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Epidemiology of hypoglycaemia: Trends, risk factors and outcomes

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Abstract

Background: Few data are available on the burden, risk factors, and outcomes of hospitalisation for hypoglycaemia. Newer glucose-lowering medications, such as glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium–glucose cotransporter 2 (SGLT2) inhibitors, have been associated with a lower risk of hypoglycaemia in individual randomised controlled trials (RCTs); yet, they have not been systematically compared to older therapies. Lastly, recent observations have also suggested an association between hypoglycaemia and cardiovascular mortality.

Methods: This research is structured in three parts. First, I used the NHS Hospital Episode Statistics data to: examine trends of admissions for hypoglycaemia in England between 2005 and 2014; define risk factors for admissions and differences in outcomes; develop and validate prognostic models to calculate risk of inpatient death and length of hospital stay. Second, I compared the risk of hypoglycaemia for once-weekly GLP-1RAs and SGLT2 inhibitors vs other medications with network meta-analyses of RCTs. Third, I investigated the relationship between fasting plasma glucose and risk of arrhythmias in a cohort study, aiming to clarify the pathophysiological mechanisms linking hypoglycaemia to cardiovascular disease.

Results: Admissions for hypoglycaemia increased between 2005 and 2010, with more stable trends thereafter. Differences exist across regions in England for both trends and risk factors for admissions: these findings have been instrumental for the development of a tool to calculate individual risk of inpatient mortality and length of hospital stay. Meta-analyses indicated a lower risk of hypoglycaemia for GLP-1RAs and SGLT2 inhibitors compared to older glucose-lowering therapies. Lastly, in the cohort analysis, there was an inverse relationship between fasting plasma glucose and risk of arrhythmias.

Conclusion: This thesis can broaden understanding of the burden of hospitalisation for hypoglycaemia and elucidate the link between hypoglycaemia and cardiovascular disease. These results could also assist decision makers in the adoption of individual- and population-level strategies.

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List of Abbreviations (alphabetical order)

ADA	American Diabetes Association
CVD	Cardiovascular Disease
EASD	European Association for the Study of Diabetes
eGFR	Estimated Glomerular Filtration Rate
FPG	Fasting Plasma Glucose
GLP-1RAs	Glucagon-like peptide-1 receptor agonists
HES	Hospital Episode Statistics
HR	Hazard Ratio
ICD–10	International Classification of Diseases, 10th revision
IDDM	Insulin-dependent Diabetes Mellitus
IMD–10	Deciles of Index of Multiple Deprivation
KIHD	Kuopio Ischaemic Heart Disease
NIDDM	Non-Insulin-dependent Diabetes Mellitus
NMA	Network Meta-Analysis
OR	Odds ratio
PROGRESS	PROGnosis RESearch Strategy
RCT	Randomised Controlled Trial
SCD	Sudden Cardiac Death
SD	Standard Deviation
SGLT1	Sodium–Glucose cotransporter 1
SGLT2	Sodium–Glucose cotransporter 2
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus

Publications related to this thesis (chronological order)

Zaccardi F, Webb DR, Kurl S, Khunti K, Davies MJ, Laukkanen JA. Inverse association between fasting plasma glucose and risk of ventricular arrhythmias. Diabetologia. 2015; 58:1797-802.

Zaccardi F, Htike ZZ, Webb DR, Khunti K, Davies MJ. Benefits and Harms of Once-Weekly Glucagon-like Peptide-1 Receptor Agonist Treatments: A Systematic Review and Network Meta-analysis. Ann Intern Med. 2016; 164:102-13.

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Zaccardi F, Webb DR, Htike ZZ, Youssef D, Khunti K, Davies MJ. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. Diabetes Obes Metab. 2016; 18:783-94.

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Zaccardi F, Webb DR, Davies MJ, Dhalwani NN, Gray LJ, Chatterjee S, Housley G, Shaw D, Hatton JW, Khunti K. Predicting hospital stay, mortality and readmission in people admitted for hypoglycaemia: prognostic models derivation and validation. Diabetologia. 2017; 60:1007-1015.

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Chapter One: Research rationale and thesis organisation

This PhD thesis focuses on the epidemiology of hypoglycaemia. Hypoglycaemia is a common side effect of glucose-lowering therapies, negatively affects quality of life, and is potentially associated with an increased risk of cardiovascular and all-cause mortality. Given the demographic changes in industrialised and emerging countries and the related shift in health problems (from communicable to non-communicable diseases), the incidence and prevalence of diabetes mellitus are projected to increase dramatically. A greater prevalence of diabetes in general, and in older people in particular, will potentially result in an increase incidence and prevalence of hypoglycaemia in frail people with multiple morbidities.

Following a brief introduction describing clinical aspects of hypoglycaemia (**chapter 2**), this thesis describes the research I have conducted. Using microdata (individual participant data) and macrodata (study-level data), I have organised my research in three parts (**Table 1.1**). First, I have used Hospital Episode Statistics (HES) microdata which includes all hospital admissions to National Health Service (NHS) trusts in England to: A) investigate trends of hospital admissions for hypoglycaemia and of outcomes length of stay, readmissions, and inpatient mortality following hospitalisation, in the period between 2005 and 2014 in England; B) characterise risk factors for admissions for hypoglycaemia and differences in these outcomes, using a case-control design; C) develop and validate prognostic models for these outcomes. Hospital admissions have been investigated from these three prospectives in **chapter 3**. This part of the thesis is related to hypoglycaemia recorded in HES; as such, the focus was on "all" hypoglycaemic episodes and could not be specifically related to diabetes therapies.

Second, to help interpret the results of hospital admissions trends and to compare the risk of hypoglycaemia with newer vs older glucose-lowering therapies, I have used available macrodata from randomised controlled trials (RCTs) to perform systematic reviews and network meta-analyses of once-weekly glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium–glucose cotransporter 2 (SGLT2) inhibitors (**chapter 4**), as they are potentially associated with a lower risk of hypoglycaemia. This chapter therefore focuses on hypoglycaemia related to diabetes therapies (iatrogenic hypoglycaemia).

Lastly, individual data from the Kuopio Ischemic Heart Disease prospective study have been used to clarify the relationship between low fasting plasma glucose and risk of arrhythmic disorders, with the aim to elucidate possible pathophysiological mechanisms linking hypoglycaemia to cardiovascular risk (**chapter 5**).

For each investigation, results were interpreted and put in context of available evidence synthesised with systematic reviews of the literature. As a rule, key results are reported in the main text while findings of further analyses (i.e., sensitivity analyses) or summaries of available evidence are shown in the appendices (**chapter 7**), following the conclusions (**chapter 6**).

Table 1.1: Data, analyses, and goals of the research

Data source	Data type	Main methodology	Goal	Chapter
Hospital Episode Statistics (HES), England 2005-2014	Microdata Administrative database	Logistic and Poisson regression	To define trends of hospital admissions for hypoglycaemia and of outcomes length of stay, readmissions, and inpatient mortality following admission (A)	3
		Multivariate meta-analysis	To identify risk factors for hospital admissions for hypoglycaemia and differences in these outcomes (B)	
		Model development, validation, and performance indices	To develop and validate prognostic models for these outcomes (C)	
Published Literature	Macrodata RCTs	Multivariate network meta-analysis	Quantify the risk of hypoglycaemia comparing newer vs older glucose-lowering therapies: once-weekly glucagon-like peptide-1 receptor agonists (D) and sodium–glucose cotransporter 2 inhibitors (E)	4
Kuopio Ischemic Heart Disease Study (KIHD)	Microdata Prospective study	Cox time-to-event analysis	Clarify the relationship between low fasting glucose and risk of arrhythmias to elucidate the pathophysiology of hypoglycaemia and cardiovascular risk	5

Chapter Two: Introduction

Hypoglycaemia in diabetes

Diabetes mellitus is a cardiometabolic disorder associated with an increased risk of cardiovascular diseases (CVDs) [1, 2]. Its most common form, type 2 diabetes mellitus (T2DM), is characterised by a defect in insulin function (insulin resistance) which is initially compensated for by an increased synthesis of insulin (hyperinsulinaemia). With progression of the disease, β-cells are no longer able to produce enough insulin and hyperglycaemia develops [3]. Conversely, in the majority of type 1 diabetes mellitus (T1DM) patients an immune-mediated destruction of β-cells results in a moderate to severe degree of insulinopenia (lack of insulin) [3]. Large epidemiological studies have demonstrated a two- to three-time increased risk of CVD events in T2DM compared to subjects without diabetes [1, 2] while for T1DM data are less clear, although the risk has been reported to be up to ten times higher [4, 5].

Although hyperglycaemia defines diabetes (diagnostic abnormality) [6], the potential causal link between glucose levels and CVD complications has been demonstrated in long-term randomised controlled trials (RCTs). The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (EDIC/DCCT) study [7], in subjects with type 1 diabetes, and 10-year follow-up of the United Kingdom Prospective Diabetes Study (UKPDS) study [8], in type 2 diabetes, have demonstrated a reduction of CVD events associated with a reduction of glucose levels. Many glucose-lowering drugs are available to complement lifestyle change in people with diabetes. With some exceptions, a "side effect" of glucose-lowering therapies is an increased risk of hypoglycaemia (iatrogenic hypoglycaemia). In particular, in most patients with longstanding diabetes the achievement of acceptable glucose control is possible only with insulin, which has been consistently associated with a significant risk of hypoglycaemia in both observational studies and large randomised controlled trials [9].

Although early clinical trials have demonstrated a reduction of CVD events associated with glucose control, recent "near-to-normal" glucose targets (ACCORD, ADVANCE, and VADT RCTs) have surprisingly demonstrated a nonsignificant reduction or even an increased risk of events in intensively-treated subjects with T2DM [10]. These observations have driven extensive research aiming to identify contributory factors, among which previous cardiovascular disease and autonomic neuropathy seem to be the most relevant [11, 12]. Hypoglycaemia has also been considered one of the potential reasons [13]. Episodes of hypoglycaemia have long been recognised as a "side-effect" of commonly prescribed diabetes medication and their impact on quality of life is well-known. Extensive *post-hoc* observational analyses of randomised controlled

trials, meta-analyses, and “real-world” data have confirmed the strong association between hypoglycaemia events and risk of all-cause and cardiovascular mortality although they have also added uncertainty as to the true causal role of hypoglycaemia [14-17].

Clinical characteristics and classification of hypoglycaemia

Hypoglycaemia results from an imbalance between glucose availability and glucose utilization [18], the latter depending on insulin concentrations and tissue sensitivity to insulin. In most cases, excessive insulin effects are either secondary to an overstimulation of pancreatic insulin secretion (for example, by therapeutic secretagogues) or inappropriately high external insulin doses; however, factors increasing insulin sensitivity, such as physical activity, can also contribute to the development of hypoglycaemia. In their presence, low glucose levels stimulate sympathoadrenal (also known as adrenergic or neurogenic) feedback mechanisms to restore normal glucose levels essential to maintain normal cerebral function (counter-regulatory response) [19]. These adrenergic symptoms, along with effects related to neuroglycopenia (low glucose for brain cell metabolism), define the spectrum of clinical symptoms during an episode of hypoglycaemia. Neurogenic symptoms include tremor, palpitations, anxiety (which are catecholamine mediated) along with sweating, hunger, and paresthesias (which are cholinergic) while neuroglycopenic symptoms include fatigue, confusion, weakness, behavioural changes, seizures, loss of consciousness and coma, brain damage and death [20]. The physiological activation of adrenergic response may be dysfunctional in older patients and in patients with longstanding diabetes [19]: this explains experimental and clinical observations demonstrating that symptoms may develop in different patients at different glucose values. The threshold for responses to hypoglycaemia is higher if the glucose required to stimulate the response is lower and is influenced by the presence of autonomic neuropathy (lower threshold) [21, 22].

In the last two decades, several definitions/classifications have been proposed for hypoglycaemia, which could have contributed to the limited epidemiological research in this area [23]. Along with heterogeneity of the populations investigated (i.e., different absolute risk of hypoglycaemia), inconsistent methods to assess hypoglycaemia and dissimilarities in its definitions have significantly hindered the possibility to systematically compare the prevalence and incidence of hypoglycaemia across regions and over time. In 2013, the American Diabetes Association and The Endocrine Society (ADA/ES) proposed five “types” of hypoglycaemia according to the presence of the symptoms and glucose levels [24]: 1) *severe*: the episode requires assistance of another person, independent of glucose value; 2) *documented symptomatic*: the episode is characterised by symptoms of hypoglycaemia and glucose level ≤3.9

mmol/l (70 mg/dl); 3) *asymptomatic* (formerly *biochemical*): the episode is characterised only by glucose level ≤3.9 mmol/l; 4) *probable symptomatic*: symptoms of hypoglycaemia without available glucose level; 5) *pseudo-hypoglycaemia*: symptoms of hypoglycaemia with glucose level >3.9 mmol/l. However, as the glycaemic thresholds for symptoms of hypoglycaemia and for counter-regulatory response vary among patients with diabetes and within the same patient as a function of glucose control and hypoglycaemia experience, it is would be more appropriate to define hypoglycaemia according only to the symptoms, without any "numerical" threshold. These observations constituted the background of the ADA/ES definition of hypoglycaemia as "all episodes of an abnormally low plasma glucose concentration that expose the individual to potential harm" [24]. Nonetheless, in 2017 the International Hypoglycaemia Study Group (IHSG) proposed a different classification of hypoglycaemia [25], according to three levels: *level 1*, for glucose values ≤3.9 mmol/l; *level 2*, for glucose value <3.0 mmol/l (54 mg/dl); *level 3*, severe hypoglycaemia with cognitive impairment requiring third party assistance. One of the main reasons behind this newly proposed classification is the possibility to compare the effectiveness of pharmacological and non-pharmacological interventions in reducing the risk of hypoglycaemia and facilitate quantitative systematic evidence (i.e., meta-analysis) of determinants, trends, and outcomes related to hypoglycaemia. From this perspective, the IHSG position statement will undoubtedly facilitate future research in the field of hypoglycaemia, particularly its epidemiology. In this thesis, although the identification of hypoglycaemia relied on the ICD–10 (International Classification of Diseases, 10th revision) codes, heterogeneous definitions and assessment of hypoglycaemia are possible in HES data; as such, differences across regions and over-time could be partly related to variable exposure definition, yet the quantification of its impact on the results is difficult. Similarly, for intervention studies definitions are generally the same only in RCTs of the same sponsoring company: this could favour drugs tested in RCTs where thresholds to define a hypoglycaemia event were lower (i.e., less hypoglycaemic events).

Mechanisms of hypoglycaemia-associated complications

Different mechanisms have been proposed to explain the relationship between hypoglycaemia and the increased risk of cardiovascular events and mortality observed in observational studies. They can be broadly classified in four partially overlapping groups: arrhythmic, inflammatory, haemorrheological, and vascular. The sympathoadrenal activation during the episode of hypoglycaemia results in the release of epinephrine which, in turn, stimulates hepatic gluconeogenesis and increases heart rate and stroke volume. Experimental studies in subjects

with diabetes have shown several arrhythmic abnormalities when an electrocardiogram is simultaneously performed with a hyperinsulinaemic-hypoglycaemic clamp [26]. During the state of controlled hypoglycaemia, electrocardiographic changes observed include lengthening of the corrected QT interval, increased QT dispersion with a greater heterogeneity of repolarization, and T-wave symmetry: these abnormalities are potentially associated with an increased risk of ventricular tachycardia, ventricular fibrillation, and sudden death (fatal arrhythmias) [27]. Notably, arrhythmias have also been reported during nocturnal spontaneous hypoglycaemia in subjects with continuous glucose and electrocardiogram monitoring [28]. While arrhythmic changes are likely mediated by β-adrenergic receptors (in animal models, their pharmacological inhibition prevents most of the electrocardiographic abnormalities [29]), hypoglycaemia can be proarrhythmic via other mechanisms, including insulin-induced hypokalaemia and a direct effect of lack of glucose for myocardiocytes.

Several studies have also demonstrated higher levels of pro-inflammatory cytokines during hypoglycaemia, particularly tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), IL-8, IL-1β, soluble CD40L, intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1, and vascular endothelial growth factor (VEGF) [27]. These changes occur in parallel with haemorrheological alterations, including higher levels of fibrinogen, factor VIII, plasminogen activator inhibitor-1, and soluble P-selectin levels and an enhanced platelet activation/aggregation. Together, these alterations contribute to a prothrombotic state and an abnormal fibrinolytic balance. More recently, an impaired nitric oxide (NO)-mediated vasodilation has been described during hyperinsulinaemic-hypoglycaemic clamp, particularly for repeated episodes of hypoglycaemia [30], indicating a role for endothelial dysfunction as another possible mechanism related to cardiovascular complications. Overall, the available evidence from experimental studies suggests that a combination of inflammatory and haemorrheological changes contribute to an increased risk of coronary atherosclerosis and atherothrombosis, a harmful substrate on which the sympathoadrenal activation determines the fatal arrhythmic episode.

Although hypoglycaemia has been associated with cardiovascular events and mortality in epidemiological observations and potential mechanisms have been described in experimental human and animal studies, it is not possible to definitely exclude that, in some circumstances, hypoglycaemia represents only a marker of other conditions associated with an increased risk of cardiovascular disease (i.e., a confounder). Hypoglycaemia is associated with diabetes-related complications (mainly chronic kidney disease, autonomic neuropathy), longer duration of diabetes, worse diabetes control, and frailty [31]: these factors could indeed be the “real cause” behind the increased risk of events, making hypoglycaemia only a “innocent bystander”. In the

analyses of observational data reported in this thesis, associations have been adjusted for multiple factors to account for potential confounders, although statistical adjustment does not demonstrate a causal link between the exposure (hypoglycaemia) and the outcome (cardiovascular complications) [32].

Risk factors for hypoglycaemia

Within the limitation of the definition of hypoglycaemia, in the last three decades several studies have identified potential risk factors for hypoglycaemia. Age has been consistently shown to be associated with hypoglycaemia in both type 1 and type 2 diabetes: the incidence of severe hypoglycaemia is around twice as high in subjects with type 1 diabetes older than 60 years compared to <60 years (4.0 vs 2.4 episodes person/year [33]). Other studies have reported a U-shape association, the risk being higher for young children and elderly patients [34, 35], possibly reflecting the phenotype type 1 and insulin-treated type 2, respectively. The duration of disease, in type 1 diabetes [36], and of insulin treatment, in type 2 diabetes [37], have also been related to the risk of hypoglycaemia. In RCTs, intensive glucose control increases the risk of severe hypoglycaemia in both type 1 [38, 39] and type 2 diabetes [40-42].

Patients with diabetes-related complications, particularly chronic kidney disease [43, 44] and autonomic neuropathy [21], experience higher rates of hypoglycaemia. Although both conditions could be a marker of longstanding (or not well controlled) diabetes, their presence directly influences the risk of hypoglycaemia by reducing the clearance of several glucose-lowering drugs [45] and the counter-regulatory response to hypoglycaemia [21], respectively. Notably, the association between diabetes complications and risk of hypoglycaemia could be seen in the context of an increased risk of hypoglycaemic episodes in frail people with multimorbidity. Frailty is defined as a “condition characterized by a reduction in physiological reserve and in the ability to resist physical or psychological stressors” [31], can be measured using different indices [46], and is positively associated with multimorbidity [47]. In large primary care databases, there are generally no specific measures of frailty although some “electronic” frailty indices have been developed and validated using information routinely available in these databases [48, 49]. Similarly, administrative hospital databases have no specific information on frailty, yet the Charlson comorbidity score is commonly used as a surrogate marker because it can be accurately estimated from the ICD codes. The relationship between frailty and hypoglycaemia is complex and likely bidirectional [31, 50]: hypoglycaemia increases the risk of cognitive impairment, falls and fractures, and lower treatment adherence

and daily activities, all risk factors for frailty; on the other hand, frailty has been associated with a 1.3 to 6.1 increased risk of severe hypoglycaemia [51].

Also dementia has been also associated with an increased risk of hypoglycaemia. Similar to frailty, the relationship between dementia and hypoglycaemia is bidirectional [52], as there is both evidence of a higher risk of dementia in patients experiencing hypoglycaemia [53] and of hypoglycaemia in patients with dementia [54]. The relationship between social deprivation and hypoglycaemia is less clear: a recent systematic review has evidenced contradictory associations of socio–economic status and area–level deprivation with hypoglycaemia in patients with type 1 diabetes [55]. This finding may be attributable to the heterogeneous assessment of socio–economic status across the included studies: similar to frailty, several measures are available to assess socio–economic status, including income, employment, education, or insurance status. In large epidemiological studies, socio-economic status is measured differently according to the nature of the data and the country. In the UK, the Index of Multiple Deprivation (IMD) is a well-established measure of multiple deprivation based on a combination of seven distinct domains of deprivation, including: income; employment; education, skills and training; health and disability; crime; barriers to housing and services; and living environment deprivation [56]. IMD is updated yearly to describe the pattern of deprivation in the UK and is regularly used in the analysis of both primary care databases and HES.

Lastly, a key determinant of the risk of hypoglycaemia is glucose-lowering therapy. Insulin secretagogues (sulphonylureas and glinides) and insulin are well-recognised potential cause of iatrogenic hypoglycaemia, which is responsible for around 25% of all emergency hospitalizations for adverse drug events in US adults 65 years of age or older (13.9% insulin; 10.7% oral hypoglycaemic agents [57]). There is therefore a need to reduce the burden of hypoglycaemia, with positive impact at both individual- and population-level. Other glucose-lowering drugs have the potential to reduce the burden of iatrogenic hypoglycaemia given their pharmacological properties. Insulin secretagogues and insulin increase the risk of hypoglycaemia as they alter the levels of circulating endogenous and exogenous insulin, respectively. Conversely, metformin and thiazolidinediones enhance peripheral insulin sensitivity; α-glucosidase inhibitors reduce the intestinal absorption of glucose; incretin mimetics (dipeptidyl peptidase-4 inhibitors (DPP-4i) and glucagon-like peptide-1 receptor agonists (GLP-1RAs)) increase endogenous and exogenous levels of glucagon-like peptide-1, respectively, which has a glucose-dependent mode of action (the glucose-lowering effect, mediated by insulin release, is positively related to glucose levels); and sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce tubular glucose reuptake thus resulting in an enhanced glycosuria [58]. All these therapies should not, in principle, cause

hypoglycaemia, yet they could possibly increase the risk in combination with secretagogues or insulin.

Overall, the available evidence about risk factors for hypoglycaemia would suggest a complex syndemic of biological, clinical, demographical, and socio-economic elements which interplay in determining the individual risk of hypoglycaemia [59].

PROGnosis RESearch Strategy (PROGRESS)

In the definition of the goals of this research, in particular of those reported in **chapter 3**, I have followed the PROGnosis RESearch Strategy (PROGRESS) partnership recommendations. The main aim of prognosis research is to understand and improve future outcomes in people with a given disease or health condition. However, the quality of prognosis research is poor and new standards need to be defined and improved. Within this remit, the PROGRESS partnership developed methods and recommendations to improve prognosis research and reduce its gap with translational, health impact [60]. These recommendations have been reported within four interlinked themes: 1) fundamental prognosis research; 2) prognostic factor research; 3) prognostic model research; 4) stratified medicine research.

Any prognostic research should firstly describe and quantify future outcomes in people with a specific disease or health condition (*fundamental prognosis research*). This initial step is required to clarify the overall impact of current diagnostic and treatment practices (average prognosis, i.e. change in diabetes-related mortality in the last three decades) and the specific impact of potential factors associated with the outcomes (specific prognosis, i.e. diabetes-related mortality in ethnic minorities). Quantitative information on prognosis is also instrumental for public health policy makers to model the burden of a disease in order to develop population-level strategies.

The second step consists in the identification of potential prognostic factors for the disease under investigation (*prognostic factor research*) [61]. Prognostic factors (i.e., blood-based biomarker, bioimaging, anthropometric, demographic, or social factor) are generally measured at a certain point during the natural history of the disease and are associated with subsequent endpoint/outcome. A well-known example is total cholesterol (prognostic factor) and cardiovascular mortality (outcome). In large prospective databases, information on prognostic factors is available for multiple time points and multiple, repeated measurements of one or more factors can be used.

The third step (*prognostic model research*) is complementary to the second and has three main phases [62]: a) prognostic model development (including internal validation); b) external,

spatiotemporal validation; c) investigations of impact in clinical practice (clinical decision model). Notably, a significant association between a risk factor and an outcome does not necessarily results in an improvement of risk prediction performance when the risk factor is included in the model [63]. Furthermore, while the literature is abundant on fundamental prognosis research and prognostic factor research, the number of available prognostic models is limited and relatively few, of those developed, have been implemented in clinical practice. These two observations underline the crucial role of this step in the direction of prognostic research improvement. It should be also noted that prognostic models may underperform over time (mainly because of the therapeutic changes and different average prognosis); therefore, existing models need to be improved by recalibration or adding novel predictors.

The last step (*stratified medicine research*) is the final goal of prognosis research [64] and refers to targeting treatments according to the risk characteristics shared by a subgroup of patients (i.e., personalised medicine). For example, treatments could be stratified by the absolute risk (i.e., initiating statin treatment according to absolute risk of cardiovascular disease quantified with a prognostic model in step three) or the presence of individual factors (i.e., immunotherapy according to the presence of the cellular HER-2 receptor in breast cancer).

In **chapter 3** of the thesis, I have followed the PROGRESS suggestions (**Table 1.1**). I have firstly described trends of hospital admissions for hypoglycaemia and of outcomes length of stay, readmissions, and inpatient mortality following admissions (*fundamental prognosis research*, *average prognosis of patients*; **part A**); then, I have identified risk factors for hospital admissions and outcomes differences following hospitalisation (*prognostic factor research* and *specific prognosis of patients*, respectively; **part B**); lastly, I have developed and validated a risk prediction model for the three outcomes (*prognostic model research*; **part C**). The fourth step (*stratified medicine research*) is ongoing, as the prognostic model is being implemented as a mobile app to guide clinical decision according to the absolute risk of the outcomes.

Chapter Three: Admissions to hospital for severe hypoglycaemia

Summary

In this chapter, I investigated temporal trends of hospital admissions for hypoglycaemia in England using HES data. Then, in an observational case-control study, I explored differences in risk factors for admissions and outcomes following admissions (that is, inpatient mortality, length of hospitalisation, and readmissions). Lastly, I have developed and temporally validated a risk model which predict the three outcomes using individual patient data. The trend analysis showed a rise in hospital admissions for hypoglycaemia between 2005 and 2010 and a stable trend between 2010 and 2014. The risk of admissions reaches a nadir at 60 years old, with significant differences across ethnicity (lower risk of admissions for South-East Asians and higher for Caribbeans). The risk score showed good calibration and discrimination when estimating length of hospital stay and risk of in-hospital death while the accuracy for predicting the probability of readmission was modest.

Background

Most hypoglycaemic episodes are of mild severity and self–treated by patients. Conversely, severe episodes are less common (1–2 episodes per year in insulin–treated patients), need third party assistance, and are potentially associated with short– and long–term risk of complications such as convulsions, injuries, permanent impairment of cognitive function, and death [17, 65, 66]. Some of these episodes require attendance at accident and emergency departments or hospital admission. Although hospital admissions are considered the “tip of the iceberg”, they represent a significant burden for patients and have significant resource implications [67], with a mean estimated cost per admission for hypoglycaemia in England of ~£1,000 and a total annual direct cost in the UK of ~£13 million [68, 69].

Given the rise in diabetes prevalence and ageing population [70, 71], it may be assumed the number of admissions to hospital due to hypoglycaemia have increased in recent years. Trends have been described in North America [72-76], Japan [77], and Italy [78] while detailed analyses for other countries are lacking. Published studies have also identified clinical, demographic, and socioeconomic factors associated with the risk of hypoglycaemia [9, 79], although evidence from large observational studies is more limited. The identification and estimation of risk factors could help identify at–risk patients and guide the implementation of appropriate individual– and population–level prevention strategies. Moreover, differences in length of hospitalisation and

risk of mortality and readmissions between subjects with diabetes admitted for hypoglycaemia and those without hypoglycaemia have not been investigated.

Risk prediction models are essential for implementing stratified/personalised interventions (PROGRESS step 3) [62]. In the field of hypoglycaemia, prediction models have been developed to estimate the probability of: inpatient hypoglycaemia [80]; hypoglycaemia within 24 hours [81]; severe hypoglycaemia within 6 months [82]; hypoglycaemia within 12 months [83]; and emergency or hospitalisation for hypoglycaemia within 12 months [84]. Inconsistently, these models used self-monitored blood glucose, biochemical, anthropometric, and medication data. Several risk prediction models have also been developed and validated for risk of inpatient mortality, length of hospital stay, and hospital readmission in different clinical settings, particularly cardiovascular diseases [85-89]. To date, however, no model is available for patients admitted to hospital for hypoglycaemia. As these admissions are generally characterised by a lower risk of inpatient death (2-4%) and a shorter length of stay (usually <24 hours) compared to admissions for other medical reasons [69, 85, 90-92], the applicability of available prediction models to patients admitted for hypoglycaemia would result in biased risk estimates.

Aims

Within this context, the aims of this first part of the research were:

1. To characterise trends of hospital admissions for hypoglycaemia and of the outcomes length of stay, readmissions, and inpatient mortality following hospitalisation during 2005-2014 in England (**part A**)
2. To investigate risk factors for admissions for hypoglycaemia and differences in these outcomes (**part B**)
3. To develop and validate a risk prediction model for these outcomes (**part C**)

Data source

To investigate trends, risk factors, differences in outcomes, and develop prognostic models, I have used data from the HES [93]. HES is a record-based system that covers all National Health Service trusts in England, including acute hospitals, primary care trusts and mental health trusts and contains details of all admissions, outpatient appointments and accident and emergency attendances. Data are collected during patient's time at hospital and are submitted to allow hospitals to be paid for the care delivered. However, HES data are also designed to enable secondary use: as of 15 November 2016, there were 760 PubMed reports using “hospital episode statistics [title/abstract]” search keywords, from 2 reports in 1994 (minimum) to 136 in

2016 (maximum). For these analyses, I have extracted data on all admissions for hypoglycaemia and on the outcomes length of hospital stay, inpatient mortality, and readmissions between 1/1/2005 and 31/12/2014. Included episodes reported the first ICD–10 diagnosis field E160 (drug–induced hypoglycaemia without coma), E161 (other hypoglycaemia), or E162 (hypoglycaemia, unspecified) and E10+ (diabetes type 1) or E11+ (diabetes type 2) in any of the remaining ICD–10 fields (from 2nd to 20th). For all episodes, data were available on age, sex, ethnicity, region of usual residence, start and end date of the episode, admission and discharge method, IMD and Charlson comorbidity score [94] (**Appendix A, Table A1**). Charlson score is one of the most used index to quantify multimorbidity in epidemiological studies. It combines information on the prevalence of comorbid conditions such as heart disease, cancer, AIDS by assigning to them a score of 1, 2, 3, or 6; the total score, obtained by the sum of each score, is a strong predictor of one-year mortality [94]. Simulations studies have confirmed the utility of the Charlson score instead of individual comorbidity variables in health services and epidemiological research [95]. However, the score is assigned according to the presence/absence of the disease (i.e., binary), disregarding the continuous nature of disease severity.

A. Trends of admissions to hospital for hypoglycaemia in England

Analytical approach

To examine trends of hospital admissions for hypoglycaemia, I first calculated absolute number of admissions by region (East, East Midlands, London, North East, North West, South East, South West, West Midlands, and Yorkshire–Humber) and age groups (<20 years old; 20–29; 30–39; 40–49; 50–59; 60–69; 70–79; ≥80). Second, for each age–group, sex, and ethnicity (White, Caribbean, Indian, Pakistani, other, not available), I estimated mean IMD–10 (deciles of IMD) and Charlson score [94] and group-specific total number of admissions; adjusted trends were then estimated with Poisson regression, which is the statistical method used to analyse count data. Poisson model can account for different exposures (i.e., number of hypoglycaemia over time or region); in this specific analysis, however, the number of events has been summarised per calendar year and considered for the entire England; therefore, no exposure was added (i.e., count only model). Because Poisson regression assumes that the variance is equal to the mean, the assumption has been relaxed using robust standard error, as previously suggested [96]. Third, to account for trends of overall hospital admissions in England and changes of diabetes prevalence, total hospital admissions and prevalence of diabetes were obtained from publicly available HES reports [93, 97]; I used logistic regression to estimate trends accounting for total hospital admissions (i.e., proportions) and Poisson regression to calculate rates using the

number of admissions for hypoglycaemia as numerator and the year mid-point prevalence of diabetes as denominator/exposure. Rates were reported only from 2010 to 2014 and only for subjects aged 17 or older to be consistent with available prevalence data.

Length of hospital stay (categorised in five ordered groups of similar size: same day discharge; day after discharge; two to three days; four to eight days; nine or more days), inpatient mortality, and one-month readmissions were also calculated from HES data. I have applied an ordered logistic regression, adjusted for age, sex, ethnicity, IMD–10, and Charlson score, to assess trend over time of hospital length of stay and a logistic regression with the same covariates to characterise trends for hospital mortality and one–month readmissions. An ordered logistic regression (also known as proportional odds model) is used when the outcome/response is ordinal (length of stay) and the data meet the proportional odds assumption; it can be considered an extension of the logistic regression (binary outcome). Odds ratios of risk factors were pooled across regions by random–effects meta–analyses and heterogeneity in the associations was estimated by the I^2 statistic [98]. The two-step meta-analytical approach combines estimates of several parameters (coefficients of the covariates) over different regions: the advantage of this approach, over a one-step approach (all regions considered together), is the possibility to visualise in forest plots and quantify differences across regions, which are numerically shown by larger I^2 values (as a general indication, I^2 >30% indicate moderate heterogeneity; >50% substantial; and >75% considerable). Heterogeneity suggests that the association between the exposure and the outcome investigated differs across regions. For all analyses, I considered calendar time as a factor variable allowing trends to be non-linear and used the first available year as baseline.

Stata, version 14.1 (Stata Corp, College Station, Texas), was used for all analyses, and results are reported with 95% confidence intervals (CIs).

Results

Characteristics of admissions for hypoglycaemia

From 1/1/2005 to 31/12/2014, in England there were a total of 101,475 hospital admissions for hypoglycaemia in 79,172 people, of which 65,248 (82%) had a single episode (**Table 3.A1**). Almost 50% admissions occurred in females and 81% in White Caucasian; the mean Charlson score was 2.0 (**Table 3.A2**). A greater number of admissions occurred with increasing age, with subjects aged 60 or older accounting for 72% of total cases (**Table 3.A2, Figure 3.A1**); the largest number of admission was in North–West (18169, 17.9%) while the lowest in North–East (6940,

6.8%). Adjusted for sex, ethnicity, IMD–10, and Charlson comorbidity score, age showed a J–shaped relationship with admissions (**Figure 3.A2**).

Temporal trends

The crude number of admissions increased progressively over time, from 7,868 in 2005 to 11,756 in 2010 (49% increase), and then remained more stable until 2014 (10,977; 39% increase from baseline) (**Figure 3.A3**); the trend was similar after adjusting for risk factors, with a rate ratio of 1.53 (95% CI: 1.29 to 1.81) comparing 2014 to 2005 (**Figure 3.A4**). When admissions for hypoglycaemia were estimated per total hospital admissions, there was an increase from 2005 for all the following years, with a peak in 2010/11 and a subsequent decline (**Figure 3.A5**). Total admissions progressively increased from 12.7 million in 2005/6 to 15.5 million in 2013/14 (22% increase) while 63 admissions for hypoglycaemia per 100,000 total admissions were recorded in 2005/6, increasing to 79 in 2010/11 (24% increase), and then declining to 72 in 2013/14 (14% increase from baseline). Similarly, adjusting for diabetes prevalence, there was a decline between 2010/11 and 2013/14: diabetes prevalence in people aged 17 or older increased from 2.39 million in 2010/11 to 2.75 million in 2013/14 (16% increase) while admissions decreased from 11,133 to 10,653 (4% decrease), resulting in rates declining from 4.64 admissions for hypoglycaemia/1000 person-years with diabetes in 2010/11 to 3.86 in 2013/14 (rate ratio 2013/14 vs 2010/11: 0.83; 0.81 to 0.85) (**Figure 3.A6**).

Hospital length of stay, mortality, and readmissions

Around 24%, 47%, 68%, and 75% of all admissions resulted in a length of hospital stay ≤24 hours, ≤48 hours, ≤5 days, and ≤7 days, respectively (**Figure 3.A7**). Female sex, older age, higher Charlson score, and lower IMD–10 (i.e., more deprived) were significantly associated with a longer length of hospital stay, while Indian ethnicity was associated with a shorter stay (**Figure 3.A8**). Heterogeneity across regions in the associations between the risk factors and length of stay was moderate to high (I^2 from 30% to 97%) (**Figure 3.A8 and 3.A9**). The crude proportion of same day discharge increased from 21.4% (1685 out of 7486 admissions) in 2005 to 24.9% (2730 out of 10,974) in 2014. In the analysis adjusted for risk factors, the proportion being discharged on the same day of admission increased by 43.8% (95% CI: 33.9 to 53.6), from 18.9 (16.8 to 20.9) per 100 admissions in 2005 to 27.1 (25.1 to 29.1) in 2014 (**Figure 3.A10**).

Three percent of all admissions resulted in hospital death (3109 out of 101,475). Age and Charlson score were independently associated with higher mortality (**Figure 3.A8**), with moderate–high heterogeneity across regions (I^2 from 23% to 90%; **Figure 3.A8 and 3.A9**). The

crude inpatient mortality decreased from 3.6% (280 out of 7860 admissions) in 2005 to 2.7% (296 out of 10,976) in 2014 and the risk factors–adjusted inpatient death declined by 46.3% (95% CI: 40.4 to 52.2), from 4.2 (3.8 to 4.7) per 100 admissions in 2005 to 2.3 (2.0 to 2.5) in 2014 (**Figure 3.A10**).

During the study period, almost 18% of all admissions for hypoglycaemia occurred in people with a previous episode (**Table 3.A1**); of these readmissions, around 23% occurred within one–month. One–month readmissions decreased significantly over time, accounting for 48.1% of total readmission in 2005 and for 17.9% in 2014. Adjusted for risk factors, one–month readmissions declined by 63.0% (95% CI: 58.6 to 67.4), from 48.1% (43.6 to 52.5) per 100 readmissions in 2005 to 17.8% (16.5 to 19.1) in 2014 (**Figure 3.A10**). None of the included risk factors was independently associated with one–month readmission (**Figure 3.A8 and 3.A9**).

Regional differences

During the study period, improved trends for the three outcomes were to some extent different across regions. Comparing 2014 to 2005, substantial heterogeneity was found for same day discharge (I^2 63%; 95% CI: 24 to 82), with the highest and lowest changes for West and East Midlands, respectively (**Figure 3.A11**). On the other hand, there was lower heterogeneity for both mortality (I^2 0%; 0 to 65; highest and lowest changes for West Midlands and Yorkshire–Humber, respectively) and one–month readmission (I^2 36%; 0 to 70; highest and lowest changes for South East and Yorkshire–Humber, respectively) (**Figure 3.A11**).

Interpretation in the context of available evidence

Using national hospital admissions data for England, there was an increasing trend of admissions for hypoglycaemia from 2005 to 2014: admissions increased steadily during the first five years and stabilised from 2010 onwards; the trend was similar after adjusting for potential risk factors. Accounting for total hospitalisation there was an increase until 2010 followed by subsequent decline while accounting for diabetes prevalence there was a decline between 2010 and 2014. In people admitted for hypoglycaemia, hospital length of stay, in–hospital mortality, and one–month readmission declined consistently over the 10–year study period, with some differences across regions.

While previous similar research reporting on the burden of hospital admissions for hypoglycaemia were performed at regional level or relied on data from representative samples to estimate trends at a national level (**Appendix A, Table A2**), in this analysis I have used all hospital admissions for hypoglycaemia at a national level in England. Lipska et al. [72], relying

upon health insurance data to collect information on admissions for hypoglycaemia and national surveys to calculate diabetes prevalence, estimated trends of hospital admissions for hypoglycaemia in people aged 65 years or older at national level evidencing an absolute increase between 1999 and 2007 and a subsequent decline, with a significant 11% increase of sex–, age–, and ethnicity–adjusted rate comparing 2011 to 1999. Accounting for diabetes prevalence, however, there was a progressive decline during the entire study period. Trends have been reported in three other studies in US and Canada, yet the outcomes were slightly different. Wang et al. showed crude and age–adjusted decline of US emergency department visits in adults with diabetes between 2006 and 2011 [76], while Pathak et al. reported no clinically meaningful age– and sex–adjusted trend of US emergency department visits or hospitalisation between 2005 and 2001 in people ≥20 years old [75]. Clemens et al. found in people ≥65 years old with diabetes an absolute increase in emergency department visits or hospitalisations for hypoglycaemia from 2002 to 2006 and then a decline until 2013 while a continuous decline was found accounting for diabetes prevalence [73]. These observational studies, however, did not distinguish between type 1 and type 2 diabetes and reported trends adjusted (or stratified) only for basic characteristics which are potentially associated with severe hypoglycaemia. Moreover, some analyses were restricted to specific age ranges, making generalisation not possible, or did not account for changes in diabetes prevalence.

There was significant inter-regional heterogeneity in the impact of risk factors on the three outcomes length of stay, mortality, and one-month readmissions. Heterogeneity was lower for sex compared to age, social deprivation, and comorbidities, and was greater for length of stay and one–month readmissions than for mortality. Such divergences could possibly be related to a genuine clinical diversity of patients (attributable to factors other than those considered in the analysis) or to differences in nonclinical causes affecting the three outcomes (i.e., admission policies) and could explain differences in the improvements of the three outcomes between 2005 and 2014. Notably, differences in these outcomes across regions should be interpreted in the context of health inequalities in England already proven for other risk factors (such as alcohol consumption, smoking, childhood obesity) and outcomes (such as life expectancy and cause-specific mortality rates) [99]. In this perspective, the results of this analysis confirm and reinforce the observations of many regional variations and health gaps in England.

Although a major strength of this research is the availability of some 100,000 hospital admissions in England for ten years with information on several potential risk factors and on region of residence, it should be noted that HES data are collected for administrative rather than research purposes and there is a potential risk about completeness and accuracy. Diagnostic criteria might be not consistent with some form of subjectivity in the coding across hospitals, particularly for comorbidities [100]. Furthermore,

data are sensitive to variation between hospitals or over time in admission thresholds and information is not complete for ethnicity [100, 101]. Moreover, data on other potentially relevant risk factors which could explain these findings, such as glucose-lowering medications, are not available in HES and it was not possible to estimate admission rates accounting for diabetes prevalence before 2010 as publicly available data report prevalence only from 2010 and for subjects aged 17 or older.

Given the forecasted population ageing, the rise in multimorbidity prevalence, the increase of diabetes prevalence [102, 103], and the risk of potential overtreatment in older people [104], these results indicate that further measures will be required to at least maintain stable the absolute number of hospital admissions for hypoglycaemia in subsequent years. Older people, in particular, require a more careful balance between glucose control and risk of hypoglycaemia than middle–aged patients as the risk of complications following an episode is probably greater than the potential benefit of long–term cardiovascular risk reduction [105]. The publication of RCTs in 2008–2009 and subsequent analyses suggesting a possible hypoglycaemia–mortality link [10], the development of guidelines recommending "personalised" approaches for glucose control, and the availability of new drugs associated with a lower risk of hypoglycaemia [106], could potentially contribute, along with other factors, to the declining trend in hospital admissions and readmissions for hypoglycaemia. Moreover, screening activity for type 2 diabetes has dramatically increased over the last years and is now recommended in many countries, including the UK; this could theoretically influence the results, being people diagnosed earlier at a lower risk of hypoglycaemia (shorter duration of disease). The reduction of length of hospital stay and in–hospital mortality following admissions, on the other hand, could be attributed to tighter glucose control during hospitalisation (a narrower glucose control avoiding frequent hypo and hyperglycaemic episodes has been associated with better hospital outcomes) [107-111] or to a general improvement in hospital mortality in England [112-114].

In conclusion, this analysis describes a rise in overall hospital admissions for hypoglycaemia counterbalanced by a reduction of length of hospital stay, mortality, and readmissions over the decade 2005–2014. Region-specific data about the heterogeneous impact of risk factors on outcomes following admissions could be instrumental to tailor interventions. The availability in future of data for multiple stages, from the episode of hypoglycaemia to the hospital admission, will clarify the best approach to reduce the burden of hospital admissions for hypoglycaemia and identify at what level (population or single patients) resources should be allocated.

Tables and Figures

Table 3.A1: Overall frequency of hospital admissions for hypoglycaemia, England 2005-2014

Admission (N)	Frequency	%	Cumulative %	Total Admissions
1	65,248	82.4	82.4	65,248
2	9,698	12.3	94.7	19,396
3	2,488	3.1	97.8	7,464
4	872	1.1	98.9	3,488
5	387	0.5	99.4	1,935
6	171	0.2	99.6	1,026
7	113	0.1	99.8	791
8	63	0.1	99.8	504
9	42	0.1	99.9	378
≥10	90	0.1	100	1,245
Total	**79,172**	**100.00**		**101,475**

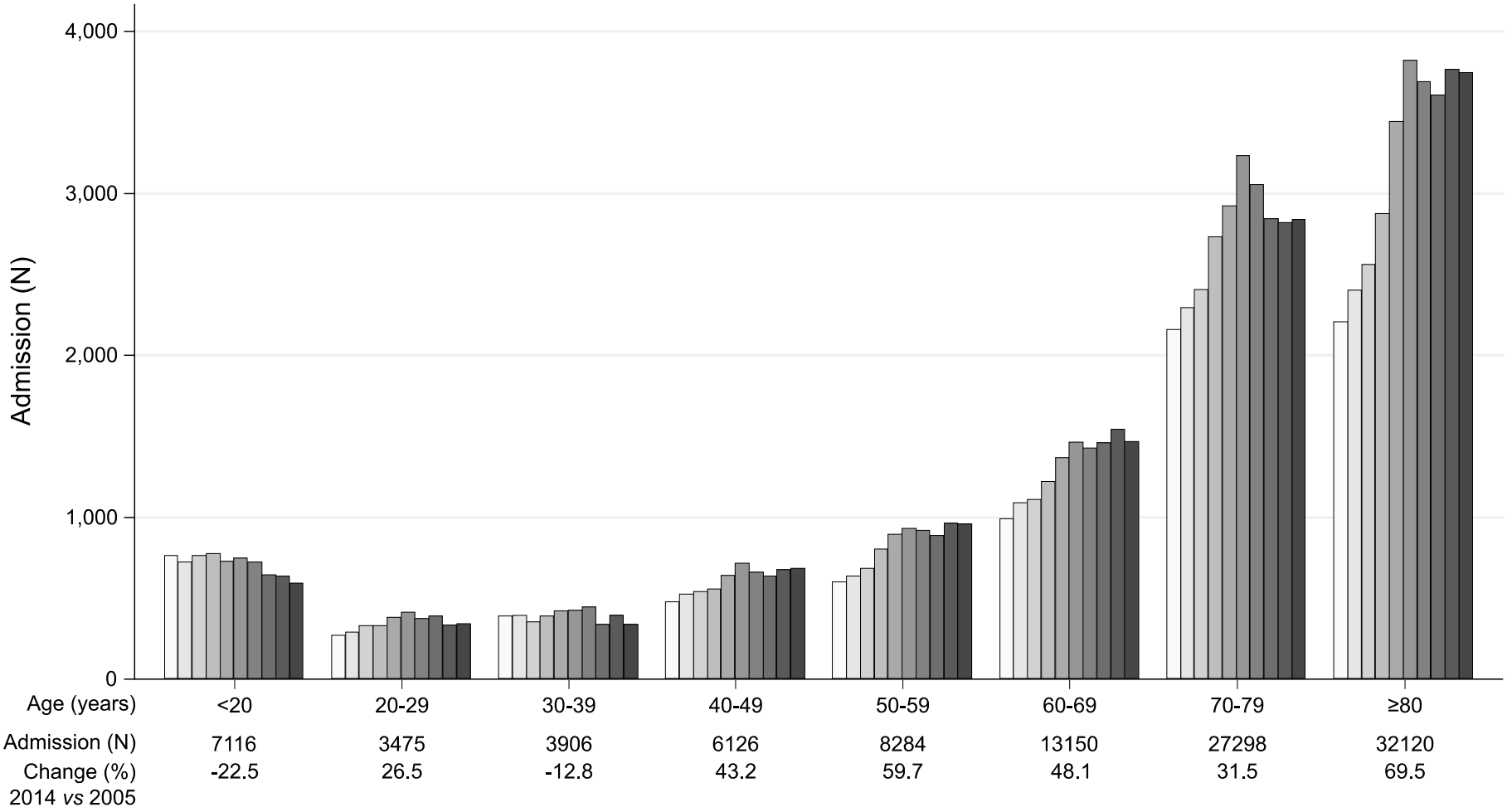
Table 3.A2: Characteristic of subjects admitted to hospital for hypoglycaemia, by region and overall, England 2005-2014

	East England	East Midlands	London	North East	North West	South East	South West	West Midlands	Yorkshire Humber	England
Total admissions – N	9460	8949	15319	6940	18169	11892	8441	11208	11097	101475
Age at admission – Years										
<20	767 (8.1)	526 (5.9)	736 (4.8)	526 (7.6)	1410 (7.8)	1052 (8.9)	652 (7.7)	712 (6.4)	735 (6.6)	7116 (7.0)
20-29	329 (3.5)	297 (3.3)	454 (3.0)	300 (4.3)	734 (4.0)	398 (3.4)	267 (3.2)	364 (3.3)	332 (3.0)	3475 (3.4)
30-39	342 (3.6)	373 (4.2)	513 (3.4)	298 (4.3)	794 (4.4)	422 (3.6)	356 (4.2)	391 (3.5)	417 (3.8)	3906 (3.9)
40-49	479 (5.1)	526 (5.9)	871 (5.7)	464 (6.7)	1154 (6.4)	720 (6.1)	514 (6.1)	715 (6.4)	683 (6.2)	6126 (6.0)
50-59	683 (7.2)	698 (7.8)	1354 (8.8)	637 (9.2)	1653 (9.1)	885 (7.4)	627 (7.4)	909 (8.1)	838 (7.6)	8284 (8.2)
60-69	1075 (11.4)	1085 (12.1)	2257 (14.7)	920 (13.3)	2501 (13.8)	1418 (11.9)	1066 (12.6)	1395 (12.5)	1433 (12.9)	13150 (13.0)
70-79	2400 (25.4)	2405 (26.9)	4545 (29.7)	1920 (27.7)	4784 (26.3)	2940 (24.7)	2116 (25.1)	3121 (27.9)	3067 (27.6)	27298 (26.9)
≥80	3385 (35.8)	3039 (34.0)	4589 (30.0)	1875 (27.0)	5139 (28.3)	4057 (34.1)	2843 (33.7)	3601 (32.1)	3592 (32.4)	32120 (31.7)
Sex (Female)	4613 (48.8)	4362 (48.7)	7265 (47.4)	3545 (51.1)	8862 (48.8)	5846 (49.2)	4055 (48.0)	5623 (50.2)	5562 (50.1)	49733 (49.0)
Charlson index	2.1 ± 1.5	2.0 ± 1.5	2.1 ± 1.5	2.0 ± 1.4	2.0 ± 1.4	2.0 ± 1.4	2.0 ± 1.5	2.1 ± 1.5	1.9 ± 1.4	2.0 ± 1.5
IMD-10*										
Least deprived 10%	803 (8.5)	486 (5.4)	272 (1.8)	147 (2.1)	589 (3.2)	1721 (14.5)	548 (6.5)	441 (3.9)	400 (3.6)	5407 (5.3)
Less deprived 10-20%	949 (10.1)	726 (8.1)	562 (3.7)	271 (3.9)	987 (5.4)	1338 (11.3)	702 (8.3)	528 (4.7)	544 (4.9)	6607 (6.5)
Less deprived 20-30%	1089 (11.5)	683 (7.6)	669 (4.4)	340 (4.9)	1023 (5.6)	1365 (11.5)	813 (9.6)	740 (6.6)	791 (7.1)	7513 (7.4)
Less deprived 30-40%	1081 (11.5)	907 (10.1)	963 (6.3)	362 (5.2)	1132 (6.2)	1330 (11.2)	938 (11.1)	806 (7.2)	827 (7.5)	8346 (8.2)
Less deprived 40-50%	1150 (12.2)	819 (9.2)	1252 (8.2)	426 (6.2)	1336 (7.4)	1395 (11.7)	1021 (12.1)	897 (8.0)	915 (8.3)	9211 (9.1)
More deprived 10-20%	636 (6.7)	1211 (13.5)	3280 (21.5)	1334 (19.3)	2626 (14.5)	882 (7.4)	755 (9.0)	1761 (15.7)	1553 (14.0)	14038 (13.9)
More deprived 20-30%	960 (10.2)	1055 (11.8)	2793 (18.3)	1008 (14.6)	2105 (11.6)	1057 (8.9)	843 (10.0)	1387 (12.4)	1289 (11.6)	12497 (12.3)
More deprived 30-40%	1200 (12.7)	1068 (11.9)	2023 (13.2)	779 (11.3)	1626 (9.0)	1132 (9.5)	1067 (12.7)	1006 (9.0)	1007 (9.1)	10908 (10.8)
More deprived 40-50%	1209 (12.8)	926 (10.4)	1457 (9.5)	575 (8.3)	1466 (8.1)	1221 (10.3)	1212 (14.4)	1060 (9.5)	926 (8.4)	10052 (9.9)
Most deprived 10%	368 (3.9)	1066 (11.9)	2009 (13.2)	1682 (24.3)	5265 (29.0)	443 (3.7)	531 (6.3)	2577 (23.0)	2839 (25.6)	16780 (16.6)
Ethnicity										
White	8162 (86.3)	7770 (86.8)	8047 (52.5)	6569 (94.7)	15879 (87.4)	10174 (85.6)	7543 (89.4)	8870 (79.1)	9590 (86.4)	82604 (81.4)
Not available	757 (8.0)	374 (4.2)	911 (6.0)	262 (3.8)	1223 (6.7)	1189 (10.0)	675 (8.0)	539 (4.8)	722 (6.5)	6652 (6.6)
Other	244 (2.6)	189 (2.1)	2924 (19.1)	52 (0.8)	421 (2.3)	260 (2.2)	120 (1.4)	345 (3.1)	211 (1.9)	4766 (4.7)
Caribbean (Black or Black British)	101 (1.1)	144 (1.6)	1917 (12.5)	4 (0.1)	158 (0.9)	59 (0.5)	62 (0.7)	603 (5.4)	118 (1.1)	3166 (3.1)
Indian (Asian or Asian British)	98 (1.0)	425 (4.8)	1201 (7.8)	27 (0.4)	143 (0.8)	120 (1.0)	30 (0.4)	473 (4.2)	99 (0.9)	2616 (2.6)
Pakistani (Asian or Asian British)	98 (1.0)	47 (0.5)	319 (2.1)	26 (0.4)	345 (1.9)	90 (0.8)	11 (0.1)	378 (3.4)	357 (3.2)	1671 (1.7)
Cardiovascular disease (Yes)	1961 (20.7)	1667 (18.6)	3005 (19.6)	1186 (17.1)	3349 (18.4)	2269 (19.1)	1698 (20.1)	2355 (21.0)	1996 (18.0)	19486 (19.2)

* IMD (Index of Multiple Deprivation) score in deciles

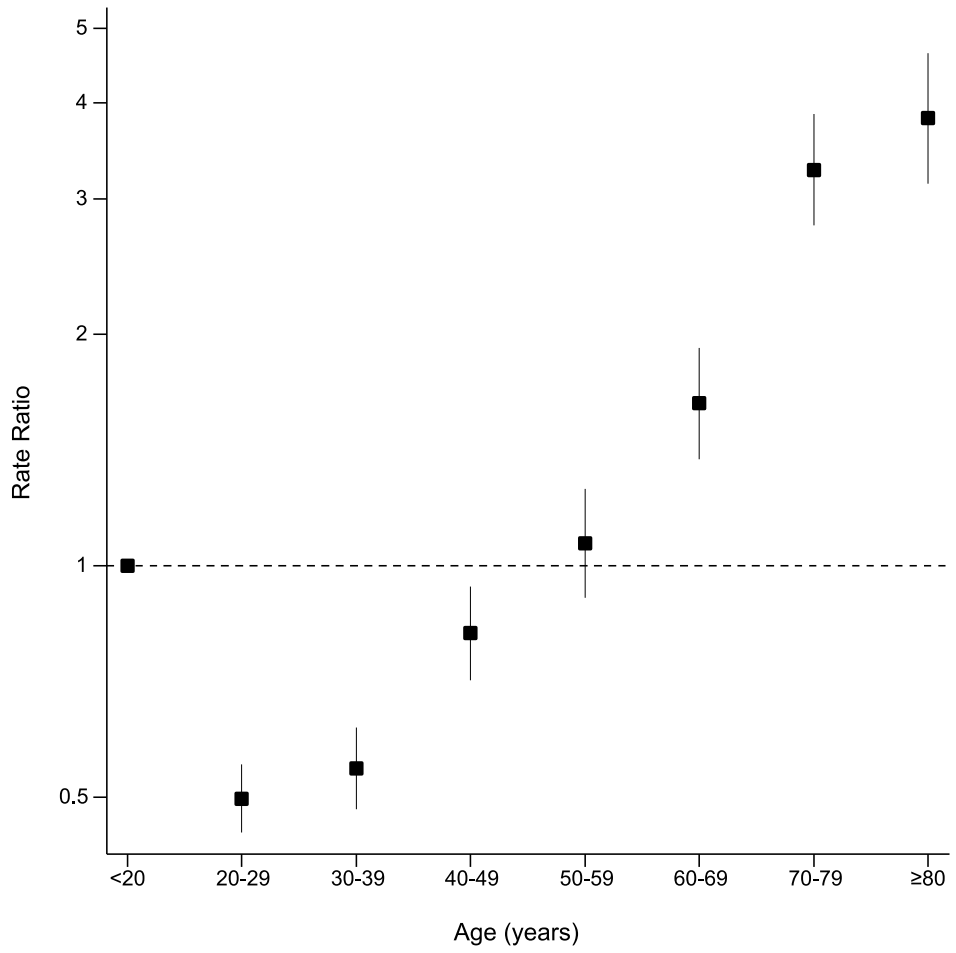
Data are reported as mean ± standard deviation or number (percentage)

Figure 3.A1: Crude total hospital admissions for hypoglycaemia, England 2005–2014



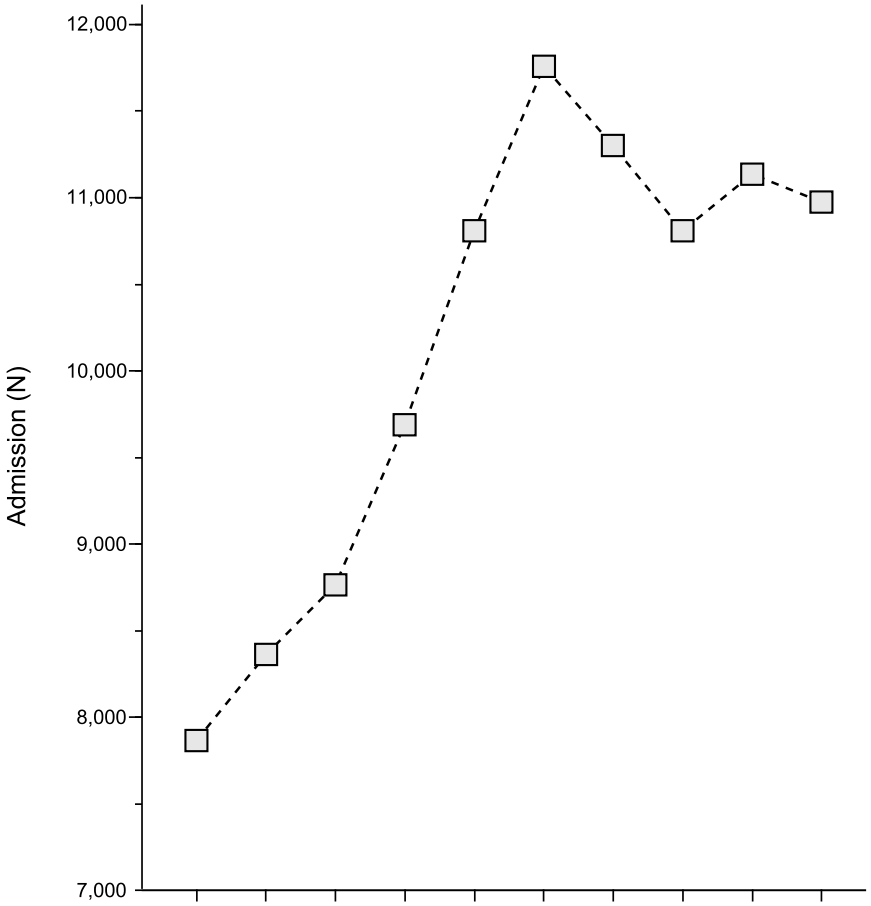
From left to right (progressively darker gradations of grey), columns indicate calendar years 2005 to 2014. Differences are reported comparing 2014 *vs* 2005 (changes in %).
Overall, there were 101,475 admissions

Figure 3.A2: Rate ratios of hospital admissions for hypoglycaemia by age, England 2005-2014



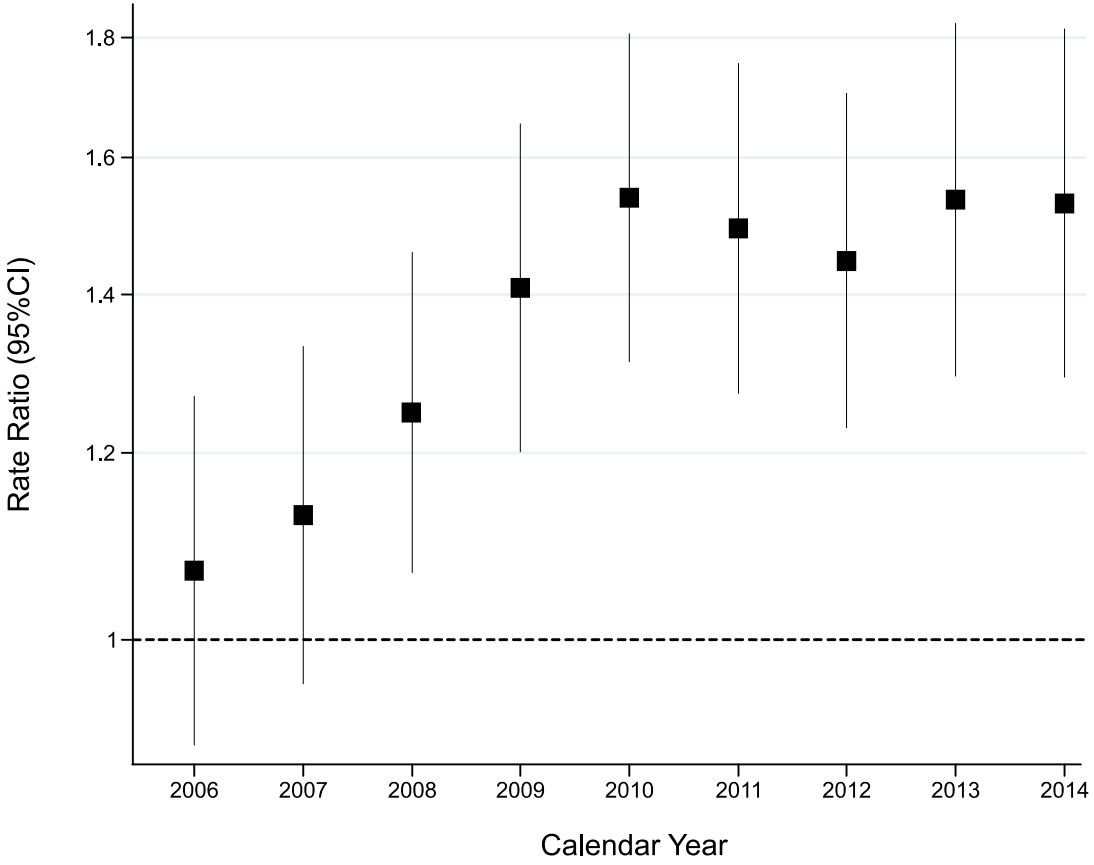
Rate ratios, estimated for the entire study period and adjusted for sex, IMD-10, and Charlson score, are compared to age <20 years old (reference, 1). Bars indicate 95% CIs

Figure 3.A3: Trends of crude hospital admissions for hypoglycaemia, England 2005-2014



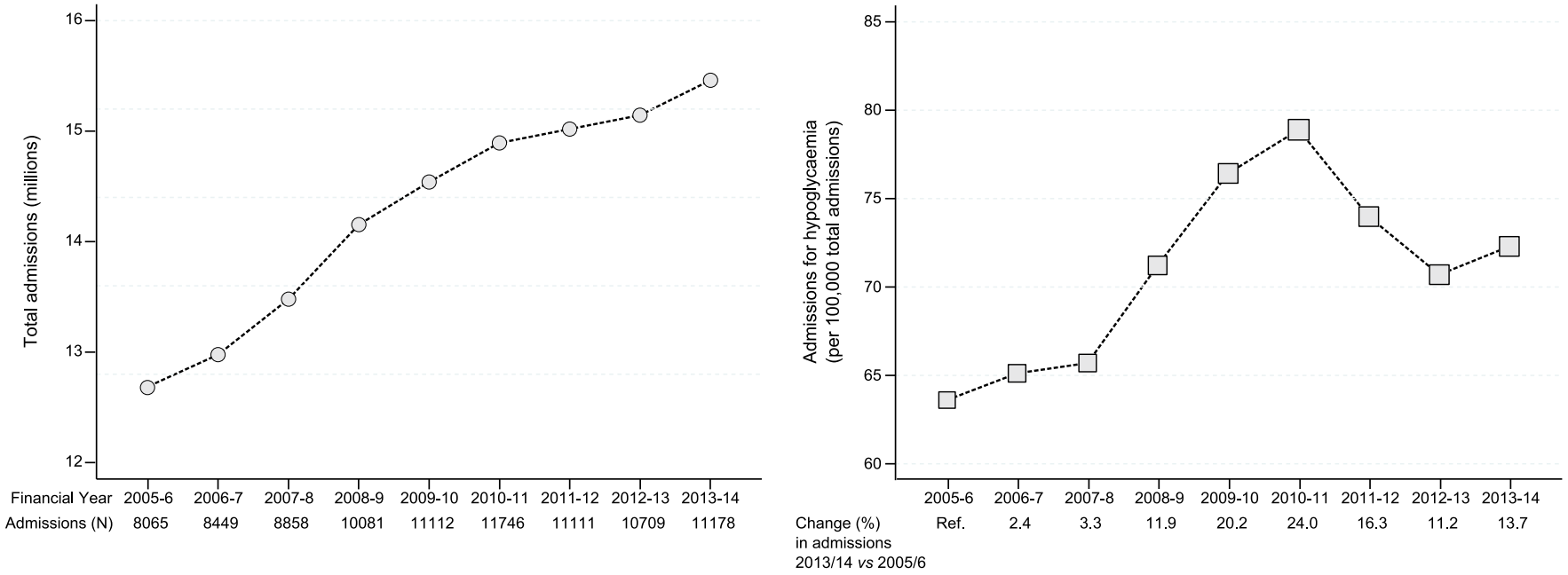
Calendar Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Admissions (N)	7868	8365	8764	9691	10809	11756	11299	10810	11136	10977
Change (%) 2014 *vs* 2005	Ref.	6.3	11.4	23.2	37.4	49.4	43.6	37.4	41.5	39.5

Figure 3.A4: Adjusted rate ratios of hospital admissions for hypoglycaemia, England 2005-2014



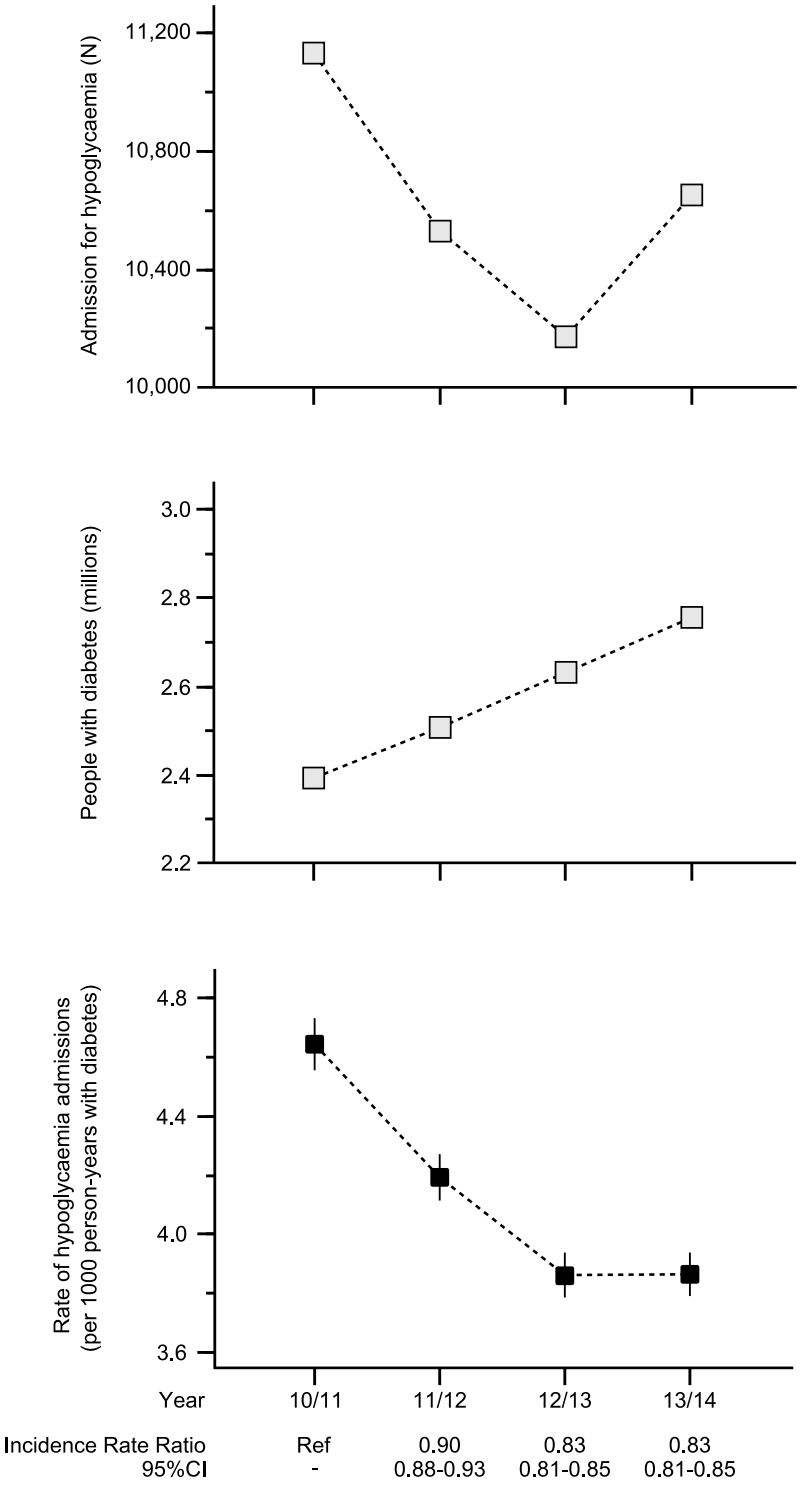
Rate ratios, adjusted for age, sex, index of multiple deprivation, and Charlson score, are compared to 2005 (reference year, black dotted line)

Figure 3.A5: Trends of hospital admissions for hypoglycaemia, adjusted for total hospital admissions, England 2005-2014



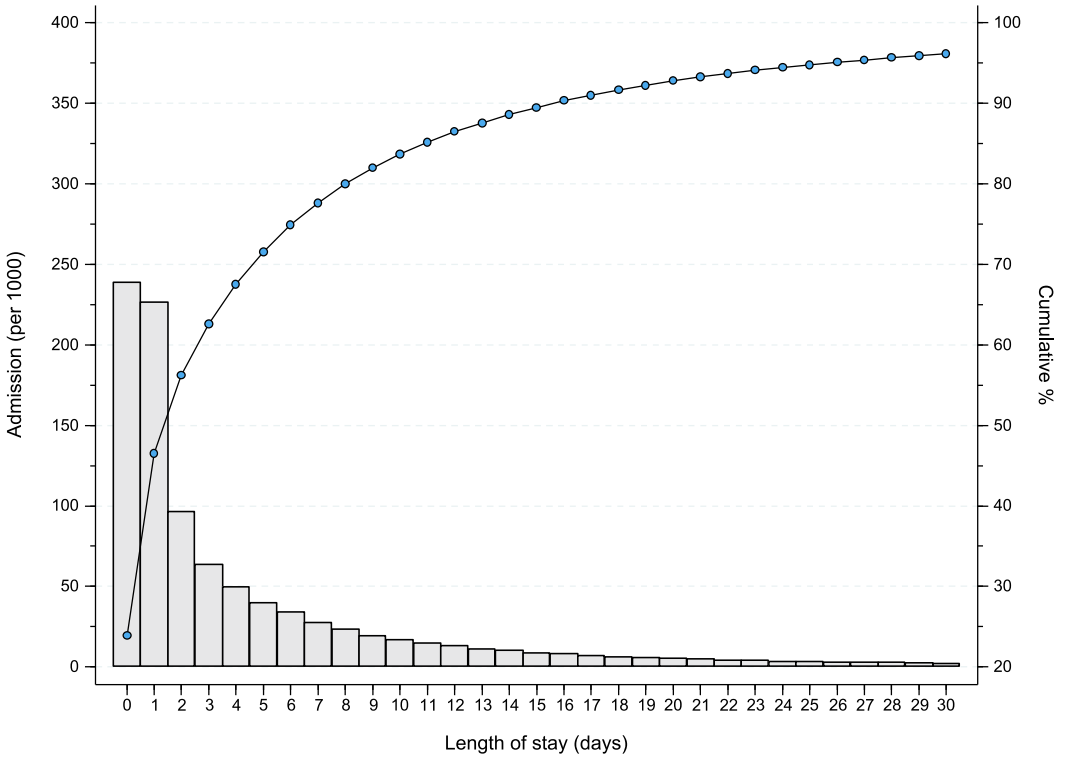
Circles (left) and squares (right) indicate total hospital admissions (in millions) and hospital admissions for hypoglycaemia per 100,000 total admissions, respectively, from April, 1 to March, 31 of the following year (financial year). The size of squares is proportional to the crude number of hospital admissions for hypoglycaemia (Figure 3.A3).

Figure 3.A6: Trends of crude hospital admissions for hypoglycaemia (top), prevalence of diabetes (middle), and prevalence-adjusted admissions (bottom), England 2010-2014



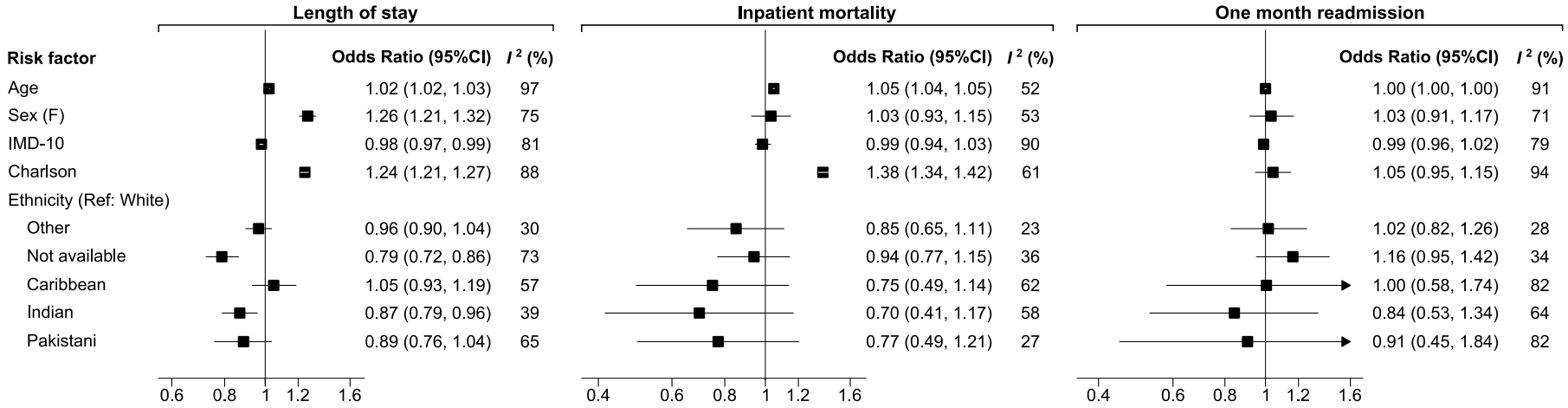
Prevalence (P) of diabetes were estimated on March 31 of each year in people 17 years of age or older. For the time intervals shown, the mid-point prevalence has been used as denominator, i.e., year 11/12 estimated as: 0.5*(P on March 31, 2011 + P on March 31, 2012). Admissions (numerator) are estimated for the same time interval. Bars in the bottom graph indicate 95% CIs

Figure 3.A7: Distribution of length of hospital stay in people admitted for hypoglycaemia, England 2005-2014



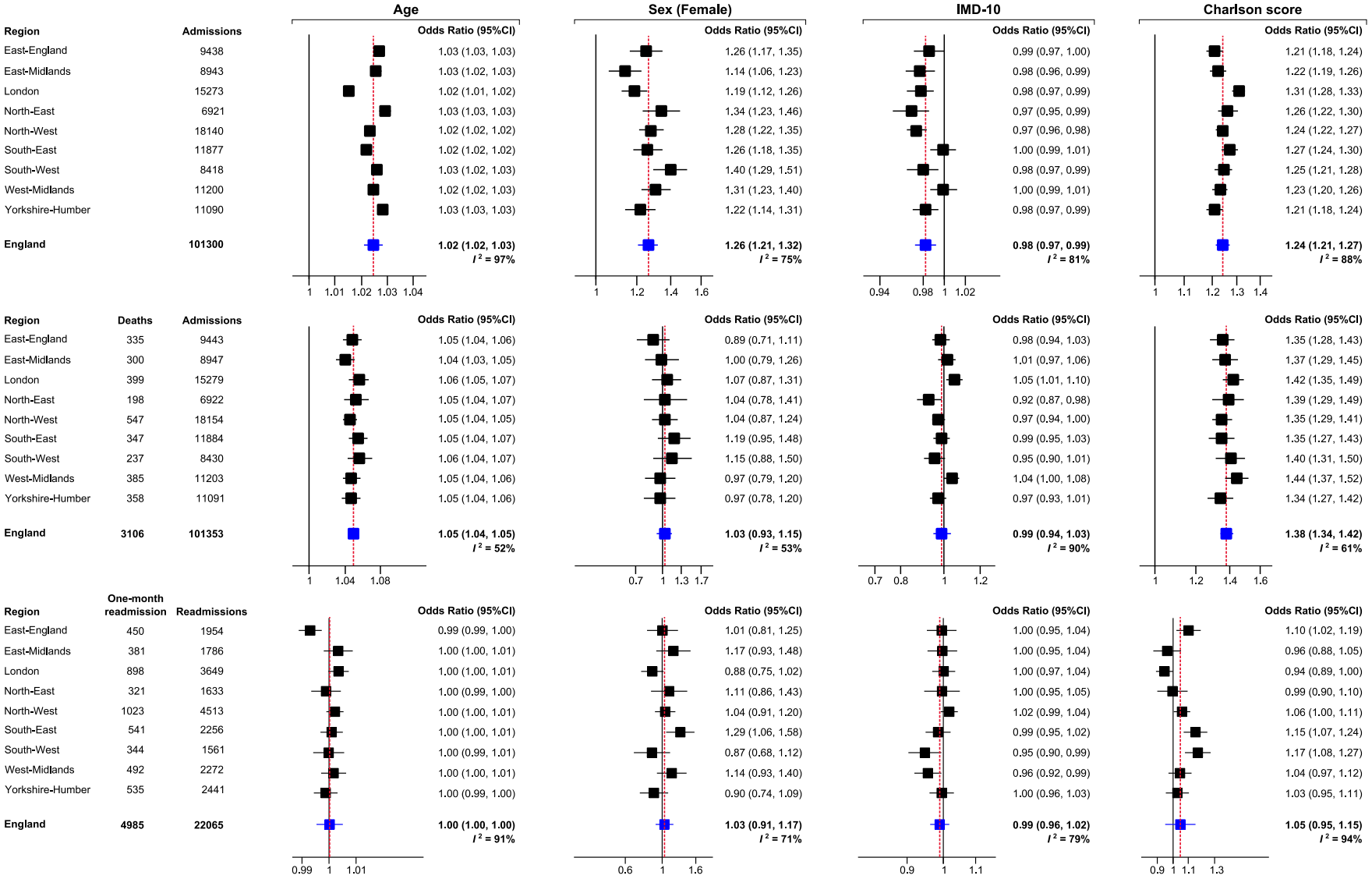
Continuous line indicates the cumulative distribution

Figure 3.A8: Risk factors for length of hospital stay, inpatient mortality, and one-month readmission in people admitted for hypoglycaemia, England 2005-2014



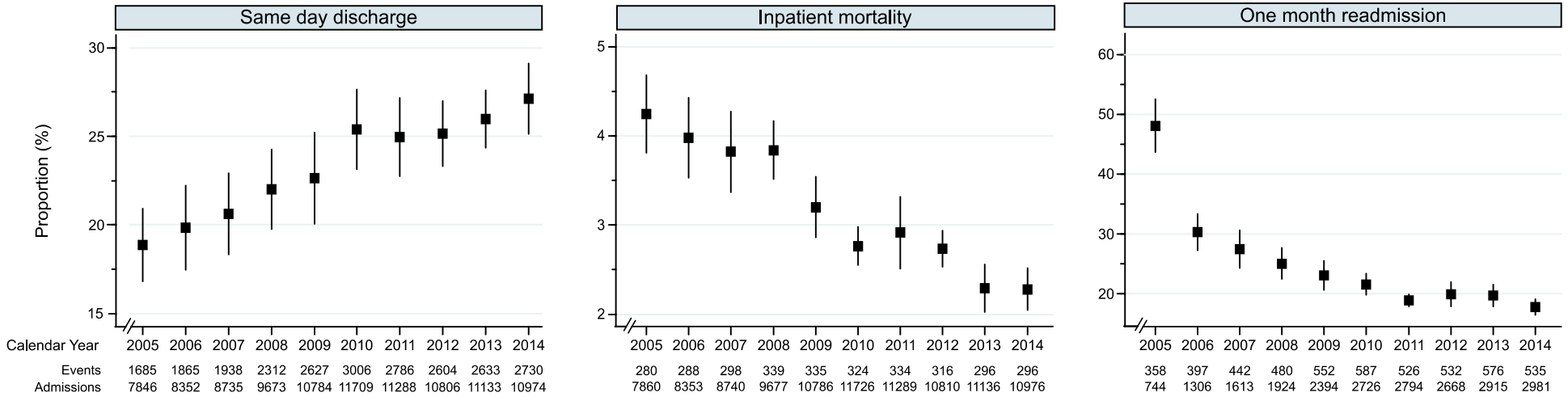
Odds ratios, adjusted for risk factors shown and calendar year, are reported per unit change of age, Charlson score, and IMD-10 (deciles of Index of Multiple Deprivation)

Figure 3.A9: Region-specific odds ratios for length of stay, inpatient mortality, and one-month readmission, England 2005-2014



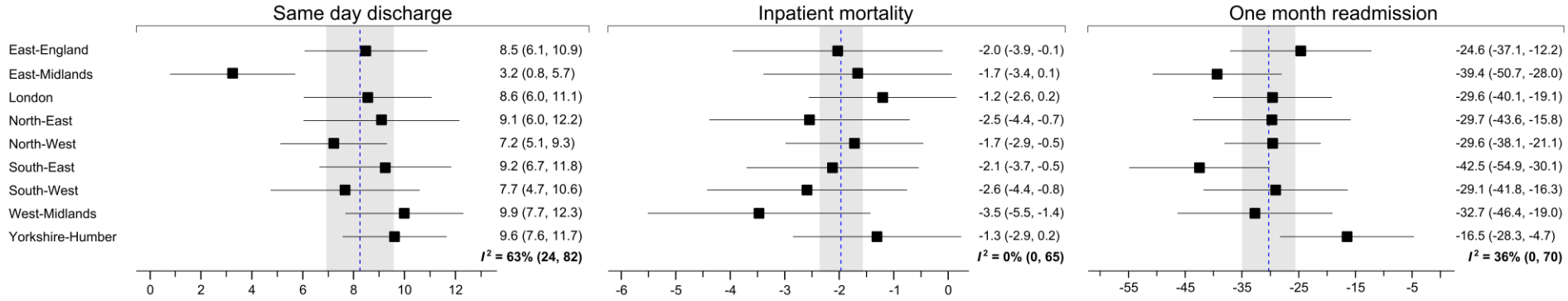
Odds Ratios reported per unit change of age, Charlson score, and IMD-10 (deciles of Index of Multiple Deprivation). Estimates for the single factor adjusted for the others shown plus ethnicity and calendar year. Red dotted lines indicate the meta-analysis overall estimates.

Figure 3.A10: Trends of length of stay, inpatient mortality, and one-month readmission, England 2005-2014



Estimates adjusted for age, sex, ethnicity, IMD-10, and Charlson score. Bars indicate 95%CI

Figure 3.A11: Region-specific same day discharge, inpatient mortality, and one-month readmission comparing 2014 vs 2005



Estimates, adjusted for age, sex, ethnicity, IMD-10, and Charlson score, indicate absolute changes per 100 admissions comparing 2014 vs 2005. For example, in Yorkshire-Humber, 9.6 more admissions out of 100 (i.e., 9.6%) resulted in same day discharge comparing 2014 to 2005. Similarly, 1.3 less deaths per 100 admissions and 16.5 less one-month readmissions per 100 readmissions occurred in the same period and for the same area. Dotted lines and the 95%CI shadow areas indicate the national average for England.

B. Risk factors and outcomes differences following admissions to hospital for hypoglycaemia in England

Analytical approach

To investigate risk factors for admissions and differences in length of hospital stay, inpatient mortality, and readmissions, three random control admissions were randomly selected for each case admission. The control/case ratio of three was based on previous methodological studies showing no significant statistical power advantage for values greater than three-four controls per case [115]. A control admission was defined in subjects with diabetes (ICD–10 codes E10+ or E11+ in any position) and without hypoglycaemia as the main reason for admission (ICD–10 codes E160, E161, or E162 in the first position). Characteristics of case and control are reported as mean and standard deviation, median and interquartile range, or number and percentage, as appropriate. Odds ratios (ORs) of hypoglycaemia–related admission for the risk factor age, sex, ethnicity (African, Bangladeshi, Caribbean, Indian, Pakistani, White, other, and not available), IMD–10 (deciles of IMD), and Charlson score were estimated by fitting logistic regression with calendar year as a factor variable (reference year, 2005) and modelling age with restricted cubic spline (five knots at 5, 27.5, 50, 72.5, and 95 percentiles of age distribution). This age transformation was chosen given the non–linear relationship between age and risk of admission for hypoglycaemia evidenced in the previous analysis investigating trends; all other analyses included untransformed age. Logistic regression models, adjusted for the same risk factors and calendar year, were fitted to estimate the odds of death in people admitted for hypoglycaemia compared to the twenty most common reasons of admission in controls and to calculate the odds of hospital readmission for hypoglycaemia in people admitted for hypoglycaemia versus readmission for any cause in people not admitted for hypoglycaemia. Lastly, an adjusted negative binomial regression (which is, compared to a Poisson regression, a generalisation for modelling over-dispersed count outcome variables where variance and mean are not equivalent) was applied to estimate the ratio of hospital stay in case admissions versus control admissions. Regression was performed following a two–stage approach, with region–specific coefficients pooled across regions by random–effects meta–analyses and heterogeneity in the associations estimated by the I^2 statistic.

Two sensitivity analyses were performed. First, using restricted cubic spline with seven (at 2.5, 18.3, 34.2, 50, 65.8, 81.7, 97.5 percentiles) knots. Second, including admissions where the ICD–10 codes for hypoglycaemia were between position 2 and 5 as cases. Moreover, in HES diabetes phenotypes are codified as “insulin–dependent” (E10+) or “non–insulin–dependent” (E11+). Although they should in principle correspond respectively to type 1 and type 2 diabetes, a

definite diagnosis of diabetes type is sometimes difficult and inaccuracies are possible. Given the difference in the association between admission for hypoglycaemia and age by diabetes type, a supplementary analysis, stratified by diabetes phenotype, has also been performed.
Stata, version 14.1 (Stata Corp, College Station, Texas), was used for all analyses and results are reported with 95% confidence intervals (CIs).

Results

Differences in baseline characteristics between case and control admissions (101,475 and 304,425, respectively) are reported in **Table 3.B1 and 3.B2**. Mean Charlson scores were 2.01 and 2.24 for case and controls admissions, respectively, and admissions occurred more in males than females and in older than younger subjects, although there were more admissions in subjects younger than 20 years old (7.0%) compared to the age group 20–29 (3.4%), 30–39 (3.9%), and 40–49 years (6.0%). A similar pattern of age distribution was found for the 304,425 control admissions, yet the increase for subjects younger than 20 years was less pronounced. In control admissions, around 10% reported "chest pain, unspecified", "urinary tract infection, site not specified", or "unspecified acute lower respiratory infection" as first code (**Table 3.B3**), while ICD–10 codes for hypoglycaemia were reported in the second position in 1,381 out of 300,166 (0.46%) available codes and in third position in 868 out of 287,428 (0.30%) (**Appendix B, Table B1**).

The relationship between age and risk of admission for hypoglycaemia, adjusted for sex, ethnicity, IMD–10, Charlson score, and calendar year, was U–shaped until the age of around 85 years old with nadir at 60 years. Compared to the nadir, the risk was progressively higher in younger (OR 1.12, 1.51, 2.26, 3.49, and 5.40 at 50, 40, 30, 20, and 10 years old, respectively) and older subjects, with an OR of 1.83 at the age of 85 and a subsequent steady decline (**Figure 3.B1**). There was no significant association between sex and risk of admission for hypoglycaemia (OR 1.01; 95% CI: 0.97 to 1.05, comparing women *vs* men) (**Figure 3.B2**); conversely, all other risk factors were significantly related to risk of admission for hypoglycaemia. With the exception of African ethnicity, other ethnic groups had lower or higher risk compared to Caucasians, from a 42% reduction in Pakistani (OR 0.58; 0.53 to 0.63) to a 59% increase in Caribbean (OR 1.59; 1.46 to 1.75). Greater social deprivation and lower comorbidity score were associated with a higher risk of admission for hypoglycaemia, being ORs 1.02 (1.02 to 1.03) and 0.91 (0.90 to 0.93) per unit increase of IMD–10 and Charlson score, respectively. Moderate to high heterogeneity was found across regions in the associations of risk factors (I^2 51% to 91%), particularly for Indian ethnicity, sex, and Charlson score.

Results were similar in sensitivity analyses using different splines or with a different definition of case admissions (3,260 admissions; **Appendix B, Table B1**).

Amongst the comorbidities related to admission for hypoglycaemia, "diabetic retinopathy" was associated with the highest absolute risk (7.2 per 1,000 admissions; 10.1 *vs* 2.9 per 1,000 admissions in hypoglycaemia *vs* non–hypoglycaemia), followed by "non–insulin–dependent diabetes with ophthalmological complications" (5.3 per 1,000), "convulsions" (5.0 per 1,000), "dementia" (4.5 per 1,000), "hypothyroidism" (4.4 per 1,000), and chronic renal failure (4.0 per 1,000) (**Figure 3.B3**).

Length of hospital stay, readmission, and inpatient mortality

Length of hospital stay was shorter in case compared to control admissions (median [interquartile range]: 2 [1–7] *vs* 4 [1–10], respectively; p<0.001). Adjusted for age, sex, ethnicity, social deprivation, Charlson score, and calendar year, length of stay was 26% shorter in people admitted for hypoglycaemia (ratio length of stay hypoglycaemia *vs* non–hypoglycaemia admissions: 0.74; 95% CI: 0.71 to 0.77); there was high heterogeneity across regions (I^2 94%; 92 to 96), with the highest and lowest differences for London (33% shorter) and West Midlands (19% shorter), respectively (**Figure 3.B4**).

Readmission risk for hypoglycaemia was higher compared to readmission for any–cause in control admissions (**Figure 3.B4**). The overall OR was 1.65 (95% CI: 1.55 to 1.76) with high heterogeneity across regions (I^2 88%; 79 to 93); the risk was lowest for East Midlands (1.51; 1.40 to 1.63) and highest for London (OR 1.93; 1.82 to 2.05).

The risk of inpatient mortality differed significantly in relation to the main reason for hospital admission (i.e., first ICD–10 code) in controls; **Figure 3.B5** depicts the odds of mortality for hypoglycaemia admissions *vs* the twenty most common reasons for hospitalisation in control admissions (35.2% of all control admissions; **Table 3.B3**). While "angina pectoris", "chest pain", "atrial fibrillation/flutter", or "unstable angina" were associated with a lower risk of inpatient mortality (ORs from 0.14 to 0.54) compared to hypoglycaemia, no differences in mortality were found for admissions of subjects with "insulin–dependent or non–insulin–dependent diabetes without complications", "syncope/collapse", "cellulitis of limb", or "insulin–dependent diabetes mellitus with ketoacidosis". Conversely, the mortality risk was significantly higher for "acute lower respiratory infection", "congestive heart failure", "acute myocardial infarction", "acute renal failure", or "pneumonia" (ORs from 1.64 to 7.82) (**Figure 3.B5**). Moderate to high heterogeneity was found across regions for cause–specific mortality (I^2 20% to 76%).

Sensitivity analysis including cases with 2nd to 5th ICD–10 codes for hypoglycaemia yielded the same results for the three outcomes.

Supplementary analysis: age and risk of admission by diabetes type

After the exclusion of participants with inconsistent coding of diabetes type (details of sample definition reported in the **Appendix B, Tables B2 and Figure B1**), 338,199 participants contributing to 387,780 admissions were included in analyses; characteristics of admissions by diabetes type are reported in **Appendix B, Table B3**. In subjects with "insulin–dependent diabetes mellitus", the relationship between age and risk of admission for hypoglycaemia, adjusted for sex, ethnicity, IMD–10, Charlson score, and calendar year, demonstrated a U–shaped curve with higher risk in patients younger than 20 and older than 70 years (**Appendix B, Figure B2**). Conversely, in patients with "non–insulin–dependent diabetes" the risk was progressively higher only in subjects older than 60 years.

Interpretation in the context of available evidence

In the previous chapter, I have reported the impact of risk factors on the outcomes length of hospital stay, readmissions, and inpatient death: women, elderly patients, higher Charlson score, and lower IMD–10 (i.e., more deprived) were associated with a longer length of hospital stay (**Figure 3.A8**). However, as data were available only for hypoglycaemia-related admissions, it was not possible to quantify the impact of demographic and clinical factors on the risk of admission. In this chapter, using a case-control design, I have quantified risk factors for admission for hypoglycaemia and, accounting for them, estimated differences in the three outcomes following the admission. The results indicate that age, social deprivation, multimorbidity (particularly visual impairment, dementia, and renal failure), and ethnicity are important determinants of admission for hypoglycaemia; readmission for hypoglycaemia is greater than the risk of readmission for any cause in subjects not admitted for hypoglycaemia; time to discharge and mortality are significantly lower following hospitalisation for hypoglycaemia; and differences for length of stay, readmission, and mortality comparing hypoglycaemia *vs* non–hypoglycaemia differ across regions.

Previous observational analyses have investigated risk factors for severe hypoglycaemia or emergency visit/hospital admission for hypoglycaemia. Using the UK–based General Practice Research Database, Bruderer et al. identified retrospectively risk factors for severe hypoglycaemia with a nested case–control design including 690 participants with type 2 diabetes and hypoglycaemia and a selection of 6,900 controls without any recorded hypoglycaemic event [35]. They showed an increased risk of severe hypoglycaemia in older people with renal failure, cognitive impairment/dementia, or treated with insulin or sulphonylurea. Using a similar database in Germany, Kostev et al. identified younger age,

diabetes duration, and several diseases (renal failure, autonomic neuropathy, dementia, and depression) as risk factors for 3,221 ICD–10 defined hypoglycaemic events in ~33,000 insulin–treated subjects with type 2 diabetes [116]. Other observational studies, as well as post–hoc analyses of randomised control trials, have confirmed the relevance of age, comorbidities, and use of insulin and insulin-secretagogues as risk factors for emergency visit/hospital admission for hypoglycaemia [74, 75, 117-119].

Given the increased risk of hypoglycaemia in younger subjects with type 1 diabetes and the limited and conflicting epidemiological evidence about age and hospital admission for hypoglycaemia, in this significantly larger study age was modelled to ascertain whether its relationship with hospitalisation was non–linear. Compared to 60 years old, a progressive increase in relative risk for younger and older subjects was observed; the shape of association, of note, accounted for other potential risk factors and was robust to statistical modelling (i.e., different splines). This relationship was further investigated in a supplementary analysis stratified by diabetes type. Within the limitations of diabetes phenotyping in HES, a higher risk of admissions in both younger and older patients with "insulin–dependent" diabetes was noticed while for "non–insulin–dependent" diabetes the risk increased only in patients older than 60 years. Importantly, the absolute number of admissions was much greater in older than younger patients as admissions in subjects older than 70 years contribute by ~60% to the overall number of hospitalisations (i.e. ~5,900 per year).

I have also investigated the impact of specific comorbidities on the risk of admission for hypoglycaemia, evidencing that retinopathy is roughly 3–times more common in subjects admitted for hypoglycaemia, with an absolute difference of 0.7% (1% and 0.3% in hypoglycaemia *vs* non–hypoglycaemia, respectively). "Ophthalmological complications" in "insulin–dependent" or "non–insulin–dependent" diabetes were also amongst the most common co–reported ICD codes, along with chronic kidney failure and dementia. While suboptimal glucose control could be associated with both a higher prevalence of comorbidities and a greater risk of hospital admissions for hypoglycaemia, nonetheless the reduced clearance of several glucose–lowering drugs in patients with kidney failure [120] and the higher risk of incorrect administration of insulin doses in patients with dementia or retinopathy may also explain these findings [121]. Of note, the presence of complications (particularly retinopathy when compared to dementia and kidney failure) could in this regard also be a surrogate marker of diabetes duration or of a higher degree of insulin deficiency, which are linked to a greater risk of severe hypoglycaemia.

This is the first study to explore ethnic differences for admissions for hypoglycaemia using national–level data in England. Compared to white Caucasians, people of Pakistani, Bangladeshi, and Indian ethnicity had lower whilst Caribbeans had a higher risk of hospitalisation for

hypoglycaemia. Previous studies have reported an increased rate of emergency department visits or admissions for hypoglycaemia in black (African–American race) compared to white patients in North American populations [72, 117, 122] while in England a study found ~2.5–times higher risk of diabetes–related hospitalisation in South Asians vs White British [123]. Multiple clinical, socioeconomic, or cultural factors could help elucidate differences across ethnicities. In fact, previous data have suggested less aggressive management of glucose in south Asian patients – Pakistani, Indian, and Bangladeshi in this study – compared to white Europeans [124, 125], and this could explain the lower rate of admissions evidenced in this study. Moreover, there is evidence of a greater concern amongst south Asians about insulin initiation and hypoglycaemia [126], of lower adherence to oral glucose–lowering drugs [127], of fewer prescriptions of insulin therapy [128, 129], and of reduced awareness of diabetes and its complications [130]. All these factors could result in worse glucose control and potentially explain the lower risk of hypoglycaemia. However, these findings should be considered in the context of previous evidence indicating differences in hospital admissions across ethnicities for several other medical conditions and health–related outcomes [131, 132]. Further investigation is required to disentangle the specific contribution of clinical, socioeconomic, and cultural factors on the risk of severe hypoglycaemia and healthcare resource utilisation in different ethnicities.

In contrast with these findings, in a small retrospective audit including ~1,500 subjects with diabetes Tan et al. showed a longer hospital stay and an overall higher inpatient mortality in patients admitted for hypoglycaemia *vs* non–hypoglycaemia (10.3 *vs* 7.3 days and 14.5% *vs* 5.2%, respectively) [133]. The paucity of other comparative assessments for length of stay, mortality, and readmission limited a broader comparison with these data. This is particularly important for readmissions because the probability of readmission in people admitted for hypoglycaemia was 65% higher compared to the risk of readmissions for any other cause. The identification of risk factors for readmissions would therefore significantly impact on the overall number of hospitalisation for hypoglycaemia and associated healthcare costs.

As for trend analyses, there was heterogeneity across regions of England in the association of risk factors with hospitalisation for hypoglycaemia and for the outcomes length of stay, readmission, and mortality. Whilst heterogeneity was moderate to high for ethnicity, it was considerably higher (I^2>75%) for sex, Charlson score, length of stay, and readmissions; regional differences in mortality risk, on the other hand, were largely dependent on the reason of control admissions. Heterogeneity may be related to differences in clinical unmeasured factors or to variations in nonclinical aspects associated with admissions and outcomes. Of note, regional

variations have been reported for several other health indicators and should be interpreted in conjunction with the results on ethnicity and social deprivation [99, 134].

The results of this analysis have important clinical and public health ramification. The observation of a different risk in subject of diverse ethnicity would suggest a holistic approach which should take into account clinical, socioeconomic, and cultural factors. Specific education pathways to recognise and treat hypoglycaemia and to increase the diversity and cultural competency of health-care professionals may address and reduce health-care disparities among ethnic minorities. Similarly, the identification of a specific pattern of age and comorbidities will help target specific groups of patients, such as younger patients and elderly patients with multiple morbidities.

A major limitation of this analysis is the unavailability in HES of information on glucose-lowering therapy, which can possibly be a confounding factor in the associations investigated.

In conclusion, the identification of potential risk factors can help identifying at–risk groups and implement appropriate strategies. Further clinical and socio–demographic studies are required to confirm and expand upon these results findings, particularly the observed ethnicity differences.

Tables and Figures

Table 3.B1: Characteristics of hospital admissions for hypoglycaemia and non–hypoglycaemia

	Admission		
Characteristic	**Hypoglycaemia**	**Non-hypoglycaemia**	**Total**
Admissions (N)	101475	304425	405900
Age at admission (Years)			
<20	7116 (7.0)	6402 (2.1)	13518 (3.3)
20–29	3475 (3.4)	5383 (1.8)	8858 (2.2)
30–39	3906 (3.9)	8717 (2.9)	12623 (3.1)
40–49	6126 (6.0)	20503 (6.7)	26629 (6.6)
50–59	8284 (8.2)	36116 (11.9)	44400 (10.9)
60–69	13150 (13.0)	58572 (19.2)	71722 (17.7)
70–79	27298 (26.9)	86142 (28.3)	113440 (28.0)
≥80	32120 (31.7)	82590 (27.1)	114710 (28.3)
Sex			
Females	49733 (49.0)	143257 (47.1)	192990 (47.6)
Males	51741 (51.0)	161160 (52.9)	212901 (52.5)
Charlson index	2.01 ± 1.45	2.24 ± 1.57	2.19 ± 1.54
IMD-10			
Least deprived 10%	5407 (5.3)	18695 (6.2)	24102 (6.0)
Less deprived 10-20%	6607 (6.5)	22173 (7.3)	28780 (7.1)
Less deprived 20-30%	7513 (7.4)	24323 (8.0)	31836 (7.9)
Less deprived 30-40%	8346 (8.2)	26408 (8.7)	34754 (8.6)
Less deprived 40-50%	9211 (9.1)	28316 (9.3)	37527 (9.3)
More deprived 10-20%	14038 (13.9)	39548 (13.0)	53586 (13.2)
More deprived 20-30%	12497 (12.3)	35771 (11.8)	48268 (11.9)
More deprived 30-40%	10908 (10.8)	32386 (10.7)	43294 (10.7)
More deprived 40-50%	10052 (9.9)	30678 (10.1)	40730 (10.1)
Most deprived 10%	16780 (16.6)	45735 (15.0)	62515 (15.4)
Ethnicity			
African (Black or Black British)	796 (0.8)	2064 (0.7)	2860 (0.7)
Bangladeshi (Asian or Asian British)	547 (0.5)	2549 (0.8)	3096 (0.8)
Caribbean (Black or Black British)	3166 (3.1)	5201 (1.7)	8367 (2.1)
Indian (Asian or Asian British)	2616 (2.6)	9301 (3.1)	11917 (2.9)
Not available	6652 (6.6)	24697 (8.1)	31349 (7.7)
Other	3423 (3.4)	10254 (3.4)	13677 (3.4)
Pakistani (Asian or Asian British)	1671 (1.7)	8129 (2.7)	9800 (2.4)
White	82604 (81.4)	242230 (79.6)	324834 (80.0)

IMD-10 (Index of Multiple Deprivation) score in deciles
Data reported as mean ± standard deviation or number (percentage)
All characteristic variables were statistically different comparing hypoglycaemia *vs* non–hypoglycaemia (p<0.001)

Table 3.B2: Frequency of hospital admissions for hypoglycaemia and non–hypoglycaemia

	Frequency – n (%)		
Number of admissions	**Hypoglycaemia**	**Non-hypoglycaemia**	**Total**
1	65,248 (82.41)	234,212 (88.21)	299,460 (86.88)
2	9,698 (12.25)	25,850 (9.74)	35,548 (10.31)
3	2,488 (3.14)	4,149 (1.56)	6,637 (1.93)
4	872 (1.10)	869 (0.33)	1,741 (0.51)
5	387 (0.49)	262 (0.10)	649 (0.19)
6	171 (0.22)	104 (0.04)	275 (0.08)
7	113 (0.14)	39 (0.01)	152 (0.04)
8	63 (0.08)	16 (0.01)	79 (0.02)
9	42 (0.05)	7 (0.00)	49 (0.01)
≥10	90 (0.11)	16 (0.01)	106 (0.03)
Total	79,172 (100)	265,524 (100)	344,696 (100)

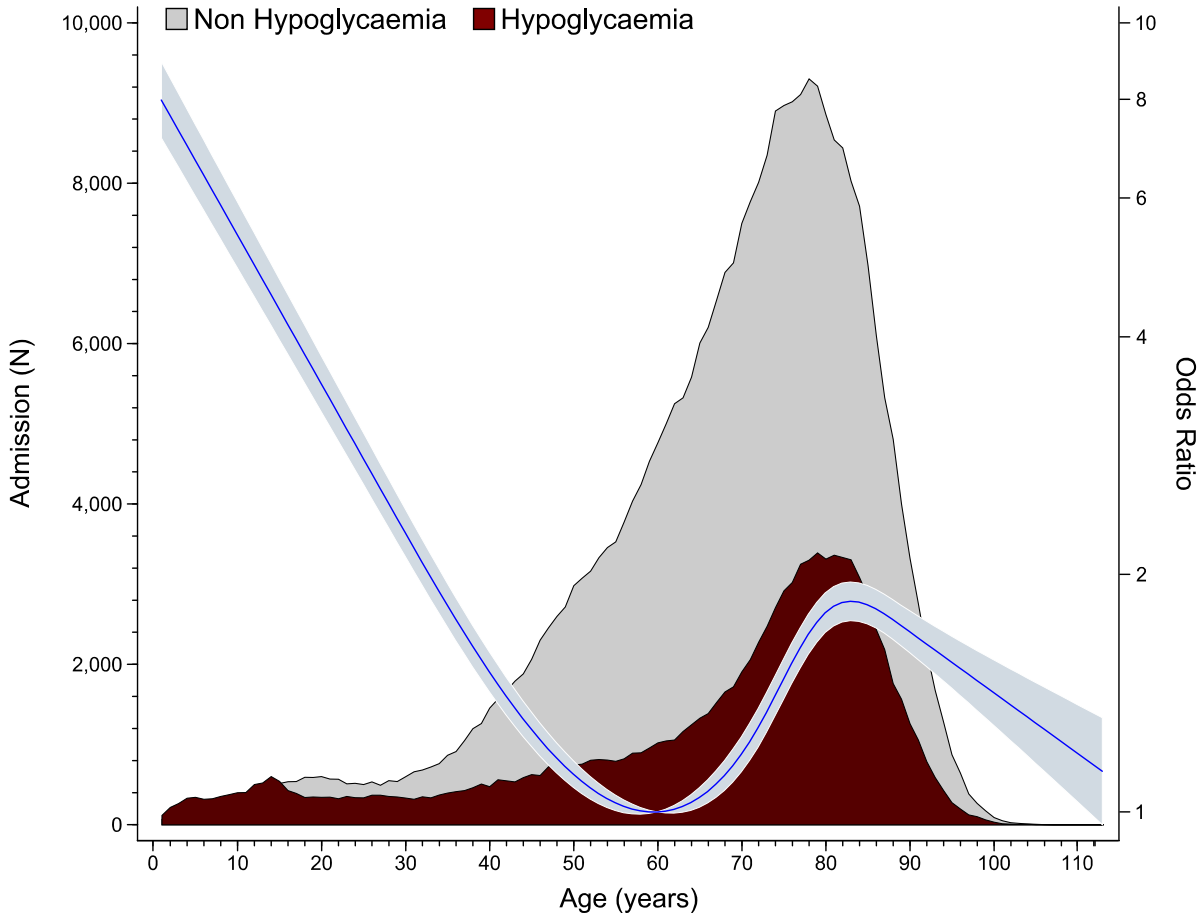
Table 3.B3: First ICD-10 code for admissions in participants with diabetes and without hypoglycaemia

ICD 10 definition	ICD-10 code	Frequency	%	Cumulative %
Chest pain, unspecified	R074	13,157	3.87	3.87
Urinary tract infection, site not specified	N390	12,731	3.74	7.61
Unspecified acute lower respiratory infection	J22X	7,160	2.11	9.72
Syncope and collapse	R55X	7,070	2.08	11.80
Congestive heart failure	I500	7,016	2.06	13.86
Lobar pneumonia, unspecified	J181	6,858	2.02	15.88
IDDM with ketoacidosis	E101	6,024	1.77	17.65
Unstable angina	I200	5,645	1.66	19.31
Cellulitis of other parts of limb	L031	5,351	1.57	20.89
COPD with acute lower respiratory infection	J440	5,251	1.54	22.43
Atrial fibrillation and flutter	I48X	4,915	1.45	23.88
Other chest pain	R073	4,790	1.41	25.28
Pneumonia, unspecified	J189	4,598	1.35	26.64
NIDDM without complications	E119	4,563	1.34	27.98
IDDM without complications	E109	4,285	1.26	29.24
Acute myocardial infarction, unspecified	I219	4,154	1.22	30.46
Noninfective gastroenteritis and colitis, unspecified	K529	4,128	1.21	31.68
Acute renal failure, unspecified	N179	4,055	1.19	32.87
Other and unspecified abdominal pain	R104	3,904	1.15	34.02
Angina pectoris, unspecified	I209	3,867	1.14	35.15
COPD with acute exacerbation, unspecified	J441	3,778	1.11	36.26
Dyspnoea	R060	3,734	1.10	37.36
Cerebral infarction, unspecified	I639	3,718	1.09	38.46
Fracture of neck of femur	S720	3,196	0.94	39.40
Senility	R54X	3,041	0.89	40.29
Nausea and vomiting	R11X	2,860	0.84	41.13
Left ventricular failure	I501	2,752	0.81	41.94
Precordial pain	R072	2,616	0.77	42.71
Disorientation, unspecified	R410	2,597	0.76	43.47
Constipation	K590	2,428	0.71	44.19
NIDDM with peripheral circulatory complication	E115	2,302	0.68	44.87
Pain localized to upper abdomen	R101	2,297	0.68	45.54
Asthma, unspecified	J459	2,213	0.65	46.19
Transient cerebral ischaemic attack, unspecified	G459	2,002	0.59	46.78
Anaemia, unspecified	D649	2,001	0.59	47.37
Headache	R51X	1,988	0.58	47.95
Septicaemia, unspecified	A419	1,970	0.58	48.53
Ulcer of lower limb, not elsewhere classified	L97X	1,857	0.55	49.08
Retention of urine	R33X	1,854	0.55	49.63

ICD-10 codes accounting for 50% of all admissions are shown and listed in decreasing order of frequency

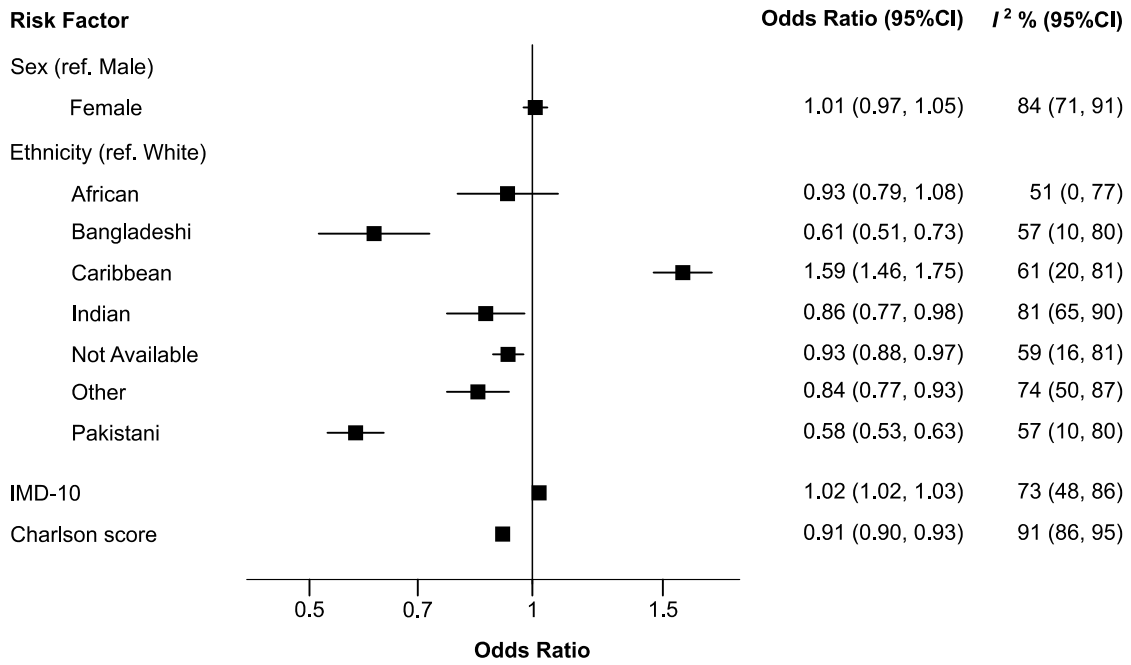
COPD: Chronic obstruct pulmonary disease
IDDM: Insulin-dependent diabetes mellitus
NIDDM: Non-insulin-depend diabetes mellitus

Figure 3.B1: Age-specific odds ratios of admission for hypoglycaemia



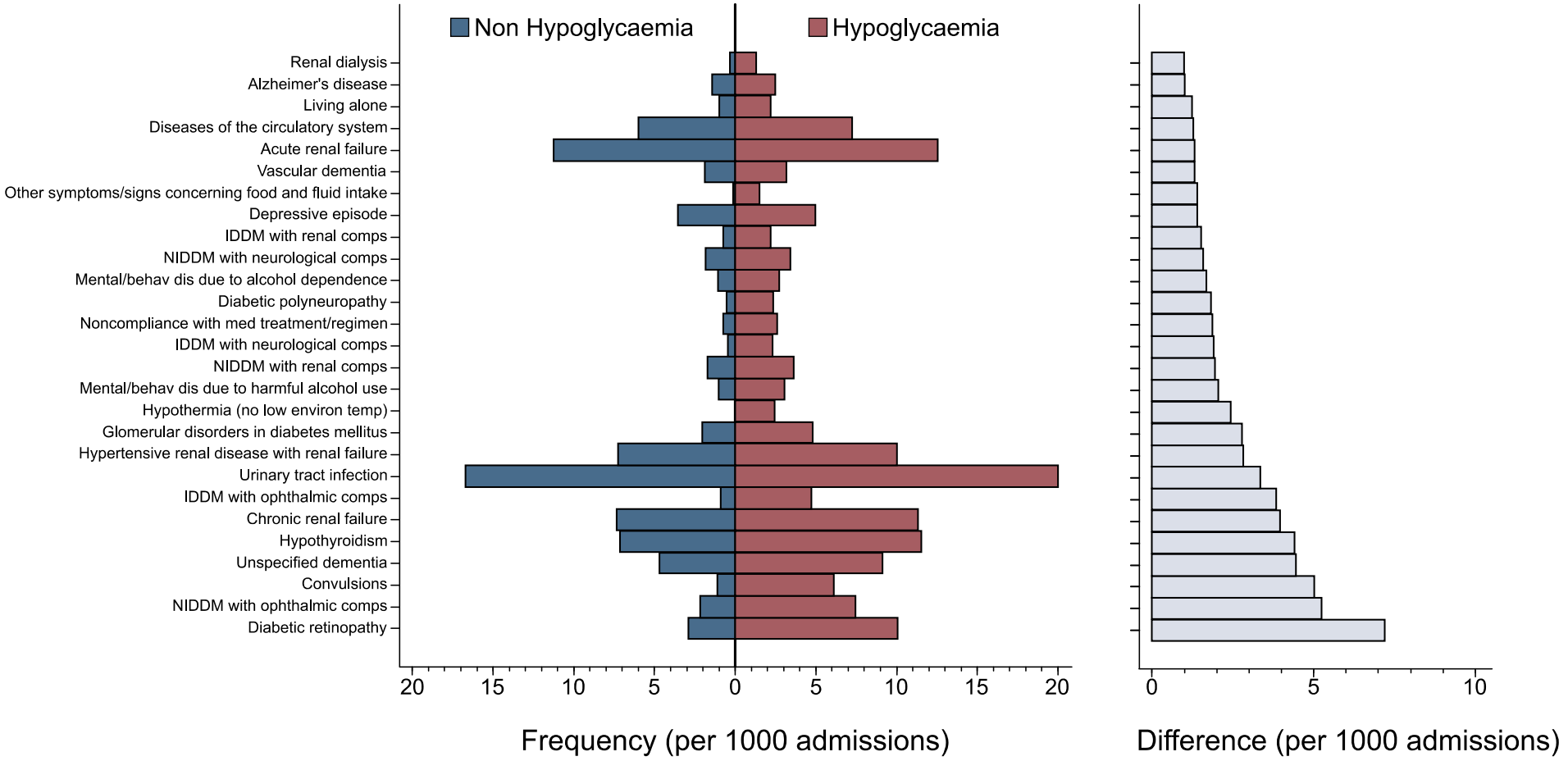
Estimates, adjusted for sex, ethnicity, IMD-10, Charlson score, and calendar year, are reported comparing admissions for hypoglycaemia vs non-hypoglycaemia.
The line indicates age-specific odds ratios relative to age 60 years old, with 95%CI (shadow)

Figure 3.B2: Risk factors for admission for hypoglycaemia



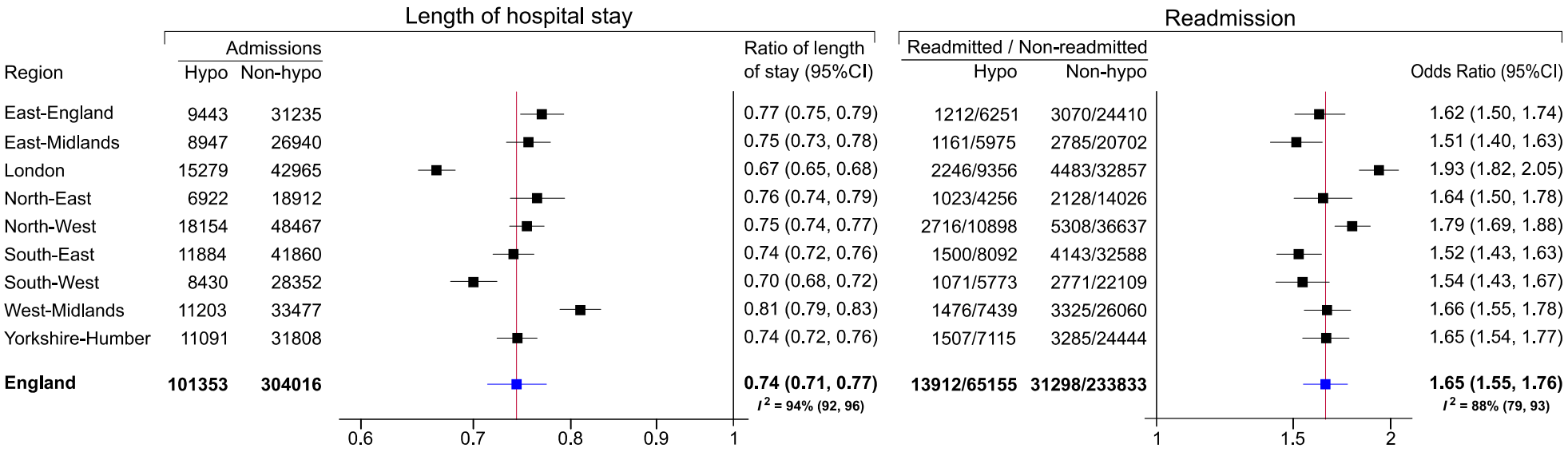
Estimates adjusted for risk factors shown plus age and calendar year. Odds ratios reported per unit increase of IMD-10 (more deprived) and Charlson score (greater multimorbidity)

Figure 3.B3: ICD-10 code frequencies in case and control admissions



Frequencies >1 per 1000, estimated using ICD-10 codes in the first 5 positions, are shown. IDDM: Insulin-dependent diabetes mellitus; **NIDDM**: Non-insulin-dependent diabetes mellitus.

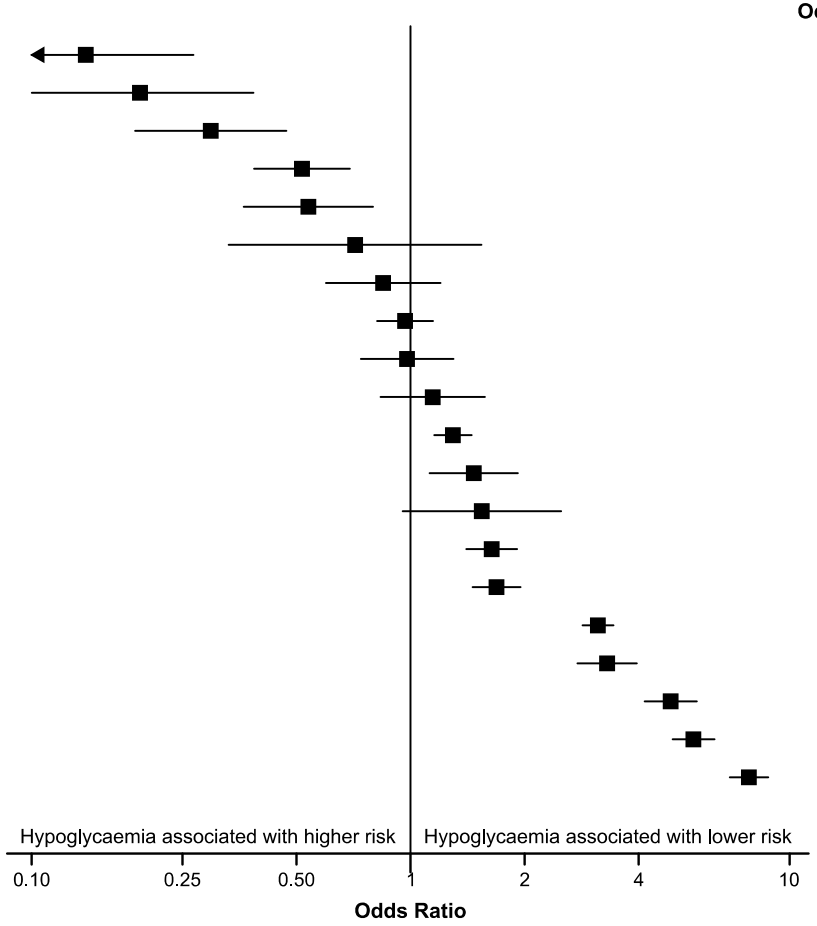
Figure 3.B4: Length of stay and risk of readmission comparing admissions for hypoglycaemia vs non-hypoglycaemia, by region



Estimates, adjusted for age, sex, ethnicity, IMD-10, Charlson score, and calendar year, are reported comparing admissions for hypoglycaemia vs non-hypoglycaemia.
Overall, hospital stay was 26% shorter and risk of readmissions 65% higher in people admitted for hypoglycaemia

Figure 3.B5: Risk of inpatient mortality comparing hypoglycaemia to other common reasons of admission

First ICD code	Number of Deaths	Number of Admissions	Odds Ratio (95%CI)	I^2 % (95%CI)
Angina pectoris, unspecified	12	3420	0.14 (0.07, 0.27)	23 (0, 63)
Other chest pain	14	4266	0.19 (0.10, 0.38)	36 (0, 71)
Chest pain, unspecified	79	11795	0.30 (0.19, 0.47)	76 (53, 87)
Atrial fibrillation and flutter	77	4405	0.52 (0.39, 0.69)	37 (0, 71)
Unstable angina	89	5075	0.54 (0.36, 0.80)	67 (34, 84)
IDDM without complications	9	3820	0.71 (0.33, 1.54)	20 (0, 62)
NIDDM without complications	90	4073	0.85 (0.60, 1.20)	60 (17, 81)
Syncope and collapse	215	6350	0.97 (0.82, 1.15)	29 (0, 67)
Cellulitis of other parts of limb	136	4804	0.98 (0.74, 1.30)	60 (16, 81)
Other and unspecified abdominal pain	89	3503	1.14 (0.83, 1.57)	52 (0, 78)
Urinary tract infection, site not specified	573	11431	1.29 (1.15, 1.45)	34 (0, 69)
Noninfective gastroenteritis and colitis, unspecified	179	3665	1.47 (1.12, 1.92)	65 (28, 83)
IDDM with ketoacidosis	32	5369	1.54 (0.95, 2.50)	43 (0, 74)
Unspecified acute lower respiratory infection	398	6376	1.64 (1.40, 1.91)	49 (0, 76)
COPD with acute lower respiratory infection	303	4677	1.69 (1.46, 1.95)	27 (0, 66)
Congestive heart failure	932	6369	3.12 (2.84, 3.43)	26 (0, 65)
Acute myocardial infarction, unspecified	469	3727	3.30 (2.76, 3.96)	64 (27, 82)
Acute renal failure, unspecified	662	3648	4.86 (4.14, 5.70)	63 (24, 82)
Lobar pneumonia, unspecified	1084	6128	5.58 (4.92, 6.34)	62 (21, 81)
Pneumonia, unspecified	963	4120	7.82 (6.96, 8.78)	46 (0, 75)



Estimates, adjusted for age, sex, ethnicity, IMD-10, Charlson score, and calendar year, are reported comparing admissions for hypoglycaemia (reference, 1) vs the twenty most common reasons of admission (1st ICD code). For hypoglycaemia there were 3,106 deaths in 101,353 admissions.
IDDM: Insulin-dependent diabetes mellitus; **NIDDM**: Non-insulin-dependent diabetes mellitus; **COPD**: Chronic obstructive pulmonary disease.

C. Risk stratification and precision medicine: prognostic models for patients admitted for hypoglycaemia

Analytical approach

For the current analysis, I have defined two temporally-distinct derivation and validation samples within HES. In the derivation samples, admissions in 2013 for inpatient mortality and 2010-2012 for one-month readmission and length of hospitalisation (defined as 24hr-discharge) have been included; corresponding years for validation samples were 2014 for inpatient mortality and 2013-2014 for one-month readmission and length of hospitalisation. These time frames were selected because the previous analysis evidenced more stable trends of these outcomes during these years (**Figure 3.A10**).

The three outcomes inpatient mortality, one-month readmission for hypoglycaemia, and 24hr-discharge were modelled using complete-case logistic regressions. Two prognostic models were defined: the first ("base" model) included age, transformed with a cubic spline with five knots to account for the non-linearity of the relationship between age and hospital admission for hypoglycaemia previosly evidenced, sex, ethnicity (White, Other), region (East-Midlands, London, North-East, North-West, South-East, South-West, West-Midlands, Yorkshire and Humber), social deprivation (deciles of IMD), and Charlson score for all three outcomes. In the second model ("disease" model), the twenty most common ICD-10 comorbidities reported in position 2nd to 6th were added to the base model: comorbidities were identified for each outcome and are reported in **Table 3.C1**. After their inclusion, a stepwise backward elimination of individual factors was applied using the ordinary Akaike's information criterion to define the final set of variables [135].

Performance of regression models was assessed with Nagelkerke R^2, discrimination, and calibration. For a specific model, R^2 indicates the additional variation in the outcomes compared to a model with only the intercept. For a logistic regression, discrimination corresponds to the area under the receiver operating characteristic curve (C-index): a value of 0.5 indicates model discrimination no better than chance while a value of 1 perfect discrimination [136]. Observed outcomes by decile of predictions were plotted to graphically assess calibration and calculate calibration slope and intercept: values around 1 for slope and 0 for intercept indicate correct calibration [137].

Models were internally validated with 300 bootstrap samples to assess possible optimism and temporally by recalculating indices of discrimination, plotting observed vs predicted outcomes, and estimating calibration slope and intercept. Finally, a calculator based on recalibrated models

using the calibration slope and intercept obtained in validation samples has been developed [138].

Analyses were performed following the general framework proposed by Harrell [139] and Steyerberg and Vergouwe [138] and results are reported in line with TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) recommendations [140]. Stata 14.1 and R 3.2.3 (package rms [139]) were used for all analyses and results are reported with 95% CIs; p-value <0.05 was considered statistically significant.

Results

Characteristics of derivation and validation sample

Of 22,113 available admissions for inpatient mortality, one admission (0.005%) was excluded due to missing data on age; of 55,978 available admissions for one-month readmission and 24hr-discharge, 41 admissions were excluded for one-month readmission (0.073%) and 68 for length of hospital stay (0.121%).

Characteristics of the remaining admissions with complete data, by outcome and sample, are shown in **Table 3.C2**. No major differences were found between the derivation and validation samples. Most admissions occurred in patients older than 60 years and of White ethnicity; there were slightly more admissions in males than females and Charlson scores were slightly higher in validation samples. The outcome-specific top twenty most common diseases covered approximately 50% of all reported comorbidities (**Table 3.C1**): of these, two for readmission and 15 for 24hr-discharge were included in the final models after the stepwise backward elimination. Multivariable associations between variables and outcomes in derivation samples are reported in **Figure 3.C1** for base models and **Table 3.C3** for disease models; performance measures are summarised in **Table 3.C4** and calibration plots are depicted in **Figure 3.C2**.

Model development and internal validation

The base and disease models for inpatient mortality were developed from 11,136 admissions and 296 (2.7%) deaths (**Table 3.C2**). Age and Charlson score were significantly associated with the risk of inpatient mortality in both the base and disease model (**Figure 3.C1 and Table 3.C3**). Discrimination was very similar comparing the two models: the base model showed a C-index of 0.77 (95% CI: 0.75 to 0.80), with minimal over-fitting in bootstrap validation (bias-corrected C-index 0.75) while the disease model achieved a C-index of 0.78 (0.75 to 0.80) with a bias-corrected value of 0.77 (**Table 3.C4**). The prognostic models for one-month readmission were derived from 1789 one-month readmissions among 33,825 admissions (5.3%). Ethnicity and

region were significantly associated with risk of readmissions in both the base and disease model. Discriminations were modest, being C-index 0.57 (0.56 to 0.59) and 0.57 (0.56 to 0.58) for the base and disease model, respectively; bias-corrected C-indices yielded similar results (**Table 3.C4**). Lastly, prognostic models for 24hr-discharge were developed from 8396 24hr-discharge among 33,803 admissions (24.8%). All variables of the base model were associated with 24hr-discharge; in the disease model, 15 further variables were included, of which 12 were associated with the outcome (**Table 3.C3**). C-indices were 0.68 (0.67 to 0.69) for the base model and 0.69 (0.68 to 0.69) for the disease model, with similar bias-corrected values (**Table 3.C4**). Both models showed good calibration for inpatient mortality and 24hr-discharge; conversely, one-month readmission models had poor calibration, with no spread between deciles of predicted risk (**Figure 3.C2**).

Temporal validation

The temporal validation of the two models showed values slightly lower than those obtained in the derivation sample and very similar comparing base and disease models (**Table 3.C4**). For inpatient mortality (296 events among 10,976 admissions; 2.7%), C-indices were 0.74 (0.71 to 0.76) for the base and 0.74 (0.72 to 0.77) for the disease model; corresponding values for one-month readmission (1207 events among 22,112 admissions; 5.5%) were 0.55 (0.54 to 0.57) and 0.55 (0.53 to 0.56); and for 24hr-discharge (5363 events among 22,107 admissions; 24.3%), 0.66 (0.65 to 0.67) and 0.67 (0.66 to 0.68). Calibration plots showed good agreement between observed and predicted risk for inpatient mortality and 24hr-discharge; however, a slightly higher predicted than observed risk was evident for the base model in the last (tenth) risk group (**Figure 3.C2**).

Individual risk calculator

Coefficients obtained in the logistic regressions for inpatient mortality and 24hr-discharge were used to develop an Excel calculator to estimate individual absolute predicted risk based on variables included in the base model; for both outcomes, models were recalibrated using the calibration slope and intercept estimated in the validation samples (**Table 3.C4**). One-month readmission was not included because of the poor performance of models for this outcome and the calculator was developed using only base models following criteria of parsimony, simplicity, and given the negligible differences in the performance between the base and disease models. The calculator allows the input of individual data on age, sex, ethnicity, Charlson score, and England postcode (for social deprivation) for two patients to visually inspect the impact of changing a single variable; the Excel graphical interface is shown in **Appendix C, Figure C1**.

Interpretation in the context of available evidence

Two prognostic models have been developed, internally and temporally validated, for length of hospital stay, mortality, and readmission using a large sample of hospital admissions for hypoglycaemia in England. The two models performed well and without meaningful differences between them in the prediction of inpatient mortality and length of hospital stay, defined in this study as same-day discharge. Conversely, models failed to accurately predict one-month readmission for hypoglycaemia: in fact, the same variables used for inpatient mortality and length of stay did not accurately predict the risk one-month readmissions, underlying the possibility that other, unmeasured factors are more relevant in identifying patients at higher risk of recurrent admissions for hypoglycaemia and confirming the previous two analyses. For all outcomes, model performances were similar in temporal validations. These findings allowed the development of a tool to assess individual risk based on basic information which are routinely collected in patients admitted to English National Health Service hospital trusts (an example is reported in **Appendix C, Figure C1**).

Few models to predict the risk of hypoglycaemia are available. Based on a sample of around 10,000 admissions in people with diabetes, Stuart et al. developed and internally validated (C-index 0.73) a model including routine biochemical data to predict the risk of hypoglycaemia (defined as blood glucose <4 mmol/l) during hospitalisation [80]. Schroeder et al. developed in 31,674 individuals with pharmacologically-treated diabetes and externally validated in two cohorts (38,764 and 12,035 participants) two models to predict the risk of severe hypoglycaemia (emergency departments and inpatient encounters using ICD codes) within 6 months [82]. The two models included 16 and 6 variables (age, diabetes type, HbA1c, eGFR, history of a hypoglycaemic event in the prior year, and insulin use) and both performed well in terms of calibration and discrimination (C-index in the external cohorts, 0.80-0.84). Another model has been developed and internally validated in 195 patients with insulin-treated type 2 diabetes using the mean and standard deviation of self-monitored blood glucose over 8 weeks (C-index 0.75) to predict the risk of hypoglycaemia (blood glucose ≤3.33 mmol/l) within 12 months [83]. Recently, more advanced analytical methods (machine learning) have been used to predict the risk of hypoglycaemia within 24 hours [81] and emergency or hospitalisation admission for hypoglycaemia within 12 months [84]. In the first study, Sudharsan et al. developed and validated an algorithm to predict hypoglycaemia (<3.9 mmol/l) with a sensitivity of 92% and specificity of 70%. In the second, Karter et al. used recursive partitioning with a split-sample design to develop (206,435 participants with type 2 diabetes) and validate in two cohorts (1,335,966 and 14,972 participants) a risk prediction model for hypoglycaemia-related

emergency department or hospital admission. From an initial set of 156 potential predictor variables based on literature review, the final model included six variables (number of prior episodes of hypoglycaemia-related utilization, insulin use, sulfonylurea use, prior year emergency department use, chronic kidney disease stage, and age) with a C-index in the external cohorts of 0.79-0.81. However, this model only stratifies the risk (high, >5%; intermediate, 1%-5%; or low <1%) and does not estimate the absolute risk for an individual patient.

In the last few years, clinical risk models have also been developed and validated for inpatient mortality in different settings, including people with myocardial infarction [85], valve replacement [86], abdominal aortic aneurism [87], or admitted to intensive care unit [141]. Similarly, validated models for readmissions are available for all-cause and cause-specific readmissions, such as cardiovascular, gastrointestinal, or pulmonary diseases [88, 142-146]. More limited are validated models for length of hospital stay, available for example for patients with chronic obstructive pulmonary disease [147], gastrointestinal bleeding [148], or stroke [89]. Studies aimed to develop clinical prediction models are appreciably different in terms of variables accessibility, model specification procedures, temporal and geographical settings and, more importantly, studied populations. It is therefore not surprising that the final variables included in the models, the strength of their associations with outcomes, and the occurrence of the outcomes are inconsistent across studies. This is in part due to differences in the aetiology and pathophysiology of diseases (which could influence, for example, the selection of variables) as well as to differences in their severity (for example, risk of inpatient death following decompensated heart failure *vs* hypoglycaemia). Therefore, the precise definition of a homogeneous population to whom the prediction models apply is of crucial importance. As of November 2016, no model has been developed to predict hospital outcomes in patients admitted for hypoglycaemia.

The algorithm developed could is being implemented in a web/mobile app to evaluate the benefit for patients and health-care systems of estimating and acknowledging the risk of inpatient death and length of hospital stay. While factors associated with an increased risk of complications, death, longer hospitalisation or readmission have been described for diabetic ketoacidosis [149-154], to date the approach to hypoglycaemia has consisted in the normalisation of physiological glucose levels without any stratification of the individual risk after hospitalisation. The possibility to estimate the risk could help decision makers in identifying high-risk patients and implementing tailored strategies, on top of glucose normalisation. Ideally, a RCT should assess whether the use of the algorithm would results in potential benefits for patients and health care systems (i.e., shorter length of hospitalisation and reduced risk of mortality).

A major strength of this study is the availability of a nation-wide large database with detailed information on hospital admissions with virtually no missing data. At the same time, several points should be considered for the interpretation of these findings.

This analysis shares the same limitations previously reported for the other two analyses. First, only variables available in HES database were used and important prognostic variables such as glucose-lowering medications (particularly insulin therapy) and diabetes duration which could be particularly relevant for one-month readmission, were not available. However, a recent systematic review has confirmed initial observations about the poor to moderate performance of risk models for one-month hospital readmissions [144], even in those including an extensive panel of potential predictors [88]. Moreover, although several studies have evidenced multiple clinical risk factors for severe hypoglycaemia, the large majority of these analyses reported only associations which do not necessarily translate into better prognostic ability [63]. Given the substantial cost associated with hospital readmissions in the UK and the high prevalence of one-month readmission in patients admitted for hypoglycaemia [72, 155] (also evidenced in the previous analysis), further studies are warranted to address this important knowledge, clinical, and public health gap.

Second, variable selection in prognostic models is well recognised as the most difficult step in model development. At two extremes, selection of variables can be based only on the expert knowledge of subject matter or only on statistical methods, although the latter approach has been criticised for unstable selection of predictors and bias estimation of associations [138]. In this analysis, two models were tested: a simple model, responding to criteria of parsimony and clinical knowledge, based only on six variables and a second model, with more detailed specification of comorbidities, based on a statistical method to define the final set of variables. The performance of the two models, however, was very similar and that justified the use of variables included in the base model for predicting individual risk.

Third, notwithstanding the importance and the implications of length of stay as a quality indicator across hospitals [156], there are still methodological uncertainties about the best modelling approach to analyse such data: logistic regression estimating discharge at meaningful time points, time-to-event analysis, or mixture models have been variably suggested, with unclear advantages in simulation studies of one method over another [157-159]. Accounting for HES database characteristics, however, I opted to perform a logistic regression using 24hr as the time point. Indeed, in HES length of stay can be calculated as the difference between two dates, thus resulting in admissions of length of zero (24hr-discharge, i.e. same date for entry and exit) or within multiples of 1 day. As about 25% of discharges occurred in 24 hours, time-to-event analysis was not a suitable approach to analyse these data. In similar circumstances where a

significant proportion of discharge occurs within 24 hours, a more detailed description of length of hospitalisation with time-to-event analysis is possible only if length of stay is reported in fractional days (i.e. hours).

Lastly, a validation of models was performed using admissions in two different periods (temporal validation): these results, therefore, pertain in principle only to admissions for hypoglycaemia in England. A fully external validation (temporal and spatial) is required to validate models accounting for geographical and temporal differences.

While further validation studies are required, this risk model is a simple and pragmatic tool which can potentially improve the quality of care through personalised approaches and optimise resource allocation. Future randomised controlled trials should be designed to randomly assign patients to the use of the risk score and evaluate whether its application results in improved outcomes.

Tables and Figures

Table 3.C1: Outcome-specific top 20 most common diseases (ICD code position 2nd to 6th)

Inpatient mortality					Included*
ICD-10	**Disease**	**N**	**%**	**Cumulative %**	
E119	NIDDM without complications	13,455	14.3	14.3	✓
I10X	Essential (primary) hypertension	6,852	7.3	21.5	✓
E109	IDDM without complications	5,892	6.2	27.7	
I48X	Atrial fibrillation and flutter	2,138	2.3	30.0	
Y423	Insulin and oral hypoglycaemic [antidiabetic] drugs	1,938	2.1	32.1	
N179	Acute renal failure, unspecified	1,748	1.9	33.9	✓
N390	Urinary tract infection, site not specified	1,741	1.8	35.8	
N189	Chronic renal failure, unspecified	1,601	1.7	37.5	
I259	Chronic ischaemic heart disease, unspecified	1,573	1.7	39.1	✓
E780	Pure hypercholesterolaemia	1,481	1.6	40.7	
I252	Old myocardial infarction	1,262	1.3	42.0	✓
E039	Hypothyroidism, unspecified	1,062	1.1	43.1	
F171	Mental & behavioural disease due use tobacco: harmful use	1,046	1.1	44.3	
J459	Asthma, unspecified	1,039	1.1	45.4	
H360	Diabetic retinopathy	1,025	1.1	46.4	
I500	Congestive heart failure	996	1.1	47.5	
J449	COPD, unspecified	992	1.1	48.5	
F03X	Unspecified dementia	970	1.0	49.6	
R296	Repeated falls	917	1.0	50.5	
I209	Angina pectoris, unspecified	900	1.0	51.5	
Other	-	45,814	48.5	100.0	
TOTAL		**94,442**	**100.0**		

One month readmission (R) and 24hr discharge (24d)					Included*	
ICD-10	**Disease**	**N**	**%**	**Cumulative %**	**R**	**24d**
E119	NIDDM without complications	34,191	14.8	14.8	✓	✓
I10X	Essential (primary) hypertension	16,521	7.1	21.9		✓
E109	IDDM without complications	15,034	6.5	28.4		✓
I48X	Atrial fibrillation and flutter	5,256	2.3	30.6		✓
Y423	Insulin and oral hypoglycaemic [antidiabetic] drugs	4,508	1.9	32.6		
N390	Urinary tract infection, site not specified	4,331	1.9	34.5		✓
E780	Pure hypercholesterolaemia	4,086	1.8	36.2		✓
N179	Acute renal failure, unspecified	3,460	1.5	37.7		✓
N189	Chronic renal failure, unspecified	3,105	1.3	39.1	✓	
I259	Chronic ischaemic heart disease, unspecified	3,100	1.3	40.4		✓
E039	Hypothyroidism, unspecified	2,857	1.2	41.6		✓
I209	Angina pectoris, unspecified	2,710	1.2	42.8		✓
I258	Other forms of chronic ischaemic heart disease	2,653	1.1	43.9		✓
J459	Asthma, unspecified	2,599	1.1	45.1		
F03X	Unspecified dementia	2,427	1.0	46.1		✓
I500	Congestive heart failure	2,365	1.0	47.1		✓
J449	COPD, unspecified	2,355	1.0	48.2		
H360	Diabetic retinopathy	2,319	1.0	49.2		✓
Z867	Personal history of diseases of the circulatory system	2,055	0.9	50.0		✓
F171	Mental & behavioural disease due use tobacco: harmful use	1,997	0.9	50.9		
Other	-	113,730	49.1	100.0		
TOTAL		**231,659**	**100.0**			

* Initial models included age (spline with 5 knots), sex, ethnicity, region, IMD-10, Charlson score, and outcome-specific top 20 most common diseases (admissions in 2013-2014 for inpatient mortality; 2010-2014 for readmission [R] and 24hr discharge [24d]). Final models were defined with a stepwise back elimination and included variables indicated with ✓ (odds ratios reported in Table 3.C3).
COPD: Chronic obstructive pulmonary disease; **IDDM**: Insulin-dependent diabetes mellitus; **NIDDM**: Non-insulin-dependent diabetes mellitus

Table 3.C2: Characteristics of admissions to hospital for hypoglycaemia

	DERIVATION			VALIDATION		
Characteristic	**Inpatient mortality**	**One month readmission**	**24hr discharge**	**Inpatient mortality**	**One month readmission**	**24hr discharge**
Calendar year	2013	2010-2012	2010-2012	2014	2013-2014	2013-2014
Admission (n)	11136	33825	33803	10976	22112	22107
Participant (n)	9937	28554	28533	9819	19057	19054
Death (n)	296	-	-	296	-	-
Readmission (n)	-	1789	-	-	1207	-
24hr-discharge (n)	-	-	8396	-	-	5363
Age at admission (Years)						
<20	638 (5.7)	2121 (6.3)	2121 (6.3)	594 (5.4)	1232 (5.6)	1232 (5.6)
20-29	334 (3.0)	1182 (3.5)	1182 (3.5)	344 (3.1)	678 (3.1)	678 (3.1)
30-39	395 (3.6)	1207 (3.6)	1206 (3.6)	341 (3.1)	736 (3.3)	736 (3.3)
40-49	678 (6.1)	2008 (5.9)	2007 (5.9)	686 (6.3)	1364 (6.2)	1362 (6.2)
50-59	964 (8.7)	2730 (8.1)	2730 (8.1)	960 (8.8)	1924 (8.7)	1924 (8.7)
60-69	1542 (13.9)	4348 (12.9)	4347 (12.9)	1468 (13.4)	3010 (13.6)	3010 (13.6)
70-79	2818 (25.3)	9120 (27.0)	9118 (27.0)	2840 (25.9)	5658 (25.6)	5656 (25.6)
≥80	3767 (33.8)	11109 (32.8)	11092 (32.8)	3743 (34.1)	7510 (34.0)	7509 (34.0)
Sex						
Females	5430 (48.8)	16518 (48.8)	16506 (48.8)	5257 (47.9)	10687 (48.3)	10686 (48.3)
Males	5706 (51.2)	17307 (51.2)	17297 (51.2)	5719 (52.1)	11425 (51.7)	11421 (51.7)
Charlson index	2.29 ± 1.62	2.04 ± 1.46	2.04 ± 1.46	2.37 ± 1.61	2.33 ± 1.62	2.33 ± 1.62
IMD-10						
Least deprived 10%	607 (5.5)	1828 (5.4)	1826 (5.4)	633 (5.8)	1240 (5.6)	1240 (5.6)
Less deprived 10-20%	768 (6.9)	2241 (6.6)	2240 (6.6)	671 (6.1)	1439 (6.5)	1439 (6.5)
Less deprived 20-30%	857 (7.7)	2459 (7.3)	2458 (7.3)	806 (7.3)	1663 (7.5)	1663 (7.5)
Less deprived 30-40%	917 (8.2)	2863 (8.5)	2861 (8.5)	842 (7.7)	1759 (8.0)	1759 (8.0)
Less deprived 40-50%	1027 (9.2)	3108 (9.2)	3103 (9.2)	949 (8.7)	1976 (8.9)	1976 (8.9)
More deprived 10-20%	1436 (12.9)	4747 (14.0)	4743 (14.0)	1563 (14.2)	2999 (13.6)	2999 (13.6)
More deprived 20-30%	1359 (12.2)	4223 (12.5)	4222 (12.5)	1369 (12.5)	2728 (12.3)	2727 (12.3)
More deprived 30-40%	1195 (10.7)	3538 (10.5)	3537 (10.5)	1192 (10.9)	2387 (10.8)	2387 (10.8)
More deprived 40-50%	1101 (9.9)	3314 (9.8)	3312 (9.8)	1174 (10.7)	2275 (10.3)	2273 (10.3)
Most deprived 10%	1869 (16.8)	5504 (16.3)	5501 (16.3)	1777 (16.2)	3646 (16.5)	3644 (16.5)
Ethnicity						
White	9225 (82.8)	28185 (83.3)	28166 (83.3)	9030 (82.3)	18255 (82.6)	18250 (82.6)
Other	1911 (17.2)	5640 (16.7)	5637 (16.7)	1946 (17.7)	3857 (17.4)	3857 (17.4)

Data reported as mean ± standard deviation or number (percentage); IMD-10 (Index of Multiple Deprivation) score in deciles. Complete-case data (i.e., non-missing) are shown – there was 1 missing information for inpatient mortality (age); 41 for readmission (1 age and 40 IMD-10); and 68 for length of hospital stay (1 age, 34 IMD-10, 27 time to discharge, and 6 both IMD-10 and time to discharge).

Table 3.C3: Outcome-specific odds ratios of variables included in "disease" models

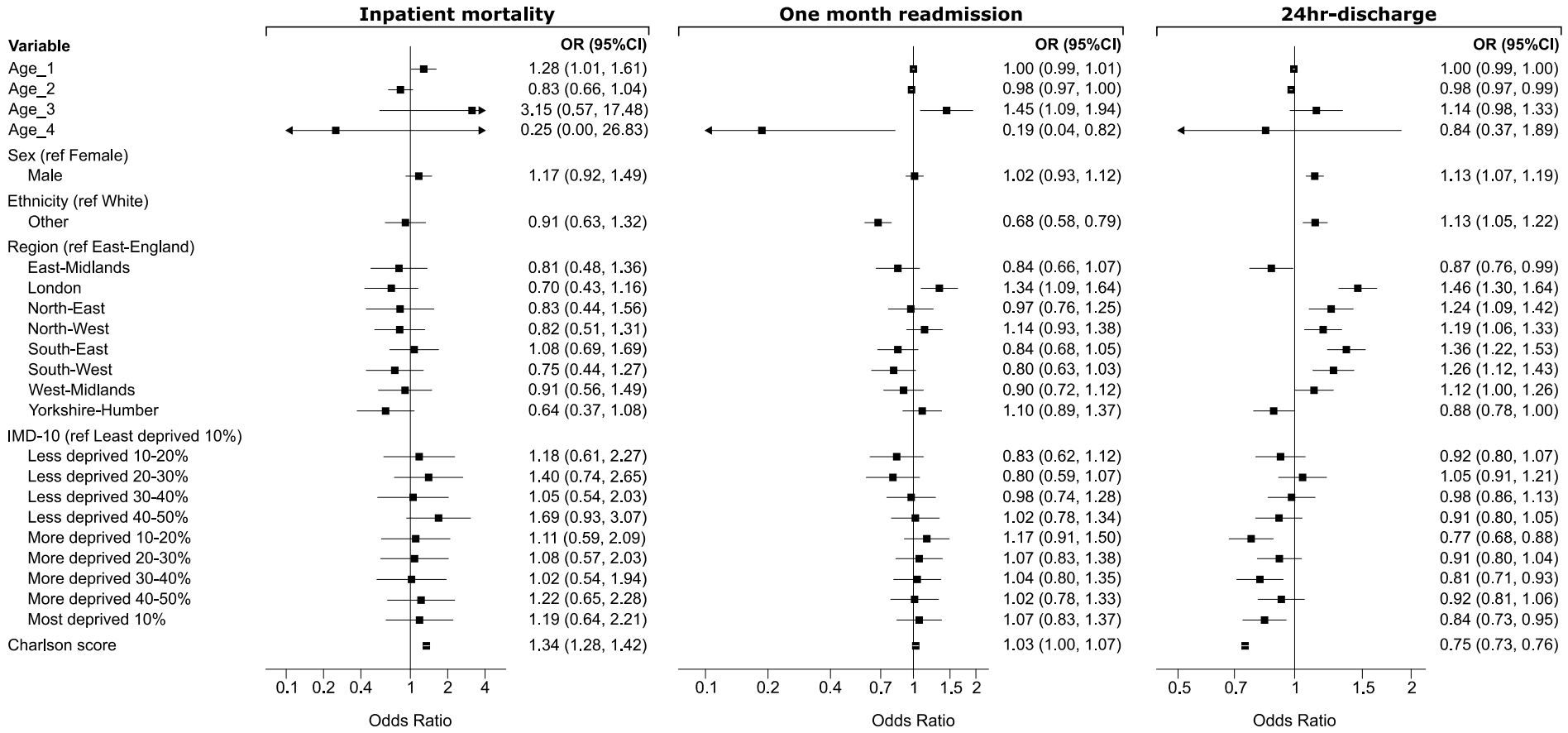
Variable		Odds Ratio (95% confidence interval)		
		Inpatient mortality	One month readmission	24hr discharge
Age (unit increase)		1.05 (1.04, 1.07)	0.99 (0.99, 1.00)	0.98 (0.98, 0.99)
Sex (Male vs Female)		-	-	1.15 (1.10, 1.22)
Ethnicity (Other vs White)		-	0.69 (0.59, 0.80)	1.12 (1.04, 1.21)
Region (ref East-England)				
East-Midlands		-	0.87 (0.68, 1.10)	0.88 (0.77, 1.00)
London		-	1.41 (1.15, 1.72)	1.48 (1.32, 1.66)
North-East		-	1.02 (0.80, 1.31)	1.26 (1.10, 1.44)
North-West		-	1.18 (0.98, 1.43)	1.19 (1.06, 1.32)
South-East		-	0.84 (0.68, 1.05)	1.36 (1.21, 1.52)
South-West		-	0.81 (0.64, 1.04)	1.26 (1.11, 1.42)
West-Midlands		-	0.94 (0.75, 1.17)	1.12 (0.99, 1.25)
Yorkshire-Humber		-	1.15 (0.93, 1.42)	0.88 (0.78, 1.00)
IMD-10 (ref Least deprived 10%)				
Less deprived 10-20%		-	-	0.92 (0.79, 1.07)
Less deprived 20-30%		-	-	1.05 (0.91, 1.21)
Less deprived 30-40%		-	-	0.99 (0.86, 1.14)
Less deprived 40-50%		-	-	0.91 (0.80, 1.05)
More deprived 10-20%		-	-	0.80 (0.70, 0.91)
More deprived 20-30%		-	-	0.94 (0.82, 1.07)
More deprived 30-40%		-	-	0.83 (0.72, 0.95)
More deprived 40-50%		-	-	0.94 (0.82, 1.08)
Most deprived 10%		-	-	0.87 (0.76, 0.99)
Charlson score (unit increase)		1.36 (1.29, 1.43)	1.03 (0.99, 1.06)	0.76 (0.74, 0.78)
Presence of disease	**ICD-10**			
Hypothyroidism, unspecified	E039	-	-	0.73 (0.56, 0.96)
IDDM without complications	E109	-	-	2.55 (1.24, 5.28)
NIDDM without complications	E119	2.43 (1.30, 4.54)	0.51 (0.26, 0.99)	0.47 (0.33, 0.66)
Pure hypercholesterolaemia	E780	-	-	0.82 (0.68, 1.00)
Unspecified dementia	F03X	-	-	0.61 (0.43, 0.87)
Diabetic retinopathy	H360	-	-	0.61 (0.36, 1.05)
Essential (primary) hypertension	I10X	0.68 (0.41, 1.14)	-	0.56 (0.48, 0.64)
Angina pectoris, unspecified	I209	-	-	0.71 (0.52, 0.96)
Old myocardial infarction	I252	0.41 (0.13, 1.33)	-	-
Other forms of CIHD	I258	-	-	0.56 (0.43, 0.74)
CIHD, unspecified	I259	0.49 (0.18, 1.34)	-	0.54 (0.39, 0.76)
Atrial fibrillation and flutter	I48X	-	-	0.50 (0.39, 0.66)
Congestive heart failure	I500	-	-	0.66 (0.44, 0.98)
Acute renal failure, unspecified	N179	2.97 (1.14, 7.73)	-	0.20 (0.09, 0.46)
Chronic renal failure, unspecified	N189	-	1.51 (0.97, 2.34)	-
UTI, site not specified	N390	-	-	0.24 (0.11, 0.52)
Hx of the circulatory system	Z867	-	-	0.82 (0.67, 1.02)
Constant (exp)		0.00022	0.07933	1.42862

CIHD: chronic ischaemic heart disease
Hx: personal history of diseases
IDDM: insulin-dependent diabetes mellitus
NIDDM: non-insulin-dependent diabetes mellitus
UTI: Urinary tract infection

Table 3.C4: Model performance indices in derivation and validation samples

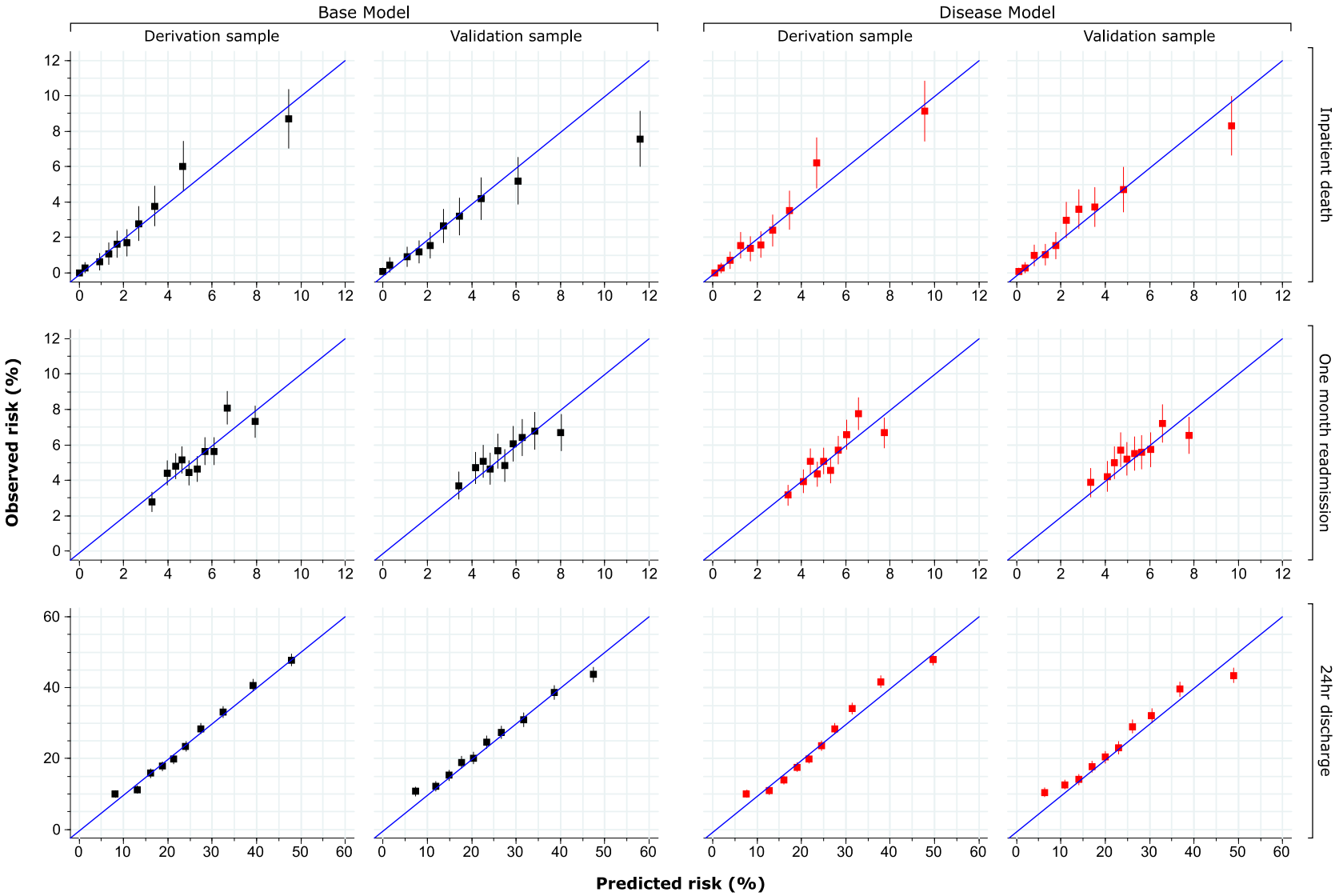
Model	DERIVATION			VALIDATION			
	Nagelkerke R^2	C-index (95% CI)	Bias-corrected C-index	Nagelkerke R^2	C-index (95% CI)	Calibration Slope	Calibration Intercept
Inpatient mortality							
Base	12.1	0.77 (0.75, 0.80)	0.75	8.1	0.74 (0.71, 0.76)	0.77	0.00
Disease	11.8	0.78 (0.75, 0.80)	0.77	9.0	0.74 (0.72, 0.77)	0.86	-0.01
One-month readmission							
Base	1.0	0.57 (0.56, 0.59)	0.56	0.5	0.55 (0.54, 0.57)	0.70	0.03
Disease	0.9	0.57 (0.56, 0.58)	0.56	0.4	0.55 (0.53, 0.56)	0.66	0.03
24hr-discharge							
Base	10.6	0.68 (0.67, 0.69)	0.68	8.4	0.66 (0.65, 0.67)	0.83	0.04
Disease	11.1	0.69 (0.68, 0.69)	0.69	8.9	0.67 (0.66, 0.68)	0.82	0.05

Figure 3.C1: Associations of variables with outcomes for base model (derivation samples)



Age_1, Age_2, Age_3, and Age_4 indicate restricted cubic spline transformation of age; IMD-10: Deciles of index of multiple deprivation. Odds ratios are reported per unit increase of Charlson score. Constants of the models were: -16.864 for inpatient mortality; -2.701 for one-month readmission; and 0.086 for 24hr-discharge

Figure 3.C2: Calibration plots for base and disease models in derivation and validation samples



Chapter Four: Risk of hypoglycaemia in RCTs of GLP-1R agonists and SGLT2 inhibitors

Summary

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium–glucose cotransporter 2 (SGLT2) inhibitors are two new classes of glucose-lowering drugs. Given their pharmacological properties [160, 161], these drugs are expected to reduce hyperglycaemia without increasing rates of hypoglycaemia. In individual RCTs, GLP-1RAs and SGLT2 inhibitors have shown similar glucose-lowering efficacy without an increased risk of hypoglycaemia when compared to older therapies (particularly sulphonylurea and insulin). As a rising use of GLP-1RAs and SGLT2 inhibitors has been reported in England during the last years [106], this could contribute, along with other reasons, to the declining trends of admissions to hospital for hypoglycaemia. In this chapter, the glucose-lowering efficacy and the risk of hypoglycaemia of GLP-1RAs and SGLT2 inhibitors have been systematically assessed combining RCT data with a network meta-analytical approach. Results indicate that these newer drugs reduce hyperglycaemia with a significantly lower risk of hypoglycaemia compared to older therapies.

Glucagon-like peptide-1 receptor agonists

As in normal subjects levels of insulin are greater following oral administration of glucose compared to levels achieved with an isoglycaemic intravenous glucose challenge, it was postulated that specific hormones stimulating insulin secretion (incretins) are synthesised and released by gut cells following enteral nutrient ingestion. In the last 30 years, extensive research has identified GLP-1 as one of the major incretins which stimulates glucose-dependent insulin secretion in preclinical and clinical studies [162]. Furthermore, GLP-1 inhibits glucagon secretion, slows gastric emptying, and reduces food intake [163].

In subjects with type 2 diabetes, there is a reduced “incretin effect”, with lower plasma levels of GLP-1 following food ingestion compared to subjects without diabetes [163]. This pathophysiological observation prompted experiments to increase levels of this hormone with external administration of modified GLP-1 (Glucagon-like peptide-1 receptor agonists, GLP-1RAs). In individual clinical studies, GLP-1RAs improve glucose control and reduce body weight, without an increased risk of hypoglycaemia [160]. In fact, given their glucose-dependent mode of action (the effects are dependent on glucose levels [164]), high dose of GLP-1RAs should not increase the risk of hypoglycaemia.

GLP-1RAs are recommended by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) in patients on metformin with or without another glucose-lowering treatment if individualised HbA1c targets are not achieved [165]. The first two approved GLP-1RAs are administered as subcutaneous daily injections ("daily" GLP-1RAs; twice-daily exenatide and once-daily liraglutide). More recently, GLP-1RAs have been made available via once-weekly administration, thus reducing the number of injections and potentially improving patient's compliance [160]. Several RCTs have also assessed the efficacy and safety of once-weekly GLP-1RAs compared to daily GLP-1RAs or other glucose-lowering therapies although no direct comparisons between once-weekly GLP-1RAs are available (as of September 2015).

Sodium–glucose cotransporter 2 inhibitors

A new class of glucose–lowering pharmacotherapy, which act by the inhibiting renal glucose reabsorption in the kidney, has also been recently introduced [166]. In physiological conditions, glycosuria arises when the tubular threshold for glucose reabsorption is exceeded. As SGLT2 is the major cotransporter involved in tubular glucose reuptake, inhibitors of its activity have been developed with the aim of enhancing glycosuria and reducing blood glucose levels [161]. The efficacy and safety of SGLT2 inhibitors have been investigated in individual RCTs showing improved glucose control and a reduction of body weight and blood pressure with a low risk of hypoglycaemia [161]. Like GLP-1RAs, these drugs are recommended by ADA/EASD as a treatment option in patients on metformin with or without another glucose–lowering treatment [165] and no direct comparisons between specific SGLT2 inhibitors are available (November 2015).

Analytical models to synthesise evidence: frequentist multivariate network meta-analysis

"Classical" pairwise meta-analysis of RCTs allows the estimation of an overall treatment effect combining data from studies which are deemed homogenous enough to be pooled together. In recent years, network meta-analysis (NMA; also known as mixed-treatment comparison analysis) has rapidly emerged as a new methodology for the comparison of different drugs combining "direct" (i.e., pairwise) and "indirect" evidence. While for a pairwise meta-analysis studies can be pooled together when they report on the same comparison (for example, RCT 1: A vs Placebo; RCT 2: A vs Placebo; RCT 3: A vs Placebo), in a NMA all studies are included as long as there is a common treatment across RCTs (i.e., "connected network"; for example, RCT 1: A

vs B; RCT 2: B vs C; the indirect estimation is possible between A vs C because B is common to both RCTs). Network meta-analysis has therefore advantages over conventional pairwise meta-analysis, as it combines direct and indirect evidence to compare multiple interventions, particularly when "head-to-head" RCTs are not available. An attractive feature of a NMA is also the possibility to rank treatments according to their comparative effectiveness.

Network meta-analysis models were initially developed within the framework of Bayesian statistics. Recently, multivariate random-effects meta-analytical methods have been proposed within the frequentist framework [167, 168] and a suite of programs has been developed to perform network meta-analysis in Stata [169]. This suite relies on the updated version of the *mvmeta* Stata command (version 3.1.3; 22 Jul 2015) [170]; the analysis assumes that all treatment contrasts have the same heterogeneity variance [167]. Frequentist methods have some key advantages: first, they aim to speed up computation, avoid sensitivity to the choice of priors and avoid Monte Carlo error; second, multivariate random-effects analyses are two-stage estimation procedures, unlike the one-stage Bayesian procedure; third, models can be easily fitted with common statistical softwares.

Similarly to pairwise meta-analysis, key elements should be considered when performing and interpreting a NMA. A NMA can be graphically summarised using "circles", which represent an intervention as a node and "lines", which connect nodes and represent direct comparisons between two interventions [171]. As the size of the nodes is proportional to the number of participants (or RCTs) while the width of the lines is proportional to the number of RCTs comparing every pair of nodes, by visually examining the network of nodes and lines it is possible to understand how many treatments have been compared in "head-to-head" RCTs, which of the treatments are connected indirectly through one or more common comparators, and the level of evidence for each comparison [172]. An imbalance of evidence for each intervention (i.e., multiple studies comparing the same pair and very few other pairs) may affect the reliability of the overall comparative estimates [173]. Along with the network "geometry", it is also relevant to consider both heterogeneity and incoherence. As in pairwise meta-analysis, heterogeneity can be measured using I^2 and indicates whether estimates across multiple studies are "statistically" heterogeneous. However, the absence of statistical heterogeneity does not exclude the presence of heterogeneity among the pooled studies (i.e., differences in exposure or outcome definition or assessment, dissimilar populations). Of note, in a NMA heterogeneity should be assessed both within direct comparisons and between indirect comparisons. Moreover, in a frequentist multivariate NMA it is assumed that all treatment contrasts have the same heterogeneity variance [167]: in this case, the standard deviation of the between-studies heterogeneity (tau [τ]) can be reported instead of I^2. The presence of heterogeneity among

comparisons increases the likelihood of divergences between estimates obtained from direct vs indirect comparisons. Such divergence is defined “incoherence” or “inconsistency” [172]. Transitivity, which is linked to the concepts of heterogeneity and coherence, is another important element to consider in a NMA. The transitivity assumption is satisfied when RCTs comparing different pairs of treatments do not differ with respect to effect modifiers [174] (i.e., comparing the risk of hypoglycaemia for drug A, B, and C, the RCTs A vs B and A vs C do not significantly differ in terms of factor which could potentially influence the risk of hypoglycaemia, for example age or concomitant glucose-lowering therapies). Small study effects (publication bias) is generally assessed using funnel plots and (when possible) with formal tests (i.e., Egger’s test). This is common, however, for pairwise meta-analysis, while the interpretation of a funnel plot for a network meta-analysis is challenging and different from a pairwise analysis because there is not a common reference line of symmetry [171]; moreover, no formal test for funnel plot asymmetry for frequentist network meta-analysis is to date available.

D. Glucose control and risk of hypoglycaemia of GLP-1RAs agonists

Data sources and extraction

This systematic review and network meta-analysis was conducted to compare the efficacy and safety of the recent formulations of GLP-1RAs (i.e., once-weekly; albiglutide, dulaglutide, once-weekly exenatide, semaglutide, and taspoglutide) with each other and versus other glucose-lowering therapies; comparisons between once-weekly and daily GLP-1RAs indicate a better glucose control with a similar risk of hypoglycaemia for weekly formulations [175]. The study was performed according to standard guidelines for the conduct and reporting of systematic reviews and network meta-analysis [176-178]. From inception to September 26th 2015, PubMed, ISI Web of Science, the Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, fda.gov and ema.europa.eu/ema reports and major diabetes conference abstracts (ADA and EASD from 2012 onwards) were sought. Reference lists of eligible studies, as well as systematic reviews and meta-analyses of GLP-1RAs, were manually scanned for additional relevant studies. No language restriction was applied. For PubMed, the search used the keywords: “Exenatide” OR “Taspoglutide” OR “Albiglutide” OR “Dulaglutide” OR “Semaglutide”, limited to “Humans” and “Randomized Controlled Trial”. Detailed information on the search strategy for other databases is provided in **Figure 4.D1**.

Phase 3 RCTs in adults with type 2 diabetes lasting 24 weeks or more were included. RCTs with at least one once-weekly GLP-1RAs (any dose of albiglutide, dulaglutide, once-weekly exenatide, semaglutide, and taspoglutide) arm were included, regardless of the comparator (placebo or

another glucose-lowering drug). As glucose control and risk of hypoglycaemia are related, to be included RCTs were required to report data on HbA1c (glycated haemoglobin, a biomarker of mean glucose control in the last 3-4 months) or hypoglycaemic events. RCTs with patients with chronic kidney disease were excluded while taspoglutide RCTs were included as they contribute to indirect estimations, although its clinical trial programme was stopped in 2010 and development since suspended.

Extracted data included study characteristics and outcome measured (arm-specific number of participants, mean difference and standard error (or standard deviation) for HbA1c; total number of participants and participants with hypoglycaemic events). As the definitions of hypoglycaemia are expected to differ across RCTs, to reduce heterogeneity data were collected separately for documented and/or symptomatic hypoglycaemia and severe hypoglycaemia. Data were extracted, using a standardised electronic extraction sheet, by intention to treat; when published studies reported outcomes for different durations of follow-up, the longest was used. When it was not possible to extract relevant information for the primary outcome from published reports, trial results were searched in ClinicalTrials.gov and study authors were contacted. Study-level quality was assessed by using the items reported in the Cochrane risk of bias tool (random sequence generation, allocation concealment, blinding of participants/personnel and outcome assessment, incomplete data and selective reporting) [179].

Search and selection of RCTs, data extraction, and quality assessments were also independently performed by other members of the research team with disagreements resolved by arbitration.

Analytical approach

Stata 14 (Stata Corp, College Station, TX, USA) was used for all analyses and results are reported with 95% confidence intervals (CI) with a single digit approximation in the text to be consistent with results available from clinical labs. Pairwise random-effects meta-analyses were performed with the Knapp-Hartung method [180]. Stata commands were used to perform network meta-analysis as multivariate random-effects meta-analysis and meta-regression [169]; *network rank* command was used to estimate the ranking probabilities and the *netleague* command to report relative treatment effects for all pairwise comparisons estimated with the network meta-analysis [181].

Given their similar clinical pharmacology, in this analysis twice-daily exenatide and once-daily liraglutide treatments were combined in one group (i.e., daily GLP-1RA therapies) as were glargine and detemir treatments (i.e., basal insulins). Albiglutide was defined as a single group

because the majority of RCTs were designed to titrate (if necessary) the drug to 50mg and dose-specific data were available only for two studies [182, 183] (for these studies data of 50mg dose were used).

For both pairwise and network meta-analyses, arm-specific mean difference from baseline and odds ratio (OR) as effect measure for continuous and dichotomous data, respectively; 0.5 was added when studies reported 0 events in one treatment arm [167]. For both HbA1c and hypoglycaemia, available evidence was summarised by network diagram [171]. Results are presented against a common comparator (placebo) in forest plots and comparisons across GLP-1RAs are shown in forest plots and tables; ranking probabilities are displayed graphically [184]. Within the networks, consistency between direct and indirect evidence was assessed by using the 'design by treatment' interaction model [168]. For hypoglycaemic events, a sensitivity analysis was performed excluding trials in which once-weekly GLP-1RAs were combined either to insulin or sulphonylurea.

Results

Study Characteristics

Of 1065 identified records, 35 reports (31 full-text articles, 2 studies in ClinicalTrials.gov, and 2 abstracts) based on 34 unique RCTs fulfilled inclusion criteria (**Figure 4.D1; references are reported in Appendix D**). No RCT for semaglutide was found. Included RCTs were published between October 2008 and September 2015, with a total of 21,106 participants with type 2 diabetes, and lasting 24 to 156 weeks (**Table 4.D1**). Overall, the risk of bias for the domains included in the Cochrane tool of risk assessment were judged to be low, high, and unclear in 51.0%, 24.5%, and 24.5% of the cases, respectively (**Table 4.D2**). In 24 out of 34 RCTs (70.6%), a high risk of bias was present for the domain "incomplete outcome data" and an unclear risk for "blinding of outcome assessment", while 21 RCTs (62%) had a high risk for the "blinding of participants and personnel" domain. Conversely, the risk of bias for "random sequence generation", "allocation concealment", and selective reporting was considered low. The completion rate ranged from 60 to 97%, with 25 RCTs using the last-observation carried forward imputation for incomplete data outcome and 9 a mixed-effects model for repeated measure (**Table 4.D3**). Thirteen RCTs used the last observation before hyperglycaemia rescue while data handling for rescued patients was not reported in 21 studies. Other characteristics of the included studies are reported in **Tables 4.D4–4.D6**.

HbA1c

Network maps of evidence are graphically displayed in **Figure 4.D2**. Combining direct and indirect evidence, the network meta-analysis showed a mean HbA1c reduction compared to placebo of -1.4% (95% CI: -1.6, -1.2) [-15.2 mmol/mol; -17.6, -12.8] for dulaglutide 1.5mg; -1.3% (-1.5, -1.1) [-14.3 mmol/mol; -16.6, -11.9] for once-weekly exenatide; -1.2% (-1.4, -1.0) [-13.1 mmol/mol; -15.4, -10.9] for dulaglutide 0.75mg; -1.1% (-1.3, -0.9) [-12.2 mmol/mol; -14.3, -10.2] for taspoglutide 20mg; -1.0% (-1.2, -0.8) [-10.8 mmol/mol; -12.8, -9.0] for albiglutide; and -1.0% (-1.2, -0.8) [-10.7 mmol/mol; -12.9, -8.5] for taspoglutide 10mg (**Figure 4.D3**). Statistical inconsistency for the whole network was not significant (p=0.499). Comparisons across once-weekly GLP-1RAs showed a greater reduction of HbA1c with dulaglutide 1.5mg compared to dulaglutide 0.75mg, albiglutide, and taspoglutide 10mg and 20mg, while no difference was observed in comparison with once-weekly exenatide (**Table 4.D7**). The ranking probabilities for each drug included in the analysis are shown in **Figure 4.D4.** Sensitivity analyses considering separate daily GLP-1RAs (once-daily liraglutide and twice-daily exenatide) and basal insulins (detemir and glargine) showed results consistent with the main analysis (**Table 4.D8**). The estimates from studies with a follow-up duration of 24 to 26 weeks (28 RCTs) similarly showed a greater HbA1c reduction with dulaglutide 1.5mg, although no difference was found compared to albiglutide, possibly due to the small number of albiglutide studies of in this analysis compared to the main analysis (3 vs 8; **Table 4.D9**).

Hypoglycaemia

Based on 30 RCTs, network meta-analysis showed an increased risk of documented and/or symptomatic hypoglycaemia for albiglutide (odds ratio: 1.82; 95% CI: 1.05, 3.15), taspoglutide 10mg (1.94; 1.03, 3.62), once-weekly exenatide (2.08; 1.14, 3.82), dulaglutide 0.75mg (2.51; 1.39, 4.54), and dulaglutide 1.5mg (2.69; 1.51, 4.82), but not for taspoglutide 20mg (1.69; 0.92, 3.14) when compared to placebo (**Figure 4.D3**). The risk of hypoglycaemia was lower for all GLP-1RAs compared to insulins (particularly basal) and glimepiride (**Figure 4.D3** and **Table 4.D10**).

No differences were found among once-weekly GLP-1RAs (**Table 4.D10** and **Table 4.D11**). Sensitivity analyses without grouping basal insulins and daily GLP-1RAs and excluding studies with background therapy including sulphonylurea and/or insulin showed similar results (**Table 4.D8** and **4.D12**, respectively). Due to the presence of a disconnected network (only HARMONY 6 reported data on albiglutide and rapid insulin), the sensitivity analysis limited to studies with a follow-up duration of 24 to 26 weeks was not possible. Few cases of severe hypoglycaemia were reported limiting the possibility of performing a formal analysis. Statistical inconsistency for the whole network of documented and/or symptomatic hypoglycaemia was not significant (p=0.427).

Interpretation in the context of available evidence

Using a network meta-analysis, this study assessed the comparative efficacy and safety of once-weekly GLP-1RAs against each other and versus other glucose-lowering drugs for HbA1c and hypoglycaemia. The results suggested differences in relation to HbA1c, with a slightly greater reduction for dulaglutide 1.5mg. Conversely, the risk of documented and/or symptomatic hypoglycaemic was not different among once-weekly GLP-1RAs.

Previous network meta-analyses (PubMed search, September 2015) have investigated the efficacy and safety of GLP-1RAs in type 2 diabetes patients [185-194], with limited data on once-weekly GLP-1RAs. Moreover, single or few outcomes were reported, making it difficult to formulate a balanced overall assessment of GLP1-RAs therapies. This study included data from recent RCTs and compared once-weekly GLP-1RAs for both HbA1c and hypoglycaemia against each other and versus other well-established therapies. Its aim was to assist decision makers execute 'patient-centred' care by balancing potential risks and benefits of individual drugs. Beyond HbA1c, therapeutic decisions should be based on other outcomes, including side effects. These results could help clinicians to follow ADA/EASD recommendations [165], as both efficacy and safety outcomes have been assessed.

Similar to other glucose-lowering agents [165], once-weekly GLP-1RAs reduced HbA1c from 0.9% to 1.4% when compared to placebo. Among once-weekly GLP-1RAs, the highest difference was found in favour of dulaglutide 1.5mg vs taspoglutide 10mg (0.4%). Of note, comparisons among licensed drugs showed no differences between once-weekly exenatide and the maintenance dose of dulaglutide (1.5mg) for HbA1c and both treatments reduced HbA1c to a better extent compared to albiglutide. Although the risk of hypoglycaemia was not different comparing once-weekly GLP-1RAs, it was lower compared to basal insulin and glimepiride. Overall, these results indicate that: 1) any once-weekly GLP-1RA reduces HbA1c; 2) dulaglutide 1.5mg and once-weekly exenatide are similarly effective and better than other once-weekly GLP-1RAs (particularly albiglutide), sulphonylureas, or insulin; 3) any once-weekly GLP-1RA is associated with a lower risk of hypoglycaemia compared to sulphonylureas or insulin.

There are some limitations of this study. First, this is a study-level meta-analysis based only on available articles, abstracts, and web documents. They are more likely to report 'positive' findings compared to unpublished reports. Second, the magnitude of HbA1c reduction could depend on baseline HbA1c, as higher reductions are typically associated with higher baseline HbA1c values [195]. Yet, most of the studies reported baseline-adjusted HbA1c differences and each once-weekly GLP-1RA has been evaluated in a wide range of patients and HbA1c. Third,

studies with the longest duration for the main analysis were selected to better reflect “real world” conditions, where in reality these drugs are used for many months to years. Sensitivity analyses to assess the impact of study duration were performed although the limited number of albiglutide RCTs made it difficult to derive definitive conclusions. Of note, the lower effects of albiglutide on HbA1c would suggest a reduced efficacy of this drug which is in line with the pharmacological properties of albiglutide, whose large molecular weight (~73kDa) reduces blood-brain barrier crossing and speculatively modulates central nervous system effects [196]. Fourth, the small number of events and heterogeneity of its definition did not allow analyses of severe hypoglycaemia. Fifth, the absence of significant differences for several cardiometabolic risk factors does not necessarily mean the absence of a difference for ‘hard’ cardiovascular outcomes. Sixth, in three studies with zero events in one arm the standard 0.5 continuity correction was used. While the influence of this correction on summary estimates has been investigated in the context of pairwise meta-analysis [197], little is known about the degree to which zero event arms and the 0.5 correction affect network meta-analysis estimates. Results should therefore be interpreted with caution and further research is needed in this area. Lastly, RCTs are not independent as they “cluster” within the same sponsoring company. RCTs of the same company are indeed more similar than RCTs of different companies (i.e., follow-up duration, outcome definition and assessment, rescue design, data analysis and reporting, and results sharing). Although it is difficult to avoid this limitation, it should be considered while interpreting combined data from RCTs. This is particularly relevant for hypoglycaemia, as differences in the definitions and assessment may be present within the same classification (i.e., “documented hypoglycaemia”). On the other hand, this was the first attempt to summarise available data on once-weekly GLP-1RAs with detailed data on study, drug, and outcome-specific number of participants to help the reader interpret the results.

In conclusion, available data indicate that GLP1-RA treatments are effective in reducing HbA1c and are associated with a lower risk of hypoglycaemia compared to sulfonylureas and basal insulin.

Note

In this systematic review, the last day of electronic search for RCTs was September 26th 2015; since then, other RCTs assessing HbA1c reduction and risk of hypoglycaemia for once-weekly GLP-1RAs have been published.

Tables and Figures

Table 4.D1: Baseline characteristics of the included studies

Author	Acronym	Year	Background Therapy	Once-weekly GLP-1	Comparator(s)	Study duration (weeks)	Total sample size (N)	Females (%)	Age* (years)	Diabetes duration* (years)	HbA1c* (%)
Wysham	Award 1	2014	MET+TZD	DUL 0.75/1.5mg	PLA, Exenatide BID	52	976	41.6	55.6	9.0	8.1
Giorgino	Award 2	2015	MET±OADs, SU±OADs	DUL 0.75/1.5mg	Glargine	78	810	48.7	56.7	9.0	8.1
Umpierrez	Award 3	2014	Diet+Exercise	DUL 0.75/1.5mg	MET	52	807	55.9	55.5	3.0	7.6
Blonde	Award 4	2015	Insulin (Basal/Basal+Prandial/Premixed)±OADs	DUL 0.75/1.5mg§	Glargine§	52	884	46.5	59.4	12.7	8.5
Weinstock	Award 5	2015	MET	DUL 0.75/1.5mg	Sitagliptin	104	921	52.7	54.1	7.0	8.1
Dungan	Award 6	2014	MET	DUL 1.5mg	Liraglutide QD	26	599	52.1	56.7	7.2	8.1
Drucker	Duration 1	2008	MET, SU, TZD, or any two combination	EOW 2mg	Exenatide BID	30	295	46.8	55.0	6.0	8.3
Bergenstal	Duration 2	2010	MET	EOW 2mg	PIO, Sitagliptin	26	491	47.3	52.3	5.7	8.5
Diamant ||	Duration 3	2014	MET±SU	EOW 2mg	Glargine	156	456	46.7	58.0	7.9	8.3
Russell-Jones	Duration 4	2012	Diet+Exercise	EOW 2mg	PIO, Sitagliptin, MET	26	820	42.1	53.9	2.7	8.5
Blevins	Duration 5	2011	MET, SU, TZD, or any combination	EOW 2mg	Exenatide BID	24	252	42.5	55.5	7.0	8.5
Buse	Duration 6	2013	MET, SU, MET + SU, MET+PIO	EOW 2mg	Liraglutide QD	26	911	45.2	57.0	8.5	8.5
Reusch	Harmony 1	2014	PIO±MET	ALB 30mg	PLA	52	301	40.2	55.0	7.9	8.1
Nauck	Harmony 2	2013	Diet+Exercise	ALB 30/50mg¶	PLA	52	296	46.0	53.0	4.0	8.1
Ahren	Harmony 3	2014	MET	ALB 30 to 50mg	PLA, Sitagliptin, Glimepiride	104	1012	53.5	54.4	6.0	8.1
Weissman	Harmony 4	2014	MET±SU	ALB 30 to 50mg	Glargine	52	745	43.9	55.4	8.7	8.3
Home	Harmony 5	2015	MET+SU	ALB 30 to 50mg	PLA, PIO	52	663	46.8	55.2	8.9	8.2
Rosenstock	Harmony 6	2014	Glargine/Detemir/NPH±OADs	ALB 30 to 50mg	Lispro	26	563	52.9	55.5	11.0	8.5
Pratley	Harmony 7	2014	MET, SU, TZD, or any combination	ALB 30 to 50mg	Liraglutide QD	32	812	49.6	55.6	8.3	8.2
Raz	T-Emerge 1	2012	Diet+Exercise	TAS 10/20mg	PLA	24	368	60.3	55.0	2.4	7.6
Rosenstock	T-Emerge 2	2013	MET, TZD, MET+TZD	TAS 10/20mg	Exenatide BID	52**	1149	47.4	56.9	6.7	8.3
Henry	T-Emerge 3	2012	MET+PIO	TAS 10/20mg	PLA	24	313	46.7	54.2	7.7	8.1
Bergenstal	T-Emerge 4	2012	MET	TAS 10/20mg	PLA, Sitagliptin	52†	546	44.6	55.9	5.9	8.0
Nauck	T-Emerge 5	2012	MET+SU	TAS 10/20mg	Glargine	24	1028	48.3	57.7	9.5	8.3
Pratley	T-Emerge 6	2013	SU±MET	TAS 10/20mg	PIO	24	740	50.4	56.4	8.8	8.3
Hollander	T-Emerge 7	2013	MET	TAS 20mg	PLA	24	292	59.2	53.5	5.1	7.5
Miyagawa	-	2015	Diet+Exercise	DUL 0.75mg	PLA, Liraglutide QD	26	487	18.7	57.4	6.6	8.1
Araki	-	2015	SUs, BIGs, SUs+BIGs	DUL 0.75mg	Glargine	26	361	28.5	56.8	8.8	8.0
NCT01648582	-	2015	MET, SU, MET+SU	DUL 0.75/1.5mg	Glargine	52	770	45.4	54.9	-	-
Wang	-	2015	Diet+Exercise±OAD	DUL 0.75/1.5mg	Glimepiride	26	807	46.1	52.8	3.7	7.9
Davies	-	2013	MET±SU	EOW 2mg	Detemir	26	216	33.8	58.5	7.5	8.4
Inagaki	-	2012	BIG, BIG+TZD, BIG+SU, BIG+TZD+SU	EOW 2mg	Glargine	26	427	32.1	56.8	9.0	8.5
Ji	-	2013	MET, SU, TZD, MET+SU, MET+TZD, SU+TZD	EOW 2mg	Exenatide BID	26	678	45.9	55.5	8.1	8.7
NCT01733758	-	2015	Diet + Exercise, OAD	ALB 30/50mg¶	PLA, Liraglutide QD	24	330	25.1	57.8	-	8.1

* When not reported for the overall population, values have been estimated as weighted means; § Both arms added also insulin Lispro; || Data from 156 weeks (year 2014) for continuous outcomes; data from 26 weeks (year 2010) for hypoglycaemic events; ¶ Data and analyses are reported for the higher dose (50mg); ** 104 weeks for side effects; † 156 weeks for hypoglycaemia. **ALB:** Albiglutide; **BID:** Twice daily; **BIG:** Biguanide; **DUL:** Dulaglutide; **EOW:** Once-weekly Exenatide; **MET**: Metformin; **NPH**: Neutral Protamine Hagedorn insulin; **OAD**: Oral antihyperglycaemic drug; **PIO**: Pioglitazone; **PLA:** Placebo; **QD:** Once-daily; **SU**: Sulphonylurea; **TAS:** Taspoglutide; **TZD**: Thiazolidinedione

Table 4.D2: Assessment of risk of bias in individual studies

	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting
DULAGLUTIDE						
AWARD 1	L	L	H	U	H	L
AWARD 2	U	H	H	U	H	L
AWARD 3	L	L	L	U	H	L
AWARD 4	L	H	H	U	H	L
AWARD 5	L	L	H	H	H	L
AWARD 6	L	L	H	L	U	L
Miyagawa	L	L	H	U	U	L
Araki	L	L	H	H	U	L
NCT01648582	U	U	H	H	U	U
Wang	U	U	U	U	U	U
ONCE WEEKLY EXENATIDE						
DURATION 1	L	L	H	L	H	L
DURATION 2	L	L	L	L	H	L
DURATION 3	L	L	H	L	U	L
DURATION 4	L	L	L	U	U	L
DURATION 5	L	L	H	L	H	L
DURATION 6	L	L	H	U	U	L
Davies	L	L	H	U	H	L
Inagaki	L	L	H	U	H	L
Ji	L	L	H	U	U	L
ALBIGLUTIDE						
HARMONY 1	L	L	L	U	H	L
HARMONY 2	U	U	U	U	H	U
HARMONY 3	L	L	L	U	H	L
HARMONY 4	L	L	H	U	H	L
HARMONY 5	L	L	L	U	H	L
HARMONY 6	L	L	H	U	H	L
HARMONY 7	L	L	H	U	H	L
NCT01733758	U	U	U	U	U	U
TASPOGLUTIDE						
T-EMERGE 1	L	L	L	U	H	L
T-EMERGE 2	L	L	H	L	H	L
T-EMERGE 3	L	L	L	U	H	L
T-EMERGE 4	L	L	H	L	H	L
T-EMERGE 5	L	L	H	U	H	L
T-EMERGE 6	L	L	L	U	H	L
T-EMERGE 7	L	L	L	U	H	L

L = Low Risk**; H =** High Risk**; U =** Unclear Risk

Table 4.D3: Handling of rescue and missing data for the included studies

First Author	Acronym	Duration (weeks)	Completion Rate (%)	Statistical methods for drop-out/missing data (HbA1c)	Data handling for rescued patients
Wysham	Award 1	52	88.1	LOCF (Supplementary analysis MMRM, data not reported)	Last value before rescue
Giorgino	Award 2	78	89.3	LOCF (Supplementary analysis MMRM, data not reported)	Last value before rescue
Umpierrez	Award 3	52	80.7	LOCF (Supplementary analysis MMRM, data not reported)	Last value before rescue
Blonde	Award 4	52	77.1	LOCF (Supplementary analysis MMRM, data not reported)	Last value before rescue
Weinstock	Award 5	104	59.8	LOCF (Supplementary analysis MMRM with similar results, data not reported)	Last value before rescue
Dungan	Award 6	26	89.8	MMRM (Supplementary analysis LOCF)	Last value before rescue
Drucker	Duration 1	30	87.5	LOCF	Not reported
Bergenstal	Duration 2	26	75.3	LOCF	Not reported
Diamant *	Duration 3	156	64.0	MMRM	Not reported
Russell-Jones	Duration 4	26	84.9	MMRM	Not reported
Blevins	Duration 5	24	81.0	LOCF (Supplementary analysis MMRM with similar results, data reported)	Not reported
Buse	Duration 6	26	86.7	MMRM	Not reported
Reusch	Harmony 1	52	80.0	LOCF	Last value before rescue
Nauck	Harmony 2	52	NR	LOCF	Last value before rescue
Ahren	Harmony 3	104	67.4	LOCF	Last value before rescue
Weissman	Harmony 4	52	76.9	LOCF	Last value before rescue
Home	Harmony 5	52	79.6	LOCF	Last value before rescue
Rosenstock	Harmony 6	26	89.1	LOCF	Last value before rescue
Pratley	Harmony 7	32	81.6	LOCF	Last value before rescue
Raz	T-Emerge 1	24	94.9	LOCF	Not reported
Rosenstock	T-Emerge 2	52	65.9	LOCF	Not reported
Henry	T-Emerge 3	24	85.3	LOCF	Not reported
Bergenstal	T-Emerge 4	52	65.6	LOCF	Not reported
Nauck	T-Emerge 5	24	81.8	LOCF	Not reported
Pratley	T-Emerge 6	24	82.2	LOCF	Not reported
Hollander	T-Emerge 7	24	83.9	LOCF	Not reported
Miyagawa	-	26	93.9	MMRM	Not reported
Araki	-	26	97.0	MMRM	Not reported
NCT01648582	-	52	87.1	MMRM	Not reported
Wang	-	26	91.3	MMRM	Not reported
Davies	-	26	86.0	LOCF (Supplementary analysis MMRM, data not reported)	Not reported
Inagaki	-	26	92.3	LOCF	Not reported
Ji	-	26	84.5	MMRM	Not reported
NCT01733758	-	24	92.7	LOCF	Not reported

LOCF: last observation carried forward; **MMRM**: Mixed model for repeated measures; **NR**: Not reported

* Duration 26 weeks; completion rate 91.7%

Table 4.D4: Number of study-specific participants (left) and drug-specific arms and participants (right) for HbA1c

First Author	Acronym	N	Drug	N
Wysham	Award 1	835	Once-weekly Exenatide	9
Giorgino	Award 2	807		2045
Umpierrez	Award 3	807	Daily GLP-1RAs	10
Blonde	Award 4	884		2654
Weinstock	Award 5	921	Pioglitazone	4
Dungan	Award 6	599		851
Drucker	Duration 1	295	Sitagliptin	5
Bergenstal	Duration 2	491		1123
Diamant*	Duration 3	456	Basal Insulins	9
Russell-Jones	Duration 4	820		2092
Blevins	Duration 5	252	Metformin	2
Buse	Duration 6	911		514
Reusch	Harmony 1	301	Taspoglutide 10mg	6
Nauck	Harmony 2	195		1389
Ahren	Harmony 3	1012	Taspoglutide 20mg	7
Weissman	Harmony 4	745		1563
Home	Harmony 5	648	Placebo	9
Rosenstock	Harmony 6	563		970
Pratley	Harmony 7	812	Albiglutide	8
Raz	T-Emerge 1	368		2154
Rosenstock	T-Emerge 2	1149	Rapid Insulin	1
Henry	T-Emerge 3	313		281
Bergenstal	T-Emerge 4	546	Dulaglutide 1.5mg	8
Nauck	T-Emerge 5	1028		2240
Pratley	T-Emerge 6	740	Dulaglutide 0.75mg	9
Hollander	T-Emerge 7	292		2395
Miyagawa	-	484	Glimepiride	2
Araki	-	361		575
NCT01648582	-	770	-	-
Wang	-	790		-
Davies	-	216	-	-
Inagaki	-	427		-
Ji	-	678	-	-
NCT01733758	-	330		-
TOTAL No. of			**TOTAL No. of**	
STUDIES		**34**	**ARMS**	**89**
PARTICIPANTS		**20846**	**PARTICIPANTS**	**20846**

* Data reported for 156 weeks

Table 4.D5: Number of study-specific cases and participants for hypoglycaemia

Study		Hypoglycaemic Events		Study		Hypoglycaemic Events	
First Author	**Acronym**	**DSH**	**SH**	**First Author**	**Acronym**	**DSH**	**SH**
Wysham	Award 1	108 976	2 97	Rosenstock	T-Emerge 2	198 117	1 1173
Giorgino	Award 2	350 807	4 80	Henry	T-Emerge 3	3 324	0 324
Umpierrez	Award 3	97 807	0 80	Bergenstal	T-Emerge 4	54 563	0 563
Blonde	Award 4	732 884	32 88	Nauck	T-Emerge 5	14 103	0 1037
Weinstock	Award 5	92 921	0 92	Pratley	T-Emerge 6	107 751	7 751
Dungan	Award 6	43 599	0 59	Hollander	T-Emerge 7	1 304	0 304
Drucker	Duration 1	17 293	0 29	Miyagawa	-	- -	0 487
Bergenstal	Duration 2	8 491	0 49	Araki	-	- -	0 361
Diamant*	Duration 3	98 456	3 45	NCT01648582	-	- -	- -
Russell-Jones	Duration 4	34 820	0 82	Wang	-	24 805	0 805
Blevins	Duration 5	9 252	0 25	Davies	-	11 216	0 216
Buse	Duration 6	91 911	0 91	Inagaki	-	62 427	1 427
Reusch	Harmony 1	7 301	2 30	Ji	-	134 678	1 678
Nauck	Harmony 2	3 196	0 19	NCT01733758	-	- -	- -
Ahren	Harmony 3	73 1012	0 10				
Weissman	Harmony 4	154 745	3 74	**TOTAL No. of CASES^**		**287**	**62**
Home	Harmony 5	115 663	4 66	**PARTICIPANTS**		**191**	**1964**
Rosenstock	Harmony 6	129 566	2 56	**STUDIES**		**30**	**31**
Pratley	Harmony 7	95 812	0 81				
Raz	T-Emerge 1	12 368	- -				

DSH=Documented and/or symptomatic hypoglycaemic events; **SH**=Severe hypoglycaemic events
* Hypoglycaemic events at 26 weeks
^ With at least one event

Table 4.D6: Number of drug-specific arms, cases with event, and participants for hypoglycaemia

	Hypoglycaemic events	
Drug	**DSH**	**SH**
Once-weekly Exenatide	9 188 2045	9 1 2045
Daily GLP-1RAs	8 324 2425	9 4 2564
Pioglitazone	4 116 862	4 4 862
Sitagliptin	5 60 1130	5 0 1130
Basal Insulins	7 575 1661	8 21 1841
Metformin	2 44 514	2 0 514
Taspoglutide 10mg	6 123 1412	5 2 1296
Taspoglutide 20mg	7 117 1586	6 4 1457
Placebo	8 24 981	8 0 928
Albiglutide	7 227 2013	7 5 2013
Rapid Insulin	1 84 281	1 2 281
Dulaglutide 1.5mg	7 476 1987	7 12 1987
Dulaglutide 0.75mg	6 444 1685	8 7 2146
Glimepiride	2 73 576	2 0 576
TOTAL No. of		
ARMS	**79**	**81**
CASES^	**2875**	**62**
PARTICIPANTS	**19158**	**19640**

DSH=Documented and/or symptomatic hypoglycaemic events;
SH=Severe hypoglycaemic events
^ With at least one event

Table 4.D7: Comparison of once-weekly GLP-1RAs vs other glucose-lowering drugs for HbA1c

HbA1c (%)													
													PLA
												dGLP1	**1.08 (0.89,1.27)**
											SITA	**-0.37 (-0.58,-0.16)**	**0.71 (0.50,0.93)**
										RAPID	0.12 (-0.35,0.59)	-0.25 (-0.71,0.21)	**0.83 (0.38,1.28)**
									PIO	0.29 (-0.18,0.77)	**0.41 (0.18,0.65)**	0.04 (-0.19,0.28)	**1.12 (0.90,1.35)**
								MET	0.01 (-0.30,0.32)	0.31 (-0.21,0.82)	**0.43 (0.13,0.72)**	0.06 (-0.23,0.35)	**1.14 (0.83,1.44)**
							GLIM	-0.36 (-0.72,0.01)	**-0.34 (-0.67,-0.02)**	-0.05 (-0.56,0.45)	0.07 (-0.22,0.36)	**-0.30 (-0.59,-0.01)**	**0.78 (0.49,1.07)**
						BASAL	0.21 (-0.08,0.50)	-0.15 (-0.44,0.14)	-0.14 (-0.38,0.11)	0.16 (-0.31,0.62)	**0.28 (0.06,0.50)**	-0.09 (-0.28,0.10)	**0.99 (0.78,1.20)**
					DUL 1.5	**0.40 (0.23,0.58)**	**0.61 (0.33,0.89)**	0.26 (-0.02,0.54)	**0.27 (0.02,0.52)**	**0.56 (0.09,1.03)**	**0.68 (0.47,0.90)**	**0.31 (0.13,0.50)**	**1.39 (1.17,1.61)**
				DUL 0.75	**-0.19 (-0.34,-0.04)**	**0.22 (0.05,0.38)**	**0.43 (0.15,0.70)**	0.07 (-0.21,0.35)	0.08 (-0.17,0.33)	0.37 (-0.10,0.84)	**0.49 (0.28,0.71)**	0.13 (-0.06,0.31)	**1.20 (1.00,1.41)**
			ALB	-0.21 (-0.43,0.01)	**-0.40 (-0.63,-0.18)**	0.00 (-0.21,0.21)	0.21 (-0.08,0.50)	-0.15 (-0.46,0.17)	-0.13 (-0.37,0.10)	0.16 (-0.25,0.57)	**0.28 (0.06,0.51)**	-0.09 (-0.28,0.11)	**0.99 (0.82,1.17)**
		TAS 20	0.13 (-0.10,0.35)	-0.09 (-0.31,0.14)	**-0.27 (-0.51,-0.04)**	0.13 (-0.09,0.35)	**0.34 (0.03,0.65)**	-0.02 (-0.33,0.30)	-0.01 (-0.24,0.23)	0.29 (-0.18,0.76)	**0.41 (0.19,0.63)**	0.04 (-0.17,0.25)	**1.12 (0.93,1.31)**
	TAS 10	-0.14 (-0.31,0.03)	-0.01 (-0.24,0.22)	-0.22 (-0.46,0.01)	**-0.41 (-0.65,-0.17)**	-0.01 (-0.23,0.22)	0.20 (-0.11,0.52)	-0.16 (-0.47,0.16)	-0.14 (-0.39,0.10)	0.15 (-0.33,0.62)	**0.27 (0.04,0.50)**	-0.10 (-0.32,0.12)	**0.98 (0.78,1.18)**
EOW	**0.33 (0.09,0.56)**	0.19 (-0.04,0.42)	**0.32 (0.10,0.54)**	0.10 (-0.10,0.30)	-0.09 (-0.29,0.12)	**0.32 (0.14,0.50)**	**0.53 (0.23,0.83)**	0.17 (-0.12,0.46)	0.18 (-0.05,0.41)	**0.48 (0.01,0.94)**	**0.60 (0.38,0.81)**	**0.23 (0.06,0.40)**	**1.31 (1.09,1.52)**

ALB=Albiglutide; **BASAL**=Basal insulin; **dGLP1**=Daily GLP-1RAs; **DUL 0.75**=Dulaglutide 0.75mg; **DUL 1.5**=Dulaglutide 1.5mg; **EOW**=Once-weekly Exenatide; **GLIM**=Glimepiride; **MET**=Metformin; **PIO**=Pioglitazone; **PLA**=Placebo; **RAPID**=Rapid insulin; **SITA**=Sitagliptin; **TAS 10**=Taspoglutide 10mg; **TAS 20**=Taspoglutide 20mg

Data are reported as mean difference (95% confidence interval) and indicate column-to-row differences [i.e., compared to Placebo, Once-weekly Exenatide reduces HbA1c of 1.31%]. Statistically significant differences are in bold.

Table 4.D8: Sensitivity analyses for HbA1c and documented and/or symptomatic hypoglycaemia

HbA1c (mean difference, %)

Separate basal insulins (detemir & glargine) and daily GLP-1RAs (EBID and LQD)

					DUL 1.5
				DUL 0.75	**-0.19 (-0.33,-0.06)**
			ALB	-0.16 (-0.35,0.04)	**-0.35 (-0.54,-0.15)**
		TAS 20	0.04 (-0.16,0.24)	-0.11 (-0.31,0.09)	**-0.30 (-0.51,-0.10)**
	TAS 10	-0.14 (-0.29,0.01)	-0.10 (-0.31,0.11)	**-0.26 (-0.46,-0.05)**	**-0.45 (-0.66,-0.24)**
EOW	**0.28 (0.07,0.49)**	0.14 (-0.07,0.34)	0.18 (-0.02,0.38)	0.02 (-0.16,0.21)	-0.17 (-0.35,0.02)

Studies with duration 24 to 26 weeks

					DUL 1.5
				DUL 0.75	-0.16 (-0.32,0.00)
			ALB	-0.03 (-0.38,0.31)	-0.19 (-0.54,0.16)
		TAS 20	-0.03 (-0.38,0.33)	-0.06 (-0.30,0.18)	-0.22 (-0.46,0.02)
	TAS 10	-0.13 (-0.32,0.05)	-0.16 (-0.52,0.20)	-0.19 (-0.44,0.05)	**-0.35 (-0.60,-0.10)**
EOW	**0.27 (0.01,0.52)**	0.13 (-0.11,0.38)	0.10 (-0.24,0.45)	0.07 (-0.15,0.29)	-0.09 (-0.31,0.14)

Documented and/or symptomatic hypoglycaemia (odds ratio)

Separate basal insulins (detemir & glargine) and daily GLP-1RAs (EBID and LQD)

					DUL 1.5
				DUL 0.75	1.04 (0.80,1.36)
			ALB	**1.53 (1.00,2.33)**	**1.59 (1.06,2.39)**
		TAS 20	0.88 (0.54,1.44)	1.34 (0.83,2.16)	1.40 (0.87,2.24)
	TAS 10	0.88 (0.62,1.24)	0.77 (0.47,1.27)	1.18 (0.73,1.90)	1.23 (0.76,1.97)
EOW	1.07 (0.66,1.72)	0.94 (0.58,1.51)	0.82 (0.54,1.26)	1.26 (0.86,1.85)	1.31 (0.91,1.90)

Studies with duration 24 to 26 weeks*

					DUL 1.5
				DUL 0.75	-
			ALB	-	-
		TAS 20	-	-	-
	TAS 10	-	-	-	-
EOW	-	-	-	-	-

Data are reported as mean difference (95% confidence interval) for HbA1c and indicate column-to-row differences [i.e. top left, compared to Dulaglutide 0.75mg, Dulaglutide 1.5mg reduces HbA1c of 0.19% (95% CI: 0.06 to 0.33)]. Data are reported as odds ratio (95% confidence interval) and indicate column-to-row ratios for hypoglycaemic events [i.e. bottom left, compared to Dulaglutide 0.75mg, Dulaglutide 1.5mg treatment is associated with an odds ratio of hypoglycaemia of 1.04 (95% CI: 0.80 to 1.36)]. Statistically significant differences are in bold. **EBID**=Twice-daily Exenatide; **LQD**=Once-daily Liraglutide; **EOW**=Once-weekly Exenatide; **TAS 10**=Taspoglutide 10mg; **TAS 20**=Taspoglutide 20mg; **ALB**=Albiglutide; **DUL 0.75**=Dulaglutide 0.75mg; **DUL 1.5**=Dulaglutide 1.5mg.

* This analysis was not possible given the availability of only one study with Albiglutide (HARMONY 6), thus resulting in a disconnected network (isolated comparison Albiglutide vs Rapid insulin).

Table 4.D9: Number of RCTs with available information in the main and sensitivity analysis including studies with 24 to 26 weeks of follow-up

		Once-weekly GLP-1RAs					
Outcome	**Analysis**	**Once-weekly exenatide**	**Taspoglutide 10mg**	**Taspoglutide 20mg**	**Albiglutide**	**Dulaglutide 0.75mg**	**Dulaglutide 1.5mg**
HbA1c	Main	9	6	7	8	9	8
	24-26 weeks studies	8	6	7	3	9	8
Documented and/or symptomatic hypoglycaemia	Main	9	6	7	7	6	7
	24-26 weeks studies	8	4	5	1	4	5

Table 4.D10: Comparison of once-weekly GLP-1RAs vs other glucose-lowering drugs for hypoglycaemia

Documented and/or symptomatic hypoglycaemia													
													PLA
												dGLP1	**0.39 (0.22,0.69)**
											SITA	1.38 (0.86,2.22)	0.54 (0.28,1.01)
										RAPID	0.45 (0.20,1.04)	0.62 (0.29,1.34)	**0.24 (0.10,0.56)**
									PIO	1.64 (0.73,3.67)	0.74 (0.42,1.29)	1.01 (0.62,1.66)	**0.40 (0.22,0.72)**
								MET	0.99 (0.51,1.93)	1.62 (0.65,4.01)	0.73 (0.39,1.37)	1.00 (0.56,1.80)	**0.39 (0.19,0.82)**
							GLIM	**0.19 (0.09,0.42)**	**0.19 (0.09,0.39)**	**0.31 (0.12,0.76)**	**0.14 (0.07,0.27)**	**0.19 (0.10,0.37)**	**0.07 (0.04,0.15)**
						BASAL	**3.31 (1.72,6.37)**	0.63 (0.35,1.12)	0.62 (0.37,1.05)	1.01 (0.47,2.19)	**0.46 (0.28,0.75)**	**0.63 (0.43,0.92)**	**0.24 (0.14,0.44)**
					DUL 1.5	**1.52 (1.07,2.14)**	**5.01 (2.65,9.46)**	0.95 (0.55,1.62)	0.94 (0.55,1.60)	1.54 (0.70,3.39)	0.69 (0.44,1.09)	0.95 (0.66,1.38)	**0.37 (0.21,0.66)**
				DUL 0.75	1.07 (0.80,1.45)	**1.63 (1.14,2.33)**	**5.38 (2.81,10.30)**	1.02 (0.59,1.75)	1.01 (0.59,1.73)	1.65 (0.74,3.67)	0.74 (0.46,1.19)	1.02 (0.69,1.51)	**0.40 (0.22,0.72)**
			ALB	1.38 (0.86,2.20)	1.48 (0.94,2.33)	**2.25 (1.47,3.42)**	**7.42 (3.95,13.97)**	1.41 (0.74,2.66)	1.39 (0.86,2.26)	**2.27 (1.19,4.35)**	1.02 (0.60,1.73)	1.41 (0.93,2.13)	**0.55 (0.32,0.95)**
		TAS 20	1.07 (0.64,1.80)	1.48 (0.88,2.48)	1.59 (0.96,2.63)	**2.41 (1.45,3.99)**	**7.96 (3.89,16.32)**	1.51 (0.77,2.94)	1.49 (0.91,2.44)	**2.44 (1.06,5.59)**	1.10 (0.65,1.85)	1.51 (0.97,2.36)	0.59 (0.32,1.09)
	TAS 10	0.88 (0.60,1.29)	0.94 (0.56,1.59)	1.30 (0.77,2.19)	1.39 (0.83,2.32)	**2.11 (1.26,3.53)**	**6.98 (3.39,14.36)**	1.32 (0.67,2.59)	1.31 (0.80,2.15)	2.14 (0.93,4.92)	0.96 (0.57,1.62)	1.33 (0.85,2.08)	**0.52 (0.28,0.97)**
EOW	0.93 (0.55,1.55)	0.81 (0.49,1.35)	0.87 (0.55,1.38)	1.20 (0.79,1.84)	1.29 (0.86,1.94)	**1.96 (1.36,2.81)**	**6.47 (3.28,12.77)**	1.22 (0.68,2.21)	1.21 (0.71,2.06)	1.98 (0.89,4.39)	0.89 (0.54,1.48)	1.23 (0.88,1.71)	**0.48 (0.26,0.88)**

ALB=Albiglutide; **BASAL**=Basal insulin; **dGLP1**=Daily GLP-1RAs; **DUL 0.75**=Dulaglutide 0.75mg; **DUL 1.5**=Dulaglutide 1.5mg; **EOW**=Once-weekly Exenatide; **GLIM**=Glimepiride; **MET**=Metformin; **PIO**=Pioglitazone; **PLA**=Placebo; **RAPID**=Rapid insulin; **SITA**=Sitagliptin; **TAS 10**=Taspoglutide 10mg; **TAS 20**=Taspoglutide 20mg

Data are reported as odds ratio (95% confidence interval) and indicate column-to-row ratios [i.e., compared Once-weekly Exenatide, Placebo is associated with an odds ratio of 0.48 of hypoglycaemia, or equivalently Once-weekly Exenatide increases the risk by an odds ratio of 2.08 (=1/0.48)]. Statistically significant differences are in bold.

Table 4.D11: Comparisons of once-weekly GLP-1RAs for documented and/or symptomatic hypoglycaemia

Documented and/or symptomatic hypoglycaemia					
					DUL 1.5
				DUL 0.75	1.07 (0.80,1.45)
			ALB	1.38 (0.86,2.20)	1.48 (0.94,2.33)
		TAS 20	1.07 (0.64,1.80)	1.48 (0.88,2.48)	1.59 (0.96,2.63)
	TAS 10	0.88 (0.60,1.29)	0.94 (0.56,1.59)	1.30 (0.77,2.19)	1.39 (0.83,2.32)
EOW	0.93 (0.55,1.55)	0.81 (0.49,1.35)	0.87 (0.55,1.38)	1.20 (0.79,1.84)	1.29 (0.86,1.94)

Data are reported as odds ratio (95% confidence interval) and indicate column-to-row ratios [i.e., compared to Dulaglutide 0.75mg, Dulaglutide 1.5mg treatment is associated with an odds ratio of hypoglycaemia of 1.07 (95% CI: 0.80 to 1.45)]. Statistically significant differences are in bold. **EOW**= Once-weekly Exenatide; **TAS 10**=Taspoglutide 10mg; **TAS 20**=Taspoglutide 20mg; **ALB**=Albiglutide; **DUL 0.75**=Dulaglutide 0.75mg; **DUL 1.5**=Dulaglutide 1.5mg

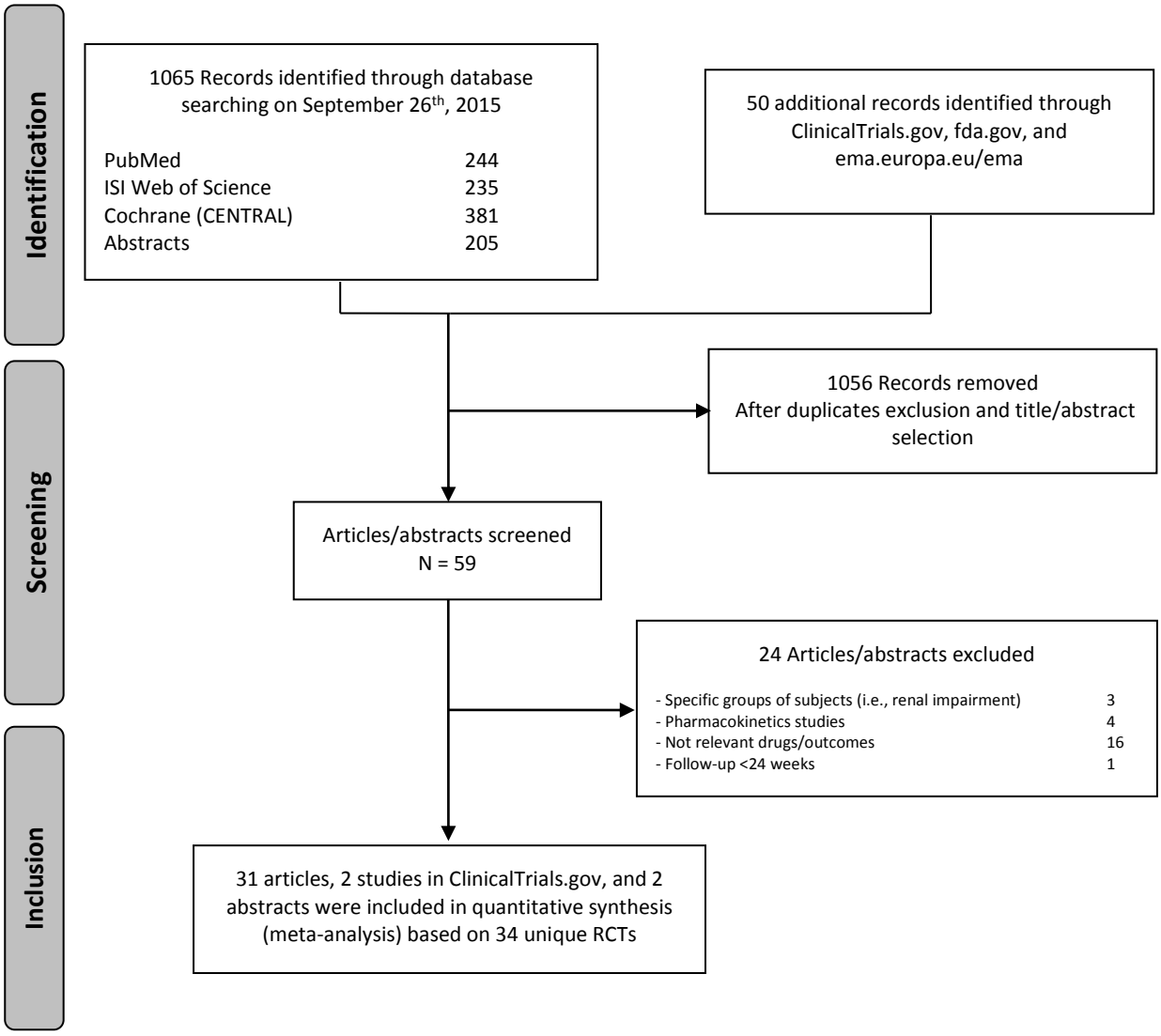
Table 4.D12: Sensitivity analyses for hypoglycaemic events excluding studies with background sulphonylurea and/or insulin

Documented and/or symptomatic hypoglycaemia					
					DUL 1.5
				DUL 0.75	1.28 (0.88,1.86)
			ALB	1.15 (0.43,3.07)	1.47 (0.55,3.90)
		TAS 20	1.00 (0.37,2.73)	1.15 (0.63,2.08)	1.47 (0.83,2.59)
	TAS 10	0.88 (0.58,1.36)	0.89 (0.32,2.43)	1.02 (0.57,1.82)	1.30 (0.75,2.27)
EOW	0.90 (0.35,2.31)	0.80 (0.31,2.03)	0.80 (0.24,2.69)	0.91 (0.38,2.19)	1.17 (0.49,2.78)

Data are reported as odds ratio (95% confidence interval) and indicate column-to-row ratios [i.e., compared to Dulaglutide 0.75mg, Dulaglutide 1.5mg treatment is associated with an odds ratio of hypoglycaemic events of 1.28 (95% CI: 0.88 to 1.86)]. **EOW**=Once-weekly Exenatide; **TAS 10**=Taspoglutide 10mg; **TAS 20**=Taspoglutide 20mg; **ALB**=Albiglutide; **DUL 0.75**=Dulaglutide 0.75mg; **DUL 1.5**=Dulaglutide 1.5mg.

Studies included in the analysis (n=14): AWARD 1, 3, 5, 6; DURATION 2, 4; HARMONY 1 to 3; T-EMERGE 1 to 4, 7.

Figure 4.D1: Study flow diagram: progression of papers through the review process



Search Strategy

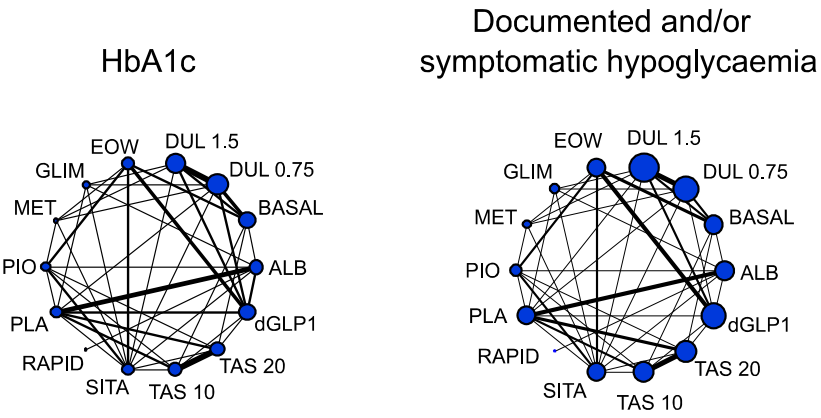
PubMed, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) articles published in any language before September 26th, 2015 were identified. Electronic search was supplemented by scanning reference lists of all relevant articles, including reviews, by hand searching of relevant journals. Additionally, clinical trials in ClinicalTrials.gov, fda.gov, and ema.europa.eu/ema and in major diabetes conference abstract (ADA and EASD databases from 2012 onwards) were searched.

For **PubMed** database, the search was: *"*Exenatide" OR "Taspoglutide" OR "Albiglutide" OR "Dulaglutide" OR "Semaglutide"
Limits: Humans and Randomized Controlled Trial

Web of Science
TOPIC: (Exenatide) OR TOPIC: (Taspoglutide) OR TOPIC: (Albiglutide) OR TOPIC: (Dulaglutide) OR TOPIC: (Semaglutide)

Cochrane Library
Exenatide [All Text] OR Taspoglutide [All Text] OR Albiglutide [All Text] OR Dulaglutide [All Text] OR Semaglutide [All Text]

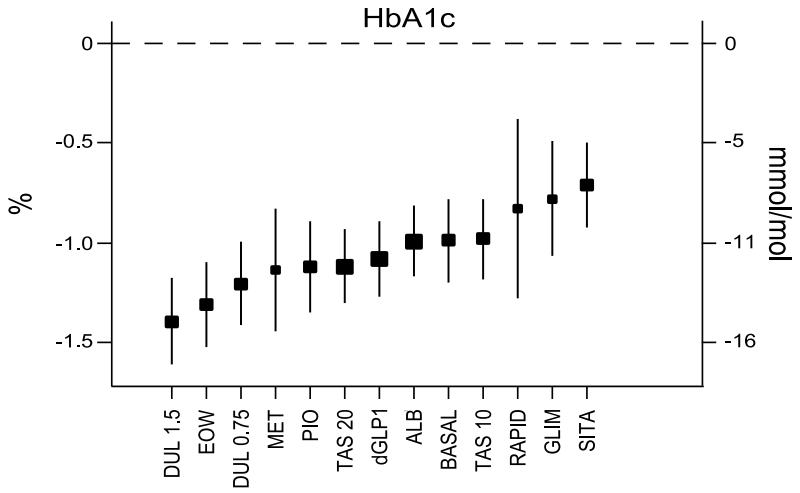
Figure 4.D2: Network maps for HbA1c and hypoglycaemia

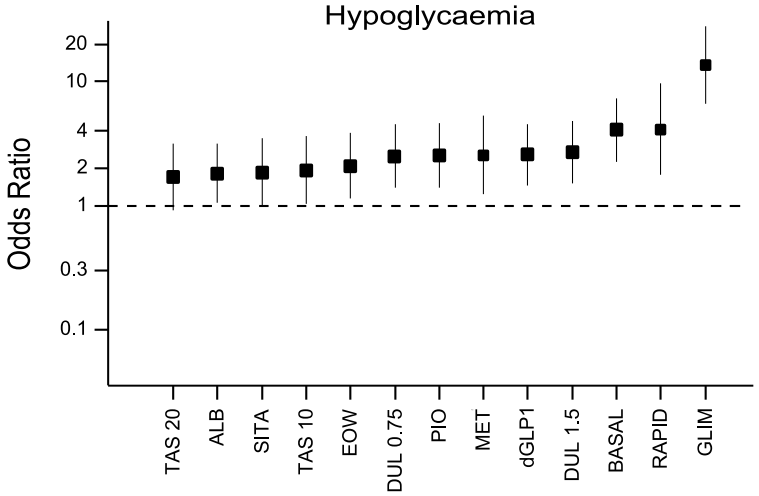


Nodes represent the competing treatments and their size is proportional to the number of participants; edges represent the available direct comparisons between pairs of treatments and their width is proportional to the number of trials comparing every pair.

ALB=Albiglutide; **BASAL**=Basal insulin; **dGLP1**=Daily GLP-1RAs; **DUL 0.75**=Dulaglutide 0.75mg; **DUL 1.5**=Dulaglutide 1.5mg; **EOW**=Once-weekly Exenatide; **GLIM**=Glimepiride; **MET**=Metformin; **PIO**=Pioglitazone; **PLA**=Placebo; **RAPID**=Rapid insulin; **SITA**=Sitagliptin; **TAS 10**=Taspoglutide 10mg; **TAS 20**=Taspoglutide 20mg

Figure 4.D3: Differences vs placebo (dotted lines) for HbA1c and hypoglycaemia for the drugs included in the network meta-analysis





HbA1c (%) Difference vs Placebo (95% CI)	
DUL 1.5=Dulaglutide 1.5mg	-1.39 (-1.61, -1.17)
EOW=Once-weekly Exenatide	-1.31 (-1.52, -1.09)
DUL 0.75=Dulaglutide 0.75mg	-1.20 (-1.41, -1.00)
MET=Metformin	-1.14 (-1.44, -0.83)
PIO=Pioglitazone	-1.12 (-1.35, -0.90)
TAS 20=Taspoglutide 20mg	-1.12 (-1.31, -0.93)
dGLP1=Daily GLP-1RAs	-1.08 (-1.27, -0.89)
ALB=Albiglutide	-0.99 (-1.17, -0.82)
BASAL=Basal insulins	-0.99 (-1.20, -0.78)
TAS 10=Taspoglutide 10mg	-0.98 (-1.18, -0.78)
RAPID=Rapid insulin	-0.83 (-1.28, -0.38)
GLIM=Glimepiride	-0.78 (-1.07, -0.49)
SITA=Sitagliptin	-0.71 (-0.93, -0.50)

Hypoglycaemia (odds ratios) difference vs Placebo (95% CI)	
TAS 20=Taspoglutide 20mg	1.70 (0.92, 3.14)
ALB=Albiglutide	1.86 (0.99, 3.52)
SITA=Sitagliptin	1.86 (0.99, 3.52)
TAS 10=Taspoglutide 10mg	1.94 (1.03, 3.62)
EOW=Once-weekly Exenatide	2.09 (1.14, 3.82)
DUL 0.75=Dulaglutide 0.75mg	2.51 (1.39, 4.54)
PIO=Pioglitazone	2.53 (1.38, 4.63)
MET=Metformin	2.56 (1.22, 5.34)
dGLP1=Daily GLP-1RAs	2.57 (1.46, 4.52)
DUL 1.5=Dulaglutide 1.5mg	2.70 (1.51, 4.82)
BASAL=Basal insulins	4.09 (2.27, 7.35)
RAPID=Rapid insulin	4.14 (1.77, 9.67)
GLIM=Glimepiride	13.51 (6.59, 27.69)

Figure 4.D4: Rank probabilities for HbA1c, by drug

Each bar indicates the probability for the specific rank. For example, for HbA1c Dulaglutide 1.5mg has the highest probability to be the best (rank 1st) and Placebo the worst (rank 14th).

E. Glucose control and risk of hypoglycaemia of SGLT2 inhibitors

Data sources and extraction

This analysis was conducted to assess the comparative efficacy and safety of SGLT2 inhibitors canagliflozin, dapagliflozin, and empagliflozin against each other and versus other glucose-lowering therapies. PubMed, ISI Web of Science, and the Cochrane Library were searched for RCTs published in any language from inception until November 3rd, 2015. RCTs lasting at least 24 weeks and reporting data on HbA1c or hypoglycaemia had to compare licensed doses of canagliflozin (100mg or 300mg), dapagliflozin (5mg or 10mg), or empagliflozin (10mg or 25mg) with placebo or other glucose–lowering drugs in adults with type 2 diabetes. RCTs including patients with chronic kidney disease alone at baseline were excluded. Reference lists of eligible studies, as well as systematic reviews and meta-analyses of SGLT2 inhibitors, were manually scanned for additional relevant studies.

After the identification of the studies, information was extracted using a standardised electronic extraction sheet on: first author name, clinical trial registration number, year of journal article publication, background glucose–lowering therapy, SGLT2 inhibitor(s) and comparator(s), duration of follow-up, sample size, gender distribution, age, diabetes duration, baseline HbA1c, and outcome measured. Outcomes data were as arm–specific counts (i.e., number of participants, mean difference and standard error (or standard deviation) for continuous outcomes in patients with baseline and at least one post-baseline measurement); total number of participants and participants with event for hypoglycaemia (all hypoglycaemic events) in patients who were randomised and received treatment; or contrast–based estimations (i.e., pairwise comparisons). When studies reported outcomes data for different durations of follow-up, the longest was used. Data were retrieved from ClinicalTrials.gov when it was not possible to extract relevant information from the published report. Study quality was assessed using the Cochrane risk of bias tool [11].

Search and selection of RCTs, data extraction, and quality assessments were also independently performed by other members of the research team with disagreements resolved by arbitration.

Analytical approach

The analysis followed the same principles and approaches reported for the GLP-1RA network meta-analysis. Stata 14.1 (Stata Corp, College Station, TX, USA) was used for all analyses and results are reported with 95% CI and a single digit approximation in the text to be consistent with results available from clinical labs. Pairwise random–effects meta–analyses were

performed using the DerSimonian and Laird method [198]. Network meta–analyses were based on the method of multivariate meta–analysis [167, 169, 170]. Results were reported with 95% confidence intervals; p<0.05 was considered statistically significant.

In three–arm trials reporting contrasted-based estimates for continuous outcomes, pairwise comparisons were available only for two out of the three possible contrasts (i.e., A *vs* B and B *vs* C, but not A *vs* C, where A, B, and C denote the three arms); in these cases, given the presence of correlations between the treatment differences, the standard error (σ) of the missing contrast was estimated using the formula: $\sigma^2_{AC} = \sigma^2_{AB} + \sigma^2_{BC} - 2\rho\sigma_{AB}\sigma_{BC}$ [199]. As ρ values (correlations) were not reported, in the main analysis a value similar to those obtained from other comparable studies included in this systematic review (ρ=0.5) was used, as previously advocated [199].

Linagliptin and sitagliptin were combined in a single group (dipeptidyl peptidase–4 inhibitors, DPP–4i) and glimepiride and gliclazide in another (sulphonylurea). For these analyses, it was assumed that participants of the included RCTs could be randomly allocated to any of the three treatments being compared (on average, the baseline characteristics of participants are similar as the treatments are tested for a wide range of patients).

Results

From 2174 identified records, 79 reports underwent full-text assessment; after further selection (**Figure 4.E1**), 38 unique RCTs fulfilled inclusion criteria (**Table 4.E1; references are reported in Appendix E**). RCTs were published between 2012 and 2015 and included 23,997 (range, 136–2072) participants with type 2 diabetes; 34 (89.5%) were multinational RCTs. Baseline HbA1c, age, and disease duration weighted means were 8.1%, 58 years old, and 8 years, respectively; 57% were males and follow up duration ranged from 24 to 208 weeks. Other characteristics of the RCTs, such as study-, drug-, and outcome-specific available data, are reported in **Tables 4.E2–E4**.

Overall, the risk of bias for the domains included in the Cochrane tool of risk assessment were judged to be low, high, and unclear in 89.5%, 1.8%, and 8.7% of the cases, respectively; high or unclear domain-specific bias was lowest for blinding of outcome assessment (2.7%) and highest for random sequence generation (15.8%) (**Table 4.E5**). The risk of bias was high or unclear in 1.8%, 10.8%, and 16.7% of canagliflozin, dapagliflozin, and empagliflozin RCTs, respectively. Networks of evidence for both outcomes are graphically displayed in **Figure 4.E2**.

HbA1c

Data on HbA1c were available from all RCTs. The results of the network meta–analysis showed a mean HbA1c reduction, compared to placebo, of -0.9% (-1.0 to -0.8) [-9.4 mmol/mol; -10.5 to

-8.3] for canagliflozin 300mg; -0.8% (-0.9 to -0.7) [-8.3 mmol/mol; -9.4 to -7.2] for canagliflozin 100mg; -0.7% (-0.8 to -0.6) [-7.1 mmol/mol; -8.1 to -6.0] for empagliflozin 25mg; -0.7% (-0.7 to -0.6) [-7.1 mmol/mol; -8.0 to -6.2] for dapagliflozin 10mg; -0.6% (-0.7 to -0.5) [-6.6 mmol/mol; -7.7 to -5.5] for empagliflozin 10mg; and -0.6% (-0.7 to -0.4) [-6.1 mmol/mol; -7.3 to -4.8] for dapagliflozin 5mg (**Table 4.E6; Figure 4.E3**). Comparisons across SGLT2 inhibitors showed greater HbA1c reductions with canagliflozin 300mg compared to all other SGLT2 drugs (from -0.3% [-3.3 mmol/mol] vs dapagliflozin 5mg to -0.1% [-1.1 mmol/mol] vs canagliflozin 100mg) and no significant differences between dapagliflozin and empagliflozin at different doses (**Table 4.E6**). **Figure 4.E4** shows SGLT2 inhibitors according to the ranking probabilities. There was a no inconsistency for the whole network (p=0.123).

Hypoglycaemia

Data on hypoglycaemic events were available from 37 RCTs, reporting a total of 4347 participants with event. The results of the network meta–analysis showed an increased risk of hypoglycaemia compared to placebo for canagliflozin 300mg and 100mg, with respective ORs of 1.6 (1.3 to 1.9) and 1.5 (1.3 to 1.8) (**Table 4.E7; Figure 4.E3**). Among SGLT2 inhibitors, canagliflozin at both doses was associated with higher risk of hypoglycaemia compared to dapagliflozin 10mg (ORs 1.5) and empagliflozin 10mg (ORs 1.4) (**Table 4.E7**). Any SGLT2 inhibitor carried a lower risk of hypoglycaemia compared to sulphonylureas. There was no inconsistency for the whole network (p=0.866). Ranking probabilities are graphically displayed in **Figure 4.E4**. In a sensitivity analysis excluding studies with insulin or sulfonylurea as background therapy, canagliflozin at both doses increased the risk of hypoglycaemia compared to dapagliflozin 10mg (ORs 1.7 to 1.9), although no significant differences were found versus placebo for all SGLT2 inhibitors (**Table 4.E8**).

Interpretation in the context of available evidence

Several randomised clinical trials have investigated the efficacy and safety of SGLT2 inhibitors compared to placebo or other glucose-lowering drugs (sulphonylurea, DPP–4i, or metformin); however, as of November 2015, no direct 'head-to-head' trials comparing SGLT2 inhibitors have been reported or are ongoing, thus limiting the possibility of a direct evaluation of their comparative clinical profiles. As network meta–analysis allows indirect assessment between treatments when direct evidence is unavailable, this approach was used to compare SGLT2 inhibitors with each other and versus other glucose-lowering therapies for HbA1c and hypoglycaemia.

While previous network meta-analysis assessed the efficacy and safety of a single SGLT2 inhibitor [200-203] or restricted the analyses only to efficacy outcomes and in patients with type 2 diabetes inadequately controlled with diet and exercise alone or metformin monotherapy [204], in this analysis data were collected data for inhibitors clinically available in most countries and for indications usually considered when choosing glucose–lowering drugs, such as HbA1c and hypoglycaemia, to provide a comprehensive picture of these inhibitors.

When compared to placebo, all SGLT2 inhibitors improved glucose control (0.6% to 0.9% decrease in HbA1c); although they did not increase the risk of hypoglycaemia as they do not stimulate insulin secretion [161], the risk was ∼50% greater for both canagliflozin doses but not different for empagliflozin and dapagliflozin when compared to placebo. Of note, the increased canagliflozin risk was nominally lower than metformin and significantly lower than sulphonylurea (~9–fold). Moreover, when the analysis was restricted to studies without background sulphonylurea or insulin, the risk of hypoglycaemia for all SGLT2 inhibitors was similar to placebo. This would suggest an imbalance of insulin or sulfonylurea use across studies where SGLT2 inhibitors were compared to placebo or some heterogeneity possibly due to study design (insulin studies are more likely to be open label and treat-to-target with no stable doses during trial).

Along with changes versus placebo, differences between SGLT2 inhibitors were found. The highest dose of canagliflozin reduced HbA1c to a greater extent compared to dapagliflozin and empagliflozin at any dose and increased the risk of hypoglycaemia compared to dapagliflozin also accounting for different background therapies. The differences observed for some clinical outcomes could in part be attributed to outcome definition, study design and/or analysis, or intrinsic pharmacological properties of individual drugs. Indeed, in addition to SGLT2, the SGLT1 receptor has also been implicated in glucose regulation [205], and each inhibitor is known to have a different receptor selectivity profile (for SGLT2 over SGLT1, >2500-fold with empagliflozin; >1200-fold with dapagliflozin; and >250-fold with canagliflozin) [206]. The results indicating a better glucose control by canagliflozin would therefore underline the glucometabolic relevance of SGLT1 inhibition and support recent results on dual SGLT1/SGLT2 blockade [207, 208]. Overall, these results indicate that: 1) any SGLT2 inhibitor reduces HbA1c, with canagliflozin 300mg performing better than other inhibitors; 2) canagliflozin 300mg reduces HbA1c to a greater extent compared to sulphonylureas; 3) any SGLT2 inhibitor carries a lower risk of hypoglycaemia compared to sulphonylureas; 4) canagliflozin 300mg is associated with a higher risk of hypoglycaemia compared to dapagliflozin 10mg and empagliflozin 10mg, possibly in light of the its greater HbA1c reduction.

This analysis shares the same limitations reported for GLP-1RAs network meta-analysis, including: 1) it is based only on data published in journal articles or available on ClinicalTrials.gov; 2) across RCTs, ethnicities of participants included, follow-up durations, or outcomes selection, definition, and ascertainment (particularly for hypoglycaemia) could to some extent differ; 3) RCTs are "clustered" within the same sponsoring company. Conversely, this was the first attempt to summarise available data on SGLT2 inhibitors with detailed data on study, drug, and outcome-specific number of participants.

In conclusion, SGLT2 inhibitors improved HbA1c in patients with type 2 diabetes with no clinically significant increased risk of hypoglycaemia. Future RCTs comparing SGLT2 inhibitors with each other and versus other glucose-lowering therapies would further delineate their comparative efficacy and tolerability and clarify whether their use in a larger fraction of patients with diabetes could potentially reduce the incidence of hypoglycaemia.

Note

In this systematic review, the last day of electronic search for RCTs was November 3rd, 2015; since then, other RCTs assessing HbA1c reduction and risk of hypoglycaemia for SGLT2 inhibitors have been published.

Tables and Figures

Table 4.E1: Baseline characteristics of the included studies

First Author	Year	Background Therapy	SGLT2 inhibitor	Comparator(s)	Study duration (weeks)	Total sample size (N)	Males (%)	Age [a] (years)	Diabetes duration [a] (years)	HbA1c [a] (%)
Inagaki	2014	Diet + PA	Cana 100mg	Placebo	24	183	65.0	58.3	5.2	8.0
Bode	2015	Diet ± OADs ± insulin	Cana 100mg, Cana 300mg	Placebo	104	714	55.5	63.6	11.7	7.8
Forst	2014	Met + Pio	Cana 100mg, Cana 300mg	Placebo	26	342	63.2	57.3	10.5	8.0
Neal	2015	Insulin ± OADs	Cana 100mg, Cana 300mg	Placebo	52	2072	66.1	62.7	16.2	8.3
Stenlof	2013	Diet + PA	Cana 100mg, Cana 300mg	Placebo	26	584	44.2	55.4	4.3	8.0
Wilding	2013	Met + SU	Cana 100mg, Cana 300mg	Placebo	52	469	51.0	56.8	9.6	8.1
Lavalle-Gonzalez	2013	Met	Cana 100mg, Cana 300mg	Placebo, DPP–4i	26	1284	47.1	55.4	6.9	7.9
Leiter	2015	Met	Cana 100mg, Cana 300mg	SU	104	1450	52.1	56.2	6.6	7.8
Schernthaner	2013	Met + SU	Cana 300mg	DPP–4i	52	755	55.9	56.7	9.6	8.1
Bailey	2012	Diet + PA	Dapa 5mg	Placebo	24	136	50.7	52.4	1.3	7.9
Bailey	2013	Met	Dapa 5mg, Dapa 10mg	Placebo	102	409	54.3	53.6	6.1	8.1
Ji	2014	Diet + PA	Dapa 5mg, Dapa 10mg	Placebo	24	393	65.4	51.3	1.4	8.3
Kaku	2014	Diet + PA	Dapa 5mg, Dapa 10mg	Placebo	24	261	59.4	58.8	4.9	7.5
Rosenstock	2012	Pio	Dapa 5mg, Dapa 10mg	Placebo	24	420	49.5	53.5	5.5	8.4
Strojek	2014	Glimepiride	Dapa 5mg, Dapa 10mg	Placebo	48	438	47.5	59.8	7.3	8.1
Bailey	2015	Diet + PA	Dapa 5mg, Dapa 10mg	Met	102	209	45.9	52.0	1.8	7.9
Henry	2012	Diet + PA	Dapa 5mg, Dapa 10mg	Met	24	831	46.8	52.0	1.8	9.1
Bolinder	2014	Met	Dapa 10mg	Placebo	102	180	55.6	60.7	5.7	7.2
Cefalu	2015	OADs ± Insulin	Dapa 10mg	Placebo	52	914	68.3	62.9	12.4	8.1
Jabbour	2014	Sita ± Met	Dapa 10mg	Placebo	48	447	54.8	54.9	5.7	8.0
Leiter	2014	OADs + Insulin	Dapa 10mg	Placebo	52	962	66.9	63.7	13.2	8.0
Matthaei	2015	Met + SU	Dapa 10mg	Placebo	52	218	48.6	61.0	9.5	8.2
Mathieu	2015	Saxa + Met	Dapa 10mg	Placebo	24	320	45.6	55.1	7.6	8.2
Wilding	2014	Insulin ± OADs	Dapa 10mg	Placebo	104	387	47.0	59.1	13.9	8.5
Rosenstock*	2015	Met	Dapa 10mg	DPP–4i	24	355	51.5	54.5	7.8	8.9
Del Prato	2015	Met	Dapa 10mg	SU	208	801	55.1	58.4	6.4	7.7
Haering	2015	Met + SU	Empa 10mg, Empa 25mg	Placebo	76	666	50.9	57.1	8.5	8.1
Kovacs	2015	Pio ± Met	Empa 10mg, Empa 25mg	Placebo	76	498	48.4	54.5	5.5	8.1
Merker	2015	Met	Empa 10mg, Empa 25mg	Placebo	76	637	71.3	55.7	6.3	7.9
Rosenstock	2014	Insulin ± Met	Empa 10mg, Empa 25mg	Placebo	52	563	45.5	56.7	10.5	8.3
Rosenstock**	2015	Insulin	Empa 10mg, Empa 25mg	Placebo	78	494	55.9	58.8	7.0	8.3
Roden	2013	Diet + PA	Empa 10mg, Empa 25mg	Placebo, DPP–4i	24	899	61.3	55.0	3.3	7.9
Lewin[b]	2015	Diet + PA	Empa 10mg, Empa 25mg	DPP–4i	52	405	53.3	54.6	3.5	8.0
DeFronzo[b]	2015	Diet + PA + Met	Empa 10mg, Empa 25mg	DPP–4i	52	405	51.1	55.9	6.5	8.0
Ferrannini[c]	2013	Diet + PA, Met	Empa 10mg, Empa 25mg	Met, DPP–4i	90	659	50.7	59.5	4.6	8.0
Araki[d]	2015	AGI, Biguanide, DPP–4i, Glinide, TZD, SU	Empa 10mg, Empa 25mg	Met	52	1160	72.0	60.3	6.9	7.9
Kadowaki	2015	Diet + PA ± OAD (no TZD)	Empa 10mg, Empa 25mg	-	52	532	74.8	57.6	NR	7.9
Ridderstrale	2014	Diet + PA + Met	Empa 25mg	SU	104	1545	55.2	55.9	5.6	7.9

AGI, α-glucosidase inhibitor; **Cana**, Canagliflozin; **Dapa**, Dapagliflozin; **DPP–4i**, Dipeptidyl peptidase–4 inhibitor; **Empa**, Empagliflozin; **Met**, Metformin; **NR**, Not reported; **OADs**, Oral glucose–lowering drugs; **PA**, Physical activity; **Pio**, Pioglitazone; **Saxa**, Saxagliptin; **Sita**, Sitagliptin; **SU**, Sulphonylurea; **TZD**, Thiazolidinedione . [a] When not reported for the overall population, values have been estimated as weighted means; [b] Data for HbA1c at 24 weeks; [c] Comparators were metformin (background, Diet + PA) or DPP–4i (background, metformin); data for blood pressure at 78 weeks; age reported as median; [d] Data reported by background therapy; metformin as open-label comparator for SU background therapy. * Diabetes Care 2015: 38:376–383; ** Diabetes Obes Metab 2015: 17:936–948

Table 4.E2: Number of study-specific participants (left) and drug-specific arms and participants (right) for HbA1c

First Author	N	Study	N
Araki	1160	Canagliflozin 100mg	8
Bailey (2012)	134		2302
Bailey (2013)	409	Canagliflozin 300mg	8
Bailey (2015)	209		2577
Bode	714	Dapagliflozin 5mg	8
Bolinder	176		957
Cefalu	394	Dapagliflozin 10mg	16
DeFronzo	368		2397
Del Prato	150	Empagliflozin 10mg	17
Ferrannini	556		2329
Forst	339	Empagliflozin 25mg	18
Haering	427		3084
Henry	810	Dipeptidyl peptidase–4 inhibitor	7
Inagaki	183		1345
Jabbour	447	Metformin	5
Ji	393		592
Kadowaki	532	Placebo	26
Kaku	261		4247
Kovacs	498	Sulphonylurea	3
Lavalle-Gonzalez	1260		1333
Leiter (2014)	503	-	-
Leiter (2015)	1450		-
Lewin	352	-	-
Mathieu	320		-
Matthaei	132	-	-
Merker	637		-
Neal	1967	-	-
Ridderstrale	1545		-
Roden	762	-	-
Rosenstock (2012)	415		-
Rosenstock (2014)	566	-	-
Rosenstock (2015)*	350		-
Rosenstock (2015)**	294	-	-
Schernthaner	739		-
Stenlof	574	-	-
Strojek	434		-
Wilding (2013)	457	-	-
Wilding (2014)	246		-
Total number of		**Total number of**	
Studies	**38**	**Arms**	**116**
Participants	**21163**	**Participants**	**21163**

* Diabetes Obes Metab 2015: 17:936–948. ** Diabetes Care 2015: 38:376–383

Table 4.E3: Number of total participants and participants with hypoglycaemic events, by study

Study	All Hypoglycaemia	Study	All Hypoglycaemia
Araki	27 1160	Rosenstock (2012)	4 420
Bailey (2012)	1 136	Rosenstock (2014)	320 563
Bailey (2013)	22 409	Rosenstock (2015)	178 494
Bailey (2015)	7 209	Rosenstock (2015)	4 355
Bode	311 714	Schernthaner	345 755
Bolinder	9 182	Stenlof	18 584
Cefalu	237 922	Strojek	42 442
DeFronzo	10 405	Wilding (2013)	141 469
Del Prato	232 814	Wilding (2014)	241 393
Ferrannini	14 659		
Forst	9 342		
Haering	130 666		
Henry	8 831		
Inagaki	9 183		
Jabbour	26 451		
Ji	4 393		
Kadowaki	2 532		
Kaku	2 261		
Kovacs	15 498		
Lavalle-Gonzalez	- -		
Leiter (2014)	258 965		
Leiter (2015)	290 1450		
Lewin	6 405		
Mathieu	2 320		
Matthaei	26 218		
Merker	26 637		
Neal	1138 2072		
Ridderstrale	229 1545	**Total number of**	
Roden	4 899	**Participants with events** **Participants** **Studies**	**4347** **22753** **37**

Table 4.E4: Number of drug-specific arms, participants with event, and total participants for hypoglycaemia

Drug	All Hypoglycaemia
Canagliflozin 100mg	7 622 1971
Canagliflozin 300mg	7 797 2255
Dapagliflozin 5mg	8 27 972
Dapagliflozin 10mg	16 462 3244
Empagliflozin 10mg	17 245 2544
Empagliflozin 25mg	18 283 3296
Dipeptidyl peptidase–4 inhibitor	6 176 1096
Metformin	5 17 603
Placebo	25 1098 5102
Sulphonylurea	3 620 1670
Total number of	
Arms	**112**
Participants with event	**4347**
Participants	**22753**

Table 4.E5: Assessment of risk of bias in individual studies

Study – First Author	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding Of Outcome Assessment	Incomplete Outcome Data	Selective Reporting
CANAGLIFLOZIN						
Bode	L	L	L	L	L	L
Forst	L	L	L	L	L	L
Inagaki	L	L	L	L	L	L
Lavalle-Gonzalez	L	L	L	L	L	L
Leiter (2015)	L	L	L	L	L	L
Neal	L	L	L	L	L	L
Schernthaner	L	L	L	L	L	L
Stenlof	U	L	L	L	L	L
Wilding (2013)	L	L	L	L	L	L
DAPAGLIFLOZIN						
Bailey (2012)	L	L	L	L	L	L
Bailey (2013)	L	L	L	L	L	L
Bailey (2015)	L	L	L	L	L	L
Bolinder	L	L	L	L	L	L
Cefalu	L	L	L	L	L	L
Del Prato	L	L	L	L	U	L
Henry	L	L	L	L	L	U
Jabbour	U	U	L	L	L	L
Ji	L	L	L	L	L	L
Kaku	U	U	U	U	L	L
Leiter (2014)	L	L	L	L	U	L
Mathieu	L	L	L	L	L	L
Matthaei	L	L	L	L	L	L
Rosenstock (2012)	U	U	L	L	L	L
Rosenstock (2015)	L	L	L	L	L	L
Strojek	L	L	L	L	L	L
Wilding (2014)	L	L	L	L	L	L
EMPAGLIFLOZIN						
Araki	L	L	L	L	L	L
DeFronzo	L	L	L	L	U	U
Ferrannini	U	U	U	L	L	L
Haering	L	L	L	L	L	L
Kadowaki	L	L	L	L	H	H
Kovacs	L	L	L	L	L	L
Lewin	L	L	L	L	H	H
Merker	U	U	U	L	L	L
Ridderstrale	L	L	L	L	L	L
Roden	L	L	L	L	L	L
Rosenstock (2014)	L	L	L	L	L	L
Rosenstock (2015)	L	L	L	L	L	L

L = Low Risk**; H =** High Risk**; U =** Unclear Risk

Table 4.E6: Comparison of SGLT2 inhibitors vs other glucose-lowering drugs for HbA1c

HbA1c (%)									
									Placebo
								DPP-4 inhibitor	**0.56 (0.45,0.67)**
							Sulphonylurea	-0.00 (-0.18,0.17)	**0.56 (0.40,0.71)**
						Metformin	0.06 (-0.15,0.27)	0.05 (-0.12,0.23)	**0.61 (0.46,0.77)**
					Canagliflozin 300mg	**0.25 (0.07,0.42)**	**0.31 (0.14,0.47)**	**0.30 (0.17,0.43)**	**0.86 (0.76,0.96)**
				Canagliflozin 100mg	**-0.10 (-0.20,-0.00)**	0.14 (-0.03,0.32)	**0.20 (0.04,0.37)**	**0.20 (0.07,0.33)**	**0.76 (0.66,0.86)**
			Dapagliflozin 10mg	-0.11 (-0.23,0.02)	**-0.21 (-0.34,-0.09)**	0.04 (-0.12,0.19)	0.10 (-0.07,0.26)	0.09 (-0.04,0.22)	**0.65 (0.57,0.73)**
		Dapagliflozin 5mg	-0.09 (-0.21,0.02)	**-0.20 (-0.35,-0.05)**	**-0.30 (-0.45,-0.16)**	-0.06 (-0.23,0.11)	0.00 (-0.19,0.19)	-0.00 (-0.16,0.15)	**0.56 (0.44,0.67)**
	Empagliflozin 25mg	0.09 (-0.05,0.24)	-0.00 (-0.12,0.12)	-0.11 (-0.24,0.02)	**-0.21 (-0.34,-0.09)**	0.03 (-0.12,0.19)	0.09 (-0.07,0.25)	0.09 (-0.02,0.20)	**0.65 (0.55,0.74)**
Empagliflozin 10mg	-0.05 (-0.12,0.02)	0.04 (-0.10,0.19)	-0.05 (-0.17,0.07)	**-0.16 (-0.29,-0.03)**	**-0.26 (-0.39,-0.13)**	-0.02 (-0.17,0.14)	0.04 (-0.12,0.21)	0.04 (-0.07,0.15)	**0.60 (0.50,0.70)**

Data are reported as mean difference (95% confidence interval) and indicate column-to-row differences [i.e., compared to Placebo, Canagliflozin 300mg reduces HbA1c of 0.86%]. Statistically significant differences are in bold.

Table 4.E7: Comparison of SGLT2 inhibitors vs other glucose-lowering drugs for hypoglycaemia

All hypoglycaemia									
									Placebo
								DPP-4 inhibitor	0.75 (0.54,1.06)
							Sulphonylurea	**0.10 (0.07,0.15)**	**0.07 (0.06,0.10)**
						Metformin	**6.61 (3.20,13.65)**	0.66 (0.30,1.41)	**0.49 (0.25,0.99)**
					Canagliflozin 300mg	1.30 (0.64,2.66)	**8.61 (6.61,11.21)**	0.85 (0.63,1.16)	**0.64 (0.53,0.78)**
				Canagliflozin 100mg	1.02 (0.85,1.24)	1.33 (0.65,2.72)	**8.81 (6.75,11.50)**	0.87 (0.62,1.23)	**0.66 (0.55,0.79)**
			Dapagliflozin 10mg	**1.48 (1.16,1.89)**	**1.51 (1.18,1.94)**	1.97 (0.98,3.96)	**13.04 (9.84,17.29)**	1.29 (0.89,1.88)	0.97 (0.82,1.16)
		Dapagliflozin 5mg	0.96 (0.58,1.56)	1.42 (0.84,2.39)	1.45 (0.85,2.45)	1.89 (0.82,4.31)	**12.47 (7.20,21.59)**	1.24 (0.68,2.24)	0.93 (0.57,1.52)
	Empagliflozin 25mg	0.87 (0.50,1.49)	0.83 (0.63,1.09)	1.22 (0.93,1.61)	1.25 (0.95,1.66)	1.63 (0.81,3.28)	**10.79 (8.11,14.34)**	1.07 (0.73,1.57)	0.80 (0.64,1.01)
Empagliflozin 10mg	1.12 (0.88,1.41)	0.97 (0.56,1.67)	0.92 (0.69,1.24)	**1.37 (1.02,1.84)**	**1.40 (1.04,1.88)**	1.82 (0.90,3.69)	**12.06 (8.73,16.66)**	1.20 (0.80,1.78)	0.90 (0.70,1.15)

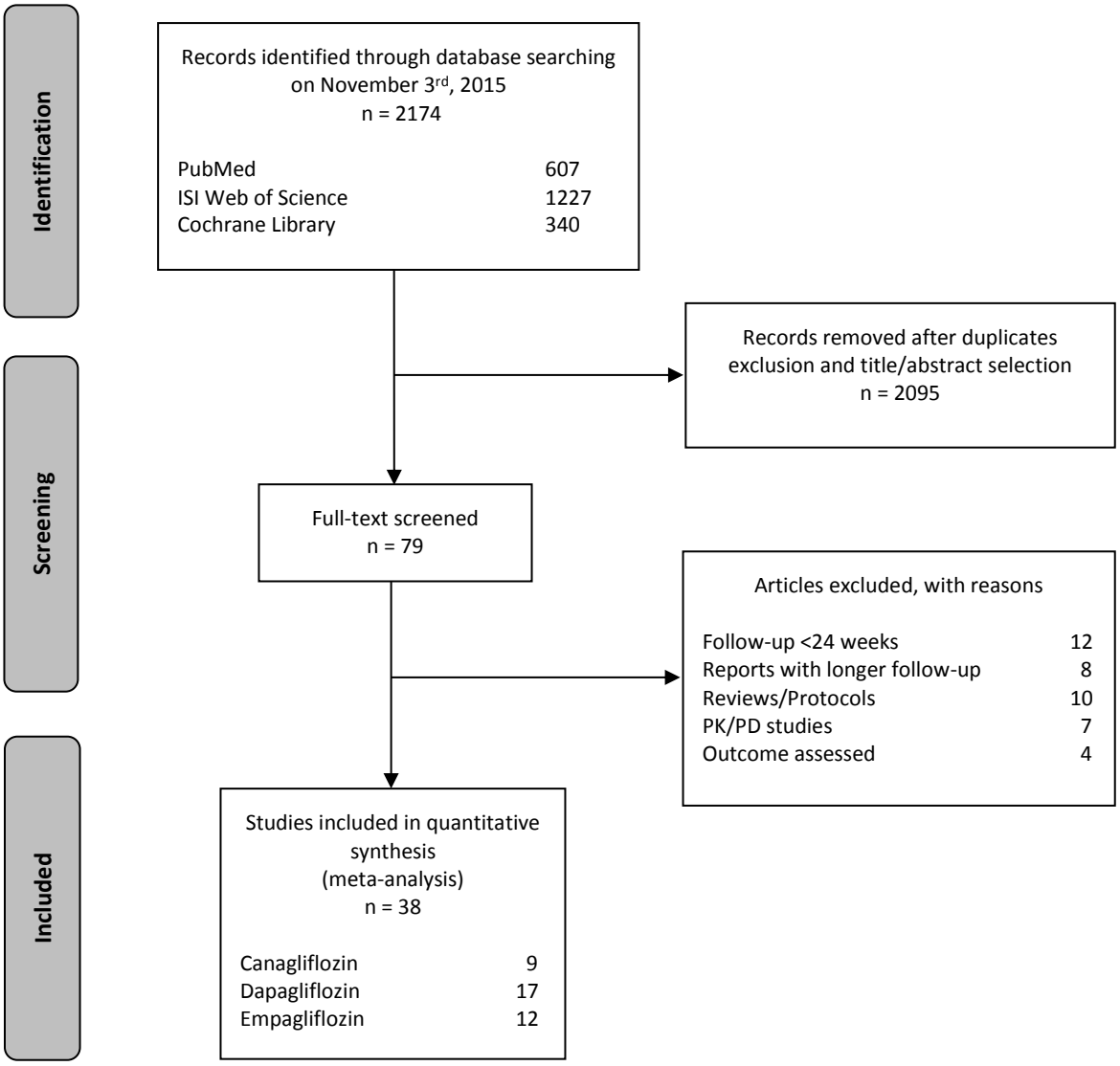
Data are reported as odds ratio (95% confidence interval) and indicate column-to-row ratios [i.e., compared to Canagliflozin 300mg, Placebo is associated with an odds ratio of 0.64 of hypoglycaemia, or equivalently Canagliflozin 300mg increases the risk by an odds ratio of 1.56 (=1/0.64)]. Statistically significant differences are in bold.

Table 4.E8: Comparisons of SGLT2 inhibitors for hypoglycaemia excluding studies with sulphonylurea or insulin as background therapy

All hypoglycaemia						
						Placebo
					Canagliflozin 300mg	0.64 (0.38,1.08)
				Canagliflozin 100mg	1.16 (0.77,1.76)	0.75 (0.45,1.25)
			Dapagliflozin 10mg	**1.66 (1.00,2.74)**	**1.92 (1.16,3.17)**	1.24 (0.81,1.89)
		Dapagliflozin 5mg	0.88 (0.43,1.84)	1.46 (0.64,3.36)	1.70 (0.74,3.90)	1.09 (0.53,2.25)
	Empagliflozin 25mg	0.64 (0.28,1.44)	**0.56 (0.35,0.91)**	0.93 (0.58,1.52)	1.08 (0.67,1.75)	0.70 (0.44,1.12)
Empagliflozin 10mg	1.27 (0.73,2.20)	0.81 (0.33,2.01)	0.72 (0.37,1.38)	1.18 (0.60,2.35)	1.37 (0.69,2.72)	0.89 (0.48,1.64)

Data are reported as odds ratio (95% confidence interval) and indicate column-to-row ratios [i.e., compared to Canagliflozin 300mg, Placebo is associated with an odds ratio of 0.64 of hypoglycaemia, or equivalently Canagliflozin 300mg increases the risk by an odds ratio of 1.6 (=1/0.64)]. Statistically significant differences are in bold.

Figure 4.E1: Study flow diagram: progression of papers through the review process



Abbreviations
PK, Pharmacokinetics; **PD**, Pharmacodynamics

Search Strategy

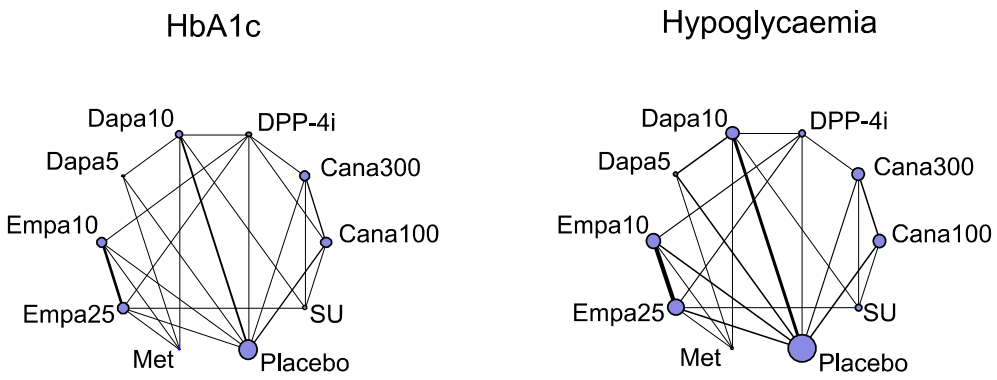
PubMed, Web of Science, and Cochrane Library articles published in any language before November 3rd, 2015 were identified. Electronic search was supplemented by scanning reference lists of all relevant articles, including reviews, by hand searching of relevant journals. For the three databases, the searches were:

PubMed
Canagliflozin [All Fields] OR Dapagliflozin [All Fields] OR Empagliflozin [All Fields]

Web of Science
TOPIC: (Canagliflozin) OR TOPIC: (Dapagliflozin) OR TOPIC: (Empagliflozin)

Cochrane Library
Canagliflozin [All Text] OR Dapagliflozin [All Text] OR Empagliflozin [All Text]

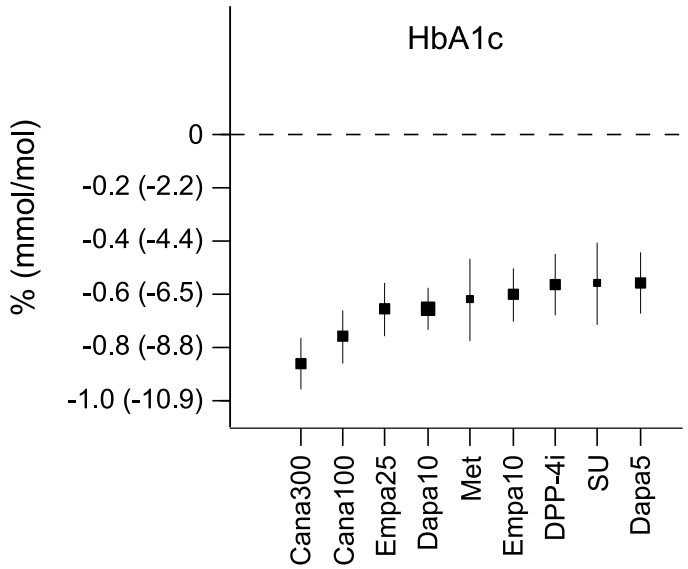
Figure 4.E2: Network maps for HbA1c and hypoglycaemia

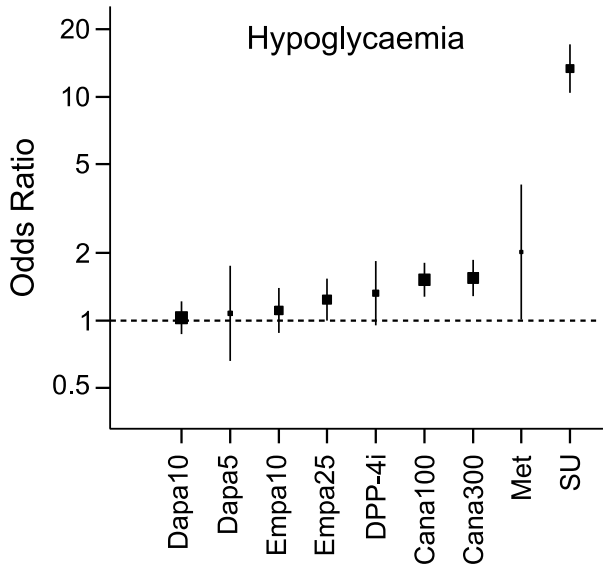


Nodes represent the competing treatments and their size is proportional to the number of participants; edges represent the available direct comparisons between pairs of treatments and their width is proportional to the number of trials comparing every pair.

Abbreviations
Cana100=Canagliflozin 100mg; **Cana300**=Canagliflozin 300mg; **Dapa5**=Dapagliflozin 5mg; **Dapa10**=Dapagliflozin 10mg; **Empa10**=Empagliflozin 10mg; **Empa25**=Empagliflozin 25mg; **DPP-4i**= Dipeptidyl peptidase-4 inhibitor; **Met**=Metformin; **SU**=Sulphonylurea

Figure 4.E3: Differences vs Placebo (dotted lines) for HbA1c and hypoglycaemia for the drugs included in the network meta-analysis

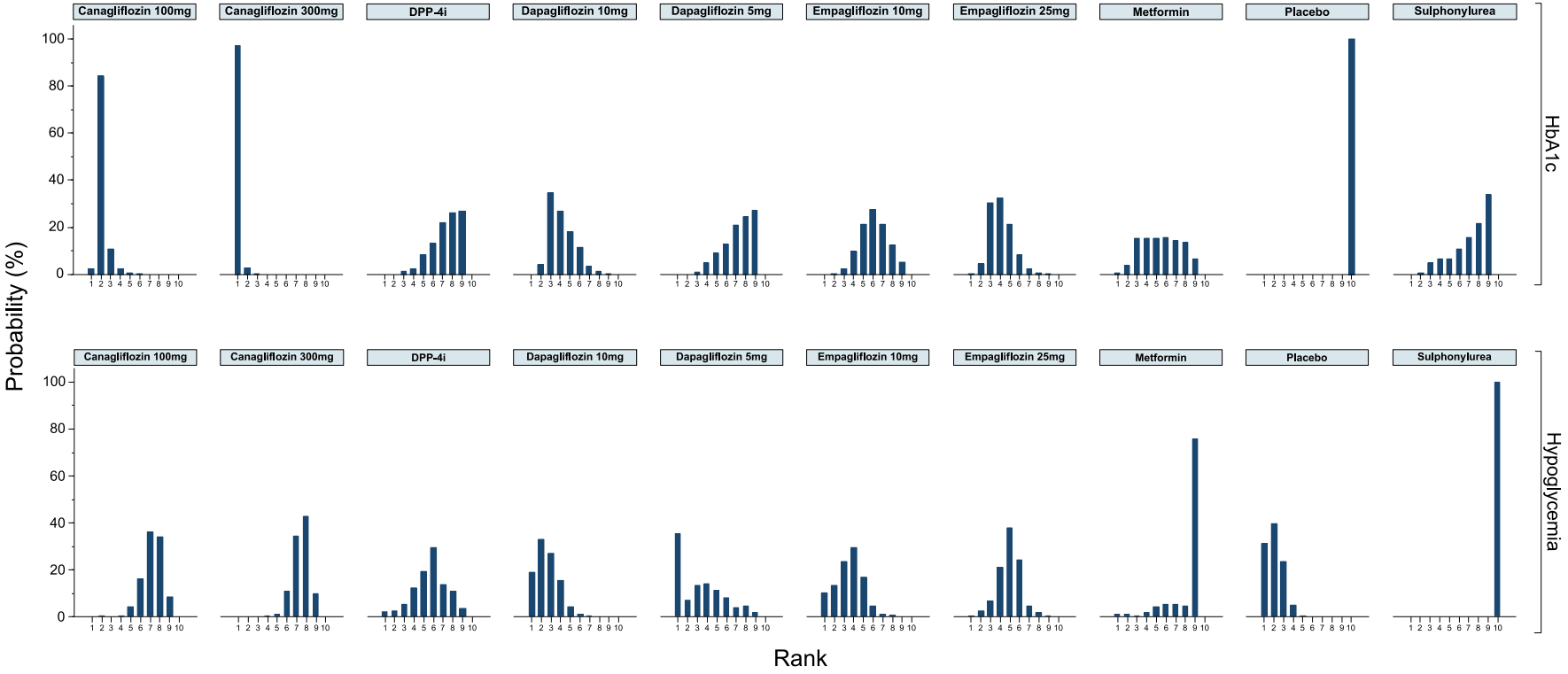




HbA1c (%) Difference vs Placebo (95% CI)	
Cana300=Canagliflozin 300mg	-0.86 (-0.96, -0.76)
Cana100=Canagliflozin 100mg	-0.76 (-0.86, -0.66)
Empa25=Empagliflozin 25mg	-0.65 (-0.74, -0.55)
Dapa10=Dapagliflozin 10mg	-0.65 (-0.73, -0.57)
Met=Metformin	-0.61 (-0.77, -0.46)
Empa10=Empagliflozin 10mg	-0.60 (-0.70, -0.50)
Dapa5=Dapagliflozin 5mg	-0.56 (-0.67, -0.44)
SU=Sulphonylurea	-0.56 (-0.71, -0.40)
DPP-4i=Dipeptidyl peptidase-4 inhibitor	-0.56 (-0.67, -0.45)

Hypoglycaemia (odds ratios) difference vs Placebo (95% CI)	
Dapa10=Dapagliflozin 10mg	1.03 (0.86,1.22)
Dapa5=Dapagliflozin 5mg	1.08 (0.66,1.76)
Empa10=Empagliflozin 10mg	1.11 (0.87,1.42)
Empa25=Empagliflozin 25mg	1.24 (0.99,1.56)
DPP-4i=Dipeptidyl peptidase-4 inhibitor	1.33 (0.95,1.87)
Cana100=Canagliflozin 100mg	1.52 (1.27,1.83)
Cana300=Canagliflozin 300mg	1.56 (1.28,1.89)
Met=Metformin	2.03 (1.01,4.07)
SU=Sulphonylurea	13.41 (10.36,17.35)

Figure 4.E4: Ranking probabilities for HbA1c and hypoglycaemia, by drug



Each bar indicates the probability for the specific rank. For example, for HbA1c Canagliflozin 300mg has the highest probability to be the best (rank 1st) and Placebo the worst (rank 10th). For Hypoglycaemia, Sulphonylurea has the highest probability to rank worst (10th).

DPP-4i: Dipeptidyl peptidase-4 inhibitor

Chapter Five: Hypoglycaemia and cardiovascular disease

Summary

In this chapter I used individual-level data from the KIHD prospective study to investigate the relationship between fasting plasma glucose (FPG) and risk of arrhythmias in subjects without diabetes. The rationale behind the analysis is the observation of an increased risk of cardiovascular events for low levels of FPG as well as the experimental evidence of cardiac rhythm abnormalities associated with hypoglycaemia. The results indicated that lower levels of FPG are associated with an increased risk of ventricular arrhythmias. These findings could help clarify the complex relationship between hypoglycaemia and cardiovascular disease.

Background

Large prospective observational studies have shown a nonlinear "J-shaped" relationship between FPG and major cardiovascular events in subjects without diabetes [1, 2, 209-211]. Whilst increased risk associated with higher values of FPG is commonly related to more severe atherosclerosis, the link between lower FPG values and the risk of cardiovascular events is not fully understood. It has been proposed that a lower FPG could be a marker of conditions associated with an increased risk although this hypothesis has not been confirmed [209, 212].

Cardiac rhythm disturbances, and ventricular arrhythmias in particular, are considered to be the final event in a chain of complications leading to cardiac death from atherothrombotic occlusion of coronary arteries [213]. However, arrhythmic abnormalities can be also caused by hypoglycaemia [13, 28, 214], potentially explaining the lack of efficacy in reducing fatal events in a randomized clinical trial of intensively-treated type 2 diabetic subjects [10].

To help clarify epidemiological and clinical trial observations, the association between fasting plasma glucose and risk of incident ventricular tachycardia or fibrillation was evaluated in a general male population (i.e., not selected on the basis of pre-existing disease) who participated in the Kuopio Ischaemic Heart Disease (KIHD) prospective study [215].

Kuopio Ischaemic Heart Disease study

The KIHD study was designed to investigate risk predictors for atherosclerotic cardiovascular outcomes in a population-based sample of men from Eastern Finland. Subjects were a randomly selected sample of 3433 men 42 to 60 years of age resident in the town of Kuopio or its surrounding rural communities, and baseline examinations were conducted between 1984 and 1989. Of those invited, 2682 (78.1%) participated in the study. After the exclusion of 162 subjects

with prevalent diabetes (either having regular treatment with an oral hypoglycaemic agent, insulin therapy, or having treatment only with diet while also having a FPG level of at least 7.0 mmol/l) and 38 with missing information on FPG, 2482 participants were included in the analyses.

Fasting blood samples and measurements were taken between 8 and 10 am. The resting systolic blood pressure was measured with a random-zero sphygmomanometer (Hawksley, Lancing England) by two trained nurses using the following protocol: after supine rest of 5 minutes, 3 measurements in supine, 1 in standing and 2 in sitting position with 5-minute intervals. The systolic blood pressure was taken as the mean of all 6 measurements [216]. Baseline diseases, smoking habits and years of education were assessed by self-administered questionnaires. The diagnosis of chronic diseases was checked during a medical examination by the internist. Alcohol consumption was assessed using the Nordic Alcohol Consumption Inventory [216]. Body mass index was computed as the ratio of weight in kilograms to the square of height in meters.

All incident ventricular tachycardia or fibrillation cases that occurred from study baseline (March 1984 - December 1989) through 2012 were included. Annually updated data on new incident outcome events were obtained by computer linkage to the national hospital discharge register, and ICD-9 (427.41) or ICD-10 (I47.2, I49.0) codes were used to define ventricular arrhythmias. The definition of non-sustained, sustained ventricular tachycardia and/or ventricular fibrillation was based on electrocardiography. Documents were cross-checked in detail by two physicians, and an independent events committee blinded to clinical data performed the classification of outcomes [217]. There were no losses to follow-up.

Analytical approach

For all the analyses, natural logarithm transformed values of the non-normal distributed variables C-reactive protein, triacylglycerols, and alcohol consumption were used. Descriptive data are presented as means and standard deviations (SDs) for continuous variables and numbers and percentages for categorical ones; their differences were estimated with ANOVA and $\chi 2$ test, respectively. Correlation coefficients were calculated to assess the correlation between FPG levels and other continuous variables, whereas mean differences between groups were calculated for categorical factors.

Analyses of the associations between FPG and outcomes were performed with Cox-regression, which is the most popular statistical model for the analysis of survival (time-to-event) data. Cox regression is defined a semiparametric model because the regression portion of the model is parametric but the model does not assume any particular form of the hazard function. When

the main interest is the effect of covariate(s) and not the hazard function, the Cox model may be preferred to others. Conversely, flexible parametric models should be preferred when the investigator is interested in both the hazard function and the effects of the covariates [218, 219]. Two key assumptions of the Cox model are: a) non-informative censoring, which is satisfied if censoring of individual subjects are not related to the probability of an event occurring; b) proportional hazard, which assumes that predictors act multiplicatively on the hazard function. In this analysis, this assumption was verified for all variables by inspection of the plots of the Schoenfeld residual (the observed minus the expected values of the covariates at each failure time): a plot of residuals against time showing a non-random pattern indicates that the proportional hazard assumption is violated [218]. To assess the shape of the association, hazard ratios (HRs) were estimated within quartiles of FPG relative to the bottom quartile against the mean FPG level in each quartile and 95% confidence intervals (CIs) were estimated from variances attributed to the groups to reflect the amount of information within each group (including the reference category [220]). To assess the independence of any association between FPG and incident cases of ventricular arrhythmias, HRs were calculated by quartiles and per 1 mmol/l higher baseline FPG with progressive adjustment for potential confounders selected on the basis of their previously established role as predictive cardiovascular risk factors. Two-sided analyses were performed using Stata version 13 (Stata Corp, College Station, TX, USA) and results are presented at the 95% level.

Results

At baseline, 32% were smokers, mean (SD) age was 53 (5) years and mean FPG 4.6 (0.5) mmol/l; characteristics of the study participants by quartile of fasting plasma glucose are reported in **Table 5.1**. With the exception of systolic blood pressure and triacylglycerols, levels of other cardiometabolic risk factors were not significantly different in subjects who had an arrhythmic event throughout the follow-up as compared to subjects who had not (**Table 5.2**). During a median follow-up time of 23.3 (interquartile range: 18.5-25.3) years, there were 74 (2.9%) cases of ventricular arrhythmias, with a crude incidence rate of 1.43 (95% CI: 1.14, 1.80) per 1000 person-years.

The relationship between 1 mmol/l higher baseline FPG and incident ventricular tachycardia or fibrillation events, adjusted for potential confounders, is reported in **Table 5.3** and HRs by quartiles of FPG are shown in **Appendix F, Table F1**. In the analysis adjusted for age, systolic blood pressure, current smoking, LDL and HDL cholesterol, and C-Reactive protein, 1 mmol/l higher baseline FPG was associated with a HR of 0.58 (95% CI: 0.34, 0.98) of ventricular

arrhythmic events; progressive adjustment for body mass index, alcohol consumption, triacylglycerols, and history of ischaemic heart disease at baseline did not materially change the estimate (**Table 5.3; Figure 5.1**). Similarly, additional inclusion of glomerular filtration rate, use of β-blockers, serum sodium, and serum potassium resulted in comparable associations (**Tables 5.3 and F1**).

Interpretation in the context of available evidence

These results suggest that, in a general male population, lower fasting plasma glucose levels are associated with a higher risk of ventricular tachycardia/fibrillation independently from other cardiovascular risk factors. Although nondiabetic hyperglycaemic states have been associated with major vascular events, the precise relationship between FPG and cardiovascular outcomes remains unclear. A graded continuous [221, 222], threshold [223], or "J-shaped" relationship [1, 2, 209-211] have been reported. The reasons behind these divergences are unclear, being possibly related to different study characteristics and methods or due to inherent diversity in subjects involved. In studies showing a "J-shaped" association, the nadir has been reported between 3.3 and 5.6 mmol/l; further to this, it has been suggested that low glucose values could be a marker of conditions associated with an increased risk of vascular events, such as liver or kidney dysfunction [224]; this hypothesis, however, has not been clearly confirmed.

Experimental studies have shown that low plasma glucose levels can cause ventricular electrophysiological abnormalities (i.e., QT interval prolongation) associated with an increased risk of ventricular arrhythmias in individuals with and without diabetes [13, 28, 214]. Hypoglycaemia can indeed increase the risk of ventricular arrhythmias through direct (effect of low glucose on ion channels [225]) and indirect (hypokalaemia, catecholamine release) mechanisms. However, no study has prospectively demonstrated a link between FPG and risk of ventricular arrhythmic events in subjects without diabetes.

These results have important ramifications. First, although large epidemiological studies tend to combine outcomes, the heterogeneity of mechanisms eventually resulting in what collectively (and simplistically) is classified as a single outcome is increasingly recognized, for both cardiovascular [226, 227] and other diseases [228, 229]. These results could suggest that, across the range of FPG, increased risk at upper and lower extremities could be attributable to different pathophysiological pathways leading to the same-defined outcome and underline that a better definition of the multiple mechanisms driving cardiovascular disease outcomes is essential. Second, these findings could further help interpret recent trials and observational analyses in subjects with type 2 diabetes mellitus showing an increased cardiovascular risk in intensively-

treated patients, possibly related to higher rates of hypoglycaemia [10, 11, 16]. From this perspective, these results would support hypoglycaemia as a plausible mechanism that could contribute to increased cardiovascular mortality during intensive glycaemic therapy.

In a previous analysis exploring the association between FPG and sudden cardiac death (SCD) in nondiabetic subjects from the general population, a positive relationship has been evidenced [230]. Notably, of 190 SCDs events occurred during the follow-up, 157 SCDs were out-of-hospital events: therefore, for the large majority of events (82.6%) it was not possible to assess the presence of ventricular arrhythmias. While SCD is generally considered to be the consequence of ventricular fibrillation/tachycardia, it is also well-know that other causes can lead to SCD as well, and only about 50% of SCD events are attributable to ventricular fibrillation/tachycardia [231]. This could explain the divergence in the relationship between FPG/SCD and FPG/ventricular arrhythmias, and further underlines as the identification of multiple mechanisms behind cardiovascular outcomes is critical.

The interpretation of these results should consider the limitations of this study. First, a generalisation of these findings is limited by the study population, consisting of middle-age Finnish men only; these results need to be confirmed in other ethnic groups. Second, no information on the nature of ventricular arrhythmic events was recorded. Third, the association evidenced does not necessarily indicate a cause-effect relationship between FPG and arrhythmic disorders. Although experimental studies would support a causal link, low FPG could be a confounder of a condition increasing the risk of ventricular arrhythmias. Furthermore, as participants in the fourth quartile of FPG experienced a greater risk of fatal coronary heart disease, an incomplete assessment of ventricular arrhythmias could be possible and should be considering while interpreting these results. Fourth, the independence of association between FPG and ventricular arrhythmias has been assessed by adjusting for several well-known and potential confounders, including drugs for hypertension and dyslipidaemia; however, baseline data on other specific medications (i.e., diuretics) were not available. Notably, adjustment is a common statistical methodology to assess the effect of a single factor keeping all others constant (*ceteris paribus*). The degree of the association between the exposure and the outcome can be considered an indirect estimate of the causality of the association [232], yet adjustment does not account for the complex interaction (statistical and biological) among factors included in the model [32]. On the other hand, strengths of this study include the rigorous measurement of baseline risk factors, the large and homogeneous community-based sample, and the long-term follow-up.

In this population of male subjects without diabetes, FPG was inversely associated with incident risk of ventricular arrhythmias. These results could help clarify the complex association between glucose, hypoglycaemia, and cardiovascular disease.

Tables and Figures

Table 5.1: Baseline characteristics of the study participants (N=2482) by quartile of fasting plasma glucose

	Fasting plasma glucose quartiles, mmol/l [min-max]				
Characteristics	**1st [3.2-4.3]**	**2nd [4.4-4.5]**	**3rd [4.6-4.9]**	**4th [5.0-6.2]**	**p for trend**
Sample size, % (n)	32.4 (804)	19.0 (473)	28.4 (704)	20.2 (501)	-
Age, years	52.7 (5.2)	53.0 (5.1)	53.2 (5.0)	53.0 (5.1)	0.137
Body mass index, kg/m^2	25.6 (3.1)	26.7 (3.1)	27.0 (3.3)	27.9 (3.8)	<0.001
Systolic blood pressure, mmHg	131 (16)	134 (17)	134 (17)	137 (17)	<0.001
LDL cholesterol, mmol/l	3.99 (0.99)	4.05 (1.04)	4.10 (1.02)	4.04 (1.00)	0.135
HDL cholesterol, mmol/l	1.32 (0.32)	1.29 (0.28)	1.30 (0.30)	1.28 (0.30)	0.055
Triacylglycerols[a], mmol/l	1.02 (0.76-1.40)	1.11 (0.79-1.54)	1.17 (0.79-1.54)	1.18 (0.83-1.76)	<0.001
Fasting plasma glucose, mmol/l	4.1 (0.2)	4.4 (0.1)	4.7 (0.1)	5.3 (0.3)	<0.001
Sodium, mmol/l	140.9 (1.4)	140.8 (1.5)	140.8 (1.5)	140.6 (1.7)	0.001
Potassium, mmol/l	3.9 (0.3)	3.9 (0.3)	3.9 (0.3)	3.9 (0.3)	0.777
Glomerular filtration rate[b], ml/min/1.73m^2	78 (13)	79 (14)	79 (13)	81 (18)	<0.001
High sensitivity C-reactive protein[a], mg/l	1.17 (0.63-2.24)	1.23 (0.70-2.33)	1.25 (0.73-2.27)	1.55 (0.81-2.83)	<0.001
Alcohol consumption[a], g/week	27 (6-76)	37 (5-88)	25 (5-90)	43 (7-121)	0.008
Previously Diagnosed Diseases					
Current smoking	33.9 (273)	33.8 (160)	29.5 (208)	32.1 (161)	0.192
Ischaemic heart disease	24.0 (193)	20.9 (99)	25.4 (179)	25.7 (129)	0.283
Hypertension	25.1 (202)	28.2 (133)	30.3 (212)	28.8 (165)	0.001
Heart failure[c]	4.6 (37)	6.7 (32)	7.6 (53)	8.2 (41)	0.006
Cerebrovascular disease	2.1 (17)	2.5 (12)	0.8 (6)	2.9 (15)	0.915
Claudication	3.4 (27)	2.9 (14)	4.8 (34)	4.2 (21)	0.191
Pulmonary disease[d]	13.3 (95)	14.2 (60)	14.6 (94)	12.4 (56)	0.905
Cancer	1.9 (15)	1.9 (9)	1.9 (14)	1.6 (8)	0.822
Regular Use of Medications					
Antidyslipidaemic	0.8 (7)	0.2 (1)	0.4 (3)	0.9 (5)	0.967
Antihypertensive	18.8 (151)	18.4 (87)	22.1 (156)	24.7 (124)	0.005
β-blockers	14.8 (119)	14.4 (68)	18.6 (131)	19.9 (100)	0.004
Acetylsalicylic acid	7.6 (61)	4.9 (23)	7.5 (53)	8.4 (42)	0.453
Incident events					
Fatal coronary heart disease	11.6 (93)	12.0 (57)	11.4 (80)	17.6 (88)	0.012
Type 2 diabetes mellitus	2.5 (20)	4.2 (20)	6.7 (47)	12.9 (65)	<0.001

Unless otherwise stated, data are reported as mean (standard deviation) for continuous variables and as % (number) for categorical ones.
LDL: Low-density lipoprotein; HDL: High density lipoprotein. [a] Data reported as median and interquartile range; [b] Estimated with the MDRD formula: 175 x (Creatinine/88.4)$^{-1.154}$ x Age$^{-0.203}$
[c] Diagnosis based on clinical findings and symptoms and/or echocardiography; [d] Including bronchial asthma, chronic obstructive pulmonary disease and pulmonary tuberculosis

Table 5.2: Baseline characteristic of study participants (N=2482) according to incident ventricular arrhythmias during follow-up

Variable	Ventricular Tachycardia/Fibrillation		p-Value
	Yes (N=74)	No (N=2408)	
Age (years)	54.0 ± 4.2	52.9 ± 5.2	0.078
Body mass index (kg/m^2)	27.4 ± 3.4	26.7 ± 3.4	0.067
Systolic blood pressure (mmHg)	139 ± 20	133 ± 17	0.001
LDL-Cholesterol (mmol/l)	4.08 ± 1.18	4.05 ± 1.01	0.764
HDL-Cholesterol (mmol/l)	1.27 ± 0.31	1.30 ± 0.30	0.452
Triacylglycerols (mmol/l) [a]	1.24 (0.87–1.79)	1.10 (0.80–1.53)	0.034
Fasting plasma glucose (mmol/l)	4.5 ± 0.4	4.6 ± 0.5	0.089
Serum sodium (mmol/l)	140 ± 1	140 ± 2	0.506
Serum potassium (mmol/l)	3.9 ± 0.3	3.9 ± 0.3	0.783
Glomerular filtration rate [b] (ml/min/1.73m^2)	77 ± 15	79 ± 15	0.192
C-Reactive protein (mg/l) [a]	1.31 (0.82–2.34)	1.26 (0.69–2.39)	0.566
Alcohol consumption (g/week) [a]	37 (9-93)	31 (6-89)	0.372
Current smoking (Yes)	30% (22)	32% (780)	0.629
History of ischaemic heart disease (Yes)	32% (24)	24% (576)	0.092

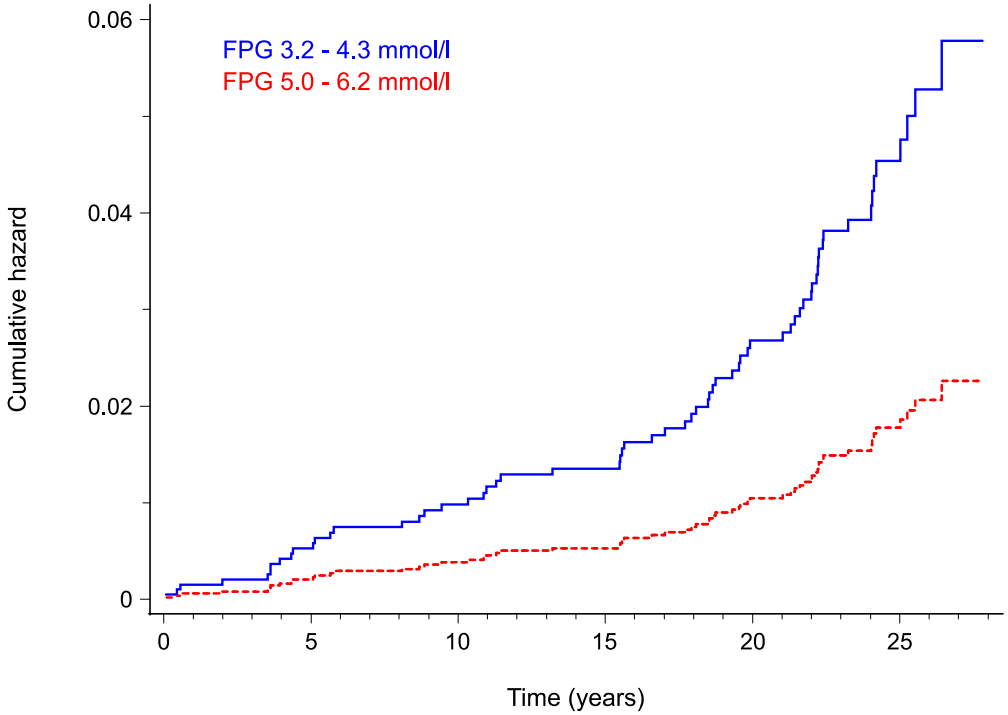
Unless otherwise stated, values are reported as mean ± standard deviation or % (n)
LDL: Low-density lipoprotein; HDL: High-density lipoprotein
[a] Median and interquartile range
[b] Estimated with the MDRD formula: $175 \times (\text{Creatinine}/88.4)^{-1.154} \times \text{Age}^{-0.203}$

Table 5.3: Hazard ratio (HR) of ventricular tachycardia/fibrillation per 1 mmol/l higher baseline fasting plasma glucose

Level of Adjustment	HR (95% CI)	p-Value
Age, SBP, Smoking, LDL, HDL, C-Reactive protein	0.58 (0.34, 0.98)	0.042
Above + Body mass index, Alcohol consumption, Triacylglycerols	0.50 (0.28, 0.89)	0.019
Above + Ischaemic Heart Disease	0.50 (0.28, 0.89)	0.020
Above + eGFR, β-blockers	0.51 (0.28, 0.92)	0.025

CI: confidence interval; SBP: Systolic blood pressure; LDL: Low-density lipoprotein cholesterol; HDL: High-density lipoprotein cholesterol; eGFR: Estimated glomerular filtration rate

Figure 5.1: Cumulative Hazards of Ventricular Arrhythmias comparing top vs bottom quartiles of baseline fasting plasma glucose



Hazard ratio higher (dotted line) vs lower (solid line) quartile of fasting plasma glucose: 0.39 (95% CI: 0.19, 0.78), adjusted for age, systolic blood pressure, LDL- and HDL-cholesterol, smoking status, C-reactive protein, body mass index, alcohol consumption, triacylglycerols, and prevalent ischaemic heart disease.
Range fasting plasma glucose quartiles: lower, 3.2-4.3 mmol/l; higher, 5.0-6.2 mmol/l.

Chapter Six: Conclusions

Summary of findings

The analyses I have conducted indicate that hypoglycaemia has a major impact on patients with diabetes and represents a significant public health burden. In **chapter 3A**, I have shown increasing trends of hospital admissions for hypoglycaemia in England between 2005 and 2014, in line with the findings from studies conducted in other countries, such as US Japan, and Italy. However, the number of hospitalisations accounting for diabetes prevalence is currently in decline, suggesting that the increasing trends are likely related to a higher prevalence of diabetes with a decreasing number of admissions per patient. Moreover, in **chapter 3B**, I have evidenced important differences comparing admissions for hypoglycaemia vs those for other causes in patients with diabetes, both in terms of risk factors and outcomes following the hospitalisation. A U-shape relationship between age and risk of admission for hypoglycaemia, likely related to the age-diabetes phenotype distribution, indicates higher risks for younger and elderly patients. Of note, ethnicity and comorbidities (particularly retinopathy, dementia, and chronic kidney disease) are strongly related to risk of admission for hypoglycaemia. In **chapter 3C**, a model has been developed using simple clinical information to predict the risk of inpatient death, length of hospitalisation, and hospital readmission. The model can accurately predict the risk of death and length of hospital stay after admission for hypoglycaemia but the same prognostic indicators do not adequately identify patients at higher risk of readmission, in line with previous models validated in patients admitted for other medical conditions.

To put the epidemiological evidence in context, I have examined whether newer glucose-lowering therapies, namely once-weekly GLP-1RAs and SGLT2 inhibitors, are associated with a reduced risk of hypoglycaemia compared to older therapies, particularly sulphonylureas and insulin. In light of the pharmacological properties of these two classes of medications (which should reduce glucose without a parallel increase of hypoglycaemia) and their increasing use in England, I have systematically synthesised the available evidence from RCTs with network meta-analyses, which have the advantage of combining together direct and indirect evidence. The results for once-weekly GLP-1RAs (**chapter 4D**) indicate that any GLP-1RA reduces HbA1c and is associated with a lower risk of hypoglycaemia compared to sulphonylureas or insulin. Similarly, any SGLT2 inhibitor reduces HbA1c and carries a lower risk of hypoglycaemia compared to sulphonylureas (**chapter 4E**). Lastly, to help clarify the U-shape relationship between glucose levels and risk of cardiovascular events observed in large epidemiological studies and the long-term association between severe hypoglycaemia and mortality found in post-hoc analyses of

RCTs, I have investigated the relationship between fasting plasma glucose and risk of ventricular arrhythmias in subjects without diabetes from the general population, evidencing an increased risk for lower levels of glucose (**chapter 5**).

Public health and clinical implication

The first and most immediate application of these results is the implementation of the algorithm developed in **chapter 3C** to assess its impact on the risk of inpatient death and length of hospital stay.

The more stable trends of admissions for hypoglycaemia between 2010 and 2014 could be related to the availability of drugs associated with a lower risk of hypoglycaemia (individual level changes) and to the variation in hospital admission policies (public health level changes). A better understanding of the relative importance and contribution of individual and public health factors in determining the risk of hypoglycaemia-related admissions is essential. The predicted increase of diabetes prevalence in England indicates that further effort is required in the future to keep constant the number of hospital admissions for hypoglycaemia (i.e., further reduction of number of admissions per patient with diabetes). As the results indicate a decreasing number of admissions per patient with diabetes, appropriate strategies to reduce the burden of hypoglycaemia at individual level (i.e., structured education, psychological support, glucose self-monitoring, therapies associated with a lower risk of hypoglycaemia) are being implemented. Strategies at population/public health level, conversely, should be further improved, as also supported by the findings of relevant regional and ethnic differences. Health inequalities between regions and ethnic groups is a well-known, characterised, and described problem in England; such a complex phenomenon requires structural changes targeting the syndemic of a disease rather than its apparently separate clinical, social, and economic determinants.

Current guidelines for the management of hyperglycaemia in subjects with type 2 diabetes advocate a personalised approach which accounts for the benefit and harms of individual therapies. Beyond HbA1c, therapeutic decisions should be based on their overall effects on multiple outcomes, of which hypoglycaemia has central importance. The results of this thesis confirm that once-weekly GLP-1RAs and SGLT2 inhibitors are associated with a lower risk of hypoglycaemia and suggest their use when the risk (and fear) of hypoglycaemia is a major barrier to achieving personalised glucose targets.

Strengths and weaknesses

The major strength of the individual-level analyses is the availability of a large, complete, and, in the case of HES, national-level database which allowed the estimation of precise figures related to trends, risk factors, and associations. However, HES has important limitations, particularly the unavailability of data for medications and other relevant risk factors (i.e., anthropometric and lifestyle variables); furthermore, it is an administrative database not primarily designed for research. Conversely, KIHD is a classical prospective cohort study, whose data are very detailed yet population-specific (Finnish males).

For both individual-level and meta-analytical studies, it should be highlighted the limitation of heterogeneous definition and assessment of hypoglycaemia. Various definitions and methods of assessment could result in significant differences in the rates of hypoglycaemia across RCTs which, in turn, may influence the overall meta-analytical estimates. A standardisation of hypoglycaemia definition and assessment is the *sine qua non* it will not be possible to precisely describe the burden of hypoglycaemia across regions and over-time and compare the risk of iatrogenic hypoglycaemia for multiple therapies. Once a more standardised approach will be adopted, differences between future findings with those reported in this thesis will help quantify the impact of heterogeneous classifications and definitions on the epidemiology of hypoglycaemia and its complications.

Future research

It remains unclear whether hypoglycaemia is simply a marker or a causal factor for cardiovascular and all-cause mortality. The observation of an inverse association between fasting glucose and risk of ventricular arrhythmias provides some insights into the possible pathophysiological mechanisms linking glucose and cardiovascular disease, although the definitive answer about the nature of the hypoglycaemia-mortality link remains elusive. In contrast to the classical "dualism" association or causation, however, it is possible that hypoglycaemia could act as both a biomarker of an increased risk of mortality in long-term observational studies (without being in the casual pathway) and, at the same time, be the cause of death in acute, severe episodes of hypoglycaemia.

From an epidemiological perspective, further studies are required to develop and validate models to predict the risk of severe hypoglycaemia in outpatients and the probability of hospital readmission given the significant proportion (and cost) of readmission in patients admitted for hypoglycaemia. Moreover, the results of **chapter 3 part A** and **B** could be compared with an estimation of the global burden of hypoglycaemia. Data from the World Health Organisation on the "underlying" cause of death from death certificates and population estimates by countries

and over-time would widen understanding for the global burden of hypoglycaemia, in particular hypoglycaemia-related deaths. Complementing such data with those of age-specific prevalence of diabetes will also allow quantification of the relative impact of population pyramids, prevalence of diabetes, and geographical differences on the risk of death-related hypoglycaemia.

The control of glucose levels to reduce the risk of hyperglycaemia-related complications is an essential principle of diabetes medicine. The publication of RCTs showing a neutral or negative impact of intensive glucose control in subjects with established type 2 diabetes, however, has partly changed this perspective, fuelling the development of two related concepts: the "metabolic memory" (or "legacy effect") and the personalised approach to the treatment of hyperglycaemia. Metabolic memory refers to the observation that the benefits of intensified glycaemic control early in the course of diabetes are demonstrable only after long-term observation, for both microvascular and macrovascular complications [233]. As intensive glucose control increases the risk of short and possibly long-term hypoglycaemia-related complications and its effect is evident after several years of treatment, clinicians face the problem of balancing pros and cons of intensive glucose reduction for the individual patient (personalised medicine). However, as long as positive and negative effects of intervention are quantified in terms of relative measures (i.e., hazard ratio, a standard in RCTs), there will be limited possibilities to apply a stratified, patient-centred approach. Rather, absolute risks should guide practice. The results of this thesis underline the relevance of estimating the absolute risk of severe hypoglycaemia and the need to balance it with the risk of hyperglycaemia-related complications. The availability of large datasets and the possibility to implement machine learning and artificial intelligence algorithms will be instrumental to estimate or classify the individual absolute risk of complications related to intensive glucose control. Once validated models will be available, decision makers will be able to complement them with clinical judgment in deciding whether the intensification of glucose control or, conversely, a reduction of the treatment (deintensification) is the most appropriate approach to avoid acute and long-term complications.

Chapter Seven: Appendices

Appendix A

Table A1 | Criteria to identify HES admissions for hypoglycaemia
Emergency admission methods [ADMIMETH]: **- 21:** Accident and emergency or dental casualty department of the Health Care Provider **- 22:** GP: after a request for immediate admission has been made direct to a Hospital Provider, i.e. not through a Bed bureau, by a GP or deputy **- 23:** Bed bureau **- 24:** Consultant Clinic, of this or another Health Care Provider **- 25:** Admission via Mental Health Crisis Resolution Team **- 2A:** Accident and Emergency Department of another provider where the patient had not been admitted **- 2B:** Transfer of an admitted patient from another Hospital Provider in an emergency **- 2C:** Baby born at home as intended **- 2D:** Other emergency admission **- 28:** Other means: - admitted from the Accident and Emergency Department of another provider where they had not been admitted - transfer of an admitted patient from another Hospital Provider in an emergency - baby born at home as intended
Episode status [EPISTAT]: **- 3**: Finished episode
Patient classification [CLASSPAT]: **- 1:** Ordinary admission **- 2**: Day case admission
Episode order [EPIORDER]: **- 1:** Admitting episode
***ICD-10 Hypoglycaemia primary diagnosis code [DIAG_01]:** - E160 - E161 - E162 *** ICD-10 Diabetes diagnosis code [DIAG_02 – DIAG_20]:** - E10+ (Diabetes Type 1) - E11+ (Diabetes Type 2)
Date episode ended [EPIEND]: 01/01/2005 – 31/12/2014

* Fourteen [DIAG_01 – DIAG_14] codes were available before April 2007

Further details are available at:
http://www.hscic.gov.uk/hesdatadictionary

Table A2 | Selected similar studies reporting on emergency treatment or hospital admission for hypoglycaemia*

First author (*Ref*)	Country	Data source	Period	Outcome	Main findings
Barranco RJ *Diabet Med 2015;32:1520-6*	Andalusia, Spain	All hypoglycaemic episode calls in the region of Andalusia recorded in the Health Emergency Public Company database	1/1/2012 31/12/2012	Emergency treatment for hypoglycaemia	8,683 calls for hypoglycaemia 80 (95%CI: 78-83) per 10,000 pyrs with diabetes 85% required medical assistance (of which 21% referred to hospital) Older age significant risk factor for ED visit and hospitalisation
Budnitz DS *N Engl J Med 2011;365:2002-12*	US	National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance People ≥65 years old	1/1/2007 31/12/2009	Hospitalisation after ED visits for adverse drug events	Of ~100,000 estimated hospitalisation/year, 13.9% and 10.7% due to unintentional insulin and oral hypoglycaemic agents overdose, respectively Older age significant risk factor for hospitalisation
Clemens KK † *PLoS One 2015; 10:e0137596*	Ontario, Canada	Canadian Institute for Health Information's Discharge Abstract Database and the National Ambulatory Care Reporting System database People ≥65 years old	1/4/2002 31/3/2013	ED or hospitalization visits for hypoglycaemia	Increase in absolute events until mid-2006 (~1.7%) and then decline (~1.3% in Oct 2012) Decline from the beginning of the study when adjusted for prevalence of treated diabetes (~0.75% in Apr 2002 to ~0.45% in Oct 2012) Age not significant risk factor for ED or hospitalization
Farmer AJ *Diabet Med 2012;29:1447-50*	South Central England	South Central Ambulance Service National Health Service Trust	12/2009 11/2010	Emergency ambulance assistance and ED visits for hypoglycaemia	4,801 overall calls, of which 35.3% were taken to hospital Estimated calls from 1,431 (55-64 years old) to 9,919 (15-24 years old) per 100,000 people with diabetes Older age significant risk factor for ED visits
Geller AI *JAMA Internal Medicine 2014; 174:678-86*	US	National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance for ED visits and National Health Interview Survey for insulin use	1/1/2007 31/12/2011	ED visits and emergency hospitalisations for insulin-related hypoglycaemia	~98,000 estimated ED visits/year (of which 1/3 resulted in hospitalisation) 13.7 and 34.9 ED visits/1,000 pyrs in <18 and ≥80 years old, respectively Older age significant risk factor for ED visit and hospitalisation
Khalid JM *Int J Clin Pract 2014;68:40-8*	England	General Practice Research Database linked to Hospital Episode Statistics database People ≥18 years old with type 2 diabetes	1/2006 12/2012	Hospital admissions for hypoglycaemia	Rate of admission, 30 per 10,000 pyrs Hypoglycaemia accounting for 1.2% of all diabetes-related admissions Older age significant risk factor for hospitalisation

Table A2 (cont'd) | Selected similar studies reporting on emergency treatment or hospital admissions for hypoglycaemia*					
First author (*Ref*)	**Country**	**Data source**	**Period**	**Outcome**	**Main findings**
Khunti K *Prim Care Diabetes 2013; 7:159-65*	East Midlands England	All emergency ambulance calls recorded in East Midlands Ambulance Service NHS Trust database	1/11/2010 28/2/2011	Emergency ambulance and hospital ED visits for hypoglycaemia	523 calls for hypoglycaemia 276 per 10,000 pyrs with diabetes 30% referred to hospital Older age not significant risk factor for hospital ED visits
Lipska KJ † *JAMA Internal Medicine 2014; 174:1116-24*	US	Medicare beneficiaries for hospital admissions and Behavioral Risk Factors Surveillance System for prevalence of diabetes People ≥65 years old	1999 2011	Hospital admissions for hypoglycaemia 30-day and 1-year mortality 30-day readmission	Rates increase from 94 (in 1999) to 130 (2007) per 100,000 pyrs and then decline until 2011 Incidence Rate Ratio 2011 vs 1999, 1.11 (95%CI, 1.08-1.13), adjusted for age, sex, race Decline from the beginning of the study of admission adjusted for diabetes prevalence 30-day and 1-year mortality adjusted odds ratios, 2010 vs 1999: 0.87 (95%CI, 0.81-0.95) and 0.82 (0.78-0.85), respectively 30-day readmission adjusted odds ratios, 2010 vs 1999: 0.93 (0.89-0.97) Older age significant risk factor for length of stay and mortality
McEwan P *BMJ Open Diabetes Research and Care 2015;3:e000057*	England	General Practice Research Database linked to Hospital Episode Statistics database People ≥18 years old	1/1/2002 30/10/2012	Hospital admissions for hypoglycaemia in insulin-treated patients Length of hospital stay In-hospital mortality following the episode	1490 hospitalisation contributed by 1131 patients Mean length of stay 11.9 days Older age significant risk factor for length of stay and mortality
Pathak RD † *Diabetes Care 2016;39:363–70*	US	Insured diabetes patient cohort with data from electronic health records in the US outside of the Veterans Administration (SUPREME-DM DataLink) People ≥20 years old	1/1/2005 31/12/2011	ED or hospitalization visits for hypoglycaemia	Hypoglycaemia rate range: 136-159 per 10,000 pyrs with diabetes No clinically meaningful rate trend during the study period Older age significant risk factor for ED visit and hospitalisation

Table A2 (cont'd) | Selected similar studies reporting on emergency treatment or hospital admissions for hypoglycaemia*					
First author (*Ref*)	**Country**	**Data source**	**Period**	**Outcome**	**Main findings**
Veronese G *Nutr Metab Cardiovasc Dis. 2016; Jan 18 [Epub]*	Italy	All cases with an acceptance diagnosis of hypoglycaemia collected by 46 EDs (HYPOTHESIS study) People ≥18 years old	1/2011 6/2012	ED or hospitalization visits for hypoglycaemia	3,516 ED visits (52% admitted via emergency ambulance) 49.8%, 17.2%, and 33.1% were discharged, received short-term observation (<24h), and were admitted to hospital, respectively Older age significant risk factor for ED visit and hospitalisation
Wang J † *PLoS One 2015; 10:e0134917*	US	Agency for Healthcare Research and Quality's Nationwide Emergency Department Sample for ED visits and National Health Interview Survey for diabetes prevalence People ≥18 years old	2006 2011	ED visits for hypoglycaemia	ED visits decline from 308,232 in 2006 to 282,254 in 2011 22% age-adjusted rate decline, from 1.8 to 1.4 per 100 persons with diabetes Older age significant risk factor for ED visits

* Studies with observation ending at least in 2006
† Studies assessing temporal trends

ED: Emergency department
Pyrs: Person-years

Appendix B

Table B1: ICD-10 codes for hypoglycaemia in control admissions, by position

ICD code			
Position	**Hypoglycaemia**	**Reported**	**%**
1	0	304425	0.000
2	1381	300166	0.460
3	868	287428	0.302
4	602	261416	0.230
5	409	223044	0.183
6	241	178873	0.135
7	153	135759	0.113
8	113	98802	0.114
9	57	71126	0.080
10	56	49635	0.113
11	35	34291	0.102
12	21	23461	0.090
13	18	14562	0.124
14	5	6484	0.077
15	1	2237	0.045
16	1	1587	0.063
17	1	960	0.104
18	0	661	0.000
19	0	461	0.000
20	1	312	0.321

ICD-10 codes for hypoglycaemia: E160, E161, E162

Details of supplementary analysis by diabetes type

For this analysis, I first explored the accuracy of diabetes type in this HES database.

In the initial database of 405,900 admissions in 344,696 patients, I investigated consistency of diabetes coding by assessing how many admissions reported E10+ or E11+. I found that 204 admissions in 200 patients reported both diabetes codes; therefore I excluded all admissions (i.e., also those reporting a single code) of these patients from the database (402 total admissions excluded).

Among the remaining 405,498 admissions in 344,496 patients, there were 299,345 patients who had a single admission and 45,151 patients with two or more admissions. In these readmitted patients, I assessed consistency of diabetes coding over multiple admissions. Table B2 shows that 86.1% (38,854 patients) had a consistent coding while the reaming 13.9% (6,297 patients) had at least one change.

Table B2: Consistency of diabetes type coding in multiple admissions

Number of times diagnosis code changed	Number of patients	%	Cumulative %
0	38,854	86.1	86.1
1	5,121	11.3	97.4
2	925	2.1	99.4
3	147	0.3	99.8
4	56	0.1	99.9
5	24	0.1	100.0
6	18	0.0	100.0
7	3	0.0	100.0
8	1	0.0	100.0
9	1	0.0	100.0
12	1	0.0	100.0
Total	**45,151**	**100**	**-**

As a final step, all 17,718 admissions of patients with inconsistent diagnosis from the initial 405,498 admissions were excluded, leaving 387,780 admissions in 338,199 participants for the analyses (Figure B2).

Figure B1 | Flow chart of sample size determination process for analyses stratified by diabetes type

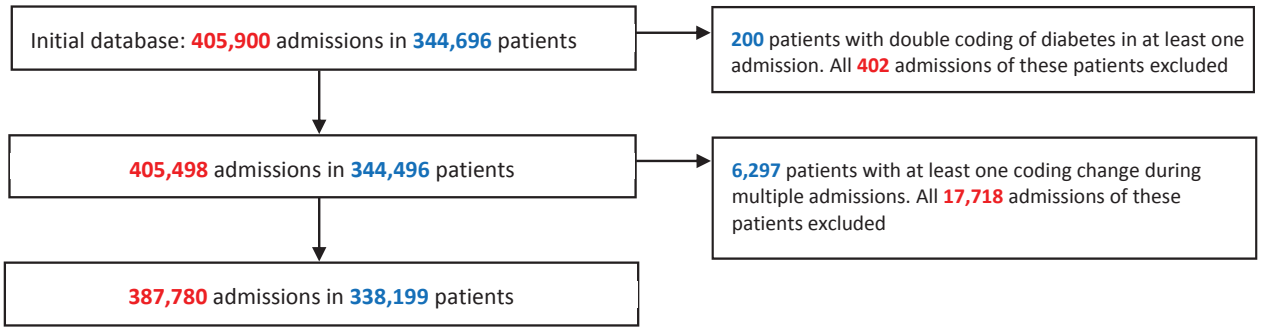
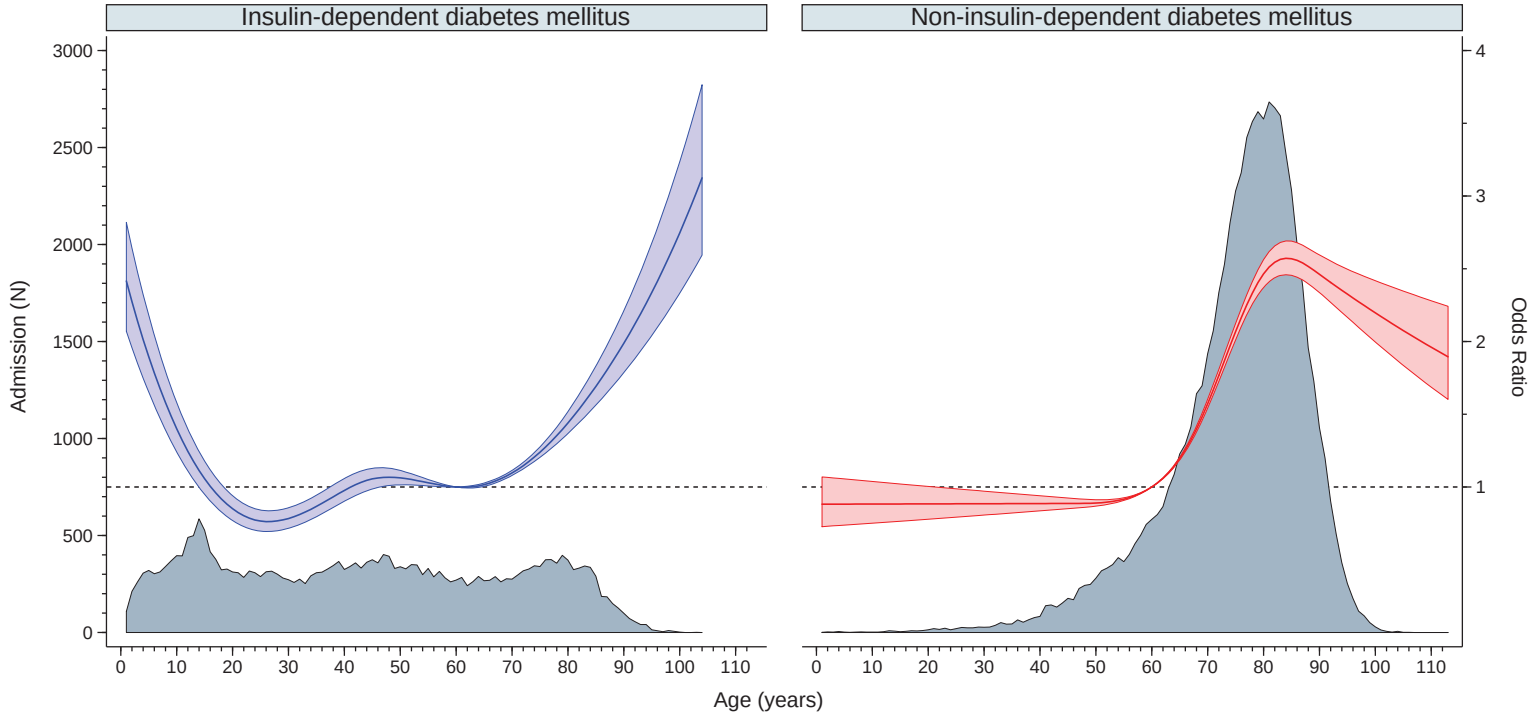


Table B3: Characteristics of hospital admissions for hypoglycaemia and non-hypoglycaemia, by diabetes type

Characteristic	Insulin-dependent diabetes mellitus		Non-insulin-dependent diabetes mellitus	
	Hypo	Non-hypo	Hypo	Non-hypo
Admissions (N)	28740	31701	62849	264490
Age at admission (Years)				
<20	6876 (23.9)	6089 (19.2)	82 (0.1)	242 (0.1)
20-29	3028 (10.5)	3974 (12.5)	208 (0.3)	1143 (0.4)
30-39	3006 (10.5)	3745 (11.8)	491 (0.8)	4438 (1.7)
40-49	3577 (12.5)	4310 (13.6)	1709 (2.7)	15039 (5.7)
50-59	3138 (10.9)	3738 (11.8)	3950 (6.3)	30957 (11.7)
60-69	2708 (9.4)	3571 (11.3)	8853 (14.1)	53259 (20.1)
70-79	3406 (11.9)	3789 (12.0)	21271 (33.8)	80403 (30.4)
≥80	3001 (10.4)	2485 (7.8)	26285 (41.8)	79009 (29.9)
Sex				
Females	13033 (45.3)	15222 (48.0)	32044 (51.0)	124150 (46.9)
Males	15707 (54.7)	16478 (52.0)	30804 (49.0)	140333 (53.1)
Charlson score	1.55 ± 1.10	1.79 ± 1.32	2.25 ± 1.56	2.30 ± 1.59
IMD-10				
Least deprived 10%	1765 (6.2)	2191 (6.9)	3104 (4.9)	16135 (6.1)
Less deprived 10-20%	1992 (6.9)	2418 (7.6)	4059 (6.5)	19308 (7.3)
Less deprived 20-30%	2267 (7.9)	2529 (8.0)	4586 (7.3)	21252 (8.1)
Less deprived 30-40%	2347 (8.2)	2723 (8.6)	5190 (8.3)	23091 (8.7)
Less deprived 40-50%	2496 (8.7)	2934 (9.3)	5828 (9.3)	24651 (9.3)
More deprived 10-20%	3843 (13.4)	4096 (13.0)	8782 (14.0)	34213 (13.0)
More deprived 20-30%	3411 (11.9)	3725 (11.8)	7799 (12.4)	30919 (11.7)
More deprived 30-40%	3131 (10.9)	3338 (10.6)	6697 (10.7)	28193 (10.7)
More deprived 40-50%	2888 (10.1)	3165 (10.0)	6219 (9.9)	26684 (10.1)
Most deprived 10%	4555 (15.9)	4522 (14.3)	10523 (16.8)	39713 (15.0)
Ethnicity				
African (Black or Black British)	233 (0.8)	239 (0.8)	492 (0.8)	1772 (0.7)
Bangladeshi (Asian or Asian British)	57 (0.2)	98 (0.3)	474 (0.8)	2399 (0.9)
Caribbean (Black or Black British)	327 (1.1)	409 (1.3)	2573 (4.1)	4632 (1.8)
Indian (Asian or Asian British)	413 (1.4)	633 (2.0)	1999 (3.2)	8383 (3.2)
Not available	2278 (7.9)	3113 (9.8)	3953 (6.3)	21055 (8.0)
Other	933 (3.3)	1090 (3.4)	2206 (3.5)	8922 (3.4)
Pakistani (Asian or Asian British)	425 (1.5)	529 (1.7)	1146 (1.8)	7293 (2.8)
White	24074 (83.8)	25590 (80.7)	50006 (79.6)	210034 (79.4)

Data reported as mean ± standard deviation or number (percentage); IMD-10 (Index of Multiple Deprivation) score in deciles
All characteristic variables were statistically different ($p<0.001$) comparing hypoglycaemia *vs* non-hypoglycaemia for insulin-dependent and non-insulin-dependent diabetes

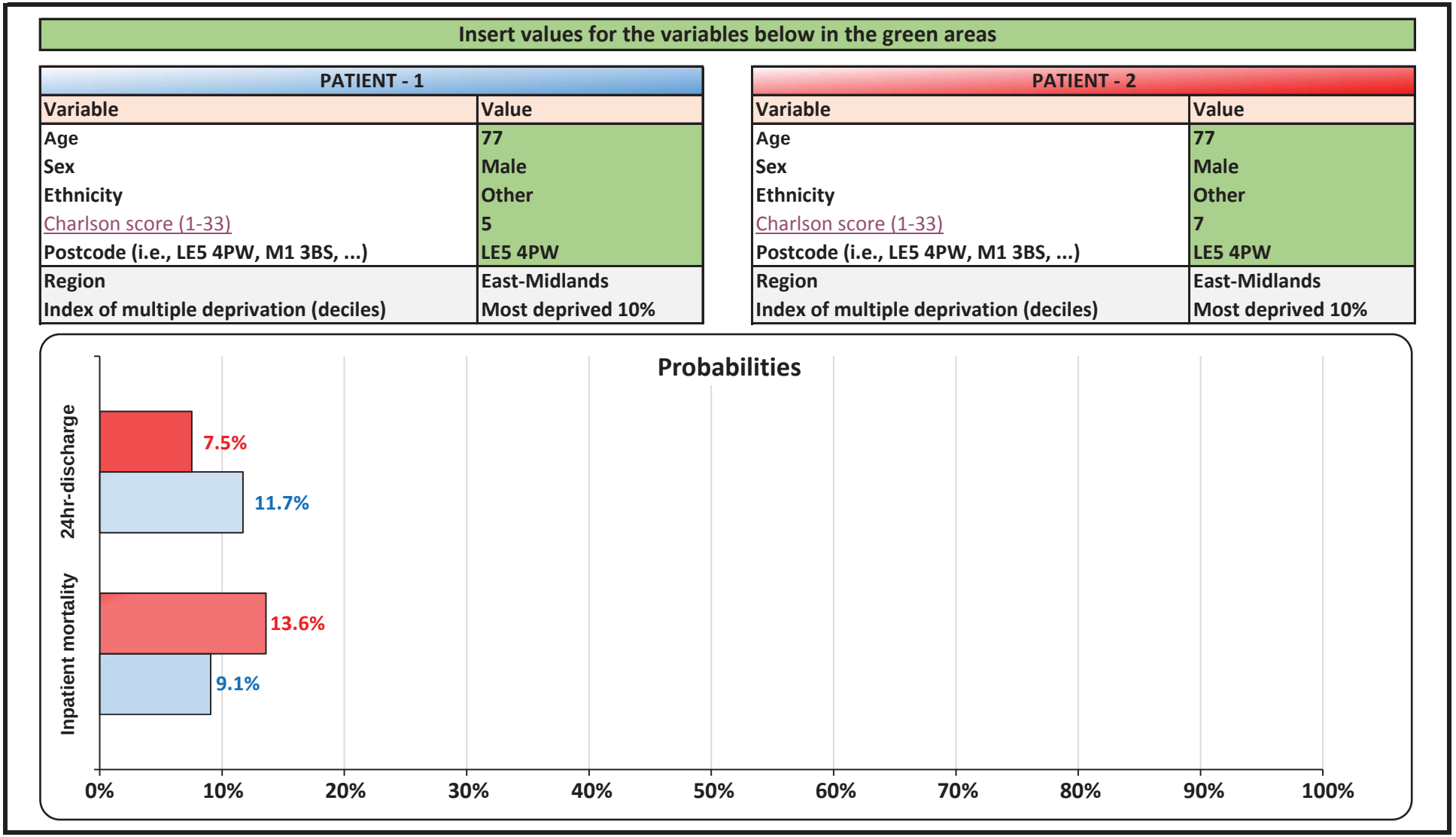
Figure B2 | Age-specific odds ratios of hospital admission for hypoglycaemia, by diabetes type



Estimates, adjusted for sex, ethnicity, IMD-10, Charlson score, and calendar year, are reported comparing admissions for hypoglycaemia vs non-hypoglycaemia. The line indicates age-specific odds ratios relative to age 60 years old with 95%CI (shadow). Grey areas show absolute number of admissions for hypoglycaemia.

Appendix C

Figure C1: Example of individual risk estimates for two patients



In this example, the two patients differ only for Charlson score (5 for patient-1 and 7 for patient-2); such difference results in dissimilar probabilities of being discharged in 24hrs and of in-hospital death. This example also illustrates how different values of a single variable can impact on the absolute risk of the two outcomes. In the Excel file, values can be modified to dynamically assess the changes of the absolute risks.

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Appendix F

Table F1: Hazard ratios for ventricular fibrillation/tachycardia according to quartiles of baseline fasting plasma glucose in progressive multivariable-adjusted models

	Fasting plasma glucose (mmol/l)			
Quartiles	**Quartile 1st**	**Quartile 2nd**	**Quartile 3rd**	**Quartile 4th**
Mean [Min-Max]	**4.1 [3.2-4.3]**	**4.4 [4.4-4.5]**	**4.7 [4.6-4.9]**	**5.3 [5.0-6.2]**
Progressive adjustment				
Age	1.00 (0.69, 1.44)	0.77 (0.44, 1.33)	0.89 (0.60, 1.34)	0.56 (0.29, 1.07)
Systolic blood pressure	1.00 (0.69, 1.46)	0.72 (0.42, 1.24)	0.84 (0.56, 1.25)	0.49 (0.25, 0.93)
LDL cholesterol	1.00 (0.69, 1.46)	0.72 (0.42, 1.24)	0.84 (0.56, 1.25)	0.48 (0.25, 0.93)
Smoking	1.00 (0.69, 1.46)	0.72 (0.42, 1.24)	0.84 (0.57, 1.26)	0.49 (0.25, 0.94)
HDL cholesterol	1.00 (0.69, 1.46)	0.72 (0.42, 1.23)	0.84 (0.56, 1.26)	0.49 (0.25, 0.94)
Log_e C-reactive protein	1.00 (0.69, 1.46)	0.71 (0.41, 1.22)	0.84 (0.56, 1.25)	0.48 (0.25, 0.92)
Body mass index	1.00 (0.68, 1.47)	0.69 (0.40, 1.18)	0.80 (0.53, 1.18)	0.44 (0.23, 0.85)
Log_e alcohol consumption	1.00 (0.66, 1.51)	0.57 (0.31, 1.06)	0.76 (0.49, 1.16)	0.40 (0.20, 0.81)
Log_e triacylglycerols	1.00 (0.66, 1.51)	0.57 (0.31, 1.06)	0.75 (0.49, 1.14)	0.38 (0.19, 0.78)
Ischaemic heart disease	1.00 (0.66, 1.51)	0.58 (0.31, 1.08)	0.75 (0.49, 1.14)	0.39 (0.19, 0.78)
Glomerular filtration rate	1.00 (0.65, 1.54)	0.59 (0.32, 1.01)	0.79 (0.52, 1.22)	0.40 (0.19, 0.82)
β-blockers use	1.00 (0.65, 1.53)	0.62 (0.33, 1.16)	0.79 (0.52, 1.22)	0.41 (0.20, 0.83)
Serum sodium	1.00 (0.65, 1.53)	0.63 (0.34, 1.17)	0.76 (0.49, 1.17)	0.42 (0.20, 0.85)
Serum potassium	1.00 (0.65, 1.53)	0.64 (0.34, 1.19)	0.76 (0.48, 1.18)	0.42 (0.21, 0.85)

The table indicates the number of variables included in the models (i.e., the first model is only age-adjusted, the second is adjusted for age and systolic blood pressure, the final is adjusted for all variables). Number of participants by quartile is reported in Table D1. Log_e: natural logarithm

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