The use and safety of oral anticoagulants in patients with type 2 diabetes mellitus in the UK

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Declaration

I, Hassan H Alwafi confirm that the work presented in this report is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

Type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CVDs) often coexist. Oral anticoagulants (OACs) are prescribed for the management of CVDs. However, the safety of OACs in T2DM patients remains unclear. This PhD research aimed to evaluate the use and safety of OACs in T2DM patients.

The Health Improvement Network primary care database of the United Kingdom was used to achieve the project aims. Firstly, a systematic review and meta-analysis were conducted to review the literature. Secondly, a drug utilisation study was conducted to evaluate the prescribing of OACs in T2DM. Then, two studies were conducted to explore the epidemiology and treatment of AF in T2DM. Finally, an analytical cohort study using the propensity score and Cox regression models was conducted to investigate the safety of the use of OACs and oral hypoglycaemic agents (OHAs) in T2DM.

The pooled average of the prevalence of hypoglycaemia in diabetes was 11.0% (95% confidence intervals, 7.0% – 17.0%). The prevalence of OACs prescribing increased by 50.8% from 4.4% (4.2% – 4.6%) in 2001 to 6.6% (6.5% – 6.7%) in 2015. The prevalence of AF increased from 2.7% (2.5% – 2.8%) in 2001 to 5.0% (4.9% – 5.1%) in 2016. T2DM patients with AF, aged 60-79, males, and BMI ≥25, were more likely to receive OAC. The cohort study results showed that compared with sulfonylurea only, concurrent use of warfarin and sulfonylureas, increased the risk of hypoglycaemia and

bleeding, (HR 1.38, (1.10 – 1.75)), (HR 1.12, (1.01 – 1.24)), respectively. However, there was no association between the use of DOACs and sulfonylureas concurrently and the risk of hypoglycaemia, (HR 0.54, (0.27 – 1.10)).

In conclusion, the prevalence of AF and the use of OACs in T2DM patients have increased over the last decade. T2DM patients are at a higher risk of developing serious adverse events when warfarin and sulfonylureas are used concurrently.

Thesis overview

This thesis summarises the work that has been conducted during the past three years. It includes an introduction to the topic of this PhD, a systematic review of the literature through which a knowledge gap was identified, and it includes details of the studies that were conducted during this PhD project. An outline of the objectives and studies for this PhD work is shown below (Figure 1). Details of the studies are available in further chapters of this thesis.

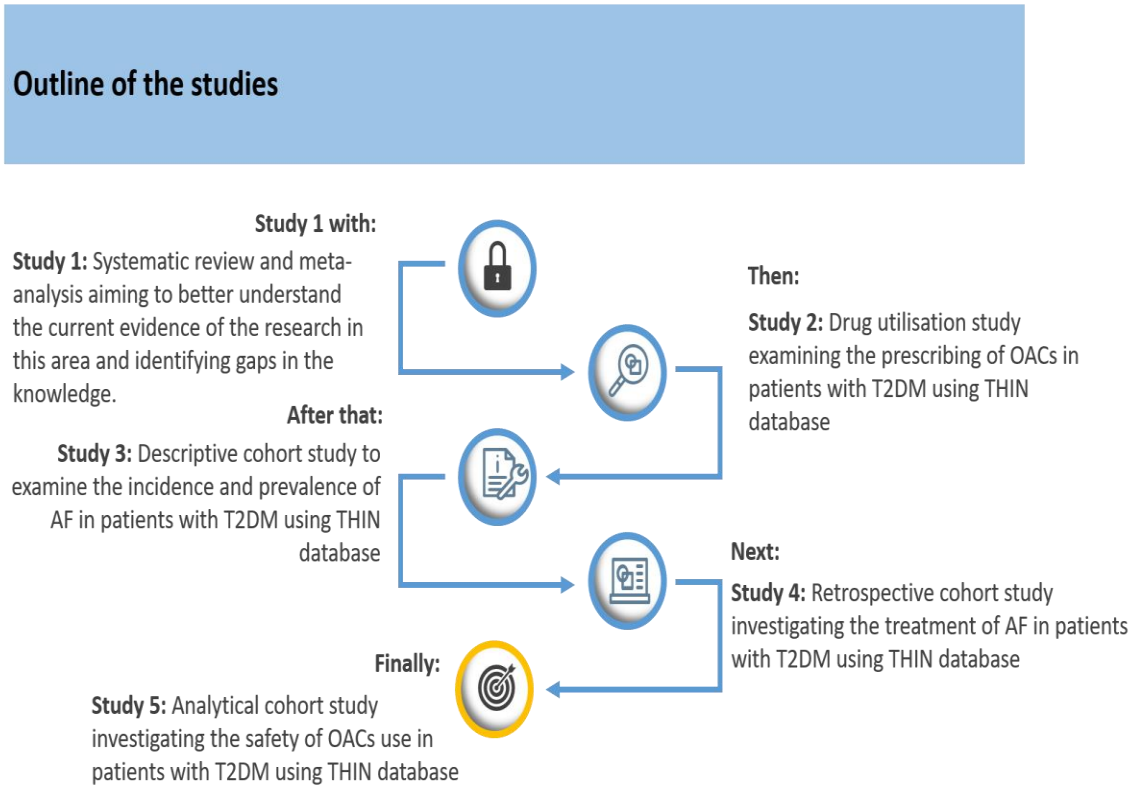

Figure 1: An outline of the studies for this PhD work

Impact of this PhD project

The studies presented in this thesis may have the potential to be beneficial to both clinical practice and academia. This PhD project highlighted that hypoglycaemia is a very common event in patients with Type 2 Diabetes Miletus (T2DM). Doctors and health care providers should be aware of the risk factors associated with hypoglycaemia and raise awareness among their patients about the different strategies to prevent hypoglycaemia. This research highlighted that the prevalence of atrial fibrillation (AF) and the use of oral anticoagulants (OACs) in patients with T2DM are increasing, particularly among male patients and the older population. In addition, this PhD project demonstrated the underuse of OACs in patients with AF and T2DM. However, since the introduction of direct oral anticoagulants (DOACs) in 2011, the initiation rate of OACs in patients with T2DM and AF has increased significantly. The findings of this PhD project have several potential impacts/influences on current clinical practice, including 1) informing health policy about the co-existence of T2DM and AF; 2) raising awareness about the clinical practice of clinicians, and 3) supporting adherence to NICE guidelines (CG180) which were updated in 2014. In addition, the results of this PhD project could help future researchers to gain a better understanding of the characteristics and directions of these two common disease populations. The findings reported in this thesis can make health care providers aware of possible drug-to-drug interactions (e.g. concurrent use of OACs and oral hypoglycaemic agents) that may lead to serious medical complications, including hypoglycaemia and bleeding.

This can ultimately support and guide them to prescribe the optimal therapy for patients with T2DM, and to avoid one of the most common complications of OACs, i.e. bleeding. Doctors, pharmacists and other health care providers must be aware of such interactions for the safety of their patients and must be vigilant when prescribing these medications concurrently.

Future research could be developed from the findings and the limitations highlighted in this PhD project. This could include: 1) applying the same methodologies and replicating the studies on different populations to validate the results of this project; 2) replicating the methodologies that have been used in this project by conducting a study on a larger scale on patients using DOACs; 3) replicating the same methodology to investigate the effect of OAC medications in reducing cardiovascular incidents such as stroke and heart attacks; 4) applying the same methodologies (analytical and descriptive studies from clinical perspectives) to other life-threatening and costly adverse drug events; 5) conducting further qualitative studies to explore factors affecting doctors' practice linked to adverse drug reactions, and 6) conducting further qualitative studies to explore factors affecting patients' problem-solving abilities, awareness and strategies that could decrease the incidence of experiencing adverse drug events in patients with T2DM, specifically hypoglycaemia or bleeding.

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Abbreviations

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	Angiotensin converting enzyme
ACEI	Angiotensin converting enzyme inhibitor
ADA	American diabetes association
AHD	Additional health data
ADE	Adverse drug events
ADR	Adverse drug reaction
AHD	Additional health data
AF	Atrial fibrillation
AMR	AMR
ARBs	Angiotensin II receptor blockers
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in AF
BARC	Bleeding Academic Research Consortium
BB	Beta blocker
BMI	Body mass index
BNF	British National Formulary

CABG	coronary artery bypass graft
CCB	Calcium channel blocker
CHA_2DS_2	Congestive heart failure, Hypertension, Age≥75 years, Diabetes mellitus, previous Stroke/transient ischaemic attack
CHA_2DS_2-VASc	Congestive heart failure, Hypertension, Age≥75, Diabetes, Stroke, Vascular disease, Age 65–74 and Sex category (female)
CI	Confidence interval
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CNS	Central nervous system
CT	Computed tomography
CVA	Cerebro vascular accident
CVD	Cardiovascular disease
CPRD	The Clinical Practice Research Datalink
CYP 450	Cytochrome P450
CYP2C9	Cytochrome P2C9
DC	Decilitre
DDP-4	Dipeptidyl peptidase-4
DM	Diabetes mellitus
DOACs	Direct oral anticoagulants
DUS	Drug utilisation study

DVT	Deep vein thrombosis
EMA	European medicine agency
EHRs	Electronic health records
ENGAGE AF-TIMI 48	The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48
FBS	Fasting blood glucose
FDA	Food and Drug Administration
FFA	Free fatty acids
GIB	Gastrointestinal bleeding
GLP-1	Glucagon-like peptide-1
GP	General practitioner
GPRD	General Practice Research Database
HbA1c	Glycated haemoglobin A1c
HHS	Hyperosmolar hyperglycaemic state
HIV	Human immunodeficiency virus
HR	Hazard ratio
HTN	Hypertension
ICD	International Classification of Diseases
ICH	Institute of Child Health
ICPE	International Conference on Pharmacoepidemiology and Therapeutics Risk Management

IDDM	Insulin dependent diabetes mellitus
IDF	International Diabetes Federation
INR	International normalized ratio
IR	Incidence rate
ITS	Interrupted time series analysis
KATP	ATP-sensitive potassium channel
L	Litre
MODY	Maturity-onset diabetes among young people
MG	Milligram
MOOSE	Meta-analysis of Observational Studies in Epidemiology
MRI	Magnetic resonance imaging
NA	Not available
NHS	National Health Service
NIDDM	Non-insulin dependent diabetes mellitus
NICE	National Institute for Health and Care Excellence
NOAC	New oral anticoagulants
NSAIDS	Nonsteroidal anti-inflammatory drugs
OACs	Oral anticoagulants
OGTT	Oral glucose tolerance test
OHA	Oral hypoglycaemic agents
OR	Odds ratio

OTC	Over the counter
PATFLAG	Patient flag
PE	Pulmonary embolism
PG	Plasma glucose
PPARs	Peroxisome proliferator-activated receptors
PPIOAC	Proportions of patients with T2DM who initiated OAC
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PROSPERO	Prospective register of systematic reviews
PUD	Peptic ulcer disease
PVD	Peripheral vascular disease
PY	Patients years
RCT	Randomised clinical trial
RE-LY	Randomized Evaluation of Long-term Anticoagulant Therapy)
ROCKET	Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation
RR	Relative risk
SD	Standard deviation
SCCS	Self-controlled case series
SE	Standard error

SGLT2	Sodium-glucose linked transporter Inhibitors
SoP	School of Pharmacy
SUs	sulfonylureas
SRC	Scientific Review Committee
STROBE	Strengthening the reporting of observational studies in epidemiology
THIN	The Health Improvement Network
TTT	Treatment regimen
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
UK	United Kingdom
UKPDS	The UK Prospective Diabetes Study
VKA	Vitamin K antagonists
UCL	University College London
US	United States
VTE	Venous thromboembolism

Disseminated work from this thesis

Publications:

- Three manuscripts have been published based on the work conducted in this PhD project. These manuscripts are based on the content presented in chapters 2, 5, 6 and 7, and are cited below.

  1-Alwafi, H., Wei, L., Naser, A. Y., Mongkhon, P., Tse, G., Man, K. K. C., Bell, J. S., Ilomaki, J., Fang, G. & Wong, I. C. K. 2020. Trends in oral anticoagulant prescribing in individuals with type 2 diabetes mellitus: a population-based study in the UK. BMJ Open, 10, e034573.

  2-Alwafi, H., Wong, I. C. K., Banerjee, A., Mongkhon, P., Whittlesea, C., Naser, A. Y., Lau, W. C. Y. & Wei, L. 2020. Epidemiology and treatment of atrial fibrillation in patients with type 2 diabetes in the UK, 2001–2016. Scientific Reports, 10, 12468.

  3-**Alwafi, H**., Alsharif, A. A., Wei, L., Langan, D., Naser, A. Y., Mongkhon, P., Bell, J. S., Ilomaki, J., Al Metwazi, M. S., Man, K. K. C., Fang, G. & Wong, I. C. K. 2020. Incidence and prevalence of hypoglycaemia in type 1 and type 2 diabetes individuals: A systematic review and meta-analysis. Diabetes Res Clin Pract, 170, 108522.

- One manuscript based on the content of chapter 8 is being prepared for publication in a peer review journal.

Publication outside of the PhD work:

1- Naser, A. Y., Wong, I. C. K., Whittlesea, C., **Alwafi, H**., Abuirmeileh, A., Alsairafi, Z. K., Turkistani, F. M., Bokhari, N. S., Beykloo, M. Y., Al-Taweel, D., Almane, M. B. & Wei, L. 2019.Attitudes and perceptions towards hypoglycaemia in patients with diabetes mellitus: A multinational cross-sectional study. PLoS One, 14, e0222275.

2- Naser, A. Y., **Alwafi, H**. & Alsairafi, Z. 2020. Cost of hospitalisation and length of stay due to hypoglycaemia in patients with diabetes mellitus: a cross-sectional study. Pharm Pract (Granada), 18, 1847.

3- Mongkhon, P., **Alwafi, H**., Fanning, L., Lau, W. C. Y., Wei, L., Kongkaew, C. & Wong, I. C. K. 2020. Patterns and factors influencing oral anticoagulant prescription in people with atrial fibrillation and dementia: Results from UK primary care. Br J Clin Pharmacol.

4- Naser, A. Y., Dahmash, E. Z., Al-Rousan, R., **Alwafi, H**., Alrawashdeh, H. M., Ghoul, I., Abidine, A., Bokhary, M. A., Al-Hadithi, H. T., Ali, D., Abuthawabeh, R., Abdelwahab, G. M., Alhartani, Y. J., Al Muhaisen, H., Dagash, A. & Alyami, H. S. 2020. Mental health status of the general population, healthcare professionals, and university students during 2019 coronavirus disease outbreak in Jordan: A cross-sectional study. Brain Behav, 10, e01730.

5- Shabrawishi, M., Al-Gethamy, M. M., Naser, A. Y., Ghazawi, M. A., Alsharif, G. F., Obaid, E. F., Melebari, H. A., Alamri, D. M., Brinji, A. S., Al Jehani, F. H., Almaimani, W., Ekram, R. A., Alkhatib, K. H. & **Alwafi, H**. 2020. Clinical, radiological and therapeutic characteristics of patients with COVID-19 in Saudi Arabia. PLoS One, 15, e0237130.

6- Naser, A. Y., Alsairafi, Z., **Alwafi, H**., Mohammad Turkistani, F., Saud Bokhari, N., Alenazi, B., Zmaily Dahmash, E. & Alyami, H. S. 2021. The perspectives of physicians regarding antidiabetic therapy de-intensification and factors affecting their treatment choices-A cross-sectional study. Int J Clin Pract, 75, e13662.

Conference presentations:

I have presented work from this thesis in national and international conferences. A break-down of these posters is listed in the following;

1-British Journal of Clinical Pharmacology “Pharmacology 2019”. Edinburgh, United Kingdom, 15-17 December 2019.

Abstract tittle: Trends in oral anticoagulant prescribing in individuals with type 2 diabetes mellitus: a population-based study in the UK.

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2- The 35th International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ICPE 2019). Pennsylvania, United States, 24 - 28 August 2019.

Abstract tittle: Trends in oral anticoagulant prescribing in individuals with type 2 diabetes mellitus: a population-based study in the UK.

3- The 4th Scientific Meeting for Medication Safety. "Reducing Burden of Prescription Drugs". Riyadh, Saudi Arabia, 29 November 2018.

Abstract tittle: Trends in oral anticoagulant prescribing in individuals with type 2 diabetes mellitus: a population-based study in the UK.

4- The 18th Annual Meeting of the International Society of Pharmacovigilance (ISOP) ‘‘Pharmacovigilance without borders’’. Geneva (Switzerland), 11-14 November 2018.

Abstract tittle: Prevalence and Risk Factors of Hypoglycaemia in Diabetes Patients: Systematic Review and Meta-analysis of Observational Studies.

5- The 34th International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ICPE 2019). Prague, Czech Republic 22 – 26 August 2018.

Abstract tittle: Incidence and episodes of hypoglycaemia in type 2 diabetes patients: A systematic review and meta-analysis of observational studies.

Available; https://onlinelibrary.wiley.com/doi/full/10.1002/pds.4629.

6- The 34th International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ICPE 2019). Prague, Czech Republic 22 – 26 August 2018.

Abstract tittle: The rate of hypoglycaemic events in individuals with type 1 diabetes; Systematic review and meta-analysis of observational studies.

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Chapter 1 Introduction

1.1 Chapter overview

This chapter provides a detailed information for the reader about the background of type 2 diabetes (T2DM), which is the study population for the main analysis of this PhD work.

1.2 Diabetes

Diabetes mellitus is one of the most common chronic diseases in the United Kingdom (UK) and worldwide and has become a major global public health concern (Ogurtsova et al., 2017). It represents a group of metabolic diseases whose characteristics include increased blood sugar levels (hyperglycaemia) that result from a defect in the normal physiological function of insulin (National Institute for Health and Care Excellence, 2015). Diabetes is caused by different mechanisms; these include deficiency of insulin secretion and insulin resistance (American Diabetes Association, 2018a). The long-term effect of hyperglycaemia is associated with an increased risk of developing organ damage and different macro and microvascular complications, including: cardiac, renal and retinal complications (American Diabetes Association, 2018a).

1.2.1 Prevalence

The prevalence of the disease has significantly increased over the last 30 years. According to the International Diabetes Federation (IDF) report in 2019 (International Diabetes Federation, 2019), it is estimated that 463 million people in the world are

living with diabetes, compared with 30 million in 1985 (International Diabetes Federation, 2019). In the UK, the prevalence of diabetes cases has doubled over the last three decades (Sharma et al., 2016, Zghebi et al., 2017). In 2019, It was estimated that around 4 million people in the UK have diabetes, and 90% of those were diagnosed with T2DM diabetes mellitus (Diabetes UK, 2019). In 2015, the National Institute for Health and Care Excellence (NICE) guidelines reported that in England, diabetes prevalence has increased by 53% between 2006 and 2013 (National Institute for Health and Care Excellence, 2015). According to the NICE guidelines in 2015, around 6.7% of the population of England has diabetes (National Institute for Health and Care Excellence, 2015). Using a national health database in the UK, Sharma et al. estimated a rise in diabetes prevalence from 2.39 % in 2000 to 5.32 % in 2013 (Sharma et al., 2016), with similar results being reported in different studies in the UK (Gonzalez et al., 2009, Zghebi et al., 2017). The life expectancy of patients with diabetes is affected by diabetes complications and it is shortened by up to 15 years compared to the general population (National Institute for Health and Care Excellence, 2015).

1.2.2 Pathophysiology

The pathophysiology of the disease involves different pathogens; these include autoimmune destruction of the pancreatic beta-cells resulting in the deficiency of insulin secretion and others, including abnormalities which cause a reduction in the sensitivity and resistance to insulin action (American Diabetes Association, 2018a).

Inadequate secretion of insulin and reduced response of tissues to insulin at certain points in the complex mechanism of hormonal action causes the deficient insulin actions and the increased level of blood sugar (American Diabetes Association, 2018a). Different pathogens are related to different types of diabetes mellitus and the disease can be classified according to these pathogeneses.

1.2.3 Classification

For many years, diabetes was classified into two main categories: insulin dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM) (American Diabetes Association, 2018a). However, this has been changed into a classification based on the etiology of the disease (Who, 1999). The general categories of the current classifications are: type 1 diabetes mellitus (T1DM), T2DM, gestational diabetes mellitus, and specific types of diabetes due to other causes (Genuth et al., 2003).

T1DM is the result of the destruction of beta-cells, which leads to the absolute deficiency of insulin (American Diabetes Association, 2018a, Genuth et al., 2003). It is an autoimmune disease and is often related to genetic or environmental factor. T2DM is the result of a progressive process of insulin secretion defect coupled with insulin resistance (Genuth et al., 2003, American Diabetes Association, 2018a). It represents about 90% of diabetes cases, and it is related to different environmental and lifestyle causes, as well as physical inactivity and obesity (American Diabetes Association, 2018a, Genuth et al., 2003). Other types include gestational diabetes

mellitus, which is often diagnosed in pregnant mothers in their second or third trimesters, and in most of the cases the disease will resolve itself at the end of the pregnancy (American Diabetes Association, 2018a, Genuth et al., 2003). However, the etiology of gestational diabetes is not well understood. Other types are specific, each having their own causes (American Diabetes Association, 2018a). These types include monogenic diabetes syndromes such as; neonatal diabetes, as well as maturity-onset diabetes among young people (MODY) (American Diabetes Association, 2018a). Others include chemical or drug-induced diabetes, which can occur in the treatment of human immunodeficiency virus (HIV) or after an organ transplant (American Diabetes Association, 2018a). It was traditionally thought that T1DM only affects children while T2DM only affects adults. However, this paradigm is no longer true as both diseases occur in both adults and children (American Diabetes Association, 2018a). Adults with T2DM may exhibit symptoms of T1DM, while in some cases children with T1DM may exhibit the symptoms of T2DM (American Diabetes Association, 2018a, Genuth et al., 2003)

1.2.4 Clinical presentation

The symptoms by which diabetes can present include polyphagia, polydipsia, polyuria, weight loss and blurred vision (National Institute for Health and Care Excellence, 2015). In addition, chronic hyperglycaemia may also be characterised by growth impairment. Patients could be at higher risk of developing infections due to their decreased immunity (American Diabetes Association, 2018a).

1.2.5 Complications

Diabetes complications could range from acute to chronic events in which the effect is not noticed for several years. Uncontrolled diabetes and high levels of blood sugar could cause acute life-threatening conditions such as ketoacidosis and hyperosmolar hyperglycaemic state (HHS). These two events are marked by high levels of hyperglycaemia; however, they differ by the presence of acidosis and the level of hyperglycaemia. Diabetic ketoacidosis is characterized by the presence of acidosis, the level of blood glucose and increased body ketones (Kitabchi et al., 2009). HHS occurs when the blood sugar level increases to dangerous levels, in some cases it reaches up to 1000mg/dL (Kitabchi et al., 2009). Hyperosmolarity, hyperglycaemia, dehydration and neurological symptoms are the characteristics of HHS (Kitabchi et al., 2009). The two events are usually treated by rehydration, correction of blood sugars to normal levels, and by replacing body electrolytes (Kitabchi et al., 2009).

In other cases, the complications of diabetes are long-term and may include macro and microvascular complications (Hemmingsen et al., 2011, Fowler, 2008). Patients with diabetes are at higher risk of developing macrovascular events such as coronary heart disease, peripheral and cerebral vascular diseases. This was highlighted in many studies including the prospective diabetes study in the UK (Hemmingsen et al., 2011). Microvascular events are also of high importance, especially as they may develop slowly and without being noticed. Microvascular events include retinopathy, which may also accompany vision loss (Fowler, 2008). Nephropathy is also a long-

term microvascular event that could lead to renal failure (Ruospo et al., 2017, Coca et al., 2012). Another long-term condition is neuropathy, which places the patient at the risk of foot ulcers (Fowler, 2008). Other complications caused by diabetes that could be identified include: autonomic neuropathy, which causes genitourinary; gastrointestinal events; and sexual dysfunction (Fowler, 2008).

Hypoglycaemia is another common complication which is mainly related to the treatment of diabetes. It is characterised by a significantly low blood sugar level (Seaquist et al., 2013). This complication may result from the instant effect of an administered drug, consumption of less food, or a sudden increase in physical activities (Seaquist et al., 2013). Hypoglycaemia is treated by fast-acting carbohydrates whenever the blood sugar level hits 70 mg/dL (Seaquist et al., 2013). Hypoglycaemia will be discussed in detail later in this dissertation

1.2.6 Diagnosis

The diagnosis of diabetes mellitus can be confirmed by different diagnostic tests. The first procedure entails the utilisation of glycated haemoglobin AIC criterion, HbA1c ≥6.5% (48 mmol/L.) (American Diabetes Association, 2018a, National Institute for Health and Care Excellence, 2015). Alternatively, two methods can be applied; the first involves a fasting blood glucose (FBS) level of at least 126 mg/l, which is equivalent to 7.0 mmol/L, within two different time intervals (American Diabetes Association, 2018a, National Institute for Health and Care Excellence, 2015).

However, for these results to be valid, an individual must have fasted for at least 8 hours before the test. The second test involves the 2-h value of the plasma glucose (2-h PG) value over 75-g score on the oral glucose tolerance test (OGTT) (American Diabetes Association, 2018a, National Institute for Health and Care Excellence, 2015). In most cases, the HbAIc test is preferred over the FPG and the OGTT because it is significantly more convenient and does not disrupt individual daily activity (American Diabetes Association, 2018a, National Institute for Health and Care Excellence, 2015). Moreover, fasting is not necessary when carrying out the test. Nonetheless, when conducting all forms of diagnosis for diabetes mellitus, in the case of an absence of unequivocal hyperglycaemia, all outcomes must be confirmed by repeat testing within 24 hours (American Diabetes Association, 2018a, National Institute for Health and Care Excellence, 2015).

1.2.7 Diabetes management

There is a wide range of diabetes management. However, the type of treatment will depend on the type of diabetes. Patients with T1DM will usually require the administration of exogenous insulin. On the other hand, patients with T2DM can be managed by a wide range of treatment, including lifestyle modifications and pharmacological treatment. Prevention of T2DM is a very important strategy in the management of the disease; this has been recommended by many guidelines and by consensus (American Diabetes Association, 2018a, National Institute for Health and Care Excellence, 2015). Physical activity, exercise, diet control and weight reduction

are among the most important methods to prevent diabetes or to control the disease (National Institute for Health and Care Excellence, 2015).

1.2.7.1 Pharmacological treatment of T2DM

Multiple classes of medications are available for the treatment of T2DM. Doctors follow the national or international guidelines for the medical management; however, some patients require tailoring of the treatment, and in such cases, doctors can choose from different classes of medications (America Diabetes Association, 2017, National Institute for Health and Care Excellence, 2015, Chaudhury et al., 2017). T2DM medications can be classified into insulin and oral hypoglycaemic agents (OHAs) (non-insulin). OHAs include; biguanides, sulfonylureas, acrobose, meglitinides, thiazolidinedione, dipeptidylpeptidase-4 inhibitors, sodium glucose co-transporter 2 inhibitors and glucagon-like peptide-1 receptor agonists (Chaudhury et al., 2017, National Institute for Health and Care Excellence, 2015).

Biguanides

Metformin is the only available agent in this drug class and is also the first line therapy for the treatment of T2DM, as recommended by the guidelines (American Diabetes Association, 2018a, National Institute for Health and Care Excellence, 2015, Sharma et al., 2016). It is also the most prescribed medication for the treatment of T2DM (Sharma et al., 2016) . This drug works by increasing the sensitivity of the body tissues

to insulin (Viollet et al., 2012). As such, administration of the drug enables the body to utilise insulin more efficiently than before (Viollet et al., 2012). Metformin also regulates the blood sugar levels by lowering the production of glucose by the liver (Viollet et al., 2012). Metformin is not metabolised by the liver, and is excreted unchanged in the urine (Graham et al., 2011). However, the administration of metformin is associated with diarrhoea and vomiting as side effects (Chaudhury et al., 2017). Also, it is contraindicated in patients with increased risk of lactic acidosis, some cases of kidney diseases where the creatinine level is > 1.7 mg/dL and in cases of cirrhotic liver disease effect (Misbin, 2004, Chaudhury et al., 2017).

Sulfonylureas

Sulfonylureas (SUs) are among the most prescribed antidiabetic medications, and in many guidelines they are recommended as a second-line therapy or addition therapy with metformin (America Diabetes Association, 2017, National Institute for Health and Care Excellence, 2015). Sulfonylureas act by lowering the blood glucose level by increasing insulin secretion in the pancreas and by blocking the ATP-sensitive potassium (KATP) channels (Proks et al., 2002). The first generation sulfonylureas (tolbutamide, tolazamide, acetohexamide and chlorpropamide) have a longer duration of action and have hypoglycaemic side effects. Second generation drugs (glibenclamide, gliclazide, glimepiride, and glipizide) are safer in terms of hypoglycaemia and studies have proven that it is as potent as the first generations (Abrahamson, 2015, Chaudhury et al., 2017). Sulfonylureas are metabolised in the

liver by the cytochrome P450 (CYP) 2C9 isoenzyme (Aquilante, 2010). The use of sulfonylureas can be associated with minor side effects such as headache, nausea and weight gain (Abrahamson, 2015). Sulfonylureas are also contraindicated in cases of liver and renal diseases (Chaudhury et al., 2017). This risk of hypoglycaemia and sulfonylureas use will be discussed in detail later in this chapter.

Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase-4 (DDP-4) inhibitors (gliptins) include alogliptin, anagliptin, gemigliptin, linagliptin, saxagliptin, sitagliptin, teneligliptin, and vildagliptin. This class of antidiabetic medication can be used as a single or added therapy (National Institute for Health and Care Excellence, 2015). They act by inhibiting the destruction of the incretins, the glucose-dependent insulin otropic peptide and GLP-1 (Thornberry and Gallwitz, 2009). DDP-4 are largely metabolised in the liver and excreted by the kidney (Except for linagliptin) (Chen et al., 2015, Chaudhury et al., 2017). This class has not been linked to a higher incidence of hypoglycaemia compared with other OHAs (Chaudhury et al., 2017). The most common side effects associated with the use of these medications are nasopharyngitis, upper respiratory tract infection, and headache (Chaudhury et al., 2017).

Thiazolidinedione

Thiazolidinedione (TZDs) include rosiglitazone and pioglitazone. They act by increasing sensitivity to insulin (Hauner, 2002). The mechanism of action of this class is by activating the nuclear transcription factor PPAR. It also facilitates glucose uptake in numerous tissues, including adipose, muscle, and liver, therefore increasing insulin sensitivity (Hauner, 2002). TZDs are metabolised in the liver through the CYP450 enzymes (Scheen, 2007). This class of antidiabetic medication is recommended to be used as an added therapy (National Institute for Health and Care Excellence, 2014). The most common side effects of TZDs are GI symptoms, fluid retention, fracture, weight gain (Chaudhury et al., 2017)

Meglitinides

This class of medication includes repaglinide and nateglinide, which are non-sulfonylurea secretagogues, and are characterised by their rapid response and short half-life. Meglitinides has a similar mechanism of action of sulfonylureas, i.e., by increasing insulin secretion (Chaudhury et al., 2017). However, the binding of meglitinides to the receptor of Beta cells of the pancreas is weaker than with sulfonylurea (Chaudhury et al., 2017). Meglitinides are metabolised in the liver through the CYP450 enzymes (Pakkir Maideen et al., 2018). The most common side effects of meglitinides are GI symptoms, gastritis and flu-like symptoms (U.S. National Library of Medicine, 2018).

Sodium-glucose linked transporter (SGLT2) inhibitors

Sodium-glucose linked transporter (SGLT2) inhibitors, including canagliflozin, dapagliflozin, and empagliflozin, are a new class of antidiabetic medication (Brown et al., 2019). Dapagliflozin was the first SGLT2 inhibitors to receive marketing authorisation by the EMA in 2012 (European Medicine Agency, 2012). It acts by blocking the reabsorption of glucose in the proximal renal tubules (Brown et al., 2019). This class could be suitable for patients who have been suffering from diabetes for a long period of time, and their pancreatic cells are no longer producing insulin (Chaudhury et al., 2017, National Institute for Health and Care Excellence, 2015). However, it is associated with a higher risk of urinary tract infection and diabetic ketoacidosis (Liu et al., 2017).

Glucagon-like peptide-1 Receptor Agonists

Glucagon-like peptide-1 receptor (GLP-1) agonists include albiglutide, dulaglutide, exenatide, liraglutide and lixisenatide (Hinnen, 2017). This class has multiple beneficial effects in diabetes including; decrease of glucagon concentrations, improve insulin sensitivity, decrease fatty acid concentrations, and decrease body weight (Hinnen, 2017). This class of antidiabetic medication is usually prescribed in combination with other anti-hyperglycaemic agents (Chaudhury et al., 2017, National Institute for Health and Care Excellence, 2015). The most common side effect of GLP1 are GI symptoms, headache and nasopharyngitis (Filippatos et al., 2014).

Alpha-Glucosidase inhibitors

This class of medication includes acarbose and miglitol. It acts by decreasing the absorption of sugar in the intestine by inhibiting the action of intestinal alpha-glucosidase receptors (Chaudhury et al., 2017). This class can be used in combination of with other OHAs (National Institute for Health and Care Excellence, 2015). However, the main advantage of this class is that they do not increase the possibility of weight gain (Hollander, 2007). The major common side effect of Alpha-Glucosidase inhibitors are flatulence and loose stools (Hollander, 2007).

1.2.7.2 Guidelines recommendation

Both The NICE guidelines (National Institute for Health and Care Excellence, 2015) and the American Diabetes Association (ADA) (America Diabetes Association, 2017) recommend similar strategies for controlling blood sugar levels. However, there are some variations regarding the intensification of treatment. Figure 2 outlines the management of T2DM in adults. The NICE guidelines recommend starting treatment with single therapy metformin for all patients who did not respond to lifestyle modification and their haemoglobin A1c (HbA1c) is > 6.5% (National Institute for Health and Care Excellence, 2015). NICE also recommends intensifying the patient's treatment with a dual therapy if the HbA1c is over >7.5% (National Institute for Health and Care Excellence, 2015), while the ADA guidelines recommend to start dual therapy only if the HbA1c is more than > 9% (America Diabetes Association, 2017).

Combination therapy usually consists of a sulfonylurea and metformin; however, selection of metformin with any of the following is possible: pioglitazone, SGLT2 inhibitor, DDP-4 inhibitor (National Institute for Health and Care Excellence, 2015). If the blood glucose level remains uncontrolled, further intensification with a triple therapy is recommended. This includes metformin with a SU and any of the following: pioglitazone, SGLT2 inhibitor, DDP-4 inhibitor. In cases where the blood glucose level is not controlled and the HbA1c is > 9 %, doctors should consider the application of injectable insulin in their treatment (National Institute for Health and Care Excellence, 2015).

In cases where metformin is contraindicated or not tolerated, a DPP-4 inhibitor or a sulfonylurea, or pioglitazone are prescribed for the initial treatment of T2DM among adult patients (National Institute for Health and Care Excellence, 2015). Even though pioglitazone is an effective drug in the management of diabetes, it is associated with the increased risk of cardiovascular conditions, bone fracture, and bladder cancer (Schernthaner et al., 2013). Adults with T2DM should adopt a lifestyle change and recommended a diet or adopt the lifestyle change, recommended diet and a single drug that does not increase the risk of hypoglycaemia.

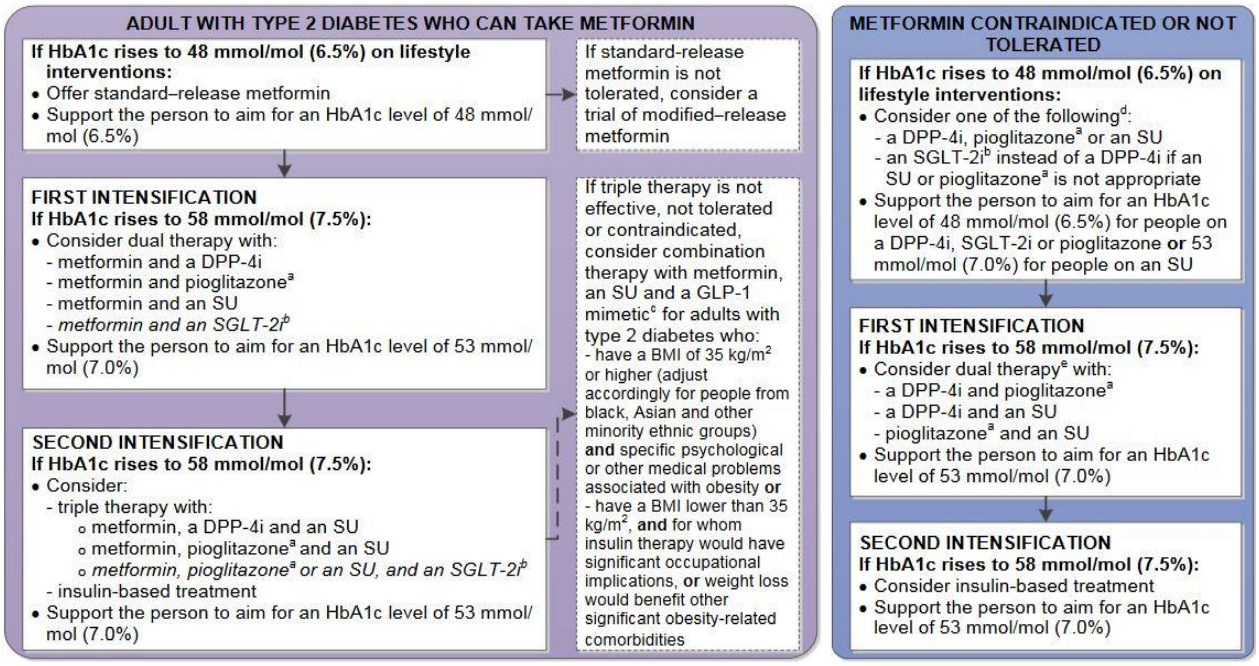

Figure 2: Management of type 2 diabetes in adults

Source of data: (National Institute for Health and Care Excellence, 2015)

SU: Sulfonylureas, DDP-4I: Dipeptidyl peptidase-4 inhibitors, SGLT2: Sodium-glucose linked transporter

1.2.8 Cost of diabetes

Diabetes is a chronic illness and is often associated with comorbidities and complications. The economic impact of diabetes is very high, and in some European countries such as; Spain and Germany diabetes expenditures can consume up to 10% of the total health expenditures (International Diabetes Federation, 2019). According to the IDF report in 2019, diabetes caused at least USD 760 billion dollars in health

expenditure in 2019 worldwide (International Diabetes Federation, 2019). The economic impact of diabetes are related to the burden of its complications, and to the indirect cost of the disease, and specifically to inpatient care and procedures due to diabetes complications such as myocardial infarction (Kanavos, 2012). In the IDF report in 2019, the direct cost of diabetes in Germany was around €43.8 billion and €20.2 [£14.1] billion in the UK (International Diabetes Federation, 2019). The United States (US) reported direct diabetes costs standing at about $327 billion in 2017 (American Diabetes Association, 2018b). Given these numbers published, the cost of diabetes is having a serious impact on the economy and health expenditures of most western countries.

1.3 Diabetes and cardiovascular diseases

T2DM patients are at a higher risk of developing macro and microvascular events such as cardiovascular diseases, diabetic retinopathy/nephropathy, and renal failure (Bailey et al., 2014, Mozaffarian et al., 2016). Cardiovascular diseases are amongst the leading causes of mortality worldwide (World Health Organization, 2018). In the UK, approximately 27% of all causes of mortality are due to cardiovascular diseases (British Heart Foundation, 2020). Diabetes and cardiovascular diseases are often coexistent, with many diabetes patients suffering from cardiovascular complications (Celis-Morales et al., 2017, Dinesh Shah et al., 2015, Movahed et al., 2005). Cardiovascular disease is associated with high rates of mortality and morbidity among patients with diabetes (White et al., 2016). Furthermore, it has been reported that

diabetes is an independent risk factor for many cardiac diseases including atrial fibrillations (Movahed et al., 2005), deep venous thrombosis (Bai et al., 2015) and strokes (Janghorbani et al., 2007), which will be discussed below.

1.3.1 **Atrial fibrillation**

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias (De Sensi et al., 2015), the disease can be associated with high rates of mortality and morbidity (Odutayo et al., 2016). The prevalence of AF is about 1.5% in the UK, the prevalence is increased with age, rising to about 9 % in the elder population (Townsend N, 2017). AF is associated with an increased risk of thromboembolic events and life-threatening emergencies (Odutayo et al., 2016).

Diabetes has been reported to be an independent risk factor that increases the risk of AF, and the association between both diseases is well documented (Pallisgaard et al., 2016, Movahed et al., 2005, Nichols et al., 2009). The Framingham study reported that diabetes was a risk factor for AF, the odds ratios were 1.4 and 1.6 for both men and women, respectively (Wolf et al., 1991). Besides this, a large cohort study on the Danish populations reported that the incidence of AF among the population with diabetes was higher compared to the general population, the incidence rate was 2.34 (95% CI, 1.52 – 3.60) (Pallisgaard et al., 2016). The prevalence of AF among patients with diabetes was about 3.5 % in Nichols's study (Nichols et al., 2009).

Diabetes and AF can be associated with serious and life-threatening complications. This association can be further explained by the fact that AF is an independent risk factor for developing thromboembolic events with a 3 fold increased risk (Lin et al., 1996), while diabetes is also an independent risk factor to develop thromboembolic events and haemorrhagic stroke (Sarwar et al., 2010). Therefore, patients diagnosed with both diseases can be at higher risk of developing serious thromboembolic events and major clinical complications.

The first-line treatment for AF is often pharmacological treatment with either rate control or anti-arrhythmic agents for rhythm control (Camm et al., 2012, January et al., 2019, National Institute for Health and Care Excellence, 2014). A key element in the management of AF is the use of oral anticoagulants (OACs) to prevent thromboembolic complications (National Institute for Health and Care Excellence, 2014). Warfarin was the most common oral anticoagulants used for the management of AF, however, since 2011, direct oral anticoagulants (DOACs) have been introduced into the market and have been replacing warfarin in the treatment of AF (Adderley et al., 2019, Alwafi et al., 2020b). OACs will be further discussed in the following sections.

1.3.2 **Venous thromboembolism**

Deep vein thrombosis (DVT) and pulmonary embolism (PE), collectively named as venous thromboembolism (VTE), can be associated with a significant morbidity and

mortality (Beckman et al., 2010). Data from the previous studies suggest that an estimated average annual incidence rate of overall VTE among persons of European ancestry ranges from 104 to 183 per 100,000 person-years (Spencer et al., 2009, Heit et al., 2016). Multiple risk factors have been indicated to increase the risk of VTE, including: cancer, trauma, recent surgery and hypercoagulability states (Kyrle and Eichinger, 2005).

Patient with diabetes are at higher risk of VTE and many patients diagnosed with VTE are suffering from diabetes (Bai et al., 2015). A study by Piazza et al, estimated that about 19.1% of patients with DVT had a history of diabetes (Piazza et al., 2012). In addition, several studies have reported that diabetes was associated with an increased risk of VTE (Bai et al., 2015, Stein et al., 2009). Diabetes is characterised by increased levels of glucose which over time may lead to a permeant damage in the blood vessels due to a poor blood supply and endothelial cells lining of the vessels that may provoke the incidence of thrombosis (Grant, 2007). Therefore, patients with diabetes can be at a high risk of developing serious thromboembolic events.

1.3.3 Stroke

Stroke is one of the leading causes of death in the UK for both males and females (Office for National Statistics, 2020), (Figure 3) and (Figure 4). Stroke can be associated with different disabilities such as vision, speech, eating, and walking difficulties (Lee et al., 2011). In the UK, there are more than 100,000 strokes new

cases each year and around 36,000 deaths each year (British Heart Foundation, 2020). The incidence of stroke was around 1.04 per 1000 patients in the UK, in 2008 (Lee et al., 2011).

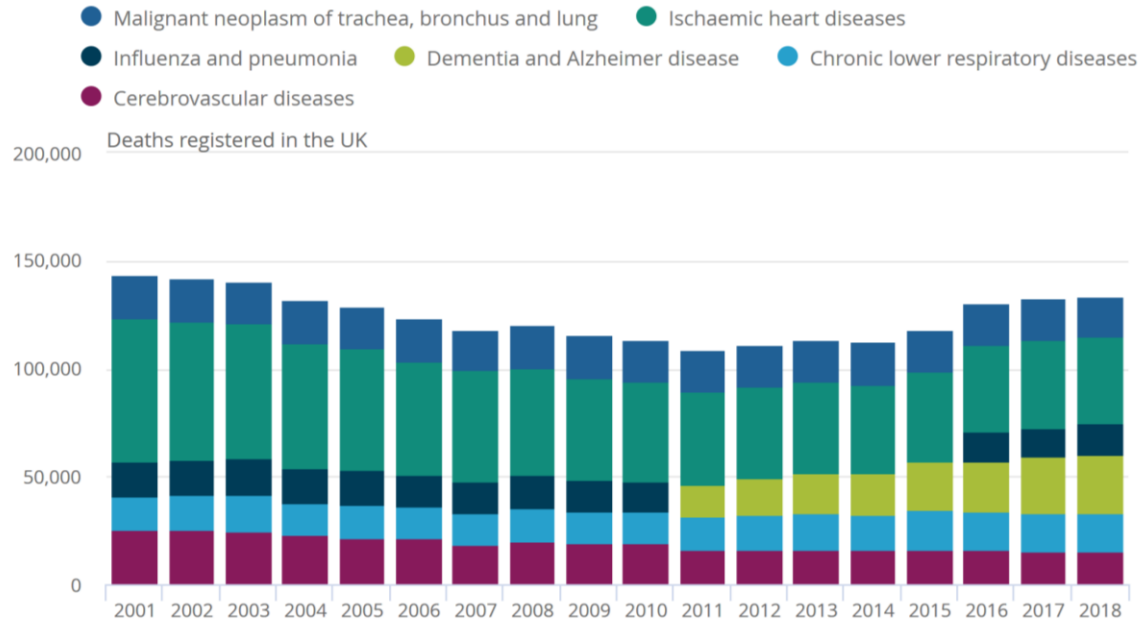

Figure 3: Deaths registered in the UK by leading causes of death, males, all ages, 2001 to 2018

Source of data: Office for National Statistics (Office for National Statistics, 2020)

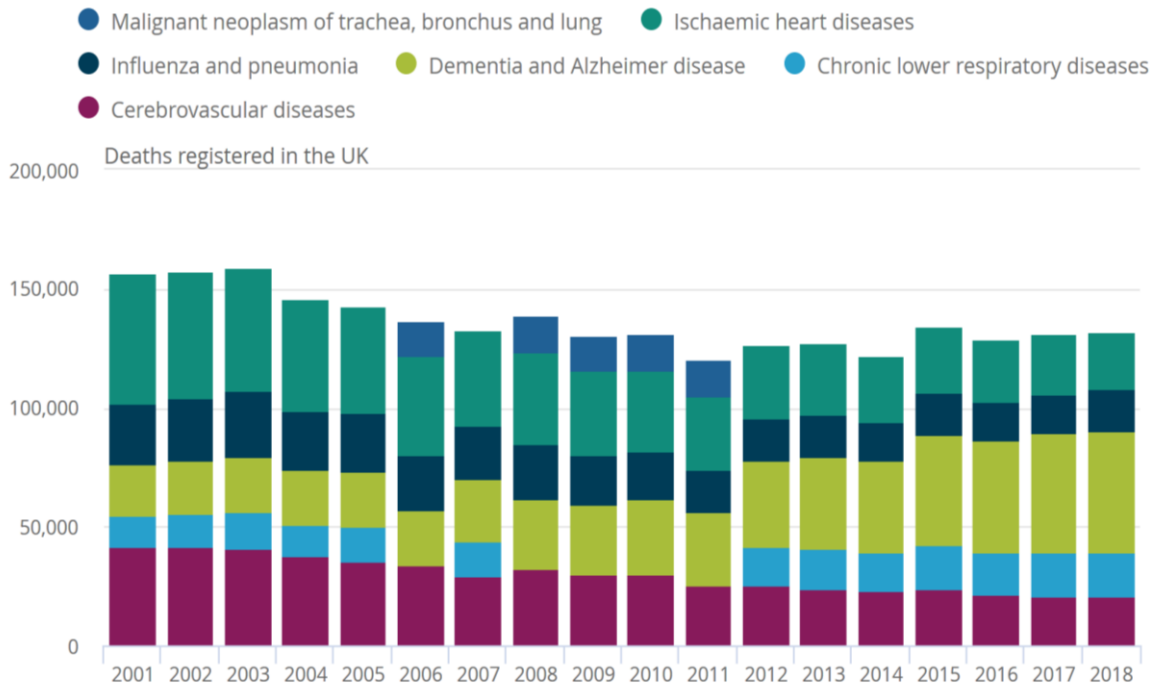

Figure 4: Deaths registered in the UK by leading causes of death, females, all ages, 2001 to 2018

Source of data: Office for National Statistics (Office for National Statistics, 2020)

Age is the single most important risk factor associated with stroke, and this risk doubles every successive 10 years after age 55 (Wolf et al., 1992). Other risk factors include: being of African American ethnicity, diabetes, hypertension, cardiac diseases, smoking, and hyperlipidaemia and oral contraceptive medications (Sacco et al., 1997). The clinical symptoms of stroke include numbness, weakness or paralysis, slurred speech, blurred vision, confusion, and severe headache (Powers et al., 2019).

Stroke can be prevented by lifestyle change and pharmacological treatment with thromboprophylaxis medications such as antiplatelets and anticoagulant drugs in

people with high risk (Antithrombotic Trialists' Collaboration, 2002, Ageno et al., 2012). For example, among patients with AF or DVT anticoagulant medications are commonly prescribed for the prevention of stroke (National Institute for Health and Care Excellence, 2014).

1.3.4 Oral anticoagulants

Oral anticoagulants (OACs) are medications that prevent the formation of blood clots in the vessels (arteries or veins) (Sugerman, 2013). The main indication for their use is for the management of AF (January et al., 2019, Ageno et al., 2012). However, it is also widely prescribed for the prevention and treatment of cardiovascular diseases, including stroke, arrhythmia, and venous and arterial thrombosis (Altiok and Marx, 2018, Loo et al., 2017).

There are different types of oral anticoagulant medications, vitamin K antagonists (VKAs) such as warfarin and non-vitamin K antagonist such as DOACs (Harter et al., 2015). In the following, types of OACs will be discussed briefly.

Vitamin K antagonists

Warfarin and other coumarins including; acenocoumarol, phenprocoumon, fluindione are used in a variety of clinical indications. These medications were discovered in more than 60 years ago, and they have been prescribed for many years as the only available OACs (Mekaj et al., 2015). However, warfarin is the most frequently used

OACs among these medications (Mekaj et al., 2015). Warfarin acts by blocking the function of the enzyme vitamin K-epoxide, which is required for the formation of the active form of vitamin K-dependent clotting factors, and thus it blocks the synthesis of vitamin K-dependent coagulation factors, including Factors II, VII, IX, X, and proteins C and S (Hirsh and Fuster, 1994), (Figure 5). Warfarin is metabolised in both the liver and kidney (Horton and Bushwick, 1999). Warfarin is known for its potential for several drug-interactions (Ament P, 2000). The use of warfarin can be associated with serious clinical complications such as bleeding due to its narrow therapeutic index (Harter et al., 2015, Alquwaizani et al., 2013). Therefore, in practice, its effect is usually monitored by international normalized ratio (INR) level while being prescribed for patients (Harter et al., 2015).

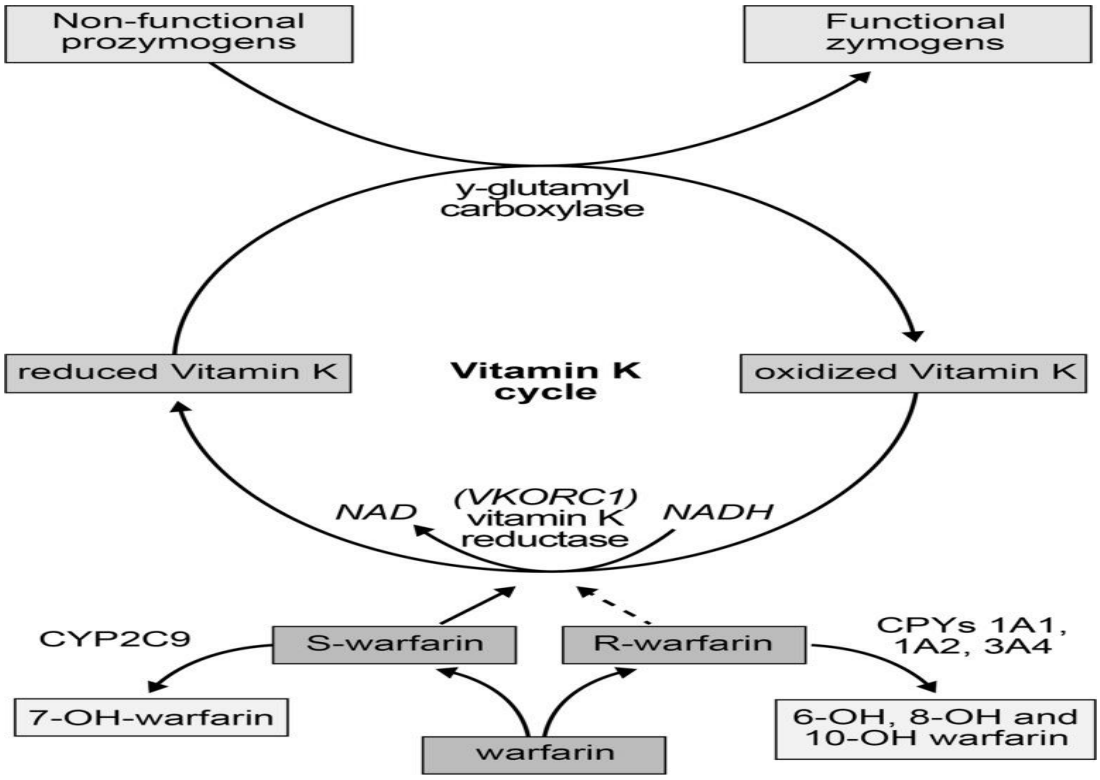

Figure 5: Pharmacology and mechanism of action of warfarin

Source of data: (Nutescu et al., 2016)

Direct oral anticoagulants

In the last 10 years, new types of oral anticoagulants, i.e., DOACs have been introduced for the treatment of different cardiovascular events, and many guidelines recommend them as a first-line therapy for the management of cardiovascular diseases (January et al., 2019, National Institute for Health and Care Excellence, 2014). Unlike warfarin, these medications are selective for one specific coagulation factor, either thrombin or activated factor Xa (Mekaj et al., 2015), (Figure 6). These include: factor Xa inhibitors, such as rivaroxaban, apixaban and edoxaban, and the

direct thrombin inhibitor, such as dabigatran (Koenig-Oberhuber and Filipovic, 2016), (Table 1). The advantages of DOACs compared to warfarin is that they have less drug-drug interactions, and they can be given with a fixed dose and therefore, they don't require regular monitoring and interactions (Altiok and Marx, 2018).

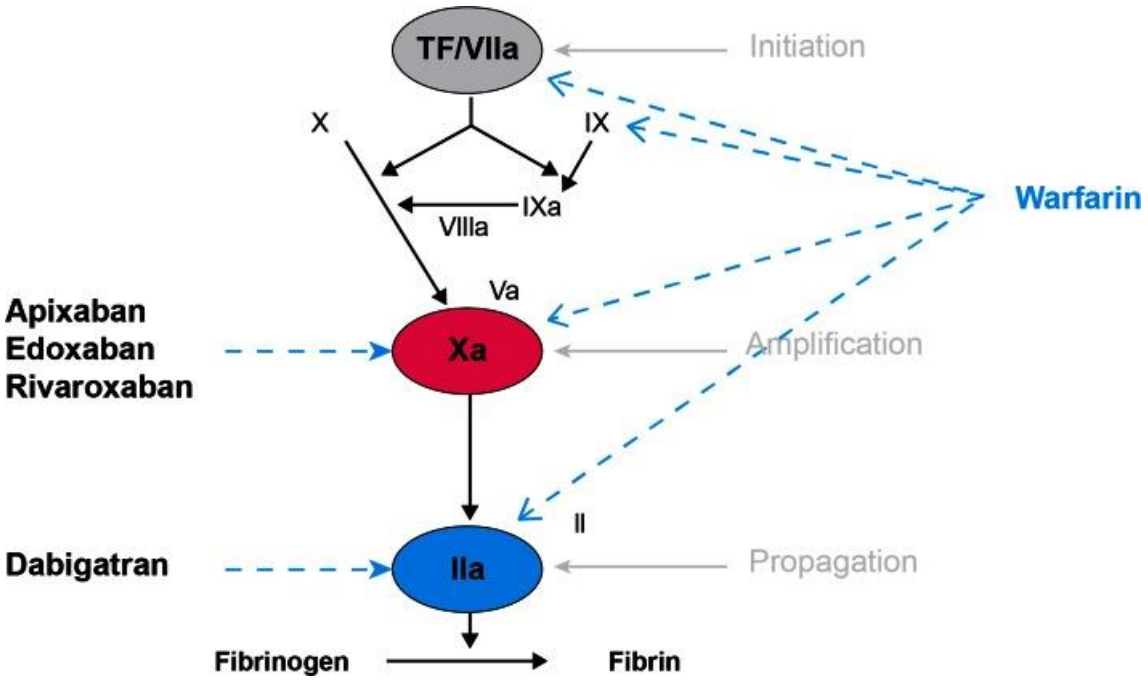

Figure 6: Mechanism of action of direct oral anticoagulants

Source of data: (Nutescu et al., 2016)

Table 1: Types of direct oral anticoagulants

DOACs	Trial	Marketing date	Mechanism of action
Dabigatran	The RE-LY study (Randomized Evaluation of Long-term Anticoagulant Therapy) (Connolly et al., 2009).	Dabigatran etexilate was the first DOACs to be authorized as an alternative to warfarin in the management of AF (Mekaj et al., 2015). The EMA first approved its marketing authorization in 2008 (European Medicine Agency, 2008a).	The mechanism of action of dabigatran is by binding reversibly to the active site of factor IIa, and therefore, it acts as a direct thrombin inhibitor (factor IIa), and it prevents the conversion of fibrinogen intro fibrin (Ganetsky et al., 2011).
Rivaroxaban	The ROCKET AF study (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) (Patel et al., 2011).	It received its marketing authorization by the EMA in 2008 (European Medicine Agency, 2008b).	It acts by binding directly and reversibly to Factor Xa, thus decreasing the formation of thrombin (Hinojar et al., 2015).
Apixaban	The Apixaban for Reduction in Stroke and Other Thromboembolic Events in AF (ARISTOTLE) study (Granger et al., 2011).	The EMA proved its marketing authorization in 2011 (European Medicine Agency, 2011).	It acts similar to rivaroxaban, as a direct, reversible, competitive, and selective inhibitor of factor Xa (Mekaj et al., 2015).
Edoxaban	The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial (Giugliano et al., 2013).	It was approved for marketing by the EMA in 2015 (European Medicine Agency, 2015).	It acts as a reversible and specific factor Xa inhibitor with an approximate 10,000-fold selectivity for factor Xa over thrombin (Mekaj et al., 2015).

1.4 Diabetes and adverse drug reaction

Patients with T2DM are at an increased risk of developing adverse drug reactions (ADRs) due to their multiple comorbidities, renal impairment and multiple uses of the drugs (Mangoni and Jackson, 2004). In a study by Veeren and Weiss, more than 5.6 million emergency hospital admissions for ADRs were reported in 2014/2015 in the UK (Veeren and Weiss, 2017). The majority of these admissions, were attributed to antidiabetic medications, including sulfonylureas, which contributing to the second greatest cause of the increase in admissions due to ADRs in the UK (Veeren and Weiss, 2017). In a systematic review reporting on ADR hospitalisations worldwide, Hamid et al. in 2014 reported that 33.9 % and 9 % of all ADRs were due to cardiovascular and antidiabetic medications, respectively (Al Hamid et al., 2014). Furthermore, according to the prescription cost analysis report provided by the NHS: about 60 million prescriptions in 2016 were either for anticoagulants or antidiabetics medications" in England (Prescribing and Medicines Team Health and Social Care Information Centre, 2015). In 2014, the US Department of Health & Human Services reported antidiabetic medications and drug-induced hypoglycaemia as one of the top priority targets in reducing ADRs (U.S Department of Health and Human Services, 2014).

1.4.1 Adverse drug reactions related to sulfonylureas

The ADA and NICE's guidelines both recommend the use of a SU as add-on treatment when metformin therapy fails to achieve glycaemic control or when there is a contraindicated to use metformin (America Diabetes Association, 2017, National Institute for Health and Care Excellence, 2015). Hypoglycaemia in users of SUs is an expected event, especially after a six month period (Jennings et al., 1989, Bodmer et al., 2008). Many studies have documented the increased risk of hypoglycaemia among SUs users, especially in patients using long-acting SUs (Tessier et al., 1994, Gangji et al., 2007, van Staa et al., 1997). A study of 120,903 new users of non-insulin antidiabetic medications in the UK found that those patients treated with sulfonylureas were at a higher risk of developing hypoglycaemia compared to users of metformin (adjusted HR 2.50, 95% CI, 2.23 – 2.82) (van Dalem et al., 2016).

Patients with T2DM are at an increased risk of developing multiple comorbidities, including renal impairment and liver failure (Mangoni and Jackson, 2004). SU medications are partially or totally metabolized by the liver and excreted by the kidneys (Sola et al., 2015). Therefore, SUs users are at increased risks of experiencing adverse effects, especially among the older age group, patients using multiple medications or those with other comorbidities (Sola et al., 2015, Alsahli and Gerich, 2014). Further, the risk of hypoglycaemia in SUs is increased with the co-administration of certain medications. SUs are at higher risk of an increase of their action, and a potential increase in the risk of hypoglycaemia with drugs that inhibit

hepatic CYP450 and CYP2C9 substrates such as amiodarone and warfarin, respectively (Triplitt, 2006), or that displace plasma protein binding such as warfarin (May and Schindler, 2016).

The mechanism of the interaction is that the other drug (proposed as causing the interaction) will displace the SU drug from its binding with the proteins and make it more available in the circulation, therefore, increasing its effect and resulting in hypoglycaemia (May and Schindler, 2016). The other mechanism of interaction with drugs is when SUs are substrates of CYP2C9 and therefore, medications that induce or inhibit CYP2C9 can affect the metabolism of SUs (May and Schindler, 2016). Medications that inhibit CYP450, and specifically CYP2C9, can prolong the action of SUs, and increase their plasma level (May and Schindler, 2016, Tirkkonen et al., 2010). Different medications have been previously documented in the literature to cause hypoglycaemia through this mechanism, including: amiodarone, ranitidine, bosentan, trimethoprim, fluconazole and fluoxetine (Murad et al., 2009). Leonard et al. studied the association between the use of SUs and several anti-hyperlipidaemia medications among 592,872 patients using an electronic health record (Leonard et al., 2016). The authors reported that hypoglycaemia was highly associated with those patients treated with both SUs and fibrate, the hazard ratio ranging from 1.37 to 1.63, based on the type of SU (Leonard et al., 2016). Another study in Finland reported that about 20% of patients with T2DM treated with SUs had a clinically relevant interaction (Tirkkonen et al., 2010).

1.4.2 The safety and concurrent use of warfarin and sulfonylureas

Warfarin and SUs are largely metabolized by the liver, and specifically by the CYP450 enzymes (Aquilante, 2010, Sola et al., 2015, Kaminsky and Zhang, 1997). There is a possibility that one drug can affect the metabolism of the other by competing for the CYP2C9 enzyme, especially when given at higher doses, leading to an inhibition of the clearance of the primary drug by preventing its transformation into an inactive metabolite. Coexisting evidence on pharmacokinetic theories relating to the displaced plasma protein binding and hepatic metabolism through CYP2C9 as a potential cause of drug-drug interaction between warfarin and sulfonylureas has been reported (Triplitt, 2006, Benet and Hoener, 2002). In addition, three case reports showed a possible drug-drug interaction between warfarin and glibenclamide (Namazi S, 2005, Naganuma et al., 2003, Armstrong G, 1991). However, there is limited evidence of large-scale epidemiological studies about the potential interaction between sulfonylureas and warfarin in patients with T2DM. Two observational studies reported that patients who concurrently used warfarin with either sulfonylureas or metformin had an increased risk of admission due to hypoglycaemia (Romley et al., 2015, Nam et al., 2018).

Warfarin is a drug with a narrow therapeutic index, meaning that a small difference in the dosage or concentration in the blood could lead to accumulation to a toxic level (Kuruvilla and Gurk-Turner, 2001). Therefore, this may lead to unwanted therapeutics

effects that may also increase when co-administered with other drugs that share similar pharmacokinetics (Kuruvilla and Gurk-Turner, 2001).

The use of warfarin and sulfonylureas concurrently can increase the action of both drugs leading to serious complications such as hypoglycaemia and bleeding. The latter events will be discussed in the following sections with more details on the primary objective of this thesis (hypoglycaemia).

1.4.3 Hypoglycaemia

Hypoglycaemia is an acute and serious event of diabetes treatment that can lead to different complications (Seaquist et al., 2013). Hypoglycaemia can be defined as a low level of blood glucose (National Institute for Health and Care Excellence, 2015). Several studies including the Prospective Diabetes Study and the Diabetes Control and Complications Trials have found that intensive glucose control could prevent diabetes-related complications (King et al., 1999, Nathan, 2014), however, hypoglycaemia is an important limitation in the treatment of diabetes (Cryer, 2004). Hypoglycaemia is very common among diabetes patients, especially patients treated with insulin or sulfonylureas (Edridge et al., 2015, Lipska et al., 2014). It can range from being mild symptomatic to a more severe form, requiring hospitalisation (Briscoe and Davis, 2006). Hypoglycaemia can also lead to cardiac and neurological complication in patients with diabetes (Diedrich et al., 2002).

1.4.3.1 Prevalence

The prevalence rate of hypoglycaemia has significantly increased in the last three decades (Zaccardi et al., 2016). Lipska et al, in the United States reported high rates of hypoglycaemia between 1999 to 2011, admissions for hypoglycaemia increased by 11.7% (from 94 to 105 admissions per 100,000 person-years) (Lipska et al., 2014). Similar studies in the UK reported higher rates of hypoglycaemia admissions (Zhong et al., 2017, Zaccardi et al., 2016). Zhong et al. reported that the incidence of hypoglycaemia in adults with T1DM increased to 14.80 hospitalisations per 1,000 person-years between 1998 and 2013 (adjusted IRR 1.67, 95% CI, 1.14 – 2.43), while the incidence for T2DM increased to 1.19 hospitalisations per 1,000 person-years between 1998 and 2013 (adjusted IRR, 1.52, 95% CI, 0.68 – 3.38) (Zhong et al., 2017). A systematic review and meta-analysis investigating the incidence and prevalence of hypoglycaemia in diabetes patients reported that the prevalence of mild hypoglycaemia in T2DM patients is about 45%, while it was reported as only 6 % for severe hypoglycaemia (Edridge et al., 2015).

1.4.3.2 Pathophysiology

The normal physiology of hypoglycaemia depends mainly on six components: 1) a decrease in insulin production, 2) an increase in secretion of epinephrine and glucagon, as well as other neurohormones, to increase the production of glucose, 3) neurological symptoms and cognitive impairment, 4) a reduction in glucose uptake by

the adipose tissue, which will preserve the remaining glucose in the circulation, 5) adipose tissue lipolysis and release of free fatty acids (FFA), which will result in preserving a significant amount of glucose as the tissues will utilise FFA in replacement of glucose, 6) growth hormone and cortisol which increase the production of glucose (Briscoe and Davis, 2006, Cryer, 2004). In diabetes, both T1DM and advanced T2DM, the exogenous use of insulin or the use of insulin secretagogues will result in a reduction in the glucose level (Briscoe and Davis, 2006). However, insulin production will not be decreased due to the action of exogenous medications; also, the glucagon and epinephrine levels will not increase and therefore, the levels of glucose in the blood will remain low, resulting in hypoglycaemia (Briscoe and Davis, 2006).

1.4.3.3 Risk factors for hypoglycaemia

Multiple risk factors have been identified to increase the risk of the developing of hypoglycaemia. These risk factors can induce the risk of hypoglycaemia through different mechanisms, which include: an increase in the administration of exogenous insulin products (including OHAs); a reduction in endogenous glucose production; increase in the utilisation and consumption of endogenous glucose; a reduction in the administration of exogenous glucose or by a reduction in insulin clearance (Seaquist et al., 2013, International Hypoglycaemia Study Group, 2015), however, there are many risk factors that could be related to the mechanisms mentioned above.

Skipping meals or performing extensive exercise could result in hypoglycaemia by utilising all the glucose or by reducing the exogenous intake of glucose (Lin et al., 2010, Maran et al., 2010, Riddell and Milliken, 2011). Older people are at increased risk of developing hypoglycaemia; this can be related to their comorbidities and the use of multiple medications (Borzi et al., 2016, The Diabetes Control Complications Trial Research Group, 1993, International Hypoglycaemia Study Group, 2015). Chronic kidney disease (CKD) is a common complication of diabetes and often coexists with diabetes. Patients with CKD can be at higher risk of hypoglycaemia due to the defect in the excretion function of the kidneys that can result in an increase in the circulating antidiabetic medications or insulin (Kim et al., 2016b, Moen et al., 2009). Dementia, which is another disease of the elderly, can increase the risk of hypoglycaemia by a different mechanism: these patients can forget the dosage instructions and mistakenly administer a higher dosage of their diabetic medication, which can lead to severe hypoglycaemia (Yaffe et al., 2013). A study by Kim et al., using a Korean health database and entailing about 300,000 patients, revealed that patients with different comorbidities had a higher risk of hypoglycaemia. These comorbidities included cardiovascular diseases, CKD and dementia (Kim et al., 2016b).

Drug-induced hypoglycaemia is very common: this can be either due to intensive therapy, multiple use of medications or through drug interactions (International Hypoglycaemia Study Group, 2015, Murad et al., 2009). Further, this can be explained

differently either by dose-related issues with antidiabetic medications or by interactions due to the use of concurrent medications, such as warfarin, statins, aspirin and Angiotensin converting enzyme inhibitors (ACEIs) (Murad et al., 2009).

Intensive treatment, with increased dosage or multiple uses of antidiabetic therapies, could result in hypoglycaemia by increasing the effect of insulin (Boussageon et al., 2011). Although many studies have recommended the intensification of diabetes treatment (King et al., 1999), recent studies and guidelines have suggested that intensive therapy may increase the risk of hypoglycaemia (Boussageon et al., 2011, National Institute for Health and Care Excellence, 2015).

Drug-drug interactions also play a major role in the development of hypoglycaemia. It has been documented that different medications could result in hypoglycaemia (Murad et al., 2009). This is often due to an increase in the action of insulin or other OHAs (Holstein and Egberts, 2003, Czech et al., 2015). Medication such as statins and beta blockers and ACEIs have been documented to interact with sulfonylurea and result in hypoglycaemia (Murad et al., 2009). Antibiotics such as quininolones also have been found to cause hypoglycaemia (Garber et al., 2009, Murad et al., 2009). Other risk factors in developing hypoglycaemia can be related to the age of patients and their cognitive behaviour (Abdelhafiz et al., 2015). Warfarin is another commonly prescribed medicine, especially among the elderly, has been documented to cause hypoglycaemia when concomitantly used with sulfonylureas (Romley et al., 2015, Nam et al., 2018). The latter will be the topic of this PhD, and will be discussed and

studied in detail in the following chapters.

It has also been documented in the literature that patients who experienced previous attacks of hypoglycaemia, and who have a longer duration since first being diagnosed with diabetes, are at higher risk of developing the condition. Risk factors for hypoglycaemia in patients with diabetes will be discussed into details in the next chapter.

1.4.3.4 Symptoms

Hypoglycaemia can be mild to moderate or it can be severe. Symptoms of hypoglycaemia can appear at any point when blood glucose levels are below 70 mg/dL (American Diabetes Association, 2018a, National Institute for Health and Care Excellence, 2015). The symptoms of hypoglycaemia can be divided into two main categories: neurogenic symptoms, where patients can experience symptoms such as: shaking, trembling, anxiety, nervousness, palpitations, clamminess, sweating, dry mouth, hunger, pallor, pupil dilation (Cryer, 2004). These symptoms are usually mediated by the release of catecholamines (adrenaline and noradrenaline) and acetylcholine (Briscoe and Davis, 2006). Other symptoms could be related to neuroglycopenic causes, where there is not enough blood reaching the brain and patients start to experience behavioural and cognitive problems such as: abnormal mentation, irritability, confusion, difficulty in thinking, difficulty speaking, ataxia, paresthesia, headaches, stupor, seizures, coma or death (if untreated) (Briscoe and

Davis, 2006).

1.4.3.5 Diagnosis

According to the International Hypoglycaemia Study Group hypoglycaemia can be classified into three major levels. The first level, also known as hypoglycaemia alert, is blood glucose level below 70 mg/dL (3.9 mmol/L). The second is level is known as clinically significant hypoglycaemia and the blood glucose level is < 54 mg/dL (3.0 mmol/L) (International Hypoglycaemia Study Group, 2017). Both the first and the second levels can be self-treated without the need for external assistance (International Hypoglycaemia Study Group, 2017). The third level is severe hypoglycaemia, where the blood glucose level is not necessarily specified, but is always associated with severe cognitive impairment and the need for external assistance to recovery (International Hypoglycaemia Study Group, 2017). However, the ADA classify hypoglycaemia into different types, including: severe hypoglycaemia, for which the patient will need assistance from another person; documented symptomatic hypoglycaemia, at which the patient experience the typical symptoms of hypoglycaemia accompanied by blood glucose level ≤ 3.9 mmol/L (70 mg/dL) (Seaquist et al., 2013); asymptomatic hypoglycaemia, where the blood glucose level is ≤ 3.9 mmol/L (70 mg/d, but the patient does not experience symptoms; and relative hypoglycaemia, where the blood glucose level is > 3.9 mmol/L (70 mg/dL), but the patient experiences typical symptoms of hypoglycaemia (Seaquist et al., 2013).

1.4.3.6 Treatment of hypoglycaemia

For the conscious patient, and where the hypoglycaemia is above < 54 mg/dL (3.0 mmol/L), 10-20 g of glucose should be administered in the form of liquids or granulated sugar. This should be repeated within 15 minutes. Once the blood glucose level returns to normal, the patient should consume a meal or snack to prevent any recurrence (National Institute for Health and Care Excellence, 2015). In severe cases of hypoglycaemia or clinically significant hypoglycaemia, where the blood glucose level is below < 54 mg/dL (3.0 mmol/L), glucagon injections should be given to avoid serious complications. Alternatively, I.V glucose 20% should be administered to the patients in order to restore normal blood glucose levels (National Institute for Health and Care Excellence, 2015).

1.4.3.7 Complications

Hypoglycaemia is associated with various complications, including: dementia, seizures and decreased cognitive function (Kalra et al., 2013, Whitmer et al., 2009). Another serious complication is increased risk of cardiac mortality (Khunti et al., 2015). Autonomic dysfunction and disturbance of the sympathetic nervous system during hypoglycaemic attacks can lead to cardiac arrhythmias (Adler et al., 2009). Also, it has been documented that hypoglycaemia can increase the risk of coronary heart diseases, this is because it can affect the autonomic nervous system leading to an increase in the contractility of the muscles, an increase in stroke volume and an

increase in cardiac output; therefore, leading to cardiac load (Pan et al., 1986, Khunti et al., 2015).

Giving that all of these complications could result due to hypoglycaemic events, it is therefore, important to highlight that hypoglycaemia can be a major health risk in daily life tasks, and can affect the quality of life of patients with diabetes.

1.4.3.8 Cost of hypoglycaemia

Hypoglycaemia, and especially severe hypoglycaemia that requires hospital admission, is associated with high costs and a significant economic impact. In the last five years, many studies have been conducted to estimate the direct (e.g., drug-related, medical procedures, hospitalisations, etc.) and the indirect costs of hypoglycaemia (Parekh et al., 2017, Jonsson et al., 2006, Jakubczyk et al., 2016). In the UK, a retrospective cohort study using the national database and including 1131 patients reported that the mean cost per admission for hypoglycaemia was £1034 (95% CI, £855 to £1253) (McEwan et al., 2015). Another study in the UK estimated the cost of hypoglycaemia using data from the UK hypoglycaemia study group, the authors reported that the estimated cost of a hypoglycaemic episode could range from £2,152 for severe cases to £1.67 for non-severe cases (Parekh et al., 2015).In the US, a large cohort study was conducted compromising 536,581 patients and with approximately 1.21 million person-years of follow-up, the authors reported that the mean cost of a hypoglycaemia admission was $17,564, then $1387 for an emergency

department visit, and $394 for an outpatient visit (Quilliam et al., 2011b). Similar higher rates of cost were reported in Spain, Sweden, Korea and other countries (Jonsson et al., 2006, Parekh et al., 2017, Kim et al., 2016a).

1.4.4 Bleeding

Bleeding (sometimes called ‘haemorrhage’) is one of the most serious and life-threatening medical emergencies (Fitzmaurice et al., 2002). It can be defined as an acute blood loss from blood vessels (Johnson, 2020). Bleeding can either be external (outside the body) such as when superficial damage occurs due to trauma or a wound, or it can be internal, such as when organ damage occurs (Johnson, 2020). Bleeding can be minor, such as when the superficial vessels are damaged causing swelling and petechial, or it can be major as a result of a rupture in major vessels causing significant body damage including vital signs instability or severe clinical symptoms (Johnson, 2020).

1.4.4.1 Definition of bleeding

The definition of bleeding can be heterogeneous, and several clinical trials have used different definitions (Mehran et al., 2011). Major bleeding can be defined as a fatal event, e.g., symptomatic bleeding in a critical area or an organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular bleeding, or it can be defined as bleeding that causes a drop in the haemoglobin level

to 20 g/L^{-1} (1.24 $mmol/L^{-1}$) or that leads to a transfusion of two or more units of whole blood or red blood cells (Schulman and Kearon, 2005). Minor bleeding could be defined as overt bleeding or bleeding that made the patient stop taking medication (Schulman and Kearon, 2005, Mehran et al., 2011). The Bleeding Academic Research Consortium (BARC) defined bleeding based on six categories (from 0 to 5) (Mehran et al., 2011). Type 0 is no bleeding; type 1 is not actionable and does not require treatment; type 2 is any clinically overt sign of haemorrhage that requires treatment or hospitalisation or further investigations; type 3a is overt bleeding plus a haemoglobin drop 3 to < 5 g/dL, while type 3b is overt bleeding plus a haemoglobin drop > 5 g/dL, and type 3c is intracranial haemorrhage; type 4 is CABG related bleeding within 48 hours; type 5a is probable fatal bleeding and type 5b is definite fatal bleeding (Mehran et al., 2011).

1.4.4.2 Aetiology of bleeding

Bleeding can occur due to various conditions and causes, including traumatic injuries (such as: gunshots, car accidents or other types of trauma), bleeding disorders (such as: Von Willebrand disease and haemophilia), bleeding due to adverse drug reactions (such as: warfarin or antiplatelets use), or it can be due to other causes (such as: inoperative or postoperative trauma or post massive transfusion (Gopinath et al., 2014). However, in this thesis, only bleeding due to adverse drug reactions is discussed in detail.

1.4.4.3 Bleeding and adverse drug reactions

Major and minor bleeding can occur due to adverse drug reactions to different medications, including anticoagulants, antiplatelets and antithrombotics medications (Fitzmaurice et al., 2002, Mehran et al., 2011). During normal physiological circumstances, the function of platelets, active biological blood components, and tissue factors enhance the coagulation cascade to maintain body haemostasis (De Caterina et al., 2013). This physiology is interrupted when some medications such as OACs or antiplatelets are ingested (De Caterina et al., 2013). However, the exact mechanism through which bleeding due to adverse reactions occurs is unclear. Some perceptions may arise from the fact that these medications may increase the blood pressure or local stress leading to bleeding. Other hypotheses arise from the fact that these medications cause subclinical hematomas, which may in turn grow and lead to serious bleeding events (Hart et al., 1995).

1.4.4.4 Epidemiology of bleeding

The risk of bleeding with the administration of drugs that interfere with the homeostasis of the blood such as oral anticoagulants, antiplatelets and antithrombotics is well established (Hernandez et al., 2015, De Berardis et al., 2012, Adeboyeje et al., 2017). However, the risk of bleeding associated with the use of anticoagulants can be higher compared with antiplatelet medications. This was highlighted by a meta-analysis where the authors reported that the risk of bleeding when patients are using aspirin or

clopidogrel compared to warfarin in non-randomized trials is (RR, 0.87; 95% CI, 0.77 – 0.99) (Melkonian et al., 2017). Furthermore, the incidence of bleeding associated with the use of warfarin was 0.32 per 100 patient–years (95% CI, 0.27 – 0.37), compared to 0.16 per 100 patient–years (95% CI, 0.12 – 0.20) when DOACs are used (Melkonian et al., 2017). Another study in the UK by Gallagher et al. in 2014 reported that the incidence of bleeding events requiring hospitalisation is 3.8 per 100 patients-years among warfarin users (Gallagher et al., 2014). Similar results were reported in the US, with the incidence of major bleeding as 6.0 per 100 patients-years among warfarin users, compared to 2.8 per 100 patients-years with dabigatran and 5.0 per 100 patients-years with rivaroxaban (Adeboyeje et al., 2017).

1.4.4.5 Symptoms

Bleeding symptoms may vary based on the anatomical position and the amount of blood loss (Johnson, 2020). Patients with bleeding experience a wide range of symptoms including tachycardia, hypotension, slow capillary refill time, tachypnea, dehydration, decreased urine output, muscle weakness, inability to speak, confusion and coma (Van Iersel et al., 2012, Gutierrez et al., 2004).

1.4.4.6 Evaluation and diagnosis

The evaluation and approach for a patient with bleeding start with a detailed history of the patient’s medical history, including medications use, history of bleeding disorders,

and recent trauma. This is followed by a complete physical examination of the patients (Kim et al., 2014, Hemphill et al., 2015). Blood tests, nasogastric tube insertion, upper and lower endoscopies, computed tomography (CT) and magnetic resonance imaging (MRI) may also be needed based on the clinical judgment of the doctors (Hemphill et al., 2015, Kim et al., 2014).

1.4.4.7 Management of bleeding

The management of patients with bleeding will depend mainly on the cause of the bleeding. However, in cases where patients are in critical situations and severe cases, patients are likely to require intravenous fluid administrations to reverse the dehydration (Johnson, 2020). In addition, patients may require some oxygen and a blood transfusion depending on the severity of the loss of blood (Johnson, 2020). In addition, in some cases, patients may require antidote administrations to reverse the action of some blood thinners and antiplatelet medications. Other patients may also require surgical operations to evacuate the bleeding (Hemphill et al., 2015) or intervention endoscopies (National Institute for Health and Clinical Excellence, 2012).

1.4.4.7.1 Complications of bleeding

Major bleeding is associated with high rates of morbidity, mortality, and disability (Feigin et al., 2003). The mortality rate is higher in the first week after a haemorrhagic event, and the case fatality at one month could range from 30% to 40%, depending

on the type of haemorrhage (Gonzalez-Perez et al., 2013). In a study in the UK using electronic health records data, the authors reported that 56-day mortality after a first stroke was 12% (Lee et al., 2011). Another study in the UK investigated the short-term case fatality and the long-term case fatality after a haemorrhagic stroke, the authors reported that the risk of death was higher among the patients with a stroke compared with others, with more than one-third of the patients suffering from a haemorrhagic stroke dying within the first month after the event (Gonzalez-Perez et al., 2013). Similarly, mortality rates associated with gastrointestinal bleeding (GIB) are high. In a systematic review, the authors reported that the mortality rate associated with GIB is about 7.4% (95% CI, 7.2 – 7.6) (Straube et al., 2009).

1.5 Summary of general introduction

This chapter identified that diabetes is a highly prevalent disease and is associated with significant morbidity and mortality including cardiovascular comorbidities. Sulfonylureas are used in the second line management of diabetes and, in some cases, are prescribed as first line therapy. Type 2 diabetes is often coexistent with cardiac comorbidities including AF. Patients with diabetes and other comorbid diseases are likely to utilise multiple medications including antidiabetics and anticoagulants; therefore, these patients are at higher risk of experiencing adverse drug events and are at higher risk of hypoglycaemia and bleeding.

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Chapter 2 Incidence, prevalence and risk factors of hypoglycaemia in type 1 and type 2 diabetes patients treated with insulin and oral hypoglycaemic agents; a systematic review and meta-analysis

The prevalence and incidence parts of the findings from this chapter have been published in the Diabetes Research and Clinical Practice journal, under the title: “Incidence and Prevalence of Hypoglycaemia in Type 1 and Type 2 Diabetes Individuals: A Systematic Review and Meta-analysis”. Refer to Figure 7 below.

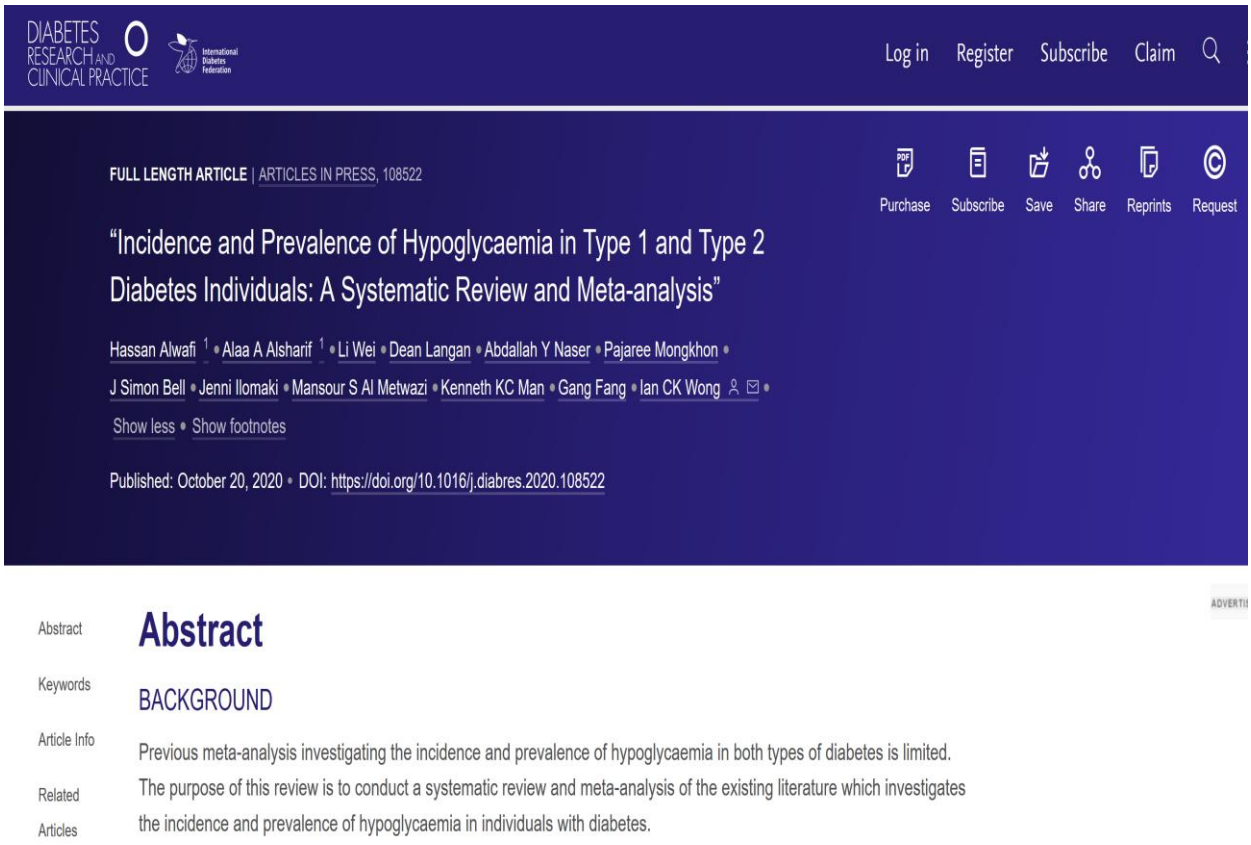


Figure 7: A capture picture from Diabetes Research and Clinical Practice journal website which represent the publication of this chapter

2.1 Chapter overview

This chapter will enable us to explore the literature, better understand the current knowledge and to identify knowledge gaps relating to the topic of this PhD.

2.2 Background

Diabetes is a major public health concern which is affecting about 460 million patients in the world (Guariguata et al., 2014, Ogurtsova et al., 2017). Patients with diabetes require continuous medical care to achieve the optimal glycaemic control in order to prevent the development of its complications (McCoy et al., 2016). Optimal glycaemic control can be achieved with intensive antidiabetic treatment; however, it is also associated with an increased risk of hypoglycaemia (McCoy et al., 2016). Hypoglycaemia is an acute complication that is associated with the treatment of diabetes using insulin or antidiabetic agents (Gehlaut et al., 2015). Hypoglycaemia can significantly affect the quality of life of diabetes patients and could lead to serious side effects and emergencies including; falling down, micro and macrovascular events, seizures, cognitive impairment, comas, and death (Clayton et al., 2013, Stargardt et al., 2009). According to the American Diabetes Association guidelines (ADA) "*hypoglycaemia can be defined as blood glucose level lower than 70 mg/dl (3.9 mmol/l)*"(American Diabetes Association, 2018a). Symptoms of hypoglycaemia range from simple hunger or thirst to mild symptoms such as diaphoresis, tachycardia, irritability or blurred vision, or to more severe symptoms such as confusion, seizures

and comas requiring third-party assistance and/or hospitalisation (American Diabetes Association, 2018a).

Rates of hypoglycaemia have significantly increased in the last three decades (Lipska et al., 2014, Zaccardi et al., 2016). One study in the United States in 2014 reported higher rates of hypoglycaemia compared to hyperglycaemia (Lipska et al., 2014). Similar studies in the UK reported higher rates of hypoglycaemia admissions (Zaccardi et al., 2016, Zhong et al., 2017). Tight glycaemic control and prevention of macrovascular and microvascular complications is an important aim in the management of diabetes (American Diabetes Association, 2018a). However, this approach is often associated with higher rates of hypoglycaemic attacks (The Diabetes Control Complications Trial Research Group, 1993, Gerstein et al., 2008). Other risk factors that could lead to the development of hypoglycaemia include uncontrolled diabetes, older age, dementia, increased exercise, skipping meals, sulfonylureas and insulin overdose (American Diabetes Association, 2018a, Nicolucci et al., 2015, van Dalem et al., 2016).

Previous systematic reviews and meta-analysis investigating the incidence, prevalence and risk factors of hypoglycaemia in diabetes patients are limited, and the majority of the published reviews focused on randomised clinical trials settings (RCT) (Phung et al., 2010) (Rosenstock et al., 2005, Waugh et al., 2010, Montvida et al., 2018). However, RCTs often underestimate the frequency of hypoglycaemia and are not reflective of the real-world burden (Elliott et al., 2016). In addition, since 2014,

newer drugs with a lower risk of hypoglycaemia have been more frequently used. Besides this, to the best of my knowledge, there are no previous reviews that have investigated the incidence and prevalence rates of hypoglycaemia in patients with type 1 diabetes.

Given the fact that there is a knowledge gap and the lack of studies, this systemic review aimed to investigate the incidence, prevalence, and risk factors of hypoglycaemia among type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) diabetes patients treated with insulin and oral antidiabetic agents.

2.3 Research question

What are the incidence, prevalence and risk factors of hypoglycaemia in T1DM and T2DM patients treated with insulin and oral antidiabetic agents?

2.4 Aims and objectives

The overall aim of this study was to review the literature about the incidence, prevalence and risk factors of hypoglycaemia in T1DM and T2DM patients.

2.4.1 Objectives

1) To investigate the incidence and the prevalence of hypoglycaemia in T1DM and T2DM patients.

2) To investigate the risk factors of hypoglycaemia in T1DM and T2DM patients.

2.5 Methods

This review was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) (Moher et al., 2009) and the meta-analysis of observational studies in epidemiology (MOOSE) (Stroup et al., 2000) to ensure clear and comprehensive reporting (Appendix 1). The study protocol was registered with PROSPERO (Ref: CRD42017077013). For details refer to (Appendix 2).

2.5.1 Search strategy

I used an extensive search strategy developed by a specialised librarian to search electronic bibliographic databases: PubMed, the Excerpta Medica dataBASE (Embase) and the Cochrane library up to October 2018. A combination of MeSH terms and keywords with both English and American spellings have been used to identify relevant studies. The search terms used covered; diabetes mellitus, type 1 diabetes, type 2 diabetes, incidence of hypoglycaemia, prevalence of hypoglycaemia, events of hypoglycaemia, episodes of hypoglycaemia, rates of hypoglycaemia, risk factors, relative risk, rate risk, OR, HR and IR. A detailed search strategy for PubMed and Embase can be found in Appendix 3.

2.5.2 Types of studies included

Only observational studies were included in this review.

2.5.3 Study population

The study population was T1DM and T2DM individuals, sampled from any primary, secondary or tertiary care settings, without any restrictions on the ethnic groups or sociodemographic characteristics. In addition, no limitations regarding the classification and severity of hypoglycaemia (mild or severe) were applied in this study.

2.5.4 Inclusion criteria

- English language papers.
- Studies that reported hypoglycaemia as a primary or a secondary objective (outcome of the study).
- The study population was diagnosed with diabetes mellitus.
- Patients must be on antidiabetic treatment including insulin and oral antidiabetic.
- Studies that were published as full-text papers.
- The incidence and/or prevalence, or risk factors of hypoglycaemia in T1DM and T2DM was reported.
- The incidence and/or prevalence of hypoglycaemia in T1DM and T2DM was reported.

- The number of patients with diabetes who experienced hypoglycaemia and/or the incidence of hypoglycaemic episodes was reported (or data were available to determine these numbers).
- Observational studies (cohort, case controls and cross sectional studies).

2.5.5 Exclusion criteria

1- RCTs, interventional studies, case reports, case series, narrative reviews, commentaries, editorials, book chapters, and duplicate publications.
2- Gestational diabetes.
3- Animal studies.
4- Conference proceedings or abstracts.
5- Studies that did not have quantitative measurements (results that can be pooled in the analysis) or studies that provided insufficient information to calculate the incidence and/or the prevalence of hypoglycaemia were excluded.
6- Studies that did not clearly describe the calculation method used to estimate the incidence or provide enough information (e.g. number of events or person years) to calculate the incidence rate were excluded.

2.5.6 Types of outcome measure

Primary outcome

Incidence, and prevalence of hypoglycaemia in patients with T1DM and T2DM.

Secondary outcome

Risk factors of hypoglycaemia in patients with T1DM and T2DM.

2.6 Data collection and data synthesis

2.6.1 Selection of studies

Duplicate publications were removed, and titles and abstracts were screened independently by two reviewers (HA, AA) in order to identify studies that met the inclusion criteria. Citations that were not clear from the title and the abstract screening were reviewed independently as full text papers. Whenever there has been a scientific disagreement regarding the relevance of a particular study between the two reviewers, a third reviewer (AN) has been consulted. A detailed flow chart is listed in Figure 8.

2.6.2 Data extraction

Data extraction was performed independently by two reviewers (HA and AA) using the pre-specified data extraction form. The following data were extracted from each included article: 1) study details (including study design, study duration, year published, author's name, and country in which the study was conducted); 2) population details (including sample size, mean age, ethnicity, mean HbA1c (glycated haemoglobin A1c), sex, treatment regimens, type of diabetes and diabetes duration); 3) data source (self-report questionnaires, prospective diaries, hospital charts, clinical

data registries, emergency department admission records and electronic healthcare databases); and 4) definition of hypoglycaemia used in the study: International Classification of Diseases (ICD) codes, third party assistance, blood glucose level or symptoms of hypoglycaemia. I extracted hypoglycaemia data for the percentage of patients with diabetes who experienced a hypoglycaemic event and the incidence rate of hypoglycaemia (defined as the number of episodes per 1000 person-years). In addition, I extracted outcome data for the risk factors of hypoglycaemia (IR, OR, HR, RR).

2.6.3 Quality assessment

Two reviewers (HA, AA) independently assessed all the studies for methodological quality and risk of bias. I used the Newcastle Ottawa scale for observational studies (Wells et al., 2000), which was modified to meet the requirement of this review (Herzog et al., 2013, Magliano et al., 2019). A total of six criteria have been evaluated, and it included the following: 1) representativeness of the population; 2) sample size; 3) confounder adjustments; 4) statistical analysis; 5) missing data; and 6) methodology to report the outcome of interest and methods to detect the outcome of interest or to report it. Each criteria rated using a scale ranging from 0 to 3, where 3 represented the highest quality, and the highest overall score is 18. In addition, I categorised the quality assessment score into three categories, > 14 good quality, ≥ 14 moderate quality < 7, and low quality ≤ 7 points. A separate calculation for the quality of the studies included in the meta-analysis were also performed. This is because some of

the studies included in the meta-analysis were of descriptive nature only and therefore, it was not possible to asses them based on the confounder adjustments.

2.6.4 Data synthesis and analysis

The incidence rates reported by the authors of each study were normalized to rates per 1000 person-years when it was not provided in this format in the original research article. The standard error (SE) was calculated whenever it was not reported in the original research article. For the meta-analysis related to prevalence, only studies that were of one year (12 months) duration were included in the prevalence calculation. Overall analysis for both T1DM and T2DM was conducted. However, I also conducted a subgroup analysis based on the following variables: type of diabetes (T1DM and T2DM), country or location of the study, treatment regimen and source of the data. Sensitivity analysis was conducted to investigate the pooled estimate of prevalence after removing outlier studies (Conceicao et al., 2017, Henderson et al., 2003). Data source was categorized into two groups: self-reported (where hypoglycaemia was reported by patients through surveys) and electronic databases (where hypoglycaemia was reported by a healthcare provider through healthcare databases or clinical data registries). A random effects model was used to estimate the prevalence and incidence rates. All analyses were performed using R, the package *meta* (Schwarzer, 2007). The function *metaprop* was used for analysis of prevalence, which uses a logit transformation of the outcome. The function *metarate* was used for analysis of incidence rates, using a natural log transformation. Asymmetry of

prevalence results was assessed via funnel plots with pseudo 95% confidence interval around the fixed effect.

2.7 Results

2.7.1 Results of the search (included studies)

The search identified 35,007 studies, from which 29,652 were screened for relevant titles, and only 2,918 were screened for abstract. Nine hundred and fifty-three citations were screened for full text and only 145 studies were included in the systematic review, from which only 72 studies were included in the meta-analysis. A detailed flow chart of the studies included in the review is summarised in Figure 8.

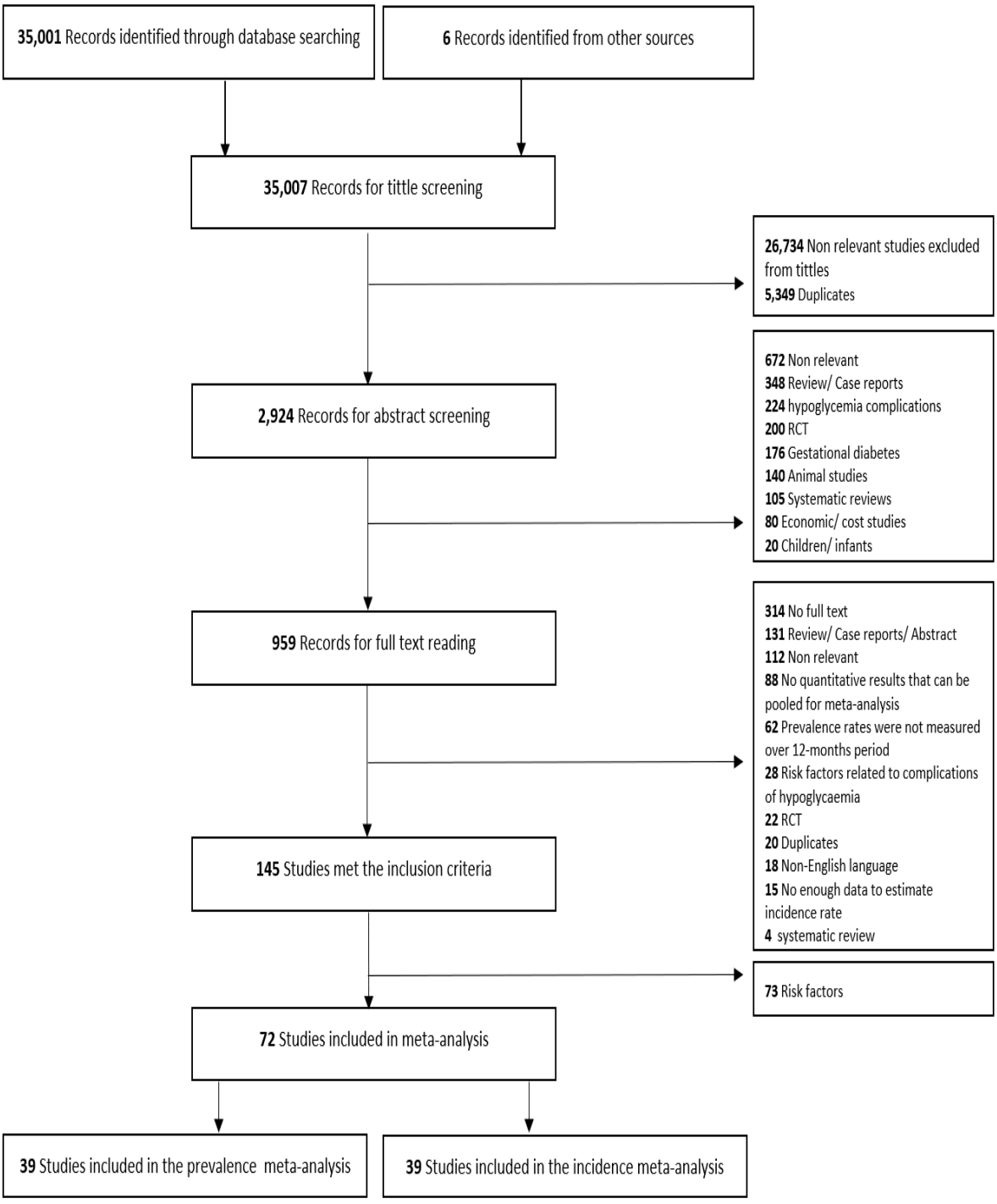


Figure 8: Flow chart of studies included in the meta-analysis

2.7.2 Summary of included studies

Descriptive characteristics including authors, year of publication, country, sample source, study design, sample size, type of diabetes, mean age, gender, diabetes duration and definition of hypoglycaemia are summarised in Appendix 4. The citations included in this review were from the year of 1989 to the year of 2018 (Figure 9).

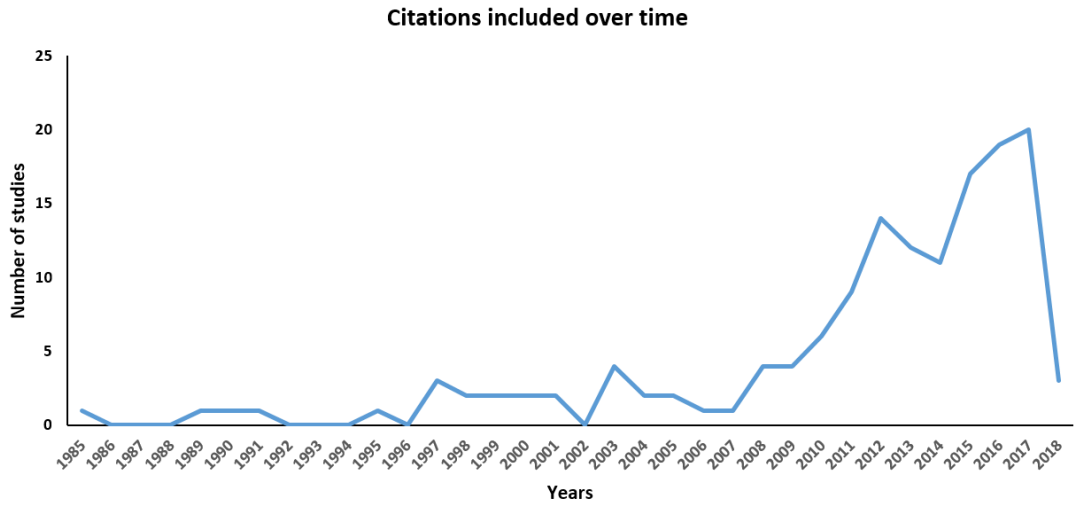


Figure 9: Citations included in the systematic review and meta-analysis over time

The majority of studies were in Europe (66) 46%, followed by North America (46) 31%, Asia (23) 16%, Australia (5) 3%, and multinational studies (4) 3%, while the data for location in one study was missing. Seventy-one citations included in this review were on T2DM, while 27 citations were on T1DM and the remaining studies were either for both types of diabetes or not specified by the authors. All of the studies were observational, 88% of studies were retrospective (n=128), and 12% were prospective

(n=17). Around 52% of the studies were based on the electronic health records database (n=81), while 42% were self-reported studies (n=61), and the remaining studies were not mentioned by the original research article. The ethnicity of the populations was poorly reported. The definition of hypoglycaemia was very heterogeneous between studies included in this review, with some studies reporting it as the need for third-party assistance; others defined it as loss of consciousness, and some studies depended only on the ICD codes. Insulin was the most prevalent type of treatment used in the studies included in this review 21% (n=31), followed by a combination of oral antidiabetic medications and insulin 17% (n=25), only oral antidiabetic medications 12% (n=18) and sulfonylureas 8% (n=12), while the data for the remaining studies were not available. (For details on the characteristics of the studies included in this review, refer to Appendix 4). A summary of the characteristics of studies included is presented in Table 2.

Table 2: Summary of the characteristics of studies included

	Location	Type of diabetes	Study design	Data source	Type of treatment
	Europe (46%)	T2DM (49%)	Retrospective (88%)	Electronic health records (52%)	Insulin (21%)
	North America (31%)	T1DM (19%)	Prospective (12%)	Self-reported studies (42%)	Combination of oral antidiabetic medications and insulin (17%)
	Asia (16%)	Both types of diabetes (32%)	-	-	only oral antidiabetic medications (12%)
	Australia (3%)	-	-	-	Sulfonylureas (8%)
	Multinational (3%)	-	-	-	-

2.7.3 Quality of studies included

The modified Newcastle Ottawa scale was used to assess the quality of the studies in this review. The quality of studies included in this review varied considerably, however, this could be due to different reasons including the variation in the year of publication, the definition of the hypoglycaemia, or the study design integrated to do the study. The majority of the studies were of good quality (70%), and had a score of more than 14, however, there are some studies that reported moderate quality evidence. Studies

published based on data sampled from electronic health databases (either hospital electronic health records or national database) were better in quality than studies published using data from self-reporting. Full details of the quality of the studies included in this review are provided in Table 3.

Table 3: Quality of the studies included in the review

Author	Year of publication	Representative population	Sample size	Confounders adjustments	Appropriate statistical analysis	Missing data	Methodology of the outcome measurement	Methods to detect hypoglycaemia	**Total**
(Jabbar et al., 2017)	2017	3	1	2	3	0	3	1	13
(Lee et al., 2017)	2017	3	2	2	2	2	3	3	17
(Allen et al., 2001)	2001	3	1	1	2	3	3	3	16
(Akirov et al., 2018)	2018	3	2	0	3	0	3	2	13
(Aung et al., 2012)	2012	3	2	0	3	0	3	3	14
(Barkai et al., 1998)	1989	2	1	1	2	0	2	2	10
(Basu et al., 2017)	2017	3	3	3	2	0	2	3	16
(Berkowitz et al., 2012)	2012	2	3	1	2	1	2	2	13
(Birkebaek et al., 2017)	2017	3	3	3	3	3	3	3	21
(Blasetti et al., 2011)	2011	3	1	1	2	0	3	3	13
(Bognetti et al., 1997)	1997	2	1	2	3	0	3	3	14
(Borzi et al., 2016)	2016	3	3	2	3	0	3	3	17
(ter Braak et al., 2000)	2000	3	3	3	3	3	3	3	21

Author	Year of publication	Representative population	Sample size	Confounders adjustments	Appropriate statistical analysis	Missing data	Methodology of the outcome measurement	Methods to detect hypoglycaemia	**Total**
(Bramlage et al., 2012)	2012	2	2	1	2	0	3	1	11
(Bron et al., 2012)	2012	3	3	3	3	0	3	3	18
(Bruce et al., 2009)	2009	2	2	3	3	1	3	3	17
(Bruderer et al., 2014)	2014	2	1	2	2	2	2	2	13
(Buyken et al., 1998)	1998	3	3	3	3	1	3	3	19
(Cherubini et al., 2013)	2013	3	3	3	3	1	3	3	19
(Chou et al., 2013)	2012	3	3	3	3	1	3	3	19
(Alexiu et al., 2017)	2017	3	3	0	3	3	3	3	18
(Conceicao et al., 2017)	2017	2	1	0	2	2	3	3	13
(Corsonello et al., 1999)	2017	2	3	2	2	3	2	1	15
(Davis et al., 1998)	1998	3	2	2	3	0	3	3	16
(Davis et al., 2010)	2010	3	1	1	3	0	3	2	13
(Davis et al., 2011)	2011	2	1	1	2	0	3	3	12
(Dendy et al., 2014)	2014	3	3	0	2	0	2	2	12
(Derijks et al., 2008)	2008	3	3	3	3	0	3	3	18

Author	Year of publication	Representative population	Sample size	Confounders adjustments	Appropriate statistical analysis	Missing data	Methodology of the outcome measurement	Methods to detect hypoglycaemia	**Total**
(Desjardins et al., 2014)	2014	2	1	2	3	0	2	3	13
(Deusenberry et al., 2012)	2012	2	2	3	2	2	1	2	14
(Donnelly et al., 2005)	2004	3	3	3	3	0	3	3	18
(Duran-Nah et al., 2008)	2008	3	1	3	2	3	3	3	18
(Egger et al., 1991)	1991	3	3	3	3	3	3	3	21
(Elwen et al., 2015)	2015	2	1	2	3	0	1	3	12
(Endo et al., 2000)	2000	3	1	1	1	0	3	3	12
(Eriksson et al., 2016)	2016	3	3	3	3	0	3	3	18
(Faerch et al., 2011)	2011	3	2	1	2	0	3	3	14
(Feher et al., 2016)	2016	2	1	1	1	1	1	1	8
(Fang et al., 2015)	2013	2	2	3	3	0	3	3	16
(Farmer et al., 2012)	2012	2	2	1	2	2	1	2	12
(Feil et al., 2011)	2011	3	3	3	3	1	3	3	19
(Freathy et al., 2006)	2006	3	3	3	3	1	3	3	19

Author	Year of publication	Representative population	Sample size	Confounders adjustments	Appropriate statistical analysis	Missing data	Methodology of the outcome measurement	Methods to detect hypoglycaemia	**Total**
(Fu et al., 2014)	2014	3	3	3	3	0	3	3	18
(Ganz et al., 2014)	2014	3	3	3	3	0	3	3	18
(Geller et al., 2014)	2014	3	3	1	3	0	3	3	16
(Green et al., 2012)	2012	3	2	3	0	3	3	14	3
(Gu et al., 2016)	2016	3	3	3	3	2	3	3	20
(Guisasola et al., 2008)	2008	2	2	2	3	1	3	2	15
(Henderson et al., 2003)	2013	3	3	3	3	2	3	3	20
(Herings et al., 1995)	1995	3	3	3	3	3	3	3	21
(Hirai et al., 2007)	2007	1	1	1	2	1	2	3	11
(Holstein et al., 2009)	2009	2	1	3	3	0	3	3	15
Holstein et al 2011 (Holstein et al., 2011)	2011	2	1	0	1	0	2	2	8
(Honkasalo et al., 2011)	2011	3	3	3	3	1	3	3	19
(Ishikawa et al., 2017)	2017	3	3	3	3	3	3	3	21

Author	Year of publication	Representative population	Sample size	Confounders adjustments	Appropriate statistical analysis	Missing data	Methodology of the outcome measurement	Methods to detect hypoglycaemia	**Total**
(Ishtiak-Ahmed et al., 2017)	2017	3	3	3	3	0	3	3	18
(Yun et al., 2018)	2018	3	3	0	3	0	3	3	15
(Yun et al., 2015)	2015								0
(Jeon et al., 2016)	2016	3	3	3	3	0	3	3	18
(Jick et al., 1990)	1990	3	3	2	1	3	3	3	18
(Johnston et al., 2012)	2012	3	3	3	3	1	3	3	16
(Johansen et al., 2015a)	2015	3	3	3	3	1	3	3	19
(Kajiwara et al., 2015)	2015	3	3	0	2	0	0	0	8
(Karges et al., 2015)	2015	3	3	3	3	0	3	3	18
(Karter et al., 2017)	2017	3	3	3	3	0	3	3	18
(Katon et al., 2013)	2013	3	3	3	3	3	3	3	21
(Katz et al., 2012)	2012	2	2	2	3	0	2	2	13
(Kim et al., 2016b)	2012	3	3	3	3	0	3	3	18
(Kostev et al., 2014)	2014	0	0	3	3	0	1	2	9
(Kostev et al., 2015)	2015	3	3	3	3	0	3	3	18
(Leckie et al., 2005)	2005	3	3	3	3	1	3	3	19

Author	Year of publication	Representative population	Sample size	Confounders adjustments	Appropriate statistical analysis	Missing data	Methodology of the outcome measurement	Methods to detect hypoglycaemia	**Total**
(Leese et al., 2003)	2003	3	3	1	3	1	3	3	17
(Leonard et al., 2016)	2016	3	3	3	3	0	3	3	18
(Li et al., 2014)	2014	3	3	3	3	1	3	3	19
(Lin et al., 2010)	2010	3	3	3	3	0	3	3	18
(Lipska et al., 2013)	2013	3	3	3	3	3	3	3	21
(Lipska et al., 2014)	2014	3	3	3	3	0	3	3	18
(Loke et al., 2010)	2010	2	1	0	1	2	2	2	10
(Lundkvist et al., 2005)	2005	3	3	1	3	1	3	3	17
(Ly et al., 2009)	2009	3	3	3	3	1	3	3	19
(Maltoni et al., 2013)	2013	2	1	0	2	3	3	3	14
(Mantovani et al., 2016)	2016	3	1	1	2	0	3	3	13
(Mauricio et al., 2015)	2016	3	3	3	3	3	3	3	21
(McCoy et al., 2016)	2016	3	3	3	3	0	3	3	18
(Miller et al., 2001)	2001	3	2	1	1	2	3	3	15
(Alonso-Moran et al., 2015)	2015	3	3	3	3	3	3	3	21

Author	Year of publication	Representative population	Sample size	Confounders adjustments	Appropriate statistical analysis	Missing data	Methodology of the outcome measurement	Methods to detect hypoglycaemia	**Total**
(Morris et al., 1997)	1997	3	1	1	2	2	2	2	13
(Muhlhauser et al., 1985)	1985	3	2	1	3	1	3	3	16
(Muhlhauser et al., 1998)	1998	3	3	3	3	0	3	3	18
(Muller et al., 2017)	2017	3	3	3	3	3	3	3	21
(Murata et al., 2005)	2004	3	2	3	3	3	3	3	20
(Nam et al., 2018)	2018	3	3	3	3	3	3	3	21
(Nunes et al., 2016)	2016	3	3	3	3	2	3	3	20
(Nunes et al., 2017)	2017	3	3	3	3	3	3	3	21
(Odawara et al., 2014)	2014	3	3	3	3	3	3	3	21
(Olsen et al., 2014)	2014	3	3	3	3	3	3	3	21
(Yu et al., 2018)	2017	3	3	3	3	3	3	3	21
(Ooi et al., 2011)	2011	2	1	2	0	0	3	3	15
(Pathak et al., 2016)	2016	3	3	3	3	0	3	3	18
(Lyngsie et al., 2016)	2016	3	3	0	3	3	3	3	18
(Pedersen-Bjergaard et al., 2003)	2003	1	2	3	3	0	3	2	14

Author	Year of publication	Representative population	Sample size	Confounders adjustments	Appropriate statistical analysis	Missing data	Methodology of the outcome measurement	Methods to detect hypoglycaemia	**Total**
(Pedersen-Bjergaard et al., 2004)	2004	2	3	3	3	1	3	3	18
(Pilemann-Lyberg et al., 2015)	2016	2	2	1	2	2	1	2	12
(Pirags et al., 2012)	2012	3	2	2	3	3	3	3	19
(Quilliam et al., 2011a)	2011	3	3	3	3	0	3	3	18
(Radosevich et al., 2015)	2015	3	3	3	3	0	3	3	18
(Ragia et al., 2012)	2013	2	1	3	3	0	3	1	13
(Rajendran et al., 2015)	2015	3	1	2	2	0	2	3	13
(Raju et al., 2016)	2016	3	3	3	3	0	3	3	18
(Rathmann et al., 2013)	2013	2	3	2	3	0	1	1	12
Ren et al 2016 (Ren et al., 2016)	2016	3	2	2	2	0	3	3	15
(Romley et al., 2015)	2015	3	3	2	3	0	3	3	17

Author	Year of publication	Representative population	Sample size	Confounders adjustments	Appropriate statistical analysis	Missing data	Methodology of the outcome measurement	Methods to detect hypoglycaemia	**Total**
(Roumie et al., 2016)	2015	3	3	3	3	0	3	3	18
(Rubin et al., 2011)	2011	3	2	3	3	3	3	3	20
(Sako et al., 2015)	2015	3	3	3	3	0	3	2	17
(Samann et al., 2013)	2013	3	3	3	3	1	3	3	19
(Sarkar et al., 2010)	2010	2	3	1	3	1	2	2	14
(Sato et al., 2010)	2010	2	1	2	2	1	2	1	11
(Schloot et al., 2016)	2016	1	2	3	3	1	3	3	16
(Seewi et al., 2008)	2008	2	1	2	2	0	2	2	11
(Seligman et al., 2010)	2010	3	3	3	3	0	3	3	18
(Shriraam et al., 2017)	2017	3	3	3	3	1	3	3	19
(Solomon et al., 2013)	2013	3	3	3	2	0	3	3	17
(Sreenan et al., 2014)	2014	1	1	2	2	2	2	2	12
(Strandberg et al., 2015)	2017	3	3	3	3	0	3	3	18

Author	Year of publication	Representative population	Sample size	Confounders adjustments	Appropriate statistical analysis	Missing data	Methodology of the outcome measurement	Methods to detect hypoglycaemia	**Total**
(Stuart et al., 2017)	2017	1	2	2	2	2	2	1	12
(Takeishi et al., 2016)	2016	3	1	2	3	0	1	3	13
(Tan et al., 2015)	2015	3	3	3	1	0	3	3	16
(Thamer et al., 1999)	1999	3	3	2	3	0	2	3	16
(Tschope et al., 2012)	2012	3	2	2	3	0	2	2	14
(Tschope et al., 2011)	2012	3	3	3	3	3	3		18
(Van Keulen et al., 2015)	2015	3	3	2	3	0	2	3	16
(Vlckova et al., 2010)	2009	3	2	2	3	1	3	2	16
(Wang et al., 2015)	2015	3	3	3	3	0	3	3	18
(Weinstock et al., 2013)	2013	2	3	3	3	1	3	3	18
(Weir et al., 2011)	2010	3	3	3	3	3	3	3	21
(Williams et al., 2014)	2014	3	3	3	3	3	3	3	21

Author	Year of publication	Representative population	Sample size	Confounders adjustments	Appropriate statistical analysis	Missing data	Methodology of the outcome measurement	Methods to detect hypoglycaemia	**Total**
(Wohland et al., 2017)	2017	3	3	3	3	1	3	3	19
(Chu et al., 2017)	2017	3	3	3	3	0	3	3	18
(Cho and Cho, 2018)	2018	3	3	3	3	0	3	3	18
(Yu et al., 2016)	2016	2	3	2	3	0	3	3	16
(Ikeda et al., 2018)	2018	3	3	3	3	0	3	3	18
(Yun et al., 2013)	2013	1	1	3	3	3	3	3	17
(Zaccardi et al., 2017)	2016	3	3	3	3	0	3	3	18
(Zhong et al., 2017)	2017	3	3	3	3	3	3	3	21

Methodology of the outcome measurements (Percentage, OR, RR, IR, HR); Methods to detect hypoglycaemia (ICD codes, self-reported or lab test)

2.7.4 Prevalence of hypoglycaemia

Only studies that measured hypoglycaemia prevalence over a 12-months period were included in the meta-analysis, and this resulted in 39 studies being included with a total of 2,462,810 patients with diabetes (Table 4). The prevalence of hypoglycaemia varied between studies, some citations reported a high prevalence rate of 73% (Henderson et al., 2003), while other citations reported low prevalence rate of less than 1% (Conceicao et al., 2017). Pooled average prevalence of hypoglycaemia in diabetes was 11.0 % (95% CI, 7.0 – 17.0) (Figure 10). The pooled estimate of prevalence of hypoglycaemia was 12.0 % (95% CI, 8.0 – 17.0) after sensitivity analysis of removing two studies (Henderson et al., 2003, Conceicao et al., 2017) (Figure 11). However, the 39 studies included in the meta-analysis of prevalence had a high level of heterogeneity (I-squared = 100.0 %). There was large variation between studies in terms of hypoglycaemia definitions, year of publications, geographical locations, study designs and data source.

Table 4: Characteristics of studies included in the prevalence meta-analysis

Author (s)	Year of publication	Country (s)	Study design	Sample size	Follow up	Sample Source	DM type	Treatment	Prevalence (%)
(Jabbar et al., 2017)	2017	Multinational	retrospectively	3250	1 year	Self-reported	T2DM	A combination of oral and insulin	7.1
(Akirov et al., 2018)	2018	N/A	prospective	5301	1 year	Self-reported	Both types of diabetes	A combination of oral and insulin	15
(Aung et al., 2012)	2012	Europe	retrospectively	1066	1 year	Self-reported	T2DM	A combination of oral and insulin	8
(Bognetti et al., 1997)	1997	Europe	retrospectively	187	1 year	Self-reported	Both types of diabetes	Insulin only	19.2
(Bramlage et al., 2012)	2012	Europe	retrospectively	3810	1 year	Self-reported	T2DM	A combination of oral and insulin	10.7
(Buyken et al., 1998)	1998	Europe	retrospectively	2065	1 year	Self-reported	T1DM	Insulin only	31.8
(Cherubini et al., 2013)	2013	Europe	retrospectively	2025	1 year	Self-reported	T2DM	Insulin only	5
(Conceicao et al., 2017)	2017	Europe	retrospectively	425706	1 year	Self-reported	Both types of diabetes	A combination of oral and insulin	0.074

Author (s)	Year of publication	Country (s)	Study design	Sample size	Follow up	Sample Source	DM type	Treatment	Prevalence (%)
(Deusenberry et al., 2012)	2012	North America	retrospectively	692	1 year	Database	T2DM	sulfonylureas	19
(Faerch et al., 2011)	2011	Europe	prospective	128	1 year	Self-reported	T1DM	Insulin only	38
(Feher et al., 2016)	2016	Europe	retrospectively	1569	1 year	Self-reported	T2DM	A combination of oral and insulin	62
(Farmer et al., 2012)	2012	Europe	retrospectively	3562	1 year	Database	Both types of diabetes	NA	2.1
(Green et al., 2012)	2012	North America	retrospectively	3000	1 year	Self-reported	T2DM	NA	23
(Guisasola et al., 2008)	2008	Europe	retrospectively	1709	1 year	Self-reported	T2DM	A combination of oral only	38.4
(Henderson et al., 2003)	2003	Europe	retrospectively	215	1 year	Self-reported	T2DM	Insulin only	73
(Hirai et al., 2007)	2007	North America	retrospectively	537	1 year	Self-reported	T1DM	Insulin only	14.3
(Honkasalo et al., 2011)	2011	Europe	retrospectively	1005	1 year	Self-reported	T2DM	NA	12.3
(Honkasalo et al., 2011)	2011	Europe	retrospectively	771	1 year	Self-reported	T1DM	Insulin only	31
(Yun et al., 2018)	2018	Asia	retrospectively	1366692	1 year	Database	T2DM	NA	2.7

Author (s)	Year of publication	Country (s)	Study design	Sample size	Follow up	Sample Source	DM type	Treatment	Prevalence (%)
(Johnston et al., 2012)	2012	North America	retrospectively	361210	1 year	Database	T2DM	A combination of oral only	4.7
(Kostev et al., 2014)	2013	Europe	retrospectively	32545	1 year	Database	T2DM	Insulin only	2.2
(Leese et al., 2003)	2003	Europe	retrospectively	977	1 year	Database	T1DM	Insulin only	7.1
(Leese et al., 2003)	2003	Europe	retrospectively	7678	1 year	Database	T2DM	A combination of oral and insulin	1.1
(Lipska et al., 2013)	2013	North America	retrospectively	9094	1 year	Database	T2DM	A combination of oral and insulin	10.8
(Muhlhauser et al., 1985)	1985	Europe	prospective	384	1 year	Self-reported	T1DM	Insulin only	14.6
(Murata et al., 2005)	2003	North America	prospective	344	1 year	Self-reported	T2DM	A combination of oral and insulin	51.2
(Nunes et al., 2017)	2017	North America	retrospectively	143635	1 year	Database	T2DM	sulfonylureas	8.5
(Olsen et al., 2014)	2014	Europe	retrospectively	440	1 year	Self-reported	T1DM	Insulin only	37
(Ooi et al., 2011)	2011	Asia	retrospectively	170	1 year	Self-reported	T2DM	A combination of oral and insulin	61.8

Author (s)	Year of publication	Country (s)	Study design	Sample size	Follow up	Sample Source	DM type	Treatment	Prevalence (%)
(Pedersen-Bjergaard et al., 2004)	2004	Europe	retrospectively	1076	1 year	Self-reported	T1DM	Insulin only	36.7
(Pirags et al., 2012)	2012	Multinational	prospective	991	1 year	Self-reported	T1DM	Insulin only	2.5
(Rajendran et al., 2015)	2015	Europe	retrospectively	132	1 year	Database	Both types of diabetes	A combination of oral and insulin	1
(Samann et al., 2013)	2013	Europe	retrospectively	373	1 year	Self-reported	T1DM	A combination of oral and insulin	1.3
(Samann et al., 2013)	2013	Europe	retrospectively	4481	1 year	Self-reported	T2DM	A combination of oral and insulin	0.5
(Sarkar et al., 2010)	2010	North America	retrospectively	14357	1 year	Self-reported	T2DM	A combination of oral and insulin	11
(Schloot et al., 2016)	2015	Europe	retrospectively	29485	1 year	Database	T2DM	sulfonylureas	2.8
(Seligman et al., 2010)	2011	North America	retrospectively	711	1 year	Self-reported	T2DM	NA	28
(Shriraam et al., 2017)	2017	Asia	retrospectively	366	1 year	Self-reported	T2DM	A combination of oral and insulin	23

Author (s)	Year of publication	Country (s)	Study design	Sample size	Follow up	Sample Source	DM type	Treatment	Prevalence (%)
(Stuart et al., 2017)	2017	Europe	retrospectively	9584	1 year	Self-reported	Both types of diabetes	A combination of oral and insulin	13.8
(Tschope et al., 2012)	2012	Europe	prospective	3347	1 year	Self-reported	T2DM	A combination of oral only	14.1
(Weinstock et al., 2013)	2013	North America	retrospectively	4973	1 year	Self-reported	T1DM	A combination of oral and insulin	11.8
(Chu et al., 2017)	2017	Asia	retrospectively	20845	1 year	Database	Both types of diabetes	NA	14.48

Abbreviations: NA: Not available, DM: diabetes mellitus

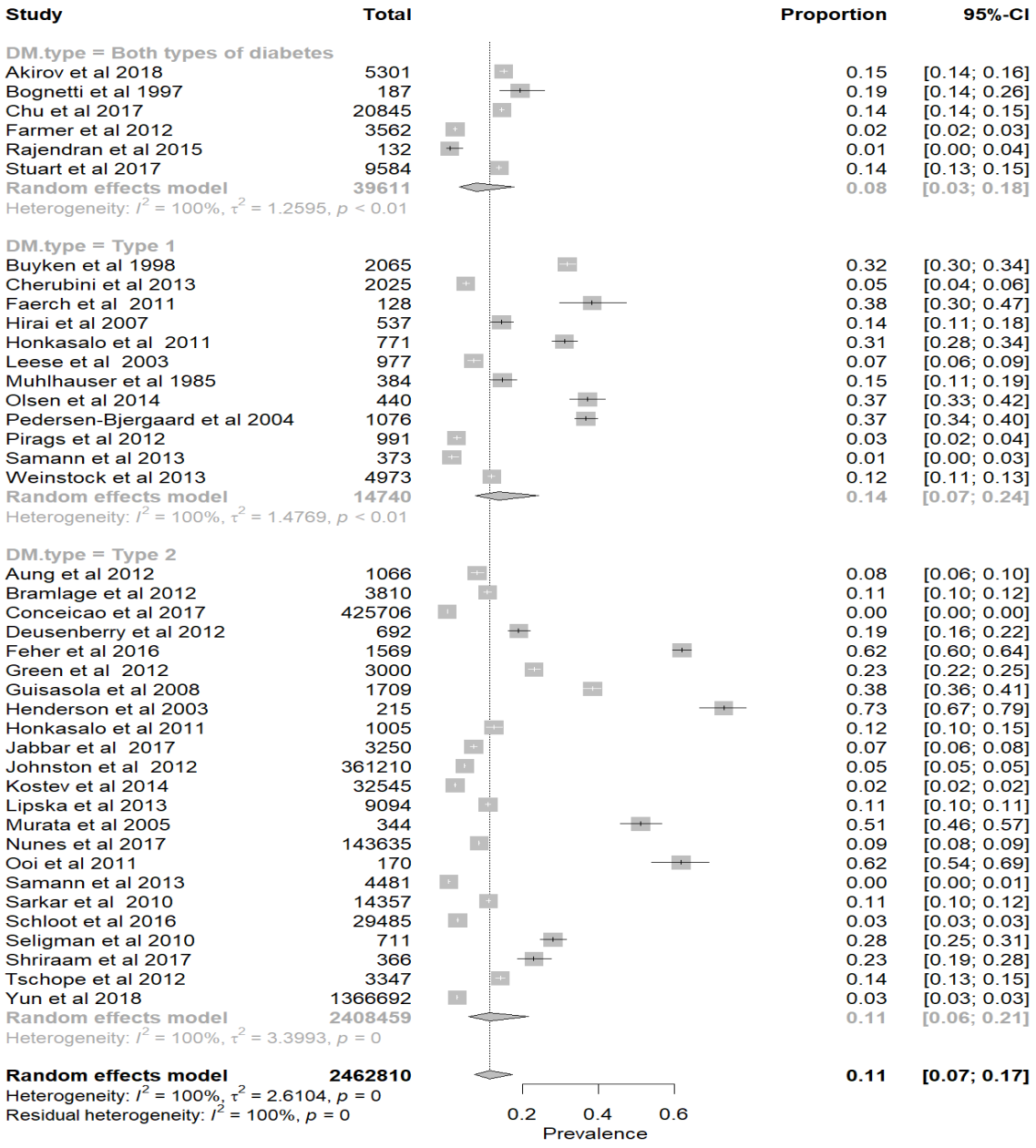


Figure 10: Forest plot of prevalence meta-analysis of hypoglycaemia in both types of diabetes.

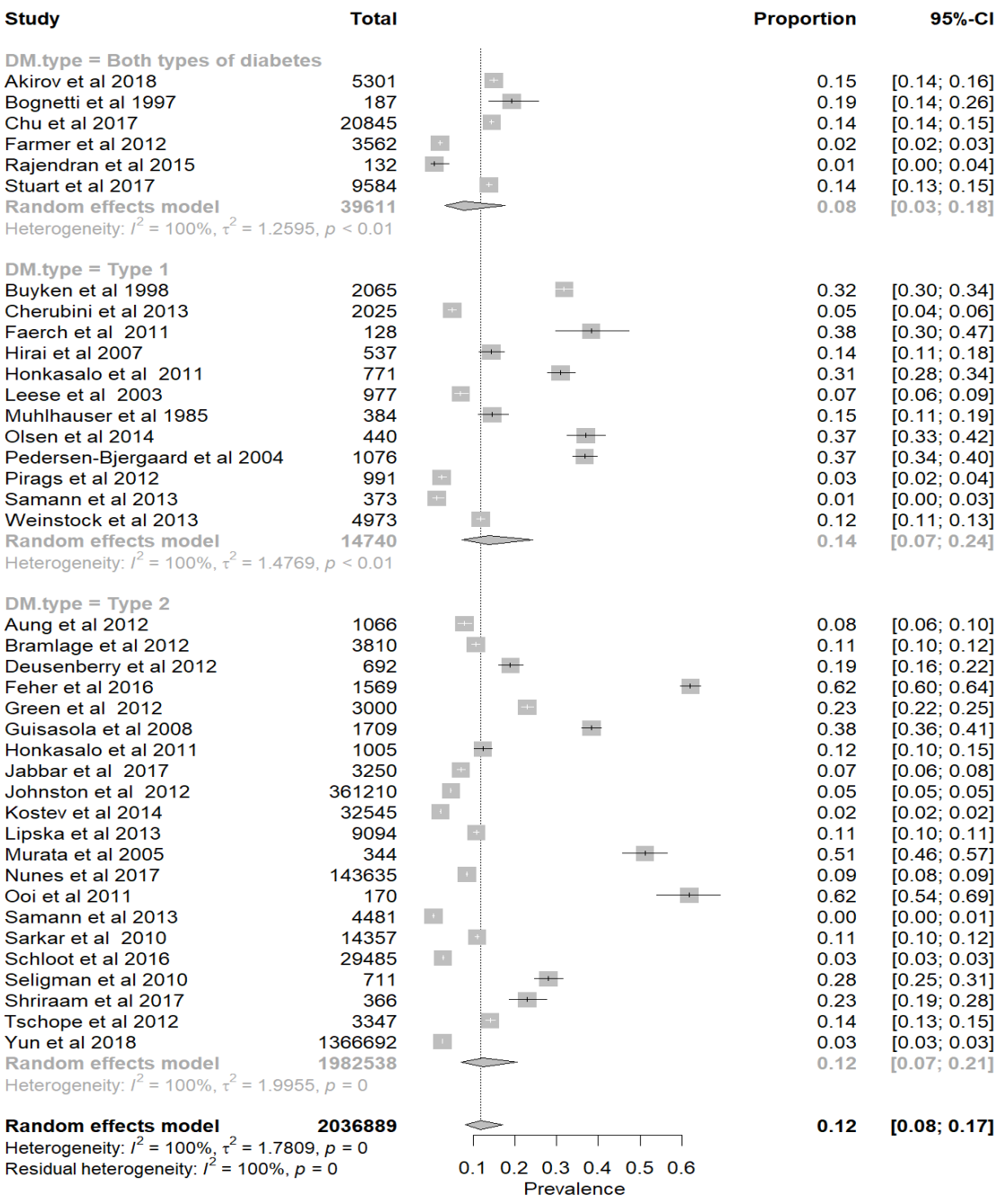


Figure 11: Forest plot of prevalence meta-analysis of hypoglycaemia in both types of diabetes after sensitivity analysis.

2.7.4.1 Subgroup analysis

When stratifying by type of diabetes, the pooled average prevalence of hypoglycaemia for T1DM and T2DM were 14.0 % (95% CI, 7.0 – 24.0) and 11.0 % (95% CI, 6.0 – 21.0), respectively. Further stratification by geographical location showed that the average prevalence of hypoglycaemia for studies based in Europe and North America was 10.0 % (95% CI, 5.0 – 19.0) and 15.0 % (95% CI, 10.0 – 23.0), respectively, while, it was higher in Asia 18.0 % (95% CI, 5.0 – 47.0) (Figure 12). The average prevalence when stratified by data source varied among studies. Self-reported studies had a higher pooled average than studies using electronic health records: pooled average prevalence of hypoglycaemia was 15.0 % (95% CI, 9.0 – 24.0) and 5.0 % (95% CI, 3.0 – 8.0), respectively (Figure 13). When stratified by treatment regimen, studies that included only patients using insulin had higher prevalence of hypoglycaemia 17.0 % (95% CI, 10.0 – 27.0), compared to studies that included patients using sulfonylureas 8.0 % (95% CI, 3.0 – 18.0) (Figure 14).

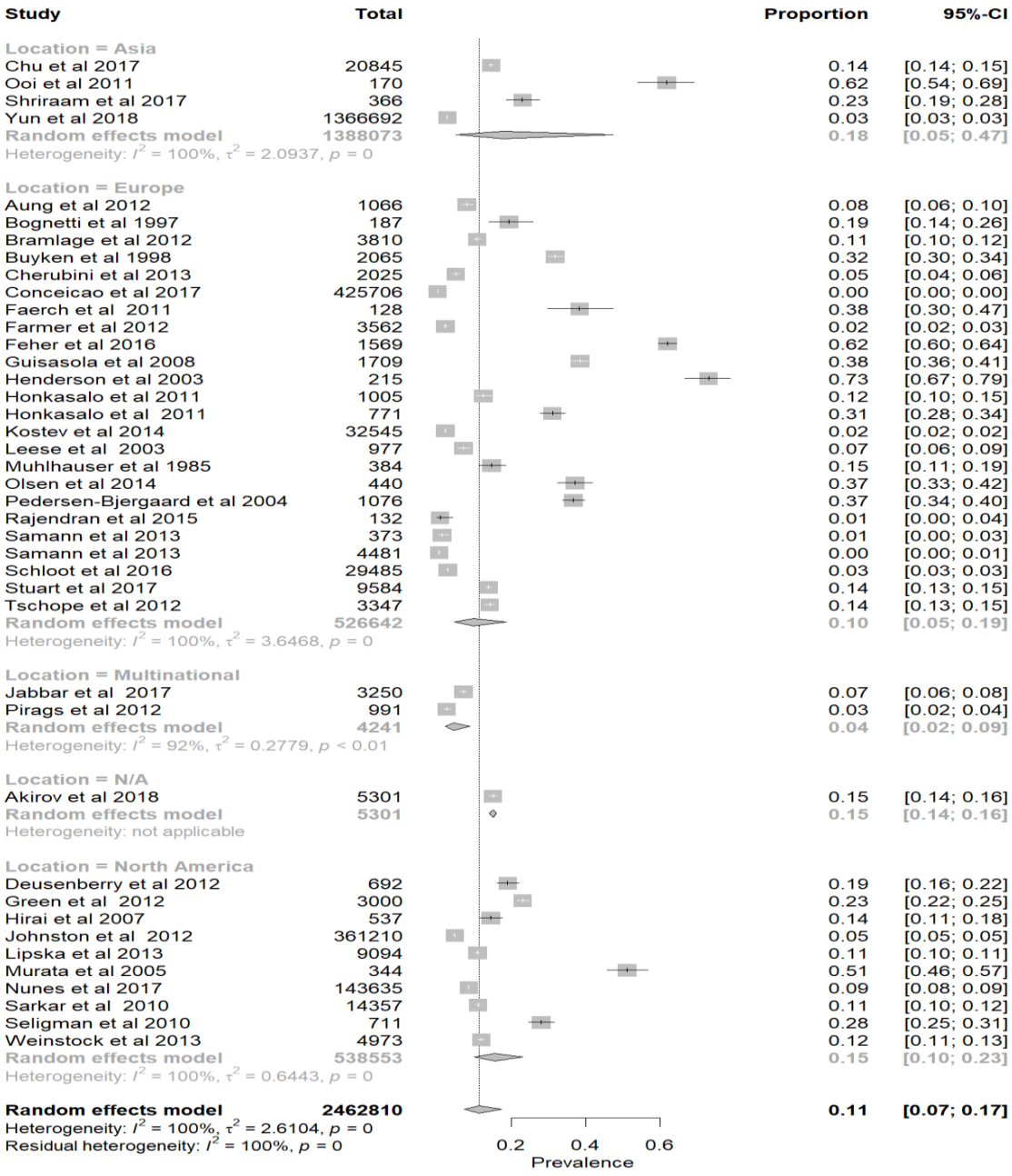


Figure 12: Forest plot of prevalence of hypoglycaemia meta-analysis stratified by location.

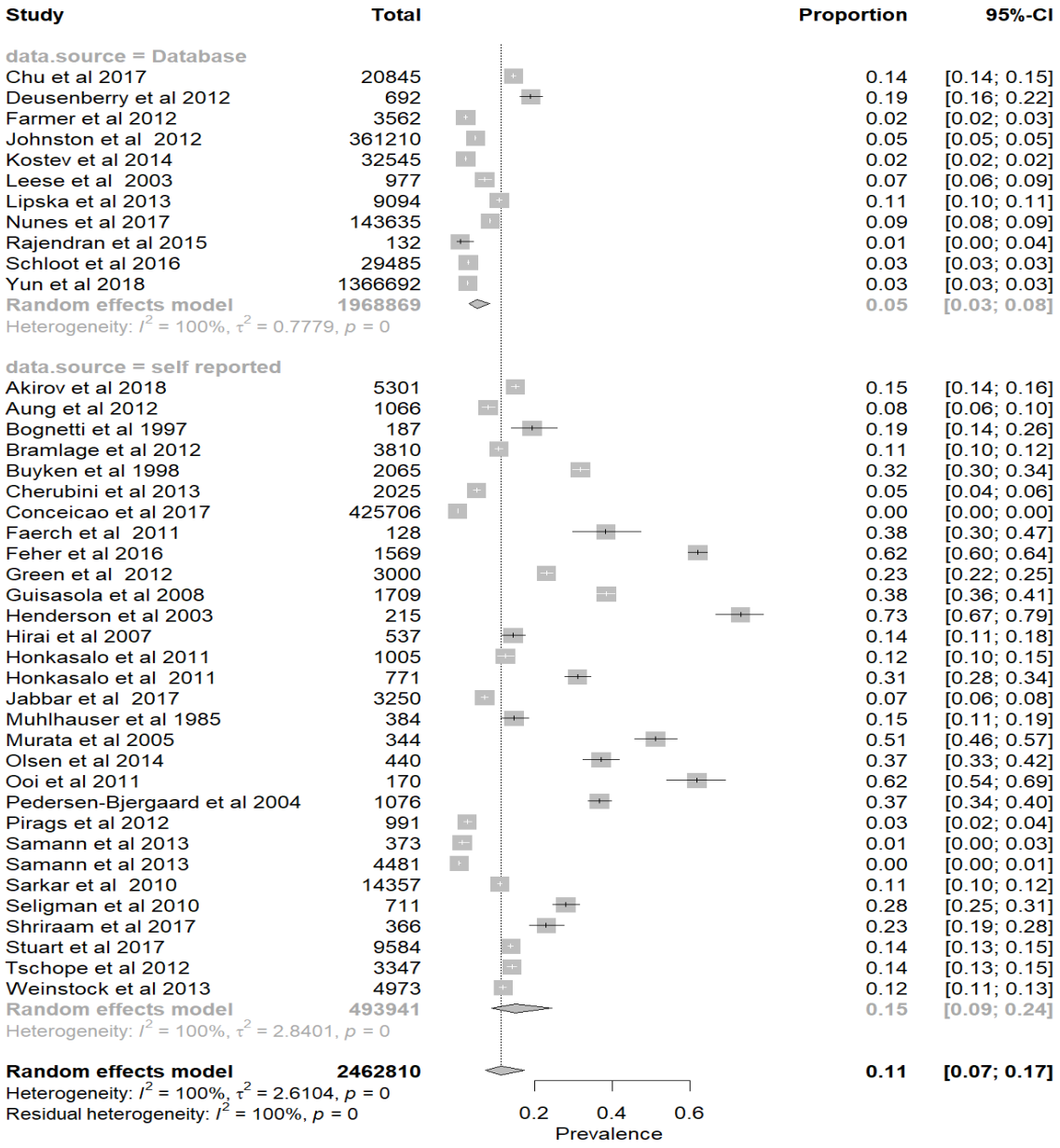


Figure 13: Forest plot of prevalence of hypoglycaemia meta-analysis stratified by data source.

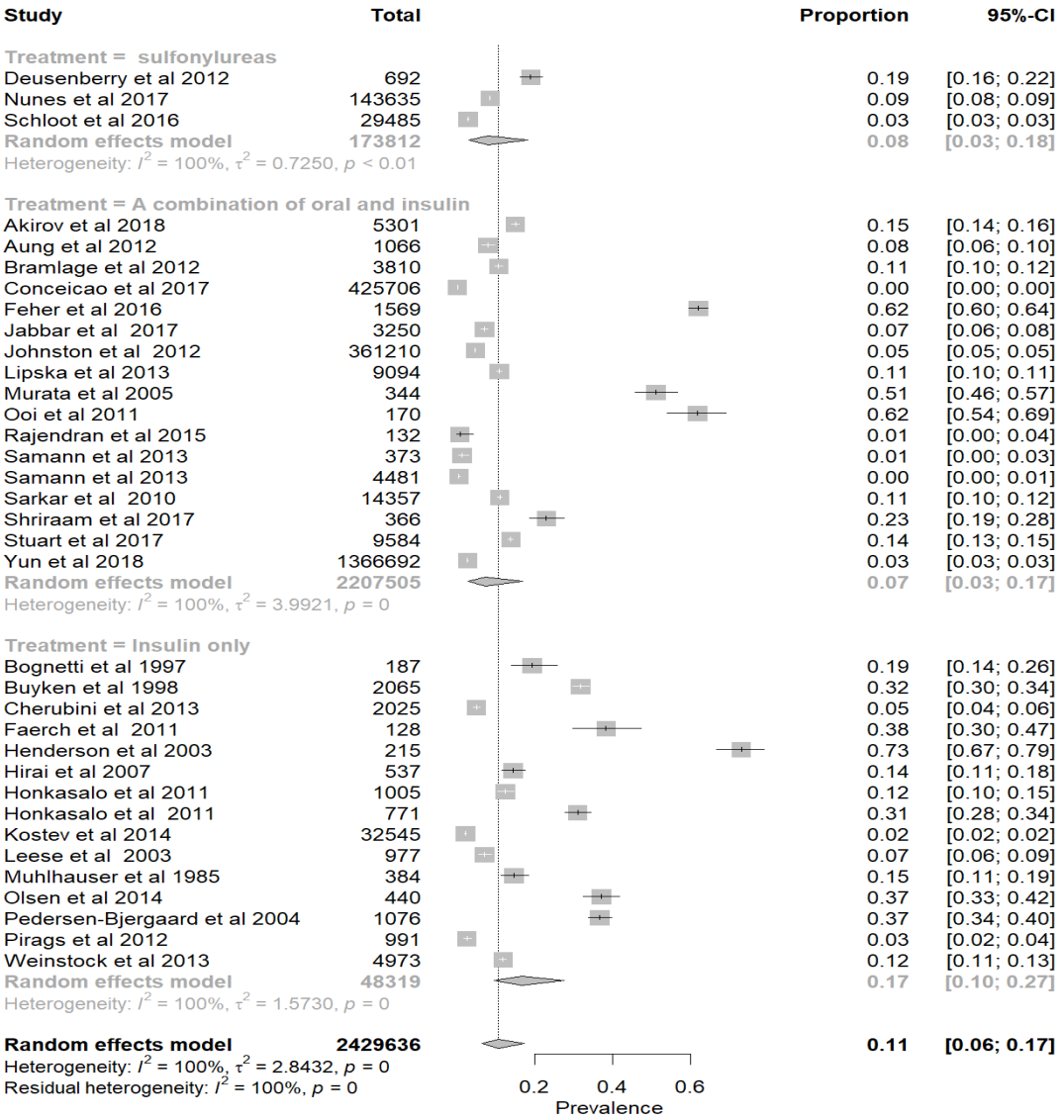


Figure 14: Forest plot of prevalence of hypoglycaemia meta-analysis stratified by treatment.

Further stratification by combining studies from similar geographical location, study design and data source showed that the pooled estimate of prevalence of hypoglycaemia was 35.0 % (95% CI, 32.0 – 38.0) (I^2=59%) among studies that were

cross-sectional in design, self-reported in source of data, and were conducted in Europe (Figure 15). While the pooled estimate of prevalence of hypoglycaemia was 11.0 % (95% CI, 11.0 – 13.0) (I^2=38%) among studies that were cross-sectional in design, self-reported in source of data, and were conducted in North America (Figure 16).

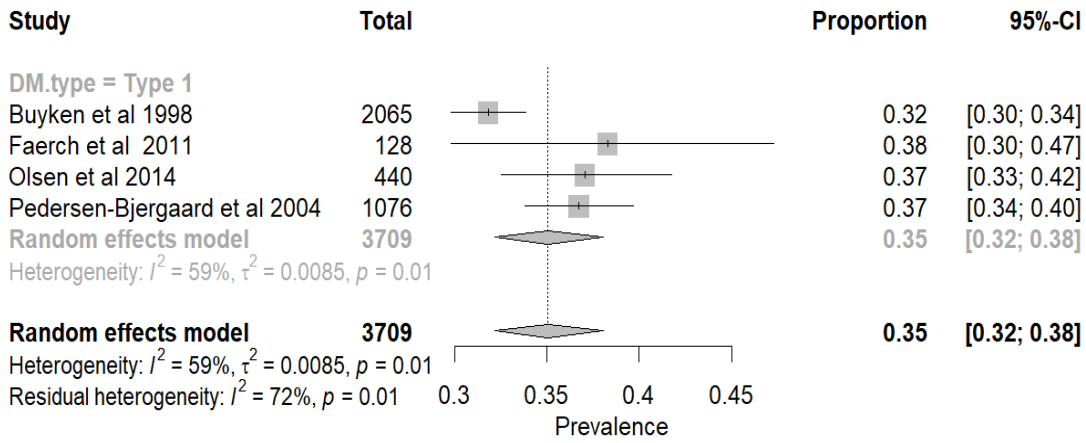


Figure 15: Forest plot of prevalence of hypoglycaemia meta-analysis stratified by European studies, self-reported and cross-sectional studies.

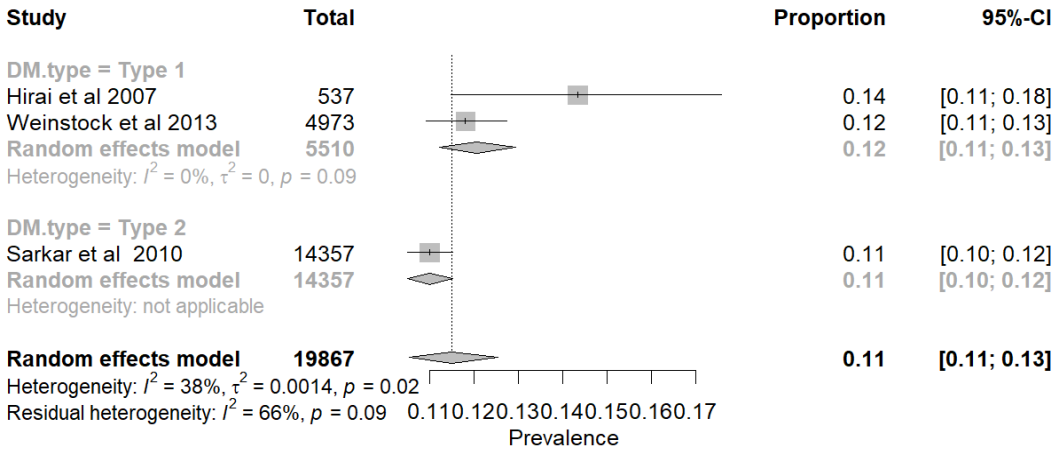


Figure 16: Forest plot of prevalence of hypoglycaemia meta-analysis stratified by North American studies, self-reported and cross-sectional studies.

2.7.5 Incidence of hypoglycaemia

A total of 39 studies involving 45,768,950 patients met the inclusion criteria and were included in the meta-analysis (Table 5). The pooled incidence rates of hypoglycaemia was 64.1 episodes per 1,000 person-years (95% CI, 29.4 – 139.7) (Figure 17).

The pooled hypoglycaemia incidence rate stratified by diabetes type was 156.5 episodes per 1,000 person-years (95% CI, 61.6 – 397.6) for patients with T1DM and 40.9 episodes per 1,000-person years (95% CI, 9.5 - 174.9) for patients with T2DM (Figure 17). Based on data source, the incidence rate of self-reported hypoglycaemia showed a pooled average rate of 160.0 episodes per 1,000 person years (95% CI, 28.3 – 903.6) and 43.3 episodes per 1,000 person-years (95% CI, 19.2 - 97.3) obtained from databases (Figure 18). Furthermore, the average incidence rates were 222.6 episodes per 1,000 person-years (95% CI, 91.9 – 539.3) for patients with diabetes using insulin, while it was 18.0 episodes per 1,000 person years (95% CI, 1.8 – 178.2) for patients on combination therapy of both insulin and oral hypoglycaemia agent. (Figure 19).

Table 5: Details of the studies included in the incidence meta-analysis.

Author	Year of publication	Geographical region	Sample size	Sample Source	DM type	TTT regimen	Incidence rate Per 100 Pys
(Barkai et al., 1998)	1998	NA	130	Self-reported	T1DM	Insulin	38.5
(Birkebaek et al., 2017)	2017	Europe	8806	Database	T1DM	Insulin	6
(Pedersen-Bjergaard et al., 2003)	2003	Europe	171	Database	T1DM	Insulin	110
(Blasetti et al., 2011)	2011	Europe	195	Database	T1DM	Insulin	9.4
(Bognetti et al., 1997)	1997	Europe	187	Self-reported	Both types of diabetes	NA	14.9
(Bron et al., 2012)	2012	North America	212061	Database	T2DM	Oral medication only	5.4
(Cherubini et al., 2013)	2013	Europe	2025	Database	T1DM	Insulin	7.7
(Alexiu et al., 2017)	2017	North America	232898	Database	Both types of diabetes	A combination of oral and insulin	26.63
(Davis et al., 2010)	2010	Australia	616	Self-reported	T2DM	NA	1.7

Author	Year of publication	Geographical region	Sample size	Sample Source	DM type	TTT regimen	Incidence rate Per 100 Pys
(Davis et al., 1998)	1998	Australia	709	Self-reported	T1DM	Insulin	23.2
(Donnelly et al., 2005)	2004	Europe	173	Self-reported	T2DM	Insulin	1636
(Donnelly et al., 2005)	2004	Europe	94	Database	T1DM	Insulin	4289
(Henderson et al., 2003)	2003	Europe	215	Self-reported	T2DM	Insulin	28
(Ishtiak-Ahmed et al., 2017)	2017	Europe	17230	Database	T1DM	Insulin	3.38
(Johansen et al., 2015b)	2015	Europe	3320	Database	T1DM	Insulin	15.1
(Karges et al., 2015)	2015	North America	31330	Database	T1DM	Insulin	4.81
(Katz et al., 2012)	2012	Australia	255	Self-reported	T1DM	Insulin	37.6
(Kim et al., 2016b)	2016	Asia	307107	Database	T2DM	A combination of oral and insulin	0.933

Author	Year of publication	Geographical region	Sample size	Sample Source	DM type	TTT regimen	Incidence rate Per 100 Pys
(Leckie et al., 2005)	2005	Europe	243	Database	Both types of diabetes	Insulin	98
(Leese et al., 2003)	2003	Europe	977	Database	T1DM	Insulin	11.5
(Leonard et al., 2016)	2016	North America	592872	Database	T2DM	Oral medication only	5.8
(Lipska et al., 2014)	2014	North America	33952331	Database	Both types of diabetes	NA	0.105
(Lundkvist et al., 2005)	2005	Europe	309	Self-reported	T2DM	A combination of oral and insulin	0.0072
(Ly et al., 2009)	2009	Europe	656	Self-reported	T1DM	Insulin	24.5
(Maltoni et al., 2013)	2013	Europe	269	Self-reported	T1DM	Insulin	15.6
(Alonso-Moran et al., 2015)	2015	Europe	134413	Database	T2DM	NA	63

Author	Year of publication	Geographical region	Sample size	Sample Source	DM type	TTT regimen	Incidence rate Per 100 Pys
(Muller et al., 2017)	2017	Europe	7900000	Database	T2DM	A combination of oral and insulin	0.49
(Murata et al., 2005)	2003	North America	344	Self-reported	T2DM	A combination of oral and insulin	610
(Nunes et al., 2016)	2016	North America	844683	Database	T2DM	Oral medication only	6.28
(Odawara et al., 2014)	2014	Asia	4219	Database	T2DM	A combination of oral and insulin	3.5
(Pathak et al., 2016)	2016	North America	917440	Database	Both types of diabetes	NA	1.47
(Lyngsie et al., 2016)	2016	Europe	307016	Database	Both types of diabetes	NA	0.7
(Pilemann-Lyberg et al., 2015)	2015	Europe	3156	Database	T2DM	Oral medication only	0.43
(Pirags et al., 2012)	2012	Australia	991	Self-reported	T1DM	Insulin	4

Author	Year of publication	Geographical region	Sample size	Sample Source	DM type	TTT regimen	Incidence rate Per 100 Pys
(Raju et al., 2016)	2016	North America	11536	Database	T2DM	Oral medication only	3.37
(Sako et al., 2015)	2015	Asia	25071	Database	Both types of diabetes	NA	0.412
(Wang et al., 2015)	2015	North America	63972	Database	Both types of diabetes	NA	1.4
(Ikeda et al., 2018)	2018	Asia	166806	Database	T2DM	A combination of oral and insulin	0.37
(Yun et al., 2013)	2013	Asia	878	Database	T2DM	A combination of oral and insulin	1.55
(Zhong et al., 2017)	2017	Europe	23246	Database	T1DM	Insulin	1.48

Abbreviations: TTT: treatment regimen, DM: diabetes mellitus, NA: not available, IR: incidence rate. PY: patients years, T1DM: type 1 diabetes mellitus, T2DM: type 2 diabetes mellitus

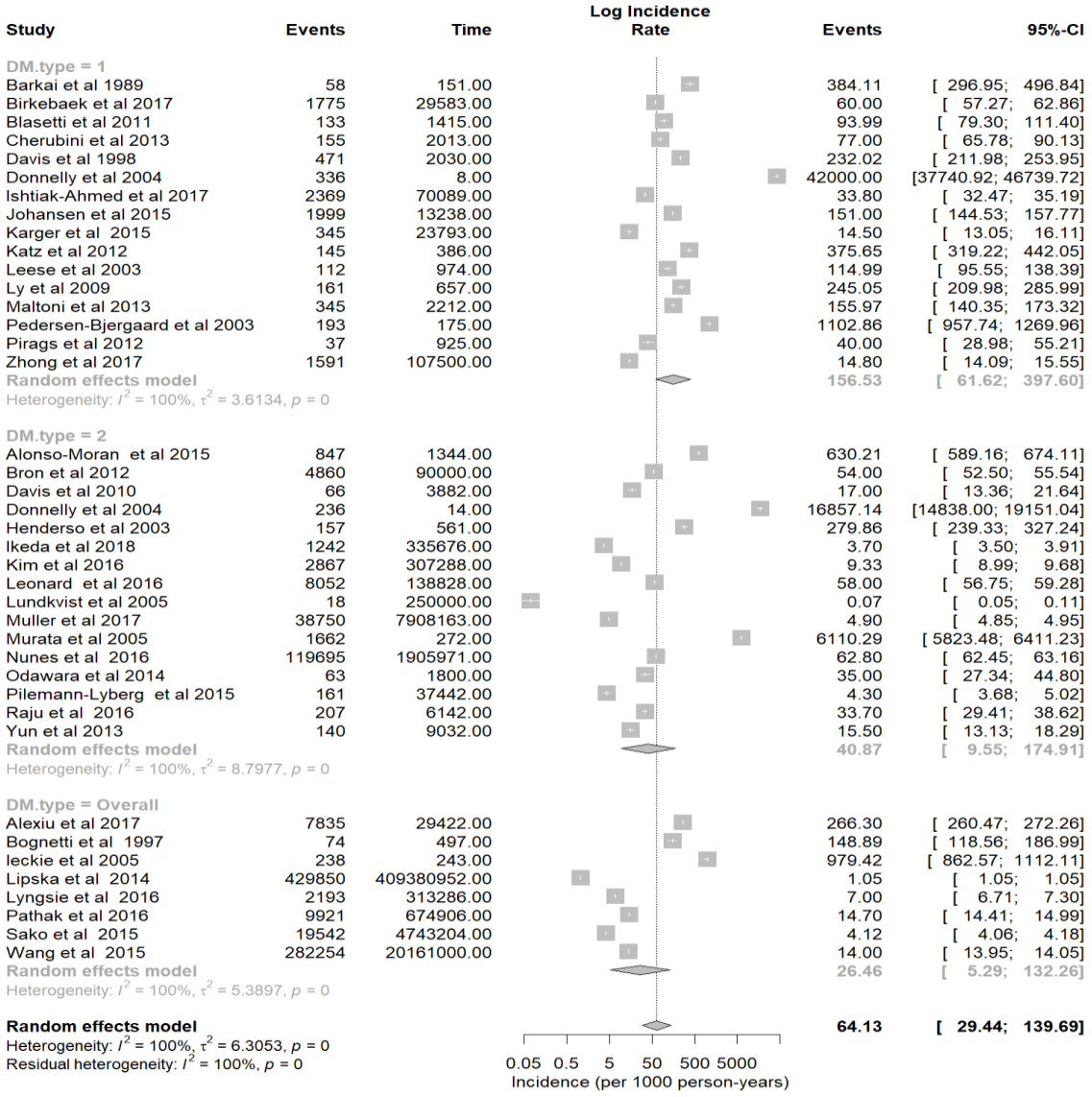


Figure 17: Forest plot of incidence rate of hypoglycaemia (episode per 1000 person-years) meta-analysis stratified by type of diabetes.

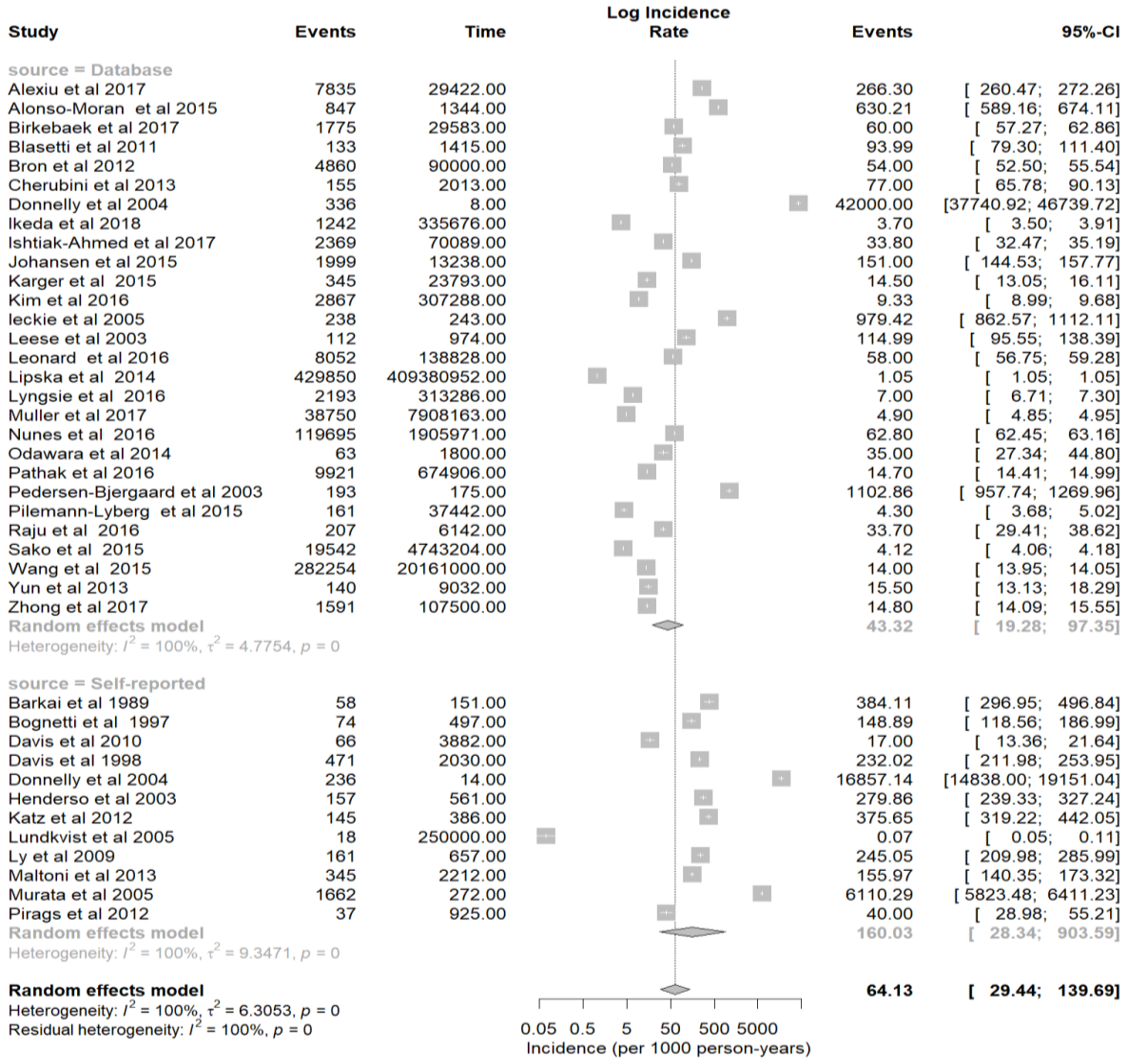


Figure 18: Forest plot of incidence rate of hypoglycaemia meta-analysis stratified by data source.

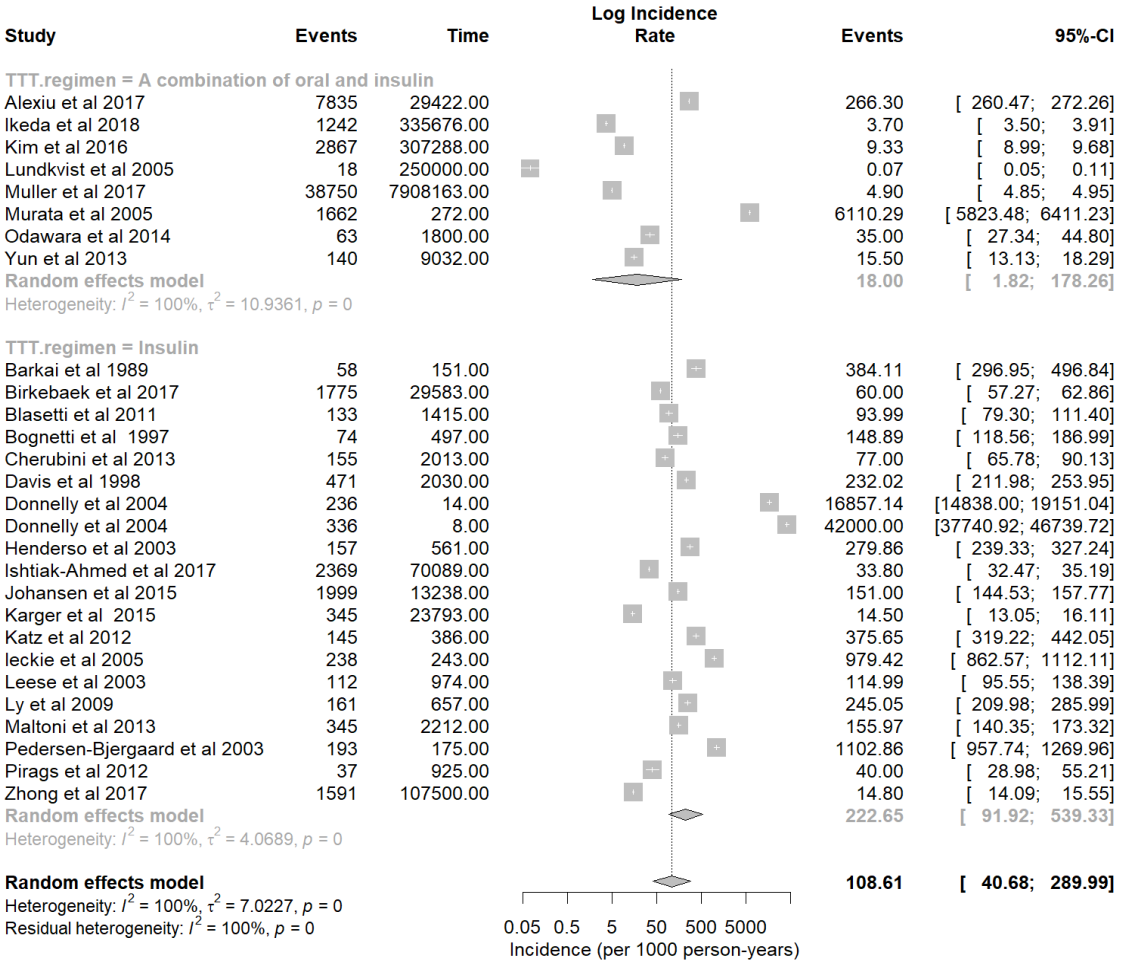


Figure 19: Forest plot of incidence rate of hypoglycaemia stratified by treatment regimen.

2.7.6 Publication bias

Funnel plots comparing the transformed effect sizes with the estimated standard error was generated for the prevalence and the incidence, respectively, to investigate the

relationship between the outcome and size of the studies. The funnel plots were asymmetric and show a stark contrast between the results of the fixed effect and random-effects models, with most studies falling outside the dotted confidence interval within which we would expect 95% of studies to reside assuming a fixed effect holds (Figure 20).

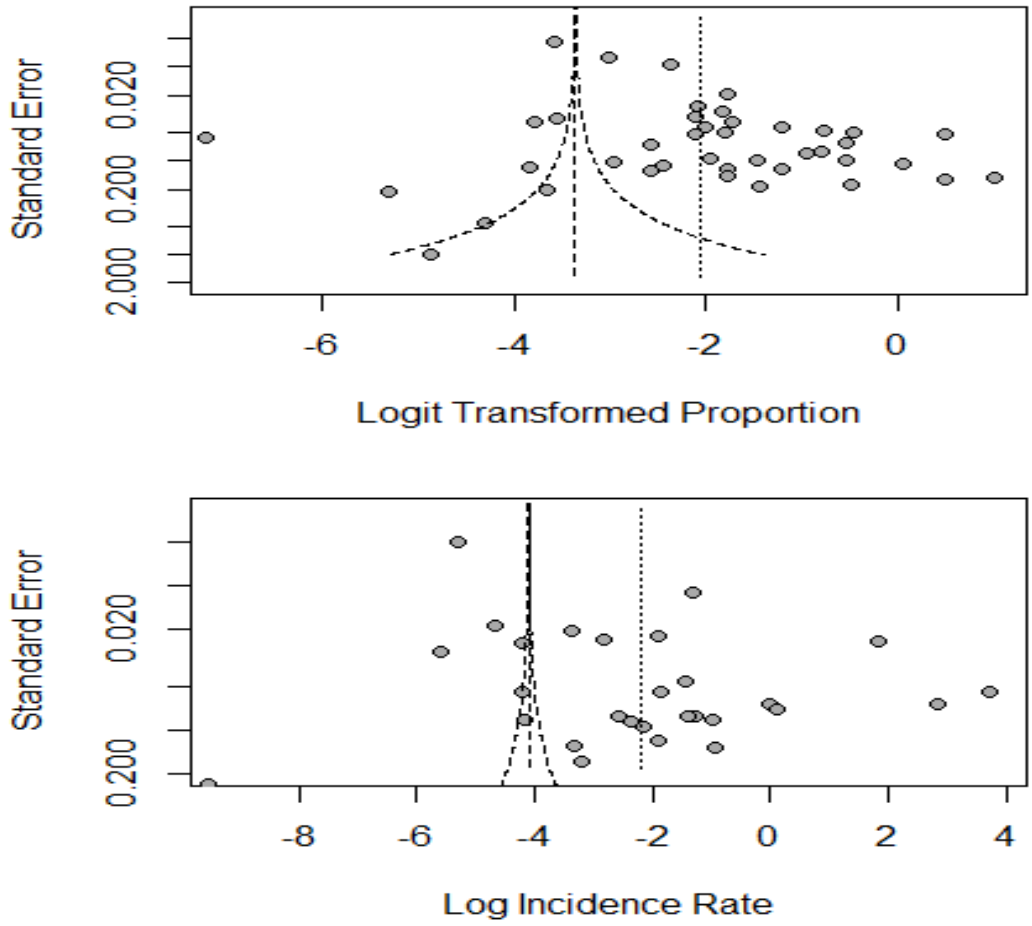


Figure 20: Funnel plots of standard error by the logit of the prevalence/incidence with observed estimates.

Funnel plot for prevalence and incidence on the transformed scale, presented with pseudo 95% confidence interval around the fixed effect. The separate vertical line corresponds to the pooled effect from the random-effects model.

2.7.7 Risk factors

A total of 145 citations were included in this systematic review, from which only 101 studies reported risk factors that were associated with hypoglycaemia in patients with diabetes. Some of the studies reported multiple risk factors in their study and this was noted in citations that studied clinical or demographic characteristics. Different risk factors have been reported in this review; some of the risk factors were significantly associated with an increased risk of hypoglycaemia, while others were found to be protective factors of hypoglycaemia. Studies included in this review were also different in their study design as some of the citations were prospective, while others were retrospective. Risk factors included in this review were further categorised into four categories: 1) demographics which included 26 studies; 2) drug-induced hypoglycaemia which included 50 studies; 3) comorbidities which included 23 studies; 4) others which included 38 studies.

2.7.7.1 Demographics

The demographic risk factors reported in this review are age, gender, HbA1c, diabetes duration, race and body mass index (BMI). Seven studies measured age and the risk of hypoglycaemia. However, there was a controversy in the results between studies. All of the studies used data from the electronic health records databases, and they reported that old age was an independent risk factor for hypoglycaemia, while one study by (Guisasola et al., 2008), used self-reporting data and the authors reported

that old age was a protective factor for hypoglycaemia, OR 0.98 (95%CI 0.97–0.99). In addition, this study had a smaller sample size in comparison to the other citations.

In terms of HbA1c, there were eight studies that examined the risk of hypoglycaemia and the levels of HbA1c. Notably, there was a variation in the results between citations. Six studies reported that higher levels of HbA1c were associated with an increased risk of hypoglycaemia (Weinstock et al., 2013, Gu et al., 2016, Williams et al., 2014, Alonso-Moran et al., 2015, Fang et al., 2015, Mauricio et al., 2015), these studies were also different in the data source. Two studies were self-reported studies while two studies were based on data from databases. On the other hand, four studies demonstrated that a low level of HbA1c was associated with an increased risk of hypoglycaemia (Li et al., 2014, Yu et al., 2016, Tschope et al., 2012, Egger et al., 1991), these studies were all based on data from self-reporting hypoglycaemia. In regard to the difference in gender, there were six studies that measured the association between gender and risk of hypoglycaemia. Four studies reported that the risk of hypoglycaemia was increased among female patients (Kajiwara et al., 2015, Samann et al., 2013, Vlckova et al., 2010, Zaccardi et al., 2017), and one study reported no risk difference (Dendy et al., 2014), while one study by Li and colleagues (Li et al., 2014), reported that male patients were at higher risk of hypoglycaemia. However, this study had a relatively small sample size in comparison to the other studies (Li et al., 2014). Diabetes duration was reported by four studies in this review; all of the studies demonstrated a higher risk of hypoglycaemia with longer diabetes

duration, and the highest odds ratio was OR 4.14 (95% CI, 3.03 – 5.67) which was reported by (Gu et al., 2016). Regarding the race as a risk factor for hypoglycaemia, one study by (Karter et al., 2017) examined this association and the authors reported that the risk is increased among African and Asian populations, where the incidence rates were IR 4.3 (95% CI, 2.1 – 6.5) and 3.9 (95% CI, 3.6 – 12), respectively. However, this study reported no risk difference among Latin and white populations. For full details on demographics risk factors, see Table 6.

Table 6: Studies reported demographics risk factors of hypoglycaemia in both types diabetes

Author	Age	Race	BMI	Gender	HbA1C	Diabetes duration
(Tschope et al., 2011)					↑ Low HbA1c OR 1.68 (1.31-2.14)	
(Borzi et al., 2016)	↑ OR 1.39 (1.00 -193)					
(Gu et al., 2016)	↑ OR 1.33 (0.78–2.28)		↓ Risk of Low BMI OR: 0.86 (0.82–0.90)		↑ High HbA1c OR 2.14 (0.87- 5.24).	↑ OR 4.14 (3.03–5.67)
(Elwen et al., 2015)	↑RR 1.041 (1.014-1.069)					
(Dendy et al., 2014)				No risk male OR 0.91 (0.55, 1.49)		
(Duran-Nah et al., 2008)						↑ OR 1.119 (1.05-1.2)
(Kajiwara et al., 2015)				↑ Risk female OR 2.04 (1.22–3.41)		
(Bramlage et al., 2012)						↑ OR 1.29 (0.97-1.71)
(Yu et al., 2016)					↑ Risk low HbA1c OR 1.66 (1.21- 2.28).	

Author	Age	Race	BMI	Gender	HbA1C	Diabetes duration
(Karter et al., 2017)		No risk White IR - 0.9 (−4.4 –2.8). No risk Latina IR 0.5 (−0.6 – 1.7). ↑ African IR 4.3 (2.1–6.5) ↑ Asian IR 3.9 (−3.6–12)				
(Karges et al., 2015)	↑ Risk of 15-20 years RR 1.63 (1.32–2.02)					
(Samann et al., 2013)				↑ female patients OR (2.84, 1.19, 6.70)		
(Bruderer et al., 2014)	↑ OR 2.27(1.65–3.12)					
(Vlckova et al., 2010)				↑ risk of female HR 2.05 (1.24- 3.41)		
(Deusenberry et al., 2012)	↑ OR 3.07					
(Li et al., 2014)			↓ High BMI RR 0.62 ↑ Low BMI RR 1.44	↑ male gender RR 1.71	↑ low HbA1C RR=1.46	↑ RR=1.22

Author	Age	Race	BMI	Gender	HbA1C	Diabetes duration
(Weinstock et al., 2013)					↑ HbA1C=9-10 OR=6.26 (3.99, 9.83)	
(Williams et al., 2014)					↑ high HbA1C OR 1.17 (1.13, 1.21)	
(Egger et al., 1991)					↑ low HbA1C OR 4.5 (1.9-10.5)	
(Alonso-Moran et al., 2015)					↑ HbA1C > 9 OR 2.216	
(Guisasola et al., 2008)	↓ OR 0.98 (0.97–0.99)		↓ OR 0.990 (0.984–0.997)			
(Zaccardi et al., 2017)		African (0.93 (0.79-1.8). ↓ Bangladeshi 0.61 (0.51-0.73). ↑ Caribbean (1.59 (1.46-1.75). ↓Indian (0.86 (0.77-0.93). ↓Pakistani 0.58 (0.53-0.63)		↑ female 1.01 (0.97-1.05)		
(Chu et al., 2017)						

Author	Age	Race	BMI	Gender	HbA1C	Diabetes duration
(Fang et al., 2015)					↑ OR = 6.4	
(Mauricio et al., 2015)					↑ OR, 3.70 [95% CI, 3.41-4.00]	

Abbreviations: HbA1c: glycated haemoglobin, BMI: body mass index, OR: odds ratio, IR: incidence rate, HR: hazard ratio, RR: relative risk

2.7.7.2 Drug induced hypoglycaemia

2.7.7.2.1 Antidiabetic medications

Insulin and sulfonylureas were the highest risk factors reported to increase the risk of hypoglycaemia in patients with diabetes. All of the studies demonstrated that insulin is an independent risk factor for hypoglycaemia in diabetes patients. Muller et al, reported the highest risk of hypoglycaemia associated with the use of insulin OR 14.6 (95% CI, 13.3 – 15.9) (Muller et al., 2017). Sulfonylureas were the second highest antidiabetic drug to be associated with an increased risk of hypoglycaemia, with all of the studies reporting that sulfonylureas are associated with a higher risk for hypoglycaemia. However, one study by (Rathmann et al., 2013) reported that sulfonylurea can be a protective factor with odds ratio of 0.21 (95% CI, 0.08 – 0.57). Regarding other types of oral antidiabetic medications including dipeptidyl peptidase-4 (DDP-4), metformin and thiazolidinedione, three studies examined the association of their use and the risk of hypoglycaemia. However, all of the studies demonstrated that these medications can be a protective factor for hypoglycaemia. Patients treated with intensive therapy were also associated with a higher risk of hypoglycaemia; Seven studies measured this association, and the highest odds ratio was reported by (Fu et al., 2014), OR 4.74 (95% CI, 3.67 – 6.06). Polypharmacy was also reported to increase the risk of hypoglycaemia, (Duran-Nah et al., 2008), reported that polypharmacy can increase the risk of hypoglycaemia by four-folds.

2.7.7.2.2 Non-antidiabetic medications

Multiple cardiac medications have been demonstrated to increase the risk of hypoglycaemia among diabetes patients. Hypertensive patients treated with beta blocker (BB) were at higher risk of developing hypoglycaemia. This was reported by four studies (Thamer et al., 1999, ter Braak et al., 2000, Lin et al., 2010, Quilliam et al., 2011a), with the highest odds ratio reported by (Lin et al., 2010) OR 4.48 (95% CI, 2.33 – 8.61), however, one study reported that there is no risk of hypoglycaemia associated with the use of BB (Corsonello et al., 1999). Regarding angiotensin-converting enzyme inhibitors (ACEI), three studies reported that there is an increased risk of hypoglycaemia with ACEI (Lin et al., 2010, Herings et al., 1995, Pedersen-Bjergaard et al., 2003), while one study demonstrated that there is no risk (Corsonello et al., 1999). Regarding calcium channel blockers (CCB), one study reported CCB can be a protective factor of hypoglycaemia, OR 0.19 (95% CI, 0.08 – 0.46) (Lin et al., 2010). However, (Thamer et al., 1999), reported different results, the authors reported that CCB can increase the risk of hypoglycaemia in diabetes patients, OR 1.1 (95% CI, 0.5 – 2.6).

Anticoagulant medications were also reported to increase the risk of hypoglycaemia up to 20%, this association was highlighted by (Romley et al., 2015), where the authors examined the association of use of warfarin and risk of hypoglycaemia by using a national database in the US. The study was a retrospective cohort analysis over 71,895 patients who are using warfarin with a coexistent sulfonylurea. The authors

found an increased risk of hypoglycaemia when warfarin is used with sulfonylureas in patients with T2DM, the adjusted odds ratio was OR 1.22 (95% CI, 1.05 – 1.42). Davis et al also reported that anticoagulants are associated with an increased risk of hypoglycaemia in diabetes, OR 2.93 (95% CI, 1.0 – 8.1) patients (Davis et al., 2010). In addition, another observational study in the US on national database reported a similar increased risk of hypoglycaemia when warfarin is used concomitantly with sulfonylureas or metformin (Nam et al., 2018).

Antihyperlipedmic and antidepressant medications were also reported by (Lindner et al., 2013) and (Derijks et al., 2008), to increase the risk of hypoglycaemia in patients with diabetes. In addition, antibiotics medications have been reported to increase the risk of hypoglycaemia, this was demonstrated in many studies and on different types of antibiotics including fluoroquinolones, co-trimoxazole and trimethoprim. The highest antibiotic reported to be associated with an increased risk of hypoglycaemia was Co-trimoxazole, OR 3.89 (95% CI, 2.29 – 6.60) (Tan et al., 2015). For full details on drug induce hypoglycaemia as a risk factors for hypoglycaemia, see Table 7.

Table 7: Studies reported drug induced risk factors of hypoglycaemia in both types diabetes

Author	Polypharmacy	Intensive therapy	Insulin	SU	Oral antidiabetic other than SU	Cardiac	CNS	Antibiotics
(Lee et al., 2017)		↑ HR 2.20; 95% CI 1.28–3.76)						
(Bron et al., 2012)			↑ HR 2.10 (1.98-2.24)					
(Fu et al., 2014)		↑ OR 4.74 (3.67-6.06)	↑ OR 4.20 (3.39-5.19)	↑ OR 3.94 (3.42-4.55)				

Author	Polypharmacy	Intensive therapy	Insulin	SU	Oral antidiabetic other than SU	Cardiac	CNS	Antibiotics
(Solomon et al., 2013)			↑ Risk of premix insulin HR 2.12 (1.26–3.55) ↑ Risk of Rapid acting insulin HR 2.75 (1.88-4.04) ↑ Risk of Ishophane insulin HR 2.19 (1.36–3.52) ↑ Risk of detemir insulin HR 1.20 (0.43–3.34)					
(Cho and Cho, 2018)		↑ HR 2.20; 95% CI 1.28–3.76)			HRs (95% CI), ↓ 0.39 (0.18-0.83) metformin and THZ versus metformin + SU			

Author	Polypharmacy	Intensive therapy	Insulin	SU	Oral antidiabetic other than SU	Cardiac	CNS	Antibiotics
(Yu et al., 2018)				↑ HR, 4.53; 95% CI, 2.76-7.45). SU Vs metfromin				
(Strandberg et al., 2015)			No Risk of glargine insulin HR 0.92 (0.74-1.15) ↓ Risk of detemir insulin HR 0.70 (0.51-0.94)					

Author	Polypharmacy	Intensive therapy	Insulin	SU	Oral antidiabetic other than SU	Cardiac	CNS	Antibiotics
(Radosevich et al., 2015)			↑ 0.05 to <1 units/kg OR 3.04 (0.97–9.55) ↑ > 1 units/kg OR 4.57 (1.45-14.41) ↑ 4 TO < 8 units/kg OR 2.76 (0.80–9.51) ↑ > 8 units/kg OR 4.17 (1.18-14.75)					
(Geller et al., 2014)			↑ RR 2.5 (1.5 -4.3)					

Author	Polypharmacy	Intensive therapy	Insulin	SU	Oral antidiabetic other than SU	Cardiac	CNS	Antibiotics
(Rubin et al., 2011)			↑ 0.6–0.8 units/kg OR 2.10 (1.08–4.09) ↑ > 0.8 units/kg: OR 2.95 (1.54–5.65) ↑ 0.2–0.4 units/kg OR 1.08 [(0.64–1.81) ↑ 0.4–0.6 units/kg OR 1.60 (0.90–2.86)					
(Davis et al., 2010)			↑ Risk of long acting insulin HR 4.29 (2.44–7.55)	↑ HR 1.15 (0.65–2.0)		↑ Anticoagulant OR 2.93 (1.06–8.1)		
(Wohland et al., 2017)			↑ NPH Insulin OR 3.68 (1.64, 8.91)					

Author	Polypharmacy	Intensive therapy	Insulin	SU	Oral antidiabetic other than SU	Cardiac	CNS	Antibiotics
(Mantovani et al., 2016)				↑ OR 1.61 (0.32–8.02)				
(Tschope et al., 2011)				↑ OR 2.58 (2.03-3.29)	↓ Metformin OR 0.64 (0.50-0.82) ↓ DDP-4 OR 0.34 (0.16-0.70) ↓Thiazolidinedione OR 0.50 (0.28-0.89)			
				↑ OR 2.25 (2.06–2.70)	↓ Metformin 0.62 (0.53–0.73)	↑ beta blocker OR 1.20 (1.78 –2.26)		↑fluoroquinolones OR 2.59 (3.82–5.77) ↑ Trimethoprim 1.97 (2.68–5.41)
(Rathmann et al., 2013)				↓ OR 0.21 (0.08–0.57)				

Author	Polypharmacy	Intensive therapy	Insulin	SU	Oral antidiabetic other than SU	Cardiac	CNS	Antibiotics
(McCoy et al., 2016)		↑ OR 3.04 (1.9 - 4.18)						
(Allen et al., 2001)		↑ OR 1.6 (1.3–1.9)						
(Roumie et al., 2016)		↑ OR 1.39 (1.12–1.72)						
(Eriksson et al., 2016)		↑ HR 2.07 (1.11–3.86)						
(Duran-Nah et al., 2008)	↑ OR 4.9 (0.7 - 35.1)							
(Lin et al., 2010)	↑ OR 2.93 (1.63 - 5.28)					↑ beta blocker OR 4.48 (2.33 - 8.61) ↓ CCB OR 0.19 (0.08-0.46)		
(Derijks et al., 2008)							↑ antidepressant OR 2.75 (1.31–5.77)	

Author	Polypharmacy	Intensive therapy	Insulin	SU	Oral antidiabetic other than SU	Cardiac	CNS	Antibiotics
(Thamer et al., 1999)						↑ ACEI 1.5 (0.8 to 2.8) ↑ BB 2.3 (0.9 to 6.1) ↑ CCB 1.1 (0.5 to 2.6) ↑ Diuretic 1.4 (0.7 to 2.7)		
(Morris et al., 1997)						↑ OR 4.3 (1.2-16.0)		
(Romley et al., 2015)						↑ Anticoagulant OR 1.22 (1.05 - 1.42)		

Author	Polypharmacy	Intensive therapy	Insulin	SU	Oral antidiabetic other than SU	Cardiac	CNS	Antibiotics
(Nam et al., 2018)						↑ Glimepiride + Warfarin 1.47 (1.07-2.02). ↑ Glimepiride + Warfarin 1.20 (0.98-1.46). ↑ Glimepiride + Warfarin 1.09 (0.88-1.35) . ↑ Glimepiride + Warfarin 1.73 (1.38-2.16)		
(Bramlage et al., 2012)				↑ OR 1.71 (1.17-2.49)				

(Leonard et al., 2016)						↑ Risk of gemfibrozil (fibrates) OR 1.57 (1.22-2.03) ↑ Risk of fenofibrate (fibrates) OR 1.63 (1.29-2.06) No risk Risk of atorvastatin OR 0.92 (0.77-1.09) ↓ Risk of simvastatin OR 0.83 (0.70-0.99) No Risk of lovastatin OR 0.89 (0.69-1.16) No risk of rosuvastatin OR 0.87 (0.67-1.13)		

Author	Polypharmacy	Intensive therapy	Insulin	SU	Oral antidiabetic other than SU	Cardiac	CNS	Antibiotics
(Van Keulen et al., 2015)							↑ Antipsychotic OR 2.27 (1.46-3.54)	
(Holstein et al., 2011)			↑ OR 1.61 (0.84-3.09)					
(Takeishi et al., 2016)			↑ OR 1.40 (0.55-3.59)		↓ Metformin OR 0.67 (0.28-1.61) ↓ DDP-4 OR 2.11 (0.85-5.24) ↓Thiazolidinedione OR 0.50 (0.28-0.89)			
(Corsonello et al., 1999)						No risk Beta blocker OR 0.95 (0.13-7.20) No risk ACEI OR 0.5 (0.19-1.55)		

Author	Polypharmacy	Intensive therapy	Insulin	SU	Oral antidiabetic other than SU	Cardiac	CNS	Antibiotics
(Lundkvist et al., 2005)			↑ OR 5.55					
(Jick et al., 1990)			↑ RR 1.3 (0.5, 3.5)					
(Samann et al., 2013)			↑ (OR= 3.43 (1.31, 8.96)					
(Bruderer et al., 2014)			↑ OR 11.83 (9.00–15.54)	↑ OR 4.45 (3.53–5.60) SU + CYP substrates ↓ OR 0.72 (0.39 - 1.34)				
(Muller et al., 2017)			↑ OR 14.613.3–15.9)					
(Tschope et al., 2012)			↑ OR2.99 (2.27-3.95)					
(Freathy et al., 2006)			↑ OR 2.77 (1.36-5.62)					

Author	Polypharmacy	Intensive therapy	Insulin	SU	Oral antidiabetic other than SU	Cardiac	CNS	Antibiotics
(Vlckova et al., 2010)			↑ HR = 3.11 (CI 1.64 -5.88)	↑ HR = 4.15 (CI 1.74- 9.91)				
(ter Braak et al., 2000)			↑ (OR1.3 (1.0–1.6)			↑ beta blocker OR 14.9 (2.1–107.4)		
(Ishtiak-Ahmed et al., 2017)			↑ OR 2.17 (1.16–4.08)					
(Deusenberry et al., 2012)			↑ OR 3.01					
(Ragia et al., 2012)				↑ OR 3.218 (1.116–9.285)				
(Pedersen-Bjergaard et al., 2003)						↑ ACEI RR 2.9 (1.0–8.2)		
(Herings et al., 1995)						↑ ACEI OR 2.8 (1.4-12.2)		

Author	Polypharmacy	Intensive therapy	Insulin	SU	Oral antidiabetic other than SU	Cardiac	CNS	Antibiotics
(Tan et al., 2015)								↑ Co-trimoxazole OR 3.89 (2.29–6.60)
(Chou et al., 2013)								↑ Moxifloxacin OR 2.13(1.44–3.14) ↑ Levofloxacin OR 1.79 (1.33–2.42) ↑ Ciprofloxacin OR 1.45 1.07–2.00)

Abbreviations: OR: odds ratio, HR: hazard ratio, RR: relative risk, SU: sulfonylureas, BB: beta blockers, CCB: calcium channel blockers, ACEI: angiotensin converting enzyme inhibitor, CNS: central nervous system, CYP: cytochrome P450

2.7.7.3 Comorbidities

In terms of comorbidities as a risk factor for hypoglycaemia, chronic kidney disease (CKD) was the highest disease to be reported with an increased risk of hypoglycaemia. Ten studies reported that CKD can increase the risk of hypoglycaemia. The highest OR was reported by (Weir et al., 2011), OR 6.0 (95% CI, 3.8 – 9.5). Cardiovascular diseases were also reported to increase the risk of hypoglycaemia in patients with diabetes. Six studies in this review highlighted this association, (Endo et al., 2000) demonstrated that the risk of hypoglycaemia was increased by seven-folds in cardiovascular patients and patients with diabetes, while (Dendy et al., 2014) reported that the risk of hypoglycaemia in cardiovascular patients with diabetes is OR 1.25 (95% CI, 0.76 – 2.10). Cerebrovascular accident (CVA) has been reported by four studies in this review, all of the studies reported that CVA can increase the risk of hypoglycaemia in diabetes patients. Dementia and depression were also reported to increase the risk of hypoglycaemia, six citations studied the risk of hypoglycaemia associated with dementia. (Bruce et al., 2009) reported that dementia can increase the risk of hypoglycaemia by three-folds. While five studies demonstrated that depression can increase the risk of hypoglycaemia, one study by (Wohland et al., 2017), reported that depression is a protective factor for hypoglycaemia OR 0.14 (95% CI, 0.02 – 0.51). Similar results were also reported among other diseases and complications to increase the risk of hypoglycaemia including retinopathy,

nephropathy and cirrhosis. For more details on comorbidities as a risk factors for hypoglycaemia, see Table 8.

Table 8: Studies reported comorbidities risk factors of hypoglycaemia in both types diabetes

Author	CKD	Depression	Dementia	CVD	CVA	Cirrhosis	Micro complication
(Lee et al., 2017)			↑ HR 1.57; 95% CI 1.33–1.84				
(Kim et al., 2016b)	↑ OR 2.52		↑ OR 1.93	↑ OR 1.7 (1.57-1.83)	↑ OR 1.78 (1.64-1.94)		
(Davis et al., 2010)	↑ OR 2.90 (1.68–5.00)						
(Wohland et al., 2017)		↓ OR 0.14 (0.02- 0.51)					
(Mantovani et al., 2016)	↑ OR 2.42 (1.11–8.09)					↑ OR 6.76 (1.24–36.8)	
(Quilliam et al., 2011a)	↑ OR 2.22 (6.49 – 10.81)			↑ OR 2.33 (8.86–13.64)	↑ 2.78 (6.37–14.52)		
(Borzi et al., 2016)	↑ OR 1.32 (1.02-1.72)		↑ OR 1.32(1.02-1.72)				
(Dendy et al., 2014)	↑ OR 1.64 (0.96 - 2.80)			↑ OR 1.25 (0.76 - 2.10)		↑ OR 1.51 (0.73-3.12)	

(Endo et al., 2000)				↑ OR 7.0 (1.0-47)			
(Duran-Nah et al., 2008)	↑ OR 3.0 (1.2 - 7.7)						
(Kostev et al., 2015)					↑ OR 1.90 (1.03- 3.50)		
(Lin et al., 2010)				↑ OR 3.38 (1.91- 6.01)			
(Bramlage et al., 2012)		↑ OR 4.24 (2.35-7.65)		↑ OR 1.61 (1.02-2.53)	↑ OR 1.94 (1.04-3.59)		
(Bruderer et al., 2014)	↑ OR 1.34(1.04–1.71)		↑ OR 2.00 (1.37–2.91)				
(Tschope et al., 2012)		↑ (OR= 1.81; 1.14-2.88)					↑ diabetic retinopathy OR 3.27 (1.07-30.02)
(ter Braak et al., 2000)							↑ nephropathy OR 3.9 (1.5–10.4)
(Deusenberry et al., 2012)	↑ OR 3.64						
(Lin et al., 2010)							↑ neuropathy RR (1.89)
(Honkasalo et al., 2011)		↑ (OR 1.6 (1.0–2.6)					
(Weir et al., 2011)	↑ OR 6.0 (3.8–9.5)						

(Katon et al., 2013)		↑ HR 1.42 (1.03-1.96)					
(Bruce et al., 2009)			↑ HR 3.00 (1.06–8.48)				
(Feil et al., 2011)			↑ OR=1.58 (1.53–1.62)				

Abbreviations: OR: odds ratio, HR: hazard ratio, RR: relative risk, CVA: cerebro vascular accident, CVD: cardio vascular disease, CKD: chronic kidney disease

2.7.7.4 Other risk factors

Multiple risk factors were also reported to increase the risk of hypoglycaemia (for more details, refer to, Table 9). Previous attacks of hypoglycaemia were highly reported in the literature, ten studies highlighted the associations between previous hypoglycaemia and the risk of developing new events. The highest odds ratio reported was by (Dendy et al., 2014), OR 38.7 (95% CI, 20.4 – 73.3). Missing meals, fasting, impaired awareness and serum ACE activity were all demonstrated to increase the risk of hypoglycaemia in diabetes patients, and have been reported in this review.

Table 9: Studies reported all other risk factors of hypoglycaemia in both types diabetes

Author	Previous hypoglycaemia	Impaired awareness	Missing meals	Smoking	Care of patients	Low socioeconomic	Post dinner dietary intake	Biomarkers
(Lee et al., 2017)								↑ HR microalbuminuria (HR 1.95; 95% CI 1.23–3.07)
(Davis et al., 2010)	↑ HR 6.59 (2.62–16.60)							
(Wohland et al., 2017)		↑ OR 2.06 (1.09-3.93)			↑ No monitoring OR 4.88 (1.41 - 22.63).			
(Quilliam et al., 2011a)	↑ OR 9.48 (4.95–18.15)							
(Loke et al., 2010)			↑ RR of 1.60 (1.05- 2.43)					

(Ishtiak-Ahmed et al., 2017)	↑ HR 3.19 (2.62–3.88)			↑ HR 1.11(0.89-1.39)				
(Barkai et al., 1998)		↑ OR 5.8 (2.3-13.2)						
(Ganz et al., 2014)	↑ OR 8.08 (5.99-10.91)							
(Dendy et al., 2014)	↑ OR 38.7 (20.47-73.33)							
(Endo et al., 2000)	↑ OR 15 (0.77 - 297)		↑ OR 81 (3.6-1 84)					
(Duran-Nah et al., 2008)	↑ OR 2.9 (1.3 - 6.5)		↑ OR 19.8 (9.1-43.1)			↑ OR 3.7 (1.4-10.0)		
(Muhlhauser et al., 1998)	↑ HR 2.73 (1.7-4.25)							↑ C-peptide level HR 4.0, CI 1.2-12.7

(Jeon et al., 2016)	↑ OR 22.0 (6.05 – 80.0)				↑ No monitoring OR 4.43 (1.30–15.1)			
(Kostev et al., 2015)	↑ OR 11.27 (6.6 - 18.99)							
(Lin et al., 2010)			↑ OR 3.50 (1.97 - 6.22)					
(Faerch et al., 2011)								↑ Serum ACE activity RR 1.32 (1.14 - 1.55)
(Pedersen-Bjergaard et al., 2003)								↑ Serum ACE activity RR 1.4 (1.2-1.6)
(Davis et al., 2011)								↑ Serum ACE activity H.R 2.35 (1.13–1.53)
(Sarkar et al., 2010)			↑ Fasting OR 1.4 (1.1–1.7)					

(Seewi et al., 2008)								↑ Insulin binding OR 4.8 (1.5-15.2)
(Berkowitz et al., 2012)						↑ Risk of low income OR 1.51(1.19-1.91)		
(Basu et al., 2017)						↑ OR 1.07 (1.02–1.12)		
(Seligman et al., 2010)						↑ OR 2.95 (1.48-5.91)		
(Desjardins et al., 2014)							↑ OR 1.16 (1.04–1.29)	
(Sato et al., 2010)							↑ OR: 1.65	ABCC gene Ser Allele ↑ OR 1.65
(Ren et al., 2016)								↑ Uric acid OR 3.03 (2.13–4.32)

(Holstein et al., 2009)								No risk KCNJ11(E23K) OR 0.68 (0.34 – 1.35)
(Deusenberry et al., 2012)		↑ OR 2.06 (1.09-3.93)			↑ Nursing home OR 4.88 (1.41 - 22.63).			
(Li et al., 2014)				↑ RR 1.48		↑ RR 2.09		
(Honkasalo et al., 2011)			↑ Fasting RR of 1.60 (1.05- 2.43)					
(Feil et al., 2011)		↑ OR 5.8 (2.3-13.2)						
(Sreenan et al., 2014)	↑ T1D OR 2.21 [1.51- 3.22] ↑ T2D OR = 16.65 (8.66- 32.02)							
(Seligman et al., 2010)			↑ OR 19.8 (9.1-43.1)			↑ OR= 2.95 (1.48-5.91)		

(Weinstock et al., 2013)						↑ Low socioeconomic OR 2.23 (1.53 -3.26) ↑ No insurance OR=2.08 (1.58-2.74) ↑ Learning problems OR 3.72 (2.28- 6.05)		
(Alonso-Moran et al., 2015)			↑ OR 3.50 (1.97 - 6.22)					
(Hirai et al., 2007)				↑ OR 2.40 (CI 1.30–4.40)				
(Chu et al., 2017)	↑ HR 1.19 (1.18-1.32)							

(Jabbar et al., 2017)	↑ OR 7.80; 95% CI 5.31–11.4							

Abbreviations: T1DM: type 1 diabetes mellitus, T2DM: type 2 diabetes mellitus, OR: odds ratio, IR: incidence rate, HR: hazard ratio, RR: relative risk, ACE: angiotensin converting enzyme

2.8 Discussion

The objectives of this systematic review were to investigate the incidence, prevalence and risk factors of hypoglycaemia in patients with T1DM and T2DM. The pooled estimate of prevalence, incidence and episodes of hypoglycaemia in diabetes patients were calculated, and further subgroup analysis was conducted, based on different variables including type of treatment, the source of study sample, and location of the studies included.

The pooled prevalence of hypoglycaemia in diabetes was 11.0 % (95% CI, 7.0 – 17.0); the pooled average of incidence rates of hypoglycaemia was 64.1 episodes per 1,000 person-years (95% CI, 29.4 – 139.7). The incidence and the prevalence of hypoglycaemia in patients with T1DM were higher compared to patients with T2DM; the prevalence: 14.0 % (95% CI, 7.0 – 24.0) and 11.0 % (95% CI, 6.0 – 21.0), for T1DM and T2DM, respectively; the incidence: 156.5 episodes per 1,000 person-years (95% CI, 61.6 – 397.6) experienced by patients with T1DM and 40.9 episodes per 1,000-person years (95% CI, 9.5 – 174.9) experienced by patients with T2DM, respectively. In addition, this review highlighted that both the incidence and the prevalence are higher among patients with diabetes using insulin-based therapy compared to patients on oral combination based therapy or sulfonylureas-based therapy. In addition, this review has identified multiple risk factors that can increase the risk of hypoglycaemia in patients with diabetes including intensified antidiabetic therapy, dementia, previous hypoglycaemia diabetes duration and other risk factors.

Previous reviews investigating the incidence and prevalence of hypoglycaemia in T1DM and T2DM in observational studies are limited. Two previous systematic reviews only examined the incidence and the prevalence of severe/mild to moderate hypoglycaemia in T2DM; however, they did not investigate hypoglycaemia in T1DM and did not report an overall estimate for the prevalence or the incidence of hypoglycaemia in T2DM (Edridge et al., 2015, Bloomfield et al., 2012). A meta-analysis on clinical trials investigating the proportions of hypoglycaemia in patients with T2DM reported that the pooled average of the prevalence of hypoglycaemia in patients with diabetes and treated with sulfonylureas is 10.1 % (95% CI, 7.3 – 13.8%), which was slightly higher than the pooled average reported in this study 8.0 % (95% CI, 3.0 – 22.0%) (Schopman et al., 2014). In addition, in three clinical trials that were included in their review, the proportion of hypoglycaemia in patients with diabetes and treated with insulin ranged from 8.0 % to 56.0 %, thus, the estimate reported in this study for the prevalence of hypoglycaemia in patients treated with insulin were in the same range of these studies (Schopman et al., 2014).

The result of this meta-analysis demonstrates that the prevalence and incidence of hypoglycaemia are high as shown above, and that hypoglycaemia is a very common complication that many patients with diabetes might experience. However, it is important to mention that the risk of hypoglycaemia is different between both types of diabetes (UK Hypoglycaemia Study Group, 2007), patients with T1DM have a higher risk of hypoglycaemia compared to patients with T2DM, which was highlighted in this

study. These high numbers could be related to the fact that recent guidelines recommend intensification of diabetes treatment to control the blood sugar levels and to prevent macrovascular and microvascular complications, which may put the patients under higher risk of experiencing hypoglycaemic events (Nathan et al., 1993). A recent study by Naser et al. has found that patients with diabetes who were using intensive antidiabetic therapy were five-folds at higher risk of hypoglycaemia compared to patients using antidiabetic monotherapy (Naser et al., 2018).

The results reported in this study showed a lower rate of prevalence and incidence of hypoglycaemia in T2DM compared with the previously published systematic review (Edridge et al., 2015). However, this could be due to the fact that their results were reported based on the severity of hypoglycaemia (mild and severe), and they did not have any estimation on the overall rates of hypoglycaemia prevalence and incidence. The reason that I did not conduct any stratification by the severity of the disease, is that the definition of hypoglycaemia varied significantly between studies published in the literature, with no clear definition that can make a margin for the classification. Therefore, this would affect the estimation of the incidence and prevalence rates. In addition, there is a gap of three years between this study and the previous one, and I included more recent studies, which could be a reason for this difference in results. However, the pooled estimate of the prevalence of hypoglycaemia that was demonstrated in this review can fall between the results of mild hypoglycaemic

episodes and severe hypoglycaemic episodes which was estimated by a previous systematic review (Edridge et al., 2015).

The sample source of publications included in this review varied considerably, and the quality of evidence also varied between studies. Studies that were self-reported had higher incidence rates of hypoglycaemia compared to studies that were based on health record database. Self-reported citations are more likely to be biased to report mild cases of hypoglycaemia and, therefore, may overestimate the prevalence of hypoglycaemia. Studies reporting hypoglycaemia by recruiting patients using continuous blood glucose monitors, or by reporting hypoglycaemia based on self-reported questionnaires, are likely to report higher rates of hypoglycaemic episodes compared to databases. This may be explained by the fact that patients are unlikely to visit the GP or the emergency department unless it is a severe case and, therefore, the rates of hypoglycaemia in this group would be less compared to the self-reported group. However, this is also influenced by precision of individual review, which can be poor, especially for non-severe hypoglycaemic events. It is further dependent upon the patient's ability to perceive hypoglycaemia when it happens, which is restricted by impaired hypoglycaemia awareness, and to accurately separate them from symptoms inconsequential to hypoglycaemia. Moreover, only 5% of self-reported hypoglycaemic events were managed by the healthcare system or emergency medical services (Silbert et al., 2018). On the other hand, health record databases are more likely to

report more severe cases of hypoglycaemia that requires either emergency visits or hospital admissions, in which the events are confirmed by healthcare professionals.

The prevalence of hypoglycaemia varied by the geographical location of the studies included in this review; for instance, the pooled estimate of the prevalence of hypoglycaemia in Asia was higher compared to other geographical locations. Differences in ethnicity, education and cultural behaviours between Asians and Western populations may affect the rates of occurrence of hypoglycaemia (Goh et al., 2017). A study found that patients with diabetes in Asia had lower awareness of the symptoms and causes of hypoglycaemia compared with other regions (Hussein et al., 2017). In addition, fasting during Ramadan, which lasts one lunar month, places Asians at greater risk of hypoglycaemia, as shown by the Epidemiology of Diabetes and Ramadan study (Salti et al., 2004). These factors may contribute to the variation in the prevalence of hypoglycaemia in Asia compared to Europe and North America.

Furthermore, studies at which the patients were based on insulin treatment had a higher incidence rates of hypoglycaemia compared to oral combination therapy and studies that were based on a combination of oral and insulin. Insulin and sulfonylurea based antidiabetic therapies are commonly associated with hypoglycaemic events (Cryer, 2004, Umpierrez and Korytkowski, 2016). The higher risk of hypoglycaemia with the use of insulin or sulfonylurea among patients with diabetes is due to their mechanism of action which is mainly based on triggering the pancreatic secretion of insulin inside the body (for sulfonylurea-based therapy) or the administration of

exogenous insulin formulations (Proks et al., 2002), while the mechanism of action of other antidiabetic therapies is based on increasing the sensitivity of insulin and limiting the absorption of glucose, leading to a lower risk of experiencing hypoglycaemic events (Luna and Feinglos, 2001). However, it is important to highlight that other risk factors could also increase the risk of hypoglycaemia such as polypharmacy and drug-induced hypoglycaemia (Murad et al., 2009, Peron et al., 2015).

In regard to risk factors of hypoglycaemia in patients with diabetes. Antidiabetic medications and non-anti diabetic medications have been reported to increase the risk of hypoglycaemia. Insulin was the highest anti-hyperglycaemia medication to increase the risk of hypoglycaemia: this was even highlighted by some of the studies reporting the incidence and prevalence of hypoglycaemia and was also highlighted previously in the analysis of this review. The second anti-hyperglycaemia medication that was demonstrated to increase the risk of hypoglycaemia is sulfonylureas; two studies reported that SUs can increase the risk of hypoglycaemia up to four-fold (Bruderer et al., 2014, Vlckova et al., 2010). However, this can be due to different reasons including: the fact that SUs are metabolised by CYP450 in the liver (Tirkkonen et al., 2010) and, therefore, SUs users are at higher risk of experiencing drug-drug interactions when SUs are concurrently used with other medications metabolised by the CYP450. Medications that are metabolised by the CYP450 can increase the effect of each other (Tirkkonen et al., 2010), and in situations where SUs are used, patients may experience hypoglycaemia due to the enhancement of SUs effect.

Antihypertensive medications, anticoagulants, antibiotics and other medications were reported in this review to increase the risk of hypoglycaemia in patients with diabetes. However, the mechanism of how these drugs can increase the risk of hypoglycaemia is not well understood and were not reported. Some of these medications are also metabolised by CYP 450 and therefore they can interact with SUs and increase the risk of hypoglycaemia. This was highlighted by two studies, Romley et al. (Romley et al., 2015) and Leonard et al., (Leonard et al., 2016) which narrated that warfarin anticoagulants and statins antihyperlipidemics can increase the risk of hypoglycaemia. The authors of these studies hypothesised that this could be due to a drug-drug interaction via the CYP450 system. Romley et al. (Romley et al., 2015) also reported that admission due to hypoglycaemia is increased among patients receiving concurrent treatment of both SUs and warfarin compared to patients receiving SUs alone (OR 1.22, 95% CI, 1.05 – 1.42); these results are based on a large-scale retrospective study that included 465,918 patients with diabetes. Similarly, Nam et al narrated that anticoagulants can increase the risk of hypoglycaemia using another big database in the US (Nam et al., 2018). Both studies used a self-controlled case series design, where the same patients will account for both the exposure and non-exposed periods of follow up. However, the association between the use of anticoagulants and the risk of hypoglycaemia remains unclear, and untested in other populations.

Previous hypoglycaemia appears to be one of the strongest risk factors for hypoglycaemia, and it was reported by ten studies in this review. The risk of

hypoglycaemia ranged from a three to a 22-fold increase when there is a history of a previous attack of hypoglycaemia. This could be explained by the fact that previous hypoglycaemia can lead to autonomic insufficiency, a state of confusion in which patients may experience hypoglycaemia without being aware of the symptoms of low glucose levels in the blood (Cryer, 2004).

Comorbidities including CKD were also among the strongest risk factors to be reported by studies included in this review, with ten studies reporting that CKD can increase the risk of hypoglycaemia (a two to six-fold increase). Patients with CKD have a poor clearance of insulin from their body, and so will be at higher risk of hyperinsulinemia and, therefore, increased risk of hypoglycaemia (Cryer, 2004).

Demographics including age were also reported in this review to increase the risk of hypoglycaemia. Elder patients are at higher risk of experiencing multiple comorbidities and the use of multiple medications (Davis et al., 2011). Also, elder populations may experience dementia and loss of memory and, therefore, these patients are at higher risk of misuse of their antidiabetic medications (Bruce et al., 2009, Abdelhafiz et al., 2015).

The quality of studies included in this review varied between the studies, the health records databases studies were better in quality compared to self-reported studies. Health record databases mainly use the international classification of disease (ICD) system or hospital codes that was entered by either doctors or health care

professional, so it might be more accurate than self-reported diagnosis, however, it is important to mention that even health record databases are subject to misreporting or under reporting bias (Leong et al., 2013).

In recent years, hypoglycaemia has been a major importance of research and clinical practice, this was even highlighted after the publication of some post-hoc RCTs showing an increased risk of complications and death in patients experiencing hypoglycaemia (Frier, 2010, Mellbin et al., 2009, Skyler et al., 2009). This study, demonstrated that hypoglycaemia is a common event among patients with diabetes in real-life in both T1DM and T2DM, and that multiple risk factors can increase the risk of hypoglycaemia. More research should focus on identifying risk factors and predictors of hypoglycaemia, including newer oral hypoglycaemic agents such as glucagon-like peptide-1 (GLP) and sodium-glucose linked transporter (SGLT2) inhibitors. Furthermore, hypoglycaemia can be a major public health issue, especially that diabetes is highly prevalent in the general population (Ogurtsova et al., 2017), therefore, health care providers must be aware of such event and monitor their patients on continuous basis and more importantly to educate their patients about their disease and its associated events. Further, cost effective approaches based on personalized management should be suggested to prevent such unnecessary events of hypoglycaemia. In addition, this systemic review has identified many knowledge gaps regarding the risk factors of hypoglycaemia in diabetes. Precisely, for the aim of this thesis, this review has identified a knowledge gap about the use of oral

anticoagulant and the risk of hypoglycaemia in patients with. Only two studies by Romley et al (Romley et al., 2015) and Nam et al (Nam et al., 2018) studied the risk of warfarin use concurrently with antidiabetic medications and the risk of hypoglycaemia in T2DM patients. Both studies were conducted using an American database. In addition, both studies reported that warfarin use concurrently with sulfonylurea can increase the risk of hypoglycaemia in T2DM patients. However, this association needs more investigation, and perhaps on a different population.

2.8.1 Strengths

To the best of my knowledge, this is the first systematic review and meta-analysis to review the incidence and prevalence of hypoglycaemia in patients with T1DM and T2DM. Unlike previous published meta-analysis, I standardize the prevalence to 1 year to allow appropriate data pooling meta-analytically and interpretation. I included observational studies, which reported the prevalence and incidence rates of hypoglycaemia in diabetes population representing real-life situations. RCTs considered as the gold standard for demonstrating clinical efficacy. However, the rates and nature of hypoglycaemic events reported from clinical trials may not be generalized to real-world practice. Large, RCTs generally included patients who are restricted to their suggested regimens, subjected to close monitoring and support than patients in routine clinical practice. In addition, patients with history of severe hypoglycaemia, elderly or poor health status are often not included in RCTs (Elliott et al., 2016). Therefore, the results of this study are likely to be generalisable to all

patients with diabetes. This systematic review and meta-analysis reviewed a large number of studies covering the topic: incidence, prevalence and risk factors of hypoglycaemia in T1DM and T2DM patients. The data extracted in this review covers a wide range of information previously published in the literature. Two independent reviewers assessed the quality of evidence and extracted the data in this review. Furthermore, a third reviewer was involved for any disagreement in the screening of studies between the two authors. The search strategy of this review was comprehensive, and I did not have any restrictions on the keywords used to conduct this review. In addition, in the meta-analysis of this review I did not include studies that did not clearly describe their statistical analysis; this was to avoid any misconception or over-estimation of the incidence rates.

2.8.2 Limitations

Heterogeneity between studies was high, which was not explained by any of the study level covariates considered in the subgroup analysis. Therefore, the high heterogeneity is likely to be due to study characteristics which were not measured or reported in the original citations (Barendregt et al., 2013). Moreover, high statistical heterogeneity is more frequent in meta-analyses of prevalence compared to meta-analyses of binary outcomes (Alba et al., 2016). Furthermore, the results reported in this study showed an evidence of asymmetry and publication bias as presented in the funnel plot. However, it is important to highlight that unlike studies that report associations or measure an outcome risk, burden of diseases studies are likely to be

descriptive studies or as part of secondary objectives of research and therefore, it is reasonable to assume that there is no under-reporting. The definition of hypoglycaemic episodes varied between studies; therefore, it was not possible to stratify the results based on the severity of hypoglycaemia. In addition, due to the difference in study designs between studies included in this review (questionnaire/medical records/database), it should be recognized that this causes difficulties when combining results across studies, resulting in under or over reporting of hypoglycaemic episodes; however, I tackled this issue by stratifying the pooled average based on data sources.

2.9 Conclusion

Hypoglycaemia is a very common event among both T1DM and T2DM. The frequency of hypoglycaemia among patients treated with insulin and sulfonylureas was higher compared to other antidiabetic medications and to patients with T2DM. Multiple risk factors can increase the risk of hypoglycaemia; some of these risk factors are well documented, while others need to be more deeply investigated. However, the quality of information available in the literature largely varied. Over the last 10 years, the quality of the evidence has improved compared to previous published studies. Studies using data from health records databases had a higher quality in recording the incidence and prevalence of hypoglycaemia. Further studies on this topic across the world and especially among third world countries are warranted.

2.10 Context of this chapter in overall work

This systematic review has reviewed the existing knowledge about the incidence, prevalence and risk factors of hypoglycaemia in patients with both T1DM and T2DM. This will help in better understanding the current knowledge about this topic and will provide a better insight in the design and structure of the following studies. In addition, several gaps were identified in the literature, most importantly it identified one gap about the association of the concurrent use of warfarin and sulfonylureas and the risk of hypoglycaemia, which were further studied in this PhD project.

Chapter 3 Aims and objectives

3.1 Rational of thesis

As described in previous chapters, Type 2 Diabetes Miletus (T2DM) is a highly prevalent disease, and it is associated with a wide range of comorbidities and complications. Patients with T2DM are likely to be prescribed oral anticoagulants (OACs) for the management of cardiac comorbidities, including atrial fibrillation (AF). However, there is a relatively limited research about the safety of OACs in patients with T2DM.

In the previous chapter, a systematic review and a meta-analysis on the incidence, prevalence and risk factors of hypoglycaemia in patients with Type 1 Diabetes Miletus (T1DM) and T2DM was conducted. It summarised the literature, and it also highlighted that there is a gap in current literature with regards to the safety of the use of OACs and risk of hypoglycaemia. The greatest limitation in current literature is that only two observational studies in the United States have investigated the association of OACs and the risk of hypoglycaemia in a real-world setting. In addition, there are no previous studies that investigated the safety of the concurrent use of OACs and oral hypoglycaemic agents (OHAs) in patients with T2DM. This proves the need for more research and expansion on the safety of OACs in patients with T2DM among different populations across the world.

3.2 Research questions

Does concurrent use of OACs and OHAs increase the risk of hypoglycaemia and bleedings?

3.3 Aim

The overall aim of this PhD work was to evaluate the drug utilisation and the safety of OACs in patients with T2DM using a UK primary care database, The Health Improvement Network Database (THIN) database.

3.4 Objectives

The specific objectives of this PhD project were:

1. To examine the prescribing trends of OACs in patients with T2DM.
2. To assess annual trends in the prevalence and incidence of AF in patients with T2DM.
3. To examine the treatment of AF in patients with T2DM.
    I. To assess the trend of OACs initiation in patients with T2DM and AF.
    II. To evaluate the effect of the introduction of Direct Oral Anticoagulants (DOACs) on the OACs prescribing in patients with T2DM and AF.
    III. To investigate factors associated with prescribing of OACs in patients with T2DM and AF.

4. To investigate the safety of the use of OACs in patients with T2DM.
    I. To investigate the association of the concurrent use of warfarin and sulfonylureas and the risk of hypoglycaemia.
    II. To investigate the association of the concurrent use of warfarin and sulfonylureas and the risk of bleeding.

Objectives 1-3 were addressed by Chapters 5-7. The drug utilisation study (chapter 5) and the descriptive cohort (chapter 6), explored the amount of the problem as an initial step in the evaluation of the safety of OACs in patients with T2DM. The drug utilisation study investigated the trends in the prevalence of prescribing of OACs in patients with T2DM. The descriptive cohort (chapter 6) investigated the trends in incidence and prevalence of AF in patients with T2DM. Chapter 7 examined the treatment of AF (the main indication of OACs) in patients with T2DM. The analytical cohort study (Chapter 8) addressed objective 4 by investigating the association of the concurrent use of warfarin and sulfonylureas and the risk of hypoglycaemia and bleeding.

Chapter 4 Methodology

4.1 Chapter overview

This chapter provides a brief overview of the study designs. In addition, it justifies the use of the observational study design for the evaluation of the safety of the use of oral anticoagulants (OACs) in patients with type 2 diabetes mellitus (T2DM). This is followed by a description of the big data and electronic health databases. It also provides a detailed description of The Health Improvement Network (THIN) primary care database, which was used as the data source for this PhD project. The history of the development of THIN, data structure, data quality, strength and limitations of the database are discussed in this chapter. This chapter also describes the criteria which were used to identify the cohort of patients with T2DM, which was the main population in the main analysis of this PhD project.

4.2 Pharmacoepidemiology

Pharmacoepidemiology investigates and evaluates drug use in large populations (Storm, 2012). This includes the safety, efficacy, and drug utilisation at population health level (Storm, 2012). The word ‘pharmacoepidemiology’ constitutes two well-known components; pharma and epidemiology. Therefore, pharmacoepidemiology can be described as an emerging field that builds bridges between clinical pharmacology and epidemiology (Storm, 2012). Pharmacoepidemiology has a wide range of applications, including 1) studying the patterns and the trends of drug use in populations, an example of which can be seen in the study by Alwafi and colleagues,

where the authors examined the prevalence of OAC prescribing in patients with T2DM (Alwafi et al., 2020b); 2) adherence to medication use, an example of which can be seen in the study by Banerjee and colleagues, where the authors explored the adherence and persistence of OACs in patients with AF using primary care data in the United Kingdom (UK) (Banerjee et al., 2020). Another example is the study by Wilkinson and colleagues, where the authors investigated the adherence to clinical guidelines in the management of diabetes in the UK (Wilkinson et al., 2018) ; and 3) the efficacy and safety of medication use in the population, which also include phase 4 studies (post-marketing authorisation assessment studies) (Hilmer et al., 2011); an example of this can also be seen in the study by Fanning and colleagues, where the authors investigated the safety and effectiveness of OACs versus warfarin use in patients with AF and dementia (Fanning et al., 2020). Another example is the study by Wei and colleagues, where the authors investigated the safety of 5α-reductase inhibitors and the incidence of diabetes using a large UK primary care data (Wei et al., 2019).

4.3 Study design in pharmacoepidemiological studies

There are two main types of study designs in pharmacoepidemiological studies, descriptive and analytical studies.

4.3.1 Descriptive studies

Descriptive studies aim to explore and describe health problems, drug use, clinical practice and outcomes of specific diseases or medications. They usually aim to answer exploratory questions and/or generate a hypothesis (Grimes and Schulz, 2002, Süt, 2014). The analysis of descriptive studies usually focuses on the description of the problem in a specific time-point or over some time. Descriptive studies may consist of descriptive statistics, frequency distributions, and calculating rates such as incidence and prevalence (Süt, 2014). In addition, descriptive studies highlights the need for future research, or it predicts a specific problem. However, descriptive studies are limited by the fact that it cannot draw a causal inference or causation (Grimes and Schulz, 2002). Descriptive studies typically include several study designs, such as 1) case-reports, 2) case series, 3) ecological studies, 4) drug utilisation studies, and 5) cross-sectional descriptive studies (Süt, 2014). Case reports and case series studies typically describe a single or series of events or adverse drug reactions in a single or a few patients, which are related to a novel condition or a rare disease (Thaker et al., 2015). Ecological studies examine trends in medication use or disease over some time or across different geographical locations and associate them with trends in presumed exposure to build a hypothesis (Thaker et al., 2015). Drug utilisation studies usually identify and explore questions related to the prescribing, adherence, dispensing and impact of interventions or guidelines on medication use (Lee, 2012). While cross-sectional descriptive studies identify and analyse health

problems related to the epidemiology of diseases such as incidence and prevalence (Mann, 2012).

4.3.2 Analytical studies

Analytical studies usually aim to test a hypothesis or answer a clinical question related to the association between an exposure and an outcome (Ranganathan and Aggarwal, 2019). This type of study is typically categorised into experimental studies, including randomised trials and observational studies such as cohort and case-control studies (Süt, 2014). Experimental studies, also called interventional studies, randomise patients to either receiving the treatment of interest or the control group (Thiese, 2014). On the other hand, observational studies, also called non-interventional studies, observe patients receiving or not receiving the treatment of interest to discover the association between exposure and an event or outcome (Thaker et al., 2015). Observational studies answer a research question without the influence of randomisation (Grimes and Schulz, 2002). Analytical observational studies can be classified into several categories; however, the most common types are analytical cross-sectional studies, case-control studies, and cohort studies.

Analytical cross-sectional studies investigate data from a population at a specific time-point (snapshot), and they usually lack a follow-up time. They usually study the potential association between exposure and outcomes; however, they fail to determine whether the results of an outcome were from the exposure. Therefore, it is difficult to

interpret the results. In addition, analytical cross-sectional studies usually compare disease or medication prevalence between multiple groups (Süt, 2014).

Case-control studies compare the case and control groups in terms of the existence of certain factors to identify potential outcomes or associations (Ranganathan and Aggarwal, 2019). This study design proceeds by identifying the outcome and the past exposure is compared with the control group and is typically a retrospective study design (Thaker et al., 2015). Case-control studies typically allow the testing of multiple exposures and relate them to a single outcome, and therefore this type of study design is useful to conduct clinical research that aims to identify risk factors and determinants of diseases (Ranganathan and Aggarwal, 2019).

Cohort studies divide a population with similar characteristics into exposed and non-exposed groups that are followed over a certain period to determine the existence of an outcome (Thaker et al., 2015). Cohort studies can be designed as retrospective or prospective studies (Thaker et al., 2015). A key strength in this type of study design is that it allows the testing of multiple outcomes for a given exposure. In addition, it allows the calculation of the rates of disease in the exposed and unexposed groups over time (Mann, 2012).

While the study designs mentioned above are well established in the literature and are widely used in pharmacoepidemiology, Other advanced study designs are more frequently used nowadays and more applicable in electronic health database research

such as the self-controlled case series (SCCS) designs and the case-crossover design (Gault et al., 2017). The self-controlled design is an epidemiological observational study design, where the comparison between the exposure and non-exposure is made within the same patient (case only) but at different times. These designs provide the advantage of controlling for time varying confounders (Gault et al., 2017). The SCCS study design can be an alternative method to the traditional cohort study design, especially in cases where the exposure of interest is transient and is only prescribed for a short time and is not a chronic medication such as antibiotics use (Petersen et al., 2016). The case-crossover design is a similar design to the case-control study. However, the case-crossover design is a beneficial method used to examine the effect of transient exposure on the incidence of an acute event immediately preceding the event of interest (Gault et al., 2017). Similar to the SCCS design, it measures the risk of the exposure within the same patients but at different risk windows (Maclure and Mittleman, 2000).

In this PhD project, a descriptive drug utilisation study, analytical cross-sectional study and analytical cohort study were conducted.

4.4 Strengths and limitations of the observational studies for the evaluation of the safety of medications.

Randomised controlled trials (RCTs) are considered the gold standard study design for the evaluation of the safety of medications (Silverman, 2009). They ensure that the only difference between the two treatment groups is the intervention of interest in the trial. However, several biases and restrictions can limit the applicability and the generalisability of an RCT. The cost of conducting an RCT and the recruitment of patients are some of the major challenges in an RCT (Pearce et al., 2015). Furthermore, one of the major limitations in the design of an RCT is the strict inclusion and exclusion criteria, and the study sample that makes it different from what is seen in routine practice and real-world settings (Booth and Tannock, 2014).

Observational studies using routinely collected data can provide important information for the practice guidelines and policymakers. They can be used as an alternative design to address some of the limitations in RCTs, such as recruiting older patients or those with several comorbidities. Observational studies can monitor patients and assess the safety of medications for a longer follow-up period compared to an RCT (Boyko, 2013). In addition, unlike RCTs, observational studies have the advantages of using data from big registries and databases, where a large number of patients can be recruited to test a specific hypothesis, and thus provide important insights into real-world practice and the generalisability of the results (Booth and Tannock, 2014).

Observational studies lack the randomisation between two groups receiving treatment. This may lead to biased results and conclusions where the comparison between both groups is not fair at the beginning of the follow-up period (Boyko, 2013). For example, a study might conclude that a drug is not safe for a specific population whereas the population tested were at higher risk from the beginning of the follow-up period. However, this kind of bias and other biases can be tackled and minimised by identifying the confounding variables that might affect both the outcome of interest and the exposures and by applying some epidemiological and statistical approaches such as the propensity score matching and adjustment methods (Boyko, 2013), which have been used in this PhD project and are explained in further detail in the following chapters.

4.5 Big data and electronic health records in drug safety research

Big data can be defined as the collection and combination of high velocity, high volume and high variety datasets that provide important information and patterns. One of the major applications of big data is using electronic health records (EHRs) in medical research (Vezyridis and Timmons, 2016). EHRs are big sources of data because of their complexity, variations, and number of patients and/or medications that they can provide (Hemingway et al., 2017).

In the UK, the health care system is structured and organised around primary and secondary care settings. The majority of the patients are registered with a general

practitioner in primary care, as it is considered the first point of health care in the UK (The Scottish Parliamen, 2016, Department of Health and Social Care, 2013). Patients can then be referred if needed to a secondary health care provider such as hospitals. Secondary health care providers and clinicians can also feedback the GP and the primary care whenever a patient is discharged from secondary care (Vezyridis and Timmons, 2016). Several EHRs and databases are available for medical research in the UK, which provide access to routinely collected data either from primary care or secondary care settings (Vezyridis and Timmons, 2016). Primary care databases have been of more interest and more frequently used in medical research in the last twenty years in the UK. The main primary care databases and that have the most contribution to scientific research and publication in the UK are; The Clinical Practice Research Datalink (CPRD), THIN and QResearch (Figure 21) (Vezyridis and Timmons, 2016). The THIN database was used as the data source of this PhD project and is discussed in detail in the following sections.

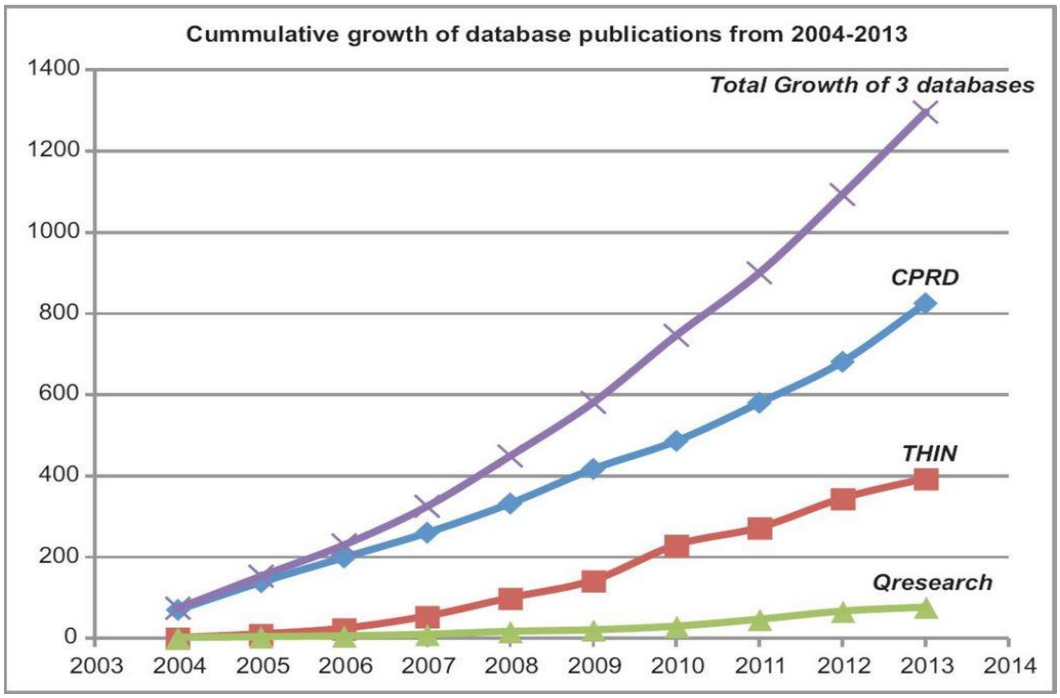


Figure 21: Cumulative growth of database publications from 2004–2013.

Source of data: (Mannan et al., 2017)

4.6 Data source (THIN database)

4.6.1 History of THIN

The roots for the development of the THIN database go back to the 1980s. Several factors including the need to computerise patients' records, the need to find a way to detect adverse drug reactions, and the lack of resources to conduct pharmacoepidemiological studies have led to the development of VAMP Health LTD, which set up a computerised system (vision) to record routinely collected data by GPs.

VAMP also developed the first primary care databases in the UK (Hall, 1992). The latter was then named The General Practice Research Database (GPRD) (now is known as CPRD) after it was donated to the UK Department of Health in 1994 (Walley and Mantgani, 1997). In 2003, ln Practice Systems Ltd. (INPS) (which is the new name of the VAMP company who developed the vision system), and Cegedim Healthcare Software collaborated to establish the THIN database (Mannan et al., 2017).

4.6.2 Summary of THIN

THIN is one of the two well-known primary care databases in the UK. It collects longitudinal anonymised administrative data on patients demographic, disease diagnosis, management and prescribing from UK primary care and participating GPs throughout the UK, dating back to 1994 (The Health Improvement Network, 2019). It has data from over 744 practices with more than 15 million individuals, of which around 4 million are active patients and currently registered with THIN (IQVIA, 2018), and it is representative of about 6.2% of the UK population (Blak et al., 2011). THIN is generalisable to the UK population, particularly in terms of demographics, disease distribution and medication use (Blak et al., 2011).THIN has been validated for epidemiological research purposes (Brauer et al., 2019, McCarthy et al., 2013, McCarthy et al., 2012a, McCarthy et al., 2012b, Mongkhon et al., 2020b, Fanning et al., 2020). Data are collected during patients' routine consultations (visits) with GPs from the time when a patient registers at a general practice affiliated with THIN until they die or transfer out of practice (leave the practice) (Lewis et al., 2007), or the last

data collection of the practices. THIN data is stored across several sets of files created for each practice. This includes information on demographics, diagnosis, treatments and additional health data (Blak et al., 2011). THIN also provides information on referrals that are made by GPs to secondary hospitals and anonymised free texts that are written by doctors or healthcare providers.

4.6.3 Ethics

Data collection for THIN was approved by the National Health Service (NHS) South-East Multi-centre Research Ethics Committee in 2003. To obtain approval for individual studies, study protocols are reviewed by an independent Scientific Review Committee (SRC), which is led by CSD Medical Research UK. THIN data are anonymised and unidentifiable, thus the need for informed consent from patients is waived by the THIN SRC.

4.6.4 Data quality

There are several elements of data quality in THIN. The patient's flag is one of these data quality measurements as it indicates the integrity of the data for the patient. Using an internal validated algorithm that is inbuilt in THIN, patients are categorised based on their data integrity. In this PhD project, I have included only patients flagged A or C, as these two categories represent acceptable data integrity. Other measures of data quality that are embedded within THIN include the acceptable mortality reporting

(AMR) date (Maguire et al., 2009). Data from practices that met the acceptable mortality reporting (AMR) measures of quality assurance for THIN data were included in this PhD project. The AMR date is the year that data reporting is deemed to be complete, based on information derived from the Office for National Statistics (Maguire et al., 2009).

4.6.5 Data structure

THIN data is structured in seven main files. Patient records across all of the seven files can be linked by a specific variable called “patid” (Figure 22). Data was stored in SAS format. Figure 23 provides an example of the therapy file. The information recorded in each file is discussed below;

1- Patient file: this includes demographic information such as age, gender, the date that the patient registered at the practice, the date the patient left the practice, patient registration status, year of birth, patients residing at the same address, or members of the same family linked to the same practice using a household identifier number.
2- Medical file: this includes data on the medical history of patients, such as medical diagnosis and date of diagnosis. Medical conditions are recorded using the Read Clinical Classification version 2 (Read code), which will be discussed in the following section. THIN also provides some free text information that is collected from secondary care and referrals letters.

3- Therapy file: this includes prescribing data, including the date of prescription, drug names, formulation, drug codes, dosage, the quantity prescribed, the duration of the prescription and BNF codes. Medication can be identified using drug codes, which will be discussed later in this chapter.

4- Additional health data (AHD) file: THIN contains additional data on lifestyle and preventative healthcare including height, weight, body mass index (BMI), blood pressure, smoking, alcohol, pregnancy, birth, death, immunisation and lab results.

5- Postcode variable indicator files: these include social deprivation information in the form of quintiles of Townsend score.

6- Consultation records file: this includes information on the time and duration (time patient record remained opened) of the consultation.

7- Practice record (ancillary file): this file contains information on the THIN practices including location, status field (which is an indicator of whether the practice is currently contributing), and vision date (which is when the practice started using the vision practice management software to record consultations).

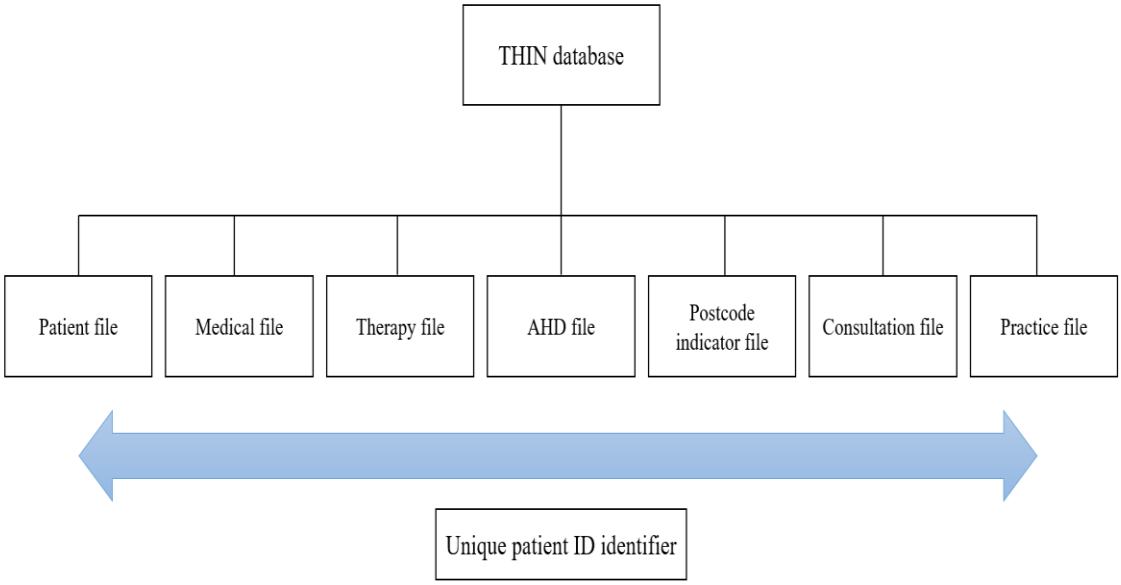


Figure 22: Data structure in the THIN database and the linkage between files via the patient ID.

	patid	drugcode	doscode	prscqty	prscdays	bnf	packsize	dosgval	pracid	prscdate	new_id
1	00Pr	60768979	6o2t	28.00000	000	02080200	0000081	-1.00	a6641	20/12/2016	a6641_00Pr
2	00rZ	60768979	0000010	28.00000	000	02080200	0000081	-1.00	a6641	24/10/2014	a6641_00rZ
3	011y	60768979	5Zjq	28.00000	000	02080200	0000081	-1.00	a6641	16/06/2014	a6641_011y
4	011y	60770979	0000014	56.00000	000	02080200	0000081	1.00	a6641	18/07/2014	a6641_011y
5	011y	60770979	0000014	56.00000	000	02080200	0000081	1.00	a6641	30/09/2014	a6641_011y
6	011y	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	28/10/2014	a6641_011y
7	011y	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	22/12/2014	a6641_011y
8	011y	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	16/02/2015	a6641_011y
9	011y	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	01/05/2015	a6641_011y
10	011y	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	13/05/2015	a6641_011y
11	011y	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	17/07/2015	a6641_011y
12	011y	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	28/09/2015	a6641_011y
13	011y	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	02/12/2015	a6641_011y
14	011y	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	05/02/2016	a6641_011y
15	011y	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	05/04/2016	a6641_011y
16	011y	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	23/05/2016	a6641_011y
17	011y	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	20/07/2016	a6641_011y
18	011y	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	02/09/2016	a6641_011y
19	011y	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	05/10/2016	a6641_011y
20	011y	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	30/11/2016	a6641_011y
21	011y	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	18/01/2017	a6641_011y
22	011y	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	21/03/2017	a6641_011y
23	011y	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	08/05/2017	a6641_011y
24	011y	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	03/07/2017	a6641_011y
25	011y	60770979	0000014	28.00000	28	02080200	0000081	1.00	a6641	27/07/2017	a6641_011y
26	011y	60770979	0000014	28.00000	28	02080200	0000081	1.00	a6641	29/08/2017	a6641_011y
27	011y	60770979	0000014	28.00000	28	02080200	0000081	1.00	a6641	15/09/2017	a6641_011y
28	013u	60770979	5tCO	28.00000	000	02080200	0000081	-1.00	a6641	04/02/2015	a6641_013u
29	013u	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	27/02/2015	a6641_013u
30	013u	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	27/04/2015	a6641_013u
31	013u	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	27/07/2015	a6641_013u
32	013u	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	17/09/2015	a6641_013u
33	013u	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	09/11/2015	a6641_013u
34	013u	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	31/12/2015	a6641_013u
35	013u	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	26/02/2016	a6641_013u
36	013u	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	25/04/2016	a6641_013u
37	013u	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	13/06/2016	a6641_013u
38	013u	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	08/08/2016	a6641_013u
39	013u	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	13/10/2016	a6641_013u
40	013u	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	05/12/2016	a6641_013u
41	013u	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	31/01/2017	a6641_013u
42	013u	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	27/03/2017	a6641_013u
43	013u	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	30/05/2017	a6641_013u
44	013u	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	24/07/2017	a6641_013u
45	013u	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	18/09/2017	a6641_013u
46	01U	60768979	0000014	56.00000	000	02080200	0000081	1.00	a6641	22/07/2013	a6641_01UM
47	01U	60770979	0000014	56.00000	56	02080200	0000081	1.00	a6641	06/08/2013	a6641_01UM

Figure 23: An example of the therapy file.

4.6.6 Identification of outcomes, confounders, and exposures

Patients with different health conditions (diagnosis) and symptoms can be identified in THIN using a code list of Read codes. The Read codes, which are also known as clinical terms, are clinical terminologies used to describe the care, diagnosis of diseases and treatments of patients (Dave and Petersen, 2009, NHS Digital, 2018). The code list was initially adopted by the British Health Service in 1990 (Bonney et al., 2017). It is used to manage primary care data in electronic health records in the UK. Read codes are formed in a hierarchical system of codes and structured similarly to the International Classification of Diseases (ICD) (NHS Digital, 2018). Using the THIN dictionary, outcomes and confounders of interest can be identified using Read codes (an example of the Read codes is listed below in Table 10). To ensure the validity of the selection of the population of interest, Read codes were selected and validated with reference to clinicians' comments and by comparing my list to previously published studies. A similar list of drug codes was also created to help in identifying the medications (exposures) of interest; these codes were identified using the British National Formulary (BNF) (Table 11). The THIN dictionary is given in Excel spreadsheets and the relevant Read codes, and drug codes were extracted and then imported into SAS format to extract the data from the THIN datasets.

Table 10: An example of the read codes

Read code	Read term	Clinical event
J68.00	Gastrointestinal haemorrhage	Bleeding
J680.00	Haematemesis	Bleeding
J680.11	Vomiting of blood	Bleeding
J681.00	Melaena	Bleeding
C10yy00	Other specified diabetes mellitus with other spec comps	Diabetes
C10E.11	Type I diabetes mellitus	Diabetes
C10FC00	Type 2 diabetes mellitus with nephropathy	Diabetes
C106.00	Diabetes mellitus with neurological manifestation	Diabetes
66Ad.00	Hypoglycaemic attack requiring 3rd party assistance	Hypoglycaemia
C110z00	Hypoglycaemic coma NOS	Hypoglycaemia
C108E11	Type I diabetes mellitus with hypoglycaemic coma	Hypoglycaemia
G2...00	Hypertensive disease	Hypertension
G20.11	High blood pressure	Hypertension
G20.00	Essential hypertension	Hypertension
G65..00	Transient cerebral ischaemia	Stroke
G64.12	Infarction - cerebral	Stroke
G66.11	CVA unspecified	Stroke

Table 11: An example of drug codes used in the identification of medications

Drug codes	generic name	Bnfcode
83971998	Dabigatran etexilate 110mg capsules	02.08.02.00
80953998	Rivaroxaban 20mg tablets	02.08.02.00
61036979	Warfarin 1mg tablets	02.08.02.00
97322997	Human insulin 100iu/ml preloaded injection pen	06.01.01.01
86045998	Human insulin 1mg unit dose blisters	06.01.01.01
97057997	Glibenclamide 2.5mg tablets	06.01.02.01
96283997	Gliclazide 30mg modified-release tablets	06.01.02.01
62836979	Gliclazide 40mg tablets	06.01.02.01
95272992	Metformin 250 mg tab	06.01.02.02
54786979	Metformin 500mg modified-release tablets	06.01.02.02
98016979	Amlodipine 5mg tablets	02.06.02.00
95382992	Paracetamol 125 mg tab	04.07.01.00
97883996	Flucloxacillin 500mg powder for solution for injection vials	05.01.01.02
96256998	Amoxicillin 125mg sugar free chewable tablets	05.01.01.03
87251998	Citalopram 10mg tablets	04.03.03.00

4.6.7 Strengths and limitations of the THIN database

There are several advantages and benefits of using the THIN database in medical research in general. One major advantage of THIN is the large sample size of patient's records that can be included in a single study, in which this data is representative of

about 6 % of the entire UK population (Blak et al., 2011). Another advantage of using THIN is access to real-life (real-world) data with consultations, diagnosis and treatment details during routine GP visits (Blak et al., 2011). THIN has also been validated for epidemiological research by several studies (Lewis et al., 2007). In addition, THIN offers longitudinal primary care data which is important when studying epidemiology and the treatment of chronic illness such as T2DM, as patients with T2DM are mainly managed in primary care settings with multiple visits and treatment refills (Willens et al., 2011).

However, the THIN database has some limitations. Firstly, there is the risk of underestimating the prescription rate as the THIN database only contains information from the primary care setting, and, therefore, prescribing for patients treated in different health care settings (secondary, tertiary, private) is not possible, which can create gaps in the data recorded by THIN on the treatment of patients. Secondly, adherence to medications is a limitation in the THIN database and other EHRs databases, as it is not possible to guarantee that patients are taking their medications. However, this issue can also be found in other types of data sources and pharmacoepidemiological research and trials, and is not exclusive to the THIN database (Zhang et al., 2014). In addition, several techniques can tackle this issue, for example, looking at repeated prescriptions and counting the pills patients are dispensing that may indicate continuation and adherence (Banerjee et al., 2020). Thirdly, THIN has no over the counter (OTC) drug information, and it has some missing

data for blood pressure levels, body mass index (BMI), smoking and alcohol use. However, this issue can be tackled by applying some advanced statistical methods such as multiple imputations (Pedersen et al., 2017).

4.7 Identification of patients with T2DM

4.7.1 Overview

The study population of this PhD project was patients with T2DM. Therefore, the process of identification of patients with T2DM is described in this chapter. Other populations investigated in this PhD project are discussed later in this thesis.

4.7.2 Diabetes cohort identification

Data from practices that met the AMR measures of quality assurance for THIN data were used in this PhD project. Patients were included only if they had an observation period of at least 12 months prior to T2DM diagnosis and were registered with their general practice during the study period of 2001-2017. Patients with T2DM aged ≥ 18 years were identified from the entire THIN population using the Read codes produced by previous THIN studies. However, some of the Read codes were non-specific for any type of diabetes (see Table 12. below). Therefore, I used specific criteria to limit the misclassification of the type of diabetes and to avoid under-reporting. Patients with T2DM were identified based on the following criteria of having 1) a diagnostic code for T2DM (using Read codes), or 2) a diagnostic code for any type of diabetes and a

record of any oral hypoglycaemic agent prescription. Patients who had a diagnostic code for T2DM accounted for 92.7% of the entire cohort, while the remaining met criteria two. Patients with a non-specific code for T2DM and who only had records for insulin prescription were excluded because they may have T1DM, although their age at the first event is taken into account. T2DM is typically diagnosed over the age of 30 years; however, the rate of young-onset T2DM is increasing (Ogurtsova et al., 2017). Therefore, I only excluded children (less than 18 years old) who were more likely to have T1DM.

Table 12: An example of Read codes used in the identification of patients with diabetes

Read code	Read term	Diabetes type
C10yy00	Other specified diabetes mellitus with other spec comps	Nonspecific
C104y00	Other specified diabetes mellitus with renal complications	Nonspecific
C104y00	Other specified diabetes mellitus with renal complications	Nonspecific
C10ED00	Type 1 diabetes mellitus with nephropathy	T1DM
C10EM00	Type 1 diabetes mellitus with ketoacidosis	T1DM
C10E.11	Type I diabetes mellitus	T1DM
C10FC00	Type 2 diabetes mellitus with nephropathy	T2DM
C10F500	Type 2 diabetes mellitus with gangrene	T2DM
C10F.11	Type II diabetes mellitus	T2DM

4.8 Summary of this chapter

This chapter summarised important details about the structure and quality of THIN database. In addition, the process of identification of diagnosis, medications and most

importantly, the main study population in this PhD project (patients with T2DM), were described. This will inform the reader about the THIN database and its strengths and limitations. It will also help to better understand some of the variables and terminologies that will be mentioned later in this thesis.

Chapter 5 Trends in Oral Anticoagulant Prescribing in patients with Type 2 Diabetes Mellitus: A Population-based Study in the United Kingdom

The findings from this chapter have been published in the British Medical Journal Open, under the title: “Trends in Oral Anticoagulant Prescribing in Individuals with Type 2 Diabetes Mellitus: A Population-based Study in the United Kingdom”. Refer to Figure 24 below.

Figure 24: A capture picture from BMJ open website which represent the publication of this chapter.

5.1 Chapter overview

In this chapter, patients with Type 2 Diabetes Miletus (T2DM) who were identified in Chapter 4 were further investigated. I examined the number of patients with T2DM and using oral anticoagulants (OACs) over 15 years period. The changes in prescribing pattern in the last years helps in understanding the clinical characteristics of patients with T2DM and using OACs.

5.2 Background

T2DM is one of the most common chronic diseases worldwide and has become a major global public health concern (Ogurtsova et al., 2017). The prevalence of the disease has significantly increased over the last 30 years. According to the International Diabetes Federation (IDF) report in 2019, it is estimated that 463 million people in the world are living with diabetes (International Diabetes Federation, 2019). In England, the prevalence of diabetes is about 6.7%, it has increased by 53% between 2006 and 2013 (National Institute for Health and Care Excellence, 2015).

T2DM and cardiovascular diseases (CVDs) often coexist with many patients with T2DM experiencing cardiovascular complications (Mozaffarian et al., 2016). CVDs including cardiac arrhythmias, venous thromboembolism, and ischaemic heart disease are among the leading causes of mortality worldwide in patients with T2DM (Nichols et al., 2014). In the UK, approximately 27% and 25% of all causes of mortality

amongst males and females respectively are due to cardiovascular diseases (British Heart Foundation, 2020). Diabetes and CVDs are often coexistent, with many diabetes patients suffering from cardiovascular complications (Movahed et al., 2005, Dinesh Shah et al., 2015).

Anticoagulants are widely prescribed for the prevention and treatment of atrial fibrillation (AF), stroke, venous and arterial thrombosis. When prescribed for venous thromboembolism, oral anticoagulant (OAC) treatment is typically of short duration, but it can be lifelong treatment when prescribed for AF (National Institute for Health and Care Excellence, 2014, National Institute for Health and Care Excellence (NICE), 2014, January et al., 2019).

T2DM is one of the main risk factors contributing in CHA_2DS_2 score (Congestive heart failure, Hypertension, Age≥75 years, Diabetes mellitus, previous Stroke/transient ischaemic attack (TIA) (2 points)), which is a prediction of the risk of stroke and guides the optimisation of management in patients with AF (Gage et al., 2001). In 2010, CHA_2DS_2-VASc (Congestive heart failure/left ventricular dysfunction, Hypertension, Age≥75 (2 points), Diabetes, Stroke (2 points) –Vascular disease, Age 65–74 and Sex category (female)) was adapted from the previous score (Lip et al., 2010), and it is now recommended by most of the current guidelines, in which patients with AF are likely to be prescribed OAC if they score two or more in the total score (January et al., 2019, National Institute for Health and Care Excellence, 2014). In addition, since the introduction of direct oral anticoagulants (DOACs) in 2011, several guidelines

recommended their use for indications such as atrial fibrillation (January et al., 2019, National Institute for Health and Care Excellence, 2014). DOACs have much more predictable pharmacokinetics and pharmacodynamics, and are less prone for drug interactions when compared with warfarin (20). However, OAC use in patients with T2DM remains unclear, with limited studies focused on their use in patients with T2DM (Hamada and Gulliford, 2015, Łabuz-Roszak et al., 2017).

Previous studies have demonstrated that the prevalence of AF in patients with T2DM ranges from 3.5% to 14.9% (Movahed et al., 2005, Murphy et al., 2007, Nichols et al., 2009), and that patients with T2DM have 40% higher risk of developing AF compared to patients without T2DM (Dublin et al., 2010). Investigating OAC use in patients with T2DM is important due to the high number of patients, the possibility of drug-drug interactions, and the potential association with serious adverse events such as bleeding and hypoglycaemia (National Institute for Health and Clinical Excellence, 2017, Ament P, 2000). This was highlighted in particular among patients with T2DM in previous large-scale epidemiological studies and in multiple case reports where warfarin was associated with an increased risk of hypoglycaemia (Nam et al., 2018, Leonard et al., 2016). It has been suggested that displaced plasma protein and Cytochrome P450 (CYP450) hepatic metabolic pathway could be potential mechanisms for the increased risk of hypoglycaemia (Leonard et al., 2016, Romley et al., 2015, Nam et al., 2018, Namazi S, 2005).

5.3 Aims and objectives

Given the recent update in guidelines for OAC prescribing, and the limited research on their use in patients with T2DM, this research aimed to describe the prescribing patterns of OAC medications in patients with T2DM in the UK population as an important step in investigating its safety within this high risk population.

5.3.1 Primary objective

The primary objective of this study was to examine the prescribing trends of OAC medications in patients with T2DM from 2001 to 2015, stratified by age, gender and therapeutic classifications.

5.3.2 Study design

An observational retrospective drug utilisation study

5.3.3 Secondary objective

The secondary objective was to compare the trend in OAC use in patients with AF, with and without T2DM, given that AF is the main indication for OAC use (Loo et al., 2017).

5.4 Methods

5.4.1 Data source

This study used The Health Improvement Network (THIN) primary care database in the UK. For details, refer to Chapter 4, Section 4.10.

5.4.2 Ethical consideration

The present study is based on anonymised and unidentifiable THIN data, thus the need for informed consent was waived by the THIN scientific review committee (SRC). This study was reviewed and scientific approval was obtained by THIN SRC in 2018 (Reference: 18THIN009) (Appendix 5). The research was reported in accordance with strengthening the reporting of observational studies in epidemiology (STROBE) Statement (Appendix 6). Patients were not involved in the design of the study.

5.4.3 Study population

Data from practices that met the acceptable mortality reporting (AMR) measures of quality assurance for THIN data were used in this study (Maguire et al., 2009). The start date was defined as the date of the first record for T2DM diagnosis. Patients were included only if they had an observation period of at least 12 months prior to their start date and were registered with the general practice during the study period. The end date was the date were patients left the practice, died or transferred out. Patients with

T2DM aged ≥ 18 and registered with the THIN database between 2001 and 2015 (of which data were only available up to) were identified based on the criteria described in chapter 4 section 4.10. Patients with T2DM receiving at least one prescription of OAC medication were identified. Oral anticoagulant medications were consigned into three categories: warfarin, DOACs (apixaban, rivaroxaban, dabigatran and edoxaban), and other anticoagulant medications (acenocoumarol, pentosan polysulfate and phenindione) (Figure 25).

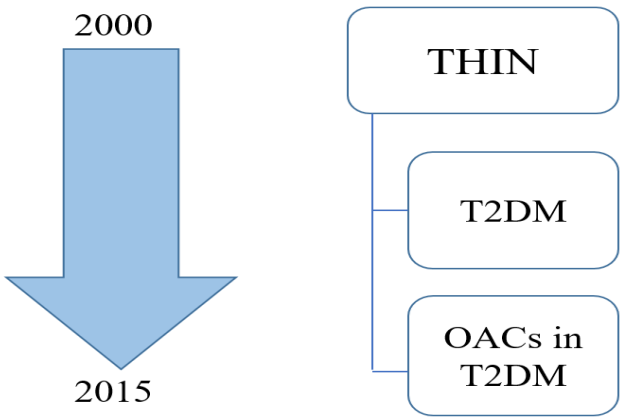


Figure 25: Flow chart of the population included in the study.

For the second objective, patients with AF aged ≥ 18 years and registered with THIN were identified using Read codes. The prescribing of OAC medications in patients with AF with and without T2DM involved a two-step cohort identification (Figure 26). The first step was designed to identify patients with AF with coexisting T2DM, and the latest

first record between AF and T2DM was counted as the start date (coexisting of both diseases) for this cohort. The second step involved identifying patients with AF without a diagnosis of T2DM, and the start date for these patients was the first recorded AF diagnosis. Patients who developed AF first and T2DM later contributed to the AF only cohort and then to the AF and T2DM cohort.

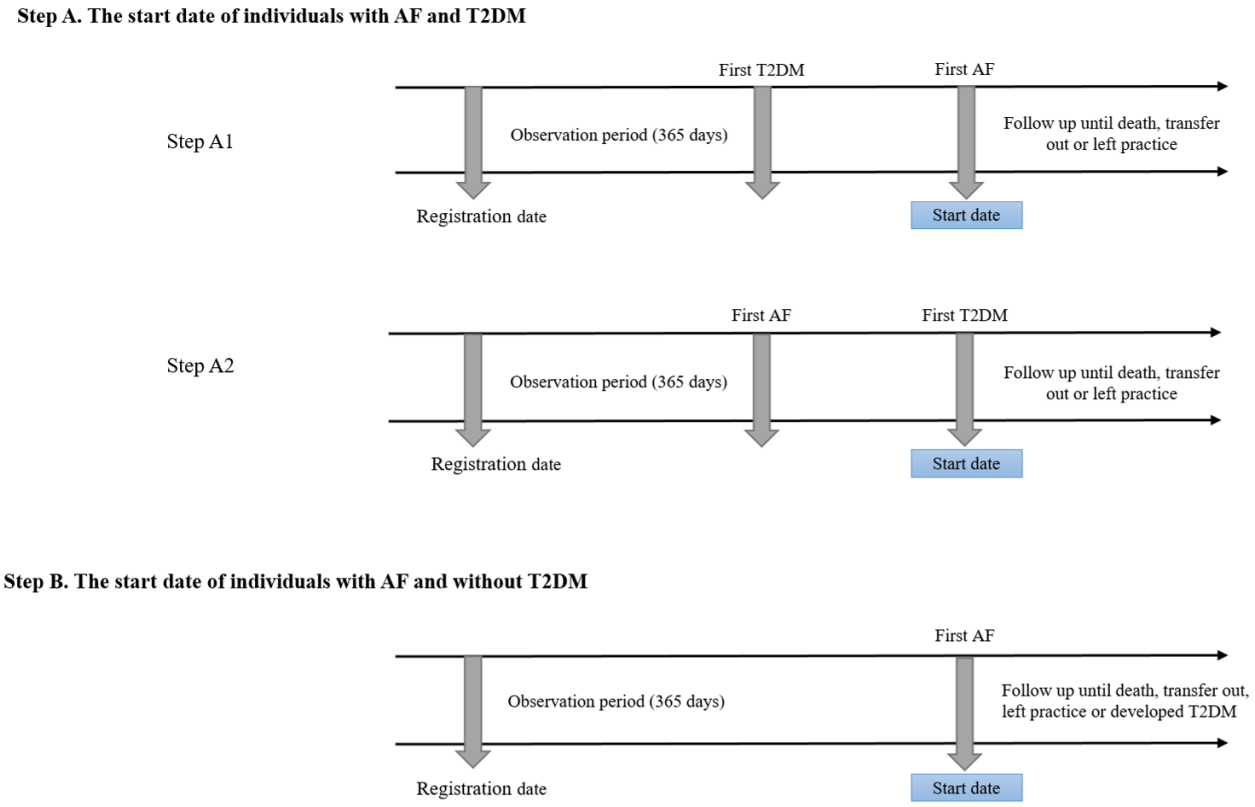


Figure 26: Methods to identify the study population of AF patients with and without T2DM.

Registration date: is the date of a patient's registration with the general practice; AF: Atrial fibrillation; T2DM: Type 2 diabetes mellitus. Patients who developed AF first and T2DM later (Step A2) contributed to the AF only cohort (Step B) until they developed T2DM

5.4.4 Study variables

The following variables were used to describe the population demographics. The characteristics of the study population were identified at the time of the first OAC prescription.

1- Demographics: Age, gender, alcohol and smoking status
2- Comorbidities history including; AF, deep vein thrombosis (DVT), stroke, coronary heart disease, chronic kidney disease (CKD), heart failure, hypertension, Hyperlipidaemia, chronic obstructive pulmonary disease (COPD), bleeding, peptic ulcer disease, peripheral vascular disease, depression and liver diseases. Theses variables were identified using diagnosis records of Read codes (details of Read code are listed in Appendix 7). Baseline characteristic were measured over the 12-month period preceding the first OAC prescription
3- Medications use including; aspirin, antiplatelet, statins, beta blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, diuretics and digoxin. These medications were identified using drug codes (Appendix 8). Medication use was assessed over the 6-month period preceding the first OAC prescription.
4- CHA2DS2-VASc score (Lip et al., 2010); several international guidelines recommend using this score to calculate stroke risk in patients with AF (January et al., 2019, National Institute for Health and Care Excellence, 2014).

CHA2DS2-VASc score ranges from 0 to 9 (higher score indicates a higher risk for stroke). The element of the score includes the following:

- Congestive cardiac failure (1 point), including right side and left side heart failure which are identified by Read codes.
- Hypertension (HTN) (1 point), including primary and secondary hypertension, identified by Read codes.
- Age ≥75 years (doubled points).
- Diabetes mellitus (1 points), including T1DM and T2DM, identified by Read codes.
- Age 65 to 74 years (1 point)
- Prior stroke or TIA or systemic embolism (doubled points), this includes ischaemic stroke, TIA and excludes haemorrhagic stroke and venous infarctions. Thromboembolism includes arterial embolic disease and excludes thrombosis and venous embolic disease, which are included in vascular diseases
- Vascular disease (1 point), includes coronary artery disease, peripheral vascular disease and arterial and venous thrombosis, identified by Read codes.
- Females sex (1 point).

5- HAS-BLED score; several international guidelines recommend using this score to calculate bleeding risk with OAC medications (National Institute for Health

and Care Excellence, 2014, January et al., 2019). HAS-BLED score ranges from 0 to 8 (as labile INR not included in calculation), a higher score indicates a higher risk for bleeding. These elements of the score includes the following;

- Hypertension (1 point): as described for CHA2DS2-VASc score previously.
- Renal disease (1 points) including CKD, renal impairment, chronic dialysis, transplant and end stage renal disease. This was identified by Read codes.
- Liver disease (1 points) including includes chronic hepatic disease (cirrhosis, hepatitis, fatty liver and fibrosis), chronic hepatitis and liver transplantation.
- Prior stroke (1 point): as described for CHA2DS2-VASc score previously.
- Prior major bleeding includes any previous bleed; defined based on the International Society of Thrombosis and Haemostasis guidance as major bleeding where the bleed occurs in a critical area or organ or requires a blood transfusion (Schulman and Kearon, 2005).
- Age > 65 years (1 point)
- Medications that predispose to bleeding (1 point each), this includes nonsteroidal anti-inflammatory drugs (NSAIDs) or antiplatelet drugs.
- Alcohol use (1 point).

5.5 Outcomes

5.5.1 Primary outcomes

The primary outcome was the prevalence of OACs prescribing in patients with T2DM between 2001 and 2015, stratified by age, gender and therapeutic classifications.

5.5.2 Secondary outcomes

Secondary outcome was the prevalence in OAC prescribing in patients with AF, with and without T2DM.

5.6 Data analysis

Descriptive statistics were used to describe patient's demographics, and comorbidities. Continuous data were reported as mean ± standard deviation (SD), and categorical data was reported as percentages (frequencies). The prevalence of OAC medications presented per 100 persons with 95% confidence intervals (CIs) were calculated on an annual basis by dividing the number of all patients prescribed OAC medications in a particular year over the mid-year population of patients with T2DM in the same calendar year, stratified by age, gender and therapeutic classifications.

$$\frac{Number\ of\ \ T2DM\ patients\ prescribed\ OAC\ medications\ during\ year\ X}{Total\ number\ of\ T2DM\ patients\ in\ year\ X}$$

For the secondary objective: the trend in OAC use in AF patients with T2DM, was calculated on an annual basis by dividing the number of AF patients with T2DM prescribed OAC medications in a particular year over the mid-year population of AF patients with T2DM in the same calendar year. The trend in OAC use in patients with AF and without T2DM was calculated by dividing the number of AF patients without T2DM prescribed OAC medications in a particular year over the mid-year population of AF patients without T2DM in the same calendar year. The prescribing trend of OAC medications was assessed using Poisson model. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

5.6.1 Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of this research.

5.7 Results

5.7.1 Demographics and characteristics

From the entire THIN population, 361,635 patients with T2DM were identified between 2001 and 2015 were identified, of whom 36,570 received a prescription for OAC. Characteristics of the entire cohort included in this study are presented at the time of first OAC prescription. The average age of patients at the time of first OAC prescription was 72 (SD, 10.2) years old, and the majority of patients were male (59.9%). Around 64.6% of patients were diagnosed with AF and 22.2% were diagnosed with venous thromboembolism diseases. Baseline demographics of the study sample are described in Table 13.

Table 13: Characteristics of the study sample at the time of first OAC prescription

Demographics	T2DM patients receiving OAC (%)
Total	**36,570 (100%)**
Age (Mean ± SD)*	72 ± 10.2
Gender (Male)	21,586 (59.9)
Social	
Smoking	3,598 (10.0)
Alcohol drinking	23,879 (69.6)
Geographical location	
England	24,436 (66.8)
Scotland	5,479 (14.9)
Wales	5,051 (13.8)
Ireland	1,604 (4.3)
Comorbidities**	
Atrial fibrillation	23,655 (64.6)
Venous thromboembolisms	8,127 (22.2)
Stroke	7,441 (20.3)
Coronary heart diseases	12,606 (34.4)
Chronic kidney diseases	10,097 (27.6)
Heart failure	8,181 (22.3)
Hypertension	25,342 (69.3)
Hyperlipidaemia	8,563 (23.4)
COPD	3,815 (10.4)

PUD	10,266 (28.0)
PVD	3,522 (9.6)
Bleeding	8,062 (22.0)
Depression	8,186 (22.8)
Mild liver disease	146 (0.4)
Moderate to severe liver disease	209 (0.5)
Medications	
Aspirin	13,940 (38.1)
Other anti-platelets	2,736 (7.4)
Statin	25,138 (68.7)
BB	18,503 (50.6)
CCB	13,597 (37.1)
ACEIs/ARBs	25,490 (69.7)
Diuretics	16,796 (45.9)
Digoxin	11,867 (32.4)
Antidiabetic medications	
Metformin	20,235 (55.3)
Sulfonylurea	9,617 (26,3)
Thiazolidinediones	1,587 (4.3)
DDP-4	1,244 (3.4)
Meglitinide	152 (0.4)
SGLT	52 (0.1)
GLP	320 (0.9)

CHA_2DS_2-VASc Score[a]	
< 2	723 (3.06)
≥ 2	22,923 (96.4)
HASBLED[b]	
< 2	1,413 (6.0)
≥ 2	22,242 (94.0)

*Standard deviation ±; Alcohol missing: (10.5%), Smoking missing (3.2%); OAC: Oral anticoagulant; SD: Standard deviation; COPD: Chronic obstructive pulmonary disease; PUD: Peptic ulcer disease; PVD: Peripheral vascular disease; BB: Beta-blocker; CCB: Calcium channel blocker; ACEIs: Angiotensin converting enzyme inhibitors; ARBs: Angiotensin II receptor blockers; a; CHA2DS2-VASc indicates patients with congestive cardiac failure, hypertension, age ≥75 years (doubled), diabetes mellitus, age 65 to 74 years, prior stroke or transient ischemic attack or systemic embolism (doubled), vascular disease, and gender category (women). CHA2DS2-VASc score ranges from 0 to 9 (higher score indicates a higher risk for stroke); b; HAS-BLED indicates patients with hypertension, renal disease, liver disease, prior stroke, prior major bleeding, age > 65 years, medications that predispose to bleeding (NSAIDs or antiplatelet drugs), alcohol use (labile INR not included). HAS-BLED score ranges from 0 to 8 (as labile INR not included in calculation), a higher score indicates a higher risk for bleeding.

5.7.2 Trends in prescribing prevalence of oral anticoagulant medications in T2DM

Between 2001 and 2015, the prescribing prevalence of OACs in patients with T2DM increased by 50.0% from 4.4 (95% CI, 4.2–4.6) in 2001 to 6.6 (95% CI, 6.5–6.7) in 2015 per 100 persons with T2DM, p<0.001, with an average increase of 3.2% per year (Figure 27).

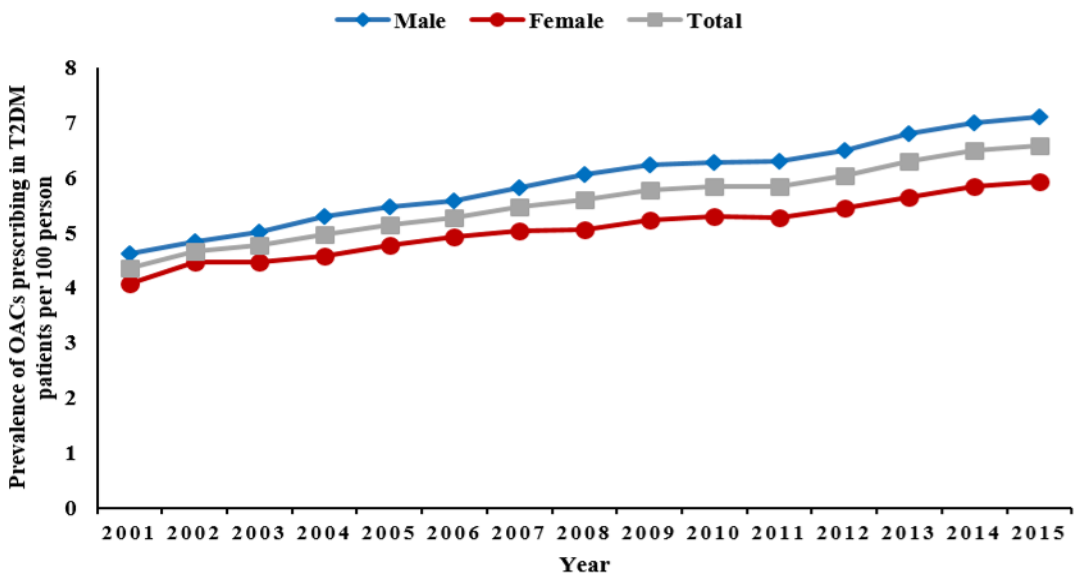


Figure 27: Prescribing prevalence of oral anticoagulant medications in patients with T2DM stratified by gender.

5.7.2.1 Trends in prevalence of oral anticoagulant prescribing stratified by gender

The changes in prevalence of OAC prescribing between 2001 and 2015 stratified by gender are shown in Figure 27. The prescribing prevalence of OAC medications among males increased by 54.3% from 4.6 (95% CI, 4.3 – 4.9) to 7.1 (95% CI, 6.9 – 7.2) per 100 persons with T2DM, while the prescribing prevalence of OAC medications among females increased from 4.0 (95% CI, 3.8 – 4.4) to 5.9 (95% CI, 5.8 – 6.1) per 100 persons with T2DM, with an overall increase of 47.5%.

5.7.2.2 Trends in prevalence of oral anticoagulant prescribing stratified by age

Similarly, the prescribing prevalence of OAC medications varied among patients from the different age groups. The prevalence of OAC medications among patients aged 75 years or above increased from 7.1 (95% CI, 6.6 – 7.6) in 2001 to 11.6 (95% CI, 11.4 – 11.9) in 2015 per 100 persons with T2DM. However, it was clearly lower among younger patients, which increased from 5.7 (95% CI, 5.2 – 6.1) in 2001 to 6.5 (95% CI, 6.3 – 6.6) in 2015 per 100 persons with T2DM, for patients aged between 65-74 years, and from 2.0 (95% CI, 1.8 – 2.2) in 2001 to 2.2 (95% CI 2.1 – 2.3) in 2015 per 100 persons with T2DM, for patients aged below 65 years (Figure 28).

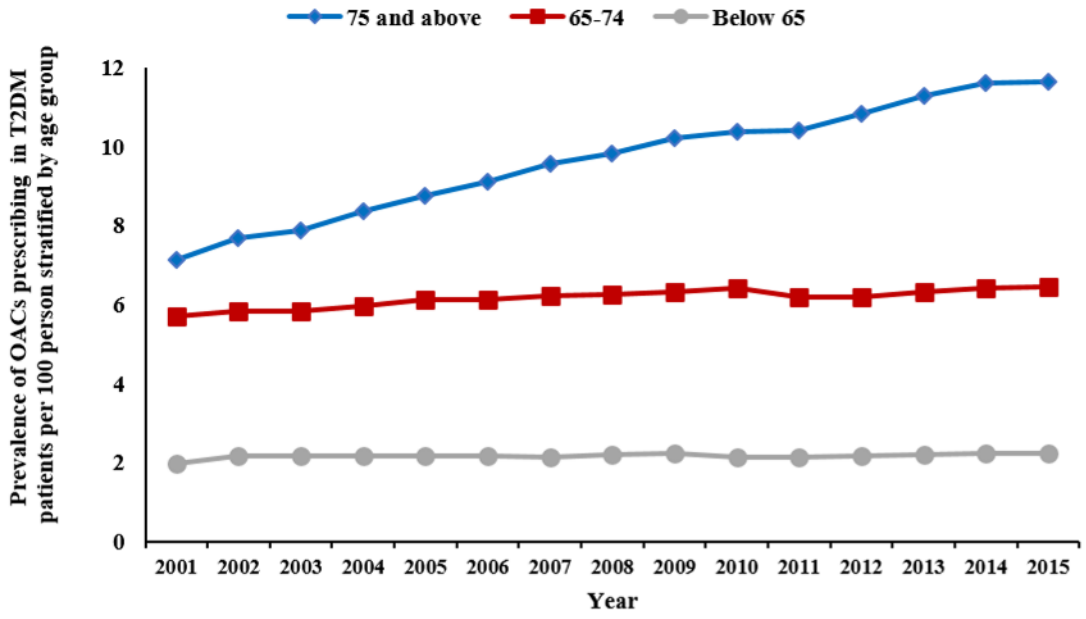


Figure 28: Prescribing prevalence of oral anticoagulant medications in patients with T2DM stratified by age.

5.7.2.3 Trends in prevalence of oral anticoagulant prescribing stratified by medication

Although warfarin was the most common OAC prescribed during the entire study period (86.3%), its use declined from 98.9 (95% CI, 98.4 – 99.4) in 2001 to 85.1 (95% CI, 84.6 – 85.7) in 2015 per 100 persons with T2DM. In contrast, there was a corresponding increase in the proportion of patients who used DOACs from 0.1 (95% CI, 0.08 – 0.23) in 2010 to 17.6 (95% CI, 17.1 – 18.2) in 2015 per 100 persons with T2DM. Other OACs, including acenocoumarol and phenindione were less likely to be

prescribed during the entire study period (0.03%), their prescribing rate decreased from 1.1 (95% CI, 0.7 – 1.7) in 2001 to 0.4 (95% CI, 0.3 – 0.5) in 2015 per 100 persons with T2DM (Figure 29). In addition, a small percentage of patients with T2DM using OAC were prescribed different OAC classes during the same year ranging from less than 1% in 2010 to 3% in 2015.

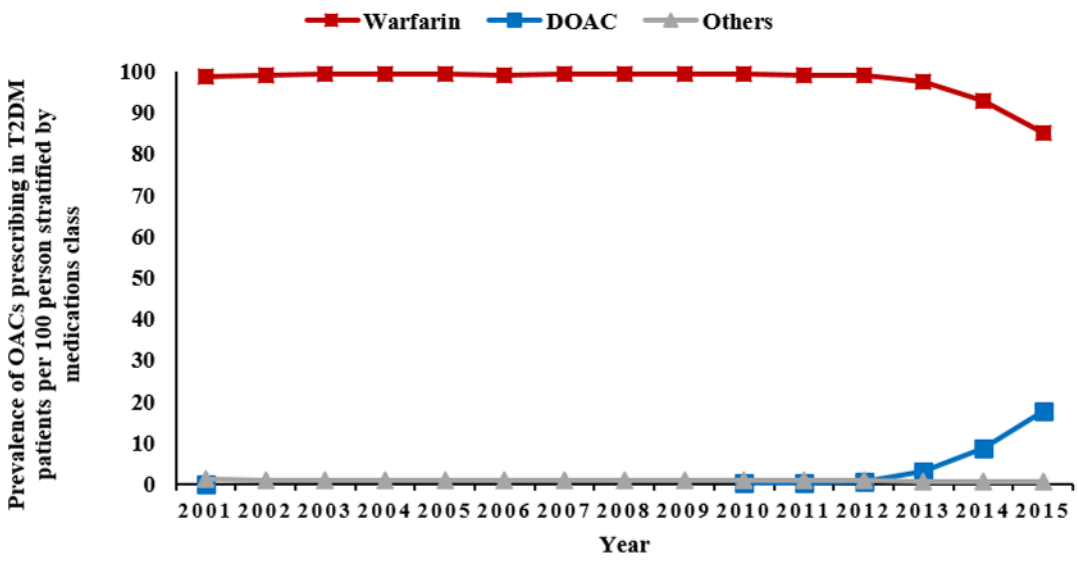


Figure 29: Prescribing prevalence of oral anticoagulant medications in patients with T2DM stratified by medications class.

Further stratification by individual OAC drug treatment showed that the prescribing prevalence of rivaroxaban markedly increased from 0.1 (95% CI, 0.05 – 0.2) in 2010 to 10.9 (95% CI, 10.5 – 11.4) in 2015 per 100 persons with T2DM, while the prescribing prevalence of dabigatran increased to a lesser degree from 0.03 (95% CI, 0.001 –

0.07) in 2010 to 2.7 (95% CI, 2.5–2.9) in 2015 per 100 persons with T2DM. In addition, the prescribing prevalence of apixaban increased from 0.05 (95% CI, 0.01 – 0.08) in 2010 to 4.36 (95% CI, 4.1 – 4.6) in 2015 per 100 persons with T2DM (Figure 30).

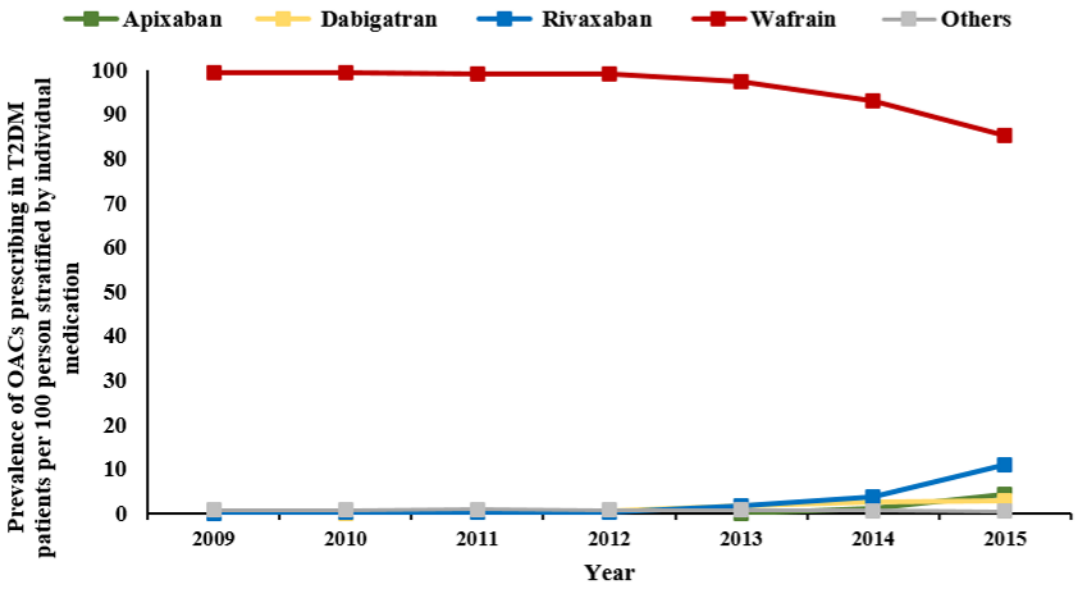


Figure 30: Prescribing prevalence of oral anticoagulant medications in patients with T2DM stratified by individual medication.

5.7.2.4 Trends in prescribing prevalence of oral anticoagulants in patients with atrial fibrillation with and without T2DM

The prescribing prevalence of OACs in patients with AF with and without coexisting T2DM maintained a parallel increase. Patients with AF and T2DM had a higher rate of OAC medications prescribing compared to those without T2DM (38.2% vs. 26.4%,

respectively). The prevalence of prescribing ranged from 46.6 (95% CI, 43.5 – 49.7) in 2001 to 59.0 (95% CI, 58.3 – 60.0) in 2015 per 100 persons for patients with AF and T2DM, and from 36.0 (95% CI, 35.1 – 36.7) to 49.7 (95% CI, 49.4 – 50.0) per 100 persons between 2001 and 2015 for patients with AF without T2DM (Figure 31).

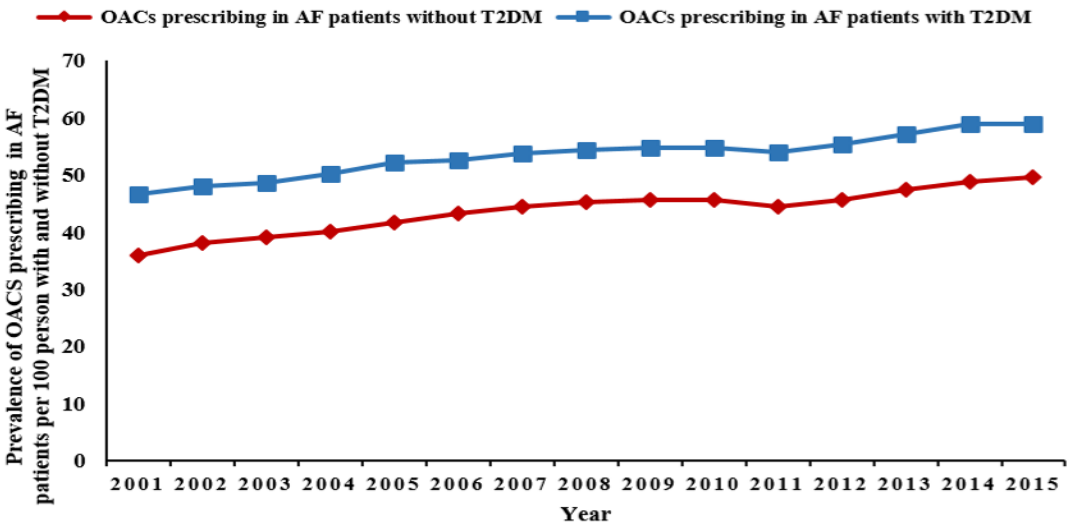


Figure 31: Prescribing prevalence of oral anticoagulant medications in AF patients with and without T2DM.

5.8 Discussion

This study investigated the drug utilisation pattern of OAC medications in patients with T2DM, and in patients with AF, with and without T2DM. The key findings are: 1) the prescribing prevalence of OACs in patients with T2DM has increased markedly between 2001 and 2015, 2) the increase in the prescribing prevalence of OACs was

not consistent across patients of different gender and age group, males and patients aged 75 years and above had a higher prescribing prevalence compared to females and patients younger than 75 years, 3) the prescribing of DOACs is clearly replacing the prescribing of warfarin since their introduction to the UK market in 2011.

Previous studies investigating the trend of OACs prescribing in patients with T2DM are limited. A previous study by Hamada *et al*. examined the trend of cardiovascular medication prescribing in patients with diabetes aged 80 years or above in the UK between 1990 to 2010, concluding that the prescribing of OACs in patients with T2DM had increased from 5% in 1999 to 19% in 2010 (Hamada and Gulliford, 2015). These results showed similar trends to this study in the increase of OACs prescriptions in T2DM. However, the results of this study showed that OAC prescriptions increased less sharply, which is explicable by restriction of their population to include only patients aged 80 years and older. Despite this, age is considered a risk factor for many conditions for which OACs are indicated, and the results showed an increased rate of OACs prescribing among patients aged 75 years and above, which was also similar to a previous study that used primary care data in the UK (Loo et al., 2017). Furthermore, an increasing prescribing prevalence of DOACs in the last few years have been reported in several studies that examined the trend of OACs in the general population or in patients with AF across different countries (Loo et al., 2017, Gadsboll et al., 2017, Alalwan et al., 2017). Alalwan *et al*., using data from MarketScan Medicare, reported that DOACs increased from 1.39% (95% CI, 1.34 –1.44%) in 2010

to 28.33% (95% CI, 28.14 – 28.52%) in 2014 (Alalwan et al., 2017). Similarly, Loo *et al*. found that the rate of initiation of DOAC increased significantly, particularly from 2012 onwards, with a 17-fold increase from 2012 to 2015 (RR 17.68; 95% CI, 12.16 – 25.71) (Loo et al., 2017). The findings presented in this study, and specifically related to DOACs' prescribing trend are in line with previous findings, however, it is important to highlight that those studies concerned the general population and were not specific to T2DM (Loo et al., 2017, Gadsboll et al., 2017, Alalwan et al., 2017).

This study showed that since the introduction of DOACs, patients with T2DM using OACs were prescribed different classes of OAC, possibly due to patients switching from one class to another. DOACs have been reported to be non-inferior to warfarin in the prevention of major strokes and embolic events in different clinical trials and observational studies (Patel et al., 2011, Granger et al., 2011, Connolly et al., 2009, Larsen et al., 2013, Vinogradova et al., 2018). Evidence from meta-analyses showing better efficacy and non-inferior safety when comparing DOACs and warfarin could be a reason for the paradigm shift in favouring the prescribing of DOACs (Hicks et al., 2016, Ruff et al., 2014). This led in a change in the UK National Institute for Health and Care Excellence (NICE) guidance for the management of AF, and as of 2014, DOACs have been recommended as first-line therapy for AF (National Institute for Health and Care Excellence, 2014). However, it is crucial to recognise that older people with comorbidities were excluded or underrepresented in the pivotal clinical trials of DOACs and therefore, DOACs should be prescribed with caution and strict

monitoring in this population (Fanning et al., 2017). Another major issue with warfarin is that it is more prone to several drug-food and drug-drug interactions (Ament P, 2000, Di Minno et al., 2017), which could explain why DOACs are being prescribed more favourably in the recent years compared to warfarin, especially accounting for elements such as ageing and polypharmacy. Nonetheless, a major advantage for DOACs is their wider therapeutic index and that it does not require regular monitoring during intake for international normalized ratio (INR) compared to warfarin (Mekaj et al., 2015, Kimmel, 2008, Tse et al., 2018).

The results of this study highlighted that patients with T2DM receiving OACs have a high risk profile of cardiovascular comorbidities including hypertension, coronary heart disease, heart failure, peripheral vascular diseases and hyperlipidaemia (Table 13), in which it could be associated with the initiation of OAC prescribing (Łabuz-Roszak et al., 2017). However, due to the nature of this descriptive study it is difficult to draw this conclusion and further studies to investigate this association are needed.

As expected, the results of this study showed that AF was the main indication for OAC prescriptions among patients with T2DM. Several international guidelines, including those from the US (January et al., 2019), Europe (Kirchhof et al., 2016) and the UK (National Institute for Health and Care Excellence, 2014) have recommended the use of OACs in patients with AF based on $CHADS_2$ (Gage et al., 2001) and CHA_2DS_2-VASc score (Lip et al., 2010). This was also in line with the results of this study as it showed that patients with AF and coexisting T2DM had a higher rate of OACs

prescribing compared to patients with AF without T2DM. However, the results showed a higher prescribing rate of OAC among males compared to females that is similar to other studies that highlighted the higher prevalence of OAC prescribing amongst males (Kjerpeseth et al., 2017, Scowcroft et al., 2013).

5.8.1 Strengths and limitations

To the best of my knowledge, this was the first study that examined the overall and stratified trend of OAC medication prescribing in patients with T2DM over a 15-year period. This study used a clinical record primary care research database which was representative of the UK general population. However, this study has some limitations. Firstly, underestimation of OAC prescribing as THIN database only contains information from the primary care setting, and therefore, it was not possible to include patients treated in different health care settings (secondary, tertiary, private) in the study, and this can create gaps in the data recorded by THIN on the treatment of individuals. However, the UK National Health Service (NHS) heavily subsidies the treatment of chronic illness and the majority of patients with chronic illness are looked after by primary care; therefore, the findings of this study should not be affected significantly. Secondly, patients were identified using relevant Read code lists and algorithms. Codes were selected with reference to clinicians' comments and previously published studies. However, as described in the methods section, there is a possibility of misclassification in identifying patients with T2DM. This may have led to overestimation of T2DM diagnoses in the study, however, it is also important to

mention that patients who had a diagnostic code for T2DM contributed to over 92% of the study cohort. Therefore, it is reasonable to assume that this did not have a major impact on the findings of this study. THIN is a medical record database and therefore, similar to other clinical databases, It was not possible to confirm if patients were adherent. Furthermore, in the secondary objective of this study I did not adjust for CHA_2DS_2-VASc in the comparison between the trend in OAC use in patients with AF, with and without T2DM. However, CHA_2DS_2-VASc was introduced in 2010 (Lip et al., 2010), and was only implemented in the NICE guidelines in 2014 (National Institute for Health and Care Excellence, 2014), considering that the study end date was 2015, the practice will not be reflected in the study period.

Future studies are warranted to investigate the safety of the concurrent use of antidiabetic medications and OAC medications for possible drug-drug interactions, especially when warfarin is the drug of choice. However, with DOACs being relatively new to the market and rapidly replacing warfarin, it is imperative to investigate the effect of concomitant use of this class of medication and the risk of hypoglycaemia or bleeding. This will identify medications that are associated with higher risk, and thus improve the safety of OAC use in patients with T2DM.

5.9 Conclusions

Prescribing of OACs in patients with T2DM increased from 2001 to 2015. This study highlights a clear change in prescribing pattern towards DOAC use compared to

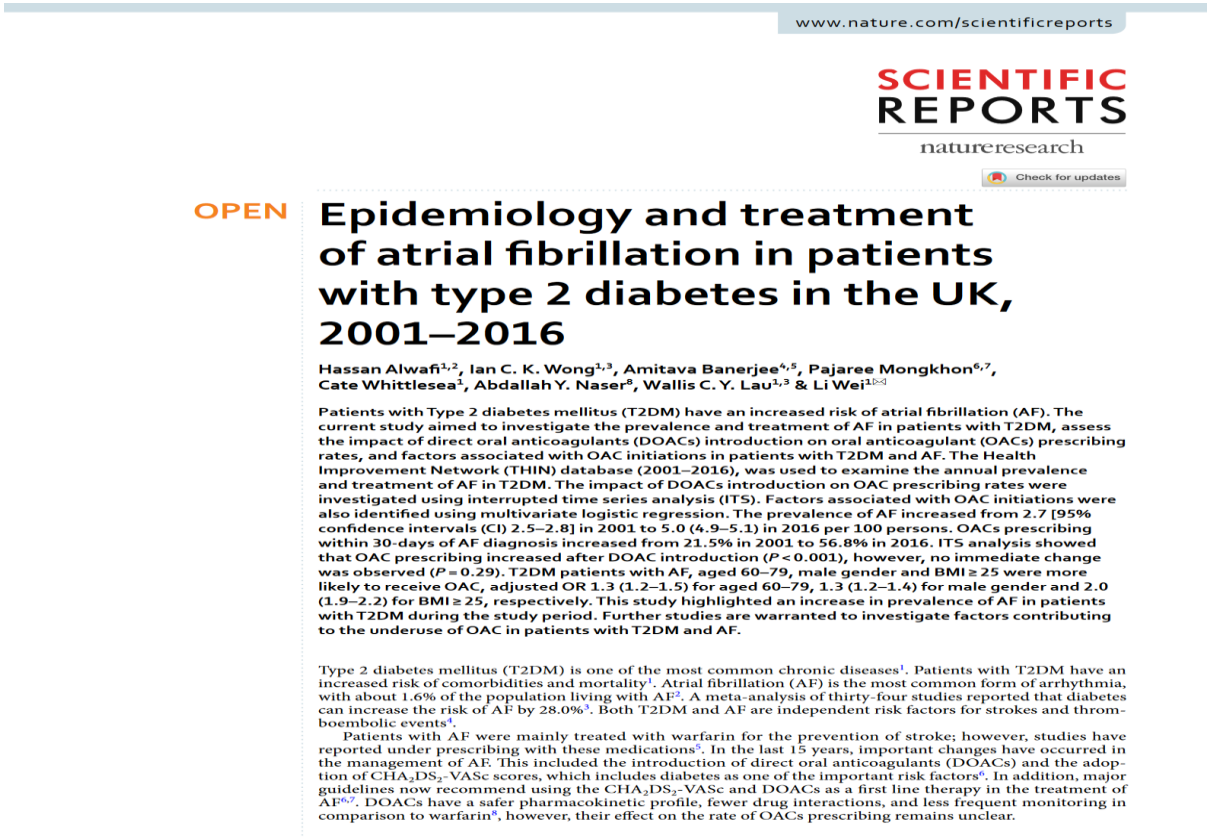
warfarin since its introduction to the UK market, which is consistent with UK guidelines. However, there is a lack of studies examining their safety when used in patients with T2DM. Further studies are warranted to investigate the safety of the concurrent use of antidiabetic and OAC medications for possible drug-drug interactions.

5.10 Context of this chapter in overall work

This study demonstrated that around 6% of patients with T2DM are using OACs, and that the prescribing prevalence of OACs in patients with T2DM is increasing. It also showed that around 26% of the patients using OACs are also utilising sulfonylureas. This will help in better understanding the current practice and will emphasize on the need for further research to study the association between the use of OACs and anti-diabetic medications, which will be discussed in the following chapters.

Chapter 6 Incidence and prevalence of Atrial Fibrillation in Patients with Type 2 Diabetes in the UK, 2001-2016

The prevalence part of the findings from this chapter have been published in the Scientific Reports journal, under the title: “Epidemiology and treatment of atrial fibrillation in patients with type 2 diabetes in the UK, 2001–2016”. Refer to Figure 32 below.



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Epidemiology and treatment of atrial fibrillation in patients with type 2 diabetes in the UK, 2001–2016

Hassan Alwafi[1,2], Ian C. K. Wong[1,3], Amitava Banerjee[4,5], Pajaree Mongkhon[6,7], Cate Whittlesea[1], Abdallah Y. Naser[8], Wallis C. Y. Lau[1,3] & Li Wei[1]✉

Patients with Type 2 diabetes mellitus (T2DM) have an increased risk of atrial fibrillation (AF). The current study aimed to investigate the prevalence and treatment of AF in patients with T2DM, assess the impact of direct oral anticoagulants (DOACs) introduction on oral anticoagulant (OACs) prescribing rates, and factors associated with OAC initiations in patients with T2DM and AF. The Health Improvement Network (THIN) database (2001–2016), was used to examine the annual prevalence and treatment of AF in T2DM. The impact of DOACs introduction on OAC prescribing rates were investigated using interrupted time series analysis (ITS). Factors associated with OAC initiations were also identified using multivariate logistic regression. The prevalence of AF increased from 2.7 [95% confidence intervals (CI) 2.5–2.8] in 2001 to 5.0 (4.9–5.1) in 2016 per 100 persons. OACs prescribing within 30-days of AF diagnosis increased from 21.5% in 2001 to 56.8% in 2016. ITS analysis showed that OAC prescribing increased after DOAC introduction ($P < 0.001$), however, no immediate change was observed ($P = 0.29$). T2DM patients with AF, aged 60–79, male gender and BMI ≥ 25 were more likely to receive OAC, adjusted OR 1.3 (1.2–1.5) for aged 60–79, 1.3 (1.2–1.4) for male gender and 2.0 (1.9–2.2) for BMI ≥ 25, respectively. This study highlighted an increase in prevalence of AF in patients with T2DM during the study period. Further studies are warranted to investigate factors contributing to the underuse of OAC in patients with T2DM and AF.

Type 2 diabetes mellitus (T2DM) is one of the most common chronic diseases[1]. Patients with T2DM have an increased risk of comorbidities and mortality[1]. Atrial fibrillation (AF) is the most common form of arrhythmia, with about 1.6% of the population living with AF[2]. A meta-analysis of thirty-four studies reported that diabetes can increase the risk of AF by 28.0%[3]. Both T2DM and AF are independent risk factors for strokes and thromboembolic events[4].

Patients with AF were mainly treated with warfarin for the prevention of stroke; however, studies have reported under prescribing with these medications[5]. In the last 15 years, important changes have occurred in the management of AF. This included the introduction of direct oral anticoagulants (DOACs) and the adoption of CHA_2DS_2-VASc scores, which includes diabetes as one of the important risk factors[6]. In addition, major guidelines now recommend using the CHA_2DS_2-VASc and DOACs as a first line therapy in the treatment of AF[6,7]. DOACs have a safer pharmacokinetic profile, fewer drug interactions, and less frequent monitoring in comparison to warfarin[8], however, their effect on the rate of OACs prescribing remains unclear.

Figure 32: A capture picture from Scientific Reports journal website which represent the publication of this chapter.

6.1 Chapter overview

In Chapter 5, it was highlighted that atrial fibrillation (AF) is the main indication for receiving oral anticoagulants (OACs) in patients with Type 2 diabetes mellitus (T2DM). Therefore, in this chapter I investigated the incidence and prevalence of AF in patients with T2DM. The findings of this chapter helps health professionals in better understanding the coexistence of both diseases and the extent of the problem over the last 16 years.

6.2 Background

Patients with T2DM have an increased risk of cardiac comorbidities including AF, making it a major concern for public health (Diabetes UK, 2013). AF is the most common form of arrhythmia, with about 1.6% of the population living with AF (Nichols et al., 2014).

The relationship between T2DM and the development of AF has been described previously, glucose levels and insulin resistance were linked to directly affect the myocardium and therefore, leading to structural and electrical remodelling of the heart and thereby leading to the development of AF and ventricular hypertrophy (Sun and Hu, 2010, Bohne et al., 2019). In addition, other studies have reported that the inflammation produced by the metabolic syndrome with its main components obesity

and hypertension to be a major risk factor for the development of AF in patients with T2DM (Bell and Goncalves, 2019).

Previous studies have reported the association of AF and T2DM, this includes a meta-analysis of thirty-four studies that reported that pre-diabetes and diabetes could increase the risk of AF by 20% and 28%, respectively. Patients with AF and T2DM have an increased risk of comorbidities and mortality (Banerjee et al., 2020, Sarwar et al., 2010), this was highlighted in a national wide cohort study in the United States that included more than 9,000 patients which concluded that patients with T2DM were associated with a worse quality of life, worsen symptoms of AF and increased risk of hospitalisation and death (Echouffo-Tcheugui et al., 2017). Both diseases can increase the risk of stroke and mortality (Kamel et al., 2016).

Diabetes is one of the main risk factors contributing in CHA_2DS_2 score, which is a prediction of risk of stroke and guides the optimisation of management in patients with AF (Gage et al., 2001). In 2010, CHA_2DS_2-VASc was adapted from the previous score (Lip et al., 2010), and it is now recommended by most of the current guidelines (January et al., 2019, National Institute for Health and Care Excellence, 2014), in which patients with AF are likely to be prescribed OAC if they score two or more in the total score.

Previous studies that examined the incidence and prevalence of AF among patients with T2DM are limited. Estimating the burden of AF in patients with T2DM across the

United Kingdom (UK) population will help to develop a better understanding of the co-existence of both conditions and explore population levels trend in order to plan health policy.

6.3 Aims and objectives

The overall aim of the study was to investigate the epidemiology of AF in patients with T2DM from 2001 to 2016.

6.3.1 Primary objective

The primary objective of this study was to examine the trends of the prevalence of AF in patients with T2DM from 2001 to 2016.

6.3.2 Secondary objective

The secondary objective of this study was to estimate the incidence of AF among patients with T2DM from 2001 to 2016.

6.4 Methods

6.4.1 Study design

An observational retrospective descriptive cohort study.

6.4.2 Data source

This study used The Health Improvement Network (THIN) primary care data in the UK. For details, refer to Chapter 4, section 4.10.

6.4.3 Ethical consideration

This study was reviewed and scientific approval was obtained by THIN scientific review committee in 2018 (18THIN009) (Appendix 5). The research was reported in accordance with strengthening the reporting of observational studies in epidemiology (STROBE) Statement. For details refer to Appendix 9. Patients were not involved in the design of the study.

6.4.4 Study population

Data from practices that met the acceptable mortality reporting (AMR) measures of quality assurance for THIN data were used in this study (Maguire et al., 2009). Patients with T2DM aged ≥18 years old and registered within THIN database between 2001 and 2016 were included in the study. Only patients who were registered with the general practice for at least 12 months prior to the first T2DM diagnosis being recorded were included. They were identified based on the criteria defined in chapter 4, section 4.10. T2DM patients who had a record of AF were identified on/or after their diagnosis of T2DM using the AF Read codes, and the first record of AF was defined as the start

date. Patients with valvular heart disease were excluded. Patients were censored if they left the practices, transferred out or died during the study period.

6.4.5 Study variables

Comorbidity history including; stroke, coronary heart disease, chronic kidney disease (CKD), heart failure, hypertension, hyperlipidaemia, chronic obstructive pulmonary disease (COPD), peptic ulcer disease, peripheral vascular disease, and depression. Theses variables were identified using Read codes (details of Read code are listed in Appendix 7). Baseline characteristic were measured over the 12-month period preceding the T2DM diagnosis. Medications use including; aspirin, antiplatelet, statins, beta blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, diuretics and digoxin. These medications were identified using drug codes (Appendix 8). Medication use was assessed over the 6-month period preceding T2DM diagnosis.

6.4.6 Outcomes

The primary outcome was the prevalence of AF in patients with T2DM from 2001 to 2016. The secondary outcome was the incidence of AF in patients with T2DM during the same period.

6.4.7 Data analysis

Descriptive statistics were used to describe patients' demographics, and comorbidities. Continuous data were reported as mean ± standard deviation (SD), and categorical data were reported as number (percentage). The prevalence of AF in patients with T2DM was presented per 100 patients with 95% confidence intervals (CIs), and was calculated annually by dividing the number of all T2DM patients diagnosed with AF during the particular year over the mid-year population of patients with T2DM in the same calendar year during the study period.

$$\frac{Number\ of\ patients\ with\ T2DM\ diagnosed\ with\ AF\ in\ a\ particular\ yar}{Number\ of\ patients\ with\ T2DM\ in\ that\ particualr\ year}$$

Only the first record of AF during the study period was used for calculating the incidence rate, i.e. dividing the number of T2DM patients with a first record of AF in a particular year over the mid-year population of patients with T2DM at risk in the same calendar year.

$$\frac{Number\ of\ patients\ with\ T2DM\ with\ a\ first\ record\ of\ AF\ in\ a\ particular\ year}{Number\ of\ patients\ with\ T2DM\ at\ risk\ in\ that\ particualr\ year}$$

Trends of the incidence and prevalence of AF were further stratified by age and gender. Temporal trends in the distribution of the incidence and prevalence were assessed using a Poisson method. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

6.4.8 Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of this research.

6.5 Results

6.5.1 Demographics and characteristics

During the study period of 2001 and 2016, a total of 23,124 patients with T2DM and diagnosed with AF were identified. The average age of the AF patients was 66.9 (SD= 11.1) years old. The majority of the patients were male (58.4%). The baseline demographics of the AF patients are described in Table 14.

Table 14: Baseline characteristics of the AF patients

Demographics	T2DM patients with AF (%)
Total	**23,124 (100%)**
Age (Mean ± SD)*	66.9 ± 11.1
Gender (Male)	13,515 (58.4)
Comorbidities**	
Hypertension	11,411 (49.3)
Coronary Heart Disease	4,641 (20.0)
Heart Failure	1,146 (4.9)

Cerebrovascular Accidents	1,463 (6.3)
Peripheral Vascular Disease	751 (3.2)
Chronic Kidney Disease	1,085 (4.6)
Chronic Obstructive Pulmonary Disease	1,097 (4.7)
Depression	3,221 (13.3)
Hyperlipidaemia	2,624 (11.2)
Peptic Ulcer Disease	3,956 (17.1)
Cardiovascular Medications**	
Beta-Blockers	8,288 (35.8)
ACEIs/ARBs	6,687 (28.4)
Aspirin	6,259 (27.2)
Calcium Channel Blockers	6,965 (30.1)
Statins	5,521 (23.88)
Diuretics	4,416 (19.0)
Digoxin	1,400 (6.0)

* Standard deviation ± ; ** At the time of T2DM diagnosis

Abbreviations: ACEIs: Angiotensin Converting Blockers; ARBs: Angiotensin II receptor blockers

6.5.2 Prevalence of AF in patients with T2DM

Between 2001 and 2016, the prevalence of AF in patients with T2DM increased by 89.5% from 2.7% (95% CI, 2.6 – 2.8) in 2001 to 5.0% (95% CI, 4.9 – 5.1) in 2016, $p<0.001$, with an average increase of 5.6% per year (Figure 33).

6.5.2.1 Prevalence of AF in patients with T2DM stratified by gender

The changes in prevalence of AF between 2001 and 2016 stratified by gender are shown in Figure 33. Similar increase trends were observed for the first two years and then men started to have a higher increase rate over the study period than women. The prevalence of AF among males increased by from 2.7% (95% CI, 2.5 – 2.9) in 2001 to 5.5% (95% CI, 5.4 – 5.6) in 2016, p<0.001, with an average increase of 6.4% per year. The prevalence of AF among females increased from 2.6% (95% CI, 2.4 – 2.8) in 2001 to 4.4% (95% CI, 4.3 – 4.6) in 2016, p<0.001, with an average increase of 4.3% per year.

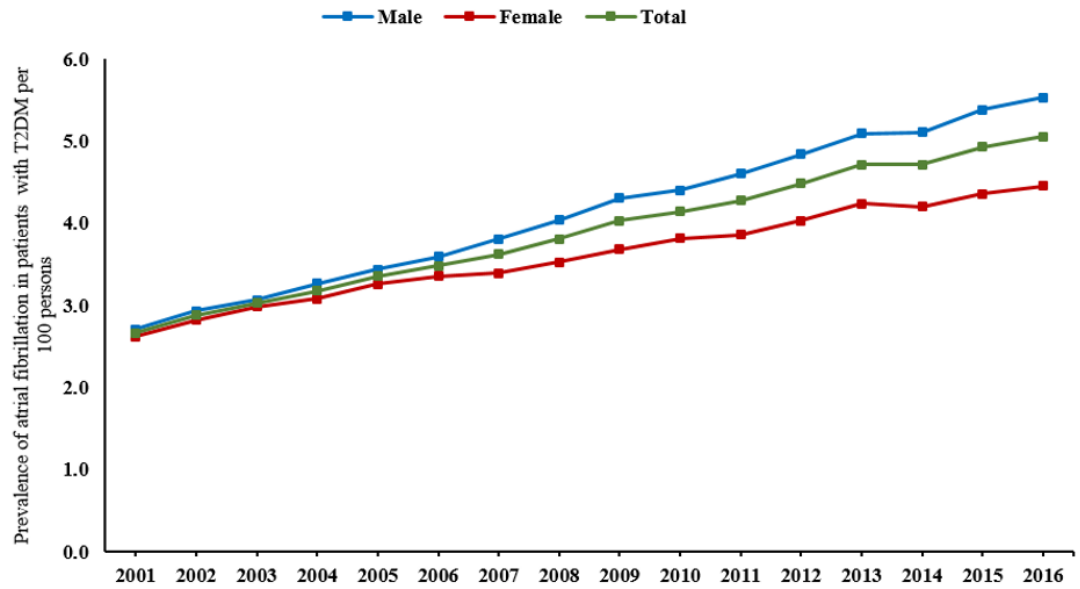

Figure 33: Prevalence of atrial fibrillation in patients with T2DM stratified by gender.

6.5.2.2 Prevalence of AF in patients with T2DM stratified by age group

The prevalence of AF varied among the different age groups. The prevalence of AF among patients aged 75 years and above increased by 80% from 5.5% (95% CI, 5.1 – 5.8) in 2001 to 9.9% (95% CI, 9.7 – 10.0) in 2016, p<0.001, with an average increase of 5.0% per year. There was about 43 – 55% increase in AF prevalence among younger patients from 3.0% (95% CI, 2.7– 3.2) in 2001 to 4.3% (95% CI, 4.2 – 4.4) in 2016, p<0.001, for patients aged between 65-74 years, from 0.8% (95% CI, 0.7– 0.9) in 2001 to 1.2% (95% CI, 1.2 – 1.3) in 2016 p<0.001, for patients aged below 65 years, with an average increase of 2.7% – 3.4% per year, respectively (Figure 34).

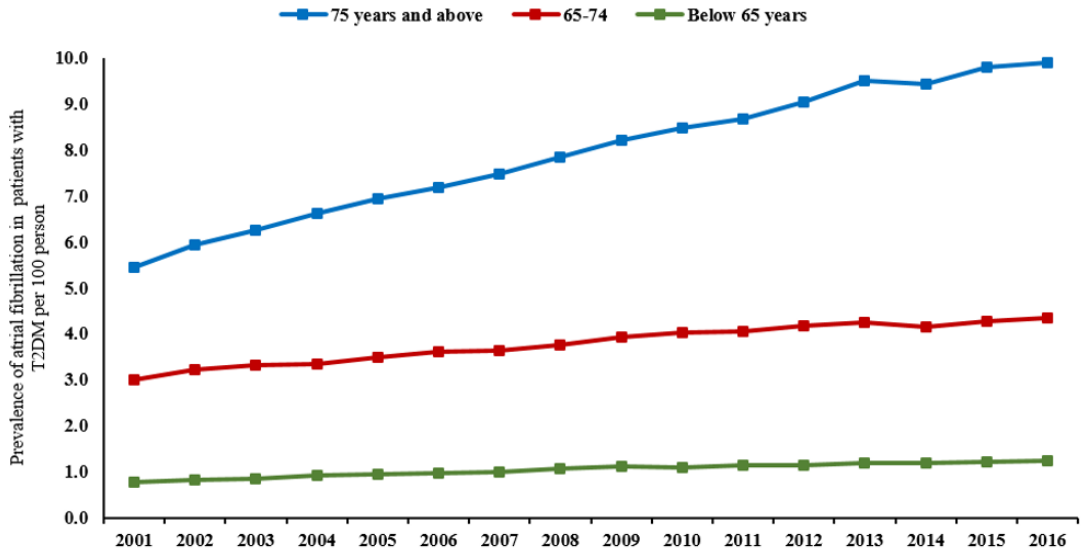

Figure 34: Prevalence rate of atrial fibrillation in patients with T2DM stratified by age group.

6.5.3 Incidence of atrial fibrillation in T2DM

Between 2001 and 2016, the incidence of AF in patients with T2DM decreased from 1.0% (95% CI, 0.9 – 1.0) in 2001 to 0.7% (95% CI, 0.6 – 0.8) in 2016, p<0.001, with an average decrease of 1.7% per year (Figure 35).

6.5.3.1 Incidence of atrial fibrillation in T2DM stratified by gender

The changes in the incidence of AF between 2001 and 2016 stratified by gender are shown in Figure 35. The incidence of AF among males decreased from 1.0% (95% CI, 0.9 – 1.1) in 2001 to 0.8% (95% CI, 0.7 – 0.8) in 2016, p=0.003, while the incidence

among females decreased from 1.0% (95% CI, 0.9 – 1.1) in 2001 to 0.6% (95% CI, 0.6 – 0.7) in 2016, p=0.003 (Figure 35).

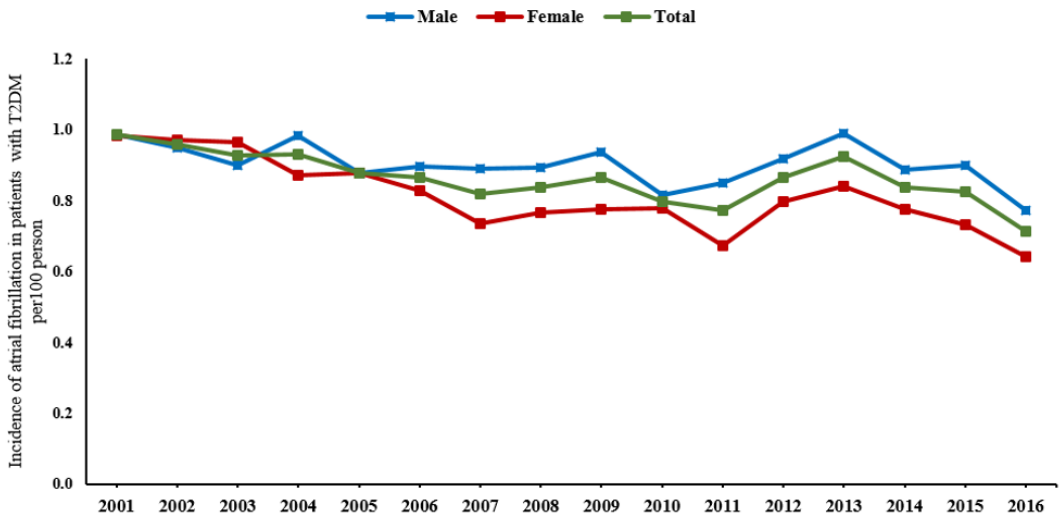

Figure 35: Incidence of atrial fibrillation in patients with T2DM stratified by gender.

6.5.3.2 Incidence of atrial fibrillation in T2DM stratified by age group

The incidence of AF varied among patients with diabetes from the different age groups (Figure 36). The incidence of AF among patient aged 75 years and above decreased from 2.0% (95% CI, 1.7 – 2.1) in 2001 to 1.3% (95% CI, 1.2– 1.3) in 2016, p<0.001. The decrease in the incidence of AF among the younger patients who were aged 65-74 years, and below 65 was lower than that for elderly, which decreased from 1.0% (95% CI, 0.9 – 1.2) in 2001 to 0.7% (95% CI, 0.7 – 0.8) in 2016, p<0.001, and from 0.4% (95% CI, 0.3 – 0.3) in 2001 to 0.3% (95% CI, 0.2 – 0.3) in 2016, p=0.012, respectively. (Figure 36).

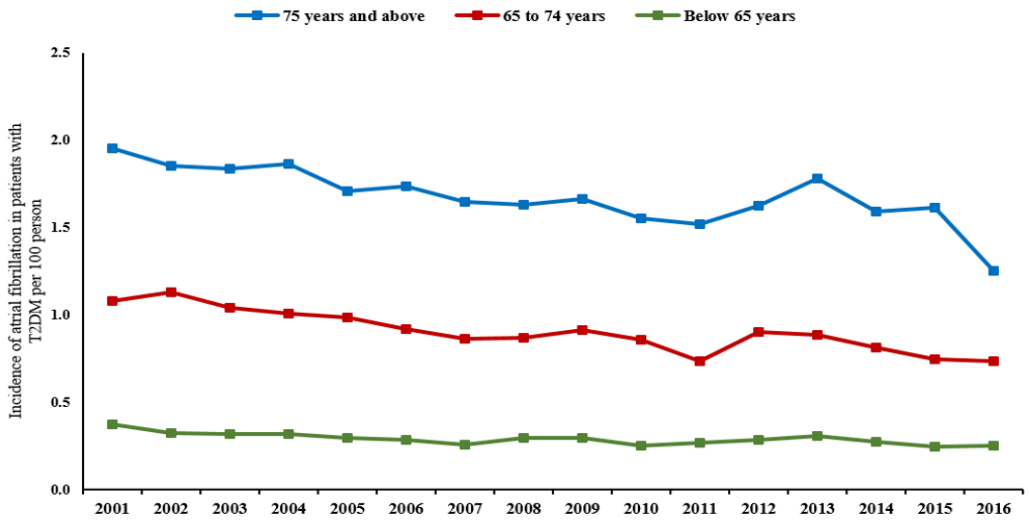

Figure 36: Incidence of atrial fibrillation in patients with T2DM stratified by age group.

6.6 Discussion

In this population-based study, I investigated the trend in the prevalence and incidence of AF in patients with T2DM over a 16-year period. The key findings were: 1) the prevalence of AF in patients with T2DM has increased between 2001 and 2016, the increase in the prevalence of AF was not consistent across patients age and gender, males and patients aged 75 years and above had a higher prevalence rate compared to females and patients younger than 75 years, and 2) the incidence of AF in patients with T2DM slightly decreased during the study period.

Previous studies reporting the prevalence of AF in patients with T2DM are lacking, however, there are few studies that reported the prevalence of AF in patients with T2DM as part of their analysis of a high-risk population or during measuring the

association risk of AF and T2DM. A study by Adderley et al., using a national UK database, reported that the prevalence of AF in the UK general population increased from 2.0% in 2000 to 3.2% in 2016 (Adderley et al., 2019) . The authors reported that the prevalence of AF was higher among those aged 65 years and above and was higher among male patients which was supported by the findings of this study in the T2DM patients. The results of this study showed a higher prevalence trend among male patients and among those aged 65 years and above which was similar to their results. In addition, the increase of AF prevalence in patients with T2DM over the years could also be related to an evolved doctors' sensibility and consequent more aggressive search for AF (Welton et al., 2017).

Ageing is an important risk factor for AF and the prevalence of AF increases with age, in the Framingham study it was reported that the prevalence of AF increased by 0.5% for those aged 50-59 years compared to 8.8% for those aged 80-89 years (Wolf et al., 1991). Furthermore, in a pooled analysis of four large European community based studies it was reported that cumulative incidence of AF increased markedly after the age of 50 for men and 60 for women, meaning that men could develop AF with an average of 10 years earlier than women (Magnussen et al., 2017). This study was conducted in a T2DM population. It showed a higher trend in the prevalence of AF in males and patients aged 75 years and above compared to females and patients younger than 75 years. This was similar to published data for the general population (Magnussen et al., 2017, Wolf et al., 1991).

Previous studies reported the association of T2DM and AF; however, the mechanism of the development of AF in patients with T2DM is not fully understood. It has been suggested that the metabolic process in patients with T2DM, including the inflammatory response and the atrial remodelling, might play a major role in the association between both diseases (Sun and Hu, 2010, Tadic and Cuspidi, 2015, Goudis et al., 2015). In addition, patients with T2DM have a high cardiac risk-profile and a higher body mass index. These are known risk factors for AF, which was highlighted in this study (Shulman et al., 2018, Gallagher et al., 2019).

T2DM and AF are both highly prevalent in the general population with about 6.0%-7.0% of the population having diabetes (Sharma et al., 2016), and about 1.5%-2.9% of the population have AF (England, 2017, Adderley et al., 2019). T2DM and AF have also been linked to several comorbidities and increased risk of stroke and mortality. It is therefore important to recognise the coexistence of both conditions to increase the awareness and to closely monitor this population. Several guidelines, including the National Institute for Health and Care Excellence (NICE) rely on the CHA_2DS_2–VASc score, in which T2DM is a criterion for score calculation and have recommended the use of OACs in patients with atrial fibrillation in order to prevent future stoke events (National Institute for Health and Care Excellence, 2014, January et al., 2019). Furthermore, it is important to highlight the risk of possible adverse drug reactions when both conditions coexist especially giving that recent studies have highlighted a

possible drug-drug interactions between antidiabetic medications and oral anticoagulants (Romley et al., 2015, Nam et al., 2018).

Future studies are warranted to investigate risk factors related to the development of AF in patients with T2DM including the association of antidiabetic medications and atrial fibrillation, as this will identify medications that are associated with higher risks, and thus improve the quality of life for these patients.

6.6.1 Strengths and limitations

To the best of my knowledge, this is the first study that examined the overall and stratified trend of the prevalence and the incidence of AF in patients with T2DM over a 16-years period. This study used clinical record primary care database which is representative of the UK general population, however, this study has some limitations. THIN is an administrative database and it only provides information of primary care setting, and therefore, underestimation of the prevalence and the incidence of AF in patients with T2DM would be possible as THIN was not able to include patients from different health care setting (secondary, tertiary, private) in the study.

6.7 Conclusions

This study highlighted that there is an increase in prevalence of AF in patients with T2DM in the past 16 years, and that AF is more prevalent among elderly and male patients. In addition, this study showed that the incidence of having new incident of

AF among patients with T2DM remained stable over 16 years period. Further studies to investigate risk factors related to the development of AF among patients with diabetes are warranted.

6.8 Context of this chapter in overall work

This study demonstrated that there is an increase in the prevalence of AF in patients with T2DM. The findings of this chapter and the previous chapter are clearly showing that both T2DM and AF are growing and a lot of patients are suffering from both diseases. Therefore, a majority of these patients are likely to be prescribed OAC medications.

Chapter 7 Patterns and Factors Associated with Oral Anticoagulant Therapy in Atrial Fibrillation Patients with T2DM in the UK Primary Care from 2001-2016

The findings from this chapter have been published in the Scientific Reports journal, under the title: “epidemiology and treatment of atrial fibrillation in patients with type 2 diabetes in the UK, 2001–2016”. Refer to Figure 32 in Chapter 6.

7.1 Chapter overview

In the previous chapters (chapters 5,6), it was highlighted that atrial fibrillation (AF) is the main indication for receiving oral anticoagulants (OACs) in patients with Type 2 diabetes mellitus (T2DM), and that the prevalence of AF has increased in patients with T2DM over the last 16 years. Therefore, in this chapter, I will explore the patterns and factors associated with OACs treatment in patients with T2DM and AF. In addition, the effect of the introduction of direct oral anticoagulants (DOACs) on the rate on OACs prescribing is examined in this chapter.

7.2 Background

Patients with T2DM have an increased risk of cardiac diseases such as AF (Pallisgaard et al., 2016, Movahed et al., 2005). AF is a heart condition that causes cardiac rhythm disturbances and consequently ineffective atrial contraction (January et al., 2019). T2DM and AF are associated with increased risk of mortality, strokes, thromboembolic events and other cardiovascular comorbidities (Banerjee et al., 2012, Sarwar et al., 2010). In a large cohort study of more than 9,000 AF patients, AF

patients with T2DM were associated with a worse quality of life, worsen symptoms of AF and an increased risk of hospitalisation and death (Echouffo-Tcheugui et al., 2017). Patients with AF were mainly treated with warfarin for the prevention of stroke; however, studies have reported under prescribing or poor adherence with these medications (Guo et al., 2018, Weisbord et al., 2001, Ogilvie et al., 2010). In the last 15 years, important changes have occurred in the management of AF. This included the introduction of DOACs and the adoption of both CHA_2DS_2 and CHA_2DS_2-VASc scores, which are tools to help in the assessment of stroke risk and in the management of AF. Diabetes is one of the important risk factors in these calculations (Gage et al., 2001, Lip et al., 2010). In addition, major guidelines now recommend using the CHA_2DS_2-VASc and DOACs as a first line therapy in the treatment of AF (January et al., 2019, National Institute for Health and Care Excellence, 2014). DOACs have a safer pharmacokinetic profile, fewer drug interactions, and less frequent monitoring in comparison to warfarin (Burn and Pirmohamed, 2018), however, their effect on the rate of OACs prescribing remains unclear. In addition, there are limited studies that investigated the treatment of AF among patients with T2DM.

7.3 Aims and objectives

The overall aim of this study is to examine the treatment of AF in patients with T2DM.

7.3.1 Primary objective

The primary objective of this study was to investigate the proportions of patients with T2DM who were initiated OAC on/or after AF diagnosis from 2001 to 2016.

7.3.2 Secondary objective

The secondary objective of this study were to assess the impact on OAC prescribing rates after the introduction of DOACs, and to investigate the factors associated with the initiation of warfarin versus DOAC in patients with T2DM and AF.

7.4 Methods

7.4.1 Study design

A longitudinal observational study.

7.4.2 Data source

This study used The Health Improvement Network (THIN) primary care data in the UK. For details, refer to Chapter 4, section 4.10.

7.4.3 Ethical consideration

This study was reviewed and scientific approval was obtained by THIN scientific review committee in 2018 (18THIN009) (Appendix 5). The research was reported in accordance with strengthening the reporting of observational studies in epidemiology (STROBE) Statement. For details refer to section and Appendix 10.

7.4.4 Study population

Details of the study population including patients with T2DM and AF have been described previously in Chapter 4, section 4.10, and Chapter 5, section 6.4.4. Patients with T2DM and AF who received at least one prescription of OAC were identified.

7.4.4.1 OAC use in patients with T2DM and AF

Patients with T2DM who received OAC prescription on/or after the diagnosis of AF were identified using drug codes from the British National Formulary (BNF) and the drug dictionary provided by THIN, and were included in the treatment analysis. Patients who received OAC prescription prior to the diagnosis of AF were excluded from the treatment analysis, as they were likely to be received OAC for other indications than AF. Patients were divided into two groups; one group received OAC prescription and a second group who did not receive OAC prescription. Further stratification by type of OAC into Warfarin and DOACs (dabigatran, apixaban,

rivaroxaban, and edoxaban) were also undertaken (selection of the study cohort is presented in Figure 37).

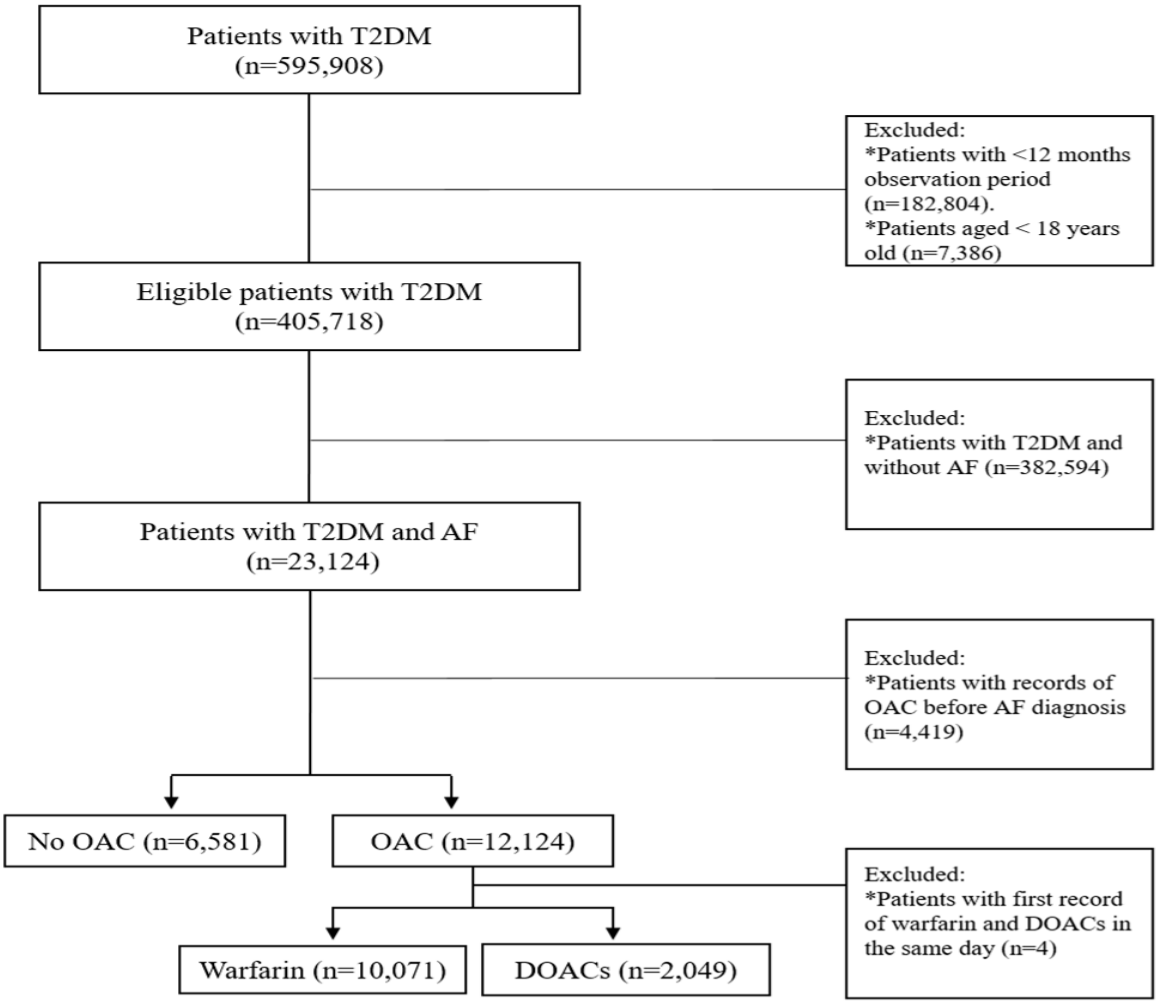

Figure 37: Selection of study population.

AF: Atrial fibrillation; DOAC: Direct oral anticoagulant; OAC: Oral anticoagulant; T2DM: Type 2 diabetes mellitus

7.4.4.2 Factors associated with warfarin versus DOAC use

Factors associated with warfarin and DOAC included age, gender, smoking status (never-smoked, ex-smoker and current smoker) alcohol consumption (never drinker, ex-drinker and current drinker, body mass index (BMI), coronary heart disease (CHD), heart failure, hypertension, hyperlipidaemia, chronic kidney disease (CKD), and liver diseases. These comorbidities were identified at any time on/or before the first OAC prescription using Read codes (Appendix 7). Medications including antiplatelet drugs, antihypertensive drugs, and lipid-lowering drugs, were identified using drug codes within 180-days on/or before the first OAC prescription (Appendix 8). In addition, we included polypharmacy as a covariate in the study and it was defined as the use of ≥4 chronic cardiac medications (Payne and Avery, 2011). CHA_2DS_2-VASc score for stoke risk and HASBLED score for risk of bleeding were also calculated (Refer to Chatper 5, section 5.4.4 for further details on CHA_2DS_2-VASc and HASBLED scores) (Lip et al., 2010, Deirdre and Gregory, 2012).

7.4.5 Outcomes

The primary outcome was the proportions of patients with T2DM who were initiated OAC on/or after AF diagnosis. Secondary outcomes of this study were the impact on OAC prescribing rates after the introduction of DOACs, and factors associated with OAC initiation in patients with T2DM and AF.

7.4.6 Data analysis

Descriptive statistics were used to describe patients' demographics, and comorbidities. Continuous data were reported as mean ± standard deviation (SD), and categorical data were reported as number (percentage). Data analysis for each objective is described in details in the following;

7.4.6.1 OAC treatment after AF diagnosis

The proportions of patients with T2DM who initiated OAC (PPIOAC) on/or after AF diagnosis from 2001 to 2016 was calculated annually using the following equation.

$$PPIOAC = \frac{Number\ of\ patients\ with\ T2DM\ who\ received\ OAC\ on/or\ after\ the\ diagnosis\ of\ AF\ in\ a\ particular\ year}{Number\ of\ patients\ with\ T2DM\ and\ were\ diagnosed\ with\ AF\ in\ that\ particualr\ year}$$

Only patients who received OAC prescriptions within 30-days of AF diagnosis were accounted as OAC users (Received OAC). However, we also conducted sensitivity analysis by accounting for patients who received OAC prescriptions within 90-days and within 1-year of AF diagnosis.

7.4.6.2 Effect of the introduction of DOACs on OAC prescribing

To examine the impact of the introduction of DOACs on the rate of OAC initiation, we used an interrupted time series analysis (ITS).

7.4.6.2.1 Interrupted time series analysis (ITS)

ITS design is one of the most powerful quasi-experimental designs and is used widely in the evaluation of public health interventions (Biglan et al., 2000). ITS design has been used to evaluate several policy and guidelines intervention including smoking banning (Bernal et al., 2016), the introduction of new medications (Komen et al., 2017), and adherence to guidelines or clinical decisions (Emmerick et al., 2017, Sheibani et al., 2017).

7.4.6.2.2 Features of ITS models in this study

An ITS model involves a set of data taken repeatedly over time before and after the implementation of an intervention, where in this study, DOACs are considered the intervention. The model works by extrapolating the pre-intervention trend and the post intervention period. Any changes in the outcome in the post intervention period is then evaluated in relation to the intervention (Wagner et al., 2002).

7.4.6.2.3 Application of ITS models in this study

Data were plotted graphically over time. In addition, we fitted a segmented regression analysis using a Poisson regression (Wagner et al., 2002). Durbin-Watson test was used to control for first order autocorrelation that may lead to an overestimations of the significance of an intervention (Durbin and Watson, 1950). Residual analyses were conducted, and showed no evidence of autocorrelations. The following equation was

used in the regression analysis; $Yt = \beta0 + \beta1Tt + \beta2Xt + \beta3XtTt + \epsilon t$. Where Yt; is the rate of OAC initiation, β0 reflects the rate of OAC initiation at the beginning of the period (at time 0), β1 represents the change in OAC initiation use that is independent from the intervention (for trend pre-intervention); β2 captures the change in level of the rate of OAC initiation after the intervention (for change in level, immediately after intervention); and β3 estimates the change in trend in the rate of OAC initiation after the intervention (for change in trend post-intervention). Whereas the error term εt represents the random variability unexplained by the model Overall, we included 44 data points (quarterly); representing repeated OAC prescriptions from July-October 2005 up to April-July 2016. DOACs were first authorized for the treatment of non-valvular AF in 2011, therefore, we accounted for the intervention in this model from the first quarter of the next calendar year (January-April 2012). I did not account for seasonal variations as the outcome is unlikely to be affected.

7.4.6.3 Factors associated with warfarin versus DOACs use

Univariable and multivariable logistic regression were used to identify factors associated with the initiation of OACs prescribing in patients with T2DM and AF compared with no OAC prescribing, and stratified by OAC type (warfarin Vs. DOACs). Unadjusted and adjusted odds ratios (OR) with 95% confidence intervals (CIs) were estimated for all the aforementioned baseline covariates. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

7.4.7 Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of this research.

7.5 Results

7.5.1 Demographics and characteristics

During the study period of 2001 and 2016, a total of 405,718 patients with T2DM were identified of whom only 23,124 patients with T2DM and AF were included. Of the 23,124 patients with T2TM and AF, 12,124 (52.4%) received OAC prescription at some point on/or after the diagnosis of AF. Patients who received OACs were slightly younger compared to patients who did not receive OACs prescriptions (73.4 vs 77.5 years). In addition, male patients received more OACs in comparison to females. Besides this, patients who received OAC had a higher BMI index compared to patients who did not receive OACs prescriptions (54.8% vs 41. 0%).The cardiovascular profile of patients who received OACs were similar to patients who did not receive OACs including their score in CHA_2DS_2-VASc risk assessment, as (97%) in both groups fell in CHA_2DS_2-VASc ≥2 category. The characteristics of patients receiving OAC (stratified by medication class) vs. patients who did not receive OACs prescription are summarised in (Table 15).

Table 15: Baseline characteristics of patients with T2DM and AF

Characteristic	OAC (n=12,124)	No OAC (n=6,581)	Warfarin (n=10,071)	DOAC (n=2,049)
Age (Mean ± SD)*	73.4± 9.1	77.5 ± 10.5	73.6 ± 8.9	75.2± 9.6
Gender (Male)	7,446 (61.4)	3,456 (52.5)	6,231 (61.8)	1,213 (59.2)
Never-smoker	5,450 (45.3)	3,099 (47,9)	4,443 (44.5)	999 (48.8)
Ex-smoker	5,445 (45.3)	2,650 (40.9)	4,692 (47.0)	871 (42.5)
Current-smoker	1,121 (9.3)	717 (11.0)	855 (8.5)	179 (8.7)
Never-drinker	2,778 (23.9)	1,831 (29.8)	2,287 (23.7)	549 (27.5)
Ex-drinker	604 (5.2)	323 (5.3)	509 (5.2)	130 (6.5)
Current-drinker	8,235 (70.8)	3,976 (64.8)	6,875 (71.1)	1,319 (66.0)
BMI < 25	1,503 (12.5)	1,525 (24.2)	1,213 (12.2)	292 (14.3)
BMI 25-30	3,891 (32.6)	2,181 (34.6)	3,239 (32.7)	655 (32.1)
BMI ≥ 30	6,544 (54.8)	2,581 (41.0)	5,454 (55.1)	1,089 (53.4)
CHA_2DS_2-VASc Score [a] <2	279 (2.3)	151 (2.3)	206 (2.0)	37 (1.8)
CHA_2DS_2-VASc Score [a] ≥2	11,845 (97.7)	6,430 (97.7)	9,865 (98.0)	2,012 (98.2)
HASBLED[b] <2	517 (4.2)	340 (5.2)	355 (3.5)	77 (3.8)
HASBLED[b] ≥2	11,670 (95.7)	6,241 (94.8))	9,716 (96.5)	1,972 (96.2)
Coronary heart disease	4,052 (33.4)	2,216 (33.6)	3,511 (34.8)	665 (32.4)
Heart failure	1,885 (15.5)	1,237 (18.8)	1,959 (19.4)	342 (16.7)
Hypertension	9,365 (77.2)	4,813 (73.1)	7,829 (77.7)	1,620 (79.0)
Hyperlipidaemia	3,085 (25.4)	1,440 (21.9)	2,595 (25.7)	544 (26.5)
Stroke /TIA	2,094 (17.3)	1,257 (19.1)	1,957 (19.4)	451 (22.0)
Bleeding	2,511 (20.7)	1448 (22.0)	2,114 (21.0)	516 (25.2)
Chronic Kidney Disease	3,644 (30.0)	2,101 (31.9)	3,225 (32.0)	750 (36.6)
Aspirin	7,369 (60.8)	4,058 (61.7)	6,568 (65.2)	1,123 (54.8)
ACEs /ARBs	8,843 (72.9)	4,159 (63.2)	7,809 (77.5)	1,515 (74.0)

Beta-Blockers	5,882 (48.5)	2,515 (38.2)	6,127 (60.9)	1,423 (69.4)
Calcium Channel Blockers	5,525 (45.6)	2,508 (38.1)	4,687 (46.5)	915 (44.6)
Statins	8,904 (73.4)	4,000 (60.8)	7,693 (76.3)	1.598 (78.0)
Polypharmacy	3,324 (27.4)	1,542 (23.4)	3,983 (39.5)	732 (35.7)

*Standard deviation ±; OAC: oral anticoagulant; DOAC: direct oral anticoagulant; BMI: body mass index; ACEIs: Angiotensin converting enzyme inhibitors; ARBs: Angiotensin II receptor blockers. a CHA_2DS_2-VASc indicates patients with congestive cardiac failure, hypertension, age ≥75 years (doubled), diabetes mellitus, age 65 to 74 years, prior stroke or transient ischemic attack or systemic embolism (doubled), vascular disease, and gender category (women). CHA 2 DS 2 -VASc score ranges from 0 to 9 (higher score indicates higher risk for stroke); b HAS-BLED indicates patients with hypertension, renal disease, liver disease, prior stroke, prior major bleeding, age 65 years, medications that predispose to bleeding (NSAIDs or antiplatelet drugs), alcohol use (INR not included). HAS-BLED score ranges from 0 to 8 (as INR not included in calculation), a higher score indicates a higher risk for bleeding. Missing BMI, n=480 (2.6%) Alcohol, missing, n= 958 (5.0%) Smoking, missing, n=223 (1.2%)

7.5.2 OACs treatment in patients with T2DM and AF

The proportions of patients with T2DM who received an OAC prescription within 30-days of AF diagnosis increased from 21.5% in 2001 to 56.8% in 2016, p<0.001. In sensitivity analysis, the proportions of patients with T2DM who received an OAC prescription within 90-days of AF diagnosis was higher, 29.8% in 2001 to 69.9% in 2016, p<0.001. In addition, the proportions of patients with T2DM who received an OAC prescription within 1-year after the diagnosis of AF was markedly higher in comparison to 30-days and 90-days from diagnosis, ranging from 39.4% in 2001 to 78.0% 2016, p<0.001 (Figure 38).

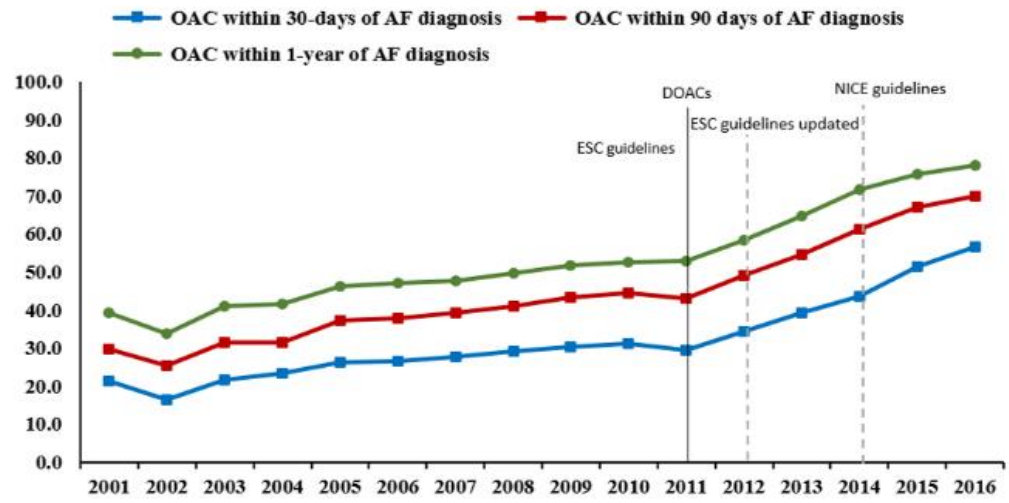

Figure 38: Proportion of T2DM patients who initiated OAC treatment after the diagnosis of AF, 2001-2016.

7.5.3 Effect of the introduction of DOACs on OAC prescribing

The overall quarterly proportions of patients with T2DM who received OAC prescription on/or after 30-days of AF is presented in (Figure 39). There was no immediate change in the rate of OAC prescribing after the introduction of DOACs (P= 0.29). However, the rate of OAC initiation then increased gradually (P <.0001) (Table 16).

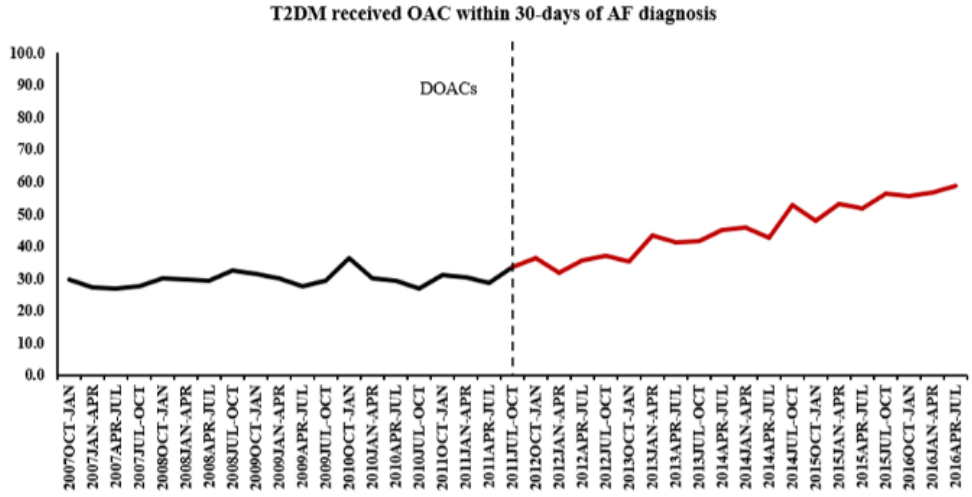

Figure 39: Quarterly proportions of patients with T2DM who received OAC prescription after 30-days of AF, 2001-2016.

Table 16: Interrupted time series analysis model on the changes before and after the introduction of DOACs in OAC prescribing.

Variable	IRR (95%CI)	Standard Error	P-value
Change in level (immediate effect)	1.00 (0.99-1.01)	0.056	0.299
Change in trend post intervention	1.02 (1.01-1.03)	0.004	<.0001

Abbreviations: CI, confidence interval; IRR, incidence rate ratio;

7.5.4 Factors associated with initiation of OAC prescription versus non-OAC

In the multivariable logistic regression analysis, males were 30.0% more likely to initiate OAC compared to females (adjusted OR 1.3; 95% CI, 1.2 – 1.4). Patients aged 65-74 were more likely to receive OAC prescription (adjusted OR 1.3; 95% CI, 1.2 – 1.5) compared to patients younger than 65 years, while elderly patients aged ≥75 were less likely to receive OAC prescription (adjusted OR 0.8; 95% CI, 0.7 – 0.9). BMI ratios (BMI 25-29 and BMI ≥ 30) were significantly associated with OAC initiation compared to BMI <25 (adjusted OR 1.6; 95% CI, 1.4 – 1.7) and (adjusted OR 2.0; 95% CI, 1.9 – 2.2), respectively). In addition, the use of angiotensin converting enzyme inhibitor (ACEI) / angiotensin II receptor blockers (ARB), beta blockers (BB), calcium channels blockers (CCBs) and statins was a strong predictor to initiate OAC, while use of aspirin and polypharmacy were protective factors against the initiation of OAC. Table 17 presents details of the results from a logistic regression model.

7.5.5 Factors associated with initiation of warfarin versus DOACs

In the multivariable logistic regression analysis, T2DM patients with AF aged ≥75 years (adjusted OR 0.7; 95% CI, 0.6-0.8) were more likely to be prescribed DOACs compared with patients age under 65 years old. Male gender was associated with higher odds of receiving DOACs compared to females (adjusted OR 0.9; 95% CI, 0.8 – 1.0). In addition, having a history of bleeding (adjusted OR 0.8; 95% CI, 0.7 – 0.9), CKD (adjusted OR 0.9; 95% CI, 0.8 – 0.9), stroke (adjusted OR 0.9; 95% CI, 0.8 – 1.0) or history of using beta-blockers (BB) (adjusted OR 0.6; 95% CI, 0.5 – 0.7) were significantly associated with higher odds of initiating DOACs In contrast, T2DM patients with AF who had a history of using aspirin and ACEs/ARBs were significantly associated with higher odds of initiating warfarin (adjusted OR 1.5; 95% CI, 1.4 – 1.7) and (adjusted OR 1.1; 95% CI, 1.0 – 1.3), respectively) (Table 17).

Table 17: Factors associated with initiation of warfarin versus DOACs in patients with T2DM and AF

Variables	OAC versus non-OAC				Warfarin versus DOACs			
	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age < 65	Reference		Reference		Reference		Reference	
Age 65-74	1.2 (1.1-1.4)	<.0001	1.3 (1.2- 1.5)	<.0001	0.9 (0.8-1.1)	0.491	0.8 (0.7-1.0)	0.081
Age ≥ 75	0.6 (0.5- 0.6)	<.0001	0.8 (0.7- 0.9)	<.0001	0.7 (0.6-0.8)	<.0001	0.6 (0.5-0.8)	<.0001
Male sex (%)	1.40 (1.3-1.5)	<.0001	1.3 (1.2-1.4)	<.0001	1.1 (1.0-1.2)	0.073	0.9 (0.8-1.0)	0.038
Never-smoked	Reference		Reference		Reference		Reference	
Ex-smoker	1.1 (1.0-1.2)	<.0001	1.0 (0.9-1.1)	0.914	1.2 (1.1-1.3)	<.0001	1.1 (1.0-1.3)	0.019
Current-smoker	0.9 (0.8-1.0)	0.012	0.8 (0.7-0.9)	<.0001	1.0 (0.8-1.3)	0.588	0.9 (0.8-1.1)	0.459
Never-drink	Reference		Reference		Reference		Reference	
Ex-drinker	1.2 (1.1-1.4)	0.006	1.0 (0.9-1.2)	0.354	0.9 (0.8-1.2)	0.618	0.9 (0.7-1.1)	0.432
Current-drinker	1.3 (1.3-1.4)	<.0001	1.2 (1.1-1.3)	<.0001	1.3 (1.1-1.4)	<.0001	1.2 (1.0-1.3)	0.003
BMI < 25	Reference		Reference		Reference		Reference	
BMI 25-29	1.8 (1.7-2.0)	<.0001	1.6 (1.4-1.7)	<.0001	1.2 (1.0-1.4)	0.025	1.1 (0.9- 1.3)	0.204
BMI ≥ 30	2.6 (2.4-2.8)	<.0001	2.0 (1.9-2.2)	<.0001	1.2 (1.0-1.4)	0.012	1.0 (0.9 1.2)	0.720
CHA_2DS_2-VASc Score <2	Reference		Reference		Reference		Reference	
CHA_2DS_2-VASc Score ≥2	1.0 (0.8-1.2)	0.863	1.1 (0.8-1.4)	0.385	0.9 (0.6-1.3)	0.695	1.0 (0.7-1.6)	0.863
HASBLED <2	Reference		Reference		Reference		Reference	
HASBLED ≥2	1.1 (0.9-1.3)	0.367	0.9 (0.8-1.2)	0.726	1.2 (0.9-1.5)	0.241	1.2 (0.8- 1.6)	0.361
Coronary heart disease	1.0 (0.9-1.0)	0.339	0.9 (0.8-0.9)	<.0001	1.1 (1.0-1.3)	0.035	1.1 (0.9- 1.2)	0.337
Heart Failure	0.8 (0.7-0.9)	<.0001	0.9 (0.8-0.9)	0.001	1.2 (1.0-1.3)	0.009	1.2 (1.0-1.3)	0.025
Hypertension	1.2 (1.1-1.3)	<.0001	0.9 (0.9-1.0)	0.160	0.9 (0.8-1.0)	0.297	0.9 (0.8-1.1)	0.331

Hyperlipidaemia	1.2 (1.1-1.3)	<.0001	1.0 (1.0-1.1)	0.224	1.0 (0.9-1.1)	0.624	1.0 (0.9-1.1)	0.605
Stroke/TIA	0.9 (0.8-1.0)	0.006	1.0 (0.9-1.1)	0.621	0.9 (0.7-1.0)	0.010	0.9 (0.8-1.0)	0.045
Bleeding	0.9 (0.8-1.0)	0.010	0.9 (0.8-1.0)	0.029	0.8 (0.7-0.8)	<.0001	0.8 (0.7-0.9)	<.0001
Chronic Kidney Disease	0.9 (0.8-1.0)	<.0001	0.9 (0.9-1.0)	0.205	0.8 (0.7-0.9)	.0008	0.9 (0.8-1.0)	0.041
Aspirin	1.0 (0.9-1.1)	0.334	0.9 (0.8-0.9)	<.0001	1.5 (1.4-1.7)	<.0001	1.5 (1.4-1.7)	<.0001
ACEI/ARB	1.5 (1.4 1.6)	<.0001	1.3 (1.2-1.4)	<.0001	1.2 (1.1-1.4)	<.0001	1.2 (1.0-1.3)	0.019
Beta-blockers	1.5 (1.4-1.6)	<.0001	1.5 (1.4- 1.6)	<.0001	0.7 (0.6-7.0)	<.0001	0.6 (0.5-0.7)	<.0001
Calcium Channel Blockers	1.3 (1.2-1.4)	<.0001	1.3 (1.2- 1.4)	<.0001	1.0 (1.0-1.2)	0.109	1.0 (0.9-1.1)	0.884
Statin	1.7 (1.6-1.8)	<.0001	1.5 (1.4 1.6)	<.0001	0.9 (0.8-1.0)	0.343	0.8 (0.7- 1.0)	0.011
Polypharmacy	1.2 (1.1-1.3)	<.0001	0.8 (0.7-0.9)	<.0001	0.8 (0.8-1.0)	<.0001	1.2 (1.0-1.3)	0.015

BMI: body mass index; ACEIs: Angiotensin converting enzyme inhibitors; ARBs: Angiotensin II receptor blockers. a CHA_2DS_2-VASc indicates patients with congestive cardiac failure, hypertension, age ≥75 years (doubled), diabetes mellitus, age 65 to 74 years, prior stroke or transient ischemic attack or systemic embolism (doubled), vascular disease, and gender category (women). CHA 2 DS 2 -VASc score ranges from 0 to 9 (higher score indicates higher risk for stroke); b HAS-BLED indicates patients with hypertension, renal disease, liver disease, prior stroke, prior major bleeding, age 65 years, medications that predispose to bleeding (NSAIDs or antiplatelet drugs), alcohol use (INR not included). HAS-BLED score ranges from 0 to 8 (as INR not included in calculation), a higher score indicates a higher risk for bleeding. Missing BMI, n=178 (1.4%) Alcohol, missing, n= 451 (3.7%) Smoking, missing, n=81 (0.6%). Missing data were removed from the analysis

7.6 Discussion

This study examined the treatment of AF in patients with T2DM over a 16-year period. I investigated the proportion of patients with T2DM who were initiated OACs on/or after AF diagnosis. In addition, the effect of the introduction of DOACs on the rate of OACs prescribing was examined, and moreover I investigated risk factors associated with OAC initiation in patients with T2DM and AF.

The study findings demonstrated that the proportion of patients with T2DM who were initiated on an OAC after AF diagnosis increased between 2001 and 2016. However, there were an underuse of OACs prescribing in patients with T2DM and AF. In addition, in the ITS models, I found that the rate of OAC initiation after the introduction of DOACs was increased, however, this change was not immediate. Finally, in the multivariable logistic regression analysis, the study demonstrated that being male, patients aged 65-74, BMI ≥ 25 and patients using ACEI/ARB, BB, CCBs and statins were strong predictors for OAC initiation, while age ≥75 and history of previous bleeding were protective factors against OAC initiation. In addition, I found that age ≥75 years, previous bleeding or stroke/TIA and history of CKD, were strong predictors for DOACs initiation.

Several studies have reported the increase of OAC prescribing over the last decade in the general population and in patients with atrial fibrillation. In addition, in Chapter 5, I highlighted the increase of OACs prescribing in patients with T2DM (Alwafi et al., 2020b). Although, the study demonstrated that the rate of OAC initiation has increased over time, the study also highlighted the possible underuse of OAC in this population. Particularly if we take into consideration that the majority of the patients were eligible for anticoagulation, based on the CHA_2DS_2–VASc score, as shown in Table 17. There

were 44% of the study patients in 2016 who still did not receive OAC within 30-days of AF diagnosis (Figure 38). The results were in line with previous studies that reported similar characteristics and trends of OAC prescribing in patients with AF. In a study that included more than 900,000 patients, the authors concluded that there are still a large percentage of patients who did not receive OACs prescriptions and that the availability of DOACs do not address the issue of under prescribing (Rose et al., 2019b). Similarly in a systematic review that was published in 2016, the authors summarised their review by the fact that available data from the literature about clinical practice and prescribing of OAC suggest that there is a suboptimal use of OAC in patients with AF (Alamneh et al., 2016). However, it is important to mention that there are other factors that doctors might consider before prescribing an OAC to their patients including risk of bleeding, older age and risk of falls (Wehbe and Yadlapati, 2016). Future research investigating factors associated with underuse of OACs is needed including qualitative studies to focus of the behavioural aspect of both doctors and patients. In addition, applying a risk-benefit assessment in prescribing of OACs is a crucial element in the management of patients with AF (Kirchhof et al., 2016).

In this study, I found that the rate of OAC initiation after the introduction of DOACs increased significantly, however, this change was not immediate. This could be explained because new drugs are prescribed with a greater caution due to uncertainties in regards to their effectiveness and safety (Lublóy, 2014). In addition, unlike banning policy where the intervention requires immediate response, prescribing patterns are likely to be influenced by other factors including, updates in guidelines recommendation. This was highlighted by Komen et al, who reported that the update

in the European Guidelines was associated with an increase DOACs initiations (Komen et al., 2017).

The study also identified some of the individual-level characteristics that may influence the overall and the type of OAC prescribing. BMI ≥25 and male gender were strong predictors for the initiating of OAC. These results were also in line with a previous large observational study where the authors reported that both BMI ≥25 and male gender are likely to influence the OAC prescribing (Rose et al., 2019a, Katz David et al., 2017).

Other predictors including; the use of ACEI/ARB, BB, CCBs and statins were also associated with the initiation of OAC prescribing. This could be explained by the fact that these medications are commonly indicated for the management of cardiac diseases, where hypertension, peripheral vascular diseases, stroke and congestive heart failures are all criteria in CHA_2DS_2–VASc score calculations (Lip et al., 2010).

However, the results of this study demonstrated that the use of aspirin was negatively associated with OAC prescribing. Aspirin is one of the criteria in HASBLED score (Deirdre and Gregory, 2012) , in which it is given a total of 1 point in the total score which predicts the risk of bleeding and therefore, it reasonable to assume that patients who use aspirin are less likely to receive OAC.

In the multivariate analysis of the factors that may influence the type of OAC prescribing, I found that both age ≥ 75 years and having a history of previous bleeding were significant predictors of DOAC prescribing. Several randomized trials studies have shown safer and non-inferiority of DOACs use in patients with AF (Granger et al., 2011, Patel et al., 2011, Connolly et al., 2009). In addition, recent observational studies have demonstrated a safer profile of DOACs compared to warfarin

(Vinogradova et al., 2018), and less bleeding events among patients with AF ≥ 90 years of age (Chao et al., 2018). Furthermore, having a history of CKD was associated with more likelihood of receiving DOACs. This finding was in line with some evidence-based literature, as DOACs showed favourable safety and efficacy profile in patients with CKD (Malhotra et al., 2019).

7.6.1 Strengths and limitations

This study has several strengths. Firstly, to the best of my knowledge, this is the first study that examined the treatment of AF in patients with T2DM over a 16-year period. Secondly, this study used a primary care database, which is representative of the UK general population. We included a large sample size in the study, it is therefore, reasonable to assume that the results are generalisable. In addition, we used ITS design which is a powerful methodological design to evaluate the effect of the introduction of OACs in patients with T2DM. ITS design has several advantages, this include; 1) it can control the effect of secular trends in a time series of outcome measures. This is important because it minimize the effect the sloping downward in the pre-intervention period, and therefore, avoiding the incorrectly attribute in the annual reduction in the rate to the intervention when it is actually due to other factors (Penfold and Zhang, 2013); and, 2) ITS provides an easily and clear interpretation of the results even in the absence of the complicated statistical methods (Penfold and Zhang, 2013).

However, there are some limitations in this study. As described in previous chapters, THIN only provides information of primary care setting, and therefore, underestimation of the prevalence and treatment of AF in T2DM would be possible as THIN was not

able to include patients from other health care settings. Patients were identified using relevant Read code lists and algorithms. Therefore, we were not able to do data stratification based on AF type (i.e. paroxysmal, persistent, permanent) and management strategy (i.e. rhythm vs. rate control), which may influence OAC prescription rates. This may have led to bias in the study due to under-reporting or misreporting; however, this issue was mitigated by validating the codes with clinicians and previously published studies. Observational studies are subject to confounding factors and bias due to lack of randomisation at baseline, and this may have biased the findings of this study in determining the factors actors associated with OACs use (Kahlert et al., 2017). However, I tackled this issue by adjusting for all base-line characteristics in the regression model. Finally, ITS design is subject to history bias, which include other factors or events that occurred at the same time of the intervention that may have biased the results (Wagner et al., 2002). However, I used quarterly data in the analysis to minimize the effect of other factors that could bias the results (Shadish et al., 2002).

7.7 Conclusions

The proportions of patients with T2DM who received OACs after AF diagnosis has increased during the study period. However, this study also demonstrated an underuse of OACs in Patients with T2DM and AF. Males, elder populations and patients with history of stroke or bleeding were more likely to receive DOACs prescriptions. Further studies at individual and clinical practice level are warranted to investigate the factors associated with the underuse of OAC in patients with T2DM

and AF in order to help in providing better responses and interventions in the management of this high-risk population.

7.8 Context of this chapter in overall work

The finding of this chapter demonstrates that there is an increase in the trend of OACs in patients with T2DM and AF. In addition, it showed that the introduction of DOACs increased the trend of OACs significantly. These results are in line with the results demonstrated in Chapter 5. In addition, the results of this chapter showed that male, older age, and patients with history of bleeding or stroke are less likely to warfarin. These results, and other patient's characteristics results that were demonstrated in this chapter guided me in the design and methods of the next chapter.

Chapter 8 The safety of the concurrent use of oral anticoagulants medications and sulfonylureas in patients with type 2 diabetes in the UK: A population based cohort study

8.1 Chapter overview

In Chapter 2, one of the findings was the association of warfarin and sulfonylureas and the risk of hypoglycaemia. Then Chapter 5 highlighted that the prevalence of oral anticoagulants (OACs) use in patients with type 2 diabetes mellitus (T2DM) was around 6.6% in 2015. Therefore, in this chapter, I investigated the association of concurrent use of warfarin and sulfonylureas and the risk of hypoglycaemia and bleeding.

8.2 Background

Patients with T2DM often suffer from cardiovascular complications (Celis-Morales et al., 2017, Dinesh Shah et al., 2015, Guariguata et al., 2014). Cardiovascular diseases (CVDs), including atrial fibrillation (AF), and stroke are among the leading causes of mortality worldwide (World Health Organization, 2018).

Patients with T2DM are initially treated with metformin therapy to control blood glucose levels, however, for many patients with T2DM this type of treatment fails to control the blood sugar levels, and they are often prescribed addition treatments or alternative therapies (National Institute for Health and Care Excellence, 2015). The most common second-line therapy of T2DM is sulfonylureas (Sharma et al., 2016), which can be given as a monotherapy or add-on treatment with metformin (National Institute for Health and Care Excellence, 2015).

T2DM diabetes patients are at an increased risk of developing adverse drug reactions (ADRs) due to their multiple comorbidities, renal impairment and multiple uses of drugs

(Mangoni and Jackson, 2004). In a systematic review of ADRs hospitalisation worldwide, Al Hamid et al. reported that 33.9% and 9% of all ADRs were due to cardiovascular and antidiabetic medications (Al Hamid et al., 2014). Similarly, the United States Health and Human Services Department reported that “Warfarin accounts for about 33% of all hospitalisation due to adverse drug events (ADEs), while it is 10.7% for oral hypoglycaemic agents” (U.S Department of Health and Human Services, 2014). Together, the use of warfarin and sulfonylurea accounted for approximately 44% of all ADE-related hospitalisation (U.S Department of Health and Human Services, 2014).

OACs are widely prescribed for the prevention and treatment of CVDs including stroke, myocardial infarction (MI), AF, venous and arterial thrombosis (Camm et al., 2012, National Institute for Health and Care Excellence, 2014, Ageno et al., 2012). However, their use may be considered a public health concern, mainly due to their large prescribing, high possibilities of drug-drug interactions, and their association with serious emergency events, such as bleeding and hypoglycaemia (Ament P, 2000, National Institute for Health and Care Excellence, 2017, Di Minno et al., 2017). In the last few years, Direct Oral Anticoagulant (DOAC) medications have been introduced for the treatment of different CVDs, and many guidelines recommend these as a first-line therapy for the management of AF (Ageno et al., 2012, Camm et al., 2012, National Institute for Health and Care Excellence, 2014). The use of DOACs has several advantages over warfarin including fewer drug-drug interactions and predictable pharmacokinetics and pharmacodynamics (Mekaj et al., 2015). However, their use is expensive currently in 2020 when compared to warfarin, and there is no standardised test to monitor their level in the blood (Burn and Pirmohamed, 2018).

Hypoglycaemia is an expected dose-related complication of sulfonylureas (Sola et al., 2015), which can be potentiated by several risk factors including drug-drug interaction via inhibition of hepatic cytochrome P450 (CYP) enzymes which are responsible for the metabolism of sulfonylureas (Kirchheiner et al., 2005). Drug-drug interactions resulting in the risk of hypoglycaemia are widely documented in the literature (May and Schindler, 2016). Similarly, bleeding is one of the most serious and life-threatening medical emergencies (Fitzmaurice et al., 2002, Mehran et al., 2011) that can occur due to ADRs (Fitzmaurice et al., 2002, Mehran et al., 2011).

Coexisting evidence on pharmacokinetic theories relating the displaced plasma protein binding and hepatic metabolism through CYP450 as a potential cause of drug-drug interactions between warfarin and sulfonylureas have been reported (Triplitt, 2006, Benet and Hoener, 2002). Also, two case reports showed a possible drug-drug interaction between warfarin and glibenclamide (Namazi S, 2005, Naganuma et al., 2003). However, there is limited evidence of large-scale epidemiological studies about the potential interaction between sulfonylureas and warfarin in patients with T2DM. Two previous studies in the United States reported a significant association when warfarin and sulfonylurea are used concurrently and the risk of hypoglycaemia (Romley et al., 2015, Nam et al., 2018). However, both studies used a self-controlled series design, where a major limitation of this design is that patients health status may be different during the exposure period, and patients are sicker in periods of the exposure (Hallas and Pottegård, 2014). Besides, Romley et al. only included patients aged > 65 years old in their study, and therefore, their results may not be generalised to the entire populations (Romley et al., 2015).

Given the fact that diabetes and AF are highly prevalent, and that antidiabetic and anticoagulant medications are largely prescribed concomitantly (Quilliam et al., 2011a), and in view of the lack of evidence in the literature, this research aimed to investigate the association between the use of OACs with co-existence sulfonylurea and the risk of hypoglycaemia and bleeding.

8.3 Evidence before this study

To review the current knowledge on the safety of the use of OACs in patients with T2DM, I searched the Medline and Embase databases up to the 6 September 2019 for all studies that examined this issue. The following keywords were used in the search process ((“Hypoglycaemia OR Bleeding)))” AND “Adverse Drug Events OR Adverse Drug Reactions OR Side Effects OR Risk Factors” AND “Insulin OR Hypoglycemic Agents OR antidiabetic medications” AND “Anticoagulants OR oral anticoagulants OR Direct oral anticoagulants OR DOAC OR NOAC”. I included any randomised controlled trials (RCTs) or observational studies that explored the safety of the use of OACs in patients with T2DM. The safety outcomes of interest were hypoglycaemia and bleeding of any type or severity.

The search identified a total of 3,976 articles, from which only six studies were related to the topic of interest, three studies of which were observational studies (one cohort studies and two self-controlled case series studies) (Nam et al., 2018, Romley et al., 2015, Baker et al., 2019) and three studies were RCTs (Ezekowitz et al., 2015, Bansilal et al., 2015, Brambatti et al., 2015) .

8.3.1 Hypoglycaemia

Among the six studies identified, only two observational studies reported hypoglycaemia. A study by Nam et al. reported that the co-administration of warfarin and sulfonylurea or metformin was associated with a higher risk of hypoglycaemic events. The co-administration of glimepiride with warfarin was also associated with a higher risk of hypoglycaemic events (hazard ratio (HR) 1.47; 95% CI, 1.07 – 2.02) (Nam et al., 2018). The second study by Romley et al. found that patients who were using warfarin with sulfonylureas (glipizide or glimepiride) were at higher risk of hypoglycaemia compared to patients who were not using warfarin (HR: 1.22; 95% CI, 1.05 – 1.42) (Romley et al., 2015).

8.3.2 Bleeding

The only observational study that explored the safety in term of bleeding events, by Baker et al. (2019), found that the risk of major bleeding events did not differ significantly between patients with diabetes mellitus who are using rivaroxaban or warfarin (HR 0.95; 95% CI, 0.79 – 1.15) (Baker et al., 2019). The three randomized controlled trials in this systematic review confirmed that in patients with diabetes the use of warfarin as an anticoagulant therapy was associated with a higher risk of bleeding compared to other anticoagulant options. Ezekowitz et al. reported that patients with diabetes who were using apixaban had a lower rate of any bleeding compared to patients on warfarin (HR 0.72; (95% CI. 0.65 – 0.80) (Ezekowitz et al., 2015). Bansilal et al. found that the rate of major bleeding events was slightly lower among users of rivaroxaban compared to warfarin users (3.79 vs. 3.90 / per 100 patient-years) in patients with diabetes Also, Brambatti et al. reported that dabigatran

had a lower risk of intracranial bleeding at a low dose (110mg) compared to warfarin (HR 0.26; (95% CI, 0.11 – 0.65) (Brambatti et al., 2015).

8.4 Aims and objectives of this study

The aim of this study was to investigate the safety of the use of OACs in patients with T2DM.

8.4.1 Primary objective

The primary objective of this study was to investigate the association of the concurrent use of oral anticoagulants and sulfonylureas and the risk of hypoglycaemia in patients with T2DM.

8.4.2 Secondary objective

Secondary objective of this study was to investigate the association of the concurrent use of oral anticoagulants and sulfonylureas and the risk of bleeding in patients with T2DM.

8.5 Methods

8.5.1 Study design

This was a population-based cohort study. I constructed cohorts of patients with T2DM from 2001 to 2017 and investigated the association of the concurrent use of OACs and sulfonylureas and the risk of hypoglycaemia and bleeding.

8.5.2 Data source

This study used The Health Improvement Network (THIN) primary care data in the United Kingdom (UK). For details, refer to chapter 4, section 4.10.

8.5.3 Ethical consideration

This study was reviewed and scientific approval was obtained by THIN scientific review committee in 2018 (18THIN046) (Appendix 11). The research was reported in accordance with strengthening the reporting of observational studies in epidemiology (STROBE) Statement. For details refer to section and Appendix 12.

8.5.4 Study cohort

Data from practices that met the acceptable mortality reporting (AMR) measures of quality assurance for THIN data were used in this study (Maguire et al., 2009). The study population included people aged at least 18, with a recorded diagnosis of T2DM. They were identified based on the criteria defined in Chapter 4, Section 4.10. To ensure accurate measurement of medical history, I included patients only if they had an observation period of at least 12 months before the first T2DM diagnosis and were registered with the general practice during the study period. Patients were followed up until the end of September 2017 and were censored if they experienced the outcome of interest, died, left their general practice during the study period, or stopped medications during the overlapping period of both medications. I excluded patients diagnosed with Type 1 Diabetes Miletus (T1DM) or patients diagnosed with malignancy or metastatic tumours.

The study covered a period of 17 calendar years (2001-2017), and three separate but similar analyses were carried out. The first and second analyses comprised patients with T2DM who received at least one prescription for one of the OACs of interest (including warfarin (Analysis 1) or DOACs (Analysis 2)) and sulfonylureas, and were identified using drug codes recorded in THIN. A third analysis comprised patients with T2DM who received at least one prescription for warfarin and sulfonylureas, and were identified using drug codes recorded in THIN. The index date (start date) was defined as the date on which users were first co-exposed (concurrently) and used both medications (OACs and sulfonylureas), regardless of which medication is first. Patients with records of prescriptions of both medications during the follow up were included in the study. Patients were included with either method: a) if sulfonylurea prescription was between the first and last warfarin prescriptions then the date of sulfonylurea was accounted as the index date, b) if warfarin prescription was between the first and last sulfonylurea prescriptions then the date of warfarin was accounted as the index date (for further illustration see Figure 40). Patients who did not meet these criteria were categorised as ‘no overlap’ and excluded.

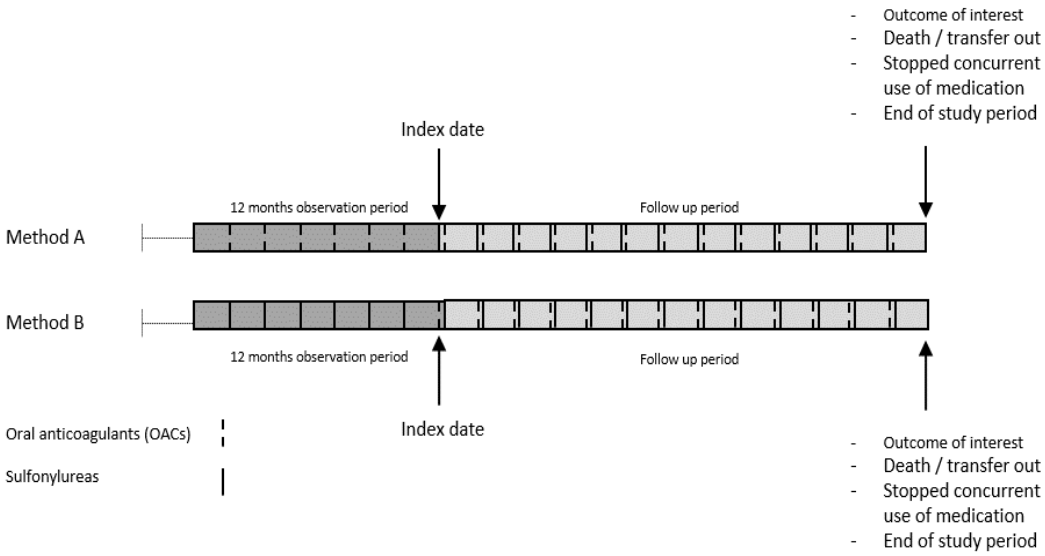

Figure 40. Methods for cohort entry.

8.5.5 Exposure definition

The exposure of interest was person-time concomitantly exposed to OACs and sulfonylureas after the diagnosis of T2DM. OACs included warfarin and DOACs (dabigatran, apixaban, rivaroxaban and edoxaban). Patients with records of acenocoumarol or phenindione only were not included, because of the very low number of patients and because it is very unlikely to be prescribed in the UK, as shown in Chapter 5. Sulfonylureas were of a second generation and included: glipizide, glyburide and glimepiride. As described in the previous section, several comparison groups were identified in this study. For the primary objective, I compared patients using OACs (warfarin or DOACs) and sulfonylureas concurrently, versus patients using sulfonylureas without OACs (Analyses 1 and 2). For the secondary objective,

we compared patients using warfarin and sulfonylureas concurrently, versus patients using warfarin without sulfonylurea (Analysis 3). I did not have a comparison group of DOACs and sulfonylureas concurrently versus patients using DOACs, because of the minimal number of patients with T2DM and using DOACs only without sulfonylureas. For DOACs and sulfonylureas versus sulfonylureas, only patients who were new users from 2011 onwards were included, as DOACs were first approved on the market from 2011. For further details on the comparison groups, Refer to Table 18.

Table 18. Details of exposure and comparator groups

	Exposure group	non-exposure group	Outcome
First analysis	Sulfonylureas + warfarin	Sulfonylureas (no OACs)	Hypoglycaemia
Second analysis	Sulfonylureas + DOACs	Sulfonylureas (no OACs)	Hypoglycaemia
Third analysis	Sulfonylureas + warfarin	Warfarin	Bleeding

8.5.6 Study outcomes

8.5.6.1 Primary outcome

The primary outcome was incident hypoglycaemia during the follow up time defined as the first record of hypoglycaemia after the index date. Hypoglycaemia was identified based on Read codes (Appendix 7).

8.5.6.2 Secondary outcome

The secondary outcomes were incident bleeding defined as the first record of bleeding after the index date. Bleeding was identified based on Read codes (Appendix 7).

8.5.7 Study covariates

Demographics, comorbidities and medications associated with developing hypoglycaemia or bleeding were included as covariates. These covariates were selected based on the results of Chapter 2, previous studies (Leonard et al., 2016, Nam et al., 2018) and with reference to clinicians. They included; age, gender, smoking status (never-smoked, ex-smoker and current smoker), body mass index (BMI), alcohol consumption (never-drink, ex-drinker and current drinker), Townsend deprivation score, CVDs, history of hyperglycaemia, history of Hyperlipidaemia, history of hypertension (HTN), history of chronic kidney disease (CKD), history of liver disease, history of stroke/ transient ischaemic attack (TIA), history of AF, history of deep vein thrombosis (DVT), history of anxiety, history of depression, history of chronic obstructive pulmonary disease (COPD), history of bleeding, history of peripheral vascular disease (PVD), multiple antidiabetic use (intensification), history of beta-blockers (BBs) use, history of angiotensin converting enzyme inhibitor (ACEIs) use, history of angiotensin II receptor blocker inhibitor (ARBs) use, history of calcium channels blockers (CCBs) use, history of statins use, history of proton pump inhibitors (PPIs) use, history of corticosteroids use, history of aspirin use, history of antiplatelets use. Finally, a HAS-BLED score (without INR results) was also estimated at baseline to measure the risk of bleeding. Information for comorbidities was evaluated at any

time on/or before the index date and was identified using Read codes. Medications were identified using drug codes within 180-days on/or before the start date. We did not account for INR results because the data was not complete. Details of the Read codes are provided in Appendix 7.

8.5.8 Propensity score matching

Propensity scores are statistical methods about the conditional probability to assign treatments between groups based on a set of baseline covariates when estimating the effect or association of treatment and an outcome (Rosenbaum and Rubin, 1983). It makes the distribution of baseline variables similar between the exposure and non-exposure groups (Rosenbaum and Rubin, 1983) There are different types of the propensity score, including; propensity score matching, stratification, inverse probability of treatment weighting (IPTW), and adjustment covariates using the propensity score (Austin, 2011). Previous articles using large datasets have demonstrated that both PS matching and IPTW are efficient and precise in reducing the imbalance between the exposure and non-exposure groups at baseline (Lunceford and Davidian, 2004, Austin, 2009b). In this study, I have used the propensity score matching in the main analysis, and I also conducted the IPTW as part of the sensitivity analysis.

Propensity score matching for each patient to minimise potential bias due to non-randomised allocation was used to generate matched cohorts that are different in the treatment exposures, but with reduced or eliminated effect concerning other unmeasured characteristics (Austin, 2011). Also, to address confounding by

indication, when patients with T2DM with more severe illness are likely to be treated with insulin, sulfonylurea or multiple antidiabetic medications or patients with T2DM using OACs might be prescribed OACs for different indications, I included the following variables (index-date, AF, DVT and stroke/TIA) in the PS model (Okoli et al., 2014). The procedure includes creating a matched dataset between the exposure and non-exposure groups (Austin, 2011). First, we used a logistic regression model to estimate the propensity score for each individual, and the aforementioned variables (covariates) were the confounding variables at baseline and were inserted in the propensity score model. Choosing the variables included in the PS model is essential to reduce the bias and therefore, these covariates were selecting based on their relation to either the outcome or both the exposure and the outcome (Brookhart et al., 2006). Second, using SAS software macro, comparator cohorts matched by propensity score (within ±0.05, comprising 1:1 controls for each exposed patients with concurrent use of sulfonylurea and OACs) were created using patients prescribed sulfonylureas in Analyses (1 and 2), and warfarin in analysis 3. Propensity score matching based on one to one ratio is the most common technique, and it allows precise and robust estimates especially in studies with large sample sizes (Rassen et al., 2012, Austin, 2011).

Absolute Standardised Differences (ASD) for all baseline variables were calculated to assess the differences in patient characteristics and covariates balance between treatment groups before and after the propensity score matching. Previous researchers have suggested a cut-offs point ranging from 0.1 to 0.25 for ASD (Lau et al., 2017, Austin, 2009a, Normand et al., 2001). Therefore, characteristics with an ASD greater than 0.2 after propensity score matching were included as covariates in the subsequent regression model.

8.5.9 Statistical analysis

Patient characteristics were presented as a number (percentage) for categorical variables and as a mean (±SD) for continuous variables. Crude incidence rates were calculated by dividing the number of hypoglycaemia events by person-time at risk, and were expressed as rates per 1000 person-years. Person-time was calculated as the time from the index date until the end of follow up. The Cox proportional hazard model before and after propensity score was used to estimate the time to an event, and to investigate the association between the use of OACs with co-existent sulfonylurea and the risk of hypoglycaemia and/or bleeding; results were presented as HR with 95% CI. I performed Kaplan-Meier survival curves plots on the matched datasets to compare outcomes among the cohorts over time. The hazard assumption was examined by both visual graphs and by applying tests using ph statement (proc PHREG) in SAS v9.4. In the primary analysis, the analysis was conducted on complete case analysis and according to the initial and latest treatment, regardless of subsequent changes to their exposure status. In all statistical analyses, a 2-sided P value less than 0.05 was considered statistically significant. All analysis was performed using SAS version 9.4 (SAS Institute).

8.5.10 Sensitivity analysis

To confirm the robustness of the results I conducted multiple approaches in sensitivity analyses as follows;

(i) I re-analysed the data taking into account subsequent changes in the exposure status. Patients were censored if they suspended treatment that allowed a grace

period to account for potential incomplete adherence. A 90-days gap after the expected end date of any prescription, where the gap between expected prescription end date and the start date of any subsequent prescription would be no more than 90 days.

(ii) To assess the robustness of the results, re-analysing the data using the IPTW method to address the difference between groups at baseline and to estimate population average treatment effects based of PS were conducted (Austin and Stuart, 2015). The IPTW uses weights based on the propensity score calculated to create an artificial data-set that are similar in the baseline characteristics (Austin, 2011). The stabilised IPTW was calculated by multiplying the IPTW by the marginal probability of receiving the actual treatment (Austin and Stuart, 2015). Stabilisation was used to reduce the variability of the IPTW weights (Xu et al., 2010). The predictor variables inserted in the IPTW models included the same covariates as in the PS matching.

(iii) PS trimming for the IPTW was also conducted, where patients receiving the treatment contrary to prediction were excluded. I re-analysed the IPTW based on (1st percentile of the PS distribution in exposure and the 99th percentile of the PS in non-exposed treated) (Lee et al., 2011b).

(iv) The missing data on smoking status, BMI, alcohol consumption and Townsend scores were imputed by the multiple imputation (MI) method (Pedersen et al., 2017)). MI is a helpful statistical method when dealing with missing data (Yuan, 2005). The rationale for using the MI in epidemiological studies arises from the fact that some covariates may be related to the outcome of interest which thereby may bias the

overall conclusion when missing at large proportions (Sterne et al., 2009). Besides, when using PS analysis some patients may be excluded from the matching because of the missing values in some variables, and therefore, when data are imputed, the matching datasets may be different (Leyrat et al., 2019). MI of observational data is widely used in the literature, and it has proven its efficiency (White and Carlin, 2010, Choi et al., 2019). It works by replacing the missing values with a set of probable values by creating multiple synthetic complete datasets to estimate the propensity score for each patient (Leyrat et al., 2019, Yuan, 2005) and then apply Rubins rule, where individual estimates and standard errors (SE) from each of the imputed datasets are combined into an overall MI estimate and SE to determine the treatment effect (Marshall et al., 2009). Previous studies suggested including the outcome of interest in the MI model (Leyrat et al., 2019), and to create at least 10 imputed datasets (Bartlett and Morris, 2015). In this study, all PS covariates, the outcome and survival time were included in the MI model, and 25 imputed datasets were generated, analysed separately and then combined using Rubin's rule.

(V) To assess the robustness of the results of the second analysis (sulfonylureas and DOACs vs sulfonylureas only), re-analysing of the data taking into account the differences in the median follow-up time was also conducted in the matching analysis.

8.5.11 Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of this research.

8.6 Results

8.6.1 Patient's characteristics

A total of 418,613 individuals with T2DM were identified, of whom only 178,084 received a prescription for sulfonylureas and OACs at some point during the study period between 2001 and 2017. Around 49,317 (22%) patients in the warfarin group (Analysis 1) and 16,413 (17.5%) patients in the DOACs group (Analysis 2) were excluded for missing data in the main analysis. Finally, after we applied exclusion criteria, 109,040 using warfarin and sulfonylureas (Analysis 1) and 77,296 using DOACs and sulfonylureas (Analysis 2) were identified and included in the complete case analysis, respectively. Details of the identification of the study cohort, including the study cohort of patients included in Analyses 1, 2 and 3 (secondary outcome) are presented in Figure 41 and Appendices 13 – 14.

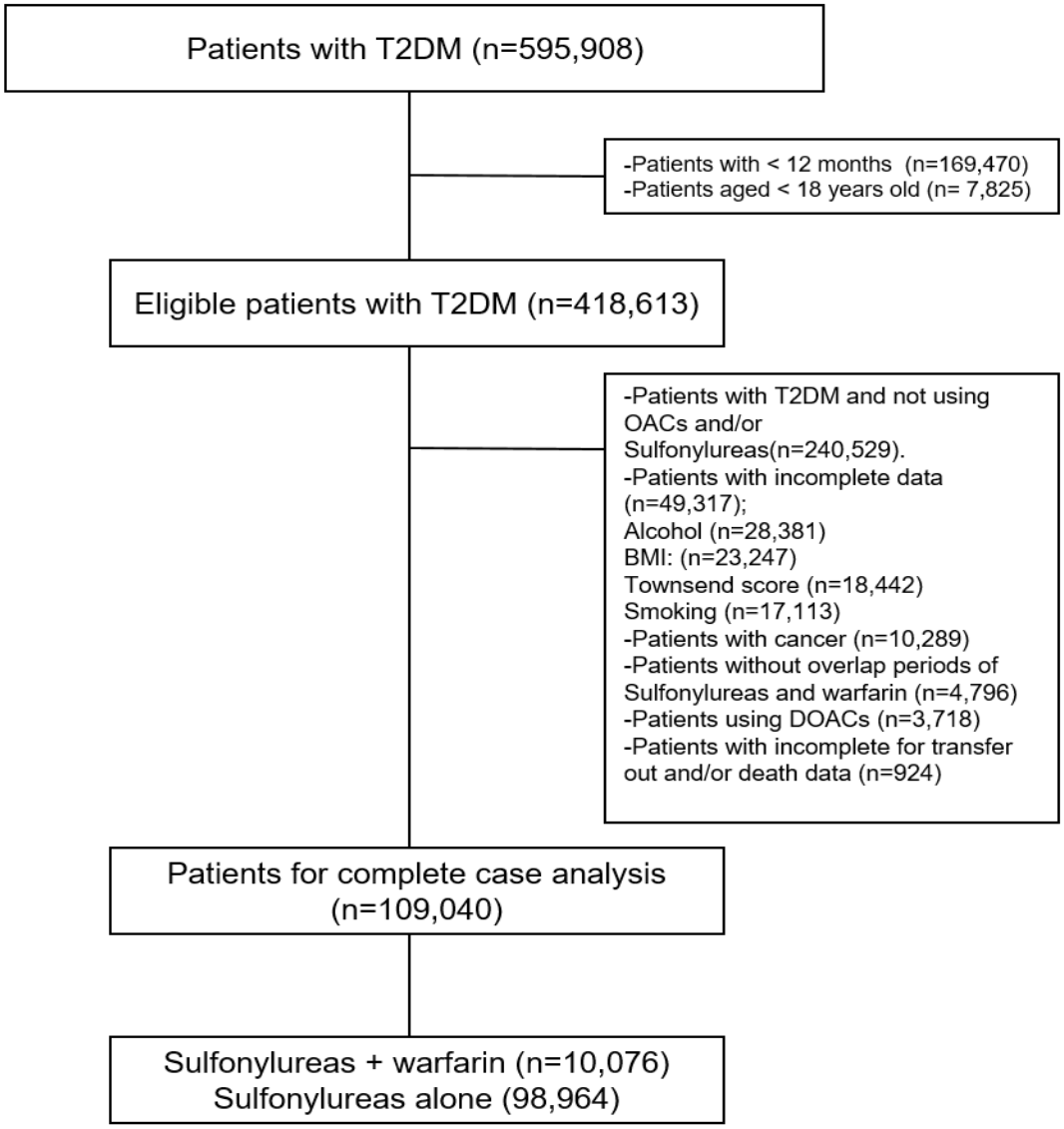

Figure 41. Study flow chart.

Below I will describe the characteristics of patients included in Analysis 1 (warfarin with sulfonylureas vs sulfonylureas only). Details of the other two comparisons, Analysis 2 and Analysis 3, are presented in Tables 19 – 20.

At baseline, before propensity score matching, the mean age was higher among patients who received warfarin with sulfonylureas compared to patients who received

sulfonylureas only (mean age: 73.3 vs 61.0). The distribution of male to female percentages was nearly similar between the two groups (61% vs 57%). At least 50% of the study population had a BMI ≥30, with nearly similar BMI ratios in patients who received warfarin with sulfonylureas compared to patients who received sulfonylureas only.

The cardiovascular profile was significantly different between the two groups. Patients who received warfarin concomitantly with sulfonylureas had a higher cardiovascular profile compared to patients who received sulfonylureas only, CVDs (14.7% vs 4.5%), HTN (68% vs 50%), stroke/TIA (19% vs 5.7%), AF (61% vs 1.8%), and DVT (21% vs 2%). Other common comorbidities were that patients who received warfarin with sulfonylureas were more likely to have a history of COPD and CKD compared to patients who received sulfonylureas only. However, the mental health profile including depression and anxiety showed little difference between patients who received warfarin with sulfonylureas and patients who received sulfonylureas only (20% vs 23%) and (13% vs 15%), respectively. After matching, all baseline patients' characteristics had standardised differences less than 0.2 (Table 19 and Figure 42). Details of the study characteristics, including patient characteristics of Analysis 2 (DOACs with sulfonylureas vs sulfonylureas), and Analysis 3 (warfarin with sulfonylureas vs sulfonylureas) are presented in Table 20 and Figure 43 for Analysis 2, and in Appendices 15 – 16 for Analysis 3.

Table 19. Patient's characteristics among the cohort of first analysis (sulfonylureas and warfarin versus sulfonylureas only)

Variable	Before propensity scree matching No. (%) of participant				After propensity scree matching No. (%) of participant		
	All (n=109,040)	Sulfonylureas + warfarin (n= 10,076)	Sulfonylureas (n= 98,964)	Crude ASD	Sulfonylureas + warfarin (n= 5,379)	Sulfonylureas (n= 5,379)	Matched ASD
Demographics							
Age mean (SD)	62.0 (12.9)	73.3 (10.0)	61.0 (12.8)	0.918	69.9 (10.8)	70.0 (11.8)	0.054
Male, n (%)	70,883 (57.3)	6,918 (61.1)	63,965 (57.0)	0.083	3,114 (57.89)	3041 (56.53)	-0.027
BMI				0.037			0.038
BMI < 25	20,206 (16,3)	1,715 (15.5)	18,491 (16.5)	-	877 (16.3)	923 (17.1)	-
BMI 25-30	42,293 (34,2	3,942 (34.8)	38,351 (34.2)	-	1837 (34.1)	1894 (35.2)	-
BMI ≥ 30	61,006 (49.4)	5,665 (50.0)	55,341 (49.3)	-	2665 (49.5)	2562 (47.6)	-
Smoking				0.228			-0.011
Non-smokers	100,717 (81.5)	10,068 (88.9)	90,649 (80.8)	-	4673 (86.8)	4652 (86.4)	-
Smokers	22,788 (18.5)	1,254 (11.0)	21,534 (19.2)	-	706 (13.3)	727 (13.5)	-
Alcohol				0.035			0.006
Non-drinker	37,503 (30.3)	3,604 (31.8)	33,899 (30.2)	-	1740 (32.3)	1757 (32.6)	-
Drinker	86,002 (69.7)	7,718 (68.2)	78,284 (69.8)	-	3639 (67.7)	3622 (67.3)	-
Townsend				0.053			0.036
1 (Least deprived)	21200 (19.4)	2026 (20.1)	19174 (19.4)	-	1075 (19.9)	1021 (19.0)	-
2	21695 (19.9)	2140 (21.2)	19555 (19.7)	-	1091 (20.3)	1057 (19.6)	-
3	23941 (22.0)	2168 (21.6)	21773 (22.0)	-	1149 (21.4)	1203 (22.4)	-
4	23690 (21.7)	2167 (21.5)	21523 (21.7)	-	1199 (22.3)	1222 (22.7)	-
5 (Most deprived)	18514 (17.0)	1575 (15.6)	16939 (17.2)	-	865 (16.0)	876 (16.3)	-
Comorbid conditions, n (%)							
CVDs	6709 (5.4)	1670 (14.7)	5039 (4.5)	0.353	684 (12.7)	656 (12.2)	-0.016
Hypertension	64243 (52.0)	7693 (68.0)	56550 (50.4)	0.363	3399 (63.2)	3370 (62.6)	0.011
Stroke/TIA	8583 (7.0)	2154 (19.0)	6429 (5.7)	0.412	838 (15.6)	866 (16.1)	-0.014
Bleeding	17414 (14.1)	2112 (18.6)	15302 (13.6)	0.137	1009 (18.7)	970 (18.0)	-0.019
Hyperlipidaemia	22399 (18.1)	2652 (23.4)	19747 (17.6)	0.144	1187 (22.0)	1194 (22.2)	-0.003
AF	8925 (7.3)	6952 (61.4)	1973 (1.8)	1.673	1862 (34.6)	1750 (32.5)	0.044

DVT	4703 (4.0)	2403 (21.2)	2300 (2.0)	0.627	1453 (27.0)	1571 (29.2)	-0.049
Chronic kidney disease	14007 (11.3)	3016 (26.6)	10991 (9.8)	0.447	1099 (20.4)	1105 (20.5)	-0.003
COPD	6289 (5.0)	1208 (10.7)	5081 (4.5)	0.233	481 (9.0)	518 (9.6)	-0.024
Hyperglycaemia	3873 (3.4)	422 (3.7)	3451 (3.0)	0.036	212 (3.9)	216 (4.0)	-0.004
Liver diseases	737 (0.5)	59 (0.5)	678 (0.6)	0.011	36 (0.7)	49 (0.9)	-0.027
Depression	28257 (22.9)	2323 (20.5)	25934 (23.1)	0.063	1202 (22.3)	1254 (23.3)	-0.023
Anxiety	19096 (15.5)	1542 (13.6)	17554 (15.6)	0.057	811 (15.0)	843 (15.7)	-0.017
Baseline medication use, n (%)							
Aspirin use	39242 (31.8)	4264 (37.6)	34978 (31.8)	0.137	2223 (41.3)	2480 (46.1)	-0.096
Antiplatelet drugs use	4352 (3.5)	716 (6.3)	3636 (3.2)	0.145	368 (6.8)	394 (7.3)	-0.019
Beta blockers use	28927 (23.4)	5264 (46.5)	23663 (21.0)	0.558	1943 (36.1)	36.12 (38.8)	-0.055
ACEs /ARBs use	58306 (47.2)	8061 (71.2)	50245 (44.8)	0.555	3337 (62.0)	3328 (61.9)	0.003
Corticosteroids use	8130 (6.6)	1276 (11.2)	6854 (6.1)	0.184	578 (10.7)	616 (11.4)	-0.022
Multiple antidiabetic medications use (intensification)	84,540 (68.4)	7705 (68.0)	76835 (68.5)	0.009	3559 (66.1)	3425 (63.7)	0.052

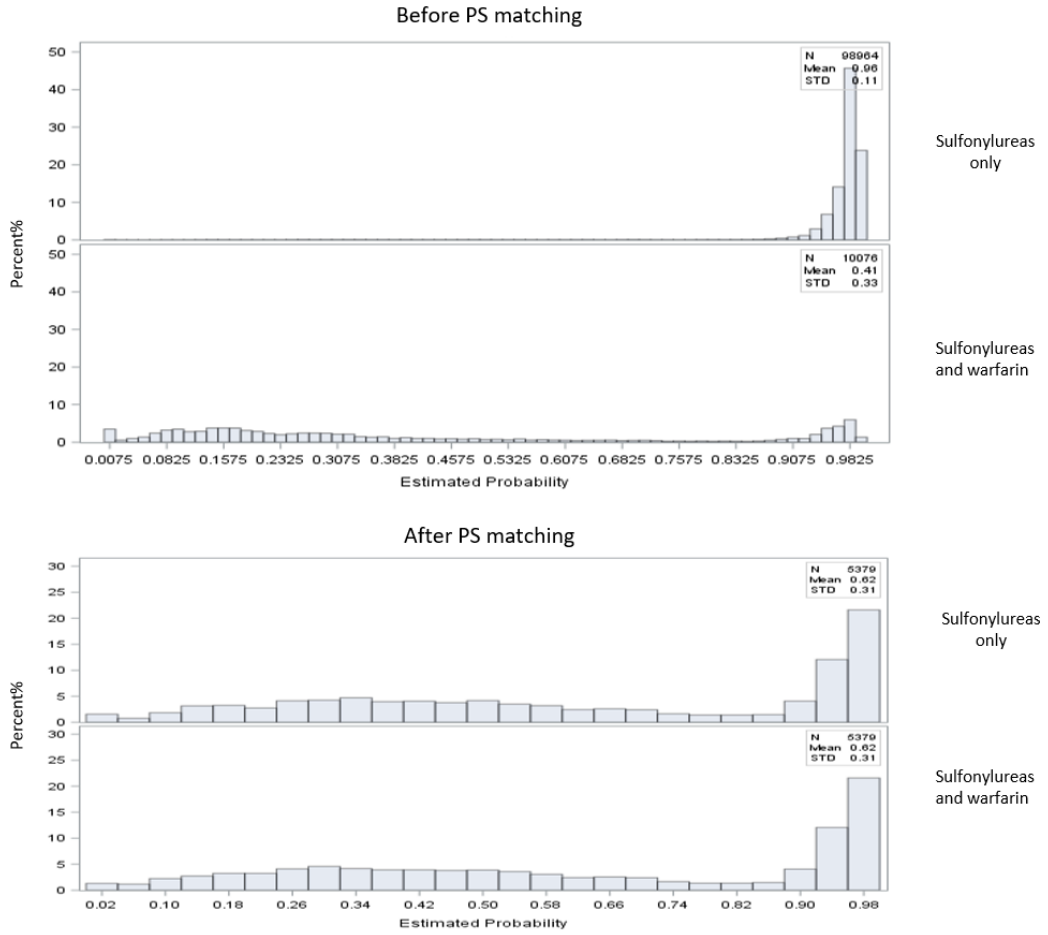

Figure 42. Absolute standardised difference before and after matching of patients receiving sulfonylureas and warfarin versus sulfonylureas only.

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Table 20. Patient's characteristics among the cohort of second analysis (sulfonylureas and DOACs versus sulfonylureas only)

Variable	Before propensity scree matching No. (%) of participant				After propensity scree matching No. (%) of participant		
	All (n=77,296)	Sulfonylureas + DOACs (n= 1,045)	Sulfonylureas (n= 76,251)	Crude ASD	Sulfonylureas + DOACs (n= 1,027)	Sulfonylureas (n= 1,027)	Matched ASD
Demographics							
Age mean (SD)	63.9 (SD13.1)	73 (10.2)	63.7 (13.0)	0.793	73.3 (10.3)	74.3 (11.1)	0.106
Male, n (%)	45,112 (58.3)	645 (61.7)	44,467 (58.3)	0.070	632 (61.5)	608 (59.2)	-0.048
BMI				0.088			0.080
BMI < 25	10910 (14.1)	124 (11.8)	10786 (14.1)	-	120 (11.7)	133 (13.0)	
BMI 25-30	25143 (32.5)	322 (30.8)	24821 (32.5)	-	318 (31.0)	346 (33.7)	
BMI ≥ 30	41243 (53.3)	599 (57.3)	40644 (53.3)	-	589 (57.3)	548 (53.4)	
Smoking				0.111			0.015
Non-smokers	64954 (84.0)	918 (88.0)	64036 (84.0)	-	903 (88.0)	908 (88.4)	-
Smokers	12342 (16.0)	127 (12.0)	12215 (16.0)	-	124 (12.0)	119 (11.6)	-
Alcohol				0.079			0.044
Non-drinker	24607 (32.0)	371 (35.5)	242316 (32.0)	-	364 (35.4)	386 (37.6)	-
Drinker	52689 (68.0)	674 (64.5)	52015 (68.0)	-	663 (64.5)	641 (62.4)	-
Townsend				0.087			0.055
1 (Least deprived)	14950 (19.3)	195 (18.7)	14755 (19.3)	-	190 (18.5)	184 (18.0)	-
2	15403 (20.0)	199 (19.0)	15204 (19.9)	-	196 (19.0)	201 (19.6)	-
3	17042 (22.0)	238 (22.8)	16804 (22.0)	-	233 (22.7)	214 (20.9)	-
4	16654 (21.5)	204 (19.5)	16450 (21.6)	-	201 (19.6)	216 (21.0)	-
5 (Most deprived)	13247 (17.1)	209 (20.0)	13038 (17.1)	-	207 (20.1)	212 (20.6)	-
Comorbid conditions, n (%)							
CVDs	4308 (5.5)	185 (17.7)	4123 (5.4)	0.393	175 (17.0)	194 (18.9)	-0.048
Hypertension	46371 (60.0)	776 (74.2)	45595 (60.0)	0.311	763 (74.3)	778 (75.7)	-0.034
Stroke/TIA	5700 (7.3)	229 (22.0)	5471 (7.1)	0.428	219 (21.3)	235 (22.9)	0.038
Bleeding	13882 (18.0)	285 (27.3)	13597 (18.0)	0.227	277 (27.0)	310 (30.2)	-0.071
Hyperlipidaemia	17699 (23.0)	230 (22.0)	17469 (22.9)	0.022	229 (22.3)	245 (22.8)	-0.037
AF	2313 (3.0)	645 (61.7)	1668 (2.1)	1.658	627 (61.0)	621 (60.5)	0.012

DVT	2215 (2.9)	162 (15.5)	2053 (2.7)	0.457	159 (15.5)	201 (19.6)	-0.108
Chronic kidney disease	17295 (22.4)	364 (34.4)	16931 (22.2)	0.282	360 (35.0)	402 (39.0)	-0.085
COPD	4176 (5.4)	120 (11.4)	4056 (5.3)	0.224	118 (11.5)	134 (13.0)	-0.048
Hyperglycaemia	2778 (3.6)	37 (3.5)	2741 (3.6)	0.003	36 (33.5)	33 (33.2)	0.016
Liver diseases	527 (0.7)	10 (1.0)	517 (0.7)	0.031	10 (1.0)	11 (0.9)	-0.010
Depression	21066 (27.3)	303 (29.0)	20763 (27.3)	0.039	295 (28.7)	304 (29.6)	-0.019
Anxiety	14160 (18.3)	202 (19.3)	13958 (18.3)	0.026	199 (19.3)	201 (19.6)	-0.005
Baseline medication use, n (%)							
Aspirin use	32006 (41.4)	480 (46.0)	31526 (41.3)	0.093	476 (46.3)	526 (51.2)	-0.098
Antiplatelet drugs use	3644 (4.7)	172 (16.5)	3472 (4.5)	0.396	166 (16.1)	180 (17.5)	-0.036
Beta blockers use	18316 (23.7)	659 (63.0)	17657 (23.1)	0.880	642 (62.5)	622 (60.5)	0.040
ACEIs /ARBs use	47369 (61.2)	761 (73.0)	46608 (61.1)	0.251	745 (72.5)	748 (72.8)	-0.007
Corticosteroids use	5051 (6.5)	161 (15.4)	4890 (6.4)	0.291	154 (15.0)	156 (15.2)	-0.005
Multiple antidiabetic medications use (intensification)	65600 (85.5)	875 (83.7)	64725 (85.4)	0.032	857 (83.4)	835 (81.3)	0.056

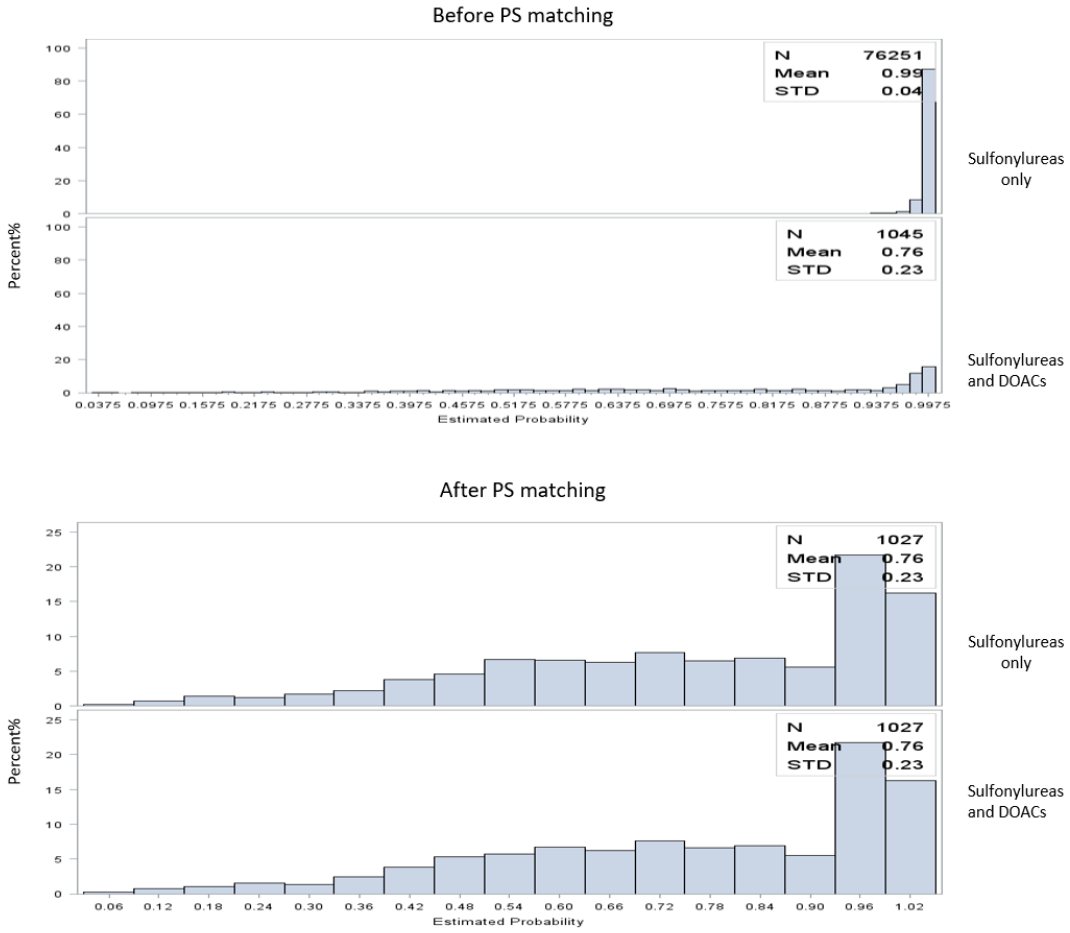

Figure 43: Absolute standardised difference before and after matching of patients receiving sulfonylureas and DOACs versus sulfonylureas only

8.6.2 Hypoglycaemia

8.6.2.1 Warfarin with sulfonylureas vs sulfonylureas

Users of warfarin with sulfonylureas contributed to 34,422.40 person-years of concomitant exposure, during which 578 hypoglycaemia events were recorded (crude incidence rates = 16.7 per 1000 person-years), while users of sulfonylureas only contributed to 526,422.49 person-years, during which 7307 hypoglycaemia events were recorded (crude incidence rates = 13.8 per 1000 person-years). The risk of developing hypoglycaemia was higher for patients receiving warfarin with sulfonylureas compared to patients receiving sulfonylureas alone (HR 1.20; 95% CI, 1.10 – 1.30), p=<0,0001), Table 21.

8.6.2.1.1 DOACs with sulfonylureas vs sulfonylureas

Patients using DOACs with sulfonylureas concomitantly contributed to a total of 957 person-years, during which I identified 14 hypoglycaemic events (crude incidence rates = 15.0 per 1000 person-years), while in the non-exposed group (sulfonylureas only), with a total of 246,345.65 person-years, I identified 4,514 hypoglycaemia events (crude incidence rates = 18.0 per 1000 person-years). The risk of developing hypoglycaemia was lower for patients receiving DOACs with sulfonylureas compared to patients receiving sulfonylureas alone. However, this was not statistically significant (HR 0.66; 95% CI, 0.39 – 1.11, p=0.118), Table 21.

Table 21. Number of events, incidence rates and crude HR, for risk of hypoglycaemia

Exposure group	No. of event	Person-years at risk, year	IR, per 1000 person-years (95% CI)	Crude HR (95% CI), p-value
Sulfonylurea+warfarin (n=10,076)	578	34422.40	16.7	1.20 (1.10 – 1.30)
Ref= Sulfonylurea only (n=98,964)	7307	526422.49	13.8	
Sulfonylurea+DOAC *(n=1,045)	14	956.9	15.0	0.66 (0.39- 1.11)
Ref= Sulfonylurea only * (n=76251)	4514	246345.6	18.0	

* This analysis included patients only from 2011 onward.

8.6.2.2 Propensity score matched analysis

8.6.2.2.1 Warfarin with sulfonylureas vs sulfonylureas

After matching 5,379 patients in each group, there were a total of 15,959.04 of concomitant exposure, during which I identified 285 hypoglycaemia events (incidence rates = 17.8 per 1000 person-years), while users of sulfonylureas only contributed to 21,028.52 person-years, during which I identified 304 hypoglycaemia events (incidence rates = 14.4 per 1000 person-years). The risk of hypoglycaemia was 38% higher in patients with concomitant use of warfarin with sulfonylureas, compared to sulfonylureas alone users (HR 1.38; 95% CI, 1.10 – 1.76, P= 0.010), Table 22. Kaplan-Meier curves for the incidence of hypoglycaemia of first analysis (sulfonylureas and warfarin versus sulfonylureas only) are shown in Figure 44.

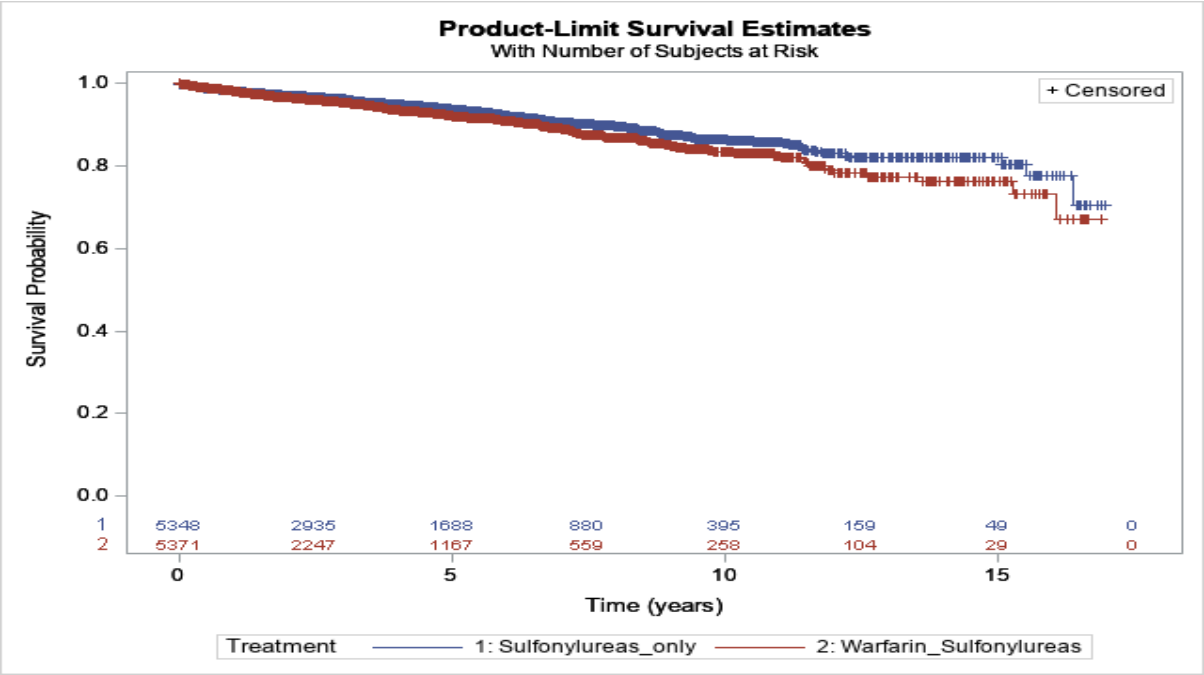

Figure 44. Kaplan-Meier curves for the incidence of hypoglycaemia during the follow-up period.

8.6.2.2.2 DOACs with sulfonylureas vs sulfonylureas

The results of the matching cohorts produced a total of 1,027 in each group, with a total of 942, and 2,532 person-years, during which I identified 14 and 60 hypoglycaemic events (incidence rates =14.8 per 1000 person-years and 23.7 per 1000 person-years) exposure and non-exposure groups, respectively, Table 22. The risk of developing hypoglycaemia was again lower for patients receiving DOACs with sulfonylureas compared to patients receiving sulfonylureas alone (HR 0.54; 95% CI, 0.27 – 1.10, P=0.091). However, this was not statistically significant (Table 22). Kaplan-Meier curves for the incidence of hypoglycaemia of second analysis (sulfonylureas and DOACs versus sulfonylureas only) are shown in Appendix 17.

Table 22. Number of events, incidence rates and matched HR, for risk of hypoglycaemia for the matched cohort

Exposure group	No. of event	Person-years at risk, year	IR, per 1000 person-years (95% CI)	Matched HR (95% CI), p-value
Sulfonylurea+warfarin (n=5379)	285	15959.04	17.8	1.38 (1.10-1.75)
Ref= Sulfonylurea only (n=5379)	304	21028.52	14.4	1.00
Sulfonylurea+DOAC *(n=1027)	14	942.2	14.8	0.54 (0.27- 1.10)
Ref= Sulfonylurea only * (n=1027)	60	2532.0	23.7	1.00

* This analysis included patients only from 2011 onward.

8.6.2.3 Sensitivity analysis

The results of the sensitivity analyses are presented in Tables 23-25. When re-analysing the data taking into account only patients who received subsequent prescriptions within no more than 90-days, the risk of hypoglycaemia was higher in patients receiving warfarin with sulfonylureas compared to patients receiving sulfonylurea alone (HR 1.14; 95% CI, 1.01 – 1.30, P= 0.032), Table 23. However, the results of the matching analysis based on 90-days grace period showed non-statistically significant results between both groups (HR 1.10; 95% CI, 0.71 – 1.22, P= 0.634), Table 23.

Table 23. Cox proportional hazard (Un-adjusted/Adjusted/Matched) for risk of hypoglycaemia 90-days

Exposure group	Un-adjusted hazard-ratio (95% CI)	Adjusted hazard-ratio (95% CI)	Matched by propensity score (95%CI)
Warfarin+ sulfonylureas Ref=Sulfonylurea only	1.14 (1.01- 1.30)	1.00 (0.85- 1.15)	1.10 (0.71- 1.22)
DOACs+ sulfonylureas Ref=Sulfonylurea only	1.05 (0.70- 1.60)	0.79 (0.52- 1.21)	0.80 (0.44- 1.40)

Results from the inverse probability of treatment weighting (IPTW) were similar to main analyses. Patients had a higher risk of hypoglycaemia by 24% when receiving warfarin with sulfonylureas compared to patients receiving sulfonylureas alone (HR 1.24; 95% CI, 1.20- 1.25, P= <0.0001) (Table 24). The results of IPTW were different from main analysis when comparing patients receiving DOACs and sulfonylureas concomitantly against patients receiving sulfonylureas alone. The risk of hypoglycaemia was again lower for patients receiving DOACs and sulfonylureas, but significant in the IPTW analysis (HR 0.56; 95% CI, 0.36 – 0.90, P= 0.011). Results from the inverse probability of treatment weighting (IPTW), including PS trimming, are presented in Table 24.

Table 24. Cox proportional hazard results from IPWT analysis

Exposure group	IPWT (95% CI)	IPWT (95%CI) 1%-99% percentile
Warfarin+ sulfonylureas Ref=Sulfonylurea only	1.24 (1.20-1.25)	1.12 (1.01- 1.24)
DOACs+ sulfonylureas Ref=Sulfonylurea only	0.56 (0.36- 0.90)	0.39 (0.244- 0.60)

Results from multiple imputations were also similar to the main analyses, demonstrating warfarin with sulfonylureas treatment was associated with a higher risk of hypoglycaemia compared to sulfonylureas alone (HR=1.08; 95% CI, 1.03 – 1.13; p=<0.001), Table 25.

Table 25. Cox proportional hazard results from multiple imputation method (m=25)

Exposure group	Crude HR (95% CI)	P-value	Matched HR (95% CI)	P-value
Warfarin+ Sulfonylureas Ref=Sulfonylurea only	1.22 (1.13-1.32)	<0.0001	1.08 (1.03-1.13)	<0.0001
DOACs+ Sulfonylureas Ref=Sulfonylurea only	0.9 (0.59-1.36)	0.593	0.54 (0.46 -0.62)	<0.0001

When re-analysing the data of Analysis 2, taking into account the difference in the median follow-up, the results did not differ from the main analysis when comparing patients receiving DOACs and sulfonylureas concomitantly, against patients receiving sulfonylureas alone. The risk of hypoglycaemia was lower for patients receiving DOACs and sulfonylureas, but not significant in the matching analysis (HR 0.429; 95% CI, 0.11 – 1.66, P=0.220).

8.6.3 Bleeding

Users of warfarin with sulfonylureas contributed to 29,177.47 person-years of concomitant exposure, during which we identified 1,570 bleeding events (crude incidence rates = 53.8 per 1000 person-years), while users of warfarin only contributed to 38,534.68 person-years), during which we identified 1,696 bleeding events (crude incidence rates = 44.0 per 1000 person-years). The risk of developing bleeding was higher for patients receiving warfarin with sulfonylureas compared to patients receiving warfarin alone (HR 1.21; 95% CI, 1.13 – 1.30, P=<0.0001), Table 26.

Table 26. Number of events, incidence rates and crude HR, for risk of bleeding

Exposure group	No. of event	Person-years at risk, year	IR, per 1000 person-years	Crude HR (95% CI)
Sulfonylureas+ warfarin (n= 10,076)	1570	29,177.47	53.8	1.21 (1.14-1.30)
Ref= Warfarin only (n= 12,898)	1696	38,534.68	44.0	1.00

8.6.3.1 Propensity score matched analysis

The matching analysis containing 9,918 patients in each group produced 28,838.29 of concomitant exposure, during which 1,548 bleeding events (matched incidence rates = 53.6 per 1000 person-years) were reported, while users of warfarin only contributed to 30,068.24 person-years, during which 1,307 bleeding events (matched incidence rates = 43.4 per 1000 person-years) were reported, Table 27. The risk of developing bleeding was again higher by 12% for patients receiving warfarin with sulfonylureas compared to patients receiving warfarin alone (HR 1.12; 95% CI, 1.01 – 1.24,

P=0.028), Table 27. Kaplan-Meier curves for the incidence of bleeding of third analysis (sulfonylureas and warfarin versus warfarin only) are shown in Figure 45.

Table 27. Number of events, incidence rates and matched HR, for risk of bleeding for the matched cohort

Exposure group	No. of event	Person-years at risk, year	IR, per 1000 person-years	Matched HR (95% CI)
Sulfonylurea+ warfarin (n= 9,918)	1545	28752.62	53.7	1.12 (1.01-1.24)
Ref= Warfarin only (n= 9,918)	1303	29940.07	43.5	1.00

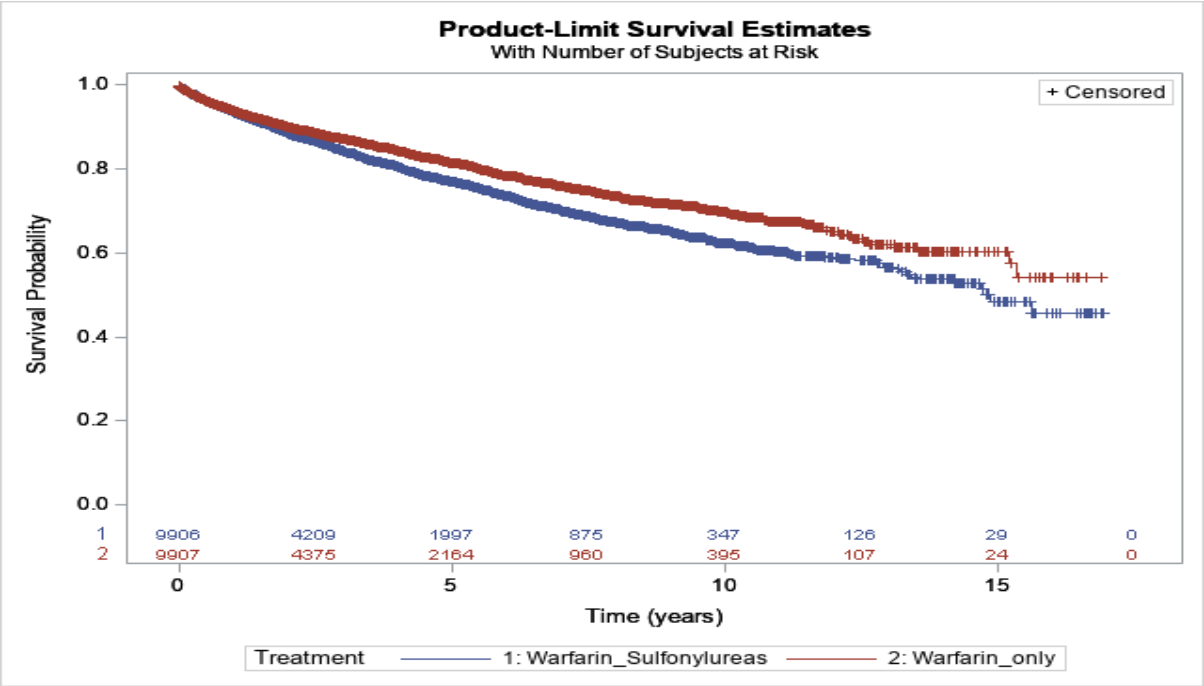

Figure 45. Kaplan-Meier curves for the incidence of bleeding during the follow-up period.

8.6.3.2 Sensitivity analysis

The analysis of the 90-day grace period (prescription for not more than 90 days) showed that the bleeding was higher in patients receiving warfarin with sulfonylureas compared to patients receiving warfarin alone (HR 1.40; 95% CI, 1.32 – 1.52, P=<0.0001). Similarly, the results of the matching analysis based on a 90-day grace period, showed an increased risk of bleeding in patients receiving warfarin with sulfonylureas (HR 1.41; 95% CI, 1.26 – 1.57, P=<0.0001), Table 28.

Table 28. Cox proportional hazard (Un-adjusted/Adjusted/Matched) for risk of bleeding-90-days

Exposure group	Un-adjusted hazard-ratio (95% CI)	Adjusted hazard-ratio (95% CI)	Matched by propensity score (95%CI)
Sulfonylurea+ warfarin	1.42 (1.32- 1.52)	1.45 (1.35-1.56)	1.41 (1.26-1.57)
Ref=warfarin only			

Results from the inverse probability of treatment weighting (IPTW) were similar to main analyses. Patients receiving warfarin with sulfonylureas had a higher risk of bleeding when sulfonylureas compared to patients receiving warfarin alone (HR 1.21; 95% CI, 1.16 – 1.27, P=<0.0001). Results from the inverse probability of treatment weighting (IPTW), including PS trimming, are presented in Table 29.

Table 29. Cox proportional hazard results from IPWT analysis

Exposure group	IPWT (95% CI)	IPWT (95%CI) 1%-99% percentile
Sulfonylurea+ warfarin	1.21 (1.16- 1.27)	1.22 (1.16- 1.28)
Ref=warfarin only		

When re-analysing the data by multiple imputations, the results were also similar to main analyses demonstrating warfarin with sulfonylureas treatment was associated with a higher risk of bleeding compared to warfarin alone (HR=1.23; 95% CI, 1.11-1.30; p=<0.001), Table 30.

Table 30. Cox proportional hazard results from multiple imputation method (m=25)

Exposure group	Crude HR (95% CI)	P-value	Matched HR (95% CI)	P-value
Warfarin+ sulfonylureas	1.23 (1.12- 1.30)	<0.0001	1.37 (1.24- 1.51)	<0.0001
Ref=Warfarin only				

8.7 Discussion

In this large population-based study in UK primary care, I investigated the association between the concurrent use of OACs and sulfonylureas and the risk of hypoglycaemia and bleeding in patients with T2DM. The study found that warfarin was associated with 38% and 15% of increased risks of hypoglycaemia and/or bleeding when used with sulfonylureas concurrently in patients with T2DM, (HR 1.38; 95% CI, 1.10 – 1.75 and HR 1.12; 95% CI, 1.01 – 1.24), respectively. In addition, I found no evidence of an association between the use of DOACs and sulfonylureas concurrently and the risk of hypoglycaemia (HR 0.54; 95% CI, 0.27 – 1.10). The study results support the hypothesis that warfarin is associated with an increased risk of hypoglycaemia or bleeding when given concomitantly with sulfonylureas in patients with T2DM.

8.7.1 Comparison with other studies

The present study findings are consistent with two previous large database studies in the United States (Romley et al., 2015, Nam et al., 2018). Romley et al. used pharmacy and medical data from Medicare beneficiaries between 2006 and 2011 and included more than 465,918 patients with diabetes in their study. The authors reported that the concurrent use of warfarin and sulfonylureas is associated with a 22% higher risk for

hypoglycaemia (Romley et al., 2015). Similarly, Nam et al. using data from five Medicaid programmes and Medicare claims, reported an elevated rate of serious hypoglycaemia when warfarin was given concomitantly with sulfonylureas (glipizide, glyburide, glyburide), (RR, 1.72; 95% CI, 1.29 – 2.29), (RR, 1.57; 95% CI, 1.15 – 2.15), and (RR, 1.56; 95% CI, 0.97 – 2.50), respectively (Nam et al., 2018). However, the two previous studies did not include patients receiving DOACs in their studies. In this study, I had a longer follow-up than the other two studies, and I used a different design and analytic approaches. The two previous studies used a self-controlled case series cohort design, where quarters of concurrent use of warfarin and sulfonylureas were compared with quarters without warfarin use within the same patients (Hallas and Pottegård, 2014). However, in my study, I used a cohort design, and I compared exposure and comparators groups. Self-controlled case series design inherently controls for time-invariant confounders, and it controls for the unmeasured confounders. This is because it compares the same patients, but across different risk windows (Hallas and Pottegård, 2014), while its disadvantages arise from the fact that patients are sicker, and have a severe disease during exposure periods, which may increase the risk of bias (Hallas and Pottegård, 2014). Romley et al. included only patients with diabetes older than 65 years, which meant that the results could be generalised only to patients of the older age group (Romley et al., 2015). On the other hand, I accounted for all age groups of adults in the study, and I aimed to generalise the results to the entire population, even though OACs are more likely prescribed for the older population. However, the younger population is also prescribed OACs, which may better reflect current clinical practice (Adderley et al., 2019, Alwafi et al., 2020b).

Unlike previous studies, I accounted for important risk factors in the study such as smoking and alcohol status, social deprivation and BMI. These are well-established risk factors for bleeding and/or hypoglycaemia (Wolf et al., 1988, Pujades-Rodriguez et al., 2014, Tsai et al., 2015), and adjusting or matching patient characteristics based on these variables is important to reduce the risk of bias. Furthermore, there were more females included in the previous two studies, 58% in Romley et al.'s study (Romley et al., 2015) and 65% in the study by Nam et al., (Nam et al., 2018), compared to around 40% females in my study. However, it is important to highlight that even though the gender ratio in the general UK and US population is nearly equal (UK Government, 2018, U.S. Census BureauU.S. Census Bureau, 2019), males are more likely to have cardiovascular and diabetes diseases compared to females (Gao et al., 2019).

Despite some differences in the study population characteristics, health care systems and locations, and the study design and analytical methods used, the results of this study were consistent with the previous two studies (Romley et al., 2015, Nam et al., 2018), and support the finding that warfarin use concurrently with sulfonylureas may be associated with a higher risk for hypoglycaemia incidents.

Previous studies that investigated the concurrent use of OACs with sulfonylureas and the risk of bleeding are limited. Three randomised trials investigated the safety of DOACs and warfarin in patients with T2DM (Bansilal et al., 2015, Ezekowitz et al., 2015, Brambatti et al., 2015). Ezekowitz et al. reported that patients who were using apixaban had a lower rate of any type of bleeding compared to patients on warfarin (HR: 0.73; 95% CI 0.65 – 0.81). Bansilal et al. in their study reported that the rate of major bleeding events was lower among users of rivaroxaban compared to warfarin

users (3.79 vs. 3.90 / per 100 patient-years). Also, Brambatti et al. reported that users of dabigatran had a lower risk of intracranial bleeding at a low dose (110mg) compared to warfarin (HR 0.26; 95% CI, 0.11 – 0.65). Besides this, a recent observational study using a large database from the United States reported that when compared with warfarin, apixaban (HR 0.60; 95% CI, 0.56 – 0.65) and dabigatran (HR 0.78; 95% CI, 0.69 – 0.88) were associated with a significantly lower risk of major bleeding (Lip et al., 2020). The results of this study showed that warfarin was associated with an increased risk of bleeding when given concomitantly with sulfonylureas, (HR 1.12; 95% CI, 1.01 – 1.24). However, it is important to highlight that in my study, the study population was limited to patients with T2DM and using both warfarin and sulfonylureas, while previous studies included patients with T2DM and AF without any inclusive criteria or restrictions based on a specific antidiabetic medication, and further studies to investigate the association of concurrent use of warfarin and sulfonylureas and the risk of bleeding are needed.

8.7.2 Potential mechanisms

The underlying mechanism of action for the concurrent use of warfarin with sulfonylureas and increased risk of hypoglycaemia or bleeding is unclear. Previous pre-clinical hypotheses suggest some potential mechanisms for this association through a drug-drug interaction between the warfarin and sulfonylureas. First, there may be a displaced protein binding mechanism, where interaction between warfarin and sulfonylureas may occur on the site of the protein binding, and thus warfarin may enhance the plasma concentration of sulfonylureas in the blood, and hence increase its activity and risk of hypoglycaemia (Triplitt, 2006). However, previous studies and

reviews have described this mechanism of drug interaction to be overestimated and not to have meaningful clinical effects, as it only applies to data from in vitro studies, or to drugs that are given through loading intravenous doses (McElnay and D'Arcy, 1983, Rolan, 1994). Second, a drug-drug interaction through inhibition of the cytochrome CYP2C9 hepatic metabolic pathway has also been suggested. Warfarin, glimepiride, and glipizide are all largely metabolised by hepatic cytochrome CYP2C9 (Triplitt, 2006), and therefore, warfarin may limit the rate at which the sulfonylurea can be metabolised in the liver (Bibi, 2008). This mechanism may explain the findings of my study, especially the fact that widely used drug references warn that the concurrent use of warfarin with sulfonylureas may increase the risk of bleeding (IBM Watson MicromedexWatson Micromedex, 2019, Facts & Comparisons Lexicomp, 2018) However, no previous human studies exist to validate this hypothesis, and future studies to investigate this association are needed**.**

Furthermore, pre-clinical studies have suggested that osteocalcin which is one of the important bone proteins produced by the bone (Wei and Karsenty, 2015), is involved in the metabolism of glucose and insulin sensitivity through the process of bone mineralisation and formation, which requires high energy (Booth et al., 2013). It has been postulated that the uncarboxylated form of osteocalcin enhances the glucose tolerance by the beta cells in the pancreatic islets and increases the insulin sensitivity in peripheral tissues (Booth et al., 2013). However, this function is mainly dependent on Vitamin K, and therefore, administration of warfarin may block the activation of the carboxylation forum of osteocalcin and thus increase the uncarboxylated forum in the plasma (Booth et al., 2013). In vitro studies have suggested stimulation in the production of undercarboxylated osteocalcin by insulin through a positive feedback

mechanism between the pancreas, adipose tissue and bone, which in turn enhances insulin production and sensitivity (Zanatta et al., 2014).

Combined, these mechanisms may explain the effect of warfarin in lowering the blood glucose level when used with sulfonylureas concurrently, especially with prolonged exposure and more prolonged diabetes. However, warfarin has also been associated with an increased risk of hypoglycaemia when given with metformin concomitantly (Nam et al., 2018), which may support the previous hypothesis that warfarin may have a primarily hypoglycaemic effect, instead of drug-drug interaction with sulfonylureas (Yamagishi, 2019). However, warfarin's effects on blood sugar have not previously been studied in human studies (Booth et al., 2013), and future research is needed to elucidate the mechanisms of this drug interaction.

8.7.3 Meaning of the study

Several important drug references have warned that warfarin may have some drug interactions when given with sulfonylureas. However, this possible drug interaction has not been studied extensively or appreciated in the literature. My study provides the first evidence for this drug interaction of two widely used medications in the UK, and it is also consistent with the findings from the previous studies in the US.

8.7.4 Implications for practice and research

OACs treatment is likely to be indicated for old age patients with T2DM (Alwafi et al., 2020b). Patients with T2DM receiving these medications are older and more susceptible to metabolic and drug interaction. Besides this, patients with T2DM are likely to suffer from AF and other comorbidities when they are older (Alwafi et al.,

2020c), and therefore to be at risk of polypharmacy and drug-drug interactions (Mallet et al., 2007). Doctors and clinical pharmacists must be vigilant when prescribing warfarin with sulfonylureas and must be alert to both immediate and delayed-onset hypoglycaemia or bleeding when prescribing this drug combination. Clinical surveillance, frequent blood glucose measurements, INR monitoring, diet changes and patient education may be necessary to reduce the risk of hypoglycaemia or bleeding if patients are prescribed these medications together (Wolpert, 2007, Snipelisky and Kusumoto, 2013). The National Quality Forum in the United States has some recommendations regarding warfarin treatment; for example, patients receiving warfarin with anti-infective medications should have some specific measures including INR testing within three to seven days of starting both medications (Centers for Medicar and Medicaid Services, 2020). Similar measures may be applied to patients receiving warfarin and sulfonylureas.

Additionally, given that DOACs are widely available nowadays, these medications may be an alternative therapeutic when OACs and sulfonylureas are indicated in patients with T2DM. DOACs have a more predictable pharmacokinetic profile and have less drug-drug interactions (Melkonian et al., 2017). However, they are more expensive than warfarin (Melkonian et al., 2017) and in many cases, warfarin remains the treatment of choice for many patients. In such cases, where warfarin is still prescribed, other OHAs such as metformin, SGLT2 and GLP-1 may be an alternative treatment for patients requiring both OACs and OHAs in their management plan.

The findings of this study have implications for further research in this area. First, a potential drug-drug interaction between warfarin and sulfonylureas is identified.

However, no clinical human trials have previously investigated this association or reported such incidents and therefore, future studies are needed to confirm this association, especially since warfarin and sulfonylurea are widely used worldwide and in patients with T2DM (Alwafi et al., 2020b, Sharma et al., 2016). This research has also highlighted a possible protective effect of DOACs against hypoglycaemia when prescribed with sulfonylureas; however, the sample size was small, and I did not have a long follow-up time. Therefore, considering these results in the context of the currently available literature, I underline the need for future research with a longer follow-up time, and large sample sizes to examine the association of DOACs and sulfonylureas and the risk of hypoglycaemia or bleeding in patients with T2DM.

8.7.5 Strength of the study

The study has several strengths and results should be interpreted in the context of these strengths. First; this study used the cohort design, which is one of the top-level evidence-based research designs in medicine (Burns et al., 2011), and it also enabled us to examine multiple exposures and outcomes (Mann, 2012). Second, this study had a long follow-up period compared to the previous studies that published data from the US (Nam et al., 2018, Romley et al., 2015). Third, this study used data from large healthcare databases which have clinical and prescribing data of more than 15 million cumulative patients, covering approximately 6.0% of the UK population (Blak et al., 2011), and I included more than 400,000 patients with T2DM. It is, therefore, reasonable to assume that the findings are generalised and may broadly reflect real-world practice in the UK. Fourth, I used an established algorithm to identify patients with T2DM, and to minimise the misclassification of type of diabetes (Alwafi et al.,

2020b, Alwafi et al., 2020c). Fifth, the study filled some of the limited knowledge gaps of previous studies in the US by investigating the association of concurrent use of OACs and sulfonylureas and the risk of hypoglycaemia, and the study included important risk factors for hypoglycaemia and/or bleeding in the analysis such as; social deprivation, smoking, alcohol and BMI. Sixth, I used propensity score matching and weighting methods, which are powerful statistical methods used to control for the confounders between the exposure and comparator groups and to reduce risk of bias in observational studies (Austin, 2011). One of the advantages of PS matching is that it produces a good covariate balance in most circumstances (Austin, 2011), while the IPWT can create a pseudo population with perfect covariate balance, and it retains data without a huge loss in sample size (Austin, 2011). In this study, I used the PS matching in the main analysis; however, to confirm the robustness of the results, I also used the IPWT in the sensitivity analysis. Some of the advantages and disadvantages of using the different types of PS are listed in Table 31. In addition, I conducted several sensitivity analyses that suggest the results are robust, including multiple prescriptions grace periods, IPWT and multiple imputations.

Table 31. Advantages and disadvantages of different types of propensity score methods

Analysis method	Advantage	Disadvantage
Stratification	• Retains data from all study participant • Provides effect estimates for every stratum	• May not account for strong confounding
Matching	• Provides excellent covariate balance	• Some patients are unmatched leading to information excluded from the analysis

	• Simple to analyse, present and interpret	
Inverse probability treatment weighting	• Retains data from all study participant • Simple to analyse, present and interpret • Creates an artificial pseudo population with perfect covariate balance	• Can be unstable when extreme weights exist
Covariate adjustment	• Performed well • Analyses the entire study population	• Subject to residual and unmeasured confounding • This method is no longer considered best practice

8.7.6 Limitations

This study has some limitations. First, this study is an observational cohort study, and unlike RCTs, the possibility of confounding may still have remained (Austin, 2011). Second, due to the emergency nature of the outcomes of interest in this study (hypoglycaemia and bleeding), there could be a limitation of the study as THIN only provides information in the primary care setting, and I did not have access to hospital data. Also, mild hypoglycaemia is less complicated and can be treated easily with the administration of any source of glucose including juice or food, and, in many cases, it is self-managed by the patients at home. Therefore, patients may not report such events to the doctors, and this could lead to underestimations of the cases. Third, medication use was not directly measured, and since warfarin doses are adjusted according to the INR, the GP record may not be completely accurate; and I did not have data for INR levels, which is potentially informative during the prescribing of warfarin. In addition, THIN is an administrative database and therefore, data on medication adherence, the actual ingestion of medications or diet is lacking. However,

I tackled this by conducting a sensitivity analysis to account only for prescription refills of fewer than 90 days.

8.8 Conclusion

In summary, the study found that warfarin was associated with an increased risk of hypoglycaemia and bleeding when given concomitantly with sulfonylureas in patients with T2DM. The results of the study provide real-world evidence of possible drug-drug interactions and answer the hypothesis of this PhD project about the safety of the concurrent use of warfarin and sulfonylureas. In addition, this research found no evidence of an increased risk of hypoglycaemia when DOACs are prescribed with coexistent sulfonylureas. The decision to prescribe warfarin with coexistent sulfonylureas to patients with T2DM should be carefully evaluated in the context of other risk factors of hypoglycaemia or bleeding, and the availability of alternative medications. Future studies are needed to validate the finding of the protective effect of DOACs and sulfonylureas on hypoglycaemia/bleeding on larger sample size and longer follow-up periods.

8.9 Context of this chapter in overall work

The study design and methods used in this chapter enabled us to investigate the research question of this PhD thesis. The findings of this study identified important adverse events such as hypoglycaemia and bleeding when two common medications (warfarin and sulfonylureas) are concurrently used in patients with T2DM. These results are in line with previous large observational studies. Several implications for practice and research have been also provided in this chapter.

Chapter 9 Overall Discussion and Conclusion

9.1 Chapter overview

This chapter highlights the main findings from this PhD work, which explored the drug utilisation and safety of the use of oral anticoagulants (OACs) among patients with type 2 diabetes mellitus (T2DM). The previous chapters' results are summarised to provide the key information and implications for both clinical practice and future research. The strengths and limitations of this research are evaluated prior to the overall conclusion.

The current PhD research explored the drug utilisation and safety of the use of OACs medications among patients with diabetes using different study designs. Firstly, a systematic review was conducted to investigate the prevalence and risk factors of hypoglycaemia among patients with diabetes and to identify gaps in the knowledge (Chapter two). The systemic review identified multiple research gaps, including a possible increased risk of hypoglycaemia when sulfonylureas and OACs (warfarin) are used concurrently among patients with T2DM. This was followed by investigating the trends in OACs prescribing in patients with T2DM, and to examine the amount of problem as an initial step in the evaluation of the safety study (Chapter five). This study highlighted an increasing trend in the prevalence of OACs among patients with T2DM, and it also demonstrated that atrial fibrillation is the main indication for OACs prescribing in patients with T2DM. This was followed by two studies to evaluate the epidemiology and treatment of a clinically important and prevalent disease among the diabetic population. These studies aimed to explore the incidence and prevalence of AF in patients with T2DM and to investigate the patterns and factors associated with OACs therapy prescribing in AF patients with T2DM (Chapter six and seven). Finally,

I assessed the safety of the concurrent use of OACs medications and sulfonylureas in patients with type 2 diabetes as there is a potential drug-drug interaction between these two medications which was reported in previous literature (Chapter eight). This study which used a cohort study design aimed to investigate the safety of OACs in patients with diabetes concerning the incidence of hypoglycaemia and bleeding.

9.2 Summary of the main findings

This PhD research evaluated the drug utilisation and safety of the use of OAC medications among patients with T2DM. To achieve the aims and objectives of this PhD, I employed different study designs. The key findings of each study are described below. A summary of the main findings is shown at the end of this section in Figure 46.

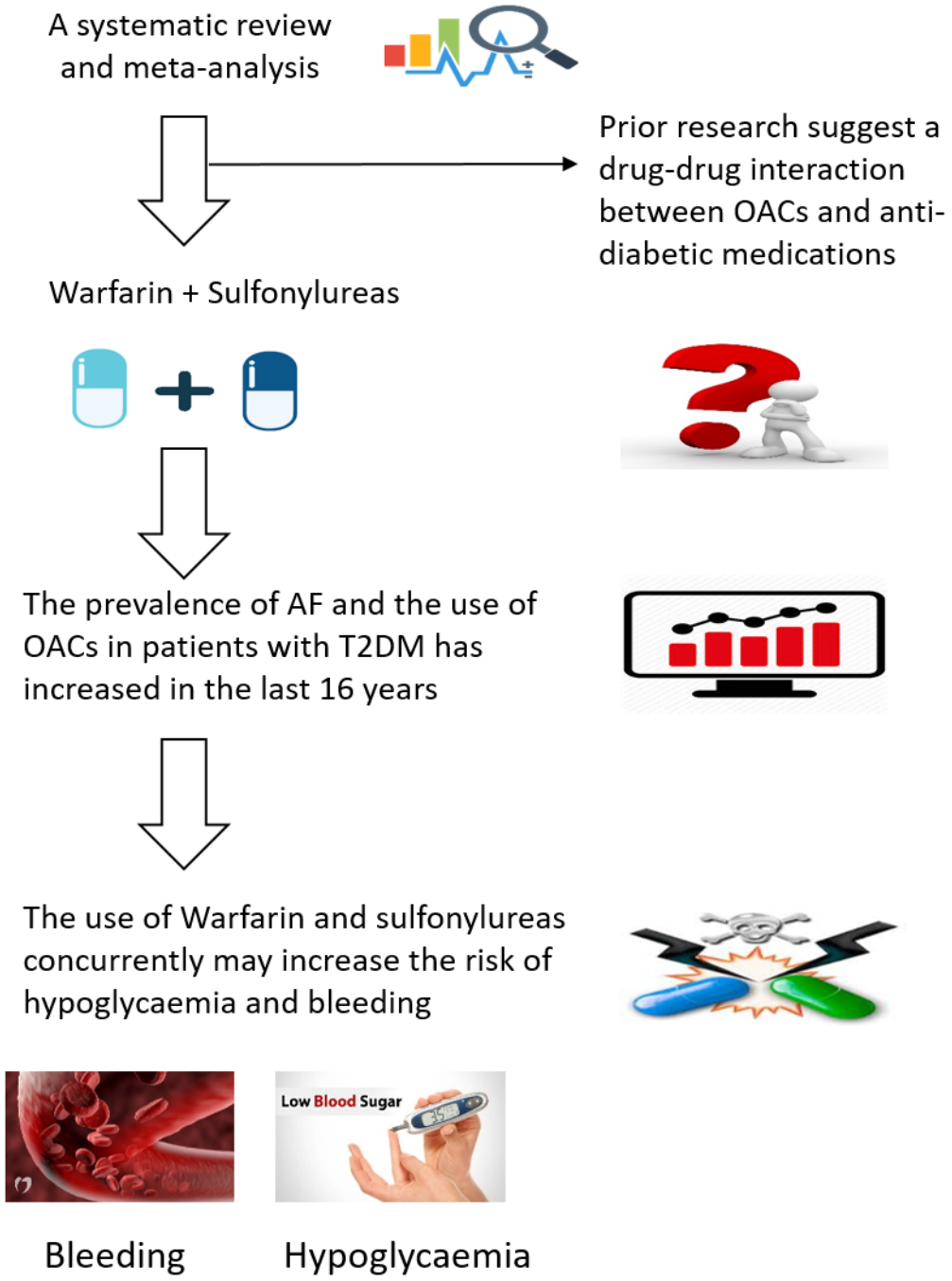

Figure 46. Summary of the main findings of this PhD work.

9.2.1 Incidence, prevalence and risk factors of hypoglycaemia in type 1 and type 2 diabetes patients treated with insulin and oral hypoglycaemic agents: a systematic review and meta-analysis (Chapter 2)

First, a systematic review and meta-analysis were conducted to understand the current evidence from the research in this area and to identify the gaps in the knowledge (Chapter 2). The study found that hypoglycaemia is a common event in patients with diabetes. The pooled average of the prevalence of hypoglycaemia in diabetes was 11.0 % (95% CI, 7.0 – 17.0) from a total of 2,462,810 individuals with diabetes. The study also highlighted different risk factors associated with hypoglycaemia among patients with diabetes, of which I was interested specifically in drug-induced hypoglycaemia related to the concurrent use of OACs and antidiabetic medications.

9.2.2 Trends in Oral Anticoagulant Prescribing in Patients with Type 2 Diabetes Mellitus: A Population-based Study in the United Kingdom (Chapter 5)

This study informed us about the number of patients with T2DM receiving OACs and the trend of prescribing of OACs in patients with T2DM in the last 15 years. It also helped us to better understand the clinical characteristics of patients with T2DM using OACs. The prevalence of OAC prescribing increased by 50.0% from 4.4 (95% CI, 4.2 – 4.6) per 100 persons in 2001 to 6.6 (95% CI, 6.5 – 6.7) per 100 persons in 2015. The prevalence of warfarin prescribing decreased by 14.0% from 98.9 (95% CI, 98.4 – 99.4) per 100 persons in 2001 to 85.1 (95% CI, 84.6 – 85.7) per 100 persons in 2015. This corresponded with increased prescribing of direct oral anticoagulants (DOACs) during the same period from 0.1 (95% CI, 0.08 – 0.23) per 100 persons in

2010 to 17.6 (95% CI, 17.1 – 18.2) per 100 persons in 2015. In addition, this study also highlighted that Atrial Fibrillation (AF) is the main indication for OAC prescribing in patients with T2DM, with around 64% of the patients who received OACs diagnosed with AF.

9.2.3 Incidence and prevalence of atrial fibrillation in patients with T2DM (Chapter 6)

The drug utilisation study (Chapter 5) showed that AF was the main indication for OAC prescribing in patients with T2DM. In addition, previous research has suggested an increased risk of AF in patients with diabetes (Movahed et al., 2005, Pallisgaard et al., 2016). However, no large population-based studies have previously investigated the incidence and prevalence of AF in patients with T2DM. Therefore, in this study, I explored the trends in the incidence and prevalence of AF in patients with T2DM (Chapter 6). I found that the prevalence of AF among patients with T2DM increased from 2.7 (95% CI, 2.5 – 2.8) per 100 persons in 2001 to 5.0 (95% CI, 4.9 – 5.1) per 100 persons in 2016.

9.2.4 Patterns and factors associated with oral anticoagulant therapy in atrial fibrillation patients with T2DM in the UK from 2001-2016 (Chapter 7)

In Chapters 5 and 6, it was suggested that AF is the main indication for OAC prescribing in patients with T2DM, and that the prevalence of AF is increasing among patients with T2DM. Patients with AF are eligible for OAC use if they meet the criteria of CHA_2DS_2-VAS score, which is recommended by the clinical guidelines in the management of AF (National Institute for Health and Care Excellence, 2014, January

et al., 2019). Diabetes is one of the essential elements in this tool (Lip et al., 2010). Therefore, patients with AF and diabetes are likely to meet the criteria for OAC prescribing. Given these factors together, in this study, I investigate the patterns and factors associated with OAC treatment in patients with AF and T2DM.

I found that OAC prescribing within 30-days of AF diagnosis increased from 21.5% in 2001 to 56.8% in 2016. Using an interrupted time series design, the results of this study also showed that OAC prescribing increased after DOAC introduction (P= <0.001); however, no immediate change was observed (P= 0.29).

9.2.5 The safety of the concurrent use of oral anticoagulant medications and sulfonylureas in patients with type 2 diabetes in the UK: A population-based cohort study (Chapter 8)

The systematic review and meta-analysis study (Chapter 2) highlighted the association between OAC use and risk of hypoglycaemia. It also stressed that this topic is under-researched, and few studies have examined this association. Therefore, in this analytical cohort study, I aimed to investigate the association between the use of OACs with co-existence of sulfonylurea and the risk of hypoglycaemia and bleeding (Chapter 8).

The study showed that warfarin is associated with an increased risk of hypoglycaemia and/or bleeding when used concurrently with sulfonylureas in patients with T2DM, (HR 1.38; 95% CI, 1.10 – 1.75) for hypoglycaemia and (HR 1.12; 95% CI, 1.01 – 1.24) for bleeding, respectively. However, I found no evidence of an association between the

concurrent use of DOACs and sulfonylureas and the risk of hypoglycaemia (HR 0.54; 95% CI, 0.27 – 1.10, P= 0.091).

9.3 Contribution to knowledge

It is well established that T2DM and cardiovascular diseases (CVDs) often coexist (Dinesh Shah et al., 2015), and that patients with T2DM are likely to receive OACs for the management of cardiac comorbidities, such as AF (Alwafi et al., 2020b). However, there was limited research that have investigated the use of OACs in patients with T2DM. The study findings presented in chapters (5, 6, 7, and 8) will be discussed in the context of the existing literature in this chapter.

9.3.1 The trend of OAC use in patients with T2DM in the UK

The results showed that OAC use in patients with T2DM increased between 2001 and 2015. These results were in line with a previous study by (Hamada and Gulliford, 2015). However, it is important to highlight that their study focused on elderly patients with diabetes (aged 80 and above). Other studies that investigated the trend of OAC use in the general AF population or sub-populations also had similar results to the results reported in this PhD. For example, two studies by (Loo et al., 2017) and (Adderley et al., 2019) highlighted that OAC use has increased since the year 2000. These authors also reported a higher trend in the use of OACs among older patients and male patients, which was also in line with my results (Loo et al., 2017, Adderley et al., 2019). Another recent study by (Mongkhon et al., 2020a) using the THIN database reported that the trend in OACs use in patients with AF and dementia

increased between 2000 and 2015. The authors also reported a higher trend among the elderly population, which was also in line with the results of my PhD work.

AF is a disease of the elderly population (Chen et al., 2018) and therefore, it is expected that older patients have a higher prevalence of receiving OAC medications. In addition, patients with T2DM are more likely to suffer from diabetes complications when their blood sugar levels are uncontrolled or when they are older (American Diabetes Association, 2018a). In Chapter 7, the results showed that patients with AF and T2DM aged 65–74 were 30% more likely to receive an OAC prescription compared to patients younger than 65 years. These facts support the results showing a higher trend of OAC use in the elderly population. In Chapter 6, the results showed that the prevalence of AF increased in patients with T2DM between 2001 and 2016 (Alwafi et al., 2020c). Diabetes is a criterion for OAC use in the CHA_2DS_2-VAS score, and since AF is the main indication of OAC use as highlighted in Chapter 5, it is reasonable to expect such an increase in the trend of OAC prescribing for patients with T2DM.

The results of the drug utilisation study (Chapter 5), also showed that the prescribing of DOACs is largely replacing warfarin. These results were similar to other studies (Mongkhon et al., 2020a, Loo et al., 2017). DOACs have a safer pharmacokinetic profile, fewer drug interactions, and less frequent monitoring is required in comparison to warfarin, which may explain the changes in current practice (Vinogradova et al., 2018, Mekaj et al., 2015).

9.3.2 Underuse of OACs in T2DM

The results of Chapter 7 demonstrated that the proportion of patients with T2DM who were initiated on an OAC after AF diagnosis increased between 2001 and 2016. It also highlighted the underuse of OAC prescribing in patients with T2DM and AF, as about 44% of the study patients in 2016 did not receive an OAC within 30-days of AF diagnosis.

However, this percentage of underuse was lower after investigating the consumption of OACs after 90 days and after one year (Figure 38). These results are also in line with previous studies that highlighted this issue (Rose et al., 2019a).

An explanation for this may be that doctors usually consider multiple approaches in their management of patients with AF. Some doctors may include risk-benefit assessment (Wehbe and Yadlapati, 2016), and calculation of the bleeding risk before prescribing OACs (Deirdre and Gregory, 2012). In addition, lack of adherence to guidelines or a lack of time spent in identifying and diagnosing comorbidities may also contribute to the underuse of OACs. Another important reason is that AF may present with an acute symptom (National Institute for Health and Care Excellence, 2014), and one of the main aspects in the management of AF is that patients are likely to be initiated on OACs in the emergency department when they are first diagnosed with AF. Transferring the data from different healthcare settings may not reflect the actual utilisation of OACs at the primary care level, especially in the early stages of diagnosis (Wang et al., 2016).

9.3.3 The safety of the use of OACs in patients with T2DM

Doctors and researchers in previous studies have expressed their concern about the safety of the use of warfarin in patients with T2DM (Yamagishi, 2019). These concerns arise from the fact that warfarin is a problematic medication, with multiple drug interactions (Ament P, 2000), increased risk of bleeding (Snipelisky and Kusumoto, 2013), and has a narrow therapeutic window (Teklay et al., 2014). The results in the analytical cohort study (Chapter 8), showed that warfarin could increase the risk of hypoglycaemia and bleeding when given concurrently with sulfonylureas. These results may be justified by preclinical theories involving CYP2C9 interactions (Ament P, 2000) and displace plasma protein bindings (Triplitt, 2006). This also supports results from previous studies (Nam et al., 2018, Romley et al., 2015). However, the exact mechanism of this possible interaction between warfarin and sulfonylureas remains unclear, and further research is needed.

The results from my study showed that the risk of developing hypoglycaemia was lower for patients receiving DOACs with sulfonylureas compared to patients receiving sulfonylureas alone (HR 0.54; 95% CI, 0.27 – 1.10), however, this was not statistically significant, P= 0.091. While future research with a larger sample size and longer follow-up time is needed, other studies have also demonstrated that DOACs are safer in patients with T2DM (Lip et al., 2020).

Since the introduction of DOACs, there has been a clear shift towards DOACs compared to warfarin. In addition, the results of Chapter 5 support the growing evidence concerning the increase in the prescribing of DOACs compared to warfarin

in the last few years. Yet, warfarin is largely prescribed for the management of AF (Alalwan et al., 2017, Alwafi et al., 2020b, Mongkhon et al., 2020a). DOACs have fewer drug interactions and more predictable pharmacokinetics compared to warfarin (Mekaj et al., 2015). Previous large randomised controlled trials (RCTs) demonstrated better or non-inferior results on the safety and efficacy of DOCAs compared to warfarin in patients with T2DM (Ezekowitz et al., 2015, Bansilal et al., 2015, Brambatti et al., 2015). These, together with the real-world findings of this thesis, suggest that DOACs may be a safer option when prescribing OACs for patients with T2DM, especially in the setting where patients with T2DM are prescribed sulfonylurea medications.

9.4 Strengths and limitations

This section emphasises the overall strengths and limitations of this PhD project. The strengths and limitations of each study have been stated at the end of Chapters 2, 5, 6, 7 and 8. There are three important aspects which are key strengths of this PhD work, the first being the employment of different study designs and advanced statistical methods to investigate the drug use and the safety of the use of OACs among patients with T2DM. In this thesis, I analysed the data using traditional regression analysis. However, I also applied advanced statistical methods, such as propensity score matching, inverse probability weighting and multiple imputations, to address the known confounding and missing data issues. I also used several methodological concepts, such as the active comparator design and the interrupted time-series design. The reason for using multiple statistical approaches was to make sure that the results remained consistent across the different methods. Second, all studies were conducted using a large primary care database, which was representative of the actual clinical

practice of the UK population, and it provided insight into real-world practice. Third, all studies were the first of their kind in the UK to answer some crucial questions from actual clinical practice and to highlight under-researched areas for future work.

This PhD work has some clinical and methodological limitations to acknowledge. In the meta-analysis study, there was a high level of heterogeneity between studies, which was not explained by any of the variables stratified in the subgroup analysis. However, high statistical heterogeneity is frequent in meta-analyses of prevalence compared to meta-analyses of binary outcomes (Alba et al., 2016), and the high level of heterogeneity is likely to be due to study characteristics that were not measured or reported in the original citations (Barendregt et al., 2013). Furthermore, a major limitation in systematic reviews and meta-analysis is publication bias (Sutton et al., 2000), where studies with significant results are more likely to be published compared to studies with non-significant results (Hopewell et al., 2009). However, to address this issue, I used the funnel plot test to present the data graphically and to detect the existence of publication bias. The results showed evidence of asymmetry and publication bias. However, it is important to highlight that, unlike studies that report associations or measure an outcome risk, burden of diseases studies are likely to be descriptive studies or part of secondary objectives of the research and therefore, it is reasonable to assume that there is no under-reporting. In this thesis, I focused on the safety of the concurrent use of OACs and sulfonylureas, and I did not examine other types of oral hypoglycaemic agents. This is because, as highlighted in Chapter 2, section 2.7.7.2.2, previous literature from the United States suggested drug-drug interactions between warfarin and sulfonylureas and therefore, this PhD project aimed to investigate this association in the UK setting. Adherence and actual ingestion of

medications are one of the limitations of electronic health record databases, which may bias the findings of this study. However, I conducted several sensitivity analyses, including accounting only for prescription refills of less than 90-days in the analytical cohort study (Chapter 8). Finally, one of the limitations of observational study designs is the lack of randomisation and the challenges of controlling for residual confounders (Austin, 2011).

9.5 Implications for clinical practice and public health

The findings of this PhD work focused on a high-risk population. This enabled the researcher to provide implications for practice that addressed the research question from multiple dimensions.

First, the results of the systematic review showed that hypoglycaemia is a common event (Alwafi et al., 2020a); however, many of the risk factors that were identified to increase the risk of hypoglycaemia are preventable. Doctors and health care practitioner (HCPs) must be aware of such predictors. HCPs should be cautious when prescribing intensive antidiabetic therapy or when prescribing medications that increase the risk of hypoglycaemia (Naser et al., 2018), especially when managing patients with multiple comorbidities and polypharmacy (McCoy et al., 2020). In addition, HCPs are strongly encouraged to educate patients about the symptoms of hypoglycaemia and how to self-manage any hypoglycaemic event (Naser et al., 2019). Such practice is associated with better disease control, and less possibility of suffering from its adverse events (Tomky, 2005).

Second, the criteria used in this research to help in identifying patients with T2DM in large electronic health care database may have a broader application beyond the studies in this thesis. It can be used in future database studies to help in minimising the under-reporting and misclassification of T2DM.

Third, the findings provided some timely and useful updates of primary care practice on the prescribing of OAC medications in patients with T2DM. The results of this thesis reflect the actual clinical practice in the UK and adherence to the guidelines. It emphasises that the clinical practice in the UK is mainly driven by science and scientific guidelines. Despite this, we also identified underuse of OACs in patients with T2DM, which may further inform scientific committees and policy guidelines.

Fourth, the study examining trends in the incidence and prevalence of AF in T2DM provided important information regarding the rising prevalence of AF in patients with T2DM in the UK. This is a major public health concern, especially the fact that both diseases are associated with significant comorbidities and mortality (National Institute for Health and Care Excellence, 2014, National Institute for Health and Care Excellence, 2015). Additional economic burdens and strains on the National Health Service (NHS) are likely to arise if these two conditions continue to increase. It is, therefore, important to investigate the current practice of the management of patients with T2DM to identify the possible need for further training and support in clinical practice and research to ensure effective management for patients.

Finally, this thesis evaluated the safety of the concurrent use of commonly prescribed medications, which enabled the researcher to identify a major adverse event that was also avoidable. The results provided some suggestions for improvement in order to

increase the safety of prescribing of OACs for patients with T2DM. HCPs must be extra vigilant when prescribing warfarin with sulfonylureas in patients with T2DM as it is associated with a higher risk of hypoglycaemia and bleeding. Frequent monitoring, benefit-risk assessment, medications review, optimising treatment and patient awareness should be the approaches when prescribing these medications concurrently (Hughes, 2008, Gray et al., 2018). In addition, alternative medications with a lower risk of hypoglycaemia, such as new oral hypoglycaemic agents should be considered during the prescribing of OACs for patients with T2DM. The findings of this PhD project provide important information for scientific committees and guidelines on this association, especially because it involved a large sample size of patients and it was consistent with previous studies.

9.6 Implications for future research

Several gaps in the knowledge and suggestions for future research have been identified in this PhD project. However, due to limited time and funding, it was not feasible to answer all of these questions in my PhD work.

The results of the systematic review highlighted multiple gaps in the literature on the risk factors of hypoglycaemia, which can be investigated in future research. In my PhD work, I only focused on the safety of OACs in patients with T2DM.

The findings of Chapter 6 demonstrated an increase in the prevalence of AF in patients with T2DM. However, the factors associated with the development of AF among patients with T2DM remain unclear, and future studies are needed. In addition, future research should examine the factors associated with under-prescribing of OACs in

patients with T2DM and AF. Studies should also focus on the individual and clinical practice level, for example, studies on the attitude and perception of HCPs during the management of patients with T2DM and AF, and to examine factors that influence prescribing decisions of doctors.

In this thesis, I examined the safety of the use of OACs in patients with T2DM. However, my research focused on the safety of the concurrent use of OACs and sulfonylureas. Future studies on the safety of the concurrent use of OACs and other antidiabetic medications are warranted, especially the fact that, as highlighted in the drug utilisation study (Chapter 5), OAC prescribing is common in patients with T2DM.

Cost-effectiveness is also an important element in the management of disease and making choices of medications use, especially when there are several choices of treatment (Hill, 2012). However, this has not been examined in this PhD work.

Another area of future research is the long-term safety of DOACs in patients with T2DM, which I was not able to study because of the small sample size and the short follow-up period, as they were only authorised for use in late 2011.

RCTs are the gold standard of methods to investigate the safety and effectiveness of medication use. Future RCTs to investigate the long-term effectiveness of the concurrent use of OACs and OHAs against stroke or myocardial ischemia are also needed.

9.7 Conclusion

This PhD work contributed to the current knowledge of the prescribing pattern and safety of the use of OACs among patients with T2DM. In this thesis, I found that hypoglycaemia is a very common adverse event among patients with type 1 diabetes and type 2 diabetes. The findings from my PhD work also showed that there has been a clear increase in the prescribing of OACs and in the prevalence of AF among patients with T2DM over the past 16 years. Since the introduction of DOACs into the market in 2011, there has been a significant increase in the rate of OAC prescribing in patients with T2DM, and there has been a clear shift in the prescribing of DOACs instead of warfarin. These results from the initial studies laid the foundation for the main focus of this thesis, which was the evaluation of the safety of OACs in patients with T2DM.

The findings from this thesis indicated several research gaps for future research, specifically concerning the factors associated with underuse of OACs and concerning the safety of DOAC use in patients with T2DM. It also highlighted an important and preventable adverse event when two commonly prescribed medications are used together. Healthcare providers should consider these factors when prescribing OACs for patients with T2DM in order to provide safer and better outcomes during their clinical management.

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Appendices

Appendix 1. MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	89-91
2	Hypothesis statement	91
3	Description of study outcome(s)	94
4	Type of exposure or intervention used	91
5	Type of study designs used	91
6	Study population	93,94
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	92
8	Search strategy, including time period included in the synthesis and key words	92
9	Effort to include all available studies, including contact with authors	91-94
10	Databases and registries searched	92
11	Search software used, name and version, including special features used (eg, explosion)	92
12	Use of hand searching (eg, reference lists of obtained articles)	92
13	List of citations located and those excluded, including justification	Figure 8, Appendix 4
14	Method of addressing articles published in languages other than English	NA
15	Method of handling abstracts and unpublished studies	NA
16	Description of any contact with authors	NA
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	91-94
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	95-97
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	95-97
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	95-97
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	96
22	Assessment of heterogeneity	97
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	97
24	Provision of appropriate tables and graphics	Figures 8-20, Tables 3-5, Appendix 4
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figure 8-20

26	Table giving descriptive information for each study included	Tables 4,5 and Appendix 4
27	Results of sensitivity testing (eg, subgroup analysis)	123-137
28	Indication of statistical uncertainty of findings	115

Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	138-139
30	Justification for exclusion (eg, exclusion of non-English language citations)	Figure 8
31	Assessment of quality of included studies	102-103, Table 3
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	NA
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	177-188
34	Guidelines for future research	185-187
35	Disclosure of funding source	NA

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.200

Appendix 2. PROSPERO protocol of the systematic review and meta-analysis

Incidence, prevalence and risk factors of hypoglycemia in type I and type II diabetes mellitus individuals treated with insulin and oral hypoglycemic agents; a systematic review

Hassan Alwafi, Alaa Al sharif, Abdullah Naser, Li Wei, Simon Bell, Jenni Ilomak, Gang Fang, Mansour Al Metwazi, Ian Wong

Citation

Hassan Alwafi, Alaa Al sharif, Abdullah Naser, Li Wei, Simon Bell, Jenni Ilomak, Gang Fang, Mansour Al Metwazi, Ian Wong. Incidence, prevalence and risk factors of hypoglycemia in type I and type II diabetes mellitus individuals treated with insulin and oral hypoglycemic agents; a systematic review. PROSPERO 2017 CRD42017077013 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017077013

Review question

What are the incidence, prevalence and risk factors of hypoglycemia in type I and type II diabetes mellitus individuals treated with insulin and oral hypoglycemic agents?

Searches

PubMed, Embase and Cochrane Library will be searched for observational studies looking at hypoglycemia in humans with type I and type II diabetes mellitus.

Types of study to be included

1- Observational studies will be included. 2- Published as full-text papers.

Condition or domain being studied

We will study hypoglycemia in type I and type II diabetes mellitus individuals.

Participants/population

Inclusion criteria
1- The study population is in type I, type II or mixed type I and II diabetes mellitus individuals, sampled from any primary, secondary or tertiary care settings, without any restrictions on the ethnic groups or sociodemographic characteristics.
2- Reported hypoglycemia as primary/secondary objective (an outcome of interest).
Exclusion criteria:
1. Interventional studies, case reports, case series, narrative reviews, commentary, editorial, book chapters, other summaries, and duplicate publications.
2. Gestational diabetes
3. Animal studies.

Intervention(s), exposure(s)

Anti-diabetic medications and/or non-pharmacological treatment, if applicable.

Comparator(s)/control

No control group.

Context

Primary outcome(s)

Hypoglycaemia incidence / prevalence.

Secondary outcome(s)

Title

Incidence, prevalence and risk factors of hypoglycaemia in type I and type II diabetes mellitus individuals treated with insulin and oral hypoglycaemic agents; a systematic review

Citation

Hassan Alwafi, Alaa Al sharif, Abdullah Naser, Li Wei, Simon Bell, Jenni Ilomak, Gang Fang, Mansour Al Metwazi, Ian Wong. Incidence, prevalence and risk factors of hypoglycaemia in type I and type II diabetes mellitus individuals treated with insulin and oral hypoglycaemic agents; a systematic review. PROSPERO 2017 CRD42017077013 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42017077013

Review question

What are the incidence, prevalence and risk factors of hypoglycaemia in type I and type II diabetes mellitus individuals treated with insulin and oral hypoglycaemic agents?

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2- Reported hypoglycaemia as primary/secondary objective (an outcome of interest).

Exclusion criteria:

1. Interventional studies, case reports, case series, narrative reviews, commentary, editorial, book chapters, other summaries, and duplicate publications.

2. Gestational diabetes

3. Animal studies.

Intervention(s), exposure(s)

Anti-diabetic medications and/or non-pharmacological treatment, if applicable.

Comparator(s)/control

No control group.

Main outcome(s)

Hypoglycaemia incidence / prevalence.

Additional outcome(s)

Hypoglycaemia risk factors.

Risk of bias (quality) assessment

The Newcastle-Ottawa Scale (NOS) for the assessment of the methodological quality of the included studies and minimization of bias will be used. Two independent reviewers (H.A and A.A) will assess the studies selection. Two independent reviewers (H.A and A.A) will undertake quality assessment and allocate stars for adherence to the pre-specified criteria. We will classify studies into a low, medium and high risk of bias. We will consider the risk of bias in the study while synthesizing available evidence. We will perform the sensitivity analysis by including and excluding studies with high risk of bias.

Strategy for data synthesis

If studies are sufficiently homogeneous in terms of design, we will conduct meta-analyses. Study results will be summarized using prevalence and incidence rates and the association of risk factors with hypoglycaemia will be reported as relative risk or odds ratio at 95% confidence interval. If required, sensitivity analysis will be conducted to assess heterogeneity by patient characteristics (age, gender) and publication type (risk of bias).

A systematic narrative synthesis will be provided with information presented in the text and tables to summarize and explain the characteristics and findings of the included studies.

Analysis of subgroups or subsets

None planned.

Organisational affiliation of the review

University College London

Review team members and their organisational affiliations

Dr Hassan Alwafi. University College London

Mrs Alaa Al sharif. University College London

Mr Abdullah Naser. University College London

Dr Li Wei. University College London

Dr Simon Bell. Monash University

Dr Jenni Ilomak. Monash university

Dr Gang Fang. University of North Carolina at Chapel Hill

Dr Mansour Al Metwazi. King Saud University

Professor Ian Wong. University College London

Type and method of review

Systematic review

Anticipated or actual start date

24 July 2017

Anticipated completion date

01 December 2017

Funding sources/sponsors

None

Conflicts of interest

None known

Language

English

Country

England

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Diabetes Mellitus, Type 2; Humans; Hypoglycaemia; Hypoglycaemic Agents; Incidence; Insulin; Prevalence; Risk Factors

Date of registration in PROSPERO

16 October 2017

Date of first submission

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	No	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Appendix 3. Search strategy for the systematic review and meta-analysis

Embase database search strategy

Key word	Mesh terms	Terms as free text
Diabetes	Diabetes mellitus	Diabetes Diabetes Complications [MeSH Descriptor] Diabetic
Diabet*		
Hypoglycaemia	Experimental hypoglycaemia	Experimental hypoglycaemia, Experimentally induced hypoglycaemia, Experimentally induced hypoglycaemia
	hypoglycaemia	conditioned hypoglycaemia, conditioned hypoglycaemia, hypoglycaemia, hypoglycaemic reaction , hypoglycaemic reaction, insulin reaction, ketotic hypoglycaemia, ketotic hypoglycaemia, late hypoglycaemic syndrome, reactive hypoglycaemia, reactive hypoglycaemia, spontaneous hypoglycaemia, spontaneous hypoglycaemia
	Insulin hypoglycaemia	hypoglycaemia,insulin, hypoglycaemia,insulin dependent, hypoglycaemia ,insulin, hypoglycaemia ,insulin dependent, insulin hypoglycaemia
	Nocturnal hypoglycaemia	Nocturnal hypoglycaemia

1- Diabetes , 2- Diabetes mellitus, 3- Diabetes Complications, 4- Diabetic, 5- Diabet*

6- 1 OR 2 OR 3 OR 4 OR 5

7- Hypoglycaemia, 8- Experimental hypoglycaemia, 9- Experimental hypoglycaemia , 10- Experimentally induced hypoglycaemia, 11- Experimentally induced hypoglycaemia , 12- Hypoglycaemia , 13- Conditioned hypoglycaemia, 14- Conditioned hypoglycaemia , 15- hypoglycaemic reaction, 16- Hypoglycaemic reaction, 17- insulin reaction, 18- ketotic hypoglycaemia, 19- ketotic hypoglycaemia , 20- Late hypoglycaemic syndrome, 21- Reactive hypoglycaemia, 22- Reactive hypoglycaemia , 23- Spontaneous hypoglycaemia, 24- Spontaneous hypoglycaemia , 25- Insulin hypoglycaemia , 26- hypoglycaemia, insulin, 27- hypoglycaemia, insulin dependent, 28- hypoglycaemia , insulin, 29- hypoglycaemia , insulin dependent, 30- Insulin hypoglycaemia, 31- Nocturnal hypoglycaemia

32- 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31

33- Incidence, 34- Incidence rate, 35- Rate, incidence

36- 33 OR 34 OR 35

37- Prevalence, 38- Prevalence study

39- 37 OR 38

40- Risk factor, 41- Relative risk, 42- Risk factors

43- 40 OR 41 OR 42

44- 43 OR 36 OR 39

45- odds ratio, 46- rate risk

47- 45 OR 46

48- 44 OR 47

49- 6 AND 32 AND 48

Total number of studies identified in Embase: 11,410

PubMed database search strategy

	Key words	Mesh terms	Terms as free text	Search
A	Incidence	Incidence	Incidences	("Incidence"[Mesh]) OR incidence*
B	Prevalence	Prevalence	Prevalences	("Prevalence"[Mesh]) OR prevalence*
C	Risk factor	Risk factor	Factor, Risk, Factors, Risk Risk Factor, Population at Risk, Risk, Population at Populations at Risk Risk, Populations at	(((((((("Risk Factors"[Mesh]) OR risk factor*)) OR Factor, Risk) OR Factors, Risk) OR Risk Factor) OR Population at Risk) OR Risk, Population at) OR Populations at Risk) OR Risk, Populations at
D	Rate risk		Rate risks	Rate risk OR rate risks
E	Relative risk		Relative risks	(relative risks) OR relative risk
F	Odds ratio		Odds ratios	(odds ratios) OR odds ratio
G	hypoglycaemia	Hypoglycaemia	Postprandial Hypoglycaemia Hypoglycaemia , Postprandial Reactive Hypoglycaemia Hypoglycaemia , Reactive Fasting Hypoglycaemia Hypoglycaemia , Fasting	(((((((("Hypoglycaemia "[Mesh]) OR hypoglyc*) OR Postprandial Hypoglycaemia) OR Hypoglycaemia , Postprandial) OR Reactive Hypoglycaemia) OR Hypoglycaemia , Reactive) OR Fasting Hypoglycaemia

			Postabsorptive Hypoglycaemia Hypoglycaemia , Postabsorptive	) OR Hypoglycaemia , Fasting) OR Postabsorptive Hypoglycaemia) OR Hypoglycaemia , Postabsorptive
H	episode			episode*
I	event			event*
J	diabetes	Diabetes mellitus		(diabet*) OR "Diabetes Mellitus"[Mesh]

1- (A) OR (B) OR (C) OR (D) OR (E) OR (F) OR (H) OR (I)
2- G AND 1
3- J AND 2

Total number of studies identified in PubMed: 23,591

Appendix 4. Characteristics of all studies included in the systematic review and meta-analysis

Author	Country	Study design	Sample size	Sample Source	Diabetes type	Mean age	Sex M/F	Diabetes duration	Treatment regimens	Prevalence data	Incidence data	Risk factors	Definition of hypoglycaemia
(Jabbar et al., 2017)	Multinational	Retrospective	3250	Self-reported	T2DM	54.7	M48.5%	NA	NA	Yes	No	No	NA
(Akirov et al., 2018)	NA	Prospective	5301	Self-reported	Both types of diabetes	73 ± 13	M 51%	12 ± 11	A combination of oral or Insulin	Yes	No	No	Hypoglycaemia and serious hypoglycaemia were defined as at least one blood glucose measurement ≤ 70 and < 54 mg/dl.
(Lee et al., 2017)	North America	Prospective	1206	Self-reported	T2DM	64	54%	NA	NA	No	No	Yes	ICD codes
(Allen et al., 2001)	North America	Retrospective	415	Self-reported	T1DM	NA	M 51.3,% F 48.7 %	NA	Insulin	No	No	Yes	Frequent hypoglycaemia was defined as approximately two to four times per week or more, and severe hypoglycaemia was defined as loss of consciousness during an insulin reaction.
(Aung et al., 2012)	Europe	Retrospective	1066	Self-reported	T2DM	67.9 ± 4.2	M 51%	8.1 SD ±6.5	A combination of oral and insulin	Yes	No	No	Severe hypoglycaemia was defined as self-reported episodes of hypoglycaemia requiring external help.
(Barkai et al., 1998)	Europe	Prospective	130	Self-reported	T1DM	NA	M 52.3 %	NA	Insulin	No	Yes	No	A hypoglycaemic event was defined as an episode which was accompanied by typical common symptoms of hypoglycaemia and which was corrected by oral carbohydrate, parenteral glucose or glucagon therapy, irrespective of whether hypoglycaemia had been demonstrated by blood glucose measurement. Severe hypoglycaemia was defined as any event requiring the assistance of another person for treatment
(Basu et al., 2017)	North America	Retrospective	560,503	Database	NA	49.7	M 48.7%, F 51.3%	NA	NA	No	No	Yes	ICD codes
(Berkowitz et al., 2012)	North America	Retrospective	14,357	Self-reported	T2DM	58 SD ± 10	M 51%, F 49 %	10 SD ± 8	A combination of oral and insulin	No	No	Yes	Severe hypoglycaemia was defined as an event that required assistance from another person who actively administered carbohydrate, glucagon or other resuscitative actions and was associated with either a blood glucose level less than 3.9 mmol⁄l (< 70mg⁄dl) or prompt recovery after restoring normoglycaemia

(Birkebaek et al., 2017)	Europe	Retrospective	8806	Database	T1DM	11	M 52%	5.1±3.1 years	NA	No	Yes	No	SH was defined in accordance with the guidelines of the International Society of Pediatric and Adolescent Diabetes as an event associated with severe neuroglycopenia resulting in coma or seizure and requiring parenteral therapy (glucagon or intravenous glucose)
(Pedersen-Bjergaard et al., 2003)	Europe	Prospective	171	Self-reported	T1DM	44 ± 12	M 54%	19 ±11 years	Insulin	No	Yes	Yes	Severe hypoglycaemia was defined as hypoglycaemic episodes with a need for assistance from other persons in order to restore glucose levels.
(Blasetti et al., 2011)	Europe	Prospective	195	Database	T1DM	13.9 ± 6.6	M 51.79 %	NA	Insulin	No	Yes	No	< 50 mg/dl associated with altered status of consciousness including seizure or coma or confessional state
(Bognetti et al., 1997)	Europe	Retrospective	187	Self-reported	NA	NA	M 56.1%	NA	Insulin	Yes	Yes	No	NA
(Borzi et al., 2016)	Europe	Retrospective	3,167	Self-reported	T2DM	75.2 SD ± 11.2	M 50.7%,F 49.3 %	NA	NA	No	No	Yes	Hypoglycaemic episodes had to be symptomatic with a blood glucose level <3.89 mmol/L and/or specific treatment for hypoglycaemia.
(ter Braak et al., 2000)	Europe	Retrospective	195	Self-reported	T1DM	Uncomplicated hyop 39 ± 12 Hypoglycemic coma 44 ± 14	NA	Uncomplicated hyop 22 SD ± 10 Hypoglycemic coma 24 SD ± 13	Insulin	No	No	Yes	SH was defined as all episodes for which help from others was required divided into uncomplicated SH (i.e., SH episodes not complicated by coma, seizure, or treatment with glucagon or intravenous dextrose) and hypoglycaemic coma (i.e., SH complicated by coma, seizure, or treatment with glucagon or intravenous dextrose)
(Bramlage et al., 2012)	Europe	Retrospective	3810	Self-reported	T2DM	NA	M 48.9%	NA	A combination of oral only	Yes	No	No	Patients with mild hypoglycaemia were defined as being with or without specific symptoms but manageable without help. These were usually detected by self-measurements of blood glucose (<2.22 mmol/l; 40 mg/dl in any case; 2.22-2.78 mmol/l or 50 mg/dl in case of symptoms) . Patients with moderate hypoglycaemia experienced symptoms of hypoglycaemia and required assistance from a second person (e.g. a relative or friend), but no attention of a medical professional was necessary. Patients with severe hypoglycaemia were seeking medical attention or were admitted to hospital because of hypoglycaemia

(Bron et al., 2012)	Europe	Retrospective	212061	Database	T2DM	53.9 ± 10.6	M 56 %	NA	A combination of oral and insulin	No	Yes	No	ICD codes
(Bruce et al., 2009)	Australia	Retrospective	302	Database	NA	NA	NA	NA	NA	No	No	Yes	Severe hypoglycaemia required ED visit or hospitalisation
(Bruderer et al., 2014)	Europe	Retrospective	130,761	Database	T2DM	61.7	NA	NA	A combination of oral and insulin	No	No	Yes	To define severe hypoglycaemia, we required one of the following records: (i) a code for hypoglycaemia requiring third party assistance; (ii) a code for hypoglycaemic coma; (iii) a code for hypoglycaemia or a blood glucose level <3.0 mmol/l followed by emergency admission to hospital or by death within 30
(Buyken et al., 1998)	Europe	Retrospective	2065	Self-reported	T1DM	32.7± 10.2	M 50.9	14.8 ±9.5 years	Insulin	Yes	No	No	Severe hypoglycaemia (requiring the help of another person)
(Cherubini et al., 2013)	Europe	Retrospective	2025	Self-reported	T1DM	12.4 ± 3.8	M 53 %	5.6 ± 3.5 years	Insulin	Yes	Yes	No	Hypoglycaemia was defined as any episode leading to hospitalisation or requiring the administration of glucagon because the patient was unconscious or had seizures
(Chou et al., 2013)	Asia	Retrospective	78, 433	NA	NA	NA	NA	NA	NA	No	No	Yes	Severe hypoglycaemia required ED visit or hospitalisation
(Alexiu et al., 2017)	North America	Retrospective	232898	Database	Both types of diabetes	NA	NA	NA	A combination of oral and insulin	No	Yes	No	Mild, moderate, and severe hypoglycaemia severity is typically defined on the basis of service use, medical setting, and/or hospitalisation
(Conceicao et al., 2017)	Europe	Retrospective	425706	Self-reported	T2DM	NA	NA	NA	A combination of oral and insulin	Yes	No	No	ER admissions
(Corsonello et al., 1999)	Europe	Retrospective	3,477	Database	Both types of diabetes	71.4	NA	NA	A combination of oral and insulin	No	No	Yes	NA
(Davis et al., 2011)	Australia	Retrospective	602	Database	T2DM	66.5 SD ± 9.9	M 51.8%	NA	NA	No	No	Yes	An episode in which a patient with a subnormal blood/plasma/ serum glucose required documented health service use (ambulance attendance, emergency department attendance, or hospitalisation) and hypoglycaemia was the primary diagnosis

(Davis et al., 2010)	Australia	Retrospective	616	Database	T2DM	6.7 ± 9.8	M 52.3%	7.7 years	NA	No	Yes	No	NA
(Davis et al., 1998)	Australia	Prospective	709	Self-reported	T1DM	12.3 ± 4.4	M 52 %	4.9 years	Insulin	No	Yes	No	Moderate hypoglycaemia defined as hypoglycaemia requiring the assistance of another person for treatment and severe hypoglycaemia as an event resulting in coma or convulsion.
(Deusenberry et al., 2012)	North America	Retrospective	692	Database	T2DM	NA	M 51.3 %	NA	Sulfonylureas	Yes	No	No	Glucose <70 mg/dl
(Dendy et al., 2014)	North America	Retrospective	5,026	Database	Both types of diabetes	67.6 SD± 13.2	M 62%, F 38%	NA	NA	No	No	Yes	Hypoglycaemia was defined as a glucose measurement < 70 mg/dL.
(Derijks et al., 2008)	North America	Retrospective	2,446	Database	Both types of diabetes	69	NA	NA	A combination of oral and insulin	No	No	Yes	NA
(Desjardins et al., 2014)	North America	Retrospective	108	Self-reported	T1DM	46.4	M 53%	NA	Insulin	No	No	Yes	NA
(Duran-Nah et al., 2008)	North America	Retrospective	282	Hospital based	T2DM	NA	M 67.6% , F 32.4%	13.7 SD ± 8.3	NA	No	No	Yes	Defined as glucose concentration less than or equal to 4 mmol/L (72 mg/dL)
(Donnelly et al., 2005)	Europe	Prospective	267	Database	Both types of diabetes	NA	NA	NA	Insulin	No	Yes	No	Patients were encouraged to use their own glucose meter to take their recording), together with the nature of the remedial action taken and whether the episode required assistance of a third party (i.e. severe hypoglycaemia
(Egger et al., 1991)	Europe	Retrospective	155	Self-reported	T1DM	12.6 SD± 4.6	NA	5.5 SD ± 4.0	NA	No	No	Yes	Grade 1, minor signs, self-management possible; grade 2, moderate signs, patient dependent on external help but no loss of consciousness; grade 3, unconscious-ness with documented low blood glucose and/or immediate response to glucose or glucagon
(Elwen et al., 2015)	Europe	Retrospective	1,156	Self-reported	Both types of diabetes	61	M 60 %, F 40 %	NA	A combination of oral and insulin	No	No	Yes	Capillary blood glucose (CBG) levels were less than 4 mmol/L at attendance of the emergency crew.

(Endo et al., 2000)	North America	Retrospective	38	Database	T2DM	6.9+ SD ± .1	M 78%, F 28%	22 SD ± 7.7	Sulfonylureas	No	No	Yes	glucose 54 mg/dL requiring intravenous glucose administration with or without concurrent therapy for longer than 12 hours were included as case patient
(Eriksson et al., 2016)	Europe	Retrospective	52,760	Database	T2DM	64.4 SD ± 11.8	M 59.8 %, F 40.1 %	NA	A combination of oral only	No	No	Yes	ICD codes
(Fang et al., 2015)	Asia	Retrospective	291	Hospital based	T2DM	75.7	NA	16.7 SD ±9.6	A combination of oral only and insulin	No	No	Yes	NA
(Faerch et al., 2011)	Europe	Prospective	128	Self-reported	T1DM	45± 12 years	M 56.2%	19±11 years	Insulin	Yes	No	No	Severe hypoglycaemia was defined as an episode at which the patient needs assistance from another person to restore the blood glucose level
(Feher et al., 2016)	Europe	Retrospective	1569	Self-reported	T2DM	NA	M 66%	NA	A combination of oral and insulin	Yes	No	No	As: feeling hungry, sweating, dizziness, tiredness (fatigue), blurred vision, trembling or shakiness, fast pulse or palpitations, tingling lips, irritability, difficulty concentrating, confusion, and disorderly or irrational behaviour, which may be mistaken for drunkenness. 'Mild hypoglycaemia ' was defined as any of the above symptoms where a third party was not required, and 'severe hypoglycaemia was defined as the above symptoms with third party involvement or where there was loss of consciousness
(Farmer et al., 2012)	Europe	Retrospective	3562	Self-reported	NA	NA	NA	NA	NA	Yes	No	No	NA
(Feil et al., 2011)	North America	Retrospective	497900	Database	NA	NA	NA	NA	NA	No	No	Yes	ICD codes
(Freathy et al., 2006)	Europe	Retrospective	308	Self-reported	T2DM	54 .5	M 54 .5/ 45.5%	10 (5-14)	A combination of oral only and insulin	No	No	Yes	Definitions of mild (self-treated) and severe (requiring help from another person to effect recovery)
(Fu et al., 2014)	North America	Retrospective	887,182	Database	T2DM	NA	M 52.25%, F 47.75%	NA	A combination of oral only and insulin	No	No	Yes	NA
(Ganz et al., 2014)	North America	Retrospective	7,235	Database	T2DM	60.82 SD 11.65	M 49.3 %,F 50.70 %	NA	Insulin	No	No	Yes	SH events were defined as events requiring medical attention with the appropriate SH diagnosis codes attached to outpatient, inpatient, or

													emergency department visits or by a recorded glucose level of 40 mg/dL. + ICD CODES
(Geller et al., 2014)	North America	Retrospective	8,100	Self-reported	NA	NA	M 49.6% , F 50.4%	NA	Insulin	No	No	Yes	(1) Clinical documentation of related clinically relevant hypoglycaemia (BG<70mg/dL (2) “insulin overdose” or “insulin reaction,” or (3) An error in insulin use (e.g: administration of the wrong insulin dose)
(Green et al., 2012)	North America	Retrospective	3000	Self-reported	T2DM	NA	NA	NA	NA	Yes	No	No	Hypoglycaemia was based on self-reported low blood sugar
(Gu et al., 2016)	Asia	Retrospective	6,633	Self-reported	T2DM	56.31 SD ± 10.57	M 56% , F43%	NA	NA	No	No	Yes	Mild hypoglycaemia was defined as having one or more episodes of hypoglycaemia with symptoms (e.g., palpitations, hunger,sweating, tremulousness, weakness, fatigue, dizziness, and anxiety) in one month prior to the survey
(Guisasola et al., 2008)	Europe	Retrospective	1709	Self-reported	T2DM	62.9 ± 10.6	M 54.9%	7.8 SD ± 5.1	A combination of oral only	Yes	No	No	NA
(Henderson et al., 2003)	Europe	Retrospective	215	Self-reported	T2DM	68	NA	NA	Insulin	Yes	Yes	No	Mild hypoglycaemia was defined by the ability to have self-treated the episode and severe hypoglycaemia as having required external assistance to effect recovery.
(Herings et al., 1995)	Europe	Retrospective	748	Database	NA	NA	NA	NA	A combination of oral only	No	No	Yes	ICD codes
(Hirai et al., 2007)	North America	Retrospective	537	Self-reported	T1DM	45.3 ± 9.9	M 50.1%	31.3 ± 7.9 years	Insulin	Yes	No	No	Severe hypoglycaemia required ED visit or hospitalisation
(Holstein et al., 2009)	Europe	Retrospective	97	Hospital based	T2DM	75.2 SD ± 10.4	M 53%, F47 %	8.6 SD ± 11.3	Sulfonylureas	No	No	Yes	symptomatic event requiring treatment with intravenous glucose and was confirmed by a blood glucose measurement of < 50 mg / dl (< 2.8
(Holstein et al., 2011)	Europe	Prospective	264	Hospital based	T2DM	NA	NA	NA	Sulfonylureas	No	No	Yes	Defined by the requirement for intravenous glucose or glucagon injection and blood glucose value of <2.8 mmol/l
(Honkasalo et al., 2011)	Europe	Retrospective	1776	Self-reported	Both types of diabetes	61.6± 13.5 years	NA	12.8 ± 11.0 years	insulin	Yes	No	Yes	SH was defined as a condition for which the patient needs the assistance of another person to recover from a hypoglycaemic

													episode as used by the UK Hypoglycaemia Study Group
(Ishikawa et al., 2017)	Asia	Retrospective	170	Database	T2DM	74.1	NA	NA	A combination of oral and insulin	No	No	Yes	NA
(Ishtiak-Ahmed et al., 2017)	Europe	Retrospective	17230	Database	T1DM	NA	M 57.3 %	NA	Insulin	Yes	Yes	No	Defined as an event when it required an outpatient, inpatient, or emergency care visit with the previously mentioned corresponding diagnostic code to icd codes-10 for HH
(Jeon et al., 2016)	Asia	Retrospective	NA	Database	NA	66.3 SD ± 10.0	M 59 %, F 41%	14.1 SD ±8.8	NA	No	No	Yes	Severe hypoglycaemia is defined as a state of low blood glucose that requires the assistance of another person
(Jick et al., 1990)	Europe	Retrospective	121	Database	NA	NA	NA	NA	A combination of oral only	No	No	Yes	ICD codes
(Yun et al., 2018)	Asia	Retrospective	1366692	Database	T2DM	57.7± 11.7	M 59.3%	NA	NA	Yes	No		ICD codes
(Johansen et al., 2015a)	Europe	Retrospective	3320	Database	T1DM	NA	M 52.4%	NA	Insulin	No	Yes	No	Severe hypoglycaemia was defined according to ISPAD guidelines; a hypoglycaemic event leading to loss of consciousness and/or seizure
(Johnston et al., 2012)	North America	Retrospective	361210	Database	T2DM	NA	NA	NA	A combination of oral and insulin	Yes	No	No	ICD codes
(Karges et al., 2015)	Europe	Retrospective	31330	Database	NA	12.7 ± 9.2	M 52.8 %	NA	Insulin	No	Yes	No	NA
(Karter et al., 2017)	North America	Retrospective	NA	Database	NA	61.4± SD 13.7	M 52.8 %, F 47.2 %	NA	A combination of oral and insulin	No	No	Yes	ICD codes
(Katz et al., 2012)	North America	Prospective	255	Self-reported	T1DM	12.2	M 49%	4.4years	Insulin	No	Yes	No	hypoglycaemia requiring assistance from another person for oral treatment and hypoglycaemia with seizure/coma (altered consciousness) as determined by report of seizure or coma, requirement for parenteral therapy (i.e., glucagon or intravenous dextrose), or use of emergency services

(Katon et al., 2013)	North America	Retrospective	4,117	Hospital based	T2DM	63.4 (13.4)	M/F 51.9/48.1	9.6 (9.4)	NA	No	No	Yes	ICD codes
(Kajiwara et al., 2015)	Asia	Retrospective	2,119	Self-reported	NA	68.4 SD ± 11.6	NA	NA	NA	No	No	Yes	NA
Kim et al (2016) (Kim et al., 2016b)	Asia	Retrospective	307107	Database	T2DM	NA	M 41.7%	NA	A combination of oral and insulin	No	Yes	No	ICD codes
Kostev et al (2014) (Kostev et al., 2014)	Europe	Retrospective	32545	Database	T2DM	70.2	M 50.3%	NA	Insulin	Yes	No	No	NA
(Kostev et al., 2015)	Europe	Retrospective	10,842	Database	T2DM	70.2±11.2 years	NA	NA	Insulin	No	No	Yes	ICD codes
(Leckie et al., 2005)	Europe	Prospective	243	Self-reported	NA	NA	NA	NA	Insulin	No	Yes	No	Mild hypoglycaemia was defined as any symptomatic episode that was self-treated. Severe hypoglycaemia was defined as an episode that required treatment by another person and was associated either with a blood glucose concentration of ↕2.8 mmol/l or with prompt recovery after administration of oral carbohydrate, or the parenteral administration of dextrose or glucagon
(Leese et al., 2003)	Europe	Retrospective	977	Database	T1DM	NA	NA	NA	Insulin	Yes	Yes	No	Episodes of severe hypoglycaemia were defined as blood glucose <3.5 mmol/l associated with the need for treatment with glucagon or intravenous dextrose to effect recovery or paramedic confirmation of hypoglycaemia with rapid recovery following treatment
(Leonard et al., 2016)	North America	Retrospective	592872	Database	T2DM	NA	NA	NA	Sulfonylureas	No	Yes	No	ICD CODES
(Li et al., 2014)	Asia	Retrospective	611	Hospital based	T1DM	NA	M 47.3/ F 53.7%	NA	NA	No	No	Yes	NA
(Lin et al., 2010)	Asia	Retrospective	233	Database	T2DM	74.1 SD ± 9.8	M 41 %, F 59 %	NA	NA	No	No	Yes	Defined severe hypoglycaemia using the American Diabetes Association criteria as an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative action.

(Lipska et al., 2013)	North America	Retrospective	9094	Database	T2DM	59.5± 9.8	NA	10.6± 8.4 years	A combination of oral and insulin	Yes	No	No	History of hypoglycaemia was based upon at least one emergency department or inpatient visit for hypoglycaemia during the pre-observation period identified using previously validated ICD CODES-9 codes
(Lipska et al., 2014)	North America	Retrospective	33952331	Database	NA	NA	NA	NA	NA	No	Yes	No	ICD codes
(Loke et al., 2010)	Asia	Prospective	61	Self-reported	T2DM	NA	NA	NA	NA	No	No	Yes	Severe hypoglycaemia was defined as a hypoglycaemic episode severe enough to require the assistance of another person
(Lundkvist et al., 2005)	Europe	Retrospective	309	Hospital based	T2DM	65 SD ±11	M 60 / F40%	NA	A combination of oral and insulin	No	Yes	Yes	Symptomatic hypoglycaemia was considered biochemically verified by a blood glucose concentration less than 3.3 mmol/l. Severe hypoglycaemia was de fined as a hypo glycaemic event for which the patient required as assistance from another per son to re solve the situation. Mild hypoglycaemia was defined as manageable by the patient (e.g., by eating a sandwich)
Ly et al (2009) (Ly et al., 2009)	Australia	Retrospective	656	Self-reported	T1DM	12.8 ±4.0	M 48.3%	5.4 ± 3.9 years	Insulin	No	Yes	No	Severe hypoglycaemia was defined as an event leading to loss of consciousness or seizure. Recurrent hypoglycaemia was defined as the occurrence of 2 episodes of severe hypoglycaemia in the preceding year.
(Maltoni et al., 2013)	Europe	Retrospective	269	Self-reported	T1DM	NA	M 50.2%	NA	Insulin	No	Yes	No	Hypoglycaemic episode as severe, we used ISPAD guidelines 2011 defining SH as an event of coma, seizures and/or altered mental status requiring third-party assistance
(Mauricio et al., 2015)	Multinational	Retrospective	40,627	Database	T2DM	63.3	NA	NA	A combination of oral and insulin	No	No	Yes	ICD codes
(Mantovani et al., 2016)	Europe	Retrospective	520	Hospital based	Both types of diabetes	72 SD ± 16	M 55 % , F 45 %	22 SD ± 11	A combination of oral and insulin	No	No	Yes	We electronically searched for the terms “hypoglycaemia” or “hypoglycaemic event” in the discharge diagnosis from the hospital, or for recorded blood glucose levels less than 3.8 mmol/L.
(McCoy et al., 2016)	North America	Retrospective	31,542	Database	T2DM	58.0 SD	M 51.9%, F 49.1%	NA	A combination of oral only	No	No	Yes	ICD codes

(Miller et al., 2001)	North America	Retrospective	1,055	Self-reported	T2DM	60.9 SD ± 0.4	M 28.2%, F 71.8%	10.8 SD ± 0.3	A combination of oral and insulin	No	No	Yes	Hypoglycaemia was defined as typical symptoms relieved by eating, and/or blood glucose level of less than 60 mg/dL (<3.3 mmol/L)
(Alonso-Moran et al., 2015)	Europe	Retrospective	134413	Database	T2DM	NA	M 53.9%	NA	NA	No	Yes	No	ICD codes
(Morris et al., 1997)	Europe	Retrospective	504	Database	Both types of diabetes	NA	NA	NA	A combination of oral only	No	No	Yes	NA
(Muhlhauser et al., 1985)	Europe	Retrospective	384	Self-reported	T1DM	30±13 years	NA	12±9 years	Insulin	Yes	No	No	hypoglycaemia with loss of consciousness treated with glucagon or intravenous glucose,as
(Muhlhauser et al., 1998)	Europe	Prospective	684	Self-reported	T1DM	36 SD ± 11	M 59% , F 41 %	NA	NA	No	No	Yes	NA
(Muller et al., 2017)	Europe	Retrospective	7900000	Database	T2DM	NA	NA	NA	A combination of oral and insulin	No	Yes	No	ICD codes
(Murata et al., 2005)	North America	Prospective	344	Database	T2DM	65.5±9.7 years	M 96.5%	14.7 ± 9.9 years	A combination of oral and insulin	Yes	Yes	No	Glucose <60 mg/dl
(Nam et al.)	North America	Retrospective	3467	Database	T2DM	NA	NA	NA	A combination of oral only	No	No	Yes	ICD codes
(Nunes et al., 2017)	North America	Retrospective	143635	Database	T2DM	NA	NA	NA	Sulfonylureas	Yes	No	No	ICD codes
(Nunes et al., 2016)	North America	Retrospective	844683	Database	T2DM	NA	M 48.5 %	NA	A combination of oral only	No	Yes	No	NA
(Odawara et al., 2014)	Asia	Retrospective	4219	Self-reported	T2DM	62.8 ± 12.1	M 58.9%	5.7 years	A combination of oral and insulin	No	Yes	No	Severe hypoglycaemia included hypoglycaemic episodes satisfying any of the following serious AEs criteria; 1) resulted in death, 2) life-threatening, 3) required or prolonged inpatient hospitalisation, 4) persistently or significantly disabling/ incapacitating, 5) a congenital anomaly, and/or 6) medically important.
(Olsen et al., 2014)	Europe	Retrospective	440	Self-reported	T1DM	NA	M 51.0%	NA	Insulin	Yes	No	No	NA

(Yu et al., 2018)	Europe	Retrospective	14012	Database	T2DM	NA	NA	NA	A combination of oral and insulin	No	No	Yes	Read codes
(Ooi et al., 2011)	Asia	Retrospective	170	Self-reported	T2DM	67.32 +5.45	M41.2%	9.00 ±6.77	A combination of oral and insulin	Yes	No	No	NA
(Pathak et al., 2016)	North America	Prospective	917440	Database	NA	57.9 ± 13.2	M 52.1%	NA	NA	No	Yes	No	ICD CODES
(Lyngsie et al., 2016)	Europe	Retrospective	307016	Database	NA	NA	NA	NA	NA	No	Yes	No	ICD codes
(Pedersen-Bjergaard et al., 2004)	Europe	Retrospective	1076	Self-reported	T1DM	NA	M 55.5%	NA	Insulin	Yes	No	Yes	Mild hypoglycaemic events were reported for the previous week, defined as episodes with symptoms of hypoglycaemia manageable by the patient. Severe hypoglycaemic events were defined as episodes where assistance from others was needed to restore blood glucose and were reported for the preceding one- and two-year periods.
(Pilemann-Lyberg et al., 2015)	Europe	Prospective	161	Database	T2DM	76±12 years	M 54 %	NA	Sulfonylureas	No	Yes	No	We defined a severe hypoglycaemic event as an episode requiring external help
(Pirags et al., 2012)	Multinational	Prospective	991	Self-reported	T2DM	57.9±10.1	M 52.2%	9.2± 5.9 years	Insulin	Yes	Yes	No	Severe hypoglycaemia was defined as an event that required assistance from another person who actively administered carbohydrate, glucagon or other resuscitative actions and was associated with either a blood glucose level less than 3.9 mmol⁄l (< 70mg⁄dl) or prompt recovery after restoring normoglycaemia
(Quilliam et al., 2011a)	North America	Retrospective	14,729	Database	T2DM	56.4 SD ± 7.0	M 51%, F 49 %	NA	NA	No	No	Yes	ICD codes
(Radosevich et al., 2015)	North America	Retrospective	122	Database	NA	59.5 SD ± 17.8	M 43 %, F 53%	NA	Insulin	No	No	Yes	Hypoglycaemia was defined as a glucose measurement < 70 mg/dL.
(Rajendran et al., 2015)	Asia	Retrospective	132	Database	Both types of diabetes	59±20	M 52.2%	NA	A combination of oral and insulin	Yes	No	No	NA

(Ragia et al., 2012)	Europe	Retrospective	176	NA	T2DM	NA	NA	NA	Sulfonylureas	No	No	Yes	NA
(Raju et al., 2016)	North America	Retrospective	11536	Database	T2DM	55.7 ± 10.1	M 58.8%	NA	A combination of oral only	No	Yes	No	NA
(Rathmann et al., 2013)	Europe	Retrospective	50,294	Database	T2DM	NA	NA	NA	A combination of oral only	No	No	Yes	ICD codes
(Ren et al., 2016)	Asia	Retrospective	6,713	Self-reported	T2DM	56.38+-10	M 56 %, F 44%	NA	NA	No	No	Yes	Asymptomatic hypoglycaemia was defined as plasma glucose ≤3.9 mmol/L but without any symptoms in 1 month before hospitalisation. Mild hypoglycaemia was defined as having one or more episodes of hypoglycaemia with symptom in 1 month prior to the hospitalisation. Severe hypoglycaemia was defined as having one or more episodes of hypoglycaemia that needed assistance from other people in 3 months before hospitalisation
(Romley et al., 2015)	North America	Retrospective	465, 918	Database	T2DM	74.6 SD ± 7.5	M 42.2%, F 57.8 %	NA	Sulfonylureas	No	No	No	ICD codes
(Rubin et al., 2011)	North America	Retrospective	1,990	Database	NA	NA	NA	NA	Insulin	No	No	No	Defined by a POC glucose ,70 mg/dL after the first 24 h of admission
(Roumie et al., 2016)	North America	Retrospective	178,341	Database	NA	NA	NA	NA	A combination of oral and insulin	No	No	No	Hypoglycaemia was defined as hospital admission or an emergency department visit for hypoglycaemia, or an outpatient blood glucose value of less than 3.3 mmol/L / ICD CODES
(Sako et al., 2015)	Asia	Retrospective	25071	Database	NA	73.4 ± 13.1	M 53.3%	NA	NA	No	Yes	No	ICD codes
(Sarkar et al., 2010)	North America	Retrospective	14357	Self-reported	T2DM	58 ± 10	M 51 %	10 ± 8 years	A combination of oral and insulin	Yes	No	No	We asked participants in the past year, how many times have you had a severe low blood sugar reaction, such as passing out or needing help to treat the reaction?
(Samann et al., 2013)	Europe	Retrospective	sample of participants with type	Hospital based	Both types of diabetes	T1D 49 SD ± 16 T2d 66 SD ± 10	T1D M 58/ F 42% T2D M 56 / F 44%	T1D 20 SD +13 T2D 8 SD ± 7	A combination of oral and insulin	Yes	No	Yes	SH was defined as hypoglycaemia with coma or the need for intravenous glucose or intramuscular glucagon injection

			1 (n = 373) and type 2 diabetes (n = 4,481) Total = 4,854										
(Sato et al., 2010)	Asia	Retrospective	32	Hospital based	T2DM	74.8 SD ± 8.5	M 37% , F 63%	14.9 SD ± 10.2	Sulfonylureas	No	No	Yes	Symptoms + < 50 mg/dl (2.8 mmol/l) + I.V glucose administration
(Schloot et al., 2016)	Europe	Retrospective	29485	Database	T2DM	NA	M 51.1%	NA	Sulfonylureas	Yes	No	No	NA
(Seligman et al., 2010)	North America	Retrospective	711	Self-reported	T2DM	NA	NA	NA	NA	Yes	No	No	NA
(Seewi et al., 2008)	Europe	Retrospective	73	Self-reported	T1DM	NA	NA	NA	Insulin	No	No	Yes	History, and potential explanation of severe hypoglycaemia (grade 2: requiring external help because of diminished consciousness, and grade 3: coma, seizure, loss of consciousness
(Shriraam et al., 2017)	Asia	Retrospective	366	Self-reported	T2DM	NA	M 23.5%	10.9± 5.9 years	A combination of oral and insulin	Yes	No	No	Severe hypoglycaemia required ED visit or hospitalisation
(Solomon et al., 2013)	North America	Retrospective	8,626	Database	T2DM	56.4	M 50.9 %, F 49.1%	NA	Insulin	No	No	Yes	NA
(Sreenan et al., 2014)	Europe	Retrospective	T1DM (*n* = 7,420) or T2DM (*n* = 12,981)	NA	Both types of diabetes	T1D 41.4 SD ± 16.8 T2D 60.6 SD ± 10.8	NA	T1D 16.4 SD ± 12.5 T2D 11.2 SD ± 7.5	Insulin			No	SHEs were defined as an episode with symptoms of neuroglycopenia, in which the patient was unable to treat himself/herself and third-party intervention was needed, and where the patient had one of the following characteristics: (i) blood glucose <2.8 mmol/L (<50 mg/dL) or (ii) reversal of symptoms after food intake, glucagon or intravenous glucose administration.
(Stuart et al., 2017)	North America	Retrospective	9584	Self-reported	NA	NA	NA	NA	A combination of oral and	Yes	No	No	Glucose <4 mmol/L
(Strandberg et al., 2015)	Europe	Retrospective	16,985	Database	Both types of diabetes	NA	NA	NA	Insulin	No	No	Yes	ICD codes

(Takeishi et al., 2016)	Asia	Retrospective	106	Hospital based	T2DM	66.6 SD ± 11.0	M 52.8, F 47.2 %	14.7 SD ± 10.7	A combination of oral and insulin	No	No	Yes	Nocturnal hypoglycaemia was defined as a blood glucose level of <70 mg/dL occurring from 0 am to 8 am.
(Tan et al., 2015)	North America	Retrospective	37,086	Database	NA	NA	NA	NA	Sulfonylureas	No	No	Yes	NA
(Thamer et al., 1999)	North America	Retrospective	1,779	Database	NA	NA	M 41.8 % , female 58.2 %	NA	A combination of oral and insulin	No	No	Yes	NA
(Tschope et al., 2012)	Europe	Retrospective	3347	Self-reported	T2DM	68.6	M 51.7 %	NA	NA	Yes	No	Yes	NA
(Tschope et al., 2011)	Europe	Retrospective	3,808	Self-reported	T2DM	NA	M 53.1 %	NA	NA	No	No	Yes	NA
(Van Keulen et al., 2015)	Europe	Retrospective	4,732	Database	NA	79.4 SD ± 6.5	NA	NA	NA	No	No	Yes	NA
(Vlckova et al., 2010)	Europe	Retrospective	12 ,772	Database	NA	60.9	M 53/ F 47%	NA	NA	No	No	Yes	Hypoglycaemia was defined as an event recorded by GPs on the green forms. blood glucose or low blood sugar.
(Wang et al., 2015)	North America	Retrospective	63972	Database	NA	M 48.4%	NA	NA	NA	No	Yes	No	ICD codes
(Weinstock et al., 2013)	North America	Retrospective	4973	Database	T1DM	NA	M 46%	NA	NA	Yes	No	No	SH was defined as an episode in which the assistance of another individual was needed or glucagon was given.
(Weir et al., 2011)	North America	Retrospective	364	Self-reported	NA	NA	M 50.5 / F 49.5%	NA	A combination of oral and insulin	No	No	Yes	Severe hypoglycaemia required ED visit or hospitalisation
(Williams et al., 2014)	North America	Retrospective	24,751	Hospital based	Both types of diabetes	63.7 (12.1)	M 49.5/ F 51.5%	NA	NA	No	No	Yes	ICD codes
(Wohland et al., 2017)	Europe	Retrospective	92,794	Database	T1DM	48.2 SD ± 19.1	M 55.8%, F 44.2%	24.9 SD ± 15.7	Insulin	No	No	Yes	SH was defined as an event requiring treatment with intravenous glucose or glucagon administration and being confirmed by a blood glucose measurement of <2.8 mmol/l.
(Chu et al., 2017)	Asia	Retrospective	20845	Database	Both types of diabetes	NA	NA	NA	NA	Yes	No	Yes	ICD codes

(Cho and Cho, 2018)	Asia	Retrospective	5693	Database	T2DM	NA	53.1%	NA	A combination of oral and insulin	No	No	Yes	ICD codes
(Yu et al., 2016)	Multinational	Retrospective	4,399	Self-reported	T2DM	59.5	M 52 %, F 48 %	NA	A combination of oral only	No	No	Yes	NA
(Ikeda et al., 2018)	Asia	Retrospective	166806	Database	T2DM	66.2 ± 11.8	M 62.1%	NA	A combination of oral and insulin	No	Yes	No	ICD codes
(Yun et al., 2013)	Asia	Retrospective	878	Database	T2DM	55.3 ± 9.8	NA	9.8 6 ± 6.5 years	A combination of oral and insulin	No	Yes	No	Hypoglycaemia episodes requiring the assistance of another person to actively administer carbohydrate, other resuscitative actions, hospitalisation, or medical care in an emergency department.
(Yun et al., 2015)	Korea	Prospective	624	Hospital based	T2DM	61.2 SD ±10.2	M 48/ F 42 %	12.9 SD ±7.6	A combination of oral and insulin	No	No	Yes	Hypoglycaemic episodes requiring the assistance of medical care in an emergency department or hospitalisation
(Zaccardi et al., 2017)	Europe	Retrospective	405900	Database	Both types of diabetes	NA	52.5%	NA	NA	No	No	Yes	ICD codes
(Zhong et al., 2017)	Europe	Retrospective	23246	Database	T1DM	NA	NA	NA	NA	No	Yes	No	ICD codes

Appendix 5. Approved study protocol for Chapters 5, 6 and 7

SRC Feedback

Researcher Name: Hassan Alwafi
Organisation: UCL School of Pharmacy
SRC Reference Number: 18THIN009
Date: 2nd March 2018
Study title: Trends in utilization of oral anticoagulants in patients with type 2 diabetes mellitus; A population based study in the United Kingdom.

Committee opinion: Approved

The following feedback has been supplied by the SRC.

Notes from the Chair:

Approved

Approved documents:

Approved document	Version	Date
SRC_Protocol_18THIN009_v2_21-02-2018	2	21/02/2018
SRC_Feedback_18THIN009_Response		

We are pleased to inform that you can proceed with the study as this is now approved. IQVIA will let the relevant Ethics committee know this study has been approved by the SRC.

Once the study has been completed and published, it is important for you to inform IQVIA in order for us to advise the SRC and your reference number to be closed.

References to all published studies are added to our website enabling other researchers to become aware of your work. In order to identify your study as using the THIN database, we recommend that you include the words “The Health Improvement Network (THIN)” within your title. Copies of publication(s), where available, will be appreciated.

I wish you and your team all the best with the study progression.

Appendix 6. STROBE checklist for chapter 5

Strengthening the reporting of observational studies in epidemiology (STROBE) checklist

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract		Not applicable
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3,4	Abstract
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	220-220	Background
Objectives	3	State specific objectives, including any prespecified hypotheses	223	Aims and objectives
Methods				
Study design	4	Present key elements of study design early in the paper	224-226	Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	224-226	Methods
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	224-226	Methods
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	231	Methods
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	224-232	Methods
Bias	9	Describe any efforts to address potential sources of bias		Not applicable
Study size	10	Explain how the study size was arrived at	233	Results

Continue on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	231-232	Methods
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	231-232	Methods
		(*b*) Describe any methods used to examine subgroups and interactions	231-232	Methods
		(*c*) Explain how missing data were addressed		Not applicable
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	231-232	Methods
		(*e*) Describe any sensitivity analyses		Not applicable
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	233	Results
		(b) Give reasons for non-participation at each stage		Not applicable
		(c) Consider use of a flow diagram	Figure 25	Methods
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	232-242	Results
		(b) Indicate number of participants with missing data for each variable of interest		Not applicable
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)		Not applicable
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time		Not applicable
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		Not applicable
		Cross-sectional study—Report numbers of outcome events or summary measures	232-242	Results
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included		Not applicable
		(*b*) Report category boundaries when continuous variables were categorized		Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		Not applicable

Continue on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	232-242	Results
Discussion				
Key results	18	Summarise key results with reference to study objectives	242-247	Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	247	Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	242-247	Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	242-247	Discussion
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based		Not applicable

Note: The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Appendix 7. Read codes list

Read code	Read term	Clinical event
J615z13	Cirrhosis of liver NOS	Severe liver disease
G85..11	Oesophageal varices	Severe liver disease
J614200	Chronic aggressive hepatitis	Severe liver disease
J615300	Diffuse nodular cirrhosis	Severe liver disease
J612.00	Alcoholic cirrhosis of liver	Severe liver disease
J623.00	Portal hypertension	Severe liver disease
J616000	Primary biliary cirrhosis	Severe liver disease
Jyu7100	[X]Other and unspecified cirrhosis of liver	Severe liver disease
J61..00	Cirrhosis and chronic liver disease	Severe liver disease
C350012	Pigmentary cirrhosis of liver	Severe liver disease
G852300	Oesophageal varices in alcoholic cirrhosis of the liver	Severe liver disease
J616.00	Biliary cirrhosis	Severe liver disease
J624.00	Hepatorenal syndrome	Severe liver disease
G858.00	Oesophageal varices NOS	Severe liver disease
760C300	Fibreoptic endoscopic injection sclerotherapy oesoph varices	Severe liver disease
J616100	Secondary biliary cirrhosis	Severe liver disease
J615z00	Non-alcoholic cirrhosis NOS	Severe liver disease
J615.00	Cirrhosis - non alcoholic	Severe liver disease
760C500	Fibreoptic endoscopic banding of oesophageal varices	Severe liver disease
J635300	Toxic liver disease with chronic persistent hepatitis	Severe liver disease
J615z12	Cryptogenic cirrhosis of liver	Severe liver disease
C310400	Glycogenosis with hepatic cirrhosis	Severe liver disease
7609z00	Open operation on oesophageal varices NOS	Severe liver disease
7609400	Open injection sclerotherapy to oesophageal varices	Severe liver disease
J615z11	Macronodular cirrhosis of liver	Severe liver disease
7609	Open operations on oesophageal varices	Severe liver disease
G850.00	Oesophageal varices with bleeding	Severe liver disease
G852200	Oesophageal varices in cirrhosis of the liver	Severe liver disease
J615700	Cardiac portal cirrhosis	Severe liver disease
G857.00	Gastric varices	Severe liver disease
G851.00	Oesophageal varices without bleeding	Severe liver disease
J62..00	Liver abscess and sequelae of chronic liver disease	Severe liver disease
J635500	Toxic liver disease with chronic active hepatitis	Severe liver disease
J615600	Capsular portal cirrhosis	Severe liver disease
7609300	Local ligation of oesophageal varices	Severe liver disease
J635600	Toxic liver disease with fibrosis and cirrhosis of liver	Severe liver disease
G852.00	Oesophageal varices in diseases EC	Severe liver disease
J615400	Fatty portal cirrhosis	Severe liver disease
760F400	Rigid oesophagoscopic banding of oesophageal varices	Severe liver disease
760F300	Rigid oesophagoscopic injection sclerotherapy oesoph varices	Severe liver disease
J615.11	Portal cirrhosis	Severe liver disease

J62y.00	Other sequelae of chronic liver disease	Severe liver disease
J615H00	Infectious cirrhosis NOS	Severe liver disease
J615y00	Portal cirrhosis unspecified	Severe liver disease
J615812	Indian childhood cirrhosis	Severe liver disease
J616z00	Biliary cirrhosis NOS	Severe liver disease
G852z00	Oesophageal varices in diseases EC NOS	Severe liver disease
J635400	Toxic liver disease with chronic lobular hepatitis	Severe liver disease
A704000	Viral hepatitis C with coma	Severe liver disease
J612.11	Florid cirrhosis	Severe liver disease
A702.00	Viral hepatitis B with coma	Severe liver disease
J615100	Multilobular portal cirrhosis	Severe liver disease
G852100	Oesophageal varices without bleeding in diseases EC	Severe liver disease
J615D00	Bacterial portal cirrhosis	Severe liver disease
J616200	Biliary cirrhosis of children	Severe liver disease
J615500	Hypertrophic portal cirrhosis	Severe liver disease
J615800	Juvenile portal cirrhosis	Severe liver disease
G852000	Oesophageal varices with bleeding in diseases EC	Severe liver disease
J615C00	Xanthomatous portal cirrhosis	Severe liver disease
J612.12	Laennec's cirrhosis	Severe liver disease
C370800	Cystic fibrosis related cirrhosis	Severe liver disease
Gyu9400	[X]Oesophageal varices in diseases classified elsewhere	Severe liver disease
J62z.00	Liver abscess and chronic liver disease causing sequelae NOS	Severe liver disease
J614.00	Chronic hepatitis	Mild liver disease
A705000	Viral hepatitis C without mention of hepatic coma	Mild liver disease
A703.00	Viral (serum) hepatitis B	Mild liver disease
65Q7.00	Viral hepatitis carrier	Mild liver disease
J617000	Chronic alcoholic hepatitis	Mild liver disease
J617.00	Alcoholic hepatitis	Mild liver disease
J614111	Autoimmune chronic active hepatitis	Mild liver disease
J614100	Chronic active hepatitis	Mild liver disease
J61z.00	Chronic liver disease NOS	Mild liver disease
ZV02B00	[V]Hepatitis B carrier	Mild liver disease
J614z00	Chronic hepatitis NOS	Mild liver disease
ZV02600	[V]Viral hepatitis carrier	Mild liver disease
J63B.00	Autoimmune hepatitis	Mild liver disease
J612000	Alcoholic fibrosis and sclerosis of liver	Mild liver disease
J614000	Chronic persistent hepatitis	Mild liver disease
A707000	Chronic viral hepatitis B with delta-agent	Mild liver disease
J61y400	Hepatic fibrosis	Mild liver disease
C376100	Alpha-1-antitrypsin hepatitis	Mild liver disease
C32y511	Hepatic familial steatosis	Mild liver disease
A707.00	Chronic viral hepatitis	Mild liver disease
J63X.00	Granulomatous hepatitis, not elsewhere classified	Mild liver disease
ZV02C00	[V]Hepatitis C carrier	Mild liver disease
J63y100	Nonspecific reactive hepatitis	Mild liver disease

A707200	Chronic viral hepatitis C	Mild liver disease
141E.00	History of hepatitis B	Mild liver disease
J630.00	Chronic passive liver congestion	Mild liver disease
A707X00	Chronic viral hepatitis, unspecified	Mild liver disease
J61yz00	Other non-alcoholic chronic liver disease NOS	Mild liver disease
Q48yz11	Congenital hepatic fibrosis	Mild liver disease
J61y300	Portal fibrosis without cirrhosis	Mild liver disease
A707100	Chronic viral hepatitis B without delta-agent	Mild liver disease
J631.00	Hepatitis in viral diseases EC	Mild liver disease
J61y.00	Other non-alcoholic chronic liver disease	Mild liver disease
Q409100	Congenital hepatitis B infection	Mild liver disease
J614300	Recurrent hepatitis	Mild liver disease
J600200	Acute yellow atrophy	Mild liver disease
J614y00	Chronic hepatitis unspecified	Mild liver disease
J61y500	Hepatic sclerosis	Mild liver disease
J614400	Chronic lobular hepatitis	Mild liver disease
J601200	Subacute yellow atrophy	Mild liver disease
J615z15	Hepatic fibrosis	Mild liver disease
9kV..00	Hepatitis C screening positive - enhanced services admin	Mild liver disease
J61y800	Nonalcoholic steatohepatitis	Mild liver disease
9kR..00	Chronic hepatitis annual review - enhanced services admin	Mild liver disease
J61y600	Hepatic fibrosis with hepatic sclerosis	Mild liver disease
9NgR.00	On hepatitis C treatment plan	Mild liver disease
L414.00	Postnatal deep vein thrombosis	DVT
L414.11	DVT - deep venous thrombosis, postnatal	DVT
L414.12	Phlegmasia alba dolens - obstetric	DVT
L414000	Postnatal deep vein thrombosis unspecified	DVT
L414100	Postnatal deep vein thrombosis - delivered with p/n comp	DVT
L414200	Postnatal deep vein thrombosis with postnatal complication	DVT
L414z00	Postnatal deep vein thrombosis NOS	DVT
G801.11	Deep vein thrombosis	DVT
G801.12	Deep vein thrombosis, leg	DVT
G801.13	DVT - Deep vein thrombosis	DVT
G801C00	Deep vein thrombosis of leg related to air travel	DVT
G801D00	Deep vein thrombosis of lower limb	DVT
G801E00	Deep vein thrombosis of leg related to intravenous drug use	DVT
G801F00	Deep vein thrombosis of peroneal vein	DVT
G801G00	Recurrent deep vein thrombosis	DVT
G801G00	Recurrent deep vein thrombosis	DVT
G801H00	Unprovoked deep vein thrombosis	DVT
G802000	Thrombosis of vein of leg	DVT
Eu32.12	[X]Single episode of psychogenic depression	Depression
Eu32.13	[X]Single episode of reactive depression	Depression
Eu32212	[X]Single episode major depression w'out psychotic symptoms	Depression
Eu32213	[X]Single episode vital depression w'out psychotic symptoms	Depression

Eu32311	[X]Single episode of major depression and psychotic symptoms	Depression
Eu32312	[X]Single episode of psychogenic depressive psychosis	Depression
Eu32313	[X]Single episode of psychotic depression	Depression
Eu32314	[X]Single episode of reactive depressive psychosis	Depression
Eu32400	[X]Mild depression	Depression
Eu32500	[X]Major depression, mild	Depression
Eu32600	[X]Major depression, moderately severe	Depression
Eu32700	[X]Major depression, severe without psychotic symptoms	Depression
Eu32800	[X]Major depression, severe with psychotic symptoms	Depression
Eu32900	[X]Single major depr ep, severe with psych, psych in remiss	Depression
Eu32A00	[X]Recurr major depr ep, severe with psych, psych in remiss	Depression
Eu32B00	[X]Antenatal depression	Depression
Eu32y00	[X]Other depressive episodes	Depression
Eu32y11	[X]Atypical depression	Depression
Eu32y12	[X]Single episode of masked depression NOS	Depression
Eu32z00	[X]Depressive episode, unspecified	Depression
Eu32z11	[X]Depression NOS	Depression
Eu32z12	[X]Depressive disorder NOS	Depression
Eu32z13	[X]Prolonged single episode of reactive depression	Depression
Eu32z14	[X] Reactive depression NOS	Depression
Eu33.00	[X]Recurrent depressive disorder	Depression
Eu33.11	[X]Recurrent episodes of depressive reaction	Depression
Eu33.12	[X]Recurrent episodes of psychogenic depression	Depression
Eu33.13	[X]Recurrent episodes of reactive depression	Depression
Eu33.14	[X]Seasonal depressive disorder	Depression
Eu33211	[X]Endogenous depression without psychotic symptoms	Depression
Eu33212	[X]Major depression, recurrent without psychotic symptoms	Depression
Eu33213	[X]Manic-depress psychosis,depressd,no psychotic symptoms	Depression
Eu33214	[X]Vital depression, recurrent without psychotic symptoms	Depression
Eu33300	[X]Recurrent depress disorder cur epi severe with psyc symp	Depression
Eu33311	[X]Endogenous depression with psychotic symptoms	Depression
Eu33312	[X]Manic-depress psychosis,depressed type+psychotic symptoms	Depression
Eu33313	[X]Recurr severe episodes/major depression+psychotic symptom	Depression
Eu33314	[X]Recurr severe episodes/psychogenic depressive psychosis	Depression
Eu33315	[X]Recurrent severe episodes of psychotic depression	Depression
Eu33316	[X]Recurrent severe episodes/reactive depressive psychosis	Depression
Eu33400	[X]Recurrent depressive disorder, currently in remission	Depression
Eu33y00	[X]Other recurrent depressive disorders	Depression
Eu33z00	[X]Recurrent depressive disorder, unspecified	Depression
Eu33z11	[X]Monopolar depression NOS	Depression
Eu34113	[X]Neurotic depression	Depression
Eu34114	[X]Persistant anxiety depression	Depression
Eu41211	[X]Mild anxiety depression	Depression
Eu53011	[X]Postnatal depression NOS	Depression
Eu53012	[X]Postpartum depression NOS	Depression

PE03.00	Depressions in skull	Depression
Q018.00	Fetus or neonate affected by maternal postnatal depression	Depression
Q482000	Newborn cerebral depression	Depression
R007z13	[D]Postoperative depression	Depression
ZR2A.00	Beck depression inventory	Depression
ZR2A.11	BDI - Beck depression inventory	Depression
ZR2h.00	Brief depression rating scale	Depression
ZR2h.11	BDRS - Brief depression rating scale	Depression
ZR3L.00	Child depression scale	Depression
ZR3L.11	CDS - Child depression scale	Depression
ZR3L100	Child depression scale, second research edition	Depression
ZR7..00	Depression anxiety scale	Depression
ZR8..00	Depression self rating scale	Depression
ZR8..11	DSRS - Depression self rating scale	Depression
ZRBY.00	Edinburgh postnatal depression scale	Depression
ZRBY.11	EPDS - Edinburgh postnatal depression scale	Depression
ZRL6.00	Geriatric depression scale	Depression
ZRL6.11	GDS - Geriatric depression scale	Depression
ZRL6.12	Geriatric depression score	Depression
ZRLr.00	Hospital anxiety and depression scale	Depression
ZRLr.11	HAD - Hospital anxiety and depression scale	Depression
ZRLr.12	HADS - Hospital anxiety and depression scale	Depression
ZRLU.00	Hamilton rating scale for depression	Depression
ZRLU.11	HAMD - Hamilton rating scale for depression	Depression
ZRLU.12	HRSD - Hamilton rating scale for depression	Depression
ZRrc.00	Zung self-rating depression scale	Depression
ZRrc.11	SDS - Zung self-rating depression scale	Depression
ZRrI.00	Wakefield self-assessment depression inventory	Depression
ZRrY.00	WHO depression scale	Depression
ZRVM.00	Leeds scale for the self-assessment of anxiety & depression	Depression
ZV79000	[V]Screening for depression	Depression
115X.00	No history of depression	Depression
12K8.00	Maternal postnatal depression	Depression
13Y3.00	Manic-depression association member	Depression
1465	H/O: depression	Depression
1B1U.00	Symptoms of depression	Depression
1JJ..00	Suspected depression	Depression
212S.00	Depression resolved	Depression
32E4.00	ECG: S-T depression	Depression
3885	Edinburgh postnatal depression scale	Depression
388a.00	Depression anxiety stress scales stress score	Depression
388b.00	Depression anxiety stress scales anxiety score	Depression
388g.00	Beck depression inventory second edition score	Depression
388J.00	Hospital anxiety and depression scale	Depression
388K.00	Geriatric depression scale	Depression

388l.00	BASDEC - Brief Assessment Schedule Depression Cards score	Depression
388P.00	HAD scale: depression score	Depression
388Z.00	Depression anxiety stress scales depression score	Depression
38Dp.00	HAMD - Hamilton rating scale for depression	Depression
38Dp.11	HRSD - Hamilton rating scale for depression	Depression
38Dq.00	MADRS - Montgomery-Asberg depression rating scale	Depression
38GJ000	EuroQol five dimension five level anxiety depression score	Depression
62T1.00	Puerperal depression	Depression
6891000	Assessment using Whooley depression screen	Depression
6896	Depression screening using questions	Depression
6G00.00	Postnatal depression counselling	Depression
8BK0.00	Depression management programme	Depression
8HHq.00	Referral for guided self-help for depression	Depression
8I3F.00	Edinburgh postnatal depression scale at 8 months declined	Depression
8I3G.00	Edinburgh postnatal depression scale declined	Depression
8ID..00	Postnatal depression not discussed	Depression
8ID..00	Postnatal depression not discussed	Depression
8IH3100	Depression screening declined	Depression
8IH5200	Referral for guided self-help for depression declined	Depression
9H90.00	Depression annual review	Depression
9H91.00	Depression medication review	Depression
9H92.00	Depression interim review	Depression
9HA0.00	On depression register	Depression
9HA1.00	Removed from depression register	Depression
9hC..00	Exception reporting: depression quality indicators	Depression
9hC0.00	Excepted from depression quality indicators: Patient unsuita	Depression
9hC1.00	Excepted from depression quality indicators: Informed dissen	Depression
9k4..00	Depression - enhanced services administration	Depression
9k40.00	Depression - enhanced service completed	Depression
9kQ..00	On full dose long term treatment depression - enh serv admin	Depression
9kQ..11	On full dose long term treatment for depression	Depression
9Ov..00	Depression monitoring administration	Depression
9Ov0.00	Depression monitoring first letter	Depression
9Ov1.00	Depression monitoring second letter	Depression
9Ov2.00	Depression monitoring third letter	Depression
9Ov3.00	Depression monitoring verbal invite	Depression
9Ov4.00	Depression monitoring telephone invite	Depression
E113700	Recurrent depression	Depression
E11z200	Masked depression	Depression
E130.11	Psychotic reactive depression	Depression
E135.00	Agitated depression	Depression
E200300	Anxiety with depression	Depression
E204.00	Neurotic depression reactive type	Depression
E204.11	Postnatal depression	Depression
E2B0.00	Postviral depression	Depression

E2B1.00	Chronic depression	Depression
Eu20400	[X]Post-schizophrenic depression	Depression
G700.00	Aortic atherosclerosis	PVD
G73z000	Intermittent claudication	PVD
G73..12	Ischaemia of legs	PVD
G73zz00	Peripheral vascular disease NOS	PVD
G73z.00	Peripheral vascular disease NOS	PVD
G73yz00	Other specified peripheral vascular disease NOS	PVD
R054.00	D]Gangrene	PVD
G73..11	Peripheral ischaemic vascular disease	PVD
G73..00	Other peripheral vascular disease	PVD
M271.12	Ischaemic leg ulcer	PVD
G73..13	Peripheral ischaemia	PVD
G73z011	Claudication	PVD
G732.00	Peripheral gangrene	PVD
G732100	Gangrene of foot	PVD
C10F500	Type 2 diabetes mellitus with gangrene	PVD
G702.00	Extremity artery atheroma	PVD
G742z00	Peripheral arterial embolism and thrombosis NOS	PVD
G702z00	Extremity artery atheroma NOS	PVD
G731000	Buerger's disease	PVD
G73y100	Peripheral angiopathic disease EC NOS	PVD
M271000	Ischaemic ulcer diabetic foot	PVD
R054300	[D]Widespread diabetic foot gangrene,Diabetes mellitus with gangrene	PVD
C107.11	Diabetes with gangrene	PVD
C107.12	Diabetes mellitus, adult with gangrene"	PVD
C107200	Diabetic peripheral angiopathy	PVD
G73y000	Thromboangiitis obliterans	PVD
G731.00	Diabetes mellitus with peripheral circulatory disorder	PVD
C107.00	D]Gangrene NOS	PVD
R054z00	Type 2 diabetes mellitus with peripheral angiopathy	PVD
C10FF00	Other specified peripheral vascular disease	PVD
G73y.00	Presenile gangrene	PVD
G731100	Non-insulin dependent diabetes mellitus with gangrene	PVD
C109500	Type 2 diabetes mellitus with gangrene	PVD
C109512	Non-insulin-dependent d m with peripheral angiopath	PVD
C109F00	Type II diabetes mellitus with peripheral angiopathy	PVD
C109F11	NIDDM with peripheral circulatory disorder	PVD
C107400	Insulin dependent diabetes mellitus with gangrene	PVD
C108600	Type 2 diabetes mellitus with peripheral angiopathy	PVD
C109F12	Type II diabetes mellitus with gangrene	PVD
C109511	Diabetes mellitus, adult, + peripheral circulatory disorder"	PVD
C107100	Insulin dependent diab mell with peripheral angiopathy	PVD
C108G00	Diabetes mellitus NOS with peripheral circulatory disorder	PVD

C107z00	Thromboangiitis obliterans NOS	PVD
G731z00	IDDM with peripheral circulatory disorder	PVD
C107300	Type 1 diabetes mellitus with gangrene	PVD
C10E600	Diabetes mellitus, juvenile +peripheral circulatory disorder"	PVD
C107000	X]Other specified peripheral vascular diseases	PVD
Gyu7400	Type 1 diabetes mellitus with peripheral angiopathy	PVD
C10EG00	Ischaemic foot	PVD
G733.00	Referred for peripheral artery disease assessment	PVD
8HlP.00	Vascular claudication	PVD
G73z012	Type I diabetes mellitus with gangrene	PVD
J101.00	Oesophagitis	PUD
J101100	Reflux oesophagitis	PUD
J101112	Gastro-oesophageal reflux with oesophagitis	PUD
J101113	Oesophageal reflux with oesophagitis	PUD
J101114	Peptic oesophagitis	PUD
J101200	Chemical oesophagitis	PUD
J101300	Postoperative oesophagitis	PUD
J101400	Gangrenous oesophagitis	PUD
J101500	Phlegmonous oesophagitis	PUD
J101611	Barrett's oesophagus	PUD
J101y00	Other specified oesophagitis	PUD
J101z00	Oesophagitis NOS	PUD
J102.00	Ulcer of oesophagus	PUD
J102000	Peptic ulcer of oesophagus	PUD
J102100	Fungal ulcer of oesophagus	PUD
J102200	Oesophageal ulcer due to aspirin	PUD
J102300	Oesophageal ulcer due to chemicals	PUD
J102400	Oesophageal ulcer due to medicines	PUD
J102500	Barrett's ulcer of oesophagus	PUD
J102z00	Ulcer of oesophagus NOS	PUD
J10y600	Barrett's oesophagus	PUD
J11..00	Gastric ulcer - (GU)	PUD
J11..11	Prepyloric ulcer	PUD
J11..12	Pyloric ulcer	PUD
J110.00	Acute gastric ulcer	PUD
J110000	Acute gastric ulcer without mention of complication	PUD
J110100	Acute gastric ulcer with haemorrhage	PUD
J110111	Bleeding acute gastric ulcer	PUD
J110200	Acute gastric ulcer with perforation	PUD
J110400	Acute gastric ulcer with obstruction	PUD
J110y00	Acute gastric ulcer unspecified	PUD
J110z00	Acute gastric ulcer NOS	PUD
J111.00	Chronic gastric ulcer	PUD
J111000	Chronic gastric ulcer without mention of complication	PUD
J111100	Chronic gastric ulcer with haemorrhage	PUD

J111111	Bleeding chronic gastric ulcer	PUD
J111200	Chronic gastric ulcer with perforation	PUD
J111211	Perforated chronic gastric ulcer	PUD
J111400	Chronic gastric ulcer with obstruction	PUD
J111y00	Chronic gastric ulcer unspecified	PUD
J111z00	Chronic gastric ulcer NOS	PUD
J112.00	Anti-platelet induced gastric ulcer	PUD
J112z00	Anti-platelet induced gastric ulcer NOS	PUD
J113.00	Non steroidal anti inflammatory drug induced gastric ulcer	PUD
J113z00	Non steroidal anti inflammatory drug induced gastric ulc NOS	PUD
J11y.00	Unspecified gastric ulcer	PUD
J11y000	Unspecified gastric ulcer without mention of complication	PUD
J11y200	Unspecified gastric ulcer with perforation	PUD
J11y400	Unspecified gastric ulcer with obstruction	PUD
J11yz00	Unspecified gastric ulcer NOS	PUD
J11z.00	Gastric ulcer NOS	PUD
J11z.11	Gastric erosions	PUD
J11z.12	Multiple gastric ulcers	PUD
J12..00	Duodenal ulcer - (DU)	PUD
J120.00	Acute duodenal ulcer	PUD
J120000	Acute duodenal ulcer without mention of complication	PUD
J120200	Acute duodenal ulcer with perforation	PUD
J120400	Acute duodenal ulcer with obstruction	PUD
J120y00	Acute duodenal ulcer unspecified	PUD
J120z00	Acute duodenal ulcer NOS	PUD
J121.00	Chronic duodenal ulcer	PUD
J121000	Chronic duodenal ulcer without mention of complication	PUD
J121200	Chronic duodenal ulcer with perforation	PUD
J121211	Perforated chronic duodenal ulcer	PUD
J121400	Chronic duodenal ulcer with obstruction	PUD
J121y00	Chronic duodenal ulcer unspecified	PUD
J121z00	Chronic duodenal ulcer NOS	PUD
J122.00	Duodenal ulcer disease	PUD
J123.00	Duodenal erosion	PUD
J124.00	Recurrent duodenal ulcer	PUD
J125.00	Anti-platelet induced duodenal ulcer	PUD
J125z00	Anti-platelet induced duodenal ulcer NOS	PUD
J126.00	Non steroidal anti inflammatory drug induced duodenal ulcer	PUD
J126z00	Non steroidal anti inflammatory drug induced duoden ulc NOS	PUD
J12y.00	Unspecified duodenal ulcer	PUD
J12y000	Unspecified duodenal ulcer without mention of complication	PUD
J12y200	Unspecified duodenal ulcer with perforation	PUD
J12y400	Unspecified duodenal ulcer with obstruction	PUD
J12yz00	Unspecified duodenal ulcer NOS	PUD
J12z.00	Duodenal ulcer NOS	PUD

J13..00	Peptic ulcer - (PU) site unspecified	PUD
J13..11	Stress ulcer NOS	PUD
J130.00	Acute peptic ulcer	PUD
J130000	Acute peptic ulcer without mention of complication	PUD
J130200	Acute peptic ulcer with perforation	PUD
J130400	Acute peptic ulcer with obstruction	PUD
J130y00	Acute peptic ulcer unspecified	PUD
J130z00	Acute peptic ulcer NOS	PUD
J131.00	Chronic peptic ulcer	PUD
J131000	Chronic peptic ulcer without mention of complication	PUD
J131200	Chronic peptic ulcer with perforation	PUD
J131400	Chronic peptic ulcer with obstruction	PUD
J131y00	Chronic peptic ulcer unspecified	PUD
J131z00	Chronic peptic ulcer NOS	PUD
J13y.00	Unspecified peptic ulcer	PUD
J13y000	Unspecified peptic ulcer without mention of complication	PUD
J13y200	Unspecified peptic ulcer with perforation	PUD
J13y400	Unspecified peptic ulcer with obstruction	PUD
J13yz00	Unspecified peptic ulcer NOS	PUD
J13z.00	Peptic ulcer NOS	PUD
J14..00	Gastrojejunal ulcer (GJU)	PUD
J14..11	Anastomotic ulcer	PUD
J14..12	Gastrocolic ulcer	PUD
J14..13	Jejunal ulcer	PUD
J14..14	Marginal ulcer	PUD
J14..15	Stomal ulcer	PUD
J140.00	Acute gastrojejunal ulcer	PUD
J140000	Acute gastrojejunal ulcer without mention of complication	PUD
J140400	Acute gastrojejunal ulcer with obstruction	PUD
J140y00	Acute gastrojejunal ulcer unspecified	PUD
J140z00	Acute gastrojejunal ulcer NOS	PUD
J141.00	Chronic gastrojejunal ulcer	PUD
J141000	Chronic gastrojejunal ulcer without mention of complication	PUD
J141200	Chronic gastrojejunal ulcer with perforation	PUD
J141400	Chronic gastrojejunal ulcer with obstruction	PUD
J141y00	Chronic gastrojejunal ulcer unspecified	PUD
J141z00	Chronic gastrojejunal ulcer NOS	PUD
J14y.00	Unspecified gastrojejunal ulcer	PUD
J14y000	Unspecified gastrojejunal ulcer without mention complication	PUD
J14y200	Unspecified gastrojejunal ulcer with perforation	PUD
J14y400	Unspecified gastrojejunal ulcer with obstruction	PUD
J14yz00	Unspecified gastrojejunal ulcer NOS	PUD
J14z.00	Gastrojejunal ulcer NOS	PUD
J15..00	Gastritis and duodenitis	PUD
J150.00	Acute gastritis	PUD

J150000	Acute haemorrhagic gastritis	PUD
J151.00	Chronic gastritis	PUD
J151000	Chronic atrophic gastritis	PUD
J151100	Chronic inflammatory gastritis	PUD
J151200	Chronic superficial gastritis	PUD
J151z00	Chronic gastritis NOS	PUD
J152.00	Gastric mucosal hypertrophy	PUD
J153.00	Alcoholic gastritis	PUD
J154.00	Other specified gastritis	PUD
J154200	Irritant gastritis	PUD
J154300	Corrosive gastritis	PUD
J154400	Helicobacter gastritis	PUD
J154z00	Other specified gastritis NOS	PUD
J155.00	Gastritis unspecified	PUD
J156.00	Gastroduodenitis unspecified	PUD
J157.00	Duodenitis	PUD
J15z.00	Gastritis and duodenitis NOS	PUD
J16y400	Dyspepsia	PUD
H32..00	Emphysema	COPD
H3...11	Chronic obstructive airways disease	COPD
H3...00	Chronic obstructive pulmonary disease	COPD
H312200	Acute exacerbation of chronic obstructive airways disease	COPD
H31..00	Chronic bronchitis	COPD
H3z..00	Chronic obstructive airways disease NOS	COPD
H312000	Chronic asthmatic bronchitis	COPD
H312011	Chronic wheezy bronchitis	COPD
H3y1.00	Chron obstruct pulmonary dis wth acute exacerbation, unspec	COPD
H38..00	Severe chronic obstructive pulmonary disease	COPD
H37..00	Moderate chronic obstructive pulmonary disease	COPD
H36..00	Mild chronic obstructive pulmonary disease	COPD
H322.00	Centrilobular emphysema	COPD
H311.00	Mucopurulent chronic bronchitis	COPD
H3y..00	Other specified chronic obstructive airways disease	COPD
H312100	Emphysematous bronchitis	COPD
H31z.00	Chronic bronchitis NOS	COPD
H310000	Chronic catarrhal bronchitis	COPD
H32yz00	Other emphysema NOS	COPD
H310100	Smokers cough	COPD
H3y0.00	Chronic obstruct pulmonary dis with acute lower resp infectn	COPD
H320z00	Chronic bullous emphysema NOS	COPD
H31y000	Chronic tracheitis	COPD
H313.00	Mixed simple and mucopurulent chronic bronchitis	COPD
H310.00	Simple chronic bronchitis	COPD
H312300	Bronchiolitis obliterans	COPD
H320.00	Chronic bullous emphysema	COPD

H312.00	Obstructive chronic bronchitis	COPD
H32z.00	Emphysema NOS	COPD
H3z..11	Chronic obstructive pulmonary disease NOS	COPD
H311100	Fetid chronic bronchitis	COPD
H311000	Purulent chronic bronchitis	COPD
H32y.00	Other emphysema	COPD
H312z00	Obstructive chronic bronchitis NOS	COPD
H31y100	Chronic tracheobronchitis	COPD
H321.00	Panlobular emphysema	COPD
H320000	Segmental bullous emphysema	COPD
H32y111	Acute interstitial emphysema	COPD
H320200	Giant bullous emphysema	COPD
H310z00	Simple chronic bronchitis NOS	COPD
H311z00	Mucopurulent chronic bronchitis NOS	COPD
H32y200	MacLeod's unilateral emphysema	COPD
H31y.00	Other chronic bronchitis	COPD
H3y..11	Other specified chronic obstructive pulmonary disease	COPD
H31yz00	Other chronic bronchitis NOS	COPD
H320100	Zonal bullous emphysema	COPD
H32y100	Atrophic (senile) emphysema	COPD
H32y000	Acute vesicular emphysema	COPD
H39..00	Very severe chronic obstructive pulmonary disease	COPD
14OX.00	At risk of chronic obstructive pulmonary disease exacerbation	COPD
H320300	Bullous emphysema with collapse	COPD
14B3.12	History of chronic obstructive pulmonary disease	COPD
H320311	Tension pneumatocoele	COPD
H3A..00	End stage chronic obstructive airways disease	COPD
1442	H/O: raised blood lipids	hyperlipidaemia
44O3.00	Serum lipids borderline raised	hyperlipidaemia
44O4.00	Serum lipids high	hyperlipidaemia
44O6.00	Lipids abnormal	hyperlipidaemia
44P3.00	Serum cholesterol raised	hyperlipidaemia
44P4.00	Serum cholesterol very high	hyperlipidaemia
44Q3.00	Serum triglycerides raised	hyperlipidaemia
687B.00	Hyperlipidaemia risk assessment with New Zealand table	hyperlipidaemia
8CR3.00	Hyperlipidaemia clinical management plan	hyperlipidaemia
C320.00	Pure hypercholesterolaemia	hyperlipidaemia
C320.11	Familial hypercholesterolaemia	hyperlipidaemia
C320.13	Low density lipoproteinaemia	hyperlipidaemia
C320000	Familial hypercholesterolaemia	hyperlipidaemia
C320100	Hyperbetalipoproteinaemia	hyperlipidaemia
C320200	Hyperlipidaemia, group A	hyperlipidaemia
C320300	Low-density-lipoprotein-type (LDL) hyperlipoproteinaemia	hyperlipidaemia
C320400	Fredrickson's hyperlipoproteinaemia, type IIa	hyperlipidaemia
C320y00	Other specified pure hypercholesterolaemia	hyperlipidaemia

C320z00	Pure hypercholesterolaemia NOS	hyperlipidaemia
C322.00	Mixed hyperlipidaemia	hyperlipidaemia
C324.00	Hyperlipidaemia NOS	hyperlipidaemia
C325100	Hypo-alpha-lipoproteinaemia	hyperlipidaemia
C325200	Hypo-beta-lipoproteinaemia	hyperlipidaemia
C325300	A-beta-lipoproteinaemia	hyperlipidaemia
Cyu8D00	[X]Other hyperlipidaemia	hyperlipidaemia
ZC2CJ00	Dietary advice for hyperlipidaemia	hyperlipidaemia
ZV65317	[V]Dietary surveillance in hypercholesterolaemia	hyperlipidaemia
G580.00	Congestive heart failure	Heart failure
G581.00	Left ventricular failure	Heart failure
G58..11	Cardiac failure	Heart failure
G58..00	Heart failure	Heart failure
G580.11	Congestive cardiac failure	Heart failure
G58z.00	Heart failure NOS	Heart failure
G581000	Acute left ventricular failure	Heart failure
G581.13	Impaired left ventricular function	Heart failure
G580.14	Biventricular failure	Heart failure
1O1..00	Heart failure confirmed	Heart failure
G580.12	Right heart failure	Heart failure
G580.13	Right ventricular failure	Heart failure
G580300	Compensated cardiac failure	Heart failure
G58z.12	Cardiac failure NOS	Heart failure
G232.00	Hypertensive heart&renal dis wth (congestive) heart failure	Heart failure
G1yz100	Rheumatic left ventricular failure	Heart failure
G581.11	Asthma - cardiac	Heart failure
G580000	Acute congestive heart failure	Heart failure
G580200	Decompensated cardiac failure	Heart failure
G582.00	Acute heart failure	Heart failure
G580100	Chronic congestive heart failure	Heart failure
G581.12	Pulmonary oedema - acute	Heart failure
G234.00	Hyperten heart&renal dis+both(congestv)heart and renal fail	Heart failure
662T.00	Congestive heart failure monitoring	Heart failure
G58z.11	Weak heart	Heart failure
9N0k.00	Seen in heart failure clinic	Heart failure
662g.00	New York Heart Association classification - class II	Heart failure
14A6.00	H/O: heart failure	Heart failure
8HBE.00	Heart failure follow-up	Heart failure
662f.00	New York Heart Association classification - class I	Heart failure
662h.00	New York Heart Association classification - class III	Heart failure
R2y1000	[D]Cardiorespiratory failure	Heart failure
8B29.00	Cardiac failure therapy	Heart failure
ZRad.00	New York Heart Assoc classification heart failure symptoms	Heart failure
662W.00	Heart failure annual review	Heart failure
8H2S.00	Admit heart failure emergency	Heart failure

14AM.00	H/O: Heart failure in last year	Heart failure
G557100	Beriberi heart disease	Heart failure
662i.00	New York Heart Association classification - class IV	Heart failure
G211100	Benign hypertensive heart disease with CCF	Heart failure
G21z100	Hypertensive heart disease NOS with CCF	Heart failure
SP11111	Heart failure as a complication of care	Heart failure
G210100	Malignant hypertensive heart disease with CCF	Heart failure
G580400	Congestive heart failure due to valvular disease	Heart failure
G5y4z00	Post cardiac operation heart failure NOS	Heart failure
G583.11	HFNEF - heart failure with normal ejection fraction	Heart failure
G583.00	Heart failure with normal ejection fraction	Heart failure
G30..00	Acute myocardial infarction	CHD
7928z00	Transluminal balloon angioplasty of coronary artery NOS	CHD
792..11	Coronary artery bypass graft operations	CHD
G30..14	Heart attack	CHD
G340.12	Coronary artery disease	CHD
G33z300	Angina on effort	CHD
G33..00	Angina pectoris	CHD
G311.13	Unstable angina	CHD
G340.11	Triple vessel disease of the heart	CHD
G3z..00	Ischaemic heart disease NOS	CHD
G30..15	MI - acute myocardial infarction	CHD
G308.00	Inferior myocardial infarction NOS	CHD
G341000	Ventricular cardiac aneurysm	CHD
G30..12	Coronary thrombosis	CHD
7928	Transluminal balloon angioplasty of coronary artery	CHD
792Dy00	Other specified other bypass of coronary artery	CHD
G307.00	Acute subendocardial infarction	CHD
G340000	Single coronary vessel disease	CHD
G32..00	Old myocardial infarction	CHD
G311.11	Crescendo angina	CHD
ZV45K00	[V]Presence of coronary artery bypass graft	CHD
G340100	Double coronary vessel disease	CHD
G301.00	Other specified anterior myocardial infarction	CHD
G340.00	Coronary atherosclerosis	CHD
ZV45K11	[V]Presence of coronary artery bypass graft - CABG	CHD
7928.11	Percutaneous balloon coronary angioplasty	CHD
7927500	Open angioplasty of coronary artery	CHD
792..00	Coronary artery operations	CHD
7929y00	Other therapeutic transluminal op on coronary artery OS	CHD
G341.00	Aneurysm of heart	CHD
14A5.00	H/O: angina pectoris	CHD
ZV45L00	[V]Status following coronary angioplasty NOS	CHD
7921.11	Other autograft bypass of coronary artery	CHD
7920y00	Saphenous vein graft replacement of coronary artery OS	CHD

G343.00	Ischaemic cardiomyopathy	CHD
G311100	Unstable angina	CHD
7920200	Saphenous vein graft replacement of three coronary arteries	CHD
7921z00	Other autograft replacement of coronary artery NOS	CHD
7920100	Saphenous vein graft replacement of two coronary arteries	CHD
G33z200	Syncope anginosa	CHD
7920.11	Saphenous vein graft bypass of coronary artery	CHD
G37..00	Cardiac syndrome X	CHD
7920000	Saphenous vein graft replacement of one coronary artery	CHD
G302.00	Acute inferolateral infarction	CHD
7929400	Insertion of coronary artery stent	CHD
G31y000	Acute coronary insufficiency	CHD
G31y.00	Other acute and subacute ischaemic heart disease	CHD
7921	Other autograft replacement of coronary artery	CHD
G307000	Acute non-Q wave infarction	CHD
G33z500	Post infarct angina	CHD
7921200	Autograft replacement of three coronary arteries NEC	CHD
G307100	Acute non-ST segment elevation myocardial infarction	CHD
792z.00	Coronary artery operations NOS	CHD
G331.11	Variant angina pectoris	CHD
7920300	Saphenous vein graft replacement of four+ coronary arteries	CHD
G311500	Acute coronary syndrome	CHD
G300.00	Acute anterolateral infarction	CHD
G30X000	Acute ST segment elevation myocardial infarction	CHD
SP07600	Coronary artery bypass graft occlusion	CHD
G33z700	Stable angina	CHD
G331.00	Prinzmetal's angina	CHD
G30..11	Attack - heart	CHD
G30..16	Thrombosis - coronary	CHD
G30z.00	Acute myocardial infarction NOS	CHD
G301z00	Anterior myocardial infarction NOS	CHD
G305.00	Lateral myocardial infarction NOS	CHD
G310.11	Dressler's syndrome	CHD
G34z.00	Other chronic ischaemic heart disease NOS	CHD
G32..11	Healed myocardial infarction	CHD
G30A.00	Mural thrombosis	CHD
G311200	Angina at rest	CHD
G32..12	Personal history of myocardial infarction	CHD
G30..17	Silent myocardial infarction	CHD
G301100	Acute anteroseptal infarction	CHD
G311400	Worsening angina	CHD
G330000	Nocturnal angina	CHD
7920	Saphenous vein graft replacement of coronary artery	CHD
ZV45800	[V]Presence of coronary angioplasty implant and graft	CHD
7928000	Percut transluminal balloon angioplasty one coronary artery	CHD

G35..00	Subsequent myocardial infarction	CHD
G34z000	Asymptomatic coronary heart disease	CHD
ZV45700	[V]Presence of aortocoronary bypass graft	CHD
7929300	Rotary blade coronary angioplasty	CHD
7923z00	Prosthetic replacement of coronary artery NOS	CHD
7923	Prosthetic replacement of coronary artery	CHD
7921100	Autograft replacement of two coronary arteries NEC	CHD
G311.14	Angina at rest	CHD
G330.00	Angina decubitus	CHD
7A6G100	Peroperative angioplasty	CHD
G31y300	Transient myocardial ischaemia	CHD
792B000	Endarterectomy of coronary artery NEC	CHD
G3y..00	Other specified ischaemic heart disease	CHD
7925311	LIMA single anastomosis	CHD
7929000	Percutaneous transluminal laser coronary angioplasty	CHD
G34y100	Chronic myocardial ischaemia	CHD
G310.00	Postmyocardial infarction syndrome	CHD
G361.00	Atrial septal defect/curr comp folow acut myocardal infarct	CHD
G304.00	Posterior myocardial infarction NOS	CHD
G360.00	Haemopericardium/current comp folow acut myocard infarct	CHD
G34y000	Chronic coronary insufficiency	CHD
7929	Other therapeutic transluminal operations on coronary artery	CHD
G33z.00	Angina pectoris NOS	CHD
G33z600	New onset angina	CHD
G341.11	Cardiac aneurysm	CHD
G31..00	Other acute and subacute ischaemic heart disease	CHD
G31yz00	Other acute and subacute ischaemic heart disease NOS	CHD
G34..00	Other chronic ischaemic heart disease	CHD
G33zz00	Angina pectoris NOS	CHD
G30y000	Acute atrial infarction	CHD
7925.11	Creation of bypass from mammary artery to coronary artery	CHD
G344.00	Silent myocardial ischaemia	CHD
G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI	CHD
G303.00	Acute inferoposterior infarction	CHD
G30X.00	Acute transmural myocardial infarction of unspecif site	CHD
G330z00	Angina decubitus NOS	CHD
G309.00	Acute Q-wave infarct	CHD
G30..13	Cardiac rupture following myocardial infarction (MI)	CHD
7925100	Double implant of mammary arteries into coronary arteries	CHD
7924200	Revision of bypass for three coronary arteries	CHD
7922	Allograft replacement of coronary artery	CHD
792y.00	Other specified operations on coronary artery	CHD
7929z00	Other therapeutic transluminal op on coronary artery NOS	CHD
G38..00	Postoperative myocardial infarction	CHD
G33z400	Ischaemic chest pain	CHD

7922.11	Allograft bypass of coronary artery	CHD
G30B.00	Acute posterolateral myocardial infarction	CHD
7924	Revision of bypass for coronary artery	CHD
792Dz00	Other bypass of coronary artery NOS	CHD
792B.00	Repair of coronary artery NEC	CHD
7929100	Percut transluminal coronary thrombolysis with streptokinase	CHD
7925000	Double anastomosis of mammary arteries to coronary arteries	CHD
7928100	Percut translum balloon angioplasty mult coronary arteries	CHD
G311300	Refractory angina	CHD
G34y.00	Other specified chronic ischaemic heart disease	CHD
G30y.00	Other acute myocardial infarction	CHD
792D.00	Other bypass of coronary artery	CHD
792A.00	Diagnostic transluminal operations on coronary artery	CHD
G501.00	Post infarction pericarditis	CHD
14A3.00	H/O: myocardial infarct <60	CHD
G34yz00	Other specified chronic ischaemic heart disease NOS	CHD
7923.11	Prosthetic bypass of coronary artery	CHD
G36..00	Certain current complication follow acute myocardial infarct	CHD
G311.00	Preinfarction syndrome	CHD
G342.00	Atherosclerotic cardiovascular disease	CHD
G332.00	Coronary artery spasm	CHD
G362.00	Ventricle septal defect/ acute myocardial infarct	CHD
7925	Connection of mammary artery to coronary artery	CHD
7925y00	Connection of mammary artery to coronary artery OS	CHD
G351.00	Subsequent myocardial infarction of inferior wall	CHD
7A54500	Rotary blade angioplasty	CHD
G312.00	Coronary thrombosis not resulting in myocardial infarction	CHD
Gyu3000	[X]Other forms of angina pectoris	CHD
G311.12	Impending infarction	CHD
G31y200	Subendocardial ischaemia	CHD
14A4.00	H/O: myocardial infarct >60	CHD
G301000	Acute anteroapical infarction	CHD
7929111	Percut translum coronary thrombolytic therapy- streptokinase	CHD
G30y200	Acute septal infarction	CHD
7928y00	Transluminal balloon angioplasty of coronary artery OS	CHD
G341z00	Aneurysm of heart NOS	CHD
7927z00	Other open operation on coronary artery NOS	CHD
G384.00	Postoperative subendocardial myocardial infarction	CHD
7929500	Insertion of drug-eluting coronary artery stent	CHD
7928200	Percut translum balloon angioplasty bypass graft coronary a	CHD
7921300	Autograft replacement of four of more coronary arteries NEC	CHD
793G.00	Perc translumin balloon angioplasty stenting coronary artery	CHD
7921000	Autograft replacement of one coronary artery NEC	CHD
792Bz00	Repair of coronary artery NOS	CHD
7925200	Single anast mammary art to left ant descend coronary art	CHD

7922300	Allograft replacement of four or more coronary arteries	CHD
G350.00	Subsequent myocardial infarction of anterior wall	CHD
7922200	Allograft replacement of three coronary arteries	CHD
G30yz00	Other acute myocardial infarction NOS	CHD
G380.00	Postoperative transmural myocardial infarction anterior wall	CHD
G35X.00	Subsequent myocardial infarction of unspecified site	CHD
G381.00	Postoperative transmural myocardial infarction inferior wall	CHD
7927	Other open operations on coronary artery	CHD
7927300	Transposition of coronary artery NEC	CHD
7922z00	Allograft replacement of coronary artery NOS	CHD
7925011	LIMA sequential anastomosis	CHD
14AH.00	H/O: Myocardial infarction in last year	CHD
7925300	Single anastomosis of mammary artery to coronary artery NEC	CHD
7920z00	Saphenous vein graft replacement coronary artery NOS	CHD
7927400	Exploration of coronary artery	CHD
7924000	Revision of bypass for one coronary artery	CHD
G311z00	Preinfarction syndrome NOS	CHD
G33z100	Stenocardia	CHD
792C000	Replacement of coronary arteries using multiple methods	CHD
G311011	MI - myocardial infarction aborted	CHD
792C.00	Other replacement of coronary artery	CHD
792Ay00	Diagnostic transluminal operation on coronary artery OS	CHD
7925z00	Connection of mammary artery to coronary artery NOS	CHD
14AJ.00	H/O: Angina in last year	CHD
7922100	Allograft replacement of two coronary arteries	CHD
7924z00	Revision of bypass for coronary artery NOS	CHD
G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI	CHD
G341200	Aneurysm of coronary vessels	CHD
7922y00	Other specified allograft replacement of coronary artery	CHD
G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct	CHD
793G000	Perc translum ball angio insert 1-2 drug elut stents cor art	CHD
7926300	Single implantation thoracic artery into coronary artery NEC	CHD
793Gz00	Perc translum balloon angioplasty stenting coronary art NOS	CHD
792Az00	Diagnostic transluminal operation on coronary artery NOS	CHD
7921y00	Other autograft replacement of coronary artery OS	CHD
7926000	Double anastom thoracic arteries to coronary arteries NEC	CHD
G30y100	Acute papillary muscle infarction	CHD
7924500	Revision of implantation of thoracic artery into heart	CHD
G306.00	True posterior myocardial infarction	CHD
7A6H300	Prosthetic graft patch angioplasty	CHD
7923200	Prosthetic replacement of three coronary arteries	CHD
G33z000	Status anginosus	CHD
7929200	Percut translum inject therap subst to coronary artery NEC	CHD
7923100	Prosthetic replacement of two coronary arteries	CHD
7A6H400	Percutaneous transluminal angioplasty of vascular graft	CHD

G341100	Other cardiac wall aneurysm	CHD
7924100	Revision of bypass for two coronary arteries	CHD
7926200	Single anastomosis of thoracic artery to coronary artery NEC	CHD
7923300	Prosthetic replacement of four or more coronary arteries	CHD
7925312	RIMA single anastomosis	CHD
7925400	Single implantation of mammary artery into coronary artery	CHD
G31y100	Microinfarction of heart	CHD
G38z.00	Postoperative myocardial infarction, unspecified	CHD
792By00	Other specified repair of coronary artery	CHD
G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct	CHD
7922000	Allograft replacement of one coronary artery	CHD
792Cz00	Replacement of coronary artery NOS	CHD
G353.00	Subsequent myocardial infarction of other sites	CHD
7926z00	Connection of other thoracic artery to coronary artery NOS	CHD
793G200	Perc translum balloon angioplasty insert 1-2 stents cor art	CHD
7928300	Percut translum cutting balloon angioplasty coronary artery	CHD
793G100	Perc tran ball angio ins 3 or more drug elut stents cor art	CHD
G341300	Acquired atrioventricular fistula of heart	CHD
7925012	RIMA sequential anastomosis	CHD
7923000	Prosthetic replacement of one coronary artery	CHD
793G300	Percutaneous cor balloon angiop 3 more stents cor art NEC	CHD
7929600	Percutaneous transluminal atherectomy of coronary artery	CHD
793H000	Percutaneous transluminal balloon dilation cardiac conduit	CHD
792Cy00	Other specified replacement of coronary artery	CHD
7927y00	Other specified other open operation on coronary artery	CHD
7926	Connection of other thoracic artery to coronary artery	CHD
Gyu3400	[X]Acute transmural myocardial infarction of unspecif site	CHD
7924y00	Other specified revision of bypass for coronary artery	CHD
Gyu3600	[X]Subsequent myocardial infarction of unspecified site	CHD
7924300	Revision of bypass for four or more coronary arteries	CHD
G341111	Mural cardiac aneurysm	CHD
G39..00	Coronary microvascular disease	CHD
G383.00	Postoperative transmural myocardial infarction unspec site	CHD
Gyu3500	[X]Subsequent myocardial infarction of other sites	CHD
K011.00	Nephrotic syndrome with membranous glomerulonephritis	CKD
K00..00	Acute glomerulonephritis	CKD
K0...00	Nephritis, nephrosis and nephrotic syndrome	CKD
7L1A100	Peritoneal dialysis	CKD
K01..00	Nephrotic syndrome	CKD
K07z.00	Renal sclerosis NOS	CKD
G22..00	Hypertensive renal disease	CKD
K02y200	Chronic focal glomerulonephritis	CKD
K06..11	Uraemia NOS	CKD
K00..11	Acute nephritis	CKD
K04z.00	Acute renal failure NOS	CKD

K072.00	Glomerulosclerosis	CKD
7L1B000	Insertion of ambulatory peritoneal dialysis catheter	CKD
K0C0.00	Analgesic nephropathy	CKD
K0A..00	Glomerular disease	CKD
K0A0.00	Acute nephritic syndrome	CKD
14D1.00	H/O: nephritis	CKD
K010.00	Nephrotic syndrome with proliferative glomerulonephritis	CKD
K05..11	Chronic uraemia	CKD
J624.00	Hepatorenal syndrome	CKD
K021.00	Chronic membranous glomerulonephritis	CKD
7L1A.11	Dialysis for renal failure	CKD
K03..12	Nephropathy, unspecified	CKD
K01z.00	Nephrotic syndrome NOS	CKD
K02..11	Nephritis - chronic	CKD
K032.00	Membranoproliferative nephritis unspecified	CKD
K02yz00	Other chronic glomerulonephritis NOS	CKD
K0z..00	Nephritis, nephrosis and nephrotic syndrome NOS	CKD
K030.00	Proliferative nephritis unspecified	CKD
K190X00	Persistent proteinuria, unspecified	CKD
C104.00	Diabetes mellitus with renal manifestation	CKD
C104.11	Diabetic nephropathy	CKD
C104000	Diabetes mellitus, juvenile type, with renal manifestation	CKD
C104100	Diabetes mellitus, adult onset, with renal manifestation	CKD
C104z00	Diabetes mellitus with nephropathy NOS	CKD
D215.00	Anaemia secondary to renal failure	CKD
D215000	Anaemia secondary to chronic renal failure	CKD
8L50.00	Renal transplant planned	CKD
K017.00	Nephrotic syn difus mesangial prolifertiv glomerulonephritis	CKD
K018.00	Nephrotic syn,difus endocapilary proliftv glomerulonephritis	CKD
K019.00	Nephrotic syn,diffuse mesangiocapillary glomerulonephritis	CKD
K01A.00	Nephrotic syndrome, dense deposit disease	CKD
K01B.00	Nephrotic syndrome, diffuse crescentic glomerulonephritis	CKD
G22..11	Nephrosclerosis	CKD
G220.00	Malignant hypertensive renal disease	CKD
G221.00	Benign hypertensive renal disease	CKD
G222.00	Hypertensive renal disease with renal failure	CKD
G22z.00	Hypertensive renal disease NOS	CKD
G22z.11	Renal hypertension	CKD
C109011	Type II diabetes mellitus with renal complications	CKD
C109012	Type 2 diabetes mellitus with renal complications	CKD
C10FL00	Type 2 diabetes mellitus with persistent proteinuria	CKD
C10FL11	Type II diabetes mellitus with persistent proteinuria	CKD
C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria	CKD
C10FM11	Type II diabetes mellitus with persistent microalbuminuria	CKD
K016.00	Nephrotic syndrome, diffuse membranous glomerulonephritis	CKD

F374A00	Polyneuropathy in uraemia	CKD
K00y000	Acute glomerulonephritis in diseases EC	CKD
14V2.00	H/O: renal dialysis	CKD
14V2.11	H/O: kidney dialysis	CKD
K00..12	Bright's disease	CKD
K00z.00	Acute glomerulonephritis NOS	CKD
K13yz00	Other kidney and ureteric disorders NOS	CKD
K13yz11	Salt-losing nephritis	CKD
K13z.00	Kidney and ureter disease NOS	CKD
K13z000	Non-functioning kidney	CKD
K0A3.00	Chronic nephritic syndrome	CKD
K032600	Berger's IgA or IgG nephropathy	CKD
C345.00	Gout due to impairment of renal function	CKD
G232.00	Hypertensive heart&renal dis wth (congestive) heart failure	CKD
G233.00	Hypertensive heart and renal disease with renal failure	CKD
G234.00	Hyperten heart&renal dis+both(congestv)heart and renal fail	CKD
K01x411	Lupus nephritis	CKD
ZV45100	[V]Renal dialysis status	CKD
K015.00	Nephrotic syndrome, focal and segmental glomerular lesions	CKD
D310100	Henoch-Schonlein nephritis	CKD
7L1B100	Removal of ambulatory peritoneal dialysis catheter	CKD
K014.00	Nephrotic syndrome, minor glomerular abnormality	CKD
K03T.00	Tubulo-interstit nephritis, not specif as acute or chron	CKD
K032400	Familial glomerulonephritis in Alport's syndrome	CKD
K0C..00	Drug/heavy-metal-induced tubulo-interstitial and tub conditn	CKD
C109C12	Type 2 diabetes mellitus with nephropathy	CKD
K08yz00	Other impaired renal function disorder NOS	CKD
K08z.00	Impaired renal function disorder NOS	CKD
K06..00	Renal failure unspecified	CKD
K06..12	Kidney failure unspecified	CKD
K060.00	Renal impairment	CKD
K07..00	Renal sclerosis unspecified	CKD
7B06300	Exploration of renal transplant	CKD
K03y.00	Other nephritis and nephrosis unspecified	CKD
K03y000	Other nephritis and nephrosis in diseases EC	CKD
K03y100	Other exudative nephritis	CKD
K01wz00	Congenital nephrotic syndrome NOS	CKD
K01x.00	Nephrotic syndrome in diseases EC	CKD
K01x000	Nephrotic syndrome in amyloidosis	CKD
K01x100	Nephrotic syndrome in diabetes mellitus	CKD
K000.00	Acute proliferative glomerulonephritis	CKD
K013.00	Nephrotic syndrome with minimal change glomerulonephritis	CKD
K05..13	Chronic kidney disease	CKD
K050.00	End stage renal failure	CKD
K05..00	Chronic renal failure	CKD

K060.11	Impaired renal function	CKD
K08..00	Impaired renal function disorder	CKD
Kyu0000	[X]Glomerular disorders in infectious+parasitic diseases CE	CKD
Kyu0100	[X]Glomerular disorders in neoplastic diseases CE	CKD
Kyu0200	[X]Glomerulr disordrs/bld dis+disordr inv immune mechansm CE	CKD
Kyu0300	[X]Glomerular disorders in diabetes mellitus	CKD
Kyu0400	[X]Glomerulr disordr/oth endocrine,nutritnl+metabolic dis CE	CKD
Kyu0500	[X]Glomerular disordrs/systemic disordrs/connectiv tissue CE	CKD
Kyu0600	[X]Glomerular disorders in other diseases CE	CKD
Kyu0700	[X]Rapidly progressive nephritic syndrome, other	CKD
Kyu0800	[X]Unspecif nephritic syndr, minor glomerular abnormality	CKD
Kyu0900	[X]Unsp nephrit synd, diff mesang prolif glomerulonephritis	CKD
Kyu0A00	[X]Unsp nephrit synd, diff endocap prolif glomerulonephritis	CKD
Kyu0B00	[X]Unspecified nephritic syndrome, dense deposit disease	CKD
Kyu0C00	[X]Unspecif nephr synd, diff concentric glomerulonephritis	CKD
Kyu0D00	[X]Isolated proteinuria, with oth specif morpholog changes	CKD
Kyu0E00	[X]Isolated proteinuria, with unspecified morpholog changes	CKD
Kyu0F00	[X]Hereditary nephropathy, unspecif morphological changes	CKD
Kyu1.00	[X]Renal tubulo-interstitial diseases	CKD
Kyu1000	[X]Other chronic tubulo-interstitial nephritis	CKD
Kyu1100	[X]Other and unspecified hydronephrosis	CKD
Kyu1200	[X]Other obstructive and reflux uropathy	CKD
Kyu1300	[X]Obstructive and reflux uropathy, unspecified	CKD
Kyu1400	[X]Nephropathy induced by other drugs+biological substances	CKD
Kyu1500	[X]Toxic nephropathy, not elsewhere classified	CKD
Kyu1600	[X]Other specified renal tubulo-interstitial diseases	CKD
Kyu1700	[X]Renal tubulo-interstitial disordr/infect+parasitic dis CE	CKD
Kyu1800	[X]Renal tubulo-interstitial disordrs/neoplastic diseases CE	CKD
Kyu1900	[X]Renal tub-interstl disord/bld dis+disord invl imm mech CE	CKD
Kyu1A00	[X]Renal tubulo-interstitial disorders/metabolic diseases CE	CKD
Kyu1B00	[X]Renal tubul-interstitl disordrs/connectv tissu disordr CE	CKD
Kyu1C00	[X]Renal tubulo-interstitial disorders/transplant rejection	CKD
Kyu1D00	[X]Renal tubulo-interstitial disorders in other diseases CE	CKD
Kyu1E00	[X]Tubulo-interstit nephritis, not specif as acute or chron	CKD
Kyu1F00	[X]Hydronephrosis with ureteral stricture NEC	CKD
Kyu2.00	[X]Renal failure	CKD
Kyu2000	[X]Other acute renal failure	CKD
Kyu2100	[X]Other chronic renal failure	CKD
K0E..00	Acute-on-chronic renal failure	CKD
C108D00	Insulin dependent diabetes mellitus with nephropathy	CKD
C108D11	Type I diabetes mellitus with nephropathy	CKD
C108D12	Type 1 diabetes mellitus with nephropathy	CKD
1Z1..00	Chronic renal impairment	CKD
1Z10.00	Chronic kidney disease stage 1	CKD
1Z11.00	Chronic kidney disease stage 2	CKD

1Z12.00	Chronic kidney disease stage 3	CKD
1Z13.00	Chronic kidney disease stage 4	CKD
1Z14.00	Chronic kidney disease stage 5	CKD
1Z15.00	Chronic kidney disease stage 3A	CKD
1Z16.00	Chronic kidney disease stage 3B	CKD
1Z17.00	Chronic kidney disease stage 1 with proteinuria	CKD
1Z17.11	CKD stage 1 with proteinuria	CKD
1Z18.00	Chronic kidney disease stage 1 without proteinuria	CKD
1Z18.11	CKD stage 1 without proteinuria	CKD
1Z19.00	Chronic kidney disease stage 2 with proteinuria	CKD
1Z19.11	CKD stage 2 with proteinuria	CKD
1Z1A.00	Chronic kidney disease stage 2 without proteinuria	CKD
1Z1A.11	CKD stage 2 without proteinuria	CKD
1Z1B.00	Chronic kidney disease stage 3 with proteinuria	CKD
1Z1B.11	CKD stage 3 with proteinuria	CKD
1Z1C.00	Chronic kidney disease stage 3 without proteinuria	CKD
1Z1C.11	CKD stage 3 without proteinuria	CKD
1Z1D.00	Chronic kidney disease stage 3A with proteinuria	CKD
1Z1D.11	CKD stage 3A with proteinuria	CKD
1Z1E.00	Chronic kidney disease stage 3A without proteinuria	CKD
1Z1E.11	CKD stage 3A without proteinuria	CKD
1Z1F.00	Chronic kidney disease stage 3B with proteinuria	CKD
1Z1F.11	CKD stage 3B with proteinuria	CKD
1Z1G.00	Chronic kidney disease stage 3B without proteinuria	CKD
1Z1G.11	CKD stage 3B without proteinuria	CKD
1Z1H.00	Chronic kidney disease stage 4 with proteinuria	CKD
1Z1H.11	CKD stage 4 with proteinuria	CKD
1Z1J.00	Chronic kidney disease stage 4 without proteinuria	CKD
1Z1J.11	CKD stage 4 without proteinuria	CKD
1Z1K.00	Chronic kidney disease stage 5 with proteinuria	CKD
1Z1K.11	CKD stage 5 with proteinuria	CKD
1Z1L.00	Chronic kidney disease stage 5 without proteinuria	CKD
1Z1L.11	CKD stage 5 without proteinuria	CKD
1Z1M.00	CKD with GFR category G1 & albuminuria category A1	CKD
1Z1N.00	CKD with GFR category G1 & albuminuria category A2	CKD
1Z1P.00	CKD with GFR category G1 & albuminuria category A3	CKD
1Z1Q.00	CKD with GFR category G2 & albuminuria category A1	CKD
1Z1R.00	CKD with GFR category G2 & albuminuria category A2	CKD
1Z1S.00	CKD with GFR category G2 & albuminuria category A3	CKD
1Z1T.00	CKD with GFR category G3a & albuminuria category A1	CKD
1Z1V.00	CKD with GFR category G3a & albuminuria category A2	CKD
1Z1W.00	CKD with GFR category G3a & albuminuria category A3	CKD
1Z1X.00	CKD with GFR category G3b & albuminuria category A1	CKD
1Z1Y.00	CKD with GFR category G3b & albuminuria category A2	CKD
1Z1Z.00	CKD with GFR category G3b & albuminuria category A3	CKD

C10yy00	Other specified diabetes mellitus with other spec comps	Diabetes
C10FC00	Type 2 diabetes mellitus with nephropathy	Diabetes
C10F500	Type 2 diabetes mellitus with gangrene	Diabetes
66AI.00	Diabetic - good control	Diabetes
C104y00	Other specified diabetes mellitus with renal complications	Diabetes
C100100	Diabetes mellitus, adult onset, no mention of complication	Diabetes
C100111	Maturity onset diabetes	Diabetes
C103.00	Diabetes mellitus with ketoacidotic coma	Diabetes
C106.00	Diabetes mellitus with neurological manifestation	Diabetes
C106.13	Diabetes mellitus with polyneuropathy	Diabetes
C104.00	Diabetes mellitus with renal manifestation	Diabetes
13L4.11	Diabetic child	Diabetes
C109600	Non-insulin-dependent diabetes mellitus with retinopathy	Diabetes
C109.12	Type 2 diabetes mellitus	Diabetes
66AL.00	Diabetic-uncooperative patient	Diabetes
C109G11	Type II diabetes mellitus with arthropathy	Diabetes
C109012	Type 2 diabetes mellitus with renal complications	Diabetes
C109.13	Type II diabetes mellitus	Diabetes
C109J12	Insulin treated Type II diabetes mellitus	Diabetes
C109J00	Insulin treated Type 2 diabetes mellitus	Diabetes
C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria	Diabetes
C10FB00	Type 2 diabetes mellitus with polyneuropathy	Diabetes
C10F600	Type 2 diabetes mellitus with retinopathy	Diabetes
C10F000	Type 2 diabetes mellitus with renal complications	Diabetes
C102.00	Diabetes mellitus with hyperosmolar coma	Diabetes
66AJz00	Diabetic - poor control NOS	Diabetes
C10N.00	Secondary diabetes mellitus	Diabetes
C106z00	Diabetes mellitus NOS with neurological manifestation	Diabetes
C10F.11	Type II diabetes mellitus	Diabetes
C109711	Type II diabetes mellitus - poor control	Diabetes
C109G00	Non-insulin dependent diabetes mellitus with arthropathy	Diabetes
C109C12	Type 2 diabetes mellitus with nephropathy	Diabetes
C10FQ00	Type 2 diabetes mellitus with exudative maculopathy	Diabetes
C10F700	Type 2 diabetes mellitus - poor control	Diabetes
C10FL00	Type 2 diabetes mellitus with persistent proteinuria	Diabetes
66AV.00	Diabetic on insulin and oral treatment	Diabetes
C109900	Non-insulin-dependent diabetes mellitus without complication	Diabetes
C107.11	Diabetes mellitus with gangrene	Diabetes
C107.12	Diabetes with gangrene	Diabetes
C10FN00	Type 2 diabetes mellitus with ketoacidosis	Diabetes
C105.00	Diabetes mellitus with ophthalmic manifestation	Diabetes
C109612	Type 2 diabetes mellitus with retinopathy	Diabetes
C102100	Diabetes mellitus, adult onset, with hyperosmolar coma	Diabetes
C10F311	Type II diabetes mellitus with multiple complications	Diabetes
C109D00	Non-insulin dependent diabetes mellitus with hypoglyca coma	Diabetes
C10M.00	Lipoatrophic diabetes mellitus	Diabetes
66AK.00	Diabetic - cooperative patient	Diabetes
C109E12	Type 2 diabetes mellitus with diabetic cataract	Diabetes
C10FE00	Type 2 diabetes mellitus with diabetic cataract	Diabetes
C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy	Diabetes
C10z.00	Diabetes mellitus with unspecified complication	Diabetes
C109712	Type 2 diabetes mellitus - poor control	Diabetes
C109212	Type 2 diabetes mellitus with neurological complications	Diabetes
C109512	Type 2 diabetes mellitus with gangrene	Diabetes
C108y00	Other specified diabetes mellitus with multiple comps	Diabetes
C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma	Diabetes

C10F711	Type II diabetes mellitus - poor control	Diabetes
C10F100	Type 2 diabetes mellitus with ophthalmic complications	Diabetes
C105y00	Other specified diabetes mellitus with ophthalmic complicatn	Diabetes
C109B11	Type II diabetes mellitus with polyneuropathy	Diabetes
C109H11	Type II diabetes mellitus with neuropathic arthropathy	Diabetes
C10F900	Type 2 diabetes mellitus without complication	Diabetes
C109E11	Type II diabetes mellitus with diabetic cataract	Diabetes
C10F400	Type 2 diabetes mellitus with ulcer	Diabetes
C10F611	Type II diabetes mellitus with retinopathy	Diabetes
C109G12	Type 2 diabetes mellitus with arthropathy	Diabetes
C109011	Type II diabetes mellitus with renal complications	Diabetes
C109100	Non-insulin-dependent diabetes mellitus with ophthalm comps	Diabetes
C10FB11	Type II diabetes mellitus with polyneuropathy	Diabetes
L180600	Pre-existing diabetes mellitus, non-insulin-dependent	Diabetes
C109A11	Type II diabetes mellitus with mononeuropathy	Diabetes
C100z00	Diabetes mellitus NOS with no mention of complication	Diabetes
C10G.00	Secondary pancreatic diabetes mellitus	Diabetes
C10FP00	Type 2 diabetes mellitus with ketoacidotic coma	Diabetes
Cyu2.00	[X]Diabetes mellitus	Diabetes
C10A.00	Malnutrition-related diabetes mellitus	Diabetes
C109000	Non-insulin-dependent diabetes mellitus with renal comps	Diabetes
C10F911	Type II diabetes mellitus without complication	Diabetes
C101100	Diabetes mellitus, adult onset, with ketoacidosis	Diabetes
C109F11	Type II diabetes mellitus with peripheral angiopathy	Diabetes
C109411	Type II diabetes mellitus with ulcer	Diabetes
L180X00	Pre-existing diabetes mellitus, unspecified	Diabetes
C109200	Non-insulin-dependent diabetes mellitus with neuro comps	Diabetes
C109D11	Type II diabetes mellitus with hypoglycaemic coma	Diabetes
C107400	NIDDM with peripheral circulatory disorder	Diabetes
C10F011	Type II diabetes mellitus with renal complications	Diabetes
C109611	Type II diabetes mellitus with retinopathy	Diabetes
C10FG00	Type 2 diabetes mellitus with arthropathy	Diabetes
C103y00	Other specified diabetes mellitus with coma	Diabetes
C109C00	Non-insulin dependent diabetes mellitus with nephropathy	Diabetes
C109111	Type II diabetes mellitus with ophthalmic complications	Diabetes
C10D.11	Maturity onset diabetes in youth type 2	Diabetes
C109F12	Type 2 diabetes mellitus with peripheral angiopathy	Diabetes
C10FL11	Type II diabetes mellitus with persistent proteinuria	Diabetes
C109D12	Type 2 diabetes mellitus with hypoglycaemic coma	Diabetes
C106y00	Other specified diabetes mellitus with neurological comps	Diabetes
C109511	Type II diabetes mellitus with gangrene	Diabetes
C109300	Non-insulin-dependent diabetes mellitus with multiple comps	Diabetes
C10FA00	Type 2 diabetes mellitus with mononeuropathy	Diabetes
C107100	Diabetes mellitus, adult, + peripheral circulatory disorder	Diabetes
C10y100	Diabetes mellitus, adult, + other specified manifestation	Diabetes
C10FR00	Type 2 diabetes mellitus with gastroparesis	Diabetes
C10z100	Diabetes mellitus, adult onset, + unspecified complication	Diabetes
C10zy00	Other specified diabetes mellitus with unspecified comps	Diabetes
C10zz00	Diabetes mellitus NOS with unspecified complication	Diabetes
C108z00	Unspecified diabetes mellitus with multiple complications	Diabetes
C109C11	Type II diabetes mellitus with nephropathy	Diabetes
C107z00	Diabetes mellitus NOS with peripheral circulatory disorder	Diabetes
C103z00	Diabetes mellitus NOS with ketoacidotic coma	Diabetes
C10F300	Type 2 diabetes mellitus with multiple complications	Diabetes
C109412	Type 2 diabetes mellitus with ulcer	Diabetes
C10A000	Malnutrition-related diabetes mellitus with coma	Diabetes

C109H12	Type 2 diabetes mellitus with neuropathic arthropathy	Diabetes
C109211	Type II diabetes mellitus with neurological complications	Diabetes
C103100	Diabetes mellitus, adult onset, with ketoacidotic coma	Diabetes
C109E00	Non-insulin depend diabetes mellitus with diabetic cataract	Diabetes
C109112	Type 2 diabetes mellitus with ophthalmic complications	Diabetes
C107000	Diabetes mellitus, juvenile +peripheral circulatory disorder	Diabetes
C100112	Non-insulin dependent diabetes mellitus	Diabetes
C10..00	Diabetes mellitus	Diabetes
C10F.00	Type 2 diabetes mellitus	Diabetes
C101.00	Diabetes mellitus with ketoacidosis	Diabetes
66A4.00	Diabetic on oral treatment	Diabetes
66AJ.00	Diabetic - poor control	Diabetes
C109.00	Non-insulin dependent diabetes mellitus	Diabetes
C109.11	NIDDM - Non-insulin dependent diabetes mellitus	Diabetes
1434	H/O: diabetes mellitus	Diabetes
66A3.00	Diabetic on diet only	Diabetes
C106.12	Diabetes mellitus with neuropathy	Diabetes
C109700	Non-insulin dependent diabetes mellitus - poor control	Diabetes
66A5.00	Diabetic on insulin	Diabetes
66AJ.11	Unstable diabetes	Diabetes
C10yz00	Diabetes mellitus NOS with other specified manifestation	Diabetes
C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy	Diabetes
C102z00	Diabetes mellitus NOS with hyperosmolar coma	Diabetes
C10FM11	Type II diabetes mellitus with persistent microalbuminuria	Diabetes
C10F411	Type II diabetes mellitus with ulcer	Diabetes
C10N100	Cystic fibrosis related diabetes mellitus	Diabetes
C10FE11	Type II diabetes mellitus with diabetic cataract	Diabetes
C10N000	Secondary diabetes mellitus without complication	Diabetes
C10FA11	Type II diabetes mellitus with mononeuropathy	Diabetes
C10G000	Secondary pancreatic diabetes mellitus without complication	Diabetes
C10F211	Type II diabetes mellitus with neurological complications	Diabetes
C10FD11	Type II diabetes mellitus with hypoglycaemic coma	Diabetes
C10y.00	Diabetes mellitus with other specified manifestation	Diabetes
C107200	Diabetes mellitus, adult with gangrene	Diabetes
C10A100	Malnutrition-related diabetes mellitus with ketoacidosis	Diabetes
C10F200	Type 2 diabetes mellitus with neurological complications	Diabetes
C105z00	Diabetes mellitus NOS with ophthalmic manifestation	Diabetes
C109400	Non-insulin dependent diabetes mellitus with ulcer	Diabetes
C104100	Diabetes mellitus, adult onset, with renal manifestation	Diabetes
C104z00	Diabetes mellitus with nephropathy NOS	Diabetes
C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy	Diabetes
C107.00	Diabetes mellitus with peripheral circulatory disorder	Diabetes
C10D.00	Diabetes mellitus autosomal dominant type 2	Diabetes
C109J11	Insulin treated non-insulin dependent diabetes mellitus	Diabetes
C10FF00	Type 2 diabetes mellitus with peripheral angiopathy	Diabetes
C101y00	Other specified diabetes mellitus with ketoacidosis	Diabetes
C100.00	Diabetes mellitus with no mention of complication	Diabetes
C106100	Diabetes mellitus, adult onset, + neurological manifestation	Diabetes
C109500	Non-insulin dependent diabetes mellitus with gangrene	Diabetes
C105100	Diabetes mellitus, adult onset, + ophthalmic manifestation	Diabetes
Cyu2000	[X]Other specified diabetes mellitus	Diabetes
C101z00	Diabetes mellitus NOS with ketoacidosis	Diabetes
Cyu2300	[X]Unspecified diabetes mellitus with renal complications	Diabetes
C10A500	Malnutritn-relat diabetes melitus wth periph circul complctn	Diabetes
C10F111	Type II diabetes mellitus with ophthalmic complications	Diabetes
66As.00	Diabetic on subcutaneous treatment	Diabetes

C10FC11	Type II diabetes mellitus with nephropathy	Diabetes
C10FG11	Type II diabetes mellitus with arthropathy	Diabetes
C10F511	Type II diabetes mellitus with gangrene	Diabetes
C10FF11	Type II diabetes mellitus with peripheral angiopathy	Diabetes
C109912	Type 2 diabetes mellitus without complication	Diabetes
C10FP11	Type II diabetes mellitus with ketoacidotic coma	Diabetes
C10FN11	Type II diabetes mellitus with ketoacidosis	Diabetes
C109312	Type 2 diabetes mellitus with multiple complications	Diabetes
C109911	Type II diabetes mellitus without complication	Diabetes
L180700	Pre-existing malnutrition-related diabetes mellitus	Diabetes
C10FH11	Type II diabetes mellitus with neuropathic arthropathy	Diabetes
J68..00	Gastrointestinal haemorrhage	Bleeding
J680.00	Haematemesis	Bleeding
J680.11	Vomiting of blood	Bleeding
J681.00	Melaena	Bleeding
J681.11	Blood in stool	Bleeding
J681.12	Altered blood in stools	Bleeding
J681.13	Blood in stools altered	Bleeding
J68z.00	Gastrointestinal haemorrhage unspecified	Bleeding
J68z.11	GIB - Gastrointestinal bleeding	Bleeding
J68z000	Gastric haemorrhage NOS	Bleeding
J68z100	Intestinal haemorrhage NOS	Bleeding
J68z200	Upper gastrointestinal haemorrhage	Bleeding
J68zz00	Gastrointestinal tract haemorrhage NOS	Bleeding
G850.00	Oesophageal varices with bleeding	Bleeding
J12y100	Unspecified duodenal ulcer with haemorrhage	Bleeding
J120100	Acute duodenal ulcer with haemorrhage	Bleeding
J121100	Chronic duodenal ulcer with haemorrhage	Bleeding
J121111	Bleeding chronic duodenal ulcer	Bleeding
19E4.12	C/O - melaena	Bleeding
J110100	Acute gastric ulcer with haemorrhage	Bleeding
J110111	Bleeding acute gastric ulcer	Bleeding
1994.00	Vomiting blood - fresh	Bleeding
1994.11	Blood in vomit - symptom	Bleeding
1995.00	Vomiting blood - coffee ground	Bleeding
J111111	Bleeding chronic gastric ulcer	Bleeding
J11y100	Unspecified gastric ulcer with haemorrhage	Bleeding
J120300	Acute duodenal ulcer with haemorrhage and perforation	Bleeding
J121300	Chronic duodenal ulcer with haemorrhage and perforation	Bleeding
J11yy00	Unspec gastric ulcer; unspec haemorrhage and/or perforation	Bleeding
J11y300	Unspecified gastric ulcer with haemorrhage and perforation	Bleeding
J13y100	Unspecified peptic ulcer with haemorrhage	Bleeding
J13y300	Unspecified peptic ulcer with haemorrhage and perforation	Bleeding
J110300	Acute gastric ulcer with haemorrhage and perforation	Bleeding
J111300	Chronic gastric ulcer with haemorrhage and perforation	Bleeding
J140100	Acute gastrojejunal ulcer with haemorrhage	Bleeding
J140300	Acute gastrojejunal ulcer with haemorrhage and perforation	Bleeding
J12y300	Unspecified duodenal ulcer with haemorrhage and perforation	Bleeding
G60..00	Subarachnoid haemorrhage	Bleeding
G61..00	Intracerebral haemorrhage	Bleeding
G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage	Bleeding
G61..12	Stroke due to intracerebral haemorrhage	Bleeding
G610.00	Cortical haemorrhage	Bleeding
G611.00	Internal capsule haemorrhage	Bleeding
G612.00	Basal nucleus haemorrhage	Bleeding
G613.00	Cerebellar haemorrhage	Bleeding

G614.00	Pontine haemorrhage	Bleeding
G615.00	Bulbar haemorrhage	Bleeding
G616.00	External capsule haemorrhage	Bleeding
G617.00	Intracerebral haemorrhage, intraventricular	Bleeding
G618.00	Intracerebral haemorrhage, multiple localized	Bleeding
G619.00	Lobar cerebral haemorrhage	Bleeding
G61X.00	Intracerebral haemorrhage in hemisphere, unspecified	Bleeding
G61X000	Left sided intracerebral haemorrhage, unspecified	Bleeding
G61X100	Right sided intracerebral haemorrhage, unspecified	Bleeding
G61z.00	Intracerebral haemorrhage NOS	Bleeding
G62..00	Other and unspecified intracranial haemorrhage	Bleeding
G620.00	Extradural haemorrhage - nontraumatic	Bleeding
G621.00	Subdural haemorrhage - nontraumatic	Bleeding
G622.00	Subdural haematoma - nontraumatic	Bleeding
G623.00	Subdural haemorrhage NOS	Bleeding
G62z.00	Intracranial haemorrhage NOS	Bleeding
S624.11	Epidural haematoma following injury	Bleeding
S626.00	Epidural haemorrhage	Bleeding
G60z.00	Subarachnoid haemorrhage NOS	Bleeding
G601.00	Subarachnoid haemorrhage from carotid siphon and bifurcation	Bleeding
G602.00	Subarachnoid haemorrhage from middle cerebral artery	Bleeding
G603.00	Subarachnoid haemorrhage from anterior communicating artery	Bleeding
G604.00	Subarachnoid haemorrhage from posterior communicating artery	Bleeding
G605.00	Subarachnoid haemorrhage from basilar artery	Bleeding
G606.00	Subarachnoid haemorrhage from vertebral artery	Bleeding
G60X.00	Subarachnoid haemorrh from intracranial artery, unspecif	Bleeding
Gyu6.00	[X]Cerebrovascular diseases	Bleeding
Gyu6000	[X]Subarachnoid haemorrhage from other intracranial arteries	Bleeding
Gyu6100	[X]Other subarachnoid haemorrhage	Bleeding
Gyu6200	[X]Other intracerebral haemorrhage	Bleeding
S62..00	Cerebral haemorrhage following injury	Bleeding
S62..11	Extradural haemorrhage following injury	Bleeding
S62..12	Subarachnoid haemorrhage following injury	Bleeding
S62..13	Subdural haemorrhage following injury	Bleeding
S62..14	Traumatic cerebral haemorrhage	Bleeding
S620.00	Closed traumatic subarachnoid haemorrhage	Bleeding
S620.11	Middle meningeal haemmorhage following injury	Bleeding
S621.00	Open traumatic subarachnoid haemorrhage	Bleeding
S622.00	Closed traumatic subdural haemorrhage	Bleeding
S623.00	Open traumatic subdural haemorrhage	Bleeding
S624.00	Closed traumatic extradural haemorrhage	Bleeding
S625.00	Open traumatic extradural haemorrhage	Bleeding
S627.00	Traumatic subarachnoid haemorrhage	Bleeding
S628.00	Traumatic subdural haemorrhage	Bleeding
S629.00	Traumatic subdural haematoma	Bleeding
S629000	Traumatic subdural haematoma without open intracranial wound	Bleeding
S629100	Traumatic subdural haematoma with open intracranial wound	Bleeding
S62A.00	Traumatic extradural haematoma	Bleeding
S62A000	Traumatic extradural haemat without open intracranial wound	Bleeding
S62A100	Traumatic extradural haematoma with open intracranial wound	Bleeding
S62z.00	Cerebral haemorrhage following injury NOS	Bleeding
S63..00	Other cerebral haemorrhage following injury	Bleeding
S630.12	Intracranial haematoma following injury	Bleeding
S63z.00	Other cerebral haemorrhage following injury NOS	Bleeding
J68..00	Gastrointestinal haemorrhage	Bleeding
66Ad.00	Hypoglycaemic attack requiring 3rd party assistance	Hypoglycaemia

C108E00	Insulin dependent diabetes mellitus with hypoglycaemic coma	Hypoglycaemia
C108E11	Type I diabetes mellitus with hypoglycaemic coma	Hypoglycaemia
C108E12	Type 1 diabetes mellitus with hypoglycaemic coma	Hypoglycaemia
C109D00	Non-insulin dependent diabetes mellitus with hypoglyca coma	Hypoglycaemia
C109D11	Type II diabetes mellitus with hypoglycaemic coma	Hypoglycaemia
C109D12	Type 2 diabetes mellitus with hypoglycaemic coma	Hypoglycaemia
C10EE00	Type 1 diabetes mellitus with hypoglycaemic coma	Hypoglycaemia
C10EE11	Type I diabetes mellitus with hypoglycaemic coma	Hypoglycaemia
C10EE12	Insulin dependent diabetes mellitus with hypoglycaemic coma	Hypoglycaemia
C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma	Hypoglycaemia
C10FD11	Type II diabetes mellitus with hypoglycaemic coma	Hypoglycaemia
C110.00	Hypoglycaemic coma	Hypoglycaemia
C110z00	Hypoglycaemic coma NOS	Hypoglycaemia
C112.00	Hypoglycaemia unspecified	Hypoglycaemia
C112000	Reactive hypoglycaemia NOS	Hypoglycaemia
C112100	Spontaneous hypoglycaemia NOS	Hypoglycaemia
C112z00	Hypoglycaemia unspecified NOS	Hypoglycaemia
C116.00	Other hypoglycaemia	Hypoglycaemia
C116000	Post-prandial hypoglycaemia	Hypoglycaemia
C11y100	Drug-induced hypoglycaemia without coma	Hypoglycaemia
Cyu3000	[X]Other hypoglycaemia	Hypoglycaemia
F374500	Polyneuropathy in hypoglycaemia	Hypoglycaemia
G2...00	Hypertensive disease	Hypertension
G20..11	High blood pressure	Hypertension
G20..00	Essential hypertension	Hypertension
G201.00	Benign essential hypertension	Hypertension
G20z.11	Hypertension NOS	Hypertension
G202.00	Systolic hypertension	Hypertension
G2z..00	Hypertensive disease NOS	Hypertension
G24..00	Secondary hypertension	Hypertension
G20z.00	Essential hypertension NOS	Hypertension
G200.00	Malignant essential hypertension	Hypertension
G24z.00	Secondary hypertension NOS	Hypertension
G2y..00	Other specified hypertensive disease	Hypertension
G241000	Secondary benign renovascular hypertension	Hypertension
G24z100	Hypertension secondary to drug	Hypertension
G24z000	Secondary renovascular hypertension NOS	Hypertension
G240.00	Secondary malignant hypertension	Hypertension
G244.00	Hypertension secondary to endocrine disorders	Hypertension
G24zz00	Secondary hypertension NOS	Hypertension
G241z00	Secondary benign hypertension NOS	Hypertension
G241.00	Secondary benign hypertension	Hypertension
G240000	Secondary malignant renovascular hypertension	Hypertension
Gyu2.00	[X]Hypertensive diseases	Hypertension
G240z00	Secondary malignant hypertension NOS	Hypertension
G203.00	Diastolic hypertension	Hypertension
Gyu2000	[X]Other secondary hypertension	Hypertension
G65..00	Transient cerebral ischaemia	Stroke
G64..12	Infarction - cerebral	Stroke
G66..11	CVA unspecified	Stroke
G65..12	Transient ischaemic attack	Stroke
G66..00	Stroke and cerebrovascular accident unspecified	Stroke
G65z.00	Transient cerebral ischaemia NOS	Stroke
G64z.00	Cerebral infarction NOS	Stroke
G64z111	Lateral medullary syndrome	Stroke
G64..11	CVA - cerebral artery occlusion	Stroke

G64z.12	Cerebellar infarction	Stroke
G66..13	CVA - Cerebrovascular accident unspecified	Stroke
G64..13	Stroke due to cerebral arterial occlusion	Stroke
G66..12	Stroke unspecified	Stroke
G667.00	Left sided CVA	Stroke
G663.00	Brain stem stroke syndrome	Stroke
G64..00	Cerebral arterial occlusion	Stroke
G64z200	Left sided cerebral infarction	Stroke
G64z300	Right sided cerebral infarction	Stroke
G668.00	Right sided CVA	Stroke
G641.00	Cerebral embolism	Stroke
G64z.11	Brainstem infarction NOS	Stroke
G65zz00	Transient cerebral ischaemia NOS	Stroke
G65z100	Intermittent cerebral ischaemia	Stroke
G640.00	Cerebral thrombosis	Stroke
G664.00	Cerebellar stroke syndrome	Stroke
G660.00	Middle cerebral artery syndrome	Stroke
G662.00	Posterior cerebral artery syndrome	Stroke
G661.00	Anterior cerebral artery syndrome	Stroke
G65y.00	Other transient cerebral ischaemia	Stroke
G63y000	Cerebral infarct due to thrombosis of precerebral arteries	Stroke
G63y100	Cerebral infarction due to embolism of precerebral arteries	Stroke
G64z000	Brainstem infarction	Stroke
G64z400	Infarction of basal ganglia	Stroke
G641000	Cerebral infarction due to embolism of cerebral arteries	Stroke
G665.00	Pure motor lacunar syndrome	Stroke
G6X..00	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs	Stroke
G641.11	Cerebral embolus	Stroke
G640000	Cerebral infarction due to thrombosis of cerebral arteries	Stroke
G676000	Cereb infarct due cerebral venous thrombosis, nonpyogenic	Stroke
G6W..00	Cereb infarct due unsp occlus/stenos precerebr arteries	Stroke
G653.00	Carotid artery syndrome hemispheric	Stroke
G612.00	Basal nucleus haemorrhage	Stroke
G665.00	Pure motor lacunar syndrome	Stroke
G6X..00	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs	Stroke
G641.11	Cerebral embolus	Stroke
G640000	Cerebral infarction due to thrombosis of cerebral arteries	Stroke
G676000	Cereb infarct due cerebral venous thrombosis, nonpyogenic	Stroke
G665.00	Pure motor lacunar syndrome	Stroke
G6X..00	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs	Stroke
G641.11	Cerebral embolus	Stroke
G654.00	Multiple and bilateral precerebral artery syndromes	Stroke
G666.00	Pure sensory lacunar syndrome	Stroke
Gyu6400	[X]Other cerebral infarction	Stroke
G65z000	Impending cerebral ischaemia	Stroke
Gyu6500	[X]Occlusion and stenosis of other precerebral arteries	Stroke
Gyu6300	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs	Stroke
Gyu6600	[X]Occlusion and stenosis of other cerebral arteries	Stroke
Gyu6G00	[X]Cereb infarct due unsp occlus/stenos precerebr arteries	Stroke
ZV12D00	[V]Personal history of transient ischaemic attack	Stroke
G573200	Paroxysmal atrial fibrillation	Atrial fibrillation
G573000	Atrial fibrillation	Atrial fibrillation
G573100	Atrial flutter	Atrial fibrillation
G573.00	Atrial fibrillation and flutter	Atrial fibrillation
G573z00	Atrial fibrillation and flutter NOS	Atrial fibrillation
G573300	Non-rheumatic atrial fibrillation	Atrial fibrillation

G573500	Persistent atrial fibrillation	Atrial fibrillation
G573400	Permanent atrial fibrillation	Atrial fibrillation
G573700	Chronic atrial fibrillation	Atrial fibrillation

Appendix 8. Drug codes list

Drugcode	Generic name	BNF
96749998	Acenocoumarol 1mg tablets	02.08.02.00
99138998	Acenocoumarol 1mg tablets	02.08.02.00
96749997	Acenocoumarol 4mg tablets	02.08.02.00
99138997	Acenocoumarol 4mg tablets	02.08.02.00
81167998	Apixaban 2.5mg tablets	02.08.02.00
81168998	Apixaban 2.5mg tablets	02.08.02.00
53246979	Apixaban 5mg tablets	02.08.02.00
53247979	Apixaban 5mg tablets	02.08.02.00
92313998	Coumarin 100mg capsules	02.08.02.00
83971998	Dabigatran etexilate 110mg capsules	02.08.02.00
83974998	Dabigatran etexilate 110mg capsules	02.08.02.00
81214998	Dabigatran etexilate 150mg capsules	02.08.02.00
81215998	Dabigatran etexilate 150mg capsules	02.08.02.00
83972998	Dabigatran etexilate 75mg capsules	02.08.02.00
83973998	Dabigatran etexilate 75mg capsules	02.08.02.00
46896978	Edoxaban 30mg tablets	02.08.02.00
46897978	Edoxaban 30mg tablets	02.08.02.00
46894978	Edoxaban 60mg tablets	02.08.02.00
46895978	Edoxaban 60mg tablets	02.08.02.00
95556998	Phenindione 10mg tablets	02.08.02.00
96447990	Phenindione 10mg tablets	02.08.02.00
98293998	Phenindione 10mg tablets	02.08.02.00
95556997	Phenindione 25mg tablets	02.08.02.00
98293997	Phenindione 25mg tablets	02.08.02.00
95556996	Phenindione 50mg tablets	02.08.02.00
98293996	Phenindione 50mg tablets	02.08.02.00
83418998	Rivaroxaban 10mg tablets	02.08.02.00
83425998	Rivaroxaban 10mg tablets	02.08.02.00
60769979	Rivaroxaban 15mg tablets	02.08.02.00
60770979	Rivaroxaban 15mg tablets	02.08.02.00
80955998	Rivaroxaban 15mg tablets	02.08.02.00
80956998	Rivaroxaban 15mg tablets	02.08.02.00
59453978	Rivaroxaban 2.5mg tablets	02.08.02.00
59454978	Rivaroxaban 2.5mg tablets	02.08.02.00
60767979	Rivaroxaban 20mg tablets	02.08.02.00
60768979	Rivaroxaban 20mg tablets	02.08.02.00
80953998	Rivaroxaban 20mg tablets	02.08.02.00
80954998	Rivaroxaban 20mg tablets	02.08.02.00
95741992	Warfarin 10 mg tab	02.08.02.00
61036979	Warfarin 1mg tablets	02.08.02.00
83005998	Warfarin 1mg tablets	02.08.02.00
94879990	Warfarin 1mg tablets	02.08.02.00
95514990	Warfarin 1mg tablets	02.08.02.00
95617998	Warfarin 1mg tablets	02.08.02.00
96163990	Warfarin 1mg tablets	02.08.02.00
96308990	Warfarin 1mg tablets	02.08.02.00
96318990	Warfarin 1mg tablets	02.08.02.00
97089990	Warfarin 1mg tablets	02.08.02.00
97700979	Warfarin 1mg tablets	02.08.02.00
97701979	Warfarin 1mg tablets	02.08.02.00
97702979	Warfarin 1mg tablets	02.08.02.00
97711990	Warfarin 1mg tablets	02.08.02.00
97941990	Warfarin 1mg tablets	02.08.02.00

98014990	Warfarin 1mg tablets	02.08.02.00
98031990	Warfarin 1mg tablets	02.08.02.00
98289998	Warfarin 1mg tablets	02.08.02.00
99034990	Warfarin 1mg tablets	02.08.02.00
99035990	Warfarin 1mg tablets	02.08.02.00
99331990	Warfarin 1mg tablets	02.08.02.00
84565998	Warfarin 1mg/5ml oral suspension	02.08.02.00
62209979	Warfarin 1mg/ml oral suspension sugar free	02.08.02.00
79051979	Warfarin 1mg/ml oral suspension sugar free	02.08.02.00
81727998	Warfarin 1mg/ml oral suspension sugar free	02.08.02.00
85529998	Warfarin 1mg/ml oral suspension sugar free	02.08.02.00
94878990	Warfarin 3mg tablets	02.08.02.00
95617997	Warfarin 3mg tablets	02.08.02.00
96162990	Warfarin 3mg tablets	02.08.02.00
96318989	Warfarin 3mg tablets	02.08.02.00
97089989	Warfarin 3mg tablets	02.08.02.00
97696979	Warfarin 3mg tablets	02.08.02.00
97711989	Warfarin 3mg tablets	02.08.02.00
97941989	Warfarin 3mg tablets	02.08.02.00
98014989	Warfarin 3mg tablets	02.08.02.00
98031989	Warfarin 3mg tablets	02.08.02.00
98289997	Warfarin 3mg tablets	02.08.02.00
99034989	Warfarin 3mg tablets	02.08.02.00
99331989	Warfarin 3mg tablets	02.08.02.00
86425998	Warfarin 3mg/5ml oral solution	02.08.02.00
58667979	Warfarin 500microgram tablets	02.08.02.00
88944998	Warfarin 500microgram tablets	02.08.02.00
92245998	Warfarin 500microgram tablets	02.08.02.00
93227990	Warfarin 500microgram tablets	02.08.02.00
93532990	Warfarin 500microgram tablets	02.08.02.00
95630990	Warfarin 500microgram tablets	02.08.02.00
97688979	Warfarin 500microgram tablets	02.08.02.00
97690979	Warfarin 500microgram tablets	02.08.02.00
95232990	Warfarin 5mg tablets	02.08.02.00
95617996	Warfarin 5mg tablets	02.08.02.00
96161990	Warfarin 5mg tablets	02.08.02.00
96308988	Warfarin 5mg tablets	02.08.02.00
96318988	Warfarin 5mg tablets	02.08.02.00
97089988	Warfarin 5mg tablets	02.08.02.00
97694979	Warfarin 5mg tablets	02.08.02.00
97711988	Warfarin 5mg tablets	02.08.02.00
97941988	Warfarin 5mg tablets	02.08.02.00
98014988	Warfarin 5mg tablets	02.08.02.00
98031988	Warfarin 5mg tablets	02.08.02.00
98289996	Warfarin 5mg tablets	02.08.02.00
99034988	Warfarin 5mg tablets	02.08.02.00
99331988	Warfarin 5mg tablets	02.08.02.00
83977998	Warfarin 5mg/5ml oral solution	02.08.02.00
98906998	Warfarin sodium 1mg tablets	02.08.02.00
98906997	Warfarin sodium 3mg tablets	02.08.02.00
98906996	Warfarin sodium 5mg tablets	02.08.02.00
83976998	Warfarin sodium 5mg/ml oral suspension	02.08.02.00
87007998	Pentosan polysulfate sodium 100mg capsules	07.04.03.00
87008998	Pentosan polysulfate sodium 100mg capsules	07.04.03.00

30538978	Warfarin 1mg capsules	No BNF codes
79061979	Warfarin 1mg/5ml oral solution	No BNF codes
66298979	Warfarin 2.5mg/5ml oral solution	No BNF codes
79057979	Warfarin 2mg/5ml oral suspension	No BNF codes
90048979	Warfarin 4mg tablets	No BNF codes
90049979	Warfarin 4mg tablets	No BNF codes
76350978	Phenprocoumon 3mg tablets	No BNF codes
78556978	Pentosan polysulfate sodium 100mg capsules	No BNF codes
94513998	Aspirin 100mg effervescent tablets	02.09.00.00
94589998	Aspirin 100mg effervescent tablets	02.09.00.00
93099998	Aspirin 100mg modified release tablets	02.09.00.00
96877992	Aspirin 100mg modified release tablets	02.09.00.00
98776996	Aspirin 100mg modified-release tablets	02.09.00.00
94709996	Aspirin 162.5mg capsules	02.09.00.00
83013998	Aspirin 162.5mg modified release capsules	02.09.00.00
83014998	Aspirin 162.5mg modified-release capsules	02.09.00.00
94513997	Aspirin 300mg effervescent tablets	02.09.00.00
94589997	Aspirin 300mg effervescent tablets	02.09.00.00
94709997	Aspirin 300mg effervescent tablets sugar free	02.09.00.00
92706998	Aspirin 300mg gastro-resistant tablets	02.09.00.00
93099997	Aspirin 300mg modified release tablets	02.09.00.00
94216997	Aspirin 300mg modified-release tablets	02.09.00.00
94676992	Aspirin 37.5 mg tab	02.09.00.00
99881992	Aspirin 40 mg cap	02.09.00.00
94074992	Aspirin 40 mg tab	02.09.00.00
99880992	Aspirin 50 mg cap	02.09.00.00
99893992	Aspirin 60 mg tab	02.09.00.00
52811979	Aspirin 75mg dispersible tablets	02.09.00.00
83322978	Aspirin 75mg dispersible tablets	02.09.00.00
91537998	Aspirin 75mg dispersible tablets	02.09.00.00
94465990	Aspirin 75mg dispersible tablets	02.09.00.00
94688990	Aspirin 75mg dispersible tablets	02.09.00.00
95310990	Aspirin 75mg dispersible tablets	02.09.00.00
95352990	Aspirin 75mg dispersible tablets	02.09.00.00
96007990	Aspirin 75mg dispersible tablets	02.09.00.00
96201990	Aspirin 75mg dispersible tablets	02.09.00.00
97160998	Aspirin 75mg dispersible tablets	02.09.00.00
97241990	Aspirin 75mg dispersible tablets	02.09.00.00
97649979	Aspirin 75mg dispersible tablets	02.09.00.00
97652979	Aspirin 75mg dispersible tablets	02.09.00.00
97656979	Aspirin 75mg dispersible tablets	02.09.00.00
97657979	Aspirin 75mg dispersible tablets	02.09.00.00
97677989	Aspirin 75mg dispersible tablets	02.09.00.00

97918990	Aspirin 75mg dispersible tablets	02.09.00.00
98142990	Aspirin 75mg dispersible tablets	02.09.00.00
98513989	Aspirin 75mg dispersible tablets	02.09.00.00
98592990	Aspirin 75mg dispersible tablets	02.09.00.00
98776998	Aspirin 75mg dispersible tablets	02.09.00.00
99282989	Aspirin 75mg dispersible tablets	02.09.00.00
99807990	Aspirin 75mg dispersible tablets	02.09.00.00
99808990	Aspirin 75mg dispersible tablets	02.09.00.00
99810988	Aspirin 75mg dispersible tablets	02.09.00.00
52809979	Aspirin 75mg gastro-resistant tablets	02.09.00.00
83320978	Aspirin 75mg gastro-resistant tablets	02.09.00.00
88820998	Aspirin 75mg gastro-resistant tablets	02.09.00.00
89218998	Aspirin 75mg gastro-resistant tablets	02.09.00.00
89625998	Aspirin 75mg gastro-resistant tablets	02.09.00.00
90143998	Aspirin 75mg gastro-resistant tablets	02.09.00.00
90711998	Aspirin 75mg gastro-resistant tablets	02.09.00.00
91537997	Aspirin 75mg gastro-resistant tablets	02.09.00.00
92015998	Aspirin 75mg gastro-resistant tablets	02.09.00.00
92340990	Aspirin 75mg gastro-resistant tablets	02.09.00.00
94441990	Aspirin 75mg gastro-resistant tablets	02.09.00.00
96390990	Aspirin 75mg gastro-resistant tablets	02.09.00.00
96436990	Aspirin 75mg gastro-resistant tablets	02.09.00.00
96444990	Aspirin 75mg gastro-resistant tablets	02.09.00.00
96988989	Aspirin 75mg gastro-resistant tablets	02.09.00.00
97097990	Aspirin 75mg gastro-resistant tablets	02.09.00.00
97160990	Aspirin 75mg gastro-resistant tablets	02.09.00.00
97182990	Aspirin 75mg gastro-resistant tablets	02.09.00.00
97241989	Aspirin 75mg gastro-resistant tablets	02.09.00.00
97537990	Aspirin 75mg gastro-resistant tablets	02.09.00.00
97644979	Aspirin 75mg gastro-resistant tablets	02.09.00.00
98776997	Aspirin 75mg gastro-resistant tablets	02.09.00.00
99282988	Aspirin 75mg gastro-resistant tablets	02.09.00.00
99334996	Aspirin 75mg gastro-resistant tablets	02.09.00.00
52810979	Aspirin 75mg tablets	02.09.00.00
93575998	Aspirin 75mg tablets	02.09.00.00
93576998	Aspirin 75mg tablets	02.09.00.00
97645979	Aspirin 75mg tablets	02.09.00.00
97646979	Aspirin 75mg tablets	02.09.00.00
97647979	Aspirin 75mg tablets	02.09.00.00
94075992	Aspirin disp 37.5 mg tab	02.09.00.00
94669992	Aspirin soluble 100 mg tab	02.09.00.00
94672992	Aspirin soluble 40 mg cap	02.09.00.00
94677992	Aspirin soluble 50 mg tab	02.09.00.00
96878992	Aspirin sr 100 mg tab	02.09.00.00
96569992	Aspirin sr 300 mg tab	02.09.00.00

55833979	Aspirin 100mg capsules	00.00.00.00
69726979	Aspirin 100mg/5ml oral solution	00.00.00.00
69718979	Aspirin 25mg/5ml oral suspension	00.00.00.00
69698979	Aspirin 75mg/5ml oral suspension	00.00.00.00
90731997	Aspirin 150mg / isosorbide mononitrate 60mg modified-release tablets	02.06.01.00
90731998	Aspirin 75mg / isosorbide mononitrate 60mg modified-release tablets	02.06.01.00
83921998	Clopidogrel 300mg tablets	02.09.00.00
83922998	Clopidogrel 300mg tablets	02.09.00.00
53672979	Clopidogrel 75mg tablets	02.09.00.00
76945978	Clopidogrel 75mg tablets	02.09.00.00
82684998	Clopidogrel 75mg tablets	02.09.00.00
82800978	Clopidogrel 75mg tablets	02.09.00.00
89385998	Clopidogrel 75mg tablets	02.09.00.00
89393998	Clopidogrel 75mg tablets	02.09.00.00
91979990	Clopidogrel 75mg tablets	02.09.00.00
92249990	Clopidogrel 75mg tablets	02.09.00.00
92267990	Clopidogrel 75mg tablets	02.09.00.00
92367990	Clopidogrel 75mg tablets	02.09.00.00
97615979	Clopidogrel 75mg tablets	02.09.00.00
97618979	Clopidogrel 75mg tablets	02.09.00.00
97622979	Clopidogrel 75mg tablets	02.09.00.00
97624979	Clopidogrel 75mg tablets	02.09.00.00
97628979	Clopidogrel 75mg tablets	02.09.00.00
83026998	Prasugrel 10mg tablets	02.09.00.00
83028998	Prasugrel 10mg tablets	02.09.00.00
83027998	Prasugrel 5mg tablets	02.09.00.00
83029998	Prasugrel 5mg tablets	02.09.00.00
81711998	Ticagrelor 90mg tablets	02.09.00.00
81712998	Ticagrelor 90mg tablets	02.09.00.00
61215979	Atorvastatin 10mg chewable tablets sugar free	02.12.00.00
81050998	Atorvastatin 10mg chewable tablets sugar free	02.12.00.00
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57833979	Atorvastatin 10mg tablets	02.12.00.00
58658979	Atorvastatin 10mg tablets	02.12.00.00
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89311998	Atorvastatin 10mg tablets	02.12.00.00
61212979	Atorvastatin 20mg chewable tablets sugar free	02.12.00.00
61213979	Atorvastatin 20mg chewable tablets sugar free	02.12.00.00
81048998	Atorvastatin 20mg chewable tablets sugar free	02.12.00.00
81049998	Atorvastatin 20mg chewable tablets sugar free	02.12.00.00
57832979	Atorvastatin 20mg tablets	02.12.00.00
58650979	Atorvastatin 20mg tablets	02.12.00.00

58653979	Atorvastatin 20mg tablets	02.12.00.00
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82592978	Atorvastatin 20mg tablets	02.12.00.00
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89311997	Atorvastatin 20mg tablets	02.12.00.00
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89311996	Atorvastatin 40mg tablets	02.12.00.00
97756979	Atorvastatin 40mg tablets	02.12.00.00
58151979	Atorvastatin 60mg tablets	02.12.00.00
58706979	Atorvastatin 80mg tablets	02.12.00.00
58711979	Atorvastatin 80mg tablets	02.12.00.00
90309998	Atorvastatin 80mg tablets	02.12.00.00
90310998	Atorvastatin 80mg tablets	02.12.00.00
99957979	Atorvastatin 80mg tablets	02.12.00.00
89154998	Cerivastatin 100microgram tablets	02.12.00.00
89154997	Cerivastatin 200microgram tablets	02.12.00.00
89154996	Cerivastatin 300microgram tablets	02.12.00.00
92448998	Cerivastatin 400microgram tablets	02.12.00.00
92448997	Cerivastatin 800microgram tablets	02.12.00.00
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89153997	Cerivastatin sodium 200mcg tablets	02.12.00.00
97612979	Cerivastatin sodium 200mcg tablets	02.12.00.00
89153996	Cerivastatin sodium 300mcg tablets	02.12.00.00
97377979	Cerivastatin sodium 300mcg tablets	02.12.00.00
92447998	Cerivastatin sodium 400mcg tablets	02.12.00.00
64588979	Atorvastatin 10mg/5ml oral solution	00.00.00.00
64586979	Atorvastatin 10mg/5ml oral suspension	00.00.00.00
64636979	Atorvastatin 20mg/5ml oral solution	00.00.00.00
64634979	Atorvastatin 20mg/5ml oral suspension	00.00.00.00
58153979	Atorvastatin 30mg tablets	00.00.00.00
64584979	Atorvastatin 40mg/5ml oral solution	00.00.00.00
64582979	Atorvastatin 40mg/5ml oral suspension	00.00.00.00
79256979	Simvastatin 10mg/5ml oral suspension	00.00.00.00
59480979	Fluvastatin 20mg capsules	02.12.00.00
92804998	Fluvastatin 20mg capsules	02.12.00.00
92805998	Fluvastatin 20mg capsules	02.12.00.00
97424979	Fluvastatin 20mg capsules	02.12.00.00
97430979	Fluvastatin 20mg capsules	02.12.00.00
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92805997	Fluvastatin 40mg capsules	02.12.00.00

91194998	Fluvastatin 80mg modified-release tablets	02.12.00.00
92804996	Fluvastatin 80mg modified-release tablets	02.12.00.00
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93244998	Pravastatin 10mg tablets	02.12.00.00
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94831990	Pravastatin 10mg tablets	02.12.00.00
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93243997	Pravastatin 20mg tablets	02.12.00.00
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94830990	Pravastatin 20mg tablets	02.12.00.00
94850990	Pravastatin 20mg tablets	02.12.00.00
97454979	Pravastatin 20mg tablets	02.12.00.00
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93244996	Pravastatin 40mg tablets	02.12.00.00
94849990	Pravastatin 40mg tablets	02.12.00.00
88534998	Rosuvastatin 10mg tablets	02.12.00.00
92409998	Rosuvastatin 10mg tablets	02.12.00.00
89321979	Rosuvastatin 20mg tablets	02.12.00.00
90973998	Rosuvastatin 20mg tablets	02.12.00.00
92408998	Rosuvastatin 20mg tablets	02.12.00.00
92410998	Rosuvastatin 40mg tablets	02.12.00.00
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86468998	Rosuvastatin 5mg tablets	02.12.00.00
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97508979	Simvastatin 10mg tablets	02.12.00.00

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97518979	Simvastatin 10mg tablets	02.12.00.00
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86798998	Simvastatin 20mg / Ezetimibe 10mg tablets	02.12.00.00
89119979	Simvastatin 20mg / Ezetimibe 10mg tablets	02.12.00.00
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95550990	Simvastatin 20mg tablets	02.12.00.00
97489979	Simvastatin 20mg tablets	02.12.00.00
97494979	Simvastatin 20mg tablets	02.12.00.00
97495979	Simvastatin 20mg tablets	02.12.00.00
79254979	Simvastatin 20mg/5ml oral suspension	02.12.00.00
62597979	Simvastatin 20mg/5ml oral suspension sugar free	02.12.00.00
92154990	Simvastatin 20mg/5ml oral suspension sugar free	02.12.00.00
86788998	Simvastatin 40mg / Ezetimibe 10mg tablets	02.12.00.00
86795998	Simvastatin 40mg / Ezetimibe 10mg tablets	02.12.00.00
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87916998	Simvastatin 40mg tablets	02.12.00.00
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93620996	Simvastatin 40mg tablets	02.12.00.00
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95474990	Simvastatin 40mg tablets	02.12.00.00

95478990	Simvastatin 40mg tablets	02.12.00.00
95481990	Simvastatin 40mg tablets	02.12.00.00
95486990	Simvastatin 40mg tablets	02.12.00.00
95493990	Simvastatin 40mg tablets	02.12.00.00
95501990	Simvastatin 40mg tablets	02.12.00.00
95549990	Simvastatin 40mg tablets	02.12.00.00
97476979	Simvastatin 40mg tablets	02.12.00.00
97478979	Simvastatin 40mg tablets	02.12.00.00
97482979	Simvastatin 40mg tablets	02.12.00.00
62570979	Simvastatin 40mg/5ml oral suspension sugar free	02.12.00.00
64839979	Simvastatin 40mg/5ml oral suspension sugar free	02.12.00.00
83099998	Simvastatin 40mg/5ml oral suspension sugar free	02.12.00.00
86787998	Simvastatin 80mg / Ezetimibe 10mg tablets	02.12.00.00
86791998	Simvastatin 80mg / Ezetimibe 10mg tablets	02.12.00.00
86794998	Simvastatin 80mg / Ezetimibe 10mg tablets	02.12.00.00
83030998	Simvastatin 80mg tablets	02.12.00.00
92220998	Simvastatin 80mg tablets	02.12.00.00
92471998	Simvastatin 80mg tablets	02.12.00.00
94927990	Simvastatin 80mg tablets	02.12.00.00
95185990	Simvastatin 80mg tablets	02.12.00.00
95442990	Simvastatin 80mg tablets	02.12.00.00
95448990	Simvastatin 80mg tablets	02.12.00.00
95500990	Simvastatin 80mg tablets	02.12.00.00
86020998	Simvastatin 20mg/5ml oral solution sugar free	02.12.04.00

Appendix 9. STROBE checklist for chapter 6

Strengthening the reporting of observational studies in epidemiology (STROBE) checklist.

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract		Not applicable
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3,4	Abstract
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	251-252	Background
Objectives	3	State specific objectives, including any prespecified hypotheses	253	Aims and objectives
Methods				
Study design	4	Present key elements of study design early in the paper	253-254	Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	254-255	Methods
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	253-256	Methods
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	253-254	Methods
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	253-254	Methods
Bias	9	Describe any efforts to address potential sources of bias		Not applicable
Study size	10	Explain how the study size was arrived at	257	Results

Continue on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	256	Methods
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	256	Methods
		(*b*) Describe any methods used to examine subgroups and interactions	256	Methods
		(*c*) Explain how missing data were addressed		Not applicable
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	256	Methods
		(*e*) Describe any sensitivity analyses		Not applicable
Results				
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	257	Results
		(b) Give reasons for non-participation at each stage	256	Methods
		(c) Consider use of a flow diagram		Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	257-258	Results, Table 14
		(b) Indicate number of participants with missing data for each variable of interest		Not applicable
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)		Not applicable
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time		Not applicable
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		Not applicable
		Cross-sectional study—Report numbers of outcome events or summary measures	257-263	Results
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included		Not applicable
		(*b*) Report category boundaries when continuous variables were categorized		Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		Not applicable

Continue on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	257-263	Results
Discussion				
Key results	18	Summarise key results with reference to study objectives	263	Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	265-266	Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	263-266	Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	263-266	Discussion
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based		Not applicable

Note: The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Appendix 10. STROBE checklist for chapter 7

Strengthening the reporting of observational studies in epidemiology (STROBE) checklist.

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract		Not applicable
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3,4	Abstract
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	269-270	Background
Objectives	3	State specific objectives, including any prespecified hypotheses	270-271	Aims and objectives
Methods				
Study design	4	Present key elements of study design early in the paper	271	Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	271	Methods
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	271-277	Methods

		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	271-277	Methods
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	271-277	Methods
Bias	9	Describe any efforts to address potential sources of bias	277	Methods
Study size	10	Explain how the study size was arrived at	278	Results

Continue on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	275-277	Methods
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	275-277	Methods
		(*b*) Describe any methods used to examine subgroups and interactions	275-277	Methods
		(*c*) Explain how missing data were addressed	280	Results, Table 15

		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	275-277	Methods
		(e) Describe any sensitivity analyses	275-277	Methods
Results				
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	278-286	Methods, Results
		(b) Give reasons for non-participation at each stage	278	Results
		(c) Consider use of a flow diagram	273	Methods, Figure 37
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	278-280	Results, Table 15
		(b) Indicate number of participants with missing data for each variable of interest	280	Results, Tables 15
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)		Not applicable
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time		Not applicable
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		Not applicable

		Cross-sectional study—Report numbers of outcome events or summary measures	278-286	Results
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	283-286	Results, Table 17
		(*b*) Report category boundaries when continuous variables were categorized		Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	278-286	Results
Discussion				
Key results	18	Summarise key results with reference to study objectives	287	Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	287-291	Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	287-291	Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	287-291	Discussion
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based		Not applicable

Note: The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Appendix 11. Approved study protocol for Chapter 8

SRC Feedback

Researcher Name: Hassan Alwafi
Organisation: UCL School of Pharmacy
SRC Reference Number: 18THIN046
Date: 27th September 2018
Study title: The safety and the protective effect of the concurrent use of warfarin and sulfonylureas in patients with type 2 diabetes in the United Kingdom.

Committee opinion: Approved

The following feedback has been supplied by the SRC.

Notes from the Chair:

Approved

Approved documents:

Approved document	Version	Date
SRC_Protocol_18THIN046_v3_26-09-2018	3	26/09/2018
Researcher_Response__18THIN046		

We are pleased to inform that you can proceed with the study as this is now approved. IQVIA will let the relevant Ethics committee know this study has been approved by the SRC.

Once the study has been completed and published, it is important for you to inform IQVIA in order for us to advise the SRC and your reference number to be closed.

References to all published studies are added to our website enabling other researchers to become aware of your work. In order to identify your study as using the THIN database, we recommend that you include the words "The Health Improvement Network (THIN)" within your title. Copies of publication(s), where available, will be appreciated.

I wish you and your team all the best with the study progression.

Appendix 12. STROBE checklist for chapter 8

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract		Not applicable
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3,4	Abstract
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	294-297	Background
Objectives	3	State specific objectives, including any prespecified hypotheses	297,299	Background, Aims and objectives
Methods				
Study design	4	Present key elements of study design early in the paper	299	Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	300	Methods
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	300-301	Methods

		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	305-309	Methods
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	304-306	Methods
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	304-306	Methods
Bias	9	Describe any efforts to address potential sources of bias	305-309	Methods
Study size	10	Explain how the study size was arrived at	310-311	Results, Figure 40 and Appendices 13 – 14
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	305-309	Methods
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	305-309	Methods
		(*b*) Describe any methods used to examine subgroups and interactions	305-309	Methods
		(*c*) Explain how missing data were addressed	305-309	Methods
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	305-309	Methods

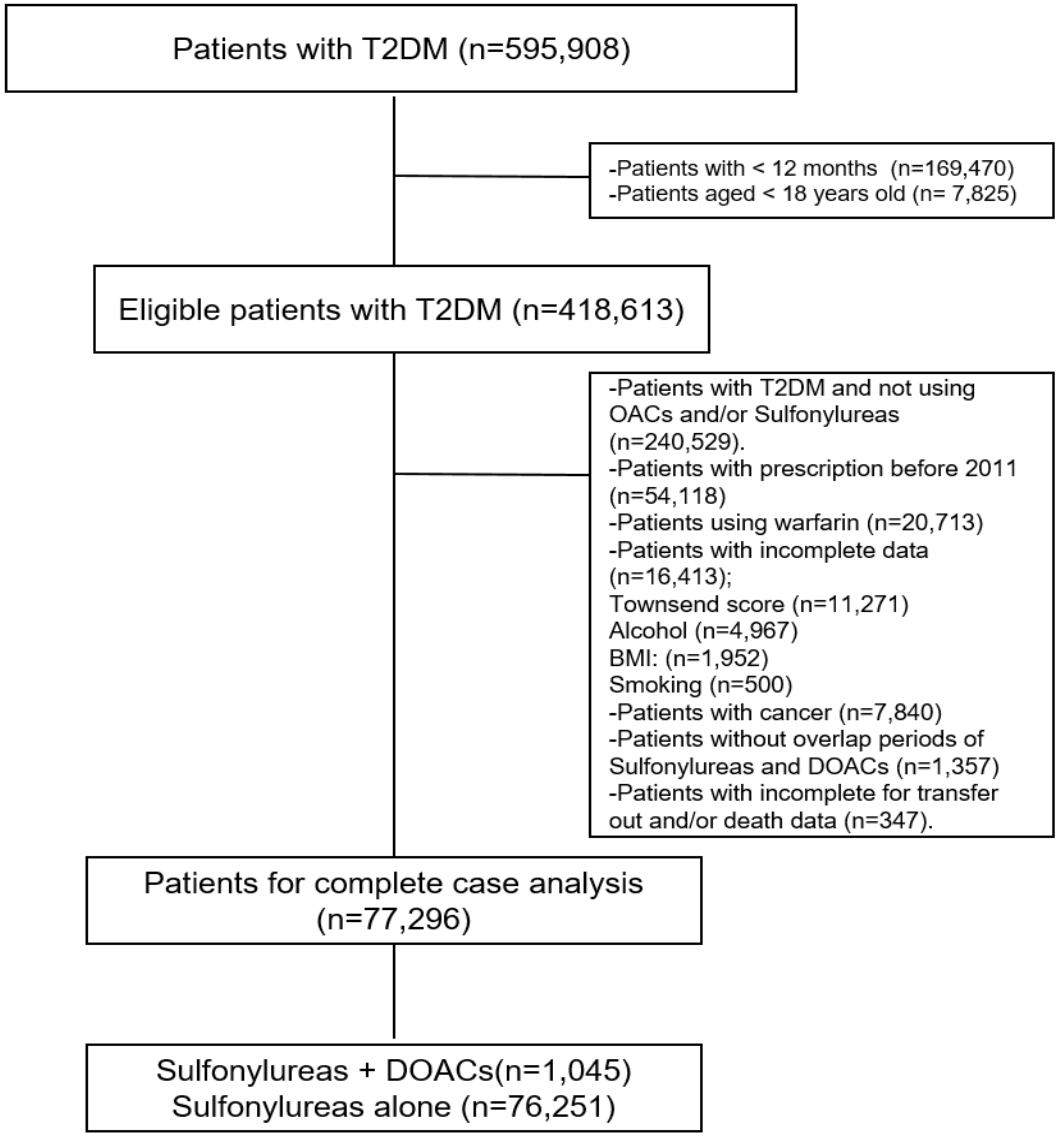
		Case-control study—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy		
		(e) Describe any sensitivity analyses	305-309	Methods
Results				
Participants				
	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	310-311	Results, Figure 41 and Appendices 13 – 14
		(b) Give reasons for non-participation at each stage	310-311	Results, Figure 41 and Appendices 13 – 14
		(c) Consider use of a flow diagram	311	Results, Figure 41 and Appendices 13 – 14
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	311-317	Results, Table 19,20 and Appendix 15

		(b) Indicate number of participants with missing data for each variable of interest	310-311	Results, Figure 41 and Appendices 13 – 14
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	319-328	Results
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	319-328	Results
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		Not applicable
		Cross-sectional study—Report numbers of outcome events or summary measures		Not applicable
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	319-328	Results
		(*b*) Report category boundaries when continuous variables were categorized		Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	319-328	Results
Discussion				
Key results	18	Summarise key results with reference to study objectives	329	Discussion

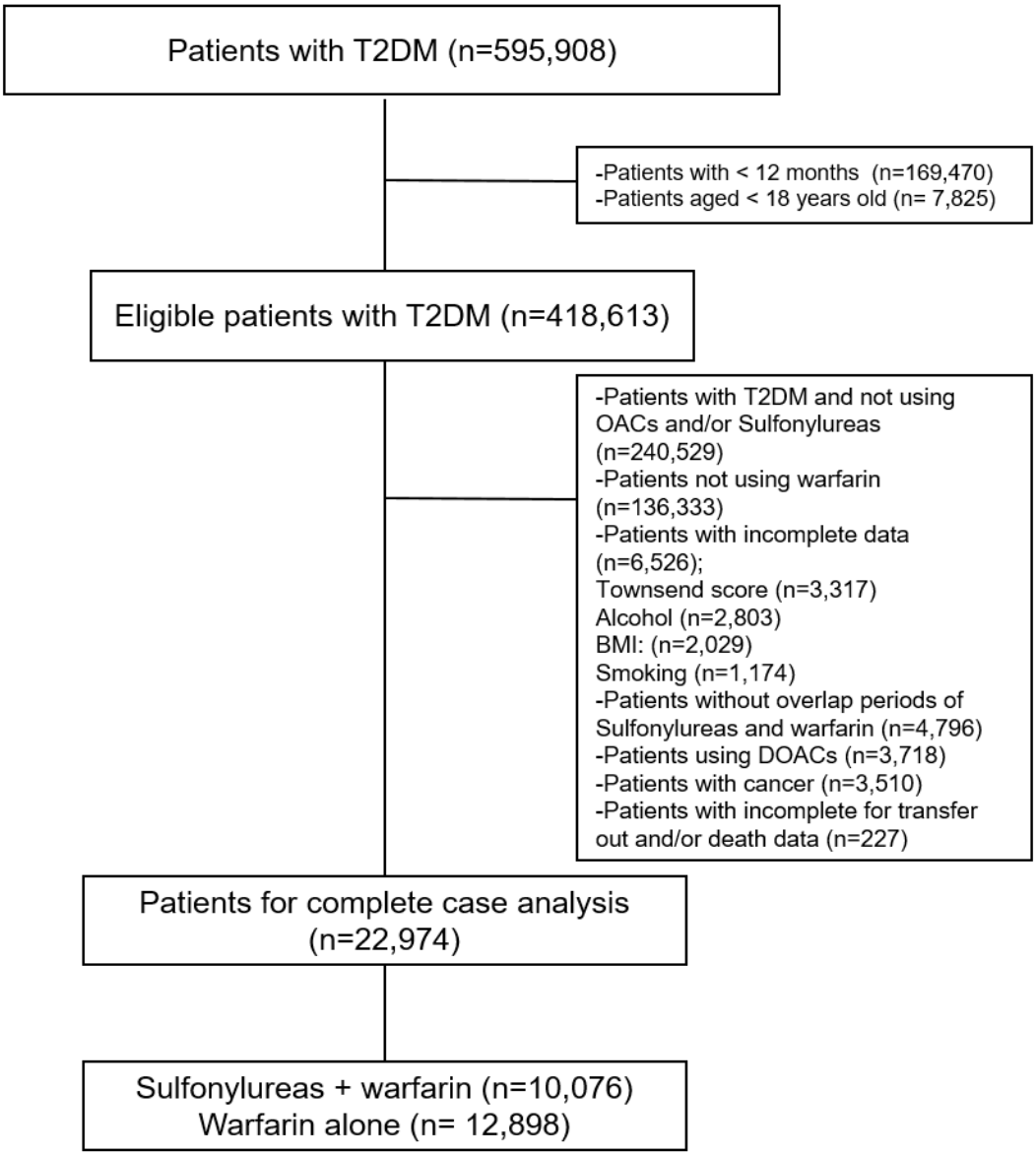
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	329-338	Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	329-338	Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	329-338	Discussion
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based		Not applicable

Note: The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Appendix 13. Flow chart of second analysis


Patients with T2DM (n=595,908)
-Patients with < 12 months (n=169,470)
-Patients aged < 18 years old (n= 7,825)
Eligible patients with T2DM (n=418,613)
-Patients with T2DM and not using OACs and/or Sulfonylureas (n=240,529).
-Patients with prescription before 2011 (n=54,118)
-Patients using warfarin (n=20,713)
-Patients with incomplete data (n=16,413);
Townsend score (n=11,271)
Alcohol (n=4,967)
BMI: (n=1,952)
Smoking (n=500)
-Patients with cancer (n=7,840)
-Patients without overlap periods of Sulfonylureas and DOACs (n=1,357)
-Patients with incomplete for transfer out and/or death data (n=347).
Patients for complete case analysis (n=77,296)
Sulfonylureas + DOACs(n=1,045)
Sulfonylureas alone (n=76,251)

Appendix 14. Flow chart of third analysis

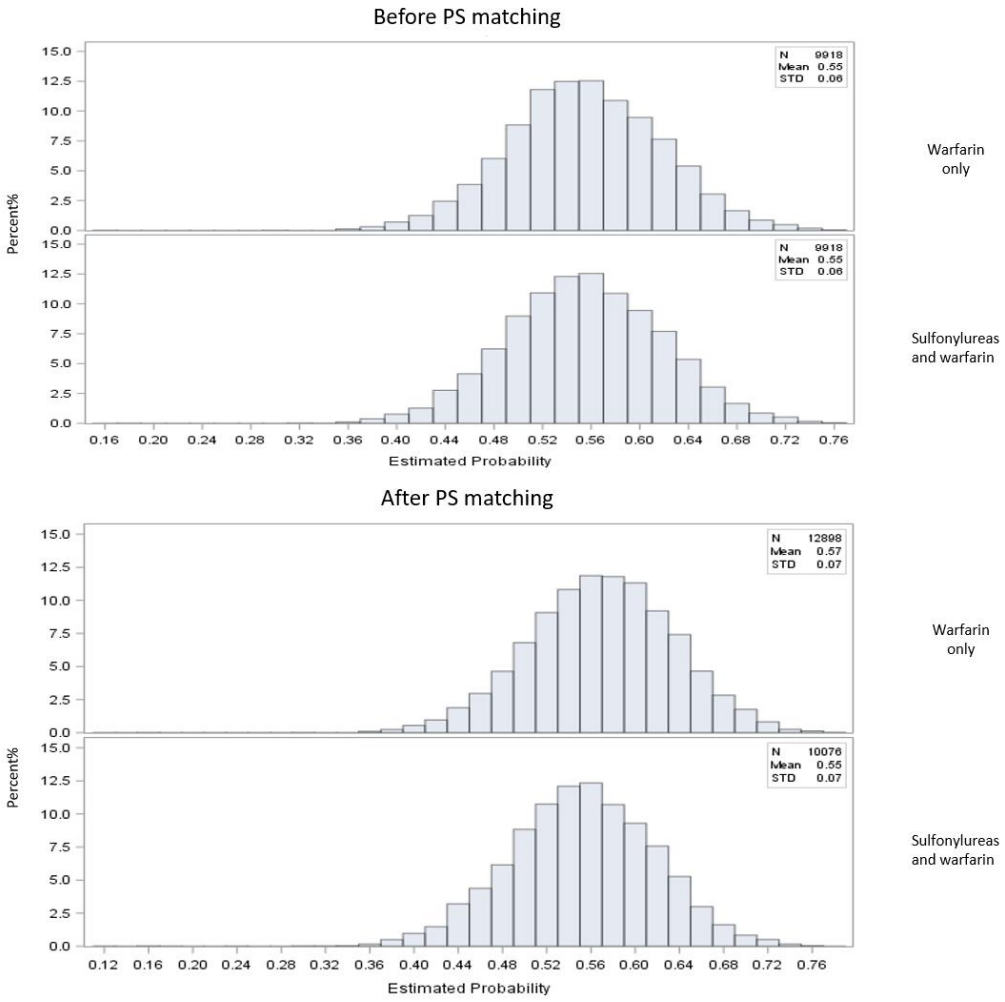

Patients with T2DM (n=595,908)
-Patients with < 12 months (n=169,470)
-Patients aged < 18 years old (n= 7,825)
Eligible patients with T2DM (n=418,613)
-Patients with T2DM and not using OACs and/or Sulfonylureas (n=240,529)
-Patients not using warfarin (n=136,333)
-Patients with incomplete data (n=6,526);
Townsend score (n=3,317)
Alcohol (n=2,803)
BMI: (n=2,029)
Smoking (n=1,174)
-Patients without overlap periods of Sulfonylureas and warfarin (n=4,796)
-Patients using DOACs (n=3,718)
-Patients with cancer (n=3,510)
-Patients with incomplete for transfer out and/or death data (n=227)
Patients for complete case analysis (n=22,974)
Sulfonylureas + warfarin (n=10,076)
Warfarin alone (n= 12,898)

Appendix 15. Patient's characteristics among the cohort of third analysis sulfonylureas and warfarin versus warfarin only

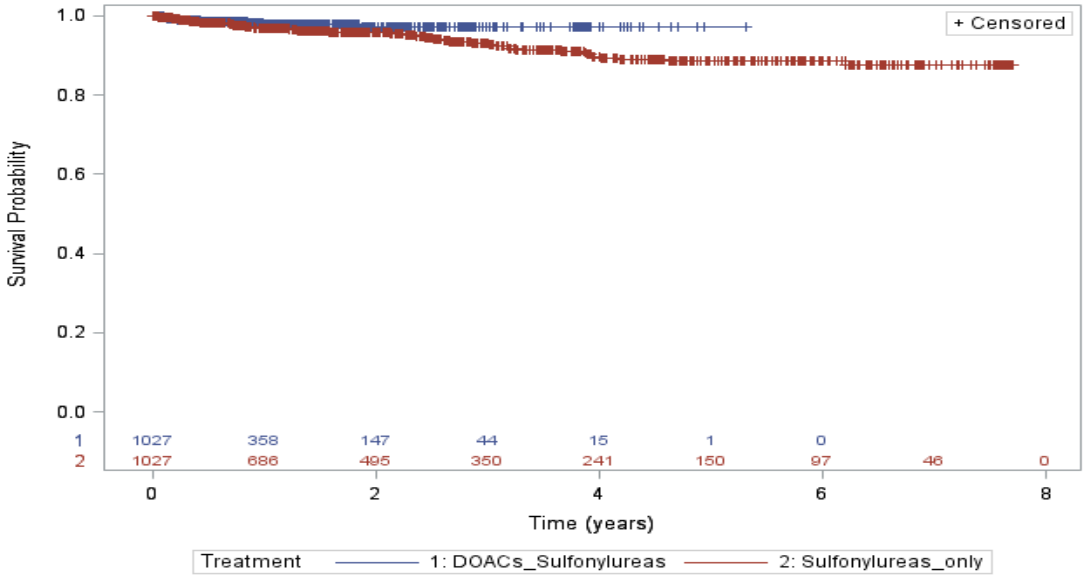
Variable	Before propensity score matching No. (%) of participant				After propensity score matching No. (%) of participant		
	All (n=22,974)	Sulfonylureas + Warfarin (n= 10,076)	Warfarin (n= 12,898)	Crude ASD	Sulfonylureas + Warfarin (n= 9,918)	Warfarin (n= 9,918)	Matched ASD
Demographics							
Age mean (SD)	72.1 (10.1)	71.5 (10.0)	72.4 (10.2)	0.0089	71.6 (9.9)	71.7 (10.4)	0.0975
Male, n (%)	13944 (60.7)	6148 (61.0)	7796 (60.4)	0.0095	6054 (61.0)	6100 (61.5)	-0.0117
BMI				0.0089			0.0264
BMI < 25	3478 (15.1)	1550 (15.4)	1928 (15.0)		1490 (15.0)	1521 (15.3)	
BMI 25-30	7834(34.1)	3486 (34.6)	4348 (33.7)		3420 (34.5)	3415 (34.4)	
BMI ≥ 30	11662 (50.)	5040 (50.0)	6622 (51.3)		5008 (50.5)	4982 (50.2)	
Smoking				0.0046			0.0246
Non-smokers	20615 (89.7)	8999 (89.3)	11616 (90.0)		8865 (89.3)	8879 (89.5)	
Smokers	2359 (10.3)	1077 (10.3)	1282 (10.0)		1053 (10.6)	1039 (10.5)	
Alcohol				-0.0094			-0.0741
Non-drinker	6780 (29.5)	3165 (31.4)	3615 (28.0)		3057 (30.8)	3014 (30.4)	
Drinker	16194 (70.5)	6911 (68.6)	9283 (72.0)		6861 (69.1)	6904 (69.6)	
Townsend				0.0135			0.0806
1 (Least deprived)	4827 (21.0)	2026 (20.1)	2801 (21.7)		2008 (20.2)	2010 (20.3)	
2	5103 (22.2)	2140 (21.2)	2963 (23.0)		2127 (21.4)	2128 (21.5)	
3	4958 (21.6)	2168 (21.5)	2790 (21.6)		2149 (21.7)	2163 (21.9)	
4	4764 (20.7)	2167 (21.5)	2597 (20.1)		2108 (21.2)	2136 (21.5)	
5 (Most deprived)	3322 (14.4)	1575 (15.6)	1747 (13.5)		1526 (15.4)	1481 (15.0)	
Comorbid conditions, n (%)							
CVDs	3477 (15.1)	1507 (15.0)	1970 (15.3)	0.0031	1483 (15.0)	1472 (14.9)	-0.0089
Hypertension	15785 (68.7)	6835 (67.8)	8950 (69.3)	-0.0002	6754 (68.1)	6755 (68.1)	-0.0335
Stroke/TIA	4483 (19.5)	1927 (19.1)	2556 (19.8)	0.0041	1899 (19.1)	1883 (19.0)	-0.0175
Bleeding	4697 (20.4)	1884 (18.7)	2813 (21.8)	0.0008	1879 (19.0)	1876 (19.0)	-0.0775

Hyperlipidaemia	5454 (23.7)	2381 (23.6)	3073 (23.8)	0.0038	2342 (23.6)	2326 (23.4)	-0.0046
AF	14810 (64.5)	6229 (62.0)	8581 (66.5)	0.0025	6187 (62.4)	6199 (62.5)	-0.0983
DVT	4814 (21.0)	2149 (21.3)	2665 (21.0)	-0.0057	2108 (21.2)	2131 (21.5)	0.0163
PVDs	2116 (9.2)	1029 (10.2)	1087 (8.4)	0.0065	979 (9.9)	960 (9.7)	0.0614
Chronic kidney disease	5853 (25.5)	2662 (26.4)	3191 (24.7)	-0.0110	2607 (26.3)	2655 (26.7)	0.0385
COPD	2343 (10.2)	1052 (10.4)	1291 (10.0)	-0.0013	1033 (10.4)	1037 (10.4)	0.0142
PUDs	6200 (27.0)	2690 (26.7)	3510 (27.2)	0.0068	2650 (26.7)	2620 (26.4)	-0.0116
Liver diseases	126 (0.5)	53 (0.5)	73 (0.6)	-0.0028	52 (0.5)	54 (0.5)	-0.0054
Depression	4896 (21.3)	2105 (20.9)	2791 (21.6)	0.0015	2082 (21.0)	2076 (20.9)	-0.0183
Anxiety	3357 (14.6)	1382 (13.7)	1975 (15.3)	0.0070	1374 (13.8)	1350 (13.6)	-0.0453
HAS-BLED risk	20951 (91.1)	9098 (90.2)	11853 (91.9)	0.0000	8983 (90.6)	8983 (90.6)	-0.0563
Baseline medication use, n (%)							
Aspirin use	8414 (36.6)	3782 (37.5)	4632 (36.0)	-0.0013	3700 (37.3)	3706 (37.3)	0.0337
Antiplatelet drugs use	1426 (6.4)	629 (6.4)	797 (6.4)	0.0033	629 (6.3)	620 (6.2)	0.0026
Beta blockers use	11357 (49.4)	4690 (46.5)	6667 (51.7)	-0.0121	4670 (47.0)	4730 (47.7)	-0.1030
ACEs /ARBs use	15786 (68.7)	7160 (71.0)	8626 (66.8)	0.0047	7020 (70.8)	6999 (70.6)	0.0905
CCBs use	8583 (37.3)	3754 (37.2)	4829 (37.4)	0.0010	3704 (37.4)	3699 (37.3)	-0.0038
Statins use	15505 (67.5)	6740 (66.8)	8765 (68.0)	0.0011	6645 (67.0)	6640 (69.9)	-0.0227
PPI use	7754 (33.7)	3307 (32.9)	4447 (34.5)	0.0006	3278 (33.0)	3275 (33.0)	-0.0351

Appendix 16. Absolute standardised difference before and after matching of patients receiving sulfonylureas and warfarin versus warfarin only


Before PS matching
N 9918
Mean 0.55
STD 0.06
Warfarin only
N 9918
Mean 0.55
STD 0.06
Sulfonylureas and warfarin
Percent%
Estimated Probability
After PS matching
N 12898
Mean 0.57
STD 0.07
Warfarin only
N 10076
Mean 0.55
STD 0.07
Sulfonylureas and warfarin
Percent%
Estimated Probability

Appendix 17. Kaplan-Meier curves for the incidence of hypoglycaemia during follow-up period.


+ Censored
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
1 1027 358 147 44 15 1 0
2 1027 686 495 350 241 150 97 46 0
0
2
4
6
8
Time (years)
Treatment
1: DOACs_Sulfonylureas
2: Sulfonylureas_only