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PHARMACOEPIDEMIOLOGY OF DIABETES MELLITUS IN A NATIONAL POPULATION

A thesis submitted to the University of Dublin, Trinity College
in fulfilment of the requirement for the degree of
Doctor of Philosophy (Pharmacology & Therapeutics)

NUR LISA ZAHARAN

December 2010

DECLARATION

I the undersigned declare that this thesis is entirely my own work and has not been previously been submitted as an exercise for a degree at this or any other University.

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ACKNOWLEDGEMENTS

ACKNOWLEDGEMENTS

All the praises and thanks are to Allah, the Most Gracious, the Most Merciful.

A million of thanks go to Dr Kathleen Bennett for guiding me from the start of my journey towards a higher degree. I am very fortunate to have a wonderful lady for a supervisor. Your support throughout this research is invaluable. Your encouragement, your ideas, your statistical knowledge, your prompt responses to any queries and most importantly your laughter and friendship have carried me through. To the late Professor John Feely who passed away in the middle of this journey, you will always be remembered for your wisdom, your kindness, your enthusiasm and support. To Professor David Williams, I am grateful for your critical eyes and guidance in completing this thesis. To Professor Michael Rowan, I appreciate your guidance in pursuing my PhD plans.

I would like to express my deep gratitude to the collaborators in Connolly Hospital and St James's Hospital. To Professor Seamus Sreenan, Dr Ana Rakovic Tisdall and a great team behind, I greatly appreciate the extra hours that you have put into this research. To Professor John Nolan and Lisa Killarney, I hope this research will pave the way for more linkage studies in the future. I wish also to acknowledge the HSE-PCRS for providing the databases in which this research is based. I am particularly grateful to Professor Datin Dr Zahurin Mohamed and all the staffs at the Department of Pharmacology, University of Malaya for giving me the opportunity to embark into this exciting journey. I wish to acknowledge the financial support from both the University of Malaya and the Malaysian Ministry of Higher Education.

To the lecturers and staffs in the Department of Pharmacology and Therapeutics, Trinity College Dublin, thank you for making my journey memorable. I will miss our tea breaks very much. To my postgraduate officemates, Jenny Svard, Omar AlSharef, Alan Kennedy and Dr Noor Jatoi, I wish all of you the very best in your future. To Professor Deidre Murphy, thank you for making this submission possible by helping me survive childbirth with the help of God. To all my Malaysians and Irish friends in Ireland especially Alhusna, Ain, Mel, kak Basmah and Kak Tuty, thank you for sharing many wonderful memories together. I am very blessed to have friends like you.

To my dearest family; ayah Wan Md Adnan, opah Teh Bahizah, Nur Haniza, Zeti Hidayah, Muhammad Ayub, Fatimah Zafira, Muhammad Amirul Hareez, Wan Nazirah, Wan Najmiyyah, Wan Nahariah, Wan Ahmad Asyraf, Zaizul Azizi, Hamidi, Shams Amir and Ahmad- thank you for your prayers. I have been away for so long and have missed so many family events. I hope we can share many happy memories ahead. To arwah Mak-Wan Jariah and tokki Hj Yusoff, you are always in my prayers. Words cannot capture my gratitude to my dearest mother, Dr Noriah Hj Yusoff and father, Zaharan Mat Alipiah. You were there for me from the beginning of my creation. I pray that Allah rewards you with nothing less than Paradise.

To my beloved husband Wan Ahmad Hafiz; you have put a lot of effort into this thesis with your prayer, encouragement, patience and love. Let the completion of this thesis be the beginning of a new chapter in our life back in Malaysia. I love you very much. To my beautiful daughter, Wan Amatullah Husna, you have accompanied me during the long hours of thesis writing from the moment you started life inside me. You have grown so much in the meantime. This thesis is dedicated to you.

SUMMARY

Diabetes is associated with significant morbidity and mortality from microvascular and macrovascular complications. It is projected that the prevalence of diabetes will increase worldwide especially in the elderly population [1]. The increase in the prevalence of diabetes and its debilitating consequences will have a significant impact on the individual patient and the health care services. The burden of diabetes has increased research interests with the release of novel pharmacotherapy for diabetes in the last few years, publication of guidelines by experts in the field and a paradigm shift towards patient centred care. This thesis aims to examine the pharmacoepidemiology of diabetes mellitus in the Irish population using information derived primarily from a national pharmacy claims database. Most patients with diabetes in Ireland are covered under two different community drug schemes and this provides a unique opportunity to examine the different patterns of prescribing for diabetes in a national population.

The patient population with treated type 1 and type 2 diabetes were identified from either the General Medical Services (GMS) scheme or Long Term Illness (LTI) scheme available through the Health Service Executive-Primary Care Reimbursement Services (HSE-PCRS). A retrospective cohort study was performed from 1st January 2003 to 31st December 2007 to examine the prevalence and incidence of treated diabetes in paediatric and adults. The prescribing of antidiabetic and preventative cardiovascular therapies as well as the variations in the prescribing of these agents across gender, age groups, community drug schemes and the different health regions was examined during this 5-year study period.

Adherence to antidiabetic and preventative cardiovascular therapies in patients with newly treated type 2 diabetes and predictors of non-adherence was measured from prescription refill records in a 365-day period. A prospective cohort study was performed in Connolly hospital, Blanchardstown, Dublin to examine self-reported adherence, influence of beliefs towards medicine on adherence and the correlation between self-reported adherence and adherence using prescription refill records. The relationship between adherence and intermediate clinical outcomes such as HbA1c, blood pressure levels and cholesterol levels was examined by linking the information from the HSE-PCRS database to information obtained from the DIAMOND database a database of diabetes patients attending outpatient clinics in St. James's Hospital, Dublin in a retrospective cohort study. Linkage study was also performed using the patient population from Connolly Hospital.

Two different epidemiological study designs were chosen to examine the risk of new-onset diabetes with commonly prescribed pharmacological agents using data from the GMS scheme from 1st January 2001 to 31st March 2009. Case-control studies were performed to examine the risk of new onset diabetes with corticosteroids and antidepressants. Retrospective cohort studies were used to examine the risk of new onset diabetes with statins and antihypertensives. Dose and duration response relationships of these agents with new onset diabetes were determined. Statistical analyses were carried out using SAS version 9.1 (SAS, Cary, NY). Significance at $p<0.05$ was assumed throughout.

Overall, the prevalence and incidence of treated diabetes had significantly increased in the adult population with higher prevalence observed in males and those 65 years and above. The age-adjusted prevalence of treated diabetes in Ireland was 2.7% in 2007. Regional variations were observed with highest prevalence in the Midland region and lowest in the Eastern region. The incidence of type 2 diabetes increased in both genders and in those between 45 to 64 years of age. The prevalence of type 1 diabetes remained stable at 0.2% in the paediatric population with no significant gender and regional variations observed. The same trend was observed in the incidence of type 1 diabetes in this group.

There has been a change in the prescribing of insulin in patients with diabetes with a decline in the prescribing of human insulin and an increase in the prescribing of the newer and more expensive insulin analogues particularly insulin glargine, insulin aspart and insulin detemir. A decline in the prescribing of intermediate-acting insulin, either alone or combined with fast-acting insulin was accompanied by an increase in the prescribing of fast-acting and long-acting insulin. Older agents such as metformin and sulphonylureas were preferred over newer oral antidiabetic agents in patients with type 2 diabetes with an increase in the prescribing of metformin and a decrease in the prescribing for sulphonylureas. The prescribing of rosiglitazone had increased before declining in 2006 after controversies regarding its adverse effects in the general population. An increase in the prescribing of glucose monitoring kits, oral combination agents and insulin was observed. Improvements in the prescribing for preventative cardiovascular therapies were observed each year with more than two thirds of patients with diabetes were prescribed antihypertensives, lipid lowering agents and antiplatelet agents. ACE inhibitors and angiotensin receptor blockers were prescribed to two thirds of patients. There has been an increase in the prescribing of atorvastatin and rosuvastatin compared to the generic simvastatin. Gender, age, socioeconomic and differences were observed in the prescribing of antidiabetic and preventative cardiovascular therapies for patients with diabetes in the Irish population. Regional variations were also observed with the Midlands and the Eastern region consistently showed better prescribing compared to other regions.

A third of patients with type 2 diabetes did not adhere to their prescribed medications. Predictors of non-adherence were younger age, eligibility for the GMS scheme, concurrent insulin prescribing and neurological conditions. Perceived necessity increased the likelihood of medication adherence. Although most patients reported high adherence to medications, their prescription refill records showed otherwise. Those with low self-reported adherence were more likely to miss their hospital appointment. However, there was no consistent relationship between adherence to medications and intermediate clinical outcomes observed in the selected patient populations.

Increased risk of new onset diabetes was observed with oral and very potent corticosteroids, all classes of antidepressants (TCAs, SSRIs, SNRIs, other) and all types of statins (rosuvastatin, atorvastatin, simvastatin, pravastatin and fluvastatin). Increased risk of new onset diabetes was observed in the combination of beta blocker and diuretic compared to ACE inhibitor and diuretic. A dose response relationship was observed with certain individual antidepressants and individual statins. A duration response relationship was observed with oral and very potent topical corticosteroids, all classes of antidepressants, statins and major classes of antihypertensive.

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4S	Scandinavian Survival Simvastatin Study
ACCORD	Action to Control Cardiovascular Risk in Diabetes Trial
ACEI	Angiotensin converting enzyme inhibitor
ADA	American Diabetes Association
ADOPT	A Diabetes Outcome Progression Trial
ADVANCE	Action in Diabetes and Vascular disease trial
AGE	Advanced glycation end-products
ALLHAT	The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial
ALPINE	Antihypertensive treatment and Lipid Profile In a North of Sweden Efficacy evaluation
ARB	Angiotensin II receptor blocker
ASCOT-BPLA	Blood Pressure Lowering Arm of Anglo-Scandinavian Cardiac Outcome Trial
ASCOT-LLA	Anglo-Scandinavian Cardiac Outcomes Trial- Lipid Lowering Arm
ATC	Anatomical Therapeutic Classification
BMI	Body Mass Index
BMQ	Beliefs about Medicines Questionnaire
CARDS	Collaborative Atorvastatin Diabetes Study
CAPP	Captopril Prevention Project
CHARM	Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity Trial
CI	Confidence interval
CODEIRE	Cost of Diabetes in EIRE
COMET	Carvedilol Or Metoprolol European Trial
COPD	Chronic obstructive pulmonary disease
CSII	Continuous Subcutaneous Insulin Infusion
CTT	Cholesterol Treatment Trialist

DCCT	The Diabetes Control and Complication Trial
DCCT-EDIC	Diabetes Control and Complication Trial – Epidemiology of Diabetes Interventions and Complication
DDD	Defined daily dose
DECODE	Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe
DISC	Diabetes Shared Care Project
DPP-4 Inhibitor	Dipeptidyl peptidase 4 inhibitor
DPS	Drug Payment Scheme
DREAM	Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication trial
EDIC	Epidemiology of Diabetes Interventions and Complications
ESC	European Society of Cardiology
EURODIAB	The Epidemiology and Prevention of Diabetes
GIP	Gastric inhibitory polypeptide
GLP 1	Glucagon-like-peptide 1
GLUT	Glucose transporter
GMS	General Medical Services
GMS-PB	General Medical Scheme Payment Board
GP	General Practitioner
GPRD	General Practice Research Database
HDL	High Density Lipoprotein
HIPE	Hospital In-Patient Enquiry
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HOPE	Heart Outcomes Prevention Evaluation Trial
HR	Hazard ratio
HSE-PCRS	Health Service Executive- Primary Care Reimbursement Services
HTD	High Tech Drugs
IBD	Inflammatory bowel disease
IHD	Ischaemic heart disease
INSIGHT	International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment
INVEST	International Verapamil SR-Trandolapril Study

JUPITER	Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin trial
LDL	Low density lipoprotein
LIFE	Losartan Intervention for Endpoint Reduction trial
LTI	Long term illness
MAO	Monoamine oxidase Inhibitor
MARS	Medication Adherence Rating Scale
MEMO	Medicine Monitoring Unit
MI	Myocardial infarction
MPR	Medication Possession Ratio
NAVIGATOR	Nateglinide and Valsartan in Impaired Glucose Tolerance Outcome Research trial
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NPH	Neutral Protamine Hagedorn
OR	Odds ratio
PDC	Proportion of Days Covered
PBS	Public Health Observatory—Brent PCT—ScHARR
PEACE	Prevention of Events with an ACE inhibitor
PHARMO	Institute for Drug Outcomes Research
PPAR	Peroxisome proliferator-activated Receptor
PPI	Proton pump inhibitor
PROactive	Prospective Pioglitazone Clinical Trials in Macrovascular Events
PROSPER	Prospective Study of Pravastatin in the Elderly at Risk trial
PROVE-IT TIMI	Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction
RCT	Randomized Controlled Trial
ScHARR	School of Health and Related Research, University of Sheffield
SD	Standard Deviation
SHEP	Systolic Hypertension in the Elderly Program trial
SLÁN	Survey of lifestyle attitude and nutrition
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SOLVD	Studies of Left Ventricular Dysfunction trial
SSRI	Selective Serotonin Reuptake Inhibitor

STAR	Study of Trandolapril/Verapamil SR And Insulin Resistance
SUR	Sulphonylurea Receptor
TCA	Tricyclic antidepressant
UK	United Kingdom
UKPDS	United Kingdom Prospective Diabetes Study
VALUE	Valsartan Antihypertensive Long-term Use Evaluation trial
WHO	World Health Organisation
WHO- DIAMOND	World Health Organisation Multinational Project for Childhood Diabetes (Diabetes Mondiale)
WOSCOPS	West Of Scotland Coronary Prevention Study
YHPHO	Yorkshire & Humber Public Health Observatory

CHAPTER ONE

CHAPTER 1 : INTRODUCTION

1.1 BACKGROUND OF RESEARCH TOPIC

1.1.1 Burden of diabetes mellitus

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both [2]. The World Health Organization (WHO) provides the international standards for diagnosis and classification of diabetes. The most recent guideline from the WHO and American Diabetes Association (ADA) agreed on the diagnosis of diabetes based on fasting glucose level of ≥ 7.0 mmol/L. A 2 hour oral glucose tolerance test was also recommended by the WHO with diabetes diagnosed when the plasma glucose values are 11.1 mmol/L and above [3]. Glycated haemoglobin (HbA1c) is a useful measure of metabolic control and the efficacy of antidiabetic treatment. It provides an integrated summary of circadian blood glucose during the preceding 6–8 weeks as a mean value, equivalent to the lifespan of erythrocytes [4]. There are two main types of diabetes, type 1 and type 2 diabetes. Type 1 diabetes results from insufficient insulin production due to destruction of the beta cells of the pancreas. It usually affects younger aged patients and multiple aetiologies have been suggested as contributors to the development of this condition. Type 2 diabetes typically develops after middle age and results from reduced secretion of insulin or increased insulin resistance. Patients may have impaired glucose tolerance or impaired fasting glucose, also known as the pre-diabetes state before developing type 2 diabetes [3]. The risk factors for the development of type 2 diabetes are obesity, physical inactivity, and genetic factors [1]. The WHO estimated that in 2000, 171 million individuals had diabetes and this figure was expected to increase to 366 million individuals by 2030, particularly for those over 65 years of age [1].

The prevalence of type 2 diabetes in Ireland is expected to increase due to increasing rates of obesity and the increasing elderly population [5]. In 2007, the ingredient cost of diabetes medications borne by the Irish government through the reimbursement schemes was €19 million [6]. However, diabetes patients often require therapies for other complications and thus the medication costs will be far greater. The Cost of Diabetes in EIRE (CODEIRE) study estimated that the cost for treating diagnosed type 2 diabetes patients in Ireland was 377.2 million euro [7]. Those with diabetes are also associated with higher all-cause mortality rates compared to the general population [8, 9]. With the increasing prevalence of diabetes, this research is performed

to examine the prevalence of treated diabetes in a national population using pharmacy claims database for comparison with previous Irish studies. As there have been no previous studies performed to examine the incidence of type 2 diabetes in the adult population in this country, this study estimates the incidence of treated type 2 diabetes using the same pharmacy claims database. The lack of research on the prevalence and incidence of type 1 diabetes in the Irish paediatric population also needs to be addressed. This study also aims to provide estimates of the prevalence and incidence of treated type 1 diabetes in the paediatric population.

The mainstay of treatment for type 1 diabetes is insulin. The availability of insulin treatment has changed with human insulin replacing animal insulin worldwide [10]. The more expensive insulin analogues were introduced to the market in the late 1990s and are gradually replacing human insulin especially in the more developed countries [11]. Little is known about the prescribing pattern of insulin therapies for patients with type 1 diabetes in Ireland. With a variety of insulin preparation for prescribers to choose from, this study was undertaken to examine the trends and the variations in the prescribing of this agent in the Irish population with type 1 diabetes. Type 2 diabetes is treated with lifestyle changes and therapeutically with oral antidiabetic agents. Some patients may require a combination of oral agents and some may progress to insulin to control their diabetes. Sulphonylureas and metformin have been used extensively in diabetic patients before the emergence of the new class of drugs such as thiazolidinediones (glitazones), meglitinides, dipeptidyl peptidase 4 (DPP-4) inhibitors and incretin mimetics [12]. These novel agents are prescribed at higher costs and currently the glitazones accounts for most of the prescribing costs for diabetes treatment in Ireland [3]. No significant differences were observed in the reduction of HbA1c level as marker of glucose control between the different oral antidiabetic agents with the exception of alpha glucosidase inhibitors [12]. However, antidiabetic agents have different side effect profiles and may have different potential advantages in terms of cardiovascular risk factors modification such as lipid profiles, blood pressure control and overall reduction in cardiovascular events [12-14]. Recent interests have emerged in determining the safety risks with these novel agents, particularly with rosiglitazone, that have been reported to have higher adverse profiles in those with diabetes with an increased risk of myocardial infarction [15, 16]. The choice of agents for patients with type 2 diabetes and the factors influencing prescribing will be examined in this study in light of recent developments in relation to antidiabetic agents. The prescribing of combination agent and insulin therapies and the time to initiation of these agents in newly treated type 2 diabetes will also be determined as marker of glucose control. The pattern of glucose monitoring kits prescribing in patients with type 2 diabetes will be examined to determine the preference of practitioners regarding these.

Diabetes mellitus is associated with macrovascular diseases such as ischaemic heart disease, cerebrovascular disease and peripheral arterial disease [1]. The risk of cardiovascular disease is increased 2- 4 fold in those with diabetes [17-19]. There is a continuous relationship between HbA1c and cardiovascular risk with greatest risk observed in those with HbA1c level of 5.6 to 6.1% [20]. For every 1% increase in HbA1c there is a 19% increase in the odds of myocardial infarction (MI) [21]. Cardiovascular disease accounts for about 80% of mortality in patients with diabetes with 75% of this due to coronary heart disease and 25% due to cerebrovascular, peripheral and other macrovascular disease [22]. Peripheral arterial disease in patients with diabetes is the most common cause of non-traumatic lower limb amputation [23]. Hyperglycaemia is strongly related with microvascular diseases such as diabetic retinopathy, nephropathy and neuropathy in patients with diabetes [24-26]. About 30% of patients will develop overt diabetic nephropathy and this is the most common cause of chronic kidney disease and end stage renal failure acquiring dialysis [5]. The risk of cardiovascular disease also increases substantially with the onset of diabetic nephropathy [27, 28]. The rate of severe visual impairment from diabetic retinopathy was 3% and rate of blindness was 1.2% [29]. Diabetic retinopathy was shown to be the most common cause of blindness in the UK in the 16 to 64 age group [30]. The EuroDiab Prospective Complications Study has demonstrated that microvascular complications are important predictors for future mortality in patients with diabetes [31, 32]. In addition, diabetes mellitus is also associated with other complications such as erectile dysfunction [33], heart failure [34], atrial fibrillation [35] and depression [36].

Long term clinical studies such as the United Kingdom Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complication Trial (DCCT) have shown that intensive treatments using oral antidiabetic agents or insulin with goal of achieving near normal glucose levels were shown to significantly reduce microvascular complications [24, 25, 37]. The effect of intensive glycaemic control in reducing microvascular complications was still observed in the Diabetes Control and Complication Trial – Epidemiology of Diabetes Interventions and Complication (DCCT-EDIC) follow up study, 13-14 years after the completion of the initial study [24, 38, 39] and in the 10-year follow up of the UKPDS study [40]. Compared to microvascular complications, the UKPDS was not powered to examine the effect of intensive glycaemic control on reduction of macrovascular complications. However, there was a slight reduction in myocardial infarction risk (16%) in those with intensive treatment compared with conventionally treated patients [41]. Intensive glycaemic control was also not shown to reduce cardiovascular complications in more recent studies such as the Actions to Control Cardiovascular Risk in Diabetes (ACCORD) and Action in Diabetes and Vascular disease (ADVANCE) studies. More controversially, intensive glycaemic control was associated with increased risk of mortality in the

ACCORD study [42]. Tight blood pressure control has been demonstrated to significantly reduce the risk of both microvascular complications and macrovascular complications in the UKPDS study [43, 44]. The micro and macrovascular risk reduction with tight blood pressure control, however, was not sustained in the 10-year follow up [45]. In addition, prevention of cardiovascular disease in patients with diabetes also incorporate management of dyslipidaemia with lipid lowering agents such as 3-hydroxy-3-methylglutaryl-coenzyme A (HMG Co-A) reductase inhibitors or statins and measures to reduce atherosclerotic risk with antiplatelet agents such as acetyl salicylic acid or aspirin [5]. Previous study found an under prescribing of cardiovascular preventative therapies in patients with diabetes [46]. Gender and age bias has also been reported in the prescribing of cardiovascular preventative therapies in Ireland [47]. In addition, regional variations in cardiovascular preventative therapies prescribing in patients with diabetes has been observed [48]. This study is undertaken to examine the trends in prescribing of cardiovascular preventative therapies in patients with diabetes and to determine whether there has been an improvement in cardiovascular prescribing over the years In Ireland.

As with other chronic conditions, adherence to medication-taking as prescribed can complicate management of diabetes [49]. Non-adherence to antidiabetic medications and preventative cardiovascular therapies were associated with increased morbidity and mortality [50-52]. This study aims to determine the level of adherence to medications in patients with type 2 diabetes and factors influencing adherence to therapy in from pharmacy claims databases and from patients attending specialised outpatient clinics in Dublin. The relationship between adherence to these medications and intermediate clinical outcomes such as glucose control, blood pressure control and lipid control will also be examined.

With the increasing prevalence and incidence of diabetes, factors that can increase the risk of developing new onset diabetes need to be examined. Commonly prescribed pharmacological agents such as thiazides, beta blockers and corticosteroids have been associated with increased risk of diabetes [53]. Recently, interests have also emerged in the risk of new onset diabetes with the commonly prescribed antidepressants and statins [54, 55]. There is a need to determine the risk of diabetes with these commonly used pharmacological agents in a national population. Dose and duration relationship between these agents and diabetes will be examined.

1.1.2 Pharmacoepidemiology research using computerized databases

Over the past few years, there has been a surge in the use of computerized health care databases for health research purposes. These databases are used for clinical research planning, pharmacoepidemiology studies, clinical epidemiology studies, pharmacovigilance studies, pharmacoeconomic studies and health service planning. Amongst the widely used databases in

EUROPE are the General Practice Research Database (GPRD) in the UK, Institute for Drug Outcome Research (PHARMO) database in the Netherland and Medicine Monitoring Unit (MEMO) in Scotland [56]. The Nordic countries also have established population based database since 1960s and these countries have a long tradition of using registry based epidemiological research [57]. In Canada, the first and most established population based database on prescription data was the Saskatchewan Health in the province of Saskatchewan in 1975 [58]. The United States also have several large databases with data on medications dispensed such as Medicaid. However, most of the databases from United States were set up by insurance companies and thus only cover selected populations. Some of these databases consist of information on prescribed drugs such as the PHARMO databases and MEMO databases linked to clinical records while others such as the UK GPRD have clinical information integrated into the database [56]. Some of these databases such as the GPRD and PHARMO have been validated and shown to be robust for research purposes [59-61]. In order to maintain good standard, a database needs to be maintained to ensure the completeness, continuity and plausibility of electronic data recording.

Although randomized controlled trials (RCTs) are the gold standard in evaluating pharmacological therapies, there are inherent limitations of RCTs. They are usually not large enough to accurately measure infrequent adverse outcomes, expensive and not designed to examine long term outcomes [62]. These population based databases are large and are usually representative of the population as compared to selected patient population in hospital settings or randomized controlled trial settings. Longitudinal databases enable retrospective and prospective population based observational studies to be performed over a long period of years. These databases are relatively inexpensive. For outcome studies, the use of these databases provide objective means to evaluate drug exposure and thus reduces recall and interview bias [63].

Confounding bias is a commonly encountered problem in pharmacoepidemiological studies using automated databases. Information in these databases may be incomplete with regards to potential confounders such as smoking, alcohol, body mass indices, co-morbidities and family histories which may be important in some research areas. Pharmacy claims databases also do not typically contain information regarding medications obtained without a prescription. This information may be an important confounder for the drug being investigated. Information on prescribed medications may also not be captured if the drug is obtained outside the particular drug scheme plan [63].

The studies in this thesis were performed using the Irish Health Service Executive- Primary Care Reimbursement Services (HSE-PCRS) pharmacy claims database. This pharmacy claims database has been used widely for pharmacoepidemiological studies in this country [47, 48, 64].

The use of the HSE-PCRS databases allows prescribing across gender, age groups, drug schemes and health regions to be examined objectively in the Irish population. In Ireland, patients with diabetes are entitled to free medicines under two schemes, the General Medical Services (GMS) and the Long Term Illness (LTI) scheme. This provides a unique opportunity to examine the pharmacoepidemiology of diabetes in the Irish population. These two schemes will be described in details in Chapter 2.

The main limitation of the HSE-PCRS is the lack of clinical diagnoses and original prescriptions as written by the clinicians in the database as compared to other national population databases. To overcome this problem, prescribed medications were used as proxy for diseases of interest. This approach lacks specificity for certain conditions as some drugs have broad licensed indications; however, this method has been used and validated in other settings [65-68]. In addition, the use of medications as proxies of diseases cannot identify conditions that are not managed by standard drug therapy or conditions for which there are no drug therapies. The lack of detailed clinical diagnosis in the database also put a limitation into the investigation of individual patient factors and differences in drug indication that may influence prescribing trends. To obtain clinical outcomes for the study on adherence to medications in this thesis, record linkage between the HSE-PCRS and hospital records was performed in a pilot study of patients from two major teaching hospitals in Dublin, Ireland.

The additional knowledge from this research will help assist in the future planning of health care to improve the care for patients with diabetes in Ireland.

1.2 RESEARCH AIMS AND OBJECTIVES

1.2.1 Research aims

Diabetes is a chronic disorder associated with many debilitating complications and increased morbidity and mortality as well as increased health care expenditure. With the projected increase in the prevalence of diabetes worldwide especially in the elderly populations and the emergence of new pharmacotherapy for diabetes, the impact of diabetes in the population needs to be examined. This thesis aims to examine the pharmacoepidemiology of diabetes mellitus in the Irish primary care population using information derived primarily from national pharmacy claims databases. Most patients with diabetes in Ireland would be covered under two community drug schemes and this provides a unique opportunity to examine the different aspects of prescribing for diabetes in a national population. This thesis will bring together the prevalence and incidence of treated diabetes in the Irish population, the trends in the utilization of antidiabetic therapies and preventative cardiovascular therapies and the

variations and inequalities in the prescribing of these medications. This thesis will examine adherence to antidiabetic medications and cardiovascular preventative therapies using the pharmacy claims database and two cohorts of patients attending outpatient diabetes clinics from two major teaching hospitals. In addition, the risk of new onset diabetes with commonly prescribed pharmacological agents will be examined in the national population.

1.2.2 Research objectives

1.2.2.1 Epidemiology of treated diabetes mellitus in Ireland from national pharmacy claims databases

1) To examine the prevalence of treated type 1 diabetes in the paediatric population and both treated type 1 and type 2 diabetes in adults in Ireland from 2003 to 2007 using national pharmacy claims databases
2) To examine the 5-year trends in the national incidence of treated type 2 diabetes in adults and type 1 diabetes in the paediatric population
3) To stratify and compare patients with diabetes according to gender, age groups, community drug schemes and health regions

1.2.2.2 Utilization of antidiabetic therapies in Ireland

1) To examine the trends in prescribing of antidiabetic therapies, both established and novel agents, and glucose monitoring kits in adults and children with type 1 and type 2 diabetes
2) To examine the variations and inequalities in the prescribing of antidiabetic therapies across gender, age groups, community drug schemes and health regions.

1.2.2.3 Preventative cardiovascular therapies prescribing in patients with diabetes in Ireland

1) To examine the prevalence of ischaemic heart disease in patients with diabetes from 2003 to 2007
2) To examine the prescribing trends for preventative cardiovascular therapies in patients over 45 years of age with diabetes and the variations in prescribing of these agents according to age groups, gender, drug schemes, types of diabetes and health regions.
3) To examine the time to initiation of preventative cardiovascular therapies, the choice of cardiovascular therapies and factors influencing choice of cardiovascular therapy in patients with newly treated type 2 diabetes

1.2.2.4 Adherence to pharmacotherapy in patients with type 2 diabetes

1) To examine the trends in adherence to oral antidiabetic medications and preventative cardiovascular therapies in patients with newly treated type 2 diabetes
2) To identify the predictors of non-adherence to medications in patients with type 2 diabetes using a pharmacy claims database and self-reported questionnaires
3) To examine the relationship between self-reported adherence and adherence as measured using prescription refill records in patients with type 2 diabetes attending a diabetes outpatient clinic in Connolly Hospital, Blanchardstown
4) To examine beliefs and attitude towards medication taking and to examine the relationship between beliefs towards medication taking and actual with medication-taking behaviour
5) To examine the relationship between adherence to medication and intermediate clinical outcomes such as HbA1c levels, systolic and diastolic blood pressure and cholesterol levels

1.2.2.5 Risk of diabetes with commonly prescribed pharmacological agents in a national population

1) To ascertain the risk of new onset diabetes associated with commonly prescribed pharmacological agents – corticosteroids, antidepressants, statins and antihypertensives, in the Irish primary care population
2) To examine the dose or duration response relationship between these pharmacological agents and new-onset diabetes.

1.3 THESIS OUTLINE

1.3.1.1 Chapter 2: Materials and methods

This chapter describes the pharmacy claims databases and patient population included in this research. This chapter also includes description on study designs and statistical analysis performed.

1.3.1.2 Chapter 3: Epidemiology of treated diabetes mellitus in Ireland from national pharmacy claims databases

This chapter examines the prevalence of treated diabetes, both type 1 and type 2, by gender, age groups and health regions in Ireland in a retrospective cohort study using a pharmacy

claims database over a 5-year period from 2003 to 2007 in the adult population. In addition, the prevalence of those prescribed glucose monitoring kits only is examined as a marker for lifestyle – controlled type 2 diabetes. The incidence of treated type 2 diabetes in the adult population and the risk of incident type 2 diabetes according to gender, age groups and health regions were also examined using the same database. The prevalence and the incidence of treated type 1 diabetes in the paediatric population over the same 5-year study period was examined and discussed separately in Section 3.2 of this chapter.

1.3.1.3 Chapter 4: Utilization of antidiabetic therapies in Ireland

Section 4.1 of this chapter examines the trends in the prescribing of insulin therapies in patients with type 1 diabetes, both in the adults and paediatric population in the same 5-year period as described in Chapter three. The overall prescribing for the different preparations (fast-acting, intermediate-acting, long-acting) and types (human insulin and insulin analogues- lispro, aspart, glulisine, glargine and detemir) of insulin and the variations across gender, age groups, community drug schemes and health regions were examined using the pharmacy claims database. Section 4.2 in this chapter examines the choice of antidiabetic therapy for patients with type 2 diabetes and the factors influencing prescribing in the light of recent developments with antidiabetic agents. The prescribing of oral combination agents and insulin therapies and the time to initiation of these agents in newly treated type 2 diabetes were determined as marker of deteriorating glucose control. In addition, the pattern of glucose monitoring kits prescribed was examined in the cohort of patients with treated type 2 diabetes.

1.3.1.4 Chapter 5: Preventative cardiovascular therapies prescribing in patients with diabetes in Ireland

Chapter 5 examines the trends in the prescribing of cardiovascular preventative therapies in patients over 45 years of age in the general population with diabetes and in a cohort of patients with diabetes and ischaemic heart disease (IHD). These agents are statins, antihypertensives (Angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), beta blockers, calcium channel blockers, diuretics and other antihypertensives) and antiplatelet agents (aspirin and clopidogrel). This chapter also explore inequalities in the prescribing of preventative cardiovascular therapies in the Irish population with diabetes. The time to initiation of preventative cardiovascular therapies in patients over 45 years old with newly treated type 2 diabetes and the choice of agents in this population were determined in this chapter.

1.3.1.5 Chapter 6: Adherence to medications in patients with type 2 diabetes

This chapter examines the adherence to antidiabetic medications, lipid lowering agents, antihypertensives and antiplatelet agents in patients with newly treated type 2 diabetes using prescription refill records. Adherence is measured using the medication possession ratio (MPR) over a 365-day period. Demographic factors associated with increased risk of non-adherence to these medications were examined. A prospective cohort study was performed in patients attending the Diabetes Centre in Connolly hospital to examine self-reported adherence in these patients, the factors predicting adherence and the relationship between beliefs towards medicines and adherence. Information from the pharmacy claims database was linked to these patients to examine the relationship between adherence measured from prescription refill records and self-reported adherence. In addition, the relationship between adherence to medication and intermediate clinical outcomes such as HbA1c, systolic and diastolic blood pressure, total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides was examined in this cohort using the linked information. The relationship between adherence and intermediate clinical outcomes was also examined using a retrospective cohort study linking the information from the DIAMOND database of St James' hospital to the pharmacy claims database.

1.3.1.6 Chapter 7: Risk of new onset diabetes with commonly prescribed medications in a national population

This chapter examines the risk of new onset diabetes. The risk of new onset diabetes with corticosteroids of differing routes of administration (oral, inhaled, topical, nasal and eye/ear drops) was examined using a case control study design. The relationship between dose and duration of prescribed corticosteroids with new onset diabetes in this population was also examined. In Section 7.2, a case control study was performed to examine the risk of new onset diabetes with different classes of antidepressants (tricyclic antidepressants (TCA), selective serotonin reuptake inhibitor (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI) and other antidepressants) as well as individual antidepressants. A dose and duration response relationship between antidepressants and new onset diabetes was also examined. In Section 7.3, a retrospective cohort study was used to examine the relationship between the different statins (atorvastatin, rosuvastatin, simvastatin, pravastatin and fluvastatin) with the development of new onset diabetes in the Irish population. A retrospective cohort study was used to examine the risk of new onset diabetes with different classes of antihypertensive agents, either as monotherapy or as combination agents in Section 7.4.

1.3.1.7 Chapter 8: Conclusion

In this chapter the conclusions from the different studies are presented and future directions are discussed.

CHAPTER 2 : MATERIALS AND METHODS

2.1 Database

2.1.1 National pharmacy claims database

This study was performed using primarily the Irish Health Service Executive - Primary Care Reimbursement Services (HSE-PCRS) national pharmacy claims database. The HSE-PCRS was formerly known as the General Medical Services Payment Board (GMS-PB). The HSE-PCRS provides financial reimbursement to primary care contractors including the provision of prescription medications under a number of different schemes.

General Medical Services (GMS) scheme The eligibility for this scheme is means tested for those less than 70 years of age and free for all 70 years old and over from July 2001 to December 2008. The scheme is, therefore, over represented by females and the elderly. The scheme covers approximately 32% of the total population in Ireland, or 1.35 million individuals in 2008.

Drug Payment Scheme (DPS) Patients without the eligibility for the GMS scheme can avail of the DPS scheme. This scheme ensures that an individual of family has to pay no more than a monthly threshold amount (€100 as of 1st January 2009) for approved medicines in a calendar month. The scheme covers approximately 38% of the total population in Ireland, approximately 1.58 million individuals in 2008.

Long Term Illness (LTI) scheme This scheme provides all patients not eligible for the GMS scheme but suffering from one or more of a schedule of illnesses with necessary medications for treatment of their conditions. Diabetes is among the clinical conditions covered under the Long Term Illness (LTI) scheme. The scheme covers approximately 3% of the total population in Ireland, approximately 120,000 individuals in 2008.

High Tech Drugs (HTD) This scheme provides patients prescribed high tech medications such as immunosuppressants or anti-cancer drugs access to their medications free of charge through the community pharmacies.

The HSE-PCRS database records all prescriptions dispensed by pharmacist throughout Ireland for claims purposes from the schemes. For administrative purposes, the country was

divided into 8 health regions: Eastern (EHB), Midland (MHB), Mid-Western (MWH), North Eastern (NEH), North Western (NWH), South Eastern (SEH), Southern (SHB) and Western (WHB) regions. Full details on medication dispensed were recorded in the database such as date of dispensing, the exact product being dispensed (brand, strength and pack size), the quantity dispensed and cost of each item. Medications dispensed were recorded using the World Health Organization (WHO) Anatomical Therapeutic Classification (ATC) code. In addition, each prescription record includes a unique patient identifier, basic demographic information such as age group and gender.

Although the GMS database may not be representative of the entire Irish population, as the elderly, females and the socially disadvantaged are overrepresented, it is estimated to account for 70% of all medicines prescribed in the primary care population. The HSE-PCRS database has been used widely for research purposes on drug utilization in Ireland. For the purpose of the studies undertaken, the pharmacy claims databases from the GMS and LTI schemes for patients with diabetes were used in order to capture almost all the prescribing for patients with diabetes at national level. A small proportion of patients (<5%) who receive their prescriptions from the DPS scheme may have been excluded. This estimate of 5% of patients in the DPS scheme was obtained from the HSE-PCRS annual financial report [6] and was in keeping with the samples of patient population from Connolly and St James Hospital.

The information for 2008 from the LTI database was not available for these studies due to technical problems with the database. Thus, for studies using data from both the GMS and LTI scheme, the study period from 1st January 2003 until 31st December 2007 was chosen. For studies using data from the GMS scheme only (Chapter 5), the study period was extended until 31st March 2009. Further limitations of the database are discussed in the individual chapters.

2.1.2 DIAMOND database

St James's hospital is Ireland's largest teaching hospital and is affiliated to Trinity College Dublin. Approximately 8,000 patients attended the diabetes outpatient clinic and their clinical information is recorded in the DIAMOND database during each visit to the hospital. Demographic information such as gender, age, address, date of birth, smoking status, alcohol intake and GP information are available from the database. Clinical information available were types of diabetes, physical examinations such as BMI, systolic and diastolic blood pressure and biochemical measurements such as HbA1c, lipid profiles, renal profiles and thyroid profiles. Administrative information such as reasons for each visit, non-attendance of appointment, referral to diabetes services and attending clinicians or other allied health professionals were also recorded in the database.

Patients with type 2 diabetes under the GMS schemes with their first visits to the diabetes centre from 1st January 2007 to 31st December 2007 were identified from the DIAMOND database (n=156). The information obtained from the DIAMOND database was linked to the pharmacy claims database to examine the relationship between medication adherence from prescription refill record and intermediate clinical outcome. Record linkage was made possible via the unique GMS number recorded in the Hospital In-Patient Enquiry (HIPE) system. This is discussed in more detail in Section 5.1.5.

2.2 Patient population

A prospective cohort study to examine beliefs towards medicine and adherence to medications was carried out at the Diabetes Day Centre, Connolly Hospital, Blanchardstown. The Connolly hospital is a major teaching hospital affiliated to the Royal College of Surgeons Ireland. Patients with type 2 diabetes newly presenting to the diabetes outpatient clinic were identified from 1st July 2008 to 31st December 2008. To detect a correlation of p=0.2 or greater with 5% significance, a study with 80% power requires 153 patients to be recruited. A total of 152 patients took part in this study and were given questionnaires to provide information on; background demographics; self-reported adherence and beliefs towards medicine. These patients were invited for an annual follow up appointment from 1st April 2010 to 5th August 2010 and were given the same questionnaires. Information on clinical measurements of these patients was obtained from the outpatient clinic at the baseline and follow up visits. Record linkage was performed whereby the information from these patients was linked to the pharmacy claims database to examine medication adherence from prescription refill records. From the 152 patients recruited at the start of the study, only 120 patients attended the follow up visit whilst only 86 patients were available for record linkage study. Thus, this study was underpowered to examine the relationship between adherence to medications and clinical outcomes. This is discussed in more detail in Section 5.1.5.

2.3 Ethical approval

Ethical approval for the study using the Connolly hospital patient population was obtained from Faculty of Health Sciences Research Ethics Committee of Trinity College Dublin and Research Ethics Committee of Connolly Hospital. Ethical approval for the study using the DIAMOND database from St James's Hospital was obtained from St James's Hospital and Federated Dublin Voluntary Hospitals Joint Research Ethics Committee.

2.4 Study designs

Most of the studies included in this thesis were retrospective cohort studies using information from the pharmacy claims database and hospital based databases (Chapter 6). Case control studies were performed for the study on the risk of new onset diabetes with corticosteroids and antidepressants (Chapter 7). A prospective cohort study was performed in the patient population with type 2 diabetes attending the diabetes centre at Connolly Hospital, Blanchardstown (Chapter 6). A detailed explanation of the patient population is given in each chapter of this thesis.

2.5 Statistical analysis

Statistical analysis performed is explained in detail in the corresponding chapters. SAS statistical software version 9.1 (SAS, Cary, N.Y) was used for all statistical analysis. Significance at $p<0.05$ was assumed throughout. Continuous variables are presented as means with standard deviation for normally distributed variables or medians, while categorical variable are presented as percentages. Incidence rates are presented as rate per 100,000 population and rates of prescribing are presented as rates per 1000 patients. For regression analysis, results are presented as odds ratio (OR) or hazards ratio (HR) with 95% confidence interval (CI). P values are presented as * for values of 0.04 to 0.001, ** for values less than 0.001 to 0.0001 and *** for values less than 0.0001.

CHAPTER 3 : EPIDEMIOLOGY OF TREATED DIABETES MELLITUS IN IRELAND FROM NATIONAL PHARMACY CLAIMS DATABASES

3.1 Epidemiology of treated diabetes mellitus in the Irish adult population

3.1.1 Background

The WHO estimated that in 2000, the prevalence of global diabetes in adults was at 2.8% (171 million individuals). This figure is expected to increase to 4.4% (366 million individuals) by 2030, particularly for those over 65 years of age. The WHO estimates were based on demographic changes with the assumption that other risk factor levels such as obesity and physical activity remain constant in developed countries or are accounted for by urbanization in developing countries. The estimates were derived from data obtained from 40 countries and extrapolated to the rest of the 191 WHO countries [1]. A recent study performed by the International Diabetes Federation (IDF) estimated that in year 2010, the global prevalence of diabetes in adults aged 20 to 79 years will be at 6.4% (285 million individuals) and in year 2030 the estimated prevalence is expected to increase to 7.7% (439 million individuals). For developed countries, a 38% increase in prevalence is expected for those aged 60 years and over. Compared to the WHO estimates, these IDF estimates were extrapolated from studies on diabetes prevalence from 91 countries and diabetes prevalence estimates were available for all 216 nations in the world. The studies included in the IDF estimates were those assessed using a population-based methodology and were identified using Medline and contact with IDF offices [69].

The prevalence of diabetes has been shown to vary greatly between European countries. In 2007, the IDF estimated the overall prevalence of diabetes in Europe to be at 8.4% (53.2 million individuals) with the highest prevalence of diabetes found in Germany (11.8%) and the lowest in Iceland (2.0%) [70]. In 2010, the recent IDF study estimated that the prevalence of diabetes to be at 8.6% or equivalent to 55.4 million individuals [71]. The Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe (DECODE) study estimated that the prevalence of diabetes in 9 European countries was less than 10% in those less than 60 years old and between 10-20% in those 60 to 79 years old [72]. A study performed in various sentinel practices in eight European countries showed that the prevalence of diabetes per 1,000 population was lowest in Slovenia (16/1,000) and highest in Croatia (33/1,000) with gender differences [73].

In Ireland, there have been few studies that have estimated the prevalence of diabetes. The Cork and Kerry Diabetes Heart Disease Study in 1998 sampled 1,018 patients aged 50-69

years old from 17 general practices. It was estimated that the prevalence of type 2 diabetes in this cohort was 3.9% with 30% of these being undiagnosed [74]. The Department of Health and Children undertook a cross sectional national survey in the Survey of Lifestyle, Attitudes and Nutrition (SLÁN) study in 2007. In a questionnaire of chronic illnesses in 10,184 individuals, 3% were reported to have had diabetes in the past 12 months [75]. The IDF estimated that the prevalence of diabetes in Ireland in 2007 to be 5.6% (n=169,000) in those aged 20-79 years old with the highest prevalence in those aged over 60 years old (n=77,800) [70]. In 2010, the IDF estimated that the prevalence of diabetes in Ireland increased to 5.7% [71].

The Irish Diabetes Prevalence Working Group utilized the Public Health Observatory—Brent PCT—ScHARR (PBS) Population Prevalence Model to estimate the prevalence of both diagnosed and undiagnosed diabetes in the population stratified by age and gender in 2005. This prevalence model was developed by the Yorkshire and Humber Public Health Observatory (YHPO), Brent National Health Service (NHS) Primary Care Trust, and the University of Sheffield School of Health and Related Research (ScHARR). Using this model, it was estimated that 4.7% of all adults over 20 years old had diabetes (type 1 and type 2 combined). Diabetes prevalence was estimated to be higher in adult females at 5.4% compared to adult males at 4.0% and increasing with age from 0.6% in those 20-29 years old, 3.0% in those 30-59 years old and 13.8% in those 60 years old and over. Diabetes prevalence was estimated to be highest in the Western region (5.2%) and lowest in the Dublin Mid-Leinster region (4.4%). The PBS model estimated that the prevalence of type 1 diabetes in the adult population to be at 0.4% (n=12,011) and higher in males (0.5%) compared to females (0.3%). For type 2 diabetes, it was estimated that the prevalence in the Irish adult population was 4.3% and higher in females (5.1%) compared to males (3.5%) [76].

Another recent study was performed by the Institute of Public Health Ireland to examine the prevalence of chronic conditions including diabetes and to project future burden of disease in Ireland. Data on diabetes were derived from 3 studies performed in England; the Coventry Diabetes study (1991), the London-Brent study (1993) and the Welsh study (2002). It was estimated that the prevalence of diabetes (type 1 and 2 combined) in adults 20 years old and over in year 2007 was at 4.5%. This figure is estimated to increase to 5.9% by year 2020. Higher prevalence of diabetes was found in females (5.1%) compared to males (3.9%) and increases with age with 13.2% prevalence rate in those 60 years old and over. Prevalence rate also varied between regions with lowest rate found in Dublin. Diabetes is more prevalent in the most socio-economically deprived areas [77].

This chapter examines the prevalence of treated diabetes using both the GMS and LTI schemes from the national pharmacy claims database for comparison with previous Irish studies. Prevalence of treated diabetes in Ireland is examined by gender, age groups and regions, in a

retrospective cohort study, using the national prescription databases over a 5-year period from 2003 to 2007 in the adult population. In addition, the prevalence of those prescribed glucose monitoring kits only is examined as marker of lifestyle-controlled type 2 diabetes. As there have been no previous studies performed to estimate the incidence of type 2 diabetes in the adult population in this country, this chapter also estimates the incidence of treated type 2 diabetes using the same pharmacy claims database. Both type 1 and type 2 diabetes are life-long conditions associated with complications that can be debilitating to the individuals and translates into increasing health burden for the state. Estimates of prevalence and incidence of diabetes will help contribute to improving policy toward a targeted diabetes service nationwide.

3.1.2 Specific objectives

1) To examine national trends in the prevalence of both treated type 1 and type 2 diabetes in the adult population from 2003 to 2007 according to gender, age groups, calendar year and health regions using pharmacy claims databases.
2) To examine national trends in the prescribing of glucose monitoring kits only as proxy of lifestyle managed type 2 diabetes in Ireland.
3) To examine national trends in the incidence of treated type 2 diabetes in the adult population in Ireland from 2004 to 2007 according to gender, age groups, calendar year and health regions using pharmacy claims.

3.1.3 Methods

3.1.3.1 Prevalence of treated diabetes in the adult population

The HSE-PCRS databases were used to identify patients, aged 16 years old and over prescribed oral anti-diabetic agents or insulin therapies under both the GMS and the LTI schemes from 1st January 2003 to 31st December 2007 in Ireland. Type 1 diabetes patients were identified as those prescribed insulin only while type 2 diabetes patients were identified as those prescribed oral anti-diabetic agents either alone or in combination with insulin. Individuals prescribed glucose monitoring kits only were examined separately and taken as surrogate for life-style controlled type 2 diabetes. Individuals were classified according to gender, age groups (16-24 years, 25-44 years old, 45-64 years old and ≥ 65 years old) and health regions (Eastern, Midland, Mid-Western, North Eastern, North Western, South Eastern, Southern and Western).

Age-adjusted prevalence for both treated type 1 and type 2 diabetes were calculated using direct standardized methods assuming equal distribution of population for the different age groups and presented as percentage of cases in the population according to gender and health

regions for each calendar year. The denominator for calendar year 2003 to 2005 was determined using the population census for 2002 while the population census for year 2006 was used as denominator for calendar year 2006 to 2007. The age-specific prevalence of both type 1 and type 2 diabetes for the different age groups were also examined for each of the health regions. Test for linear trend was used to determine the trend in diabetes prevalence over time using regression analysis. The prevalence of diet and lifestyle controlled diabetes was also examined by the prescribing of glucose monitoring kit using the same methods as described.

3.1.3.2 Incidence of treated type 2 diabetes in the adult population

The HSE-PCRS databases were used to identify patients, aged 16 years old and over newly prescribed oral anti-diabetic agents in Ireland under both the GMS and the LTI scheme from 1st January 2004 to 31st December 2007. Year 2003 was used as a run-in period to exclude prevalent treated diabetes in this population. Cases of diabetes were classified by gender, age groups, health regions and calendar year at initiation of antidiabetic treatment.

The incidence rate of type 2 diabetes was calculated as cases of new diabetes per 100 000 population per person year over the 4-year study period. The denominator for calendar year 2004 to 2005 was determined using the population census for 2002 while population census for 2006 was used for calendar year 2006 to 2007. Each person is assumed to contribute to a full calendar year. Age-adjustment for incidence rates was performed using the standard population of the different age groups. Age-specific incidence rates were also calculated for each age group. 95% CI were estimated assuming a Poisson distribution. A Poisson (log-linear) regression model was used to analyse the incidence rates by gender, age groups, calendar year and regions.

3.1.4 Results

3.1.4.1 Prevalence of treated diabetes mellitus (both type 1 and type 2) in the adult Irish population

The age-adjusted national prevalence of treated type 1 and type 2 diabetes in adults 16 years and over in Ireland was 2.1% in 2003 and increased with each calendar year ($p<0.0001$) to 2.7% in 2007 as shown in Figure 3.1.1. Higher age-adjusted prevalence rate was observed in males compared to females with prevalence of 2.4% in 2003 and 3.1% in 2007. In females, the age-adjusted prevalence rate was 1.8% in 2003 and rose to 2.3% in 2003. Significant increase in prevalence over the study period was observed in both genders ($p<0.0001$). Age-specific prevalence rate of treated diabetes increased with age groups with highest increase observed in those 65 years old and over during the study period ($p<0.0001$) as shown in Figure 3.1.2. In 2007,

the age-specific prevalence rate was 0.4% in 16-24 years old, 0.8% in 25-44 years old, 3.3% in 45-64 years old and 9.9% in those over 65 years old.

Regional variations

There was wide variation in the age-adjusted prevalence of treated diabetes across the country. Consistently, the highest prevalence rate was observed in the Midland for all the calendar years with prevalence of 2.7% in 2003 and 3.5% in 2007. The Eastern region had the lowest prevalence rate with prevalence of 1.7% in 2003 and 2.3% in 2007. In males, the highest prevalence rate of diabetes was observed in Mid-Western region (Figure 3.1.3). The lowest diabetes prevalence rate in males was seen in South-Eastern region throughout the study period. In females, the highest diabetes prevalence rate was in Midland region while the lowest prevalence rate was observed in Eastern region throughout the study period (Figure 3.1.4).

The age-specific prevalence rate also varied within the country. The Eastern region had the lowest prevalence rate in all age groups except in those 65 years old and over from 2003 to 2007 as presented in Table 3.1.1. The lowest prevalence rate in those 65 years old and over was found in the Southern region throughout the study period. The highest diabetes prevalence rate in those aged 16 to 24 years old was observed in North-Western region. Midland region had the highest diabetes prevalence rate in those aged 25 years old and above.

Figure 3.1.1: National age-adjusted prevalence of treated diabetes mellitus (both type 1 and type 2) in adult population according to gender from 2003 to 2007 (n=number of patients)

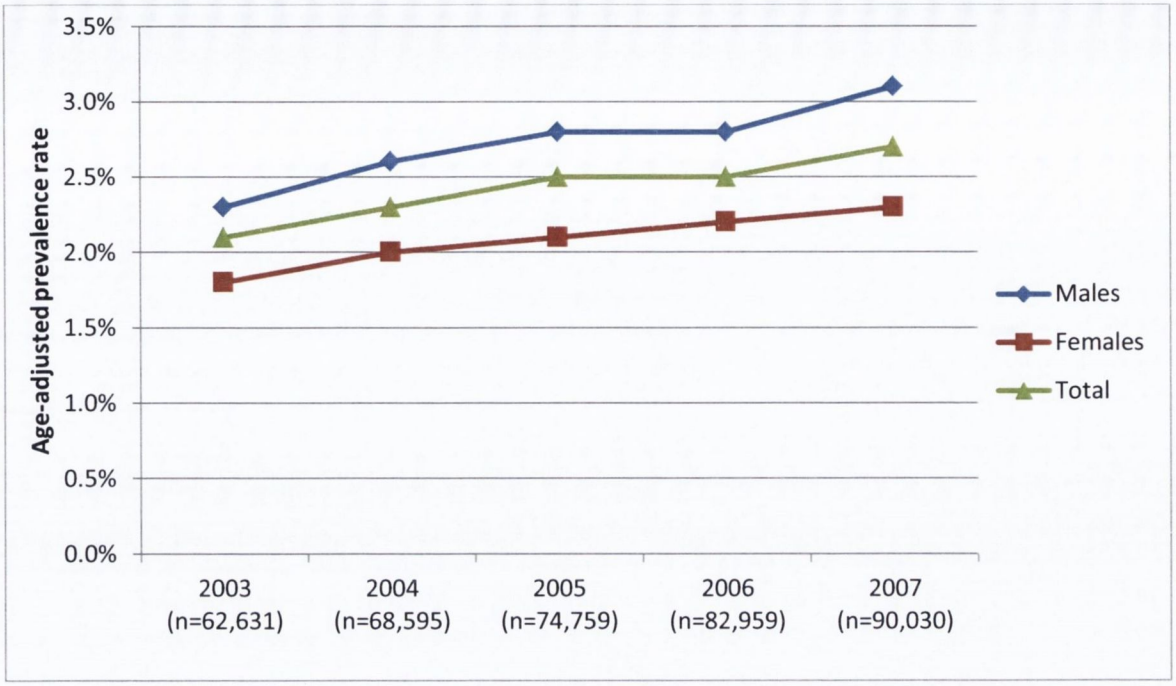


Figure 3.1.2: National age-specific prevalence of treated diabetes mellitus (both type 1 and type 2) in adult population from year 2003 to 2007

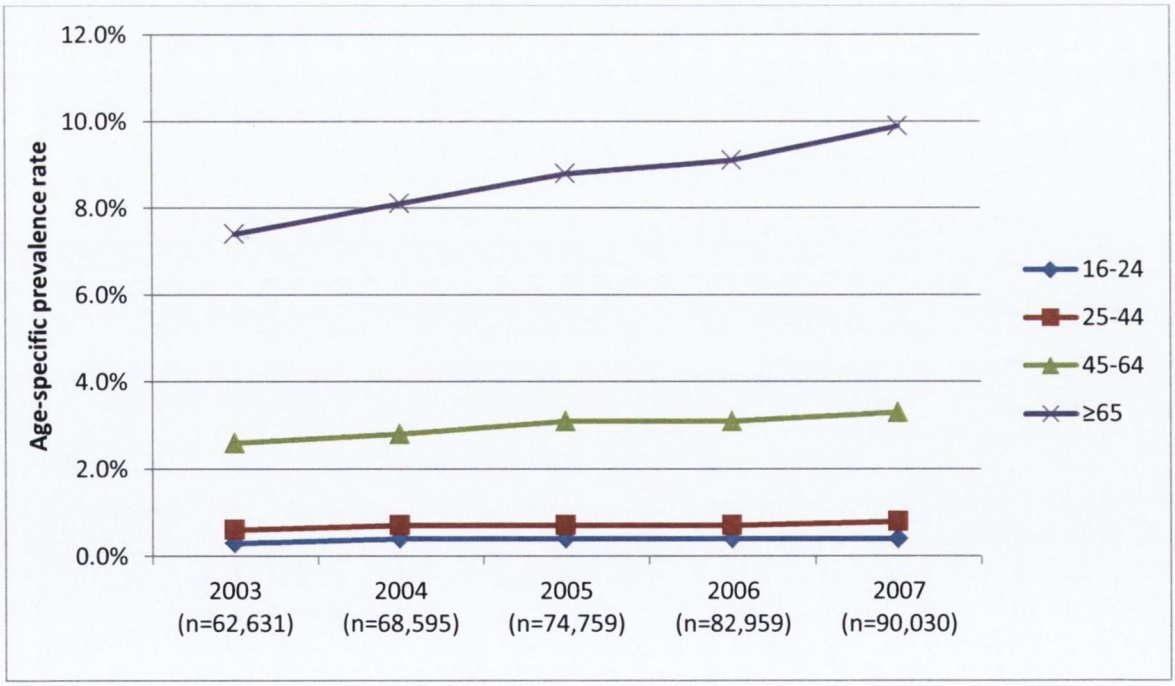


Figure 3.1.3: Age-adjusted prevalence of diabetes mellitus (type 1 and type 2) in males by regions from 2003 to 2007

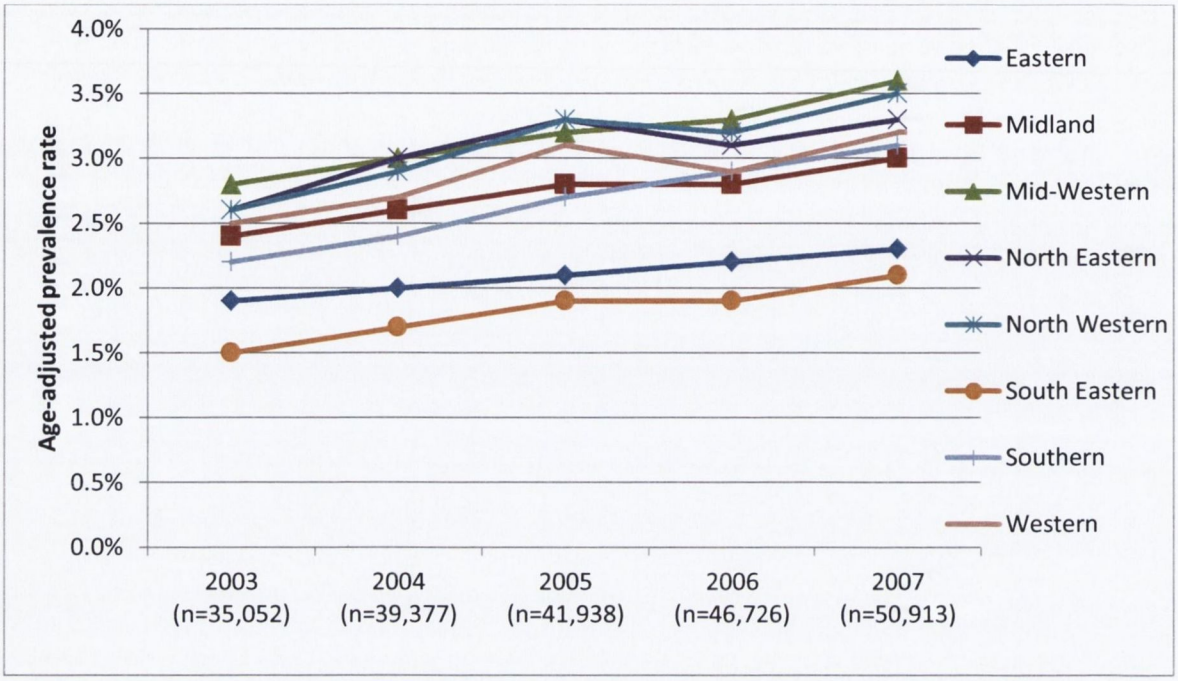


Figure 3.1.4 : Age-adjusted prevalence of diabetes mellitus (type 1 and type 2) in females by regions from 2003 to 2007

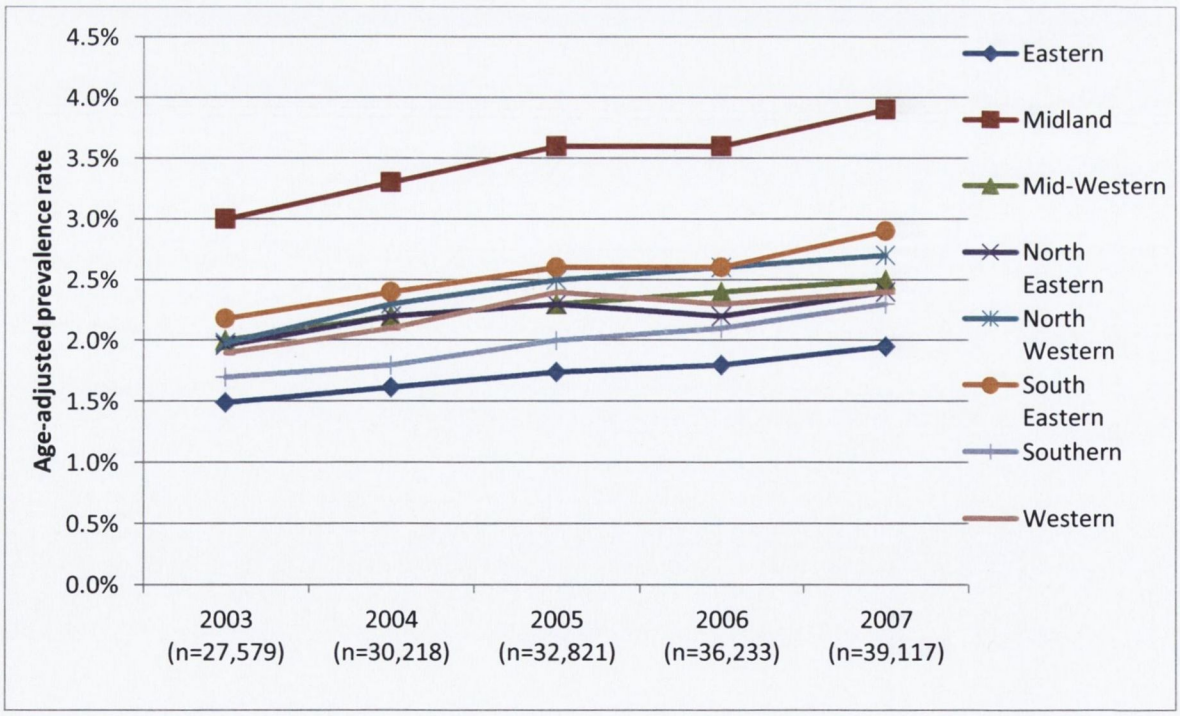


Table 3.1.1: Frequency and age-specific prevalence of diabetes mellitus (both type 1 and type 2) in adults by regions from 2003 to 2007

Year and Health regions	Frequency				Age-specific prevalence			
	16-24	25-44	45-64	≥65	16-24	25-44	45-64	≥65
2003								
Eastern	566	2,078	5,730	10,084	0.3%	0.5%	2.0%	7.4%
Midland	154	525	1,672	2,239	0.5%	0.8%	3.5%	8.5%
Mid-Western	186	709	2,308	3,120	0.4%	0.7%	3.1%	7.9%
North-Eastern	192	751	2,128	2,881	0.4%	0.7%	3.0%	7.9%
North- Western	151	409	1,269	1,997	0.5%	0.7%	2.6%	6.9%
South-Eastern	249	895	3,011	4,063	0.4%	0.7%	3.2%	8.2%
Southern	284	961	2,996	4,610	0.3%	0.6%	2.3%	6.6%
Western	239	679	2,198	3,297	0.4%	0.6%	2.6%	6.7%
2004								
Eastern	552	2,125	5,917	11,240	0.2%	0.5%	2.1%	8.2%
Midland	163	594	1,821	2,425	0.5%	0.9%	3.5%	9.3%
Mid-Western	206	793	2,581	3,292	0.4%	0.8%	3.3%	8.3%
North-Eastern	208	904	2,499	3,186	0.4%	0.9%	3.5%	8.7%
North- Western	164	467	1,494	2,181	0.5%	0.8%	3.0%	7.5%
South-Eastern	271	1,034	3,366	4,437	0.5%	0.8%	3.6%	8.9%
Southern	325	1,096	3,358	4,840	0.4%	0.6%	2.6%	7.0%
Western	263	757	2,435	3,600	0.5%	0.7%	2.9%	7.3%
2005								
Eastern	570	2,214	6,107	12,340	0.2%	0.5%	2.1%	9.0%
Midland	181	654	2,053	2,608	0.6%	1.0%	4.3%	9.9%
Mid-Western	222	820	2,775	3,455	0.4%	0.8%	3.7%	8.7%
North-Eastern	217	972	2,695	3,463	0.4%	0.9%	3.7%	9.5%
North- Western	172	503	1,739	2,416	0.6%	0.8%	3.5%	8.3%
South-Eastern	281	1,097	3,780	4,945	0.5%	0.9%	4.1%	9.9%
Southern	331	1,217	3,699	5,204	0.4%	0.7%	2.9%	7.5%
Western	299	883	2,804	4,043	0.5%	0.8%	3.3%	8.2%
2006								
Eastern	552	2,461	6,771	13,885	0.3%	0.5%	2.4%	10.3%
Midland	184	740	2,291	2,896	0.6%	1.0%	4.2%	10.5%
Mid-Western	223	897	3,064	3,785	0.4%	0.8%	3.7%	9.1%
North-Eastern	252	1,029	3,014	3,690	0.5%	0.8%	3.6%	9.4%
North- Western	182	593	1,892	2,634	0.6%	0.9%	3.4%	8.5%
South-Eastern	311	1,254	4,164	5,489	0.5%	0.9%	4.0%	10.1%
Southern	395	1,542	4,338	5,836	0.5%	0.8%	3.1%	7.9%
Western	290	954	2,963	4,295	0.5%	0.8%	3.1%	8.2%
2007								
Eastern	564	2,575	7,278	15,220	0.3%	0.5%	2.6%	11.2%
Midland	188	807	2,495	3,193	0.6%	1.0%	4.5%	11.5%
Mid-Western	242	987	3,324	4,075	0.5%	0.9%	4.0%	9.8%
North-Eastern	264	1,126	3,255	3,975	0.5%	0.9%	3.9%	10.1%
North- Western	181	635	2,059	2,839	0.6%	1.0%	3.7%	9.2%
South-Eastern	345	1,416	4,598	5,972	0.6%	1.0%	4.4%	11.0%
Southern	426	1,655	4,748	6,400	0.5%	0.9%	3.4%	8.6%
Western	293	1,029	3,200	4,666	0.5%	0.8%	3.4%	9.0%

3.1.4.2 Prevalence of treated type 1 diabetes mellitus in the adult Irish population

The age-adjusted national prevalence of type 1 diabetes in adults was stable throughout the study period with a prevalence of 0.4% from 2003 to 2006 and increasing to 0.5% in 2007 (Figure 3.1.5). Higher age-adjusted prevalence rate was observed in males compared to females. Age-adjusted prevalence rate of type 1 diabetes was constant at 0.4% in females over the 5-year study period while in males the prevalence increased from 0.4% in 2003 to 0.5% in 2007. Age-specific prevalence rate of treated type 1 diabetes increased with age groups as shown in Figure 3.1.6. During the study period, the age-specific prevalence of treated type 1 diabetes increased by only 0.1% for each age group.

Regional variations

Less variation was observed in the age-adjusted prevalence rate of type 1 diabetes between different regions in the country (Table 3.1.2) as compared to the prevalence of both type 1 and type 2 diabetes combined. In 2003, the age-adjusted prevalence of type 1 diabetes was 0.3% in the Eastern region, 0.4% in the South Eastern, Southern and Western regions and 0.5% elsewhere. Little increase in prevalence rates was observed across regions in 2007 with the prevalence of 0.4% in the Eastern region, 0.6% in the North Eastern region and 0.5% elsewhere. Little variation was also observed in the age-specific prevalence of type 1 diabetes in adult (Table 3.1.3). The Eastern region also had the lowest age-specific prevalence rate of treated type 1 diabetes in all age groups except in those 65 years and over.

Figure 3.1.5: National age-adjusted prevalence of treated type 1 diabetes mellitus in adult population according to gender from 2003 to 2007

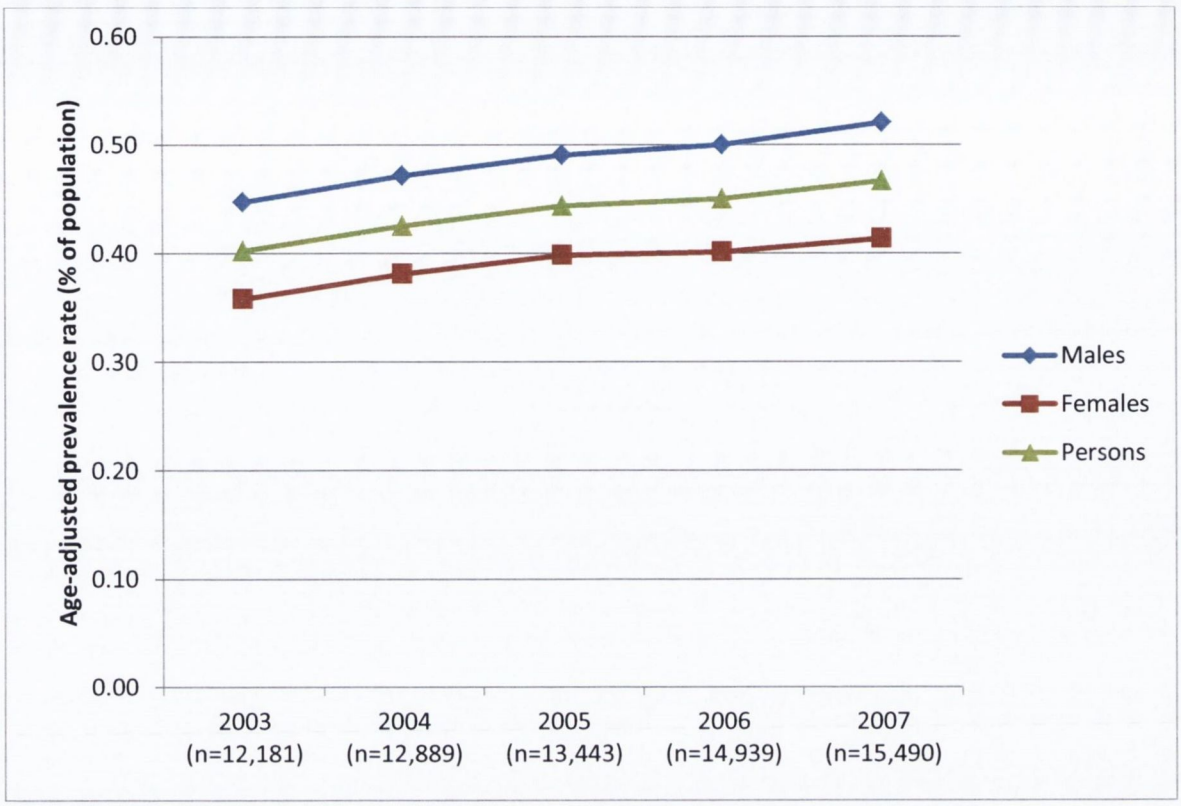


Figure 3.1.6: National age-specific prevalence of treated type 1 diabetes mellitus in the adult population from 2003 to 2007

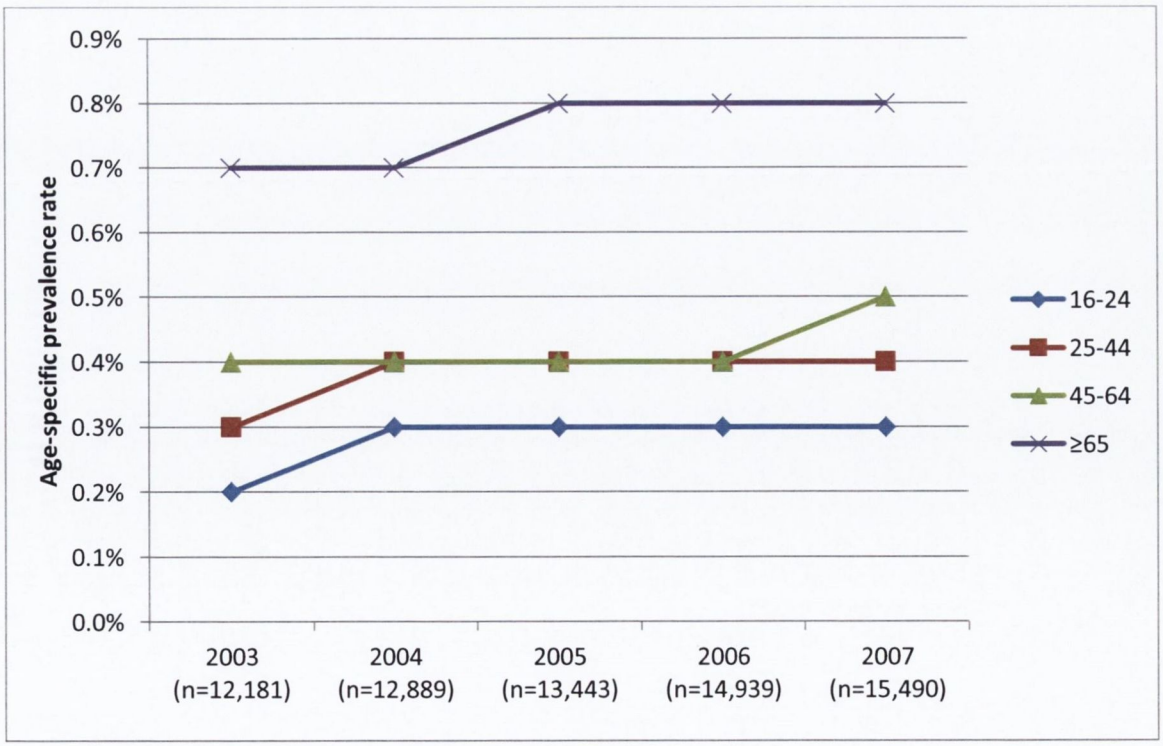


Table 3.1.2: Frequency and age-adjusted prevalence of type 1 diabetes mellitus in adults by regions from 2003 to 2007

Year and health regions	Frequency			Age-adjusted prevalence rate (%)		
	Males	Females	Total	Males	Females	Total
2003						
Eastern	1,855	1,707	3,562	0.3%	0.3%	0.3%
Midland	484	375	859	0.6%	0.4%	0.5%
Mid-Western	686	547	1233	0.5%	0.4%	0.5%
North-Eastern	665	549	1214	0.5%	0.4%	0.5%
North- Western	450	366	816	0.5%	0.4%	0.5%
South-Eastern	814	638	1452	0.4%	0.4%	0.4%
Southern	995	783	1778	0.4%	0.3%	0.4%
Western	720	547	1267	0.5%	0.4%	0.4%
2004						
Eastern	1,880	1,731	3,611	0.3%	0.3%	0.3%
Midland	480	422	902	0.6%	0.5%	0.5%
Mid-Western	724	560	1,284	0.5%	0.4%	0.5%
North-Eastern	804	632	1,436	0.6%	0.5%	0.5%
North- Western	473	377	850	0.6%	0.5%	0.5%
South-Eastern	835	692	1,527	0.4%	0.4%	0.5%
Southern	1,077	849	1,926	0.5%	0.4%	0.4%
Western	756	597	1,353	0.5%	0.4%	0.5%
2005						
Eastern	1,926	1,830	3,756	0.4%	0.3%	0.3%
Midland	513	415	928	0.6%	0.4%	0.5%
Mid-Western	713	586	1,299	0.5%	0.4%	0.5%
North-Eastern	847	655	1,502	0.6%	0.5%	0.6%
North- Western	490	394	884	0.6%	0.5%	0.5%
South-Eastern	879	713	1,592	0.4%	0.4%	0.5%
Southern	1,132	895	2,027	0.5%	0.4%	0.4%
Western	813	642	1,455	0.5%	0.4%	0.5%
2006						
Eastern	2,213	1,983	4,196	0.4%	0.3%	0.4%
Midland	548	432	980	0.6%	0.4%	0.5%
Mid-Western	735	605	1,340	0.5%	0.4%	0.5%
North-Eastern	886	699	1,585	0.6%	0.5%	0.5%
North- Western	553	431	984	0.6%	0.5%	0.5%
South-Eastern	951	780	1,731	0.4%	0.4%	0.5%
Southern	1,475	1,096	2,571	0.6%	0.4%	0.5%
Western	879	673	1,552	0.5%	0.4%	0.5%
2007						
Eastern	2,260	1,983	4,243	0.4%	0.3%	0.4%
Midland	568	457	1,025	0.6%	0.4%	0.5%
Mid-Western	743	613	1,356	0.5%	0.4%	0.5%
North-Eastern	903	745	1,675	0.6%	0.5%	0.6%
North- Western	559	446	1,005	0.6%	0.5%	0.5%
South-Eastern	1,046	815	1,861	0.5%	0.5%	0.5%
Southern	1,547	1,145	2,692	0.6%	0.5%	0.5%
Western	929	704	1,633	0.6%	0.4%	0.5%

Table 3.1.3: Frequency and age-specific prevalence of type 1 diabetes mellitus in adults by regions from 2003 to 2007

Year and Health regions	Frequency				Age-specific prevalence			
	16-24	25-44	45-64	≥65	16-24	25-44	45-64	≥65
2003								
Eastern	412	1,192	913	1,045	0.2%	0.3%	0.3%	0.8%
Midland	127	287	239	206	0.4%	0.4%	0.5%	0.8%
Mid-Western	154	416	364	299	0.3%	0.4%	0.5%	0.8%
North-Eastern	162	426	357	269	0.3%	0.4%	0.5%	0.7%
North- Western	132	243	233	208	0.4%	0.4%	0.5%	0.7%
South-Eastern	211	508	426	307	0.4%	0.4%	0.5%	0.6%
Southern	239	567	491	481	0.3%	0.3%	0.4%	0.7%
Western	184	377	368	338	0.3%	0.4%	0.4%	0.7%
2004								
Eastern	409	1,196	922	1,084	0.2%	0.3%	0.3%	0.8%
Midland	133	312	255	202	0.4%	0.5%	0.4%	0.8%
Mid-Western	173	427	382	302	0.3%	0.4%	0.5%	0.8%
North-Eastern	184	429	424	299	0.4%	0.5%	0.6%	0.8%
North- Western	137	254	261	198	0.5%	0.4%	0.5%	0.7%
South-Eastern	216	553	425	333	0.4%	0.4%	0.5%	0.7%
Southern	267	624	531	504	0.3%	0.4%	0.4%	0.7%
Western	194	415	375	369	0.3%	0.4%	0.4%	0.7%
2005								
Eastern	402	1,184	968	1,202	0.2%	0.3%	0.3%	0.9%
Midland	142	337	244	205	0.5%	0.5%	0.5%	0.8%
Mid-Western	187	433	389	290	0.4%	0.4%	0.5%	0.7%
North-Eastern	189	560	446	307	0.4%	0.5%	0.6%	0.8%
North- Western	138	267	261	218	0.5%	0.4%	0.5%	0.7%
South-Eastern	223	566	456	347	0.4%	0.5%	0.5%	0.7%
Southern	285	671	562	509	0.3%	0.4%	0.4%	0.7%
Western	211	469	407	368	0.4%	0.4%	0.5%	0.7%
2006								
Eastern	413	1,298	1,109	1,376	0.2%	0.3%	0.4%	1.0%
Midland	140	359	271	210	0.4%	0.5%	0.5%	0.8%
Mid-Western	183	472	388	297	0.4%	0.4%	0.5%	0.7%
North-Eastern	205	551	484	345	0.4%	0.4%	0.6%	0.9%
North- Western	149	319	275	241	0.5%	0.5%	0.5%	0.8%
South-Eastern	242	630	472	387	0.4%	0.5%	0.4%	0.7%
Southern	336	925	776	534	0.4%	0.5%	0.5%	0.7%
Western	224	502	420	406	0.4%	0.4%	0.4%	0.8%
2007								
Eastern	415	1300	1129	1,399	0.2%	0.3%	0.4%	1.0%
Midland	136	383	273	233	0.4%	0.5%	0.5%	0.8%
Mid-Western	195	480	396	285	0.4%	0.4%	0.5%	0.7%
North-Eastern	217	597	496	365	0.4%	0.5%	0.6%	0.9%
North- Western	152	325	293	235	0.5%	0.5%	0.5%	0.8%
South-Eastern	275	673	503	410	0.5%	0.5%	0.5%	0.7%
Southern	364	967	797	564	0.4%	0.5%	0.6%	0.8%
Western	231	537	457	408	0.4%	0.4%	0.5%	0.8%

3.1.4.3 Prevalence of treated type 2 diabetes mellitus in the adult population

The age-adjusted national prevalence of type 2 in adults aged 16 years and over in Ireland was 1.7% in 2003 rising to 2.2% in 2007 (Figure 3.1.7). As with type 1 diabetes, higher age-adjusted prevalence rates were observed in adult males compared to females. In males, the age-adjusted prevalence was 1.9% in 2003 and continued to increase to 2.6% in year 2007 while in females; the prevalence rate was 1.4% in 2003 increasing to 1.9% in 2007. There was an overall increase in the prevalence of treated type 2 diabetes with higher age groups (Figure 3.1.8). In 2003, the national age-specific prevalence rate was very low in those 16-24 year olds at 0.1%, however, the prevalence increased to 7.1% in those aged 65 years and over. In 2007, a higher prevalence rate was observed in those aged 25 years and above with a prevalence of 0.4% in 25-44 year olds, 2.9% in 45-64 year olds and 9.1% in those 65 years old and over. The prevalence of type 2 diabetes was lower than type 1 diabetes in those aged below 45 years during the 5-year study period.

The highest prevalence of treated type 2 diabetes was observed in the Midland region for both genders. In 2007, only the Eastern and Southern regions had lower age-adjusted prevalence of type 2 diabetes compared to the national prevalence. In males, the lowest prevalence rate was in the South- Eastern region (Figure 3.1.9) while in females the lowest prevalence rate was found in the Eastern region (Figure 3.1.10). For the age-specific prevalence of type 2 diabetes, the Midland region had the highest prevalence rate for all the different age groups (Table 3.1.4). The Eastern region had the lowest age-specific prevalence rate of treated type 2 diabetes in those aged between 25 to 64 years from 2003 to 2007. The lowest prevalence rate in those 65 years and over was found in the Southern region throughout the study period.

Figure 3.1.7 : National age-adjusted prevalence of treated type 2 diabetes mellitus in the adult population according to gender from 2003 to 2007

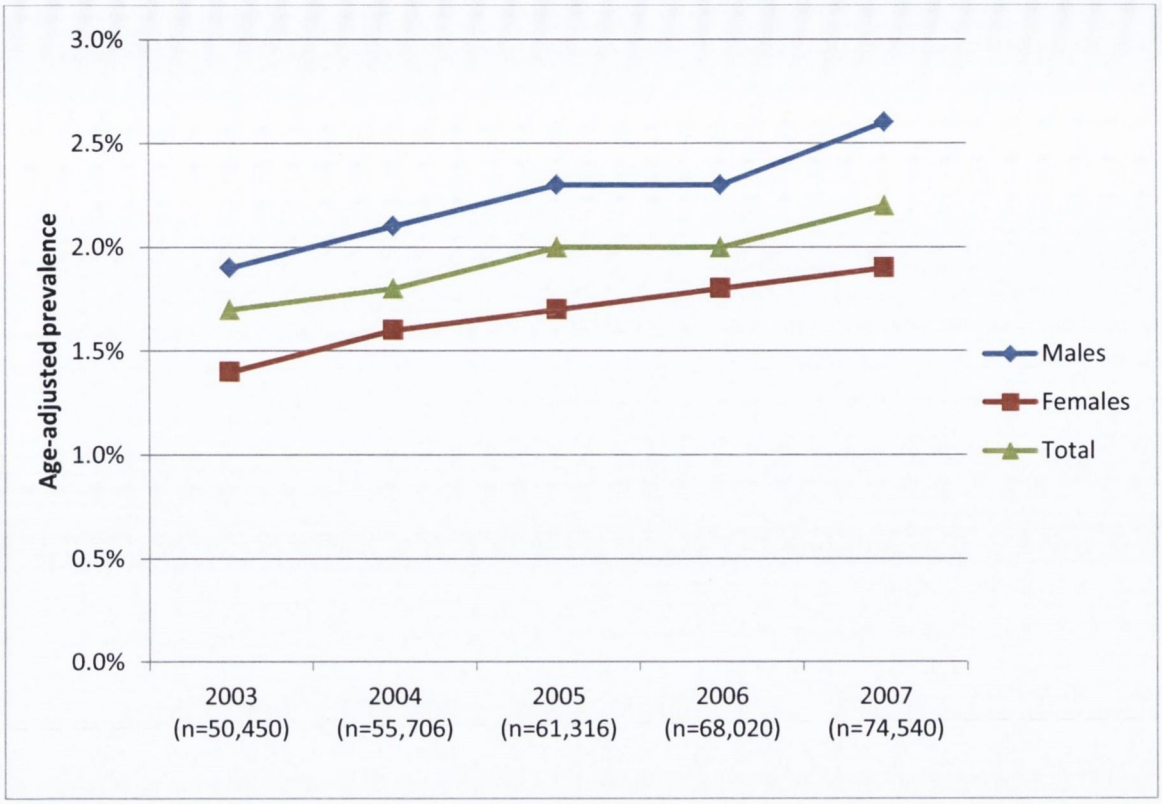


Figure 3.1.8 : National age-specific prevalence of treated type 2 diabetes mellitus in the adult population from 2003 to 2007

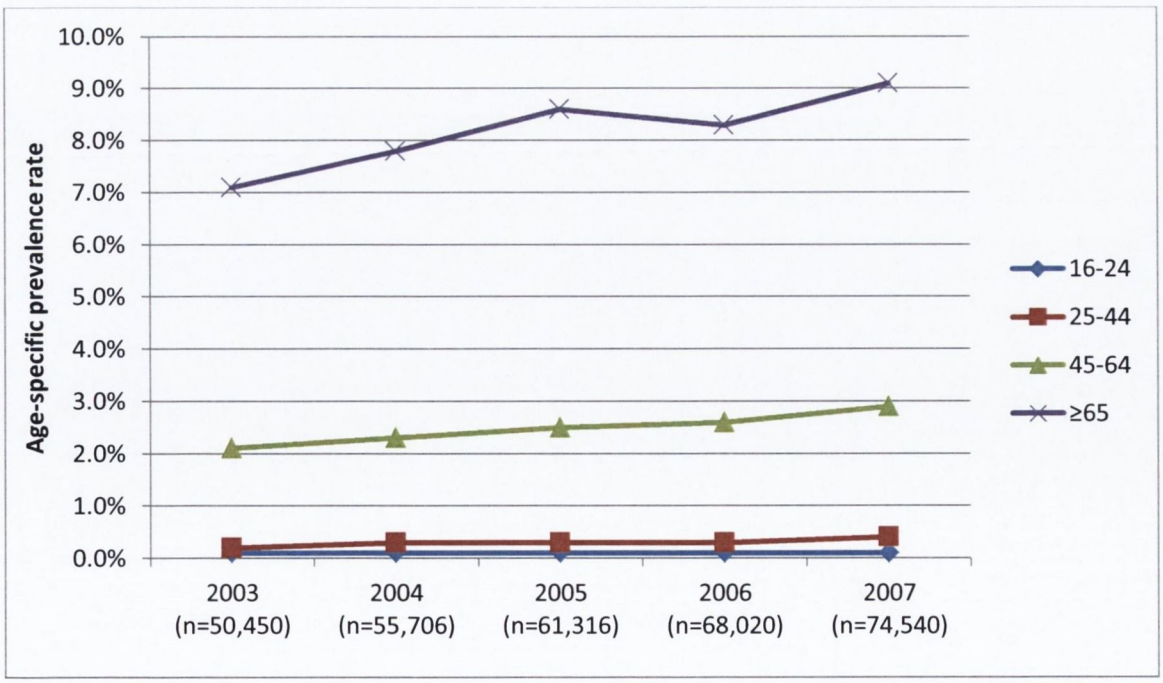


Figure 3.1.9: Age-adjusted prevalence of treated type 2 diabetes mellitus in males by regions from 2003 to 2007

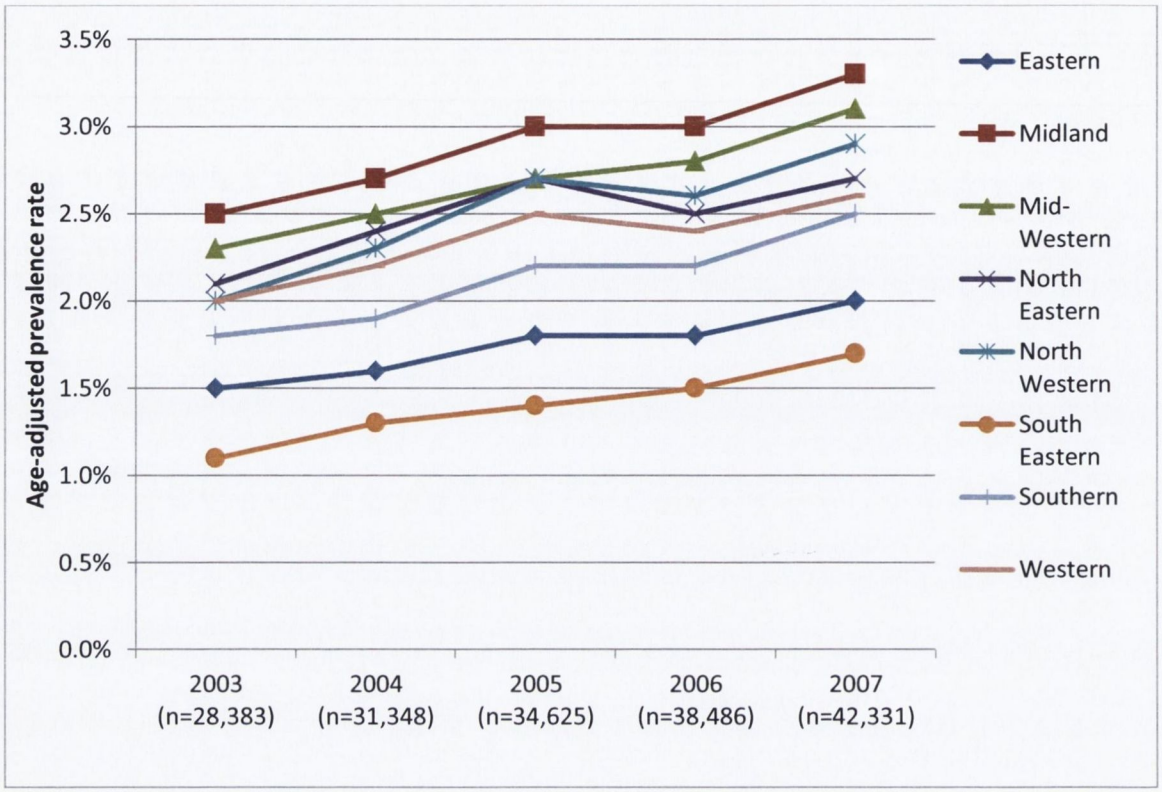


Figure 3.1.10: Age-adjusted prevalence of treated type 2 diabetes mellitus in females by regions from 2003 to 2007

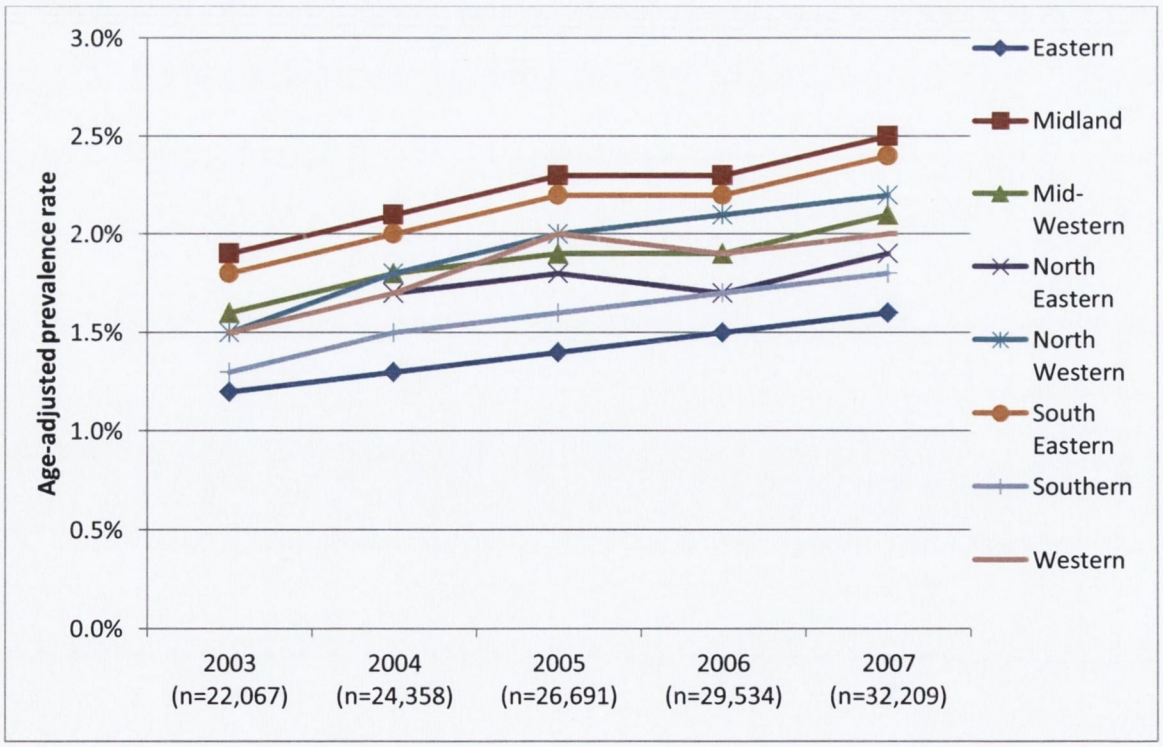


Table 3.1.4: Frequency and age-specific prevalence of type 2 diabetes mellitus in adults by regions from 2003 to 2007

Year and Health regions	Frequency				Age-specific prevalence			
	16-<25	25-<45	45-<65	≥65	16-<25	25-<45	45-<65	≥65
2003								
Eastern	154	886	4,817	9,039	0.1%	0.2%	1.6%	7.1%
Midland	27	238	1,433	2,033	0.1%	0.4%	2.9%	8.3%
Mid-Western	32	293	1,944	2,821	0.1%	0.3%	2.5%	7.6%
North-Eastern	30	325	1,771	2,612	0.1%	0.3%	2.4%	7.6%
North- Western	19	166	1,036	1,789	0.1%	0.3%	2.0%	6.5%
South-Eastern	38	387	2,585	3,756	0.1%	0.3%	2.7%	8.1%
Southern	45	394	2,505	4,129	0.1%	0.2%	1.9%	6.4%
Western	55	302	1,830	2,959	0.1%	0.3%	2.1%	6.4%
2004								
Eastern	143	929	4,995	10,156	0.1%	0.2%	1.7%	8.0%
Midland	30	282	1,566	2,223	0.1%	0.4%	3.2%	9.1%
Mid-Western	33	366	2,199	2,990	0.1%	0.4%	2.8%	8.1%
North-Eastern	24	375	2,075	2,887	0.1%	0.4%	2.8%	8.4%
North- Western	27	213	1,233	1,983	0.1%	0.4%	2.4%	7.2%
South-Eastern	55	481	2,941	4,104	0.1%	0.4%	3.1%	8.8%
Southern	58	472	2,827	4,336	0.1%	0.3%	2.1%	6.7%
Western	69	342	2,060	3,231	0.1%	0.3%	2.4%	7.0%
2005								
Eastern	168	1030	5,139	11,138	0.1%	0.2%	1.7%	8.8%
Midland	39	317	1,809	2,403	0.1%	0.5%	3.7%	9.8%
Mid-Western	35	387	2,386	3,165	0.1%	0.4%	3.1%	8.6%
North-Eastern	28	412	2,249	3,156	0.1%	0.4%	3.0%	9.2%
North- Western	34	236	1,478	2,198	0.1%	0.4%	2.9%	8.0%
South-Eastern	58	531	3,324	4,598	0.1%	0.4%	3.5%	9.9%
Southern	46	546	3,137	4,695	0.1%	0.3%	2.4%	7.2%
Western	88	414	2,397	3,675	0.2%	0.4%	2.8%	7.9%
2006								
Eastern	139	1,163	5,662	12,509	0.1%	0.2%	2.0%	9.2%
Midland	44	381	2,020	2,686	0.1%	0.5%	3.7%	9.7%
Mid-Western	40	425	2,676	3,488	0.1%	0.4%	3.2%	8.4%
North-Eastern	47	478	2,530	3,345	0.1%	0.4%	3.0%	8.5%
North- Western	33	274	1,617	2,393	0.1%	0.4%	2.9%	7.8%
South-Eastern	69	624	3,692	5,102	0.1%	0.4%	3.5%	9.4%
Southern	59	617	3,562	5,302	0.1%	0.3%	2.5%	7.1%
Western	66	452	2,543	3,889	0.1%	0.4%	2.7%	7.5%
2007								
Eastern	149	1,275	6,149	13,821	0.1%	0.3%	2.2%	10.2%
Midland	52	424	2,222	2,960	0.2%	0.5%	4.1%	10.7%
Mid-Western	47	507	2,928	3,790	0.1%	0.5%	3.5%	9.1%
North-Eastern	47	529	2,759	3,610	0.1%	0.4%	3.3%	9.2%
North- Western	29	310	1,766	2,604	0.1%	0.5%	3.1%	8.4%
South-Eastern	70	743	4,095	5,562	0.1%	0.5%	3.9%	10.2%
Southern	62	688	3,951	5,836	0.1%	0.4%	2.8%	7.9%
Western	62	492	2,743	4,258	0.1%	0.4%	2.9%	8.2%

3.1.4.4 Prevalence of prescribed glucose monitoring kits only in the adult population

There was only a slight increase in the prevalence of prescribed glucose monitoring kits in the Irish population. In 2003, the prevalence was 0.6% and this increased to 0.7% in 2007. There was a higher prevalence rate in males (0.6%) compared to females (0.5%) in 2003 but by 2007, a similar rate was observed in both genders (0.7%). The age-specific prevalence increased with age (Figure 3.1.11). In 2007, the age-specific prevalence was only 0.2% in those less than 25 years old, 0.3% in those between 25 to 44 years and 0.8% in those 45-64 years old. The prevalence rate increased to 2.3% in those 65 years old and over.

Regional variations

The lowest age-adjusted prevalence of prescribed glucose monitoring kits only in both males and females was observed in the Eastern region and the highest was observed in the Midland region (Figure 3.1.12, Figure 3.1.13). In 2007, the prevalence rate in Midland region was 1.2% in males and 1.0% in females, double the prevalence observed in the Eastern region (0.5%). Less variation was observed between regions for those below 45 years (Table 3.1.5). The Midland region had the highest prevalence rate of prescribed glucose monitoring kits for those aged 45 years and above.

Figure 3.1.11: National age-specific prevalence of prescribed glucose monitoring kits only in the adult population from 2003 to 2007

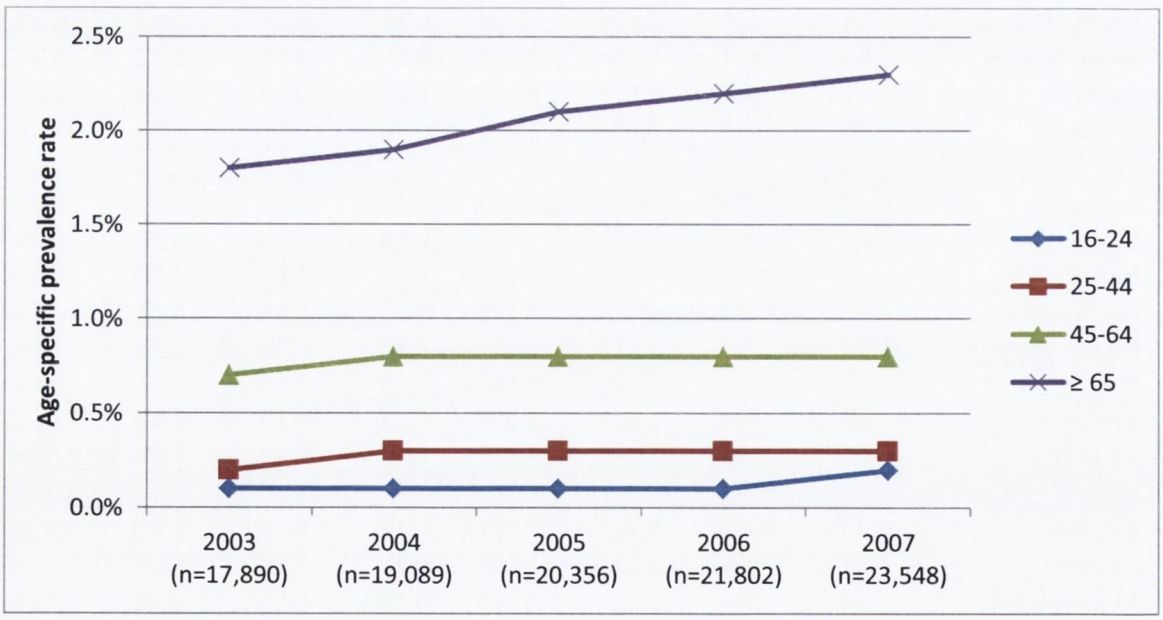


Figure 3.1.12: Age-adjusted prevalence of prescribed glucose monitoring kits in males by regions from 2003 to 2007

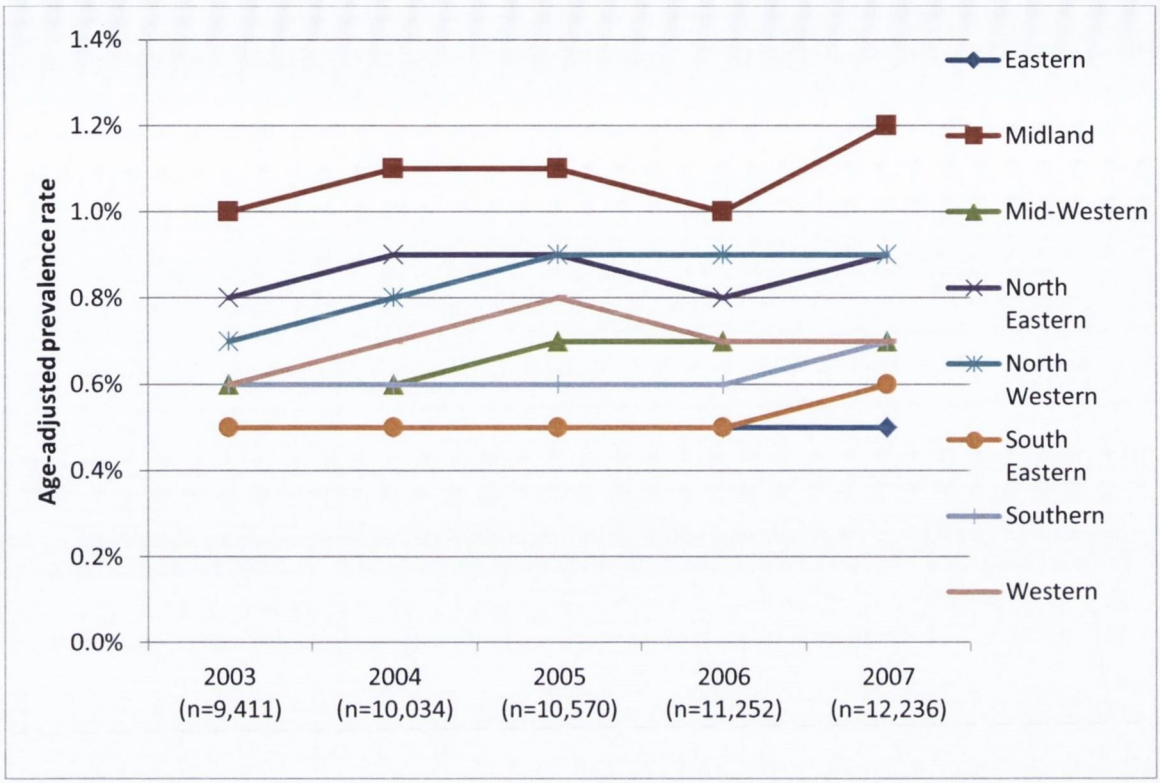


Figure 3.1.13: Age-adjusted prevalence of prescribed glucose monitoring kits in females by regions from 2003 to 2007

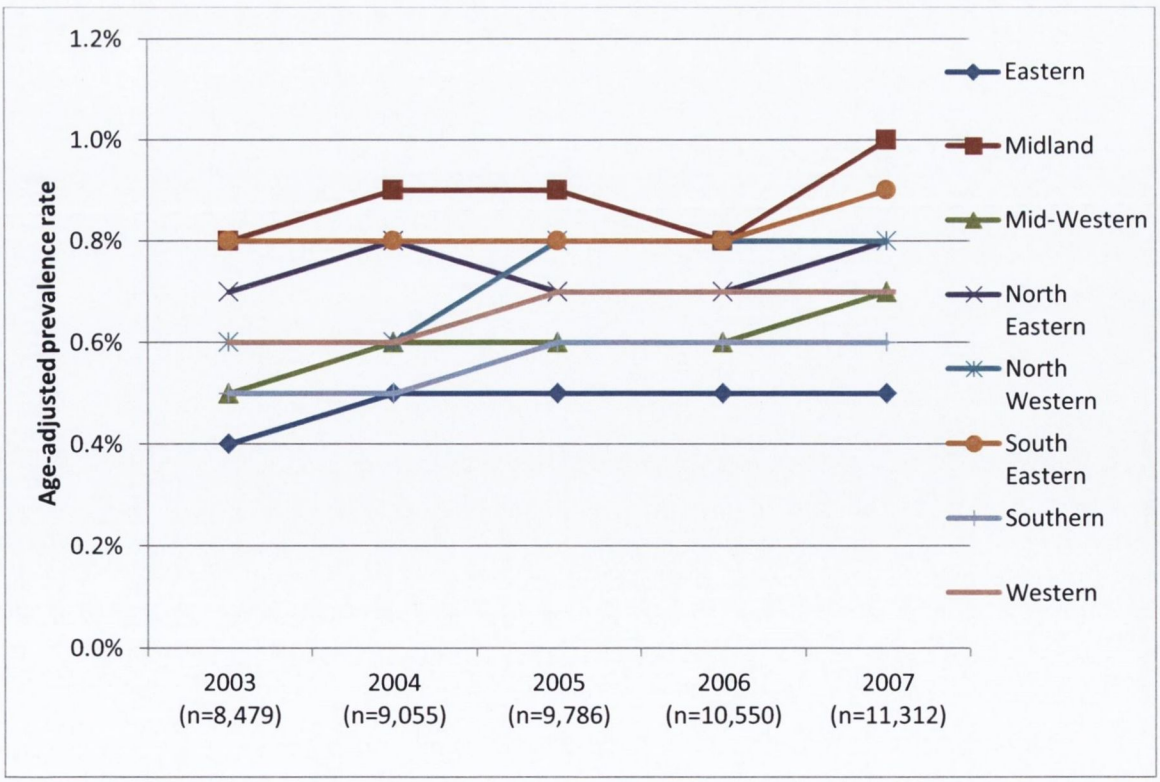


Table 3.1.5: Frequency and age-specific prevalence of prescribed glucose monitoring kits only in adults by regions from 2003 to 2007

Year and Health regions	Frequency				Age-specific prevalence			
	16-24	25-44	45-64	≥65	16-24	25-44	45-64	≥65
2003								
Eastern	201	806	1,682	2,561	0.1%	0.2%	0.6%	1.9%
Midland	57	215	516	628	0.2%	0.3%	1.1%	2.4%
Mid-Western	64	276	536	594	0.1%	0.3%	0.7%	1.5%
North-Eastern	81	350	732	806	0.2%	0.3%	1.0%	2.2%
North- Western	54	178	403	486	0.2%	0.3%	0.8%	1.7%
South-Eastern	113	435	946	1,103	0.2%	0.4%	1.0%	2.2%
Southern	111	445	833	954	0.2%	0.3%	0.6%	1.4%
Western	82	260	593	789	0.2%	0.2%	0.7%	1.6%
2004								
Eastern	195	803	1,611	2,797	0.1%	0.2%	0.6%	2.1%
Midland	55	255	569	730	0.2%	0.4%	1.2%	2.8%
Mid-Western	63	290	590	707	0.1%	0.3%	0.8%	1.8%
North-Eastern	91	406	821	799	0.2%	0.4%	1.1%	2.2%
North- Western	52	189	432	508	0.2%	0.3%	0.9%	1.7%
South-Eastern	110	489	973	1,082	0.2%	0.4%	1.0%	2.2%
Southern	102	446	919	968	0.1%	0.3%	0.7%	1.4%
Western	97	324	709	854	0.2%	0.3%	0.8%	1.7%
2005								
Eastern	167	783	1,597	2,934	0.1%	0.2%	0.6%	2.1%
Midland	61	236	594	696	0.2%	0.4%	1.2%	2.7%
Mid-Western	58	352	640	729	0.1%	0.4%	0.9%	1.8%
North-Eastern	80	395	761	872	0.2%	0.4%	1.1%	2.4%
North- Western	55	210	505	611	0.2%	0.3%	1.0%	2.1%
South-Eastern	115	482	1,024	1,233	0.2%	0.4%	1.1%	2.5%
Southern	127	525	990	1,141	0.1%	0.3%	0.8%	1.6%
Western	117	382	762	919	0.2%	0.4%	0.9%	1.9%
2006								
Eastern	202	862	1,694	3,286	0.1%	0.2%	0.6%	2.4%
Midland	52	258	624	735	0.2%	0.3%	1.1%	2.7%
Mid-Western	58	322	633	813	0.1%	0.3%	0.8%	1.9%
North-Eastern	82	432	886	943	0.2%	0.3%	1.1%	2.4%
North- Western	63	247	542	711	0.2%	0.4%	1.0%	2.3%
South-Eastern	102	467	1,064	1,370	0.2%	0.3%	1.0%	2.5%
Southern	126	573	1,102	1,223	0.1%	0.3%	0.8%	1.6%
Western	87	356	750	1,137	0.2%	0.3%	0.8%	2.2%
2007								
Eastern	183	879	1,668	3,552	0.1%	0.2%	0.6%	2.6%
Midland	67	323	708	820	0.2%	0.4%	1.3%	3.0%
Mid-Western	81	390	717	828	0.2%	0.3%	0.9%	2.0%
North-Eastern	109	467	966	988	0.2%	0.4%	1.2%	2.5%
North- Western	74	293	552	689	0.2%	0.4%	1.0%	2.2%
South-Eastern	152	610	1,278	1,494	0.3%	0.4%	1.2%	2.7%
Southern	155	683	1,157	1,329	0.2%	0.4%	0.8%	1.8%
Western	111	421	774	1,030	0.2%	0.3%	0.8%	2.0%

3.1.4.5 Incidence of treated type 2 diabetes mellitus in the adult population

There was a significant increase in the incidence of type 2 diabetes in the adult population over the 4-year study period ($p<0.0001$). The national age-adjusted incidence rate of type 2 diabetes per 1,000 adult population was 4.70 (95% CI 4.62, 4.78) in 2004 and increased to 5.01 (95% CI 4.93, 5.08) in 2007 (Figure 3.1.14). In males the age-adjusted incidence rate for 2004 was 5.31 (95% CI 5.20, 5.43) and in females was 4.10 (95% CI 4.00, 4.20.35). The incidence rates increased in 2007 to 5.64 (95% CI 5.52, 5.75) in males and 4.38 (95% CI 4.28, 4.48) in females. The age-specific incidence rate of type 2 diabetes in adults was highest in those aged 65 years and over at 16.68 (95% CI 16.30, 17.07) in 2004, which decreased slightly by 2007 to 16.44 (95% CI 16.25, 16.62) (Figure 3.1.15).

The overall age adjusted incidence rate of type 2 diabetes per 1,000 adult population per year during the 4-year study period was 4.82 (95% CI 4.78, 4.86), with males at 5.44 (95% CI 5.39, 5.50) and females at 4.21 (95% CI 4.16, 4.26, Table 3.1.6). The overall age-specific incidence rate of type 2 diabetes per 1,000 adult population during the study period was 0.63 (95% CI 0.60, 0.66) in those 16 to 24 years old, 1.37 (95% CI 1.34, 1.40) in those aged 25 to 44 years old, 6.55 (95% CI 6.46, 6.62) in those aged 45 to 64 and 16.43 (95% CI 16.25, 16.63) in those 65 years and over (Table 3.1.7). Females had significantly lower risk of incident type 2 diabetes compared to males with adjusted incidence rate ratio of 0.67 (95% CI 0.66, 0.68) as shown in Table 3.1.8. Risk of incidence type 2 diabetes increased with age with 45 to 64 year olds (10.32 [95% CI 10.16, 10.48]) and 65 year olds and over (32.58 [95% CI 32.09, 33.07]) having higher rates compared to those 16 to 44 year olds.

Regional variations

The highest age-adjusted incidence rate was observed in South-Eastern region and the lowest in the Southern region. The South-Eastern region had the highest age-adjusted incidence rates in both males and females while the Southern region had the lowest age-adjusted incidence rates in both males and females. The Midland region had the highest incidence rate of treated type 2 diabetes for those aged 16 to 24 years, the South- Eastern region for those aged 25 to 44 years and for those aged 45 to 64 years and the Eastern region for those aged 65 years and over. The Southern region had the lowest incidence rates compared to other regions for all the four different age groups.

Figure 3.1.14: National age-adjusted incidence rate of type 2 diabetes mellitus in the adult population (per 1,000 population per year) according to gender from 2004 to 2007

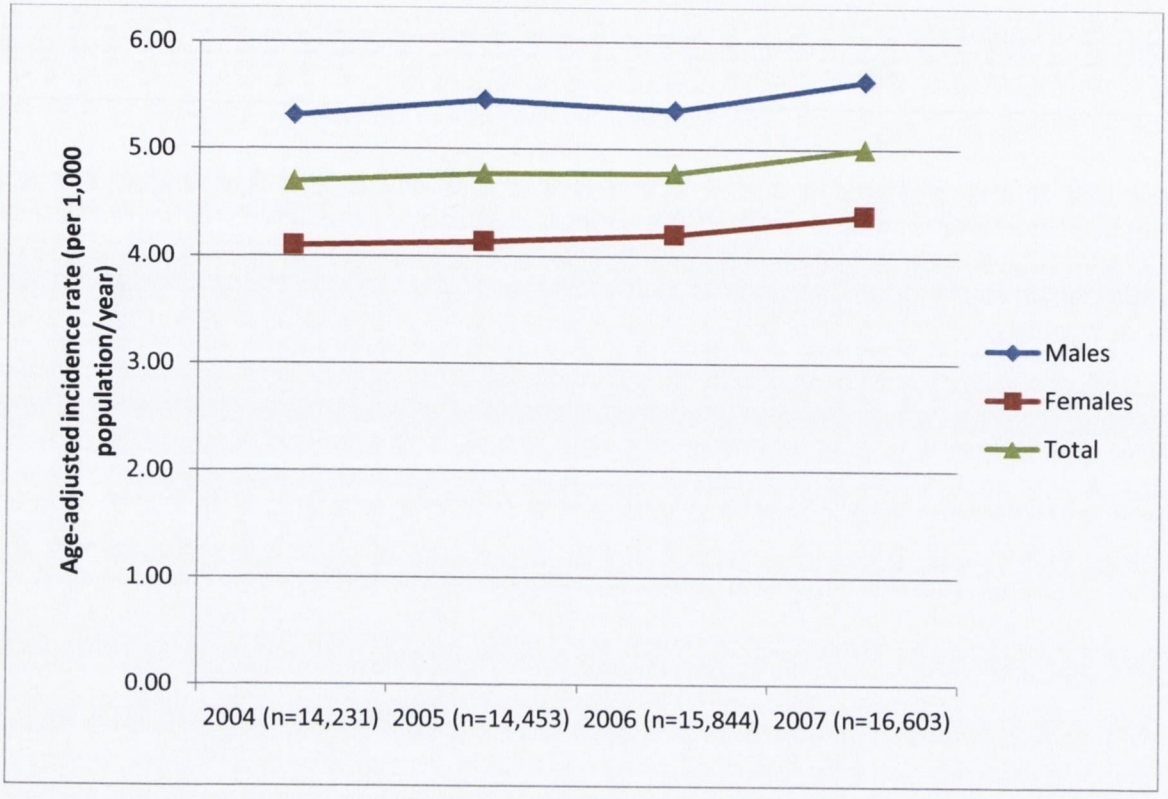


Figure 3.1.15: National age-specific incidence rate of type 2 diabetes mellitus in the adult population (per 1,000 population per year) from 2004 to 2007

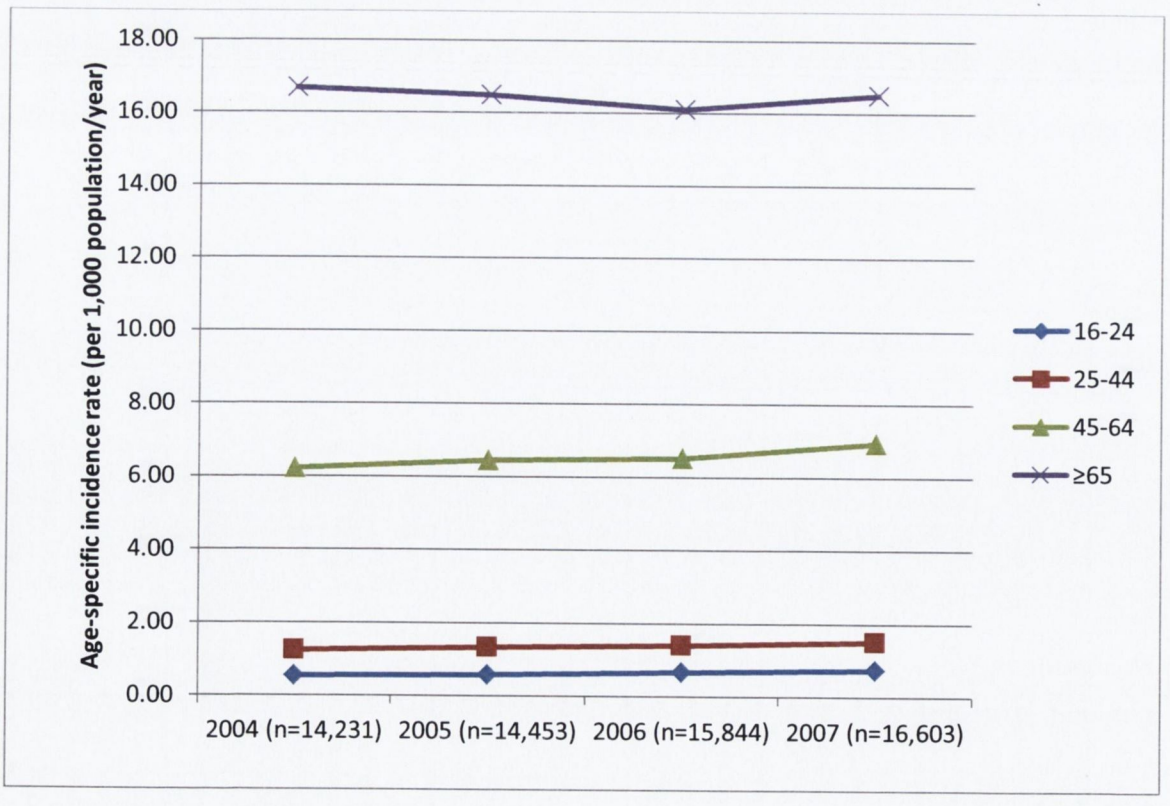


Table 3.1.6: Frequency and age-adjusted incidence rate of type 2 diabetes mellitus in the adult population (per 1,000 adult population per year) by gender and regions from 2004 to 2007

Health Regions	Frequency			Age-adjusted incidence rate (per 1,000 adult population per year) with 95% CI		
	Males	Females	Total	Males	Females	Total
Eastern	11,727	10,463	22,190	5.27 (5.17, 5.37)	4.42 (4.34, 4.51)	4.96 (4.90, 5.03)
Midland	2,318	1,720	4,038	6.35 (6.09, 6.61)	4.81 (4.59, 5.04)	5.59 (5.42, 5.76)
Mid-Western	3,061	2,077	5,138	5.61 (5.41, 5.81)	3.83 (3.66, 4.00)	4.59 (4.47, 4.72)
North Eastern	3,115	2,122	5,237	5.54 (5.35, 5.74)	3.81 (3.65, 3.98)	4.68 (4.55, 4.81)
North Western	2,002	1,563	3,565	5.74 (5.49, 5.99)	4.45 (4.23, 4.67)	5.09 (4.92, 5.26)
South Eastern	4,563	3,288	7,851	6.65 (6.46, 6.85)	4.85 (4.69, 5.02)	5.79 (5.66, 5.92)
Southern	4,154	3,143	7,297	4.45 (4.32, 4.59)	3.32 (3.21, 3.44)	3.88 (3.80, 3.97)
Western	3,374	2,563	5,937	5.44 (5.25, 5.62)	4.14 (3.98, 4.30)	4.80 (4.68, 4.92)

Table 3.1.7: Frequency and age-specific incidence rate of type 2 diabetes mellitus in the adult population (per 1,000 adult population per year) by region from 2004 to 2007

Health regions	Frequency				Age-specific incidence rate (per 1,000 adult population per year) with 95% CI			
	16-24	25-44	45-64	≥65	16-24	25-44	45-64	≥65
Eastern	462	2,036	6,595	13,097	0.54 (0.49, 0.59)	1.09 (1.05, 1.14)	5.81 (5.67, 5.95)	24.11 (23.70,24.53)
Midland	131	516	1,668	1,732	1.04 (0.87,1.23)	1.81 (1.66, 1.98)	8.16 (7.77, 8.56)	16.08 (15.33, 16.85)
Mid-Western	118	649	2,227	2,144	0.59 (0.49, 0.71)	1.57 (1.45, 1.70)	7.10 (6.80, 7.40)	13.21 (12.66, 13.79)
North Eastern	130	691	2,168	2,248	0.67 (0.56, 0.79)	1.50 (1.39, 1.61)	6.97 (6.68, 7.27)	14.82 (14.21, 15.44)
North Western	97	405	1,463	1,600	0.82 (0.66, 1.00)	1.61 (1.45, 1.77)	6.97 (6.61, 7.33)	13.34 (12.70, 14.01)
South Eastern	183	971	3,520	3,177	0.79 (0.68, 0.91)	1.86 (1.75, 1.98)	8.91 (8.61, 9.21)	15.24 (14.72, 15.78)
Southern	176	914	3,041	3,166	0.53 (0.47, 0.62)	1.26 (1.18, 1.35)	5.60 (5.40, 5.80)	11.03 (10.65, 11.42)
Western	213	721	2,378	2,625	0.96 (0.84, 1.10)	1.58 (1.47, 1.70)	6.67 (6.40, 6.94)	12.95 (12.46, 13.46)

Table 3.1.8: Risk of incident type 2 diabetes mellitus in the adult population according to patient characteristics presented as adjusted incidence rate ratio with 95% CI and *p*-values

Characteristics		Unadjusted incidence rate ratio (95% CI), *p*	Adjusted incidence rate ratio† (95% CI), *p*
Gender□	Female (n=26,995)	0.75 (0.74, 0.75) ***	0.67 (0.66, 0.68), ***
Age group◊	45-64 years (n=23,034)	10.40 (10.24, 10.57) ***	10.32 (10.16, 10.48) **
	≥ 65 years (n=29,721)	32.15 (31.66, 32.63) ***	32.58 (32.09, 33.07) ***
Health region∞	Midland (n=4,038)	2.16 (2.14, 2.18) ***	1.88 (1.86, 1.91) ***
	Mid-Western (n=5,138)	1.39 (1.37, 1.41) ***	1.20 (1.19, 1.22) ***
	North-Eastern (n=5,237)	1.35 (1.33, 1.37) ***	1.24 (1.23, 1.28) ***
	North-Western (n=3,565)	1.44 (1.42, 1.46) ***	1.14 (1.12, 1.16) ***
	South-Eastern (n=7,851)	1.63 (1.61, 1.65) ***	1.35 (1.33, 1.37) ***
	Southern (n=7,297)	1.18 (1.17, 1.19) ***	1.02 (1.00, 1.03), 0.01
	Western (n=5,937)	1.33 (1.31, 1.35) ***	1.09 (1.07, 1.11) ***

† Adjusted for age groups, gender, calendar year at start of diabetes treatment and regions
□ Reference category males (n=34,181)
◊ Reference category age 16-44 years (n=8,376)
∞ Reference category Eastern region (n=22,190)

3.1.5 Discussion

Overall trend

The prevalence of treated diabetes in Ireland is significantly increasing year on year with a higher prevalence found in males compared to females. The prevalence of treated diabetes increased with age with the highest prevalence observed in those aged 65 years and over. Variations in the prevalence were observed across the country with the lowest rate found in the Eastern region and highest in the Midland region. The prevalence of treated type 1 diabetes was fairly stable over the study period for both genders and age groups with lowest prevalence observed in the Eastern region. Unlike type 1 diabetes, the prevalence of type 2 diabetes in adults significantly increased in both genders and in those aged 45 years and over. The prevalence rate of type 2 diabetes was higher also in males compared to females and in those with higher age groups. There was also an increase in the prescribing of glucose monitoring kits in those not receiving anti-diabetic prescriptions. In addition, the incidence of type 2 diabetes significantly increased in both genders; however, the increase in age-specific incidence was confined to those aged 45 to 65 years only.

The overall prevalence of diabetes found in this study was lower than the previous Irish estimates [70, 76]. Due to the differences in methodology in the estimation of diabetes prevalence between this study and other Irish studies, direct comparison of prevalence rates is difficult and may be confounded. The estimate of diabetes prevalence by the IDF was based on international averages while the estimates by the Public Health Institute are based mainly on UK population data [70, 76]. The development of PBS model was limited by the paucity of high quality representative population based studies that can be used to derive reference rates in modelling diabetes prevalence. Thus the model combined the prevalence rates from a number of different UK studies [78]. In addition, compared to this study, the estimates using the PBS model took into account the social demographic of local areas and projection of prevalence on total diabetes burden in the population [76]. All of these factors may have a role in explaining the different prevalence results obtained in the different studies.

Only treated diabetes was included in this study and this would have under-estimated the true prevalence of diabetes. However, those with treated diabetes represent those in need of aggressive management and at risk of complications and thus determining the prevalence of this population is important. Patients with early stage type 2 diabetes being managed with lifestyle interventions only and others who may be undiagnosed were not included. Most estimates in other studies included untreated and undiagnosed diabetes.

If the prescribing of glucose monitoring kits were taken as marker of type 2 diabetes managed with lifestyle interventions, only a slight increase in the prevalence of type 2 diabetes were observed in this study and still consistently lower than other Irish estimates. However, as the pharmacy claims database does not contain clinical information, the reasons for a patient to be initiated glucose monitoring kits could not be determined. The patients may be initiated glucose monitoring kits for gestational diabetes, metabolic syndrome, or due to concurrent medications such as high dose of corticosteroids. The use of glucose monitoring kits for patients with lifestyle controlled diabetes is not indicated by diabetes guidelines [5, 79] and thus the use of these kits as proxy for lifestyle controlled diabetes may not be clinically appropriate. Further validation studies need to be performed to ascertain the status of patients prescribed the glucose monitoring kits in the population.

In the UKPDS study, 27% of participants were initially randomized to lifestyle interventions. However, only approximately 10% of patients were maintained on diet after 10 years [41]. The proportion of known diabetes in Ireland was estimated to be at 76% out of the total diabetes patients [80]. The IDF estimated that in 2007, 59,000 individuals had impaired glucose tolerance in which 50% is estimated to develop diabetes in the next five years if no lifestyle changes are made [70]. This study can be utilized together with other Irish studies to provide useful measures to estimate the prevalence of untreated diabetes in the population. The estimate of type 1 diabetes in the adult population in 2005 at 0.4% was similar to the previous Irish estimate using the PBS model [76].

In contrast to the previous Irish studies, the current study found a higher prevalence of treated diabetes in adult males compared to females. Age-adjustment was carried out in the current study when calculating the prevalence by gender while other Irish studies applied the direct measure of prevalence. The WHO study observed a higher prevalence in males less than 60 years of age while a higher prevalence was observed in females for those aged 60 years and above but overall higher prevalence in females. It was suggested that the difference in prevalence was due to greater number of older females compared to older males in most countries and increasing prevalence rate with increasing age [1].

The increasing prevalence of treated diabetes, especially type 2 diabetes, with higher age group was consistent with findings from other studies in Ireland and globally [1, 76, 77]. This study also found an increase in the prescribing of glucose monitoring kits only especially in those 65 years and over. Type 2 diabetes is rare before the age of 25 years old although the prevalence of type 2 diabetes in adolescents is on the increase [81]. Other Irish studies included adults over 20 years of age [76, 77] while this study included adults from 16 years of age and above. The age groups used to calculate the age-specific prevalence rate differed between this study and other

Irish estimates [76, 77] making the comparison of prevalence between each specific age group difficult. Risk factors for diabetes such as weight gain especially abdominal weight gain, increased waist circumference, obesity and physical inactivity increases with age. As discussed above, diabetes may also be undiagnosed or managed with lifestyle interventions for years before being treated and thus many elderly patients with diabetes will be on treatment compared to younger patients.

Regional variations

The low prevalence rate of diabetes in the Eastern region was consistent with other studies [76, 77]. This may have been due to underlying differences in the demographic of population in the Eastern region. The Eastern region consisting of Dublin, Kildare and Wicklow is the largest region in Ireland. For those aged 65 years and over, the prevalence of diabetes in the Eastern region was comparable to other regions suggesting that the differences observed were mainly in the younger aged population. This study found that the highest prevalence of diabetes in the country was identified in the Midland region for both genders and most age groups. The PBS model estimated that the highest prevalence rate of diabetes in the country was found in the Western region [76] while the most recent Institute of Public Health study estimated that prevalence was higher in Cork and Kerry which made up the Southern region [77].

The regional variations of diabetes prevalence may be explained by the differences in the utilization of health services for diabetes between regions rather than prevalence of diabetes per se. The Midland region has one of the longest established primary care lead diabetes programs under the Midland HSE Diabetes Structured Care Programme in Ireland dedicated to improve the quality of care for patients with diabetes [82]. This program started in 1997 through partnership between GPs with interest in diabetes, the Department of Public Health and Planning in the Midland Health board and recently a consultant endocrinologist [83]. Under this program, patients with diabetes are managed in primary care with extra support provided including diabetes nurse specialists, enhanced access to dietetic, ophthalmology and chiropody services and fast track referral to vascular services. In addition, educational input and support for the development of local clinical guidelines, protocols and quality assurance system are provided for participating GPs. By 2010, 67 GPs in 30 practices were involved in this project and over 3,700 patients with diabetes were registered in the program. Significant clinical improvement in terms of glycaemic control, progression to diabetic complications and cardiovascular risk factors have been observed under this program [83]. The Midland shared care diabetes program could serve as a model of successful diabetes structured care and could be extended nationwide to other regions in Ireland.

The increasing prevalence of diabetes, especially of type 2 diabetes is consistent with other Irish, European and global projections. With the increasing prevalence of diabetes with higher age groups, the current trend of increasing ageing population will translate into increasing prevalence of diabetes overall. Increasing prevalence of overweight and obesity compounded by sedentary lifestyle and higher caloric intake in the population contributes to the increasing prevalence of diabetes. The increasing prevalence and incidence of diabetes is of concern given the complications and the associated costs.

Strengths and limitations

The national prescribing databases used for this study were population-based and therefore captured almost all prescribing for the known and treated diabetes in Ireland. The retrospective data collection enabled a longitudinal history of prescribed medications over a 5-year period at an individual level to be examined objectively. This study was based on observational data using pharmacy claims database with no diagnostic or outcome information. However, disease specific therapy; oral anti-diabetic agents and insulin were used as surrogate for diabetes. In addition, we cannot estimate the true prevalence and incidence of diabetes, as described earlier, only those treated with anti-diabetic agents. Use of insulin may have misclassified those with type 2 diabetes being treated with insulin only as type 1 diabetes patients especially in older patients. The estimate of incidence of type 2 diabetes in this study was also likely to include patients with previously untreated prevalent diabetes or prevalent diabetes patients previously not registered under both drug schemes. Other Irish studies have been able to estimate prevalence at regional and also local health area level. Due to the limitations in the prescribing database, this study only examined the diabetes prevalence rates for the eight health regions. The prevalence rates of diabetes at county levels were not examined.

3.2 Epidemiology of treated diabetes in the Irish paediatric population

3.2.1 Background

The Epidemiology and Prevention of Diabetes (EURODIAB) and the WHO Multinational Project for Childhood Diabetes-Diabetes Mondiale (WHO DIAMOND) prospective registries provided much of the evidence on the epidemiology of type 1 diabetes in the paediatric population in Europe and the rest of the world [84, 85]. The WHO DIAMOND registry included 112 centres from 57 countries in the world with a total of 43,013 newly diagnosed type 1 diabetes cases from 84 million paediatric population from 1990 to 1999 [84]. 44 European countries participated in the EURODIAB registry and most of the European countries in the DIAMOND study were members of the EURODIAB registry. The EURODIAB registry recorded 29,311 new cases of type 1 diabetes in those below 15 years old during a 15-year period from year 1989 to 2003 [85] . However, Ireland did not participate in either of these paediatric diabetes registries.

The WHO DIAMOND data found an increased trend in the incidence of type 1 diabetes in paediatric population below 15 years of age worldwide except in Central America and West Indies from 1990 to 1999. The average annual increase in incidence was 2.8% (95% CI 2.4, 3.2). The highest incidence rates were observed in European and North American population. Overall, no significant differences in type 1 diabetes incidence rates were observed between boys and girls. Incidence rates of type 1 diabetes increased with age and peaked at puberty. Those aged 5 to 9 years old had a 1.62 (95% CI 1.57, 1.66) times higher risk and those aged 10 to 14 years old had a 1.94 (95% CI 1.89, 1.98) higher risk of type 1 diabetes compared to the paediatric population aged 0 to 4 years old. The increase in annual incidence rates was higher in younger aged groups with 4.0% (95% CI 3.1, 4.9) in those aged 0 to 4 years old, 3.0% (95% CI 2.4, 3.7) in those aged 5 to 9 years old and 2.1% (95% CI 1.5, 2.7) in those aged 10 to 14 years old. Incidence continued to increase post puberty only in boys [84]. The EURODIAB study (1989-2003) also showed significant increases in incidence of type 1 diabetes over the study period in most participating countries with overall annual increase estimated to be at 3.9% (95% CI 3.6, 4.2). The highest increase in annual incidence was in Katowice, Poland at 9.3% (95% CI 7.8, 10.8). No significant difference in rates of incidence increase between genders was observed. The EURODIAB group also projected that the number of new cases with type 1 diabetes in Europe to be approximately 15,000 (24% 0 to 4 years old; 35% 5 to 9 years old and 41% 10 to 14 years old) in 2005. This figure is expected to rise to 24,400 by 2020 (29% 0 to 4 years old; 37% 5 to 9 years old and 34% 10 to 14 years old) [85].

The incidence of type 1 diabetes differed between countries. Worldwide, the highest incidence rate was observed in Finland (40/100,000) and the lowest incidence rate in Zuni region

in China and Venezuela (0.1/100,000 population/year) according to the WHO DIAMOND study [84]. Variation in type 1 diabetes was also observed between neighbouring countries, exemplified by the different incidence rates amongst the Scandinavian countries. Between year 1999 to 2003 Finland had the highest incidence rate (52.6/100,000) followed by Sweden (34.6/100,000) while the incidence rate in Norway (24.6/100,000) and Denmark (22.9/100,000) were comparatively lower [85]. There was also variation in the incidence in type 1 diabetes within a country. Countries such as Finland, Italy and UK showed large variations in type 1 diabetes within the country [86, 87]. In Italy, Sardinia had an incidence rate of 36.9/100,000 while other regions in peninsular Italy had an incidence rate of 8.4/100,000 [88].

In 1988, it was estimated that the incidence rate was 6.8/100,000 population in Ireland compared to 19.8/100,000 population found in Scotland [89]. An Irish study performed in 1997 using the same case ascertainment method as the WHO DIAMOND study estimated that the incidence of type 1 diabetes in those under 15 years of age was 16.3/100,000 (95% CI 14.2, 18.5) and put Ireland amongst the countries with the highest incidence of type 1 diabetes during the study period [90]. The highest incidence rate of type 1 diabetes was observed in those between 5 to 10 years old at 21.3/100,000 (95% CI 16.2, 27.4) with a boys to girls ratio of 1.09: 1. This figure was obtained from prospective data reporting by paediatricians through the Irish Paediatric Surveillance Unit and survey of adult physicians, endocrinologist and specialist nurses. The incidence rate was higher than the European average from the EURODIAB study in the period between 1989 and 1994 [90]. The incidence in Northern Ireland during 1989 to 2003 was estimated to be 24.7/100,000 in those less than 15 years [87]. The more recent PBS model estimated that the prevalence of type 1 diabetes in the paediatric population aged 0 to 19 years old was 0.2% (n=2,229) in 2005. No difference between genders was expected in this estimate with a prevalence in boys (n=1,105) and girls (n=1,124) both at 0.2%. No differences in the prevalence of type 1 diabetes in the paediatric population between the different regions within Ireland was found using the model [76]. The IDF projected that in 2010, the incidence of type 1 diabetes is 0.2% while the prevalence is estimated to be at 1.0% [71].

Many hypotheses have emerged to explain the worldwide increased incidence of type 1 diabetes in the paediatric population. Genetic susceptibility and environmental factors such as viral infection during pregnancy, increasing maternal age, early exposure to cow's milk, viral infections and childhood obesity have been implicated [91]. Another popular theory was the hygiene hypothesis, whereby a reduction in exposure to infectious diseases in early childhood lead to immaturity of the immune system and hence increased the risk of immunological conditions such as type 1 diabetes [92].

The lack of research on the prevalence and incidence of type 1 diabetes in the Irish paediatric population need to be addressed. This study aims to provide estimates of the prevalence and incidence of treated type 1 diabetes in the paediatric population (<16 years old) and to examine the trends in childhood type 1 diabetes over a 5-year period. This knowledge would allow comparison between different Irish regions as well as across European countries.

3.2.2 Specific objectives

1) To examine the trends in the prevalence of treated type 1 in the Irish paediatric population (<16 years) from 2003 to 2007 according to gender, age groups and health regions.
2) To examine the trends in the incidence of treated type 1 diabetes in the paediatric population from 2004 to 2007 according to age groups, gender and region of residence.

3.2.3 Methods

3.2.3.1 Prevalence of treated type 1 diabetes in the paediatric population

The HSE-PCRS databases were used to identify patients below 16 years old prescribed insulin therapies in Ireland under both the GMS and the LTI scheme from 1st January 2003 to 31st December 2007. Prevalence of type 1 diabetes and linear trend was examined using the same methods as described for the adult population (Section 3.1.3.1).

3.2.3.2 Incidence of treated type 1 diabetes in the paediatric population

The HSE-PCRS databases were used to identify patients less than 16 years old newly prescribed insulin therapies in Ireland under both the GMS and the LTI scheme from 1st January 2004 to 31st December 2007. 2003 was used as run-in period to exclude prevalent type 1 diabetes in this population. Cases of diabetes were classified by gender, age groups (<5 years old, 5 to 11 years old, 12 to 15 years old), health regions and year at start of insulin treatment. Incidence of treated type 1 diabetes was calculated using the same methods as described above for calculating incidence in the adult population (section 3.1.3.2).

3.2.4 Results

3.2.4.1 Prevalence of type 1 diabetes mellitus in the paediatric population

The age-adjusted prevalence of type 1 diabetes in the paediatric population remained stable at 0.2% in both boys and girls from 2003 to 2007 in Ireland. The age-specific prevalence

rate of treated type 1 diabetes increased with age groups with the prevalence rate at 0.1% in those <5 years old, 0.2% in those 5 to 11 years old and 0.3% in those 12 to 15 years old. The prevalence rate for each age group remained constant throughout the study period.

The lowest age-adjusted prevalence rate of treated type 1 diabetes in the paediatric population was observed in the Eastern region for all the calendar years in both genders (Table 3.2.1). The Eastern region also had the lowest prevalence rate of treated type 1 diabetes in all age groups from 2003 to 2007 (Table 3.2.2). Unlike the prevalence of diabetes in the adult population, the age-adjusted and age-specific prevalence rates of type 1 diabetes in the paediatric population remained stable in most regions in Ireland.

3.2.4.2 Incidence of type 1 diabetes mellitus in the paediatric population

The overall age adjusted incidence rate of type 1 diabetes per 100,000 paediatric population per year during the study period was 28.33 (95% CI 26.62, 30.11) with boys at 27.59 (95% CI 25.23, 30.06) and girls at 29.06 (95% CI 26.66, 31.69) (Table 3.2.3). The highest age-adjusted incidence rate was observed in North-Western region and the lowest was observed in the Eastern region (Table 3.2.3). The highest age-adjusted incidence rate in boys was in North-Western while in girls was in Southern region. The Eastern region had the lowest age-adjusted incidence rates in both boys and girls. No significant changes were observed in the national age-adjusted incidence rate during the study period.

The overall age-specific incidence rate of type 1 diabetes per 100,000 paediatric population during the study period was 16.81 (95% CI 14.53, 19.35) in those less than 5 years old, 34.45 (95% CI 31.59, 37.50) in those 5 to 11 years and 33.22 (95% CI 29.59, 37.17) in those between 12 and 15 years as presented in Table 3.2.4. North Western region (39.40 [95% CI 25.73, 57.73]) had the highest incidence rates for those less than 5 years old, Southern region (53.43 [95% CI 44.33, 63.80] for those 5 to 11 years old and Midland region (49.90 [95% CI 33.42, 71.67]) for those 12 to 15 years old. The Eastern region had the lowest incidence rates compared to other regions for all the three age groups.

No significant differences were observed in the incidence of type 1 diabetes between boys and girls (Table 3.2.5). Those aged 5 to 11 years had a 1.98 (95% CI 1.72, 2.30) higher risk and those aged 12 to 15 years had a 1.99 (95% CI 1.70, 2.33) higher risk of treated type 1 diabetes compared to those less than 5 years old. All regions demonstrated a significantly higher risk of type 1 diabetes in the paediatric population compared to those from Eastern region.

Table 3.2.1: Frequency and age-adjusted prevalence of type 1 diabetes in paediatric population by gender and regions from 2003 to 2007

Year and Health regions	Frequency			Age-adjusted prevalence rate (%)		
	Boys	Girls	Persons	Boys	Girls	Persons
2003						
Eastern	163	169	332	0.1%	0.1%	0.1%
Midland	41	48	89	0.1%	0.2%	0.2%
Mid-Western	52	78	130	0.1%	0.2%	0.2%
North-Eastern	69	60	129	0.2%	0.1%	0.1%
North- Western	69	51	120	0.3%	0.2%	0.2%
South-Eastern	95	78	173	0.2%	0.2%	0.2%
Southern	112	90	202	0.2%	0.1%	0.1%
Western	81	75	156	0.2%	0.2%	0.2%
2004						
Eastern	137	143	280	0.1%	0.1%	0.1%
Midland	50	51	101	0.2%	0.2%	0.2%
Mid-Western	54	74	128	0.1%	0.2%	0.2%
North-Eastern	75	70	145	0.2%	0.2%	0.2%
North- Western	71	56	127	0.3%	0.2%	0.2%
South-Eastern	102	88	190	0.2%	0.2%	0.2%
Southern	133	115	248	0.2%	0.2%	0.2%
Western	86	78	164	0.2%	0.2%	0.2%
2005						
Eastern	130	131	261	0.1%	0.1%	0.1%
Midland	50	59	109	0.2%	0.2%	0.2%
Mid-Western	55	72	127	0.1%	0.2%	0.2%
North-Eastern	87	82	169	0.2%	0.2%	0.2%
North- Western	74	61	135	0.3%	0.2%	0.2%
South-Eastern	101	89	190	0.2%	0.2%	0.2%
Southern	127	109	236	0.2%	0.2%	0.2%
Western	91	82	173	0.2%	0.2%	0.2%
2006						
Eastern	124	142	266	0.1%	0.1%	0.1%
Midland	43	66	109	0.1%	0.2%	0.2%
Mid-Western	63	73	136	0.2%	0.2%	0.2%
North-Eastern	98	90	188	0.2%	0.2%	0.2%
North- Western	84	72	156	0.3%	0.3%	0.3%
South-Eastern	117	94	211	0.2%	0.2%	0.2%
Southern	143	133	276	0.2%	0.2%	0.2%
Western	88	74	162	0.2%	0.2%	0.2%
2007						
Eastern	133	139	272	0.1%	0.1%	0.1%
Midland	47	65	112	0.2%	0.2%	0.2%
Mid-Western	2	75	137	0.2%	0.2%	0.2%
North-Eastern	86	94	180	0.2%	0.2%	0.2%
North- Western	85	66	151	0.3%	0.2%	0.3%
South-Eastern	105	108	213	0.2%	0.2%	0.2%
Southern	142	141	283	0.2%	0.2%	0.2%
Western	92	76	168	0.2%	0.2%	0.2%

Table 3.2.2: Frequency and age-specific prevalence of type 1 diabetes in paediatric population by regions from 2003 to 2007

Year and Health region	Frequency			Age-specific prevalence rate (%)		
	0-4 years	5-11 years	12-15 years	0-5 years	5-11 years	12-15 years
2003						
Eastern	36	168	128	<0.1%	0.1%	0.2%
Midland	9	39	41	0.1%	0.2%	0.3%
Mid-Western	13	59	58	0.1%	0.2%	0.3%
North-Eastern	12	64	53	<0.1%	0.2%	0.2%
North- Western	13	65	42	0.1%	0.3%	0.3%
South-Eastern	22	77	74	0.1%	0.2%	0.3%
Southern	26	101	75	0.1%	0.2%	0.2%
Western	21	75	60	0.1%	0.2%	0.2%
2004						
Eastern	26	136	118	<0.1%	0.1%	0.2%
Midland	13	37	51	0.1%	0.2%	0.3%
Mid-Western	13	60	55	0.1%	0.2%	0.3%
North-Eastern	12	78	55	<0.1%	0.2%	0.2%
North- Western	16	68	43	0.1%	0.3%	0.3%
South-Eastern	25	79	86	0.1%	0.2%	0.3%
Southern	28	120	100	0.1%	0.2%	0.3%
Western	22	78	64	0.1%	0.2%	0.3%
2005						
Eastern	21	113	127	<0.1%	0.1%	0.2%
Midland	12	49	48	0.1%	0.2%	0.3%
Mid-Western	10	65	52	<0.1%	0.2%	0.2%
North-Eastern	11	88	70	<0.1%	0.2%	0.3%
North- Western	21	64	50	0.1%	0.3%	0.3%
South-Eastern	24	87	79	0.1%	0.2%	0.3%
Southern	26	119	91	0.1%	0.2%	0.3%
Western	20	83	70	0.1%	0.2%	0.3%
2006						
Eastern	18	112	136	<0.1%	0.1%	0.2%
Midland	12	55	42	0.1%	0.2%	0.3%
Mid-Western	13	66	57	0.1%	0.2%	0.3%
North-Eastern	14	97	77	<0.1%	0.2%	0.3%
North- Western	21	82	53	0.1%	0.3%	0.4%
South-Eastern	21	100	90	0.1%	0.2%	0.3%
Southern	27	132	117	0.1%	0.2%	0.4%
Western	15	80	67	0.1%	0.2%	0.3%
2007						
Eastern	15	122	135	<0.1%	0.1%	0.2%
Midland	17	53	42	0.1%	0.2%	0.3%
Mid-Western	8	68	61	<0.1%	0.2%	0.3%
North-Eastern	12	90	78	<0.1%	0.2%	0.3%
North- Western	18	78	55	0.1%	0.3%	0.4%
South-Eastern	15	114	84	<0.1%	0.2%	0.3%
Southern	25	126	132	0.1%	0.2%	0.4%
Western	16	81	71	0.1%	0.2%	0.3%

Table 3.2.3: Frequency and age-adjusted incidence rate of type 1 diabetes mellitus (per 100,000 paediatric population per year) with 95% CI by gender and regions from 2004 to 2007

Health Regions	Frequency			Age-adjusted incidence rate (per 100,000 population per year, 95% CI)		
	Boys	Girls	Persons	Boys	Girls	Persons
Eastern	136	112	248	21.82 (18.31, 25.82)	19.00 (15.64, 22.86)	20.45 (17.99, 23.16)
Midland	52	59	111	31.25 (22.00, 43.07)	42.51 (31.34, 56.36)	36.74 (29.35, 45.44)
Mid-Western	58	57	98	31.91 (23.76,41.95)	34.64 (25.95,45.31)	33.24 (27.16,40.28)
North Eastern	79	95	174	32.49 (24.79,41.82)	42.90 (33.75,53.78)	37.56 (31.49,44.45)
North Western	58	63	121	50.15 (37.87,65.12)	37.97 (27.12,51.70)	44.23 (35.83,54.02)
South Eastern	85	90	175	38.31 (30.42,47.65)	36.76 (28.86,46.15)	37.55 (31.87,43.95)
Southern	118	124	242	39.19 (32.06,47.45)	43.25 (35.58,52.09)	41.18 (35.87,47.05)
Western	84	67	151	36.65 (28.34,46.62)	30.46 (22.75,39.95)	33.58 (27.77,40.19)
National	675	673	1,348	27.59 (25.23,30.06)	29.06 (26.66,31.69)	28.83 (26.62,30.11)

Table 3.2.4: Frequency and age-specific incidence rate of type 1 diabetes mellitus (per 100,000 paediatric population per year) with 95% CI by regions from 2004 to 2007

Health regions	Frequency			Age-specific incidence rate (per 100,000 population per year, 95% CI)		
	<5 years	5-<12 years	12-<16 years	<5 years	5-<12 years	12-<16 years
Eastern	41	132	75	10.20 (7.32, 13.84)	25.75 (21.54, 30.54)	25.15 (19.78, 31.52)
Midland	30	48	39	29.72 (18.62,44.99)	34.37 (23.74, 47.9)	49.90 (33.42,71.67)
Mid-Western	6	51	41	18.33 (10.86,28.96)	36.29 (26.84,47.97)	46.50 (32.73,64.09)
North-Eastern	21	101	52	19.45 (12.33,29.19)	45.03 (35.04,56.99)	48.87 (35.36,65.83)
North-Western	27	66	28	39.40 (25.73,57.73)	50.25 (36.92,66.82)	39.40 (25.35,60.01)
South-Eastern	31	90	54	20.08 (13.12,29.43)	47.54 (37.92,58.85)	42.22 (30.79,56.49)
Southern	43	133	66	23.14 (16.37,31.76)	53.43 (44.33,63.80)	42.59 (32.25,55.18)
Western	38	64	49	19.48 (12.06,26.78)	37.87 (28.68,49.06)	42.86 (30.62,58.37)
National	254	689	405	16.81 (14.53,19.35)	34.45 (31.59,37.50)	33.22 (29.59,37.17)

Table 3.2.5: Risk of incidence type 1 diabetes in paediatric population according to patient characteristics presented as adjusted incidence rate ratio with 95% CI from 2004 to 2007

Characteristics		Unadjusted incidence rate ratio	Adjusted incidence rate ratio†
Gender□	Girls (n=673)	1.05 (0.94, 1.16), ns	1.05 (0.94, 1.16), ns
Age group◊	5-11 years (n=689)	2.00 (1.74, 2.32) ***	1.98 (1.72, 2.30) ***
	12-15 years (n=405)	2.00 (1.72, 2.36) ***	1.99 (1.70, 2.33) ***
Health region∞	Midland (n=111)	2.35 (1.87, 2.93), ***	2.33 (1.85, 2.90) ***
	Mid-Western (n=98)	1.80 (1.44, 2.24), ***	1.78 (1.42, 2.21) ***
	North-Eastern (n=174)	2.35 (1.94, 2.85), ***	2.35 (1.93, 2.85) ***
	North-Western (n=121)	2.72 (2.19, 3.37) ***	2.68 (2.15, 3.32), ***
	South-Eastern (n=175)	2.07 (1.71, 2.51) ***	2.05 (1.69, 2.49) ***
	Southern (n=242)	2.25 (1.89, 2.69) ***	2.23 (1.87, 2.66), ***
	Western (n=151)	2.10 (1.71, 2.57) ***	2.07 (1.69, 2.54), ***

† Adjusted for gender, age groups, calendar year at start of insulin therapies and regions

□ Reference category boys (n=675)

◊Reference category age < 5 years (n=254)

∞Reference category Eastern region (n=248)

3.2.5 Discussion

Overall trend

The age-adjusted prevalence of type 1 diabetes in the paediatric population in Ireland in both genders was stable at 0.2% over the 5 year study period across all regions. The prevalence of type 1 diabetes increased with age with highest prevalence observed in those 12 years old and above. The age-specific prevalence also remained stable throughout the years in all age groups across all regions. The incidence of type 1 diabetes in the paediatric population also did not show significant changes over the study period. The highest age-specific incidence rate was observed in those aged 5 to 11 years old. No significant gender differences were observed in the prevalence and incidence of type 1 diabetes in paediatric population. All regions showed higher prevalence and incidence of type 1 diabetes compared to the Eastern region.

It is difficult to compare the estimate of type 1 diabetes obtained from this study to other larger studies examining paediatric cases of type 1 diabetes due to different case definitions and different age groups used. This study examined the prevalence and incidence of treated type 1 diabetes by identifying the paediatric population prescribed insulin through the pharmacy claims database. Case ascertainment was unable to be carried out as no diagnosis was available in the pharmacy claims database and completeness of the database in terms of childhood prescribing was unable to be determined. Other studies used capture-recapture method that requires two independent sources of case identification, primary and secondary sources to ascertain diabetes cases included in their studies [93]. The capture recapture method would therefore be more accurate in estimation of incidence type 1 diabetes in a childhood population compared to the estimate obtained in this study. Some may not avail of the free prescribed medications under both schemes available in Ireland and thus would not be captured in this study, but this is likely to be small. In addition, some patients with prevalent diabetes may be registered in the schemes late in the course of their diabetes and may be included as incident diabetes.

The prevalence of type 1 diabetes in the paediatric population in this study was similar to the estimate obtained using the PBS model [76]. However, this study observed a high incidence of type 1 diabetes compared to other previous estimates in Ireland [87, 90]. The incidence found in this study puts Ireland amongst the countries with highest incidence of paediatric diabetes in Europe, at fourth place just below the rate found in the neighbouring Northern Ireland (29.8/100,000) in the period of 1999-2003 according to the EURODIAB study [85]. As mentioned above, the age group included in this study differed to other studies in which the paediatric population included in this study was less than 16 years old compared to less than 15 years old for other studies.

This study did not demonstrate an increase in the incidence of type 1 diabetes over the study period as observed in the WHO DIAMOND and EURODIAB study. Compared to other studies on paediatric incidence of type 1 diabetes [84, 85, 90], the period chosen for this study is more recent. This could explain the higher incidence rate of diabetes compared to the other European countries and previous Irish estimates and the relatively stable incidence over the years. Some Northern European countries also showed levelling of incidence rate after recording of high incidence rate of type 1 diabetes [94].

Gender and age variations

As with other studies on type 1 diabetes in paediatric population, no significant gender differences were observed in this study. For those in the age group of less than 5 year old in which direct comparison was able to be made with other studies, a higher incidence rate was observed compared to the 1997 Irish estimate. The increase is to be expected if the worldwide increase in the incidence of diabetes especially in the youngest age group also occurred in Ireland in the period between this study and the previous Irish study.

Regional variations

The variation in type 1 incidence rate across different regions in Ireland is consistent with studies performed in the Northern Ireland and UK [87]. The study in Northern Ireland had showed differences in incidence rate between different areas with lowest rates found in urban areas such as Belfast and Derry [87]. This is reflected in this study as the Eastern region consisting of Dublin, Kildare and Wicklow having the lowest incidence rate. A higher incidence of type 1 diabetes in remote areas and less populated areas was also observed in Northern Ireland [95]. This could explain the higher incidence observed in other regions in Ireland compared to the Eastern region. Cardwell *et al* suggested that the higher incidence of type 1 diabetes in urban areas may be explained by the hygiene hypothesis. Children from urban areas may have more social contact and thus earlier and more frequent exposure to childhood infection thought to be protective of type 1 diabetes [87, 92]. However, due to small number of patients from different regions in Ireland, random variation may also explain the differences observed between the different regions. Ecological analysis was not performed across smaller geographical areas due to limitations in the database. Some studies have also demonstrated seasonal variation in the incidence of type 1 diabetes with peaks during winter months and troughs during summer time while some have not [96, 97]. One Irish study in 1997 demonstrated seasonal effects of birth months and months of clinical onset of diabetes in the incidence of type 1 diabetes in males population only [98]. This study, however, did not examine seasonal variation in the incidence of treated type 1 diabetes in this population.

In contrast to type 1 diabetes, few studies have examined the incidence of type 2 diabetes in the paediatric population. Increased incidence of type 2 diabetes has been observed in Europe and in the UK is most probably due to the increasing prevalence of obesity in the paediatric population over the last few years [81, 99]. However, it is more difficult to determine the true incidence of type 2 diabetes in paediatric population as most will be undiagnosed and even those diagnosed may be managed with lifestyle intervention during the early course of the disease. As no clinical diagnosis is available, this study did not attempt to estimate the prevalence and incidence of type 2 diabetes in the Irish paediatric population. The prevalence of obesity in the paediatric population in Ireland is however on the increase [100] and thus a corresponding increase prevalence of type 2 diabetes in this population would be expected in the next coming years.

CHAPTER 4 : UTILIZATION OF ANTIDIABETIC THERAPIES IN IRELAND

4.1 Trends in the prescribing of antidiabetic therapies in patients with type 1 diabetes

4.1.1 Background

The mainstay of treatment for patients with type 1 diabetes mellitus is insulin which was discovered in 1921 from beef and pork pancreases by a team of scientists from the University of Toronto [10]. Animal insulin was associated with an increased risk of allergic reaction due to antibody formation and lipoatrophy at injection sites [101]. In 1982, application of genetic engineering enabled insulin to be produced using recombinant DNA technology to replace the animal source of insulin in most parts of the world [102]. This recombinant insulin or also called human insulin was easily manufactured and less immunogenic compared to animal insulin [103]. However, human insulin was found to be inferior to animal insulin in terms of glycaemic control and had an increased risk of hypoglycaemic episodes [104, 105]. The more expensive insulin analogues were developed and introduced to the market after 1996 and these analogues are now gradually replacing human insulin especially in the more developed countries.

Insulin therapies are administered as subcutaneous injections and are available as short- or rapid-acting as well as intermediate-acting and long-acting preparations. Short acting insulin is given before meal to increase the level of circulating insulin and thus target postprandial hyperglycaemia [106]. The first short-acting insulin analogue to be developed was insulin lispro followed by insulin aspart and most recently, insulin glulisine [106]. Insulin analogues were shown to produce rapid onset of action and rapid return to baseline compared to short-acting human insulin [107]. Intermediate-acting insulin is produced by combining insulin with neutral protamine, also known as Neutral Protamine Hagedorn insulin or NPH insulin [106]. Intermediate-acting insulin is also available as combined or premixed preparation with fast-acting insulin. Long-acting insulin is used at bedtime or in the morning to provide basal insulin replacement [106]. Insulin glargine, the first of long-acting insulin analogues is produced by substitution of glycine for asparagine and addition of two arginine molecules to the insulin chain. Insulin glargine was the first long-acting insulin analogue and this was followed by insulin detemir which was just marketed in 2004. Long-acting insulin analogues are slowly released into the circulation resulting in prolonged insulin absorption compared to human insulin [108].

Conventionally, in patients with type 1 diabetes, a basal bolus insulin regime is used with once or twice daily long-acting insulin injection coupled with meal time injection of short-acting insulin. Premixed combination human insulin was designed to target prandial glucose as well as to prolong the duration of action of insulin in the body. Premixed insulin offers convenience to patients and accuracy of insulin delivery. In addition, premixed insulin analogues containing mixtures of rapid acting insulin with addition of protamine have been developed and have been shown to offer better postprandial glucose control with similar long term glycaemic control compared to premixed human insulin [109].

The inhaled insulin, Exubera, was developed to address some of the problems concerning injections in type 1 diabetes and to reduce the number of daily insulin injections. Exubera was shown to provide similar efficacy with better treatment satisfaction compared to subcutaneous human insulin [110]. However, inhaled insulin was associated with reduced pulmonary function, necessitating pulmonary function test in those to be initiated with this agent [111]. Unfortunately, in 2007, inhaled insulin was withdrawn from the market due to adverse effects on pulmonary function and lack of response from the diabetes market [112]. Improvement in insulin delivery devices such as insulin pen therapy over the years has provided convenient, pain-free injections and more accurate delivery of insulin. Insulin pen devices are discrete and help the patient to overcome issues such as needle phobias and social embarrassment with insulin injection [113, 114]. Devices such as continuous subcutaneous insulin infusion (CSII) were developed in 1976 to deliver continuous basal insulin and patient activated meal time insulin [115]. Treatment of patients with type 1 diabetes using CSII were associated with significant improvement in glucose control and lower incidence of hypoglycaemia compared to traditional delivery methods in both paediatric and adult population [116]. However, CSII is costly and the uptake is still at low level in Europe [117].

Little is known about the prescribing pattern of insulin therapies for patients with type 1 diabetes in Ireland. With a variety of insulin preparation for prescribers to choose from, this study was undertaken to examine the trends and the variations in the prescribing of this agent in the Irish population with type 1 diabetes.

4.1.2 Specific objectives

1) To examine the overall prescribing trends of insulin therapies in both the Irish adult and paediatric populations with type 1 diabetes from 2003 to 2007

2) To examine the variations in the prescribing of insulin therapies across gender, age groups, drug schemes and health regions in Ireland.

4.1.3 Methods

4.1.3.1 Trends in the prescribing of insulin in prevalent patients with type 1 diabetes

The HSE-PCRS database was used to identify patients prescribed insulin only from 1st January 2003 to 31st December 2007 under both the GMS and the LTI schemes in Ireland. Insulin preparations examined were fast-acting insulin, intermediate-acting insulin, long-acting insulin, intermediate-and fast-acting premixed insulin and inhaled insulin. In addition, human insulin and insulin analogues; insulin lispro, insulin aspart, insulin glulisine, insulin glargine and insulin detemir were identified.

The percentages of patients with type 1 diabetes prescribed insulin were calculated each year over the study period. Adjusted logistic regression was used to examine variations in the prescribing of different preparation and types of insulin across gender, age groups (age groups 0-4, 5-11 and 12-15 for the paediatric population and age groups 16-44, 45-64 and 65 years above for adults), community drug schemes (GMS and LTI schemes) and health regions. Results are presented as adjusted OR with 95% CIs.

4.1.4 Results

4.1.4.1 Prescribing of insulin in adult patients with prevalent type 1 diabetes

Overall trend in the prescribing of insulin

Overall, there was a significant increase in the prescribing of insulin in adults with type 1 diabetes during the 5-year study period ($p<0.0001$). A change in the prescribing pattern of the different insulin preparations was observed between 2003 and 2007. A significant increase in patients being prescribed fast-acting insulin and doubling of patients being prescribed long-acting insulin was observed during this study period ($p<0.0001$, Figure 4.1.1). A decline in patients being prescribed both preparations of intermediate-acting insulin was observed ($p<0.0001$). The overall uptake of inhaled insulin was very low in patients with type 1 diabetes in Ireland during the study period (0.1%).

The change in the prescribing trend over the years in adult type 1 diabetes patients was also observed with the different types of insulin. In 2003, nearly ninety percent of patients were prescribed human insulin (Figure 4.1.2). This declined to only a third of patients by 2007. The total prescribing of insulin analogues such as insulin aspart, insulin glargine, insulin detemir and insulin glulisine increased significantly over the study period ($p<0.0001$) while the total prescribing of insulin lispro was relatively stable. Insulin aspart was the most prescribed insulin analogues. Less than ten percent of patients were prescribed other fast-acting insulin analogues; insulin lispro and

insulin glulisine. The introduction of insulin detemir to the Irish market in 2004 saw the increase in the prescribing of this agent and it was prescribed a third of patients by 2007 ($p<0.0001$).

Gender, age and socioeconomic variations in the prescribing of insulin

Females were less likely to be prescribed premixed insulin but more likely to receive other insulin preparations compared to males (Table 4.1.1). Females were more likely to be prescribed insulin analogues compared to males (Table 4.1.2). The same pattern was observed when those eligible under the LTI scheme were compared to those eligible under the GMS scheme. Patients with type 1 diabetes over 45 years of age were more likely to receive the premixed insulin but less likely to receive other preparations of insulin compared to those less than 45 years of age. Those over 65 years old were more than 4 times as likely to be prescribed premixed insulin compared to those less than 45 years of age. Those over 45 years of age were more likely to receive the less expensive human insulin and less likely to receive insulin analogues compared to younger patients.

Regional variations in the prescribing of insulin

The prescribing of insulin differed across the country during the study period as shown in Figure 4.1.3 to Figure 4.1.11 respectively. The national trend of significant increase in the prescribing of fast- and long-acting insulin and significant decrease in the prescribing of intermediate- and premixed insulin was observed in all regions during the study period. Consistent with the national trend, the prescribing of human insulin declined significantly while the prescribing of insulin analogue increased over the 5-year period in all regions.

Compared to the Eastern region, patients from all other regions except the North Eastern region were less likely to receive fast-acting insulin (Table 4.1.1). Those in Southern region were more likely to be prescribed intermediate-acting insulin compared to those in the Eastern region. Long- acting insulin was more likely to be prescribed in the Midland, North Eastern and Western regions and less likely to be prescribed in the Mid-Western, North Western and Southern regions compared to the Eastern region. Patients from most other regions were more likely to prescribed premixed insulin compared to the Eastern region except those from the Midland, North Eastern and North Western regions.

Patients from most other regions were more likely to be prescribed human insulin compared to the Eastern region with the exception of the Western region (Table 4.1.2). Those from the Mid-Western region were more than twice as likely to be prescribed human insulin but were less likely to be prescribed the different insulin analogues compared to those from the Eastern region. Those from Southern, South Eastern and North Eastern regions were more likely to be prescribed insulin detemir while those from the North Western and Western were more likely to be prescribed insulin glargine compared to the Eastern region. Those from the Midland,

Southern and Western regions were more likely to be prescribed insulin aspart compared to the Eastern region. Only the South Eastern and Western region were more likely to be prescribed other fast acting insulin analogues compared to the Eastern region.

Figure 4.1.1: Trends in the prescribing of insulin according to preparations in adults with type 1 diabetes from 2003 to 2007 (note: patients may be prescribed ≥ one medication in a year)

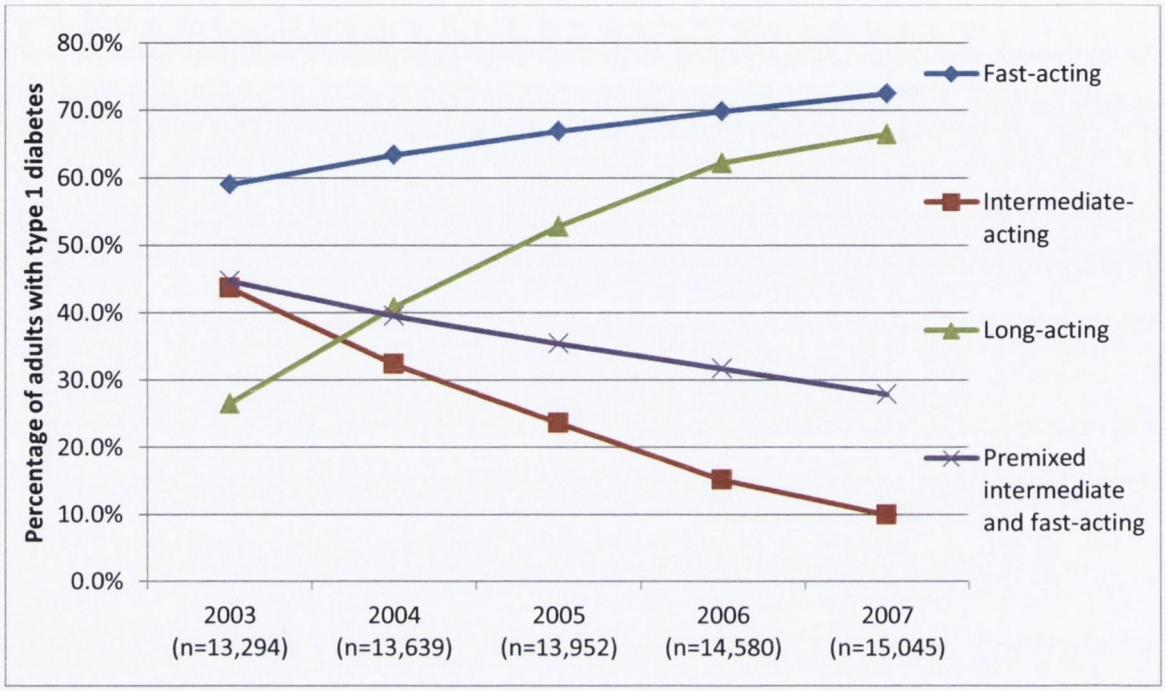


Figure 4.1.2: Trends in the prescribing of insulin according to type in adults with type 1 diabetes from 2003 to 2007 (note: patients may be prescribed ≥ one medication in a year)

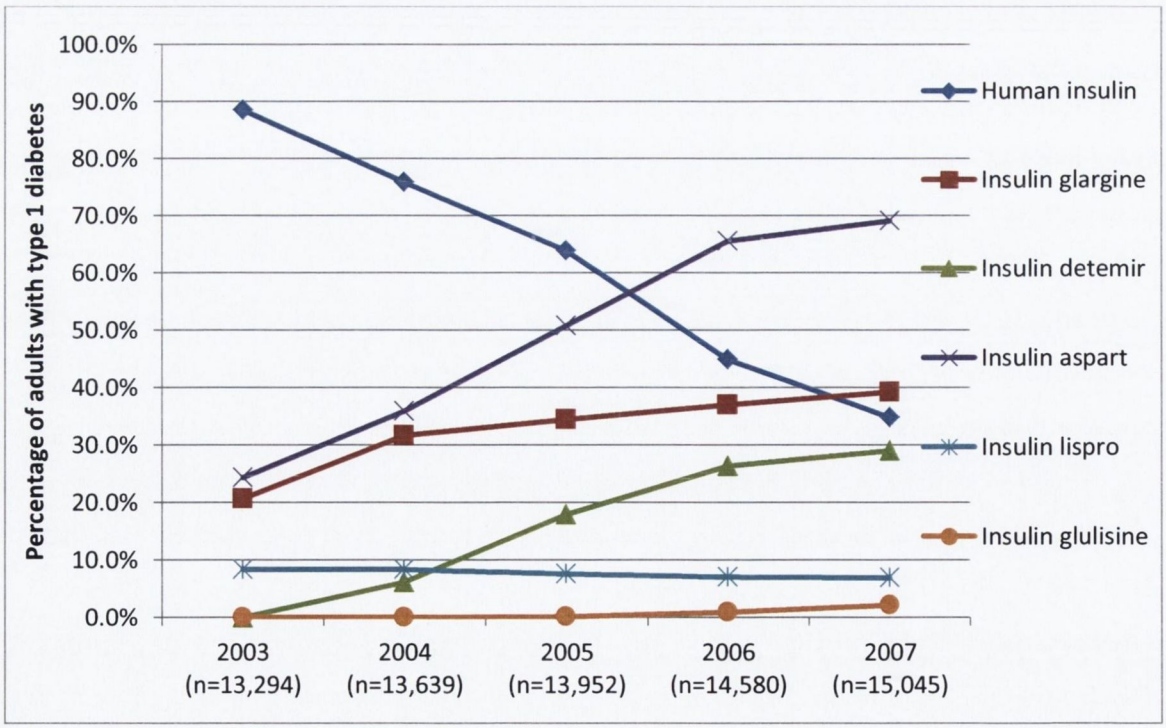


Figure 4.1.3: Trends in the prescribing of fast-acting insulin in adults with type 1 diabetes according to health regions from 2003 to 2007 (note: patients may be prescribed ≥ one medication in a year)

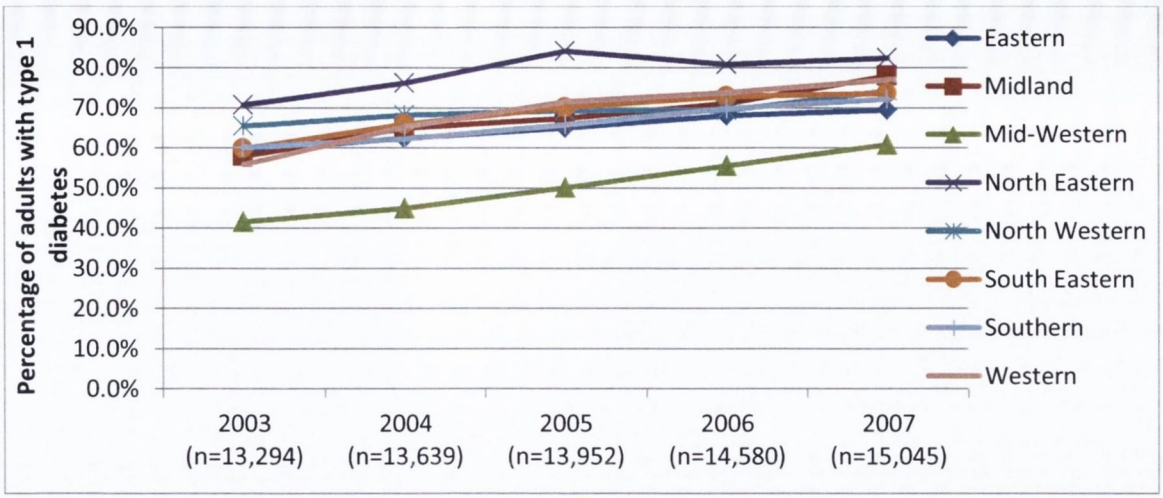


Figure 4.1.4: Trends in the prescribing of intermediate-acting insulin in adults with type 1 diabetes according to health regions from 2003 to 2007 (note: patients may be prescribed ≥ one medication in a year)

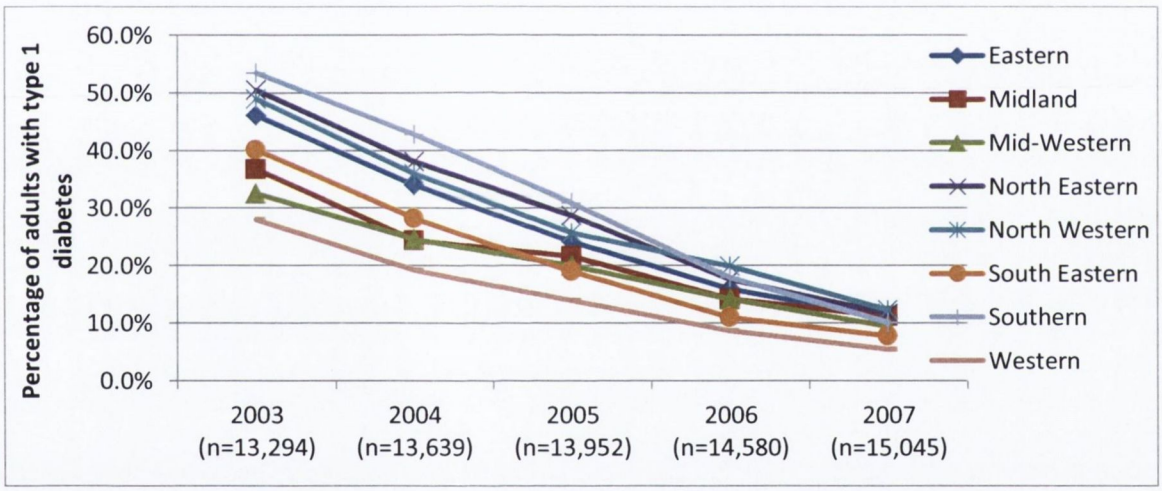


Figure 4.1.5: Trends in the prescribing of long-acting insulin in adults with type 1 diabetes according to health regions from 2003 to 2007 (note: patients may be prescribed ≥ one medication in a year)

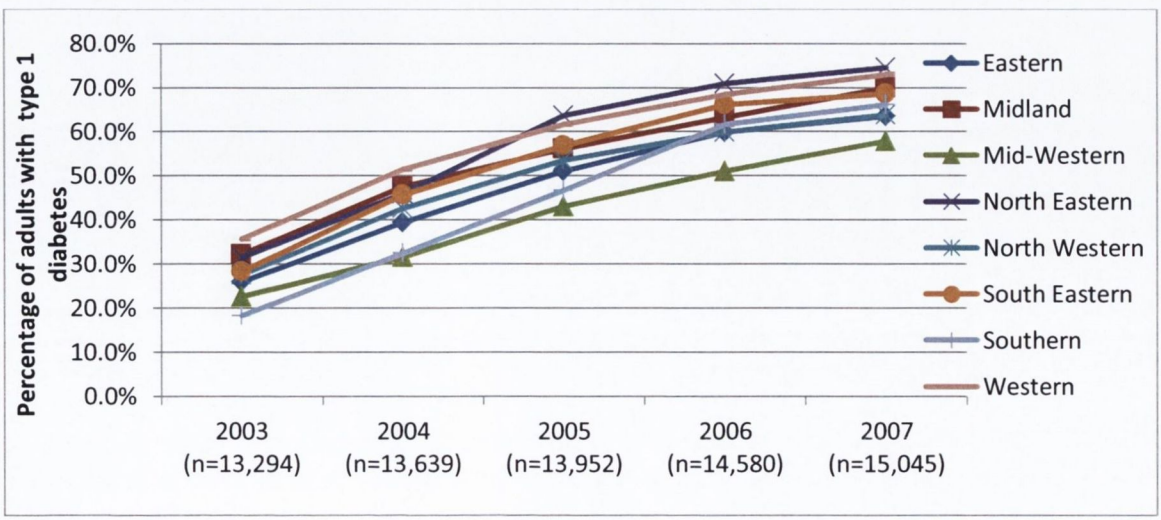


Figure 4.1.6: Trends in the prescribing of biphasic insulin in adults with type 1 diabetes according to health regions from 2003 to 2007 (note: patients may be prescribed ≥ one medication in a year)

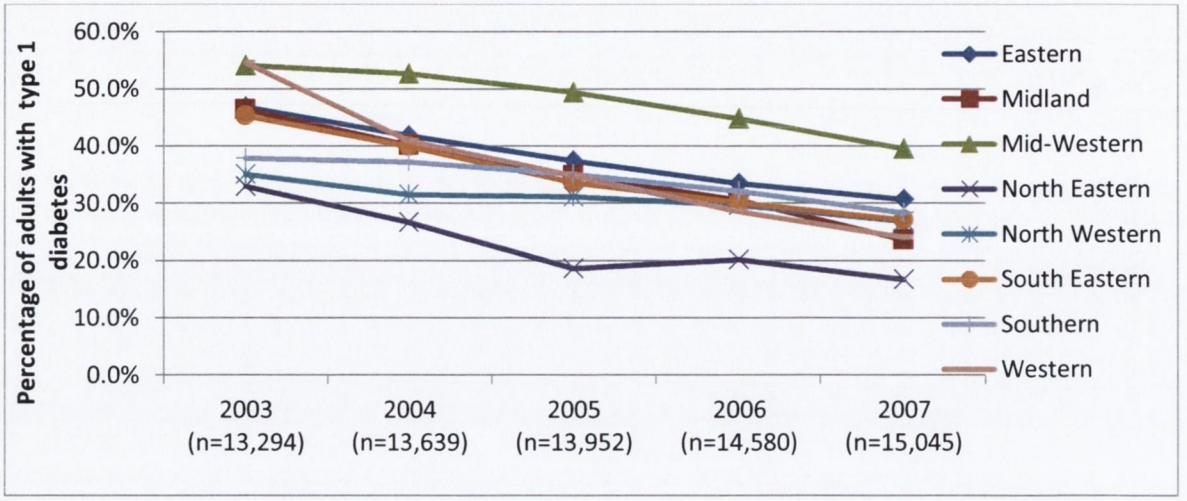


Figure 4.1.7: Trends in the prescribing of human insulin in adults with type 1 diabetes according to health regions from 2003 to 2007 (note: patients may be prescribed ≥ one medication in a year)

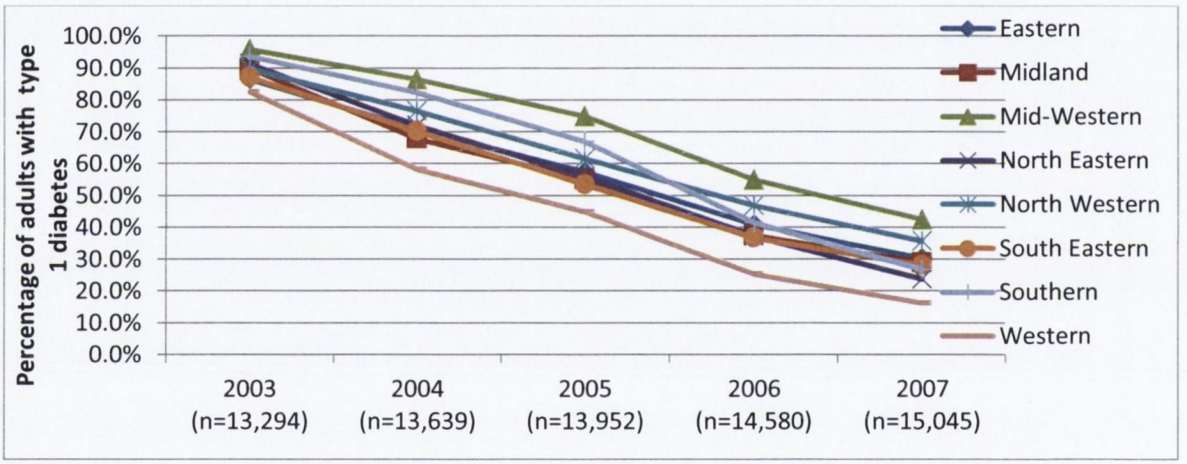


Figure 4.1.8: Trends in the prescribing of insulin aspart in adults with type 1 diabetes according to health regions from 2003 to 2007 (note: patients may be prescribed ≥ one medication in a year)

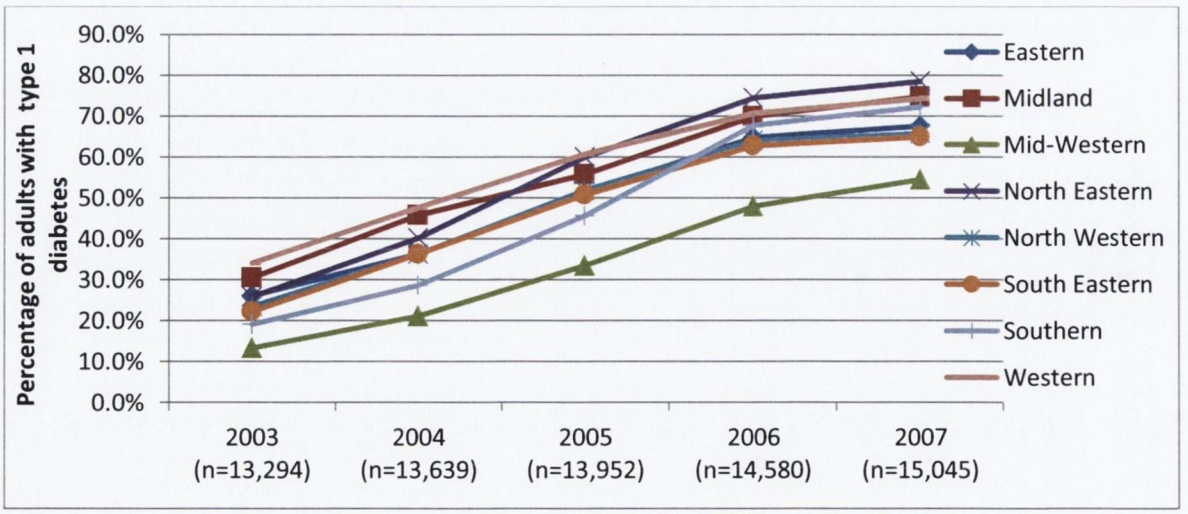


Figure 4.1.9: Trends in the prescribing of insulin glargine in adults with type 1 diabetes according to health regions from 2003 to 2007 (note: patients may be prescribed ≥ one medication in a year)

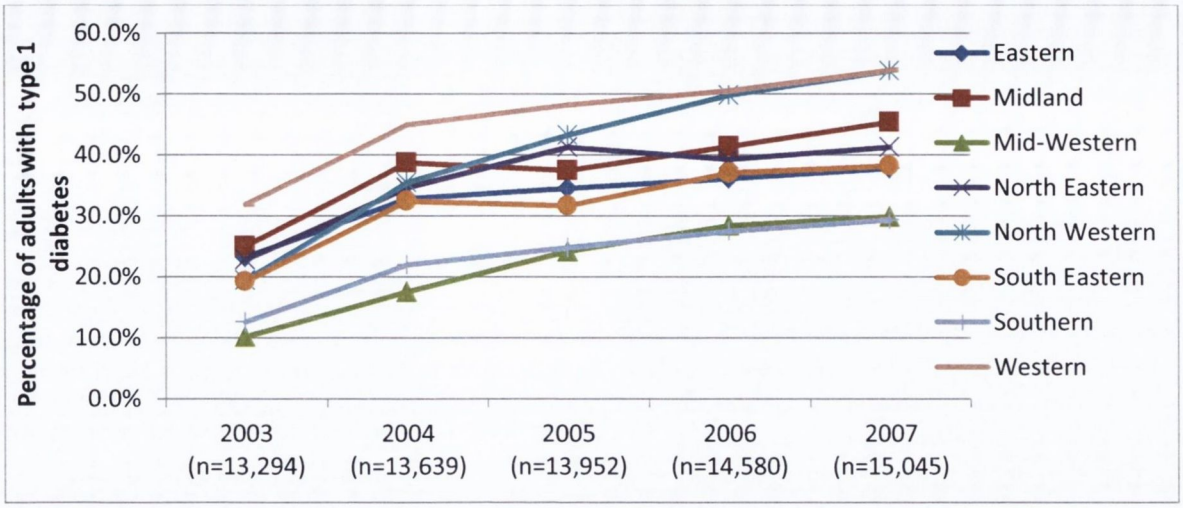


Figure 4.1.10: Trends in the prescribing of insulin detemir in adults with type 1 diabetes according to health regions from 2003 to 2007 (note: patients may be prescribed ≥ one medication in a year)

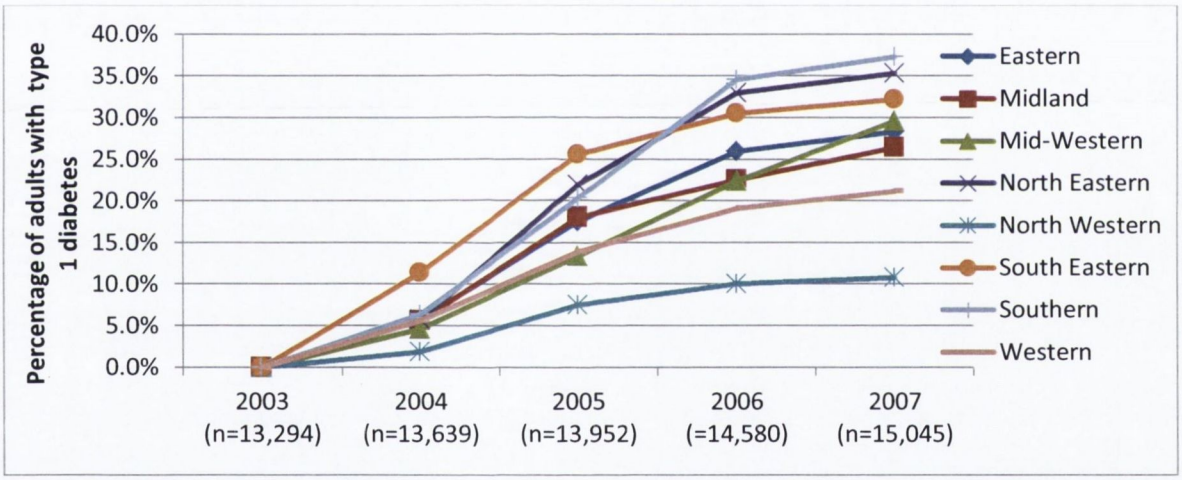


Figure 4.1.11: Trends in the prescribing of insulin lispro and glulisine in adults with type 1 diabetes according to health regions from 2003 to 2007 (note: patients may be prescribed ≥ one medication in a year)

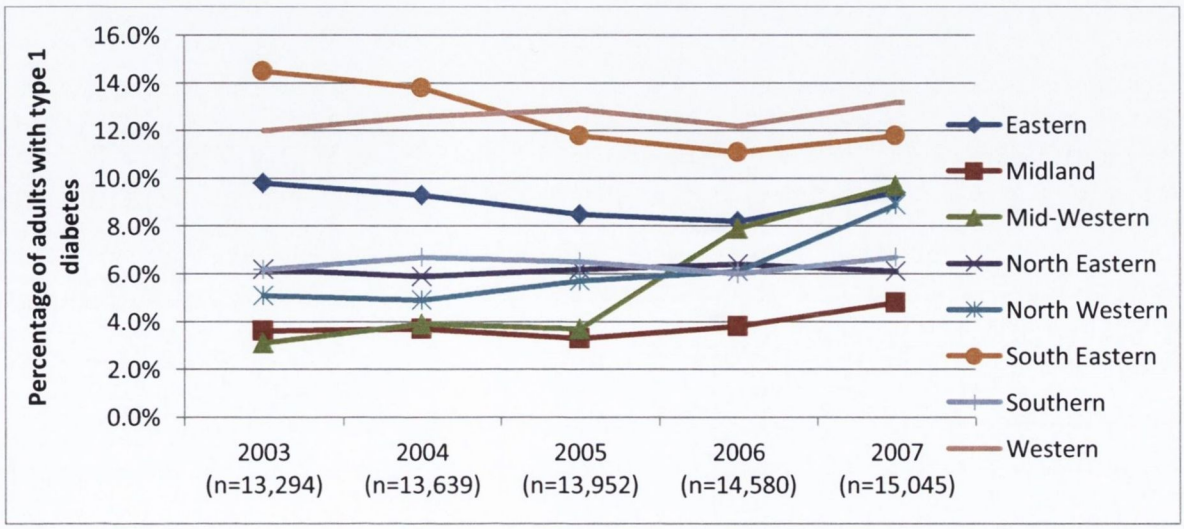


Table 4.1.1: Variations in the prescribing of different insulin preparations in adults with type 1 diabetes presented as adjusted OR with 95% CI

Patient characteristics		Fast-acting	Intermediate-acting	Long-acting	Premixed
		OR† (95% CI), *p*	OR† (95% CI), *p*	OR† (95% CI), *p*	OR † (95% CI), *p*
Gender□	Female (n=10,857)	1.26 (1.22,1.31) ***	1.23 (1.18, 1.28) ***	1.05 (1.02, 1.09) *	0.82 (0.79, 0.85) ***
Age group◊	45-64 (n=6,427)	0.42 (0.41,0.44) ***	0.67 (0.64, 0.70) ***	0.73 (0.70, 0.75) ***	1.88 (1.81, 1.96) ***
	≥65 (n=5,863)	0.15 (0.14, 0.16) ***	0.44 (0.42, 0.46) ***	0.35 (0.33, 0.36) ***	4.17 (3.99, 4.36) ***
Drug scheme ¥	LTI (n=10,482)	1.88 (1.81, 1.96) ***	1.27 (1.22, 1.32) ***	1.49 (1.44, 1.55) ***	0.59 (0.57, 0.62) ***
Health region∞	Midland (n=1,499)	0.91 (0.84, 0.98) *	0.71 (0.65,0.77) ***	1.12 (1.05, 1.20) **	1.07 (0.99, 1.15) ns
	Mid-Western (n=1,722)	0.37 (0.34, 0.39) ***	0.63 (0.59, 0.68) ***	0.62 (0.58, 0.66) ***	1.98 (1.86, 2.11) ***
	North Eastern (n=1,801)	1.38 (1.28,1.48) ***	1.00 (0.94, 1.07) ns	1.15 (1.08, 1.23) ***	0.66 (0.62, 0.71) ***
	North Western (n=1,290)	0.92 (0.85, 0.99) *	1.04 (0.96, 1.13) ns	0.88 (0.82, 0.94) **	0.90 (0.83, 0.97) *
	South Eastern (n=2,177)	0.80 (0.75, 0.85) ***	0.64 (0.60, 0.68) ***	1.01 (0.95, 1.07) ns	1.19 (1.12, 1.26) ***
	Southern (n=3,250)	0.71 (0.68,0.75) ***	1.13 (1.07,1.19) ***	0.70 (0.67, 0.74) ***	1.13 (1.07, 1.19) ***
	Western (n=2,107)	0.84 (0.79,0.89) ***	0.41 (0.38, 0.44) ***	1.29 (1.22, 1.37) ***	1.26 (1.19, 1.34) ***

† Adjusted for gender, age groups, drug schemes, calendar years and health regions

□ Reference category males (n=12,467)

◊ Reference category age 16-44 years (n=11,725)

¥ Reference category GMS scheme (n=13,533)

∞ Reference category Eastern region (n=10,169)

Table 4.1.2: Variations in the prescribing of different insulin types in adults with type 1 diabetes presented as adjusted OR with 95% CI

Patient characteristics		Human insulin OR† (95% CI), *p*	Insulin aspart OR† (95% CI), *p*	Insulin glargine OR † (95% CI), *p*	Insulin detemir OR † (95% CI), *p*	Other analogues OR † (95% CI), *p*
Gender□	Female (n=10,857)	0.99 (0.95, 1.02) ns	1.13 (1.09, 1.17) ***	1.04 (1.01, 1.08) *	1.13 (1.08, 1.18) ***	1.09 (1.03, 1.16) ***
Age group◊	45-64 (n=6,427)	1.18 (1.14, 1.24) ***	0.65 (0.62, 0.67) ***	0.73 (0.71, 0.76) ***	0.90 (0.85, 0.94) ***	0.79 (0.75, 0.84) ***
	≥65 (n=5,863)	1.96 (1.87, 2.06) ***	0.35 (0.33, 0.36) ***	0.38 (0.36, 0.40) ***	0.59 (0.56, 0.63) ***	0.29 (0.26, 0.33) ***
Drug scheme¥	LTI (n=10,482)	0.79 (0.76, 0.82) ***	1.40 (1.35, 1.46) ***	1.47 (1.42, 1.52) ***	1.17 (1.11, 1.23) ***	1.76 (1.65, 1.87) ***
Health region∞	Midland (n=1,499)	1.03 (0.96, 1.11) ns	1.16 (1.09, 1.25) ***	1.07 (1.00, 1.15) ns	0.85 (0.78, 0.94) **	0.33 (0.28, 0.38) ***
	Mid-Western (n=1,722)	2.39 (2.22, 2.56) ***	0.41 (0.38, 0.43) ***	0.48 (0.45, 0.52) ***	0.80 (0.73, 0.88) ***	0.50 (0.44, 0.56) ***
	North Eastern (n=1,801)	1.13 (1.06, 1.21) **	1.06 (0.99, 1.13) ns	0.88 (0.83, 0.93) ***	1.18 (1.09, 1.27) ***	0.48 (0.42, 0.53) ***
	North Western (n=1,290)	1.48 (1.37, 1.52) ***	0.80 (0.74, 0.86) ns	1.20 (1.11, 1.28) ***	0.29 (0.26, 0.33) ***	0.52 (0.46, 0.60) ***
	South Eastern (n=2,177)	1.03 (0.97, 1.09) ns	0.74 (0.70, 0.78) ***	0.77 (0.73, 0.82) ***	1.25 (1.17, 1.35) ***	1.15 (1.05, 1.25) *
	Southern (n=3,250)	1.44 (1.37, 1.52) ***	1.25 (1.17, 1.32) ***	0.50 (0.47, 0.52) ***	1.25 (1.18, 1.33) ***	0.56 (0.51, 0.61) ***
	Western (n=2,107)	0.59 (0.56, 0.63) ***	1.25 (1.17, 1.32) ***	1.49 (1.41, 1.58) ***	0.64 (0.59, 0.70) ***	1.22 (1.12, 1.33) ***

† Adjusted for gender, age groups, drug schemes, calendar years, and health regions

□ Reference category males (n=12,467)

◊ Reference category age 16-44 years (n=11,725)

¥ Reference category GMS scheme (n=13,533)

∞ Reference category Eastern region (n=10,169)

4.1.4.2 Prescribing of insulin in paediatric population with type 1 diabetes

Overall trend

In 2003, most of the prescribing for insulin in paediatric patients with type 1 diabetes were made up of premixed fast- and intermediate-acting insulin, however, a decrease in the prescribing of this agent was observed over the years ($p<0.0001$). As in adults, there was also a significant decrease in the prescribing of intermediate-acting ($p<0.0001$) and significant increases in the prescribing of fast-acting ($p<0.0001$) and long-acting insulin ($p<0.0001$) in paediatric patients with type 1 diabetes (Figure 4.1.12).

The same trend of declining utilization of human insulin in adults with type 1 diabetes was also observed in the paediatric population ($p<0.0001$, Figure 4.1.13). Most paediatric patients with type 1 diabetes were prescribed human insulin early in the study period. In contrast to adults with type 1 diabetes, more than half of paediatric patients were still being prescribed human insulin in 2007. This was followed by a significant increases in the total prescribing of some insulin analogues; insulin aspart, glargine and detemir ($p<0.0001$). However, a significant decrease in the prescribing of insulin lispro ($p<0.0001$) was also observed. A steep rise in the prescribing of insulin aspart was observed with more than three quarter patients being prescribed this agent in 2007 ($p<0.0001$). Increases in the percentage of paediatric patients being prescribed long-acting insulin analogues ($p<0.0001$) were also observed with prescribing of insulin detemir overtaking insulin glargine by 2007.

Gender, age and socioeconomic variations

No significant gender differences were observed in the prescribing of the different preparation of insulin in paediatric patients with type 1 diabetes (Table 4.1.3). Those over 5 years old were less likely to be prescribed intermediate-acting insulin but more likely to be prescribed long-acting insulin compared to those less than 5 years old. Those 12 years old and over were more likely to be prescribed fast-acting insulin and less likely to be prescribed premixed insulin compared to those less than 5 years old. As in adult patients, paediatric patients eligible under the LTI scheme were less likely to be prescribed premixed insulin and more likely to be prescribed all other insulin preparations compared to those eligible under the GMS scheme.

The prescribing of the different insulin types in paediatric patients with type 1 diabetes also showed no significant gender differences (Table 4.1.4). No significant differences was observed in the prescribing in patients 5 to 11 years old compared to those less than 5 years old except in the prescribing of insulin glargine. Those 12 years old and over were more likely to be prescribed the different insulin analogues except insulin lispro and glulisine but less likely to be prescribed human insulin compared to those less than 5 years old. Paediatric patients under the

LTI scheme were more likely to be prescribed the more expensive insulin analogues compared to those under the GMS scheme.

Regional variations

Due to the small number of paediatric patients with type 1 diabetes in the country, wide variations were observed across the regions in the prescribing of insulin in this cohort. In 2003, some 90% of paediatric patients with type 1 diabetes from the North Eastern were prescribed fast-acting insulin compared to 30% of patients in the North Western region. In 2007, more than three quarter of paediatric patients with type 1 diabetes were prescribed fast-acting insulin in all regions except in North Western. In 2007, more than half of paediatric patients with type 1 diabetes were prescribed long-acting insulin except Midland regions whereby only a third of patients were prescribed this agent. The Western region had the highest prescribing of premixed insulin but the lowest prescribing of intermediate-acting insulin compared to other regions throughout the study period. Compared to the Eastern regions, patients from most other regions were less likely to be prescribed fast-acting, intermediate-acting and long-acting insulin but were more likely to be prescribed premixed insulin (Table 4.1.3). The exception was observed in the Southern region whereby, paediatric patients with type 1 diabetes were more likely to be prescribed long-acting insulin compared to those from the Eastern region.

In 2003, human insulin was prescribed to at least ninety percent of paediatric patients with type 1 diabetes with the highest prescribing observed in the Midland at nearly 100%. By 2007, prescribing of human insulin declined in all regions. Some eighty percent of patients in Midland were still being prescribed human insulin in 2007 compared to only a third in the Southern region. The Southern region had the most patients being prescribed insulin aspart and insulin glargine compared to other regions in 2003. The prescribing of insulin detemir also increased in all regions since its introduction in 2004 with the lowest uptake observed in the North Western region throughout the study period. The prescribing of other short acting insulin analogues were less than ten percent except in the Eastern and South Eastern region. Paediatric patients from most other regions were less likely to be prescribed the different types of insulin analogues compared to those from the Eastern region (Table 4.1.4). Paediatric patients from the Midland and the South Eastern region were more likely to be prescribed human insulin compared to those from the Eastern region. Those from the Southern and Western region were less likely to be prescribed human insulin compared to those from the Eastern region. Paediatric patients from the Southern region, however, were more likely to be prescribed insulin aspart and insulin glargine compared to those from the Eastern region.

Figure 4.1.12: Trends in the prescribing of insulin according to preparations in paediatric population with type 1 diabetes from 2003 to 2007 (note: patients may be prescribed ≥ one medication in a year)

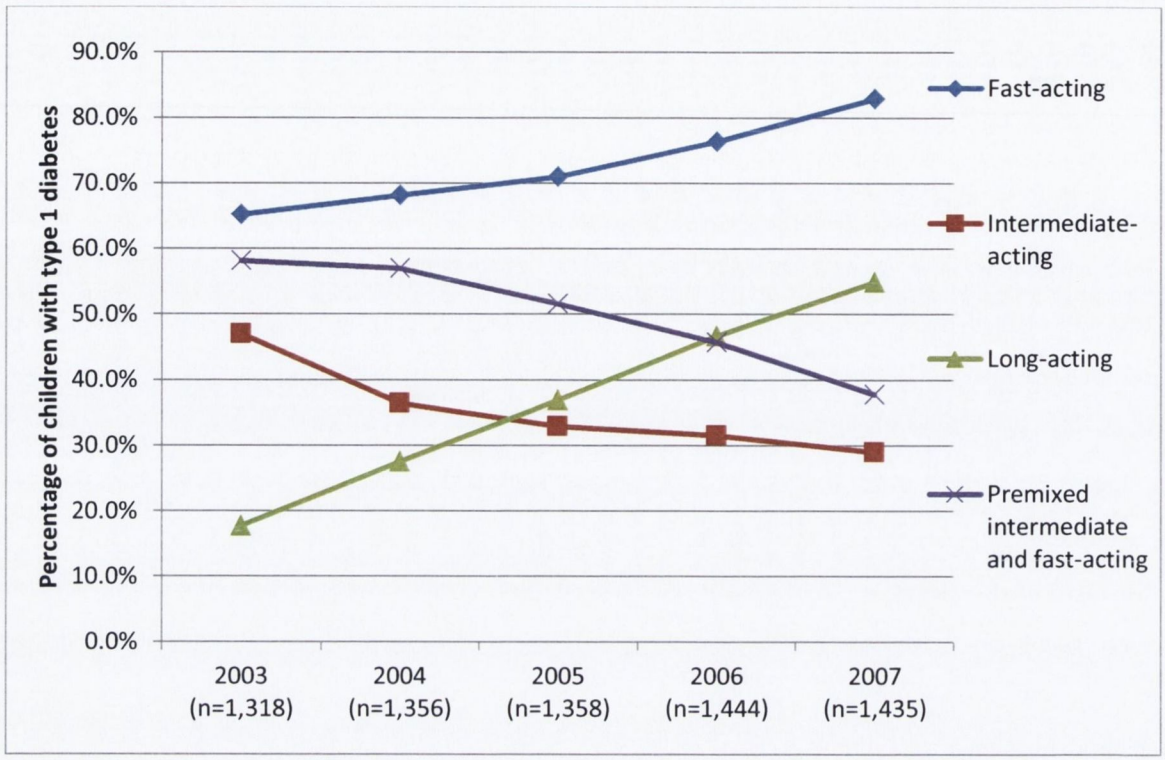


Figure 4.1.13: Trends in the prescribing of insulin according to types in paediatric population with type 1 diabetes from 2003 to 2007 (note: patients may be prescribed ≥ one medication in a year)

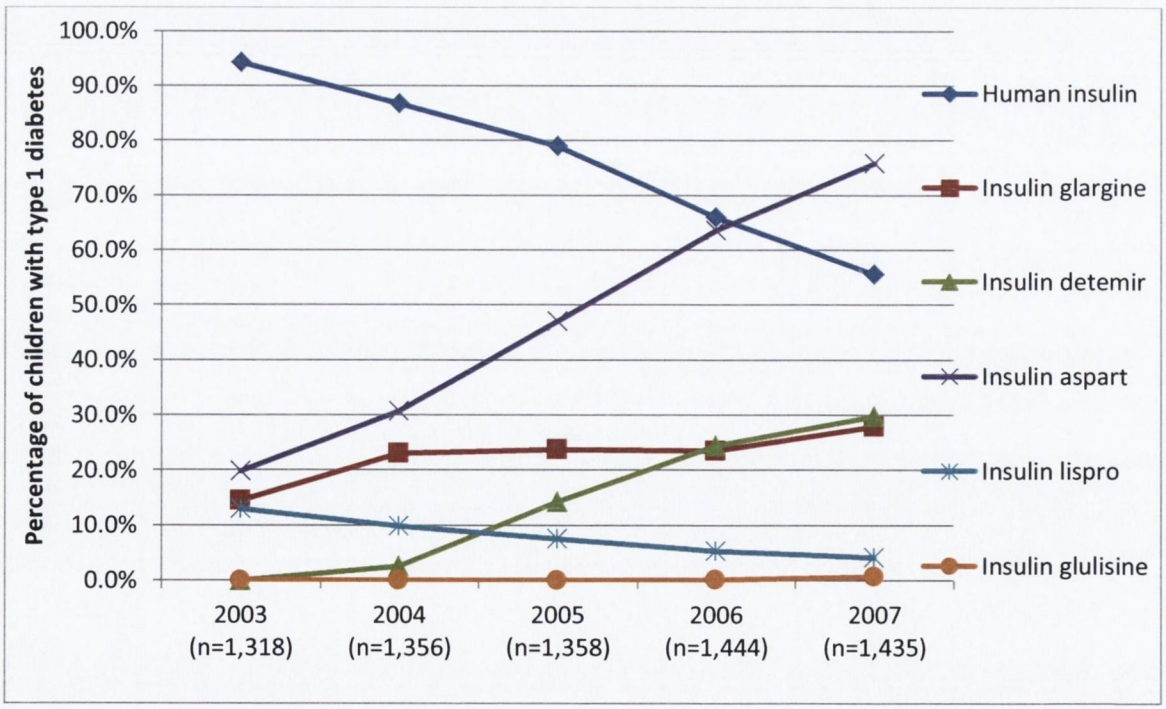


Table 4.1.3: Variations in the prescribing of different insulin preparation in paediatric population with type 1 diabetes presented as adjusted OR with 95% CI

Patient characteristics		Fast-acting	Intermediate-acting	Long-acting	Premixed
		OR† (95% CI), *p*	OR† (95% CI), *p*	OR† (95% CI), *p*	OR† (95% CI), *p*
Gender□	Female (n=1,266)	0.97 (0.86, 1.09) ns	0.99 (0.89, 1.11) ns	1.04 (0.93, 1.16) ns	0.98 (0.88, 1.08) ns
Age group◊	5-11 (n=1,284)	0.82 (0.66, 1.03) ns	0.74 (0.59, 0.92) *	1.49 (1.17, 1.91) **	1.21 (0.98, 1.49) ns
	12-15 (n=961)	1.39 (1.11, 1.75) *	0.43 (0.35, 0.54) ***	5.04 (3.95, 6.44) ***	0.75 (0.61, 0.92) *
Drug scheme¥	LTI (n=1,718)	1.66 (1.46, 1.89) ***	1.19 (1.04, 1.36) *	1.71 (1.50, 1.95) ***	0.74 (0.61, 0.92) ***
Health Region∞	Midland (n=189)	0.31 (0.24, 0.40) ***	0.43 (0.35, 0.53) ***	0.73 (0.59, 0.91) *	2.42 (1.96, 2.99) ***
	Mid-Western (n=232)	0.58 (0.46, 0.75) ***	0.24 (0.19, 0.29) ***	0.93 (0.75, 1.15) ns	3.16 (2.58, 3.85) ***
	North Eastern (n=265)	0.92 (0.71, 1.18) ns	0.74 (0.61, 0.88) **	1.03 (0.84, 1.25) ns	1.51 (1.33, 1.89) ***
	North Western (n=245)	0.13 (0.11, 0.17) ***	0.09 (0.07, 0.12) ***	0.73 (0.59, 0.91) *	6.93 (5.60, 8.56) ***
	South Eastern (n=326)	0.54 (0.43, 0.67) ***	0.65 (0.55, 0.77) ***	1.05 (0.87, 1.27) ns	1.59 (1.33, 1.90) ***
	Southern (n=409)	0.35 (0.29, 0.43) ***	0.12 (0.10, 0.15) ***	2.01 (1.69, 2.38) ***	2.80 (2.38, 3.30) ***
	Western (n=264)	0.24 (0.20, 0.30) ***	0.06 (0.04, 0.08) ***	0.57 (0.46, 0.71) ***	0.89 (0.76, 1.05) ns

† Adjusted for gender, age groups, drug schemes, calendar years and health regions

□ Reference category males (n=1,304)

◊ Reference category age <5 years (n=362)

¥ Reference category GMS scheme (n=891)

∞ Reference category Eastern region (n=679)

Table 4.1.4: Variations in the prescribing of different insulin types in paediatric population with type 1 diabetes presented as adjusted OR with 95% CI

Patient characteristics		Human insulin OR† (95% CI), *p*	Insulin aspart OR† (95% CI), *p*	Insulin glargine OR † (95% CI), *p*	Insulin detemir OR † (95% CI), *p*	Other analogues OR† (95% CI), *p*
Gender□	Female (n=1,266)	1.00 (0.88, 1.13) ns	0.98 (0.87, 1.09) ns	1.04 (0.92, 1.18) ns	1.07 (0.93, 1.24) ns	0.97 (0.81, 1.17) ns
Age group◊	5-11 (n=1,284)	1.14 (0.87, 1.49) ns	0.90 (0.73, 1.12) ns	1.93 (1.36, 2.72) **	1.26 (0.90, 1.77) ns	1.15 (0.76, 1.72) ns
	12-15 (n=961)	0.36 (0.28, 0.47) ***	1.96 (1.57, 2.44) ***	7.66 (5.45, 10.79) ***	1.91 (1.37, 2.68) **	1.51 (1.00, 2.25) ns
Drug scheme¥	LTI (n=1,718)	0.77 (0.67, 0.90) **	1.72 (1.51, 1.95) ***	1.61 (1.39, 1.87) ***	1.34 (1.12, 1.59) **	2.44 (1.89, 2.15) ***
Health region∞	Midland (n=189)	1.69 (1.26, 2.27) **	0.56 (0.45, 0.71) ***	0.62 (0.47, 0.82) ***	0.57 (0.41, 0.80) **	0.35 (0.23, 0.52) ***
	Mid-Western (n=232)	1.00 (0.78, 1.28) ns	0.92 (0.74, 1.14) ns	0.64 (0.49, 0.82) ***	1.24 (0.94, 1.62) ns	0.44 (0.32, 0.62) ***
	North Eastern (n=265)	1.04 (0.83, 1.32) ns	0.55 (0.45, 0.68) ***	0.94 (0.75, 1.18) ns	0.93 (0.72, 1.21) ns	0.31 (0.22, 0.45) ***
	North Western (n=245)	0.96 (0.75, 1.22) ns	0.51 (0.41, 0.63) ***	0.95 (0.74, 1.20) ns	0.49 (0.36, 0.67) ***	0.11 (0.06, 0.20) ***
	South Eastern (n=326)	1.30 (1.03, 1.63) *	0.76 (0.63, 0.91) *	0.68 (0.54, 0.84) **	1.20 (0.94, 1.53) ns	0.63 (0.48, 0.81) ***
	Southern (n=409)	0.40 (0.33, 0.48) ***	1.66 (1.39, 1.98) ***	2.24 (1.87, 2.68) ***	0.82 (0.65, 1.03) ns	0.30 (0.22, 0.41) ***
	Western (n=264)	0.64 (0.51, 0.80) ***	0.80 (0.66, 0.98) ***	0.50 (0.39, 0.64) ***	0.87 (0.66, 1.14) ns	0.22 (0.15, 0.33) ***

† Adjusted for gender, age groups, drug schemes, calendar years, and health regions

□ Reference category males (n=1,304)

◊ Reference category age <5 years (n=362)

¥ Reference category GMS scheme (n=891)

∞ Reference category Eastern region (n=679)

4.1.5 Discussion

Overall trend

There has been an increase in the total prescribing of insulin in both adults and paediatric patients with type 1 diabetes in Ireland. The prescribing of insulin has shown an increase in some European countries such as England (1991-2004)[118-120] and Germany (1994 and 2003) [121]. The prescribing of insulin in countries such as Belgium, Portugal and Italy, however, have stabilised around the same study period [121]. The increase in the prescribing of insulin analogues for paediatric patients with type 1 diabetes were also observed in Germany and Austria (1995-2007).The current study is more recent compared to the study performed in Europe but includes the same time period as covered in the Germany and Austria childhood study. An increase in the prescribing of insulin may reflect an increase in the prevalence of type 1 diabetes as discussed in Section 3.1.5 and Section 3.2.5. Prescribing of short- and long-acting insulin has increased with a move towards insulin analogues in both paediatric and adult population. There has also been a decline in the prescribing of intermediate-acting insulin, either alone or premixed with fast-acting insulin. Although much publicized, inhaled insulin did not receive the anticipated response from Irish prescribers before its discontinuation from the market by Pfizer in October 2007 [119].

Short-acting insulin provides flexibility to the management of diabetes patients. Short-acting insulin is absorbed faster than other insulin preparation and provides rapid effects of insulin to regulate glucose levels at meal times [106]. Short-acting human insulin needs to be injected thirty minutes before meal and many patients did not observe this requirement [122]. The absorption of human insulin injected subcutaneously was erratic and did not fully mimic the physiological action of insulin in the body. Short-acting human insulin also tends to cause postprandial hyperglycaemia and also hypoglycaemic episodes 3 to 5 hours after injection [106]. Thus patients are advised to snack in between main meals to prevent this problem and this lead to increased caloric intake and weight gain. Insulin itself is an anabolic hormone which promotes weight gain [123]. Short-acting insulin analogues can be administered just prior to meal or 15 minutes after meal and thus are more convenient especially in paediatric patients [124, 125]. Comparable control of hyperglycaemia was observed between short-acting human insulin and analogues with less frequent episodes of severe hypoglycaemia in those prescribed insulin analogues albeit at higher cost [107, 126]. The reduction of hypoglycaemic events is quite important as hypoglycaemia is a major limiting factor in achieving glycaemic goal in patients with type 1 diabetes [127]. In the paediatric population, no significant improvement of overall glucose control and reduction of severe hypoglycaemia were demonstrated with analogues compared to human insulin [128]. However, significant improvement of postprandial hyperglycaemia with

reduction of nocturnal hypoglycaemia was observed in this population [128]. Short-acting insulin analogues also showed improvement with regards to quality of life due to flexibility of treatment, higher satisfaction with treatment and better adherence to treatment [107, 129]. Although there is still a lack of data on long term safety and effects on diabetic complications with short acting analogues [107, 126], worldwide, the sales of short-acting insulin analogues have already exceeded the sales of short-acting human insulin in 2005 [130].

Insulin aspart was the agent of choice amongst the short-acting insulin analogues in Ireland. Reduction of HbA1c was higher in patients prescribed insulin aspart as well as improvement in postprandial glucose control and reduction of major nocturnal hypoglycaemia compared to human insulin in many clinical trials [131]. Although insulin lispro was the first short-acting insulin analogue in the market, the uptake for insulin lispro was quite low in Ireland with only around 10% of patients prescribed this agent in both paediatric and adult populations. In addition, the prescribing of insulin lispro was on the decline in the paediatric population. Insulin lispro has demonstrated better postprandial glycaemic control and reduction in hypoglycaemia with similar overall glycaemic control and severe hypoglycaemic events compared to human insulin [132]. No significant difference in the risk of hypoglycaemia was observed between insulin lispro and human insulin in the prepubertal paediatric population [133]. The uptake for the newly introduced insulin glulisine was very low especially in the paediatric population. Insulin glulisine was shown to be effective in achieving glycaemic control in patients with type 1 diabetes compared to human insulin and is as effective as insulin lispro. However, more studies are needed to compare insulin glulisine with insulin aspart in patients with type 1 diabetes [134].

The prescribing of intermediate-acting insulin may have declined due to several factors such as the variable pharmacokinetic profiles of this agent with high variability of insulin absorption rate between patients and within an individual, a pronounced and variable peak effects and a dose dependant duration of action [106]. Long acting insulin was shown to be superior in terms of nocturnal glucose control compared to intermediate-acting insulin [135]. Long-acting human insulin also had less than the ideal duration of action time compared to physiological insulin [106]. The production of long-acting human insulin with the addition of zinc suspension (Ultra Lente and Humulin L lente) by the Eli Lilly company were discontinued in 2005 due to rapid decline in the prescribing of this agent in the face of newer long-acting insulin analogues. Long acting insulin analogues provides an ideal smooth, 24 hour basal insulin supply compared to NPH insulin [129].

Long-acting analogues demonstrated reduced nocturnal hypoglycaemic events, a frequent problem with intermediate- or long-acting human insulin [136]. Long acting insulin analogues also had a small but significant advantage on overall glucose control compared to NPH

human insulin [136]. In paediatric patients, long-acting insulin analogues were associated with improvement of hypoglycaemia with no significant benefit on glucose control [128]. There has been a rapid increase in the prescribing of insulin detemir since its launch in the Irish market in 2004 with almost one third of patients with type 1 diabetes were prescribed this agent by 2007. In the paediatric patients, the prescribing of insulin detemir has surpassed insulin glargine. Insulin detemir was shown to exhibit less variability in glycaemic control and reduced risk of hypoglycaemia compared to human insulin and insulin glargine [108]. Insulin detemir also demonstrated less weight gain compared to human insulin, an effect not demonstrated with insulin glargine in both adult and paediatric populations [136, 137]. Population based studies have linked the use of insulin analogues especially glargine with cancer such as breast cancer [138-140]. Consensus statements from international diabetes bodies such as the American Diabetes Association criticized the limitations of these studies and suggested further long term clinical research to evaluate this issue [141]. Other studies did not show an increased risk of cancer with use of analogues [142, 143].

Similar to intermediate acting insulin, premixed human insulin is associated with considerable variable onset and duration of action and variable peak insulin level as well as lacking flexibility in terms of insulin requirement [106, 109]. These problems may deter the prescribing of this combination agent in this population. With the decline in the prescribing of premixed human insulin combinations, there is an increasing trend towards prescribing of basal bolus regime using insulin analogues. The combination of insulin glargine and insulin lispro as well as combination of insulin detemir and insulin aspart have been shown to improve overall glycaemic control and reduce nocturnal hypoglycaemia in patients with type 1 diabetes compared to combination human insulin [144, 145].

Gender, age and community drug schemes variations

Variations in the prescribing of antidiabetic agents in the diabetic population were observed across gender, age groups and drug schemes. Inequalities in the prescribing of preventative cardiovascular therapies in patients with diabetes have been described previously in Ireland [146]. In the adult population, males, older patients and those eligible under the GMS schemes were less likely to be prescribed the newer more expensive insulin analogues. Pharmaceutical marketing may account for the differential preferences in the prescribing of insulin in this population. Both short- and long-acting insulin analogues have been shown to reduce hypoglycaemic events which are more frequently a problem in the elderly compared to human insulin [145]. Some may prefer to continue prescribing human insulin in older patients as no significant differences of glycaemic control was observed between analogues and human insulin [107, 126, 136]. There were also insufficient data to compare insulin analogues to human

insulin in terms of reducing long term diabetes-related complications or mortality [126]. Premixed insulin is favoured for patients with type 2 diabetes instead of the basal bolus regime, thus the higher prescribing of this agent in the elderly population may in actual fact represent patients with type 2 diabetes who have switched to insulin therapies only [147].

The safety of insulin in pregnancy needs to be considered in female patients of reproductive age. Human insulin is generally considered safe to be used in pregnancy [148]. Insulin aspart was associated with fewer foetal losses and preterm delivery compared to human insulin [149]. Insulin lispro was not shown to cross the placenta [150] and no significant differences were observed between insulin lispro and human insulin for both maternal and foetal outcome in pregnant women [132]. Insulin glargine was not recommended previously for pregnant women but recent population based studies have demonstrated that the incidence of congenital malformation were similar to human insulin [151]. At present, no published data are available on the use of the newer insulin analogues, insulin detemir and insulin glulisine in pregnancy [151].

In the paediatric population, treatment of type 1 diabetes is more challenging as paediatric patients are more likely to have unpredictable meal and sleep times, lack of ability for self-care, the need for supervision outside home, limited sites for insulin injection, increased insulin sensitivity, neurological vulnerability to hypoglycaemia and frequent infectious disease [152]. Insulin treatment may be perceived as complex and inconvenient due to multiple injections and dose adjustment required in addition to the constant need for glucose monitoring and lifestyle changes to be made [152]. The transition from childhood to adolescent in patients with type 1 diabetes is also associated with changing insulin sensitivity related to sexual maturity and physical growth, reduced adherence to treatment and concurrent psychological disorders [152, 153]. Psychological disorders such as mood disorders, anxiety, eating problems and depression are frequently reported in adolescents with type 1 diabetes [154]. Pre or postprandial short-acting insulin analogues allows flexibility in adjusting insulin therapy in the paediatric population [155]. In the adolescent population, insulin glargine was associated with greater treatment satisfaction compared to human insulin [128]. The weight gain observed with insulin therapy is also a barrier in the treatment of type 1 diabetes especially in the adolescent population. In this regards, insulin detemir, with its weight sparing effect is a promising agent for use in adolescents [156].

Although patients eligible under the GMS scheme represent those with lower socioeconomic background (less than 70 years old) compared to those eligible under the LTI schemes, patients under both schemes are able to obtain their antidiabetic medications free of charge. Thus, no differences in prescribing should be observed between these two schemes. However, there was a higher prescribing of the more expensive insulin analogues in those eligible

under the LTI schemes, in both paediatric and adult populations, compared to those eligible under the GMS scheme. Previous study did not show significant difference in the prescribing of cardiovascular medications in people with diabetes between the two schemes [146]. The findings in this study are consistent with studies performed using the NHS in England whereby inequalities in diabetes care and treatment across socio-economic status were observed despite provision of equal access for all patients with diabetes by the government [157]. Diabetes-related hospital admission, cardiovascular events and mortality are more common in patients with diabetes of lower socioeconomic status [158-161]. A study in Canada show that those with lower socioeconomic status are more likely to be referred to diabetes care services and this may be attributable to higher burden of disease in these patients [162]. In England, increases in the prescribing of insulin was significantly higher in those with lower compared to higher socioeconomic status [157]. Studies have shown that different clinical outcomes still persist despite improvement in the equality of care across socioeconomic status [160, 163]. Thus universal health care system itself may not address inequalities in diabetes care and outcomes [157]. Patients with higher socioeconomic status were shown to be more willing to pay significantly more for better glucose control and to avoid adverse events compared to those with lower socioeconomic status [164]. Prescribers have to weigh the higher cost and the overall benefits of insulin analogues compared to human insulin when choosing insulin therapy to be prescribed. Diabetes specialists may have a role in tackling inequalities in diabetes care by providing equitable and cost-effective treatments as well as education to patients with diabetes [165]. Comprehensive home and community based interventions has been shown to improve clinical outcomes in adolescents with poorly controlled type 1 diabetes from lower socioeconomic status [166].

Regional variations in the prescribing of insulin

Regional variation was observed in the prescribing of insulin especially in the uptake of the newer and more expensive insulin analogues in this study. Regional variation had also been observed previously in the prescribing of cardiovascular therapies for patients with and without diabetes [48]. This may be partly explained by random variation due to small number of patients with type 1 diabetes especially in paediatric population. The choice of insulin may depend on local professional expertise, the provision of support in the hospital and primary care settings and individual preferences of both patients and the diabetes care team [167]. In addition, variations in prescribing may reflect the differences in the clinical need of the population [168].

Due to the large numbers of general practitioners (GPs) and hospital clinicians within a health region, it is not possible to explain these variations in terms of individual clinician behaviour. In the neighbouring UK, the prescribing of new drugs in the population by GPs was

influenced by the type of drug and the perceived risk. Some GPs are more receptive to change than others [169] and an individual GPs early experience of using particular drugs may strongly influence their subsequent prescribing [170]. It was also shown that those who prescribe new drugs early after its introduction to the marker have larger lists of patients and rely on pharmaceutical information compared to those who prescribe these drugs later in their practice [171]. Pharmaceutical marketing has also been shown to contribute greatly to better awareness of a new drug in the market [172]. Influences of pharmaceutical marketing especially with the newer insulin analogues where evidence of superiority is still lacking may explain the variations in the prescribing of the different long- and short acting insulin analogues in this population [48].

Variations in the prescribing of antidiabetic drugs have been shown in two neighbouring towns in Sweden where it was suggested that prescribing may be influenced by differences in practice between specialized diabetes clinicians and non-specialist clinicians [173]. The interface between secondary and primary care is also important in terms of prescribing and hospital clinicians may influence prescribing in primary care. Clinical specialists have been shown to be influenced by research evidence and scientific meetings [170]. Initiation of a new drug by hospital consultants influences its future use by GPs [170]. This may partly explain the consistently higher prescribing of the different insulin analogues in the Eastern, Midland, Southern and Western regions where the major teaching hospitals are located and, in the case of the Midland region, where shared care practices are in place.

The variations between regions may also be due to differences in the socioeconomic status as described above. Only a quarter of population in the Eastern regions were covered under the GMS scheme compared to nearly half in the North Western region and approximately a third of population in other regions [6]. The differences in drug budgeting between health regions may also influence the prescribing especially for newer and more expensive drugs.

Future direction for treatment of type 1 diabetes

With lessons learned from the fate of Exubera, attempts at developing inhaled insulin were abandoned with the exception of technosphere insulin [174]. In contrast to Exubera, technosphere insulin is designed to be more user friendly and is shown to be safe in terms of pulmonary function to date [175]. However, technosphere insulin is still at clinical trial stage in 2010 [176]. Although many different oral insulin formulations were tested in animal studies, currently oral insulin has yet to make it to clinical studies [174]. Islet cell transplant was demonstrated to be a successful procedure in 2000, however, this technology has not taken off in Europe. In patients who have undergone islet cell transplant, 85% had to be reinstituted with insulin treatment, albeit with lower requirement, with time to insulin of around 15 months [177]. Patients also have to be prescribed immunosuppressants to avoid rejection problems [177]. Stem

cell therapy held the promise of novel approach in future treatment of type 1 diabetes with the advantage of no risk to donor and low risk of rejection compared to islet cell transplant. However, stem cells have limited availability and more clinical research is needed in this area [178].

Isolated emphasis on insulin treatments and delivery systems has limited potential in the management of paediatric with type 1 diabetes and psychosocial issues needs to be tackled as part of diabetes care [179]. Special attention to aspects such as family dynamics, pubertal changes and other psychological issues are essential in management of paediatric patients [152]. Family based psychosocial interventions, educational summer camps, coping skills training can be utilized to optimize glycaemic controls in these patients [180-182].

Strengths and limitations

Compared to other studies on utilization of antidiabetic agents [121, 183] this study is able to capture the prescribing of insulin therapy at individual levels of prescription. As such, prescribing of insulin was able to be examined across age, gender, regions and drug schemes. This allows variations and inequalities in the prescribing to be examined in this population. This study, however, is limited to only data up to 31st December 2007 and thus the trends in the prescribing of newer agents such as premixed insulin analogues may not be representative. Due to limitations in the database, the prescribing of CSII in this population was not examined.

As diagnostic information and clinical information are not available in the prescribing database, therefore the possible reasons for initiation and changes of different insulin regimes in individual patients cannot be determined. As such, the variations observed in insulin prescribing may simply be due to the different burden of type 1 diabetes in different individuals. In addition, the differences in the prescribing for diabetes were only examined according to the eight health regions and not smaller local areas. Thus the influence of local socioeconomic on prescribing was not able to be examined. The cost-effectiveness analysis of the different insulin types in order to allow comparisons between these agents to be more accurately made in this population was not performed.

This study was able to capture all insulin prescribing in the Irish population and thus accurately reflect the prescribing of insulin at the primary care level. Health care providers should be aware of the changing trends in the prescribing of insulin and the inequalities in the prescribing of insulin in this population. Education and training on evidence-based therapies should be made accessible to health care providers to counter the influence of pharmaceutical marketing especially in the prescribing of the newer and more expensive insulin. This would help to ensure that all patients receive evidence-based treatment irrespective of gender, age, socioeconomic status and geographical location.

4.2 Trends in the prescribing of antidiabetic therapies in patients with type 2 diabetes

4.2.1 Background

Metformin and sulphonylureas have been used extensively in patients with type 2 diabetes before the emergence of new classes of drugs such as α-glucosidase inhibitors, thiazolidinediones (glitazones), meglitinides, dipeptidyl-peptidase-4 (DPP-4) inhibitors and glucacon-like-peptide-1 (GLP-1) receptor agonists. Biguanides were developed during the 1950s from the plant, *Galega officinalis,* historically used for the treatment of diabetes in Europe. Most biguanide agents were associated with increased risk of lactic acidosis resulting in the withdrawal of these agents in the 1970s except for metformin [184]. Metformin improves peripheral tissue sensitivity to insulin [185] and improves glucose metabolism by reducing hepatic glucose production and gastrointestinal glucose absorption [186]. Sulphonylureas as insulin secretagogues have also been around as treatment of type 2 diabetes since 1954 [14]. Sulphonylureas stimulate insulin secretion from beta-cells in pancreas by binding to the sulphonylurea receptor (SUR-1) therefore are dependent on adequate beta cell functions. Second-generation sulphonylureas were developed in the 1970s, for example, glibenclamide, gliclazide and glipizide to replace the older generation sulphonylureas such as tolbutamide, chlorpropamide and tolazamide while glimepiride was introduced in late 1990s [13, 14].

The search for better insulin secretagogues for diabetes patients led to the discovery of the meglitinides, the non-sulphonylureas component of glibenclamide. Derivatives of meglitinides were developed such as repaglinide and nateglinide; these bind to the SUR1 receptor of the beta cells at a site distinct from sulphonylureas. These agents are also known as prandial insulin releasers due to the rapid but short lived insulin secretion stimulated by these agents post-meal [187]. Acarbose, introduced in early 1990s was the first of α-glucosidase inhibitors and the only one available in Ireland. This agent inhibits the intestinal α-glucosidase enzymes in the intestine resulting in delayed rate of glucose absorption and thus reduces postprandial hyperglycaemia [188]. Thiazolidinediones, also known as glitazones, (insulin sensitizing agents), were introduced in the late 1990s and act via stimulation of a nuclear receptor peroxisome proliferator-activated receptor δ (PPARδ). By binding to this nuclear receptor glitazones can affect a number of different genes regulating glucose and fat metabolism especially in adipose tissues, liver and skeletal muscle. The first glitazone on the market, troglitazone had to be withdrawn due to concerns about fatal liver toxicity. Liver toxicity was not an issue with the later glitazone agents, pioglitazone and rosiglitazone. Recent interests have emerged in determining the safety risks associated with rosiglitazone and pioglitazone in the general diabetic population [15, 189].

Incretin hormones such as Gastric Inhibitory polypeptide (GIP) and glucagon-like-peptide-1 (GLP-1) are responsible for augmentation of insulin response induced by a meal. Thus incretin hormones are suitable targets to reduce postprandial hyperglycaemia in patients with type 2 diabetes. The GLP-1 receptor agonist such as exenatide works as an incretin mimetic and was isolated from the salivary gland of the *gila* monster, a lizard found in the deserts of Arizona. Exenatide was only approved in Europe in late 2006 and can only be administered as subcutaneous injection while liraglutide was a more recent incretin mimetic in the market. Recent safety concerns have emerged linking exenatide to increased risk of pancreatic cancer. DPP-4 inhibitors such as sitagliptin and vildagliptin were developed to prolong the duration of incretin hormones action in the body by preventing degradation of incretin hormones by DPP-4 enzyme.

No significant differences were observed in the reduction of HbA1c level as a marker of glucose control between the different oral antidiabetic agents with the exception of alpha glucosidase inhibitors [12]. However, antidiabetic agents have different side effect profiles and may have different potential advantages in terms of cardiovascular risk factors modification such as lipid profiles, blood pressure control and overall reduction in cardiovascular events [12, 14]. As diabetes progresses with worsening of insulin resistance and reduced insulin secretion, the need for early introduction of combination oral agents or insulin has been recognised when treatment with monotherapy agent has failed [190]. Fixed-combinations are also available to enhance adherence to treatment. Some patients may need to be treated with insulin alone at later stages of their diabetes when beta cell functions are exhausted.

The choice of agents for patients with type 2 diabetes and the factors influencing prescribing will be examined in this study in light of recent developments in relation to antidiabetic agents. The prescribing of combination agents and insulin therapies and the time to initiation of these agents in newly treated type 2 diabetes will also be determined as a marker of glucose control. The pattern of glucose monitoring kits prescribing in patients with type 2 diabetes will be examined to determine the preference of practitioners regarding these.

4.2.2 Specific objectives

1) To examine the prescribing trends of antidiabetic therapies in the adult population with type 2 diabetes from 2003 to 2007

2) To examine the choice of antidiabetic therapies in adults with newly treated type 2 diabetes from 2004 to 2007

3) To examine the variations in the prescribing of antidiabetic therapies in patients with type 2 diabetes across age groups, gender, drug schemes, cardiovascular comorbidities and health regions.

4) To examine the time to initiation of combination of oral antidiabetic agents or insulin and switching of oral antidiabetic agents in patients with newly treated type 2 diabetes

4.2.3 Methods

4.2.3.1 Trends in the prescribing of antidiabetic therapies in prevalent type 2 diabetes patients

Adult patients with treated type 2 diabetes were identified according to the methods described in section 3.1.3.1. Classes of oral antidiabetic agents examined were biguanides, sulphonylureas, glitazones, α-glucosidase inhibitors, meglitinides, DPP-4 inhibitors, GLP-1 inhibitors and fixed oral combination agents. Prescribing of insulin and glucose monitoring kits were also examined in the cohort of patients with type 2 diabetes. Individual oral antidiabetic agents and combination therapies were also identified. The individual agents examined were metformin, glimepiride, gliclazide, glibenclamide, glipizide, acarbose rosiglitazone, pioglitazone, repaglinide, nateglinide, sitagliptin and exenatide.

The percentages of patients with type 2 diabetes prescribed different classes of antidiabetic therapies, individual monotherapy agents, oral combination therapies, insulin and glucose monitoring kits were calculated in the 5-year period. The prescribing trend of antidiabetic agents over time was examined using logistic regression analysis.

4.2.3.2 Trends in the prescribing of antidiabetic therapies in newly treated type 2 diabetes patients

Patients with newly treated type 2 diabetes were identified using the methods described in section 3.1.3.2. The choice of antidiabetic agents at initiation of diabetes treatment was examined and statistical analysis was performed similar to the methods described in section 4.2.3.1.

4.2.3.3 *Time to switching of therapies, combination oral therapies and addition of insulin in newly treated type 2 diabetes patients*

Patients with newly treated type 2 diabetes in the adult population were identified using the methods described in section 3.1.3.2. Patients were followed up from the first antidiabetic treatment until (1) switching of prescription to another oral antidiabetic agents (2) addition of another oral antidiabetic agent (3) addition of insulin (4) replacement of oral antidiabetic agent with insulin or (5) end of study period by 31st December 2007. Kaplan-Meier Survival analysis was used to determine the time to switching of therapies, either combination oral agents or insulin prescribing in patients with newly treated type 2 diabetes.

4.2.4 Results

4.2.4.1 *Trends in the prescribing of antidiabetic therapies in patients with prevalent type 2 diabetes*

Overall trend

An increased rate of metformin prescribing in patients with type 2 diabetes was observed while the prescribing of sulphonylureas decreased over the 5-year period ($p<0.0001$) in this population (Figure 4.2.1). Prescribing of glitazones increased until 2005 and then declined afterwards ($p<0.0001$). Less than 10% of patients with type 2 diabetes were prescribed other oral antidiabetic agents although there was a significant increase in patients were being prescribed fixed combination agents during the study period ($p<0.0001$). In the cohort of patients prescribed monotherapy only, the prescribing of metformin as monotherapy agent increased significantly from half of patients with type 2 diabetes in 2003 to two third of patients in 2007 (Figure 4.2.2). The prescribing of monotherapy sulphonylurea on the other hand decreased from half of patients with type 2 diabetes in 2003 to only a third of patients in 2007. Less than two percent of patients were prescribed monotherapy of antidiabetic agents other than metformin and sulphonylureas. In the cohorts of patients prescribed sulphonylureas, the agent of choice was gliclazide (Figure 4.2.3) and in those prescribed glitazones, the agent of choice was rosiglitazone (96%). However, the prescribing for pioglitazone significantly increased over the study period ($p<0.0001$) especially after the decline in rosiglitazone prescribing after 2005.

There was a significant increase in the prescribing of oral antidiabetic combination therapies and insulin ($p<0.0001$) in patients with type 2 diabetes over the years (Figure 4.2.4). In 2007, nearly half of those being prescribed combination therapy in the same prescription form received metformin and sulphonylureas (Figure 4.2.5). The prescribing of glucose monitoring kits

had also increased in patients with type 2 diabetes (61% in 2003, 70% in 2007, $p<0.0001$). In the cohort of patients prescribed both oral antidiabetic agents and insulin, metformin and insulin was the first choice combination during the study period (Figure 4.2.6). Some 4% of patients were prescribed the combination of glitazone and insulin in 2007. In 2003, the most prescribed insulin in this group was premixed fast-and intermediate-acting insulin (Figure 4.2.7). However, in 2007, the most prescribed insulin in this group was long-acting insulin and only a third of patients were being prescribed premixed insulin. Two thirds of patients on combination were prescribed human insulin in 2003 and this figure decreased by just one fifth of patients in 2007 (Figure 4.2.8). 90% of patients in this cohort were also prescribed glucose monitoring kits in 2007.

Regional variation

Consistent with the national trends in the prescribing of oral antidiabetic agents, there was an increase in the prescribing of metformin (Figure 4.2.9) and decrease in the prescribing of sulphonylureas (Figure 4.2.10) in adults with type 2 diabetes across all regions. In 2003, both metformin and sulphonylureas were being prescribed in some two thirds of patients with diabetes in most regions. The Eastern region had the highest percentage of patients prescribed metformin back in 2003 while the Western region had the highest percentage of patients prescribed sulphonylureas. In 2003, more than five percent of patients were being prescribed glitazones in all regions with some ten percent of patients being prescribed glitazones in the North Western region (Figure 4.2.11). In 2007, most regions prescribed glitazones to less than ten percent of patients. Less than five percent of patients were being prescribed other oral antidiabetic agents across the country during the study period. An increase in the prescribing of fixed combination oral antidiabetic agents were observed in all regions with the highest percentage observed in the Southern region (Figure 4.2.12).

Compared to the Eastern region, patients from most other regions with the exception of the South Eastern region were less likely to be prescribed metformin (Table 4.2.1). Those from the Midland, North Eastern and the Western region were more likely to be prescribed sulphonylureas while those from the rest of the country were less likely to be prescribed sulphonylureas compared to the Eastern region. Glitazones were more likely to be prescribed to patients from the North Western and Southern region compared to the Eastern region and less likely to be prescribed to patients from the Midland, North Eastern and Western regions. Patients from most regions were more likely to be prescribed other oral antidiabetic agents compared to those from the Eastern region (Appendix 1). The same pattern was also observed in the prescribing of fixed combination agents with the exception of the North Eastern and South Eastern regions. In comparison to patients from the Eastern region, patients from other regions were less likely to be prescribed oral combination therapy or insulin except patients from the Midland for oral

combination therapy. Patients with type 2 diabetes from other regions in the country were less likely to be prescribed glucose monitoring kits compared to patients from the Eastern region.

Gender, age and drug scheme variation

As for patients with type 1 diabetes, there were also gender and age variations in the prescribing of antidiabetic agents in patients with type 2 diabetes in Ireland (Table 4.2.1). Female patients were more likely to be prescribed metformin and glitazones but less likely to be prescribed sulphonylureas compared to males. Metformin was significantly less likely to be prescribed while sulphonylureas were more likely to be prescribed in those aged ≥ 45 when compared to younger patients aged 16-44 years old. Those aged over 65 years were also less likely to be prescribed glitazones and fixed combination agents compared to younger patients. Patients eligible under the LTI scheme were more likely to be prescribed the newer and more expensive agents such as glitazones, meglitinides and incretin modulators compared to GMS patients.

Females were less likely to be prescribed oral antidiabetic combination therapy compared to males though they were more likely to be prescribed insulin (Table 4.2.2). Those 45 years and over were more likely to be prescribed combination therapy compared to younger patients but less likely to be prescribed insulin in combination with oral antidiabetic agents. Those eligible under the LTI scheme were more likely to be prescribed both oral combination therapy and insulin compared to patients eligible under the GMS scheme. With regards to the prescribing of glucose monitoring kits in type 2 diabetes patients, females and those 45 years and over were more likely to be prescribed the kit compared to males and younger aged patients. Those eligible under the LTI scheme were more likely to be prescribed glucose monitoring kits compared to GMS patients.

Figure 4.2.1: Trends in the prescribing of oral antidiabetic agents in patients with type 2 diabetes from 2003 to 2007 (note: patients may be prescribed ≥ one medication in a year)

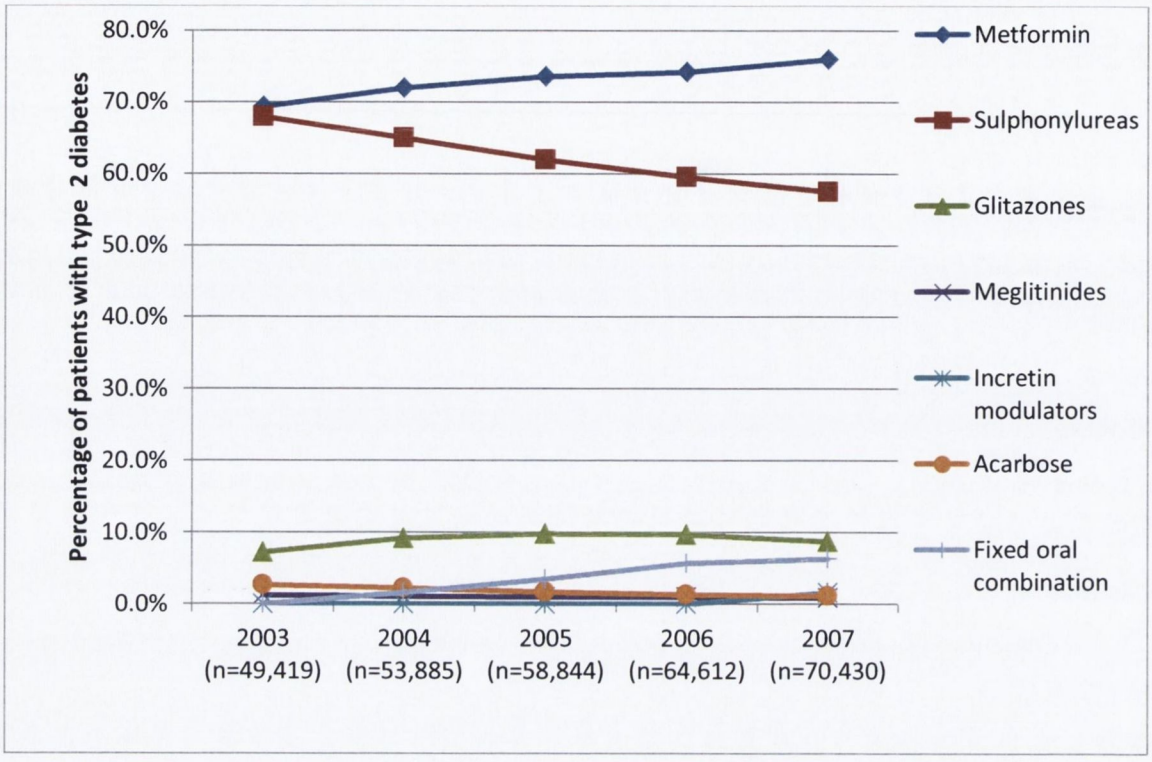


Figure 4.2.2: Choice of antidiabetic agents in patients with type 2 diabetes prescribed monotherapy only from 2003 to 2007

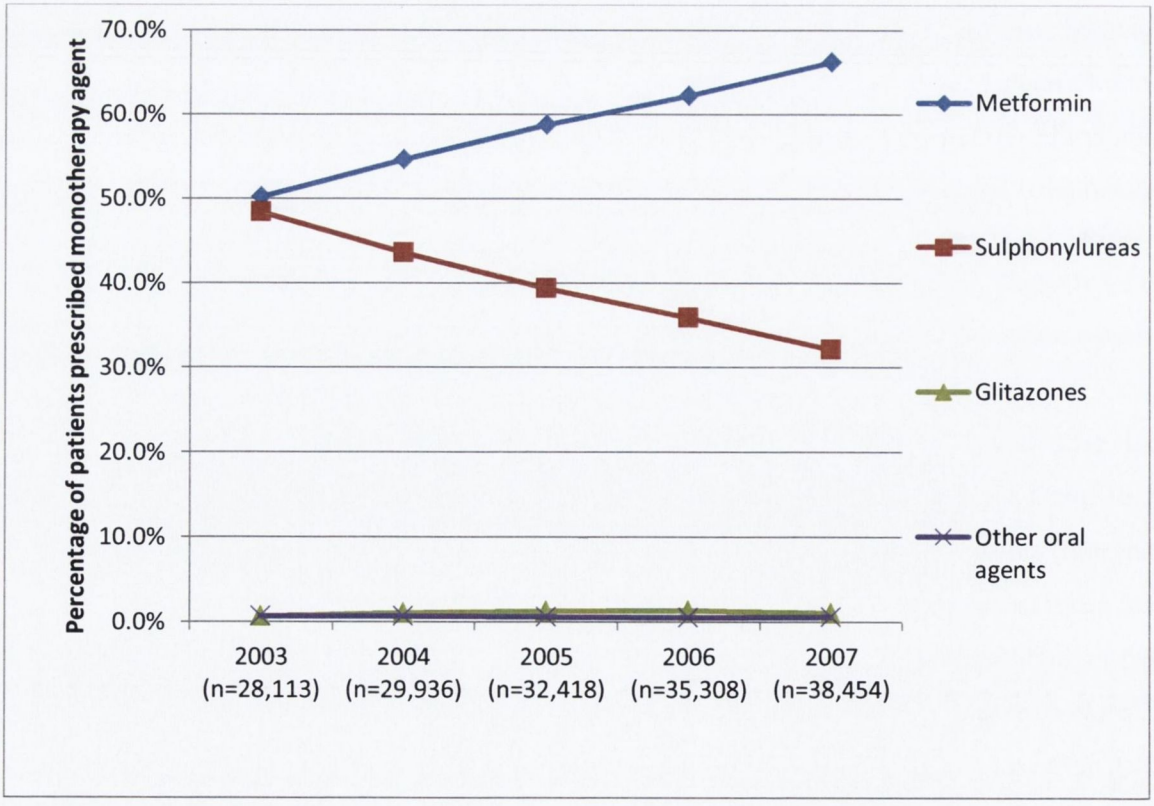


Figure 4.2.3: Choice of sulphonylurea agent in patients with type 2 diabetes prescribed this agent from 2003 to 2007 (note: patients may be prescribed ≥ one medication in a year)

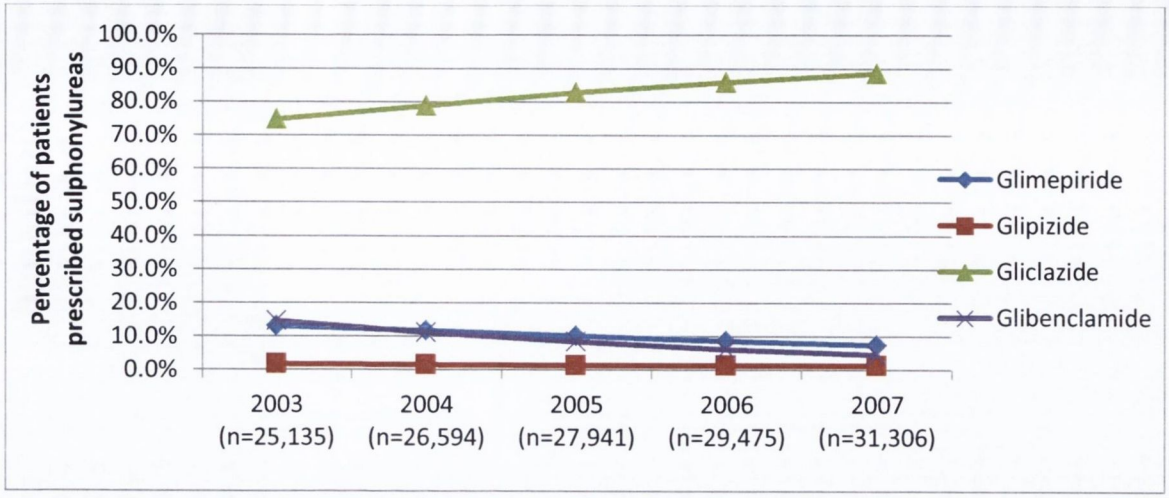


Figure 4.2.4: Trends in the prescribing of oral antidiabetic combination therapies and insulin in patients with type 2 diabetes from 2003 to 2007

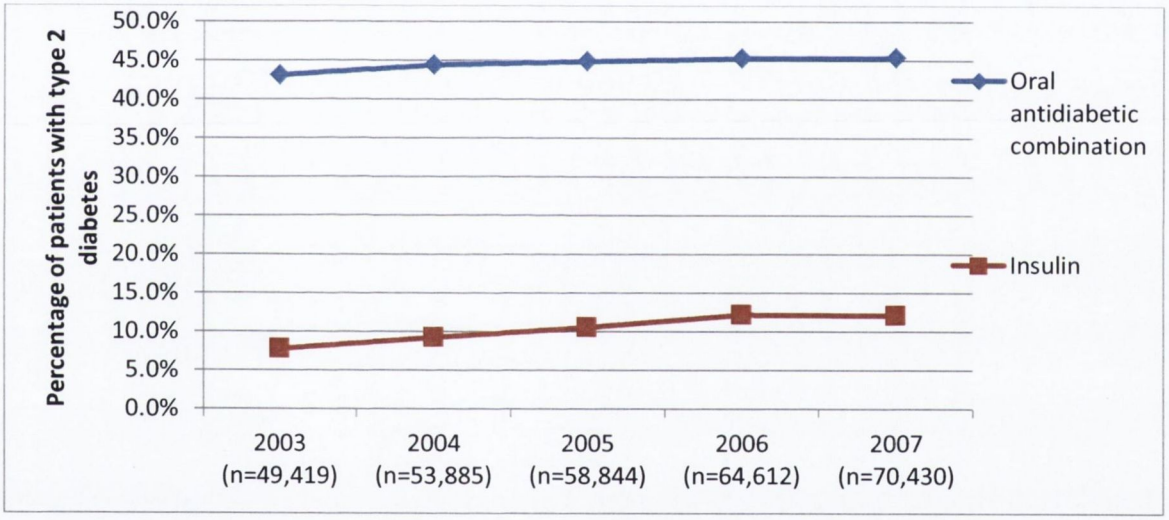


Figure 4.2.5: Choice of combination in the cohort prescribed double oral antidiabetic agents in the same prescription claim form from 2003 to 2007

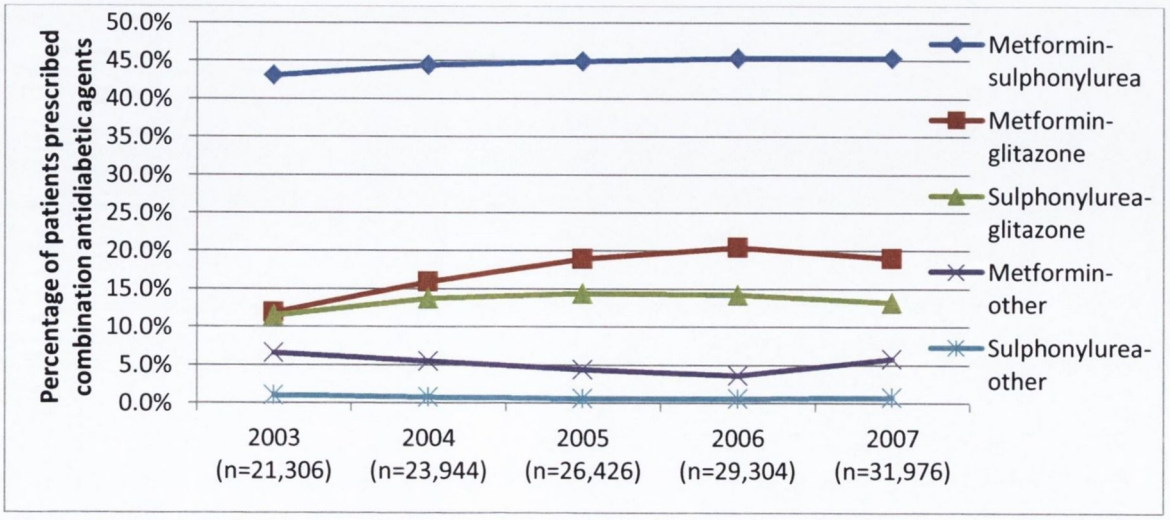


Figure 4.2.6 : Choice of combination in the cohort with type 2 diabetes prescribed both oral antidiabetic agents and insulin in the same prescription claim form from 2003 to 2007

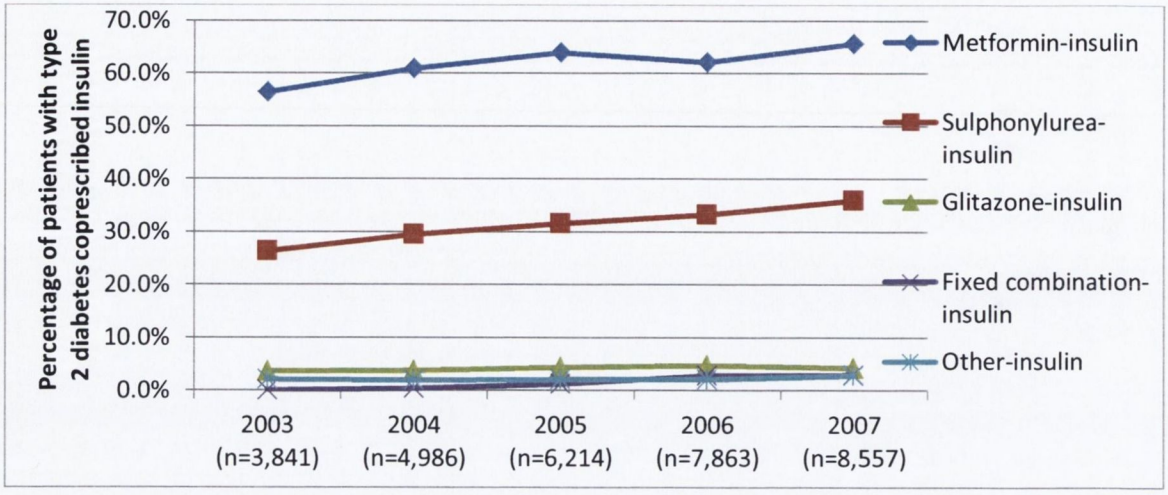


Figure 4.2.7: Choice of insulin preparation in the cohort of patients with type 2 diabetes prescribed insulin from 2003 to 2007 (note: patients may be prescribed ≥ one medication in a year)

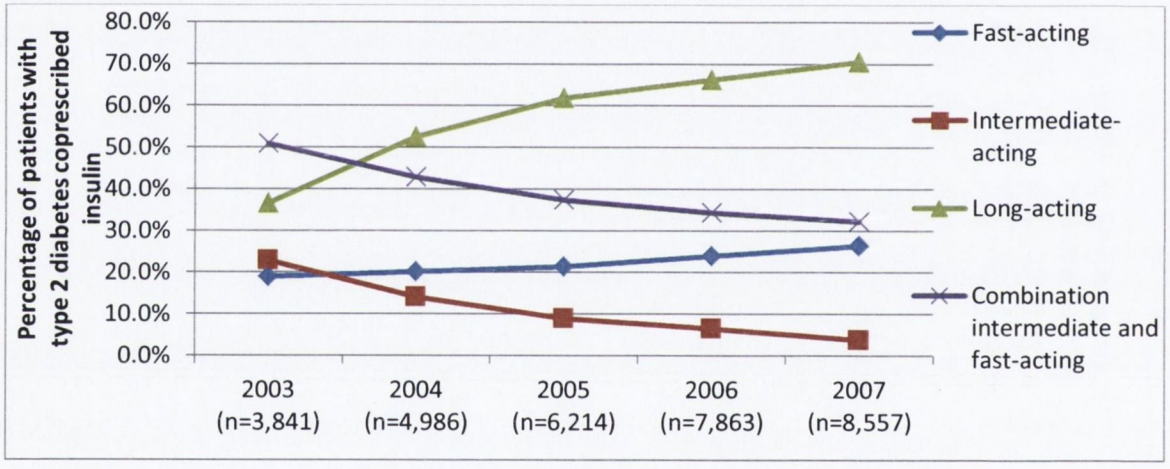


Figure 4.2.8: Choice of insulin types in the cohort with type 2 diabetes prescribed insulin from 2003 to 2007 (note: patients may be prescribed ≥ one medication in a year)

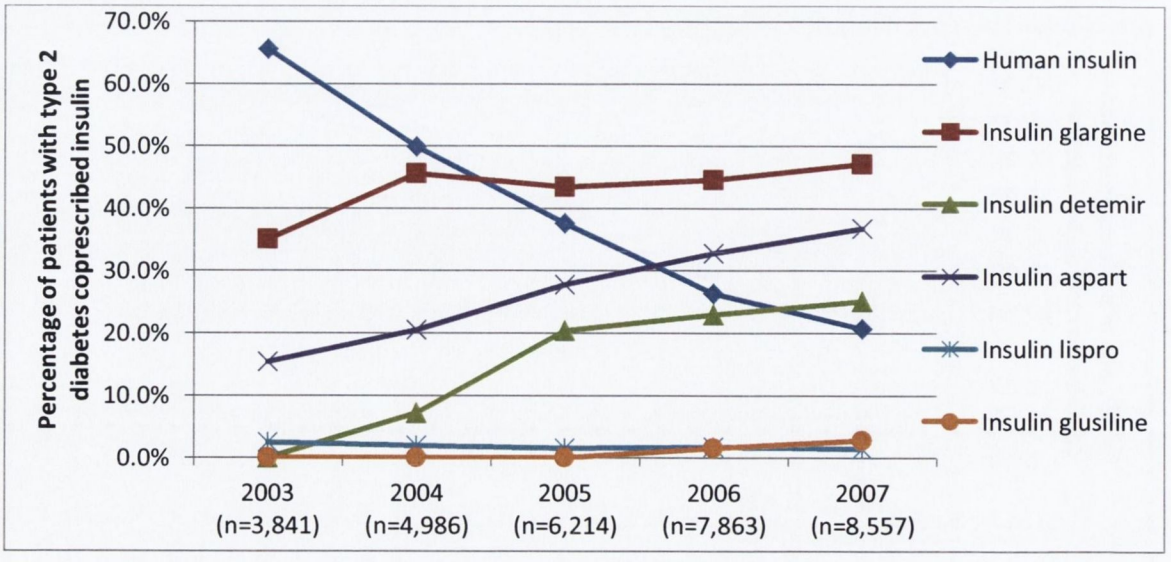


Figure 4.2.9: Trends in the prescribing of metformin in patients with type 2 diabetes according to health regions from 2003 to 2007 (note: patients may be prescribed ≥ one medication in a year)

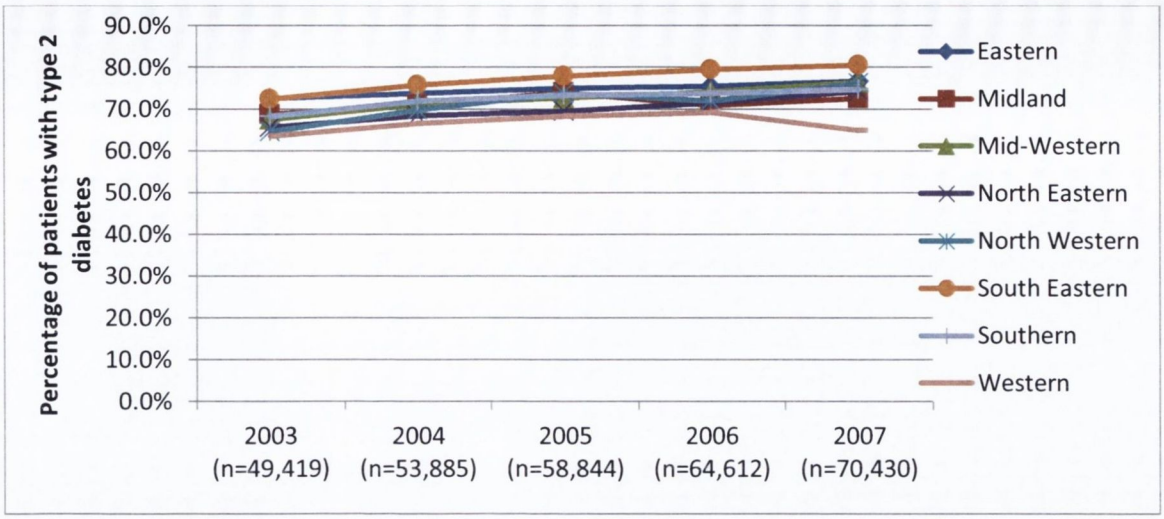


Figure 4.2.10: Trends in the prescribing of sulphonylureas in adults with type 2 diabetes according to health regions from 2003 to 2007 (note: patients may be prescribed ≥ one medication in a year)

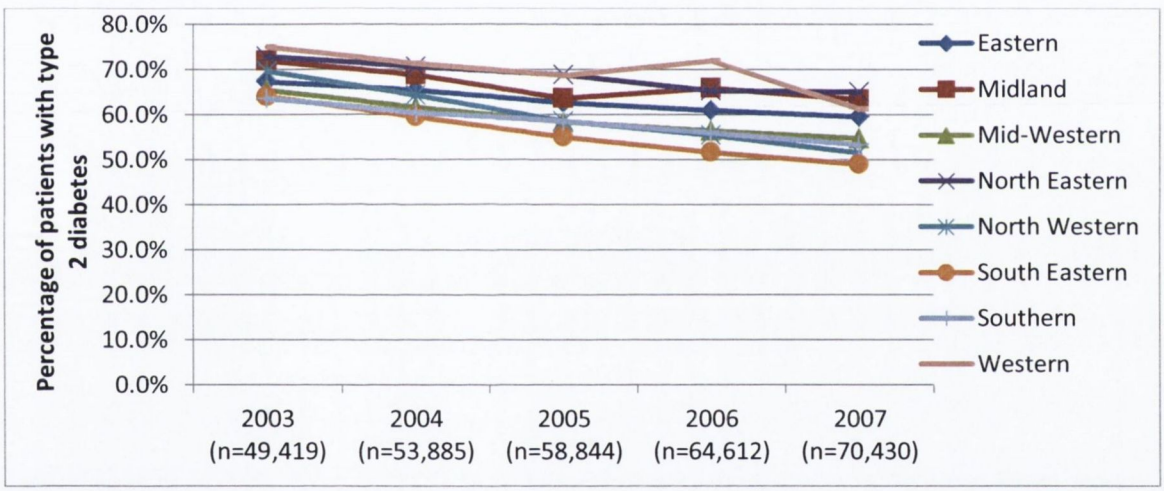


Figure 4.2.11: Trends in the prescribing of glitazones in patients with type 2 diabetes according to health regions from 2003 to 2007 (note: patients may be prescribed ≥ one medication in a year)

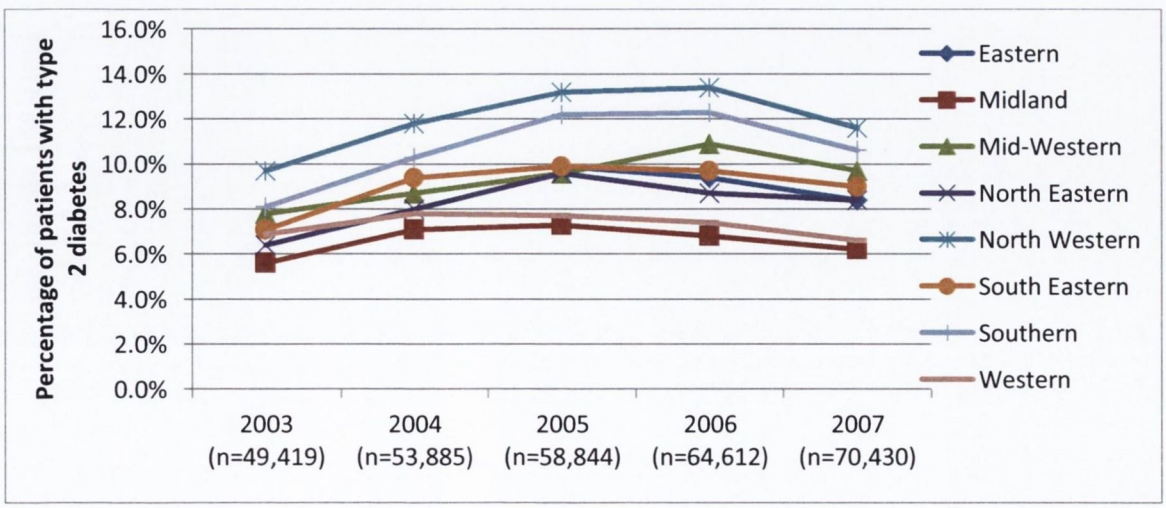


Figure 4.2.12: Trends in the prescribing of fixed combination therapies in patients with type 2 diabetes according to health regions from 2003 to 2007 (note: patients may be prescribed ≥ one medication in a year)

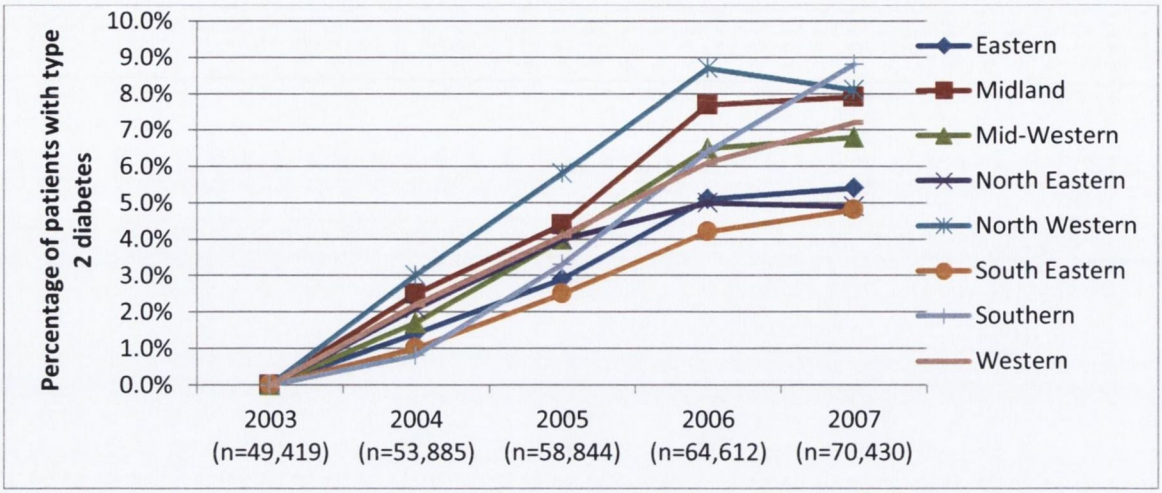


Table 4.2.1: Variations in the prescribing of oral anti-diabetes therapies for adult type 2 diabetes patients presented as adjusted OR with 95 % CI

Patient characteristics		Metformin OR† (95% CI), p	Sulphonylurea OR† (95% CI), p	Glitazones OR† (95% CI), p
Gender□	Female (n=44,219)	1.06 (1.05,1.08) ***	0.87 (0.85,0.88) ***	1.08 (1.05,1.11) ***
Age group◊	45-64 (n=22,845)	0.85 (0.82,0.88)***	1.78 (1.72,1.83)***	1.18 (1.12,1.24)***
	>65 (n=47,519)	0.52 (0.50,0.54)***	2.59 (2.51, 2.67)***	0.94 (0.89,0.99)*
Drug scheme¥	LTI (n=23,859)	1.11 (1.09,1.13)***	0.99 (0.97,1.01) ns	1.20 (1.16,1.24)***
Health region∞	Midland (n=7,386)	0.76 (0.73,0.78)***	1.30 (1.26,1.34)***	0.70 (0.66,0.74)***
	Mid-Western (n=7,392)	0.83 (0.81,0.86)***	0.87 (0.86,0.91)***	1.01 (0.96,1.06)ns
	North Eastern (n=5,388)	0.73 (0.71,0.75)***	1.33 (1.29,1.38)***	0.85 (0.80,0.89)***
	North Western (n=4,836)	0.81 (0.78,0.84)***	0.88 (0.85,0.91)***	1.35 (1.28,1.42)***
	South Eastern (n=9,645)	1.07 (1.04,1.11)***	0.76 (0.75,0.78)***	0.96 (0.92,1.00) ns
	Southern (n=11,149)	0.84 (0.82,0.86)***	0.84 (0.82,0.86)***	1.19 (1.14,1.23)***
	Western (n=7,169)	0.68 (0.66,0.70)***	1.30 (1.26,1.34)***	0.80 (0.73,0.81)***

† Adjusted for gender, age groups, drug schemes, calendar years and health regions
□ Reference category males (n=56,902)
◊ Reference category age 16-44 years (n=7,441)
¥ Reference category GMS scheme (n=77,805)
∞Reference category Eastern region (n=48,699)

Table 4.2.2: Variations in the prescribing of oral combination therapies and insulin in adults with type 2 diabetes presented as adjusted OR with 95% CI

Patient characteristics		Oral combination therapy OR† (95% CI), *p*	Insulin OR† (95% CI), *p*	Glucose monitoring kits OR† (95% CI), *p*
Gender□	Female (n=44,219)	0.94 (0.93,0.95)***	1.06 (1.03,1.09)***	1.04 (1.02,1.06)***
Age group◊	45-64 (n=22,845)	1.42 (1.38,1.47)***	0.56 (0.54,0.59)***	1.11 (1.08,1.15)***
	>65 (n=47,519)	2.01 (1.83,2,20)***	0.72 (0.63,0.82)***	2.81 (2.58,3.06)***
Drug scheme¥	LTI (n=23,859)	1.20 (1.17,1.22)***	1.27 (1.24,1.31)***	1.90 (1.85,1.94)***
Health region∞	Midland (n=7,386)	1.03 (1.00,1.22)*	0.87 (0.83,0.91)***	1.02 (0.99,1.05) ns
	Mid-Western (n=7,392)	0.83 (0.81,0.85)***	0.53 (0.51,0.56)***	0.59 (0.58,0.61)***
	North Eastern (n=5,388)	0.98 (0.95,1.01)ns	0.59 (0.56,0.62)***	0.89 (0.87,0.92)***
	North Western (n=4,836)	0.91 (0.88,0.94)***	0.70 (0.67,0.74)***	0.52 (0.50,0.53)***
	South Eastern (n=9,645)	0.83 (0.81,0.85)***	0.60 (0.62,0.68)***	0.86 (0.83,0.88)***
	Southern (n=11,149)	0.84 (0.82,0.86)***	0.65 (0.62,0.68)***	0.57 (0.55,0.58)***
	Western (n=7,169)	0.95 (0.92,0.97)**	0.61 (0.58,0.64)***	0.65 (0.63,0.67)***

† Adjusted for gender, age groups, drug schemes, calendar years and health regions
□ Reference category males (n=56,902)
◊ Reference category age 16-44 years (n=7,441)
¥ Reference category GMS scheme (n=77,805)
∞ Reference category Eastern region (n=48,699)

4.2.4.2 Trends in the prescribing of antidiabetic therapies in newly treated type 2 diabetes patients

Overall trend

In the cohort of adults with newly treated type 2 diabetes, the initial antidiabetic agent of choice was metformin throughout the 4-year study period (Figure 4.2.13). Similar to the trend in prevalent type 2 diabetes, a significant increase in metformin prescribing was observed while there was a decrease in sulphonylurea prescribing ($p<0.0001$) as the initial choice of antidiabetic agent. The prescribing of all other agents including glitazones as initial antidiabetic agents was less than ten percent with a significant decrease in prescribing of glitazones and an increase in the prescribing of fixed combination therapy ($p<0.0001$) during the study period.

Gender, age and drug scheme variation

Females were more likely to be initiated on metformin but less likely to receive sulphonylureas and fixed combination agents compared to males (Table 4.2.3). As in prevalent diabetes, those aged 45 years and above were less likely to be initiated on metformin but more likely to be prescribed sulphonylureas compared to younger adult patients. Those 65 years and over were more likely to be initiated on other agents and less likely to be prescribed fixed combination agents compared to younger patients. Patients with incident diabetes eligible under the LTI scheme were more likely to be initiated with metformin or fixed combination agents but less likely to be prescribed sulphonylureas compared to patients eligible under the GMS scheme.

Regional variations

Patients with incident diabetes in the Midlands, North Eastern and Western regions were less likely to be initiated on metformin but more likely to be initiated on sulphonylureas compared to those from the Eastern region. Those from the South Eastern region were more likely to be started on metformin but less likely to be prescribed sulphonylureas. Those from the North Western and the Southern region were also less likely to be prescribed sulphonylureas compared to the Eastern region. Those from most other regions were less likely to be initiated with glitazones compared to the Eastern region whilst more likely to be initiated with fixed combination agents. Those from South Eastern region were more likely to be initiated on other antidiabetic agents; however, they were less likely to be prescribed fixed combination agents compared to those from the Eastern region.

Figure 4.2.13: Choice of oral antidiabetic agents at initiation of treatment in adults with incident type 2 diabetes (note: patients may be prescribed ≥ one medication in a year)

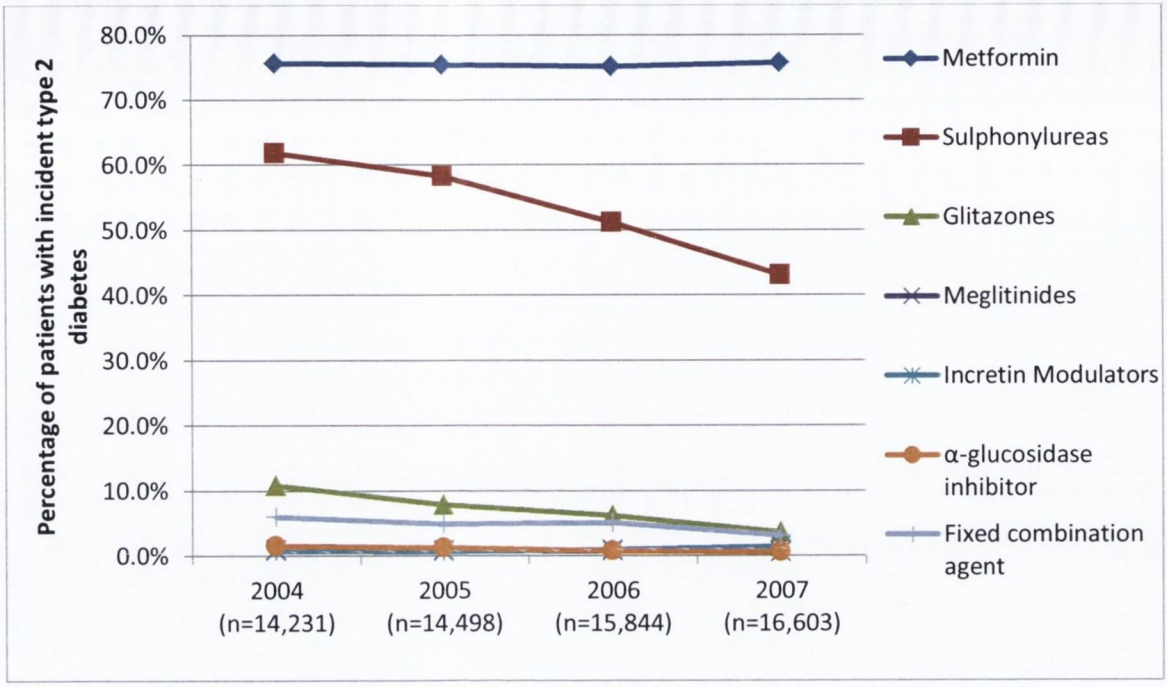


Table 4.2.3: Variations in the prescribing of oral antidiabetic therapies at initiation of treatment in patients with incident type 2 diabetes presented as adjusted OR with 95 % CI

Patient characteristics		Metformin OR†(95% CI), *p*	Sulphonylureas OR†(95% CI), *p*	Glitazones OR†(95% CI), *p*	Other agents OR †(95% CI), *p*
Gender□	Female (n=29,379)	1.04 (1.01,1.08) *	0.84 (0.82, 0.87) ***	1.02 (0.94, 1.10) ns	1.00 (0.88, 1.14) ns
Age group ◊	45-64 (n=25,229)	0.75 (0.71, 0.79) ***	1.35 (1.28, 1.42) ***	0.99 (0.88,1.12) ns	0.89 (0.72, 1.10) ns
	>65 (n=32,529)	0.50 (0.47, 0.53) ***	1.99 (1.89, 2.09) ***	0.94 (0.84, 1.06) ns	1.26 (1.03, 1.55) *
Drug scheme¥	LTI (n=12,564)	1.07 (1.02, 1.13) *	0.91 (0.87,0.95) ***	1.09 (0.98, 1.22) ns	0.84 (0.70, 1.03) ns
Health region∞	Midland (n=7,028)	0.86 (0.81, 0.91) ***	1.47 (1.39, 1.56) ***	0.84 (0.73, 0.96) *	0.99 (0.79, 1.24) ns
	Mid-Western (n=6,689)	0.94 (0.89, 1.00) ns	1.00 (0.95, 1.06) ns	1.00 (0.88, 1.15) ns	1.39 (1.13, 1.72) *
	North Eastern (n=5,279)	0.78 (0.73, 0.83) ***	1.27 (1.20, 1.35) ***	0.71 (0.60, 0.84) ***	0.83 (0.63, 1.09) ns
	North Western (n=3,825)	0.93 (0.87, 1.00) ns	0.72 (0.67, 0.78) ***	1.10 (0.94, 1.29) ns	0.77 (0.56, 1.06) ns
	South Eastern (n=7,990)	1.33 (1.25, 1.41) ***	0.64 (0.61, 0.68) ***	0.78 (0.69, 0.90) **	1.35 (1.12, 1.64) *
	Southern (n=7,521)	1.01 (0.95, 1.07) ns	0.79 (0.75, 0.84) ***	0.81 (0.70, 0.92) *	0.69 (0.53, 0.89) *
	Western (n=6,008)	0.69 (0.65, 0.73) ***	1.15 (1.09, 1.22) ***	0.76 (0.65, 0.88) **	0.71 (0.54, 0.93) *

† Adjusted for gender, age groups, drug schemes, year at initiation of antidiabetic treatment and health regions

□ Reference category males (n=37,497)

◊ Reference category age 16-44 years (n=9,005)

¥ Reference category GMS scheme (n=54,402)

∞Reference category Eastern region (n=22,626)

4.2.4.3 Time to switching of therapies, combination oral therapies and addition of insulin in newly treated type 2 diabetes patients

Overall trend

In patients newly initiated antidiabetic treatment between 2004 and 2007, 16% were switched to another oral antidiabetic agent while 25% were prescribed additional oral antidiabetic treatment as combined therapy. Insulin was added to initial oral antidiabetic treatment in 6% of patients while another 3% of patients were switched to insulin therapy after initial oral antidiabetic treatment. Most patients had an addition of or switched to another agent within three months of initial antidiabetic treatment. The Kaplan-Meier plots of the probability of additional oral antidiabetic or insulin are presented in Figure 4.2.14 and Figure 4.2.15, respectively. Kaplan-Meier plots of the probability of switching to another oral antidiabetic agent or insulin are presented in Figure 4.2.16 and Figure 4.2.17. Those prescribed antidiabetic agents other than metformin were less likely to be added another agent or switched to insulin compared to metformin as initial antidiabetic agent (Table 4.2.4).

Gender, age and drug scheme variation

Female patients with newly treated type 2 diabetes were less likely to be prescribed additional oral antidiabetic therapies compared to males (Table 4.2.4). No significant gender differences were observed in the prescribing of insulin in patients with incident type 2 diabetes. Those over 45 years old were more likely to be prescribed additional oral antidiabetic agents after initial treatment. However, those aged between 45 to 64 years old were less likely to be switched to another oral agents or insulin compared to younger patients. Those over 65 years old were slightly more likely to be switched to another antidiabetic agent but were less likely to be prescribed insulin after initiation of treatment with oral antidiabetic agents compared to younger patients. Those eligible under the LTI scheme were more likely to be switched to another oral antidiabetic agent and also to be prescribed insulin, either alone or as combination with oral agents compared to those eligible under the GMS scheme.

Regional variations

Patients with newly treated type 2 diabetes from the Midlands were less likely to be added another oral antidiabetic agent to initial therapy but were more likely to be switched to another oral agent compared to those from the Eastern region (Table 4.2.4). Meanwhile, those from other regions were more likely to be added another oral antidiabetic agents and less likely to be switched to another oral agent or insulin compared to those from the Eastern region. Those from North Western regions were more likely while those from most other regions were less likely to be added insulin to their initial regime compared to the Eastern region.

Figure 4.2.14: Kaplan-Meier plot of the cumulative probability of additional oral agents to initial antidiabetic agent in patients with newly treated type 2 diabetes

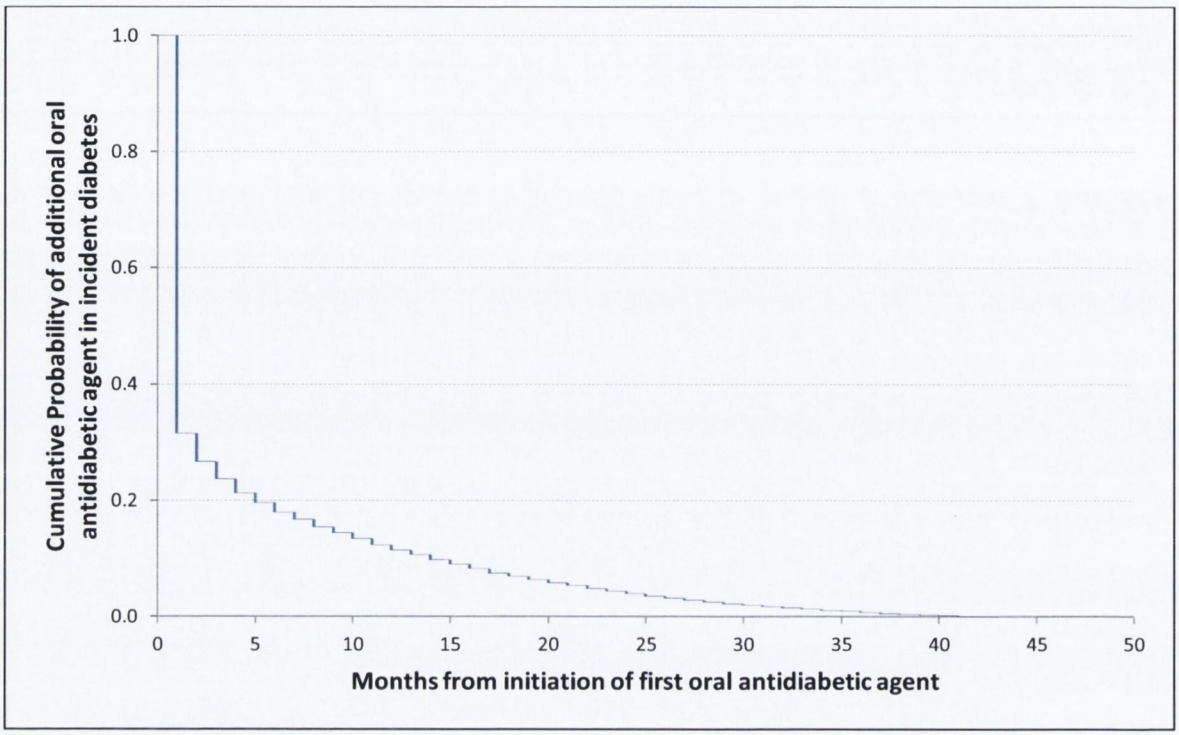


Figure 4.2.15: Kaplan-Meier plot of the cumulative probability of insulin addition to initial antidiabetic agent in patients with newly treated type 2 diabetes

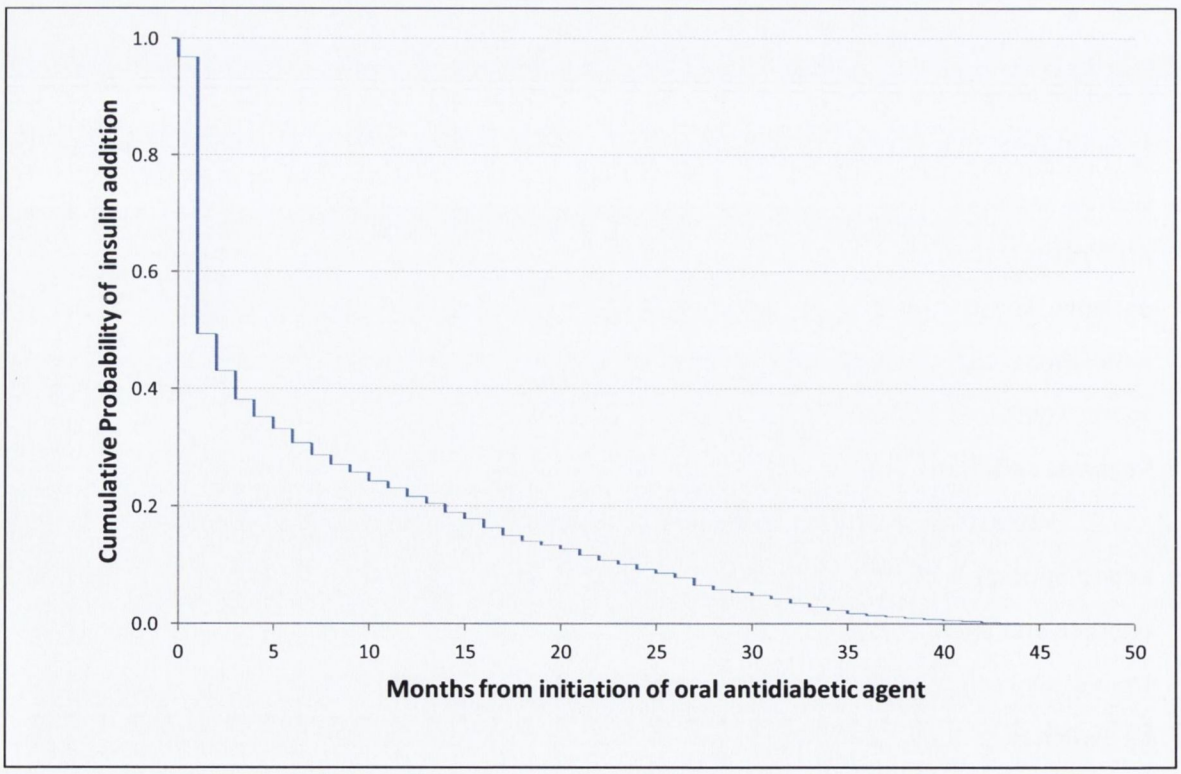


Figure 4.2.16: Kaplan-Meier plot of the cumulative probability switching to another antidiabetic agent in patients with newly treated type 2 diabetes

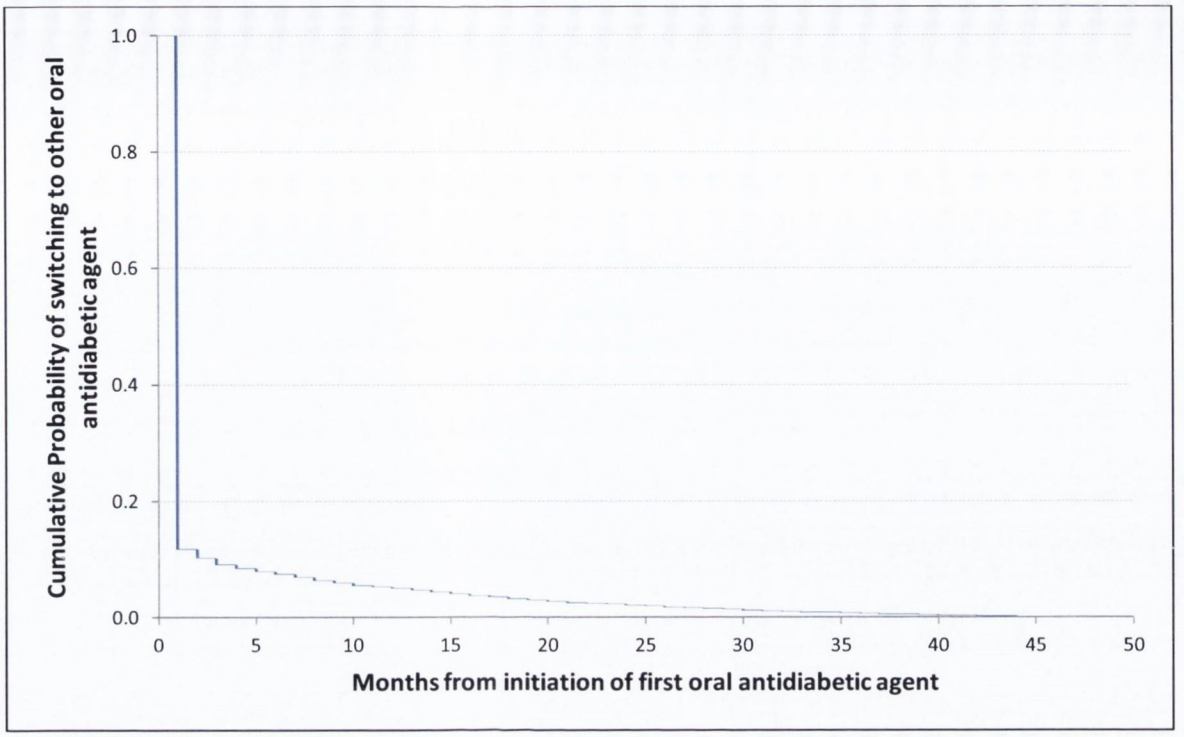


Figure 4.2.17: Kaplan-Meier plot of the cumulative probability switching to insulin in patients with newly treated type 2 diabetes

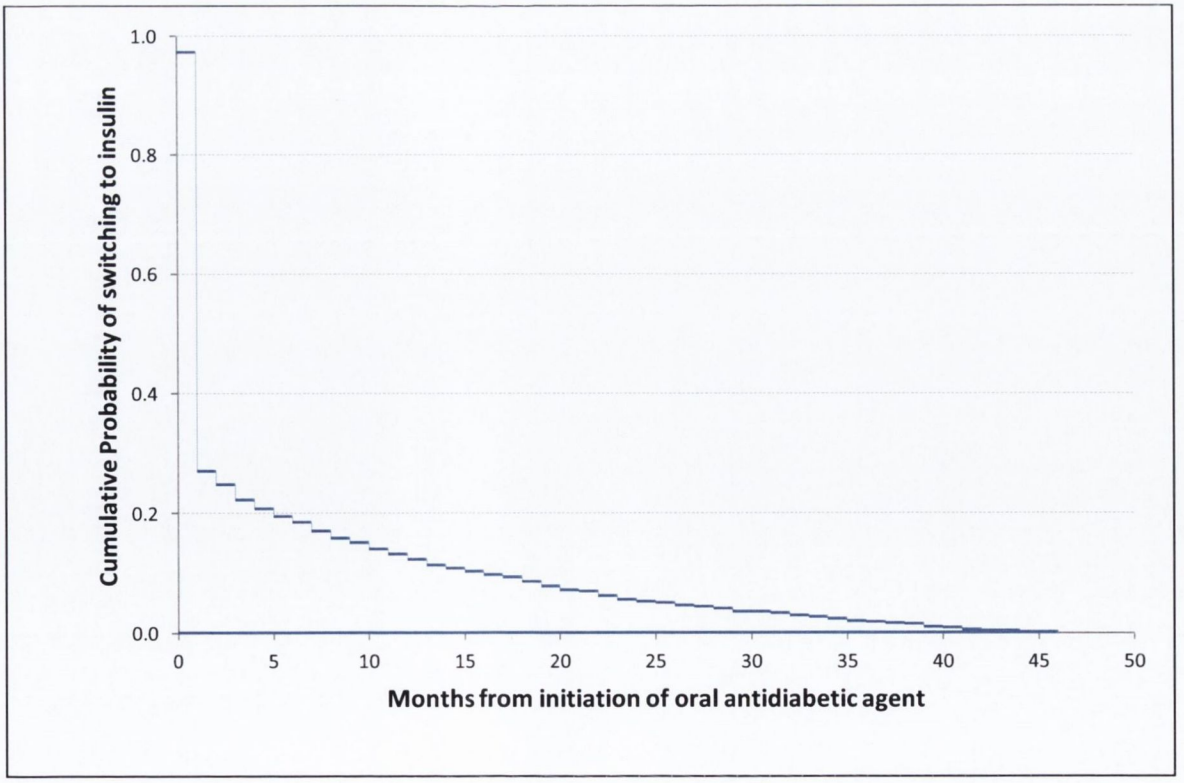


Table 4.2.4: Factors influencing the change in diabetes treatment regime in adults with newly treated type 2 diabetes presented as OR with 95% CI

Patient characteristics		Addition of oral agents OR†(95% CI), *p*	Switched to oral agents OR†(95% CI), *p*	Addition of insulin OR†(95% CI), *p*	Switched to insulin OR†(95% CI), *p*
Gender□	Female (n=29,379)	0.82 (0.79, 0.84) ***	0.97 (0.93, 1.01) ns	1.03 (0.97, 1.09) ns	1.05 (0.97, 1.14) ns
Age group◊	45-64 (n=25,229)	1.62 (1.54, 1.71) ***	0.82 (0.77, 0.87) ***	0.94 (0.87, 1.03) ns	0.55 (0.49, 0.61) ***
	>65 (n=32,529)	1.21 (1.15, 1.28) ***	1.10 (1.03, 1.17) *	0.60 (0.55, 0.66) ***	0.51 (0.46, 0.57) ***
Drug scheme x	LTI (n=12,564)	0.98 (0.93, 1.02) ns	1.18 (1.11, 1.25) ***	1.39 (1.28, 1.50) ***	2.02 (1.81, 2.25) ***
Health region∞	Midland (n=7,028)	0.92 (0.86, 0.98) *	1.60 (1.51, 1.70) ***	0.81 (0.72, 0.90) **	0.70 (0.61, 0.80) ***
	Mid-Western (n=6,689)	1.23 (1.15, 1.31) ***	0.90 (0.84, 0.96) *	0.66 (0.58, 0.74) ***	0.50 (0.43, 0.58) ***
	North Eastern (n=5,279)	2.24 (2.11, 2.39) ***	0.40 (0.36, 0.44) ***	0.93 (0.83, 1.05) ns	0.35 (0.29, 0.42) ***
	North Western (n=3,825)	1.58 (1.47, 1.70) ***	0.35 (0.31, 0.39) ***	1.33 (1.18, 1.51) ***	0.42 (0.34, 0.52) ***
	South Eastern (n=7,990)	1.58 (1.49, 1.67) ***	0.31 (0.28, 0.33) ***	0.97 (0.88, 1.08) ns	0.33 (0.28, 0.39) ***
	Southern (n=7,521)	1.67 (1.58, 1.77) ***	0.37 (0.34, 0.40) ***	0.88 (0.79, 0.98) *|	0.36 (0.31, 0.43) ***
	Western (n=6,008)	1.74 (1.64, 1.85) ***	0.44 (0.40, 0.48) ***	0.88 (0.78, 0.99) *	0.48 (0.41, 0.56) ***
Initial agent σ	Sulphonylureas (30,399)	0.50 (0.48, 0.52) ***	0.32 (0.30, 0.33) ***	0.54 (0.49, 0.58) ***	0.94 (0.86, 1.04) ns
	Glitazones (n=2,862)	0.36 (0.29, 0.44) ***	0.33 (0.26, 0.43) ***	0.73 (0.54, 0.99) *	1.13 (0.78, 1.63) ns
	Fixed combination (n=1,562)	0.19 (0.16, 0.25) ***	0.21 (0.16, 0.28) ***	0.58 (0.43, 0.80) **	1.02 (0.72, 1.43) ns
	Other oral agents (n=999)	0.23 (0.16, 0.33) ***	0.26 (0.17, 0.39) ***	1.24 (0.85, 1.82) ns	1.80 (1.16, 2.79) *

† Adjusted for gender, age groups, drug schemes, year at initiation of antidiabetic treatment, health regions and initial oral antidiabetic agent

□ Reference category males (n=37,497)

◊ Reference category age 16-44 years (n=9,005)

x Reference category GMS scheme (n=54,402)

∞Reference category Eastern region (n=22,626)

σ Reference category metformin (n=45,748)

4.2.5 Discussion

Overall trend

Similar to findings from other European countries [121] and consistent with the increasing prevalence of diabetes, an increase in the prescribing of antidiabetic agents was observed in patients with type 2 diabetes in Ireland. In the earlier part of the study, the prescribing of metformin and sulphonylureas was similar. However, the prescribing of metformin has continued to surpass sulphonylureas over the years in patients with prevalent and incident type 2 diabetes. This may be due to changes in guidelines over the study period with preference for sulphonylureas in guidelines prior to 2005 [191] and preference for metformin after 2005 as first line therapy in patients with type 2 diabetes [190]. Prescribing of rosiglitazone was on the decline after year 2006. The uptake of novel agents has been low in Ireland even as combination therapy. There has also been an increase in the prescribing of oral antidiabetic combination therapy either separately or as fixed preparation as well as an increase in the prescribing of insulin. Studies on the utilization of antidiabetic agents in Europe and UK revealed similar prescribing pattern as found in this study [6, 121, 192].

Oral antidiabetic agents for type 2 diabetes

Metformin is preferred in many diabetes guidelines as first line pharmacological therapy in patients with type 2 diabetes [5, 152]. In addition to its glucose lowering effects, metformin also improves cardiovascular risk factors such as weight, lipids and diastolic blood pressure compared to other antidiabetic agents [193]. Metformin was shown to significantly reduce the risk of myocardial infarction in overweight patients [194] and cardiovascular mortality compared to sulphonylureas [195, 196]. However, metformin is contraindicated in patients with impaired renal function, cardiac or respiratory insufficiencies, liver disease, alcohol abuse and history of metabolic acidosis [14]. Although previously metformin was reported to be associated with lactic acidosis, meta-analyses have shown that there was no increased risk of lactic acidosis in those prescribed metformin compared to other antidiabetic agents [12, 197].

Treatment with sulphonylureas has an increased risk of hypoglycaemia, a side effect rarely seen with metformin. In the UKPDS study, 20% of patients treated with sulphonylureas reported episodes of hypoglycaemic events [41]. The newer, extended release formulation of glipizide and gliclazide is associated with reduced risk of hypoglycaemia compared to older agents [13]. Weight gain is also common with sulphonylureas due to the anabolic effects of insulin in the body [13, 41]. In addition, sulphonylureas have the potential to interact with other medications such as warfarin and salicylate with resultant hypoglycaemia. Tolbutamide, a sulphonylurea agent was associated with increased cardiovascular events in the University Group Diabetes Program in

the 1970s [198]. Other studies have also shown that sulphonylureas were associated with increased cardiovascular mortality compared to metformin [195, 199-201]. However, studies such as the UKPDS, Steno-2 and A Diabetes Outcome Progression Trial (ADOPT) did not demonstrate an increased risk of cardiovascular events or mortality with sulphonylureas in patients with diabetes [41, 202-204]. The ADOPT study found reduced incidence of cardiovascular events in those prescribed glibenclamide compared to metformin and rosiglitazone [205]. Gliclazide was the agent of choice in the cohort of patients with type 2 diabetes prescribed sulphonylureas in this study. Gliclazide and glimepiride were associated with lower risk of myocardial infarction and mortality post-myocardial infarction compared to older generation sulphonylureas such as glibenclamide and glipizide in population based studies [201, 206]. Gliclazide also had lower risk of hypoglycaemia compared to glimepiride [207].

Most novel antidiabetic agents are only recommended as second line therapy or as an add-on therapy in selected patients [5, 190]. These agents have yet to demonstrate greater efficacy and long term clinical advantages compared to metformin and sulphonylureas [12]. Long term safety of these agents for use in the general population with diabetes has yet to be determined. The low prescribing of novel agents in this population may also be due to subjective grounds such as prescribers' knowledge and familiarity with older antidiabetic drug such as metformin and sulphonylureas compared to newer antidiabetic agents. Financial implications may contribute to the low prescribing of these agents as most of these agents are still not available as generic and the cost is driven by pharmaceutical marketing. In 2005, the cost of prescribing rosiglitazone (ingredient cost only) in Ireland was nearly €3 million [208].

The prescribing of rosiglitazone was declining after 2006 while the prescribing of pioglitazone was increasing. A meta-analysis performed showed that rosiglitazone significantly increased the risk of MI with pooled relative risk (RR) of 1.42 (95% CI 1.06, 1.91) and heart failure (RR=2.09, 95% CI 1.52, 2.88) compared to controls [16]. Another meta-analysis of 42 randomized clinical trials also reported similar increased risk of MI with rosiglitazone compared to controls (OR=1.43, 95% CI 1.03, 1.98) [126]. A Cochrane meta-analysis reported that rosiglitazone increased the risk of oedema and is associated with significant weight gain but without benefit on glycaemic control or improvement in morbidity, mortality, cost and health related quality of life as compared to other hypoglycaemic agents [209]. On the other hand, the Prospective Pioglitazone Clinical Trial in Macrovascular Events (Proactive) demonstrated that pioglitazone had a non-significant reduced risk of coronary and peripheral vascular events with significant benefit observed in terms of secondary end points; death, myocardial infarction or stroke. However, like rosiglitazone, this trial found that pioglitazone increased the risk of congestive heart failure. A

meta-analysis found that pioglitazone significantly reduced the risk of composite end point (death, myocardial infarction or stroke) with HR of 0.82 (95% CI 0.72, 0.94) [189].

The prescribing of meglitinides was stable during the study period at around 2% of patients with type 2 diabetes in this population. Meglitinides, as prandial glucose regulators are suitable for patients with irregular meal times, albeit the need for multiple daily dosages [210]. Similar risk of hypoglycaemia was observed with repaglinide compared to sulphonylureas while weight gain was generally greater compared to metformin [12]. Meglitinides were not shown to be associated with increased cardiovascular events, however, long term data especially on morbidity and mortality in patients prescribed meglitinides are lacking [211]. The prescribing of acarbose has significantly declined in this population. Similar to meglitinides, acarbose also reduces postprandial hyperglycaemia [188]. Although acarbose is not as effective in reducing HbA1c as other antidiabetic agents [12], it has been shown to have additional cardiovascular advantages by reducing triglycerides, systolic blood pressure and risk of myocardial infarction [212, 213]. Acarbose does not cause weight gain and has low risk of hypoglycaemia [214], however, the use is limited by gastrointestinal side effects such as flatulence and diarrhoea. Another disadvantage of acarbose is the need to be taken with meals and patients have to include a diet rich in complex carbohydrate [215].

The incretin modulators, exenatide and sitagliptin have only been marketed in the Irish population since 2007 with very little uptake. Subcutaneous exenatide injections are shown to be effective in glycaemic control with the added advantage of promoting weight loss compared to placebo [216]. However, currently exenatide is only recommended for use in combination therapy and may be considered as an alternative to insulin. Although comparable HbA1c reduction was observed with exenatide compared to insulin in patients already on either metformin or sulphonylureas, exenatide offers advantage in terms of reducing of postprandial hyperglycaemia and promoting weight loss [217, 218]. The DPP-4 inhibitor, sitagliptin is weight neutral and has unmarked side effects profile thus making it suitable as add-on therapy to other oral agents such as metformin [219]. However, both the incretin mimetics and DPP-4 inhibitors are relatively new and thus require longer clinical evaluations to determine the safety profiles and long term outcomes of these agents when used in the general population.

Combination oral antidiabetic therapies

Nearly half of patients with newly treated diabetes in this study needed a change in treatment regime after initiation of antidiabetic therapies. The change in treatment regime was mostly done early after the initiation of first antidiabetic agent. Due to limitation in the database, it is not possible to examine the duration of diabetes and patients identified as newly treated diabetes may already have diabetes prior to inclusion in the prescribing database. Thus, this may

be the possible reason for the early addition of another oral antidiabetic agent in these patients. Studies have shown that initial monotherapy with antidiabetic agents is often unsuccessful at achieving glycaemic goals [220, 221]. In the UKPDS study, only half of patients were able to maintain HbA1c below 7.0% with monotherapy at 3 years follow up. At 9 years follow up less than a quarter of patients were maintained on monotherapy sulphonylureas and 13% on monotherapy metformin (obese patients only) [221]. A population based study in the UK population using the GPRD demonstrated that more than 80% of patients failed to consistently maintain HbA1c of less than 7.0% after 3 years of initiation of monotherapy with either metformin or sulphonylureas [220]. The failure of monotherapy in patients with type 2 diabetes may be due loss of insulin responsiveness and progressive reduction in insulin secretion. In the ADOPT study, it was demonstrated that the progressive loss of beta cell functions after diagnosis of type 2 diabetes was similar between metformin, glibenclamide and rosiglitazone [205].

The combination of metformin and sulphonylureas is the commonest combination for oral antidiabetic agents. There were concerns regarding the increased risk of cardiovascular disease and mortality in those receiving this combination [194, 199, 222]. Other studies, however, have shown that the combination of these agents is safe [223, 224]. The combination of metformin and sulphonylureas were shown to be equally effective in improving glycaemic control compared to glitazone and sulphonylurea combination with differential effects on lipid profiles [225]. The combination of glitazone and sulphonylureas was associated with significant weight gain compared to the combination of metformin and sulphonylureas [226]. There is no clinical advantage in combining meglitinides with sulphonylureas since these agents exert their action by binding at the same receptors, the SUR1, albeit at different sites [210]. Exenatide can be combined with metformin or sulphonylureas with resultant better glycaemic control and beneficial effects on weight than monotherapy [227]. Addition of a third agent with failure of dual therapy is sometimes used with combination of metformin, sulphonylureas and glitazones. This triple therapy combination was found to be safe and allows glucose targets to be reached before insulin is needed [228]. This triple therapy combination is more expensive than the addition of insulin and guidelines recommend the use of triple therapy only when circumstances make it difficult to use insulin and patients are already close to target glycaemic control [190].

Insulin in type 2 diabetes

Guidelines have recommended early insulin addition in those not achieving control by metformin alone [5, 190]. Use of insulin in type 2 diabetes has been shown to improve insulin sensitivity, reduce hyperglycaemic-induced insulin resistance and improve insulin secretion by beta cells in the pancreas [229]. Intensive glucose control with insulin in patients with type 2

diabetes has been shown to decrease microvascular complications [41]. Compared to patients with type 1 diabetes, insulin treatment in patients with type 2 diabetes was not usually associated with severe hypoglycaemia [230]. However, the use of insulin in type 2 diabetes is also associated with significant weight gain which may result in limitation of its use in obese or overweight patients [231]. Insulin and oral hypoglycaemic agent combination showed benefits on glucose control compared to once daily human insulin alone. However, when administered twice daily either as basal bolus or premixed insulin, insulin only was superior to combination with oral agents [232]. When combined with metformin, the increase in weight after insulin treatment is significantly reduced. Combination of insulin and metformin is preferred as it improves glucose control and reduces the need for high dose insulin. Insulin and sulphonylureas has no beneficial effect compared to insulin alone while increasing weight gain [232]. Although the insulin and glitazone combination has been reported to be associated with a high risk of oedema [233], some 4% of patients were being prescribed both these agents in Ireland in 2007. The combination of exenatide and insulin is promising and showed significant reduction of HbA1c, weight and reduce insulin requirement [234].

Traditionally, long-acting basal human insulin was added to existing oral antidiabetic agents when optimized oral therapy is inadequate to achieve and maintain target glucose level. Biphasic premixed insulin consisting of rapid-acting combined with long-acting showed beneficial effect on postprandial and basal glucose control in patients with type 2 diabetes as well as providing convenience to patients. Compared to patients with type 1 diabetes, the basal bolus regime with multiple insulin injections is less favoured in patients with type 2 diabetes [147]. Long-acting insulin analogues, insulin glargine and insulin detemir and more recently, biphasic premixed insulin analogues have also been studied for use in patients with type 2 diabetes as alternative to human insulin. In patients already prescribed sulphonylureas or metformin, insulin glargine has not shown significant differences in terms of HbA1c levels reduction and weight gain compared to long acting human insulin [235]. The addition of insulin glargine or detemir in patients with type 2 diabetes has the advantage of reduced incidence of hypoglycaemia compared to human insulin [236]. However, until long term efficacy and data are available, a cautious approach is suggested with both insulin glargine and detemir [237]. A similar degree of overall glycaemic control with beneficial effects on postprandial hyperglycaemia was observed when biphasic premixed analogues were compared to biphasic premixed human insulin with reduced hypoglycaemic risk [238]. Combination of oral antidiabetic agents and biphasic insulin analogues were shown to produce better glycaemic control in patients with type 2 diabetes compared with long-acting analogues only [239]. Insulin aspart, lispro and glulisine in combination with long acting analogues have all been studied in patients with type 2 diabetes in basal bolus

approach compared to human insulin. Similar to patients with type 1 diabetes, insulin analogues reduces weight gain, hypoglycaemia and variation in glucose levels compared to human insulin [147].

Glucose monitoring kits

Another issue in the management of type 2 diabetes is the prescribing of glucose monitoring kits in those not using insulin. There has been an increase in the prescribing of glucose monitoring kits in this patient population. The use of glucose monitoring kits was also on the rise in the UK population [240]. Although self-monitoring of blood glucose might be effective in improving glycaemic control in patients with type 2 diabetes, large clinical trials are needed to confirm this potential benefit [241]. The IDF recommended glucose monitoring in selected patients such as those recently diagnosed with type 2 diabetes, on insulin, changes in medications, hypoglycaemia problems, keen to tighten glucose control or with intercurrent illness. The NICE guideline recommends that self-monitoring should not be considered as stand-alone intervention but used in conjunction with appropriate therapy [79]. In the UK NHS 17 million pounds were spent on glucose monitoring kits and it was suggested that many patients with type 2 diabetes were using self-monitoring kits unnecessarily [242]. Health care providers should be made aware of the current increasing trend of glucose monitoring kits prescribing and a clear local guideline should be provided with regards to the prescribing of these kits.

Gender, age, drug scheme and regional variations

Variations in the prescribing of antidiabetic agents in diabetic population were observed across age groups, gender, drug schemes and regions in this study. There was a preference for sulphonylureas over metformin in the prescribing for older type 2 diabetes patients. The prescribing of sulphonylureas was as high as metformin in 2003 and prescribers may have chosen to continue with the same therapy in older aged patients. The presence of comorbidities such as congestive heart failure, renal failure and liver failure in older patients may render the prescribing of metformin inappropriate [243]. The commonly encountered gastrointestinal side effects of metformin may not be tolerated by older patients. There may also be perceived increased risk of lactic acidosis with metformin, however, advanced age per se is not a contraindication to metformin and does not increase the risk of lactic acidosis [12, 243]. The risk of hypoglycaemia associated with sulphonylureas is increased by 36% in older compared to younger patients [244]. Multiple factors may contribute to the increased susceptibility to sulphonylurea-induced hypoglycaemia in older patients such as polypharmacy, cognitive impairment and reduced liver or kidney function [245]. On the other hand, sulphonylureas has the advantage of extensive clinical experience in older persons [243]. Glitazones has been associated with increased risk of oedema, congestive heart failure, macular oedema and fracture (post-menopausal women), all of which

are increased in older patients [243]. Older patients with type 2 diabetes were less likely to be prescribed insulin compared to younger patients but more likely of combination therapy. The problems in insulin delivery, the need for self-glucose monitoring and risk of hypoglycaemia may deter some from prescribing insulin to these patients. Patients eligible under the LTI scheme were more likely to be prescribed expensive agents such as glitazones, meglitinides and incretin modulators than those eligible under the GMS scheme, suggesting socioeconomic differences in prescribing. As for type 1 diabetes, regional variations were observed in the prescribing of antidiabetic agents in patients with type 2 diabetes. The possible reasons for socioeconomic and regional variations have been discussed in Section 3.1.5.

Strengths and limitations

This study was performed using data from the prescription database up to 31st December 2007 only. Therefore, the trends in the prescribing of newer agents such as repaglinide, exenatide and sitagliptin were only captured at the end of this study and thus may account for the low prescribing of these agents. Most of these novel agents are still covered by patent and thus generic options are still not available at this moment. It is expected that there will be an increase uptake of this agents as second line therapy after the fall of the glitazones and after generic preparations are available. The fixed combination of metformin and sitagliptin (Janumet) has just entered the Irish market in 2008 and thus this combination was not examined in this study. The choice of oral antidiabetic agents by prescribers may be made on many clinical grounds. As diagnostic information and clinical information such as duration of diabetes, hospital admissions, comorbidities and social circumstances are not available in the prescribing database, the possible reasons for the choosing an oral antidiabetic agent in individual patients cannot be determined. It is also difficult to determine the circumstances that lead to a change in therapy in these patients although one can speculate in accordance with findings from other studies. In addition to diabetes, metformin may also be prescribed for treatment of infertility problems in those with polycystic ovarian syndrome (PCOS). However, this use of metformin is still unlicensed [246] and thus it is expected that the number of patients prescribed this agent for this condition is small.

In conclusion, there has been a change in the prescribing trends for oral antidiabetic agents in the Irish population with type 2 diabetes with a trend towards metformin as per local and international diabetes guidelines [5, 190]. This shows that health care providers are receptive to clinical guidelines. However, inequalities in the prescribing of oral antidiabetic agents were observed especially in the elderly population and in those from lower socioeconomic backgrounds. A structured and co-ordinated approach to diabetes health care as exemplified by the Midlands diabetes services is needed to improve standards of care in patients with diabetes and to reduce inequalities in the prescribing of antidiabetic therapies across the country.

CHAPTER 5 : PREVENTATIVE CARDIOVASCULAR THERAPIES PRESCRIBING IN PATIENTS WITH DIABETES IN IRELAND

5.1 Trends in the prescribing of preventative cardiovascular therapies in patients with diabetes

5.1.1 Background

Cardiovascular disease accounts for about 80% of mortality in patients with diabetes. The risk of cardiovascular mortality is 2-3 times higher in men and 3-5 times higher in women with diabetes than those without [17, 18]. Morbidity and mortality from cardiovascular disease is also higher in women with diabetes compared to men without diabetes [17]. In Ireland, mortality rates from cardiovascular disease have decreased by 47% between 1985 and 2000 [247] and by 30% between 2000 and 2005 [248]. However, cardiovascular disease remains the most common cause of death, currently accounting for one-third of all deaths and one in five premature deaths [249].

The proposed mechanisms of increased cardiovascular disease in patients with diabetes include hyperglycaemia, insulin resistance, oxidative stress, thrombogenic propensity and lipid disorders [250]. Hyperglycaemia is associated with increased cardiovascular morbidity and mortality in both patients with type 1 and type 2 diabetes [251, 252]. A meta-analysis of epidemiological studies found a progressive relationship between plasma glucose and the incidence of cardiovascular events even in people without diabetes [252]. Hyperglycaemia may affect vascular functions leading to endothelial dysfunction and reduced nitric oxide bioavailability and this is implicated in atherogenesis [253]. Hyperglycaemia also stimulates the production of advanced glycation end-product (AGE) which has adverse effects on vascular functions and increases the release of proinflammatory cytokines [254]. In addition, hyperglycaemia may increase the tendency for atherosclerotic plaque to rupture leading to overt cardiovascular events. The magnitude of insulin resistance is directly related to cardiovascular outcomes. Insulin resistance is associated with impaired endothelium dependant vasodilation. Oxidative stress also plays a key role in endothelial dysfunction and atherosclerotic process in patients with diabetes. Increased oxidative stress affects endothelial functions via a number of pathways and increases the release of proinflammatory cytokines [255]. In addition, the risk for cardiovascular disease is also linked to platelet dysfunction and coagulation disorders in patients with diabetes [256].

The risk of cardiovascular disease in patients with diabetes increases with age [257]. Duration of diabetes also has a strong relationship with cardiovascular mortality [258]. In contrast to the general population, acute and fatal cardiovascular events are more frequent in women compared to men with diabetes [259]. Pre-menopausal women with diabetes lose their relative protection against cardiovascular disease compared to men [17]. In addition, other risk factors for cardiovascular disease are also more common in those with diabetes. Hypertension is at least twice as common in patients with diabetes and was associated with both macro and microvascular complications in the UKPDS study [44]. Dyslipidaemia is also common in patients with diabetes and may include lowered HDL cholesterol, increased LDL and total cholesterol and increased triglycerides [260]. Large population based studies in Finland over 7- and 18-year periods found that patients with diabetes had as high a risk of MI as those with previous acute MI but without diabetes [261, 262]. Therefore, those with diabetes are considered as having similar risk to those with established coronary heart disease. However, other studies in different populations have found conflicting results especially among men [196, 263, 264] and a recent meta-analysis of observational studies did not support the concept of diabetes being of equivalent risk to those with established coronary heart disease [265].

The Irish college of general practice guideline on type 2 diabetes care recommends that patients with diabetes and hypertension should be treated aggressively with the aim of achieving targets below 135mmHg for systolic blood pressure of (or 140mmHg in those over 65) and below 80mmHg for diastolic blood pressure using lifestyle modifications and drug therapy. It is recommended that the initial antihypertensives used should be with agents that have been demonstrated to reduce cardiovascular events in patients with diabetes such as ACEIs or ARBs, diuretics, calcium channel blockers and beta blockers, avoiding the use of atenolol. This guideline also recommends lipid levels to be managed to achieve total cholesterol of <4.5 mmol/l, LDL cholesterol of <2.5mmol/l, HDL cholesterol of >1.0 mmol/l and triglycerides <2.0mmol/l. Statins should be prescribed in all patients with diabetes who fail to meet these lipid targets or those with concurrent cardiovascular risk factors. Second generation statins such as atorvastatin and simvastatin should be prescribed if triglycerides are > 2.3mmol/l and LDL is > 2.5 mmol/l, followed by Omega 3 fish oils and then fibrates as a third line therapy. Nicotinic acid may be prescribed to achieve target HDL level. This guideline also recommends the use of aspirin in all patients with diabetes who are over 40 years of age or earlier in those with concurrent cardiovascular risk factors [5].

A previous study in Ireland has shown that there was an increased rate of preventative cardiovascular therapies prescribing in patients with IHD over the years [266]. However, there was also found to be an under prescribing of cardiovascular preventative therapies in patients

with diabetes [46]. Gender and age bias have also been reported in the prescribing of cardiovascular preventative therapies in Ireland [47]. In addition, regional variations in cardiovascular preventative therapies prescribing in patients with diabetes have been observed [48]. This study is undertaken to examine the trends in prescribing of cardiovascular preventative therapies over a 5 year period and to determine whether there has been an improvement in cardiovascular prescribing over the years In Ireland.

5.1.2 Specific objectives

1) To examine the prevalence of IHD in patients with treated diabetes in Ireland from 2003 to 2007
2) To determine the prescribing trends of preventative cardiovascular therapies in patients with diabetes from 2003 to 2007.
3) To examine the variations in the prescribing of preventative cardiovascular therapies for patients with diabetes according to gender, age groups, drug schemes, types of diabetes, cardiovascular co-morbidities and health regions.
4) To determine the choice of cardiovascular agents, the time to initiation of preventative cardiovascular therapies and factors influencing prescribing of cardiovascular therapies in patients with newly treated type 2 diabetes.

5.1.3 Methods

5.1.3.1 Trends in the prescribing of preventative cardiovascular therapies in patients with prevalent diabetes

The HSE-PCRS database was used to identify patients with treated diabetes (both type 1 and type 2) from 1st January 2003 to 31st December 2007 as described in Section 3.1.3.1. As guidelines on cardiovascular prevention in diabetes focused on patients over 40 years of age [5], only patients 45 years old and over were included in the study (n=93,633). In addition, patients with IHD were identified in the diabetes cohort as those prescribed either nitrate or nicorandil during the study period (n=8,340). Nitrate prescribing has been shown to be a useful surrogate marker for coronary heart disease with a sensitivity of approximately 73% and specificity of 96% [267].

Cardiovascular therapies examined were lipid lowering agents, aspirin/clopidogrel and antihypertensives in diabetic patients with and without IHD. The prescribing trends for the major antihypertensive classes (ACEIs, ARBS, beta blockers, calcium channel blockers and diuretics) and combination of antihypertensive agents were also examined in patients with diabetes. In addition,

the choice of lipid lowering agents (atorvastatin, simvastatin, pravastatin, fluvastatin, rosuvastatin, ezetimibe, fibrates and nicotinic acid) were also examined in the cohort of patients prescribed lipid lowering therapies.

The percentage of patients with diabetes, with or without IHD, prescribed preventative cardiovascular therapies was calculated for each calendar year over the 5-year period. Logistic regression was used to examine the variations in cardiovascular therapies prescribing across gender, age groups, type of diabetes, drug schemes and health regions. A test for linear trend was used to examine trends in cardiovascular therapies prescribing over time.

5.1.3.2 Trends in prescribing of preventative cardiovascular therapies in patients with newly treated type 2 diabetes

Newly treated type 2 diabetes patients aged 45 years old and above were identified as described in Section 3.1.3.2 from 1st January 2004 to 31st December 2006 (n=32,491). Patients were followed up longitudinally until 31st December 2007. Patients prescribed all statins, aspirin/clopidogrel, and antihypertensives prior to initiation of antidiabetic therapies were excluded (n=5,672). Each cardiovascular agent was analysed separately and patients prescribed these agents prior to diabetes were excluded (statins (n=3,382), aspirin/clopidogrel (n=5,491) and antihypertensives (n=12,578)).

Cox proportional hazard was used to examine the relationship between time taken to initiation of preventative cardiovascular and gender, age groups, year at initiation of antidiabetic therapies, initial oral antidiabetic agents and other prior cardiovascular medications. Kaplan-Meier survival analysis was used to plot the time to prescribing of cardiovascular therapies in newly treated diabetes patients prescribed each agent.

5.1.4 Results

5.1.4.1 Trends in prescribing of preventative cardiovascular therapies in patients with prevalent diabetes

Overall trends

There was a significant decrease in the prevalence of IHD in patients with treated diabetes in Ireland from 2003 to 2007 (p=0.0001, Figure 5.1.1). There was a significant increase in the prescribing of preventative cardiovascular therapies in patients over 45 years old with diabetes over the 5-year period (p<0.0001, Figure 5.1.2). In 2003, half of the patients with diabetes were prescribed aspirin/clopidogrel and statins. This increased to more than two thirds of patients being prescribed aspirin/clopidogrel and statins in 2007. Three quarter of patients

with diabetes were already on antihypertensives back in 2003 and this increased to more than eighty percent in 2007. More than two thirds of patients were being prescribed ACEIs or ARBs (Figure 5.1.3). Although beta blockers were only prescribed in around one third of patients with diabetes, a significant increase in the prescribing of beta blockers was observed in this cohort of patients over the study period ($p<0.0001$). There was also an increase in the prescribing of calcium channel blockers and diuretics in patients with diabetes over the years. A significant increase in the prescribing of combination antihypertensive therapy was observed ($p<0.0001$). The first choice of combination agent in this cohort was ACEI-beta blocker followed by ACEI-calcium channel blockers (Figure 5.1.4). Increased prescribing of combination agents with ARBs was also observed during the study period ($p<0.0001$).

In the cohort of patients prescribed lipid lowering agents, atorvastatin was the most prescribed agent throughout the years with a significant increase in prescribing observed (Figure 5.1.5). Meanwhile there was a significant reduction in the prescribing of pravastatin over the years ($p<0.0001$). Only around 10% of patients were prescribed other lipid lowering agents with an increase in the prescribing of rosuvastatin ($p<0.0001$) and a decrease in the prescribing of simvastatin ($p<0.0001$) and fluvastatin ($p<0.0001$). Overall, only 2% of patients were prescribed ezetimibe and fibrates while less than 1% were prescribed nicotinic acid.

Prescribing of cardiovascular therapies in patients with diabetes and concurrent IHD

There was a higher rate of cardiovascular therapies prescribed in diabetes patients with IHD compared to the general diabetes population ($p<0.0001$) with a significant increase in prescribing during the study period ($p<0.0001$). More than seventy percent of diabetes patients with IHD had been prescribed cardiovascular preventative therapies while nearly all of these patients were being prescribed antihypertensives in 2007 (Figure 5.1.6). Over eighty five percent of these patients were prescribed antiplatelet agents and statins. There was also a significant increase in the prescribing of all major classes of antihypertensive agents in diabetic patients with IHD with the exception of calcium channel blockers ($p<0.0001$) (Figure 5.1.7).

Age, gender, type of diabetes and drug scheme variations

Female patients were more likely to receive statins and antihypertensives but less likely to receive aspirin/clopidogrel compared to males (Table 5.1.1). Females were also less likely to be prescribed beta blockers but more likely to be prescribed calcium channel blockers and diuretics compared to males (Table 5.1.2). Patients 65 years old and above were less likely to be prescribed statins but more likely to be prescribed aspirin/clopidogrel and all classes of antihypertensives compared to younger patients. Those with type 2 diabetes had a greater likelihood of receiving cardiovascular therapies compared to patients with type 1 diabetes. Patients under the LTI scheme were also less likely to be prescribed preventative cardiovascular therapies except in the

prescribing of diuretics compared to GMS patients. Patients with IHD were more than 3 times likely to be prescribed aspirin/clopidogrel and beta blockers and more than 6 times more likely to be prescribed antihypertensives compared to diabetes patients without IHD.

Regional variations

Regional variations were observed in the prescribing of cardiovascular therapies compared to prescribing in the Eastern region. With regards to aspirin, all other regions showed significantly lower prescribing compared to the Eastern region. There was higher prescribing of statins in the Midland region but lower in all other regions compared to the Eastern region. Patients in the Midland, South Eastern and Southern region were more likely while those from Mid-Western, North Western and Western region were less likely to be prescribed antihypertensives compared to those from the Eastern region. Only the Midland region and the South Eastern region showed higher prescribing of ACEIs or ARBs compared to the Eastern region. Higher prescribing of beta blockers was observed in the Southern region with patients from other regions less likely to be prescribed beta blockers compared to the Eastern region.

Figure 5.1.1: Prevalence of IHD in patients ≥45 years old with treated diabetes in Ireland from 2003 to 2007

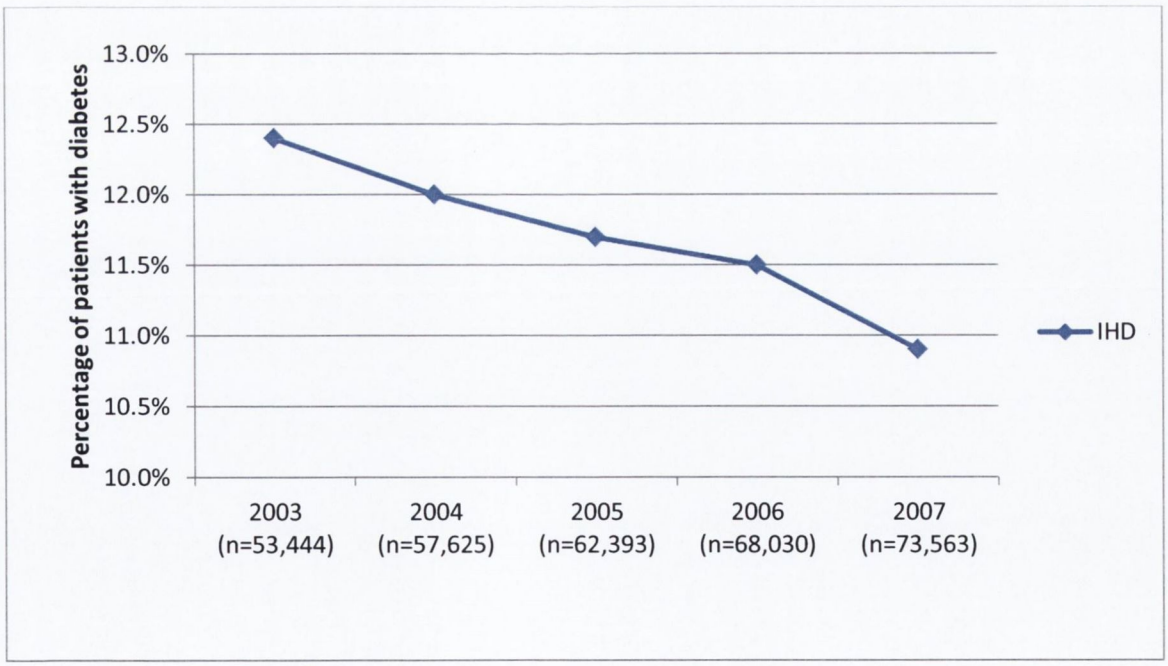


Figure 5.1.2: Overall prescribing of cardiovascular therapies in patients ≥45 years old with diabetes mellitus from 2003 to 2007 (note: patients may be prescribed ≥ one medication in a year)

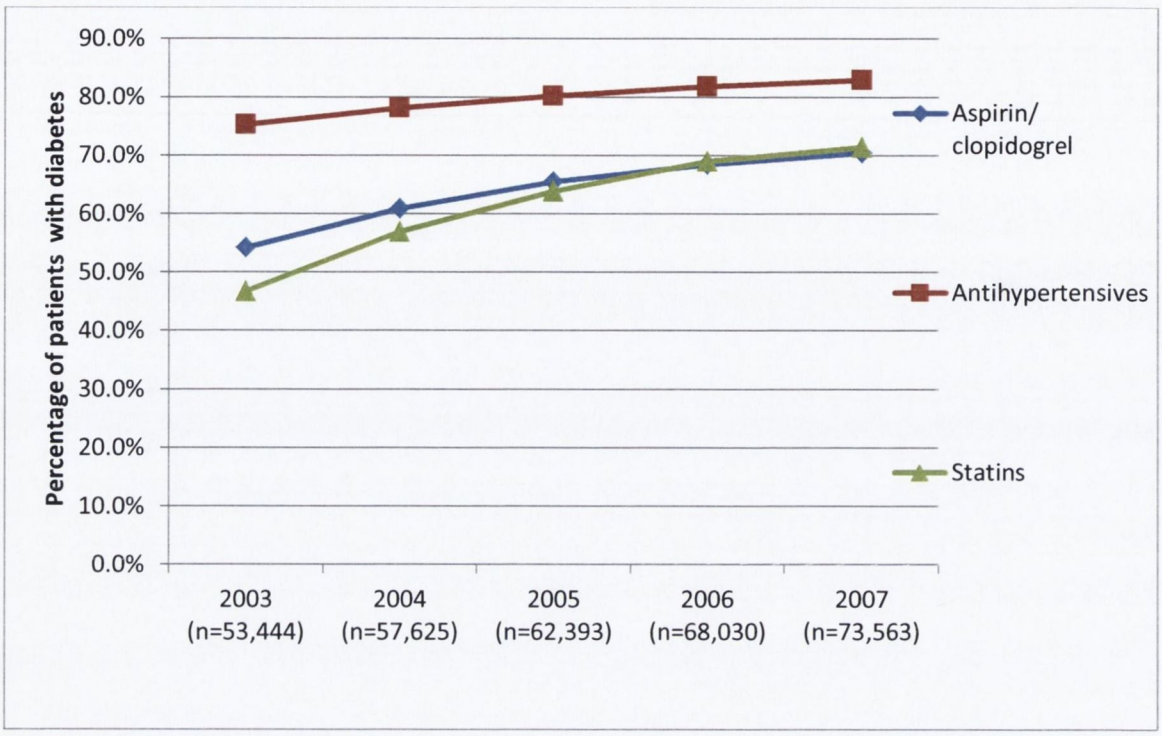


Figure 5.1.3: Choice of antihypertensive in patients ≥ 45 years old with diabetes mellitus from 2003 to 2007 (note: patients may be prescribed ≥ one medication in a year)

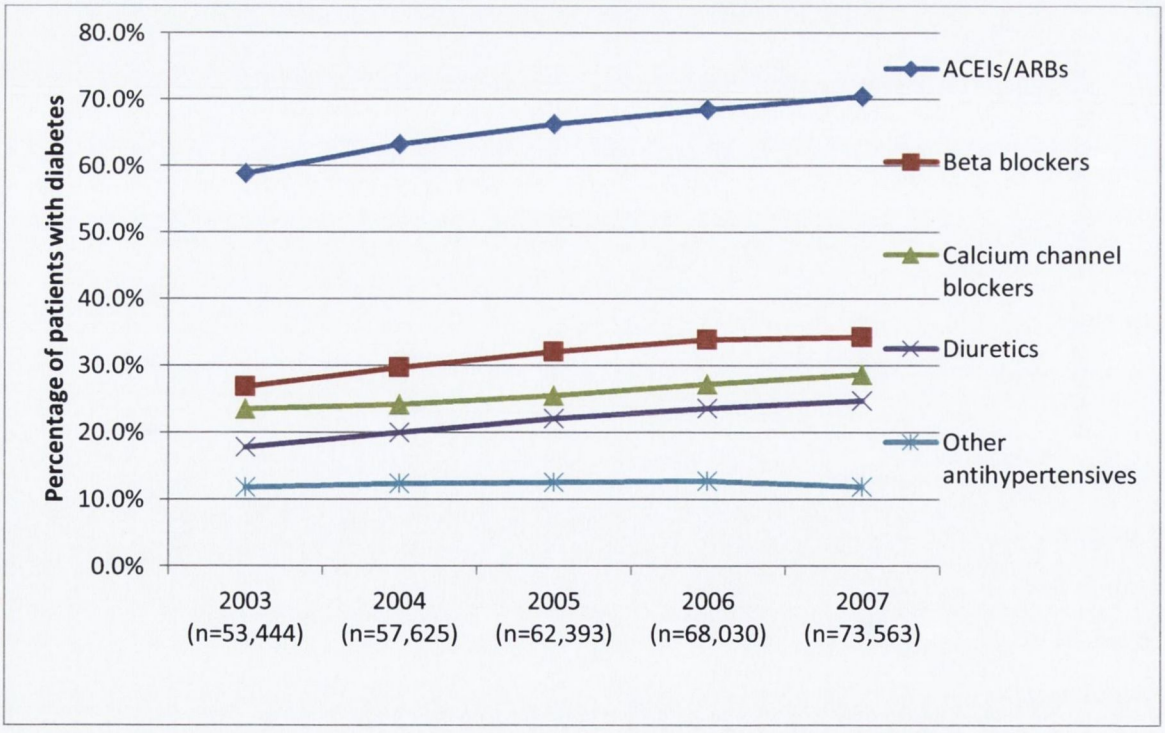


Figure 5.1.4: Choice of combination antihypertensive in the cohort of patients with diabetes prescribed combination agents in one prescription claim form only from 2003 to 2007

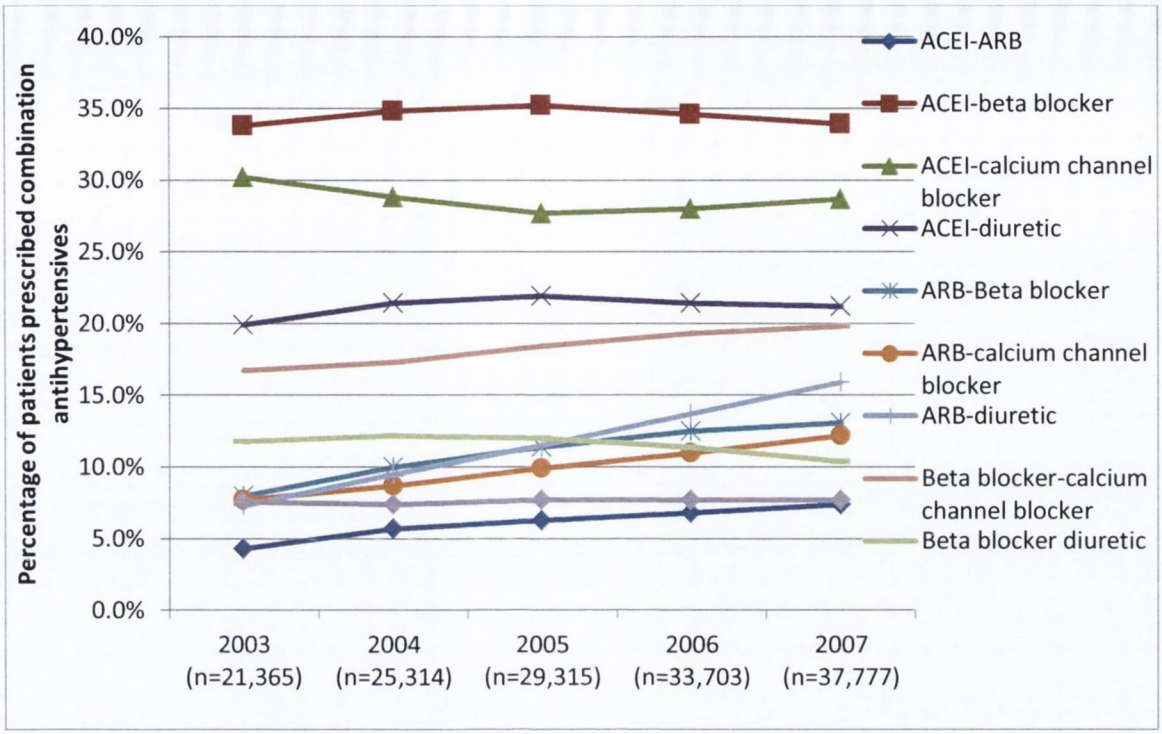


Figure 5.1.5: Choice of agents in patients ≥45 years old with diabetes mellitus prescribed lipid lowering therapies from 2003 to 2007

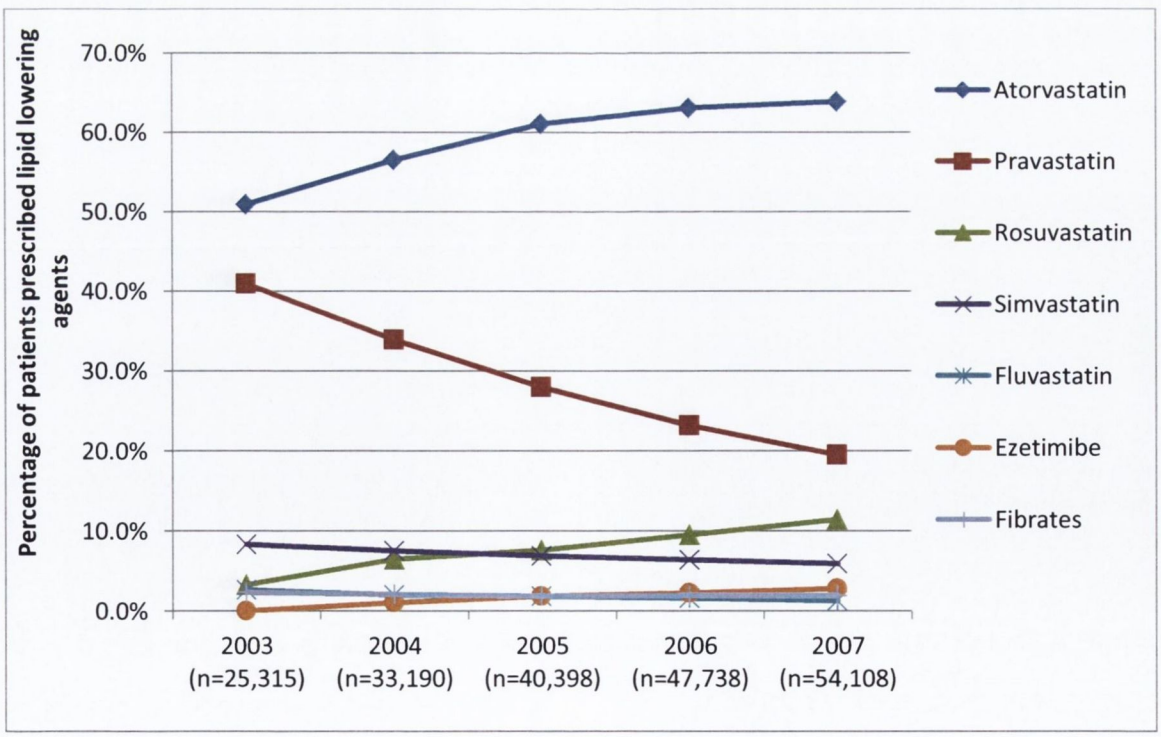


Figure 5.1.6: Trends in the prescribing of cardiovascular therapies in patients ≥ 45 years old with diabetes mellitus and concurrent IHD from 2003 to 2007 (note: patients may be prescribed ≥ one medication in a year)

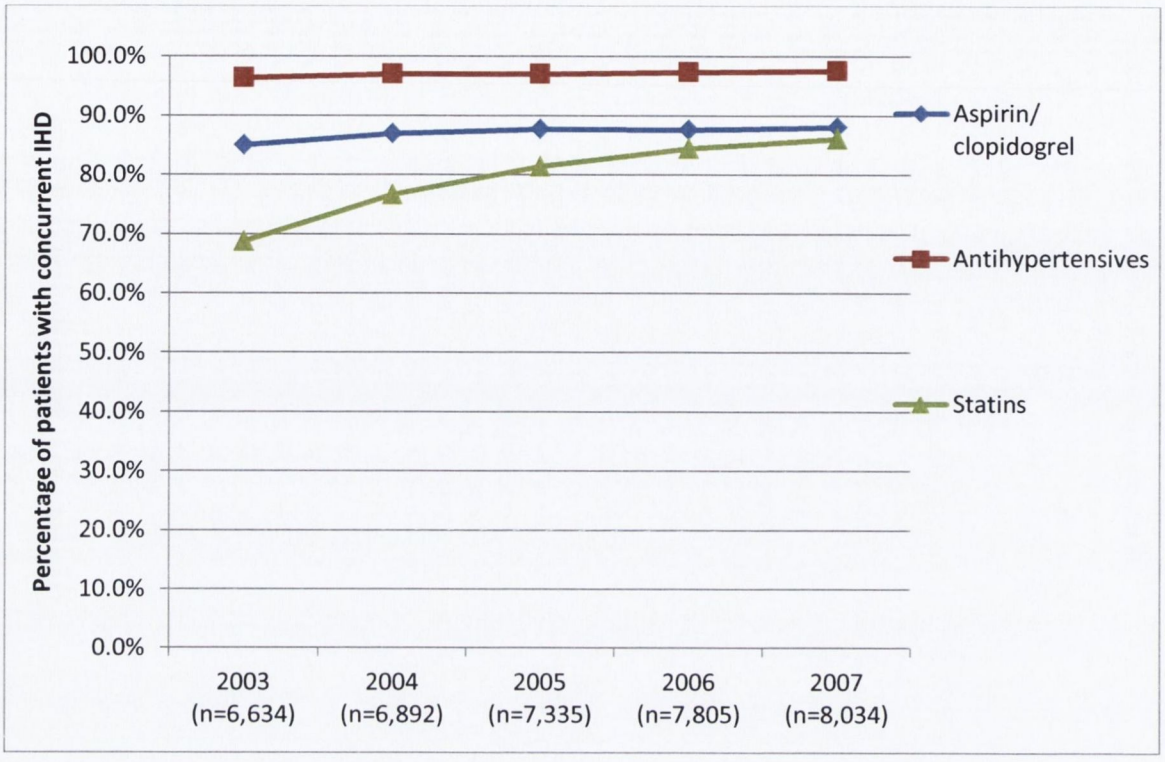


Figure 5.1.7: Trends in the prescribing of antihypertensives in patients 45 years old and above with diabetes mellitus and concurrent IHD from 2003 to 2007 (note: patients may be prescribed ≥ one medication in a year)

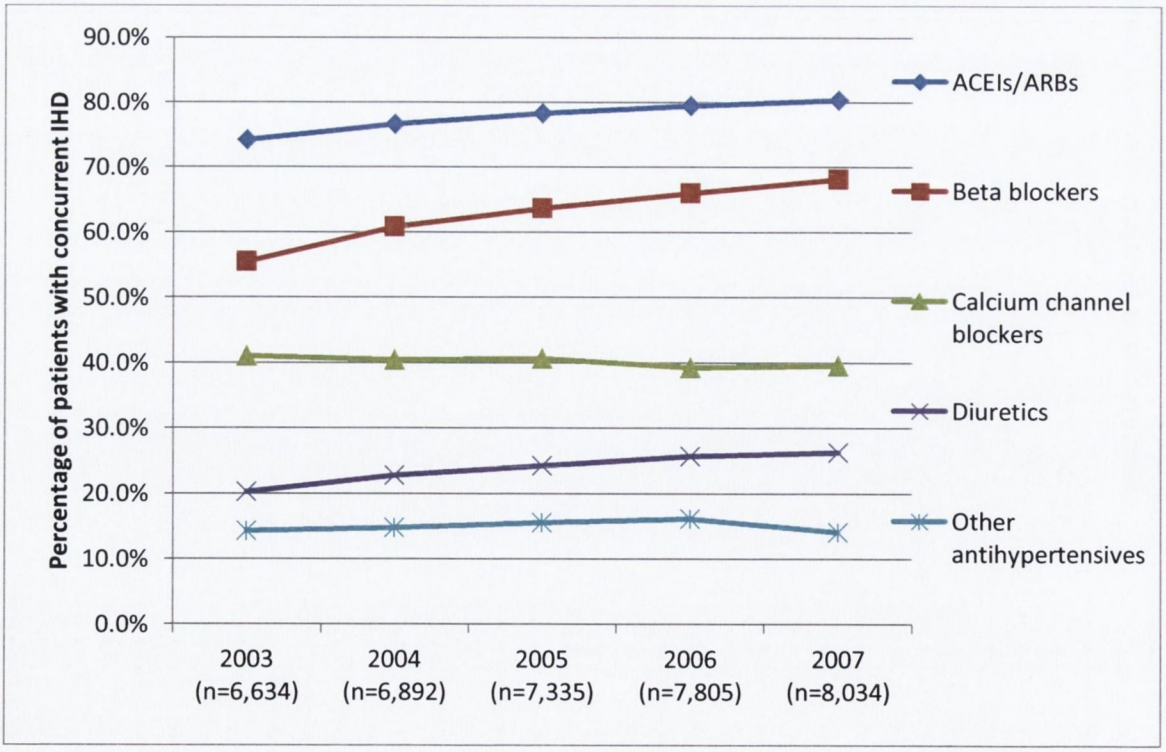


Table 5.1.1: Variations in the prescribing of preventative cardiovascular therapies in patients ≥ 45 years old with diabetes presented as adjusted OR with 95% CI

Patient characteristics		Aspirin/ clopidogrel OR⁺ (95% CI), *p*	Statins OR⁺ (95% CI), *p*	Antihypertensives OR⁺ (95% CI), *p*
Gender□	Female	0.83 (0.82,0.83) ***	1.02 (1.01, 1.02) ***	1.19 (1.19, 1.20) ***
Age group◊	≥65	1.21 (1.20, 1.22) ***	0.81 (0.80, 0.81) ***	1.72 (1.70, 1.73) ***
Type of diabetes ¥	Type 2	1.24 (1.23, 1.25) ***	1.27 (1.25, 1.28)***	1.55 (1.54, 1.56) ***
Drug scheme×	LTI	0.71 (0.71,0.72) ***	0.84 (0.83, 0.84) ***	0.50 (0.55, 0.55) ***
IHD§	IHD	3.34 (3.30, 3.37) ***	2.46 (2.43, 2.48) ***	6.21 (6.08, 6.35) ***
Health region∞	Midland	0.91 (0.90, 0.92) ***	1.41 (1.39, 1.42) ***	1.08 (1.07, 1.10) ***
	Mid-Western	0.56 (0.56, 0.57) ***	0.80 (0.79, 0.80) ***	0.93 (0.92, 0.94) ***
	North Eastern	0.70 (0.69, 0.71) ***	0.73 (0.72, 0.73) ***	1.01 (1.00, 1.02) ns
	North Western	0.52 (0.51, 0.52) ***	0.72 (0.71, 0.73) ***	0.81 (0.80, 0.82) ***
	South Eastern	0.72 (0.72, 0.73) ***	0.98 (0.97, 0.99) ***	1.05 (1.04, 1.06) ***
	Southern	0.70 (0.69, 0.70) ***	0.79 (0.79, 0.80) ***	1.05 (1.04, 1.06) ***
	Western	0.60 (0.59, 0.60) ***	0.87 (0.87, 0.88) ***	0.93 (0.92, 0.94) ***

⁺Adjusted for gender, age groups, type of diabetes, drug schemes, presence of IHD, calendar year and health regions
□ Reference category males
◊ Reference category age 45-65
¥ Reference category Type 1 diabetes
× Reference category GMS
§ Reference category diabetes patients without prescriptions for IHD
∞Reference category Eastern region

Table 5.1.2: Variations in the prescribing of antihypertensives in patients over 45 years old with diabetes presented as adjusted OR with 95% CI

Patient characteristics		ACEIs/ARBs OR⁺ (95% CI)*p*	Beta blockers OR⁺ (95% CI) *p*	CCB OR⁺ (95% CI) *p*	Diuretics OR⁺ (95% CI) *p*
Gender□	Female	1.00 (0.99, 1.00) ns	0.97 (0.96, 0.97) ***	1.07 (1.06, 1.07) ***	1.37 (1.36, 1.37) ***
Age group◊	≥65	1.17 (1.16, 1.17) ***	1.19 (1.19, 1.20) ***	1.46 (1.45, 1.47) ***	1.41 (1.40, 1.42) ***
Type of diabetes ¥	Type 2	1.17 (1.16, 1.18) ***	1.37 (1.35, 1.38) ***	1.14 (1.13, 1.15) ***	1.47 (1.45, 1.49) ***
Drug scheme×	LTI	0.76 (0.75, 0.76) ***	0.67 (0.66, 0.67) ***	0.69 (0.68, 0.69) ***	0.78 (0.77, 0.78) ***
IHD§	IHD	1.47 (1.46, 1.49) ***	3.60 (3.56, 3.63) ***	1.73 (1.72, 1.75) ***	0.86 (0.84, 0.86) ***
Health region∞	Midland	1.13 (1.12, 1.14) ***	0.88 (0.87, 0.89) ***	0.82 (0.81, 0.83) ***	0.92 (0.90, 0.93) ***
	Mid-Western	0.86 (0.85, 0.87) ***	0.87 (0.86, 0.87) ***	0.79 (0.79, 0.80) ***	1.13 (1.12, 1.15) ***
	North Eastern	0.97 (0.96, 0.98) ***	0.86 (0.85, 0.87) ***	0.83 (0.82, 0.84) ***	0.89 (0.88, 0.90) ***
	North Western	0.84 (0.83, 0.85) ***	0.80 (0.79, 0.81) ***	0.89 (0.88, 0.90) ***	1.03 (1.02, 1.05) ***
	South Eastern	1.11 (1.10, 1.11) ***	0.95 (0.94, 0.95) ***	0.87 (0.86, 0.88) ***	1.41 (1.39, 1.42) ***
	Southern	0.99 (0.98, 1.00) **	1.30 (1.29, 1.31) ***	0.77 (0.77, 0.78) ***	1.24 (1.23, 1.26) ***
	Western	0.89 (0.88, 0.90) ***	0.81 (0.80, 0.81) ***	0.86 (0.85, 0.87) ***	1.12 (1.10, 1.13) ***

⁺Adjusted for gender, age groups, type of diabetes, drug schemes, presence of IHD, calendar year and health regions
□ Reference category males
◊ Reference category age 45-65
¥ Reference category Type 1 diabetes
× Reference category GMS scheme
§ Reference category diabetes patients without prescriptions for IHD
∞Reference category Eastern region

5.1.4.2 *Trends in prescribing of preventative cardiovascular therapies in patients with newly treated type 2 diabetes*

There were 32,491 patients with newly treated diabetes from 2004 to 2006 after exclusion of patients who received all three classes of cardiovascular therapies prior to diabetes. Of those, 10% had received statins, 17% aspirin/clopidogrel, 37% all antihypertensives (16% ACE-Is, 6% ARBs and 14% BBs) prior to initiating treatment for diabetes. After initiation of antidiabetic therapy the percentages of patients prescribed cardiovascular therapies was 70% for aspirin/clopidogrel, 76% statins and 88% all antihypertensives during this study period. The first choice of antihypertensives in newly treated diabetes patients was ACEIs/ARBs (73%) followed by beta blockers (34%), calcium channel blockers (27%) and diuretics (24%).

Most patients were prescribed preventative cardiovascular therapies within 3 months of starting anti-diabetic therapy. The time to initiation of the various cardiovascular agents is presented in Figure 5.1.8, Figure 5.1.9 and Figure 5.1.10. Newly treated type 2 diabetes patients were more likely to receive cardiovascular preventative therapy with higher prescribing in earlier year of initiating antidiabetic therapy ($p<0.0001$). There were no significant difference in prescribing across gender and age. Types of oral hypoglycaemic agents and prior prescribing of other cardiovascular medications showed little influence in prescribing for cardiovascular therapies.

Figure 5.1.8: Kaplan-Meier plot of the cumulative probability of aspirin/clopidogrel initiation in patients ≥ 45 years old with newly treated type 2 diabetes

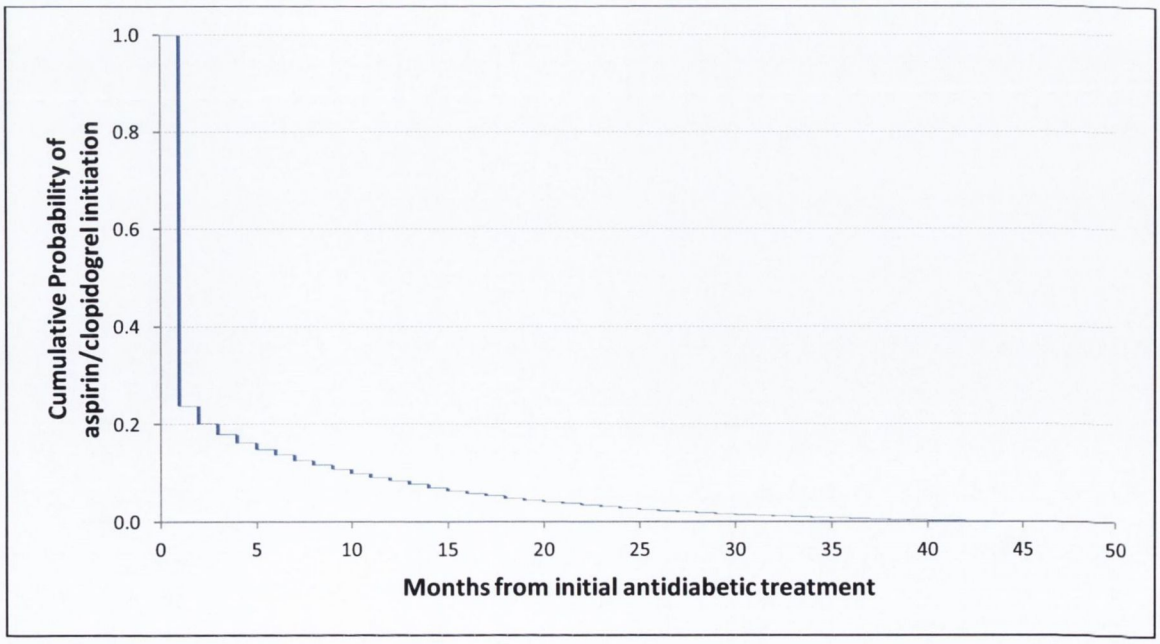


Figure 5.1.9: Kaplan-Meier plot of the cumulative probability of statins initiation in patients ≥ 45 years old with newly treated type 2 diabetes

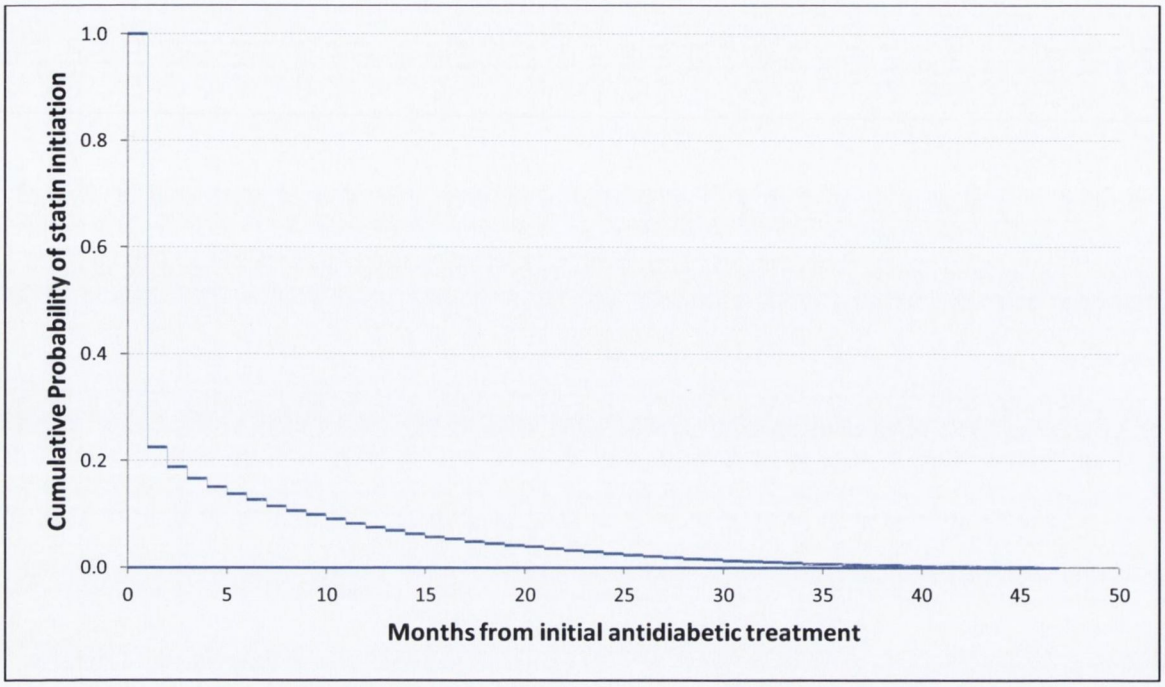
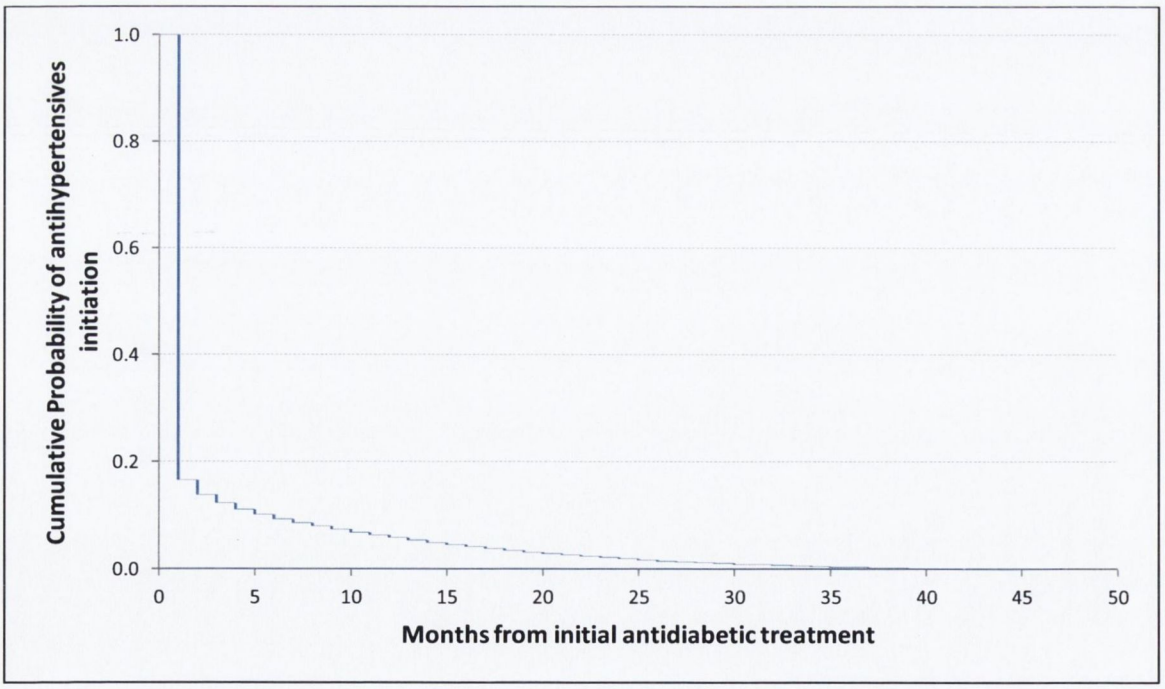


Figure 5.1.10: Kaplan-Meier plot of the cumulative probability of antihypertensives initiation in patients ≥ 45 years old with newly treated type 2 diabetes



5.1.5 Discussion

Overall trends

The prevalence of IHD in patients with treated diabetes has been declining in the Irish population. Although the prescribing of preventative cardiovascular therapies for patients with diabetes was low at the beginning of the study period, there has been an increase in the prescribing of these agents each year. More than two thirds of patients with treated diabetes were prescribed lipid lowering agents, antiplatelet agents and antihypertensives in 2007. In those with newly treated type 2 diabetes prescribed preventative cardiovascular therapies, the time taken to be initiated these agents was less than 3 months. Previous studies in Ireland in patients with IHD have also shown an increase in the prescribing of preventative cardiovascular therapies [266]. The increase in prescribing of cardiovascular therapies is consistent with the trends observed in Europe from the European Action on Secondary Prevention through Intervention to Reduce Events (EUROASPIRE) I, II and III studies [268, 269]. The overall increase in the prescribing of cardiovascular therapies in Ireland between 1985 and 2000 was found to have contributed to almost half of the decline in cardiovascular mortality in Ireland [247]. The prescribing of cardiovascular therapies such as beta blockers, aspirin and ACEIs in males and beta blockers, aspirin and calcium channel blocker in females has had an impact on the reduction of cardiovascular mortality from 1998. However, the impact of cardiovascular prescribing on mortality rates was lower in females compared to males [248]. The reduction in cardiovascular mortality may be offset by the increased prevalence of diabetes [247]. Thus, improvement in the prescribing of cardiovascular preventative therapies in patients with diabetes is important to continue the trend of decreasing cardiovascular mortality in this population.

The increase in prescribing preventative cardiovascular therapies in patients with diabetes may be attributed to national initiatives on cardiovascular prevention undertaken by the Irish health services. The first Irish cardiovascular health strategy 'Building Healthier Hearts' published in 1999 included protocols on primary and secondary prevention of cardiovascular disease in populations at risk [270].This strategy recommended that cardiovascular risk factors in patients with diabetes, even when asymptomatic, should be managed as aggressively as in patients without diabetes with pre-existing cardiovascular disease. The most recent cardiovascular policy published in 2010 also recognizes patients with diabetes as a priority group for prevention, early detection and management of cardiovascular risk [271].

Heartwatch, a secondary prevention program of coronary heart disease was initiated in the primary care setting in Ireland in 2003 and involved 20% of GPs (n=472) nationwide. This program recruited 11,542 patients with established coronary heart disease including 17% of

patients with diabetes. Clinical data under this program is centralized and thus Heartwatch provided the largest database on cardiovascular disease in primary care in Ireland [272]. Under this program, significant improvement in the prescribing of preventative cardiovascular therapies such as statins, ACEIs and beta blockers was observed [272]. There was also a significant improvement in reduction of blood pressure and cholesterol levels and improvement in the quality of care delivered by GPs who participated in this program [273]. There have been improvements in the monitoring and screening for diabetes with additional 4.2% of patients with diabetes identified in the first two years of the program and this corresponded to 29% improvement in detection rate. In addition, large increases were observed in the prescribing for statins, aspirin and ACEIs in patients with diabetes. By two years of the program, statins were prescribed to 91% of patients with diabetes [273].

Prescribing of lipid lowering agents

The prescribing of statins in patients with treated diabetes in the Irish population has increased for primary and secondary cardiovascular prevention. A meta-analysis by the Cholesterol Treatment Trialist (CTT) collaborators has demonstrated that participants with diabetes treated with statins had a 9% reduction in all-cause mortality and 21% reduction in major vascular events per mmol/L LDL cholesterol reduction [274]. The proportional effects of statins were similar irrespective of baseline characteristics of patients. This meta-analysis included 14 landmark clinical trials on statins such as Scandinavian Survival Simvastatin Study (4S), West of Scotland Coronary Prevention Study (WOSCOPS), Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), Anglo-Scandinavian Cardiac Outcomes Trial- Lipid Lowering Arm (ASCOT-LLA) and Collaborative Atorvastatin Diabetes Study (CARDS) [274]. However, a recent meta-analysis did not demonstrate significant reductions in all-cause mortality in patients prescribed statins for primary prevention including those with diabetes compared to placebo [275]. The prescribing of statins in Ireland is amongst the highest in Europe [268, 276]. This is translated into a significantly better lipid control in the Irish population compared to other European countries as in the EUROASPIRE III study [268]. Statins accounted for the largest expenditure on medications by the Irish health services in 2006 [277]. However, the prescribing of statins as secondary preventative measures in those at risk of cardiovascular disease has been demonstrated to be cost effective with less than €7000 per life years gained [278].

There has been an increase in the prescribing of atorvastatin and rosuvastatin in patients with treated diabetes with a concurrent decrease in the prescribing of pravastatin, fluvastatin and simvastatin. Pharmaceutical marketing strategies may account for the preferences in statins prescribing. Pravastatin, simvastatin, atorvastatin and rosuvastatin was shown to be effective in both primary and secondary prevention of cardiovascular disease compared to placebo in

patients with diabetes [274]. Pravastatin and fluvastatin represent first generation statins and are low in potency as compared to newer generation statins [279]. In terms of cholesterol lowering effects, meta-analysis on RCTs with head to head comparison between statins showed a significant but clinically minor difference (<7%) between the different types of statins with only rosuvastatin and atorvastatin (20mg or higher) reducing LDL cholesterol by more than 40% [280]. Intensive high dose statins have been shown to reduce cardiovascular events and mortality in patients post-acute coronary events and also in those with cardiovascular risk factors [281]. Simvastatin and pravastatin are now available as generic preparations and have thus become cheaper than atorvastatin. In contrast to other European countries, most prescribing of statins in Ireland are branded preparations accounting for the high cost born by the Irish health system [277]. The Heart Protection Study has shown that the generic simvastatin regimen producing a mean reduction of about 1 mmol/L of LDL, was cost effective even in those at risk of a major vascular event as low as about 1% per year [282].

The use of other lipid lowering agents such as fibrates was very low in Ireland compared to other European countries [268]. Fibrates and omega 3 fatty acid were recommended only as third line therapy or additional therapy if statins failed to achieve target cholesterol level in patients with diabetes [5]. Fibrates were shown to reduce LDL and increase HDL but have a modest impact on reduction of cardiovascular events [283]. The combination of statins with a fibrate especially gemfibrozil increases the risk of rhabdomyolysis especially in older patients with diabetes [284]. Ezetimibe has been shown to effectively achieve 17-18% reduction of LDL cholesterol [283] and can be used alone or in combination with statins. A fixed preparation of ezetimibe and simvastatin, recently available in the market has been shown to improve lipid profile without an increase in side effect profiles [285]. Omega-3-fatty acid was shown to reduce cardiovascular events and has recently been endorsed by the American Heart Association for use as secondary preventative therapy in those with coronary heart disease [283].

Prescribing of antiplatelet agents

Similar to the trends observed in the prescribing of statins, there has been an increase in the prescribing of antiplatelet agents especially of aspirin in both primary and secondary prevention setting. The use of antiplatelet agents such as aspirin and clopidogrel has been shown to prevent progression of atherosclerotic plaques and is thus effective in reducing cardiovascular morbidity and mortality [286]. However, specific studies in patients with diabetes showed equivocal results. The Antiplatelet Trialist Collaboration Meta-Analysis only showed slight and non-significant reduction in cardiovascular events in patients with diabetes with use of aspirin for primary prevention [287]. Other more recent meta-analyses on patients with diabetes also found a non-significant reduction of cardiovascular events with aspirin as primary preventative therapy

[288, 289]. However, the regular use of aspirin is reasonable in the prevention of cardiovascular disease in patients with diabetes and concurrent cardiovascular risk factors [289]. Clopidogrel as secondary preventative therapy has also been shown to be beneficial in reducing vascular events in patients with diabetes [290]. The ADA currently recommends clopidogrel as adjunctive therapy in patients with diabetes at very high risk of cardiovascular disease of as alternative therapy in patients who are intolerant to aspirin [291].The combination of aspirin and clopidogrel in patients with diabetes showed no significant benefit on prevention of cardiovascular events compared to aspirin alone but increased the risk of major bleeding [292].

Prescribing of antihypertensive agents

There has also been an increase in prescribing of all antihypertensives in patients with treated diabetes with over eighty percent of patients aged 45 years old and over being prescribed an antihypertensive agent(s) in this population. In the general diabetes population, ACEIs and ARBs were the first choice agents. In the cohort of patients with diabetes and concurrent IHD, in addition to increased prescribing of ACEIs and ARBs there has been an increase in the prescribing of beta blockers and a reduction in the prescribing of calcium channel blockers. Studies have shown that controlling concurrent hypertension in patients with diabetes leads to substantially reduced risk of cardiovascular morbidity and mortality with the added benefit of reducing risk for microvascular events. The reduced risk of cardiovascular disease with improved control of hypertension in patients with diabetes is substantially greater than that observed in the general population with similar blood pressure level [293]. Previous studies have also shown an increase in the prescribing of antihypertensives such as ACEIs, ARBs and calcium channel blockers in Ireland [64]. The pattern observed in the prescribing of antihypertensive in this population is similar to those observed elsewhere in Europe during the same study period [294, 295]. However, compared to other European countries, the prescribing of beta blockers for secondary prevention is high in Ireland while the prescribing of ACEIs and diuretics is somewhat lower [268]. The presence of diabetes has been shown to have an influence in the prescribing of antihypertensives in the general Irish population with the avoidance of beta blockers in this population [296].

The benefit of ACEIs and ARBs in patients with diabetes is beyond blood pressure lowering in patients with diabetes. ACEIs and ARBs are also prescribed for microalbuminuria [297], cardiac failure [298] and post myocardial infarction [299]. Due to the limitation of no diagnostic information in the database, it is not possible to ascertain the reason for commencement of ACEIs or ARBs in this cohort. Compared to ACEI, ARBs offer less cardiovascular protection and thus ACEIs is preferred for cardiovascular prevention unless patients are intolerant to ACEIs in which substitution with ARBs is reasonable [300]. There were no significant differences in risk of myocardial infarction and cardiovascular mortality between ACEIs or ARBs compared to calcium

channel blockers or thiazide diuretics [301]. Controversies regarding the use of beta blockers in patients with diabetes have not deterred prescribers from choosing this agent especially in those with concurrent IHD. Guidelines on hypertension treatment no longer favour the prescribing of beta blockers in patients with or without diabetes except in those with established coronary heart disease [301]. The previously recommended ABCD antihypertensive regime (ACEIs or ARBs and beta blockers in those less than 55 years of age and calcium channel blockers and diuretics in those over 55 years) was replaced in favour of the ACD regime [302] Recent meta-analyses demonstrated that the use of beta blockers as first line therapy in hypertension was associated with increased risk of stroke with no benefit on cardiovascular morbidity and mortality compared with other antihypertensive agents. However, beta blockers were shown to reduce mortality in those with previous myocardial infarction [303, 304]. Beta blockers as well as thiazide diuretics are associated with increased risk of new onset diabetes in those at risk of diabetes and worsened glycaemic control while ACEIs or ARBs were associated with reduced risk of new onset diabetes and this will be discussed in Chapter 7 (Section 7.4.5).

The need to control blood pressure tightly in patients with diabetes may necessitate the need for combination antihypertensive therapy either as separate agents or fixed dose combinations. Most patients prescribed double combination therapy were being prescribed ACEI based combination antihypertensives. Increased prescribing of combination with ARBs was also observed. The European Society of Cardiology (ESC) recognizes the need for combination antihypertensive in patients with diabetes and recommends ACEIs or ARBs as part of hypertension management [305]. The use of ACEI or ARB with beta blocker in patients with diabetes is indicated for secondary prevention post coronary heart disease or for heart failure The combination of ACEIs or ARBs with calcium channel blockers was shown to reduce the risk of major cardiovascular events with improved metabolic outcome compared to diuretic based combinations [306]. The combination of both ACEI and ARB targeting the renin angiotensin system showed no significant difference in terms of lowering blood pressure and reducing proteinuria compared to ACEI alone [307]. Although the combination of thiazide and beta blockers was not recommended in patients with hypertension due to increased risk of new onset diabetes, the use of these agents in patients with established diabetes is reasonable [302].

Gender, age, types of diabetes and drug scheme variations

Consistent with other studies, females were more likely to be prescribed statins in this population [46, 48, 277]. This may be due to greater awareness of cholesterol levels and treatment in females [277]. These findings, however, contrast those in the DCCT/EDIC study cohort in the US and Canada population whereby females were shown to be less likely to receive statins, aspirin and ACEI or ARBs. Women in the DCCT/EDIC study were shown to be less likely to

be prescribed statins even in the subset with high LDL cholesterol levels [308]. Older patients were less likely to be prescribed statins compared to younger patients. This may be due to increased comorbidities and caution because of side effects associated with statins in these patients. Adverse effects of statins such as myalgia, myopathy, which can lead to rhabdomyolysis and abnormal liver function are increased with advanced age [309]. However, studies have shown that the benefit of statins on reduction of cardiovascular events and mortality also extend to the elderly population [310]. In contrast to statins, females were less likely whilst elderly patients were more likely to be prescribed aspirin/clopidogrel compared to males and younger patients respectively. The higher prescribing of aspirin in males and elderly may be due to the increased risk of cardiovascular disease in this population. The elderly were more likely to be prescribed all types of antihypertensives compared to younger patients and this may be due to increased prevalence of hypertension in the elderly diabetic population and increased risk of cardiovascular disease in these patients [257].

This study showed that patients with type 2 diabetes were more likely to be prescribed cardiovascular preventative therapies compared to those with type 1 diabetes. Patients with type 2 diabetes may present to the primary care with multiple cardiovascular risk factors as these patients were generally older and more overweight compared to patients with type 1 diabetes. Cardiovascular mortality accounts for 44% of patients with type 1 and 52% of patients with type 2 diabetes [311]. Guideline for integrated care including cardiovascular prevention for patients with diabetes in Ireland focus more on patients with type 2 diabetes compared to patients with type 1 diabetes [5]. Thus there is also a need to develop a working guideline on cardiovascular prevention for patients with type 1 diabetes in Ireland.

Compared to the prescribing of antidiabetic therapies, those under the LTI scheme were less likely to be prescribed cardiovascular preventative therapies compared with the GMS population. A previous study in 2003 did not demonstrate significant differences between the two schemes with regards to prescribing of cardiovascular medications [146]. As the GMS scheme covered all patients over 70 years old after July 2001, most of the prescribing of cardiovascular therapies would have been initiated under the GMS scheme. The differences between the two schemes may represent the differences in the burden of cardiovascular diseases itself across different socioeconomic groups. A previous study has shown that there was an inverse relationship between socioeconomic and cardiovascular disease [312]. In addition, aspirin was not available for reimbursement under the LTI scheme in 2003. The procedure to claim for cardiovascular medications in patients with diabetes under the LTI scheme was not as straightforward as antidiabetic therapies thus patients under the LTI scheme may also opt to pay for cardiovascular medications on their own. The HSE community drug schemes should facilitate

easy access to antidiabetic and cardiovascular medications for patients under the LTI scheme. Initiatives should be taken by the pharmacists and the HSE to increase the awareness of patients eligible under the LTI scheme of their access to free cardiovascular medications.

Regional variations

The variation in the prescribing of cardiovascular therapies in patients with diabetes across different regions in Ireland has been observed previously [48] and was also shown in this study. The variations in the prescribing is more apparent in the prescribing of statins and aspirin/clopidogrel compared to the prescribing of antihypertensives. Similar to previous studies in the diabetes population, the prescribing of preventative cardiovascular therapy is higher in the Midlands and the Eastern region compared to other regions in the country [48, 146]. All regions including the Midlands were less likely to be prescribed aspirin compared to the Eastern region. An East-West division was observed, as found previously [48, 146], with those from the Western part of the country (Mid-Western, North Western and Western) being less likely to be prescribed cardiovascular therapies especially antihypertensives, compared to those from the East. A previous study has shown that over fifty percent of GMS prescriptions in the primary care setting for cardiovascular medications were initiated by hospital clinicians [266]. In Dublin itself, there are six teaching hospitals affiliated to the three medical schools. This may explain the higher prescribing of cardiovascular therapies for patients with diabetes in the Eastern region. The structured diabetes care in the Midland has been described previously. In terms of cardiovascular prevention, audit of the Midland integrated care has demonstrated that the prescribing of cardiovascular preventative therapies in this region were extremely high with significant clinical improvement in cardiovascular risk factors observed under this program [83]. Other possible explanations for the regional variations observed in the prescribing for patients with diabetes have been discussed in Section 3.1.5 and Section 4.1.5.

Strengths and limitations

This study encompasses a 5-year study period enabling trends in prescribing of cardiovascular therapies in patients with diabetes to be examined compared to previous Irish studies. However, due to lack of diagnostic information, it is not possible to examine the reasons for initiation of cardiovascular therapy in these patients. Although duration of diabetes is also a predictor of cardiovascular mortality, the duration of diabetes in those with prevalent diabetes was not determined. Thus one may only hypothesize the reasons for the variations observed in the prescribing of cardiovascular medications across age, gender, types of diabetes, drug scheme and health regions. The use of nitrate prescription as a marker for IHD also may not truly capture populations at risk of cardiovascular disease. The validation study on the use of nitrates as marker for IHD was performed in 1998 [313]. However, the use of nitrates is still valid for studies on IHD

in population. The longitudinal prescribing of cardiovascular therapies will be examined in Chapter 6.

CHAPTER 6 : ADHERENCE TO PHARMACOTHERAPY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

6.1 Adherence to pharmacotherapy in patients with diabetes using prescription refill records and self-reported questionnaires

6.1.1 Background

The WHO defined adherence to chronic disorder as the extent to which a person's behaviour - taking medications, following diet and or executing lifestyle changes correspond with agreed recommendations from a heath care provider [49]. There are different categories of non-adherence in health care which include delay in seeking medical care, non-attendance of appointments and failure to follow instructions with regards to treatment. Adherence to medication is defined as the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen [314]. Non adherence to medications can be classified into (i) those who fail to collect medications after receiving prescriptions, (ii) those who take less than the prescribed doses or prescribed frequencies, (iii) those who forget to take the medications at times, or (iv) those who cease to continue with the prescribed medications [315]. Non adherence to treatment is common in those with chronic conditions especially in asymptomatic conditions such as hypertension and diabetes [49]. Only half of patients in developed countries adhere to long term therapy for chronic conditions [49]. Non adherence to treatment is associated with increased morbidity and mortality as well as increased health care cost [316].

Adherence to medication can be measured using direct or indirect methods. Direct methods include measurement of the drug, its metabolite or marker in the bodily fluid. Another method is using direct observation of medication taking and is more suitable in the hospital population rather than primary care population. Although more accurate than other measures, direct methods may be invasive, time consuming and costly. Indirect measures include electronic medication monitoring, assessment of clinical response, pill counting, utilization of administrative database or self-reported adherence questionnaires [317]. Measures of adherence using prescription refill records include medication possession ratio (MPR), proportion of days covered (PDC), calculation of medication-total (MED_TOT), refill compliance rate (RCR), compliance ratio (CR), medication possession ratio, modified (MPRm), continuous measure of medication gaps (CMG), continuous multiple interval measure of oversupply (CMOS), continuous single interval measure of medication acquisition (CSA), adherence ratio, refill adherence, compliance rate,

continuous multiple-refill-interval measure of medication availability (CMA), adherence index, compliance ratio, or compliance index [318]. Currently there are no universally accepted methods to determine adherence in patients with diabetes either from administrative databases or from self-reported questionnaires [319]. MPR and PDC have been shown to have the highest predictive value of hospitalizations in patients with diabetes compared to other measures of adherence using administrative claims database [319].

As discussed in previous chapters, patients with diabetes are often prescribed multiple therapies with a combination of antidiabetic agents, lipid lowering agents, antihypertensive medications and antiplatelet agents. The importance of achieving good glycaemic control with antidiabetic agents and the use of cardiovascular preventative therapies have been discussed in Section 4.1.5, Section 4.2.5 and Section 5.1.5. Thus, adherence to these medications is important in order to reduce the risk of the long term debilitating complications of diabetes. In addition, patients with diabetes are also required to adhere to other measures such as diet, physical activity and in some, self-monitoring of blood glucose as part of their diabetes self-care management [49]. A systematic review on adherence to oral antidiabetic medications in patients with diabetes found that adherence rates ranged from 36% to 93% in different retrospective and prospective study populations [314]. Non-adherence to antidiabetic medications was found to be associated with 58% increase in all-cause hospitalization and 81% increase in all-cause mortality [320]. Low adherence to antihypertensive agents has been found to be associated with increased coronary heart disease, cerebrovascular disease and chronic heart failure [50]. Statin adherence rates of more than 80% were found to be associated with lower risk of recurrent myocardial infarction and reduced mortality in patients with myocardial infarction [51]. In patients with diabetes under the Medicare program in USA, 46% were found to be non-adherent to ACEIs or ARBs in patients and this was associated with 5% increased risk for potentially avoidable hospitalizations in these patients [52].

There are several predictors that may affect adherence to treatment such as presence of psychological problems, cognitive impairment, adverse effects of medications, presence of barriers to care or medications, the complexity of medication regimen and cost of medications [321, 322]. The most salient influences on adherence are patients' beliefs about their medications and about medicines in general [323]. Amongst factors that have been associated with adherence to treatment in patients with diabetes are patients' own understanding of the treatment regimen, perception of treatment benefits, adverse effects of medications, medication costs, forgetfulness, regimen complexity, polypharmacy, difficulties in medication refills and emotional well-being [324, 325]. Patients' disease and medication beliefs have also been shown to influence adherence in patients with diabetes [326]. Identifying factors predicting adherence to

medication in patients with diabetes is important in order to identify those at risk of adherence and to drive interventions aimed to improve adherence in these patients. In addition, few studies have examined medication beliefs in patients with diabetes [326, 327].

This research is undertaken to examine the adherence to oral antidiabetic medications and cardiovascular preventative therapies in patients with type 2 diabetes from the pharmacy claims database and also from two main teaching hospitals in Ireland. Factors that influence adherence as well as the relationship between beliefs towards medicines and adherence to medications will be determined in the Irish population with type 2 diabetes. This study also explores the relationship between adherence to medications and intermediate clinical outcomes such as HbA1c, blood pressure and cholesterol levels.

6.1.2 Specific objectives

1) To examine the national trends in adherence to oral antidiabetic medications and cardiovascular preventative therapies in patients with treated type 2 diabetes using prescription refill records
2) To determine the predictors of adherence using demographic information available from the pharmacy claims database
3) To examine the correlation between self-reported adherence using questionnaires and adherence as measured from prescription refill records in patients with type 2 diabetes mellitus attending diabetes outpatient clinic
4) To examine the beliefs towards medications and its relationship with adherence to medications in patients with type 2 diabetes
5) To determine the relationship between adherence to treatment and intermediate clinical endpoints in terms of laboratory measurements and physical examinations during routine annual review of patients from two diabetes outpatient clinics.

6.1.3 Methods

6.1.3.1 Medication adherence in a population with newly treated type 2 diabetes using prescription refill records

The HSE PCRS database was used to identify patients with newly treated type 2 diabetes under both the GMS and LTI schemes from 1st January 2006 to 31st December 2006 using the methods described in Section 3.2.3 (n=10,023). These patients were followed up longitudinally to examine their medication claims from 1st January 2007 until 31st December 2007. The medication

possession ratio (MPR) was chosen as a measure of adherence for the 365-day study period. The MPR is the most commonly used method in calculating medication adherence using prescription refill records [318]. The total cumulative defined daily dose (DDD) dispensed were calculated for each class of oral antidiabetic agents. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. The DDD is a unit of measurement and does not necessarily reflect the recommended or prescribed daily dose. A patient is assumed to be prescribed 365 DDDs of oral antidiabetic agent in 365 days. MPR was calculated by dividing the total cumulative DDDs by 365 days and was expressed as percentage. PROC SQL command in SAS version 9.1 was used for this purpose. This is a crude measure of adherence as this method does not take into account changes in dosage or prescribed dosage of more or less than the stated DDDs by the WHO during the study period. Those prescribed more than 365 DDDs for oral antidiabetic agents over the study period will have higher adherence score compared to those prescribed less than 365 DDDs. In those prescribed more than one oral antidiabetic agents, an average MPR was calculated from the individual classes of oral antidiabetic agents. This may result in apparently higher adherence level in those prescribed more than one agent. Separate MPRs were calculated for lipid lowering agents, antihypertensives, antiplatelet agents and ACEIs or ARBs. Patients are considered adherent to the medications being examined if the MPR was 80% or more.

The median MPRs for each separate medication are presented. MPR scores were also divided into adherent (MPR>80%) as the percentage of patients categorized as having good adherence to medications and non-adherent (MPR<80%) as the percentage of patients categorized as having poor adherence to medications. Influence of gender, age groups, drug scheme, number of oral antidiabetic medications, prescribing of insulin and presence of chronic disease on adherence in patients with newly treated type 2 diabetes were examined using logistic regression. The prescribing of certain medications was used as surrogates for chronic diseases [328]. These chronic diseases were grouped into (i) cardiovascular diseases (cardiac arrhythmias, hypertension, dyslipidaemia, and IHD) (n=6,336), (ii) neurological diseases (Parkinson's, epilepsy and dementia) (n=1,225), (iii) psychiatric conditions (psychotics, depression, anxiety and sleep disorders) (n=3,609), (iv) rheumatological disease (gout, rheumatoid arthritis and osteoporosis) (n=926), (v) respiratory conditions (chronic obstructive pulmonary disease (COPD), asthma) (n=2,136) (vi) gastrointestinal conditions (peptic ulcer disease) (n=4,027) , (vii) endocrine disorder (hyper/hypothyroidism) n=625) (viii) sensory disease (glaucoma) (n=409) and (ix) neoplastic diseases (n=234). Univariate analysis using logistic regression were performed for each group of chronic diseases and only those with significant association with MPR score were included in the final statistical analysis.

6.1.3.2 Self-reported adherence and prescription refill adherence

A prospective cohort study was carried out at the Diabetes outpatient clinic, Connolly Hospital, Blanchardstown. The Connolly hospital is a major teaching hospital affiliated to the Royal College of Surgeons Ireland. Ethical approval was obtained from Faculty of Health Sciences Research Ethics Committee of Trinity College Dublin and Research Ethics Committee of Connolly Hospital. To detect a correlation of p=0.2 or greater with 5% significance, a study with 80% power required 153 patients to be recruited. Patients with type 2 diabetes newly presenting to the diabetes outpatient clinic were identified from 1st July 2008 to 31st December 2008. Patients were given an information leaflet and consent form to participate in the study two weeks prior to their outpatient clinic appointment date. Patients who agreed to take part (n=152, 67% males, mean (SD) age 61±13) completed their background information questionnaire, adherence questionnaire and beliefs about medicine questionnaire (Appendix 2) at the outpatient clinic. This background questionnaire included presence of limitations in activities of daily living (ADL), presence of chronic conditions, medications prescribed, smoking status, alcohol intake, social support at home, ethnicity and highest level of education (Appendix 2). The same cohort (n=152) was invited for review 2 years after the initial visit. Thirty-two patients did not re-attend for follow up visit. During their follow up review, patients were given the same background information and self-reported adherence questionnaires (n=120, 67% males, mean (SD) age 63±13). A research clinician facilitated the completion and collection of these questionnaires.

Self-reported medication adherence was examined using the 5-item Medication Adherence Report Scale (MARS) [329]. This survey assesses the likelihood of patients to take their medications as prescribed. The 5-item MARS asked respondents to rate the frequency with which they engaged in each of the five types of non-adherent behaviour. All items are rated on a 5-point scale (5=never, 4=rarely, 3=sometimes, 2=often and 1=always). Scores for each of the five items are summed to give a total score ranging from 5 to 25 where higher scored indicate higher levels of self-reported adherences. This scale can be used to grade according to their relative adherence rather than as an exact measure of when and how patients consume their medications [329]. Patients with scores of less than 20 out of 25 were categorized as non-adherent to medications.

The GMS or LTI number for individual patients were obtained from the patients by the clinician in charge to examine the longitudinal prescription refill by these patients from their baseline visit to their annual follow up review visits using the HSE PCRS pharmacy claims database. Of the original cohort, only 86 patients with a valid GMS or LTI number and prescription claim in the HSE PCRS database within the study period were identified (56% males, mean age 67±13). Thus this reduced the power of the study to examine the relationship between

adherence and clinical outcome in this cohort. MPRs for oral antidiabetic medications, lipid lowering medications and antihypertensive agents were calculated from each patient using the methods described in Section 6.1.3. The 365 day period for MPR calculation started from their baseline index visit. Those with MPR>80% were considered to have good adherence to the medications being examined in this cohort.

Logistic regression was used to examine background factors that might predict adherence using the self-reported adherence score and MPR. Spearman's correlation was used to examine the correlation between self-reported adherence and MPR from prescription refill records. SPSS 16 was used for statistical analysis.

6.1.3.3 Beliefs towards medication taking behaviour and the relationship with adherence to medications

The same cohort as described in Section 6.1.3.2 was recruited for this study to assess beliefs and attitude towards medicine and its relationship with adherence to medications, both self-reported adherence and prescription refill adherence. Beliefs and attitude towards prescribed medications were assessed using the validated Beliefs about Medicines Questionnaire (BMQ) [330]. The BMQ consists of an eighteen item questionnaire that measures beliefs about medicines and is divided into two main sections. The BMQ-Specific assesses beliefs about prescribed drugs while the BMQ-General assesses beliefs about medicines in general. The BMQ-Specific is organized into two 5-statement scales. The Necessity scale identifies beliefs about the necessity of prescribed medication, and the Concerns scale identifies concerns about prescribed medications. The BMQ-General is organized into two 4-statement scales. The Harm scale assesses beliefs that drugs are harmful, addictive, or poisons and the Overuse scale assesses beliefs that medicines are overused by clinicians. Each item of the BMQ is scored using a 5-point scale (1=strongly disagree, 2=disagree, 3=uncertain, 4= agree, and 5= strongly agree). Individual item scores are summed to generate each of the 4 scale scores. The range of the Necessity and Concern scale scores is 5 to 25 and the range of the Harm and Overuse scale scores is 4 to 20 with higher BMQ scores indicating stronger beliefs.

The internal reliability for each of the BMQ scale was examined using Cronbach alpha coefficient. The sum scores for each scale are presented as means and standard deviations. The correlations between the BMQ scores and adherence; either self-reported or by prescription refill record were examined using Spearman's correlation. The Kruskal Wallis test was used to examine the relationship between each scale and subscale of the BMQ scores and adherence as categorical variable.

6.1.3.4 Adherence to medication and relationship with intermediate clinical outcomes

Prospective cohort study

The patient population for this study was recruited from Connolly hospital and has been described in Section 6.1.3.2. Blood samples from the patients for biochemical laboratory measurements such as HbA1c, total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol and creatinine were obtained by the nurses at the diabetes centre 2 weeks prior to patients' appointment at the outpatient clinic using standardized methods. Clinical measurements such as body mass indices (BMI), sitting systolic and diastolic blood pressure were taken by the nurses at the outpatient clinic. At the follow up visit, clinical measurements were obtained as per initial appointment.

Retrospective cohort study

A retrospective cohort study was performed using the DIAMOND database held at the Diabetes Centre, St James's hospital, Dublin. Ethical approval was obtained from St James's Hospital and Federated Dublin Voluntary Hospitals Joint Research Ethics Committee. St James's hospital is Ireland's largest teaching hospital and is affiliated to Trinity College Dublin. Two endocrinology consultants are dedicated to the care of patients with diabetes in this hospital. Approximately 8,000 patients attended the diabetes outpatient clinic over a ten-year period and their clinical information is recorded in the DIAMOND database during each visit to the hospital. Demographic information such as gender, age, address, date of birth, smoking status, alcohol intake and GP information were available from the database. Clinical information available included types of diabetes, physical examinations such as BMI, systolic and diastolic blood pressure and biochemical measurements such as HbA1c, lipid profiles, renal profiles and thyroid profiles. Administrative information such as reasons for each visit, non-attendance of appointment, referral to diabetes services and attending clinicians or other allied health professionals were also recorded in the database.

Patients with type 2 diabetes under the GMS schemes with their first visits to the diabetes centre from 1st January 2007 to 31st December 2007 were identified from the DIAMOND database (n=156, 60% males, mean (SD) age 66±10). Patients were followed up until their first annual review ranging from 10th January 2007 to 31st March 2009 (Mean follow up time 1.3 years ±4, n=128). Information from these patients was linked to the HSE-PCRS pharmacy claims database using their unique GMS number. To ensure confidentiality, patient identifiers were removed once linkage was performed.

Although GMS numbers were available for all the 160 patients selected for the retrospective cohort study, only 92 patients were available for record linkage study using the

prescription claims database (50% males, mean age 69, ± 12). The other 68 patients did not have their records available in the pharmacy claims database. This may be due to several reasons such as incorrect GMS number recorded in the St James's administrative database, patients buying their own medications, hospitalizations, patients not prescribed any medications and patients who did not collect their prescribed medications.

MPR was calculated as the measure of adherence for oral antidiabetic agents, lipid lowering agent, antihypertensives and ACEI or ARBs using the methods described in Section 6.1.3.1. The 365 day period was calculated from the first visit to the hospital and in those patients who were not prescribed medications during the first visit (n=19), the 365 day period was calculated from the date of their first prescription. In 10 patients who were initiated oral antidiabetic medications after 31st March 2009, patients were followed up only up to 30th April 2010 and the MPR calculated during this time period. MPR were analysed as a continuous variable and also as a dichotomous variable with MPR>80% considered as adherent and MPR<80% considered as poor adherers to medication.

Statistical analysis

Clinical measurements are presented as percentages for categorical data and means with standard deviations for continuous measures. The paired *t*-test was used to compare the changes in clinical measurements between baseline visits and follow up annual review visits. The relationship between (1) adherence to oral antidiabetic agents and HbA1c (2) adherence to lipid lowering agent and lipid profiles (total cholesterol, triglycerides, HDL and LDL cholesterol) and (3) adherence to antihypertensives and systolic blood pressure were examined in both the prospective cohort and the retrospective cohort. Adjustments were made for gender, age groups, prescribing of insulin and presence of chronic diseases where they were found to be significantly related to adherence as per Section 6.1.3.1. A test for linear trend using multiple regression analysis was used to examine the relationship of clinical measurements and adherence (self-reported or MPR) by including the clinical measurements as continuous terms in the model. The relationship between adherence (self-reported or MPR) and clinical measurements were also examined as dichotomous variable using the values as recommended by the Irish guideline on type 2 diabetes [5] using non parametric Mann Whitney test. For this purpose HbA1c of 6.5%, systolic blood pressure of 130 mmHg and diastolic blood pressure of 80 mmHg, total cholesterol of 4.5 mmol/l, LDL cholesterol of 2.5 mmol/l, triglyceride of 2.0 mmol/l and HDL cholesterol of 1.0 mmol/l were chosen as cut off values. In addition, as non-adherence patients may have poorer clinical outcomes, the relationship between adherence to medication and the 75th quartile for clinical measurements as obtained from the initial visit was also examined. For this purpose, patients were divided into two groups, those with clinical measurements above the 75th quartile

and those with clinical measurements below the 75th quartile. Non parametric Mann Whitney test was used to examine the relationship between adherence to medications and achievement of clinical measurements below the 75th quartile.

6.1.4 Results

6.1.4.1 Medication adherence in population with newly treated type 2 diabetes using prescription refill records

10,023 patients (57% males, 71% GMS and 46% over 65 years old) were identified as patients with newly treated type 2 diabetes in 2006. 64% were on monotherapy while the rest were prescribed more than one oral antidiabetic agents. 75% were prescribed metformin, 52% sulphonylureas, 6% glitazones, 5% fixed oral combination agent, 3% other antidiabetic agents and 12% insulin. In addition, 67% were prescribed lipid lowering agents, 63% were prescribed antiplatelet agents and 75% antihypertensives with 62% being prescribed either ACEIs or ARBs.

Adherence to oral antidiabetic agents

Overall, 57% of patients with newly treated type 2 diabetes were considered adherent to oral antidiabetic medications (MPR>80%) as measured from the pharmacy claims database. Only 44% of patients under the age of 45 years old and 43% of patients concurrently being prescribed insulin were adherent to oral antidiabetic medications (Table 6.1.1). Those over 45 years old were more likely to adhere to oral antidiabetic medications compared to younger patients and those under the LTI schemes were more likely to adhere to medications compared to those under the GMS scheme. Amongst chronic diseases being examined, presence of cardiovascular diseases was associated with increased likelihood of adherence to medications while presence of neurological, gastrointestinal and psychiatric conditions was associated with reduced adherence to medications. After adjustment of other covariates, no significant relationship was observed between the presence of psychiatric conditions and gastrointestinal disease with adherence. Those prescribed metformin were more likely to adhere to medications compared to those prescribed other oral antidiabetic agents. Those prescribed two or more oral antidiabetic medication were slightly more likely to be adherent compared to those with only one medication. Patients with type 2 diabetes concurrently being prescribed insulin were significantly less likely to adhere to their oral antidiabetic medications.

Table 6.1.1: Adherence to antidiabetic medications and factors predicting adherence in patients with newly treated type 2 diabetes from 1st January 2007 to 31st December 2007

Patient characteristics		% adherent	Unadjusted OR (95% CI) *p*	Adjusted† OR (95% CI) *p*
Gender□	Males (n=5,675)	58%	-	-
	Females (n=4,337)	56%	0.92 (0.83, 1.02) ns	0.99 (0.89, 1.10) ns
Age groups◊	16-44 (n=1,452)	44%	-	-
	45-64 (n=3,973)	61%	1.96 (1.68, 2.29) ***	1.65 (1.40, 1.94) ***
	≥65 (n=4,598)	57%	1.73 (1.48, 2.02) ***	1.59 (1.34, 1.88) ***
Drug scheme ¥	GMS (n=7,133)	55%	-	-
	LTI (n=2,890)	60%	1.23 (1.11, 1.36) **	1.27 (1.92, 2.77) **
Chronic diseases∞	Cardio (n=8660)	59%	2.45 (2.05, 2.92)***	2.31 (1.92, 2.77)***
	Neurological (n=1,225)	52%	0.80 (0.69, 0.93) *	0.83 (0.71, 0.96) *
	Psychiatric (n=3,609)	54%	0.84 (0.76, 0.93) **	1.03 (0.92, 1.17) ns
	Gastrointestinal (n=4,027)	55%	0.82 (0.74, 0.91) **	0.90 (0.80,1.01) ns
No of anti-diabetic Δ	1 (n=6,463)	56%	-	-
	2 or more (n=3,558)	59%	1.15 (1.04, 1.28) *	1.18 (1.06, 1.31) *
Class of antidiabetic □	Metformin (n=7,498)	58%	1.23 (1.09, 1.40) **	1.36 (1.03, 1.78) *
	Sulphonylureas (n=5,237)	57%	1.00 (0.90,1.10) ns	1.11 (0.85, 1.44) ns
	Glitazones (n=608)	60%	1.12 (0.91, 1.36) ns	1.17 (0.92, 1.49) ns
	Fixed combination agents (n=541)	62%	1.25 (1.01, 1.54) *	1.27 (0.98, 1.65) ns
	Other (n=247)	58%	1.06 (0.77,1.44) ns	1.05 (0.75, 1.48) ns
Insulin σ	Absent (n=8,836)	59%	-	-
	Present (n=1,187)	43%	0.52 (0.44, 0.61)***	0.52 (0.44, 0.61) ***

† Adjusted for gender, age groups, drug schemes, presence of chronic diseases, number of antidiabetic medications, class of antidiabetic medications and prescribing of insulin

□ Reference category males (n=5,675)

◊ Reference category age 16-44 years (n=1,452)

¥ Reference category GMS scheme (n=7,133)

∞Reference category those without the chronic diseases being examined - cardiovascular (n=8660), neurological (n=8,798), psychiatric (n=6,414) and gastrointestinal (n=5,996)

Δ Reference category only one oral antidiabetic medication (n=6,463)

□ Reference category those prescribed antidiabetic agents other than the antidiabetic class being examined – metformin (n=2,525), sulphonylureas (n=4,786), glitazones (n=9,415), fixed combination agent (n=9,482) and other antidiabetic agent (n=9,776)

σ Reference category no insulin (n=8,836)

Adherence to lipid lowering agents in patients with type 2 diabetes

Overall, 56% of patients with newly treated type 2 diabetes demonstrated good adherence to lipid lowering agents (MPR > 80%) as measured from the pharmacy claims database. Similar to oral antidiabetic medications, those over 45 years of age and eligible for the LTI scheme were more likely to adhere to medications compared to younger aged patients and those under the GMS scheme as shown in Table 6.1.2. Those prescribed other cardiovascular medications were more likely to adhere to lipid lowering treatment compared to those without. Presence of other chronic diseases was not significantly associated with adherence to lipid lowering medications. The types of oral antidiabetic medications and the number of oral antidiabetic medications did not influence adherence to lipid lowering medications. However, prescribing of insulin was significantly associated with reduced adherence to lipid lowering medications in this cohort.

Table 6.1.2: Adherence to lipid lowering agents and factors predicting adherence in patients with newly treated type 2 diabetes from 1st January 2007 to 31st December 2007

Patient characteristics		% adherent	Unadjusted OR (95% CI), *p*	Adjusted OR (95% CI), *p*
Gender□	**Males (n=3,962)**	57%	-	-
	Females (n=2,780)	56%	0.97 (0.84, 1.11) ns	1.06 (0.94, 1.20) ns
Age groups◊	**16-44 (n=725)**	36%	-	-
	45-64 (n=2,898)	56%	2.25 (1.69, 3.01) ***	1.48 (1.21, 1.81) **
	≥65 (n=3,127)	59%	2.54 (1.92, 3.36) ***	1.44 (1.17, 1.79) **
Drug scheme ¥	**GMS (n=4,710)**	56%	-	-
	LTI (n=2,040)	57%	1.03 (0.91, 1.15) ns	1.31 (1.14, 1.51) **
Chronic diseases∞	**Cardio (n=4,241)**	58%	1.67 (1.43, 1.96)***	1.35 (1.14, 1.61) **
Insulin σ	**Absent (n=5,862)**	58%	-	-
	Present (n=888)	49%	0.71 (0.60, 0.84) ***	0.49 (0.41, 0.58) ***

† Adjusted for gender, age groups, drug schemes, presence of chronic diseases and prescribing of insulin
□ Reference category males (n=3,962)
◊ Reference category age 16-44 years (n=725)
¥ Reference category GMS scheme (n=4,710)
∞Reference category those without the chronic diseases being examined (cardiovascular, n=2,509)
σ Reference category no insulin (n=5,862)

Adherence to antihypertensive medications in patients with type 2 diabetes

61% of patients with newly treated type 2 diabetes were considered adherent (MPR>80%) to their prescribed antihypertensive medications. In those prescribed ACEIs or ARBs, 56% were considered adherent to these medications. Similar to oral antidiabetic and lipid lowering medications, those over 45 years of age and eligible for the LTI scheme were more likely to adhere to all antihypertensives (Table 6.1.3) compared to younger aged patients and those under the GMS scheme. In the cohort prescribed ACEIs or ARBs, no significant difference in adherence between GMS and LTI schemes was observed (Table 6.1.4). Those prescribed other cardiovascular medications were more likely while those with neurological conditions were less likely to adhere to antihypertensives compared to those without. Those receiving two or more oral antidiabetic medication were more likely to adhere to ACEIs or ARBs therapy. Similar to other medications being examined, those prescribed insulin were less likely to adhere to antihypertensives compared to those without.

Table 6.1.3: Adherence to antihypertensive medications and factors predicting adherence in patients with newly treated type 2 diabetes from 1st January 2007 to 31st December 2007

Patient characteristics		% adherent	Unadjusted OR (95% CI), *p*	Adjusted OR (95% CI), *p*
Gender□	**Males (n=4,293)**	59%	-	-
	Females (n=3,265)	59%	0.98 (0.88, 1.10) ns	1.04 (0.93.1.07) ns
Age groups◊	**16-44 (n=675)**	39%	-	-
	45-64 (n=2,945)	58%	2.19 (1.78, 2.69)***	2.10 (1.70, 2.58) ***
	≥65 (n=3,943)	61%	2.05 (1.67,2.51)***	1.19 (1.77, 2.71) ***
Drug scheme ¥	**GMS (n=5,648)**	59%	-	-
	LTI (n=1,915)	64%	1.24 (1.10, 1.40)**	1.31 (1.13, 1.51) **
Chronic diseases∞∞	**Cardio (n=6,003)**	62%	1.38 (1.20, 1.60) ***	1.40 (1.21, 1.62) ***
	Neuro (n=1,142)	56%	0.80 (0.69, 0.93) *	0.84 (0.72, 0.98) *
	Gastro (n=3,610)	59%	0.87 (0.78, 0.97) *	0.95 (0.84, 1.08) ns
Insulin σ	**Absent (n=6,622)**	62%	-	-
	Present (n=941)	51%	0.63 (0.54, 0.74) ***	0.66 (0.56, 0.77) ***

† Adjusted for gender, age groups, drug schemes, presence of chronic diseases and prescribing of insulin
□ Reference category males (n=4,293)
◊ Reference category age 16-44 years (n=675)
¥ Reference category GMS scheme (n=5,648)
∞∞Reference category those without the chronic diseases being examined (cardiovascular n=1,560, neurological n=6,421, and gastrointestinal n=3,953)
σ Reference category no insulin (n=6,622)

Table 6.1.4: Adherence to ACEIs or ARBs and factors predicting adherence in patients with newly treated type 2 diabetes from 1st January 2007 to 31st December 2007

Patient characteristics		% adherent	Unadjusted OR (95% CI), *p*	Adjusted OR (95% CI), *p*
Gender□	Males (n=3,619)	56%	-	-
	Females (n=2,590)	56%	1.00 (0.88, 1.13) ns	1.05 (0.93, 1.19) ns
Age	16-44 (n=549)	44%	-	-
groups◊	45-64 (n=2,522)	57%	1.75 (1.40, 2.19) ***	1.71 (1.36, 2.14) ***
	≥65 (n=3,143)	56%	1.68 (1.34, 2.10) ***	1.77 (1.40, 2.25) ***
Drug	GMS (n=4,512)	55%		-
scheme ¥	LTI (n=1,702)	58%	1.17 (1.03, 1.32) *	1.14 (0.98, 1.33) ns
Chronic	Cardio(n=5,119)	56%	1.19 (1.00, 1.40) *	1.22 (1.03, 1.44) *
diseases∞	Neuro (n=881)	51%	0.79 (0.66, 0.93) *	0.84 (0.71, 1.00) ns
	Gastrointestinal (n=2,866)	53%	0.79 (0.70, 0.90) **	0.83 (0.73, 0.95) *
No of	1 (n=3,826)	57%	-	-
anti-diabeticΔ	2 or more (n=1,702)	55%	0.87 (0.77, 0.98) *	0.88 (0.78, 0.99) *
Insulin σ	Absent (n=5,383)	57%	-	-
	Present (n=831)	45%	0.61 (0.51, 0.73) ***	0.64, 0.54, 0.76)***

† Adjusted for gender, age groups, drug schemes, presence of chronic diseases, number of antidiabetic medications and prescribing of insulin

□ Reference category males (n=3,619)

◊ Reference category age 16-44 years (n=549)

¥ Reference category GMS scheme (n=4,512)

∞Reference category those without the chronic diseases being examined (cardiovascular, n=1,095), neurological n=8,798, psychiatric n=5,333, and gastrointestinal n=3,348)

Δ Reference category only one oral antidiabetic medication (n=3,826)

σ Reference category no insulin (n=5,383)

Adherence to antiplatelet agents in patients with newly treated type 2 diabetes

In patients with newly treated type 2 diabetes being prescribed antiplatelet agents, 56% were considered adherent to antiplatelet agents (MPR > 80%). Consistent with the trends in adherence to other medications, those aged over 45 and those prescribed other cardiovascular medications were more likely to adhere to their prescribed medications compared to younger aged patients and those without cardiovascular medications (Table 6.1.5). Similarly, those prescribed insulin were less likely to adhere to antiplatelet medications. No significant differences in adherence to antiplatelet agent were observed between those eligible for the GMS and the LTI schemes.

Table 6.1.5: Adherence to antiplatelet agents and factors predicting adherence in patients with newly treated type 2 diabetes from 1st January 2007 to 31st December 2007

Patient characteristics		% adherent	Unadjusted OR (95% CI), *p*	Adjusted OR (95% CI), *p*
Gender□	**Males (n=3,759)**	56%	-	-
	Females (n=2,577)	55%	0.96 (0.86, 1.08) ns	0.98 (0.86,1.11) ns
Age	**16-44 (n=578)**	41%	-	-
groups◊	**45-64 (n=2,600)**	57%	1.93 (1.54, 2.41) ***	1.87 (1.49, 2.34) ***
	≥65 (n=3,165)	57%	1.93 (1.54, 2.41) ***	1.93 (1.53, 2.44) ***
Drug	**GMS (n=4,607)**	56%	1.02 (0.90, 1.16) ns	1.01 (0.86, 1.17) ns
scheme ¥	**LTI (n=1,736)**	56%	-	-
Chronic	**Cardio(n=6,117)**	56%	2.76 (1.88, 4.05) ***	2.71 (1.84, 3.99) ***
diseases∞	**Neuro (n=943)**	50%	0.76 (0.65, 0.90) **	0.78 (0.66, 0.92) *
	Gastrointestinal (n=3,027)	54%	0.88 (0.78, 0.99) *	0.88 (0.77, 1.00) ns
Insulin σ	**Absent (n=5,542)**	57%	-	-
	Present (n=801)	49%	0.75 (0.63, 0.89)	0.78 (0.65, 0.93) *

† Adjusted for gender, age groups, drug schemes, presence of chronic diseases and prescribing of insulin
□ Reference category males (n=3,759)
◊ Reference category age 16-44 years (n=578)
¥ Reference category GMS scheme (n=4,607)
∞Reference category those without the chronic diseases being examined (cardiovascular=226, neurological n=5,400, and gastrointestinal n=3,316)
σ Reference category no insulin (n=5,542)

6.1.4.2 Self-reported adherence and prescription refill adherence

Background of participants

The background characteristics of patients with type 2 diabetes attending the baseline visit and follow up annual visit as well as those included in the linkage study with the pharmacy claims database are presented in Table 6.1.6. At the baseline visit, 54% were prescribed metformin, 25% sulphonylureas, 3% other antidiabetic agents and 14% insulin. 51% were prescribed lipid lowering agents (49% statins) and 57% were prescribed antiplatelet agents. In patients included for the linkage study, 56% were on monotherapy while the rest were prescribed more than one oral antidiabetic agents. 81% were prescribed metformin, 42% sulphonylureas, 6% fixed oral combination agent, 2% other antidiabetic agents and 14% insulin. In addition, 90% were prescribed lipid lowering agents (86% statins), 83% were prescribed antiplatelet agents and 86% antihypertensives with 80% being prescribed either ACEIs or ARBs.

Self-reported adherence

80% of patients scored highly for self-reported adherence scale in this cohort (total score >20/25) at the baseline visit. Low self-reported adherence to medications at baseline was significantly associated with non-attendance at the follow-up visit (p<0.0001, Mann-Whitney). At the follow up visit, there was an increase in the proportion of patients who scored highly for self-reported adherence (95%). However, due to the smaller number of patients at the follow up visit, this trend did not reach statistical significance. The self-reported response for each self-reported adherence statement at baseline and at follow up are presented in Figure 6.1.1 to Figure 6.1.5 respectively. At follow up visit, more than 90% of patients reported never to statement "I alter the dose of my medicine", "I stop taking my medicines for a while" and "I decide to miss out a dose" while only 60% reported never to statement "I forget to take my medicine" and "I take less than instructed". Significant difference was observed at baseline and follow up visit for statement "I forget to take my medicine" (p<0.0001, Kruskal Wallis test between adherers and non-adherers), "I alter the dose of my medicine" (p<0.0001, Kruskal Wallis) "I decide to miss out a dose" (p=0.03, Kruskal Wallis) and "I take less than instructed" (p<0.0001, Kruskal Wallis). Those 65 years old and over were more likely to report adherence to medications at baseline compared to those under 65 years old (OR=2.14 [1.09, 4.23], p=0.03). No significant relationship between age group and self-reported adherence were observed at follow up visit. No significant association was found between self-reported adherence and gender, support at home, limitations of daily activities, smoking status, alcohol intake, total medications, diabetic medications and presence of self-reported chronic conditions at baseline or at the follow up visit.

Table 6.1.6: Background characteristics of patients with type 2 diabetes at baseline, follow up and those included in the linkage study with the pharmacy claims database

Patient characteristics		Baseline (n=152) %	Follow up (n=120) %	Linkage study × (n=86) %
Gender	Females	33%	31%	24%
Age group	≥65	41%	41%	52%
Ethnicity	White	95%	95%	97%
Social support	Living alone	15%	15%	23%
Activities of daily living	With limitations	24%	28%	18%
Highest level of education	Primary	15%	7%	13%
	Leaving cert/Equivalence	28%	34%	32%
	Diploma/Certificate	26%	27%	26%
	Primary degree	16%	17%	19%
	Higher degree/postgraduate	7%	7%	6%
Smoking status	Smoker	14%	9%	10%
	Non smoker	44%	49%	50%
	Ex-smoker	41%	41%	39%
Alcohol intake	never	26%	34%	24%
	monthly	12%	13%	8%
	<2-4 times/month	31%	27%	32%
	2-3 times/week	8%	17%	19%
	≥4 times/week	4%	8%	10%
Diabetes medications	none	12%	12%	10%
	Oral only	66%	68%	68%
	Oral and insulin	11%	7%	10%
	Insulin only	10%	12%	10%
Total medications	1	8%	5%	5%
	2-3	6%	3%	5%
	>3	86%	92%	90%
Self-reported chronic illness	Asthma/COPD	18%	16%	25%
	Heart attack	13%	12%	10%
	angina	7%	11%	10%
	stroke	8%	10%	11%
	Rheumatoid arthritis	16%	20%	21%
	Osteoarthritis	12%	22%	11%
	Chronic back pain	20%	31%	21%
	Cancer	6%	7%	6%
	Urinary problems	12%	20%	10%
	Anxiety	10%	14%	14%
	Depression	11%	12%	8%
	High blood pressure	47%	42%	50%
	High cholesterol	35%	27%	39%

×Patient characteristics from baseline visit

Figure 6.1.1: Self-reported answer provided by participants with type 2 diabetes for statement "I forget to take my medicine" at baseline and follow up outpatient visit

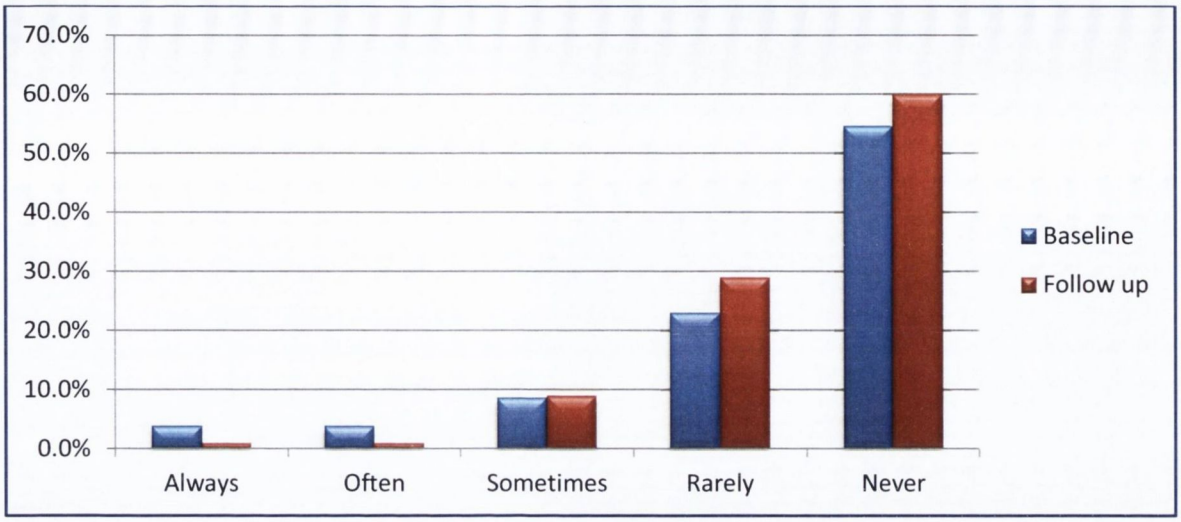


Figure 6.1.2: Self-reported answer provided by participants with type 2 diabetes for statement "I alter the dose of my medicine" at baseline and follow up outpatient visit

Figure 6.1.3: Self-reported answer provided by participants with type 2 diabetes for statement "I stop taking my medicines for a while" at baseline and follow up outpatient visit

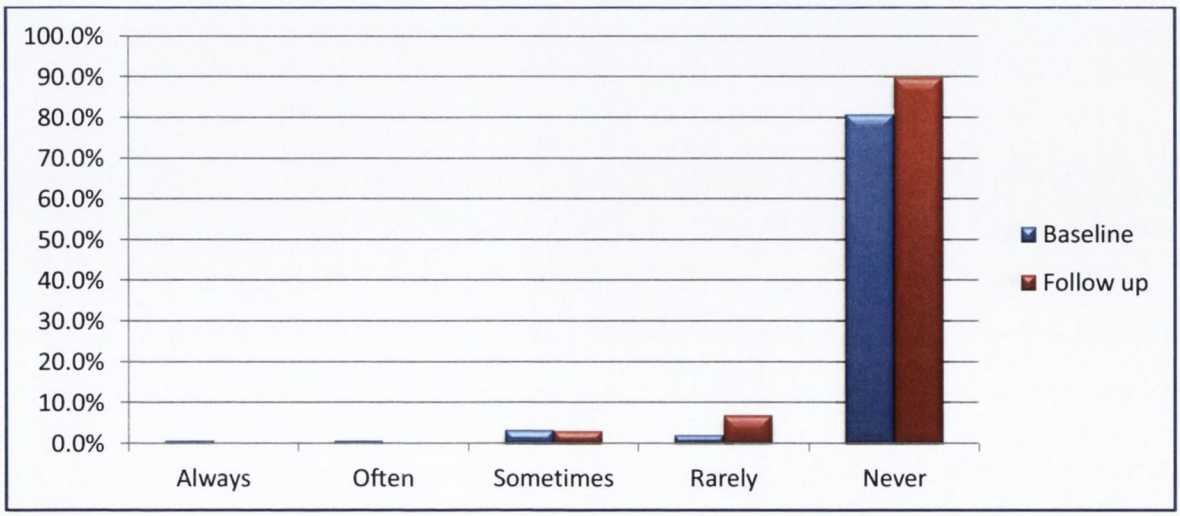


Figure 6.1.4: Self-reported answer provided by participants with type 2 diabetes for statement "I decide to miss out a dose" at baseline and follow up outpatient visit

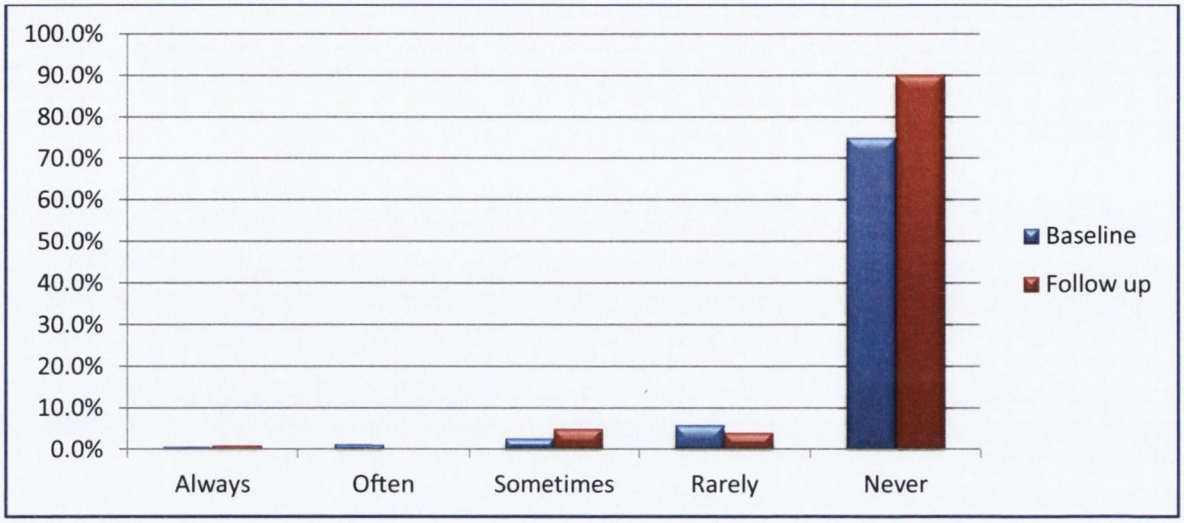
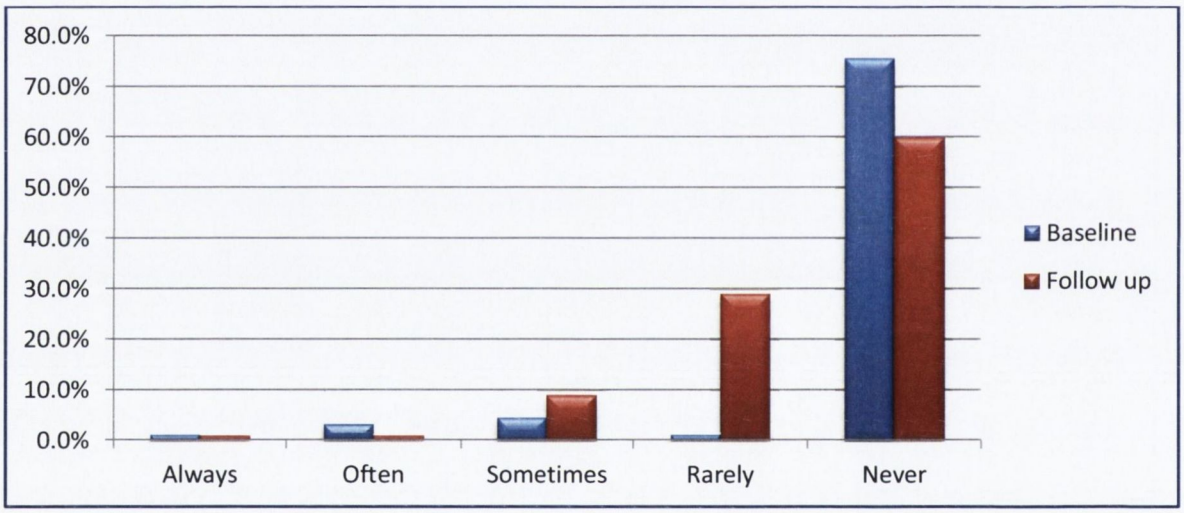


Figure 6.1.5: Self-reported answer provided by participants with type 2 diabetes for statement "I take less than instructed" at baseline and follow up outpatient visit



Prescription refill adherence

The mean adherence as measured by MPR between baseline visits to annual review to oral antidiabetic medications was 55% (SD 27%) in the cohort from Connolly hospital (n=86). The mean adherence for statins was 82% (SD 26%) and for antihypertensives was 81% (SD 23%). No significant associations were found between adherence to medications as measured using the prescription refill record and gender, age groups, social support, limitations of daily activities, smoking status, alcohol intake, antidiabetic medications, total medications and levels of education in this cohort. The study was not sufficiently powered to show a significant association, if one existed, due to the small number of patients.

Relationship between self-reported adherence and prescription refill adherence

When comparing adherence classification by MPR with self-reported adherence, 43% of patients at baseline and 40% of patients at follow up from Connolly Hospital have the same classification by both methods (Table 6.1.7). Discordant classification was found in 56% of patients at baseline and 60% of patients at follow up. As the number of patients available for record linkage study was small, there was no significant correlation found between self-reported adherence score and adherence as measured by prescription refill records in this cohort study either at baseline (ρ=0.11, Spearman's correlation) or at the follow up visit (ρ=-.17 Spearman's correlation). The proportion of patients considered adherent using self-reported questionnaires at baseline and the follow up visit and using prescription refill records are presented in Table 6.1.8.

Table 6.1.7: Classification of adherence in patients with type 2 diabetes using self-reported adherence scale and prescription refill records at baseline and follow up

Adherence classification	Baseline (n=86)	Follow up (n=86)
MPR high, self-reported high	16%	16%
MPR high, self-reported low	19%	20%
MPR low, self-reported high	37%	40%
MPR low, self-reported low	27%	24%

High MPR is defined as those with MPR≥80%, low MPR is defined as those with MPR <80%
High self-reported adherence is defined as those with scores of ≥20 out of 25, low self-reported adherence is defined as those with scores of <20 out of 25

Table 6.1.8: The proportion of patients with good adherence to medications using self-reported adherence questionnaires (score > 20/25) and prescription refill records (MPR>80%) according to background characteristics in cohort of patients from Connolly hospital, Blanchardstown

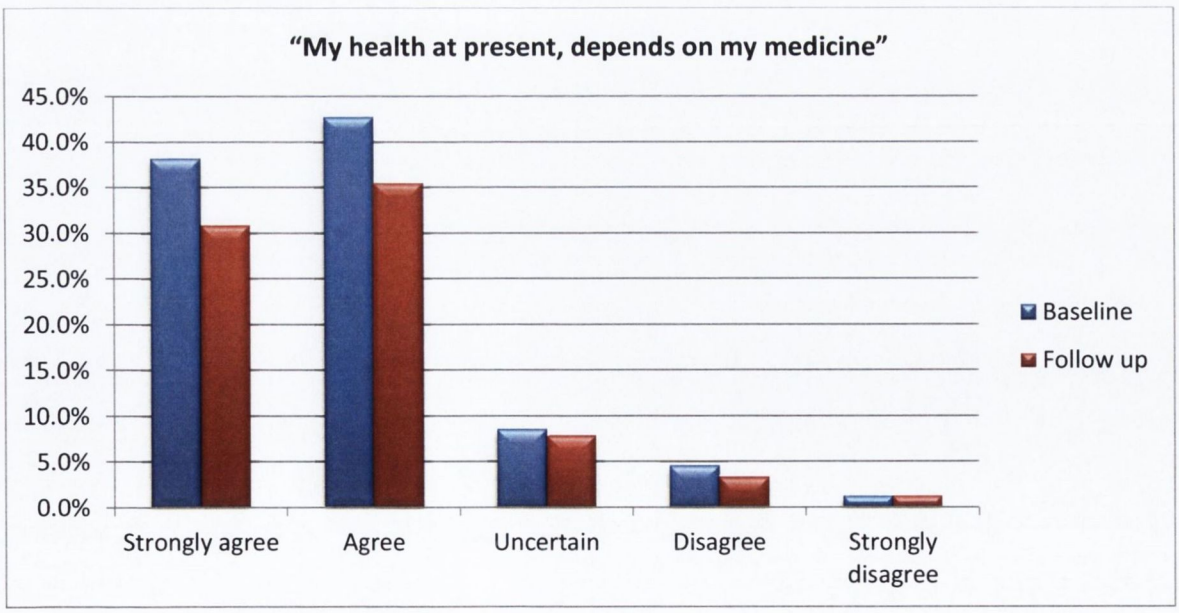
Patient Characteristics		Self-reported		Prescription refill
		Baseline (n=152)	Follow up (n=120)	(n=86)
Gender	Males	49%	50%	35%
	Females	44%	61%	33%
Age group	64 years	39%	53%	31%
	≥ 65 years	58%	55%	38%
Support	Living alone	63%	53%	53%
	Living with others	45%	52%	31%
Highest level of education	Primary	50%	61%	12%
	Leaving cert	51%	42%	50%
	Certificate/diploma	41%	55%	29%
	Primary degree	58%	50%	40%
	Higher degree	45%	43%	-
Limitations of ADL	Present	50%	57%	40%
	absent	44%	50%	35%
Smoking	Smoker	42%	27%	29%
	None smoker	47%	58%	28%
	Ex-smoker	51%	56%	45%
Alcohol	Never	56%	50%	29%
	monthly	37%	65%	40%
	<2-4 times/month	41%	51%	21%
	2-3 times/week	51%	57%	64%
	≥4 times/week	27%	27%	40%
Total medications	1	45%	44%	40%
	2	33%	63%	-
	3 or more	50%	53%	35%
Self-reported chronic illness	Asthma/COPD	50%	50%	67%
	Heart attack	47%	50%	43%
	Angina	55%	71%	57%
	Stroke	61%	60%	57%
	Rheumatoid arthritis	56%	65%	50%
	Osteoarthritis	47%	56%	50%
	Chronic back pain	55%	61%	25%
	Cancer	56%	75%	60%
	Urinary problems	39%	47%	86%
	Anxiety	58%	54%	60%
	Depression	60%	39%	57%
	High blood pressure	44%	63%	37%
	High cholesterol	44%	55%	37%

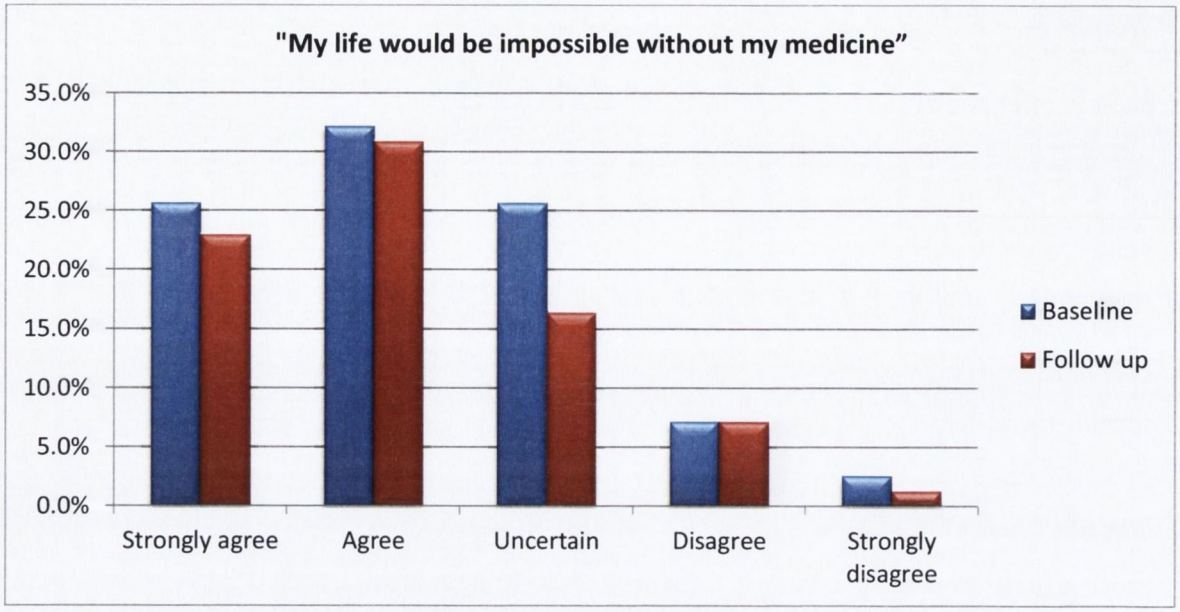
6.1.4.3 Relationship between beliefs and attitude towards medications and adherence to medications in patients with type 2 diabetes

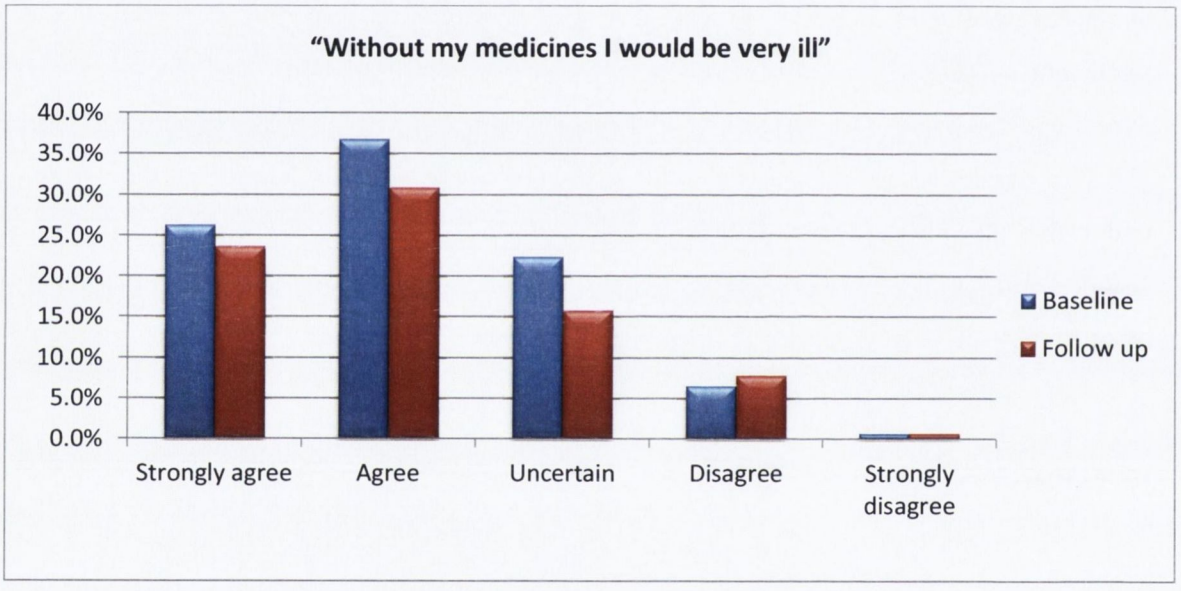
Beliefs towards medications

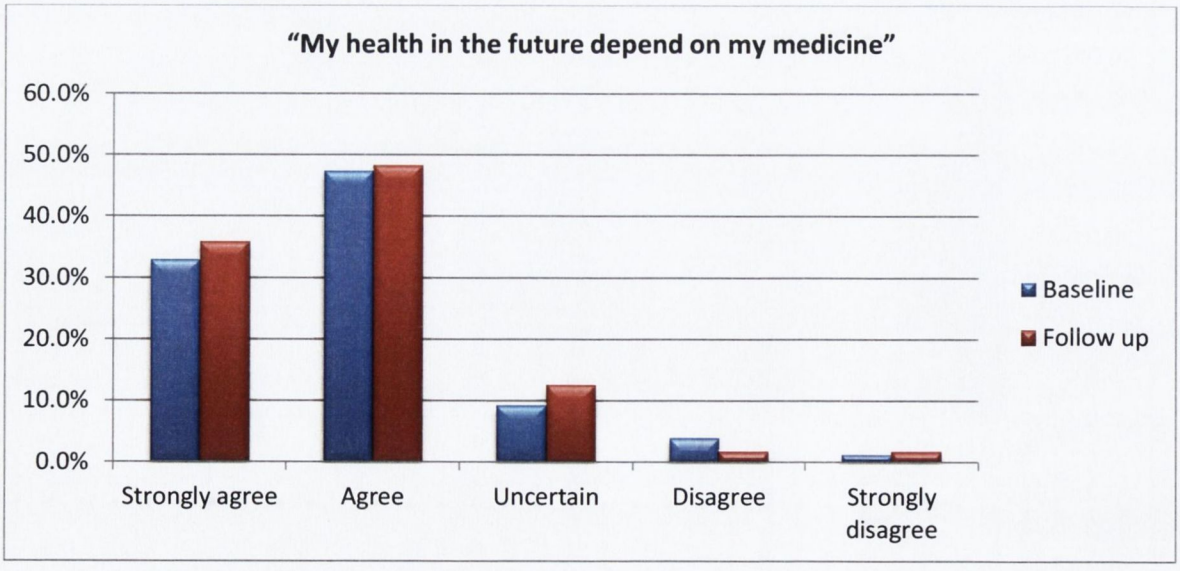
The internal reliability for all BMQ scale items in this study was high with standardized Cronbach coefficient alpha values ranging from 0.79 for general Overuse scale to 0.90 for the specific necessity scale. At baseline visit, 73% of patients scored highly on perceived necessity of prescribed medications (Specific Necessity) while a minority had concerns about their medications (Specific Concern) (28%), thought medications were overused (General Overuse) (24%) or were causing harm (General Harm) (11%). There was a significant increase in patients reporting high necessity score from baseline to follow up ($p<0.0001$, Mann Whitney). There was also a significant decrease in patients reporting high concern score at follow up visit compared to baseline ($p=0.03$, Mann Whitney). A decrease in patients reporting high Overuse and Harm score was also observed although not significant. The self-reported answer for each BMQ statement under the Specific Necessity, Specific Concern, General Overuse and General Harm scale at baseline and follow up are presented in Figure 6.1.6, Figure 6.1.7, Figure 6.1.8 and Figure 6.1.9 respectively.

Figure 6.1.6: Self-reported answers provided by participants for statements under the Specific Necessity scale at baseline and follow up visit




"My life would be impossible without my medicine"
35.0%
30.0%
25.0%
20.0%
15.0%
10.0%
5.0%
0.0%
Strongly agree
Agree
Uncertain
Disagree
Strongly disagree
Baseline
Follow up


"Without my medicines I would be very ill"
40.0%
35.0%
30.0%
25.0%
20.0%
15.0%
10.0%
5.0%
0.0%
Strongly agree
Agree
Uncertain
Disagree
Strongly disagree
Baseline
Follow up


"My health in the future depend on my medicine"
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
Strongly agree
Agree
Uncertain
Disagree
Strongly disagree
Baseline
Follow up

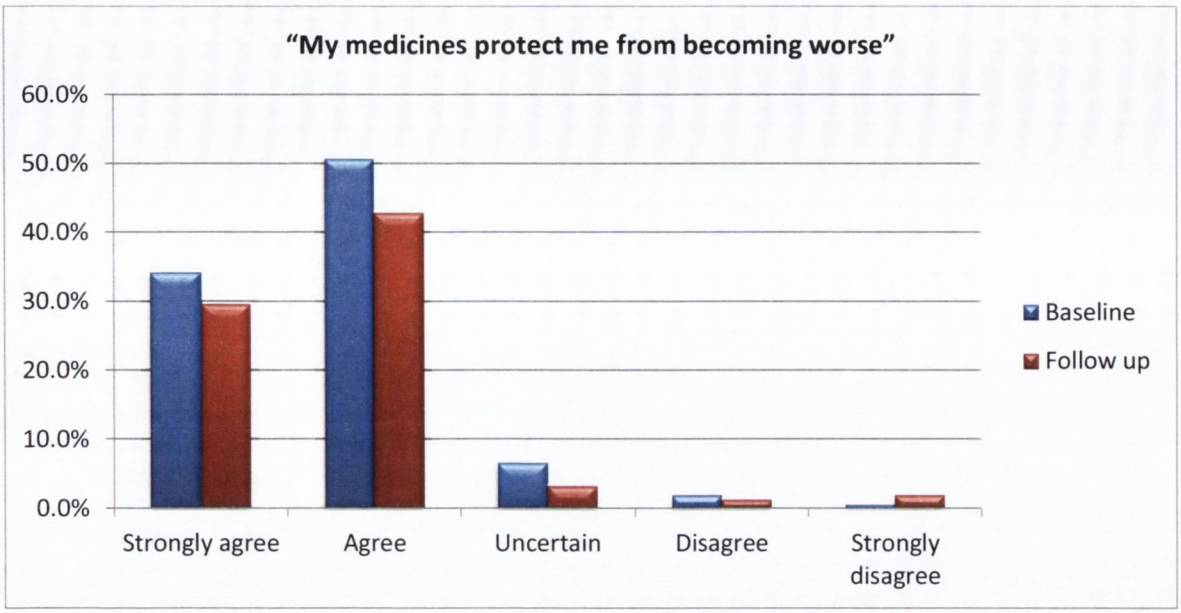
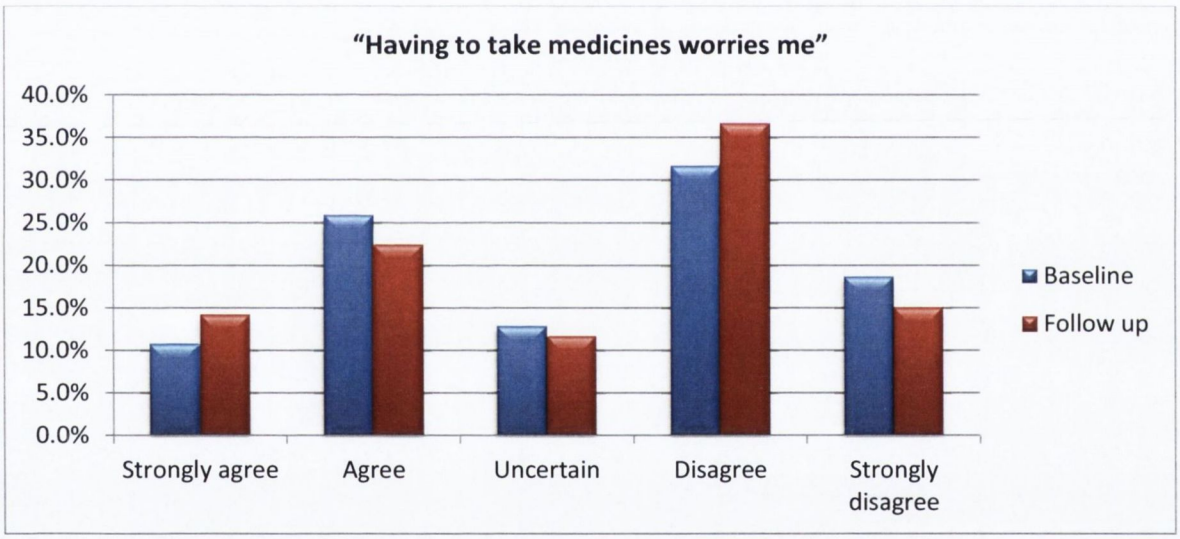
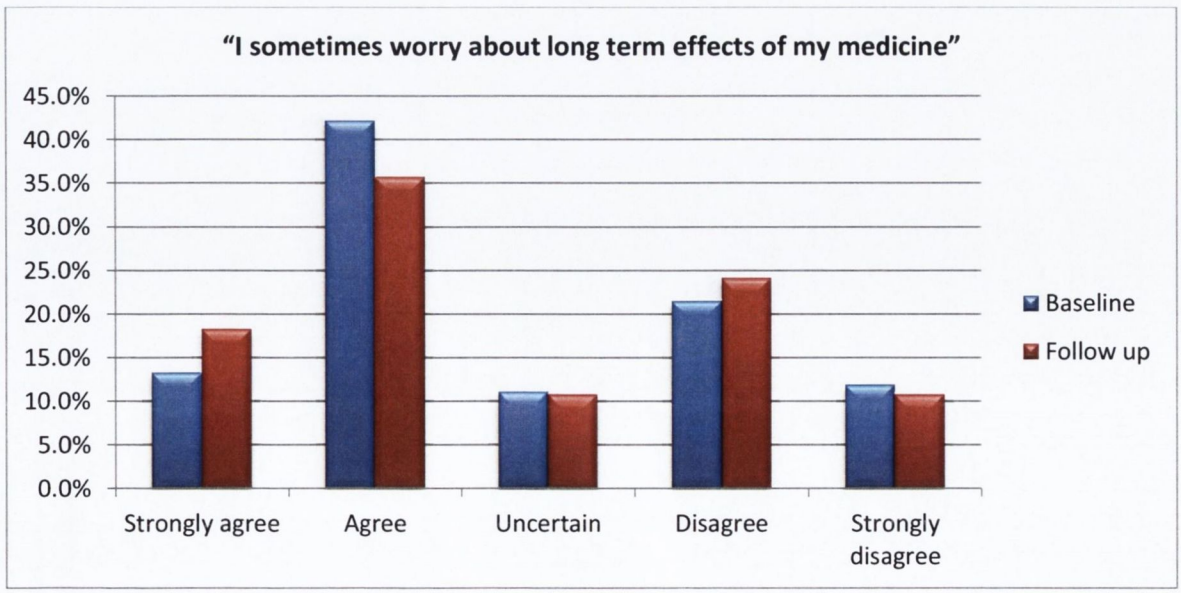
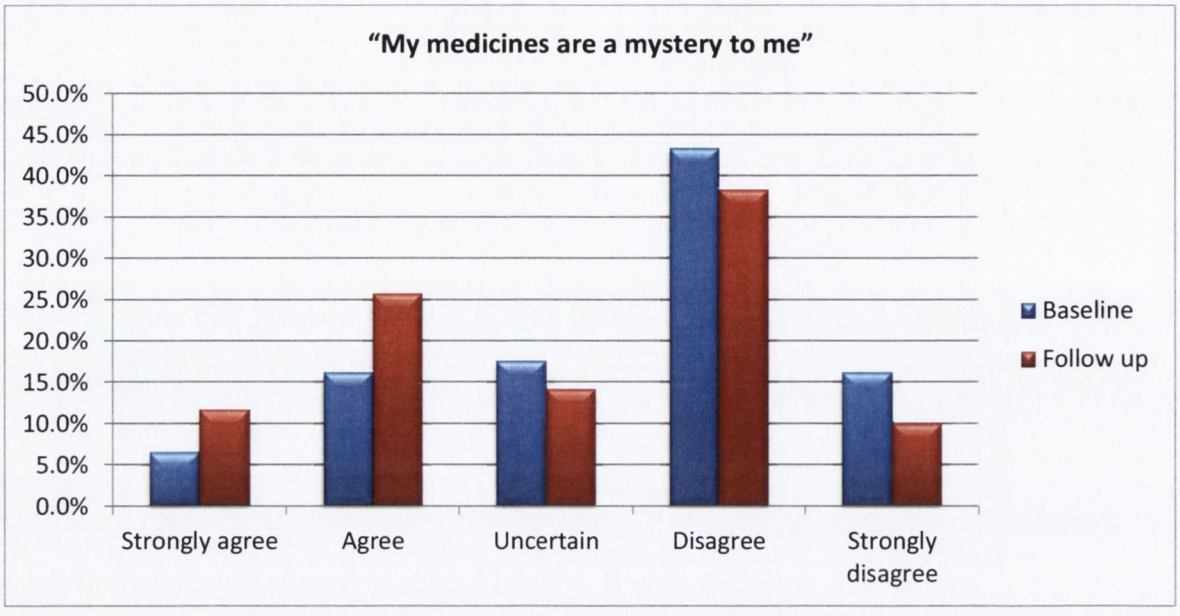
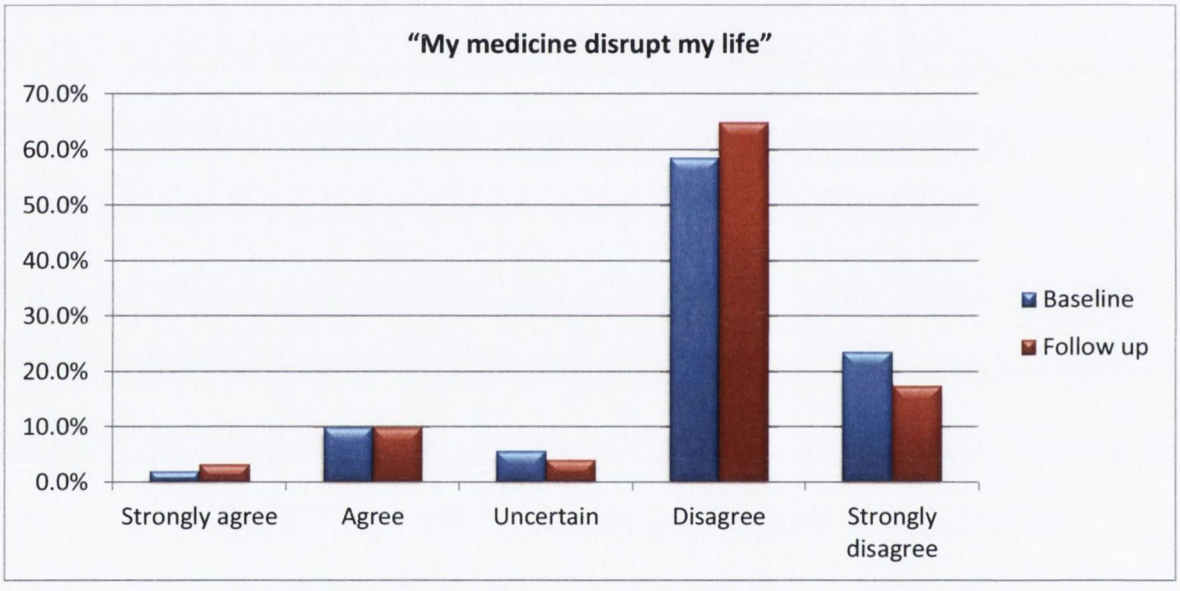


Figure 6.1.7: Self-reported answers provided by participants for statements under the Specific Concern scale at baseline and follow up visit






"My medicines are a mystery to me"
50.0%
45.0%
40.0%
35.0%
30.0%
25.0%
20.0%
15.0%
10.0%
5.0%
0.0%
Strongly agree
Agree
Uncertain
Disagree
Strongly disagree
Baseline
Follow up


"My medicine disrupt my life"
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
Strongly agree
Agree
Uncertain
Disagree
Strongly disagree
Baseline
Follow up

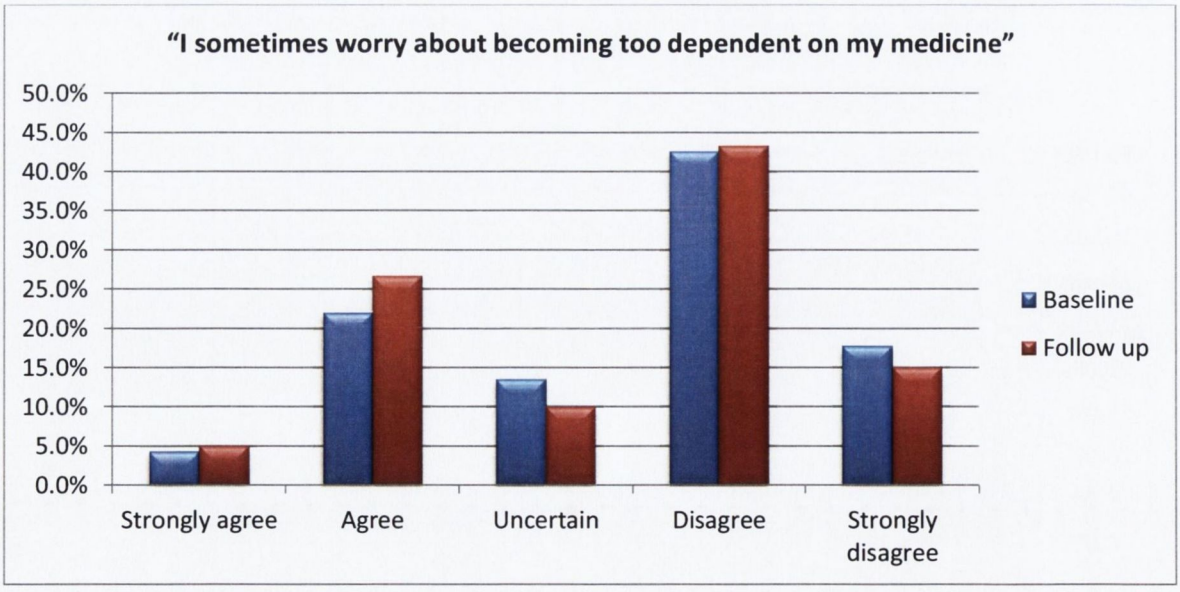
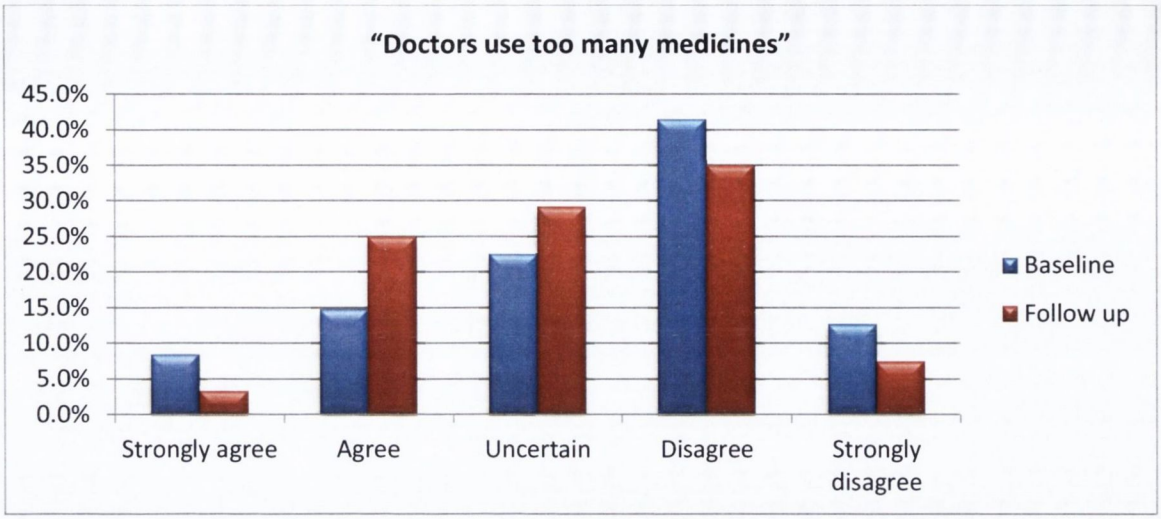
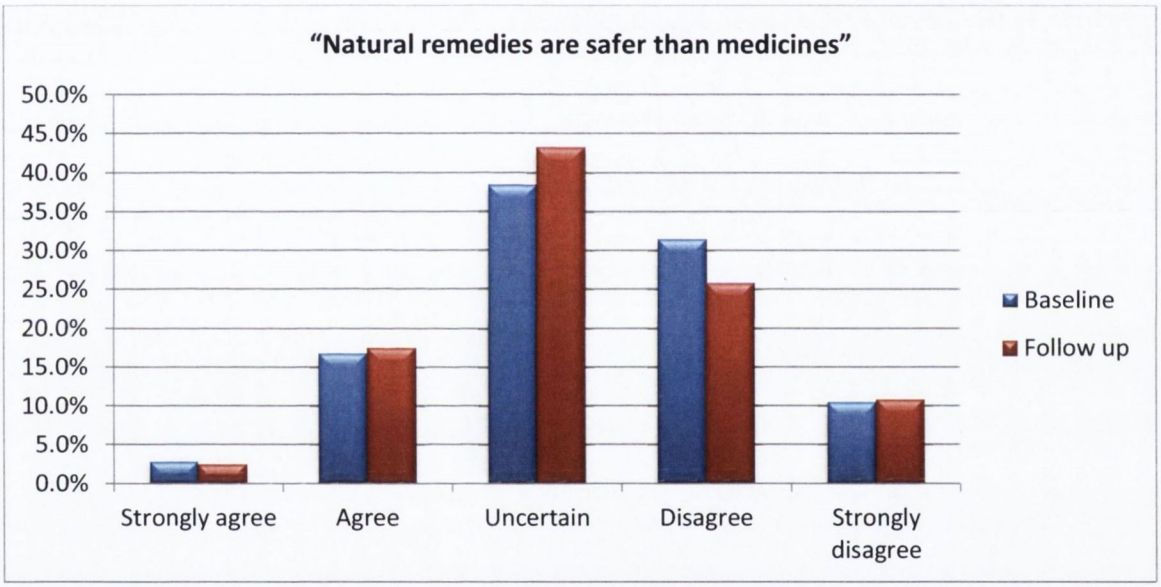
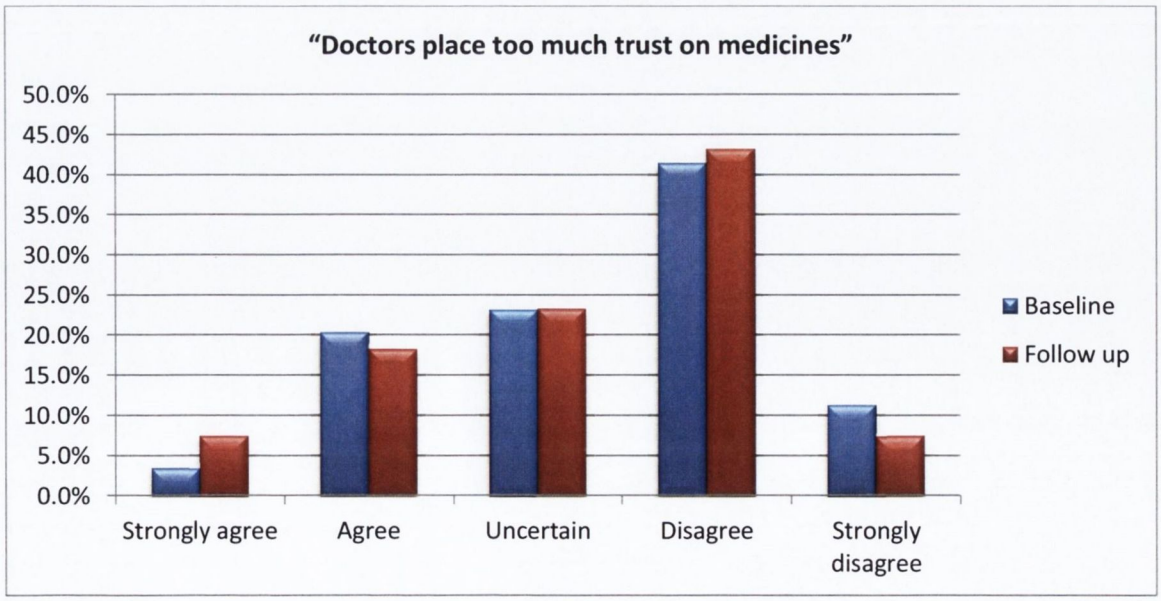

"I sometimes worry about becoming too dependent on my medicine"
50.0%
45.0%
40.0%
35.0%
30.0%
25.0%
20.0%
15.0%
10.0%
5.0%
0.0%
Strongly agree
Agree
Uncertain
Disagree
Strongly disagree
Baseline
Follow up

Figure 6.1.8: Self-reported answers provided by participants for statements under the General Overuse scale at baseline and follow up visit







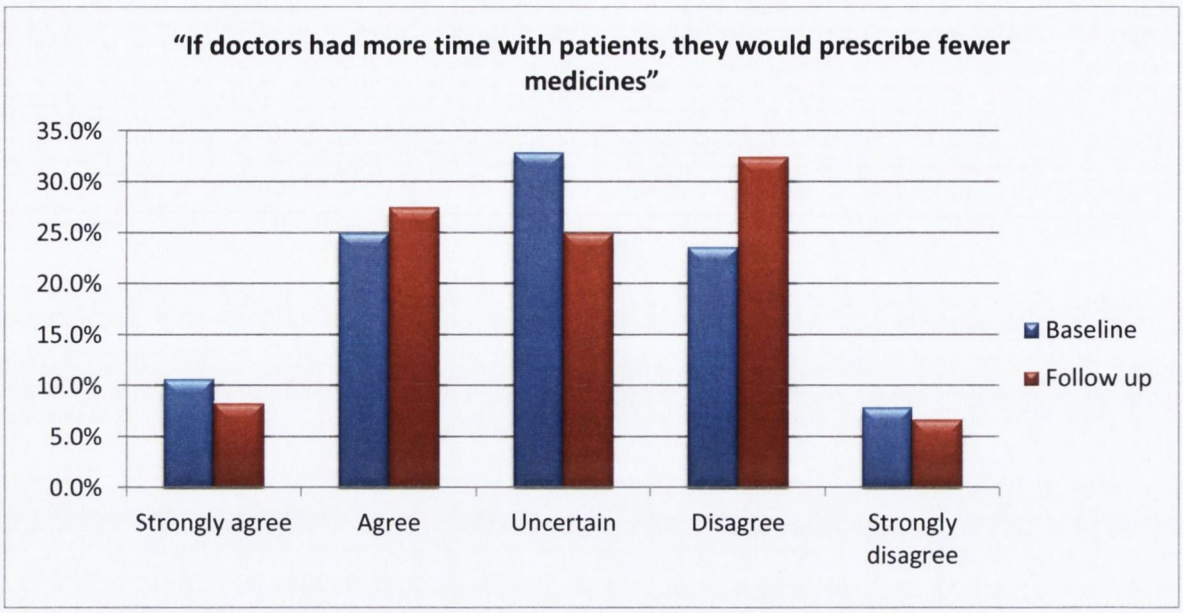
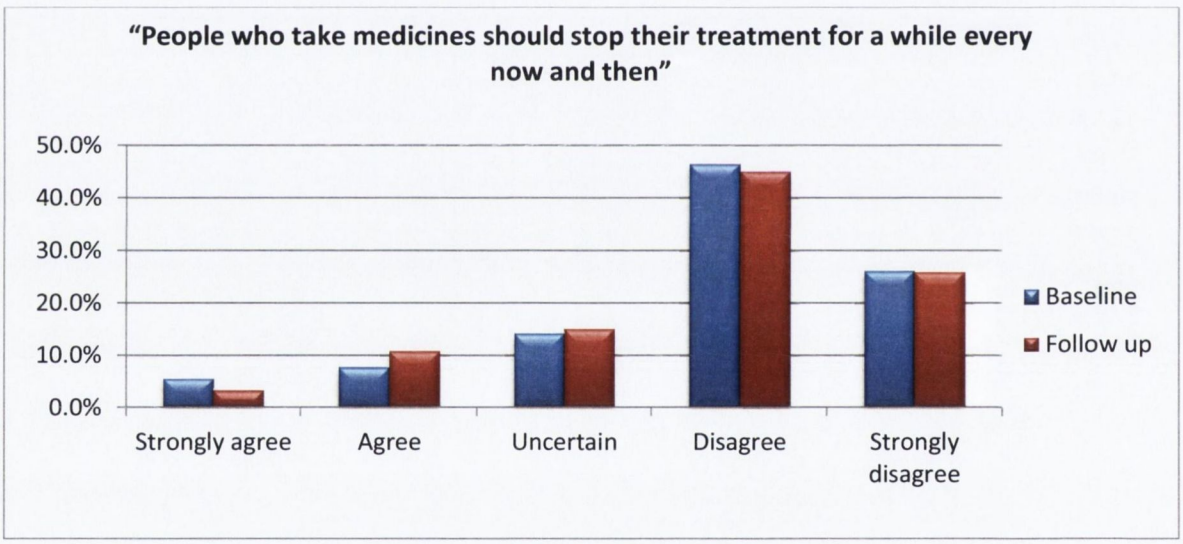
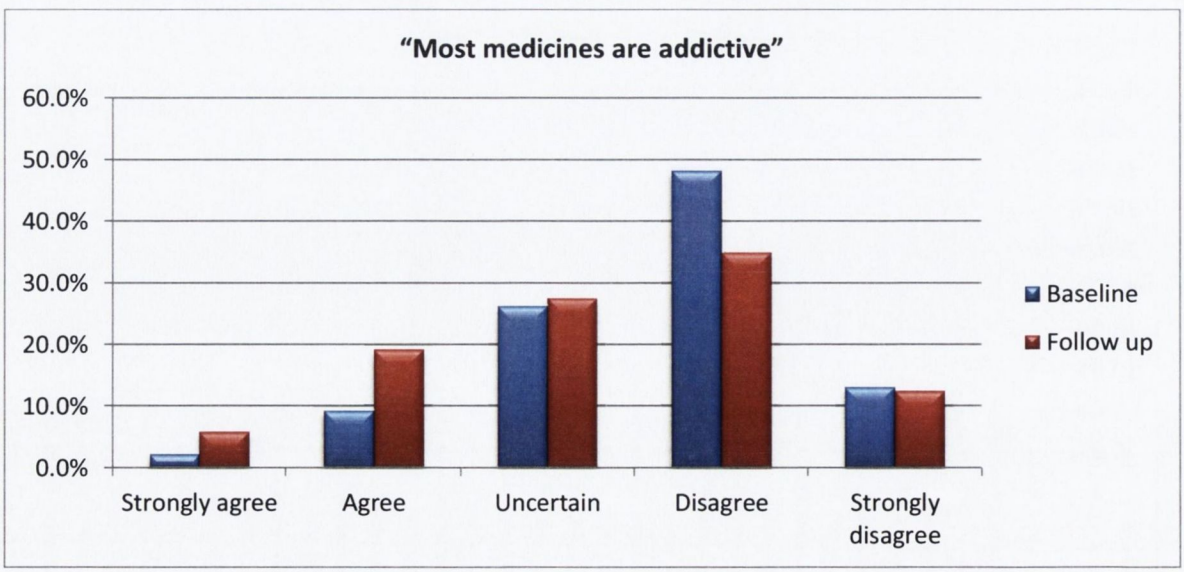
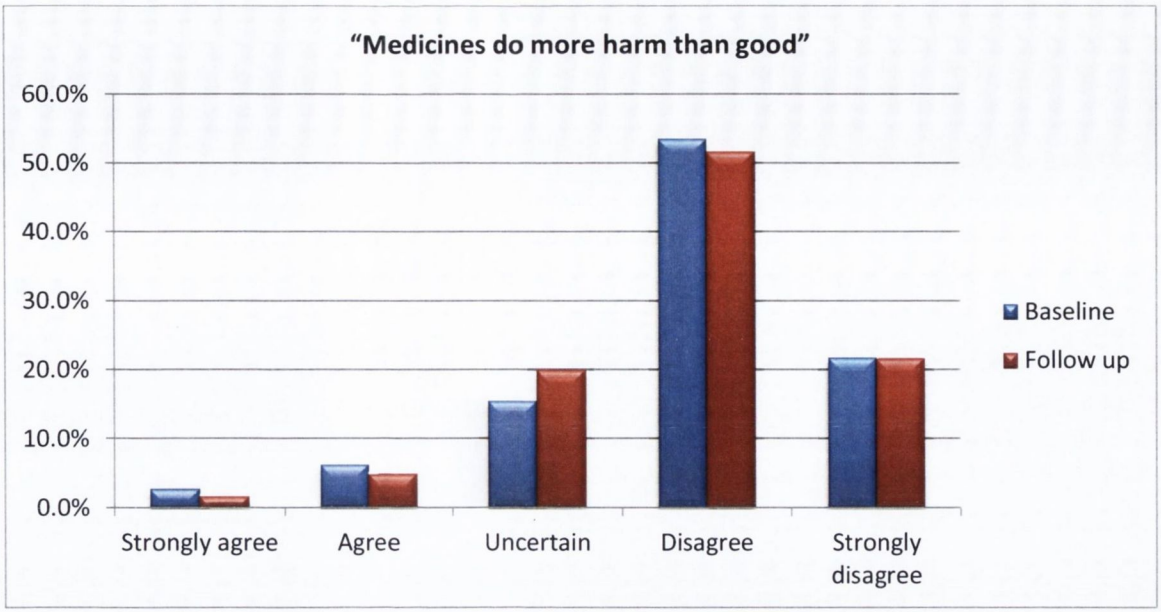
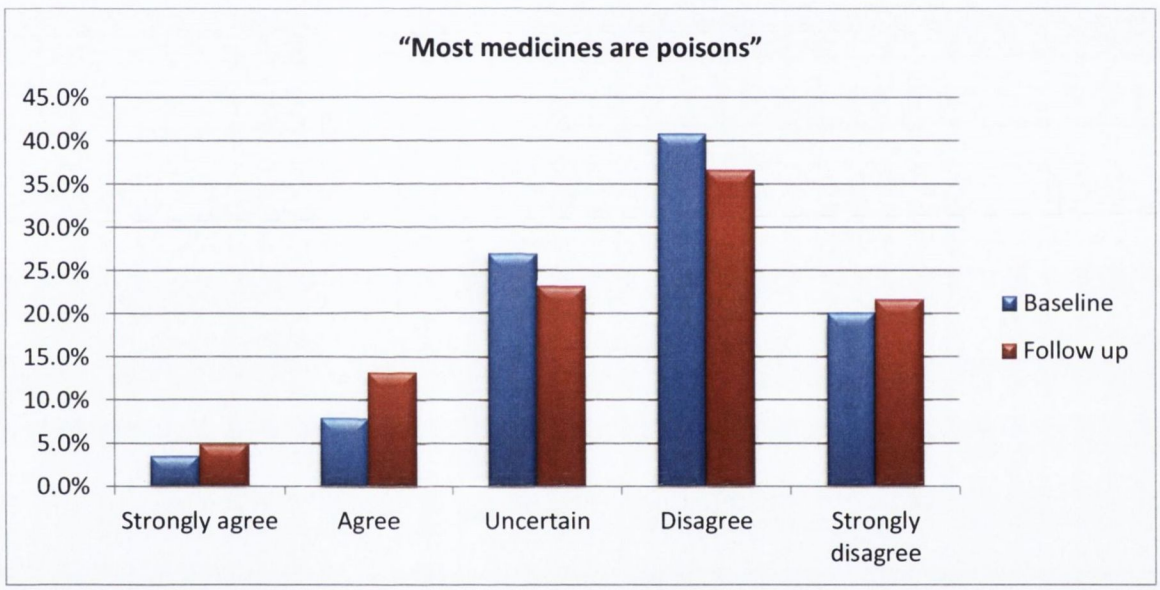


Figure 6.1.9: Self-reported answers provided by participants for statements under the General Harm scale at baseline and follow up visit









Relationship between beliefs and attitude towards medications and adherence to medications

When examined as a categorical variable, a significant relationship was demonstrated between the Necessity scale and the self-reported adherence score (p=0.008, Kruskal Wallis) at the baseline visit. Those with higher Necessity scores (total ≥20/25) were more likely to report adherence to medication (Table 6.1.9). A significant relationship between necessity and adherence using prescription refill record was also observed (p=0.03, Kruskal Wallis). No significant association between self-reported adherence and Concern, Overuse and Harm scale was observed during the baseline and follow up visits. When examined as a continuous variable, a significant negative correlation was observed between the Harm scale and self-reported adherence (ρ=-.205, p=0.02, Spearman's correlation). No significant correlation was observed between the adherence and the Necessity, Concern and Overuse scales.

Amongst the subscales in the BMQ, significant differences were only observed between responses from adherent and non-adherent patients in the statement "If doctors had more time with patients, they would prescribe fewer medicines" (p<0.0001, Wilcoxon rank test).

Table 6.1.9: Percentage of patients with high sum score (>20/25) for each scale of the beliefs about medications questionnaire stratified by adherence to medications using self-reported questionnaire and prescription refill records.

BMQ Scales	Baseline (n=152)			Follow up (n=120)			Prescription refill (n=86)		
	Total	Adhere	Non adhere	Total	Adhere	Non adhere	Total	Adhere	Non adhere
Specific Necessity	73%	74%	70%	88%	90%	88%	60%	73%	58%
Specific Concern	28%	26%	28%	14%	10%	14%	12%	5%	12%
General Overuse	24%	22%	24%	13%	10%	16%	11%	0%	17%
General Harm	11%	6%	12%	4%	3%	2%	3%	22%	6%

6.1.4.4 Relationship between adherence to medication and intermediate clinical outcome

Prospective cohort study: Connolly Hospital, Blanchardstown

The clinical measurements for these patients at the baseline visit to the outpatient clinic and at the annual follow up review are presented in Table 6.1.10. A significant increase in blood pressure was observed between the two visits. At baseline more than half of the patients had HbA1c levels more than 6.5% as recommended by the Irish guideline. This increased to more than three quarter of patients at follow up (Table 6.1.11). Less than half of the patients had higher than the recommended values for cholesterol at baseline and at follow up. A significant increase in the proportion of patients with systolic blood pressure over 130mmHg was also observed at the follow up visit. The cut off values for 75th centile in this cohort were 7.5% for HbA1c, 144 mmHg for systolic blood pressure and 90 mmHg for diastolic blood pressure, 4.80 mmol/L for total cholesterol, 2.68 mmol/L for LDL cholesterol, 1.41 mmol/L for HDL cholesterol and 2.02 mmol/L for triglycerides.

There was no significant relationship between self-reported adherence and achievement of the recommended guideline target for HbA1C, blood pressure or cholesterol level in this

patient population (Table 6.1.12). When the relationship between adherence and clinical measurements was examined using the 75th centile as cut off values, it was found that patients with HbA1c <7.5% were more likely to report higher adherence to medications at baseline visit. In addition, patients with diastolic blood pressure <90 mmHg were also more likely to report high adherence to medications at the follow up visit. No significant relationship was observed between MPR and clinical measurements when examined as continuous variables. The study was not sufficiently powered to show a significant association due to the small number of patients.

Table 6.1.10: Clinical parameters in patients with type 2 diabetes attending the outpatient clinic at Connolly hospital during their first visit and their annual review visit

Clinical measurements	Baseline (n=152) Mean, SD	Follow up (n=120) Mean, SD	Mean change , p
HbA1c (%)	7.1% (SD 1.5%)	7.2% (SD 1.3)	0.2% (SD 1.6%), ns
Systolic blood pressure (mmHg)	135 (SD 20)	146 (SD 20)	10 (SD 25)***
Diastolic blood pressure (mmHg)	82 (SD 10)	85 (SD 12)	4 (SD 15)**
Total cholesterol (mmol/l)	4.23 (SD 0.94)	4.27 (SD 0.85)	0.09 (SD 0.94), ns
Triglycerides (mmol/l)	1.71 (SD 0.92)	1.76 (0.97)	0.08 (SD 0.71), ns
HDL cholesterol (mmol/l)	1.23 (SD 0.33)	1.29 (SD 0.42)	0.04 (SD 0.20) *
LDL cholesterol (mmol/l)	2.22 (SD 0.79)	2.19 (SD 0.69)	0.01(SD 0.79) ns

Table 6.1.11: Percentage of patients with clinical measurement above the target values recommended by the Irish guideline on type 2 diabetes

Clinical measurements	Baseline visit (n=152)	Follow up (n=120)	*p*
HbA1c >6.5%	58%	78%	***
Systolic blood pressure>130 mmHg	63%	81%	*
Diastolic blood pressure> 80mmHg	67%	69%	ns
Total cholesterol> 4.5 mmol/l	39%	39%	ns
Triglycerides >2.0 mmol/l	26%	28%	ns
HDL cholesterol <1.0 mmol/l	70%	74%	ns
LDL cholesterol >2.5 mmol/l	33%	27%	ns

Table 6.1.12: Relationship between adherence to medications (antidiabetic, lipid lowering, antihypertensive agents) and clinical measurement when examined as categorical variable

Clinical measurement		Baseline (n=152)		Follow up (n=120)		Prescription refill (n=86)	
		% Adherent	*p*	% Adherent	*p*	% adherent	*p*
HbA1c×	<6.5%∞	35%	ns	27%	ns	21%	ns
	<7.5% Δ	70%	*	80%	ns	74%	ns
Systolic blood pressure	<130 mmHg∞	33%	ns	17%	ns	33%	ns
	<144mmHg Δ	70%	ns	51%	ns	44%	ns
Diastolic blood pressure	<80 mmHg∞	28%	ns	38%	ns	28%	ns
	<90mmHg Δ	75%	ns	88%	*	77%	ns
Total cholesterol	<4.5 mmol/l∞	60%	ns	63%	ns	63%	ns
	<4.80 mmol/l Δ	71%	ns	77%	ns	84%	ns
Triglycerides	<2.0 mmol/l∞	67%	ns	69%	ns	73%	ns
	<2.02 mmol/l Δ	67%	ns	69%	ns	73%	ns
LDL cholesterol	<2.5 mmol/l∞	67%	ns	82%	ns	90%	ns
	<2.68 mmol/l Δ	75%	ns	84%	ns	90%	ns
HDL cholesterol	>1 mmol/l ∞	66%	ns	70%	ns	63%	ns
	<1.41 mmol/l Δ	79%	ns	71%	ns	64%	ns

∞ recommended values by Irish guideline on type 2 diabetes
Δ values obtained from the 75th centile at the first visit

Retrospective cohort study : St James's Hospital, Dublin

Amongst the patients from St James's Hospital included in this cohort study (n=156), 88% were initiated oral antidiabetic medications at the first clinic visit while the rest were prescribed oral antidiabetic medication at a subsequent visit. 64% of patients from the James's cohort were prescribed metformin, 43% were prescribed sulphonylureas, 4% were prescribed other agents. 35% of patients were prescribed two or more oral antidiabetic agents and 6% were prescribed insulin. In addition, 73% of patients from this cohort were prescribed lipid lowering agents (61% statins), 78% antihypertensives (68% ACE/ARBs) and 71% antiplatelet agents (66% aspirin). The clinical measurements for these patients at the first visit to the outpatient clinic and at the annual review are presented in Table 6.1.13. The cut of values for 75th centile in this cohort were 7.4% for HbA1c, 148 mmHg for systolic blood pressure and 78 mmHg for diastolic blood pressure, 4.78 mmol/L for total cholesterol, 2.62 mmol/L for LDL cholesterol, 1.39 mmol/L for HDL cholesterol and 2.12 mmol/L for triglycerides.

A significant reduction was found in HbA1c level, diastolic blood pressure, total cholesterol, LDL cholesterol and serum creatinine and significant increase in HDL cholesterol between the first visit to the outpatient clinic and the annual review visit. At first visit more than three quarters of patients had HbA1c level above the recommended value by the Irish diabetes guideline (Table 6.1.14). This decreased by almost 20% during their annual review. More than half of the patients had blood pressure and total cholesterol levels above the recommended values with improvement observed at the annual review.

The median MPR for oral antidiabetic medication in this cohort was 67% with only 29% of patients considered adherent (MPR >80%). The median MPR for statins in this cohort was 92% with 76% of patients having an MPR>80% while the median MPR for antihypertensives in this cohort was also 92% with 56% considered adherent. When examined as a continuous variable, there was found to be no significant relationship between MPR score for antidiabetic medication and HbA1c levels at the annual review clinic in this cohort. No significant relationships were observed between the MPR score for lipid lowering medications and lipid profiles (total cholesterol levels, LDL cholesterol, HDL cholesterol and triglycerides). Similar findings were found for the MPR score for antihypertensive agents and blood pressure levels.

No significant relationship was observed between MPR and achievement of HbA1c levels of <6.5% (Table 6.1.15). Positive trends were observed between adherence to lipid lowering medications and achievement of recommended values for cholesterol levels, however, these were not statistically significant. Adherence to antihypertensive medications was associated with achievement of <80 mmHg diastolic blood pressure (p=0.03).

Table 6.1.13: Clinical parameters in patients with type 2 diabetes attending outpatient clinic at St James's hospital during their first visit and their annual review visit

Clinical measurements	First visit (n=160) Mean, SD	Annual review (n=128) Mean, SD	Mean change , *p*
HbA1c (%)	8.0% (SD 2.1%)	7.0% (SD 1.3%)	1.2% (SD 2.1%) ***
Systolic blood pressure (mmHg)	136 (SD 18)	134 (SD 22)	1 (SD 20.6) ns
Diastolic blood pressure (mmHg)	75 (SD 9)	70 (SD 12)	5 (SD 12) *
Total cholesterol (mmol/l)	4.52 (SD 1.05)	4.18 (SD 1.02)	0.34 (SD 0.84) *
Triglycerides (mmol/l)	1.87 (SD 1.22)	1.64 (SD 0.90)	0.19 (SD 1.06), ns
HDL cholesterol (mmol/l)	2.51 (SD 0.87)	2.16 (SD 0.85)	0.39 (SD 0.78) ***
LDL cholesterol (mmol/l)	1.18 (SD 0.32)	1.31 (SD 0.59)	-0.15 (SD0.56) *

Table 6.1.14: Percentage of patients with clinical measurement above the target values recommended by the Irish guideline on type 2 diabetes

Clinical measurements	First visit (n=156)	Annual review (n=128)	*p*
HbA1c >6.5%	78%	61%	***
Systolic blood pressure>130 mmHg	68%	56%	ns
Diastolic blood pressure> 80mmHg	49%	22%	**
Total cholesterol> 4.5 mmol/l	53%	33%	*
Triglycerides >2.0 mmol/l	33%	27%	ns
LDL cholesterol	48%	32%	*
HDL cholesterol <1.0 mmol/l	26%	19%	ns

Table 6.1.15: Relationship between adherence to medications (antidiabetic, lipid lowering, antihypertensive agents) and clinical measurement when examined as categorical variable

Clinical parameters		% Adherent (n=92)	*p*
HbA1c×	**<6.5%∞**	52%	ns
	<7.4% Δ	57%	ns
Systolic blood pressure	**<130 mmHg∞**	52%	ns
	<148 mmHg Δ	57%	ns
Diastolic blood pressure	**<80 mmHg∞**	58%	*
	<78mmHg Δ	54%	ns
Total cholesterol	**<4.5 mmol/l∞**	57%	ns
	<4.78 mmol/l Δ	59%	ns
Triglycerides	**<2.0 mmol/l∞**	55%	ns
	<2.12 mmol/l Δ	55%	ns
LDL cholesterol	**<2.5 mmol/l∞**	60%	ns
	<2.62 mmol/l Δ	60%	ns
HDL cholesterol	**>1 mmol/l ∞**	51%	ns
	<1.39 mmol/l Δ	51%	ns

∞ recommended values by Irish guideline on type 2 diabetes
Δ values obtained from the 75th centile

6.1.5 Discussion

Predictors of adherence in the Irish population with type 2 diabetes

More than a third of patients with type 2 diabetes were non adherent to their prescribed antidiabetic and cardiovascular therapies. These findings are consistent with other studies on adherence to medications in patients with type 2 diabetes [314]. Younger aged patients with newly treated type 2 diabetes were less likely to adhere to medications compared to older aged patients. Younger patients are likely to have fewer symptoms and therefore may not realize the long term consequences of poor diabetes control and may not comprehend the benefit of good adherence to treatment. Patients with lower socioeconomic background, as represented by those eligible for the GMS scheme were less likely to adhere to medications compared to those from higher socioeconomic background eligible for the LTI scheme. Demographic factors such as age, gender and race as well as socioeconomic background are non-modifiable and often inconsistent predictors of adherence to therapy [325]. Concurrent insulin treatment, as identified from prescription refill records, were shown to significantly influence adherence to oral antidiabetic medication and also adherence to cardiovascular preventative therapies in patients with type 2 diabetes.

Presence of cardiovascular comorbidities such as ischaemic heart disease using prescriptions as surrogate markers increases the likelihood of adherence. These patients may be seen more often in the primary care setting or hospital setting and may comprehend the need for the multiple medications. A 10-year study on adherence to statins and aspirin in patients with cardiovascular disease also demonstrated that patients on dual cardiovascular therapies were more likely to adhere to their prescribed medications compared to one medication only [331]. Patients with diabetes and concurrent neurological problem (Parkinson's disease, epilepsy and dementia) were less likely to adhere to their medications. This may be due to the difficulties in incorporating the complex diabetes regime into the pre-existing management of their neurological problems. Other studies have also shown the presence of cognitive impairment and psychological problems, such as depression, to be associated with reduced adherence to medications [332, 333].

Although the majority of patients in the cohort from Connolly Hospital reported good adherence to medications, only half of the patients were found to be adherent from prescription refill records. In contrast, it was shown that the self-reported adherence was significantly related to MPR in the Improving Diabetes Outcomes Study [316]. However, this discrepancy may be due to the small number of patients available for this study compared to the patients included in the Improving Diabetes Outcomes Study. A self-reported adherence questionnaire is simple to

administer and is the most useful method to examine adherence in clinical settings [317]. However, it is subject to self-presentational and recall bias. Patients may provide answers that they feel appropriate in the clinical setting rather than reflecting on their true beliefs on medicines and medication taking behaviour.

Beliefs towards medications taking behaviour and its relationship with adherence to medications in patients with type 2 diabetes

This study has shown that, in patients with type 2 diabetes attending an outpatient clinic in Dublin, most patients perceived that their prescribed medications are a necessity for their diabetes management. Less than a third have specific concerns about their prescribed medications and felt that medications are overprescribed by their clinician while only a minority felt that medicines are harmful. Longer term follow-up alleviated patients' negative views on medications. Those who scored highly for necessity were more likely to report good adherence to medication. Lower perceived harm is related to an increase in self-reported adherence.

Studies in different populations have also validated the use of BMQ questionnaire either in English or translated into other native languages as a tool to examine patients' beliefs and attitude towards their prescribed medicine and other medications in general [321, 334, 335]. Patient medication beliefs have been correlated with medication use in hyperlipidaemia, heart disease, depression and other chronic diseases. Beliefs about medicines have been shown to be related to self-reported adherence scores [321, 322, 334-337] and other measures of adherence such as the MPR from prescription refills [338] or serum concentration of medications [322]. Those who believe that their medications are a necessity and have low concerns with regards to their prescribed medications were consistently shown to report higher adherence to medications [321].

Adherence and clinical outcomes

In the prospective study of patients with type 2 diabetes attending an outpatient clinic, patients with HbA1c <7.5% were more likely to report higher adherence to medications at their initial visit. However, there was no relationship between poor self-reported adherence and achieved glycaemic, lipid or blood pressure goals at follow up. This could in part be explained by the fact that patients reporting non-adherence to medications were less likely to attend their follow-up visit. In the retrospective cohort study, a significant relationship between adherence to medication was observed between antihypertensive agents and diastolic blood pressure.

In order to examine the relationship between adherence from prescription refill records and clinical outcomes in this study, record linkages were performed between the pharmacy claims database and hospital records. Other pharmacy databases such as the PHARMO and MEMO databases are linked to clinical records and this record linkage has transformed these databases

to allow researches on drug uses and clinical outcomes to be performed. One of the weaknesses of record linked databases are the uncertain validity of diagnosis data [63]. However, validation of nearly ten thousand linked records in the PHARMO databases showed that this database was linked with a sensitivity and specificity exceeding 95% [339]. In this study, some difficulties were encountered in the process of record linkage between the Irish HSE-PCRS database and hospital records including the long process to obtain ethical approval, the difficulties in obtaining the GMS numbers from the patients in the Connolly cohort, the need for manual extraction of the hospital records and measures to maintain confidentiality of patients. In the prospective study using the cohort of patients from Connolly hospital, the GMS or LTI unique patient identifier was unavailable for more than a third of patients. Similarly, although the GMS patient identifier was available for all of patients from St James's hospital cohort in the retrospective study, the actual prescribing records for more than a third of these patients were unavailable. Some patients may not have obtained their medications under either the GMS or LTI schemes and also some may not have collected their medications at all during the one year study period. It is also possible that an incorrect GMS number recorded was recorded in the St James's HIPE system.

Both the studies performed in Connolly Hospital and in St James's Hospital were underpowered to examine the relationship between adherence to medications using prescription refill records and clinical outcomes. Inconsistent results have been obtained in other studies examining the association between adherence and HbA1c levels [316, 325, 340]. HbA1c levels are influenced by many factors and adherence may contribute to the overall achievement of target HbA1c. One study found that poor adherence, as measured using MPR was associated with higher HbA1c levels amongst those receiving two or more oral antidiabetic agents [316]. Adherence to statins therapy as reflected by MPR has been shown to be closely related to LDL cholesterol levels in patients with diabetes [341]. On the other hand, only 43% of patients with high adherence to antihypertensive medication attain their target blood pressure control [342].

It is interesting to note that there was a significant improvement in the clinical parameters from first visit to their annual visit in patients with type 2 diabetes newly presenting to the St James's diabetes centre in the retrospective cohort study. St James's hospital has an integrated diabetes care system which encompasses the services of diabetes specialists, specialist and research diabetes nurses, chiropodists, dieticians and social workers. Access to this service by a patient is recorded in the DIAMOND database. The integrated approach provides a holistic management for patients with diabetes and thus improvement in clinical parameters may be contributed by lifestyle changes in addition to pharmacological management. This model of integrated care should be extended nationwide to other tertiary and secondary centres providing

care to patients with diabetes so that more patients can benefit from the improved clinical outcomes.

Strength and limitations

Using both the GMS and LTI databases, this study was able to examine adherence to antidiabetic and cardiovascular medications in a national population using prescription refill records. All patients with diabetes received their medications free of charge from the Irish health services either through the GMS or LTI schemes, thus the measures of medication adherence were not confounded by the differing ability of patients to pay for prescribed medications. The cost of medications and the ability to pay for medications have been shown to impact on patients adherence to treatment in other studies [325].

An inherent limitation of using a pharmacy claims database for adherence studies is that it only measures medication possession and not the actual consumption of medicines. Thus the use of MPR may overestimate the true adherence level in an individual patient. Average MPR for patients taking more than one class of medication was used and thus this may overestimate adherence in this population. Access to prescriptions written by the clinicians was not available to examine the recommended regimen for patients. Thus the use of DDDs to calculate the cumulative dosage may not reflect changes of dosage as prescribed by clinicians, switching of therapies and addition of antidiabetic agents. Gaps in the prescription refill record may possibly be due to other reasons such as paying for their own medications, concurrent illness requiring hospitalizations or holidays outside the country. The use of prescription refill record also does not differentiate between non adherence and non-persistence. Persistence is defined as the duration of time from initiation to discontinuation of therapy [343]. It was shown that 10.5% of patients failed to fill the second prescription for oral antidiabetic medications and 37% discontinued their antidiabetic medications 12 months after initiation of treatment [344]. This may be the reason for lower adherence in patients co-prescribed insulin compared to those without insulin. However, this does not explain poor adherence to cardiovascular preventative therapies in patients concurrently prescribed insulin. Approximately half of patients prescribed statins discontinued their medications within six months of initiation [345]. Adherence to insulin was not examined as the database does not have the original prescriptions written by the clinicians and thus the dose of insulin needs to be injected by the patients were unable to be determined.

The self-reported adherence questionnaires and the BMQ were administered in the outpatient settings by clinicians in charge and thus there may be subject to bias as described above. The reduced power for statistical calculation may explain the lack of association between adherence to medications and clinical outcomes observed in this study. Clinical measurements from those who did not attend the follow up visit were not available and thus it was not possible

to examine the relationship between adherence and clinical measurement in non-attendees. Those who did not attend their follow up clinic had lower initial self-reported adherence score and this may be a bias in this study.

Implications of research

Identification of patients with suboptimal adherence can facilitate measures to improve adherence in the hospital and community settings. It was shown in other studies that interventions by allied health professionals in patients with type 2 diabetes did not improve adherence in those already highly adherent to medications while in those with poor adherence, inconsistent results were observed [346]. Thus, it is important to determine the baseline level of adherence in order to plan appropriate interventions targeting those at risk of poor adherence to medications.

The use of prescription refill records and self-reported adherence score could be used as a tool to identify patients at greater risk of non-adherence such as younger patients, those with concurrent insulin prescriptions, those with lower socioeconomic background and those with neurological problems. The use of self-reported adherence linked to pharmacy claims database provides a unique opportunity to capture the medication taking behaviour in this population. The use of combination measures increases the accuracy of adherence calculation [347].

In the prospective cohort study, perceived necessity of medications increased the likelihood of medication adherence and patients with higher medication adherence were more likely to have good glycaemic control at baseline. It was also shown in this prospective study that those with low self-reported adherence were more likely not to attend their annual follow up clinic. Effective communications between clinicians and other health care professionals to address necessity of treatment may improve adherence and address concerns about potential side effects with regards to treatment especially if this involves change in doses, change in medications or polypharmacy [348]. A meta-analysis showed that educational interventions have positive effects on patient knowledge, self-care behaviour, metabolic control, and psychological outcomes in patients with type 2 diabetes [166]. However, inconsistent effects were observed with educational interventions to improve adherence in patients with type 2 diabetes [349]. Other measures to improve adherence include simplification of treatment regime by choosing fixed oral dose combination such as metformin-sitagliptin, once daily longer acting preparation such as modified release sulphonylureas and use of medications with dual purposes such as ACEIs or ARBs [325].

CHAPTER SEVEN

CHAPTER 7 : RISK OF DIABETES WITH COMMONLY PRESCRIBED PHARMACOLOGICAL AGENTS IN THE PRIMARY CARE POPULATION

7.1 Risk of new onset diabetes with corticosteroids in the Irish population

7.1.1 Background

Corticosteroids possess potent anti-inflammatory and immunosuppressive properties and have become valuable treatment options for a wide range of clinical conditions since their discovery in 1935 [350]. However, multiple adverse effects of corticosteroids have also been reported in the literature and among common side effects associated with corticosteroids are adipose tissue redistribution, peptic ulcer disease, osteoporosis, cataract and hyperglycaemia [351]. Risks associated with corticosteroids inducing hyperglycaemia have been described as early as 1953 [352]. Corticosteroids even when used in an alternate day regime, were also found to be associated with alternate day hyperglycaemia [353].

In susceptible individuals, impaired glucose regulation can lead to the development of subsequent overt diabetes mellitus. The association between corticosteroid use and new onset diabetes has been shown mainly from selected clinical settings, in particular in post-transplant patients using high doses of corticosteroids as part of immunosuppressant regime [354] . Some population based studies have also recently examined the risk of new onset diabetes in those prescribed corticosteroids and found an increased risk of new onset diabetes with corticosteroids compared to the general population [355] [356-358].

Previous studies on corticosteroids and their effects on glucose have mostly focused on oral corticosteroid agents [355, 356], however, risks of new onset diabetes associated with corticosteroids when prescribed by other routes of administration in a population require consideration. This case-control study aims to examine the risk of new onset diabetes associated with corticosteroids via different routes of administration as prescribed in the Irish national population. In addition, the risk of new onset diabetes with individual corticosteroid agents is examined. This study also examines the relationship between dose and duration of prescribed corticosteroids with new onset diabetes in this population.

7.1.2 Specific objectives

1) To examine the risk of new onset diabetes with prescribed corticosteroids according to route of administration in the Irish population
2) To examine the dose-response relationship between oral corticosteroids as well as duration-response relationship between corticosteroids of different routes of administration and risk of new onset diabetes
3) To examine the risk of new onset diabetes with individual corticosteroid agents as prescribed for the Irish population

7.1.3 Methods

A case-control study was performed using the HSE-PCRS national primary care prescribing database. For the purpose of this study, patients under the GMS scheme were selected as this study requires longitudinal follow up of patients prior to initiation of anti-diabetic therapies.

Case and control definition

A total number of 2,070,137 individuals aged 25 years old and above prescribed any medicines from January 2001 to January 2009 were identified from the database. Those prescribed oral anti-diabetic agents prior to January 2008 (n=101,349), insulin only (n=16,173) or glucose monitoring kits only (n=21,754) were excluded. The year 2001 was used as run-in period to exclude individuals prescribed corticosteroids prior to the study period (n=175,968). Those newly initiating corticosteroids after or in the same month as oral anti-diabetic agents (n=814) were also excluded.

Cases (new onset diabetes) were selected from individuals newly initiating antidiabetic agents for a period of ≥3 months from January 2008 to January 2009 (n=11,132). The cases were matched according to age (within 10 year age bands) and gender with four randomly selected controls receiving no oral anti-diabetic agents during the same study period (n=44,528).

Corticosteroids exposure

Patients prescribed oral, topical, inhaled, nasal, and eye/aural drop corticosteroids by one route of administration only were identified according to the relevant ATC codes over a 7-year period prior to new onset diabetes or between January 2002 and December 2008 for controls. The selection of corticosteroid by one main route of administration only was used to reduce confounding due to co-prescriptions of corticosteroids by other routes of administration in an individual patient. Inhaled corticosteroid agents combined with long-acting beta agonist such as budesonide-formoterol and fluticasone-salmeterol combinations were excluded to reduce confounder due to use of combination agent. The total cumulative DDDs prescribed for oral

corticosteroid agents throughout the study period was calculated according to method described by the WHO [359]. A DDD for oral corticosteroid is equivalent to 10mg prednisolone, 30mg hydrocortisone, 15mg deflazacort and 1.5mg betamethasone. The total DDDs was converted to prednisolone - equivalent milligram and presented as milligram/month. Duration of exposure to corticosteroids was examined according to the number of months in which the patients were prescribed corticosteroids. Patients were considered to be exposed to a month of corticosteroid if the patient received a corticosteroid prescription for the respective month.

Risk of new onset diabetes was examined in patients prescribed monotherapy of individual corticosteroids agents. Individual agents examined were oral prednisolone (n=1,469), inhaled beclomethasone (n=511), inhaled budesonide (n=113), nasal beclomethasone (n=161), nasal fluticasone (n=167), nasal mometasone (n=143) and topical corticosteroids (n=3,266). Topical corticosteroid agents were classified according to potency using the ATC classification; weakly potent, moderately potent, potent and very potent agents. Weakly potent agents included in the analysis were hydrocortisone (n=504) and prednisolone (n=225); moderately potent agents included hydrocortisone butyrate (n=66) and alclometasone (n=23); potent agents included betamethasone (n=853) and mometasone (n=88) and very potent agents included clobetasol (n=117). Individual corticosteroid agents with small number of patients (<100) were not included in the statistical analysis.

Covariates

The use of pharmacological agents such as thiazide diuretics, beta blockers and antipsychotics shown to have some association with new onset diabetes were considered as potential confounders and thus included as covariates [53]. In addition, diseases being treated with corticosteroids may influence the risk of new onset diabetes. These include adrenal failure (Addison's disease), allergic conditions such as asthma and allergic rhinitis, inflammatory conditions such as rheumatoid arthritis, inflammatory bowel disease, connective tissue diseases such as vasculitis, dermatological conditions such as psoriasis, haematological conditions such as thrombocytopenic purpura, immunological conditions such as multiple sclerosis. In addition, corticosteroids are also used to prevent *graft –versus-host* disease following transplant and in combination with cytotoxic drugs in treatment of specific malignancies such as Hodgkin's disease and acute lymphocytic leukaemia [360]. For some of these conditions mentioned, the prescribing of other medications besides corticosteroids for these conditions can be used as surrogates for the disease of interest. These were identified using the relevant ATC codes and included as covariates: (1) anti-psoriatic agents for psoriasis (2) inhaled or systemic agents for COPD or asthma (3) intestinal anti-inflammatory agents for inflammatory bowel disease (IBD) (4) anti-rheumatic agents for rheumatoid arthritis (5) anti-neoplastic agents for neoplastic diseases and

(6) conditions requiring immunosuppressants such as post-transplant. Anti-neoplastic agents or immunosuppressants prescribed through a different scheme in Ireland, the HTD Scheme, were not included. These were etoposide, idarubicin, cyclosporine, mycophenolate and tacrolimus.

Statistical analysis

Univariate analysis was performed on possible covariates to examine the association between each co-prescribed medications of interest and new onset diabetes. Only medications with significant relationship with diabetes were included for adjustment. Conditional logistic regression stratified for age groups and gender was used to examine the association between new onset diabetes and prior prescription of corticosteroids of differing routes of administration adjusting for covariates as described above compared to those not prescribed any corticosteroids during the study period. In addition, the risks of new onset diabetes in patients prescribed individual corticosteroid agents and topical corticosteroids of differing potencies were examined. A test for linear trend was used to examine the duration and dose response relationship of prescribed corticosteroids and new onset diabetes by including duration and dose as a continuous term in the model. In addition, the dose and duration relationship was also examined as categorical variable by selected duration (≤3 months, 4-6 months and >6 months) and dosage prescribed (<60mg/month, 60-120mg/month and >120mg/month). Analysis was performed using PROC PHREG command in SAS version 9.1.

7.1.4 Results

The study comprised of 11,132 cases and 44,528 controls. The baseline characteristics of patients included in the study and the co-prescriptions of other medications of interest in both cases and controls are presented in Table 7.1.1. Covariates selected for the final analysis were thiazides, beta blockers, antipsychotics, anti-psoriatics, drugs for COPD or asthma and immunosuppressants. The percentage of cases with new onset diabetes prescribed corticosteroids via only one route of administration was 26% in cases and 18% in controls (Table 7.1.2). Of those, only 4% of cases and 3% of controls received >12 months of corticosteroids prescriptions.

The use of any corticosteroids by only one route of administration, oral, topical, inhaled and nasal corticosteroids throughout the study period was associated with an increased risk of new onset diabetes when no adjustment for other co-prescribed medications were made (OR=1.46 [95% CI 1.38, 1.55]) (Table 7.1.3). However, after adjustment, only oral corticosteroids were associated with an increased risk of new onset diabetes with adjusted OR=1.13 (1.01, 1.26). New onset diabetes was significantly associated with duration of oral corticosteroids treatment (p=0.008) OR=1.88 (95% CI 1.69, 2.11) for more than 6 months prescriptions compared to non-

users (Figure 7.1.1a). A significant linear trend relationship was observed between dosage of oral corticosteroids and new onset diabetes ($p<0.0001$) with adjusted OR of 2.51 (95% CI 1.98, 3.18) for >120 mg/month equivalent dose of prednisolone over the study period (Figure 7.1.1b).

Topical corticosteroids of differing potencies were found to be significantly associated with new onset diabetes (Table 7.1.4) before adjustment for covariates was made. Only very potent topical agents with OR=1.58 (95% CI 1.05, 2.93) showed significant association with new onset diabetes when adjusted for covariates showing a significant duration response relationship ($p=0.0001$). With regards to monotherapy of individual corticosteroid agents, most agents showed a significant risk of diabetes before adjustments for co-prescribed medications as proxy of diseases were made (Table 7.1.5). There was a significant risk of new onset diabetes in this study for topical clobetasol (OR=1.58 [95% CI 1.05, 2.39]) followed by oral prednisolone (OR=1.28[95% CI 1.12, 1.45]) with a significant linear trend for the duration of individual corticosteroids prescribed ($p=0.0001$ for clobetasol, $p<0.0001$ for oral prednisolone).

Table 7.1.1: Baseline characteristics of both cases and controls included in the corticosteroids study with univariate analysis of diabetes risk (OR with 95% CI)

Patient characteristics		Cases (n=11,132)	Controls (n=44,528)	Total (n=55,660)	OR (95% CI), *p*
Gender	**Females**	5,323 (47.8%)	21,292 (47.8%)	26,615 (47.8%)	-
Age groups	**25-44**	2,442 (21.9%)	9,768 (21.9%)	12,210 (21.9%)	-
	45-64	3,923 (35.2%)	15,692 (35.2%)	19,615 (35.2%)	-
	≥65	4,767 (42.8%)	19,068 (42.8%)	23,835 (42.8%)	-
Diabetogenic agents	**Thiazide**	1,322 (11.9%)	2,962 (6.6%)	4,284 (7.7%)	1.93 (1.80, 2.07) ***
	Beta blockers	3,221 (28.9%)	5,862 (13.2%)	9,083 (16.3%)	2.82 (2.68, 2.97) ***
	Antipsychotics	1,041 (9.3%)	2,672 (6.0%)	3,713 (6.7%)	1.62 (1.50, 1.75) ***
Co-prescriptions of other medications	**Anti-psoriatics**	143 (1.3%)	276 (0.6%)	419 (0.7%)	2.09 (1.70, 2.56) ***
	Drugs for COPD/asthma	1,752 (15.7%)	4,446 (10.0%)	6,198 (11.1%)	1.69 (1.59, 1.79) ***
	Intestinal anti-inflammatory agents	80 (0.7%)	273 (0.6%)	353 (0.6%)	1.17 (0.91, 1.51) ns
	Anti-rheumatic agents	33 (0.3%)	103 (0.2%)	136 (0.2%)	1.28 (0.87, 1.90) ns
	Anti-neoplastic agents	174 (1.6%)	609 (1.4%)	783 (1.4%)	1.15 (0.97, 1.36) ns
	Immune-suppressants	128 (1.1%)	287 (0.6%	415 (0.7%)	1.80 (1.46, 2.22) ***

Table 7.1.2: Frequency and percentages of corticosteroids prescribing according to different routes of administration and duration of use in cases and controls

Corticosteroid agents×	Cases (n=11,132) (n, %)	Controls (n=44,528) (n, %)	Total (n=55,660) (n, %)
All corticosteroids	2,889 (25.9%)	8,004 (18.0%)	10,893 (19.6%)
Oral only	1,040 (9.3%)	2,818 (6.3%)	3,858 (6.9%)
Topical only	807 (8.6%)	2,459 (5.5%)	3,266 (5.9%)
Inhaled only ∞	820 (7.4%)	1,939 (4.3%)	2,759 (5.0%)
Nasal only	171 (1.5%)	598 (1.3%)	769 (1.4%)
Eye/aural drops only	51 (0.6%)	190 (0.4%)	241 (0.4%)

× Patients prescribed corticosteroids by one route of administration only
∞ excludes combination of fluticasone-salmeterol and budesonide-formoterol

Table 7.1.3: Risk of new onset diabetes with corticosteroids according to routes of administration presented as unadjusted and adjusted OR with 95% CI

Corticosteroid agents ×	Cases (n, %)	Controls (n,%)	Unadjusted OR (95% CI), *p*	Adjusted OR (95% CI), *p*
All corticosteroids†	1,843 (17.6%)	5,476 (12.8%)	1.46 (1.38,1.55) ***	1.17 (0.86, 1.59) ns
Oral only†◊	551 (6.0%)	1,587 (4.1%)	1.51 (1.37,1.67) ***	1.13 (1.01, 1.26) *
Topical onlyΔ	807 (8.6%)	2,459 (6.2%)	1.43 (1.31, 1.55) ***	1.09 (1.00, 1.19) ns
Inhaled only □	263 (3.0%)	642 (1.7%)	1.77 (1.53, 2.05) ***	1.18 (1.00,1.39) ns
Nasal only □	171 (1.8%)	598 (1.5%)	1.22 (1.02, 1.44) *	0.97 (0.81, 1.15) ns
Eye/aural drops only ∞	51 (0.6%)	190 (0.5%)	1.17 (0.86, 1.59) ns	0.96 (0.69, 1.32) ns

×Patients prescribed corticosteroids by one route of administration only
† adjusted for co-prescriptions of thiazide diuretics, beta blockers, antipsychotics and other medications used for psoriasis, COPD/asthma, immunosuppressants
Δ adjusted for co-prescriptions of thiazide diuretics, beta blockers, antipsychotics and other medications used for psoriasis
□ adjusted for co-prescriptions of thiazide diuretics, beta blockers, antipsychotics and other medications used for COPD/asthma
∞ adjusted for co-prescriptions of thiazide diuretics, beta blockers and antipsychotics
◊ significant linear trend test for duration of corticosteroids, $p<0.05$ and risk of new onset diabetes

Figure 7.1.1: OR (95% CI) showing the relationship between new onset diabetes and a) duration of oral corticosteroid and b) dose of oral corticosteroids (equivalence to prednisolone dosage) when examined as categorical variables

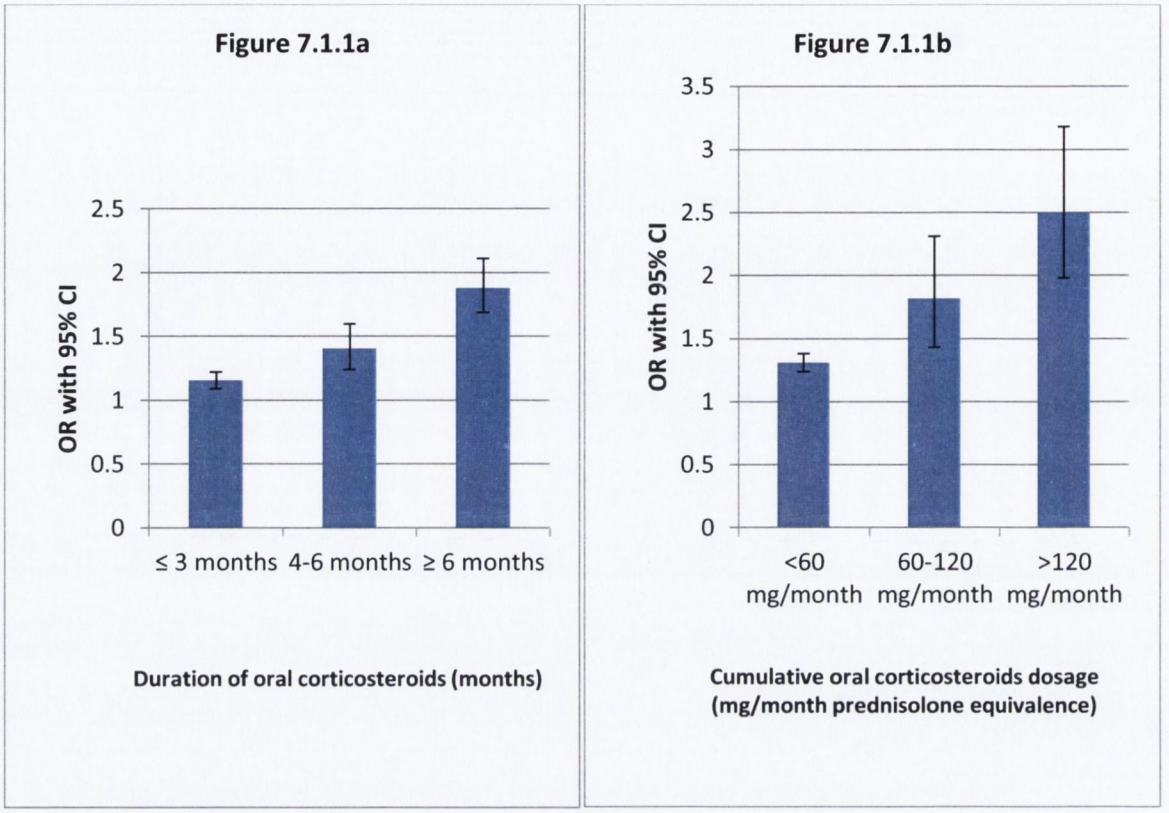


Table 7.1.4: Adjusted OR with 95% CI and linear trend test of new onset diabetes for monotherapy of topical agents according to potency and duration of use

Topical corticosteroids	Unadjusted OR (95% CI), *p*	Adjusted† OR (95% CI), *p*
Weakly potent (n=1,054)	1.48 (1.23, 1.79) ***	1.14 (0.94, 1.38), ns
Moderately potent (n=342)	1.64 (1.16, 2.32) **	1.28 (0.89, 1.85) ns
Potent (n=998)	1.48 (1.28, 1.71) ***	1.07 (0.92, 1.24) ns
Very potent (n=117)◊	1.85 (1.24, 2.75) **	1.58 (1.05, 2.39) *

† adjusted for co-prescriptions of thiazide diuretics, beta blockers, antipsychotics and anti-psoriatics
◊ significant linear trend test for duration of topical corticosteroids, $p<0.05$ and risk of new onset diabetes

Table 7.1.5: Risk of new onset diabetes with monotherapy of individual corticosteroid agents presented as unadjusted and adjusted OR with 95% CI

Individual corticosteroid agents	Unadjusted OR (95% CI), *p*	Adjusted OR (95% CI), *p*
Prednisolone (oral) †◊	1.78 (1.58,2.00) ***	1.28 (1.12, 1.45) **
Betamethasone (topical) Δ	1.47 (1.26, 1.72) ***	1.08 (0.92, 1.27) ns
Hydrocortisone (topical) Δ	1.50 (1.23, 1.84) ***	1.16 (0.94, 1.43) ns
Prednisolone (topical) Δ	1.20 (0.88, 1.65) ns	0.96 (0.70, 1.34) ns
Clobetasol (topical) Δ◊	1.85 (1.24, 2.75) **	1.58 (1.05, 2.39) *
Beclomethasone (inhaled) □	1.90 (1.57, 2.30) ***	1.06 (0.92, 1.23) ns
Budesonide (inhaled) □	2.00 (1.34, 2.98) **	1.46 (0.95, 2.23) ns
Beclomethasone (nasal) □	1.08 (0.74, 1.60) ns	0.84 (0.57, 1.26) ns
Fluticasone (nasal) □	1.46 (1.03, 2.07) *	1.09 (0.76, 1.57) ns
Mometasone (nasal) □	1.52 (1.04, 2.20) *	1.17 (0.79, 1.73)ns

† adjusted for co-prescriptions of thiazide diuretics, beta blockers, antipsychotics and other medications used for psoriasis, COPD/asthma, immunosuppressants

Δ adjusted for co-prescriptions of thiazide diuretics, beta blockers, antipsychotics and other medications used for psoriasis

□ adjusted for co-prescriptions of thiazide diuretics, beta blockers, antipsychotics and other medications used for COPD/asthma

◊ significant linear trend test for duration of individual corticosteroids, $p<0.05$ and risk of new onset diabetes

7.1.5 Discussion

Corticosteroids are commonly prescribed in the Irish population with nearly a quarter of cases and a fifth of controls in this case-control study receiving at least one prescription of corticosteroids by one route of administration only. This study has shown that oral and very potent topical corticosteroids are associated with an increased risk of new onset diabetes in the selected case-control study population. A strong dose and duration effect of oral corticosteroids was associated with new onset diabetes in this population. In addition, a duration effect for very potent topical corticosteroids was also demonstrated. Monotherapy of oral prednisolone and topical clobetasol were demonstrated to be associated with an increased risk of new onset diabetes compared to those not prescribed any corticosteroids.

In a meta-analysis of adverse drug events with oral corticosteroids in 93 randomized controlled trials, diabetes was reported more frequently in patients prescribed corticosteroids compared to placebo with a combined OR of 3.21 for more than 3 months corticosteroids [361]. Meta-analysis of oral corticosteroids in COPD patients showed an increased risk of hyperglycaemia compared to placebo with a combined OR of 4.95 (95% CI 2.47, 9.91) [362]. Studies of low dose corticosteroids, as used in rheumatoid arthritis (≤ 10 mg/day), did not report

on any increase in new onset diabetes although significant increases in mean fasting glucose were observed [363]. Corticosteroids, as used for solid organ transplant either alone or in combination with other immunosuppressive agents, have also been to induce post-transplant diabetes [354]. In addition to risk of diabetes, corticosteroids are associated with development of other independent risk factors for cardiovascular disease such as hypertension, hyperlipidaemia and obesity [364] as well as increased risk of cardiovascular disease such as myocardial infarction, heart failure and cerebrovascular disease [365].

The first population based case-control study (11,855 cases; 11,855 controls) on the risk of diabetes with corticosteroids was performed in New Jersey. This study showed that the relative risk of hyperglycaemia was RR=2.23 (95% CI 1.92, 2.59) and the risk increased with increasing dose with OR=10.34 (95% CI 3.16, 33.90) for 120 mg/day or and more of hydrocortisone-equivalent milligrams compared to non-corticosteroids users [356]. However, the study only examined the risk of initiation of hypoglycaemic therapy with recent (<120 days prior to index date) oral corticosteroids use. Our study spans a 7-year period and is not limited to recently prescribed corticosteroids. In addition, few patients were prescribed 120mg/day of hydrocortisone equivalent (>30mg/day of prednisolone equivalent) in our study population.

A more recent case control study in a primary care population (2,647 cases; 5,294 controls) performed over a 10-year period in London also found an increased risk of new onset diabetes with more than 3 prescriptions of oral corticosteroids (OR=1.36 [95% CI 1.10, 1.69]) compared to none after adjusting for propensity scores [357]. The adjusted OR for cumulative oral dose equivalent to ≥2.5 g hydrocortisone (or ≥625 mg of prednisolone equivalent) was 1.25 (95% CI 1.01, 1.54). This study also included corticosteroids by different routes of administration although not limited to those exclusively prescribed corticosteroids by only one route of administration. Similar to our study, the London study did not find any increased risk of new onset diabetes with corticosteroids by other routes of administration after adjustment. Another retrospective cohort study performed in Ontario, Canada examined the risk of diabetes in those prescribed oral or inhaled corticosteroids compared to proton pump inhibitors (PPI) in elderly patients (>65 years old) adjusting for potential diabetogenic agents and corticosteroids of differing routes of administration. Risk of diabetes was found to be increased in those prescribed oral corticosteroids with adjusted RR=2.31(95% CI 2.11, 2.54) [355].

Topical corticosteroids may induce adverse events such as hyperglycaemia via systemic absorption [366] and the systemic absorption of topical corticosteroids increases with increasing duration and dose of treatment [367]. A recent nested case-control study using the PHARMO database found an increased risk of diabetes with current use of topical corticosteroids compared to past users (adjusted OR=1.20 [95% CI 1.07, 1.36]) with a significant dose and duration response

trend between topical corticosteroids and new onset diabetes. Compared to this study, the PHARMO study on topical corticosteroids did not exclude those using concomitant oral or inhaled corticosteroids and did not adjust for co-prescribing of anti-psoriatic known to be associated with diabetes. In those with previous or no systemic or inhaled corticosteroids use, current users of topical corticosteroids were still associated with increased risk of diabetes [358]. In contrast, no increased risk of diabetes were observed with topical corticosteroids in the London population-based study [357]. Compared to the PHARMO and London study, our study found an increased risk of new onset diabetes only with very potent topical corticosteroids showing significant duration response relationship. The risk observed with this agent may be related to the greater systemic absorption and thus systemic disturbances of glucose metabolism compared to topical agents with lower potencies [368, 369].

Meta-analyses performed on inhaled corticosteroids tend not to include diabetes or hyperglycaemia as adverse events of interest [370, 371]. Similar to the findings in our study, a nested case-control study on the use of inhaled corticosteroids in the elderly did not demonstrate an increased risk of new onset diabetes with use of this agent [372]. Other population cohort studies also did not observe an increased risk of diabetes with inhaled corticosteroids [355, 357, 372]. There is a lack of research on nasal and eye/aural drop corticosteroids and the risk of new onset diabetes and our study is one of very few to have found no association.

Corticosteroids exert their effects by binding to the specific intracellular glucocorticoid receptors and thus regulating the expression of the corticosteroid responsive genes. Corticosteroids can induce a state of insulin resistance as well as reducing or suppressing the secretion of insulin from the beta cells in the pancreas. Impaired utilization of glucose in the skeletal muscles and adipose tissues with increased glucose production from the liver via the process of glucogenesis and glycogenolysis may lead to impaired glucose regulation and hyperglycaemia [373, 374]. It is possible that the relationship between prescribed corticosteroids on new onset diabetes was due to the underlying disease being treated. Some diseases commonly treated with corticosteroids are associated with risk of metabolic disturbances such as hyperglycaemia and full blown diabetes. Patients with psoriasis had an increased risk of new onset diabetes compared to the general population [375]. A prospective cohort study found an eighty percent increased risk of diabetes with COPD compared to those without COPD [376]. Transplant patients were more likely to develop post-transplant diabetes with or without corticosteroids [377].

Strengths and limitations

This study, compared to other studies described above was nationally-based and comprised patients selected from all regions in Ireland thus reducing the potentials for selection

bias. The retrospective data enabled longitudinal history of prescribed corticosteroids according to individual agents, dose, duration and potency at individual level to be examined. The selection of corticosteroids prescribed by only one route of administration was used to reduce any confounding due to concurrent use of corticosteroids by other routes of administration in an individual patient.

No diagnostic information was available from the database. However, disease specific therapy of oral antidiabetic agents was used as a proxy for diabetes. Information on other risk factors for diabetes were also not available such as medical history (obesity, gestational diabetes, polycystic ovary and metabolic disorders), family history of diabetes, smoking and body mass index known to be associated with diabetes. Use of oral antidiabetic agents only may have misclassified those with diabetes being managed by diet alone, as controls. For those under 70 years of age, eligibility for the scheme is considered a surrogate measure of lower socioeconomic status, and therefore, more likely to be associated with increased risk of diabetes [378]. The risk of new onset diabetes with intermittent compared to continuous use of corticosteroids and in those prescribed corticosteroids recently compared to past users was not examined. Although the total quantities of oral corticosteroids prescribed were recorded, data on indications for use were not available.

Prescribing of certain medications were used as proxies of diseases commonly prescribed corticosteroids and were adjusted for in the statistical analysis. The use of these proxies may still not capture all patients with those diseases and corticosteroids may be prescribed for other systemic diseases which could not be identified. The use of proxies for diseases may not capture the true severity of the disease and therefore the dose and duration relationship observed may be due to confounding by the underlying disease severity. However, the results of our study were consistent with other studies showing an increased risk of new onset diabetes with increasing duration or dosage of corticosteroids prescribed [356-358].

Implications

Corticosteroids should be used with caution for the shortest duration and lowest dose possible [379]. Careful monitoring of patients for hyperglycaemia during corticosteroids treatment may be required in patients at risk of diabetes. Baseline blood glucose, blood pressure and lipid levels may need to be measured particularly in patients commenced on long-term or high dose corticosteroids therapy [380].

Further research into the development of potent anti-inflammatory drugs to replace corticosteroids and their adverse effects is required. Novel agents targeting the glucocorticoid receptor such as the 11-beta-hydroxysteroid dehydrogenase inhibitors are being developed [381].

7.2 Risk of new onset diabetes with antidepressants in the Irish population

7.2.1 Background

Depression is a common mood disorder with the lifetime prevalence of major depressive disorder estimated to be at 6.7% in the general population [382]. The SLÁN study showed that 6% of Irish respondents were classified as having major generalised depressive disorder with Irish women more likely to have major depressive disorder compared to men [383]. Some patients experiencing depression may need to be prescribed antidepressants. Increases in prescribing of antidepressants have been observed over the past few years in the UK population [384]. In 2003, 17% of the Irish adult population covered by the GMS scheme were prescribed antidepressants [385].

The relationship between depression and diabetes is quite complex and may be bidirectional [386]. Depression itself is a common co-morbidity in patients with diabetes. The prevalence of depression in diabetes patients is estimated to be at 25.3%, with 11.4% of diabetes patients having major depressive disorder [36]. Co-morbid depression is associated with an increase in all-cause mortality in diabetes patients [387]. Increasing evidence is emerging on the association between depressive symptoms and risk of new onset diabetes in many epidemiological studies. Evidence also suggests that diabetes is associated with increased risk of new onset depression. A meta-analysis found that depressed adults had a 37% increased risk of type 2 diabetes [388]. Another recent meta-analysis on bidirectional relationship of depression and diabetes found higher risk of type 2 diabetes with depression than the previous meta-analysis at 60% whilst type 2 diabetes was associated with only modest increased risk of depression [389].

Although studies have reported an association between depression and new onset diabetes, observational studies have found conflicting results on the risk of developing new onset diabetes with the use of antidepressants in different populations [54, 390-392]. Thus, this case-control study was undertaken to examine the risk of new onset diabetes in patients prescribed antidepressants in the Irish primary care population setting. This study examined the risk of new onset diabetes according to the different classes of antidepressants and in individual antidepressants according to duration and dosage prescribed.

7.2.2 Specific objectives

1) To examine the risk of new onset diabetes with different classes of antidepressants as prescribed in the Irish primary care population

2) To examine the risk of new onset diabetes with the use of individual antidepressant agents according to duration and dosage prescribed.

7.2.3 Methods

A case-control study was performed using the HSE-PCRS database national prescribing database. For the purpose of this study, only patients under the GMS scheme were selected.

Case and control definition

A total number of 2,070,137 individuals aged 25 years old and above prescribed any medicines from January 2001 to January 2009 were identified from the HSE-PCRS database. Those prescribed oral anti-diabetic agents prior to January 2008 (n=101,349), insulin only (n=16,173) or glucose monitoring kits only (n=21,754) were excluded. The year 2001 was used as run-in period to exclude individuals prescribed antidepressants prior to the study period (n=120,065). Those newly initiating antidepressants after or in the same month as oral anti-diabetic agents (n=1,095) were also excluded.

Cases (new onset diabetes) were selected from individuals newly initiated on anti-diabetic agents for a period of ≥3 months from January 2008 to January 2009 (n=9,474). The cases were matched according to age and gender with four randomly selected controls receiving no oral anti-diabetic agents during the same study period (n=37,896).

Antidepressant exposure

Individuals prescribed only one class of antidepressants with defined daily doses (DDD) were identified (n=6,783) over a 7-year period prior to new onset diabetes or between January 2002 to December 2008 for controls. The classes of antidepressants included in the analysis were tricyclic antidepressants (TCA) (n=1,372), selective serotonin reuptake inhibitors (SSRI) (n=4,052), serotonin-norepinephrine reuptake inhibitors (SNRI) (n=790) and other antidepressants including monoamine oxidase inhibitors (n=569). In addition, individuals prescribed individual monotherapy antidepressants over the 7-year study period were examined. These were amitriptyline (n=814), dothiepin (n=297), citalopram (n=1,073), escitalopram (n=1,229), fluoxetine (n=504), sertraline (n=453), paroxetine (n=393), venlafaxine (n=646), duloxetine (n=133), mirtazapine (n=365) and trazodone (n=166). Monotherapy agents with small numbers of patients (<100) were not included in the analysis.

The total cumulative DDDs were included to determine total consumption of antidepressants prescribed over the study period. A DDD is equivalent to 75mg amitriptyline, 0.1g dothiepin, 20mg citalopram, 10mg escitalopram, 20mg fluoxetine, 50mg sertraline, 20mg paroxetine, 0.1g venlafaxine, 60mg duloxetine, 30mg mirtazapine and 0.4g trazodone. Duration of exposure to antidepressants was examined according to the number of months in which the

patients were prescribed antidepressants. Patients were considered to be exposed to one month of antidepressant if they received a prescription for the respective month.

Covariates

Thiazide diuretics, beta blockers, oral corticosteroids and antipsychotic prescriptions were considered potential confounders as discussed in section 7.1.3. In addition, patients prescribed anxiolytics (n=10,429) and hypnotics (n=11,190) were identified as these medications were often co-prescribed in patients with depression [393].

Statistical analysis

Univariate analysis was performed on possible covariates to examine the association between each co-prescribed medication of interest and new onset diabetes. Only medications with a significant relationship with new onset diabetes were included for adjustment in the final statistical analysis. Conditional logistic regression stratified for age groups and gender was used to examine the association between new onset diabetes and prior prescription of different classes of antidepressants adjusting for covariates as described above. In addition, the risk of new onset diabetes in patients prescribed monotherapy of individual antidepressants was also examined.

A test for linear trend was used to examine the duration and dose response relationship of prescribed antidepressants and new onset diabetes by including duration and dose as a continuous term in the model. In addition, the dose and duration relationship was also examined as a categorical variable by selected duration (≤3 months, 4-6 months and >6 months) and cumulative dosage prescribed (<90 DDDs, 90-180 DDDs and >180 DDDs). Analysis was performed using the PROC PHREG command in SAS.

7.2.4 Results

The study comprised of 9,474 cases and 37,896 controls. The baseline characteristics of patients included in the study and the co-prescription of other medications of interest in both cases and controls are presented in Table 7.2.1. Covariates selected for the final analysis were thiazides, beta blockers, corticosteroids, antipsychotics, anxiolytics and hypnotics. The percentage of antidepressants prescribed in cases with new onset diabetes was 17% and 14% in controls. Of these, 9% of cases and 5% of controls received >6 months of antidepressant prescriptions over the study period.

An increased risk of new onset diabetes was found in those prescribed any antidepressant, adjusted OR=1.23 (95% CI 1.15, 1.32) compared to those prescribed none. A significant risk of new onset diabetes was observed with monotherapy of SSRIs, TCAs and SNRIs with the highest risk observed with SNRI (adjusted OR=1.62 [95% CI 1.38, 1.91], Table 7.2.2). New onset diabetes was significantly associated with increased duration of antidepressant treatment,

adjusted OR=2.10 (95% CI 1.92, 2.28), comparing more than 6 months versus no prescriptions (Figure 7.2.1a). A significant linear trend was observed between dose of antidepressants and new onset diabetes (p<0.0001) with adjusted OR= 2.12 (95% CI 1.96, 2.29) for >180 cumulative DDDs compared to those prescribed none over the study period (Figure 7.2.1b). There was a significant linear association between duration of treatment and new onset diabetes after adjustment of covariates between SNRI (p<0.0001), SSRI (p<0.0001), TCA (p=0.0007) and other antidepressants (p<0.0001).

With regards to monotherapy of individual antidepressant agents, most agents except dothiepin, mirtazapine, sertraline and trazodone showed a significant increased risk of new onset diabetes with no adjustments for covariates (Table 7.2.3). After adjustment, the highest risk of new onset diabetes was observed with venlafaxine, an SNRI agent (OR=1.45, 95% CI 1.21, 1.74) followed by fluoxetine (OR=1.40, 95% CI 1.13, 1.72) and escitalopram (OR=1.29, 95% CI 1.12, 1.48). Other individual monotherapy antidepressants associated with significant risk of new onset diabetes were amitriptyline and paroxetine, after adjustment for covariates. A significant duration relationship with new onset diabetes was observed with venlafaxine (p<0.0001), mirtazapine (p<0.0001), escitalopram (p=0.0008), paroxetine (p=0.001), dothiepin (p=0.003), fluoxetine (p=0.003), citalopram (p=0.007), amitriptyline (p=0.02) and sertraline (p=0.03). There was also a significant dose (DDD) response relationship between venlafaxine (p<0.0001), escitalopram (p<0.0001), mirtazapine (p<0.0001), citalopram (p=0.001), dothiepin (p=0.001), paroxetine (p=0.002), amitriptyline (p=0.007) and sertraline (p=0.01) and new onset diabetes.

Table 7.2.1: Baseline characteristics of both cases and controls included in the antidepressants study with univariate analysis of risk of diabetes presented as OR with 95% CI

Patient characteristics		Cases (n=9,474) (n, %)	Controls (n=37,896) (n, %)	Total (n=47,370) (n, %)	OR (95% CI), p
Gender	**Females**	4,277 (44.0%)	17,108 (44.0%)	21,385 (44.0%)	-
Age groups	**25-44**	1,305 (13.4%)	5,220 (13.4%)	6,525 (13.4%)	-
	45-64	3,751 (38.6%)	15,004 (38.6%)	18,755 (38.6%)	-
	≥65	4,655 (47.9%)	18,620 (47.9%)	23,275(47.9%)	-
Diabetogenic agents	**Thiazide**	1,463 (15.1%)	4,073 (10.5%)	5,536 (11.4%)	1.54 (1.44, 1.64) ***
	Beta blockers	3,723 (38.3%)	8,175 (21.1%)	11,898 (24.5%)	2.44 (2.32, 2.56) ***
	Corticosteroids	2,648 (27.3%)	8,538 (22.0%)	11,186 (23.0%)	1.34 (1.27, 1.41) ***
	Anti-psychotics	1,688 (17.4%)	5,407 (13.9%)	7,095 (14.6%)	1.31 (1.23, 1.39) ***
Co-prescriptions of other medications	**Hypnotics**	2,504 (25.8%)	8,686 (22.4%)	11,190 (23.1%)	1.21 (1.15, 1.27) ***
	Anxiolytics	2,312 (23.8%)	8,117 (20.9%)	10,429 (21.5%)	1.19 (1.12, 1.25) ***

Table 7.2.2: Frequency and percentages of antidepressants prescribing according to different classes of antidepressants in both cases and controls

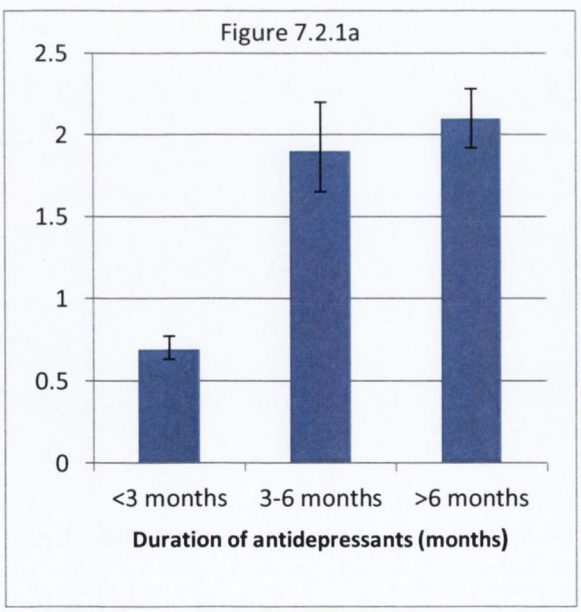
Antidepressants×	Cases (n=9,474) (n, %)	Controls (n=37,896) (n, %)	Unadjusted OR (95% CI), *p*	Adjusted† OR (95% CI), *p*
All antidepressant ◊	1,616 (17.1%)	5,167 (13.6%)	1.34 (1.26, 1.42) ***	1.23 (1.15, 1.32), ***
TCAs ◊	319 (3.4%)	1,053 (2.8%)	1.29 (1.14, 1.47) ***	1.14 (1.00, 1.30) *
SSRIs ◊	947 (10.0%)	3,105 (8.2%)	1.31 (1.21, 1.41) ***	1.20 (1.10, 1.30) ***
SNRIs ◊	227 (2.4%)	563 (1.5%)	1.73 (1.48, 2.02) ***	1.62 (1.38, 1.91) ***
Other antidepressant ◊	123 (1.3%)	446 (1.2%)	1.17 (0.96, 1.43) ns	1.11 (0.90, 1.37) ns

†OR with 95% CI adjusted for co-prescriptions of thiazide diuretics, beta blockers, oral corticosteroids and antipsychotics, anxiolytics and hypnotics

×Patients prescribed one class of antidepressants only during the study period

◊ significant linear trend test for duration of antidepressants, $p<0.05$ and risk of new onset diabetes

Figure 7.2.1: OR (95% CI) showing the relationship between new onset diabetes and a) duration of antidepressants and b) dose of antidepressants (cumulative DDDs) when examined as categorical variables (reference: no antidepressants prescribed)



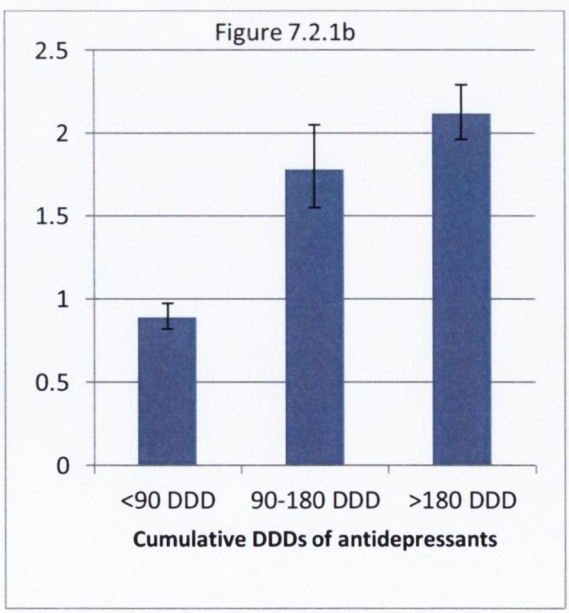


Table 7.2.3: Risk of new onset diabetes with monotherapy of individual antidepressants and linear trend test presented as unadjusted and adjusted OR with 95% CI

Individual antidepressant agents	Unadjusted	Adjusted†
	OR (95% CI), *p*	OR (95% CI), *p*
Amitriptyline ◊ □	1.37 (1.16, 1.61), **	1.20 (1.01, 1.41), *
Citalopram ◊ □	1.20 (1.03, 1.39), *	1.08 (0.93, 1.26), ns
Dothiepin ◊ □	1.29 (0.99, 1.69), ns	1.19 (0.90, 1.56), ns
Escitalopram ◊ □	1.39 (1.22, 1.59), ***	1.29 (1.12, 1.48), **
Fluoxetine ◊ □	1.47 (1.20, 1.81), **	1.40 (1.13, 1.72), **
Mirtazapine ◊ □	1.24 (0.96, 1.58), ns	1.10 (0.85, 1.42), ns
Paroxetine ◊ □	1.37 (1.09, 1.73), **	1.29 (1.02, 1.64), *
Sertraline ◊ □	1.24 (0.99, 1.55), ns	1.10 (0.88, 1.38), ns
Trazodone	1.09 (0.75, 1.59), ns	0.93 (0.59, 1.46), ns
Venlafaxine ◊ □	1.53 (1.28, 1.83), ***	1.45 (1.21, 1.74), ***

†OR with 95% CI adjusted for co-prescriptions of thiazide diuretics, beta blockers, oral corticosteroids, antipsychotics, anxiolytics and hypnotics

◊ significant linear trend test for duration adjusted for covariates, $p<0.05$ and risk of new onset diabetes

□ significant linear trend test for dose (as DDDs) as continuous variable adjusted for covariates, $p<0.05$ and risk of new onset diabetes

7.2.5 Discussion

This case-control study demonstrates that prescribed antidepressants were associated with an increased risk of new onset diabetes in this population. All classes of antidepressants (TCA, SSRI, SNRI and others) were associated with an increased risk of new onset diabetes with the highest risk observed with SNRI. A duration response relationship was also observed with the different classes of antidepressants. There was also a significant dose response relationship between amitriptyline, citalopram, fluoxetine, mirtazapine, paroxetine and venlafaxine and new onset diabetes.

The findings of this study are consistent with the recent findings on the use of antidepressants and diabetes risk in the UK primary care population using the UK GPRD [54]. Compared to this study, the nested case-control in the UK GPRD study population included those prescribed antidepressants only; untreated diabetes patients were also included as cases. The UK GPRD study demonstrated that recent long term use of antidepressants in moderate or high daily doses was associated with increased risk of diabetes (incidence rate ratio=1.84[95% CI 1.35,2.52]) and that the risk of diabetes was increased in those with recent use of amitriptyline, paroxetine and venlafaxine. However, unlike our study, fluoxetine and citalopram were found to be

protective against new onset diabetes [54]. A study on the use of antidepressants and new onset diabetes were also performed in the Netherlands using the PHARMO database [391]. The PHARMO study included prevalent use of antidepressants and in contrast to this study, the PHARMO study did not find any significant increased risk of new onset diabetes with antidepressants [391]. Another nested case control study performed using the Saskatchewan database found a higher risk of new onset diabetes in those prescribed TCAs and SSRIs concurrently with reduced risk observed with SSRIs only compared to TCAs only [392].

Many other studies have shown that SSRIs especially fluoxetine have favourable effects on glucose homeostasis in patients with or without diabetes [394, 395]. The conflicting results may possibly be by selective prescribing in this study whereby those at increased risk of diabetes were being prescribed SSRIs or SNRIs due to their protective effects. It can also be argued that the underlying depression may have influenced the outcome of this study rather than due to the antidepressants prescribed. Those with more severe or prolonged depression may be selectively prescribed the newer agents, such as SSRIs or SNRIs, with fewer side effects compared to TCAs. The study period chosen for this study was relatively recent; therefore only a small percentage of patients were prescribed monotherapy of TCAs or MAOIs.

Our study found a significant dose and duration relationship between the different classes of antidepressants and the risk of new onset diabetes as has been observed in the UK GPRD study [54]. However, it is also possible that patients on longer duration and higher doses of antidepressants are more depressed and thus at an increased risk of new onset diabetes due to the underlying depression itself. Few studies have examined the risk of new onset diabetes with depressive symptoms and antidepressants together. In a study performed amongst participants of Diabetes Prevention Program (DPP), a strong relationship was found between baseline antidepressant use and continuous antidepressant use with increased new onset diabetes in the placebo group and those in the lifestyle intervention group but not in those prescribed metformin as a preventative measure. This study, however, did not find an increased risk of diabetes with elevated depression score as a marker of severity of depression [396]. Another prospective study performed in an elderly population in Melbourne found that those with symptomatic depression were more likely to show increased risk of diabetes compared to those without symptoms, with or without antidepressants use [390].

A few hypotheses have emerged to explain the risk of new onset diabetes in those with depression. Those with depression may have disturbances in the regulation of the hypothalamic-pituitary-adrenal axis with resultant disturbances in cortisol, epinephrine, growth hormone and glucagon levels leading to impaired glucose control [397]. Depression may induce alterations of glucose transport in the body and increased inflammatory markers associated with diabetes such

as tumour necrosis factor-α, C-reactive protein and interleukin 1-β [397]. Depression is also associated with reduced insulin sensitivity, a precursor to full-blown diabetes [398]. In addition, depression may increase the risk of diabetes indirectly as the presence of depression is associated with reduced self-care activities and potentially damaging behaviour such as smoking, physical inactivity and increased caloric intake [399]. However, the findings of this study and other similar studies suggest that treatment with antidepressants may influence glucose homeostasis through direct pharmacological action. Antidepressants prescribed for depression are known to exert some adverse effects on metabolism. Many antidepressants are associated with weight gain [400], obesity [401], and dyslipidaemia [402]. These problems could lead to increased risk of metabolic syndrome, diabetes and cardiovascular disease in susceptible high risk individuals.

Limitations

Due to the lack of clinical diagnosis, depression in this population may be underestimated. Many patients with depression may not present to their general practitioner and thus remain undiagnosed without being prescribed antidepressants. Antidepressants may also be prescribed for problems other than depression such as anxiety, headache and phobia [403]. This study was also unable to adjust for the severity of depression; however, we were able to examine the dose and duration relationship of antidepressant prescribing with new onset diabetes and found significant linear trend relationships. Comorbidities associated with antidepressants such as weight gain, increased waist circumferences, dyslipidaemia and smoking status were not adjusted for. In addition, only a few individual agents were able to be examined due to restrictions of small number of patients on monotherapy of individual antidepressants during the study period. The risk of new onset diabetes with intermittent compared to continuous use of antidepressants and in those prescribed antidepressants recently compared to past users was not examined.

This study may have underestimated the true risk of new onset diabetes in those prescribed antidepressants since we were only able to capture treated diabetes. This study captured a more socially deprived population in those less than 70 years of age. Those with lower socioeconomic status as measured by educational status reporting high numbers of depressive symptoms were at increased risk of developing diabetes independent of other risk factors for developing diabetes [399]. This is a possible bias in our study.

Higher dosage and longer duration of prescribed antidepressants may increase the risk of diabetes compared to lower doses for a shorter duration. Randomized controlled trials need to be performed to assess the risk of new onset diabetes in those on antidepressants more objectively.

7.3 Risk of new onset diabetes with statins in the Irish population

7.3.1 Background

HMG-CoA reductase inhibitors or statins are a class of lipid lowering agents targeted at reducing LDL cholesterol by inhibition of cholesterol synthesis in the liver. Statins have also demonstrated other properties beyond lipid lowering such as stabilization of atherosclerotic plaques, anti-inflammatory, anti-oxidant effects and improvement of vascular endothelial damage [404]. Studies have shown that statins reduce major coronary events, coronary revascularization and stroke by about one fifth for every mmol/L reduction of LDL cholesterol [405]. Guidelines have advocated the use of statins as part of primary and secondary prevention of cardiovascular disease in patients at high risk of cardiovascular disease including those with diabetes [297]. Meta-analyses of statins have demonstrated the efficacy and safety of statins for use in large population [405]. However, statins are also associated with some adverse effects such as myopathy, elevated liver enzymes, peripheral neuropathy and rarely rhabdomyolysis [406].

In Europe, the greatest increase in statins prescribing was observed in Ireland [276]. The prevalence of their use in secondary prevention is approximately 75% in women and 77% in men aged 55-74 years, and for primary prevention 11% in men and 16% in women in the same age group [277]. In 2008, atorvastatin was the second most frequently prescribed therapy in the Irish GMS population and accounted for the largest expenditure on medications by the Irish health services The cost borne by the Irish government for all statins (ingredient cost only) in 2007 was € 141 million [6].

Recent interests has emerged on the risk of new onset diabetes in patients prescribed statins. The WOSCOPS study was the first that examined the relationship between statins and diabetes in 2001 and showed that pravastatin was associated with reduced risk of new onset diabetes OR=0.70 (95% CI 0.55, 0.99)[407] compared to placebo. A recent meta-analysis of 13 RCTs demonstrated that statins were associated with slightly increased risk of new onset diabetes OR=1.09 (95% CI 1.02, 1.17) [408]. The meta-analysis included two trials showing a positive association with new onset diabetes; the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) showed patients assigned rosuvastatin were significantly associated with increased risk of new onset diabetes compared to placebo RR=1.25 (95% CI 1.05, 1.49) [409] and the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) showed that pravastatin was associated with increased risk of new onset diabetes OR=1.32 (95% CI 1.03, 1.69) compared to placebo [410].

Only one observational population based study has been performed to examine the risk of diabetes with statins, however, the observational study did not find any significant relationship

between statins and new onset diabetes [55]. The observational study also did not examine newer agents such as rosuvastatin. With such high prescribing of statins in the Irish population and the increasing prevalence of diabetes, the risk of new onset diabetes associated with prescribed statins in this population requires consideration. This study was performed to examine the risk associated with prescribed statins in the Irish primary care population, in a retrospective cohort study. The differing effects of new onset diabetes with different types of statins and the duration and dose response relationship between prescribed statins and new onset diabetes were examined.

7.3.2 Specific objectives

1) To examine the risks of new onset diabetes in patients prescribed monotherapy of the different types of statin compared to those prescribed none in a retrospective cohort study
2) To examine the relationship between duration and dose of prescribed statins and new onset diabetes

7.3.3 Methods

A retrospective cohort study was performed using the HSE-PCRS national primary care pharmacy claims database for the GMS scheme.

Study cohort

A total number of 2,633,077 individuals aged 25 years old and above prescribed any medicines were identified from the database from January 2001 to January 2009. Those prescribed oral anti-diabetic agents prior to January 2001 (n=30,727) or insulin only (n=19,318) were excluded. The year 2001 was used as run-in period to exclude individuals prescribed any lipid lowering agents prior to the study period (n=67,426). Those newly initiating statins after 1st January 2008 (n=55,373) were excluded as were those initiating statins after or in the same month as oral anti-diabetic agents (n=23,163). Those with less than 6 months of history in the database were also excluded (n=1,203,904) to ensure patients with prevalent diabetes who joined the GMS scheme during the study period were not included as patients with new onset diabetes.

Patients with new onset diabetes were identified as individuals newly initiating oral anti-diabetic agents for period of 3 months or more from March 2002 to January 2009 (n=25,820).

Statins exposure

Patients prescribed monotherapy of the different types of statin with DDDs from 1st January 2002 to 31st December 2007 were identified from the cohort (n=197,138). The types of statin included in the analysis were atorvastatin (n=120,307), pravastatin (n=42,159), rosuvastatin

(n=20,006), simvastatin (n=11,539) and fluvastatin (n=3,127). Duration of exposure to statins was examined according to the number of months in which the patients were prescribed statins. Patients were considered to be exposed to one month of statins if they received a prescription for the respective month. The defined daily doses (DDD), was included to determine total dosage of statins prescribed over the study period. A DDD is equivalent to 15 mg simvastatin, 20 mg pravastatin, 40 mg fluvastatin, 10 mg atorvastatin and 10 mg rosuvastatin. All patients newly prescribed statins were followed up until their first prescription of any anti-diabetic agents or until 1st January 2009 in those without anti-diabetic prescriptions. Controls were selected from patients not prescribed any statins during the study period and were followed up until their first prescription of any anti-diabetic agents or until 1st January 2009 in those without anti-diabetic prescriptions

Covariates

Oral corticosteroids and antipsychotics prescriptions were considered as potential confounders as previous studies have shown some association of these agents with diabetes. Patients prescribed nitrate or nicorandil were considered to have IHD, those prescribed antihypertensive agents as having hypertension and those prescribed anti-obesity agents as having obesity. In addition, patients prescribed other lipid lowering agents were also identified; ezetimibe, fibrates, nicotinic acid and omega-3 triglycerides.

Statistical analysis

Univariate analyses were performed on possible covariates to examine the association between each co-prescribed medications of interest and diabetes. Only medications having significant relationship with diabetes were included for adjustment in the final statistical analysis. Cox proportional hazard regression was used to calculate the hazard ratio (HR) of developing new onset diabetes in the cohorts prescribed statins adjusting for age groups, gender and covariates compared to the general population cohort prescribed no statins. A test for linear trend was used to examine the duration and dose response relationship of prescribed statins and new onset diabetes by including duration and dose as a continuous term in the model. In addition, the dose and duration relationship was also examined as categorical variable by selected duration (<=6 months, 6-12 months, 12-24 months and >24 months) and dosage prescribed (<=180 DDDs, 181-360 DDDs, 361-720 DDDs and >720 DDDs). Analysis was performed using the PROC TPHREG command in SAS version 9.1.

7.3.4 Results

A total of 1,233,166 individuals were included in this retrospective cohort study and 25,820 (2.1%) individuals with new onset diabetes were identified during the study period. The baseline characteristics and risk of new onset diabetes with covariates are presented in Table 7.3.1. Covariates selected for the final analysis were antipsychotics, medications for cardiovascular comorbidities such as hypertension, IHD and obesity and lipid modifying agents such as ezetimibe, fibrates and omega-3 triglycerides. 17% of patients in the cohorts were prescribed statins during the study period with 6% receiving more than 24 months of statins.

4.7% developed diabetes compared to 2.1% in the general population cohort. An increased risk of new onset diabetes was found in those prescribed any statins (HR (adjusted) =1.18 (95% CI 1.15, 1.22)) compared to those prescribed none. A significant risk of new onset diabetes was observed with monotherapy of atorvastatin, rosuvastatin and simvastatin (Table 7.3.2). The highest risk of diabetes was observed with monotherapy of rosuvastatin (HR (adjusted) = 1.41 (95% CI 1.31, 1.52)). There was a significant linear association between duration of treatment and new onset diabetes with all types of statins ($p<0.0001$).

When examined as a categorical variable, the highest risk of new onset diabetes was observed in those prescribed more than 24 months of statin therapy with HR=1.72 (95% CI 1.64, 1.80). The hazard ratio for new onset diabetes in those receiving more than 24 months duration of statin therapy was 1.93 (95% CI 1.63, 2.28) for rosuvastatin, 1.77 (95% CI 1.67, 1.87) for atorvastatin, 1.62 (95% CI 1.20, 2.19) for fluvastatin, 1.47 (95% CI 1.23, 1.75) for simvastatin and 1.43 (95% CI 1.31, 1.56) for pravastatin (Figure 7.3.1). A significant linear association between cumulative dose (DDDs) and new onset diabetes was also observed (Figure 7.3.2). The hazard rates for new onset diabetes for more than 720 DDDs of statins were 3.21 (95% CI 2.07, 4.97) for rosuvastatin, 1.61 (95% CI 1.22, 2.13) for fluvastatin, 1.60 (95% CI 1.53, 1.67) for atorvastatin, 1.39 (95% CI 1.20, 1.61) for simvastatin and 1.33 (95% CI 1.22, 1.44) for pravastatin.

Table 7.3.1: Baseline characteristics of patients included in the statins cohort study with univariate analysis of risk of new onset diabetes presented as HR with 95% CI

Patient characteristics (n=197,138)		Total	Number with diabetes (%)	HR (95% CI), *p*
Gender⁺	Females	747,708	12,342 (1.6%)	1.01 (0.98, 1.03), ns
	25-<45	497,669	2,765 (0.6%)	-
Age groups□	45-<65	336,728	9,133 (2.7%)	1.05 (1.00, 1.09), **
	≥65	398,769	13,922 (3.5%)	1.28 (1.23, 1.34) ***
Diabetogenic	Antipsychotics	367,720	7,075 (1.9%)	1.23 (1.19, 1.27) ***
agents◊	Corticosteroids	267,863	4,696 (1.7%)	0.77 (0.75, 0.80) ***
Cardiovascular	Hypertension	531,518	15,988 (3.0%)	1.20 (1.17, 1.24) ***
comorbidities	IHD	57,197	2,132 (3.7%)	1.12 (1.08, 1.17) ***
∞	Obesity	35,722	1,095 (3.1%)	1.31 (1.23, 1.39) ***
Other lipid	Ezetimibe	8,557	254 (3.0%)	1.67 (1.47, 1.88) ***
lowering agents	Omega-3	7,187	146 (2.0%)	1.70 (1.44, 2.00) ***
Δ	Fibrates	2,149	153 (7.1%)	1.21 (1.03, 1.42) **
	Nicotinic acid	809	40 (4.9%)	1.37 (1.00, 1.86) ns

□ Reference category age 25-44 ⁺ Reference category males ◊ Reference category cohort not prescribed diabetogenic agents ∞ Reference category cohort without cardiovascular comorbidities Δ Reference category cohort not prescribed lipid lowering agents

Table 7.3.2: Frequency and risk of new onset diabetes with different types of statins presented as unadjusted and adjusted HR with 95% CI

Statins	Total	Number with diabetes (n, %)	Unadjusted HR, 95% CI, *p*	Adjusted HR, 95% CI, *p*
All statins ◊ □	197,138	9,253 (4.7%)	1.22 (1.19, 1.25) ***	1.18 (1.15, 1.22) ***
Atorvastatin ◊ □	120,307	5,608 (4.7%)	1.27 (1.24, 1.31) ***	1.23 (1.19, 1.27) ***
Pravastatin ◊ □	42,159	2,070 (4.9%)	1.00 (0.95, 1.04), ns	0.99 (0.94, 1.04), ns
Rosuvastatin ◊ □	20,006	812 (4.1%)	1.46 (1.36, 1.57), ***	1.41 (1.31, 1.52) ***
Simvastatin ◊ □	11,539	586 (5.1%)	1.17 (1.08, 1.27) **	1.15 (1.05, 1.25) **
Fluvastatin ◊ □	3,127	177 (5.7%)	1.10 (0.96, 1.29) ns	1.03 (0.89, 1.20) ns

*HR with 95% CI adjusted for gender, age groups, prescriptions of oral corticosteroids, antipsychotics, antihypertensives, medications for IHD, anti-obesity, and other lipid modifying agents

◊ significant linear trend test for duration adjusted for covariates, $p<0.05$ and risk of new onset diabetes

□ significant linear trend test for dose (as DDDs) adjusted for covariates, $p<0.05$ and risk of new onset diabetes

Figure 7.3.1: HR and 95% CI showing the relationship between new onset diabetes and duration of different types of statins when examined as categorical variables

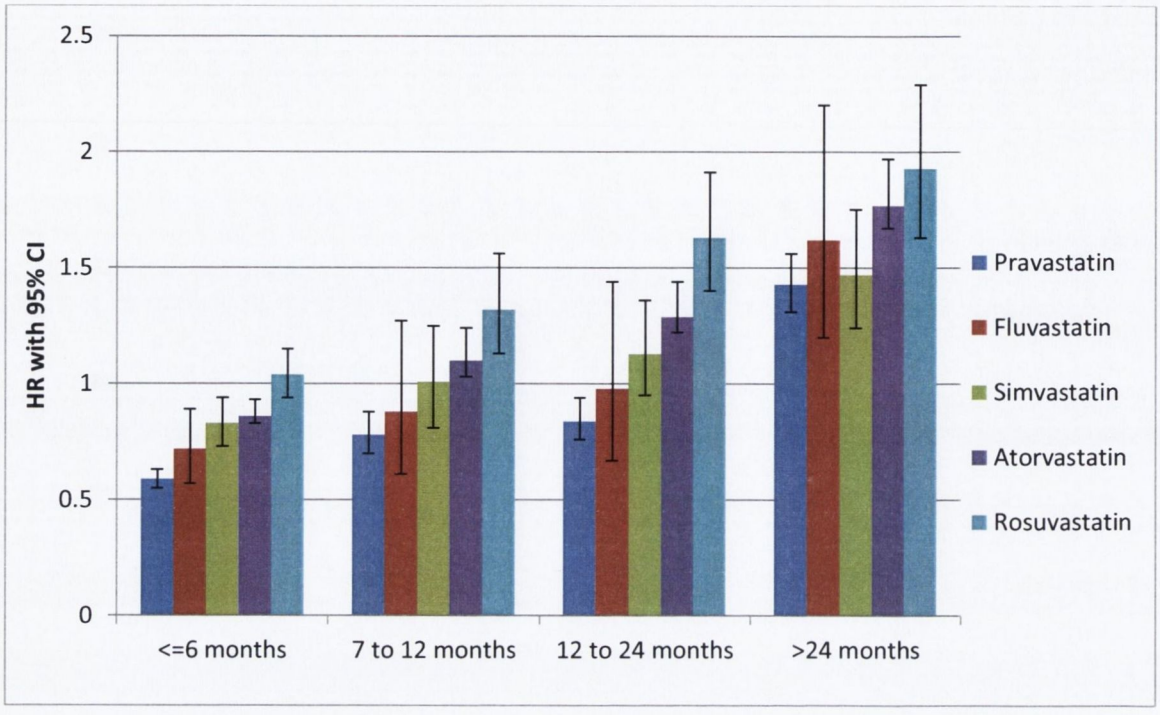
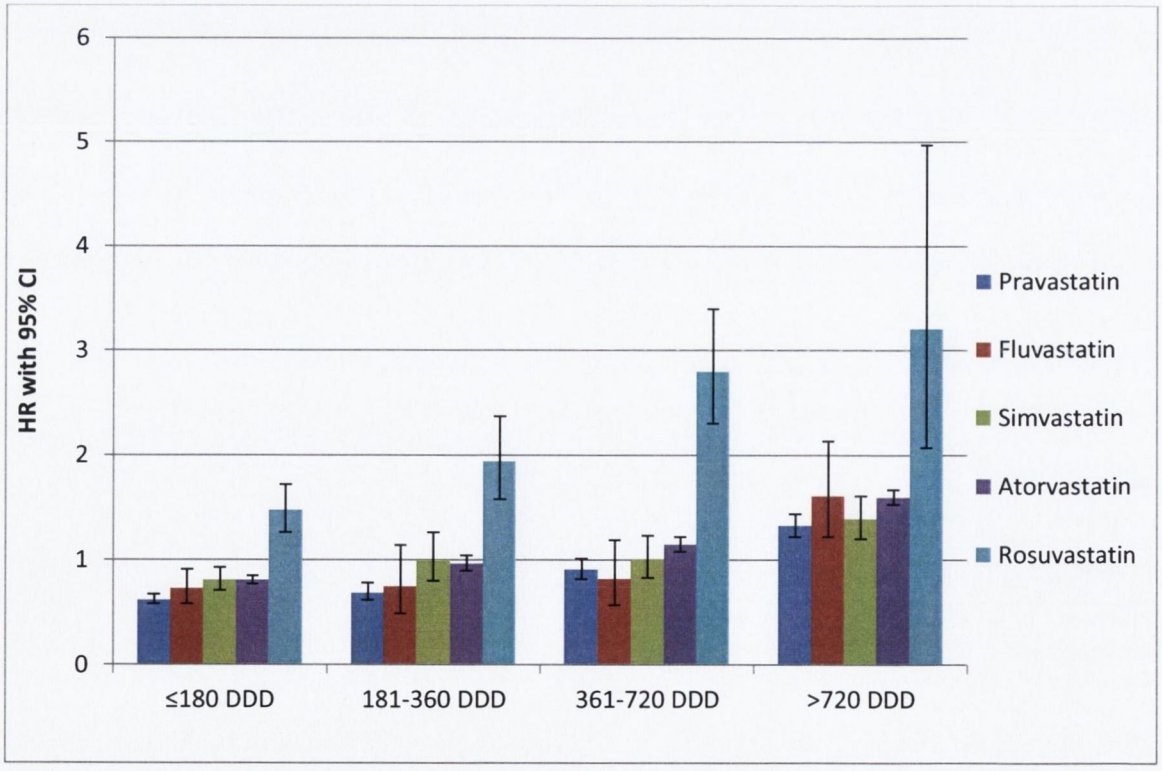


Figure 7.3.2: HR and 95% CI showing the relationship between new onset diabetes and cumulative dose (as DDD) of different types of statins when examined as categorical variables



7.3.5 Discussion

An increased risk of new onset diabetes was found in those prescribed any statins compared to those prescribed none. A significant risk of new onset diabetes was observed with monotherapy of atorvastatin, rosuvastatin and simvastatin while no significant risk was observed with pravastatin and fluvastatin. There was a significant linear association between duration of treatment and new onset diabetes with all types of statins. A significant linear association between cumulative dose of statins prescribed and new onset diabetes was also observed. The highest risk of new onset diabetes was observed with rosuvastatin in those prescribed >7.2 g (equivalent to >240 DDDs) of rosuvastatin over the study period with more than 3 times the risk of diabetes compared to the general population. Pravastatin and fluvastatin were associated with slight increased risk of new onset diabetes with longer duration and higher doses prescribed.

The findings of this study are consistent with findings from the JUPITER study in which increased risk of diabetes was found to be associated with rosuvastatin [409]. However, compared to the WOSCOPS [407] and the PROSPER study [410], this study did not observe a significant effect of pravastatin on new onset diabetes although an increased risk of new onset diabetes was observed with increasing dose and duration prescribed. The meta-analysis of 13 RCTs described above observed a similar risk of new onset diabetes between the different types of statins [408]. Another meta-analysis of 6 RCTs found a significant increased risk of new onset diabetes with any statins (OR=1.13). When the meta-analysis included the WOSCOPS trial, the risk of new onset was not significant (OR=1.06). However, the meta-analysis did not examine the differential risk of new onset diabetes with different types of statins [411]. A meta-analysis of 16 RCTs that examined the effects of statins on insulin sensitivity found a differential effect of statins types. Pravastatin was associated with significant improved insulin sensitivity while simvastatin was associated with significantly worse insulin sensitivity. When studies on atorvastatin, rosuvastatin and simvastatin were combined, significantly worse insulin sensitivity was observed compared to placebo or control [412]. The differences observed between the different RCTs, however, may be due to differences in the characteristics of patients recruited in the study with regards to risk factors for diabetes such as age, gender, BMI and baseline glucose.

A nested case control study was performed using the UK GPRD in 2004 after the WOSCOPS study to examine the protective effects of statins in the general primary care population. Compared to this study, the UK GRPD study did not observe a significant relationship between current statins users and new onset diabetes. Only simvastatin and pravastatin were examined individually due to the insufficient number of patients on other types of statins and no significant relationship between these statins and diabetes was found. The GPRD study also did

not find any evidence of a relationship between new onset diabetes and cumulative prescription or duration of statins use. Unlike this study, only a small number of patients were prescribed long term statins at the time the GRPD case control study was carried out [55].

A few hypotheses have emerged to explain the mechanism by which statins may induce new onset diabetes. Statins are associated with interference of the normal glucose metabolism involving glucose transport system (GLUT4 and GLUT1) with resultant decreased insulin sensitivity and thus impaired glucose tolerance. Statin therapy has also been found to induce insulin resistance via inhibition of isoprenoid biosynthesis, a precursor of cholesterol formation. Differences between different types of statin may be explained by the water solubility of the different statins. Lipid soluble statin such as simvastatin and atorvastatin are taken up by pancreatic cells and adipocytes and thus may attenuate insulin action by interfering with isoprenoid biosynthesis compared to the highly water soluble statins such as pravastatin [413, 414]. This would not explain the differential effects between rosuvastatin and pravastatin observed in this study as rosuvastatin, like pravastatin is a water soluble statin. However, compared to other statins, rosuvastatin has been shown to be more potent and efficacious than atorvastatin, simvastatin and rosuvastatin while sharing the same adverse effects as other types of statins [415, 416].

It is possible that the relationship between prescribed statins and new onset diabetes is due to the effects of hyperlipidaemia. The increased risk observed with other lipid modifying agents such as ezetimibe, omega-3 and fibrates in this cohort may favour confounding by indication. However, the non-significant risk of new onset diabetes found with pravastatin and fluvastatin as well as dose and duration relationship with the different types of statin argues against the effect of hyperlipidaemia on new onset diabetes per se. Other studies have also shown that increased risk of new onset diabetes is independent of lipid levels in those prescribed statin [408].

As no clinical diagnosis is available in the database, some patients with lifestyle controlled diabetes may have been missed as having diabetes. These patients may be prescribed statin as part of primary or secondary cardiovascular preventative strategy. The increased risk of new onset diabetes observed in our study may be due to unmasking of the diabetes in patients at high risk of diabetes itself. Those prescribed glucose monitoring kits only were excluded from this study to control for this bias. However, the use of glucose monitoring kits would not capture all patients with lifestyle controlled diabetes. Some patients may also have undiagnosed diabetes or the metabolic syndrome and are thus at higher risk of developing diabetes compared to the general population. If these patients were being carefully monitored by their primary care

physician this may have resulted in the increased risk of new onset diabetes observed in our study.

The risk of new onset diabetes in those prescribed statins was small compared to the overall reduction in cardiovascular events by statins. In those without diabetes, prescribing of statins significantly reduces the risk of major coronary events with 5.4 events per 255 patients treated with statin for 4 years per mmol/L reduction of LDL cholesterol compared to controls [408]. Others have shown a significant 13% reduction in all-cause mortality in patients without diabetes prescribed statins compared to controls [405]. Even in patients with established diabetes, there was a significant reduction in all-cause mortality and cardiovascular related mortality in those prescribed statins with significant reduction in major vascular events per mmol/L reduction of cholesterol [274].

The findings from this population based study on the risk of new onset diabetes with statins are consistent with other meta-analyses of randomized controlled trials [408, 411]. Prescribers have to weigh up the small risk of developing diabetes against the greater cardiovascular protection conferred by statins in patients at risk of cardiovascular disease. Prescribers may need to consider to include glucose levels in addition to liver function and creatinine kinase monitoring in those prescribed statins [417].

7.4 Risk of new onset diabetes with antihypertensive agents in the Irish population

7.4.1 Background

Hypertension is a common chronic condition associated with an increased risk of cardiovascular disease [418]. The prevalence of hypertension in Ireland is estimated to be at 25.1% in 2007 [77]. However, only half of those with hypertension were treated with antihypertensive agents [419]. The most widely prescribed antihypertensive agents in Ireland for those without diabetes were diuretics (30.7%) and beta blockers (25.8%) [296]. There was also an increase in the prescribing of ACEIs and ARBs in the Irish population over the last few years [64]. Reduction of blood pressure with the use of antihypertensive agents reduced overall mortality and cardiovascular outcomes in hypertensive patients with 35-40% reduction of stroke, 20-25% reduction in MI and 50% reduction in heart failure [420].

The effect of antihypertensive agents especially thiazides on glucose disturbance has been described since early 1960s [421, 422]. New onset diabetes is usually included as a secondary or post hoc analysis in many RCTs on antihypertensive agents. Meta-analyses consistently showed that thiazide diuretics and beta blockers were associated with increased risk of new onset diabetes. Calcium channel blockers were metabolically neutral, while ACEIs or ARBs were associated with a reduced risk of new onset diabetes [423-427]. Observational studies on the differential effects of antihypertensive agents on new onset diabetes in the general population have also demonstrated similar results as RCTs [428-431].

The Captopril Prevention Project (CAPP) trial was one of the first study to demonstrate the reduced risk of new onset diabetes in those prescribed ACEIs (captopril) compared to diuretic or/and beta blocker (RR=0.86) [432]. The ALLHAT study also demonstrated that an ACEI (lisinopril) was associated with a reduced risk of new onset diabetes compared to the diuretic (chlorthalidone) [433]. ACEIs were also associated with a reduced risk of diabetes when compared to placebo as demonstrated in the Heart Outcomes Prevention Evaluation (HOPE) trial (ramipril) [434], Prevention of Events with an ACE inhibitor (PEACE) (trandolapril) [435] and Studies of Left Ventricular Dysfunction (SOLVD) (enalapril) trials [436]. The reduced risk of new onset diabetes with ARBs was first demonstrated when losartan was compared to the beta blocker, atenolol in the Losartan Intervention for Endpoint Reduction (LIFE) trial [437]. ARBs were also associated with a reduced risk of new onset diabetes compared to calcium channel blocker (amlodipine) in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial [438] and placebo in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) trial [439]. Calcium channel blockers were associated with a reduced risk of diabetes compared to

diuretics in the International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT) [440] and ALLHAT trials (amlodipine) [433]. The risk of new onset diabetes also differed between different types of beta blockers. An increased risk of new onset diabetes was observed with non-selective beta blockers, metoprolol compared to selective beta blocker, carvedilol in the Carvedilol Or Metoprolol European Trial (COMET) [441]. There were no large scale randomized clinical trials that examined the risk of new onset diabetes with alpha blockers, vasodilators and centrally acting antihypertensive agents.

Only the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) and Nateglinide and Valsartan in Impaired Glucose Tolerance Outcome Research (NAVIGATOR) RCTs investigated the risk of new onset diabetes as their primary end point with monotherapy antihypertensive agents and enrolled patients at high risk of diabetes. No significant differences in the development of new onset diabetes were observed between those prescribed ramipril, an ACEI agent compared to placebo in the DREAM trial [442]. The NAVIGATOR trial found a significant protective effect of valsartan, an ARB agent with lifestyle modification after 5 years on new onset diabetes compared to placebo (HR=0.86) [443].

With regards to dual combination antihypertensive agents, the Study of Trandolapril/Verapamil SR And Insulin Resistance (STAR) showed that the combination of ACEI and calcium channel blocker was associated with a reduced risk of new onset diabetes compared to the ARB and diuretic combination [444]. In the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA), the risk of new onset diabetes was lower in those prescribed ACEI and calcium channel blocker combination compared to those prescribed beta blocker and diuretic [445]. Diuretic and beta blocker combination was found to be associated with an increased risk of new onset diabetes compared to an ARB and calcium channel blocker in the Antihypertensive treatment and Lipid Profile In a North of Sweden Efficacy evaluation (ALPINE) study [446]. The International Verapamil SR-Trandolapril Study (INVEST) found that combination of thiazide and beta blocker (atenolol) increased the risk of new onset diabetes while the combination of ACEI and calcium channel blocker reduced the risk of new onset diabetes compared to atenolol alone.

There is a lack of cohort studies on the risk of new onset diabetes with prescribed antihypertensives in the general population [431]. With the increasing use of antihypertensives in the population and the changing trends towards the use of ACEIs or ARBs [64], this study was performed to examine the risk associated with prescribed antihypertensive agents in the Irish primary care population, in a retrospective cohort study. The study examined the differing effects of new onset diabetes with different classes of monotherapy antihypertensives or dual

combination therapy and the duration relationship between prescribed antihypertensive agents and new onset diabetes.

7.4.2 Specific objectives

1) To examine the risks of new onset diabetes in patients prescribed monotherapy of the different classes of antihypertensive agents compared to those prescribed no antihypertensives in a retrospective cohort study
2) To examine the relationship between duration of prescribed antihypertensives and new onset diabetes
3) To examine the risk of new onset diabetes with different dual combination of antihypertensive agents prescribed in the same prescription claim form only

7.4.3 Methods

A retrospective cohort study was performed using the HSE-PCRS national primary care prescribing database for the GMS scheme.

Study cohort

A total number of 2,633,077 individuals aged 25 years old and above prescribed any medicines were identified from the database from January 2001 to January 2009. Those prescribed oral anti-diabetic agents prior to January 2001 (n=30,727) or insulin only (n=19,318) were excluded. The year 2001 was used as run-in period to exclude individuals prescribed any antihypertensives prior to the study period (n=268,587). Those newly initiating antihypertensives after 1st January 2008 (n=70,258) were excluded and so were those initiating antihypertensives after or in the same month as oral anti-diabetic agents (n=18,815). Those with less than 6 months of history in the database were also excluded (n=898,474).

Patients with new onset diabetes were identified as individuals newly initiating oral anti-diabetic agents for period of 3 months or more from March 2002 to January 2009 (n=19,756).

Antihypertensive therapies exposure

Patients prescribed monotherapy of the different classes antihypertensive agents from 1st January 2002 to 31st December 2007 (n=116,039) were identified from the cohort. These were ACEIs, ARBs, beta blockers, calcium channel blockers, thiazide, potassium sparing (k-sparing) diuretics, other diuretics, alpha blockers, vasodilators and centrally acting antihypertensives. Patients who were switched from one class of antihypertensive to another were not included in the analysis. Patients prescribed dual combination antihypertensive therapies in the same prescription claim form (n=34,456) during the study period were also identified. Dual combinations of antihypertensive therapies with less than 100 patients were not included in the

final analysis. Dual combination included were ACEI-diuretic, ARB-diuretic, beta blocker-diuretic, ACEI-calcium channel blocker, ACEI-beta blocker, ARB-calcium channel blocker and beta blocker-calcium channel blocker. Due to the limitation in the ATC classification and the prescribing database, thiazides, K-sparing diuretics and other diuretics were grouped together as diuretic when examined as dual combination agents.

Duration of exposure to antihypertensives was categorized into ≤6 months, 7-12 months, 12-24 months and >24 months. All patients newly prescribed antihypertensives were followed up until their first prescription of any anti-diabetic agents or until 1st January 2009 in those without anti-diabetic prescriptions. Controls were selected from patients not prescribed any antihypertensives during the study period and were followed up until their first prescription of any anti-diabetic agents or until 1st January 2009 in those without anti-diabetic prescriptions.

Covariates

Oral corticosteroids and antipsychotic prescriptions were considered as potential confounders. In addition, patients prescribed nitrate or nicorandil as marker of IHD and those prescribed lipid lowering agents as marker of hyperlipidaemia were identified as important cardiovascular co-morbidities.

Statistical analysis

Univariate analysis was performed on possible covariates to examine the association between each co-prescribed medications of interest and diabetes. Only medications with significant relationship with diabetes were included for adjustment in the final statistical analysis. Cox proportional hazard regression was used to calculate the hazard ratio (HR) and 95% CI of developing new onset diabetes in the monotherapy cohort adjusting for age groups, gender and covariates as described above compared to those prescribed no antihypertensives. The cohort prescribed double combination antihypertensive therapies was compared to those prescribed the combination of ACEIs and diuretics. A test for linear trend was used to examine the duration response relationship of prescribed monotherapy of different classes of antihypertensives and new onset diabetes by including duration as a continuous term in the model. In addition, the duration relationship was also examined as categorical variable. Analysis was performed using PROC TPHREG command in SAS version 9.1.

7.4.4 Results

A total of 866,674 individuals were included in this retrospective cohort study. Amongst those, 2.3% (n=19,756) of patients with new onset diabetes were identified. The baseline characteristics and risk of new onset diabetes with chosen covariates are presented in Table 7.4.1.

Covariates selected for the final analysis were antipsychotics, corticosteroids and medications for cardiovascular comorbidities.

16.7% of patients in the cohort were prescribed monotherapy of antihypertensives during the study period with 3.5% received more than 24 months prescriptions of antihypertensives. Patients prescribed any antihypertensives were associated with a reduced risk of diabetes compared to the general population prescribed none with HR (adjusted) = 0.86 (95% CI 0.83, 0.89). Those prescribed monotherapy of beta blockers, ACEIs, thiazides and alpha blockers were all associated with a reduced risk of new onset diabetes compared to the general population (Table 7.4.2). No significant risk was observed in those prescribed other classes of antihypertensives compared to the general population. There was, however, a significant linear association between duration of treatment and new onset diabetes with major classes of antihypertensives; ACEIs, ARBs, beta blockers, calcium channel blockers and thiazides ($p<0.0001$). When examined as categorical variables, those prescribed more than 24 months of antihypertensives were associated with increased risk of new onset diabetes compared to those prescribed none with HR=1.44 (95% CI 1.34, 1.56). The HR of new onset diabetes with more than 24 months prescriptions of antihypertensives was 1.68 (95% CI 1.29, 2.19) for ARBs, 1.53 (95% CI 1.34, 1.75) for beta blockers, 1.50 (95% CI 1.18, 1.90) for calcium channel blockers, 1.41 (95% CI 1.12, 1.77) for thiazides and 1.40 (95% CI 1.22, 1.61) for ACEIs (Figure 7.4.1).

In the cohort of patients prescribed dual combination therapy, only the combination of beta blockers and diuretics in the same prescription claim form was significantly associated with an increased risk of new onset diabetes compared to combination of ACEIs and diuretics with HR= 1.20 (95% CI 1.02,1.42)(Table 7.4.3). No significant differences in risk of new onset diabetes were observed with other dual combinations of antihypertensives compared to the combination of ACEIs and diuretics.

Table 7.4.1: Baseline characteristics of patients included in the antihypertensive cohort study with univariate analysis of risk of new onset diabetes presented as HR with 95% CI

Patient characteristics (n=312,591)		Total	Number with diabetes (n, %)	OR (95% CI), *p*
Gender □	Females	509,272	8,852 (1.7%)	0.99 (0.96, 1.02), ns
Age groups+	25-<45	337,705	3,149 (0.9%)	1.00
	45-<65	249,738	7,523 (3.0%)	1.04 (1.00, 1.08), ns
	≥65	264,852	9,004 (3.4%)	1.14 (1.10, 1.19), ***
Diabetogenic agents◊	Antipsychotics	186,918	3,321 (1.8%)	1.21 (1.17, 1.26), ***
	Corticosteroids	258,019	4,974 (1.9%)	1.29 (1.25, 1.33), ***
Cardiovascular comorbidities∞	IHD	43,011	1,622 (3.8%)	1.15 (1.09, 1.21), ***
	Hyperlipidaemia	217,064	7,412 (3.4%)	1.35 (1.31, 1.39), ***

□ Reference category age 25-44 Reference category males Reference category cohort with no diabetogenic agents Reference category cohort with no cardiovascular comorbidities

Table 7.4.2: Risk of new onset diabetes with different classes of antihypertensives prescribed as monotherapy only compared to those prescribed none antihypertensives (HR with 95% CI)

Monotherapy of antihypertensives	Total	Total with diabetes	Unadjusted HR (95% CI), *p*	Adjusted† HR (95% CI), *p*
All antihypertensives	116,039	4,790 (4.1%)	0.91 (0.88,0.94) ***	0.86 (0.83, 0.89) ***
Beta blockers	41,141	1,272 (3.1%)	1.00 (0.94, 1.06), ns	0.92 (0.87, 0.99), *
ACEIs	23,147	1,594 (6.9%)	0.85 (0.80, 0.90), ***	0.80 (0.75, 0.84), ***
Thiazides	17,123	569 (3.3%)	0.91 (0.84, 0.99), *	0.98 (0.80, 0.96), **
Calcium channel blockers	15,163	632 (4.2%)	0.85 (0.78, 0.92), ***	0.83 (0.77, 0.91), ***
ARBs	8,702	428 (4.9%)	0.96 (0.87, 1.06), ns	0.92 (0.83, 1.01), ns
Vasodilators	5,091	59 (1.2%)	1.14 (0.88, 1.47), ns	1.15 (0.89, 1.49), ns
K-Sparing diuretics	2,140	74 (3.5%)	1.00 (0.80, 1.27), ns	0.96 (0.76, 1.20), ns
Alpha blockers	1,617	82 (5.1%)	0.70 (0.56, 0.87), **	0.72 (0.58, 0.90), **
Other diuretics	1,564	71 (4.5%)	0.75 (0.60, 0.95), *	0.81 (0.64, 1.03), ns
Centrally acting antihypertensives	351	9 (2.6%)	0.70 (0.36, 1.35), ns	0.68 (0.35, 1.30), ns

† Adjusted for gender, age groups, co-prescriptions of antipsychotics and corticosteroids and cardiovascular comorbidities

Figure 7.4.1: HR and 95% CI showing the relationship between new onset diabetes and duration of different classes of antihypertensives when examined as categorical variables

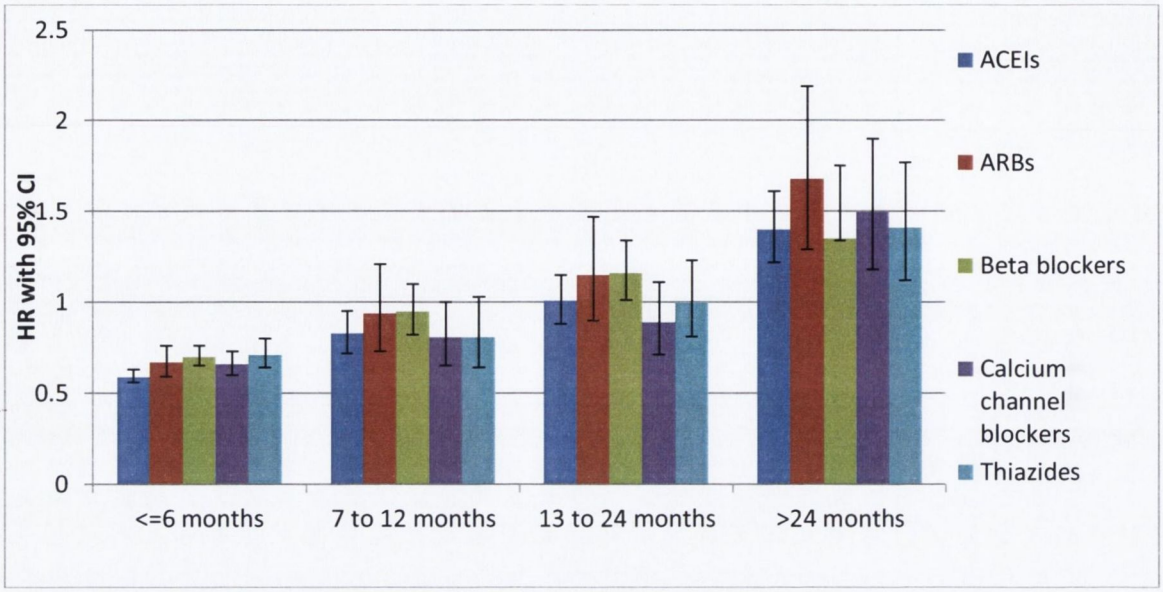


Table 7.4.3 : Risk of new onset diabetes with different dual combination of antihypertensives prescribed in the same prescription claim form only compared to dual combination of ACEIs and diuretic (HR with 95% CI)

Double combination antihypertensive agents	Total	Total with diabetes	Unadjusted HR (95% CI), *p*	Adjusted† HR (95% CI), *p*
ACEI – diuretic	7,400	331 (4.5%)	1.00	1.00
ARB- diuretic	10,286	356 (3.5%)	0.90 (0.77, 1.04), ns	0.86 (0.74, 1.00), ns
Beta-blocker-diuretic	4,900	262 (5.3%)	1.30 (1.11, 1.53), 0.001	1.20 (1.02, 1.42), 0.03
ACEI- calcium channel blocker	845	33 (3.9%)	0.89 (0.62, 1.27), ns	0.89 (0.62, 1.27), ns
ACEI- beta blocker	358	20 (5.6%)	1.61 (1.02, 2.53), 0.04	1.57(1.00, 2.48), ns
ARB-calcium channel blocker	381	11 (2.9%)	0.84 (0.46, 1.52), ns	0.79 (0.44, 1.45), ns
Beta blocker- calcium channel blocker	100	9 (9.0%)	1.52 (0.79, 2.96), ns	1.39 (0.72, 2.71), ns

† Adjusted for gender, age groups, co-prescriptions of antipsychotics and corticosteroids and cardiovascular comorbidities

7.4.5 Discussion

Patients prescribed any antihypertensive agents were associated with reduced risk of diabetes compared to the general population prescribed no antihypertensive agents. There was, however, a significant linear association between duration of treatment and increased risk of new onset diabetes with the major classes of antihypertensive agents; ACEIs, ARBs, beta blockers, calcium channel blockers and thiazides. Those prescribed >24 months of antihypertensive agents were associated with an increased risk of new onset diabetes compared to those prescribed none. In the cohort of patients prescribed dual combination therapy, only the combination of beta blockers and diuretics was significantly associated with an increased risk of new onset diabetes compared to the combination of ACEIs and diuretics.

Although direct comparisons cannot be made with the RCTs on monotherapy antihypertensive described above, no significant relationship was observed with ARBs and new onset diabetes while reduced risk of diabetes was observed with ACEIs in our study. An increased risk of new onset diabetes was observed in this study population after 2 years of treatment with both ACEIs and ARBs monotherapy. This study observed similar results as the RCTs on dual combination agents where higher risks of new onset diabetes were observed with diuretic and beta blocker combinations. However, this study did not find an increased risk of new onset diabetes with an ACEI and calcium channel blocker combination or ARBs and diuretic combination compared to ACEI and diuretic combination.

A retrospective cohort study on the risk of new onset diabetes with antihypertensives in a primary care population was performed previously using the UK GPRD. Only those prescribed antihypertensives were included in the UK GPRD study and thus direct comparison to this study cannot be made in those prescribed monotherapy antihypertensives [431]. Only calcium channel blockers were associated with a significantly increased risk of new onset diabetes compared to monotherapy of ACEI in the UK GPRD population HR=1.27 (95% CI 1.07, 1.51). Similar to this study, in those prescribed dual combination antihypertensive therapy the GPRD study found that thiazide and beta blockers combination were associated with increased risk of diabetes compared to ACEI and thiazide combination HR=1.37 (95% CI 1.10, 1.70). However, calcium channel blockers and thiazide combination were also associated with an increased risk of new onset diabetes compared to ACEI and thiazide combination HR=1.44 (95% CI 1.13, 1.83) in the UK GPRD study which was not found in our study. The period chosen for our study was relatively recent compared to the UK GPRD and thus was able to examine the risk of new onset diabetes with newer agents such as ARBs and alpha blockers [431].

Various theories have been put forward to explain the mechanisms in which antihypertensives may induce new onset diabetes. Thiazides may induce new onset diabetes by lowering serum potassium or magnesium level and thus lead to impaired insulin secretion. Thiazides are also associated with reduced peripheral insulin sensitivity independent of serum potassium levels. In addition, thiazides may also increase serum aldosterone which are usually associated with cardiometabolic syndrome [447]. Beta blockers association with new onset diabetes may be due to the combination of weight gain, reduced insulin secretion, impaired insulin sensitivity, changes in lipid metabolism, and peripheral vasoconstriction [448, 449]. ACEIs and ARBs are associated with improved insulin sensitivity and glucose metabolism. The improved insulin sensitivity may be due to kinin accumulation with these agents [450]. Other potential mechanisms for the protective effects of ACEIs and ARBs are (i) protective effect of pancreatic beta cell function (ii) improved insulin sensitivity by improving blood flow to skeletal muscle (iii) inhibition of deleterious effects of angiotensin II on insulin pathways (iv) improved glucose transport (GLUT-4) (v) facilitation of differentiation of adipocyte cells and (vi) activation of the PPAR-gamma [451].

The high risk of new onset diabetes in those prescribed long term monotherapy of ACEIs or ARBs may be due to confounding by indication or selective prescribing in these cohorts. Patients with lifestyle controlled diabetes may be prescribed ACEIs or ARBs as part of cardiovascular preventative therapy. As discussed in Section 7.3.5, patients prescribed glucose monitoring kits only were excluded from this cohort study. Patients may also be prescribed ACEIs or ARBs to prevent microvascular complications such as nephropathy in those at risk. This study is recent compared to most meta-analyses described above and thus there may be selective prescribing of ACEIs and ARBs by primary care physicians in hypertensive patients with higher risk of developing new onset diabetes. This database could not identify patients with impaired glucose tolerance, abdominal obesity or metabolic syndrome at higher risk of diabetes compared to general population.

This study did not include the daily defined dosage of prescribed antihypertensives and thus a dose response relationship between antihypertensives and new onset diabetes was not examined. However, this study did examine the relationship between duration of prescribed antihypertensives and new onset diabetes as continuous and categorical variables. The increased risk of new onset diabetes with longer duration prescribed favours a dose response relationship. There may be residual confounding when dual combination antihypertensives were examined as the decision to add a second antihypertensive agent and the choice of second agent may be multifactorial.

Implications

The VALUE trial found that patients who developed new onset diabetes during treatment with antihypertensives had significantly higher cardiac morbidity especially congestive cardiac failure compared to those without diabetes HR=1.43 (95% CI 1.16, 1.77). The cardiac morbidity was intermediate between those already with diabetes and those without diabetes at the end of study[452]. The ALLHAT trial on the other hand had not shown that the reduced risk of new onset diabetes by ACEIs translate into reduced cardiovascular disease during the study period [433]. The Systolic Hypertension in the Elderly Program trial (SHEP) found that although new onset diabetes was associated with increased cardiovascular and total mortality, no significant increased risk was found in those with new onset diabetes randomized to thiazide diuretics compared to those randomized to placebo.

An observational study on patients with hypertension mostly treated with thiazide diuretics or beta blockers with follow up time of 28 years demonstrated an increased risk of stroke, MI and mortality in those who developed new onset diabetes compared to those without [453]. Other observational studies also demonstrated non-significant increased cardiovascular morbidity associated with new onset diabetes in those treated with antihypertensive agents [454, 455]. This underlines the importance of recognizing the patients on antihypertensives at risk of developing new onset diabetes.

The differential effects of antihypertensives on risk of developing new onset diabetes may influence the prescribing of these agents in those at high risk of diabetes. The Joint British and National Institute for Clinical Excellence (NICE) guideline for uncomplicated hypertension advocated the use of ACEIs (or ARBs if ACEIs poorly tolerated) in younger patients and calcium channel blockers and diuretics for older patients as first line treatment compared to previous recommendations which included beta blockers. Although thiazides are also associated with new onset diabetes, use of a thiazide is still cost effective and preferred for uncomplicated hypertension in terms of cardiovascular disease prevention. NICE also advises against combining beta blockers with thiazide type diuretics to reduce the risk of diabetes [456].

In conclusion, consistent with other population based studies and randomized controlled trials, this study has also shown an increased risk of diabetes with increasing duration of antihypertensives prescribed. Thus, health care providers need to be cautious especially in starting the combination of thiazide and beta blockers in those at high risk of diabetes.

CHAPTER 8 : CONCLUSION

8.1 Conclusion of thesis

Diabetes prevalence has been increasing over time in both adults and the paediatric population. Epidemiology of diabetes, prescribing and utilization trends of pharmacological therapies in patients with diabetes at national level are important to inform and target diabetes services nationwide. This research has shown that the prevalence of treated diabetes in the Irish adult population is significantly increasing. In 2007, the prevalence of treated diabetes in adults was 2.7% for both type 1 and type 2 combined. A higher prevalence of treated diabetes was found in males and those over 65 years of age with variations in prevalence rates observed across the country. The Eastern region had the lowest prevalence of treated diabetes while the Midland region had the highest prevalence rate. The apparently higher prevalence of diabetes in the Midlands may be due to higher utilization of health services for diabetes in this region where integrated and structured diabetes shared care is in place since 1997. The incidence of type 2 diabetes is also on the increase especially in those aged between 45 to 65 years of age. This is consistent with the global trends contributed to by increasing prevalence of obesity and sedentary lifestyle. In contrast, no significant change in prevalence and incidence of type 1 diabetes and no significant difference between genders and health regions were observed within the study period in the paediatric and adolescent populations.

There has been a change in the prescribing trends for insulin in patients with type 1 diabetes, in both adults and the paediatric population; results showed a significant decline in the prescribing of human insulin and a significant increase in the prescribing of the newer and more expensive insulin analogues especially insulin glargine, insulin detemir and insulin aspart. Insulin analogues have advantages over human insulin in terms of the reduction in hypoglycaemic episodes although superiority in terms of glycaemic control has not been established [107]. This finding suggests that pharmaceutical marketing may play an important part in determining prescribing practice rather than evidence-based care in a country where there is a lack of restriction on drug cost and, in contrast to patients with type 2 diabetes, there is a lack of clinical guidelines for the care of patients with type 1 diabetes.

In accordance with guidelines on type 2 diabetes the prescribing for metformin has increased and has surpassed sulphonylureas as first choice agents for both prevalent and incident type 2 diabetes in the Irish population [5, 190]. The prescribing of rosiglitazone declined significantly in 2006 after controversies regarding the adverse effects of these agents shown in other population based studies [15, 16]. The uptake of other novel agents such as meglitinides and incretin mimetics were very low during this study period. In addition, there has been an increase in the prescribing of glucose monitoring kits, oral antidiabetic combinations and insulin in patients with type 2 diabetes. Inequalities in the prescribing of insulin and oral antidiabetic agents were observed especially in the elderly population and in those from lower socioeconomic backgrounds. Significant variations were also observed in the prescribing of antidiabetic therapies across the country.

The prevalence of IHD in patients with diabetes has been declining in this population. Although previous studies have shown an under-prescribing of cardiovascular preventative therapies [46, 47], there has been an increase in the prescribing of antihypertensive, antiplatelet and lipid lowering agents in patients with diabetes year on year. In those with newly treated type 2 diabetes, the time to initiation of these cardiovascular preventative therapies was less than 3 months. For lipid lowering agents, there has been an increase more recently in the prescribing of the more expensive atorvastatin and rosuvastatin compared to the generic simvastatin. ACEIs and ARBs are commonly prescribed in this population; these have been shown to exert benefit beyond blood pressure lowering in patients with diabetes. The improvement in cardiovascular prescribing is in line with guidelines on cardiovascular prevention and may be contributed to by the government cardiovascular health policies as well as primary care initiatives such as the Heartwatch program. Gender, age and regional differences in prescribing were observed particularly for statins and aspirin. The prescribing of cardiovascular preventative therapies in the Eastern and the Midland regions were consistently higher compared to other regions; this may be accounted for by the presence of many teaching hospitals affiliated to medical universities in the Eastern region and the presence of integrated diabetes services in the Midlands.

With the improvements in the prescribing of antidiabetic therapies and associated preventative cardiovascular therapies, adherence to these medications is important for these improvements to be translated into better glycaemic control and reduction in complications. More than one third of patients with type 2 diabetes were non-adherent to their prescribed antidiabetic and preventative cardiovascular therapies. Predictors of non-adherence in the study population with type 2 diabetes were: younger patients, those from lower socioeconomic background (as indicated by GMS scheme eligibility), those prescribed insulin and those with concurrent neurological problems. Although most patients reported high adherence to

medications, their prescription refill records showed otherwise. Those with low self-reported adherence were more likely to miss their clinic appointment. Those who believed that their medications were necessary were more likely to report adherence to medications. The use of self-reported adherence linked to pharmacy claims database provides a unique opportunity to capture the medication taking behaviour in this population. Although no consistent relationship was observed between adherence to medications and intermediate clinical outcomes in the cohort studies, this finding might be explained by the fact that each study was underpowered. A properly powered study would provide more relevant information and is recommended.

This study examined the risk of new onset diabetes with certain commonly prescribed pharmacological agents and found an increased risk of diabetes with corticosteroids, antidepressants, statins and beta blocker-diuretic antihypertensive combinations. Both oral and very potent topical corticosteroids were shown to be associated with increased risk of new onset diabetes in the selected case-control study population. Another case control study in this population demonstrated that all classes of prescribed antidepressants were associated with an increased risk of new onset diabetes with the highest risk observed with SNRIs. There was also a significant dose response relationship between certain individual antidepressants and new onset diabetes. Although statins are recommended as preventative cardiovascular therapy in patients with diabetes, a significant increased risk of new onset diabetes was observed with atorvastatin, rosuvastatin and simvastatin. A significant linear association between dose as well as duration of treatment with new onset diabetes was observed with all classes of statins. A reduced risk of new onset diabetes was shown in individuals prescribed antihypertensive agents compared to the general population. However, a significant linear association between duration of major classes of antihypertensive treatment (ACEIs, ARBs, beta blockers, calcium channel blockers and thiazides) and increased risk of new onset diabetes was observed. The combination of beta blockers and diuretics was significantly associated with increased risk of new onset diabetes compared to combination of ACEIs and diuretics. Guidelines on hypertension generally discourage the use of this combination in patients at risk of developing diabetes [457]. This study was performed using information derived from a pharmacy claims database and was thus limited by the lack of diagnostic information and other clinical information. Further population based studies using record linkage or randomized controlled trials would provide validation of these findings. However, this study has provided interesting preliminary findings on the risk of new onset diabetes with commonly prescribed medications.

8.2 Recommendations

The increasing prevalence of diabetes and its complications will have a significant impact on the Irish health care services. It is difficult to compare the estimates of diabetes prevalence across the different studies due to differences in methodology. This research only examined treated diabetes in those with pharmacy claims records. A diabetes register whereby all patients with known diabetes, either treated or managed with lifestyle interventions recorded in one database will allow a more accurate determination of diabetes cases. The DIAMOND database in St James's Hospital is a good example of a diabetes register in the hospital population with records maintained by administrative staff, clinicians, diabetes nurses and other healthcare professionals. Hospital based diabetes registers such as the DIAMOND database should be set up in other secondary and tertiary centres. This would facilitate audits on the care of patients with diabetes in hospital settings and would enhance research efforts on diabetes in the Irish population.

The availability of the HSE-PCRS database has provided valuable data on diabetes in the Irish population. Few national based population studies have been undertaken to examine issues related to prescribing in patients with diabetes. The use of the HSE-PCRS database in looking at prescribing trends provides an opportunity to provide feedback and comparative information on certain aspects of prescribing at the different levels of care. As Ireland currently is lacking in standardized computerized clinical records, the use of the pharmacy claims database may be a pragmatic means of examining disease prevalence in the population. This methodology offers the possibility of international comparison of disease prevalence, drug utilization and adherence to medications in the management of chronic conditions exemplified by diabetes. Compared to other studies based on administrative databases such as in the UK, Netherlands and the Nordic countries, studies using the Irish pharmacy claims database is limited by the lack of diagnostic information available, clinical records and prescribing information by clinicians. A more definitive study would require the use of oral glucose tolerance testing or fasting glucose to diagnose diabetes which was outside the scope of this study. The use of medications as proxy of diseases needs to be continuously revised as new drug treatments emerge. Pharmacy data are collected in other European countries, thus there is the possibility of developing a consensus on surrogate markers for diseases, which could facilitate international comparison of disease and treatments using standardised methodology and validation against data with clinical diagnosis.

With advancements in technology, it should be possible in the future for information obtained in the primary care and hospital settings to be centralized in a common database/registry. The UK GPRD is a prime example whereby details regarding each visit to the

primary care practitioner, any hospitalizations, social background and prescribing records issued are recorded. This validated database is now considered a gold standard for population based studies [458, 459]. The availability of this type of database in Ireland would facilitate more population based research and would enable comparisons to other populations. Specifically for diabetes, a more comprehensive database would facilitate research on diabetes complications such as nephropathy, retinopathy and diabetic neuropathy, which is currently lacking in this population.

To improve standards of care in patients with diabetes and to reduce inequalities in prescribing of antidiabetic therapies across the country, a systematic approach to diabetes health care delivery is needed. A structured and co-ordinated approach is required to ensure all patients receive evidence-based diabetes treatment, irrespective of their age, gender, socioeconomic status or geographical location. The influence of pharmaceutical marketing on primary care physicians in the prescribing of newer and expensive antidiabetic therapies should be equalized with education and training on evidence-based therapies for diabetes. Effective dissemination of information and support to access information resources should be made available to GPs. Guidelines on the management of type 1 diabetes should also be made available to GPs as there is a lack of guideline for these patients especially in terms of managing diabetic complications.

The Structured Diabetes care in the Midland region has shown significant improvements in the clinical outcomes and care of patients with diabetes at the Midland level [83] and thus this integrated care could be extended to other regions in Ireland and to other countries as well. It has been shown in this study that the prescribing for patients with diabetes in this region was consistently better compared to other regions in Ireland. For this program to be successful at national level, participation by general practitioners with an interest in diabetes, together with diabetes specialists at secondary and tertiary level, needs to be encouraged. A smaller integrated care project for patients with diabetes in Dublin, The North Dublin Diabetes Shared Care Project (DISC) project, has also shown significant improvement in diabetes care and delivery as well as psychosocial outcomes [460]. Although a Cochrane review indicated that there was no evidence to support the widespread introduction of shared care for chronic diseases management, the majority of studies included in the review were of relatively short duration in contrast to the Midlands shared care [461].

This study only examined the prescribing of antidiabetic therapies until 2007. Agents such as sitagliptin and exenatide were just coming on the market in Ireland during this study period. A combination of metformin and sitagliptin was only marketed in Ireland in 2008. Therefore, this study needs to be extended to incorporate the recent availability of these new antidiabetic medications. More recently, rosiglitazone monotherapy and rosiglitazone combinations were

withdrawn from the European market due to concerns regarding cardiovascular risks. The changes in prescribing of oral antidiabetic medications following this measure needs to be examined further.

Primary care-based health initiatives such as the Heartwatch program have been shown to improve delivery of care for patients in terms of cardiovascular prescribing, and should be extended to include more GPs at national level to benefit the whole population in Ireland. Although targeted at patients with established cardiovascular disease only, this pilot primary care program with its integrated database has also been shown to improve screening for patients with diabetes and uptake of cardiovascular therapies in this high risk population. Extension of this program to the whole population would ensure equity and access to services in patients with cardiovascular diseases. In addition, the Irish government should continue to improve their existing policies on prevention and management of cardiovascular disease in the population as a whole. These policies could serve as a working example to other countries with low prescribing of cardiovascular preventative therapies.

Record linkages between pharmacy database and hospital record provide a golden opportunity for drug utilization researches. The PHARMO database in the Netherlands is one example of how record linkages can facilitate research on drug prescribing and clinical outcomes. One part of this research project attempted to link the hospital based data from two major teaching hospitals to the HSE-PCRS database. However, it was only possible to link a small number of patients in these linkage studies. Future linkage studies with larger numbers of patients could provide more insight into the relationship between prescribing and clinical outcomes. In order for record linkages between the HSE-PCRS and hospital records to be utilized and be on par with other established linked databases, some administrative aspects need to be improved. Amongst improvements that could be undertaken include accurate recording of the GMS or LTI patient identifier in the hospital system, enhanced measures to protect confidentiality of patients, improvement of computerized hospital records, provision of facilities for extraction of hospital records and support for researchers involved with record linkage research.

The use of prescription refill records and self-reported adherence score could be used as a tool to identify patients at greater risk of nonadherence and interventions to improve adherence can be targeted to these patients. The self-reported adherence questionnaire was easy to administer in the clinical setting and may help to identify those at risk of non-adherence. Time spent at the clinic explaining the necessity of taking prescribed medications and to allay any concerns may help improve adherence to treatment.

The risk of new onset diabetes with commonly prescribed medications in the general Irish population needs to be quantified to allow appropriate assessment of benefits and risks of these

medications. Higher dosage and longer duration of prescribed antidepressants and corticosteroids increase the risk of diabetes compared to lower dose for shorter duration. Thus the chronic prescribing of these agents need to be reviewed especially amongst those at higher risk of diabetes. Randomized controlled trials need to be performed to assess the risk of new onset diabetes in those on antidepressants more objectively. Prescribers may need to weigh up the small additional risk of developing diabetes against the greater cardiovascular protection conferred by antihypertensives and statins in patients at risk of developing cardiovascular disease. Prescribers may also need to consider glucose test in those prescribed these medications.

Appendix 1: Variations in the prescribing of acarbose, meglitinides and incretin modulators for adult type 2 diabetes patients presented as adjusted OR with 95 % CI

Patient characteristics		Acarbose OR† (95% CI), p	Meglitinides OR† (95% CI), p	Incretin modulators OR† (95% CI), p
Gender□	Female (n=44,219)	0.93(0.88,0.98)***	1.01 (0.95,1.07) ns	0.94 (0.84, 1.05) ns
Age group◊	45-64 (n=22,845)	1.71(1.48,1.98)***	1.15 (1.03,1.28)*	0.93 (0.74, 1.17) ns
	>65 (n=47,519)	2.04(1.77,2.35) ***	1.19(1.06,1.33)**	0.62 (0.50, 0.78)***
Drug scheme[x]	LTI (n=23,859)	0.81(0.75,0.88) ***	4.72(4.42,5.03)***	2.57 (2.18, 3.04)***
CV co-morbidities Δ	HTN (n=70,619)	1.51 (1.37, 1.67)***	1.38 (1.20, 1.57)***	1.36 (1.15, 1.62) **
	IHD (n=14,181)	1.10 (1.01, 1.41) *	1.10 (0.98, 1.24) ns	0.97 (0.81, 1.15) ns
	Hyperlipidaemia (n=57,677)	1.23 (1.15, 1.32)***	1.10 (1.00, 1.21) *	1.76 (1.52, 2.02)***
Health region∞	Midland (n=7,386)	2.15(1.93,2.39)***	0.48(0.40,0.57)***	0.45 (0.33, 0.63)***
	Mid-Western (n=7,392)	1.35(1.20,1.51)***	0.80(0.70,0.91)**	1.78 (1.49, 2.14)***
	North Eastern (n=5,388)	2.68(2.43,2.96)***	0.52(0.44,0.60)***	0.73 (0.54, 0.98) *
	North Western (n=4,836)	1.87(1.65,2.12)***	0.82(0.70,0.91)*	0.87 (0.65, 1.15) ns
	South Eastern (n=9,645)	2.86(2.63,3.12)***	1.29(1.17,1.43)***	0.79 (0.63, 0.99) *
	Southern (n=11,149)	1.94(1.77,2.13)***	5.00(4.62,5.41)***	1.82 (1.55, 2.13)***
	Western (n=7,169)	1.49(1.33,1.66)***	1.16(1.03,1.30)*	1.11(0.89, 1.38) ns

† Adjusted for gender, age groups, drug schemes, calendar years and health regions □ Reference category males (n=56,902) ◊ Reference category age 16-44 years (n=7,441) [x] Reference category GMS scheme (n=77,805)
Δ Reference category no cardiovascular morbidities (n=31, 502 for hypertension, n=86,940 for IHD and n=43,444 for hyperlipidaemia) ∞Reference category Eastern region (n=48,699)

Appendix 2: Questionnaire for patients attending diabetes outpatients at Connolly Hospital, Blanchardstown

PLEASE COMPLETE THE QUESTIONNAIRE BY TICKING THE APPROPRIATE BOXES.

Demographics

1) Are you? Male□ Female□
2) What age are you? _____ Years old
3) Is your daily activity limited by a long term illness, health problems or disability? Yes □ No □
4) EUROPEAN Health Survey (EHIS) (Modified_)
   Have you had any of the following condition diagnosed by the doctor?

	Condition	Yes	No
B1	Asthma		
B2	Chronic bronchitis, chronic obstructive lung (pulmonary) disease, emphysema		
B3	Heart Attack		
B4	Angina		
B5	Stroke		
B6	Rheumatoid Arthritis (inflammation of the joints)		
B7	Osteoarthritis (Arthosis, joint degeneration)		
B8	Lower back pain or other chronic back pain condition		
B9	Cancer (malignant tumour including leukaemia and lymphoma)		
B10	Urinary incontinence, problems in controlling the bladder		
B11	Anxiety		
B12	Depression		
B13	Others, please specify		

5) In the last 12 months, have you been told by a doctor that you have a high blood pressure? Yes□ No□
6) In the last 12 months, have you been told by a doctor that you have high cholesterol? Yes□ No□
7) What medications do you have to take for your diabetes (high blood sugar)?
   None□ Tablets□ insulin injection□ tablets and insulin □
8) How many different medications other than for diabetes are on your prescription?_____
9) In total, how many tablets per day do you have to take?_____

10) Which of these are you currently?
Smoker□ Non-smoker□ Smoker □___ years

11) How often do you have a drink containing alcohol?
Never□ monthly□ less 2-4 times a month□
2-3 times a week□ 4 or more times a week□

12) Who do you live with at home?
Alone□ with family/friends□

13) What is your ethnic/cultural background?
White□ Black□ Asian□ Others/Mixed□

14) What is the highest level of education you have completed to date? Please tick one only

	Some primary	
C1	Primary or equivalent	
C2	Leaving certificate or equivalent	
C3	Diploma/certificate	
C4	Primary degree	
C5	Postgraduate degree/Higher degree	
C6	Refusal	

Here are some ways in which people have said that they use their medicines. For each of the statements, please tick the box which applies to you

		Always	Often	Sometimes	Rarely	Never
M1	I forget to take my medicines					
M2	I alter the dose of my medicines					
M3	I stop taking my medicines for a while					
M4	I decide to miss out a dose					
M5	I take less than instructed					

Beliefs about Medicines Questionnaire

These are statements that other people have made about medicines. Please show how much you agree or disagree with them by ticking the appropriate box. There are no right or wrong answers. We are interested in your personal view.

	Views about Medicines	Strongly Agree	Agree	Uncertain	Disagree	Strongly disagree
BG1	My health at present, depends on my medicines					
BG2	My life would be impossible without my medicines					
BG3	Without medicines I would be very ill					
BG4	My health in the future depend on my medicines					
BG5	My medicines protect me from becoming worse					
BG6	Having to take medicines worries me					
BG7	I sometimes worry about long-term effects of my medicine					
BG8	My medicines are a mystery to me					
BG9	My medicines disrupt my life					
BG10	I sometimes worry about becoming too dependent on medicines					
BG11	Doctors use too many medicines					
BG12	Natural remedies are safer than medicines					
BG13	Doctors place too much trust on medicines					
BG14	If doctors had more time with patients, they would prescribe fewer medicines					
BG15	People who take medicines should stop their treatment for a while every now and then					
BG16	Most medicines are addictive					
BG17	Medicines do more harm than good					
BG18	Most medicines are poisons					

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE. PLEASE PLACE IN THE STAMP-ADDRESSED ENVELOPE PROVIDED.

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