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Comorbidity and Type 2 Diabetes : Prevalence, type and impact on cost and health-related behaviours.

A thesis submitted to the University of Dublin, Trinity College for the degree of Doctor of Philosophy

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Declaration

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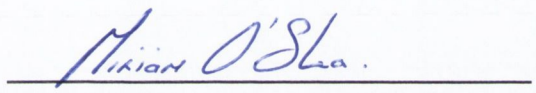

Miriam Pauline O'Shea

September 2014

Summary

Comorbidity is the co-existence of one or more additional conditions in patients with a specified medical condition. It is highly prevalent in patients with diabetes and may be related (concordant) or unrelated (discordant) to diabetes. Few studies in Ireland have investigated the presence or impact comorbidity in patients with Type 2 Diabetes Mellitus (T2DM). International studies have shown that the presence of comorbidity in patients with diabetes has negative implications in terms of the patient, economy, and society. Until recently however, the majority of these studies focused, only, on the presence and/or impact of concordant comorbidity. The overall aim of this thesis was to investigate the prevalence, type, and cost of both concordant and discordant comorbidity and its impact on adherence and self-care in patients with T2DM in Ireland by: (i) estimating the prevalence, type and ingredient drug cost of comorbidity associated with medication treated T2DM in both the adult and elderly population, that were eligible for inclusion in the General Medical Services (GMS) scheme in 2010, (ii) examining the influence of comorbidity and region of residence on adherence (the degree to which a patient takes their medication as prescribed) and persistence (the length of time that a patient remains on their medication) to oral anti-hyperglycaemic (OAH) agents in the GMS eligible population and (iii) investigating the impact of comorbidity on diabetes self-care and health-related quality of life (HRQoL) in a diabetes population attending an outpatient department in an Irish hospital. This thesis is composed of five studies.

The first four studies are based on analysis of prescription claims data obtained from the Health Service Executive – Primary Care Reimbursement Service. The first two studies found that, during 2010, the prevalence of treated T2DM in the GMS eligible adult (25 – 64 years) (N=674,026) and elderly (≥65 years) (N=445,180) population was 3.1% (N=21,877) and 9.7% (N=43,165) respectively. The median number of comorbid conditions was significantly higher in patients with treated T2DM, compared to those without T2DM, in both the adult (3 vs. 0 $p<0.0001$) and elderly (5 vs. 3, $p<0.0001$) patient populations. The higher level of comorbidity in patients with treated T2DM was associated with a significant increase in drug costs compared to those without T2DM with an average increase in costs of €717.29 in the adult and €439.26 in the elderly respectively. Concordant and discordant comorbid conditions were common in adult and elderly patients with T2DM. The third study examined the influence of comorbidity on medication taking behaviour in new users of any OAH therapy (N=21,280). The overall rate of persistence and adherence to OAH therapy was 74% and 70% respectively at 6 months, and 62.6% and 66.6% respectively at 12 months post initiation. The rate of persistence and adherence to OAH agents was shown to increase with increasing number of

comorbid conditions. When comorbidity was stratified by type, patients with only concordant conditions were significantly more likely to be persistent at 6 (OR 1.45, 95% CI 1.28, 1.65) and 12 months (OR 1.22, 95% CI 1.09, 1.38) when compared to patients either with no or with both types of comorbidity. In contrast, patients with only discordant conditions were significantly less likely to be persistent at 6 (OR 0.40, 95% CI 0.35, 0.46) and 12 months post initiation (OR 0.43, 95% CI 0.38, 0.50). Results for adherence were similar. The results of the fourth study (N=11,035) suggest there was little variability between the four HSE administrative regions in terms of patient medication taking behaviour. The Southern region had the lowest rates for both non-persistence (HR 0.86, 95% CI 0.80, 0.94) and non-adherence (OR 0.83 95% CI 0.74, 0.93). The presence of any type of comorbidity (versus no comorbidity) was shown to be associated with a lower risk of both non-persistence and non-adherence to OAH therapy in all regions. The results presented in fifth study relate to the responses (N=159) received from an anonymised cross-sectional questionnaire that was sent to 498 T2DM patients that had attended an outpatient diabetes clinic in St James's Hospital Dublin. In relation to diabetes self-care, type of comorbidity was significantly associated with physical activity. Respondents with no comorbid conditions had the highest median value for physical activity, while those with both types of comorbidity had the lowest. In terms of HRQoL, the presence of discordant comorbidity either on its own or in combination with concordant comorbidity was also associated with a significant decline in EQ-5D score compared to no complications / comorbid conditions. The presence of concordant comorbidity on its own was not found to significantly affect EQ-5D scores.

The studies presented in this thesis are currently among the few in Ireland to examine the presence and / or impact of comorbidity in patients with T2DM. The results of the first two studies provide baseline prevalence for concordant and discordant comorbid conditions in the adult and elderly GMS eligible population with treated T2DM. The results of these studies suggest that both types of comorbidity are highly prevalent in these patients. The drug costs associated with the treatment of both types of comorbidity was found to be considerably higher in patients with T2DM when compared to other patients. The economic cost of treating concordant conditions in patients with diabetes has been recognised in the international literature. The results presented in this thesis add to the existing literature by presenting costs relating to the treatment of discordant comorbidity. Previous international studies have also suggested that the presence of comorbid conditions may have a deleterious impact on patient medication taking behaviour and HRQoL in patients with T2DM. The results presented in this thesis add to this literature by showing that the presence of discordant comorbid conditions is associated with lower persistence and adherence to OAH agents and reduced HRQoL.

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Dedication

This thesis is dedicated in loving memory of my paternal grandmother,

Pauline O'Shea (nee Kearney)

19th May 1922 (Cork) – 7th October 2013 (Dublin)

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List of Abbreviations

95% CI	95% Confidence Interval
ACG	Adjusted Clinical Groups system
AMNCH	Adelaide Meath, incorporating the National Children's Hospital
ATC	Anatomical Therapeutic Chemical
CDS	Chronic Disease Score
CHD	Coronary Heart Disease
CIRS	Cumulative Index Illness Rating System
CODE	Community Orientated Diabetes Education
CODE - 2	The Cost of Diabetes in Europe – Type 2
CODEIRE	Cost of Diabetes in Eire
CPD	Continuing Professional Development
DDC	Diabetes Day Centre
DEAG	Diabetes Expert Advisory Group
DESMOND	Diabetes Education and Self-management for Ongoing and Diagnosed
DOHC	Department of Health & Children
DPS	Drugs Payment Scheme
DUSOI	Duke Severity Illness Checklist
EMM	Electronic Medication Monitors
EQ-5D	EuroQoL – 5 Dimension
ESRD	End Stage Renal Disease
FPG	Fasting Plasma Glucose
GMS	General Medical Scheme
HbA1c	Glycosylated Haemoglobin
HIPE	Hospital Inpatient Enquiry
HRQoL	Health-related Quality of Life
HRR	Hospital Referral Region
HRs	Hazard Ratio
HSE	Health Service Executive
HSE-PCRS	Health Service Executive - Primary Care Reimbursement Service

ICGP	Irish College of General Practitioners
IDF	International Diabetes Federation
IPCRN	Irish Primary Care Research Network
IQR	Inter-quartile range
LTI	Long Term Illness Scheme
MI	Myocardial Infarction
MPR	Medication Possession Ratio
MMAS	Morisky Medication Adherence Scale
NI	Northern Ireland
NIHSWS	Northern Ireland Health and Social Wellbeing Survey
OAH	Oral Anti-Hyperglycaemic
OGTT	Oral Glucose Tolerance Test
OR	Odds Ratio
OTC	Over-the-counter
PAD	Peripheral Arterial Disease
PCOS	Polycystic Ovary Syndrome
PPIs	Proton Pump Inhibitor
QoL	Quality of Life
RCT	Randomised Control Trial
RoI	Republic of Ireland
SCQ	Self-Administered Comorbidity Questionnaire
SCV	Systematic Component of Variance
SD	Standard deviation
SDSCA	Summary of Diabetes Self-Care Activities Scale
SF-36	Short Form - 36
SIP	Sickness Impact Profile
SJH	St James's Hospital
SLAN	Survey of Lifestyle, Attitudes and Nutrition
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TILDA	The Irish Longitudinal Study on Ageing
VAS	Visual Analogue Scale
WHO	World Health Organisation
X-PERT	Expert Patient Education versus Routine Treatment

Publications

- O'Shea M*, Teeling M, Bennett K. *The prevalence and ingredient cost of chronic comorbidity in the Irish elderly population with medication treated type 2 diabetes: A retrospective cross-sectional study using a national pharmacy claims database.* BMC Health Services Research, 2013 13:23. Doi: 10.1186/1472-6963-13-23. (*Chapter 3*)

- O'Shea MP*, Teeling M, Bennett K. *An observational study examining the effect of comorbidity on the rates of persistence and adherence to newly initiated oral anti-hyperglycaemic agents.* Pharmacoepidemiology and Drug Safety, 2013 22(12):1336-44. Doi: 10.1002/pds.3535. (*Chapter 5*)

- O'Shea MP*, Teeling M, Bennett K. *Regional variation in medication taking behaviour of new users of oral anti-hyperglycaemic therapy in Ireland.* Irish Journal of Medical Science, 2014 [Epub ahead of print] Doi: 10.1007/s 11845-014-1132-1. (*Chapter 6*).

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* *Corresponding author.*

Chapter 1: Background to the research topic

1.1 Introduction

The purpose of this chapter is to provide an introduction to the research topics covered in this thesis. As type 2 diabetes mellitus is the index condition in all five studies presented in this thesis, the chapter begins with an overview of literature relating to diabetes mellitus with respect to its clinical characteristics, epidemiology and economic implications. This is followed by a synopsis of the literature relating to comorbidity, the wider topic of multimorbidity and the prevalence and impact of comorbidity in patients with diabetes. An overview of the literature relating to each of the study outcomes is subsequently provided. The final section of this chapter details the overall aim and objectives of this thesis as well as providing an outline of the content of subsequent chapters.

1.2 Diabetes

Insulin and Diabetes Mellitus

Insulin is a hormone that is produced by beta cells in the pancreas. It is secreted postpradially in response to an increase in blood glucose and amino acids. The primary function of insulin is to regulate the concentration of glucose in the blood. It does this in three ways, first by promoting the uptake of glucose by peripheral tissues (mainly skeletal muscle), and then by the simultaneous promotion of glycogenesis and inhibition of glucagon secretion (1). Diabetes Mellitus is a group of chronic metabolic disorders defined by a persistent increase in blood glucose concentration (known as hyperglycaemia), which is caused by deficiencies in the secretion and / or function of insulin (2). There are several symptoms associated with pronounced hyperglycaemia including increased frequency of urination, excessive thirst, weight loss, increased hunger and blurred vision (2).

Types of diabetes

There are two main types of diabetes mellitus. Type 1 diabetes mellitus (T1DM) is an autoimmune disease which results in the destruction of pancreatic beta-cell islets, and complete insulin deficiency (3). In order for survival, patients with T1DM are required to take insulin to prevent the development of ketoacidosis (3). Although the specific etiology is unknown, risk factors for the condition include family history, ethnicity (higher in Caucasians than other ethnicities), and certain childhood viral infections (4). At present, there are no identified means of preventing the onset of T1DM (4). Genetic markers and

serological evidence of autoimmune pathologic processes in the pancreatic islets can be used to identify individuals at increased risk of developing T1DM (2). The number of cases of T1DM is relatively low (<10%) in comparison to the number of cases of type 2 diabetes mellitus (T2DM) (>90%) world-wide (3).

T2DM is defined by insulin resistance and / or a relative deficiency in the secretion of insulin (3). T2DM usually occurs in adults over the age of 40 years (5) however, the incidence of this condition is increasing in younger patients (6, 7) primarily as a result of a rise in the prevalence of obesity (8). T2DM generally starts with insulin resistance (4), indicated by a reduction in the expected physiological action of insulin with regards to both the removal of glucose from skeletal muscle and inhibition of glucogenesis in the liver (9). In the early stages of the condition, normoglycaemia is maintained by the secretion of additional insulin (10). However, as the condition develops, the manufacture of insulin slowly decreases, resulting in the gradual increase in the concentration of glucose in the blood (10).

In contrast to T1DM, which, is normally diagnosed quickly after the acute presentation of characteristic symptoms, T2DM is generally diagnosed following an extended asymptomatic period (11). Many people with T2DM are only diagnosed when complications occur (12).

Age, race or ethnicity, family history, history of gestational diabetes, low birth weight are considered to be non-modifiable risk factors for T2DM (4). In contrast, increased body mass index (BMI), physical inactivity, poor nutrition, hypertension, smoking and alcohol use are considered to modifiable risk factors (4). In addition, the presence of psychological conditions including depression and anxiety has been associated with an increased risk of T2DM development (13, 14)

Diagnosis

Opportunistic screening for T2DM is frequently targeted towards people with risk factors for the condition (15), which is often how asymptomatic patients are diagnosed. The opportunistic screening of T2DM should be considered for all individuals $\geq$45 years, (especially those with a BMI>25kg/m^2) presenting with risk factors for diabetes and should be repeated every 3 years if the results are normal (16). The screening of younger individuals should be considered in those that are overweight (BMI >25kg/m^2) and have additional risk factors, for example, a first degree relative diagnosed with T2DM (16).

Traditionally, diabetes was diagnosed based on the results of either the fasting plasma glucose (FPG) or the 2 hour value in the 75g oral glucose tolerance test (OGTT) (17). In 2009, an expert panel of international diabetes professionals proposed that the diagnosis of diabetes could also be made using a glycosylated haemoglobin (HbA_{1c}) measurement of >48mmol/mol (equivalent to $\geq$6.5%) (18). This has since been recognised a valid measure by the World Health Organisation (WHO)(19). HbA_{1c} is a standard biomarker for glycaemic control, which reflects mean plasma glucose level over a 2-3 month period (17). In an asymptomatic person a single abnormal plasma glucose or HbA_{1c} level should not be used to diagnose diabetes; diagnosis should be confirmed with at least one additional HbA_{1c} or fasting glucose test (19).

Complications

Diabetes is associated with a wide range of both microvascular and macrovascular complications (20). Macrovascular diseases associated with diabetes include ischaemic heart disease, cerebrovascular disease and peripheral arterial disease (PAD) (20). The presence of diabetes infers a 2-to-4 fold greater risk of developing coronary artery disease (21). There is a 19% increase in the risk of myocardial infarction (MI) for every 1% increase in HbA_{1c} (22). Furthermore, patients with T2DM have a similar risk of myocardial infarction (MI) as non-diabetic patients with established coronary heart disease (CHD) (23). The presence of diabetes also increases the risk of stroke in all age groups (20). The prognosis for patients with diabetes who have had a stroke is also worse than for people without diabetes (20). PAD is defined by constriction of the arteries in the extremities (20). The symptoms of PAD include leg pain on rest, loss of foot hair, discoloration and/or coolness of the feet and diminished or absent peripheral pulses (24). In patients with PAD, lower – extremity amputation is more common in patients with diabetes compared to those without (20).

Microvascular complications associated with diabetes include diabetic retinopathy, nephropathy and neuropathy. Diabetic retinopathy is the most common microvascular complication in patients with diabetes (25) and is the most frequent cause of incident blindness in adults between the ages of 20 – 74 years (26). Evidence of diabetic retinopathy is present in up to 40% of patients newly diagnosed with T2DM (27). Factors strongly associated with the development and progression of diabetic retinopathy include inadequate glycaemic control, hypertension and duration of diabetes (27). Diabetic nephropathy is the primary cause of end-stage renal disease (ESRD) and between 20 – 40% of patients with diabetes will develop nephropathy at some point (26). Key elements in the management of diabetic nephropathy include glycaemic control and the treatment of

hypertension (27). Diabetic neuropathy refers to a variety of neurological conditions that are connected with diabetes (27). The maintenance of good glycaemic control can help reduce progression of neuropathies (27). In addition to these macrovascular and microvascular conditions, diabetes is also associated with dental disease, impaired resistance to infections and macrosomia (large babies) and other birth complications among pregnant women with diabetes (4).

Mortality

Individuals with diabetes have an excess risk of premature mortality when compared to their peers without the condition (28, 29). The most common cause of death in patients with diabetes is cardiovascular disease (29, 30). The International Diabetes Federation (IDF) recently estimated that in 2013, 5.1 million people aged 20 – 79 years, died world-wide as a result of diabetes. This accounts for 8.4% of all-cause mortality globally within this age range (12). It is, however, difficult to estimate diabetes related mortality due to the lack of reliable mortality data in some countries and also because diabetes is infrequently documented as a cause of, or contributing factor to death (28).

1.3 Epidemiology

In order to correctly allocate healthcare and other resources for patients with diabetes, it is necessary to have estimates of the current and future prevalence of diabetes (31). The studies summarised in this section include both global and Irish prevalence estimates for diabetes. The global estimates pertain to both T1DM and T2DM, while the Irish estimates relate predominantly to prevalence estimates for T2DM.

Global prevalence

A study commissioned by the WHO, estimated that in the year 2000, 171 million adults worldwide had diabetes; which represents a global prevalence of 2.8%. This figure is projected to increase to 366 million adults (4.4%) by 2030 (32). The IDF carried out a more recent study in 2009, which estimated that in 2010, 285 million adults worldwide aged 20-79 years, would have diabetes representing a global prevalence of 6.4%. This study projected that the global prevalence of diabetes would increase to 7.7% (439 million individuals) by the year 2030 (31). In terms of regional diabetes burden, the IDF estimated that in 2013 approximately 56.3 million people in Europe, aged between 20 – 79 years had diabetes. This equates to a prevalence of 6.8%, which is projected to increase to 7.1% (68.9 million people) by the year 2035 (12).

Irish prevalence

In Ireland, currently there is no national register of diabetes patients, however a number of studies have estimated the prevalence of diabetes using various methodologies. A study carried out in 1998, 'The Cork and Kerry Heart disease and diabetes study', estimated that the prevalence of T2DM was 3.9% in a cohort of 1,018 patients aged 50 – 69 years from 17 general practices in Cork and Kerry. This study found that 30% of patients with T2DM were previously undiagnosed (33). Another study published in 2003 by Smith SM *et al* collected data over an 18 month period (1997-1998) from 41 general practices nationwide. This study found that the prevalence of T2DM was 9.2% in patients that were over the age of 40 years, 23.5% of which were undiagnosed previously (34). Usher *et al* used prescribing data from 2003 to estimate the prevalence of pharmacologically-treated diabetes in patients that were eligible for inclusion in one of two community health schemes – the General Medical Scheme (GMS) and the Long-term Illness scheme (LTI). The study found that the prevalence of treated diabetes was 2% overall (35). The Yorkshire and Humber Public Health Observatory Brent PCT-ScHARR (PBS) Population Prevalence Model was used in 2005 by The Irish Diabetes Prevalence Working Group to estimate the prevalence of both diagnosed and undiagnosed diabetes in Ireland. This model estimated that in 2005 the prevalence of T2DM in adults over 20 years was 4.3%. The use of this model predicted that the prevalence will increase to 5.9% by the year 2020 (36).

The results of the Survey of Lifestyle, Attitudes and Nutrition (SLAN), a national cross sectional questionnaire study carried out in 2007, by the Department of Health and Children (DOHC), found that 3.5% of the adult cohort (n=10,364 individuals) had been diagnosed with diabetes. Diabetes was found to be significantly more prevalent in older patients increasing from 0.7% amongst adults 18 – 44 years to 6.1% amongst adults $\geq$45 years. There was no significant difference in the prevalence of diagnosed diabetes between the sexes (37). The analysis of baseline data collected during the first wave of data collection in The Irish Longitudinal Study on Ageing (TILDA) (2009/10) found that one in twelve of adults (8%) included in this nationally representative cohort of people over 50, reported having received a diagnosis of diabetes. Further analysis of the TILDA data showed that the prevalence of diabetes increased by age from 6% in adults aged 50 – 64 years to 11.1% in those $\geq$75 years. However, in contrast to the SLAN study, the prevalence of diabetes was shown to differ by sex, with men reporting a diagnosis of diabetes more frequently compared to women (38). The most recent estimate of T2DM prevalence in Ireland was published in 2013 by Gallagher *et al.* This study utilised prescribing data from both the Republic of Ireland (RoI) and Northern Ireland (NI) to

examine the management of T2DM in two demographically similar populations with different health care systems. Based on analysis of prescribing data this study estimated that the prevalence of T2DM in RoI was 2.8% in 2009 and 3.1% in 2010 (39).

1.4 Economic cost of diabetes

Economic analyses have established that diabetes presents a significant economic burden society (40). Economic costs associated with diabetes can be split into direct costs (medical costs related to disease management or healthcare) and indirect costs (absenteeism from work, long-term disability and premature mortality) (40). Better knowledge relating to the economic implications of diabetes assists policymakers and encourages pro-active decisions aimed at reducing the prevalence of diabetes (41). The wide variety of methods and data sources used in economic analyses means that it is difficult to estimate the overall economic impact of diabetes or make suitable comparisons between studies (40).

Global

According to a study commissioned by the International Diabetes Federation, an estimated $376 billion American dollars (USD) was used globally in 2010 for the treatment of diabetes and related complications accounting for approximately 12% of the world's total health expenditure. This is projected to surpass $490 (USD) billion by 2030. An estimated prevalence of diabetes was obtained from studies carried out in 91 countries. Estimates of population size and health expenditures were obtained from both the United Nations and World Health Organisation (42).

Europe

In 2002, The Cost of Diabetes in Europe – Type 2 (CODE-2) study assessed the healthcare related cost of T2DM in eight European countries (Belgium, France, Germany, Italy, The Netherlands, Spain, Sweden and the UK). This study estimated that the overall cost of the T2DM in these 8 countries was €29 billion (1999 values) equating to a mean of €2834 per patient per annum (43, 44). The majority of costs related to the management of complications associated with diabetes (45).

In the United Kingdom, a recent study by Hex *et al,* estimated that in 2010/2011 the total cost attributed to diabetes was approximately £23.7 billion consisting of £9.8 billion direct costs (£8.8 billion for T2DM) and £13.9 billion in indirect costs (£13 billion for T2DM). The overall cost equates to approximately 10% of the total UK health care budget. As in

previous studies the treatment of diabetes-related complications accounted for a significant proportion of the direct health costs (46).

Ireland

The Cost of Diabetes in EIRE (CODEIRE) study estimated that the total cost of treating diagnosed T2DM in Ireland was 377.2 million euros from 1999-2000, which corresponded to 4.1% of the national healthcare expenditure for that period. Hospitalisation for the treatment of diabetes-related complications accounted for nearly half of the expenditure overall. This study did not examine indirect costs associated with diabetes (47).

1.5 Multimorbidity and Comorbidity.

Definition of multimorbidity and comorbidity

An increasing number of patients are now living with multiple chronic conditions due to advances in medical care and population aging (48). The occurrence of multiple conditions is associated with reduced quality of life, increased disability and higher health care costs (49). The presence of two or more chronic or acute medical conditions in the same individual is referred to as multimorbidity (50). In contrast, comorbidity is defined as the co-existence of one or more additional conditions in persons with a specified index medical condition (51). A complication may be defined as "the existence of a second disease when the occurrence of an index disease is required" (52). Complications are etiologically associated with the natural history or treatment of the index condition (53). It is important that these conditions be accurately classified so as to prevent an inaccurate estimation of the comorbidity burden (54).

Types of co-morbidity

A number of different frameworks have been developed that categorise comorbid conditions according to their influence on the clinical management of the index condition (51). The most recent of these frameworks was developed by Piette & Kerr (55), and has since been used in a number of published studies (56-58). The original paper classified chronic comorbid conditions as being either concordant or discordant with diabetes. Concordant comorbid conditions are those associated with diabetes, i.e. they represent part of the same overall pathophysiological risk profile or share the same medical management plan (55). In contrast, discordant conditions are not pathophysiologically associated with diabetes and consequently their management may be different (55).

Measuring multimorbidity / comorbidity

"To assess the impact of multimorbidity, it is necessary to measure it" (59). Methods used to assess the burden of multimorbidity may be grouped into 2 distinct categories: simple disease counts (which are based on the sum of diseases present in an individual) and indices (based on a variety of conditions, which have each been given differential weight based on disease severity, prognosis or use of resources) (59). Comorbidity indices are calculated from diagnosis data obtained from different sources, including medical records or administrative databases, or derived by proxy diagnosis from pharmacy claims data (60). Comorbidity indices are developed for particular purposes and they differ in their initial objective and context (61). The use and attributes of a variety of different methods to measure comorbidity have been discussed in the published literature (59, 62, 63). According to a systematic review carried out by Huntley *et al,* the most frequently used measures of comorbidity in primary care and community based studies are disease counts, Charlson index, the Adjusted Clinical Groups (ACG) system, Cumulative Index Illness Rating System (CIRS), Chronic Disease Score (CDS) and the Duke Severity Illness Checklist (DUSOI) (59). The characteristics and applications of these measures are summarised in *table 1.1.* The selection of a particular comorbidity measure for research purposes should be based on the data available and the outcome of interest (59). It should be noted, however, that comorbidity indices are frequently tailored by researchers to meet the requirements of a particular study (61).

Table 1.1 Summary of the characteristics and application of some of the most commonly used measures of multimorbidity in outpatient settings*

Measure	*Original Derivation / Validation Populations*	*Information needed*	*Original Purpose of Score*	*How information is used*	*Comment*
Disease count	Varies across studies	Disease counts derived from medical reports / clinician diagnosis or patient self-reports.	Varies across studies	Sum of individual diseases / conditions per individual	No weighting of diseases in terms of prognosis or severity of disease
Chronic Disease Score (CDS) / RxRisk Model	Original CDS: adult HMO** enrollees from a single US HMO. Revised CDS derived and validated in 254,694 adult members of a US HMO. RxRisk derived and validated in large samples of US HMO members.	Automated pharmacy data	To develop a stable measure of chronic disease status using routine pharmacy data rather than chart review.	Original CDS considered 17 disease states weighted by experts. Score based on history of dispensed drugs for 1 year, adjusted for age and sex. Subsequent versions expanded the number of diseases.	Limited number of diseases Weighting of original CDS based on consensus rather than evidence (addressed by subsequent versions)
Charlson Index	Derived in 559 hospitalised patients in US. Validated in patients undergoing treatment for breast cancer	Various versions are available; 17 – 22 disease categories, including age. Available in different formats Free	To predict 1 year mortality among patients admitted to hospital. adapted to predict costs	Each disease is given a weighting of 1 – 6 and weighted scores are summated; this score can also be combined with age. Variations have been developed to use ICD-9 data.	Limited number of diseases. Needs information about the severity of some conditions.
Adjusted Clinical Group (ACG) System	Derived and validated in US using large HMO databases. Validation sample also included Medicaid patients.	Age, sex and diagnosis codes from medical records or insurance claims coded using the ICD or Red code systems. Software needed which has a license fee.	Originally devised to predict morbidity burden and use of health care resources.	Collapsed into Initial Codes then to calculate ADGs; CADGs; MACs; ACGs**. Each ACG includes individuals with a similar pattern of morbidity and similar expected resource use	Need to buy software. Based on reliability of claims or record data.
Cumulative Index Rating Scale (CIRS)	Hospitalised men in the US and subsequently older adults in an outpatient setting	A rating scale consisting of 14 body systems categories that can be filled in by trained assessors directly during clinical consultation or from medical records. Free access.	To assess the medical burden of chronic illness.	Each body system has a severity rating of 0 – 4, which are summated to create a total score (0 – 56) or presented as an index based on the number of categories scoring 2 or more. Several variations exist.	Requires training based on manual. Broad body system groups. Prognoses vary among types of conditions and may have improved since index was devised
Duke Severity Illness Checklist index(DUSOI)	Developed in 249 adult patients attending a family practice in the US	Severity of illness checklist for measuring a person's illness severity. Can be filled in during clinical consultation or from medical	To quantify the burden of illness as measured by the physician	Each diagnosis is rated on 4 levels: symptom, complication, prognosis without treatment, prognosis with treatment.	Subjective judgment is required on the part of the assessor. Training needed Available from Author.

*** Adapted from Huntley AL, Johnson R, Purdy S *et al* (59)**

**** Acronyms: (HMO) Health Maintenance Organisation; (CDS) Chronic Disease Score; (ACGs) Adjusted Clinical Group; (ADGs) Aggregated Diagnosis Groups; (CADGs) Collapsed Aggregated Groups; (MAC) Major Ambulatory Categories; (ACGs) Ambulatory Care Groups; (CIRS) Cumulative Index Rating System; (DUSOI) Duke Severity Illness Checklist Index.**

Global burden of multimorbidity

The use of different indices to measure multimorbidity in previous studies makes it difficult to compare the prevalence of multimorbidity in different patient populations (64). In contrast to research examining the epidemiology of single conditions, the results for multimorbidity has been shown to vary extensively between studies (48). A systematic review of the literature conducted by Marengoni *et al* in 2011 identified 12 studies (published between 1990 and 2010) that examined the prevalence of multimorbidity in various countries. This study noted that while the majority of the research studies included in the review defined multimorbidity as the co-occurrence of $\geq$2 medical conditions, it was also defined as the co-occurrence of $\geq$3 medical conditions in a number of studies. The results of the review found that the prevalence of multimorbidity, taking into account all age groups, ranged between 20% - 30%. However, the prevalence of multimorbidity was considerably higher (55% - 98%) in studies that only examined the older age group (>60 years) (49).

Multimorbidity in Ireland

There have been a number of published studies that have examined the prevalence of multimorbidity in Ireland using different methods in different patient settings. A study by Naughton C *et al*, used national pharmacy claims data from 2003 to estimate the prevalence of pharmacologically treated multimorbidity in the Irish population $\geq$70 years. This study found that at least 60% of the elderly population was treated for at least two chronic conditions (65). More recently, analysis carried out on the first wave of data (2009/10) from The Irish Longitudinal Study on Ageing (TILDA) study reported that the prevalence of multimorbidity was 53.8% in this nationally representative sample of adults $\geq$50 years (66). Another study conducted in 2011 investigated the prevalence of multimorbidity in patients >50 years of age in three primary care practices (n=3,309 patients) in the West of Ireland using patient medical records and found the prevalence of multimorbidity to be 66.2% (67). The most recent study, published in 2013, used data from both the Northern Ireland Health and Social Wellbeing Survey (NIHSWS) 2005 and the Survey of Lifestyle, Attitudes and Nutrition (SLAN) 2007 to examine the impact of combinations of chronic conditions on disability and quality of life (QoL) in patients $\geq$50 years (n=6159). This study categorised chronic conditions into four groups; cardiovascular disease, chronic pain, diabetes or respiratory disease. The study reported that 11% of the study population had a chronic condition from at least two of the four disease categories (64).

Management of Multimorbidity

Physicians, particularly those working in specific areas of medicine including general practice, psychiatry and geriatrics, often face difficulties in caring for patients with multimorbidity (68). For example, the many medical and pharmacological requirements of patients with multimorbidity need to be comprehensively addressed within a relatively short consultation period. However, the presence of medically dominant and / or symptomatic conditions in such patients, can take up a considerable amount of the consultation time and result in less consideration being given to the patient's other medical conditions (68). Furthermore, there may be disagreement between the patient and physician as to the relative importance of each condition (69). Differences in prioritisation may result in poor patient adherence (69). Continuity of care used in conjunction with a holistic approach to patient care can assist therapeutic decision making for both clinicians and patients, while also taking into consideration, patient preferences, priorities and individual circumstances (70).

There is a dearth of information in relation to the medical management of patients with multimorbidity (71). At present, the majority of evidence based clinical guidelines concentrate on the treatment of a single chronic condition and their related complications (72-74). Current clinical guidelines present few specific recommendations relating to the treatment of comorbid conditions (74). The use of clinical guidelines may therefore have limited applicability to patients with multiple conditions (74). In order to increase the relevance of clinical guidelines in terms of the management of patients with multimorbidity, it has been proposed that guidelines should highlight synergistic or conflicting recommendations by cross-referencing other relevant guidelines (73). Furthermore, the inclusion of a small number of clinical vignettes, which relate to combinations of comorbid conditions frequently encountered in clinical practice, may help to address some of the difficulties encountered by health professionals trying to summarise the recommendations from several different guidelines (73).

1.6 The burden of comorbidity in patients with diabetes.

Prevalence of comorbidity in patients with diabetes

The occurrence of comorbidity is very common in patients with diabetes. Previous research has shown that the majority of patients with diabetes in the United States have at least one additional condition (75), while as many as 40% of patients have three or more comorbid conditions (76). Studies conducted in Europe have also reported a high rate of comorbidity in patients with diabetes. For example, the results of a comprehensive

longitudinal study carried out in primary care in newly diagnosed T2DM patients in the Netherlands found that approximately 85% of patients had at least one additional chronic condition at the time of their diagnosis and, of the minority of patients that did not have any comorbid condition initially, 25% were subsequently diagnosed with another condition within twelve months of their diabetes diagnosis (77). Furthermore, a recent Irish study found that 90% of patients with T2DM eligible for enrollment in a randomised control trial (RCT), carried out in primary care setting, had at least one comorbid condition, while 25% had $\geq$4 comorbidities (78).

Impact of comorbidity on diabetes-related self-care

The presence of comorbidity can have a major influence on a patient's capacity to manage their diabetes-related self-care (79). Depending on the symptoms and severity of the comorbid condition(s) present, patients' prioritisation and self-management may be compromised and / or complicated (80). A higher symptom burden has been shown to adversely affect a patient's ability to adhere to recommendations for self-care with respect to diet, exercise, and medication regimens (81).

The presence of comorbid depression in patients with diabetes has been linked with poorer adherence to medications and lifestyle recommendations (82, 83). This effect is not unique to patients with clinical depression; even mild cases of depression can have a negative effect on adherence to self-care recommendations (84). Depression has been shown to decrease the motivation of patients to follow self-care practices (85). In addition, both the presence and severity of chronic pain have been shown to have an adverse effect on diabetes related self-care, particularly with respect to engaging in specific activities such as participating in regular physical exercise (86).

A qualitative study by Beverly *et al* found that patients with comorbid conditions often perceived their other conditions as being more important than diabetes. Patients prioritised other conditions over diabetes by selectively attending to the self-management of the condition(s), which they perceived as more important or severe (87). Another study found that patients receiving chemotherapy for the treatment of cancer prioritised their cancer over the management of their diabetes. After undergoing chemotherapy, the performance of diabetes self-care activities was found to have decreased substantially (81).

1.7 Treatment, persistence, adherence and self-care.

Goal of diabetes treatment

The main objectives of treating diabetes are to normalise blood glucose levels and prevent diabetes-related complications (88). It has been established by several randomised control trials (RCTs) that intensive glycaemic control reduces the risk of patients developing microvascular complications (89-91). The role of intensive glycaemic control in the prevention of macrovascular complication is, however, less certain (30, 92-94).

Defining glycaemic control

A HbA_{1c} level of less than 7% (<53mmol / mol) is considered an acceptable target measure of glycaemic control for many patients with diabetes. However, it is recognised that the glycaemic target set for particular patients should reflect their specific needs (26). Tighter glycaemic targets (e.g. HbA_{1c} 6.0 – 6.5%, 42 – 48mmol / mol) may be considered for patients meeting specific criteria such as long life expectancy, recent diabetes diagnosis and absence of major cardiovascular disease, provided that they can be achieved without increasing the incidence of adverse effect such as hypoglycaemia (25, 26). In contrast, it may be necessary to consider a less strict HbA_{1c} target level (<8%) for certain patients including those with a shorter life expectancy, serious diabetes-related complications or other comorbid medical condition, and in those presenting with a history of severe hypoglycaemia (26, 30).

Therapeutic options for the treatment of type 2 diabetes

Patients with newly diagnosed T2DM are required to initiate lifestyle changes, such as, weight loss, and modifications in diet and levels of physical activity (95). The majority of these patients will also require oral anti-hyperglycaemic (OAH) agents in order to achieve satisfactory glycaemic control (95). In order to achieve adequate glycaemic control it has been estimated that approximately 70% of patients with T2DM require pharmacotherapy (96). There are at present five separate therapeutic classes of OAH agents used in the treatment of patients with T2DM (10). According to a review of the literature by Inzucchi the majority of OAH agents are capable of a 1 – 2% reduction in HbA_{1c} level when compared to placebo agents (10).

According to clinical guidelines for the management of T2DM, which were commissioned by the United Kingdom's National Institute for Health and Care Excellence (NICE), the first approach used to obtain glycaemic control in patients with newly diagnosed T2DM should involve a trial period of lifestyle modifications, followed by the initiation of metformin

monotherapy if HbA1c remains above 6.5% (97) *(Figure 1.1)*. A sulphonylurea may be initiated in patients that do not tolerate metformin or in cases where its use is contraindicated (97). If this initial strategy does not achieve or cannot maintain adequate glycaemic control, another anti-hyperglycaemic agent should be added to the initial treatment regimen (97). In order to maintain adequate glycaemic control, it is common for patients with T2DM to require ≥2 anti-hyperglycaemic agents with different mechanisms of action (98). Research suggests that HbA_{1c} is reduced by between 0.9% - 1.1% for each new class of OAH added to the initial therapy (26). Due to the progressive nature of T2DM, it is often necessary to introduce different OAH agents with alternative mechanisms of action, at various stages of the disease (98). Insulin may also be introduced to counteract the effect of insulin depletion due to advanced beta-cell destruction or to treat severe insulin resistance (98). It is estimated that 60% of patients will eventually need insulin for adequate glycaemic control due to the progressive nature of T2DM (99). In spite of the treatments available, the Cost of Diabetes in Europe – type 2 (CODE-2) study found that only 28% of European patients treated for T2DM obtained satisfactory glycaemic control (88).

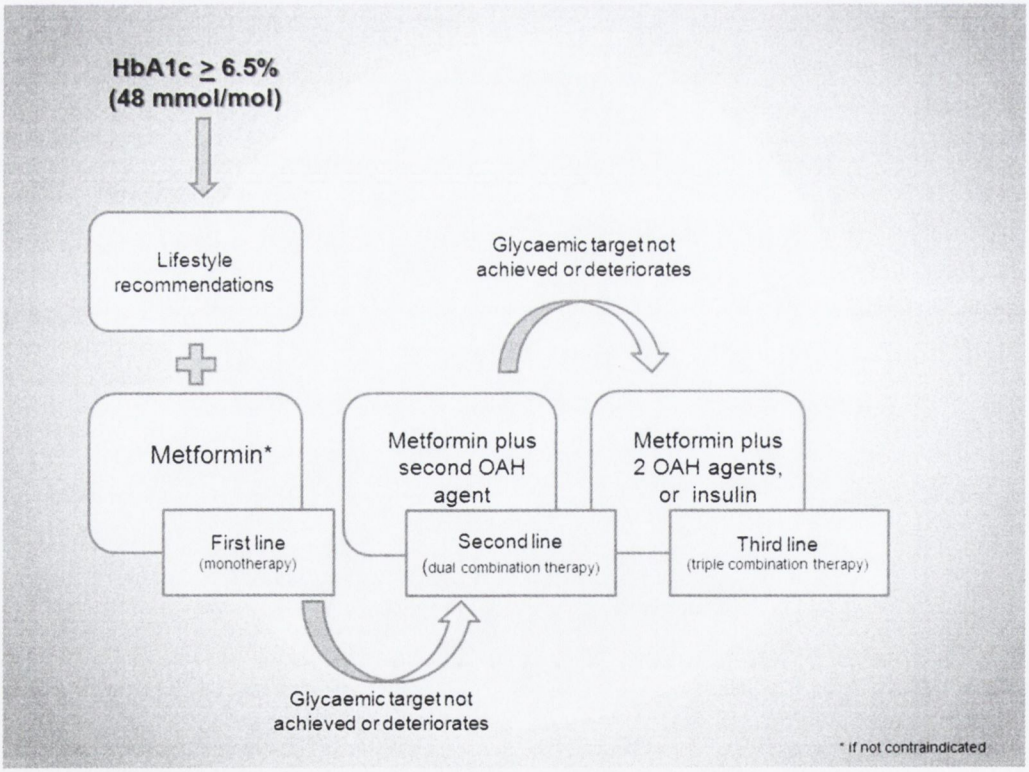

Figure 1-1Example of a treatment pathway for a patient with type 2 diabetes (based on NICE guideline) (97).

Defining medication persistence and adherence

The use of medications by patients can be defined in terms of two distinctive patterns of patient behaviour, medication persistence and adherence (100). Medication persistence is defined as the "*duration of time from initiation to discontinuation of therapy*" (101), whereas medication adherence (synonym medication compliance) refers to "*the extent to which patients take medications as prescribed by their health care providers*"(102). The clinical outcome of therapy is affected by both medication persistence and adherence; therefore, both behaviours should be independently evaluated in order to fully examine medication taking behaviour (101).

Methods for measuring medication adherence

At present, however, there is no consensus on a gold standard method for assessing medication adherence (103). Medication taking behaviour may be measured using ether direct or indirect methods (102). Examples of direct methods include examining the concentration of a drug or associated metabolite in the patient's blood plasma or urine, or through direct observation of medication taking behaviour (102). Direct methods have a number of disadvantages including being expensive and tedious to perform, potentially subject to alteration by the patient (102) and impractical to carry out in large population of patients (104). Indirect methods include evaluating clinical responses, patient self-report, performing pill counts, using electronic medication monitors and examination of prescription refill data (102).

Information obtained from pharmacy / administrative databases are increasingly being used to assess patient medication taking behaviour in different health care settings (104). However, the use of pharmacy claims data to evaluate patient medication taking behaviour has several limitations (104). One limitation is that although the data may provide an accurate description of medication possession, it does not measure actual medication consumption (104). The use of prescription claims data can, therefore, overestimate the true level of medication adherence in a study population (105). In addition, the use of either short (e.g. <63 days) or long (e.g. >90 days) evaluation periods have the potential to introduce biases in the estimation of medication adherence when using this type of data (105). However, in spite of these limitations, the use of pharmacy claims data provides an effective way of estimating medication taking behaviours in large real world patient populations (104), using methods that are convenient, impartial, clinically non-invasive and cheap to obtain (105). Furthermore, the results of a study by Pladevall *et al* found that estimates of medication adherence based on pharmacy claims data were representative of clinical outcomes (106).

Persistence can be determined by examining medication refill activity from either the initiation of treatment or a specific point in time, in the case of a prevalent disease, to a point in time defined as the end of the observation period (101). A pre-determined number of days between prescription refills, reflecting a permissible gap in medication, must be defined (101). Persistence may be reported as either a continuous or dichotomous (persistent versus non-persistent) variable (101). The percentage of patients that remain persistent at 12 months post index date is a frequently used measure of persistence (107).

The Medication Possession Ratio (MPR) is a frequently used measure of medication adherence (107). It is a proxy measurement based on prescription refill activity and refers to the number of doses dispensed with respect to time covered by the prescription. Values for MPR can range from 0 – 1 or can be reported as percentages (0% - 100%). Better adherence is denoted by higher MPR values (108). Even though, there is no agreement as to a value that represents adequate adherence (102), a MPR $\geq$80% has been often used arbitrarily to denote satisfactory medication adherence (109, 110).

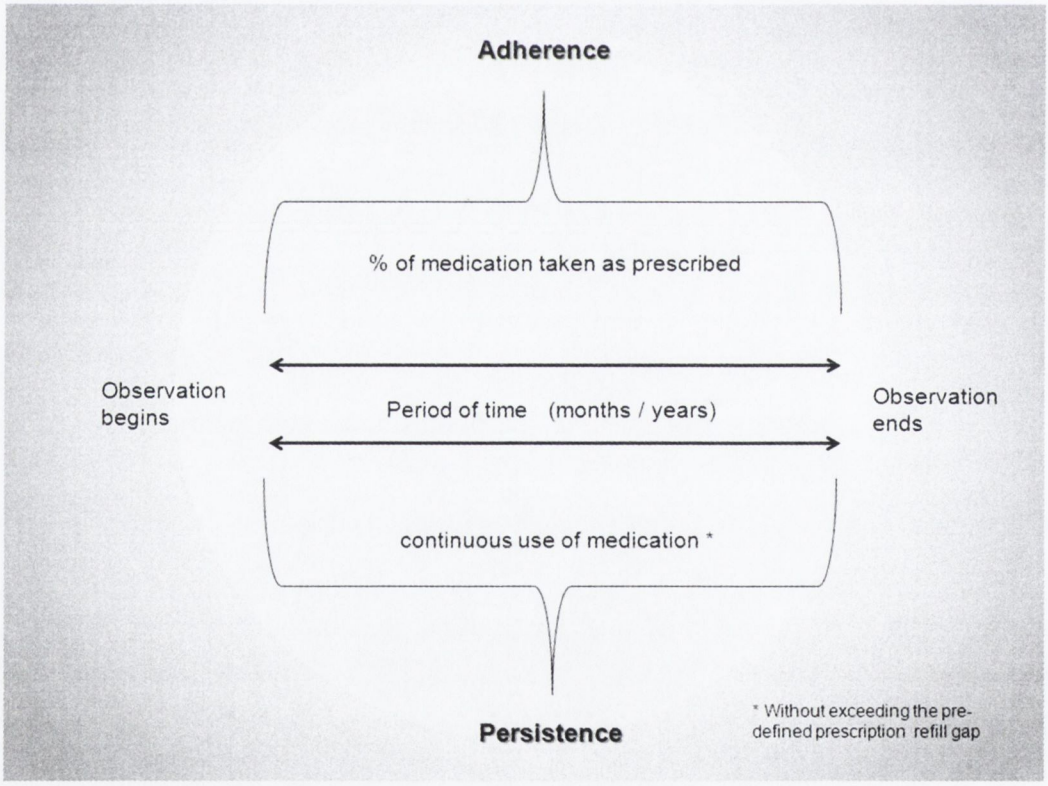

Figure 1-2 Definitions of Medication persistence and adherence *(adapted from Cramer et al, 2008)* (101)

Consequences of non-adherence

The use of pharmacotherapy has a central role in the prevention and successful management of chronic medical conditions (111). However, patients with chronic conditions are frequently non-adherent to their medications (95). Previous research has indicated that between 40% – 50% of patients with chronic medical conditions do not take their medication as prescribed (111). In a report issued by the WHO in 2003, non-adherence to medication was recognised as a significant cause of avoidable morbidity, mortality and economic cost to health systems (88). Factors that affect medication adherence can be separated into several distinct groups including patient-related factors, therapy-related factors, health system factors, socioeconomic factors and disease related factors (*Table 1.2*) (88, 112).

Table 1.2 Categories of factors related to medication adherence (Adapted from Jin et al, 2008)(112)

Category	*Factors*
Patient-related factors	• Demographics: *Age, Ethnicity, Sex, Education, Marriage status.* • Psychosocial Factors: *Beliefs, Motivation, Attitude.* • Patient-doctor relationship • Health literacy • knowledge • Physical difficulties • Tobacco or alcohol use • Forgetfulness • History of good adherence
Medication –related factors	• Route of administration • Regimen complexity • Length of treatment • Degree of behavioural change needed • Taste of medication if used orally • Requirements for storage
Factors relating to the health service	• Limited accessibility • Long waiting time • Difficulty in getting prescription filled • Dissatisfactory visits to the clinic
Social and economic factors	• Difficulty taking time off work • Cost and income • Social support
Factors related to the medical condition	• symptoms • Severity

Healthcare professionals view medication adherence as a key clinical issue for two reasons;

(1) Non-adherence may have significant implications on treatment efficacy and clinical outcomes (112); according to a meta-analysis by Di Matteo *et al*, medication adherence, versus non-adherence, decreases the likelihood of an ineffective / poor therapeutic result by 26% (113).

(2) In addition, non-adherence is associated with increased economic cost, for example, non-adherence has been associated with increased use of emergency services, hospital admissions and higher therapeutic costs. Previous research has estimated that 25% of hospitalisations in Australia and 33% – 69% of drug-related hospital admissions in the USA were as a result of medication non-adherence (112).

Adherence and persistence of treatment in Diabetes

Patients with diabetes are frequently non-adherent to their medication (95). The results of a meta-analysis found that, in patients with diabetes, the mean adherence was 67.5%, which is less than that reported for many other chronic conditions (114). Patient adherence to anti-hyperglycaemic medication has been shown to decline over time (109). Non-persistence occurs frequently in the first year of treatment, with over a third of patients failing to refill their prescriptions during this period (109). Previous research has shown that non-adherence to anti-hyperglycaemic therapy is associated with poor glycaemic control, a higher risk of requiring hospital care (115, 116) and all-cause mortality (117).

A number of reviews have been written that document barriers to medication adherence in patients with diabetes (118). According to the literature, the most frequently encountered barriers to medication adherence in patients with diabetes include regimen complexity, high dosage frequency (>2 daily), cost of treatment, poor self-efficacy, lack of education, the presence of depression, or adverse effects of treatment and related anxiety (118). Adherence to medication may also be influenced by the patients' perception of their own health. Research has shown that adherence was better in patients with poorer self-perceived health and in those who considered themselves more vulnerable to negative outcomes associated with diabetes (96).

1.8 Diabetes Self-care

Self-management may be defined as "*the individual's ability to manage symptoms, treatment, physical and psychosocial consequences and lifestyle changes inherent in living with a chronic condition*" (119). An essential part of chronic disease management is the empowerment of the individual to manage their own condition (120). Previous research has demonstrated that in those with chronic conditions, increased participation in everyday self-management activities can lead to an improvement in health-related behaviours, health status and healthcare use (120).

In those with T2DM, lifestyle modification represents the basis for disease self-management. Essential aspects of diabetes self-management associated with lifestyle include healthy eating, appropriate weight management, engagement in regular exercise, moderate consumption of alcohol and smoking cessation (121). According to the published literature, good diabetes self-management is positively associated with a number of different patient-related outcomes including glycaemic control, diabetes-related complications and quality of life (QoL). Furthermore, diabetes self-care has also been shown to be positively associated with health care use and cost (122).

In spite of the known benefits, many with diabetes are not able to adhere to the lifestyle and behavioural changes that are recommended (123). It has been estimated that between 60% - 80% of patients experience difficulty in adhering to the dietary and exercise recommendations associated with the management of diabetes (82). Diabetes self-management may be supported or obstructed by a number of different factors related to either the individual patient and / or their environment (*Table 1.3*) (124).

Table 1.3 Potential Issues associated with management of diabetes*

Category	Factors
Patient issues	• Knowledge • Empowerment • Health literacy • Motivation • Beliefs about health • Self-efficacy • Coping mechanism • Problem solving capacity • Locus of control • Mental health issues – depression & anxiety • Forgetfulness • Excessive alcohol use • Comorbid conditions that may interfere with diabetes care
Environmental issues	• Social support • Support from health professionals • Socio-economic factors • Distance from health-care provider • Other responsibilities and interests • Factors linked to the availability of good quality health care, nutritious foods, exercise opportunities etc.

Adapted from Ahola A.J. & Groop P.H (2013) (124)

Patient comprehension of their illness is necessary for optimal self-care (125). Studies have suggested that insufficient patient knowledge is one of the principle barriers effecting diabetes self-management (124). Furthermore, the absence of formal diabetes education in patients with diabetes has been linked with a 4 fold increased risk of developing major complications related to diabetes (126).

The goal of self-management support is to teach patients with chronic conditions how to take an active role in the care of their health problems, through the use of systematic interventions, which aim to enhance the competency and confidence of the patient in relation to the management of their chronic illness (127). The results of a previous meta-analysis suggest that in patients with diabetes, self-management interventions are associated, at least in the short term, with increased patient knowledge relating to diabetes and an improvement in self-monitoring and dietary related behaviours (124). If

these improvements are to be maintained in the long term, patient education may need to be repeated at intervals (128).

1.9 Health-related quality of life

Health-related quality of life (HRQoL) is a term used to describe "*the way in which health, illness and medical treatment impact on quality of life (QoL)*" (129). HRQoL is recognised as an important patient related outcome measure in both clinical and health service research (130). In addition to traditional outcome measures, such as mortality and morbidity, HRQoL is now frequently used in randomised control trials (RCT) (131). Furthermore, instruments of HRQoL are also used in healthcare related economic evaluations (132).

In patients with T2DM maximizing HRQoL is important, as significant associations have been found between poor HRQoL and unfavorable clinical outcomes such as, poor therapeutic response, disease progression and increased risk of mortality (129). HRQoL may be measured using either disease specific or generic instruments (133). The use of disease specific instruments enables a detailed evaluation of how a particular condition may influence patient HRQoL; however, their usefulness is limited to the comparison of populations with the same index condition (134). In contrast, generic instruments examine overall patient well-being and the capacity to perform everyday activities and enables the comparison of HRQoL across populations with different medical conditions (134). Some of the most commonly used generic HRQoL instruments are: the Short Form – 36 (SF – 36), the Sickness Impact Profile (SIP), the Nottingham Health Profile and the EuroQoL – 5 Dimension (EQ-5D) (131). A number of experts have advocated the use of both general health status and disease specific instruments in studies examining HRQoL (135).

Patients with diabetes generally report lower HRQoL when compared to persons who do not have a chronic condition (134, 136). A number of factors including increased age, female sex, lower standard of education, lower economic status, and longer disease duration have been shown to be associated with reduced HRQoL in those with diabetes (137). Furthermore, chronic complications related to diabetes have also been shown to have an adverse effect on patient HRQoL. The presence of more than one complication generally reduces HRQoL even further (134, 138). Other studies have also indicated that the presence (139, 140) and number of comorbid conditions can adversely influence HRQoL in patients with T2DM (130, 141, 142).

1.10 Regional variation

All patients should have equal access to comprehensive healthcare irrespective of their means or geographical location (143). Practice variation may reveal inconsistencies in patient care and / or inefficiencies in the use of healthcare resources between or within regions (143). Comparative studies of healthcare resources and outcomes in different geographic areas have been used to evaluate healthcare delivery and direct health policy (144). Evaluation of well- as opposed to poorly- performing localities may help to ascertain means of enhancing performance (145).

To take an example, comparative research indicates that surgical procedures vary between countries and geographical regions (146). Variation in such procedures has been shown to result primarily from divergent physician views relating to indication of surgery, and from the degree to which physicians take patient preferences into account when making therapeutic decisions (146). Regional variations have also been observed in patterns of medication prescribing, hospitalisation rates (146) and healthcare expenditure (147). The implications of variation, both economically and in terms of health outcomes, means that variations, are increasingly being regarded as indicators of health system performance and the quality of care received by patients (148).

In Ireland, few published studies have investigated regional variation in relation to healthcare provision or spending. However, regional variation in prescribing has been documented for both anti-diabetic medication (143, 149) and secondary preventative cardiovascular therapy (143). Such variations may signify discrepancies in the delivery of diabetes-related care (149).

1.11 Aim of this research

Drawing on evidence from the international literature, this chapter has shown that comorbidity, the co-existence of one or more additional conditions in patients with a specified medical condition, is highly prevalent in patients with diabetes. It has shown that comorbid conditions may be related (concordant) or unrelated (discordant) to diabetes. In addition international studies have shown that the presence of comorbidity in patients with diabetes have negative implications in terms of the patient, health service and economy. Until recently, however, the majority of these studies have focused, only, on the presence and/or impact of concordant comorbidity. In Ireland few studies have investigated the presence or impact comorbidity in patients with diabetes. The aim of this research is to investigate the

prevalence, type and potential implications of comorbidity in patients with T2DM in Ireland, in terms of cost and impact on medication taking and self-care by the following objectives:

1. To establish the prevalence and ingredient drug cost of comorbidity associated with pharmacologically treated T2DM in the GMS eligible adult and older populations in Ireland.
2. To examine the influence of comorbidity and region of residence on OAH agents' adherence and persistence in the GMS eligible population.
3. To investigate the impact of comorbidity on diabetes self-care and health-related quality of life in a diabetes population attending an Irish hospital outpatient department.

1.12 Thesis outline

The thesis is presented as follows:

Chapter two: Materials and Methods

This chapter describes the Health Service Executive – Primary Care Reimbursement Service (HSE-PCRS) pharmacy claims database, the General Medical Services (GMS) Scheme, provides a brief summary of indices used to measure comorbidity in the first four studies and of the validated instruments that were adapted for use in the final questionnaire study.

Chapter 3: The prevalence and ingredient cost of chronic comorbidity in the Irish elderly population with medication treated Type 2 diabetes: A retrospective cross-sectional study using a national pharmacy claims database.

This chapter presents the published outcomes of a retrospective cross-sectional study, which used data from the HSE-PCRS from 2010, to examine the prevalence, type and medication cost of chronic comorbid conditions in the elderly (≥65 years) GMS eligible population with pharmacologically treated T2DM.

Chapter 4: The prevalence and ingredient cost of chronic comorbidity in young and middle aged GMS eligible adults with pharmacologically treated type 2 diabetes.

This chapter presents a retrospective cross-sectional study, which investigated the prevalence, type and medication cost of chronic comorbidity in both young (25 – 44 years) and middle aged (45 – 64 years) adults eligible for inclusion in the GMS scheme, using data obtained from the HSE-PCRS for 2010.

Chapter 5: An observational study examining the effect of comorbidity on the rates persistence and adherence to newly imitated oral anti-hyperglycaemic agents.

This chapter presents the published outcomes of retrospective cohort study, which used data obtained from the HSE-PCRS, to investigate the effect of presence and type of comorbidity on patient medication taking behaviours. The study identified a cohort of incident users of oral anti-hyperglycaemic agents (≥25 years) and followed their prescription refill activity to examine both persistence and adherence to OAH therapy at 6 and 12 months post therapy initiation.

Chapter 6: Regional variation in medication taking behaviour of new users of oral anti-hyperglycaemic therapy in Ireland.

This chapter presents the findings of a retrospective cohort study, which examined whether there were any regional differences in medication taking behaviours with regard to OAH therapy in GMS eligible patients (≥25 years), who initiated therapy between 2009/10. This study also examined whether there was any disparity in the co-prescription of medication for comorbid conditions between different regions and the subsequent effect of comorbidity on medication taking behaviour in those regions. This chapter has been submitted as an original manuscript for consideration to an academic journal.

Chapter 7: An observational study examining the effect of comorbidity on the rates of persistence and adherence to newly initiated oral anti-hyperglycaemic agents

This chapter presents the findings of a cross-sectional questionnaire study, which examined the effect of the number and type of comorbid conditions on HRQoL and diabetes-related self-care in patients with T2DM that had attended the diabetes day centre in large hospital in Dublin. This chapter has been submitted as an original manuscript for consideration to an academic journal and is currently undergoing peer review.

Chapter 8: Thesis Conclusions

This chapter provides an overview of the conclusions from each of the different studies presented in this thesis, their implications, and outlines areas future research.

Chapter 2: Materials and Methods

2.1Databases

2.1.1 The Health Service Executive - Primary Care Reimbursement Service database.

The Health Service Executive – Primary Care Reimbursement Service (HSE-PCRS) database is primarily used as a means of reimbursing primary care contractors for the provision of both healthcare and prescription medication through a variety of different community health schemes, including the General Medical Services scheme (GMS) (150). The HSE reimburses community pharmacies, through the PCRS, for the cost of each pharmaceutical item dispensed to patients covered by the community health schemes (151). The cost of each item is calculated based on the sum of ingredient drug cost (ex-factory price* + whole sale mark-up), the dispensing fee / retail mark-up and value added tax (VAT)†. Items dispensed under the GMS scheme are not subject to a retail mark-up (151). The HSE-PCRS database contains the ingredient cost, dispensing fee and VAT for each pharmaceutical item covered under the community health schemes (153). Medications recorded in the HSE-PCRS database are coded using the WHO Anatomical Therapeutic Chemical (ATC) classification system (154). The HSE-PCRS database contains demographic information such as sex, age and region of residence. However, it does not contain any diagnostic information relating to the patient or data relating to over the counter (OTC) medication which may be obtained without a prescription (155). The database has, however, been used previously for research purposes, to examine prescribing patterns (143, 149), prescribing practices (155) and economic implications (156).

2.1.2 The General Medical Services (GMS) Scheme

The General Medical Services (GMS) scheme provides eligible individuals, referred to as "medical card patients" with access to subsidised primary and secondary health care and routine dental services. Prior to October 2010 eligible patients were also provided with prescription medications free of charge. A nominal fee of €0.50 per prescription item was introduced in the 2010 budget. This increased to €1.50 per item in 2013. Eligibility is

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* ***Ex-factory price***: *The price of a particular drug item determined in accordance with the relevant agreement in force at that particular time between the Health Service Executive and representative bodies of manufacturers and importers of such items (152.).*

† VAT is 0% on oral medications and at the standard rate for other preparations (151).

based on Irish residency and on the outcome of a gross means income assessment. The weekly income threshold for GMS scheme eligibility is dependent on the marital status and age of the claimant (150). The GMS scheme is over represented by the elderly, females and the socially disadvantaged (149). According to the latest figures available from the HSE-PCRS, 1.7 million individuals, approximately 37% of the total population, were eligible for inclusion in the GMS scheme at the end of 2011 (157).

2.2 Comorbidity indices

2.2.1 RxRisk index

The RxRisk index was developed as a risk assessment instrument utilising automated ambulatory pharmacy data to identify chronic conditions and future health costs (158). It was developed by modifying the Chronic Disease Score (158). Development of the RxRisk included the construction of tables containing therapeutic classes and representative agents for selected chronic conditions (158). The validity of these conditions and therapeutic classes was reviewed by physicians during the development process. There are separate adult and paediatric forms of the RxRisk index (158). Twenty-six disease classes are included in the adult index (158). An individual may be classified as having one of the conditions in the index, if they have one prescription filled for the classified condition during a given timeframe (158).

2.2.2 RxRisk V index

The RxRiskV index was developed by adapting the RxRisk to include additional disease categories for assessing disease burden among older aged patients (>65 years) in the Veteran Health Administration (159). It is calculated from the sum of 45 potential disease groups derived from prescribing data using ATC classification codes (159). As with the RxRisk, individuals are classified as having a condition included in the RxRiskV, if dispensed at $\geq$1 prescription for the condition during a given time period (159).

2.2.3 Modification of the RxRisk and RxRisk V

The RxRisk and RxRiskV indices were adapted for the purposes of this research to include ATC codes for medications currently licensed in Ireland. Appendix 1 & 2 lists the ATC codes in the modified indices. Individuals are assumed to have one of the diseases included in the indices if they received three or more consecutive prescriptions of medication representing a specific disease class. Diabetes, although included in the RxRisk and RxRiskV, was removed from the modified indices as it was the index condition in this study.

2.3 Synopsis of validated instruments used in the Questionnaire study

2.3.1 The Morisky Medication Adherence Scale.

The Morisky Medication Adherence Scale is a frequently used adherence screening instrument (160). It was originally developed to assess medication adherence in patients with hypertension (161). Additional adherence studies have since validated the scale's reliability in other types of medication and in different patient settings (162-165). The Morisky scale is short and easy to use (160). It consists of four dichotomous yes/no questions that relate to previous medication use (160). Scoring of the Morisky scale is as follows; 1 point for yes; 0 point for no. A total score of 0 = high adherence, 1 - 2 points = medium adherence, 3 - 4 points = low adherence (165).

2.3.2 The EuroQoL- 5 Dimension (EQ-5D)

The EuroQoL - 5 Dimension (EQ-5D) is a standardised instrument that provides a single index value for health status (166). It has been validated for use in many languages (166). The EQ-5D has been designed for self-completion and is short and cognitively simple to use (166). It has been extensively used in patients with a wide range of health conditions (167-169) including diabetes (170, 171). The instrument is composed of a five item descriptive system of health states (it includes one item for each of the following; mobility, self-care, usual activity, pain/discomfort, and anxiety/ depression) and a visual analogue scale (VAS), (170). By utilising preference weights obtained from a sample population a single utility index score can be derived from the scores of the five health states (167). The original preference weights derived from samples of the UK population (172) are widely used (167).

2.3.3 The Summary of Diabetes Self-Care Activities Scale (SDSCA)

The Summary of Diabetes Self-Care Activities Scale (SDSCA) is a previously validated short self-report instrument, which measures the frequency of self-management activities across different aspects of the diabetes regimen, by the patient over the previous week (173). It consists of a number of items relating to diabetes self-care including general diet, specific diet, exercise, blood glucose testing, foot care and smoking (173). The SDSCA was originally developed in the US, but has since been translated into a variety of languages and used in several different countries (174-176). On the basis of a review of seven studies that had used the SDSCA a revised scale was proposed (173). The revised scale consists of 14 new questions in addition to a core set of 11 items, which had been included in the previous scale (173).

2.3.4 The Self-Administered Comorbidity Questionnaire (SCQ).

The Self-Administered Comorbidity Questionnaire (SCQ) is a brief validated self-administered comorbidity assessment instrument (177). It contains a list of twelve common medical problems, frequently addressed in general practice and often included in other comorbidity indices, for example diabetes, heart disease and kidney disease. Additional space is provided for the patient to specify three additional conditions, not included on the list. For each medical problem the patient is asked three yes/no dichotomous questions; i) Do you have the problem? ii) Do you receive treatment for it? and iii) Does it limit your activities? Positive answers to each question are scored 1 point. The maximum total score, which may be obtained by a patient, is 45 points if all 15 conditions are included; if the non-specified conditions are removed the maximum total is 36 points (177). Previous research has shown that the SCQ has a modest correlation with the frequently used medical record based Carlson Comorbidity Index (177). The SCQ has been used in several studies to assess comorbidity in patients with different index conditions (178-180) .

2.4 Ethical approval and methodological challenges.

The studies that used data obtained from the HSE-PCRS (Chapters 3 – 6), did not require ethical approval from a research ethics committee. A specific agreement between the HSE-PCRS and the Department of Pharmacology and Therapeutics (Trinity College Dublin) allows for the secondary analysis of PCRS data for specific research purposes by staff and students affiliated with the department. Informed patient consent was not required for these studies as the use of anonymised data puts it outside the remit of the Data Protection Act (181-183).

Ethical approval for the patient questionnaire study (Chapter 7) was obtained from the Joint Research Ethics Committee of St James's Hospital and The Adelaide Meath and National Children's Hospital Tallaght (AMNCH) (*Appendix 4*). The selection of potential participants from the hospital based administrative database (DIAMOND) in the Diabetes Day Centre (DDC) in St James's Hospital presented a number of methodological challenges, which were subsequently overcome. Permission to recruit potential participants from patients recorded in the DIAMOND database was required. This was sought and obtained from the Consultant Endocrinologist in charge of the DDC. The personal nature of the data contained within DIAMOND (184) meant that in order to remain compliant with the Data Protection Act (181, 182), only a member of hospital staff could access the database. The retrieval of data required for this study was facilitated by the Clinical Nurse Manager, who organised for the extraction of relevant data to be conducted by an administrator within the DDC. The candidate provided a list of 500

randomised numbers that had been previously generated (www.randomization.com). The Clinical Nurse Manager also facilitated the sending out of the patient questionnaires.

2.5 Statistical analysis

The statistical analysis performed is explained in detail in the data analysis section of each individual chapter. SAS statistical software version 9.1 (SAS, Cary, NY) was used for the statistical analysis. Statistical significance at $p<0.05$ was assumed for all statistical tests. Categorical variables are presented as percentages. For the logistic regression analysis results are presented as Odds Ratio (OR) with 95% confidence intervals (CI). For Cox proportional hazard analysis results are presented as Hazard Ratios (HR) with 95%CI. The results of the bootstrapping analyses in Chapter 3 and 4 are presented in Euro (€). The nonparametric Mann Whitney and Kruskal Wallis tests were used in the univariate analysis to assess the association between EQ-5D score and other covariates.

Chapter 3: The prevalence and ingredient cost of chronic comorbidity in the Irish elderly population with medication treated type 2 diabetes: A retrospective cross-sectional study using a national pharmacy claims database.

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3.1 Abstract

Background: Comorbidity in patients with diabetes is associated with poorer health and increased cost. The aim of this study was to investigate the prevalence and ingredient cost of comorbidity in patients ≥65 years with and without medication treated type 2 diabetes using a national pharmacy claims database.

Methods: The Irish Health Service Executive Primary Care Reimbursement Service pharmacy claims database, which includes all prescribing to individuals covered by the General Medical Services scheme, was used to identify the study population (≥65 years). Patients with medication treated type 2 diabetes (T2DM) were identified using the prescription of oral anti-hyperglycaemic agents alone or in combination with insulin as a proxy for disease diagnosis. The prevalence and ingredient prescribing cost of treated chronic comorbidity in the study population with and without medication treated T2DM were ascertained using a modified version of the RxRiskV index, a prescription based comorbidity index. The association between T2DM and comorbid conditions was assessed using logistic regression adjusting for age and sex. Bootstrapping was used to ascertain the mean annual ingredient cost of treated comorbidity. Statistical significance at $p<0.05$ was assumed.

Results: In 2010, 43,165 of 445,180 GMS eligible individuals (9.7%) were identified as having received medication for T2DM. The median number of comorbid conditions was significantly higher in those with T2DM compared to without (median 5 vs. 3 respectively; $p<0.001$). Individuals with T2DM were more likely to have ≥5 comorbidities when compared to those without (OR=2.82, 95% CI=2.76-2.88, $p<0.0001$). The mean annual ingredient cost for comorbidity was higher in the study population with T2DM (€1238.67, 95% CI = €1238.20 - €1239.14) compared to those without the condition (€799.28, 95% CI = €799.14 - € 799.41).

Conclusions: Individuals with T2DM were more likely to have a higher number of treated comorbid conditions than those without and this was associated with higher ingredient

costs. This has important policy and economic consequences for the planning and provision of future health services in Ireland, given the expected increase in T2DM and other chronic conditions.

3.2 Background

Diabetes is increasingly being recognised as a major global health concern (3). The prevalence of diabetes has increased globally (185) and it is projected that worldwide the prevalence will increase from an estimated 2.8% in the year 2000 to 4.8% by 2030 (32). This increase has been attributed to a rise in the incidence of type 2 diabetes (T2DM) (3), the most common type of diabetes (2), and has been driven primarily by increasing levels of obesity, inactivity and population aging (3).

Comorbidity, the co-existence of one or more additional conditions in persons with a specified index medical condition (52), is highly prevalent in patients with diabetes (75). In the United States the majority of adults with diabetes have more than one comorbid condition (75) and 40% have 3 or more conditions (76). A number of different frameworks have been developed that categorise comorbid conditions according to their influence on the clinical management of the index condition (51). The most recent was developed by Piette & Kerr (79) and has since been used in a number of published studies (56, 186, 187). The original paper classified chronic comorbid conditions as being either concordant or discordant with diabetes. Concordant conditions are those associated with diabetes, i.e. they represent part of the same overall pathophysiological risk profile and share the same medical management plan (e.g. hypertension, ischemic heart disease, and hyperlipidaemia) (56, 79). In contrast, discordant conditions are not pathophysiologically associated with diabetes and consequently their management may be different (e.g. arthritis, chronic obstructive pulmonary disease, depression) (56, 79).

In terms of the patient, comorbidity is associated with reduced health status, decreased quality of life and increased risk of mortality (52). Patients with diabetes are required to manage their condition in order to obtain and maintain optimal outcome measures (188). Depending on the symptoms and severity of the comorbid condition(s) present, patients' prioritisation and self-management may be compromised and / or complicated (80, 87). Patients with multiple conditions may encounter conflicting medical advice and fragmented care pathways which may provide a barrier to effective self-management (87, 189). The management of comorbid conditions may also indirectly affect diabetes self-care by representing an additional demand on patient time, effort and financial resources (79).

In terms of the health service, comorbidity is associated with increased health care utilisation (190) and economic cost (191-194). In the Irish CODEIRE study, which estimated the economic cost of diabetes in Ireland, complications related to diabetes accounted for the majority (61.7%) of all patient costs (47). This is consistent with the results of previous research conducted in Europe (44). However, these studies did not include any cost analysis relating to discordant comorbidity.

It is evident from the published literature, that comorbidity has substantial implications in terms of self-care and health service provision. At present, few Irish studies have examined the subject of comorbidity in relation to diabetes. Those that have been published have concentrated on the prevalence or impact of a single comorbid condition (195-197). The aim of this study was to investigate and estimate the prevalence, type and ingredient cost of chronic comorbid conditions occurring in elderly Irish individuals with T2DM, compared to those without T2DM ,using a modified version of the RxRisk V comorbidity index, based on data obtained from a national pharmacy claims database.

3.3 Methods

A retrospective cross-sectional study, utilising the Irish Health Service Executive Primary Care Reimbursement Service (HSE-PCRS) national pharmacy claims database was conducted using data from 2010. The HSE-PCRS database is used primarily to provide financial reimbursement to health care professionals involved in primary care for the provision of health services and prescription medications under a number of different state provided health care schemes, including the General Medical Services scheme (GMS) (150). The GMS scheme provides eligible individuals, termed "medical card" patients, with access to free health care, routine dental services and prescription medication (150). Eligibility for the GMS scheme is based on an individual being ordinarily resident in Ireland and the outcome of a gross income means assessment. The weekly income threshold for GMS scheme eligibility is dependent on the marital status and age of the claimant (150). Older individuals aged $\geq$70 years were automatically entitled to a medical card regardless of their income from July 2001 – Dec 2008 (150). In 2010 the GMS scheme covered half (50.4%) of the Irish population aged between 65-69 years and 98.4% of the population aged $\geq$70 years or more (based on population estimates) (198, 199).

The HSE-PCRS collates information on dispensed prescribed medication for the GMS scheme on a monthly basis. Medications dispensed through the GMS scheme are recorded in the HSE-PCRS and are coded using the WHO Anatomical Therapeutic Chemical (ATC) classification system. The ingredient drug cost (derived from the sum of

the ex-factory price and whole sale mark-up), pharmacist dispensing fee and value added tax (VAT) for each medication, dispensed to GMS eligible patients are recorded in the HSE-PCRS database. This information is used to calculate the total cost of each item dispensed through the GMS and other community health schemes (153). In addition to providing details on medications dispensed to eligible individuals, the HSE-PCRS pharmacy claims database also contains demographic information about the claimant such as age, sex and region of residence. The HSE-PCRS pharmacy claims database does not contain clinical information regarding diagnosis, clinical outcome or over the counter (OTC) medication which may be obtained without a prescription (155). Permission to use this database for research purposes was obtained from the HSE-PCRS.

The study population consisted of elderly individuals aged ≥65 years who were eligible for inclusion in the GMS scheme and who had received medication documented in the HSE-PCRS database during the study period. The eligible elderly cohort were categorised by sex and subdivided into three age groups; 65-69, 70-74 and ≥75 years. Individuals with T2DM were identified using the prescription of any oral anti-hyperglycaemic (OAH) agent (ATC, A10B) either prescribed alone or in combination with any type of insulin (ATC, A10A), as a proxy for disease diagnosis. For the purposes of this paper the study population identified as having received medication for T2DM are referred to as the T2DM group. Individuals who did not receive any OAH agents during the study period were used as the comparator group for the analysis, and are referred to as the non T2DM group.

The burden of pharmacologically treated comorbidity in both the T2DM and the non T2DM group was ascertained using a modified version of RxRiskV index. The RxRiskV is a previously validated pharmaceutical based comorbidity index which is calculated from the sum of 45 potential disease groups derived from prescribing data using ATC classification codes (159). The RxRiskV index was adapted for the purposes of the current study to include updated ATC codes for medications currently licensed in Ireland. Appendix 1 lists the medications and ATC codes used in the current study. In its original form, individuals were classified as having one of the conditions listed in the RxRiskV index if they had received at least one prescription filled for a disease class during a given study period (159). This was modified in the present study to reflect the chronic nature of disease categories listed in the RxRiskV index. In the present study individuals were assumed to have one of the diseases if they received at least three consecutive prescriptions of a medication representing a specific disease class. In order to include the maximum number of elderly individuals fitting these criteria the study period was extended to sixteen months to include the last two months of 2009 and the first two months of 2011. Diabetes

was excluded from the modified version of the RxRisk V index as it was the disease of interest. This modified version of the RxRisk V index is referred to as RxRiskV (mod). Ethical approval for this study was not required as the analysis for this study was carried out on an anonymised database.

3.4 Data analysis

The comorbidity score was determined by calculating the maximum RxRiskV (mod) score for each individual and then grouping them according to their T2DM status. As the proportion of the study cohort with more than 10 conditions was small (0.78%) individuals with $\geq$10 were grouped together into a single category. The median comorbidity level, inter quartile range and the prevalence of the most common comorbid conditions defined by the RxRiskV (mod) was calculated in those with and without T2DM. The association between T2DM and individual conditions in the RxRiskV (mod) index was assessed using the chi^2 test. The median number of comorbid conditions in the T2DM group was chosen as a proxy measurement to define low (<median) versus high (>=median) comorbidity. The association between T2DM and low versus high comorbidity was subsequently examined using the chi^2 test. Logistic regression analysis was performed to examine the relationship between the comorbid conditions and T2DM and adjusted for age (ref: 65-69 years) and sex (ref: female). The resulting associations are displayed as adjusted odds ratios with 95% confidence intervals (OR, 95%CI).

The total annual ingredient cost was calculated by summing the medication cost for each category included in the RxRiskV (mod) index for 2010. Bootstrapping was used to allow the comparison of means given the skewness of the cost data and replicated 2000 times so as to attain the 95% confidence interval (200). The cost data were subsequently stratified by age, sex, T2DM status and number of comorbid conditions. SAS version 9.1 was used for the data analysis. Statistical significance at $p < 0.05$ was assumed.

3.5 Results

During January to December 2010, 445,180 individuals aged $\geq$ 65 received at least three consecutive prescriptions recorded in the HSE-PCRS pharmacy claims database. Forty three per cent (191690 individuals) of the sample population were male. Half (50.3%) of the individuals were $\geq$75 years, 26.9% were 70 - 74 years and 22.8% were aged 65-69 years. In the study cohort 43165 individuals received three or more consecutive prescriptions for OAH agents. This represents a prevalence of 9.7% for T2DM in this elderly population. The prevalence of T2DM in this population was significantly higher in males (12.1%) compared to females (7.9%) ($p<0.0001$). The prevalence of T2DM was

highest in the middle age category 70 - 74 years, (10.1%) and lowest in the oldest study population ≥75 years (9.4%) ($p<0.0001$).

The median number of comorbid conditions was found to be significantly higher in the elderly cohort with T2DM (5 conditions, IQR 3-6) compared to the non T2DM group (3 conditions, IQR 1-5). The association between low versus high comorbidity was significant (X^2 =16355, df =10, $p <0.0001$). The odds of having ≥ 5 comorbid conditions was almost three times higher in the T2DM group compared with the non T2DM group (OR=2.82, 95% CI = 2.76-2.88, $p<0.0001$). In the study population with T2DM, females in the youngest (65-69 years) and middle (70-74 years) age categories had a higher median number of comorbid conditions when compared to males (5 vs. 4 conditions) (*Table 3.1*). In the non T2DM group there was no significant difference in the median number of comorbid conditions when stratified by age group and sex (*Table 3.1*).

The prevalence of 35 of the 45 conditions listed in the RxRiskV (mod) index was significantly higher in the group with T2DM than in the non T2DM group. The results from the logistic regression analysis on individual comorbid conditions included in the RxRiskV (mod) index with a prevalence of ≥10% in the elderly study cohort showed an increased likelihood of individuals with T2DM having received a prescription for these conditions. The prevalence of co-prescribing and the odds ratios adjusted for age and sex are summarised in *table 3.2.*

The majority of comorbidity in the group with T2DM related to concordant conditions or therapies associated with the cardiovascular system (CVS). A number of discordant conditions, were also significantly co-prescribed more often in the cohort with T2DM ($p<0.0001$). The most prevalent of these were gastric reflux and peptic ulcer, depression and chronic airway disease. The prevalence of co-prescribed medication for osteoporosis was, however, significantly lower in the cohort with T2DM (OR = 0.73, 95%CI = 0.70-0.75, $p<0.0001$) when compared to the control group.

Table 3.1 Median number of comorbid conditions stratified by age, sex and T2DM status (Total n = 445,180.)

Sex	*Age*	*T2DM group (n 43165)*	*T2DM Median no. of comorbid conditions [IQR]*	*Non T2DM Group (n 402015)*	*Control Median no. of comorbid conditions [IQR]*
Male					
	65 - 69	5535	4 [3 – 6]	38606	3 [1 – 4]
	70 - 74	6948	4 [3 – 6]	50023	3 [1 – 5]
	≥75	10690	5 [3 – 6]	79888	4 [2 – 5]
Female					
	65 - 69	4610	5 [3 – 6]	52770	3 [1 – 4]
	70 - 74	5109	5 [4 – 6]	57726	3 [1 – 5]
	≥75	10273	5 [4 – 7]	123002	4 [2 – 6]

Table 3.2 Chronic medical conditions included in the RxRiskV (mod) index with ≥10% prevalence in the study population.

RxRiskV(mod) category	*Non T2DM (%)*	*T2DM (%)*	*Adjusted ** Odds Ratio*	*95% CI*
Concordant conditions /therapies				
Cardiovascular system				
Hyperlipidaemia	42.6	78.5	4.95	4.83 - 5.06
Anti-platelet agents*	39.8	71.7	3.84	3.76 - 3.93
Heart disease	39.4	61.4	2.44	2.39 - 2.49
Hypertension	21.7	32.2	1.79	1.75 - 1.83
Discordant conditions /therapies				
Digestive system				
Gastric reflux and peptic ulcer	34.5	46.4	1.67	1.63 - 1.70
Mental health				
Depression	16.0	20.5	1.46	1.43 - 1.50
Respiratory system				
Chronic airway disease	14.4	18.6	1.35	1.32 - 1.40
Musculoskeletal				
Osteoporosis	14.3	9.3	0.73	0.70 - 0.75
Pain management				
Anti-inflammatory agents	13.0	14.1	1.14	1.11 - 1.18
Pain (Opiates)	10	12.9	1.40	1.38 - 1.47

* Non-specific marker for cardiovascular disease
** Adjusted for age and sex

The mean annual ingredient cost of comorbidity in the study population with T2DM was higher (€1238.67, 95% CI = €1238.20 - €1239.14) than for the control group (€799.28, 95% CI = €799.14 - € 799.41). When the cost data was stratified by age and sex, a similar significant difference between groups was observed in both men and women with the mean ingredient cost of comorbidity increasing with increasing age (*Table 3.3*). The mean drug ingredient cost of comorbidity was higher in women compared to men across all age categories in the study population with T2DM, and was also higher in women in the middle (70-74 years) and oldest (≥75 years) age categories in the study population without T2DM (*Table 3.3*). Further analysis of the cost data, stratified by number of comorbid conditions, found that the mean annual ingredient cost of chronic comorbidity was higher in the non T2DM group compared to the group with T2DM in patients with a low number (≤2) of comorbid conditions. Conversely, in the study population with a high number (≥4) of comorbid conditions, the mean annual ingredient cost was higher in the T2DM group compared to the group without T2DM. There was no difference in the mean annual ingredient cost between the two groups in patients with three comorbid conditions. These results are summarised in *Table 3.3*

Table 3.3 Mean annual ingredient cost of chronic comorbidity in the study population with and without T2DM

Sex	*Age (yrs.)*	*T2DM group (€)*	*Non T2DM group (€)*	*Cost ratio **
Male				
	65-69	**1183. 43** [1182.12, 1184.75]	**683. 85** [683.41, 684.28]	1.73
	70-74	**1184. 35** [1183.22, 1185.47]	**744. 02** [743.67, 744.37]	1.59
	≥75	**1245. 51** [1244.65, 1246.36]	**871. 33** [871.02, 871.65]	1.45
Female				
	65-69	**1223. 89** [1222.43, 1225.31]	**667.52** [667.16, 667.88]	1.83
	70-74	**1293. 06** [1291.74, 1294.38]	**764.89** [764.57, 765.22]	1.69
	≥75	**1279. 10** [1278.05, 1280.14]	**882.95** [882.71, 883.18]	1.45
No. of comorbid conditions				
0		**0**	**0**	1
1		**193. 45** [192.82, 194.08]	**225.02** [224.86, 225.17]	0.86
2		**386. 59** [385.99, 387.20]	**414.52** [414.34, 414.69]	0.93
3		**628. 65** [628.10, 629.21]	**628.35** [628.15, 628.54]	1
4		**897. 08** [896.42, 897.74]	**874.86** [874.60 , 875.11]	1.03
5		**1186. 88** [1186.14, 1187.62]	**1153.70** [1153.38, 1154.02]	1.03
6		**1485. 14** [1484.16, 1486.13]	**1454.08** [1153.38, 1154.02]	1.02
7		**1807.74** [1806.40, 1809.08]	**1764.68** [1764.05, 1765.31]	1.02
8		**2130. 86** [2129.05, 2132.67]	**2078.91** [2078.03, 2079.79]	1.03
9		**2461. 44** [2458.71, 2464.17]	**2436.44** [2435.00, 2437.87]	1.01
≥10		**3151. 03** [3146.39, 3155.67]	**3023.80** [3022.13, 3025.46]	1.04

[95% Confidence Interval]
*T2DM group: non T2DM group.

3.6 Discussion

This is the first large scale study using a national pharmacy claims database in Ireland to investigate the prevalence, type and ingredient cost of comorbidity present in the elderly GMS eligible population (≥65 years) with and without T2DM. It has also successfully modified the RxRiskV index to include the ATC codes of pharmacological agents currently licensed for use in Ireland and strengthened the definition of "chronic" used in the original version, by specifying that an individual must have received a minimum of three consecutive prescriptions for a disease class. The results show that during the study period the elderly population with T2DM had a higher level of comorbidity and associated drug costs when compared to the non T2DM group. These results are similar to the findings of previous studies that investigated comorbidity in diabetic populations in Finland and Australia (201, 202).

Overall cardiovascular-related concordant conditions accounted for a substantial proportion of the comorbidity in the study cohort both with and without T2DM. A higher level of cardiovascular-related comorbidity in patients with T2DM has been reported before (201, 203) and reflects the established association between T2DM and conditions affecting the cardiovascular system (204). The high rate of co-prescription of anti-platelet therapy, anti-hypertensive medication and cholesterol lowering agents in patients with T2DM also suggests prescriber adherence to the current Irish cardiovascular health policy which advocates active and aggressive management of cardiovascular risk factors in individuals with diabetes (205).

The most prevalent discordant comorbid conditions in the current study were gastric reflux/peptic ulcer, depression and chronic airway disease. This is consistent with the findings of a previous Australian study that used RxRiskV index to examine the level of comorbidity in a cohort of veterans with T2DM (202). It is possible that the higher frequency of co-prescribing treatment for gastric reflux/ peptic ulcer in the cohort with T2DM may reflect the use of proton pump inhibitors (PPIs) as a gastroprotective agent in patients taking the OAH agents rather than the presence of gastrointestinal morbidity.

Previous studies that have investigated comorbidity in populations with diabetes have also reported an increase in the prevalence of depression (206, 207). The frequency of co-prescription of anti-depressant medication in the current study was significantly higher in the cohort with T2DM. There is conflicting evidence as to whether there may be a physiological basis for the observed association between diabetes and depression or

whether it is due to psychosocial stress associated with having a chronic condition (208). There is evidence, however, to suggest that the presence of comorbid depression in individuals with diabetes is associated with poorer medication adherence (209) and an increased risk of diabetes related complications (210). It is imperative therefore, that depression in patients with T2DM is recognised and treated given the adverse outcomes associated with such comorbidity.

Osteoporosis was the only condition included in the RxRiskV (mod) index with a prevalence of $\geq$10% in the study cohort as a whole that was prescribed far less frequently in the cohort with T2DM. This finding is perhaps unexpected as a recent meta-analysis demonstrated that individuals with diabetes have an increased risk of various types of bone fracture (211). The result of a previous study, which also utilised PCRS data, suggested that anti-osteoporotic medication in general is under-prescribed with only a fifth of GMS eligible patients who potentially had osteoporosis prescribed medication (212). It is possible that the result of the present study may infer a further inadequacy in the level of prescribing of anti-osteoporotic medication in elderly patients with T2DM.

Research has shown that elderly patients with multiple unrelated medical conditions may be undertreated (213). Health professionals attending to patients with chronic conditions must remain vigilant for other disorders to ensure they are treated appropriately (213). This is particularly important, considering information relating to the care of patients with multiple conditions is scarce (52). Evidence based guidelines established for the treatment of diabetes and other major chronic conditions have focused too narrowly on the management of single conditions (79) and may not be appropriate for patients with comorbidity unrelated to the index condition. This should be taken into consideration when proposing new health strategies. Policy makers should alter the focus of initiatives away from individual diseases towards policies that reflect the holistic requirements of individuals with multiple conditions (76, 214).

The economic liability posed by diabetes has been discussed extensively in the published literature (47). It has been well documented that the treatment of complications associated with diabetes account for the majority of the economic cost associated with patient care (47). The cost analysis presented in the current study focuses solely on the ingredient cost of prescription drugs and did not include other expenses such as health care utilisation or patient out-of-pocket expenses. The results of the current analysis suggest that the treatment of comorbid conditions (both concordant and discordant) pose a significant additional annual ingredient cost in the GMS eligible elderly population with T2DM

compared to the study population without the condition. It would, therefore, be advisable that both types of comorbidity be taken into consideration in future economic evaluations of costs associated with diabetes.

The results of this study have important clinical implications for both patients and health professionals. There are also substantial economic implications for decision makers responsible for providing the most cost-effective health care. The results of the current study indicate that those with T2DM have a greater number of comorbid conditions, both related and unrelated to diabetes, and that these are associated with substantial increased cost. Increased education and earlier intervention programme for patients with diabetes are needed so as to avoid the costly consequences of poor adherence and management of their condition. A structured management care programme provided in general practice, in conjunction with a multi-disciplinary team of health professionals; with direct and immediate access to specialist services as required, would facilitate this greatly. In Ireland, this type of programme has been implemented in the Midlands health region for patients with diabetes and has produced encouraging results (215). The nationwide implementation of this type of programme could yield an overall improvement in patient management and costs associated with diabetes.

The present study has a number of limitations. The HSE-PCRS pharmacy claims database upon which the data for this study was based does not contain clinical diagnoses. As a result patients with T2DM were identified in study population using the prescription of any OAH agents, with or without insulin, as a proxy for disease diagnosis. This definition was unable to take into account patients with T2DM who were treated using diet alone. In spite of this methodological limitation it is likely that the present study has captured the majority of diagnosed T2DM in the study population, given the results of a previous community based study that reported that the majority of patients (74%) with T2DM were treated with OAH agents (34). In addition, the current study was unable to take into account patients with medication treated T2DM who did not meet the eligibility criteria for the GMS scheme. It is possible that non medical card patients may have received their diabetes medication through other community drug schemes such as the Long Term Illness (LTI) scheme or Drugs Payment Scheme (DPS) or paid for their medications privately. In 2010, medical card holders represented a very high proportion of the Irish elderly population $\geq$ 70 years (98.4%). It is, therefore, likely that the results of the present study represent an accurate account of medication treated T2DM, comorbidity and the associated ingredient cost in this age group. For the age group 65-69 years, only half are eligible for the GMS scheme, which may represent a slightly more deprived and

sicker population. Previous research has indicated that medical card holders on average visit their doctor more frequently per year (216) and have poorer health (217) when compared to non medical card holders. There are limitations to using the bootstrapping methods including the assumption that the distribution of the data from the sample is a reasonable estimate of the population distribution from which it came. Given the very large sample size and the high percentage of the population captured this is unlikely to be a major source of bias. There may also have been some sampling error in the selection of random samples in the bootstrap procedure, but with 2000 samples chosen this is unlikely. Finally, a medication listed for one disease category in the RxRiskV (mod) may have a number of indications for use. In order to limit the effect of this in the present study, medications with more than one indication were assigned to a single disease category based on their major therapeutic use. This assessment was carried out in consultation with a clinician with expertise in pharmacology and regulatory affairs.

3.7 Conclusions

This study has shown that older patients with T2DM in Ireland have a greater prevalence of comorbidity when compared to those without the condition. It has also shown increased economic cost in terms of drug expenditure for both concordant and discordant comorbidity in this study population. These findings highlight the need for health policy makers and economists to ensure that both concordant and discordant comorbid conditions are taken into account when planning for future health care needs of those with diabetes.

Chapter 4: The prevalence and ingredient cost of chronic comorbidity in young and middle aged GMS eligible adults with pharmacologically treated type 2 diabetes

4.1 Abstract

Background: The presence of comorbidity in patients with type 2 diabetes (T2DM) is associated with negative outcomes for both patients and the health service. The aim of this study was to examine the prevalence and ingredient cost of chronic comorbidity in young and middle aged adults (25 - 64 years) with and without pharmacologically treated T2DM

Methods: The Irish Health Service Executive Primary Care Reimbursement Service pharmacy claims database, was used to identify the study population aged 25 - 64 years who were eligible for inclusion in the General Medical Scheme (GMS). The prescription of any oral anti-hyperglycaemic agents prescribed either alone or in combination with insulin was used as a proxy for disease diagnosis for pharmacologically treated T2DM. The prevalence and ingredient cost of treated chronic comorbidity in the study population with and without pharmacologically treated T2DM were ascertained using a modified version of the RxRisk index, a prescription based comorbidity index. Logistic regression analysis, adjusting for age and sex, was used to assess the association between T2DM and comorbid conditions. The mean annual ingredient cost of pharmacologically treated comorbidity was obtained using bootstrapping.

Results: In 2010, 21,877 of 674,026 GMS eligible individuals (3.14%) were identified as having received OAH medication for T2DM. The median number of comorbid conditions was significantly higher in those with T2DM compared to without (median 3 vs. 0 respectively; $p<0.0001$). In adjusted analysis patients with T2DM were more likely to have ≥ 3 comorbidities when compared to those without the condition (OR=7.17, 95% CI = 6.95, 7.39, $p<0.0001$). The mean annual ingredient cost of comorbidity in the study population with T2DM was higher (€981.73, 95% CI = €981.02, €982.45) compared to those without the condition (€264.44, 95% CI = €264.37, €264.51).

Conclusions: Adult GMS eligible patients with treated T2DM had a higher number of chronic treated comorbidities compared to those without T2DM with associated higher ingredient drug costs. This has implications for society both in terms of loss of productivity through ill-health and increased economic expenditure. Policy should, therefore, prioritise measures to prevent or delay the onset of T2DM in this age group.

4.2 Background

Type 2 diabetes mellitus (T2DM) is the most prevalent form of diabetes, accounting for approximately 90% of cases of the condition worldwide (11). Increasing age is an important non-modifiable risk factor for the development of the disease (4), with diagnosis most frequently made in patients over the age of 40 years and highest in those aged between 60 - 70 years (5). However, the results of a number of studies suggest that the average age of onset for T2DM is decreasing (7, 218) due to the increase in the prevalence of obesity (8).

Younger adults with T2DM are more likely to report worse diabetes self-care, higher diabetes-related distress and poorer glycaemic control, when compared to older patients with the condition (219). In addition, younger patients are more likely to require insulin therapy compared to older patients (220). Previous studies have also suggested that patients diagnosed with T2DM at a younger age may develop serious diabetes-related complications faster than patients who acquire T2DM later in life (221).

The co-occurrence of one or more medical conditions in a patient with a specified index disorder (e.g. diabetes) is referred to as comorbidity (52). Comorbidity is common in patients with T2DM (78), and has been classified as being either concordant or discordant with diabetes (79). Concordant conditions are those which are associated with diabetes, they represent part of the same overall pathophysiological risk profile and are likely to share a similar medical management plan (79). In contrast, discordant conditions are regarded as discrete entities (i.e. they do not share a pathophysiological association with diabetes) and as a consequence their medical management may be different (79).

The presence of comorbidity in patients with T2DM may complicate its treatment (222) and has been shown to have a negative effect on patient's quality of life (139, 140), diabetes self-care (87) and the risk of mortality (52). Furthermore, comorbidity has also been shown to have adverse implications for the provision of health services, as it is associated with higher health care utilisation (190, 223) and increased economic cost (192, 193). Many of the studies that have investigated the prevalence and / or impact of comorbidity in patients with T2DM have concentrated solely on cohorts of elderly patients ($\geq$65 years) (202, 224, 225) The aim of this study was to examine and estimate the prevalence, type and ingredient cost of both concordant and discordant chronic comorbid conditions in young and middle aged adults with pharmacologically treated T2DM compared to a cohort of patients without the condition.

4.3 Methods

The Data Source

A retrospective cross-sectional study, using national pharmacy claims data obtained from the Irish Health Service Executive Primary Care Reimbursement Service (HSE-PCRS) was carried out using dispensing data from 2010. The primary function of the HSE-PCRS is to reimburse the provision of health care services and prescription medication in Ireland, provided through a number of national schemes, including the General Medical Services scheme (GMS) (150). This scheme provides free healthcare and prescription medication to patients meeting certain eligibility criteria, which are based on Irish residence and the outcome of an income assessment (150). The GMS scheme is over represented by women, children and older adults aged 70 years and over. Approximately one third of the Irish population overall are eligible for inclusion in the GMS.

Prescription medications dispensed through the GMS scheme are recorded in the HSE-PCRS database using the World Health Organisation (WHO) Anatomical Therapeutic Chemical (ATC) classification system (155). The ingredient drug cost (derived from the sum of the ex-factory price and whole sale mark-up), pharmacist dispensing fee and value added tax (VAT) for each medication, dispensed to GMS eligible patients are recorded in the HSE-PCRS database. This information is used to calculate the total cost of each item dispensed through the GMS and other community health schemes (153). In addition, the HSE-PCRS pharmacy claims database also collates basic demographic information, including the age, sex and region of residence of each patient. The database does not, however, collect any clinical information relating to the patient (155). Permission to use the HSE-PCRS data for research purposes was obtained from the HSE-PCRS. Approval by an ethics committee for the present study was not required as anonymised data were used.

Study population

The study population was composed of GMS eligible adults, aged between 25 – 64 years, who were dispensed prescription medication as recorded in the HSE-PCRS database during the study period. The dispensing of any oral anti-hyperglycaemic (OAH) agent (ATC A10B) either alone or in combination with any type of insulin (ATC A10A) was used as a proxy diagnosis for T2DM. For the purpose of this analysis, patients who were dispensed OAH therapy (with or without insulin) were referred to as the T2DM group. In keeping with previous diabetes research, patients with T2DM aged between $\leq$44 years were categorised as having early onset T2DM, whereas patients aged $\geq$ 45 years were categorised as having usual onset T2DM (220, 226). GMS eligible patients who were not

dispensed OAH therapy at any time were used as the comparator group, and are referred to as the control group.

Comorbidity

The prevalence of treated comorbidity in both patient cohorts was determined using a modified version of RxRisk index. The RxRisk is a validated pharmaceutical based comorbidity index, calculated from the sum of 26 potential disease groups that are derived from prescribing data using ATC classification codes (158). The RxRisk index was modified for the purpose of this study to include a list of revised ATC codes for medications that are currently licensed for use in Ireland. The medications and ATC codes included in the modified index are listed in Appendix 2.

A person may be classified as having any of the conditions included in the RxRisk provided that they were dispensed at least one medication for a disease class during the study period (158). For the purpose of the present study, patients were classified as having one of the disease classes in a modified RxRisk index if they were dispensed a minimum of three consecutive monthly prescriptions of a medication representing a specific disease class. This revision was made in order to represent the chronic nature of the conditions included in the modified index. In addition, although diabetes is included in the original version of the RxRisk, the condition was removed from the revised index as it was the disease of interest. This revised form of the RxRisk index, adapted for use in the present study, is subsequently referred to as the RxRisk (mod). In order to capture of largest number of patients fitting the eligibility criteria for chronicity; the study period was extended to sixteen months, so as to take into account patients who were dispensed medication pertaining to a specific condition in either the last two months of 2009 or the first two months of 2011.

In order to examine the overall prevalence and ingredient cost of different types of comorbidity, two comorbidity sub-scores were developed. Chronic conditions and therapies included in the modified index assessed to be concordant with diabetes (cardiovascular condition/therapies) were used to develop the concordant sub-score. All other conditions and therapeutic agents were used to develop the discordant comorbidity sub-score. Subsequently a single variable was derived to categorise whether comorbid conditions were absent, concordant only, discordant only, or both concordant and discordant.

4.4 Data analysis

The comorbidity score was ascertained by calculating the maximum RxRisk (mod) score for each patient and then classified according to their diabetes status. As the percentage of patients with 10 or more conditions was very small (0.01%), patients falling into this category were classified as a single group. The median number of comorbid conditions, inter quartile range and the prevalence of the most common comorbid conditions defined by the RxRisk (mod) was calculated in those with and without the index condition. The chi square test was used to examine the association between T2DM and individual conditions in the RxRisk (mod) index. The median number of comorbid conditions in the T2DM group was chosen as a proxy measurement to define low (<median) versus high (>=median) comorbidity. The chi square test was also used to assess the association between T2DM and low versus high comorbidity.

Logistic regression analysis was used to assess the association between T2DM different types of comorbidity (ref: no comorbidity), adjusting for age (ref: 25 – 34 years) and sex (ref: female). In addition, logistic regression analysis was also used to assess potential associations between specific comorbid conditions and T2DM, adjusting for age and sex. The results of these analyses are presented as adjusted Odds Ratios (ORs) with 95% confidence intervals (95%CI).

The total annual ingredient cost was calculated by adding the medication cost for each category included in the RxRisk (mod) for the study period. The bootstrapping method was used to allow the comparison of means given the skewness of the cost data and replicated 2000 times so as to attain the 95% confidence interval (200). The cost data were then stratified by age, sex, T2DM status, number and type of comorbid conditions. SAS version 9.1 was used for the data analysis. Statistical significance at $p < 0.05$ was assumed.

4.5 Results

A total of 695,903 individuals aged 25-64 years, were eligible for inclusion in the present study. Forty four per cent (303,869 individuals) of the study population were male. In the study cohort 21,877 individuals received three or more consecutive prescriptions for OAH agents. This represents a prevalence of 3.1% for treated T2DM in the study population. The vast majority (84%) of these patients were in the normal age range ($\geq$45 years) for T2DM. The prevalence of T2DM was highest in the oldest (55 – 64 years) age category compared to the youngest age group (25 – 34 years) ($p<0.0001$). The prevalence of

treated T2DM in this population was higher in males (4.0%) compared to females (2.5%) which was statistically significant ($p < 0.0001$).

The majority (94%) of patients with pharmacologically treated T2DM were prescribed medication for at least one medical condition or therapy included in the RxRisk (mod) index compared to 41% of the control group ($p<0.0001$). The median number of comorbid conditions was also found to be significantly higher in the adult cohort with treated T2DM (3 comorbid conditions, IQR 2-5) compared to the control group (0 comorbid conditions) ($p<0.0001$) (*Table 4.1*). The association between T2DM and low versus high comorbidity was significant ($p<0.0001$). The odds of having $\geq$ 3 comorbid conditions was seven times higher in the T2DM group compared with the control group (OR=7.17, 95% CI = 6.95, 7.39, $p<0.0001$). In those with T2DM, males in the youngest (25 - 34 years) age category had a higher median number of comorbid conditions when compared to females (2 vs. 1 condition) (*Table 4.1*).

Table 4.1 Median number of comorbid conditions stratified by age, sex and T2DM status (Total n = 695,903.)

Sex	*Age*	*T2DM group (n 21,877)*	*T2DM Median no. of comorbid conditions [IQR]*	*Non T2DM Group (n 674,026)*	*Control Median no. of comorbid conditions [IQR]*
Male					
	25 – 34	300	2 [1 – 3]	78685	0 [0 – 0]
	35 – 44	1398	2 [1 – 4]	79381	0 [0 – 1]
	45 – 54	3540	3 [2 – 4]	67192	0 [0 – 2]
	55 – 64	6893	4[3 – 5]	66480	1 [0 – 3]
Female					
	25 – 34	594	1 [0 – 2]	124163	0 [0 – 0]
	35 – 44	1163	2 [1 – 4]	101431	0 [0 – 1]
	45 – 54	2658	3 [2 – 5]	77700	1 [0 – 2]
	55 – 64	5331	4 [3 – 5]	78994	2 [0 – 3]

The results of logistic regression analysis found that patients with treated T2DM were significantly more likely to be co-prescribed treatment for a concordant and / or discordant comorbidity when compared to the control group (*Table 4.2*). The prevalence of 22 of the 26 conditions listed in the RxRisk index, were significantly higher in the group with treated T2DM compared with the control group. Logistic regression analysis on individual comorbid conditions included in the RxRisk (mod) index with a prevalence of $\geq$5% in the study cohort showed an increased likelihood of patients with T2DM having received a prescription for these conditions. The prevalence of co-prescribing and the odds ratios adjusted for age and sex are summarised in *table 4.3*. The majority of comorbidity in the group with T2DM related to concordant comorbid conditions or therapies associated with the cardiovascular system (CVS). A number of specific discordant conditions, were also found to be co-prescribed more often in patients with T2DM compared to the control group ($p<0.0001$). The most prevalent of these were gastric reflux and peptic ulcer, depression and rheumatoid arthritis (*Table 4.3*).

Table 4.2 Adjusted OR for different types of comorbid conditions in patients with and without T2DM

Type of comorbidity	*Non T2DM (%)*	*T2DM (%)*	*Adjusted * Odds Ratio*	*95% CI*
No comorbid conditions	58.83	5.78	1.0	n/a
Discordant comorbidity only	22.95	7.57	3.14	2.92 – 3.38
Concordant comorbidity only	5.86	26.18	34.37	32.23 – 36.66
Both concordant and discordant comorbid conditions	12.36	60.47	37.95	35.70 – 40.35

*Adjusted for age, and sex

Table 4.3 Chronic medical conditions included in the RxRisk (mod) index with ≥5% prevalence in the study population.

RxRisk (mod) category	*Non T2DM (%)*	*T2DM (%)*	*Adjusted ** Odds Ratio*	*95% CI*
Concordant conditions /therapies				
Cardiovascular system				
Hyperlipidemia	11.5	75.0	14.94	14.4 – 15.5
Anti-platelet agents*	6.6	60.1	12.66	12.3 – 13.1
Heart disease	8.8	42.3	4.02	3.9 – 4.1
Hypertension	4.6	23.4	3.33	3.2 – 3.5
Discordant conditions /therapies				
Digestive system				
Gastric reflux and peptic ulcer	13.2	37.6	2.40	2.3 – 2.5
Mental health				
Depression	13.5	24.3	1.77	1.7 – 1.8
Anxiety	5.8	10.1	1.36	1.3 – 1.4
Respiratory system				
Asthma	6.9	17.4	2.00	1.9 – 2.0
Musculoskeletal				
Rheumatoid arthritis	8.3	18.0	1.56	1.5 – 1.6
Neurological				
Epilepsy	4.8	11.1	1.97	1.9 – 2.0

* Non-specific marker for cardiovascular disease

** Adjusted for age and sex

The mean annual ingredient cost of comorbidity in the study population with T2DM was much higher (€981.73, 95% CI = €981.02, €982.45) compared with the control group (€264.44, 95% CI = €264.37, €264.51). When the cost data was stratified by age and sex, a significant difference between the T2DM and the control group was observed in both men and women with the mean ingredient cost of comorbidity increasing with increasing age (*Table 4.4*). The mean drug ingredient cost of comorbidity was higher in women compared to men in all but the youngest age category in those with T2DM but, in contrast it was higher in men across all age categories in the control group (*Table 4.4*).

Table 4.4 Mean annual ingredient cost of chronic comorbidity in the study population with and without T2DM by sex and age.

Sex	*Age (yrs.)*	*T2DM group* *Cost in Euro (€)*	*Non T2DM group* *Cost in Euro (€)*	*Cost ratio **
Male				
	25 – 34	**689.07** [680.34 – 697.81]	**141.76** [141.58 – 141.94]	4.86
	35 – 44	**723.81** [721.28 – 726.34]	**214.11** [213.91 – 214.31]	3.38
	45 – 54	**981.38** [978.95 – 983.82]	**357.52** [357.26 – 357.79]	2.75
	55 – 64	**1018.53** [1017.44 – 1019.62]	**488.32** [488.05 – 488.60]	2.09
Female				
	25 – 34	**497.20** [493.56 – 500.85]	**88.38** [88.28 – 88.48]	5.63
	35 – 44	**765.26** [762.29 – 768.23]	**173.33** [173.18 – 173.49]	4.42
	45 – 54	**1042.03** [1040.11 – 1043.95]	**342.33** [342.10 – 342.56]	3.04
	55 – 64	**1088.38** [1087.11 – 1089.64]	**486.94** [486.70 – 487.19]	2.24

[95% Confidence Interval]
* T2DM group: non T2DM group

Examination of the cost data, stratified by the number of comorbid conditions, found that the mean annual ingredient cost of chronic comorbidity was higher in patients in the control group with up to 4 comorbid conditions when compared to patients with T2DM with the same number of comorbid conditions (*Table 4.5*). In contrast, in the study population with 7 or more chronic comorbid conditions, the mean annual ingredient cost was significantly higher in patients with T2DM than in the control group (*Table 4.5*). The results

for the population with 5 or 6 comorbid conditions did not follow any particular trend (*Table 4.5*).

The stratification of the cost data by type of comorbidity found that the ingredient cost of comorbidity was higher in patients with T2DM compared to controls regardless of type of comorbidity present (*Table 4.5*). Additional examination of the cost data, stratified by age and comorbidity type, found that ingredient cost of chronic comorbidity was higher in patients with usual onset T2DM compared to those with early onset T2DM (*Table 4.6*).

Table 4.5 Mean annual ingredient cost of chronic comorbidity in the study population with and without T2DM by number and type of comorbidity.

	T2DM group Cost in Euro (€)	Non T2DM group Cost in Euro (€)	Cost ratio *
No. of comorbid conditions			
0	**0**	**0**	1
1	**225.67** [225.02 – 226.31]	**240.11** [239.99 – 240.23]	0.93
2	**445.18** [444.44 – 445.92]	**523.36** [523.12 – 523.61]	0.85
3	**721.54** [720.63 – 722.46]	**807.33** [806.97 – 807.69]	0.89
4	**1050.61** [1049.50 – 1051.72]	**1120.33** [1119.81 – 1120.85]	0.94
5	**1477.40** [1475.62 – 1479.19]	**1444.13** [1443.38 – 1444.87]	1.02
6	**1815.04** [1812.69 – 1817.40]	**1833.18** [1831.93 – 1834.44]	0.99
7	**2277.75** [2273.93 – 2281.57]	**2244.06** [2241.93 – 2246.20]	1.02
8	**2833.85** [2826.44 – 2841. 25]	**2700.49** [2696.79 – 2704.19]	1.05
9	**3447.40** [3434.67 – 3460.13]	**3332.46** [3324.21 – 3340.71]	1.03
≥10	**5046.22** [4937.08 – 5155.37]	**4106.79** [4074.68 – 4138.89]	1.23
Type of comorbidity			
Concordant only.	**433.66** [433.25 – 434.07]	**287.97** [287.84 – 288.11]	1.51
Discordant only.	**778.07** [775.51 – 780.63]	**526.68** [526.50 – 526.87]	1.48
Both concordant and discordant.	**1338.05** [1337.03 – 1339.07]	**1024.98** [1024.68 – 1025.69]	1.31

* T2DM group: non T2DM group

Table 4.6 Mean annual ingredient cost of chronic comorbidity in the study population with and without T2DM stratified by age category and comorbidity type

Age	*Type of comorbidity*	*T2DM group* *Cost in Euro (€)*	*Non T2DM group* *Cost in Euro (€)*	*Cost ratio **
25 – 44 years				
	All comorbid conditions	696.79 [695.04 – 698.53]	147.85 [147.77 – 147.93]	4.71
	Concordant conditions only	336.02 [335.07 – 336.97]	213.87 [213.60 – 214.30]	1.57
	Discordant conditions only	751.02 [746.76 – 755.29]	496.54 [496.29 – 496.79]	1.51
	Both concordant and discordant conditions	1246.53 [1242.99 – 1250.07]	1008.70 [1007.74 – 1009.65]	1.24
45 – 64 years				
	All comorbid conditions	1034.53 [1033.74 – 1035.32]	418.57 [418.45 – 418.69]	2.47
	Concordant conditions only	450.78 [450.32 – 451.24]	306.84 [306.69 – 306.99]	1.50
	Discordant conditions only	795.65 [792.44 – 798.87]	564.16 [563.87 – 564.44]	1.41
	Both concordant and discordant conditions	1347.65 [1346.60 – 1348.70]	1027.82 [1027.49 – 1028.14]	1.31

[95% Confidence Interval] * T2DM group: non T2DM group

4.6 Discussion

The results of this study found that during 2010, the prevalence of chronic comorbidity and its associated ingredient drug costs were significantly higher in GMS eligible young and middle aged adults (25 – 64 years) with pharmacologically treated T2DM than in a control group. These findings are similar to results presented in a previous study for the elderly GMS eligible population (≥65 years) with T2DM (225).

In keeping with the findings of previous research, concordant conditions associated with the cardiovascular system were found significantly more often in the patients with T2DM compared to controls (77, 201, 203). This is unsurprising as it is well known that patients with diabetes have an increased risk of developing cardiovascular disease (23). The high rate of co-prescribed anti-platelet therapy, anti-hypertensive medication and cholesterol lowering agents for hyperlipidemia in patients with T2DM is also consistent with the findings of a recent Irish study by Teljeur el al, which examined the prevalence of comorbidity in a cohort of patients with T2DM in a general practice setting (78), and may be reflective of physicians taking into account Irish clinical guidelines relating to cardiovascular health which advocate the active management of cardiovascular risk factors in individuals with diabetes (227).

In terms of discordant conditions, the higher prevalence of gastric reflux / peptic ulcer in patients with T2DM compared to the control group is consistent with the finding of previous Irish research in elderly GMS patients (≥65 years) (225). In addition, two Japanese studies have also reported a higher incidence of gastroesophageal reflux disease (GERD) in patients with T2DM compared to individuals without diabetes (228, 229). A number of hypotheses including increased prevalence of obesity in patients with T2DM, and decreased salivary rate have been put forward as possible explanations for this observed association. Further research is required to understand the actual cause of this apparent association (229). However, it is also possible that the higher frequency of prescribed treatment for gastric reflux / peptic ulcer in patients with T2DM, may not relate to the existence of gastrointestinal morbidity but the use of such these agents for gastro-protective purposes in patients prescribed OAH agents (225).

The higher prevalence of depression in patient with T2DM reported in this study is consistent with the findings of previous studies (206-208). It is not apparent from the existing literature whether there is a pathophysiological basis for this observed association, or, if the increase is due to confounding environmental factors (208).

However, the outcome of previous research has shown that the presence of comorbid depression in patients with diabetes is negatively associated with medication adherence (209), glycaemic control (230) and quality of life (231). The presence of depression has also been found to be associated with increased risk of developing diabetes-related complications (210) and should, therefore, be proactively treated aggressively if present.

The economic consequences of diabetes have been discussed extensively in previous research (47). The treatment of diabetes-related complications has been shown to account for most of the economic burden related to healthcare in patients with T2DM in both Ireland and Europe (43, 47). However, these studies did not include the economic cost of discordant comorbid conditions. The results of the current study highlight the significant additional annual drug cost of both concordant and discordant comorbidity in young and middle aged patients receiving treatment for T2DM compared to the control group without the condition. The cost analysis in this study only concentrated on the ingredient cost of prescription medication and did not include other possible expenses such as G.P fees or patient out-of-pocket expenses. Consideration should, therefore, be given to both concordant and discordant comorbidity in future economic analyses of costs associated with diabetes.

The results of the present study have a number of important clinical and economic implications. The presence of comorbid conditions has been shown to significantly reduce the amount of time, energy and financial resources patients have to adequately care for their diabetes (79). Inadequate self-care may lead to the development of diabetes-related complications, which are a major cause of patient morbidity, mortality (232) and economic cost (43, 47). The occurrence of T2DM and comorbid conditions also has indirect economic implications for society, through loss of productivity due to ill-health (233). Policy makers should, therefore, aim to prevent the onset of T2DM by promoting the importance of healthy eating and physical activity, so as to reduce the overall prevalence of important risk factors such as obesity in the population (234). In addition, the screening of patients with risk factors for T2DM should be actively conducted as per the recommendations provided in clinical guidelines pertaining to diabetes, which have been developed by a number of organisations including the Irish College of General Practitioners (16). Early detection of type 2 diabetes should be encouraged, in order to delay the development and progression of diabetes-related complications (234).

The methods used in the present study have several inherent limitations. The HSE-PCRS pharmacy claims database is primarily used to reimburse pharmaceutical costs in Ireland

and does not contain medical diagnoses or clinical outcomes. As a result, patients with T2DM were identified by proxy, using the prescription of any oral anti-hyperglycaemic agents, with or without insulin as an indicator of disease. This definition was unable to take into account the proportion of patients diagnosed with T2DM, treated with diet and exercise alone. It is therefore possible, that the present study has underestimated the true prevalence of treated T2DM in the study population. Furthermore, the present study was unable to take into account patients prescribed pharmacotherapy for T2DM who were not eligible for inclusion in the GMS scheme. These patients may have received treatment through other community drug schemes such as the Long Term Illness (LTI) scheme, the Drug Payment Scheme (DPS).

In addition, there is also the possibility that medications listed for any given disease category included the RxRisk (mod) may have a number of licensed indications for use. In order to minimise the implication of this in the present study, medicines with more than one indication were allocated to a single disease category that reflected the major therapeutic use. It is also possible that a proportion of women of reproductive age were prescribed metformin for the symptomatic relief of Polycystic Ovary Syndrome (PCOS) rather than for the treatment of T2DM, even though metformin is not currently licensed in Ireland for this purpose (235). Finally, the use of the bootstrapping procedure also poses a number of limitations. The primary limitation is the assumption that the distribution of the data from the sample is a realistic estimate of the distribution in the original population. It is unlikely, however, that this would have been a significant source of bias due to the very large sample size in the present study.

4.7 Conclusions

This study has shown that the prevalence of both concordant and discordant comorbid condition is higher in young and middle aged GMS eligible adults with pharmacologically treated T2DM compared to adults of the same age without the condition. It has also found that the increased prevalence of comorbidity was associated with a significant increase in drug related expenditure. In terms of health strategy, policy makers should be aware that these factors are taken into account when planning for the future, given that the expected increase in the prevalence in T2DM and its earlier onset will have implications for health care provision and drug related cost in the future.

Chapter 5: An observational study examining the effect of comorbidity on the rates of persistence and adherence to newly initiated oral anti-hyperglycaemic agents

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5.1 Abstract

Purpose: To examine whether the type of comorbid condition affects medication persistence and adherence in patients initiating oral anti-hyperglycaemic (OAH) therapy.

Methods: The Irish Health Services Executive pharmacy claims database was used to identify a cohort of incident OAH therapy users (ATC A10B), ≥25 years, between June 2009 and December 2010. Persistence and adherence were examined at 6 and 12 months post therapy initiation. Comorbidity was ascertained using modified versions of the RxRisk and RxRisk-V indices, and classified as either concordant or discordant with diabetes. Adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) were determined in relation to comorbidity using logistic regression analysis, adjusting for age, gender, and type of OAH prescribed.

Results: In the study cohort (n=21,280), persistence was 74.0% and 62.6% and adherence 70.0% and 66.7% for all OAHs at 6 and 12 months respectively. Patients with only concordant comorbidity were significantly more likely to be persistent at 6 (OR 1.45, 95%CI 1.28, 1.65) and 12 months (OR 1.22, 95%CI 1.09, 1.38). Patients with only discordant comorbidity were significantly less likely to be persistent at 6 (OR 0.40, 95%CI 0.35, 0.46) and 12 months (OR 0.43 95%CI 0.38, 0.50) ($p<0.0001$). Results were similar for adherence.

Conclusion: The study suggests that the persistence and adherence of OAH therapy in incident users are affected by the type of comorbidity present; this may help in identifying effective interventions aimed at optimising medication use.

5.2 Background

Chronic disease management frequently involves the long term use of medication (236). In order to obtain the desired therapeutic effect, patients are required to take their medication as prescribed (237). The use of medications by patients can be defined in terms of two distinctive patterns of patient behaviour: medication persistence and adherence (101, 238). Non-persistence and inadequate adherence to prescribed therapy are associated with poorer clinical outcomes and increased health care expenditure (113, 239-241).

The benefit of pharmacotherapy in obtaining and sustaining glycaemic control in patients with Type 2 Diabetes Mellitus (T2DM) is well recognised (118). However, in spite of the wide variety of effective glucose lowering agents available, less than half of patients with T2DM will attain adequate glycaemic control (238). Medication non-adherence is one of a number of causes of poor glycaemic control (115). Previous research has indicated that non-adherent patients are at increased risk of developing diabetes-related complications, all-cause hospitalisation and all-cause mortality (117). A systematic review reported that adherence to oral anti-hyperglycaemic (OAH) therapy varied widely in different studies, ranging from 36% – 93% (242).

In view of the chronic nature of diabetes, persistence is also a key factor in the success of long-term pharmacological therapy, in terms of obtaining and sustaining glycaemic control and thus preventing complications (243). However, previous research has reported that persistence with anti-diabetic medication declines over time (244); with one study finding that 37% of patients had discontinued their diabetes medication within 12 months of initiation (109).

Comorbidity is highly prevalent in patients with diabetes (75, 76) and studies have suggested that increased number (245) and severity of comorbid condition may affect medication adherence (246). According to a framework developed by Piette and Kerr, comorbid conditions may be classified as being either concordant or discordant with diabetes (79). Concordant conditions are associated with diabetes, represent part of the same overall pathophysiological risk profile and have similar treatment strategies (79). Examples include hypertension, hyperlipidaemia and ischaemic heart disease (56). In contrast, discordant conditions are unrelated to diabetes development and consequently their management may be different e.g. osteoporosis, arthritis and depression (56, 79). The effect of different types of comorbidity on persistence and adherence to newly initiated OAH therapy has not been previously examined. The purpose of the present study was to investigate whether the number and type of comorbid condition (concordant

and discordant) had an effect on medication persistence or adherence among incident users of OAH therapy in Ireland between 2009 - 2010.

5.3 Methods

Data source

This retrospective cohort study was conducted using data obtained from the Irish Health Service Executive Primary Care Reimbursement Service (HSE-PCRS) pharmacy claims database. The HSE-PCRS is a national database, and is primarily used to reimburse pharmacy claims in Ireland. The HSE-PCRS database collates information on dispensed prescribed medication for individuals included in the General Medical Services (GMS) Scheme. This scheme provides eligible individuals with free health care, medication and limited dental care. Eligibility is based on Irish residence and the outcome of a gross income means assessment.

Between 2009 and 2011, approximately one third of the Irish population aged ≥25 years were eligible for inclusion in the GMS scheme. Women, children and those over the age of 65 years are over represented in this scheme. Medications dispensed through the scheme are recorded in the HSE-PCRS database and are coded using the World Health Organisation (WHO) Anatomical Therapeutic Chemical (ATC) classification system. In addition to prescription data, the HSE-PCRS database also contains basic demographic information, such as sex, age and region of residence. It does not contain any clinical information regarding diagnosis or clinical outcomes. Permission to use the HSE-PCRS database for research purposes was obtained from the HSE-PCRS. Ethical committee approval for this study was not required as the data were anonymised.

Study population

A study cohort of GMS eligible patients with T2DM, aged ≥25 years, was identified from the HSE-PCRS database, using the prescription of any OAH agent (ATC, A10B) as a proxy for disease diagnosis. Patients were classified as incident users of OAH therapy if they initiated treatment between June 2009 and December 2010, having no recorded prescription claim for any OAH agent in the previous 6 months. Patients were eligible for inclusion in the present study if they could be followed for a minimum of six months post OAH initiation (*figure* 5.1). The prescription refill of OAH agents for this cohort was followed until August 2011. In order to determine if the initial OAH agent prescribed had an effect on subsequent persistence and adherence, the cohort was separated into four treatment groups. These were categorised as follows; (i) patients receiving metformin monotherapy (ATC, A10BA02) (ii) patients receiving sulphonylurea monotherapy (ATC, A10BB) (iii) patients receiving metformin and a sulphonylurea as dual therapy (ATC

A10BD02) and (iv) patients receiving other OAH agents including alpha-glucosidase inhibitors (ATC, A10BF), thiazolidiniones (ATC, A10BG), Dipeptidyl peptidase-4 inhibitors (DPP-4) (ATC, A10BH), combinations of OAH agents (ATC, A10BD except A10BD02) and other oral anti-diabetic medications (ATC, A10BX). Patients prescribed insulin either as a monotherapy or in combination with an OAH agent were excluded from the analysis, as an estimate of insulin adherence cannot be obtained from pharmacy claims data (247).

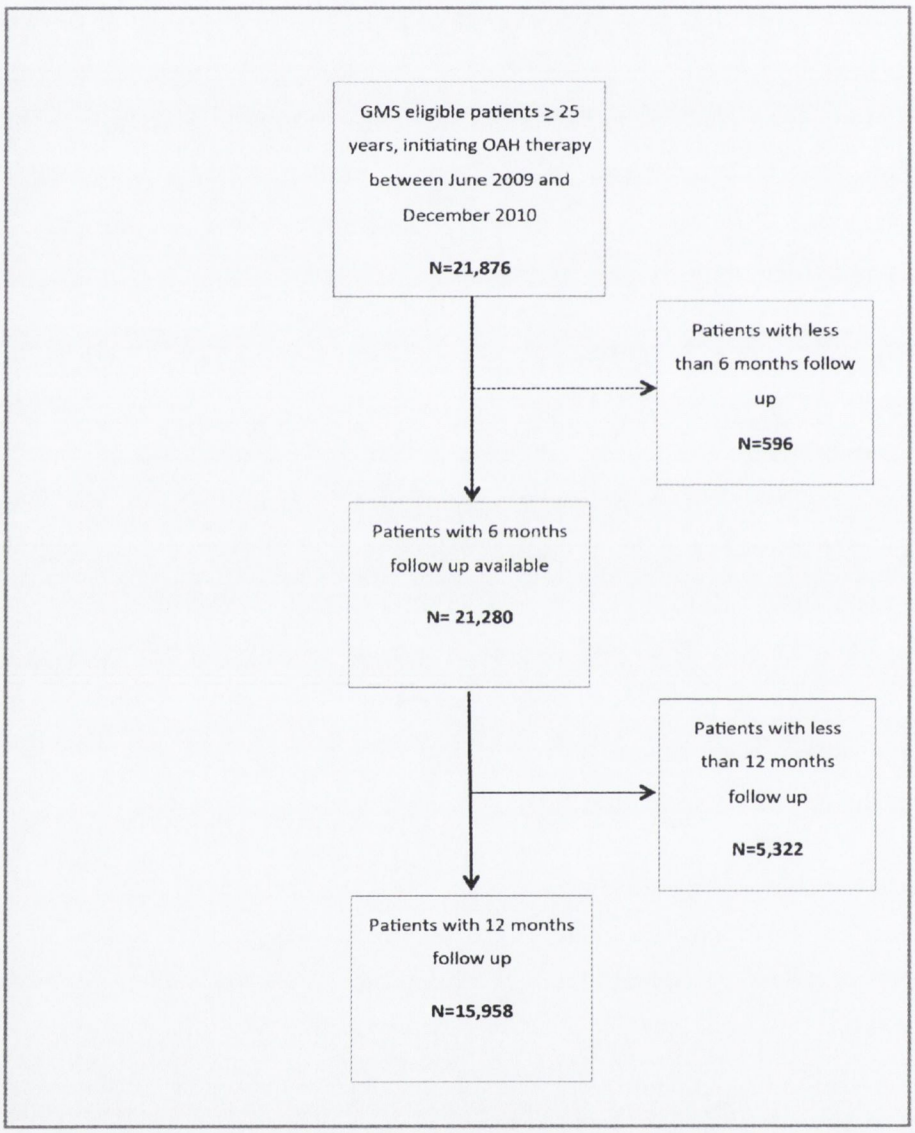

Figure 5-1 Study flow chart

Persistence

Persistence was measured from the initial dispensing of the OAH prescription until the end of the study period if the patient remained on their therapy.

GMS eligible patients should only receive a maximum of one months' supply at any time. To adjust for variation in pack size for the different OAH agents, each patient was assumed to receive only one months' supply, and the quantity of tablets/capsules was converted to days' supply. For example, if the quantity dispensed was 60, this was divided by 2 for 30 days' supply. A prescription refill gap of 63 days was used to define non-persistence in the present study. At present, there is no standard definition as to what constitutes an appropriate permissible gap (length of time) between consecutive prescriptions (248). The length of permissible gaps reported in the published literature ranges from 15 – 120 days (248). While other studies have used the number of days' supply multiplied by 1.5 or 3 to define the permissible gap (248). In this study the permissible gap of 63 days equates to 9 weeks between prescription refills. This length of time was chosen as GMS patients should be dispensed their prescribed medication on a monthly basis and a gap of 63 days would mean that it is likely that they did not receive medication for a consecutive period of greater than two months. For the purpose of the present analysis, patients who were prescribed an additional OAH agent to be used in combination with the initial OAH agent were considered persistent unless they subsequently were found to discontinue their initial agent. The proportion of patients remaining persistent with all OAH agents was examined at 6 and 12 months post therapy initiation, where follow-up data were available. Subsequently, persistence was examined in the four treatment groups above. A sensitivity analysis was conducted by altering the allowable refill gap from 63 days to 35 and 91 days.

Adherence

The medication possession ratio (MPR) was used to estimate adherence to OAH agents at 6 and 12 months post therapy initiation. MPR was calculated in the present study, as the number of days of medication obtained by a patient during a specified period, divided by the number of days in the specified period, multiplied by 100. Although there is no agreed standard for what represents acceptable adherence (102), in keeping with previous diabetes research a cut-off measure for satisfactory adherence was defined as a MPR of $\geq$80% (109, 110). For the purposes of the present analysis, the MPR was calculated for the index medication received by a patient, subsequent addition.

Comorbidity

The prevalence of treated comorbidity in the study cohort was ascertained using modified versions of RxRisk and RxRisk-V indices. The RxRisk and RxRisk-V are validated

pharmaceutical based comorbidity indices, calculated from the sum of 26 and 45 potential disease groups respectively (158, 159). The RxRisk index was originally developed as a risk assessment instrument that utilised automated ambulatory pharmacy data to identify chronic conditions and future health costs (158). Development of the RxRisk index included the construction of tables containing therapeutic classes and representative agents for selected chronic conditions (158). The validity of these conditions and therapeutic classes was reviewed by physicians during the development process (158). The RxRisk-V index was developed by adapting the RxRisk to include additional disease categories for assessing disease burden among patients in the Veteran Health Administration (159). In both indices individuals are classified as having a condition if dispensed at least 1 prescription for the condition during a given time period (159).

The modifications made to the RxRisk-V index for use with the HSE-PCRS data are discussed elsewhere (249). The RxRisk index was modified for the purposes of the present study using similar methods. Diabetes was removed from the modified indices as it was the index disease. The modified RxRisk index was used to calculate a comorbidity score for individuals aged 25 to 64 years, whereas the modified RxRisk-V index was used to ascertain a comorbidity score for individuals aged $\geq$ 65 years. As the proportion of the study cohort with $\geq$7 conditions was relatively small (12%), individuals with $\geq$7 comorbid conditions were grouped into a single category.

In order to determine the effect of different types of comorbid conditions on persistence and adherence to OAH therapy, two comorbidity sub-scores were developed. Chronic conditions and therapies included in the modified indices assessed to be concordant with diabetes (cardiovascular condition/therapies) were used to develop the concordant sub-score. All other conditions and therapeutic agents were used to develop the discordant comorbidity sub-score. The list of conditions and ATC codes used in these sub-scores are summarised in appendices I and II.

5.4 Data analysis

Descriptive statistics for categorical variables are presented as percentages. The univariate association between persistence and adherence to OAH therapy, and covariates gender, age comorbidity score and type, and initial OAH therapy were assessed using the chi^2 test. Binary dependent variables of persistence/non-persistence and adherence/non-adherence were used. Adjusted ORs and 95% CIs for both persistence and adherence were subsequently determined using logistic regression analysis, adjusting for age (reference 25-34 years), gender (reference female), index OAH agent (reference metformin monotherapy), and comorbidity score (reference no

comorbidity) and type - concordant comorbidity only (reference patients with no and both comorbidities) and discordant comorbidity only (reference patients with no and both comorbidities). SAS® v 9.1 (SAS Institute Inc. Cary, USA) was used for the data analysis. Statistical significance at $p < 0.05$ was assumed.

5.5 Results

A total of 21,280 GMS patients met the eligibility criteria for inclusion in the present study. Fifty four percent (n=11,494) of the study cohort were male. Over seventy two percent (n=15,363) of the study cohort were aged ≥55 years. The majority (64.2%) of the study cohort were prescribed metformin as a monotherapy (ATC, A10BA02) and seventy nine percent (n=16,832) were prescribed any monotherapy of metformin or a sulphonylurea. Comorbidities were highly prevalent, with the vast majority of the study cohort (83.4%) prescribed medication for at least one other chronic comorbid condition. Most of the study cohort (54.6%) was co-prescribed medication for both concordant and discordant comorbidities. Twenty percent (n=4262) of the study cohort were prescribed medication for only concordant conditions while an additional 8.8% of the cohort were prescribed medication for only discordant conditions *(table 5.1)*.

Table 5.1 Characteristics of study population at 6 and 12 months post-initiation with OAH therapy

Characteristics	*6 months (n=21,280)*		*12 months (n=15,958)*	
Age (years)	*N*	*% of total N*	*N*	*% of total N*
25 - 34	965	4.53	716	4.49
35 - 44	1828	8.59	1363	8.54
45 - 54	3124	14.68	2365	14.82
55 - 64	4785	22.49	3606	22.6
65 - 69	2865	13.46	2117	13.27
70 - 74	3404	16.00	2555	16.01
≥75	4309	20.25	3236	20.28
Sex				
Female	9786	45.99	7357	46.1
Male	11494	54.01	8601	53.9
Comorbidity score				
0	3525	16.56	2391	14.98
1	2048	9.62	1461	9.16
2	2701	12.69	2007	12.58
3	3089	14.52	2343	14.68
4	3145	14.78	2426	15.2
5	2454	11.53	1936	12.13
6	1751	8.23	1372	8.60
≥7	2567	12.06	2022	12.67
Index OAH therapy				
Metformin monotherapy	13662	64.2	10324	64.69
Sulphonylurea monotherapy	3170	14.9	2438	15.28
Metformin and sulphonylurea dual therapy	2537	11.92	1856	11.63
Other OAH agents (inc combinations)	1911	8.98	1340	8.40
Comorbidity type				
Concordant comorbidity only	4262	20.03	3203	20.07
Discordant comorbidity only	1868	8.78	1354	8.48
Both concordant and discordant comorbidity	11625	54.63	9010	56.46
Depression	4092	19.23	3171	19.87

Persistence

The overall proportion of patients that remained persistent to OAH therapy at 6 and 12 months post initiation was 74.0% and 62.6% respectively. The descriptive patterns of persistence in the study cohort stratified by age, gender, initial OAH agent, comorbidity score and type are summarised in *table 5.2*. In the adjusted analyses, patients prescribed medication for at least one chronic comorbid condition, were significantly more likely to remain persistent to their medication when compared to patients without any comorbidity ($p<0.0001$) (*table 5.2*). The cohort with only concordant comorbidity was also significantly more likely to be persistent when compared to the rest of the study cohort ($p=0.0008$) (*table 5.2*). In contrast, the cohort of patients with only discordant comorbidity were significantly less likely to remain persistent when compared to the rest of the study cohort ($p<0.0001$) (*table 5.2*).

Older patients were significantly ($p<0.0001$) more likely to persist with OAH therapy at 6 and 12 months post initiation, when compared to the youngest age group (25-34 years), except in the very oldest age group ($\geq$75 years) (*table 5.2*). Men were more likely to be persistent with OAH therapy at 6 ($p=0.0002$) and 12 months ($p=0.0018$) post initiation when compared to women (*table 5.2*). When considering index OAH therapy patients initially prescribed sulphonylurea monotherapy or other OAH agents were significantly less likely to remain persistent, compared to metformin monotherapy ($p<0.0001$) (*table 5.2*). The overall pattern of persistence remained consistent following the sensitivity analysis (Appendix III).

Table 5.2 Persistence with OAH therapy at 6 and 12 months post initiation, adjusting for age, sex, number of comorbid conditions, index OAH treatment and type of comorbidity.

Variable	*6 months (N=21,280)*			*12months (N=15,958)*		
Age (years)	Persistence (%)	Adjusted Odds Ratio	95%CI	Persistence (%)	Adjusted Odds Ratio	95%CI
25 - 34	42.4	1.0	n/a	28.2	1.0	n/a
35 - 44	64.0	1.60	1.35 - 1.91	51.0	1.71	1.39 - 2.12
45 - 54	73.8	1.72	1.45 - 2.03	61.8	1.86	1.52 - 2.28
55 - 64	78.8	1.86	1.58 - 2.19	68.1	2.07	1.70 - 2.58
65 - 69	81.2	1.80	1.50 - 2.15	71.6	2.09	1.69 - 2.58
70 - 74	79.5	1.55	1.30 - 1.85	69.3	1.88	1.53 - 2.31
≥75	70.9	1.01	0.85 - 1.20	58.3	1.22	1.00 - 1.49
Sex						
Female	71.6	1.0	n/a	59.9	1.0	n/a
Male	76.0	1.14	1.07 - 1.22	64.8	1.12	1.04 - 1.20
Comorbidity score						
0	37.7	1.0	n/a	23.7	1.0	n/a
1	70.3	4.97	4.20 - 5.88	53.4	4.56	3.80 - 5.48
2	79.9	6.38	5.54 - 7.36	68.3	6.63	5.67 - 7.75
3	81.6	7.01	6.16 - 7.97	70.8	7.32	6.34 - 8.45
4	83.5	8.19	7.23 - 9.28	72.8	8.05	7.01 - 9.23
5	85.0	9.70	8.46 - 11.13	74.8	9.21	7.96 - 10.66
6	83.7	9.16	7.87 - 10.66	73.3	8.76	7.46 - 10.27
≥7	82.2	8.89	7.78 - 10.15	68.8	7.50	6.50 - 8.67

Table 5.2 (continued)

Variable	*6 months (N=21,280)*			*12months (N=15,958)*		
Index OAH therapy	Persistence (%)	Adjusted Odds Ratio	95%CI	Persistence (%)	Adjusted Odds Ratio	95%CI
Metformin monotherapy	75.7	1.0	n/a	64.5	1.00	n/a
Sulphonylurea monotherapy	66.8	0.66	0.60 - 0.73	53.8	0.66	0.60 - 0.72
Dual therapy *	76.7	1.05	0.94 - 1.18	65.5	0.97	0.87 - 1.09
Other OAH agents (inc combinations)	69.9	0.70	0.62 - 0.78	59.4	0.73	0.64 - 0.83
Comorbidity type						
Concordant comorbidity only**	85.6	1.45	1.28 - 1.65	72.8	1.22	1.09 - 1.38
Discordant comorbidity only **	58.9	0.40	0.35 - 0.46	44.1	0.43	0.38 - 0.50

* Metformin with a sulphonylurea. ** Reference: patients with no and both comorbidities.

Table 5.3 Adherence to OAH therapy at 6 and 12 months post initiation, adjusting for age, sex, number of comorbid conditions, index OAH treatment and type of comorbidity.

Variable	*6 months (N=21,280)*			*12months (N=15,958)*		
Age (years)	Adherence (MPR)	Adjusted Odds Ratio	95%CI	Adherence (MPR)	Adjusted Odds Ratio	95%CI
25 - 34	35.0	1.0	n/a	29.2	1.0	n/a
35 - 44	55.1	1.45	1.21 - 1.73	50.6	1.51	1.22 - 1.87
45 - 54	68.2	1.71	1.44 - 2.02	65.5	1.93	1.57 - 2.37
55 - 64	74.9	1.96	1.66 - 2.31	72.5	2.18	1.78 - 2.66
65 - 69	78.4	1.98	1.66 - 2.37	76.2	2.16	1.74 - 2.68
70 - 74	76.8	1.74	1.46 - 2.07	74.1	1.92	1.55 - 2.36
≥75	68.8	1.18	1.00 - 1.40	64.0	1.23	1.00 - 1.51
Sex						
Female	67.0	1.0	n/a	63.6	1.0	n/a
Male	72.4	1.19	1.11 - 1.27	69.3	1.18	1.09 - 1.27
Comorbidity score						
0	31.1	1.0	n/a	23.8	1.0	n/a
1	63.0	4.32	3.68 - 5.07	55.6	4.50	3.73 - 5.43
2	74.4	5.84	5.10 - 6.68	71.3	6.98	5.95 - 8.18
3	77.7	6.90	6.10 - 7.81	74.5	8.22	7.10 - 9.51
4	80.8	8.55	7.57 - 9.64	78.7	10.64	9.22 - 12.27
5	82.8	10.24	8.97 - 11.70	79.6	11.73	10.08 - 13.66
6	82.5	10.44	8.99 - 12.11	78.8	11.62	9.83 - 13.74
≥7	80.8	9.84	8.63 - 11.21	76.8	11.06	9.51 - 12.86

Table 5.3 (continued)

Variable	*6 months (N=21,280)*			*12months (N=15,958)*		
Index OAH therapy	Adherence (MPR)	Adjusted Odds Ratio	95%CI	Adherence (MPR)	Adjusted Odds Ratio	95%CI
Metformin monotherapy	70.4	1.0	n/a	67.7	1.00	n/a
Sulphonylurea monotherapy	64.4	0.77	0.70 - 0.84	59.8	0.72	0.65 - 0.80
Dual therapy *	72.1	1.08	0.97 - 1.20	67.4	0.90	0.80 - 1.01
Other OAH agents (inc combinations)	72.8	1.14	1.02 - 1.29	70.2	1.08	0.94 - 1.24
Comorbidity type						
Concordant comorbidity only**	80.8	1.43	1.28 - 1.61	77.3	1.42	1.26 - 1.62
Discordant comorbidity only **	53.4	0.47	0.41 - 0.54	46.9	0.46	0.40 - 0.54

* Metformin with a sulphonylurea. ** Reference: patients with no and both comorbidities

Adherence

In this study, the overall pattern of adherence to OAH therapy was found to be broadly similar to that described for persistence. The adherence rate for all OAH agents, as measured by the MPR, was 70.0% and 66.7% at 6 and 12 months respectively. The descriptive patterns of adherence stratified by age, gender, initial OAH agent, comorbidity score and type are summarised in *table 5.3*.

The impact of comorbidity on adherence rates was similar to the results obtained for the persistence analysis. Patients who were co-prescribed treatment for at least one comorbid condition were significantly more likely to remain adherent to OAH therapy when compared to patients not prescribed treatment for any comorbid condition ($p<0.0001$) (*table 5.3*). Patients prescribed medications for concordant conditions only versus not, were significantly more likely to be adherent to OAH therapy ($p<0.0001$) (*table 5.3*). In contrast, patients who were only co-prescribed medications for discordant conditions only versus not, were significantly less likely to be adherent to OAH ($p<0.0001$) (*table 5.3*).

Older patients were significantly more likely to persist with OAH therapy at 6 and 12 months post initiation, when compared to the youngest age group (25-34 years) ($p<0.05$) (*table 5.2*). Men were statistically more likely to be persistent with OAH therapy compared to women ($p<0.0001$) (*table 5.3*). Patients initially prescribed sulphonylurea monotherapy or other OAH agents were found to be significantly less likely to be persistent when compared to patients receiving metformin monotherapy ($p=0.03$) (*table 5.3*).

5.6 Discussion

In this study, the overall rate of persistence and adherence to OAH therapy was high at 6 and 12 months post therapy initiation. At 6 months post-initiation medication persistence was shown to be 74% and adherence 70%. By 12 months this had reduced to 62.6% for persistence and 66.6% for adherence. Persistence and adherence increased with increasing number of comorbid conditions. Comorbidity was found to be positively associated with both persistence and adherence rates at 6 and 12 months. When comorbid conditions were stratified by comorbidity type, the results found that the presence of concordant comorbidity was positively associated with medication persistence and adherence. In contrast, however, the presence of discordant comorbidity was negatively associated with medication persistence and adherence. This is the first large observational study to specifically examine the effect of both concordant and discordant comorbidity on the use of newly initiated OAH therapy in patients with T2DM. Age, gender, and initial OAH therapy differences were also found to have a significant effect on persistence and adherence rates in the present study.

Diabetes patients with no comorbid conditions were found to have the lowest rates of persistence and adherence to OAH therapy, whereas, those with any or multiple comorbid conditions had increased levels of both persistence and adherence. A similar effect was found in a study by Shalansky *et al*, which found that an increasing number of medications (up to 10) were associated with better adherence to cardiovascular therapies (250). However, the results of previous studies examining the effect of comorbidity on anti-diabetic medication have not been consistent. Some studies have shown that an increased number of comorbid conditions or a higher number of co-prescribed medications (used as a proxy measure of comorbidity) was associated with better adherence to anti-diabetic medications (96, 115, 117). A possible reason for this, according to a study by Rozenfeld Y *et al*, is that patients with a greater number of comorbid conditions may be more knowledgeable with regards to diabetes and its complications, and this may consequently encourage them to remain adherent to their diabetes treatment regimen (115). Furthermore, previous research has also shown a positive correlation between perceived medication necessity in patients with chronic conditions and medication adherence (251). In contrast however, other studies have described an inverse association between increased numbers of comorbid conditions or co-prescriptions and anti-diabetic medication adherence (103). This lack of consistency in the published literature may be due to the variety of methodologies applied to assess comorbidity status, such as diagnostic and prescription level, and in differing populations studied.

Few studies have examined the effect of different types of comorbidity on medication persistence and adherence in relation to the treatment of diabetes. There are, however, a number of published studies that have looked at the effect of different types of comorbidity on adherence to anti-hypertensive medication. The results of these studies suggest that comorbidities related to the cardiovascular system (concordant conditions) are associated with better adherence to anti-hypertensive agents, (252, 253) whereas, in contrast, conditions unrelated to the cardiovascular system (discordant conditions) are inversely associated with adherence to anti-hypertensive agents (254-256). In terms of diabetes, it has previously been suggested that self-management may be compromised and/or complicated depending on the symptoms and severity of the comorbid condition(s) present (80, 87). Previous research has also indicated that the medical management of diabetes may be influenced by the type of comorbidity present. For example, in an Australian study, the presence of discordant comorbidity was shown to be negatively correlated with intensification of anti-diabetic treatment (224).

A number of studies have also shown that specific symptomatic comorbid conditions (e.g. depression) can be particularly disruptive to diabetes care and medication persistence and adherence (82, 257, 258). The most recent of these studies, found that the co-prescription of anti-depressant medication was associated with 42% increased likelihood of discontinuing anti-hyperglycaemic medication in a large cohort of Australian veterans who had recently been initiated on either metformin or a sulphonylurea (258). In the present study, however, the co-prescription of anti-depressant medication alone was not found to be significantly associated with poorer rates of persistence or adherence to OAH therapy (Appendix IV).

In terms of age, gender and initial OAH therapy differences influencing medication taking behaviour, this study found that male gender was associated with an increased rate of persistence and adherence. It also found that increasing age was positively associated with medication persistence (with the exception of the oldest age group) and adherence (in all age groups). Previous studies have found conflicting results as to the effect of gender on the adherence and persistence of OAH therapy. A study by Yang Y *et al* reported that male gender was associated with increased adherence to OAH therapy (245); in contrast a study by Rozenfeld Y *et al* did not find gender to be a significant indicator of medication taking behaviour (115). The results of the previous studies with regards to age are more consistent, with a number of studies suggesting that increased age is positively associated with improved persistence (109) and adherence to OAH therapy (115, 245, 259). The results of the present study also suggest that patients initiated on metformin monotherapy, were more likely to remain persistent when compared to patients initiated on sulphonylurea monotherapy. This is consistent with the results of previous studies that have examined discontinuation rates in patients' newly prescribed OAH therapy (243, 260).

The use of comprehensive pharmacy claims data, such as the HSE-PCRS database, provides an important estimate of medication persistence and adherence in large patient populations in the real world setting (104), using methods that are convenient, inexpensive and clinically non-invasive (105). Furthermore, the results of previous research suggest that adherence estimates obtained using pharmacy claims data are associated with relevant clinical outcome measures (105). However, as with other studies that have investigated medication persistence and adherence, the use of pharmacy claims data in this study is associated with intrinsic limitations. One limitation is that although the data may provide an accurate description of medication possession, it cannot measure actual medication consumption (104). The use of pharmacy claims data may, therefore, overestimate the true level of medication adherence in a study population (105). In

addition in our definition of initiators of OAH we also may have included a small proportion of prevalent users of OAH. This would have arisen as some patients, who had recently joined the GMS medical card scheme and were identified as new users of OAH, may have already been dispensed OAH previously.

In terms of non-persistence it was assumed that patients who had a prescription refill gap of more than 63 days had discontinued therapy. It is possible, however, that these patients may have switched therapy because of treatment failure or adverse side effects. In patients who initiated OAH therapy either on metformin or a sulphonylurea monotherapy (n=16836, 70%) the level of switching between treatments in this study was relatively low (6.4%) and it is, therefore, unlikely that this would have a large effect on the results. The follow up period used in the present study of 12 months from OAH initiation was relatively short in comparison to a number of recent studies that have investigated persistence to OAH therapy over longer periods (243, 258) . However, non-persistence is also associated with side effects of therapies which occur early after initiation, so we are likely to have captured most of this. The HSE-PCRS pharmacy claims database does not contain medical diagnoses, therefore treatment was used as a proxy diagnoses for both T2DM and comorbidity. Some medications however, may have a number of indications e.g. ACE-inhibitors. In order to limit the effect of this in the present study, medications with more than one indication were assigned to a single disease category reflecting their major therapeutic use (249). The analysis presented in this study was restricted only to patients eligible for inclusion in the GMS scheme. The other community scheme under which diabetes patients are treated – the Long Term Illness scheme (LTI) represents less socially deprived patients who have previously been shown to have better levels of adherence (184). Limiting the analysis to the GMS scheme, may have therefore, introduced a certain amount of selection bias into this study. It should be noted however that a previous study found that that the majority (65%) of patients prescribed treatment for diabetes (type 1 and type 2) in Ireland were eligible for inclusion in the GMS scheme (35).

5.7 Conclusions

Inadequate adherence to anti-diabetic therapy is a major cause of diabetes complications and their related human, social and financial costs (88). Frequently cited risk factors for non-adherence include difficulties with the prescribed course of therapy (eg. medication side effects), inadequate medical advice, poor doctor-patient rapport, forgetfulness, discrepancy between patient and provider with regard to treatment necessity and the high cost of medication (261). From a clinical perspective the results of the present study

suggest that patients with discordant comorbidity or early-onset T2DM may require additional support in order to remain persistent / adherent to their OAH therapy regimen. Health professionals should encourage those likely to be non-persistent and/or non-adherent of the importance of taking their medications in reducing future complications. The use of Motivational Interviewing (MI) as a method of patient counselling in patients with T2DM, has been shown to have beneficial effect on range of aspects associated with better glycaemic control including; disease comprehension, beliefs about treatment, prevention and behaviour change (262).The results of the present study also add to the existing literature by providing evidence that suggests that the presence of concordant and discordant comorbid conditions effect persistence and adherence to OAH therapy in different ways. This may be of benefit to health care professionals and researchers working to develop interventions to optimise medication use in patients with T2DM and other chronic diseases.

Chapter 6: Regional variation in medication taking behaviour of new users of oral anti-hyperglycaemic therapy in Ireland.

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6.1 Abstract

Purpose: To investigate whether there are regional differences in non-persistence and non-adherence to oral anti-hyperglycaemic agents in patients initiating therapy and examine if any association exists between different types of comorbidity in terms of medication taking behaviour.

Methods: The Irish Health Services Executive (HSE) pharmacy claims database was used to identify new users of metformin or sulphonylureas, aged ≥25 years, initiating therapy between June 2009 and December 2010. Non-persistence and non-adherence were examined up to 12 months post initiation. Comorbidity was assessed using modified versions of the RxRisk and RxRisk-V indices, and was classified as either concordant and/or discordant with diabetes. Adjusted hazard ratios (HRs) and 95% confidence intervals (95%CIs) for non-persistence were determined in relation to both HSE region and comorbidity type using Cox proportional hazards model, adjusting for age, sex and initial OAH prescribed. Logistic regression analysis, adjusting for these covariates, was used to determine the adjusted odds ratios (ORs) and 95% CIs for non-adherence for both HSE region and comorbidity type.

Results: There was little overall difference between regions in terms of patient medication taking behaviour. The largest reduction for both non-persistence (HR 0.86, 95%CI 0.80, 0.94) and non-adherence (OR 0.83, 95%CI 0.74, 0.93) was observed in the South. The presence of any comorbidity was associated with a reduction in the risk of non-persistence and non-adherence.

Conclusions: Interventions to optimise medication taking in patients with T2DM should be implemented nationally to improve the overall level of adherence and persistence in Ireland, especially in patients with no comorbidity.

6.2 Background

Diabetes Mellitus is a group of chronic metabolic disorders characterised by persistent hyperglycaemia and caused by defects in the secretion and / or function of insulin (2). It is associated with a wide range of microvascular and macrovascular complications (4). A reduction in plasma glucose concentration has been shown to reduce the risk of diabetes-related complications (26).

In patients with type 2 diabetes mellitus (T2DM), the value of oral anti-hyperglycaemic (OAH) therapy in terms of improved glycaemic control is well established (10). The long term success of pharmacotherapy is however, dependent on patients continuing to take their medication as prescribed (243). Poor adherence reduces the effectiveness of pharmacotherapy, resulting in increased morbidity, mortality and higher costs for the health system (263, 264). Adherence to medication may be affected by a number of factors, related to the patient, provider and / or the health service (102, 118). Additional studies have also suggested that the number (245) and severity (246) of comorbid conditions, as well as specific types of comorbidity (e.g. depression) (258), may also affect patients use of anti-diabetic medication.

In Ireland, patients diagnosed with T2DM were traditionally referred to specialist diabetes services in a hospital setting (265). During the last 10 years, more emphasis has been given to the management of diabetes in primary care, due to the increasing number of patients with the condition (266). Previous research has suggested that the care of patients with diabetes in primary care in Ireland is frequently unstructured (267). There are, however a small number of high quality initiatives within the Irish health care system that have been found to deliver inclusive and organised diabetes-related care (268). Previous research investigating trends in prescribing of anti-diabetic medication and use of secondary preventative cardiovascular therapies in Ireland has shown significant regional variation in prescribing practices (143). This may have been related to the geographical location of these diabetes care initiatives (143). It is not known, however, whether geographic variation exists in relation to patient medication taking behaviour. The aims of the present study were to: (i) investigate whether there are regional differences in non-persistence and non-adherence to OAH agents in patients initiating therapy between 2009 and 2010, and (ii) examine if any association exists between different types of comorbidity in terms of medication taking behaviour.

6.3 Methods

Data source

This retrospective cohort study was carried out using data obtained from the Health Service Executive Primary Care Reimbursement Service (HSE-PCRS) pharmacy claims database. The HSE-PCRS is a national database used primarily to reimburse the provision of health care services and prescription medication in Ireland, through a number of national schemes, including the General Medical Services (GMS) scheme. In 2011, the GMS scheme provided free healthcare including medications, subject to specific eligibility criteria based on means testing, to approximately 37% of the Irish population (1,694,063 individuals) (157). The GMS scheme is over represented by women, children and older adults (≥65 years). Prescription medications dispensed through the scheme are recorded in the HSE-PCRS database using the World Health Organisation (WHO) Anatomical Therapeutic Chemical (ATC) classification system. The HSE-PCRS database also collates basic demographic information pertaining to each GMS claimant including age, sex and region. It does not, however, contain any clinical data. Consent to use the HSE-PCRS data for research purposes was acquired from the HSE-PCRS. Approval by an ethics committee for the present study was not required as anonymised data were used.

Health Service Executive regions

In Ireland, the Health Service Executive (HSE) is responsible for the provision of health services and social care. For administrative purposes, the HSE is divided into four regions of approximately equal proportion in terms of population size: HSE Dublin Mid-Leinster, HSE Dublin North-East, HSE South and HSE-West. In 2011, HSE-West had the largest number of individuals eligible for inclusion in the GMS scheme (n=472, 174), while in contrast HSE-Dublin North-East had the lowest number of eligible individuals (n=357, 838)(157). The HSE region of each GMS claimant is documented in the HSE-PCRS pharmacy claims database.

Study cohort

The prescription of any OAH agent (ATC, A10B) was used to identify a cohort of GMS eligible patients, aged ≥25 years, that had received treatment for type 2 diabetes. Patients were eligible for inclusion in the present study if data was available for a minimum of twelve months post OAH initiation. Eligible patients were subsequently classified as incident users of OAH therapy, if they were dispensed either metformin (ATC, A10BA02) or a sulphonylurea (ATC, A10BB) as a monotherapy between June 2009 and December 2010, having no prescription claim documented in the HSE-PCRS database for any anti-diabetic agent in the previous 6 months. In addition, patients were also required to have

been eligible for inclusion in the GMS scheme for ≥3 months prior to their initial OAH prescription claim (*figure* 6.1). The prescription refill patterns of these patients were subsequently followed from OAH initiation until August 2011.

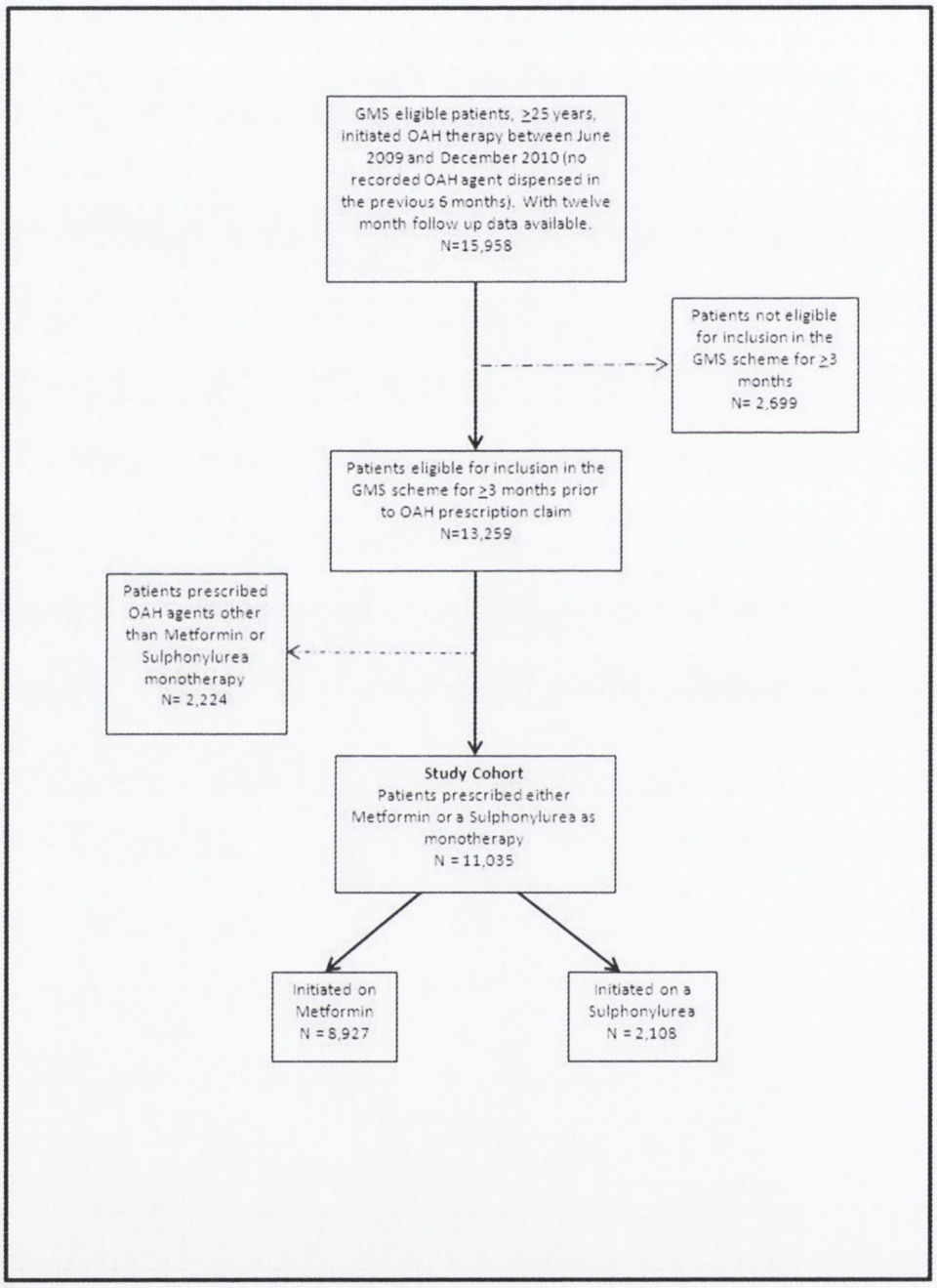

Figure 6.1 Flow chart of study cohort

Definition of study outcomes

For the purposes of the present study, discontinuation of OAH therapy (non-persistence) was defined as a prescription refill gap of ≥63 days at any time up to 12 months after the initial dispensing. Patients eligible for inclusion in the GMS scheme can only be dispensed a maximum of one months' supply of any medication at one particular time. In order to correct for differences in dosage or pack size, patients were assumed only to have been dispensed the number of tablets/capsules equal to one months' supply of medication. The quantity of tablets/capsules was then converted to a days' supply by dividing the quantity of tablets/capsules by a number that would give a 30 day supply of that medication. For the purpose of the present study, patients with a prescription refill gap of ≥63 days were assumed not to have received any OAH medication for a period of greater than two consecutive months. Time to non-persistence with OAH therapy was examined using a Cox Proportional Hazards model.

The medication possession ratio (MPR) was used to estimate non-adherence to either metformin or a sulphonylurea from the initial date that they were dispensed to 12 months post therapy initiation. For the purposes of the present study, MPR was calculated as the number of days of medication obtained by a patient during a specified period, divided by the number of days in the specified period, multiplied by 100. In keeping with previous research the cut-off measure for non-adherence was defined as a MPR of ≤80% (109).

Comorbidity

The prevalence of treated comorbidity in the study cohort was ascertained using modified versions of RxRisk and RxRisk-V indices. The RxRisk and RxRisk-V are validated pharmaceutical based comorbidity indices, calculated from the sum of 26 and 45 potential disease groups respectively (158, 159). The modifications made to the RxRisk-V index are relevant to the Irish setting and have been discussed previously in detail (225). Similar modifications were made to the RxRisk index. As diabetes was the index condition in the present study, it was removed from both of the modified indices. The modified RxRisk was used to ascertain the number of comorbid conditions in patients aged 25 - 64 years whereas the modified RxRisk-V index was used for older patients aged ≥65 years. In order to determine the effect of different types of comorbidity on persistence and adherence to OAH therapy, a variable was derived to indicate whether comorbid conditions were absent, concordant only, discordant only, or both concordant and discordant.

6.4 Data analysis

Descriptive statistics for categorical variables are presented as percentages. The univariate association between non-persistence and non-adherence (MPR ≤80%) to HSE region and type of comorbidity were assessed using the Chi square test. A Cox Proportional Hazards model adjusted for the following covariates; age (reference: 25-34 years), sex (reference: female), initial OAH agent (reference: metformin monotherapy), HSE region (reference: Dublin Mid-Leinster), and type of comorbid condition (reference: no comorbidity) and with persistence censored was used to examine time to non-persistence with OAH therapy. The resulting associations are displayed as adjusted hazard ratios with 95% confidence intervals (HR, 95%CI). A logistic regression model, adjusting for the same covariates, was subsequently preformed to examine the relationship between OAH non-adherence and type of comorbidity. The resulting associations for the logistic regression analysis are displayed as adjusted odds ratios with 95% confidence intervals (OR, 95%CI). The systematic component of variance (SCV) indicates the level of variability in the data that can be attributed to heterogeneity between HSE regions. The SCV and 95% CIs presented for both non-persistence and non-adherence by HSE-region was estimated using multilevel logistic regression analysis. SAS® v 9.1 (SAS Institute Inc, Cary, USA) and STATA®v 11 were used for the data analysis. Statistical significance at $p < 0.05$ was assumed in all cases.

6.5 Results

A total of 11,035 patients were eligible for inclusion in the present study (*figure 6.1*). The majority of patients (80.9%) were initially prescribed metformin (*table 6.1*). Fifty-one percent of the study cohort was male and 73% of patients were aged 45 years or more (*table 6.1*). In terms of regions of residence, HSE region Dublin Mid-Leinster had the highest number of eligible patients (n=3,084), representing 28% of the study cohort. In contrast, the HSE region Dublin North-East was found to have the lowest proportion (17.4%) of patients eligible for inclusion in the present study (*table 6.1*). The majority of patients in this study cohort (85%) were found to have been dispensed medication for at least one comorbid condition and nearly 57% of patients were dispensed medication for both concordant and discordant comorbid conditions (*table 6.1*). The prevalence of co-prescribing for the different types of comorbid conditions was not found to differ significantly between the four HSE regions (*table* 6.2).

Table 6.1 Characteristics of the study cohort (N=11,035).

Characteristics	*N*	*% of total N*
Age (years)		
25 - 34	546	4.95
35 - 44	912	8.26
45 - 54	1522	13.79
55 - 64	2241	20.31
65 - 69	1340	12.14
70 - 74	1773	16.07
≥75	2701	24.48
Sex		
Female	5359	48.56
Male	5676	51.44
Index OAH therapy		
Metformin monotherapy	8927	80.90
Sulphonylurea monotherapy	2108	11.35
Type of Comorbidity		
No comorbid conditions	1653	14.98
Concordant condition only	2089	18.93
Discordant conditions only	1018	9.23
Both concordant and discordant conditions	6275	56.86
HSE region		
Dublin Mid-Leinster	3084	27.95
Dublin North East	1925	17.44
West	2944	26.68
South	3082	27.93

The overall proportion of patients who remained non-persistent and non-adherent to OAH agents in this cohort was 39% and 35.3% respectively 12 months post therapy initiation. In the univariate analysis, the proportion of patients that remained persistent with OAH therapy was found to differ significantly between the four HSE-regions (X^2 =31.91, df=3, p<0.0001) (*table 6.2*). A similar result was found in terms of medication adherence (X^2 =33.94, df=3, p<0.0001) (*table 6.2*).

The results of the Cox proportional hazards model, after adjusting for age, sex and initial OAH therapy, found that the risk of non-persistence was significantly lower in patients residing in HSE region South and West (*table 6.3*). In terms of non-adherence to OAH therapy, patients in HSE regions South and Dublin North-East were significantly less likely

to be non-adherent twelve months post OAH initiation (*table 6.3*). There was no evidence of significant heterogeneity (SCV value) between the four HSE regions (*table 6.3*).

In multivariate analysis the presence of comorbidity was found to influence both the risk of non-persistence and non-adherence to OAH therapy at 12 months post initiation. The risk of non-persistence was significantly lower in those that had also been dispensed pharmacotherapy for concordant and / or discordant comorbid conditions when compared to patients with no comorbid conditions (*table 6.3*). The likelihood of non-adherence to OAH therapy showed a similar pattern (*table 6.3*).

Table 6.2 Medication use and comorbidity type by HSE region at 12 months post OAH initiation

Variable	*HSE region Dublin Mid-Leinster N=3,084*		*HSE region Dublin North-East N=1,925*		*HSE region West N=2,944*		*HSE region South N=3,082*	
Medication use	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Non-persistent	1239	41.93	724	37.61	1192	40.49	1092	35.43
Non-adherent	1174	38.07	641	33.33	1100	37.36	986	31.99
Type of comorbidity								
None	494	16.02	272	14.13	493	16.75	394	12.78
Concordant only	570	18.48	377	19.58	541	18.38	601	19.50
Discordant only	298	9.66	134	6.96	283	9.61	303	9.83
Both concordant and discordant comorbidity	1722	55.84	1142	59.32	1627	55.26	1784	57.88

Table 6.3 Non-persistence and non-adherence to OAH therapy 12 months post initiation, adjusted for age, sex and initial OAH

Variables	*Non-persistent*	*HR**	*95% CI*	*Non-adherent*	*OR***	*95% CI*
HSE region						
Dublin Mid-Leinster	41.9	1		38.1	1	
Dublin North East	37.6	0.93	0.84 - 1.01	33.3	0.87	0.76 – 0.99
West	40.5	0.96	0.89 - 1.04	37.4	0.95	0.85 – 1.07
South	35.4	0.86	0.80 - 0.94	32.0	0.83	0.74 – 0.93
Comorbidity Type						
none	76.7	1		77.9	1	
concordant only	28.3	0.22	0.20 – 0.24	24.7	0.11	0.10 – 0.13
discordant only	56.7	0.53	0.48 - 0.58	53.7	0.33	0.28 – 0.40
both concordant and discordant	29.7	0.22	0.21 - 0.24	24.7	0.11	0.09 – 0.12
Systematic component of variance		0.004	0.001 - 0.028		0.004	0.001 - 0.03

* Time to non-persistence ** Non-adherence

6.6 Discussion

This is the first study conducted in an Irish setting to investigate regional variation in medication taking behaviour. The results of this study showed that there was little variability between HSE regions in terms of patient medication taking behaviour. Reductions were found, however, in terms of non-persistence in HSE regions South and West, and in HSE regions South and Dublin North-East in relation to non-adherence. Furthermore, the co-prescription of pharmacotherapy related to different types of comorbidity was not found to differ significantly between the HSE regions. The presence of any type of comorbidity was, however, associated with an overall reduction in the risk of non-persistence and non-adherence to OAH therapy in all four regions.

Regional variation in health care may reflect important differences in quality and/or patient access (269, 270). The existing literature related to regional variation, has concentrated mainly on differences in the rate of medical procedures (271-273) hospital admissions (274) and on prescribing practices (143, 275). In contrast, relatively few studies have investigated regional variation in medication taking behaviour (276).

A study by Gibson et al, examined regional variation in medication adherence for 11 different chronic conditions across hospital referral regions (HRRs) in the United States (US) and found that the variation in adherence to prescription medication was small across the HRRs (276). Another study by Zhang *et al*, also found that adherence to pharmacotherapy for heart failure did not vary substantially in Medicare patients across the HRRs (277). In contrast, two other studies have reported the presence of regional variation in adherence to anti-diabetic medications (278, 279). The first study, carried out by Egede *et al,* used data obtained from the US Veterans Health Administration (VHA) National Patient Care and Pharmacy Benefits Management databases. Medication adherence was examined using the MPR and adequate adherence was defined as MPR $\geq$80%. The five geographic regions in this study were based on the VHA Veteran Integrated Service Networks (VISNs). Significant regional differences in MPR were reported, as well as race/ethnicity and urban/rural interactions (278). The second more recent study, conducted by Curkendall *et al* also reported regional variation in regional variation in adherence and persistence to anti-diabetic medication (279). This study, used US Census geographic regions, and found that patients with T2DM residing in the southern states were less likely to remain either persistent or adherent to anti-hyperglycaemic medication when compared to patients living in other parts of the United States (279). However, the authors were unable to determine if other factors, e.g. health attitudes and beliefs, and ethnicity, may have contributed to the observed differences in

medication taking between regions and suggested that further research in this area may be required (279).

Disparities between or within regions frequently suggest inconsistencies in the implementation of best practice and evidence based medicine (145). The comparison of regional data may, therefore, enable the identification of structures and/or processes that improve outcomes in well performing regions (145). Although some variation was noted between HSE regions, it is probably of limited clinical importance. This may suggest that factors that promote medication persistence and adherence, such as the provision of diabetes self-management education programmes or advice from health professionals, did not vary substantially between the HSE regions.

Relatively few studies have focused on the potential effect of different types of comorbidity on medication taking behaviours in patients with diabetes. Furthermore, the research that has been carried out has predominantly investigated the effect of specific symptomatic comorbid conditions on adherence, such as depression (257, 258, 280). However, a number of studies have examined the effect of different types of comorbidity on adherence to anti-hypertensive medication. The results of these, suggest that concordant conditions, such as those affecting the cardiovascular system, are associated with better adherence to anti-hypertensive medication (252, 253) whereas discordant conditions, unrelated to the cardiovascular system, were found to be associated with poorer adherence to anti-hypertensive medication (254, 255). In contrast, the results of the present study, found that the presence of any type of comorbidity was associated with improved medication taking behaviour in patients prescribed OAH therapy. These findings are in keeping with research, which suggested that patients with a higher comorbidity burden may be more knowledgeable about diabetes and its related complications, and therefore, may be more likely to adhere to their anti-diabetic regimen (115).

The use of pharmacy claims data to investigate medication taking behaviour is associated with a number of inherent limitations. It is accepted that although the use of pharmacy claims data may present an accurate depiction of medication possession, it is unable to determine actual medication consumption (104). The utilisation of pharmacy claims data may, therefore, overestimate the true rate medication adherence in a given population (105). With regard to non-persistence, it is also possible that patients, who had a prescription refill gap of 63 day or more, may have erroneously been assumed to have discontinued therapy, when they had actually switched treatments due to adverse side effects or treatment failure. It is unlikely however, that this had a large effect on the results presented as the level of treatment switching was relatively low in this study. An

additional limitation of the present study was that the follow up period of 12 months from OAH initiation, was comparatively short compared to the follow up periods presented in a number of recent persistence studies (243, 281). Due to the lack of clinical information in the HSE-PCRS database, dispensed medications were used as a proxy diagnosis for both T2DM and other conditions. There are, however, limitations associated with this, as some medications have a number of licensed indications (e.g. ACE-inhibitors). To minimise the effect of this, medications with more than one indication were assigned to a single disease category reflecting their major therapeutic use. It is possible, however, a small proportion of the female cohort aged 25 – 44 years (n=833) may have been prescribed metformin for the symptomatic relief of Polycystic Ovary Syndrome (PCOS), even though it is not licenced for this purpose in Ireland. Furthermore, the present analysis was limited to only GMS eligible patients and did not include diabetes patients who received their medication through other community schemes, such as the Long Term Illness (LTI) scheme. The LTI scheme is a non-means tested national scheme that provides medications free of charge to patients diagnosed with specific chronic conditions. Approximately 35% of patients diagnosed with T2DM are covered by the LTI scheme (35), and as a result this may have introduced a certain amount of selection bias into the present study.

6.7 Conclusions

The results of the present study suggest that patients without comorbid conditions may require additional support in order to remain persistent and / or adherent to their prescribed OAH regimen. Individuals who are likely to become non-adherent or non-persistent should be provided with additional professional advice and support on the importance of taking their medications in reducing the likelihood of chronic complications. The results of the present study suggest that, although, medication taking behaviour does not substantially differ by region in Ireland, it is affected by the presence of any comorbidity. Therefore, any intervention planned to optimise medication taking behaviour in patients with T2DM should be implemented on a national basis with particular emphasis on those without any apparent comorbidity.

Chapter 7: Comorbidity, health-related quality of life and self-care in Type 2 diabetes: A cross-sectional study in outpatient population.

Under review: the Irish Journal of Medical Science

7.1 Abstract

Background: Comorbidity is common in patients with type 2 diabetes (T2DM) and is associated with reduced health-related quality of life (HRQoL) and self-care. The aim of this study was to examine the impact of comorbidity on HRQoL and self-care in T2DM patients attending an outpatient setting.

Methods: A cross-sectional anonymised questionnaire was sent to 498 patients with T2DM, aged 25-80 years, previously attending (August 2011 and July 2012) an outpatient diabetes service in a Dublin hospital. The EuroQoL-5 Dimension (EQ-5D) and a modified Summary of Diabetes Self-Care Activities Scale were used to assess HRQoL and self-care respectively. Comorbidity was assessed using a simplified version of the Self-Administered Comorbidity Questionnaire. Mann-Whitney and Kruskal-Wallis tests were used to examine the association between EQ-5D index scores or self-care, and the number and type of comorbid conditions. Multiple linear regression analysis, adjusted for age and sex, was used to examine the association between EQ-5D score, comorbidity score and type.

Results: EQ-5D scores decreased with an increasing number of comorbid conditions and with discordant comorbidity (p=0.0001). Type of comorbidity was associated with physical activity. The highest level of physical activity was reported in respondents with no comorbidity (median 4.5 IQR 3 – 6), while the lowest was in patients with both concordant and discordant comorbidity (median 2.5 IQR 0 – 5).

Conclusions: Health professionals should be aware of the fall in HRQoL associated with comorbidity. This should be taken into account in the management of patients with T2DM. Patients with discordant comorbidity should be advised and supported to maintain adequate levels of physical activity.

7.2 Background

Type 2 diabetes mellitus (T2DM) is associated with a wide range of both macrovascular and microvascular complications. Continuous self-care and medical management are necessary in order to prevent or manage the onset of these complications (282). In addition, diabetes related self-care is associated with better patient quality of life, lower mortality and reduced health care expenditure (99). However, diabetes self-care is often difficult for patients to maintain (123). Optimal treatment of T2DM requires patients to adhere to a multi-faceted regimen including maintenance of a healthy diet, physical activity, weight control, self-monitoring of blood glucose levels and often adherence to prescribed medication (283). Patients with T2DM frequently experience other medical conditions (comorbid) conditions that may be pathophysiologically related (concordant) or unrelated (discordant) to their diabetes (79). Previous research has shown that the presence of comorbidity is a significant barrier to participation in diabetes related self-care (99).

Health Related Quality of Life (HRQoL) is a term used to describe the effect of health, sickness and therapy on a person's quality of life (129). The importance of HRQoL as a patient outcome parameter in both clinical and health service research has increased during the last two decades (130). Measures of HRQoL can also be used to examine differences in patient health status resulting from disease progression or the acquisition of complications (138). Previous research has shown that individuals with T2DM have a lower HRQoL compared to individuals without the condition (136) and that the development of complications further reduces patient HRQoL (284).

There have been few published studies relating to HRQoL or the performance of self-care activities in patients with T2DM in Ireland. The aim of this study was to examine the effect of the number and type of comorbid conditions on HRQoL and diabetes-related self-care in a cohort of patients with T2DM recently attending a diabetes outpatient service in a large Dublin hospital.

7.3 Methods

Participant selection & recruitment

St James's hospital (SJH) is a large university teaching hospital, located in Dublin. The Diabetes Day Centre (DDC) provides outpatient services for those with diabetes (type 1 and 2). Over the last decade, approximately 8,000 patients with T2DM have attended the DDC (184). Clinical, demographic and administrative information for each patient referred to the DDC is recorded in a hospital based administrative database (DIAMOND), and is

updated after each outpatient appointment (184). Individuals were eligible for inclusion in the present study, if they had a diagnosis of T2DM, were aged 25 - 80 years and had attended the DDC in SJH on at least one occasion between August 2011 and July 2012.

A preliminary list of 2000 patients matching the inclusion criteria was generated. From this list a random sample of 500 patients was selected using a list of random numbers (www.randomization.com). Two patients were subsequently excluded from the cohort of potential participants, because no valid community dwelling address was available for them. The remaining 498 potential participants were sent a copy of the questionnaire to return via a pre-paid envelope. Potential participants were advised that, due to the anonymous format of the questionnaire, completion would be taken as consent to participate in the study. Ethical approval for this study was obtained from St James's Hospital and The Adelaide, Meath incorporating the National Children's Hospital (SJH/AMNCH) Joint Research Ethics Committee.

Instrument development & design

The questionnaire used in the present study, was constructed using a number of previously validated instruments and questions derived from the published literature. A pilot study was carried out on a small number of patients attending the DDC (n=17). The final questionnaire was separated into four sections and was composed of 42 questions.

Section one contained a series of demographic and socio-economic questions, relating to age, gender, education, employment, marital and health insurance status of the respondent. The second section examined their current HRQoL using the EuroQoL 5 Dimension (EQ-5D) instrument. The EQ-5D is a standardised instrument that provides a single utility value for health status (285). The EQ-5D has been extensively used in patients with a wide range of health conditions (169, 286) including diabetes (171, 287) and is short and cognitively simple to use (169). The instrument is composed of a five item descriptive system of health states (one item for each of the following; mobility, self-care, usual activity, pain/discomfort, and anxiety / depression) and a visual analogue scale (VAS) (167). By utilising preference weights obtained from a sample population, a single utility index score can be derived from the scores of the five health states (167). The original preference weights derived from samples of the UK population were used in the present study (172).

Section three of the questionnaire addressed current diabetes status (including duration, diabetes-related complications and treatment) medication adherence and diabetes-related self-care. Patient adherence to glucose lowering medication was assessed using the Morisky Medication Adherence Scale (MMAS). The MMAS consists of four dichotomous

yes/no questions relating to previous medication use (160). Scoring of the scale is as follows; 1 point for yes; 0 point for no. A total score of 0 = high adherence, 1 - 2 points = moderate adherence, 3 - 4 points = low adherence (165). The sub-section of the questionnaire relating to diabetes self-care was taken, with minor adjustment, from the Summary of Diabetes Self-Care Activities (SDSCA) scale (173). The SDSCA scale measures the frequency of self-care activities across six different areas relating to diabetes self-care (general diet, specific diet, exercise, blood glucose testing, foot care and smoking) by the patient over the previous seven days (173).

Section four of the questionnaire, relating to comorbidity, used a simplified version of the Self-administered Comorbidity Questionnaire (SCQ) (177), containing 12 common medical problems. The SCQ has been used in several studies to assess comorbidity in patients with different index conditions (288, 289). The simplified SCQ was used to calculate a comorbidity score for each respondent. As the proportion of respondents that reported 4 or more comorbid conditions was relatively small, they were grouped together for the purpose of analysis. In order to determine the effect of different types of comorbidity on HRQoL and diabetes self-care, two comorbidity sub-scores were also developed. The first was composed of conditions considered to be concordant with diabetes (heart disease, kidney disease and hypertension) and the second was composed of conditions considered to be discordant to diabetes (lung disease, ulcer or stomach disease, liver disease, anaemia or other blood disease, cancer, depression, osteoarthritis, back pain, and rheumatoid arthritis).

Sample size calculation

A sample size calculation was conducted to estimate the correlation between comorbidity and the outcomes of interest (e.g. HRQoL) of 0.2 or greater, with 80% power and two-sided significance of 5%. The number required was n=200. However, given the expected response rate of 50%, the sample size was doubled to 400, and further inflated by 25% to take into account the possibility of respondents not having any comorbid conditions giving a total sample size of 500 patients.

7.4 Data analysis

Data from the returned questionnaires was entered into a database (Microsoft Access 2010, Microsoft Corporation). Descriptive statistics for categorical variables are presented as percentages and continuous data as medians with interquartile ranges (IQR). The univariate association between EQ-5D index scores and socio-demographic covariates, comorbidity score (as based on the modified SCQ) and type of comorbidity (concordant alone, discordant alone, both concordant and discordant or none) were assessed using

nonparametric Mann - Whitney and the Kruskal - Wallis tests. Multiple linear regression analysis was used to investigate the association between EQ-5D index scores and comorbidity score and type (reference: none), adjusting for age (reference: 25 - 44 years) and gender (reference: female). Beta coefficients and standard errors are provided. The beta coefficient can be used to interpret both the direction and effect size of a given exposure. A beta coefficient value that is not significantly different from zero is interpreted as meaning that there is no association between two variables (supportive of the Null Hypothesis). A positive value significantly different from zero indicates that there is a positive association, while a negative significant value is indicative of a negative association (290). The further away from zero (either positive or negative) the beta coefficient is, the greater the effect of the exposure in terms of its clinical significance. Similar statistical analyses were conducted for all individual subscales of the SDSCA scale. SAS v 9.1 (SAS Institute Inc, Cary, USA) was used for all data analyses. Significance at $p < 0.05$ was assumed.

7.5 Results

A total of 159 of 498 (32%) questionnaires were completed and returned. In terms of demographic characteristics, 60% of respondents were male and over 78% were aged 55 years or more. The majority of respondents stated that they were currently married or co-habiting with a partner (64.9%) and that they were retired or not in employment (71.6%). In relation to formal education, 46.5% of respondents had completed secondary education while an additional 19.4% had completed a third level or postgraduate qualification.

Over half of the respondents (55.3%), were diagnosed with diabetes for more than 6 years duration. Almost all respondents (96.8%) stated that they were currently being treated for their diabetes, with the vast majority (87.2%) prescribed some form of pharmacological therapy to control their blood glucose level. Most of the respondents (59.6%) were prescribed oral anti-hyperglycaemic (OAH) agents, while an additional 20.5% were prescribed OAH agents in combination with insulin. The majority of patient prescribed glucose lowering medication (68.3%) reported that they were fully adherent according to MMAS criteria (MMAS score 0), while an additional 29.6% were shown to be moderately adherent (MMAS score 1-2). Most of the respondents (85%) reported that they had received some form of education about their diabetes. The demographic and diabetes-related characteristics of respondents are summarised in *table 7.1*.

Comorbidity was highly prevalent in the present study, with the vast majority (77.9%) reporting the presence of at least one common medical problem included in the modified SCQ. The most common comorbidity reported was hypertension (59%) (Table 7.1.1). The

median number of comorbid conditions was 1 (IQR 1 – 3). Thirty-seven per cent (N=57) reported having both concordant and discordant comorbid conditions, 27% (N=42) reported only concordant conditions while an additional 13.6% reported only discordant conditions. Seventy-one respondents (45.5%) reported the acquisition of at least one diabetes-related complication.

Table 7.1 Demographic characteristics of questionnaire respondents (N=159)

Characteristics	*N*	*%*
Sex	154	
Male	92	59.7
Female	62	40.3
Age	155	
25 - 44	10	6.5
45 - 54	23	14.8
55 – 64	44	28.4
65 - 69	28	18.1
70 – 74	27	17.4
75 - 80	23	14.8
Marital status	*154*	
Single	24	15.6
Separated / Divorced	16	10.4
Married / Co-habiting	100	64.9
Widowed	14	9.1
Formal Education	154	
Primary	52	33.8
Second level	72	46.8
Third level and above	30	19.5
Employment status	155	
Employed	44	28.4
Unemployed / Retired	111	71.6
Diabetes duration	158	
less than 1 yr.	6	3.80
1 - 3 yrs.	29	18.35
3 - 6 yrs.	36	22.78
6 - 9 yrs.	25	15.82
more than 10 yrs.	62	39.24
Type of treatment	156	
Not currently receiving treatment	5	3.21
Diet	15	9.62
Oral anti-hyperglycaemic agents (OAH)	93	59.62
Insulin	4	2.56
OAH and insulin	32	20.51
OAH and other injectable agent ex insulin	7	4.49
Diabetes related education*		
Group classes	30	19.61
Individual advice from a health professional	92	60.13
Reading material related to diabetes	84	54.9
Internet	27	17.65
Other	9	5.88

Table 7.1.1 Prevalence of the 12 common conditions included in the SCQ (N=154)

Condition	*N*	*%*
Heart disease	27	17.53
Hypertension	91	59.09
Kidney disease	13	8.44
Lung disease	12	7.79
Stomach disease	16	10.39
Liver disease	5	3.25
Blood disorder	12	7.79
Cancer	4	2.6
Depression	19	12.34
Osteoporosis	22	14.29
Back pain	28	18.18
Rheumatoid arthritis	17	11.04

A utility score for the EQ-5D was calculated for 88.7% of respondents (*table 7.2*). The median EQ-5D index score for this cohort was 0.80, IQR 0.69 – 1.00 (mean 0.76 + SD 0.27). The median VAS score was 75 IQR 60 – 89 (mean 72 + SD 19.32). In univariate analysis, respondents reporting the presence of at least one complication related to their diabetes had a lower median EQ-5D score when compared to respondents without a diabetes-related complication (p=0.0003) (*table 7.2*). In addition, an increasing number of comorbid conditions was statistically associated with a decline in median EQ-5D scores (p<0.0001) (*table 7.2*). The type of comorbidity present was also found to have a significant effect on EQ-5D index scores (p<0001) (*table* 7.2). The median EQ-5D score for respondents reporting only discordant comorbid conditions was lower than those who reported only concordant comorbid conditions (*table* 7.2). Respondents reporting the presence of both concordant and discordant comorbid conditions had the lowest median EQ-5D score (*table* 7.2). Demographic variables including gender, age and marital status and diabetes-related factors, such as duration and type of treatment, were not found to be statistically associated with median EQ-5D scores in univariate analysis (*table 7.2*).

Table 7.2 EQ-5D median scores; stratified by demographic and diabetes-related variables as well as comorbidity status.

Variables	N	Median EQ-5D index score (IQR)	P value
Entire cohort	141	0.80 (0.69 – 1.00)	
Sex			0.08
Male	82	0.82 (0.73 – 1.00)	
Female	56	0.74 (0.67 – 0.92)	
Age group			0.83
25 – 44 yrs.	10	0.92 (0.73 – 1.00)	
45 – 54 yrs.	22	0.85 (0.73 – 1.00)	
55 – 64 yrs.	42	0.80 (0.73 - 1.00)	
65 – 69 yrs.	26	0.83 (0.66 – 1.00)	
70 – 74 yrs.	22	0.80 (0.69 – 1.00)	
75 – 80 yrs.	19	0.80 (0.69 – 1.00)	
Marital status			0.69
Single	23	0.80 (0.73 – 1.00)	
Married or co-habiting	94	0.80 (0.73 – 1.00)	
Separated or divorced	16	0.76 (0.64 – 0.92)	
Widowed	12	0.79 (0.67 – 0.93)	
Formal education			0.19
Primary	44	0.80 (0.73 – 0.85)	
Secondary	67	0.80 (0.66 – 1.00)	
Third level and higher	29	0.85 (0.73 – 1.00)	
Diabetes treatment			0.24
Diet alone	14	1.00 (0.73 – 1.00)	
OAH therapy	85	0.80 (0.69 – 1.00)	
Insulin	2	0.85 (0.85 – 0.85)	
OAH and insulin	29	0.76 (0.67 – 0.90)	
OAH and other injectable	6	0.77 (0.19 – 0.85)	
Diabetes duration			0.52
0 - 3 yrs.	32	0.76 (0.71 – 1.00)	
3 – 6 yrs.	32	0.76 (0.71 – 1.00)	
6 – 9 yrs.	21	0.85 (0.66 – 1.00)	
10 yrs. or more.	55	0.80 (0.66 – 0.85)	
Diabetes-related complications			0.0003
Present	65	0.73 (0.66 – 0.85)	
Absent	74	0.85 (0.73 – 1.00)	
Diabetes education			0.26
Yes	117	0.80 (0.73 – 1.00)	
No	20	0.76 (0.47 – 0.93)	
Comorbidity type			<0.0001
None	31	1.00 (0.85 – 1.00)	
Concordant comorbidity only	36	0.87 (0.80 – 1.00)	
Discordant comorbidity only	19	0.73 (0.62 – 0.85)	
Both concordant and discordant comorbidity	52	0.71 (0.52 – 0.80)	
Number of comorbid condition			<0.0001
0	31	1.00 (0.85 – 1.00)	
1	40	0.85 (0.78 – 1.00)	
2	30	0.76 (0.66 – 0.85)	
3	23	0.69 (0.52 – 0.80)	
≥4	14	0.35 (0.00 – 0.69)	

Table 7.3 Multiple Linear Regression model examining predictors of EQ-5D index score [a]

Variable	*Beta Coefficient*	*SE*	*P value*
Diabetes complications present vs absent	-0.16	0.05	0.001
SQC score vs. no comorbid conditions	-0.14	0.02	<0.0001
Concordant comorbidity alone [b]	-0.07	0.06	0.22
Discordant comorbidity alone [b]	-0.28	0.07	0.0001
Both concordant and discordant comorbidity [b]	-0.32	0.06	<0.0001

[a] adjusted for age and sex
[b] compared to no comorbid conditions

In this study, multiple linear regression, adjusting for age and sex, found that the presence of at least one diabetes-related complication was associated with a statistically significant decrease in EQ-5D index scores (p=0.001) (*table 7.3*). The beta coefficient can be used to assess effect size. For instance, in this example, the beta coefficient is minus 0.16, which means that HRQoL, as assessed using the EQ-5D, is lower in those with diabetes-related complications by 0.16 points on the EQ-5D scale compared to those without. Furthermore, an increasing number of comorbid conditions (SCQ score) and either the presence of discordant comorbidity alone (p=0.0001) or in combination with concordant comorbidity was also significantly associated with a decline in EQ-5D index score (p<0.0001) (*table 7.3*). In contrast, the presence of concordant comorbidity alone was not found to have any statistically significant effect on EQ-5D index scores (*table 7.3*).

In terms of self-care activities, the presence of diabetes-related complications or an increasing number of comorbid conditions was not found to be statistically associated with any aspect of diabetes self-care included in the SDSCA scale. Type of comorbidity was found to be significantly associated with participation in physical activity (p=0.04), but not with the other areas of diabetes self-care. Respondents with no comorbidity had the highest median value 4.5 (IQR 3 – 6) for physical activity. This indicates that on average, these individuals participated in any physical activity for at least 30 minutes as part of their daily routine (example house cleaning), or had taken part in a specific aerobic exercise session (example swimming, cycling etc.) on approximately 5 days in the previous week. In contrast, respondents reporting both concordant and discordant comorbidity had the lowest median value 2.5 (IQR 0 – 5) for the physical activity subscale, while similar values were observed for those reporting either only concordant (median 4.0, IQR=3 – 6.5) or discordant comorbidity (median 3.75, IQR=2 – 5.5).

7.6 Discussion

The results of the current study found that patient HRQoL as measured using the EQ-5D index was negatively associated with the presence of diabetes-related complications, as well as with the number and type of comorbid conditions present. In contrast, the presence of diabetes-related complications and an increasing number of comorbid conditions was not found to be associated with any specific aspects of diabetes-related self-care, as measured using the SDSCA. Type of comorbidity was, however, found to be associated with the physical activity subscale of the SDSCA, with those having both discordant and concordant comorbidity reporting the lowest level of physical activity.

In terms of HRQoL, the negative effect of diabetes-related complications described in this study, is in keeping with the results of previous research, which have consistently shown a correlation between the presence of complications and reduced HRQoL in patients with T2DM (291, 292). Furthermore, the negative association of increasing number of comorbid conditions with decreasing HRQoL is consistent with the findings from other studies (142, 293).

Previous research has indicated that a number of common medical conditions are associated with the lower HRQoL in patients with T2DM. These have included conditions related to the cardiovascular system that are concordant to diabetes, such as, myocardial infarction (294), heart disease (295) and heart failure (294) and discordant conditions including depression (129, 294) and osteoarthritis (130).The results of this study also suggest that the presence of discordant comorbid conditions either alone or in combination with concordant comorbid conditions have a detrimental effect on patient HRQoL. However, in contrast to previous research, the presence of concordant comorbidity alone was not, in the current study, associated with a lower HRQoL. It is possible that the high prevalence of reported hypertension (59%) in patients with concordant conditions in the present study, may have contributed to this finding. Hypertension is mainly an asymptomatic condition. Previous research has shown that asymptomatic conditions have less impact on patient HRQoL compared to symptomatic conditions such osteoarthritis (130).

In terms of self-care, patients with comorbidity have often reported difficulty in relation to diabetes self-care (99). The management of comorbid conditions with diabetes has been shown to significantly reduce the amount of time, energy and financial resources patients have to adequately care for their diabetes (79). In addition, depending on the severity of the comorbid condition(s) present, diabetes self-care can be complicated and its priority reduced (80, 87). Previous research found that the presence of discordant comorbidity is

associated with a reduction in the ability to perform diabetes self-care activities (80). In contrast, no area of diabetes self-care measured in the present study was found to be negatively affected by an increasing number of comorbid conditions or the presence of diabetes related complications.

Type of comorbidity was found to be significantly associated with participation in physical activity, but not with the other aspects of diabetes-related self-care. Respondents with both concordant and discordant comorbidity had the lowest level of reported engagement in physical activity. It is likely that the high level of morbidity reported by these respondents may have limited their ability to engage in physical activity. Previous research has indicated that the presence of serious illness is often cited by patients as a reason for reduced physical activity (296, 297). In addition, it has also been shown that symptoms such as joint pain and fatigue often prevent participation in physical activity, even in individuals that are aware of the importance of exercise (298).

Overall, the relatively high level of diabetes self-care reported in the present study may have been influenced by the fact that the majority of respondents reported having had some form of diabetes education. Previous research has indicated that patients are more likely to carry out diabetes related self-care activities if they are more knowledgeable about their diabetes (299) or have received self-care training (300). Diabetes self-care education programmes utilising behavioural altering techniques (e.g. cognitive reframing) have been associated with improved clinical outcomes in many different countries (301). However, further patient education and on-going support may be required if improvements to clinical outcomes and self-management behaviours are to be sustained in the long term (128).

In Ireland there are a number of examples of structured education programmes relating to diabetes self-care available to patients with T2DM, including Community Orientated Diabetes Education (CODE), Diabetes Education and Self-Management for Ongoing and Diagnosed (DESMOND), and Expert Patient Education versus Routine Treatment (X-PERT) Ireland (302). These have been reviewed by the Diabetes Expert Advisory Group (DEAG) education and empowerment subgroup (303). These programmes provide information on living with diabetes, its treatment, self-care requirements and possible complications. Diabetes educators can help provide additional information and support to patients with discordant comorbidity in order to optimise diabetes-related self-care.

The present study has a number of strengths, specifically in terms of the methods used. The use of a random sampling reduced the possibility of selection bias. In addition, the questionnaire used a number of instruments that have been previously validated and

psychometrically tested for use in similar patient populations. The use of an anonymous postal format also encouraged respondents to respond in a more truthful manner.

The main limitation was the low response rate (32%) as a result it is possible that some of the reported associations, including those relating to individual components of the SDSCA scale may have been underpowered except for exercise where a significant association was observed. The provision of a second, perhaps shorter version of the questionnaire, sent a couple of weeks after the initial questionnaire, may have increased the response rate in the present study (304). Limiting the recruitment of patients in the present study to individuals that had attended a specialist diabetes clinic in a hospital setting may have reduced the generalisability of the results. Diabetes care is provided to patients in Ireland through a number of different pathways including mixed care, hospital led care, shared care and primary care led arrangements (268). Patients receiving care in different settings may have disparate characteristics and / or treatment requirements. For example, the percentage of patients who reported that they were treated using diet alone in the present study (12%) is considerably less than the of participants treated using diet alone in a previous Irish study conducted in general practice (22.7%) (305). The low response rate and the single study site location may have introduced bias in those responding compared to non-responders and may have affected the generalisability of the results. There also may have been some overlap between respondents reporting concordant comorbidity and diabetes-related complications.

7.7 Conclusions

Health professionals and policy makers should be aware of the lower HRQoL associated with the increasing numbers of comorbid conditions, diabetes-related complications, discordant comorbidity and the cumulative effects of having both concordant and discordant comorbidity present when deciding on the overall management of patients with T2DM. Patients with discordant comorbidity should be actively encouraged to engage in diabetes-related education and should be given additional advice relating to improving their diabetes care and other conditions as well as with support to enable participation in physical activity.

Chapter 8: Thesis Conclusion

8.1 Summary of main research findings.

The overall aim of this thesis was to investigate the prevalence, type and potential implications of comorbidity in patients with T2DM in Ireland, in terms of cost and impact on medication taking and self-care by the following objectives:

1. Investigation of the prevalence, type and ingredient drug cost of comorbidity associated with pharmacologically treated T2DM in the GMS eligible adult and elderly populations in Ireland.
2. Examination of the influence of comorbidity and region of residence on adherence and persistence to oral anti-hyperglycaemic (OAH) agents in the GMS eligible population.
3. Investigation of the impact of comorbidity on diabetes self-care and health-related quality of life (HRQoL) in a diabetes population attending an Irish hospital outpatient department.

The results of the first two studies presented in this thesis (Chapter 3 & 4) relate to the first research objective. The results of these two studies found that during 2010, the prevalence of medication treated T2DM in the GMS eligible adult (25 – 64 years) and elderly (≥65 years) population was 3.1% and 9.7% respectively. These studies also found that that the median number of comorbid conditions was significantly higher in patients with medication treated T2DM, when compared with those without the condition, in both the adult (3 vs. 0 comorbid conditions) and elderly (5 vs. 3 comorbid conditions) patient populations.

The higher level of comorbidity in the elderly GMS eligible population with medication treated T2DM, compared to their peers without the condition, is consistent with the findings of previous research (201, 202). To date, however, relatively few studies have examined the presence of multiple conditions in younger adults (189, 306). The results of the research presented in chapter 4, show that the presence of a higher number of comorbid conditions in patients with medication treated T2DM is not only confined to elderly, but that it is also an issue which can affect both young (25 – 44 years) and middle aged (45 – 64 years) patients with T2DM.

The higher level of comorbidity in patients with medication treated T2DM was associated with a significant increase in drug expenditure in patients with T2DM compared to those without, equating to a mean difference of €717.29 in the adult and €439.26 in the elderly cohort. Diabetes-related (i.e. concordant) comorbid conditions associated with the cardiovascular system, namely hyperlipidemia, heart disease, anti-platelet therapy and hypertension, were shown to account for a substantial proportion of treated comorbidity in both the adult and elderly GMS population, with and without T2DM. Gastric reflux / peptic ulcer and depression were found to be the most prevalent co-prescribed discordant conditions in both the adult and elderly cohorts. Irrespective of age category, the prevalences of these conditions were individually found to be higher in the patient cohort with medication treated T2DM compared to the cohort without the condition.

There is extensive literature detailing the economic consequences of diabetes (42, 43, 46, 47). To date, most of this research has concentrated on direct costs of diabetes-related care and complications. The results of the research presented in chapter 3 and 4 of this thesis, add to this literature by demonstrating the additional drug cost of both concordant and discordant comorbidity in the elderly and adult patients with T2DM.

The results of the two studies presented in chapter 5 and 6 relate to the second research objective. The first of these studies (Chapter 5) examined the influence of comorbidity on medication taking behaviour in new users (designated as no prescription claim in the previous six months) of any OAH therapy. The overall rate of persistence and adherence to OAH therapy persistence was 74% and adherence 70% at 6 months, and 62.6% for persistence and 66.6% for adherence at 12 months post initiation. The presence of comorbidity was very common among this patient cohort, with the vast majority (83.4%) prescribed medication for at least one chronic comorbid condition in addition to their anti-diabetic medication. The presence and type of comorbid condition was shown to influence medication taking behaviour in this study.

Patients who were not in receipt of any medication for comorbid conditions were found to have the lowest rates of persistence and adherence to OAH therapy. In contrast the rate of persistence and adherence to OAH agents was shown to increase with rising numbers of comorbid conditions. Furthermore, when comorbidity was stratified by type, patients with only concordant conditions were significantly more likely to be persistent at 6 (OR 1.45) and 12 months (OR 1.22) when compared to patients either without any comorbidity or with both types of comorbidity. In contrast patients with only discordant conditions were significantly less likely to be persistent at 6 (OR 0.40) and 12 months post initiation (OR

0.43 when compared to the same reference group). A similar trend was observed with regards to adherence to OAH therapy at both 6 and 12 month post therapy initiation.

The second study (Chapter 6) examined the influence of both region of residence and comorbidity on patient medication behaviour in new users of either metformin or a sulphonylurea 12 months post therapy initiation. The results of this study showed that, overall, there was little variability between the four HSE administrative regions in terms of patient medication taking behaviour. The largest reduction for both non-persistence and non-adherence was observed in HSE region South. In addition, the co-prescription of medication for the treatment of different types of comorbidity did not differ significantly between the four HSE regions. The presence of any type of comorbidity (versus no comorbidity) was shown to be associated with a reduced risk of both non-persistence and non-adherence to OAH therapy in all four HSE regions.

Poor medication taking behaviour in patients with diabetes contributes to inadequate glycaemic control (115), which is associated with the development of diabetes-related complications (117). Previous studies that have examined the effect of comorbidity on medication taking behaviour in patient's prescribed anti-hyperglycaemic medication have presented conflicting results (103, 115). The results of the research presented in chapter 5 and 6, add to the existing literature by demonstrating that the presence of comorbidity was associated with better medication taking behaviour in a large cohort of patients up to 12 months post OAH initiation.

In addition, few studies have looked at the potential impact of different types of comorbid conditions on medication taking behaviours. The studies which have been published have concentrated on medication taking behaviour of patients prescribed anti-hypertensive medications (253, 254, 256). The research presented in this thesis, adds to the existing literature by providing evidence to suggest that different types of comorbid conditions have different effects on medication taking behaviour in patients newly prescribed oral anti-hyperglycaemic therapy.

Few studies have examined regional variation in relation to medication taking behaviour (276). Examination of regional data may be useful in identifying areas of the country, which may benefit from the introduction of a targeted intervention to improve medication taking behaviour. The overall lack of clinically important variation in medication taking behaviour between regions, demonstrated in chapter 6, may suggest that factors that facilitate patient medication taking, such as the provision of diabetes-related education,

did not vary substantially between regions. This suggests that future interventions aimed at optimising medication taking behaviour in patient's prescribed OAH therapy, should be contemplated on a national basis with the aim of improving the overall level of both persistence and adherence nationally.

The results presented in the Chapter 7 relate to the last research objective and are based on the analysis of questionnaire data, which was provided by patients with diabetes that had attended the diabetes day centre in St James's Hospital, Dublin. Similar to the other studies in this thesis, the presence of comorbidity was very common in this study population, with the majority of patients (77.9%) reporting the presence of at least one other medical problem in addition to their diabetes. The median number of comorbid conditions in patients that took part in this study was 1 (IQR 1 – 3), which is considerably less than the median values in the previous GMS studies reported in this thesis. It is likely, however, that this may relate to the relatively small number of conditions included in the SCQ instrument rather than an actual lower prevalence of comorbidity. It is also possible that study participants may have failed to recall or include conditions when filling out the self-completed questionnaire.

In terms of diabetes self-care, type of comorbidity was found to be significantly associated with the physical activity subscale of the SDSCA. Respondents with no comorbid conditions had the highest median value for physical activity compared to those with both types of comorbid conditions. Type of comorbidity was not found to be associated with any of the other SDSCA subscales. In addition, the presence of diabetes-related complications or an increasing number of comorbid conditions were not shown to be associated with any diabetes-related self-care activities. According to the Morisky scale 68% per cent of participants in this study reported being fully adherent with their anti-diabetic medication, while an additional 29% reported moderate adherence. This is higher than the rate of adherence reported in the GMS studies. The data relating to disease duration shows that nearly 98% of participants were prevalent cases diagnosed with T2DM for $\geq$12 month. The data from GMS studies relates to incident cases only. Previous research has shown that the greatest decline in medication persistence and adherence occurs within the first twelve months (ref). The high percentage of prevalent cases in this study may have influenced the observed rate of adherence.

In terms of HRQoL, diabetes-related complications and an increasing number of comorbid conditions were associated with a significant decrease in EQ-5D (HRQoL) score compared to no complications / comorbid conditions. Furthermore, the presence of discordant comorbidity either on its own or in combination with concordant comorbidity

was also associated with a significant decline in EQ-5D score compared to no complications / comorbid conditions. The presence of concordant comorbidity on its own was not, however, found to significantly affect the EQ-5D scores of the respondents.

8.2 Main limitations

The limitations of each of the five studies presented in this thesis have been discussed previously in detail in each of the relevant chapters. This section provides the most pertinent limitations and their implications with respect to the validity of the outcomes reported in this thesis.

In Ireland, blood glucose lowering medications are provided to all patients with diabetes (>95%) through one of two community health schemes, the GMS and the long term illness (LTI) scheme (184). Given that the LTI scheme covers only a limited number of medicines associated with diabetes, it was not possible to ascertain the level of comorbidity in patients that received their anti-diabetic medication through the LTI. The results presented in the first four studies of this thesis, therefore, only relate to GMS eligible patients.

The HSE-PCRS pharmacy claims database does not contain any clinical information or medical diagnoses. For the purpose of the first four studies presented in this thesis, patients with T2DM were identified using the prescription of OAH medication as a proxy for disease diagnosis. One of the main limitations of using this method was that it was unable to identify patients with diagnosed T2DM who were only modifying their lifestyle without medical intervention. It is, therefore, likely that the prevalence / incidence of T2DM reported in each of the four studies, which used the HSE-PCRS database, represents an underestimate of the true prevalence / incidence of this condition in the GMS eligible population.

The prevalence of comorbid conditions in each of the four GMS based studies was also ascertained by proxy, using modified versions of the prescription based RxRisk and RxRisk V indices. The use of prescription based comorbidity indices, although pragmatic due to the data available, limited the identification of comorbidity to conditions that were treated using pharmacotherapy. A further limitation was that medication listed for specific conditions included the indices may have several indications. In order to minimise the potential for disease misclassification, which may have led to over or under estimation of the prevalence of a particular disease, the major therapeutic use was used to assign specific therapeutic agents to represent a single disease.

In spite of the aforementioned limitations, recent research has shown that the HSE-PCRS database is a relatively accurate and up-to-date source of information about medication dispensed through the GMS scheme (307). In addition, the raw data supplied by the HSE-PCRS for the purpose of the first four studies presented in this thesis, were cleaned and checked prior to any statistical analyses being carried out. Subsequent inclusion criteria, for example age categories, excluded any patients with missing or age outside of the specified ranges from the data files. All results from the analyses were verified and checked for consistency. All data manipulation and statistical analyses were performed using SAS (version 9.1), which is a large powerful statistics package that has been used in many previous pharmacoepidemiological studies for manipulating and analysing large datasets.

8.3 Implications and future directions

The results of the first two studies presented in this thesis provide a baseline estimate of a broad range of comorbid condition in GMS eligible patients, with and without medically treated T2DM, in an adult and older aged population. Few previous Irish studies have examined the occurrence or impact of comorbid conditions in patients with diabetes (195-197). Furthermore, the majority of those that have been published have only looked at the occurrence or impact of relatively few comorbid conditions. A recent study by Teljeur et al, investigated the prevalence of different comorbid conditions in patients with T2DM in primary care, however, the study was smaller (n=425) and was limited to patients over the age of 50 years (78). Evidence from research conducted in other developed countries suggests that the age of onset of T2DM is decreasing (7, 218). It is important, therefore, to incorporate a wider range of age groups into T2DM research.

The results of the research in this thesis show that the treatment of comorbid conditions in GMS eligible patients with T2DM is associated with increased annual drug expenditure. If the prevalence of comorbidity increases in line with the projected increase in prevalence of T2DM, the cost of treating diabetes and comorbid conditions will have major financial implications for the health service in the future. Furthermore, previous research has shown that patients with multiple medical conditions attend their primary care physician more often and are hospitalised more frequently, compared to patients with fewer medical conditions (67). Therefore, any increase in the prevalence of comorbidity in patients with T2DM may also have important implications in terms of both the provision and financing of future health care services. Further research on the prevalence of both concordant and discordant comorbid conditions over time may provide useful information on the prevalence and types of comorbidity in patients with T2DM, which may be potentially

useful in the planning future health services. Epidemiological trend analyses carried out in large populations normally presents data that has been collated over an extended period of time (≥10 years) (308). Previous research by Zaharan et al, has shown that HSE-PCRS data may be successfully used to retrospectively analyse epidemiological trends in prescribing over such a period (149).

As economic evaluations relating to the costs of T2DM have only included costs estimates relating to concordant conditions and/or diabetes-related complications, further research should consider other costs associated with discordant conditions which were significant. Linkage of the GMS and Hospital Inpatient Enquiry (HIPE) system data may be able to provide a means of examining the utilisation of hospital inpatient services with the aim of estimating costs in patients with T2DM with different types of comorbid conditions. Each patient who is eligible for inclusion in the GMS scheme has a unique medical card number. This number is recorded upon each admission of a GMS eligible patient to an acute hospital partaking in the collection of HIPE data (62 hospitals nationally) but at present is not part of the data provided to the national HIPE database (309). The presence of such information in hospital HIPE databases, has, however, allowed for linkage between the HSE-PCRS data and HIPE data for specific hospitals (309, 310). Linked data from these two sources have been used in previous research (309, 310). Other sources of data relating to the provision of diabetes care, such as that currently being compiled by the Irish Primary Care Research Network (IPCRN), may provide a means of investigating the cost and utilisation of health services outside of the hospital setting. Furthermore, the examination of linked death registry data may potentially provide a means of examining premature mortality in this population of patients.

In terms of governance, the main concern associated with the linkage of such data sources, relates to the protection of individual privacy and the maintenance of data confidentiality (311). Under the Data Protection Acts, the data controller (i.e. the admitting hospital or the primary care physician / practice in this case), has a statutory obligation, to ensure that patient data remains confidential (183). In addition, the data controller is also responsible for obtaining informed explicit consent from the patient before identifiable data may be used for research purposes (183). Subsequent to consent being obtained from the patient, adequate safeguards must be put in place in order to ensure that personal patient data is used only for the purpose which consent was obtained and that access is restricted to only those with permission to use it (183). Electronic data should be stored on encrypted devices, while paper files should be stored in locked cabinets. Although, the removal of personal identifiers from a linked dataset may remove the need for informed

patient consent, as was the case with the linkage of the HIPE and PCRS data (309, 310), researchers still need to be mindful of data security issues and take appropriate action (183).

There is currently little information available to health professionals relating to the management of patients with multiple chronic conditions (71). Most evidence based guidelines and clinical research focuses on the management of single conditions and their related complications (72, 73). The high prevalence of both concordant and discordant comorbid conditions in patients with T2DM, as shown in this and other research (77) highlights the need to reassess the focus of current chronic disease management towards the growing number of patients with multiple chronic conditions (312). According to a recent systematic review, which included a synthesis of the qualitative literature, clinicians working in general practice frequently encounter a variety of challenges in the management of patients with multiple conditions (313). These relate to four distinct domains including; disorganisation and fragmentation of health care, inadequacy of evidence base and clinical guidelines and difficulties in the deliverance of patient centred care and shared decision making (313). The authors concluded that although, no single intervention would necessarily improve the care of patients with multiple conditions, identification of these four domains may serve as useful as targets for future intervention studies (313).

In order for pharmacotherapy to be effective it needs to be taken as prescribed (237). However, it is well recognised that patients with chronic conditions, including diabetes frequently do not take their medication as recommended (95). In patients with diabetes non-adherence to anti-hyperglycaemic therapy is associated with poorer glycaemic control (115), which may lead to the development and / or progression of diabetes-related complications (242). The treatment of diabetes-related complications has significant financial implications for both the health service and society as a whole (46, 233). Improving medication taking behaviour in patients with diabetes should, therefore, be seen as a priority for health service research and policy.

The results of the two studies pertaining to medication persistence and adherence presented in this thesis, found that the presence of comorbidity was associated with better medication taking behaviours. Previous research has suggested that patients with multiple conditions may be more knowledgeable about their diabetes leading to improved medication taking behaviour (115). However, research using administrative / pharmacy claims data is unable to assess particular reasons why some patients fail to take their

medications as prescribed. Further research incorporating qualitative methods may provide more in-depth patient-level information on behaviours such as medication taking, which may help to inform the development of interventions aimed at improving medication taking behaviour.

In spite of the low response rate, the results of the questionnaire study demonstrated the negative effect of both diabetes-related complications and an increasing number of comorbid conditions on HRQoL, which is consistent with the outcomes of other research in this area (130, 140, 141). Continuing Professional Development (CPD) training courses recognised by professional bodies, such as the Irish College of General Practitioners (ICGP) or An Board Altranais, could be used as a means of disseminating information to health professionals about the negative effect of both diabetes-related complications and comorbidities on patient HRQoL.

Participation in regular physical activity is an important aspect of diabetes related self-care, which has been shown to have a positive effect on glycaemic control (314), cholesterol and blood pressure levels (315). However, many patients with diabetes find it difficult to adhere to recommendations relating to physical activity, citing personal (e.g. tiredness) and environmental barriers (e.g. lack of local facilities) to engaging in physical activity (297). The results of the questionnaire study, found that type of comorbidity influenced engagement in physical activity. The physical limitations imposed by different combinations of comorbid conditions need to be taken into consideration when recommending physical activity to patients with diabetes. Health professionals should work in conjunction with their patients to identify realistic ways of increasing physical activity.

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Appendix I: RxRisk V (mod)

List of ATC codes used in the modified RxRisk V index stratified by diabetes discordant and concordant comorbid conditions

Discordant conditions/therapies	***ATC code***
Alcohol dependency	N07BB03, N07BB04, N07BB01
Allergies	R0AC,R01AD, R06AD02, R06AD03, R06AD04, R06AD05, R06AD06, R06AD07, R06AD08, R06AD09, R06AD52, R06AD55, R06AE, R06AK, R06AX [***excluding*** R0AX27, R06AX28, R06AX53, R06AX58]
Anxiety	N05BA01 – N05BA12, N05BB01
Benign prostate hypertrophy	G04CA02 – G04CA03.
Bipolar disorder	N0AN01
Dementia	N06DA02, N06DA03,N06DA04, N06DX
Depression	N06A
End stage renal disease	B03XA, V03AE02, V03AE03, A11CC
Epilepsy	N03AA01 – N03AA04, N03AA30, N03AB01 – N03AB05, N03AB52, N03AB54, N03AC01, N03AC02, N03AC03, N03AD01, N03AD02, N03AD03, N03AD51, N03AE01, N03AF01, N03AF02, N03AG01, N03AG02, N03AG03, N03AG04, N03AG05, N03AG06, N03AX.
Gastric-oesophageal reflux disorder and peptic ulcer	A02B
Glaucoma	S01EA01 – S01EA05, S01EA51, S01EB01 – S01EB03, S01EC03, S01EC04, S01ED01 – S01ED06, S01ED51, S01ED52, S01ED54, S01EE01 – S01EE04, S0EX01, S0EX02.
Gout	M04AA01 – M04AA03, M04AA51, M04AB01 – M04AB04, M04AC01.
Hepatitis C	J0AB54
HIV	J05AE01 – J05AE08, J05AF01 – J05AF11, J05AG01 – J05AG03, J05AR01 – J05AR06, J05AX07
Hyperkalaemia	V03AE01
Hyperthyroidism	H03AA01, H03AA02
Inflammatory bowel disease	A07EC01 - A07EC04, A07EA

Discordant conditions/therapies	*ATC codes*
Malignancies	L01AA01 – L01AA08, L01AB, L01AC, L01AD, L01AG01, L01AX, L01BA01, L01BA03, L01BA04, L01BB02 – L01BB07, L01BC, L01CA, L01CB,L01CC01,L01CD,L01CX01, L01DA01, L01DB, L01DC,L01XA, L01XB01, L01XC, L01XD01, L01XD03 - L01XD06, L01XE, L02BA01, L02BA02, L02BG02 – L02BG04, L02BG06, L02BB01, L02BB03, L02AE02, L02AE04, L02AB01.
Migraine	N02CA01, N02CA02, N02CA04, N02CA07, N02CA51, N02CA52, N02CA72, N02CB01, N02CC01 – N02CC07, N02CX01
Osteoporosis	M05BA, M05BB, M05BX03, G03XC01, A12AX92.
Pain - Opiates	N02AA, N02AB, N02AC01, N02AC03 – NO2AC05, N02AC52, N02AC54, N02AC74, NO2AD01, N02AD02, N02AE01, N02AF01, N02AF02, N02AG, N02AX01, N02AX02, N02AX52, N02AX05.
Pain – Anti-inflammatory agents	M01AB, M01AC01, M01AC02, M01AC04 – M01AC06, M01AE, M01AG, M01AH, N02BE51, N02BA01.
Pancreatic insufficiency	A09AA02
Parkinson's disease	N04AA01 – N04AA05, N04AA08 – N04AA12, N04AB01, N04AB02, N04AC01, N04AC30, N04BA01 – N04BA06, N04BB01, N04BC01 – N04BC07, N04BD01, N04BX01, N04BX02, N0BC09, N0BD02.
Psoriasis	D05BB01, D05BB02, D05AX
Psychotic illness	N05AA, N05AB, N05AC, N05AD, N05AE, N05AF, N05AG, N05AH, N05AL, N05AN01, N05AX
Chronic airways disease.	R03AC, R03AK, R03BA, R03AB, R03BC01, R03BC03, R03BX01, R03CA02, R03CB, R03CC, R03CC53, R03DA, R03DB, R03DC, R03BB.
Smoking cessation	N07BA01, N07BA03.
Steroid responsive disease (Systemic corticosteroid use)	H02AB, H02AA.
Transplant	L04AA01 – L04AA06, L04AA08 - L04AA12, L04AA14 - L04AA19, L04AA21, L04AD02, L04AX01.
Tuberculosis	J04AB04, J04AB05, J04AB30, J04AC01, J04AC51, J04AD01, J04AD02, J04AD03, J04AK01, J04AK02.
Neurogenic bladder and urinary incontinence.	V07AN
Ostomy	V027AS

Concordant conditions/therapies	
Anti-coagulation therapy	B0AA03, B01AA04, B01AA07 – B01AA11, B01AB01, B01AB02, B01AB04 – B01AB06, B01AB10.
Anti-platelet therapy	B01AC04 – B01AC19, B01AC30, B01AC22, B01AC23.
Arrhythmia	C01AA05, C01BA01 – C01BD01.
Angina	C01DA02, C01DA04, C01DA05, C01DA07 – C01DA09.
Chronic heart failure	***Must have both loop diuretic:*** C03CA, C03CB, C03CC01, C03DA ***and an ace inhibitor:*** C09AA01 – C09AA10, C09CA06, C09CA07, C09CA01, C09CA03.
Hyperlipidemia	C01AA, C10AB, C10AC, C10AD, C10AX, C10BA, CA0BX.
Hypertension	C03AA, C03AB, C03AH, C03AX01, C02CA04, C03BA02 – C03BA11, C03DB01, C03DB02, C03EA, C09BA02, C09BA03 – C009BA09, C09BB, C09DB, C09DA01 – C09DA07, C02AB01, C02AB02, C02AC01 – C02AC05, C02DB02 – C02DB04, C02DC01, C02DD01,C02DG01, C02KA01, C02KB01, C02KC01, C02KD01, C02KX01, C09XA.
Heart disease	C07AA01 – C07AA07, C07AA12, C07AA14 – C07AA17, C07AA19, C07AA23, C07AA27, C07AA57, C07AB, C07AG01, C07AG02, C07BA02, C07BA05 – C07BA07, C07BA12, C07BA68, C07BB02 - C07BB07, C07BB52, C07BG01, C07CA02, C07CA03, C07CA17, C07CA23, C07CB02, C07CB03, C07CB53, C07CG01, C07DA06, C07DB01, C07FA05, C07FB02, C07FB03, C07FB07, C08CA01 - C08CA15, C08CA55, C08CX01, C08DA01, C08DA02, C08DA51, C08DB01.

Appendix II: RxRisk (mod)

List of ATC codes used in the modified RxRisk V index stratified by diabetes discordant and concordant comorbid conditions

Discordant conditions /therapies	*ATC code*
Anxiety	N05BA01 – N05BA12, N05BB01
Asthma	R03AA, R03AB, R03AC, R03AH, R03AK, R03BA, R03BB, R03BC, R03BX, R03CA, R03CB, R03CC, R03CK, R03DA, R03DB, R03DX.
Bipolar disorder	N05AN01
Depression	N06A
Epilepsy	N03AA01 – N03AA04, N03AA30, N03AB01 – N03AB05, N03AB52, N03AB54, N03AC01, N03AC02, N03AC03, N03AD01, N03AD02, N03AD03, N03AD51, N03AE01, N03AF01, N03AF02, N03AG01, N03AG02, N03AG03, N03AG04, N03AG05, N03AG06, N03AX.
End stage renal disease	B03XA, V03AE02, V03AE03, A11CC
Gastric-oesophageal reflux disorder and peptic ulcer	A02B
Gout	M04AA01 – M04AA03, M04AA51, M04AB01 – M04AB04, M04AC01.
HIV	J05AE01 – J05AE08, J05AF01 – J05AF11, J05AG01 – J05AG03, J05AR01 – J05AR06, J05AX07
Inflammatory bowel disease	A07EC01 - A07EC04, A07EA.
Liver disease	A05AA, A05AB, A05AX, A05BA, J05AF05, J05AF07, J05AF11.
Malignancy	L01AA01 – L01AA08, L01AB, L01AC, L01AD, L01AG01, L01AX, L01BA01, L01BA03, L01BA04, L01BB02 – L01BB07, L01BC, L01CA, L01CB, L01CC01,L01CD,L01CX01, L01DA01, L01DB, L01DC,L01XA, L01XB01, L01XC, L01XD01, L01XD03 - L01XD06, L01XE, L02BA01, L02BA02, L02BG02 – L02BG04, L02BG06, L02BB01, L02BB03, L02AE02, L02AE04, L02AB01.
Parkinson's disease	N04AA01 – N04AA05, N04AA08 – N04AA12, N04AB01, N04AB02, N04AC01, N04AC30, N04BA01 – N04BA06, N04BB01, N04BC01 – N04BC07, N04BD01, N04BX01, N04BX02, N0BC09, N0BD02.
Psychotic illness	N05AA, N05AB, N05AC, N05AD, N05AE, N05AF, N05AG, N05AH, N05AL, N05AN01, N05AX
Rheumatoid arthritis	M01AA, M01AB, M01AC, M01AE, M01AG, M01AH, M01AX, M01BA, M01BX, M01CA, M01CB, M01CC, M02AA, M02AB, M02AC, M02AX, L01BA01, L04AB, L04AD01, L04AX03, L04AX04, L04AA13.
Thyroid problems	H03AA01, H03AA02.
Transplant	L04AA01 – L04AA06, L04AA08 - L04AA12, L04AA14 - L04AA19, L04AA21, L04AD02, L04AX01.
Tuberculosis	J04AB04, J04AB05, J04AB30, J04AC01, J04AC51, J04AD01, J04AD02, J04AD03, J04AK01, J04AK02

Concordant conditions/ therapies	*ATC code*
Anti-coagulation therapy	B0AA03, B01AA04, B01AA07 – B01AA11, B01AB01, B01AB02, B01AB04 – B01AB06, B01AB10.
Anti-platelet therapy	B01AC04 – B01AC19, B01AC30, B01AC22, B01AC23.
Heart disease	C07AA01 – C07AA07, C07AA12, C07AA14 – C07AA17, C07AA19, C07AA23, C07AA27, C07AA57, C07AB, C07AG01, C07AG02, C07BA02, C07BA05 – C07BA07, C07BA12, C07BA68, C07BB02 - C07BB07, C07BB52, C07BG01, C07CA02, C07CA03, C07CA17, C07CA23, C07CB02, C07CB03, C07CB53, C07CG01, C07DA06, C07DB01, C07FA05, C07FB02, C07FB03, C07FB07, C08CA01 - C08CA15, C08CA55, C08CX01, C08DA01, C08DA02, C08DA51, C08DB01.
Hyperlipidemia	C01AA, C10AB, C10AC, C10AD, C10AX, C10BA, CA0BX.
Hypertension	C03AA, C03AB, C03AH, C03AX01, C02CA04, C03BA02 – C03BA11, C03DB01, C03DB02, C03EA, C09BA02, C09BA03 – C009BA09, C09BB, C09DB, C09DA01 – C09DA07, C02AB01, C02AB02, C02AC01 – C02AC05, C02DB02 – C02DB04, C02DC01, C02DD01,C02DG01, C02KA01, C02KB01, C02KC01, C02KD01, C02KX01, C09XA.

Appendix III

Appendix III.1 Persistence with OAH therapy at 6 months post initiation, adjusting for age, sex, number of comorbid conditions, index OAH treatment and type of comorbidity.

Variable	*35 day refill gap*			*91 day refill gap*		
Age (years)	Persistence (%)	Adjusted Odds Ratio	95%CI	Persistence (%)	Adjusted Odds Ratio	95%CI
25 - 34	33.4	1.0	n/a	47.9	1.0	n/a
35 - 44	53.3	1.46	1.22 – 1.74	67.9	1.52	1.28 – 1.81
45 - 54	65.9	1.69	1.43 – 2.01	77.2	1.64	1.39 – 1.94
55 - 64	72.5	1.92	1.63 – 2.28	81.6	1.75	1.49 – 2.06
65 - 69	75.2	1.85	1.55 – 2.21	83.4	1.64	1.37 – 1.97
70 - 74	73.5	1.63	1.37 – 1.94	82.0	1.43	1.20 – 1.70
≥75	65.2	1.14	0.96 – 1.35	73.9	0.92	0.79 – 1.09
Sex						
Female	64.2	1.0	n/a	74.8	1.0	n/a
Male	69.6	1.19	1.11 – 1.26	78.8	1.13	1.06 – 1.20
Comorbidity score						
0	29.0	1.0	n/a	42.6	1.0	n/a
1	60.7	4.30	3.67 – 5.04	73.7	4.95	4.15 – 5.90
2	71.9	5.68	4.97 – 6.48	83.2	6.62	5.70 – 7.69
3	74.9	6.57	5.82 – 7.41	85.0	7.38	6.45 – 8.45
4	77.8	7.93	7.04 – 8.92	85.8	8.10	7.11 – 9.21
5	79.6	9.35	8.23 – 10.63	87.6	10.01	8.67 – 11.58
6	79.0	9.33	8.09 – 10.76	85.6	8.84	7.55 – 10.34
≥7	77.3	8.99	7.91 – 10.20	83.9	8.36	7.29 – 9.58

Appendix III.1 cont.

Variable	*35 day refill gap*			*91 day refill gap*		
Index OAH therapy	Persistence (%)	Adjusted Odds Ratio	95%CI	Persistence (%)	Adjusted Odds Ratio	95%CI
Metformin monotherapy	68.6	1.0	n/a	78.7	1.0	n/a
Sulphonylurea monotherapy	60.5	0.71	0.65 – 0.78	70.5	0.68	0.61 – 0.75
Dual therapy *	71.0	1.12	1.31 – 1.63	79.3	1.03	0.92 – 1.15
Other OAH agents (inc combinations)	62.9	0.73	0.65 – 0.81	72.5	0.66	0.59 – 0.75
Comorbidity type						
Concordant comorbidity only**	78.8	1.46	1.31 – 1.63	88.3	1.50	1.31 – 1.72
Discordant comorbidity only **	49.8	0.46	0.40 – 0.52	62.9	0.38	0.33 – 0.44

* Metformin with a sulphonylurea. ** Reference: patients with no and both comorbidities.

Appendix III.2 Persistence with OAH therapy at 12 months post initiation, adjusting for age, sex, number of comorbid conditions, index OAH treatment and type of comorbidity.

Variable	*35 day refill gap*			*91 day refill gap*		
Age (years)	Persistence (%)	Adjusted Odds Ratio	95%CI	Persistence (%)	Adjusted Odds Ratio	95%CI
25 - 34	22.0	1.0	n/a	32.8	1.0	n/a
35 - 44	39.6	1.41	1.13 – 1.77	55.3	1.63	1.33 – 2.01
45 - 54	52.1	1.67	1.35 – 2.07	66.2	1.80	1.48 – 2.20
55 - 64	60.3	1.98	1.60 – 2.44	71.6	1.94	1.60 – 2.35
65 - 69	64.2	2.01	1.62 – 2.51	74.8	1.93	1.57 – 2.38
70 - 74	62.3	1.86	1.50 – 2.31	72.1	1.68	1.37 – 2.06
≥75	51.6	1.27	1.02 – 1.57	61.3	1.09	0.89 – 1.32
Sex						
Female	51.7	1.0	n/a	63.4	1.0	n/a
Male	57.2	1.15	1.08 – 1.23	68.4	1.13	1.05 – 1.22
Comorbidity score						
0	16.4	1.0	n/a	27.2	1.0	n/a
1	43.4	4.39	3.62 – 5.27	57.8	4.64	3.86 – 5.58
2	58.8	6.49	5.51 – 7.59	72.6	6.92	5.91 – 8.11
3	62.7	7.53	6.49 – 8.73	74.5	7.53	6.52 – 8.70
4	65.5	8.56	7.42 – 9.88	75.8	8.06	7.02 – 9.25
5	67.7	9.79	8.43 – 11.38	78.4	9.65	8.32 – 11.20
6	65.2	8.98	7.64 – 10.55	75.8	8.62	7.34 – 10.12
≥7	62.3	8.31	7.16 – 9.66	71.9	7.56	6.54 – 8.73

Appendix III.2 cont.

Variable	*35 day refill gap*			*91 day refill gap*		
Index OAH therapy	Persistence (%)	Adjusted Odds Ratio	95%CI	Persistence (%)	Adjusted Odds Ratio	95%CI
Metformin monotherapy	56.4	1.0	n/a	68.1	1.0	n/a
Sulphonylurea monotherapy	46.4	0.68	0.62 – 0.75	57.7	0.66	0.60 – 0.73
Dual therapy *	58.0	1.00	0.90 – 1.12	68.5	0.95	0.84 – 1.07
Other OAH agents (inc combinations)	52.1	0.77	0.68 – 0.88	62.8	0.71	0.63 – 0.81
Comorbidity type						
Concordant comorbidity only**	64.6	1.29	1.16 – 1.44	76.4	1.22	1.08 – 1.38
Discordant comorbidity only **	35.4	0.48	0.41 – 0.56	49.0	0.43	0.37 – 0.50

Appendix IV

IV.1 Persistence with OAH at 6 and 12 months post therapy initiation, adjusting for age, sex, comorbidity score, index OAH therapy and depression.

Variable	*6 months (N=21,280)*			*12months (N=15,958)*		
Age (years)	Persistence (%)	Adjusted Odds Ratio	95%CI	Persistence (%)	Adjusted Odds Ratio	95%CI
25 - 34	42.4	1.00	n/a	28.2	1.00	n/a
35 - 44	64.0	1.73	1.45 - 2.06	51.0	1.85	1.50 - 2.29
45 - 54	73.8	1.90	1.61 - 2.25	61.8	2.07	1.70 - 2.53
55 - 64	78.8	2.09	1.78 - 2.46	68.1	2.32	1.91 - 2.82
65 - 69	81.2	2.01	1.68 - 2.40	71.6	2.35	1.91 - 2.91
70 - 74	79.5	1.77	1.49 - 2.11	69.3	2.13	1.73 - 2.61
≥75	70.9	1.13	0.95 - 1.33	58.3	1.36	1.11 - 1.67
Sex						
Female	71.6	1.00	n/a	59.9	1.00	n/a
Male	76.0	1.18	1.10 - 1.26	64.8	1.15	1.07 - 1.23
Comorbidity score						
0	37.7	1.00	n/a	23.7	1.00	n/a
1	70.3	3.73	3.33 - 4.19	53.4	3.53	3.08 - 4.06
2	79.9	6.12	5.44 - 6.88	68.3	6.08	5.32 - 6.94
3	81.6	7.18	6.38 - 8.08	70.8	7.15	6.27 - 8.16
4	83.5	8.03	7.10 - 9.08	72.8	7.75	6.77 - 8.87
5	85.0	8.82	7.69 - 10.11	74.8	8.63	7.45 - 9.98
6	83.7	10.13	8.59 - 11.94	73.3	8.43	7.14 - 9.96
≥7	82.2	8.02	6.93 - 9.28	68.8	6.89	5.90 - 8.04
Index OAH therapy						
Metformin monotherapy	75.7	1.00	n/a	64.5	1.00	n/a
Sulphonylurea monotherapy	66.8	0.64	0.58 - 0.70	53.8	0.64	0.58 - 0.70
Metformin and sulphonylurea dual therapy	76.7	1.05	0.94 - 1.17	65.5	0.98	0.87 - 1.09
Other OAH agents (inc combinations)	69.9	0.71	0.63 - 0.79	59.4	0.74	0.65 - 0.84
Depression						
Anti-depressant vs. no anti-depressant	79.9	0.95	0.87 - 1.04	68.2	0.97	0.88 - 1.07

IV.2 Adherence with OAH at 6 and 12 months post therapy initiation, adjusting for age, sex, comorbidity score, index OAH therapy and depression.

Variable	*6 months (N=21,280)*			*12months (N=15,958)*		
Age (years)	*Adherence (MPR)*	*Adjusted Odds Ratio*	*95%CI*	*Adherence (MPR)*	*Adjusted Odds Ratio*	*95%CI*
25 - 34	35.0	1.00	n/a	29.15	1.00	n/a
35 - 44	55.1	1.56	1.31 - 1.86	50.55	1.64	1.32 - 2.03
45 - 54	68.2	1.88	1.59 - 2.23	65.54	2.14	1.75 - 2.63
55 - 64	74.9	2.18	1.85 - 2.57	72.49	2.43	1.99 - 2.97
65 - 69	78.4	2.19	1.83 - 2.62	76.24	2.42	1.95 - 3.00
70 - 74	76.8	1.96	1.65 - 2.34	74.05	2.16	1.75 - 2.66
≥75	68.8	1.30	1.10 - 1.54	64.03	1.36	1.11 - 1.67
Sex						
Female	67.0	1.00	n/a	63.56	1.00	n/a
Male	72.4	1.22	1.14 - 1.30	69.3	1.21	1.12 - 1.30
Comorbidity score						
0	31.1	1.00	n/a	23.8	1.00	n/a
1	63.0	3.51	3.13 - 3.93	55.6	3.72	3.25 - 4.28
2	74.4	6.02	5.38 - 6.74	71.3	7.15	6.25 - 8.18
3	77.7	7.35	6.55 - 8.24	74.5	8.69	7.59 - 9.96
4	80.8	8.18	7.27 - 9.21	78.7	10.30	8.96 - 11.85
5	82.8	9.71	8.49 - 11.09	79.6	11.11	9.54 - 12.93
6	82.5	10.89	9.29 - 12.77	78.8	11.83	9.14 - 14.11
≥7	80.8	9.01	7.81 - 10.40	76.8	10.19	8.66 - 11.99
Index OAH therapy						
Metformin monotherapy	70.4	1.00	n/a	67.7	1.00	n/a
Sulphonylurea monotherapy	64.4	0.74	0.68 - 0.81	59.8	0.70	0.63 - 0.77
Dual therapy*	72.1	1.08	1.97 - 1.19	67.4	0.91	0.81 - 1.02
Other OAH agents (inc combinations)	72.8	1.15	1.02 - 1.29	70.2	1.09	0.95 - 1.25
Depression						
Anti-depressant vs. no anti-depressant	77.0	0.99	0.91 - 1.08	73.3	0.97	0.88 - 1.06

Appendix V: Ethical Approval

THE ADELAIDE & MEATH HOSPITAL, DUBLIN
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Secretariat Fax 4142371

Ms. Miriam O'Shea
Department of Pharmacology and Therapeutics
School of Medicine
University of Dublin
Trinity College
Dublin 2

June 20th 2012

Re: A Questionnaire Study Investigating the Impact of Co morbidity on Diabetes Self Care, Medication Adherence, Disease Prioritisation and Quality of Life in Adults with Type 2 Diabetes Attending a Dublin Hospital.

Please quote this reference in any follow up to this letter: 2012/06/10 Chairman's Action

Dear Miriam,

Thank you for your recent submission of the above proposal to the SJH/AMNCH Research Ethics Committee.

The Chairman, having reviewed the proposal has given ethical approval on behalf of the SJH/AMNCH Research Ethics Committee.

Yours sincerely

Ms. Ursula Ryan
Secretary,
SJH/AMNCH Research Ethics Committee

Appendix VI: Patient Questionnaire

Department of Pharmacology and Therapeutics.

Trinity Centre for Health Sciences,

St James's Hospital,

Dublin 8

A survey looking at the impact of comorbidity on diabetes self-care, medication adherence, disease prioritisation and quality of life in adults with type 2 diabetes

Introduction and instructions

Dear participant,

There are four main sections in this questionnaire. Each section has a specific purpose and is composed of a series of short questions. For the majority of questions you will be required to indicate your answer by placing a tick in the appropriate box or boxes. However this format changes for certain questions within the questionnaire to make it easier to provide the information.

Please read the questions carefully and follow the instructions provided along the way. You are requested to answer all of the questions that are relevant to you.

Thank you for your interest in this study and taking the time to fill in this questionnaire.

The information which you will provide in this questionnaire will help better inform research about living with type 2 diabetes and other conditions in Ireland.

About you

In this section of the questionnaire we would like to find out some information about you. ***Please answer each of the following questions by placing tick in the box which represents the SINGLE best answer.***

Q1. What age group are you in?

25-34 years ☐ 35-44 years ☐ 45-54 years ☐

55-64 years ☐ 65-69 years ☐ 70-74 years ☐

75-80 years ☐

Q2. Gender:

Male ☐ Female ☐

Q3. What is your *current* marital status?

Single (never married)	☐
Separated / Divorced	☐
Married or living with partner	☐
Widowed	☐

Q4. What is the *highest* level of education that you have completed?

Primary education	☐
Secondary level	☐
Third level (i.e. Institute of Technology or University)	☐
Postgraduate (i.e. Master's Degree or PhD)	☐

Q5 Are you currently *formally* employed (working for payment or profit)?

Yes ☐ No ☐

Q6. Do you have any of following? *(Please tick All of the boxes that apply)*

Medical card	☐
A Long Term Illness (LTI) green book	☐
Private Health Insurance	☐

Your health

In this section of the questionnaire we wish to know about your health in general.

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Q7. Mobility

I have no problems in walking about	☐
I have some problems in walking about	☐
I am confined to bed	☐

Q8. Self - care

I have no problems washing or dressing myself	☐
I have some problems washing or dressing myself	☐
I am unable to wash or dress myself	☐

Q9. Usual Activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities	☐
I have some problems with performing my usual activities	☐
I am unable to perform my usual activities	☐

Q10. Pain / Discomfort

I have no pain or discomfort	☐
I have moderate pain or discomfort	☐
I have extreme pain or discomfort	☐

Q11. Anxiety / Depression

I am not anxious or depressed	☐
I am moderately anxious or depressed	☐
I am extremely anxious or depressed	☐

Q12. To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state

Diabetes and you

In this section of the questionnaire we would like to find out some information about your diabetes. It has been divided into a number of sub-sections. Please follow the instructions given under each sub-heading in order to answer the questions in each section.

Duration of diabetes and complications

The following questions relate to your diabetes diagnosis and any health problems which you may have as a result of having diabetes.

Please answer each of the following questions by placing a tick in the box which represents the best single answer to the question, unless otherwise stated.

Q13 How long have you been diagnosed with diabetes?

Less than 1 year ☐ 1-3 years ☐ 3-6years ☐

6 – 9 years ☐ 10 or more years ☐

Q14. Has your diabetes caused any other health problems?

Yes	☐
No	☐
Do n't know	☐

(If No or Do n't know, please go to the sub-section entitled "Treatment")

(14a) If Yes, has your diabetes caused any of the following health problems? ***(Please tick ALL of the boxes that apply)***

Problems with your kidneys	☐
Problems with your eyes, treated by an ophthalmologist	☐
Problems with your legs or feet (e.g. leg ulcers)	☐
Problems with your heart or circulation	☐
Other health problem *Please specify:* _____	☐

Treatment

The following series of questions relate to your current diabetes treatment.

Please answer each of the following questions by placing a tick in the box which represents the best SINGLE answer to the question, unless otherwise stated.

Q15 Are you currently being treated for your diabetes?

Yes ☐ No ☐

(If No, please go to the sub-section entitled "Measuring your blood sugar")

(15a) If *Yes*, what is the current treatment being used to control your diabetes *(Please tick ONE box only)*

Diet alone ***(If diet alone, please skip to question 21)***	☐
Tablets	☐
Insulin	☐
A combination of tablets and insulin	☐
A combination of tablets and injectable medication other than insulin	☐

Q16 On how many of the last SEVEN DAYS did you take your recommended diabetes medication *(Please CIRCLE the appropriate number of days)*

0 1 2 3 4 5 6 7

Q17. Do you ever forget to take your medicine?

Yes ☐ No ☐

Q18. Are you careless at times about taking your medicine?

Yes ☐ No ☐

Q19. When you feel better do you sometimes stop taking your medicine?

Yes ☐ No ☐

Q20. Sometimes, if you feel worse, when you are taking the medicine do you stop?

Yes ☐ No ☐

Q21. In the *PAST YEAR* has your doctor made *ANY* changes to your diabetes treatment?

Yes ☐ No ☐ **(If *No*, please go to question 22)**

(21a) If *Yes*, why were these changes to your diabetes treatment made? (*Please place tick ALL of the boxes that apply*)

Blood sugar levels were too high	☐
Blood sugar levels were too low	☐
Side effects from the diabetes treatment	☐
Other	☐

Please specify: _____

Measuring your blood sugar

The following series of questions are about measuring your blood sugar.

Please answer each of the following questions by placing a TICK in the box which represents the best SINGLE answer to the question UNLESS OTHERWISE STATED.

Q22. Do you have a machine to measure your blood sugar (glucose) level?

Yes ☐ No ☐

Q23. As part of caring for your diabetes, has a doctor or other health professional ever told you to measure your blood sugar (glucose) levels?

Yes ☐ No ☐

(If No, please go to the sub-section entitled "Diabetes self-care activities")

(23a) If Yes, on how many of the last SEVEN days did you test your blood sugar? (*Please CIRCLE the appropriate number of days)*

0 1 2 3 4 5 6 7

(23b) On how many of the last SEVEN days did you test your blood sugar the number of times as recommended by your doctor or other health professional? (*Please CIRCLE the appropriate number of days*)

0 1 2 3 4 5 6 7

(23c) Do you keep a record of your blood sugar test results?

Yes	☐
No	☐
Only unusual values	☐

Diabetes self - care activities

The following series of questions ask you about your diabetes management activities during the past seven days. If you were sick during the past seven days, please think back to the last seven days that you were not sick.

To answer each question please CIRCLE the appropriate number of days.

Q24 How many of the last SEVEN DAYS have you followed a specific or recommended eating plan?

0 1 2 3 4 5 6 7

Q25. On average, over the past month, how many DAYS PER WEEK have you followed your eating plan?

0 1 2 3 4 5 6 7

Q26. On how many of the last SEVEN DAYS did you eat five or more servings of fruit and vegetables?

0 1 2 3 4 5 6 7

Q27. On how many of the last SEVEN DAYS did you eat high fat foods such as red meat or full fat dairy products?

0 1 2 3 4 5 6 7

Q28. On how many of the last SEVEN DAYS did you check your feet?

0 1 2 3 4 5 6 7

Q29. On how many of the last SEVEN DAYS did you check your shoes?

0 1 2 3 4 5 6 7

Q30. On how many of the last SEVEN DAYS did you participate in at least 30 minutes of physical activity? (*Total minutes of continuous activity, including walking*)

0 1 2 3 4 5 6 7

Q31. On how many of the last SEVEN DAYS did you participate in a specific aerobic exercise session (such as swimming, walking, cycling etc.) other than what you do around the house or as part of your work?

0 1 2 3 4 5 6 7

(31a) If you did *NOT* participate in any specific aerobic exercise session please indicate the *MAIN* reason? (*Please tick ONE box only*).

Not interested	☐
Interested but not willing to spend the time	☐
No time to do it	☐
Injury /disability / or medical condition	☐
Cost of activity	☐
Other	☐

Please specify: _____

Weight management

The following series of questions relate to weight management.

Please answer each of the following questions by placing a tick in the box which represents the best SINGLE answer to the question, unless otherwise stated.

Q32. In the past 12 months has a doctor, nurse or other health professional given you dietary advice?

Yes ☐ No ☐

Q33. Are you actively trying to manage your weight at the present time?

Yes ☐ No ☐

(If No, please go to the sub-section entitled "Smoking")

(33a) If Yes, is it to lose, gain or maintain weight?

Lose weight	☐

Maintain weight	☐
Gain weight	☐

(If *GAIN WEIGHT* *please go to sub-section entitled "Smoking"*)

(33b) Are you using the any of the following to lose or maintain weight? *(Please tick Yes or No for each line)*

Eating fewer calories	Yes ☐	No ☐
Eating less fat	Yes ☐	No ☐
Taking exercise	Yes ☐	No ☐

Smoking History

In the following series of question we would like some information on cigarette use past and present. Please fill out this section of the questionnaire even if you have never smoked. ***Please answer the questions by placing a tick in the box which represents the best SINGLE answer to the question.***

Q34. Have you EVER smoked? (Ever smoked = more than 100 cigarettes in your lifetime).

Yes ☐ No ☐

(If No, please go to sub-section entitled "Diabetes education")

(34a) If yes, do you now smoke every day, some day or not at all?

Every day	☐
Some days	☐
Not at all	☐

(If Not at all, please go to sub-section entitled "Diabetes education")

(34b) If you currently smoke every day or on some days, how many cigarettes on average do you smoke per day?

1- 5 cigarettes ☐ 5-10 cigarettes ☐ 10 - 15 cigarettes☐

15 - 20 cigarettes ☐ More than 20 cigarettes ☐

Diabetes education

In the following series of questions we would like to know about any education you may have received about living with diabetes and the people that help you look after yourself. ***Please answer each of the following questions by placing a tick in the box which represents the best SINGLE answer to the question, unless otherwise stated.***

Q35. Have you ever received diabetes education?

Yes ☐ No ☐

(***If No, please go to the section entitled "Other medical conditions"***)

(35 a) If Yes, what format did it take? (Please tick ALL of the boxes that apply)

Series of classes conducted by a health professional or diabetes educator	☐
One-to-one advice from a health professional	☐
Leaflets / brochures from a health clinic	☐
Website related to diabetes	☐
Other *Please specify:* _____	☐

Q36 In terms of health professionals who helps or encourages you *the most* to look after your diabetes? (*Please place a tick in ONE box only*)

Consultant endocrinologist or their team	☐
GP	☐
Diabetes nurses	☐
Other health professional *Please specify:* _____	☐
No one	☐

Q37 In terms of other people (family or friends) who helps or encourages you *the most* to look after your diabetes? (*Please place a tick in ONE box only*)

Husband / Wife or Partner	☐
Other family members	☐
Friends	☐
Other	☐

Please specify: _____

No one	☐

Other medical conditions

In this section of the questionnaire we ask about medical conditions, ***other than diabetes***, that you may have at the moment or have experienced in the past. ***Please answer each of the following questions by placing a tick in the box which represents the best SINGLE answer to the question, unless otherwise stated.***

Q38 Apart from your diabetes do you have any other medical condition?

Yes, I have one other condition ☐ Yes, I have 2 other conditions☐

Yes I have 3 or more other conditions☐ No, I only have diabetes ☐ **(If No, *please go to end of questionnaire)***

Q39. Were these medical conditions diagnosed?

Yes, all were diagnosed ☐ Yes, some of the conditions were diagnosed ☐

No, they were not diagnosed ☐

Q40. Are you currently receiving treatment or medication for your other condition(s)?

Yes, I am receiving treatment or medication for my other medical conditions	☐
Yes, I am receiving treatment for some of my other medical conditions	☐
No, I am not receiving treatment or medication for my other medical conditions	☐

Q41. Are you currently being treated for any of the following common health problems ***(Please tick ALL of the boxes that apply)***

Heart disease	☐
High Blood Pressure	☐
High Cholesterol	☐
Lung disease (eg Asthma, COPD)	☐
Ulcer or other stomach disease	☐
Kidney disease	☐
Liver disease	☐

Anaemia or other blood condition	☐
Cancer	☐
Depression	☐
Osteoarthritis	☐
Back pain	☐
Rheumatoid arthritis	☐

Q42 Do you have any other medical conditions that have not been included on this list?

Yes ☐ No ☐

(42a) If Yes, please state the name(s) of the condition(s) in the space provided below ***(Please print in BLOCK CAPITALS)***

_____

Q43. Do you have a medical condition that is more important (takes priority) over your diabetes or your other medical condition(s)

Yes ☐ No ☐

(43a) If Yes, please write down the name of the condition in the space provide below (***please write down one condition only and use block capitals letters***)

_____

(43b) Below is a list of possible reasons why some individuals prioritise one condition over others. (***Please tick a SINGLE box that correspond to the MAIN reason why you prioritise the condition named in Q 39 part a)***

It affects my quality of life	☐
It is painful	☐
It affects my mobility or causes some other physical limitation	☐
It affects my breathing	☐
The symptoms are embarrassing	☐
The symptoms are unpredictable	☐

Medicines do not seem to improve it	☐
It could be life threatening	☐
It may lead to other conditions	☐
Other reason	☐

Please specify: _____

Thank you for taking the time to complete this questionnaire. ***If you have any concerns regarding your health please contact your doctor or the diabetes clinic in St James's Hospital***

Appendix VII: Presentations

O'Shea MP, Teeling M, Bennett K. Comorbidity and adherence to oral anti-hyperglycaemic agents in Ireland. *Pharmacoepidemiology and Drug Safety* 2012, **21**:(Suppl.3): 1 – 481. doi:10.111/j1399-5448.2012.03324x (Poster presentation 28th International Conference on Pharmacoepidemiology and Therapeutic Risk Management August 23 – 26th 2012, Barcelona Spain)

O'Shea MP, Teeling M, Bennett K, Comorbidity in Type 2 Diabetes in Ireland.
(Poster presentation EuroPRevent conference, European Society of Cardiology.3rd – 5th May 2012, Dublin Ireland)

O'Shea M, Teeling M, Bennett K. Comorbidity in the Irish elderly population with treated Type 2 diabetes mellitus *Pharmacoepidemiology and Drug Safety* 2011, **20** :(S1 – S4): 1 – 481. doi:10.1002/pds (Oral presentation, Prescribing and Research in Medicine Management UK and Ireland (PRIMM) 22nd Annual Meeting, 17th February 2011, London England)

O'Shea M, Teeling M, Bennett K. Potentially inappropriate prescribing in the Irish elderly population with treated Type 2 diabetes mellitus *Pharmacoepidemiology and Drug Safety* 2011, **20** :(S1 – S4): 1 – 481. doi:10.1002/pds (Poster presentation 22nd Annual PRIMM meeting 17th February 2011, London, England)