The Effects of Glycemic Control and Thiazolidinediones on the Risk of Congestive Heart Failure among Patients with Type 2 Diabetes

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ABSTRACT

The objectives of this thesis are to describe prescription patterns of anti-diabetic therapy among patients with type 2 diabetes and to examine the effects of glycemic control and the oral anti-diabetic thiazolidinedione medications on the risk of incident congestive heart failure in a population-based study. Pertinent data were extracted from the United Kingdom's General Practice Research Database, a clinical database that records information from over 400 practices and contains over 39 million person-years of observation.

The first study describes prescription patterns of anti-diabetic medical therapy. There was a substantial increase in the prescription of anti-diabetic medications during the study period from 2000 to 2006. This increase was particularly evident for thiazolidinediones and metformin.

The second study examines the effect of glycemic control, measured by hemoglobin A1c, on the risk of heart failure in a nested case-control study. As part of this study, the effects of misclassification of hemoglobin A1c on this relationship were assessed. Increasing hemoglobin A1c was associated with an increased rate of heart failure. Although patients with hemoglobin A1c values ≥ 8% had an increase in heart failure, those with an hemoglobin A1c between 7% and 8% had a similar rate as those with hemoglobin A1c < 7%. Measurement error adjustment did not appreciably alter this relationship.

The third study uses a nested case-control design to estimate the effect of thiazolidinediones on the risk of incident heart failure. This study found no definitive evidence that thiazolidinediones are associated with an increased rate of

incident heart failure, although a potentially clinically important effect could not be excluded.

In conclusion, this thesis found that prescription of anti-diabetic medications increased dramatically during the study period. In addition, this thesis failed to find a benefit with intensive glycemic control in the reduction of the risk of heart failure, but poor control was associated with an increased risk. Unlike previous studies with restricted populations demonstrating an increased risk of heart failure with thiazolidinediones, we could not conclusively show an increased risk with thiazolidinediones in this population-based study.

RÉSUMÉ

Les objectifs de cette thèse étaient de décrire les modes de prescription de traitement anti-diabétique chez les patients atteints du diabète de type 2 et d'examiner les effets du contrôle glycémique ainsi que des médicaments anti-diabétiques thiazolidinediones sur l'incidence d'insuffisance cardiaque congestive (ICC) dans cette population. Les données pertinentes furent extraites de la *General Practice Research Database*, une banque de données cliniques qui compile l'information de plus de 400 pratiques et qui contient plus de 39 millions personnes-années d'observation.

La première étude décrit les modes de prescription de traitements anti-diabétique oraux. Elle démontre une augmentation substantielle des prescriptions de médications anti-diabétiques pendant la période étudiée (2000-2006). Cette augmentation fut particulièrement évidente pour les thiazolidinediones et la metformine.

La deuxième étude examine l'effet du contrôle glycémique, mesuré par l'hémoglobine glyquée, sur l'incidence d'ICC dans une étude cas-témoin nichée. Les effets des erreurs de classification de l'hémoglobine glyquée furent évalués. Une augmentation de l'hémoglobine glyquée était associée à une augmentation du taux d'ICC. Bien que les patients ayant une hémoglobine glyquée $\geq 8\%$ avaient une augmentation d'ICC, ceux ayant une hémoglobine glyquée entre 7% et 8% avaient un taux d'ICC similaire à ceux ayant une hémoglobine glyquée $< 7\%$. L'ajustement pour les erreurs de mesure n'a pas sensiblement changé cette observation.

Enfin, la troisième étude, une étude de cas-témoin nichée, examine les effets des thiazolidinediones sur l'incidence d'ICC. Cette étude n'a pu identifier de façon définitive une association entre les thiazolidinediones et une augmentation du taux d'incidence d'ICC, bien qu'un effet potentiellement cliniquement important n'a pu être exclu.

En conclusion, cette thèse démontre que les prescriptions de médicaments anti-diabétiques ont dramatiquement augmenté lors de la période étudiée. De plus, cette thèse ne parvient pas à démontrer l'avantage d'un contrôle glycémique serré en ce qui concerne la réduction du risque d'ICC, bien qu'un mauvais contrôle glycémique était associé à une augmentation du risque d'ICC. Contrairement aux études précédentes conduites chez des populations restreintes et mettant en évidence une augmentation d'ICC avec l'utilisation des thiazolidinediones, nous n'avons pas pu démontrer de façon conclusive une augmentation du risque dans la population générale.

SUGGESTED SHORT TITLE

Glycemic Control, Thiazolidinediones, and the Risk of Heart Failure

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STATEMENT OF ORIGINALITY

This doctoral thesis makes a number of original contributions. This work provides important information regarding the epidemiology of diabetes. The description of prescription trends of anti-diabetic medications offers key insight into current treatment practices in the United Kingdom and highlights a shift towards more aggressive pharmacological management of patients with type 2 diabetes. Although recent studies have examined trends in the United States, this study illustrates a contemporary view of practices in the United Kingdom. In addition, the investigation of the effects of glycemic control on the risk of incident congestive heart failure contributes to our understanding of the etiology of this disease among patients with type 2 diabetes. The results of these studies have important public health consequences.

This research also has important clinical implications. The investigations of the effects of glycemic control and thiazolidinediones on the risk of incident congestive heart failure provide important information regarding these effects in patients in actual clinical practice rather than the controlled and highly selected setting of a clinical trial. Unlike previous observational studies, our thiazolidinedione assessment focused on incident cases, and the results of this study suggest that any increased heart failure risk is likely lower than reported in clinical trials. The finding of no benefit of very aggressive glycemic control contributes to the ongoing debate regarding the clinical merits of this management strategy while extending this debate to the issue of congestive heart failure.

In addition, there are methodological contributions to the area of pharmacoepidemiology in general and General Practice Research Database studies in particular. Although previous General Practice Research Database studies have used hemoglobin A1c as an outcome, as a potential confounder, or to assess the prevalence of poor glycemic control, to our knowledge this represents the first use of hemoglobin A1c as an exposure. In doing so, this study expands the use of clinical data that are available in the General Practice Research Database but typically not found in administrative databases. This work also examines the impact of error in the measurement of hemoglobin A1c on its effect on the risk of congestive heart failure, which revealed that measurement error did not substantially affect this relationship. Moreover, this analysis further extends the use of Bayesian techniques in pharmacoepidemiology and the General Practice Research Database, which to date have been dominated by frequentist methods. Finally, the examination of the effect of thiazolidinediones on the risk of heart failure included models with and without adjustment for hemoglobin A1c; the results of these analyses were virtually identical and suggest that glycemic control has smaller confounding effects than originally thought. This finding is reassuring since these data are typically not available in administrative databases used in pharmacoepidemiologic research.

CONTRIBUTIONS OF AUTHORS

There are 3 manuscripts included in this thesis. Within each manuscript, the authors' contributions have been described as part of the standard formatting used for submitted manuscripts. To facilitate the evaluation of this integrated thesis, a more detailed description of these contributions is provided below.

The first manuscript describes trends in the prescription of anti-diabetic medications in the United Kingdom (Chapter 5). I conceived of the study idea, designed the study, constructed the database, designed and conducted the statistical analyses, and drafted the manuscript. Dr. Brophy also contributed to the study design, and Dr. Joseph contributed to the design of the statistical analyses. Dr. Suissa provided online access to the General Practice Research Database. Drs. Brophy, Joseph, Boivin, and Suissa were involved in revising the article for important intellectual content.

The second manuscript is a nested case-control study examining the effect of glycemic control, measured by hemoglobin A1c on the risk of congestive heart failure (Chapter 6). I conceived of the study idea. Dr. Brophy and I designed the study, and I constructed the nested case-control database. Dr. Brophy also assisted in the definition of congestive heart failure, and Drs. Brophy and Boivin assisted in the interpretation of clinical data. Dr. Joseph and I designed the statistical analyses, which I conducted. Dr. Joseph also provided important technical support with WinBUGS. Dr. Suissa contributed to the acquisition of the data. All authors were involved in revising the article for important intellectual content.

The third manuscript is a population-based nested case-control study examining thiazolidinediones and the risk of incident congestive heart failure (Chapter 7). Dr. Brophy and I conceived of the study idea. I designed the study, with Drs. Brophy and Boivin providing helpful study design suggestions. This study, as will the other 2 observational studies, relied on data obtained by Dr. Suissa. I constructed the database, conducted all data analyses, and drafted the manuscript. All authors were involved in revising the article for important intellectual content and data interpretation.

Funding for this work was provided as part of an operating grant from the Canadian Institutes of Health Research. I was actively involved in all aspects of obtaining this funding. I participated fully with Dr. Brophy, playing an integral role in all aspects of this process, including the formulation of the research questions, development of the study design, and the drafting of the protocol. I also participated fully in obtaining research ethics approval from both the Scientific and Ethical Advisory Board of the General Practice Research Database and McGill University Health Centre.

ABBREVIATIONS

ACE	Angiotensin Converting Enzyme
ACS	Acute Coronary Syndrome
ADA	American Diabetes Association
ADOPT	A Diabetes Outcome Progression Trial
ACCORD	Action to Control Cardiovascular Risk in Diabetes Trial
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation Trial
APPROACH	Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Diabetes Patients with Cardiovascular History Trial
ARBs	Angiotensin II Receptor Blockers
CABG	Coronary Artery Bypass Graft Surgery
CHARM	Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity Program
CHF	Congestive Heart Failure
CI	Confidence Interval
CIMT	Carotid Intima-Media Thickness
COPD	Chronic Obstructive Pulmonary Disorder
COX	Cyclooxygenase
CrI	Credible Interval
CRP	C-Reactive Protein
CVD	Cardiovascular
DREAM	Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication
FDA	Food and Drug Administration
GSK	GlaxoSmithKline
GPRD	General Practice Research Database
FDA	Food and Drug Administration
HbA1c	Hemoglobin AIC or Glycosylated Hemoglobin
HDL	High-Density Lipoprotein
HR	Hazard Ratio
IQR	Inter-Quartile Range
LDL	Low-Density Lipoprotein
MeSH	Medical Subject Headings
MI	Myocardial Infarction
NSAIDs	Non-Steroidal Anti-Inflammatory Drug
NHS	National Health Service
NA	Not Applicable
NR	Not Reported
OR	Odds Ratio
OXMIS	Oxford Medical Information System
PCI	Percutaneous Coronary Intervention

PERISCOPE	Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation Trial
PROactive	Prospective Pioglitazone Clinical Trial In Macrovascular Events Trial
PPAR	Peroxisone-Proliferator-Activated Receptor
RAMQ	Régie de l'Assurance Maladie du Québec
RECORD	Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes Trial
RR	Rate Ratio
RRR	Relative Risk Reduction
SD	Standard Deviation
SEAG	Scientific and Ethical Advisory Group
TZDs	Thiazolidinediones
U.K.	United Kingdom
UKPDS	United Kingdom Prospective Diabetes Study
U.S.	United States
VADT	Veterans Affairs Diabetes Trial
WMD	Weight Mean Difference

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CHAPTER 1 – INTRODUCTION

1.1 Type 2 Diabetes Mellitus

Type 2 diabetes is a metabolic condition characterized by decreased insulin sensitivity and thus, poor glucose control (1-6). Approximately 7% of the Canadian population have type 2 diabetes, with 60,000 new cases diagnosed each year (7). In addition, the prevalence of type 2 diabetes has been increasing dramatically over time. For example, in the U.S., its prevalence rose by over 61% between 1990 and 2001 (8). This increase is due to a number of factors, including an aging population (9), an obesity epidemic that is affecting the Western World (10), increased childhood obesity (11), and declining levels of physical activity (12).

Diabetes is the 7th leading cause of death in Canada (7), with the majority of these deaths in patients with type 2 diabetes and attributable to cardiovascular disease. Diabetes is responsible for 21% of deaths due to ischemic heart disease and 13% of deaths due to stroke worldwide (13). Duration of diabetes is also an important predictor of the incidence of cardiovascular disease and cardiovascular death among diabetics. For every 10-year increase in the duration of diabetes, there is a relative increase of 38% in the risk of cardiovascular disease and a 86% increase in the risk of cardiovascular death (14). Other complications of diabetes include limb amputation, nephropathy, neuropathy, retinopathy, and stroke (7), most of which are due to the vascular effects of this disease.

The importance of tight glycemic control among patients with type 2 diabetes and its effect on clinical outcomes has been examined in a number of studies, including UKPDS 33 (15), ADVANCE (16), and ACCORD (17). Glycemic control is monitored using a variety of tests, including blood and urine glucose tests and urine ketone tests (18). However, these tests measure day-to-day glycemic levels, which are prone to fluctuations. Consequently, most treatment guidelines focus on glycosylated hemoglobin (HbA1c) (1, 19, 20), which provides an average measure of glycemic control over the preceding 3 months. Most guidelines recommend a treatment target of HbA1c < 7% (19), with recent guidelines now advocating lower HbA1c targets among patients with increased cardiovascular risk (20). However, trials have produced inconsistent results regarding association between glycemic control and clinically relevant endpoints; these conflicting results have led to increased debate regarding the role of surrogate endpoints in trials (21).

Most treatment guidelines advocate the use of diet and exercise as first line therapy for type 2 diabetes (1, 22, 23). However, these lifestyle interventions are often inadequate (24). Pharmacological therapy is therefore central to the management of type 2 diabetes. A number of pharmacological therapies have been shown to be effective at controlling hyperglycemia in patients with type 2 diabetes, including alpha-glucosidase inhibitors (e.g., acarbose), biguanide (e.g., metformin), insulin, insulin secretagogues (e.g., sulfonylureas [gliclazide, glimepiride, glyburide], nonsulfonylureas [nateglinide, repaglinide]), anti-obesity agents (e.g., orlistat, rimonabant)(1, 20), and insulin sensitizers (e.g.,

thiazolidinediones (TZDs) [pioglitazone, rosiglitazone]). The efficacy and cardiovascular safety of TZDs has recently become a controversial issue among clinicians, researchers, and regulatory agencies and consequently, the remainder of this thesis focuses on TZD use in patients with type 2 diabetes.

1.2 Thiazolidinediones

TZDs are a class of anti-hyperglycemic agent that target tissue insulin sensitivity (25-27). There are currently 2 TZDs available in North America: pioglitazone (Actos®) and rosiglitazone (Avandia®). A third TZD, troglitazone (Rezulin®), received regulatory approval but has since been withdrawn from the market due to liver toxicity (28). Initial concerns regarding the toxicity of troglitazone were raised in 1997. Despite these warnings, it was only withdrawn from the U.S. market in 2000. This delay, combined with the cardio-toxicity of murglitazaar (29, 30), which was similar mechanistically to TZDs, highlight the need for vigilance regarding the safety of the TZDs. TZDs are prescribed as monotherapy and in combination with other anti-hyperglycemic agents (28). The mechanism of TZDs has been described previously (25-27).

The effects of TZDs on diabetic outcomes, cardiovascular risk factors, and cardiovascular outcomes have been examined extensively (31-73). TZDs decrease HbA1c by approximately 1% (57), with larger doses of TZD eliciting greater decreases in HbA1c. Available evidence suggests that pioglitazone and rosiglitazone result in similar decreases in HbA1c (41, 47). TZDs also appear to decrease systolic and diastolic blood pressure (67), increase serum adiponectin (65), and may increase exercise capacity (74). In addition, TZDs decrease central

obesity by redistributing body fat (26) and have pleiotropic effects on platelet function and coagulation (75). Pioglitazone appears to slow carotid intima-media thickness (CIMT) progression, a marker of atherosclerosis, more than glimepiride (76). In a meta-analysis, Chiquette et al. found that pioglitazone lowered triglycerides, increased high-density lipoprotein (HDL), and had no detectable effect on low-density lipoprotein (LDL) or total cholesterol (47). Conversely, rosiglitazone was associated with clinically important increases in LDL and total cholesterol. Rosiglitazone use was also associated with a small but important increase in HDL and, unlike pioglitazone, did not appear to affect triglycerides. Both TZDs result in substantial weight gain compared with placebo (47). Rosiglitazone also decreases the incidence of type 2 diabetes when used among those with impaired fasting glucose or impaired glucose tolerance (40, 77, 78).

1.3 Cardiovascular Effects of Thiazolidinediones

To date, there has only been 1 completed randomized, double-blind trial specifically designed to prospectively examine the effect of TZDs on cardiovascular outcomes (39). In the PROactive study, the investigators found that pioglitazone had no effect on their primary composite endpoint but appeared to reduce the occurrence of one of their secondary endpoint, which was a composite of all-cause mortality, MI, and stroke. Due in part to the authors' focus on this secondary analysis in their conclusions, the results of the PROactive trial have been interpreted with caution (79-81).

Recently, safety concerns have arisen concerning the cardiovascular effects of rosiglitazone. Using data from the GlaxoSmithKline (GSK) and Food

and Drug Administration (FDA) websites and published rosiglitazone trials, Nissen and Wolski examined the effect of rosiglitazone on the risk of MI and death from cardiovascular causes (55). The authors found that rosiglitazone was associated with an increased in MI and may be associated with increased death from cardiovascular causes. Although this meta-analysis had important limitations (48, 69, 73, 82), meta-analyses conducted by the GSK and the FDA confirmed these results (50, 51) and, in 2007, the FDA reviewed the cardiovascular safety of rosiglitazone (83, 84). During this meeting, the Advisory Committee concluded that rosiglitazone increased the risk of MI. Consequently, although rosiglitazone was not withdrawn from the market, it received a 'black box' warning, and the committee has requested that other studies be conducted. With limited data available concerning the cardiovascular effects of rosiglitazone (85), the safety of rosiglitazone remains a controversial issue (48, 59, 82, 85-87) while awaiting the results of ongoing trials such as RECORD. Concerns regarding potentially increased rates of MI do not extend to pioglitazone, which appears to decrease the occurrence of cardiovascular events (54).

1.4 Thiazolidinediones and Congestive Heart Failure

Although much attention, particularly in the lay press, has been focused on the potential increase in MI with rosiglitazone, TZDs have also been linked to congestive heart failure (CHF). Although the mechanism of these CHF effects remains incompletely understood, it appears to be partially related to increased sodium reabsorption via the renal PPARγ pathway (70). A number of case studies and small observational studies have suggested that pioglitazone and rosiglitazone

are associated with an increased risk of CHF (88-96). The association between TZD use and CHF has also been examined in clinical trials and recent meta-analyses. In the DREAM trial, rosiglitazone was associated with an increase in CHF compared with placebo (40). The PROactive study (39) and recent meta-analyses support this observed increase in CHF (97, 98), and another meta-analysis suggests that rosiglitazone may increase the risk of edema more than pioglitazone (43). However, as described in detail in Chapter 2, these studies have important limitations. Nonetheless, as a result of these findings, both pioglitazone and rosiglitazone have received 'black box' warnings from the FDA alerting physicians and patients to this potential danger (84).

Despite these warnings, physicians continue to prescribe TZDs. There remains a need to examine the potential cardio-toxic effects of TZDs in an unselected population representative of those receiving it in practice. If these agents are associated with a substantial increase in CHF, a condition with which moderate and severe cases have l-year survival rates that are less than 50% (99), patients, physicians, and regulatory agencies must be alerted to this danger. Conversely, if this risk is minimal or non-existent, the safety profile of TZDs would be enhanced.

1.5 The General Practice Research Database

The General Practice Research Database (GPRD), which serves as the data source for this thesis, is a clinical database linking data from over 400 general practices in the United Kingdome (U.K.) (100). The GRPD has been used extensively in pharmacoepidemiologic studies, including studies of type 2

diabetes (101-104) and CHF (101). It serves as a representative sample of approximately 5% of the U.K. population (105) and contains data regarding patient demographics, lifestyle variables, clinical diagnoses, procedures, prescriptions issued, blood pressure readings, and laboratory data such as HbA1c and total cholesterol. These laboratory data, as well as lifestyle variables such as BMI and smoking, are typically missing from large administrative databases. These attributes make the GPRD well suited as a data source to examine the cardiovascular effects of TZDs.

1.6 Objectives

The overall objective of this thesis is to examine the effects of glycemic control and TZDs, including rosiglitazone and pioglitazone, on the risk of incident CHF among patients with type 2 diabetes. The specific study objectives are:

1. To describe recent trends in the prescription of anti-diabetic medications among patients with type 2 diabetes.
2. To determine the effect of glycemic control, measured by HbA1c, on the risk of CHF among patients in the GPRD with type 2 diabetes.
3. To examine the effect of error in the measurement of HbA1c on the estimates of the effect of glycemic control on the risk of CHF among patients with type 2 diabetes.
4. To compare the risk of incident CHF among patients with type 2 diabetes receiving TZDs, including rosiglitazone and pioglitazone, with that of patients with type 2 diabetes not receiving TZDs.

1.7 Overview of Thesis

The remainder of this thesis addresses these objectives. Chapter 2 provides a critical analysis of the trials that have examined these agents, as well as systematic reviews and meta-analyses of the cardiovascular effects of TZDs. It also summarizes previous observational studies that investigated the effect of TZDs on the risk of CHF. In addition, Chapter 2 describes key studies that assessed the ability of HbA1c to predict cardiovascular events. Chapter 3 provides an overview of the methods used in this thesis. Chapter 4 contains a brief description of the cohort of patients with type 2 diabetes that serves as the data sources for studies described in Chapters 5-7. Chapter 5, which includes the first manuscript, involves a description of recent trends in the prescription of anti-diabetic medications. Chapter 6, which contains the second manuscript, examines the effect of glycemic control, measured by HbA1c, on the risk of CHF among patients with type 2 diabetes and discusses the potential role of measurement error in assessing this relationship. Chapter 7, which contains the third manuscript, involves a nested case-control study that examines the association between prescription of TZDs and the risk of incident CHF. This chapter also examines survival among cases exposed to TZDs relative to those not exposed to TZDs. Finally, Chapter 8 discusses the implications of this work and provides general conclusions of this thesis.

CHAPTER 2 – LITERATURE REVIEW

There exists a substantial literature examining the cardiovascular effects of TZDs. To place this thesis into context of existing knowledge and to underscore the contributions of this work, this chapter comprehensively and critically reviews the literature available up to February 2009. This assessment includes 4 parts. In the first part (Section 2.1), the large RCTs examining the cardiovascular effects of TZDs are reviewed. These RCTs include those that served as the data sources for systematic reviews and meta-analyses as well as recently published RCTs that continue to shape our current knowledge base. The second part (Section 2.2) is a systematic overview of systematic reviews and meta-analyses examining the effect of TZDs on cardiovascular events, including all-cause and cardiovascular mortality, MI, CHF, revascularization procedures, and edema, a possible symptom of CHF. In the third part (Section 2.3), the pharmacoepidemiologic studies that have assessed the effect of TZDs on the risk of CHF are discussed. Finally, since the benefits of TZDs are purportedly achieved through improved glycemic control, RCTs examining the effect of glycemic control on cardiovascular events are reviewed (Section 2.4).

2.1 Thiazolidinedione Trials

There have been a small number of trials examining the cardiovascular effects of TZDs (Table 2.1). To highlight the strengths and limitations of these trials as well as the systematic reviews and meta-analyses that include their data, these large, outcome-driven trials are critically reviewed in the following pages.

There have been 3 large, outcome-driven trials examining the safety and efficacy of rosiglitazone. Two of these trials, ADOPT and DREAM, were mandated by the FDA as a condition of receiving approval (106). Unfortunately, both trials had several design limitations, and their clinical utility remains unclear. Neither trial was designed to examine the effect of rosiglitazone on cardiovascular outcomes (107) but rather were designed to examine diabetic ones (i.e., progression to insulin and progression to type 2 diabetes, respectively).

In A Diabetes Outcome Progression Trial (ADOPT), 4,360 patients with newly-diagnosed type 2 diabetes who had not previously received an anti-diabetic agent were randomized to metformin (500 mg/day), glyburide (2.5 mg/day), or rosiglitazone (4 mg/day) monotherapy (108, 109). Daily dosages were titrated to maximal dosages of 2,000 mg, 15 mg, and 8 mg, respectively. A total of 9 patients were excluded prior to receiving their assigned therapy, resulting in a final sample of 4,351 patients being included in their intention-to-treat analyses. The median follow-up time was 4.0 years, and the primary endpoint was monotherapy treatment failure. Treatment failure was defined as confirmed hyperglycemia (>180 mg/dL) on consecutive fasting plasma glucose tests 6 weeks apart while on maximum dosage. Secondary endpoints include time to treatment failure. Cardiovascular endpoints were not included as part of the primary or secondary endpoints of ADOPT but were included as part of adverse event reporting. Patients randomized to rosiglitazone monotherapy had a lower rate of treatment failure compared with those randomized to metformin (hazard ratio [HR] = 0.68, 95% confidence interval (CI) = 0.55, 0.85) or glyburide (HR = 0.37,

95% CI = 0.30, 0.45). The proportions of overall adverse events were similar between groups however, rosiglitazone was associated with an increase in edema and weight gain. The comparison of CHF risk between the rosiglitazone-treated group and thoat of the metformin-treated group was inconclusive (22 cases vs 19 cases, OR = 1.15, 95% CI = 0.62, 2.18) but the risk of CHF was higher among rosiglitazone-treated patients than among those in the glyburide-treated group (22 cases vs 9 cases, OR = 2.44, 95% CI = 1.14, 5.59).

In the DREAM trial, a double-blind, placebo-controlled, 2x2 factorial design trial, 5,269 patients with impaired fasting glucose or impaired glucose tolerance were randomized to rosiglitazone or placebo and followed for a median of 3 years (40, 77, 78). Patients were concurrently randomized to ramipril or placebo as part of the factorial design. The primary endpoint of the rosiglitazone component of the DREAM trial was a composite endpoint of incident type 2 diabetes or death. Patients randomized to rosiglitazone were substantially less likely to develop the primary endpoint than those randomized to placebo (HR = 0.40, 95% CI = 0.35, 0.46). This difference was completely driven by the occurrence of diabetes (HR = 0.38, 95% CI = 0.33, 0.44). There was insufficient evidence to draw any conclusions regarding the effect of rosiglitazone on mortality (HR = 0.91, 95% CI = 0.55, 1.49). Although the point estimates of secondary analyses suggested that rosiglitazone may increase the risk of MI (HR = 1.66, 95% CI = 0.73, 3.80), stroke (HR = 1.39, 95% CI = 0.44, 4.40), cardiovascular death (HR = 1.20, 95% CI = 0.52, 2.77), new angina (HR = 1.20, 95% CI = 0.66, 2.17), or revascularization (HR = 1.29, 95% CI = 0.79, 2.14),

these estimates were accompanied by wide CIs and were inconclusive. These wide CIs were due, in part, to the low cardiovascular event rate in these pre-diabetic patients, who are at lower cardiovascular risk compared with frank diabetics. Despite their low cardiovascular risk, rosiglitazone was associated with a substantial increase in CHF compared with placebo (14 cases vs 2 cases, HR = 7.03, 95% CI = 1.60, 30.9).

Following the publication of the Nissen and Wolski meta-analysis, Home and colleagues conducted an unplanned interim analysis of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial, a randomized, open-label non-inferiority trial (110). In this trial, whose primary endpoint was hospitalization or death from cardiovascular causes, 4,447 patients with poor glycemic control while receiving metformin and a sulfonylurea were randomized to rosiglitazone or usual care, with all patients continuing their metformin and sulfonylurea therapy. This interim analysis, conducted after a mean of 3.75 years of follow-up, did not reveal an increased risk of hospitalization or death from cardiovascular causes with rosiglitazone (HR = 1.08, 95% CI = 0.89, 1.31). In addition, although wide 95% CIs prevent strong conclusions from being drawn, the interim analysis did not find an increased risk of MI (HR = 1.16, 95% CI = 0.75, 1.81). However, rosiglitazone was again associated with a substantial increase in the incidence of CHF (HR = 2.24, 95% CI = 1.27, 3.97). The final results of the RECORD trial will hopefully clarify the cardiovascular safety of rosiglitazone.

In addition to these 3 outcome-driven trials, the effect of rosiglitazone on the prevention of the progression of atherosclerosis was recently examined in the APPROACH trial (111, 112). In this multi-center, double-blind RCT, the results of which were presented in the Late Breaking Clinical Trial Session of the 2008 American Heart Association Scientific Sessions (111), 672 patients with type 2 diabetes and coronary artery disease were randomized to rosiglitazone or glipizide. The primary endpoint was change in percent atheroma volume. Although patients randomized to rosiglitazone experienced a decrease in atheroma volume of 0.21% while those randomized to glipizide experienced an increase of 0.43%, the overall difference in change in atheroma volume was inconclusive (treatment difference = -0.64%, 95% CI = -1.46%, 0.17%). There were a similar proportion of adjudicated cardiovascular events, consisting of all-cause mortality, non-fatal MI, non-fatal stroke, coronary revascularization, and hospitalization for ischemia, among those randomized to rosiglitazone (11.7%) and among those randomized to glipizide (11.2%). With only 11 cases of CHF occurring in this trial (8 and 3, respectively), there are insufficient data to draw conclusions regarding the effect of rosiglitazone on the incidence of CHF from the APPROACH trial.

There have also been two large trials examining the safety and efficacy of pioglitazone. In PERISCOPE, a double-blind, randomized RCT similar in design to APPROACH, 543 patients with diabetes and coronary artery disease who underwent intravascular ultrasound were randomized to either glimepiride or pioglitazone for 18 months (42). Dosages were titrated from 1 to 4 mg and 15 to

45 mg, respectively. Repeat intravascular ultrasound was completed in 360 of these patients. The primary outcome of PERISCOPE was progression of coronary atherosclerosis, which was assessed using the change in percent atheroma volume. Unlike in APPROACH, the PERISCOPE authors found that those randomized to glimepiride experienced a mean increase of 0.73% (95% CI = 0.33%, 1.12%) atheroma volume whereas those randomized to pioglitazone experienced a mean decrease of 0.16% (95% CI = -0.57%, 0.25%), suggesting that pioglitazone decreases the progression of coronary atherosclerosis. There were no differences in cardiovascular death, non-cardiovascular death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, or coronary revascularization between those randomized to glimepiride and those randomized to pioglitazone. In addition, there was no difference in hospitalizations for CHF. However, with only 9 hospitalizations for CHF (5 in the glimepiride arm and 4 in the pioglitazone arm), there are insufficient data to draw conclusions regarding the effect of pioglitazone on the incidence of CHF in this trial.

PERISCOPE has a number of limitations. First, over a third of patients did not complete the follow-up ultrasound and were thus excluded from the primary analysis (113). Although the authors attempt to account for these missing data using multiple imputation, this technique is not a replacement for having the data that are missing and is based on unverifiable assumptions. Consequently, although the use of multiple imputation is preferable to deleting missing patients (which may result in a selection bias), the possibility of bias remains. Second, the clinical significance of the observed treatment difference of approximately 1% is

unknown (113), particularly given the similar event rates in both treatment arms. Third, some have argued that the observed atherosclerosis progression and higher HbA1c among those randomized to glimepiride may be due to inadequate dosage titration in this group (114).

The PROactive study is the only randomized, double-blind trial specifically designed to examine the effect of TZDs on cardiovascular outcomes that has been completed to date. In the PROactive study, Dormandy and colleagues randomized 5,238 patients with type 2 diabetes and evidence of macrovascular disease to pioglitazone or placebo (39), in addition to their previously prescribed anti-diabetic medications. Pioglitazone was titrated from 15 to 45 mg, and the primary endpoint was a composite of all-cause mortality, non-fatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankles. The mean follow-up time was 34.5 months. Pioglitazone had no effect on their primary endpoint (HR = 0.90, 95% C I= 0.80, 1.02). However, pioglitazone appeared to reduce the occurrence of one of the secondary endpoints, a composite of all-cause mortality, MI, and stroke (HR = 0.84, 95% CI = 0.72, 0.98). In the PROactive study, patients randomized to pioglitazone also experienced an increased risk of 'any report of CHF' compared with those randomized to placebo (281 cases vs 198 cases, OR = 1.49, 95% CI = 1.23, 1.80). However, there was no difference in fatal CHF (25 cases vs 22 cases, OR = 1.15, 95% CI = 0.64, 2.04). The low case fatality rates (8.9% and 11.1%, respectively) suggest that

some of these patients may be misdiagnosed peripheral edema rather than true CHF.

With neutral results for their primary composite endpoint, the authors of PROactive inappropriately focus on their secondary analysis in their conclusions. Some have suggested that the results of this trial should not be disregarded just because of a poor choice in primary endpoint (115) and that discrepancy between the two endpoints was a dilution of effects due to the inappropriate inclusion of procedure endpoints in the primary analysis (116). However, others have argued that such post-hoc rationalization should be avoided (80). Furthermore, as discussed in a series of letters to the editor (79-81), the main secondary composite endpoint was not included in the published study protocol (117). This endpoint was, however, specified prior to unblinding and submitted to the FDA (118). Nonetheless, this inconsistency, combined with a neutral primary endpoint, has left the interpretations of the effect of pioglitazone on macrovascular events controversial.

Despite the availability of these trials, our knowledge regarding the cardiovascular effects of TZDs remains limited, particularly with respect to CHF. First, in the PROactive study, the 'any reported CHF endpoint' was not adjudicated by the Endpoints Evaluation Committee (39). Thus, information bias, particularly due to misclassification of outcome, remains an important possibility, particularly in light of their low case fatality rate. For example, it is unknown if these endpoints represent true CHF or misdiagnosed peripheral edema. Second, trials involve highly selected patients and are typically not representative of

patients in actual practice (119). For example, the DREAM trial involved patients with impaired glucose tolerance rather than patients with type 2 diabetes; these patients were at lower risk of CHF. As a result, the DREAM trial included only 16 cases of CHF. The generalizability of results of these trials remains unclear. In the real world, patients who have had diabetes for long durations are at increased risk of CHF and the risk of TZD-induced CHF may be amplified in these patients. Thus, there remains a need to examine the potential increased risk of CHF in an unselected, representative population.

2.2 Systematic Reviews and Meta-Analyses of Thiazolinediediones

The cardiovascular effects of TZDs have also been investigated in a number of systematic reviews and meta-analyses. We systematically searched PubMed to identify all systematic reviews and meta-analyses of RCTs published in English examining the effects of TZDs on cardiovascular events in patients with type 2 diabetes, impaired glucose tolerance, or the metabolic syndrome. We searched PubMed using the PubMed Clinical Query (120) for systematic reviews and the Shojania and Bero (121) search strategy for systematic reviews (Table 2.2). Using keywords and Medical Subject Headings (MeSH), we then searched for TZDs, including both pioglitazone and rosiglitazone. Results were limited to those involving human subjects and to those published between 1966 and February 2009. References of included studies were hand-searched for additional systematic reviews and meta-analyses.

We identified all systematic reviews and meta-analysis examining the cardiovascular effect of TZDs as a class and those specific to pioglitazone or

rosiglitazone. Systematic reviews and meta-analyses of troglitazone, a TZD that was removed from the market due to liver toxicity (28), were excluded. We also restricted our overview to those that examined cardiovascular events, including CHF, MI, coronary restenosis, all-cause or cardiovascular mortality, and peripheral edema, a symptom of CHF and the most common side effect of TZDs. We excluded all narrative reviews, letters, and editorials. In addition, we excluded systematic reviews and meta-analysis of basic science as well as those that examined TZD use in patients other than those with type 2 diabetes, impaired glucose tolerance, or the metabolic syndrome.

Our literature search identified a total of 228 potentially relevant articles (Figure 2.1). After applying our inclusion and exclusion criteria, we excluded 212 articles, leaving 16 systematic reviews and meta-analysis that were eligible for inclusion. An additional 5 meta-analyses were identified from a manual search of references of previous studies, resulting in a total of 21 systematic reviews and meta-analyses being included in this systematic overview (43-46, 48, 50, 51, 53-56, 59, 62-64, 66, 68-71, 73).

A total of 12 TZD systematic reviews and meta-analyses assessed the effects of TZDs on either all-cause or cardiovascular mortality (45, 48, 50, 51, 53-55, 63, 68, 69, 71, 73) (Table 2.3). These studies include 1 meta-analysis that examined the effect of TZDs as a class on mortality (53). Lago and colleagues identified 7 RCTs that compared the incidence of cardiovascular mortality among those randomized to TZD or active or placebo control (53). The authors concluded that the risk of cardiovascular mortality was not increased among those

randomized to TZD (relative risk = 0.93, 95% CI = 0.67, 1.29) but emphasized the need for longer follow-up to conclusively address this issue.

The effect of rosiglitazone on all-cause and cardiovascular mortality is inconclusive (Table 2.3). Nine of 11 systematic reviews and meta-analyses estimated that the relative risk for the effect of rosiglitazone on cardiovascular mortality is > 1.0, with relative risks ranging from 0.90 (95% CI = 0.63, 1.26) (71) to 2.37 (95% CI = 1.38, 4.07) (69). However, these estimates are accompanied by wide CIs, leading most authors to conclude that further studies are needed. The relative risks for all-cause mortality were similar.

There were important variations in the estimated cardiovascular death effects of rosiglitazone despite the use of relatively similar data sources (Table 2.4). This is well illustrated by a series of meta-analyses that analyzed the same data and demonstrates that these results are strongly affected by the inclusion of zero-event trials, choice of estimator, analytical approach, and comparator (45, 48, 55, 69, 73). Using trial data from the GSK website and 2 large, published RCTs, Nissen and Wolski used the Peto method to obtain an OR = 1.64 (95% CI = 0.98, 2.74) and concluded that there was a 'borderline' statistically significant increase in cardiovascular death (55). However, this analysis had some limitations including the exclusion of zero-event trials, and it has been suggested that although the Peto method is preferable for rare events under some circumstances, it may not be well suited for meta-analyses of studies with large imbalances in treatment and control groups (122). Using the same data sources as Nissen and Wolski (55), Friedrich and colleagues found that the estimated risk varied with

analytical approach and method used to account for zero-event trials, with all estimates suggesting an increased risk (Table 2.3). However, when examining this relationship using risk differences instead of ORs, the effects were less prominent. Addition of data from the RECORD trial (110) did not affect these estimates. Friedman and colleagues then repeated these analyses but restricted inclusion to those in which the only difference between treatment arms was the presence of absence of rosiglitazone (31 trials), which increased the risk estimates. In addition, Shuster and colleagues used multiple analytical methods, including a random-effects model that enabled them to include all trials with zero-events (relative risk = 2.37, 95% CI = 1.38, 4.07) (69). The effects of analytical approach and zero-event trials were also investigated by Bracken (45) and Diamond and colleagues (48).

The inclusion of unpublished RCTs also appears to influence the estimated effect on cardiovascular mortality. Meta-analyses that relied exclusively on published RCTs generally found smaller cardiovascular mortality effects (53, 68, 71) than those that included unpublished data from the manufacturer (either patient-level data or from the GSK website) (45, 48, 50, 51, 55, 69, 73). Thus, conventional literature searches that rely solely on electronic citations of published material are likely inadequate due to publication bias. To decrease this potential bias, pharmaceutical companies should be encouraged to make unpublished data available through online registries such as that maintained by GSK (123), and this finding highlights the importance of clinical trial registration (124).

Duration of follow-up may also play a role in explaining the variability in treatment effects (73). Singh and colleagues restricted inclusion to RCTs with at least 12 months of follow-up (71) and concluded that there was no significant increased risk (relative risk = 0.90, 95% CI = 0.63, 1.26). In contrast, most meta-analyses that included short-term studies reported relative risks >1.

Despite the variability in analytical approaches, data sources, and inclusion criteria, the 95% CIs of the majority of meta-analyses suggest that beneficial effects of rosiglitzone on cardiovascular mortality are unlikely.

Two meta-analyses have examined the effect of pioglitazone on mortality (53, 54). Both analyses were inconclusive, highlighting the need for further large RCTs examining the effect of pioglitazone on this endpoint.

The effect of rosiglitazone on the risk of MI has been examined extensively in 9 previous systematic reviews and meta-analyses (Table 2.5) (45, 48, 50, 51, 55, 59, 69, 71, 73). The previously-described meta-analysis conducted by Nissen and Wolski found that rosiglitazone was associated with an increased risk of MI (OR = 1.43, 95% CI = 1.03, 1.98) (55). Similarly, Psaty and Furberg (59), who incorporated the results of the RECORD trial (110) with the data presented by Nissen and Wolski, concluded that there was evidence of harmful effects of rosiglitazone with respect to MI (OR = 1.33, 95% CI = 1.02, 1.72). Meta-analyses of short-term trials conducted by the GSK (51, 98) and the FDA (50, 83) yielded results that were consistent with those reported elsewhere. However, GSK concluded that there was no consistent evidence of harm when examining the totality of available data, which included the GSK meta-analysis

and the results of the ADOPT (109), DREAM (40), and RECORD (110) trials. The FDA analysis resulted in ORs that varied from 1.38 (95% CI = 1.1, 1.8) to 1.5 (95% CI = 0.9, 2.7), depending on analytical method, but these results were inconclusive once insulin trials were excluded (total ischemic events: OR = 1.3, 95% CI = 1.0, 1.7; serious ischemic events: OR = 1.35, 95% CI = 0.9, 2.0). The FDA reviewer also raised concerns about the appropriateness of using a single estimate across all studies and all patients (50).

As with cardiovascular death, the choice of analytical approach, inclusion of zero-event trials, choice of estimator, and choice of comparator greatly influenced the estimates and conclusions of meta-analyses examining rosiglitazone's effect on MI (45, 48, 69, 73). Shuster and colleagues (69) used a random-effects model and included 6 zero-event trials excluded by Nissen and Wolski to obtain a relative risk = 1.51 (95% CI = 0.91, 2.48). Diamond and colleagues employed a variety of fixed-effects models and both constant and treatment continuity corrections to obtain ORs that ranged from 1.26 (95% CI = 0.93, 1.69) with a Mantel-Haenszel fixed-effects model with a constant continuity correction for all zero-event trials to 1.43 (95% CI = 1.03, 1.98) with the Peto method without continuity correction (48). In light of this variability, the authors concluded that the MI risk of rosiglitazone is uncertain. Similar results were obtained by Bracken (45) and Friedrich and colleagues (73), both of whom also demonstrated that there is no evidence of an increased risk when examining this relationship using risk differences. Results from the meta-analysis by Friedrich and colleagues also suggest that these estimates may underestimate the risk of MI

with rosiglitazone; restriction to trials where the only difference between the treatment groups is the presence or absence of rosiglitazone produced ORs that ranged from 1.42 (95% CI = 0.94, 2.15) to 1.91 (95% CI = 1.16, 3.06).

The conflicting nature of the results and conclusions drawn from meta-analyses examining the effect of rosiglitazone on MI highlights the need for the use of appropriate analyses and the importance of sensitivity analyses. Many investigators choose a fixed- or random-effects approach based on tests of heterogeneity. However, such tests are often grossly underpowered and, from a theoretical perspective, it is unlikely that the assumption of no between-study variability is ever completely satisfied. At the very least, random effects analyses should be performed (and reported) as sensitivity analyses. If using a fixed-effects model, sensitivity analyses should also include the use of different fixed-effects weighting procedures (e.g., Peto, inverse variance weighting, Mantel-Haenszel). Given the underlying assumptions of meta-analyses, an assessment of the robustness of the available data is essential to ensure that conclusions are consistent with the available evidence.

Regardless of analytical approach, all meta-analyses addressing this issue have reported point estimates consistent with a clinically-relevant increased risk of MI with accompanying 95% CIs that suggest the risk is either clinically equivalent to control or clinically harmful. Virtually none of these studies have estimates compatible with a clinical benefit with respect to MI.

In contrast, the effect of pioglitazone on the risk of MI has only been examined in 1 meta-analysis to date. In this study, Lincoff and colleagues (54)

obtained patient-level data from the manufacturer and, using a fixed-effects Cox proportional hazards model, found that pioglitazone decreased the rate of MI by 19% compared with placebo and active comparators (HR = 0.81, 95% CI = 0.64, 1.02). This meta-analysis is largely based on the findings of the PROactive trial (39), which contributed 5,238 of 16,390 patients included in this meta-analysis and is heavily weighted in their fixed-effects model.

The source of the apparent discordant effects of pioglitazone and rosiglitazone on MI remains poorly understood. Both agents appear to have similar effects on HbA1c (56, 57), but they appear to have different effects on other cardiovascular risk factors, which may partially explain the observed differences in MI effects. A meta-analysis of early TZD trials suggests that rosiglitazone has minimal effect on triglycerides (weighted mean difference = -1.1 mg/dL, 95% CI = -14.5, 12.3 mg/dL) and increases total cholesterol (21.3 mg/dL, 95% CI = 17.7, 24.9 mg/dL) and LDL (15.3 mg/dL, 95% CI = 13.0, 17.5 mg/dL) whereas pioglitazone has beneficial effects on triglycerides (-39.7 mg/dL, 95% CI = -53.0, -26.4 mg/dL) and neutral effects on LDL (-0.4 mg/dL, 95% CI = -4.7, 3.9 mg/dL) and total cholesterol (-0.1 mg/dL, 95% CI = -5.3, 5.1 mg/dL) (47). Both agents increase HDL, with pioglitazone resulting in a slightly larger increase.

The effects of pioglitazone and rosiglitazone on lipid profiles were directly compared in a multi-center RCT conducted in 802 patients with type 2 diabetes and untreated dyslipidemia (125). Compared with rosiglitazone, pioglitazone resulted in decreased triglycerides (-26.9 mg/dL, 95% CI = -35.4, -

18.4 mg/dL), LDL (-7.5 mg/dL, 95% CI = -12.8, -2.2 mg/dL), and total cholesterol (-10.2 mg/dL, 95% CI = -13.0, -7.4 mg/dL), improved total-to-HDL cholesterol ratio (-1, 95% CI = -1.3, -0.7), and increased HDL (7.1 mg/dL, 95% CI = 3.8, 10.4 mg/dL). Meta-analyses have also compared the effects of pioglitazione and rosiglitazone, albeit indirectly (43, 56); these comparisons produced similar results as those reported in this RCT. Further research into the mechanism of these agents is required to fully understanding the root of the different effects of these agents on the risk of MI.

As a result of their differing effects on MI and cardiovascular death, treatment guidelines now include different recommendations for pioglitazone and rosiglitazone (126). In a consensus statement issued by the American Diabetes Association and the European Association for the Study of Diabetes regarding the medical management of hyperglycemia among patients with type 2 diabetes, pioglitazone is listed as a less validated therapy and relegated as a second tier treatment option to be considered in specific situations (e.g., where hypoglycemia could be particularly dangerous). Despite acknowledged increases in CHF, edema (both discussed below), and fracture, the authors included pioglitazone as part of the treatment algorithm due to its favorable effects of lipid profiles, its potential cardiovascular benefits (as demonstrated by PROactive (39) and the meta-analysis by Lincoff and colleagues (54)), and the rarity of hypoglycemia associated with its use. Rosiglitazone is not recommended because of the concerns regarding its effects of MI and cardiovascular death.

Although much attention has focused on the effects of TZDs (particularly rosiglitazone) on MI and cardiovascular mortality, their effects on the risk of CHF have also been investigated in 3 systematic reviews (44, 56, 63) and 4 meta-analyses (53, 54, 70, 71) (Table 2.6). With the large majority of trials (including ADOPT, DREAM, RECORD, and PROactive) (39, 40, 109, 110) excluding patients with prevalent CHF, virtually all cases of CHF reported in these systematic reviews and meta-analyses were incident cases.

The CHF effects of TZDs as a medication class have been examined by 1 systematic review (44) and 2 meta-analyses (53, 70); all reported CHF increases associated with TZDs. In a meta-analysis restricted to placebo-controlled RCTs, Singh and colleagues found that TZDs were associated with a substantial increase in CHF (OR = 2.10, 95% CI = 1.08, 4.08) (70). A smaller increase was reported in a second meta-analysis, which included both placebo- and active-control (53).

In addition, 2 systematic reviews (53, 63) and 1 meta-analysis (71) have assessed the CHF effects of rosiglitazone and 1 systematic review (56) and 2 meta-analyses (53, 54) have examined the CHF effects of pioglitazone (Table 2.6). Both agents increase the risk of CHF, with rosiglitazone resulting in a larger increase relative to pioglitazone. Rosiglitazone meta-analyses estimate that it approximately doubles the rate of CHF relative to placebo- or active-control (53, 71). In contrast, Lincoff and colleagues found that pioglitazone increased the rate of CHF by 40% in their patient-level meta-analysis (HR = 1.41, 95% CI = 1.14, 1.76). Similar effects have been reported elsewhere (53).

The number of meta-analyses examining the CHF effects of these agents is relatively small compared with those that have examined their effects on MI and cardiovascular death. This is primarily due to the publicity generated by the meta-analysis by Nissen and Wolski (55); 8 meta-analyses (45, 48, 50, 51, 59, 69, 71, 73) examining rosiglitazone's potentially deleterious effects on MI were published soon after its publication. As a result, the CHF effects of TZDs remain underreported and their public health consequences potentially underestimated.

The effects of TZDs on composite cardiovascular endpoints have been examined in many systematic reviews and meta-analyses (Table 2.7) (46, 50, 51, 54, 56, 63, 64, 68). This includes the FDA's assessment of the cardiovascular effects of rosiglitazone (50). In this meta-analysis of short-term RCTs, the authors found that there was no definitive evidence that rosiglitazone increased the risk of a composite endpoint of cardiovascular death, myocardial infarction, and stroke (OR = 1.20, 95% CI = 0.8, 1.8). Similar results were obtained in other meta-analyses, highlighting the potentially increased risk but underscoring the need for additional studies to conclusively address the effect of rosiglitazone on composite cardiovascular outcomes (51, 63, 68).

The effect of pioglitazone on composite cardiovascular outcomes is more promising (Table 2.7). Using patient-level data from the manufacturer, Lincoff et al. found that pioglitazone decreased the rate of a composite outcome of all-cause mortality, MI, and stroke (HR = 0.82, 95% CI = 0.72, 0.94), as well as a composite endpoint of all-cause mortality and MI (HR = 0.85, 95% CI = 0.73, 0.99) (54). Composite endpoints that include CHF were less promising. In

addition, Selvin et al. used published results to examine the effect of pioglitazone on a composite measure of cardiovascular morbidity and concluded that no significant association was present (OR = 0.88, 95% CI = 0.78, 1.00) (68). Despite the authors' interpretation, which appears to be based solely on the absence of statistical significance, these results suggest that pioglitazone decreases cardiovascular morbidity; approximately 97.5% of estimates are below an OR of 1. In addition, as with MI, many of the composite endpoint results are dominated by the results of the large PROactive trial (39).

The effects of TZDs on rates of coronary restenosis and revascularization procedures among patients who had previously undergone coronary stenting have been investigated in 2 meta-analyses (Table 2.8). In a meta-analysis involving data from 5 RCTs (n = 235), Rosmarakis and colleagues (66) examined the effects of TZDs among patients with and without diabetes and found that patients randomized to TZDs had substantially lower rates of coronary restenosis (OR = 0.29, 95% CI = 0.15, 0.56) and target lesion revascularization (OR = 0.24, 95% CI = 0.09, 0.61). Despite these apparent benefits, the authors appropriately concluded that large, double-blind RCTs are required before implementing these findings into practice.

In another meta-analysis, Riche and colleagues (62) investigated the effects of TZDs on the risk of target vessel revascularization using data from 7 RCTs (n = 608). Using a random-effects model, the investigators found that patients randomized to TZDs had a lower risk of target vessel revascularization compared with those randomized to standard care (relative risk = 0.35, 95% CI =

0.22, 0.57). The beneficial effects appeared to be greater among patients in pioglitazone trials (relative risk = 0.24, 95% CI = 0.11, 0.51) than among those in rosiglitazone trials (relative risk = 0.45, 95% CI = 0.25, 0.83). Similar results were obtained among patients with and without diabetes.

Despite the apparent benefits associated with their use among patients who had previously received a coronary stent, these results should be interpreted with caution. Both meta-analyses are based on a relatively small number of RCTs and these RCTs had small sample sizes. Consequently, the large beneficial effects on restenosis and revascularization rates may be the result of publication bias. Large RCTs powered to examine these endpoints are required to conclusively address the use of TZDs in this patient population.

Finally, 3 previous systematic reviews (44, 46, 56) and 3 meta-analyses (43, 63, 64) have also estimated the risk of edema, a possible symptom of CHF and the most common side effect of TZDs (Table 2.9). Most systematic reviews and meta-analyses suggest that TZDs result in a 2- to 3-fold relative increase in the risk of edema, with some estimating the OR to be as high as 3.75 (43). As was the case with MI, the analytical approach employed appears to have important effects on these estimates. For example, Berlie and colleagues (43) identified 26 RCTs (n = 15,332) and pooled data across studies using both fixed- and random-effects meta-analyses. Although both analyses identified a substantial increase in edema, the point estimates of these analyses varied considerably (fixed-effects: OR = 2.26, 95% CI = 2.02, 2.53; random-effects: OR = 2.65, 95% CI = 2.19, 3.20).

The only systematic review or meta-analysis that did not conclude that TZDs were associated with an increased risk of edema was the systematic review conducted by Norris and colleagues (56). In this study, the authors identified 10 RCTs (1 rosiglitazone and 9 pioglitazone) that examined the effect of TZDs on peripheral edema. Although most RCTs suggested that edema may be higher among those randomized to TZDs, the authors' conclusions were based on overall adverse event rates, which were similar between treatment groups. The authors also emphasized that adverse event data were limited and the quality of the reporting of these data varied from fair to poor.

Berlie and colleagues compared pioglitazone and rosiglitazone indirectly (43). The authors found that, compared with pioglitazone, rosiglitazone was associated with a substantial increase in edema (OR = 2.74, 95% CI = 2.33, 3.14).

In conclusion, previous systematic reviews and meta-analyses suggest that rosiglitazone likely increases the risk of cardiovascular death and MI. The estimates and conclusions from these meta-analyses were heterogeneous (particularly with respect to MI), varying with analytical approach, inclusion of zero-event trials, choice of comparator and estimator, and inclusion of unpublished data. However, point estimates consistently suggest that rosiglitazone has clinically important harmful effects on these outcomes and accompanying CIs suggest that the likelihood of benefit is low. In contrast, pioglitazone appears to reduce the risk of MI and has clinically neutral effects on cardiovascular mortality. Both TZDs substantially increase the risk of CHF and edema, with rosiglitazone appearing to result in a larger increase than

pioglitazone. However, these systematic reviews and meta-analyses are based on data from RCTs that were conducted in highly-selected patient populations. The cardiovascular effects of TZDs in unselected patients remain understudied.

2.3 Observational Studies Examining Thiazolidinediones and Congestive Heart Failure

To date, there have been 7 observational studies that examined the effect of TZDs on the risk of CHF (88, 89, 94-96, 127, 128) (Table 2.10), half of which were published since this thesis was initiated. Delea and colleagues investigated the effect of TZDs on the risk of incident CHF using data from the Pharmetrics Integrated Outcomes health claims database (89). This study, which was funded by Novartis, included patients with type 2 diabetes who filled a prescription for an oral anti-diabetic agent from 1995 to 2001. Cohort entry was defined as the first prescription for a TZD (pioglitazone, rosiglitazone, or troglitazone) among exposed patients (n = 5,441). Patients who did not receive a TZD but filled prescriptions for oral anti-diabetic agents during the pre-index period were selected in a 5:1 ratio as the referent group (n = 28,103). The authors found that patients prescribed TZDs had a substantial increase in CHF (HR = 1.76, 95% CI = 1.43, 2.18). As discussed in a subsequent letter to the editor (129), this study had important limitations, including an inadequate referent group. Exposed patients consisted of those who were initiating TZD therapy (likely due to poor glycemic control) whereas the referent group was comprised of patients who were maintaining existing oral anti-diabetic medical therapy. Consequently, the results of this comparison are likely strongly affected by confounding by indication. In addition, although the authors adjusted for baseline differences, there was no

adjustment for medication use or comorbidities that arose during follow-up, resulting in residual confounding. In light of these limitations, the results of this study should be interpreted with caution.

Rajagopalan and colleagues compared the risk of hospitalization for CHF among patients prescribed pioglitazone and those prescribed insulin using data from the PharMetrics Patient-Centric database (96). In this study, which was funded and conducted by Takeda Pharmaceuticals (the manufacturer of pioglitazone), 1,668 pioglitazone patients of the 1,123,645 patients with type 2 diabetes in the database were matched to 1,668 insulin-prescribed controls using propensity scores. Compared with those prescribed insulin, patients prescribed pioglitazone had a substantially lower rate of hospitalization for primary or secondary diagnosis of CHF (HR = 0.50, 95% CI = 0.33, 0.76) and of hospitalization for CHF (HR = 0.26, 95% CI = 0.14, 0.51). However, patients prescribed insulin are typically much sicker than those prescribed oral anti-diabetic agents, and the use of propensity score analysis only accounts for measured confounders. Thus, it is very likely that these results are biased due to residual confounding due to unmeasured variables, including severity of disease and confounding by indication.

In a case-control study using data from Medicaid, Hartung and colleagues assessed TZD use among patients with type 2 diabetes hospitalized for CHF and those hospitalized for any other condition (95). TZD exposure was defined as any use of pioglitazone, rosiglitazone, or troglitazone (which has since been withdrawn from the market) in the 60 days prior to hospitalization. Using

frequency matching on sex, race, and age (caliper of 10 years), the authors identified 288 cases of CHF and 1,652 corresponding controls. TZDs were not associated with hospitalization for CHF, although the small number of cases (59 of which were exposed) prevent definitive conclusions from being drawn from these data (OR = 1.37, 95% CI = 0.98, 1.92). Furthermore, the choice of comparison group also represents an important limitation. TZDs have been linked to an increase in fractures among women (130), rosiglitazone may increase the risk of MI (55), and troglitazone was removed from the market because of potentially fatal hepatic effects (28), and the inclusion of patients hospitalized for any of these conditions as part of the control group would underestimate the CHF effects of TZDs.

In another study, Karter and colleagues used a new-user cohort to examine the association between pioglitazone and hospitalization for CHF (94). Using data from the Kaiser Permanente Medical Care Program, the authors identified all patients who initiated anti-diabetic medical therapy between October 1999 and November 2001 (n = 23,440), including 3,556 patients who initiated pioglitazone during this time. After adjusting for potential confounders (including HbA1c), pioglitazone was not associated with an increased rate of hospitalization for CHF compared with sulfonylureas, although wide CIs include clinically meaningful effects (HR = 1.28, 95% CI = 0.85, 1.92). The lack of precision of these estimates is due, in part, to a relatively short follow-up period (mean = 10.2 months), which limited the number of observed hospitalizations.

In response to the controversy surrounding rosiglitazone's potential increase in MI, 3 additional studies recently examined the effects of TZDs on the risk of CHF as part of an assessment of their global cardiovascular effects (88, 127, 128). Lipscombe and colleagues conducted a nested case-control study among patients aged ≥ 66 years with type 2 diabetes (n = 159,026) using provincial health care databases from Ontario, and cases were defined as an emergency room visit or hospitalization for CHF (88). A total of 17% of patients had prevalent CHF prior to the index date. The authors identified 12,491 cases and 61,827 controls. After adjusting for potential confounders, current TZD monotherapy (HR = 1.60, 95% CI = 1.21, 2.10) and current TZD combination therapy (HR = 1.31, 95% CI = 1.17, 1.47) were associated with an increased rate of hospitalization compared with current use of other oral combination therapy. These increased rates were larger for rosiglitazone (current monotherapy: HR = 1.98, 95% CI = 1.44, 2.72; current combination therapy: HR = 1.43, 95% CI = 1.25, 1.81) than pioglitazone (current monotherapy: HR = 0.91, 95% CI = 0.52, 1.59; current combination therapy: HR = 1.09, 95% CI = 0.90, 1.32).

Most recently, Habib and colleagues conducted a time-updated propensity score analysis among patients aged ≥ 18 years with type 2 diabetes who filled at least 1 prescription for an oral anti-diabetic agent between January 2000 and December 2006 (128). Data were obtained from a large health maintenance organization (HMO) for a total of 19,171 patients, 8.9% of whom had prevalent CHF. Compared with other oral anti-diabetic agents, TZDs increased the rate of hospitalization for CHF (HR = 1.24, 95% CI = 1.07, 1.44).

Finally, Winkelmayer and colleagues compared the cardiovascular effects of rosiglitazone and pioglitazone in elderly Medicare patients with type 2 diabetes who were initiating TZD therapy (127). The authors identified 14,101 new users of rosiglitazone and 14,260 new users of pioglitazone. A total of 22.4% and 21.1% of these patients had prevalent CHF at the time of cohort entry, respectively. Compared with those prescribed pioglitazone, patients prescribed rosiglitazone had an increased rate of hospitalization for CHF (HR = 1.13, 95% CI = 1.01, 1.26). Although these data are important in assessing the relative CHF effects of pioglitazone and rosiglitazone, they do not address their CHF effects relative to other anti-diabetic therapies.

Although 7 observational studies have examined the CHF effects of TZDs, important study limitations restrict the inferences that can be drawn from their results. These limitations include inappropriate referent groups in early TZD studies, the use of which led to results that are likely strongly affected by confounding by indication (89, 96). Six of the 7 studies did not adjust for glycemic control (88, 89, 95, 96, 127, 128); these studies are therefore likely confounded by disease severity, an independent risk factor for CHF. The 3 most recent studies included patients with prevalent CHF in their study populations (88, 127, 128), and 2 of these studies involved restricted study populations (88, 127). Consequently, the effect of TZDs on the risk of incident CHF in the general population of patients with type 2 diabetes remains unknown.

2.4 Glycemic Control Trials

There have also been a number of trials examining the effect of tight glycemic control on clinical outcomes (Table 2.11). These studies include sub-studies of the United Kingdom Prospective Diabetes Study (UKPDS), one of the largest trials ever conducted in patients with diabetes (131). In the UKPDS 33 trial, 3,867 patients with type 2 diabetes were randomized to intensive blood glucose control (target fasting blood glucose < 6 mmol/L) or conventional treatment and followed these patients for 10-years (15). All patients underwent a dietary intervention during a 3 month run-in period, and intensive therapy consisted of a sulphonylurea with or without insulin. Compared with patients in the conventional treatment arm (7.9%, 95% CI = 6.9%, 8.8%), patients in the intensive therapy arm had an 11% reduction in HbA1c (7.0%, 95% CI = 6.2%, 8.2%). In UKPDS 33, there were 3 primary composite endpoints: 1) any diabetes-related endpoint, defined as sudden death, death from hyperglycemia or hypoglycemia, MI, angina, CHF, stroke, renal failure, amputation, vitreous hemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction; 2) diabetes-related death, defined as death from MI, stroke, peripheral vascular disease, renal disease, hyperglycemia or hypoglycemia, or sudden death; and 3) all-cause mortality. Other clinical events examined included microvascular events, defined as retinopathy requiring photocoagulation, vitreous haemorrhage, and/or fatal or non-fatal renal failure. Patients randomized to intensive glucose control had a 12% relative risk reduction (RRR) in any diabetes-related outcome (95% CI = 1%, 21%) and 25% RRR in the occurrence of

microvascular events (95% CI = 7%, 40%). There were no detectable differences in diabetes-related deaths (RRR = 10%, 95% CI = -11%, 27%) or all-cause mortality (RRR = 6%, 95% CI = -10%, 20%). These similar event rates may be due to a substantial number of patients randomized to diet crossing over to more intensive therapy (131). Those randomized to intensive therapy experienced greater weight gain and, not surprisingly, had higher rates of hypoglycemia. Although the investigators examined the effect of intensive glucose control on CHF, there were insufficient data to draw meaningful conclusions from this analysis (RRR = 9%, 95% CI = -52%, 46%).

In UKPDS 34, data were combined from 2 UKPDS sub-studies to examine the effect of intensive blood-glucose in patients who were overweight with newly-diagnosed type 2 diabetes (132). In the first sub-study, a total of 753 patients were randomized starting in 1977 to intensive blood-glucose lowering with metformin or conventional therapy consisting primarily of diet. Data for these patients were combined with those for 537 patients from the second sub-study, who had been randomized to sulphonylureas but remained poorly controlled. These latter patients were then randomized to sulphonylurea and metformin or sulphonulurea only. After a median of 10.7 years of follow-up, patients randomized to intensive therapy had substantial reductions in diabetes-related endpoints (as defined above) (RRR = 32%, 95%CI = 13%, 47%), diabetes-related death (RRR = 42%, 95% CI = 9%, 63%), and all cause mortality (RRR = 36%, 95%CI = 9%, 55%) compared with those randomized to conventional therapy. In addition, those randomized to both sulfonylureas and metformin in the

second sub-study had a substantially increased risk of diabetes-related death compared with those randomized to sulfonylureas only (relative increased risk = 96%, 95% CI = 2%, 275%), highlighting the potential dangers associated with overly aggressive management.

Following the conclusion of the interventional phase of the UKPDS trial, 1,525 patients were monitored for 10-years (133). This follow-up study (UKPDS 80) was purely observational; no attempts were made to maintain their allocated treatment regiments. The first 5 years of follow-up were conducted via clinic visit, with the remaining 5 years occurring via questionnaire. After one year, all groups had similar levels of HbA1c. However, patients who had been randomized to intensive therapy, consisting of a sulfonylurea with or without insulin, experienced fewer adverse events compared with those randomized to diet alone (any diabetes-related endpoint: risk ratio = 0.91, 95% CI = 0.83, 0.99; all-cause mortality: risk ratio = 0.83, 95% CI = 0.79, 0.96; MI: risk ratio = 0.85, 95% CI = 0.74, 0.97; microvascular disease: risk ratio = 0.76, 95% CI = 0.64, 0.89). Among overweight patients, those randomized to metformin had lower all-cause mortality (risk ratio = 0.73, 95% CI = 0.59, 0.89), diabetes-related endpoints (risk ratio = 0.79; 95% CI = 0.66, 0.95), and MI (risk ratio = 0.67, 95% CI = 0.51, 0.89). Consequently, despite similar HbA1c levels during this follow-up period, intensive therapy appeared to improve long-term outcomes, highlighting the ambiguity surrounding HbA1c as a predictor of clinical events. Furthermore, the mechanism behind this ‘legacy effect’, linking early changes in HbA1c with long-term outcomes, remains poorly understood (134).

Other trials that examined the effect of glucose lowering on mortality and cardiovascular outcomes include the recently published ADVANCE (16) and ACCORD (17) trials. In the ADVANCE trial, over 11,000 patients with type 2 diabetes were randomized to intensive or standard glucose control (16). Intensive therapy involved an HbA1c treatment target of 6.5%. After a median of 5 years of follow-up, intensive glucose control reduced the incidence of their primary endpoint, a composite of macro- and microvascular events (HR = 0.90, 95% CI = 0.82, 0.98). This difference was primarily due to a 21% relative reduction in nephropathy (HR = 0.79, 95% CI = 0.66, 0.93). There was no difference in their composite endpoint of major macrovascular events (HR = 0.94, 95% CI = 0.84, 1.06) or new or worsening retinopathy (HR = 0.95, 95% CI = 0.82, 1.10). There was also no difference in all-cause mortality (HR = 0.93, 95% CI = 0.93, 1.06). Some have argued that ADVANCE's 5-year follow-up may have been insufficient to allow the survival curves to separate (134). However, such post-hoc hypotheses should be interpreted with caution.

The ACCORD trial (17) randomized over 10,000 patients with type 2 diabetes who had either established cardiovascular disease or additional cardiovascular risk factors to intensive therapy (targeting an HbA1c<6%) or standard therapy (targeting an HbA1c between 7.0 and 7.9) and followed them for a mean of 3.5 years. The investigators found that intensive therapy resulted in a 22% relative increase in all-cause mortality (95% CI = 1%, 46%). Some have hypothesized that the excess mortality may be due to the use of an increased number of anti-diabetic drug classes among those randomized to intensive therapy

(135) whereas others have suggested that the increased mortality may be due to increased use of rosiglitazone in the intensive-therapy arm (136). In addition, it has been suggested that important differences in patient characteristics (obesity in particular) may explain the differing conclusions drawn from ADVANCE and ACCORD (137). Nonetheless, these conflicting nature of the ADVANCE and ACCORD results have further fueled the debate regarding the role of surrogate endpoints in clinical trials (21). These results have also highlighted the trade-off between the beneficial effects of intensive therapy on microvascular events and the potential increase in other adverse events (138).

The clinical utility of HbA1c has also been examined in patients with CHF. The Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program involved a total of 2,412 patients who had undergone at least 1 HbA1c test, 907 of whom had previously-diagnosed type 2 diabetes (139). These patients were followed for a median of 34 months. The authors found that, after adjusting for potential confounders, a 1% increase in HbA1c was associated with a small but important increase in their primary composite endpoint of cardiovascular death or worsening CHF (HR = 1.14, 95% CI = 1.07, 1.21). This increase was consistently present for both components of this composite endpoint (cardiovascular death: HR = 1.13, 95% CI = 1.04, 1.22; worsening CHF: HR = 1.13, 95% CI = 1.05, 1.21), as well as for all-cause mortality (HR = 1.14, 95% CI = 1.06, 1.23). The authors also found the presence of a dose-response relationship, with the risks of their primary composite endpoint, cardiovascular death, worsening CHF, and all-cause mortality all

increasing with increasing HbA1c category. Secondary analyses stratified by the presence or absence of diabetes suggest that increasing HbA1c is a greater predictor of these 4 outcomes among those without diabetes compared with those with diabetes. Although these results suggest that HbA1c is an important predictor of worsening CHF, its role in predicting incident CHF remains unclear.

Most recently, the effects of intensive glucose control on cardiovascular outcomes were examined in the Veterans Affairs Diabetes Trial (VADT) (140). In this open-label trial, over 1,700 military veterans with BMI $\geq$ 27 kg/m^2 and inadequate glucose control while receiving maximal dosages of an oral anti-diabetic therapy or insulin were randomized to intensive glucose therapy, consisting of metformin and rosiglitazone at maximal dosages, or standard therapy, consisting of the same agents at half of the maximal dosages. Insulin therapy was then added to these treatment regiments, when HbA1c was > 6% in the intensive group and > 9% in the standard therapy group. The primary endpoint of VADT was time to the first occurrence of a composite cardiovascular endpoint that included MI, stroke, cardiovascular death, new or worsening CHF, surgical intervention for cardiac, cerebrovascular, or peripheral vascular disease, inoperable coronary artery disease, and amputations for ischemic gangrene. In VADT, intensive therapy was not associated with the time to their primary composite endpoint (HR = 0.88, 95% CI = 0.74, 1.05), cardiovascular death (HR = 0.81, 95% CI = 0.32, 2.14), or all-cause mortality (HR = 1.07, 95% CI = 0.81, 1.42).

The inconsistent nature of the results of these trials, particularly those of ADVANCE and ACCORD, may affect the recommended HbA1c target, particularly among those at high-cardiovascular risk, while awaiting the results of ongoing trials (e.g., HEART2D, ORIGIN, BARI 2D)(141). While awaiting these results, the American Diabetes Association (ADA) continues to advocate for an HbA1c target < 7% due to its beneficial effects on microvascular complications. Although tight glycemic control will continue to be the hallmark of clinical management of patients with type 2 diabetes, additional studies are required to identify the optimal HbA1c target. Furthermore, studies are needed to further delineate the clinical utility of HbA1c as a predictor of clinical events such as incident CHF.

Table 2.1 Overview of major thiazolidinedione trials.

Study	Intervention	Follow-Up (Years)	Endpoint	TZD (n/N)	Control (n/N)	Hazard Ratio (95% CI)
Rosiglitazone:						
ADOPT 2006 (109)	Rosiglitazone (4-8 mg/day) vs Metformin (500-2,000 mg/day	4.0	Monotherapy Treatment Failure	143/1,393	207/1,397	0.68 (0.55, 0.85)
			CHF	22/1,393	19/1,397	1.15 (0.62, 2.18)*
	Rosiglitazone (4-8 mg/day) vs Glyburide (2.5-15 mg/day)		Monotherapy Treatment Failure	143/1,393	311/1,337	0.37 (0.30, 0.45)
			CHF	22/1,393	9/1,337	2.44 (1.14, 5.59)*
DREAM 2006 (40)	Rosiglitazone (8 mg) vs Placebo	3.0	Incident Diabetes or Death	306/2,635	686/2,634	0.40 (0.35, 0.46)
			Incident Diabetes	280/2,635	658/2,634	0.38 (0.33, 0.44)
			Death	30/2,635	33/2,634	0.91 (0.55, 1.49)
			CVD Event	75/2,635	55/2,634	1.37 (0.97, 1.94)
			MI	15/2,635	9/2,634	1.66 (0.73, 3.80)
			Stroke	7/2,635	5/2,634	1.39 (0.44, 4.40)
			CVD Death	12/2,635	10/2,634	1.20 (0.52, 2.77)
			New Angina	24/2,635	20/2,634	1.20 (0.52, 2.77)
			Revascularization	35/2,635	27/2,634	1.29 (0.78, 2.14)
			CHF	14/2,635	2/2,634	7.00 (1.60, 30.9)
RECORD 2008 (110)	Rosiglitazone + Metformin + Sulfonylurea vs Metformin + Sulfonylurea	3.75	CVD Hospitalization or Death†	217/2,220	202/2,227	1.08 (0.89, 1.31)
			All-Cause Mortality†	74	80	0.93 (0.67, 1.27)
			MI†	43	37	1.16 (0.75, 1.81)
			CHF†	38	17	2.24 (1.27, 3.97)
APPROACH 2008 (111)	Rosiglitazone (titrated to 8 mg/day) vs Glipizide (titrated to 15 mg/day)	1.5	Change in Percent Atheroma Volume	NR	NR	-0.64% (-1.46%, 0.17%)††
			CVD Composite Endpoint	39/333	38/339	1.05 (0.65, 1.70) ‡‡
			All-Cause Mortality	8/339	7/339	1.17 (0.41, 3.42) ‡‡
			CHF	8/339	3/339	2.75 (0.75, 12.9) ‡‡

Study	Intervention	Follow-Up (Years)	Endpoint	TZD (n/N)	Control (n/N)	Hazard Ratio (95% CI)
Pioglitazone:						
PERISCOPE 2008 (42)	Pioglitazone (15-45 mg/day) vs Glimepiride (1-4 mg/day)	1.5	Change in Atheroma Volume	-0.16% (0.33%, 1.12%)‡	0.73% (0.33%, 1.12%)‡	NR
			CVD Death, Non-fatal MI or Stroke	5/270	6/273	0.84 (0.23, 2.91)*
			CVD Event	41/270	40/273	1.04 (0.65, 1.68)
			CHF Hospitalization	4/270	5/273	0.81 (0.19, 3.22)
PROactive 2005 (39)	Pioglitazone (1545 mg/day) vs Placebo	2.9	All-cause mortality, MI, Stroke, ACS, Coronary or Peripheral Revascularization, Amputations	514/2,605	572/2,633	0.90 (0.80, 1.02)
			All-cause mortality, MI, Stroke	301/2,605	358/2,605	0.84 (0.72, 0.98)
			Any Report of CHF	281/2,605	198/2,605	1.49 (1.23, 1.80)*
			Fatal CHF	25/2,605	22/2,605	1.15 (0.64, 2.04)*

Abbreviations: ADOPT: A Diabetes Outcome Progression Trial; APPROACH: Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Diabetes Patients with Cardiovascular History Trial; CHF: Congestive Heart Failure; CVD: Cardiovascular DREAM: Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication; MI: Myocardiac Infarction; NR: Not Reported; PERISCOPE: Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation Trial; PROactive: Prospective Pioglitazone Clinical Trial In Macrovascular Events Trial; RECORD: Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes Trial; TZD: Thiazolidinediones.

* Effect measure reported was the odds ratio rather than hazard ratio.

† Only includes adjudicated events.

†† Data were reported as a treatment difference with a corresponding 95% confidence interval.

‡ Data were reported as change from baseline with corresponding 95% confidence intervals.

‡‡ Data represent odds ratios and 95% CIs calculated from published count data.

Table 2.2. Pubmed search strategy for systematic reviews and meta-analyses of thiazolidinediones*.

Search Number	Description	Number of Publications
#1†	(systematic review*[tiab] OR systematic literature review* OR meta-analysis[pt] OR meta-analysis[ti] OR metaanalysis[ti] OR meta-analyses[ti] OR evidence-based medicine OR (evidence-based AND (guideline[tiab] OR guidelines[tiab] OR recommendations)) OR (evidence based AND (guideline [tiab] OR guidelines[tiab] OR recommendation*)) OR consensus development conference[pt] OR health planning guidelines OR guideline[pt] OR Cochrane database syst rev OR acp journal club OR health technol assess OR evid rep technol assess summ OR evid based dent OR evid based nurs OR evid based ment health OR clin evid) OR ((systematic[tiab] OR systematically OR critical [tiab] OR (study[tiab] AND selection[tiab]) OR (predetermined OR inclusion AND criteri*) OR exclusion criteri* OR "main outcome measures" OR "standard of care" OR "standards of care") AND (survey[tiab] OR surveys [tiab] OR overview* OR review[tiab] OR reviews[tiab] OR search* OR hand search OR analysis[tiab] OR critique[tiab] OR appraisal OR (reduction AND risk AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication[tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR unpublished OR citation OR citations OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references OR trials[tiab] OR meta-analysis[mh] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome)) NOT (case report[ti] OR editorial[ti] OR editorial[pt] OR letter[pt] OR newspaper article[pt])	158,420
#2‡	((meta-analysis [pt] OR meta-analysis [tw] OR metanalysis [tw]) OR ((review [pt] OR guideline [pt] OR consensus [ti] OR guideline* [ti] OR literature [ti] OR overview [ti] OR review [ti]) AND ((Cochrane [tw] OR Medline [tw] OR CINAHL [tw] OR (National [tw] AND Library [tw])) OR (handsearch*[tw] OR search* [tw] OR searching [tw]) AND (hand [tw] OR manual [tw] OR electronic [tw] OR bibliographi* [tw] OR database* OR (Cochrane [tw] OR Medline [tw] OR CINAHL [tw] OR (National [tw] AND Library [tw])))) OR ((synthesis [ti] OR overview [ti] OR review [ti] OR survey [ti]) AND (systematic[ti] OR critical [ti] OR methodologic [ti] OR quantitative [ti] OR qualitative [ti] OR literature [ti] OR evidence [ti] OR evidence-based [ti]))) BUT NOT (case* [ti] OR report [ti] OR editorial [pt] OR comment [pt] OR letter [pt])	83,371
#3	#1 OR #2	197,709
#4	("Thiazolidinediones"[Mesh] OR "PPAR gamma"[Mesh] OR "rosiglitazone"[Substance Name] OR "pioglitazone"[Substance Name] OR "rosiglitazone"[tiab] OR "pioglitazone"[tiab] OR glitazone*[tiab] OR Thiazolidinedione*[tiab] OR TZD*[tiab] OR (("peroxisome proliferatoractivated receptor"[tiab] OR "PPAR"[tiab]) AND ("agonist"[tiab] OR "activator"[tiab])) OR (("peroxisome proliferator-activated receptor"[tiab] OR "PPAR"[tiab]) AND "gamma"[tiab]) OR "avandia"[tiab] OR "actos"[tiab])	12,278
#5	#3 AND #4	304
#6	#5 Limited to English	278
#7	#6 Limited to Human	228

* The literature search was conducted on February 9, 2009.
†Search #1 corresponds to Pubmed's Clinical Query search filter for systematic reviews (120).
‡ Search #2 corresponds to the Shojania and Bero filter for systematic reviews (121).

Table 2.3. Systematic reviews and meta-analyses that examined the effect of thiazolidinediones on all-cause and cardiovascular mortality.

Study	Populations	Minimum Duration of RCTs (weeks)	Analytical Approach	Correction for Zero-Event Trials	Number of Trials (Number of Patients)	Comparator	Type of Mortality	Treatment Effect (95% CI)	Conclusions
TZDs									
Lago 2007 (53)	Pre-DM or T2DM	NR	Random Effects	Yes	7 (n=20,191)	Placebo or Active	CV	RR=0.93 (0.67, 1.29)	Risk not increased; longer follow-up is needed.
Rosiglitazone									
Bracken 2007 (45)	T2DM, IGT, IFG, or Chronic Psoriasis	24	Fixed Effects (Peto)	Yes (0.5)	42 (n=27,847)	Placebo or Active	CV	OR=1.15 (0.81, 1.64)	Results sensitive to choice of estimator; weakens inferences that can be drawn from Nissen's meta-analysis. Addition of RECORD data does not impact conclusions.
			Fixed Effects (MH)	Yes (0.5)	42 (n=27,847)	Placebo or Active	CV	RR=1.07 (0.76, 1.49)	
			Fixed Effects (MH)	Yes (0.5)	42 (n=27,847)	Placebo or Active	CV	OR=1.07 (0.76, 1.50)	
			Fixed Effects (MH)	Yes (0.5)	42 (n=27,847)	Placebo or Active	CV	RD=0.00 (0.00, 0.00)	
Diamond 2007 (48)	T2DM, IGT, IFG, or Chronic Psoriasis	24	Fixed Effects (Peto)	Excluded	23 (NR)	Placebo or Active	CV	OR=1.64 (0.98, 2.74)	Risk is uncertain – definitive RCT is required.
			Fixed Effects (IV)‡	Yes (TAC)	23 (NR)	Placebo or Active	CV	OR=1.46 (0.88, 2.42)	
			Fixed Effects (IV)‡	Yes (CC)	23 (NR)	Placebo or Active	CV	OR=1.31 (0.80, 2.13)	
			Fixed Effects (MH)	Yes (TAC)	23 (NR)	Placebo or Active	CV	OR=1.51 (0.94, 2.44)	
			Fixed Effects (MH)	Yes (CC)	23 (NR)	Placebo or Active	CV	OR=1.33 (0.83, 2.13)	
			Fixed Effects (MH)	Yes (TAC+)	42 (n=27,847)	Placebo or Active	CV	OR=1.39 (0.91, 2.13)	
			Fixed Effects (MH)	Yes (CC+)	42 (n=27,847)	Placebo or Active	CV	OR=1.17 (0.77, 1.77)	
Friedrich 2009 (73)	NR	24	Fixed Effects (Peto)	Excluded	38 (n=18,953)	Placebo or Active	CV	OR=1.64 (0.98, 2.74)	Increased or decreased risk and presence or absence of statistical significance vary with choice of analytical method; ongoing trials may provide additional information but all point
			Fixed Effects (IV)	Excluded	38 (n=18,953)	Placebo or Active	CV	OR=1.31 (0.80, 2.13)	
			Fixed Effects (MH)	Yes (CC)	38 (n=18,953)	Placebo or Active	CV	OR=1.33 (0.83, 2.13)	
			Fixed Effects (MH)	Yes (TCC)	38 (n=18,953)	Placebo or Active	CV	OR=1.51 (0.94, 2.44)	
			Fixed Effects (MH)	Yes (Empiric)	38 (n=18,953)	Placebo or Active	CV	OR=1.58 (0.97, 2.55)	
			Fixed Effects (Exact)	NA	38 (n=18,953)	Placebo or Active	CV	OR=1.66 (0.95, 2.98)	
			Bayesian	NA	38 (n=18,953)	Placebo or Active	CV	OR=1.74 (0.99, 2.89)	
			Fixed Effects (Peto)	Excluded	39 (n=23,400)	Placebo or Active	CV	OR=1.08 (0.78, 1.51)	

Study	Populations	Minimum Duration of RCTs (weeks)	Analytical Approach	Correction for Zero-Event Trials	Number of Trials (Number of Patients)	Comparator	Type of Mortality	Treatment Effect (95% CI)	Conclusions
			Fixed Effects (IV)	Excluded	39 (n=23,400)	Placebo or Active	CV	OR=1.00 (0.72, 1.38)	estimates suggest
			Fixed Effects (MH)	Yes (CC)	39 (n=23,400)	Placebo or Active	CV	OR=1.02 (0.74, 1.40)	increased risk.
			Fixed Effects (MH)	Yes (TCC)	39 (n=23,400)	Placebo or Active	CV	OR=1.07 (0.78, 1.48)	
			Fixed Effects (MH)	Yes (Empiric)	39 (n=23,400)	Placebo or Active	CV	OR=1.07 (0.78, 1.46)	
			Fixed Effects (Exact)	NA	39 (n=23,400)	Placebo or Active	CV	OR=1.08 (0.76, 1.53)	
			Bayesian	NA	39 (n=23,400)	Placebo or Active	CV	OR=1.09 (0.77, 1.51)	
			Fixed Effects (Peto)	Excluded	31 (NR)	Placebo or Active[¥]	CV	OR=1.87 (1.06, 3.31)	
			Fixed Effects (IV)	Excluded	31 (NR)	Placebo or Active[¥]	CV	OR=1.40 (0.82, 2.38)	
			Fixed Effects (MH)	Yes (CC)	31 (NR)	Placebo or Active[¥]	CV	OR=1.43 (0.85, 2.38)	
			Fixed Effects (MH)	Yes (TCC)	31 (NR)	Placebo or Active[¥]	CV	OR=1.66 (0.97, 2.81)	
			Fixed Effects (MH)	Yes (Empiric)	31 (NR)	Placebo or Active[¥]	CV	OR=1.79 (1.04, 3.06)	
			Fixed Effects (Exact)	NA	31 (NR)	Placebo or Active[¥]	CV	OR=1.94 (1.02, 3.86)	
			Bayesian	NA	31 (NR)	Placebo or Active[¥]	CV	OR=2.12 (1.09, 3.84)	
			Fixed Effects (Peto)	NA	54 (NR)	Placebo or Active	CV	RD=0.10 (-0.04, 0.25)	
			Fixed Effects (Peto)	NA	55 (NR)	Placebo or Active	CV	RD=0.03 (-0.13, 0.20)	
			Fixed Effects (Peto)	NA	41 (NR)	Placebo or Active[¥]	CV	RD=0.15 (-0.03, 0.33)	
FDA 2007 (50) [‡‡]	T2DM	NR	Exact test stratified by meta-analysis group	Yes (0.5)	42 (n=14,237)	Placebo or Active (Including Insulin)	CV	OR=1.7 (0.7, 5)	No definitive evidence
			Fixed Effects (MH)		42 (n=14,237)	Placebo or Active (Including Insulin)	CV	OR=1.6 (0.7, 3.8)	Mortality data are limited
			Fixed Effects (MH)	Yes (0.5)	42 (n=14,237)	Placebo or Active (Including Insulin)	ACM	OR=1.7 (0.8, 3.4)	
GSK 2007 (51, 98) [‡‡]	T2DM	NR	Patient-Level Cox Proportional Hazards	NR	42 (n=14,237)	Placebo or Active (Including Insulin)	CV	HR=1.9 (0.8, 4.6)	No consistent evidence of increased risk; further studies are needed
Lago 2007 (53)	Pre-DM or T2DM	NR	Random Effects	Yes	5 (n=14,491)	Placebo or Active	CV	RR=0.91 (0.63, 1.32)	Risk not increased; longer follow-up is needed.
Nissen 2007 (55)	T2DM, IGT, IFG, or Chronic	24	Fixed Effects (Peto)	Excluded	23 (NR)	Placebo or Active	CV	OR=1.64 (0.98, 2.74)	Increased risk with borderline statistical significance
	Psoriasis		Fixed Effects (Peto)	Excluded	NR	Placebo or Active	ACM	OR=1.18 (0.89, 1.55)	NR
Richter 2007 (63)	T2DM	24	NA	NA	1 (n=2,910)	Metformin	ACM	OR=1.10 (0.67, 1.81)	Patient-orientated

Study	Populations	Minimum Duration of RCTs (weeks)	Analytical Approach	Correction for Zero-Event Trials	Number of Trials (Number of Patients)	Comparator	Type of Mortality	Treatment Effect (95% CI)	Conclusions
					1 (n=2,897)	Glyburide	ACM	OR=1.09 (0.64, 1.84)	outcome studies needed
Selvin 2008 (68)	T2DM	12	Fixed Effects (MH)†	Excluded	5 (n=3,202)	Placebo or Active	CV	OR=1.03 (0.30, 3.53)	Increased risk but not significant, possibly due to small number of studies to date.
					6 (n=2,927)		ACM	OR=1.21 (0.39, 3.77)	Increased risk but not significant, possibly due to small number of studies to date.
Shuster 2007 (69)	T2DM, IGT, IFG, or Chronic Psoriasis	24	Random Effects	NR	42 (n=27,847) + 6 (NR)€	Placebo or Active	CV	RR=2.37 (1.38, 4.07)	Random-effects = better analytical approach
			Fixed-Effects Cox Analysis	NR	42 (n=27,847)	Placebo or Active	CV	RR=1.66 (0.97, 2.83)	because of weighting of large studies
			Fixed-Effects Logistic Regression	NR	42 (n=27,847)	Placebo or Active	CV	RR=1.66 (0.98, 2.84)	
			STATXACT	NR	42 (n=27,847)	Placebo or Active	CV	RR=1.66 (0.95, 2.98)	
			STATXACT (Asymptomatic)	NR	42 (n=27,847)	Placebo or Active	CV	RR=1.69 (0.98, 2..93)	
Singh 2007 (71)	T2DM, IGT, or IFG	52	Fixed Effects‡	NR	4 (n=14,291)	Placebo or Active	CV	RR=0.90 (0.63, 1.26)	No significant increased risk
Pioglitazone									
Lago 2007 (53)	Pre-DM or T2DM	NR	Random Effects	Yes	2 (n=5,700)	Placebo or Active	CV	RR=1.01 (0.51, 2.01)	Risk not increased; longer follow-up is needed.
Lincoff 2007 (54)	T2DM	NR	Patient-Level Fixed Effects Cox Model	Excluded	19 (n=16,390)	Placebo or Active	ACM	HR=0.92 (0.76, 1.11)	NR
Selvin 2008 (68)	T2DM	12	Fixed Effects (MH) †	Excluded	2 (n=5,566)	Placebo or Active	CV	NA	NR

Abbreviations: ACM=all-cause mortality; CC=constant correction for continuity; CC+= constant correction for continuity that includes all zero-event trials; CHF=congestive heart failure; CI=confidence interval; DM=diabetes mellitus; CV=cardiovascular; HR=hazard ratio; IFG=impaired fasting glucose;

IGT=impaired glucose tolerance; IV=inverse variance; MH=Mantel-Haenszel; NA=not applicable; NR=not reported; OR=odds ratio, RD=risk difference; RR=relative risk; T2DM=type 2 diabetes mellitus; TAC=treatment arm correction for continuity; TAC+= treatment arm correction for continuity that includes all zero-event trials; TZDs=thiazolidinediones.

†Sensitivity analyses included the use of Peto fixed effects analyses, which produced similar results as those reported here.

‡ Sensitivity analyses included the use of random effects analyses, which produced similar results as those reported here.

‡‡Multiple analyses with multiple comparison groups were conducted. In addition, data from 3 long-term RCTs (ADOPT, DREAM, and RECORD) (40, 109, 110) were also presented. These data were not presented here due to space constraints.

¥Restricted to studies where the only difference between the 2 treatment groups is the presence or absence of rosiglitazone.

€ This analysis included the 42 trials from the Nissen meta-analysis as well as 6 that we excluded from the Nissen meta-analysis because they included 0 events.

Table 2.4. Systematic reviews and meta-analyses that examined the effect of thiazolidinediones on the risk of myocardial infarction.

Study	Populations	Minimum Duration of RCTs (weeks)	Analytical Approach	Correction for Zero-Event Trials	Number of Trials (Number of Patients)	Comparator	Treatment Effect (95% CI)	Conclusions
Rosiglitazone								
Bracken 2007 (45)	T2DM, IGT, IFG, or Chronic Psoriasis	24	Fixed Effects (Peto)	Yes (0.5)	42 (n=27,847)	Placebo or Active	OR=1.33 (1.02, 1.73)	Results sensitive to choice of estimator; weakens inferences that can be drawn from Nissen's meta-analysis. Addition of RECORD data does not impact conclusions.
			Fixed Effects (MH)	Yes (0.5)	42 (n=27,847)	Placebo or Active	RR=1.24 (0.97, 1.58)	
			Fixed Effects (MH)	Yes (0.5)	42 (n=27,847)	Placebo or Active	OR=1.24 (0.97, 1.58)	
			Fixed Effects (MH)	Yes (0.5)	42 (n=27,847)	Placebo or Active	RD=0.00 (0.00, 0.00)	
Diamond 2007 (48)	T2DM, IGT, IFG, or Chronic Psoriasis	24	Fixed Effects (Peto)	Excluded	23 (NR)	Placebo or Active	OR=1.43 (1.03, 1.98)	Risk is uncertain – definitive RCT is required.
			Fixed Effects (IV) *	Yes (TAC)	23 (NR)	Placebo or Active	OR=1.34 (0.97, 1.84)	
			Fixed Effects (IV) *	Yes (CC)	23 (NR)	Placebo or Active	OR=1.29 (0.94, 1.76)	
			Fixed Effects (MH)	Yes (TAC)	23 (NR)	Placebo or Active	OR=1.36 (1.00, 1.84)	
			Fixed Effects (MH)	Yes (CC)	23 (NR)	Placebo or Active	OR=1.28 (0.95, 1.72)	
			Fixed Effects (MH)	Yes (TAC+)	42 (n=27,847)	Placebo or Active	OR=1.35 (1.00, 1.82)	
			Fixed Effects (MH)	Yes (CC+)	42 (n=27,847)	Placebo or Active	OR=1.26 (0.93, 1.69)	
FDA 2007 (50) †	T2DM	NR	Fixed Effects (MH)	Yes (0.5)	42 (n=14,237)	Placebo or Active (Including Insulin)	OR=1.4 (1.1, 1.8) €	Statistically significant increase
			Exact test stratified by meta-analysis group	Yes (0.5)	42 (n=14,237)	Placebo or Active (Including Insulin)	OR=1.4 (1.0, 2.1) ¥	Borderline statistically significant increase; not significant when excluding insulin trials
			Fixed Effects (MH)	Yes (0.5)	42 (n=14,237)	Placebo or Active (Including Insulin)	OR=1.38 (1.1, 1.8) €	Statistically significant increase but pooling across all patients and all studies may not be sufficient to describe risk
			Exact test stratified by meta-analysis group	Excluded	37 (n=13,266)	Placebo or Active (Excluding Insulin)	OR=1.3 (1.0, 1.7) €	
			Exact test stratified by meta-analysis group	Excluded	37 (n=13,266)	Placebo or Active (Excluding Insulin)	OR=1.35 (0.9, 2.0) ¥	
			Exact test stratified by meta-analysis group	Excluded	42 (n=14,237)	Placebo or Active (Including Insulin)	OR=1.5 (0.9, 2.7)	No definitive evidence
			Fixed Effects (MH)	Yes (0.5)	42 (n=14,237)	Placebo or Active	OR=1.44 (0.98, 2.1) ¥	NR

Study	Populations	Minimum Duration of RCTs (weeks)	Analytical Approach	Correction for Zero-Event Trials	Number of Trials (Number of Patients)	Comparator (Including Insulin)	Treatment Effect (95% CI)	Conclusions
GSK 2007 (51, 98)†	T2DM	NR	Patient-Level Cox Proportional Hazards†	NR	42 (n=14,237)	Placebo or Active	HR=1.31 (1.01, 1.70)	No consistent evidence of increased risk; further studies are needed
Friedrich 2009 (73)	NR	24	Fixed Effects (Peto)	Excluded	38 (n=18,953)	Placebo or Active	OR=1.43 (1.03, 1.98)	Increased or decreased risk and presence or absence of statistical significance vary with choice of analytical method; ongoing trials may provide additional information but all point estimates suggest increased risk.
			Fixed Effects (IV)	Excluded	38 (n=18,953)	Placebo or Active	OR=1.29 (0.94, 1.76)	
			Fixed Effects (MH)	Yes (CC)	38 (n=18,953)	Placebo or Active	OR=1.28 (0.95, 1.72)	
			Fixed Effects (MH)	Yes (TCC)	38 (n=18,953)	Placebo or Active	OR=1.36 (1.00, 1.84)	
			Fixed Effects (MH)	Yes (Empiric)	38 (n=18,953)	Placebo or Active	OR=1.41 (1.04, 1.91)	
			Fixed Effects (Exact)	NA	38 (n=18,953)	Placebo or Active	OR=1.43 (1.02, 2.01)	
			Bayesian	NA	38 (n=18,953)	Placebo or Active	OR=1.45 (1.03, 1.98)	
			Fixed Effects (Peto)	Excluded	39 (n=23,400)	Placebo or Active	OR=1.35 (1.04, 1.75)	
			Fixed Effects (IV)	Excluded	39 (n=23,400)	Placebo or Active	OR=1.27 (0.99, 1.63)	
			Fixed Effects (MH)	Yes (CC)	39 (n=23,400)	Placebo or Active	OR=1.26 (0.99, 1.61)	
			Fixed Effects (MH)	Yes (TCC)	39 (n=23,400)	Placebo or Active	OR=1.31 (1.03, 1.68)	
			Fixed Effects (MH)	Yes (Empiric)	39 (n=23,400)	Placebo or Active	OR=1.34 (1.05, 1.72)	
			Fixed Effects (Exact)	NA	39 (n=23,400)	Placebo or Active	OR=1.33 (1.01, 1.75)	
			Bayesian	NA	39 (n=23,400)	Placebo or Active	OR=1.36 (1.04, 1.76)	
			Fixed Effects (Peto)	Excluded	31 (NR)	Placebo or Active‡‡	OR=1.77 (1.12, 2.80)	
			Fixed Effects (IV)	Excluded	31 (NR)	Placebo or Active‡‡	OR=1.44 (0.93, 2.24)	
			Fixed Effects (MH)	Yes (CC)	31 (NR)	Placebo or Active‡‡	OR=1.42 (0.94, 2.15)	
			Fixed Effects (MH)	Yes (TCC)	31 (NR)	Placebo or Active‡‡	OR=1.57 (1.03, 2.40)	
			Fixed Effects (MH)	Yes (Empiric)	31 (NR)	Placebo or Active‡‡	OR=1.74 (1.14, 2.68)	
			Fixed Effects (Exact)	NA	31 (NR)	Placebo or Active‡‡	OR=1.82 (1.10, 3.12)	
			Bayesian	NA	31 (NR)	Placebo or Active‡‡	OR=1.91 (1.16, 3.06)	
			Fixed Effects (Peto)	NA	54 (NR)	Placebo or Active	RD=0.19 (-0.01, 0.39)	
			Fixed Effects (Peto)	NA	55 (NR)	Placebo or Active	RD=0.22 (0.01, 0.43)	
			Fixed Effects (Peto)	NA	41 (NR)	Placebo or Active‡‡	RD=0.21, 0.01, 0.41)	
Nissen 2007 (55)	T2DM, IGT, IFG, or Chronic Psoriasis	24	Fixed Effects (Peto)	Excluded	42 (n=27,847)	Placebo or Active	OR=1.43 (1.03, 1.98)	Increased risk
Psaty 2007 (59)	T2DM,	24	Fixed Effects (IV)	NR	43 (n=32,290)	Placebo or Active	OR=1.33 (1.02, 1.72)	Evidence of harm;

Study	Populations	Minimum Duration of RCTs (weeks)	Analytical Approach	Correction for Zero-Event Trials	Number of Trials (Number of Patients)	Comparator	Treatment Effect (95% CI)	Conclusions
	IGT, IFG, or Chronic Psoriasis							likelihood of benefit remote
Singh 2007 (71)	T2DM, IGT, IFG, or Chronic Psoriasis	52	Fixed Effects*	NR	4 (n=14,291)	Placebo or Active	OR=1.42 (1.06, 1.91)	Increased risk
Shuster 2007 (69)	T2DM, IGT, IFG, or Chronic Psoriasis	24	Random Effects	NA	42 (n=27,847) + 6 (NR)‡	Placebo or Active	RR=1.51 (0.91, 2.48)	Random-effects = better analytical approach because of weighting of large studies
			Fixed-Effects Cox Analysis	NR	42 (n=27,847)	Placebo or Active	RR=1.43 (1.03, 1.96)	
			Fixed-Effects Logistic Regression	NR	42 (n=27,847)	Placebo or Active	RR=1.43 (1.03, 1.98)	
			STATXACT	NR	42 (n=27,847)	Placebo or Active	RR=1.43 (1.01, 1.98)	
			STATXACT (Asymptomatic)	NR	42 (n=27,847)	Placebo or Active	RR=1.43 (1.03, 1.98)	
Pioglitazone								
Lincoff 2007 (54)	T2DM	NR	Patient-Level Fixed Effects Cox Model	Excluded	19 (n=16,390)	Placebo or Active	HR=0.81 (0.64, 1.02)	NR

Abbreviations: CC=constant correction for continuity; CC+= constant correction for continuity that includes all zero-event trials; CI=confidence interval; HR=hazard ratio; IFG=impaired fasting glucose; IGT=impaired glucose tolerance; IV=inverse variance; NR=not reported; OR=odds ratio, RD=risk difference; RR=relative risk; T2DM=type 2 diabetes mellitus; TAC=treatment arm correction for continuity; TAC+= treatment arm correction for continuity that includes all zero-event trials.

* Sensitivity analyses included the use of random effects analyses, which produced similar results as those reported here.

† Multiple analyses with multiple comparison groups were conducted. In addition, data from 3 long-term RCTs (ADOPT, DREAM, and RECORD) (40, 109, 110) were also presented. These data were not presented here due to space constraints.

‡ This analysis included the 42 trials from the Nissen meta-analysis as well as 6 that we excluded from the Nissen meta-analysis because they included 0 events.

‡‡ Restricted to studies where the only difference between the 2 treatment groups is the presence or absence of rosiglitazone.

€ Denotes total ischemic events.

¥ Denotes serious ischemic events.

Table 2.5. Data sources of systematic reviews and meta-analyses that examined the effect of thiazolidinediones on cardiovascular outcomes.

	Data Source																					
Study	Cinhal	Cochrane Database of Systematic Reviews	Cochrane Register of Trials	Current Research in Britain Register	DARE	Databases of Ongoing Trials	EMBASE	FDA Website	GSK Trial Registry	Hand-Search of References	Meeting Abstracts	Medline/PubMed	MRC Clinical Trials Register	NIH Clinical Trials Register	Nissen's Data*	Office of Health Economics Health Economics Evaluations Database	Patient-Level Data from Manufacturer	'Published Trials'†	RECORD Trial††	Science Citation Index	UK National Research Register	UK National Health Service Centre for Reviews and Dissemination databases
Berlie 2006 (43)	X	X	X				X				X£	X										
Bolen 2007 (44)			X				X			X		X										
Bracken 2007 (45)															X				X			
Chilcott 2001 (46)		X	X	X			X			X		X	X	X		X				X	X	X
Diamond 2007 (48)															X							
FDA 2007 (50)																	X					
Fridrich 2009 (73)									X										X			
GSK 2007 (51, 98)																	X					
Lago 2007 (53)		X‡	X‡		X		X			X	X£€	X										
Lincoff 2007 (54)																	X					
Nissen 2007 (55)								X	X						X			X				
Norris 2007 (56)		X	X				X			X		X										
Psaty 2007 (59)															X				X			
Riche 2007 (62)	X	X¥	X¥				X			X	X£	X										
Richter 2007 (63)		X‡	X‡			X	X			X		X										
Richter 2006 (64)		X‡	X‡			X	X			X		X										

	Data Source																					
Study	Cinhal	Cochrane Database of Systematic Reviews	Cochrane Register of Trials	Current Research in Britain Register	DARE	Databases of Ongoing Trials	EMBASE	FDA Website	GSK Trial Registry	Hand-Search of References	Meeting Abstracts	Medline/PubMed	MRC Clinical Trials Register	NIH Clinical Trials Register	Nissen's Data*	Office of Health Economics Health Economics Evaluations Database	Patient-Level Data from Manufacturer	'Published Trials'†	RECORD Trial††	Science Citation Index	UK National Research Register	UK National Health Service Centre for Reviews and Dissemination databases
Rosmarakis 2007 (66)										X		X										
Selvin 2008 (68)			X				X			X		X										
Shuster 2007 (69)															X							
Singh 2007 (70)									X			X										
Singh 2007 (71)								X	X			X										

Abbreviations: DARE= Database of Abstracts of Reviews of Effects; FDA= Food and Drug Administration; GSK=GlaxoSmithKline; UK=United Kingdom;
* The authors re-analyzed data presented in the meta-analysis conducted by Nissen and Wolski (55) rather than those identified through a literature search.
† The authors incorporated data from 2 published RCTs but did not report the details of their literature search.
†† The authors incorporated the results from the interim analysis of the RECORD trial (110).
‡ The authors reported Cochrane Library as a data source but did not specify whether this consisted of the Cochrane Database of Systematic Reviews or the Cochrane Register of Trials.
¥ The authors reported Cochrane database as a data source but did not specify whether this consisted of the Cochrane Database of Systematic Reviews or the Cochrane Register of Trials.
£ Abstracts include those presented at the American College of Cardiology, American Diabetes Association, and the American Heart Association Scientific Sessions.
€ Abstracts include those presented at the European Society of Cardiology.

Table 2.6. Systematic reviews and meta-analyses that examined the effect of thiazolidinediones on the risk of congestive heart failure.

Study	Populations	Minimum Duration of RCTs (weeks)	Analytical Approach	Correction for Zero-Event Trials	Number of Trials (Number of Patients)	Comparator	Treatment Effect (95% CI)	Conclusions
<u>TZDs</u>								
Bolen 2007 (44)	T2DM	12	NA	NA	2 (n=376)	Sulfonylurea	RD: 1.0% to 2.2%	Increased risk
					3 (n=1,028)	Sulfonylurea*	RD: 0.7% to 1.2%	
Lago 2007 (53)	Pre-DM or T2DM	NR	Random Effects	Yes	7 (n=20,191)	Placebo or Active	RR=1.72 (1.21, 2.42)	
Singh 2007 (70)	NR	26	Random Effects	NR	3 (n=8,361)	Placebo	OR=2.10 (1.08, 4.08)	Increased risk
<u>Rosiglitazone</u>								
Lago 2007 (53)	Pre-DM or T2DM	NR	Random Effects	Yes	5 (n=14,491)	Placebo or Active	RR=2.18 (1.44, 3.32)	Increased risk
Ritcher 2007 (63)	T2DM	24	NA	NA	1 (n=2,910)	Metformin	OR=1.15 (0.62, 2.18)	Patient-orientated outcome studies needed
					1 (n=2,897)	Glyburide	OR=2.44 (1.14, 5.59)	
Singh 2007 (71)	T2DM, IFG, or IGT	52	Fixed Effects‡	NR	4 (n=14,291)	Placebo or Active	RR=2.09 (1.52, 2.88)	Increased risk
<u>Piogltiazone</u>								
Lago 2007 (53)	Pre-DM or T2DM	NR	Random Effects	Yes	2 (n=5,700)	Placebo or Active	RR=1.32 (1.04, 1.68)	Increased risk
Lincoff 2007 (54)	T2DM	NR	Patient-Level Fixed Effects Cox Model‡	Excluded	19 (n=16,390)	Placebo or Active	HR=1.41 (1.14, 1.76) ‡‡	Increased risk
Norris 2007 (56)	Pre-DM, T2DM, or MetS	NR	NA	NA	3 (n=5,820)	Placebo or Active	RD=1% to 12.5%	Limited data and fair to poor quality of reporting for adverse events; generally no difference in adverse event rates between pioglitazone and placebo.

Abbreviations: CHF=congestive heart failure; CI=confidence interval; DM=diabetes mellitus; HR=hazard ratio; IFG=impaired fasting glucose; IGT=impaired glucose tolerance; MetS=metabolic syndrome; NA=not applicable; NR=not reported; OR=odds ratio, RD=risk difference; RR=relative risk; T2DM=type 2 diabetes mellitus; TZDs=thiazolidinediones.

*This represents a comparison of TZDs and sulfonylurea combination therapy vs sulfonylurea therapy alone.

‡ Sensitivity analyses included analyses with random-effects that produced similar results.

‡‡Denotes serious CHF.

Table 2.7. Systematic reviews and meta-analyses that examined the effect of thiazolidinediones on composite cardiovascular outcomes.

Study	Populations	Minimum Duration of RCTs (weeks)	Analytical Approach	Number of Trials (Number of Patients)	Comparator	Outcome	Treatment Effect (95% CI)	Conclusions
Rosiglitazone								
Norris 2007 (56)	Pre-DM, T2DM, or MetS	NR	NA	2 (n=635)	Placebo	Cardiac-Related Endpoints	RD=0.2% to 1.0%	Limited data and fair to poor quality of reporting for adverse events; generally no difference in adverse event rates between rosiglitazone and placebo.
FDA 2007 (50)‡	T2DM	NR	Fixed Effects (MH)	42 (n=14,237)	Placebo or Active (Including Insulin)	CV Mortality/MI/Stroke	OR=1.20 (0.8, 1.8)‡	No definitive evidence
			Exact test stratified by meta-analysis group	37 (n=13,266)	Placebo or Active (Excluding Insulin)	CV Mortality/MI/Stroke	OR=1.1 (0.7, 1.7)	
GSK 2007 (51, 98)‡	T2DM	NR	Patient-Level Cox Proportional Hazards	42 (n=14,237)	Placebo or Active (Including Insulin)	CV Mortality/MI/Stroke	HR=1.16 (0.8, 1.7)	No consistent evidence of increased risk
Selvin 2008 (68)	T2DM	12	Fixed Effects (MH)*	5 (n=1,338)	Placebo or Active	CVD Morbidity	OR=1.68 (0.92, 3.06)	Increased risk but not significant, possibly due to small number of studies.
Richter 2007 (63)	T2DM	24	NA	1 (n=2,910)	Metformin	CVD (Serious)	OR=1.06 (0.71, 1.61)	Patient-orientated outcome studies needed
					Metformin	CVD (Total)	OR=1.07 (0.74, 1.55)	
				1 (n=2,897)	Glyburide	CVD (Serious)	OR=1.89 (1.18, 3.11)	
					Glyburide	CVD (Total)	OR=1.52 (1.02, 2.28)	
Pioglitazone								
Chilcott 2001 (46)	T2DM	12	NA	11 (n=3,169)	Placebo or Active	Cardiac Events	NR†	Increased
Lincoff 2007 (54)	T2DM	NR	Patient-Level Fixed Effects Cox Model	19 (n=16,390)	Placebo or Active	ACM/MI/Stroke	HR=0.82 (0.72, 0.94)	Significantly lower
						ACM/MI	HR=0.85 (0.73, 0.99)	NR
						ACM/Serious CHF	HR=1.11 (0.96, 1.29)	Not significantly increased
						ACM/MI/Stroke/Serious	HR=0.96 (0.85, 1.09)	NR

Study	Populations	Minimum Duration of RCTs (weeks)	Analytical Approach	Number of Trials (Number of Patients)	Comparator	Outcome	Treatment Effect (95% CI)	Conclusions
Norris 2007 (56)	Pre-DM, T2DM, or MetS	NR	NA	3 (n=1,525)	Placebo	CHF Cardiac-Related Endpoints	RD=0.9% to 2.7%	Limited data and fair to poor quality of reporting for adverse events; generally no difference in adverse event rates between pioglitazone and placebo.
Richter 2006 (64)	T2DM	24	NA	1 (n=5,238)	Placebo	ACM/MI/Stroke	HR=0.84 (0.72, 0.98)	Results from only trial available are hypothesis-generating and should be confirmed
Selvin 2008 (68)	T2DM	12	Fixed Effects (MH)*	6 (n=9,287)	Placebo or Active	CVD Morbidity	OR=0.88 (0.78, 1.00)	No significant association observed

Abbreviations: ACM=all cause mortaliy; CHF=congestive heart failure; CI=confidence interval; CV=cardiovascular; CVD=cardiovascular disease; DM=diabetes mellitus; HR=hazard ratio; MetS=metabolic syndrome; MH=Mantel-Haenszel; MI=myocardial infarction; NA=not applicable; NR=not reported; OR=odds ratio, RD=risk difference; T2DM=type 2 diabetes mellitus.

* Sensitivity analyses included the use of Peto fixed effects analyses, which produced similar results as those reported here.

† The authors reported that 6 cardiovascular events had been reported at the time of their review: 1 patient had left ventricular hypertrophy and 5 patients had cardiomegaly. The authors concluded that cardiac effects were more frequent in patients receiving pioglitazone.

‡ In sensitivity analyses, Cox proportional hazards models and exact logistic regression were also used and produced similar results.

‡ Multiple analyses with multiple comparison groups were conducted. In addition, data from 3 long-term RCTs (ADOPT, DREAM, and RECORD) (40, 109, 110) were also presented. These data were not presented here due to space constraints.

Table 2.8. Systematic reviews and meta-analyses that examined the effect of thiazolidinediones on risks of coronary restenosis and revascularization procedures among patients with and without diabetes who underwent percutaneous coronary intervention.

Study	Minimum Duration of RCTs (weeks)	Analytical Approach	Number of Trials (Number of Patients)	Comparator	Intervention	Treatment Effect (95% CI)	Conclusions
Coronary Restenosis							
Rosmarakis 2007 (66)	26	Random Effects	3 (n=170)	Other Anti-Diabetic Therapy (for Diabetic Patients) or No Anti-Diabetic Therapy (for Non-Diabetic Patients)	TZDs	OR=0.29 (0.15, 0.56)	Potential benefit – large RCTs needed
Target Lesion Revascularization							
Rosmarakis 2007 (66)	26	Random Effects	4 (n=197)	Other Anti-Diabetic Therapy (for Diabetic Patients) or No Anti-Diabetic Therapy (for Non-Diabetic Patients)	TZDs	OR=0.24 (0.09, 0.61)	Potential benefit – large RCTs needed
Target Vessel Revascularization							
Riche 2007 (62)	26	Random Effects	7 (n=608)	Standard of Care	TZDs	RR=0.35 (0.22, 0.57)	Significant benefit
			4 (n=466)	Standard of Care	Rosiglitazone	RR=0.45 (0.25, 0.83)	Significant benefit
			3 (n=140)	Standard of Care	Pioglitazone	RR=0.24 (0.11, 0.51)	Significant benefit

Abbreviations: CI=confidence interval; OR=odds ratio, RR=relative risk; TZDs=thiazolidinediones.

Table 2.9. Systematic reviews and meta-analyses that examined the effect of thiazolidinediones on the risk of edema.

Study	Populations	Minimum Duration of RCTs (weeks)	Analytical Approach	Number of Trials (Number of Patients)	Comparator	Treatment Effect (95% CI)	Conclusions
TZDs							
Berlie 2006 (43)	T2DM	NR	Fixed Effects (MH)	26 (n=15,332)	Placebo or Active	OR=2.26 (2.02, 2.53)	Increased risk
			Random Effects	26 (n=15,332)	Placebo or Active	OR=2.65 (2.19, 3.20)	
Bolen 2007 (44)	T2DM	12	NA	5 (n=1,921)	Sulfonylurea	RD=4.2% to 21.2%	Increased risk
				4 (n=2,712)	Metformin	RD=2.4% to 10.5%	
				3 (n=1,439)	Metformin*	RD=2% to 5.2%	
				3 (n=1,028)	Sulfonylurea†	RD=6.6% to 14%	
				2 (n=248)	Meglitinides	RD=2% to 3%	
Rosiglitazone							
Berlie 2006 (43)	T2DM	NR	Random Effects	9 (n=3,683)	Placebo or Active	OR=3.75 (2.70, 5.20)	Increased risk; risk appears to be higher than with pioglitazone
Norris 2007 (56)	Pre-DM, T2DM, or MetS	NR	NA	1 (n=908)	Placebo	RD=2.5% to 5%	Limited data and fair to poor quality of reporting for adverse events; generally no difference in adverse event rates between rosiglitazone and placebo.
Richter 2007 (63)	T2DM	24	Fixed Effects	9 (n=4,739)	Placebo or Active (Including Insulin)	OR=2.27 (1.83, 2.81)	Increased risk
Pioglitazone							
Berlie 2006 (43)	T2DM	NR	Random Effects	17 (n=11,529)	Placebo or Active	OR=2.42 (1.90, 3.08)	Increased risk; risk appears to be lower than with rosiglitazone
Norris 2007 (56)	Pre-DM, T2DM, or	NR	NA	9 (n=908)	Placebo or Active	RD=0% to 9%	Limited data and fair to poor

Study	Populations	Minimum Duration of RCTs (weeks)	Analytical Approach	Number of Trials (Number of Patients)	Comparator	Treatment Effect (95% CI)	Conclusions
	MetS						quality of reporting for adverse events; generally no difference in adverse event rates between pioglitazone and placebo.
Chilcott 2001 (46)	T2DM	12	NA	11 (n=3,169)	Placebo or Active	NR‡	Increased risk
Richter 2006 (64)	T2DM	24	Fixed Effects	18 (n=11, 565)	Placebo or Active	OR=1.98 (1.78, 2.20)	Increased risk

Abbreviations: CI=confidence interval; DM=diabetes mellitus; MetS=metabolic syndrome; MH=Mantel-Haenszel; NA=not applicable; NR=not reported; OR=odds ratio, RD=risk difference; T2DM=type 2 diabetes mellitus; TZDs=thiazolidinediones.

*This represents a comparison of TZDs and metformin combination therapy vs metformin therapy alone.

†This represents a comparison of TZDs and sulfonulurea combination therapy vs sulfonylurea therapy alone.

‡ The authors cite FDA documents that suggest there is a risk difference of 3.4% and 3 Japanese studies that report an incidence among pioglitazone-treated patients ranging 1.5% to 11.7% but do not provide corresponding data for controls.

Table 2.10 Overview of pharmacoepidemiologic studies that examined the effect of thiazolidinediones on congestive heart failure.

Study	Study Design	Population	Data Source	Comparator	Endpoint	Relative Risk (95% CI)	Sponsor
Delea 2003 (89)	Cohort	Patients Aged ≥ 18 Years with T2DM who Filled Prescriptions for Oral Anti-Diabetic Agents (n=33,544)	Pharmetrics Integrated Outcomes	TZD-exposed vs Unexposed	Diagnosis of Incident CHF	HR=1.76 (1.43, 2.17)	Novartis
Rajagopalan 2004 (96)	Propensity-Matched Cohort	Patients Aged ≥ 18 Years with T2DM (1,668 Cases, 1,668 Controls)	PharMetrics Patient-Centric	Pioglitazone vs Insulin	Primary or Secondary Diagnosis of Incident CHF	HR=0.50 (0.33, 0.76)	Takeda
					Hospitalization for CHF	HR=0.26 (0.14, 0.51)	
Hartung 2005 (95)	Case Control	Patients Aged ≥ 18 Years with T2DM (288 Cases, 1,652 Controls)	Oregon Medicaid	TZD-Exposed vs Unexposed	Hospitalization for Incident CHF	OR=1.37 (0.98, 1.92)	NR
Karter 2005 (94)	New Users Cohort	Patients with T2DM (n=23,440)	Kaiser Permanente Medical Care Program with Type 2 Diabetes	Pioglitazone vs Sulphonylureas	Hospitalization for Incident CHF	HR=1.28 (0.85, 1.92)	ADA
Lipscombe 2007 (88)	Nested Case-Control	Patients Aged ≥ 66 Years with T2DM (n=159,026)	Ontario Drug Benefit Plan	Current TZD Monotherapy vs Other Oral Agents	ER Visit or Hospitalization for Incident or Prevalent CHF	RR=1.60 (1.21, 2.10)	Ontario Ministry of Health and Long-Term Care
				Current TZD Combination vs Other Oral Anti-Diabetic Agents		RR=1.31 (1.17, 1.47)	

Study	Study Design	Population	Data Source	Comparator	Endpoint	Relative Risk (95% CI)	Sponsor
Winkelmayer 2008 (127)	Inception Cohort (n=28,361)	Elderly Patients with T2DM	New Jersey Pharmaceutical Assistance for the Aged and Disabled Program	Rosiglitazone vs Pioglitazone	Hospitalization for CHF	IRR=1.11 (1.03, 1.19)	AHA, Satellite Healthcare, Inc., and Investigator Initiated Grants from Amgen, Fresenius Medical Care, and GSK
Habib 2009 (128)	Time-Updated Propensity-Adjusted Cohort (n=19,171)	Patients Aged ≥ 18 Years with T2DM and Prescribed Oral Anti-Diabetic Agents	Integrated Health System in Michigan	TZD vs Other Oral Agents	Hospitalization for CHF	HR=1.24 (1.07, 1.44)	Fund for Henry Ford Hospital and NIH

Abbreviations: ADA=American Diabetes Association; AHA=American Heart Association; CI=confidence interval; HR=hazard ratio; IRR=incidence rate ratio; NIH=National Institutes of Health; NR=not reported; OR=odds ratio; RR=rate ratio; T2DM=type 2 diabetes mellitus.

Table 2.11. Overview of major studies that examined the effect of glycemic control on clinical events.

Study	Intervention	Follow-Up (Years)	Endpoint	Intensive Therapy (n/N)	Control (n/N)	Hazard Ratio (95% CI)
UKPDS 33 1998 (15)	Sulfonylurea ± Insulin vs Diet	10.0	Any Diabetes-related Endpoint	963/2,729	438/1,138	0.88 (0.79, 0.99)
			Diabetes-related Death	285/2,729	129/1,138	0.90 (0.73, 1.11)
			All-cause Mortality	489/2,729	213/1,138	0.94 (0.80, 1.10)
			CHF	80	36	0.91 (0.54, 1.52)
UKPDS 34 1998 (132)	Metformin vs Diet	10.7	Any Diabetes-related Endpoint	98/342	160/411	0.68 (0.53, 0.87)
			Diabetes-related Death	28/342	66/411	0.56 (0.37, 0.91
			All-cause Mortality	50/342	80/411	0.64 (0.45, 0.91)
	Chlorpropamide, Glibenclamide, or Insulin vs Diet	10.7	Any Diabetes-related Endpoint	350/941	160/411	0.93 (0.77, 1.12
			Diabetes-related Death	103/941	66/411	0.80 (0.58, 1.11)
			All-cause Mortality	150/941	80/411	0.92 (0.71, 1.18)
	Sulfonylurea + Metformin vs Sulfonulurea Alone		Any Diabetes-related Endpoint	81/268	82/269	1.04 (0.77, 1.42)
			Diabetes-related Death	26/268	14/269	1.96 (1.02, 3.75)
			All-cause Mortality	47/268	31/269	1.60 (1.02, 2.52)
UKPDS 80 2008 (133)	Sulfonylurea ± Insulin vs Diet	30.0	Any Diabetes-related Endpoint	1,571/2,729	686/1,138	0.91 (0.83, 0.99)
			Diabetes-related Death	618/2,729	297/1,138	0.83 (0.73, 0.96)
			All-cause Mortality	1,162/2,729	537/1,138	0.87 (0.79, 0.96)
	Metformin vs Diet		Any Diabetes-related Endpoint	209/342	262/411	0.79 (0.66, 0.95)
			Diabetes-related Death	81/342	120/411	0.70 (0.53, 0.92
			All-cause Mortality	152/342	217/411	0.73 (0.59, 0.89)
ADVANCE 2008 (16)	Target HbA1c=6.5% vs Target HbA1c=7.0%	5.0	Macrovascular + Microvascular Events	1,009/5,571	1,116/5,569	0.90 (0.82, 0.98)
			Macrovascular Events	557/5,571	590/5,569	0.94 (0.84. 1.06)
			Microvascular Events	526/5,571	605/5,569	0.84 (0.77, 0.97)
			All-Cause Mortality	498/5,571	533/5,569	0.93 (0.83, 1.06)
			CHF	220/5,571	231/5,569	0.95 (0.79, 1.14)

Study	Intervention	Follow-Up (Years)	Endpoint	Intensive Therapy (n/N)	Control (n/N)	Hazard Ratio (95% CI)
ACCORD 2008 (17)	Target HbA1c=6.0% vs Target HbA1c=7.0-7.9%	3.5	Non-fatal MI, Non-fatal Stroke, or CVD Death	352/5,128	371/5,123	0.90 (0.78, 1.04)
			All-Cause Mortality	257/5,128	203/5,123	1.22 (1.01, 1.46)
			Fatal or Non-Fatal CHF	152/5,128	124/5,123	1.18 (0.93, 1.49)
CHARM 2008 (139)*	Observational Study Examining HbA1c as Continuous Variable – No Intervention	2.8	CVD Death or CHF hospitalization	NR	NR	1.18 (1.13, 1.24)
			CVD Death	NR	NR	1.19 (1.12, 1.27)
			Worsening CHF	NR	NR	1.18 (1.11, 1.24)
			All-Cause Mortality	NR	NR	1.18 (1.11, 1.25)
VADT 2009 (140)	Metfomin + Rosiglitazone at Maximum Dosage vs Metfomin + Rosiglitazone at Half Dosage		MI, Stroke, CVD Death, New or Worsening CHF, Surgical Interventions, CAD, or Amputations	263/892	301/899	0.88 (0.74, 1.05)
			CVD Death	40/892	33/899	0.81 (0.32, 2.14)
			All-Cause Mortality	102/892	95/899	1.07 (0.81, 1.42)

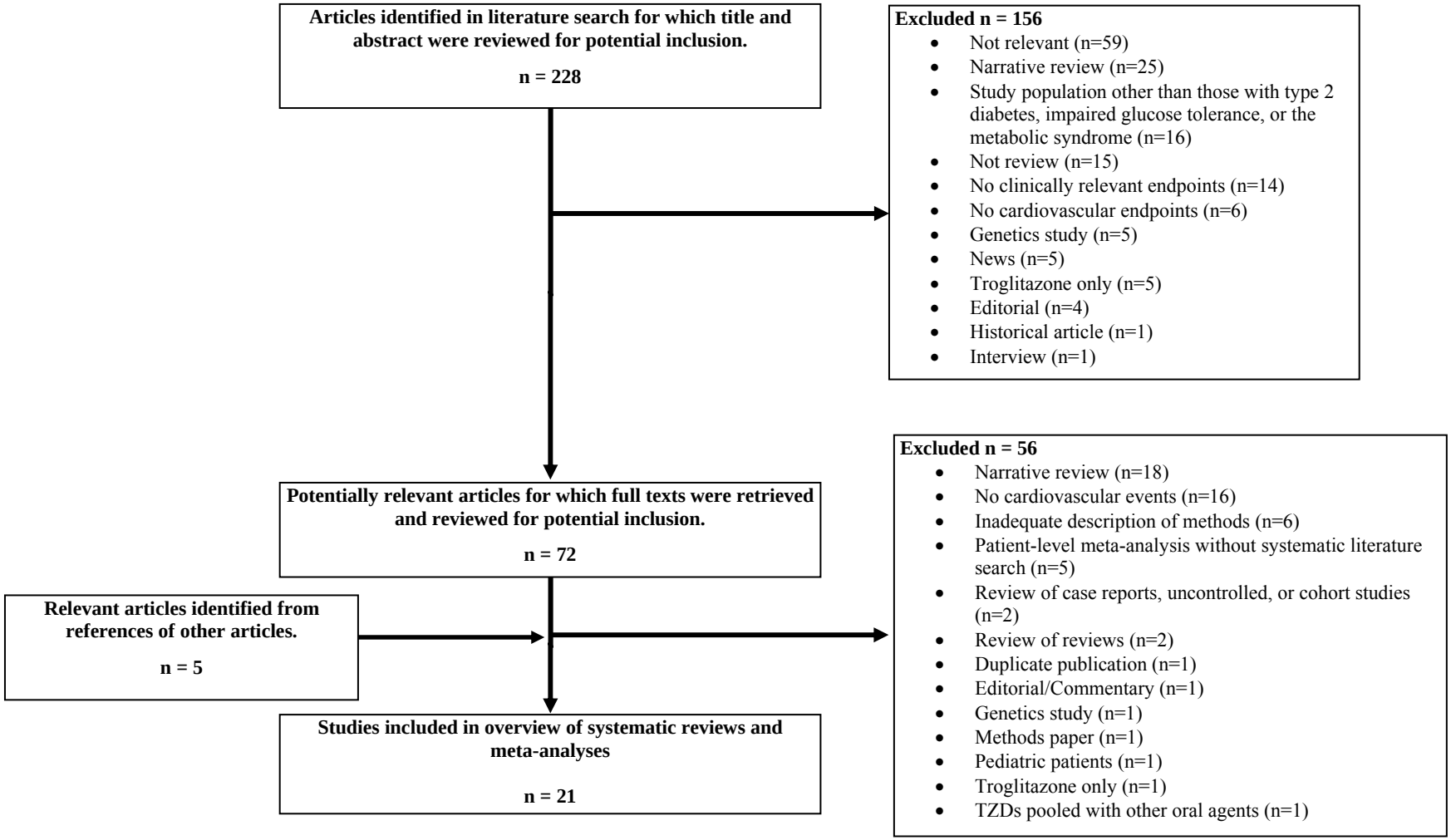
Abbreviations: ACCORD: Action to Control Cardiovascular Risk in Diabetes Trial; ADVANCE:Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation Trial; CHARM: CHF: Congestive Heart Failure; CVD: Cardiovascular; NR: Not Reported; UKPDS: United Kingdom Prospective Diabetes Study VADT: Veterans Affairs Diabetes Trial

* CHARM was conducted in patients with congestive heart failure. All other studies were conducted in patients with type 2 diabetes.

FIGURE LEGEND

Figure 2.1. Flow diagram of literature search to identify systematic reviews and meta-analysis of the cardiovascular effects of thiazolidinediones.

Figure 2.1


Articles identified in literature search for which title and abstract were reviewed for potential inclusion.
n = 228
Excluded n = 156
Not relevant (n=59)
Narrative review (n=25)
Study population other than those with type 2 diabetes, impaired glucose tolerance, or the metabolic syndrome (n=16)
Not review (n=15)
No clinically relevant endpoints (n=14)
No cardiovascular endpoints (n=6)
Genetics study (n=5)
News (n=5)
Troglitazone only (n=5)
Editorial (n=4)
Historical article (n=1)
Interview (n=1)
Potentially relevant articles for which full texts were retrieved and reviewed for potential inclusion.
n = 72
Excluded n = 56
Narrative review (n=18)
No cardiovascular events (n=16)
Inadequate description of methods (n=6)
Patient-level meta-analysis without systematic literature search (n=5)
Review of case reports, uncontrolled, or cohort studies (n=2)
Review of reviews (n=2)
Duplicate publication (n=1)
Editorial/Commentary (n=1)
Genetics study (n=1)
Methods paper (n=1)
Pediatric patients (n=1)
Troglitazone only (n=1)
TZDs pooled with other oral agents (n=1)
Relevant articles identified from references of other articles.
n = 5
Studies included in overview of systematic reviews and meta-analyses
n = 21

CHAPTER 3 - METHODS

To accomplish the objectives of this thesis (Chapter 1) and address some of the current knowledge gaps (Chapters 1 and 2), a series of 3 observational studies was conducted. The first study describes trends in the prescription of anti-diabetic medical therapy. The second study examines the effect of glycemic control on the risk of CHF among patients with type 2 diabetes, and the third study investigates the effect of TZDs on the risk of CHF in this patient population. These studies are discussed in detail in Chapters 5, 6, and 7. In the present chapter, overall methods of this thesis are described. In addition, methodological details specific to the 3 studies that were omitted from the corresponding manuscripts for the sake of brevity are provided.

3.1 Data Source

The 3 studies were conducted using data extracted from the GPRD. The GPRD is a clinical database that links the electronic medical records of over 400 general medical practices in the U.K. (100, 105). This database, which is owned by the U.K. Department of Health, has been used extensively for research purposes, serving as the data source for over 600 peer-reviewed publications (142), including studies of type 2 diabetes (101, 143), CHF (101, 144-146), and prescription practices (147). The GPRD contains a demographically-representative sample of approximately 5% of the U.K. population (105) and has over 39 million person-years of observation available for research purposes (100). Data available in the GPRD include demographic information, clinical diagnoses, and prescriptions issued (105). Diagnosis information is based on a combination

of National Health Service (NHS) Clinical Term codes (commonly called READ codes) (148, 149) and Oxford Medical Information System (OXMIS) codes. Prescription data are based on the Prescription Pricing Authority coding system (105). Unlike purely administrative databases such as Québec's Régie de l'Assurance Maladie du Québec (RAMQ), the GPRD also contains lifestyle variables (e.g., smoking status, BMI), and clinical data such as blood pressure readings and laboratory test results (e.g., HbA1c, total cholesterol).

The validity of GPRD has been examined extensively in previous studies (105, 150-154). Jick and colleagues compared the GPRD computer records to the corresponding paper-based records of 2,491 patients who were prescribed non-steroidal anti-inflammatory drugs (150). Of these patients, 1,191 had a consultation with a specialist in their paper-based record (865 outpatient referrals and 326 inpatient referrals). The sensitivity of the electronic records of diagnoses found in these paper-based records was 87%. In another study, Pringle and colleagues examined the validity of GPRD diabetes data using data from 4 practices (153). The sensitivity of a diagnosis of type 2 diabetes was 97%. Furthermore, compared with the paper-based records, the electronic records contained 82% of all diagnoses and 100% of all prescriptions. These studies suggest that GPRD data are valid.

Current quality assurance processes help ensure that these data are of high quality. Physicians and clerical staff at GPRD practices also undergo extensive training, and data validity is examined to ensure that all practices meet minimum validity thresholds before a practice becomes 'up-to-standard' (105). The NHS

has also implemented a Quality and Outcomes Framework (155, 156), which uses data recorded in the GPRD to guide physician reimbursement. Physicians and their staff therefore have incentives to ensure that all relevant data are entered in the GPRD.

The GPRD represents an excellent data source for the 3 studies conducted in this thesis. The GPRD provides a representative sample of the U.K. population, making the results of these studies generalizable. This large sample also allows for the precise estimation of effects. Furthermore, the presence of clinical data not typically found in large, administrative databases reduces the amount of bias due to residual confounding. This is particularly important for studies involving patients with diabetes, where glycemic control, a marker of disease severity measured by HbA1c, may represent an important confounder. The presence of these data also allows for an examination of the effect of glycemic control on clinical outcomes such as CHF; such studies cannot be conducted in most administrative databases. Finally, the GPRD contains prescriptions issued, rather than prescriptions filled, and is thus an appropriate data source for studies examining prescribing patterns such as that presented in Chapter 5 of this thesis.

3.2 Creation of Cohort of Patients with Type 2 Diabetes

As part of this thesis, a cohort of patients with type 2 diabetes was constructed (Figure 3.1). The first step of this process was the identification of patients with type 2 diabetes. Patients were considered to have type 2 diabetes if at least one of the following criteria was met: a) a READ or OXMIS code in

patient's electronic record indicating a clinical diagnosis of type 2 diabetes; b) an HbA1c test value > 7%; or c) ≥ 2 prescription for anti-diabetic medications, including insulin, metformin, sulfonylureas, TZDs, and other anti-diabetic medications. Data for these variables were downloaded from the GPRD data server to identify the patients that met there criteria. The list of READ and OXMIS codes, identified using the GPRD Medical Dictionary (Version 0.3.7 - Evaluation Release) (157), that formed our clinical diagnosis criteria is found in Appendix 1. Patients with diagnoses of diabetes induced by steroid use as well as those with gestational diabetes were excluded. Patients with type 1 diabetes and patients with codes indicating the presence suspected but not confirmed diabetes (e.g., diabetes screening) were also excluded. A list of all codes used to exclude patients is provided in Appendix 1.

Although a number of diagnostic laboratory tests exists to diagnose or monitor type 2 diabetes, the laboratory test component of our diabetes definition was restricted to the use of HbA1c testing for a number of reasons. First, fasting and non-fasting blood glucose tests are prone to fluctuations due to recent dietary intake while HbA1c provides an average measure of glycemic control over the preceding 3 months. Second, it is not possible to assess compliance with fasting requirements of certain blood tests from the available data, making the validity of fasting glucose tests unclear. Finally, although non-fasting blood glucose test results are available in the GPRD, few patients undergo routine, non-fasting blood glucose tests in the U.K.. HbA1c testing is part of the NHS's Quality and Outcomes Framework (155), which guides reimbursement for care of patients

with diabetes. These guidelines state that, to receive full reimbursement for caring for a patient with diabetes, an HbA1c test must be conducted at least every 15 months. Thus, despite the availability of other measures of glycemic control, HbA1c represents the only readily available and valid test that could be used to identify patients with diabetes. The threshold of 7% was selected as that is the most commonly used threshold in treatment guidelines for type 2 diabetes (19).

HbA1c data required substantial data cleaning, a process that involved 3 general steps. In the first step, all tests preceding 1996 (i.e., 4 years before the start of the study period) were excluded. GPRD data quality has improved greatly over time, and the validity of these early test results was questionable. Furthermore, any patient with HbA1c test results > 7% prior to 1996 but no record of a clinical diagnosis of diabetes, medical treatment for diabetes, or another positive HbA1c test after 1996 is unlikely to have diabetes. The second step of this cleaning process focused on the test result units. Although HbA1c is typically presented as a percentage, it can also be expressed as an average blood glucose in mmol/L or in mg/dL. Data reported in these units were converted to percentages using the following formula (158):

$$\text{HbA1c in \%} = (\text{Average Plasma Glucose in mg/dL} + 77.3)/35.6$$

$$\text{HbA1c in \%} = (\text{Average Plasma Glucose in mmol/L} + 4.29)/1.98$$

All HbA1c results with numeric values but missing units (16.8% of HbA1c tests) were assumed to be percentages, the most common method used to express these data. These steps increased the number of HbA1c tests expressed as percentages from 64% to 83% of all tests. The remaining tests were assumed to

have incorrect unit but were retained for further data cleaning. The third step involved cleaning the test result values. The range of plausible HbA1c values was assumed to be from 3% to 20%; approximately 90% of HbA1c test results were within this range. All test results that were outside of this range were excluded. These cleaned HbA1c data formed the basis for the second component of the diabetes definition used in this thesis.

The third component of the definition was ≥ 2 prescriptions for anti-diabetic medications, including insulin, metformin, sulfonylurea, TZDs, and other oral anti-diabetic medications. Prescriptions were identified and sorted, and the date of the second prescription was used as the potential date of cohort entry. Only one prescription was counted per day. Consequently, if a patient received 2 prescriptions on the same day, they were not eligible for cohort entry based on this criterion until their next prescription.

If patients met more than 1 of the criteria used to define type 2 diabetes, the criteria that was met first was used to define the occurrence of diabetes. In addition, our study was restricted to patients who were aged ≥ 30 years at the time of diabetes. Patients who met our diabetes criteria prior to the age of 30 years were considered to have a high probability of having type 1 diabetes and were therefore excluded. Patients who were listed as 'not acceptable' in the GPRD, indicating poor data quality for a given patient, were also excluded. A list of unique identifiers for patients who met our criteria for type 2 diabetes were then uploaded to the GPRD server, and all data for these patients were downloaded for database construction, including demographic information, prescriptions,

diagnostic codes, and laboratory test data. These data were used to construct a cohort database and 2 nested case-control databases, which were used to conduct the 3 studies described in Chapters 5, 6, and 7.

Cohort entry was defined as the latest of the following 4 dates: 1) the date at which the patient met our criteria for type 2 diabetes; 2) the date of registration at the practice; 3) the date the practice became 'up-to-standard'; or 4) January 1st, 2000. The arbitrary date of January 1st, 2000 was selected as the earliest possible date for cohort entry as TZDs only entered the U.K. market in 2000 (159). Thus, patients with diabetes were not eligible for exposure to TZDs prior to this time. If the date of cohort entry was based on prescription data (as part of our diabetes criteria), the date of the second prescription was used to avoid immortal time bias (160-162). Patients were eligible to enter the cohort between January 1st, 2000 and December 31st, 2005. In the descriptive study and the nested case-control study examining the effect of TZDs on the risk of CHF, the cohort was restricted to patients with at least 1 year of history in the GPRD prior to cohort entry to ensure sufficient observation time for assessment of comorbidities and previous medical history. In the nested case-control study examining the effects of glycemic control on the risk of CHF, the cohort was restricted to patients with at least 2 years in the GPRD to ensure that all patients had at least 1 year of history in the GPRD prior to the 1-year HbA1c assessment period.

The entry criteria resulted in the creation of a cohort of patients with prevalent and incident diabetes. The descriptive study involved the use of this full cohort as well as a sub-cohort that was restricted to patients with incident type

2 diabetes to avoid confounding due to duration of disease. Restricting the 2 nested case-control studies to patients with incident type 2 diabetes may have been preferable due to the potential confounding related to disease duration, a risk factor for adverse outcomes (163). However, practical limitations rendered the use of an incident cohort for the 2 nested case-control studies not feasible. These limitations include an insufficient sample size to estimate clinically relevant effects due to relatively low rates of CHF, particularly among those with incident diabetes. These limitations were compounded by relatively low rates of TZD prescription in the early years of the study period. Consequently, rather than relying on restriction, these studies involved statistical adjustment for duration of diabetes (discussed below).

Different criteria were used to define cohort exit in the 3 observational studies. In the first, which describes prescription trends, cohort exit was defined as the earliest of the following 3 dates: 1) the date the patient transferred out of the GPRD medical practice; 2) the date of the most recent data upload from the practice to the GPRD; 3) December 31st, 2006. In the 2 nested case-control studies, the date of CHF diagnosis was incorporated as a fourth component of the cohort exit date definition. The date of cohort exit was defined by the date of whichever component occurred first.

3.3 Case-Control Selection

In the 2 case control studies, cases were defined as patients with a first diagnosis of CHF. Potential controls were matched on age (caliper of 3 years), calendar date, and GPRD practice, and up to 10 controls per case were selected.

The date of CHF diagnosis defined the index date for cases, and this calendar date defined the index date among corresponding controls. Matching factors included calendar date to prevent confounding due to changes that occurred during the study period. These changes included increasing prescription of anti-diabetic medication in general and TZDs in particular (Chapter 5), decreasing cardiovascular mortality among patients with diabetes (164), and changes in type 2 diabetes treatment guidelines (20, 165-167). GPRD practice was used as a matching variable to minimize the confounding effects of variability in treatment practices, GPRD coding practices, and HbA1c testing practices. Matching on GPRD practice also inherently matches on geographic variations in treatments and outcomes; previous studies have illustrated important variability in cardiovascular outcomes throughout the U.K. (168, 169). Age is an important risk factors for CHF and is tightly correlated with duration of diabetes, a key measure of severity of diabetes. Thus, controls were also caliper matched on age.

It would have been ideal to also match on duration of diabetes. However, due to sparse risk sets (primarily due to matching on GPRD practice), such matching was not feasible. In these studies, duration of diabetes was defined as the difference in years between the date at which the patient met our diabetes criteria and their index date. This time represents a proxy of their true duration of diabetes as diabetes is a prevalent, progressive condition that, unlike an acute MI, is not marked by the onset of acute symptoms. In addition, the definition of the true duration of diabetes is more difficult in the GPRD than other large databases due to patients who switch practices. When patients switch practices, they are

assigned a new unique identifier, and their previous data are not transferred to their new patient file. Previous clinical diagnoses are typically included in the new patient file as part of the medical history taken during registration at the new medical practice but previous prescriptions and laboratory test results are not included as part of this new record. Despite these limitations, duration of diabetes was included as a potential confounder in multivariable models, minimizing its potential confounding effects.

3.4 Data Analysis

In the first study of this thesis, trends in the prescription of anti-diabetic medications are described as prescriptions per 100,000 person-years. In the third study, the effect of TZDs on the risk of incident CHF is examined using (frequentist) conditional logistic regression analyses. Both of these studies involved the use of standard analytical techniques, which are described in detail in Chapters 5 and 7, respectively.

In the second study, the effects of glycemic control on the risk of CHF among patients with type 2 diabetes were assessed using Bayesian conditional logistic regression analyses, an analytical approach that has been described in detail elsewhere (170). Briefly, a likelihood function was constructed such that the numerator employed the data for the case of each matched set and the denominator employed the data for the entire matched set (i.e., cases and corresponding controls). The product of these terms across all matched sets produced the global likelihood function that, when combined with prior distributions through Bayes Theorem, provided the desired posterior distributions.

Low information normal distributions were used as prior densities for all regression parameters. In particular, we used a truncated normal density with mean 0 and standard deviation of 10, truncated at -2 and 2. The use of this distribution resulted in a relatively flat prior density over the range -2 to 2, which covers all plausible values on the logit scale. A 1,000 iteration burn-in was used to ensure model convergence, and 10,000 iterations were used to create the posterior distribution. This median of the posterior distribution was used to estimate the rate ratio (RR), and the 2.5 and 97.5 percentiles were used to estimate the corresponding 95% credible interval (CrI), the Bayesian equivalent to the frequentist CI. Several runs from dispersed starting values were carried out to ensure convergence.

The use of Bayesian techniques offered important advantages, especially in terms of greater flexibility in statistical modelling. In particular, the use of Bayesian modelling allowed for relatively easy adjustment for measurement error (171), as only a small change to the likelihood function is required to carry out a similar case-control analysis that adjusts for any variable measured with error. In this study, we adjusted for error in the assessment of HbA1c, which can occur due to natural fluctuations in HbA1c within the body as well as laboratory error (172). Additional error can be introduced in the recording of these data; this error was not considered in this analysis.

The Bayesian approach to measurement error adjustment relies on the use of 3 conditional independence sub-models (171). The disease sub-model expresses the outcome Y (i.e., CHF) as a function of an exposure X (i.e., HbA1c

free of measurement error). The measurement sub-model expresses the observed surrogate Z (i.e., HbA1c with measurement error) as a function of X and the measurement error variance. Finally, the exposure sub-model expresses X as a function of population parameters, such as the population distribution of HbA1c, and other risk factors for Y, if applicable. The product of these conditional sub-models and their corresponding prior densities produces the posterior distribution of the measurement error adjusted relative risk estimating the effect of X (i.e., the true HbA1c) on Y (i.e., CHF).

Previous studies suggest that the standard deviation of the HbA1c measurement error is 0.47% (172). Thus, a uniform prior distribution that varied from 0.45% and 0.50% was used to estimate the standard deviation of the HbA1c measurement error. In sensitivity analyses, a uniform(0.10, 0.50) prior distribution was used to allow for a broader range of standard deviation values. These measurement error models involved the use of a 1,000 iteration burn-in and 40,000 iterations to estimate measurement error-adjusted RRs.

Sensitivity analyses included adjustment for additional potential confounders, including comorbidities, BMI, smoking status, non-diabetic medication prescriptions, total cholesterol, and blood pressure, and the assessment of HbA1c as a continuous variable. In addition, our primary regression analyses were repeated using frequentist methods.

Bayesian analyses were conducted in WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge, United Kingdom). Sample WinBUGS code, including adjustment for HbA1c measurement error, is found in Appendix 2.

Frequentist sensitivity analyses were conducted using SAS (Version 9.1.3. Cary, NC).

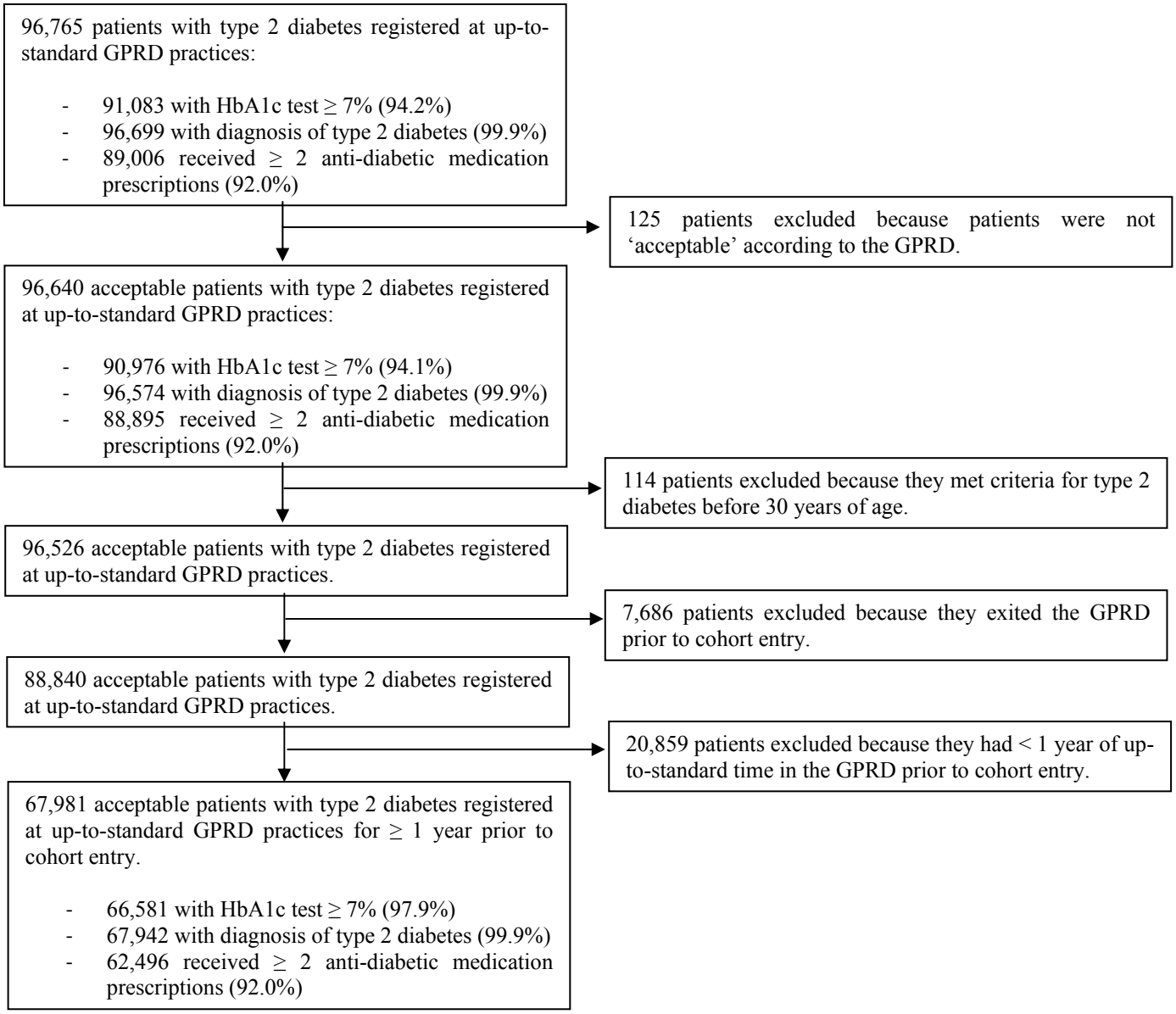
3.5 Ethics

For this thesis, ethical approval was obtained from two sources. Ethical approval was obtained from the McGill University Health Centre Research Ethics Board (Appendix 3). Approval was also obtained from the Scientific and Ethical Advisory Group (SEAG) of the GPRD (Appendix 4). The SEAG, which has since been renamed the Independent Scientific Advisory Committee, is responsible for the scientific and ethical review of all studies conducted with GPRD data (173).

FIGURE LEGEND

Figure 3.1 Flow diagram depicting construction of cohort of patients with type 2 diabetes.

Figure 3.1


96,765 patients with type 2 diabetes registered at up-to-standard GPRD practices:
- 91,083 with HbA1c test ≥ 7% (94.2%)
- 96,699 with diagnosis of type 2 diabetes (99.9%)
- 89,006 received ≥ 2 anti-diabetic medication prescriptions (92.0%)
125 patients excluded because patients were not 'acceptable' according to the GPRD.
96,640 acceptable patients with type 2 diabetes registered at up-to-standard GPRD practices:
- 90,976 with HbA1c test ≥ 7% (94.1%)
- 96,574 with diagnosis of type 2 diabetes (99.9%)
- 88,895 received ≥ 2 anti-diabetic medication prescriptions (92.0%)
114 patients excluded because they met criteria for type 2 diabetes before 30 years of age.
96,526 acceptable patients with type 2 diabetes registered at up-to-standard GPRD practices.
7,686 patients excluded because they exited the GPRD prior to cohort entry.
88,840 acceptable patients with type 2 diabetes registered at up-to-standard GPRD practices.
20,859 patients excluded because they had < 1 year of up-to-standard time in the GPRD prior to cohort entry.
67,981 acceptable patients with type 2 diabetes registered at up-to-standard GPRD practices for ≥ 1 year prior to cohort entry.
- 66,581 with HbA1c test ≥ 7% (97.9%)
- 67,942 with diagnosis of type 2 diabetes (99.9%)
- 62,496 received ≥ 2 anti-diabetic medication prescriptions (92.0%)

CHAPTER 4 – COHORT DESCRIPTION

The 3 observational studies presented in this thesis involve data from subsets of a cohort of patients with type 2 diabetes in the U.K. In this chapter, the characteristics of this overall cohort are described to provide a thorough understanding of the patient population under investigation.

4.1 Patient and Cohort Characteristics

The baseline and clinical characteristics of patients with type 2 diabetes included in our cohort are found in Table 4.1. The mean age of patients was 64.1 years (SD = 12.7) at cohort entry, and the 54.8% were male. The majority of patients were obese (41%) or overweight (35%), and 21.9% of patients had coronary artery disease. Approximately 8% of patients had a history of MI, and less than 5% of patients had previously undergone coronary revascularization (3.0% had previously undergone CABG and 1.6% had previously undergone PCI). The prevalence of CHF was 6.7% in this population.

At cohort entry, the median duration of diabetes in this cohort was 1.0 years (IQR = 0, 6.7), and only a small number of patients had diabetic complications. The mean HbA1c in the year before cohort entry was 8.3% (SD = 1.9%). In addition, prescription of anti-diabetic medications in the 90 days prior to cohort entry was relatively low, with only 20.4% of patients prescribed metformin and 11.2% of patients prescribed insulin. Thus, although this cohort is one of prevalent type 2 diabetics, the majority of patients had relatively uncomplicated diabetes that had been diagnosed fairly recently at cohort entry.

4.2 Heterogeneity of Entry Criteria

A potential limitation was that our cohort entry criteria were somewhat heterogeneous, with patients entering based on a clinical diagnosis of type 2 diabetes, an abnormal HbA1c test result, or ≥ 2 prescriptions for anti-diabetic medications. However, >90% of patients met all 3 criteria at some point during their time in the GPRD (Figure 4.2). In addition, >98% met at least two of these criteria. The majority of patients who did not meet the third criteria appear to have diet-controlled diabetes. Thus, although the entry criteria may have been somewhat heterogeneous, their use resulted in a fairly homogeneous study population. These data also demonstrate the validity of GPRD data.

Table 4.1. Baseline demographic and clinical characteristics of patients with type 2 diabetes in the General Practice Research Database at cohort entry.

Characteristic[†]	Patients (n = 67,981)
Demographic	
Male, n (%)	37,217 (54.8)
Age (Years) [Mean ± SD]	64.1 ± 12.7
Lifestyle Variables	
Body Mass Index (kg/m^2)	
Mean ± SD	29.8 ± 6.1
Missing, n (%)	2,912 (4.3)
Smoking, n (%)	
Current	10,567 (15.5)
Past	22,794 (33.5)
No	33,719 (49.6)
Missing	901 (1.3)
Comorbidities, n (%)	
Atrial Fibrillation	3,707 (5.5)
Cerebrovascular Disease	6,394 (9.4)
Chronic Obstructive Pulmonary Disease	2,680 (3.9)
Congestive Heart Failure	4,519 (6.7)
Coronary Artery Disease	14,912 (21.9)
Dyslipidemia	11,166 (16.4)
Hypertension	30,963 (45.6)
Myocardial Infarction	5,515 (8.1)
Peripheral Vascular Disease	2,052 (3.0)
Previous Coronary Angiogram	2,937 (4.3)
Previous Coronary Artery Bypass Graft Surgery	2,004 (3.0)
Previous Percutaneous Coronary Intervention	1,070 (1.6)
Renal Failure	643 (1.0)
Stroke	2,097 (3.1)
Rheumatoid Arthritis	7,053 (10.4)
Unstable Angina (including ACS)	1,408 (2.1)
Diabetic Complications, n (%)	
Amputations	528 (0.8)
Blindness	556 (0.8)
Nethropathy	963 (1.4)
Neuropathy	2,358 (3.5)
Retinopathy	5,047 (7.4)

Characteristic[†]	Patients (n = 67,981)
Medication Use, n (%)	
ACE Inhibitors	1,402 (2.1)
ARBs	2,657 (3.9)
Aspirin	16,657 (24.5)
Beta-Blockers	13,957 (20.5)
Calcium Channel Blockers	14,592 (21.5)
COX-2 Inhibitors	1,292 (1.9)
Digoxin	3,373 (5.0)
Diuretics and Other Anti-Hypertensive Agents	21,925 (32.3)
Nitrates	8,542 (12.6)
Statins	11,855 (17.4)
Diabetic Medications, n (%)	
Insulin	7,611 (11.2)
Metformin	13,879 (20.4)
Sulfonylureas	17,643 (26.0)
TZDs	2 (0)
Pioglitazone	0 (0)
Rosiglitazone	2 (0)
Other Oral Antidiabetics	1,569 (2.3)
Duration of Diabetes (Years)	
Mean ± SD	4.2 ± 6.3
Median (IQR)	1.0 (0.0, 6.7)
Laboratory and Clinical Tests	
HbA1c Test	
Test in Previous Year, n (%)	33,049 (48.6)
Mean HbA1c [%][‡]	
Mean ± SD	8.3 ± 1.9
Median (IQR)	7.9 (7.0, 9.3)
Total Cholesterol Test	
Test in Previous Year, n (%)	33,077 (48.7)
Mean Total Cholesterol [mmol/L][‡]	
Mean ± SD	5.6 ± 1.1
Median (IQR)	5.5 (4.8, 6.3)
Systolic Blood Pressure	
Reading in Previous Year, n (%)	52,109 (76.7)
Mean Systolic Blood Pressure [mm Hg][‡]	
Mean ± SD	147.7 ± 18.8
Median (IQR)	147.0 (135.0, 160.0)

Characteristic[†]	Patients (n = 67,981)
Diastolic Blood Pressure	
Reading in Previous Year, n (%)	52,090 (76.6)
Mean Diastolic Blood Pressure [mm Hg][‡]	
Mean ± SD	83.2 ± 9.7
Median (IQR)	82.5 (77.7, 90.0)
Cohort Characteristics	
Duration of Follow-up (Years)	
Mean ± SD	4.8 ± 2.2
Median (IQR)	5.2 (2.9, 7.0)
Time from Registration at Practice to Cohort Entry (Years)	
Mean ± SD	18.0 ± 14.0
Median (IQR)	13.3 (7.7, 25.1)
Time from Up-to-Standard to Cohort Entry (Years)	
Mean ± SD	8.5 ± 4.0
Median (IQR)	9.8 (4.8, 11.0)

Abbreviations: ACE: angiotensin converting enzyme; ACS: acute coronary syndrome; ARBs: angiotensin II receptor blockers; COX: Cyclooxygenase; HbA1c: hemoglobin A1c; IQR: inter-quartile range; SD: standard deviation; TZDs: thiazolidinediones

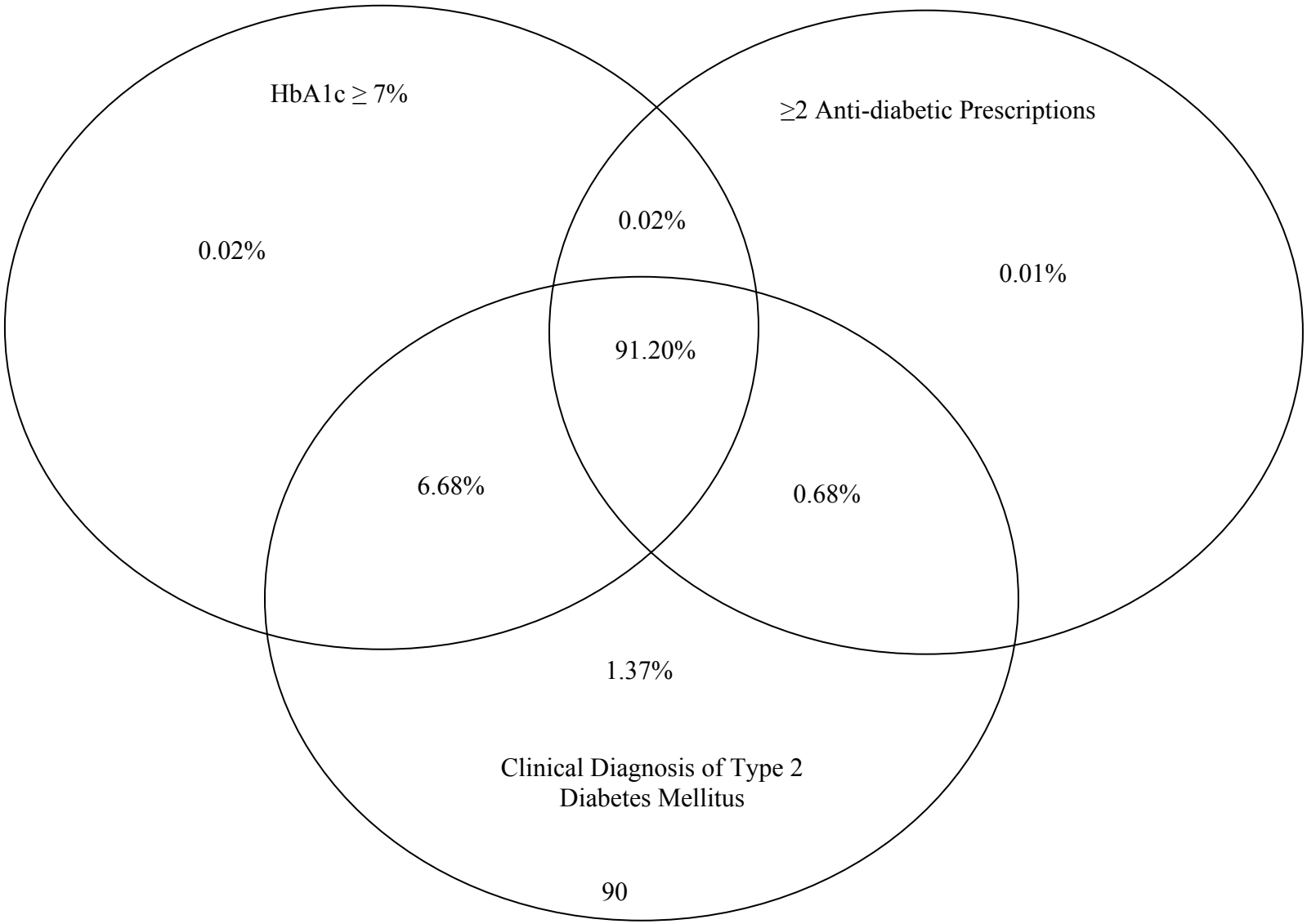
[†] Comorbidities are based on any previous diagnosis in the GPRD occurring prior to cohort entry. Medication data are for the 90 days prior to cohort entry, and blood pressure and HbA1c data are for the year prior to cohort entry.

[‡] Among those with a test in the year prior to cohort entry.

FIGURE LEGEND

Figure 4.1 Breakdown of patients by cohort entry criteria.

Figure 4.1


HbA1c ≥ 7%
≥2 Anti-diabetic Prescriptions
0.02%
0.02%
0.01%
91.20%
6.68%
0.68%
1.37%
Clinical Diagnosis of Type 2 Diabetes Mellitus
90

CHAPTER 5 – TRENDS IN PRESCRIPTION OF ANTI-DIABETIC MEDICATIONS

5.1 Preface to Manuscript #1

Chapters 1 and 2 describe the currently available evidence that suggests that, although TZDs have favorable effects on glycemic control, they may also have cardio-toxic effects resulting in a potentially increased risk in CHF. These chapters also illustrate gaps in this currently available literature. However, before examining the potential effects of glycemic control (Chapter 6) and TZDs (Chapter 7) on the risk of incident CHF, a description of the use of these agents is warranted. Recent treatment guidelines for patients with type 2 diabetes promote increasingly aggressive glycemic control in this patient population (1, 19, 20, 23, 167) but physician adherence to these guidelines remains unknown. Furthermore, if these agents are infrequently prescribed in patients with type 2 diabetes, any increased risk of CHF associated with their use would have a minimal public health impact. Conversely, if they are frequently prescribed in this patient population, the public health consequences of an increased risk of incident CHF could be significant. The remainder of this chapter therefore describes trends in the prescription of anti-diabetic medications in the U.K.

Trends in the Prescription of Anti-Diabetic Medications in the United Kingdom: A Population-Based Analysis

Running Title: Trends in Anti-Diabetic Medications

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Word Count: 1,331

Figures: 1

Authors Contributions: KBF conceived of the study idea, and KBF and JMB contributed to the study design. SS contributed to the acquisition of data. KBF drafted the manuscript and conducted the statistical analyses. All authors were involved in revising the article for important intellectual content, interpreting the data, and approved the final version to be published.

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Competing Interests: None.

Keywords: Diabetes, medical therapy, prescribing patterns.

ABSTRACT

Purpose: Over the last decade, guidelines for the treatment of type 2 diabetes have increasingly favored tighter glycemic control, necessitating the use of more aggressive pharmacological therapy. The objective of this study was to describe trends in the prescription of anti-diabetic medications among patients with type 2 diabetes in the United Kingdom (U.K.).

Methods: Using the U.K. General Practice Research Database, we constructed a cohort of patients with type 2 diabetes. Diabetes was defined as the presence of a diagnosis of diabetes, HbA1c $\geq$ 7%, or $\geq$ 2 prescriptions for anti-diabetic medications. Analyses were conducted for the full cohort as well as a sub-cohort with incident diabetes.

Results: Our full cohort involved 67,981 patients and a total of 320,089 patient-years, and our sub-cohort involved 30,234 patients with incident diabetes and 111,890 patient-years. From 2000 to 2006, there was a substantial increase in the prescription rate of anti-diabetic medications. Overall, there were 9.6 prescriptions/patient-year in 2000, and this had increased to 14.8 prescriptions/patient-year in 2006. The greatest relative increase occurred in the prescription of thiazolidinediones. The greatest absolute increase occurred in the prescription of metformin, which surpassed sulfonylureas as the most commonly prescribed anti-diabetic medication among patients with type 2 diabetes in 2002. Among those with incident diabetes, overall prescription rates were 4.6 prescriptions/patient-year in 2000 and 13.6 prescriptions/patient-year in 2006.

Conclusions: There was a substantial increase between 2000 and 2006 in the U.K. in the prescription of anti-diabetic medications. This increasingly aggressive pharmacological management is consistent with recent practice guidelines.

INTRODUCTION

Over the last decade, guidelines for the treatment of type 2 diabetes have increasingly favored tighter glycemic control (1-5), necessitating the use of more aggressive pharmacological therapy. However, the changes in prescribing patterns of anti-diabetic medications during this period remain poorly documented. Our objective was therefore to describe recent trends in the prescription of anti-diabetic medications among patients with type 2 diabetes in the United Kingdom (U.K.).

METHODS

Using data from the General Practice Research Database (GPRD), we constructed a cohort of patients with type 2 diabetes from January 1st, 2000 to December 31, 2006. The GPRD has been described in detail previously (6) and used extensively in pharmacoepidemiologic studies (7;8). Briefly, this database links over 400 general practices and provides a representative sample of approximately 5% of the U.K. population (6). Data include demographic information, clinical diagnoses, prescriptions issued, and laboratory data.

Diabetes was defined as the presence of a clinical diagnosis of type 2 diabetes, an HbA1c test $\geq 7\%$, or ≥ 2 prescriptions for anti-diabetic medications. We excluded all patients with a diagnostic code of type 1 diabetes mellitus as well as those diagnosed with type 2 diabetes before the age of 30 years. Cohort entry was defined as the latest of the following 4 events: 1) date of registration at the GPRD practice; 2) date at which the GRPD practice became up-to-standard with respect to data validity; 3) date at which the patient met at least one component of our definition for type 2 diabetes; 4) January 1st, 2000. If

prescription data were used to define cohort entry, the date of cohort entry was defined by the date of the second prescription for an anti-diabetic medication. Cohort entry could occur between January 1st, 2000 and December 31st, 2005. Patients were followed until transfer to another practice, death, the date of the latest data upload from the practice to the GPRD, or December 31st, 2006, whichever came first. We limited our study to patients with ≥ 1 year of history in the GPRD prior to cohort entry.

We grouped prescriptions for anti-diabetic medications by medication class, including insulin, metformin, sulfonylureas, thiazolidinediones (TZDs), and other oral anti-diabetic agents. Prescription rates were calculated by year and are presented as prescriptions per patient-year. Prescription rates for the full cohort were calculated to describe population-level prescribing practices. In addition, we conducted analyses restricted to a sub-cohort of patients with incident diabetes to account for confounding by duration of disease and describe changes in prescribing patterns.

Ethical approval was obtained from the McGill University Health Centre (MUHC) Research Ethics Board and from the Scientific and Ethical Advisory Group (SEAG) of the GPRD.

RESULTS

Our full cohort involved 67,981 patients with type 2 diabetes, contributing a total of 320,089 patient-years, and our sub-cohort included 30,234 patients with incident type 2 diabetes and a total of 111,890 patient-years. Among all patients,

the mean age at cohort entry was 64.0 years (standard deviation = 12.7), and 55% were male. In addition, 8% had a previous myocardial infarction and 46% had hypertension. The mean HbA1c in the year before cohort entry was 8.3% (standard deviation = 1.9%).

Between 2000 and 2006, prescription rates of anti-diabetic medications increased with time (Figure 5.1a). Overall, there were 9.6 prescriptions/patient-year in 2000. By 2006, the overall prescription rate of anti-diabetic medications had increased to 14.8 prescriptions/patient-year. The greatest relative increase occurred in the prescription of TZDs. The greatest absolute increase occurred in the prescription of metformin, which surpassed sulfonlyureas as the most commonly prescribed anti-diabetic medication among patients with type 2 diabetes in 2002. Prescription of sulfonylureas and other oral anti-diabetic agents decreased modestly over time. During this period, there was also a small but important increase in the prescription of insulin, which increased by approximately 10%.

Among patients with incident diabetes, there was a substantial increase in prescription rates between 2000 and 2006 (Figure 5.1b). During this time, the overall prescription rate increased from 4.6 prescriptions/patient-year to 13.6 prescriptions/patient-year. Prescription rates for TZDs and metformin increased dramatically during the study period. In addition, important increases in the prescription of insulin in patients with incident diabetes were observed.

DISCUSSION

We found sharp increases in the overall prescription of anti-diabetic medications between 2000 and 2006. The greatest increases were observed in metformin and TZDs. TZDs entered the market place early in the study period and were characterized by rapid uptake. There was also an increase in the prescription of insulin during this period, particularly among patients with incident type 2 diabetes. Prescription patterns among patients with incident disease suggest that physicians are being increasingly aggressive in the pharmacological treatment of type 2 diabetes.

This pattern of increasingly aggressive prescription of anti-diabetic medications is consistent with most treatment guidelines (1-5). Although most guidelines recommend an HbA1c < 7%, many now recommend lower HbA1c targets and suggest tailoring treatment targets based on individuals' risk of microvascular and macrovascular complications (1). In addition, the American Diabetes Association now recommends targeting as close to normal HbA1c as possible without inducing hypoglycemia (2).

The effect of aggressive management of type 2 diabetes on clinical outcomes remains unclear. Recently, the effect of intensive therapy to target normal HbA1c was examined in the ACCORD Trial (9). In this trial, over 10,000 patients with established cardiovascular disease or additional cardiovascular risk factors were randomized to intensive therapy to target an HbA1c < 6% or usual care. The investigators found that patients randomized to intensive therapy had higher mortality compared with those randomized to usual care. In contrast, the

ADVANCE Trial (10), which randomized more than 11,000 patients with type 2 diabetes, found that intensive glucose control targeting an HbA1c < 6.5% was associated with a decrease in their primary endpoint, a composite of incident macro- and microvascular events, but had no effect on mortality or major macrovascular events. In light of these conflicting results, there is a need to examine the effect of the observed shift towards more aggressive anti-diabetic therapy on outcomes in actual practice.

Our study has a number of strengths. First, the GPRD data provide a representative sample of the U.K. population. These data are well validated and have been the source of over 600 peer-reviewed publications (11). Second, the GPRD records prescriptions issued rather than prescriptions filled (6). Consequently, it is a good data source for studies examining physician prescription patterns at the population level.

Our study also has potential limitations. First, we have not accounted for the duration of prescriptions, which typically vary from 28 to 90 days in the GPRD. However, it is unlikely that these durations differ systematically over time. Second, our cohort was somewhat heterogeneous, consisting of patients with a clinical diagnosis of type 2 diabetes, an abnormal HbA1c test result, or treated for type 2 diabetes. However, greater than 90% of patients met all 3 criteria and greater than 98% met at least two of these criteria while in the GPRD. Third, medication data in the GPRD represent prescriptions issued rather than prescriptions filled or taken. Thus, although these data are ideal for measuring prescription patterns, there is likely imperfect patient adherence to these

prescriptions. Finally, it is possible that the observed increase in prescriptions was the result of temporal changes in patient population, including changes in the mix of patients in the cohort and increasing diabetes duration. However, to assess the impact of duration of diabetes, we repeated analyses among a sub-cohort of patients with incident type 2 diabetes. These analyses suggest that increasing duration of diabetes and changes in the mix of patients are unlikely explanations for the observed changes in prescriptions and that physicians are utilizing more aggressive pharmacological management during the study period.

CONCLUSION

There was a substantial increase between 2000 and 2006 in the U.K. in the prescription rate of anti-diabetic medications among patients with type 2 diabetes. This increasingly aggressive pharmacological management is consistent with recent practice guidelines. However, the effect of these prescription trends on clinical outcomes at the population level remains unknown.

TAKE-HOME MESSAGES

- There was a substantial increase between 2000 and 2006 in the U.K. in the prescription rate of anti-diabetic medications among patients with type 2 diabetes.
- The greatest increase was observed in metformin and TZDs.
- Future studies need to examine the effect of these prescription trends on population-level clinical outcomes.

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FIGURE LEGEND

Figure 5.1. Trends in the prescription of anti-diabetic medications among patients with type 2 diabetes in the United Kingdom between 2000 and 2006. a) Full cohort; b) Sub-cohort of patients with incident type 2 diabetes. Prescription rates are presented as prescriptions per patient-year.

Figure 5.1a

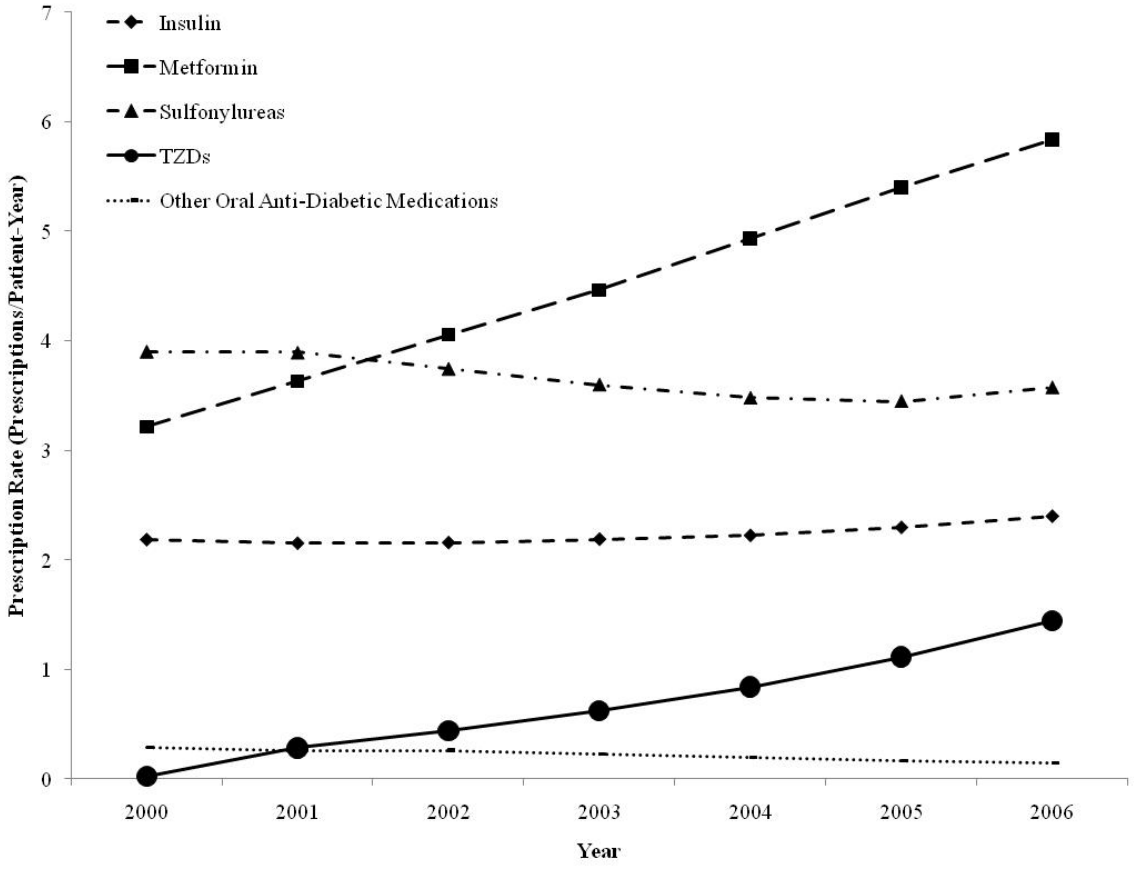
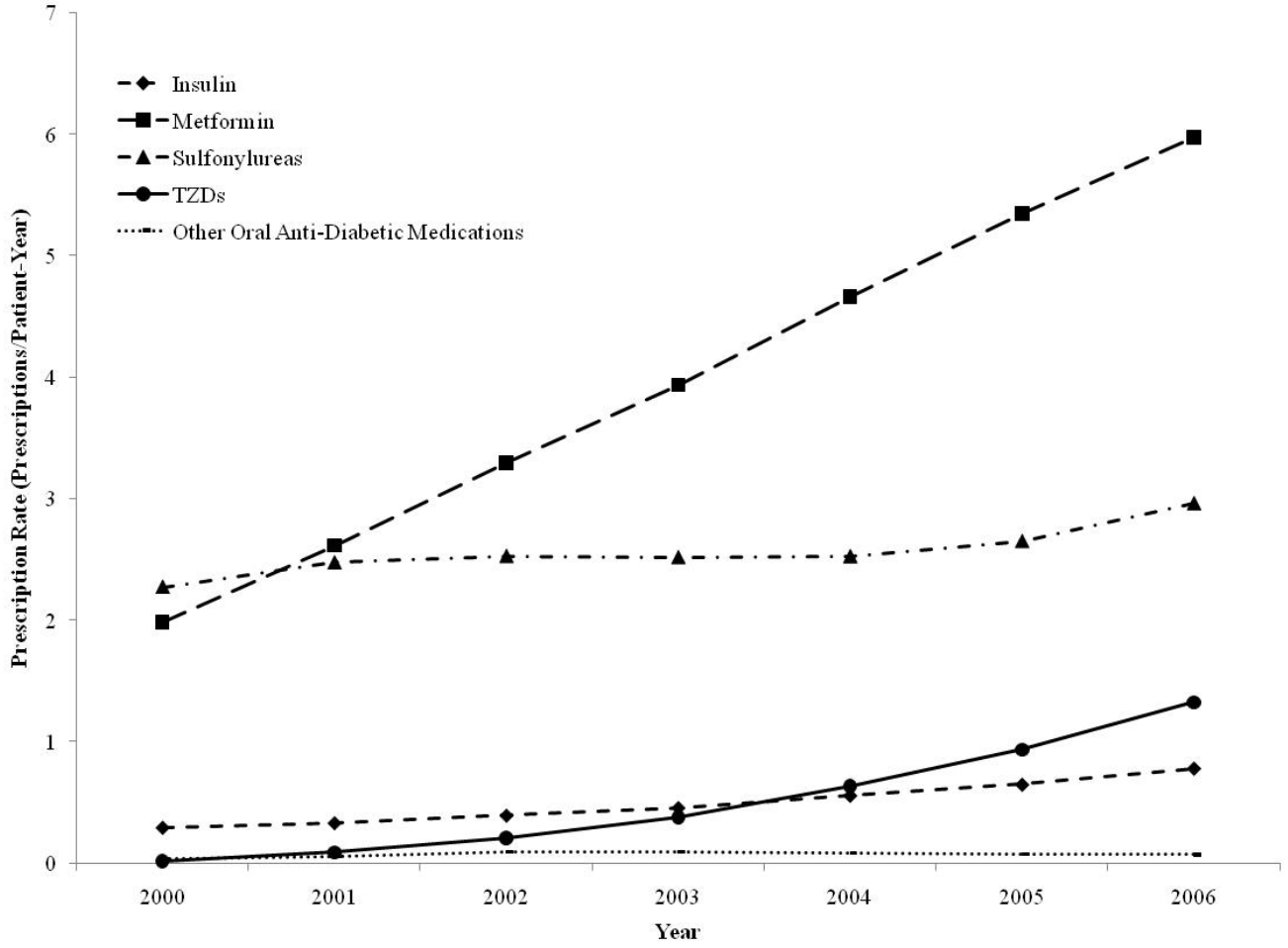

Insulin
Metformin
Sulfonylureas
TZDs
Other Oral Anti-Diabetic Medications
Prescription Rate (Prescriptions/Patient-Year)
0
1
2
3
4
5
6
7
2000
2001
2002
2003
2004
2005
2006
Year

Figure 5.1b


Insulin
Metformin
Sulfonylureas
TZDs
Other Oral Anti-Diabetic Medications
Prescription Rate (Prescriptions/Patient-Year)
0
1
2
3
4
5
6
7
2000
2001
2002
2003
2004
2005
2006
Year

CHAPTER 6 –GLYCEMIC CONTROL AND THE RISK OF CHF

6.1 Preface to Manuscript #2

As described in Chapter 5, the prescription of anti-diabetic medications has increased dramatically over time. This increase is particularly striking for TZDs, which entered the market early in the study period and were characterized by rapid update. The sharp increase in the prescription of TZDs is likely the result of aggressive promotion and advertising by their manufacturers and recent changes in treatment guidelines for patients with type 2 diabetes (1, 19, 20, 23, 167). These changes included recommendations for increasing aggressive glycemic control, particularly among those at high cardiovascular risk (19). Although changes in prescribing patterns suggest that these new treatment targets have been incorporated into clinical practice, the effect of glycemic control on clinical outcomes remains controversial. To address this issue, a population-based nested case-control study was conducted to assess the effect of glycemic control on the risk of CHF among patients with type 2 diabetes. The remainder of this chapter describes this study.

The Effect of Glycemic Control on the Risk of Congestive Heart Failure among Patients with Type 2 Diabetes Mellitus: A Population-Based Nested Case-Control Study

Running Title: HbA1c and CHF

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Authors Contributions: KBF conceived of the study idea, and JMB and KBF contributed to the design of the study. KBF conducted the statistical analyses and drafted the manuscript. LJ contributed to the design of the statistical analyses. SS contributed to the acquisition of data. All authors were involved in revising the article for important intellectual content, interpreting the data, and approved the final version to be published.

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Competing Interests: None.

Keywords: Congestive Heart Failure, Glycemic Control, Type 2 Diabetes Mellitus, HbA1c, General Practice Research Database.

ABSTRACT

Background: Although glycemic control as measured by hemoglobin A1c (HbA1c) is a central component to most treatment guidelines for type 2 diabetes, its impact on the risk of cardiovascular events is controversial.

Methods: We conducted a nested case-control study using data from the General Practice Research Database to examine the effect of glycemic control on the risk of congestive heart failure (CHF) among patients with type 2 diabetes. Cases were defined as patients with incident CHF, and up to 10 controls were matched on age, medical practice, and calendar date. Bayesian conditional logistic regression models were used and, in additional analyses, the effects of error in the measurement of HbA1c were considered.

Results: We identified 2,545 CHF cases and 23,559 matched controls. After adjusting for age, sex, use of anti-diabetic medications prior to HbA1c assessment, and diabetes duration, patients with an HbA1c between 7% and 8% had a similar CHF rate as those with an HbA1c < 7% (rate ratio [RR] = 0.98, 95% credible interval [CrI] = 0.88, 1.09). However, patients with higher HbA1c values had increased CHF rates compared with those with an HbA1c < 7% (8% ≤ HbA1c < 9%: RR = 1.17, 95% CrI = 1.03, 1.33; 9% ≤ HbA1c < 10%: RR = 1.09, 95% CrI = 0.92, 1.27; HbA1c ≥ 10%: 1.17, 95% CrI = 0.98, 1.38). In a sensitivity analysis using HbA1c as a continuous variable, an increase of 1% was associated with an increase in the rate of CHF (adjusted RR = 1.03, 95% CrI = 1.00, 1.06). Taking into account possible error in HbA1c measurement did not appreciably alter these results.

Conclusions: Increasing HbA1c was associated with an increase in CHF among patients with diabetes. However, our results suggest there is no benefit to extremely aggressive glycemic control with respect to CHF. Further research in identifying the optimal HbA1c target should consider incident CHF among the cardiovascular endpoints investigated.

INTRODUCTION

Glycemic control, as measured by hemoglobin A1c (HbA1c), is a central component of most treatment guidelines for type 2 diabetes (1-5). Most guidelines recommend an HbA1c < 7% but lower treatment targets are also being recommended, particularly for those at high cardiovascular risk (2). The risks and benefits of aggressive glycemic control remain poorly understood.

The effect of aggressive glycemic control has recently been examined in 2 large randomized controlled trials of patients with type 2 diabetes at high cardiovascular risk (6-8). In the ADVANCE Trial, patients randomized to intensive glycemic control had a similar risk of macrovascular events, including cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, as those randomized to standard glycemic targets (7). However, the ACCORD Trial was prematurely stopped after 3.5 years of follow-up due to increased mortality among patients randomized to intensive glycemic control. These results have further fueled the ongoing debate regarding the effect of glycemic control on clinical outcomes, particularly among those at high cardiovascular risk.

The effects of glycemic control have also been examined in diabetic and non-diabetic patients with congestive heart failure (CHF), where increasing HbA1c was found to be associated with an increasing rate of cardiovascular death, hospitalization for CHF, and all-cause mortality (9). However, the effect of glycemic control on the risk of incident CHF in an unselected diabetic population remains unstudied. We therefore conducted a population-based nested

case-control study among patients with type 2 diabetes to examine the effect of glycemic control, measured by HbA1c, on the risk of incident CHF.

METHODS

Data Source

Data were extracted from the General Practice Research Database (GPRD), a clinical database that links electronic medical records for over 400 general medical practices in the United Kingdom (U.K.) (10). The GPRD has been described in detail elsewhere (10). Briefly, the GPRD contains a demographically-representative sample of approximately 5% of the U.K. population. With over 39 million person-years of observation (11), the GPRD has served as the data source for over 600 peer-reviewed publications (12). The GPRD contains demographic information (e.g., birth year, sex), medical diagnoses, and detailed information regarding medication prescriptions (10). Unlike most administrative databases, the GPRD also contains clinical data such as smoking status, body mass index (BMI), systolic and diastolic blood pressure, and laboratory tests such as total cholesterol and HbA1c. The availability of these HbA1c data make the GPRD well suited for studies of patients with type 2 diabetes, particularly those examining the importance of glycemic control. To ensure that GPRD data are of high quality, a number of quality assurance protocols have been developed (13). In addition, previous studies have compared GPRD data with corresponding data from medical charts, and these studies have found GPRD data to be valid (14-16).

Study Population

This case-control study was conducted within a cohort of patients with type 2 diabetes. Patients were defined as having type 2 diabetes if they met one of the following 3 criteria: 1) a National Health Service (NHS) Clinical Term code (commonly called a READ code) (17, 18) or Oxford Medical Information System (OXMIS) code in their electronic patient-file indicating a clinical diagnosis of type 2 diabetes; 2) an HbA1c test value ≥ 7%; or 3) ≥ 2 prescriptions for anti-diabetic medications. Cohort entry was defined as the latest of the following 4 dates: 1) the date that the patient met our criteria for type 2 diabetes; 2) the date that the patient's general practice became 'up-to-standard' with respect to GPRD data validity; 3) the date that the patient registered at the GPRD practice; or 4) January 1st, 2000. If cohort entry was based on prescription of anti-diabetic medications, cohort entry was defined as the date of the second prescription. Patients were eligible to enter this cohort anytime between January 1st, 2000 and December 31st, 2005. We restricted our study to those with ≥ 2 years of 'up-to-standard' time in the GPRD prior to cohort entry. Patients with type 1 diabetes and those with diagnosis of type 2 diabetes before the age of 30 years were excluded. These latter patients were excluded as they likely had type 1 diabetes. In addition, we excluded due to questionable data validity patients who were not 'acceptable' according to the GPRD as well as those from practices that were not 'up-to-standard'. Patients with a history of CHF were also excluded. Follow-up continued until a first diagnosis of CHF or until the date at

which the patient left the general practice, the date of the practice's latest data upload, or December 31st, 2006, whichever occurred first.

Case-Control Selection

Cases were defined as patients with a first clinical diagnosis of CHF. Eligible controls were matched on age (caliper of 3 years), GPRD medical practice, and calendar date, and up to 10 controls per case were randomly selected from each risk set. Index date was defined as the date of CHF diagnosis for cases, and the corresponding calendar date was used among matched controls.

Exposure Assessment

We used HbA1c, a central component of most treatment guidelines (1-5) and part of the NHS' Quality and Outcomes Framework which guides reimbursement for the treatment of patients with diabetes in the U.K. (13), as a measure of glycemic control. Although typically expressed as a percentage, a small number of tests were expressed as the average plasma glucose in mmol/L or in mg/dL; these data were converted to the more traditional format (19). All tests with values of HbA1c <3% or >20% were considered to represent implausible values and were excluded. The mean of all HbA1c test values in the year prior to the index date was used to estimate glycemic control among cases and controls (Figure 6.1). Patients with no HbA1c test values during this exposure assessment period were excluded.

Covariate Assessment

Demographic and clinical covariates were also defined using GPRD data. Baseline demographic information and lifestyle variables (e.g., smoking status,

BMI) were extracted from the GPRD patient file. Age was defined as the age in years at index date. Medical comorbidities were defined using READ and OXMIS codes. To ensure that these potential confounders were not the result of poor glycemic control during the HbA1c assessment period, we restricted comorbidities to those that were diagnosed prior to this period (i.e., diagnosis date ≥ 1 year before index date) (Figure 6.1). Similarly, medication use was defined using prescriptions issued in the 90 days prior to HbA1c assessment. Systolic blood pressure, diastolic blood pressure, and total cholesterol were defined using the mean test values in the year prior to HbA1c assessment. Finally, duration of diabetes was approximated using the time in years between the date at which patients met our diabetes criteria and their index date.

Statistical Analyses

Data were analyzed using Bayesian conditional logistic regression models (20). In our primary analysis, 3 models were constructed to examine the effect of HbA1c on the risk of CHF. These models examined HbA1c as a categorical variable and used the following categories: < 7%, 8% to 9%, 9% to 10%, and ≥ 10%. The first model was a univariate analysis, using HbA1c alone. To identify potential confounders, we visually inspected the associations between candidate variables and HbA1c using box plots and examined the effects of these variables on the risk of CHF via univariate conditional logistic regression. Variables with some evidence of effect on CHF that were also associated with HbA1c were considered as potential confounders and included in the second and third regression models. The second model adjusted for sex, which was forced into the

model, and the following potential confounders: age, and prescriptions for anti-diabetic medications (including thiazolidinediones, insulin, metformin, sulfonylureas, and other anti-diabetic medications) in the 90 days prior to the HbA1c assessment period. The third model also adjusted for duration of diabetes. Our primary analysis involved HbA1c as a categorical variable as our a priori hypothesis was that any potential effect was likely non-linear. We used low information prior distributions for all beta coefficients. The posterior distribution obtained from the conditional logistic model was used to estimate the rate ratio (RR) and corresponding 95% credible interval (CrI), the Bayesian analogue to the confidence interval. Several runs from dispersed starting values were carried out to ensure convergence.

One advantage with the use of Bayesian methods is the ability to adjust for measurement error, a process that has been described in detail elsewhere (21). Measurement of HbA1c is prone to error due to both natural fluctuations within the body as well as imperfect laboratory measurement. Previous studies suggest that the true HbA1c value is within 0.94% of the measured value 95% of the time (22). This measurement error was incorporated into our 3 previously-described conditional logistic models (code available from the authors upon request). Measurement error was estimated using a uniform prior distribution for the standard deviation of the measurement error that varied from 0.45% and 0.50%. For models that included measurement error, we used a 1,000 iteration burn-in and 40,000 iterations to estimate measurement error-adjusted RRs.

We conducted a number of sensitivity analyses. These analyses included changing the prior density for the standard deviation of HbA1c measurement error from uniform(0.45, 0.50) to uniform(0.10, 0.50). We also examined HbA1c as a continuous variable, and in additional analyses, we adjusted for other potential confounders, including BMI, smoking status, comorbidities, prescription of cardiovascular medications, systolic and diastolic blood pressure, and total cholesterol. Finally, we repeated our primary analyses (without measurement error adjustment) using frequentist methods.

All Bayesian analyses were conducted using WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge, United Kingdom), and frequentist sensitivity analyses were conducted using SAS (Version 9.1.3. Cary, NC).

Ethics

Ethical approval was obtained from the Scientific and Ethical Advisory Group (SEAG) of the GPRD and the McGill University Health Centre Research Ethics Board.

RESULTS

Patient Characteristics

Our final study cohort contained 57,165 patients with type 2 diabetes (Figure 6.2). From this cohort, 2,545 cases of incident CHF and 23,559 corresponding matched controls were identified.

Baseline demographic and clinical characteristics of cases and controls are presented in Table 6.1. Compared with controls, cases were more likely to be male and, despite caliper matching on age, were slightly older. Cases were also

more likely to have cardiovascular comorbidities, including atrial fibrillation, coronary artery disease, and myocardial infarction. In addition, cases were more likely to have previously undergone coronary revascularization (percutenous coronary intervention or coronary artery bypass surgery) and were more likely to have been prescribed aspirin, calcium channel blockers, and anti-hypertensive medications such as ACE inhibitors, diuretics, and digoxin. However, cases and controls had a similar frequency of prescription of statins and beta-blockers. Important differences were also present in history of diabetes; cases had a longer duration of diabetes and were more likely to be prescribed insulin than corresponding controls.

Effect of Glycemic Control on CHF

In univariate analyses, patients with an HbA1c between 7% and 8% had a similar rate of CHF as those with an HbA1c < 7% whereas those in the other 3 HbA1c categories had an increased rate of CHF relative to those with HbA1c < 7% (Table 6.2). However, after adjusting for age, sex, and use of anti-diabetic medications prior to the HbA1c assessment period, this increased CHF rate was attenuated. Similar results were obtained when also adjusting for duration of diabetes.

Effect of Error in Measurement of HbA1c

The inclusion of HbA1c measurement error in the analyses attenuated the estimated increase in CHF among those with an HbA1c between 7% and 8% as well as among those with an HbA1c between 9% and 10%, but did not

substantially affect the RRs among those in the other HbA1c categories (Table 6.2).

Sensitivity Analyses

In sensitivity analyses, we examined HbA1c as a continuous variable. After adjusting for age, sex, use of anti-diabetic medications, and duration of diabetes, an absolute increase in HbA1c of 1% was associated with an increased rate of CHF (RR = 1.03, 95% CrI = 1.00, 1.06). Taking into account error in HbA1c measurement did not appreciably affect this relationship.

We also used a less informative prior distribution that allowed for a smaller variance for measurement error. This analysis suggested that the amount of measurement error present was lower than the amount estimated in our primary analyses. Nonetheless, this smaller variance did not substantively affect our results (data not shown). In additional sensitivity analyses, we also adjusted for other potential confounders, including BMI, smoking status, comorbidities, prescription of cardiovascular medications, systolic and diastolic blood pressure, and total cholesterol. The results obtained in these sensitivity analyses were consistent with those of our primary analyses, both with and without measurement error adjustment (data not shown). Finally, our frequentist sensitivity analyses produced results that were virtually identical to our primary Bayesian analyses (without measurement error adjustment).

DISCUSSION

Our study examined the effect of glycemic control, measured by HbA1c, on the risk of incident CHF among patients with type 2 diabetes and the impact of

HbA1c measurement error on this relationship. Increasing HbA1c was associated with an increased rate of CHF in this patient population and measurement error due to both natural fluctuations in HbA1c and laboratory error had only minimal impact on this relationship. An absolute increase in HbA1c of 1% was associated with a 3% increase in CHF (RR = 1.03, 95% CrI = 1.00, 1.06), and patients with HbA1c values ≥ 10% had a CHF rate that was 17% higher than those with good glycemic control. Although patients with HbA1c values ≥ 8% may have a clinically-relevant increased rate of CHF, those with an HbA1c between 7% and 8% have a similar rate as those with HbA1c < 7%.

These results have important implications. Although a 1% increase in HbA1c was associated with an apparently modest 3% increase in the rate of CHF, this increase has important public health consequences when extended across the range of HbA1c values. The magnitude of these effects is illustrated by the 20% increase in CHF among those with HbA1c ≥10%. In addition, most treatment guidelines for type 2 diabetes focus on HbA1c treatment targets (1-5). Many of these guidelines recommend a target value of 7%, with some recommending more aggressive glycemic control (2). However, although our results are consistent with glycemic control having an effect on clinical outcomes, particularly among those with poor control, we also found no benefit to very aggressive glycemic control. Thus, our findings also highlight possible limitations of current HbA1c treatment targets when examining CHF as an outcome.

The importance of glycemic control has recently been examined in a number of large studies, some of which appear to provide inconsistent results regarding the effect of aggressive glycemic control on clinical outcomes among patients with type 2 diabetes and high cardiovascular risk (6, 7). In the ADVANCE Trial, 11,140 patients were randomized to either intensive glycemic control (target HbA1c<6.5%) or standard glycemic control (7). After a median follow-up of 5 years, patients randomized to intensive control had a decreased rate of microvascular events (hazard ratio [HR] = 0.86, 95% confidence interval [CI] = 0.77, 0.97) but a similar rate of macrovascular events (HR = 0.94, 95% CI = 0.84, 1.06), cardiovascular mortality (HR = 0.88, 95% CI = 0.74, 1.04), and all-cause mortality (HR = 0.93, 95% CI = 0.83, 1.06). In contrast, patients randomized to intensive glycemic control in the ACCORD Trial (n = 10,251), consisting of a target HbA1c < 6%, experienced increased mortality (HR = 1.22, 95% CI = 1.01, 1.46) compared with those randomized to standard glycemic control (6). Furthermore, the UKPDS 80 study, an observational 10-year follow-up of over 1,500 patients who participated in the interventional phase of the UKPDS trial, found that patients randomized to aggressive glycemic control had lower rates of all-cause mortality, myocardial infarction, and diabetes-related endpoints despite similar HbA1c values during this follow-up period (23). This 'legacy effect', linking early changes in HbA1c with long-term outcomes, remains poorly understood (24). Most recently, the Veterans Affairs Diabetes Trial (VADT) (25) examined the effects of aggressive glycemic control among over 1,700 overweight military veterans with poorly-controlled diabetes. In this

open-label trial, aggressive therapy was not associated with the time to the primary composite cardiovascular endpoint, cardiovascular death, or all-cause mortality. Our results are consistent with the ADVANCE trial and VADT and support the assertion that there is no benefit for cardiovascular outcomes to extremely aggressive glycemic control.

The role of glyemic control among those with prevalent CHF has also been investigated. In the CHARM program, a 1% increase in HbA1c was associated with an increased rate in their primary composite endpoint of cardiovascular death or worsening CHF (HR = 1.14, 95% CI = 1.07, 1.21) as well as both components of this composite endpoint (cardiovascular death: HR = 1.13, 95% CI = 1.04, 1.22; worsening CHF: HR = 1.13, 95% CI = 1.05, 1.21) (9). In secondary analyses, the authors stratified their results by the presence or absence of diabetes, which revealed that poor glycemic control had more prominent CHF effects among patients without diabetes (HR = 1.31, 95% CI = 1.14, 1.50) than among those with diabetes (HR = 1.13, 95% CI = 1.05, 1.22). The results of CHARM study demonstrate the harmful effects of poor glycemic control among patients with prevalent CHF, and these findings highlight the need to avoid the increased risk of incident CHF associated with poor glycemic control observed in the present study.

Our study has a number of strengths. First, our study involved a large, population-based cohort of patients with type 2 diabetes. Our study population was unselected and included a broad spectrum of patients, ranging from those with newly-diagnosed, diet-controlled diabetes to those with previous

complications of diabetes at very high risk of cardiovascular disease. In addition, although our study was limited to patients who underwent HbA1c testing and not all patients had the same number of HbA1c tests during the assessment period, our study involved the patients who had clinical indications for HbA1c testing. Second, the GPRD contains clinical data not available in most administrative databases. Thus, this database represents one of the few large, population-based databases in which this question could be addressed. Third, using Bayesian modeling, we adjusted for error in the measurement of HbA1c. These analyses revealed that the estimated effects of glycemic control are robust to misclassification of HbA1c due to natural fluctuations in HbA1c level and laboratory measurement error. Finally, we conducted a number of sensitivity analyses, including adjusting for additional potential confounders and increasing the variance of the potential HbA1c measurement error. These sensitivity analyses produced similar results to those of our primary analyses.

Our study also has potential limitations. First, our study is observational in nature, and our cases and controls were not well balanced for some important variables. Thus, our results may be affected by confounding. However, we adjusted for these imbalances in our multivariable models. We also conducted multiple sensitivity analyses in which we adjusted for other potential confounders, and these analyses produced estimates that were similar to those reported in our primary analysis. Although confounding may explain some of the smaller effects that were observed, it is unlike to account for the larger effects observed among those with poor and very poor glycemic control. Furthermore,

since our exposure is a biological measure rather than a medication or procedure, it is unlikely that confounding by indication had important effects on our results. Nonetheless, confounding due to unmeasured variables remains a potential limitation. Second, we excluded patients with missing HbA1c data. Although their exclusion may have affected the precision of our results, it is unlikely to have biased our effect measures as the HbA1c test results of patients who were included in this study are unlikely to result in a different beta coefficient (and therefore rate ratio) than those of patients who were excluded. Finally, although we adjusted for misclassification of HbA1c, misclassification may have also occurred when identifying patients with type 2 diabetes and at CHF diagnosis. Previous studies have assessed the accuracy of diabetes diagnoses in the GPRD, and these studies have found that these data are valid (14). Furthermore, over 90% of patients included in our study met all 3 diabetes criteria and over 98% met at least 2 of these criteria at some point during follow-up, suggesting that the number of patients included in this study who do not have type 2 diabetes is minimal. HbA1c data were collected prospectively and thus, any misclassification of CHF status would likely be non-differential, resulting in an underestimation of the effect of glycemic control on the risk of CHF.

CONCLUSIONS

Increasing HbA1c, a measure of poorer glycemic control, was associated with an increase in CHF among patients with type 2 diabetes. This relationship, which persisted after adjusting for potential misclassification of HbA1c, has

important public health consequences. Patients with poorer glycemic control have an increased incidence of CHF, a potentially fatal condition. In addition, our CHF results support the findings of previous studies that there is no cardiovascular benefit to extremely aggressive glycemic control. There remains a need to further investigate the optimal HbA1c treatment target for patients with type 2 diabetes, and these studies should include CHF among cardiovascular events investigated.

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Table 6.1. Baseline demographic and clinical characteristics of congestive heart failure cases and matched controls*.

Characteristic†	Cases (n = 2,545)	Controls (n = 23,559)
Demographic		
Male, n (%)	1,470 (57.8)	12,107 (51.4)
Age (Years) [Mean ± SD]	73.8 ± 9.2	72.8 ± 8.6
Lifestyle Variables		
Body Mass Index (kg/m^2)		
Mean ± SD	29.7 ± 6.4	28.7 ± 5.5
Missing, n (%)	109 (4.3)	627 (2.3)
Smoking, n (%)		
Current	275 (10.8)	2,622 (11.1)
Past	1,096 (43.1)	8,715 (37.0)
No	1,148 (45.1)	12,057 (51.2)
Missing	26 (1.0)	165 (0.7)
Comorbidities, n (%)		
Atrial Fibrillation	341 (13.4)	1,416 (6.0)
Cerebrovascular Disease	509 (20.0)	3,168 (13.5)
Chronic Obstructive Pulmonary Disease	233 (9.2)	1,063 (4.5)
Coronary Artery Disease	1,166 (45.8)	6,199 (26.3)
Dyslipidemia	664 (26.1)	5,821 (24.7)
Hypertension	1,620 (63.7)	13,971 (59.3)
Myocardial Infarction	478 (18.8)	2,041 (8.7)
Peripheral Vascular Disease	244 (9.6)	1,136 (4.8)
Previous Coronary Angiogram	269 (10.6)	1,209 (5.1)
Previous Coronary Artery Bypass Graft Surgery	212 (8.3)	826 (3.5)
Previous Percutaneous Coronary Intervention	92 (3.6)	463 (2.0)
Stroke	172 (6.8)	1,063 (4.5)
Renal Failure	89 (3.5)	346 (1.5)
Rheumatoid Arthritis	393 (15.4)	3,182 (13.5)
Unstable Angina (including ACS)	132 (5.2)	579 (2.5)
Diabetic Complications, n (%)		
Amputations	69 (2.7)	225 (1.0)
Blindness	47 (1.9)	263 (1.1)
Nethropathy	133 (5.2)	521 (2.2)
Neuropathy	277 (10.9)	1,589 (6.7)
Retinopathy	502 (19.7)	3,365 (14.3)
Medication Use, n (%)		
ACE Inhibitors	1,099 (43.2)	8,316 (35.3)
ARBs	254 (10.0)	1,978 (8.4)
Aspirin	1,208 (47.5)	8,483 (36.0)
Beta-Blockers	649 (25.5)	5,425 (23.0)

Characteristic[†]	Cases (n = 2,545)	Controls (n = 23,559)
Calcium Channel Blockers	967 (38.0)	6,772 (28.7)
COX-2 Inhibitors	57 (2.2)	433 (1.8)
Digoxin	246 (9.7)	896 (3.8)
Diuretics and Other Anti-Hypertensive Agents	1,275 (50.1)	7,944 (33.7)
Nitrates	600 (23.6)	2,383 (10.1)
Statins	1,021 (40.1)	8,800 (37.4)
Diabetic Medications, n (%)		
Insulin	562 (22.1)	3,363 (14.3)
Metformin	1,096 (43.1)	9,624 (40.9)
Sulfonylureas	1,041 (40.9)	9,423 (40.0)
TZDs	136 (5.3)	1,075 (4.6)
Pioglitazone	33 (1.3)	307 (1.3)
Rosiglitazone	103 (4.1)	771 (3.3)
Other Oral Antidiabetics	54 (2.1)	511 (2.2)
Duration of Diabetes (Years)		
Mean ± SD	10.1 ± 7.8	8.4 ± 7.2
Median (IQR)	8.6 (4.0, 14.1)	6.5 (3.1, 11.9)
Laboratory Tests		
Total Cholesterol Test		
Test in Previous Year, n (%)	1,678 (65.9)	15,872 (67.4)
Mean Total Cholesterol [mmol/L][‡]		
Mean ± SD	4.9 ± 1.0	5.0 ± 1.0
Median (IQR)	4.8 (4.2, 5.5)	4.9 (4.3, 5.7)
Systolic Blood Pressure		
Reading in Previous Year, n (%)	2,277 (89.5)	21,122 (89.7)
Mean Systolic Blood Pressure [mm Hg][‡]		
Mean ± SD	148.1 ± 18.1	147.1 ± 16.9
Median (IQR)	147.0 (136.0, 160.0)	146.0 (136.0, 157.4)
Diastolic Blood Pressure		
Reading in Previous Year, n (%)	2,276 (89.4)	21,118 (89.7)
Mean Diastolic Blood Pressure [mm Hg][‡]		
Mean ± SD	79.0 ± 9.2	79.3 ± 8.6
Median (IQR)	79.0 (72.7, 85.0)	80.0 (73.5, 85.0)
Follow-up Time (Years)[Mean ± SD]	3.1 ± 2.0	2.9 ± 1.9

Abbreviations: ACE: angiotensin converting enzyme; ACS: acute coronary syndrome; ARBs: angiotensin II receptor blockers; COX: Cyclooxygenase; HbA1c: hemoglobin A1c; IQR: inter-quartile range; SD: standard deviation; TZDs: thiazolidinediones

* Cases and controls were matched for practice, age (± 3 years), and index date.

[†] HbA1c was assessed in the 1 year prior to the index date. Comorbidities are based on any previous diagnosis in the GPRD occurring prior to the HbA1c assessment period. Medication data are for the 90 days prior to HbA1c assessment period, and laboratory test data are for the year prior to the HbA1c assessment period.

[‡] Among those with a test in the year prior to HbA1c assessment.

Table 6.2. Effect of glycemic control, measured by HbA1c, on the risk of congestive heart failure.

Model*	Variable	Cases (n/2545, %)	Controls (n/23,559, %)	Model 1: Crude		Model 2: Adjusted for Age, Sex, and Anti-Diabetic Medications		Model 3: Adjusted for Age, Sex, Anti-Diabetic Medications, and Duration of Diabetes	
Not Adjusted for Misclassification of HbA1c				RR	95% CrI	RR	95% CrI	RR	95% CrI
	HbA1c ≥ 10%	220 (8.6)	1,744 (7.4)	1.35	1.14, 1.59	1.18	0.99, 1.39	1.17	0.98, 1.38
	9% ≤ HbA1c < 10%	245 (9.6)	2,011 (8.5)	1.29	1.10, 1.50	1.11	0.94, 1.29	1.09	0.92, 1.27
	8% ≤ HbA1c < 9%	537 (21.1)	4,164 (17.7)	1.36	1.20, 1.53	1.19	1.05, 1.35	1.17	1.03, 1.33
	7% ≤ HbA1c < 8%	800 (31.4)	8,064 (34.2)	1.03	0.93, 1.15	0.98	0.88, 1.09	0.98	0.88, 1.09
	HbA1c < 7%	743 (29.2)	7,476 (31.7)	1.00	Reference	1.00	Reference	1.00	Reference
Adjusted for Misclassification of HbA1c									
	HbA1c ≥ 10%	220 (8.6)	1,744 (7.4)	1.35	1.11, 1.65	1.19	0.97, 1.45	1.17	0.96, 1.43
	9% ≤ HbA1c < 10%	245 (9.6)	2,011 (8.5)	1.13	0.85, 1.44	0.94	0.70, 1.21	0.92	0.69, 1.18
	8% ≤ HbA1c < 9%	537 (21.1)	4,164 (17.7)	1.54	1.32, 1.80	1.32	1.12, 1.55	1.30	1.10, 1.52
	7% ≤ HbA1c < 8%	800 (31.4)	8,064 (34.2)	0.89	0.72, 1.09	0.85	0.69, 1.04	0.85	0.69, 1.03
	HbA1c < 7%	743 (29.2)	7,476 (31.7)	1.00	Reference	1.00	Reference	1.00	Reference

Abbreviations: CrI = credible interval; HbA1c = hemoglobin A1c; RR = rate ratio.
*All models are matched on age (±3 years), practice, and calendar date.

FIGURE LEGEND

Figure 6.1. Description of HbA1c and covariate assessment.

Figure 6.2. Flow diagram of construction of database of patients with type 2 diabetes in the GPRD.

Figure 6.1

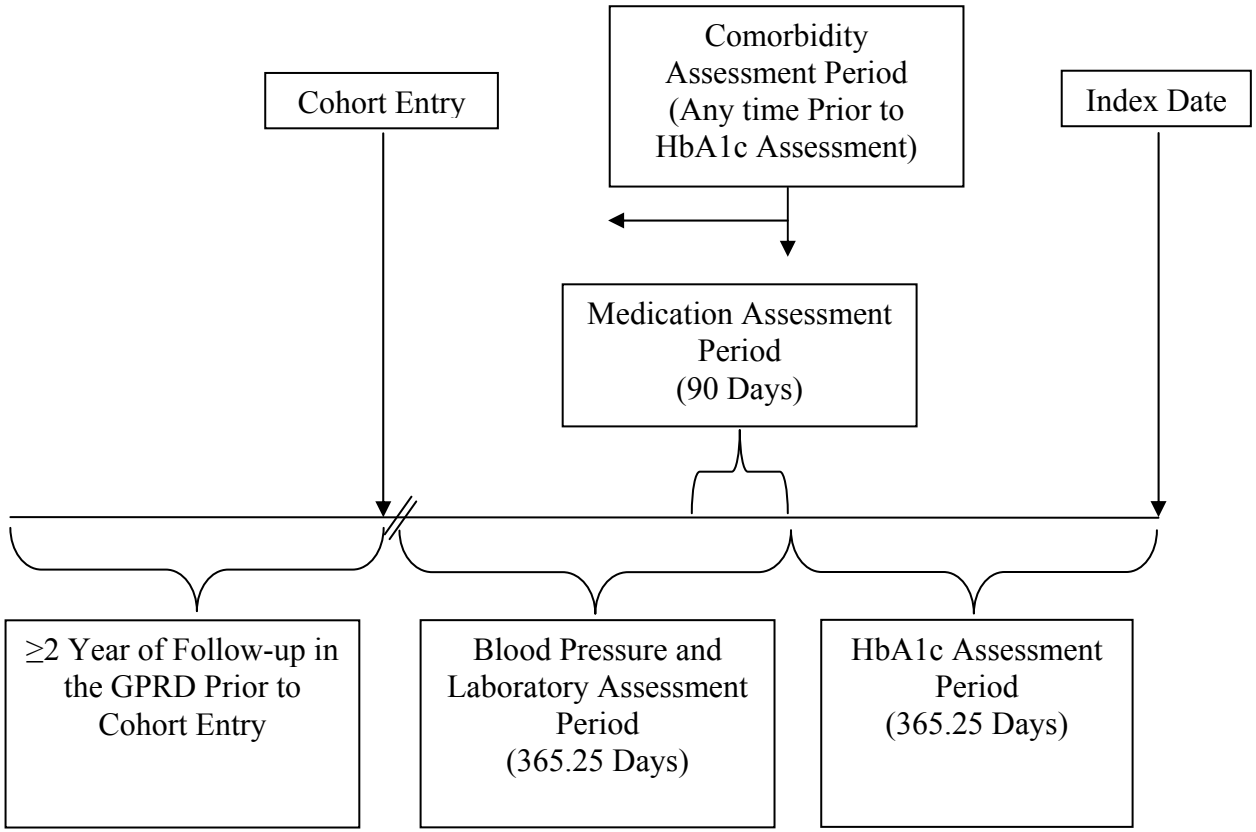
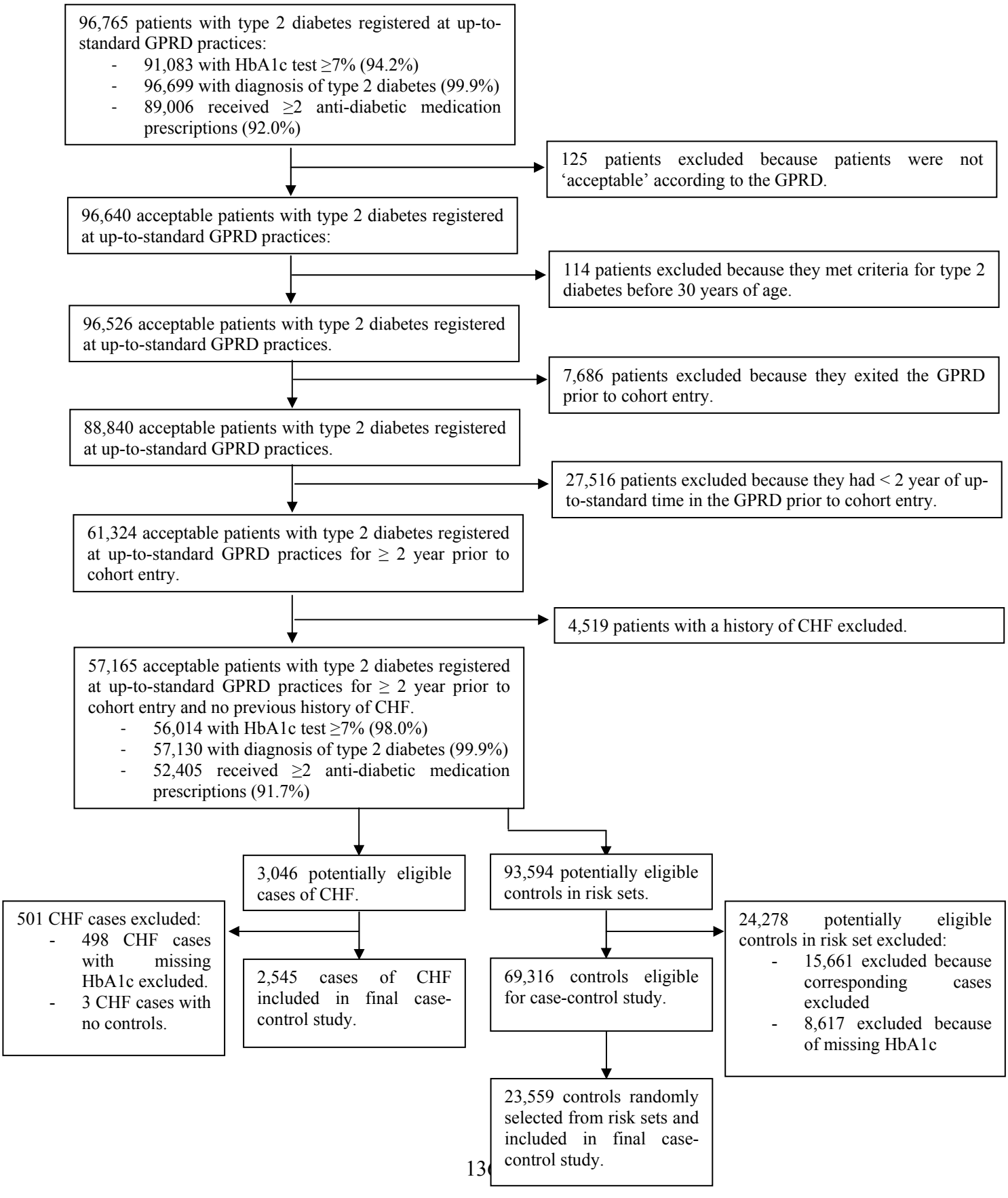

Cohort Entry
Comorbidity Assessment Period (Any time Prior to HbA1c Assessment)
Index Date
Medication Assessment Period (90 Days)
≥2 Year of Follow-up in the GPRD Prior to Cohort Entry
Blood Pressure and Laboratory Assessment Period (365.25 Days)
HbA1c Assessment Period (365.25 Days)

Figure 6.2


96,765 patients with type 2 diabetes registered at up-to-standard GPRD practices:
- 91,083 with HbA1c test ≥7% (94.2%)
- 96,699 with diagnosis of type 2 diabetes (99.9%)
- 89,006 received ≥2 anti-diabetic medication prescriptions (92.0%)
125 patients excluded because patients were not 'acceptable' according to the GPRD.
96,640 acceptable patients with type 2 diabetes registered at up-to-standard GPRD practices:
114 patients excluded because they met criteria for type 2 diabetes before 30 years of age.
96,526 acceptable patients with type 2 diabetes registered at up-to-standard GPRD practices.
7,686 patients excluded because they exited the GPRD prior to cohort entry.
88,840 acceptable patients with type 2 diabetes registered at up-to-standard GPRD practices.
27,516 patients excluded because they had < 2 year of up-to-standard time in the GPRD prior to cohort entry.
61,324 acceptable patients with type 2 diabetes registered at up-to-standard GPRD practices for ≥ 2 year prior to cohort entry.
4,519 patients with a history of CHF excluded.
57,165 acceptable patients with type 2 diabetes registered at up-to-standard GPRD practices for ≥ 2 year prior to cohort entry and no previous history of CHF.
- 56,014 with HbA1c test ≥7% (98.0%)
- 57,130 with diagnosis of type 2 diabetes (99.9%)
- 52,405 received ≥2 anti-diabetic medication prescriptions (91.7%)
3,046 potentially eligible cases of CHF.
93,594 potentially eligible controls in risk sets.
501 CHF cases excluded:
- 498 CHF cases with missing HbA1c excluded.
- 3 CHF cases with no controls.
2,545 cases of CHF included in final case-control study.
69,316 controls eligible for case-control study.
24,278 potentially eligible controls in risk set excluded:
- 15,661 excluded because corresponding cases excluded
- 8,617 excluded because of missing HbA1c
23,559 controls randomly selected from risk sets and included in final case-control study.

6.3 Supplementary Material

In the preceding manuscript, the results of the primary analyses of this study were presented. Although general conclusions of sensitivity analyses were presented in the manuscript, a detailed description of the results of these analyses were not included due to space constraints. These analyses and their corresponding results are described in detail below. In addition, the results of exploratory analyses that examined the potential presence of a threshold effect are provided.

6.3.1 Sensitivity Analyses

Additional analyses were conducted to examine the effects of other potential confounders. These analyses included unadjusted conditional logistic regression models to identify risk factors for CHF, the outcome of interest. These analyses revealed that many of the variables presented in Table 6.1 are risk factors for CHF in this patient population (Table 6.3). To identify which of these variables were also associated with HbA1c, our exposure, bivariate analyses were conducted; box plots were used to visually assess the association between HbA1c and binary or categorical variables (Figure 6.3), and correlation matrices were used to examine the association between HbA1c and continuous variables (Table 6.4). Although over 35 box plots were constructed, only 3 have been included in this supplementary material for the sake of brevity. The remaining box plots are available upon request. These bivariate analyses revealed that only prescription of anti-diabetic medications prior to the HbA1c assessment period were associated with HbA1c test values, and analyses adjusting for these variables were

presented in the accompanying manuscript. Nonetheless, regression analyses adjusting for other potential confounders were conducted (Table 6.5). Adjustment for age, sex, lifestyle variables (e.g., smoking, BMI), comorbidities, medication prescriptions, complications of diabetes, systolic and diastolic blood pressure, and total cholesterol did not appreciably shift our point estimates, further underscoring that these variables were not acting as important confounders in this study.

In additional sensitivity analyses, the prior density for the standard deviation of HbA1c measurement error was changed from uniform (0.45, 0.50) to uniform (0.10, 0.50). These analyses indicated that, in these data, the HbA1c measurement error is likely less that that reported elsewhere in the literature (172). Despite this finding, our primary analyses employed the higher valued prior density obtained by summarizing data available from the literature, as greater HbA1c error represents a more conservative assumption. Both analyses produced similar results, and overall conclusions are consistent with those from analyses that do not account for HbA1c measurement error.

In measurement error analyses, the estimated true (i.e., measurement error adjusted) HbA1c values of a small number of cases and controls were tracked to ensure that our measurement error adjustments were shifting observed HbA1c values towards the expected population distribution. These data illustrate that observed data are being shifted towards a mean value of 7.75, the expected mean of the population (Table 6.6).

Despite care taken in assessing convergence of our Gibbs sampler chains, our primary analyses were repeated using frequentist methods in additional

sensitivity analyses to ensure convergence. When not adjusting for measurement error, the results from Bayesian and frequentist analyses should be very similar. These analyses, which involved conditional logistic regression analyses conducted in SAS (Version 9.1.3. Cary, NC), did not include measurement error adjustment, which cannot be done using a frequentist approach. These sensitivity analyses produced results that were virtually identical to those of the primary Bayesian analysis (Table 6.7).

6.3.2 Threshold Analyses

Exploratory analyses were conducted to examine the potential presence of a threshold effect of HbA1c on the risk of CHF. In these analyses, HbA1c was categorized into 15 strata (<6.5%, 6.5%-7%, 7%-7.5%, 7.5%-8%, 8%-8.5%, 8.5%-9%, 9%-9.5%, 9.5%-10%, 10%-10.5%, 10.5%-11%, 11%-11.5%, 11.5%-12%, 12%-12.5%, 12.5%-13%, and ≥13%). A total of 14 indicator variables (<6.5% served as the reference group) were included in our conditional logistic model, which adjusted for age, sex, prescription of anti-diabetic medications, and duration of diabetes. This analysis did not identify any obvious threshold effect (Figure 6.4).

Table 6.3 Univariate predictors of congestive heart failure among patients with type 2 diabetes.

Variable	Rate Ratio	95% CI
Male	1.33	1.22, 1.44
Age (years)	1.07	1.05, 1.10
Smoking		
Current	1.17	1.02, 1.35
Past	1.39	1.27, 1.52
Never	1.00	Reference
BMI (kg/m^2)	1.04	1.03, 1.05
Atrial Fibrillation	2.36	2.07, 2.69
Cerebrovascular Disease	1.59	1.43, 1.77
COPD	2.13	1.83, 2.48
Coronary Artery Disease	2.45	2.25, 2.67
Dyslipidemia	1.14	1.03, 1.26
Hypertension	1.24	1.14, 1.35
Myocardial Infarction	2.47	2.21, 2.75
Peripheral Vascular Disease	2.13	1.84, 2.47
Previous CABG	2.59	2.21, 3.04
Previous Coronary Angiogram	2.36	2.05, 2.72
Previous PCI	1.97	1.57, 2.48
Renal Failure	2.47	1.94, 3.14
Rheumatoid Arthritis	1.17	1.04, 1.32
Stroke	1.55	1.31, 1.84
Unstable Angina	2.26	1.86, 2.76
ACE Inhibitors	1.47	1.35, 1.60
ARBs	1.27	1.10, 1.47
Aspirin	1.69	1.55, 1.84
Beta-Blockers	1.17	1.06, 1.29
Calcium Channel Blockers	1.56	1.43, 1.70
COX-2 Inhibitors	1.27	0.96, 1.69
Digoxin	2.59	2.23, 3.02
Diuretics or Other Anti-Hypertensive Agents	2.01	1.85, 2.20
Nitrates	2.8	2.52, 3.10
Statins	1.24	1.12, 1.36
Diastolic Blood Pressure (mmHg) ‡	1.00	0.99, 1.00
Systolic Blood Pressure (mmHg) ‡	1.00	1.00, 1.01
Total Cholesterol (mmol/L)‡	0.85	0.80, 0.90
Insulin	1.78	1.61, 1.97
Metformin	1.14	1.05, 1.24
Other Oral Anti-Diabetic Agents	1.02	0.76, 1.35
Pioglitazone	1.03	0.71, 1.49
Rosiglitazone	1.31	1.05, 1.62
Sulfonylureas	1.02	0.94, 1.11
Duration of Diabetes (years)	1.03	1.03, 1.04

Abbreviations: ACE: angiotensin converting enzyme; ARBs: angiotensin II receptor blockers; BMI: body mass index; CABG: coronary artery bypass graft

surgery; COPD: chronic obstructive pulmonary disease; COX: Cyclooxygenase; PCI: percutaneous coronary intervention.
*All models are univariate but matched on age, practice, and index date.
‡ Among those with a test in the previous year.

Table 6.4 Correlation matrix for continuous potential confounders and HbA1c among patients with type 2 diabetes.

	HbA1c (%)	Age (Years)	BMI (kg/m^2)	Diastolic Blood Pressure (mmHg)	Systolic Blood Pressure (mmHg)	Total Cholesterol (mmol/L)	Duration of Diabetes (Years)
HbA1c (%)	1.00	-0.13	0.08	0.07	0.05	0.09	0.13
Age (Years)	-0.13	1.00	-0.30	-0.18	0.14	-0.04	0.14
BMI (kg/m^2)	0.08	-0.30	1.00	0.15	0.03	-0.0006	-0.09
Diastolic Blood Pressure (mmHg)	0.07	-0.18	0.15	1.00	0.19	0.49	-0.17
Systolic Blood Pressure (mmHg)	0.05	0.14	0.03	0.19	1.00	0.15	0.04
Total Cholesterol (mmol/L)	0.09	-0.04	-0.0006	0.49	0.15	1.00	-0.11
Duration of Diabetes (Years)	0.13	0.14	-0.09	-0.17	0.04	-0.11	1.00

Table 6.5. Additional conditional logistic regression analyses examining effect of glycemic control, measured by HbA1c, on the risk of congestive heart failure.

Model*	Variable	Cases (n/2,545, %)	Controls (n/23,559, %)	Bayesian Conditional Logistic Regression Analysis			
				Not Adjusted for Misclassification of HbA1c		Adjusted for Misclassification of HbA1c	
				RR	95% CrI	RR	95% CrI
1	HbA1c≥10%	220 (8.6)	1,744 (7.4)	1.35	1.14, 1.59	1.35	1.11, 1.65
	9%≤ HbA1c<10%	245 (9.6)	2,011 (8.5)	1.29	1.10, 1.50	1.13	0.85, 1.44
	8%≤ HbA1c<9%	537 (21.1)	4,164 (17.7)	1.36	1.20, 1.53	1.54	1.32, 1.80
	7%≤ HbA1c<8%	800 (31.4)	8,064 (34.2)	1.03	0.93, 1.15	0.89	0.72, 1.09
	HbA1c<7%	743 (29.2)	7,476 (31.7)	1.00	Reference	1.00	Reference
2	HbA1c≥10%	220 (8.6)	1,744 (7.4)	1.38	1.17, 1.62	1.40	1.14, 1.69
	9%≤ HbA1c<10%	245 (9.6)	2,011 (8.5)	1.30	1.12, 1.53	1.14	0.86, 1.46
	8%≤ HbA1c<9%	537 (21.1)	4,164 (17.7)	1.36	1.21, 1.53	1.55	1.32, 1.81
	7%≤ HbA1c<8%	800 (31.4)	8,064 (34.2)	1.03	0.93, 1.15	0.90	0.73, 1.10
	HbA1c<7%	743 (29.2)	7,476 (31.7)	1.00	Reference	1.00	Reference
3†	HbA1c≥10%	217 (8.6)	1,713 (7.4)	1.39	1.17, 1.64	1.40	1.14, 1.71
	9%≤ HbA1c<10%	244 (9.7)	1,983 (8.5)	1.31	1.12, 1.54	1.17	0.89, 1.51
	8%≤ HbA1c<9%	531 (21.1)	4,100 (17.7)	1.36	1.21, 1.54	1.55	1.32, 1.81
	7%≤ HbA1c<8%	792 (31.5)	7,958 (34.3)	1.03	0.93, 1.16	0.91	0.74, 1.12
	HbA1c<7%	734 (29.2)	7,453 (32.1)	1.00	Reference	1.00	Reference

Model*	Variable	Cases (n/2,545, %)	Controls (n/23,559, %)	Bayesian Conditional Logistic Regression Analysis			
				Not Adjusted for Misclassification of HbA1c		Adjusted for Misclassification of HbA1c	
				RR	95% CrI	RR	95% CrI
4‡	HbA1c≥10%	206 (8.5)	1,605 (7.3)	1.30	1.09, 1.53	1.31	1.06, 1.61
	9%≤ HbA1c<10%	234 (9.7)	1,889 (8.5)	1.25	1.06, 1.46	1.07	0.81, 1.39
	8%≤ HbA1c<9%	510 (21.0)	3,922 (17.7)	1.30	1.15, 1.47	1.49	1.26, 1.74
	7%≤ HbA1c<8%	764 (31.4)	7,615 (34.4)	1.00	0.90, 1.12	0.87	0.70, 1.06
	HbA1c<7%	719 (29.6)	7,100 (32.1)	1.00	Reference	1.00	Reference
5§	HbA1c≥10%	206 (8.5)	1,594 (7.2)	1.31	1.10, 1.54	1.32	1.07, 1.62
	9%≤ HbA1c<10%	234 (9.6)	1,880 (8.5)	1.25	1.07, 1.46	1.09	0.81, 1.41
	8%≤ HbA1c<9%	507 (20.9)	3,904 (17.7)	1.30	1.15, 1.47	1.49	1.26, 1.74
	7%≤ HbA1c<8%	763 (31.5)	7,579 (34.4)	1.01	0.90, 1.12	0.88	0.71, 1.08
	HbA1c<7%	716 (29.5)	7,062 (32.1)	1.00	Reference	1.00	Reference
6§	HbA1c≥10%	206 (8.5)	1,594 (7.2)	1.30	1.09, 1.55	1.33	1.08, 1.64
	9%≤ HbA1c<10%	234 (9.6)	1,880 (8.5)	1.22	1.03, 1.43	1.00	0.74, 1.31
	8%≤ HbA1c<9%	507 (20.9)	3,904 (17.7)	1.29	1.14, 1.47	1.50	1.26, 1.76
	7%≤ HbA1c<8%	763 (31.5)	7,579 (34.4)	1.00	0.89, 1.11	0.84	0.68, 1.04
	HbA1c<7%	716 (29.5)	7,062 (32.1)	1.00	Reference	1.00	Reference
7§	HbA1c≥10%	206 (8.5)	1,594 (7.2)	1.30	1.10, 1.56	1.35	1.09, 1.67
	9%≤ HbA1c<10%	234 (9.6)	1,880 (8.5)	1.21	1.03, 1.43	0.98	0.71, 1.29

Model*	Variable	Cases (n/2,545, %)	Controls (n/23,559, %)	Bayesian Conditional Logistic Regression Analysis			
				Not Adjusted for Misclassification of HbA1c		Adjusted for Misclassification of HbA1c	
				RR	95% CrI	RR	95% CrI
	8%≤ HbA1c<9%	507 (20.9)	3,904 (17.7)	1.27	1.12, 1.45	1.48	1.25, 1.74
	7%≤ HbA1c<8%	763 (31.5)	7,579 (34.4)	0.99	0.88, 1.11	0.83	0.66, 1.03
	HbA1c<7%	716 (29.5)	7,062 (32.1)	1.00	Reference	1.00	Reference
8§	HbA1c≥10%	206 (8.5)	1,594 (7.2)	1.17	0.98, 1.40	1.21	0.98, 1.50
	9%≤ HbA1c<10%	234 (9.6)	1,880 (8.5)	1.08	0.91, 1.28	0.84	0.61, 1.12
	8%≤ HbA1c<9%	507 (20.9)	3,904 (17.7)	1.16	1.02, 1.33	1.33	1.11, 1.58
	7%≤ HbA1c<8%	763 (31.5)	7,579 (34.4)	0.95	0.85, 1.07	0.80	0.64, 0.98
	HbA1c<7%	716 (29.5)	7,062 (32.1)	1.00	Reference	1.00	Reference
9§	HbA1c≥10%	206 (8.5)	1,594 (7.2)	1.13	0.94, 1.36	1.18	0.95, 1.46
	9%≤ HbA1c<10%	234 (9.6)	1,880 (8.5)	1.05	0.88, 1.25	0.82	0.60, 1.10
	8%≤ HbA1c<9%	507 (20.9)	3,904 (17.7)	1.14	1.00, 1.30	1.30	1.09, 1.54
	7%≤ HbA1c<8%	763 (31.5)	7,579 (34.4)	0.95	0.85, 1.07	0.81	0.64, 1.00
	HbA1c<7%	716 (29.5)	7,062 (32.1)	1.00	Reference	1.00	Reference
10£	HbA1c≥10%	151 (6.9)	764 (5.6)	1.08	0.88, 1.34	1.08	0.83, 1.39
	9%≤ HbA1c<10%	204 (9.3)	1,000 (7.3)	1.09	0.91, 1.32	0.94	0.66, 1.29
	8%≤ HbA1c<9%	445 (20.2)	2,329 (16.9)	1.14	0.99, 1.32	1.29	1.05, 1.57
	7%≤ HbA1c<8%	713 (32.4)	4,942 (35.9)	0.94	0.83, 1.05	0.84	0.66, 1.05
	HbA1c<7%	690 (31.3)	4,717 (34.3)	1.00	Reference	1.00	Reference

*All models are matched on age, practice, and index date. The models are adjusted for the following variables: Model 1: No adjustment; Model 2: Age and Sex; Model 3: Age, Sex, Smoking[†]; Model 4: Age, Sex, BMI[‡]; Model 5: Age, Sex, BMI, Smoking[†,‡]; Model 6: Age, Sex, BMI, Smoking, Diagnoses[†,‡]; Model 7: Age, Sex, BMI, Smoking, Diagnoses, Non-Diabetic Medications[†,‡]; Model 8: Age, Sex, BMI, Smoking, Diagnoses, Non-Diabetic and Diabetic Medications[†,‡]; Model 9: Age, Sex, BMI, Smoking, Diagnoses, Non-Diabetic and Diabetic Medications, and Duration of Diabetes[†,‡]; Model 10: Age, Sex, BMI, Smoking, Diagnoses, Non-Diabetic and Diabetic Medications, Duration of Diabetes, Total Cholesterol, and Systolic and Diastolic Blood Pressure.[†,‡,§];

† Patients with missing smoking data were excluded from this analysis (27 cases and 352 controls).

‡ Patients with missing BMI data were excluded from this analysis (112 cases and 1,428 controls).

§ Patients with missing smoking or BMI data were excluded from this analysis (119 cases and 1,540 controls)

£Patients with missing smoking, BMI, total cholesterol, systolic blood pressure, or diastolic blood pressure data were excluded from this analysis (342 cases and 9,807 controls).

Table 6.6. Observed and estimated true (measurement error adjusted) HbA1c test values for a sample of CHF cases and controls.

Matched Set Number	Case/Control Status	Observed HbA1c (%)	Estimated True HbA1c (Adjusted for Measurement Error)(%)
1	Case	7.625	7.632
1	Control #1	7.3	7.308
10	Case	9.1	7.485
10	Control #1	6.15	6.945
100	Case	6.4	6.485
100	Control #1	5.95	6.04
200	Case	6.95	6.995
200	Control #1	8.9	8.85
250	Case	11.66	11.47
250	Control #1	8.075	8.064

Table 6.7 Frequentist analyses examining the effect of glycemic control, measured by HbA1c, on the risk of congestive heart failure*.

Variable	Cases (n/2545)	Controls (n/23,559)	Model 1: Crude		Model 2: Adjusted for Age, Sex, and Diabetic Medication		Model 3: Adjusted for Age, Sex, Diabetic Medication, and Duration of Diabetes	
			RR	95% CI	RR	95% CI	RR	95% CI
HbA1c ≥ 10%	220 (8.6)	1,744 (7.4)	1.35	1.14, 1.59	1.18	1.00, 1.40	1.17	0.99, 1.38
9% ≤ HbA1c < 10%	245 (9.6)	2,011 (8.5)	1.29	1.11, 1.51	1.11	0.94, 1.30	1.09	0.93, 1.28
8% ≤ HbA1c < 9%	537 (21.1)	4,164 (17.7)	1.36	1.20, 1.53	1.19	1.05, 1.35	1.18	1.04, 1.33
7% ≤ HbA1c < 8%	800 (31.4)	8,064 (34.2)	1.03	0.92, 1.15	0.98	0.88, 1.09	0.98	0.88, 1.09
HbA1c < 7%	743 (29.2)	7,476 (31.7)	1.00	Reference	1.00	Reference	1.00	Reference

Abbreviations: CI = confidence interval; HbA1c = hemoglobin A1c; RR = rate ratio.
*All models are matched on age (±3 years), practice, and calendar date.

FIGURE LEGEND

Figure 6.3 Box plots describing association between HbA1c and potential confounders. a. Male sex; b. Prescription of insulin; c. History of myocardial infarction.

Figure 6.4 Effect of HbA1c on the risk of congestive heart failure among patients with type 2 diabetes. Error bars represent 95% confidence intervals. Cases and controls were matched on age, practice, and calendar date, and analyses were adjusted for age, sex, prescription of anti-diabetic medications, and duration of diabetes.

FIGURES

Figure 6.3a.

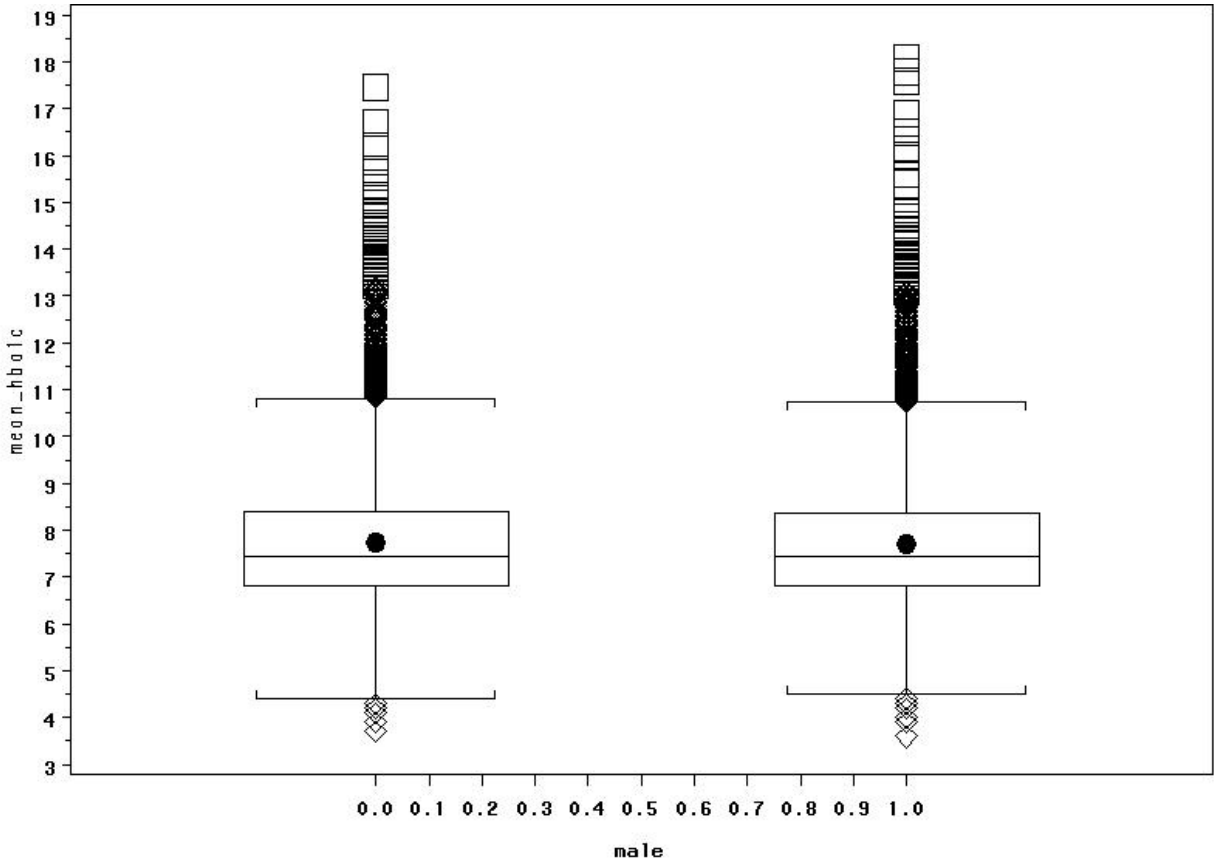
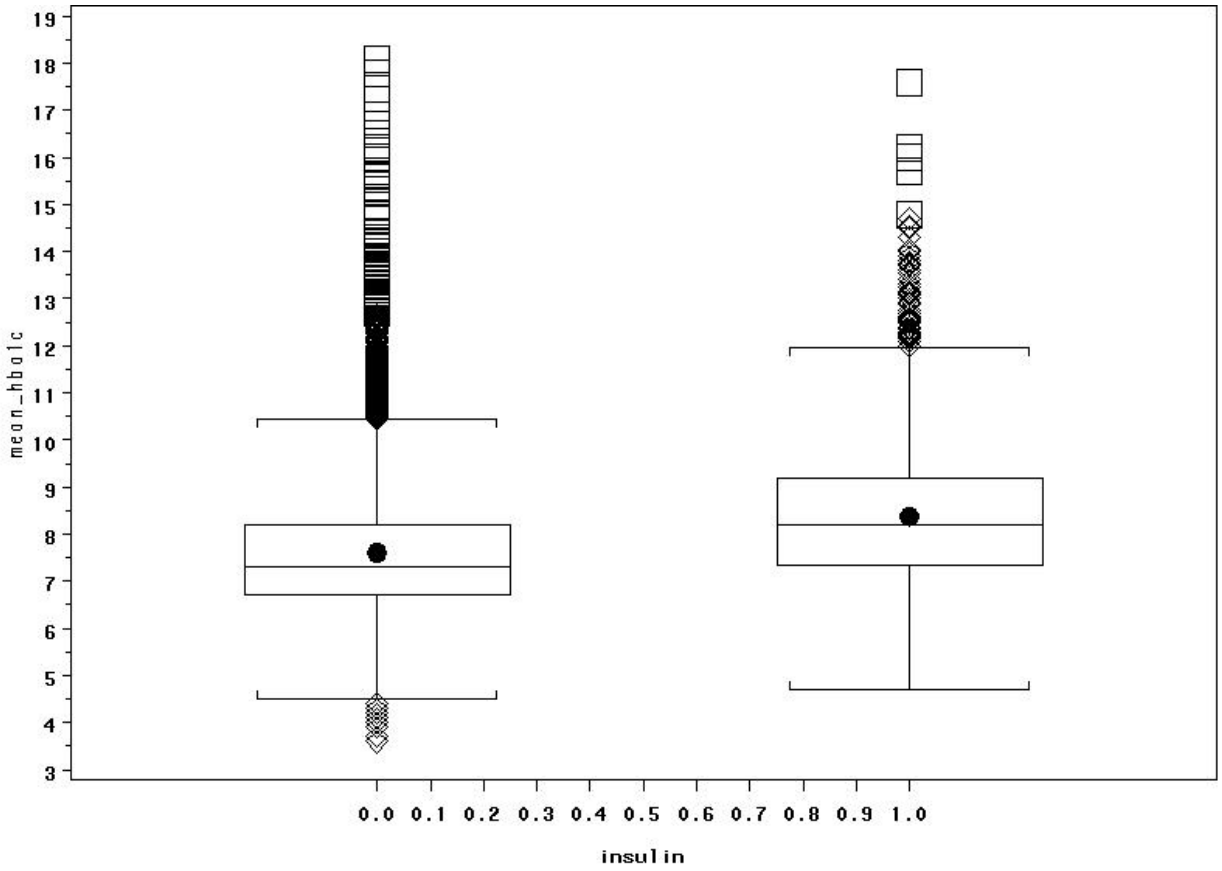


Figure 6.3b.


mean_hbalc
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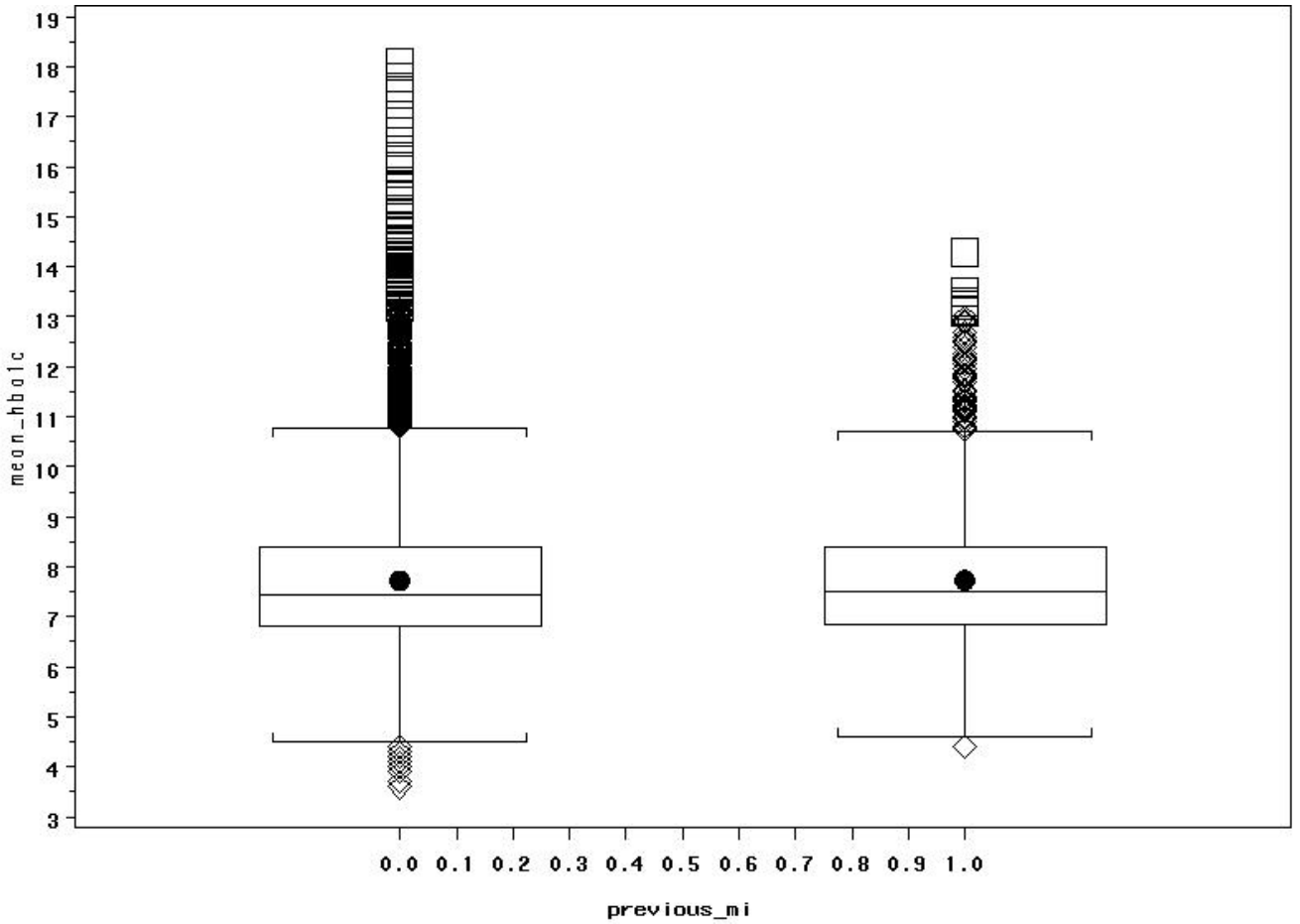
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
insulin

Figure 6.3c.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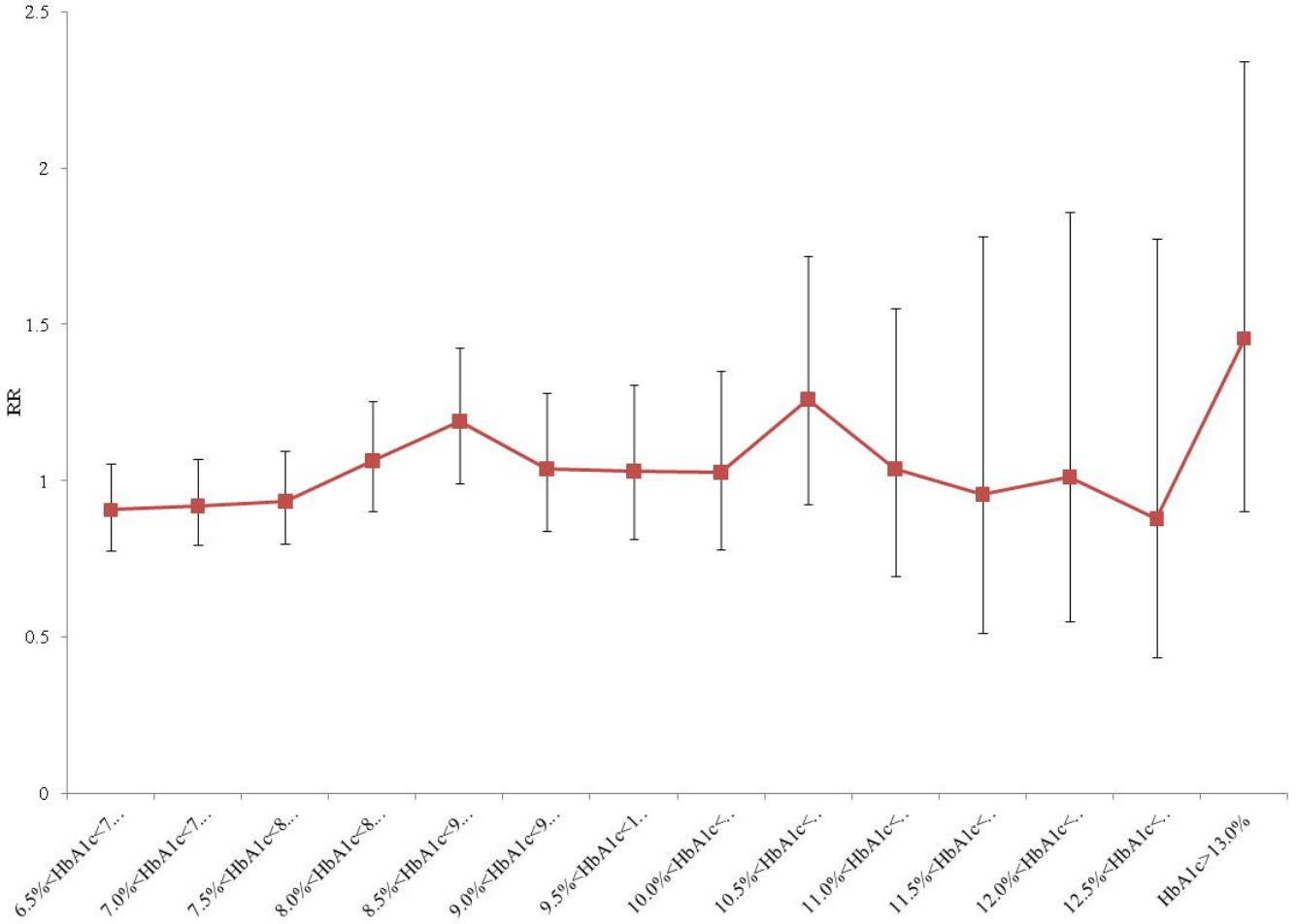
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
previous_mi

Figure 6.4


2.5
2
1.5
1
0.5
0
RR
6.5%<HbA1c<7...
7.0%<HbA1c<7...
7.5%<HbA1c<8...
8.0%<HbA1c<8...
8.5%<HbA1c<9...
9.0%<HbA1c<9...
9.5%<HbA1c<1...
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11.5%<HbA1c<...
12.0%<HbA1c<...
12.5%<HbA1c<...
HbA1c>13.0%

CHAPTER 7 – Thiazolidinediones and the Risk of Congestive Heart Failure

7.1 Preface to Manuscript #3

TZDs received regulatory approval on the basis that they improve glycemic control (174). Previous meta-analyses suggest that TZDs decrease HbA1c by approximately 1% (47, 57, 58). Although the effects of glycemic control on clinical outcomes are controversial (15, 17, 131, 132, 138, 140, 141, 175-177), our study delineated these effects with respect to CHF (Chapter 6). There was no evidence of benefit to very aggressive glycemic control; however, poor control was associated with an increased rate of CHF. On average, a 1% decrease in HbA1c (the expected treatment benefit of TZD therapy) was associated with a 3% decrease in the rate of CHF.

Despite these apparent beneficial effects, recent clinical trials and meta-analyses have linked TZDs to a potential increase in the risk of CHF (39, 40, 53, 70, 71, 97, 98). Patients participating in clinical trials are inherently different than those seen in everyday practice (119) and, as a result, these results are of questionable generalizability. Furthermore, previous observational studies examining the effect of TZDs on the risk of CHF were conducted in restricted populations (88, 127) and included patients with a history of CHF as part of their study populations (88, 128). The effect of TZDs on the risk of incident CHF in a real world setting therefore remains unknown. In this chapter, a population-based nested case-control study addresses this issue.

Thiazolidinediones and the Risk of Incident Congestive Heart Failure among Patients with Type 2 Diabetes Mellitus

Running Title: TZDs and CHF

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Authors Contributions: KBF and JMB conceived of the study idea, and JMB, JFB, LJ, and KBF contributed to the design of the study. KBF conducted the statistical analyses and drafted the manuscript. SS contributed to the acquisition of data. All authors were involved in revising the article for important intellectual content, interpreting the data, and approved the final version to be published.

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Competing Interests: None.

Keywords: Congestive Heart Failure, Thiazolidinediones, Pioglitazone, Rosiglitazone, Type 2 Diabetes Mellitus.

ABSTRACT

Background: Recent clinical trials suggest that thiazolidinediones (TZDs) may increase the risk of congestive heart failure (CHF). However, the effect of TZDs on the risk of incident CHF in unselected populations has not been thoroughly investigated.

Methods: Using data from the United Kingdom's General Practice Research Database, we conducted a case-control study within a population-based cohort of patients with type 2 diabetes. Cases were identified by a clinical diagnosis of incident CHF between January 1st, 2000 and December 31st, 2006 and were then classified as possible or probable cases using prescription data. Up to 10 controls were matched on age, physician practice, and calendar date. A drug exposure window of 90 days was used in the primary analysis, which compared patients prescribed TZDs to those with no prescriptions for anti-diabetic medications. Data were analyzed by conditional logistic regression.

Results: We identified 3,405 incident cases (2,632 probable and 773 possible) of CHF and 32,042 corresponding controls. TZDs were prescribed in 6.4% of cases and 6.1% of controls. We found no definitive evidence that TZDs are associated with an increased incident rate of possible or probable CHF but are unable to exclude a small but clinically meaningful increase in the rate of CHF (adjusted rate ratio (RR) = 1.19, 95% CI = 0.96, 1.48 and adjusted RR = 1.15, 95% CI = 0.89, 1.47, respectively). In a secondary sensitivity analysis using a 30-day exposure-window, similar results were observed (adjusted RR = 1.28, 95% CI =

1.01, 1.65). Compared with metformin monotherapy, TZD therapy was associated with an increased rate of CHF (RR = 1.38, 95% CI = 1.12, 1.71).

Conclusions: Given the totality of the evidence from this and previous studies, the probability of an increased risk for CHF with these agents remains high. However, any increase in CHF risk associated with TZDs may be lower than previously reported.

INTRODUCTION

Data from recent clinical trials and meta-analyses suggest that thiazolidinediones (TZDs) may increase the risk of congestive heart failure (CHF) (1-6). However, these studies included highly-selected patient populations with limited follow-up time and only a small number of CHF cases. For example, in the DREAM trial of 5,269 patients with impaired glucose tolerance or impaired fasting glucose (3), rosiglitazone-treated patients had a 7-fold increase in CHF (hazard ratio [HR] = 7.0, 95% confidence interval [CI] = (1.60, 30.9) but with only 16 cases, definitive conclusions are obviously impossible. Patients seen in routine practice also typically have more comorbidities than those who participate in clinical trials, and the effect of TZDs on the risk of incident CHF in the general population of patients with type 2 diabetes has not been thoroughly investigated. We therefore examined the effect of TZDs on the risk of incident CHF using a case-control study nested within a large, representative, population-based cohort.

METHODS

Data Source

The General Practice Research Database (GPRD) is a clinical database that has been used extensively in pharmacoepidemiologic studies, serving as the data source for over 600 peer-reviewed publications (7), including several studies of type 2 diabetes (8-10) and CHF (11-13). The GPRD links medical records from over 400 general practices in the United Kingdom (U.K.), forming a demographically-representative sample of 5% of the U.K. population (14) and

containing over 39 million person-years of follow-up data (15). The GPRD contains detailed information regarding demographic characteristics, clinical diagnoses, and prescriptions issued. In addition, unlike most administrative databases, GPRD data include clinical information such as body mass index (BMI), smoking status, and laboratory test results. The availability of hemoglobin A1c (HbA1c), which serves as a primary parameter of most diabetes treatment guidelines (16), makes the GPRD particularly well suited for studies of patients with type 2 diabetes. A number of quality assurance protocols have also been implemented in the GPRD, ensuring that these data are of valid (17). Previous studies have examined the validity of diabetes diagnoses. For example, Pringle and colleagues analyzed the GPRD records of 4 GPRD practices (18). The investigators found that a diagnosis of type 2 diabetes had a sensitivity of 97%. In addition, the same investigators compared the electronic records to the physical patient charts and found that 82% of all diagnoses and 100% of all prescriptions were captured in the computer records.

Study Population

We created a cohort of patients with type 2 diabetes and no previous diagnosis of CHF. The presence of type 2 diabetes was defined as the presence of any of the following 3 criteria in the patients electronic medical record: 1) a National Health Service (NHS) Clinical Term (commonly called READ) (19, 20) or Oxford Medical Information System (OXMIS) code indicating clinical diagnosis of type 2 diabetes (14); 2) an HbA1c test result $\geq$ 7%; or 3) $\geq$ 2 prescriptions for an anti-diabetic medication. Cohort entry was defined as the

latest of the following: the date at which the patient met our criteria for type 2 diabetes, the date at which the medical practice was considered to be "up-to-standard" based on GPRD data validity criteria, or the patient's registration date at the GPRD practice. If prescriptions of anti-diabetic medications were used to define cohort entry, we used the date of the second prescription as the date of cohort entry. For patients who met these criteria prior to the year 2000, we used January 1st, 2000 as the date of cohort entry. We did not consider person-time prior to this date as neither rosiglitazone or pioglitazone were available prior to 2000 (21). We restricted our cohort to those who met the criteria for cohort entry before December 31st, 2005. We excluded all patients with type 1 diabetes and those diagnosed with diabetes at age < 30 years as these had a high probability of being type 1. We also excluded all patients with < 1 year of follow-up history in the GPRD before cohort entry and those with a previous diagnosis of CHF. Due to concerns regarding data validity, patients who were classified as not 'acceptable' according to the GPRD as well as those from practices that were not 'up-to-standard' were excluded. Patients were followed until the date of diagnosis of CHF, the date at which they left the medical practice, the date of the last data upload from the practice to the GPRD, or December 31st, 2006, whichever came first.

Case-Control Selection

From our cohort of patients with type 2 diabetes, we identified all patients with a first clinical diagnosis of CHF. From these patients, two case series were constructed. In the first, we included all patients with a clinical diagnosis of CHF

and refer to these as possible cases. We also used a more restricted probable case definition by limiting our analysis to cases with a clinical diagnosis of CHF and either a) prescriptions for ≥ 2 of following medication classes in the 90 days after CHF diagnosis: digoxin, ACE inhibitors/angiotensin receptor blockers (ARBs), and other anti-hypertensive agents including diuretics; or b) who died of any cause in the 90 days following CHF diagnosis. For both case series, eligible controls were matched on calendar date, GPRD practice, and birth year (caliper of 3 years), and up to 10 controls per case were randomly selected from each risk set. Index date was defined as the date of CHF diagnosis for each CHF case and as the corresponding calendar date for matched controls.

Exposure Assessment

Diabetic medications were classified as TZDs, insulin, metformin, sulfonylureas, or other. Diabetic patients not prescribed 1 of these classes of medications were categorized as unexposed. Exposure was defined as any prescription for a given medication in the 90 days preceding the index date. The 90-day exposure window was selected a priori because this was felt to be the etiologically pertinent time window. Medications were then grouped into the following mutually-exclusive exposure categories: TZDs (with or without non-TZD oral anti-diabetics), metformin monotherapy, sulfonylurea monotherapy, other monotherapy, non-TZD combination oral therapy, any insulin, and unexposed.

Covariates

Covariate data including demographic (e.g., birth year, sex) and clinical characteristics (e.g., smoking status, BMI) were also extracted from the GPRD. We categorized smoking status as current, past, or never smoker. Comorbidities and diabetic complications were defined using READ and OXMIS codes as any clinical diagnosis or referral occurring any time before the index date. Laboratory covariates, including HbA1c and total cholesterol, and systolic and diastolic blood pressure were defined using the mean value of tests from the year preceding the index date. Finally, we used the time in years between when a patient met our diabetes definition and the index date as a proxy for duration of diabetes.

Statistical Analyses

Our time-matched nested case-control study was analyzed using conditional logistic regression, with the estimated odds ratio approximating the rate ratio (RR). Anti-diabetic medications were assessed as described above with unexposed as the reference category since the CHF effects of other anti-diabetic medications remain poorly delineated. The use of this reference category also facilitates comparison of our analyses with those of clinical trials, where patients are typically randomized to TZD or placebo. Three models were created to examine the effect of TZDs on the risk of CHF for each case series: 1) a 'crude' model; 2) an adjusted model that included demographic and clinical characteristics, comorbidities, medication prescriptions, diabetic complications, systolic and diastolic blood pressure, total cholesterol, and duration of diabetes;

and 3) a fully-adjusted model that also included HbA1c. This final model estimates the effect of TZDs independent of any risks of poorly controlled diabetes, an independent risk factor for CHF (22). These analyses were then repeated with 2 indicator variables for pioglitazone or rosiglitazone to examine the effects of the individual TZDs. In sensitivity analyses, we examined the effect of using a 30-day exposure-window instead of the 90-day window used in our primary analyses. In addition, we investigated whether a history of myocardial infarction modified the effect of TZDs on the risk of CHF as patients with a history of myocardial infarction may be at an increased risk due to existing myocardial damage. We also used metformin as our reference category to facilitate comparison of our results with those from the ADOPT trial (6).

All analyses were conducted using SAS 9.1.3 (Cary, NC).

RESULTS

Our final cohort consisted of 63,462 patients with type 2 diabetes and no previous history of CHF (Figure 7.1). From this cohort, we identified 3,405 possible or probable cases of CHF and 32,042 corresponding controls. The cases included 2,632 probable cases. Overall, each case had a mean of 9.4 (SD = 1.8) matched controls (median = 10).

Patient Characteristics

In both case series, cases were more likely to be male, had a higher BMI, and had more comorbidities than controls (Table 7.1). Particularly prominent differences include differences in history of coronary artery disease, myocardial

infarction, and stroke. Higher proportions of cases were also prescribed cardiovascular medications in the 90 days prior to index date, including ACE inhibitors, aspirin, digoxin, nitrates, and other anti-hypertensive agents including diuretics. Compared with controls, cases had a slightly longer duration of diabetes but had similar mean HbA1c levels. In addition, cases were more likely to have had amputations, nethropathy, or neuropathy but had a similar history of retinopathy.

Differences in anti-diabetic medical therapy were also present (Table 7.1). A higher proportion of cases were prescribed insulin compared with controls, and a lower proportion of cases were unexposed. The proportions of patients receiving metformin or sulfonylureas were similar between groups. The proportion of patients prescribed TZDs was low in both cases and controls. The patterns of diabetic treatment regiments for cases and controls are described in Table 7.2.

Effect of TZDs on CHF

We found no definitive evidence that TZDs were associated with an increased rate of incident CHF compared with patients who were unexposed to anti-diabetic medical therapy (adjusted RR = 1.19, 95% CI = 0.96, 1.48) (Table 7.3). This result was similar in patients prescribed pioglitazone (adjusted RR = 1.12, 95% CI = 0.78, 1.59) and in those prescribed rosiglitazone (adjusted RR = 1.20, 95% CI = 0.95, 1.53). Similar results were also obtained when our analyses were restricted to probable CHF cases.

Sensitivity analyses using a 30-day exposure-window produced similar results to those reported in our primary analyses (adjusted RR = 1.28, 95% CI = 1.01, 1.65). In addition, there was no evidence that a history of myocardial infarction modified the effect of TZDs on the rate of CHF (RR for interaction: 1.08, 95% CI = 0.70, 1.67). Compared with metformin monotherapy, TZD therapy was associated with an increased rate of CHF (RR = 1.38, 95% CI = 1.12, 1.71).

DISCUSSION

We did not find definitive evidence linking the prescription of TZDs to an increased rate of incident CHF. Our results were consistent with an 18% increase in CHF; however, a lack of precision in our estimates prevents us from conclusively ruling out no effect or a small but clinically important increase in CHF. Results for pioglitazone and rosiglitazone appear to be similar, and we found no modifying role for previous heart disease, using past myocardial infarction as a marker. It should also be remembered that we investigated only incident CHF cases and, although not definite, our results support the FDA's decision to include a 'black box' warning for incident CHF for pioglitazone and rosiglitazone (23, 24). This revised labeling also includes warning of CHF exacerbations for these agents, a population and research question not addressed in this study.

The effect of TZDs on the risk of CHF has been examined in a number of clinical trials and meta-analyses (1-6). These previous studies include three large completed clinical trials, ADOPT (6), DREAM (3), and PROactive (2). In

ADOPT, patients with newly-diagnosed type 2 diabetes were randomized to metformin, glyburide, or rosiglitazone (6). The risk of CHF was higher in patients randomized to rosiglitazone than in those randomized to glyburide (OR = 2.44, 95% CI = 1.14, 5.59). The comparison of rosiglitazone with metformin was inconclusive, with the accompanying confidence interval including both clinically important benefits and harm (OR = 1.15, 95% CI = 0.62, 2.18). In DREAM patients with impaired glucose tolerance or fasting glucose randomized to rosiglitazone had a substantially higher CHF compared with those randomized to placebo (HR = 7.01, 95% CI = 1.6, 30.9) (3). However, this analysis involved a total of only 16 cases. In PROactive, patients with type 2 diabetes and evidence of macrovascular disease were randomized to pioglitazone or placebo, in addition to their existing diabetic therapy (2). Patients randomized to pioglitazone had more reported CHF (OR = 1.49, 95% CI = 1.23, 1.80) compared with those randomized to placebo but had a similar risk of fatal CHF (OR = 1.15, 95% CI = 0.64, 2.04). An interim analysis of RECORD showed that rosiglitazone, used as an add-on therapy to existing metformin and sulfonylurea therapy, was associated with an increased rate of CHF (HR = 2.15, 95% CI = 1.30, 3.57) compared to metformin and sulfonylurea only (1). ADOPT (6), DREAM (3), and RECORD (1) all excluded patients with CHF, and PROactive excluded all patients with New York Heart Association Class 2, 3, or 4 (2).

Recent meta-analyses have also found that TZDs increase the rate of CHF (4, 5). Using patient-level data from 19 trials, Lincoff and colleagues found pioglitazone was associated with an increased rate of CHF compared with active

or placebo control (HR = 1.41, 95% CI = 1.14, 1.76) (5). Singh and colleagues conducted a meta-analysis of 4 RCTs with at least 12 months of follow-up and found that rosiglitazone was associated with a substantial increase in the risk of CHF compared with placebo or active comparator (relative risk: 2.09, 95% CI = 1.52, 2.88) (4).

The results of the present study are most comparable with those of the ADOPT trial (6). The ADOPT trial, which used patients randomized to metformin as one of their comparison groups, reported a similar estimate as that reported in the sensitivity analysis of the present study. However, with our much larger sample size, our estimate is accompanied by more precise corresponding confidence limits. Unlike DREAM (3), PROactive (2), and RECORD (1), we did not find a definitive association between TZDs and CHF. The differences in results between our study and these previous ones are likely due to differences in study population, study drug, and comparison group. None of the patients included in our study would have been eligible for DREAM (3) and only a small proportion of the patients in the present study would have been eligible for PROactive (2) or RECORD (1). Furthermore, patients who participate in trials are intrinsically different than those found in everyday clinical practice (25), underscoring the difficulties in extrapolating from clinical trial results to routine clinical decision-making.

The effect of TZDs on the risk of CHF has also been examined in a number of observational studies (26-31). However, early observational studies (26-28) had methodological limitations while more recent studies (29-31) are

more informative. Of the recent studies, one involving pioglitazone was inconclusive (HR = 1.28, 95% CI = 0.85, 1.92) (29) while two others found an increased risk of hospitalization for CHF (30, 31). However, these studies have included patients with prevalent CHF cases, which complicates the interpretation of the risk of TZDs. Nonetheless, our results are consistent with those of previous observational studies (29-31).

Our study has a number of strengths. First, our study involved a representative population-based sample of subjects with type 2 diabetes in the U.K. Consequently, our results are more generalizable than those obtained from randomized controlled trials conducted in highly-selected patient populations. In addition, unlike previous observational studies (30, 31), our study involved a broader spectrum of patients and focused on the risk of incident CHF. Second, our population-based sample contained a large number of CHF cases, overcoming a major limitation of most TZD trials to date (> 6 times the number of CHF cases than in the largest completed trial) (2). Finally, our study involved data extracted from the GPRD and thus included clinical data such as HbA1c that are typically missing from administrative databases. The availability of HbA1c is particularly important when studying patients with diabetes as severity of disease is often viewed as a source of important residual confounding. In the present study, adjustment for HbA1c did not affect our treatment estimates. The consistency of these results is reassuring; they demonstrate that the results of the present study are robust and suggest that studies that do not include adjustment for glycemic control may have less residual confounding than originally believed.

Our study also has potential limitations. First, our study is observational in nature and therefore may be affected by biases inherent to this design, including confounding by indication and other unmeasured variables. To minimize the potential effects of confounding, we matched on age, practice, and calendar date. We also adjusted for a number of potential confounders, the effects of which are illustrated by the attenuation of treatment effects between crude and adjusted models (particularly among insulin users). In addition, we conducted a number of sensitivity analyses, including analyses with and without adjustment for HbA1c, that produced similar results to those of our primary analyses, suggesting our results are robust. The use of TZDs (both pioglitazone and rosiglitazone) in patients with CHF or at high risk of CHF is presently contraindicated by regulatory agencies (23). It is therefore possible that physicians are appropriately prescribing TZDs to patients who are deemed to have a low risk of CHF. Thus, if anything, the potential confounding by indication present in this study may result in an underestimation of the true CHF risk of TZDs.

Our results may be affected by misclassification bias, particularly at the level of outcome assessment. However, our analysis restricted to probable cases of CHF revealed similar results to our more inclusive analysis, suggesting that any outcome misclassification bias is likely to minimal. Exposure misclassification may also occur, particularly when medication data are derived from prescriptions issued rather than prescriptions filled (14). Such exposure misclassification, if present, would likely to be non-differential leading to a

dilution of effect and possibly contributing to the observed null association. Finally, there were low rates of prescription of TZDs during much of our study period, which limited our ability to accurately estimate clinically meaningful differences, as evidenced by wide confidence intervals that do not rule out potentially important effects. Nonetheless, our study sample was sufficiently large to rule out larger increases in CHF such as those reported elsewhere (3).

CONCLUSIONS

Our study examined the effect of TZD prescription on the risk of incident CHF among patients with type 2 diabetes in a large, population-based cohort. We found no definitive association between TZDs and an increased rate of CHF in this population, although the upper limit of our confidence interval did include effects that are clinically important. However given the totality of the evidence from this and previous studies, the probability of an increased risk for CHF with TZDs remains high but any increase in CHF risk associated with their use is likely lower than previously reported.

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Table 7.1. Baseline demographic and clinical characteristics of congestive heart failure cases and matched controls at index date*.

Characteristic†	Possible and Probable Case Analysis††		Probable Case Analysis††	
	Cases (n = 3,405)	Controls (n = 32,042)	Cases (n = 2,632)	Controls (n = 24,903)
Demographic				
Male, n (%)	1,934 (56.8)	16,591 (51.8)	1,502 (57.1)	12,842 (51.6)
Age (Years) [Mean ± SD]	73.4 ± 9.5	72.6 ± 9.0	73.3 ± 9.4	72.5 ± 9.0
Lifestyle Variables				
Body Mass Index (kg/m^2)				
Mean ± SD	29.8 ± 6.4	28.6 ± 5.5	29.9 ± 6.5	28.6 ± 5.5
Missing, n (%)	177 (5.2)	1,063 (3.3)	133 (5.0)	786 (3.2)
Smoking, n (%)				
Current	391 (11.5)	3,648 (11.4)	297 (11.2)	2,819 (11.3)
Previous	1,445 (42.4)	11,691 (36.5)	1,116 (42.4)	9,098 (36.5)
No	1,529 (44.9)	16,448 (51.3)	1,189 (45.2)	12,795 (51.4)
Missing	40 (1.1)	255 (0.01)	30 (1.1)	191 (0.7)
Comorbidities, n (%)				
Atrial Fibrillation	697 (20.5)	2,135 (6.7)	599 (22.8)	1,671 (6.7)
Cerebrovascular Disease	774 (22.7)	4,744 (14.8)	587 (22.3)	3,645 (14.6)
COPD	366 (10.8)	1,549 (4.8)	286 (10.9)	1,173 (4.7)
Coronary Artery Disease	1,926 (56.6)	8,664 (27.0)	1,497 (56.9)	6,728 (27.0)
Dyslipidemia	940 (27.6)	8,368 (26.1)	719 (27.3)	6,562 (26.4)
Hypertension	2,231 (65.5)	19,739 (61.6)	1,789 (68.0)	15,492 (62.2)
Myocardial Infarction	930 (27.3)	3,042 (9.5)	736 (28.0)	2,367 (9.5)
Peripheral Vascular Disease	386 (11.3)	1,803 (5.6)	299 (11.4)	1,384 (5.6)
Previous CABG	321 (9.4)	1,201 (3.8)	258 (9.8)	928 (3.7)
Previous Coronary Angiogram	441 (13.0)	1,719 (5.4)	347 (13.2)	1,365 (5.5)
Previous PCI	155 (4.6)	649 (2.0)	116 (4.4)	512 (2.1)
Renal Failure	222 (6.5)	649 (2.0)	142 (5.4)	503 (2.0)
Rheumatoid Arthritis	543 (16.0)	4,391 (13.7)	403 (15.3)	3,392 (13.6)
Stroke	271 (8.0)	1,570 (4.9)	208 (7.9)	1,205 (4.8)

Characteristic[†]	Possible and Probable Case Analysis[††] Cases (n = 3,405)	Possible and Probable Case Analysis[††] Controls (n = 32,042)	Probable Case Analysis[††] Cases (n = 2,632)	Probable Case Analysis[††] Controls (n = 24,903)
Unstable Angina	232 (6.8)	865 (2.7)	182 (6.9)	686 (2.8)
Diabetic History				
Duration of Diabetes [Years]				
Mean ± SD	9.9 ± 7.7	8.4 ± 7.2	10.1 ± 7.8	8.4 ± 7.2
Median (IQR)	8.4 (3.9, 14.0)	6.6 (3.1, 12.0)	8.9 (4.0, 14.3)	6.6 (3.1, 11.9)
Complications, n (%)				
Amputations	110 (3.2)	407 (1.3)	86 (3.3)	316 (1.3)
Nethropathy	287 (8.4)	911 (2.8)	195 (7.4)	709 (2.9)
Neuropathy	393 (11.5)	2,407 (7.5)	304 (11.6)	1,844 (7.4)
Retinopathy	784 (16.0)	5,351 (16.7)	620 (23.6)	4,145 (16.6)
Medication Use, n (%)				
ACE Inhibitors	1,854 (54.5)	12,607 (39.4)	1,600 (60.8)	9,896 (39.7)
ARBs	438 (12.9)	3,133 (9.8)	383 (14.6)	2,540 (10.2)
Aspirin	1,747 (51.3)	12,732 (39.7)	1,381 (52.5)	9,983 (40.1)
Beta-Blockers	1,011 (29.7)	7,661 (23.9)	789 (30.0)	6,021 (24.2)
Calcium Channel Blockers	1,228 (36.1)	9,496 (29.6)	960 (36.5)	7,477 (30.0)
COX-2 Inhibitors	96 (6.8)	620 (1.9)	72 (2.7)	486 (2.0)
Digoxin	481 (14.1)	1,328 (4.1)	448 (17.0)	1,051 (4.2)
Diuretics or Other Anti-Hypertensive Agents	2,470 (72.5)	11,553 (36.1)	2,039 (77.5)	9,064 (36.4)
Nitrates	961 (28.2)	3,352 (10.5)	762 (29.0)	2,610 (10.5)
Non-Aspirin Antiplatelets	300 (8.8)	1,328 (4.1)	235 (8.9)	1,026 (4.1)
Non-Statin Lipid Therapies	96 (2.8)	786 (2.5)	77 (2.5)	633 (2.5)
Other NSAIDS	448 (13.2)	4,047 (12.6)	347 (13.2)	3,152 (12.7)
Statins	1,602 (47.1)	13,888 (43.3)	1,282 (48.7)	10,989 (44.1)
Warfarin	429 (12.6)	1,288 (4.0)	360 (13.7)	1,022 (4.1)
Diabetic Medications, n (%)				
Insulin	922 (27.1)	5,353 (16.7)	757 (28.8)	4,165 (16.7)
Metformin	1,450 (42.6)	14,484 (45.2)	1,175 (44.6)	11,396 (45.8)

Characteristic[†]	Possible and Probable Case Analysis[††] Cases (n = 3,405)	Possible and Probable Case Analysis[††] Controls (n = 32,042)	Probable Case Analysis[††] Cases (n = 2,632)	Probable Case Analysis[††] Controls (n = 24,903)
Sulfonylureas	1,415 (41.6)	13,525 (42.2)	1,068 (40.6)	10,545 (42.3)
TZDs	218 (6.4)	1,953 (6.1)	180 (6.8)	1,585 (6.4)
Pioglitazone	60 (1.8)	510 (1.6)	52 (2.0)	409 (1.6)
Rosiglitazone	159 (4.7)	1,453 (4.5)	129 (4.9)	1,186 (4.8)
Other Oral Antidiabetics	77 (2.3)	687 (2.1)	56 (2.1)	548 (2.2)
Laboratory Tests				
HbA1c				
Test in Previous Year, n (%)	2,844 (83.5)	27,294 (85.2)	2,230 (84.7)	21,327 (85.6)
Mean HbA1c [%]				
HbA1c ≤7%, n (%)	830 (24.4)	8,738 (27.3)	633 (24.1)	6,784 (27.2)
7< HbA1c ≤8, n (%)	903 (26.5)	9,190 (28.7)	709 (26.7)	7,211 (29.0)
8< HbA1c ≤9, n (%)	585 (17.2)	4,945 (15.4)	462 (17.6)	3,830 (15.4)
9< HbA1c ≤10, n (%)	274 (8.1)	2,457 (7.7)	219 (8.3)	1,938 (7.8)
HbA1c >10, n (%)	252 (7.4)	1,964 (6.2)	213 (8.1)	1,564 (6.3)
Missing, n (%)	561 (16.5)	4,748 (14.8)	402 (15.3)	3,576 (14.4)
Mean Total Cholesterol [mmol/L][‡]				
Reading in Previous Year, n (%)	2,413 (70.9)	23,582 (73.6)	1,901 (72.2)	18,517 (74.4)
Mean ± SD	4.8 ± 1.0	4.9 ± 1.0	4.7 ± 1.0	4.9 ± 1.0
Median (IQR)	4.6 (4.0, 5.3)	4.8 (4.2, 5.5)	4.6 (4.0, 5.3)	4.8 (4.2, 5.5)
Systolic Blood Pressure				
Reading in Previous Year, n (%)	3,131 (92.0)	29,258 (91.3)	2,435 (92.5)	22,845 (91.7)
Mean Systolic Blood Pressure [mm Hg][‡]				
Mean ± SD	144.8 ± 18.4	145.4 ± 16.6	144.9 ± 18.5	145.3 ± 16.6
Median (IQR)	143.5 (133.0, 156.0)	144.3 (134.8, 155.0)	143.7 (133.3, 155.7)	144.3 (134.7, 155.0)
Diastolic Blood Pressure				
Reading in Previous Year, n (%)	3,129 (91.9)	29,243 (91.3)	2,434 (92.5)	22,834 (91.7)
Mean Diastolic Blood Pressure [mm Hg][‡]				
Mean ± SD	77.9 ± 9.1	78.3 ± 8.6	77.9 ± 9.3	78.3 ± 8.6
Median (IQR)	77.8 (71.7, 83.1)	78.7 (72.5, 83.8)	77.5 (71.5, 83.3)	78.7 (72.5, 83.6)

Abbreviations: ACE: angiotensin converting enzyme; ARBs: angiotensin II receptor blockers; CABG: coronary artery bypass graft surgery; COPD: chronic obstructive pulmonary disorder; COX: Cyclooxygenase; HbA1c: hemoglobin A1c; IQR: inter-quartile range; NSAIDs: non-steroidal anti-inflammatory drug; PCI: percutaneous coronary intervention; SD: standard deviation; TZDs: Thiazolidinediones.

* Cases and controls were matched for practice, age (± 3 years), and calendar date.

† Comorbidities and diabetic complications are based on any previous diagnosis in the GPRD prior to index date. Medication data are for the 90 days prior to index date, and laboratory test data are for the year prior to index date.

†† The possible and probable case analysis includes all cases with a clinical diagnosis of congestive heart failure. The probable case analysis was restricted to cases with a clinical diagnosis of congestive heart failure and either a) prescriptions for ≥ 2 of following medication classes in the 90 days after CHF diagnosis: digoxin, ACE inhibitors/ARBs, and diuretics or other anti-hypertensive agents; or b) who died in the 90 days following CHF diagnosis.

‡ Among those with a test in the previous year.

Table 7.2. Patterns of diabetic therapy among patients with type 2 diabetes who were diagnosed with congestive heart failure and their matched controls*.

	Possible and Probable Case Analysis††		Probable Case Analysis††	
Mutually Exclusive Treatment Category†	Cases (n = 3,405)	Controls (n = 32,042)	Cases (n = 2,632)	Controls (n = 24,903)
TZDs	205 (6.0)	1,897 (5.9)	167 (6.3)	1,541 (6.2)
Any Insulin	922 (27.1)	5,353 (16.7)	757 (28.8)	4,155 (16.7)
Non-TZD Oral Combination Therapy	660 (19.4)	6,579 (20.5)	512 (19.5)	5,168 (20.8)
Sulfonylurea Monotherapy	585 (17.2)	5,648 (17.6)	418 (15.9)	4,324 (17.3)
Metformin Monotherapy	410 (12.0)	5,270 (16.4)	330 (12.5)	4,130 (16.6)
Other Oral Monotherapy	7 (0.2)	79 (0.2)	3 (0.1)	60 (0.2)
Unexposed	616 (18.1)	7,216 (22.5)	445 (22.5)	5,525 (22.1)

Abbreviations: TZDs: thiazolidinediones

* Cases and controls were matched for practice, age (± 3 years), and calendar date.

† Medication data are for the 90 days prior to index date. The TZD treatment category includes TZD prescriptions with and without prescriptions for non-TZD oral agents.

†† The possible and probable case analysis includes all cases with a clinical diagnosis of congestive heart failure. The probable case analysis was restricted to cases with a clinical diagnosis of congestive heart failure and either a) prescriptions for ≥ 2 of following medication classes in the 90 days after CHF diagnosis: digoxin, ACE inhibitors/ARBs, and diuretics or other anti-hypertensive agents; or b) who died in the 90 days following CHF diagnosis.

Table 7.3. Effect of thiazolidinediones on the risk of incident congestive heart failure among patients with type 2 diabetes*.

Variable	Crude RR	Crude 95% CI	Adjusted Model A†,‡ RR	Adjusted Model A†,‡ 95% CI	Adjusted Model B†,‡‡ RR	Adjusted Model B†,‡‡ 95% CI
Possible and Probable Case Analysis††:						
TZDs	1.37	1.15, 1.62	1.20	0.97, 1.48	1.19	0.96, 1.48
Pioglitazone	1.39	1.03, 1.88	1.11	0.79, 1.58	1.12	0.78, 1.59
Rosiglitazone	1.34	1.11, 1.63	1.22	0.96, 1.54	1.20	0.95, 1.53
Any Insulin	2.17	1.94, 2.42	1.16	0.98, 1.38	1.14	0.95, 1.36
Non-TZD Oral Combination Therapy	1.23	1.09, 1.38	1.07	0.91, 1.25	1.06	0.90, 1.25
Sulfonylurea Monotherapy	1.20	1.06, 1.35	1.07	0.91, 1.26	1.06	0.90, 1.26
Metformin Monotherapy	0.95	0.83, 1.08	0.86	0.72, 1.02	0.86	0.72, 1.02
Other Oral Monotherapy	1.10	0.50, 2.41	1.28	0.50, 3.24	1.29	0.51, 3.29
Unexposed	1.00	Reference	1.00	Reference	1.00	Reference
Probable Case Analysis††:						
TZDs	1.44	1.19, 1.76	1.18	0.92, 1.50	1.15	0.89, 1.47
Pioglitazone	1.56	1.12, 2.17	1.18	0.80, 1.76	1.17	0.79, 1.74
Rosiglitazone	1.39	1.12, 1.73	1.16	0.88, 1.52	1.12	0.85, 1.48
Any Insulin	2.43	2.14, 2.76	1.22	1.00, 1.49	1.15	0.94, 1.42
Non-TZD Oral Combination Therapy	1.28	1.12, 1.47	1.04	0.86, 1.25	1.01	0.83, 1.22
Sulfonylurea Monotherapy	1.18	1.02, 1.36	1.02	0.84, 1.24	1.00	0.82, 1.22
Metformin Monotherapy	1.04	0.89, 1.20	0.91	0.75, 1.11	0.90	0.74, 1.10
Other Oral Monotherapy	0.65	0.20, 2.08	0.96	0.27, 3.44	0.97	0.27, 3.48
Unexposed	1.00	Reference	1.00	Reference	1.00	Reference

Abbreviations: CI: confidence interval; HbA1c: hemoglobin A1c; RR: rate ratio; TZDs: thiazolidinediones.

***** Cases and controls were matched for practice, age (± 3 years), and calendar date.

† Comorbidities and diabetic complications are based on any previous diagnosis in the GPRD. Medication data are for the 90 days prior to index date, and laboratory test data are for the year prior to index date.

†† The possible and probable case analysis includes all cases with a clinical diagnosis of congestive heart failure. The probable case analysis was restricted to cases with a clinical diagnosis of congestive heart failure and either a) prescriptions for ≥2 of following medication classes in the 90 days after CHF diagnosis: digoxin, ACE inhibitors/ARBs, and diuretics or other anti-hypertensive agents; or b) who died in the 90 days following CHF diagnosis.

‡ Model A: Adjusted for age, sex, smoking, bmi, clinical diagnoses (atrial fibrillation, cerebrovascular disease, chronic obstructive pulmonary disease, coronary artery disease, dyslipidemia, hypertension, peripheral vascular disease, previous cardiac angiogram, previous coronary artery bypass graft surgery, previous myocardial infarction, previous percutaneous coronary intervention, previous stroke, rheumatoid arthritis, renal

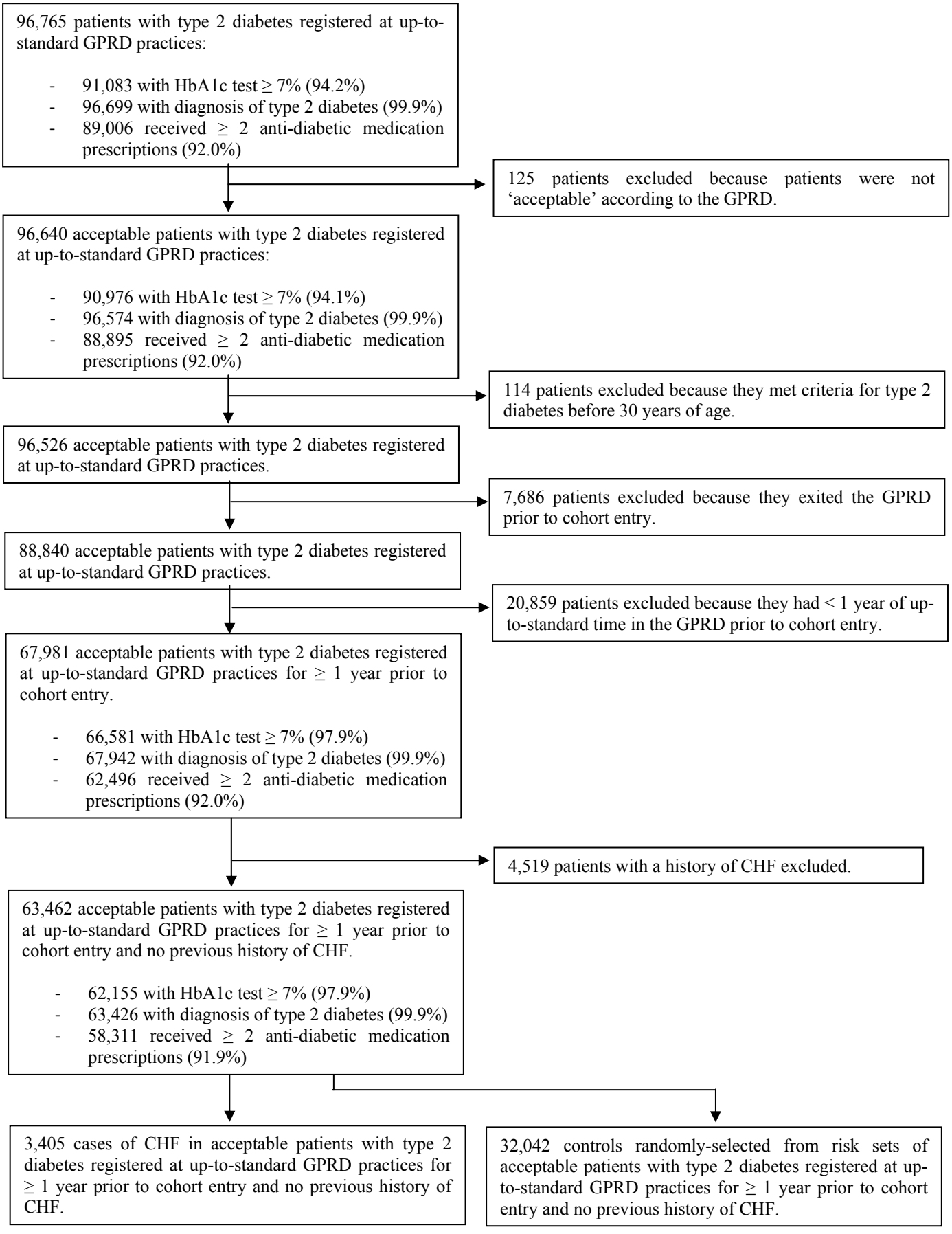
failure, and unstable angina), medication prescriptions (angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBS), aspirin, beta-blockers, calcium channel blockers, cyclooxygenase (COX) 2 inhibitors, digoxin, diuretics and other anti-hypertension therapies, nitrates, and statins), mean systolic blood pressure, mean diastolic blood pressure, mean total cholesterol, previous complications of diabetes (blindness, nethropathy, neuropathy, and retinopathy), and duration of diabetes (<5 years, 5≥ years and <10 years, and ≥ 10 years). Patients with missing smoking, BMI, mean systolic blood pressure, mean diastolic blood pressure, or mean total cholesterol were excluded from this analysis.

‡‡ Model B: Adjusted for Model A variables and HbA1c. Patients with missing HbA1c were excluded from this analysis.

FIGURE LEGEND

Figure 7.1. Flow diagram describing construction of nested case-control study database of patients with type-2 diabetes mellitus identified in the General Practice Research Database.

Figure 7.1.


96,765 patients with type 2 diabetes registered at up-to-standard GPRD practices:
- 91,083 with HbA1c test ≥ 7% (94.2%)
- 96,699 with diagnosis of type 2 diabetes (99.9%)
- 89,006 received ≥ 2 anti-diabetic medication prescriptions (92.0%)
125 patients excluded because patients were not 'acceptable' according to the GPRD.
96,640 acceptable patients with type 2 diabetes registered at up-to-standard GPRD practices:
- 90,976 with HbA1c test ≥ 7% (94.1%)
- 96,574 with diagnosis of type 2 diabetes (99.9%)
- 88,895 received ≥ 2 anti-diabetic medication prescriptions (92.0%)
114 patients excluded because they met criteria for type 2 diabetes before 30 years of age.
96,526 acceptable patients with type 2 diabetes registered at up-to-standard GPRD practices.
7,686 patients excluded because they exited the GPRD prior to cohort entry.
88,840 acceptable patients with type 2 diabetes registered at up-to-standard GPRD practices.
20,859 patients excluded because they had < 1 year of up-to-standard time in the GPRD prior to cohort entry.
67,981 acceptable patients with type 2 diabetes registered at up-to-standard GPRD practices for ≥ 1 year prior to cohort entry.
- 66,581 with HbA1c test ≥ 7% (97.9%)
- 67,942 with diagnosis of type 2 diabetes (99.9%)
- 62,496 received ≥ 2 anti-diabetic medication prescriptions (92.0%)
4,519 patients with a history of CHF excluded.
63,462 acceptable patients with type 2 diabetes registered at up-to-standard GPRD practices for ≥ 1 year prior to cohort entry and no previous history of CHF.
- 62,155 with HbA1c test ≥ 7% (97.9%)
- 63,426 with diagnosis of type 2 diabetes (99.9%)
- 58,311 received ≥ 2 anti-diabetic medication prescriptions (91.9%)
3,405 cases of CHF in acceptable patients with type 2 diabetes registered at up-to-standard GPRD practices for ≥ 1 year prior to cohort entry and no previous history of CHF.
32,042 controls randomly-selected from risk sets of acceptable patients with type 2 diabetes registered at up-to-standard GPRD practices for ≥ 1 year prior to cohort entry and no previous history of CHF.

7.3 Supplementary Material

Previous reports suggest that the peripheral edema induced by TZDs may be reversible (178), and the PROactive trial showed that, although TZDs may increase the rate of CHF, they do not increase the rate of fatal CHF (39). However, the prognosis of patients who develop CHF after exposure to TZDs remains unclear. We therefore compared the mortality rate among CHF cases exposed to TZDs to that of patients unexposed to TZDs using the case series from our nested case-control study.

Using our CHF case-series, we constructed a sub-cohort in which we categorized cases as either exposed or unexposed to TZDs, with exposure defined as any prescription for TZDs in the 90 days prior to the date of CHF diagnosis. We then followed these patients until death, the most recent data upload from the practice to the GPRD, departure from the practice, or end of follow-up (December 31st, 2006). The mortality rates of these two groups were calculated in deaths per 1,000 person-years and described using Kaplan-Meier survival analysis. Mortality rates were then compared using Cox proportional hazards in both crude and adjusted models. The proportionality of hazards assumption was assessed graphically using log-log plots.

There was a high mortality rate among incident CHF cases (Table 7.4). In the period following diagnosis of CHF, there were a total of 1,630 deaths (mean duration of follow-up: 2.5 years [SD = 2.0]; median: 2.0 years). Among possible and probable CHF cases, a total of 69 deaths occurred in CHF cases who had been exposed to TZDs in the 90 days prior to CHF diagnosis, and 1,561 deaths

occurred in unexposed CHF cases. Among probable cases, there were 58 and 1,231 deaths, respectively. Our comparison of mortality rates among TZD-exposed CHF cases and those not exposed to TZDs was inconclusive, with 95% CIs that include both unity and clinically relevant lower mortality rates among those exposed to TZDs (Figure 7.2, Table 7.4). Further research examining the reversibility of TZD-exposed CHF is therefore needed.

Table 7.4 Mortality among patients with type 2 diabetes and thiazolidinedione-exposed congestive heart failure compared with those with non-thiazolidinedione-exposed congestive heart failure.

Type of CHF	Deaths [n/N]	Person-Years	Mortality Rate [n/1,000 PYs]	95% CI	Crude HR	Crude 95% CI	Age- and Sex-Adjusted Model HR	Age- and Sex-Adjusted Model 95% CI	Fully-Adjusted Model*† HR	Fully-Adjusted Model*† 95% CI
Possible and Probable Cases††										
TZD-Exposed CHF	69/218	396.2	174.2	136.5, 219.1	0.83	0.65, 1.06	0.88	0.70, 1.13	0.90	0.69, 1.18
Non-TZD-Exposed CHF	1,561/3,187	8,010.6	194.9	185.4, 204.7	1.00	Reference	1.00	Reference	1.00	Reference
Probable Cases††										
TZD-Exposed CHF	58/180	325.0	178.4	136.8, 229.1	0.79	0.60, 1.02	0.82	0.63, 1.07	0.84	0.63, 1.13
Non-TZD-Exposed CHF	1,231/2,452	5,950.2	206.9	196.6, 219.7	1.00	Reference	1.00	Reference	1.00	Reference

Abbreviations: CHF: congestive heart failure; CI: confidence interval; HbA1c: hemoglobin A1c; HR: hazard ratio; PY = person-years; TZDs: thiazolidinediones.

* Comorbidities and diabetic complications are based on any previous diagnosis in the GPRD. Medication data are for the 90 days prior to diagnosis of CHF, and laboratory test data are for the year prior to CHF diagnosis.

† Adjusted for age, sex, smoking, bmi, clinical diagnoses (atrial fibrillation, cerebrovascular disease, chronic obstructive pulmonary disease, coronary artery disease, dyslipidemia, hypertension, peripheral vascular disease, previous cardiac angiogram, previous coronary artery bypass graft surgery, previous myocardial infarction, previous percutaneous coronary intervention, previous stroke, rheumatoid arthritis, renal failure, and unstable angina), medication prescriptions (angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBS), aspirin, beta-blockers, calcium channel blockers, cyclooxygenase (COX) 2 inhibitors, digoxin, diuretics and other anti-hypertension therapies, nitrates, and statins), mean systolic blood pressure, mean diastolic blood pressure, previous complications of diabetes (blindness, nethropathy, neuropathy, and retinopathy), duration of diabetes (< 5 years, 5 ≥ years and < 10 years, and ≥ 10 years), and year of CHF diagnosis.

†† Possible and probable case analysis includes all cases with a clinical diagnosis of congestive heart failure. Probable case analysis was restricted to cases with a clinical diagnosis of congestive heart failure and either a) a prescription for ≥2 of following medication classes in the 90 days after CHF diagnosis: digoxin, ACE inhibitor/ARB, and a diuretic or other anti-hypertensive agent; or b) died in the 90 days following CHF diagnosis.

FIGURE LEGEND

Figure 7.2 Kaplan-Meier analysis comparing survival among cases with TZD-exposed CHF with those not exposed to TZDs. A) Possible and probable CHF cases. B) Probable CHF cases.

Figure 7.2a

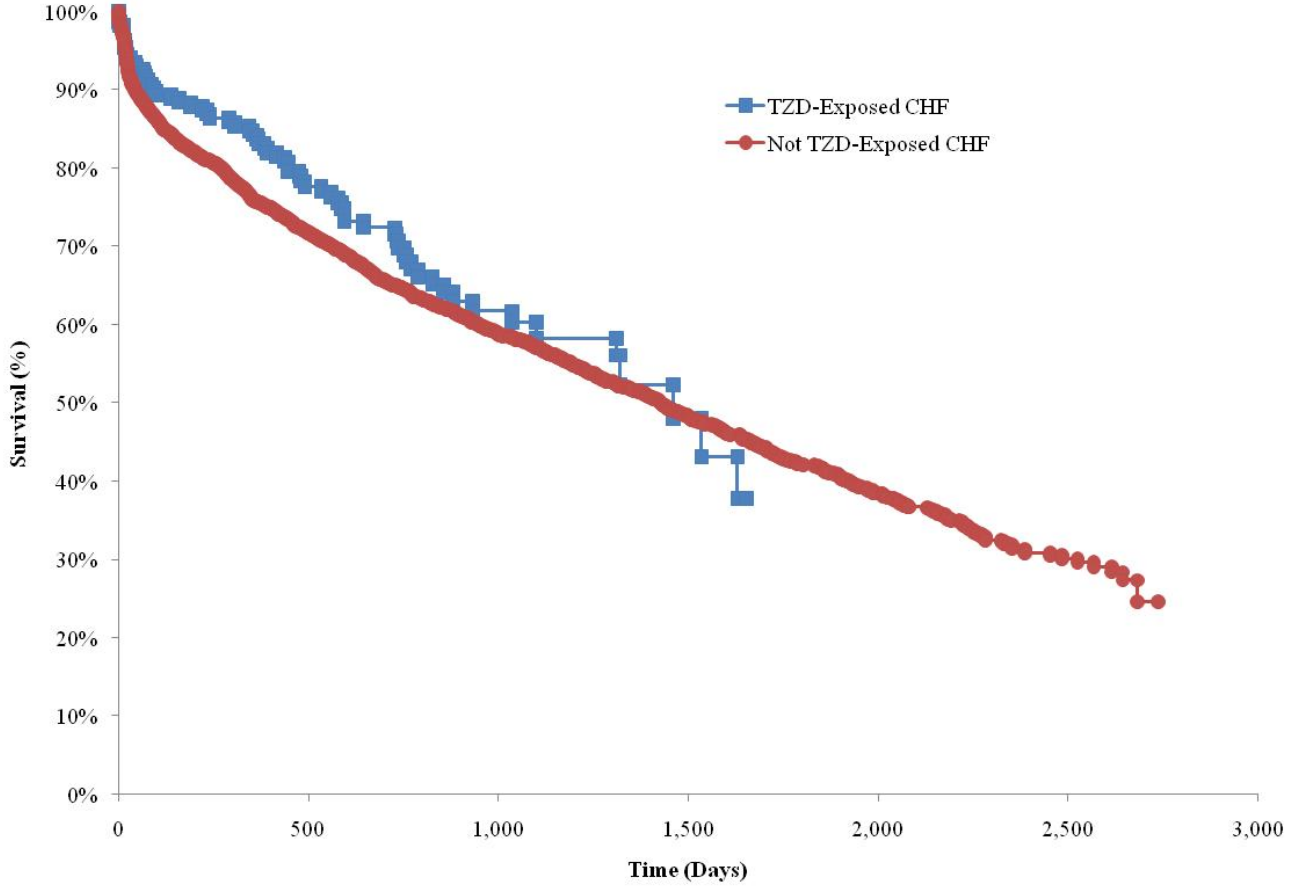
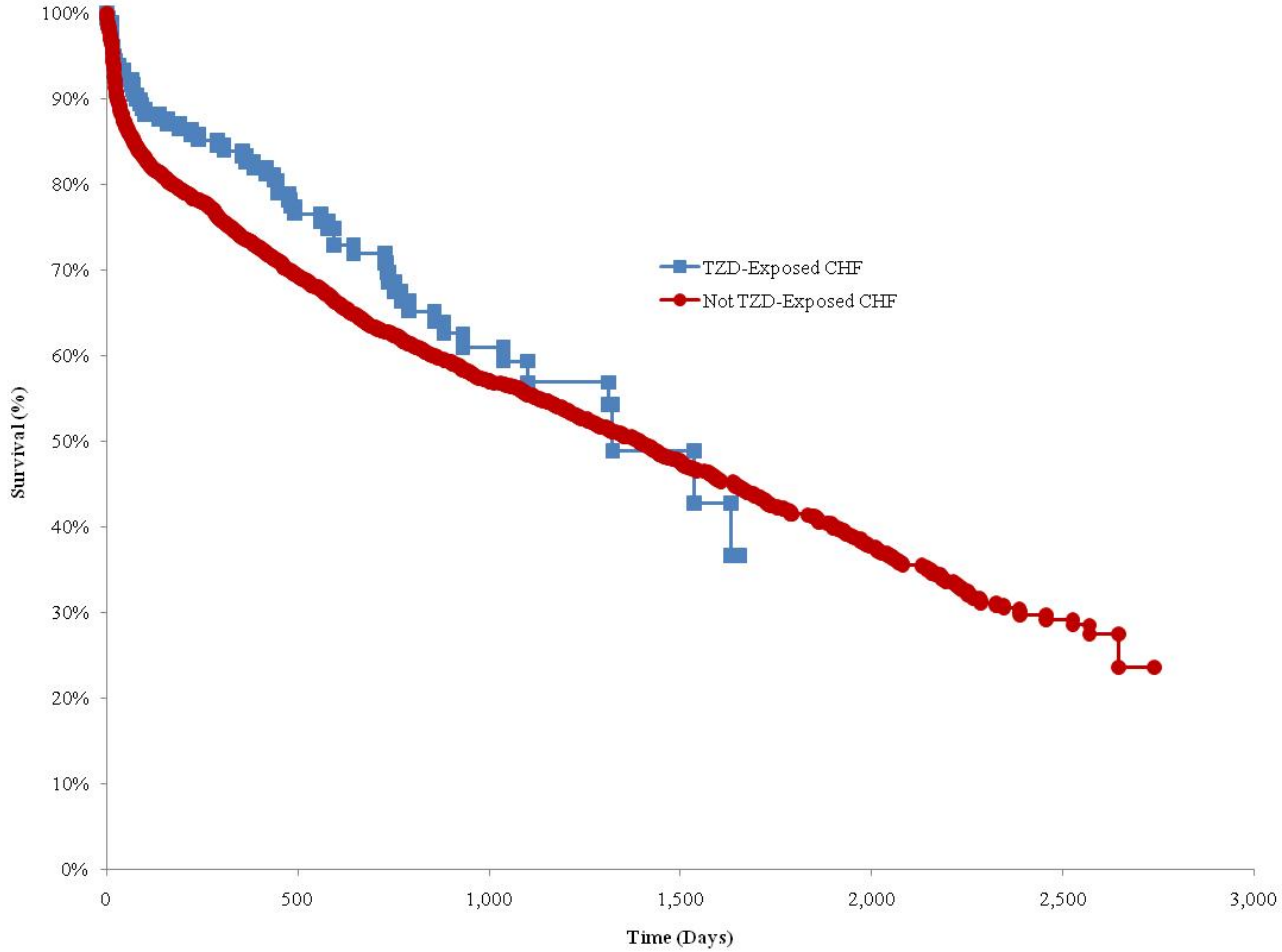

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Survival (%)
0
500
1,000
1,500
2,000
2,500
3,000
Time (Days)
TZD-Exposed CHF
Not TZD-Exposed CHF

Figure 7.2b


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Survival (%)
0
500
1,000
1,500
2,000
2,500
3,000
Time (Days)
TZD-Exposed CHF
Not TZD-Exposed CHF

CHAPTER 8 – DISCUSSION AND OVERALL CONCLUSIONS

This thesis was designed to assess recent prescription patterns and the effects of glycemic control and TZDs on the risk of incident CHF among patients with type 2 diabetes. Our investigation revealed the prescription of anti-diabetic medical therapy increased greatly between 2000 and 2006, with the largest increases occurring with metformin and TZDs. In addition, we found that poor glycemic control increases the rate of incident CHF in this patient population. This increase, which includes an approximate 20% increase among those with HbA1c $\geq$ 10%, has important public health consequences. Although poor glycemic control resulted in an increased rate of CHF, patients with HbA1c values between 7% and 8% had similar rates as those with HbA1c < 7%, suggesting that very aggressive glycemic control does not have beneficial effects with respect to this outcome. Our adjustment for HbA1c measurement error did not affect this relationship.

In our population-based assessment, TZDs were not definitely associated with an increased rate of CHF. However, our estimates were accompanied by wide 95% CIs, and these CIs included clinically important effects. These results, which do not contradict the FDA-issued 'black box' warning (179, 180), are reassuring compared to previous estimates, which included ORs as high as 7 (40). Our lower estimates may in part be explained by our exclusion of patients with a history of CHF, who may be more susceptible to TZD-induced CHF due to their existing myocardial damage. Other key differences include study settings (e.g.,

real world vs. clinical trial) and the use of less restricted populations than examined in other observational studies (88, 128).

Although reassuring compared with previous reports (39, 40, 53, 70, 71, 88, 97, 98), the findings of our TZD analysis do not completely appease concerns regarding their safety profile. The 95% CIs that accompanied our estimates included both clinically important harmful effects and equivalence to the reference group (i.e., unexposed). The probability that TZDs have any benefits with respect to CHF is therefore low, notwithstanding their beneficial effects on glycemic control. Previous studies suggest that the use of TZDs results in a 1% decrease in HbA1c (47, 57, 58), an effect that should decrease the rate of CHF by 3% in this patient population (as discussed in Chapter 6). However, our point estimate suggests that prescription of TZDs may increase the rate of CHF by 19%, and the upper bound of our corresponding 95% CI indicates that this effect may be as high as 48%. In addition, previous studies have linked TZDs to an increased risk of fracture in women (130) and rosiglitazone to a potentially increased risk of MI (55) (as discussed in Chapter 2). Given the frequency with which these agents are prescribed (Chapter 5) and the totality of the evidence regarding potential safety issues related to these agents, the deleterious public health consequences may be large.

Clinically, physicians often prescribe TZDs as an alternative to starting insulin therapy in patients already receiving other oral agents at maximum dosages. However, these agents should be prescribed with caution. The benefits of very aggressive glycemic control are controversial (16, 17, 138, 177, 181, 182)

(including no benefit with respect to CHF, as demonstrated in this thesis), and patients with very poor control are unlikely to achieve sufficient benefit from TZD therapy to avoid insulin. If TZD therapy is used, available evidence suggests that pioglitazone possesses a more favorable safety profile (126). Although we were unable to thoroughly assess the TZD-specific risks due to low prescription rates for pioglitazone, previous studies suggest that pioglitazone and rosiglitazone likely have different cardiovascular effects (127). Unlike rosiglitazone, which may increase the risk of MI and cardiovascular death (55, 71), pioglitazone appears to decrease cardiovascular events (39, 54) and slows the progression of atherosclerosis (42). Other benefits with pioglitazone may include lower rates of CHF than rosiglitazone (127).

The findings of this thesis and those of other TZD studies have important regulatory implications. As is true with all currently available anti-diabetic agents, FDA approval was based on the glucose lowering ability of the therapy (174). Improved glycemic control lowers the risk of microvascular events (15) but the link between glycemic control and macrovascular events is less clear than originally thought. The recent publication of the 10-year follow-up of the UKPDS study (133) suggests that tight glycemic control may have beneficial long-term effects on survival but short- and medium-term studies found that tight glycemic control either had no effect on mortality (16, 140) or was associated with increased mortality (17). In addition, as suggested by our results, TZDs have deleterious CHF effects despite their favorable effects on HbA1c (109).

This evidence, combined with rosiglitazone's potential increase in MI, adds fuel to the ongoing debate regarding the role of surrogate endpoints in regulatory approval (83, 183). A reliance on RCTs powered to examine hard cardiovascular endpoints as part of regulatory approval would undoubtedly lengthen an already long process (174). Nonetheless, given the inherently high cardiovascular risk of patients with diabetes, there is an ongoing call for such trials to be included as part of the approval process (83, 183). As discussed in the literature review of this thesis (Chapter 2), the PROactive trial remains the only completed large RCT powered to examine the effect of a TZD (pioglitazone) on cardiovascular events. The conduct of 2 RCTs was mandated by the FDA when it granted regulatory approval for rosiglitazone (106). The first RCT (ADOPT) examined the effect of rosiglitazone on progression to insulin therapy (109), and the second (DREAM) investigated its effect on the risk of developing diabetes among patients with impaired fasting glucose (40). Neither trial was designed to assess the cardiovascular effects of rosiglitazone. These effects are being assessed in the ongoing RECORD study (110); follow-up for RECORD should be completed in 2009 (110), approximately a decade after rosiglitazone received FDA approval.

In response to the controversy surrounding rosiglitazone's MI effects, the Endocrinologic and Metabolic Drugs Advisory Committee of the FDA recommended that applications for regulatory approval of new anti-diabetic medications include a comparison of cardiovascular events from phase 2 and phase 3 trials (184). The Committee suggested that the upper limit of the relative

risk of this comparison be no greater than 1.8. If it is between 1.3 and 1.8 with a favorable risk-benefit ratio, they recommended that a sufficiently large post-marking RCT be conducted to ensure that the upper limit of the interval is less than 1.3 to conclusively address cardiovascular safety of new anti-diabetic agents.

Future pharmacoepidemiologic studies should be undertaken to identify which patients are at the greatest risk for CHF and other adverse events. The FDA's Sentinel Initiative (185), which links data from multiple administrative databases, may represent an ideal data source to estimate these subgroup-specific risks. Other unresolved issues include the impact of timing of TZD exposure on the risk of adverse outcomes and the pharmacogenetics of these agents.

This thesis investigated the effect of glycemic control on the risk of CHF; additional studies are needed to extend this work to other macrovascular events and to identify the optimal HbA1c treatment target. The use of TZDs should be avoided in such trials due to their questionable safety profile. For example, some have argued that the increased mortality observed in the ACCORD trial (17) among those randomized to intensive therapy may be due to increased use of rosiglitazone in the intensive-therapy arm (136).

The limitations of the three epidemiologic studies contained in this thesis are discussed briefly as part of the corresponding manuscripts presented in Chapters 5, 6, and 7; however, further discussion regarding some of these limitations is warranted. Our population-based sample involved over 3,400 CHF cases, representing a 6-fold increase over the total number of cases in the largest TZD RCT conducted to date, but was underpowered for definitive conclusions.

Consequently, some estimates are accompanied by wide confidence (or credible) intervals. This is particularly true in our examination of TZDs (Chapter 7). Despite the increasing prescription of TZDs over the course of the study period, there remained a relatively small number of exposed cases and imprecise treatment effects because of an underlying decreasing rate of CHF. This limitation, which inhibited our ability to examine the effects of specific TZDs, also prevented the use of marginal structural models to adjust for HbA1c. Inverse probability of treatment weighted estimation in marginal structural models represents a useful method of adjusting for time-varying confounders when assessing the causal effects of time-varying exposures (186, 187). These methods would have been an appropriate method to adjust for time-dependent confounding by glycemic control. However, rare exposures result in model instability due to the re-weighting methods. With only 5% of cases exposed to TZDs, the use of these methods was not attempted in this thesis. To account for confounding due to HbA1c, separate models were created with and without HbA1c adjustment. The former estimated the effect of TZDs confounded by HbA1c, and the latter estimated the effect of TZDs without the confounding due to HbA1c and independent of any benefits achieved through improved glycemic control. Both models produced very similar results, suggesting that glycemic control had minimal confounding effects.

The studies presented in this thesis were observational in nature and thus may be affected by biases inherent to such designs. In particular, there is the possibility of confounding by indication and residual confounding by other

variables. To minimize confounding, a number of strategies were implemented in the design and analysis of these studies. Design strategies included restricting our descriptive study to incident diabetics in sensitivity analyses to assess the effect of duration of diabetes. In addition, we matched on age, GPRD practice, and calendar date in the case-control studies. The rationale for matching on these variables is presented in detail in Chapter 3. Unfortunately, due to sparse risk sets, matching on duration of diabetes or incident/prevalent disease status was not feasible. Analytical strategies involved the use of multivariable conditional logistic regression to adjust for potential confounders. Sensitivity analyses included adjustment for additional potential confounders, and these analyses produced results that were similar to our primary analyses, suggesting that our results were robust. Nonetheless, residual confounding due to unmeasured variables remains a possible limitation.

Misclassification of disease status, exposure, or outcome represent other potential limitations. However, as described earlier in this thesis, the GPRD contains prospectively collected and validated data and has many processes in place to insure that its data are of high quality (155). Previous validation studies suggest that diabetes-related data in the GPRD are valid (153). Furthermore, the 3 components of our diabetes definition (clinical diagnosis, elevated HbA1c, anti-diabetic medical therapy) displayed high consistency, with over 90% of patients meeting all 3 criteria and over 98% meeting at least 2 of these criteria. The large majority of the patients who did not meet all 3 criteria did not receive anti-diabetic medical therapy; these patients are likely diet-controlled. Consequently,

it is unlikely that misclassification of diabetes status had a substantial effect on our results. Although 95% of prescriptions issued to the patient are recorded in the GPRD (105), these data represent prescriptions issued rather than filled, and poor adherence may result in misclassified TZD status. Moreover, misclassification of HbA1c due to natural fluctuations in the body and laboratory error represents an addition potential source of error; this misclassification was accounted for analytically in our Bayesian modeling, which suggested that the error associated with this measure is relatively small and did not impact our results. Finally, misclassification of CHF may have resulted in non-differential misclassification and represents a possible explanation for the null results obtained in our assessment of TZDs.

Despite these limitations, pharmacoepidemiologic studies such as the present one offer several advantages for the study of unintended drug effects. These advantages include an examination of a representative sample of unselected patients rather than highly-selected patients included in clinical trials and an investigation of how medications are used in actual clinical practice instead of an artificial laboratory setting. The use of large population-based data sources also allows for the identification of rare but serious side effects. For example, cessation of dual anti-platelet therapy among patients with drug-eluting stents can result in late-stent thrombosis, a rare but potentially fatal side effect not seen in RCTs (188). Concerns regarding this adverse event surfaced largely due to observational, post-marketing surveillance of this technology (189, 190). Similarly, despite some early signals in clinical trial data (191), observational

studies were critical in establishing that rofecoxib (Vioxx©) was associated with harmful cardiovascular effects (192-196). One reason that RCTs failed to identify this safety concern is that they did not investigate the use of rofecoxib in patients at high cardiovascular risk (197); these patients represented approximately 40% of patients using rofecoxib in actual practice (196). Despite their inherent limitations, observational studies play a critical role in establishing the safety of medications and devices.

Conclusions

During the period of 2000 to 2006, there was a substantial increase in the prescription of anti-diabetic medications among patients with type 2 diabetes. This shift is consistent with changes in treatment guidelines, yet the effect of this aggressive management remains controversial. Our population-based examination of the effect of glycemic control on the risk of CHF did not find a benefit with intensive glycemic control in this patient population. Nevertheless, poor control was associated with an increased risk, and the magnitude of this increased risk combined with the increasing prevalence of diabetes suggests that poor and very poor glycemic control has increasingly important public health consequences. This work extends other research findings questioning the benefits of intensive glycemic control to the field of CHF.

Unlike previous studies with restricted populations demonstrating an increased risk of CHF with TZDs, we could not conclusively show an increased risk in this population-based study. However, the present study ruled out any benefit associated with the use of TZDs with respect to CHF. Given the totality

of evidence regarding their cardiovascular risks (including increased CHF) and benefits, TZDs should be prescribed with extreme caution.

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Ref Type: Journal (Full)

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APPENDIX 1

DIAGNOSTIC CODES USED TO DEFINE TYPE 2 DIABETES

Appendix 1.1 Diagnoses included as part of the clinical diagnosis of type 2 diabetes definition.

GPRD Medical Code	Read / OXMIS Term	Number of Clinical Events
205846.00	Refuses Diabetes Monitoring	284
206457.00	Non-Insulin-Dependent Diabetes Mellitus	35,461
206458.00	Non-Insulin-Dependent Diabetes Mellitus With Neuro Comps	3
206459.00	Non-Insulin-Dependent Diabetes Mellitus With Retinopathy	65
206461.00	Diabetes Mellitus With Other Specified Manifestation	5
215440.00	Diabetes Mellitus With Neuropathy	2,255
215441.00	Other Specified Diabetes Mellitus With Multiple Comps	2
215442.00	Non-Insulin Dependent Diabetes Mellitus With Nephropathy	1
215444.00	Diabetes Mellitus, Adult, + Other Specified Manifestation	2
222267.00	Diabetes: Shared Care Programme	5,765
223870.00	Diabetes Monitoring 3rd Letter	276
224503.00	Other Specified Diabetes Mellitus With Renal Complications	5
224505.00	Diabetes Mellitus NOS With Neurological Manifestation	25
231370.00	Unstable Diabetes	320
233007.00	Diabetes Clinic Administration	3,103
233603.00	Maturity Onset Diabetes	15,658
233604.00	Diabetes Mellitus, Adult Onset, + Ophthalmic Manifestation	30
233605.00	Diabetes With Gangrene	33
233608.00	Non-Insulin Dependent Diabetes Mellitus With Gangrene	5
234597.00	Nephrotic Syndrome In Diabetes Mellitus	59
234597.00	Nephrotic Syndrome In Diabetes Mellitus	59
242641.00	Non-Insulin Dependent Diabetes Mellitus	58,194
242643.00	Diabetes Mellitus With Polyneuropathy	2
242648.00	Non-Insulin-Dependent Diabetes Mellitus With Renal Comps	8
242650.00	Non-Insulin Dependent Diabetes Mellitus With Ulcer	94
242653.00	Diabetes Mellitus NOS With Other Specified Manifestation	3
242655.00	Diabetes Mellitus, Adult Onset, + Unspecified Complication	4
242656.00	Diabetes Mellitus NOS With Unspecified Complication	7
251250.00	Diabetes Monitoring Admin.	565,254
251251.00	Diabetes Monitoring 2nd Letter	860
251807.00	Unspecified Diabetes Mellitus With Multiple Complications	1
251808.00	Non-Insulin-Dependent Diabetes Mellitus Without Complication	60
258117.00	Foot Abnormality - Diabetes Related	139
260430.00	Attends Diabetes Monitoring	3,4119
260431.00	Diabetes Monitored	4,197
260432.00	Diabetes Monitoring Admin.NOS	212
261002.00	Diabetes Mellitus, Adult Onset, With Renal Manifestation	15
261003.00	Diabetes Mellitis With Nephropathy NOS	40
261004.00	Diabetes Mellitus With Gangrene	106
261408.00	Polyneuropathy In Diabetes	390
264936.00	[V]Dietary Counselling In Diabetes Mellitus	121
267312.00	Retinal Abnormality - Diabetes Related	46
270268.00	Diabetes Mellitus	307,986
270269.00	Diabetes Mellitus, Adult Onset, No Mention Of Complication	8,105
270270.00	Diabetes Mellitus With Peripheral Circulatory Disorder	124
270271.00	Diabetes Mellitus, Adult, + Peripheral Circulatory Disorder	3
270274.00	Non-Insulin Dependent Diabetes Mellitus With Polyneuropathy	5

GPRD Medical Code	Read / OXMIS Term	Number of Clinical Events
270372.00	[X]Diabetes Mellitus	2
278715.00	Diabetes Monitoring Default	1,923
279341.00	Diabetes Mellitus NOS With No Mention Of Complication	46
279342.00	Diabetes Mellitus With Renal Manifestation	263
279343.00	Diabetes Mellitus, Adult With Gangrene	13
279344.00	NIDDM - Non-Insulin Dependent Diabetes Mellitus	2,374
279345.00	Non-Insulin Dependent Diabetes Mellitus With Mononeuropathy	3
279348.00	Diabetes Mellitus With Unspecified Complication	10
279691.00	Autonomic Neuropathy Due To Diabetes	442
280482.00	Pre-Existing Diabetes Mellitus, Unspecified	1
286217.00	Has Seen Dietician - Diabetes	1,335
287862.00	Diabetes Monitoring 1st Letter	5,784
288454.00	Diabetes Mellitus, Adult Onset, With Ketoacidosis	9
288455.00	Diabetes Mellitus With Hyperosmolar Coma	90
288458.00	Diabetes Mellitus NOS With Ophthalmic Manifestation	4
288459.00	Diabetes Mellitus NOS With Peripheral Circulatory Disorder	23
288460.00	Type 2 Diabetes Mellitus	25,115
288461.00	Non-Insulin-Dependent Diabetes Mellitus With Ophthalm Comps	2
288523.00	Renal Diabetes	12
295380.00	Diabetes: Practice Programme	25,980
295381.00	Diabetes Management Plan Given	5,664
297029.00	Attending Diabetes Clinic	4,083
297051.00	Diabetes Monitor.Verbal Invite	98
297052.00	Diabetes Monitor.Phone Invite	167
297053.00	Diabetes Monitor. Check Done	13,191
297725.00	Diabetes Mellitus With No Mention Of Complication	296
297726.00	Diabetes Mellitus, Adult Onset, With Hyperosmolar Coma	5
297727.00	Diabetes Mellitus NOS With Hyperosmolar Coma	1
297728.00	Diabetes Mellitus, Adult Onset, With Ketoacidotic Coma	1
297729.00	Diabetes Mellitus NOS With Ketoacidotic Coma	1
297730.00	Diabetes Mellitus With Ophthalmic Manifestation	341
297731.00	Diabetes Mellitus With Neurological Manifestation	733
297732.00	Diabetes Mellitus, Adult Onset, + Neurological Manifestation	29
297733.00	Other Specified Diabetes Mellitus With Neurological Comps	6
297738.00	Non-Insulin Dependant Diabetes Mellitus - Poor Control	329
297739.00	Other Specified Diabetes Mellitus With Other Spec Comps	3
302788.00	Type II Diabetes Mellitus	2168
307957.00	Type II Diabetes Mellitus - Poor Control	18
308094.00	Type II Diabetes Mellitus With Gangrene	5
308119.00	Type II Diabetes Mellitus With Ulcer	12
308463.00	Type 2 Diabetes Mellitus With Retinopathy	6
308504.00	Type 2 Diabetes Mellitus With Diabetic Cataract	7
308703.00	Dietary Advice For Diabetes Mellitus	698
308826.00	Foot Abnormality - Diabetes Related	197
308830.00	Type II Diabetes Mellitus With Retinopathy	9
308851.00	Type II Diabetes Mellitus With Polyneuropathy	2
308872.00	Type II Diabetes Mellitus With Nephropathy	5
309007.00	Type 2 Diabetes Mellitus With Neuropathic Arthropathy	3
309010.00	Type 2 Diabetes Mellitus With Peripheral Angiopathy	1
309143.00	Type II Diabetes Mellitus With Hypoglycaemic Coma	2
309275.00	Type II Diabetes Mellitus With Renal Complications	2

GPRD Medical Code	Read / OXMIS Term	Number of Clinical Events
309300.00	Insulin Treated Type 2 Diabetes Mellitus	1,559
309572.00	Diabetes Care By Hospital Only	1,503
309614.00	Type II Diabetes Mellitus With Diabetic Cataract	4
309628.00	Type 2 Diabetes Mellitus With Nephropathy	7
309658.00	Insulin Treated Non-Insulin Dependent Diabetes Mellitus	8
309704.00	Non-Insulin Dependent Diabetes Mellitus With Arthropathy	4
309738.00	Type 2 Diabetes Mellitus With Neurological Complications	3
309758.00	Type 2 Diabetes Mellitus With Ophthalmic Complications	1
310005.00	Type 2 Diabetes Mellitus - Poor Control	15
310061.00	Type II Diabetes Mellitus With Neuropathic Arthropathy	2
331538.00	Type 2 Diabetes Mellitus With Renal Complications	2
331810.00	Type 2 Diabetes Mellitus With Ulcer	5
331823.00	Non-Insulin Dependent Diabetes Mellitus With Hypoglyca Coma	3
331925.00	Insulin Treated Type II Diabetes Mellitus	10
332060.00	Diabetes Medication Review	1,992
332066.00	Maturity Onset Diabetes In Youth Type 2	5
333249.00	Type II Diabetes Mellitus With Neurological Complications	2
333576.00	Type 2 Diabetes Mellitus With Hypoglycaemic Coma	2
339527.00	Hyperosmolar Non-Ketotic State In Type 2 Diabetes Mellitus	4
339633.00	Type 2 Diabetes Mellitus	27,361
339960.00	Type 2 Diabetes Mellitus With Nephropathy	177
339961.00	Insulin Treated Type 2 Diabetes Mellitus	747
340163.00	Non-Insulin Depend Diabetes Mellitus With Diabetic Cataract	1
340257.00	Type 2 Diabetes Mellitus With Neuropathic Arthropathy	13
340332.00	Type II Diabetes Mellitus With Peripheral Angiopathy	3
340350.00	Dietary Advice For Type II Diabetes	14
340357.00	Type 2 Diabetes Mellitus With Retinopathy	41
340367.00	Type 2 Diabetes Mellitus Without Complication	2
340474.00	Type 2 Diabetes Mellitus With Persistent Microalbuminuria	277
340507.00	Type II Diabetes Mellitus With Mononeuropathy	1
340973.00	Type 2 Diabetes Mellitus With Mononeuropathy	21
341003.00	Type 2 Diabetes Mellitus With Ketoacidosis	56
341078.00	Hyperosmolar Non-Ketotic State In Type 2 Diabetes Mellitus	16
341116.00	Type 2 Diabetes Mellitus With Persistent Proteinuria	61
341127.00	Type 2 Diabetes Mellitus With Peripheral Angiopathy	4
341264.00	Type 2 Diabetes Mellitus With Neurological Complications	8
341286.00	Type 2 Diabetes Mellitus With Diabetic Cataract	4
341302.00	Type 2 Diabetes Mellitus - Poor Control	39
341357.00	Type 2 Diabetes Mellitus With Ulcer	15
341459.00	Type 2 Diabetes Mellitus With Renal Complications	12
341509.00	Type 2 Diabetes Mellitus With Gangrene	1
341557.00	Patient On Maximal Tolerated Therapy For Diabetes	756
341680.00	Diabetes Mellitus Autosomal Dominant Type 2	23
341801.00	Type 2 Diabetes Mellitus With Polyneuropathy	27
342035.00	Maturity Onset Diabetes In Youth	15
342185.00	Type 2 Diabetes Mellitus With Exudative Maculopathy	7
342313.00	Type 2 Diabetes Mellitus With Ketoacidotic Coma	1
342317.00	Type 2 Diabetes Mellitus With Hypoglycaemic Coma	7
342400.00	Exception Reporting: Diabetes Quality Indicators	152
343145.00	Diabetes Clinic Satisfaction Questionnaire	2
343531.00	Type II Diabetes Mellitus With Arthropathy	1
343565.00	Type 2 Diabetes Mellitus With Arthropathy	1

GPRD Medical Code	Read / OXMIS Term	Number of Clinical Events
343650.00	Diabetes Mellitus Autosomal Dominant	2
343930.00	Pan Retinal Photocoagulation For Diabetes	37
344027.00	Type 2 Diabetes Mellitus With Multiple Complications	1
344028.00	Type 2 Diabetes Mellitus With Arthropathy	1
344412.00	Type II Diabetes Mellitus	1
344495.00	Lipoatrophic Diabetes Mellitus	1
231371.00	Brittle Diabetes	544
201928.00	Diabetic Glomerulosclerosis	10
210870.00	Gangrene Diabetic	32
229069.00	Diabetic Acidosis	33
247152.00	Diabetic Diarrhoea	44
256382.00	Diabetes Chemical (Abnormal Biochemistry	83
283819.00	Coma Diabetic	121
283822.00	Hyperosmolar Diabetic State	58
292948.00	Abscess Diabetic	2
306134.00	Unstable Diabetic	272
303251.00	Niddm (Non-Insulin Dependent Diabetes)	4,270
303253.00	Maturity Onset Diabetes Mellitus Insulin	20
303254.00	Maturity Onset Diabetes(Mellitus) Non-In	22
303255.00	Maturity Onset Diabetes (Mellitus)	537
303256.00	Diabetes	139,896
303259.00	Dietary Control Diabetes	391
303260.00	Hypoglycaemics Oral Diabetes	57
306131.00	Hypoglycaemia In Diabetes Mellitus	652
301930.00	Diabetes - Good Control	8,152
243795.00	Pre-Existing Diabetes Mellitus, Non-Insulin-Dependent	13
283438.00	Diabetes - Poor Control	14,879
298869.00	Pre-Existing Diabetes Mellitus, Insulin-Dependent	244
303250.00	Sugar Diabetes	40

Appendix 1.2 List of codes excluded from codes used to define clinical diagnosis of type 2 diabetes.

GPRD Medical Code	Read / OXMIS Term	Number of Clinical Events
274750.00	Diabetes Insipidus	483
202605.00	Syndrome Diabetic Congenital Due Materna	1
229070.00	Diabetes Pregnancy	150
266548.00	Iatrogenic Diabetes Mellitus	3
248905.00	Retinal Abnormality - Non-Diabetes	14
221663.00	Foot Abnormality - Non-Diabetes	31
308503.00	Foot Abnormality - Non-Diabetes	64
340806.00	Diabetes: Shared Care In Pregnancy - Diabetol And Obstet	5
206460.00	Diabetes Mellitus Induced By Steroids	107
270276.00	Steroid Induced Diabetes Mellitus Without Complication	56
343055.00	Secondary Pancreatic Diabetes Mellitus	4
215445.00	Steroid Induced Diabetes	143
288469.00	Diabetes Insipidus	591
279356.00	Diabetes Insipidus - Pituitary	1
280297.00	Nephrogenic Diabetes Insipidus	62
216578.00	Diabetes Mellitus - Unspec Whether In Pregnancy/Puerperium	1
289607.00	Diabetes Mellitus During Pregnancy - Baby Not Yet Delivered	8
280481.00	Diabetes Mellitus Arising In Pregnancy	53
207594.00	Gestational Diabetes Mellitus	1,926
289609.00	Gestational Diabetes Mellitus	932
252954.00	Diabetes Mellitus In Pregnancy/Childbirth/Puerperium Nos	2
206460.00	Diabetes Mellitus Induced By Steroids	107
207594.00	Gestational Diabetes Mellitus	1,926
215445.00	Steroid Induced Diabetes	143
221663.00	Foot Abnormality - Non-Diabetes	31
229070.00	Diabetes Pregnancy	150
237301.00	[V]Family History Of Diabetes Mellitus	83
202605.00	Syndrome Diabetic Congenital Due Materna	1
216578.00	Diabetes Mellitus - Unspec Whether In Pregnancy/Puerperium	1
248905.00	Retinal Abnormality - Non-Diabetes	14
258811.00	Diabetes Mellitus Screen	382,815
252954.00	Diabetes Mellitus In Pregnancy/Childbirth/Puerperium Nos	2
266548.00	Iatrogenic Diabetes Mellitus	3
274142.00	[V]Screening For Diabetes Mellitus (Dm)	30
274750.00	Diabetes Insipidus	483
270276.00	Steroid Induced Diabetes Mellitus Without Complication	56
279356.00	Diabetes Insipidus - Pituitary	1
280481.00	Diabetes Mellitus Arising In Pregnancy	53
280297.00	Nephrogenic Diabetes Insipidus	62
289607.00	Diabetes Mellitus During Pregnancy - Baby Not Yet Delivered	8
289609.00	Gestational Diabetes Mellitus	932
288469.00	Diabetes Insipidus	591
308503.00	Foot Abnormality - Non-Diabetes	64
340806.00	Diabetes: Shared Care In Pregnancy - Diabetol And Obstet	5
343055.00	Secondary Pancreatic Diabetes Mellitus	4
344436.00	Informed Consent For Diabetes National Audit	1
228676.00	Diabetes Check Up	27,092
274451.00	High Risk Diabetes (Mellitus)	3
302787.00	Type I Diabetes Mellitus	545

GPRD Medical Code	Read / OXMIS Term	Number of Clinical Events
303252.00	Diabetes Mellitus Insulin Dependant	13,245
206451.00	Insulin Dependent Diabetes Mellitus	11,805
206455.00	Insulin-Dependent Diabetes Mellitus With Renal Complications	11
206456.00	Insulin Dependent Diabetes Mellitus With Nephropathy	2
233607.00	Insulin Dependent Diabetes Mellitus	10,014
242647.00	Insulin Dependent Diabetes Mellitus With Retinopathy	153
251805.00	Diabetes Mellitus, Juvenile Type, No Mention Of Complication	318
251806.00	Insulin-Dependent Diabetes Mellitus With Neurological Comps	3
261005.00	Type 1 Diabetes Mellitus	3,265
261006.00	Insulin Dependent Diabetes Mellitus With Multiple Complicatn	2
261007.00	Insulin Dependent Diabetes Mellitus - Poor Control	109
261008.00	Insulin Dependent Diabetes Mellitus With Mononeuropathy	1
270273.00	Iddm-Insulin Dependent Diabetes Mellitus	2,987
288456.00	Diabetes Mellitus, Juvenile Type, + Ophthalmic Manifestation	1
288463.00	Diabetes Mellitus, Juvenile, + Other Specified Manifestation	1
297734.00	Insulin Dependent Diabetes Mellitus With Ulcer	97
297735.00	Insulin Dependent Diabetes Mellitus With Gangrene	6
297736.00	Insulin Dependent Diabetes Maturity Onset	435
297737.00	Insulin Dependent Diabetes Mellitus With Polyneuropathy	6
308004.00	Type I Diabetes Mellitus With Hypoglycaemic Coma	11
308067.00	Type I Diabetes Mellitus Maturity Onset	4
308089.00	Insulin Dependent Diabetes Mellitus With Hypoglycaemic Coma	31
308370.00	Type I Diabetes Mellitus With Arthropathy	2
308820.00	Type I Diabetes Mellitus - Poor Control	11
308871.00	Type I Diabetes Mellitus With Diabetic Cataract	3
308934.00	Insulin Dependent Diabetes Mellitus With Arthropathy	3
308948.00	Type 1 Diabetes Mellitus With Retinopathy	6
309125.00	Type 1 Diabetes Mellitus - Poor Control	1
309757.00	Type I Diabetes Mellitus With Nephropathy	3
309863.00	Unstable Type I Diabetes Mellitus	2
332948.00	Type I Diabetes Mellitus With Ulcer	4
332953.00	Type I Diabetes Mellitus With Retinopathy	6
333621.00	Type 1 Diabetes Mellitus With Neuropathic Arthropathy	3
336008.00	Type I Diabetes Mellitus With Neurological Complications	1
339632.00	Type 1 Diabetes Mellitus	3,953
339986.00	Type 1 Diabetes Mellitus With Retinopathy	24
340162.00	Type 1 Diabetes Mellitus With Renal Complications	3
340230.00	Type 1 Diabetes Mellitus With Arthropathy	3
340463.00	Perceived Control Of Insulin-Dependent Diabetes	37
340580.00	Type 1 Diabetes Mellitus With Ketoacidosis	267
340814.00	Type 1 Diabetes Mellitus With Hypoglycaemic Coma	5
340865.00	Type 1 Diabetes Mellitus With Hypoglycaemic Coma	1
340987.00	Type 1 Diabetes Mellitus With Renal Complications	4
341002.00	Type 1 Diabetes Mellitus With Ketoacidotic Coma	14
341126.00	Type 1 Diabetes Mellitus - Poor Control	19
341139.00	Type 1 Diabetes Mellitus Maturity Onset	2
341221.00	Type 1 Diabetes Mellitus With Ophthalmic Complications	3
341356.00	Unstable Type 1 Diabetes Mellitus	3
341409.00	Type 1 Diabetes Mellitus With Persistent Microalbuminuria	36
341598.00	Type 1 Diabetes Mellitus With Ulcer	6
341800.00	Type 1 Diabetes Mellitus With Polyneuropathy	4
341836.00	Type 1 Diabetes Mellitus With Neurological Complications	1
341856.00	Type 1 Diabetes Mellitus With Persistent Proteinuria	20

GPRD Medical Code	Read / OXMIS Term	Number of Clinical Events
342036.00	Type 1 Diabetes Mellitus With Neuropathic Arthropathy	5
342516.00	Type 1 Diabetes Mellitus With Exudative Maculopathy	2
342681.00	Type I Diabetes Mellitus With Mononeuropathy	1
342740.00	Type I Diabetes Mellitus With Ketoacidosis	1
343003.00	Type 1 Diabetes Mellitus With Neurological Complications	1
343345.00	Type 1 Diabetes Mellitus With Diabetic Cataract	2
343699.00	Dietary Advice For Type I Diabetes	1
344076.00	Insulin Dependent Diabetes Mellitus	1
344338.00	Type 1 Diabetes Mellitus With Gangrene	1
215438.00	Diabetes Mellitus, Juvenile Type, With Ketoacidosis	17
224500.00	Diabetes Mellitus, Juvenile Type, With Ketoacidotic Coma	2
224502.00	Diabetes Mellitus, Juvenile Type, With Renal Manifestation	1
233606.00	Diabetes Mellitus, Juvenile +Peripheral Circulatory Disorder	1
242642.00	Other Specified Diabetes Mellitus With Ketoacidosis	3
242644.00	Diabetes Mellitus, Juvenile, + Neurological Manifestation	3
242654.00	Diabetes Mellitus, Juvenile Type, + Unspecified Complication	1
261095.00	[X]Other Specified Diabetes Mellitus	2
288457.00	Other Specified Diabetes Mellitus With Ophthalmic Complicatn	3
340333.00	Type 1 Diabetes Mellitus With Nephropathy	57
239414.00	At Risk Of Diabetes Mellitus	1,802
206452.00	Diabetes Mellitus With Ketoacidotic Coma	45
215437.00	Diabetes Mellitus With Ketoacidosis	4,497
215439.00	Diabetes Mellitus Nos With Ketoacidosis	36
224507.00	Insulin-Dependent Diabetes Without Complication	4
233609.00	Malnutrition-Related Diabetes Mellitus With Ketoacidosis	25
242645.00	Insulin-Dependent Diabetes Mellitus With Ophthalmic Comps	4
242646.00	Unstable Insulin Dependent Diabetes Mellitus	27
261009.00	Malnutrition-Related Diabetes Mellitus With Coma	1
308715.00	Insulin Dependent Diabetes Mellitus With Diabetic Cataract	5
331568.00	Type I Diabetes Mellitus With Renal Complications	3
292951.00	Diabetic Acetonaemia	196
303261.00	Precoma Diabetic	5
303262.00	Ketoacidosis Diabetic	918
303263.00	Ketosis Diabetic	116

APPENDIX 2

WINBUGS CODE FOR BAYESIAN CONDITIONAL LOGISTIC REGRESSION WITH MEASUREMENT ERROR ADJUSTMENT

```
# Conditional Logistic Regression Model for Analysis of Effect of HbA1c on CHF
# Based on Mukherjee B, Sinha S, Ghosh M. Bayesian analysis for case-control studies: a review article. Handbook of Statistics 2005;793-819.
# Programmer: Kristian Filion
# March 9th, 2009
# Age, Sex, BMI, Smoking, Diagnosis, Non-Diabetes and Diabetes Medications, Duration of Diabetes, and Laboratory Tests Adjusted
# With Adjustment for HbA1c Measurement Error

model
{
        for (i in 1:2203)       # Loop over 2203 Matched Sets - Remaining Sets Excluded Due to Missing Data
                                # The dataset is ordered such that the case appears first in each matched set.
                                # The numerator contains data for cases; the denominator contains data for the entire matched set.

        {
        numerator_part1[i]<-exp(beta1*hba1c_7_8.pop[i,1] + beta2*hba1c_8_9.pop[i,1] + beta3*hba1c_9_10.pop[i,1] +
beta4*hba1c_10.pop[i,1] + beta5*age[i,1] + beta6*male[i,1] + beta7*bmi[i,1] + beta8*smoking_current[i,1] +
beta9*smoking_past[i,1] +  beta10*ua_acs[i,1] + beta11*afib[i,1] + beta12*angiogram[i,1] + beta13*cabg[i,1] + beta14*cad[i,1] +
beta15*cerebrovascular[i,1] + beta16*copd[i,1] + beta17*dyslipidemia[i,1] + beta18*ht[i,1] + beta19*previous_mi[i,1] +
beta20*previous_stroke[i,1] + beta21*pvd[i,1] + beta22*ra[i,1] + beta23*pci[i,1] + beta24*renal_failure[i,1])

        numerator_part2[i]<-exp(beta25*ace_i[i,1] + beta26*arbs[i,1] + beta27*asa_any[i,1] + beta28*beta_blockers[i,1] +
beta29*ca_blockers[i,1] + beta30*digoxin[i,1] + beta31*diuretics_other_ht[i,1] + beta32*nitrates[i,1] + beta33*statins[i,1] +
beta34*cox_inhibitors[i,1] + beta35*rosiglitazone_any[i,1] + beta36*pioglitazone[i,1] + beta37*insulin[i,1] + beta38*metformin[i,1]
+ beta39*sulfonylureas[i,1] + beta40*other_oral_anti_dm[i,1] + beta41*duration_dm_at_index[i,1] +
beta42*mean_total_cholesterol[i,1] + beta43*mean_systolic[i,1] + beta44*mean_diastolic[i,1])

# The numerator is split into 2 because the length of the line exceeds the limit in Winbugs.  The same occurs in the denominator.
```

```
        numerator[i]<-numerator_part1[i]*numerator_part2[i]


    for (j in 1:J[i])

    {
        denominator_part1[i,j]<-exp(beta1*hba1c_7_8.pop[i,j] + beta2*hba1c_8_9.pop[i,j] + beta3*hba1c_9_10.pop[i,j] +
beta4*hba1c_10.pop[i,j] + beta5*age[i,j] + beta6*male[i,j] + beta7*bmi[i,j] + beta8*smoking_current[i,j] + beta9*smoking_past[i,j] +
beta10*ua_acs[i,j] + beta11*afib[i,j] + beta12*angiogram[i,j] + beta13*cabg[i,j] + beta14*cad[i,j] + beta15*cerebrovascular[i,j] +
beta16*copd[i,j] + beta17*dyslipidemia[i,j] + beta18*ht[i,j] + beta19*previous_mi[i,j] + beta20*previous_stroke[i,j] + beta21*pvd[i,j]
+ beta22*ra[i,j] + beta23*pci[i,j] + beta24*renal_failure[i,j])

        denominator_part2[i,j]<-exp(beta25*ace_i[i,j] + beta26*arbs[i,j] + beta27*asa_any[i,j] + beta28*beta_blockers[i,j] +
beta29*ca_blockers[i,j] + beta30*digoxin[i,j] + beta31*diuretics_other_ht[i,j] + beta32*nitrates[i,j] + beta33*statins[i,j] +
beta34*cox_inhibitors[i,j] + beta35*rosiglitazone_any[i,j] + beta36*pioglitazone[i,j] + beta37*insulin[i,j] + beta38*metformin[i,j] +
beta39*sulfonylureas[i,j] + beta40*other_oral_anti_dm[i,j] + beta41*duration_dm_at_index[i,j] + beta42*mean_total_cholesterol[i,j]
+ beta43*mean_systolic[i,j] + beta44*mean_diastolic[i,j])

        denominator[i,j]<-denominator_part1[i,j]*denominator_part2[i,j]


        hba1c[i,j] ~ dnorm(hba1c.true[i,j], tau.error)      # HbA1c is the measured value from the GPRD.  HbA1c.true is the
                                                            theoretical value free of measurement error.  Tau.error is the amount of
                                                            measurement error.
                                                            # This is the measurement model
```

```
        hba1c.true[i,j] ~ dnorm(7.75,0.25)          # Using available data, we have hypothesized that the true population
                                                    mean for HbA1c is 7.75% and the corresponding tau is 0.25 (SD=2)
                                                    # This is the exposure model

        hba1c_10.pop[i,j]<-step(hba1c.true[i,j]-10) # The step function creates a binary variable such that, if the statement is
                                                    true, the variable is equal to 1.  Otherwise, it is equal to 0.

        hba1c_9.pop[i,j]<-step(hba1c.true[i,j]-9)   # In these lines, binary variables are created for the theoretical true values
                                                    of HbA1c, with HbA1c_10 indicating an HbA1c greater than 10

        hba1c_8.pop[i,j]<-step(hba1c.true[i,j]-8)   # and HbA1c_9_10 indicating an HbA1c between 9 and 10.  The other
                                                    HbA1c variables are coded similarly.
        hba1c_7.pop[i,j]<-step(hba1c.true[i,j]-7)
        hba1c_9_10.pop[i,j]<-step(hba1c_9.pop[i,j]-hba1c_10.pop[i,j]-0.5)
        hba1c_8_9.pop[i,j]<-step(hba1c_8.pop[i,j]-hba1c_9.pop[i,j]-0.5)
        hba1c_7_8.pop[i,j]<-step(hba1c_7.pop[i,j]-hba1c_8.pop[i,j]-0.5)
    }
        likelihood[i]<-numerator[i]/sum(denominator[i, 1:J[i]])

}

 beta1  ~  dnorm(0, 0.01) I(-2, 2)          #  Prior for beta1
 beta2  ~  dnorm(0, 0.01) I(-2, 2)          #  Prior for beta2
 beta3  ~  dnorm(0, 0.01) I(-2, 2)          #  Prior for beta3
 beta4  ~  dnorm(0, 0.01) I(-2, 2)          #  Prior for beta4
 beta5  ~  dnorm(0, 0.01) I(-2, 2)          #  Prior for beta5
 beta6  ~  dnorm(0, 0.01) I(-2, 2)          #  Prior for beta6
 beta7  ~  dnorm(0, 0.01) I(-2, 2)          #  Prior for beta7
```

```
beta8 ~ dnorm(0, 0.01) I(-2, 2)          # Prior for beta8
beta9 ~ dnorm(0, 0.01) I(-2, 2)          # Prior for beta9
beta10 ~ dnorm(0, 0.01) I(-2, 2)         # Prior for beta10
beta11 ~ dnorm(0, 0.01) I(-2, 2)         # Prior for beta11
beta12 ~ dnorm(0, 0.01) I(-2, 2)         # Prior for beta12
beta13 ~ dnorm(0, 0.01) I(-2, 2)         # Prior for beta13
beta14 ~ dnorm(0, 0.01) I(-2, 2)         # Prior for beta14
beta15 ~ dnorm(0, 0.01) I(-2, 2)         # Prior for beta15
beta16 ~ dnorm(0, 0.01) I(-2, 2)         # Prior for beta16
beta17 ~ dnorm(0, 0.01) I(-2, 2)         # Prior for beta17
beta18 ~ dnorm(0, 0.01) I(-2, 2)         # Prior for beta18
beta19 ~ dnorm(0, 0.01) I(-2, 2)         # Prior for beta19
beta20 ~ dnorm(0, 0.01) I(-2, 2)         # Prior for beta20
beta21 ~ dnorm(0, 0.01) I(-2, 2)         # Prior for beta21
beta22 ~ dnorm(0, 0.01) I(-2, 2)          # Prior for beta22
beta23 ~ dnorm(0, 0.01) I(-2, 2)         # Prior for beta23
beta24 ~ dnorm(0, 0.01) I(-2, 2)         # Prior for beta24
beta25 ~ dnorm(0, 0.01) I(-2, 2)          # Prior for beta25
beta26 ~ dnorm(0, 0.01) I(-2, 2)         # Prior for beta26
beta27 ~ dnorm(0, 0.01) I(-2, 2)         # Prior for beta27
beta28 ~ dnorm(0, 0.01) I(-2, 2)         # Prior for beta28
beta29 ~ dnorm(0, 0.01) I(-2, 2)         # Prior for beta29
beta30 ~ dnorm(0, 0.01) I(-2, 2)         # Prior for beta30
beta31 ~ dnorm(0, 0.01) I(-2, 2)         # Prior for beta31
beta32 ~ dnorm(0, 0.01) I(-2, 2)          # Prior for beta32
beta33 ~ dnorm(0, 0.01) I(-2, 2)         # Prior for beta33
beta34 ~ dnorm(0, 0.01) I(-2, 2)          # Prior for beta34
beta35 ~ dnorm(0, 0.01) I(-2, 2)          # Prior for beta35
```

```
beta36  ~  dnorm(0, 0.01) I(-2, 2)          #  Prior for beta36
beta37  ~  dnorm(0, 0.01) I(-2, 2)          #  Prior for beta37
beta38  ~  dnorm(0, 0.01) I(-2, 2)          #  Prior for beta38
beta39  ~  dnorm(0, 0.01) I(-2, 2)          #  Prior for beta39
beta40  ~  dnorm(0, 0.01) I(-2, 2)          #  Prior for beta40
beta41  ~  dnorm(0, 0.01) I(-2, 2)          #  Prior for beta41
beta42  ~  dnorm(0, 0.01) I(-2, 2)          #  Prior for beta42
beta43  ~  dnorm(0, 0.01) I(-2, 2)          #  Prior for beta43
beta44  ~  dnorm(0, 0.01) I(-2, 2)          #  Prior for beta44
tau.error<-1/(sigma.error*sigma.error)      # Winbugs relies on tau, rather than sigma.  Here, tau.error is converted to sigma.error,
                                            which is defined in the next line.

sigma.error ~ dunif(0.45, 0.50)             # From the literature, we expect SD=0.47 for the measurement error of HbA1c.  We have
                                            therefore used a prior for sigma.error that ranges from 0.45 to 0.50.

or.hba1c_7_8.pop <- exp(beta1)
or.hba1c_8_9.pop <- exp(beta2)
or.hba1c_9_10.pop <- exp(beta3)
or.hba1c_10.pop <- exp(beta4)
or.age           <- exp(beta5)
or.male          <- exp(beta6)
or.bmi           <- exp(beta7)
or.smoking.current <- exp(beta8)
or.smoking.past        <- exp(beta9)
or.ua_acs <- exp(beta10)
or.afib <- exp(beta11)
or.angiogram <- exp(beta12)
or.cabg <- exp(beta13)
```

```
or.cad <- exp(beta14)
or.cerebrovascular <- exp(beta15)
or.copd <- exp(beta16)
or.dyslipidemia <- exp(beta17)
or.ht<- exp(beta18)
or.previous_mi <- exp(beta19)
or.previous_stroke <- exp(beta20)
or.pvd <- exp(beta21)
or.ra <- exp(beta22)
or.pci <- exp(beta23)
or.renal_failure <- exp(beta24)
or.ace_i <- exp(beta25)
or.arbs <- exp(beta26)
or.asa_any <- exp(beta27)
or.beta_blockers <- exp(beta28)
or.ca_blockers <- exp(beta29)
or.digoxin <- exp(beta30)
or.diuretics_other_ht <- exp(beta31)
or.nitrates <- exp(beta32)
or.statins <- exp(beta33)
or.cox_inhibitors <- exp(beta34)
or.rosiglitazone_any<- exp(beta35)
or.pioglitazone<- exp(beta36)
or.insulin<- exp(beta37)
or.metformin<- exp(beta38)
or.sulfonylureas<- exp(beta39)
or.other_oral_anti_dm<- exp(beta40)
or.duration_dm_at_index<- exp(beta41)
```

```
or.mean_total_cholesterol<- exp(beta42)
or.mean_systolic<- exp(beta43)
or.mean_diastolic<- exp(beta44)


                    C <- 1                          # This needs to be large enough to ensure all p[i]'s < 1
                    for (i in 1:2203) {             # There are 2,203 matched sets
                            ones[i] <- 1            # This is a trick to get WinBUGS to multiply the lines (numerator
                                                    # and denominator) from each subject together and creates the
                                                    # overall likelihood function.
                            p[i] <- likelihood[i] / C
                            ones[i] ~ dbern(p[i])
                    }

}
```

APPENDIX 3

ETHICS APPROVAL FROM THE MCGILL UNIVERSITY HEALTH CENTRE RESEARCH ETHICS BOARD

Centre universitaire de santé McGill
McGill University Health Centre
Les meilleurs soins pour la vie
The Best Care for Life

Bureau d'éthique de la recherche
Office of Research Ethics

May 22, 2008

Dr. James Brophy
MUHC – RVH
Room R4.12

Re: "The Effect of Diabetes Mellitus on the Development, Treatment, and Outcomes of Congestive Heart Failure"

Dear Dr. Brophy:

We have received an Application for Continuing Review for the research study referenced above. The report was presented for review at the convened meeting of the SDR Committee on May 21, 2008. It was found to be acceptable for ongoing conduct at the McGill University Health Centre, and was entered accordingly, into the minutes of the meeting. At the MUHC, sponsored research activities that require US federal assurance are conducted under Federal Wide Assurance (FWA) 00000840.

The re-approval for the study was provided until May 20, 2009.

All research involving human subjects requires review at a recurring interval. It is the responsibility of the principal investigator to submit an Application for Continuing Review to the REB prior to the expiration of approval to comply with the regulation for continuing review of "at least once per year".

However, should the research conclude for any reason prior to the next required review, you are required to submit a Termination Report to the Committee once the data analysis is complete to give an account of the study findings and publication status.

Should any revision to the study, or other unanticipated development occur prior to the next required review, you must advise the REB without delay. Regulation does not permit initiation of a proposed study modification prior to REB approval for the amendment.

We trust this will prove satisfactory to you.

Best Wishes,

Thomas Maniatis, MD, MSc, FRCPC
Chair,
SDR REB

Cc: SDR-06-013

687, avenue des Pins ouest, S11, Montréal (Québec) H3A 1A1, Tél.: 514-934-1934, Poste 36077/34323, Téléc.: 514-843-1486

APPENDIX 4

ETHICS APPROVAL FROM THE SCIENTIFIC AND ETHICAL ADVISORY BOARD OF THE GENERAL PRACTICE RESEARCH DATABASE

GPRD
Excellence in Public Health Research

RESTRICTED-COMMERCIAL

Scientific & Ethical Advisory Group

SEAG EVALUATION OF PROTOCOLS

FEED-BACK TO APPLICANTS

CONFIDENTIAL ***by e-mail***

PROTOCOL NO: 776R

PROTOCOL TITLE: The effect of diabetes mellitus on the development, treatment, and outcomes of congestive heart failure

APPLICANT: James Brophy, MD, PhD, Director (Technology assessment unit), McGill University

APPROVED ☒	APPROVED SUBJECT TO MINOR AMENDMENT (resubmission not required) ☐	REVISION/ RESUBMISSION REQUESTED ☐	REJECTED ☐

COMMENTS Protocol 776R is approved

DATE: 2 February 2006