Assessing the effectiveness of adding gliclazide or pioglitazone in patients with type 2 diabetes using post-market observational data

Ting-Yu Wang, MD
Department of Epidemiology and Biostatistics, McGill University, Montreal

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CONTRIBUTION OF AUTHORS

TW, RT, WD and TS had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

TW developed the study concept and design, researched the data, ran the analysis and wrote the thesis.

RT and WD developed the study concept and design, reviewed/edited the thesis, supervised the study and obtained the funding (Funding Sources: CIHR).

TS helped with the analysis, ran the functional principal component analysis and provided patients' projected glycated hemoglobin.

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ABSTRACT

Background: Both observational and experimental studies have shown substantial differences between pre-market evidence of efficacy and post-market evaluation of effectiveness, which highlights the need to evaluate both efficacy and effectiveness of new therapies. However, in diabetes, the direct comparison between effectiveness and efficacy on glycemic control is challenging given the non-systematic timing of the measurement of glycated hemoglobin (HbA1c) in real-life practice

Objectives: To estimate the effectiveness and efficacy of adding pioglitazone or gliclazide to metformin in an adult population with type 2 diabetes using novel methods to estimate glycemic control and compare it to results obtained in an efficacy randomized controlled trial (RCT). The secondary aim is to examine the effectiveness of these medications in a subgroup of population who are usually excluded from efficacy trials, but in whom the medication is still prescribed: patients older than 75 years old.

Methods: A retrospective cohort study was conducted using a large UK anonymised primary care research database, the Clinical Practice Research Datalink, to examine the effectiveness of pioglitazone and metformin compared with gliclazide and metformin. The population was selected to match the inclusion and exclusion criteria from a published RCT. HbA1c change between week 0 and 52, estimated using each patient's values during the follow-up by functional principal component analysis, was compared to the RCT results. Sensitivity analyses were conducted to assess the impact of limiting the analysis to patients whose medication dosage and adherence were similar to that achieved in the RCT. The same method was used to evaluate the comparative effectiveness in those over 75 years old who were excluded from the RCT.

Results: The pioglitazone or gliclazide groups had a similar HbA1c change (pioglitazone -0.53%, 95%CI -0.69, -0.37 compared to gliclazide -0.46%, 95%CI -0.55, -0.36; difference between groups -0.08, 95% CI - 0.27, 0.10), which was less than the change observed in the RCT (-0.99% and -1.01% respectively). However, when limited to the subgroup of patients with equivalent medication dosage and adherence to that achieved in the RCT, our results approached those from the RCT: -1.11% (95%CI -1.52, -0.69,) and -0.69% (95%CI -0.97, -0.41) respectively. For patients over the age of 75, the addition of pioglitazone led to a change in HbA1c of -0.62% (95%CI -1.30, 0.07) compared to gliclazide -0.19% (95%CI -0.39, 0.00); difference between groups -0.24% (95%CI -0.73, 0.25).

Conclusion: The addition of either pioglitazone or gliclazide to metformin resulted in similar reduction in the HbA1c by 0.5%, and approached results obtained in the RCT when restricted to patients with comparable adherence and medication dosage. Similar results were obtained for those over the age of 75, but were non-conclusive given the small sample size.

RÉSUMÉ

Contexte: Plusieurs études ont démontré une différence entre l'efficacité obtenue pré et post marché, ce qui démontre la nécessité d'évaluer l'efficacité post marché. Par contre, la comparaison entre l'efficacité pré et post marché est difficile à cause des mesures non-systématiques de l'hémoglobine glyquée (HbA1c).

Objectifs: Déterminer l'efficacité d'ajouter la pioglitazone ou gliclazide au metformin dans une population avec le diabète de type 2 utilisant une nouvelle méthode pour estimer le contrôle de la glycémie et comparer à l'efficacité obtenue dans un essai randomisé contrôlé (ERC). Notre deuxième but est de déterminer l'efficacité dans un sous-groupe exclus de l'ERC, mais qui reçoive encore le médicament : patients âgés plus que 75 ans.

Méthodes: Une cohorte rétrospective était déterminée utilisant un grand réseau de données du Royaume Uni (Clinical Practice Research Datalink) pour examiner l'efficacité de pioglitazone et metformin comparant à celui du gliclazide et metformin. La population était sélectionnée pour ressembler aux critères d'inclusion et d'exclusion d'un ERC publié. La différence d'hémoglobine glyquée entre les semaines 0 et 52, estimée utilisant les résultats de chaque patient durant la période de suivi par analyse en composantes principales, est comparée aux résultats de l'ERC. Subséquemment, une analyse était faite pour les patients avec un dosage médicamenteux et adhérence similaire à celui de l'ERC. La même méthode était utilisée pour évaluer l'efficacité dans une population supérieure à l'âge de 75 ans qui étaient exclus de l'ERC.

Résultats: L'ajout de la pioglitazone ou gliclazide ont un changement similaire de HbA1c (pioglitazone -0.53%, IC 95% -0.69, -0.37 comparée à gliclazide -0.46%, IC 95% -0.55, -0.36; différence entre ces groupes -0.08, IC 95% - 0.27, 0.10), ce qui est moindre que le changement observé dans le ERC (-0.99% and -1.01% respectivement). Par contre, quand l'analyse était

restreinte au sous-groupe ayant un dosage médicamenteux et adhérence similaire à celui de l'ERC, nos résultats rapprochent ceux de l'ERC : -1.11% (IC 95% -1.52, -0.69,) and -0.69% (IC 95% -0.97, -0.41) respectivement. Pour les patients plus vieux que 75 ans, l'addition du pioglitazone est associée à un changement de HbA1c de 0.62% (IC 95% -1.30, 0.07) comparé au gliclazide -0.19% (IC 95% -0.39, 0.00); différence entre ces groupes -0.24% (95%CI -0.73, 0.25).

Conclusion: L'ajout de la pioglitazone ou gliclazide à metformin mène à une réduction de HbA1c de 0.5%, et celui-ci rapproche les résultats obtenus par l'ERC quand l'analyse est restreinte aux patients ayant une adhérence et dosage médicamenteux similaire. Les résultats sont similaires pour les patients âgés plus que 75 ans, mais pas de conclusion définie peut être établie étant donné du petit nombre de patients.

ABBREVIATIONS

CPRD:	Clinical Practice Research Datalink
EMR:	Electronic medical record
FPCA:	Functional principal component analysis
HbA1c:	Glycated hemoglobin
OHA:	Oral hypoglycemic agent
RCT:	Randomized controlled trial
SU:	Sulfonylurea
TZD:	Thiazolidinedione

PREFACE

The following is a manuscript-based thesis that evaluated the comparative effectiveness of adding pioglitazone or gliclazide to metformin using electronic medical record (EMR) and comparing it to results obtained from a randomized controlled trial (RCT). Many drugs have been developed to control diabetes, and all are rigorously tested in RCTs to determine their safety and efficacy, as per regulatory requirements. Subsequently, several studies, often RCTs, are done to test the medication's efficacy under specific controlled settings. However, some studies have shown substantial differences between efficacy and effectiveness, which highlight the need for assessing effectiveness in the evaluation of the benefit of new therapies.

The direct comparison between effectiveness and efficacy on glycemic control is challenging given the non-systematic timing of the measurement of glycated hemoglobin (HbA1c) in real-life practice. A statistical technique called functional principal component analysis (FPCA) is used to address the sparse and irregularly observed longitudinal data in the EMR. The projection of HbA1c using FPCA at specific time points allowed us to undertake a comparative study of the effectiveness of second-line oral hypoglycemic agents (OHAs) for diabetes in an observational cohort of patients with results obtained from RCTs. Specifically, similar inclusion and exclusion criteria to the RCT by Matthews et al[1] was used to compare the effectiveness of adding either pioglitazone or gliclazide to metformin in the lowering of the HbA1c, and subsequently compared to the results obtained in Matthew's RCT. An additional analysis was done to assess whether effectiveness approximated efficacy by restricting to a subset of patients with similar adherence and medication dosage to the RCT. To our knowledge, this was the first study comparing effectiveness using observational trials to results obtained from RCTs for second-line treatment of diabetes. Our secondary aim was to examine the

effectiveness of these medications in a subgroup of population who was excluded from the RCT, but in whom the medication was still prescribed: patients older than 75 years old.

CHAPTER 1 – INTRODUCTION: TYPE 2 DIABETES

1.1 Epidemiology

Over the last few decades, demographic and lifestyle changes have together contributed to the growing burden of diabetes worldwide. In Canada alone, more than 9 million individuals have been diagnosed with diabetes or pre-diabetes[2]. The proportion of people with diagnosed diabetes increases with age, with the sharpest increase occurring after the age of 40 and is consistently higher in males compared to females[3]. By 2030, the World Health Organization projects that diabetes will be the seventh leading cause of death[4]. The disease is associated with excess morbidities — including atherosclerosis, nephropathy, retinopathy, cardiovascular disease and depression [5, 6] — as well as early mortality, therefore leading to high socio-economic cost.

1.2 Pathophysiology

Insulin, a hormone produced by the pancreas (specifically, the beta-cells), is essential to our survival. Being the primary anabolic hormone, one of its major functions is the stimulation of glucose uptake by muscle and adipose tissue. For numerous reasons, a lack of insulin (either absolute or relative) in the body can occur and lead to the development of diabetes. There are 4 different types of diabetes: type 1 diabetes, type 2 diabetes, gestational diabetes and other types of diabetes. The current thesis will focus on only one of the types: type 2 diabetes.

Type 2 diabetes, simplified as diabetes for the purpose of this thesis, results from varying degrees of insulin resistance and relative insulin deficiency[7]. Risk factors associated with diabetes include age $\geq$ 40 years, first degree relative with type 2 diabetes, members of high risk populations (i.e. Aboriginal, African, Asian, Hispanic, or South Asian descent), history of pre-

diabetes, history of gestational diabetes mellitus or delivery of a macrosomic infant, presence of end organ damage associated with diabetes (i.e. microvascular and macrovascular), presence of vascular risk factors (i.e. HDL cholesterol level <1.0mmol/L in males, <1.3mmol/L in females, triglycerides ≥1.7mmol/L, hypertension, overweight, abdominal obesity), presence of associated diseases such as polycystic ovarian syndrome, acanthosis nigricans, psychiatric disorders (i.e. bipolar disorder, depression, schizophrenia), HIV infection, obstructive sleep apnea and use of drugs associated with diabetes (i.e. glucocorticoids, atypical antipsychotics, HAART)[8].

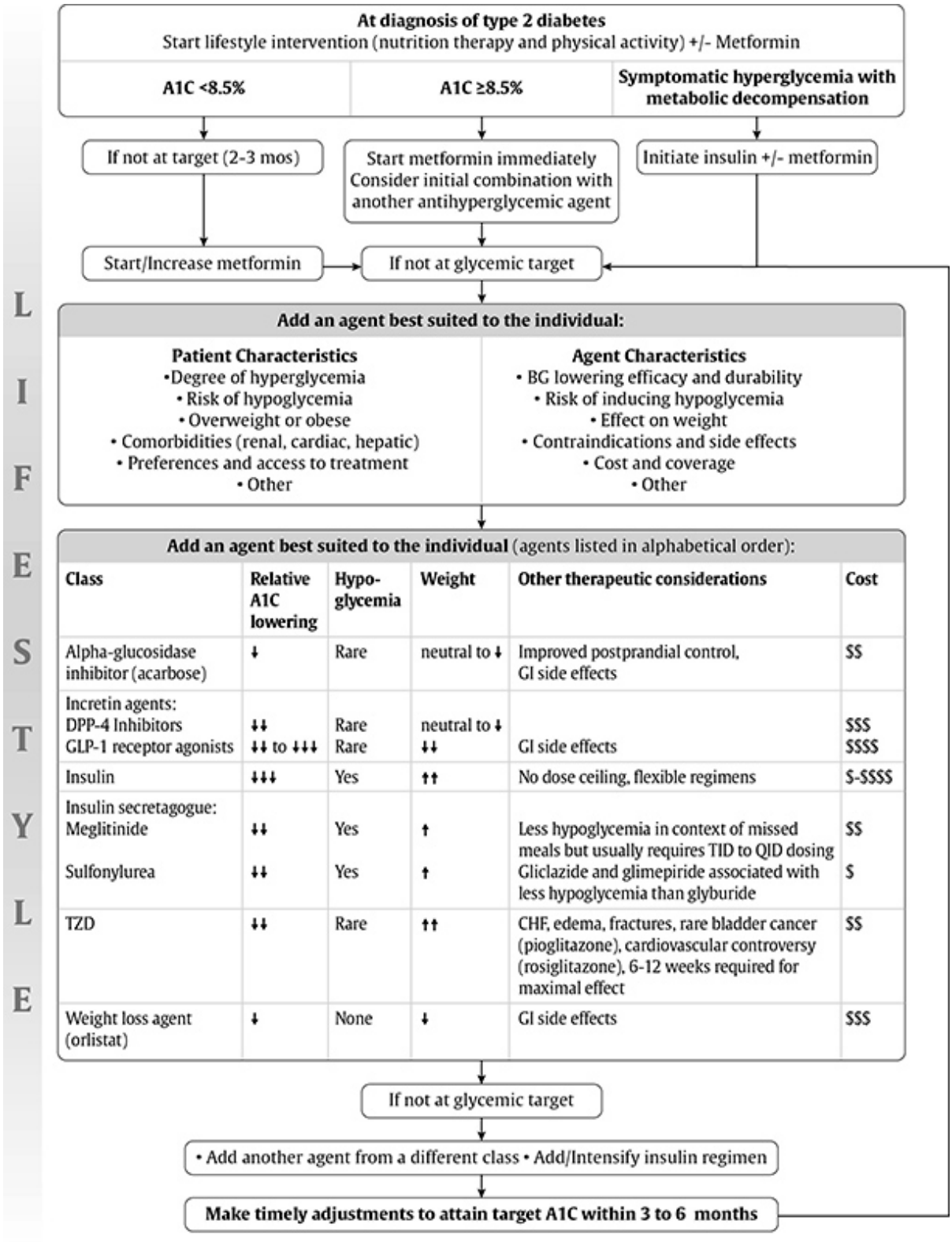
Due to insulin resistance and relative insulin deficiency, patients develop hyperglycemia with eventual possible microvascular and macrovascular complications[9]. The most common microvascular complication of diabetes is diabetic retinopathy, responsible for approximately 10 000 new cases of blindness every year in the United States[10]. The other microvascular complications include diabetic neuropathy and nephropathy. While microvascular complications lead to high morbidities, the macrovascular complications can lead to mortality. The central pathological mechanism in the macrovascular complications of diabetes is atherosclerosis, which is the narrowing of arterial walls throughout the body. In addition, patients with diabetes also have increased platelet adhesion and hypercoagulability which put them at higher risk of developing cardiovascular diseases such as coronary artery disease, peripheral arterial disease and stroke[9].

1.3 Treatment

Given the excess morbidities associated with diabetes, it is important to decrease patients' cardiovascular risk using different approaches (achievement and maintenance of healthy body weight, healthy diet, regular physical activity, smoking cessation, optimal glycemic control, optimal blood pressure control, vascular protective medications)[11]. This thesis focuses on only

one, yet very important, aspect in the management of diabetes: optimal glycemic control. Therapy in most individuals with diabetes are targeted to achieve a glycated hemoglobin (HbA1C) ≤7.0% in order to reduce the risk of microvascular and macrovascular complications[12]. At the time diabetes is diagnosed, patients are counselled to start lifestyle intervention with nutrition therapy and physical activity, along with metformin. However, if patients remain uncontrolled, a second hypoglycemic agent is usually added. Which second agent to start is subject to the physician's choice based on the patient's and agent's characteristics, and there is currently no consensus about optimal second line treatment choice[13]. There are numerous classes of medication that can be added to metformin: an alpha-glucosidase inhibitor, an incretin agent (DPP-4 inhibitors and GLP-1 receptor agonists), insulin, a meglitinide, a sulfonylurea (SU), a thiazolidinedione (TZD) and/or a weight loss agent. Each class has a different mechanism of action, blood glucose lowering efficacy, risk of hypoglycemia, effect on weight, contraindication and side effects, and cost difference (figure 1-1)[13].

Figure 1-1: Management of hyperglycemia in type 2 diabetes



Adapted from CDA 2013 guidelines[13]

Because of flatulence with the alpha-glucosidase inhibitors and patients' fear of needles with insulin, two commonly used medications after metformin were the SUs and TZDs. However, the use of TZDs has been decreasing due to their side effects, while the newer agents, the incretin agents, are gaining popularity. SUs act by binding to the SU receptors in the pancreas which cause the stimulation of insulin secretion, and thus lowering the HbA1c by 1-2%[14]. Therefore, SUs are useful only in patients with some remaining beta-cell function. Also, given that they stimulate insulin production, their side effects include hypoglycemia and weight gain. On the other hand, TZDs, by activating the peroxisome proliferator-activated receptors, increase insulin sensitivity by increasing glucose utilization and decreasing glucose production. Therefore, they do not lead to hypoglycemia. Another advantage of TZDs is a possible preservation of pancreatic beta-cell function[15]. TZDs also lower HbA1c by approximately 1-1.5%[16], but are more expensive compared to SUs[13]. However, despite these advantages, they can cause other serious side effects such as congestive heart failure, edema, fractures, bladder cancer, and questionable cardiovascular complications; therefore their use has been declining. The different classes of medication are summarized in figure 1-1[13].

CHAPTER 2 – LITERATURE REVIEW

Chapter 2 summarizes the existing knowledge on the efficacy of oral hypoglycemic agents (OHAs), and the gaps between effectiveness and efficacy seen in various studies.

2.1 Efficacy of OHAs

The Canadian Agency for Drugs and Technologies in Health has recently published a report on second-line pharmacotherapy for type 2 diabetes, showing that it is most cost-effective to add sulfonyureas (SUs) as the second-line therapy[17]. Recent guidelines, including the one published by the Canadian Diabetes Association (2013), recommend metformin as the initial OHA, but the second-line treatment recommendation remains unclear regarding long-term complications of diabetes and quality of life (such as weight gain and mild hypoglycemia)[13, 18]. Several studies have been published on comparisons between first line agents alone or the addition of second line agents, but there have been limited direct head-to-head comparison of second line OHAs.

When used as monotherapies, studies showed that thiazolidinediones (TZDs) and SUs had an efficacy in reducing the glycated hemoglobin (HbA1c) by approximately 1%[19, 20]. When used as combination therapies, a systematic review done by Bolen et al.[19] showed that the addition of a second agent provided an additive efficacy with an additional 1% reduction in HbA1c. Likewise, a meta-analysis done by Phung et al[21] studying the effect of OHAs added to metformin showed that the addition of a TZD to metformin led to a reduction of HbA1c by 1.00% (95%CI 0.38, 1.62) while the reduction was 0.79% (95%CI 0.43, 1.15) for the addition of a SU. Similarly, a randomized controlled trial (RCT) network meta-analysis by Liu et al[22] demonstrated that the mean HbA1c reduction of adding either a TZD or a SU to metformin was 0.82% (0.82, 95%CI 0.66, 0.98 for TZDs and 0.82, 95%CI 0.70, 0.95 for SUs), with no

difference between these two classes (0.00, 95%CI −0.16, 0.16). After adjusting for baseline HbA1c, adding a TZD still led to a reduction of 0.82% (95%CI 0.67, 0.97) and adding a SU resulted in a reduction of 0.84% (95%CI 0.73, 0.96), with no difference between these two classes (0.02, 95%CI -0.13, 0.17).

Although OHAs provide similar efficacy in the reduction of HbA1c, an important factor affecting such reduction is baseline HbA1c where a higher baseline HbA1c is associated with a greater HbA1c reduction. Bloomgarden et al.[23] showed that the reduction in HbA1c with active therapy for those with baseline HbA1c under 8% was only 0.1-0.2% compared to control, while for those with baseline between 8.0-8.9% was 0.6% and when the baseline HbA1c was greater than 8.9%, the reduction was between 1.0-1.2%. This was also seen in the study by Phung et al.[21], where for those with baseline HbA1c<8%, adding a TZD reduced HbA1c by 0.62% (95%CI 0.39, 0.88) and a SU by 0.57% (95%CI 0.39, 0.75); for those with baseline HbA1c ≥8%, the reduction was greater in both groups, where for TZDs was 1.02% (95%CI 0.69, 1.39) and SUs was 0.97% (95%CI 0.62, 1.35). Similar results were seen in the meta-analysis done by Sherifali et al.[20], where after adjustment for drug class, medication dose, diabetes duration and baseline HbA1c, they found that the addition of an OHA led to a 0.2-0.5% greater decline for each increase in percentage of baseline HbA1c.

It has also been shown that treatment duration affects the change in HbA1c. In the study by Phung et al.[21], in those treated for 12-24 weeks, the HbA1c reduction in TZD group was 0.75% (95%CI 0.24, 1.14) and 0.53% (95%CI 0.20, 0.88) in SU group. When the patients were treated for over 24 weeks, the HbA1c reduction was also higher in both groups, but not as steep as the first 12-24 weeks: 0.95% (95%CI 0.73, 1.27) for TZDs and 0.99% (95%CI 0.78, 1.26) for SUs. This was also seen in the meta-analysis by Sherifali et al[20], where they found that the

greatest pooled treatment effect with maximum doses of SUs was after 12 weeks of therapy, while for TZDs was 13-18 weeks. It was also shown that the increase in dose yielded a further decrease in HbA1c initially, with maximum effect achieved by 3-6 months. These meta-analyses are summarized in table 2-1.

Table 2-1: Key findings on efficacy of oral hypoglycemic agents by meta-analyses

Author	Comparison	Change in HbA1c (%)
Bolen et al.[19]	Monotherapies: • TZD • SU • Metformin	Approximately -1%
	Combination therapies: • Metformin + TZD vs Metformin • SU + TZD vs SU • Metformin + SU vs Metformin • Metformin + SU vs SU	Additive efficacy: additional -1% reduction with second agent
Sherifali et al.[20]	SU vs placebo	Approximately -1.25%
	TZD vs placebo	Approximately -1.25 to -1%
	Any OHA, for every 1% higher baseline HbA1c	-0.5 (95%CI -0.9, -0.1)
	Any OHA, for every 1 year greater diabetes duration	-0.03 (95%CI -0.1, 0.1)
Phung et al.[21]	Metformin + TZD	-1.00 (95%CI -1.62, -0.38)
	• Baseline HbA1c<8%	• -0.62 (95%CI -0.88, -0.39)
	• Baseline HbA1c>8%	• -1.02 (95%CI -1.39, -0.69)
	• Treated for 12-24 weeks	• -0.75 (95%CI -1.14, -0.24)
	• Treated for over 24 weeks	• -0.95 (95%CI -1.27, -0.73)
	Meformin + SU	-0.79 (95%CI -1.15, -0.43)
	• Baseline HbA1c<8%	• -0.57 (95%CI -0.75, -0.39)
	• Baseline HbA1c>8%	• -0.97 (95%CI -1.35, -0.62)
	• Treated for 12-24 weeks	• -0.53 (95%CI -0.88, -0.20)
	• Treated for over 24 weeks	• -0.99 (95%CI -1.26, -0.78)
Liu et al[22]	Addition of 2nd OHA to metformin	
	• TZD	• -0.82% (95%CI -0.98, -0.66)
	• SU	• -0.82% (95%CI -0.95, -0.70)
	Addition of 2nd OHA to metformin (adjusted for baseline HbA1c)	
	• TZD	• -0.82 (95%CI -0.97, -0.67)
	• SU	• -0.84 (95%CI -0.96, -0.73)
Bloomgarden et al[23]	Any OHA, with varying baseline HbA1c	
	• 6.0-6.9%	• -0.2
	• 7.0-7.9%	• -0.1
	• 8.0-8.9%	• -0.6
	• 9.0-9.9%	• -1.0
	• 10.0-11.8%	• -1.2

2.2 Gap between efficacy and effectiveness

Many drugs have been developed to control diabetes, and all are rigorously tested in pre-market RCTs to determine their safety and efficacy, as per regulatory requirements [24-26]. For a new drug to be approved into the market, the drug has to undergo standardized evaluation in three phases. Phase 1 includes human pharmacology, examining drug tolerance, metabolism, and interactions and describing pharmacokinetics and pharmacodynamics; phase 2 includes therapeutic exploratory studies, looking at effects of various doses and using biomarkers as the outcome; phase 3 consists of therapeutic confirmatory studies, demonstrating clinical use and establishing the safety profile[27]. In contrast there is no systematic approach used to evaluate the comparative effectiveness of new drugs once they are approved for market; issues that are critical in deciding if coverage of higher cost drugs are warranted.

Of interest, some studies have shown substantial differences between pre-market evidence of efficacy and post-market evaluation of effectiveness, in both observational and experimental studies[28-31], which highlight the need to evaluate both efficacy and effectiveness in the evaluation of the benefit of new therapies. One of the reasons is the lack of supervision in real-life practice leading to decreased adherence and compliance[29, 32, 33]. For instance, in an observational study comparing effectiveness to efficacy for anticoagulation, Gottlieb et al.[34] showed that patients were in the target range on 50% of the days and higher than the target range on 30% of the days. The RCT, on the other hand, reported staying in the target range for 68% (range 44-83%) of the days and higher than target range only on 8% of the days. One possible reason was the monitoring interval being between 36.3 and 40.9 days in practice compared to 21 to 28 days in the RCTs.

Another class of medication where a major discrepancy is seen is the oral contraceptives. According to a review, 7-9% of people who used oral contraceptives had unwanted pregnancy, which was much higher than the 0.1% pregnancy rate shown with efficacy trials[35]. Another reason explaining the difference between effectiveness and efficacy are the intrinsic and extrinsic factors that can affect the pharmacodynamics (for example: glucose control and risk of hypoglycemia in the use of insulin can be affected by patients' physical activity) or the pharmacokinetics (for example: increased toxicity of several medication with the consumption of grapefruit juice) of the drug[36].

Also, in practice, physicians often prescribe medication to patients who do not match the strict inclusion criteria of phase 3 RCTs[37]. For example, a retrospective study done in one academic center showed that out of the 120 new patients with osteoporosis, no more than 21% would have been accepted in the 4 large multicenter trials based on the trials' inclusion and exclusion criteria[37]. Another study, using the National Epidemiological Survey on Alcohol and Related Conditions database, revealed that more than 7 out of 10 participants with generalized anxiety disorder would be excluded by at least one criterion using a standard set of eligibility criteria representative of generalized anxiety disorder pharmacological and psychotherapy clinical trials[38]. In addition, phase 3 RCTs are often performed in a specific center or certain ethnicity, and may not be generalizable to other settings or races[39].

Statins, being the mostly commonly prescribed drug to decrease low-density lipoprotein, is a perfect example illustrating discrepancies between trials and real-life practice. Statins have been shown to reduce the risk of cardiovascular events in both primary and secondary prevention trials; however, they have also been shown to cause muscle-related adverse events and elevation of liver enzymes. In RCTs, such adverse events were noted to occur in only 5% of the patients,

but in clinical practice, it was shown to occur in as many as 20% of patients[40]. Such discrepancy may be attributed to all the aforementioned reasons: RCTs excluded older subjects or patients with multiple comorbidities; alcohol use may affect the pharmacokinetics of the medication, and heavy alcohol users were excluded; and more rigorous application of diagnostic criteria for statin-associated myopathy were used in RCTs than in clinical practice[41]. In addition, there is low adherence to statins in real-life practice; only 25.4% patients would continue taking it for primary prevention and 40.1% for secondary prevention over a 2-year period [42]. For all of these reasons, there is consensus that greater investment should be made in post-market studies of effectiveness by pragmatic randomized trials and non-experimental observational studies.

2.3 Bridging the gap between effectiveness and efficacy in diabetes

There are increasing demands to understand post-licensing effectiveness. In Canada, a division called Marketed Health Products Directorate coordinates Canadian post-marketing surveillance and has developed a Federal Regulatory Post-Market Surveillance Strategy 2007-2012[43]. It also provides a website for Canadians to access Health Canada's post-market surveillance programs and new safety information[44]. In the United States, founded in 1993, doctors and general public can report adverse reactions to drugs on MedWatch[45]. Furthermore, there are also institutes focusing on clinical effectiveness. In 2009, the American Recovery and Reinvestment Act allotted 1.1 billion USD to support for comparative effectiveness research[46], by the Agency for Healthcare Research and Quality; comparative effectiveness research was defined as "the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition, or to improve the delivery of care. The purpose of comparative effectiveness research is to assist consumers,

clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels." In 2010, the Patient-Centered Outcomes Research Institute was established and has a focus of examining relative health outcomes, clinical effectiveness and appropriateness of medical treatments using existing studies and conducting its own[47].

Knowing there is a gap between effectiveness and efficacy, it is important to assess the effectiveness of OHAs in glycemic control in real-life practice. However, the direct comparison between effectiveness and efficacy is challenging[48]. In order to assess effectiveness of OHAs, frequent HbA1c measurements are needed. Up to now, the challenge in doing such effectiveness studies in real-world practice was the high costs of assembling post-market disease registries and manually extracting information from paper records, as well as the lack of laboratory information being available at regular standardized intervals. With the advent of electronic medical records (EMR), digital post-market disease registries can be assembled. Also, linked laboratory databases are increasingly available and used in pharmacosurveillance studies[49, 50]. However, in diabetes, the major challenge in using EMRs to assess OHA's effectiveness in the reduction of HbA1c is the randomness of blood tests results, where the timing of the HbA1c is different for each patient and there is often insufficient measurement of HbA1c to compare to efficacy studies.

One solution to address the sparse and irregularly observed longitudinal data in clinical practice is the use of a statistical technique, functional principal component analysis (FPCA), to predict values at specific time-points. FPCA allows a trajectory of change to be estimated for a continuous variable through time, based on the individual's own data points as well as patterns of change within the whole population[51]. It is a statistical method where it first estimates a smooth population mean curve across all time-points, and a covariance function using pooled

data. It then uses the individual's data (at least two points required) and the covariance function along with the error variance, to estimate a trajectory of the individual residuals. The estimated population mean curve and the estimated residual trajectory is combined to provide a projected value at any time point[51]. A recent study validating the use of FPCA in projecting HbA1c at specific time points showed high predictive accuracy with more than four in five predicted values within 0.4 units, equivalent to laboratory measurement error (appendix A).

2.4 Objectives

In diabetes, guidelines recommend metformin as the initial OHA, but the second-line treatment recommendation is unclear[18, 52]. Several efficacy studies have been published showing that OHAs reduce HbA1c by approximately 1%. However, some studies have shown substantial differences between efficacy and effectiveness, which highlight the need of comparing such results in the evaluation of the benefit of new therapies.

The objectives of this thesis were:

1. To estimate the effectiveness and efficacy of adding pioglitazone or gliclazide to metformin in an adult population with type 2 diabetes using novel methods to estimate glycemic control and compare it to results obtained in an efficacy RCT

2. To examine effectiveness of these medications in a subgroup of population who are usually excluded from efficacy trials, but in whom the medication are still prescribed: patients older than 75 years old.

2.5 Approach to study design

A retrospective cohort study was conducted using a large UK anonymised primary care research database, the Clinical Practice Research Datalink (CPRD). In order to directly compare effectiveness to efficacy, a RCT evaluating the efficacy of adding two specific OHAs from

different classes to metformin was chosen. The population was selected to match the inclusion and exclusion criteria from a published RCT by Matthews et al.[1] ("Long-term therapy with addition of pioglitazone to metformin compared with the addition of gliclazide to metformin in patients with type 2 diabetes: a randomized, comparative study"). Several RCTs comparing two specific OHAs were considered but this one was chosen since it compared the two most commonly used OHAs in UK in the recent years. Glycated hemoglobin (HbA1c) at 52 weeks was estimated using each patient's values during follow-up by FPCA, and compared to RCT results. Subsequently, sensitivity analyses were conducted to assess the impact of limiting the analysis to patients whose medication dosage were similar to that used in the RCT and who have adhered to the full 12-months treatment. The same method was applied to the additional analysis, except now restricted to those over the age of 75.

CHAPTER 3 - MANUSCRIPT

Assessing the effectiveness of adding gliclazide or pioglitazone in patients with type 2 diabetes using post-market observational data

Ting-Yu Wang[1,2,3], Therese Sheppard[4], William G Dixon[4], Robyn Tamblyn[1,3]

[1]Departments of Medicine, McGill University, Montreal, Quebec, Canada
[2]Department of Endocrinology, McGill University, Montreal, Quebec, Canada
[3]Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada
[4]Arthritis Research UK Centre for Epidemiology, Manchester Academic Health Science Centre, The University of Manchester, UK

3.1 Abstract

Background: Both observational and experimental studies have shown substantial differences between pre-market evidence of efficacy and post-market evaluation of effectiveness, which highlights the need to evaluate both efficacy and effectiveness of new therapies. However, in diabetes, the direct comparison between effectiveness and efficacy on glycemic control is challenging given the non-systematic timing of the measurement of glycated hemoglobin (HbA1c) in real-life practice.

Objectives: To estimate the effectiveness and efficacy of adding pioglitazone or gliclazide to metformin in an adult population with type 2 diabetes using novel methods to estimate glycemic control and compare it to results obtained in an efficacy randomized controlled trial (RCT).

Methods: A retrospective cohort study was conducted using a large UK anonymised primary care research database, the Clinical Practice Research Datalink, to examine the effectiveness of pioglitazone and metformin compared with gliclazide and metformin. The population was selected to match the inclusion and exclusion criteria from a published RCT. HbA1c change between week 0 and 52, estimated using each patient's values during the follow-up by functional principal component analysis, was compared to the RCT results. Sensitivity analyses were conducted to assess the impact of limiting the analysis to patients whose medication dosage and adherence were similar to that achieved in the RCT. A multivariate linear regression analysis was used to estimate the difference in HbA1c between treatment groups adjusting for potential confounders that may affect the change in HbA1c.

Results: The pioglitazone or gliclazide groups had similar HbA1c reduction (pioglitazone 0.53%, 95%CI 0.37, 0.69 vs gliclazide 0.46%, 95%CI 0.36, 0.55; difference between groups 0.08, 95% CI -0.10, 0.27), which was less than the reduction observed in the RCT (0.99% and 1.01%

respectively). However, when limited to the subgroup of patients with equivalent medication dosage and adherence to that achieved in the RCT, our results approached those from the RCT: 1.11% (95%CI 0.69, 1.52) and 0.69% (95%CI 0.41, 0.97) respectively. Older age, longer disease duration, and baseline level of HbA1c influenced the magnitude of the change in HbA1c.

Conclusion: The addition of either pioglitazone or gliclazide to metformin resulted in similar reduction in the HbA1c by 0.5%, and approached results obtained in the RCT when restricted to patients with similar adherence and medication dosage.

Word count: 367

3.2 Background

By 2030, the World Health Organization projects that diabetes will be the seventh leading cause of death[4]. Many drugs have been developed to control diabetes, and all are rigorously tested in randomized controlled trials (RCTs) to determine their safety and efficacy, as per regulatory requirements [24-26]. In contrast there is no systematic approach used to evaluate the comparative effectiveness of new drugs once they are approved for market. Of interest, some studies have shown substantial differences between pre-market evidence of efficacy and post-market evaluation of effectiveness, in both observational and experimental studies, possibly due to decreased adherence, different populations and comorbidities[28-31, 34, 35]. These studies highlight the need to evaluate both efficacy and effectiveness in the evaluation of the benefit of new therapies. For instance, in an observational study comparing effectiveness to efficacy for anticoagulation, it showed that patients in routine clinical practice were in the target range on 50% of the days and higher than the target range on 30% of the days. The RCT, on the other hand, reported staying in the target range for 68% (range 44-83%) of the days and higher than target range only on 8% of the days[34]. Another class of medication where a major discrepancy was seen was the effectiveness of oral contraceptives. According to a review, 7-9% of people who used oral contraceptives had unwanted pregnancy, which was much higher than the 0.1% pregnancy rate shown with efficacy trials[35].

In diabetes, guidelines recommend metformin as the initial oral hypoglycemic agent (OHA), but the optimal choice for second-line treatment is unclear[18, 52]. Two commonly prescribed classes are sulfonylureas (SUs) and thiazolidinediones (TZDs)[13]. Both have demonstrated similar efficacy in controlling blood glucose in efficacy trials but with different

side effects and higher cost for TZDs[13]. There has been limited head-to-head comparison of their effectiveness as second line agents.

Given effectiveness could differ from efficacy, there are now increasing demands to evaluate post-market effectiveness in clinical practice[46, 47]. However, this has been challenging for multiple reasons[48]. In order to assess effectiveness of OHAs, frequent glycated hemoglobin (HbA1c) measurements are needed. Up to now, the challenge in doing such effectiveness studies in real-world practice was the high costs of assembling post-market disease registries and manually extracting information from paper records, as well as the lack of laboratory information being available at regular standardized intervals. With the advent of electronic medical records (EMR), digital post-market disease registries can be assembled. Also, linked laboratory databases are increasingly available and used in pharmacosurveillance studies[49, 50]. However, in diabetes, the major challenge in using EMRs to assess OHA's effectiveness in the reduction of HbA1c is the randomness of blood tests results. The timing of the HbA1c is different for each patient and there is often insufficient measurement of HbA1c to compare to efficacy studies.

One solution to address the sparse and irregularly observed longitudinal data in clinical practice is the use of a statistical technique, functional principal component analysis (FPCA), to predict values at specific time-points. FPCA allows a trajectory of change to be estimated for a continuous variable through time, based on the individual's own data points as well as patterns of change within the whole population [51]. It is a statistical method where it first estimates a smooth population mean curve across all time-points, and a covariance function using pooled data. It then uses the individual's data (at least two points required) and the covariance function along with the error variance, to estimate a trajectory of the individual residuals. The estimated

population mean curve and the estimated residual trajectory is combined to provide a projected value at any time point[51]. A recent study validating the use of FPCA in projecting HbA1c at specific time points showed high predictive accuracy with more than four in five predicted values within 0.4 units, equivalent to laboratory measurement error (appendix A).

The objective of this study was to estimate the effectiveness and efficacy of adding pioglitazone or gliclazide to metformin in an adult population with type 2 diabetes using novel methods to estimate glycemic control and compare it to results obtained in an efficacy RCT.

3.3 Methods

3.3.1 Context

The Clinical Practice Research Datalink (CPRD), an UK primary care EMR research database, was used for this study. As of March 2011, it contains records from over 12 million patients contributing 64 million person years of prospectively recorded high-quality primary healthcare data[53, 54]. Information, either by written text or READ codes, is continuously recorded for each patient, including a record of each consultation, diagnoses, prescribed medicines, and basic demographic data. CPRD has a long history of validation studies, and has been used for many pharmaco-epidemiological studies[55, 56]. This study has been approved by the ISAC Committee of CPRD (11_154A).

3.3.2 Study design

A retrospective cohort of patients with type 2 diabetes who were on at least one OHA between 2007-2012 was assembled from the CPRD, and followed for 52 weeks after the start of

pioglitazone or gliclazide as the second line treatment. The population was selected to match the inclusion and exclusion criteria from a published RCT by Matthews et al.[1] ("Long-term therapy with addition of pioglitazone to metformin compared with the addition of gliclazide to metformin in patients with type 2 diabetes: a randomized, comparative study"). Several RCTs comparing two specific OHAs were considered but this one was chosen since it compared the two most commonly used OHAs in UK in the recent years. READ codes were also used to identify type 2 diabetes (code list available on request from the authors). The date of the addition of the second OHA, either pioglitazone or gliclazide, was defined as the cohort entry date, when baseline information was collected. Glycated hemoglobin (HbA1c) at 52 weeks was estimated using each patient's values during follow-up by FPCA, and compared to RCT results. Subsequently, sensitivity analyses were conducted to assess the impact of limiting the analysis to patients whose medication dosage were similar to that achieved in the RCT and who have adhered to the full 12-months treatment.

3.3.3 Population

Using the inclusion and exclusion criteria of the RCT by Matthews et al. [1], patients were included if they were between ages 35 to 75, with baseline HbA1c between 7.5% and 11%, and who were on metformin (with no gaps of more than 30 days) for at least three months prior to the start of second line treatment with pioglitazone or gliclazide. Patients with type 1 diabetes, history of myocardial infarction, transient ischaemic attacks or stroke in the previous 6 months and cancer within 10 years were excluded (table 3-1, 3-2).

To sample patients similar to the RCT, patients were excluded if they had gaps of more than 30 days in treatment between their active prescriptions (either metformin, pioglitazone or

gliclazide) during the follow-up since non-compliance was rarely seen in the RCT given the close follow-up. As FPCA projects a trajectory change, patients who had less than 2 measured HbA1c in the follow-up period were also excluded.

3.3.4 Drug Exposure Measurement at Baseline and Follow-Up

Mean baseline metformin dose was calculated for the three months prior to study entry, by only adding the active prescriptions and dividing it by the number of prescription days; gaps between prescriptions were not accounted for. During the study year, mean metformin, gliclazide and pioglitazone dose were also calculated in the same way. In order to compare mean dosing between both drugs, doses were converted to a percentage of the maximum daily dosing (45mg for pioglitazone and 320mg for gliclazide). A 12-months completion percentage was defined as the percentage of patients who completed a 12 month study, in which a patient must be on either pioglitazone or gliclazide along with metformin for at least 12 months with no switch or third agent added, and who did not leave the practice or died during this period.

3.3.5 Primary Outcome

FPCA was used to estimate each patient's HbA1c based on the population mean curve and individual's trajectory [51]. To approximate the RCT where they had frequent HbA1c measurements at pre-determined times, HbA1c was estimated for week 0, 4, 8, 12, 16, 24, 32, 42 and 52 using FPCA. The primary outcome was the change of HbA1c from time 0 to week 52. The percentage of patients achieving a target HbA1c of less than 7% at 12 months was also calculated.

3.3.6 Potential Confounders

Potential confounders including disease duration, baseline HbA1c and age were measured at cohort entry, while number of physician visits for the assessment of diabetes was measured during the follow-up time. Disease duration could attenuate the effect of treatment since pancreas function may decrease over time; gliclazides (SU) function by stimulating insulin production from the pancreas[57] compared to pioglitazones (TZD) which decrease insulin resistance through the activation of peroxisome proliferator-activated receptors[58]. The duration of diabetes was calculated using the difference between the first READ code for diabetes and the cohort entry. Baseline HbA1c was estimated by FPCA and taken into account because drugs lower the HbA1c more when the baseline HbA1c was higher [20, 23]. As older patients may be more likely to receive pioglitazones since they do not cause hypoglycaemia, age was measured at cohort entry. Frequency of visits for diabetes may also affect HbA1c as this may lead to increased titration of medication, more frequent assessment of glycemic control, and diabetes teaching. The number of general practitioner visits for assessment of their diabetes was determined by READ codes.

3.3.7 Analysis

Descriptive statistics were employed to characterize the study population and outcome. The mean change of estimated HbA1c between week 0 and 52 on gliclazide or pioglitazone was examined for all patients. If patients contravened the RCT protocol by an addition of a third drug, discontinuation of metformin or pioglitazone or gliclazide, death during the study, or transfer out of practice prior to the end of follow-up, the last projected HbA1c (at either week 4, 8, 12, 16, 24, 32 or 42) prior to the study exit was considered to be the final HbA1c. The difference between

effectiveness of pioglitazone with metformin compared to gliclazide with metformin on glycemic control between baseline and week 52 was estimated using multivariate linear regression analysis. The model included potential confounders: duration of diabetes, baseline HbA1c, age, and diabetes visit frequency.

In order to examine whether effectiveness approximated efficacy, a secondary analysis was performed first by trying to mimic the RCT's adherence, which was done by limiting the analysis to only include patients who completed a 12-months course of treatment. An additional analysis was also conducted where the cohort was further restricted to only those with comparable mean dosage of pioglitazone and gliclazide to the RCT. Results of this analysis were then compared to findings from the RCT by Matthews et al. All analyses were performed using STATA software 12.0.

3.4 Results

During the period of 2007-2012, 203 662 patients with diabetes were on at least one OHA, in which 178 894 received metformin. Of the 48 883 who were subsequently started on a second OHA, 21 235 received an OHA other than gliclazide or pioglitazone, and 26 530 were excluded for being on metformin for less than 3 months (n=3577) or had gaps in metformin of more than 30 days within the 90 days prior to the second OHA (n=22 953). Out of the 912 patients initiated on gliclazide and 206 on pioglitazone, 41 had cancer within 10 years of cohort entry (0 had myocardial infarction, transient ischaemic attacks or stroke in the previous 6 months); 161 patients had only one measured HbA1c value during the cohort time; and 393 did not match in age or HbA1c criteria at cohort entry (132 patients were less than 35 or over 75 years old, 315 had HbA1c of less than 7.5% or higher than 11%; in which 54 patients did not

meet both criteria). Out of the 523 patients, 368 had no gaps over 30 days in their medication during follow-up (82 pioglitazone, 286 gliclazide) and were used for primary analysis (figure 3-1).

When comparing the pioglitazone group to the gliclazide group, there were no major differences in their baseline characteristics (table 3-3). When comparing to the RCT, this study population was similar except for fewer females in our cohort (39.0% pioglitazone and 42.7% gliclazide vs 49.2% and 50.8% in the RCT respectively) (table 3-3).

3.4.1 Change in HbA1c

The pioglitazone group had similar metformin dosage, duration of treatment and number of visits when compared to the gliclazide group (table 3-4). Their HbA1c reduction was also similar, where those on pioglitazone achieved a reduction of 0.53% (95%CI 0.37, 0.69) while those on gliclazide had a reduction of 0.46% (95%CI 0.36, 0.55); with no difference between groups 0.05 (95%CI -0.23, 0.32) (table 3-4 and 3-5). The pioglitazone group attained a higher mean medication dose compared to the gliclazide group (53.3% vs 40.9% respectively) with a higher number of 12-months completion percentage (61.0% vs 54.2%). After a year of treatment, only 12.2% in the pioglitazone group and 12.9% in the gliclazide group achieved a target HbA1c of less than 7% (table 3-4). When the change of HbA1c was plotted by time, both drugs showed similar results with a reduction throughout the year (figure3- 2).

When compared to the RCT, lower mean medication dosing (24mg pioglitazone, 131mg gliclazide in this study vs. 39mg and 212mg in the RCT), lower 12-months completion percentage (61.0% and 54.2% vs. 82.3% and 86.6% respectively), lower mean duration of treatment (9.5 and 9.6 months vs. 11 months in both medication), and lesser HbA1c reduction

(0.53% and 0.49% vs 0.99% and 1.01%) were seen (table 3-4). The multivariate linear regression analysis showed no significant difference in the comparative effectiveness of pioglitazone and gliclazide as second-line treatment (difference: -0.08; 95% CI -0.27, 0.10). As expected each percentage increase in baseline HbA1c led to a change of -0.16% (95%CI -0.26, -0.06), and every 10 years increase in age led to a change of -0.11% (95%CI -0.19, -0.02). On the other hand, each additional year with diabetes was associated with an increase in HbA1c by 0.03% (95%CI 0.02, 0.05); while the other confounders (gender, drugs and visit frequency) did not affect the treatment outcome (table 3-5).

3.4.2 Secondary analysis (sensitivity analysis)

Out of the 368 patients, only 205 patients completed a 12 month follow-up with no addition of a third agent, death or discontinuation of the drug. Similar to the primary analysis, there were no differences between the piogliazone group and the gliclazide group. When compared to the RCT, this new cohort of 205 patients was similar except for fewer females (appendix 3-1). After completing the 12 month follow-up, the pioglitazone group had slightly higher mean dose. Compared to the primary analysis, there was higher success in achieving target HbA1c, but most still did not achieve a target of ≤7% (20.0% with pioglitazone and 21.3% with gliclazide); the HbA1c reduction from baseline was higher with pioglitazone (0.76, 95%CI 0.52, 0.99) compared to gliclazide (0.67, 95%CI 0.53, 0.81), but both drug groups still showed a lesser reduction than seen in the RCT (appendix 3-2). Of the covariates in the multivariate analysis, baseline HbA1c and disease duration were still associated with changes in HbA1c reduction, but age had no significant association once adjusted for the other variables (appendix 3-3).

Of these 205 patients, when further restricted to those with mean pioglitazone and gliclazide dose similar to the RCT, there were 14 in the pioglitazone and 47 in the gliclazide group. This study still included fewer females compared to the RCT, especially in the pioglitazone group (appendix 3-4). After 1 year of treatment, the reduction in HbA1c was similar to the RCT: this study showed a reduction of 1.11% (95%CI 0.69, 1.52) with pioglitazone and 0.69% (95%CI 0.41, 0.97) with gliclazide, with no difference between groups 0.32 (95%CI -0.25, 0.88); while the RCT showed a reduction of 0.99% and 1.01% respectively (table 3-6, appendix 3-5). Baseline HbA1c was significantly associated with HbA1c reduction, but disease duration no longer influenced the HbA1c reduction (appendix 3-5).

3.5 Discussion

Using FPCA methods, HbA1c was estimated at one year for all patients, enabling us to examine the real-world change in HbA1C following the addition of either pioglitazone or gliclazide to metformin, and to then compare the results to those reported from the RCT. Based on a RCT network meta-analysis[22], the mean HbA1c reduction of adding either a thiazolidinedione (TZD) or a sulfonylurea (SU) to metformin was 0.82% (95%CI 0.66, 0.98) for TZDs and 0.82 (95%CI 0.70, 0.95) for SUs with no difference between these two classes (0.00, 95% CI −0.16, 0.16). Another meta-analysis also showed no difference between SUs and TZDs in terms of HbA1c reduction[19]. Similarly, Matthews et al showed a reduction of HbA1c of 0.99% for adding pioglitazones and 1.01% for adding gliclazides. Unlike efficacy trials, this study showed a decreased effectiveness with a reduction in HbA1c of 0.53% (95%CI 0.37, 0.69) and 0.46% (95%CI 0.36, 0.55) respectively, but also no difference between these two drugs.

Like other studies, this study also showed a decreased effectiveness compared to efficacy trials, possibly due to many intrinsic and extrinsic factors such as physician prescribing behavior, patients' adherence, patients' comorbidities[36]. The main factors in this study accounting for such difference were patients' adherence and medication dose. When a secondary analysis restricting to those who had prescriptions for the whole 12 month period was done, the extent of HbA1c reduction approached that of the RCT. This suggests that much of the difference was attributable to non-adherence. An additional analysis limiting to those with mean dose of pioglitazone and gliclazide similar to the RCT showed a greater reduction in HbA1c, which was similar to efficacy trials. Given the lack of evidence in the effectiveness of adding a second OHA, physicians often extrapolate results from efficacy trials and apply them to real life practice. This study demonstrated that given the way in which pioglitazone or gliclazide are co-prescribed with metformin in UK general practice, the improvement in HbA1C was only half of those from efficacy trials. In addition, this study showed that only 12% of patients with a mean baseline HbA1c of 8.5% started on either drug reached a target of HbA1c<7% within one year of therapy

Older age, longer disease duration, and baseline level of HbA1c influenced the magnitude of the change in HbA1c. However, once restricted to patients with medication dosage and adherence similar to that achieved in the RCT, baseline HbA1c remained the only factor influencing the reduction in HbA1c, which has been seen in many studies[20, 21, 23].

3.6 Strengths and limitations

Using CPRD, a large number of patients with good clinical and prescription information was sampled. Although HbA1c results were irregularly spaced, HbA1c was estimated one year using FPCA, allowing a comparison between real-world effectiveness and results reported within clinical trials. This technique has been validated by testing its ability to estimate known but

hidden values (appendix A). Whilst the primary results showed a lower reduction of HbA1c compared to the RCT, our sensitivity analysis of continuous, high-dose patients showed equivalent results in the observational study and the RCT. This provides further reassurance about the validity of the FPCA technique to estimate accurately HbA1c change through time.

This study had several limitations. The exposure was defined using prescriptions; therefore, like any pharmaco-epidemiological study, it could not be known whether the prescription was actually administered or subsequently taken by the patient[59]. Despite having another RCT done by the same group but examining efficacy of these drugs at two years[60], this RCT was chosen because of the limited numbers of patients who completed a one year protocol; therefore a two year analysis was not attempted. This limited our knowledge in the long term effectiveness of these drugs, but should not bias our results in either group.

For those who did not complete a 12 month period, the last projected HbA1c was used. However, given the FPCA projected HbA1c by developing an estimated curve using all measurements, their subsequent blood tests could have affected the HbA1c projection. Also, by using the last projected HbA1c instead of the closest HbA1c could bias the result (for example: those who were excluded from the study at week 51.9, HbA1c at week 42 was used instead of week 52's even though technically the projection at week 52 would be more accurate). Therefore, effectiveness of the drug could actually be different (either higher or lower) than presented. However, to follow the design of the RCT as closely as possible, the last measured HbA1C was considered as the final HbA1c. In addition, a secondary analysis was done with only complete cases and showed a greater reduction in HbA1c with no difference between the two agents, confirming that effectiveness in the real-life practice seemed to be less than the efficacy shown in trials.

Another possible bias which occurs in observational studies is channelling bias, where patients are actively selected to receive one treatment in favour of another, and where the reason for that treatment decision is also associated with the outcome of interest. Although similar in efficacy, the two drugs are known to have different side effect profiles. SUs are known to cause hypoglycemia and weight gain while TZDs could sometimes cause congestive heart failure, edema, fractures, bladder cancer and questionable cardiovascular complications[14]. This could have biased the results if patients with certain characteristics (for example, elderly patients) were prescribed one drug preferentially, and such patients were more (or less) likely to respond to treatment. However, the baseline characteristics showed that both groups were similar. Whilst unmeasured confounding is possible, it is difficult to think of such a confounder that is also associated with treatment response. For the same reason, there were fewer patients in the pioglitazone group compared to the gliclazide group, with also possible unmeasured confounding. However, their baseline characteristics were similar and therefore should not affect the analysis.

As FPCA projects a trajectory change, patients who had less than 2 measured HbA1c in the follow-up period were excluded. Because of the different timing of patients' blood tests, a baseline HbA1c (at time 0) could be not obtained, and therefore, we were unable to determine whether the excluded populations were similar to those from the analysis as baseline HbA1c was one of the main inclusion criteria to the study. These patients could be different in many ways such as being less compliant or had less severe disease; however, this should affect both groups in similar fashion and should not bias the comparison between drugs.

A few RCT inclusion criteria could not be replicated in this observational study due to insufficient information. These included fasting c-peptide and females who were either postmenopausal, sterilized or using satisfactory contraception. In the RCT, one of the inclusion

criteria was an entry dose of metformin being at ≥50% of the maximum recommended dose or at the maximum tolerated dose for over 3 months. Given that the maximum tolerated dose could not be determined, all patients on metformin with no gaps in the 3 months prior to cohort entry were included. A few exclusion criteria involving certain medical illnesses (history of substance abuse, acute malabsorption or chronic pancreatitis, familial polyposis coli and ketoacidosis) were also not reproduced, but given their rarity, it should be of limited impact. The exclusion criteria of symptomatic heart failure in the previous 10 years could not be confirmed since READ codes may not accurately reproduce this and may lead to unnecessary exclusion of patients; furthermore, this should not affect the analysis (as patients with heart failure are usually not prescribed TZDs due to the possibility of worsening heart failure).

3.7 Conclusion

There is currently clinical equipoise about which second OHA should be added to metformin. It is thus important to examine real-world data to see if these drugs are equal in their effectiveness. This study showed that the addition of either pioglitazone or gliclazide to metformin resulted in similar effectiveness in the reduction of HbA1c by 0.5% at one year. Decisions should not be solely guided by effectiveness, and therefore other factors such as safety profile, cost, and clinician and patient preference should be considered while making the choice. Patients who had continuous use of a second drug for the full one year period, and at the higher doses as used in RCTs, did have a greater improvement in HbA1C of 0.7-1%, as seen in efficacy trials. This suggests some of the lesser reduction in the primary results were explained by non-adherence and lower prescribed doses. Future research using this novel technique could be used

looking at effectiveness of other OHAs or in population excluded from RCTs (such as elderly population).

Competing interests
There are no author conflicts to declare with regard to this manuscript.

Authors' contributions
TW, TS, RT and WD had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
TW developed the study concept and design, ran the analysis, wrote the manuscript and researched data. RT and WD developed the study concept and design, reviewed/edited the manuscript, supervised the study and obtained funding (Funding Sources: CIHR).
TS helped with the analysis, ran the functional principal component analysis and provided patients' projected glycated hemoglobin, and reviewed/edited the manuscript

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3.8 Tables and Figures

Table 3-1: Inclusion criteria of this study comparing it to Matthews et al.

Matthews et al.	This study
• Type 2 diabetes • Inadequately managed with metformin alone (at ≥50% of the maximum recommended dose or at the maximum tolerated dose for ≥ 3 months) • Age between 35-75 years • HbA1c ≥7.5% or ≤11.0% • Stable or worsening glycaemic control for ≥ 3 months prior to screening • Fasting C-peptide of ≥1.5ng/ml • Female patients had to be postmenopausal, sterilized or using satisfactory contraception	• Type 2 diabetes • On metformin for ≥ 3 months with no gaps in their treatment • Age between 35-75 years • HbA1c ≥7.5% or ≤11.0% • On metformin for over 3 months and started on either pioglitazone or gliclazide

Table 3-2: Exclusion criteria of this study comparing it to Matthews et al.

Matthews et al.	This study
• Type 1 diabetes • Ketoacidosis, myocardial infarction, transient ischaemic attacks or stroke in the previous 6 months • Symptomatic heart failure, acute malabsorption or chronic pancreatitis, familial polyposis coli, malignant disease in the previous 10 years • Previous treatment with insulin, gliclazide, pioglitazone or other sulphonylureas or TZD • Substance abuse • Pregnant or breastfeeding women	• Type 1 diabetes • Myocardial infarction, transient ischaemic attacks or stroke in the previous 6 months • Malignant disease in the previous 10 years • Only on metformin, and started on either pioglitazone or gliclazide • Gaps of over 30 days in either metformin, gliclazide or pioglitazone • Less than 2 measured HbA1c in the follow-up period

Table 3-3:Comparison of baseline characteristics between patients in this study's cohort and those by Matthews et al.

	This study				Matthews et al.			
	Metformin + Pioglitazone n=82		Metformin + Gliclazide n=286		Metformin + Pioglitazone n=317		Metformin + Gliclazide n=313	
Sex	**n (%)**				**n (%)**			
• Female	32 (39.0)		122 (42.7)		156 (49.2)		159 (50.8)	
• Male	50 (61.0)		164 (57.3)		161 (50.8)		154 (49.2)	
	$\bar{x}$ ± SD [range]				**$\bar{x}$ ± SD [range]**			
Age (years)	57.4 ± 8.9	[38-74]	58.5 ± 9.9	[35-75]	56 ± 9.2	[35-74]	57 ± 9.0	[34-75]
Duration of diabetes (years)	5.0 ± 4.4	[0.1-20.8]	4.9 ± 4.7	[0-33.3]	5.8 ±5.1	[0.2-30.9]	5.5 ± 5.1	[0.2-34.7]
Daily metformin dose (mg/day)	1722 ± 575	[500-3400]	1646 ± 581	[500-3000]	1726	[500-3000]	1705	[500-3000]
HbA1c (%)	8.53 ± 0.73	[7.5-10.3]	8.63 ± 0.88	[7.5-10.9]	8.71 ± 1.00	[6.6-12.1]	8.53 ± 0.89	[6.9-11.3]

Table 3-4: Comparison of 2nd line OHA at 12 months between this study's cohort and those by Matthews et al.

	This study				Matthews et al.	
	Metformin + Pioglitazone n=82		Metformin + Gliclazide n=286		Metformin + Pioglitazone n=317	Metformin + Gliclazide n=313
	$\bar{x}$ ± SD (95% CI)				**$\bar{x}$**	
HbA1c change (%)	-0.53 ± 0.08	(-0.69, -0.37)	-0.46 ± 0.05	(-0.55, -0.36)	-0.99	-1.01
Medication dose (mg)	23.5 ± 0.9	(21.7, 25.3)	131.3 ± 4.3	(122.8, 140.0)	39	212
Mean medication dose as %	53.3	(48.9, 55.6)	40.9	(38.4, 43.8)	86.7	66.3
Mean metformin dose	1909 ± 61	(1787, 2031)	1827 ± 32	(1764, 1891)	-	-
Mean duration of treatment (month)	9.5 ± 0.4	(8.6, 10.3)	9.6 ± 0.2	(9.1, 10.0)	11	11
Number of visits for diabetes	3.3 ± 0.2	(2.9,3.7)	3.3 ± 0.1	(3.0, 3.6)	-	-
	n (%)				**%**	
Completed 12 month of treatment	50 (61.0)		155 (54.2)		82.3	86.6
Achieving target of ≤7% at 1 year	10 (12.2)		37 (12.9)		-	-

Table 3-5: Multivariate analysis for change of HbA1c at 12 months

	Estimate (95% CI)	**p-value**
Baseline HbA1c	-0.16 (-0.26, -0.06)	<0.01
Male gender	-0.12 (-0.27, 0.04)	0.16
Disease duration (per one year increase)	0.03 (0.02, 0.05)	<0.01
Age (per 10 year increase)	-0.11 (-0.19, -0.02)	0.02
Pioglitazone + metformin use (ref: Gliclazide + metformin)	-0.08 (-0.27, 0.10)	0.38
Number of visits for diabetes	0.03 (-0.00, 0.07)	0.08

Table 3-6: Sensitivity analaysis*: Comparison of 2nd line OHA at 12 months between this study's cohort and those by Matthews et al.

	This study				Matthews et al.	
	Metformin + Pioglitazone n=14		Metformin + Gliclazide n=47		Metformin + Pioglitazone n=317	Metformin + Gliclazide n=313
	$\bar{x}$ ± SD (95% CI)				**$\bar{x}$**	
HbA1c change (%)	-1.11 ± 0.19	(-1.52, -0.69)	-0.69 ± 0.14	(-0.97, -0.41)	-0.99	-1.01
Medication dose (mg)	31.9 ± 1.2	(29.4, 34.5)	201.2 ± 8.2	(184.6, 217.8)	39	212
Mean medication dose as %	70.9	(64.4, 75.6)	62.9	(57.8, 68.1)	86.7	66.3
Mean metformin dose	2090 ± 161	(1742, 2437)	1806 ± 69.7	(1666, 1947)	-	-
Mean duration of treatment (month)	12	-	12	-	11	11
Number of visits for diabetes	2.8 ± 0.5	(1.8,3.8)	3.4 ± 0.1	(2.8-4.0)	-	-
	n(%)				**%**	
Completed 12 month of treatment	14 (100)		49 (100)		82.3	86.6
Achieving target of ≤7% at 1 year	3 (21.4)		9 (19.2)		-	-

*restricted to those who completed the12 month of treatment (no addition of a third agent, death or discontinuation of the drug) with mean dose of pioglitazone and gliclazide similar to those of Matthews et al.

Figure 3-1:Patient selection from the CPRD between 2007-2012

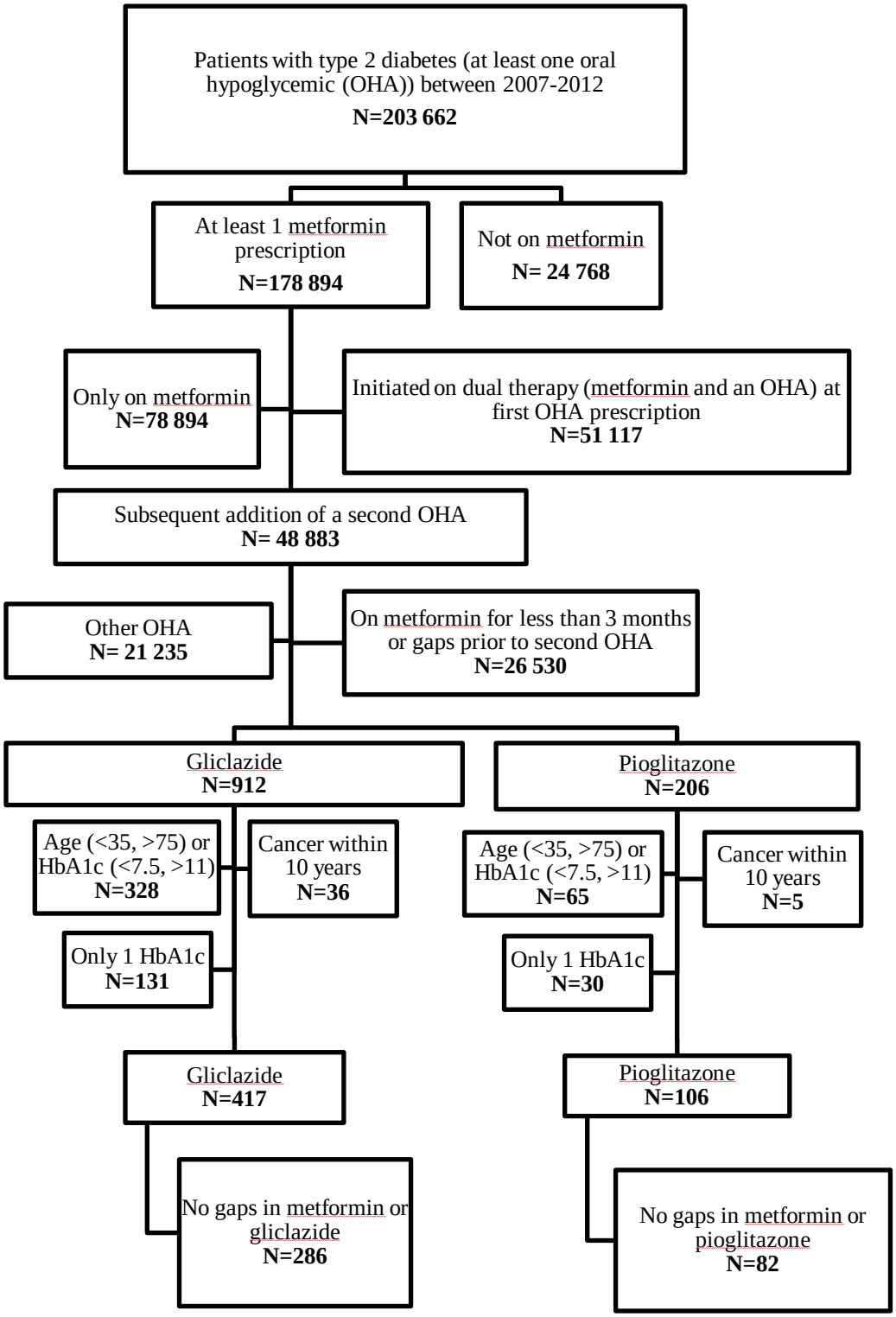
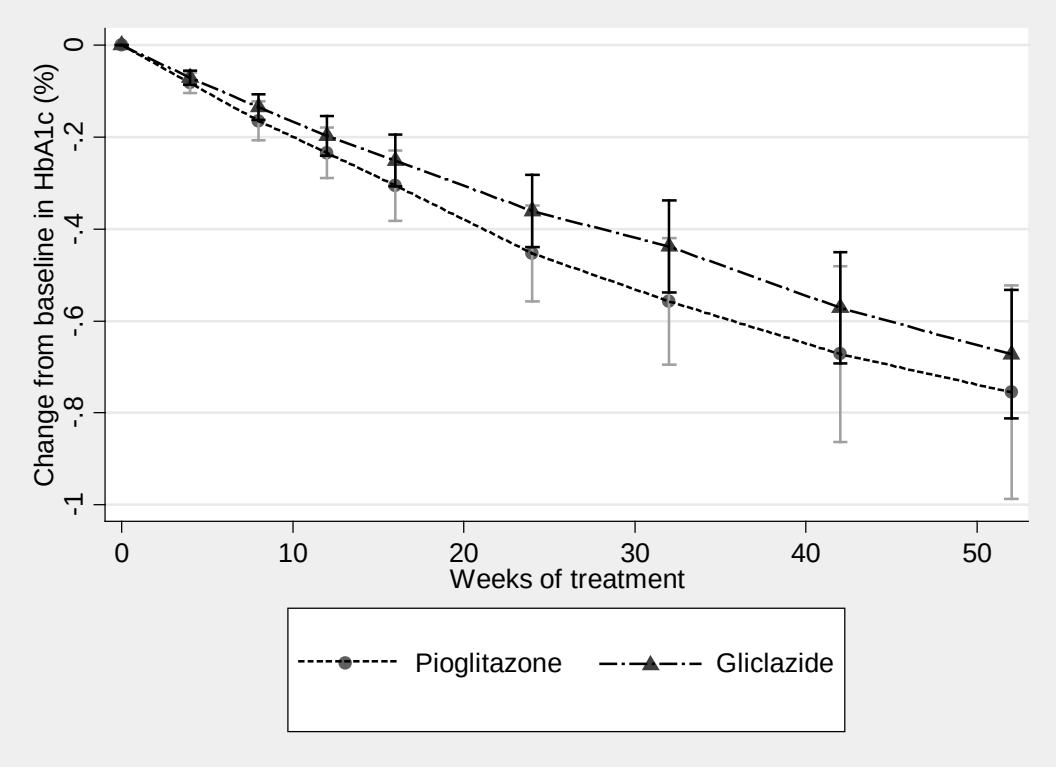


Figure 3-2: Mean change of HbA1c (%) from baseline and its 95% CI by drugs over time



Number of patients by weeks of treatment

	0	4	8	12	16	24	32	42	52
Pioglitazone	82	79	75	73	64	60	57	51	50
Gliclazide	286	279	265	247	234	221	207	185	162

Mean change of HbA1c (%) from baseline and its 95% CI by drugs over time

	0	4	8	12	16	24	32	42	52
Pioglitazone	0	0.08 (0.06,0.10)	0.16 (0.12,0.21)	0.23 (0.18,0.29)	0.31 (0.23,0.38)	0.45 (0.35,0.56)	0.56 (0.42,0.70)	0.67 (0.48,0.86)	0.76 (0.52,0.99)
Gliclazide	0	0.07 (0.06,0.19)	0.13 (0.11,0.16)	0.20 (0.15,0.24)	0.25 (0.31,0.25)	0.36 (0.28,0.44)	0.44 (0.34,0.54)	0.57 (0.45,0.69)	0.67 (0.53,0.81)

3.9 Appendix

Appendix 3-1: Sensitivity analysis*: Comparison of baseline characteristics between patients in this study's cohort and those by Matthews et al.

	This study				Matthews et al.			
	Metformin + Pioglitazone n=50		Metformin + Gliclazide n=155		Metformin + Pioglitazone n=317		Metformin + Gliclazide n=313	
Sex	**n (%)**				**n (%)**			
• Female	17 (34.0)		63 (40.6)		156 (49.2)		159 (50.8)	
• Male	33 (66.0)		92 (59.4)		161 (50.8)		154 (49.2)	
	$\bar{x}$ ± SD [range]				**$\bar{x}$ ± SD [range]**			
Age (years)	57.4 ± 9.0	[39-74]	58.5 ± 9.5	[36-75]	56 ± 9.2	[35-74]	57 ± 9.0	[34-75]
Duration of diabetes (years)	3.8 ± 3.0	[0.4 – 13.8]	4.9 ± 4.9	[0.23-22.8]	5.8 ±5.1	[0.2-30.9]	5.5 ± 5.1	[0.2-34.7]
Daily metformin dose (mg/day)	1676 ±521	[500-3400]	1643 ± 540	[500-3000]	1726	[500-3000]	1705	[500-3000]
HbA1c (%)	8.50 ± 0.70	[7.5-10.3]	8.56 ± 0.84	[7.5-10.9]	8.71 ± 1.00	[6.6-12.1]	8.53 ± 0.89	[6.9-11.3]

*restricted to those who completed 12 months of treatment (no addition of a third agent, death or discontinuation of the drug)

Appendix 3-2: Sensitivity analysis*: Comparison of 2nd line OHA at 12 months between this study's cohort and those by Matthews et al.

	This study				Matthews et al.	
	Metformin + Pioglitazone n=50		Metformin + Gliclazide n=155		Metformin + Pioglitazone n=317	Metformin + Gliclazide n=313
	$\bar{x}$ ± SD (95% CI)				**$\bar{x}$**	
HbA1c change (%)	-0.76 ± 0.12	(-0.99, -0.52)	-0.67 ± 0.07	(-0.81, -0.53)	-0.99	-1.01
Medication dose (mg)	22.7 ± 1.1	(20.6, 24.8)	124.0 ± 5.1	(113.9, 134.2)	39	212
Mean medication dose as %	51.1	(16.7, 55.6)	38.8	(35.6, 41.9)	86.7	66.3
Mean metformin dose	1853 ± 73	(1705, 2000)	1838 ± 40.4	(1759, 1918)	-	-
Mean duration of treatment (month)	9.5 ± 0.4	(8.6, 10.3)	9.6 ± 0.2	(9.1, 10.0)	11	11
Number of visits for diabetes	3.4 ± 0.2	(2.9,3.9)	3.0 ± 0.1	(2.7-3.3)	-	-
	n (%)				**%**	
Completed 12 month of treatment	50 (100.0)		155 (100.0)		82.3	86.6
Achieving target of ≤7% at 1 year	10 (20.0)		33 (21.3)		-	-

*restricted to those who completed 12 months of treatment (no addition of a third agent, death or discontinuation of the drug)

Appendix 3-3: Sensitivity analysis*: Multivariate analysis for change of HbA1c at 12 months

	Estimate (95% CI)	p-value
Baseline HbA1c	-0.28 (-0.43, -0.12)	<0.01
Male gender	-0.21 (-0.45, 0.04)	0.09
Disease duration (per one year increase)	0.04 (0.01, 0.07)	<0.01
Age (per 10 year increase)	-0.11 (-0.24, 0.02)	0.10
Pioglitazone + metformin use (ref: Gliclazide + metformin)	-0.05 (-0.32, 0.23)	0.71
Number of visits for diabetes	0.03 (-0.4, 0.09)	0.48

*restricted to those who completed 12 months of treatment (no addition of a third agent, death or discontinuation of the drug)

Appendix 3-4: Sensitivity analysis*: Comparison of baseline characteristics between patients in this study's cohort and those by Matthews et al.

	This study				Matthews et al.			
	Metformin + Pioglitazone n=14		Metformin + Gliclazide n=47		Metformin + Pioglitazone n=317		Metformin + Gliclazide n=313	
Sex	**n (%)**				**n (%)**			
• Female	3 (21.4)		22 (46.8)		156 (49.2)		159 (50.8)	
• Male	11 (78.6)		25 (43.2)		161 (50.8)		154 (49.2)	
	$\bar{x}$ ± SD [range]				**$\bar{x}$ ± SD [range]**			
Age (years)	58.9 ± 11.0	[42-74]	58.3 ± 9.9	[39-75]	56 ± 9.2	[35-74]	57 ± 9.0	[34-75]
Duration of diabetes (years)	3.9 ± 3.8	[0.5 – 13.8]	5.5 ± 4.6	[0.3-20.5]	5.8 ±5.1	[0.2-30.9]	5.5 ± 5.1	[0.2-34.7]
Daily metformin dose (mg/day)	1606 ±726	[500-3400]	1649 ± 569	[580-3000]	1726	[500-3000]	1705	[500-3000]
HbA1c (%)	8.64 ± 0.71	[7.8-10.0]	8.7 ± 0.89	[7.5-10.8]	8.71 ± 1.00	[6.6-12.1]	8.53 ± 0.89	[6.9-11.3]

*restricted to those who completed the12 month of treatment (no addition of a third agent, death or discontinuation of the drug) with mean dose of pioglitazone and gliclazide similar to those of Matthews et al.

Appendix 3-5: Sensitivity analysis*: Multivariate analysis for change of HbA1c at 12 months

	Estimate (95% CI)	p-value
Baseline HbA1c	-0.42 (-0.75, -0.09)	0.01
Male gender	0.01 (-0.49, 0.51)	0.96
Disease duration (per one year increase)	0.04 (-0.01, 0.10)	0.11
Age (per 10 year increase)	-0.13 (-0.38, 0.12)	0.29
Pioglitazone + metformin use (ref: Gliclazide + metformin)	-0.32 (-0.88, 0.25)	0.27
Number of visits for diabetes	0.09 (-0.03, 0.21)	0.12

*restricted to those who completed the12 month of treatment (no addition of a third agent, death or discontinuation of the drug) with mean dose of pioglitazone and gliclazide similar to those of Matthews et al.

CHAPTER 4 – EFFECTIVENESS IN ELDERLY PATIENTS

4.1 Rationale

Randomized controlled trials (RCTs), particularly pre-market efficacy studies conducted to meet regulatory requirements, are often done with population that is not necessarily representative of the general population that would use the drug. Patients are otherwise healthy with many exclusion criteria such as extreme of ages (young or elderly), comorbidities (such as liver or renal disease) and pregnancy[48, 61]. However, physicians still need to treat patients who are excluded from efficacy trials. Thus, given the lack of evidence in these populations and without better evidence published, physicians often extrapolate results from these trials and apply them to patients who are usually excluded from the studies[37, 38].

Chapter 3 demonstrated that effectiveness of adding pioglitazone or gliclazide to metformin measured in a cohort of diabetics assembled from an electronic medical record (EMR) database, was lower than the results obtained in the RCT. In the sensitivity analyses, where we approximated the RCT completion rate and mean medication dosage, we were able to obtain similar results to the RCT and to those from previous studies examining oral hypoglycemic agent's (OHA) efficacy. This suggests that the functional principal component analysis (FPCA) technique may be a valid method for estimating glycated hemoglobin (HbA1c). This new method allowed us to answer questions that have not been previously addressed: to examine the real-world effectiveness of OHAs in patients who are over the age of 75. These results were compared to the effectiveness obtained for those aged between 35-75 years old. Although the functional principal component analysis (FPCA) was not validated in age strata, there is no reason why this technique will work differentially at different ages.

4.2 Design and Study Population

A retrospective cohort of patients with type 2 diabetes who were on at least one OHA between 2007-2012 was assembled from the Clinical Practice Research Datalink (CPRD), and followed for 52 weeks after the start of pioglitazone or gliclazide as the second line treatment. READ codes were also used to identify type 2 diabetes (code list available on request from the authors). The date of the addition of the second OHA, either pioglitazone or gliclazide, was defined as the cohort entry date, when baseline information was collected.

Modifying the age criteria, but using all the other inclusion and exclusion criteria of the RCT by Matthews et al.[1], patients were included if they were over 75, with baseline HbA1c between 7.5% and 11% at cohort entry and who were on metformin (with no gaps of more than 30 days) for at least three months prior to the start of second line treatment with pioglitazone or gliclazide. Patients with type 1 diabetes, history of myocardial infarction, transient ischaemic attacks or stroke in the previous 6 months and cancer within 10 years were excluded (READ code list available on request). To sample patients similar to the RCT, patients were excluded if they had gaps of more than 30 days in treatment between their active prescription (either metformin, pioglitazone or gliclazide) since non-compliance was rarely seen in the RCT. As FPCA projects a trajectory change, patients who had less than 2 measured HbA1c in the follow-up period were also excluded.

4.3 Drug Exposure Measurement at Baseline and Follow-Up

Baseline characteristics (age, baseline HbA1c, disease duration) were measured the same way as outlined in Chapter 3 for the younger diabetic cohort, and defined at cohort entry with the initiation of gliclazide or pioglitazone. Number of physician visits for diabetes was measured during the follow-up time using READ codes (READ code list available on request). Mean

medication dose was calculated by adding the daily doses of active prescriptions and dividing it by the number of prescription days.

4.4 Analysis

Descriptive statistics were employed to characterize the study population and outcome. The mean change of estimated HbA1c between week 0 and 52 on gliclazide or pioglitazone was examined for all patients. If patients contravened the RCT protocol by an addition of a third drug, discontinuation of metformin or pioglitazone or gliclazide, death during the study or transfer out of practice prior to the end of follow-up, the last projected HbA1c by FPCA prior to the study exit was considered to be the final HbA1c (week 52). The effectiveness obtained for patients over 75 years old were then compared with the effectiveness obtained for patients who were between the age of 35 to 75 years.

The difference between effectiveness of pioglitazone with metformin compared to gliclazide with metformin on glycemic control between baseline and week 52 for patients over the age of 75 was estimated using multivariate linear regression analysis. The model included the same potential confounders as described in chapter 3: duration of diabetes, baseline HbA1c, age, and diabetes visits frequency. All analyses were performed using STATA software 12.0.

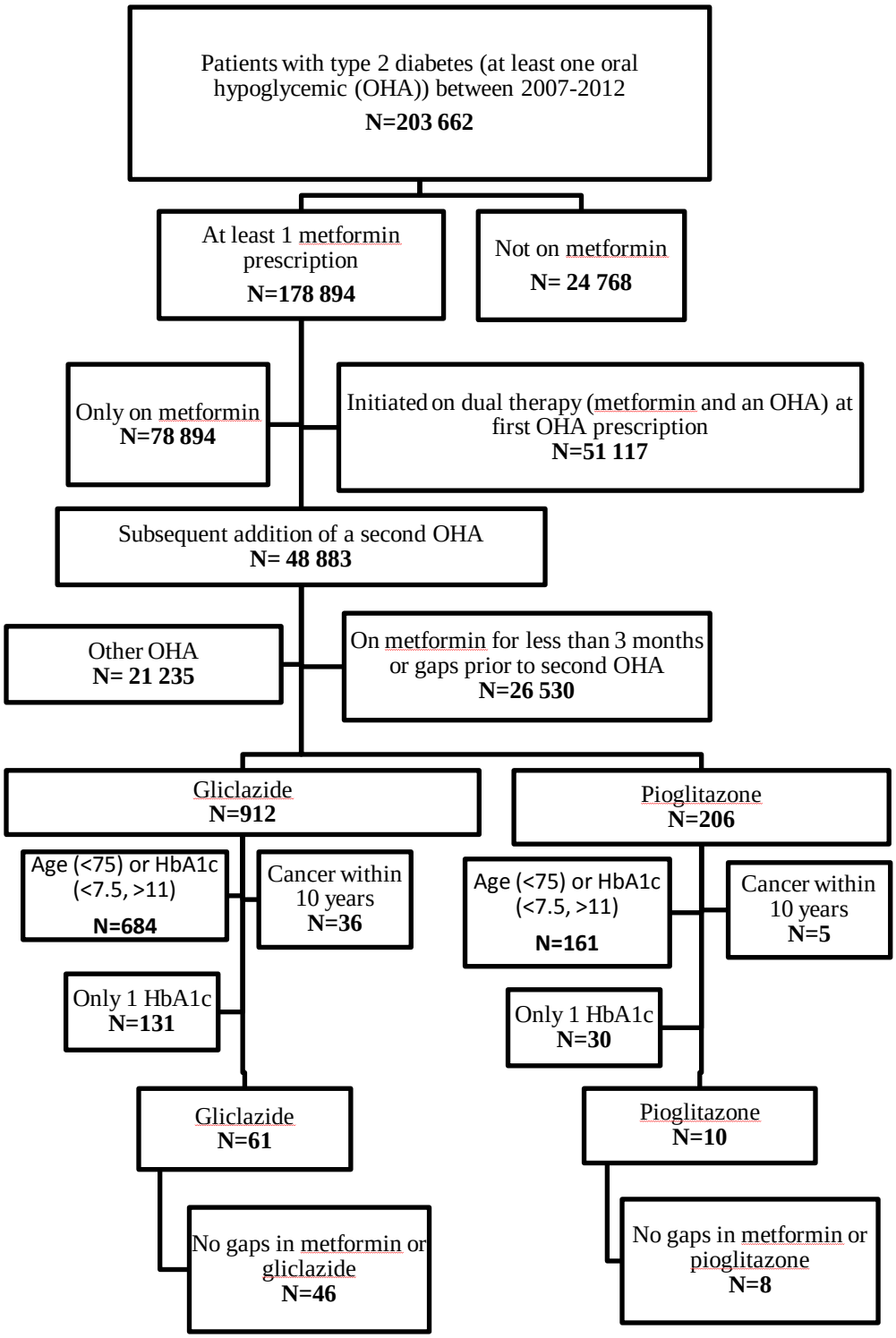
4.5 Results

During the period of 2007 to 2012, 203 662 patients with diabetes were on at least one OHA, of which 178 894 received metformin. Of the 48 883 who were subsequently started on a second OHA, 21 235 received an OHA other than gliclazide or pioglitazone, and 26 530 were excluded for being on metformin for less than 3 months (n=3577) or had gaps in metformin of more than 30 days within the 90 days prior to the second OHA (n=22 953). Out of the 912 patients initiated on gliclazide and 206 on pioglitazone, 41 had cancer within 10 years of cohort

entry (0 had myocardial infarction, transient ischaemic attacks or stroke in the previous 6 months); 161 patients had only one measured HbA1c value during the 52 weeks of follow-up; and 845 did not meet the inclusion criteria of age or HbA1c at cohort entry (792 patients were 75 years old or younger, and 315 had HbA1c of less than 7.5% or higher than 11%; in which 262 patients did not meet in criteria both categories). Out of the 71 patients, 54 had no gaps in their medication (8 pioglitazone, 46 gliclazide) and were used for the analysis (figure 4-1).

When comparing the pioglitazone group to the gliclazide group, there were no major differences in their baseline characteristics. When compared to those who were between 35-75 years old, this new study population was older but otherwise similar except for the duration of diabetes where it was higher: 13.5 years (95%CI 1.3, 53.6) for pioglitazone and 9.2 years (95%CI 0.4, 28.8) for gliclazide vs 5 (95%CI 0.1, 20.8) and 4.9 (95%CI 0, 33.3) in the original cohort respectively (table 4-1). This difference is not statistically significant due to the low power caused by the small sample size.

Figure 4-1:Patient selection from the CPRD between 2007-2012



The pioglitazone group had non-statistically significant higher metformin dosage, mean medication dose and number of visits when compared to the gliclazide group (table 4-2). The pioglitazone group also had a higher 12 months completion percentage (62.5% vs 45.7%). In addition, the HbA1c reduction in patients on pioglitazone was also non-statistically higher: those on pioglitazone achieved a HbA1c change of -0.62% (95%CI -1.3, 0.07) while those on gliclazide had a change of -0.19% (95%CI -0.39, 0.00), with both groups' 95%CI crossing the null, no statistically significant difference seen between groups -0.24 (95%CI -0.73, 0.25). After a year of treatment, only 12.5% in the pioglitazone group and 4.4% in the gliclazide group achieved a target HbA1c of less than 7% (table 4-2 and 4-3).

When compared to the original age cohort (age 35-75), patients over the age of 75 had non-significant lower mean medication dosing (20mg pioglitazone, 125mg gliclazide in those over 75 years old vs 24mg and 131mg in those aged between 35-75), lower completion percentage in the gliclazide group only (45.7% vs 54.2%) and similar mean duration of treatment (9.3 and 8.4 months vs 9.5 and 9.6 months) (table 4-2). In patients over 75 years old, the HbA1c change was -0.62% (95%CI -1.3, 0.07) for pioglitazone and -0.19% (95%CI -0.39, 0.00) for gliclazide vs -0.53% (95%CI -0.69, -0.37) and -0.46% (95%CI -0.55, -0.36) respectively in those aged between 35-75 (table 4-2). Similar to the analysis in the younger age group, the main factor associated with the magnitude of the reduction in HbA1c was baseline HbA1c where each percentage increase in baseline HbA1c led to a change of -0.55% (95%CI -082, -0.29) when a second OHA was added, with no difference between the addition of either pioglitazone or gliclazide (table 4-3).

Table 4-1:Comparison of baseline characteristics by age group

	Age >75				Age 35-75			
	Metformin + Pioglitazone n=8		Metformin + Gliclazide n=46		Metformin + Pioglitazone n=82		Metformin + Gliclazide n=286	
Sex	**n (%)**				**n (%)**			
• Female	32 (39.0)		122 (42.7)		32 (39.0)		122 (42.7)	
• Male	50 (61.0)		164 (57.3)		50 (61.0)		164 (57.3)	
	$\bar{x}$ ± SD [range]				**$\bar{x}$ ± SD [range]**			
Age (years)	79.3 ± 2.8	[76-83]	80.9 ± 8.9	[76-87]	57.4 ± 8.9	[38-74]	58.5 ± 9.9	[35-75]
Duration of diabetes (years)	13.5 ± 16.9	[1.3-53.6]	9.2 ± 7.4	[0.4-28.8]	5.0 ± 4.4	[0.1-20.8]	4.9 ± 4.7	[0-33.3]
Daily metformin dose (mg/day)	1824 ± 435	[1000-2550]	1625 ± 606	[500-3000]	1722 ± 575	[500-3400]	1646 ± 581	[500-3000]
HbA1c (%)	8.53 ± 0.97	[7.6-10.5]	8.17 ± 0.60	[7.5-10.3]	8.53 ± 0.73	[7.5-10.3]	8.63 ± 0.88	[7.5-10.9]

Table 4-2: Comparison of 2nd line OHA at 12 months by age group

	Age >75				Age 35-75			
	Metformin + Pioglitazone n=8		Metformin + Gliclazide n=46		Metformin + Pioglitazone n=82		Metformin + Gliclazide n=286	
	$\bar{x}$ ± SD (95% CI)				**$\bar{x}$ ± SD (95% CI)**			
HbA1c change (%)	-0.62 ± 0.29	(-1.30, 0.07)	-0.19 ± 0.10	(-0.39, 0.00)	-0.53 ± 0.08	(-0.69, -0.37)	-0.46 ± 0.05	(-0.55, -0.36)
Medication dose (mg)	20.5 ± 2.7	(14.1, 26.8)	124.7 ± 12.9	(98.8, 150.7)	23.5 ± 0.9	(21.7, 25.3)	131.3 ± 4.3	(122.8, 140.0)
Mean medication dose as %	44.4	(31.1, 60.0)	39.1	(30.9, 47.1)	53.3	(48.9, 55.6)	40.9	(38.4, 43.8)
Mean metformin dose	1979 ± 131	(1668, 2290)	1768 ± 99	(1568, 1968)	1909 ± 61	(1787, 2031)	1827 ± 32	(1764, 1891)
Mean duration of treatment (month)	9.3 ± 1.3	(6.3, 12.4)	8.4 ± 0.6	(7.2, 9.7)	9.5 ± 0.4	(8.6, 10.3)	9.6 ± 0.2	(9.1, 10.0)
Number of visits	3.4 ± 1.1	(0.9,5.9)	2.8 ± 0.3	(2.3, 3.3)	3.3 ± 0.2	(2.9,3.7)	3.3 ± 0.1	(3.0, 3.6)
	n (%)				**%**			
Completed 12 month of treatment	5 (62.5)		21 (45.7)		50 (61.0)		155 (54.2)	
Achieving target of ≤7% at 1 year	1 (12.5)		2 (4.4)		10 (12.2)		37 (12.9)	

Table 4-3: Multivariate analysis for change of HbA1c at 12 months

	Estimate (95% CI)	**p-value**
Baseline HbA1c	-0.55 (-0.82, -0.29)	<0.01
Male gender	0.15 (-0.22, 0.52)	0.41
Disease duration (per one year increase)	-0.002 (-0.02, 0.02)	0.79
Age (per 10 year increase)	0.03 (-0.49, 0.56)	0.90
Pioglitazone + metformin use (ref: Gliclazide + metformin)	-0.24 (-0.73, 0.25)	0.32
Number of general practitioner visits	0.04 (-0.05, 0.13)	0.32

4.6 Discussion

In patients over the age of 75, the pioglitazone group had non-statistically significant higher metformin dosage, mean medication dose, number of visits and higher 12 months completion percentage when compared to the gliclazide group (table 4-1). The HbA1c change for those over 75 years old was non-significantly higher for the pioglitazone group (-0.62%, 95%CI -1.3, 0.07) compared to the gliclazide group (-0.19%, 95%CI -0.39, 0.00); and there was no statistically significant difference between groups in the multivariate analysis -0.24 (95%CI -0.73, 0.25). When this was compared to those between the age of 35-75 (pioglitazone -0.53, 95%CI -0.69, -0.37 and gliclazide -0.46, 95%CI -0.55, -0.36), it showed the use of pioglitazone was as effective in the elderly as the younger age group, with a reduction in HbA1c of approximately 0.5%; however, the use of gliclazide in those over the age of 75 seemed to be less effective with a reduction of only 0.2%, but it was not statistically significant due to the small sample size.

The main difference between analyses done in the older age group and younger age group was age, which could be the potential hypothesis explaining the difference in HbA1c reduction. As humans age, there are pancreatic, insulin receptor and post-receptor changes[62]. It has been observed that insulin resistance increases in the elderly, and that there may be impaired replication of pancreatic beta-cells[63, 64]. Given gliclazides (family of sulfonylureas, SUs) function by stimulating insulin production from the pancreas[57] versus pioglitazones (family of thiazolidinedione, TZDs) which decrease insulin resistance through the activation of peroxisome proliferator-activated receptors and possibly also preserving beta-cell function[58, 65], there could be a possible decrease of gliclazide effect with age. Also, a study by Kahn et al.[65] showed that levels of beta-cell function declined in patients treated with either metformin, SUs

or TZDs, but greatest in the SU group where the annual rate of decline was 6.1% but only 2.0% in the TZD group.

These results suggested that the use of pioglitazone was more effective in the elderly population compared to the addition of gliclazide, however, given the small number of patients, for both medications when used in patients over 75 years old, the 95% CI crossed the null. Furthermore, the multivariate analysis done also showed no difference between drugs, with the only factor affecting the change in HbA1c being baseline HbA1c.

4.7 Strengths and limitations

With the FPCA technique (validated in chapter 3 and paper in appendix A), we were able to examine the effectiveness of adding pioglitazone to metformin or gliclazide to metformin in a subgroup of population usually excluded from trials.

The main limitation is the small number of patients, where there were only 8 patients in the pioglitazone group and 46 in the gliclazide group; leading to a lack of power. We only had a 56% power to identify a large effect. In addition, there were other possible unmeasured confounders such as weight, physical activities, other comorbidities (for example: renal failure with long standing diabetes)[62] which could affect the change of HbA1c in the elderly. As people age, there is often decreased physical activity with associated weight gain (especially adipose tissue), leading to increased insulin resistance[66, 67] and subsequently, higher HbA1c. This may mask the effect of OHAs and make OHAs seem less effective; however, this should affect patients in both groups, and should not lead to difference between groups. Also, given TZDs are known to cause serious side effects (congestive heart failure, edema, fractures, bladder cancer and questionable cardiovascular complications), channelling bias could occur where physicians prescribe TZDs to healthier patients, and therefore bias the effect of SUs toward the

null. However, such bias was not seen in the younger population; instead, the effectiveness of pioglitazone or gliclazide was similar in the original cohort (age 35-75).

There were several limitations in this analysis. Many limitations occurred in both our younger age trial inclusion group (chapter 3) and this current analysis (older age exclusion group), and were already described in chapter 3. As mentioned in chapter 3, like any pharmaco-epidemiological study, it could not be known whether the prescription was actually dispensed or subsequently taken by the patient. Channeling bias could occur where physicians prescribed either a SU or a TZD due to patients' baseline characteristics and drug's properties. However, our baseline characteristics showed no difference between groups. For those who ended the study prematurely, the last projected HbA1c was used instead of the closest value, which could be problematic since FPCA project HbA1c by developing an estimated curve using all measurements and therefore their subsequent blood tests could have affected the HbA1c projection. Unless the frequency of testing, or truncation of follow-up was related to the effectiveness of the drug, patients in both groups should be affected, therefore, should not lead to difference in effectiveness between the addition of pioglitazone or gliclazide, or difference between the young and older population. As FPCA projects a trajectory change, patients who had less than 2 measured HbA1c in the follow-up period were excluded. Because of the different timing of patients' blood tests, a baseline HbA1c (at time 0) could be not obtained, and therefore, we were unable to determine whether the excluded populations were similar to those from the analysis as baseline HbA1c was one of the main inclusion criteria to the study. These patients could be different in many ways such as being less compliant or had less severe disease; however, this should affect both groups in similar fashion and should not bias the comparison between drugs.

4.7 Conclusion

Due to the lack of RCTs in treatment of diabetes for patients older than 75 years old, it is unclear how effective the addition of pioglitazone or gliclazide to metformin is in this age group. Compared to those aged between 35-75, the addition of pioglitazone resulted in similar HbA1c reduction of 0.62%, while gliclazide showed a possible decreased effectiveness with a reduction of HbA1c by 0.19% in the elderly population. This decreased effectiveness could be possibly explained by the medication's pharmacodynamics combined with aging. However, given the small sample size, both 95% confidence interval crossed the null and therefore no definite conclusion could be made. Adjusting for confounders, there was no statistically significant difference between the addition of either drug in the reduction of HbA1c. Larger studies, by either including patients for longer period of time (for example: ten years instead of five) or by using several EMR databases, should be done to confirm this finding.

CHAPTER 5 – DISCUSSION

5.1 Implications

Diabetes, associated with multiple medical morbidities and early mortality, is increasing in prevalence[4]. Consequently, many drugs have been developed with the aim of controlling blood glucose and all have been rigorously studied in randomised controlled trials (RCTs) to determine their efficacy. According to guidelines, metformin is the initial oral hypoglycemic agent (OHA) prescribed to patients with type 2 diabetes[13, 18], but the second OHA to add remains controversial. Our literature review examining efficacy of second line OHAs showed that the addition of either a thiazolidinedione (TZD) or a sulfonylurea (SU) to metformin reduces glycated hemoglobin (HbA1c) by approximately 1%. However, it has also been shown that there are differences between efficacy and effectiveness. Pragmatic trials and observational studies that evaluate the effectiveness of OHAs are crucial for both clinical decision-making and cost-effective drug policy decisions. A major challenge in using increasingly accessible electronic medical record (EMR) data to assess effectiveness is the sparse and irregularly measured HbA1c in day to day practice. Using projected HbA1c from functional principal component analysis (FPCA), a novel method, we were able to compare the effectiveness between the addition of either pioglitazone or gliclazide to metformin in the lowering of the HbA1c.

Unlike the previous studies [19, 21, 22] and the RCT by Matthews et al.[1] where the efficacy was approximately 1% for either drug, our study showed a decreased effectiveness with a reduction in HbA1c of 0.53% (95%CI 0.37, 0.69) for pioglitazone and 0.46% (95%CI 0.36, 0.55) for gliclazide, but also no difference between these two drugs. Similar to the meta-analysis by Bolen et al[19] and Sherifali et al.[20], our study showed that each percentage increase in baseline HbA1c led to a further reduction by 0.16% (95%CI 0.06, 0.26) with a second OHA

addition. In addition, similar to results shown by Phung et al.[21] and Sherifali et al.[20], our study showed that HbA1c reduction occurred throughout the year.

According to the Canadian Diabetes Association 2013 guidelines[13], the target HbA1c level should be attained within 3 to 6 months. However, this is often not achieved. Our study showed that only 12% of patients with a mean baseline HbA1c of 8.5% started on either drug reached a target of HbA1c<7% within one year of therapy. Similarly, a report published in 2011 showed fewer than half of the US population achieved a target HbA1c of less than 7%[68] while another study by Rossi et al.[69] showed that only 43.1% of the 114 249 Italian patients achieved the target. Overall, our study provided useful clinical information, as it showed that the addition of either pioglitazone or gliclazide to metformin led to a reduction in HbA1c of 0.5% instead of the popular belief of 1%, with a peak effect by 16 weeks.

Due to the lack of better evidence, physicians extrapolate the results of RCTs to subpopulations who were excluded from RCTs. Therefore, after verifying that the functional principal component analysis (FPCA) method of estimating HbA1c with observational data could approximate the RCT results when limited to those who were adherent and who received an equivalent drug dose, we have performed subsequent analysis in the effectiveness of adding pioglitazone or gliclazide to metformin in patients over the age of 75. As expected, perhaps due to higher insulin resistance associated with aging and possible impaired replication of pancreatic beta-cells[63, 64], pioglitazone was as effective (-0.62%, 95%CI -1.3, 0.07) in the elderly while gliclazide appeared to be less effective (-0.19%, 95%CI -0.39, 0.00); although these differences were not statistically significant due to the small sample size.

5.2 Limitations

There are several limitations to both our analyses (chapter 3 and 4). Like any pharmaco-epidemiological study, it could not be known whether the prescription was actually dispensed or subsequently taken by the patient. Channeling bias could occur where physicians prescribed either SU or TZD due to patients' baseline characteristics and drug's properties. However, our baseline characteristics showed no difference between groups. For those who ended the study prematurely, the last projected HbA1c was used instead of the closest value, which could be problematic since FPCA projects HbA1c by developing an estimated curve using all measurements and therefore their subsequent blood tests could have affected the HbA1c projection. Unless the frequency of testing, or truncation of follow-up was related to the effectiveness of the drug, they should affect patients in both groups, and should not lead to difference in effectiveness between the addition of pioglitazone or gliclazide. In addition, a sensitivity analysis including only those who completed the 12 months follow-up was done and showed no difference in effectiveness between both drugs.

In addition to limitations outlined in chapter 3, our study also suffered other limitations that are associated with non-experimental observational studies. First, there was a substantial difference in the follow-up experience in actual practice than occurred in the efficacy RCT either due to an addition of a third agent, discontinuing of the medication for any reason prior to 12-months completion or switch between gliclazide and pioglitazone. Only half of the patients completed a full year study, with a mean duration of treatment of 9.5 months. However, given that both groups (pioglitazone or gliclazide) were similar, it should not lead to selection bias. Furthermore, a sensitivity analysis was done by only including complete cases, and also showed no difference in effectiveness between medications.

A commonly encountered problem in assessing effectiveness using electronic medical record (EMR) is the heterogeneity of the study population. For this reason, we chose a well-defined study cohort using similar inclusion and exclusion criteria to the RCT by Matthews et al[1]. With similar baseline characteristics to the RCT, our cohort seemed fairly homogeneous.

A few RCT inclusion criteria could not be replicated in our observational study due to insufficient information. In the RCT, one of the inclusion criteria was an entry dose of metformin being at ≥50% of the maximum recommended dose or at the maximum tolerated dose for over 3 months. Given we were not able to determine the maximum tolerated dose and by including only those who achieved more than 50% of the maximum recommended dose, we could be inducing bias (excluding those who can not tolerate a high dose, or those with renal failure), we included all patients with metformin prescriptions with no gaps in the 3 months prior to cohort entry. The RCT only included patients who had stable or worsening glycaemic control for over 3 months prior to screening, which was not well defined. Given that this should be the reason of the second OHA addition, we believed that this inclusion criterion was met. Another inclusion criterion in the RCT was C-peptide level being over ≥0.5nmol/L, which could not be reproduced as C-peptide is not routinely done outside of research context for type 2 diabetes. In the RCT, women were required to be postmenopausal, sterilized or using satisfactory contraception, while pregnant or breastfeeding women were excluded. Due to the lack of such information, and by only including post-menopausal women, bias could be introduced; we therefore did not include this criterion in our study. Other aspects that could not be reproduced in the study design were the dose-titration and dietary advice. In the RCT, patients were randomized to a 16-week forced dose-titration phase and a 36-week maintenance phase. Patients were seen every four weeks with

an assessment for dose titration. Cessation of titration or down-titration was permitted only on the basis of tolerability issues, including actual hypoglycaemia or increased risk of hypoglycaemia. Since this was a retrospective observational study, we could not replicate such titration and close follow-up, and therefore, we did not exclude patients who continued to have dose-titration after 16 weeks. Few exclusion criteria involving certain medical illnesses could also not be reproduced, but given their rarity, it should be of limited impact; these included a history of substance abuse, acute malabsorption or chronic pancreatitis, familial polyposis coli and ketoacidosis. The exclusion criteria of symptomatic heart failure in the previous 10 years could not be confirmed since READ codes may not accurately reproduce this and may lead to unnecessary exclusion of patients; furthermore, this should not affect the analysis (as patients with heart failure are usually not prescribed TZDs due to the possibility of causing heart failure).

The last limitation occurred in the additional analysis in the elderly population aged 75 and over. The sample size was small, and the power was only 56% to detect large effects; thus, no conclusive result could be obtained.

5.3 Future research

Using projected HbA1c values from FPCA, our study allowed us to compare effectiveness to efficacy, and also further validated FPCA technique. Future research using this technique could be used looking at effectiveness of other OHAs, especially the new ones such as the incretin agents (DPP-4 and GLP-1 analogues). In addition, given patients could be prescribed three OHAs, it would be of interest to compare the effectiveness of the third OHA, which had not been done in RCTs.

Another important area where further research should be done is to look at the effectiveness of OHAs in subsets of population excluded from RCTs. We performed additional

analysis in those aged 75 years and older, but did not have a large enough sample size for a definite conclusion. The next step would be to examine OHAs effectiveness in a larger elderly population or younger patients (less than 18 years old), patients with comorbidities (such as renal failure) and patients who are at the extreme of baseline HbA1c when the OHA was started (such as <7.5% or higher than 11%).

CHAPTER 6 – CONCLUSION

Many drugs have been developed to control diabetes and studied to determine their efficacy, but little is known about how well these drugs work in the real-life practice and in people excluded from efficacy trials. There is currently clinical equipoise about which second oral hypoglycemic agent (OHA) should be added to metformin. It is thus important to examine real-world data to see if these drugs are equal in their effectiveness. Our study showed that the addition of either pioglitazone or gliclazide to metformin resulted in similar effectiveness in the reduction of glycated hemoglobin (HbA1c) by 0.5% at one year. Decisions should not be solely guided by effectiveness, and therefore other factors such as safety profile, cost, and clinician and patient preference should be considered while making the choice. Patients who had continuous use of a second drug for the full one year period, and at the higher doses as used in randomized controlled trials (RCTs), had a greater improvement in HbA1C of 0.7-1% as seen in efficacy trials. This suggests some of the lesser reduction in the primary results were explained by non-adherence and lower prescribed doses.

When the analysis was done in a subgroup usually excluded by efficacy trials, patients over the age of 75, the addition of pioglitazone reduced HbA1c by 0.62% while the addition of gliclazide reduced it by 0.19%. The addition of pioglitazone seemed to be as effective, but gliclazide seemed to be less effective in the elderly population; however, given the small sample size, when used in patients over 75 years old, no firm conclusion could be made. Further studies should be done in this group and other subsets of patients excluded from efficacy trials; the effectiveness of other OHAs could also benefit from further studies.

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APPENDIX A: Paper validating FPCA

(This paper has been submitted to Epidemiology)

How to measure change at one year when no measurement at one year exists: Using functional principal component analysis to estimate HbA1C in patients with diabetes

Therese Sheppard [1], Robyn Tamblyn [2 3], Michal Abrahamowicz [2 4], William G Dixon [1 5]

[1] Arthritis Research UK Centre for Epidemiology, Manchester Academic Health Science Centre, The University of Manchester, UK

[2] Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Canada

[3] Clinical and Health Informatics Research Group, McGill University, Montreal, Canada

[4] Division of Clinical Epidemiology, McGill University Health Center, Montreal, Canada

[5] Health eResearch Centre, Manchester Academic Health Science Centre, The University of Manchester, UK

Abstract

Background

A common primary outcome in healthcare studies is change in a continuous variable over a pre-specified time period. Measurements in observational research using data collected as part of routine clinical practice are dependent on when patients visit their clinicians, resulting in data that can be sparse and irregularly spaced. Measuring change at pre-specified time points is therefore challenging. Functional principal component analysis (FPCA) allows estimation of individual trajectories throughout time, developed using an individual's data points and patterns of change in the whole population. This study aims to demonstrate the application of FPCA in epidemiology and examine its performance using the example of haemoglobin A1C (HbA1C) in diabetes.

Methods

HbA1C measurements were collected from new users of oral hypoglycaemic medication. A continuous-in-time HbA1C estimation was developed for patients with at least two measurements over a 30 month period using FPCA. Additional trajectories were estimated after omitting known, or incorporating historical, HbA1C results. The influence of the number and range of known values on the mean prediction error was explored.

Results

The predictive accuracy of FPCA was high, with more than four in five predicted values

within 0.4 units, equivalent to laboratory measurement error. Omission of the final data point and inclusion of historical data worsened predictive accuracy. High variability in HbA1C values and fewer data points led to higher mean prediction errors.

Conclusions

FPCA allows prediction of individual trajectories for sparse longitudinal data, facilitating estimation of change from baseline to any specified time-point in observational studies.

Background

Opportunities for observational research will increase significantly over the coming years with the expansion of electronic health records, and investment in e-infrastructure for research, distributed data networks and patient-centred research (1-3). Analysis of data collected for the primary purpose of healthcare delivery rather than research generates methodological challenges. Good progress is being made in many areas, for example understanding how to study the same question across different geographical settings with different healthcare systems (4), and how to adjust for confounders that are defined and measured differently in different settings (2). However, less attention has been paid to the challenge of how to deal with data collected at irregular time intervals.

Randomised controlled trials (RCTs) are widely viewed as the optimal study design for testing the efficacy of new treatments. This study design allows investigators to assign an intervention in a selected population and measure outcomes at pre-specified time intervals. For example, trials of new oral hypoglycaemic drugs examine the change in glycosylated haemoglobin (HbA1C) from baseline to pre-specified endpoints (e.g. week 24 (5) or week 104 (6)). However, RCTs have several accepted limitations. First, drugs often do not perform as well in clinical practice as the trials suggest for a range of biological and behavioural reasons (7). Second, RCTs have strict inclusion and exclusion criteria. For example, oral hypoglycaemic trials have excluded elderly patients (8) and those with comorbidities including renal insufficiency, liver disease, cardiovascular disease, pulmonary disease and alcohol abuse (9). Clinicians still prescribe to patients with these comorbidities, yet effectiveness in these populations remains unknown. Furthermore, combination therapy of multiple drugs is seldom studied in RCTs and evidence of the comparative effectiveness and safety of different combinations are lacking. There is therefore a need to conduct observational research using data collected in 'real-world' settings.

One of the significant challenges in real-life studies of drug use is defining an effectiveness outcome comparable between individual patients, given the varied patterns of assessment timing. In a clinical trial, patients are brought back for assessment at pre-specified intervals. In contrast, in real-life, patients can visit their doctor at any time-point. It thus becomes impossible to measure the change in HbA1C at, for example, week 104 unless the patient has visited their doctor that week. Yet, if we want to use post-market observational research to fill knowledge gaps, for example to assess the effectiveness of oral hypoglycaemics in patients with renal impairment, we need to compare changes in HbA1C over an agreed time interval. Options such as selecting the closest temporal measurement as a surrogate for the value at a given time-point (10), linear interpolation i.e. 'joining the dots' and assuming a linear change between each sequential measurement (11), or averaging measures over a yearly interval (12) require assumptions that may be inconsistent with the true nature of longitudinal processes under study. Moreover, it fails to take advantage of all available data about trends in an individual's glycaemic control that may influence response to treatment as well as the expected value at any

given time-point. There is a need to make more efficient use of all information contained in the repeated but irregularly spaced and usually sparse visit-based measures.

Statistical techniques such as functional principal component analysis (FPCA) exist to model sparse longitudinal data, although are not widely used in epidemiology. The aim of these techniques is to develop a continuous-in-time estimation (or 'trajectory') of changes in a continuous variable through time, based on the individual's own data points as well as patterns of change within the whole population (13). Developing a patient-specific estimated trajectory throughout the study period would allow estimation of expected change from baseline to any time-point of interest. This would enable observational effectiveness studies to be conducted in populations excluded from RCTs using the same outcome as defined in the original trial (eg change in HbA1C from drug initiation to 12 months). It would allow examination of combination therapy over a pre-specified time interval. Also, it could facilitate consideration of the longitudinal evolution of changes from baseline to endpoint, rather than just the total change. If validated, such methodology could be applied to any continuous variable outcome that is measured at irregularly spaced visits or assessment times in clinical practice.

The aim of this study was therefore to employ functional principal component analysis methods to develop and validate estimated trajectories for HbA1C in a cohort of patients with diabetes from UK primary care. Specific objectives included 1) estimating the mean prediction error by comparing estimated to known values actually observed at specific time-points, 2) examining the impact of using fewer of the known values or adding additional historical data points and 3) assessing the influence of disease stability and number of measurements on the prediction error.

Methods

Study Population

Adult patients with diabetes were identified in the Clinical Practice Research Datalink (CPRD - formerly General Practice Research Database (GPRD)), a UK database of anonymised primary care electronic medical records covering an active population of over 8M people (14). CPRD includes information about all clinical encounters in primary care, including laboratory tests requested by the general practitioner. Patients participating in CPRD are thought to be representative of the UK population.

The sampling frame for this study was adult patients with type II diabetes defined by READ codes (code list available on request from the authors) or who had any prescribed hypoglycaemic medication between 1987 and July 2011. Practices were excluded if their last collection date preceded the study end date, or the practice did not meet minimum data quality documentation standards, as assessed by CPRD, throughout the study period. We restricted analysis to new users of oral hypoglycaemic medication in the period July 1 2007 to Dec 31 2008 (defined as first ever use of an oral hypoglycaemic) in order to generate a more homogeneous cohort.

Patients were then required to have at least two HbA1C measurements in the study period Jan 1 2009 to June 30 2011 (Figure 1). The UK Quality and Outcomes Framework incentivises general practitioners to measure HbA1C at least once every 15 months for patients with diabetes (15), meaning nearly all patients should have two or more measurements in our two and a half year study window. Patients who died or transferred out of practice, and were thus not eligible for the full 30 months' follow-up, were excluded. The study was approved by the Independent Scientific Advisory Committee of CPRD.

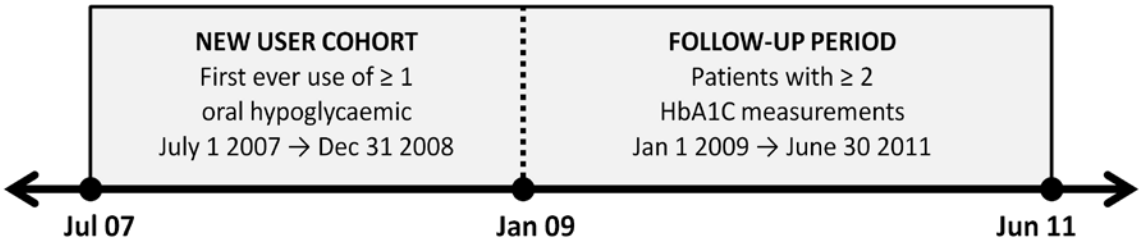

Figure 1. Establishment of cohort of new users of oral hypoglycaemics during July 07 – Jan 09, with 30 month follow-up period from Jan 09 – Jun 11

Statistical analysis

Estimation of trajectories

Trajectories were estimated, separately for each individual patient, over a 30-month time window from Jan 1 2009 to June 30 2011 using the functional principal component analysis method described by Peng and Paul (13) (Figure 2). Details of the methods and signposting to the statistical code are included in the online Appendix. In brief, the technique estimates subject-specific trajectories throughout time by combining the information from that individual with estimates obtained from the entire study sample.

Three different models were used to estimate trajectories in order to examine performance using mean prediction error (see below) under various circumstances. The primary analysis (Model 1) used all available data points within the study period (the squares in Figure 2). Model 2 re-fitted trajectories for all patients after temporarily excluding the final data point for one in four randomly selected patients (hollow square, Figure 2). This second model was developed to allow estimation of prediction error at times when the outcomes for some patients may not have been measured and could not contribute to the estimated trajectory. Model 3 sought to examine whether the prediction error could be improved by extending the observation time window and thus including more known, historical data points. To this end, the estimated trajectory was refitted for Model 3 using data points within a longer study window, from July 1 2007 to June 30 2011. This is represented by inclusion of both the squares and the triangles in Figure 2 in the prediction model.

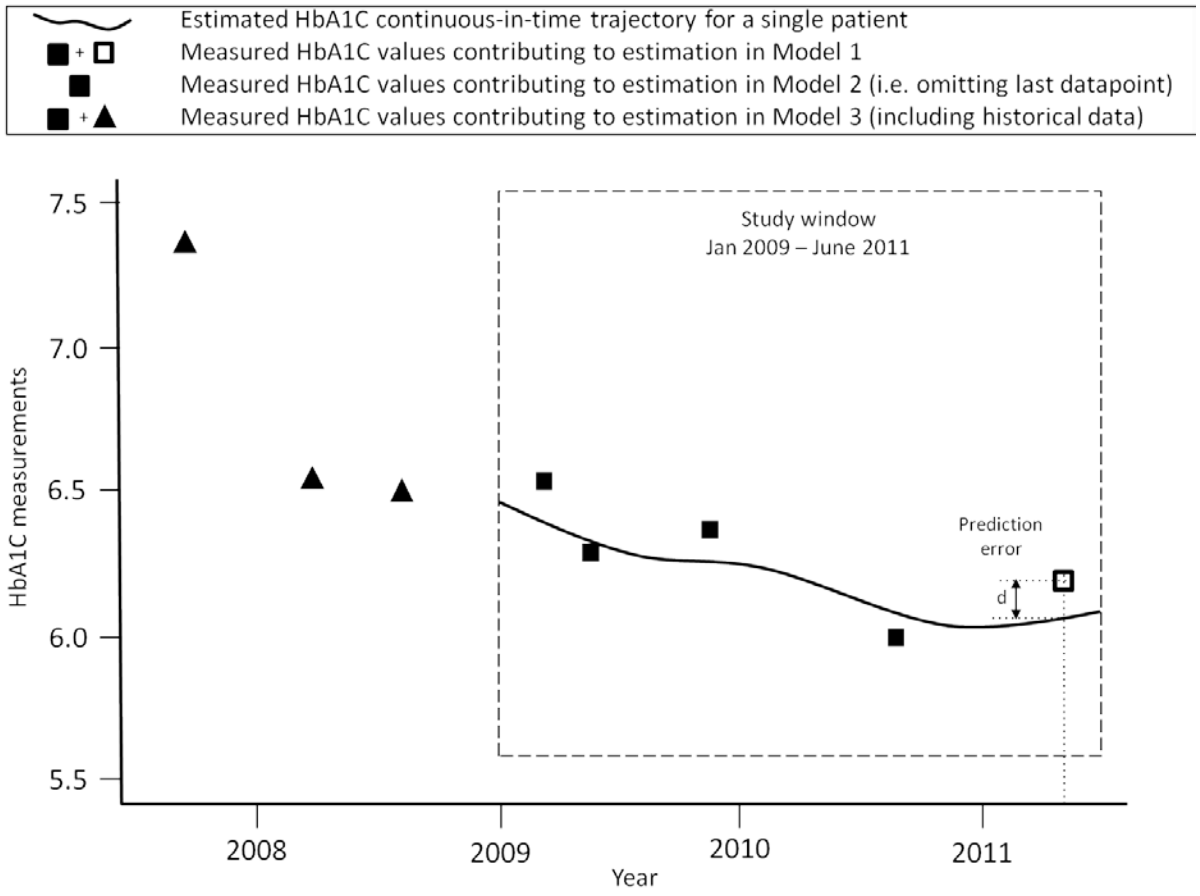

Figure 2. Schematic of a single patient's HbA1C measurements, estimated trajectory and prediction error

Triangles and squares represent true measured values for a single patient.

The curve represents the estimated HbA1C trajectory through time for that patient.

Prediction error is the distance from the most recent (latest) known value to the value predicted (i.e. the value on the estimated trajectory) for the same time (d).

Validation of trajectories

The predictive accuracy of estimated patient-level trajectories was assessed using the mean prediction error, i.e. the difference between the most recently observed HbA1C and the trajectory-estimated HbA1C at the corresponding time-point (distance d, Figure 2), averaged across all patients. For Model 2 (excluding last data point for one in four subjects), the mean prediction error was estimated using the distance from the last known data point (hollow square,

Figure 2) to the estimated value at that time-point for all patients (distance d, Figure 2), irrespective of whether the value contributed to the FPCA estimated trajectory. The mean prediction error was also calculated separately for the quarter of patients where the last data point was omitted from the FPCA estimation in Model 2.

To appreciate the importance of the difference between estimated and true HbA1C, we also estimated the proportion of individual prediction errors that were i) below the measurement error and ii) below a clinically meaningful difference. Measurement error of HbA1C is considered to be around 0.4 units assuming an average HbA1C value of 8% (16). We defined the clinically meaningful difference as the change in HbA1C associated with a 10% increased risk of any endpoint related to diabetes, which equates to a change in HbA1C of 0.5% (17).

Factors influencing prediction error

We anticipated that prediction errors would be affected by (i) the density of HbA1C measures in the study window, and (ii) the stability of disease control. Therefore, we performed two types of stratified analyses, in which results for Model 1 were also presented separately for (i) patients with 2-3, 4-5, 6-8, or >8 HbA1C measurements, and (ii) patients for whom the range of recorded values is <2 or ≥ 2 units of HbA1C (deemed to represent stable and unstable disease, respectively).

Results

500 643 adult patients were identified who had either a READ code for diabetes or had any prescribed hypoglycaemic medication between 1987 and July 2011. There were 20 570 patients found to be new users of this type of medication from July 1 2007 to December 31 2008 after limiting to practices that were 'up to standard' throughout follow-up, and excluding patients who died or transferred out of practice prior to June 30 2011. Of these, 16 034 patients had two or more measures between Jan 1 2009 and June 30 2011.

43% of patients were female, with a mean age of 62 years. 57% were male with a mean age of 60 years. The number of HbA1C measurements for this final cohort in the study window ranged from 2-17 with a median of 4 (IQR 3-6). The median period between measurements was 163 days (IQR 104-221).

The mean prediction error using the complete dataset for all patients within the study window (Model 1, full 30-month data) was 0.27 (sd 0.31). 80% of prediction errors were less than measurement error of 0.4 units HbA1C, and 86% were less than the clinically important difference of 0.5 units (Table 1). 64% of prediction errors were less than 0.25 units of HbA1C. Excluding the final data point for one in four subjects (Model 2) led to a slight decrease in the

predictive ability of the technique, where 73% of prediction errors were less than measurement error and 80% were less than the clinically important difference. Limiting the mean prediction error assessment to the quarter of subjects where their last HbA1C value did not contribute to the FPCA led to a mean prediction error of 0.61, with around 60% of estimates within 0.5 units. Interestingly, extending the time window used to estimate the trajectories to include data points from the more distant past (Model 3), a time period prior to their first oral hypoglycaemic use, led to a higher mean prediction error than the previous two models, with 70% predictions less than the clinically important difference of 0.5 units.

Table 1. Prediction error (difference between predicted and actual values of last observation), described as absolute difference and proportion of predictions within clinical acceptability and measurement error

	Model 1	**Model 2**	**Model 3**
	All data points	All data points	All data points
	1/'09-7/'11	1/'09-7/'11	7/'07-7/'11
		excluding final data point in 25% subjects for Models 2 & 3	
Prediction error			
Mean	0.27	0.34	0.46
Standard deviation (SD)	0.31	0.43	0.51
Median	0.18	0.21	0.30
Interquartile range (IQR)	(0.08, 0.34)	(0.10,0.42)	(0.14, 0.58)
Proportion of predictions…			
Within 0.5 units (clinically important difference)	86%	80%	70%
Within 0.4 units (measurement error)	80%	73%	62%

Model 1: Trajectories developed using all data points within study window (Jan 09 – June 11)

Model 2: Trajectories developed using same study window (Jan 09 - June 11), but exclusion of one in four random final HbA1C measurements

Model 3: Trajectories developed after exclusion of one in four random final HbA1C measurements, but including all HbA1C data points in the preceding 1.5 years (July 07 - June 11)

Stratification by the range of HbA1C, reflecting stability of disease, and number of HbA1C measurements within the two and a half year study window generated eight groups whose characteristics may influence mean prediction error (Table 2). All four groups with < 2 unit variability in HbA1C values had mean prediction errors of < 0.21 units (upper half of Table 2), > 90% of prediction errors below the clinically important difference, and > 85% below the measurement error. Furthermore, among subjects with a stable disease, the frequency of measurements had little impact on the prediction errors. The prediction error was much greater for subjects who had greater variability in their observed HbA1C measurements (lower half of Table 2). The best mean prediction error of these strata was 0.51. The proportion of predictions below the clinically important difference was between 29% and 61%. Less than 51% of prediction errors fell within measurement error for subjects whose known HbA1C values varied by more than two units in the study window. Among subjects with unstable disease, the prediction errors were by far the highest for those with the most sparse data, i.e. only two or three HbA1C measurements.

Table 2. Prediction error, stratified by the number of HbA1C measurements within the 30-month study window and by the range of HbA1C values for individual subjects within that same window

Number of HbA1C measures within study window	2 - 3	4 - 5	6 – 8	> 8
A. Range of HbA1C measures in study window < 2				
Number of subjects	4490	5322	2354	195
Prediction error				
Mean	0.18	0.17	0.19	0.21
SD	0.15	0.14	0.16	0.15
Median	0.14	0.14	0.15	0.17
IQR	(0.07, 0.25)	(0.07, 0.24)	(0.07, 0.27)	(0.08, 0.30)
Proportion of predictions…				
within 0.5 units (clinically important difference)	96%	96%	95%	95%
within 0.4 units (measurement error)	91%	92%	90%	87%

B. Range of HbA1C measures in study window >= 2				
Number of subjects	586	1479	1337	271
Prediction error				
Mean	0.76	0.58	0.50	0.54
SD	0.46	0.46	0.44	0.49
Median	0.68	0.49	0.39	0.40
IQR	(0.43, 0.98)	(0.25, 0.81)	(0.19, 0.68)	(0.19, 0.72)
Proportion of predictions…				
within 0.5 units (clinically important difference)	30%	51%	60%	61%
within 0.4 units (measurement error)	23%	41%	51%	50%

Discussion

This study shows that estimated patient-level trajectories of HbA1C can be developed with good validity in patients with diabetes. 80% or more of predictions fell within a clinically important difference and the known laboratory measurement error.

Successful estimation of patient-level trajectories for continuous variables opens up many opportunities for real-world observational research. Patients vary in the timing of their outcome assessments in routine clinical practice, rarely having their outcome measured at specified time-points. Development of continuous valid estimations throughout time in observational datasets will allow researchers to examine the change from baseline to any pre-specified time-point, irrespective of whether the patient has a measurement at that time. This will allow examination of real-world clinical effectiveness and compare to efficacy from RCTs. It will enable examination of drug effectiveness in populations excluded from RCTs. It will facilitate comparative effectiveness research for both monotherapy and any prescribed drug combination therapy. Furthermore, it allows researchers to examine the complete evolution of the continuous variable of interest from baseline to the end of the study (e.g. early versus late control of disease severity). Although we illustrate its utility for estimating HbA1C in patients with diabetes, this technique could be applied in a whole range of settings.

Empirical validation of the FPCA method in this study was based on mean prediction error, comparing the final known data point to the estimated value at that same time-point. It could be argued that inclusion of this final data point in the trajectory estimation would imply that, on

average, the curve came close to the known value at this time-point. We therefore ran a second model that ignored this final data point in a proportion of patients, to avoid this problem. The mean prediction error increased slightly, as expected, but more than 70% of patients still had estimates within the measurement error range of 0.4 units. It was not possible to remove the final data point for all patients, as defining a patient's trajectory using the FPCA method is dependent on the rest of the population. Had we removed the final data point from all patients, there would have been little population-level information at the end of the study window with which to generate the trajectories. As a consequence, our results may underestimate the prediction error for a setting where the most contemporary data are sparse for all subjects.

Our third model helped assess if one could improve the prediction error by using additional data points, from the more distant past, to inform each individual's estimated curve. Contrary to our expectations, this resulted in higher prediction errors (mean 0.46 units). Put otherwise, the potential gains due to additional HbA1C measurements were outbalanced by the bigger difference in time between these measurements and the (most recent) assessment used to estimate the prediction error. This may be because analysis was restricted to new users of oral hypoglycaemic therapy. Many data points prior to 2009 would therefore reflect time spent off treatment, whilst those within the study window reflect time on treatment. The FPCA model would not take account of the change in treatment, which is prescribed to improve glucose control. This might therefore explain why the prediction error increases with Model 3. In order to address this possibility, we will be extending the methodology to incorporate time-fixed and time-varying covariates including medication use.

Stratification by the range of HbA1C values found patients with unstable disease (range of observed HbA1C values within the study window exceeded 2 units) to have higher prediction errors. As expected, the worst performance of the model occurred when there were only three or fewer data points combined with unstable disease. However, the proportion of patients with unstable disease was less than 25%, leaving the majority with good predictions.

We were reliant on known HbA1C values to be able to validate our model. It is of clinical and research interest to know whether the technique accurately predicts patients' HbA1C values at time-points when they have *not* been measured. We addressed this to an extent in Model 2 by ignoring data points for a randomly selected subset of 25% of the study sample. It is impossible to test estimated values against unmeasured values. To get around this problem, we are extending our validation work by comparing observational studies using this technique to published RCTs. We will replicate an RCT population and treatment arms, then compare the estimated change from baseline to the RCT-specified endpoint in the two treatment arms. The technique will be further validated if our effectiveness results over the period defined in the RCT, using FPCA-estimated levels derived from sparse and irregularly spaced data, replicate the published RCT results, allowing for the known 'efficacy-effectiveness gap' (7). Finally, simulation studies could be considered to further assess the FPCA performance under a range of clinically plausible assumptions about the underlying processes and data structures.

FPCA assumes that all patients are similar, with no external influences on the measurements. In diabetes, this is clearly not true. Diabetic control is affected by diet and medication, amongst many other factors. Exclusion of time-fixed and time-varying covariates that might influence HbA1C would reduce our ability to accurately predict the true values. It is thus very reassuring that, despite this limitation, our prediction error is low. Future work will extend this model to incorporate other variables, with the goal of further improving the prediction accuracy.

In conclusion, FPCA has been shown to be a useful and valid method to estimate HbA1C through time. Although FPCA performs less well in the setting of increasingly sparse data, the mean prediction error remains within clinical acceptability for HbA1C. Planned future work includes extended validation through replicating known results from RCTs using FPCA in an observational setting, and incorporating time-fixed and time-varying covariates to improve prediction accuracy. This technique could also be tested and utilised for a range of other sparse and irregularly spaced clinical outcomes in epidemiology, and may become a useful part of the epidemiology toolkit**.**

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Online Appendix

Details of FPCA methodology when estimating subject-specific trajectories from sparse longitudinal data

In the sparse functional model, Peng and Paul [2009] consider a sample of *n* individual trajectories which are assumed to be independent realisations of a smooth random function, $X(t)$. The unknown mean of this random function, $X(t)$, is given by $\mu(t)$, and its covariance function, defined as $G(s,t) = cov\big(X(s), X(t)\big)$, represents covariance between measurements at time-points *s* and *t* within a time interval τ, rescaled so that $\tau = [0,1]$.

With $i = 1, \dots, n$ individuals and $j = 1, \dots, N_i$ time-points for subject i (notice that N_i may vary between subjects), the sparse functional data model can be expressed as follows:

$$Y_{ij} = X_i\big(t_{ij}\big) + \varepsilon_{ij}$$

$$= \mu\big(t_{ij}\big) + \pi_{ij} + \varepsilon_{ij} \qquad (1)$$

where Y_{ij} is the observed value for the ith subject at the jth observation time, t_{ij} is the corresponding jth consecutive time-point when this individual was assessed and the number of measurements, N_i, made on the ith individual is considered random, i.e. independent of the $X(t)$ trajectory. Y_{ij} is considered to be the sum of the 'true' (latent) value, $X_i\big(t_{ij}\big)$, and the measurement error, ε_{ij}, where the ε_{ij}'s are assumed to be independent and identically distributed, with mean zero and constant variance, σ^2. The value of the population mean at the corresponding time-point, t_{ij} is given by $\mu(t_{ij})$. Within individual differences from the corresponding population mean are represented by π_{ij} and these residuals have a symmetric $N_i \times N_i$ covariance matrix, where the measurements within an individual are not independent, but inherently correlated. The individual numbers of measurements, N_i, are assumed to be independent realisations of a random variable and independent of all other random variables.

Estimation of the model components of (1) is done in four steps. First, the procedure estimates a smooth population mean curve, $\mu(t)$, across all time-points, t, based on the data pooled from all individuals, using a local linear smoothing method [Fan and Gijbels 1996]. Second, the covariance function, $G(s,t)$, is estimated from the pooled data using the eigenvalues, λ_k, and corresponding eigenfunctions, ϕ_k, (i.e. the functional principal components, where $k = 1, 2, \dots, K$), as well as the measurement error variance, σ^2. The choice of K is determined automatically by the software so as to best capture the variability present in the data [Peng and

Paul's 'fpca' R package 2013 available on http://cran.r-project.org]. In the third step, best linear unbiased prediction is used to obtain estimates of the functional principal component scores, ξ_{ik}, for the ith individual, given the data from that individual together with the functional principal components and measurement error variance already estimated using all the data in the previous step. This allows the individual residual, π_{ij}, of model (1), at each time-point to be determined for each individual, since in classical functional principal component analysis, π_{ij} can be expressed as

$$\pi_{ij} = \sum_{k=1}^{K} \xi_{ik} \phi_k(t_{ij})$$

Finally, prediction of the trajectory, $X_i(t)$, for the ith individual in model (1), using the first K eigenfunctions, is achieved by combining the estimated mean curve, $\hat{\mu}(t)$, with the estimated residual component, $\hat{\pi}_{ij}$, at any time-point, t, as follows

$$\hat{X}_i^K(t) = \hat{\mu}(t) + \sum_{k=1}^{K} \hat{\xi}_{ik} \hat{\phi}_k(t) \qquad (2)$$

The continuous nature of the estimated individual trajectories in (2) means we can estimate the expected value for each individual at any given time-point within the study period, irrespective of whether the individual had an observation at that time or not, allowing estimation from the sparse and irregularly spaced data.

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