University of Alberta

Use of Insulin in Type 2 Diabetes

by

John-Michael Gamble

A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements for the degree of

Master of Science

in

Clinical Epidemiology

Department of Public Health Sciences

Edmonton, Alberta
Fall 2008

Your file Votre référence
ISBN: 978-0-494-47252-1
Our file Notre référence
ISBN: 978-0-494-47252-1

ABSTRACT

Background: Evidence surrounding the optimal treatment strategy and overall safety of using insulin in type 2 diabetes is unclear.

Methods: We conducted a systematic review to compare the efficacy of add-on therapy using basal insulin versus an additional oral antidiabetic agent in patients with type 2 diabetes and secondary failure. Using a retrospective cohort design we quantified the relationship between insulin exposure and all-cause mortality.

Results: Insulin treatment demonstrated a small but statistically significant improvement in A1C compared with the use of an additional oral agent as add-on therapy. Increasing insulin exposure was associated with an increased risk of mortality.

Conclusions: Basal insulin therapy compared to the use of an oral agent as add-on therapy produce comparable results in glycemic control. Higher level evidence is needed to further evaluate the association of insulin therapy and mortality in patients with type 2 diabetes.

ACKNOWLEDGEMENT

This work was supported by a full-time Health Research Studentship through the Alberta Heritage Foundation for Medical Research (AHFMR) and a Canada Graduate Scholarship from the Canadian Institutes of Health Research (CIHR). This thesis was supported in part by the New Emerging Team (NET) grant to the Alliance for Canadian Health Outcomes Research in Diabetes (ACHORD). The ACHORD NET grant is sponsored by the Canadian Diabetes Association, the Heart and Stroke Foundation of Canada, the Kidney Foundation of Canada and CIHR (Institute of Nutrition, Metabolism and Diabetes and the Institute of Circulatory and Respiratory Health).

Dr. Simpson is a New Investigator supported by the CIHR. Dr. Majumdar is a Population Health Investigator with the AHFMR and a New Investigator with the CIHR. Dr. Johnson holds a Canada Research Chair in Diabetes Health Outcomes, is a Health Scholar through the AHFMR and is the Chair of a New Emerging Team (NET) grant to the Alliance for Canadian Health Outcomes Research in Diabetes (ACHORD).

Chapter 3 is based in part on de-identified data provided by the Saskatchewan Department of Health. The interpretation and conclusions contained herein do not necessarily represent those of the Government of Saskatchewan or the Saskatchewan Department of Health.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1
Introduction

1.1 Introduction

Insulin was discovered in the early 1920's by a group of Canadian scientists.[1] Much advancement has been made regarding the purity and stability of insulin since its discovery and, along with the acceleration of genetic technology in the past two decades, there are now a myriad of insulin formulations to choose from today (appendix A). Insulin is one of the many treatment options for individuals living with type 2 diabetes. Type 2 diabetes is a condition occurring when the body is no longer able to produce, secrete, or use insulin and is characterized by high blood glucose.[2] Although considerable advancements in therapeutic knowledge surrounding insulin have accumulated over the years, the overall risk-benefit ratio of insulin in people with type 2 diabetes remains uncertain.

Type 2 diabetes represents 90 to 95 percent of people living with diabetes and is currently putting an indelible mark in the health and health care systems of individuals and countries respectively throughout the world. The prevalence of diabetes is increasing in epidemic proportions in Alberta, Canada,[3,4] and globally,[5,6] presenting a substantial public health burden. The prevalence is estimated to rise from a reported 171 million cases worldwide in the year 2000 to over 350 million cases by 2030.[5] Living with type 2 diabetes increases one's risk of many painful and often devastating complications. Complications of diabetes include diseases of the microvasculature such as retinopathies, neuropathies, and nephropathies and diseases of the macrovasculature such as coronary heart disease, peripheral vascular disease, and stroke. These complications translate to a substantially increased risk of amputation, kidney failure, nerve pain, and heart attack.[7] In addition to the burden of complications, life expectancy appears to be shortened by an average of five to ten years in middle aged people with type 2 diabetes.[8] Leading causes of death include cardiovascular disease and renal disease,[8] whereby cardiovascular disease is responsible for over 50% of deaths in people living with type 2 diabetes.[9]

Various treatments exist to decrease the risk of these complications, although the optimal strategy of when and how to use various medications is not yet conclusive.

Current management strategies in type 2 diabetes are multifaceted, focusing on managing a variety of cardiovascular risk factors such as hypertension, dyslipidemia, and obesity, in addition to the management of hyperglycemia.[10] Although lifestyle and diet intervention is beneficial, it is often insufficient for optimal glycemic control and pharmacological agents are required. Oral antidiabetic drugs (appendix B) are the mainstay of therapy for type 2 diabetes; however, as the condition is progressive, these agents often fail to maintain proper control of one's blood glucose over the long term.[11,12] In addition to focusing on managing hyperglycemia aggressive, cardiovascular risk reduction is essential in light of substantial evidence supporting a greater absolute impact on future morbidity and mortality.[13-16]

The treatment role of insulin has been well defined in evidence-based clinical practice guidelines.[2,17,18] Current Canadian, American, and European clinical practice guidelines [2,10] for type 2 diabetes suggest either the addition of insulin or another oral agent following inadequate control with monotherapy using an oral agent. Intensified and early initiation of insulin as a therapeutic modality for type 2 diabetes is being advocated due to its limitless ability to lower blood glucose and presumed safety. Evidence for these recommendations is based primarily on the United Kingdom Prospective Diabetes Study (UKPDS) where intensive glycemic therapy was compared to conventional glycemic therapy. Intensive antidiabetic therapy (fasting glucose target $\leq$6mmol/L) with insulin or a sulfonylurea subsequently was associated with a statistically significant 25% risk reduction for microvascular damage compared to conventional therapy (fasting glucose target >6 and $\leq$5mmol/L).[13] Although the point estimate suggested intensive therapy may be associated with a decrease in mortality in the entire study population (Relative risk 0.94), the confidence interval spanned across unity (95% Confidence interval 0.80 – 1.10). Many relevant questions regarding treatment of type 2 diabetes were unanswered, such as the benefit of long-term intensive insulin therapy.[19] The Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes (VA-CSDM) was a feasibility trial investigating the risks and benefits of intensive glycemic therapy in type 2 diabetes.[20] The study reported 24 patients (32%) in the intensive

treatment arm compared to 16 patients (20%) in the standard treatment arm experienced a cardiovascular (CV) event (p=0.10).[21] A follow-up study to the VA-CSDM named the Veteran Affairs Diabetes Trial (VADT) is designed to assess the effect of intensive glycemic control on CV events and is sufficiently powered to detect a 21% relative reduction in major CV events (CV death, myocardial infarction, stroke, congestive heart failure, revascularization and amputation).[22]

In addition to intensive insulin treatment, recent studies assessing the relationship between tight glucose control and mortality have lead to controversy over how aggressive glycemic targets should be for type 2 diabetes mellitus. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial is an ongoing multifactorial trial designed to assess cardiovascular outcomes using three different treatment interventions (www.accordtrial.org). The glycemic intervention comparing intensive glycemic control with standard glycemic control was prematurely stopped due to an unexpected increase in the number of deaths in the patients randomized to intensive glycemic therapy.[23] Results reported from the Action in Diabetes and Vascular Disease: Pretarax and Diamicron MR Controlled Evaluation (ADVANCE) trial did not support the findings of increased risk observed in the ACCORD trial, but nor did the ADVANCE treatment protocol result in any benefit in terms of reduced cardiovascular morbidity and mortality.[24] Therefore, the evidence remains unclear as to whether intensive glucose lowering therapy is beneficial with respect to mortality.

Recently treatment options for type 2 diabetes seem to be diminishing as rosiglitazone, a newer thiazolidinedione agent, has been associated with an increased risk of myocardial infarctions [25,26] and cardiovascular related mortality.[25] Controversy exists as recent meta-analyses show discordant results with cardiovascular related mortality and a recent interim analysis of an ongoing RCT suggests no evidence exists for an increase in death from cardiovascular events or all causes.[27] Also, the safety of sulfonylureas, particularly tolbutamide and glyburide has been questioned because of their potential for cardiotoxicity.[28-30] Many questions remain to be answered regarding the optimal role of insulin therapy in type 2 diabetes. Should long-term intensive insulin therapy be initiated upon diagnosis? Do we wait until all other therapeutic resources have been exhausted before introducing insulin? A common issue that often arises is whether to add insulin

therapy or add an additional oral agent when patients are failing their current oral therapy regimen.

Despite the paucity of evidence supporting the adoption of insulin as a preferred treatment in type 2 diabetes, clinicians are advocating for the earlier adoption of insulin therapy.[31] The uncertainty, potential toxicity, and limitation of lowering A1C of oral agent regimens have clinicians advocating for the use of earlier initiation of insulin therapy. A recent poll in the New England Journal of Medicine indicates that the addition of insulin is favoured by the majority of health care practitioners as an add-on agent compared to pioglitazone or exenatide in a patient whose blood sugar is uncontrolled on their current regimen.[32] By adopting insulin as the 'drug of choice' without high level evidence of undisputed RCT data to support its early introduction is relying merely on lower level evidence, primarily expert opinion. Furthermore, as mentioned we are uncertain of the long-term safety issues of using high dose insulin or lowering glucose beyond an A1C of 6% over a prolonged period in type 2 diabetes.[21,23,24]

Well designed observational studies, particularly in the absence of a RCT, provide a means to test hypotheses surrounding the long-term safety of medications. Observational studies restricted to topics of unexpected effects may often be as credible as RCTs [33]. In fact such studies are often better suited than RCTs for detecting signals related to adverse events due to adequate sample sizes.[34,35] Previous studies examining the safety of insulin use in type 2 diabetes have focused on cardiovascular disease.[36] Other safety issues have also surfaced in the literature such as the relationship between insulin and cancer.[37] All-cause mortality is an important outcome to all patients and is often an excellent measure of overall benefit in comparison with risk.[38] Mortality is an appropriate measure of overall risk-benefit for patients using insulin as the benefit of treatment is prevention of future disease, and insulin has potentially serious side effects (i.e. acute hypoglycemia).

The optimal timing and role of insulin in the treatment of type 2 diabetes is evolving. Further evidence is required to guide researchers, clinicians, policy makers, and patients. The relationship between long-term insulin use and patient oriented outcomes such as all-cause mortality remains uncertain and pharmacoepidemiological

methods provide tools to determine the true magnitude of effect in real world clinical situations beyond highly controlled RCT conditions.[39]

1.2 Objectives

The objective of this thesis is to assess questions regarding the efficacy and safety of insulin in people with type 2 diabetes. The use of well-designed epidemiological studies is essential to acquire knowledge regarding these themes. The two following papers address clinically relevant questions regarding the role of insulin in treating people with type 2 diabetes. The first paper is a quantitative systematic review (meta-analysis) assessing whether add-on therapy using basal insulin is more efficacious compared to an oral antidiabetic agent in patients failing their initial therapy with an oral agent. The second paper is a cohort study designed to quantify the relationship between insulin exposure and mortality. These two study designs, a meta-analysis and a cohort study, complement each other in providing evidence for the efficacy and safety of insulin therapy in people with type 2 diabetes.

1.3 Reference List

1. Bliss M. Resurrections in Toronto: The Emergence of Insulin. Hormone Research 2005;64:98-102.

2. Canadian Diabetes Association. 2003 Clinical Practice Guidelines. Can J Diabetes 2003;27:S1-S52.

3. Johnson JA, Vermeulen SU. Epidemiological Trends of Diabetes in Alberta. In Alberta Diabetes Atlas. Edmonton: Institute of Health Economics, 2007;11-24.

4. Ohinmaa A, Jacobs P, Simpson S et al. The projection of prevalence and cost of diabetes in Canada: 2000 to 2016. Can J Diabetes 2004;28:116-23.

5. Wild S, Roglic G, Green A et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047-53.

6. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. Diabetes Care 1998;21:1414-31.

7. MRFIT investigators. The multiple risk factor intervention trial (MRFIT). A national study of primary prevention of coronary heart disease. JAMA: The Journal of the American Medical Association 1976;235:825-7.

8. Panzram G. Mortality and survival in Type 2 (non-insulin-dependent) diabetes mellitus. Diabetologia 1987;30:123-31.

9. Morrish NJ, Wang SL, Stevens LK et al. Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. Diabetologia 2001;44:S14-21.

10. Nathan DM, Buse JB, Davidson MB et al. Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2006;29:1963-72.

11. UK Prospective Diabetes Study (UKPDS) Group. U.K. prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. Diabetes 1995;44:1249-58.

12. Harris SB, Ekoe JM, Zdanowicz Y et al. Glycemic control and morbidity in the Canadian primary care setting (results of the diabetes in Canada evaluation study). Diabetes research and clinical practice 2005;70:90-7.

13. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-53.

14. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998;317:703-13.

15. Pyorala K, Pedersen TR, Kjekshus J et al. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). Diabetes Care 1997;20:614-20.

16. Antithrombotic TC. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71-86.

17. American Diabetes Association. Standards of Medical Care in Diabetes--2008. Diabetes Care 2008;31:S12-S54.

18. Task FM, Ryden L, Standl E et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). European Heart Journal Supplements 2007;9:C3-74.

19. King P, Peacock I, Donnelly R. The UK Prospective Diabetes Study (UKPDS): clinical and therapeutic implications for type 2 diabetes. British Journal of Clinical Pharmacology 1999;48:643-8.

20. Abraira C, Colwell JA, Nuttall FQ et al. Veterans Affairs Cooperative Study on glycemic control and complications in type II diabetes (VA CSDM). Results of the feasibility trial. Veterans Affairs Cooperative Study in Type II Diabetes. Diabetes Care 1995;18:1113-23.

21. Abraira C, Colwell J, Nuttall F et al. Cardiovascular events and correlates in the Veterans Affairs Diabetes Feasibility Trial. Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes. Archives of Internal Medicine 1997;157:181-8.

22. Abraira C, Duckworth W, McCarren M et al. Design of the cooperative study on glycemic control and complications in diabetes mellitus type 2: Veterans Affairs Diabetes Trial. Journal of Diabetes and its Complications 2003;17:314-22.

23. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of Intensive Glucose Lowering in Type 2 Diabetes. The New England Journal of Medicine 2008;358:2545-59.

24. The ADVANCE Collaborative Group. Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes. The New England Journal of Medicine 2008;358:2560-72.

25. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. New England Journal of Medicine 2007;356:2457-71.

26. Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. JAMA: The Journal of the American Medical Association 2007;298:1189-95.

27. Home PD, Pocock SJ, Beck-Nielsen H et al. Rosiglitazone evaluated for cardiovascular outcomes--an interim analysis. New England Journal of Medicine 2007;357:28-38.

28. Meinert CL, Knatterud GL, Prout TE et al. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. Mortality results. Diabetes 1970;19(Suppl):789-830.

29. Simpson SH, Majumdar SR, Tsuyuki RT et al. Dose-response relation between sulfonylurea drugs and mortality in type 2 diabetes mellitus: a population-based cohort study. CMAJ 2006;174:169-74.

30. Riddle MC. Editorial: sulfonylureas differ in effects on ischemic preconditioning--is it time to retire glyburide? J.Clin.Endocrinol.Metab 2003;88:528-30.

31. Joshi SR. Role of insulin in type 2 diabetes. Journal of the Association of Physicians of India 2007;55:41-3.

32. Halperin F, Ingelfinger JR, McMahon GT. Management of Type 2 Diabetes -- Polling Results. The New England Journal of Medicine 2008;358:e8.

33. Vandenbroucke JP. When are observational studies as credible as randomised trials? The Lancet 2004;363:1728-31.

34. Avorn J. In Defense of Pharmacoepidemiology -- Embracing the Yin and Yang of Drug Research. The New England Journal of Medicine 2007;357:2219-21.

35. Ray WA. Population-Based Studies of Adverse Drug Effects. The New England Journal of Medicine 2003;349:1592-4.

36. Hirai FE, Moss SE, Klein BEK et al. Relationship of Glycemic Control, Exogenous Insulin, and C-Peptide Levels to Ischemic Heart Disease Mortality Over a 16-Year Period in People With Older-Onset Diabetes: The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR). Diabetes Care 2008;31:493-7.

37. Bowker SL, Majumdar SR, Veugelers P et al. Increased Cancer-Related Mortality for Patients With Type 2 Diabetes Who Use Sulfonylureas or Insulin. Diabetes Care 2006;29:254-8.

38. Ray WA. Observational Studies of Drugs and Mortality. The New England Journal of Medicine 2005;353:2319-21.

39. Strom B. When Should One Perform Pharmacoepidemiology Studies? In: Strom B, ed. Pharmacoepidemiology. Etobicoke: John Wiley & Sons, 2005;59-66.

CHAPTER 2

Insulin versus an oral antidiabetic agent as add-on therapy in patients with type 2 diabetes failing their current oral antidiabetic regimen: A meta-analysis.

2.1 Introduction

Lowering blood glucose decreased the risk of microvascular complications in the United Kingdom Prospective Diabetes Study (UKPDS) trial.[1] In this study, patients randomly assigned to the intensive protocol (target fasting plasma glucose (FPG) < 6 mmol/L) showed a significant reduction in microvascular complications and a trend toward reduced macrovascular complications.[1] Mainly on the basis of evidence from the UKPDS and other major diabetes clinical trials,[2,3] several organizations have formulated guidelines with clear recommendations for the initial therapy of type 2 diabetes.[4-6] However, in view of the progressive nature of type 2 diabetes,[7] patients and their clinicians will inevitably need to intensify therapy to maintain glycemic control. The decision to intensify therapy after initial success with oral antidiabetic medication has been defined as "secondary failure".[8-10] Although clinical trial evidence conveys the importance of early and sustained blood glucose control,[1,2,11] it is not clear how to proceed when initial oral antidiabetic drug therapy is no longer effective.

Current clinical practice guidelines [4-6] for type 2 diabetes recommend either the addition of insulin or another oral agent when monotherapy using an oral agent fails to achieve or maintain glycemic targets (A1C >7%). However, it is unclear which of these options is preferable.

Previous systematic reviews have not explored whether it is preferable to add insulin therapy or to add an additional oral agent in patients with secondary failure. Goudswaard and colleagues [12] focused on switching a patient's therapeutic regimen to insulin monotherapy versus adding insulin to oral antidiabetic agents. Reviews assessing combination therapy of insulin and oral antidiabetic agents have been limited to a specific class of oral antidiabetic agents, most commonly sulfonylureas,[13-15] and assessed whether combination therapy with insulin was beneficial compared with insulin monotherapy. Moreover, these previous reviews predate the launch of the newer long-acting insulins - insulin glargine and detemir.

A version of this chapter has been published. Gamble 2008. Open Medicine. 1(2):e1-13

The objective of this meta-analysis was to evaluate the evidence of the efficacy of adding basal intermediate or long-acting insulin versus the addition of another oral antidiabetic agent in people with type 2 diabetes whose current oral antidiabetic therapy was failing.

2.2 Methods

2.2.1 Search strategy

The search strategy was designed to capture the patient population, consisting of people with type 2 diabetes currently using any class of oral antidiabetic therapy; the population problem, defined as current treatment failure; the intervention of insulin glargine, detemir or NPH (neutral protamine Hagedorn); and the primary outcome measure of change in glycosylated hemoglobin (A1C). Our search strategy was developed in consultation with a research librarian well versed in the conduct of systematic reviews and in the use of MeSH (MEDLINE subject headings) and key terms.

The MEDLINE-based search strategy formed the foundation for searching in other databases. We searched the following electronic bibliographic databases from their inception until June 2007: MEDLINE, EMBASE, Cochrane Register of Controlled Trials, Web of Science, Scopus, CINAHL, International Pharmaceutical Abstracts, Academic OneFile, PASCAL, Global Health Database, LILACS, HealthSTAR, and PubMed. Other literature sources searched included: reference lists of all included studies and relevant narrative reviews; clinical trials databases (ClinicalTrials.gov; CenterWatch Clinical Trials Listing Service, and Current Controls Trials); OCLC Proceedings First and OCLC Papers First databases to identify studies presented at conferences and proceedings; and, Proquest and Index to Theses to identify relevant theses and dissertations. We contacted the pharmaceutical companies producing insulin glargine (Sanofi-Aventis), insulin detemir (NovoNordisk) and NPH (NovoNordisk, Lily) to inquire about other published or unpublished studies.

2.2.2 Selection of Studies

Citations identified in the literature search were independently screened by two reviewers (JG, SS) to select potentially relevant articles. The full articles from this list

were retrieved and subsequently reviewed by 2 reviewers (JG & LB) for inclusion in the systematic review. Inter-rater agreement at this stage was assessed using Cohen's Kappa statistic. Disagreements between reviewers were reconciled by consensus; a 3rd party intermediary was not required. Reviewers were not blinded to the authors, journal, or publisher of the studies. Non-English abstracts and articles were assessed by one reviewer (SK).

Studies were included if they had the following characteristics: RCTs, whether parallel or cross-over design; participants inadequately controlled on their current oral antidiabetic regimen, defined as an A1c>7% or a fasting plasma glucose (FPG) >7 mmol/L; participants insulin naïve at baseline; subjects randomized to the addition of either basal insulin therapy (insulin glargine, detemir, or NPH) or another oral antidiabetic agent from any class (biguanide, sulfonylurea, thiazolidinedione, non-sulfonylurea secretagogue, or glucosidase inhibitor). We use the term "basal" to mean administration of an single injection of intermediate or long-acting insulin as 100% of daily insulin dose; specifically, these would be regimens using NPH, glargine, or detemir.[4] We felt cross-over trials were suitable for our clinical question as diabetes management is a chronic condition of which we do not expect a carry-over effect of treatment in respect to blood glucose levels. Data from cross-over trials were entered as a parallel study.

In addition to the above criteria, studies must have reported (or given the information to calculate) change in A1C (%) from baseline. Glycemic control was our primary outcome, measured by change in A1C and the proportion of individuals achieving an A1C $\leq 7\%$. Secondary outcomes included change in FPG (mmol/L), change in weight (kg) and the proportion of participants experiencing ≥ 1 hypoglycemic event as defined by the study investigators.

2.2.3 Data Extraction and Management

Two reviewers (JG, LB) independently extracted the data from all articles that met our predefined eligibility criteria. Data were recorded on a standardized form, and all discrepancies were resolved by consensus. Both reviewers independently extracted data from 2 studies using a preliminary data extraction form. Minor revisions to the

extraction form were made after this trial period to provide the content found in Textbox 1. We attempted to contact authors to verify, interpret and obtain missing data. In addition to extracting data, the reviewers assessed the overall methodological quality of studies using the Jadad scale.[16] Methodological quality was assessed based on information reported in the published article only. In addition, a scale by Schulz and colleagues [17] was used to assess allocation of concealment. Funding sources for included studies were also considered.

If the mean change and its respective standard deviation were missing, we calculated the mean change from baseline by subtracting the mean baseline A1C from the mean A1C at the last follow-up date. Standard deviation (SD) was calculated using standard formulas,[18] using a correlation coefficient of 0.5 to allow estimation of the combined SDs. In one study [19] we had to estimate the values of A1C and fasting plasma glucose from inspection of graphs, as the exact values were not included in the publication and we were unable to obtain further information from the study authors. We substituted the mean SD from the other studies that used an identical comparison agent.

2.2.4 Data synthesis

We chose a random effects model for our meta-analysis, as it is more conservative than a fixed effect model and therefore less likely to overestimate treatment effects.[20] Statistical, clinical, and methodological heterogeneity were assessed to determine appropriateness of pooling data across studies. We evaluated statistical heterogeneity using the I^2 statistic. A I^2 value of greater than 50% was considered indicative of significant heterogeneity.[18] We recognized the potential for variability in key clinical characteristics such as duration of diabetes, baseline A1C, and age amongst studies. Therefore two strategies were used to explore potential sources of heterogeneity. First we used the method described by Tobias [21] to explore the impact of each study on the overall summary effect. Second, we examined pre-specified subgroups. Subgroups defined *a priori* included stratification by the type of insulin (NPH, glargine, detemir) and the comparative oral agent (metformin, thiazolidinedione, acarbose). Last we conducted sensitivity analyses on the following factors, defined *a priori*: fixed-effects versus random-effects model; parallel versus crossover design; and duration of follow-up.

All continuous variables (changes in A1C, FPG, and weight) were expressed using a weighted mean difference (WMD) and 95% confidence interval (CI). All dichotomous outcomes (proportion of subjects achieving an A1C $\leq$7%, and proportion of subjects experiencing $\geq$ 1 hypoglycemic event) were expressed using a relative risk (RR) and 95% CI. We chose RR as a measure of effect given considerations of consistency and interpretability. Publication bias was assessed by examining the symmetry of a funnel plot, where sample size is plotted against the treatment effect. A funnel plot was inspected for our primary outcome only, in view of the small number of studies that addressed our secondary outcomes.

2.3 Results

2.3.1 Search Strategy

Our search strategy identified 1234 unique citations, and an additional 26 citations were identified from grey literature sources (Fig. 1). Screening of title, abstracts, and keywords identified 54 citations potentially relevant to the review question, and the full text of these studies was retrieved. Seven non-English articles were assessed by 1 reviewer (SK), who found that none met the eligibility criteria. Two reviewers assessed the remaining 47 potentially relevant articles and found that 12 studies met the eligibility criteria independently (kappa=0.74). The reviewers arrived at a consensus that 11 studies met all of the eligibility criteria.

2.3.2 Included Studies

Baseline clinical and demographic data for each study are listed in Table 1. Seven studies[19,22-27] had a parallel design; 4 studies [28-31] used a crossover design. Crossover studies tended to have smaller sample sizes, contributing 119 to a total of 757 participants. Trial duration ranged from 12 weeks to 1 year of follow-up. Sample sizes ranged from 12 to 219 participants. Three studies used insulin glargine,[25-27] 7 studies used NPH insulin,[22,23,28-31] and 1 study did not specify the type of insulin.[19] Five studies used a thiazolidinedione (n=1 for pioglitazone and n=4 for rosiglitazone),[22,23,25-27] 5 studies used metformin,[19,24,29-31] and 1 study used acarbose [28] as comparison agents. Baseline A1C ranged from 8.8 to 11.2 %.

The overall quality of the studies was low (Jadad range 0-2), and only 1 study adequately describing an allocation of concealment method.(27) One study [28] was described as double-blinded; this was misleading, as the insulin arm was not blinded, and only the acarbose arm was masked with a placebo. Three studies [22,24,26] explicitly stated they were "open label" studies. The average percentage of dropouts per study was 13% of the number of subjects randomly assigned to a study arm. Reasons for dropouts were given in all studies, except the 2 studies that had no dropouts.[27,31] Although 2 studies described an intention to treat analysis, [23,26] in fact no study performed an intention to treat analysis.

Six studies were sponsored by a pharmaceutical company.[22,24-27] Most studies did not explicitly state their primary outcome. In the study by Rosenstock and colleagues [26] the primary outcome was identical to that of our systematic review: glycemic control measured using A1C.

2.3.3 Outcomes

To compare the overall efficacy of the two treatment options – addition of basal insulin versus another oral antidiabetic agent - outcome results from each study were pooled and an overall summary measure of effect was calculated. When all studies were pooled, the addition of basal insulin demonstrated a statistically significant improvement in A1C in comparison with the use of an oral agent as add-on therapy (WMD -0.17; 95%CI -0.33 to -0.02) (Fig. 2). The pooled analyses of the proportion of patients achieving an A1C $\leq$7% favoured addition of insulin; however, this finding did not reach statistical significance (RR 1.10; 95%CI 0.80-1.52) (Fig. 3). A third measure of glycemic control was change in FPG from baseline, where an improvement in the insulin arm versus the oral agent was found (WMD -1.29; 95%CI -1.61 to -0.98) (Fig. 4). With respect to adverse events, more patients experienced at least one hypoglycemic event in the insulin group than in the oral agent group (RR 1.42; 95%CI: 1.11-1.80) (Fig. 5). Weight gain was not pooled into an overall meta-analysis in view of the significant heterogeneity among studies (Fig. 6).

Results were categorized into clinically meaningful subgroups according to the type of insulin used. Eight studies compared a once daily injection of NPH versus an oral

antidiabetic as add-on therapy.[19,22-24,28-31] Two of these studies used a thiazolidinedione,[22,23] 5 studies used metformin [19,24,29-31] and 1 study used acarbose [28] as a comparator. No differences between groups were demonstrated for overall glycemic control as measured by change in A1C or proportion achieving an A1C ≤7% (Fig. 2).

A greater change in FPG was observed in the NPH group than in the oral group (WMD -1.64; 95%CI: -2.05 to -1.22) (Fig. 4). The proportion of participants who experienced a hypoglycemic event was higher in the NPH treated group (RR 1.89; 95%CI 1.16-3.10) (Fig. 5). There no statistically significant difference in the change in weight in kilograms from baseline between groups (WMD 0.99; 95%CI 0.36-1.62) (Fig. 6). As expected, when NPH was compared with metformin only, more weight gain was seen in the NPH group, although still statistically non-significant (WMD 1.29 95%CI 0.62-1.96).

Three studies compared the addition of insulin glargine to an oral agent.[25-27] Rosiglitazone was the only oral agent used in all 3 studies. Glycemic control did not differ significantly between groups, although the point estimates favour the addition of insulin glargine for both change in A1C (WMD -0.13; 95%CI -0.31 to 0.06) (Fig. 2) and the proportion of subjects achieving a target A1C ≤7% (RR 1.22; 95%CI 0.76-2.76) (Fig. 3). A significant difference was seen in favour of insulin for change in FPG (WMD -1.03; 95%CI -1.09 to -0.97) (Fig. 4) as well as weight gain (WMD -1.30; 95%CI -1.41 to -1.19) (Fig. 6). No difference was demonstrated between groups with respect to hypoglycemia (RR 1.29; 95%CI 0.98-1.71) (Fig. 5).

Sensitivity analyses, using a fixed-effects model, stratification by study design, or stratification by study duration, did not result in a substantial change in the magnitude or direction of the summary effect. To test the robustness of our summary measure of effect for change in A1C, we used the method developed by Tobias,[21] by which each study is omitted and the summary effect measure is compared with the original result. The WMD did not change by more than 10% with the exception that when the study by Rosenstock and colleagues [26] was omitted the WMD changed by 28% in favour of insulin treatment. The possibility of publication bias was suggested by asymmetry in the funnel plot.

2.4 Discussion

Management of type 2 diabetes mellitus is multifaceted, incorporating blood glucose, blood pressure, lipid, and weight control. Although guidelines recommend tight glucose control to reduce the risk of microvascular complications [4-6] many patients remain above recommended glycemic targets.[32] The progressive nature of type 2 diabetes further exacerbates the difficulty in achieving and maintaining glycemic control.[33] The objective of this review was to evaluate the efficacy of 2 different treatment strategies in people with type 2 diabetes in whom initial oral antidiabetic therapy had failed. We compared the addition of a basal insulin injection with the addition of another oral antidiabetic agent.

The results of this systematic review indicate that, when used as add-on therapy, basal insulin therapy and an oral agent achieve comparable glycemic control. Although insulin showed a statistically significant benefit, the difference was small and of limited clinical importance. The clinical impact of a 0.17% reduction in A1C associated with insulin therapy versus the addition of oral therapy must be viewed in light of the absence of large-scale quality trials. The 95% CI showed the potential benefit ranging from a 0.02% to a 0.33% reduction in A1C. We reported pooled estimates of the WMD in change in A1C from baseline, comparing insulin and oral agent treatment according to the type of insulin agent used. Although the overall pooled estimate favoured the addition of basal insulin, analysis stratified by insulin type to obtain an indirect comparison [34] showed no apparent difference between NPH or glargine in comparison with the addition of an oral antidiabetic agent. Another outcome of interest with respect to glycemic control was the number of patients in each treatment group who achieved a target A1C $\leq$7%.[4,5] The small number of patients who achieved an optimal A1C was likely related to the conservative dosing of insulin. A much larger magnitude of effect was observed with respect to change in FPG, but this might be expected insofar as insulin dosing was titrated on the basis of FBG levels in all of the studies. In view of the significant heterogeneity between NPH and glargine groups, the magnitude of effect must be considered in context. Insulin glargine was generally used as a third-line agent, whereas NPH was added as a second-line agent. Therefore, the magnitude of effect may have been influenced by other factors, such as differences in post-prandial blood glucose

control, which could account for the diminished effect observed in change in A1C.[26]

The relative safety of the 2 treatment strategies was evaluated using 2 secondary outcomes: proportion of subjects experiencing ≥1 hypoglycemic event, and change in weight. As expected, hypoglycemic events were more frequent in the insulin group than in the oral agent group. This appears to have been driven mostly by the large number of studies that use metformin as the comparison agent. The magnitude of effect is diminished and is statistically non-significant when only studies using a thiazolidinedione are considered. Overall, there was no difference in weight gain when insulin versus an oral agent was used as add-on therapy. The significant heterogeneity observed (I^2 92.8%; $p < 0.001$) and is explained in part by subgroup analysis. Of the 7 studies that used NPH and reported weight as an outcome measure, 4 used metformin as the comparative oral agent and showed a non-significant increase in weight gain among the NPH users (WMD 1.29; 95%CI 0.62-1.96). This is consistent with metformin use in general, which is advocated for overweight patients.[4] In the insulin glargine subgroup, insulin users experienced significantly less weight than those who used rosiglitazone as an add-on agent (WMD -1.30; 95%CI -1.41 to -1.19).

2.4.1 Limitations

Several limitations should be considered in the interpretation of our results. First, the overall quality of the studies included in the meta-analysis was poor, as indicated by the average Jadad score. We identified several recurring problems of methodology. For example, although all studies used random allocation, the process of randomization and concealment was not adequately described. Moreover, the lack of blinding was a major limitation across all studies. Proper blinding would require a double dummy design whereby participants would administer an injection and an oral tablet concurrently. Second, follow-up times were relatively short, considering that people with type 2 diabetes receive treatment for the rest of their lives. Two studies had a follow-up of 1 year.[19,23] However, the 2 treatment groups might not show comparable efficacy after 2, 5, or 10 years. Longer follow-up times would increase the external validity of the results. A third limitation is that our primary outcomes are surrogate markers and lack information on long-term outcomes such as microvascular or cardiovascular events. A

fourth consideration concerns the limit to which a triple oral therapy can lower A1C. The addition of a third oral agent is unlikely to decrease A1C levels by greater than 1.5% to 2.0%; therefore, insulin may be a more appropriate option for those who diabetes is very poorly controlled (>9.5%) with secondary oral antidiabetic therapy. Evidence for this exists in the findings from Rosenstock and colleagues,[26] which show that the glucose lowering benefit of insulin glargine, as measured by FPG, was greater when baseline A1C was ≥9.5%. A fifth limitation is the absence of data for secondary outcomes. Hypoglycemic event reporting was inconsistent, and definitions of hypoglycemia were rare (n=3).[22,26,27] Similarly, reporting on weight change was inconsistent between studies. Consistent reporting of other side-effects such as edema or pain at the injection site would aid in the applicability of the results.

Although every effort was made to minimize biases in the review process, potential biases still exist. These biases were limited to the involvement of 2 independent reviewers involved at each major stage in the review process. Publication bias was suggested by asymmetry observed on the funnel plot, although other sources of bias including selection bias, true heterogeneity, data irregularities, artefact, or chance may explain this asymmetry.[35]

The results of this systematic review are relevant for clinicians working with patients with poorly controlled type 2 diabetes who are using either a sulfonylurea as monotherapy or in combination with metformin. The choice of treatment regimens for add-on therapy should be evaluated in light of current A1C levels and risk of hypoglycemia. Non-therapeutic reasons such as cost and patient preference or adverse effects should be given adequate weight in view of the small magnitude of benefit observed for insulin use as add-on therapy. The optimal strategy for adding basal insulin therapy to an oral antidiabetic regimen remains to be demonstrated. More rigorous studies are required to establish the ideal treatment strategy for people with type 2 diabetes experiencing secondary failure on oral antidiabetic therapy.

A version of this chapter has been published. Gamble 2008. Open Medicine. 1(2):e1-13

2.4.2 Author Contributions

The authors thank Tamara Durec for assistance designing and implementing the search strategy; Stefan Kuhle for evaluating all non-English articles; Donna Dryden for providing comments on an early draft; and Dr's Raymond Reynolds, Curtis Triplitt, and Gary Ko for providing additional data from their respective studies.

JM Gamble was responsible for protocol development, searching for trials, trial selection, quality assessment, data extraction, statistical analysis, and the preparation of the first draft of this manuscript. Scot Simpson developed the research question, assisted with protocol design, independently screened for trial selection. Lauren Brown was responsible for trial selection, quality assessment of trials, data extraction. All authors contributed to interpretation of the results and provided revisions to the manuscript.

Textbox 2-1: Data extraction

General

- study identifier
- name of reviewer
- date of extraction
- bibliographic source

Study method

- design
- method of randomization
- length of study
- number lost to follow up
- number of withdrawals/dropouts
- reasons for withdrawal
- inclusion/exclusion criteria
- setting and location
- funding source

Population

- sample size
- age and gender
- current oral antidiabetic regimen
- baseline A1C (%)
- baseline body mass index (kg/m2) and/or weight (kg)
- baseline fasting plasma glucose (mmol/L)
- diabetes duration at baseline

Intervention

- type of insulin
- dose
- time of daily injection
- duration of therapy

Comparison

- type of oral antidiabetic agent
- dose, frequency
- duration of therapy

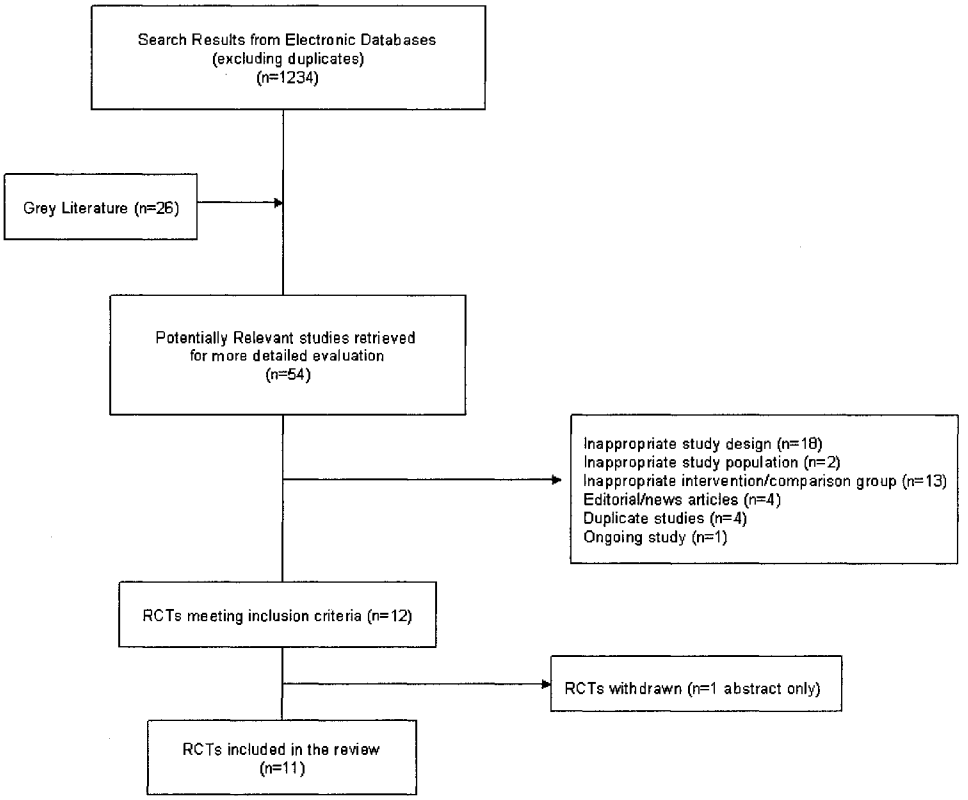
Outcomes

- primary outcomes stated
- change or follow up A1C
- change or follow up fasting glucose
- definition and number of hypoglycemic episodes
- change or follow-up weight

Analysis

- intention-to-treat or per protocol
- how authors dealt with missing data

Figure 2-1: Flow Diagram of Study Selection



A version of this chapter has been published. Gamble 2008. Open Medicine. 1(2):e1-13

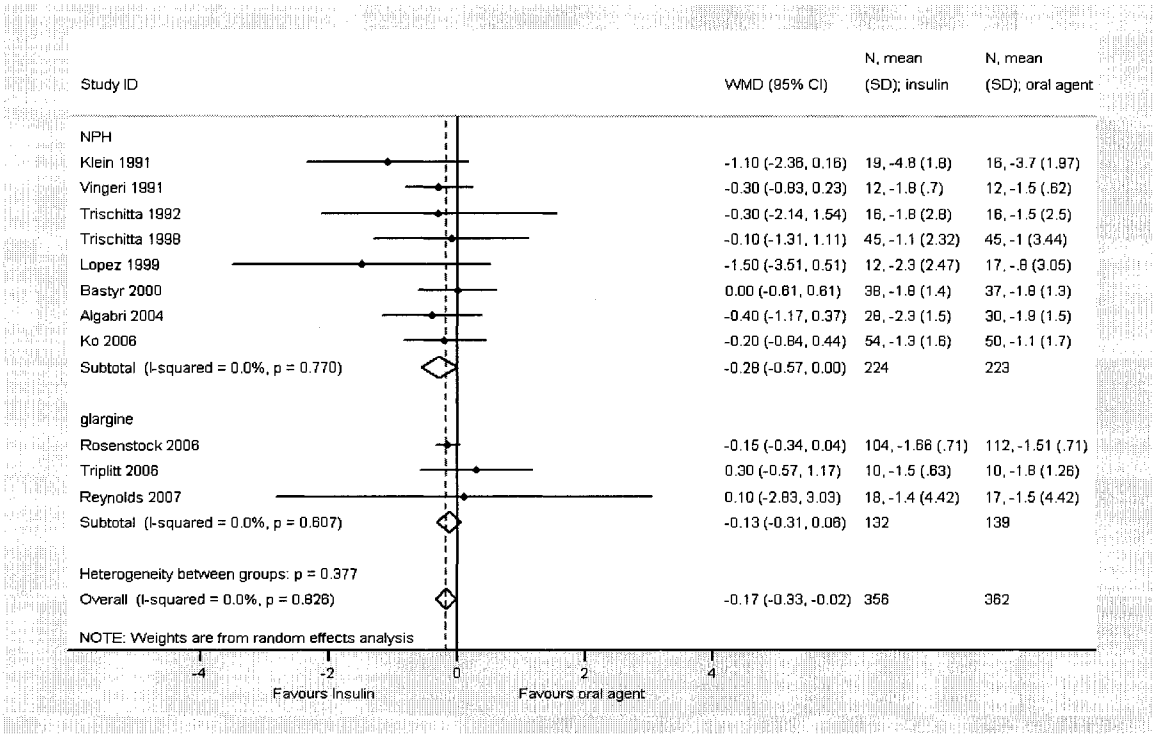
Table 2-1: Study Characteristics

Study (year), type	N*	Diabetes duration (yrs)	Age (yrs)	%M/F	BMI	A1C (%)	OAD	Duration of follow-up (wks)	Insulin Type	Oral Agent	Jadad Score	Funding Source
Aljabri (2004), P	62/58	10	58	60/40	25.5	9.9	Met+SU or Met + nateglinide	16	NPH	pioglitazone	2	Eli Lilly†
Ko‡ (2006), P	112/104	13	58	56/44	24.9	9.9	SU or Met+SU	52	NPH	rosiglitazone	1	Internal
Bastyr (2000), P	135/114	8	57	60/40	28.4	10.2	glyburide	12	NPH	metformin	1	Eli Lilly
Klein (1991), P	50/35	12	67	24/76	NR*	NR*	glibencla-mide	52	NR*	metformin	1	Unclear
Trishitta (1992), C	20/16	12	43	35/65	NR*	10.2	glyburide	16	NPH	metformin	1	Unclear
Trishitta (1998), C	50/45	13	56	24/76	27.8	9.1	glibencla-mide	16	NPH	metformin	1	Unclear
Vingeri (1991), C	12/12	12	52	NR*	NR*	NR*	glyburide	16	NPH	metformin	1	Unclear
Lopez-Alverenga (1999), C	37/29	10	53	28/72	27.3	11.2	chlorprop-amide + Met	12	NPH	acarbose	1	Bayer
Reynolds‡ (2007), P	40/35	11	61	100/0	31.6	9	Met+SU	24	Glargine	rosiglitazone	1	GSK†
Rosenst-ock (2006), P	219/216	8	56	52/48	34.1	8.8	Met +SU	24	Glargine	rosiglitazone	1	Aventis
Triplitt‡ (2006), P	20/20	8	48	40/60	30.2	9.3	Met +SU	16	Glargine	rosiglitazone	0	Aventis

* randomized / analyzed; M/F = male/female; BMI = body mass index (kg/m^2); OAD=oral antidiabetic therapy; P = parallel design; C = crossover design; NPH = neutral protamine Hagedorn; Met = metformin; SU = sulfonylurea; NR = not reported; GSK = GlaxoSmithKline. The study that did not report the type of insulin (Klein) was analyzed with the NPH studies. † Sponsor had not role in study design, analysis, or involvement in manuscript preparation.‡ Additional information was obtained from the author.

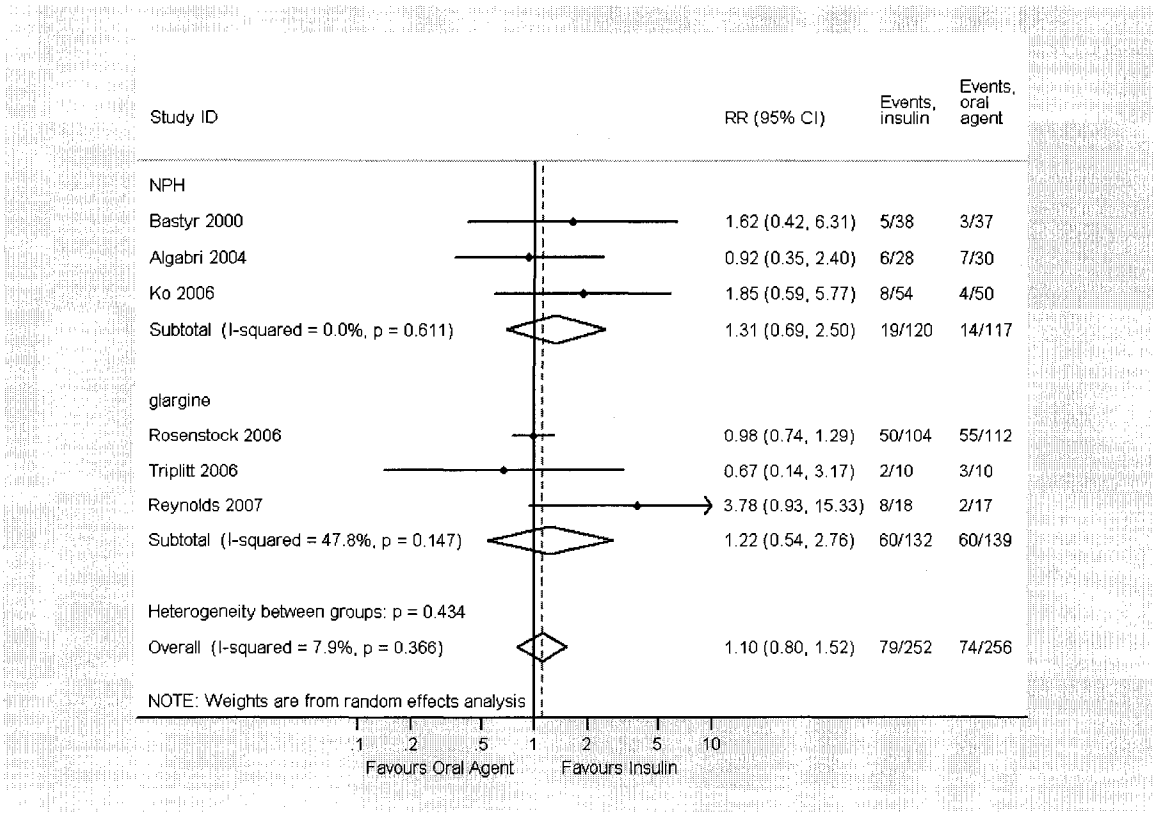
A version of this chapter has been published. Gamble 2008. Open Medicine. 1(2):e1-13

Figure 2-2: Change in A1C (%)



A version of this chapter has been published. Gamble 2008. Open Medicine. 1(2):e1-13

Figure 2-3: Proportion of Subjects Achieving a target A1C<7%



A version of this chapter has been published. Gamble 2008. Open Medicine. 1(2):e1-13

Figure 2-4: Change in Fasting Plasma Glucose (mmol/L)

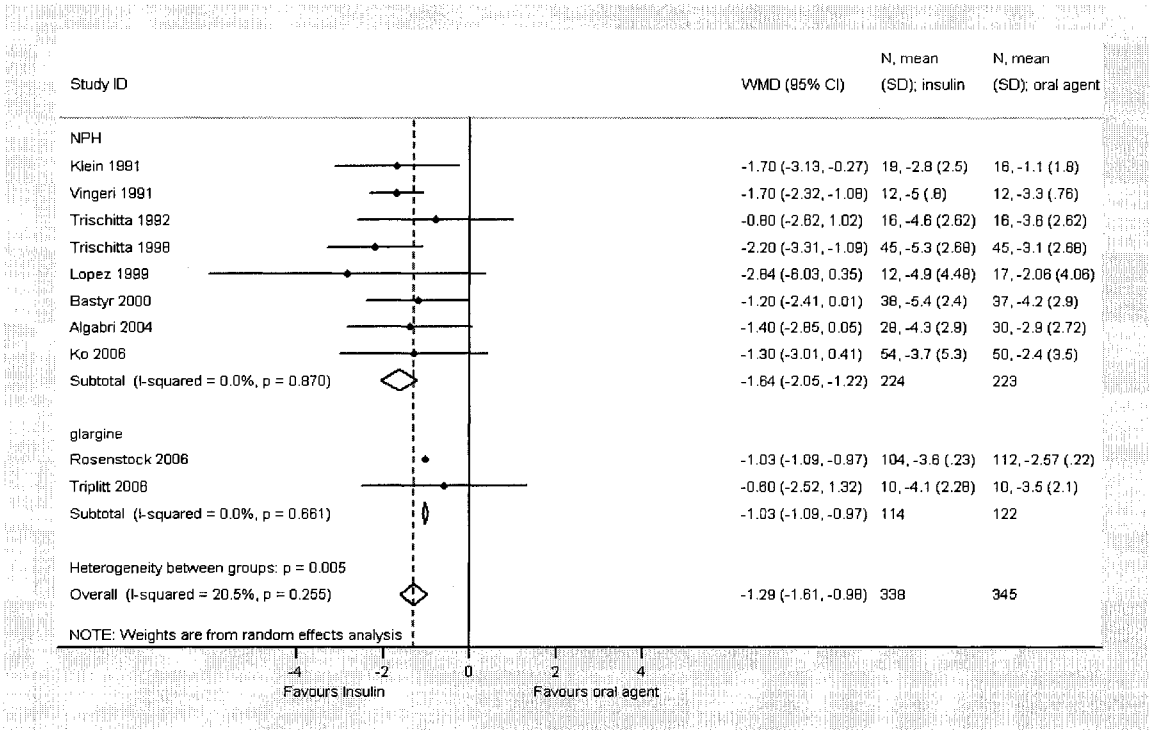
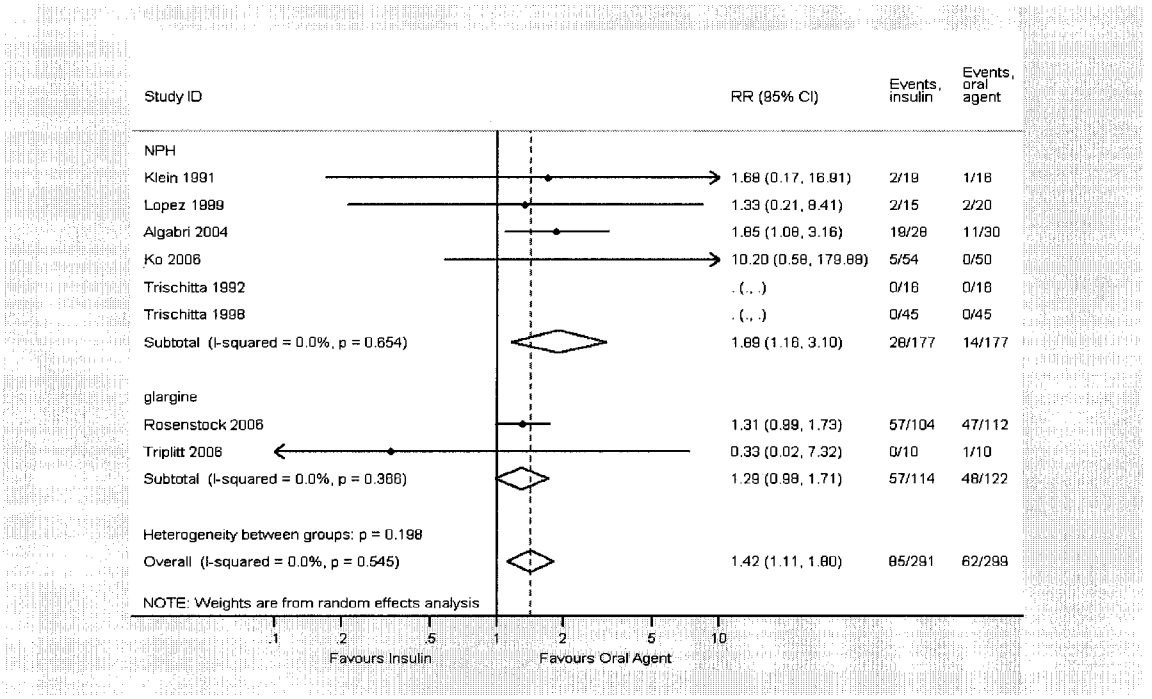
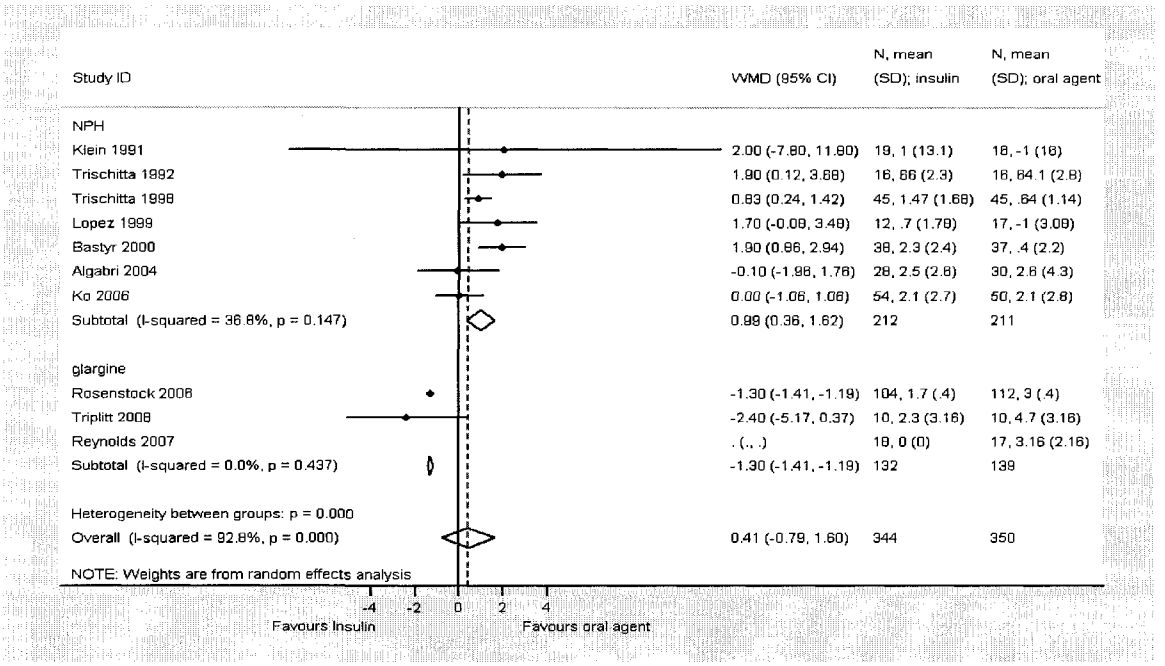


Figure 2-5: Proportion of Subjects experiencing a hypoglycemic event



A version of this chapter has been published. Gamble 2008. Open Medicine. 1(2):e1-13

Figure 2-6: Weight Change (kg)



Appendix 2-1: Medline final search strategy (Please contact authors for more details regarding other databases)

1. Drug Therapy, Combination/
2. exp Hypoglycemic Agents/
3. exp Sulfonylurea Compounds/
4. exp Biguanides/
5. exp Glucosidases/
6. Thiazolidinediones/
7. sulfonylurea$.mp.
8. sulphonylurea$.mp.
9. biguanide$.mp.
10. (thiazolidinedione$ or TZD?).mp.
11. glitazone$.mp.
12. secretagogue$.mp.
13. glimepiride.mp.
14. amaryl.mp.
15. gliclazide.mp.
16. diamicron.mp.
17. glyburide.mp.
18. glibenclamide.mp.
19. diabeta.mp.
20. metformin.mp.
21. glucophage.mp.
22. acarbose.mp.
23. alpha glucosidase inhibitor?.mp.
24. pioglitazone.mp.
25. Actos.mp.
26. rosiglitazone.mp.
27. Avandia.mp.
28. tolbutamide.mp.
29. chlorpropamide.mp.
30. 93479-97-1.rn.
31. 111025-46-8.rn.
32. 122320-73-4.rn.
33. 657-24-9.rn.
34. OAD.mp.
35. oral hypoglyc?emi$ agent$.mp.
36. oral antidiabet$ agent.mp.
37. *Diabetes Mellitus, Type 2/dt [Drug Therapy]
38. or/1-37
39. exp "Outcome Assessment (Health Care)"/
40. (treatment adj (outcome or failure)).mp.
41. insulin-naive.mp.
42. OHA failure.mp.

43. ((suboptimal$ or poor$ or glyc?emic or diabet$) adj contro?l$).mp.
44. or/39-43
45. Hemoglobin A, Glycosylated/
46. (Alc or A1c).mp.
47. HbA1c.mp.
48. GHb.mp.
49. (hemoglobin or haemoglobin).mp.
50. (glycosylated or glycated).mp.
51. HbA1.mp.
52. or/45-51
53. clinical trial.pt.
54. randomi?ed.ti,ab.
55. placebo.ti,ab.
56. dt.fs.
57. randomly.ti,ab.
58. trial.ti,ab.
59. groups.ti,ab.
60. or/53-59
61. animals/
62. humans/
63. 61 not (61 and 62)
64. 60 not 63
65. glargine.mp.
66. detemir.mp.
67. ((add-on or "add on") adj3 therap$).mp.
68. Insulin, Isophane/
69. Insulin, Long-Acting/
70. isophane.mp.
71. (long acting or longacting or long-acting).mp.
72. NPH.mp.
73. nph insulin.mp.
74. neutral protamine hagedorn.mp.
75. 53027-39-7.rn.
76. or/65-75
77. and/38,44,52,64,76

2.5 Reference List

1. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-53.

2. Ohkubo Y, Kishikawa H, Araki E et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes research and clinical practice 1995;28:103-17.

3. Abraira C, Colwell JA, Nuttall FQ et al. Veterans Affairs Cooperative Study on glycemic control and complications in type II diabetes (VA CSDM). Results of the feasibility trial. Veterans Affairs Cooperative Study in Type II Diabetes. Diabetes Care 1995;18:1113-23.

4. Canadian Diabetes Association. 2003 Clinical Practice Guidelines. Can J Diabetes 2003;27:S1-S52.

5. American Diabetes Association. Standards of Medical Care in Diabetes--2007. Diabetes Care 2007;30:S4-41.

6. Task FM, Ryden L, Standl E et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). European Heart Journal Supplements 2007;9:C3-74.

7. UK Prospective Diabetes Study (UKPDS) Group. U.K. prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. Diabetes 1995;44:1249-58.

A version of this chapter has been published. Gamble 2008. Open Medicine. 1(2):e1-13

8. Eurich DT, Simpson SH, Majumdar SR et al. Secondary failure rates associated with metformin and sulfonylurea therapy for type 2 diabetes mellitus. Pharmacotherapy 2005;25:810-6.

9. Nichols GA, Alexander CM, Girman CJ et al. Contemporary analysis of secondary failure of successful sulfonylurea therapy. Endocr Pract 2007;13:37-44.

10. Groop LC, Pelkonen R, Koskimies S et al. Secondary failure to treatment with oral antidiabetic agents in non-insulin-dependent diabetes. Diabetes Care 1986;9:129-33.

11. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. New England Journal of Medicine 1993;329:977-86.

12. Goudswaard AN, Furlong NJ, Valk GD et al. Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus. Cochrane Database of Systematic Reviews. 2004.

13. Johnson JL, Wolf SL, Kabadi UM. Efficacy of insulin and sulfonylurea combination therapy in type II diabetes. A meta-analysis of the randomized placebo-controlled trials. Archives of Internal Medicine 1996;156:259-64.

14. Peters AL, Davidson MB. Insulin plus a sulfonylurea agent for treating type 2 diabetes. Annals of Internal Medicine 1991;115:45-53.

15. Pugh JA, Wagner ML, Sawyer J et al. Is combination sulfonylurea and insulin therapy useful in NIDDM patients? A metaanalysis. Diabetes Care 1992;15:953-9.

16. Jadad AR, Moore RA, Carroll D et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled Clinical Trials 1996;17:1-12.

A version of this chapter has been published. Gamble 2008. Open Medicine. 1(2):e1-13

17. Schulz KF, Chalmers I, Hayes RJ et al. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA: The Journal of the American Medical Association 1995;273:408-12.

18. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions 4.2.6. Chichester, UK: John Wiley & Sons, LTD, 2006.

19. Klein W. Sulfonylurea-metformin-combination versus sulfonylurea-insulin-combination in secondary failures of sulfonylurea monotherapy. Results of a prospective randomized study in 50 patients. Diabete & metabolisme 1991;17:235-40.

20. Scott I, Greenberg P, Poole P et al. Cautionary tales in the interpretation of systematic reviews of therapy trials. Internal Medicine Journal 2006;36:587-99.

21. Tobias A. Assessing the influence of a single study in the meta-analysis estimate. The Stata Technical Bulletin 1999;STB-47:15-7.

22. Aljabri Khaled, Kozak Sharon E, Thompson David M. Addition of pioglitazone or bedtime insulin to maximal doses of sulfonylurea and metformin in type 2 diabetes patients with poor glucose control: A prospective, randomized trial. The American Journal of Medicine 2004;116:230-5.

23. Ko GT, Tsang PC, Wai HP et al. Rosiglitazone versus bedtime insulin in the treatment of patients with conventional oral antidiabetic drug failure: a 1-year randomized clinical trial. Advances in Therapy 2006;23:799-808.

24. Bastyr III EJ, Stuart CA, Brodows RG et al. Therapy focused on lowering postprandial glucose, not fasting glucose, may be superior for lowering HbA(1c). Diabetes Care 2000;23:1236-41.

25. Reynolds LR, Kingsley FJ, Karounos DG et al. Differential effects of rosiglitazone and insulin glargine on inflammatory markers, glycemic control, and lipids in type 2 diabetes. Diabetes research and clinical practice 2007;77:180-7.

A version of this chapter has been published. Gamble 2008. Open Medicine. 1(2):e1-13

26. Rosenstock J, Sugimoto D, Strange P et al. Triple therapy in type 2 diabetes - Insulin glargine or rosiglitazone added to combmiation therapy of sulfonylurea plus metformin in insulin-naive patients. Diabetes Care 2006;29:554-9.

27. Triplitt C, Glass L, Miyazaki Y et al. Comparison of glargine insulin versus rosiglitazone addition in poorly controlled type 2 diabetic patients on metformin plus sulfonylurea. Diabetes Care 2006;29:2371-7.

28. Lopez Alvarenga JC, Aguilar Salinas CA, Velasco Perez ML et al. Acarbose vs. bedtime NPH insulin in the treatment of secondary failures to sulphonylurea-metformin therapy in type 2 diabetes mellitus. Diabetes, obesity & metabolism 1999;1:29-35.

29. Trischitta V, Italia S, Mazzarino S et al. Comparison of combined therapies in treatment of secondary failure to glyburide. Diabetes Care 1992;15:539-42.

30. Trischitta V, I. Efficacy of combined treatments in NIDDM patients with secondary failure to sulphonylureas. Is it predictable ? J Endocrinol Invest 1998;21:744-7.

31. Vigneri R, Trischitta V, Italia S et al. Treatment of NIDDM Patients With Secondary Failure to Glyburide - Comparison of the Addition of Either Metformin or Bed-Time NPH Insulin to Glyburide. Diabetes & metabolism 1991;17:232-4.

32. Harris SB, Ekoe JM, Zdanowicz Y et al. Glycemic control and morbidity in the Canadian primary care setting (results of the diabetes in Canada evaluation study). Diabetes research and clinical practice 2005;70:90-7.

33. Turner RC, Cull CA, Frighi V et al. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA: The Journal of the American Medical Association 1999;281:2005-12.

A version of this chapter has been published. Gamble 2008. Open Medicine. 1(2):e1-13

34. Song F, Altman DG, Glenny AM et al. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. BMJ 2003;326:472.

35. Sterne JA, Egger M, Smith GD. Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis. BMJ 2001;323:7304-101.

A version of this chapter has been published. Gamble 2008. Open Medicine. 1(2):e1-13

CHAPTER 3

Insulin Use and the Risk of Mortality in Type 2 Diabetes Mellitus

3.1 Introduction

Since the discovery of insulin, the armamentarium of antidiabetic agents has increased substantially, although the optimal strategy to control hyperglycemia in people with type 2 diabetes remains unclear.[1-3] There is a mix of evidence supporting the association between either exogenous insulin therapy or endogenous hyperinsulinemia with several adverse physiological cardiovascular effects, including vasculature dysfunction,[4] weight gain,[5] and exacerbation of hypertension,[6] and dyslipidemia.[7] Two meta-analyses [8,9] have suggested endogenous hyperinsulinemia is associated with a modest increase in adverse cardiovascular events. The clinical evidence surrounding (exogenous) insulin use has been mixed with studies suggesting both harms [10-15] and benefits.[16-18] In one of the few RCTs conducted, The Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes (VA-CSDM), high versus standard doses of insulin therapy was examined in 253 patients with type 2 diabetes.[19] The study reported 24 patients (32%) who were randomly assigned to high dose insulin therapy compared to 16 patients (20%) randomly assigned to standard dose insulin therapy, who experienced a cardiovascular (CV) event ($p=0.10$).[20] The authors suggested this finding should be interpreted with caution and noted that insulin dose itself was not a significant risk factor for events.[20]

Nonetheless, because single oral antidiabetic agents are limited in their ability to lower blood glucose [21] and the progressive decline in B-cell function over time requires additional treatments from different classes [22,23], patients with type 2 diabetes often faced with the need to use insulin. However, we do not know the relative advantages and disadvantages of using higher versus lower doses of insulin in this population. Thus, the optimal strategies for treatment remain undefined. For example, should we continue combination oral antidiabetic agents with insulin to spare exposure to the latter,[24] or once insulin is started, should its use be up-titrated and considered only as monotherapy.[25] In the absence of randomized controlled trials (RCTs) to directly answer such questions, a

well-designed observational cohort study provides a means to test hypotheses surrounding insulin use and mortality at a population level; furthermore, it has been suggested that such studies are better suited than RCTs for detecting signals related to adverse events.[26,27] Therefore, we compared population-based rates of all-cause mortality in people with type 2 diabetes exposed to various levels of insulin using an observational retrospective cohort design. We hypothesized that exposure to increasing amounts of insulin would be associated with a graded increased risk of mortality.

3.2 Methods

3.2.1 Study Population

We analyzed data from the computerized linkable administrative databases of Saskatchewan Health, a provincial government department that provides universal health coverage to 99% of the approximately 1 million people in Saskatchewan, Canada.[28] Saskatchewan Health Databases have been used in numerous pharmacoepidemiological studies.[29-32] Saskatchewan Health beneficiaries eligible for prescription drug benefits, who were ≥30 years old, and who had at least one year of continuous coverage in the provincial health plan prior to their index oral antidiabetic drug dispensation were potentially eligible for inclusion. Specifically, we identified 12,272 new users of oral antidiabetic agents, defined as those eligible beneficiaries who received at least one new prescription for an antidiabetic medication between the index years of 1991-1996, and who were not treated with insulin or oral antidiabetic agents in the year prior to index.[29-31,33] Subjects were prospectively followed until death, termination of Saskatchewan Health Coverage, or until December 31, 1999, whichever occurred first.

3.2.2 Exposure and Outcome Definition

Our independent variable of interest was insulin exposure classified on an ordinal scale: no clinically important exposure (less than 3 dispensation records for insulin per year); low exposure, 3 to <9 dispensations/year (0.5 vials per month); moderate exposure, 9 to <15 dispensations/year (1 vial per month); high exposure, 15 to <21 dispensations/year (1.5 vials per month); very high exposure, ≥21 dispensations/year (2 vials per month). An average cumulative duration exposure was calculated using the sum

of insulin dispensations divided by the length of time between a subject's first insulin dispensation and their last insulin dispensation. The primary outcome was time to all-cause mortality.

3.2.3 Primary analysis

Cohort characteristics were first summarized using descriptive statistics and compared using student t-tests and chi-square tests where appropriate. Crude mortality rates were calculated for each level of insulin exposure. All person-time prior to insulin exposure contributed to the denominator of the unexposed group and person-time following insulin exposure contributed to the denominator used when calculating mortality rates among insulin users. The relationship between insulin exposure levels and all-cause mortality was assessed using time varying Cox proportional hazards models. Unadjusted and adjusted hazards ratios (HR) and 95% confidence intervals were determined using the no insulin exposure group as a reference. The amount of person-time follow-up was classified based on time spent exposed and unexposed to various levels of insulin as previously defined. The exact date of insulin initiation (insulin index date) was used to classify person-time follow-up. Therefore, prior to the insulin index date subjects were classified as non-insulin users, whereby upon insulin dispensation they were classified according to the ordinal variables used to characterize insulin exposure.

For multivariate analyses, potential confounders included in the models were age, sex, chronic disease score, severity of diabetes, and relevant medications. Age was treated as a continuous variable. Chronic disease score (CDS) provides an estimate of overall health status using patterns of prescription medications over time and has been shown to be predictive of hospitalization and mortality.[34] To further adjust for diabetes specific disease severity, a categorical variable was used to identify individuals with the absence of microvascular and macrovascular disease, the presence of either microvascular or macrovascular disease or the presence of both. Microvascular disease was identified based on any physician or hospital diagnosis for various international classification of disease (ICD-9) codes (appendix 1). Relevant medications included potentially confounding therapies that may decrease mortality, specifically angiotensin converting enzyme inhibitors (ace-I)[35], angiotensin receptor blockers (arbs), HMG Co-A

reductase inhibitors (statins)[36], beta-blockers[37], and calcium channel blockers[38]. Other selected medications associated with mortality served as covariates in our model (antiplatelets, anticoagulants, antiarrhythmics, and pentoxifylline). Although exposure to these medications will also vary with time, we choose to use time-fixed dichotomous variables for all medications except antidiabetic agents. Our rationale was that due to the high number of prevalent users of these medications prior to entering the study cohort an accurate period of unexposure and exposure was unattainable. Furthermore, attrition of susceptibles may introduce bias with prevalent users.

3.2.4 Sensitivity analysis

Multiple sensitivity analyses were performed. First, we used the insulin exposure level as the reference group. Second, we excluded subjects who died in the first 6 months and the first 12 months to examine whether early deaths significantly affected the results. Third, we excluded subjects never exposed to insulin and used a new insulin user design where individuals were followed from their first dispensation date of insulin (insulin index date).

3.3 Results

For the 12,272 new users of oral antidiabetic agents the mean age (SD) of the cohort was 65.0 (13.9) years, 55% were male, and 51% had a previous history of cardiovascular disease (Table 1). The average (SD) length of follow-up was 5.1 (2.2) years and 1280 (10%) subjects started insulin therapy. There were 257 (2%) subjects classified as low exposure, 450 (4%) as moderate, 286 (2%) as high and 215 (2%) as very high insulin exposure. There were 2681 (21.8%) deaths over the course of follow-up. A consistent graded increase in the mortality rate with increasing insulin exposure was observed (Table 2). Specifically, 2456 (22%) people died in the no exposure group (reference), 36 (14%) in the low exposure group (unadjusted hazard ratio (HR) 1.03; 95% confidence interval (CI) 0.74-1.43), 89 (20%) in the moderate (unadjusted HR 1.60; 95% CI 1.39-1.99), 57 (20%) in the high exposure group (unadjusted HR 1.82; 95% CI 1.40-2.38), and 43 (20%) in the very high exposure group (unadjusted HR 2.21; 95% CI 1.63-2.99). After adjusting for potential confounding variables, increasing levels of exposure

to insulin remained associated with a graded risk of increased mortality compared to no insulin exposure: low insulin exposure (HR 1.16; 95%CI 0.83-1.61), moderate exposure (HR 1.62; 1.31-2.01), high exposure (HR 2.58; 1.98-3.37), and very high exposure (HR 3.17; 2.33-4.31) (Table 3; Fig. 1).

3.3.1 Sensitivity analyses

First, using a low level of insulin exposure as the reference group (rather than no exposure) led to essentially the same findings (Table 3). Second, excluding subjects who died within 6 and 12 months continued to show a higher mortality risk associated with more insulin use (table 3). Third, analysis that excluded patients never exposed to insulin demonstrated results similar to the overall cohort. Specifically, compared with low insulin exposure, moderate exposure (HR 1.59; 1.07-2.38), high exposure (HR 2.00; 1.30-3.08), and very high exposure (HR 3.31; 1.45-3.66) were all associated with higher mortality (Table 4, Fig. 2).

3.4 Discussion

We found a graded risk in mortality associated with increasing insulin exposure. A consistent dose-response relationship was observed in our sensitivity analysis that excluded patients who never used insulin over 5 years of follow-up. There are two plausible explanations for our results.

First, confounding by disease severity whereby insulin simply serves as a marker for more severe diabetes. The use of multiple antidiabetic agents, including insulin, has been found to be an indicator of more severe diabetes in some retrospective studies using administrative data.[39] Therefore, individuals being dispensed insulin more frequently may have poorer glycemic control and this alone accounts for our observed association between insulin exposure and mortality. This is improbable because there is minimal randomized trial evidence that better glycemic control leads to better survival and even recent data to the contrary[40,41]. Even if we ignore the randomized trial evidence, observational data from the UKPDS reported a 14% decrease in all-cause mortality for every 1% reduction in A1C.[42] We observed an approximate 200% increase in risk among subjects exposed to very high levels of insulin compared to no insulin exposure, implying

A1C differences between these groups in excess of 14%. A difference in A1C of this magnitude is implausible. Furthermore, we attempted to adjust for diabetes severity using a categorical variable that identified the presence of both macrovascular and microvascular disease. Second, our findings may reflect the truth, that is that insulin use is not beneficial in terms of all-cause mortality. Insulin's effect on the cardiovascular system is well documented, suggesting both potential mechanisms for harm and for benefit.[4] Our findings are, in fact, broadly consistent with the VA feasibility trial.[20]

To our knowledge this study takes a unique approach in quantifying the relationship between insulin exposure and mortality. The majority of previous studies have focused on insulin's relationship with cardiovascular events or mortality and have classified insulin as a dichotomous variable.[43,44] Furthermore, many studies have simply excluded insulin from their analysis, focusing on oral antidiabetic agents and mortality risk.[30,45] Two previous observational studies have classified insulin by dose – unit/kg/day.[10,12] A recent study by Hirai and colleagues,[12] reported a consistent point estimate suggesting exogenous as well as endogenous insulin was associated with an increased risk of CV and all-cause mortality. Although statistically non-significant, the consistently high magnitude of the hazard ratios may be clinically relevant.

It is clear that many challenges exist when trying to quantify insulin exposure, especially with administrative data. One challenge is lack of dosage per day prescribed. Although the number of insulin units per day prescribed may not accurately reflect an individual's precise exposure due to dosage adjustments it would represent a close approximation of daily insulin exposure. We were limited to prescription counts only and used a cumulative summation over time of dispensations standardized to duration for each subject. In addition, beyond classifying insulin exposure, we do not know to what degree patients actually took their insulin (i.e., adherence). We included several medications associated with mortality as covariates in our statistical model. These medications reflect those used to treat the most common comorbidities affecting people with diabetes and we recognize that there are many other comorbidities and treatments that may affect mortality that we were unable to adjust for. The last major limitation of our work relates to the use of administrative databases. Unfortunately, we were unable to adjust for common clinical variables such as glycosylated hemoglobin (A1C), body mass

index (BMI), smoking status, lipid profile and kidney function; all of these factors potentially affect mortality and might contribute to residual confounding.

Our study also has several strengths to balance off these limitations. First, an identical association between insulin exposure and mortality is observed in the sensitivity analysis designed as a new user cohort as compared to the primary cohort. New user designs avoid potential bias introduced with prevalent users.[46] Second, treating insulin as a time-dependent variable avoids immortal time bias, which may underestimate risk estimates in cohort studies and is especially problematic in pharmacoepidemiology where there is a period of unexposed time prior to drug initiation.[47,48] Third, the magnitude of association observed is unlikely to be accounted for by presently known confounders such as A1c as discussed previously. Fourth, our data was collected in the 1990's where the variability in insulin formulations was considerably less than today.

Our findings suggest that increasing amounts of insulin exposure are associated with higher mortality in older patients with type 2 diabetes. We believe that until we have more solid randomized trial evidence with respect to the use of insulin, a prudent approach might be to try and achieve recommended glycemic targets with the use of as little insulin as possible. While this approach is "evidence-based" it is not necessarily consistent with national and international clinical practice guidelines.

Table 3-1: Characteristics of Baseline Cohort

	Incident Users Cohort		Reference group: no insulin		Insulin Exposure: low		moderate		high		very high		p-value
Demographic Variables	n or mean	% or sd	n or mean	% or sd	n or mean	% or sd	n or mean	% or sd	n or mean	% or sd	n or mean	% or sd	
Number of Subjects	12,272	100	11,064	90	257	2	450	4	286	2	215	2	
Age	65	14	66	13	60	15	60	15	59	14	58	14	<0.0001
Male	6,755	55	6,147	56	129	50	246	55	135	47	98	46	0.001
Chronic Disease Score	9	4	8	4	9	5	9	5	9	4	10	4	<0.0001
Severity of Diabetes													
absence of complications	1,599	13	1,392	13	52	20	86	19	45	16	24	11	<0.001
presence of microvascular or macrovascular compliations	4,975	41	4,529	41	90	35	154	34	117	41	85	40	
presence of both microvascular and macrovascular compliations	5,698	46	5,143	46	115	45	210	47	124	43	106	49	
Oral Diabetes Regimen													
Sulfonylurea monotherapy	4,729	39	4,493	41	62	24	96	21	51	18	27	13	<0.001
Metformin monotherapy	1,625	13	1,556	14	26	10	18	4	15	5	10	5	
Combination SU and MET	5,918	48	5,015	45	169	66	336	75	220	77	178	83	
Medications of Interest													
statin use	1,930	16	1,704	15	41	16	85	19	54	19	46	21	0.020
betablocker use	3,381	28	3,064	28	48	19	109	24	86	30	74	34	0.001
calcium channel blocker use	3,963	32	2,583	32	76	30	146	32	82	29	76	35	0.470
ace/arb use	6,138	50	5,506	50	120	47	223	50	158	55	131	61	0.005
diuretic use	5,326	43	4,720	43	115	45	213	47	146	51	132	61	<0.001
antiplatelet use	2,930	24	2,617	24	53	21	134	30	67	23	59	27	0.018
anticoagulant use	1,611	13	1,422	13	41	16	66	15	43	15	39	18	0.058
antiarrhythmic use	2,239	18	2,019	18	41	16	81	18	52	18	46	21	0.671
pentoxifylline use	423	3	374	3	13	5	19	4	9	3	8	4	0.543

Table 3-2: Mortality Events and Hazard Ratios for Primary Analysis

Insulin Exposure Category†	Events (n/N)	Mortality rate per 1000 p-y‡	Unadjusted HR	95% CI	p-value	Adjusted* HR	95% CI	p-value
0	2456/11064	57.62	1.00	reference		1.00	reference	
1	36/257	46.47	1.03	0.74 - 1.43	0.864	1.16	0.83 - 1.61	0.388
2	89/450	71.51	1.60	1.39 - 1.99	0.000	1.62	1.31 - 2.01	0.000
3	57/286	80.83	1.82	1.40 - 2.38	0.000	2.58	1.98 - 3.37	0.000
4	43/215	100.04	2.21	1.63 - 2.99	0.000	3.17	2.33 - 4.31	0.000

*** Adjusted for age, sex, chronic disease score, severity of diabetes, oral diabetes medications, use of selected medications (statins, betablockers, calcium channel blockers, angiotension converting enzyme inhibitors/angiotensin receptor blockers, diuretics, antiplatelets, anticoagulants, antiarrhythmics, and pentoxifylline). Oral diabetes medication regimen was treated as a time-varying covariate. † time-varying covariate (The amount of person-time follow-up was classified based on time spend unexposed or subsequently exposed to insulin. ‡ Adjusted mortality rate using true exposed time in denominator.**

Table 3-3: Adjusted Hazard Ratios and 95% Confidence Intervals for Sensitivity Analyses

	Reference as low exposure		Exclusion of Subjects who died within first 6 months		Exclusion of Subjects who died within first 12 months	
Insulin Exposure Category†	Adjusted* HR	95% CI	Adjusted* HR	95% CI	Adjusted* HR	95% CI
none	n/a	n/a	1.00	reference	1.00	reference
low	1.00	reference	1.67	1.13 - 2.48	1.67	1.12 - 2.49
moderate	1.40	0.95 - 2.07	2.59	1.92 - 3.50	2.57	1.89 - 3.49
high	2.23	1.47 - 3.39	2.96	2.10 - 4.17	2.97	2.10 - 4.19
very high	2.74	1.76 - 4.72	3.18	2.16 - 4.65	3.07	2.08 - 4.54

*** Adjusted for age, sex, chronic disease score, severity of diabetes, oral diabetes medications, use of selected medications (statins, betablockers, calcium channel blockers, angiotension coverting enzyme inhibitors/angiotensin receptor blockers, diuretics, antiplatelets, anticoagulants, antiarrhythmics, and pentoxifylline). Oral diabetes medication regimen was treated as a time-varying covariate. † time-varying covariate (The amount of person-time follow-up was classified based on time spend unexposed or subsequently exposed to insulin.**

Table 4-3: Mortality Events and Hazard Ratios for Sensitivity Analysis of Cohort Excluding non-insulin users

Insulin Exposure Category	Events (n/N)	Mortality rate per 1000 p-y†	Unadjusted HR	95% CI	p-value	Adjusted* HR	95% CI	p-value
low	36/257	46.47	1.00	reference		1.00	reference	
moderate	89/450	71.51	1.53	1.04 - 2.27	0.03	1.59	1.07 - 2.38	0.023
high	57/286	80.83	1.75	1.15 - 2.26	0.009	2.00	1.30 - 3.08	0.002
very high	43/215	100.04	2.14	1.37 - 3.33	0.001	2.31	1.45 - 3.66	<0.001

*** Adjusted for age, sex, chronic disease score, severity of diabetes, oral diabetes medications, use of selected medications (statins, betablockers, calcium channel blockers, angiotensin coverting enzyme inhibitors/angiotensin receptor blockers, diuretics, antiplatelets, anticoagulants, antiarrhythmics, and pentoxifylline). Oral diabetes medication regimen was treated as a time-varying covariate. † time-varying covariate (The amount of person-time follow-up was classified based on time spend unexposed or subsequently exposed to insulin.**

Figure 3-1: Adjusted Survival curves for all-cause mortality in patients with type 2 diabetes, stratified by insulin exposure

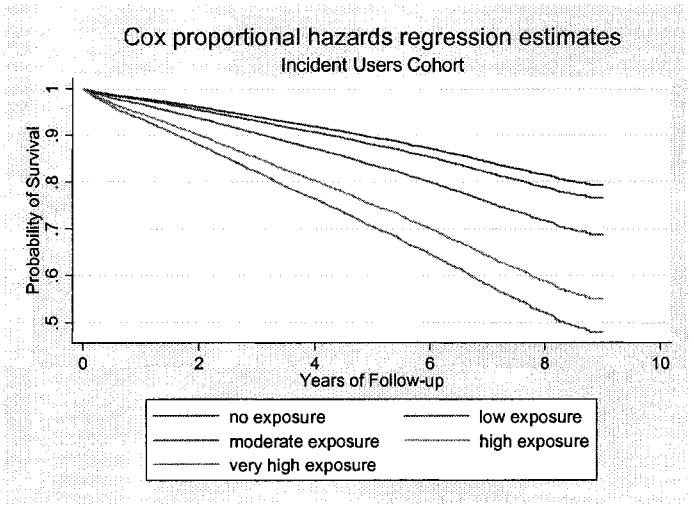
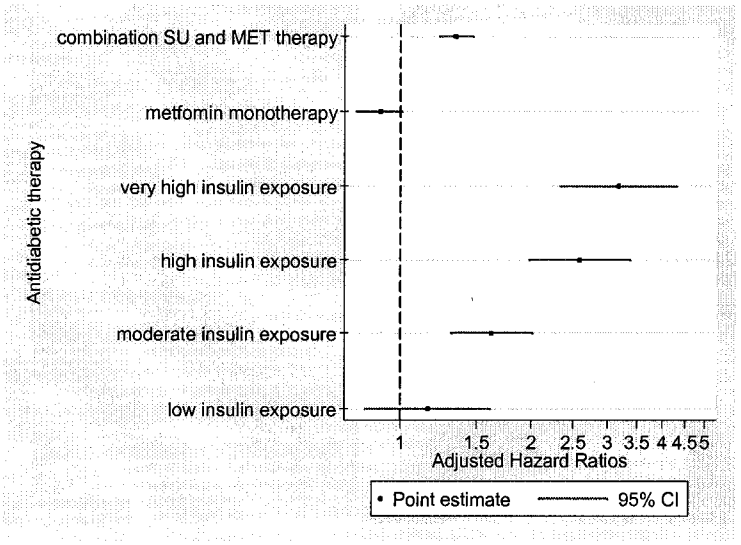


Figure 3-2: Adjusted Hazard Ratio's for all-cause mortality in patients with type 2 diabetes, stratified by antidiabetic exposure



Appendix 3-1: International Classification of Disease Diagnostic Codes used to construct Severity of Diabetes covariate.

Macrovascular Disease
Physician Diagnosis or Hospitalization for cardiovascular-related Event (ICD-9:401-429)
Physician Diagnosis or Hospitalization for cerebrovascular event (ICD-9: 430-438)
Physician Diagnosis or Hospitalization for peripheral vascular disease (ICD-9: 440-459)
Cardiovascular procedure in hospital (CCP code: 47-51.99)
Microvascular Disease
Physician Diagnosis or Hospitalization for retinopathy (ICD-9: 362-362.9, 365-365.9, 377-377.9)
Physician Diagnosis or Hospitalization for neuropathy (ICD-9: 337.1, 354-355.9, 356.8, 357.2)
Physician Diagnosis or Hospitalization for nephropathy (ICD-9: 580-588.9, 590-590.9, 593-593.9)
Amputation of limb (CCP code: 96.0-96.09, 96.1-96.19)

3.5 Reference List

1. American Diabetes Association. Standards of Medical Care in Diabetes--2007. Diabetes Care 2007;30:S4-41.

2. Canadian Diabetes Association. Pharmacologic management of type 2 diabetes. Can J Diabetes 2003;27:37-42.

3. Nathan DM, Buse JB, Davidson MB et al. Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2006;29:1963-72.

4. Muis MJ, Bots ML, Grobbee DE et al. Insulin treatment and cardiovascular disease; friend or foe? A point of view. Diabetic Medicine 2005;22:118-26.

5. Henry RR, Gumbiner B, Ditzler T et al. Intensive conventional insulin therapy for type II diabetes. Metabolic effects during a 6-mo outpatient trial. Diabetes Care 1993;16:21-31.

6. Randeree HA, Omar MA, Motala AA et al. Effect of insulin therapy on blood pressure in NIDDM patients with secondary failure. Diabetes Care 1992;15:1258-63.

7. Santen RJ, Willis PW, III, Fajans SS. Atherosclerosis in diabetes mellitus. Correlations with serum lipid levels, adiposity, and serum insulin level. Archives of Internal Medicine 1972;130:833-43.

8. Ruige JB, Assendelft WJ, Dekker JM et al. Insulin and risk of cardiovascular disease: a meta-analysis. Circulation 1998;97:996-1001.

9. Sarwar N, Sattar N, Gudnason V et al. Circulating concentrations of insulin markers and coronary heart disease: a quantitative review of 19 Western prospective studies. European Heart Journal 2007;28:2491-7.

10. Janka HU, Ziegler AG, Standl E et al. Daily insulin dose as a predictor of macrovascular disease in insulin treated non-insulin-dependent diabetics. Diabete et Metabolisme 1987;13:359-64.

11. Pocock SJ, Wang D, Pfeffer MA et al. Predictors of mortality and morbidity in patients with chronic heart failure. European Heart Journal 2006;27:65-75.

12. Hirai FE, Moss SE, Klein BE et al. Relationship of Glycemic Control, Exogenous Insulin, and C-Peptide Levels to Ischemic Heart Disease Mortality Over a 16-Year Period in People With Older-Onset Diabetes: The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR). Diabetes Care 2008;31:493-7.

13. Masoudi FA, Inzucchi SE, Wang Y et al. Thiazolidinediones, Metformin, and Outcomes in Older Patients With Diabetes and Heart Failure: An Observational Study. Circulation 2005;111:583-90.

14. Smooke S, Horwich TB, Fonarow GC. Insulin-treated diabetes is associated with a marked increase in mortality in patients with advanced heart failure. American Heart Journal 2005;149:168-74.

15. Murcia AM, Hennekens CH, Lamas GA et al. Impact of Diabetes on Mortality in Patients With Myocardial Infarction and Left Ventricular Dysfunction. Archives of Internal Medicine 2004;164:2273-9.

16. Welborn TA, Knuiman MW, Ward N et al. Serum insulin is a risk marker for coronary heart disease mortality in men but not in women. Diabetes research and clinical practice 1994;26:51-9.

17. Ferrara A, Barrett-Connor EL, Edelstein SL. Hyperinsulinemia Does Not Increase the Risk of Fatal Cardiovascular Disease in Elderly Men or Women without Diabetes: The Rancho Bernardo Study, 1984-1991. American Journal of Epidemiology 1994;140:857-69.

18. Welin L, Eriksson H, Larsson B et al. Hyperinsulinaemia is not a major coronary risk factor in elderly men. Diabetologia 1992;35:766-70.

19. Abraira C, Colwell JA, Nuttall FQ et al. Veterans Affairs Cooperative Study on glycemic control and complications in type II diabetes (VA CSDM). Results of the feasibility trial. Veterans Affairs Cooperative Study in Type II Diabetes. Diabetes Care 1995;18:1113-23.

20. Abraira C, Colwell J, Nuttall F et al. Cardiovascular events and correlates in the Veterans Affairs Diabetes Feasibility Trial. Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes. Archives of Internal Medicine 1997;157:181-8.

21. Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes: scientific review. JAMA: The Journal of the American Medical Association 2002;287:360-72.

22. Harris SB, Ekoe JM, Zdanowicz Y et al. Glycemic control and morbidity in the Canadian primary care setting (results of the diabetes in Canada evaluation study). Diabetes research and clinical practice 2005;70:90-7.

23. Johnson J, Pohar S, Secnik K et al. Utilization of diabetes medication and cost of testing supplies in Saskatchewan, 2001. BMC Health Services Research 2006;6:159.

24. Golay A, Guillet-Dauphine N, Fendel A et al. The insulin-sparing effect of metformin in insulin-treated diabetic patients. Diabetes-Metabolism Reviews 1995;11:S63-7.

25. Goudswaard AN, Furlong NJ, Valk GD et al. Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus. Cochrane Database of Systematic Reviews. 2004.

26. Avorn J. In Defense of Pharmacoepidemiology -- Embracing the Yin and Yang of Drug Research. The New England Journal of Medicine 2007;357:2219-21.

27. Ray WA. Population-Based Studies of Adverse Drug Effects. The New England Journal of Medicine 2003;349:1592-4.

28. Downey W, Beck P, McNutt M, Stang M, Osei W, Nichol J. Health Services Databases in Saskatchewan. In: Strom B, ed. Pharmacoepidemiology. Chinchester: Wiley, 2005;295-310.

29. Eurich DT, Majumdar SR, Tsuyuki RT et al. Reduced Mortality Associated With the Use of ACE Inhibitors in Patients With Type 2 Diabetes. Diabetes Care 2004;27:1330-4.

30. Johnson JA, Majumdar SR, Simpson SH et al. Decreased mortality associated with the use of metformin compared with sulfonylurea monotherapy in type 2 diabetes. Diabetes Care 2002;25:2244-8.

31. Simpson SH, Majumdar SR, Tsuyuki RT et al. Dose-response relation between sulfonylurea drugs and mortality in type 2 diabetes mellitus: a population-based cohort study. CMAJ 2006;174:169-74.

32. Bowker SL, Majumdar SR, Veugelers P et al. Increased Cancer-Related Mortality for Patients With Type 2 Diabetes Who Use Sulfonylureas or Insulin. Diabetes Care 2006;29:254-8.

33. Johnson JA, Simpson SH, Toth EL et al. Reduced cardiovascular morbidity and mortality associated with metformin use in subjects with Type 2 diabetes. Diabet.Med. 2005;22:497-502.

34. Von Korff M, Wagner EH, Saunders K. A chronic disease score from automated pharmacy data. Journal of Clinical Epidemiology 1992;45:197-203.

35. Hope trial investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. The Lancet 2000;355:253-9.

36. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383-9.

37. Haas SJ, Vos T, Gilbert RE et al. Are [beta]-blockers as efficacious in patients with diabetes mellitus as in patients without diabetes mellitus who have chronic heart failure? A meta-analysis of large-scale clinical trials. American Heart Journal 2003;146:848-53.

38. Tuomilehto J, Rastenyte D, Birkenhager WH et al. Effects of Calcium-Channel Blockade in Older Patients with Diabetes and Systolic Hypertension. The New England Journal of Medicine 1999;340:677-84.

39. Willey CJ, Andrade SE, Cohen J et al. Polypharmacy with oral antidiabetic agents: an indicator of poor glycemic control. American Journal of Managed Care 2006;12:435-40.

40. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-53.

41. Meinert CL, Knatterud GL, Prout TE et al. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. Mortality results. Diabetes 1970;19(Suppl):789-830.

42. Stratton IM, Adler AI, Neil HA et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405-12.

43. Bruno G, Merletti F, Boffetta P et al. Impact of glycaemic control, hypertension and insulin treatment on general and cause-specific mortality: an Italian population-based cohort of type II (non-insulin-dependent) diabetes mellitus. Diabetologia 1999;42:297-301.

44. Saito I, Folsom AR, Brancati FL et al. Nontraditional risk factors for coronary heart disease incidence among persons with diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. Annals of Internal Medicine 2000;133:81-91.

45. Evans JM, Ogston SA, Emslie-Smith A et al. Risk of mortality and adverse cardiovascular outcomes in type 2 diabetes: a comparison of patients treated with sulfonylureas and metformin. Diabetologia 2006;49:930-6.

46. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. American Journal of Epidemiology 2003;158:915-20.

47. Zhou Z, Rahme E, Abrahamowicz M et al. Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: a comparison of methods. American Journal of Epidemiology 2005;162:1016-23.

48. Suissa S. Immortal Time Bias in Pharmacoepidemiology. American Journal of Epidemiology 2007;Advance Access: Dec 3, 2007. (DOI:10.10393/aje/kwm324).

CHAPTER 4

General Discussion and Conclusions

4.1 General Discussion

The role of insulin in type 2 diabetes management continues to be debated amongst clinicians. This controversy is fueled by insufficient knowledge regarding the long-term safety of insulin. Therefore, we designed two epidemiological studies to tackle this issue. Two specific research questions were addressed using different methodologies – a quantitative systematic review (meta-analysis) and a retrospective cohort study. In the absence of higher levels of evidence, the thoughtful consideration of epidemiologic evidence along with the integration of biological and laboratory evidence represents the strongest approach to understanding a clinical problem and providing guidance for clinical management of patients with type 2 diabetes.

4.1.1 Two methodologies exploring insulin use

The first study, a meta-analysis exploring the role of insulin in type 2 diabetes, asked whether the addition of basal insulin or an oral agent is more effective in patients failing their current oral antidiabetic regimen. The results indicated that there is no clinically significant difference in A1C between the two options and that non-therapeutic issues must be considered (i.e. cost, patient preference) when deciding whether to add basal insulin or an additional oral agent to one's current therapeutic regimen. The second study, a cohort study, assessed the relationship between insulin exposure and mortality. We found a graded relationship between insulin exposure and all-cause mortality. This suggests that long term therapy using intensive insulin therapy may not be as safe as commonly thought.

These two studies complement each other in that they assess relevant questions of the efficacy and safety of using insulin in type 2 diabetes. The meta-analysis gathered data from experimental evidence (randomized controlled trials), and the cohort study was observational in design. These two methodologies represent two different rungs on the evidence-based medicine ladder.

4.1.2 Insulin use, Mortality and the Bradford Hill considerations

In clinical medicine it is important to consider the overall accumulation of knowledge regarding the causal relationship between a medication and health outcome. In 1965, Sir Austin Bradford Hill outlined nine viewpoints to consider when reflecting on the association between a particular exposure and a suspected outcome.[1] These viewpoints, or sometimes called considerations, are used as a template to help guide decisions as to whether a relationship between an exposure and outcome is indeed causal. Reflecting on these considerations or viewpoints is especially important in observational research due to the potential for unforeseen biases. The nine viewpoints Bradford Hill used to assess causation are: strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimental evidence and analogy.[1] Hill's viewpoints have been widely criticized for being treated as a checklist to establish a causal relationship and others have proposed a less structured approach to assessing causation.[2] Nonetheless, Hill's considerations provide a useful 'roadmap' for exploring cause-effect relationships. Alternative groupings of similar viewpoints are frequently cited in many epidemiology textbooks.[3-5] The applicability of the Bradford Hill considerations in pharmacoepidemiology has been discussed in recent publications, specifically in the application of assessing the causality of drug-induced 'side-effects'.[6,7] Using Hill's considerations as a 'roadmap' it is prudent to consider the evidence supporting a cause-effect relationship between insulin use and mortality. In an effort to be concise, not all of Hill's points will be reviewed, only those which relate specifically to this thesis.

Strength of association is measured using a quantitative measure of effect (i.e. odds ratio, relative risk, absolute risk difference, hazard ratio). Our observed hazard ratio, when comparing the risk of mortality associated with very high dose insulin compared to no clinically meaningful exposure (Adjusted hazard ratio (HR) 3.17; 95% confidence interval (CI) 2.33-4.31) or low exposure (Adjusted HR 2.31; 95% CI 1.45-3.66), could be considered a very strong association. Measures of effect, such as relative risks, beyond three are often considered very strong in epidemiology;[8] in

pharmacoepidemiology it is uncommon to find relative risks greater than two, especially for serious adverse drug reactions.[7]

In pharmacoepidemiology, the **consistency of results** among different study populations and study designs is particularly important.[7] In addition to our study, other observational studies have shown consistent point estimates suggesting insulin is associated with an increase in all-cause mortality. Hirai and colleagues [9] reported a multivariable adjusted hazard ratio of 1.12 (95% CI 0.93-1.35) for exogenous insulin compared to no insulin exposure and an adjusted HR of 1.20 (95% CI 0.85-1.69) per 1 unit/kg/day of insulin use. In other studies comparing the risk of all-cause mortality in patients with type 2 diabetes using insulin compared to diet therapy consistent results were also found. Bruno and colleagues [10] reported an adjusted relative risk of 1.71 (95% CI 1.18-2.48), Sasaki et al [11] reported an age-adjusted odds ratio of 3.31 (95% CI 2.63-4.16).

In contrast, results from randomized control trials (RCTs) have been mixed. Evidence from RCTs may be considered under two of Hill's viewpoints: consistency and experimental evidence. We have mentioned in chapter 3 that our results were broadly consistent with those from the Veterans Affairs Feasibility trial, where the investigators randomized patients to either intensive insulin therapy or conventional insulin therapy. A higher cardiovascular-related event rate was observed in the intensive arm compared to the conventional arm. Other RCTs have not specifically evaluated the risk of intensive insulin therapy but have rather randomized patients to either intensive glycemic therapy or less intensive glycemic therapy. Recently the safety of intensive lowering of blood glucose has been questioned as the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial investigators (www.accordtrial.org) choose to modify their intensive treatment arm due to an unexpected increase in the number of deaths in the intensive treatment arm. Earlier RCTs, the University Group Diabetes Program (UDGP) and the United Kingdom Prospective Diabetes Study (UKPDS) did not support evidence of increased mortality risk associated with insulin, although risk within treatment subgroups (i.e. intensive insulin treatment) was difficult to establish due to the mixing of treatments between groups.[12,13] In the UKPDS subgroup analyses where the authors looked at the

intensive treatment arms separately, insulin was associated with a statistically non-significant decrease in all-cause mortality (HR 0.93; 95% CI 0.76-1.14).[13]

The only consideration that Hill outlined that is required for a causal association is that a cause must precede an effect. In our case due to the nature of the effect (mortality) as well as the study design (cohort) the **temporal relationship** between insulin use and mortality is consistent with a cause preceding the effect. We also observed a **biological gradient** or a dose-response relationship between insulin and mortality. Although our measure of insulin exposure was very crude, nonetheless we were able to categorize individuals in discrete categories dependent on their average cumulative exposure over their entire follow-up. This was the first study to evaluate insulin exposure in this way.

There is likely not a single specific **biological mechanism** that is responsible for the observed increase in mortality. Insulin's effect on the cardiovascular system has been well described and reviewed in the literature.[14] Several harmful cardiovascular effects of insulin have been demonstrated such as increased endothelin production,[15,16] stimulations of growth factors via mitogen-activated protein kinase signaling pathway,[17] thickening of the aorta intima and arterial wall in animals,[18,19] worsening obesity,[20] increased blood pressure,[21] and increased lipids.[22] Many beneficial effects of insulin on the cardiovascular system have also been demonstrated such as increased nitric oxide production,[23,24] decreased inflammation of the endothelium.[25] Other mechanisms such as an increase in cancer-related mortality are plausible.[26]

In summary, compelling evidence exists for a cause-effect relation between insulin use and mortality as demonstrated by reviewing the Bradford Hill considerations. Nonetheless, higher quality experimental evidence (i.e. RCTs) is required to either support or refute the hypothesis that insulin use may be causally linked to mortality in type 2 diabetes.

4.1.3 Research and clinical implications

4.1.3.1 Implications for clinical practice

The results of the systematic review are relevant for practitioners working with a poorly controlled type 2 diabetes population currently using maximal doses of either a

sulfonylurea or a sulfonylurea-metformin combination. Our findings suggest that the choice of treatment regimens for add-on therapy can be made foremost using non-therapeutic reasons (i.e. medication costs, patient preference). Another implication for practice is the apparent difficulty to achieve target A1c levels in patients with secondary failure to oral antidiabetic agents. The optimal strategy for adding once daily insulin therapy to one's oral antidiabetic regimen remains to be demonstrated.

Results from the retrospective cohort study suggest that the benefits of long-term use of insulin in type 2 diabetes may not always outweigh the risks. In fact, given the absence of good RCT data, it is reasonable to suggest that practitioners be cautious in the early initiation of intensive insulin therapy. Furthermore, results from the glycemic intervention strategy in the ACCORD trial suggest that lowering blood glucose aggressively toward the normal range may in fact cause undo harm.[27]

4.1.3.2 Implications for research

More rigorous studies are required to establish the ideal treatment strategy for people with type 2 diabetes with secondary oral antidiabetic therapy. High quality RCTs are needed to evaluate the long-term safety of insulin use in type 2 diabetes. The recent RCTs Further observational studies using clinically rich datasets would allow for investigators to control for more potentially confounding factors. Important questions to address in future research include:

- Does more aggressive insulin titration translate to a benefit of the addition of a once daily insulin injection compared to the addition of an oral agent?
- What is the effect of low dose versus high dose insulin therapy on quality of life and other patient orientated outcomes?
- What is the effect of low dose versus high dose insulin therapy on non-glucocentric outcomes such as lipids, blood-pressure, and cardiovascular events?

Given the recent results from the ACCORD[27] and ADVANCE[28] trials, it is important to reflect on the implications for further research in evaluating medications for type 2 diabetes. Briefly, the ACCORD and ADVANCE trials are multi-center

randomized factorial trials designed to assess the efficacy of various treatment strategies such as glycemic, blood pressure, and lipid control in people with type 2 diabetes. The aim of the glycemic therapy arms in both the ACCORD and ADVANCE trials was to evaluate the effect of an intensive glucose lowering strategy compared to a standard glucose lowering strategy on cardiovascular (CV) events in people with type 2 diabetes. Over 10,000 patients with type 2 diabetes at an increased risk of a CV event were randomized to either intensive glucose lowering therapy (an A1C target <6% in ACCORD and <6.5% in ADVANCE) or standard glucose lowering therapy (A1C target 7-7.9% in ACCORD and ≈7% depending on local guidelines in ADVANCE). The primary outcome in the ACCORD trial was a composite of cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes). A primary composite outcome was also used in the ADVANCE trial defined as major macrovascular events (death from CV causes, nonfatal myocardial infarction, or nonfatal stroke) and major microvascular events (new or worsening nephropathy or retinopathy).

In the ACCORD trial 352 (6.9%) people experienced the primary outcome in the intensive therapy group versus 371 (7.2%) people in the standard therapy group (Hazard ratio (HR) 0.90; 95% confidence interval (CI) 0.78 to 1.04; P=0.16). In the ADVANCE trial 1009 (18.1%) people in the intensive therapy group experienced the primary outcome compared to 1116 (20.0%) people in the standard therapy group (HR 0.90; 95% CI 0.82-0.98; P=0.01). Major macrovascular events considered separately did not show a significant difference between groups (HR 0.94; 95% CI 0.84 to 1.06; P=0.32); however, major microvascular events were associated with a significant difference between treatment strategies (HR 0.86; 95% CI 0.77 to 0.97; P=0.01). The glycemic arm of the ACCORD trial was stopped early due to a 22% increase in mortality among the intensive therapy group compared to the standard therapy group (HR 1.22; 95% CI 1.01 to 1.46; P=0.04).

Both studies were appropriately powered to detect a clinically meaningful difference in major cardiovascular events between treatment strategies, however, neither study showed a meaningful benefit in terms of CV events when an intensive glucose strategy was implemented with a goal of achieving a near normal glycemic level. The results must be kept in context of the study population which included people of 62-66

years on average with 8-10 years duration of diabetes at baseline. Furthermore, 32-35% of patients had a history of a macrovascular disease. Therefore the applicability to people with a new diagnosis of type 2 diabetes at a low risk of macrovascular disease is uncertain. Interestingly, subgroup analysis in ACCORD found that people without a history of macrovascular disease were less likely to experience the primary outcome compared to those with a history.

Beyond not showing a benefit in terms of CV events, the results from ACCORD suggest harm is associated with intensive glucose lowering therapy. The potential reasons for the observed increased in mortality are many and the authors speculated that their aggressive approach to lower A1C rapidly or perhaps the level reached may be an explanation. Another practical implication of these trials is the difficulty in teasing out the individual effects of the medications used, independent of their glucose lowering effect. These trials were designed to evaluate the effects of two different glucose lowering strategies whereby numerous antidiabetic agents were used to achieve glycemic targets. There were several differences in the medications used to lower glucose between the trials (higher insulin and thiazolidinedione use in the ACCORD trial and high gliclazide use in the ADVANCE trial). Non-glucose lowering treatment differences were also apparent (ASA and statin use was much lower in the ADVANCE trial).

Although many questions remain regarding the speed and how glucose should be lowered, the consensus from the recent American Diabetes Association meeting was that our current A1C target of $\leq 7\%$ is still appropriate provided that benefits (i.e. a decrease in microvascular complications) and risks are weighed for each individual. The results from these trials do not directly support the hypothesis that more intensive insulin is responsible an increase in mortality. In fact the authors of the ACCORD trial state that differences in medications between the groups did not explain the mortality difference. Unfortunately the studies were not designed to compare different medication regimens nor were they powered to detect such differences, therefore much uncertainty remains as to whether individual medications or how we use these medications in terms of aggressiveness, timing, or dosing accounts for mortality differences. In the context of evidence from these along with other diabetes trials it is imperative to optimize interventions which we already know have a significant impact cardiovascular morbidity

and mortality such as aspirin, blood pressure reduction and statins. Ongoing trials such as HEART2D[29] and BARI2D[30] will be important to consider in the ongoing debate over the effect of glucose lowering therapies and patient important outcomes, specifically cardiovascular-related morbidity and mortality.

4.2 Conclusion

This thesis presented two studies that used different research methodologies to address questions related to the role and safety of insulin in type 2 diabetes. The results of the first study suggested that insulin is an effective therapeutic agent for individuals unable to maintain their target blood glucose on their current oral regimen. Insulin, however, does not provide a clinically meaningful improvement in A1C over the addition of another oral agent. The second study found a relationship between insulin use and increased risk of mortality suggesting that clinicians ought to be cautions in the early initiation of long term high dose insulin.

4.3 Reference List

1. Hill AB. The environment and disease: association or causation? Proc Soc Med 1965;58:295-300.

2. Rothman KJ, Greenland S. Causation and Causal Inference in Epidemiology. American Journal of Public Health 2005;95:S144-S150.

3. Strom B. Study Designs Available for Pharmacoepidemiolgy Studies. In: Strom B, ed. Pharmacoepidemiology. Chichester: John Wiley & Sons, 2005;17-28.

4. Oleckno WA. Association and Causation. In Essential Epidemiology. Long Grove: Waveland Press, 2002;123-135.

5. Szklo M, Nieto FJ. Epidemiology: Beyond the Basics. Mississauga: Jones and Bartlett Publishers Inc, 2007.

6. Perrio M, Voss S, Saad AS. Application of the Bradford Hill Criteria to Assess the Causality of Cisapride-Induced Arrhythmia: A Model for Assessing Causal Association in Pharmacovigilance. Drug Safety 2007;30:333-46.

7. Shakir SAW, Layton D. Causal Association in Pharmacovigilance and Pharmacoepidemiology: Thoughts on the Application of the Austin Bradford-Hill Criteria. Drug Safety 2002;25:467-71.

8. Oleckno WA. Comparing Rates in Epidemiology. In Essential Epidemiology. Long Grove: Waveland Press, 2002;91-122.

9. Hirai FE, Moss SE, Klein BE et al. Relationship of Glycemic Control, Exogenous Insulin, and C-Peptide Levels to Ischemic Heart Disease Mortality Over a 16-Year Period in People With Older-Onset Diabetes: The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR). Diabetes Care 2008;31:493-7.

10. Bruno G, Merletti F, Boffetta P et al. Impact of glycaemic control, hypertension and insulin treatment on general and cause-specific mortality: an Italian population-based cohort of type II (non-insulin-dependent) diabetes mellitus. Diabetologia 1999;42:297-301.

11. Sasaki A, Uehara M, Horiuchi N et al. A 15-year follow-up study of patients with non-insulin-dependent diabetes mellitus (NIDDM) in Osaka, Japan. Factors predictive of the prognosis of diabetic patients. Diabetes Research & Clinical Practice 1997;36:41-7.

12. Meinert CL, Knatterud GL, Prout TE et al. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. Mortality results. Diabetes 1970;19(Suppl):789-830.

13. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-53.

14. Muis MJ, Bots ML, Grobbee DE et al. Insulin treatment and cardiovascular disease; friend or foe? A point of view. Diabetic Medicine 2005;22:118-26.

15. Hattori Y, Kasai K, Nakamura T et al. Effect of glucose and insulin on immunoreactive endothelin-1 release from cultured porcine aortic endothelial cells. Metabolism: Clinical & Experimental 1991;40:165-9.

16. Cardillo C, Nambi SS, Kilcoyne CM et al. Insulin Stimulates Both Endothelin and Nitric Oxide Activity in the Human Forearm. Circulation 1999;100:820-5.

17. Hsueh WA, Law RE. Insulin signaling in the arterial wall. American Journal of Cardiology 1999;81:21J-4J.

18. Stout RW. Development of vascular lesions in insulin-treated animals fed a normal diet. British Medical Journal 1970;3:685-7.

19. Stout RW, Buchanan KD, Vallance-Owen J. The relationship of arterial disease and glucagon metabolism in insulin-treated chickens. Atherosclerosis 1973;18:153-62.

20. Henry RR, Gumbiner B, Ditzler T et al. Intensive conventional insulin therapy for type II diabetes. Metabolic effects during a 6-mo outpatient trial. Diabetes Care 1993;16:21-31.

21. Randeree HA, Omar MA, Motala AA et al. Effect of insulin therapy on blood pressure in NIDDM patients with secondary failure. Diabetes Care 1992;15:1258-63.

22. Santen RJ, Willis PW, III, Fajans SS. Atherosclerosis in diabetes mellitus. Correlations with serum lipid levels, adiposity, and serum insulin level. Archives of Internal Medicine 1972;130:833-43.

23. Aljada A, Dandona P. Effect of insulin on human aortic endothelial nitric oxide synthase. Metabolism: Clinical & Experimental 2000;49:147-50.

24. Zeng G, Quon MJ. Insulin-stimulated production of nitric oxide is inhibited by wortmannin. Direct measurement in vascular endothelial cells. Journal of Clinical Investigation 1996;98:894-8.

25. Dandona P, Aljada A, Mohanty P. The anti-inflammatory and potential anti-atherogenic effect of insulin: a new paradigm. Diabetologia 2002;45:924-30.

26. Bowker SL, Majumdar SR, Veugelers P et al. Increased Cancer-Related Mortality for Patients With Type 2 Diabetes Who Use Sulfonylureas or Insulin. Diabetes Care 2006;29:254-8.

27. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of Intensive Glucose Lowering in Type 2 Diabetes. The New England Journal of Medicine 2008;358:2545-59.

28. The ADVANCE Collaborative Group. Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes. The New England Journal of Medicine 2008;358:2560-72.

29. Milicevic Z, Raz I, Strojek K et al. Hyperglycemia and its effect after acute myocardial infarction on cardiovascular outcomes in patients with Type 2 diabetes mellitus (HEART2D) Study design. Journal of Diabetes & its Complications. 2005;80-7.

30. Magee MF, Isley WL, Investigators DT. Rationale, design, and methods for glycemic control in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial. American Journal of Cardiology 2006;97:20G-30G.

Appendix A: Insulin Formulations available in Canada (May 2008)

Insulin aspart
Insulin glulisine
Insulin lispro
Insulin regular
Insulin NPH
Insulin detemir
Insulin glargine
Insulin regular / NPH
Insulin lispro / lispro protamine

Appendix B: Oral Antidiabetic Agents available in Canada (May 2008)

acarbose
acetohexamide
chlorpropamide
gliclazide
glimepiride
glyburide
metformin
nateglinide
pioglitazone
repaglinide
rosiglitazone
rosiglitazone / glimepiride
rosiglitazone / metformin