Diabetes Mellitus: Patterns of Pharmaceutical Use in Manitoba

by

Kimi T. G. Guilbert

A Thesis submitted to
The Faculty of Graduate Studies in
Partial Fulfillment of the Requirements for the Degree of

MASTER OF SCIENCE

Faculty of Pharmacy
The University of Manitoba
Winnipeg, Manitoba

THE UNIVERSITY OF MANITOBA

FACULTY OF GRADUATE STUDIES

*****

COPYRIGHT PERMISSION PAGE

Diabetes Mellitus: Patterns of Pharmaceutical Use in Manitoba

BY

Kimi T.G. Guilbert

A Thesis/Practicum submitted to the Faculty of Graduate Studies of The University of Manitoba in partial fulfillment of the requirements of the degree of

MASTER OF SCIENCE

Acknowledgements

Upon initiation of this project I had a clear objective in mind--to learn more. As with many endeavors in life that are worthwhile, the path I have followed has brought me many places I did not anticipate at the beginning of my journey. In reaching the end, it is without a doubt that I did learn more, and the knowledge I have been able to take with me includes a wider spectrum than the topic of population health and medication utilization. In achieving my goal I would like to acknowledge the many people, all of whom contributed to my learning process.

Firstly, I would like to thank Dr. Colleen Metge, my advisor, for her enduring enthusiasm and knowledge in support of this research project. She provided both the original inspiration which directed me toward this area of research and the vision with which to pursue future research. To my committee members; Dr. David Collins, for his valuable advice and accessibility, and Dr. Lavern Vercaigne for sharing his knowledge and clinical skill set. A special thank-you to Dr. Jane Griffith who graciously stepped in as a committee member near the end of the project.

I would also like to thank the Manitoba Center For Health Policy for providing the structure and support needed to accomplish this type of population health research. I especially would like to acknowledge Charles Burchill, Senior Systems Analyst, and Marina Yogendran, Systems Analyst, for freely sharing their time and skill.

A special thanks to Drs. Anita Carrie and Patricia Schroeder. The many meetings they attended allowed for free dialogue and sharing of ideas which contributed greatly to the thought process, an important part of scholarship.

Many thanks to my family. Thank you to my husband, Steven Lawrie, for his support and patience. Thank you to my son, Tomi, for literally kicking me awake as I worked in the early hours of the morning and for being patient and calmly waiting for 'play-time' with Mom during your first 18 months of life. Thank-you to Naomi Guilbert and Hiroshi Koshiyama who provided me with perspective and to Fubuki Daiko for providing a much needed outlet. Thank you to Sadako Mizobuchi for your enduring support. Finally, I cannot express enough thanks to my father and mother, Norman and Sachiko Guilbert, who patiently waited for me, first to choose a career path and then to finish this project. They provided me the values, skills and attitude with which I was able to finish what I started and to acquire knowledge from the process.

TABLE OF CONTENTS

Table of Tables & Figures

ABSTRACT

Statement of the problem

The high incidence and prevalence of secondary complications from diabetes in the general population indicate that blood glucose management may not be reaching the level of control that is achievable. In other words, drug therapy is efficacious in large clinical trials but may potentially lack effectiveness within the general population. Comprehensive drug utilization would provide a strong base from which to develop interventions to close the gap between the promise of anti-diabetic drug therapy (its efficacy) and its current (lack of) effectiveness.

Methods

Using a fixed-sample panel design, several measures of drug utilization (e.g., intensity of use and cost) were applied to a Manitoba population-based cohort of persons with diabetes. Data was accessed through the Population Health Research Data Repository (PHRDR) at the Manitoba Centre for Health Policy.

Results

The healthier or less 'comorbid' and wealthier segments of the cohort appeared to have the lowest rates of drug use. Conversely, there seemed to be an increase in utilization rates which followed the cohort members as their comorbidity status increased and/or their socioeconomic status decreased. Unexpected however, was the appearance of higher access among males.

Conclusion

Pharmaceutical use patterns and prescription drug costs for persons with diabetes in the Manitoba population can be described using the population demographics available with administrative claims data. The descriptions presented are hypothesis generating; future analyses should examine apparent differences in pharmaceutical use.

Preface

The incidence and prevalence of diabetes mellitus has been increasing in epidemic proportions across the globe. Data available from the National Diabetes Surveillance Strategy (NDSS), a Canadian organization, demonstrated the prevalence in adults was 4.8% while population based studies indicate the true prevalence as much as 30 to 50% higher than NDSS.[1] This means that in Canada greater than 7% of the population may be diabetic.[2] In Manitoba alone more than 4,000 new cases are diagnosed each year, which translates into more than 55,000 Manitobans suffering from diabetes.[3] Implications of this disease, through secondary complications, include widespread damage to major biological systems within the body including blindness due to retinopathy. There is widely accepted scientific evidence from the DCCT (Diabetes Control and Complications Trial) and UKPDS (United Kingdom Prospect Diabetes Study Group) trials demonstrating that achieving euglycemia, normal blood glucose levels, results in reducing secondary complications.[4-5] A major part of this control is achieved through drug therapy.

The high incidence and prevalence of secondary complications in the general population indicate that management of blood glucose levels may not be reaching the level of control achieved in the DCCT and UKPDS trials, and outlined as goals in the Canadian Diabetes Association Clinical Practice Guidelines.[4-5] In other words, drug therapy is efficacious in large clinical trials but may potentially lack effectiveness within the general population.

Appropriate measures need to be developed to decrease the distance between the efficacy of drug therapy and effectiveness. In other words, we need to move towards better outcomes for persons with diabetes in light of our access to proven therapy. An initial step toward this goal, and the primary aim of this thesis, is to develop a comprehensive understanding of drug utilization[a,6] or pharmaceutical use[b,7] patterns in the population of Manitoba persons with diabetes which will provide a basis for designing data responsive interventions for more effective treatment of diabetes.

[a] WHO defines ***drug utilization*** as "the marketing, distribution, prescription, and use of drugs in society, with special emphasis on the resulting medical, social, and economic consequences"

[b] The term "pharmaceutical utilization" is rarely used in the literature, more often terms such as "drug utilization" or "drug use" are used. For the purpose of this thesis these terms are considered interchangeable however, "pharmaceutical use" is preferred in an effort to separate those prescribed by a physician from the use of other drugs not requiring a prescription; the latter are not tracked by the drug program information network.

CHAPTER ONE

Background: Understanding Diabetes

Diabetes mellitis is a Latin term, which roughly translates into "sweetened with honey" referring to the overflow of glucose from the blood into the urine, a condition characteristic of this chronic disease.[8] A number of different diabetic states exist, the most common being Type 1 and Type 2 Diabetes, formerly, Insulin Dependent Diabetes Mellitus (IDDM) and Non-insulin Dependent Diabetes Mellitus (NIDDM) respectively. From a prevalence perspective, diabetes is the most common endocrine disorder found in all humans.[9,3]

A. Pathophysiology

Insulin is a hormone produced in the pancreas by the beta-cells located in the Islets of Langerhans. It facilitates cellular uptake of substrates such as glucose and fatty acids into cells for utilization and promotes storage into fat tissue. Insulin also aids in the entry of amino acids into cells for the production of protein and inhibits the secretion of another hormone called glucagon. When there are low levels of glucose, fatty acids, and amino acids, glucogan produced by alpha-cells in the Islets of Langerhans, stimulates the liver to undergo glycogenolysis (hydrolyze glycogen to glucose) and lipolysis (hydrolysis of stored fat).[10] Thus, in a normal state there is a balance between glucagon and insulin allowing for storage and access to energy within the body. In a diabetic state, where insulin is not accessible, the cells are unable to uptake the available glucose, lipids and

amino acids, thus causing both a state of cell 'starvation' within the cells and an abnormal concentration of substrates in the blood plasma. This imbalance is thought to cause the widespread damage to biological systems.[9]

Persons with Type 1 diabetes make up approximately 10-20% of the diabetic population and are defined by the absence of insulin resulting from an autoimmune process in the pancreas that destroys the insulin producing beta cells.[3] Despite adequate levels of amino acids and fatty acids in the blood, the cell is unable to access these products and will eventually starve. Patients with this condition must be treated with exogenous insulin in order to survive.[9] Onset is usually, but not limited to, the juvenile years and is likely as a result of an autoimmune process.

The remaining diabetic population (80 to 90%) exhibit Type 2 diabetes.[3] These patients often have normal or above normal production of insulin. With Type 2 diabetes there is an inability to effectively utilize insulin causing a state of chronic hyperglycemia. Receptor down-regulation or decreased receptor sensitivity exhibited in this population is thought, in part, to cause the lack of insulin effectiveness and may explain the sometimes excessive production of insulin.[9]

B. Etiology

Research indicates that diabetes appears to be caused by a combination of genetic and environmental factors.[11] It is hypothesized that an individual inherits a genetic

susceptibility, and then is exposed to one or more environmental factors resulting in precipitation of diabetes.[11] Support for a genetic origin of Type 1 diabetes has been seen in studies that have revealed a concordance rate in identical twins of 50%.[11] Type 2 diabetes has also been observed to aggregate within families indicating an etiology with a strong genetic component. Studies of identical twins reveal a concordance rate of 90% and thought to be hereditary as a result of a multi-allele genetic mode of inheritance.[11-12] Epidemiologic evidence reveals that specific populations of people based on ethnicity are at higher risk for Type 2 diabetes, or at epidemic levels (Table 1).[13] This susceptibility has been theorized to be a result of evolution and is described by the 'Thrifty Gene Theory'.[14]

Table 1. Risk of Type 2 diabetes by ethnicity

.Type 2 diabetes Prevalent at Epidemic Levels in Populations Identified by Ethnicity
Expatriate Asian Indians in Fiji
South Africans
Mauritius
Bangladeshi migrants to the United Kingdom
Chinese and Creoles in Mauritius
U.S. Native Americans
Japanese Americans
Black Americans

*adapted from Reference 12.

The 'Thrifty Gene Theory' attempts to explain the vulnerability of specific populations defined by ethnicity for developing Type 2 diabetes after acculturation to a Euro-based society. It is theorized that these populations were genetically adapted to surviving

periods of inadequate food supplies, alternating with periods when food was abundant. This was achieved by having an extremely efficient capability of using insulin to store calories as fat or glucagon during periods of abundant food supplies, that would in turn be available during times of famine. However, in modern society famine conditions are rare and the constant hyperglycemic state due to over-nutrition resulting in long periods of time with high levels of insulin, and no periods of fasting, that may cause a down regulation or decreased insulin receptor sensitivity. This metabolic efficiency theory is supported by both the increased incidence of diabetes following a rising incidence of obesity, and the decrease in diabetes during historical periods of under-nutrition in many populations.[14]

Many well established risk factors including; sedentary lifestyle, poor eating habits (high intake of saturated fat), age, and malnutrition; have been identified and are outlined in Table 2. According to **Hill's Criteria of Causation,** strength of association means the larger the relative effect, the more likely the causal role of the factor.[15] A confounding factor is one that can cause or prevent the outcome of interest, is not an intermediate variable, and is associated with the factor under investigation or a determinant of diabetes. The most studied risk factor, obesity, is associated with an increased risk of Type 2 diabetes.[12-13]

Table 2. Proposed Environmental Determinants of NIDDM--based on findings from observational studies[16]

Determinant	Strength of Association	Control for Confounding Factors
High body mass index	High	Adequate
Increased central obesity	High	Adequate
Physical activity	Intermediate	Not complete
Excessive intake of energy	Intermediate	Not satisfactory
Simple carbohydrates	Weak	Not satisfactory
Saturated fats	Intermediate	Not satisfactory
Alcohol	Weak	Not satisfactory
Low intake of dietary fiber	Intermediate	Not satisfactory
Certain trace elements	Weak	Not satisfactory
Use of some antihypertensive drug	Intermediate	Not complete

*adapted from Reference 15.

There is convincing evidence that demonstrates obesity contributes to insulin resistance and may increase the incidence of Type 2 diabetes.[17] Reinforcing this relationship are data that demonstrate weight loss can improve blood glucose control, and decrease the need for drug therapy. In some people achieving a healthy weight for height ratio as determined by a measure called Body Mass Index (BMI),[18-19] may even result in euglycemia (normal blood sugar levels).[11]

In addition to the risk factors or determinants, listed in Table 2, certain events have been known to precipitate diabetes. These include infection (thought to play a causative role in Type 1 diabetes[11]), damage of beta cells through exposure to toxic substances, severe prolonged stress or trauma[11], drugs (steroids, diuretics), hormones (oral contraceptives)[11], and pancreatic disorders. In summary, it is important to understand that there is a

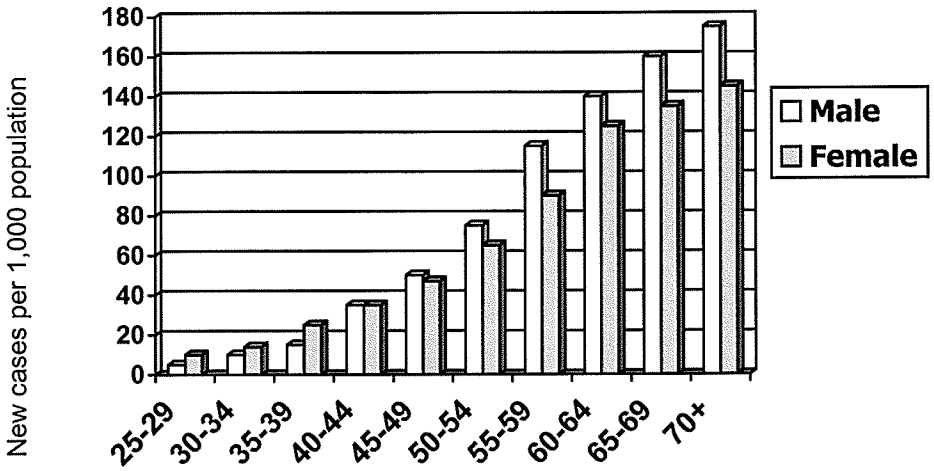
dynamic process involving multi-genetic factors and environmental or external influences in the etiology of diabetes.[11]

C. Epidemiology of Diabetes

In 1985, the World Health Organization (WHO) estimated 30 million people were afflicted with diabetes, this increased to 50 million people by 1989 and 100 million people by 1994 (a growth of 330%).[11] By the year 2025 it is estimated that approximately 300 million people will be afflicted with diabetes. [11]

In Canada, 2 million people had diabetes in 1998, and it is estimated that 3 million people will have diabetes by 2010.[2] In Manitoba, the geographic focus of this project, more than 55,000 people have DM, which translates into approximately 6% of the population.[3] Each year more then 4000 Manitobans are diagnosed with diabetes, and between 1986 and 1993 the number of prevalent cases increased by almost 60% in adults 25 years or older. [3] As age is a recognized risk factor for Type 2 diabetes it is expected that incidence and prevalence will increase as Canadians age. Figure 1. describes prevalence and incidence among Manitoba adults stratified by age and sex for 1994. [3]

Figure 1. Prevalence and Incidence of Diabetes in Manitoba, 1994



* adapted from Reference 3.

The prevalence of diabetes in developed or first world countries varies between different racial and ethnic groups. In Canada, people of aboriginal descent are 3 to 5 times more likely than the general population to have, or to develop diabetes, and are more likely to become diabetic at a younger age. Extrapolating from population data, this means 20% of First Nations women and 13% of First nations men suffer from diabetes compared to 6% of the overall population. Whilst adults, in the general population with diabetes are over 55 years of age, most aboriginal adults present with diabetes at a younger age and cases have recently been identified in children.[20] In 1980, there were no Aboriginal children identified with Type 2 diabetes but, by 1996, 43 Aboriginal children (<18 years) were diagnosed.[21] The expectation that the prevalence of diabetes among the First Nations population will triple by the year 2016 indicates an epidemic of this chronic disease is imminent resulting in a large impact on the health care system.[3] Clues to

explain these epidemiologic differences between some racial and ethnic groups might be found in epidemiological surveys.

One survey of the native populations of Canada determined age standardized point prevalence rate in 1987 using known cases of diabetes reported to local units of the Northern Medical Unit, University of Manitoba.[22] Previously, these units were managed by the Medical Services Branch of the Department of National Health and Welfare. This study included 76% of the Inuit and on-reserve registered native population of Canada. Subjects were also divided by indigenous language in an effort to better identify genetic predictors, as language is a better predictor of genetic relationship than culture area. Results from the survey indicated an association between geographical distribution and prevalence of Type 2 diabetes.[22] As study subjects moved from north to south the prevalence of Type 2 diabetes increased significantly; this same trend was observed following a west to east gradient.[22] An alternative perspective of geographic location was undertaken by examining rural and urban populations. This revealed that the highest prevalence of Type 2 diabetes occurred among the urban aboriginal population, and the lowest among the First Nations people living in remote areas.[22] These data seem to support the 'Thrifty Gene Theory' that there is a higher prevalence of Type 2 diabetes among communities faced with living in a predominately Euro-Canadian type of lifestyle to which they have become acculturated into. The increased incidence can be seen as a reflection of the drastic change from traditional lifestyle patterns of nomadic settlements of hunting, fishing and gathering.[23] The traditional lifestyle is likely to be completely

abandoned as communities adopt the lifestyle of those more southerly located near urban centers.[22-23]

D. Treatment of Diabetes

After examining the etiology and epidemiology of diabetes, it becomes clear that the ultimate therapeutic goal is to achieve a state of euglycemia. A combination of pharmacologic therapy and diet are the standard forms of treatment to mitigate the effects of hyperglycemia. In Type 1 diabetes, the only drug therapy is to replace endogenous insulin with an exogenous source of insulin, most commonly done by using synthetically produced insulin. To treat Type 2 diabetes a number of oral drugs can be utilized. These drugs have an ability to increase the amount of insulin that can be effectively utilized by the cell, and can be categorized into 5 classes determined by chemical structure and mechanism of action; see Table 3. Despite the many therapeutic differences in the drugs available they each have in common proven therapeutic efficacy. To increase both understanding of therapy, and to improve drug utilization, Canadian clinical practice guidelines for treatment of diabetes were first published in the Canadian Medical Association Journal in 1998. These were updated by the Clinical Practice Guidelines Expert Committee in 2003 and are available on the Canadian Diabetes Association website.[2]

Table 3. Common Examples of Oral Anti-diabetic Drug Treatments

Drug Class	Chemical Name	Brand Name	Mechanism of Action
Biguanide	Metformin	Glucophage	• insulin sensitizer • reduces hepatic glucose output
Sulphonylureas (Sulphonamides)	Glyburide	Diabeta	• stimulates pancreatic secretion of insulin
	Gliclazide	Diamicron	• stimulates pancreatic secretion of insulin
Alpha Glucosidase Inhibitor	Acarbose	Prandase	• inhibits glucosidase enzymes in carbohydrate digestion • decreases post-prandial glucose rise
Meglitinides	Repaglinide	Gluconorm	• stimulates pancreatic insulin secretion with a different method than sulphonylureas
Thiazolidinediones	Rosiglitazone	Avandia	• insulin sensitizer • insulin action improved in liver, muscle and adipose tissue
	Pioglitazone	Actos	• insulin sensitizer • insulin action improved in liver, muscle and adipose tissue

Evidence-based clinical practice guidelines outline management approaches for diabetes including diagnostic criteria, therapeutic strategy, goals of care and treatment, and follow-up (Appendix A). These guidelines were updated after Diabetes Control and Complications Trial and United Kingdom Prospective Diabetes Study Group trials were published which demonstrated a decrease in negative health outcomes with an increase in control of blood glucose levels and are discussed in more detail below. [4-5]

The objective of the guidelines are to provide a tool for the health care team to optimize and standardize treatment for persons with diabetes. The goals of care are outlined in Table 4. As well, specific quantitative targets were developed in these guidelines an effort to decrease morbidity and mortality. The guidelines were formed through a type of

consensus development conference of specialist and family physicians, nurse educators, dietitians, and a lawyer. The Canadian guidelines are unique among national guidelines in that they cover care of children, adolescent and special groups such as the elderly and native people.[2]

Table 4. Goals of Diabetes Care

Relieve symptoms
Prevent and treat acute and long term complications
Promote self-care
Improve quality of life
Reduce morbidity and mortality
Treat accompanying disorders

Diet is the main non-pharmacologic means of managing diabetes.[2] The first approach to diet management is the control of daily caloric intake to match the body's ability to maintain a euglycemic state.[24] By consuming too many calories the individual would become hyperglycemic, and by not eating enough a state of hypoglycemia would result. Both states are undesirable as they can cause unwanted clinical effects which may lead to immediate and long term adverse consequences.[25] Therefore, a controlled diet that is matched with exogenous insulin in persons with Type 1 diabetes or with the body's ability to produce and use insulin for persons with Type 2 diabetes is essential.[4-5] For some Type 2 patients, diet and achievement of an ideal weight may be used as an effective single therapy.[5] A loss of a relatively small amount of weight (2.5-5.0kg) has been shown to result in marked improvement of glycemic control.[5]

Without the ability to achieve euglycemia a state of either hypoglycemia or hyperglycemia results with immediate short term consequences (e.g., fainting, excessive

thirst, blurred vision), especially with Type 1 diabetes.[4] Long term secondary consequences, such as blindness and heart disease, are theorized to be a result of prolonged and sustained hyperglycemia.[26]

E. Secondary Complications of Diabetes

Following the understanding that Type 1 and Type 2 diabetes are two distinct disease states both with insulin abnormalities often leading to hyperglycemia, it is not surprising to find they share similar secondary complications when inadequate management occurs. Complications involve microvascular, macrovascular and neuropathic pathologies.[4-5,27] In Manitoba, approximately 25% of hospital admissions for heart disease and stroke occur in people with diabetes.[3]

Macrovascular complications include accelerated atherosclerotic disease in large blood vessels involving; coronary artery disease leading to acute myocardial infarction, cerebrovascular disease resulting in strokes, and peripheral vascular disease affecting circulation in the lower limbs causing claudication leading to for skin ulcers and gangrene.[28] In patients with diabetes, macrovascular disease occurs both with greater frequency (a two-three fold increase), and at an earlier age than the rest of the population.[24] In Manitoba, persons with diabetes make up half of all non-traumatic amputations performed. As well, hospitilisation for heart disease and stroke in 1991 among persons with diabetes was significantly higher than persons who were non-diabetic.[29]

Microvascular complications include pathologies related to small blood vessels and include retinopathy and nephropathy.[30] Retinopathy affects up to 80% of persons with diabetes within 15-20 years of diagnosis. Other ocular disorders associated with diabetes include senile-type cataracts, occurring at an early age, and resistant glaucoma that together with retinopathy make diabetes the leading cause of blindness in Americans.[30] Diabetic nephropathy often manifests as azotemia, (in 30% of patients with end-stage renal disease), and is a major cause of death.[30] Patients end stage renal disease associated with diabetic nephropathy are the leading conditions treated by dialysis or renal transplantation.[24] In Manitoba, over 40% of dialysis patients in 1993 were persons with diabetes, resulting in a cost of seven million dollars to provincial health care expenses.[3]

It is postulated that neuropathy is a result of metabolic abnormalities secondary to the microangiopathy of vessels supplying blood to neurons and can present as autonomic insufficiency and peripheral neuritis.[27] Over 25% of persons with diabetes may be symptomatic and clinical features include paresthesia and pain in the lower extremities, decreased vibration sense, decrease ankle and knee jerks, and decrease nerve conduction velocity.[24]

As well as suffering the highest prevalence the aboriginal population in Manitoba are also more susceptible to complications of diabetes. Data from 1991 shows that persons who are aboriginal and diabetic account for the following:[31]

- 91% lower limb amputations
- 60% hospitalizations for heart disease

- 50% hospitalizations for stroke
- 41% of hospital days
- 30% hospitalizations

It is hypothesized that the hyperglycemia present in both types of diabetes, and related metabolic changes arising from diabetes, results in metabolic abnormalities that lead in or contribute to microvascular and neurologic changes in function.[28] This hypothesis is called the *glucose hypothesis* and it proposes that eliminating hyperglycemia and maintaining glucose levels at a normal or near normal range will result in a decrease or elimination of those complications. However, opponents argue that a genetic predisposition is required, in addition to hyperglycemia, to develop microvascular complications. This argument is supported by the fact that 14 to 20% of persons with diabetes, regardless of blood glucose control do not develop microvascular complications, and 5% will develop complications regardless of how well blood glucose is controlled.[32] This observation has fueled the debate over the benefits versus risks of tight blood glucose control, until relatively recently when data from two large long term trials became available (The Diabetes Control and Complications Trial and United Kingdom Prospective Diabetes Study Group).[4-5,26]

F. Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study Group (UKPDS)

The DCCT was a multi-centered randomized cohort controlled trial in which 1441 patients were followed for a mean of 6.5 years in an effort to assess the implications of

tight glucose control in Type 1 patients.[4] The results of this trial were a landmark in the treatment of Type 1 patients. The trial enrolled two cohorts in order to explore prevention as well as treatment of sequelae to diabetes. The primary prevention cohort included patients who had Type 1 for one to five years, no retinopathy, and a urinary albumin excretion of less than 40mg per 24 hours.[4] The secondary intervention cohort included patients diagnosed as Type 1 and of one to 15 years duration, very mild to moderate non-proliferative retinopathy, and a urinary albumin excretion of less than 200mg per 24 hours.[4] Four complications of diabetes were examined; retinopathy, nephropathy, neuropathy and macrovascular disease.[4]

Retinopathy in the primary prevention cohort was not significantly different in the two treatment groups for the first 36 months, however, at this point the groups began to separate. A 50% decrease in the incidence of retinopathy after a period of 5 years between the intensive therapy primary prevention cohort, and the conventional therapy cohort was detected.[4] It was concluded that in this trial there was a 76% reduction of the adjusted mean risk of retinopathy. The secondary-intervention cohort demonstrated similar results, with intensive therapy reducing the average risk of progression by 54% during the study period.[4] As well, intensive therapy reduced the risk of severe non-proliferative retinopathy by 47%. However, it was observed that during the first year there appeared to be a higher cumulative incidence of sustained retinopathy progression in the intensive therapy group.[4,26]

The nephropathy data also showed favorable results with tight glucose control.[4] For both cohorts, there was less development of microalbuminuria and albuminuria in the

intensive-therapy group when compared with the conventional-therapy group; reducing the mean risk by 34 percent and 43 percent in the primary and secondary groups respectively.[4] There was also a risk reduction of albuminuria by 56 percent. Similar results were seen when examining neuropathy in the primary cohort. There was a 69 percent reduction in the appearance of neuropathy at five years in the cohort which showed no symptoms of neuropathy at the beginning of the study.[4] The secondary intervention cohort demonstrated a 57 percent reduction in neuropathy at five years. Finally, data on macrovascular disease showed a 41 percent risk reduction in the intensive-therapy group after combining all major cardiovascular and peripheral vascular events; although this was not statistically significant.[4]

The UKPDS was formed in 1977.[33,34,35,36,37,38] The organization's main objective was to investigate the effect of intensive blood glucose control in patient's with Type 2 diabetes.[5] In particular the group was interested in determining whether there could be a decrease in risk of microvascular and macrovascular complications similar to Type 1 patients demonstrated by DCCT. Finally, UKPDS would examine whether any particular therapy had greater benefit over others. Results of this study were published in 1998.[5] In the UKPDS trials 3,867 patients aged 25 to 65 years were entered into a multi-centered randomized cohort trial. Persons were assigned to one of two cohorts consisting of either conventional treatment or intensive glucose control. Rates of retinopathy, nephropathy, neuropathy, cardiovascular disease and hypertension were determined.[39]

With regard to retinopathy, intensively treated participants had a 25% RRR (relative risk reduction) in developing microvascular disease, a 19% RRR in retinal photocoagulation and a 24% RRR in cataract extraction.[5] As well there was a 21% RRR for the progression of retinopathy over 12 years.[5] Similarly favorable results for intensive glucose control were seen with renal endpoints. A 33% RRR was found in the development of microalbuminuria, and a 74% reduction in the number of patients who doubled their creatinine value over 12 years.[5] Neuropathy, not one of the primary endpoints of UKPDS, showed a 40% RRR in sensory nerve function deterioration as measured by a biothesiometer in the intensive glucose control cohort. Finally, a 16% RRR for development of myocardial infarction was determined although, this did not reach statistical significance; a 53% RRR in sudden death was demonstrated.[5] These results were consistent with the DCCT in supporting a more favorable outcome for the intensive glucose control group.[4]

Diabetes is a debilitating disease and long term consequences like blindness and heart disease have a large impact on morbidity and mortality. The incidence and prevalence of diabetes is increasing at almost epidemic rates across the globe and Manitoba reflects this trend (even more so when one considers that it has a large First Nations (aboriginal) population). Results from both the DCCT and UKPDS show that regardless of the type of diabetes, a policy for intensive glucose control can have a beneficial effect and the Canadian Diabetes Association Guidelines for treatment of diabetes have been changed to reflect this (Appendix A).[2] An initial step toward this goal is to acquire a more comprehensive understanding of anti-diabetic pharmaceutical use patterns.

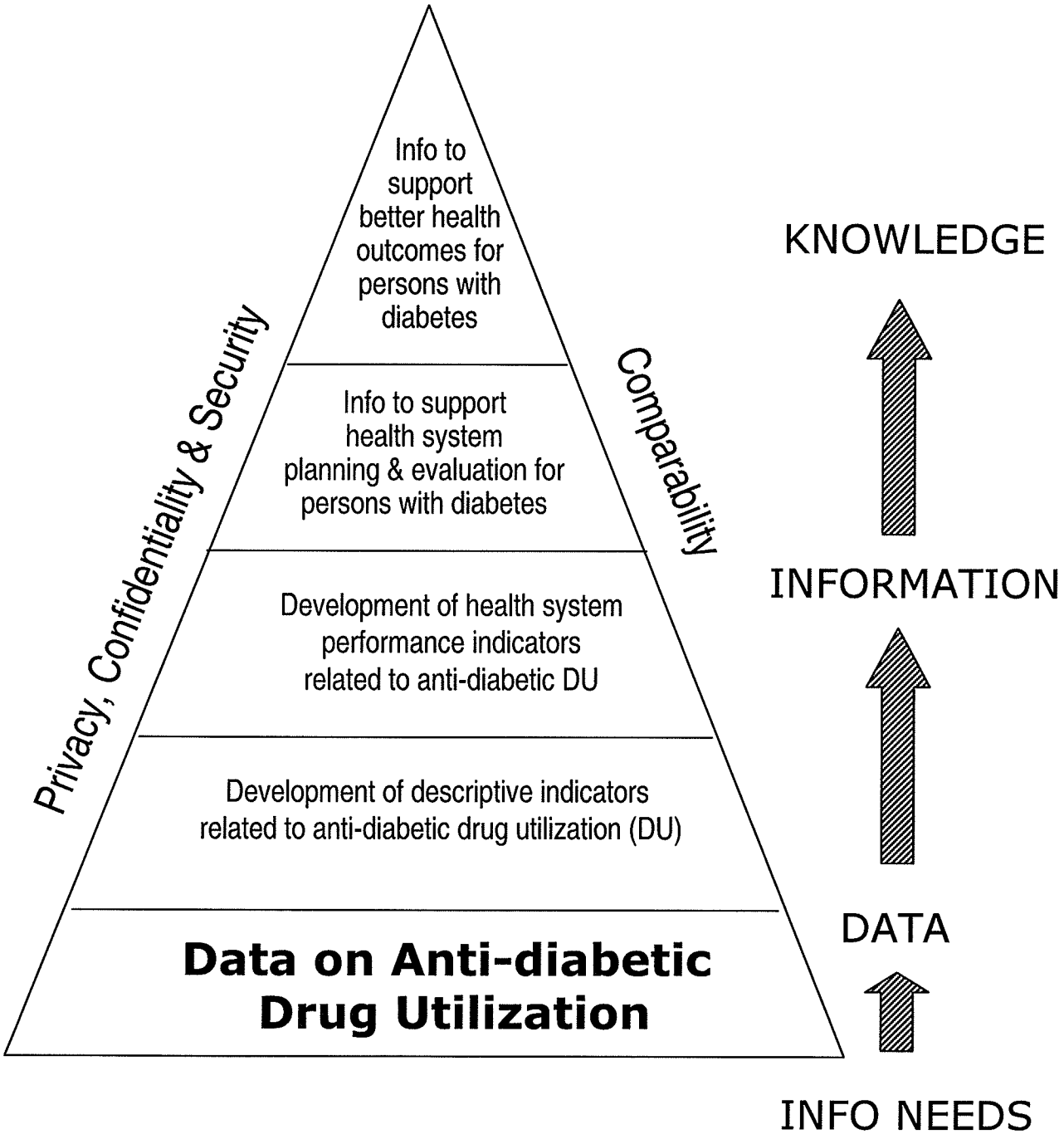
CHAPTER TWO

Literature Review

Quality assessment and improvement in diabetes care is a major issue in many countries.[40] Information on diabetes care is being demanded by policy makers, such as the Canadian Diabetes Association, health-care professionals and the general public in order to ensure that the most effective care is being provided. With the majority of diabetes oriented doctor-patient encounters in general practice resulting in a prescription for anti-diabetic pharmacotherapy, the quality of drug utilization is an important issue.[41] Quality of pharmacotherapy use in diabetes requires that each patient prescribed anti-diabetic medication receives medication appropriate to their needs.[42] As Lynn Brousseau at the Canadian Institute for Health Information (CIHI) has said, "...the quality of medication use cannot be managed or monitored unless utilization can be measured."[43]

Measuring drug utilization is a dynamic and complex matter but a necessary one to ensuring that better health outcomes are attained for persons with diabetes. Figure 2 depicts how information needs or requirements support a vision for the transformation of data (through drug utilization research) into information (quality indicators for appropriate and effective use of anti-diabetic drugs), and further into knowledge for better health outcomes.[44] The model conceptually describes a process and a continuum for the development of information about the use of anti-diabetic drugs over time. Within this model, each new stage of the process builds on the previous one, and enhances the

Figure 2. A Model for the Development of Anti-diabetic Drug Utilization Indicators



*Adapted from CIHI, 2004 (see reference in the text)
Note: The relationship between the stages is dynamic as new data must be reflected upon so that needs can be reevaluated and interventions adapted, accordingly. Comparability between provinces and across Canada is desirable and issues surrounding privacy, confidentiality and security must also guide the evolution of the stages.

ability to analyze the impact of multiple factors that may affect anti-diabetic drug use and eventually health outcomes.

The bottom level of the pyramid can be referred to as descriptive and 'hypothesis generating.' Although hypothesis generation can occur at any level, starting at the base of the pyramid provides data which first demonstrates patterns of drug use; the next logical step is to assess these patterns of use with a health services research orientation.[45] Methodologically, one would want to describe patterns of use on one dataset and assess the patterns on another:

> " (one)...strategy to protect against the acceptance of spurious or chance associations is to raise hypotheses on one set of data and test them on a separate one."[46]

In other words, to develop hypotheses and test them on the same data set may lead to erroneous conclusions. Theoretically then, the base of the pyramid should probably be comprised of two steps—first, a description of diabetes treatment patterns should be provided and then patterns of use that elicit hypotheses previously not seen should be tested or assessed in a separate process by examining them on another dataset of diabetics.

Once patterns in drug utilization are identified and hypothesis developed, testing of the hypothesis can be undertaken which will provide ability to move up the pyramid ultimately establishing programs to improve health outcomes. A literature search was undertaken to provide insight in drug utilization patterns with regard to anti-diabetic

medications. In the past several years there has been worldwide interest in anti-diabetic drug utilization at the population level.[47,48] These population studies often use data originating from large insurance databases and have taken place in many countries, although most are found in either the United States or Europe.

One of the largest studies was published in 2001 and involved a cohort of 60 million people from the Merck Medco Managed Care, a large private health insurance company based in the United States.[47] This database included 3 years of longitudinal patient-level pharmacy claims data, with a patient mix thought to be reflective of the payer mix in the general population. Compliance rates were evaluated in an effort to characterize "real world' drug utilization patterns, by examining five anti-diabetic drugs (each one representing a class of drugs). It was observed that discontinuation rates were between eight and 16 percent and upward dose changes were observed in 15 to 31 percent of the cohort, with 36 percent of patients requiring a change in choice of drug therapy. Twelve month persistence rates ranged from 31 percent to 60 percent and compliance rates varied between 70 and 80 percent. Compliance was measured by determining the sum of the days' supply of a prescription dispensed divided by the duration of therapy. Persistence was based on patient refill behavior and attempted to measure the duration of time the patient was on a particular therapy in an effort to determine if discontinuation of a drug therapy had occurred.[47]

A second study published in the same year, 2001, examined the escalation in cost of drug treatment among type 2 diabetics using the Kaiser Permanente Northwest Diabetes

Registry data collected in 1995.[48] These data reflected individuals with prepaid coverage representing approximately 20 percent of people (450,000 residents, 12,200 identified with diabetes) living in Portland, Oregon. Total annual costs of health care utilization appeared to be linked with severity of disease state; costs for patients not taking anti-diabetic drug therapy were $4,400USD, for patients on a sulfonylureas only $4,187, for patients on metformin only $4,838USD, for patients on sulfonylureas and insulin $8,856USD and patients on insulin only $7,365USD. Total per patient costs were $5,303USD and $4,365USD respectively, for patients who had received antidiabetic therapy by 1995. The researchers concluded that total cost increased as antidiabetic therapies escalated.[48]

Using the same database, Brown and Nichols published an earlier, but more extensive retrospective study using data from 1988 to 1998.[49] The cohort of 693 persons newly diagnosed patients with Type 2 diabetes were identified in 1988 and followed for 10 years. Seventy-three percent of the cohort had a change in therapy over the time period, and eight to 10 percent of the population discontinued therapy altogether. Avoidance of treatment after diagnosis was more common during the first year, and five to 10 percent of the cohort avoided contact over the entire ten year period. As well, approximately 80 percent of patients started on a sulphonylureas, added or switched to a second class of drug within ten years.[49]

Looking at a more restricted population Spooner et al. described drug utilization among patients in 1,492 Medicare and Medicaid certified long term care settings in the states of

Kansas, Maine, Mississippi, New York, and South Dakota.[50] There were 75,829 patients who were labeled with a diagnosis for diabetes identified from the cohort of 437,128 residents in between 1992 and 1996. A retrospective, cross-sectional study evaluated the prevalence and correlates of treatment of elderly diabetics in the cohort. Data were obtained using a database called, The Systematic Assessment of Geriatric Drug Use via Epidemiology, which is a population-based, integrated database that includes information obtained through the Health Care Financing Administration's Case-Mix Reimbursement and Quality Demonstration Project. The database consists of a 350-item Minimum Data Set (MDS) that included socio-demographic information, symptoms, syndromes and treatments among many other recorded variables. Not included in the dataset are HbA1c levels, or both fasting and postprandial plasma glucose concentrations. These values are indicative of a patient's control of blood glucose concentrations, therefore, demonstrate ability to manage the residents' diabetes. Along with this dataset the nursing staff recorded data of up to 18 medications taken by each resident during the seven days preceding the MDS assessment. No anti-diabetic medication was given to 47 percent of the diabetic residents and independent predictors included age, race, impaired physical ability, and impaired cognitive function. However, without laboratory value data, demonstrating ability to achieve control over blood glucose levels amongst the non-anti-diabetic medication taking population. the authors were unable to conclude adequacy of diabetic care.[50]

Much of the published literature focused on anti-diabetic drug utilization has originated in Europe. In Sweden, population based studies examining anti-diabetic drug use have

been carried out using the Tierp Study Database.[51] One of the early studies, published in 1987, by Isacson and Stalhammer, described how two point eight percent of the Tierp population were defined as diabetic and accounted for 10.2 percent of total prescriptions dispensed.[51] The study evaluated all medical records for diabetes patients at the primary health care centre, and all prescriptions for diabetes drugs filled at the local pharmacies, from 1975-1994. These data were generated by a cohort comprised of 2,125 persons. Of the 16 pharmacologic groups studied, diabetic patients had a higher rate of use in nine groups. Drug use increased in both groups with age among both the diabetic and non-diabetic groups, and females, had higher levels of pharmaceutical use.[51] Where diet treatment was emphasized, oral pharmacologic treatment decreased, but when treatment without diet was emphasized the converse was observed. Biguanide treatment increased when the guidelines emphasized better glycemic control, and diet alone decreased. When the guidelines emphasized vigorous glycemic control, sulphonylurea and insulin use increased and treatment with diet alone decreased.[51]

Another Swedish study, attempted to describe and compare the distribution of prescribed drugs in diabetic patients between 1992 and 1995.[52] Data were gathered using two cross-sectional surveys reflecting a random selection of medical records of diabetic patients from three health care centers. From these records the number of prescriptions and classification of diabetes, metabolic outcome, and concomitant hypertension were recorded. These data showed a significant increase in both the use of oral anti-diabetic drugs and treatment with more than one drug entity over time. However, during the same

period of time, metabolic state was unchanged and unsatisfactory for 40-50 percent of patients.[52]

In 1991, Benitez, Puerto, and Diaz conducted a comparative population based study of antidiabetic drug utilization between three health systems in Extramadura, a region in the Southwestern part of Spain.[53] Citizens in this region were provided access to health care through a national system, however, armed forces and civil servants were able to choose either the national system or private health insurance. Civil servants and armed forces made up 4.2 percent and 2.3 percent of the population respectively. During December of 1986, 91.8 percent of the population had care provided through the national system.[53] Study results comparing the population made of citizens and those in the civil service and armed forces were examined and expressed in DDD, an acronym for Defined Daily Dose, a unit of measurement that serves as a basis for comparison of drug use that is independent of price and dosage form differences. It was assumed that the average dose per day for a drug product used was for it's major indication in adults, and was expressed in DDD per 1000 inhabitants per day[54]. The results revealed that, overall, oral anti-diabetic treatment was the most common at 9.65 DDDs/1000 inhabitants/day and insulin use was 4.10 DDDs/1000 inhabitants/day. There was almost a threefold difference between the armed forces personnel and civil servants use of antidiabetic drugs (15.82 DDDs to 5.73 DDDs, respectively). In addition, armed forces personnel use twice the amount of insulin than do civil servants (3.82 DDDs vs. 2.02 DDDs) and three times the amount of oral antidiabetic agents (12.00 DDDs vs. 3.71 DDDs). Armed forces personnel use less insulin (3.82 DDDs vs. 4.21 DDDs) than the National Health Service

but more oral antidiabetic agents (12.00 DDDs vs. 9.86 DDDs). Sulfonyureas are the oral antidiabetic drug of choice at the rate of 9.45 DDDs/1000 inhabitants/day. The differences in utilization between the three groups, especially between the civil servants and armed forces, may be explained in part by age structure, civil servants being the youngest.[53]

Evans and MacDonald investigated the utilization and cost of drugs among diabetic and non-diabetic patients in a population based study in Tayside, Scotland.[55] A diabetes register was used to identify Type 1 and Type 2 diabetes patients. Prescription data from a database containing all the prescriptions dispensed in the community of 406,526 people in 1995 were used. After adjusting for age, Type 1 diabetics were 2.07 times more likely, and Type 2 diabetics were one point seven times more likely to be dispensed a prescription than patients without diabetes. Patients identified as diabetic accounted for 7.3 percent of the prescriptions dispensed, and when antibiotic medications were excluded this dropped to 5.5 percent. Diabetic patients accounted for a higher proportion of drug items dispensed than would be expected given the prevalence of diabetes for drug categories evaluated.[55]

Data gathered from original prescriptions, hard copies written by physicians, were examined in Hong Kong by Wu and Lung in 1998.[56] This study, called a prescription survey, was designed to examine the use of antidiabetic, antihypertensive, and lipid lowering drugs in a hospital diabetes clinic; expenditure incurred was also evaluated. All prescriptions issued over four consecutive, four week periods (total of 16 weeks) were

collected and drugs were categorized as described above. Using the 534 prescriptions collected the total cost of the dispensed medications was. Oral hypoglycemic agents accounted for 73 percent of costs with sulphonylurea and metformin being the most commonly dispensed agents. As well, 32 percent of the 534 prescriptions contained an antihypertensive drug and 8 percent a lipid lowering agent. It was determined that use of antidiabetic drugs represented a major burden on the health care system, and the high proportion of patients requiring antihypertensive and lipid lowering agents further increased expenditure in the diabetic population.[56]

While there has been a increase in published research examining the use of anti-diabetic drugs in various populations during the last five years, it is apparent that the majority of studies discussed above use samples or segments of a population. Further, they have used incomplete drug acquisition records, thereby limiting the generalizability of the findings. The most complete picture comes from a Spanish study examining the Extramadura region.[53] However, no detailed examination of the use of specific antidiabetic agents was completed, and the population was divided by primary payor rather than a relevant social indicators i.e. age, gender, geographic location and socioeconomic status. Often studies have not take into consideration factors related to co-pay, volume of drug and formulary management which would contribute to variability in drug utilization. Research completed to date has lacked the depth and breadth that would be ideal for population-based research. However, in Manitoba there exists a comprehensive database, called The Population Health Research Data Repository (which is described in greater detail below). This database provides a unique ability to provide

the breadth and depth of drug utilization information within a population that is more complete than any other center in the world. With this database and a powerful statistical analysis software packages such as SAS® patterns of drug use can be explored and formulation of hypothesis can be undertaken.

INTRODUCTION TO RESEARCH QUESTIONS

In Canada, a socialized model of medical care is followed in which the province administers it's own health care delivery and costs.[57] Manitoba, with a population of 1.1 million people, maintains an administrative database that reflects person-level transactions in the health care system.[58] This comprehensive data source provides a unique ability to examine drug utilization patterns in a population and, in particular use of anti-diabetic drugs can be comprehensively described. It is the objective of this thesis to examine the patterns of anti-diabetic drug use and to describe variability with respect to the population's geographic location, age, socioeconomic class, health status or gender. Cost of anti-diabetic pharmacotherapy also can be assessed using the available data. For the purpose of this thesis the following questions will be addressed:

1. Can patterns of pharmacologic use for persons with diabetes in the Manitoba population be described by access (to all pharmacologic entities and, specifically, to anti-diabetic pharmacotherapy) and measures of intensity of use (number of prescriptions claims, number of different drugs used and number of defined daily doses used per day and per year)? How are these patterns of use illustrated by the population's:

a. Age
b. Sex
c. Age/Sex
d. Income Quintile
e. Region of Residence
f. Comorbidity Status

2. Can the costs of pharmacologic use for anti-diabetes in the Manitoba population be determined, and can they be described by the population's:

    a. Age
    b. Age/Sex
    c. Sex
    d. Income Quintile
    e. Region of Residence
    f. Comorbidity Status

CHAPTER THREE

Research Methods

A. Introduction

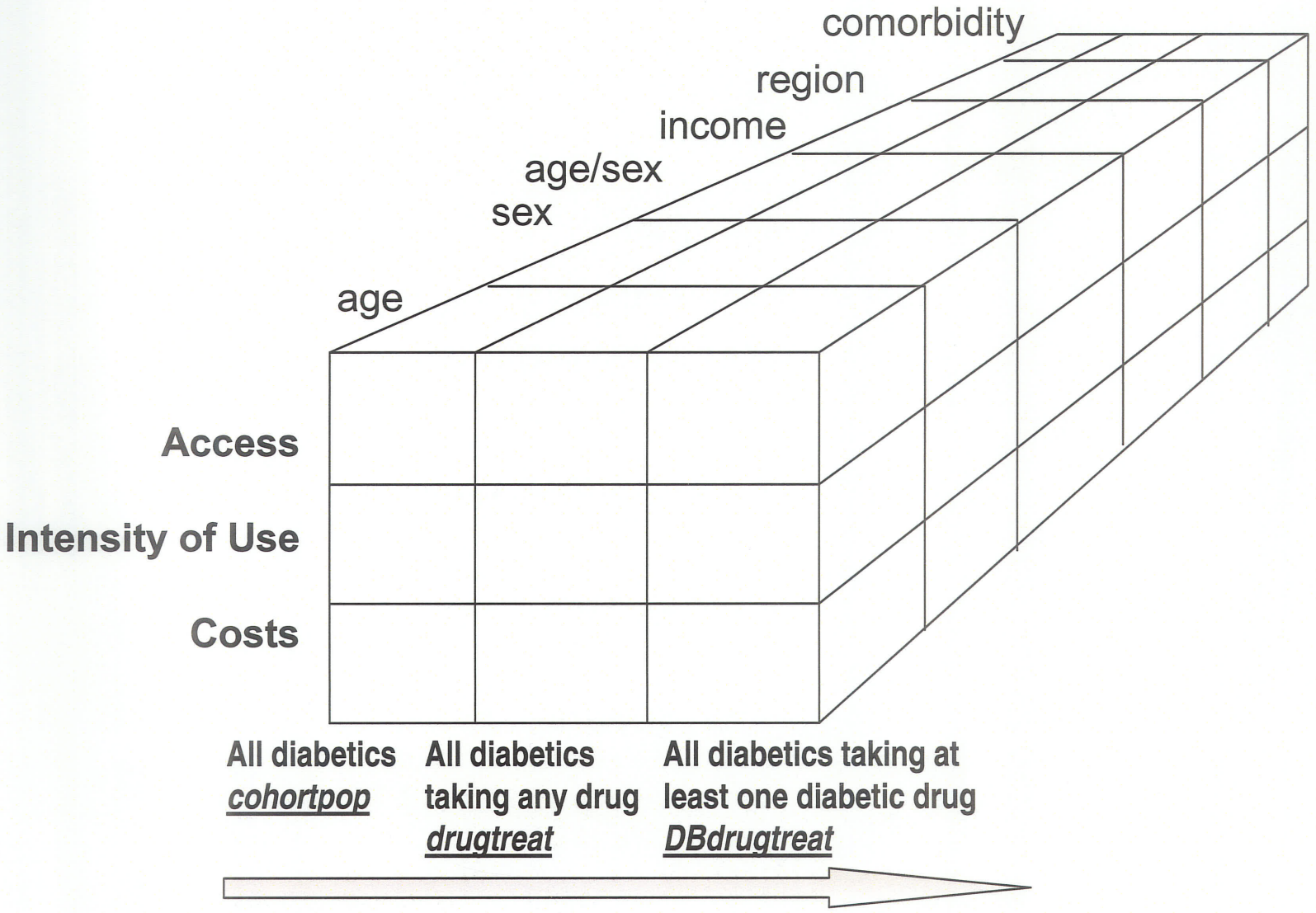
This study uses a fixed-sample panel study design to look at the use of anti-diabetic prescription medications by the Manitoba population defined as being diabetic. A variety of measures of drug utilization are used to describe access, intensity of use and costs according to the population's demographic descriptors.

B. Study Design

Using administrative claims data a panel study of persons identified as being diabetic was examined for their use of antidiabetic drugs for the fiscal years (April 1 – March 31) 1997-98, 1998-99, 1999-00, and 2000-01. All subjects included in the panel were residents of Manitoba during the period of the study. Although subjects pharmaceutical use was examined over a four years period, their age, comorbidity status, income category, and geographic area of residence were identified and indexed as of April 1, 1997. Subject's access to prescription drugs, including anti-diabetic agents, was assessed along with the frequency of antidiabetic drug use (number of claims, number of different drugs, defined daily doses), and costs of these drugs over the four year period. Figure 3. shows the overall analytical orientation that is used for this four-year panel study.

Each block in the three-dimensional diagram is divided into categories including drug utilization, and by population and cohort descriptions. Drug utilization in this thesis is

Figure 3. Analysis Orientation



described by measures categorized around the access to anti-diabetic medications (given that the subject meets the inclusion criteria as 'diabetic'), the intensity of use with regard to prescribed medications (e.g., number of prescriptions dispensed), the population's demographics (e.g., age, sex, comorbidity status), and by the three cohorts defined by the data's diabetic algorithm (Figure 6).

C. Data Source

The Population Health Research Data Repository (PHRDR), which has existed in some form since the 1970's, is housed in the Manitoba Center for Health Policy (MCHP), a university based policy research center.[58] The mission of MCHP is to provide accurate and timely information to health care decision-makers, analysts and providers, so that they can offer services that are effective and efficient in improving the health of Manitobans. The Repository contains various files which are made up of encounter-based, anonymized records of individuals who have had contact with the provincial health care system.[58] Files used in this study include the Hospital File, Medical Claims File, Personal Care Home Database, Registration File, and Drug Program Information Network Files. Each file contains unique and specific information which when merged with other files provides a detailed longitudinal description describing the healthcare received by Manitobans.

MCHP's PHRDR files can be linked using the Personal Health Identification Number (PHIN). The PHIN's in the repository are anonymized by a software program and do not resemble the actual PHINs. Each time a prescription is filled, a physician submits billing for a procedure to the province, or a patient is admitted to hospital, their PHIN can link

the patient's contacts to a health profile. Thus, various types of information are gathered and stored with regard to medical procedures, physician visits and procedures, hospital discharge information.

The Repository has become a robust database that can be used to describe and explain patterns of care and profiles of illness, as well as to explore other factors that influence health such as income, education, employment and social status. The following table describes the information contained in the files (Table 5).

The data from each of these files is housed at different parent organizations. There is no routine integration in which the files are combined, however the data they contain can be analyzed together since patient identifiers, physician and hospital numbers have been standardized across all files using encrypted identifiers. Histories can be developed for individuals, describing all care rendered by the provincially insured health system over time. Since the entire population is insured, non-participation in the Manitoba health plan is minimal. As well since registry records date back to 1970 a longitudinal picture of the population is available and software was developed to facilitate longitudinal follow-up including mobility, migration, and mortality. This database is believed to be unique in the world and it is a very carefully managed resource. With such a unique and robust database MCHP believes that confidentiality is paramount and individual records are protected with rigorous well established protocols and security measures.

Table 5. Manitoba Health Research Data Repository Files

Repository File Name	Contents	Originating Date
Hospital File	Day surgery and inpatient admission to both acute and chronic care hospitals	1970
Medical Claims File	Physician contacts in offices, hospitals, and out patient departments	1970
Registration File	Dates of coverage, with annual snapshots. An effort has been made to join the snapshot files together such that individual histories can be constructed over the entire period of the database resulting in a longitudinal population registry.	1970
Mortality File	Information on the date and cause of death and derived primarily from Vital Statistics death records	1970
Public Access Census Files	Demography, families, households, dwellings, language, immigration, ethnic origin, education, mobility and migration, income, place of work, religion	1986-1991
Drug Programs Information Network Files	Data of pharmaceuticals purchased at private retail outlets	1994 (July)
Financial Information System Data	Detailed chart of accounts and include both hospital based and non-hospital activities such as Community Health Centers, Juxtaposed Personal Care Homes, Retail pharmacies and outreach centers	
Master Formulary	A file developed under the MCHP umbrella which allows for efficient and effective analysis of DPIN by providing a classification system and other important variables linked to pharmaceutical products	1998

No patient names or addresses are contained in the Repository and any individual and family identifiers are changed by Manitoba Health or MCHP so they are not recognizable. Projects requiring access to the Repository must be approved by the

provincial Health Information Privacy Committee and/or the Research Ethics Boards, the University of Manitoba. All MCHP employees and external research associates must sign a Confidential Information Agreement and comply with terms related to the use and dissemination of information derived from the Repository. Computer output and printed output are closely regulated and are subject to strict regulations that include access to the physical research space and destruction of generated data files. Policies regarding the management of the Repository, with particular regard to confidentiality and security and any information garnered from it are reviewed on regular basis.

The files used in this study (Table 5) are used to both identify and describe the study cohort and the cohort's pharmaceutical use patterns. The primary files used to examine pharmaceutical use patterns include the Financial Information System Data file (FIS) from which cost of drug use is gathered, the Master Formulary file which allows analysis of the Drug Program Information Network (DPIN) file, and the DPIN file itself.

DPIN is an administrative claims database of prescriptions dispensed to Manitoba residents. Claims missing from the database can be identified as belonging to one of four different categories. First, internal patient drug profiles dispensed during a hospital admission are maintained within the hospital. Second, prescriptions dispensed to First Nations peoples by physicians or nurses at reserve-based nursing stations in remote rural areas of Manitoba are not submitted to DPIN. These prescriptions are typically for either short courses of drug therapy, for treatment of acute conditions such as infection or dermatitis, or an initiation/change in drug treatment. This is accepted practice in an effort

to ensure time between diagnosis and treatment is not delayed. Third, missing include a small percent of small rural long term care beds who do not submit claims through the DPIN database. Finally, pharmaceuticals dispensed in Manitoba, which are exported as international prescriptions are not submitted through DPIN.

Administration of the DPIN system is accomplished through real-time computer links to each licensed community-based pharmacy in Manitoba; these are maintained by the provincial government's Ministry of Health. Each time a Manitoba resident has a prescription filled in the community, or by a hospital outpatient department, their PHIN is used by DPIN to capture their prescription information. The system administers payment of claims under the provincial Pharmacare Program, the Nursing Home Drug Program, and the Department of Family Services Drug Benefits Program. The government pays for the total costs for the Nursing Home drug claims, the Family Services drug claims, and the non-adjudicated claims (claims from Medical Service and Winnipeg Social Services recipients).

The DPIN data files housed at the MCHP include:

- a person-specific identifier (scrambled version of a person's PHIN)
- demographic data
    - region of residence, sex, date of birth, physician and pharmacy identifiers
- the date the prescription claim was dispensed
- pharmaceutical formulation specific data

    - metric quantity of drug dispensed, drug identification number (DIN), dosage form and route, strength in metric units
- number of days supply dispensed,
- expenditure information including;
    - ingredient price per unit of drug, total ingredient price, professional dispensing fee charged, total expenditure of claim

More than 8 million prescriptions or claims are submitted to DPIN each year[c] whilst validity of the DPIN files has never been verified, entry errors with respect to the PHIN, pharmaceutical formulation, and physician are expected to be limited as any inaccuracies in these fields would constitute a medical error. Currently, any medical errors identified are brought forward to a professional administrative organization called the Manitoba Pharmaceutical Association (MPhA). MPhA has been granted powers under the provincially legislated Pharmaceutical Act to license, discipline, manage standards of practice and represent the pharmacists of Manitoba. Thus, the drive for accuracy in transcription of prescriptions results, in all probability, a highly valid dataset.

Most claims are submitted to Pharmacare, Nursing Homes, Family Services, or First Nations and Inuit Health; these are all parts of a public health insurance system. Expenditure information is adjudicated by the respective program and any errors resulting in a higher cost or inappropriate inflation of prices would likely be rejected by the insurance carrier and need to be resubmitted by the pharmacy. Errors in expenditures

[c] Based on *Pharmaceuticals: Focussing on Appropriate Utilization,* by Colleen Metge, Anita Kozyrskyj, Matt Dahl, Marina Yogendran and Noralou Roos; (June 2003)

resulting in a low cost may not be picked up by the adjudication process but would likely be identified by the pharmacy itself as it infringes on the pharmacy's profit margin. Demographic data are the responsibility of the Repository, and while pharmacy locator numbers are static physician locator numbers and individual resident addresses may fluctuate to a degree.

The number of days supply of drug is entered at the pharmacy and may or may not be specified by the physician. In instances where it is not specified by the physician the pharmacist will determine the days supply by dividing the quantity prescribed by the number of times per day a patient is instructed to take the drug. However, during a course of therapy, a patient may be instructed by their physician to take the medication more or less frequently, thus changing the days supply a prescription would provide. This can occur without the pharmacy being informed or obtaining a new prescription with up to date directions. This inaccuracy may or may not be corrected on the refill prescriptions upon the patient's next visit to the pharmacy.

The DPIN data can be linked to the DIN Master, a file developed by the Pharmaceutical Use Policy Research Office at the Faculty of Pharmacy. The DIN Master[d] takes three provincial insurance programs; Pharmacare, the Nursing Home Drug Program, and the Family Services Drug Program; along with the non-adjudicated files[e], and determines the

[d] The DIN Master file was previously known as the Master Formulary (MF) file in MCHP's programming logs. The terms can be used interchangeably.
[e] Non adjudicated claims are prescriptions dispensed that are not paid (in full or in part) by Manitoba Health, information is captured by DPIN when the prescription is submitted for screening of potential

common set of drugs between the programs. The Master Formulary contains one record for each drug identification number (DIN) with information attached such as dosage form, strength, route of administration, defined daily dose designators, ATC (Anatomical Therapeutic Chemical) code and AHFS (American Hospital Formulary Service) classification.[17] The list of drugs dispensed each year in Manitoba is updated yearly using a database called the DIN (Drug Identification Number) Master: a list representing all drugs that have been dispensed in the Manitoba since DPIN's initiation in 1995.

Two classification systems for grouping DINs are available in the DIN Master; they are the AHFS and ATC system, each system is used to group and describe related drugs. In this study, the ATC system was used to identify and group drugs. ATC is the World Health Organization's Collaborating Center for Drug Statistics Methodology classification system which classifies human medicines into different groups, using a combination letter and number code according to the organ or system on which they act, and/or therapeutic, pharmacological and chemical characteristics.[54] A unique ATC code is assigned to each pharmaceutical product, with two exceptions. First, if the same chemical is used in different formulations or strengths designed for different therapeutic purposes, a substance may be designated more than one ATC code. Second, for combination pharmaceutical products (e.g., amilzide/hydrocholorthiazide) a specific ATC code has been assigned. This same classification system also lists the DDD for many of the drugs.

---

inappropriateness (drug/drug interactions or therapeutic duplications) with other drugs previously dispensed.

D. Data Management and Cohort Identification

As described above, the PHRDR is used to describe and explain patterns of care and profiles of health and illness in Manitoba. In order to access and analyse the data within the data set MCHP has provided SAS®, a powerful statistical software tool widely used throughout the world to manage large quantities of data. In order to integrate the data located in PHRDR, sophisticated statistical tools have been developed using SAS®.

Therefore, a basic understanding of SAS® was required in order to perform the programming operations with which to analyze the data. The inclusion criteria were based on the definition used by Manitoba Health with the addition of a third consideration--the drug data available through PHRDR. The definition for diabetes is not consistent across the provinces, however, the Manitoba Health definition is consistent with the National Diabetes Surveillance System definition.[1] That definition is currently being tested for validity. Initially, Charles Burchill, a programmer with MCHP, created a separate program that identified the diabetic population using the following inclusion criteria for this study:

- A Manitoba resident with continuous provincial health coverage after April 1, 1994) and the end of the definition period (March 30, 1997).
- defined as diabetic by meeting one of the following criteria within a three-year time period:

Criteria	Repository File	Year
2 physician claims for ICD-9=250	Medical File	1994-97
1 hospital claim for ICD-9=250	Hospital File	1994-97
1 pharmaceutical claim for an antidiabetic drug (ATC=A10)	DPIN File	1996-97

The derived cohort file included the encrypted Personal Health Identification Number (PHIN) and the criteria that had been used to identify the cohort member.

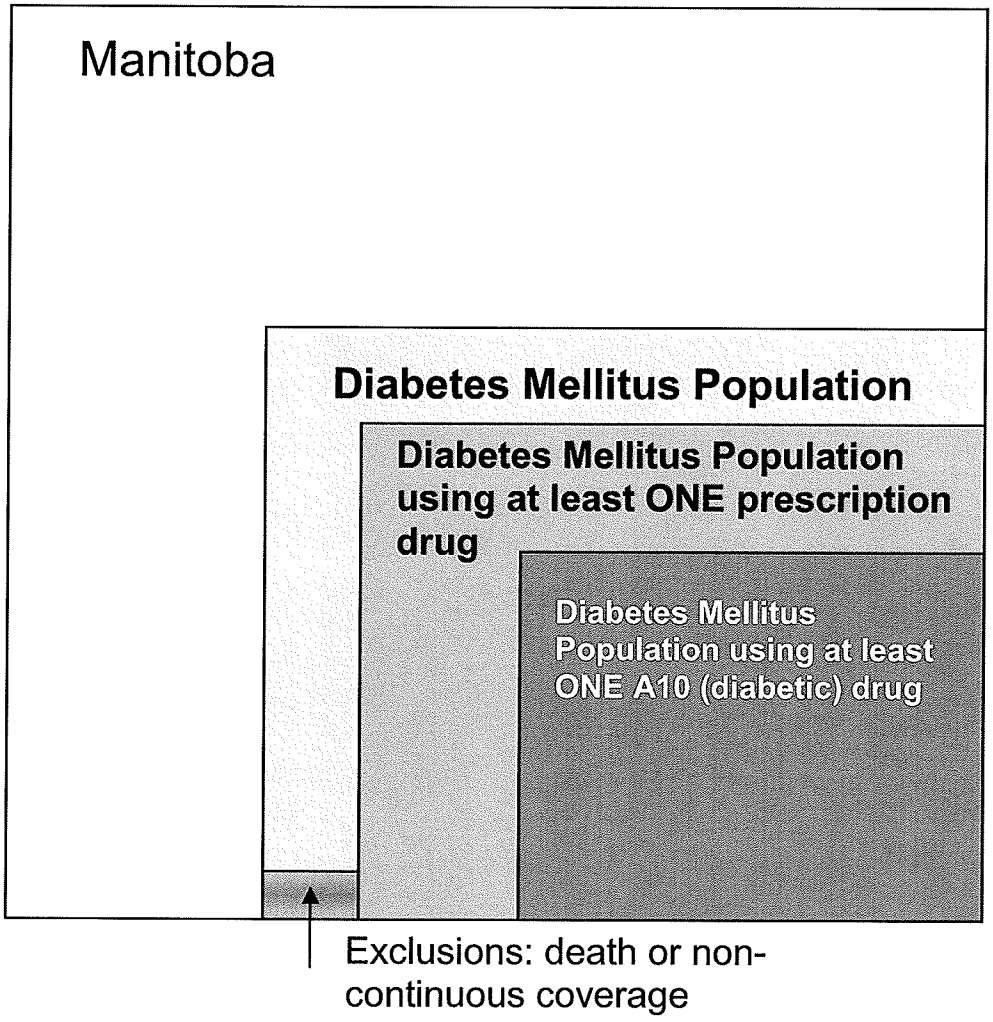
A separate program to identify any DINs missing from the DIN Master file was developed to ensure all possible antidiabetic (ATC category, A10) drugs were included in the analysis. This program merged all A10 drugs in the DIN Master history file with the DIN Master file (which has one record for each DIN that had been submitted to DPIN). The drugs in each file were identified using both ATC and generic or chemical name. The anti-diabetic drugs found in both files were merged and one record for each DIN was retained. These drug products (DINs) were then analyzed and defined daily dose (DDD), a WHO designation for average maintenance dose for the drug's main indication, ATC code, and a variable which allows for DDD calculation called 'str_new' were added to the file. A more detailed discussion of the SAS® strategy used in this study can be found in Appendix B (SAS® program).

The study period (April 1, 1997 to March 31, 2001) was then divided into four fiscal years. Each of the four years of data provided different denominators for describing

Manitoba's diabetic cohort (Figure 4). Each year was analyzed separately using only those cohort members who survived to the end of that respective year:

- April 1, 1997 to March 31, 1998
- April 1, 1998 to March 31, 1999
- April 1, 1999 to March 31, 2000
- April 1, 2000 to March 31, 2001

Figure 4. Denominator Derivation for Diabetic Population, April 1, 1997



* Not drawn to scale

E. Measurement Tools

Calculating population-based rates of access to pharmaceuticals (dispensed at least one pharmaceutical in a year), intensity of use (number of different drugs/defined daily doses), and total expenditures can be done by accessing variables from Manitoba Health datasets. For this project, these variables included: age strata, sex, age group and sex, Adjusted Diagnostic Groupings (ADGs), regional health authority (RHAs both Winnipeg and Non-Winnipeg), the 12 Winnipeg community regions, income quintile (in Winnipeg), and ATC codes for the drugs dispensed to the cohort (Appendix E). The calculated rates of population-based measures of pharmaceutical use can be described using these variables.[7] The anonymity of an individual's data is closely guarded, therefore, rates or tables, as previously stated, are not published when cells have fewer than 20 individuals in a utilization category; this regulation is mandated by MCHP to preserve privacy and confidentiality.

- **Access to care** has historically described the "...actual entry of a given population to the health care delivery system.[59] In this project, 'access' tells us what proportion of the population described as "diabetic" have received at least one A10 drug. Such a measure can help to determine if interventions, such as pharmaceuticals, are distributed on the basis of people's need for them. Inequity exists when one's income or insurance coverage predicts actual access.[59] In this project, access to pharmaceuticals can be determined by calculating the proportion of individuals receiving at least one prescription during the year. In other words, an individual who

had one or more prescription drugs dispensed during the year is counted once, independent of the total number of prescriptions dispensed to that person. The denominator is the 'study population' or the persons with diabetes identified by the algorithm used to define the study cohort. The access rate is calculated per fiscal year and is expressed as a percent of the diabetic 'study population'.[7]

- **Intensity of use**: The indicators of intensity of use are a measure of the 'burden' of pharmaceutical use being carried by the person diagnosed as diabetic. Intensity of use can be defined in a variety of ways. Four common rates are: number of prescriptions dispensed, number of different drugs dispensed, defined daily doses (DDD), and prescribed daily dose (PDD).[7] For this study we will not examine PDD due to limitations of the amount of data required to adequately describe use on a drug by drug basis.

  Number of prescriptions dispensed: This rate is the total number of prescription drug claims dispensed per 'study population' subject and per 'anti-diabetic drug (A10) using population'. The total number of prescription drug claims for A10 drugs is also described for the 'anti-diabetic drug (A10) using population'. This measure can be problematic due to the fact that days of drug supplied of specific anti-diabetic drugs varies from prescription to prescription. However, it does signify the rate at which persons visit pharmacies.

Number of *different drugs* dispensed: 'Different' drugs are defined at the 4th level of the ATC (the chemical/therapeutic/pharmacological subgroup). The rate of number of different drugs, that is all drugs, is reported as dispensed per 'study population' subject and per 'anti-diabetic drug (A10) using population' subject. This rate can be used as a proxy for co-morbidity status.

Defined Daily Dose (DDD): The defined daily dose (DDD) is the "assumed average maintenance dose per day for a drug used for its main indication in adults."[54] When calculated, it gives a rough estimation of the proportion of the population receiving the drug (or a related group of drugs) at the accepted daily dose for the drug (or drug group's) major indication. The DDD standardizes the measurement of drug utilization within and between drug entities and can be used to describe pharmaceutical use across a population particularly burden or amount of use. It must be noted however, that when using DDD two basic assumptions one made. First, the patient is taking all the medication he/she has received, and second, the drug was prescribed for it's major indication at the average maintenance dose.[54] For this project, the following DDD rate is described: the number of anti-diabetic (A10) DDDs used per 'anti-diabetic drug (A10) using population' subject.

- **Cost** of pharmaceuticals is another measure of 'burden' of pharmaceutical use. The metric used in this measure, dollars per subject per year, is an indicator that can also inform on 'equity' of the distribution of pharmaceuticals. Unexplained differences in

costs/subject based on characteristics such as income may indicate that some persons are vulnerable to health policies that may have a deleterious effect on adequate access to pharmaceuticals. In this study, cost is sum of the amount paid either by a government agency and/or the individual for their drug ingredients, professional (dispensing) fee and total prescription costs. The DPIN data include drug ingredient costs in the Pharmacare, the Nursing Home, and the Family Services data files; drug costs are imputed for the data set that is not adjudicated by Pharmacare. Dispensing fees are available from the Pharmacare and Family Services data but are unavailable from the Nursing Home file since there is a set fee per bed per month. Thus, professional fees are imputed for the Nursing Home drug data as well as for the non-adjudicated data set.[7] In this project, costs are expressed (per year) as the total cost of all drugs for each 'study population' subject, total cost of all drugs for each 'anti-diabetic drug (A10) using population' subject and total cost of antidiabetic drugs (A10) for each anti-diabetic drug (A10) using population' subject.

F. Descriptive (Demographic Variables)

The derived, original cohort file per record (= an individual) includes an encrypted PHIN, an indicator of the diabetes criteria met by the individual for inclusion in the cohort, sex and date of birth. Addition demographic data stored in the Repository were added from the other files (e.g., Registry data). These data were linked (added) to the cohort member's record using the encrypted PHIN.

- **Age**

  Age was calculated by subtracting the beginning of the study period from the date of birth; therefore, age was identified as of April 1, 1997 and was fixed throughout the four year study period. Cohort members were placed in one of nine age groups as defined in April 1, 1997 (0-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89 and 90+). By using the age at April 1, 1997 managing age was more efficient. First, the SAS® programming developed allowed a single simple calculation. Second, the cohort age groups stay together and trends over the four years of data are easier to identify.

- **Sex**

  Sex was coded in the original cohort as '1=male' or '2=female'.

- **Adjusted Diagnostic Groupings** (variable name: ADG)

  The Adjusted Diagnostic Groupings (ADG) is a marker for comorbidity status. The ADG files from 1997 were merged to the cohort file and individuals were divided amongst eight categories. Therefore, an ADG group was assigned to each subject at the beginning of the study period and did not change despite possible changes in health status between 1997 and 2001.

  The ADGs are based on the John Hopkins ACG Case-Mix System software package which uses ICD-9 codes to categorize diagnosis for individuals in a population.[60] Essentially there are 34 groupings of medical diagnoses meaning that each grouping

may involve multiple ICD-9 diagnoses. However, a person can be assigned to one of the ADG's once only despite the possibility of qualifying for that group more than once. The total number of the 34 ADGs that a person can qualify for determines the category used in the SAS® program designed for this study. Table 6 provides the following is the variable assignment used for ADGs in this study. The categories reported on for this thesis includes: non-user, 1, 2 to 3, 4 to 5, 6 to 9 and 10+. Therefore, if someone qualifies for none of the 34 ADGs then they will have an assignment of 'non-user', whereas if another person has eight ADGs then they are placed in the group who have six to nine ADGs. These categories provide a method of grouping together people according to their health status, therefore, any trends with regard to the health of the cohort can be examined.

Table 6. ACG Groupings

Number of 34 Categories cohort member qualifies for	Acg_group assignment
(.) no value in acg_group field	Missing
None	Non-user
1	1
2	2 to 3
3	2 to 3
4	4 to 5
5	4 to 5
6	6 to 9
7	6 to 9
8	6 to 9
9	6 to 9
10	10+
Greater than 10	10+
Pregnant	Preg

- **Winnipeg Area** (variable name: WPGAR)

  Residents of Winnipeg were assigned to one of 12 geographic locations determined by postal codes from the registry data (a detailed assignment map can be found in Appendix C).

- **Region** (variable name: RHA)

  Residents of Manitoba were assigned to one of 12 Regional Health Authorities (RHAs) based on their postal codes in the registry data. For reporting purposes, these RHAs were combined into four (4) Manitoba Regions to reflect the geographic location of the cohort members (Table 7; detailed map in Appendix D).

Table 7. Manitoba Regional Groupings

Geographic Region Designation	RHA
Urban	Winnipeg (K), Brandon(G)
South Rural	South Eastman(BS), Central(A), Assiniboine(GA)
Middle Rural	Parkland(E), Interlake(C), North Eastman(BN)
North Rural	Norman(D), Burntwood(FC), Churchill(FC)

- **Income Quintile** (variable names : INCQ)

  Income quintiles are geographic area measures of socioeconomic status derived from Canadian census data. Census-derived household income data, aggregated to the geographic unit of the enumeration area, were used to rank neighborhoods by average household income.[61] The top 20% of the population by mean neighborhood household income is identified as quintile 5, and the poorest 20% is defined as quintile 1.

For urban areas, U1 to U5 (from poorest 20th percentile to the wealthiest 20th percentile, respectively), the census enumeration (EA) data is linked via the MCHP postal code conversion file. It is possible for the EA data to be 0, in these cases the values are re-set to missing so they do not contribute the mean average income assigned to the postal code. Previous MCHP studies found that ranking rural populations by postal code was unsatisfactory because rural postal codes often include a large geographical area, however, steps have been taken to try to provide a weighted mean using municipality codes. A detailed description of ranking can be found in the MCHP internal website under 'Income Quintile' in the Concept Dictionary (http://www.cpe.umanitoba.ca/mchp/concept/concept.frame.shtml). It is important to note at this point that First Nations people with an urban postal code will be assigned an income quintile based on the postal code. All other First Nations people will be assigned an income quintile on the basis of their home reserve, regardless of their actual residence. The census may define populations living on the periphery of Winnipeg as rural purely based on a density rule; an example of this is East St. Paul (MCHP Concept Dictionary) which is more closely associated as Winnipeg-based residency.

G. Analysis Plan

The following restates the original research questions posed on page 31 and then describes the rates that were calculated to answer the question posed. The reader is reminded that the rates give us measures of drug utilization that will tell us if pharmaceutical use is responsive to differential health needs across the population and will help us to frame the information and knowledge needs for obtaining better health outcomes for persons with diabetes.

The following analysis plan includes the use of descriptive statistics for describing patterns of pharmaceutical use by persons with diabetes in Manitoba. The intent of the study was not to demonstrate statistical differences in measures of drug use within the population. Instead, the basis for analysis was to be first descriptive (Figure 2) and to allow for the exploration of methods to accurately summarize and report the data according to different population-based of rates use such as access, intensity, and cost. Another intent of this analysis was to determine if these rates could be reported by previously unavailable demographic descriptors such as geographic region, income quintile and a morbidity indicator in addition to the more commonly used descriptors of age and sex. The results of this study are to provide both an ability to efficiently 'target' areas to which assessment and testing could be directed and begin the work of 'development of descriptive indicators related to anti-diabetic drug utilization'—the second level of the pyramid (Figure 2).

Research Question #1:

Can the patterns of pharmacologic use for persons with diabetes in the Manitoba population be described by access (that is, the deployment of pharmacologic entities and, specifically, anti-diabetic pharmacotherapy) and measures of intensity of use (number of prescriptions claims, number of different drugs used and number of defined daily doses used per day and per year)? How are these patterns of use illustrated by the population's:

a. Age
b. Age/Sex
c. Sex
d. Income Quintile
e. Region of Residence
f. Comorbidity Status

Access Rate

The number of the diabetic 'study population' subjects (`cohortpop`) who have received at least one prescription claim for an A10 drug per fiscal year (1997-98, 1998-99, 1999-2000, 2000-01).

$$\textbf{Access} = \frac{\text{Number of persons on at least one A10 drug}}{\text{diabetes 'study' population}} \quad \frac{\texttt{DBdrugtreat}}{\texttt{cohortpop}}$$

Intensity of Use Rates

Prescription Claim rates: Intensity of use is described by the total number of prescription claims (dispensations) per year per subject. Three different claims rates are calculated:

1. `RxINTcohort` is the rate describing the number of prescription claims for any class of drug dispensed per diabetic 'study' population subject per fiscal year. In a population

of persons designated as "diabetic" it helps us to understand the burden of pharmaceutical use given a diagnosis:

$$\textbf{Rx claims per= diabetic} \quad \frac{\text{Number of prescription claims for any drug}}{\text{diabetic 'study' population subject}} \quad \frac{\textbf{totcount}}{\textbf{cohortpop}}$$

2. RxINTA10alldrug is the rate describing the number of prescription claims for any class of drugs per 'diabetic drug (A10) using population' subject per fiscal year. If one assumes that the 'A10 taking diabetic' may be sicker than the non-A10 taking diabetic, then this rate will inform on the total burden to A10 users of taking anti-diabetic and other drugs.

$$\textbf{Rx claims per = diabetic drug (A10) user} \quad \frac{\text{Number of prescription claims for any drug}}{\text{'diabetic drug (A10) using population' subject}} \quad \frac{\textbf{atc4totcount}}{\textbf{DBdrugtreat}}$$

3. RxINTA10A10 is the rate describing the number of prescription claims for A10 drugs only per 'anti-diabetic drug (A10) using population' subject per fiscal year.

$$\textbf{Diabetic drug (A10)= claims per A10 user} \quad \frac{\text{Number of prescription claims for A10 drugs}}{\text{'diabetic drug (A10) using population' subject}} \quad \frac{\textbf{A10\_count}}{\textbf{DBdrugtreat}}$$

Number of Different Drug Class rates: Intensity of use described by the total number of different drugs (defined at the 4th level of the ATC classification) dispensed per year per subject. Two different rates for different drug classes are calculated:

1. DCINTA10pop is the rate describing the number of different drug classes (all drugs) per diabetic 'study population' subject per fiscal year.

# different drugs = Per diabetic	Number of ATC 4th level drug claims (all drugs) / Diabetic 'study population' subject	**atc4_count / cohortpop**

2. DCINTA10A10 is the rate describing the number of different drug classes (all drugs) per 'anti-diabetic drug (A10) using population' subject per fiscal year.

# different drugs = per diabetic drug (A10) user	Number of ATC 4th level drug claims (all drugs) / 'diabetic drug (A10) using population' subject	**atc4_count / DBdrugtreat**

Defined Daily Dose rates: Intensity of use described by the total number of defined daily doses[f] per year per subject.

1. DDDINTall is a rate describing the number of DDDs for any A10 drug per 'anti-diabetic drug (A10) using population subject per fiscal year. Theoretically, if a subject is taking one anti-diabetic drug per year and once per day at its DDD dose, then the DDD should be equal to (or close) 365.

Total # DDDs per diabetic	Total number of DDDs for any A10 drugs / 'diabetic drug (A10) using population' subject	**DDDtotA10 / DBdrugtreat**

[f] The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults (WHO, 2004).

Research Question #2

What are the costs of pharmacologic use for diabetes in the Manitoba population and how are costs described by the population's:

a. Age
b. Age/Sex
c. Sex
d. Income Quintile
e. Region of Residence
f. Comorbidity Status

Cost Rates

Costs are expressed (per fiscal year) as the total cost of all drugs for each 'study population' subject, total cost of all drugs for each 'anti-diabetic drug (A10) using population' subject and total cost of antidiabetic drugs (A10) for each anti-diabetic drug (A10) using population' subject.

COSTPOP is the total cost per year of all drugs dispensed per cohort member per year.

$$\textbf{Cost of all dispensed drugs= per diabetic per year} = \frac{\text{Total cost of all drugs dispensed}}{\text{Diabetic 'study population' subject}} \quad \frac{\texttt{Totcost}}{\texttt{cohortpop}}$$

COSTPOPA10all is the total cost per year of all drugs dispensed per A10 user per year.

$$\textbf{Cost of all dispensed drugs= per A10 user} = \frac{\text{Total cost of all drugs dispensed}}{\text{'diabetic drug (A10) using population' subject}} \quad \frac{\texttt{TotcostA10}}{\texttt{DBdrugtreat}}$$

COSTPOPA10A10 is the total cost per year of all A10 drugs dispensed per A10 user per year.

$$\textbf{Cost of all A-10 dispensed drugs= per A10 user} = \frac{\text{Total cost of all drugs dispensed}}{\text{'diabetic drug (A10) using population' subject}} \quad \frac{\texttt{totdiabcost}}{\texttt{DBdrugtreat}}$$

The following chapter reports on the results of the analysis for Research Question #1 and Research Question #2. If one refers back to Figure 3. Analytical Orientation (page 34), it is possible to report 120 different analyses over four years (480 tables). As a result, a complete description of the study populations characteristics are outlined, followed by a sampling of the 480 results tables according to the rates outlined under G. Analysis Plan.

CHAPTER FOUR

Results

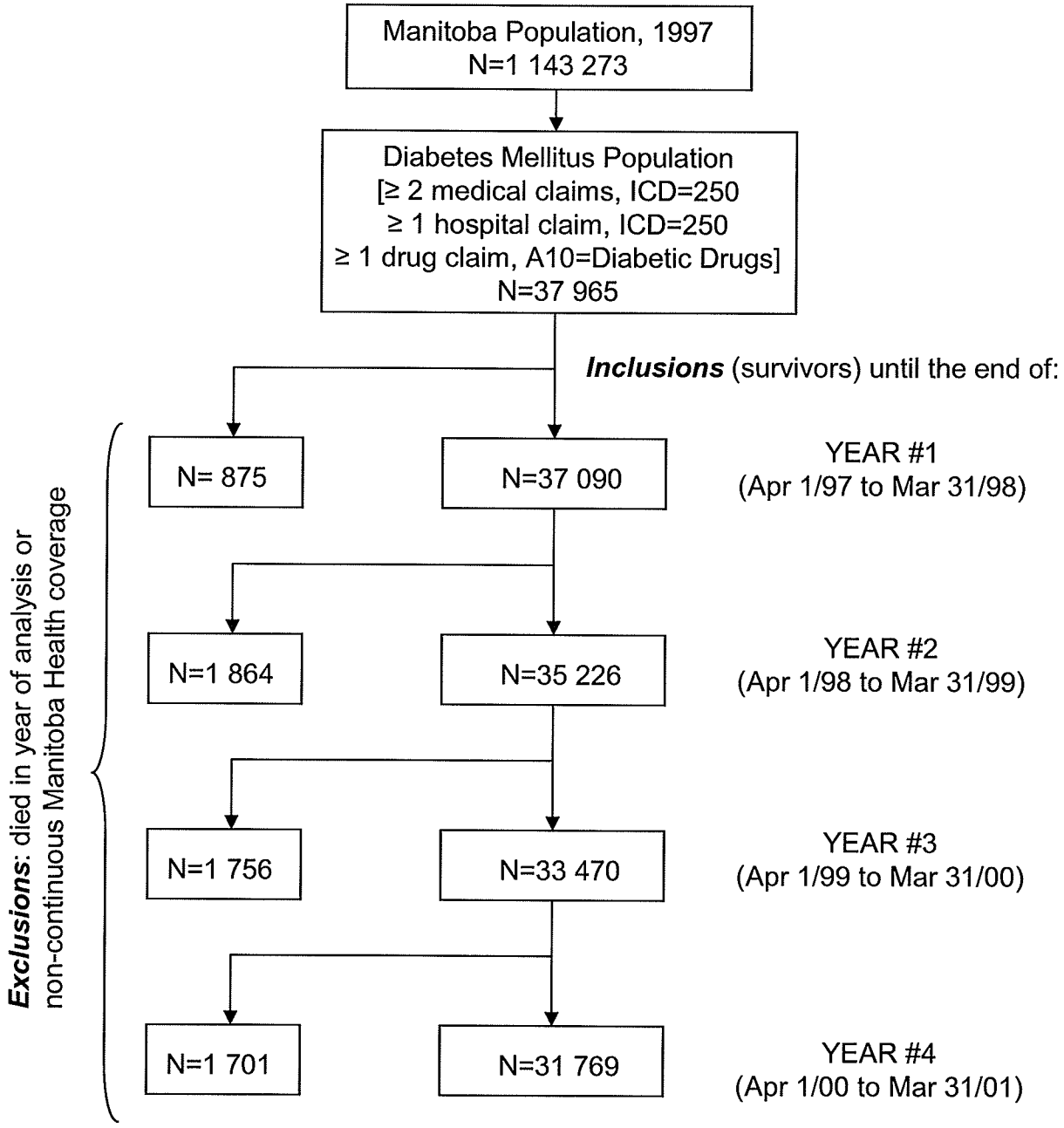
A. Cohort Characteristics

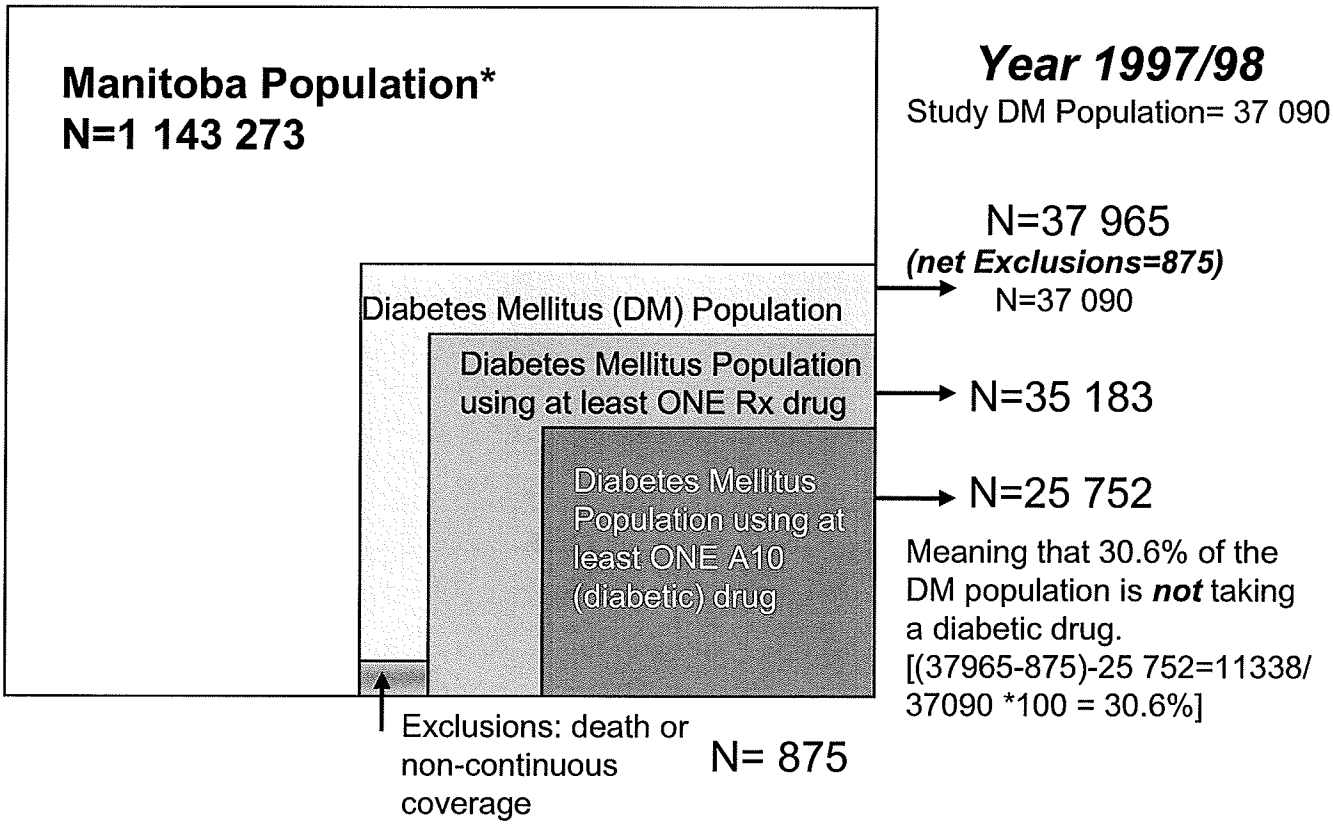
The initial cohort numbered 37,965 diabetic persons of all ages residing in Manitoba as of April 1st 1996. This population represented a three point four percent prevalence rate according to the case definition for a diabetic that was used. As the original subjects' pharmaceutical use was followed in the four paneled years, there was depletion of the original cohort size due to death and emigration from Manitoba. Figure 5 demonstrates the sample for each of the four years of analysis.

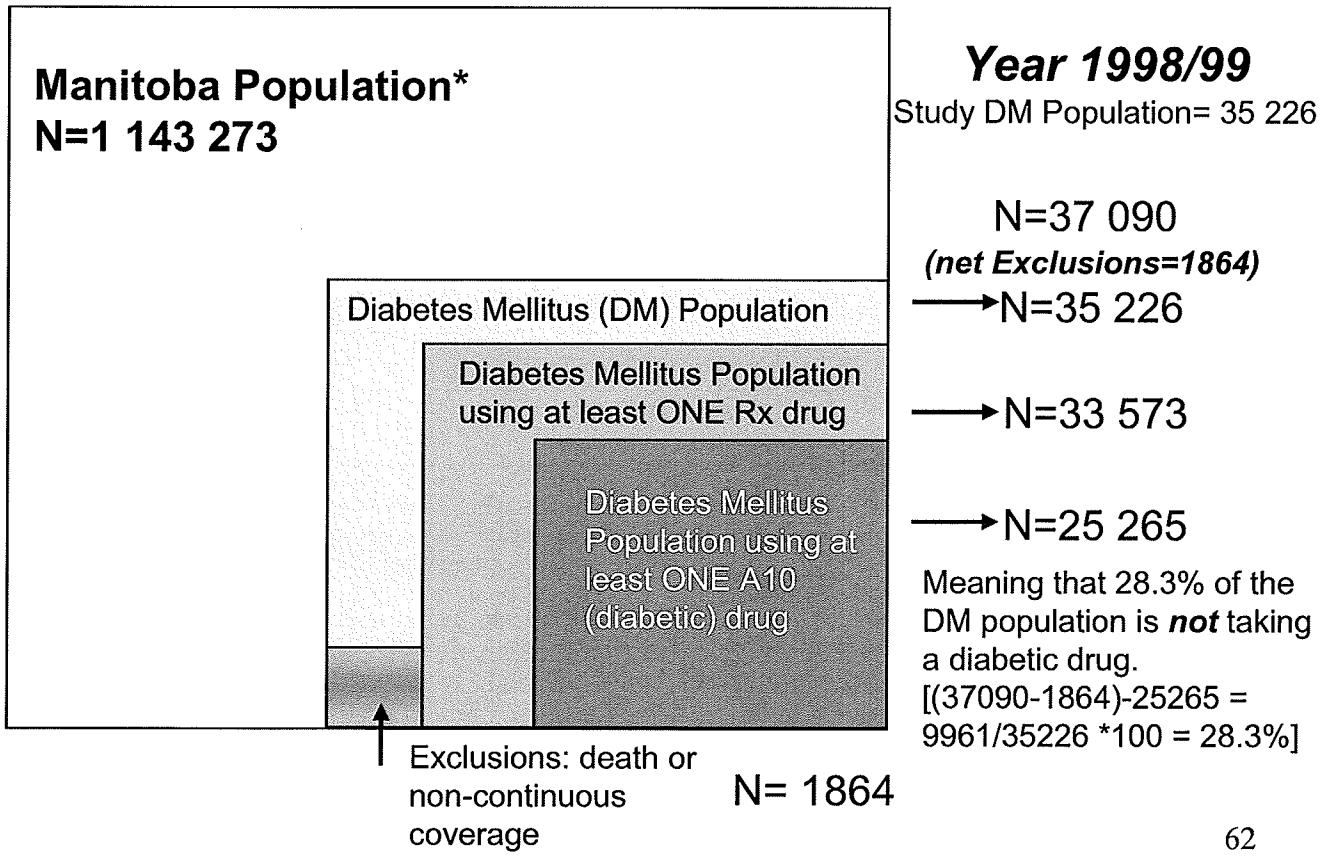
Of the 37,965 persons with diabetes identified for the 1997/98 measures, 876 were excluded from the analysis leaving 37,090. A further 1,907 diabetics were not using any prescription drugs, and of the remaining 35,183 diabetics, 9,431 were not dispensed any anti-diabetic (A10) drugs. Figures 6 and 7 account for the cohort's two populations used to calculate rates of pharmaceutical use: (1) persons with diabetes according to our definition, and (2) persons with diabetes using at least one antidiabetic (A10) drug.

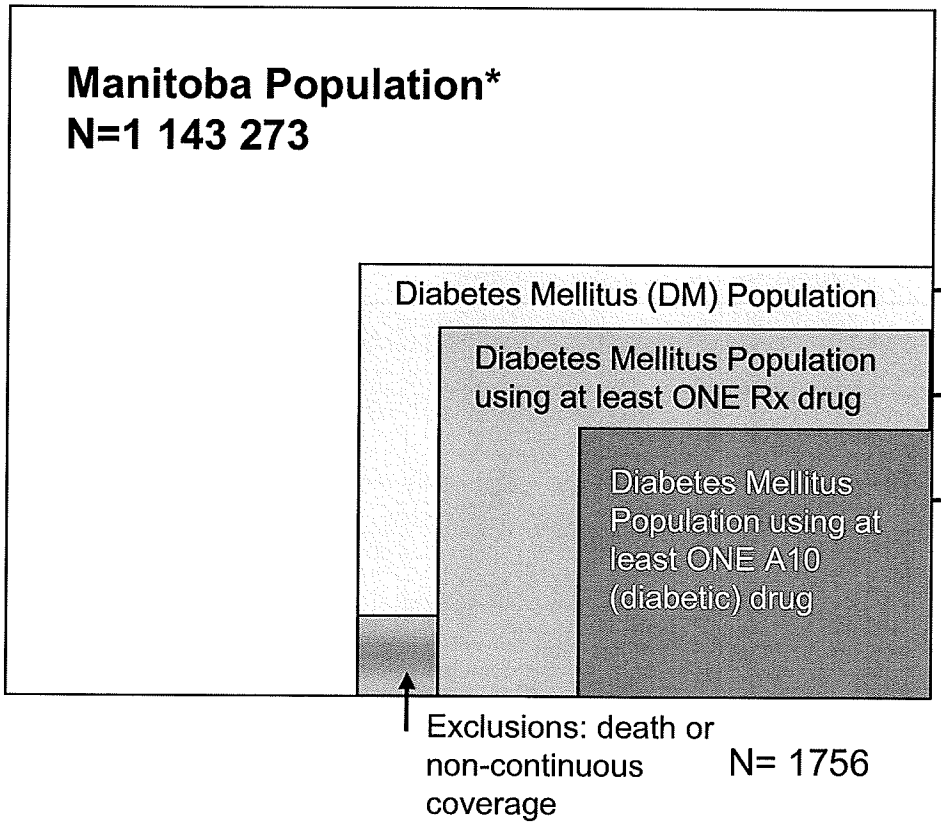
Figure 8 and Table 8 illustrate the origins of the study subjects according to the inclusion criteria (N = 37,965).

Figure 5. Cohort Derivation




Manitoba Population*
N=1 143 273
Year 1997/98
Study DM Population= 37 090
N=37 965
(net Exclusions=875)
N=37 090
Diabetes Mellitus (DM) Population
Diabetes Mellitus Population using at least ONE Rx drug
N=35 183
Diabetes Mellitus Population using at least ONE A10 (diabetic) drug
N=25 752
Meaning that 30.6% of the DM population is not taking a diabetic drug.
[(37965-875)-25 752=11338/ 37090 *100 = 30.6%]
Exclusions: death or non-continuous coverage
N= 875


Manitoba Population*
N=1 143 273
Year 1998/99
Study DM Population= 35 226
N=37 090
(net Exclusions=1864)
N=35 226
Diabetes Mellitus (DM) Population
Diabetes Mellitus Population using at least ONE Rx drug
N=33 573
Diabetes Mellitus Population using at least ONE A10 (diabetic) drug
N=25 265
Meaning that 28.3% of the DM population is not taking a diabetic drug.
[(37090-1864)-25265 = 9961/35226 *100 = 28.3%]
Exclusions: death or non-continuous coverage
N= 1864



Year 1999/00

Study DM Population= 33 470

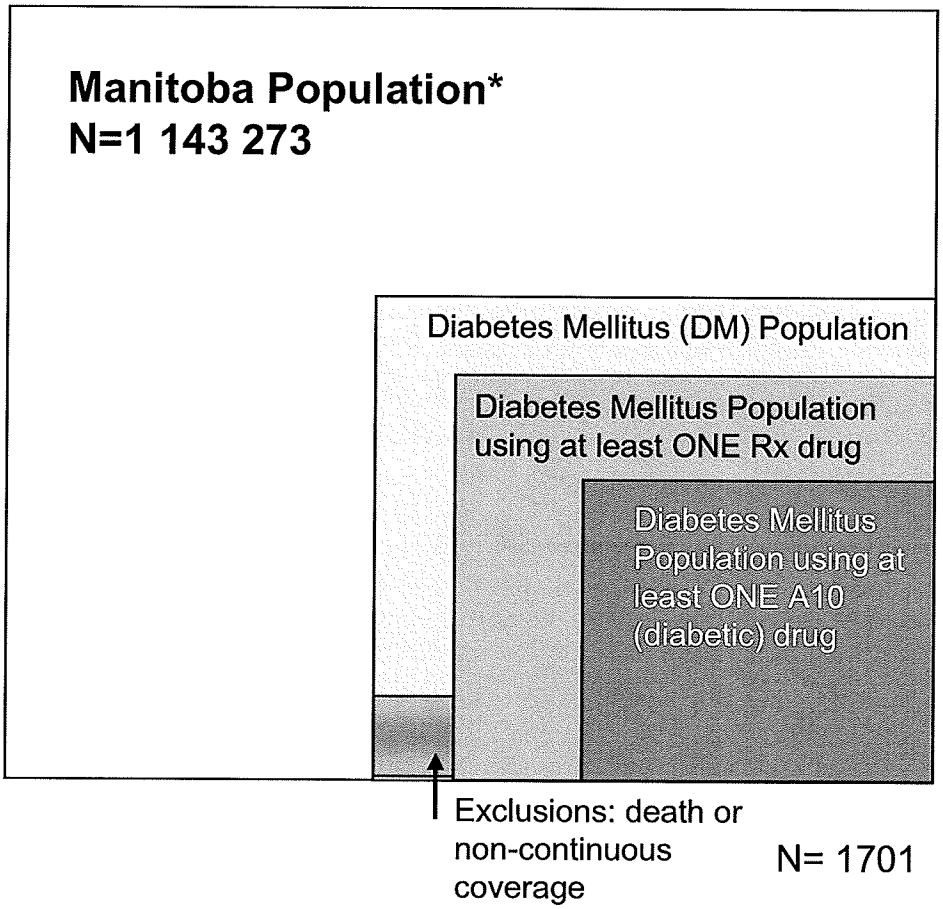
N=35 226
(net Exclusions=1756)

→ N=33 470

→ N=31 964

→ N=24 682

Meaning that 26.3% of the DM population is ***not*** taking a diabetic drug.
[(35226-1701)-24682=8788/ 33470 *100 = 26.3%]



Year 2000/01

Study DM Population= 31 769

N=33 470
(net Exclusions=1701)

→ N=31 769

→ N=30 431

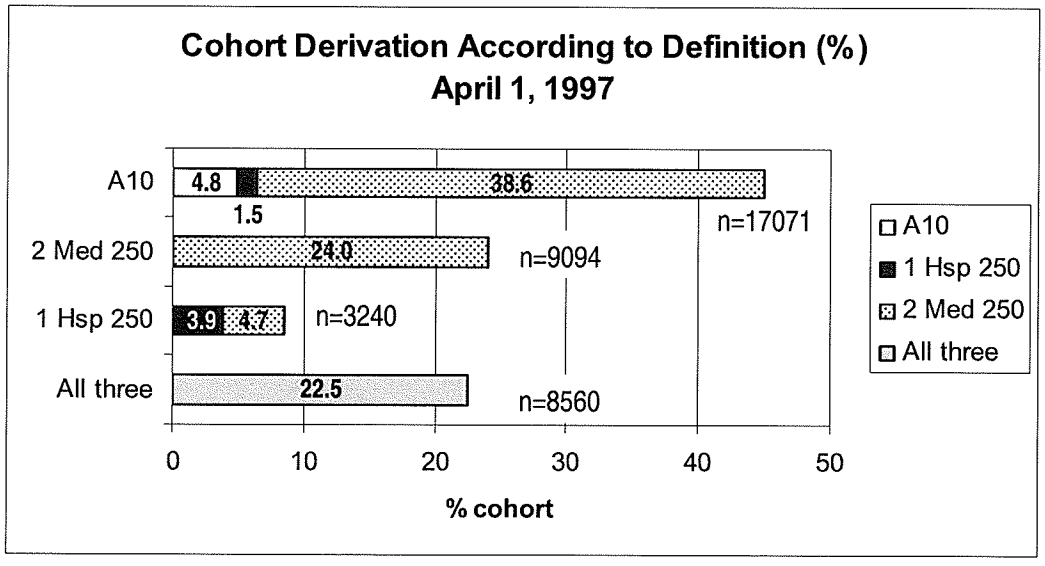
→ N=24 030

Meaning that 24.4% of the DM population is ***not*** taking a diabetic drug.
[(33470-1701)-24030=7739/ 31769 *100 = 24.4%]

Table 8. Cohort derivation according to diabetes definition

Defined as 'diabetic' by having:	N	%
≥ 1 Hospitalization ICD9 = 250 alone	1471	3.9%
≥ 2 Medical claims ICD9 = 250 alone	9094	24.0%
≥ 1 claim for an antidiabetic drug (A10) alone	1827	4.8%
≥ 1 Hospitalization ICD9 = 250 AND ≥ 2 Medical claims ICD9 = 250	1769	4.7%
≥ 1 Hospitalization ICD9 = 250 AND ≥ 1 claim for an antidiabetic drug (A10)	579	1.5%
≥ 2 Medical claims ICD9 = 250 AND ≥ 1 claim for an antidiabetic drug (A10)	14665	38.6%
Met ALL criteria: ≥ 1 Hospitalization ICD9 = 250 ≥ 2 Medical claims ICD9 = 250 AND ≥ 1 claim for an antidiabetic drug (A10)	8560	22.5%
TOTAL	37965	100.0%

Figure 8. Percent of cohort derived according to diabetes definition (100%=37965), 1997



Tables 9 and 10 and Figures 9 and 10 illustrate the cohort's characteristics. Data are presented in contrast to the general Manitoba population (1997).

Table 9. Comparison of Manitoba's AGE Category Distribution to the Diabetic Study's AGE Category Distribution, April 1, 1997

Age category	Manitoba Population N=1143273		Diabetic Study Population N=37965		Distribution of Diabetes by Manitoba Age Category
		%		%	%
0-19	325918	28.5	597	1.6	0.18
20-29	154994	13.6	1031	2.7	0.67
30-39	180800	15.8	2531	6.7	1.40
40-49	166719	14.6	5049	13.3	3.03
50-59	115182	10.1	3705	9.8	3.22
60-69	86313	7.5	9029	23.8	10.46
70-79	71878	6.3	8491	22.4	11.81
80-89	35169	3.1	3526	9.3	10.03
90+	6300	0.6	406	1.1	6.44

Figure 9.

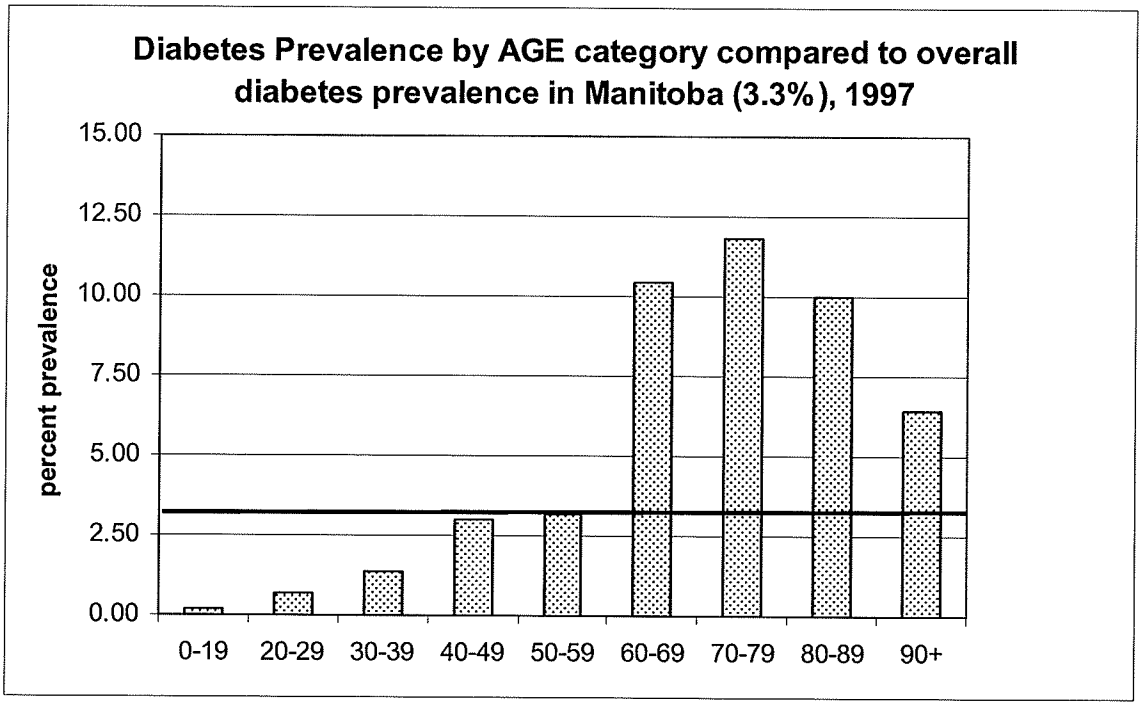


Table 10. Comparison of Manitoba's AGE & SEX Categories Distribution to the Diabetic Study's AGE & SEX Category Distribution, April 1, 1997

AGE category	Female				Male			
	Manitoba Population		Diabetic Study Population		Manitoba Population		Diabetic Study Population	
	N=579780	%	N=19309	%	N=563493	%	N=18656	%
0-19	158823	27.4	306	1.6	167095	29.7	291	1.6
20-29	77135	13.3	601	3.1	77859	13.8	430	2.3
30-39	90227	15.6	1397	7.2	90573	16.1	1134	6.1
40-49	83395	14.4	2424	12.6	83324	14.8	2625	14.1
50-59	57682	9.9	3427	17.7	57500	10.2	3878	20.8
60-69	44503	7.7	4318	22.4	41810	7.4	4716	25.3
70-79	41062	7.1	4512	23.4	30816	5.5	3979	21.3
80-89	22336	3.9	2050	10.6	12833	2.3	1476	7.9
90+	4617	0.8	279	1.4	1683	0.3	127	0.7

Figure 10.

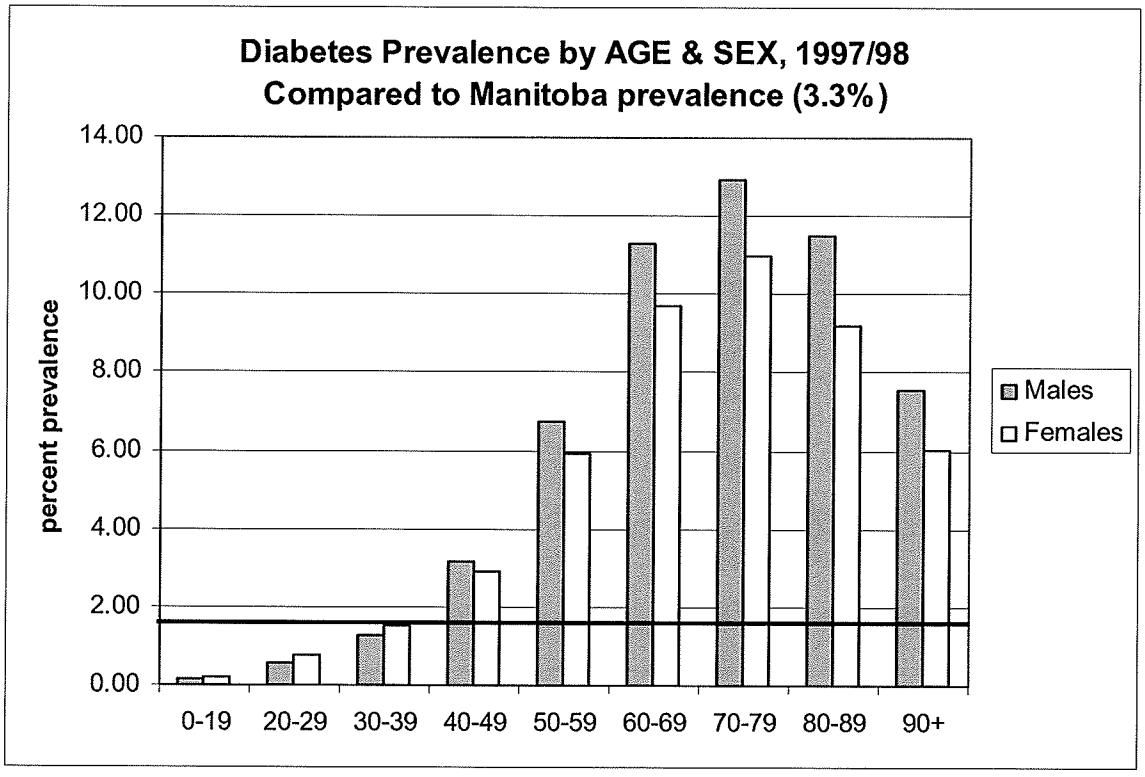
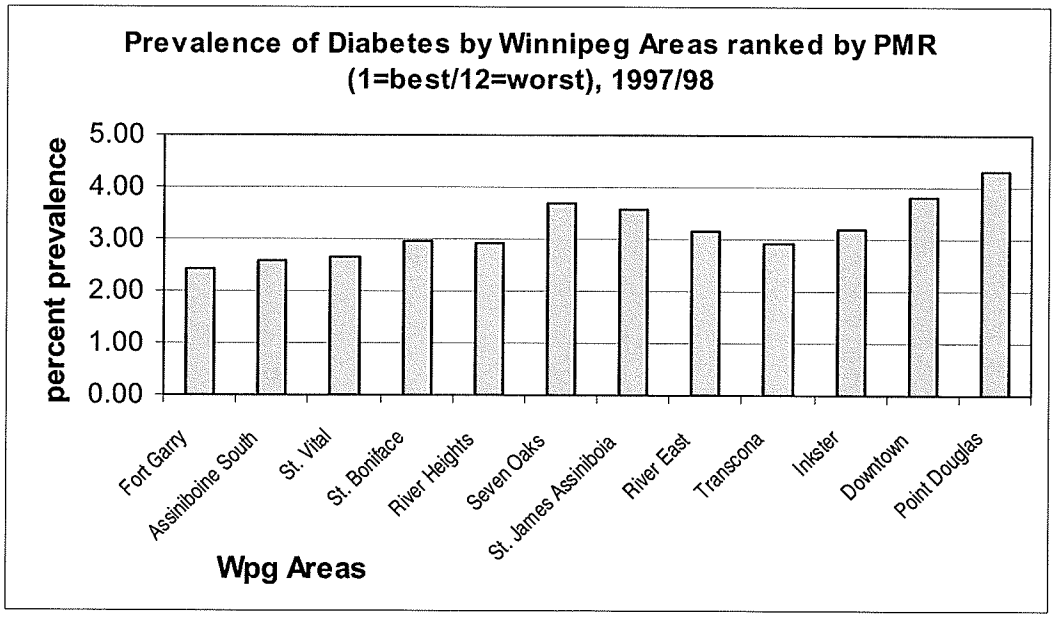


Table 11. Distribution of Diabetic Study population according to Winnipeg areas ordered by increasing premature mortality rate[g] (e.g., Point Douglas has the highest PMR in the City of Winnipeg), 1997

Winnipeg Community Areas *[ranked from lowest to highest Premature Mortality Rate (PMR) neighborhood]*	**Winnipeg Population** N=646561	%	**Diabetic Study Population** N=20663	%	**Distribution of Diabetes Population (Percent Prevalence)**
Fort Garry (03)	60417	9.3	1468	7.1	2.43
Assiniboine South (02)	36016	5.6	923	4.5	2.56
St. Vital (04)	60653	9.4	1614	7.8	2.66
St. Boniface (05)	45371	7.0	1339	6.5	2.95
River Heights (12)	56773	8.8	1667	8.1	2.94
Seven Oaks (08)	56885	8.8	2099	10.2	3.69
St. James Assiniboia (01)	60397	9.3	2159	10.4	3.57
River East (07)	90485	14.0	2839	13.7	3.14
Transcona (06)	33504	5.2	975	4.7	2.91
Inkster (09)	31350	4.8	1004	4.9	3.20
Downtown (11)	73940	11.4	2821	13.7	3.82
Point Douglas (10)	40770	6.3	1755	8.5	4.30

Figure 11.



[g] Premature mortality refers to deaths occurring among persons under 75 years of age and has been suggested by some health researchers as the best single indicator of health status and need for health care. {Charlton J, Hartley R, Silver R, Holland W. Geographical variation in mortality from conditions amenable to medical intervention in England and Wales. Lancet 1983; 1(8326 Pt 1):691-696. ; McGinnis JM, Richmond JB, Brandt En Jr, Windom RE and Mason JO. Health progress in the United States: results of the 1990 Objectives for the Nation. JAMA 1992; 268(18): 2545-52}

Table 12. Distribution of Diabetic Study population according to urban/rural geographic areas in Manitoba, 1997

	Manitoba Population		Diabetes Study Population		Distribution of Diabetes Population by geographic region
	N=1143273	%	N=37965	%	
Middle Rural	157521	13.8	6241	16.4	3.96
North Rural	71392	6.2	2809	7.4	3.93
South Rural	220576	19.3	6829	18.0	3.10
Urban (Winnipeg & Brandon)	693784	60.7	22086	58.2	3.18
Manitoba	1143273	100.0	37965	100.0	3.32

χ^2=103.53 (df=3), p<0.00001

Figure 12.

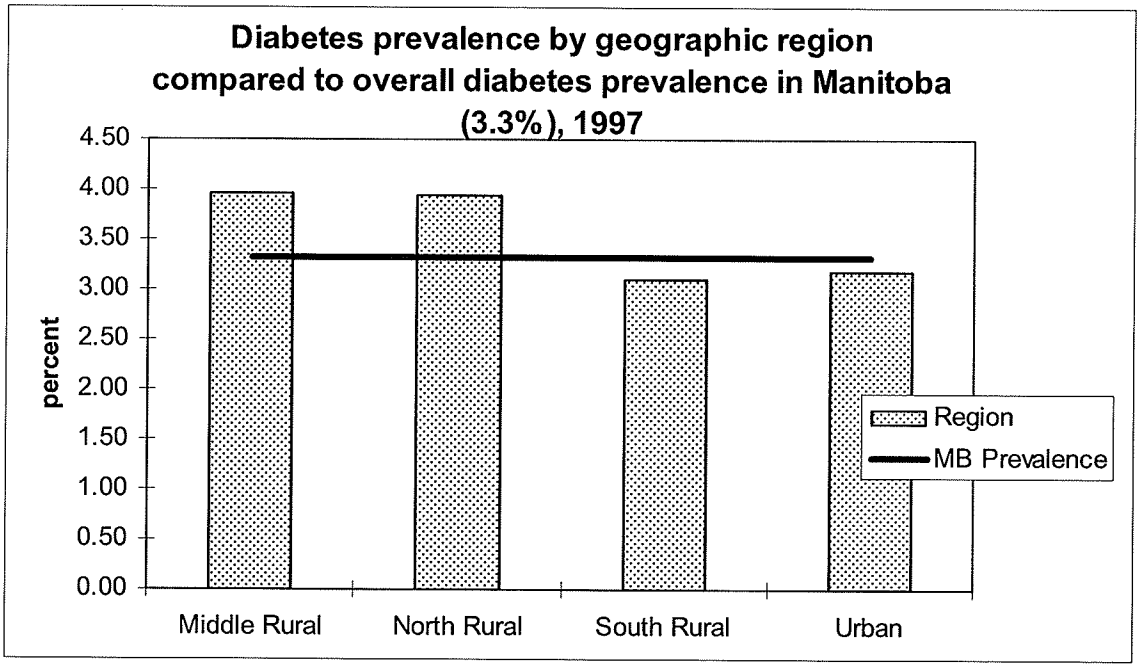


Table 13. Comparison of Manitoba's ADG Distribution to the Diabetic Study's ADG Category Distribution, April 1, 1997

ADG Categories	Manitoba Population N=1143273	%	Diabetes Study Population N=37965	%	Distribution of Diabetes Population by ADG Category
non-user	215119	18.8	1665	4.4	0.77
1	581060	50.8	9915	26.1	1.71
2 to 3	121540	10.6	8293	21.8	6.82
4 to 5	97427	8.5	7826	20.6	8.03
6 to 9	68754	6.0	7688	20.3	11.18
10+	10849	0.9	1793	4.7	16.53
missing	15380	1.3	537	1.4	3.49

Figure 13.

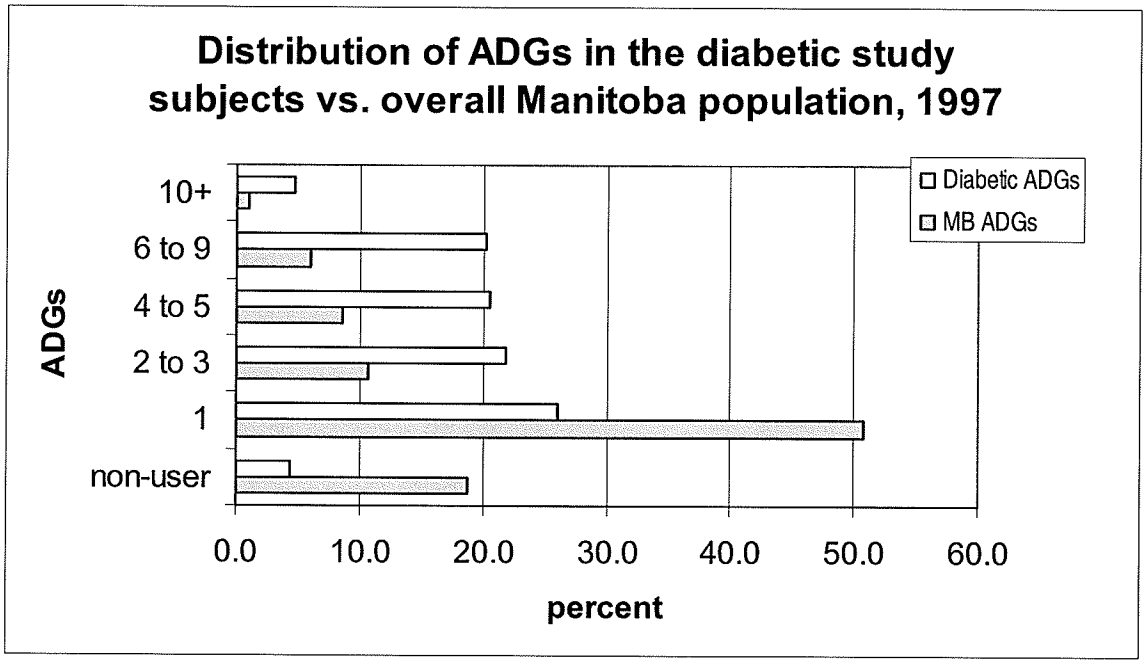
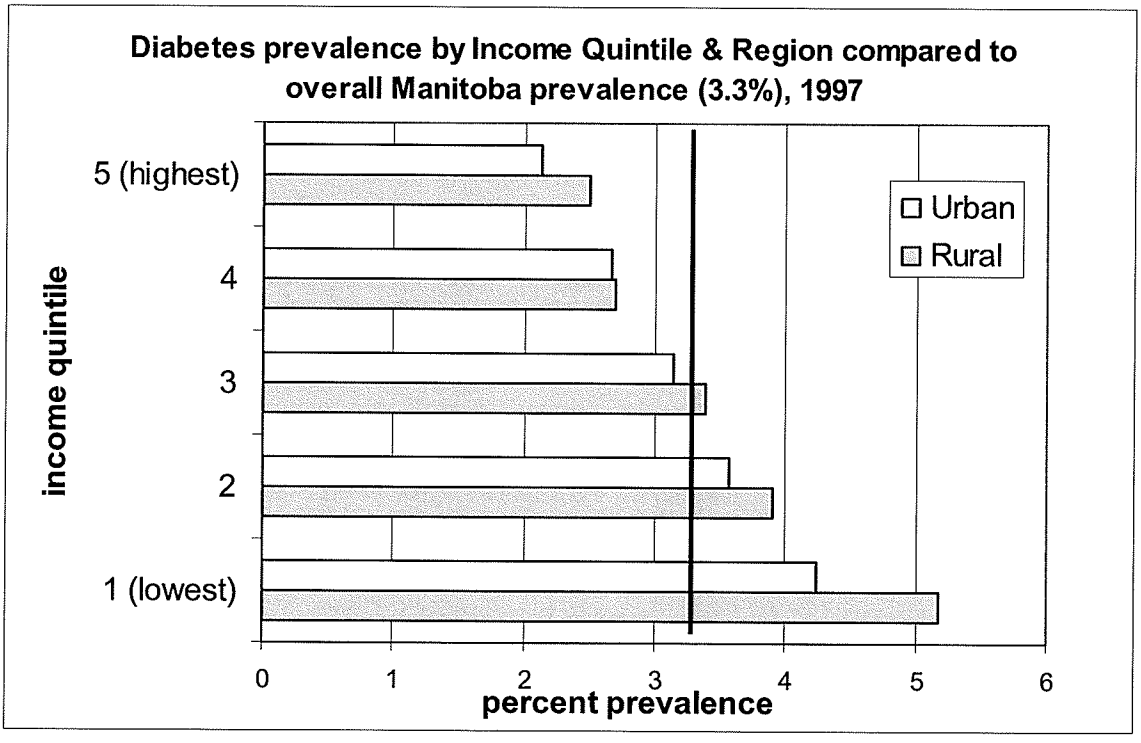


Table 14. Distribution of Diabetic Study population according to urban/rural income quintiles in Manitoba, 1997

Income Quintile (rural & urban)	Manitoba Population N=1143273	%	Diabetes Study Population N=37965	%	Distribution of Diabetes Population by Income Quintile
R1 (lowest)	89035	19.9	4610	29.2	5.18
R2	88304	19.7	3441	21.8	3.90
R3	90509	20.2	3056	19.4	3.38
R4	87947	19.7	2372	15.0	2.70
R5 (highest)	91379	20.4	2283	14.5	2.50
TOT Rural	447174		15762		
*U1 (lowest)	134828	19.7	5707	26.6	4.23
U2	136481	20.0	4858	22.7	3.56
U3	136439	20.0	4273	19.9	3.13
U4	137483	20.1	3655	17.1	2.66
*U5 (highest)	137974	20.2	2942	13.7	2.13
TOT Urban	683205		21435		
Not Found	12941	1.1	768	2.0	

Figure 14.



B. Missing Data

A very small proportion of the cohort were found to have missing descriptive variables. Table 15 outlines the two demographic variables with missing values: ACGs and income quintile.

Table 15. Number of Diabetics in Cohort with Missing Variables

	ACG	INCQ	Region	DBdrugtreat	Cohortpop
1997/98	339 (1.3%)	673 (3.0%)	0	25752	37090
1998/99	265 (1.0%)	529 (2.1%)	0	25265	35226
1999/00	231 (0.9%)	427 (1.7%)	0	24692	33470
2000/01	197 (0.8%)	358 (1.5%)	0	24030	31769

Table 16 outlines how many claims were involved in the calculation of rates for each study year. Although as many as 13.5% of claims were missing a corresponding Anatomical-Therapeutic-Chemical (ATC) code, the 'type' of drug claim could still be identified through the drug identification number's (DIN) generic product name.

Table 16. Claim Totals

	1997/98	1998/99	1999/00	2000/01
CLAIMS ALL DRUGS (cohortpop)	1202308	1235849	1287407	1356632
CLAIMS ALLDRUGS (DBdrugreat)	999523	1042390	1100117	1176087
MISSING ATC CODES	162327 (13.5%)	165609 (13.4%)	163967 (12.7%)	177737 (13.1%)
CLAIMS A10 DRUGS	260 215	269234	276504	289692

C. Considerations for Reporting Data

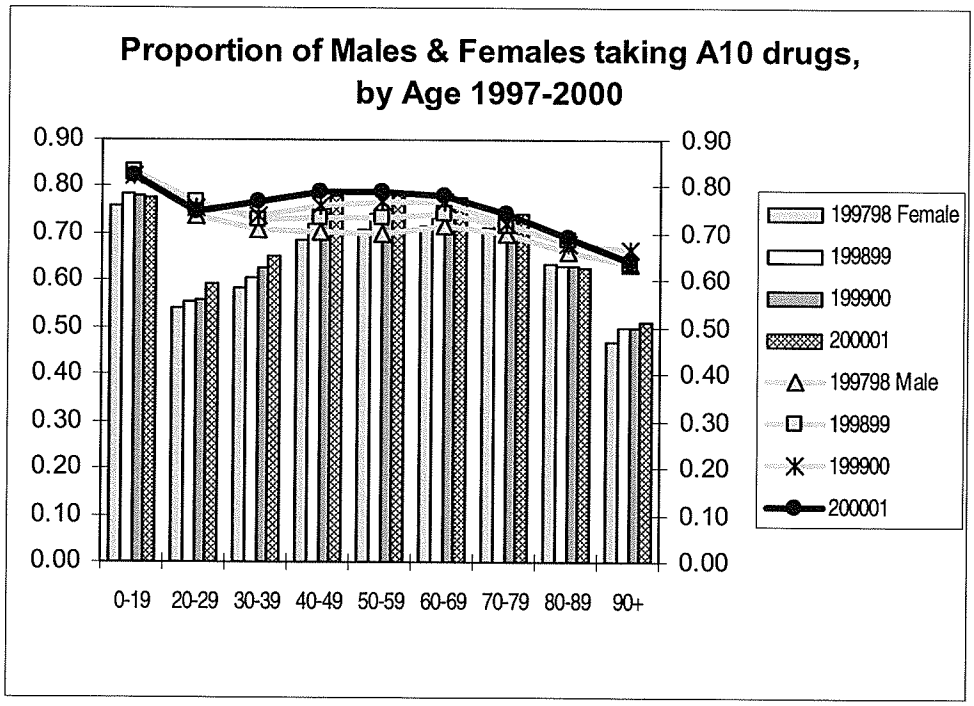
Figure 3 (p.34) demonstrates the wide number of combinations and permutations of rates that could be reported. The wealth of data resulting from this study translates into over 100 separate tables for each year, demonstrating the various demographic variables, cohort groupings, and rate/cost calculations. It would be impossible to report on all findings. The strategy chosen in reporting the data was to provide data and/or accompanying figures for one consistent descriptor of the cohort throughout the results. The age/sex descriptor was chosen, in part, because it is the most commonly used demographic in population health research. Additional figures, demonstrating the use of other demographic descriptors, were chosen to provide examples of the large volume of data gathered for this study. Consideration was made to demonstrate the hypothesis generating power of this descriptive analysis when determining which data were to be presented in the results. In other words, an effort was made to present results that may provide insight into the direction of possible future research.

In following this section, the reader is reminded that none of the differences observed have been determined to be truly statistically different, as this was not the intent of the study. The reporting style used to describe drug use between men and women uses the term "difference" only because the measures were calculated as the rate of one sex 'subtracted' from the other thus providing the terminology 'difference'. Figures were used throughout the results to provide a visual description of the cohort and to demonstrate the power of descriptive data when being used as 'hypothesis generating'.

D. Access Rates

Access for each year of data and for each demographic group was calculated as the proportion of the diabetic 'study population' subjects who had received at least one prescription claim for an A10 drug during each fiscal year of analysis. In the 1997/98 data the overall access to any drug by any member of the cohort was 69%. By the last year of study data.(2000/01) it was 76% . Access for males and females in the first year of the study was 68% and 70% respectively. There appeared to be a slightly higher rate of access among males after the population was split into age groups, and this seemed consistent throughout the 4 years of data (Figure 15).

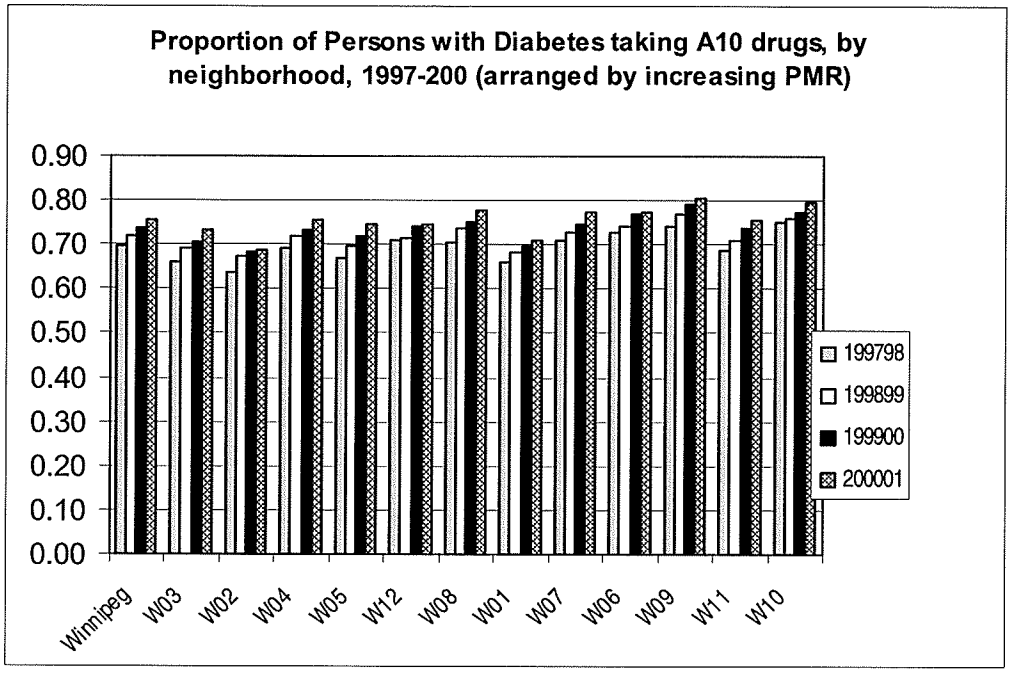
Figure 15.



When access rates are displayed according to the rank of premature mortality rates (PMR) by Winnipeg neighborhood, it shows that the area with the lowest PMR (Fort

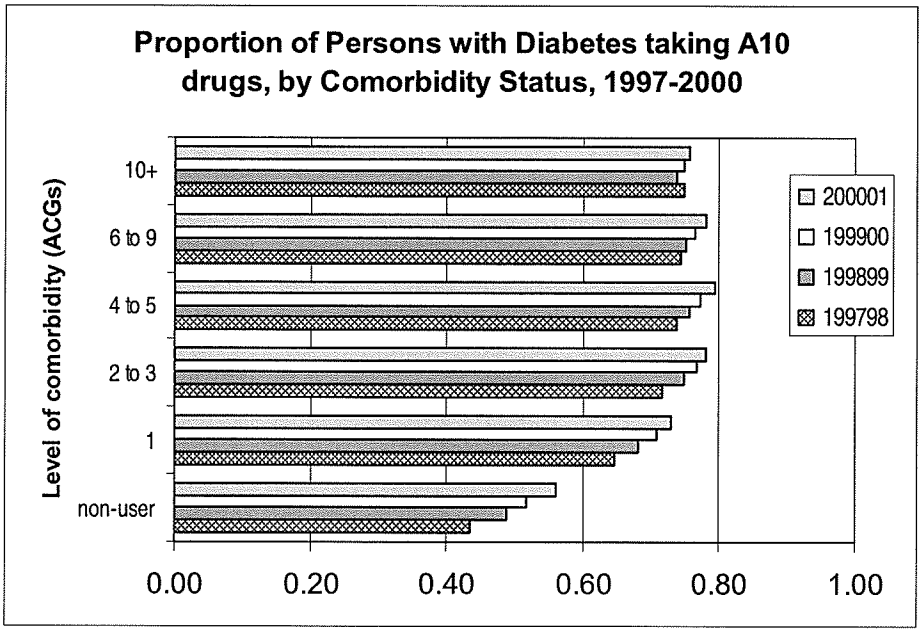
Garry, PMR 2.2) had an access rate of 73% while that of the area with the highest PMR (Point Douglas, PMR 4.8) had an access rate of 80% in 2000/01 (Figure 16).

Figure 16.



Access to anti-diabetic drugs (A10), when analyzed by level of comorbidity, appears to show an increase in the rate of access as the level of ACG increases (Figure 17).

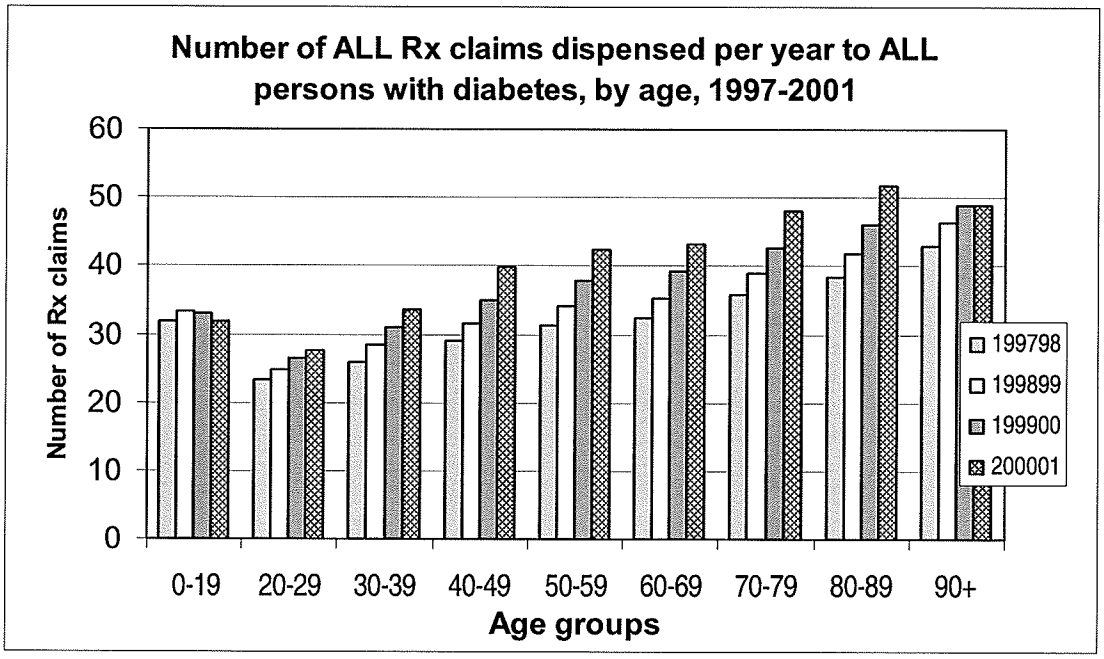
Figure 17.



E. Intensity Rates: Prescription Claims

Intensity of use rates are described by three prescription (Rx) claim rates: **Rx claims per diabetic, Rx claims per diabetic drug (A10) user** and **Diabetic drug (A10) claims per A10 user**. All rates in each age category appear to increase over the 4 year study period (Figure 18). For **Rx claims per diabetic** the rate was 32.4 prescriptions in 1997/98 and 42.7 claims per person in the study population by 2000/01.

Figure 18.



For **Rx claims per diabetic drug (A10) user** the number of drug claims in 1997/98 was 38.8 and in 2000/01 was 48.9. **Diabetic drug (A10) claims per A10 user** for A10 drug claims were 10.1 and 12.0 for 1997/98 and 2000/01 respectively (Figure 19and 20).

Figure 19.

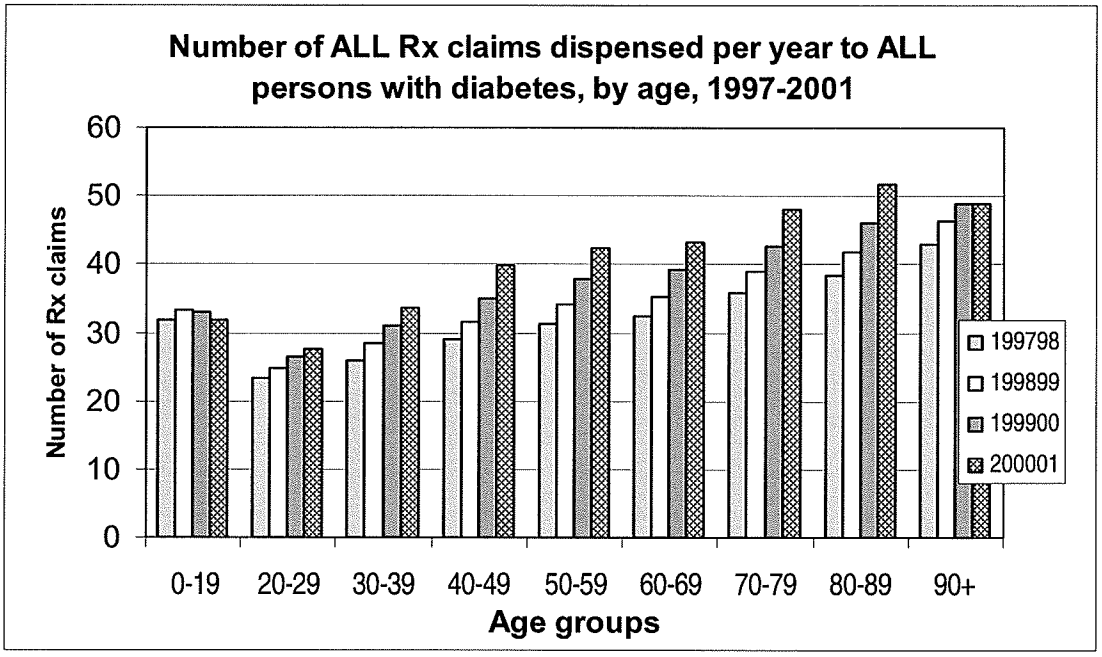
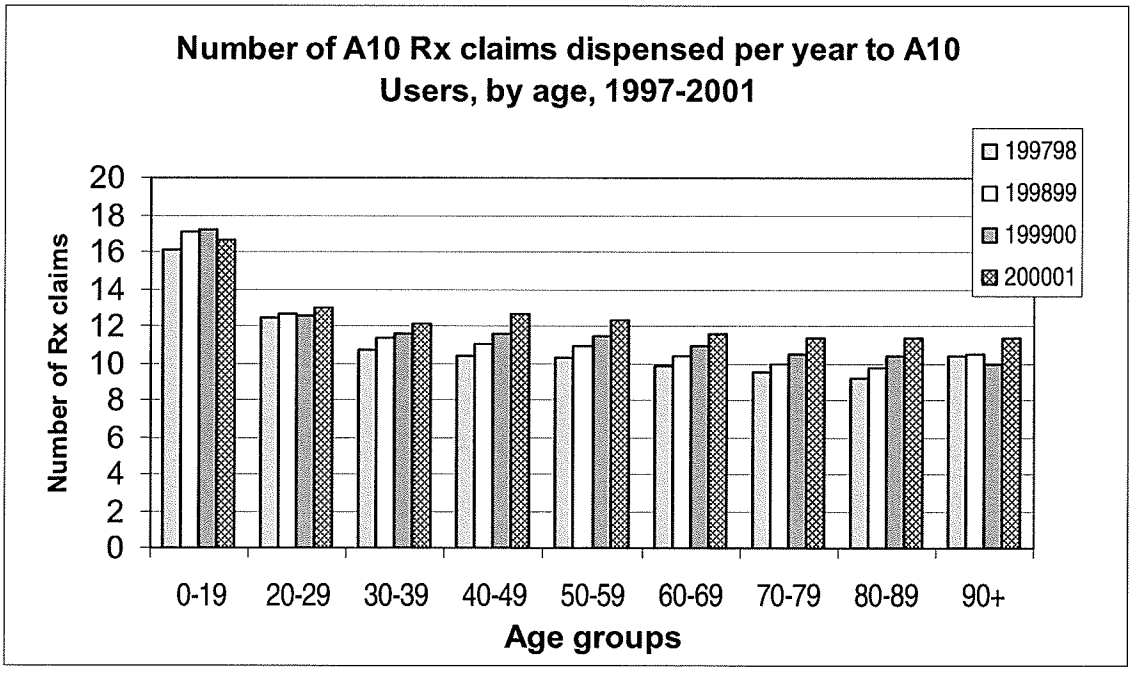


Figure 20.



Female use appeared to be consistently higher than male use in all three prescription claims rates. For **Rx claims per diabetic** the rate showed female drug users had an average yearly number of prescription claims to be 7.4 prescriptions per year more than

reported for males. The appearance of a higher prescription claim rate remained consistent over the 4 years of data. A similar appearance of a difference, reported as an average of 8.7 prescriptions, in intensity rates between males and females was reported with **Rx claims per diabetic drug (A10) user** (Table 17). Again, when examining the rates for A10 drugs only, using the rate **diabetic drug (A10) claims per A10 user**, the appearance of a gap between the sexes was examined. In 1997/98 females with diabetes appeared to have an average of 0.5 more claims than the average male .

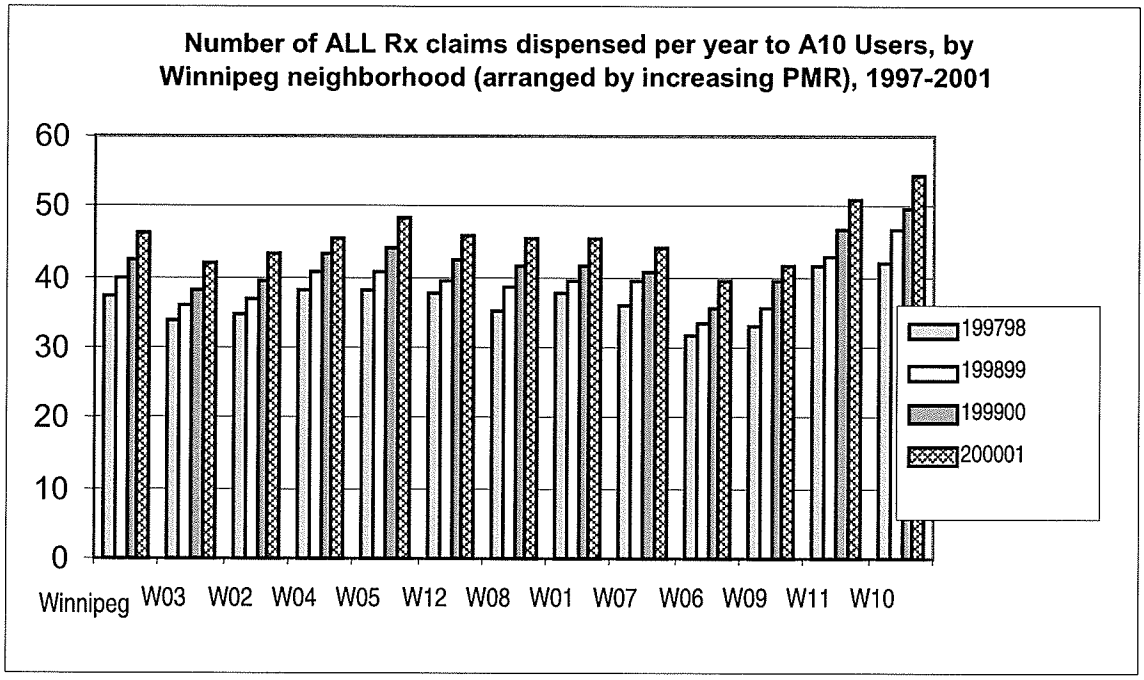
Table 17. Numbers of prescription claims for ALL drugs dispensed to the 'Anti-diabetic drug (A10) using population', by Sex, 1997/98 to 2000/01

	Female				Male			
	199/98	199899	199900	200001	199798	199899	199900	200001
0-19	40.3	41.3	41.9	41.3	36.9	38.7	37.6	35.8
20-29	36.4	38.0	39.6	42.2	28.9	30.4	31.7	32.2
30-39	36.6	39.5	41.8	44.8	32.8	35.2	37.8	38.6
40-49	41.8	44.7	47.8	53.1	30.5	32.0	35.5	40.2
50-59	43.2	45.5	49.4	53.9	32.8	35.5	38.3	43.3
60-69	42.6	45.1	48.6	52.6	34.1	36.9	40.4	44.3
70-79	43.7	47.0	51.3	57.7	38.8	41.1	44.7	50.0
80-89	46.2	50.4	55.2	63.0	42.7	45.6	50.3	55.2
90+	55.6	56.5	57.4	61.9	42.3	45.0	44.6	48.8

Reporting Winnipeg areas in order of increasing PMR from low to high for **Rx claims per diabetic,** there were 35.9 and 50.2 prescription claims (2000/01). There appeared to be an increased use of prescription drugs as the premature mortality rate increased. It should be noted, however, that Inkster (34.7) and Transcona (36.7) both had the lowest reported drug use however despite being ranked with a premature morality rate of the

ninth and tenth highest out of 12. **Rx claims per diabetic drug (A10) user** varied from to be 41.9 to 54.4 from low to high mortality rates, respectively. Inkster (32.9) and Transcona (31.5) remained exceptions and consistently report lower rates throughout the study with respect to other rate calculations (Figure 21).

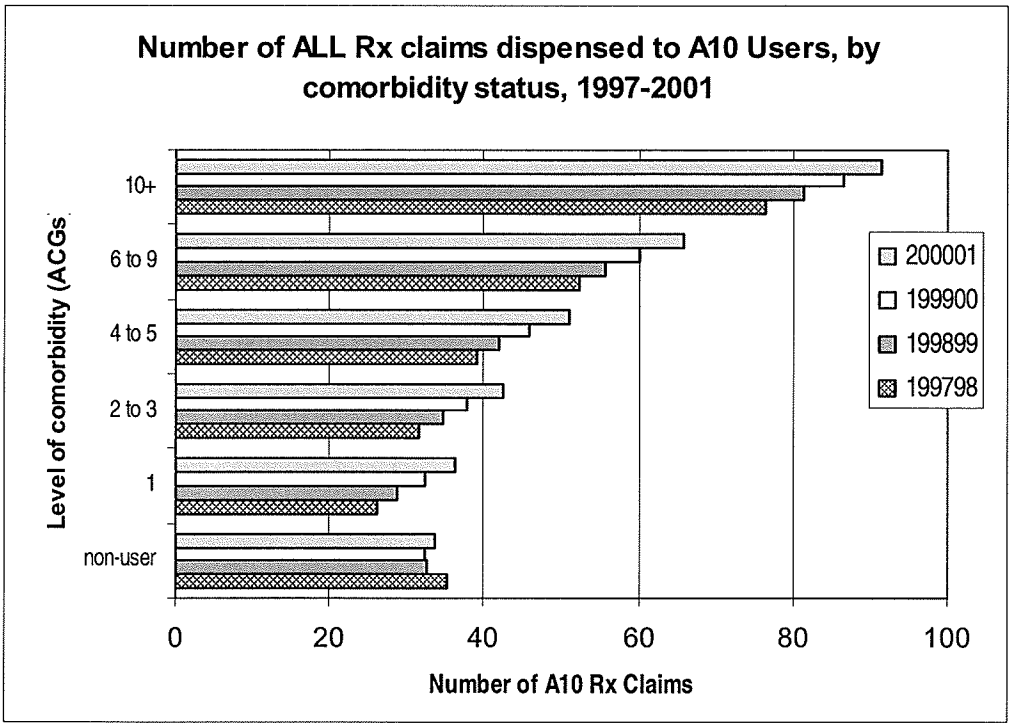
Figure 21.



Similar to the access rate there appeared to be an increase in prescription use with increasing level of comorbidity, measured by ACG's, where **Rx claims per diabetic** non-users claimed 23.5 prescriptions and 10+ claimed 59.7 prescriptions in 2000/01 data. The first year of the study had consistently lower values and there was a gradual increase throughout the four years for each of the three rates. This is also demonstrated in two other rates.

An exception to this was the non-user group who were identified as non-users in the first year of analysis, but who clearly were being dispensed prescriptions, and in some of the results have higher rate values than those with only 1 ADG as shown in the figure mentioned above (Figure 22).

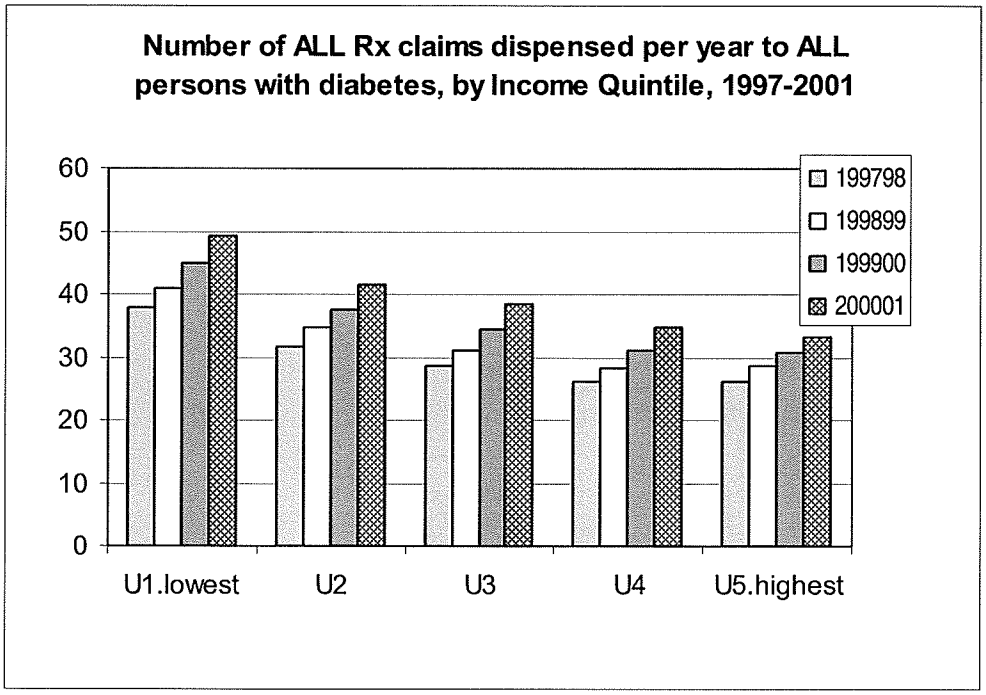
Figure 22.



There appeared to be a decrease in prescriptions per person as income quintile increased for the urban population when looking at all drugs using the rates **Rx claims per diabetic** and **Rx claims per diabetic drug (A10) user**. For example, the **Rx claims per diabetic** rate increased from 49.2 prescriptions in the lowest income quintile to 33.2 prescriptions in the highest income quintile from 2000/01 data (Figure 23). The same

trend was not seen in **diabetic drug (A10) claims per A10 user** where the number of prescriptions leveled off and stayed almost the same in the two highest income quintiles.

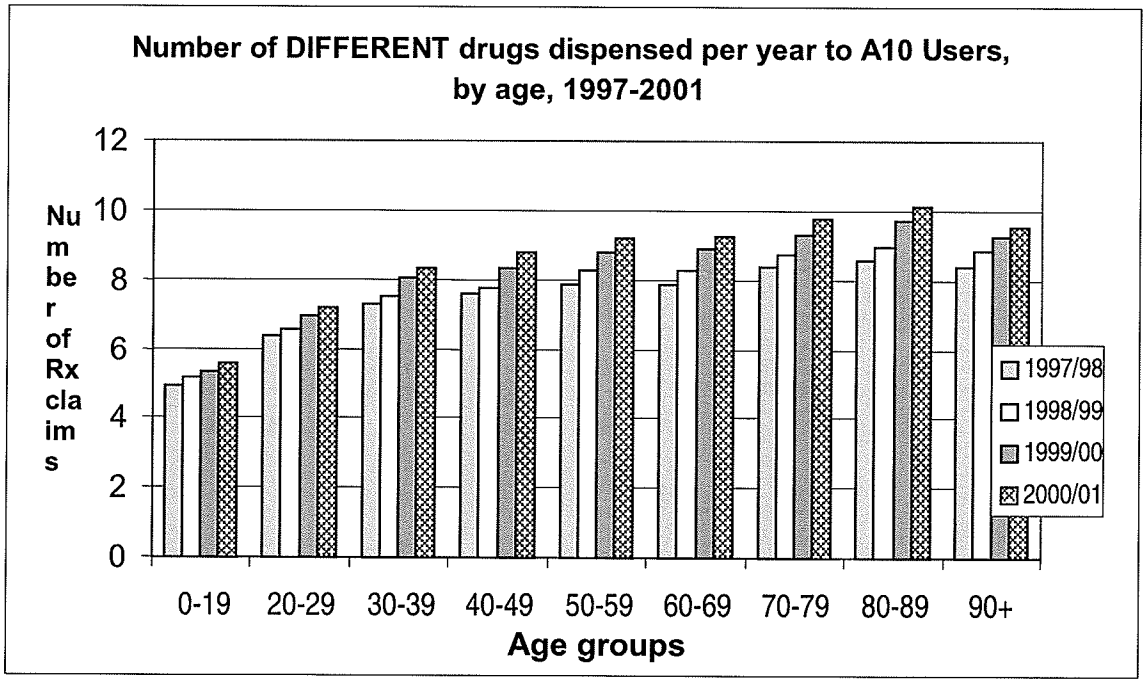
Figure 23.



F. Intensity Rates: Different Drug Classes

For measuring intensity by number of different drugs or prescription classes, rates # **different drugs per diabetic** and **# different drugs per diabetic drug (A10) user** were examined. Both rates appeared to increase over the 4 year study period. In Manitoba, for **# different drugs per diabetic**, the rate was 6.9 different classes in 1997/98 and 8.2 classes per person in the study population by 2000/01. For **# different drugs per diabetic drug (A10) user** it was 7.9 in 1997/98 and 9.1 in 2000/01 (Figure 24). The age category data are used to demonstrate this.

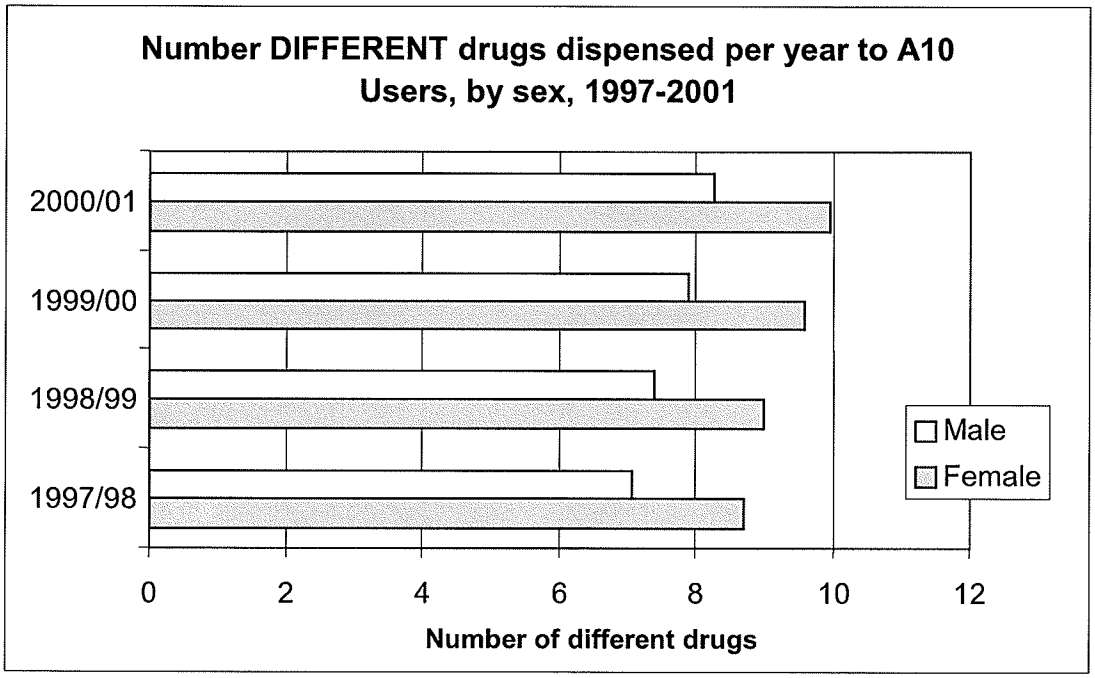
Figure 24.



Females' drug use appeared higher than males in both prescriptions class rates. The **# different drugs per diabetic** rate appeared higher among females with an average of 1.5 classes over the 4 years of data. With **# different drugs per diabetic drug (A10)**

user the average difference, over the four years of data, between males and females was 1.7 classes (Figure 25).

Figure 25.



Similar to the intensity rate by claims, the Winnipeg areas were ranked by premature mortality rates from low to high. **# different drugs classes per diabetic,** reported from low to high respectively (2000/01), were 7.4 and 9.3. Both Inkster and Transcona appear to be outliers with rates of 7.7 and 7.3 respectively. **# different drugs classes per diabetic drug (A10) user,** were 8.3 to 10.0 from low to high premature mortality rates respectively. Once again Inkster (8.5) and Transcona (8.0) were exceptions.

There appeared to be an increase in prescription use which mirrored increasing level of comorbidity for **# different drugs per diabetic drug (A10) user** where non-users

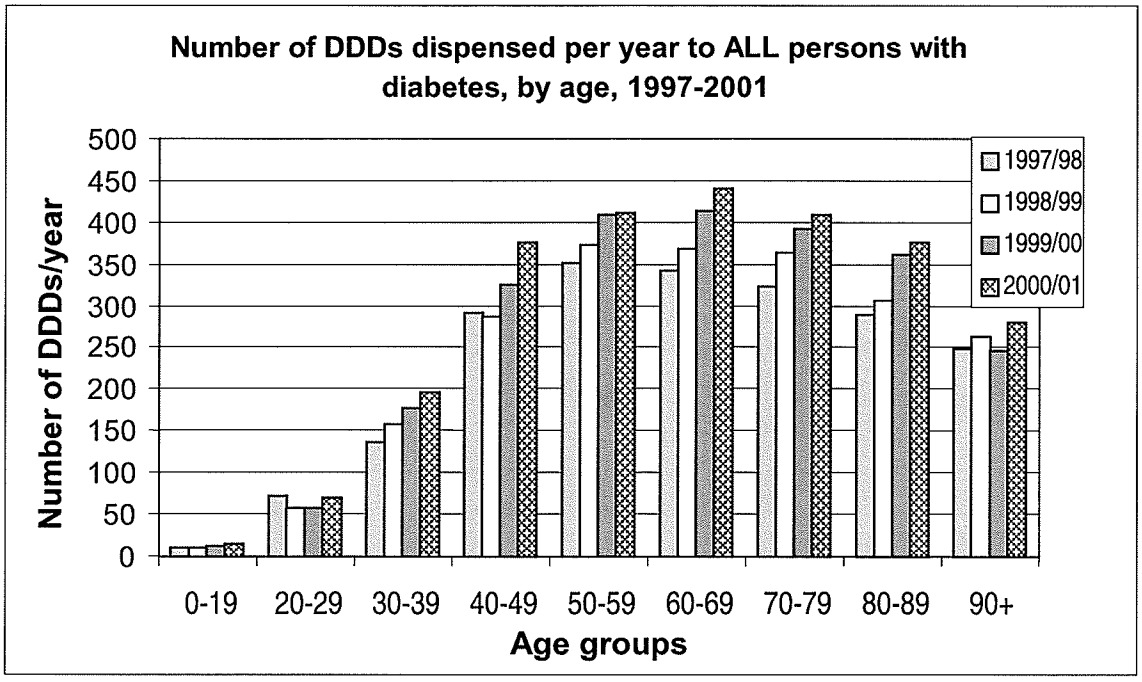
claimed 6.0 classes and 10+ claimed 16.1 classes in the 2000/01 data. There also appeared to be a gradual increase in the use of number of different drugs for the overall diabetic 'study' population throughout the four years.

When examining income quintile there appeared to be a decrease in prescriptions per person as income quintile increased for the urban population. This was observed when the rates of **# different drugs per diabetic** and **# different drugs per diabetic drug (A10)** user were calculated. The rate for **# different drugs per diabetic drug (A10) user** in the 2000/01 data for the lowest income quintile (UI) was 10 different drugs, while the highest income quintile (U5) was 8 different drugs.

G. Intensity Rates: Defined Daily Dosages

For the defined daily dose (DDD) intensity rates calculated there appeared to be an increase in standardized doses dispensed over the 4 year study period. In Manitoba, the **total # DDDs per diabetic** overall rate was 302 DDD in 1997/98 and 378 DDD in 2000/01 (Figure 26).

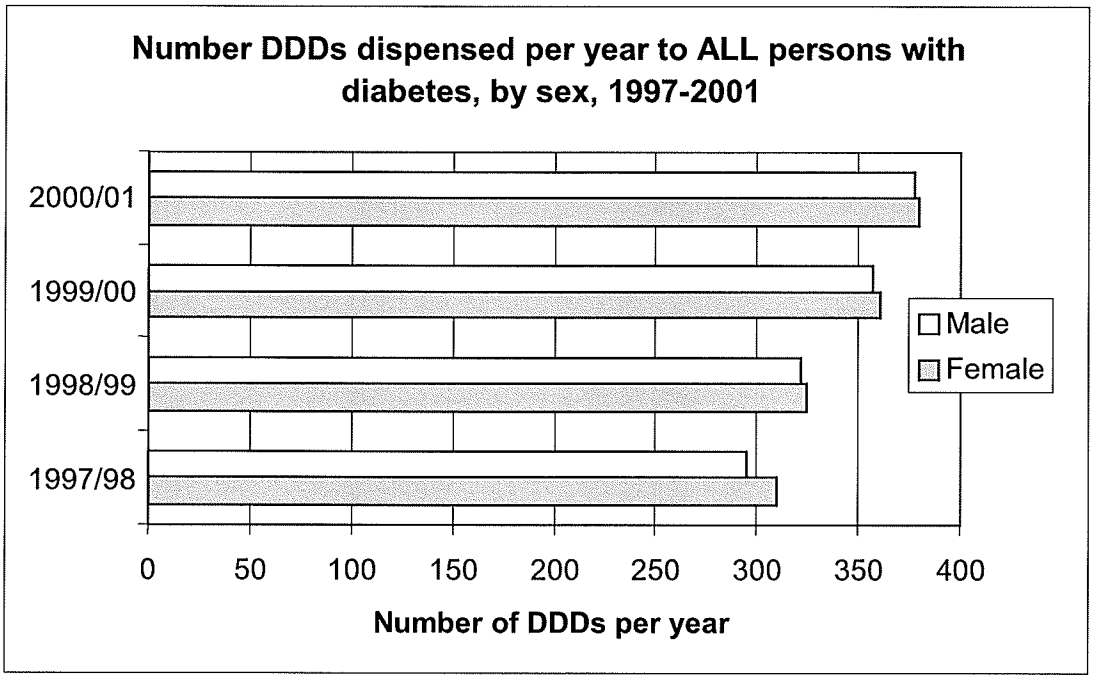
Figure 26.



Similar to the previous rates on number of claims dispensed per year reported, the total DDDs for females appeared higher than males with an average difference over the 4-years of 5.95 DDDs (Figure 27). As well, there appeared to be a decrease in DDDs per person as income quintile increased for the urban population for antidiabetic (A10) drugs. The DDD rate was 369 DDD in the lowest quintile and 326 DDD in the highest quintile from 2000/01 data.

It is important to note that DDDs were calculated only for solid oral dosage forms, and thus, insulin would not be included in the DDD calculation. Therefore, as a person with diabetes required insulin or more insulin, their dependency on oral antidiabetic agents decreased and thus the DDDs appeared to decrease even though more drug in total is required.

Figure 27.

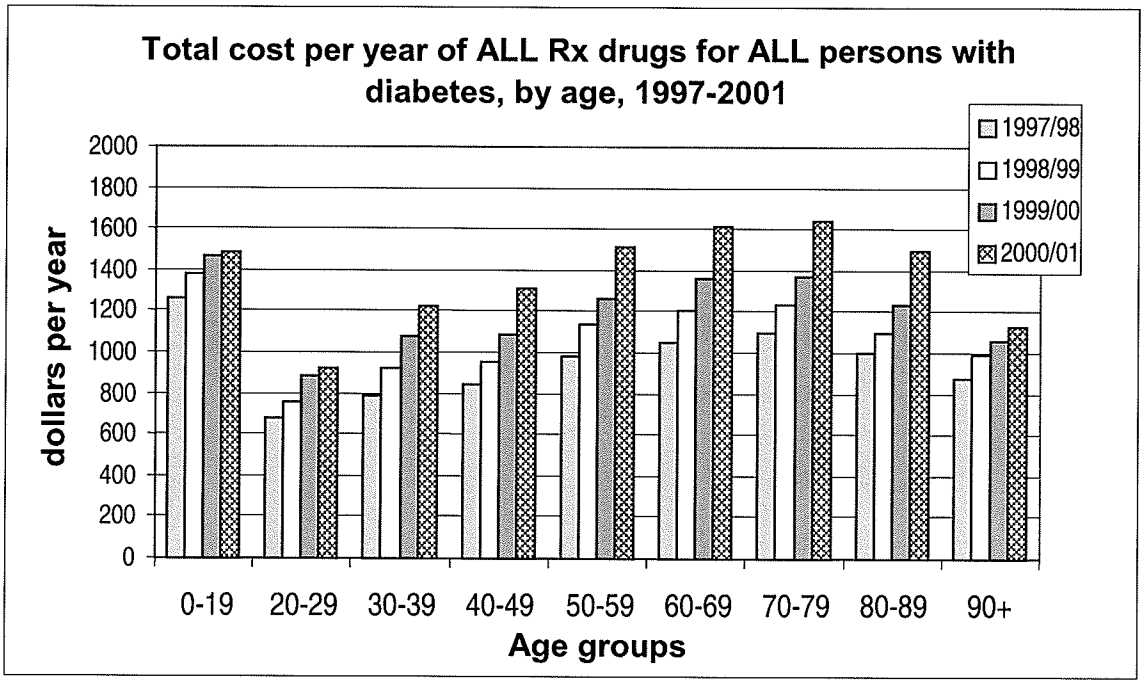


H. Costs

Costs for **cost of all drugs dispensed per diabetic per year**, **cost of all drugs dispensed per A10 user per year** and **cost of all A-10 drugs dispensed per A10 user per year** were examined over the 4 year study period. **Cost of all drugs dispensed per A10 user per year** was an average of $1182 per person in 1997/98 and $1716 per person in the diabetic drug (A10) using study population by 2000/01. **Cost of all A-10 drugs dispensed per A10 user per year** were observed to be $217 in 1997/98 and $291 in 2000/01. Finally, there appeared to be a more dramatic difference in cost when examining the results for the rate **cost of all drugs dispensed per diabetic per**

year where the initial cost per person was $989 in 1997/98 and increased to $1491 in 2000/01 (Figure 28). Age category data were used to demonstrate these trends.

Figure 28.



Again, cost for females appeared consistently higher than males in all three prescription cost measures. **Cost of all drugs dispensed per diabetic per year** among females appeared higher by an average of $90.11 over the 4 years of data, and the difference between the two groups seemed to increase from $59.02 in the first year to $110.91 in the last year. There appeared to be an even greater increase over the four years in the **cost of all drugs dispensed per A10 user per year** where the average difference between males and females was $120.26. When examining the costs for A10 drugs using the rate **cost of all A-10 drugs dispensed per A10 user per year,** there appeared to be a small but steady increase. The 1997/98 data of female persons with diabetes showed a cost of

$5.21 more than the average male and this average became $7.40 by 2000/01 (Figure 29 and 30).

Figure 29.

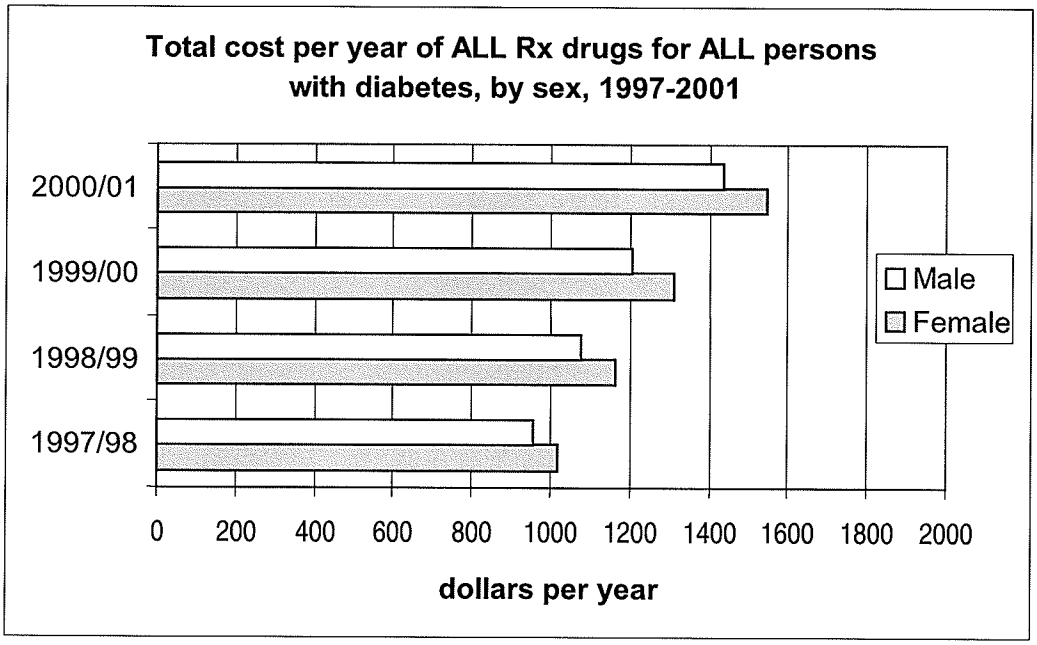
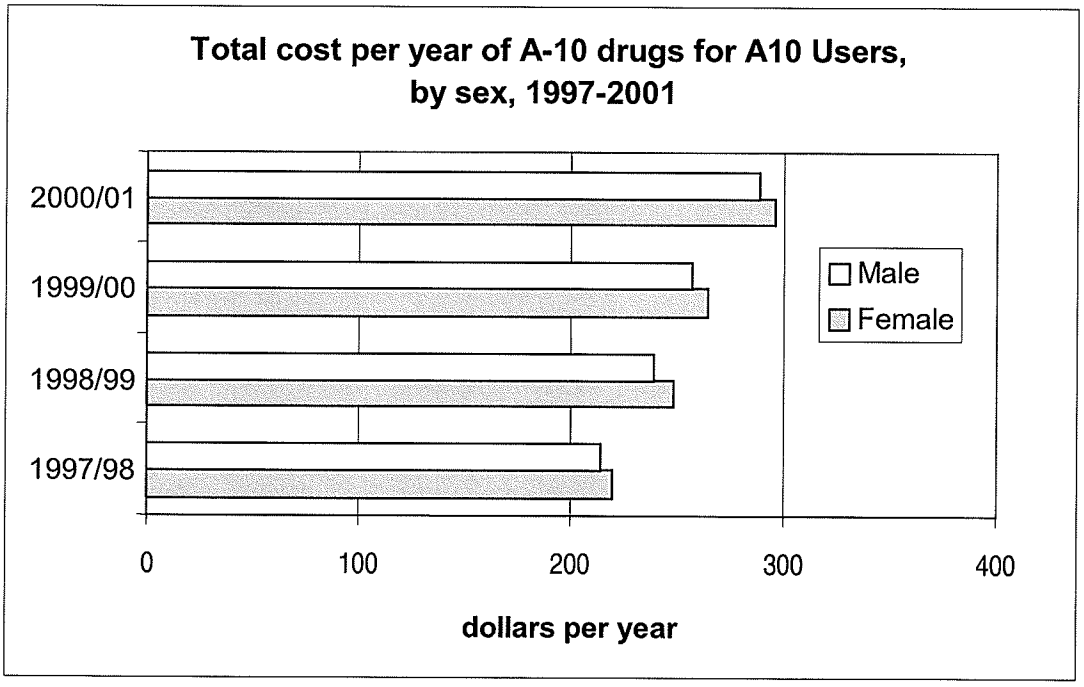


Figure 30.



CHAPTER FIVE

Discussion

This study has demonstrated that a demographic group can be followed, retrospectively and longitudinally, for four years, and that possible changes with respect to drug use patterns can be identified. Throughout the results various observations have been made which provide for the formulation of further research questions around a variety of hypotheses—and, a move up from the base of the pyramid (Figure 2).

There appear to be changes, observed in the current study, that follow predictable trends reflecting the effect of aging within a cohort of persons with diabetes and what appears to be an increase of prescription drug treatment over time, as measured by rates of access and intensity. Just as there seems to be an increase in access and intensity of pharmaceutical use, there appear to be changes with use associated with markers of comorbidity and income. The healthier or less 'comorbid', and wealthier segments of the cohort appear to have the lowest rates of drug use. Conversely, there appears to be an increase in utilization rates which follow the cohort members as their comorbidity status increase and/or their socioeconomic status decrease. As expected, geographic region of residence demonstrated an association between premature mortality rate (PMR) and the rates of drug use.

When the regions evaluated were ranked from lowest to highest with respect to premature mortality rate, there appeared to be a possible trend which demonstrated there may be lower rates of use in regions with lower PMR, and there may be an increase in rates of

pharmaceutical use as the PMR for the region increased. The regions of Inkster and Transcona were two notable areas that may exist as outliers. Both regions showed consistently lower values of rate of drug use on all measures of access, intensity and cost. Lower rates in Inkster are consistent with other MCHP research, however, an hypothesis for these lower rates has yet to be formulated (personal communication, R. Fransoo, MCHP 2005).

The magnitude of differences (i.e., female rates subtracted from male rates) in drug use among males and females for all drugs and for ATC: A10 anti-diabetic drugs was not anticipated at the commencement of this study and demonstrates the importance of hypothesis generating research. The average number of prescription claims for all drugs and the average number of different drug classes used, both demonstrated that females appeared to have consistently higher rates of use of all prescription and anti-diabetic drugs than males. These findings were similar to Evans et al.[55] The proportion of males on at least one drug therapy for diabetes, as measured by access, appeared higher than females. Access, however, is a difficult measure to interpret with respect to those persons with diabetes. Persons with type 2 diabetes are not necessarily required to be prescribed drug therapy although differences in access across the cohort do reflect trends in drug utilization.

This study has shown that a cohort of persons with diabetes and their patterns of drug use can be described using the PHRDR. From four years of Manitoba population-based data using a fixed-sample of residents and standard demographic variables, there was an

increase in prevalence ($p<0.0001$) of diabetes according to increasing comorbidity levels and decreasing income levels. In other words, the cohort groups that were defined as healthier and wealthier have a lower prevalence than those groups with a larger number of comorbidity indicators (less healthy), and lower income quintile. Geographic region of residence when ranked according to PMR demonstrated that there is a possible trend that would link increased premature mortality rate with increasing prevalence of diabetes. Rural regions reported a prevalence rate which appeared lower in the south and higher in the middle and northern regions of the province.

Prevalence in the youngest group (0-19 years of age) were equal between males and females but in the age groups 20-29 and 30-39 females had a higher prevalence. This increased prevalence is likely a reflection of those members of the cohort diagnosed with gestational diabetes. As age increased the prevalence of males with diabetes became higher than females, until the 70+ age group where females took the lead role again. The change from males to females in these older age categories is a likely a reflection of younger deaths among males and the longer expected life expectancy among females (Figure 10). The increased prevalence amongst females in the 20 to 39 age category and the higher prevalence for adult men until the 70+ age group mirrors previous finding by James et al.[62]

Prevalence of diabetes in Manitoba was determined to be 3.3% in this study, which is below the Manitoba Health estimate of 6.7 percent, and WHO estimate of 5 percent.[3,11] Reasons for this may lie in the definition of diabetes used in this study. Manitoba

Health's estimate[3] was based on an adult population aged greater than 24 years, while this study included Manitobans less than 25 years of age.[29] Given that Type 1 diabetes (juvenile type) makes up approximately 10 percent of the diabetic population and more than 95 percent of the diabetic population over 25 years of age has type 2 diabetes, the inclusion of those under the age of 25 in the prevalence calculation will result in a lower number, when compared to previous determinations of prevalence using the Manitoba Health estimates. Due to the decision to divide the age groups by decade it was not possible, due to time constraints, to regroups the data to allow for a prevalence rate using those 25 years of age and older. However, when a prevalence rate using the 1997 population older than 29 years of age was calculated using data from this study, the prevalence rate increased to 5.5% (reference population: 1997 Statistics Canada). As well, Manitoba Health's estimate has been in existence since 1985. Those people who either died or emigrated from the Manitoba population were eliminated and only the remaining survivors were totaled.[29]

James et al. stated that when using person-level information from publicly administered health care services, the quality of diagnostic and other information must be considered.[62] In this study, Manitobans were defined as diabetic using medical claim and hospitalization data reaching back three years while the drug data dated back one year. Therefore, any diabetic persons who did not have a diagnostic ICD-9 code of 250 or a drug claim for an ATC: A10 anti-diabetic drug in the definition period were not captured. This could include two groups of people, all of whom could have been diagnosed prior to April 1, 1994: (1) those persons with diabetes who are well controlled or who have other

prominent diagnoses, and whose physician did not submit an ICD-9 250 code and, (2) those persons with diabetes who had no contact with the medical system in the three year period preceding this analysis.

The cohort of 37,965 persons were first identified using data from 1994 to 1997 (Figure 5). Decisions on managing and maintaining the cohort were made based on the methods used to calculate and describe the data. In other words, how drug dispensations (prescriptions) are defined and counted--the numerator--and how different populations are defined--the denominator--were of primary importance in ensuring that the rates were an accurate reflection of the Manitoba population's use of anti-diabetic drugs.

Decisions about management of the denominator with regard to events such as emigration, death, and newly diagnosed cases of diabetes within the cohort had to be made. Such decisions impacted on how prescription utilization rates were interpreted. For example, the cohort could have been open and dynamic and allowed for immigration and emigration of cohort members. Using this model, for each of the study years, a new cohort would have been defined, thereby resulting in a *longitudinal trend* or *repeated cross-sectional design* study. Patients who emigrated or died over the study years would have been identified and eliminated from the study and newly diagnosed cases added. A decision as to which points in time were used for capturing the cohort and eliminating deaths or emigration would need to have been made. By identifying and analyzing the pharmaceutical use of this type of cohort, an accurate description of patterns of drug use amongst the entire population would have resulted. Keeping this in mind, it is likely that

the deaths would primarily have represented the less healthy cohort members and those more likely to have more prescriptions and complex drug profiles. The 'newer' cohort members, on the other hand, are more likely to have been newly diagnosed persons with diabetes and, therefore, younger and healthier with fewer overall prescription dispensations. In other words, in a longitudinal trend study the population who were sicker and used prescriptions at a higher rate would have been replaced by a healthier population who used prescriptions at a lower rate. Therefore, this model would have represented the entire population and reflected changes from year-to-year, however, any actual trends in drug use amongst the original cohort could have been hidden due to the dynamics of the cohort (its turnover).

An alternative mode of cohort definition and design was chosen for this study; it is called a *retrospective longitudinal fixed sample panel study*. The cohort was defined and identified over a three-year period prior to assessing pharmaceutical use. At the end of the three-year cohort definition period, four years of demographic and health care resource use data were identified and split into four by fiscal year (April 1 to March 31). As each year passed, the cohort members must have survived to the end of that fiscal year to be included in the corresponding year of data. In other words, four years of data were gathered (1997/98, 1998/99, 1999/2000, 2000/01), and if the cohort member survived to the end of the 2000/01 fiscal year that person was included in all four years of analysis. However, if a cohort member died in the 1999/2000 year they were included for the 1997/98 and 1998/99 years of data, and if the cohort member died before the end of the

1997/98 year the cohort member was not included in any of the results but was included in the original description of the cohort.

By the end of the study (March 31, 2001), 16.3 percent (6,196) of the cohort were excluded due to death or emigration. Included in this number were 875 diabetics who died or emigrated prior to the end of the first fiscal year and, therefore, did not contribute any data to the results. The study year 1998/99 had the most exclusions (1,864) while the following years 1999/2000 and 2000/2001 had 1,756 and 1,701 respectively.

In the rate calculations for anti-diabetic drug use, the numerator reflected information from the prescription data either the number of different drug classes or the number of prescription claims dispensed to the cohort. To be able to use this data a DIN Master file was employed that was designed to identify and label drug claims with classification codes and DDD's. As observed on analysis, 13.2 percent of dispensed claims did not have an ATC code assigned. Those drugs without an ATC are a result of missing drug identification numbers (DINs) in the DIN Master file. The DINs are used as the common merge variable between the claims data set and the DIN Master. A missing DIN from the Master Formulary file would result in an inability to capture corresponding claims from the prescription data. To avoid missing any claims for anti-diabetic drugs a program was developed. It identified any ATC: A10 drugs found in the claims data but not in the DIN Master. Excluding the anti-diabetic drug pioglitazone, (released in 2000/01 representing 299 claims, and not yet included in the Master Formulary), the 1999/00 year was found to

have the largest number of missing claims. These missing claims totaled 27 and represented 0.0001 percent of the claims for anti-diabetic drugs.

Given the richness of the PHRDR and the resulting possibilities for describing the population's use of prescription drugs, it is worth considering in more depth one of the rates of intensity used—the defined daily dose (DDD). It is important to consider that extrapolating DDD methodology to this study requires an understanding of the overall usefulness of this measure. DDD rates describe the number of assumed average maintenance dose(s) per day for a drug used for its main indication in adults.[63] Advantages of DDD include aggregation of data into meaningful therapeutic classes and the ability to identify trends in utilization and cost.[64] The data are usually gathered over a specific period and therefore reflect an average utilization over time. In this study the total number of DDDs dispensed to each subject for each year were examined. There were several methods by which this could be done. In previous research published by MCHP, the total DDD's per subject dispensed during a fiscal year were added, and then divided by 365 days to obtain the number of daily doses taken per day for all drugs. Using 365 days assumed the patient was either prescribed or received the drug for the entire year, and would not reflect those who were prescribed it mid-way through the year, or who were non-compliant and did not take the prescribed dose on a daily basis. In other words, a 365 day assumption could artificially inflate the denominator thereby deflating the DDD/day rate. In this study, the total number of DDDs dispensed per subject per fiscal year was reported to give a better understanding of 'burden of pharmaceutical use' per year per person. One is reminded at this point, that DDD rate calculations only

provide information on what is dispensed and not what is actually consumed by the patient. Therefore, it cannot be used as a measure of compliance.[54] Similar to intensity and access rates, DDDs appeared to gradually increase over the four years of the study, and females appeared to have consistently higher rates of DDD use than did males. However, unlike the intensity and access measures, there did not appear to be an increase in the differences between male and female DDDs over the four years. Finally, the number of DDDs dispensed appeared to increase as income levels decreased.

Unique to this study is access to the Population Health Research Database Repository (PHRDR) which provided the ability to gather information from a population defined by geographic boundaries, socioeconomic characteristics, and cultural similarity. The data was analyzed over four contiguous years and the cohort was followed with an ability to provide exclusion identifiers based on death or emigration from the province. Patterns of drug utilization according to access, intensity and cost were calculated based on person level data and described using a variety of demographic variables not previously reported on in persons with diabetes.

CHAPTER SIX

Conclusion

The prevalence of diabetes is increasing across the globe and more than 55,000 Manitobans have already been diagnosed with this chronic disease. Secondary complications of diabetes result in widespread damage to both macrovascular and microvascular body systems resulting in cardiovascular complications, amputations, nephropathy and neuropathy. The burden on the health care system resulting from these complications is significant. As prevalence increases, so will the expected demands to provide pharmaceuticals to prevent diabetic complications.

This study has demonstrated the need for a comprehensive understanding of pharmaceutical use data and the importance of providing an accurate picture of a cohort's drug utilization patterns. Decisions affecting numerator and denominator values, such as days supply or management of the cohort are important in accurately describing drug utilization. Despite the fact that descriptive drug-utilization research has been possible within MCHP since the late 1990s, this study provides a solid base upon which further research in a chronic disease state—diabetes--can be undertaken.

As hypothesis generating research, it provides the base upon which the next step up the pyramid (Figure 2)--identifying the information needed to develop accurate drug utilization indicators--can be attempted. Analysis in the management of the cohort inclusion and numerator values can be undertaken and statistical modeling can be undertaken more efficiently in order to test differences within demographic groupings

and between years. In order to move up the pyramid even further, to the measurement of the effectiveness of diabetic therapy, one would have to be capable of linking laboratory measures of glycosylated hemoglobin (HgA1C) to drug utilization to examine whether 'target' A1Cs have been met given drug use.

Finally, we can describe the patterns of pharmaceutical use and prescription drug costs for persons with diabetes in the Manitoba population as described by access and measures of intensity of use and we can examine these patterns of use by the population demographics available with administrative claims data.

REFERENCES

[1] Public Health Agency of Canada. National Diabetes Surveillance Strategy. Available at : http://www.phac-aspc.gc.ca/ccdpc-cpcmc/diabetes-diabete/english/strategy/ndss.html. Accessed March 26, 2005.

[2] Meltzer S, Leiter L, Daneman D, Gerstein HC, Lau D, Ludwig S, Yale JF, Zinman B, Lillie D. 1998 clinical practice guidelines for the management of diabetes in Canada.Canadian Diabetes Association. CMAJ. 1998;159 Suppl 8:S1-29. XX change to 2003 guidelines

[3] Manitoba Health. Diabetes: A Manitoba Strategy. Blanchard J, editor. 1998. Winnipeg MB, Manitoba Health.

[4] DCCT Research Group. The effect of intensive diabetes treatment on the development and progression of long-term complications in insulin-dependent diabetes mellitus. New England Journal of Medicine 1993; 329:997-986.

[5] Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998 Sep 12;352(9131):837-53.

[6] World Health Organization. The selection of essential drugs. Report of a WHO Committee. Technical Report, Series No. 615. Geneva, Switzerland, 1977.

[7] Metge C, Black C, Peterson S, Kozyrskyj AL. The population's use of pharmaceuticals. Med Care. 1999 Jun;37(6 Suppl):JS42-59.

[8] Hensyl RW, editor. Stedman's medical dictionary. Baltimore, MD: Williams and Wilkins, 1990

[9] Sherwood L, editor. Human Physiology: from cells to systems. Minneapolis/St.Paul: West Publishing Co; 1993.

[10] Van de Graaff KM, Fox SI. Concept of Human Anatomy and Physiology. 4th ed. Iowa: Wm.C.Brown Publishers, 1995.

[11] World Health Organization. Diabetes mellitus: report of a WHO study group on diabetes mellitus. Geneva, World Health Organization: WHO Technical Report Series No. 727; 1985.

[12] Knowler WC, Pettitt D, Bennett PH, Williams RC. Diabetes mellitus in the Pima Indians: genetic and evolutionary considerations. American Journal of Physical

Anthropology 1983; 62:107-114.

[13] Dyck FR, Cassidy H. Preventing non-insulin-dependent diabetes among aboriginal peoples: is exercise the answer? Chronic Deseases in Canada 1995; 16(4):175-177.

[14] Neel JV. Diabetes mellitus: a thrifty genotype rendered detrimental by 'progress'. American Journal of Human Genetics 1962; 14:353-362.

[15] Hill B. The environment and disease: association or causation. Proc R Soc Med. 1965;58:295-300

[16] Tuomilehto J, Knowler WC, Zimmet P. Primary Prevention of non-insulin-dependent diabetes mellitus. Diabetes Metabolism Reviews 1992; 8(4):399-535.

[17] Henry RR. Prospects for primary prevention of type 2 diabetes mellitus. Diabetes 1994; 3:2-5.

[18] Garrow JS and Webster J. Quetelet's index (W/H^2) as a measure of fatness. International Journal of Obesity 1985;9:147–153.

[19] Gallagher D, et al. How useful is BMI for comparison of body fatness across age, sex and ethnic groups? American Journal of Epidemiology 1996;143:228–239.

[20] Green C, Blanchard JF, Young TK, Griffith J. The epidemiology of diabetes in the Manitoba-registered First Nation population: current patterns and comparative trends. Diabetes Care. 2003 Jul;26(7):1993-8.

[21] Blanchard JF, Dean H, Anderson K, Wajda A, Ludwig S, Depew N. Incidence and prevalence of diabetes in children aged 0-14 years in Manitoba, Canada, 1985-1993. Diabetes Care. 1997 Apr;20(4):512-5.

[22] Young KT, Szathmary EJE, Evers S, Wheatley B. Geographical distributions of diabetes among the native population of Canada; a national survey. Social Science Medicine 2001; 31:129-139.

[23] Travers KD. Using Qualitative Research to Uncerstand the sociocultural origins of diabetes amonth Cape Breton Mi'kmaq. Chronic Diseases in Canada 1995; 16(4):140-143.

[24] West KM. Epidemiology of diabetes and its vascular lesions. New York: Elsevier; 1978.

[25] Deckert T, Poulsen JE, Larsen M. The prognosis of insulin dependent diabetes mellitus and the importance of supervision. Acta Med Scand Suppl. 1979;624:48-53.

[26] Reichard P, Nilsson BY, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. N Engl J Med. 1993 Jul 29;329(5):304-9.

[27] Kern TS, Engerman RL. Microvascular metabolism in diabetes. Metabolism. 1986 Apr;35(4 Suppl 1):24-7.

[28] Muls E. Diabetic control: the glucose hypothesis in post-DCCT and pre-UKPDS era. Diabetes 1990; 4(2):12-14.

[29] Blanchard J, Ludwig S, Wajda A, Dean H, Anderson K, Kendall O et al. Incidence and Prevalence of Diabetes in Manitoba, 1986-1991. Diabetes Care 1996; 19(8):807-811.

[30] Chase HP, Jackson WE, Hoops SL, Cockerham RS, Archer PG, O'Brien D. Glucose control and the renal and retinal complications of insulin-dependent diabetes.JAMA. 1989 Feb 24;261(8):1155-60.

[31] Tuomilehto-Wolf E, Tuomilehto J, Hitman GA, Nissinen A, Stengard J, Pekkanen J, Kivinen P, Kaarsalo E, Karvonen MJ. Genetic susceptibility to non-insulin dependent diabetes mellitus and glucose intolerance are located in HLA region. BMJ. 1993 Jul 17;307(6897):155-9.

[32] Deckert T, Poulsen JE, Larsen M. Prognosis of diabetics with diabetes onset before the age of thirty-one. II.Factors influencing the prognosis.Diabetologia. 1978 Jun;14(6):371-7.

[33] United Kingdom Prospective Diabetes Study (UKPDS). 13: Relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. BMJ. 1995 Jan 14;310(6972):83-8.

[34] UK Prospective Diabetes Study (UKPDS). XI: Biochemical risk factors in type 2 diabetic patients at diagnosis compared with age-matched normal subjects. Diabet Med. 1994 Jul;11(6):534-44.

[35] UK Prospective Diabetes Study (UKPDS). X. Urinary albumin excretion over 3 years in diet-treated type 2, (non-insulin-dependent) diabetic patients, and association with hypertension, hyperglycaemia and hypertriglyceridaemia. Diabetologia. 1993 Oct;36(10):1021-9.

[36] UK Prospective Diabetes Study (UKPDS). IX: Relationships of urinary albumin and N-acetylglucosaminidase to glycaemia and hypertension at diagnosis of type 2 (non-insulin-dependent) diabetes mellitus and after 3 months diet therapy. Diabetologia. 1993 Sep;36(9):835-42.

[37] UK Prospective Diabetes Study (UKPDS). VIII. Study design, progress and performance. Diabetologia. 1991 Dec;34(12):877-90.

[38] UK Prospective Diabetes Study 7: response of fasting plasma glucose to diet therapy in newly presenting type II diabetic patients, UKPDS Group. Metabolism. 1990 Sep;39(9):905-12.

[39] Gerstein CG, Hanna A, Rowe R, Leiter L, MacGregor A. CDA Position Statement Regarding the UKPDS and Revision of Diabetes Clinical Practice Guidelines Accounting for UKPDS Results. Can J Diabetes Care 1999; 23(1):15-17.

[40] Murray CJL, Lopez AD. Estimating causes of death: New methods and global and regional applications for 1990. In: WHO, Global Health Statistics: a comprehensive assessment of mortality and disability from disease, injuries and risk factors in 1990 and projected to 2020. Boston MA: Harvard University Press; 1996 Volume 1 (3) p. 120.

[41] Haaijer-Ruskamp FM, Hoven J, Mol PGM A Conceptual framework for constructing prescribing quality indicators: a proposal. WHO publication 2004).

[42] Managing drug supply. The selection, procurement, distribution and use of pharmaceuticals. USA, Management Sciences for Health in collaboration with the World Health Organization, 1997; 2004.

[43] Tools for Advancing Pharmaceuticals Management, Ottawa, November 2004.

[44] Development of drug utilization indicators: A feasibility study using existing aggregated administrative databases. Canadian Institute for Health Information; 2002.

[45] Aday LA, Begley C, Lairson D, Slater C. Evaluating the Healthcare System: Effectiveness, Efficiency and Equity. 2nd ed. Chicago, IL: Health Administration Press, 1998.

[46] Fletcher RH, Fletcher SW, Wagner EH. Clinical epidemiology: the essentials. 3rd edition. Baltimore, MD: Williams & Wilkins, 1996.

[47] Boccuzzi JS, Wogen J, Fox J, Sung JCY, Shah AB, Kim J. Utilization of Oral Hypoglycemic Agents in a Drug-Insured U.S. Population. Diabetes Care 2001; 24(8):1411-1415.

[48] Brown JB, Nichols GA, Glauber HS, Bakst AW, Schaeffer M, Kelleher CC. Health care costs associated with escalation of drug treatment in type 2 diabetes mellitus. Am J Health Syst Pharm. 2001 Jan 15;58(2):151-7.

[49] Brown JB, Nichols GA, Glauber HS, Bakst A. Ten-year follow-up of antidiabetic drug use, nonadherence, and mortality in a defined population with type 2 diabetes mellitus. Clin Ther. 1999 Jun;21(6):1045-57.

[50] Spooner JJ, Lapane KL, Hume AL, Mor V, Gambassi G. Pharmacologic treatment of diabetes in long term care. Journal of Clinical Epidemiology 1 A.D.; 54(5):525-530.

[51] Isacson D, Stalhammar J. Prescription drug use among diabetics--a population study. J Chronic Dis. 1987;40(7):651-60.

[52] Wandell PE, Brorsson B, Aberg H. Drug prescription in diabetic patients in Stockholm in 1992 and 1995—change over time. Eur J Clin Pharmacol. 1997;52(4):249-54.

[53] Benitez J, Puerto AM, Diaz JA. Differences in antidiabetic drug utilisation between three different health systems in the same national region. Eur J Clin Pharmacol. 1992;42(2):151-4.

[54]World Health Organization. World Health Organization's Centre for Drug Statistics Methodology: Guidelines for ATC classification and DDD assignment. Oslo, Norway: World Health Organization, 2004.

[55] Evans JM, MacDonald TM, Leese GP, Ruta DA, Morris AD. Impact of type 1 and type 2 diabetes on patterns and costs of drug prescribing: a population based study. Diabetes Care 2000; 23(6):770-774.

[56] Wu SYB, Lung BCH, Chang S, Lee SC, Critchley AJH, Chan JCN. Evaluation of drug usage and expenditure in a hopsital diabetes clinica. J Clin Pharm Therapeut 1998; 23:49-56.

[57] Deber RB, Hastings JE, Thompson GG. Health care in Canada: current trends and issues. J Public Health Policy. 1991 Spring;12(1):72-82.

[58] Roos NP, Black C, Roos LL, Frohlich N, DeCoster C, Mustard C, Brownell MD, Shanahan M, Fergusson P, Toll F, Carriere KC, Burchill C, Fransoo R, MacWilliam L, Bogdanovic B, Friesen D. Managing health services: how the Population Health Information System (POPULIS) works for policymakers. Med Care. 1999 Jun;37(6 Suppl):JS27-41.

[59] Andersen RM, McCutcheon A, Aday LA et al. Exploring Dimension of Access to Medical Care. Health Services Research 1983; 18(1):50-74

[60] Reid R, MacWilliam L, Verhulst L, Roos N, Atkinson M: Performance of the ACG case-mix system in two Canadian provinces. *Med Care* 2001; 39(1):86-99.

[61] Krieger N. Overcoming the absence of socioeconomic data in medical records: Validation and application of census based methodology. Am J Public Health 1992;82:703

[62] James RC, Blanchard JF, Campbell D, Clottey C, Osei W, Svenson LW, Noseworthy TW. A model for non-communicable disease surveillance in Canada: the prairie pilot diabetes surveillance system. Chronic Dis Can. 2004 Winter;25(1):7-12.

[63] World Health Organization. World Health Organization's Centre for Drug Statistics Methodology: Guidelines for ATC classificaiotn and DDD assignment. Oslo, Norway: World Health Organization, 2004.

[64]Sketris IS, Metge CJ, Ross JL, MacCara ME, Comeau DG, Kephart GC. The use of the World Health Organisation Anatomical Therapeutic Chemical/Defined Daily Dose methodology in Canada. Drug Info J 2004; 38(1):

Appendix A:

Canadian Diabetes Association

Clinical Practice Guidelines Expert Committee

2003 Clinical Practice Guidelines

Introduction

Canadian Diabetes Association
Clinical Practice Guidelines Expert Committee

RATIONALE FOR REVISION OF THE 1998 CLINICAL PRACTICE GUIDELINES

The 1998 Clinical Practice Guidelines for the Management of Diabetes in Canada (1), developed by the Clinical & Scientific Section of the Canadian Diabetes Association, were the first comprehensive, evidence-based, clinical practice guidelines for diabetes care that allowed readers to independently judge the value of the diagnostic, prognostic and therapeutic recommendations (2). Recently published evidence relevant to the prevention and management of diabetes mellitus justified a complete review of the 1998 recommendations. The Canadian Diabetes Association 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada were drafted over a 2-year period by a volunteer Expert Committee representing key stakeholders across Canada. The process included a broad-based review to ensure that the diabetes community at large had input into the document.

Canada is actively evaluating the structure and guiding principles of its healthcare system (3,4). The need to ration and appropriately allocate healthcare resources is now more commonly accepted (3-5). As the practice of medicine in Canada shifts to an evidence-based model, healthcare professionals will be under increasing pressure to update and incorporate new strategies and information into their practices. With healthcare budgets at the top of the Canadian political agenda, governments require justification of healthcare expenditures. Evidence-based guidelines will inevitably be used in funding decisions (6), and as the trend toward improved cost and efficiency in healthcare delivery continues, so will the need for guidelines (2,7).

A GROWING HEALTHCARE PROBLEM

Diabetes is a common chronic disease, and type 2 diabetes, which accounts for the vast majority of cases, has become a public health issue that is increasing significantly worldwide. The most recent available Canadian data (from the National Diabetes Surveillance Strategy [NDSS]) indicate that in 1998/1999, the physician-diagnosed prevalence of diabetes in adults (people ≥20 years of age) was 4.8% (approximately 1 054 100 people) (8). However, population-based studies have identified prevalence rates to be 30 to 50% higher (9-11), suggesting that the true prevalence may be >7%.

A number of factors predispose individuals to type 2 diabetes, including heredity, age, ethnicity and socioeconomic status. Population-specific prevalence data reveal a higher burden of disease and increasing rates of complications among certain ethnic groups (12-15). The highest rates of diabetes are seen in the lower income quintiles (16). In the 1998/1999 National Population Health Survey (17), 21.4% of people with diabetes reported low income (vs. 12.8% in the general population) and 42.7% reported not finishing secondary school (vs. 22.5% in the general population). People in lower income brackets and with fewer years of formal education also report higher rates of smoking, less physical activity and higher rates of overweight (17,18), with the latter 2 factors being major precursors of, and modifiable risk factors for, diabetes.

Demographic trends that will contribute to an increased prevalence of diabetes in Canada include an aging population (19), increasing immigration from high-risk populations (20) and growth in the Aboriginal population (21), all of which will dramatically affect health service requirements in the acute, chronic and home care sectors (8,22). Primary care providers will have to care for increasing numbers of patients with diabetes who will live longer and with more advanced stages of the disease (16). The increasing prevalence of obesity (23) in the Western World will also result in an increase in the burden of diabetes. Some authors have speculated that increases in childhood obesity and low levels of physical activity will constitute the public health crisis of the 21st century (24,25).

Diabetes is costly to both the affected individual and to society. Recent data from Ontario, Canada, indicate that diabetes shortens life spans by an average of 13 years (12). People with diabetes also have medical expenditures that are approximately 2.4 times higher than would be incurred if they did not have diabetes (26). Economic analyses of the costs of diabetes to the Canadian healthcare system have produced estimates that vary widely; however, 1 recent study calculated that the economic cost of diabetes in Canada in 1998 was between US $4.76 and $5.23 billion (27). The annual direct medical costs associated with diabetes care for patients just diagnosed with diabetes, before considering any complications, were US $573 million. Of the complications

The initial draft of this chapter was prepared by Stewart B. Harris MD MPH FCFP FACPM.

of diabetes, cardiovascular disease (CVD) was by far the costliest (US $637 million), highlighting the importance of CVD prevention in patients with diabetes (27). The direct medical and indirect productivity-related costs of diabetes in the United States (US) for 2002 were recently estimated at US $132 billion (26), representing an approximately 35% increase since 1997. Given the increase over a 5-year period in the US, the 1998 Canadian figures quoted above likely underestimate the true financial burden of the disease.

While the prevention of and cure for type 1 diabetes remain elusive, encouraging data have emerged since publication of the 1998 Clinical Practice Guidelines for the Management of Diabetes in Canada demonstrating that type 2 diabetes can be prevented (28-31). Canadian research is urgently needed to define effective strategies, tailored to specific populations, to prevent and treat obesity and to encourage physical activity. Health promotion and disease prevention strategies must also include thoughtful and coordinated government policies aimed at addressing poverty and other systemic barriers to health (3,5,18,32).

ADVOCACY AND ACCESS TO CARE

All people with diabetes should be assessed on a case-by-case basis and should not be subject to blanket discrimination in any life circumstance (e.g. education, employment, driver's licensing, insurance) because of diabetes. The healthcare system should recognize the rights of people with diabetes by striving to include them in healthcare delivery planning, and ensuring that they have timely, affordable and ongoing access to diabetes education, comprehensive treatment services provided by qualified professionals, and appropriate access to pharmaceuticals and medical devices that can improve quality of life. Such access may also prevent future interventions that are more costly and less effective. In addition, governments should commit to a strategy to ensure that the costs of medications and supplies for the management of diabetes and diabetes-related complications are not a burden to the individual or a barrier to managing the disease.

DISSEMINATION AND TRANSLATION OF GUIDELINES

Practitioners have been inundated with clinical practice guidelines during the last decade. While the effect of guidelines on family practice has been underresearched, studies on this topic have shown that guidelines have often fallen short of their intended objective to improve patient care and health outcomes (7,33,34). Therefore, the publication of guidelines should be seen as the starting point, rather than the end point, of their development and dissemination (6).

The challenges of effective dissemination and implementation of guidelines were identified by the Expert Committee, and a dissemination strategy was developed concurrently with the development of the guidelines. The current guidelines have incorporated appendices and clinical and patient tools, and identified additional resources to help clinicians adopt and implement evidence-based recommendations. In addition, the web-based version of the guidelines will be fully searchable, and will include relevant links, online risk engines and other web-based resources. Technical reviews and summary articles in subspecialty journals are planned to reach key target audiences. Evidence about prevention and management will also be translated into messages targeted to the general public and people with diabetes.

CONCLUSION

Ongoing provincial and national monitoring of people with diabetes are now possible with the establishment of the NDSS. Data generated by the NDSS will facilitate the determination of epidemiological trends, the effect of the disease on healthcare resource utilization and economic impact. A better understanding of these issues is needed to help direct healthcare policy as it relates to diabetes. In addition, existing diabetes care models need to be formally evaluated to ensure that they effectively address the needs of people with or at risk of diabetes.

The care of people with diabetes is complex. These guidelines are not intended to be a textbook on diabetes care, but rather a useful reference to help translate evidence into practice and to help direct policy. Research and new technologies and therapeutics are rapidly expanding our knowledge of and ability to manage diabetes and its related complications. This and the burgeoning worldwide epidemic make it incumbent upon healthcare professionals to remain current in this ever-changing field.

REFERENCES

1. Meltzer S, Leiter L, Daneman D, et al. 1998 clinical practice guidelines for the management of diabetes in Canada. *CMAJ.* 1998;159(suppl 8):S1-S29.
2. Haynes RB, Gerstein HC. What is evidence? In: Gerstein HC, Haynes RB, eds. *Evidence-based Diabetes Care.* Hamilton, ON: BC Decker Inc.; 2001:1-12.
3. Romanow RJ. *Building on Values. The Future of Health Care in Canada–Final Report.* Ottawa, ON: Commission on the Future of Health Care in Canada; 2002. Publication CP32-85/2002E-IN. Available at: http://www.hc-sc.gc.ca/english/care/romanow/hcc0023.html. Accessed November 7, 2003.
4. Standing Senate Committee on Social Affairs, Science and Technology. *The Health of Canadians–The Federal Role. Volume Six: Recommendations for Reform.* Ottawa, ON: The Senate; 2002. Available at: http://www.parl.gc.ca/37/2/parlbus/commbus/senate/Com-e/SOCI-E/rep-e/repoct02vol6-e.htm. Accessed November 7, 2003.
5. Vinicor F. New models of diabetes healthcare delivery. *Can J Diabetes Care.* 2001;25(suppl 2):24-30.
6. Harris S, Webster-Bogaert S, Lillie D, et al. A model for the dissemination of clinical practice guidelines—the Canadian Diabetes Association experience. *Can J Diabetes Care.* 2000;24:64-69.

7. Harris SB, Webster-Bogaert S. Evidence-based clinical practice guidelines. In: Gerstein HC, Haynes RB, eds. *Evidence-based Diabetes Care*. Hamilton, ON: BC Decker Inc.; 2001:48-61.
8. Health Canada. *Diabetes in Canada*. 2nd ed. Ottawa, ON: Centre for Chronic Disease Prevention and Control, Population and Public Health Branch, Health Canada; 2002. Available at: http://www.hc-sc.gc.ca/pphb-dgspsp/publicat/dic-dac2/english/01cover_e.html. Accessed November 7, 2003.
9. Leiter LA, Barr A, Bélanger A, et al. Diabetes Screening in Canada (DIASCAN) Study: prevalence of undiagnosed diabetes and glucose intolerance in family physician offices. *Diabetes Care*. 2001;24:1038-1043.
10. Harris MI, Flegal KM, Cowie CC, et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. The Third National Health and Nutrition Examination Survey, 1988–1994. *Diabetes Care*. 1998;21:518-524.
11. Dunstan DW, Zimmet PZ, Welborn TA, et al. The rising prevalence of diabetes and impaired glucose tolerance: the Australian Diabetes, Obesity and Lifestyle Study. *Diabetes Care*. 2002;25:829-834.
12. Manuel DG, Schultz SE. Diabetes health status and risk factors. In: Hux JE, Booth GL, Slaughter PM, et al, eds. *Diabetes in Ontario. An ICES Practice Atlas*. Toronto, ON: Institute for Clinical Evaluative Sciences; 2003:4.77-4.94. Available at: http://www.ices.on.ca. Accessed November 7, 2003.
13. *First Nations and Inuit Regional Health Survey: National Report 1999*. St. Regis, QC: First Nations and Inuit Regional Health Survey National Steering Committee; 1999. Available at: http://www.afn.ca/Programs/Health%20Secretariat/PDF's/title.pdf. Accessed November 7, 2003.
14. Shah BR, Hux JE, Zinman B. Increasing rates of ischemic heart disease in the Native population of Ontario, Canada. *Arch Intern Med*. 2000;160:1862-1866.
15. Anand SS, Yusuf S, Vuksan V, et al. Differences in risk factors, atherosclerosis, and cardiovascular disease between ethnic groups in Canada: the Study of Health Assessment and Risk in Ethnic groups (SHARE). *Lancet*. 2000;356:279-284.
16. Hux JE, Tang M. Patterns of prevalence and incidence of diabetes. In: Hux JE, Booth GL, Slaughter PM, et al, eds. *Diabetes in Ontario. An ICES Practice Atlas*. Toronto, ON: Institute for Clinical Evaluative Sciences; 2003:1.1-1.18. Available at: http://www.ices.on.ca. Accessed November 7, 2003.
17. Statistics Canada. National Population Health Survey — Household Component Longitudinal, 1998–1999. Ottawa, ON: Statistics Canada; 2000. Available at: http://www.statcan.ca/english/sdds/3225.htm#17214_3. Accessed November 7, 2003.
18. Raphael D. *Inequality is Bad for Our Hearts. Why Low Income and Social Exclusion are Major Causes of Heart Disease in Canada*. Toronto, ON: North York Heart Health Network; 2001. Available at: http://www.turningpointprogram.org/Pages/heartFullReport.pdf. Accessed November 7, 2003.
19. Statistics Canada. *Profile of the Canadian Population by Age and Sex: Canada Ages*. Ottawa, ON: Statistics Canada; 2002. Publication 96F0030XIE2001002. Available at: http://www12.statcan.ca/english/census01/Products/Analytic/companion/age/contents.cfm. Accessed November 7, 2003.
20. Statistics Canada. *Canada's Ethnocultural Portrait: The Changing Mosaic*. Ottawa, ON: Statistics Canada; 2003. Publication 96F0030XIE2001008. Available at: http://www12.statcan.ca/english/census01/Products/Analytic/companion/etoimm/contents.cfm. Accessed November 7, 2003.
21. Statistics Canada. *Aboriginal Identity Population (3), Registered Indian Status (3), Age Groups (11B), Sex (3) and Area of Residence (7) for Population, for Canada, Provinces and Territories, 2001 Census – 20% Sample Data (Aboriginal Peoples of Canada)*. Ottawa, ON: Statistics Canada; 2003. Publication 97F0011XCB2001005. Available at: http://www/statcan.ca/english/IPS/Data/97F0011XIE2001006.htm. Accessed November 7, 2003.
22. Amos AF, McCarty DJ, Zimmet P. The rising global burden of diabetes and its complications: estimates and projections to the year 2010. *Diabet Med*. 1997;14(suppl 5):S1-S85.
23. Mokdad AH, Bowman BA, Ford ES, et al. The continuing epidemics of obesity and diabetes in the United States. *JAMA*. 2001;286:1195-1200.
24. Troiano RP, Flegal KM. Overweight children and adolescents: description, epidemiology, and demographics. *Pediatrics*. 1998;101:497-504.
25. Tremblay MS, Willms JD. Secular trends in the body mass index of Canadian children. *CMAJ*. 2000;163:1429-1433.
26. American Diabetes Association. Economic costs of diabetes in the U.S. in 2002. *Diabetes Care*. 2003;26:917-932.
27. Dawson KG, Gomes D, Gerstein H, et al. The economic cost of diabetes in Canada, 1998. *Diabetes Care*. 2002;25:1303-1307.
28. Hu FB, Manson JE, Stampfer MJ, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med*. 2001;345:790-797.
29. Tuomilehto J, Lindström J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med*. 2001;344:1343-1350.
30. Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care*. 1997;20:537-544.
31. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393-403.
32. Epp J. *Achieving Health for All: A Framework for Health Promotion*. Ottawa, ON: Health Canada; 1986. Available at: http://www.frcentre.net/library/AchievingHealthForAll.pdf. Accessed November 7, 2003.
33. Harris SB, Stewart M, Brown JB, et al. Type 2 diabetes in family practice. Room for improvement. *Can Fam Physician*. 2003;49:778-785.
34. Worrall G, Chaulk P, Freake D. The effects of clinical practice guidelines on patient outcomes in primary care: a systematic review. *CMAJ*. 1997;156:1705-1712.

Definition, Classification and Diagnosis of Diabetes and Other Dysglycemic Categories

Canadian Diabetes Association
Clinical Practice Guidelines Expert Committee

DEFINITION OF DIABETES AND DYSGLYCEMIA

Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, insulin action or both. The chronic hyperglycemia of diabetes is associated with significant long-term sequelae, particularly damage, dysfunction and failure of various organs—especially the kidneys, eyes, nerves, heart and blood vessels.

Dysglycemia is a qualitative term used to describe blood glucose (BG) that is abnormal, without defining a threshold. The adoption of this term reflects uncertainty about optimal BG ranges and the current understanding that cardiovascular (CV) risk and mortality risk exist in people with even slightly elevated BG levels.

CLASSIFICATION OF DIABETES

The classification of diabetes is summarized in Table 1 and Appendix 1 (1,2).

Table 1. Classification of diabetes (1)

- **Type 1 diabetes** encompasses diabetes that is primarily a result of pancreatic beta cell destruction and that is prone to ketoacidosis. This form includes cases due to an autoimmune process and those for which the etiology of beta cell destruction is unknown.
- **Type 2 diabetes*** may range from predominant insulin resistance with relative insulin deficiency to a predominant secretory defect with insulin resistance.
- **Gestational diabetes mellitus** refers to glucose intolerance with first onset or recognition during pregnancy.
- A wide variety of relatively uncommon conditions are listed under **"other specific types."** These consist mainly of specific genetically defined forms of diabetes or diabetes associated with other diseases or drug use (see Appendix 1).

*Includes latent autoimmune diabetes in adults (LADA), the term used to describe the small number of people with apparent type 2 diabetes who appear to have immune-mediated loss of pancreatic beta cells (2).

The initial draft of this chapter was prepared by Ehud Ur MB FRCP.

DIAGNOSTIC CRITERIA

The diagnostic criteria for diabetes and the plasma glucose (PG) thresholds for other diagnostic categories are summarized in Tables 2 and 3 (1). These criteria are based on venous sample methods used in the laboratory.

Table 2. Diagnosis of diabetes

FPG ≥7.0 mmol/L
Fasting = no caloric intake for at least 8 hours
or
Casual PG ≥11.1 mmol/L + symptoms of diabetes
Casual = any time of the day, without regard to the interval since the last meal
Classic symptoms of diabetes = polyuria, polydipsia and unexplained weight loss
or
2hPG in a 75-g OGTT ≥11.1 mmol/L

A confirmatory laboratory glucose test (an FPG, casual PG, or a 2hPG in a 75-g OGTT) must be done in all cases on another day in the absence of unequivocal hyperglycemia accompanied by acute metabolic decompensation.

2hPG = 2-hour plasma glucose
FPG = fasting plasma glucose
OGTT = oral glucose tolerance test
PG = plasma glucose

Table 3. PG levels for diagnosis of IFG, IGT and diabetes

	FPG (mmol/L)		*2hPG in a 75-g OGTT (mmol/L)*
IFG	6.1–6.9		NA
IFG (isolated)	6.1–6.9	and	<7.8
IGT (isolated)	<6.1	and	7.8–11.0
IFG and IGT	6.1–6.9	and	7.8–11.0
Diabetes	≥7.0	or	≥11.1

2hPG = 2-hour plasma glucose
FPG = fasting plasma glucose
IFG = impaired fasting glucose
IGT = impaired glucose tolerance
NA = not applicable
OGTT = oral glucose tolerance test
PG = plasma glucose

Diabetes

A fasting plasma glucose (FPG) level of 7.0 mmol/L correlates most closely with a 2-hour plasma glucose (2hPG) value of ≥11.1 mmol/L in a 75-g oral glucose tolerance test (OGTT) and best predicts the development of microvascular disease (1). This permits the diagnosis of diabetes to be made on the basis of the commonly available FPG test. Although the frequency distributions of glycosylated hemoglobin (A1C) levels in some studies have characteristics similar to those obtained from FPG and 2hPG tests, the lack of standardization of the A1C test precludes its use in the diagnosis of diabetes.

Prediabetes

Elevated BG levels below the threshold for diabetes also have clinical consequences. The term 'prediabetes' is a practical and convenient term for impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) (Table 3), which place individuals at risk of developing diabetes and its complications. It is important to stress that not all individuals with prediabetes will necessarily progress to diabetes. Indeed, a significant proportion of people who are diagnosed with IGT will revert to normoglycemia. Identifying people with prediabetes, particularly in the context of the metabolic syndrome, indicates those who would benefit from CV risk factor modification.

While people with isolated IFG or isolated IGT do not have the diabetes-associated risk for microvascular disease, they have a higher risk for the development of diabetes and cardiovascular disease (CVD) (3). IGT is more strongly associated with CVD outcomes. However, individuals identified as having both IFG and IGT are at higher risk for diabetes as well as CVD. Lifestyle interventions have been shown to be highly effective in delaying or preventing the onset of diabetes in people with IGT (4,5). Evidence has not yet demonstrated reductions in CVD and total mortality.

Table 4. Clinical identification of the metabolic syndrome using NCEP ATP III criteria (9)

Risk factor	*Defining level**
FPG	≥6.1 mmol/L
BP	≥130/85 mm Hg
TG	≥1.7 mmol/L
HDL-C Men Women	 <1.0 mmol/L <1.3 mmol/L
Abdominal obesity Men Women	Waist circumference >102 cm >88 cm

*A diagnosis of metabolic syndrome is made when 3 or more of the risk determinants are present.

BP = blood pressure
FPG = fasting plasma glucose
HDL-C = high-density lipoprotein cholesterol
NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III
TG = triglyceride

Metabolic syndrome

Dysglycemia and type 2 diabetes are often manifestations of a much broader underlying disorder (6,7), including the metabolic syndrome—a highly prevalent, multifaceted condition characterized by a distinctive constellation of abnormalities that include abdominal obesity, hypertension, dyslipidemia, insulin resistance and dysglycemia. Patients with the metabolic syndrome are at significant risk of developing diabetes and CVD. Evidence now exists to support an aggressive approach to identifying people with the metabolic syndrome and treating not only the hyperglycemia, but also the associated CV risk factors, such as hypertension, dyslipidemia and abdominal obesity, with the hope of significantly reducing CV morbidity and mortality.

A lack of consensus exists regarding operational definitions of the metabolic syndrome. In 1998, the World Health Organization (8) proposed a unifying definition that includes identification of the presence of insulin resistance. More recently, the United States (US) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) provided an operational definition based on 3 or more criteria that does not require a measure of insulin resistance (Table 4) (9). Data from the Third National Health and Nutrition Survey (NHANES III), which employed the ATP III criteria, found that the overall prevalence of the metabolic syndrome in the US was approximately 20 to 25% (10).

OTHER RELEVANT GUIDELINES

Screening and Prevention, p. S10
Macrovascular Complications, Dyslipidemia and Hypertension, p. S58
Type 2 Diabetes in Children and Adolescents, p. S91

RELEVANT APPENDICES

Appendix 1: Etiologic Classification of Diabetes Mellitus, p. S118
Appendix 2: History and Examination: Initial and Follow-up Visits, p. S119

REFERENCES

1. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care.* 2003;26(suppl 1):S5-S20.
2. Turner R, Stratton I, Horton V, et al. UKPDS 25: autoantibodies to islet-cell cytoplasm and glutamic acid decarboxylase for prediction of insulin requirement in type 2 diabetes. *Lancet.* 1997;350:1288-1293.

3. Coutinho M, Gerstein HC, Wang Y, et al. The relationship between glucose and incident cardiovascular events. A meta-regression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care*. 1999; 22:233-240.
4. Tuomilehto J, Lindström J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med*. 2001; 344:1343-1350.
5. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393-403.
6. Zimmet PZ. Diabetes epidemiology as a tool to trigger diabetes research and care. *Diabetologia*. 1999;42:499-518.
7. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes*. 1988;37:1595-1607.
8. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med*. 1998;15:539-553.
9. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486-2497.
10. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the Third National Health and Nutrition Examination Survey. *JAMA*. 2002; 287:356-359.

Insulin Therapy in Type 1 Diabetes

Canadian Diabetes Association
Clinical Practice Guidelines Expert Committee

INTRODUCTION

Insulin therapy remains the mainstay of treatment for type 1 diabetes mellitus. Insulin is primarily produced by recombinant DNA technology and is formulated either as chemically identical to human insulin or as a modification of human insulin (insulin analogues) designed to improve pharmacokinetics. Animal insulins are becoming less commercially available.

Insulin preparations can be classified according to their duration of action, and further differentiated by their onset of action and peak action time (Table 1). Premixed insulin preparations are available, but are not suitable for patients with type 1 diabetes who usually need to frequently change the individual components of their insulin regimens.

INSULIN DELIVERY SYSTEMS

Insulin can be administered by syringe, pen (or pen-like device) or pump (continuous subcutaneous insulin infusion [CSII]). Insulin pen devices facilitate the use of multiple injections of insulin and their use should be encouraged. CSII therapy is a safe and effective way to deliver intensive insulin therapy for selected patients and may provide some advantages over other methods of intensive therapy (1-3).

INITIATION OF INSULIN THERAPY

Patients must receive initial and ongoing education that includes comprehensive information on how to care for and use insulin, recognition and treatment of hypoglycemia, management of sick days, adjustments for food intake and physical activity, and self-monitoring of blood glucose (SMBG).

INSULIN REGIMENS

A variety of insulin regimens have been used and studied. Insulin regimens should be adapted to an individual's treatment goals, lifestyle, diet, age, general health, motivation, capacity for hypoglycemia awareness and self-management, and social and financial circumstances. After an initial 'honeymoon period,' during which insulin requirements may decrease, insulin requirements will increase with time due to progressive beta cell destruction in both children and adults with type 1 diabetes.

The initial draft of this chapter was prepared by Ellen L. Toth MD FRCPC; Jean-François Yale MD CSPQ; Keith G. Dawson MD PhD FRCPC.

While fixed-dose regimens (conventional therapy) were previously the most commonly used regimens, and are occasionally still used, they are not preferred. The Diabetes Control and Complications Trial (DCCT) conclusively demonstrated that intensive treatment of type 1 diabetes significantly delays the onset and slows the progression of microvascular complications (4). The most successful protocols for type 1 diabetes rely on basal-bolus regimens with intermediate- or long-acting insulin, or extended long-acting insulin analogue once or twice daily as the basal insulin, and fast-acting insulin or rapid-acting insulin analogue as the bolus insulin for food intake at each meal (intensive therapy). Such protocols attempt to imitate normal pancreatic secretion, which consists of basal insulin secretion and a bolus

Table 1. Types of insulin

Insulin type/action	*Trade names*
Rapid-acting analogue (clear) Onset: 10–15 min Peak: 60–90 min Duration: 4–5 h	Humalog® (insulin lispro) NovoRapid® (insulin aspart)
Fast-acting (clear) Onset: 0.5–1 h Peak: 2–4 h Duration: 5–8 h	Humulin®-R Novolin®ge Toronto
Intermediate-acting (cloudy) Onset: 1–3 h Peak: 5–8 h Duration: up to 18 h	Humulin®-L Humulin®-N Novolin®ge NPH
Long-acting (cloudy) Onset: 3–4 h Peak: 8–15 h Duration: 22–26 h	Humulin®-U
Extended long-acting analogue Onset: 90 min Duration: 24 h	Lantus®* (insulin glargine)
Premixed (cloudy) A single vial or cartridge contains a fixed ratio of insulin (% rapid- or fast-acting to % intermediate-acting insulin)	Humalog® Mix25™ Humulin® (20/80, 30/70) Novolin®ge (10/90, 20/80, 30/70, 40/60, 50/50)

*Approved, but not yet available, in Canada

component (postprandial insulin secretion). Insulin lispro (Humalog®) and insulin aspart (NovoRapid®) should be administered 0 to 15 minutes before meals; however, since their onset of action is very fast, they can also be administered up to 15 minutes after a meal. Regular insulin should ideally be administered 30 to 45 minutes prior to a meal. Insulin lispro or insulin aspart, in combination with adequate basal insulin, is preferred to regular insulin to achieve postprandial glycemic targets and improve glycosylated hemoglobin (A1C) while minimizing the occurrence of hypoglycemia (5-11).

Insulin glargine (Lantus®) is an extended long-acting insulin analogue, approved, but not yet available, in Canada, but approved and in use in the United States and Europe. When used as a basal insulin in well-controlled patients (with regular insulin for meals), insulin glargine results in lower fasting plasma glucose (FPG) levels and less nocturnal hypoglycemia compared to once- or twice-daily NPH. No difference in A1C was observed between the 2 regimens after 6 months of treatment (12). Due to its acidic pH, insulin glargine must not be mixed with other insulins in the same syringe.

RECOMMENDATIONS

1. To achieve glycemic targets in people with type 1 diabetes, multiple daily insulin injections (3 or 4 per day) or the use of CSII as part of an intensive diabetes management regimen should be considered *[Grade A, Level 1A (4)]*.
2. Insulin aspart or insulin lispro, in combination with adequate basal insulin, is preferred to regular insulin to achieve postprandial glycemic targets and improve A1C while minimizing the occurrence of hypoglycemia *[Grade B, Level 2 (5-11)]*.
3. Insulin lispro or insulin aspart should be used when CSII is used in patients with type 1 diabetes *[Grade B, Level 2 (13,14)]*. Buffered regular insulin is equally effective in experienced insulin pump users *[Grade B, Level 2 (14)]*. (Buffered regular insulin is available only by special request through the manufacturer or Health Canada.)
4. Insulin glargine should be considered for use as the basal insulin in well-controlled patients who have problems controlling their FPG levels or to reduce overnight hypoglycemia *[Grade B, Level 2 (12)]*.

HYPOGLYCEMIA

Drug-induced hypoglycemia is a major obstacle for individuals with type 1 diabetes who are trying to achieve glycemic targets. Hypoglycemia can be severe and result in confusion, coma or seizure, requiring the assistance of other individuals. Significant risk of hypoglycemia often necessitates less stringent glycemic goals. The negative social and emotional impact of hypoglycemia may make patients reluctant to intensify therapy.

The diabetes healthcare team should review the patient's experience with hypoglycemia at each visit. This should include an estimate of cause, frequency, symptoms, recognition, severity and treatment.

Severe hypoglycemic reactions and hypoglycemia unawareness

Asymptomatic hypoglycemia is the presence of a biochemically low blood glucose (BG) level without any symptoms. Hypoglycemia unawareness occurs when the threshold for the development of autonomic warning symptoms is close to or lower than the threshold for the neuroglycopenic symptoms, such that the first signs of hypoglycemia will often be confusion or loss of consciousness. Severe hypoglycemic reactions are the primary barrier to achieving optimal glycemic control in people with type 1 diabetes (15). Severe hypoglycemic episodes occur frequently during sleep or in the absence of hypoglycemia awareness that alerts patients to take actions to correct their BG levels (16,17). Asymptomatic nocturnal hypoglycemia is common and often lasts >4 hours (16,18-21). Hypoglycemia is more likely to cause seizures during the night than during the day. To reduce the risk of asymptomatic nocturnal hypoglycemia, individuals using intensive insulin therapy should periodically monitor overnight BG levels at a time that corresponds with the peak action time of their overnight insulin.

In people with type 1 diabetes, hypoglycemia occurs at an average rate of approximately 2 episodes per week. Increasing frequency of hypoglycemia can lead to a decrease in the hormonal responses to hypoglycemia (22), which, in turn, can lead to decreased awareness of hypoglycemia and defective glucose counterregulation.

Hypoglycemia unawareness and defective glucose counterregulation are potentially reversible. Strict avoidance of hypoglycemia for a period of 2 days to 3 months has been associated with improvement in the recognition of severe hypoglycemia, in the counterregulatory hormone responses, or both (23-29).

The major risk factors for severe hypoglycemia include a prior episode of severe hypoglycemia (30-32), a current low A1C (<6.0%) (16,31,33,34), hypoglycemia unawareness (35), long duration of diabetes (33,36), autonomic neuropathy (37), adolescence (38) and preschool-age children unable to detect and/or treat mild hypoglycemia on their own (Table 2).

Table 2. Risk factors for severe hypoglycemia

- Prior episode of severe hypoglycemia
- Current low A1C (<6.0%)
- Hypoglycemia unawareness
- Long duration of diabetes
- Autonomic neuropathy
- Adolescence
- Preschool-age children unable to detect and/or treat mild hypoglycemia on their own

A1C = glycosylated hemoglobin

Patients at high risk for severe hypoglycemia should be informed of their risk and counselled, along with their significant others, on preventing and treating hypoglycemia (including use of glucagon), preventing driving and industrial accidents through SMBG and taking appropriate precautions prior to the activity, and documenting BG readings taken during sleeping hours. Individuals may need to have their insulin regimen adjusted appropriately to lower their risk.

Animal vs. human insulin

There is no significant clinical difference between animal and human insulin in terms of the symptomatic response to (39,40) or the frequency of hypoglycemia (41,42). Furthermore, there is no proof that animal insulins afford advantages regarding hypoglycemia awareness (40).

Intensive vs. conventional insulin therapy

Hypoglycemia is the most common adverse effect of intensive insulin therapy in patients with type 1 diabetes. In the DCCT, 35% of patients in the conventional treatment group and 65% in the intensive group experienced at least 1 episode of severe hypoglycemia (31). In a meta-analysis of 14 trials, the median incidence of severe hypoglycemia was 4.6 and 7.9 episodes per 100 patient-years in the conventionally treated and intensively treated patients, respectively (34). Studies have suggested that with adequate self-management education, appropriate glycemic targets, SMBG and professional support, intensive therapy may result in less hypoglycemia than reported in the DCCT (43-47).

Rapid-acting insulin analogues vs. regular insulin

Studies have found no differences in the onset, magnitude and temporal pattern of the physiologic, symptomatic and counterregulatory hormonal responses to acute hypoglycemia induced by regular human insulin compared with the rapid-acting insulin analogue lispro (48,49).

Lifestyle factors

Deviations from recommended or appropriate self-management behaviours, such as eating less food, taking more insulin and engaging in more activity, account for 85% of hypoglycemic episodes (50,51). For patients managed with fixed-dose insulin regimens, care should be taken to develop an individualized meal and activity plan that the person can and will follow (52). Adding bedtime snacks may be required to avoid nocturnal hypoglycemia (53,54).

Knowledge of the acute effects of exercise is mandatory. Low- to moderate-intensity exercise lowers BG levels both during and after the activity, increasing the risk of a hypoglycemic episode. These effects on BG levels can be modified by altering diet, insulin and the type and timing of exercise. In contrast, high-intensity exercise raises BG levels during and immediately after the event. SMBG before, during and, especially, for many hours after exercise is important for establishing the patient's response to exercise and guiding the appropriate management of exercise. If preprandial BG level is >14.0 mmol/L and urine ketone level is >8.0 mmol/L or blood ketone level is >3.0 mmol/L, exercise should not be performed, as metabolic deterioration will occur (55).

RECOMMENDATIONS

5. Risk factors for severe hypoglycemia should be identified in people with type 1 diabetes so that appropriate strategies can be used to minimize hypoglycemia *[Grade D, Consensus]*.

6. The following strategies should be implemented to reduce the risk of hypoglycemia and to increase physiologic counterregulatory responses to hypoglycemia in individuals with hypoglycemia unawareness:
   - increased frequency of SMBG, including episodic assessment during sleeping hours;
   - less stringent glycemic targets; and
   - multiple insulin injections *[Grade D, Level 4 (27,28)]*.

7. All individuals currently using insulin or starting intensive insulin therapy should be counselled about the risk and prevention of insulin-induced hypoglycemia *[Grade D, Consensus]*.

8. In an attempt to reduce the development of hypoglycemia unawareness in people with type 1 diabetes, the frequency of mild hypoglycemic episodes should be minimized (<3 episodes per week), particularly in those at high risk *[Grade D, Level 4 (22)]*.

9. To reduce the risk of asymptomatic nocturnal hypoglycemia, individuals should periodically monitor overnight BG levels at a time that corresponds with the peak action time of their overnight insulin and consume a bedtime snack with at least 15 g of carbohydrate and 15 g of protein if their bedtime BG level is <7.0 mmol/L *[Grade B, Level 2 (54)]*.

OTHER RELEVANT GUIDELINES

Organization and Delivery of Care, p. S14
Targets for Glycemic Control, p. S18
Monitoring Glycemic Control, p. S21
Physical Activity and Diabetes, p. S24
Nutrition Therapy, p. S27
Pharmacologic Management of Type 2 Diabetes, p. S37
Hypoglycemia, p. S43
Type 1 Diabetes in Children and Adolescents, p. S84
Type 2 Diabetes in Children and Adolescents, p. S91
Pre-existing Diabetes and Pregnancy, p. S94
Gestational Diabetes Mellitus, p. S99
Diabetes in the Elderly, p. S106
Perioperative Glycemic Control, p. S113
Peri-acute Coronary Syndrome Glycemic Control, p. S115

REFERENCES

1. Pickup J, Mattock M, Kerry S. Glycaemic control with continuous subcutaneous insulin infusion compared with intensive

insulin injections in patients with type 1 diabetes: meta-analysis of randomised controlled trials. *BMJ*. 2002;324:705-708.
2. Tsui E, Barnie A, Ross S, et al. Intensive insulin therapy with insulin lispro: a randomized trial of continuous subcutaneous insulin infusion versus multiple daily insulin injection. *Diabetes Care*. 2001;24:1722-1727.
3. DeVries JH, Snoek FJ, Kostense PJ, et al. A randomized trial of continuous subcutaneous insulin infusion and intensive injection therapy in type 1 diabetes for patients with long-standing poor glycemic control. *Diabetes Care*. 2002;25:2074-2080.
4. 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. *N Engl J Med*. 1993; 329:977-986.
5. Ciofetta M, Lalli C, Del Sindaco P, et al. Contribution of postprandial versus interprandial blood glucose to HbA_{1c} in type 1 diabetes on physiologic intensive therapy with lispro insulin at mealtime. *Diabetes Care*. 1999;22:795-800.
6. Raskin P, Guthrie RA, Leiter L, et al. Use of insulin aspart, a fast-acting insulin analog, as the mealtime insulin in the management of patients with type 1 diabetes. *Diabetes Care*. 2000;23:583-588.
7. Home PD, Lindholm A, Riis A. Insulin aspart vs. human insulin in the management of long-term blood glucose control in type 1 diabetes mellitus: a randomized controlled trial. *Diabet Med*. 2000;17:762-770.
8. Anderson JH Jr, Brunelle RL, Koivisto VA, et al. Reduction of postprandial hyperglycemia and frequency of hypoglycemia in IDDM patients on insulin-analog treatment. *Diabetes*. 1997;46:265-270.
9. Holleman F, Schmitt H, Rottiers R, et al. Reduced frequency of severe hypoglycemia and coma in well-controlled IDDM patients treated with insulin lispro. *Diabetes Care*. 1997; 20:1827-1832.
10. Brunelle BL, Llewelyn J, Anderson JH Jr, et al. Meta-analysis of the effect of insulin lispro on severe hypoglycemia in patients with type 1 diabetes. *Diabetes Care*. 1998;21:1726-1731.
11. Annuzzi G, Del Prato S, Arcari R, et al. Preprandial combination of lispro and NPH insulin improves overall blood glucose control in type 1 diabetic patients: a multicenter randomized crossover trial. *Nutr Metab Cardiovasc Dis*. 2001;11:168-175.
12. Ratner RE, Hirsch IB, Neifing JL, et al. Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. *Diabetes Care*. 2000;23:639-643.
13. Zinman B, Tildesley H, Chiasson J-L, et al. Insulin lispro in CSII: results of a double-blind crossover study. *Diabetes*. 1997;46:440-443.
14. Bode B, Weinstein R, Bell D, et al. Comparison of insulin aspart with buffered regular insulin and insulin lispro in continuous subcutaneous insulin infusion: a randomized study in type 1 diabetes. *Diabetes Care*. 2002;25:439-444.
15. Cryer PE. Banting lecture. Hypoglycemia: the limiting factor in the management of IDDM. *Diabetes*. 1994;43:1378-1389.
16. The DCCT Research Group. Epidemiology of severe hypoglycemia in the Diabetes Control and Complications Trial. *Am J Med*. 1991;90:450-459.
17. Daneman D, Frank M, Perlman K, et al. Severe hypoglycemia in children with insulin-dependent diabetes mellitus: frequency and predisposing factors. *J Pediatr*. 1989;115:681-685.
18. Porter PA, Byrne G, Stick S, et al. Nocturnal hypoglycaemia and sleep disturbances in young teenagers with insulin dependent diabetes mellitus. *Arch Dis Child*. 1996;75:120-123.
19. Gale EAM, Tattersall RB. Unrecognised nocturnal hypoglycaemia in insulin-treated diabetics. *Lancet*. 1979;1:1049-1052.
20. Beregszàszi M, Tubiana-Rufi N, Benali K, et al. Nocturnal hypoglycemia in children and adolescents with insulin-dependent diabetes mellitus: prevalence and risk factors. *J Pediatr*. 1997;131:27-33.
21. Vervoort G, Goldschmidt HM, van Doorn LG. Nocturnal blood glucose profiles in patients with type 1 diabetes mellitus on multiple (> or = 4) daily insulin injection regimens. *Diabet Med*. 1996;13:794-799.
22. Ovalle F, Fanelli CG, Paramore DS, et al. Brief twice-weekly episodes of hypoglycemia reduce detection of clinical hypoglycemia in type 1 diabetes mellitus. *Diabetes*. 1998; 47:1472-1479.
23. Dagogo-Jack S, Rattarasarn C, Cryer PE. Reversal of hypoglycemia unawareness, but not defective glucose counterregulation, in IDDM. *Diabetes*. 1994;43:1426-1434.
24. Fanelli C, Pampanelli S, Epifano L, et al. Long-term recovery from unawareness, deficient counterregulation and lack of cognitive dysfunction during hypoglycaemia, following institution of rational, intensive insulin therapy in IDDM. *Diabetologia*. 1994;37:1265-1276.
25. Dagogo-Jack S, Fanelli CG, Cryer PE. Durable reversal of hypoglycemia unawareness in type 1 diabetes [letter]. *Diabetes Care*. 1999;22:866-867.
26. Davis M, Mellman M, Friedman S, et al. Recovery of epinephrine response but not hypoglycemic symptom threshold after intensive therapy in type 1 diabetes. *Am J Med*. 1994;97:535-542.
27. Liu D, McManus RM, Ryan EA. Improved counter-regulatory hormonal and symptomatic responses to hypoglycemia in patients with insulin-dependent diabetes mellitus after 3 months of less strict glycemic control. *Clin Invest Med*. 1996;19:71-82.
28. Lingenfelser T, Buettner U, Martin J, et al. Improvement of impaired counterregulatory hormone response and symptom perception by short-term avoidance of hypoglycemia in IDDM. *Diabetes Care*. 1995;18:321-325.
29. Fanelli CG, Epifano L, Rambotti AM, et al. Meticulous prevention of hypoglycemia normalizes the glycemic thresholds and magnitude of most of neuroendocrine responses to, symptoms of, and cognitive function during hypoglycemia in intensively treated patients with short-term IDDM. *Diabetes*. 1993;42:1683-1689.
30. The Diabetes Control and Complications Trial Research Group. Adverse events and their association with treatment

regimens in the Diabetes Control and Complications Trial. *Diabetes Care*. 1995;18:1415-1427.
31. The Diabetes Control and Complications Trial Research Group. Hypoglycemia in the Diabetes Control and Complications Trial. *Diabetes*. 1997;46:271-286.
32. Mühlhauser I, Overmann H, Bender R, et al. Risk factors of severe hypoglycaemia in adult patients with type I diabetes—a prospective population based study. *Diabetologia*. 1998; 41:1274-1282.
33. Davis EA, Keating B, Byrne GC, et al. Hypoglycemia: incidence and clinical predictors in a large population-based sample of children and adolescents with IDDM. *Diabetes Care*. 1997;20:22-25.
34. Egger M, Davey Smith G, Stettler C, et al. Risk of adverse effects of intensified treatment in insulin-dependent diabetes mellitus: a meta-analysis. *Diabet Med*. 1997;14:919-928.
35. Gold AE, MacLeod KM, Frier BM. Frequency of severe hypoglycemia in patients with type I diabetes with impaired awareness of hypoglycemia. *Diabetes Care*. 1994;17:697-703.
36. Mokan M, Mitrakou A, Veneman T, et al. Hypoglycemia unawareness in IDDM. *Diabetes Care*. 1994;17:1397-1403.
37. Meyer C, Großmann R, Mitrakou A, et al. Effects of autonomic neuropathy on counterregulation and awareness of hypoglycemia in type 1 diabetic patients. *Diabetes Care*. 1998;21:1960-1966.
38. Diabetes Control and Complications Trial Research Group. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. *J Pediatr*. 1994;125:177-188.
39. Jacobs MA, Salobir B, Popp-Snijders C, et al. Counterregulatory hormone responses and symptoms during hypoglycaemia induced by porcine, human regular insulin, and Lys(B28), Pro(B29) human insulin analogue (insulin lispro) in healthy male volunteers. *Diabet Med*. 1997;14:248-257.
40. MacLeod KM, Gold AE, Frier BM. A comparative study of responses to acute hypoglycaemia induced by human and porcine insulins in patients with type 1 diabetes. *Diabet Med*. 1996;13:346-357.
41. MacLeod KM, Gold AE, Frier BM. Frequency, severity and symptomatology of hypoglycaemia: a comparative trial of human and porcine insulins in type 1 diabetic patients. *Diabet Med*. 1995;12:134-141.
42. Colagiuri S, Miller JJ, Petocz P. Double-blind crossover comparison of human and porcine insulins in patients reporting lack of hypoglycaemia awareness. *Lancet*. 1992;339:1432-1435.
43. Bott S, Bott U, Berger M, et al. Intensified insulin therapy and the risk of severe hypoglycaemia. *Diabetologia*. 1997;40:926-932.
44. Ahern J, Tamborlane WV. Steps to reduce the risks of severe hypoglycemia. *Diabetes Spectrum*. 1997;10:39-41.
45. Nordfeldt S, Ludvigsson J. Severe hypoglycemia in children with IDDM. A prospective population study, 1992–1994. *Diabetes Care*. 1997;20:497-503.
46. Bolli GB. How to ameliorate the problem of hypoglycemia in intensive as well as nonintensive treatment of type 1 diabetes. *Diabetes Care*. 1999;22(suppl 2):B43-B52.
47. Fanelli C, Pampanelli S, Lalli C, et al. Long-term intensive therapy of IDDM patients with clinically overt autonomic neuropathy: effects on hypoglycemia awareness and counterregulation. *Diabetes*. 1997;46:1172-1181.
48. McCrimmon RJ, Frier BM. Symptomatic and physiological responses to hypoglycaemia induced by human soluble insulin and the analogue lispro human insulin. *Diabet Med*. 1997; 14:929-936.
49. Torlone E, Fanelli C, Rambotti AM, et al. Pharmacokinetics, pharmacodynamics and glucose counterregulation following subcutaneous injection of the monomeric insulin analogue [Lys(B28),Pro(B29)] in IDDM. *Diabetologia*. 1994;37:713-720.
50. Clarke WL, Cox DJ, Gonder-Frederick LA, et al. The relationship between nonroutine use of insulin, food, and exercise and the occurrence of hypoglycemia in adults with IDDM and varying degrees of hypoglycemic awareness and metabolic control. *Diabetes Educ*. 1997;23:55-58.
51. Fritsche A, Stumvoll M, Renn W, et al. Diabetes teaching program improves glycemic control and preserves perception of hypoglycemia. *Diabetes Res Clin Pract*. 1998;40:129-135.
52. Cryer PE, Fisher JN, Shamoon H. Hypoglycemia. *Diabetes Care*. 1994;17:734-755.
53. Kaufman FR, Halvorson M, Kaufman ND. A randomized, blinded trial of uncooked cornstarch to diminish nocturnal hypoglycemia at diabetes camp. *Diabetes Res Clin Pract*. 1995;30:205-209.
54. Kalergis M, Schiffrin A, Gougeon R, et al. Impact of bedtime snack composition on prevention of nocturnal hypoglycemia in adults with type 1 diabetes undergoing intensive insulin management using lispro insulin before meals: a randomized, placebo-controlled, crossover trial. *Diabetes Care*. 2003;26:9-15.
55. American Diabetes Association. Diabetes mellitus and exercise. *Diabetes Care*. 2002;25(supp 1):S64-S68.

Pharmacologic Management of Type 2 Diabetes

Canadian Diabetes Association
Clinical Practice Guidelines Expert Committee

ORAL ANTIHYPERGLYCEMIC AGENTS, INSULIN AND COMBINATION THERAPIES

Type 2 diabetes mellitus is characterized by insulin resistance and progressive beta cell failure. While the usual therapy when diet and exercise have failed is to start with a single oral antihyperglycemic agent of any class, the use of early combination therapy is an option in the management of type 2 diabetes with oral antihyperglycemic agents. The stepwise approach described in the 1998 Clinical Practice Guidelines for the Management of Diabetes in Canada implied that it was acceptable to wait for up to 8 to 16 months before implementing aggressive therapy to treat hyperglycemia (1). However, short-term hyperglycemia can result in vascular changes, the diagnosis of type 2 diabetes is often delayed and 20 to 50% of people with type 2 diabetes present with microvascular and macrovascular complications at the time of diagnosis (2,3). Therefore, it is now recommended that the management regimens of patients with type 2 diabetes be tailored to the individual patient, aiming for glycemic targets as close to normal as possible and, in most people, as early as possible.

The initial use of combinations of submaximal doses of oral antihyperglycemic agents produces more rapid and improved glycemic control compared to monotherapy with the maximal dose of 1 agent, without a significant increase in side effects (4). Furthermore, many patients on monotherapy and with late addition of combination therapy may not attain target blood glucose (BG) levels (5). Multiple therapies may be required to achieve glycemic targets because of the progressive deterioration of glycemic control in type 2 diabetes (5). The choice of antihyperglycemic agent(s) should be based on the individual patient and the factors outlined in Table 1 (3,6-33) and Figure 1. The lag period before adding other antihyperglycemic agent(s) should be kept to a minimum, taking into account the pharmacokinetics of the different agents. With timely adjustments to and/or additions of antihyperglycemic agents, the target glycosylated hemoglobin (A1C) level should be attainable within 6 to 12 months.

A combination of oral antihyperglycemic agents and insulin often effectively controls BG levels in adults with type 2 diabetes. When insulin is added to oral antihyperglycemic agent(s), a single injection of intermediate-acting or long-acting insulin (3,34), or extended long-acting insulin analogue (insulin glargine [Lantus®], approved, but not yet available, in Canada) (14) may be added at bedtime. This approach may result in better glycemic control with a smaller dose of insulin (35) and may induce less weight gain and less hypoglycemia than the use of insulin alone (36). The combination of bedtime insulin with a biguanide (metformin) leads to less weight gain than insulin plus a sulfonylurea or twice-daily NPH insulin (11).

In individuals with type 2 diabetes, insulin therapy (without the concomitant use of oral antihyperglycemic agents) is generally used when diet, exercise, lifestyle and oral antihyperglycemic agents are not effective or are contraindicated. However, insulin may be used as the initial therapy (3), especially in the presence of marked hyperglycemia (A1C ≥9.0%). Insulin can be used temporarily during illness, pregnancy, stress, a medical procedure or surgery. There is no evidence that exogenous insulin accelerates the risk of macrovascular complications of diabetes, and its appropriate use should be encouraged (37). When insulin is used in type 2 diabetes, the insulin regimen should be tailored to achieve good metabolic control without a significant risk of hypoglycemia. With intensive glycemic control, there is an increased risk of hypoglycemia, but this risk is lower in people with type 2 diabetes than in those with type 1 diabetes. The number of insulin injections (1 to 4/day) and the time of injections may vary depending on each individual's situation (38). There is an increased risk of weight gain with insulin compared to sulfonylureas in type 2 diabetes (3). The reduction in A1C achieved with insulin therapy depends on the dosage and type of insulin.

HYPOGLYCEMIA

Drug-induced hypoglycemia is the most common cause of hypoglycemia. It is estimated that hypoglycemia of any severity occurs annually in approximately 20% of patients taking insulin secretagogues (39). Although these hypoglycemic episodes are rarely fatal, they can be associated with serious clinical sequelae. Therefore, it is important to prevent, recognize and treat hypoglycemic episodes secondary to the use of insulin secretagogues. Few large, randomized clinical trials have compared the rates of hypoglycemia between these agents.

In the United Kingdom Prospective Diabetes Study (UKPDS), the proportion of adults with type 2 diabetes who

The initial draft of this chapter was prepared by Amir Hanna MB BCh FRCPC FACP; Vincent Woo MD FRCPC; Keith G. Dawson MD PhD FRCPC; Stewart B. Harris MD MPH FCFP FACPM.

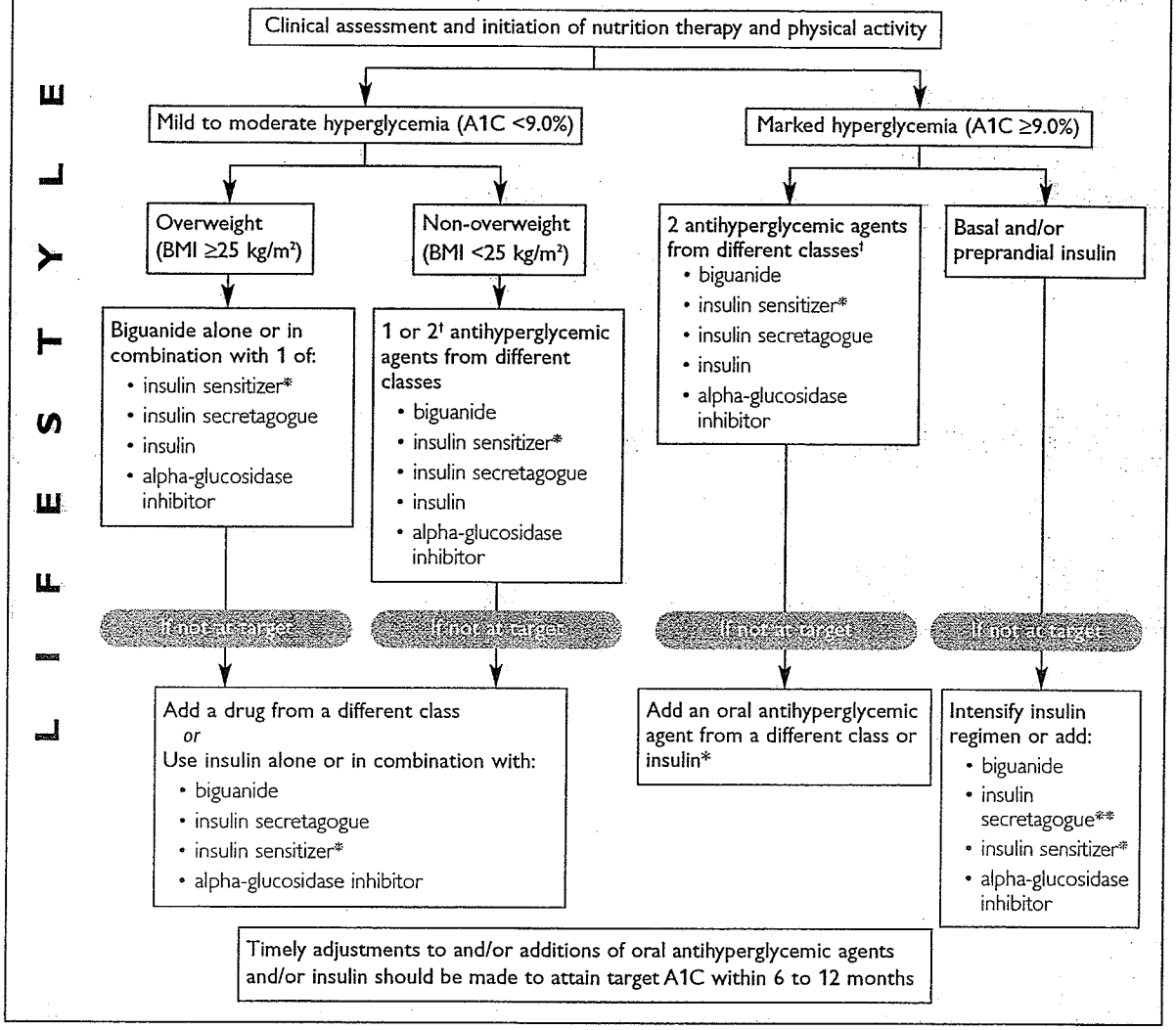
Table 1. Antihyperglycemic agents for use in type 2 diabetes

Class	*Expected decrease in A1C with monotherapy (%)*	*Therapeutic considerations*
Alpha-glucosidase inhibitor acarbose (Prandase®) (6-8)	0.5–0.8	• Not recommended as initial therapy in people with severe hyperglycemia (A1C ≥9.0%) • Mostly used in combination with other oral antihyperglycemic agents • Gastrointestinal side effects • Treat hypoglycemia with dextrose tablets, milk or honey
Biguanide metformin (Glucophage®, generic) (9,10)	1.0–1.5	• Contraindicated in patients with renal or hepatic dysfunction, or cardiac failure • Use Cockcroft-Gault formula (see "Nephropathy," p. S66) to calculate creatinine clearance (<60 mL/min indicates caution or contraindicates the use of metformin) • Associated with less weight gain than sulfonylureas and does not cause hypoglycemia • Gastrointestinal side effects
Insulin (3,11-14)	Depends on regimen	• When initiating insulin, consider adding bedtime intermediate-acting insulin, long-acting insulin or extended long-acting insulin analogue to daytime oral antihyperglycemic agents (although other regimens can be used) • Intensive insulin therapy regimen recommended if above fails to attain glycemic targets • Causes greatest reduction in A1C and has no maximal dose • Increased risk of weight gain relative to sulfonylureas and metformin
Insulin secretagogues sulfonylureas: gliclazide (Diamicron®, Diamicron® MR, generic) (15,16) glimepiride (Amaryl™) (17-19) glyburide (Diabeta®, Euglucon®, generic) (3) (note: chlorpropamide and tolbutamide are still available in Canada, but rarely used) nonsulfonylureas: nateglinide (Starlix®) (20) repaglinide (GlucoNorm®) (21-23)	1.0–1.5 0.5 (for nateglinide)	• All insulin secretagogues reduce overall glycemia similarly (except nateglinide) • Postprandial glycemia is especially reduced by nateglinide and repaglinide • Hypoglycemia and weight gain are especially common with glyburide • Consider using other class(es) of antihyperglycemic agents first in patients at high risk of hypoglycemia (e.g. the elderly) • If a sulfonylurea must be used in such individuals, gliclazide and glimepiride are associated with less hypoglycemia than glyburide • Nateglinide and repaglinide are associated with less hypoglycemia in the context of missed meals
Insulin sensitizers (TZDs) (24-32) pioglitazone (Actos®) rosiglitazone (Avandia®)	1.0–1.5	• Contraindicated in patients with hepatic dysfunction (ALT >2.5 times ULN) or significant cardiac failure • Between 6 and 12 weeks required to achieve full BG-lowering effect • Triple therapy: addition of TZD to metformin plus sulfonylurea is acceptable • May induce mild edema, fluid retention • When used in combination with insulin, may increase risk of edema and CHF. The combination of a TZD plus insulin is currently not an approved indication in Canada
Combined formulation of rosiglitazone and metformin (Avandamet™)	1.0–1.5	• See rosiglitazone and metformin
Antiobesity agent orlistat (Xenical®) (33)	0.5	• Associated with weight loss • Gastrointestinal side effects

Physicians should refer to the most current *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, Ottawa, ON) and product monographs for detailed prescribing information.

A1C = glycosylated hemoglobin
ALT = alanine transaminase
BG = blood glucose
CHF = congestive heart failure
TZD = thiazolidinedione
ULN = upper limit of normal

Figure 1. Management of hyperglycemia in type 2 diabetes[§]



THERAPEUTIC NOTES

Key adverse effects

Gastrointestinal upset, loose bowels
biguanide

Hypoglycemia
insulin, insulin secretagogues (less with gliclazide, glimepiride, nateglinide and repaglinide than with glyburide)

Edema, fluid retention
insulin sensitizers, rarely with insulin

Moderate weight gain
insulin, insulin secretagogues, insulin sensitizers

Key precautions/contraindications

Hepatic disease
glyburide, biguanide, insulin sensitizers

Significant renal insufficiency
biguanide, sulfonylureas

Significant cardiac failure
biguanide, insulin sensitizers

Sulfa allergy
sulfonylureas

[§]See Recommendations 1 to 6 for grading and level of evidence regarding components of this figure.
*When used in combination with insulin, insulin sensitizers may increase the risk of edema or CHF. The combination of an insulin sensitizer and insulin is currently not an approved indication in Canada.
**If using preprandial insulin, do not add an insulin secretagogue.
†May be given as a combined formulation: rosiglitazone and metformin (Avandamet™).

Physicians should refer to the most current *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, Ottawa, ON) and product monographs for detailed prescribing information.

A1C = glycosylated hemoglobin
BMI = body mass index
CHF = congestive heart failure

RECOMMENDATIONS

1. In people with type 2 diabetes, if glycemic targets are not achieved using lifestyle management within 2 to 3 months, antihyperglycemic agents should be initiated *[Grade A, Level 1A (3)]*. In the presence of marked hyperglycemia (A1C ≥9.0%), antihyperglycemic agents should be initiated concomitant with lifestyle counselling *[Grade D, Consensus]*.

2. If glycemic targets are not attained when a single antihyperglycemic agent is used initially, an antihyperglycemic agent or agents from other classes should be added. The lag period before adding other agent(s) should be kept to a minimum, taking into account the pharmacokinetics of the different agents. Timely adjustments to and/or additions of antihyperglycemic agents should be made in order to attain target A1C within 6 to 12 months *[Grade D, Consensus]*.

3. The choice of antihyperglycemic agent(s) should take into account the individual and the following factors:
   - Unless contraindicated, a biguanide (metformin) should be the primary drug used in overweight patients *[Grade A, Level 1A (9)]*; and
   - Other classes of antihyperglycemic agents may be used either alone or in combination to attain glycemic targets, with consideration given to the information in Table 1 and Figure 1 *[Grade D, Consensus for the order of antihyperglycemic agents listed in Figure 1]*.

4. In people with type 2 diabetes, if individual treatment goals have not been reached with a regimen of nutrition therapy, physical activity and sulfonylurea *[Grade A, Level 1A (42)]*, sulfonylurea plus metformin *[Grade A, Level 1A (34)]* or other oral antihyperglycemic agents *[Grade D, Consensus]*, insulin therapy should be initiated to improve glycemic control.

5. Combining insulin and the following oral antihyperglycemic agents (listed in alphabetical order) has been shown to be effective in people with type 2 diabetes:
   - alpha-glucosidase inhibitors (acarbose) *[Grade A, Level 1A (6,43)]*
   - biguanide (metformin) *[Grade A, Level 1A (11,44,45)]*
   - insulin secretagogues (sulfonylureas) *[Grade A, Level 1A (12)]*
   - insulin sensitizers (thiazolidinediones) *[Grade A, Level 1A (46)]*. (The combination of an insulin sensitizer plus insulin is currently not an approved indication in Canada.)

6. Insulin may be used as initial therapy in type 2 diabetes *[Grade A, Level 1A (3)]*, especially in cases of marked hyperglycemia (A1C ≥9.0%) *[Grade D, Consensus]*.

7. To safely achieve optimal postprandial glycemic control, mealtime insulin lispro or insulin aspart is preferred over regular insulin *[Grade B, Level 2 (47,48)]*.

8. When insulin given at night is added to oral antihyperglycemic agents, insulin glargine may be preferred over NPH to reduce overnight hypoglycemia *[Grade B, Level 2 (14,49)]* and weight gain *[Grade B, Level 2 (14)]*.

9. All individuals with type 2 diabetes currently using or starting therapy with insulin or insulin secretagogues should be counselled about the recognition and prevention of drug-induced hypoglycemia *[Grade D, Consensus]*.

experienced a severe hypoglycemic episode per year was significantly higher in the intensive group than in the conventional group (3), particularly for patients using insulin therapy. Although the risk of hypoglycemia was less than in the Diabetes Control and Complications Trial, each year approximately 3% of patients treated with insulin in the UKPDS experienced a severe hypoglycemic episode and 40% had a hypoglycemic episode of any severity (3).

Lower rates of hypoglycemia have been observed in patients with type 2 diabetes treated with insulin lispro (Humalog®) compared to those treated with regular insulin (40,41), with more significant reductions in overnight hypoglycemia despite similar reductions in A1C.

OTHER RELEVANT GUIDELINES

Insulin Therapy in Type 1 Diabetes, p. S32
Hypoglycemia, p. S43
Management of Obesity in Diabetes, p. S46
Type 2 Diabetes in Children and Adolescents, p. S91
Pre-existing Diabetes and Pregnancy, p. S94
Gestational Diabetes Mellitus, p. S99
Diabetes in the Elderly, p. S106

RELEVANT APPENDIX

Appendix 9: Insulin Initiation Options in People With Type 2 Diabetes, p. S135

REFERENCES

1. Meltzer S, Leiter L, Daneman D, et al. 1998 clinical practice guidelines for the management of diabetes in Canada. *CMAJ*. 1998;159(suppl 8):S1-S29.
2. Klein R, Klein BEK, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. *Arch Ophthalmol*. 1984;102:527-532.
3. 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; 352:837-853.
4. Garber AJ, Larsen J, Schneider SH, et al. Simultaneous glyburide/metformin therapy is superior to component monotherapy as an initial pharmacological treatment for type 2 diabetes. *Diabetes Obes Metab*. 2002;4:201-208.
5. 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). *JAMA*. 1999;281:2005-2012.

6. Chiasson J-L, Josse RG, Hunt JA, et al. The efficacy of acarbose in the treatment of patients with non-insulin-dependent diabetes mellitus. A multicenter controlled clinical trial. *Ann Intern Med*. 1994;121:928-935.
7. Hoffmann J, Spengler M. Efficacy of 24-week monotherapy with acarbose, glibenclamide, or placebo in NIDDM patients. The Essen Study. *Diabetes Care*. 1994;17:561-566.
8. Holman RR, Cull CA, Turner RC. A randomized double-blind trial of acarbose in type 2 diabetes shows improved glycemic control over 3 years (U.K. Prospective Diabetes Study 44). *Diabetes Care*. 1999;22:960-964.
9. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 1998;352:854-865.
10. Garber AJ, Duncan TG, Goodman AM, et al. Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial. *Am J Med*. 1997;103:491-497.
11. Yki-Järvinen H, Ryysy L, Nikkilä K, et al. Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus. A randomized, controlled trial. *Ann Intern Med*. 1999;130: 389-396.
12. Wright A, Burden ACF, Paisey RB, et al. Sulfonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U.K. Prospective Diabetes Study (UKPDS 57). *Diabetes Care*. 2002;25:330-336.
13. 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 Res Clin Pract*. 1995;28:103-117.
14. Rosenstock J, Schwartz SL, Clark CM Jr, et al. Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (HOE 901) and NPH insulin. *Diabetes Care*. 2001;24:631-636.
15. Harrower A. Gliclazide modified release: from once-daily administration to 24-hour blood glucose control. *Metabolism*. 2000;49(10 suppl 2):7-11.
16. Tessier D, Dawson K, Tétrault JP, et al. Glibenclamide vs gliclazide in type 2 diabetes of the elderly. *Diabet Med*. 1994;11:974-980.
17. Schade DS, Jovanovic L, Schneider J. A placebo-controlled, randomized study of glimepiride in patients with type 2 diabetes mellitus for whom diet therapy is unsuccessful. *J Clin Pharmacol*. 1998;38:636-641.
18. Dills DG, Schneider J. Clinical evaluation of glimepiride versus glyburide in NIDDM in a double-blind comparative study. *Horm Metab Res*. 1996;28:426-429.
19. Holstein A, Plaschke A, Egberts EH. Lower incidence of severe hypoglycaemia in patients with type 2 diabetes treated with glimepiride versus glibenclamide. *Diabetes Metab Res Rev*. 2001;17:467-473.
20. Horton ES, Clinkingbeard C, Gatlin M, et al. Nateglinide alone and in combination with metformin improves glycemic control by reducing mealtime glucose levels in type 2 diabetes. *Diabetes Care*. 2000;23:1660-1665.
21. Wolffenbuttel BHR, Landgraf R. A 1-year multicenter randomized double-blind comparison of repaglinide and glyburide for the treatment of type 2 diabetes. *Diabetes Care*. 1999;22:463-467.
22. Moses R, Slobodniuk R, Boyages S, et al. Effect of repaglinide addition to metformin monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care*. 1999;22:119-124.
23. Damsbo P, Clauson P, Marbury TC, et al. A double-blind randomized comparison of meal-related glycemic control by repaglinide and glyburide in well-controlled type 2 diabetic patients. *Diabetes Care*. 1999;22:789-794.
24. Aronoff S, Rosenblatt S, Braithwaite S, et al. Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes: a 6-month randomized placebo-controlled dose-response study. *Diabetes Care*. 2000;23:1605-1611.
25. Raskin P, Rappaport EB, Cole ST, et al. Rosiglitazone short-term monotherapy lowers fasting and post-prandial glucose in patients with type II diabetes. *Diabetologia*. 2000;43:278-284.
26. Nolan JJ, Jones NP, Patwardhan R, et al. Rosiglitazone taken once daily provides effective glycaemic control in patients with type 2 diabetes mellitus. *Diabet Med*. 2000;17:287-294.
27. Lebovitz HE, Dole JF, Patwardhan R, et al. Rosiglitazone monotherapy is effective in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2001;86:280-288.
28. Fonseca V, Rosenstock J, Patwardhan R, et al. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial. *JAMA*. 2000;283:1695-1702.
29. Kipnes MS, Krosnick A, Rendell MS, et al. Pioglitazone hydrochloride in combination with sulfonylurea therapy improves glycemic control in patients with type 2 diabetes mellitus: a randomized, placebo-controlled study. *Am J Med*. 2001;111:10-17.
30. Einhorn D, Rendell M, Rosenzweig J, et al. Pioglitazone hydrochloride in combination with metformin in the treatment of type 2 diabetes mellitus: a randomized, placebo-controlled study. *Clin Ther*. 2000;22:1395-1409.
31. Yale J-F, Valiquett TR, Ghazzi MN, et al. The effect of a thiazolidinedione drug, troglitazone, on glycemia in patients with type 2 diabetes mellitus poorly controlled with sulfonylurea and metformin. A multicenter, randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 2001;134:737-745.
32. Schwartz S, Raskin P, Fonseca V, et al. Effect of troglitazone in insulin-treated patients with type II diabetes mellitus. *N Engl J Med*. 1998;338:861-866.
33. Miles JM, Leiter L, Hollander P, et al. Effect of orlistat in overweight and obese patients with type 2 diabetes treated with metformin. *Diabetes Care*. 2002;25:1123-1128.
34. Yki-Järvinen H, Kauppila M, Kujansuu E, et al. Comparison of

insulin regimens in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med.* 1992;327:1426-1433.

35. 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. *Arch Intern Med.* 1996;156:259-264.
36. United Kingdom Prospective Diabetes Study Group. United Kingdom Prospective Diabetes Study 24: a 6-year, randomized, controlled trial comparing sulfonylurea, insulin, and metformin therapy in patients with newly diagnosed type 2 diabetes that could not be controlled with diet therapy. *Ann Intern Med.* 1998;128:165-175.
37. American Diabetes Association. Implications of the United Kingdom Prospective Diabetes Study. *Diabetes Care.* 1998; 21:2180-2184.
38. 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. *Diabetes Care.* 1995;18:1113-1123.
39. Jennings AM, Wilson RM, Ward JD. Symptomatic hypoglycemia in NIDDM patients treated with oral hypoglycemic agents. *Diabetes Care.* 1989;12:203-208.
40. Anderson JH Jr, Brunelle RL, Keohane P, et al. Mealtime treatment with insulin analog improves postprandial hyperglycemia and hypoglycemia in patients with non-insulin-dependent diabetes mellitus. *Arch Intern Med.* 1997;157:1249-1255.
41. Anderson JH Jr, Brunelle RL, Koivisto VA, et al. Improved mealtime treatment of diabetes mellitus using an insulin analogue. *Clin Ther.* 1997;19:62-72.
42. Shank ML, Del Prato S, DeFronzo RA. Bedtime insulin/daytime glipizide. Effective therapy for sulfonylurea failures in NIDDM. *Diabetes.* 1995;44:165-172.
43. Coniff RF, Shapiro JA, Seaton TB, et al. A double-blind placebo-controlled trial evaluating the safety and efficacy of acarbose for the treatment of patients with insulin-requiring type II diabetes. *Diabetes Care.* 1995;18:928-932.
44. Ponssen HH, Elte JWF, Lehert P, et al. Combined metformin and insulin therapy for patients with type 2 diabetes mellitus. *Clin Ther.* 2000;22:709-718.
45. Avilés-Santa L, Sinding J, Raskin P. Effects of metformin in patients with poorly controlled, insulin-treated type 2 diabetes mellitus. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med.* 1999;131:182-188.
46. Raskin P, Rendell M, Riddle MC, et al. A randomized trial of rosiglitazone therapy in patients with inadequately controlled insulin-treated type 2 diabetes. *Diabetes Care.* 2001;24: 1226-1232.
47. Ross SA, Zinman B, Campos RV, et al. A comparative study of insulin lispro and human regular insulin in patients with type 2 diabetes mellitus and secondary failure of oral hypoglycemic agents. *Clin Invest Med.* 2001;24:292-298.
48. Rosenfalck AM, Thorsby P, Kjems L, et al. Improved postprandial glycaemic control with insulin aspart in type 2 diabetic patients treated with insulin. *Acta Diabetol.* 2000;37:41-46.
49. Yki-Järvinen H, Dressler A, Ziemen M. Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. *Diabetes Care.* 2000;23:1130-1136.

Appendix B:
SAS Program
A Plain English Version of the Strategy
Diabetes Mellitus: Patterns of Pharmaceutical Use in Manitoba

Cohort Acquisition

Enrollment Criteria:

- A Manitoba resident with continuous provincial health coverage after April 1, 1994) and the end of the definition period (March 30, 1997).
- defined as diabetic by meeting one of the following criteria

Criteria	Repository File	Year
2 physician claims	Medical File	1994-97
1 hospital claim	Hospital File	1994-97
1 Drug Claim	DPIN File	1996-97

Cohort file included the Personal Health Identification Number and the criteria that had been used to identify the cohort member.

The study period (April 1, 1997 to March 31, 2001) had been divided into 4 fiscal years. Each analyzed separately and included only cohort members who survived to the end of that fiscal year (Figure 5).

- April 1, 1997 to March 31, 1998
- April 1, 1998 to March 31, 1999
- April 1, 1999 to March 31, 2000
- April 1, 2000 to March 31, 2001

Adding Demographic Variables to Cohort

The original cohort included Personal Health Identification Number, the diabetes criteria, sex, and date of birth therefore additional demographic data stored in the Repository were added and or labeled. These data were linked to the cohort members using the PHIN.

Age (ageg)
-age was calculated by subtracting the beginning of the study period from the date of birth therefore age was identified on April 1, 1997 and the cohort member did not increase in defined age throughout the four year study period
-cohort members were then placed in one of nine age groups as defined in April 1, 19970
Sex
-sex, defined in the original cohort, was changed from a 1/2 to a male/female label
Adjusted Clinical Groupings (ACG)
-the adjusted diagnostic groupings (ADG) from the 1997 ACG files were merged to the cohort file and divided into 8 categories therefore the ACG

was assigned at the beginning of the study period and did not change despite possible changes on health between 1997 and 2001
Winnipeg Area (WPGAR)
-residents of Winnipeg were assigned to one of 12 geographic locations determined by postal codes from the registry data.
Region (RHA)
-residents of Manitoba were assigned to one of 12 Regional Health Authorities based on their postal codes in the registry data. These RHA's were then combined into 4 Manitoba Regions which reflect geographic location of the cohort members

Acquisition of Drug Files
The original cohort file is renamed in order to preserve it's integrity. The cohort PHIN's were then used to identify drug claims which were collected into the file 'DPIN". This was done using a signature Charles Burchill programming code which ensures the dpin data collected include only those claims which exist for the cohort. Three drug files were used; dpin file, nursing home drug data, and the non-adjudicated drug claims data. The drug costs were then added to the files and a professional fee of $6.95 was imputed.

Next the DIN Master (previously known at MCHP as the Master Formulary) were added to the dpin data by merging the DIN Master data to the din's (drug identification numbers) in the din files. Finally, information for those diabetic drugs not included in the DIN Master were added by din. These drugs missing from the DIN Master were previously identified with a separate program which identified drugs in the dpin data, by chemical name, and not included in the DIN Master.

The dpin file and the cohort files were sorted by phin. New variables using the 6 level ATC were initialized. The dpin file and cohort files were then merged by phin. The resulting file dpin_alldrugs contains one observation for each claim. Each observation includes the dpin data and the patient demographic data which had been initially attached to the cohort.

The 6 level ATC codes were then grouped by a format procedure into 5 ATC categories (a10clas); BIGUAN, SULFON, ALPHA, THIAZ, INSULIN and OTHER.. A frequency was performed on these categories.

The data was sorted in ascending order by: phin, atc1 (first level atc), atc4 (fourth level atc), and then atc (5^{th} level atc).

The next section of the program involves counting and calculating variables. Definitions for each of these variables can be found in Appendix XX under 'Variable Definitions'. The data is sorted first by phin then by atc. Several 'counters' are zeroed which will count, for each new phin, each time a new occurrence for that variable appears in the data.

if first.phin then do;

```
    a10=0 ;
    atc1_count=0
    atc4_count=0 ;
    a10cl_count=0;
    totcount=0;
    totcost=0;
    totdiabcost=0;
    DDDtot = 0 ;
    DDDuser = 0 ;
    INSULIN_user = 0 ;
    tot_days = 0 ;
  end ;
```

The counters set to zero above are defined as[1]:

Variable	Definition
a10	Number of A10 claims for DB.drugtreat
atc1_count	Number of 1st level ATCs from totcount
atc4_count	Number of 4th level ATCs from totcount
a10cl_count	Number of different A10 drugs a person from DB.drugtreat is taking (i.e., class of drug defined as ATC level 4)
totcount	Number of (any) claims for FREQ & drugtreat
totcost	Total cost for all claims (includes drugcost and fee); matches 'totcount'
totdiabcost	Total cost for A10 claims (includes drugcost and fee); matches 'a10'
DDDtot	Total number of DDDs dispensed to DB.drugtreat
DDDuser	Should equal DB.drug treat
INSULIN_user	Number of persons with at least one claim for insulin
tot_days	Total number of days on A10 as counted by the 'days supply' variable in the claims data

The number of A10 drugs for each person are totaled.
The variables listed above are added with each new observation that includes that specific variable.
Using an array the DDD's, total days supply and cost are then totaled for A10 drugs and for each drug class as defined by the earlier format a10clas. For those observations with zero or missing DDD's or days not included in the adding procedure. Within this the number of people in the cohort for at least one claim for an A10 is totaled. Finally, each the number of claims for each of the 23 ATC codes are added. This will sum the number of different A10 5th level drugs a patient is taking.

Once the last observation for a phin has been reached the totals are retained and summed.

A frequency for each of the 5 classes of A10 drugs is performed.

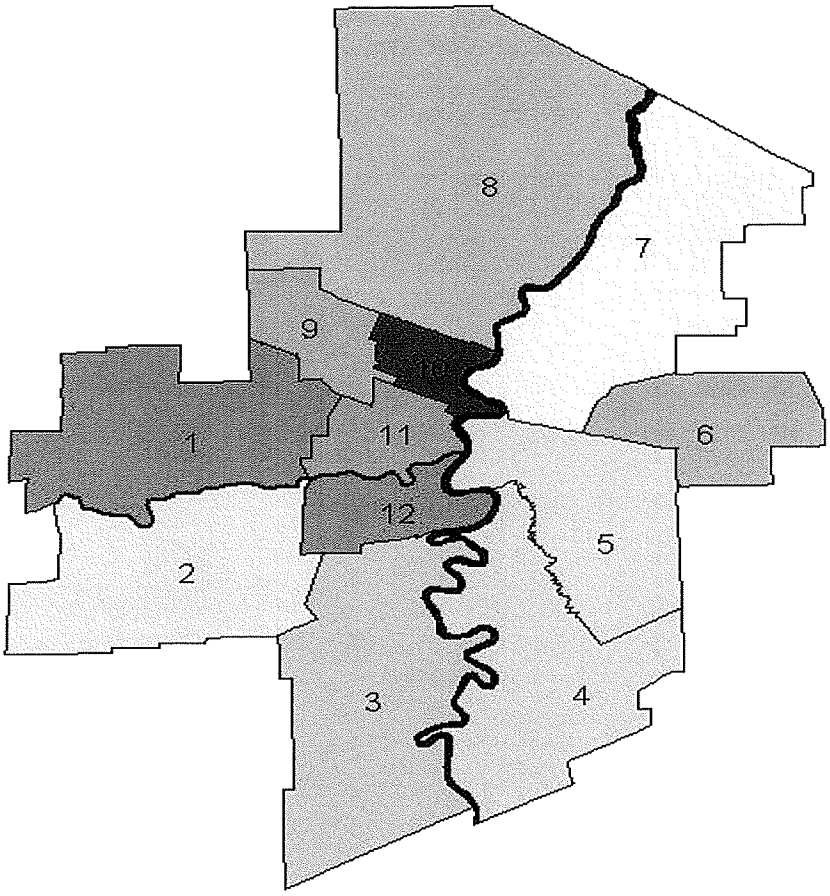
[1] A complete definition dictionary can be found in Appendix E.

A means procedure is performed on the data and any variables required to calculate rates and costs are retained. The dpin_alldrugs data and the cohort data are summed and sorted by the demographic variable (e.g.age). The cohort data is required in order to maintain the entire cohort population including those with no drug claims in the dpin data.

A new dataset is named and calculations for ACCESS, INTENSITY, and COST are calculated.

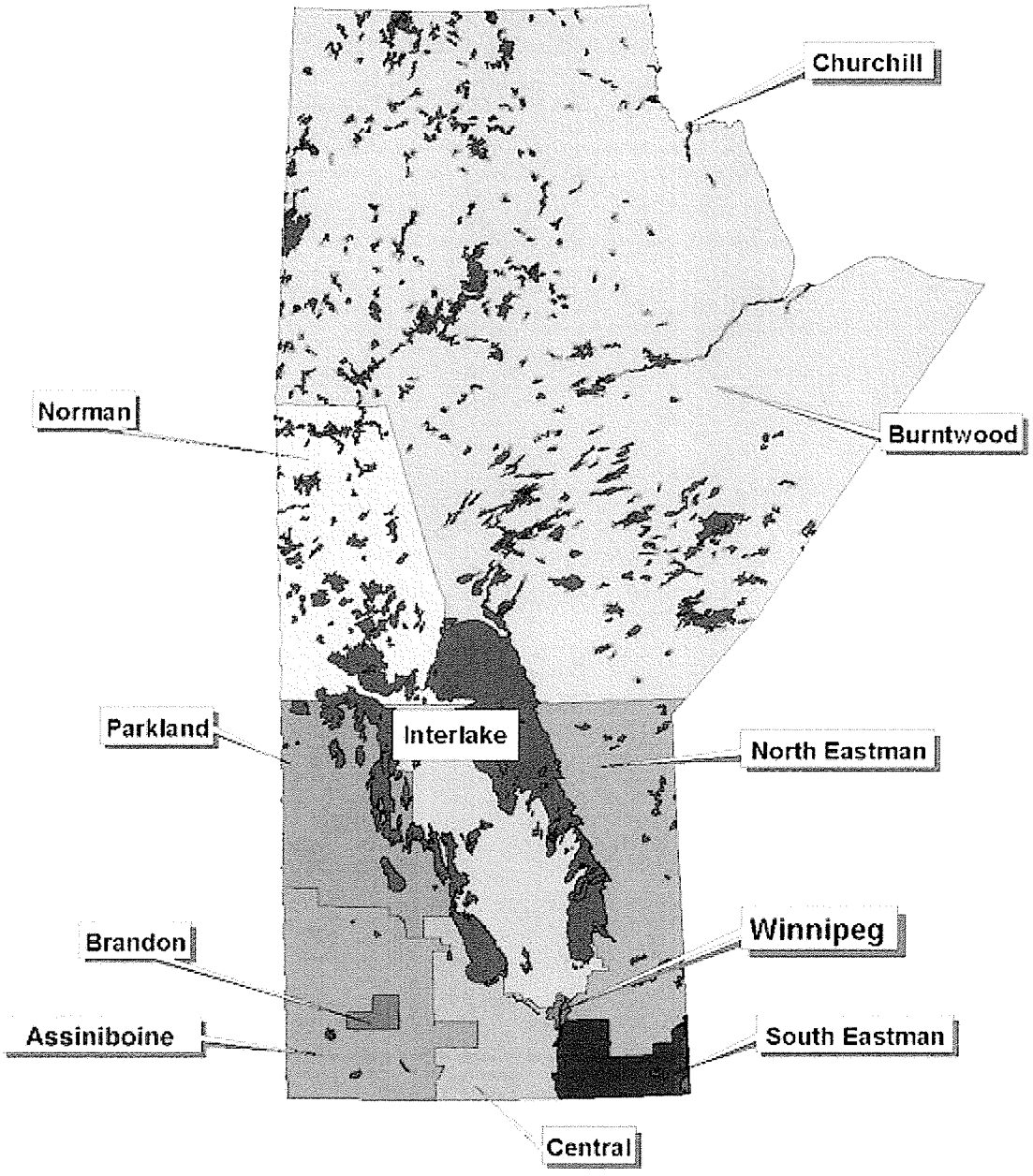
Therefore for each dpin_alldrugs data set, which contains the cohort, the demographic variables, the drug claims with the master formulary. This dataset undergoes 5 different procedures in which rates and other variables are calculated or added respectively. This is done for each year. In word format this SAS program contains approximately 32 pages of code. This program must be run for each of the four years of data.

Appendix C:
12 Winnipeg Areas



1. St.James-Assiniboea
2. Assiniboine South
3. Fort Garry
4. St.Vital
5. St.Boniface
6. Transcona
7. River East
8. Seven Oaks
9. Inkster
10. Point Douglas
11. Downtown
12. River Heights

Appendix D:
Manitoba Geographic Regions Determined by Grouping of Regional Health Authorities



Urban Region - Winnipeg and Brandon
South Region - Assiniboine, Central, and South Eastman
Middle Region - Parkland, Interlake, and North Eastman
North Region - Norman, Burntwood, and Churchill

Appendix E: Variable Definitions Used in SAS Programming

Demographic Labels Used in SAS Programming

Region	Middle Rural	North Rural	South Rural	Urban	Middle Rural is Interlake
Sex	Female	Male			
					Urban includes Brandon
Age	1	0-19			
	2	20-29			
	3	30-39			
	4	40-49			
	5	50-59			
	6	60-69			
	7	70-79			
	8	80-89			
	9	90+			

Sex/Age		Female		Male
	1	0-19	1	0-19
	2	20-29	2	20-29
	3	30-39	3	30-39
	4	40-49	4	40-49
	5	50-59	5	50-59
	6	60-69	6	60-69
	7	70-79	7	70-79
	8	80-89	8	80-89
	9	90+	9	90+

Winnipeg Areas	W01	St. James Assiniboia
	W02	Assiniboine South
	W03	Fort Garry
	W04	St. Vital
	W05	St. Boniface
	W06	Transcona
	W07	River East
	W08	Seven Oaks
	W09	Inkster
	W10	Point Douglas
	W11	Downtown
	W12	River Heights

ACGs	.	(.) means not assigned	means no visit to physician or hospital in previous year
	1	when assigned to cohort?	Assigned in year previous to start of analysis
	2 to 3		1996/97
	4 to 5		
	6 to 9		
	10+		
	non-user	ADG=0 Interpretation: healthiest	
	pregnant	pregnant only in the year that ACGs are assigned	

		1997 MIN	1997 MAX	Mean
Income	NF			
Quintile	R1	15983	29987	24998
	R2	30101	35662	32853
	R3	35681	41986	38357
	R4	42340	51034	47446
	R5	51265	77320	67047
	U1	10577	31979	25558
	U2	31979	38910	35731
	U3	38910	48042	43037
	U4	48012	60957	53755
	U5	60957	170386	77623

Variable Labels Used in SAS Programming

			Variable definition
NOTE:	There are three (3) denominators:	diabetic population	cohortpop
		diabetic population with a Rx claim	drugtreat
		diabetic population with an A10 claim	DB.drugtreat

Program:

Note: A10/all refers to two different submissions of the almost identical SAS programming

all	program submission with the entire cohort in a specific year and all associated claims
A10	program submission with cohort members who had at least one A10 claim (DB.drugtreat) and associated drug claims

Labels	A10/all	Program	
A		Demographic	(region, sex.age, Winnipeg areas, ACGs, Income Q)
B		Type or agegrp	(see sex.age) **SAS count of variable
C	all	Freq	Denominator of DM Study population with any di
	A10	Freq	Denominator of DM Study pop with a claim for A
D	all	drugtreat	= freq, numbers treated with any drug
	A10	drugtreat	= freq, numbers treated with any A10 79:79drug
E		DB.drugtreat	Number of persons on at least one A10
F	all	totcount	Number of (any) claims for drugtreat (FREQ)
	A10	totcountA10	Number of (any) claims for DB.drugtreat (which is persons who take at least one A10 drug)
G		a10	Number of A10 claims for DB.drugtreat
H	all	atc1_count	Number of 1st level ATCs for totcount
	A10	atc1_count	Number of 1st level ATCs for DB.drugtreat
I	all	atc4_count	Number of 4th level ATCs from totcount
	A10	atc4_countA10	Number of 4th level ATCs for A10s (DB.drugtreat)
J		A10_count	Number of A10 claims that a DB.drugtreat person is taking sb='G' a10
K		a10cl_count	(cl=class) Number of different A10 drugs a person from DB.drugtreat is taking (i.e., class of drug defined as ATC level 4)
L	all	totcost	Total cost for all claims (includes drugcost and fee) for 'totcount' Can calculate cost/claim
	A10	totcostA10	Total cost for all claims for DB.drugtreat; for totcountA10
M		totdiabcost	Total cost for A10 claims (includes drugcost and fee); for 'a10' (column G in outp Can calculate cost/A10 claim

The following relates only to A10 drugs:

N	DDDtot	Total number of DDDs of A10 drugs dispensed to DB.drugtreat
	DDDtotA10	Total number of DDDs of A10 drugs dispensed to DB.drugtreat
O	DDDuser	Number of persons with at least ONE DDD (does not include those on non-solid dosage forms)
P	INSULIN_user	Number of persons with at least one claim for insulin
Q	INSULIN2_user	Number of persons with at least one claim for insulin (validity check for column 'P')
R	BIGUAN_user	Number of persons using a biguanide (e.g., metformin)
S	SULFON_user	Number of persons using a sulfonamide (e.g. glyburide)
T	tot_days	Total number of days on A10 as counted by the 'days supply' variable in the claims data
U	ALPHA_user	Number of persons using a alpha-glucosidase (acarbose)
V	THIAZ_user	Number of persons using a thiazolidine (e.g., rosglitazone)
W	OTHER_user	Number of persons using 'other' antidiabetic agents (e.g., repaglinide)
X	COST_bigua	Total cost of claims for biguanides
Y	COST_sulfon	Total cost of claims for sulfonamides
Z	COST_alpha	Total cost of claims for alpha-glucosidase
AA	COST_thiaz	Total cost of claims for thiazolidines
AB	COST_other	Total cost of claims for other antidiabetic oral agents
AC	COST_insul	Total cost of claims for insulin
AD	DAY_biguan	Total number of days on biguanides as defined by the 'days supply' variable
AE	DAY_sulfon	Total number of days on sulfonamides as defined by the 'days supply' variable
AF	DAY_alpha	Total number of days on alpha-glucosidase as defined by the 'days supply' varia
AG	DAY_thiaz	Total number of days on thiazolidines as defined by the 'days supply' variable
AH	DAY_other	Total number of days on other oral antidiabetics agents as defined by the 'days supply' variable
AI	DAY_insuli	Total number of days on insulin as defined by the 'days supply' variable
AJ	DDDAY_bigu	Total number of DDDs dispensed / day of biguanides (using the sum of 'days supply' as the denominator for days)
AK	DDDAY_sulf	Total number of DDDs dispensed / day of sulfonamides (using the sum of 'days supply' as the denominator for days)
AL	DDDAY_alph	Total number of DDDs dispensed / day of alpha-glucosidase (using the sum of 'days supply' as the denominator for days)
AM	DDDAY_thia	Total number of DDDs dispensed / day of thiazolidines (using the sum of 'days supply' as the denominator for days)
AN	DDDAY_othe	Total number of DDDs dispensed / day of other oral antidiabetic agents (using the sum of 'days supply' as the denominator for days)
AO	DDDAY_insu	Total number of DDDs dispensed / day of insulin (using the sum of 'days supply' as the denominator for days)

AP		DDD_biguan	Total number of biguanide DDDs dispensed (year total)
AQ		DDD_sulfon	Total number of sulfonamide DDDs dispensed (year total)
AR		DDD_other	Total number of other antidiabetic drug DDDs dispensed (year total)
AS		DDD_alpha	Total number of alpha-glucosidase DDDs dispensed (year total)
AT		DDD_thiaz	Total number of thiazolidine DDDs dispensed (year total)
start of some rate calculations			
AU		cohortpop	Total number of persons defined as diabetic (DM Study population)
AV		ACCESS	Access to A10 drugs: DB.drugtreat / cohortpop
AW	all	RxINTcohort	Number of prescriptions dispensed to entire diabetic population: totcount / cohortpop
	A10	RxINTA10alldrug	Number of ALL drugs (prescriptions) dispensed to A10 users: totcount / DB.drugtreat
AX	all	RxINTA10A10	Number of A10 prescriptions dispensed to A10 users: A10_count / DB.drugtreat
	A10	DCINTA10A10	Number of different drugs dispensed to A10 users: atc4_countA10 / DB.drugtreat
AY	all	DCINTA10pop	Number of different (all) drugs dispensed to entire (Study DM) diabetic population: atc4_count / cohortpop
	A10	DDDINTall	Number of DDDs dispensed to A10 users (over the year): DDDtot / DB.drugtreat
AZ	all	DDDbiguan	Number of biguanide DDDs/ (days supply) day dispensed per year per user
	A10	COSTPOPA10all	Cost of any (all) drugs for A10 users: totcostA10 / DB.drugtreat
BA	all	DDD365bigu	Number of biguanide DDDs/ 365 days dispensed per year per user
	A10	DDDbiguan	Number of biguanide DDDs/ (days supply) day dispensed per year per user
BB	all	DDDsulfon	Number of sulfonamide DDDs/ (days supply) day dispensed per year per user sb close to 365 days (ideal!)
	A10	DDD365bigu	Number of biguanide DDDs/ 365 days dispensed per year per user
BC	all	DDD365slf	Number of sulfonamide DDDs/ 365 days dispensed per year per user
	A10	DDDsulfon	Number of sulfonamide DDDs/ (days supply) day dispensed per year per user
BD	all	DDDother	Number of other antidiabetic drug DDDs/ (days supply) day dispensed per year per user
	A10	DDD365slf	Number of sulfonamide DDDs/ 365 days dispensed per year per user
BE	all	DDD365othe	Number of other antidiabetic drug DDDs/ 365 days dispensed per year per user
	A10	DDDother	Number of other antidiabetic drug DDDs/ (days supply) day dispensed per year per user
BF	all	DDDalpha	Number of alpha-glucosidase DDDs/ (days supply) day dispensed per year per user
	A10	DDD365othe	Number of other antidiabetic drug DDDs/ 365 days dispensed per year per user
BG	all	DDD365alph	Number of alpha-glucosidase DDDs/ 365 days dispensed per year per user
	A10	DDDalpha	Number of alpha-glucosidase DDDs/ (days supply) day dispensed per year per user
BH	all	DDDthiaz	Number of thiazolidines DDDs/ (days supply) day dispensed per year per user
	A10	DDD365alph	Number of alpha-glucosidase DDDs/ 365 days dispensed per year per user
BI	all	DDD365thiaz	Number of thiazolidines DDDs/ 365 days dispensed per year per user
	A10	DDDthiaz	Number of thiazolidines DDDs/ (days supply) day dispensed per year per user

BJ	all	COSTPOP	Cost per year per diabetic (DM Study pop) for all drugs: totcost / cohortpop
	A10	DDD365thiaz	Number of thiazolidines DDDs/ 365 days dispensed per year per user
BK	all	COSTPOPA10	Cost per year per diabetic A10 user (DB.drugtreat) for A10 drugs: totdiabcost / DB.drugtreat
	A10	COSTPOP	Cost per year per A10 user for any (all) drugs: totcostA10 / cohortpop
BL	all	COSTbiguan	Cost per user of biguanides per year: costbigua / biguan_user
	A10	COSTPOPA10	Cost per year per diabetic A10 user (DB.drugtreat) for A10 drugs: totdiabcost / DB.drugtreat
BM	all	COSTsulfon	Cost per user of sulfonamides per year: COST_sulfon / SULFON_user
	A10	COSTbiguan	Cost per user of biguanides per year: costbigua / biguan_user
BN	all	COSTalpha	Cost per user of alpha-glucosidases per year: costbigua / biguan_user
	A10	COSTsulfon	Cost per user of sulfonamides per year: COST_sulfon / SULFON_user
BO	all	COSTthiaz	Cost per user of thiazolidines per year: cost_thiaz /thiaz_user
	A10	COSTalpha	Cost per user of alpha-glucosidases per year: cost_alpha / alpha_user
BP	all	COSTother	Cost per user of other oral anti-diabetic drugs per year: cost_other / other_user
	A10	COSTthiaz	Cost per user of thiazolidines per year: cost_thiaz / thiaz_user
BQ	all	COSTinsuli	Cost per user of insulins per year: cost_insulin /insulin_user
	A10	COSTother	Cost per user of other oral anti-diabetic drugs per year: cost_other / other_user
BR	all		
	A10	COSTinsulin	Cost per user of insulins per year: cost_insulin / insulin_user