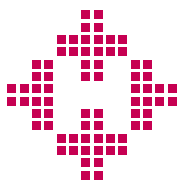# Pharmaceuticals: Focussing on Appropriate Utilization

June 2003

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## THE MANITOBA CENTRE FOR HEALTH POLICY

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Members of MCHP consult extensively with government officials, health care administrators, and clinicians to develop a research agenda that is topical and relevant. This strength along with its rigorous academic standards enable MCHP to contribute to the health policy process. MCHP undertakes several major research projects, such as this one, every year under contract to Manitoba Health. In addition, our researchers secure external funding by competing for other research grants. We are widely published and internationally recognized. Further, our researchers collaborate with a number of highly respected scientists from Canada, the United States and Europe.

We thank the University of Manitoba, Faculty of Medicine, Health Research Ethics Board for their review of this project. The Manitoba Centre for Health Policy complies with all legislative acts and regulations governing the protection and use of sensitive information. We implement strict policies and procedures to protect the privacy and security of anonymized data used to produce this report and we keep the provincial Health Information Privacy Committee informed of all work undertaken for Manitoba Health.

## ACKNOWLEDGEMENTS

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# EXECUTIVE SUMMARY

Indicators of pharmaceutical use within the current environment do not reflect a strategy for assessing the effectiveness or outcomes of prescription drugs. The assumption is that, other than death and other catastrophic events like heart attack or hip fracture, we have few population-based measures of "effect" or outcomes from the consumption of pharmaceuticals. However, indicators of both utilization and appropriateness, which are antecedents of effectiveness, are possible to measure using Manitoba Health's databases.

This project reports on the Manitoba Centre for Health Policy's (MCHP) efforts to develop methods to establish comparative benchmarks for pharmaceutical "effectiveness" by first looking at the appropriateness of pharmaceutical use. Appropriateness measures, first, whether the right drug has been prescribed for the right indication, for the right person and at the right time and dose. Following from this, effectiveness, measures the net of benefit—or what the drug is supposed to do, given appropriateness, in designated patient groups—and harm (adverse drug reactions).

Pharmaceuticals now rank as the third largest sector of health care spending in Manitoba, after hospitals and physician services (Chomiak, 2002). Most of the increase in expenditures in pharmaceuticals is due to the increased use of existing drugs and the introduction of new drugs rather than price increases per se (Patented Medicine Prices Review Board, 2000). Describing the process or appropriateness of prescribing and dispensation is essential to understanding whether scarce resources are being used efficiently and effectively in the provision of pharmaceuticals.

The objectives of this project were to:
1. Identify the influence of newer pharmaceuticals by major therapeutic class and to review their use from a population-health perspective (utilization by age, sex, age/sex, socioeconomic group, geographic area and comorbidity status).
2. Describe the extent of use of the most influential newer pharmaceuticals through application of appropriateness criteria applicable to their original indication(s) for use.
3. Determine the extent of appropriate use according to evidence-based clinical practice guidelines in persons with hypertension and post-acute myocardial infarction.

## Drug Utilization Study

All prescription drug use as captured by Manitoba Health's Drug Programs Information Network (DPIN)[1] was analyzed for the fiscal years 1996/97 to 1999/2000. Rates of drug utilization were based on dispensed prescription claims submitted to Manitoba Health by about 300 pharmacies providing pharmaceuticals to Manitoba residents.

## Drug Utilization Indicators

The primary indicator of access to pharmaceuticals is the proportion of the Manitoba population (pharmaceutical users) having dispensed to them at least one prescription drug per year. Indicators of utilization or intensity of use rates describe pharmaceutical users and/or residents by total number of prescriptions dispensed, number of different drugs and defined daily doses (DDD) used per year. Indicators of expenditure describe pharmaceutical users' and residents' cost per prescription and total costs by population characteristics and therapeutic drug class.

# Appropriateness Study

Two drug classes (agents acting on the renin-angiotensin system and serum lipid reducing agents (statins)) and two diagnoses (hypertension and acute myocardial infarction) were the subjects of the appropriateness study. Each analysis used a dynamic cohort of "new users" of a drug or "newly diagnosed" persons (with a medical condition) resident in Manitoba. The period of study for each analysis differed depending on the appropriateness criterion being applied but was in the bounds of the Manitoba Health data available from April 1, 1996 to March 31, 2000.

## Appropriateness Criteria

An appropriateness criterion was applied if there was evidence to support its implementation and if it could be measured using the administrative databases currently available. Four algorithms related to determining appropriateness and applicability to other drug classes were developed for use with Manitoba Health data.

> ***Agents Acting on the Renin-Angiotensin System and Hypertension:*** Appropriateness criteria for two of these agents, angiotensin-converting enzyme inhibitors (ACEIs) and the newer angiotensin II receptor antagonists (A2RAs), were applied to cohorts of persons first identified as "hypertensive" and with or without other comorbid conditions. All of this category's criteria are based on a "step-up"[2] approach to prescribing. We have called the prescribing indicator for appropriateness of agents acting on the renin-angiotensin system, initial therapy choice. A key question asked was, "What proportion of persons treated with the newer A2RAs have been previously treat-

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[1] DPIN is an electronic, on-line, point-of-sale prescription drug database. It links all community pharmacies (but not hospitals or nursing homes) and captures information about all Manitoba residents, including most prescriptions dispensed to Status Indians. The DPIN contains information such as: unique patient identification, age, birth date, sex, medication history, over-the-counter medication history, patient postal code, new drug prescribed, date dispensed and unique pharmacy identification number.

[2] The "step-up" approach follows the principle of applying the minimum pharmacological force necessary to achieve a stated therapeutic objective.

ed with an ACEI?" In other words, "Are the most cost-effective agents (ACEIs) being used as a first-line?"

### Serum Lipid Reducing Agents (the "statins"):
Appropriateness criteria for statins were applied once new users of the drugs were identified. Two prescribing indicators for appropriateness were examined: persistence on treatment and follow-up monitoring which are described as both length of time on treatment and rate of cholesterol monitoring.

### Treatment of Post-Acute Myocardial Infarction:
Appropriateness criteria were applied once individuals suffering a myocardial infarction were identified from Manitoba Health's hospital diagnosis data. Then, the proportion of individuals prescribed several types of pharmacological agents indicated post-acute myocardial infarction were described. The prescribing indicator for appropriateness in this case is therapy initiation.

## Results

### Drug Utilization Study

● Over eight million prescriptions were dispensed to Manitobans from community-based pharmacy settings and other outpatient locations in 1999/2000. Total expenditures (by both public and private payers (insurers and/or out-of-pocket)) were $285,982,702.

● Two-thirds of Manitobans (67.3%) have at least one prescription dispensed per year; this proportion increases to 87% (1999/2000) if one examines only older Manitobans (65 years of age and older).

*Manitobans aged 65 or older spend four times more per year on pharmaceuticals than younger residents—$708 vs. $177 per year. Yet, younger Manitobans cost about 20% more per Defined Daily Dose— $1.81/DDD vs. $1.39/DDD.*

● Older Manitoba residents (65 years of age and older) are dispensed, on average, over 21 prescriptions per year and take over five different kinds of medication; this is in contrast to younger Manitoba residents who have over five prescriptions dispensed on average per year representing about three different kinds of medication.

● Women consume, on average, about a third more doses of medication daily than men. Winnipeg residents consume marginally more doses (about 3%) than Non-Winnipeg residents.

● Older Manitoba residents expend four times more dollars per person per year for pharmaceuticals than younger residents (those less than 65 years of age) of Manitoba ($708 versus $177). Yet, when one considers expenditures per defined daily dose, the younger Manitoba residents cost about 20% more ($1.81/DDD versus $1.39/DDD).

**Appropriateness Study**

### Agents Acting on the Renin-Angiotensin System and Hypertension

- The cost per prescription for these agents increased 59.7% between 1995/96 and 1999/2000 ($12.73 to $20.33). This increase parallels the introduction of a new, and largely more expensive, class of agent-the angiotensin II receptor antagonists (A2RAs).
- ACEIs are used twice as often in those with hypertension and a comorbid condition like diabetes or congestive heart failure (10-11%) than in those with uncomplicated hypertension (5%).
- The per cent of persons with new prescriptions for A2RAs as first-line agents in newly diagnosed hypertension increased four-fold (0.5% to 2.4%) from 1996/97 to 1999/2000.
- Sixty-four percent (64%) of all new users of A2RAs in 1999/2000 did not have a previous trial with an ACEI.

### Serum Lipid Reducing Agents (the statins)

- The number of users of statins has increased by 60% between 1996/97 and 1999/2000 (25,824 to 41,344). Despite increases in utilization across all age groups, the proportion of those prescribed statins decreases significantly after the age of 80.
- Of the new users of statins in 1996/97, 9.9% had one dispensation of a statin only; 41% of new statin users appear to have been "persistent to treatment" or have remained on treatment for more than one year.
- The appropriate rate of follow-up testing is at least once per year. In Winnipeg, 45% of persistent statin users had their cholesterol levels monitored once a year.
- If one examines "persistence to treatment" in those with a previous acute myocardial infarction (an indication for a statin), 5.9% had only one dispensation of a statin and 52% remained on statin treatment after one year.

### Treatment Post-Acute Myocardial Infarction (AMI)

- In 1999/2000, 49.2% of post-AMI persons were prescribed a combination of a beta-blocker, an ACEI and/or a statin; beta-blockers were the most common single pharmaceutical intervention, post-AMI (17%), although the use of this intervention has fallen (19.3% in 1996/97 to 16.3% in 1999/2000).
- No outpatient cardiovascular drugs (including ASA) appear to be prescribed to about 17% of persons post-acute myocardial infarction (AMI).

## Conclusions

Four fiscal years of prescription drug data (1996/97-1999/2000) have been aggregated to describe, using previously developed population-based indicators, Manitoban's use of pharmacotherapy. The rates of use found are consistent with those in other Canadian jurisdictions and with previous Manitoba studies.

The main focus of this report, however, is on the appropriate use of pharmaceuticals. With many Canadian health policy-makers calling for better control of the quality of

pharmacotherapy (Commission on the Future of Health Care in Canada, 2002), MCHP has tried in this report to test the ability of Manitoba Health's databases to provide information on the appropriate use of pharmaceuticals. We have successfully developed four algorithms needed to apply appropriateness criteria that describe such subjects as rates of: (1) "step-up" prescribing, (2) therapy initiation post-medical event, (3) persistence to treatment, and (4) follow-up monitoring on chronic medications.

A caveat is warranted to the use of administrative data such as that housed at the Manitoba Centre for Health Policy for determining appropriateness of drug therapy. Many evidence-based indicators of appropriateness require kinds of information currently not available using administrative datasets. For example, cardiovascular risk stratification variables to determine the most effective use of drugs like statins as primary prevention agents for acute myocardial infarction include cholesterol levels, obesity, smoking, blood pressure readings; these variables are currently unavailable on a population-wide basis through administrative claims databases such as MCHP's Population Health Information System (POPULIS).

Table 1 is a summary of our application of four appropriateness algorithms representing seven criteria across two drug classes and two diagnoses. Only one out of seven (14%) criteria met the criterion's appropriateness standard.

The implications from these findings are significant and, in preparation for a discussion of appropriateness of pharmaceutical use in Manitoba, a number of observations come to mind to be considered:

1. It is difficult to examine appropriateness and effectiveness without knowing what is the drug's intended indication for use as well as some clinical data; can this be ameliorated?
2. Several policies around the concept of ensuring "appropriateness" could be developed and should be tested for feasibility before implementation; Can this be done? The following comprise the report's recommendations:
   a. A step-up approach to prescribing where marginal benefit of a newer drug could be realized but only after a trial of the minimum pharmacological force.
   b. The means to improve persistence to therapy after its initiation
   c. The means to encourage the initiation of therapy when indicated, especially post-acute myocardial infarction
3. A synthesis of the "appropriate use findings" from this and several other projects[3], currently underway in Manitoba, in order to gain perspective about strategies to encourage appropriate use.

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[3] MOMM: Maximizing Osteoporosis Management in Manitoba; MAAUI: Manitoba Appropriate Anti-inflammatory Use Initiative; Describing 'early adopters' of new pharmaceuticals.

**Table 1: Summary of applied appropriateness criteria**

| Criteria category | Specific criteria tested | Rate | Appropriateness assignment |
|---|---|---|---|
| **Agents acting on the renin-angiotensin system** | | | |
| 'step-up' approach[1] | Angiotensin converting enzyme inhibitor (ACEI) use should be highest in persons with hypertension (HTN) and at least one existing comorbidity (CM). | 10-11% of ACEI use is in those with HTN/CM. 5% of ACEI use in those with uncomplicated HTN. | Potentially Appropriate |
| | Treatment with an ACEI should be initiated prior to use of an angiotensin II receptor antagonist (A2RA). | 64% of new A2RA users have not been previously treated with an ACEI. | Potentially Inappropriate OVERUSE |
| | A2RA use should be highest in persons with hypertension (HTN) and at least one existing comorbidity (CM). | There are no discernible differences. | Potentially Inappropriate OVERUSE |
| | Persons with newly-diagnosed, uncomplicated HTN should not receive A2RAs as first-line therapy. | 2.4% of newly-diagnosed, uncomplicated HTNs are prescribed A2RAs initially. | Potentially Inappropriate OVERUSE |
| **Serum lipid reducing agents** | | | |
| Persistence to treatment | Persons with a previous MI are more likely to persist on treatment. | 41.1% of those without an indication vs. 51.8% of those with an indication persist. | Potentially Inappropriate UNDERUSE |
| Follow-up monitoring | The cholesterol levels of persons taking statins should be checked at least once per year, preferably every six months. | Approximately 45% have cholesterol checked at least once every year. | Potentially Inappropriate UNDERUSE |
| **Treatment post-acute myocardial infarction** | | | |
| Therapy initiation | Persons with an acute myocardial infarction (AMI) are more likely to be prescribed one of a beta-blocker, statin or an ACEI. | 17% post-AMI persons were not dispensed any prescription drugs; 50% were dispensed two or more cardiovascular drugs. | Potentially Inappropriate UNDERUSE |

[1] The "step-up" approach to prescribing is the act of applying (or prescribing) the minimum pharmacological force necessary to achieve a stated therapeutic objective when initiating therapy.

## 1.0 INTRODUCTION

Manitobans spent approximately $286 million in 1999/2000 on pharmaceuticals available outside of hospitals, yet little is known about the appropriate use of what is becoming a costly intervention. By appropriate use we mean the extent to which the pharmaceutical treatment is necessary and is the right choice. Optimally, we would like also to measure effectiveness or the extent to which the desired outcome of the pharmaceutical is obtained. The purpose of this report is to explore how Manitoba Health data could be used to inform about the appropriateness of pharmaceuticals prescribed in the ambulatory or ambulatory setting.

*This report explores how appropriate use of pharmaceuticals could be measured using Manitoba Health's databases.*

## 1.1 Factors Contributing to Pharmaceutical Expenditure Increases

Drug expenditures now rank as the third largest sector of health care spending in Manitoba, after hospitals and physician services (Chomiak, 2002). Between 1995/96 and 1999/2000 expenditures on marketed pharmaceuticals grew at an average annual rate of 13%; representing an actual (overall) 61% increase over the five-year period (Federal/Provincial/Territorial Working Group on Drug Prices, 2000). Two factors appear to be contributing to the increase in expenditures—an increased utilization of existing drugs and the introduction of new therapies.

*80% of increased expenditures for pharmaceuticals is primarily due to:*
*- The increased use of existing drugs;*
*- The introduction of new therapies.*

Factors related to this increase in expenditures have led provincial, territorial and federal health ministers to address "pharmaceuticals management" as one of eight priorities to be considered in health system renewal. Specifically, the First Ministers have agreed to work together to develop strategies for assessing the cost-effectiveness of prescription drugs[4] in order that Canadians continue to have access to new, appropriate and cost-effective drugs. Further, the First Ministers agreed that…

> "…these strategies could include the creation of a common intergovernmental advisory process to assess drugs for potential inclusion in government drug plans. They will be informed by an examination of current best practices and various means of addressing drug purchasing costs. The federal government will strengthen the surveillance of the therapeutic effect of drugs on Canadians after they have been approved for sale in Canada. This would complement ongoing work to ensure the optimal use of pharmaceuticals in health care."[5]

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[4] The definition of effectiveness is the production of a benefit in a person for treatment or prevention of disease; cost-effectiveness is an indicator (ratio) of the cost of providing an intervention (treatment or prevention) to the measure of health outcome the intervention is expected to produce. If an alternative activity produces a better outcome at the same or a lesser cost then it is more cost-effective. For pharmaceuticals, effectiveness can be described as net of benefit (the drug does what it is supposed to do) and harm (adverse drug reactions).

[5] News release. First Ministers' Meeting, Ottawa ON September 11, 2000. Communiqué on Health (ref: 800-038/004)

A common drug review (CDR) process has already been established by
Canada's Health Ministers under the auspices of the
Federal/Provincial/Territorial Advisory Committee and the Canadian
Coordinating Office for Health Technology Assessment (CCOHTA). The
CDR process will need to be informed by an examination of current best
practices (appropriateness) and through surveillance of the therapeutic effect
(effectiveness) of drugs on Canadians after they have been approved for sale
in Canada. An effort such as this is also proposed by the Health Care
Commission headed by Roy Romanow (Commission on the Future of
Health Care in Canada, 2002).

## 1.2 Effective versus Appropriate Use of Pharmaceuticals

*The ultimate objective for population-based pharmaceutical analyzes is to use benchmarks for comparing pharmaceutical outcomes among drugs.*

This project reports on the Manitoba Centre for Health Policy's efforts to
develop methods to establish benchmarks for comparing a drug's effective-
ness to other drugs with similar therapeutic mandates by first looking at
appropriateness of pharmaceutical use. *Appropriateness* is a process measure;
it is the subset of quality that is concerned with determining whether the
right thing was done for the patient. In a health system performance sense it
is the provision of care or interventions based on established standards or
evidence. *Effectiveness*, on the other hand, concerns the results or outcomes
achieved in the actual practice of healthcare with typical patients and
providers.

Within the framework of system evaluation, the question concerning effec-
tiveness could be: "To what extent is the care or intervention achieving the
desired outcome(s)?" Using the prescription of the lipid-lowering drugs,
statins, an appropriateness measure would be the rate at which these drugs
are prescribed after an acute myocardial infarction as compared to the rate
expected under best practice; an effectiveness measure would be a decrease
in coronary heart disease events and premature mortality in those prescribed
the statins. To illustrate how utilization, appropriateness and effectiveness
meld together in a framework, consider these three attributes of pharmaceu-
tical use within Donabedian's quality of care framework (Patented Medicine
Prices Review Board, 2000).

**Figure 1: Quality of Pharmacotherapy Use Framework**

*Randomized clinical trials (RCTs) provide the most valid estimate of the efficacy of a drug.*

If appropriateness has to do with measuring the extent to which the right drug is given for the right indication to the right person at the right time and dose, then what do we mean by effectiveness? Contrary to efficacy, which is the benefit the drug brings when it is taken in the context of a clinical trial or an ideal setting, effectiveness is the benefit the population derives when the drug is prescribed, dispensed and taken under real life circumstances.

*However, RCTs have limitations and real-world effectiveness studies offer us an opportunity to describe how cost-effective are pharmaceuticals.*

Why is effectiveness so important? In a clinical trial, an eligible, restricted group of persons randomly selected to take the drug (or a comparator or placebo) takes the drug for the period of time required to determine its benefit (and potential for harm). Evidence in Canada shows, however, that individuals' persistence in taking a highly efficacious drug (an HMG Co-A enzyme inhibitor or statin) to prevent heart attack is 75% less than the persistence shown through clinical trials.[6] In other words, to save one life with this drug, three times more individuals would need to be treated in real life than were found to be needed in the original (clinical trial) study.

*Other than death and catastrophic events like heart attack, most measures of the 'effect' of pharmaceutical therapy are missing from Manitoba Health's databases.*

Indicators of pharmaceutical use within the current environment do not reflect a strategy for assessing the effectiveness or outcomes of prescription drugs. The assumption is that, other than death and other catastrophic events like heart attack or hip fracture, we have few population-based measures of "effect" or outcomes from the consumption of pharmaceuticals. However, indicators of both utilization and appropriateness, which are antecedents of effectiveness, are possible to measure using Manitoba Health's databases.

Currently developed indicators can assess basic drug utilization in the population and these include: (1) access to prescription drugs, (2) utilization of prescription drugs (by therapeutic class and population descriptors like age and sex), and (3) expenditure or costs of prescription drugs. Drug utilization indicators as opposed to appropriateness indicators give us the background against which appropriateness and optimally, effectiveness can be examined.

*Several appropriateness indicators are feasible using Manitoba Health databases including:*
*- Persistence to therapy*
*- Prescribed daily doses*
*- Rates of initial prescription following an event like a heart attack*
*- Rates of "step-up" prescribing*

Indicators of appropriateness are defined by their alignment with the processes of care as established by evidence-based guidelines. Examples of these indicators include prescribing criteria around acceptable duration and dose of treatment, and rates of rule-out investigations and initial prescription following a consequential event like a heart attack (acute myocardial infarction: AMI). Although not officially an appropriateness indicator, also examined under appropriateness are the rates of step-up care. The step-up approach follows the principle of applying the minimum pharmacological

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6 Personal communication:  Dr. Jacques LeLorier (University of Montreal) studied the gap between drug efficacy and real therapeutic effectiveness in cardiovascular prevention.  He looked at the clinical trials of the drug pravastatin that showed significantly reduced total mortality (over placebo); persistence on the drug after five years was 94%.  Looking at real-life dispensations among Quebec males, persistence to the same drug fell by about 75% after the first dispensation of the drug and then, on subsequent refills, persistence fell away to almost nothing.

force necessary to achieve a stated therapeutic objective. This approach targets more powerful and costly interventions selectively towards patients in which less forceful interventions may have met with limited success and, therefore, patients may have a proven therapeutic need for more intensive treatment.[7]

## 1.3 Manitoba's Perspective on Pharmaceutical Use: Previous Analyzes

*Drug utilization review is a necessary step to understanding appropriate and cost-effective use of pharmaceuticals.*

A drug utilization analysis of Manitoba Health's Drug Programs Information Network (DPIN) was undertaken by the Manitoba Centre for Health Policy in 1996. The report, "Analysis of patterns of pharmaceutical use in Manitoba, 1996," allowed us to develop measures of pharmaceutical use for the population (Metge et al., 1999a). It also helped us to understand the research potential of what was then a new dataset. To the extent that it is helpful to report on utilization measures over time, this deliverable highlights recent findings in the use of pharmaceuticals by Manitobans.

The 1996 report found that Manitobans' use of pharmaceuticals appears to respond to the population's need for prescription drugs and that, according to DPIN data, there is a pattern of differential response to different levels of population need (Metge et al., 1999a). For example, we found that regions with the highest use of pharmaceuticals were also those areas whose residents had the poorest health and the highest level of socioeconomic risk.

*Burgeoning costs for pharmaceuticals are driving increased interest in the measurement of utilization, outcomes and efficient use of scarce health care resources.*

The appropriateness of the use of pharmaceuticals in Manitoba, however, is still relatively unknown and, with the role of pharmaceuticals ever-expanding as a component of the health care system, a more in-depth analysis was needed of this quality dimension. We were inspired by a series of reports by the Canadian Patented Medicine Prices Review Board (PMPRB) in 2001 as a place to start our appropriateness of pharmaceuticals analysis (Federal/Provincial/Territorial Working Group on Drug Prices, 2000). Specifically, these "cost driver" reports measured the role of changes in drug prices, utilization and new drugs on changes in total drug expenditures.

The provinces are facing a number of issues around the use of pharmaceuticals including their cost, utilization and outcomes for dollars spent and the efficiency of the resources allocated to this category of health care expenditures. To put the PMPRB cost driver reports into perspective, consider Table 2 which outlines the factors that alone or in combination are influencing the changes in annual costs of pharmaceuticals (Federal/Provincial/Territorial Working Group on Drug Prices, 2000).

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[7] The 'step-up' approach is in contrast to the 'step-down' approach that proposes that patients should initially be treated with the more powerful and costly alternatives only being 'stepped-down' to a less intensive intervention in strictly defined circumstances. The principal problem inherent in this approach is the universal application of a powerful and costly drug for patients in whom less intensive interventions may have been adequate and have not previously been proven to be ineffective.

**Table 2: Factors affecting total drug expenditures[1]**

| 1. | Changes in the total population. |
|---|---|
| 2. | Changes in the demographics and health status of the population (i.e., towards those with increased medication needs). |
| 3. | Changes in the unit prices of drugs (both patented and non-patented). |
| 4. | Changes in retail and wholesale mark-ups, and dispensing fees. |
| 5. | Changes in the prescribing habits of physicians (i.e., from older, less expensive medications to newer, relatively more expensive medications (± improved therapeutic effect to treat the same underlying diagnosis). |
| 6. | Changes in utilization of drugs on a per patient basis (i.e., more medications per patient per year). |
| 7. | Trends towards using drug therapy instead of other treatments (e.g., as alternatives to surgery in some cases). |
| 8. | New diseases to be treated and old diseases to be treated or better treated. |
| 9. | Extended patent protection, barriers to entry and reduction in competition. |

[1] Reproduced from Figure 1 of Federal/Provincial/Territorial Working Group on Drug Prices report, "Cost Driver Analysis of Provincial Drug Plans: Manitoba, 1995/96 – 1998/99." Patented Medicine Prices Review Board, April 2000.

*Increases in utilization and entry of new drugs were responsible for 139.4% of the increase in expenditures over a 4-year fiscal period (1995/96 to 1998/99)—base year, 1995/96.*

In the cost-driver report, (Federal/Provincial/Territorial Working Group on Drug Prices, 2000) the change in total annual expenditures is broken out into the following components: the price effect, volume (quantity) effect, entry of new drugs, exiting drugs and others (including the "cross effect" of price and volume—an interaction between changes in prices and changes in quantity). In Manitoba, on average (1995/96-1998/99) per unit price changes were responsible for 3.3% of the expenditure change, volume change or utilization was responsible for 108.6%, entry of new drugs was responsible for 30.8%, while exiting drugs and other factors were responsible for -0.3% and -42.2% of expenditure changes, respectively.

From selected factors affecting expenditures, Manitoba's population increased by 0.4% over the period 1995/96 to 1998/99 and the number of prescriptions dispensed to Manitobans increased by 10.4%; the segment of the population dispensed the most prescriptions per resident, the elderly population, also increased by 3% (Patented Medicine Prices Review Board, 2001). The cost per prescription and total expenditures on drugs increased by 58% and 30.8%, respectively (Federal/Provincial/Territorial Working Group on Drug Prices, 2000). Factors that may influence the cost of prescriptions include: the manufacturer's unit price, wholesale and retail mark-ups, changes in the size of prescriptions (i.e., the number of units dispensed

per dispensation), changes in prescribing habits of physicians (i.e., from older less expensive therapies to newer relatively more expensive ones), the trend towards using drug therapy instead of other treatments, and, the inclusion of new indications and new drugs for diseases in which drug therapy was not previously available (e.g., multiple sclerosis).

*Four classes of drugs were responsible for most of the increases in expenditures:*
*- ACE Inhibitors*
*- Statins*
*- Antidepressants*
*- Proton pump inhibitors*

If one considers the therapeutic class analysis undertaken in the cost-driver reports, there are several groups of drugs contributing proportionately more to increases in pharmaceutical expenditures than are others. At the second level of the Anatomical Therapeutic Chemical (ATC-2)[8] classification system, 16 therapeutic classes of drugs were identified based on their level of expenditures relative to other ATC-2 classes. The top four classes accounting for a substantial percentage of total expenditure were: agents acting on the renin-angiotensin system (angiotensin converting enzyme inhibitors, ACEIs-C09), serum lipid reducing agents (statins-C10), psychoanaleptics (antidepressants-N06) and antacids, drugs for treatment of peptic ulcer and flatulence (proton pump inhibitors-A02).

This report focuses on the appropriate use of agents acting on the renin-angiotensin system (C09) and serum lipid reducing agents (the statins) (C10). Utilization data for these classes of drugs are also reported on in the context of diagnoses for hypertension and acute myocardial infarction. Table 3 is a summary of how the use of these drugs has changed over the four years of this analysis (1996/97 to 1999/2000).

**Table 3: Changes in use and expenditures <u>overall</u> and for cost-driver drug classes[1]**

| | Expenditures (% total expenditures) | | Population (% total population) | | Prescriptions (% total prescriptions) | |
|---|---|---|---|---|---|---|
| | **1996/97** | **1999/2000** | **1996/97** | **1999/2000** | **1996/97** | **1999/2000** |
| **Overall pharmaceutical use:** | $195,971,131 | $285,982,711 | 1,144,460 | 1,148,074 | 7,134,300 | 8,771,033 |
| % change 1996/97-1999/2000 | 46.0% | | 0.3% | | 23.0% | |
| **By cost-driver drug class:** Agents acting on the renin-angiotensin system | $14,564,240 (7.4%) | $23,335,377 (8.2%) | 50,704 (4.4%) | 71,564 (6.2%) | 293,639 (2.7%) | 453,388 (5.2%) |
| % change 1996/97-1999/2000 | 60.2% | | 41.1% | | 54.4% | |
| Serum lipid reducing agents (the 'statins') | $12,057,762 (6.2%) | $21,154,671 (7.4%) | 25,824 (2.3%) | 41,344 (3.6%) | 137,828 (1.9%) | 244,699 (2.8%) |
| % change 1996/97- 1999/2000 | 75.5% | | 60.1% | | 77.5% | |

[1] Note that the per cent changes in this table will not reflect those identified in PMPRB's cost-driver reports because we report on all outpatient pharmaceutical use in Manitoba not just those that the Manitoba government is fiduciarily responsible for.

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[8] This is a classification system for classifying drugs, widely used in Europe. These classifications are from the WHO's Collaborating Centre for Drug Statistics Methodology. In the ATC classification system, the drugs are divided into different groups according to the organ or system on which they act and/or therapeutic and chemical characteristics. In the ATC system, drugs are classified in groups at five different levels, the final level being the drug molecule.

## 1.4 Developing Indicators of Pharmaceutical Use and Appropriateness

*Developing indicators of pharmaceutical use is this report's primary focus.*

Development of indicators of pharmaceutical appropriateness is the primary topic of this report. There are some 809 different drugs dispensed in Manitoba each year. Given the breadth of actual pharmaceutical use, then; How does one determine what indicators should be (can be) developed to look for indicators of appropriateness of pharmaceutical use?

*Evidence-based guidelines were used to develop appropriateness use indicators.*

Appropriate use indicators of these newer pharmaceuticals were developed using evidence-based clinical practice guidelines. A caveat is warranted here, however, as many evidence-based indicators of appropriateness require kinds of information currently not available using large administrative databases. For example, cardiovascular risk stratification variables to determine the most effective use of drugs like statins as primary prevention agents for acute myocardial infarction include cholesterol levels, obesity, smoking, blood pressure readings; these variables are currently unavailable on a population-wide basis through administrative claims databases such as MCHP's Population Health Information System (POPULIS).

*Information needed for some indicators of appropriateness are not available from administrative databases.*

The development of each appropriateness criterion was dependent upon two things: (1) the availability of evidence to support implementation of the criterion and (2) the ability of the administrative databases to measure it. The evidence to support each criterion applied to the data and application of each criterion to cohorts of users of the two groups of drugs (agents acting on the renin-angiotensin system and serum lipid lowering agents—statins) are specified in these chapters of the report.

### 1.4.1 Data Sources

The data available to MCHP on pharmaceutical use in Manitoba reflects virtually all prescription drug use outside of acute care hospitals. With some exceptions, the DPIN system captures nearly all prescriptions dispensed from community-based pharmacies to Manitobans. Pharmacists are obligated by professional standards to review other drugs being taken by persons before dispensing a current order; information provided by DPIN allows them to do so. Therefore, regardless of final fiduciary obligation, virtually all prescriptions dispensed for outpatient use are captured by DPIN and analyzable by the Manitoba Centre for Health Policy.

The data used for this analysis are housed in the Manitoba Centre for Health Policy and provided by Manitoba Health. Manitoba Health claims for physician visits, hospitalizations and pharmaceutical use were used to provide all indicators of utilization and appropriateness. Detail on these datasets can be found at: www.umanitoba.ca/centres/mchp/concept/. Most of the analyzes for this report were based on claims from Manitoba Health

for four fiscal years, 1996/97 to 1999/2000. Where analyzes are based on shorter time periods, they are so identified. As well, most utilization rates shown in this report have been age- and sex-adjusted (to the 1998/99 resident population of Manitoba) to account for the different demographics of Manitoba regions.

### 1.4.2 Study Period and Population

The *population frame* for each of these analyzes is a dynamic cohort of new users of the drug class under study or a cohort of those "newly diagnosed" with a condition (e.g., hypertension or acute myocardial infarction). Depending on the appropriateness criterion being operationalized, the period of study differs but it is within the bounds of Manitoba Health data from April 1, 1996 to March 31, 2000.

To account for *channelling bias*—that is, "sicker" patients disproportionately prescribed the newer, and perceived to be more potent medications, differentially-in some analyzes, users of the class were first stratified by an ambulatory comorbidity index (e.g., adjusted clinical groups[9] (ACGs) or number of different drugs) (Starfield et al., 1991; Reid et al., 2001).

### 1.4.3 Study Design

A retrospective analysis of prescription drug claims from DPIN data for fiscal years 1996/97 to 1999/2000 was used to follow a cohort of "new users" for the drug class under study. In addition to DPIN data, other data sources were used. These included files from Manitoba Health which are held in anonymized form (no names nor addresses) in the Population Health Research Data Repository (POPULIS) including data on Manitoban's use of hospitals and physicians.

An *index date* of "new use" was assigned after a determination (from earlier occurring data) that use was, in fact, new. New use is defined as use after a period of no dispensations occurring for the study drug between April 1 and July 31 of the starting fiscal year of the analysis (usually 1996/97). Once an index date was identified then an episode of drug therapy was determined using an algorithm developed and in use at MCHP. By determining episodes of therapy we could examine the extent to which the following prescribing indicators describe appropriateness: (1) extent of follow-up monitoring

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[9] The Adjusted Clinical Group (ACG) is a population/patient case-mix adjustment system developed by researchers at Johns Hopkins University School of Hygiene and Public Health in Baltimore, Maryland, U.S.A. The ACG system quantifies morbidity by grouping individuals based on their age and gender and all known medical diagnoses (which have been assigned over a defined period of time, typically one year). International Classification of Disease, version 9 (ICD-9/ICD- 9-CM) diagnosis codes for similar conditions are clustered based on expected consumption of health care resources and short-term clinical outcomes. An ACG assigned to an individual then, represents a combination of one or more diagnostic groups (up to 32) and their age and gender; ACGs help to quantify morbidity on a population basis for the purposes of stratifying individuals by their level of comorbidity.

(through tariffs indicating that laboratory orders were undertaken[10]) and, (2) persistence to therapy (i.e., given an original dispensation for the drug, how long does the person "persist" on treatment). Episodes of therapy were not required to be calculated to describe the appropriateness indicators of: (1) initial therapy choice and, (2) therapy initiation.

## 1.5 Outline of the Report

Based on an examination of Manitoba's Pharmaceutical Trends (Patented Medicine Prices Review Board, 2001) for the years from 1995 to 2000 we undertook the following:

1. A review of Manitoba's cost-driver report (PMPRB) to: (a) identify the influence of newer pharmaceuticals by major therapeutic class (by quantity or volume and effect on expenditures), and (b) review the use of these pharmaceuticals from a population perspective (age, sex, socioeconomic group, geographic area, comorbidity status).

2. A description of the extent of use of the most influential newer pharmaceuticals through application of appropriateness criteria applicable to their original indication(s) for use.

3. A determination of the extent of appropriate use according to evidence-based clinical practice guidelines in persons with hypertension and post-acute myocardial infarction.

We report on indicators of drug utilization for all pharmaceuticals dispensed in Manitoba and then on indicators of appropriateness applied to the use of two drug groups—agents acting on the renin-angiotensin system and serum lipid reducing agents (the statins). The use of these two groups of drugs are also reported on in the context of the assumption of two diagnoses—hypertension and acute myocardial infarction.

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[10] There is an unknown rate of underreporting of tariffs for laboratory orders undertaken in rural communities. Therefore, follow-up monitoring is reported for Winnipeg only. As well, some of Winnipeg's in-hospital specialists and family practitioners use in-hospital laboratories for outpatient monitoring. For example, St. Boniface has a number of endocrinologists seeing outpatients and Seven Oaks has several family practitioners who also see persons on an outpatient basis. The rate of underreporting in Winnipeg, however, is estimated to be small.

## 2.0 Drug Utilization

*Being able to "count" or describe how pharmaceuticals are used satisfies the baseline needed for accountability.*

Measuring drug utilization indicators creates a "quality assurance" system that satisfies the need for accountability (Starfield et al., 1985). Indicators of access, for example, describe for us the persons and the prescribers of their drugs (in the aggregate and not identified) that account for the largest share of pharmaceutical use or expenditures. Measures of access and utilization are important to determine the attainment of attributes of quality-like contact with care (access to pharmaceuticals) and comprehensiveness (insurance coverage for pharmaceuticals deemed "medically necessary" by the insurer).

Tognoni (1983) has noted that before one can measure the medical, social and economic consequences of pharmaceutical use, quantitative data need to be obtained on the extent and variability of the use and cost of pharmaceutical therapy. In our 1996 report on Manitobans' use of pharmaceuticals we developed indicators of access, utilization and expenditure (Metge et al., 1999b). In this report we update the 1996 findings by describing utilization and start on the road to measuring the outcomes of pharmaceutical use through a description of appropriateness of pharmacotherapy.

*Access: Per cent prescribed at least one pharmaceutical in a year.*

*Intensity of Use: Number of prescriptions or different drugs used per resident per year.*

Our primary indicator of access describes the proportion of the population using at least one prescription drug per year (pharmaceutical users). Intensity of use indicators describe pharmaceutical users by number of (1) total prescriptions dispensed by therapeutic class per resident and pharmaceutical user, (2) number of different drugs, and (3) defined daily doses[11] (DDDs). Indicators of expenditure describe pharmaceutical users and residents: (1) cost per prescription, (2) cost per DDD, and (3) total costs by population characteristics and therapeutic class.

*Expenditures: Cost per prescription per pharmaceutical user or total costs per resident per year.*

Although these indicators are reported cursorily for all pharmaceuticals dispensed in Manitoba between 1996/97 and 1999/2000, drug utilization indicators are reported in more depth for the two therapeutic classes under discussion in this paper: agents acting on the renin-angiotensin system (the angiotensin converting enzyme inhibitors (ACEIs) and the angiotensin receptor antagonists (A2RAs)) (Appendix D), and serum lipid reducing agents (the statins) (Appendix F).

## 2.1 Drug Utilization Study

### 2.1.1 Study Period and Population

Drug utilization is reported within a population-based framework meaning that all prescription claims to Manitoba residents that are registered by DPIN are counted. Rates of drug utilization are based on dispensed prescription claims submitted to Manitoba Health by about 300 pharmacies

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[11] The defined daily dose of a drug is the average dose per day of a drug when used for its major indication in everyday practice. When the number of DDDs dispensed to the population is calculated, it provides a rough estimate of the proportion of the population receiving the drug (number of residents per 1,000 population per day).

providing pharmaceuticals to Manitoba residents for the fiscal years 1996/97 to 1999/2000 (April 1 to March 31). In-hospital use of prescription drugs is not captured by DPIN and is excluded from this study.

Pharmaceutical use for Manitoba residents is reported according to the area of an individual's residence, not according to the site where the medication was purchased. Specifically, residents of Manitoba were identified and information about region of residence was obtained using the Manitoba municipal code on the Manitoba Health Registry file as of December 31st of a specified fiscal year, except for Treaty First Nations residents. For these individuals, postal code information was used to assign region of residence. Individuals were grouped by age and were assigned an age group based on age at first prescription dispensed in the fiscal year studied or reported on.

## 2.1.2 Study Design

A population-based approach was used to study the use of pharmaceuticals by Manitoba residents. Specifically, the Population Health Information System (POPULIS) developed by MCHP provided population-based information on the pharmaceutical use of Manitobans. The pharmaceutical module of POPULIS describes how the population of Manitoba uses pharmaceuticals on a fiscal-year basis (April 1 to March 31). A population's use of the health care system in general and pharmaceuticals, in particular, requires indicators of access to care (or pharmaceuticals), intensity of use by users of pharmaceuticals, and total expenditures. Rates of these indicators are reported on a fiscal-year basis and the indicators reported on are explained below.

The numerator for POPULIS pharmaceutical rates was calculated by counting or adding individuals, or individual's prescription claims, number of different drugs at ATC level 4 (ATC-4), defined daily doses (DDDs) and expenditures during the year according to their region of residence. Denominators were based on counts of individuals resident in one of 11 rural regions or 12 urban (Winnipeg) regions as per the population registry information of June 30 in each of the fiscal years.

Rates used to describe drug utilization are limited to a common set of pharmaceutical products covered by all agencies (the master formulary). A total of 5,151 drug products (DINs) covered by all plans comprised 809 discrete drug entities. Limiting the analysis to a common or master formulary results in a loss of about 13% of total claims from the DPIN dataset (Metge et al., 1999a).

The Anatomical Therapeutic Chemical (ATC) classification system for human medicines from WHO's Collaborating Centre for Drug Statistics Methodology was used to classify drug entities in the master formulary

(World Health Organization, 1995). This classification system divides drugs into different groups according to the organ or system on which they act or on their therapeutic and chemical characteristics. The first level of the code is based on a letter for the anatomical group, e.g., N for nervous system; the second level of the code is the therapeutic main group, e.g., N05 for psycholeptics (includes antipsychotics, anxiolytics, hypnotics, and sedatives); and the third level of the code is the therapeutic subgroup, e.g., N05 B for anxiolytics. There are five levels of classification in total and the fifth level is at the drug molecule level.

The reader should take note that there are inconsistencies in the DPIN field metric quantity dispensed. These inconsistencies render non-solid dosage forms unusable for calculation of defined daily doses (DDD). DDD analyzes per year, therefore, were calculated using about 65% of total claims available for analyzes. Other utilization rate calculations (indicators of access and expenditure) are not affected by this limitation.

All indicators are reported as rates. The changes in the indicators from year to year and compared to the base year (1996/97) are reported. Refer to Appendix B for a detailed account of the drug utilization indicators developed for this project.

## 2.2 Drug Utilization Results

Population-based measures of outpatient pharmaceutical use in Manitoba are based on the dispensing of over eight million prescriptions per year (1999/2000) and costing about $286 million. Table 4 is a summary of the drug utilization indicators used to describe Manitobans' use of prescription drugs to March 31, 2000. Figure 2 shows the increases in expenditures and utilization as measured by defined daily doses. Note that the proportion of the population using at least one prescription drug has remained constant.

Three categories of drug utilization indicators have been developed: (1) access to prescription drugs, (2) utilization of prescription drugs (by therapeutic class and population descriptors like age and sex), and (3) expenditure or costs of prescription drugs. Seven specific indicators spanning these categories give us measures of the population's use of prescription drugs (Appendix B). The following sections report on these drug utilization indicators.

**Table 4: Population-based measures of pharmaceutical use, 1996/97-1999/2000**

| | | | Residents | | Users |
|---|---|---|---|---|---|
| | | All | < 65 years old | ≥ 65 years old | |
| **Access indicator:** | | | | | |
| Users of pharmaceuticals | 1996/97 | 66.0 | 63.0 | 84.4 | |
| (per 100 residents) | 1997/98 | 65.7 | 62.6 | 84.9 | N/A |
| | 1998/99 | 66.9 | 63.9 | 86.1 | |
| | 1999/2000 | 67.3 | 64.2 | 87.0 | |
| **Intensity of use indicators:** | | | | | |
| Mean number of | 1996/97 | 6.2 | 4.6 | 16.6 | 9.5 |
| prescriptions per year | 1997/98 | 6.6 | 4.8 | 17.9 | 10.1 |
| | 1998/99 | 7.0 | 5.1 | 19.1 | 10.5 |
| | 1999/2000 | 7.6 | 5.5 | 21.1 | 11.4 |
| Mean number of different | 1996/97 | 3.3 | 2.9 | 5.1 | 3.3 |
| drugs used/year (USERS) | 1997/98 | 3.4 | 3.0 | 5.3 | 3.4 |
| | 1998/99 | 3.5 | 3.0 | 5.5 | 3.5 |
| | 1999/2000 | 3.7 | 3.2 | 5.9 | 3.6 |
| Mean number of defined | 1996/97 | 120 | 76 | 405 | 223 |
| daily doses (DDDs per | 1997/98 | 135 | 83 | 447 | 246 |
| year) | 1998/99 | 142 | 89 | 474 | 257 |
| | 1999/2000 | 154 | 98 | 511 | 276 |
| **Expenditure indicators:** | | | | | |
| Mean dollars per year | 1996/97 | $171 | $123 | $480 | $260 |
| | 1997/98 | 191 | 136 | 539 | 290 |
| | 1998/99 | 216 | 154 | 607 | 322 |
| | 1999/2000 | 249 | 177 | 708 | 370 |
| Mean dollars per | 1996/97 | $27.47 | $26.65 | $28.92 | $27.47 |
| prescription | 1997/98 | 28.75 | 27.96 | 30.09 | 28.75 |
| | 1998/99 | 30.63 | 29.97 | 31.76 | 30.63 |
| | 1999/2000 | 32.61 | 32.02 | 33.58 | 32.61 |

**Figure 2: Selected Population Use Characteristics, 1996/97-1999/2000**
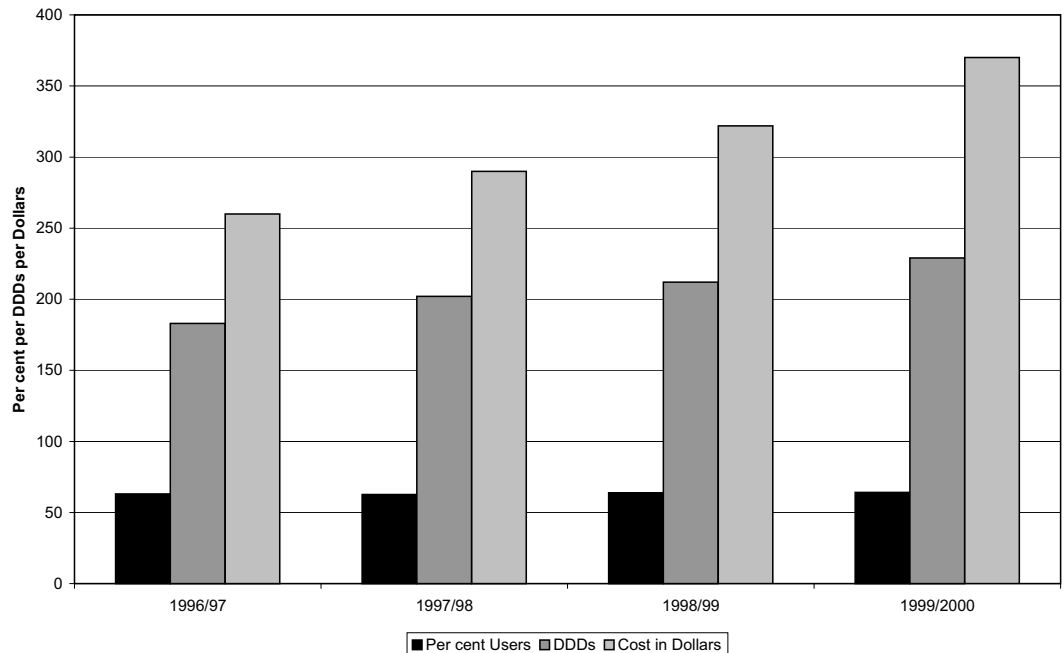
### 2.2.1 Access Indicators

At least two-thirds of Manitobans continue to be "pharmaceutical users" (residents of Manitoba dispensed at least one prescription per year) or 67.3% in 1999/2000. However, approximately 85% of older Manitobans (≥65 years old) are pharmaceutical users in any one year (in 1996/97, 84.4%; in 1999/2000, 87.0%). Figure 3 is a graphic representation of Drug Utilization Indicator #1, that is the proportion of the population using at least one prescription drug per year.

**Figure 3: Per Cent Population with Access to at Least One Prescription by Age and Sex in Manitoba, 1999/2000**
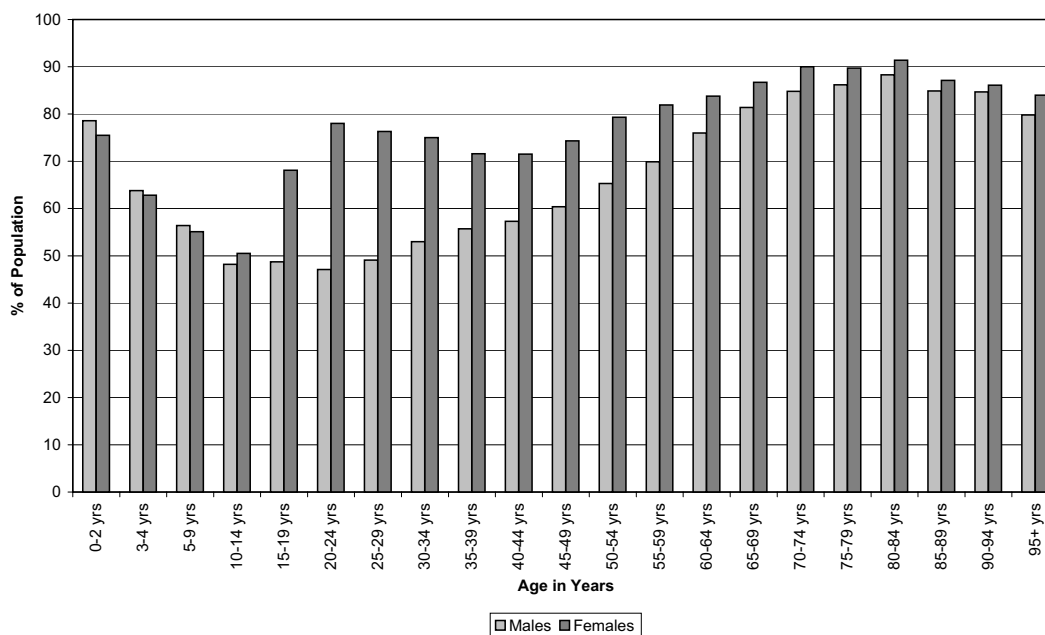


### 2.2.2 Intensity of Use Indicators

Drug Utilization Indicators (#2 to #4) describe the intensity of pharmaceutical use in the province. Indicator #2 describes the total number of prescriptions dispensed per 1,000 residents and pharmaceutical users or the mean number of prescriptions dispensed per resident. The mean number of prescriptions dispensed per resident has increased by 22.6% (6.2 in 1996/97 to 7.6 in 1999/2000); the mean number of prescriptions dispensed per pharmaceutical user has increased by 20.0% (9.5 in 1996/97 to 11.4 in 1999/2000). The most commonly dispensed group of drugs to all residents of Manitoba are drugs that act on the nervous system (ATC=N), 1,843 prescriptions dispensed per 1,000 residents in 1999/2000; the most commonly dispensed group of drugs to older residents (≥65 years old) of Manitoba are drugs that act on the cardiovascular system (ATC=C) or 7,127 prescriptions dispensed per 1,000 older Manitobans in 1999/2000. Figures 4 and 5 show

the differences in the numbers and the most frequently dispensed drugs by type and by younger (<65 years old) and older (≥65 years old) residents of Manitoba.

**Figure 4: Number of Prescriptions Dispensed per 1,000 Younger Manitoba Residents in Top Drug Categories, 1996/97-1999/2000**
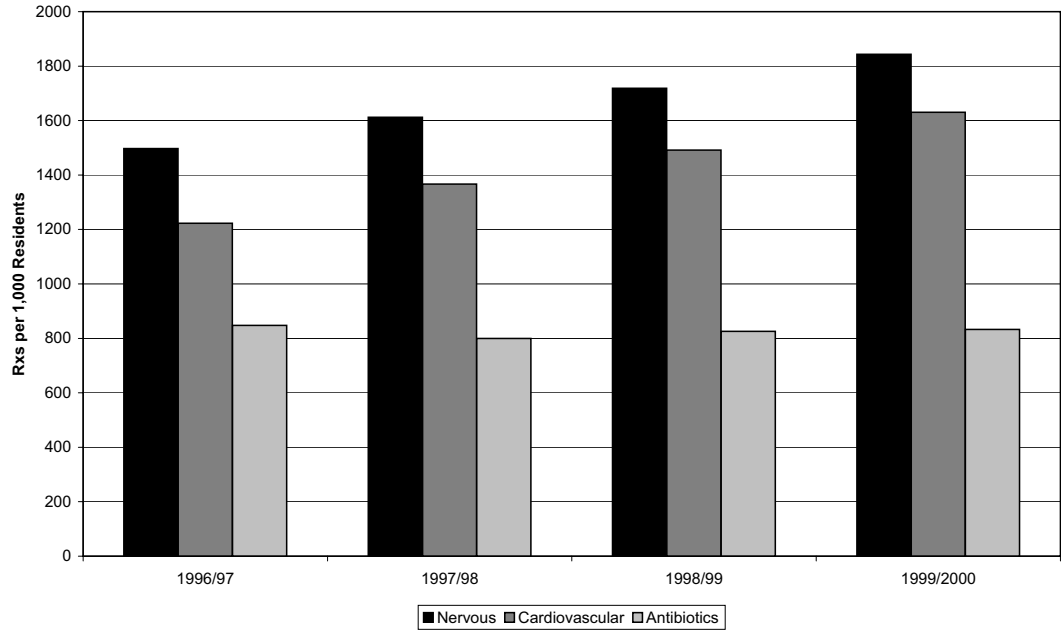


**Figure 5: Number of Prescriptions Dispensed per 1,000 Older Manitoba Residents in Top Drug Categories, 1996/97-1999/2000**
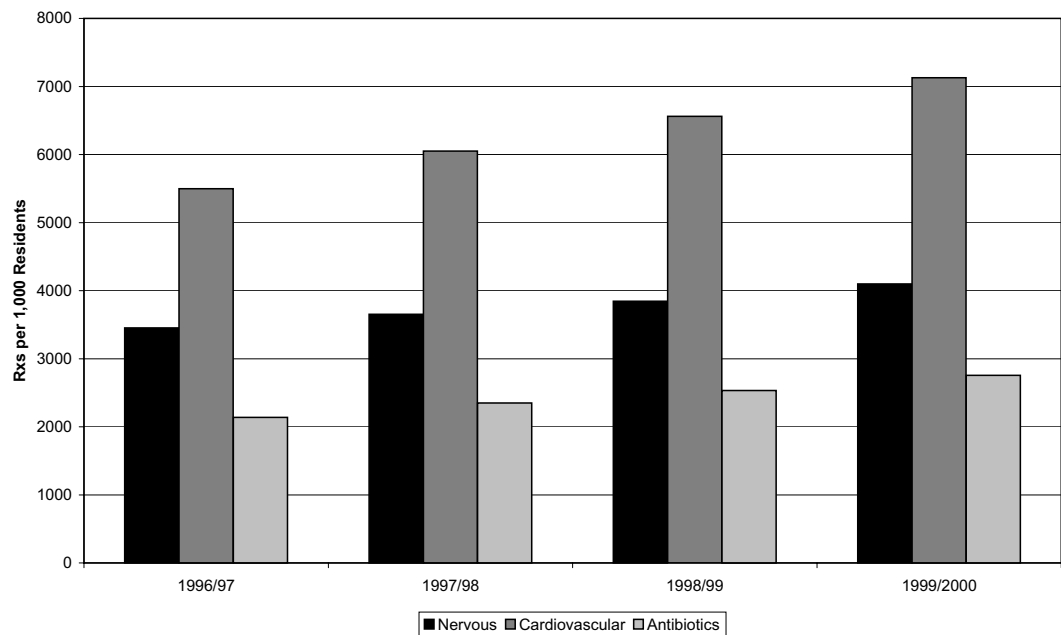
Drug Utilization Indicator #3 describes the number of different drugs dispensed to each pharmaceutical user in a year. The mean number of different drugs dispensed per user has increased by 9.1% (3.3 in 1996/97 to 3.6 in 1999/2000); the mean number of different drugs dispensed per older pharmaceutical user has increased by 15.7% (5.1 in 1996/97 to 5.9 in 1999/2000). In this analysis, we examined if the adjusted clinical group to which a pharmaceutical user was assigned would parallel the number of different drugs dispensed over a year. Figure 6 shows that, as the number of potential comorbidities rise as signified by increasing numbers of ACGs, the number of different drugs also increases.

**Figure 6: Number of Different Drugs Used by Individuals by Comorbidity Ranking (Adjusted Clinical Group), 1998/99 and 1999/2000**
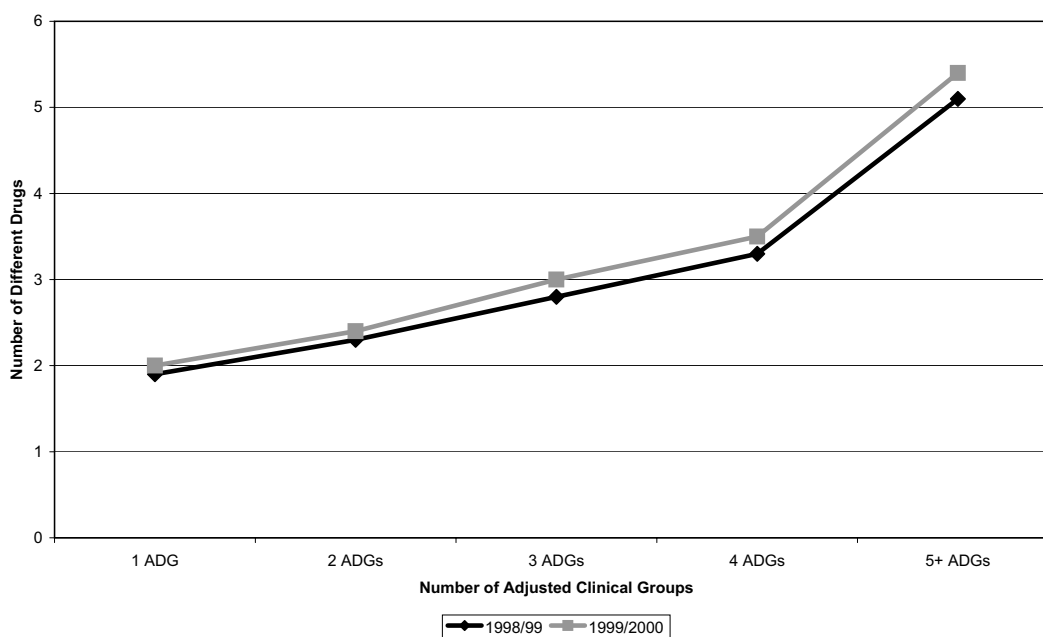


Drug Utilization Indicator #4 describes the number of defined daily doses (DDDs) used per 1,000 residents and pharmaceutical users. There are six defined daily dose (DDD) rate calculations that can be used to measure various aspects of intensity. DDDs are a technical unit of measurement meant to overcome the limitations behind simply counting prescriptions; a DDD is the average dose per day for a drug product when used for its major indication in everyday practice. We report on the number of DDDs used, on average, per year per resident (female/male and Winnipeg/Non-Winnipeg) in Table 5; the rates are equivalent to estimating how many days of treatment every resident, if placed on the drug, would have consumed in a year.

**Table 5: Average number of defined daily doses (DDDs) used per year per resident, 1996/97-1999/2000**

|  | 1996/97 | 1997/98 | 1998/99 | 1999/2000 |
|---|---|---|---|---|
| DDDs per resident per year | 124 | 135 | 142 | 153 |
| DDDs per female resident per year | 142 | 155 | 164 | 175 |
| DDDs per male resident per year | 103 | 112 | 118 | 129 |
| Ratio: female to male | 1.38 | 1.38 | 1.39 | 1.36 |
| DDDs per Winnipeg residents per year | 126 | 136 | 143 | 155 |
| DDDs per Non-Winnipeg residents per year | 120 | 132 | 140 | 150 |
| Ratio: Winnipeg to Non-Winnipeg | 1.05 | 1.03 | 1.02 | 1.03 |

## 2.2.3 Expenditure Indicators

Expenditure indicators (#5 to #7) describe the costs of prescription drugs to both pharmaceutical users and residents. The mean expenditure per prescription was $27.47 in 1996/97 and $32.61 in 1999/2000—an increase of 18.7%. Total expenditures for pharmaceuticals per resident and user were $249.10 and $370.25, respectively, for the 1999/2000 fiscal year.

Expenditure Indicator #5 describes the average cost per prescription (and by therapeutic class) and Expenditure Indicator #7 describes the total drug expenditure by population characteristics and therapeutic class. Figures 7 and 8 describe these indicators by the top ranking therapeutic classes. The bars in Figure 7 are ranked by the total value, in millions, paid by Manitobans either out-of-pocket, through insurance or as a social tax benefit by therapeutic class. The same ranking is used in Figure 8 but the bars signify the cost per prescription in each therapeutic class.

**Figure 7: Total Dollars (in millions) Spent by Manitobans on the Top Therapeutic Classes of Drugs, 1996/97-1999/2000**
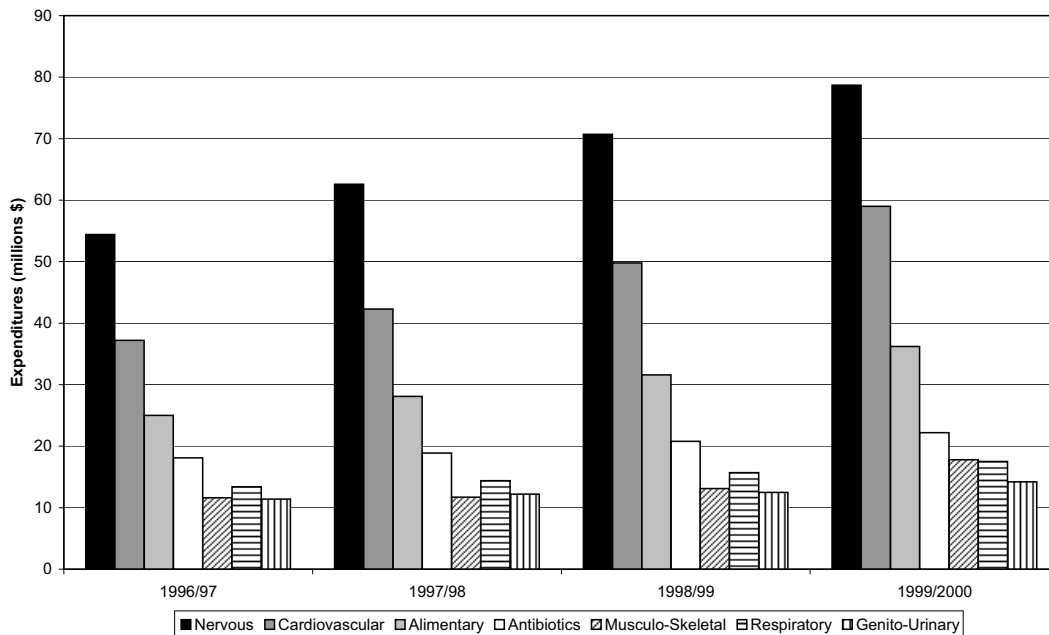


**Figure 8: Dollars Spent by Manitobans per Prescription for the Top Therapeutic Classes of Drugs, 1996/97-1999/2000**
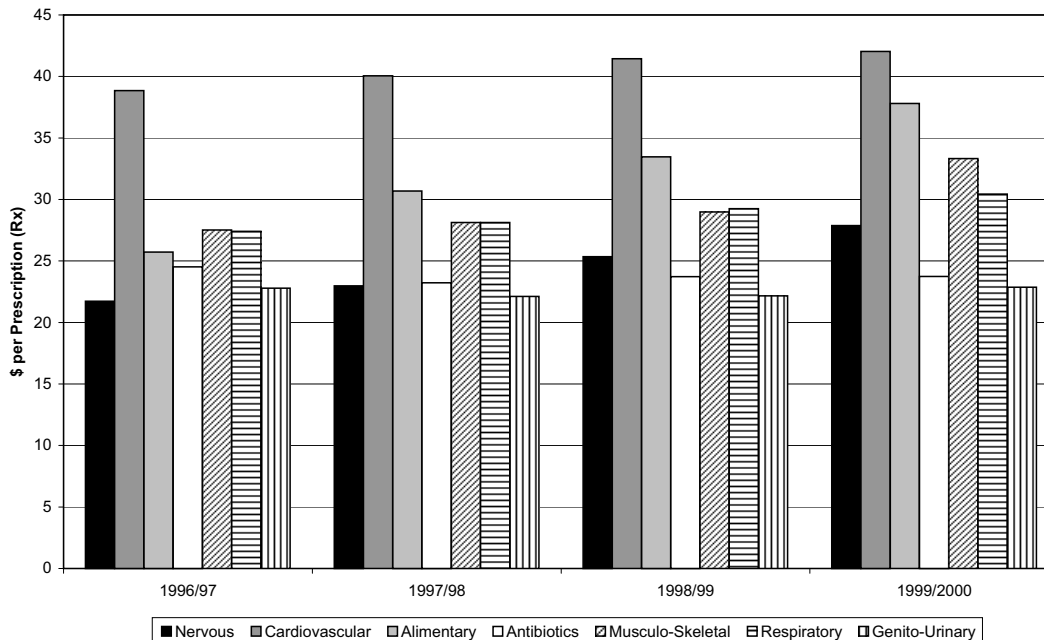


Expenditure Indicator #6 describes the average cost per defined daily dose and by therapeutic class. Figure 9 shows that older residents of Manitoba pay four times more per person for pharmaceuticals in a year than younger

residents (<65 years old) of Manitoba. Yet, when one considers the dollars spent per defined daily dose then younger residents pay about 20% more (Table 6).

**Figure 9: Dollars Spent per Younger Manitoba Resident and per Older Manitoba Resident per Year and per Defined Daily Dose (DDD), 1996/97-1999/2000**
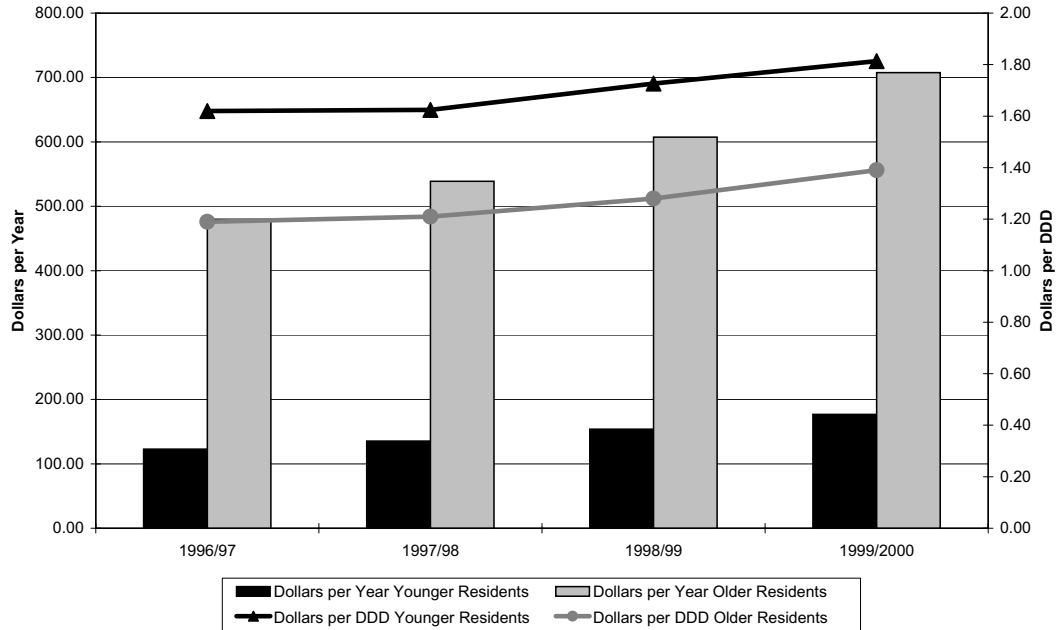


**Table 6: Expenditures per resident and per defined daily doses (DDD), 1996/97-1999/2000**

|  | 1996/97 | 1997/98 | 1998/99 | 1999/2000 |
|---|---|---|---|---|
| **Expenditures per year (in dollars per person)** |  |  |  |  |
| Manitoba residents (< 65 years old) | $122.93 | 135.50 | 153.88 | 176.72 |
| Manitoba older residents (≥ 65 years old) | $479.83 | 538.94 | 607.27 | 707.51 |
| **Expenditures per year per DDD** |  |  |  |  |
| Manitoba residents (< 65 years old) | $1.62 | 1.62 | 1.73 | 1.81 |
| Manitoba older residents (≥ 65 years old) | $1.19 | 1.21 | 1.28 | 1.39 |

To repeat, Expenditure Indicator #7 describes total drug expenditure by population characteristics and therapeutic class. Perhaps one of the most compelling ways of describing pharmaceutical use is by the expenditures that are incurred by residents of differing socioeconomic characteristics. In

previous work we have compared the health and health care use patterns of Winnipeg residents according to the average household income in the neighbourhood of residence. There is a marked difference in health status as measured by age/sex standardized death rates across the Winnipeg population. Individuals in middle-income neighbourhoods (quintile 3) have higher mortality rates than do individuals in the highest income neighbourhoods (quintile 5), whereas those in the poorest neighbourhoods demonstrated the highest rates. Table 7 describes measures of pharmaceutical use by income quintile (a population characteristic) including expenditures.

**Table 7: Pharmaceutical use measures by income quintile, Winnipeg 1999/2000**

| | Access: Per cent using at least one prescription per year | Use: Number of different drugs per user | Expenditures (in dollars) per resident | per user |
|---|---|---|---|---|
| Q5 (highest income) | 66.4 | 3.0 | $311.52 | $696.42 |
| Q4 | 68.0 | 3.2 | 301.54 | 683.51 |
| Q3 | 68.5 | 3.3 | 289.99 | 662.27 |
| Q2 | 68.9 | 3.4 | 252.32 | 556.73 |
| Q1 (lowest income) | 71.2 | 4.0 | 420.10 | 829.58 |

## 2.3 Summary of Observations: Drug Utilization in Manitoba

● Over eight million prescriptions were dispensed to Manitobans from community-based pharmacy settings and other outpatient locations in 1999/2000. Total expenditures by both public and private payers (insurers and/or out-of-pocket) were $285,982,702.

● Two-thirds of Manitobans (67.3%) have at least one prescription dispensed per year; this proportion increases to 87% (1999/2000) if one examines only older Manitobans (65 years of age and older).

● Older Manitoba residents are dispensed, on average, over 21 prescriptions per year and take over five different kinds of medication; this is in contrast to younger Manitoba residents who have over five prescriptions dispensed on average per year representing about three different kinds of medication.

● The number of prescriptions dispensed per resident has increased 20% since 1996/97; this represents a growth of about two prescriptions per resident per year.

● The three most common types of drugs dispensed are nervous system drugs, drugs acting on the cardiovascular system and antibiotics. In the older Manitobans, drugs acting on the cardiovascular system are dispensed about twice as often as nervous system drugs.

- Women consume, on average, about a third more doses of medication daily than men. Winnipeg residents consume marginally (about 3%) more doses than Non-Winnipeg residents.
- Although the total amount spent on all classes of drugs has increased since 1996 (44.7% increase in total amount spent for drugs used for the cardio-vascular system; a 58.6% increase in nervous system drug expenditures), the amount spent per prescription increased significantly for the alimentary drugs (this category includes proton pump inhibitors) from $25.73 to $37.80 per prescription (a 46.9% increase).
- Older Manitoba residents expend four times more dollars per person per year for pharmaceuticals than younger residents (those less than 65 years of age) of Manitoba ($708 versus $177). Yet, when one considers expenditures per defined daily dose, the younger Manitoba residents cost about 30% more ($1.81/DDD versus $1.39/DDD).
- All measures of pharmaceutical use in the Manitoba population are responsive to the marked difference in health status as measured by age/sex standardized death rates across the Winnipeg population. Measures of pharmaceutical use (highest income quintile versus lowest income quintile): (1) access (66.4%, 71.2%), (2) number of different drugs (3.0, 4.0), and (3) expenditures/resident ($312, $420) over the years of analysis.

## 2.4 Discussion

Over eight million prescriptions were dispensed to Manitobans from community-based pharmacy settings and other outpatient locations in 1999/2000. Total expenditures by both public and private payers (insurers and/or out-of-pocket) were $285,982,702. At the rate of $249.00 per resident, this represents an increased cost of $80 per resident over a four-year period, 1996/97-1999/2000.[12]

There was essentially no change in the proportion of Manitobans using pharmaceuticals; two-thirds of the population received at least one prescription. However, *we identified several trends in prescription utilization and costs among individuals receiving prescriptions which may explain the increased per capita costs of pharmaceuticals* that Manitobans (either out-of-pocket or through tax dollars as a social benefit) have experienced over this time period.

- The average number of prescriptions per resident increased by two prescriptions over four years (1996/97 to 1999/2000); the older Manitoban is having dispensed, on average, five more prescriptions per year than they did in 1996/97.
- The average duration of prescription treatment per younger Manitoban increased by 50 days/year, for the older Manitoba this increase since 1996/97 is over 100 more treatment days per year.

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[12] This is in line with estimates made by International Medical Statistics (IMS) and the Canadian Institute for Health Information (CIHI). Cost of prescriptions per capita (2000) according to IMS was $282.00.

• The average cost of a prescription increased by $5 for all users of pharmaceuticals in Manitoba

• An additional 400 prescriptions per 1,000 residents were dispensed for cardiovascular drugs (1996/97 to 1999/2000); in the older Manitoban (≥65 years old) cardiovascular drug use increased by 1,500 prescriptions or 1.5 prescriptions per resident

While on average, prescription costs have increased per resident, there are *specific populations of Manitobans or classes of drugs which contribute disproportionately to the increase in costs.*

• Total costs for prescription drugs for older Manitobans (versus younger Manitobans) increased more (49% vs. 44%)

• Average cost per pharmaceutical treatment day increased for all Manitobans—from $1.62 in 1996/97 to $1.81 in 1999/2000 (a 12% increase) for younger Manitobans and from $1.19 to $1.39 (a 17% increase) for older Manitobans[13]

• Total costs for nervous system drugs increased the most—59% over four years (1996/97 to 1999/2000)

• Average cost per prescription also increased the most for nervous system drugs ($21.73 to $27.88, 1996/97 to 1999/2000)

How do the specific drug classes considered in the appropriateness study place in the drug utilization study? Agents acting on the renin-angiotensin system accounted for 5.5% of total prescriptions and 8.2% of total expenditures in 1999/2000. Those in the highest income quintile (Winnipeg) use more of these agents than those in the lowest Winnipeg income quintile. The cost per prescription for these agents increased 59.7% between 1995/1996 and 1999/2000 ($12.73 to $20.33). This increase parallels the introduction of a new class of agent—the angiotensin II receptor antagonists (A2RAs).

Serum lipid reducing agents accounted for 2.8% of total prescriptions and 7.4% of total expenditures in 1999/2000. The number of users of statins has increased by 60% between 1996/97 and 1999/2000 (25,824 to 41,344). Despite the increase in utilization, the proportion of those prescribed statins decreases after the age of 80. Others have observed that advanced age and being female are risk factors for undertreatment with serum lipid reducing agents (Majumdar, 1999; Sueta et al., 1999; Miller et al., 2000; Beck et al., 2001). Unlike the use of agents acting on the angiotensin system, however, prescribing of statins appears to be equitable across income quintiles.

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[13] This could signify that older Manitobans are either dispensed generic forms more commonly, or, that choice of therapy reflects the use of older, existing pharmaceuticals.

## 2.5 Conclusion and Recommendation

Our findings are consistent with the first report made on Manitobans' use of prescription drugs: (1) two-thirds of the population have access to prescription drugs in a year, (2) females use more pharmaceuticals than males, (3) prescribing of prescription drugs appears to be responsive to need, and (4) costs are escalating due to the increased use of existing drugs and the introduction of new therapies. The POPULIS methods developed for examining rate of prescription drug use appear to be giving us rates that are consistent with national trends in increasing utilization and costs.

The ability to count and describe the prescription drugs used for the entire population of a province should not be underestimated. Drug utilization is the background against which appropriateness and, ultimately, effectiveness and outcomes can be inferred. Yet, few Canadian provinces are able to undertake such an initiative (Canadian Institute for Health Information, 2002a). The Canadian Institute for Health Information (2002a) has developed a set of nine indicators for considering the long-term use and trends in drug utilization. With the exception of being unable to count non-prescription drug use and hospital drug expenditures and determining the breakdown between publicly insured, privately insured and out-of-pocket expenditures for prescription drugs using Manitoba Health's databases, Manitoba is able to measure seven of the nine indicators.

### *Recommendation*

● Assist the Canadian Institute for Health Information and other national agencies like the Patented Medicine Prices Review Board in encouraging other jurisdictions to develop their data sources for national comparative reporting using a set of common drug utilization indicators

In a recent report synthesizing the findings of pharmaceutical projects sponsored by the Health Transition Fund (Goyer and Kennedy, 2002), a joint effort between federal, provincial, and territorial governments, there is a call for joint policies and regulations by those responsible for pharmacotherapy policy. Having more complete and consistent information on actual pharmaceutical usage will help jurisdictions negotiate more effectively with industry to share the risk of program cost increases. Manitoba can be a leader in this initiative.

## 3.0 Appropriate Use
## Agents Acting on the Renin-Angiotensin System

*Agents acting on the renin-angiotensin system relax blood vessels that lower blood pressure and make it easier for the heart to pump out blood.*

*Persons with congestive heart failure and high blood pressure benefit from these agents use.*

*Newer ACEIs and A2RAs are generally more expensive than first generation ACEIs.*

In 1998/99 cardiovascular drugs accounted for 32.7% of total drug expenditures in Manitoba. Agents acting on the renin-angiotensin system contributed to 9.9% of total prescription costs and 13.6% of the growth in overall pharmaceutical expenditures from 1995/96 to 1998/99 (Appendix C). The latter was the second-largest contribution to pharmaceutical expenditure growth in this time period. The quantity or volume effect was identified as the major factor contributing to the growth of renin-angiotensin system drugs. Expenditures for the ACEI drug, enalapril (Vasotec™), and for the A2RA drug, losartan (Cozaar®), totalled $6 million or 36.4% of total expenditures in the ACEI class of drugs.

The first ACEI, captopril, was released in the early 1980s, followed by newer, "me-too" ACEIs and then the A2RAs in the mid- to late-1990s. ACEIs and A2RAs have a similar pharmacologic action; that is, they relax the blood vessels that lower blood pressure and make it easier for the heart to pump out blood. Persons with congestive heart failure and high blood pressure (hypertension) benefit from their use. Newer ACEIs (e.g., fosinopril-Monopril®) and A2RAs (e.g., losartan-Cozaar®), are generally more expensive than first generation ACEIs (captopril-Capoten®).

## 3.1 Angiotensin-Converting Enzyme Inhibitors

All ACEIs are officially indicated for the treatment of essential hypertension. Most are indicated for the treatment of congestive heart failure, and a few are also indicated for diabetic nephropathy and left ventricular dysfunction after myocardial infarction. There is a growing literature which shows that ACEIs reduce mortality after myocardial infarction (Huckell et al., 1997).

*ACEIs are recommended as first line agents for monotherapy of uncomplicated hypertension, as an alternative to diuretics or beta-blockers.*

Beta-blockers and diuretics have long been recognized as first-line agents in essential hypertension (Ogilvie et al., 1993). The 1999 Canadian Hypertension Guidelines and subsequent updates emphasize the importance of cardiovascular risk assessment and provide recommendations for the treatment of hypertension according to the presence of cardiovascular comorbidity (Feldman, 2000). Under this classification system, ACEIs are "preferred first-line" drugs for persons with essential hypertension who also have a diagnosis of one or more of: congestive heart failure, renal failure and diabetes.

Unlike previous treatment guidelines, ACEIs are now recommended as first-line agents for monotherapy of uncomplicated hypertension, as an alternative to diuretics or beta-blockers. This recommendation has been disputed by others who claim that diuretics and beta-blockers are as or more effica-

cious than ACEIs and are considerably cheaper. However, one justification for recommending ACEIs as first-line agents may come from the hypertensive management perspective, that is, persons prescribed ACEIs as initial therapy are more persistent than those prescribed either a beta-blocker, a calcium channel blocker or a diuretic as initial treatment (Marentette et al., 2002; Degli et al., 2002; Caro et al., 1999; Hasford, 2002).

The use of beta-blockers and diuretics has decreased throughout the 1980s and 1990s, while the use of ACEIs has increased (Manolio et al., 1995; Siegel and Lopez, 1997). ACEIs accounted for 20%-25% of antihypertensives dispensed in the 1990s (Wallenius et al., 1996). In some Canadian centres, ACEIs have been prescribed twice as often to persons with hypertension and a comorbidity such as diabetes, than in hypertension alone (Laplante et al., 1998). However, others report a lesser difference in ACEI use between persons with and without cardiovascular comorbidity (Siegel, 1998). Further, the incident use of ACEIs in elderly Canadians with newly diagnosed hypertension increased from 4.1% in 1994 to 4.5% in 1997 (Maclure et al., 1998; McAlister et al., 2001).

*Appropriateness criteria for ACEIs are based on the "step-up" approach to prescribing.*

Although the "right" prescription treatment rates are unknown, the appropriateness criteria for ACEIs focus on the role of these drugs in the treatment of hypertension with and without comorbidity. The criteria are based on a step-up approach to prescribing, that is, the principle of applying the minimum pharmacological force necessary to achieve a stated therapeutic objective.

**Table 8. Angiotensin-converting enzyme inhibitor (ACEI) appropriateness criterion (#1)**

| Prescribing indicator: Initial therapy choice ["step-up" approach] | |
|---|---|
| Criterion ACEI #1 | Prevalence of ACEI use should be <u>highest</u> in persons with hypertension and existing comorbidities for which ACEI are preferred first-line agents. Prevalence of ACEI should be <u>lowest</u> in persons with uncomplicated hypertension for which ACEI are alternative first-line agents (to beta-blockers and diuretics). |
| Question | What is the prevalence of ACEI use in persons with hypertension and existing comorbidities (ACEIs indicated) and in persons with uncomplicated hypertension (ACEIs alternative first-line agent to beta-blockers and diuretics)? |
| Reasoning | ACEIs are the preferred first-line agent for persons with essential hypertension who also have a diagnosis for one or more of: congestive heart failure, renal failure and/or diabetes. |

## 3.2 Angiotensin II Receptor Antagonists

*The marginal advantage of A2RAs over ACEIs appears to be decreased adverse effects like cough and angioedema.*

A2RAs are officially indicated for the treatment of essential hypertension only. Unlike ACEIs which inhibit the production of angiotensin, A2RAs block the effects of angiotensin at the receptor level and thus, may offer more complete inhibition of angiotensin than ACEIs (Martineau and Goulet, 2001). Non-interference of the A2RAs with the production of other hormones has resulted in a lower prevalence of adverse effects normally associated with ACEIs, such as cough and angioedema. Similar to ACEIs, A2RAs enhance the management of essential hypertension. That is, persons prescribed A2RAs as initial therapy are more persistent than those prescribed either an ACEI, a beta-blocker, a calcium channel blocker or a diuretic as initial treatment (Marentette et al., 2002; Degli et al., 2002; Caro et al., 1999; Hasford, 2002).

The clinical effects of A2RAs are similar to ACEIs in terms of blood pressure lowering. However, few long-term studies have been conducted with A2RAs on cardiovascular outcomes, so that ACEIs remain the drugs of choice for hypertension in congestive heart failure, renal failure and diabetes. A2RAs are recommended when persons cannot tolerate the cough associated with ACEIs or experience other adverse effects. They may also exert renal protective effects in diabetic nephropathy. The appropriateness criteria for A2RAs focus on their use as second choice therapy in persons who cannot tolerate ACEI side effects.

**Table 9: Angiotensin II receptor antagonist (A2RA) appropriateness criteria (#2-#4)**

| Prescribing indicator: Initial therapy choice ["step-up" approach] | |
|---|---|
| Criterion A2RA #2 | Treatment with an ACEI should be initiated prior to the use of A2RAs. |
| Question | What proportion of persons treated with A2RAs have been previously treated with an ACEI? |
| Reasoning | The clinical effects of A2RAs are similar to ACEIs in terms of blood pressure lowering. Therefore, the principle of applying the minimum pharmacological forces necessary to achieve a stated therapeutic objective ("step-up" approach) should be adopted. [NOTE: If one cannot tolerate the adverse effects of ACEIs (cough, angioedema) after a 'trial', then an A2RA would be indicated.] |

| Prescribing indicator: Initial therapy choice ["step-up" approach] | |
|---|---|
| Criterion A2RA#3 | Regardless of the appropriateness of A2RA selection (criterion #2), prevalence of A2RA use should be highest in persons with hypertension and existing comorbidities for which ACEI are preferred first-line agents. |
| Question | What proportion of hypertensives with existing comorbidities are prescribed A2RAs as first-line agents for hypertension? |
| Reasoning | ACEIs are the preferred first-line agent for persons with essential hypertension who also have a diagnosis for one or more of: congestive heart failure, renal failure and/or diabetes, as the clinical effects of A2RAs are similar to ACEIs in terms of blood pressure lowering. Regardless, knowing the rate of potential 'inappropriateness' is helpful in designing interventions to minimize a "step-up"[1] approach to prescribing. |

| Prescribing indicator: Initial therapy choice ["step-up" approach] | |
|---|---|
| Criterion A2RA#4 | Persons with "newly diagnosed", uncomplicated hypertension should not receive A2RAs as first-line agents. |
| Question | What proportion of "newly diagnosed", uncomplicated hypertensives are prescribed A2RAs? |
| Reasoning | The clinical effects of A2RAs are similar to ACEIs in terms of blood pressure lowering. Therefore, the principle of applying the minimum pharmacological forces necessary to achieve a stated therapeutic objective ("step-up" approach) should be adopted. |

[1] The 'step-down' approach proposes that individuals should initially be treated with an A2RA and 'stepped-down' to a less intensive intervention (e.g., an ACEI) in defined circumstances. The problem inherent in this approach is the universal application of a powerful and costly drug in individuals in whom less intensive interventions may have been adequate and have not previously been proven to be ineffective.

## 3.3 Application of Appropriateness Criteria: Agents Acting on the Renin-Angiotensin System and Hypertension

### 3.3.1 Study Period and Population

Following the 1999 Canadian Hypertension Guidelines approach (Feldman, 2000), Manitobans treated for hypertension during 1996-2000 were stratified by the presence of cardiovascular risk factors, hypertension-related complications and other cardiovascular comorbidities. Initially, all individuals with at least one physician visit or hospitalization (primary diagnosis) for

essential hypertension and hypertensive heart or renal disease over two-year time periods (reporting year and year prior) were selected on an annual basis for the fiscal years 1996/97, 1997/98, 1998/99 and 1999/2000. Individuals were then placed into mutually exclusive categories of hypertension (see Appendix D for disease definitions) according to the following order: congestive heart and renal failure, diabetes, cardiac arrhythmias, peripheral vascular disease, coronary heart disease (including myocardial infarction), cerebrovascular disease and hyperlipidemia. Persons without these comorbidities were classified as having uncomplicated hypertension. Uncomplicated hypertension was further classified as existing hypertension and, in the absence of hypertension, cardiovascular comorbidity or antihypertensive drugs in the year prior, as a newly-diagnosed hypertensive.

The rationale for sorting persons into hypertension comorbidity categories according to the above hierarchy was to rank comorbidities by the requirement for an ACEI according to the 1999 Canadian Hypertension Guidelines (Feldman, 2000). An ACEI is the "preferred first-line" drug for congestive heart/renal failure and diabetes. It is a "preferred alternative" for persons with arrhythmias and peripheral vascular disease in the presence of contraindications to beta-blockers and diuretics and for coronary heart disease if there is a recent myocardial infarction. In persons with uncomplicated hypertension, an ACEI is an "alternative first-line" agent to a thiazide diuretic or beta-blocker as initial monotherapy therapy. In the absence of the other comorbidities, the drugs of choice for cerebrovascular disease or hyperlipidemia are similar to uncomplicated hypertension. We have labelled use of ACEIs for these conditions and uncomplicated hypertension as alternative first-line.

Only after identifying hypertensive status were new users of agents acting on the renin-angiotensin system (ACEIs and A2RAs) identified. An individual was classified as a new user if no prescription for an ACEI or A2RA (ATC:C09) was found in the DPIN claims between April 1 and July 31 of fiscal years 1996/97, 1997/98, 1998/99 and 1999/2000 (Appendix E). The analysis reports on four fiscal years of new users of agents acting on the renin-angiotensin systems classified by hypertensive status.

### 3.3.2 Analytic Approach

The appropriateness criteria for agents acting on the renin-angiotensin system focus more on the role of these drugs in the treatment of hypertension with and without comorbidity (Figure 10) rather than on their utilization alone. The criteria are based on a step-up approach to prescribing. That is, the principle of applying the minimum pharmacological force necessary to achieve a stated therapeutic objective when initiating therapy. Application of

the criteria, indicative of initial therapy choice, sought to answer four questions:

1. What is the prevalence of ACEI use in persons with hypertension and existing comorbidities (ACEIs indicated) and in persons with uncomplicated hypertension (ACEIs as alternative first-line agent to beta-blockers and diuretics)?

2. What proportion of persons treated with A2RAs have been previously treated with an ACEI?

3. What proportion of hypertensives with existing comorbidities are prescribed A2RAs as first-line agents for hypertension?

4. What proportion of newly diagnosed, uncomplicated hypertensives are prescribed A2RAs as first-line agents for hypertension?

For example, the use of ACEIs are the preferred first-line agent for persons with essential hypertension who also have a diagnosis for one or more of: congestive heart failure, renal failure and/or diabetes. Otherwise, ACEIs are alternate first-line drugs to beta-blockers and/or diuretics for the treatment of newly diagnosed hypertension without these comorbidities.

The step-up approach to prescribing is also useful to look at the appropriateness of A2RAs use. A2RAs have a lower prevalence of adverse effects normally associated with ACEIs. The clinical effects of A2RAs are similar to ACEIs in terms of blood pressure lowering. Therefore, A2RAs are usually reserved for those who cannot tolerate ACEI's side effects (cough and angioedema) and their appropriateness criteria focus on their use as a second choice of therapy in persons who cannot tolerate ACEI side effects.

**Figure 10: Agents Acting on the Renin-Angiotensin System Analysis Approach**

```
┌─────────────────────────────┐
│         Identify            │
│   essential hypertension    │
│    (HTN) as a diagnosis     │
│   1995-97 → 96/97 cohort    │
│   1996-98 → 97/98 cohort    │
│   1997-99 → 98/99 cohort    │
│   1998-00 → 99/00 cohort    │
└─────────────────────────────┘
              │
              ▼
┌─────────────────────────────┐     ┌─────────────────────────────┐
│  For each fiscal year cohort,│     │ For each fiscal year cohort, │
│  determine hypertension (HTN)│     │  identify NEW users of agents│
│   strata (mutually exclusive)│ ──▶ │ of renin-angiotensin (ACEIs  │
│  - HTN comorbidity (ranked by│     │         and A2RAs)           │
│    congestive heart or renal │     │                              │
│    failure, diabetes,        │     │       APPLY criteria         │
│    ischemic heart disease    │     │                              │
│    & other)                  │     └─────────────────────────────┘
│  - HTN (new or existing)     │
└─────────────────────────────┘
```

| Prevalence of ACEI use is highest in those with HTN and a comorbidity CRITERION #1 | Treatment with an ACEI should be initiated prior to the use of an A2RA CRITERION #2 | Prevalence of A2RA use is highest in those with HTN and a comorbidity CRITERION #3 | Newly diagnosed, uncomplicated HTN should not be treated with an A2RA CRITERION #4 |

## 3.4 Results

Approximately 125,000 Manitobans had a diagnosis of hypertension with and without existing comorbidities in 1996/97; hypertension was found among 140,000 people in 1999/2000. Comorbidities with hypertension (HT), 43%, were distributed in this population as follows: congestive heart failure (CHF) or renal failure (16%), diabetes mellitus (DM) (8%), ischaemic heart disease (IHD) (7%), hyperlipidemia (5%), arrhythmias (3%), cerebrovascular disease (3%) and peripheral vascular disease (1%). The remaining persons (57%) were designated as having uncomplicated hypertension. The proportion of persons with congestive heart/renal failure or diabetes increased in 1999/2000, while the proportion of uncomplicated hypertension decreased. The next section describes the prevalence of new use of ACEIs and A2RAs by the various levels of hypertension comorbidity.

### 3.4.1 Initial Therapy Choice (Angiotensin-Converting Enzyme Inhibitors): Criterion #1

ACEIs are the preferred first-line agent for persons with essential hypertension who also have a diagnosis for one or more of: congestive heart failure,

renal failure and/or diabetes. This criterion assumes that prevalence of ACEI use should be highest in persons with hypertension and existing comorbidities for which ACEI are preferred first-line agents and, conversely, that prevalence of ACEI should be lowest in persons with uncomplicated hypertension for which ACEI are alternative first-line agents (to beta-blockers and diuretics). Application of this criterion sought to answer the following question:

*What is the prevalence of ACEI use in persons with hypertension and existing comorbidities (ACEIs indicated) and in persons with uncomplicated hypertension (ACEIs as alternative first-line agents to beta-blockers and diuretics)?*

Seven per cent of persons with hypertension received a new prescription for an ACEI in 1996/97. This decreased slightly to 6% in the next two years then crept back up to 7% in 1999/2000. New use of ACEI prescriptions in persons with hypertension (study cohort) accounted for 19% of all ACEI users in 1996/97 and 16% of users in 1999/2000 (Figure 11).

**Figure 11: Distribution of Angiotensin-Converting Enzyme Inhibitors (ACEIs) by Prevalent Use and New Use by Diagnosis, 1996/97 and 1999/2000**
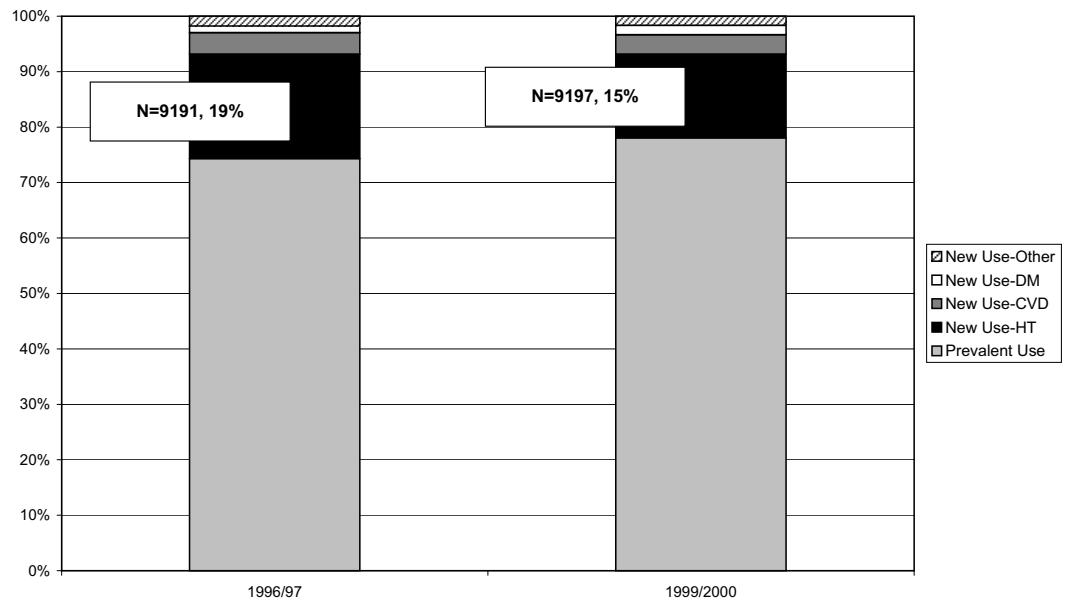


Note: Cardiovascular Disease (CVD) = Congestive Heart Failure and Ischaemic Heart Disease.

The use of ACEI decreased in all hypertension and comorbidity categories from 1996/97 to 1999/2000, with the exception that use in persons with coexisting congestive heart and diabetes remained the same (Figure 12).

**Figure 12: Per Cent of Persons with Hypertension who Received a New ACEI Prescription by Level of Comorbidity, 1996/97-1999/2000**
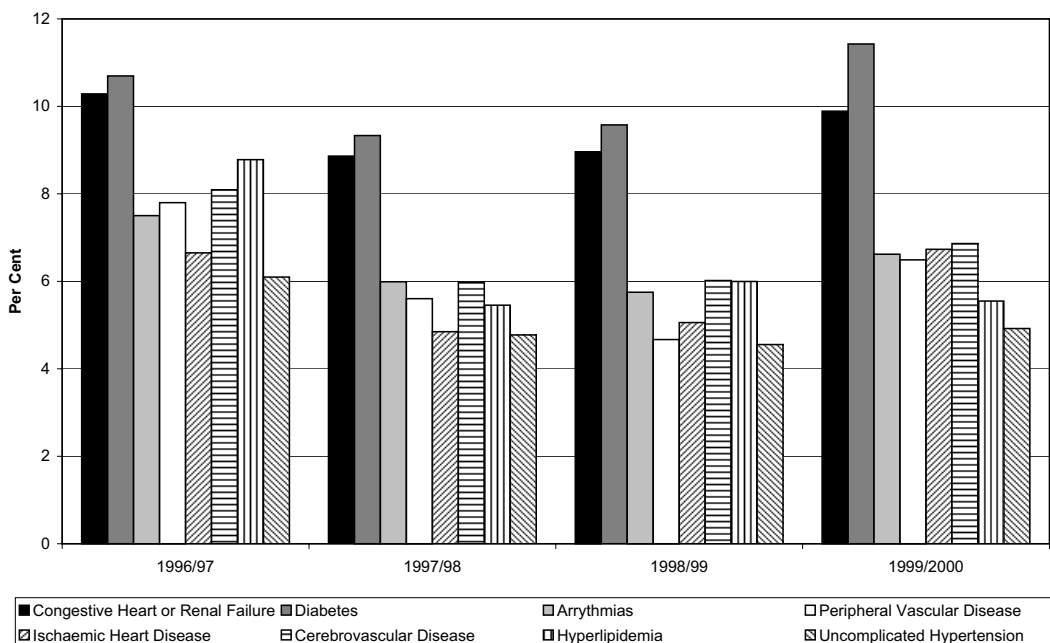


In 1999/2000, persons with hypertension and congestive heart failure or diabetes (10-11%) were more likely to receive ACEI prescriptions than persons with hypertension and other cardio/cerebrovascular comorbidities (6-7%) and persons with uncomplicated hypertension (5%). Patients with comorbidities for which ACEIs were the preferred first-line drugs of choice (congestive heart failure, renal failure and diabetes) represented a greater share of new ACEI users in 1999/2000 (41%) than in 1996/97 (34%) (Figure 13). Patients with hypertension in whom ACEIs were one of three drugs of choice, labelled as alternative first-line use in uncomplicated hypertension, hypertension with cerebrovascular disease or hyperlipidemia, were less likely to have ACEI prescriptions in 1999/2000 (48%) than in 1996/97 (55%). The proportion of patients in whom ACEIs were preferred alternative drugs (hypertension with arrhythmias, peripheral vascular disease or ischaemic heart disease) represented a constant proportion of new users over the four-year period (about 11%).

The per cent of persons with newly diagnosed uncomplicated hypertension treated with ACEI as a first-line agent (no previous treatment with beta-blockers or diuretics) hovered around 7% from 1996/97-1999/2000 (Table 10). Persons between the ages of 45 and 74 years were the most likely to be prescribed an ACEI as first-line for newly diagnosed uncomplicated hypertension.

**Figure 13: Per Cent of New ACEI Users by Role in Hypertension Treatment, 1996/97-1999/2000**
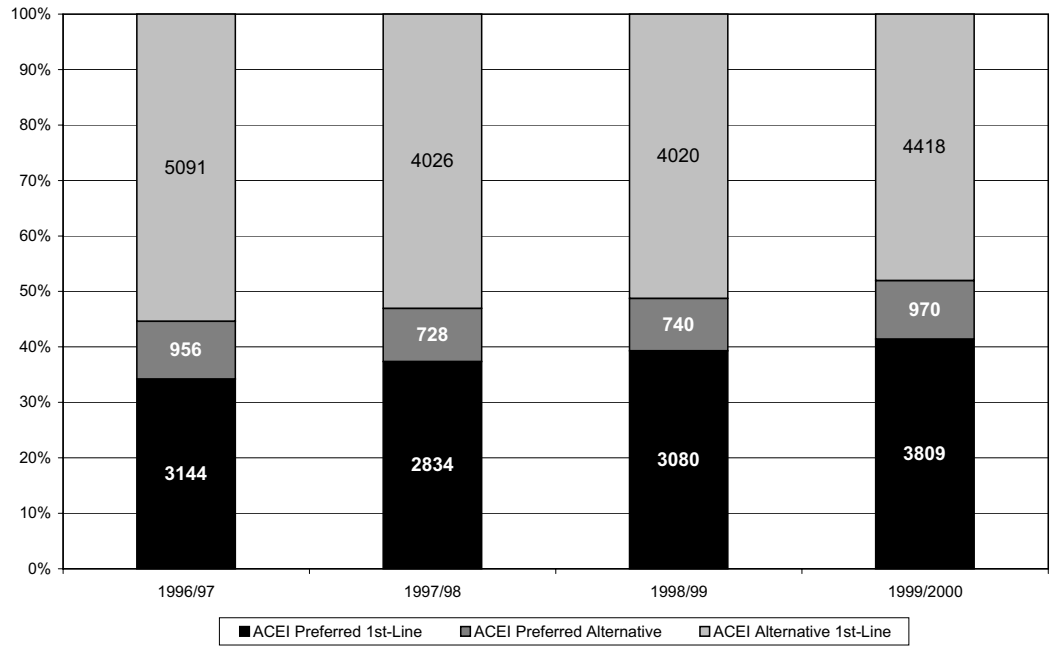


Table 10: Proportion of persons with "newly diagnosed" hypertension who have received new prescriptions for ACEI by age, 1996/97-1999/2000

| Age group | Per cent | | | |
|---|---|---|---|---|
| | 1996/97 | 1997/98 | 1998/99 | 1999/2000 |
| 20-44 years | 5.7 | 6.2 | 5.3 | 6.1 |
| 45-54 years | 8.5 | 7.4 | 7.7 | 8.1 |
| 55-74 years | 7.9 | 7.3 | 8.3 | 7.6 |
| 75+ years | 6.7 | 6.7 | 7.0 | 6.7 |
| Total | 7.2 | 6.9 | 7.1 | 7.2 |

## 3.4.2 Initial Therapy Choice (Angiotensin II Receptor Antagonists): Criteria #2 to #4

### Proportion of persons treated with A2RAs previously treated with an ACEI: Criterion #2

The clinical effects of A2RAs are similar to ACEIs in terms of blood pressure lowering. Therefore, the principle of applying the minimum pharmacological forces necessary to achieve a stated therapeutic objective (step-up approach) should be adopted. This criterion assumes that treatment with an ACEI should be initiated prior to the use of A2RAs; specifically, we wanted to answer the following:

*What proportion of persons treated with A2RAs have been previously treated with an ACEI?*

New prescriptions for A2RAs were dispensed increasingly more often over the four-year study period, growing from 1% to 3% of the hypertension population in 1999/2000. New use of A2RA prescriptions for the treatment of hypertension (study cohort) accounted for a smaller share of all A2RA users in 1999/2000 (29%) than in 1996/97 (46%). However, the actual number of users has more than tripled going from 1,244 in 1996/97 to 4,256 in 1999/2000. (Figure 14).

**Figure 14: Distribution of Angiotensin II Receptor Antagonists (A2RAs) by Prevalent Use and New Use by Diagnosis, 1996/97 and 1999/2000**



Note: Cardiovascular Disease (CVD) = Congestive Heart Failure and Ischaemic Heart Disease.
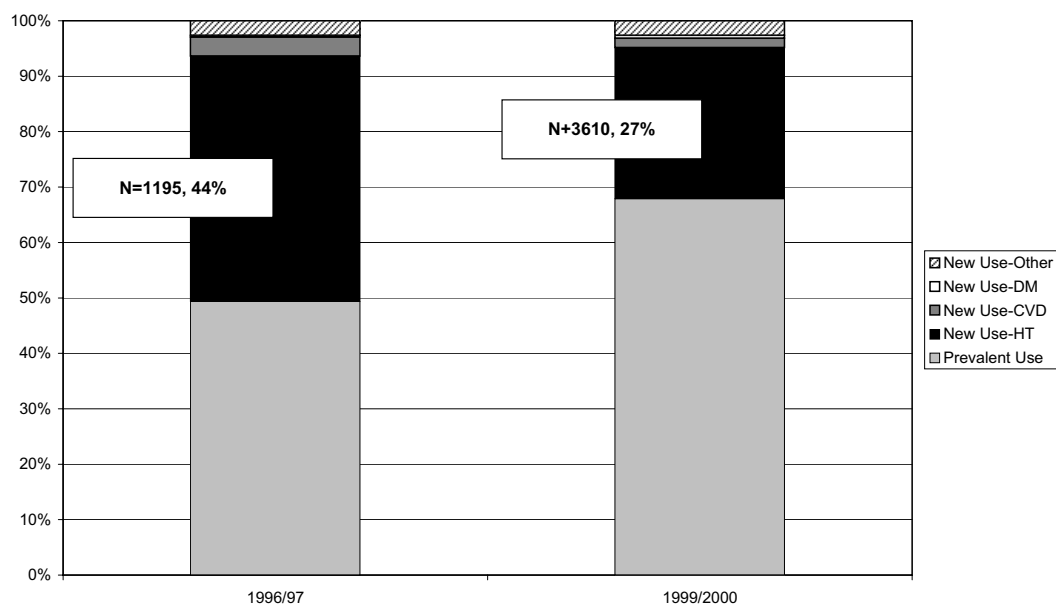
A trend of increased use of A2RAs was observed in persons with or without previous prescriptions for ACEI. The former can be labelled as "switchers." The prevalence of switchers increased from 0.4% to 1.0% of persons with hypertension. A2RA prescription users with no previous prescriptions for ACEIs experienced the steepest growth in use from 0.5% to 1.7% of persons with hypertension, accounting for 64% of all new A2RA users in 1999/2000 or an increase of 12%. This category was responsible for an increasing share of all new A2RA users (Figure 15).

**Figure 15: Per Cent of New A2RAs Users by Previous ACEI Prescriptions, 1996/97-1999/2000**
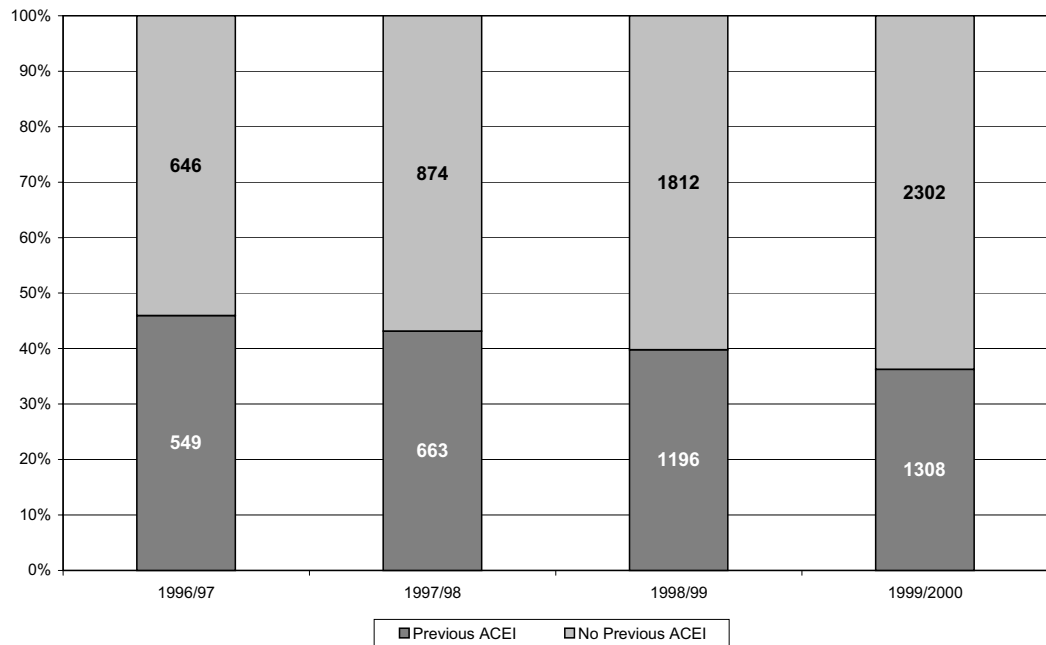


## Proportion of persons with hypertension and another comorbidity prescribed A2RAs as first-line: Criterion #3

ACEIs are the preferred first-line agent for persons with essential hypertension who also have a diagnosis for one or more of: congestive heart failure, renal failure, and/or diabetes, as the clinical effects of A2RAs are similar to ACEIs in terms of blood pressure lowering. Knowing the rate of potential "inappropriateness" is helpful in designing interventions to discourage a step-down[14] approach to prescribing. This criterion assumes that prevalence of A2RA use should be highest in persons with hypertension and existing comorbidities for which ACEI are preferred first-line agents. Treatment with an ACEI should be initiated prior to the use of A2RAs; specifically, we wanted to answer the following:

*What proportion of persons with hypertension with existing comorbidities are prescribed A2RAs as first-line agents for hypertension?*

Patterns of new A2RA use by level of comorbidity in hypertension differed by whether there was a previous trial of an ACEI. In 1996/97, new use of A2RA with previous ACEI, i.e., switching, occurred more often in the presence of comorbidities, such as congestive heart/renal failure and diabetes, than in uncomplicated hypertension (Figure 16). By 1999/2000, the prevalence rates of switching to A2RA in peripheral vascular disease and cerebrovascular disease matched those for congestive heart/renal failure and diabetes.

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[14] The 'step-down' approach proposes that individuals should initially be treated with an A2RA and 'stepped-down' to a less intensive intervention (e.g., an ACEI) in defined circumstances. The problem inherent in this approach is the universal application of a powerful and costly drug in individuals in whom less intensive interventions may have been adequate and have not previously been proven to be ineffective.

**Figure 16: Per Cent of New A2RA Users With Previous ACEI Prescriptions by Comorbidity, 1996/97-1999/2000**
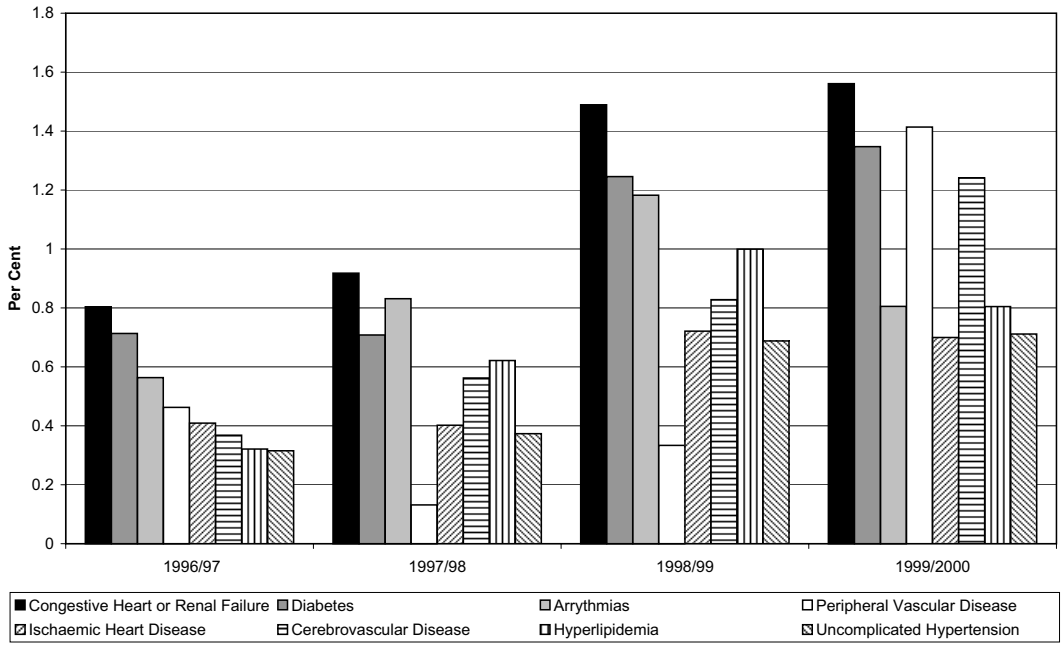


The use of new A2RAs with no previous ACEI prescriptions was similar in uncomplicated and comorbid hypertension in 1996/97. In 1999/2000 this use was higher in the presence of peripheral vascular disease and cerebrovascular disease (Figure 17).

**Figure 17: Per Cent of New A2RA Users With No Previous ACEI Prescriptions by Comorbidity, 1996/97-1999/2000**
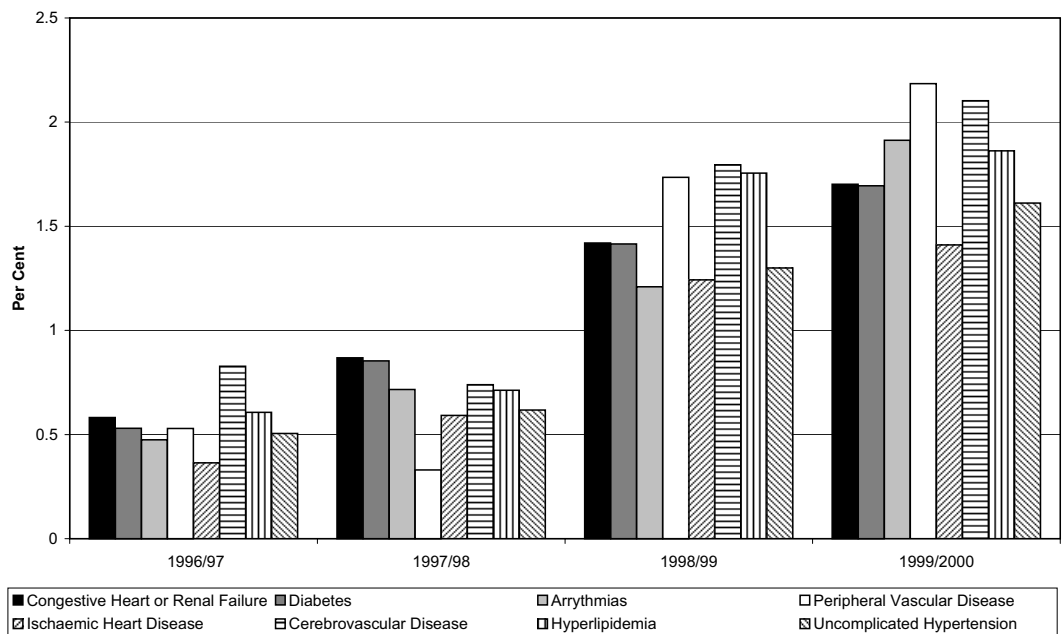
Patients with hypertension (uncomplicated hypertension, hypertension with hyperlipidemia or cerebrovascular disease) in whom ACEIs were one of three drugs of choice (beta-blockers, diuretics, ACEI) and alternative first-line agents comprised the greatest share of A2RA use without a previous trial of ACEI prescriptions (40%) and this pattern remained constant over the four-year period (Figure 18).

**Figure 18: Per Cent of New A2RAs Without Previous ACEI by Role of ACEI in the Treatment of Hypertension, 1996/97-1999/2000**



*Legend: ■ ACEI Preferred 1st-Line  ▨ ACEI Preferred Alternative  ☐ ACEI Alternative 1st-Line*
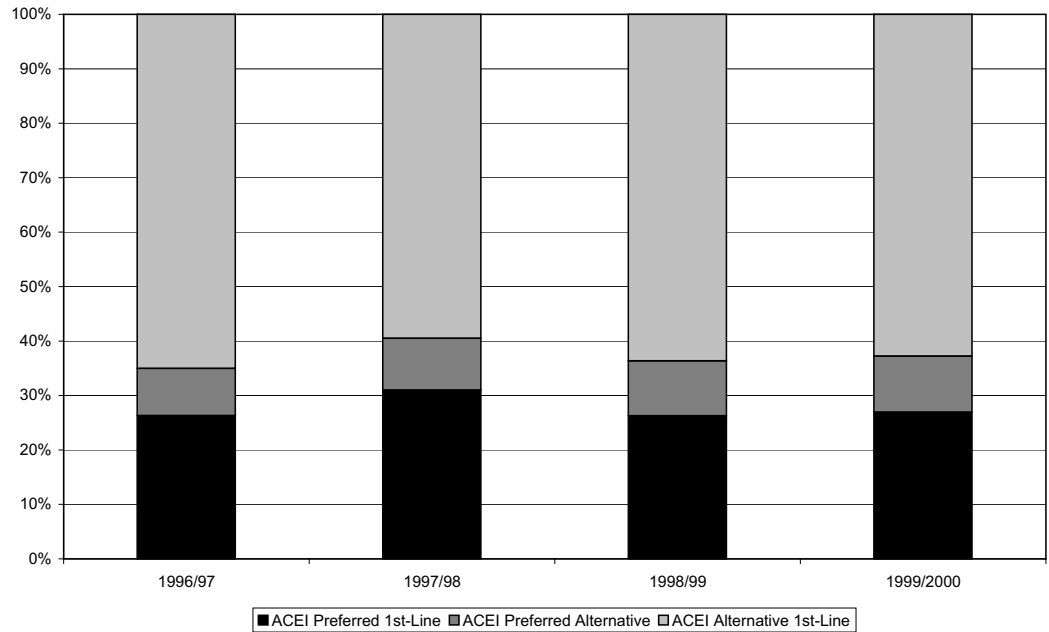
### *Proportion of persons newly diagnosed with uncomplicated hypertension and prescribed A2RAs as a first-line agent: Criterion #4*

The clinical effects of A2RAs are similar to ACEIs in terms of blood pressure lowering. This criterion assumes that persons with newly diagnosed, uncomplicated hypertension should not receive A2RAs as first-line therapy; specifically we wanted to know:

*What proportion of "newly diagnosed," uncomplicated hypertensives are prescribed A2RAs as first-line agents for hypertension?*

The per cent of persons with new prescriptions for A2RAs as first-line agents in newly diagnosed hypertension increased four-fold over the study period (Table 11). In 1999/2000, over 2% of persons fell into this category, clearly not meeting our criterion for appropriateness. Similar to the ACEIs, first-line use of A2RAs was greatest in persons 45-74 years old.

**Table 11: Proportion of persons with "newly diagnosed" hypertension who have received new prescriptions for A2RA by age, 1996/97-1999/2000**

| Age group | Per cent | | | |
|---|---|---|---|---|
|  | 1996/97 | 1997/98 | 1998/99 | 1999/2000 |
| 20-44 years | 0.4 | 0.4 | 1.7 | 1.9 |
| 45-54 years | 0.7 | 1.0 | 2.1 | 3.1 |
| 55-74 years | 0.6 | 0.6 | 2.1 | 2.6 |
| 75+ years | 0.2 | 0.7 | 1.6 | 1.5 |
| Overall Total | 0.5 | 0.7 | 2 | 2.4 |

## 3.5 Summary of Observations: Use of Agents Acting on the Renin-Angiotensin System

• Agents acting on the renin-angiotensin system accounted for 5.5% of total prescriptions and 8.2% of total expenditures in 1999/2000. Those in the highest income quintile (Winnipeg) use more of these agents than those in the lowest Winnipeg income quintile.

• The cost per prescription for these agents increased 59.7% between 1995/1996 and 1999/2000 ($12.73 to $20.33). This increase parallels the introduction of a new class of agent—the A2RAs.

• New use of the older class of these agents (ACEIs) has remained constant in those with hypertension and either diabetes or congestive heart failure; new use in uncomplicated hypertension, however, has declined.

• ACEIs are used more commonly in those with hypertension and a comorbidity like diabetes or congestive heart failure (10-11%) than in those with uncomplicated hypertension (5%).

• Sixty-four per cent of all new users of A2RAs in 1999/2000 did not have a previous trial with an ACEI.

• Persons switching from use of an ACEI to an A2RA were more likely to have hypertension and a comorbidity than uncomplicated hypertension.

• The per cent of persons with new prescriptions for A2RAs as first-line agents in newly diagnosed hypertension increased four-fold (0.5% to 2.4%) from 1996/97 to 1999/2000.

## 3.6 Discussion

• New use of ACEI prescriptions in persons with hypertension and/or diabetes or congestive heart/renal failure remained constant in Manitoba over the late 1990s, while use of ACEIs in uncomplicated hypertension or in the presence of other comorbidities has declined. *Hypertension coexisting with diabetes and congestive heart/renal failure accounted for an increasingly greater share of new ACEI use in 1999/2000.*

Our findings correspond to Laplante et al.'s (1998) observations of a two-fold greater use of ACEI in persons with hypertension and diabetes than in uncomplicated hypertension in a general practice setting. Our results also meet our appropriateness criteria for ACEIs as preferred first-line agents for these conditions.

In contrast to the findings of Maclure et al. (1998) who observed a 42% constant rate of first-line use of ACEIs, the first-line rate of ACEI use we found for uncomplicated hypertension remained constant at 7%. Although not the most cost-effective therapy, the lower rates of ACEI prescription use in newly diagnosed, uncomplicated hypertension than in hypertension with comorbidities met our criteria for appropriateness for the use of ACEIs as alternate first-line agents.

● *A2RAs were used increasingly more often over the study period in persons with and without previous ACEI prescriptions.* The former scenario represents switching, potentially due to the cough side effects of ACEIs. It occurred to a greater extent in persons with coexisting diabetes and congestive heart/renal failure than in those with uncomplicated hypertension. However, in 1999/2000, switching was also more common in persons with peripheral vascular than in uncomplicated hypertension. Peripheral vascular disease, which is common in persons with diabetes, may have represented diabetes that was not recorded in the health care data.

There is new evidence for the renal protective properties of A2RAs in diabetic nephropathy and A2RAs have been listed as alternative agents to ACEI in the first-line treatment of these patients in the 2001 Canadian Hypertension Guidelines (Garg, 2002). Interestingly, switching was also more common in persons with cerebrovascular disease in 1999/2000. This prescribing activity may have resulted from the publication of the ELITE trial that reported better survival rates and fewer side effects for persons with cerebrovascular disease taking an A2RA than an ACEI (Pitt et al., 1997). A subsequent trial reported no differences in mortality outcomes between A2RAs and ACEIs (Pitt et al., 2000), but recent trials have documented the beneficial effect of ACEI in preventing secondary stroke (Chalmers and Chapman, 2001) and further trials comparing ACEI and A2RAs are underway (Sleight, 2002).

● In 1999/2000, new A2RA use without previous ACEI prescriptions was highest in the presence of peripheral vascular disease and cerebrovascular disease. Further, treatment prevalence rates for uncomplicated hypertension were similar to those for hypertension with a comorbid condition. As of March 31, 2000 *over 2% of persons with newly diagnosed uncomplicated hypertension had received a prescription for an A2RA in the absence of prior*

*ACEI use.* These results would not meet even the most current treatment guidelines or clinical trial evidence.

A2RA use in persons without previous use of ACEIs represents inappropriate use and the trend for increased use was greater than that reported for switching. The 2001 Canadian Hypertension Guidelines now recommend that an A2RA can be prescribed as an alternative to an ACEI in patients with diabetic nephropathy. As discussed previously, peripheral vascular disease may represent diabetes. However, higher use in cerebrovascular disease, while potentially related to the ELITE trial (Pitt et al., 2000), does not meet our appropriateness criteria.

Using population-based data on prescription utilization, we determined the appropriateness of use of the cardiovascular drugs, ACEIs and A2RAs. The prevalence of hypertension found in this project was similar to the rates reported in the MCHP report by Black et al. (1999) "Comparative Indicators of Population and Health Care Use for Manitoba's Regional Health Authorities." While we can be reassured that the majority of the population with hypertension was captured, our analyzes were limited to the new use of ACEI and A2RAs as a measure of intention to treat. This design represents, maximally, 16% of all users of ACEI and 29% of all users of A2RAs. In addition, we did not describe the use of other antihypertensive agents.

## 3.7 Conclusion and Recommendations

Given that there are both new therapies (A2RAs) and existing therapies (ACEIs) in this class of drugs, we examined the extent of step-up care—that is, the prescription first of an ACEI before prescription with an A2RA. Step-up care is a proxy for the appropriateness intention that the prescription is necessary and the right choice. We wanted to know the following: (1) if use of ACEIs was more prevalent in those with hypertension and existing comorbidities than in those with uncomplicated hypertension, (2) the proportion of individuals dispensed an ACEI prior to being dispensed an A2RA (appropriate), (3) the proportion of individuals dispensed an A2RA as an initial agent for newly diagnosed, uncomplicated hypertension (inappropriate), and (4) the proportion of hypertensives with existing comorbidities prescribed A2RAs as initial agents (inappropriate).

There was a two-fold difference in the number of persons being treated with ACEIs who had hypertension and congestive heart failure or diabetes compared to those persons with uncomplicated hypertension (10% versus 5%). Of all the new A2RA users in 1999/2000, 64% had no previous trial with an ACEI. Over 2% of persons with newly diagnosed uncomplicated hypertension had received a prescription for an A2RA in the absence of prior

ACEI use. Finally, the greatest share of A2RA use without a previous trial of an ACEI (40%) was consumed by those with either uncomplicated hypertension, hypertension with either hyperlipidemia or cerebrovascular disease. Thus, there are indications that A2RAs are being inappropriately prescribed outside the criteria set, a priori and based on evidence, for this analysis.

In summary, new use of ACEIs has remained constant, while new use of A2RAs has risen among Manitobans in the 1990s. New use of A2RAs was greatest among persons with no previous use of ACEI. While new evidence supports the need of A2RAs in diabetic nephropathy as first-line agents, this is a function of clinical trial data on renal outcomes which only exists for the A2RAs and not ACEIs (Garg, 2002). A clear indication of inappropriateness was the first-line use of A2RAs for newly diagnosed uncomplicated hypertension, for which rates of use have increased four-fold. A2RAs use in uncomplicated hypertension represented a substantial share of initial A2RA use.

### Recommendation
● Policies encouraging a step-up approach to prescribing should be tested and implemented.

Several appropriate use projects are currently underway in Manitoba.[15] Lessons learned from these projects could help to design a "toolbox" of workable interventions for more cost-effective therapeutic choices to be made.

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[15] MOMM: Maximizing Osteoporosis Management in Manitoba; MAAUI: Manitoba Appropriate Anti-inflammatory Use Initiative; Describing 'early adopters' of new pharmaceuticals.

# 4.0 APPROPRIATE USE:
## SERUM LIPID REDUCING AGENTS: THE STATINS

*Statins are choles-terol-lowering drugs.  Lower cholesterol or lipid levels decrease one's risk of coro-nary heart disease (CHD) and, as a consequence one's chance of having a heart attack.*

In 1998/99 cardiovascular drugs accounted for 32.7% of total drug expendi-tures in Manitoba. Serum lipid reducing agents contributed to 9.6% of total pharmaceutical expenditures in 1998/99 and 12.6% of the growth in overall expenditures from 1995/96 to 1998/99 (Appendix F). Cardiovascular drugs, second only to nervous system drugs, contributed 24.8% of the expenditure growth in pharmaceuticals during this time period. The quantity effect or increased utilization and entry of new drugs were identified as the major fac-tors contributing to the growth in expenditure of all cardiovascular system drugs.

Abnormalities in blood lipid levels have been linked to an increase in the risk of developing coronary heart disease (CHD) (The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group, 1998). Because of the importance of CHD, considerable effort has been made to identify the major risk factors associated with the disease and to modify them by using drugs and/or making lifestyle and environmental change in order to prevent CHD occurring (primary prevention) or prevent-ing death or (further) coronary events like myocardial infarction in people with established disease (secondary prevention). Pharmacological interven-tions aimed at lowering lipid levels have been demonstrated to decrease CHD and to decrease coronary events and overall mortality (Scandinavian Simvastatin Survival Study Group et al., 1994; Sacks et al., 1996; Den Hartog et al., 2001; Kesteloot et al., 1997).

Serum lipid reducing agents of the HMG-CoA reductase inhibitor[16] class (statins) influence the rate-limiting enzyme in cholesterol synthesis. They rapidly lower serum total cholesterol, particularly low density lipoprotein (LDL) cholesterol (the "bad" cholesterol); they cause a small rise in serum high density lipoprotein (HDL) cholesterol (the "good" cholesterol). Five statins (lovastatin, pravastatin, simvastatin, atorvastatin and fluvastatin) are available for prescription in Manitoba. Pravastatin has been shown to be effective in both primary and secondary prevention (Den Hartog et al., 2001; Kesteloot et al., 1997; Arntz et al., 2000; Sacks et al., 1996; Shepherd et al., 1995). Lovastatin has been assessed for primary prevention (Downs et al., 1998) and simvastatin for secondary prevention (Scandinavian Simvastatin Survival Study Group et al., 1994).

*Persons at high risk of CHD or another heart attack are first priority for treat-ment with statins.*

The first priority for the prescription of lipid-lowering drug therapy is in patients with pre-existing cardiovascular disease (secondary prevention) (Den Hartog et al., 2001; Arntz et al., 2000; Sacks et al., 1996; Scandinavian Simvastatin Survival Study Group et al., 1994). However, the effectiveness

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[16] This group comprises agents which act as competitive inhibitors of 3-hydroxy-3-methyl-glutaryl coenzyme A reductase (HMG-CoA).

of drug treatment for lipid disorders in patients with no history of coronary heart disease (primary prevention) has been controversial (Downs et al., 1998; Pitt et al., 1995; Crouse et al., 1995; The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group, 1998; Byington et al., 1995; Huckell et al., 1997; Ogilvie et al., 1993; Feldman, 2000). Treatment for primary prevention is now seen to be linked to risk status, and lifestyle measures remain the priority in the primary prevention of CHD. A person is considered for lipid-lowering drug therapy for primary prevention of CHD usually following a trial of lifestyle changes of at least three months, when serum total cholesterol is $\geq$5.0 mmol/l and the 10 year risk of a major coronary event is $\geq$30%.

There is strong evidence that secondary prevention with a statin seems to be cost-effective for all risk subgroups (age, sex, smoking status, blood pressure, low-density lipoprotein and high-density lipoprotein cholesterol level) and is cost-saving in some high-risk subgroups (Prosser et al., 2000; Ganz et al., 2000). Primary prevention, however, may not be cost-effective for younger men and women with few risk factors (Prosser et al., 2000). Regardless, when interpreted as appropriateness, the cost-effectiveness of statins is compromised if individuals are not persistent to therapy especially when statins are used to prevent another cardiovascular event like a heart attack (MI).

## 4.1 Serum Lipid Reducing Agents (Statins): Appropriateness Criteria

*Measuring the appropriateness of statin use is difficult when an individual's risk strata are unknown.*

It is difficult to measure appropriateness in a class of drugs whose appropriateness is dependent on knowing an individual's risk strata. These risk strata are comprised of information on individuals not normally captured in an administrative database (smoking, cholesterol levels and weight). The appropriateness criteria for statins, therefore, focus on appropriateness rates that can be described using administrative data: (1) persistence on therapy given the decision to prescribe for secondary and primary prevention and (2) the rates of cholesterol monitoring for those at risk of a cardiovascular event.

**Table 12: Serum lipid reducing agents (statins) appropriateness criteria: #1 - #3**

| Prescribing indicator: Persistence on treatment | |
| --- | --- |
| Criterion statins #1 | Persons with a previous myocardial infarction are more likely to persist on treatment than those who use statins presumably as primary prevention. |
| Question | What is the persistence rate of statin use regardless of prevention status (secondary vs. primary)? What proportion of persons with a previous myocardial infarction (MI) persist on treatment with a statin? |
| Reasoning | Persons with pre-existing cardiovascular disease are the first priority for statin use; lifestyle measures remain the priority in the prevention of coronary heart disease. The effectiveness of statins in primary prevention is largely dependent on the underlying risk of coronary heart disease mortality and on the time on treatment. |
| Prescribing indicator: Follow-up monitoring | |
| Criterion statins #2 | The cholesterol levels of persons taking statins should be followed for the purpose of ensuring the statin is having the desired effect. |
| Question | What proportion of persons taking statins have their cholesterol monitored on a regular (once-yearly) basis? |
| Reasoning | Assuming that choice of therapy is appropriate and that dietary advice has been given and followed, total cholesterol should be reduced to < 5 mmol/l and LDL-cholesterol to < 3mmol/l. However, there should be evidence that these levels are being monitored. |

## 4.2 Application of Appropriateness Criteria: Serum Lipid Reducing Agents (Statins)

### 4.2.1 Study Period and Population
A cohort of new users of statins was identified from the 1996/97 and 1997/98 DPIN data. All persons who had a new prescription for a statin in fiscal years 1996/97 and 1997/98 were identified as new users. An individual was classified as a new user if no prescription for a statin (ATC:C10) occurred in the DPIN claims between April 1 and July 31 of fiscal years 1996/97 and 1997/98. The restrictive samples were used to allow for application of criteria over three years to March 31, 2000; however, only two fiscal cohorts of persons were used—1996/97 and 1997/98. An index date was assigned to all "first" prescriptions that occurred on or after August 1, 1996. From the statin perspective we could ascertain: (1) the persistence of all new users to statin therapy, and (2) the extent to which all new users of statins had their cholesterol monitored.

### 4.2.2 Analytic Approach
Appropriateness criteria for statins were applied once new users were identified (Figure 19). The number of individuals treated with at least one prescription for a statin, post-acute myocardial infarction, could also be determined. Application of criteria sought to answer two questions:

1. What is the persistence rate of statin use regardless of prevention status (secondary vs. primary)? What proportion of persons with a previous MI persist on treatment with a statin? (Persistence on treatment, Statin Criterion #1)

2. What proportion of persons taking statins have their cholesterol monitored on a regular (once-yearly) basis? (Follow-up Monitoring, Statin Criterion #2)

**Figure 19.  Serum Lipid Reducing Agents (statin) Analysis Approach**
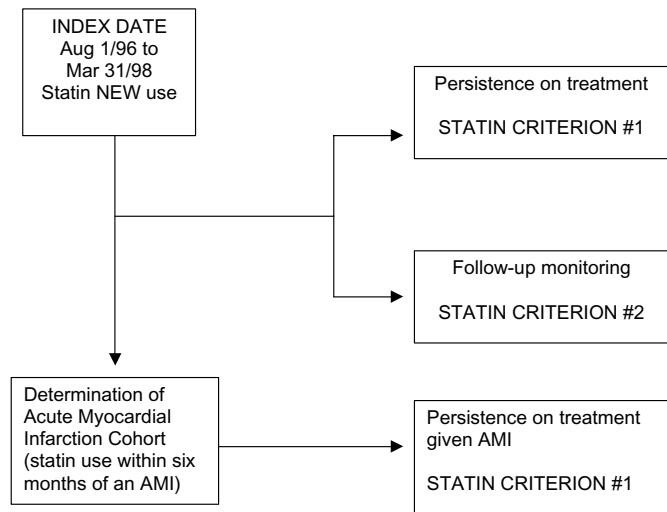


## 4.3 Results

A total of 7,273 new statin users from fiscal year 1997/98 were used to describe two appropriateness criteria for statins. Appropriateness in this class is described by two prescribing indicators: (1) persistence on therapy given the decision to prescribe for secondary and primary prevention, and (2) the rates of cholesterol monitoring for those at risk of a cardiovascular event.

### 4.3.1 Persistence on Treatment: Criterion #1

Persons with pre-existing cardiovascular disease (e.g., a previous MI) are the first priority for statin use; lifestyle measures remain the priority in the prevention of CHD. The effectiveness of statins in primary prevention is largely dependent on the underlying risk of CHD mortality and on the time on treatment. Persons with a previous MI, however, are thought more likely to persist on treatment than those who use statins, presumably as primary prevention.

The reader is reminded that indication or "reason for using a drug" is not included in the DPIN data; all indications for use are inferred either from

the drug or from associated medical or hospital claims data. In 1996/97 and 1997/98 we identified all new users of statin drugs (a first prescription between August 1 and March 31 and no prescription from the immediately preceding period of April 1 to July 31); new use was assigned an index date. Then, we identified in the six months prior to each index date, the number of new users who had a diagnosis of acute myocardial infarction (AMI). Of 7,848 new users of statins in 1996/97 (and 7,273 in 1997/98), 2.2% (2.4%) (n=170, 172) had suffered an AMI in the previous six months. Therefore, we were interested in answering the following questions:

*What is the persistence rate of statin use regardless of prevention status (secondary vs. primary)?*

*What proportion of persons with a previous myocardial infarction (MI) persist on treatment with a statin?*

Of the new users of statins in 1996/97, 9.2% or 723 persons only had one dispensation of a statin (mean duration of use 48 days, standard deviation of 31). Use was examined until March 31, 2000 and 38.1% (n=2,989 persons) of new users were persistent to treatment (Figure 20). For this analysis, "persistence" was defined as those individuals on treatment with less than a 31-day break in the quantity of drug available.

**Figure 20: Persistence to Statin Therapy, 1996/97**
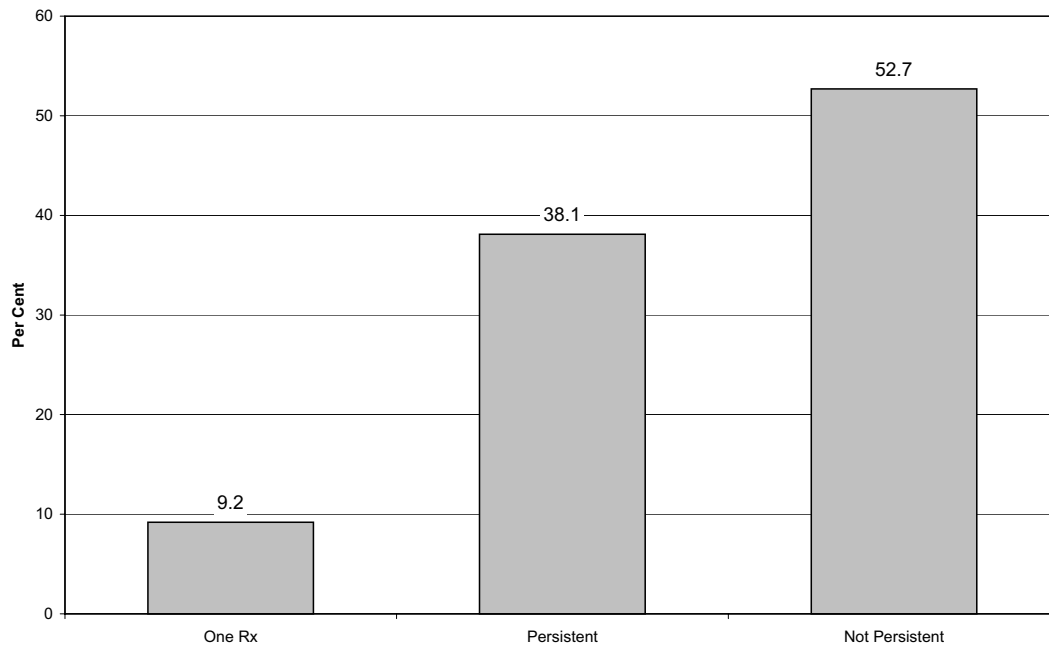
The 85 individuals who had an AMI in 1997/98 (February 1 to July 31) and were subsequently prescribed a statin were variably persistent to their prescription for statins: 5.9% had but one dispensation following their AMI, 42.3% stopped their therapy prematurely and 51.8% of individuals were persistent with statin treatment until the analysis ended in March 2000 (Figure 21).

**Figure 21: Persistence to Statin Therapy Given Previous Diagnosis for AMI, 1996/97**
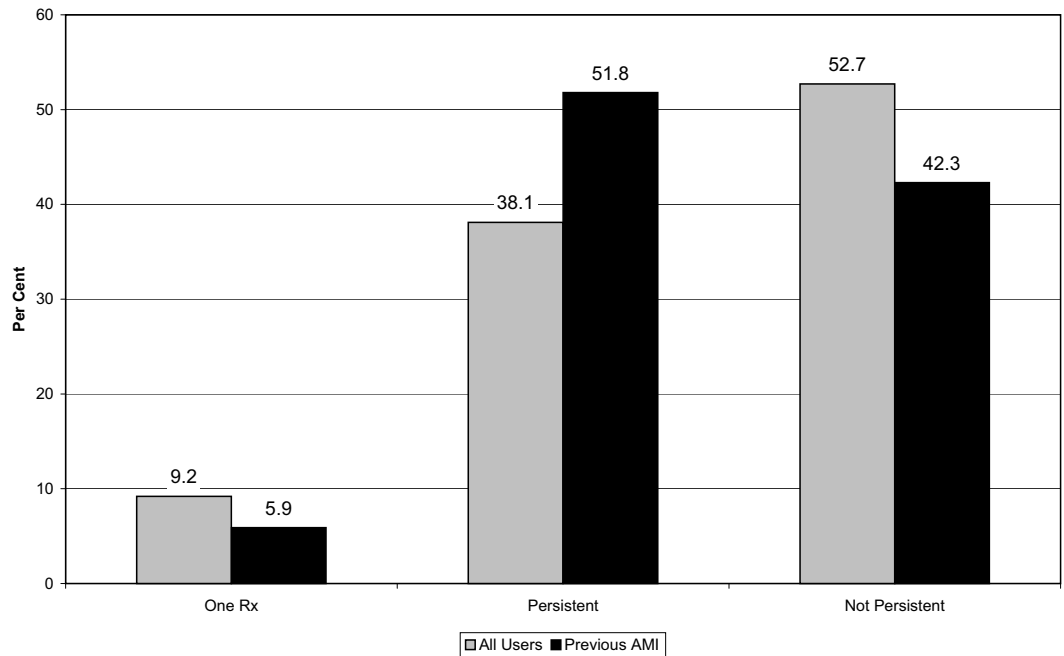


## 4.3.2 Follow-up Cholesterol Monitoring Levels: Criterion #2

Assuming that choice of therapy is appropriate and that dietary advice has been given and followed, total cholesterol should be reduced to < 5 mmol/l and LDL-cholesterol to < 3mmol/l. However, there should be evidence that these levels are being monitored for the purpose of ensuring the statin is having the desired effect. The question we were interested in answering was:

*What proportion of persons taking statins have their cholesterol monitored on a regular (once-yearly) basis?*

Using a Winnipeg-specific cohort (n=4,927) derived from the 1997/98 new statin users (n=7,273), 44.3% (n=2,184) had their cholesterol levels tested in the three years post-first prescription.

## 4.4 Summary of Observations: Serum Lipid Reducing Agents

● Serum lipid reducing agents accounted for 2.8% of total prescriptions and 7.8% of total expenditures in 1999/2000.

● The number of users of statins has increased by 60% between 1996/97 and 1999/2000 (25,824 to 41,344). Despite increases in utilization across all age groups, the proportion of those prescribed statins decreases significantly after the age of 80.

● 2.4% of new users of statins in 1997/1998 had an AMI in the six months preceding their first statin dose.

● Of the new users of statins in 1996/97, 9.9% had one dispensation of a statin only; 41% of new statin users appear to have been persistent to treatment.

● If one examines persistence to treatment in those with a previous AMI, 5.9% had one dispensation of a statin only and 52% persisted on treatment.

● The appropriate rate of follow-up testing is at least once per year. In Winnipeg, 45% of persistent statin users had their cholesterol levels monitored once a year.

## 4.5 Discussion

● In 1999/2000, 3.6% of the population had been prescribed and dispensed a statin.

Although there are no Manitoban or Canadian population-based figures on which to estimate prevalence of CHD risk, estimates from England and Scotland have determined that between 4.8% and 7.8% of the population requires secondary preventive treatment against another CHD event like heart attack. Estimates of a population-based rate for primary preventive treatment against any CHD event are based on a 30% or greater CHD risk over 10 years; these estimates range from 1.5% to 3.4% of the population.

On first glance, then, it appears that Manitobans may be underutilizing serum lipid reducing agents, at least for secondary prevention purposes. Abookire et al. (2001) found that among persons taking statins in the catchment area of a Boston hospital, 69% were being treated for primary prevention and 31% for secondary prevention or established CHD. When this use was examined according to prescribing guidelines for statins (using measures of LDL cholesterol level and risk factors), Abookire et al. reports that of those on statins with CHD, 47% (n=544) of use was overuse (i.e., LDL > 4.14 mmol/L) and 88% of those not taking statins with CHD were deemed to be underusing statins (n=1,459). In persons without CHD 69% of the 1,080 persons taking statins did not need them according to the guideline parameters and their use was deemed to be inappropriate (overuse). We were

unable to apply these same appropriateness criteria to our data as we are missing clinical and risk factor variables.

● Of the new statin users identified in 1997/1998, 2.4% of them had an AMI in the six months preceding their first statin dose (candidates for secondary prevention treatment).

This rate is similar to the one reflected in a 1998 survey of a nationally representative sample of 13,586 adults in English households (Primatesta and Poulter, 2000).

● Of the new users of statins in 1996/97 (n=7,848), 9.9% had one dispensation of a statin only (non-persistence to therapy); 41% of these new statin users appear to have been persistent to treatment after upwards of four years of treatment.

This is in contrast to the analysis reported by Catalan and LeLorier (2000) who examined persistence in new users of statins in Quebec who were social assistance recipients. Persistence at one year was found by them to be only 33%. The flip side of persistence is discontinuation. Tsuyuki and Bungard (2001) found in their meta-analysis of discontinuation rates calculated from pharmacy dispensing databases for lipid-lowering drugs that single prescription discontinuations were about 25% (versus our 10%) and that about 45% of individuals discontinued statins after one year. This rate is consistent with our findings.

● If one examines persistence to treatment in those with a previous AMI, 5.9% had one dispensation of a statin only and 52% persisted on treatment.

This is consistent with Catalan and LeLorier's (2000) findings that persistence on statin therapy was 39% better when new statin users were presumed to have pre-existing cardiovascular disease-related diagnoses or medications. It makes sense that those with asymptomatic chronic diseases, such as hyperlipidemia, likely do not experience any relief from taking these drugs but may experience real or perceived side effects—in other words, these drugs are to prevent an event which is intangible until it is experienced. (Individuals who have had a heart attack or myocardial infarction are likely to be more adherent and to continue treatment as, according to the claims data, they have already experienced an "event".)

● The appropriate rate of follow-up testing is at least once per year. In Winnipeg, 45% of persistent statin users had their cholesterol levels monitored once a year.

In a large study (n=48,586) on CHD, Sueta et al. (1999) observed a chart-documented LDL cholesterol for only 44% of patients. Abookire et al. (2001) found that cholesterol levels were monitored, on average, 2.8 times during the year. Although we recognize that there is some underreporting of cholesterol laboratory values in Manitoba Health's Winnipeg data because of hospital-based testing for patients of physicians working in hospitals it is not thought to offer an explanation for the difference between the rates of follow-up monitoring observed and those expected. It may be that physicians feel constrained about ordering laboratory tests. However, evidence-based practice guidelines specify that once LDL cholesterol levels are reaching their target that cholesterol (total, LDL and HDL) levels should be monitored regularly at 4 to 6 month intervals (Expert Panel on Detection, 2001; Fodor et al., 2000).

We were restricted in being able to apply the most commonly accepted appropriateness criteria to Manitobans' use of statins. Appropriate treatment with statins for primary and secondary prevention of a CHD event is usually based on an estimate of risk (30%) for a future evident in the next 10 years. The estimate of risk is based on data not commonly present in the Manitoba Health datasets, for example, an individual's smoking habit, total cholesterol/HDL ratio and their systolic blood pressure.

As a consequence, we examined other appropriateness criteria: (1) persistence on therapy once a statin has been initiated, and (2) rate of cholesterol monitoring post-statin treatment decision. The rate of prescription initiation with a statin post-AMI is 2.4%. Persistence to a new prescription for a statin is between 40% and 50% after one year. More persons persist on therapy if they have had a previous MI. Monitoring occurs regularly in less than 50% of those who are new users of statins.

## 4.6 Conclusions and Recommendation

The use of population-based data on statin prescription utilization gives us a limited picture of the appropriate use of this drug class. Part of determining appropriateness for statins is in determining its reason for use—as a secondary preventive treatment against another cardiovascular event like a heart attack or as primary prevention treatment against a "first" heart attack. There is unequivocal evidence for statin use as a secondary prevention agent; the same is not true for primary prevention. Regardless, it seems that there is likely underuse of statins in secondary prevention.

The suboptimal persistence we found, irrespective of primary or secondary prevention indications, constitutes a serious challenge to the effectiveness of statins as an effective therapy. In other words, if individuals are discontinu

ing statin therapy before its effect can be observed (e.g., decrease in premature mortality due to heart attack), then we are wasting scarce resources.

Measuring cholesterol levels on a regular basis appears to have some effect on persistence to statin treatment. More of those persisting on statin treatment were monitored for cholesterol levels than were those who had one dispensation or discontinued use.

In summary, there appears to be underutilization of statin therapy for secondary prevention of CHD. However, despite the rate of initial prescription for statins, the persistence on treatment is less than 50% after one year—making statin use in Manitoba a potentially cost-ineffective intervention.

### Recommendation
● The means to improve persistence after treatment is initiated should be found, tested and implemented.

To assist in the development of "means" to improve persistence on statins, several additional analyzes should be undertaken:

1. Stratifying the application of the statin appropriateness criteria by different statins (one of the statins has been removed from the market (cerivastatin) and another is about to be released onto the market (rosuvastatin) that lowers LDL cholesterol by 58% and raises HDL cholesterol by 13%); and, by a comorbidity index (as a means of possibly identifying those at risk for a recurrent MI or cardiac event)—the objective is to obtain more refined cohorts for examination of appropriate use.
2. Although we measured the rate of follow-up monitoring, the statins lend themselves to examining another appropriateness criteria—that is, follow-up monitoring for the adverse effect(s) that statins have on some users' liver function.
3. Examining the differences in appropriateness rates between specialists and family physicians (FPs) and between high, moderate and low FP prescribers of statins.
4. First, qualitatively and then quantitatively examining the motivations of physicians and patients when prescribing (or not prescribing) statins according to evidence-based risk strata.

# 5.0 APPROPRIATE USE:
## TREATMENT OF POST-ACUTE MYOCARDIAL INFARCTION

*Many persons may not be receiving optimal treatment to prevent a second heart attack.*

In 1998/99 cardiovascular drugs accounted for 32.7% of total drug expenditures in Manitoba. One of the key treatment principles in the use of these drugs is the secondary prevention of MI. In other words, survivors of a MI are at greatly increased risk of reinfarction or death. Evidence of the effectiveness of strategies to prevent such events, called secondary prevention, is convincing (Ryan et al., 1999; Antiplatelet Trialists' Collaboration, 1994; Held and Yusuf, 1993; ACE Inhibitor Myocardial Infarction Collaborative Group, 1998; Smith, 1990). Despite this, many patients may not be receiving optimal preventative treatment (Campbell et al., 1999).

Under this appropriateness topic we are considering secondary prevention of (i.e., the occurrence of another) AMI. Secondary prevention involves the reduction of preventable risk factors for future events related to atherosclerotic disease. Preventable risk factors include hypercholesterolemia, cigarette smoking, diabetes, obesity and physical inactivity. A number of pharmacological and non-pharmacological therapies have been shown to enhance survival and reduce cardiac morbidity.

The management of high cholesterol, for example, includes using drugs (statins, cholestyramine, colestipol, fibrates), exercise and an appropriate diet to lower cholesterol. The long term use of aspirin, agents acting on the renin-angiotensin system and beta-blockers, and warfarin should be considered for all post-AMI patients as they have been shown to reduce reinfarction and mortality. Although not considered below, nicotine gum and patches are available to mitigate symptoms of nicotine withdrawal; these agents are now available without a prescription. An oral prescription-only drug agent (bupropion) is also being used for smoking cessation.

## 5.1 Treatment of Post-Acute Myocardial Infarction: Appropriateness Criteria

Given a sentinel event like a heart attack (AMI) it is not difficult in Manitoba Health's datasets to measure initiation of outpatient treatment with drugs. However, we do not know what is the "right" prescription treatment rates post-AMI; as well, treatment with several of the recommended drugs post-AMI have contraindications for use. Establishing population-based treatment baseline rates though is an important goal for working towards optimal appropriateness for the secondary prevention of AMI.

**Table 13: Treatment of post-acute myocardial infarction appropriateness criterion (#1)**

| Prescribing indicator: Therapy initiation | |
| --- | --- |
| Criterion MI #1 | Persons with an evidence-based and accepted indication for use (i.e., secondary prevention for acute myocardial infarction and death) are more likely to be prescribed a statin, an agent which acts on the renin-angiotensin system (ACEI or A2RA) or a beta-blocking agent. |
| Question | What is the proportion of persons prescribed an indicated cardiovascular drug like a statin, an ACEI or A2RA or a beta-blocking agent following an acute myocardial infarction? |
| Reasoning | Many persons do not receive optimal secondary prevention after myocardial infarction despite good evidence.  At the minimum most patients (about 90%) should be taking aspirin and a beta-blocker as prevention for a secondary AMI. |

## 5.2 Treatment of Post-Acute Myocardial Infarction: Application of Appropriateness Criteria

### 5.2.1 Study Period and Population

A cohort of Manitobans with a marker for a new AMI between April 1, 1996 and March 31, 1998 was identified from hospital discharge data. All persons who had a diagnosis of ICD-9 410.0 were identified as the cohort of AMI persons. These persons were assigned to an adjusted clinical group for the purpose of examining rate of prescription use by level of comorbidity. From the perspective of diagnosis of AMI we could ascertain the rate of therapy initiation post-AMI.

### 5.2.2 Analytic Approach

The proportion of individuals prescribed several types of pharmacological agents post-AMI was identified. Rates of prescription use are reported using all persons having an AMI as the denominator.

### 5.2.3 Criteria Application

To analyze and report on the Treatment of Acute Myocardial Infarction appropriateness criterion #1 we identified the number of persons with an AMI in fiscal years April 1 to March 31, 1996 and 1997. Prescribing frequencies of beta-blockers, agents acting on the renin-angiotensin system and statins are reported. Prescribing frequencies by adjusted clinical group (ACG) membership are also reported.

## 5.3 Results

Many persons do not receive optimal secondary prevention treatment after MI despite good evidence. At the minimum, most patients (about 90%) should be taking aspirin and a beta-blocker as prevention for a secondary AMI. The focus for our research question was that persons with an evidence-based and accepted indication for use (i.e., secondary prevention for AMI and death) are more likely to be prescribed a beta-blocking agent, a statin or an agent which acts on the renin-angiotensin system (an ACEI or A2RA).

*What is the proportion of persons prescribed an indicated cardiovascular drug like a statin, an agent acting on the renin-angiotensin system (ACEIs or A2RAs), or a beta-blocking agent following an acute myocardial infarction?*

By first identifying all AMIs in a six month period (February 1 to July 31) for two fiscal years and then counting new users of cardiovascular drugs, the rate of cardiovascular drug use post-AMI is that reported in Table 14. We identified 1,971 AMIs in 1996/97, 1,897 AMIs in 1997/98 and 1,853 AMIs in 1998/99.

**Table 14: A description of cardiovascular drugs used post-myocardial infarction, 1996/97-1999/2000**

|  | 1996/97 N (%) | 1997/98 N (%) | 1999/2000 N (%) |
|---|---|---|---|
| No cardiovascular drugs prescribed | 333 (16.9%) | 341 (18.0%) | 308 (16.6%) |
| Beta (β)-blockers | 380 (19.3) | 327 (17.2) | 302 (16.3) |
| Agents acting on the renin-angiotensin system | 283 (14.4) | 210 (11.1) | 193 (10.4) |
| Serum lipid reducing agents | 61 (3.1) | 39 (2.1) | 49 (2.6) |
| Two or three of a β-blocker, ACEI or Statin | 751 (38.1) | 858 (45.2) | 912 (49.2) |
| One other cardiovascular drug | 56 (2.8) | 50 (2.6) | 40 (2.2) |
| Two or more of other CV drugs | 107 (5.4) | 72 (3.8) | 49 (2.6) |

## 5.4 Summary of Observations: Treatment of Post-Acute Myocardial Infarction

● No outpatient cardiovascular drugs appear to be prescribed to about 17% of persons post-AMI.

● In 1999/2000, 49.2% of post-AMI persons were prescribed a combination of beta blockers, agents acting on the renin-angiotensin system and/or statins; beta-blockers were the most common single pharmaceutical intervention post-AMI (17% in 1997/98) although the use of this intervention has fallen (19.3% in 1996/97 to 16.3% in 1999/2000).

## 5.5 Discussion

• No outpatient cardiovascular drugs appear to be prescribed to about 17% of persons following an AMI. In 1999/2000, 49.2% of post-AMI persons were prescribed two or three of a beta blocker, agents acting on the renin-angiotensin system or statins; beta-blockers were the most common single pharmaceutical intervention post-AMI (17% in 1997/98) although the use of this intervention has fallen (19.3% in 1996/97 to 16.3% in 1999/2000).

There are several limitations to these numbers that makes comparing them to other study results difficult. First, we have no idea what proportion of those treated post-AMI are being treated subsequent to an initial or recurrent event. Rates of therapy are much higher in those experiencing a recurrent event (Wei et al., 2002). Also, according to the most recent American Heart Association (AHA)/American College of Cardiology (ACC) (2001) guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease, most persons at risk for another heart attack are on multiple medications (Ryan et al., 1999). Yet, the most recent reports of proportion of heart attack survivors treated with different classes of cardiovascular drugs give no indication of the rate of multiple use of therapeutic interventions. Furthermore, we are unable to completely report the use of low-dose aspirin in this cohort of post-AMI survivors.

More study about prescribing post-MI is required to make any summary statements about the use of cardiovascular medications following a heart attack.

## 5.6 Conclusions and Recommendation

Prevention of a recurrent event such as a heart attack is highly desirable. Evidence has shown us in the last five years how important several pharmacotherapeutic agents are to preventing a recurring cardiac event. The criterion for this subject was simple—to understand what proportion of people are treated with cardiac therapy for prevention of another MI. We found that 17% of persons having a heart attack were not prescribed at least one prescription drug. Thus, there is evidence of underutilization of all drugs in persons previously experiencing an MI.

### *Recommendation*

• Policies to encourage appropriate therapy initiation post-acute myocardial infarction should be tested and implemented.

# 6.0 CONCLUSIONS AND RECOMMENDATIONS

The focus of this report has been on developing the methods needed to examine the appropriate use of pharmaceuticals and the application of these methods to pharmaceutical utilization data in Manitoba. Non-optimal or inappropriate use of prescription drugs is thought to be responsible, in part, for the increase in pharmacotherapy spending that has increased at least 8.6% since 2000 (Canadian Institute for Health Information, 2002b). Specifically, the chief drivers for the increased spending on prescription drugs are the change from older to newer treatments and increases in the use of existing treatments (Goyer and Kennedy, 2002). Increases in spending have focused several national policy initiatives in health care on the improvement in the use of pharmaceuticals (Expert Panel on Detection, 2001).

Although we are primarily interested in the effectiveness or outcomes of the use of pharmaceuticals, indicators of both their utilization and appropriateness are useful before one considers their effectiveness, and particularly the "cost-effectiveness" of prescription drugs. The real value of studying outcomes, according to Donabedian, lies in understanding the relationship of effectiveness to structure (drug utilization) and process (prescribing appropriateness) (Fodor et al., 2000). Drug utilization indicators such as the population's rate of access to prescription drugs, the intensity of use of drugs by various population strata like age and sex, and costs of prescription drugs are used to inform us of the background against which appropriateness and effectiveness can be examined. Appropriateness is the extent to which pharmacotherapy is necessary and the right choice, as defined by standards of care based on evidence. Only when one has drawn the background of drug use and determined whether the right choice was made for the right person for the right indication and at the right dose and time can one reasonably infer the effectiveness or outcomes of pharmacotherapy.

Four fiscal years of prescription drug data (1996/97-1999/2000) have been aggregated to describe, using previously developed population-based pharmaceutical indicators, Manitoban's use of pharmacotherapy. The rates of use found are consistent with those in other Canadian jurisdictions and with previous other Manitoba studies.

The main focus of this deliverable, however, is on the appropriate use of pharmaceuticals. With many Canadian health policy-makers calling for better control of the quality of pharmacotherapy (Commission on the Future of Health Care in Canada, 2002), the Manitoba Centre for Health Policy has tried in this report, to test the ability of Manitoba Health's databases to inform on the appropriate use of pharmaceuticals.

Indicators of appropriateness used in this study include prescribing criteria around rates of step-up prescribing, therapy initiation post a medical event (e.g., acute myocardial infarction), persistence to chronic treatment and follow-up monitoring for those on chronic medications. The step-up approach to prescribing follows the principle of using the minimum pharmacological therapy necessary to achieve a stated therapeutic objective. An important caveat to applying appropriateness indicators to the data available from Manitoba Health's administrative databases is that many evidence-based indicators of appropriateness require the kinds of information not available through health care administrative data (e.g., diagnoses, risk factors like smoking, weight, etc.)

## 6.1 Key Findings and Recommendations

### 6.1.1 Drug Utilization Study

- Over eight million prescriptions were dispensed to Manitobans from community-based pharmacy settings and other outpatient locations in 1999/2000. Total expenditures (by both public and private payers (insurers and/or out-of-pocket)) were $285,982,702.
- Two-thirds of Manitobans (67.3%) have at least one prescription dispensed per year; this proportion increases to 87% (1999/2000) if one examines only older Manitobans (65 years of age and older).
- Older Manitoba residents (65 years of age and older) are dispensed, on average, over 21 prescriptions per year and take over five different kinds of medication; this is in contrast to younger Manitoba residents who have over five prescriptions dispensed on average per year representing about three different kinds of medication.
- Older Manitoba residents expend four times more dollars per person per year for pharmaceuticals than younger residents (those less than 65 years of age) of Manitoba ($708 versus $177). Yet, when one considers expenditures per defined daily dose, the younger Manitoba residents cost about 30% more ($1.81/DDD versus $1.39/DDD).

### *Recommendation*

Assist the Canadian Institute for Health Information and other national agencies like the Patented Medicine Prices Review Board in encouraging other jurisdictions to develop their data sources for national comparative reporting using a set of common drug utilization indicators.

In a recent report synthesizing the findings of pharmaceutical projects sponsored by the Health Transition Fund, a joint effort between federal, provincial, and territorial governments, there is a call for joint policies and regulations by those responsible for pharmacotherapy policy (Expert Panel on Detection, 2001). Having more complete and consistent information on

actual pharmaceutical usage will help jurisdictions negotiate more effectively with industry to share the risk of program cost increases. Manitoba can be a leader in this initiative.

### 6.1.2 Appropriateness Study

### Agents Acting on the Renin-Angiotensin System and Hypertension

• The cost per prescription for these agents increased 59.7% between 1996/1997 and 1999/2000 ($12.73 to $20.33, respectively). This increase parallels the introduction of a new class of agent—the A2RAs.

• ACEIs are used twice as often in those with hypertension and a comorbid condition like diabetes or congestive heart failure (10% to 11%) than in those with uncomplicated hypertension (5%).

• The per cent of persons with new prescriptions for A2RAs as first-line agents in newly diagnosed hypertension increased four-fold (0.5% to 2.4%) from 1996/97 to 1999/2000.

• Sixty-four per cent (64%) of all new users of A2RAs in 1999/2000 did not have a previous trial with an ACEI.

### Recommendations

Policies encouraging a step-up approach to prescribing should be tested and implemented.

Several appropriate-use projects are currently underway in Manitoba. Lessons learned from these projects could help to design a "toolbox" of workable interventions for more cost-effective therapeutic choices.

### Serum Lipid Reducing Agents (the statins)

• The number of users of statins has increased by 60% between 1996/97 and 1999/2000 (25,824 to 41,344). Despite increases in utilization across all age groups, the proportion of those prescribed statins decreases significantly after the age of 80.

• Of the new users of statins in 1996/97, 9.9% had one dispensation of a statin only; 41% of new statin users appear to have been persistent to treatment.

• If one examines persistence to treatment in those with a previous AMI (an indication for a statin), 5.9% had only one dispensation of a statin and 52% persisted on treatment with a statin after one year.

• The appropriate rate of follow-up testing is at least once per year. In Winnipeg, 45% of persistent statin users had their cholesterol levels monitored once a year.

### Recommendation
The means to improve persistence after treatment is initiated should be found, tested and implemented.

### Treatment Post-Acute Myocardial Infarction
● In 1999/2000, 49.2% of post-AMI persons were prescribed a combination of a beta-blocker, an ACEIs and/or a statin; beta-blockers were the most common single pharmaceutical intervention, post-AMI (17% in 1997/98) although the use of this intervention has fallen (19.3% in 1996/97 to 16.3% in 1999/2000).

● No outpatient cardiovascular drugs appear to be prescribed to about 17% of persons post- AMI.

### Recommendation
Policies to encourage appropriate therapy initiation post-acute myocardial infarction should be tested and implemented.

## 6.2 Conclusions
It is clear from this analysis that the majority of the appropriateness criteria applied were judged to be "potentially" inappropriate (one out of seven, 14%). In some cases appropriateness was judged to be "potentially inappropriate OVERUSE" (e.g., rate of treatment with an A2RA before a trial of an ACEI) and in other cases, appropriateness was judged to be "potentially inappropriate UNDERUSE" (e.g., persistence to statin treatment following a heart attack). The effect of these findings on Manitoba residents, government, physicians and pharmacists is, as yet, to be determined.

The 2002 Health Transition Fund report synthesizing the findings of pharmaceutical projects, reports that "…patients' understanding of the nature of their disease and pharmacotherapy seem to show disparities between the perceptions of patients and professionals…" (Expert Panel on Detection, 2001). When given appropriate information, however, patients adapt to changes in their therapy or are motivated to control better their disease status. For example, although not reported in this deliverable, but examined by MCHP, the observed "overprescribing" of proton pump inhibitors for long-term symptomatic use of non-ulcerative dyspepsia found these disparities and patients have been willing to increase their autonomy and were "…often keen to reduce their medicine taking to a minimum." (Pollock and Grime, 2000).

Provincial drug programs, therefore, have an opportunity to take the lead in breaking down the barriers between the disjointed sectors involved in manufacturing, selling, prescribing, dispensing, using, controlling and paying for

prescription drugs (Goyer and Kennedy, 2002), so that appropriate and effective use of this most ubiquitous intervention, prescription drugs, is cost-effective. For example, a push to having everyone accept the principle of step-up care would go a long way to ensuring that Manitoba's pharmaceutical budget is spent wisely. Patients have a role in not only understanding the "step-up" versus the "step-down" approach to prescribing but also in knowing that many non-pharmacological treatments assist pharmaceuticals to be more effective. We need to understand why physicians make the choices they do when there is often good evidence to the contrary. Also, someone is going to have to assume the role of following up with patients to ensure that the pharmaceutical is doing what it is supposed to do. Is it time for changing structures so that how pharmacists interface with community-based physicians (a pharmacist co-located with a physician) serves the patient better?

### *Recommendation*
Every effort should be made by the provincial government to interconnect the physician community with patients, pharmacists, and academia in order to: (1) provide credible information on all aspects of pharmacotherapy, (2) establish the best ways to optimize the prescribing, dispensing and using of pharmacotherapies, and (3) minimize inappropriateness in the use of prescription drugs while maximizing their effectiveness.

## 6.3 Future Directions
Future efforts will focus on completing MCHP's Concept Dictionary for definitions of drug utilization indicators and appropriateness criteria with those developed so far. Our objective is to make the undertaking of this kind of analysis more efficient and effective.

Study of both the appropriateness and effectiveness (outcomes) of pharmacotherapy would be enhanced by merging clinical and/or survey-based data with the large administrative datasets. The goal of improving processes of care (appropriateness) and patient outcomes (effectiveness) would be supported with more complete information on why pharmaceuticals are prescribed in the first place. Perhaps linked to this future direction is the need that has been identified to change the way prescribing, dispensing and utilization are practised—that is, better access to "why" the drug is being prescribed in the first place.

# REFERENCES

Abookire SA, Karson AS, Fiskio J, Bates DW. Use and monitoring of "statin" lipid-lowering drugs compared with guidelines. *Arch Intern Med* 2001;161(1):53-58.

ACE Inhibitor Myocardial Infarction Collaborative Group. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. ACE Inhibitor Myocardial Infarction Collaborative Group. *Circulation* 1998;97(22):2202-2212.

Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy—I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. *BMJ* 1994;308(6921):81-106.

Arntz HR, Agrawal R, Wunderlich W, Schnitzer L, Stern R, Fischer F, Schultheiss HP. Beneficial effects of pravastatin (+/-colestyramine/niacin) initiated immediately after a coronary event (the randomized Lipid-Coronary Artery Disease [L-CAD] Study). *Am J Cardiol* 2000;86(12):1293-1298.

Beck CA, Lauzon C, Eisenberg MJ, Huynh T, Dion D, Roux R et al. Discharge prescriptions following admission for acute myocardial infarction at tertiary care and community hospitals in Quebec. *Can J Cardiol* 2001;17(1):33-40.

Black C, Roos N, Fransoo R, Martens P. *Comparative Indicators of Population Health and Health Care Use for Manitoba's Regional Health Authorities: A POPULIS Project.* Winnipeg MB: Manitoba Centre for Health Policy and Evaluation, 1999.

Byington RP, Jukema JW, Salonen JT, Pitt B, Bruschke AV, Hoen H, Furberg CD, Mancini GB. Reduction in cardiovascular events during pravastatin therapy. Pooled analysis of clinical events of the Pravastatin Atherosclerosis Intervention Program. *Circulation* 1995;92(9):2419-2425.

Campbell NR, Burgess E, Choi BC, Taylor G, Wilson E, Cleroux J, Fodor JG, Leiter LA, Spence D. Lifestyle modifications to prevent and control hypertension. 1. Methods and an overview of the Canadian recommendations. Canadian Hypertension Society, Canadian Coalition for High Blood Pressure Prevention and Control, Laboratory Centre for Disease Control at Health Canada, Heart and Stroke Foundation of Canada. *CMAJ* 1999;160(9 Suppl):S1-S6.

Canadian Institute for Health Information. *Development of Drug Utilization Indicators: A Feasibility Study Using Existing Aggregated Administrative Databases.* Ottawa ON: Canadian Institute for Health Information, 2002a.

Canadian Institute for Health Information. *National Health Expenditure Trends, 2002.* Ottawa ON, CIHI, 2002b.

Caro JJ, Speckman JL, Salas M, Raggio G, Jackson JD. Effect of initial drug choice on persistence with antihypertensive therapy: the importance of actual practice data. *CMAJ* 1999;160(1):41-46.

Catalan VS, LeLorier J. Predictors of long-term persistence on statins in a subsidized clinical population. *Value in Health* 2000;3(6):417-426.

Chalmers J, Chapman N. Challenges for the prevention of primary and secondary stroke: the importance of lowering blood pressure and total cardiovascular risk. *Blood Press* 2001;10(5-6):344-351.

Chomiak D. *Annual Report of Manitoba Health and the Annual Report of the Manitoba Health Services Insurance Plan, 2000/2001.* Winnipeg MB: Government of Manitoba, 2002b.

Commission on the Future of Health Care in Canada. *Building on Values: The Future of Health Care in Canada—Final Report.* Ottawa ON: Government of Canada, 2002.

Crouse JR, III, Byington RP, Bond MG, Espeland MA, Craven TE, Sprinkle JW, McGovern ME, Furberg CD. Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II). *Am J Cardiol* 1995;75(7):455-459.

Degli EE, Sturani A, Di Martino M, Falasca P, Novi MV, Baio G, Buda S, Volpe M. Long-term persistence with antihypertensive drugs in new patients. *J Hum Hypertens* 2002;16(6):439-444.

Den Hartog FR, Van Kalmthout PM, Van Loenhout TT, Schaafsma HJ, Rila H, Verheugt FW. Pravastatin in acute ischaemic syndromes: results of a randomised placebo-controlled trial. *Int J Clin Pract* 2001;55(5):300-304.

Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA Langendorfer A, Stein EA, Kruyer W, Gotto AM, Jr. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998;279(20):1615-1622.

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(19):2486-2497.

Federal/Provincial/Territorial Working Group on Drug Prices. *Cost driver analysis of provincial drug plans: Manitoba (1995/96 to 1998/99)*. (http://www.hc-sc.gc.ca/english/fpt2001/reports.html#3). Ottawa ON: PMPRB, April 2000.

Feldman RD, Campbell N, Larochelle P. First-line antihypertensive therapy. Task Force for the Development of the 1999 Canadian Recommendations for the Management of Hypertension. *Lancet* 2000;356(9228):509.

Fodor JG, Frohlich JJ, Genest JJ, Jr., McPherson PR. Recommendations for the management and treatment of dyslipidemia. Report of the Working Group on Hypercholesterolemia and Other Dyslipidemias. *CMAJ* 2000;162(10):1441-1447.

Ganz DA, Kuntz KM, Jacobson GA, Avorn J. Cost-effectiveness of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor therapy in older patients with myocardial infarction. *Ann Intern Med* 2000;132(10):780-787.

Garg J, Messerli AW, Bakris GL. Evaluation and treatment of patients with systemic hypertension. *Circulation* 2002;105(21):2458-2461.

Goyer R , Kennedy W. *Pharmaceutical Issues: A synthesis of Health Transition Fund Reports*. Ottawa ON: Health Canada, 2002.

Hasford J, Mimran A, Simons WR. A population-based European cohort study of persistence in newly diagnosed hypertensive patients. *J Hum Hypertens* 2002;16(8):569-575.

Held PH , Yusuf S. Effects of beta-blockers and calcium channel blockers in acute myocardial infarction. *Eur Heart J* 1993;14 Suppl F:18-25.

Huckell VF, Bernstein V, Cairns JA, Crowell R, Dagenais GR, Higginson LA et al. Angiotensin-converting enzyme inhibition in myocardial infarction--Part 1: Clinical data. *Can J Cardiol* 1997;13(2):161-169.

Kesteloot H, Claeys G, Blanckaert N, Lesaffre E. Time course of serum lipids and apolipoproteins after acute myocardial infarction: modification by pravastatin. *Acta Cardiol* 1997;52(2):107-116.

Laplante P, Niyonsenga T, Delisle E, Vanasse N, Vanasse A, Grant AM, Xhignesse M. Treatment patterns of hypertension in 1996. Data from the Quebec Family Practice, University of Sherbrooke registry. *Can Fam Physician* 1998;44:306-312.

Maclure M, Dormuth C, Naumann T, McCormack J, Rangno R, Whiteside C, Wright JM. Influences of educational interventions and adverse news about calcium-channel blockers on first-line prescribing of antihypertensive drugs to elderly people in British Columbia. *Lancet* 1998;352(9132):943-948.

Majumdar SR, Gurwitz JH, Soumerai SB. Undertreatment of hyperlipidemia in the secondary prevention of coronary artery disease. *J Gen Intern Med* 1999;14(12):711-717.

Manolio TA, Cutler JA, Furberg CD, Psaty BM, Whelton PK, Applegate WB. Trends in pharmacologic management of hypertension in the United States. *Arch Intern Med* 1995;155(8):829-837.

Marentette MA, Gerth WC, Billings DK, Zarnke KB. Antihypertensive persistence and drug class. *Can J Cardiol* 2002;18(6):649-656.

Martineau P , Goulet J. New competition in the realm of renin-angiotensin axis inhibition; the angiotensin II receptor antagonists in congestive heart failure. *Ann Pharmacother* 2001;35(1):71-84.

McAlister FA, Campbell NR, Zarnke K, Levine M, Graham ID. The management of hypertension in Canada: a review of current guidelines, their shortcomings and implications for the future. *CMAJ* 2001;164(4):517-522.

Metge CJ, Black C, Peterson S, Kozyrskyj AL, Roos N, Bogdanovic B. *Analysis of Patterns of Pharmaceutical Use in Manitoba, 1996: Key Findings.* Winnipeg MB: Manitoba Centre for Health Policy and Evaluation, 1999a.

Metge CJ, Black C, Peterson S, Kozyrskyj AL. The Population's Use of Pharmaceuticals. *Med Care* 1999b;37: JS42-JS59.

Miller M, Byington R, Hunninghake D, Pitt B, Furberg CD. Sex bias and underutilization of lipid-lowering therapy in patients with coronary artery disease at academic medical centers in the United States and Canada. Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT) Investigators. *Arch Intern Med* 2000;160(3):343-347.

Ogilvie RI, Burgess ED, Cusson JR, Feldman RD, Leiter LA, Myers MG. Report of the Canadian Hypertension Society Consensus Conference: 3.

Pharmacologic treatment of essential hypertension. *CMAJ* 1993;149(5):575-584.

Patented Medicine Prices Review Board (PMPRB). *Cost Driver Analysis of Provincial Drug Plans: British Columbia, 1990/91 - 1998/99.* Presented to Federal/Provincial/Territorial Working Group on Drug Prices. Ottawa ON, PMPRB, 2000.

Patented Medicine Prices Review Board. *PMPRB Report to the Minister of Health (Manitoba): 1995/96 - 1999/2000.* Ottawa ON, PMPRB, 2001.

Pitt B, Mancini GB, Ellis SG, Rosman HS, Park JS, McGovern ME. Pravastatin limitation of atherosclerosis in the coronary arteries (PLAC I): reduction in atherosclerosis progression and clinical events. PLAC I investigation. *J Am Coll Cardiol* 1995;26(5):1133-1139.

Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ, Konstam MA, Riegger G, Klinger GH, Neaton J, Sharma D, Thiyagarajan B. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II. *Lancet* 2000;355(9215):1582-1587.

Pitt B, Segal R, Martinez FA, Meurers G, Cowley AJ, Thomas I, Deedwania PC, Ney DE, Snavely DB, Chang PI. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet* 1997;349(9054):747-752.

Pollock K, Grime J. Patients' views on cost effectiveness of drugs are important. *BMJ* 2000;321(7271):1292.

Primatesta P , Poulter NR. Lipid concentrations and the use of lipid lowering drugs: evidence from a national cross sectional survey. *BMJ* 2000;321(7272):1322-1325.

Prosser LA, Stinnett AA, Goldman PA, Williams LW, Hunink MG, Goldman L, Weinstein MC. Cost-effectiveness of cholesterol-lowering therapies according to selected patient characteristics. *Ann Intern Med* 2000;132(10):769-779.

Reid RJ, 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.

Ryan TJ, Antman EM, Brooks NH, Califf RM, Hillis LD, Hiratzka LF, Rapaport E, Riegel B, Russell RO, Smith EE 3rd, Weaver WD, Gibbons RJ,

Alpert JS, Eagle KA, Gardner TJ, Garson A Jr, Gregoratos G, Ryan TJ, Smith SC Jr. 1999 update: ACC/AHA guidelines for the management of patients with acute myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *J Am Coll Cardiol* 1999;34(3):890-911.

Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* 1996;335(14):1001-1009.

Scandinavian Simvastatin Survival Study Group, Pyörälä K, Lehto S, Rantala A, Miettinen H, Salokannel A, Räisänen R. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344(8934):1383-1389.

Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995;333(20):1301-1307.

Siegel D, Lopez J. Trends in antihypertensive drug use in the United States: do the JNC V recommendations affect prescribing? Fifth Joint National Commission on the Detection, Evaluation, and Treatment of High Blood Pressure. *JAMA* 1997;278(21):1745-1748.

Siegel D, Lopez J, Meier J. Pharmacologic treatment of hypertension in the Department of Veterans Affairs during 1995 and 1996. *Am J Hypertens* 1998;11(11 Pt 1):1271-1278.

Sleight P. Angiotensin II and trials of cardiovascular outcomes. *Am J Cardiol* 2002;89(2A):11A-16A.

Smith P, Arnesen H, Holme I. The effect of warfarin on mortality and reinfarction after myocardial infarction. *N Engl J Med* 1990;323(3):147-152.

Starfield B, Weiner J, Mumford L, Steinwachs D. Ambulatory care groups: a categorization of diagnoses for research and management. *Health Serv Res* 1991;26(1):53-74.

Starfield B. *The effectiveness of medical care: validating clinical wisdom.* Baltimore MD: Johns Hopkins University Press, 1985.

Sueta CA, Chowdhury M, Boccuzzi SJ, Smith SC, Jr., Alexander CM, Londhe A, Lulla A, Simpson RJ, Jr. Analysis of the degree of undertreatment of hyperlipidemia and congestive heart failure secondary to coronary artery disease. *Am J Cardiol* 1999;83(9):1303-1307.

The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;339(19):1349-1357.

Tognoni G. Drug use and monitoring. In: Holland WW. *Evaluation of Health Care*. London: Oxford University Press, 1983.

Tsuyuki RT and Bungard TJ. Poor adherence with hypolipidemic drugs: a lost opportunity. *Pharmacotherapy* 2001;21(5):576-582.

Wallenius S, Peura S, Klaukka T, Enlund H. Who is using antihypertensive drugs? A prescription analysis from Finland. *Scand J Prim Health Care* 1996;14(1):54-61.

Wei L et al. Adherence to statin treatment and readmission of patients after myocardial infarction: a six year follow up study. *Heart* 88:229-233.

World Health Organization. *World Health Organization's Centre for Drug Statistics Methodology: Guidelines for ATC classification and DDD assignment*. Oslo, Norway: World Health Organization, 1995.

## GLOSSARY

### Adjusted Clinical Group (ACG)

The Adjusted Clinical Group (ACG) is a population/patient case-mix adjustment system developed by researchers at Johns Hopkins University School of Hygiene and Public Health in Baltimore, Maryland, U.S.A. The ACG system quantifies morbidity by grouping individuals based on their age and gender and all known medical diagnoses (which have been assigned over a defined period of time, typically one year). International Classification of Disease, version 9 (ICD-9/ICD-9-CM) diagnosis codes for similar conditions are clustered based on expected consumption of health care resources and short-term clinical outcomes. An ACG assigned to an individual, then, represents a combination of one or more diagnostic groups (up to 32) and their age and gender. ACGs help to quantify morbidity on a population basis for the purposes of stratifying individuals by their level of comorbidity.

### Administrative databases

With the introduction of universal medical care insurance, provincial governments developed health administrative databases for tracking hospital discharge summaries, physician billing claims, claims for prescription drugs and other health related data. Researchers study the utilization of health resources over time and the variations in rates within and across the provinces.

### Appropriateness

Appropriateness is a process measure; it is the subset of quality that is concerned with determining whether the right thing was done for the patient. In the context of the use of pharmaceuticals, appropriateness measures whether the right drug was prescribed for the right person.

### Channelling bias

The propensity of "sicker" patients to be prescribed disproportionately the newer and perceived to be more potent medications differentially.

### Cost-driver

A component that significantly influences annual changes in pharmaceutical spending in a province (for example). Major components that annually drive up pharmaceutical costs include changes in the use of older and newer drugs, price changes of older and newer drugs, and the introduction of new drugs in specific therapeutic classes or for disease groups.

### Defined daily dose (DDD)

The DDD is the assumed average maintenance dose per day for a drug used

for its main indication in adults. The rate of the number of DDDs dispensed to the population (of residents or users) per day and per year can be calculated to measure various aspects of intensity. A clinical measure can also be calculated.

### Different drugs
The number of different drugs dispensed per year per resident and per pharmaceutical user. A "different" drug is defined at the 4th level of Anatomical-Therapeutic-Chemical classification system, that is, the chemical/therapeutic/pharmacological subgroup not the drug molecule.

### Drug identification number
A number, called the "DIN", is assigned to each unique prescription drug product by the Therapeutic Products Directorate of Health Canada.

### Drug utilization indicator
A measure of how the population uses a drug (pharmaceutical). Examples of indicators include: access (the proportion of residents who are dispensed at least one prescription per year; such residents are called "pharmaceutical users"), intensity of use (total number of prescriptions, defined daily doses or number of different drugs dispensed) and expenditures (amount paid by government agency and/or individual for the drug ingredients, professional fee and total prescription cost).

### Drug programs information network (DPIN)
DPIN is an electronic, on-line, point-of-sale prescription drug database. It links all community pharmacies (but not hospitals or nursing care homes) and captures information about all Manitoba residents, including most prescriptions dispensed to status Indians. The DPIN contains information such as: unique patient identification, age, birth date, sex, medication history, over-the-counter medication history, patient postal code, new drug prescribed, date dispensed and unique pharmacy identification number.

### Drug utilization review (DUR)
Historically, DUR is a structured, ongoing organizationally authorized quality assurance process designed to ensure that drugs are used appropriately, safely and effectively.

### Effectiveness
The production of a benefit in a person for treatment or prevention of disease; cost-effectiveness is an indicator (ratio) of the cost of providing a pharmaceutical to the measure of health outcome the pharmaceutical is expected to produce. If an alternative activity produces a better outcome at the same or a lesser cost then it is more effective. Effectiveness has been described as

the net of benefit-or what the drug is supposed to do in designated patient groups-and harm (adverse drug reactions).

## Efficacy

The benefit a drug brings when it is taken in the context of a clinical trial or an ideal setting.  This is in contrast to the effectiveness of a drug which is the benefit the population derives when the drug is prescribed, dispensed and taken under real life circumstances.

## Episodes of drug therapy

Some indicators of exposure (epidemiology) and appropriateness require a measure of continuous time on therapy.  Depending on the study drug or drug class, an algorithm linking dispensing dates together and then counting total "time on therapy" is accounted for.

## First-line therapy

A synonym for the "step-up" approach to prescribing.

## Fiscal year

Manitoba Health's fiscal year is defined as starting at April 1 and ending the following year at March 31. For example the 1996-1997 fiscal year would be April 1, 1996 to March 31, 1997.   A researcher must keep the fiscal year in mind when examining the data records of Manitoba Health as they use  the April 1 to March 31 fiscal year. In other words, a data record year is the fiscal year, not the expected January 1 to December 31.

## Income quintile

Income quintiles are geographic area measures of socioeconomic status derived from Canadian 1996 census data.  Census-derived household income data, aggregated to the geographic unit of the enumeration area, are used to rank neighbourhoods by average household income.  The average (mean) household income of residents living in specific neighbourhoods are ranked from poorest to wealthiest, and then grouped into 5 income quintiles (1 being poorest and 5 being wealthiest), each quintile contains approximately 20% of the population. Income quintiles are available for both urban and rural populations, however, Winnipeg-only is usually reported.

## Index date

Index dates are usually assigned to the start of the "new use" of a prescription drug as registered on the Drug Programs Information Network. New use is usually defined as no dispensations for the drug under study for a specific person between April 1 and July 31 of the starting fiscal year of analysis. This is assumed to be a 4-month "washout" period of exposure to the study drug being analyzed. Other definitions of new use are also possible

including no use of the study drug prior to the 4-month window used in this study.

## Municipal code

Municipal codes are assigned at the time of registration or address update with Manitoba Health for publicly funded health care services. Manitoba Health relies on the resident to provide accurate information on where they live. Where possible, the information is validated, but it is virtually impossible to audit each and every registration with Manitoba Health for valid information.

## New user (new use)

No dispensations of the study drug for an individual between April 1 and July 31 of any fiscal year.

## Pharmaceutical user

A resident of Manitoba having at least one prescription drug dispensed per year in Manitoba.

## POPULIS

An integrated dataset housed at the Manitoba Centre for Health Policy (University of Manitoba). Formerly called Population Health Information System (PHIS), POPULIS was developed by MCHP to provide population based information on the health and health care utilization of Manitobans. It links the health of the population to its use of health care services and to economic and social factors. POPULIS tracks health status and health care use based on the region in which people live, not where they receive care. Analyzes can be provided at various geographic levels including Regional Health Authorities, municipalities, or hospital service areas.

## Prescribing (appropriateness) indicator

A measure that indicates the alignment of prescribing with the processes of care as established by evidence-based guidelines. Examples of these indicators include prescribing criteria addressing acceptable durations of treatment, rates of rule-out investigations, doses and rates of initial prescription following a consequential event like a heart attack (acute myocardial infarction).

## Registry file

A file containing data on the insured population organized by family registration numbers. The research registry contains information on dates of coverage, marital status and place of residence (by postal code and municipal code only; no addresses are contained in the file). Annual snapshots of this file have been received since 1970; marital status has been

reconstructed from the family information. A massive programming effort maintained over many years has joined these snapshot files together such that individual histories can be constructed over the entire period of the data base. This results in the creation of the longitudinal population registry; many checks have been done on this registry. Software has been developed to facilitate longitudinal follow-up or mobility, migration, and mortality.

## Step-up approach

The step-up approach follows the principle of applying the minimum pharmacological force necessary to achieve a stated therapeutic objective. The step-up approach is in contrast to the step-down approach that proposes that patients should initially be treated with the more powerful and costly alternatives only being stepped-down to a less intensive intervention in strictly defined circumstances. The principal problem inherent in this approach is the universal application of a powerful and costly drug for patients in whom less intensive interventions may have been adequate and have not previously been proven to be ineffective.

## APPENDIX A: ACRONYMS

A2RA        Angiotensin II Receptor Antagonists

ACEI        Angiotensin-Converting Enzyme Inhibitors

ACG         Adjusted Clinical Groups

AMI         Acute Myocardial Infarction

ATC         Anatomical-Therapeutic-Chemical (WHO classification system for drug molecules)

CDR         Common Drug Review

CHD         Coronary Heart Disease

CHF         Congestive Heart Failure

CVD         Cardiovascular Disease

DDD         Defined Daily Dose

DIN         Drug Identification Number

DM          Diabetes Mellitus

DPIN        Drug Programs Information Network

FP          Family Physician

HDL         High Density Lipoprotein

HT          Hypertension

IHD         Ischaemic Heart Disease

LDL         Low Density Lipoprotein

MI          Myocardial Infarction

PMPRB       Patented Medicine Prices Review Board

POPULIS     POPULation health Information System

## Appendix B: Drug Utilization Indicators

## B.1 Access Indicators

Access indicators describe the proportion of the population accessing at least one prescription drug in a fiscal year. Specifically, these indicators describe the persons (users) accessing pharmaceutical benefits (dispensation of at least one prescription drug in a fiscal year (Apr 01-Mar 31)) by: age, sex, age/sex, region, number of different of pharmaceuticals dispensed, and other demographic characteristics of interest at least once in a fiscal year.

> **Indicator #1:** *Proportion of the population using at least one prescription drug per year.*

How is this indicator calculated? The numerator of the rate is the number of persons (users) having at least one prescription dispensed in a fiscal year and the denominator is the number of persons possible to be covered or the resident population of Manitoba. The rate is usually reported per 1,000 residents.

## B.2 Intensity of Use Indicators

Utilization indicators describe the intensity of use, volume changes and mix of prescription drugs used by the population. Specifically, a description of the types and numbers of prescription drugs used by the population.

> **Indicator #2:** *Total number of prescriptions dispensed per 1,000 residents and pharmaceutical users and the mean number of prescriptions dispensed per resident.*
> **Indicator #3:** *The number of different drugs dispensed per pharmaceutical user.*
> **Indicator #4:** *The defined daily doses (DDDs) used per 1,000 residents and pharmaceutical users.*

How are these indicators calculated? By classifying all prescriptions using the Anatomical-Therapeutic-Chemical (ATC) classification, the numerator of each rate is the count of the:

    (1) number of prescriptions dispensed
    (2) number of different drugs dispensed
    (3) number of defined daily doses dispensed

Denominator(s) are the number of residents, users and users of specific therapeutic classes. All rates are described by: age, sex, age/sex, region, income quintile and comorbidity status.

## B.3 Expenditure Indicators

Expenditure indicators describe the costs of prescription drugs to both pharmaceutical users and residents. Expenditures are made by Manitobans either out-of-pocket or through tax dollars as a social benefit.

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**Indicator #5:** *Average cost per prescription (and by therapeutic class).*
**Indicator #6:** *Average cost per defined daily dose (DDD) (and by therapeutic class).*
**Indicator #7:** *Total drug expenditure by population characteristics and therapeutic class.*

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These rates are calculated using the following numerator/denominator combinations:

● Indicator #5: Total paid for all drug products (DINs)[17] within each ATC therapeutic class divided by total volume of prescriptions for all DINs
● Indicator #6: Total paid for all drug products (DINs) within each ATC therapeutic class divided by total DDDs dispensed for all DINs
● Indicator #7: Total paid for all drug products (DINs) within each ATC therapeutic class divided and described per user and resident by: age, sex, age/sex, region, and other demographic characteristics of interest.

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[17] DIN is 'Drug Identification Number' and is assigned to each unique prescription drug product by the Therapeutic Products Directorate.

## APPENDIX C: AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM: Drug Utilization (1996/97 to 1999/2000)
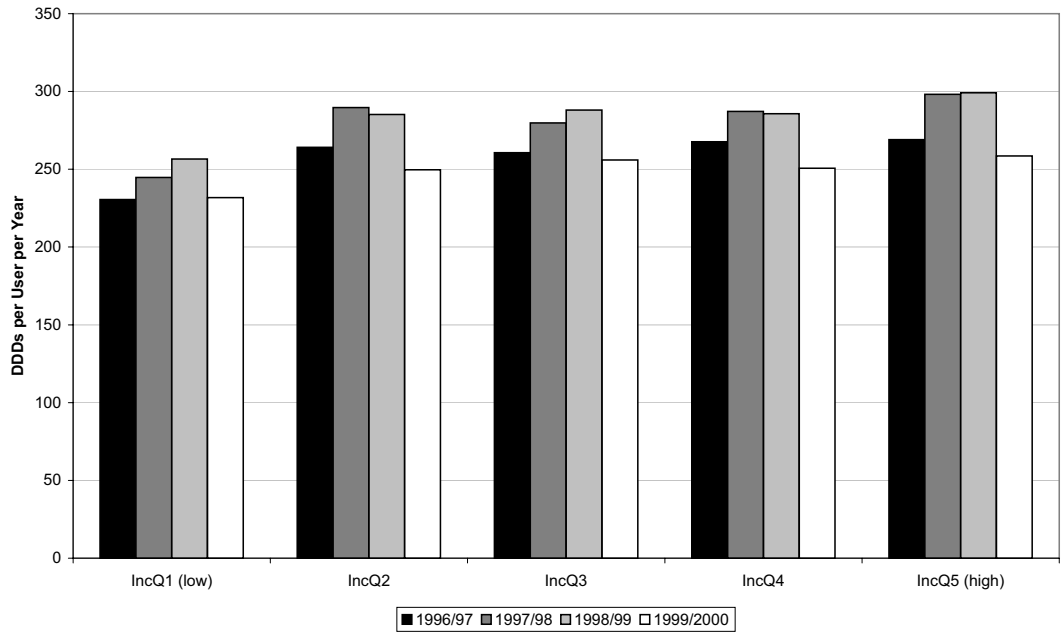
Agents acting on the renin-angiotensin system are taken by 6.2% of Manitobans in fiscal year 1999/2000. Females are dispensed approximately 16% more prescriptions for these agents than males; those 65 years of age and older are dispensed seven times more prescriptions than those less than 65 years of age. A total of 453,388 prescriptions (5.5% of the total number of prescriptions) were dispensed for this class (C09) in 1999/2000 accounting for over 8.2% of expenditures for pharmaceuticals (Table 2). Table C1 is a summary of drug utilization measures for renin-angiotensin system drugs for 1996/97-1999/2000.

**Table C1: Agents acting on the renin-angiotensin system drug utilization measures, 1996/97-1999/2000**

|  |  |  | 1996/97 | 1997/98 | 1998/99 | 1999/2000 |
|---|---|---|---|---|---|---|
| Access indicator | Per cent population | | 4.4 | 4.9 | 5.4 | 6.2 |
| Intensity of use indicators | Number of prescriptions per user per year | Overall | 5.8 | 6.1 | 6.2 | 6.3 |
|  |  | Males | 5.6 | 5.9 | 6.0 | 6.1 |
|  |  | Females | 5.9 | 6.2 | 6.4 | 6.5 |
|  |  | Non-Elderly | 5.7 | 6.0 | 6.1 | 6.2 |
|  |  | Elderly | 5.9 | 6.2 | 6.3 | 6.5 |
|  | DDDs per year | Overall | 256.9 | 281.8 | 280.8 | 246.9 |
|  |  | Males | 257.6 | 279.3 | 281.1 | 251.8 |
|  |  | Females | 256.4 | 283.9 | 280.4 | 242.7 |
|  |  | Non-Elderly | 255.8 | 276.8 | 270.6 | 241.1 |
|  |  | Elderly | 257.9 | 286.2 | 289.7 | 252.1 |
|  |  | Winnipeg | 255.2 | 276.4 | 280.2 | 246.7 |
|  |  | Non-Winnipeg | 259.0 | 288.8 | 281.6 | 247.2 |
|  | DDDs per year income quintile | Lowest (Q1): | 230.5: | 244.7: | 256.6: | 231.8: |
|  |  | Highest (Q5) | 269.1 | 298.2 | 299.1 | 258.6 |
| Expenditure indicators | Dollars per user per year | Overall | $153.47 | $314.74 | $325.57 | $326.08 |

The defined daily dose calculations are based on the average daily dose for treatment of mild to moderate hypertension. DDDs have remained relatively stable over the four years of analysis (1996/97-1999/2000) at about 267 DDDs per user per year or 75% of the average daily dose. Figure C1 shows a disparity between amount used and income quintile. Also of note, however, is that the number of DDDs decreased in the most recent year of analysis perhaps signifying that with an increase in the use of A2RAs, the defined daily dose calculations are closer to one for A2RAs (e.g., losartan DDD=50mg/day) than they are for ACEIs which may be greater than one (e.g., enalapril DDD=10mg/day, but doses up to 40mg/day or 4 DDDs/person are commonplace).

**Figure C1: Defined Daily Doses for Agents Acting on the Renin-Angiotensin System by Income Quintile, 1996/97-1999/2000**



Cost per resident per year prescription for agents acting on the renin-angiotensin system ranged from $12.73 in 1996/97 to $20.33 in 1999/2000 (a 59.7% increase); correspondingly, the cost per prescription also increased over the same period ($49.60 to $52.28). As seen in Figure C2, however, there was a great increase in the amount spent per user in 1997/98. The increase parallels the introduction of a new class of agents acting on the renin-angiotensin system—the A2RAs; losartan (Cozaar) received a Notice of Compliance from Health Canada in September 1995 and was listed on the Manitoba Formulary in early 1996. The increase in expenditures per user for this more expensive class would likely not start to be reflected until fiscal year 1996/97.

**Figure C2: Average Annual Cost per User of Agents Acting on the Renin-Angiotensin System, 1996/97-1999/2000**
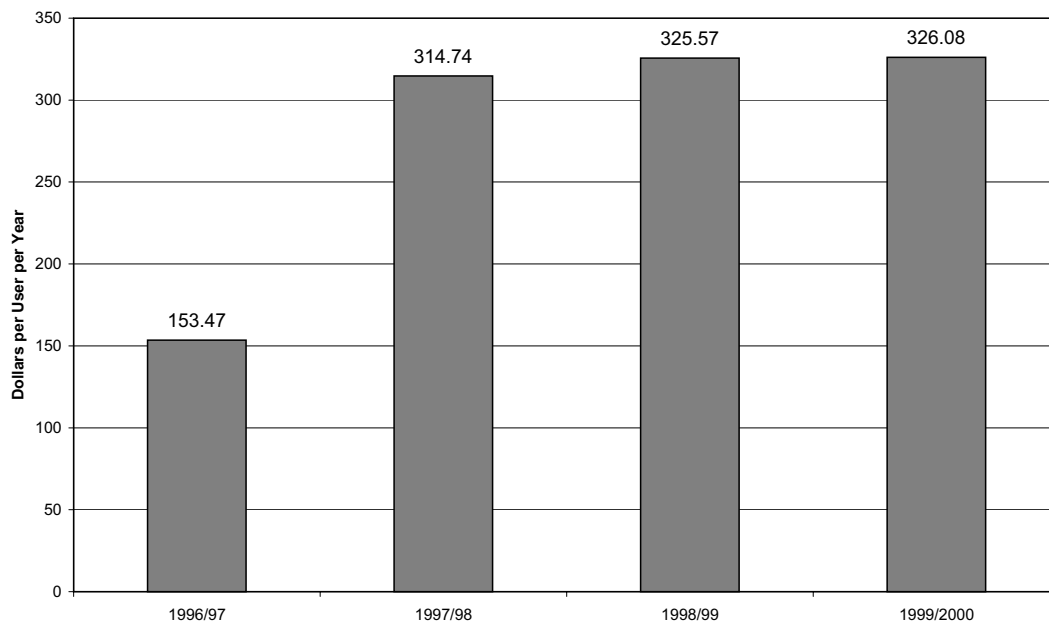
# APPENDIX D: AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM: HYPERTENSION AND COMORBIDITIES, DISEASE DEFINITIONS

| Comorbidity | Operational definition | First-line |
|---|---|---|
| Congestive heart failure or renal disease | During two years *at least* one physician visit or hospitalization (any diagnosis field) for heart failure (428), hypertensive heart disease (402), hypertensive renal disease (403), hypertensive heart and renal disease (404), chronic renal failure (585), dialysis (V451, procedure: 3995, 5498) OR one prescription for digoxin (ATC:C01A) or furosemide (ATC:C03CA01) | ACE inhibitors |
| Diabetes (need three years of physician/hospital data) | During two years *at least* one prescription for insulin or hypoglycemic drug (ATC: C01A) OR during three years at least one hospitalization or two physician visits for diabetes (250) | <60: ACE, β-blockers >60: CCA |
| Coronary artery disease | During two years *at least* one physician visit or hospitalization (any diagnosis field) for acute myocardial infarction (410), acute/subacute forms of ischaemic heart disease (411), old myocardial infarction (412), angina pectoris (413), chronic ischaemic heart disease (414), arteriosclerotic cardiovascular disease (4292) OR CABG or angioplasty (procedure: 360, 362, 363) | β-blockers |
| Arrhythmias | During two years *at least* one physician visit or hospitalization (any diagnosis field) for cardiomyopathy (425), conduction disorders (426), cardiac dysrythmias (427) OR one prescription for anti-arrhythmic (ATC: C01B) | Avoid β-blocker for specific disorders |
| Peripheral vascular disease | During two years *at least* one physician visit or hospitalization (any diagnosis field) for other peripheral vascular disease (443) OR one prescription for pentoxyfylline | Avoid β-blocker |
| Cerebrovascular disease | During two years *at least* one physician visit or hospitalization (any diagnosis field) for subarachnoid haemorrhage (430), intracerebral haemorrhage (431), other intracranial haemorrhage (432), occlusion of precerebral arteries (433), occlusion of cerebral arteries (434), transient cerebral ischaemia (435), acute cerebrovascular disease (436), other cerebrovascular disease (437), late effects of cerebrovascular disease (438) OR one prescription for antiplatelet drug (ATC: B01AC) | ACE not necessary |
| Hyperlipidemia | During two years *at least* one prescription for cholesterol-lowering drug (ATC: C10A) | ACE not necessary |

## Appendix E: Agents Acting on the Renin-Angiotensin System: Criteria Application

The following offers more detail on how the cohorts were derived in order to apply the appropriateness criteria:

### ACEI Appropriateness Criterion #1 (INITIAL THERAPY CHOICE)
"Prevalence of ACEI use should be highest in persons with hypertension and existing comorbidities for which ACEIs are preferred first-line agents. Prevalence of ACEIs should be lowest in persons with uncomplicated hypertension for which ACEIs are alternative first-line agents (to beta-blockers and diuretics)."

### A2RA Appropriateness Criterion #2 (INITIAL THERAPY CHOICE)
"Treatment with an ACEI should be initiated prior to the use of A2RAs."

### A2RA Appropriateness Criterion #3 (INITIAL THERAPY CHOICE)
"Regardless of the appropriateness of A2RA selection (criterion #2), prevalence of A2RA use should be highest in persons with hypertension and existing comorbidities for which ACEIs are preferred first-line agents."

### A2RA Appropriateness Criterion #4 (INITIAL THERAPY CHOICE)
"Persons with newly diagnosed, uncomplicated hypertension should not receive A2RAs as first-line agents."

We used all individuals with at least one physician visit or hospitalization (primary diagnosis) for essential hypertension and hypertensive heart or renal disease over two-year time periods. These individuals were placed into mutually exclusive categories of hypertension according to comorbidity status. Rates of adherence to the initial therapy choice are reported by criterion.

All questions on the appropriate use of agents acting on the renin-angiotensin system were answered using a cohort similar to the one derived in the following Figure E1. The total number of NEW users (with hypertension) of ACEIs or A2RAs for fiscal year 1999/2000 was 13,355 compared to 10,695 in fiscal year 1996/97.

**Figure E1: Obtaining the 1999/2000 ACEI/A2RA Cohort for Appropriateness Analysis**



**N=138,191
Persons identified with
Essential Hypertension**

Distribution of

essential

hypertension by

Congestive heart or renal failure
N=23509 (17.0% HTN)

Diabetes mellitus (DM)
N=12987 (9.4% HTN)

Ischemic heart disease (IHD)
N=9003 (6.5% HTN)

Other comorbidities (PVD, CVD,
arrythmias, hyperlipidemia)
N=17803 (12.9% HTN)

Uncomplicated hypertension
Existing N=57715 (41.8% HTN)
New N=17174 (12.4% HTN)

**N=9547
NEW ACEI USERS**

**N=3808
NEW A2RA USERS**

<u>Summary</u>
**N=13,355** persons in fiscal year 1999/00
were identified as NEW users of either an ACEI
or an A2RA. These persons comprise one
(1999/00) of four fiscal year STUDY cohorts.

## APPENDIX F: SERUM LIPID REDUCING AGENTS (THE STATINS) DRUG UTILIZATION (1996/97 TO 1999/2000)

Serum lipid reducing agents of the HMG-CoA reductase inhibitor class (statins) are taken by approximately 3.6% of Manitobans (1999/2000 data). In 1999/2000 there were approximately 6% more males (37 users/1,000 population) taking statins than females (35 users/1000 population). The elderly (123 users/1,000 population) are at least five times more likely to be on statins than those less than 65 years of age (22 users/1,000 population). A total of 244,699 prescriptions (2.4% total number prescriptions) were dispensed for this class (C10) in 1999/2000 accounting for over 7.4% of expenditures for pharmaceuticals in Manitoba.

**Table F1: Serum lipid reducing agents (statins) drug utilization measures, 1996/97-1999/2000**

| | | | 1996/97 | 1997/98 | 1998/99 | 1999/2000 |
|---|---|---|---|---|---|---|
| Access indicator | Per cent population | | 2.3 | 2.7 | 3.1 | 3.6 |
| Intensity of use indicators | Number of prescriptions per user per year | Overall | 5.3 | 5.7 | 5.8 | 5.9 |
| | | Males | 5.4 | 5.7 | 5.8 | 5.9 |
| | | Females | 5.3 | 5.7 | 5.8 | 6.0 |
| | | Non-Elderly | 5.3 | 5.6 | 5.8 | 5.8 |
| | | Elderly | 5.4 | 5.9 | 5.9 | 6.0 |
| | DDDs per year | Overall | 186.7 | 193.9 | 182.2 | 201.2 |
| | | Males | 181.8 | 189.0 | 175.4 | 195.1 |
| | | Females | 191.4 | 198.8 | 189.1 | 207.4 |
| | | Non-Elderly | 189.3 | 167.7 | 164.8 | 179.8 |
| | | Elderly | 183.3 | 226.0 | 202.8 | 225.7 |
| | | Winnipeg | 180.7 | 185.6 | 176.5 | 187.8 |
| | | Non-Winnipeg | 196.1 | 207.3 | 191.2 | 220.8 |
| | DDDs per year income quintile | Lowest (Q1): | 170.0: | 182.1: | 170.8: | 181.1: |
| | | Highest (Q5) | 182.0 | 183.6 | 171.0 | 182.0 |
| Expenditure indicators | Dollars per user per year | Overall | $466.92 | $314.74 | $325.57 | $326.08 |

The defined daily dose calculations are based on the average daily dose for treatment of hypercholesterolemia (hyperlipidemia). DDDs have increased slightly over the four years of analysis (1996/97-1999/2000) and are now 201 DDDs per user per year or 55% of the average daily dose. Cost per resident per year prescription for serum lipid reducing agents ranged from $10.54 in 1996/97 to $18.43 in 1999/2000 (a 74.9% increase); however, the cost per prescription has remained relatively over the same period—average $86.80 (range: 85.97-87.48). The number of users has gone up significantly, about 60% from 1996/97 to 1999/2000 (n=25,824 in 1996/97 to n=41,344 in 1999/2000). Figure F1 shows, however, that despite the increase in utilization there is a decreased selection for statins based on increasing age over 80.

**Figure F1: Per Cent of Population With Access to at Least One Statin Prescription, 1996/97-1999/2000**

## APPENDIX G: SERUM LIPID REDUCING AGENTS: CRITERIA APPLICATION

Persistence on statin treatment was determined first by separating out those "new users" of statins from August 1, 1997 to November 30, 1999 who had an index date for a statin but no further statin prescriptions. November 30, 1999 was chosen because one could not be assured that those with one prescription dispensation after November 30, 1999 really had only one prescription dispensed. Once the "n=one prescription" cohort was identified two further cohorts were identified: (1) individuals taking a statin continuously (from index date to the truncated end, March 31, 2000) and, (2) individuals taking a statin continuously but appearing to stop before March 31, 2000.

A variable called "potential time on treatment" (PTTx) was calculated for each person on more than one statin prescription; PTTx was calculated as the number of days from index date to stop date (March 31, 2000). A "duration of treatment" variable comprised of the medication interval, in days, from one dispensation to the next was calculated plus the last designated days supply. If duration of treatment was determined to be less than or equal to 30 days less than PTTx then the person was designated as has having persisted on treatment. If duration of treatment was more than 30 days less than PTTx then the person was designated as having not persisted on treatment. For example, for an individual having their first prescription dispensed on September 1, 1998, their PTTx is 578 days (Sept 1/98 to Mar 31/00); if their duration of treatment variable was equal to or greater than 547 days then this person was designated as being persistent to therapy. It was determined that at 30 days the drug's effect likely declines significantly. Consider the example just given: an index date of September 1, 1998 and a PTTx date of 578 days (minus 30 days) for a critical value of 548 days; duration of treatment, however, is calculated to be 183 days (last day of dispensing of January 31, 1999 + 30 days supply).

For individuals whose hyperlipidemia is controlled by statins, cholesterol level should be measured at 4 to 6 weeks, and then again at three months. If the goals of lowering total serum cholesterol levels is achieved, then measurement of cholesterol levels should be done every four months or more frequently when drugs requiring closer follow-up are used, to monitor the cholesterol response and possible side effects of therapy, and LDL-cholesterol performed yearly. Physicians' Current Procedural Terminology for triglycerides (9154) and total serum cholesterol levels (9075) were used to determine the rate of cholesterol monitoring in "new users" of statins in fiscal years 1996/97 and 1997/98. Rates of cholesterol monitoring were determined for the year of first dispensation and for the two subsequent years in Winnipeg residents who were new users of statins.

### Criteria Application

The following offers more detail on how the cohorts were derived in order to apply the appropriateness criteria:

### Statin Appropriateness Criterion #1 (PERSISTENCE TO TREATMENT):

"Persons with a previous myocardial infarction are more likely to persist on treatment than those who use statins presumably as primary prevention."

### Statin Appropriateness Criterion #2 (FOLLOW-UP MONITORING):

"The cholesterol levels of persons taking statins should be followed for the purpose of ensuring the statin is having the desired effect."

We identified all new users of statins (n=7,273) and, from this group, also selected for application of appropriateness criteria. In the case of Criterion #2, we selected new users of statins who were Winnipeg residents (n=4,927).