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OPTIMAL THERAPY REPORT

COMPUS

March 2008

Current Utilization of Insulin Products in Canada



Supporting Informed Decisions

À l'appui des décisions éclairées

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ABBREVIATIONS

A1c	glycosylated hemoglobin
DCCT	Diabetes Control and Complications Trial
DM	diabetes mellitus
HI	human insulin (conventional)
IA	insulin analogue
IAsp	insulin aspart
ID	identifying number
IDet	insulin detemir
IGlar	insulin glargine
ILis	insulin lispro
LAIA	long-acting insulin analogues
NPH	neutral protamine Hagedorn
OAD	oral antidiabetic agent
RAIA	rapid-acting insulin analogues
P1	look-back period
P2	analysis period
P3	look-ahead period
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
UKPDS	United Kingdom Prospective Diabetes Study

1 INTRODUCTION

1.1 COMPUS

In March 2004, the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) was launched by the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) — now the Canadian Agency for Drugs and Technologies in Health (CADTH) — as a service to federal, provincial, and territorial jurisdictions, and other stakeholders. COMPUS is a nationally coordinated program, funded by Health Canada.

The goal of COMPUS is to optimize drug-related health outcomes and the cost-effective use of drugs by identifying and promoting optimal drug prescribing and use. Where possible, COMPUS builds on existing applicable Canadian and international initiatives and research. COMPUS achieves its goals through three main approaches:

- identifying evidence-based optimal therapy in prescribing and use of specific drugs
- identifying gaps in clinical practice, then proposing evidence-based interventions to address these gaps
- supporting the implementation of these interventions.

Direction and advice are provided to COMPUS through various channels, including stakeholder input and expert advice, including the following:

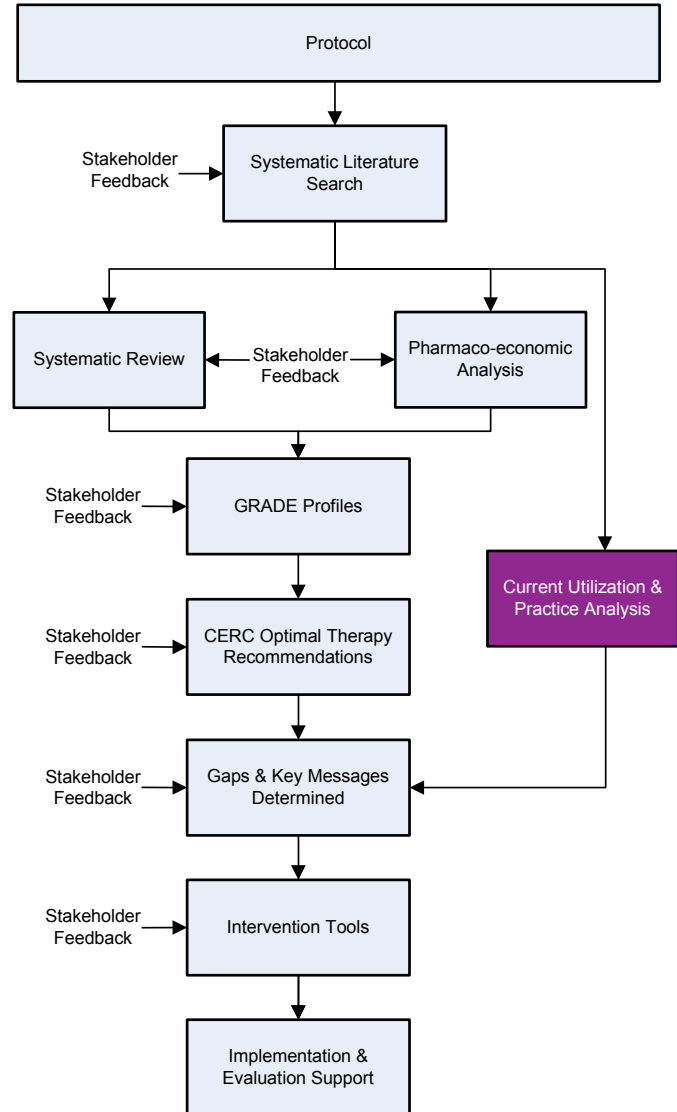
COMPUS Advisory Committee (CAC): the CAC is comprised of representatives from the Federal/Provincial/Territorial health ministries and related health organizations.

COMPUS Expert Review Committee (CERC): CERC is an expert advisory body of health and other professionals with expertise in drug therapy and evaluation of evidence.

1.2 Project overview

Once a topic is selected, COMPUS undertakes concurrent activities related to many of the key areas in the COMPUS procedure. Many of these activities involve consultations with our advisory committees, expert committees, and other interested stakeholders.

To identify and promote the implementation of evidence-based and cost-effective optimal therapy in the prescribing and use of long- and rapid-acting insulin analogues, COMPUS followed the process outlined in the flow chart to the right. This report represents Current Utilization Analysis step (purple box).



1.3 Background

Diabetes mellitus (DM) is a chronic disease characterized by the body's inability to produce sufficient insulin [type 1 DM (T1DM)] and, or properly, use insulin [type 2 DM (T2DM)].¹ Globally, approximately 177 million people have DM, the majority of whom have T2DM (90% to 95%),² and this number is expected to increase to 300 million by 2025.³ In Canada, an estimated 1 million (4.8%) Canadians aged 20 years and older were diagnosed with DM in 1998/99.² As nearly 2.7% of the adult population have undiagnosed T2DM,⁴ true prevalence of this disorder may be closer to 1.9 million.⁵

When not adequately controlled, DM may result in long-term, diabetes-related microvascular (e.g., retinopathy, neuropathy, and nephropathy) and macrovascular (e.g., coronary artery disease, peripheral artery disease, and cerebrovascular disease) complications. Consequently, both duration and quality of life may be significantly diminished in these patients.² In Canada, an estimated 6,137 deaths in 1999 were directly attributable to DM,² and a further 41,500 deaths were indirectly related to this disorder.³ By 2050, the number of deaths directly attributable to DM is likely to increase to almost 17,500 deaths annually.² In addition, far fewer people with DM (64.5%), compared to individuals without DM (90.8%), report their health to be "good or better" ($p < 0.05$).²

Evidence from the Diabetes Control and Complications Trial (DCCT)⁶, conducted in North America, and the United Kingdom Prospective Diabetes Study (UKPDS)⁷ demonstrated the value of maintaining tight glycemic control [glycosylated hemoglobin (A1c) values of $< 7.0\%$] in preventing or delaying the onset of long-term, diabetes-related complications.

To manage glycemic control, patients with T1DM require insulin therapy.⁴ Patients with T2DM are often initially controlled with lifestyle modifications (i.e., weight control, proper nutrition, and adequate exercise). For patients with T2DM who are not well-controlled with lifestyle modifications, medications, including oral antidiabetic agents (OADs), play an important role.⁸

1.4 Technology description

Two main types of insulin agents were available in Canada at the time of this analysis: human insulins (HIs) and insulin analogues (IAs).⁴ The HIs are biosynthetic insulin products prepared using recombinant DNA technology. They are available in short-, intermediate-, and long-acting formulations. When used in combination, HIs span the prandial and basal components of insulin replacement.

The pharmacokinetic and pharmacodynamic profiles of HIs, however, are such that they do not always replicate basal and meal-time endogenous insulin secretion and, subsequently, may not provide optimal glycemic control.⁹ The IAs were developed in an attempt to address the limitations of HIs. These agents target the basal-bolus components separately.⁹ Rapid-acting IAs (RAIAs) mimic the short action of endogenous meal-time insulin secretion.⁹ Long-acting IAs (LAIAs) promote a prolonged, non-fluctuating basal level of insulin activity.⁹ Insulin agents included in this analysis were RAIAs – insulin lispro (ILis), insulin aspart (IAsp); LAIAs – insulin glargine (IGlar), insulin detemir (IDet); short-acting HI; and intermediate-acting HI – neutral protamine Hagedorn (NPH).

1.5 Issue

More than \$181 million was spent on the purchase of insulin agents in Canadian retail pharmacies in 2005, an increase of 17.5% over 2004.¹⁰ It has been suggested that the recent growth in expenditures has been driven largely by “conversion” of patients from HIs to IAs.¹¹ Thus, the objective of the current report was to explore the utilization patterns of HIs and IAs in Canada.

2 METHODS

A retrospective utilization analysis of insulin agents, regarding numbers of prescriptions, market share, and costs, in Canada over an 18-month period between February 2005 and July 2006 was performed.

2.1 Data sources

Data for this report were provided by IMS Health Consulting and Services (IMS). IMS collects data from over 65,000 sources in Canada including pharmacies, pharmaceutical manufacturers, wholesalers and physicians. More than 250 million data transactions are analyzed each year, providing objective and reasonably representative information on health care trends for pharmacologic analysis.¹² IMS maintains databases of prescriptions dispensed and sold, of disease treatment patterns and longitudinal data on the prescription activity of de-identified patients over time.

This store-based collection of de-identified patient data from approximately 3,000 pharmacies represents all geographic regions and all sectors of the economy providing insights into chronic, retail-based markets. IMS tracks over 17 million de-identified patients (more than 200 million anonymous prescriptions annually).

De-identified patient data from the IMS Patient Longitudinal Database for the period of February 2005 to July 2006 were selected for analyses of prescribing trends. The Longitudinal Database contains anonymized patient-level data; patients cannot be identified by name, however, each person has a unique identifying number (ID) associated with their records. The database does not include information about diagnosis.

The Longitudinal Database contains records for 1.2 million de-identified patients being treated for DM from 10 Canadian provinces. Available data represent approximately 41% of retail pharmacies and 55% of the total insulin diabetes market in Canada.

2.2 Data classification

Only new patients with T1DM, or new insulin starts for patients with T2DM, were included in the analysis. In order to identify these patients, three time frames were defined, as described below.

Look-back period (P1)

The look-back period (P1) covered a time span of 12 months, from January 2005 to February 2004. The look-back period enabled the identification of patients who were considered to be “new insulin starts” in the Analysis period (P2).

Analysis period (P2)

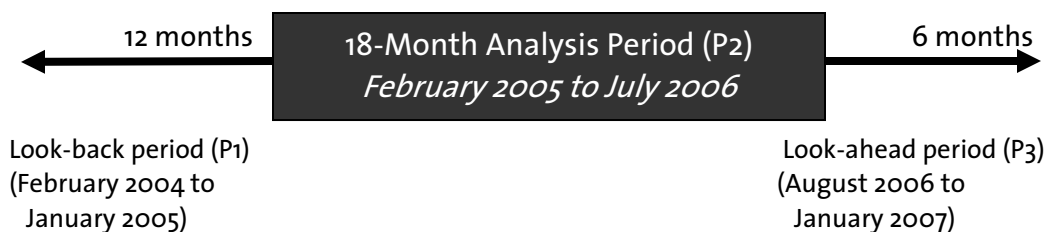
The period of analysis was the 18 months beginning in February 2005 and ending in July 2006. Data from this period were used in the current analysis.

Look-ahead period (P3)

The look-ahead period (P3) covered a time span of six months, from August 2006 to January 2007. The look-ahead period allowed cessation and switching of therapy to be accurately identified.

Patients were classified as “switching” medication if they stopped one therapy and began another medication that had not been part of their initial treatment regimen, between initiation and the end of the look-ahead period (P3).

Figure 1: Study and time periods



2.3 Classification of patients by type of DM

Patients were classified as having type 1 or type 2 DM, according to the following rules:

Type 1 diabetes

Patients were considered to have T1DM if they had never been prescribed any diabetes therapy, were younger than 30 years of age, and were initiated on an insulin agent during the analysis period (Figure 1, P2).

New insulin-treated patients with type 2 diabetes

Patients were considered to have T2DM if they had been prescribed ≥ 1 OAD during the look-back period (P1, Figure 1) and received their first prescription of insulin (with or without ≥ 1 OAD) during the analysis period (Figure 1, P2).

The classified data were cleaned and validated prior to inclusion in the analyses. Care was taken to ensure that patients who had been assigned multiple IDs (i.e., patients who were seen at more than one pharmacy or assigned more than one ID), or several patients mistakenly assigned the same ID, were not included in the dataset. Exclusion criteria were used to filter out unusable patient records and to avoid including patients who became eligible only near the end of the study period, and patients for which there were no provincial data. Patient records were excluded if they received fewer than six prescriptions in the dataset, or more than four prescriptions in one day – more than 150 prescriptions in

total over the study period; or, if their record did not contain information on their resident province. It was assumed that once initiated on diabetes-related treatment, patients would remain on some form of therapy for diabetes.

2.4 Analysis

Descriptive statistics describing therapeutic insulin regimens initially dispensed to patients with either T1DM or T2DM are reported. Demographic characteristics, switching patterns, and variation in use of insulin agents across age groups and provinces were examined.

3 RESULTS

3.1 Demographic characteristics

After data validation, the final dataset contained 30,954 de-identified patients with DM who were initiated on insulin therapy. Of these patients, 4,405 (14.23%) were classified as having T1DM, and 26,549 (85.77%) as having T2DM. The distribution of new insulin users by gender, type of DM, and age is presented in Table 1.

Table 1: Percentage distribution of de-identified patients classified as new insulin-treated patients with DM, by gender, type of DM, and age		
Category	Type 1	Type 2
Gender		
Male	52.4%	52.11%
Female	47.6%	47.89%
Age (Years)		
≤20	48.74%	0.90%
21 to 30	51.26%	1.44%
31 to 44	-	8.96%
45 to 64	-	44.91%
≥65	-	43.79%

DM= diabetes mellitus

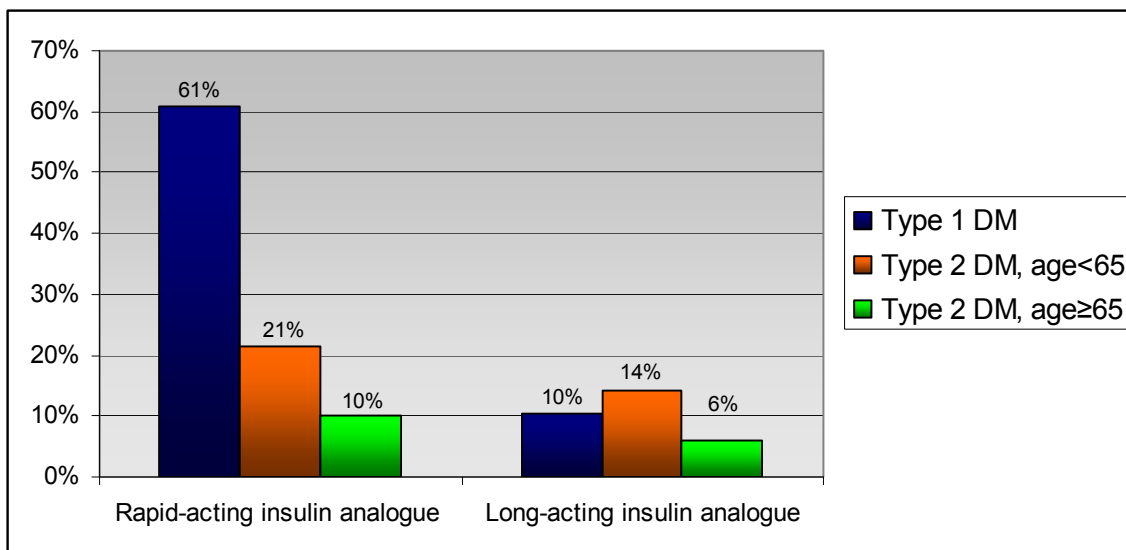
Source: *IMS Health Canada. Longitudinal Database- IMS Health Consulting Analysis*

Time Period: February 2005-July 2006

3.2 Use of IAs as initial therapy in patients with DM in Canada

Among the 4,405 patients classified as having T1DM, 2,685 (61%) were initially prescribed a RAIA and 462 (10%) were prescribed a LAIA. For younger patients with T2DM – that is, patients aged <65 years – 3,189 (21%) were initially prescribed a RAIA and 2,098 (14%) were prescribed a LAIA. Among elderly patients with T2DM – that is patients ≥65 years of age – 1,158 (10%) were initially prescribed a RAIA and 711 (6%) were prescribed a LAIA (Figure 2).

Figure 2: Percentage of patients in Canada initiated on RAIAs and LAIAs as mono-therapy or combination therapy, by type of DM



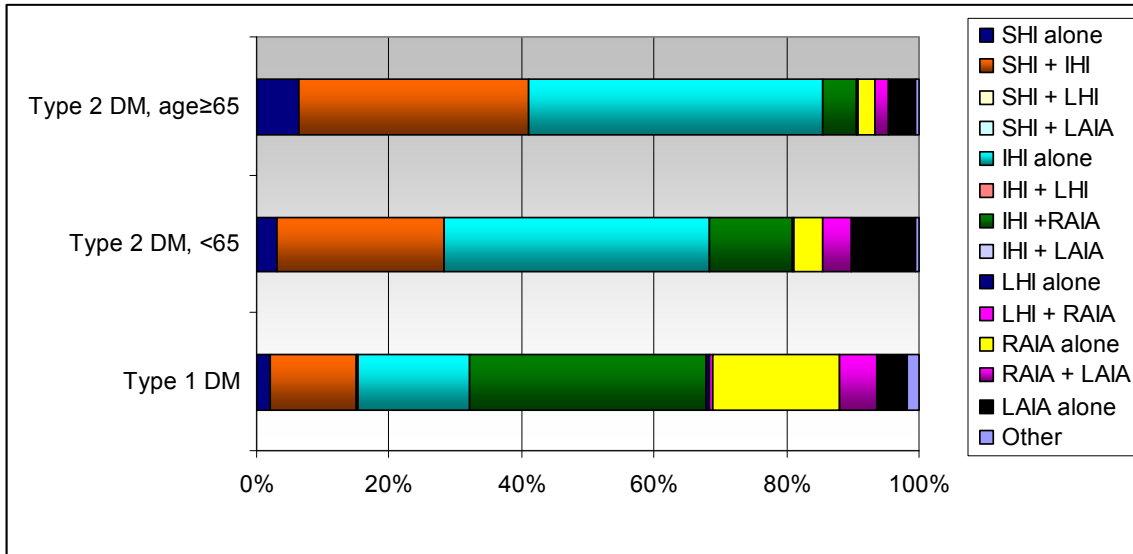
DM=diabetes mellitus; LAIA=long-acting insulin analogues; RAIA=rapid-acting insulin analogues
 Source: *IMS Health Canada. Longitudinal Database- IMS Health Consulting Analysis**
 Time Period: February 2005-July 2006

3.3 Insulin treatment regimens in patients with DM in Canada

The majority (50%) of patients with T1DM were initiated on combination therapy consisting of intermediate-acting HI and short-acting HI or a RAIA. Approximately 6% of patients were initiated on a combination of LAIAs and RAIAs (Figure 3).

Of those patients with T2DM who required insulin therapy, the majority were initiated on intermediate acting HI monotherapy. Combination therapy with intermediate-acting HI and short-acting HI, was initial therapy for 25% and 35% of young and elderly patients, respectively (Figure 3).

Figure 3: Percentage distribution of patients prescribed insulin regimens in Canada, by type of DM



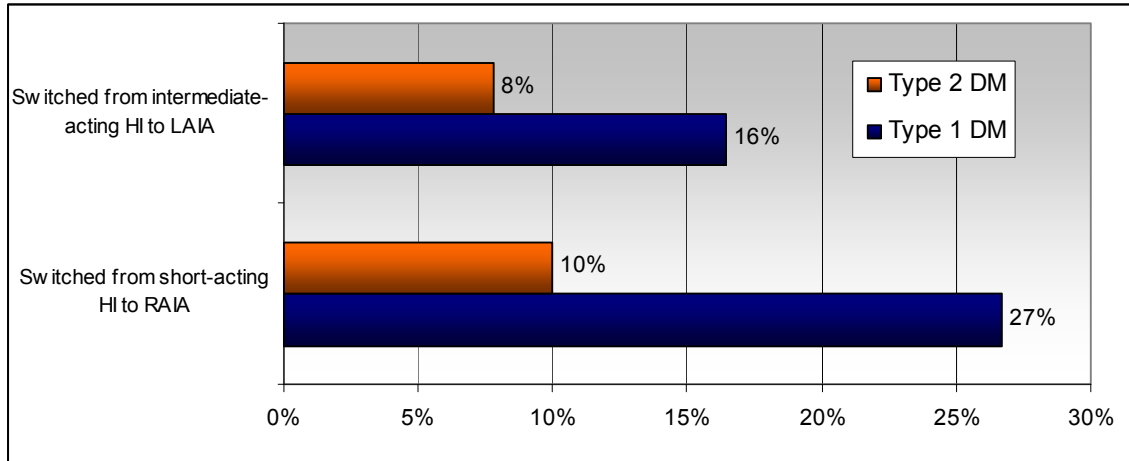
DM=diabetes mellitus; IHI= intermediate-acting human insulin; LAIA= long-acting insulin analogue; LHI=long-acting human insulin; RAIA= rapid-acting insulin analogue; SHI=short-acting human insulin
 Source: *IMS Health Canada. Longitudinal Database- IMS Health Consulting Analysis**
 Time Period: February 2005-July 2006

3.4 Switching patterns of patients with DM prescribed HI

Of patients with T1DM and T2DM who were initially prescribed short-acting HI, 27% and 10% switched to RAIAs, respectively. The median time to switch agents was 128 days for patients with T1DM, and 163 days for patients with T2DM (Figure 4).

In patients with T1DM and T2DM who were initially prescribed intermediate-acting HI, 16% and 8% switched to LAIAs, respectively. The median time to switch agents was 163 days for patients with T1DM, and 152 days for patients with T2DM (Figure 4).

Figure 4: Switching patterns of patients with T1DM and T2DM in Canada initially prescribed short- or intermediate-acting HI as monotherapy or combination therapy before switching to IAs



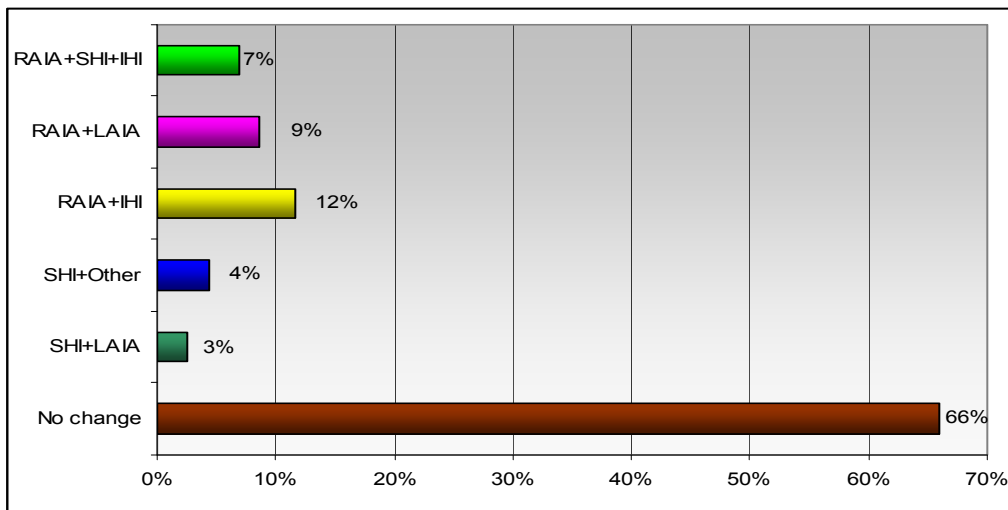
DM=diabetes mellitus; HI=human insulin; IAs=insulin analogues; RAI= rapid-acting insulin analogue; LAIA= long-acting insulin analogue; T1DM=type 1 DM; T2DM=type 2 DM

Source: IMS Health Canada. Longitudinal Database- IMS Health Consulting Analysis*

Time Period: February 2005-July 2006

The majority of patients with T1DM who were initially prescribed a basal-bolus combination therapy consisting of intermediate-acting and short-acting HI remained on their initial therapy. However, 12% of patients switched their bolus insulin to a RAI, and 7% switched their basal-bolus combination to a RAI and LAIA combination (Figure 5).

Figure 5: Switching patterns of patients with T1DM in Canada initially prescribed combination therapy with intermediate- and short-acting HI



DM=diabetes mellitus; HI=human insulin; IHI= intermediate acting human insulin; LAIA= long-acting insulin analogue; RAI= rapid-acting insulin analogue; SHI=short-acting human insulin; T1DM=type 1 DM

Source: IMS Health Canada Longitudinal Database- IMS Health Consulting Analysis*

Time Period: February 2005-July 2006

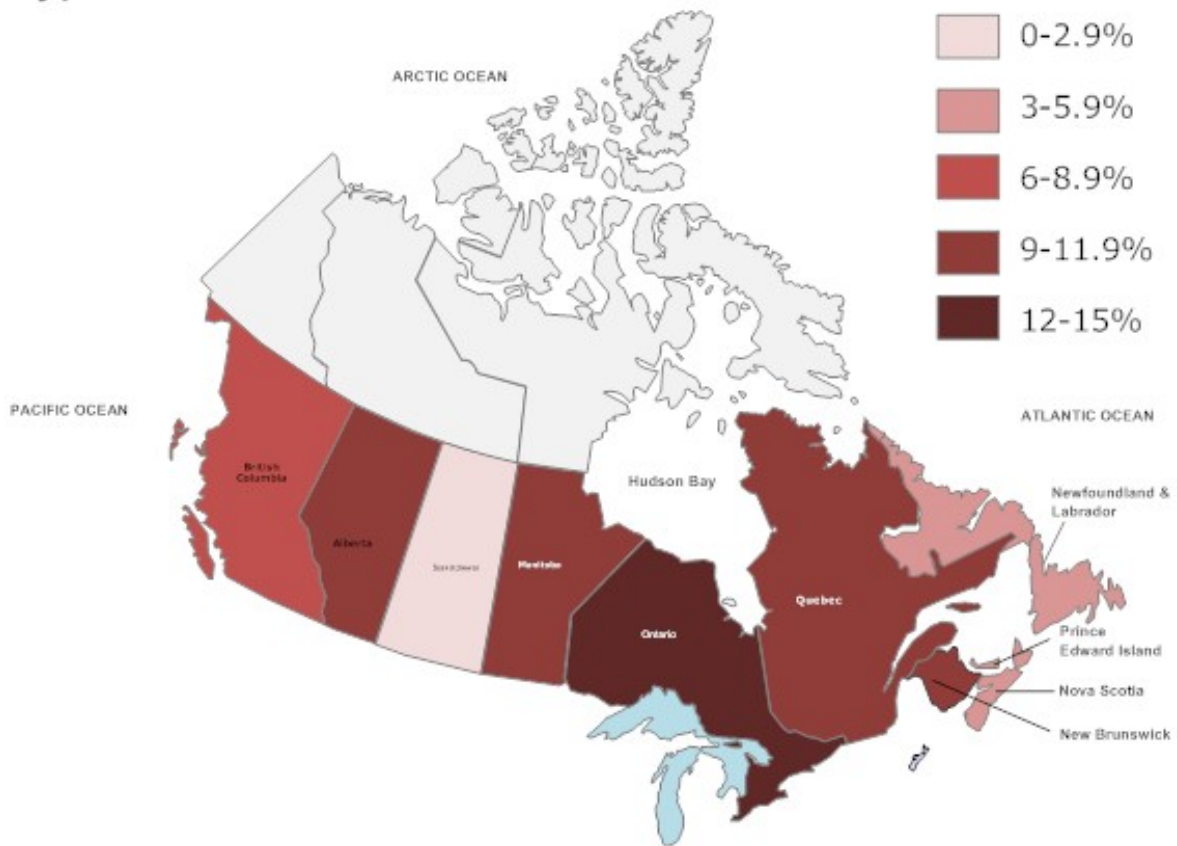
3.5 Geographic variation in the use of IAs across Canada, as initiation therapy in patients with DM

Figure 6: Geographic variation in the use of LAIAs in patients with T1DM (a), and T2DM (b), in Canada

(a) Long-acting IAs

Substantially more patients with T1DM were initiated on LAIAs in Ontario (12.32%) and Alberta (11.60%) than in Saskatchewan (2.96%) and Nova Scotia (3.47%).

Type 1 DM



Source: IMS Health Canada Longitudinal Database- IMS Health Consulting Analysis

Figure 6: Geographic variation in the use of LAIAs in patients with T1DM (a), and T2DM (b), in Canada

(b) Long-acting IAs

For patients with T2DM, substantially more prescriptions for LAIAs as initiation therapy were dispensed in Ontario (11.81%) and Alberta (14.85%) than in Québec (5.55%) and Manitoba (6.59%). (See Figure 6.)

Type 2 DM



Source: IMS Health Canada Longitudinal Database- IMS Health Consulting Analysis

Figure 7: Geographic variation in the use of RAIAs in patients with T1DM (a) and T2DM (b) in Canada

(a) *Rapid-acting IAs*

Substantially more patients with T1DM were initiated on RAIAs in New Brunswick (74.05%) and Nova Scotia (71.53%) than in Saskatchewan (37.87%) and British Columbia (41.23%).

Type 1 DM



Source: IMS Health Canada Longitudinal Database- IMS Health Consulting Analysis

Figure 7: Geographic variation in the use of RAIAs in patients with T1DM (a) and T2DM (b) in Canada

(b) Rapid-acting IAs

For patients with T2DM, substantially more prescriptions for RAIAs, as initiation therapy, were dispensed in Québec (21.05%) and Ontario (17.58%) than in British Columbia (7.37%) and Saskatchewan (10.41%) (Figure 7)

Type 2 DM

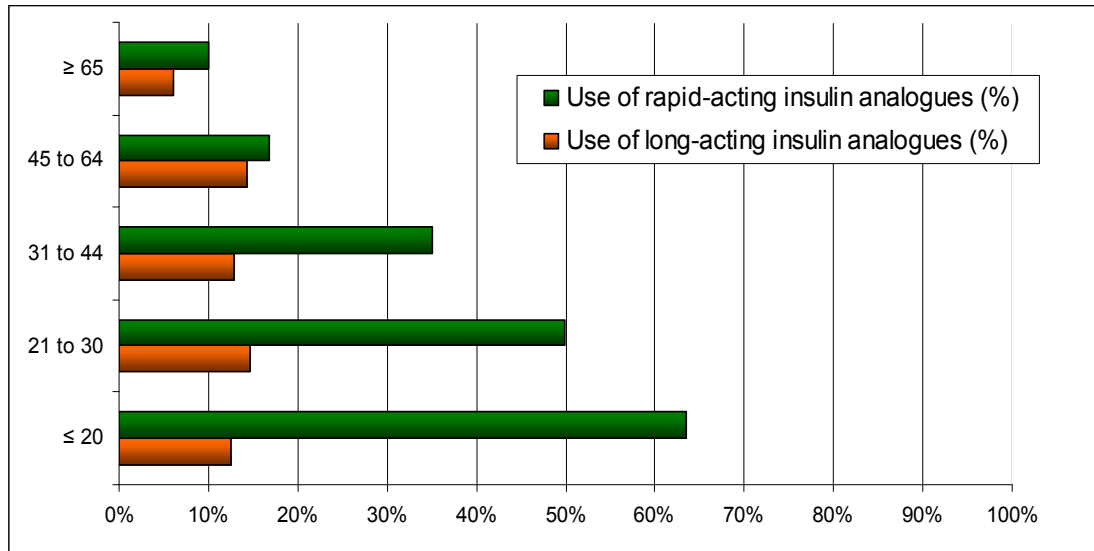


Source: IMS Health Canada Longitudinal Database- IMS Health Consulting Analysis

3.6 Variation in use of LAIAs and RAIAs as initiation therapy, by age, in patients in Canada with T2DM

There is a steady decrease in the use of RAlA as age increases. In contrast, there is a relatively constant use of LAIA for patients' aged <65, and a sudden drop among the senior population (i.e., age ≥ 65). (See Figure 8.)

Figure 8: Use of LAIAs and RAIAs, by age, in patients with T2DM in Canada



LAIAs=long-acting insulin analogues; RAIAs=rapid-acting insulin analogues; T2DM=type 2 diabetes mellitus
Source: *IMS Health Canada Longitudinal Database- IMS Health Consulting Analysis**
Time Period: February 2005-July 2006

4 LIMITATIONS

Several limitations of this study warrant mention. First, data were collected from a sample of pharmacies throughout Canada. This data sample represents 41% of Canadian pharmacies, and not all provinces had equal coverage. Coverage ranged from 73% in New Brunswick to 22% of pharmacies in Saskatchewan.

Second, there are inherent concerns with using data collected from a specific time frame to represent changes over time. The time period covered may be subject to influences that are not present at other time periods, causing spurious results. Influences could result from patients hearing about new drug options, drug manufacturer representatives, or the introduction of new drugs or the discontinuation of others. There are no means of capturing the various factors that may be affecting the data, yet such factors may exert influence on the results. Although this is a problem with any cross-sectional dataset, it is a problem that must be taken into consideration when interpreting results. Furthermore, as with other cross-sectional data, the window of time used may not have been sufficient to capture changes to treatment regimens.

Third, the Longitudinal Database does not contain diagnostic codes. Identification and classification of patients with T1DM or T2DM was determined by a set of rules for which there was no direct means of validating the results. Consequently, the results of some of the demographic findings should be interpreted with caution and may be an artefact of the rules used to classify groups of patients.

Finally, although specific criteria were applied to the data in order to filter unusable records, it may not have been possible to catch errors and omissions that occurred at participating pharmacies during the entry or transmission of data.

5 DISCUSSION AND CONCLUSION

In the current analysis, classification of disease status by therapy suggested that 14% and 86% of patients initiated on an insulin agent in Canada have T1DM and T2DM, respectively. These estimates are similar to those of a large cohort study where 17% and 83% of insulin-treated patients had T1DM and T2DM, respectively¹³.

Despite the limitations of this study, as discussed above, there are a number of lessons to be learned. Patients with T1DM were most often prescribed short-acting HI (13%) or RAIA (36%) in combination with intermediate-acting HI. When short- or intermediate-acting HI was prescribed as initial therapy, few patients (27% and 16%, respectively) switched to insulin analogue use. Only 10% of patients with T1DM were initially prescribed a LAIA, and 6% received both a RAIA and a LAIA.

As might be expected, the pattern of prescribing for patients with T2DM differed from that observed for patients with T1DM. For young patients (aged <65 years) with T2DM, 21% were initially prescribed a therapeutic regimen that included a RAIA, 14% received a regimen that included a LAIA, and 5% received both a RAIA and a LAIA. In contrast, for older patients (aged \geq 65 years) with T2DM, 10% initially received a RAIA and 6% a LAIA.

This difference in prescribing between elderly and young patients, with T2DM, may in part be attributable to differences in coverage/access to insulin products. For instance, most provinces in Canada have publicly-funded drug coverage for elderly patients; however, for the time period of the current analysis, few jurisdictions provided reimbursement for LAIA. In fact, only Québec¹⁵ reimbursed for a LAIA (i.e., insulin glargine) during part of the analysis period.¹⁶ Thus, elderly patients covered by a publicly-funded drug plan may have been more likely to receive insulin NPH than a LAIA. For RAIA use, the difference in prescribing between elderly and young patients, with T2DM, is not as readily apparent and further research is necessary.

Patterns of medication-switching for patients with T2DM were similar to that observed for patients with T1DM. That is, of those who initially received short- or intermediate-acting HI for the management of T2DM, regardless of age, 9% and 10%, respectively, switched to an insulin analogue.

Geographic variation in prescribing of insulin analogues across Canada was apparent. For example, prescribing of insulin analogues was lower in Saskatchewan than in Ontario. This variation may be due to differences in demographic characteristics or in coverage/access to insulin products across jurisdictions. The current data did not allow investigation of the

geographic variation and again further research is necessary to establish the association, if any, between prescribing patterns, demographics and policy.

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