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Original Research

The Impact of Mandatory Nonmedical Switching From Originator to Biosimilar Insulin Glargine

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ABSTRACT

Purpose: This study monitors for early changes in health services utilization after a mandatory policy to switch patients from originator to biosimilar insulin glargine in British Columbia, Canada.

Methods: We conducted a prospective cohort study of patients treated with originator insulin glargine. The policy cohort included patients treated with originator insulin glargine in the 6 months before the policy change (May 27, 2019). Three historical control cohorts included users of originator insulin glargine during the 6 months before May 27 each year in 2016, 2017, and 2018. Patients who discontinued or switched use of the originator insulin glargine and those without cost coverage by the provincial drug plan were excluded. Using likelihood ratios, we compared the daily use of medications, outpatient visits, and hospitalizations in the 12 months after the policy change with the daily use in 3 historical control cohorts. A sustained likelihood ratio above a predefined threshold of 7.1 was interpreted as an early signal of a possible policy impact.

Findings: Each cohort included 15,344 to 17,310 patients. In the first year of the policy, we observed increases in (1) insulin glargine use (the cumulative incidence increased by 2.5% compared with the mean of the 3 historical cohorts), (2) oral antidiabetic medication use (increased by 2.8%), and (3) outpatient visits (increased by 1.4%). Likelihood ratios greater than the threshold of 7.1 were detected for these 3 outcomes.

Implications: We observed marginal changes in health services utilization without detecting signals of negative health impacts on patients targeted by the British Columbia policy of mandatory switching from originator to biosimilar insulin glargine. (*Clin Ther.* 2022;000:1–14.) © 2022 Elsevier Inc.

Key words: biosimilar pharmaceuticals, diabetes mellitus, drug switching, insulin glargine, policy, prospective study.

INTRODUCTION

As worldwide spending on diabetes[1,2] and diabetes treatment[3] continues to increase, public and private drug plan administrators are motivated to consider new coverage policies to keep costs under control. Insulin glargine, a long-acting insulin analogue, is a relatively costly antidiabetic medication that contributes significantly to spending for the health care system and individual patients with diabetes.[4–6] In Canada, the annual cost of insulin glargine in 2018 was an estimated CAD$273 million.[7]

One recent option to optimize health care spending on antidiabetic treatment is to use less costly biosimilar insulin products.[5,8–10] The biosimilars are versions of authorized biological drugs that have similar physicochemical characteristics, efficacy, and safety.[11] For the biosimilar insulin glargine, systematic reviews of randomized clinical trials,[12,13] analyses of real-world data,[14–18] and a pharmacovigilance study[19] have found a similar efficacy and safety profile compared with the originator product. However, because of concerns of some patients and physicians that the biosimilar insulin glargine is associated with more adverse effects or injection reactions than the originator product,[20,21] the growth in market share of these biosimilars has been slow in the United Stated[22] and even slower in Canada.[10]

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In British Columbia, Canada, the cost of insulin glargine is covered by the provincial drug plan PharmaCare through the Limited Coverage Drug Program.[23] On May 27, 2019, the British Columbia Ministry of Health announced a new coverage policy, Phase 1 of the Biosimilars Initiative, which introduced a financial incentive to switch from originator to biosimilar insulin glargine.[24] The policy required patients to switch from originator to biosimilar insulin glargine within a 6-month transition period (May 27, 2019, to November 25, 2019) to maintain coverage. After November 25, 2019, PharmaCare only covered the cost of the biosimilar insulin glargine; coverage for the originator insulin glargine was provided under special clinical circumstances. Individuals enrolled in the First Nations Health Authority were not affected by this policy.[24] This rapid monitoring analysis was planned to detect early signals of change in health services utilization during the first year of the Biosimilars Initiative for insulin glargine. The objective of the study was to compare trends of antidiabetic drug use and health services utilization among insulin glargine users in the year after the policy launch to historical trends.

PARTICIPANTS AND METHODS

Study Design and Setting

We conducted a prospective cohort study of patients treated with originator insulin glargine and who were targeted by the British Columbia's Biosimilars Initiative. Patients were identified based on prescriptions between November 27, 2015, and May 26, 2019, and followed up to May 25, 2020 (previously May 26, 2020). British Columbia residents are eligible for public health insurance under the provincial Medical Services Plan, which covers the cost of medically necessary physician services. Residents are also eligible for optional public drug coverage under the provincial PharmaCare program, which helps to cover the costs of eligible prescription drugs, medical supplies, and pharmacy services. Of 9 different PharmaCare plans, the largest is the income-based Fair PharmaCare plan, in which individuals receive coverage after reaching their annual deductible determined by net income.

Data Source

We analyzed data from the British Columbia Ministry of Health databases, which included linked and anonymized information on registration to the provincial health plan and demographic characteristics; data on prescription drugs filled in community pharmacies (PharmaNet); and diagnoses and procedures from fee-for-service visits to physicians and other practitioners, hospital discharges abstracts (Discharge Abstract Database), and discharges from emergency departments (National Ambulatory Care Reporting System). We did not include federally insured individuals[25] and those enrolled in the First Nations Health Authority.[26] The study protocol was approved by the University of British Columbia Clinical Research Ethics Board.

Utilization of Biosimilar Insulin Glargine in British Columbia

Using longitudinal data, we explored biosimilar utilization (uptake) by individuals enrolled in the British Columbia Medical Services Plan between August 2018 (when biosimilar insulin glargine was first covered by PharmaCare) and May 2020. We presented trends in biosimilar utilization as monthly percentages of all insulin glargine prescriptions filled in community pharmacies, regardless of payer. We also presented data for prescriptions covered by PharmaCare (ie, prescriptions paid by PharmaCare or considered toward the annual deductible requirements).[27]

Study Participants

We identified eligible study participants from a source population of individuals enrolled in the provincial Medical Services Plan anytime between November 27, 2015, and May 27, 2019, the day of the policy launch. For the main analysis, we constructed one prospective policy (intervention) cohort and 3 historical (control) cohorts from the source population. The policy cohort included patients with at least 1 prescription for originator insulin glargine in the 6-month identification period that ended on May 26, 2019. The historical cohort included patients who filled at least 1 prescription for originator insulin glargine in each of the 6-month identification periods that ended on May 26 for the years 2016, 2017, and 2018. We excluded patients who were not targeted by the Biosimilars Initiative (Supplemental Table I): those who discontinued or switched from the originator insulin glargine before entering the cohort on May 27 or those without PharmaCare coverage for insulin glargine. Patients with a follow-up of <1 month were also excluded. Patients were eligible to be included in >1 cohort, depending on their drug use. Illustrations

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of the study design are available in Supplemental Figures 1 and 2. We examined the following patient characteristics for each cohort: age, sex, duration of diabetes (based on the earliest first diagnosis of diabetes or the earliest first prescription of insulin or oral antidiabetic medications), diabetes mellitus type (based on a modification of a tree-structured model[28]), health services utilization in the year before cohort entry (prior medication use, physician visits, or hospital admissions), and comorbidities (measured using the Charlson comorbidity index[29]).

Primary Outcomes

We measured the cumulative incidence of drug utilization and health services outcomes for the 4 cohorts. The main drug utilization outcomes included refilling of insulin glargine (originator or biosimilar), discontinuation and switching of insulin glargine, the use of oral antidiabetic medications, and initiation of a new oral antidiabetic medication. The main health services examined were visits to physicians (any speciality) and nurse practitioners regardless of the diagnosis; visits to physicians (any speciality) and nurse practitioners for a diagnosis of diabetes or imbalance in serum glucose; visits to specialists in internal medicine, geriatric medicine, or endocrinology; inpatient hospital discharges; visits to emergency departments; and discharges from hospital or emergency department with a diagnosis of blood glucose imbalance (hypoglycemia or hyperglycemia). Detailed definitions of the outcomes are reported in Supplemental Table II.

Additional Outcomes

We also presented daily trends of the following outcome measures by cohort: mean quantity of insulin glargine dispensed in units, mean number of days using oral antidiabetic medications, and mean number of outpatient visits to physicians and nurse practitioners. Finally, we explored treatment scenarios in patients from the policy cohort who did not switch to the biosimilar insulin glargine.

Statistical Analysis

We calculated cumulative incidence differences between the policy (intervention) cohort and the mean of the historical (control) cohorts on each successive day during the follow-up period; the historical mean cumulative incidence served as the expected utilization trend in the absence of policy impact. Missing data or data of patients with incomplete follow-up were treated with the last observation carried forward approach. A difference of 0 was interpreted as no effect of the policy on the outcome. Because we measured outcomes daily and reported the results monthly to the Ministry of Health, we did not use statistical tests. In statistical testing, the α error is set for a single comparison.[30] To estimate the strength of the evidence and the degree to which one hypothesis is better supported over another,[31] we used likelihood ratios, defined as the likelihood of the observed cumulative incidence difference relative to no difference. The interpretation of a likelihood ratio remains the same regardless of how many times the data are updated.[32,33] With reference to a $P = 0.05$ and a z score of 1.96, a predefined threshold used to identify a signal was a likelihood ratio of $e^{1.96} = 7.1$, which is interpreted as the observed difference being approximately 7.1 times more likely than a difference of zero and is analogous to an frequentist type 1 error of $\alpha = 0.05$. A signal was detected when repeated updates in the analysis denoted a sustained likelihood ratio of $\geq$7.1 for at least 30 days. Likelihood ratios are less stable in the early days of follow-up because of small number of events; hence, we did not present data from the first 31 days (1 month) of follow-up. As follow-up progressed, likelihood ratios became more stable. The methods were published previously.[33,34]

RESULTS

Utilization of Biosimilar Insulin Glargine in British Columbia

An anticipated increase in the use of the biosimilar insulin glargine was observed after the launch of the Biosimilars Initiative (Figure 1, Supplemental Table III). During the 8 months before the policy launch, 9.1% of insulin glargine prescription refills in British Columbia were for the biosimilar product. Six months after the end of the transition period of the policy, the biosimilar insulin glargine accounted for 79.0% of prescription refills for insulin glargine. During this posttransition period, the biosimilar insulin glargine accounted for 99.2% of prescription refills for insulin glargine covered by PharmaCare.

Rapid Monitoring Cohorts

The policy cohort included 15,344 patients who used originator insulin glargine during the 6-month identification period (Figure 2). The 3 historical cohorts

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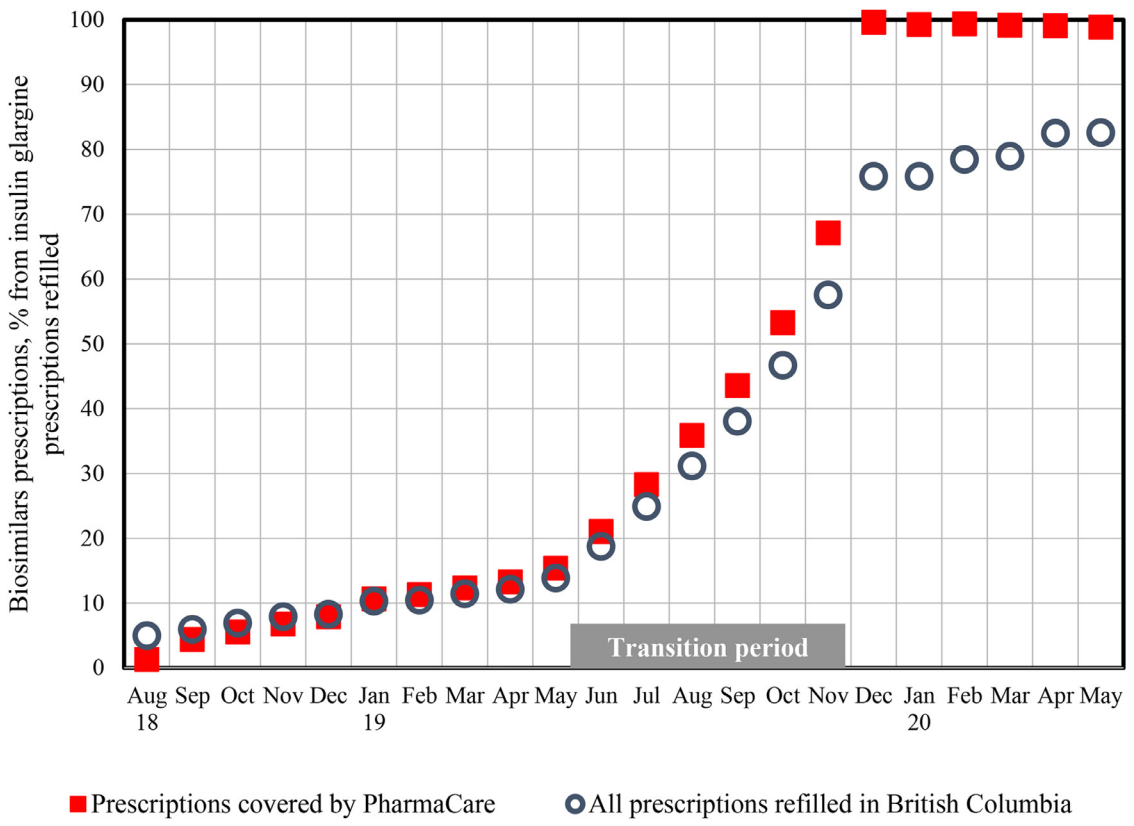

Figure 1. Utilization of the biosimilar insulin glargine by payer in British Columbia from August 2018 to May 2020. Data are presented from August 2018, when coverage for insulin glargine was approved by the British Columbia drug plan PharmaCare. Almost all (99.6%) of the PharmaCare prescriptions for insulin glargine in December 2019 were for the biosimilar. We observed a small decrease in biosimilar prescriptions later (from 99.6% to 98.9% in May 2020), when more patients were eligible for coverage for the originator insulin glargine under special clinical circumstances.

included 15,968 to 17,310 patients with diabetes. The most common exclusion criteria were the absence of PharmaCare coverage (26.6%–29.4% of the patients in each cohort) and discontinuation of treatment (13.3%–14.7%) (Figure 2). The median age of patients in the 4 cohorts ranged from 63.0 to 65.0 years, and 6676 (43.5%) to 7598 (43.9%) of the patients were female (Table I). Most patients were treated for type 2 diabetes mellitus (10,527/15,968 [65.9%] to 10,544/10,544 [68.7%]), and the median duration of diabetes ranged from 18.0 to 19.8 years. Prior medication use, physician visits, hospital admissions, and comorbidities were similar across the cohorts based on data in the year before cohort entry.

By the end of the 6-month transition period, 5938 patients (38.7%) of the policy cohort had transitioned to biosimilar insulin glargine, and at the end of the 1-year follow-up period, 12,044 patients (78.5%) had transitioned (Supplemental Figure 3) versus 3300 patients (21.5%) who had not transitioned. In addition, 424 patients (2.8%) in the policy cohort transitioned back to the originator insulin glargine after using the biosimilar product. Most of the patients who did not transition to biosimlar insulin glargine continued to refill the originator insulin glargine and paid out of pocket or through plans and programs other than PharmaCare (Supplemental Table IV).

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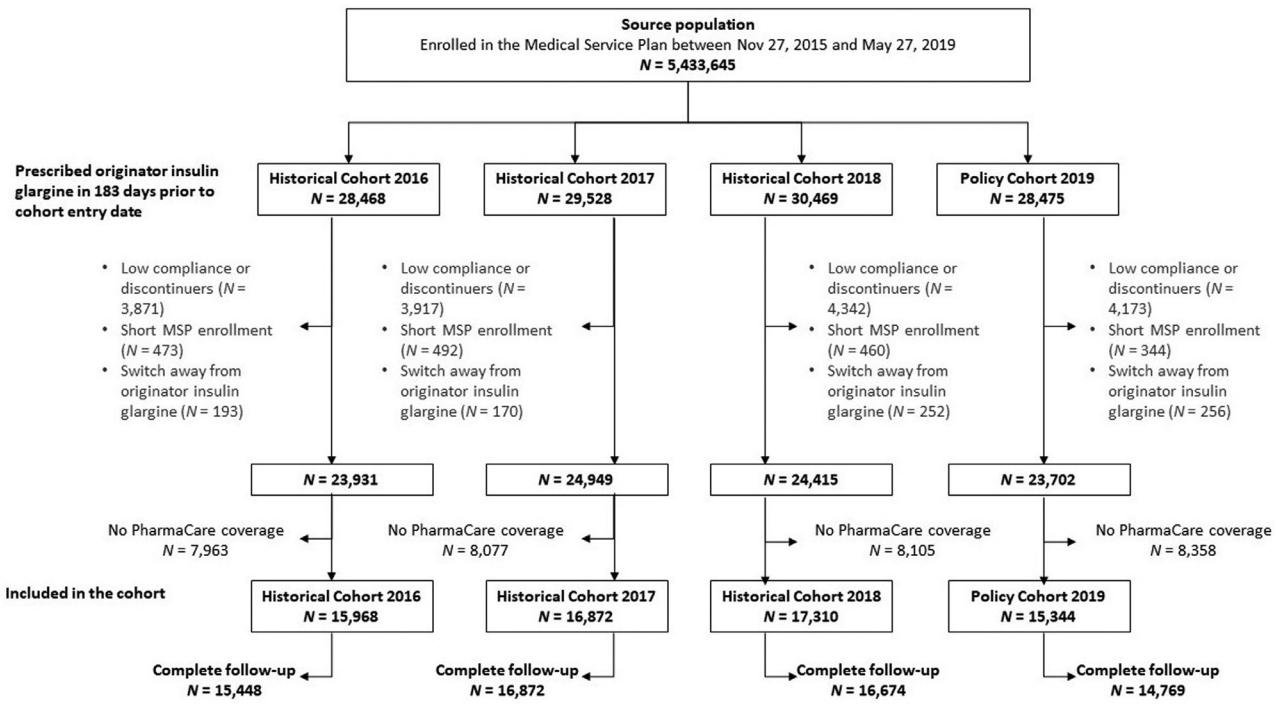

Figure 2. Patient flow diagram for the 3 historical cohorts and the policy cohort. MSP = Medical Services Plan.

Trends in Drug and Health Services Utilization

We detected early signals of an impact from the policy on drug utilization outcomes (Figure 3, Supplemental Table V). The cumulative incidence of insulin glargine prescription refilling by patients in the policy cohort was higher than anticipated, and likelihood ratios were sustained at >7.1 of the threshold from day 91 for the first refilling (maximal cumulative incidence difference of +2.0%), from day 148 for the second refilling (maximal cumulative incidence difference of +1.5%), from day 275 for the third refilling (maximal cumulative incidence difference of +2.2%), and from day 290 for the fourth refilling of insulin glargine (maximal cumulative incidence difference of +2.7%). We also detected a decrease in the cumulative incidence of discontinuing use of insulin glargine between days 32 and 155 and from day 276 (cumulative incidence difference of up to −2.2%, likelihood ratio >7.1). There was a decrease in switching to another long-acting insulin from day 48 onward (cumulative incidence difference of up to −1.3%, likelihood ratio >7.1). We detected a sustained increase in the use of oral antidiabetic medication throughout the follow-up (maximal cumulative incidence difference of +2.8%, likelihood ratio >7.1) and an increase in initation of use of a new oral antidiabetic medication from day 96 (maximal cumulative incidence difference of +2.5%, likelihood ratio >7.1). Although the likelihood ratios for primary outcomes reached the signal threshold, the magnitude of differences was small (up to +2.8%). Trends observed for the secondary drug outcomes matched the trends for the primary drug outcomes. We observed an increase of up to 3.3% in quantity (units) of insulin glargine dispensed from day 290 (Supplemental Figure 4) and an increase of up to 7.0% in the mean number of days with oral antidiabetic medications for the policy cohort (Supplemental Figure 5). To further explore the increase in the use of oral antidiabetic medications, we conducted an ad hoc analysis and detected an increase in the use of the sodium glucose cotransporter 2 (SGLT2) inhibitors among patients in the policy cohort throughout the follow-up period (cumulative incidence difference of 3.8%, likelihood ratios ≥7.1) (Supplemental Figure 6). Oral glucagon-like peptide 1 agonists, which were available in Canada beginning April 2020, were not

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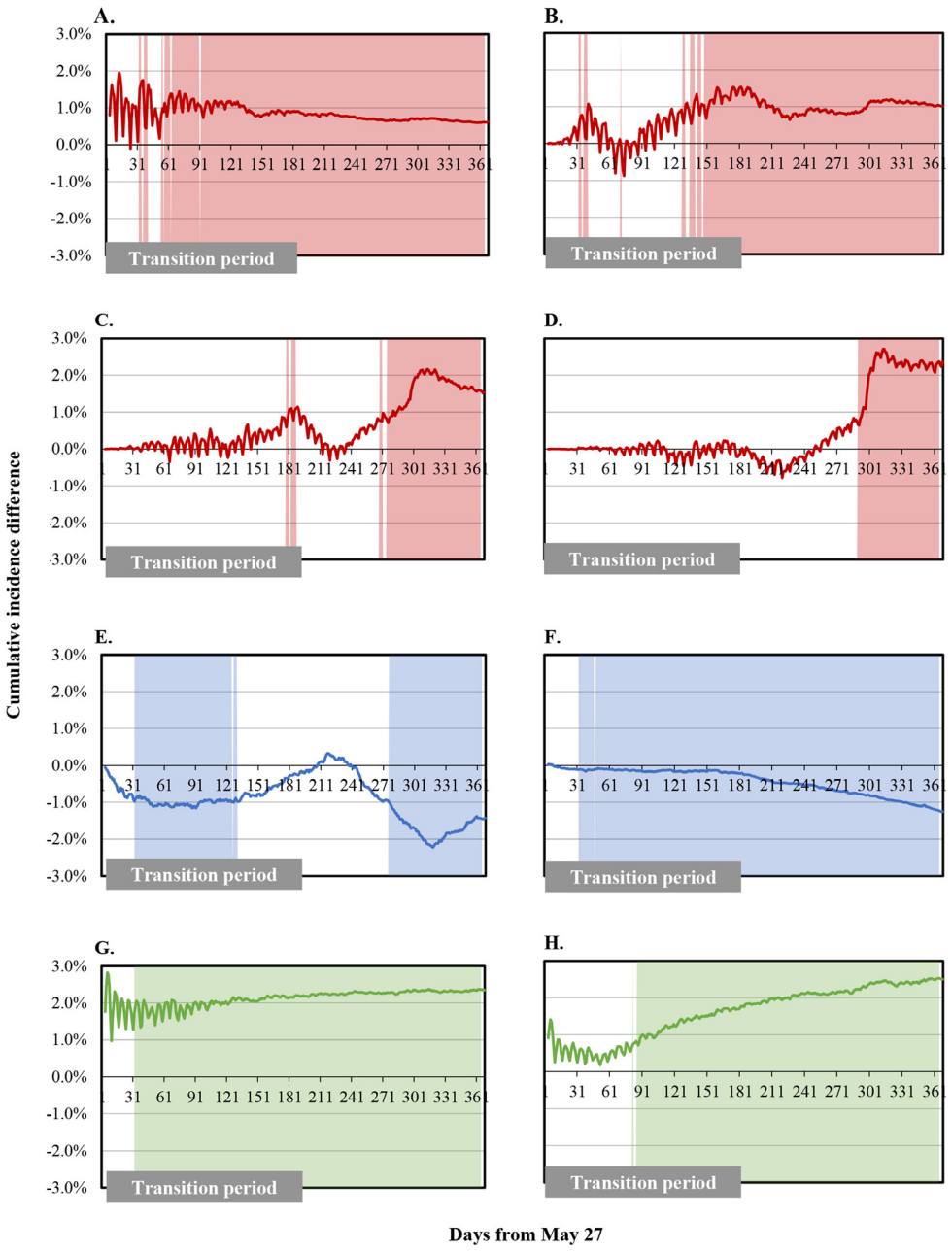

Figure 3. Drug utilization outcomes (cumulative incidence difference by day of follow-up). The lines represent the cumulative incidence difference between the policy cohort and the mean of historical cohorts for the first (A), second (B), third (C), and fourth (D) refilling of insulin glargine (originator or biosimilar), discontinuation of insulin glargine (E), switching to another different long-acting insulin (F), the first refilling of an oral antidiabetic medication (G), and initiation of an antidiabetic drug after 6 months without this drug (H). Values >0 should be interpreted as an increase in this outcome for patients included in the policy cohort.

Shaded areas represent days with likelihood ratios >7.1. Likelihood ratios were not computed during the first 31 days of follow-up. A cumulative incidence difference between the policy and historical cohorts was considered a signal if the likelihood ratio was sustained above the threshold of 7.1 for at least 30 days.

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Table I. Patient characteristics by cohort.

Characteristic	Historical cohorts			Policy cohort, 2019 (n = 15,344)
	2016 (n = 15,968)	2017 (n = 16,872)	2018 (n = 17,310)	
Age, median (range), y	63.0 (2.0–105.0)	64.0 (2.0–105.0)	64.0 (3.0–106.0)	65.0 (4.0–101.0)
Age <18 years, No. (%)	210 (1.3)	214 (1.3)	221 (1.3)	145 (0.9)
Female, No. (%)	6921 (43.3)	7327 (43.4)	7598 (43.9)	6676 (43.5)
Duration of diabetes, median (range), y[a]	18.0 (0.0-31.4)	18.4 (0.0-32.4)	18.9 (0.0-33.4)	19.8 (0.8-34.4)
Diabetes mellitus type, No. (%)[b]				
Type 1	2130 (13.3)	2197 (13.0)	2230 (12.9)	1943 (12.7)
Type 2	10,527 (65.9)	11,313 (67.1)	11,769 (68.0)	10,544 (68.7)
Unknown	3311 (20.7)	3362 (19.9)	3311 (19.1)	2857 (18.6)
Health services utilization in the year before cohort entry, median (range)				
No. of different oral antidiabetic medications	1.0 (0.0–5.0)	1.0 (0.0–6.0)	1.0 (0.0–6.0)	1.0 (0.0–6.0)
No. of different medications	11.0 (1.0–57.0)	11.0 (1.0–44.0)	11.0 (1.0–51.0)	11.0 (1.0–48.0)
No. of visits to physician's offices, median (range)[c]	18.0 (0.0–262.0)	18.0 (0.0–272.0)	18.0 (0.0–278.0)	18.0 (0.0–303.0)
Patients admitted to hospital, No. (%)	5338 (33.4)	5678 (33.7)	5847 (33.8)	5000 (32.6)
Charlson Comorbidity Index[d]				
0	6958 (43.6)	7285 (43.2)	7444 (43.0)	6592 (43.0)
1–2	5113 (32.0)	5444 (32.3)	5530 (31.9)	4834 (31.5)
≥3	3897 (24.4)	4143 (24.6)	4336 (25.0)	3918 (25.5)

[a] On the basis of the first diagnosis of diabetes or first prescription of insulin or oral antidiabetic medications, whichever was earlier.
[b] Type 1 and type 2 diabetes mellitus were identified based on a modification of a tree-structured model by Lo-Ciganic et al.[29]
[c] Visits to physicians or nurse practitioners, excluding visits to emergency department, hospital day care, private medical or surgical facility, and inpatients visits.
[d] Charlson Comorbidity Index[30] included complicated diabetes mellitus.

dispensed for the policy cohort during the follow-up period.

Trends of first and second outpatient visits to physicians (any specialty, any diagnosis) and nurse practitioners remained the same in the policy cohort compared with the historical cohorts (Figure 4, Supplemental Table V). We detected a signal of an increase in third visits between days 162 and 313 (maximal cumulative incidence difference of 1.1%, likelihood ratio >7.1) and fourth visits between days 147 and 229 (maximal cumulative incidence difference of 1.4%, likelihood ratio >7.1). Overall, we did not observe a difference in the mean number of outpatient visits to physicians and nurse practitioners during the 1-year follow-up; patients had a mean of 23 to 24 visits in each cohort (Supplemental Figure 7). We detected

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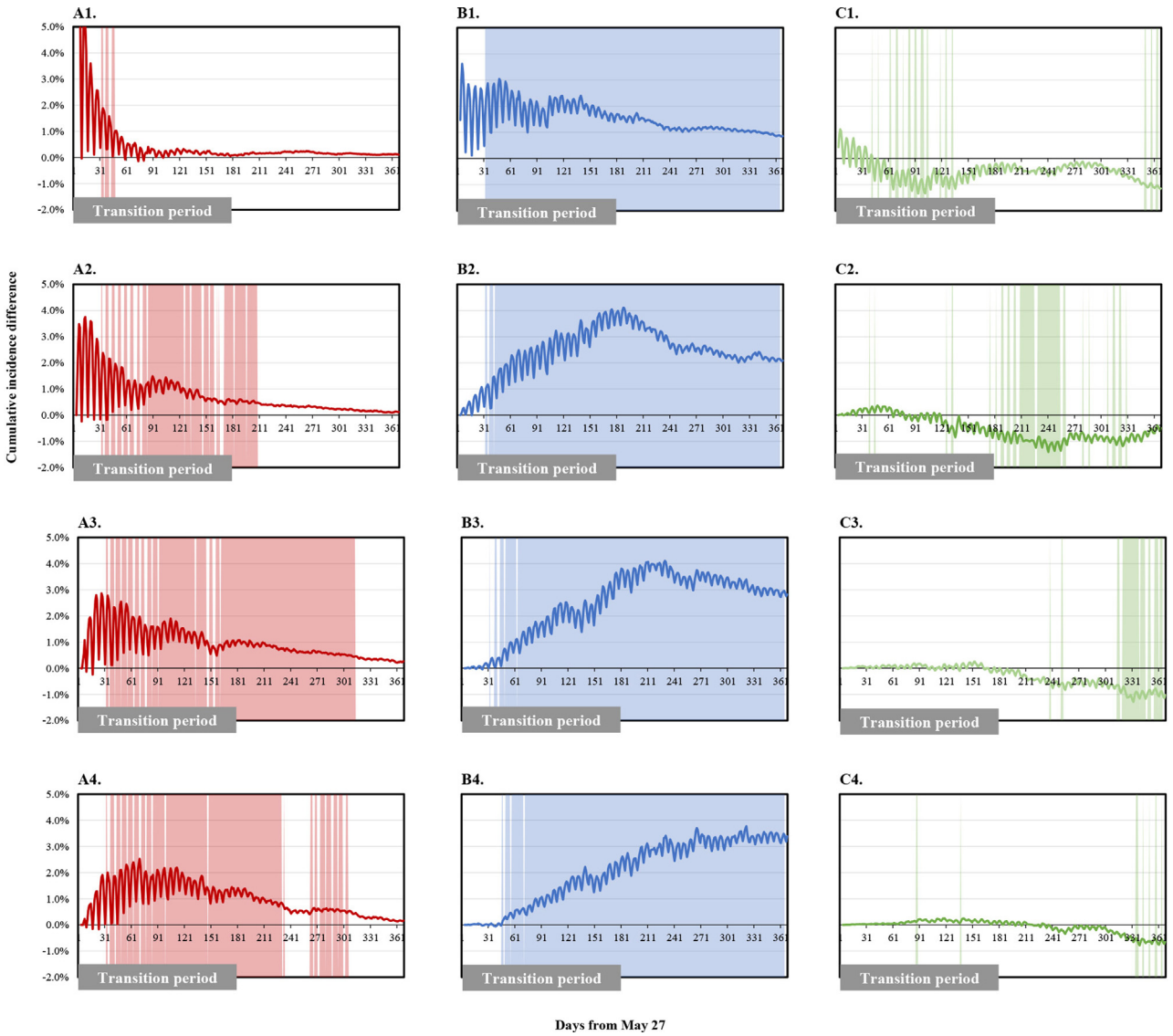

Figure 4. Visits to a physician (cumulative incidence difference by day of follow-up). The lines represent the cumulative incidence difference between the policy cohort and the mean of historical cohorts for the first 4 visits to (A) a physician of any specialty or nurse practitioner, (B) a physician of any specialty or nurse practitioner with a diagnosis of diabetes or imbalance in blood glucose, and (C) to a specialist (internal medicine, geriatric medicine, or endocrinology). Values >0 should be interpreted as an increase in visits for patients included in the policy cohort. Shaded areas represent days with likelihood ratios >7.1. Likelihood ratios were not computed during the first 31 days of follow-up. A cumulative incidence difference between the policy and historical cohorts was considered a signal if the likelihood ratio was sustained above the threshold of 7.1 for at least 30 days.

signals of an increase in visits with a diagnosis of diabetes or serum glucose imbalance up to 4.1%. Likelihood ratios were sustained at >7.1 throughout the study period for first visits and from days 43, 64, and 72 for the second, third, and fourth visits with a diagnosis of diabetes or serum glucose imbalance, respectively. No differences were found in visits to a specialist (Figure 4). In an ad hoc analysis, we observed

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among the source population of British Columbia residents from 2016 to 2019 that 77% of insulin glargine prescriptions were by family practitioners.

No impact of the policy was found on visits to emergency departments and discharges from hospital or emergency department with a diagnosis of blood glucose imbalance (hypoglycemia or hyperglycemia) (Figure 5, Supplemental Table V). We observed a small (+0.6%) and transient (lasted 32 days) increase in hospital discharges.

DISCUSSION

This is the first study to monitor the impacts of a mandatory nonmedical switching policy from originator to biosimilar insulin glargine. As anticipated, the market share of biosimilar insulin glargine among all insulin glargine products increased as patients initiated or switched to biosimilar insulin glargine after the launch of the Biosimilars Initiative. The impact of the financial incentive introduced by similar policies has previously been reported in the United States; Medicaid market share of the biosimilar insulin glargine increased quickly after the approval of this product.[22] We detected unanticipated increases in the use of (any) insulin glargine and oral antidiabetic medications, specifically SGLT2 inhibitors, among patients in the policy cohort compared with those in the historical cohorts. We also observed an anticipated increase in visits to physicians.

The unanticipated increase in insulin glargine prescription refilling and in the quantity of medication dispensed for patients in the policy cohort was detected. One explanation may be that patients who switched to the biosimilar product required higher doses of insulin glargine to control blood glucose levels. However, this explanation is unlikely because previous studies have found similar efficacy and effectiveness of originator and biosimilar insulin glargine[12–18] with no dose adjustment required.[15,35] Research indicates that switching from originator to biosimilar insulin glargine is associated with further lowering of blood glucose, even without an increase in insulin dose.[36] A second explanation may be related to the observed decrease in discontinuation and switching away from insulin glargine. To the best of our knowledge, no studies have been published on persistence or adherence after switching from originator to biosimilar insulin glargine. Studies of other biosimilars observed similar[37] or longer[38] persistence on biosimilar products. An alternative explanation may be that the observed increase in cumulative incidence of the third and fourth insulin glargine refilling may have been an impact of the COVID-19 pandemic, specifically, the result of patients stockpiling medications for chronic conditions in the early days of the pandemic.[39]

Increases were detected in refilling prescriptions and initiating use of oral antidiabetics overall. These increases in the use of oral antidiabetic medications were mainly attributable to the increased use of SGLT2 inhibitors. We found that the proportions of patients with type 2 diabetes and those with a previous history of oral antidiabetic therapy in the policy cohort were similar to those in the historical cohorts. Therefore, the observed differences were unlikely to be attributable to confounders related to diabetes type. The most likely explanation is that these trends were unrelated to the Biosimilars Initiative but rather associated with new recommendations for antidiabetic pharmacotherapy and new PharmaCare coverage for empagliflozin. New diabetes guidelines from 2019 recommended adding SGLT2 inhibitors for patients with established atherosclerotic cardiovascular disease[21,40] or poor glycemic control (instead of intensifying the insulin therapy).[21] The new guidelines could also explain the observed decrease in discontinuing or switching use from insulin glargine. In addition, at the time of the launch of the Biosimilars Initiative, PharmaCare added cost coverage for the first SGLT2 inhibitor empagliflozin,[41] which was followed by an anticipated increase in the use of this medication.

Finally, the observed increase in visits to a physician was anticipated after the policy launch. Similar increases were found after switch policies for other biosimilar medications[42–45] because patients visited their prescribing physician to discuss switching and its possible effects.

One of the main strengths of this study is the generalizability of the findings. This large population-based study used administrative data from a universal health care system that provides services to all British Columbians. Moreover, using our rapid monitoring method, we were able to provide policymakers with timely assessments of the impacts of the policy—usually within a couple of weeks of receiving the utilization data. The use of likelihood ratios allowed for multiple comparisons and could be implemented in other evaluation studies. This study also has several limitations. The signals we measured were associations

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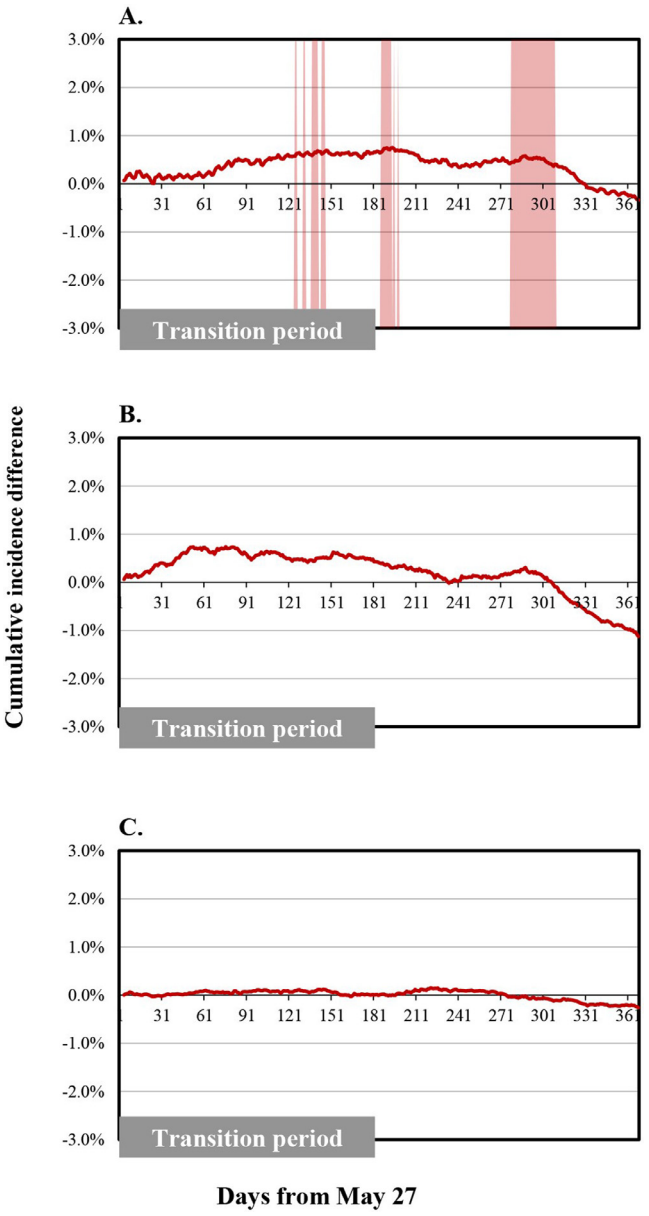

Figure 5. Cumulative incidence difference by day of follow-up: inpatient hospital discharges (A), visits to emergency department (B), and discharges from hospital or emergency department with a diagnosis of blood glucose imbalance (hypoglycemia or hyperglycemia) (C). The lines represent the cumulative incidence difference between the policy cohort and the mean of historical cohorts. Values >0 should be interpreted as an increase in the policy cohort. Shaded areas represent days with likelihood ratios >7.1. Likelihood ratios were not computed during the first 31 days of follow-up. A cumulative incidence difference between the policy and historical cohorts was considered a signal if the likelihood ratio was sustained above the threshold of 7.1 for at least 30 days.

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only and may be explained by unmeasured factors. We did not account for correlations because of repeated measures of the same patient included in multiple cohorts. In addition, the follow-up was limited to 1 year and therefore we were unable to detect possible delayed impacts. We did not assess clinical outcomes directly but rather assessed outcome proxies. Finally, the study was designed to detect signals of possible impacts; additional hypothesis-testing studies are warranted to investigate unanticipated and unexplained outcomes.

CONCLUSIONS

Two key conclusions can be drawn from this analysis. First, a financial incentive for patients had a large impact on medication use in this study. Most patients in our population switched from an originator product, which was no longer covered by PharmaCare, to the reimbursed biosimilar drug. Second, regulatory and reimbursement agencies can be assured that no signals of negative impacts on health services use were detected during the first year of the mandatory switching policy. The results of this analysis should encourage decision makers and health care managers to consider similar biosimilar policies as part of a broad approach to optimize treatments—leveraging the health care savings from such policies to increase access to improved treatment options.

DECLARATION OF INTEREST

None declared.

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APPENDIX SUPPLEMENTARY MATERIALS

Table S1. Study design cohort exclusion criteria.

Criterion	Details
Discontinued the originator insulin glargine before cohort entry	Without remaining supply of the originator insulin glargine on May 27, or without a refill in the 100 days before (excluding) May 27 (February 15 – May 26). Mean days supplied for prescriptions of the originator insulin glargine during the identification period were 39.9 days, median 30 days. Over 99% of the refills were dispensed within 100 days of the previous dispensation of originator insulin glargine.
Switched to another long-acting insulin before cohort entry	Dispensing of any of the following medications between the originator refill date and May 26: a refill record of insulin detemir, insulin degludec, or insulin glargine in the products Soliqua, Toujeo SoloStar and Toujeo DoubleStar.
Transitioned to an insulin glargine biosimilar before cohort entry	Dispensing of an insulin glargine biosimilar (Basaglar) between the originator refill date and May 26.
Short follow-up	End of health plan enrollment during the first month of follow-up (from May 28 to June 27).
No PharmaCare coverage	Zero refills of originator insulin glargine accepted by PharmaCare during the identification period.

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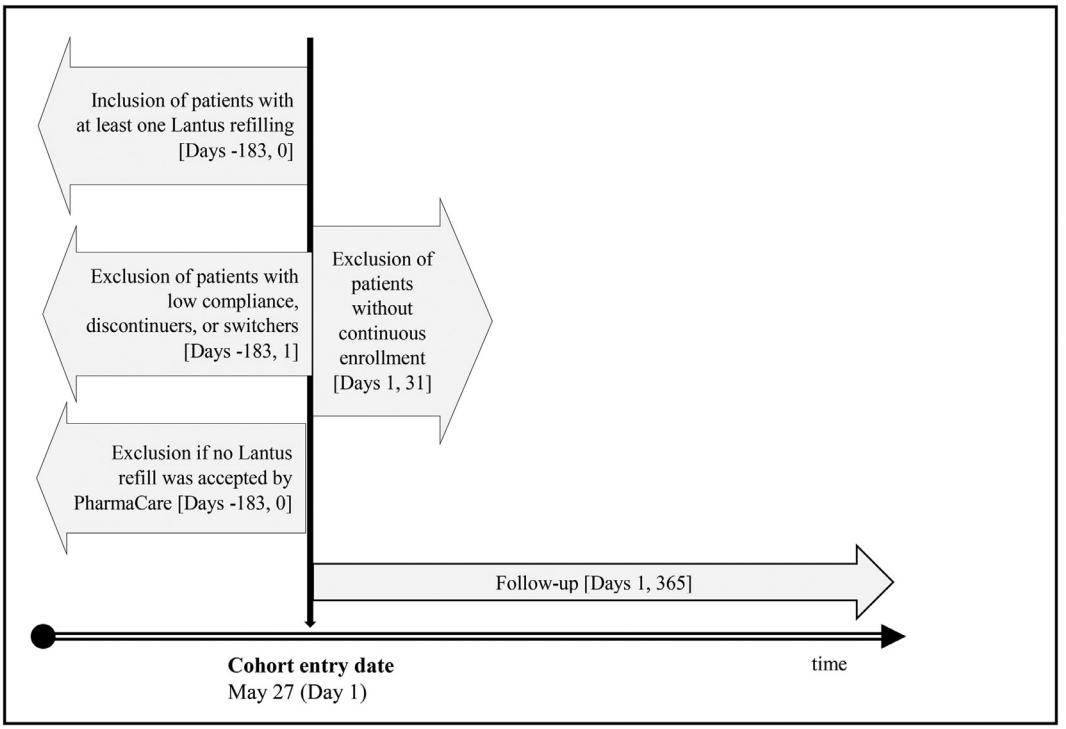
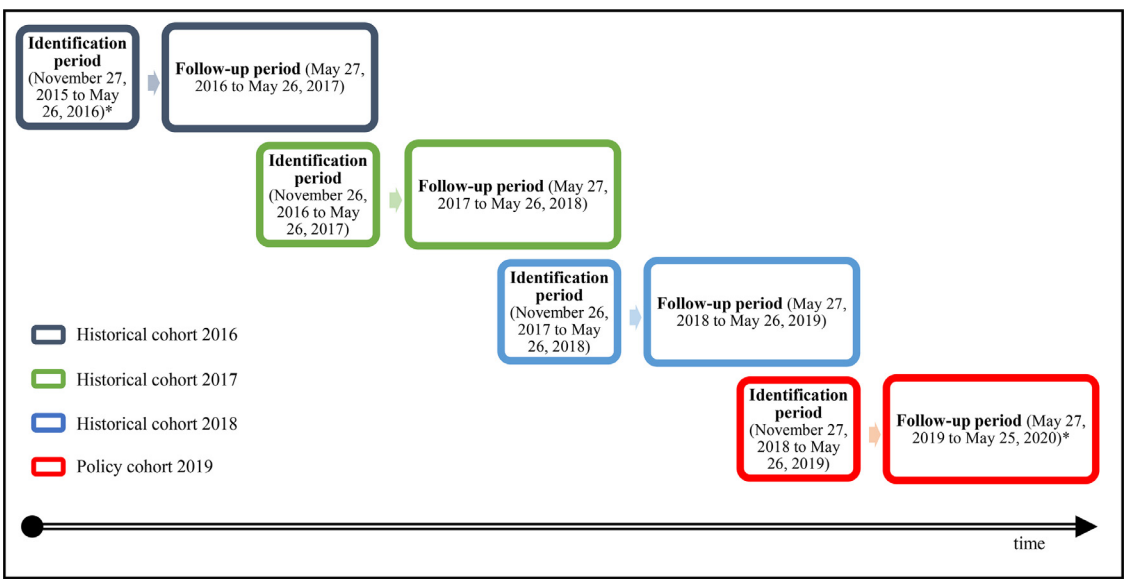


Supplemental Figure S1. Study Design: Rapid Monitoring Cohort of Users of Originator Insulin Glargine.



Supplemental Figure S2. Study Design: Identification and Follow-up Periods.

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Table S2. Study design outcome definitions. ATC, Anatomical Therapeutic Chemical; ICD, International Statistical Classification of Diseases and Related Health Problems.

Outcome	Definition	Data Source	Comments
Main Outcomes			
Drug Outcomes			
Transition to the biosimilar insulin glargine	First refill of biosimilar insulin glargine from (and including) May 27, 2019 to May 25, 2020	PharmaNet	Assessed for the policy cohort only
Refills of insulin glargine (originator or biosimilar)	First, second, third, and fourth refilling events of insulin glargine (Lantus or Basaglar) for patients in each cohort. ATC code A10AE04	PharmaNet	
Discontinuation of insulin glargine	Exhaustion of insulin glargine days' supply (originator or biosimilar) before a medication-free gap longer than 60 days; or switch to another long-acting insulin. ATC codes: insulin detemir A10AE05; insulin degludec A10AE06, A10AE56; Toujeo Solostar A10AE04; Soliqua A10AE54	PharmaNet	
Switch away from insulin glargine	First refill of another long-acting insulin ATC codes: insulin detemir A10AE05; insulin degludec A10AE06, A10AE56; Toujeo Solostar A10AE04; Soliqua A10AE54	PharmaNet	
Use of oral antidiabetic medications	First refill of an oral antidiabetic medication. ATC codes A10B: metformin A10BA02; glibenclamide A10BB01; chlorpropamide A10BB02; tolbutamide A10BB03; gliclazide A10BB09; glimepiride A10BB12; metformin and rosiglitazone A10BD03; metformin and sitagliptin A10BD07; metformin and saxagliptin A10BD10; metformin and linagliptin A10BD11; metformin and alogliptin A10BD13; metformin and dapagliflozin A10BD15; metformin and canagliflozin A10BD16; linagliptin and empagliflozin A10BD19; metformin and empagliflozin A10BD20; acarbose A10BF01; rosiglitazone A10BG02; pioglitazone A10BG03; sitagliptin A10BH01; saxagliptin A10BH03; alogliptin A10BH04; linagliptin A10BH05; exenatide A10BJ01; liraglutide A10BJ02; lixisenatide A10BJ03; dulaglutide A10BJ05; semaglutide A10BJ06; dapagliflozin A10BK01; canagliflozin A10BK02; empagliflozin A10BK03; ertugliflozin A10BK04; repaglinide A10BX02; nateglinide A10BX03	PharmaNet	

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Table S2. (*continued*)

Outcome	Definition	Data Source	Comments
Initiation of a new oral antidiabetic medication	First refill of an oral antidiabetic medication without dispensing of this medication in the prior 6 months. ATC codes A10B: metformin A10BA02; glibenclamide A10BB01; chlorpropamide A10BB02; tolbutamide A10BB03; gliclazide A10BB09; glimepiride A10BB12; metformin and rosiglitazone A10BD03; metformin and sitagliptin A10BD07; metformin and saxagliptin A10BD10; metformin and linagliptin A10BD11; metformin and alogliptin A10BD13; metformin and dapagliflozin A10BD15; metformin and canagliflozin A10BD16; linagliptin and empagliflozin A10BD19; metformin and empagliflozin A10BD20; acarbose A10BF01; rosiglitazone A10BG02; pioglitazone A10BG03; sitagliptin A10BH01; saxagliptin A10BH03; alogliptin A10BH04; linagliptin A10BH05; exenatide A10BJ01; liraglutide A10BJ02; lixisenatide A10BJ03; dulaglutide A10BJ05; semaglutide A10BJ06; dapagliflozin A10BK01; canagliflozin A10BK02; empagliflozin A10BK03; ertugliflozin A10BK04; repaglinide A10BX02; nateglinide A10BX03	PharmaNet	
Other Health Services			
Visits to physicians (any speciality) and nurse practitioners	Visits in an outpatient setting (excludes hospital inpatient, hospital emergency, hospital day care (surgery), and private medical/surgical facilities)	Fee-for-service visits to physicians and other providers	
Visits with a diagnosis of diabetes or imbalance in serum glucose	Visits to physicians and nurse practitioners with diagnosis codes (ICD-9) 249.x, 250.x, 251.0, 251.1, 251.2, 790.2	Fee-for-service visits to physicians and other providers	
Visits to specialists	Visits to physicians with a specialty in internal medicine, geriatric medicine, and endocrinology	Fee-for-service visits to physicians and other providers	

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Table S2. (*continued*)

Outcome	Definition	Data Source	Comments
Inpatient hospital discharges	Discharge from hospital for any cause, excluding same-day discharges	Discharge Abstract Database	Data from the Discharge Abstract Database were not available for the last two months of the post-policy period due delayed updates to this database
Visits to emergency departments	Discharge from emergency department, excluding visits associated with a hospital admission or death on/after arrival	National Ambulatory Care Reporting System	
Discharges from hospital or emergency department with a diagnosis of blood glucose imbalance (hypo- or hyperglycemia)	Discharges from hospital or emergency department (as defined above) with diagnosis codes (ICD-10) E10.0, E11.0, E12.0, E13.0, E14.0, E10,1, E11.1, E12.1, E13.1, E14.1, E15, E16.2	Discharge Abstract Database, National Ambulatory Care Reporting System	
Secondary Outcomes			
Average cumulative quantity of insulin glargine (Lantus or Basaglar) dispensed per patient, in units	Computed as the cumulative quantity of insulin glargine dispensed daily divided by the total number of patients in the cohort. The cumulative quantity were calculated from the strength of the product and the number of packages dispensed.	PharmaNet	

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Table S2. (*continued*)

Outcome	Definition	Data Source	Comments
Average cumulative number of days on oral antidiabetic medications	Days were calculated based on days supply in the disepnsing records. ATC codes A10B:: metformin A10BA02; glibenclamide A10BB01; chlorpropamide A10BB02; tolbutamide A10BB03; gliclazide A10BB09; glimepiride A10BB12; metformin and rosiglitazone A10BD03; metformin and sitagliptin A10BD07; metformin and saxagliptin A10BD10; metformin and linagliptin A10BD11; metformin and alogliptin A10BD13; metformin and dapagliflozin A10BD15; metformin and canagliflozin A10BD16; linagliptin and empagliflozin A10BD19; metformin and empagliflozin A10BD20; acarbose A10BF01; rosiglitazone A10BG02; pioglitazone A10BG03; sitagliptin A10BH01; saxagliptin A10BH03; alogliptin A10BH04; linagliptin A10BH05; exenatide A10BJ01; liraglutide A10BJ02; lixisenatide A10BJ03; dulaglutide A10BJ05; semaglutide A10BJ06; dapagliflozin A10BK01; canagliflozin A10BK02; empagliflozin A10BK03; ertugliflozin A10BK04; repaglinide A10BX02; nateglinide A10BX03	PharmaNet	
Average cumulative number of outpatient visits to physicians and nurse practitioners	Visits in an outpatient setting (excludes hospital inpatient, hospital emergency, hospital day care (surgery), and private medical/surgical facilities)	Fee-for-service visits to physicians and other providers	
Potential reasons for not switching to a biosimilar	Among patients without exposure to the biosimilar at any time during follow-up, the potential reasons were: switch to another long-acting insulin, continued on the originator after the transition period, died or emigrated from the province, had medication to cover the end of follow-up, or discontinued the use of insulin glargine	PharmaNet	Assessed for the policy cohort only

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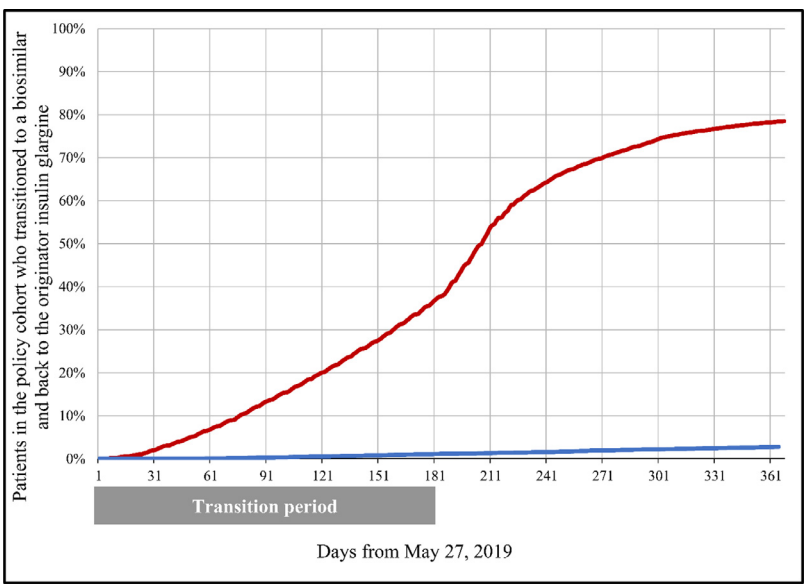
Table S3. The biosimilar insulin glargine (IGla) by payer in British Columbia

	Before policy launch (September 2018 – April 2019)	After the end of transition period (November 2019 – May 2020)
Prescriptions covered by PharmaCare		
Number of IGla prescriptions per month	10,457	10,113
Number of biosimilar IGla prescriptions per month (% from all IGla precriptions)	931 (8.9)	10,035 (99.2)
All British Columbia prescriptions		
Number of IGla prescriptions per month	15,697	16,443
Number of biosimilar IGla prescriptions per month (% from all IGla precriptions)	1,430 (9.1)	12,993 (79.0)



Supplemental Figure S3. Transitioning to the biosimilar insulin glargine (red) and transitioning back (blue) for the policy cohort. The red line presents cumulative incidence of transitioning, defined as the first prescription refill of the biosimilar insulin glargine during the follow-up. The blue line presents cumulative incidence of transitioning back, defined as the first prescription refill of the originator insulin glargine after using its biosimilar.

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Table S4. Number of outcome events during the follow-up, by cohort

Outcome	Historical Cohorts 2016 (n = 15,968)	2017 (n = 16,872)	2018 (n = 17,310)	Policy Cohort 2019 (n = 15,344)
Follow-up patient-years, total (mean)	15,707 (0.98)	16,586 (0.98)	17004 (0.98)	15065 (0.98)
First refilling of insulin glargine (originator or biosimilar)	15,456	16,382	16,691	14,944
Second refilling of insulin glargine (originator or biosimilar)	14,853	15,724	15,946	14,392
Third refilling of insulin glargine (originator or biosimilar)	13,793	14,507	14,755	13,410
Fourth refilling of insulin glargine (originator or biosimilar)	11,934	12,516	12,728	11,740
Discontinuation of insulin glargine	4,679	5,129	5,274	4,965
Switching to another long-acting insulin	470	670	687	364
First refilling of an oral antidiabetic medication	9,177	9,762	10,270	9,249
Initiation of an antidiabetic medication after 6 months without this drug	5,563	5,781	6,075	5,713
First visit to a physician of any specialty or nurse practitioner	15,800	16,687	17,109	15,192
Second visit to a physician of any specialty or nurse practitioner	15,660	16,515	16,964	15,053
Third visit to a physician of any specialty or nurse practitioner	15,461	16,323	16,767	14,892
Fourth visit to a physician of any specialty or nurse practitioner	15,227	16,113	16,543	14,671
First visit to a physician of any specialty or nurse practitioner with a diagnosis of diabetes or imbalance in blood glucose	15,119	15,975	16,395	14,671
Second visit to a physician of any specialty or nurse practitioner with a diagnosis of diabetes or imbalance in blood glucose	13,880	14,739	15,110	13,707
Third visit to a physician of any specialty or nurse practitioner with a diagnosis of diabetes or imbalance in blood glucose	12,181	13,070	13,308	12,239
Fourth visit to a physician of any specialty or nurse practitioner with a diagnosis of diabetes or imbalance in blood glucose	10,132	10,907	11,188	10,363
First visit to a specialist (internal medicine, geriatric medicine, or endocrinology)	8,560	9,034	9,321	8,084
Second visit to a specialist (internal medicine, geriatric medicine, or endocrinology)	5,979	6,314	6,484	5,676

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Table S4. (*continued*)

Outcome	Historical Cohorts 2016 (n = 15,968)	2017 (n = 16,872)	2018 (n = 17,310)	Policy Cohort 2019 (n = 15,344)
Third visit to a specialist (internal medicine, geriatric medicine, or endocrinology)	3,872	4,042	4,052	3,532
Fourth visit to a specialist (internal medicine, geriatric medicine, or endocrinology)	2,314	2,395	2,393	2,115
Inpatient hospital discharges	3,279	3,619	3,737	3,199
Visits to emergency department	4,481	4,796	4,993	4,192
Discharges from hospital or emergency department with a diagnosis of blood glucose imbalance (hypo- or hyperglycemia)	927	1,066	1,083	900

Table S5. Potential reasons for not switching to a biosimilar.

Potential Reason	N (% of non-switchers)
Switched away from originator insulin glargine to another long-acting insulin without experiencing biosimilar insulin glargine, either before or after this switching[a]	255 (7.7)
to insulin degludec	192 (5.8)
to insulin detemir	22 (0.7)
to Toujeo Solostar or Soliqua	43 (1.3)
Continued to refill originator insulin glargine after the transition period but starting on November 26th, the medication was	
paid by PharmaCare	10 (0.3)
paid out-of-pocket or through plans/programs other than PharmaCare	2,031 (61.5)
Died or emegrated from the province	309 (9.4)
Had medication to cover May 25, 2020	0 (0)
Discontinued the use of insulin glargine[b], or unknown[c]	695 (21.0)

[a] Numbers are smaller than in manuscript **Figure 3E** because patients who received the biosimilars before or after switching to different long-acting insulin were not included here.

[b] Please refer to **Supplemental Table S2** for a definition of discontinuation. Numbers are smaller than in manuscript **Figure 3F** because the figure included all patients, and not only non-switchers.

[c] We considered status as unknown when discontinuation could not be discerned (i.e., less than 60 days had passed since the end of days' supply of the last dispensation). There were fewer than 6 patients with this status; this number is masked to comply with privacy requirements.

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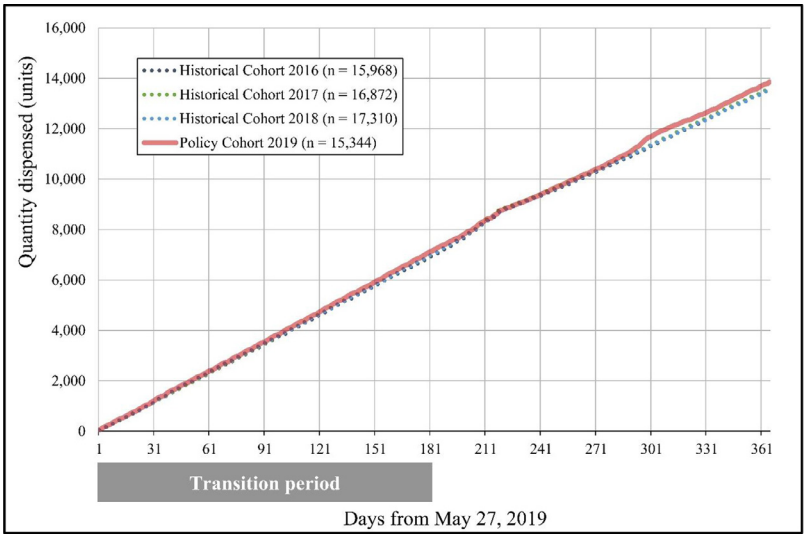

Supplemental Figure S4. Average quantity of insulin glargine dispensed in units, by cohort. Trends in the historical cohorts were homogeneous throughout the follow-up. By the end of the one-year follow-up, patients were dispensed between 13,528 and 13,605 units of insulin glargine on average. Patients in the policy cohort were dispensed a greater quantity of insulin glargine on average than in the historical cohorts. On average, around 13,850 units were dispensed per patient within one year of follow-up. We observed a noticeable increase in quantities dispensed starting on Day 294 (March 15, 2020) which may suggest patient stockpiling behavior during the COVID-19 pandemic.

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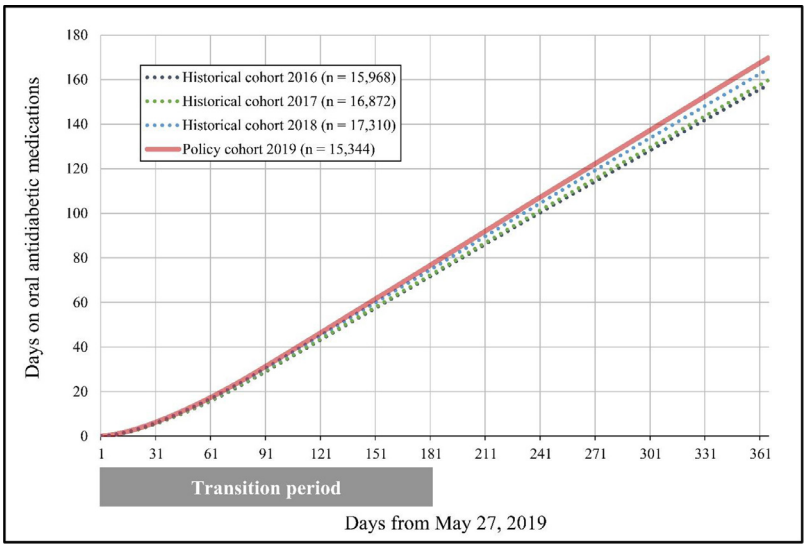

Supplemental Figure S5. Average number of days on oral antidiabetic medications, by cohort. We used the dispensing date and days' supply in the pharmacy records to identify the number of days on treatment. We computed the cumulative number of person-days on treatment during each of the 365 days of follow-up and divided this cumulative number by the number of patients in the cohort to plot the average cumulative number of days on treatment. By 365 days of follow-up, patients in the policy cohort were dispensed 170 days' supply of oral antidiabetic medications on average, compared with 158 to 165 days' supply in the historical cohorts.

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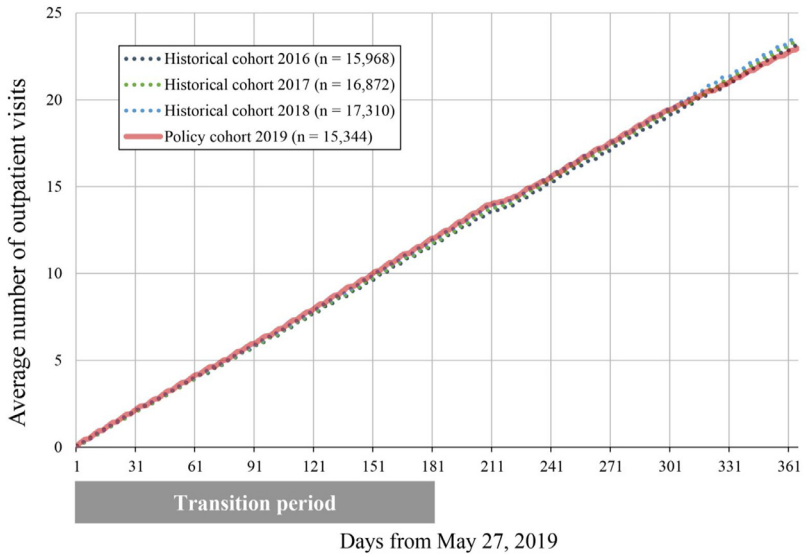
Supplemental Figure S6. Prescription filled for sodium-glucose cotransporter-2 (SGLT2) inhibitors (cumulative incidence difference by day of follow-up). The lines represent the cumulative incidence difference between the policy cohort and the average of policy cohort the first refill of sodium-glucose cotransporter-2 (SGLT2) inhibitors. Values > 0 should be interpreted as an increase in this outcome for patients included in the policy cohort. Shaded areas represent days with likelihood ratios > 7.1. Likelihood ratios were not computed during the first 31 days of follow-up. A cumulative incidence difference between the policy and historical cohorts was considered statistically significant if the likelihood ratio was sustained above the threshold of 7.1.



Supplemental Figure S7. Average number of outpatient visits to physicians and nurse practitioners, by cohort.

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