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Use of the FreeStyle Libre system and diabetes treatment progression in T2DM: Results from a retrospective cohort study using a Canadian private payer claims database

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Abstract

Background: Up to one-third of Canadians are estimated to be living with prediabetes or diabetes. A retrospective study using Canadian private drug claims data was conducted to investigate whether flash glucose monitoring using the FreeStyle Libre system (FSL) among people with type 2 diabetes mellitus (T2DM) in Canada can be associated with changes in treatment intensification when compared with blood glucose monitoring (BGM) alone.

Materials and Methods: Using a Canadian national private drug claims database comprising approximately 50% coverage of insured individuals in Canada, cohorts of people with T2DM using FSL or BGM were identified algorithmically based on treatment history and followed over a 24-month study period, tracking their progression in diabetes treatment therapy. The Andersen-Gill model for recurrent time-to-event data was used to evaluate whether the rate of treatment progression differs between the FSL and BGM treatment cohorts. The survival function was used to calculate comparative treatment progression probabilities between the cohorts.

Results: In total, 373 871 people with T2DM met the inclusion criteria. Across treatment (FSL) and control (BGM) groups, people using FSL had a higher probability of treatment progression compared with BGM alone, with a relative risk ranging between 1.86 and 2.81 ($p < .001$). A higher probability of treatment progression was independent of the diabetes treatment at the enrolment date (index date) or the patient status, and independent of whether patients were treatment naïve or on established diabetes therapy. Assessment of the ending treatment relative to the starting therapy indicated that dynamic treatment changes were most evident for patients in the FSL cohort and that the FSL cohort had a much greater portion of patients who ended with insulin treatment (when they started with non-insulin treatment) compared with the BGM cohort.

Conclusions: People with T2DM using FSL had a greater probability for treatment progression compared with BGM alone, irrespective of the starting therapy, which may suggest that FSL can be used to support escalation of diabetes therapy to improve therapeutic inertia in T2DM.

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KEYWORDS

continuous glucose monitoring, pharmaco-economics, real-world evidence, treatment intensification, type 2 diabetes

1 | INTRODUCTION

Data from the 2019 Diabetes Canada Cost Model¹ indicate that one-third of Canadians are living with prediabetes or diabetes, and that type 2 diabetes mellitus (T2DM) accounts for 90%-95% of cases. The cost of treating diabetes in Canada has more-than doubled from \$14 billion CAD in 2008 to just under \$30 billion CAD in 2019.¹ Successful treatment of T2DM requires the achievement and maintenance of tight glycaemic control and minimizing the risk of hypoglycaemia, as well as controlling cardiovascular risk factors and reducing or controlling weight.² However, evidence suggests that antihyperglycaemic therapy for people with T2DM is characterized by a poor attainment of glycaemic targets and a reluctance of health care professionals to escalate therapy, often because of concerns regarding hypoglycaemia.³⁻⁵ The therapeutic inertia in treatment intensification, even with evidence of suboptimal glycaemic control, results in extended periods of hyperglycaemia and the consequent increased risk of complications and reduced life expectancy.

FreeStyle Libre (FSL) flash glucose monitoring technology has been commercially available in Canada since September 2017. FSL measures glucose in the interstitial fluid using a factory-calibrated sensor and eliminates the need for routine finger prick blood glucose monitoring (BGM).⁶ Use of FSL is associated with significant improvements in glycaemic control for people living with T2DM. These have been documented in the REPLACE randomized clinical trial showing reductions in hypoglycaemia^{7,8} and large numbers of real-world studies,⁹⁻¹² showing reductions in hypoglycaemia and long-term glycosylated haemoglobin (HbA1c). Notably, reductions in HbA1c for people with T2DM who are not on intensive insulin therapy, or on non-insulin therapy, are evident after initiation of FSL.¹³⁻¹⁶ The use of FSL is also associated with a fall in hospital admissions for acute diabetes events such as diabetic ketoacidosis or severe hypoglycaemia for people with T2DM,^{17,18} including for people with T2DM on basal insulin therapy.^{19,20} However, no retrospective observational studies to date have investigated treatment progression to a more-intensive glucose lowering regimen when using FSL for glucose monitoring in comparison with BGM alone for people with T2DM.

FSL is established as a glucose monitoring option within the Canadian private payer market. The availability of more comprehensive glucose insights may allow for patients, their caregivers, physicians and nurses to optimize lifestyle and therapy for patients using FSL compared with those who use BGM alone. Detailed Canadian national private drug claims data that has validated the association between prescribing and use of the FSL system and changes in drug treatment profiles for people with T2DM. The primary aim of this study was to assess for people with T2DM in Canada the impact of using the FSL system on diabetes treatment intensification when compared with using BGM alone.

2 | METHODS

2.1 | Study design

The established Accuync secondary private drug claims database comprises approximately 50% coverage of insured individuals in Canada, with representation across all Canadian provinces. The database contains over 30 million drug claims (including for BGM and FSL) for 850 000 patients, of whom 650 000 are aged <65 years (with private payer coverage). Algorithms (Data S1, Table S1) were applied to categorize de-identified patients into T1DM, T2DM or gestational diabetes mellitus, based on their history of insulin and non-insulin drugs, alongside their BGM monitoring and FSL monitoring claims. Patients with T1DM or gestational diabetes mellitus, and any patients not aged ≥18 years, were excluded. De-identified records from T2DM patients aged >18 years, as of the enrolment date (the index date), were selected for the study and tracked longitudinally for 24 months (Figure 1). At each month over the 24-month study period, starting from the index date, a patient's drug treatment history was used to classify them into one of eight diabetes treatment categories (Table 1).

2.2 | Cohort assignment and analysis

Patients with T2DM were categorized into two main cohorts as of their index date, either 'naïve' or 'experienced' with diabetes treatment. The naïve cohort was defined as those having no previous diabetes drug or BGM claims history during the 12-month selection period. The experienced cohort was defined as those on active diabetes treatment in one of the eight treatment categories (Table 1) during the 12-month selection period. Experienced patients were enrolled with May 2018 as their index date. Naïve patients (as described above) were enrolled in each month from May 2018 to April 2019 to increase the power of the statistical analysis. In each month of the 24-month study period following the index date, each de-identified patients' treatment was classified into one of the eight categories (Table 1) and then time-aligned with month 1 to month 24 for analysis.

Patients in the treatment category 1 through 6 at the index date were placed in the 'non-insulin user' starting cohort, while those on treatment category 7 at the index date were placed in the 'insulin user' starting cohort (Data S1, Figure S1). Patients in treatment category 8 at the index date were excluded from this selection process as no further therapeutic progression was possible within the context of these eight categories for this group.

To investigate the impact of choice of glucose monitoring on treatment progression, patients were further classified into cohort

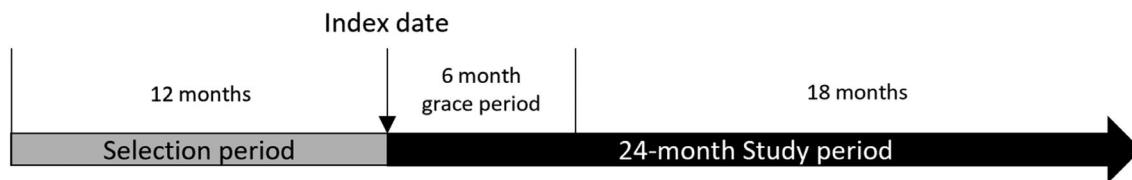


FIGURE 1 Study design. Patients were assigned to a cohort at the index date (on date enrolled in the study), based on their drug and glucose monitoring claims behaviour during a 12-month selection period before the index date (see Table 1). Selected patients were then tracked longitudinally for 24 months

TABLE 1 Treatment categories in order of progression for the purpose of the analysis

1. No diabetes drug therapy (glucose monitoring only; diet and exercise)
2. Monotherapy with non-insulin OADs
3. Dual therapy with non-insulin OADs
4. Triple therapy with non-insulin oral OADs
5. >3 non-insulin OADs
6. Injectable GLP-1 RA (\pm OADs)
7. Basal insulin therapy (\pm OADs)
8. MDI therapy (\pm OADs)

Abbreviations: GLP-1 RA, glucagon-like peptide-1 receptor agonist; MDI, multiple daily insulin injections; OAD, oral antidiabetic agents.

pairs (Data S1, Figure S1); an intervention cohort that included patients who started with, were switched to, or added FSL sensors within the first 6-month grace period after the index date and were still active on FSL at the end of the 24-month study period, and a control cohort, including patients who continued to use BGM only throughout the 24-month study period. Naïve and experienced patient categories were considered separately when tracking cohort treatment progression. To control for confounding factors, cohort selection between the FSL and BGM groups was matched by sex, socio-economic factor (low/not low as the mean household income in geographic area of the dispensing pharmacy relative to the national median) and BGM utilization at the index date (<1, 1-3 or >3 strips/day in the 6 months previously). However, the requirements of de-identifying data before analysis mean we are not able to provide information relating to specific characteristics.

Patients who started FSL more than 6 months past the index date or discontinued FSL before the end of the 24-month study period were excluded from the analysis.

2.3 | Statistical analysis

Data were analysed with SAS language for statistical analysis. The Andersen-Gill model for recurrent time-to-event data was used to evaluate whether any observed treatment progression differed between the treatment cohorts (those using FSL) compared with control cohorts (those using BGM alone). More specifically, we compare the relative risk of moving upwards in a diabetes treatment category at a given month (as assessed by the hazard ratio) after the index date

between the treatment and control groups. The Andersen-Gill model was selected to also account for the fact that more than one increment in diabetes treatment could occur for a patient during the study period. As not all patients are starting from the same diabetes treatment category at the index date, we included a covariate to control for this difference among patients. Treatment progression curves were calculated as the complement of the survival function in the model.

3 | RESULTS

3.1 | Overview of patient cohorts

In total, 373 871 patients met the inclusion criteria (T2DM, age ≥ 18 years and in treatment categories 1 through 7 at the index date). In total, 137 110 (37%) were naïve to diabetes therapy before the index date and 236 761 (63%) were on existing diabetes therapy (Table 2). Of the naïve cohort, 130 791 (95.4%) were started on non-insulin therapies at the index date, and 6319 (4.6%) were started on insulin therapy. At the index date, 208 152 (87.9%) of the experienced treatment cohort were on non-insulin therapies and 28 609 (12.1%) were on insulin therapy. The data also confirm that BGM continues to be the predominant glucose monitoring modality for people with T2DM within the recruitment parameters.

3.2 | Treatment progression during the 24-month study period

3.2.1 | Relative risk of treatment progression

The Andersen-Gill model for recurrent time-to-event data was used to evaluate the treatment progression by calculating the relative risk of moving up in treatment category over time. For all patients starting FSL, the cumulative probability of treatment progression was significantly higher than for patients who continued to use BGM alone (Table 3). Patients who were treatment-naïve at the index date were 86% more likely to have their non-insulin treatment intensified after the index date compared with the BGM cohort (Table 3; $p < .0001$) and those who were started on basal insulin therapy at the index date were 112% more likely to progress to multiple daily insulin injection (MDI) therapy compared with the BGM cohort (Table 3; $p < .0001$). The

TABLE 2 Patient numbers at index date by cohort

Comparator arms		Treatment experience at index date		
Treatment at index date	Glucose monitoring	Naïve	Experienced	Totals
Non-insulin	FSL	2748	1838	4586
	BGM	128 043	206 314	334 357
Insulin	FSL	771	1803	2574
	BGM	5548	26 806	32 354
Total		137 110	236 761	373 871

Abbreviations: BGM, blood glucose monitoring; FSL, FreeStyle Libre system.

TABLE 3 Andersen-Gill model summary of relative risk for treatment progression

Treatment at index date	Intervention cohort	Control cohort	Relative risk for progression	Relative increase in cumulative probability
Naïve	Non-insulin-FSL	Non-insulin-BGM	1.86 ($p < .0001$)	86%
	Insulin-FSL	Insulin-BGM	2.12 ($p < .0001$)	112%
Experienced	Non-insulin-FSL	Non-insulin-BGM	2.03 ($p < .0001$)	103%
	Insulin-FSL	Insulin-BGM	2.81 ($p < .0001$)	181%

Abbreviations: BGM, Self-monitoring of blood glucose; FSL, FreeStyle Libre system.

TABLE 4 Survival probability of treatment progression by the 24th month after the index date

Treatment and glucose monitoring at index date		Naïve	Experienced
Non-insulin	FSL	57.9%	51.0%
	BGM	37.3%	29.8%
Insulin	FSL	45.7%	32.2%
	BGM	25.2%	12.9%

Note: The Andersen-Gill survival probability describes the persistent occurrence over time of the non-insulin and insulin prescribing events (as described in Table 1).

Abbreviations: BGM, Self-monitoring of blood glucose; FSL, FreeStyle Libre system.

same pattern of treatment intensification was observed for patients already on diabetes therapy at the index date, with a 103% increase in cumulative probability for patients on non-insulin therapies and a 181% increase in probability of progression to MDI therapy for those on basal insulin only at the index date (Table 3; $p < .0001$ in both cases).

3.2.2 | Probability of treatment progression

The probability of treatment progression by the 24th month after the index date was calculated as the complement of the survival function. Across all cohort pairs, FSL users were found to have a higher probability of treatment progression relative to the BGM only control group by the 24th month (Table 4), irrespective of whether they were treatment naïve or experienced at the index date, or whether they were on non-insulin or insulin therapy. This analysis also showed that a higher probability of treatment progression was observed for naïve patients at the index date compared with patients who were experienced with therapy at the index date across all cohorts (Table 4).

The probability of treatment progression increases each month after the index date. Both for the treatment naïve cohort (Figure 2A) and for the experienced cohort (Figure 2B), it was observed that the probability of treatment progression is higher for the FSL group compared with the

BGM only group for all months in the study after the index date, and that the probability of treatment progression increases each month across the 24-month study period. We also observed that the FSL group had a consistently higher probability of treatment progression compared with the BGM only group irrespective of the treatment category at the index date, both for the treatment naïve and the experienced patient cohorts at the index date (Data S1, Figure S2A,B).

When comparing treatment progression for FSL users in the context of the treatment category at the index date (Figure 3), we observed that patients starting with non-insulin treatment category 2, 3 or 4 at the index date had a higher probability of treatment progression than those who were at more-advanced treatment categories 5, 6 or 7, at the index date, or those who were monitoring glucose only (category 1) at the index date. This was evident both for the treatment naïve cohort (Figure 3A) at the index date and the experienced cohort (Figure 3B). A similar pattern was observed for treatment progression for the BGM only cohort (data not shown).

3.2.3 | Patterns of treatment progression

Survival models consider the progression of recurring events. Therefore, we cross-tabulated the treatment categories at the index date

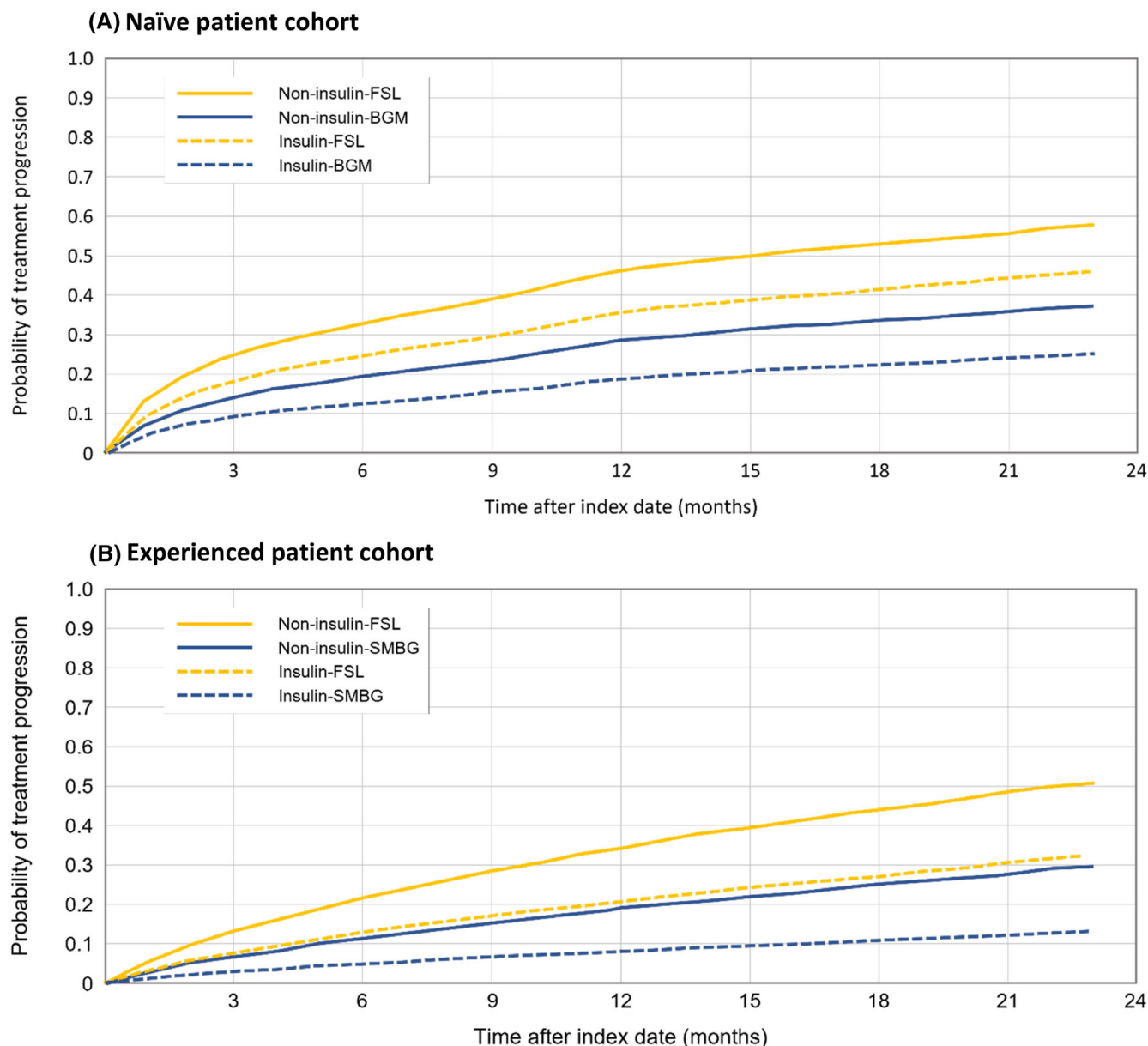


FIGURE 2 Probability of treatment progression each month after the index date. (A) Naïve patient cohort. (B) Experienced patient cohort. BGM, blood glucose monitoring; FSL, FreeStyle Libre system

with the treatment categories at the 24-month study end point. This allowed us to determine the proportion of patients who underwent treatment progression across the study compared with those who remained in the same treatment category with no progression (Table 5). Several observations may be drawn from this analysis. First, the most dynamic treatment changes were for patients in the FSL cohorts; this is observed as the percentages in the diagonal cells that indicate the proportion of patients who started and ended in the same treatment category. For the FSL group of patients (Table 5A and 5B) the proportion who had no treatment progression is much lower than the corresponding BGM-only patient group (Table 5A and 5C). This indicates that those patients using FSL had more dynamic changes in their treatment progression than those using BGM alone.

Second, a much greater portion of patients using FSL who were on a non-insulin therapy at the index date (treatment category 1-6) ended the study on insulin therapy (treatment category 7 or 8) compared with the BGM-only group. For example, among treatment-naïve patients using FSL who started in treatment category 1, 8% were on basal insulin (treatment category 7) after 24 months and 28% were on intensive insulin therapy with MDI (treatment category 8) (Table 5B). This compares with only 2% of treatment-naïve to treatment patients using BGM only who progressed to either basal or MDI insulin therapy (Table 5A). The trend for more-dynamic treatment progression for FSL users is similar across the other starting treatment categories, both for those patients naïve to treatment at the index date and those who were experienced with diabetes treatment at the index date (Table 5A-D).

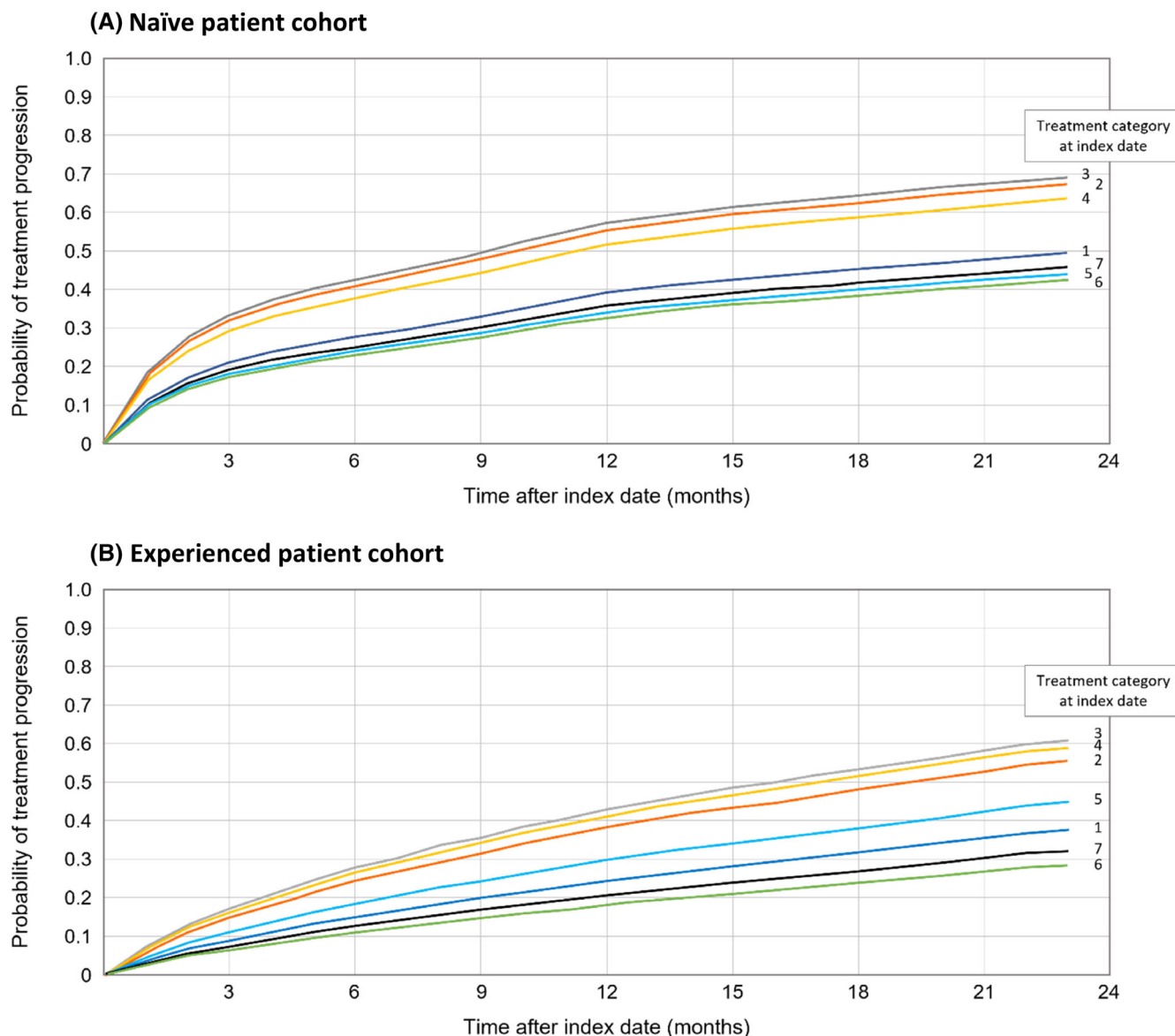


FIGURE 3 Probability of treatment progression among FreeStyle Libre system users based on treatment category at index date. (A) Naïve patient cohort. (B) Experienced patient cohort. Treatment categories are those detailed in Table 1

4 | DISCUSSION

Canadian clinical practice guidelines for the management of T2DM²¹ suggest first-line therapy for people with diabetes and no evidence of cardiovascular disease, as either diet and exercise, metformin monotherapy, or insulin with or without metformin depending on HbA1c at the time of diagnosis. If patients are not meeting their HbA1c target, the guidelines recommend adding-on dipeptidyl peptidase-4, glucagon-like peptide receptor agonist, sodium-glucose cotransporter 2, other oral antidiabetic agents, or insulin every 3–6 months until patients reach their HbA1c target.²¹

The results reported in this study are consistent with these diabetes treatment guidelines, where we observed that patients generally progressed through treatment intensification categories over the study period. The key finding identified patients who were started on

flash glucose monitoring using FSL had a greater probability for treatment progression, irrespective of the starting therapy, compared with those patients who continued to use BGM alone after the index date. This suggests that either FSL is being prescribed in situations where the physician decides that there is a need to escalate the patient's therapy, or it is possible that after prescribing FSL the need for escalating therapy becomes more evident, with consequent treatment progression. In both scenarios it appears that FSL is being proactively initiated with patients who require more intensive or complex treatment to manage their diabetes.

This speaks to the problem of therapeutic inertia in T2DM and the unmet need for treatment intensification among people with T2DM who are failing to meet glycaemic targets on monotherapy or combination therapy with non-insulin antihyperglycaemic drugs.²² Poorly managed T2DM is associated with complications, including

TABLE 5A Ending treatment category at 24 months by treatment category at index date by choice of glucose monitoring

Naïve to therapy at index date			Treatment category at 24 months							
Cohort	Treatment category at index date*	Patients	1	2	3	4	5	6	7	8
Non-insulin-BGM	1	54,587	86%	8%	3%	1%	0%	0%	1%	1%
	2	45,931	5%	70%	15%	4%	1%	2%	2%	1%
	3	17,455	3%	12%	57%	16%	2%	4%	4%	1%
	4	6,464	2%	6%	10%	56%	11%	7%	6%	1%
	5	1,554	2%	5%	4%	11%	63%	8%	7%	1%
	6	2,052	3%	16%	10%	3%	1%	55%	10%	3%
Insulin-BGM	7	5,548	6%	13%	8%	3%	1%	2%	53%	14%
		133,591	38%	30%	15%	7%	2%	3%	5%	2%

TABLE 5B

Naïve to therapy at index date			Treatment category at 24 months							
Cohort	Treatment category at index date*	Patients	1	2	3	4	5	6	7	8
Non-insulin-FSL	1	1,576	51%	7%	3%	1%	0%	2%	8%	28%
	2	600	10%	45%	13%	4%	1%	6%	9%	12%
	3	321	5%	13%	31%	12%	2%	10%	16%	10%
	4	106	2%	7%	12%	36%	6%	8%	19%	10%
	5	26	12%	4%	4%	4%	42%	8%	19%	8%
	6	119	6%	16%	4%	1%	0%	31%	25%	17%
Insulin-FSL	7	771	12%	8%	5%	2%	0%	4%	34%	36%
		3,519	28%	14%	8%	4%	1%	5%	15%	24%

TABLE 5C

Experienced with therapy at index date			Treatment category at 24 months							
Cohort	Treatment category at index date*	Patients	1	2	3	4	5	6	7	8
Non-insulin-BGM	1	48,092	90%	5%	2%	1%	0%	0%	1%	1%
	2	72,492	4%	78%	12%	2%	0%	1%	1%	0%
	3	46,232	2%	16%	62%	13%	1%	3%	2%	0%
	4	25,231	1%	10%	14%	55%	9%	5%	5%	1%
	5	7,566	1%	8%	7%	15%	54%	9%	5%	1%
	6	6,701	2%	17%	9%	4%	0%	59%	7%	1%
Insulin-BGM	7	26,806	4%	13%	8%	3%	1%	2%	63%	6%
		233,120	21%	32%	19%	10%	3%	4%	9%	1%

TABLE 5D

Experienced with therapy at index date			Treatment category at 24 months							
Cohort	Treatment category at index date*	Patients	1	2	3	4	5	6	7	8
Non-insulin-FSL	1	598	74%	3%	1%	1%	0%	1%	5%	15%
	2	310	7%	50%	16%	6%	1%	6%	5%	9%
	3	353	5%	17%	31%	14%	2%	11%	12%	8%
	4	245	4%	7%	10%	37%	8%	16%	11%	7%
	5	126	2%	5%	3%	21%	33%	19%	15%	3%
	6	206	7%	11%	8%	2%	0%	52%	14%	6%
Insulin-FSL	7	1,803	6%	7%	5%	2%	1%	4%	52%	22%
		3,641	17%	11%	8%	6%	2%	9%	30%	16%

Abbreviations: BGM, blood glucose monitoring; FSL, FreeStyle Libre system.

*Treatment categories are those detailed in Table 1.

chronic kidney disease, neuropathy, retinopathy, cardiovascular disease and stroke^{4,23} each of which cause a reduction in quality of life and result in a significant burden on health care resources. The Diabetes Mellitus Status in Canada (DM-SCAN) survey of 5123 people with T2DM treated in primary care found that only 50% met the HbA1c target of $\leq 7.0\%$.²⁴ A second primary-care survey of 379 patients with T2DM in Canada found a high prevalence of diabetes complications.²⁵ Mean HbA1c of the patients in this study was 9.5% at the point when escalation of therapy with insulin was undertaken and the mean time from diagnosis of T2DM to initiation of insulin was 9.2 years.

For this group who experience persistent high glucose levels there is a need to individualize their treatment and optimize therapy, including the step to initiating basal insulin (treatment category 7) and subsequently intensifying insulin therapy with MDI (treatment category 8). Our data show that these escalations in therapy are occurring more frequently for the FSL user population compared with those relying on BGM alone (Table 5).

Initiation of basal-insulin therapy in T2DM is associated with a three-fold increase in the relative risk of severe hypoglycaemia,²⁶ which has been cited as a barrier to treatment intensification and adherence with therapy in this population.²⁷⁻²⁹ A study across four diabetes centres in Canada has shown that hypoglycaemia and a fear of hypoglycaemia have an impact upon people with T2DM and that this fear is greatly exacerbated following an episode of severe hypoglycaemia.³⁰ Reducing the incidence of severe hypoglycaemia among people with T2DM initiating basal-insulin therapy may therefore increase adherence with therapy and attainment of glycaemic targets. Reduced fear of hypoglycaemia is shown as an aspect of the engagement of older people with T2DM with glucose-monitoring technology in general,^{31,32} which provides a clear rationale for enabling access to FSL by health care professionals as they recommend to their patients the step to intensify treatment with basal insulin or MDI, with subsequent adherence.

In future studies it would be beneficial to be able to investigate the link between increases in treatment progression for the FSL cohort arms with lab results for HbA1c to measure the clinical benefit of the increase in treatment progression. As well, it would be beneficial to investigate the link between diabetes treatment progression and the associated use of sodium-glucose cotransporter 2 and glucagon-like peptide-1 receptor agonist drugs that have benefits for comorbidities such as cardiovascular disease and obesity.^{33,34}

It is important to point out that our study has limitations. We have presented retrospective data on people with T2DM who have been prescribed FSL, derived from an established Canadian national private drugs claims database. This does not allow us to investigate the role of factors other than FSL that may contribute to the observed association with treatment progression compared with BGM. For example, diabetes education and more-focused time with health care professionals during the FSL initiation process may have empowered the patients to improve their diabetes self-care behaviour in a way that helped them to make better decisions regarding treatment optimization after the FSL start date. Nor are we able to evaluate resource utilization, or other factors related to provider/

patient care, which would have increased the likelihood of an FSL prescription. We are also unable to refute objectively the argument that prescription of FSL was a proactive consequence of the need to intensify treatment. Equally, the reimbursement claims data does not provide information on patient health-status indicators, such as HbA1c, body mass index, smoking habits or comorbid disease, nor adherence with prescribed medications. In addition, because we have used a 24-month follow-up period, the index date for a proportion of the FSL cohort will have been close to the launch of FSL in Canada. Thus, an early-adopter bias among this group cannot be discounted. The strengths of our study are the size and broad coverage of the private claims database, large number of people with T2DM recruited, as well as inclusion of both FSL and BGM treatment groups across a 24-month longitudinal timeframe.

5 | CONCLUSIONS

We have shown that people with T2DM who started FSL flash glucose monitoring had a greater probability for treatment progression compared with those who continued to use BGM alone. This increased likelihood for treatment progression with FSL was irrespective of the treatment regimen at the index date for starting FSL. This may be interpreted to mean that glucose monitoring with FSL can help physicians and patients make the decision to escalate therapy, improve therapeutic inertia, and can help monitor the impact of treatment changes and the need for further intensification of therapy.

AUTHOR CONTRIBUTIONS

This study was designed by SBH and FLG. Both authors worked collaboratively to review and prepare the final manuscript.

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CONFLICT OF INTEREST

SBH has received speaker honoraria and consulted for Abbott, AstraZenica, Bayer, Eli Lilly, Janssen, NovoNordisk, and Sanofi. FLG is an employee of Abbott Diabetes Care.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/dom.15025>.

DATA AVAILABILITY STATEMENT

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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