Real-world Canagliflozin Utilization: Glycemic Control Among Patients With Type 2 Diabetes Mellitus—A Multi-Database Synthesis

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ABSTRACT

Purpose: Randomized controlled trials have found that treatment of type 2 diabetes mellitus with canagliflozin, a sodium glucose co-transporter 2 inhibitor, is associated with significant reductions in glycosylated hemoglobin (HbA_{1c}) levels. However, very few studies have evaluated the effectiveness of sodium glucose co-transporter 2 inhibitors in a real-world context. This data synthesis aims to examine the demographic characteristics and glycemic control among patients treated with canagliflozin in clinical practice, using results obtained from 2 US-specific retrospective administrative claims databases.

Methods: Data included in the synthesis were derived from 2 large claims databases (the Optum Research Database and the Inovalon MORE^2 Registry, Research Edition) and were obtained from 3 recently published retrospective observational studies of adult patients with type 2 diabetes mellitus who were treated with canagliflozin. Two of the studies used the Optum database (3-month and 6-month follow-up) and 1 study used the Inovalon database (mean follow-up of 4 months). Patient demographic characteristics, clinical characteristics, treatment utilization, and achievement of glycemic goals at baseline and after canagliflozin treatment were evaluated across the 3 studies. Results were assessed using univariate descriptive statistics.

Findings: Baseline demographic characteristics were generally similar between the Optum and Inovalon cohorts. Mean baseline HbA_{1c} was 8.7% in the Optum and 8.3% in the Inovalon cohort. Seventy-five percent of the Optum (3-month study) cohort and 74% of the Inovalon cohort used 2 or more antihyperglycemic agents. During follow-up, in both cohorts, the proportion of patients who achieved tight glycemic control (HbA_{1c} $<7.0\%$) more than doubled, while the proportion who had poor control (HbA_{1c} $\geq 9.0\%$) decreased by approximately 50%. Among patients who had baseline HbA_{1c} $\geq 7.0\%$, 21% of the Optum cohort and 24% of the Inovalon cohort achieved tight glycemic control (HbA_{1c} $<7.0\%$), and the proportion of patients achieving HbA_{1c} $<8.0\%$ more than doubled in both cohorts (from 30% to 61% in the Optum cohort, and from 33% to 69% in the Inovalon cohort).

Implications: This synthesis of real-world data from 2 large patient databases suggests that treatment of type 2 diabetes mellitus with canagliflozin is associated with significant and consistent improvements in glycemic control. Patients with varying HbA_{1c} control and multiple antihyperglycemic agent use were able to lower their HbA_{1c} levels with canagliflozin treatment. Additional studies with longer follow-up would be beneficial to evaluate the durability of the real-world effectiveness of canagliflozin. (*Clin Ther.* 2016;38:2071–2082)

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INTRODUCTION

It has long been recognized that the attainment of glycemic goals, usually defined as being at or below a threshold of glycosylated hemoglobin (HbA_{1c}), has clear benefits in the reduction of the long-term risk of diabetes-related complications.[1,2] Guidelines issued by the American Association of Clinical Endocrinologists and American College of Endocrinology, and joint guidelines by the American Diabetes Association and the European Association for the Study of Diabetes, recommend metformin as a first-line antihyperglycemic agent (AHA) for patients whose glycemic control cannot be adequately maintained with lifestyle modifications alone. With declining glycemic control, add-on therapy using 1 or more AHAs is recommended.[3–6]

These treatment guidelines include sodium glucose co-transporter 2 (SGLT2) inhibitors as one of the many treatment options for patients with type 2 diabetes mellitus (T2DM). Furthermore, the American Association of Clinical Endocrinologists and American College of Endocrinology, as well as the American Diabetes Association and the European Association for the Study of Diabetes guidelines recommend SGLT2 inhibitors as one of the first oral options after metformin.[5–8] SGLT2 inhibitors increase urinary glucose excretion and lower blood glucose levels by blocking the reabsorption of filtered glucose in the kidneys. This unique insulin-independent mode of action means that their effectiveness is unlikely to be affected by deterioration of β-cell function, and that they can be combined with other glucose-lowering agents with different mechanistic pathways.[9]

Three SGLT2 inhibitors are currently approved for use in the United States: canagliflozin, dapagliflozin, and empagliflozin. Phase III clinical trials have found that these new treatments significantly reduce HbA_{1c} from baseline values when used as monotherapy and as add-on therapy with other oral AHAs and/or insulin.[10] In recent systematic reviews, quantitative synthesis, or meta-analyses of trials of SGLT2 inhibitors, canagliflozin, dapagliflozin, and empagliflozin were associated with mean HbA_{1c} reductions of −0.73% (95% CI, −0.84% to −0.61%),[11] −0.52% (95% CI, −0.60 to −0.45),[12] and −0.66% (95% CI, −0.76% to −0.57%),[13] respectively, when combined with other AHAs or insulin at the higher prescribed drug doses. Additionally, canagliflozin has been found to reduce postprandial glucose excursions when administered before a meal, likely due to the transient inhibition of SGLT1 in the gastrointestinal tract.[14,15]

Canagliflozin was approved by the US Food and Drug Administration in March 2013 based on the results of 9 clinical trials involving more than 10,285 patients with T2DM. In a Phase III trial of patients with T2DM inadequately controlled with metformin plus sulfonylurea, the addition of canagliflozin 300 mg provided a significantly greater reduction in HbA_{1c} from baseline compared with sitagliptin 100 mg at 52 weeks.[16] Subsequently, an analysis of pooled data from 2 Phase III studies[16,17] assessed quality measures related to glycemic control (the proportion of patients achieving HbA_{1c} goals of $<7.0\%$ or $<8.0\%$ or continuing to have poor control $>9.0\%$) at 52 weeks.[18] The results of this analysis found that canagliflozin 100 mg provided comparable or superior attainment of glycemic goals, and canagliflozin 300 mg was superior to sitagliptin, with a greater proportion of patients achieving HbA_{1c} $<7.0\%$ or $<8.0\%$, and a smaller proportion of patients with HbA_{1c} $>9.0\%$.[18] When canagliflozin (100 mg/d or 300 mg/d) was compared with glimepiride (titrated up to 6–8 mg/d) as add-on therapy for patients with T2DM inadequately controlled with metformin, both doses of canagliflozin were non-inferior, and canagliflozin 300 mg provided superior glycemic control compared with glimepiride, with a greater portion of patients achieving and maintaining an HbA_{1c} $\leq 7.0\%$ over 104 weeks.[19]

While the use of SGLT2 inhibitors has been investigated in numerous randomized controlled trials (RCTs) to establish their tolerability and efficacy, very few studies have evaluated their effectiveness in a real-world context. Compared with RCTs, observational studies provide the opportunity to evaluate clinically relevant outcomes in a more representative patient population in a real-world context.[20] RCTs have strict restrictions on participant inclusion criteria and medication adherence and, therefore, may not fully reflect the effectiveness of a drug as it is used in clinical practice.[20,21] Real-world data on effectiveness are increasingly being requested by policy makers and