When Insulin Therapy Fails: The Impact of SGLT2 Inhibitors in Patients With Type 2 Diabetes

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Insulin is the most effective therapy for achieving optimal glycemic control; however, many patients with type 2 diabetes on an intensified treatment regimen fail to achieve the recommended HbA_{1c} target (1,2) and face the risk of adverse effects such as hypoglycemia and weight gain (3). The addition of sodium–glucose cotransporter 2 (SGLT2) inhibitors to a regimen of insulin therapy in this patient population has the potential to mitigate insulin-related weight gain and risk of hypoglycemia, with the added benefit of insulin dose reduction (4). Randomized controlled trials (RCTs) have shown improved clinical outcomes of SGLT2 inhibitors as monotherapy and as an add-on to oral and insulin therapy, but there is a paucity of real-world (RW) studies evaluating similar outcomes.

Data extracted from WebDR (5) was used to evaluate the RW clinical impact of SGLT2 inhibitors (initiation of canagliflozin or dapagliflozin between February 2014 and December 2016) as an add-on to insulin therapy in patients with type 2 diabetes not achieving glycemic targets (those with HbA_{1c} >7% [>53 mmol/mol]). Empagliflozin was excluded because of inadequate sample size. Ethical approval was obtained from Western University's Research Ethics Board.

A total of 411 patients met the study criteria. The study population had a mean age of 57 years, diabetes duration of 15 years, HbA_{1c} of 9.01% (75 mmol/mol), BMI of 36.3 kg/m^2, and median baseline insulin dose of 75 IU/day, with 33.4% on >100 IU/day and 71.8% presenting with one or more diabetes-related complications. Multiple regression analysis, adjusted for age, sex, and duration of diabetes, showed that both drugs were associated with a significant reduction in HbA_{1c}, blood pressure, weight, and insulin dose at 3 and 6 months postinitiation (Table 1). Of particular interest in our research was the substantial insulin dose reduction observed in patients on a high insulin regimen (>100 IU/day). Canagliflozin use resulted in a reduction of the insulin dose by 17 IU at 3 and 6 months in patients on 101–200 IU/day. Patients on >200 IU of insulin/day experienced a reduction of 21 and 23 IU at 3 and 6 months, respectively, with canagliflozin and 77 and 71 IU at 3 and 6 months, respectively, with dapagliflozin. Despite these positive clinical outcomes and benefits, a relatively small percentage of patients achieved the glycemic target after SGLT2 addition.

Unique aspects of our RW research include the high proportion of patients on an intensified insulin regimen with suboptimal glycemic control, high BMI, and high rate of complications, reflecting a population typically excluded from RCTs. Despite the fact that hypoglycemia has been identified as a concern in patients using SGLT2 inhibitors in combination with insulin, we were unable to report hypoglycemia events because of inconsistent documentation in WebDR. This RW study plays an important role in the evaluation of treatment patterns and health outcomes and can supplement knowledge gained from RCTs. This research is the first in North America to exclusively examine the RW impact of SGLT2 inhibitors in patients with type 2 diabetes treated with insulin and highlights the advantage of adding an SGLT2 inhibitor to improve glycemic control, blood pressure, and weight and to reduce insulin dose.

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Duality of Interest. S.B.H. has served on advisory panels and as a consultant for Abbott Diabetes Care, AstraZeneca, Merck Canada, Janssen Pharmaceuticals, Boehringer Ingelheim, Sanofi, Eli Lilly Canada, and Novo Nordisk A/S. S.B.H. received research grants for this study and other studies from Boehringer Ingelheim, Janssen Pharmaceuticals, AstraZeneca, Novo Nordisk A/S, Sanofi, and Abbott. S.M.R. has served on advisory panels for and has spoken at scientific meetings sponsored by Sanofi, Novo Nordisk, Abbott, AstraZeneca, Servier, Boehringer Ingelheim, Eli Lilly Canada,

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Table 1—Baseline characteristics of study patients at the time of canagliflozin or dapagliflozin initiation and mean change from baseline in clinical outcomes at 3 and 6 months

	Canagliflozin ($N = 290$)					Dapagliflozin ($N = 121$)				
Parameters	Baseline	Δ BL-3M	*P* value	Δ BL-6M	*P* value	Baseline	Δ BL-3M	*P* value	Δ BL-6M	*P* value
HbA_{1c}, %	9.03 ± 1.5	−0.69	<0.00	−0.88	<0.00	9.13 ± 1.5	−0.59	<0.00	−0.71	<0.00
HbA_{1c}, mmol/mol	75.2 ± 15.9	−7.00	<0.00	−9.00	<0.00	76.3 ± 15.9	−6.00	<0.00	−8.00	<0.00
HbA_{1c} at target,* %	0.0	15.5	<0.00	21.1	<0.00	0.0	13.3	0.00	10.0	0.00
Weight, kg	107.2 ± 27.8	−1.40	0.00	−2.99	<0.00	102.2 ± 22.9	−0.96	0.00	−1.60	<0.00
SBP, mmHg	131.7 ± 16.1	−5.10	<0.00	−6.40	<0.00	128.8 ± 14.2	−7.97	<0.00	−4.70	0.00
DBP, mmHg	76.4 ± 9.4	−3.35	<0.00	−2.30	0.00	76.9 ± 9.9	−5.79	<0.00	−1.43	0.21
LDL-C, mmol/L	1.9 ± 0.7	−0.01	0.70	−0.01	0.87	1.9 ± 0.8	−0.12	0.07	−0.15	0.03
HDL-C, mmol/L	1.1 ± 0.3	0.02	0.05	0.02	0.07	1.1 ± 0.3	−0.00	0.65	0.01	0.18
TC, mmol/L	3.9 ± 1.1	−0.01	0.84	0.00	0.94	4.2 ± 1.5	−0.12	0.11	−0.15	0.05
TG, mmol/L	2.3 ± 2.4	−0.06	0.26	−0.08	0.14	3.1 ± 4.0	−0.14	0.14	−0.15	0.09
ACR, mg/mmol	15.3 ± 59.8	−3.20	0.31	−0.56	0.85	11.0 ± 23.6	0.30	0.82	−0.03	0.97
eGFR, mL/min	87.5 ± 16.4	−3.39	<0.00	−2.90	0.00	89.5 ± 16.4	−0.46	0.74	−0.91	0.51
SCr, μmol/L	68.2 ± 16.4	3.64	<0.00	3.24	<0.00	69.4 ± 15.7	2.19	0.07	2.60	0.03
K, mmol/L	4.4 ± 0.4	0.08	0.00	0.07	0.01	4.5 ± 0.5	0.03	0.38	0.03	0.34
Insulin/day, IU	98.2 ± 83.8	−5.19	0.05	−5.80	0.03	90.1 ± 67.8	−3.40	0.36	−5.44	0.20
Basal	228 (78.6)					96 (79.2)				
Prandial	56 (19.5)					25 (20.8)				
Premixed	6 (1.9)					0 (0)				
Insulin/day, IU										
0–100	190 (65.5)	1.53	0.55	0.76	0.77	85 (70.2)	0.22	0.94	−0.36	0.90
101–200	73 (25.2)	−17.22	<0.00	−17.0	0.00	29 (23.8)	2.4	0.84	−4.05	0.05
>200	27 (9.4)	−21.38	0.29	−23.1	0.26	7 (5.9)	−77.4	0.02	−71.0	0.03
Insulin/weight/day, IU/kg/day										
0.1–0.4	80 (27.5)	0.03	0.25	0.06	0.00	27 (22.6)	0.07	0.18	0.08	0.12
0.5–1.0	111 (38.2)	−0.06	0.09	−0.02	0.60	59 (48.4)	0.04	0.44	0.01	0.79
1.1–2.0	77 (26.4)	−0.15	0.00	−0.13	0.01	27 (22.6)	−0.05	0.69	−0.10	0.42
>2.0	23 (7.9)	−0.34	0.28	−0.39	0.20	8 (6.5)	−0.57	0.01	−0.55	0.01

Baseline values are mean ± SD or *n* (%) unless otherwise indicated. Δ BL-3M, mean change from baseline in clinical outcomes at 3 months; Δ BL-6M, mean change from baseline in clinical outcomes at 6 months; ACR, albumin-to-creatinine ratio; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, HDL cholesterol; K, potassium; LDL-C, LDL cholesterol; SBP, systolic blood pressure; SCr, serum creatinine; TC, total cholesterol; TG, triglycerides. *HbA_{1c} <7% (<53 mmol/mol).

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Prior Presentation. Results obtained from the canagliflozin and dapagliflozin data were presented as posters at the 77th Scientific Sessions of the American Diabetes Association, San Diego, CA, 9–13 June 2017.

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