Brief Research Report
DOI: 10.22374/1710-6222.24.1.2

LACK OF HEALTH-RELATED QUALITY OF LIFE AND PATIENT-CENTRED OUTCOME MEASURES IN RANDOMIZED CONTROLLED TRIALS CONDUCTED FOR DIABETES PHARMACOTHERAPY: SGLT-2 RECEPTOR INHIBITORS AS AN EXAMPLE

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Submitted: October 13, 2016. Accepted: November 2, 2016. Published January 9, 2017.

ABSTRACT

Background
Use of SGLT-2 receptor inhibitors has been associated with weight loss and a low rate of hypoglycemia in comparison to sulfonylureas. These factors may improve health-related quality of life for patients with diabetes.

Objective
To systematically explore randomized controlled trials (RCTs) involving SGLT-2 receptor inhibitors that reported health-related quality of life changes.

Methods
A systematic review of SGLT-2 receptor inhibitors clinical trials, limited to RCTs and English language, was conducted utilizing PubMed databases.

Results
One-hundred and eighteen RCTs were reviewed and 62 RCTs meeting the inclusion criteria were assessed. All 62 RCTs reported body mass index (BMI) changes and HgbA1c reduction. Measures of health-related quality-of-life (HRQoL) were reported in only 2 RCTs. Both studies illustrate improvement in HRQoL domains for SGLT-2 receptor inhibitors in comparison to the other arms in the RCTs.

Conclusion
Only a small portion of RCTs involving SGLT-2 receptor inhibitors reported on HRQoL. Because of the potential for weight loss and hypoglycemia avoidance to improve HRQoL, future studies of SGLT-2 receptor inhibitors should measure and report on patient-centred outcomes such as HRQoL.

Key Words: *diabetes, sulfonylurea, hypoglycemia, obesity, quality of life, SGLT-2*

BACKGROUND

Health-related quality-of-life (HRQoL) and other patient-centred outcomes are crucial for a comprehensive evaluation of treatment effectiveness. This has been a focus of attention for randomized controlled trials (RCTs) of chronic diseases for the past decade. For example, in RTCs of patients with chronic leukemia and myelodysplastic syndromes the use of patient-centred outcome components of HRQoL and symptom assessment has increased in recent years.[1] Similarly, HRQoL has been measured in RCTs involving gastrointestinal surgical diseases.[2]

Evaluation of quality of life in patients with diabetes is becoming an important aspect of care[3]. Several instruments have been utilized for assessing quality of life in diabetes.[3] Inclusion of HRQoL in RCTs is feasible and can provide unique information to facilitate clinical decision-making. However, the

extent that HRQoL is measured in RCTs for diabetes, a chronic disease, has not been determined.

SGLT-2 receptor inhibitors use has been associated with weight loss and a low rate of hypoglycemia in comparison to sulfonylurea (SU) use. These factors may improve HRQoL for patients with diabetes. Evidence illustrates that weight loss and avoidance of hypoglycemia will increase the feeling of well-being and quality of life among patients with diabetes.[4–6] The objective of this study was to systematically review RCTs conducted on SGLT-2 inhibitors and assess them for measuring and reporting HRQoL changes and patient-centred outcomes.

METHOD

A systematic review of SGLT-2 receptor inhibitors limited to RCTs and English language was conducted utilizing PubMed databases. The search was conducted in PubMed using medication names including "canagliflozin," "dapagliflozin," and "empagliflozin," and with a filter for RCTs. The search date was limited to publications prior to January 16th, 2016.

RESULTS

A total of 118 RCTs were reviewed and 62 RCTs met the inclusion criteria (English language RCTs). Studies were excluded from the analysis if they were limited to either PK/PD outcomes or non-glucose related outcome RCTs, were short-term studies (under 12 weeks), or were duplicate published RCTs (Table 1).

All 62 RCTs reported BMI changes and HgbA1c reduction; however, only 55 studies (88%) reported hypoglycemia events. Measures of HRQoL were reported only in 2 RCTs (1.5%); 1 study on dapagliflozin[7] and 1 study on canagliflozin[8]. Both studies illustrate improvements in HRQoL domains for SGLT-2 receptor inhibitors in comparison to the other arms in the RCTs (detailed in the discussion section).

DISCUSSION

Diabetes is a chronic disease with high incidence and prevalence, and a significant burden of illness due to complications.[9] The main goal in clinical practice in managing diabetes with non-pharmacological and pharmacological therapies is to reduce the burden of illness and complications due to diabetes.[10] Reducing blood glucose and other risk factors will lead to diminishing in comorbidities and improving quality of life in patients with diabetes in long term.[10,11] Yet diabetes pharmacotherapy that leads to hypoglycemia and weight gain are correlated with disutility and reduction in HRQoL.[12] From the patient's perspective a reduction in weight gain, or even better weight loss, and the avoidance of hypoglycemia are an important outcomes for medications used in the treatment of diabetes treatment.[4–6,13–15]

Therefore, in the context of RCTs, demonstrating and evaluating the burden of hypoglycemia and obesity/weight gain on HRQoL is important. The association between hypoglycemia and HRQoL using both an objectively confirmed and a patient-reported measure of hypoglycemia was conducted.[16] Less than 6% of patients experienced at least one objectively confirmed hypoglycemic event and about half the patients reported unacceptably low blood sugars. The association between the number of objectively confirmed hypoglycemic events and HRQoL was not statistically significant, while the patient-reported

TABLE 1 Results

	Dapagliflozin	Canagliflozin	Empagliflozin	Total
Total citations	48	44	26	118
Excluded (pharmacokinetic/pharmacodynamic study, non-related outcome study, short term study, or duplicate)	22	19	15	56
Included	26	25	11	62
Reported body mass index changes	26	25	11	62
Reported hypoglycemia events	23	22	10	55
Reported health-related quality-of-life measure	1	1	0	2
	4% (2%)	4% (2%)	0%	3% (1.5%)

frequency of hypoglycemia was statistically significantly related to all SF-36 scores ($P < 0.001$), except physical functioning; patients reporting greater perceived frequency of hypoglycemia had worse HRQoL. The study concluded that using a patient-reported measure of hypoglycemia in the context of a clinical trial could enable the burden of hypoglycemia for patients to be demonstrated.

The current literature review illustrates that despite evidence for improving HRQoL with weight loss and hypoglycemia avoidance, only a small portion of RCTs involving SGLT-2 receptor inhibitors reported HRQoL measures. One study evaluated change in HRQoL associated with ongoing weight change among patients with type 2 diabetes treated with dapagliflozin versus dapagliflozin plus metformin in a double-blind, randomized, placebo-controlled study with a 78-week extension assessing body weight.[7] Patients also completed the "Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes Weight Questionnaire-9" (SHIELD-WQ-9), a weight change-related HRQoL survey. The study illustrated that patients in the dapagliflozin arm had significantly greater weight loss than patients receiving the placebo over 102 weeks ($p < 0.05$). This corresponded to a numerically greater proportion of dapagliflozin treated patients reporting ongoing weight loss and associated improvements in most HRQoL domains at 3 different evaluation points (weeks 24, 50, and 102) than the placebo-treated patients. For example, a statistically significant greater proportion of dapagliflozin-treated patients reported improvement in overall HRQoL at week 24 (29.3%) as compared with placebo-treated patients (14.0% p=0.02).

A second study explored the impact of the average weight loss with canagliflozin treatment. This study employed 2 HRQoL instruments for outcome measures: weight-related quality of life was measured by the Impact of Weight on Quality of Life-Lite (IWQOL-Lite) questionnaire, and satisfaction with physical health and emotional health was measured by the Current Health Satisfaction Questionnaire (CHES-Q)[8]. Logistic regressions showed that a weight loss of 5 pounds (the mean amount of weight loss associated with canagliflozin treatment in the study) was associated with significant improvements in weight-related quality of life and satisfaction with physical and emotional health. In fact, those subjects who lost 5 pounds or more were approximately 2 times more likely to experience improvements than those who lost less than 5 pounds or gained weight.

At a policy level, recently the Patient-Centered Outcomes Research Institute (PCORI) eliminated the restriction of utilizing quality-adjusted life-years (QALYs) in research funded by this institution.[17] This is an important message in the level of policy making and being able to incorporate patient-centred outcomes such as QALYs into cost-effectiveness and comparative studies. This will facilitate a better understanding of the value of different treatments from patients' perspectives.[17]

For the future studies, this pattern of changes in policies call for further investment and funding for developing more accurate tools for measuring global and disease specific HRQoL during RCTs and real-world clinical settings. As new treatments and technologies are introduced or investigated for patient with diabetes, assessment of quality of life for patients with diabetes is increasingly seen as an important aspect of care. This calls for developing guidelines and recommendations for inclusion of HRQoL measures as core components of RCTs involving patients with diabetes in addition to the hard clinical outcomes and surrogate endpoints.

Source of Funding

None

Conflict of Interest

Research grants and consulting: AZ Canada.

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