Original Article

The Efficiency of SGLT2 Inhibitors in Type 2 Diabetes and their Prevention of Renal and Cardiovascular Disease

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Abstract

OBJECTIVES: To compare the effectiveness of sodium glucose co-transporter subtype 2 (SGLT2) inhibitors in preventing cardiovascular and renal disease in Type 2 diabetes patients with standard treatment.

MATERIALS AND METHODS: This study was conducted using experimental research with two-groups. All data were collected from the HIMPRO program from 1st October 2016 to 30th September 2021. A Fisher exact test was used to analyze the data to determine the relative risk reduction (RRR).

RESULTS: 237 diabetes patients were significantly eligible for SGLT2 inhibitors; 102 received SGLT2 inhibitors, and 135 received standard treatment. Annual follow-ups were scheduled for 4 consecutive years. The RRR for prevention of major adverse cardiovascular events (MACEs) in the first to fourth year were (86.8% ($p < 0.05$), 74.3% ($p < 0.05$), 67.2% ($p < 0.05$), and 66.3% ($p < 0.05$), respectively. The RRR for prevention of renal outcomes (ROs) were 55.9%, 68.8%, 83.6% ($p < 0.001$), and 84.3% ($p < 0.001$), respectively.

CONCLUSION: SGLT2 inhibitors, while being prescribed in Type-2 diabetic patients, indicated a statistically significant benefit in the prevention of cardiovascular disease in the first year and with significant benefit in preventing renal disease in the third and fourth years of use.

Keywords: type 2 diabetes, cardiovascular disease, SGLT2 inhibitors

The increase of patients with chronic illnesses is currently at a critical growth rate, especially in those with diabetes and hypertension. In 2017, there were 1,866 cases of diabetes and hypertension at Sisaket Hospital. In addition to this, trying to control hemoglobin A1c (HbA1c) levels is the target goal. Another important preferred treatment for people with type 2 diabetes is preventing microvascular and macrovascular complications. In 2008, the U.S. Food and Drug Administration (FDA) obliged pharmaceutical manufacturers to apply for approval to register new groups of diabetes medication. However, strictly conducted clinical studies should demonstrate the harmfulness to cardiovascular patients. Clinical studies were conducted by investigating deaths caused by the combined effects of cardiovascular disease, myocardial infarction, and stroke, known as major adverse cardiovascular events (MACEs).[1,2]

Sodium-glucose co-transporter inhibitors (SGLTs) are a distinct category of glucoside compounds, consisting of a glycone, and an aglycone part linked by a glucosidic bond. These molecules typically inhibit SGLT1 and SGLT2, which transfer glucose to the small intestine and ureter. Empagliflozin and Dapagliflozin are among the medications in this class available in Thailand. The sodium glucose co-transporter is involved in the absorption mechanism by hindering glucose and sodium around the proximal convoluted tubule of the nephron at the S1 and S2 segments. As a result, the distal renal tubules

receive a significant amount of glucose and sodium that must be reabsorbed in the higher renal tubules. In addition, SGLT inhibitors have the effect of preventing the occurrence of macrovascular complications.[3] The efficacy of Empagliflozin was demonstrated to be statistically effective in reducing the risk of MACEs.[4-6] In contrast, with Dapagliflozin, no change in MACEs was discovered.[7] For the prevention of nephrotic syndrome, the results from combining Empagliflozin and Dapagliflozin were statistically significant.[3]

Dapagliflozin and Empagliflozin are being used as a supplement to other treatments for type 2 diabetes. From several efficacy studies, it has been found to both help to reduce cardiovascular disease and the incidence of stroke. However, in Thailand, there are no study reports that have been conducted on cardiovascular disease, cerebrovascular disease, and renal disease. Therefore, the researchers were interested in conducting a comparative study of the effectiveness of SGLT2 inhibitors in preventing cardiovascular disease, cerebrovascular disease, and renal disease respectively. The objective of this study was to ascertain how SGLT2 inhibitors are used by internal medicine physicians.

Materials and Methods

Data collection

The study was a retrospective chart review. All data were collected from the HIMPRO program from 1 October 2016 to 30 September 2021. The protocol was approved by the Research Ethics Committee of the Sisaket hospital. The protocol approval number is 055/2564.

Statistical analysis

The study was conducted by using SPSS (version 22) with a Chi-square test. Fisher's exact test was used to analyze the data to determine relative risk reduction (RRR).

Results

The study divided a total of 237 participants across two groups: 102 people who received SGLT2 inhibitors and 135 people who received standard treatment (47 cases of Dapagliflozin and 55 cases of Empagliflozin as seen in Table 1).

Table 1: The characteristics of the patients who enrolled HIMPRO program.

Characteristics	Control n = 135	SGLT2 inhibitors n = 102
Gender		
Male	71 (52.60)	50 (49.01)
Female	64 (47.40)	52 (50.99)
Age (years; mean ± SD)	61.90 ± 9.40	57.50 ± 9.10
Body mass index (Kg/m^2; mean ± SD)	25.50 ± 4.60	27.70 ± 4.90
Estimate glomerular filtration rate; eGFR (ml/min/1.73m^2 ; mean ± SD)	71.99 ± 24.80	83.49 ± 23.50
Chronic kidney disease		
Stage 1	41 (30.37)	47 (46.09)
Stage 2	44 (32.59)	42 (41.18)
Stage 3	50 (37.04)	13 (12.75)
Albuminuria		
1+	23 (17.03)	9 (8.82)
2+	4 (2.96)	2 (1.96)
3+	10 (7.41)	3 (2.94)
4+	1(0.74)	0 (0.00)
Hemoglobin A1c (mg%; mean±SD)	8.00+2.00	9.13+2.10
Risk factor of cardiovascular disease in diabetes type 2 patient (male >55 years. or female > 60 years.)		
Once risk factors	48 (50.52)	31 (63.27)
>2 risk factors	23 (23.71)	9 (18.37)
History of coronary artery disease		
Yes	10 (7.40)	8 (7.84)
No	125 (92.60)	94 (98.16)
History of cerebrovascular disease		
Yes	7(5.19)	4 (3.92)
No	128 (94.81)	98 (96.08)
History of heart failure		
Yes	1 (0.74)	2 (1.91)
No	134 (99.26)	100 (99.09)

MACEs in patients with type 2 diabetes were prevented with SGLT2 inhibitors as opposed to those getting standard care. Cardiovascular disease prevention displayed a statistically significant improvement in the group taking SGLT2 inhibitors. It was found that RRR was 86.8% (RR= 0.132; = 0.026), 74.3% (RR = 0.257; p = 0.016), 67.2% (RR = 0.328; p = 0.037), and 66.3% (RR = 0.337; p = 0.012) in years 1, 2, 3, and 4 respectively, as shown in Table 2 and Figure 1.

The result is the prevention of renal outcomes (ROs) (eGFR<15 ml/min/1.73m^2/yr, Cr>2X, RRT and eGFR decrease > 40% from baseline) by using SGLT2 inhibitors on

patients with type 2 diabetes compared to patients receiving standard treatment. It was found that patients who were treated with SGLT2 inhibitors had a statistically significant improvement in the prevention of ROs with RRR at 55.9% (RR = 0.441; $p = 0.636$), 68.8% (RR = 0.312; $p = 0.070$), 83.6% (RR = 0.164; $p < 0.001$) and 84.3% (RR =0.157; $p < 0.001$) in years 1, 2, 3 and 4 respectively, as shown in Table 3 and Figure 2.

Table 2: The result of the MACEs outcome

Groups		Years			
		1st	2nd	3rd	4th
Control	n (N)	10 (135)	17 (134)	18 (130)	24 (115)
SGLT2 inhibitors	n (N)	1 (102)	3 (92)	4 (88)	5 (71)
	RR (RRR)	0.132 (86.8%)*	0.257 (74.3%)*	0.328 (67.2%)*	0.337 (66.3%)*
Dapagliflozin	n (N)	1 (47)	3 (39)	4 (33)	4 (30)
	RR (RRR)	0.287 (71.3)	0.606 (39.4)	0.875 (12.5)	0.639 (36.1)
Empagliflozin	n (N)	0 (55)	0 (53)	0 (50)	1 (41)
	RR (RRR)	0.122 (87.8%)	0.074 (92.6%)*	0.072 (92.8%)*	0.127 (87.3%)*

N= number of a participants; n = number of events of MACEs ; RRR = relative risk reduction * Significant $p < 0.05$

Table 3: The result of renal outcomes (ROs)

Groups		Years			
		1st	2nd	3rd	4th
Control	n (N)	3 (135)	14(134)	27 (130)	31 (115)
SGLT2 inhibitors	n (N)	1 (102)	3 (92)	3 (88)	3 (71)
	RR (RRR)	0.441 (55.9%)	0.312 (68.8%)	0.164 (83.6%)**	0.157 (84.3%)**
Dapagliflozin	n (N)	1 (47)	2(39)	2 (33)	2 (30)
	RR (RRR)	0.957 (4.3%)	0.490 (51%)	0.291 (70.9%)	0.268 (73.2%)*
Empagliflozin	n (N)	0 (55)	1(53)	1 (50)	1 (41)
	RR (RRR)	0.409 (59.1%)	0.180 (82%)	0.096 (90.4%)**	0.098 (90.2%)**

N= number of a participant; n = number of events of MACEs; RRR = relative risk reduction
* Significant $p < 0.05$, ** Significant $p < 0.001$

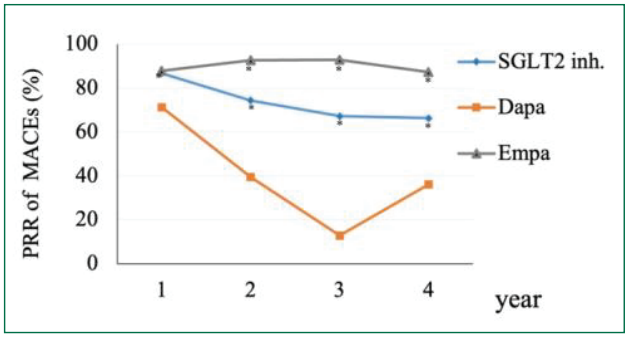


Figure 1: Preventable MACEs outcome.
(SGLT2 inh = SGLT2 inhibitors; Dapa = Dapagliflozin; Empa= Empagliflozin)
* Significant p < 0.05

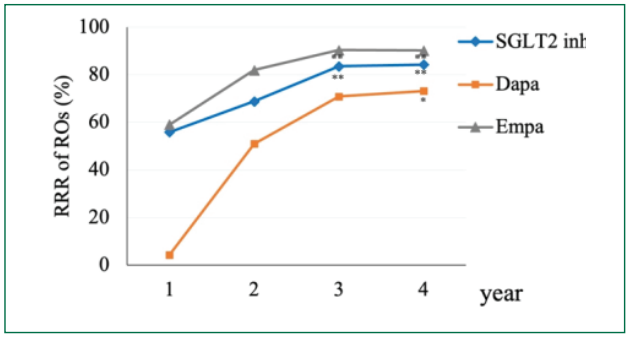


Figure 2: Preventable renal outcome (ROs).
(SGLT2 inh = SGLT2 inhibitors; Dapa = Dapagliflozin; Empa= Empagliflozin)
* Significant $p < 0.05$, ** Significant $p < 0.001$

Discussion

The comparison of the effectiveness of SGLT2 inhibitors with a different control group in preventing MACEs found that after the first year, SGLT2 inhibitors significantly reduced MACEs and this is consistent with the study of EMPAREG[8], and systematic meta-analysis by Lo, Kevin Bryan[3] and teams. Six months after starting SGLT2 inhibitor therapy, the overall impact of cardiovascular disease was lessened. The effectiveness of each of the SGLT2 inhibitors including Empagliflonzin and Dapagliflozin showed that Empagliflozin was helpful in the prevention of cardiovascular diseases, which was consistent with the research mentioned above. According to the study, Dapagliflozin was shown to protect the combined effects of cardiovascular disease, although this finding was not statistically significant, which is consistent with the study DECLARE-TIMI 85.[7]

The efficacy study comparing the SGLT2 inhibitors and the standard group in the prevention of ROs showed that

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SGLT2 inhibitors prevented the development of ROs at years 3 and 4, which is consistent with the systematic meta-analysis study by Lo, Kevin Bryan3 and teams. They found that a group with pre-study GFR levels of < 60 and > 60 (ml/min/1.73m^2/year) had a lower risk of developing the full effects of ROs and the harmful side effects caused by the medications of Empagliflozin and Dapagliflozin. The effects of each medicine were not entirely ruled out by earlier research. However, this study discovered that the medicine Dapagliflozin could prevent ROs by the fourth year after administering it, and the medicine Empagliflozin could prevent ROs by the third year of administering it.

The limitations of this current study includes the use of retrospective data from a single hospital site. The patients began receiving SGLT inhibitors as an additional medication at the beginning of the data collection period. Every year for up to four years, data was gathered on MACEs and ROs occurrences. During the study, due to some non-returning patients and some patient deaths, the study data of such participants were unable to be followed up until later. The data analyzed each year was reflective of the number of patients remaining in the cohort that year. Some information, such as the length of time since type 2 diabetes diagnosis, history of smoking, and cooperation in taking medication, cannot be followed-up on, because this is a retrospective chart review. This may have an impact on the frequency of MACEs and ROs.

Conclusion

From the first year of starting the medication, SGLT2 inhibitors used in combination with type 2 diabetes treatment was proved to help reduce cardiovascular disease and, in the third and fourth years, was proved to help in avoiding renal outcomes. The information gathered, however, is from a single hospital. Future research should be conducted in additional hospitals.

Conflict of interest

The authors declare no conflict of interest.

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