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Sodium-glucose cotransporter-2 inhibitor for renal function preservation in patients with type 2 diabetes mellitus: a Korean Diabetes Association and Korean Society of Nephrology consensus statement

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Diabetes is a leading cause of end-stage renal disease. Therefore, prevention of renal dysfunction is an important treatment goal in the management of diabetes. The data of landmark cardiovascular outcome trials of sodium-glucose cotransporter-2 (SGLT2) inhibitors showed profound reno-protective effects. The Korean Diabetes Association and the Korean Society of Nephrology reviewed clinical trials and performed a meta-analysis to assess the effects of

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© This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/ licenses/by-nc-nd/4.0/), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited. SGLT2 inhibitors on the preservation of estimated glomerular filtration rate (eGFR). We limited the data of SGLT2 inhibitors which can be prescribed in Korea. Both eGFR value and its change from the baseline were significantly more preserved in the SGLT2-inhibitor treatment group compared to the control group after 156 weeks. However, some known adverse events were increased in SGLT2 inhibitor treatment, such as genital infection, diabetic ketoacidosis, and volume depletion. We recommend long-term use of SGLT2 inhibitors in patients with type 2 diabetes mellitus (T2DM) for attenuation of renal function decline. However, we cannot generalize our recommendations due to the lack of long-term clinical trials testing the reno-protective effects of every SGLT2 inhibitor in a broad range of patients with T2DM. This recommendation can be revised and updated after the publication of several large-scale renal outcome trials.

Keywords: Diabetes mellitus, type 2, Glomerular filtration rate, Renal function, Sodium-glucose transporter-2 inhibitors

Introduction

Diabetic kidney disease (DKD) is a global problem and the prevalence and incidence are increasing strikingly. Along with the accelerating incidence of DKD, the total number of patients with end-stage renal disease (ESRD) undergoing maintenance dialysis has grown by approximately 7% to 10% per year in Korea [1-3]. DKD is the most prevalent cause of ESRD (affecting 50.2% of new ESRD patients in 2016) in Korea from 1994 [4]. All current treatment efforts in type 2 diabetes mellitus (T2DM) are devoted to the control of hyperglycemia to prevent the development of micro- and macrovascular complications. The cornerstone of therapy to prevent DKD is the strict control of the blood pressure with the reninangiotensin-aldosterone system (RAAS) blockade and blood glucose levels [5]. However, many patients with diabetes progress to chronic kidney disease (CKD) despite standard treatment. These kinds of patients usually have profound amounts of albuminuria despite the use of RAAS-blocking agents and renal function declines rapidly. Furthermore, reduced estimated glomerular filtration rate (eGFR) is independently associated with allcause mortality and cardiovascular disease [6]. There is an unmet clinical need for diabetes treatment to prevent or delay DKD progression.

Sodium-glucose cotransporter-2 (SGLT2) inhibitor is an emerging antidiabetic medication, and its cardio-protective effects has been proven from the large-scale cardiovascular outcome trials of Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes (EMPA-REG) OUTCOME [7], Canagliflozin Cardiovascular Assessment Study (CANVAS) Program [8], and Dapagliflozin Effect on Cardiovascular Events—Thrombolysis in Myocardial In-

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farction 58 (DECLARE-TIMI 58) [9]. In these studies, renal outcome was analyzed as a secondary outcome. Empagliflozin showed a 49% reduction of incident or worsening of nephropathy (progression to macroalbuminuria, doubling of the serum creatinine level, initiation of renal-replacement therapy, or death from renal disease) [10], and dapagliflozin reduced 47% of renal-specific outcomes (a sustained decline of at least 40% in eGFR to less than 60 mL/min per 1.73 m², ESRD, or death from renal or cardiovascular causes) [11]. The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial [12] was the first study to show reno-protective effects as a primary outcome from a large-scale randomized clinical trial (among 4,401 subjects with T2DM). However, canagliflozin is not available in Korea. Therefore, it is necessary to investigate the renal benefits of SGLT2 inhibitors that can be prescribed in Korea [13,14]. In real clinical practice, we monitored patients' renal functions using eGFR as described in other clinical trials assessed it. Therefore, among various renal outcomes, we aimed to analyze the eGFR after long-term treatment with SGLT2 inhibitors.

Recent recommendations regarding SGLT2 inhibitor use in patients with T2DM

In August 2019, the American Diabetes Association revised the online version of the Standards of Medical Care in Diabetes, adopting the results of the CREDENCE trial [15]. It recommended to consider SGLT2 inhibitor treatment in patients with T2DM and CKD (level of evidence C). After that, it updated the recommendation level to level of evidence A and specified the indication of SGLT2 inhibitor for patients with T2DM and DKD with an eGFR of at least 30 mL/min per 1.73 m² and albuminuria in 2020 [16]. Diabetes Canada also recommended SGLT2 inhibitor in T2DM with clinical cardiovascular disease and with an eGFR of at least 30 mL/min per 1.73 m² to reduce the risk of progression of CKD (Grade B, level 2 for empagliflozin and Grade C, level 3 for canagliflozin) in 2018 [17]. The Committee of Clinical Practice Guideline of the Korean Diabetes Association updated to the 6th Clinical Practice Guideline in 2019. In this guideline, SGLT2 inhibitor was recommended as a second-line drug, and the committee emphasized its cardioprotective effects [18]. However, it did not yet contain renal outcomes of SGLT2

inhibitor. In this statement, we firstly announced the reno-protective effects of SGLT2 inhibitor considering the situation of Korea.

Effects of SGLT2 inhibitors on renal function

Results of cardiovascular outcome trials using SGLT2 inhibitors

Neuen et al [19] reported the meta-analysis data of EM-PA-REG Outcome, CANVAS Program, CREDENCE, and DECLARE-TIMI 58. This meta-analysis demonstrated



Figure 1. Effect of sodium-glucose cotransporter-2 inhibitors (SGLT2i) on (A) estimated glomerular filtration rate (eGFR), and (B) change of eGFR from baseline.

Cl, confidence interval; IV, inverse variance; SD, standard deviation.

that SGLT2 inhibitors reduced the risk of ESRD and death due to kidney disease (relative risk of 0.67). This beneficial effect has been shown consistently across baseline eGFR levels in those studies. However, a meta-analysis result excluding the CREDENCE trial showed that the reno-protective effects were attenuated in patients with more advanced renal dysfunction at a baseline eGFR of less than 60 mL/min per 1.73 m² [20]. The inclusion and exclusion criteria of the original randomized clinical tri-

als were not the same. For example, the EMPA-REG trial [10] included subjects with their eGFRs of at least 30 mL/ min per 1.73 m², in contrast the DECLARE-TIMI 58 study [11] included subjects whose eGFRs were equal to or higher than 60 mL/min per 1.73 m². In this regard, 25.5% of subjects in the EMPA-REG study and only 7.4% of participants in DECLARE-TIMI 58 had eGFRs that were less than 60 mL/min per 1.73 m². Furthermore, a large number of participants were not followed up, and Asian pa-

В		SGLT2i		F	Placebo			Mean difference	Mean difference
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, random, 95% CI	IV, random, 95% CI
2.8.1.12 weeks Kaku K et al. 2017 Kohan DE et al. 2014 Subtotal (95% Cl) Heterogeneity: Tau ² = 6.04; Chi Test for overall effect: Z = 1.39	-1.3 -3.78 ² = 17.39, df (<i>P</i> = 0.16)	18.076 1.0228 f = 1 (<i>P</i> < 0	884 149 1,033 0.0001);	-0.7 0.4 I ² = 94%	12.571 0.2	439 70 509	47.2% 52.8% 100.0%	-0.60 [-2.27, 1.07] -4.18 [-4.35, -4.01] -2.49 [-5.99, 1.01]	
2.8.2 24 weeks Haering HU et al. 2015 Kaku K et al. 2017 Kohan DE et al. 2014 Kovacs CS et al. 2015 Merker L et al. 2015 Wiviott SD et al. 2019 Subtotal (95% CI) Heterogeneity: Tau ² = 1.00; Chi Test for overall effect: Z = 3.47	-1.89 -0.949 -3.581 -2.756 -0.792 -3.2 2 = 26.76, df (<i>P</i> = 0.0005)	12.06 16.423 1.4693 15.009 12.127 27.84 f = 5 (P < 0)	441 745 139 333 430 8,273 10,361 0.0001);	-1.9 -0.8 -0.5 -0.5 1 -1 $l^2 = 81\%$	10.1 11.08 0.92 12.5 11.2 9.2519	225 341 62 165 207 8,223 9,223	14.3% 14.8% 24.8% 9.7% 13.1% 23.2% 100.0%	0.01 [-1.72, 1.74] -0.15 [-1.81, 1.52] -3.08 [-3.42, -2.75] -2.26 [-4.75, 0.24] -1.79 [-3.70, 0.12] -2.20 [-2.83, -1.57] -1.75 [-2.74, -0.76]	*
2.8.3 52 weeks Barnett AH et al. 2014 (1) Barnett AH et al. 2014 (2) Kaku K et al. 2017 Kohan DE et al. 2014 Roden M et al. 2015 Rosenstock J et al. 2015 Wiviott SD et al. 2019 Subtotal (95% CI) Heterogeneity: Tau ² = 0.57; Chi Test for overall effect: Z = 1.74	-2.8 -2.254 -0.406 -3.261 1.569 -5.231 -3.6 2 = 31.52, df (P = 0.08)	8.2 10.807 5.454 1.5428 12.5 12.727 13.67 = 6 (<i>P</i> < 0	187 195 596 127 671 324 7,978 10,078 0.0001);	-0.3 -0.71 -0.5 -2.58 0.6 -6.3 -2.2 I ² = 81%	7.4 9.7 3.0199 1.16 9.7 13 9.0592	187 95 228 49 228 170 7,884 8,841	11.1% 6.3% 20.5% 22.0% 11.2% 6.6% 22.4% 100.0%	-2.50 [-4.08, -0.92] -1.54 [-4.01, 0.93] 0.09 [-0.49, 0.68] -0.68 [-1.10, -0.26] 0.97 [-0.61, 2.54] 1.07 [-1.33, 3.46] -1.40 [-1.76, -1.04] -0.64 [-1.36, 0.08]	
2.8.4 104 weeks Haering HU et al. 2015 Kaku K et al. 2017 Kohan DE et al. 2014 Kovacs CS et al. 2015 Merker L et al. 2015 Roden M et al. 2015 Rosenstock J et al. 2015 Wilding JP et al. 2014 Wiviott SD et al. 2019 Subtotal (95% CI) Heterogeneity: Tau ² = 0.43; Chi Test for overall effect: Z = 0.37	$\begin{array}{c} 0.1063 \\ -1.606 \\ -2.704 \\ 0.6 \\ 2.651 \\ 2.35 \\ -5.231 \\ -0.292 \\ -4.1 \end{array}$	13.519 10.501 1.4268 15.518 12.392 12.682 12.727 10.907 13.265	441 381 90 333 431 448 324 395 7,513 10,356 0.01); l ² =	0.1 -2.5 -2.38 4.3 4.2 0.6 -6.3 1.4 -4.2	13.1 5.8095 1.01 12.8 13.7 9.7 13 10.691 17.453	225 135 42 165 206 228 170 102 7,316 8,589	7.2% 11.8% 24.0% 5.4% 6.8% 9.6% 6.2% 23.1% 100.0%	0.01 [-2.12, 2.13] 0.89 [-0.55, 2.33] -0.32 [-0.75, 0.10] -3.70 [-6.27, -1.13] -1.55 [-3.76, 0.66] 1.75 [0.03, 3.47] 1.07 [-1.33, 3.46] -1.69 [-4.03, 0.64] 0.10 [-0.40, 0.60] -0.13 [-0.79, 0.54]	
2.8.5 156 weeks Kaku K et al. 2017 Wiviott SD et al. 2019 Subtotal (95% CI) Heterogeneity: Tau ² = 0.27; Chi Test for overall effect: Z = 2.80	-2.5 -6 ² = 1.27, df = (<i>P</i> = 0.005)	9.8995 8.5956 = 1 (<i>P</i> = 0.	98 7,098 7,196 26); I ² = 2	-2.5 -7.6 21%	7.1414 8.4132	51 6,800 6,851	11.3% 88.7% 100.0%	0.00 [-2.77, 2.77] 1.60 [1.32, 1.88] 1.42 [0.42, 2.41]	
2.8.6 208 weeks Kaku K et al. 2017 Wiviott SD et al. 2019 Subtotal (95% CI) Heterogeneity: Tau ² = 2.13; Chi Test for overall effect: Z = 1.18	-2.166 -8.2 ² = 2.25, df = (<i>P</i> = 0.24)	12.86 23.806 = 1 (<i>P</i> = 0.	90 6,050 6,140 13); I ² = 5	-1.7 -10.5 56%	4.9477 11.624	17 5,770 5,787	29.3% 70.7% 100.0%	-0.47 [-4.01, 3.08] 2.30 [1.63, 2.97] 1.49 [-0.98, 3.96]	

Test for subgroup differences: $Chi^2 = 24.35$, df = 5 (*P* = 0.0002); l² = 79.5%

Favours [placebo] Favours [SGLT2i]

Figure 1. Continued.

tients made up the minority of participants in each study, including 21.6% in the EMPA-REG study and 13.4% in the DECLARE-TIMI 58 study. For this reason, uncertainty remains about the reno-protective effect of SGLT2 inhibitor in Asian populations with reduced renal function. In this study, we reviewed current evidence considering patients' baseline renal function and performed a metaanalysis to determine whether SGLT2 inhibitor can be recommended to Korean subjects with T2DM.

Meta-analysis of large clinical trials using SGLT2 inhibitors

Search strategy and selection criteria

We searched PubMed, Embase, and the Cochrane Central Register of Controlled Library up to March 2020, using search terms including "dapagliflozin," "empagliflozin," "ipragliflozin," and "ertugliflozin," which are drugs available in Korea. We included long-term largescale randomized placebo controlled trials whose treatment duration was at least 52 weeks in T2DM patients with more than 100 participants in total. No studies on ipragliflozin and ertugliflozin met these criteria. Finally, we included 12 articles for 11 clinical studies (Supplementary Table 1 and Supplementary Fig. 1, available online) [9,10,21–30]. In this meta-analysis, the final eGFR or delta eGFR from baseline was compared between the SGLT2-inhibitor treatment group and placebo-control according to the method presented in the original studies, and we analyzed the data of low and high doses of empagliflozin separately.

А		SGLT2i			Placebo			Mean difference	Mean dif	ference	
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, random, 95% CI	IV, random	n, 95% CI	
2.2.1 52 weeks Barnett AH et al. 2014 (1) Barnett AH et al. 2014 (2) Bailey CJ et al. 2013 Haering H et al. 2015 Kaku K et al. 2017 Kohan DE et al. 2014 Merker L et al. 2015 Roden M et al. 2015 Rosenstock J et al. 2015 Wilding JP et al. 2014 Subtotal (95% CI) Heterogeneity: $Tau2 = 0.03$ Test for overall effect: Z =	-0.31 -0.32 -0.72041 -0.75102 -0.45 -0.34 -0.75071 -0.70018 -0.66325 -0.91866 ; Chi ² = 29.6 8.10 (P < 0.	0.7131 2.699551 0.63386 2.346172 4.395452 0.16 1.025812 2.849365 1.824279 0.879242 33, df = 9 (<i>P</i> 00001)	118 227 292 441 483 30 420 671 228 509 3,419 = 0.00	0.11 0.02 0.08 0 -0.05 -0.06 -0.1 0.09 -0.01 -0.47 005); l ² = 7	0.6723 0.8949 1.6402 1.5 4.3909 0.18 1.438749 0.754983 0.754983 0.754983 0.7512	123 66 74 225 482 13 207 228 113 157 1,688	12.8% 6.3% 9.0% 4.2% 14.7% 11.3% 10.7% 10.1% 13.9% 100.0%	$\begin{array}{c} -0.42 \ [-0.60, \ -0.24] \\ -0.34 \ [-0.75, \ 0.07] \\ -0.80 \ [-1.18, \ -0.42] \\ -0.75 \ [-1.04, \ -0.46] \\ -0.40 \ [-0.95, \ 0.15] \\ -0.28 \ [-0.39, \ -0.17] \\ -0.65 \ [-0.87, \ -0.43] \\ -0.79 \ [-1.03, \ -0.55] \\ -0.65 \ [-0.91, \ -0.40] \\ -0.45 \ [-0.59, \ -0.31] \\ -0.54 \ [-0.67, \ -0.41] \end{array}$	+ + + + + + + + + + + + + + + + + + +	_	
2.2.2 104 weeks Bailey CJ et al. 2013 Haering H et al. 2015 Kaku K et al. 2017 Kohan DE et al. 2014 Kovacs CS et al. 2015 Roden M et al. 2015 Roden M et al. 2015 Wilding JP et al. 2015 Wilding JP et al. 2015 Subtotal (95% CI) Heterogeneity: Tau ² = 0.02 Test for overall effect: Z =	-0.63571 -0.7 -0.45936 -0.95444 -0.72235 -0.69516 -0.66097 -0.54641 -0.75614 ; Chi ² = 14.3 8.68 (<i>P</i> < 0.	0.670086 1.456006 6.376544 1.589732 1.200479 2.225796 2.671054 1.449939 0.770037 87, df = 8 (<i>P</i> 00001)	140 213 846 18 149 248 372 237 399 2,622 = 0.07	0.02 0.1 -0.05 -0.67 -0.05 0.1 0.13 0.01 -0.43); l ² = 449	0.5674 0.87178 4.118252 0.82 0.668132 0.83666 0.697424 1.058301 0.887 %	28 76 424 31 70 76 112 107 928	15.2% 13.1% 4.7% 1.5% 11.8% 10.4% 13.5% 18.4% 100.0%	-0.66 [-0.89, -0.42] -0.80 [-1.08, -0.52] -0.41 [-0.99, 0.17] -0.28 [-1.37, 0.80] -0.67 [-0.98, -0.37] -0.80 [-1.13, -0.46] -0.79 [-1.10, -0.48] -0.56 [-0.83, -0.29] -0.33 [-0.51, -0.14] -0.62 [-0.75, -0.48]	+++++++++++++++++++++++++++++++++++++++		
2.2.3 156 weeks Kaku K et al. 2017 Subtotal (95% CI) Heterogeneity: not applica Test for overall effect: Z =	-0.4248 ble 1.37 (<i>P</i> = 0.	5.894165 17)	625 625	0	3.464102	300 300	100.0% 100.0%	-0.42 [-1.03, 0.18] -0.42 [-1.03, 0.18]	-	-	
2.2.4 208 weeks Kaku K et al. 2017 Subtotal (95% CI) Heterogeneity: not applica Test for overall effect: Z =	−0.1572 ble 0.74 (<i>P</i> = 0.	2.90927 46)	100 100	0.15	1.897367	40 40	100.0% 100.0%	-0.31 [-1.13, 0.51] -0.31 [-1.13, 0.51] -2	2 -1 0		2
Test for subgroup difference	ces: Chi ² = 1	.18, df = 3 (P = 0.7	(6); $I^2 = 0^6$	%				Favours [SGLT2i]	Favours [place	bo]

Figure 2. Effect of sodium-glucose cotransporter-2 inhibitors (SGLT2i) on change of (A) glycosylated hemoglobin, (B) body weight, (C) systolic blood pressure, and (D) diastolic blood pressure.

Cl, confidence interval; IV, inverse variance; SD, standard deviation.

Effect of SGLT2 inhibitor on eGFR

First, we compared the eGFR levels at each time point between the SGLT2 inhibitor and control. As shown in Fig. 1A. SGLT2 inhibitor treatment showed a lower eGFR level than the control at 12 weeks (-1.81 mL/min per) 1.73 m^2 ; 95% confidence interval [CI] -3.03 to -0.58) and at 24 weeks (-1.33 mL/min per 1.73 m²; 95% CI, -2.52 to -0.15). However, a favorable effect on eGFR was observed after at least 156 weeks of treatment. At 208 weeks of treatment, the mean difference in eGFR was 3.96 mL/ min per 1.73 m² (95% CI, 3.13–4.80) between groups. In general, the improving trend of eGFR was observed in the SGLT2 inhibitor group as the treatment duration was prolonged. In terms of eGFR change from baseline, the mean difference was 1.42 mL/min per 1.73 m² (95% CI, 0.42 to 2.41) at 156 weeks (Fig. 1B). Therefore, SGLT2 inhibitor treatment showed reno-protective effects after long-term

treatment.

Effects of SGLT2 inhibitor on glycosylated hemoglobin, body weight, and blood pressure

The glucose-lowering effect of SGLT2 inhibitors was consistently observed: the mean difference in the decline of the glycosylated hemoglobin (HbA1c) was -0.54 (95% CI, -0.67 to -0.41) at 52 weeks and -0.62 (95% CI, -0.75 to -0.48) at 104 weeks, respectively (Fig. 2A). The magnitude of body weight reduction was also greater in the SGLT2 inhibitor treatment than control treatment group (Fig. 2B). Both the systolic and diastolic blood pressure were more significantly decreased in the SGLT2 inhibitor treatment (Fig. 2C, D).

В		SGLT2i		Plac	ebo			Mean difference	Mean difference
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, random, 95% CI	IV, random, 95% CI
Study or subgroup 2.12.1 52 weeks Barnett AH et al. 2014 (1) Barnett AH et al. 2014 (2) Bailey CJ et al. 2013 Haering HU et al. 2015 Kaku K et al. 2017 Kohan DE et al. 2014 Kavacs CS et al. 2015 Roden M et al. 2015 Roden M et al. 2015 Wilding JP et al. 2014 Subtotal (95% CI)	Mean -2.2984615 -1.17 -2.4621701 -2.7 -2.2491649 -1.46 -1.6520231 0.1975 -2.0615385 -2.2469027 -1.1764047	SD 3.24622339 2.3586 2.89110683 2.19241115 4.37582347 4.43223695 2.78479237 5.62924655 2.46560172 0.53369917 3.41349877	Total 195 118 341 241 958 173 280 416 226 509 3,585	Mean -0.44 0 0.02 -0.3 -0.8 1.1 1.2 -0.8 -0.75 -0.01 0.82	SD 2.75 2.58 2.98 1.89 4.4 4.28 2.12 3.69 1.8 0.53 3.43	Total 95 123 105 89 483 51 50 85 85 81 114 157 1,433	Weight 8.8% 9.4% 9.2% 10.2% 5.0% 8.7% 6.9% 10.4% 11.7% 9.4% 100.0%	IV, random, 95% Cl -1.86 [-2.57, -1.14] -1.17 [-1.79, -0.55] -2.48 [-3.12, -1.84] -2.40 [-2.88, -1.92] -1.45 [-1.93, -0.97] -2.65 [-3.96, -1.16] -2.85 [-3.57, -2.13] 1.00 [-0.03, 2.02] -1.31 [-1.77, -0.85] -2.24 [-2.36, -2.12] -2.00 [-2.61, -1.38] -1.79 [-2.21, -1.38]	IV, random, 95% CI
Heterogeneity: $Tau^2 = 0.38$ Test for overall effect: Z = 8	; Chi ² = 75.09, 8.45 (<i>P</i> < 0.00	, df = 10 (<i>P</i> < 0 0001)	.00001)	; I ² = 87	%				
2.12.2 104 weeks Bailey CJ et al. 2013 Haering HU et al. 2015 Kaku K et al. 2017 Kohan DE et al. 2014 Kovacs CS et al. 2015 Merker L et al. 2015 Roden M et al. 2015 Rosenstock J et al. 2015 Wilding JP et al. 2014 Subtotal (95% CI) Heterogeneity: Tau ² = 0.46 Test for overall effect: Z = 1	-1.53 -2.81 -2.45 -0.76 -0.68 -2.84 -2.84 -2.1 -1.18 ; Chi ² = 23.04, 7.02 (<i>P</i> < 0.00	3.71 3.1 5.68 5.06 3.9 4.49 3.55 6.36 4.21 odf = 8 (<i>P</i> = 0.0	264 214 716 92 333 251 371 324 405 2,970 003); I ² =	1.36 -1.2 -0.9 2.63 0.5 -0.8 -0.8 0.7 1.83	3.56 3.51 5.72 5.12 3.85 5.86 3.2 10.43 4.09	73 77 363 42 165 70 64 170 108 1,132	12.3% 12.7% 14.1% 6.2% 14.1% 8.1% 12.9% 6.9% 12.8% 100.0%	-2.89 [-3.82, -1.96] -1.61 [-2.50, -0.72] -1.55 [-2.27, -0.83] -3.39 [-5.25, -1.53] -1.18 [-1.90, -0.46] -2.04 [-3.52, -0.56] -1.04 [-1.90, -0.18] -2.80 [-4.51, -1.09] -3.01 [-3.88, -2.14] -2.03 [-2.60, -1.46]	
2.12.3 156 weeks Kaku K et al. 2017 Subtotal (95% CI) Heterogeneity: not applica Test for overall effect: Z = 2	-2.5 ble 2.99 (<i>P</i> = 0.00	5.45	661 661	-1.4	5.35	318 318	100.0% 100.0%	-1.10 [-1.82, -0.38] -1.10 [-1.82, -0.38]	-
2.12.4 208 weeks Kaku K et al. 2017 Subtotal (95% CI) Heterogeneity: not applica Test for overall effect: Z = 6	−2.1 ble 0.65 (<i>P</i> = 0.51	5.82	272 272	-1.7	5.57	124 124	100.0% 100.0%	-0.40 [-1.60, 0.80] -0.40 [-1.60, 0.80] -	

Test for subgroup differences: $Chi^2 = 8.58$, df = 3 (P = 0.04); $I^2 = 65.0\%$

Figure 2. Continued 1.

С		SGLT2i		Placebo	C		Mean difference		Mean c	difference		
Study or subgroup	Mean	SD	Total Mear	n SD	Total	Weight	IV, random, 95% CI		IV, rando	om, 95% Cl	l	
2.15.1 52 weeks												
Barnett AH et al. 2014 (1) Barnett AH et al. 2014 (2) Haering HU et al. 2015 Kaku K et al. 2017 Kohan DE et al. 2014 Kavacs CS et al. 2015	-5.9 -4.4162162 -2.909205 -4.6541754 -1.3867665 -1.44	11.7496 10.4328679 7.64680406 10.9417026 17.3218529 9.38840077	112 -0.5 148 1.8 239 0.8 958 0.7 167 4.7 175	5 11.3 3 13.3 3 6.6 11 14.1 8.5	126 65 89 483 85 50	3.8% 2.5% 11.7% 22.9% 2.1% 4.4%	-5.40 [-8.34, -2.46] -6.22 [-9.86, -2.57] -3.71 [-5.39, -2.03] -4.75 [-5.96, -3.55] -5.49 [-9.47, -1.50] -2.44 [-5.18, 0.30]					
Merker L et al. 2015 Roden M et al. 2015 Wilding JP et al. 2014 Subtotal (95% CI) Heterogeneity: Tau ² = 0.00 Test for overall effect: Z =	-4.267148 -4.1185366 -4.5702554 ; Chi ² = 5.98, o 14.12 (<i>P</i> < 0.0	9.43427129 4.98470009 19.0554697 df = 8 (<i>P</i> = 0.65 00001)	277 -0.2 410 -0.2 509 -1.5 2,995 5); l ² =0%	2 7.3 2 3.6 5 13.3	84 81 157 1,220	9.0% 39.0% 4.7% 100.0%	-4.07 [-5.98, -2.15] -3.92 [-4.84, -3.00] -3.07 [-5.73, -0.41] -4.14 [-4.71, -3.57]		 •	-		
2.15.2 104 weeks Bailey CJ et al. 2013 Haering HU et al. 2015 Kaku K et al. 2017 Kohan DE et al. 2014 Kovacs CS et al. 2015 Merker L et al. 2015 Rosenstock J et al. 2015 Subtotal (95% CI) Heterogeneity: Tau ² = 0.98 Test for overall effect: Z = 4	-0.3 -4.4 -4.5 -1.4 -2.6 -4.9 -3.1 -3.3 ; Chi ² = 12.68, 5.89 (<i>P</i> < 0.00	137 10.3 12.4 17.3 11.6 9 10.6 13.3 odf = 7 (<i>P</i> = 0.0	260 1.5 214 -2.8 858 -0.1 333 0.3 248 -0.6 370 -2.8 324 0.1 370 -2.8 324 0.1 2,775 08); l ² = 45%	5 116.2 9.6 1.2 14.1 3 11.6 6 6.7 3 10.4 13.0	72 76 426 84 165 70 64 170 1,127	0.1% 11.9% 27.4% 6.2% 14.5% 16.4% 10.7% 12.7% 100.0%	-1.80 [-33.39, 29.79] -1.60 [-4.16, 0.96] -4.40 [-5.24, -3.56] -5.50 [-9.49, -1.51] -2.90 [-5.06, -0.74] -4.30 [-6.23, -2.37] -0.30 [-3.07, 2.47] -3.40 [-5.83, -0.97] -3.33 [-4.44, -2.22]		• • • •			
2.15.3 156 weeks Kaku K et al. 2017 Subtotal (95% CI) Heterogeneity: not applica Test for overall effect: Z = 1	−5.6 ble 7.46 (<i>P</i> < 0.00	10.2	576 -0.7 576	9.9	270 270	100.0% 100.0%	-5.50 [-6.95, -4.05] -5.50 [-6.95, -4.05]		•			
2.15.4 208 weeks Kaku K et al. 2017 Subtotal (95% CI) Heterogeneity: not applica Test for overall effect: Z = (-4.2 ble 6.07 (<i>P</i> < 0.00	10.8	285 2.5 285	5 10.3	131 131	100.0% 100.0%	-6.70 [-8.86, -4.54] -6.70 [-8.86, -4.54] -	-10	-5	0 5		10
Test for subgroup difference	es: Chi ² = 10.	58, df = 3 (P =	= 0.01); I ² = 7 ²	1.6%				Favou	rs [SGLT2i]	Favours	[place	bo]

Figure 2. Continued 2.

Adverse effects of SGLT2 inhibitor

There was no difference between the SGLT2 inhibitor and control groups in hypoglycemia events and urinary tract infection (Fig. 3A, B). However, more subjects were diagnosed with genital infections (risk ratio [RR], 3.34) (Fig. 3C) and diabetic ketoacidosis (RR, 2.22) (Fig. 3D). Acute kidney injury was less in the SGLT2 inhibitor group than in the control group (RR, 0.71) (Fig. 3E), but volume depletion was slightly more common in the SGLT2 inhibitor group (RR, 1.16) (Fig. 3F).

Effects of SGLT2 inhibitor on renal function among patients with eGFRs of less than 60 mL/min per 1.73 m²

The clinical studies we included for this systemic review and meta-analysis did not enroll a sufficient number of patients with eGFRs of less than 60 mL/min per 1.73 m^2 . The patients with eGFRs of less than 60 mL/min per 1.73 m² included 7.4% of participants in the dapagliflozin study (DECLARE-TIMI 58) and 25.5% of participants in the empagliflozin study (EMPA-REG). Dapagliflozin did not demonstrate the prevention of eGFR decline in patients with eGFRs of less than 60 mL/min per 1.73 m² compared to the placebo group during four years of follow-up (P = 0.053) [11]. This negative result for preventing eGFR decline with dapagliflozin could be due to the insufficient number of enrolled patients with eGFRs of less than 60 mL/min per 1.73 m² since dapagliflozin reduced the rate of eGFR decline in patients with eGFRs of more than 60 mL/min per 1.73 m². In the empagliflozin study, patients with eGFRs of less than 60 mL/min per 1.73 m² treated with empagliflozin showed higher eGFRs compared to the placebo group from 156 weeks, while the analysis with total enrolled patients showed higher eGFRs at 104 weeks (Fig. 4A vs. Fig. 1A). In terms of the eGFR change from baseline, SGLT2 inhibitors showed a beneficial effect at 208-week treatment compared to

D		SGLT2i	1	Placebo)		Mean difference	Mean difference
Study or subgroup	Mean	SD	Total Mean	SD	Total	Weight	IV, random, 95% CI	IV, random, 95% CI
2.13.1 52 weeks Barnett AH et al. 2014 (1) Barnett AH et al. 2014 (2) Haering HU et al. 2015 Kaku K et al. 2017 Kohan DE et al. 2014 Kavacs CS et al. 2015 Merker L et al. 2015 Roden M et al. 2015 Wilding JP et al. 2014 Subtotal (95% CI) Heterogeneity: Tau ² = 0.08 Test for overall effect: Z =	-2.4 -1.8108108 -1.8476987 -1.7033403 -0.9121557 -1.916 -2.533574 -1.1897561 -2.8157957 ; Chi ² = 9.34, (5.60 (<i>P</i> < 0.00	6.1113 5.60853855 5.46035991 10.9406736 10.5817804 5.13349112 5.89056534 2.1510201 7.48176567 df = 8 (<i>P</i> = 0.3 ⁻¹ 0001)	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	6.8 5.2 4.7 11 9.6 4.9 4.6 4.5 7.6	126 65 89 483 85 50 84 81 157 1,220	8.3% 8.8% 13.8% 13.7% 3.4% 8.8% 13.7% 13.7% 13.3% 11.2% 100.0%	-1.90 [-3.51, -0.29] -2.91 [-4.46, -1.36] -0.85 [-2.04, 0.35] -1.50 [-2.70, -0.30] -0.41 [-3.01, 2.18] -2.42 [-3.97, -0.86] -1.03 [-2.24, 0.17] -0.69 [-1.69, 0.31] -1.52 [-2.87, -0.16] -1.40 [-1.89, -0.91]	
2.13.2 104 weeks Bailey CJ et al. 2013 Haering HU et al. 2015 Kaku K et al.2017 Kohan DE et al. 2014 Kovacs CS et al. 2015 Merker L et al. 2015 Roden M et al. 2015 Rosenstock J et al. 2015 Subtotal (95% Cl) Heterogeneity: Tau ² = 0.56 Test for overall effect: Z = 1	-1 -2.5 -0.9 -1.7 -2.7 -1.2 -2.2 ; Chi ² = 12.88, 3.10 (P = 0.00)	83.1 6.7 10.4 10.6 6.5 5.6 7 8.9 df = 7 (<i>P</i> = 0.0 (2)	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	67 7 10.3 9.6 6.4 4.2 6.4 7.8	72 76 426 84 165 70 64 170 1,127	0.2% 11.9% 17.9% 7.2% 17.9% 12.6% 14.4% 100.0%	0.00 [-18.48, 18.48] ← -0.90 [-2.71, 0.91] -2.50 [-3.70, -1.30] -0.40 [-3.00, 2.20] -1.90 [-3.10, -0.70] -1.10 [-2.31, 0.11] 1.00 [-0.72, 2.72] -1.90 [-3.42, -0.38] -1.27 [-2.07, -0.47]	
2.13.3 156 weeks Kaku K et al. 2017 Subtotal (95% CI) Heterogeneity: not applica Test for overall effect: Z =	-2.9 ble 2.12 (<i>P</i> = 0.03	8.5	576 -1.6 576	8.2	270 270	100.0% 100.0%	-1.30 [-2.50, -0.10] -1.30 [-2.50, -0.10]	-
2.13.4 208 weeks Kaku K et al. 2017 Subtotal (95% CI) Heterogeneity: not applica Test for overall effect: Z = 1	-2.4 ble 2.45 (<i>P</i> = 0.01	6	285 -0.9 285	5.7	131 131	100.0% 100.0%	-1.50 [-2.70, -0.30] -1.50 [-2.70, -0.30] 	
Test for subgroup difference	ces: Chi ² = 0.1	3, df = 3 (<i>P</i> = 0	$(0.99); I^2 = 0\%$					Favours [SGLT2i] Favours [placebo]

Figure 2. Continued 3.

the control group (Fig. 4B). Both SGLT2 inhibitor studies revealed the initial decrease of the eGFR after SGLT2 inhibitors treatment since the mechanism of SGLT2 inhibitors may be due to relieving vasodilation of the afferent arteriole and following decrease of glomerular hyperfiltration in diabetes [31]. This initial decrease of the eGFR after SGLT2 inhibitor treatment was more significant in patients with eGFRs of less than 60 mL/min per 1.73 m².

The risk of a sustained decrease in eGFR by at least 40% to less than 60 mL/min per 1.73 m², ESRD, or renal death was lower in the dapagliflozin group than those in the placebo group, but there was no statistical significance in patients with eGFRs of less than 60 mL/min per 1.73 m² (hazard ratio, 0.60; 95% CI, 0.35 to 1.02; P = 0.059) [11]. In the EMPA-REG study, incident or worsening nephropathy was significantly lower in the empagliflozin group with eGFRs of less than 60 mL/min per 1.73 m² than in the placebo group (hazard ratio, 0.58; 95% CI, 0.47 to 0.71; P < 0.001) [10]. The adverse events in the EMPA-REG

study were similar between the empagliflozin group and the placebo group in patients with eGFRs of 60 mL/min per 1.73 m^2 or more and in patients with eGFRs of 59 mL/ min per 1.73 m^2 or less. In our meta-analysis, patients with eGFRs of less than 60 mL/min per 1.73 m^2 showed less hypoglycemia and more genital infections in SGLT2 inhibitor treatment compared to the control (Supplementary Fig. 2).

Results of Asian-dominant research

We arbitrarily defined Asian-dominant when Asians made up more than 40% of the total subjects. Kaku et al [21] analyzed the subgroup data of the Asian population from the EMPA-REG OUTCOME trial, which was the longest and largest trial included in our meta-analysis. Asian-dominant studies showed no significant difference in eGFR change between groups (Fig. 5A). Only one study was analyzed after 156 weeks of treatment in this meta-

Α	SGL	T2i	Plac	ebo		Risk ratio	Risk	ratio
Study or subgroup	Events	Total	Events	Total	Weight	M-H, random, 95% CI	M-H, rand	om, 95% Cl
Barnett AH et al. 2014 (1)	52	187	53	187	5.8%	0.98 [0.71, 1.36]		
Barnett AH et al. 2014 (2)	48	195	23	95	3.5%	1.02 [0.66, 1.57]		<u> </u>
Bailey CJ et al. 2013	19	409	8	137	1.1%	0.80 [0.36, 1.78]		
Kohan DE et al. 2015	99 71	441	40	225	5.6%			
Kovacs CS et al. 2014	8	333	43	165	0.7%	0.57 [0.21, 1.53]		
Merker L et al. 2015	25	431	8	206	1.2%	1.49 [0.69, 3.25]		
Roden M et al. 2015	6	670	2	229	0.3%	1.03 [0.21, 5.04]		
Rosenstock J et al. 2015	117	324	60	170	8.7%	1.02 [0.80, 1.31]	_	-
Wanner C et al. 2016 (1)	391	1,212	233	607	18.6%	0.84 [0.74, 0.96]		
Wanner C et al. 2016 (2)	912	3,473	417	1,726	22.3%	1.09 [0.98, 1.20]		-
Wiviott SD et al. 2019	309 61	8 574	73	8 569	19.2%			Ē
Willow OD Ct al. 2015	01	0,014	10	0,000	0.470	0.04 [0.00, 1.17]	-	
Total (95% CI)		17,027		12,597	100.0%	0.98 [0.90, 1.07]		
Total events	2,198		1,089					
Heterogeneity: Tau ² = 0.01; Ch	hi ² = 17.25, di	f = 12 (P = 0)	$(14); I^2 = 309$	%			0.2 0.5	1 2 5
Test for overall effect: $Z = 0.43$	5(P=0.66)						Favours [SGL12]	Favours [placebo]
В	SGL	T2i	Plac	ebo		Risk ratio	Risk	ratio
Study or subgroup	Events	Total	Events	Total	Weight	M-H, random, 95% CI	M-H, rand	om, 95% Cl
Barnett AH et al. 2014 (1)	31	187	29	187	4 4%	1.07 [0.67, 1.70]		•
Barnett AH et al. 2014 (2)	23	195	15	95	2.7%	0.75 [0.41, 1.36]		
Bailey CJ et al. 2013	41	409	11	137	2.4%	1.25 [0.66, 2.36]		
Haering HU et al. 2015	73	441	36	225	6.9%	1.03 [0.72, 1.49]		
Kohan DE et al. 2014	18	168	12	84	2.1%	0.75 [0.38, 1.48]		
Kovacs CS et al. 2015	74 52	333	44	165	8.6%			-
Roden M et al. 2015	53 61	670	20	200	5.1% 4.8%	0.90 [0.59, 1.39]		
Rosenstock J et al. 2015	43	324	15	170	3.1%	1.50 [086, 2.63]		
Wanner C et al. 2016	842	4,686	423	2,333	43.2%	0.99 [0.89, 1.10]	-	-
Wilding JP et al. 2014	72	610	11	197	2.6%	2.11 [1.14, 3.91]		
Wiviott SD et al. 2019	127	8,569	133	8,574	14.2%	0.96 [0.75, 1.22]		
Total (95% CI)		17 023		12 602	100.0%			
Total events	1.458	17,020	782	12,002	100.070	0.33 [0.03, 1.03]		
Heterogeneity: $Tau^2 = 0.00$; Ch	hi ² = 12.14, di	f = 11 (<i>P</i> = 0).35); l ² = 9%				0.5 0.7	1 1.5 2
Test for overall effect: Z = 0.22	2 (<i>P</i> = 0.82)	,					Favours [SGLT2i]	Favours [placebo]
C	201	T 0:	Diag	aha		Diale natio	Dial	ratio
C Study on a state state state	SGL	.I ZI Tatal	Plac	Tatal	\\/aight		Risk M. L	
	Evenis	10121	Evenis	10(8)	weight		w−⊓, rano	011, 95% CI
Barnett AH et al. 2014 (1)	5	187	2	187	3.2%	2.50 [0.49, 12.72]		
Barnett AH et al. 2014 (2) Bailov C Lot al. 2013	12	195	6 7	95 137	7.4%	0.97 [0.38, 2.52]		
Haering HU et al. 2015	23	403	2	225	3.9%	5.87 [1.40, 24.66]		
Kohan DE et al. 2014	15	168	3	84	5.2%	2.50 [0.74, 8.40]	-	
Kovacs CS et al. 2015	24	333	5	165	7.4%	2.38 [0.92, 6.12]		
Merker L et al. 2015	38	431	1	206	2.3%	18.16 [2.51, 131.37]		
Roden M et al. 2015	29	670	4	229	6.6%	2.48 [0.88, 6.97]		
Rosenstock J et al. 2015	21	324	3	170	5.3%	3.67 [1.11, 12.14]		
Wanner C et al. 2016 (1)	234	3 473	10	1 726	11.4% 17.7%	3.21 [1.00, 0.20] 3.63 [2.52, 5.23]		
Wilding JP et al. 2014	70	610	6	197	9.0%	3.77 [1.66, 8.54]		
Wiviott SD et al. 2019	76	8,574	9	8,569	10.9%	8.44 [4.23, 16.83]		
Total (95% CI)	664	17,027	00	12,597	100.0%	3.34 [2.44, 4.57]		•
Heterogeneity: $T_{21}^2 = 0.11$	004 אי 10,17 אי	f = 12 (P = 0	90 1 08): 1 ² = 370	Va			0.01 0.1	1 10 100
Test for overall effect: $7 = 7.5$	– 19.17, 01 7 (P < 0.0000)1)		10			Favours [SGLT2i]	Favours [placebo]
		- · /					[]	The research in the rest of th
П	0.01	T O:				Diele vetie	5.1	

D	SGLT2i Placebo			ebo		Risk ratio					
Study or subgroup	Events	Total	Events	Total	Weight	M-H, random, 95% C	l	M−H, rar	ndom, 9	5% CI	
Wanner C et al. 2016 Wiviott SD et al. 2019	4 27	4,685 8,574	1 12	2,333 8,569	8.8% 91.2%	1.99 [0.22, 17.81] 2.25 [1.14, 4.44]				 }	
Total (95% CI) Total events Heterogeneity: Tau ² = 0.00; C Test for overall effect: $Z = 2.4$	31 Chi² = 0.01, df 12 (<i>P</i> = 0.02)	13,259 = 1 (<i>P</i> = 0.9	13 2); I ² = 0%	10,902	100.0%	2.22 [1.16, 4.26]	0.01 Fave	0.1 ours [SGLT2i]	1 Fa	► 10 vours [plac	100 ebo]

Figure 3. Effect of sodium-glucose cotransporter-2 inhibitors (SGLT2i) on (A) hypoglycemia, (B) urinary tract infection, (C) genital infection, (D) diabetic ketoacidosis, (E) acute kidney injury, and (F) volume depletion.

CI, confidence interval; M–H, Mantel–Haenszel.



Figure 3. Continued.

analysis; therefore, it is not conclusive as to whether Asians may experience similar benefits of renal preservation with long-term treatment of SGLT2 inhibitors compared to the non-Asian population. Other parameters, such as HbA1c, body weight, blood pressure, and adverse events were similar with meta-analysis of the total population (Fig. 5B and Supplementary Fig. 3).

Korean Diabetes Association and Korean Society of Nephrology joint consensus statement on the use of SGLT2 inhibitor in T2DM for preservation of renal function

Long-term treatment of SGLT2 inhibitor has a preventive effect on decline of renal function in some patients with T2DM; therefore, long-term treatment of SGLT2 inhibitors is recommended under continuous monitoring of renal function (i.e., eGFR) (weak recommendation, low quality of evidence).

Strength of the recommendation

Study participants were mainly from Western countries. Their baseline body mass index was near 30 kg/m^2 , which is relatively higher than that of Korean subjects with

T2DM. Furthermore, Asian-dominant studies are lacking and a meta-analysis including only Asian-dominant studies did not show statistically significant effects on renal preservation. In addition, only two studies included subjects whose eGFRs were less than 60 mL/min/1.73 m² in this analysis. The immediate decline in renal function was frequently observed in subjects with eGFRs of less than 60 mL/min per 1.73 m^2 ; therefore, more attention should be paid to this population. In this regard, we cannot recommend the use of SGLT2 inhibitors in all patients with T2DM: more studies assessing renal effects as a primary outcome and including a meaningful number of Asian patients and subjects with a broad range of renal function are necessary. However, the ongoing Dapagliflozin And Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial (NCT03036150) and EMPA-KIDNEY study (NCT03594110) are likely to provide further evidence in this field. This recommendation can be revised and updated after publication of these two landmark studies.

Quality of evidence

The authors independently assessed the risk of bias at the study level using the revised Cochrane risk-of-bias



Figure 4. Results of patients with estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m². Effect of sodium-glucose cotransporter-2 inhibitors (SGLT2i) on (A) eGFR, and (B) change of eGFR from baseline. Cl, confidence interval; IV, inverse variance; SD, standard deviation.

tool for randomized trials (risk of bias 2.0; Cochrane, London, England) and any disagreements were resolved by establishing a consensus among the authors. The risk of bias was generally low except in two studies that showed high risks of bias due to missing outcomes data (Supplementary Fig. 3). A large number of patients were not followed up with at the time of final assessment. More than 50% of participants were not followed up with in three out of 10 studies. We also do not know the distinct clinical characteristics of subjects who were followed up with successfully and those who were not. Therefore, a degree of uncertainty exists due to the high dropout rate.

Other considerations

The mainstay of prevention and treatment for CKD in T2DM included optimal treatment of hyperglycemia, dyslipidemia, obesity, and blood pressure using RAAS blockade. These general recommendations should be followed and the patient's preferences regarding both the benefits of SGLT2 inhibitors and their possible disadvantages, such as urinary frequency, unwanted body weight loss, genital infections, and cost, should be considered. We should educate patients for preventing volume depletion and genital infection. From the physician's perspective, an immediate decline in renal function is concerned, and a follow-up plan for monitoring eGFR must be developed.

Conflicts of interest

All authors have no conflicts of interest to declare.

Acknowledgments

This work was performed through the cooperation of

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B	Maan	SGLT2i	Tatal	Maan	Placebo	Tetal	\//aiabt	Mean difference		Mean	differen	ce	
Study or subgroup	wean	50	Iotal	wean	50	Iotai	vveight	IV, random, 95% CI		IV, rando	om, 95%		
3.1.1 12 weeks Barnett AH et al. 2014 (1) Wanner C et al. 2016 (1) Subtotal (95% CI) Heterogeneity: Tau ² = 0.00; Test for overall effect: Z = 5	-2.9).2997352 Chi ² = 0.14 .17 (<i>P</i> < 0.1	11.557393 17.823345 , df = 1 (<i>P</i> = 00001)	162 1,133 1,295 0.71);	$0.5 \\ 3.2 \\ I^2 = 0\%$	8.6040989 10.341591	164 558 722	27.0% 73.0% 100.0%	-3.40 [-5.61, -1.19] -2.90 [-4.25, -1.55] -3.04 [-4.19, -1.88]					
3.1.2 24 weeks Barnett AH et al. 2014 (1) Mosenzon O et al. 2019 (2) Wanner C et al. 2016 (1) Subtotal (95% CI) Heterogeneity: Tau ² = 0.44; Test for overall effect: Z = 3	-2.2 0.4 1.4506434 Chi ² = 3.59 .24 (<i>P</i> = 0.1	9.2804283 3.6658 18.525637 , df = 2 (<i>P</i> = 001)	162 576 1,088 1,826 0.17);	0.5 2.4 1.7 ² = 449	9.3430571 5.0594 18.423971 %	164 617 530 1,311	19.7% 59.0% 21.3% 100.0%	-2.70 [-4.72, -0.68] -2.00 [-2.50, -1.50] 0.25 [-2.17, 1.67] -1.77 [-2.83, -0.70]		+	-	-	
3.1.3 52 weeks Barnett AH et al. 2014 (1) Mosenzon O et al. 2019 (2) Wanner C et al. 2016 (1) Subtotal (95% CI) Heterogeneity: Tau ² = 0.43; Test for overall effect: Z = 2	-2.8 1.5 1.450643 Chi ² = 3.85 .33 (<i>P</i> = 0.1	8.2 4.7494 18.525637 , df = 2 (<i>P</i> = 02)	187 544 1,088 1,819 0.15);	-0.3 2.5 1.7 I ² = 489	7.4 6.1097 18.423971 %	187 576 530 1,293	26.3% 53.2% 20.5% 100.0%	-2.50 [-4.08, -0.92] -1.00 [-1.64, -0.36] -0.25 [-2.17, 1.67] -1.24 [-2.28, -0.20]		-+		-	
3.1.4 104 weeks Mosenzon O et al. 2019 (2) Subtotal (95% CI) Heterogeneity: not applicab Test for overall effect: Z = 2	0.2 le .18 (<i>P</i> = 0.0	2.2601	493 493	-0.2	3.4923	523 523	100.0% 100.0%	0.40 [0.04, 0.76] 0.40 [0.04, 0.76]			•		
3.1.5 156 weeks Mosenzon O et al. 2019 (2) Subtotal (95% CI) Heterogeneity: not applicab Test for overall effect: Z = 0	-1.6 le .62 (<i>P</i> = 0.5	2.1684	454 454	-1.8	6.6337	472 472	100.0% 100.0%	0.20 [-0.43, 0.83] 0.20 [-0.43, 0.83]			-		
3.1.6 208 weeks Mosenzon O et al. 2019 (2) Subtotal (95% CI) Heterogeneity: not applicab Test for overall effect: Z = 1	-2 le 3.90 (<i>P</i> < 0	1.9881	382 382	-4	2.0115	391 391	100.0% 100.0%	2.00 [1.72, 2.28] 2.00 [1.72, 2.28] 	-4	-2	0	•	4
Test for subgroup difference	es: Chi ² = 1	55.55, df = 5	5 (P < (0.0001)	; I ² = 96.8%				Favours	[placebo]	Fa	vours [SGLT2i]

Figure 4. Continued.

the Korean Diabetes Association and the Korean Society of Nephrology.

Authors' contributions

Tae Jung Oh, Ju-Young Moon, and Min Kyong Moon participated in the data collection and wrote the manuscript. Kyu Yeon Hur, Seung Hyun Ko, and Hyun Jung Kim participated in the study design and performed the statistical analysis. Tae Jung Oh, Ju-Young Moon, Kyu Yeon Hur, Seung Hyun Ko, Hyun Jung Kim, Taehee Kim, Dong Won Lee, and Min Kyong Moon participated in the conception, analysis, and interpretation of data. Seung Hyun Ko and Dong Won Lee participated in the study design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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Α		SGLT2i			Placebo			Mean difference	Mean diff	erence	
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, random, 95% CI	IV, random	, 95% CI	
4.2.1 24 weeks Haering HU et al. 2015 Kaku K et al. 2017 Kovacs CS et al. 2015 Subtotal (95% CI) Heterogeneity: Tau ² = 0.19; Cł Test for overall effect: Z = 0.85	-1.89 -0.949 -2.756 $hi^2 = 2.40,$ 5 (P = 0.3)	12.06 16.423 15.009 df = 2 (<i>P</i> 9)	441 745 333 1,519 = 0.30);	-1.9 -0.8 -0.5 ; l ² = 17%	10.1 11.08 12.5	225 341 165 731	38.4% 41.0% 20.6% 100.0%	0.01 [-1.72, 1.74] -0.15 [-1.81, 1.52] -2.26 [-4.75, 0.24] -0.52 [-1.72, 0.68]			
4.2.2 52 weeks Kaku K et al. 2017 Roden M et al. 2015 Subtotal (95% CI) Heterogeneity: Tau ² = 0.02; Cł Test for overall effect: $Z = 0.7$	-0.406 1.569 ni ² = 1.04, 1 (<i>P</i> = 0.4	5.454 12.5 df = 1 (<i>P</i> 8)	596 671 1,267 = 0.31);	-0.5 0.6 J ² = 4%	3.0199 9.7	228 228 456	86.3% 13.7% 100.0%	0.09 [-0.49, 0.68] 0.97 [-0.61, 2.54] 0.21 [-0.38, 0.80]	-	- ▶	
4.2.3 104 weeks Haering HU et al. 2015 Kaku K et al. 2017 Kovacs M et al. 2015 Roden M et al. 2015 Subtotal (95% CI) Heterogeneity: Tau ² = 3.01 ; Ch Test for overall effect: Z = 0.93	0.1063 -1.606 0.6 2.35 $ni^2 = 12.74$ 7 (P = 0.9	13.519 10.501 15.518 12.682 I, df = 3 (<i>F</i> 5)	441 381 333 448 1,603 P= 0.00	0.1 -2.5 4.3 0.6 (5); I ² = 7	13.1 5.8095 12.8 9.7 6%	225 135 165 228 753	24.0% 28.3% 21.2% 26.5% 100.0%	0.01 [-2.12, 2.13] 0.89 [-0.55, 2.33] -3.70 [-6.27, -1.13] 1.75 [0.03, 3.47] -0.07 [-2.03, 1.90]			
4.2.4 156 weeks Kaku K et al. 2017 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: Z = 0.00	-2.5 0 (<i>P</i> = 1.0	9.8995 0)	98 98	-2.5	7.1414	51 51	100.0% 100.0%	0.00 [-2.77, 2.77] 0.00 [-2.77, 2.77]	-		
4.2.5 208 weeks Kaku K et al. 2017 Subtotal (95% CI) Heterogeneity: not applicable Test for overall effect: Z = 0.26	-2.166 6 (<i>P</i> = 0.8	12.86 0)	90 90	-1.7	4.9477	17 17	100.0% 100.0%	-0.47 [-4.01, 3.08] -0.47 [-4.01, 3.08] 	-4 -2 0	2	4
Test for subgroup differences:	Chi ² = 1.2	27, df = 4	(<i>P</i> = 0.8	87); I ² = 0)%				Favours [placebo]	Favours [S	3GLT2i]

В		SGLT2i			Placebo			Mean difference		Mea	n differer	ice	
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, random, 95% CI		IV, rar	ndom, 95°	% CI	
4.6.1 52 weeks Haering HU et al. 2015 Kaku K et al. 2017 Roden M et al. 2015 Subtotal (95% CI) Heterogeneity: Tau ² = 0.1 Test for overall effect: Z	-0.75102 -0.45 -0.70018 00; Chi ² = 1. = 8.26 (<i>P</i> <	2.346172 4.395452 2.849365 62, df = 2 (<i>F</i> 0.00001)	441 483 671 1,595 P = 0.44	0 -0.05 0.09); l ² = 0%	1.5 4.3909 0.754983 %	225 482 228 935	35.4% 10.0% 54.6% 100.0%	-0.75 [-1.04, -0.46] -0.40 [-0.95, 0.15] -0.79 [-1.03, -0.55] -0.74 [-0.91, -0.56]					
4.6.2 104 weeks Haering HU et al. 2015 Kaku K et al. 2017 Kovacs M et al. 2015 Roden M et al. 2015 Subtotal (95% Cl) Heterogeneity: Tau ² = 0.1 Test for overall effect: Z	-0.7 -0.45936 -0.72235 -0.66097 00; Chi ² = 1. = 8.69 (<i>P</i> <	1.456006 6.376544 1.200479 2.671054 70, df = 3 (<i>F</i> 0.00001)	213 846 149 372 1,580 P= 0.64	0.1 -0.05 -0.05 013); I ² = 0%	0.87178 4.118252 0.668132 0.697424	76 424 31 76 607	35.3% 8.0% 29.2% 27.5% 100.0%	-0.80 [-1.08, -0.52] -0.41 [-0.99, 0.17] -0.67 [-0.98, -0.37] -0.79 [-1.10, -0.48] -0.73 [-0.89, -0.56]		+ + + +			
4.6.3 156 weeks Kaku K et al. 2017 Subtotal (95% CI) Heterogeneity: not appli Test for overall effect: Z	-0.4248 cable = 1.37 (<i>P</i> =	5.894165 0.17)	625 625	0	3.464102	300 300	100.0% 100.0%	-0.42 [-1.03, 0.18] -0.42 [-1.03, 0.18]		4			
4.6.4 208 weeks Kaku K et al. 2017 Subtotal (95% CI) Heterogeneity: not appli Test for overall effect: Z	-0.1572 cable = 0.74 (<i>P</i> =	2.90927 0.46)	100 100	0.15	1.897367	40 40	100.0% 100.0%	-0.31 [-1.13, 0.51] -0.31 [-1.13, 0.51]	-2	-1	0		2
Test for subgroup differe	ences: Chi ² =	1.92, df = 3	B (P = 0	.59); I ² =	0%				Favou	urs [SGLT2i]	Fa	avours [pla	acebo]

Figure 5. Result of Asian dominant studies. Effects of sodium-glucose cotransporter-2 inhibitors (SGLT2i) on change of (A) estimated glomerular filtration rate and (B) glycosylated hemoglobin.

Cl, confidence interval; IV, inverse variance; SD, standard deviation.

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