



## ACTING EARLY TO PROTECT RENAL: BEYOND GLYCEMIC CONTROL OF SGLT2 INHIBITORS

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### ABSTRAK

Diabetes melitus tipe 2 (DMT2) merupakan penyebab utama penyakit ginjal kronik, menyebabkan hampir setengah dari semua kasus penyakit ginjal kronik (PGK) yang membutuhkan terapi pengganti ginjal (TPG). Pada pasien DMT2 dengan PGK, gangguan kardiovaskular merupakan penyebab kematian utama. Untuk menurunkan Penyakit transporter terputut natrium-glukosa tipe 2 atau *sodium/glucose cotransporter 2 inhibitors* (SGLT2-i) merupakan golongan obat antidiabetik baru yang dikembangkan untuk menurunkan gula darah pada DMT2. Penurunan risiko komplikasi renal (albuminuria, peningkatan ureum kreatinin, penurunan laju filtrasi glomerulus, gagal ginjal, dan kematian) ditemukan secara konsisten pada uji-uji klinis SGLT2i pada populasi DMT2. Uji klinis DECLARE-TIMI58 (*Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58*, atau DECLARE) yang dilakukan pada pasien DMT2 dengan albuminuria dan penurunan laju filtrasi glomerulus 30 to 90 mL/menit/1.73 m<sup>2</sup> mengidentifikasi manfaat terapeutik untuk perlindungan fungsi ginjal dan pencegahan kejadian kardiocerebrovaskular. SGLT2i diketahui meningkatkan fungsi hemodinamik glomerulus dan mengurangi respons lokal dan sistemik yang berkontribusi terhadap patogenesis PGK atau penyakit kardiovaskular. Berdasarkan panduan Perkeni terbaru, pasien DMT2 direkomendasikan untuk mendapatkan SGLT2i untuk mengurangi risiko PGK dan CVD. Strategi implementasi yang efektif diperlukan dalam tatalaksana pasien DMT2 pada praktik klinis.

**Kata Kunci:** Dapagliflozin, DMT2, Penyakit Kardiovaskular, SGLT2i

### ABSTRACT

Type 2 Diabetes Mellitus (T2DM) is the leading cause of chronic kidney disease (CKD), accounting for almost half of all cases of kidney failure that necessitate replacement therapy. Cardiovascular disease (CVD) is the leading cause of death in patients with T2DM and CKD. To lower blood glucose levels by inhibiting glucose reabsorption in the proximal tubule, sodium/glucose cotransporter 2 inhibitors (SGLT2-i) were developed. Consistent reductions in risks for secondary kidney disease end points (albuminuria and a composite of serum creatinine doubling or 40% estimated glomerular filtration rate decline, kidney failure, or death) were recognized in clinical trials designed to demonstrate the CVD safety of SGLT2i in type 2 diabetes mellitus (T2DM), as well as reductions in CVD events. The DECLARE-TIMI58 (*Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58*, or DECLARE) trial in patients with T2DM, urinary albumin-creatinine ratio >300 mg/g, and estimated glomerular filtration rate of 30 to 90 mL/min/1.73 m<sup>2</sup> established the kidney and CVD benefits of dapagliflozin in patients with CKD. SGLT2i boost glomerular hemodynamic function and are figured to augment other local and systemic processes that contribute to the development of CKD and CVD. According to latest Indonesian Society of Endocrinologist's guideline, patients with T2DM was recommended to use SGLT2i to reduce their risk of CKD and CVD, in accordance with the clinical trial entry criteria. To achieve widespread use of these life-saving medications, effective implementation strategies are required.

**Key words:** Cardiovascular Disease, CKD, Dapagliflozin, SGLT2-i, T2DM

### INTRODUCTION

Diabetes and chronic kidney disease (CKD) frequently exist simultaneously and are linked to a higher risk of both mortality and morbidity. Diabetes was diagnosed in 10.7 million people in Indonesia, making it one of the countries with the highest absolute prevalence worldwide. Type 2 diabetes mellitus (T2DM) makes up for 90% to 95% of diabetes cases.<sup>1</sup> Diabetic kidney disease (DKD), also known as CKD in diabetes, affects 40% of people with T2DM.<sup>2</sup> Diabetes is the primary cause of CKD worldwide, causing almost half of those necessitate kidney replacement



therapy.<sup>3</sup> Patients with T2DM and CKD, on the other hand, are more likely to die than to move forwards to kidney failure.<sup>3,4</sup> The most common causes of death in T2DM and CKD patients are heart failure (HF) and atherosclerotic cardiovascular disease (ASCVD).<sup>5</sup>

Glycemic control is the foundation of excellent diabetes care. Hypertension control and the use of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) are also crucial parts of improving care for those with CKD. There are numerous glucose-lowering medications available today. Until recently, no type of glucose-lowering agent was thought to be the preferred treatment. Rather, a glycemic target determined by hemoglobin A1c (HbA1c) level was recommended. Because of safety issues, adverse effects, or a lack of evidence in people with low glomerular filtration rates, people with diabetes and CKD have had fewer options of glucose-lowering agents (GFR).

Sodium/glucose cotransporter 2 inhibitors (SGLT2i) reduce blood glucose levels by deterring glucose and sodium reabsorption in the proximal tubule.<sup>6</sup> The FDA has licensed four SGLT2i for the control of blood glucose level in people with T2DM: canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin. To assess the efficacy of dapagliflozin, a trial named The Dapagliflozin Effect on Cardiovascular Events (DECLARE-TIMI 58 or DECLARE) was conducted.<sup>7</sup> It was a randomized double-blind controlled trial assigned 17,160 T2DM patients to 10 mg of dapagliflozin daily or placebo over a 4.2 year median follow-up period (interquartile range (IQR) = 3.9-4.4). Another trial, The DAPA-CKD, trial proves that the kidney benefits of SGLT2i are independent of glucose-lowering.<sup>8</sup> Current study reviews the clinical benefits of SGLT2i in T2DM to reduce and alleviate the renal complication and thus, CVD-related complication of T2DM.

## DISCUSSION

Based on a growing body of evidence, the kidney benefits of SGLT2i appear to be largely independent of glycemic control. Their glucose-lowering effects are modest, especially in people with eGFRs of 45 mL/min/1.73 m<sup>2</sup>.<sup>9</sup> Nonetheless, kidney protection in this population is consistent and substantial. SGLT2i also have kidney benefits in people with well-controlled glycemia (HbA1c 7%) who require little additional glucose lowering.<sup>10</sup> The effects on HF and kidney disease end points were consistent regardless of diabetes status in the DAPA-HF trial, which included people with and without diabetes.<sup>11</sup> Finally, this level of kidney protection has not been observed with other glucose-lowering agents.

Because of glucosuria and natriuresis, SGLT2i promote diuresis.<sup>12</sup> Diuresis is an important mechanism for lowering blood pressure and the risk of having a heart attack.<sup>13</sup> The lack of a compensatory increase in heart rate suggests that sympathetic nervous system activity has been blunted, which may also contribute to the beneficial effects of SGLT2i when compared to other diuretics.<sup>14</sup> Furthermore, a study that combined plasma and urinary water and electrolyte data with mathematical modeling to compare the effects of dapagliflozin and bumetanide on blood and interstitial fluid volumes found that SGLT2i mobilize fluid from the interstitial compartment rather than the intravascular space.<sup>15</sup>

Reduced interstitial fluid in the kidney and proximal tubular energy requirements may alleviate cortical and outer medullary hypoxia. To assess the efficacy of Dapagliflozin in reducing cardiac event, The DECLARE-TIMI 58 trial was conducted. It randomly assigned 17,160 T2DM patients to either dapagliflozin or placebo treatment. The primary outcomes of this trial were MACE and a composite of CVD death or HF hospitalization. Unlike the EMPA-REG OUTCOME trial and the CANVAS program, the majority of DECLARE-TIMI 58 trial participants (59%; n = 10,186) did not have established ASCVD. Dapagliflozin's overall effect on MACE was not statistically significant different from placebo (HR, 0.93; 95% CI, 0.84-1.03).<sup>13</sup> The point estimate of efficacy



was numerically lower in participants with ASCVD (HR, 0.90; 95% CI, 0.79-1.02) than in those without ASCVD (HR, 1.01; 95% CI, 0.86-1.20), but neither subgroup nor the interaction achieved statistical significance.

A systematic review and meta-analysis of CVOTs with data from 34,322 patients with T2DM with or at high risk for ASCVD found that patients treated with an SGLT2i versus placebo had a 23% lower risk of CVD death or hospitalization for HF (HR, 0.77; 95% CI, 0.71-0.84).<sup>16</sup> In DECLARE-TIMI 58, hospitalizations for HF were reduced in patients with and without prevalent ASCVD, as well as those with and without a history of HF.

Patients with T2DM have a higher risk of ASCVD and HF than nondiabetic individuals.<sup>17,18</sup> However, glycemic control does not reduce the risk of these events significantly. The idea that the benefits of SGLT2i are mediated by nonglycemic mechanisms is supported by the fact that the reduction in CVD events occurred regardless of the use of other glucose-lowering agents. Furthermore, the observed CVD risk reductions in diabetes participants were unrelated to either baseline or achieved HbA1c levels.<sup>19</sup> Dapagliflozin reduced the risk of worsening HF or CVD death in DAPA-HF patients regardless of diabetes status. As a result, the mechanisms by which SGLT2i reduce the risk of HF are not due to better glycemic control. A number of potential mechanisms for the beneficial effects of SGLT2i on CVD have been proposed. Effects on volume status, natriuresis, red blood cell mass expansion, and myocardial energetics appear to be particularly plausible.

DECLARE included participants with an average baseline eGFR of 85 mL/min/1.73 m<sup>2</sup>, of whom 7.4% had an eGFR of 60 mL/min/1.73 m<sup>2</sup>. The proportion of patients with albuminuria was 30%, which was comparable to other CVOTs. This trial found that dapagliflozin significantly reduced the risk of secondary kidney disease outcomes such as a 40% reduction in eGFR to 60 mL/min/1.73 m<sup>2</sup>, kidney failure, or death from kidney disease (HR, 0.53; 95% CI, 0.43-0.66).

Treatment with SGLT2i also increases the likelihood of regressing from severely increased albuminuria to moderately increased albuminuria or normal albuminuria, as well as from moderately increased albuminuria to normal albuminuria. The albuminuria-lowering effect occurs within weeks of treatment initiation and is thought to be due to glomerular hemodynamic effects. CVOT results for the prevention of new-onset albuminuria have been less consistent. DECLARE exhibited this effect.

## **CONCLUSION**

In T2DM, Renal and CVD disease are connected. Worsening renal function adversely impact CVD outcomes. DECLARE assessed dapagliflozin's CV and renal outcomes in a broad population of T2DM. Patients enrolled in DECLARE were early in their CV risk continuum and had better preserved renal function compared to previous SGLT2 inhibitor studies assessing the ability of dapagliflozin to demonstrate early cardio-renal protection. DECLARE results showed that dapagliflozin reduced the pure renal composite endpoint by 47% (nominal p value). This benefit was consistent across baseline renal function subgroups. In other hands, DAPA-CKD has shown that Dapagliflozin shows benefit and efficacy for lower eGFR setting. DAPA-CKD also showed that SGLT2i can be a future solution for CKD Management.

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