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COMMENTARY

Dapagliflozin: Beneficial Effects Beyond Glycaemia

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Commentary

Dapagliflozin is a member of the newest antidiabetic drug class called sodium-glucose cotransporter-2 inhibitors (SGLT-2is) [1]. These target the kidney, promoting glycosuria, natriuresis and osmotic dieresis [1]. They also reduce body weight and blood pressure without causing hypoglycaemias [1]. In addition, numerous cardiovascular outcome trials have revealed favourable cardiovascular and renal effects, and so SGLT-2is are now recommended after metformin in type 2 diabetes mellitus (T2DM) subjects with established atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), or heart failure (HF), irrespective of their baseline glycated haemoglobin (HbA1c) [2].

In the Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58) trial including 17160 T2DM subjects (10186 without ASCVD) [3], dapagliflozin achieved a non-significant 7% relative risk reduction (RRR) in major adverse cardiovascular events (MACE), defined as cardiovascular death, myocardial infarction (MI), or ischaemic stroke during a median follow-up of 4.2 years. However, dapagliflozin treatment resulted in a significant 17% RRR in cardiovascular death or hospitalisation for HF, as well as a 27% RRR in hospitalisation for HF [3]. Additionally, there was a 24% RRR in the renal composite with dapagliflozin [3]. Of particular note, a pre-specified subgroup analysis from DECLARE TIMI-58 including 3584 T2DM subjects with prior MI has demonstrated that dapagliflozin significantly reduced MACE by 16% RRR in this subgroup [4].

Such impressive beneficial effects of dapagliflozin have directed further research towards HF and CKD patients. The Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients with Chronic Heart Failure (DAPA-HF) [5] included 4744 subjects with New York Heart Association (NYHA) class II-IV HF and an ejection fraction ≤ 40% with or without T2DM. The primary outcome (a composite of a worsening HF or cardiovascular death) was significantly reduced by 26% RRR during a median follow-up of 18.2 months [5]. These results allowed a new therapeutic indication of dapagliflozin, namely

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treatment of heart failure with reduced ejection fraction.

The next trial, A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease (Dapa-CKD) [6], enrolled 4304 participants with an estimated glomerular filtration rate (eGFR) 25-75 ml/minute/1.73 m2 of body-surface area and a urinary albumin-to-creatinine ratio 200-5000 mg/g, with or without T2DM. It demonstrated a significant 39% RRR in the primary outcome (a composite of a sustained eGFR decline ≥ 50%, end-stage kidney disease, or death from renal or cardiovascular causes) in patients treated with dapagliflozin compared with placebo over a median follow-up of 2.4 years [6].

Moreover, there is hope that dapagliflozin may reduce inflammation and protect from cardiovascular and renal toxicity in subjects with acute mild-moderate Coronavirus infectious disease (COVID-19), and so 2 trials are underway to examine this [7]. Results are eagerly awaited.

In summary, not only does dapagliflozin improve glycaemic control without weight gain and/or hypoglycaemias, but it also exerts significant and important beneficial effects (mainly reduction of hospitalisation for HF and of deteriorating renal disease) [3,5,6]. These effects are independent of glycaemic control, paving the way for a widening scope of therapeutic indications [8].

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