

Effect of dapagliflozin on cardiovascular outcomes in patients with type 2 diabetes according to baseline renal function and albuminuria status: Insights from DECLARE-TIMI 58

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Background: Renal dysfunction including both reduced estimated glomerular filtration rate (eGFR) and the presence of albuminuria have each been shown to predict cardiovascular (CV) outcomes. Sodium glucose co-transporter 2 inhibitors (SGLT2i), which promote glucose excretion in the kidneys, reduce CV events and hospitalizations for heart failure (HHF) in patients with type 2 diabetes mellitus (T2DM).

Purpose: To analyze the CV efficacy of dapagliflozin according to baseline renal function and albuminuria status in DECLARE-TIMI 58.

Methods: The DECLARE-TIMI 58 trial compared dapagliflozin vs. placebo in 17,160 patients with T2DM and a creatinine clearance >60 ml/min/1.73m² at enrollment. The dual primary endpoints were CV death/HHF and MACE (MI, stroke, CV death). We categorized patients according baseline eGFR [<60 vs. ≥ 60 ml/min/1.73m² according to the CKD-EPI formula] and urinary albumin:creatinine ratio (UACR) [<30 vs. ≥ 30 mg/g]. Cox regression models with interaction testing were applied. The Gail-Simon test was used to test for interaction of the absolute risk differences.

Results: In total, 5198 (30.3%) patients had albuminuria (UACR 30–300: n=4029; UACR >300: n=1169) and 1265 (7.4%) had an eGFR <60

ml/min/1.73m². Accordingly, 10958 (63.9%) patients had no manifestation of CKD, 5367 (31.3%) had either an eGFR <60 ml/min/1.73m² or albuminuria, and 548 (3.2%) patients had both manifestations. Patients with more abnormal markers had higher event rates for CV death/HHF (KM event rates at 4 years of 3.9%, 8.3%, 17.4%) and MACE (7.5%, 11.7%, and 18.9%) for no, 1, or 2 markers of CKD, respectively. The relative risk reductions for CV death/HHF and MACE were generally consistent across the subgroups (both P-interaction >0.29), though numerically greatest (42%) in patients with reduced eGFR and albuminuria. However, the absolute risk difference increased substantially in patients with greater kidney damage (absolute risk difference of CV death/HHF: –0.5%, –1.0%, and –8.3%, respectively; P-INT for ARD 0.002; Figure). See figure for MACE and component outcomes.

Conclusions: Patients with baseline renal disease had higher rates of adverse CV outcomes. Dapagliflozin reduced events with generally consistent relative risk, but reduced the absolute risk of CVD/HHF by the greatest amount in patients with kidney disease evidenced by both reduced eGFR and albuminuria.

