DICTATE-AHF trial fails to meet primary endpoint with dapagliflozin in acute heart failure

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Early initiation of the sodium glucose co-transporter 2 (SGLT2) inhibitor dapagliflozin did not result in a statistically significant improvement in diuretic efficiency relative to structured usual care in

hospitalized patients with acute decompensated heart failure (ADHF), according to late breaking research presented in a Hot Line session today at ESC Congress 2023.

Early dapagliflozin initiation did not worsen any prespecified safety outcomes, indicating dapagliflozin can be safely started upon hospital admission to rapidly optimize guideline directed medical therapy (GDMT). Exploratory analyses indicated that dapagliflozin improved decongestion and led to earlier hospital discharge.

The two primary therapeutic goals during acute decompensated heart failure hospitalization are complete decongestion and optimization of GDMT. Previous studies of diuretic combinations improved decongestion, but these diuretic combinations inherently did not optimize GDMT and were not associated with improved post-discharge outcomes. Early initiation of dapagliflozin could improve both GDMT optimization and decongestion, but the efficacy and safety of this strategy is unknown.

The DICTATE-AHF trial examined the efficacy and safety of dapagliflozin initiated within 24 hours of hospital presentation on diuretic response in patients with hypervolaemic ADHF. The study enrolled adult patients with type 2 diabetes and an estimated glomerular filtration rate (eGFR) of at least 30 mL/min/1.73m^2 admitted to hospital with ADHF and current or planned treatment with intravenous (IV) loop diuretics.

In September 2021, the protocol was amended to allow enrollment of patients with or without type 2 diabetes and to decrease the eGFR inclusion criterion to 25 mL/min/1.73m^2 due to new safety data in these groups. The main exclusion criteria were type 1 diabetes, systolic blood pressure less than 90 mmHg, serum glucose less than 80 mg/dL, use of IV inotropic therapy, and history of diabetic ketoacidosis.

Within 24 hours of hospital presentation, patients were randomly assigned in a 1:1 ratio to oral dapagliflozin 10 mg once daily or structured usual care until day 5 or hospital discharge. Natriuretic peptide concentration, standing weight, and congestion were assessed at baseline. A standardized protocol for IV loop diuretic dosing and titration every 12-24 hours was used for both study arms throughout the study period to target a urine output of 3-5 L/day.

Loop diuretic doses were titrated to a dose of at least 960 mg/day of IV furosemide equivalents before a thiazide diuretic was added. A spot urine sample was collected after the initial IV loop diuretic dose, but before dapagliflozin administration, to measure baseline diuretic-induced urine sodium, potassium, and creatinine. On day 2, timed, spot urine collections and a 24-hour urine collection were performed.

At day 5 or discharge, whichever came first, natriuretic peptide concentration, final standing weight, and a congestion assessment were performed. After hospital discharge, patients were followed to assess 30-day post-discharge outcomes.

The primary outcome was diuretic efficiency (diuretic response) expressed as the cumulative change in weight per cumulative loop diuretic dose (IV and oral) from enrollment to day 5 or discharge, if sooner. The primary outcome was compared across treatment assignment using a proportional odds regression model adjusting for baseline weight.

The trial included 240 patients. The average age was 65 years and 39% were women. After adjusting for baseline weight, the odds ratio (OR) for diuretic efficiency with dapagliflozin versus structured care was 0.65, 95% confidence interval (CI) 0.41 to 1.01, p=0.06. In the unadjusted analysis, the OR was 0.64, 95% CI 0.41 to 1.00, p=0.05. The secondary endpoints of in-hospital worsening heart failure and 30-day

readmission for heart failure or diabetes-related reasons did not differ between early dapagliflozin initiation compared to usual care.

Regarding exploratory endpoints, dapagliflozin significantly increased both 24-hour natriuresis (p=0.025) and 24-hour urine output (p=0.005), and decreased both time to completing IV diuretic therapy (p=0.006) and time to hospital discharge (p=0.007).

Early dapagliflozin initiation was safe across all diabetic and cardiorenal in-hospital outcomes, with no differences between treatment groups in the change in eGFR from baseline to end-of-study, incidence of adverse events, inpatient mortality, symptomatic hypotension, total or serious hypoglycemia events, genitourinary infections, or severe hypokalemia.

Study author Professor Zachary Cox of Lipscomb University College of Pharmacy, Nashville, US said, "Although our study did not show statistical significance for its primary endpoint, the totality of data from this trial supports the early initiation of dapagliflozin in ADHF to facilitate decongestion while rapidly and safely optimizing GDMT."

"Our findings of safety across inpatient diabetes, cardiovascular, and renal outcomes should encourage in-hospital use, which can translate to improved chronic SGLT2 inhibitor prescription, adherence, and long-term benefits."

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