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Hemodynamic signature of SGLT2 inhibition: greater early NT-proBNP and plasma volume reduction with dapagliflozin versus empagliflozin in patients with atrial fibrillation and heart failure

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Introduction: Sodium-glucose cotransporter 2 (SGLT2) inhibitors improve outcomes across the heart failure (HF) spectrum, yet potential drug-specific differences in early hemodynamic unloading are unknown, especially in patients with atrial fibrillation (AF), a group prone to congestion and biomarker variability. Whether early estimated plasma volume (ePV), computed from routine laboratory measurements, and N-terminal pro-brain natriuretic peptide (NT-proBNP) trajectories differ between SGLT2 inhibitors, and thus might inform agent selection in congestion-prone patients, remains insufficiently characterized.[1-3]

Patients and Methods: We performed a single-centre, registry-based (CaRD registry - NCT06090591) real-world analysis with time-zero defined as SGLT2 inhibitor initiation (dapagliflozin or empagliflozin). Adults with AF and HF with paired NT-proBNP and ePV measurements at baseline and approximately six months (window 6±2 months) were included. ePV was calculated by Duarte, Kaplan–Hakim, and Nadler at ≈6 months (6±2) and ≈12 months (12±2). The primary endpoint was change in NT-proBNP (ΔNT-proBNP) and change in ePV by Duarte (ΔePV) from baseline to ≈ 6 months. Group differences were tested using a two-sided Mann-Whitney test with bootstrap 95% confidence intervals (CIs) for the median difference.

Results: The primary analysis set comprised 910 patients (dapagliflozin n=470; empagliflozin n=440). Median ΔNT-proBNP at ≈6 months was −1164 pg/mL with dapagliflozin versus −754 pg/mL with empagliflozin and the median difference (empagliflozin minus dapagliflozin) was +410 pg/mL (95% CI 115–799; p=0.011). Median change in ΔePV (by Duarte) ≈6 months, was −0.314 with dapagliflozin (n=436) vs. −0.198 with empagliflozin (n=352) with median difference +0.116 (95% CI 0.0002–0.222; p=0.025). Both results are indicating a more pronounced early reduction with dapagliflozin. Regarding secondary endpoints: 1. at ≈12 months, ΔNT-proBNP medians were −1074 versus −1003 pg/mL, respectively (p=0.49); 2. at ≈12 months ΔePV by Duarte, medians were −0.397 vs. −0.311 (p=0.09); 3. findings were directionally concordant by different ePV formulas - at ≈6 months by Kaplan (−0.090 vs −0.064; p=0.063) and Nadler (−0.087 vs. −0.056; p=0.060); however, at ≈12 months, separations by Kaplan and Nadler were small and non-significant (both p>0.32); 4. Crude hospitalization rates were similar (53.1 vs. 56.4 per 100 person-years, p=NS) between empagliflozin vs. dapagliflozin; and 5. renal changes were small and non-significant.

Conclusion: This study provides a novel, non-randomized, real-world registry-based direct comparison of dapagliflozin versus empagliflozin in a large cohort, reflecting a routine HF and AF care. Our data uncover nuanced differences in their short-term physiological trajectories - a more pronounced early reduction in both decongestion (as ΔePV across 3 different formulas) and ΔNTproBNP with dapagliflozin at approximately 6 months.

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