Baseline Kidney Function and Safety and Efficacy of Dapagliflozin in Patients Hospitalized for Heart Failure: An Analysis of DAPA ACT HF-TIMI 68

Siddharth M. Patel, MD, MPH, Hiddo J.L. Heerspink, PhD, Michael G. Palazzolo, MS, Paul M. Haller, MD, PhD, Jan Bělohlávek, MD, PhD, Akshay S. Desai, MD, MPH, Jarosław Drożdż, MD, PhD, Silvio E. Inzucchi, MD, John J.V. McMurray, MD, Béla Merkely, MD, PhD, Eileen O'Meara, MD, Subodh Verma, MD, PhD, Stephen D. Wiviott, MD, Marc S. Sabatine, MD, MPH, David D. Berg, MD, MPH

BACKGROUND

- SGLT2i cause a transient decrease in eGFR before long-term kidney protective effects become apparent.
- Patients hospitalized for heart failure (HF) may be more susceptible to adverse kidney events in the context of ongoing diuresis and intensification of concomitant HF therapies.
- We sought to characterize the kidney effects of dapagliflozin in patients hospitalized for HF.

METHODS

- DAPA ACT HF-TIMI 68 enrolled patients hospitalized for HF with randomization to inpatient initiation of dapagliflozin or placebo after initial clinical stabilization.
  - Those with eGFR < 25 mL/min/1.73 m^2 or rapidly progressive renal disease were excluded.
- PEP = CV death or worsening HF.
- Key pre-specified safety outcome = kidney events composite of doubling of serum Cr, investigator-reported study drug discontinuation or hospitalization due to worsening kidney function or dialysis, or renal death.
- Change in eGFR between dapagliflozin vs. placebo across study visits was examined using least-squares mean difference.
- Sensitivity analysis performed to examine sustained doubling in Cr (at 2 consecutive visits or final Cr recorded showing doubling from baseline).
- The effect of dapagliflozin on the kidney events composite was examined by baseline eGFR treated continuously and categorically (<60 vs. ≥60 mL/min/1.73 m^2).

RESULTS

- Among 2,401 patients, the median baseline eGFR was 63 (IQR 48-82) mL/min/1.73 m^2 with 45% having an eGFR <60 mL/min/1.73 m^2.

Figure 1: Change in eGFR with Dapagliflozin vs. Placebo (on-treatment)

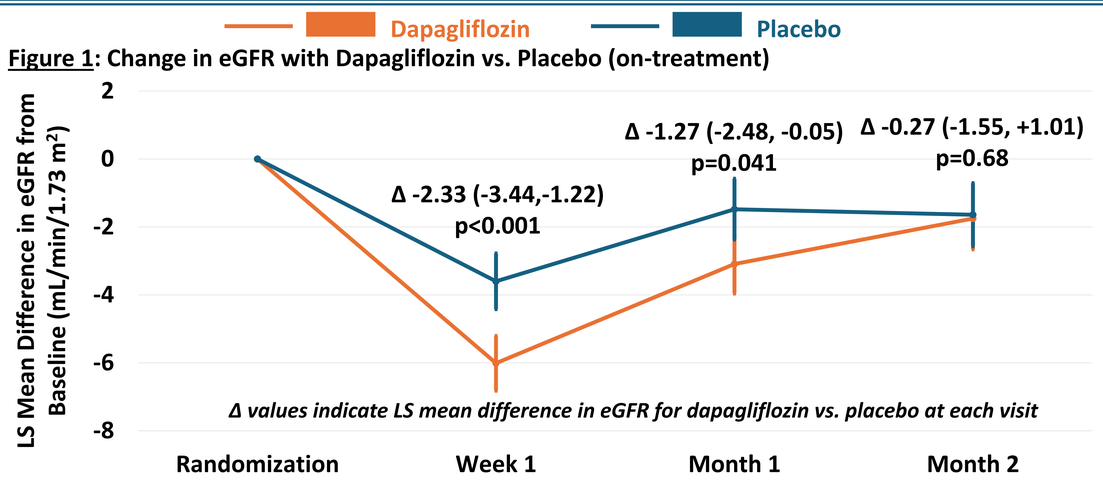


Figure 2: Adverse Kidney Events Composite and Components

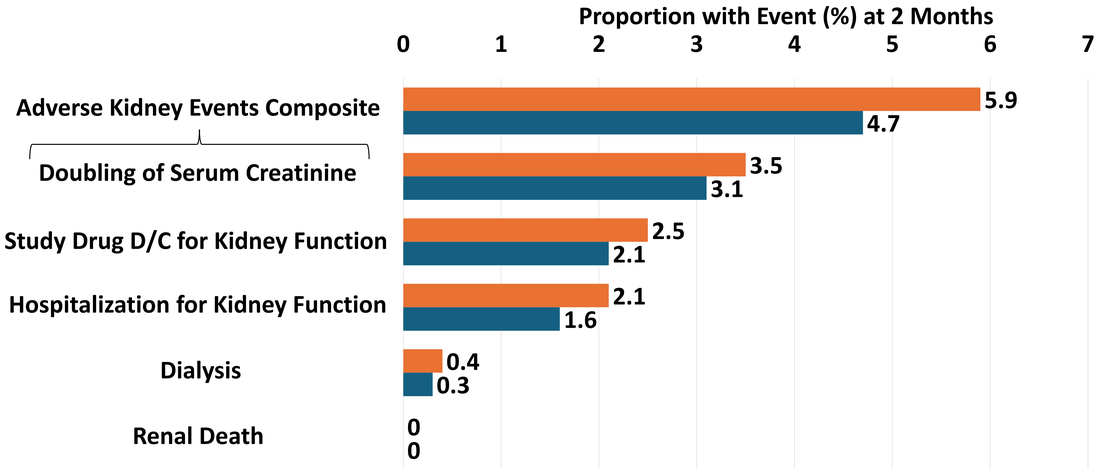
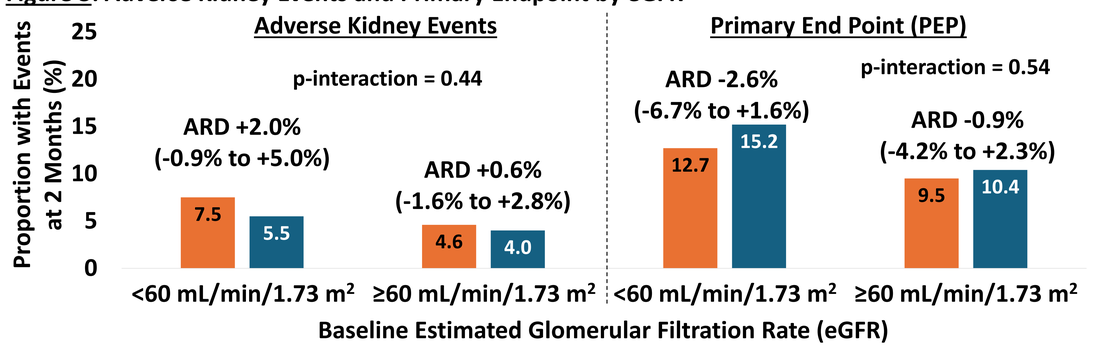


Figure 3: Adverse Kidney Events and Primary Endpoint by eGFR



RESULTS (continued)

- In-hospital initiation of dapagliflozin resulted in an initial decline in eGFR at weeks 1 and month 1, without a persistent difference by month 2 (**Figure 1**).
- The kidney composite occurred in 5.9% and 4.7% of patients in the dapagliflozin and placebo arms (ARD +1.2% [-0.6% to +3.0%]; p=0.19), with doubling of serum Cr being the most common component (**Figure 2**).
  - Events occurred predominantly within the 1st month of randomization (median 21 [IQR 8-35] days).
  - Sustained doubling of Cr occurred in 1.7% of enrolled patients without difference by treatment (1.5% in dapagliflozin arm vs. 1.9% in placebo arm; p= 0.47).
- Examined continuously, the risk for kidney events and the PEP was greater in those with lower baseline eGFR regardless of treatment (p-trend < 0.001 for each).
  - In those with baseline eGFR <60 mL/min/1.73 m^2, the ARD for kidney events with dapagliflozin was +2.0% [-0.9 to +5.0%] whereas the ARD for the PEP was -2.6% [-6.7% to +1.6%]); in those with eGFR ≥60 mL/min/1.73 m^2, the corresponding ARDs were +0.6 [-1.6% to +2.8%] and -0.9% [-4.2% to +2.3%] (**Figure 3**).

CONCLUSIONS

- In patients hospitalized for HF, dapagliflozin led to an early modest decline in eGFR which resolved by 2 months.
- Those with lower baseline eGFR were at higher risk for early adverse kidney events and the PEP.
  - Even in the subset with lower eGFR, the observed ARD with dapagliflozin for kidney events was counterbalanced by the ARD for the PEP.

DISCLOSURE OF FACULTY RELATIONSHIPS:
DAPA ACT HF-TIMI 68 was an investigator-initiated trial sponsored by the TIMI Study Group and funded by AstraZeneca. SDW is an employee of AstraZeneca. SMP, MGP, MSS, and DDB are members of the TIMI Study Group, which has received institutional research grant support through Brigham and Women's Hospital from Abbott, Abiomed, Inc., Amgen, Anthos Therapeutics, ARCA Biopharma, Inc., AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, Ionis Pharmaceuticals, Inc., Janssen Research and Development, LLC, MedImmune, Merck, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Roche, Saghmos Therapeutics, Inc., Softcell Medical Limited, The Medicines Company, Verve Therapeutics, Inc., Zora Biosciences.