Late Breaking Clinical Trial abstracts from HFSA 2019

Clinical Effectiveness of Sacubitril/valsartan among Patients Hospitalized for Heart Failure with Reduced Ejection Fraction

Stephen J. Greene[1], Steven J. Lippmann[1], Robert J. Mentz[1], Melissa A. Greiner[1], N. Chantelle Hardy[1], Chun-Lan Chang[2], Bradley G. Hammill[1], Nancy Luo[1], Marc D. Samsky[1], Paul A. Heidenreich[3], Warren K. Laskey[4], Clyde W. Yancy[5], Pamela N. Peterson[6], Lesley H. Curtis[1], Adrian F. Hernandez[1], Gregg C. Fonarow[7], Emily C. O'Brien[1]; [1]Duke University, Durham, NC; [2]Novartis, East Hanover, NJ; [3]Stanford University, Palo Alto, CA; [4]University of New Mexico, New Mexico, NM; [5]Northwestern University, Chicago, IL; [6]University of Colorado, Aurora, CO; [7]UCLA, Los Angeles, CA

Background: Sacubitril/valsartan has been highly efficacious in randomized clinical trials of patients with HFrEF. However, the effectiveness of sacubitril/valsartan in routine US clinical practice is unclear. **Methods:** This study included patients age ≥65 years who were hospitalized for HFrEF (ejection fraction ≤40%), were eligible for sacubitril/valsartan at discharge, and were enrolled in the Get With The Guidelines-Heart Failure registry linked to Medicare claims between October 2015 and September 2017. Patients prescribed sacubitril/valsartan at discharge were compared with (1) patients not prescribed sacubitril/valsartan, and (2) patients prescribed ACEI/ARB at discharge. Study endpoints were post-discharge mortality and hospitalization outcomes at 12 months. Negative control (falsification) endpoints included hospitalization for urinary tract infection and hospitalization for nutritional disorder. To adjust for selection bias, inverse probability of treatment weighting and adjustment for other HFrEF medications prescribed at discharge were performed. **Results:** Overall, 746 (8.1%) patients were discharged on sacubitril/valsartan and 8,466 (91.9%) were not. Of those not prescribed sacubitril/valsartan, 5,286 (62.4%) were prescribed an ACEI/ARB. As compared with no sacubitril/valsartan, discharge prescription of sacubitril/valsartan was independently associated with lower risk of all-cause mortality, all-cause hospitalization, and the composite of mortality or HF hospitalization at 12-month follow-up (**Table**). These findings were consistent in comparisons between sacubitril/valsartan and ACEI/ARB. Discharge sacubitril/valsartan prescription was not significantly associated with the negative control endpoints, suggesting the findings were unlikely due to residual confounding. **Conclusions:** In this contemporary real-world population of US patients hospitalized for HFrEF and eligible for sacubitril/valsartan, prescription of sacubitril/valsartan at discharge was independently associated with substantial reductions in post-discharge mortality and hospitalization. These findings suggest that the significant benefits of sacubitril/valsartan observed in clinical trials extend to patients seen in routine US clinical practice.

Table. Association Between Sacubitril/Valsartan Therapy at Hospital Discharge and Study Endpoints at 12 Months

Study Endpoint, n (%)			Hazard Ratio (95% Confidence Interval), p Value	
			Unadjusted	Inverse Weighted + Adjustment for Discharge HFrEF Medications*
Sacubitril/Valsartan versus *No* Sacubitril/Valsartan				
	Sacubitril/Valsartan (n=746)	*No* Sacubitril/Valsartan (n=8,466)		
All-cause mortality	177 (28.9)	3,054 (39.6)	0.63 (0.54-0.74), p<0.001	0.68 (0.57-0.81), p<0.001
All-cause hospitalization	405 (59.0)	5,097 (63.9)	0.81 (0.74-0.90), p<0.001	0.79 (0.71-0.89), p<0.001
All-cause mortality/ HF hospitalization	321 (48.4)	4,617 (58.6)	0.74 (0.67-0.83), p<0.001	0.72 (0.64-0.82), p<0.001
Sacubitril/Valsartan versus ACEI/ARB				
	Sacubitril/Valsartan (n=746)	ACEI/ARB (n=5,286)		
All-cause mortality	177 (28.9)	1,481 (31.5)	0.88 (0.75-1.04), p=0.13	0.83 (0.69-1.00), p=0.047
All-cause hospitalization	405 (59.0)	3,115 (63.1)	0.92 (0.83-1.01), p=0.09	0.86 (0.76-0.96), p=0.008
All-cause mortality/ HF hospitalization	321 (48.4)	2,478 (51.2)	0.95 (0.85-1.07), p=0.38	0.85 (0.74-0.97), p=0.01

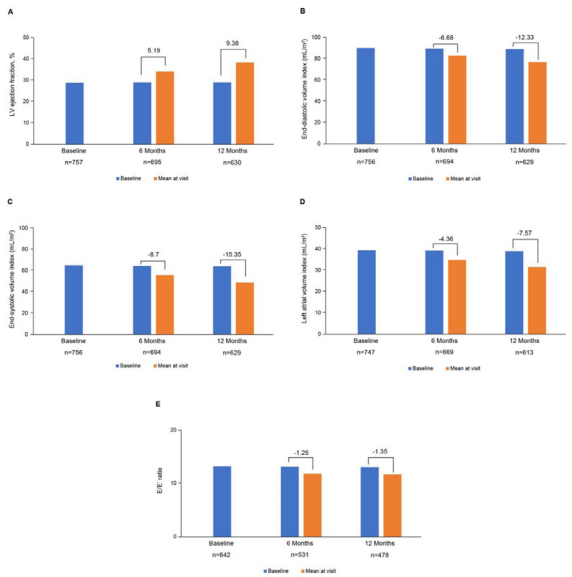
* Model reflects inverse probability of treatment weighting including 24 demographic and clinical variables, and adjustment for discharge prescription for beta-blocker and mineralocorticoid receptor antagonist therapy.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HF, heart failure; HFrEF, heart failure with reduced ejection fraction

Effects of Angiotensin Receptor/Neprilysin Inhibitor Therapy on Amino-terminal Pro-B-Type Natriuretic Peptide and Cardiac Remodeling in Heart Failure with Reduced Ejection Fraction: The PROVE-HF Study

James L. Januzzi[1], Margaret F. Prescott[2], Javed Butler[3], Michael Felker[4], Alan S. Maisel[5], Ileana Pina[6], Amil Shah[7], Ricardo Rocha[2], Kristin Williamson[2], Scott Solomon[7]; [1]Massachusetts General Hospital, Boston, MA; [2]Novartis Pharmaceuticals, Hanover, NJ; [3]University of Mississippi, Jackson, MS; [4]Duke University, Durham, NC; [5]UCSD, San Diego, CA; [6]Wayne State University, Detroit, MI; [7]Brigham and Women's Hospital, Boston, MA

Background: In patients with HFrEF, sacubitril/valsartan (sac/val) treatment improves outcomes although uncertainties regarding its mechanism of benefit exist. Reduction in NT-proBNP during HFrEF treatment is associated with reverse cardiac remodeling however such data during treatment with sac/val are lacking. **Methods:** We performed a prospective, 12 month, open-label, single-arm trial of 794 patients initiated on sac/val at 78 outpatient sites. After ACEi/ARB discontinuation, sac/val was initiated and titrated, and blood samples were obtained for NT-proBNP measurement. Echocardiograms were performed at baseline, 6 months, and 12 months and interpreted by a temporally-blinded core lab. The primary endpoint was correlation between change in NT-proBNP concentrations and change in LVEF, LVEDVi, LVESVi, LAVi or E/E' ratio at 12 months. Other objectives included change in these measures at 6 months, and outcome assessment relative to change in NT-proBNP and LVESVi. **Results:** The mean age of study patients was 65.1 years, 28.5% were women and 22.7% were Black. Participants had a baseline LVEF of 28.9%, LVEDVi of 90.1 mL/m2, LVESVi of 64.9 mL/m2, LAVi of 39.7 mL/m2, and E/E' ratio of 13.4. Following sac/val initiation, highly significant early and sustained NT-proBNP reduction was observed. Change in NT-proBNP at 12 months correlated with increased LVEF (r = -0.381; P <.001), and reduced LVEDVi (r = 0.320; P <.001) or LVESVi (r = 0.405; P <.001). Significant reverse cardiac remodeling was noted at 6 and 12 months (Figure 1). Benefits were observed in patients not receiving ACEi/ARB at study entry, those with lower NT-proBNP concentrations, and those unable to reach target sac/val dose. Shorter time to an NT-proBNP <1000 pg/mL and longer time spent <1000 pg/mL were associated with lower rates of death or HF hospitalization by 12 months (P <.05 for both). Greater reduction in NT-proBNP and LVESVi at 6 months was associated with lowest rates of subsequent death/HF hospitalization (1.3%). **Conclusions:** Among patients with HFrEF, reduction in NT-proBNP following initiation of sac/val is associated with significant reverse cardiac remodeling and fewer events, especially in those with greater reduction in NT-proBNP and LVESVi (NCT02887183).



Effects of Dapagliflozin on Biomarkers, Symptoms and Functional Status in Patients with Heart Failure with Reduced Ejection Fraction with and without Diabetes - The Define-HF Trial

Mikhail Kosiborod[1], Michael Nassif[1], Sheryl Windsor[1], Fenming Tang[1], Yevgeniy Khariton[1], Bethany Austin[1], Guillermo Umpierrez[2], Sumant Lamba[3], Stuart Katz[4], Michael Fong[5], Mansoor Husain[6], Silvio Inzucchi[7], Darren Mcguire[8], Bertram Pitt[9], Benjamin Scirica[10]; [1]Saint Lukes Mid America Heart Institute, Kansas City, MO; [2]Emory University School of Medicine, Atlanta, GA; [3]First Coast Cardiovascular Institute, Jacksonville, FL; [4]NYU Langone, New York, NY; [5]Keck Medical Center of USC, Los Angeles, CA; [6]Toronto General Hospital Research Institute, Toronto, ON; [7]Yale School of Medicine, New Haven, CT; [8]University of Texas Southwestern, Dallas, TX; [9]University of Michigan, Ann Arbor, MI; [10]Brigham and Womens Hospital, Boston, MA

Background: Three large cardiovascular outcome trials of patients with type 2 diabetes (T2D) found a reduction in hospitalizations for heart failure (HF) in patients treated with SGLT2i. However, a majority of patients in these trials did not have manifest HF, and those that did were not well characterized. Consequently, the effects of SGLT-2i in patients with established HF, specifically HF with reduced ejection fraction (HFrEF), including those with and without T2DM, have not been examined in a dedicated trial. **Methods:** The effects of dapagliflozin on biomarkers, symptoms, and functional status in patients with HFrEF (DEFINE-HF) is a 12-week multi-center, randomized, double-blind, placebo-controlled trial. From March 2016 to March 2019, 263 patients from 26 US centers were randomized 1:1 to dapagliflozin 10 mg or matching placebo. Patients with or without T2D, with LVEF ≤40%, EGFR ≥30 mL/min/m2, and NTproBNP ≥400 pg/mL were eligible for inclusion. Co-primary end points were (1) change in NTproBNP and (2) composite of proportion of patients with ≥ 5point increase in the HF disease-specific health status (assessed using KCCQ) or ≥ 20% decrease in