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

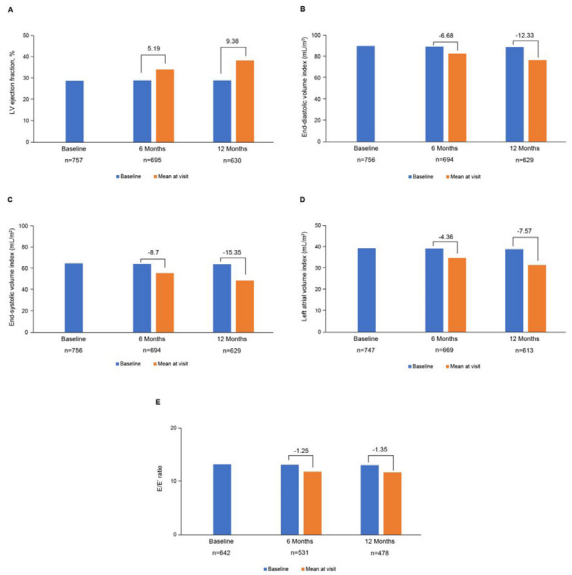
* Model reflects inverse probability of treatment weighting including 24 demographic and clinical variables, and adjustment for discharge prescription for beta-blocker and mineralocorticoid receptor antagonist therapy.

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

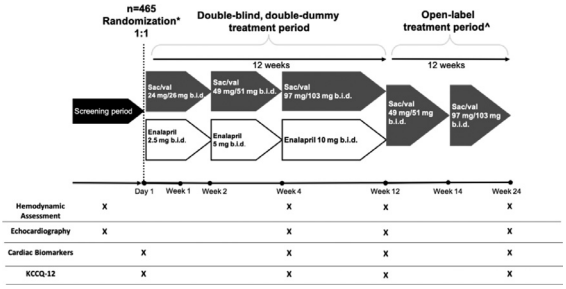
NTproBNP over 12 weeks. Key secondary endpoints included functional status based on 6-minute walk test, and change in KCCQ. Exploratory endpoints included hospitalizations for HF and urgent HF visits. **Results:** Enrollment in DEFINE-HF was completed in March 2019, with last visit scheduled in June. Baseline characteristics are consistent with other trials of high risk HFrEF patients, and are shown in the Table. Topline study results will be available in July 2019, in time for presentation at HFSA 2019. **Conclusion:** DEFINE-HF is the first dedicated multicenter randomized double-blind placebo-controlled trial of SGLT-2i in patients with established HFrEF with and without T2D. It will assess whether the SGLT2i dapagliflozin improves HF biomarkers, symptoms and functional status in this high-risk patient population.

Baseline Characteristics	
Male	193 (73.4%)
Age (years)	61.3 ± 11.5
KCCQ-os	67.3 ± 21.5
African American	97 (39.1%)
ICD	164 (62.4%)
NYHA III	91 (35.6%)
Ejection fraction (%)	26.4 ± 8.1
Diabetes	164 (62.4%)
Hx HF hosp	206 (78.3%)
Atrial Fibrillation	104 (39.5%)
NTproBNP (pg/mL)	1936 ± 2272
eGFR (mL/min)	69.2 ± 22.2
ACE/ARB	142 (54.5%)
ARNI	79 (30.0%)
Beta blockers	243 (92.4%)
MRA	155 (58.9%)
Loop diuretics	218 (82.9%)

Effects of Sacubitril-valsartan Compared with Enalapril on Arterial Hemodynamics, Cardiac Remodeling, and Quality of Life in Patients with Heart Failure and Reduced Ejection Fraction

Akshay S. Desai[1], Scott D. Solomon[1], Amil M. Shah[1], Brian L. Claggett[1], James C. Fang[2], Joseph Izzo[3], Cheryl A. Abbas[4], Ricardo A. Rocha[4], Gary F. Mitchell[5]; [1]Brigham and Women's Hospital, Boston, MA; [2]University of Utah, Salt Lake City, UT; [3]State University of Buffalo, Buffalo, NY; [4]Novartis Pharmaceuticals, East Hanover, NJ; [5]Cardiovascular Engineering, Inc., Norwood, MA

Background: Compared to angiotensin-converting enzyme inhibition alone, angiotensin receptor-neprilysin inhibition reduces cardiovascular mortality and heart failure (HF) hospitalization in patients with HF and reduced ejection fraction (HFrEF). The pathophysiologic mechanisms responsible for these clinical benefits remain unclear but may be related to effects on central hemodynamics and cardiac structure and function. We sought to determine whether treatment of HFrEF with sacubitril/valsartan improves central aortic stiffness, cardiac remodeling, biomarkers of wall stress and injury, and quality of life compared with enalapril. **Methods:** EVALUATE-HF was a prospective, randomized, multicenter, double-blind, double-dummy clinical trial of patients aged 50 or older with chronic HF, NYHA I-III symptoms, and EF of 40% or less. Participants were randomized 1:1 to treatment with sacubitril/valsartan (target dose 97/103 mg twice daily) versus enalapril (target dose 10 mg twice daily) for 12 weeks followed by open-label sacubitril/valsartan for 12 weeks (**Figure**). The primary study outcome was between group difference in change from baseline to week 12 in aortic characteristic impedance (Zc). Other prespecified outcomes included change from baseline to week 12 in levels of cardiac biomarkers and echocardiographic measures of cardiac structure and function as well as change in health-related quality of life assessed by the 12-item Kansas City Cardiomyopathy Questionnaire (KCCQ-12). **Results:** Between August 17, 2016 and January 26, 2019 we randomized 464 participants at 85 sites in the United States, of whom 231 were randomly assigned to sacubitril/valsartan and 233 to enalapril. For the overall population, mean age was 67.3 +/- 9.1 years, mean EF was 34 +/- 10%, median NTproBNP was 584 [IQR 244, 1467], 109 (23.5%) were female, 115 (24.8%) were black, 313 (67.4%) reported NYHA Class 2, and 391 (84.3%) were previously treated with an ACEi or ARB. We will present the primary results of the EVALUATE-HF study as initially submitted to the 2019 European Society of Cardiology Scientific Sessions, including the effects of sacubitril/valsartan compared with enalapril on change from baseline in central aortic stiffness, cardiac biomarkers, cardiac structure and function. We will also present new data regarding the time course and magnitude of changes in quality of life in both treatment groups during study follow up as well as the relationship of these changes to changes in cardiac structure, function, and biomarkers. **Conclusions:** EVALUATE-HF will provide important mechanistic insights into established clinical benefits of sacubitril/valsartan in HFrEF. We will present detailed quality of life outcomes for the first time at HFSA 2019.



Primary Results of the Sensible Medical Innovations Lung Fluid Status Monitor Allows Reducing Readmission Rate of Heart Failure Patients (smile) Trial

William T. Abraham[1], Stefan Anker[2], Dan Burkhoff[3], John Cleland[4], Eiran Gorodeski[5], Tiny Jaarsma[6], Roy Small[7], JoAnn Lindenfeld[8], Alan Miller[9], Stephan Ogenstad[10], Sean Pinney[11], Raymond Zimmer[12], Peter Eckman[13], Michael Koren[14], Tom McRae[15], Liviu Klein[16], Offer Amir[17], Maria Rosa Costanzo[18], Nir Uriel[3]; [1]Ohio State University, Columbus, OH; [2]Charite, Berlin, Germany; [3]Columbia, NYC, NY; [4]Univ Glasgow, Glasgow, United Kingdom; [5]Cleveland Clinic, Cleveland, OH; [6]Linköping University, Linköping, Sweden; [7]Lancaster General, Lancaster, PA; [8]Vanderbilt, Nashville, TN; [9]Univ Florida, Jacksonville, FL; [10]Statogen, Zebulon, NC; [11]Mt. Sinai, NYC, NY; [12]Cedars-Sinai, Los Angeles, CA; [13]Allina Health, Minneapolis, MN; [14]Jacksonville Center, Jacksonville, FL; [15]HCA, Nashville, TN; [16]UCSF, San Francisco, CA; [17]Poria Health, Poria, Israel; [18]Advocate Health, Naperville, IL

Background: Acute decompensated heart failure (ADHF) is associated with a high rate of readmissions and mortality. Remote dielectric sensing (ReDS) fluid monitoring provides an accurate tool for non-invasive measurement of absolute lung fluid content, providing actionable information and a new tool for managing HF. **Methods:** The SMILE trial was a prospective, multicenter, randomized clinical trial testing the hypothesis that post-discharge HF management guided by frequent in-home ReDS assessment is superior to usual care. Patients with a current hospitalization for ADHF, regardless of the LVEF, were enrolled in 43 US centers. Subjects randomized to the treatment arm were discharged home with the ReDS fluid monitor system and managed using ReDS measurements, according to protocol-defined algorithms. Control patients received usual care, without ReDS. The primary endpoint was recurrent (cumulative) ADHF hospitalizations, analyzed using the Andersen-Gill model with treatment group as the only covariate. Patients were followed for up to 9 months, until the last patient enrolled reached 3 months of follow-up. **Results:** Between October 2015 and October 2017, 268 patients were randomized - 135 to treatment and 133 to control - and followed for 6.1±3.4 months. Patients were aged 68±12 years; 30% were women and 29% had LVEF≥40%. Pre-specified analysis of the per-protocol cohort demonstrated 21 readmissions in 15 ReDS patients compared to 43 readmissions in 34 control patients (HR 0.52, 95% CI [0.31-0.87], P=0.01) or a 48% readmissions reduction (Figure). Subgroup analysis by LVEF < or ≥40% showed similar reductions in ADHF readmissions (RRR 50%, P=0.03 and 46%, P=NS, respectively), with ReDS-guided HF management. Number of days lost to ADHF hospitalization was lower (1.37 vs. 2.62 days, 48% reduction, P=0.006) and time from discharge to first ADHF readmission was longer (HR 0.45, 95% CI [0.25-0.83], P=0.01), for ReDS-guided management. There was no significant difference in mortality between groups. **Conclusions:** The SMILE trial demonstrates a substantial reduction in recurrent ADHF hospitalizations and improvement in other outcome measures in recently discharged ADHF patients managed using daily ReDS assessment of absolute lung fluid content.