Supplementary Online Content

DeVore AD, Braunwald E, Morrow DA, et al; PIONEER-HF Investigators. Initiation of angiotensin-neprilysin inhibition after acute decompensated heart failure: secondary analysis of the open-label extension of the PIONEER-HF trial. *JAMA Cardiol*. Published online December 11, 2019. doi:10.1001/jamacardio.2019.4665

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods.

Dose Titration: At the start of the open-label extension study, 13% of patients began at dose level 1 sacubitril/valsartan (24/26 mg twice daily), 19% of patients began at dose level 2 (sacubitril/valsartan 49/51 mg twice daily), and 58% of patients were at dose level 3 (97/103 mg twice daily). At 12 weeks, 13% were at dose level 1, 18% were at dose level 2 and 57% were at dose level 3.

Adjudication of Clinical Events: In the PIONEER-HF trial, clinical events were reported by sites. For the primary analysis, these investigator-reported events were utilized.[2] As reported previously, after submission of the primary analysis for publication we undertook a *post-hoc* adjudication of clinical events via a blinded Clinical Events Committee.[4] Rehospitalization for HF was defined as an admission for worsening signs or symptoms of HF resulting in the new administration of intravenous therapies, mechanical or surgical intervention, or provision of ultrafiltration, hemofiltration, or dialysis specifically for the management of persistent or worsening HF. In the **Supplemental Table**, we report clinical outcomes utilizing both unadjudicated and adjudicated data.

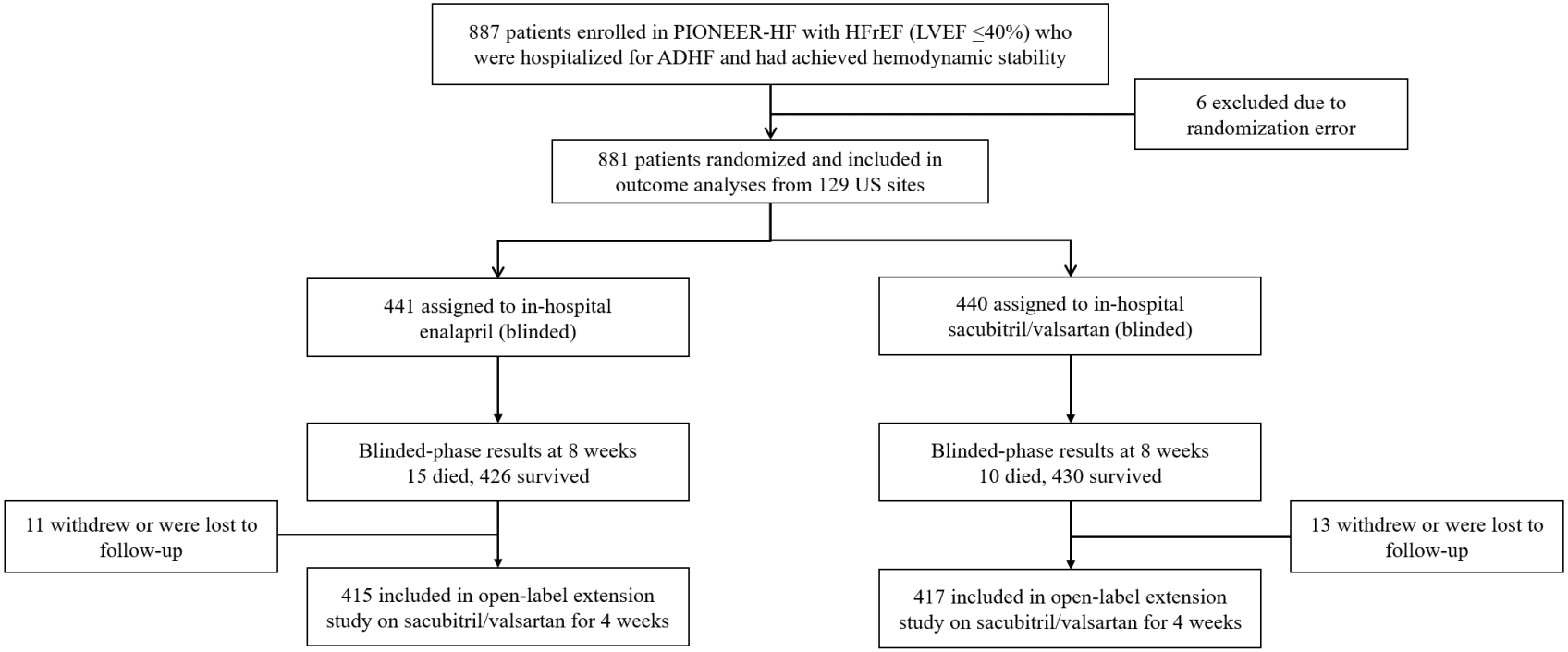
eTable. Clinical Outcomes from Baseline Over 12 Weeks

	Overall *N=881*	**In-hospital S/V followed by S/V** *N=440*	**In-hospital enalapril followed by S/V** *N=441*	**Hazard Ratio (95% CI)**	**P-value**
Composite 1 (Unadjudicated)	147 (16.69)	58 (13.18)	89 (20.18)	0.63 (0.46, 0.88)	0.007
HF Rehospitalization	125 (14.19)	50 (11.36)	75 (17.01)		
LVAD Implantation	2 (0.23)	1 (0.23)	1 (0.23)		
All-Cause Mortality	30 (3.41)	12 (2.73)	18 (4.08)		
Composite 2 (Unadjudicated)	147 (16.69)	58 (13.18)	89 (20.18)	0.63 (0.46, 0.88)	0.007
HF Rehospitalization	125 (14.19)	50 (11.36)	75 (17.01)		
All-Cause Mortality	30 (3.41)	12 (2.73)	18 (4.08)		
Composite 3 (Adjudicated)	147 (16.69)	62 (14.09)	85 (19.27)	0.71 (0.51, 0.98)	0.04
HF Rehospitalization	125 (14.19)	54 (12.27)	71 (16.10)		
LVAD Implantation	2 (0.23)	1 (0.23)	1 (0.23)		
All-cause Mortality	30 (3.41)	12 (2.73)	18 (4.08)		
Composite 4 (Adjudicated)	137 (15.55)	57 (12.95)	80 (18.14)	0.69 (0.49, 0.97)	0.03
HF Rehospitalization	125 (14.19)	54 (12.27)	71 (16.10)		
Cardiovascular Mortality	19 (2.16)	6 (1.36)	13 (2.95)		

Values shown are counts and (percentages)

CI, confidence interval; *HF,* heart failure; *LVAD,* Left Ventricular Assist Device; *no.*, number; *S/V,* sacubitril/valsartan

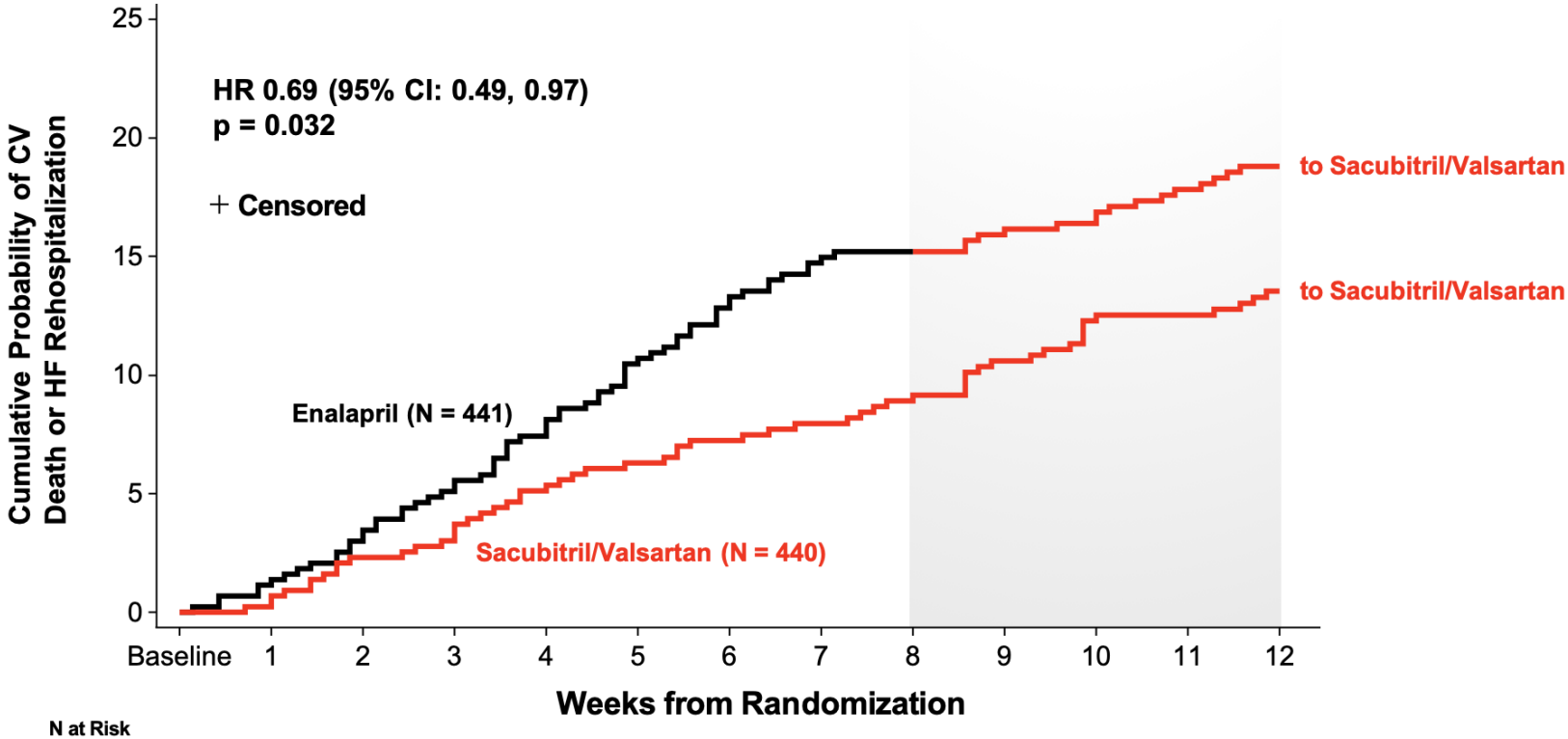
eFigure 1. Flow Diagram of the Study Design



This figure displays the initial study population, through exclusions, to the final open-label extension study population.

ADHF, acute decompensated heart failure; *HFrEF*, heart failure with reduced ejection fraction; *LVEF*, left ventricular ejection fraction; *US*, United States

eFigure 2. Effect of Sacubitril/Valsartan on Clinical Outcomes Over 12 Weeks



N at Risk	Baseline	1	2	3	4	5	6	7	8	9	10	11	12
Enalapril (n)	441	429	418	407	396	381	368	359	356	353	351	342	296
Sacubitril/Valsartan (n)	440	434	420	415	404	397	390	385	380	371	362	358	295

These data include adjudicated HF hospitalizations

This figure displays the Kaplan-Meier estimated cumulative incidence of the composite of cardiovascular death or rehospitalization for heart failure by randomized treatment arm during the double-blind period (weeks 0-8) and the open-label extension study (weeks 8-12, gray box).

CI, confidence interval; *CV*, cardiovascular, *HF*, heart failure, *HR*, hazard ratio