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# **Worsening HF Episodes Outside a Hospital Setting in Heart Failure with Preserved Ejection Fraction: the PARAGON-HF Trial**

**Running Title:** Urgent HF Visits for HFpEF

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**Tweet:** New data from #PARAGONHF: worsening HF events, even when treated in ambulatory settings, are prognostically meaningful & should be considered in future RCTs in #HFpEF.

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## **ABBREVIATIONS**

HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
KCCQ	Kansas City Cardiomyopathy Questionnaire
MAGGIC	Meta-analysis Global Group in Chronic Heart Failure
NT-proBNP	N-terminal prohormone of B-type natriuretic peptide
NYHA	New York Heart Association
PARAGON-HF	Prospective Comparison of ARNI with ARB Global Outcomes in HFpEF

## **STRUCTURED ABSTRACT**

**Background:** Episodes of worsening heart failure (HF) managed without hospitalization are common and prognostically important in HF with reduced ejection fraction (EF) . The significance of these ambulatory worsening HF events in HF with preserved EF (HFpEF) is uncertain.

**Methods:** PARAGON-HF randomly assigned 4,796 patients with HFpEF ( $\geq 45\%$ ) to treatment with sacubitril/valsartan vs. valsartan with a primary composite endpoint of total HF hospitalizations and cardiovascular death. Urgent ambulatory HF visits requiring intravenous diuretic treatment were prospectively collected and adjudicated by a blinded committee. We examined the effect of study treatment on a prespecified expanded composite of CV death and worsening HF events (including HF hospitalizations and urgent HF visits) and the effect of each type of HF event on subsequent mortality.

**Results:** Of 884 first worsening HF events, 66 (7.5%) were urgent HF visits. Patients whose first episode of worsening HF event was an urgent visit had similar age, comorbidities, baseline NT-proBNP, and MAGGIC risk scores to those in whom the first HF event was a hospitalization (all comparisons  $P > 0.05$ ). Regardless of the treatment setting, patients with a first episode of worsening HF had higher rates of subsequent death (19.2 per 100py, 95% CI: 16.9-21.8 for HF hospitalization and 10.1 per 100py, 95% CI: 5.4-18.7 for urgent HF visit) compared to those who did not experience worsening HF (death rate 4.0 per 100py, 95% CI: 3.6-4.4). Including total urgent HF visits in the composite study endpoint added 95 total events and would have shortened the trial duration needed for event accrual. The addition of urgent HF visits in a prespecified composite endpoint reinforced the treatment efficacy of sacubitril/valsartan compared with valsartan (rate ratio 0.86, 95% CI: 0.75–0.99;  $P = 0.040$ ).

**Conclusions:** Like HF hospitalizations, worsening HF events treated in the ambulatory setting are prognostically important in HFpEF. Inclusion of these events in the composite primary endpoint underscores the benefit of sacubitril/valsartan compared with valsartan in PARAGON-HF.

**Key Words:** clinical outcomes; heart failure with preserved ejection fraction; hospitalization; sacubitril/valsartan

**Clinical Trial Registration:** PARAGON-HF: ClinicalTrials.gov Identifier NCT01920711

## **CONDENSED ABSTRACT**

Of 884 first worsening heart failure (HF) events experienced by 4,796 randomized patients with chronic HF with preserved ejection fraction (HFpEF;  $\geq 45\%$ ) in the PARAGON-HF trial, 7.5% were urgent HF visits (as opposed to HF hospitalizations). Patients who first experienced urgent HF visit had higher rates of subsequent death (10.1 per 100py, 95% CI: 5.4-18.7) compared with patients who did not experience worsening HF (4.0 per 100py, 95% CI: 3.6-4.4). Treatment with sacubitril/valsartan modestly reduced the risk of the prespecified composite of the primary endpoint + urgent HF visits compared with valsartan alone (rate ratio 0.86, 95% CI: 0.75-0.99). Episodes of worsening HF requiring ambulatory intravenous treatment are prognostically meaningful and should be considered in future clinical trials evaluating patients with HFpEF.

Heart failure (HF) is a progressive clinical syndrome, punctuated by episodic clinical deterioration (1). Worsening HF episodes requiring hospitalization are strongly linked with risk for subsequent hospitalizations, deaths, and adverse patient-reported outcomes (2,3). Older adults hospitalized for HF face 5-year mortality rates of ~75%, irrespective of left ventricular ejection fraction (4). As such, hospitalization for HF is a recognized marker of disease progression, a key quality metric, and an established endpoint in clinical trials (5–7).

Hospitalizations alone may not fully capture the burden of worsening HF experienced by patients. While readmissions for HF are declining, total encounters with emergency departments and observation stays for HF are increasing in the US (8,9), potentially as a consequence of financial incentives to limit inpatient admissions. Similarly, administration of intravenous diuretics during ambulatory visits (as a proportion of total HF health system encounters) appears to be increasing slowly in the US (10). Similar shifts to ambulatory care of worsening HF have been observed outside the US (11,12). Recent clinical trials enrolling patients with HF with reduced ejection fraction (HFrEF) have accordingly incorporated worsening HF episodes treated in ambulatory settings as a component of primary study endpoints (13–19) and as enrichment criteria to enhance event rates in HFrEF (20), acknowledging their prognostic importance.

The clinical significance of these ambulatory worsening HF events in HF with preserved ejection fraction (HFpEF) is uncertain. As such, we evaluated the frequency and prognostic implications of urgent HF visits in the global PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction) trial. In addition, we evaluated the potential utility of inclusion of these events in the estimated treatment benefit of sacubitril/valsartan in HFpEF.

## **Methods**

### *Study Design and Patient Population*

The design and primary results of PARAGON-HF have been previously published (21,22). PARAGON-HF was a global, randomized, double-blind clinical trial comparing sacubitril/valsartan with valsartan in ambulatory patients with HFpEF. Key inclusion criteria included age  $\geq 50$  years, New York Heart Association (NYHA) functional class II-IV, LVEF  $\geq 45\%$ , elevated natriuretic peptides, diuretic use for at least 30 days, and evidence of structural heart disease (either left ventricular hypertrophy or left atrial enlargement). Patients

hospitalized for acute decompensated HF were ineligible until after discharge. Those tolerating sequential single-blind valsartan and sacubitril/valsartan run-in periods at half-target doses were subsequently randomized 1:1 to receive sacubitril/valsartan (target dose, 97mg/103mg twice daily) or valsartan (target dose, 160mg twice daily). Median follow-up was 35 months.

### *Clinical Endpoints*

The primary study efficacy endpoint was a composite of total (first and recurrent) HF hospitalizations and cardiovascular death. Other key secondary endpoints included cardiovascular and all-cause death. A Clinical Endpoints Committee (CEC) blinded to study drug assignment adjudicated all deaths, HF hospitalizations, and urgent HF visits. HF hospitalization was defined as events requiring an overnight stay accompanied by signs and symptoms of HF and receipt of intravenous HF therapies (diuretics, vasodilators, inotropes). Urgent HF visits were defined as receipt of intravenous HF therapies during urgent, unscheduled ambulatory clinic or emergency department visits without formal inpatient hospitalization requiring an overnight stay. An expanded worsening HF composite including cardiovascular death, total HF hospitalizations, and total urgent HF visits was a prespecified secondary analysis in the original study protocol (23).

### *Statistical Analysis*

Baseline characteristics of participants experiencing HF hospitalization as the first worsening HF event, urgent HF visit as the first worsening HF event, or no worsening HF event, were described using proportions for categorical variables, means and standard deviations for normally distributed continuous variables, and median and 25<sup>th</sup>-75<sup>th</sup> percentiles for non-normally distributed continuous variables. Characteristics were compared using analysis of variance, Kruskal-Wallis, and chi-squared tests, as appropriate. In addition, we directly compared characteristics between patients experiencing a first HF hospitalization event with those experiencing a first urgent HF visit event using Student's t, Wilcoxon rank-sum, and chi-squared tests, as appropriate.

For those experiencing at least one HF hospitalization or urgent HF visit during study follow up, rates of death following the first worsening HF event were estimated using Poisson regression and overall risk and compared to those who did not experience worsening HF using

Cox proportional hazards models. Similarly, rates of total worsening HF events and cardiovascular death after index worsening HF events were compared using a semiparametric proportional rates method of Lin, Wei, Yang, and Ying (24), stratified by geographic region. To address the possibility that sites with the capacity to provide ambulatory intravenous therapy may have enrolled patients with a different risk profile, a sensitivity analysis was performed including only sites with at least one urgent HF visit during the trial. The effect of sacubitril/valsartan compared with valsartan on the primary composite endpoint (total HF hospitalizations and cardiovascular death) and an expanded composite endpoint (including adjudicated urgent HF events) was plotted using Nelson-Aalen cumulative incidence curves and compared using the semiparametric proportional rates method, stratified by geographic region. As heterogeneity in treatment benefits of sacubitril/valsartan was observed by sex and left ventricular ejection fraction (above and below the median, 57%) in PARAGON-HF (21), we further examined treatment effects on the expanded composite endpoint in these subgroups.

The PARAGON-HF study protocol was approved by ethics committees or institutional review boards at each participating site and all patients provided written informed consent prior to study enrollment. Statistical analysis was performed using STATA version 15.1 (College Station, TX). A 2-sided p-value<0.05 was considered significant.

## Results

### *Clinical Profiles of Patients Experiencing Worsening HF Events*

Of the 4,796 randomized subjects, 884 experienced a first episode of worsening HF, of which 66 (7.5%) were urgent HF visits and 818 (92.5%) were hospitalizations for HF. Patients whose first worsening HF event was an urgent visit had similar ages, comorbidities, baseline N-terminal prohormone of B-type natriuretic peptide levels (1209 [723-2019] vs. 1160 [578-2106] pg/mL), and Meta- Analysis Global Group in Chronic Heart Failure (MAGGIC) risk scores ( $20.3 \pm 5.3$  vs.  $20.6 \pm 5.6$ ) to those whose first HF event was a HF hospitalization (all comparisons  $P>0.05$ ; **Table 1**). While baseline use of renin-angiotensin system inhibitors was more frequent among patients whose first HF event was an urgent HF visit as opposed to a HF hospitalization (93.9% vs. 82.4%;  $P=0.02$ ), use of  $\beta$ -blockers and mineralocorticoid receptor antagonists did not significantly differ ( $P>0.05$  for both; **Table 1**). The 66 participants who experienced urgent HF



visits were enrolled at 56 sites in 22 countries, with the greatest number from the United States (n=12). No site enrolled more than 2 participants who experienced urgent HF visits.

#### *Prognosis after Worsening HF Event*

Patients who experienced a first urgent HF visit (10.1 per 100py, 95% confidence interval [CI]: 5.4-18.7) or first HF hospitalization (19.2 per 100py, 95% CI: 16.9-21.8) experienced a higher rate of subsequent death than patients who did not experience worsening HF (4.0 per 100py, 95% CI: 3.6-4.4; **Central Illustration**). The risk of subsequent death was estimated to be lower after an urgent HF visit compared with after an HF hospitalization (hazard ratio 0.52, 95 CI%: 0.27-0.97; P=0.04). The proportion of deaths that were attributed to cardiovascular causes was 72% (of 231 deaths) after HF hospitalization, 60% (of 10 deaths) after urgent HF visit, and 54% (of 450 deaths) without worsening HF event.

Recognizing that all sites may not be equipped to facilitate urgent HF visits, in a sensitivity analysis restricted to patients enrolled at the 56 sites with at least 1 urgent HF visit (n=665), death rates following urgent HF visit remained lower than following HF hospitalization (10.1 per 100 py, 95% CI: 5.4-18.7 vs. 25.2 per 100 py, 95% CI: 18.3-34.5; hazard ratio 0.42, 95% CI: 0.21-0.85; P=0.02) and higher than for participants who did not experience worsening HF (4.5 per 100 py, 95% CI: 3.5-5.8).

Among the 66 patients requiring first urgent HF visits, 20 (30%) were subsequently hospitalized for HF at median 5.9 months (2.3-11.8 months). Four of these patients experienced cardiovascular death following HF hospitalization, and 2 died of cardiovascular causes without HF hospitalization. The remaining 44 patients (66%) completed study follow-up without experiencing a primary endpoint event. The rate of subsequent worsening HF events (composite cardiovascular death and any HF event) was not significantly different for both patients who first experienced urgent HF visit (55 per 100py, 95% CI: 42-72) or HF hospitalization (68 per 100py, 95% CI: 63-73], P-value for difference=0.39) (**Figure 2**).

#### *Inclusion of Urgent HF Visits in Assessing Treatment Effects of Sacubitril/Valsartan*

Use of expanded study composite endpoint including urgent HF visits added 95 total events (55 in valsartan arm, 40 in sacubitril/valsartan arm) to the primary study composite endpoint. In the original trial, sacubitril/valsartan modestly reduced the risk of the primary endpoint (rate ratio

[RR] 0.87, 95% CI: 0.75-1.005; P=0.058). The addition of urgent HF visits in a prespecified expanded composite endpoint of cardiovascular death and total worsening HF events reinforced the treatment efficacy of sacubitril/valsartan compared with valsartan alone (RR 0.86, 95% CI: 0.75–0.99; P=0.040); **Figure 3**. Consistent with heterogeneity observed in key subgroups in the main PARAGON-HF trial, sacubitril/valsartan particularly reduced cardiovascular death and total worsening HF events compared with valsartan among women and participants with lower left ventricular ejection fractions (**Table 2**).

## **Discussion**

Among patients with HFpEF enrolled in PARAGON-HF, ambulatory intravenous management of worsening HF during an urgent HF visit was far less common than HF hospitalization and modestly varied by region. While long-term mortality after an urgent HF visit was lower than that observed after HF hospitalization, total burden of subsequent cardiovascular mortality and HF events was markedly elevated after an episode of worsening HF, independent of the treatment setting. Inclusion of urgent HF visits in a composite primary endpoint in PARAGON-HF would have added 95 additional events. Based on the observed rate of urgent HF visits in PARAGON-HF, we estimate this would have shortened the time to accrual of the target number of primary events by 1.6 months. The addition of these events into an expanded composite primary endpoint in PARAGON-HF underscores a treatment benefit favoring sacubitril/valsartan compared with valsartan in HFpEF. Taken together, these data suggest that episodes of worsening HF requiring ambulatory intravenous treatment are prognostically important and represent clinically relevant endpoints for clinical trials of HFpEF.

### *Prognostic Relevance of Ambulatory Worsening HF Events in HFpEF*

Safely deferring or delaying hospitalizations is a shared goal by patients and health systems. Indeed, more patients may be receiving care in outpatient HF care units (“diuretic clinics”) in recent years (25). In addition, value-based programs that target admissions and readmissions as core quality measures have placed additional pressures to broaden capacity of ambulatory facilities in the US to provide higher acuity HF care (9). Patients may further be averse to hospitalizations in the current era of coronavirus disease 2019 (COVID-19) to limit healthcare exposure and viral transmission (26). Collectively, these factors highlight the importance of

understanding the use and clinical implications of worsening HF care delivered outside of traditional hospital encounters.

These data demonstrate that urgent HF visits are prognostically relevant with comparable trajectories of subsequent HF events as after index HF hospitalizations. In our study, patients presenting to these alternative care settings share similar characteristics and risk profiles (as determined by objective measures of disease severity, such as the validated MAGGIC risk score (27) and natriuretic peptides) as patients hospitalized for HF. It is noteworthy that while the total number of subsequent worsening HF events was comparable after an index event, subsequent mortality was lower among patients initially treated in ambulatory care compared with hospitalization settings. Importantly, not all patients who had a worsening HF event in the ambulatory setting were subsequently hospitalized (in fact only a third were), suggesting that urgent HF visits do not merely represent an early flag for subsequent HF hospitalization.

#### *Implications for Clinical Trials in HFpEF*

All-cause mortality and more recently the composite of cardiovascular death or first HF hospitalization have been traditional endpoints in clinical trials of HF therapeutics. With globalization of clinical trial programs to encompass diverse care models and recognition of their prognostic relevance, inclusion of urgent HF visits may provide a more complete portrayal of worsening HF events. Urgent HF visits appear to occur earlier than HF hospitalization during a period of worsening HF, and in two-thirds of cases represent truly *unique* events (would not have otherwise been captured by traditional composite cardiovascular endpoints). As such, for event-driven trials in HFpEF, the inclusion of these additional events would be expected to shorten, albeit modestly, the trial duration needed for event accrual. The recent VICTORIA (Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction) trial reinforced the clinical relevance of urgent HF visits in HFrEF. The trial included patients who received intravenous diuretic therapy outside a hospital setting within 3 months as a pathway of the enrollment (20). The rapid accrual of worsening HF events in this trial highlights the high-risk nature of this cohort.

Clinical trialists or sponsors may be concerned about inclusion of urgent HF visits given uncertainty around variability in care approaches. While event definitions to qualify as an urgent HF visit have been standardized in accordance to the Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials (28), ambulatory worsening HF

events may occur in various contexts, including isolated Emergency Department (treat-and-discharge) presentations, short stays in observation units, or augmentation of outpatient HF therapies. This analysis focused on the endpoint of urgent HF visits requiring intravenous therapies as this was protocol-specified and specifically adjudicated in PARAGON-HF. However, this conservative definition may identify a relatively small number of events and may miss less intensive therapeutic interventions targeting worsening HF in ambulatory care. Consistent with this observation, nationwide Medicare claims data suggest that intravenous diuretics are infrequently administered in US ambulatory clinical practice (10). PARAGON-HF was designed in 2014 at a time when experience with non-hospitalization worsening HF events was limited, and employing a recurrent events approach (as opposed to a time-to-first analysis) was already introducing an innovative adaptation. Future studies may consider more comprehensively capturing ambulatory worsening HF events (including ones that require intensification of oral diuretics or other HF therapies during an unscheduled visit) as each of these episodes of care appear to be common in clinical practice (12) and prognostically meaningful (29,30). Several clinical trials of pharmacological therapies (31), including the recent DAPA-HF (Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure) (13,30), GALACTIC-HF (Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure) (18), and SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure) (19) trials have designated urgent HF visits as a component of the primary endpoint. Similarly, urgent HF visits have been included as key endpoints of trials of cardiovascular devices in HFrEF (15–17). Other trials in HFrEF of therapies with varying mechanisms of action, including sacubitril/valsartan (29) and bucindolol (32), have simulated the impact of adding urgent HF visits to composite endpoints; this approach consistently reinforced the primary findings. In HFpEF, the ongoing DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients with PReserved Ejection Fraction Heart Failure; NCT03619213) trial includes urgent HF visits in a triple composite primary endpoint.

### *Study Limitations*

This study is subject to certain limitations. We focused specifically on adjudicated urgent HF visits which yielded a modest sample of events. As this study was embedded within a clinical

trial with specific eligibility criteria, the findings may not be generalizable to real-world clinical practice. Not all sites may have had pathways in place to facilitate urgent HF visits. However, we only identified modest variation across geographic regions in the proportion of first worsening HF events that were urgent HF visits arguing against marked variation in access to care. We further employed sensitivity analyses, restricted to sites that reported at least 1 urgent HF visit, and identified consistent findings.

### *Conclusions*

Acute care of patients with HF is diversifying in recent years. Urgent HF visits are prognostically relevant and subsequent risk of clinical progression appears comparable to that after traditional HF hospitalizations. As such, clinical trials should additionally consider these episodes of worsening HF that occur in the ambulatory settings. Measuring total episodes of worsening HF (irrespective of site or duration of care) represents a comprehensive and meaningful assessment of clinical status and healthcare utilization in HFpEF.

### **Perspectives.**

**Competency in Medical Knowledge:** Episodes of worsening HF, even those not requiring hospitalization, represent clinically important events and identify patients at risk for near-term clinical progression.

**Translational Outlook 1:** Measuring total episodes of worsening HF (irrespective of site or duration of care) represents a comprehensive and meaningful assessment of clinical status and healthcare utilization in HFpEF.

**Translational Outlook 1:** Future clinical trials evaluating patients with HFpEF should consider total episodes of worsening HF, including of urgent HF visits that occur in ambulatory settings.

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**Table 1: Baseline Characteristics of Patients Who First Experienced HF Hospitalization, Urgent HF Visit, or Did Not Experience a Worsening HF Event**

	Urgent HF Visit	HF Hospitalization	<i>P-Value</i> (Urgent HF visit vs HF Hospitalization)	No Worsening HF Event	<i>P-Value</i> (across all 3 groups)
	n=66	n=818		n=3912	
Age (years)	74 ± 9	74 ± 9	0.89	73 ± 8	<0.001
Women	29 (43.9%)	408 (49.9%)	0.35	2042 (52.2%)	0.22
Race			0.57		0.005
Asian	6 (9.1 %)	106 (13.0%)		495 (12.7%)	
Black	1 (1.5 %)	28 (3.4 %)		73 (1.9 %)	
Other	2 (3.0 %)	15 (1.8 %)		163 (4.2 %)	
White	57 (86.4%)	669 (81.8%)		3181 (81.3%)	
Geographic Region			0.26		<0.001
Asia/Pacific or other	6 (9.1 %)	143 (17.5%)		613 (15.7%)	
Central Europe	15 (22.7%)	222 (27.1%)		1478 (37.8%)	
Latin America	4 (6.1 %)	35 (4.3 %)		331 (8.5 %)	
North America	15 (22.7%)	173 (21.1%)		371 (9.5 %)	
Western Europe	26 (39.4%)	245 (30.0%)		1119 (28.6%)	
NYHA functional class			0.06		0.001
I	5 (7.6 %)	24 (2.9 %)		108 (2.8 %)	
II	51 (77.3%)	581 (71.1%)		3074 (78.6%)	
III	10 (15.2%)	207 (25.3%)		715 (18.3%)	
IV	0 (0.0 %)	5 (0.6 %)		14 (0.4 %)	
Diabetes mellitus	36 (54.5%)	421 (51.5%)	0.63	1605 (41.0%)	<0.001
Atrial fibrillation	30 (45.5%)	293 (36.0%)	0.12	1229 (31.5%)	0.004
History of stroke	8 (12.1%)	103 (12.7%)	0.90	397 (10.2%)	0.10
History of myocardial infarction	10 (15.2%)	207 (25.3%)	0.07	866 (22.1%)	0.05
Body mass index (kg/m <sup>2</sup> )	31 ± 4	31 ± 5	0.96	30 ± 5	0.012

Systolic blood pressure (mmHg)	131 ± 16	131 ± 17	0.87	130 ± 15	0.20
Heart rate (bpm)	71 ± 13	71 ± 13	0.90	70 ± 12	0.12
Screening NT-proBNP (pg/mL)	1209 [723, 2019]	1161 [578, 2106]	0.69	858 [45, 1523]	<0.001
Estimated glomerular filtration rate (mL/min/1.73m <sup>2</sup> )	63 ± 19	60 ± 19	0.21	63 ± 19	<0.001
Left ventricular ejection fraction (%)	57 ± 8	57 ± 8	0.60	57 ± 8	0.13
MAGGIC risk score	20 ± 5	21 ± 6	0.66	19 ± 6	<0.001
Diuretics	66 (100.0%)	792 (96.8%)	0.14	3727 (95.3%)	0.031
Angiotensin-converting enzyme inhibitors / Angiotensin receptor blockers	62 (93.9%)	674 (82.4%)	0.02	3403 (87.0%)	<0.001
β-blockers	55 (83.3%)	654 (80.0%)	0.51	3112 (79.6%)	0.73
Mineralocorticoid receptor antagonists	24 (36.4%)	248 (30.3%)	0.31	967 (24.7%)	<0.001

Values are n (%), mean ± standard deviation, or median [25<sup>th</sup> to 75<sup>th</sup> percentiles].

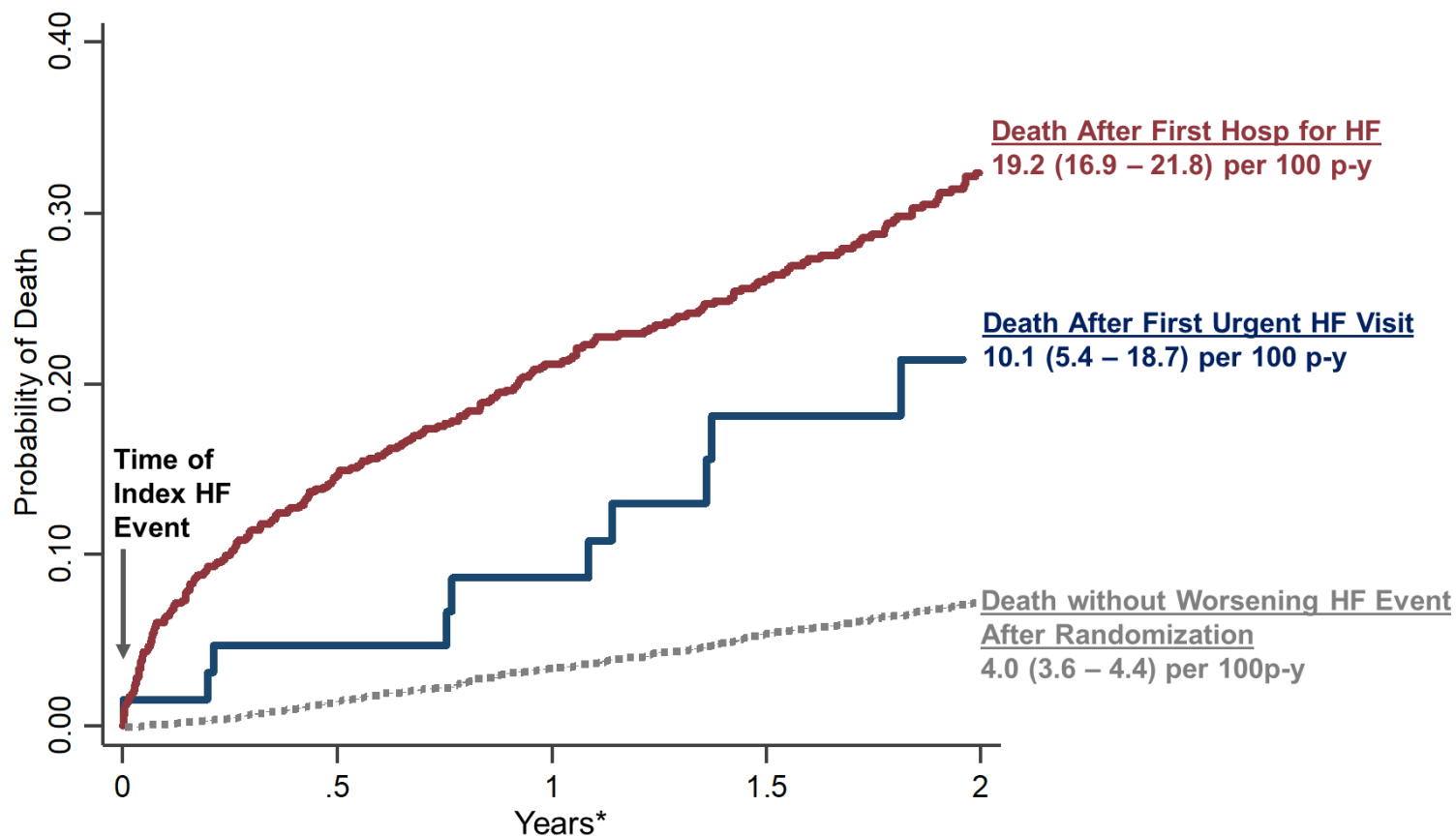
HF, heart failure; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; NYHA, New York Heart Association

**Table 2. Treatment Effect of Sacubitril/Valsartan vs. Valsartan on the Prespecified Expanded Endpoint of CV Death + Total HF Events in all PARAGON-HF Trial Participants and in Key Subgroups**

	n	Total Original Primary Events (CV Death + Total HF Hospitalizations)	Total Events if Urgent HF Visits Added	Rate Ratio (95% CI) Sacubitril/Valsartan vs. Valsartan (Prespecified Expanded Endpoint of CV Death + Total Worsening HF Events)	P-value
<b>All PARAGON-HF Participants</b>	4,796	1,903	1,998	0.86 (0.75-0.99)	0.040
<b>Women</b>	2,479	923	964	0.73 (0.60-0.91)	0.004
<b>Men</b>	2,317	980	1,034	1.00 (0.82-1.21)	0.978
<b>LVEF≤Median (57%)</b>	2,495	1,048	1,102	0.78 (0.64-0.94)	0.010
<b>LVEF&gt;Median (57%)</b>	2,301	855	896	0.98 (0.79-1.21)	0.821

Abbreviations: CI = confidence interval; CV = cardiovascular; HF = heart failure; LVEF = left ventricular ejection fraction

**Central Illustration: Death after Worsening Heart Failure (HF) Events in PARAGON-HF**



**No. at Risk**

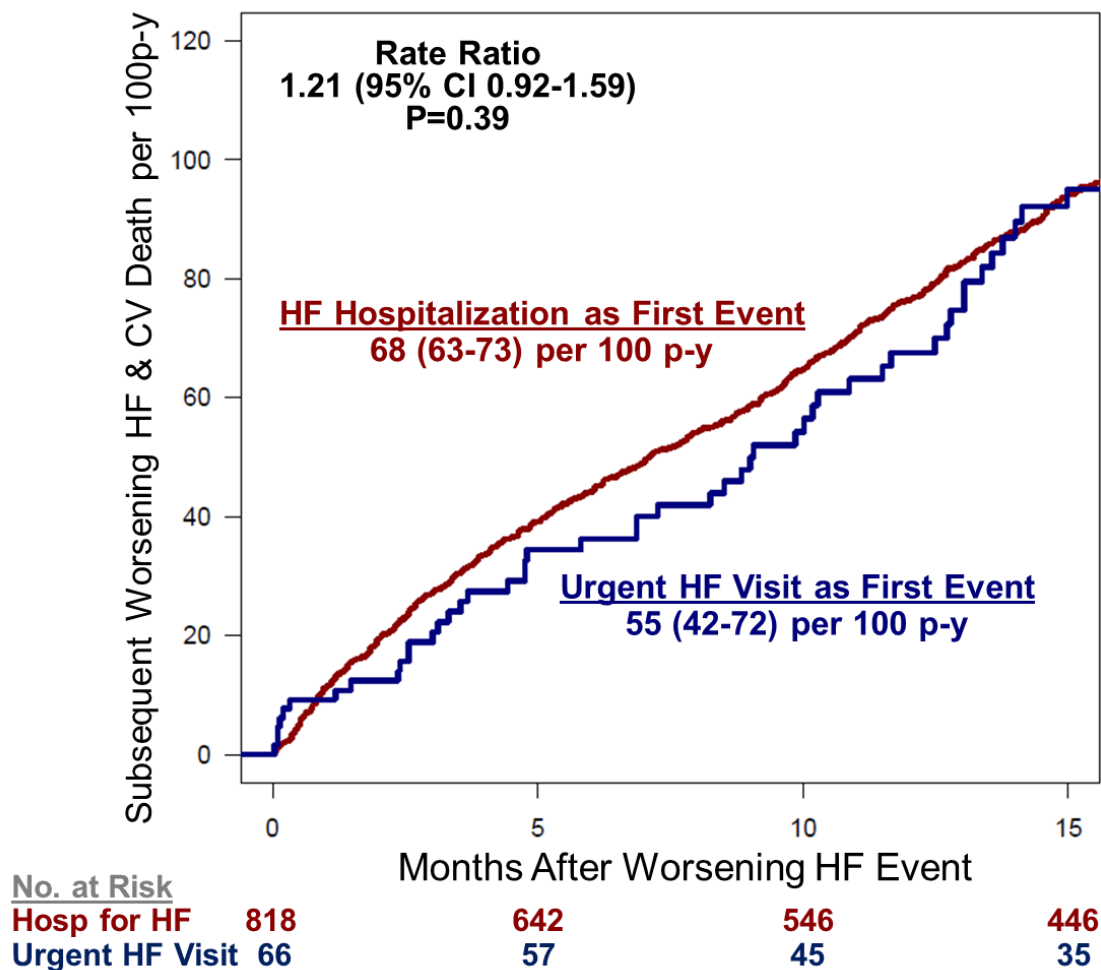
Hosp for HF	818	616	508	390	279
Urgent HF Visit	66	54	43	29	22
No Worsening HF Event	3912	3852	3774	3693	3621

\* Time scale for patients with first worsening HF events (red & blue lines) is time after worsening HF event. Time scale for patients without worsening HF event (grey dotted line) is time from randomization.

**Figure 2: Total Burden of CV death and Worsening HF Events after an Index Event**

Nelson-Aalen recurrent event cumulative hazard curves demonstrate subsequent burden of CV death and worsening HF events (either HF hospitalization or urgent HF visit) in patients whose first worsening HF event was either a HF hospitalization (red) or urgent HF visit (blue). Recurrent event analyses were performed using the semiparametric proportional rates method of Lin, Wei, Yang, and Ying and stratified by geographic region

CI, confidence interval, CV, cardiovascular; HF, heart failure.



**Figure 3: Treatment Effect of Sacubitril/Valsartan vs. Valsartan on the Primary Endpoint (Total HF Hospitalizations and CV Death, Panel A) and Primary Endpoint + Adjudicated Urgent HF Visits (Panel B)**

Nelson-Aalen recurrent event cumulative hazard curves demonstrate the incidence of the primary endpoint, total heart failure hospitalizations and cardiovascular death (left panel) and the primary endpoint + centrally adjudicated urgent HF visits (right panel). Recurrent event analyses were performed using the semiparametric proportional rates method of Lin Wei Yang and Ying and stratified by geographic region.

CI, confidence interval, CV, cardiovascular; HF, heart failure.

