Importance of Clinical Worsening of Heart Failure Treated in the Outpatient Setting

Evidence From the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF)

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Background—Many episodes of worsening of heart failure (HF) are treated by increasing oral therapy or temporary intravenous treatment in the community or emergency department (ED), without hospital admission. We studied the frequency and prognostic importance of these episodes of worsening in the Prospective Comparison of ARNI (angiotensin-receptor-neprilysin inhibitor) with ACEI (angiotensin-converting enzyme inhibitor) to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF).

Methods and Results—Outpatient intensification of HF therapy was added to an expanded composite outcome with ED visits, HF hospitalizations, and cardiovascular deaths. In an examination of first nonfatal events, 361 of 8399 patients (4.3%) had outpatient intensification of HF therapy without a subsequent event (ie, ED visit/HF hospitalizations) within 30 days; 78 of 8399 (1.0%) had an ED visit without previous outpatient intensification of HF therapy or a subsequent event within 30 days; and 1107 of 8399 (13.2%) had HF hospitalizations without a preceding event. The risk of death (in comparison with no-event patients) was similar after each manifestation of worsening: outpatient intensification of HF therapy (hazard ratio, 4.8; 95% confidence interval, 3.9–5.9); ED visit (hazard ratio, 4.5; 95% confidence interval, 3.0–6.7); HF hospitalizations (hazard ratio, 5.9; 95% confidence interval, 5.2–6.6). The expanded composite added 14% more events and shortened time to accrual of a fixed number of events. The benefit of sacubitril/valsartan over enalapril was similar to the primary outcome for the expanded composite (hazard ratio, 0.79; 95% confidence interval, 0.73–0.86) and was consistent across the components of the latter.

Conclusions—Focusing only on HF hospitalizations underestimates the frequency of worsening and the serious implications of all manifestations of worsening. For clinical trials conducted in an era of heightened efforts to avoid HF hospitalizations, inclusion of episodes of outpatient treatment intensification (and ED visits) in a composite outcome adds an important number of events and shortens the time taken to accrue a target number of end points in an event-driven trial.

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Worsening of symptoms and signs leading to hospital admission is an important event for patients with heart failure (HF), because, not only is it an unpleasant experience, but it is also a marker of heightened subsequent risk of readmission and death.[1,2] Hospital admissions also place an economic burden on patients and their families or caregivers,

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health services, and society more generally.[3,4] For these reasons, HF hospitalization has long been considered an important end point in clinical trials, and, more recently, it has become a measure of the quality of care in the United States with linkage of reimbursement to readmission rates within 30 days of discharge.[5–9] Many episodes of worsening of HF are, however, treated by augmentation of oral therapy in the community or even the use of short-term intravenous treatment. Some episodes may also lead to an emergency department (ED) visit without subsequent admission to the hospital.[10–13] Management of HF in the community or in non–ward-based hospital settings has also been encouraged recently by many organizations as a result of the reimbursement changes mentioned above.[6–9,14] Little is known, however, about the frequency and prognostic importance of such nonhospitalized episodes of worsening.[15] We have studied the occurrence and significance of these episodes in the Prospective Comparison of ARNI (angiotensin-receptor-neprilysin inhibitor) with ACEI (angiotensin-converting enzyme inhibitor) to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF).[16–18] We have also investigated the potential value of such events in an expanded composite outcome that might be of use as an end point in future clinical trials.

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Methods

Patients

The background and results of PARADIGM-HF (www.clinicaltrials.gov. identifier: NCT01035255) have been published.[16–18] The Ethics Committee of each of the 1043 participating institutions (in 47 countries) approved the protocol. All patients gave written, informed consent. In brief, PARADIGM-HF was a randomized, double-blind, and prospective comparison of the angiotensin-receptor-neprilysin inhibitor sacubitril/valsartan (formerly known as LCZ696) with enalapril in patients with chronic HF. Eligibility requirements at screening included an age of at least 18 years, New York Heart Association functional class II to IV symptoms, and a left ventricular ejection fraction of ≤40% and guideline-recommended therapy.

Trial Outcomes

The primary outcome of PARADIGM-HF was the composite of cardiovascular death or HF hospitalization. Additional prespecified exploratory end points included ED visits and outpatient intensification of HF therapy, collected by means of check box questions (yes/no) asked at each study visit. Three questions were asked in relation to outpatient intensification of HF therapy: was the dose of diuretics increased and sustained for a month (yes/no), was intravenous treatment given for HF (yes/no), or was a new drug added for the treatment of worsening HF (yes/no)? If any of these were answered in the affirmative the patients were prospectively considered to have had outpatient intensification of HF therapy.

We examined the characteristics of and subsequent survival of patients having a first event of each type and survival after each event type. In this analysis, if patients had an ED visit or were hospitalized within 30 days after intensification of therapy, they were classified as either an ED visit or HF hospitalization, respectively. If patients were hospitalized within 30 days after an ED visit, they were classified as a HF hospitalization and not an ED visit. The reference group consisted of patients who had none of these events during the trial (no-event group). We also used this analysis to estimate the reduction in time taken to accrue a certain number of composite events, comparing the expanded composite (cardiovascular death, HF hospitalization, ED visit, or outpatient intensification of therapy) with the narrowest (ie, the primary composite end point of cardiovascular death or HF hospitalization) using a time-to-first event analysis. In a sensitivity analysis, we used 7 instead of 30 days as the interval separating events.

To examine the number of unique events added by considering outpatient intensification of therapy and ED visits, we also categorized patients into 3 mutually exclusive groups for a first nonfatal event (ie, without any of the listed nonfatal events preceding the event of interest) or cardiovascular death: those having outpatient intensification of HF therapy (without a subsequent ED visit or HF hospitalization), those having an ED visit (without a subsequent HF hospitalization), and those having a HF hospitalization as their first nonfatal event.

We also examined the effect of sacubitril/valsartan in comparison with enalapril on the expanded composite outcome and its components.

Statistical Analysis

Baseline characteristics were compared by using the Kruskal-Wallis test for continuous variables and the χ^2 test for categorical variables. The association between a first event and subsequent mortality was evaluated with the use of Kaplan–Meier estimates and examined in a Cox regression model with the no-event group used as reference. The relative hazard of death following a first event was examined in a Cox proportional hazards model where an indicator of a patient's first event type was entered into the model as a time-updated covariate (with follow-up time starting at randomization) and adjusted for the effect of randomized therapy and region and then with the addition of the following baseline variables: age, sex, race, systolic blood pressure, heart rate, body mass index , serum creatinine, left ventricular ejection fraction, N-terminal pro-B-type natriuretic peptide, New York Heart Association class, ischemic etiology, hypertension, diabetes mellitus, atrial fibrillation, previous HF, myocardial infarction, stroke, previous implantable cardioverter-defibrillator, and cardiac resynchronization therapy. Hazard ratios (HRs), 95% confidence intervals (CIs), and 2-sided *P* values were calculated with the use of the Cox models. All analyses were performed using Stata version 14 (Stata Corp. College Station, TX). A *P* value of <0.05 was considered significant.

Results

Of the 8399 patients randomized, 1124 (13.4%) had outpatient intensification of therapy, 250 (3.0%) had an ED visit, 1195 (14.2%) were hospitalized for worsening HF, 1251 (14.9%) died of a cardiovascular cause, and 1546 (18.4%) died of any cause.

Among all randomized patients, 763 (9.1%) died of a cardiovascular cause without previous worsening HF hospitalization, ED visit, or intensification of therapy.

In an examination of first nonfatal events, 361 patients (4.3%) had intensification of therapy without a subsequent ED visit, hospital admission for HF, or cardiovascular death within 30 days; 78 (1.0%) had an ED visit but no previous intensification of therapy or subsequent hospital admission for worsening HF or cardiovascular death within 30 days; and 1107 patients (13.2%) had worsening HF requiring hospitalization without a preceding ED visit or intensification of therapy.

Examining mutually exclusive first nonfatal events, 223 patients (62% of 361) having intensification of therapy and 52 patients (67% of 78) experiencing an ED visit did not have a subsequent nonfatal HF event during the trial period or die of a cardiovascular cause. The numbers not

Table 1. Baseline Characteristics of Patients With Different First Manifestations of Heart Failure Worsening, or None, or Experiencing Cardiovascular Death

	None of the Events	Hospitalization for HF	Emergency Department Visit for HF	Intensification of HF Therapy	Cardiovascular Death	*P* Value
n (%)	6090 (73)	1107 (13)	78 (1)	361 (4)	763 (9)	
Age, year	63±11	64±11	66±12	65±11	64±12	<0.001
Sex (female), n (%)	1410 (23)	212 (19)	16 (21)	56 (16)	138 (18)	<0.001
Race, n (%)						
White	4016 (66)	749 (68)	43 (55)	287 (80)	449 (60)	<0.001
Black	285 (5)	82 (7)	6 (8)	17 (5)	38 (5)	
Asian	1097 (18)	188 (17)	18 (23)	28 (8)	178 (23)	
Other	692 (11)	88 (8)	11 (14)	29 (8)	98 (13)	
Region, n (%)						
North America	365 (6)	124 (11)	13 (17)	73 (20)	27 (4)	<0.001
Latin America	1091 (18)	142 (13)	13 (17)	39 (11)	148 (19)	
Western Europe and other	1516 (25)	275 (25)	13 (17)	111 (31)	136 (18)	
Central Europe	2028 (33)	384 (35)	21 (27)	110 (31)	283 (37)	
Asia	1090 (18)	182 (16)	18 (23)	28 (8)	169 (22)	
Systolic blood pressure, mm Hg	122±15	121±16	118±14	120±16	122±16	0.084
Heart rate, beats/min	72±12	74±13	74±13	72±13	73±12	<0.001
Body mass index, kg/m^2	28±5	29±6	27±6	29±6	27±6	<0.001
Serum creatinine, mg/dL	1.1±0.3	1.2±0.3	1.2±0.3	1.2±0.3	1.2±0.3	<0.001
Clinical features of heart failure						
Left ventricular ejection fraction, %	30±6	29±7	28±7	30±6	29±7	<0.001
Median BNP, pg/mL (IQR)	227 (142–407)	365 (195–723)	290 (167–528)	286 (176–560)	369 (206–689)	<0.001
Median NT-proBNP, pg/mL (IQR)	1438 (819–2737)	2367 (1208–5154)	1894 (1103–3319)	1923 (1047–3722)	2456 (1260–5189)	<0.001
NYHA functional class, n (%)						
I	309 (5)	33 (3)	7 (9)	11 (3)	29 (4)	<0.001
II	4399 (72)	736 (67)	50 (64)	249 (69)	485 (64)	
III	1332 (22)	322 (29)	21 (26)	100 (28)	243 (32)	
IV	38 (0.6)	15 (1.4)	0 (0)	1 (0.3)	6 (0.8)	
Ischemic etiology, n (%)	3593 (59)	669 (60)	44 (56)	227 (63)	503 (66)	0.004
Medical history, n (%)						
Hypertension	4252 (70)	824 (74)	59 (76)	268 (74)	537 (70)	0.012
Diabetes mellitus	1939 (32)	492 (44)	36 (46)	162 (45)	278 (36)	<0.001
Atrial fibrillation	2123 (35)	484 (44)	34 (44)	163 (45)	287 (38)	<0.001
Previous heart failure hospitalization	3663 (60)	822 (74)	53 (68)	262 (73)	474 (62)	<0.001
Myocardial infarction	2544 (42)	521 (47)	27 (35)	182 (50)	360 (47)	<0.001
Stroke	479 (8)	115 (10)	12 (15)	43 (12)	76 (10)	0.001
Treatment at randomization, n (%)						
Previous use of ACE inhibitor	4744 (78)	853 (77)	60 (77)	288 (80)	587 (77)	0.814
Previous use of ARB	1362 (22)	259 (23)	19 (24)	75 (21)	177 (23)	0.817
Diuretics	4769 (78)	979 (88)	63 (81)	307 (85)	620 (81)	<0.001
Digitalis	1755 (29)	381 (34)	27 (35)	110 (31)	266 (35)	<0.001
β-Blocker	5700 (94)	1013 (92)	69 (89)	338 (94)	691 (91)	0.002
Mineralocorticoid antagonist	3390 (56)	634 (57)	39 (50)	189 (52)	419 (55)	0.414
Implantable cardioverter-defibrillator	840 (14)	230 (21)	15 (19)	97 (27)	61 (8)	<0.001
Cardiac resynchronization therapy	383 (6)	110 (10)	7 (9)	48 (13)	26 (3)	<0.001

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; HF, heart failure; IQR, interquartile range; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and NYHA, New York Heart Association.

experiencing a nonfatal HF event or dying of any cause were 203 (56% of 361) and 48 (62% of 78) for those having intensification of therapy and ED visits, respectively. Therefore, these 2 outcomes added 278 unique events (13.7%) to the 2031 primary composite end points (cardiovascular death or HF hospitalization) accrued in PARADIGM-HF.

Baseline Characteristics

The baseline characteristics of patients with the different first manifestations of HF worsening, experiencing cardiovascular death, or having no event are shown in Table 1. Patients with any manifestation of worsening were older, less likely to be female, and more likely to have comorbidity. Patients with any manifestation of worsening also had higher B-type natriuretic peptide levels, had a worse New York Heart Association functional class, were more commonly treated with diuretics, digoxin, a defibrillating device, and cardiac resynchronization therapy, and more frequently had a history of prerandomization HF hospitalization.

Different Manifestations of Worsening and Subsequent Survival

Figure 1 shows the rate of death and Table 2 shows the unadjusted and adjusted risks of death subsequent to intensification of therapy, an ED visit, or a HF hospitalization, in comparison with patients who did not experience any manifestation of worsening. Overall, 14% of patients without any report of worsening died during the trial. The proportion dying was 32%, 31%, and 37%, respectively, for those having intensification of therapy, experiencing an ED visit, or being admitted to hospital with worsening HF. Most deaths were attributed to cardiovascular causes.

The risk of death (in comparison with no-event patients after adjustment for treatment and region only) was similar after each of the 3 manifestations of worsening: intensification of therapy (HR, 5.2; 95% CI, 4.2–6.3); ED visit (HR, 4.5; 95% CI, 3.0–6.7); and hospitalization for worsening HF (HR, 6.1; 95% CI, 5.4–6.8). Even after adjustment, the risk of death remained 3 to 5 times higher in patients experiencing some manifestation of worsening, in comparison with those who did not. When those patients who had only either a hospitalization for HF, ED visit, or intensification of therapy were analyzed, ie, they experienced that event type only, the associations between each of the event types and mortality were unchanged (Table 2).

Using a 7-day rather than 30-day interval between events (to define separate events) did not change the results (Table I in the online-only Data Supplement).

We conducted a sensitivity analysis by baseline diuretic status. In the patients not taking a diuretic (n=1661) at baseline, the risk of death was higher in those who started a diuretic during the trial (n=443; all-cause mortality=20.5%) in comparison with those who did not start a diuretic during the trial (n=1218; all-cause mortality=12.6%). Of those taking a diuretic at baseline, the risk of death in those who were taking the equivalent of <40 mg of furosemide at baseline was 16.4% and, in those taking ≥40 mg furosemide equivalent, the risk was 21.0%. The association between each of the outcomes (HF hospitalization, ED visit for HF, or intensification of therapy for HF) and the risk of all-cause mortality was similar regardless of the baseline dose of furosemide equivalent (Table II in the online-only Data Supplement). Of those who experienced an intensification of HF therapy that was attributable to an increase in diuretic dose for >1 month, the risk of death was higher in those who had an increase in dose that was ≥40 mg of furosemide equivalent in comparison with <40 mg furosemide equivalent (Table III in the online-only Data Supplement).

We also examined which medications were added for the treatment of worsening HF (n=62). This was a diuretic in 23 (37%), an mineralocorticoid receptor antagonist in 17 (27%), a β-blocker in 9 (15%), an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker in 8 (13%), and other drugs (digoxin in 2; unspecified in 3) in 5 (8%).

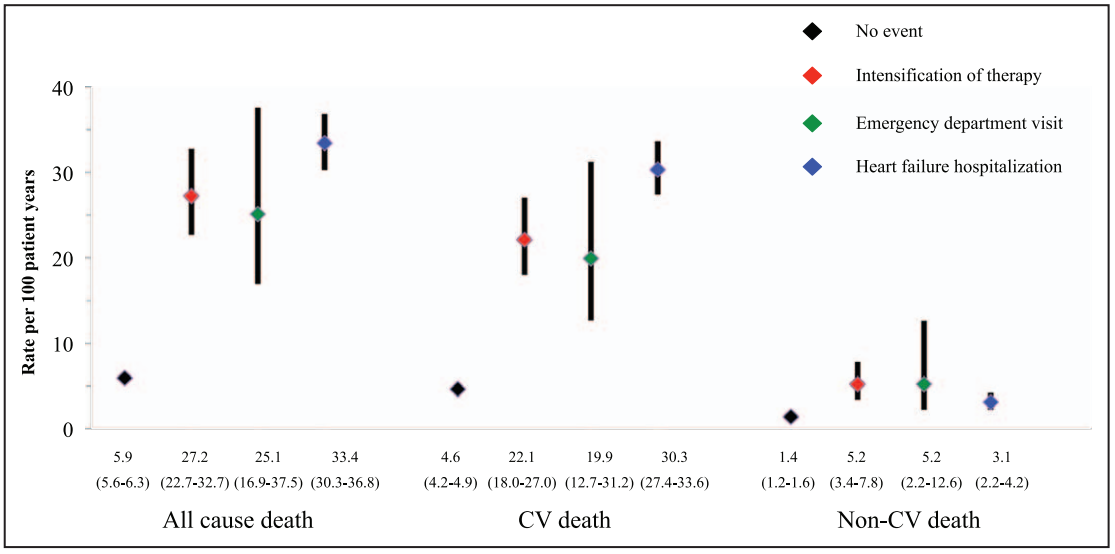

Figure 1. Mortality (%) after a first event or in patients with no event. CV indicates cardiovascular.

Table 2. Risk of All-Cause Mortality After a Hospitalization Heart Failure, Emergency Department Visit for Heart Failure, and Intensification of Therapy for Heart Failure Using a Cox Model With Event Type as the First Event Experienced and the Only Event Experienced as a Time-Updated Covariate

	None of the Events	Hospitalization for HF	Emergency Department Visit for HF	Intensification of HF Therapy
Each event as the first event experienced in a time-updated model, hazard ratio (95% CI)				
Adjusted for randomized treatment and region	1	6.1 (5.4–6.8)	4.5 (3.0–6.7)	5.2 (4.2–6.3)
Adjusted for randomized treatment, region, and baseline covariates*	1	5.3 (4.7–6.0)	3.3 (2.2–5.0)	4.6 (3.7–5.6)
Each event as the only event experienced in a time updated model, hazard ratio (95% CI)				
Adjusted for randomized treatment and region	1	5.8 (5.1–6.5)	4.1 (2.6–6.5)	4.5 (3.6–5.7)
Adjusted for randomized treatment, region, and baseline covariates*	1	5.0 (4.4–5.7)	2.9 (1.9–4.6)	4.2 (3.3–5.3)

CI indicates confidence interval; and HF, heart failure.

*Adjusted for age, sex, race, systolic blood pressure, heart rate, body mass index, serum creatinine, left ventricular ejection fraction, N-terminal pro-B-type natriuretic peptide, New York Heart Association class, ischemic etiology, hypertension, diabetes mellitus, atrial fibrillation, previous heart failure, myocardial infarction, stroke, previous implantable cardioverter-defibrillator, and cardiac resynchronization therapy.

The association between each manifestation of worsening HF and subsequent all-cause mortality was highest for intravenous treatment given for HF: dose of diuretics increased and sustained for a month (HR, 3.2; 95% CI, 2.2–5.0), intravenous treatment for HF (HR, 7.3; 95% CI, 5.5–9.6), and a new drug added for the treatment of worsening HF (HR, 3.7; 95% CI, 2.3–5.8).

Expanded Composite Outcomes and Time to Accrual of a Target Number of Events

Figure 2 shows the impact of adding intensification of therapy and ED visits to the primary composite outcome (cardiovascular death or HF hospitalization) of PARADIGM-HF. As can be seen at 1, 2, and 3 years of follow-up, an additional 177, 248, and 269 patients, respectively, had experienced a first event contributing to the expanded composite outcome in comparison with the primary end point, an increment in events of ≈14% overall. The 1- and 2-year Kaplan–Meier event rates for the primary end point were 14.2% and 24.0%, respectively, in comparison with 16.5% and 27.5%, respectively, for the expanded composite. The time taken to accrue 1000 patients with an event using the primary end point was 11 months (338 days) in comparison with 9 months (280 days) for the expanded composite.

Effect of Sacubitril/Valsartan on the Primary Composite Outcome and Expanded Composite

Figure 3 shows the effect of sacubitril/valsartan on the primary composite outcome of PARADIGM-HF, and the expanded composite outcome and the components of each of these, as well.

Sacubitril/valsartan was superior to enalapril in reducing the risk of the primary composite outcome (HR, 0.80; 95% CI, 0.73–0.87), death from cardiovascular causes (HR, 0.80; 95% CI, 0.71–0.89), and hospitalization for HF (HR, 0.79; 95% CI, 0.71–0.89).

As can be seen from Figure 4, the benefit of sacubitril/valsartan over enalapril was similar for the expanded composite (HR, 0.79; 95% CI, 0.73–0.86) and the effect of sacubitril/valsartan was consistent in relation to the additional components of this expanded composite. This effect of sacubitril/valsartan compared with enalapril on the expanded composite was also consistent across all subgroups, eg, age, sex, race, region, and medical history (data not shown).

Discussion

Our findings are relevant to both clinical practice and the conduct of future clinical trials in HF with reduced ejection fraction.

As expected, we found that worsening leading to outpatient intensification of medical therapy is common in patients with HF with reduced ejection fraction, but more surprisingly was associated with an elevation in the risk of subsequent death similar to that seen following hospital admission. Focusing only on HF hospitalization therefore underestimates the frequency of clinical worsening and fails to recognize that all manifestations of worsening have such serious implications.

For clinical trials conducted in an era of heightened efforts to avoid hospitalization in patients with HF, inclusion of episodes of outpatient intensification of medical therapy (and ED visits) in a composite outcome adds an important number of events (an increment of 14% in PARADIGM-HF) and would shorten the time taken to accrue a target number of end points in an event-driven trial. Because sacubitril/valsartan had a consistent effect on all manifestations of worsening, the benefit of sacubitril/valsartan over enalapril on the expanded composite outcome was similar to that on the primary end point in PARADIGM-HF. Therefore, use of this expanded composite could have resulted in earlier termination of the trial without any loss of sensitivity to the effect of the investigational treatment.

Although everyday clinical experience indicates that augmentation of oral therapy and even supplementation with intravenous treatment is common in patients with HF, we have

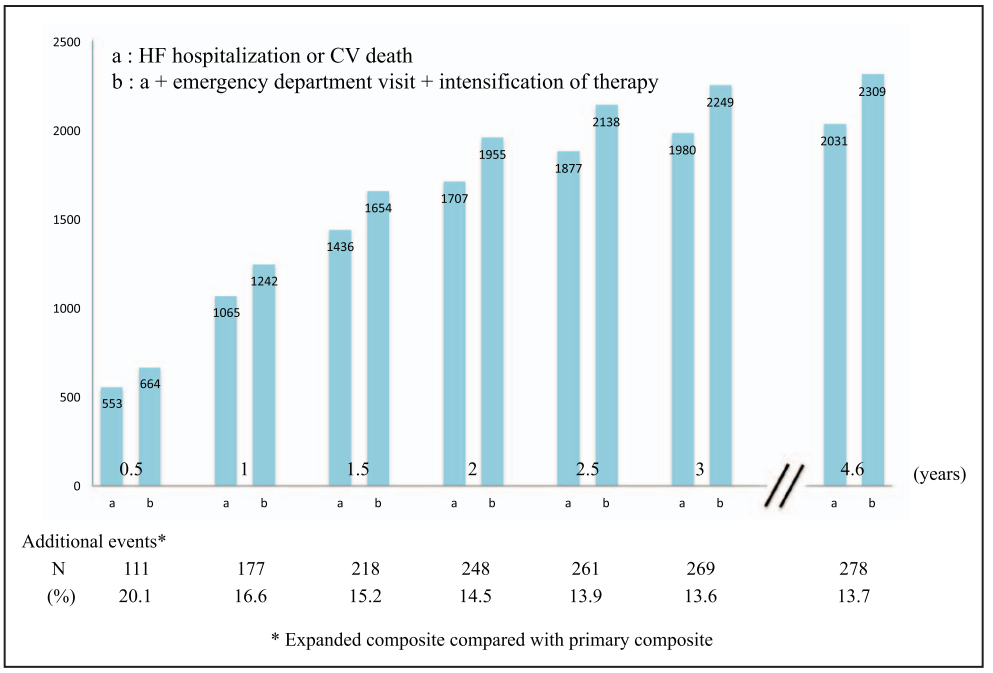

Figure 2. Impact of adding emergency department visits and outpatient intensification therapy as additional components of a composite heart failure outcome. CV indicates cardiovascular; and HF, heart failure.

been unable to find any report of how frequently such interventions occur in usual clinical practice. Asking questions about augmentation of treatment at each study visit, we found that 13.4% of patients had intensification of therapy and that two-thirds of these episodes were followed by an ED visit or HF hospitalization within 30 days. However, it should be noted that the majority of patients in PARADIGM-HF were in New York Heart Association functional class I (4.6%) or II (70.5%) after the active run-in period, and the proportion requiring intensification of therapy might be much greater in patients with more severe symptoms at baseline. The more important finding is that, even if augmentation of therapy was not followed by an ED visit or admission, it was associated with a 4-fold higher adjusted risk of subsequent death. Therefore, although these episodes were identified only by investigators checking yes in response to questions (and were not adjudicated), they were an ominous occurrence and arguably should be both a treatment target (to reduce their incidence) and a measure of outcome (eg, as part of a composite worsening end point). Not only were these episodes frequent and serious, but they were also responsive to the experimental treatment intervention in PARADIGM-HF, further supporting their use in an expanded composite end point (see below).

By contrast, ED visits were uncommonly reported (in 3% of patients) and were also frequently followed by HF hospitalization within 30 days (in 69% of cases). We believe that our investigators did not report ED visits leading directly to admission to hospital as separate events (because admission was

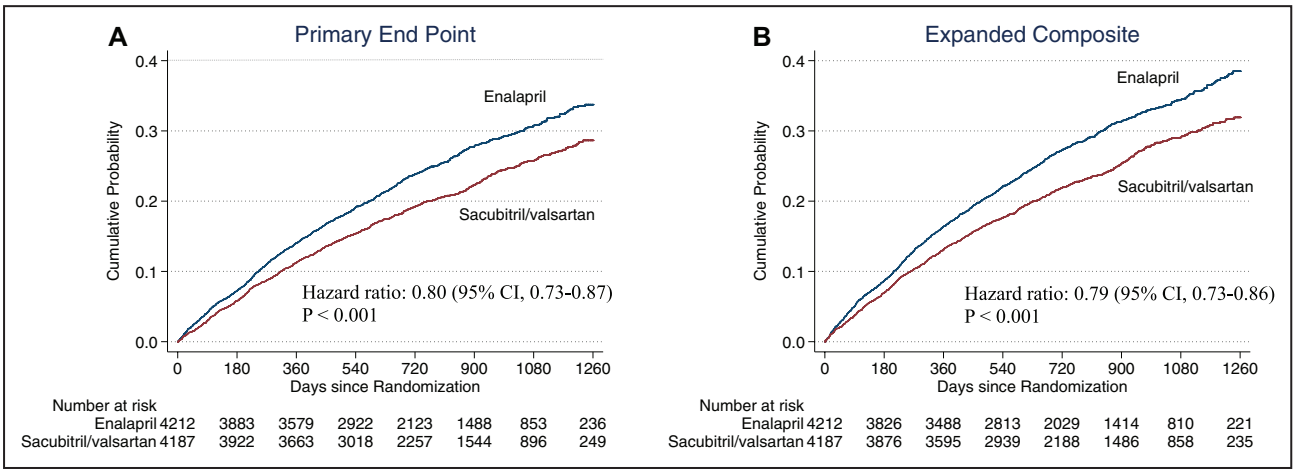

Figure 3. Kaplan–Meier curves for primary end point (**A**) and expanded composite (**B**), according to treatment group. (HR and corresponding *P* value are from the Cox model adjusted for region). CI indicates confidence interval; and HR, hazard ratio.

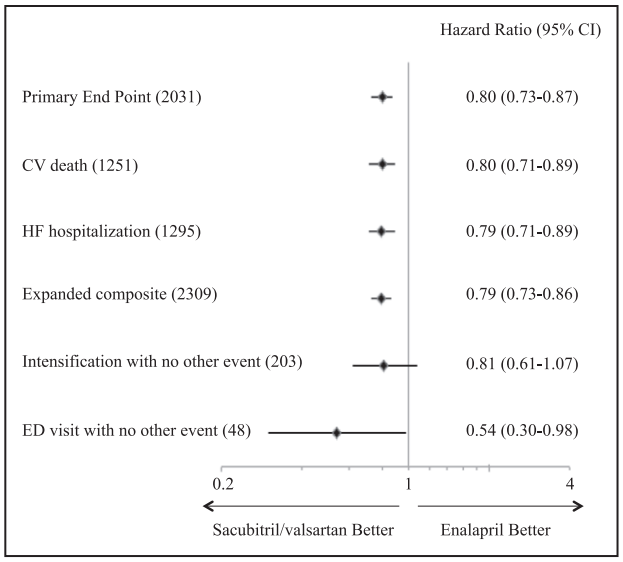

Figure 4. Effect of sacubitril/valsartan versus enalapril for each outcome. CV indicates cardiovascular; ED, emergency department; and HF, heart failure.

itself an end point). In most countries the vast majority of ED attendances with HF lead to admission, and discharge directly from the ED is very uncommon. It is likely that this explains the small proportion of such events in PARADIGM-HF. An isolated ED visit was also associated with a 4- to 5-fold higher subsequent mortality (in comparison with having no episode of worsening), and this heightened risk persisted after adjustment for other prognostic variables.

From a clinical practice perspective, we believe that there are 2 important messages from our findings. First, intensification of outpatient therapy should be carefully documented and should prompt a review of affected patients. Often the care of patients is shared and may be disjointed. Therapy may be changed by a primary care practitioner, nurse specialist, internist, or other specialist (during a hospital clinic attendance for another reason) or by a cardiologist. It is easy to overlook such changes, yet they identify a patient at high risk. Should there be a system in place to identify these changes? Such changes should prompt review of the patient – have all disease-modifying drugs been used (eg, could a mineralocorticoid receptor antagonist or digoxin be added)? Have all life-saving devices been considered (eg, cardiac resynchronization therapy and an implantable cardioverter-defibrillator)? Has the patient progressed to the point of being considered for a ventricular assist device or transplantation?

Our findings are potentially important from a clinical trials perspective as well. Although most episodes of intensification of outpatient therapy and ED visits were followed by a HF hospitalization within 30 days, approximately one-third were not. Therefore, expanding the primary composite outcome (HF hospitalization or cardiovascular death) used in PARADIGM-HF and other recent studies to include these additional components has 2 consequences. First, doing so adds unique events (an additional 14% overall). Second, it shortens the time to accrual of any given number of worsening events. This is because intensification of outpatient therapy and ED visits often occur before and therefore earlier than a HF hospitalization. These effects have the potential to reduce sample size and duration of follow-up (or increase power if sample size is maintained), although these advantages can only be realized if the additional components of the composite (and thus the overall expanded composite) are as sensitive to the effects of treatment as HF hospitalization and cardiovascular death are (although these do not always respond equally to treatment). We found that this was the case for sacubitril/valsartan, with a similar treatment effect on all components of the expanded composite outcome examined, but this might not necessarily be so for all treatments. This expanded composite may be especially relevant today given the intensive efforts to reduce admissions to the hospital for HF in the United States (and may even out the rates of worsening across geographic regions by including all manifestations of worsening irrespective of how or where they are managed). In addition, because event rates have declined as a result of the cumulative benefit of effective treatments, trials in HF with reduced ejection fraction have required larger and larger sample sizes, increasing their complexity and cost and making the development of new treatments less attractive and affordable than previously. The only other way to accrue sufficient events is to lengthen follow-up, but this too leads to higher costs and less precision because of treatment discontinuation and patient loss to follow-up. Our findings suggest that the use of the expanded composite described has the potential to reduce sample size and duration of follow-up by a modest amount and we believe that its use might be considered in future trials. We know of only a few trials in patients with chronic HF and a reduced ejection fraction that used nonhospitalized events as part of their primary end point, and each required intravenous therapy as part of the definition of these events.[15,19–21] In the Valsartan Heart Failure Trial (Val-HeFT), administration of intravenous inotropic or vasodilator drugs for ≥4 hours without hospitalization was a component of the composite coprimary outcome.[19] Of the 1524 first events, there were only 10 nonhospitalized treatment events in comparison with 801 HF hospitalizations, 42 resuscitated cardiac arrests, and 671 deaths. The Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronization trial (MADIT-CRT) included outpatient events requiring the use of intravenous decongestive therapy.[15] Of first events, 52 were outpatient events, 331 were inpatient treatment events, and 78 were deaths. The smaller proportion of outpatient events in these trials presumably reflects the requirement for intravenous therapy (as opposed to augmented or oral or intravenous therapy) and, perhaps, changing practice since publication of Val-HeFT. The individual contribution of nonhospitalized intravenous therapy to the overall primary outcome was not described separately in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure trial (COMPANION) and the Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block trial (BLOCK HF).[20,21]

Our report has some limitations. Not all of the analyses reported were prespecified. The ED visits and

intensification of oral therapy were not adjudicated (whereas HF hospitalizations and deaths were), and we do not have details of all of the drugs added to treat worsening HF. For the increase in diuretic dose component of the intensification-of-therapy end point, we required the increased to be sustained for at least a month, making this a relatively stringent component.

In conclusion, focusing only on HF hospitalization underestimates the frequency of clinical worsening and fails to recognize that other manifestations of worsening seem to have serious prognostic implications. If our findings are valid, they argue for a systematic approach in clinical practice to document episodes of nonhospitalized worsening, and their occurrence should prompt a review of affected patients. For clinical trials conducted in an era of heightened efforts to avoid hospitalization in patients with HF, inclusion of episodes of outpatient intensification of therapy (and ED visits) in a composite outcome adds a modest but important number of events and shortens the time taken to accrue a target number of end points in an event-driven trial. These additional events seem to be sensitive to the actions of effective therapy, at least as demonstrated with sacubitril/valsartan.

Disclosures

Drs Jhund, Rouleau, Solomon, Swedberg, Zile, and Packer have consulted for Novartis. Drs Rizkala, Lefkowitz, Gong, and Shi are employees of Novartis. Drs Zile and Swedberg have received honoraria from Novartis for sponsored lectures. Dr McMurray's employer, the University of Glasgow, was/is being paid for his time spent as Executive Committee member/co-chair of PARADIGM-HF. Dr Okumura reports no conflicts.

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CLINICAL PERSPECTIVE

In this study we examined the occurrence and significance of episodes of nonhospitalized worsening of heart failure, ie, those treated by augmentation of oral therapy and the use of short-term intravenous treatment in the community or emergency department by using the Prospective Comparison of ARNI (angiotensin-receptor-neprilysin inhibitor) with ACEI (angiotensin-converting enzyme inhibitor) to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF) database. These nonhospitalized episodes of worsening heart failure were associated with a 4- to 6-fold higher risk of subsequent death (in comparison with patients with no events), a risk similar to that following heart failure hospitalization. Adding these nonhospitalized episodes to a conventional composite of cardiovascular death or heart failure hospitalization increased the number of events by14% and shortened the time to accrual of a fixed number of events. The benefit of sacubitril/valsartan over enalapril was similar to the primary outcome for the expanded composite (hazard ratio, 0.79; 95% confidence interval, 0.73–0.86) and was consistent across each of the components of the expanded composite. Focusing only on heart failure hospitalization underestimates the frequency of clinical worsening and fails to recognize the serious implications of other manifestations of worsening. Clinicians should consider these nonhospitalized events as a harbinger of poor outcomes and act accordingly. For clinical trials conducted in an era of heightened efforts to avoid hospitalization in patients with heart failure, the inclusion of episodes of outpatient intensification of therapy and emergency department visits in a composite outcome adds an important number of events and shortens the time taken to accrue a target number of end points in an event-driven trial.

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Importance of Clinical Worsening of Heart Failure Treated in the Outpatient Setting: Evidence From the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF)

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SUPPLEMENTAL MATERIAL

Supplemental Table 1. Mortality (%) according to baseline diuretics dose

	No diuretic at baseline (N=1661)	Other diuretics (N=1324)	Low dose loop diuretic (<40mg furosemide equivalent*) (N=1620)	High dose loop diuretic (≥40mg furosemide equivalent*) (N=3794)
All cause death	244 (14.7%)	239 (18.1%)	265 (16.4%)	798 (21.0%)
CV death	199 (12.0%)	205 (15.5%)	215 (13.3%)	632 (16.7%)
non-CV death	45 (3.1%)	34 (3.0%)	50 (3.6%)	166 (4.4%)

* 1mg bumetanide= 40mg furosemide and 20mg torasemide= 40mg furosemide

Supplemental Table 2. Risk of all-cause mortality following a hospitalization heart failure, emergency department visit for heart failure, and intensification of therapy for heart failure using a Cox model with event type as the 1st event experienced and the only event experienced in a time-updated covariate according to baseline loop diuretic dose

	No event	Heart failure hospitalization	Emergency department visit	Intensification of therapy
Each event as the 1st event experienced in a time updated model (Hazard Ratio (95% CI)) Adjusted for randomized treatment, region and baseline covariates*				
Low dose loop diuretic (<40mg furosemide equivalent**) (N=1620)	1	5.7 (4.2-7.8)	1.6 (0.2-11.5)	4.1 (2.6-6.6)
High dose loop diuretic (≥40mg furosemide equivalent**) (N=3794)	1	5.0 (4.2-5.9)	3.6 (2.1-6.1)	5.4 (4.1-7.1)
Other diuretic (N=1324)	1	5.8 (4.2-8.0)	4.6 (1.9-10.7)	3.2 (4.2-6.1)

* Adjusted for: age, sex, race, systolic blood pressure, heart rate, body mass index (BMI), serum creatinine, left ventricular ejection fraction (LVEF), N-terminal pro-BNP (NTproBNP), New York Heart Association (NYHA) class, ischemic etiology, hypertension,

diabetes, atrial fibrillation, prior heart failure, myocardial infarction, stroke, prior implantable cardioverter-defibrillator, and cardiac resynchronization therapy.

** 1mg bumetanide= 40mg furosemide and 20mg torasemide= 40mg furosemide

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