Title: 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).

Short title: Outpatient worsening of HF in PARADIGM-HF

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ABSTRACT

Background: Many episodes of worsening of heart failure (HF) are treated by increasing oral therapy or 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 PARADIGM-HF.

Methods and Results: Outpatient intensification of HF therapy (IT) was added to an expanded composite outcome with ED visits, HF hospitalizations (HFh) and cardiovascular deaths. Examining *first* non-fatal events, 361/8399 patients (4.3%) had IT without a subsequent event (i.e. ED visit/HFh) within 30 days; 78/8399 (1.0%) had an ED visit without prior IT or a subsequent event within 30 days; and 1107/8399 (13.2%) had HFh without a preceding event. The risk of death (compared with "no event" patients) was similar after each manifestation of worsening - IT: HR=4.8(95%CI 3.9-5.9); ED visit: 4.5(3.0-6.7); HFh: 5.9(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 (HR 0.79, 0.73-0.86) and was consistent across the components of the latter.

Conclusion: Focusing only on HFh 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 HFh, 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 endpoints in an event-driven trial.

Clinical Trial Registration Information—*www.clinicaltrials.gov. Identifier: NCT01035255.*

Keywords: hospitalization, sacubitril/valsartan, neprilysin, mortality, emergency department, heart failure therapy

INTRODUCTION

Worsening of symptoms and signs leading to hospital admission is an important event for patients with heart failure as not only is it an unpleasant experience but it is also a marker of heightened subsequent risk of re-admission and death.[1,2] Hospital admissions also place an economic burden on patients and their families or caregivers, health services and society more generally.[3,4] For these reasons, heart failure hospitalization has long been considered an important endpoint in clinical trials and more recently it has become a measure of the quality of care in the USA with linkage of reimbursement to readmission rates within 30 days of discharge.[5-9] Many episodes of worsening of heart failure 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 hospital.[10-13] Management of heart failure 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 of, and prognostic importance of, such non-hospitalized episodes of worsening.[15] We have studied the occurrence and significance of these episodes in the Prospective Comparison of ARNI with ACEI 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 which might be of use as an endpoint in future clinical trials.

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. Briefly, PARADIGM-HF was a randomized, double-blind, and prospective comparison of the angiotensin-receptor-neprilysin inhibitor (ARNI) sacubitril/valsartan (formerly known as LCZ696) with enalapril in patients with chronic heart failure. Eligibility requirements at screening included an age of at least 18 years, New York Heart Association (NYHA) functional class II-IV symptoms, and an left ventricular ejection fraction of 40% or less and guideline-recommended therapy.

Trial outcomes

The primary outcome of PARADIGM-HF was the composite of cardiovascular death or heart failure hospitalization. Additional pre-specified exploratory endpoints included ED visits and outpatient intensification of heart failure 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 heart failure therapy: was the dose of diuretics increased and sustained for a month (yes/no), was intravenous treatment given for heart failure (yes/no) or was a new drug added for the treatment of worsening heart failure (yes/no)? If any of these were answered in the affirmative the patients was prospectively considered to have had outpatient intensification of heart failure 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 heart failure hospitalization, respectively. If patients were hospitalized within 30 days after an ED visit they were classified as a heart failure 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, heart failure hospitalization, ED visit or outpatient intensification of therapy) with the narrowest (i.e. the primary composite endpoint of cardiovascular death or heart failure hospitalization) using a time-to-first event analysis. In a sensitivity analysis, we used seven instead of thirty 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 three *mutually exclusive* groups for a first non-fatal event (i.e. without any of the listed non-fatal events preceding the event of interest) or cardiovascular death: those having outpatient intensification of heart failure therapy (without a subsequent ED visit or heart failure hospitalization), those having an ED visit (without a subsequent heart failure hospitalization) and those having a heart failure hospitalization as their first non-fatal event.

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

Statistical analysis

Baseline characteristics were compared using the Kruskal Wallis test for continuous variables and the chi square 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 (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. Hazard ratios (HR), 95% confidence intervals (CI), and two-sided P values were calculated with the use of the Cox models. All analyses were performed using Stata version 14 (Stata Corp. College Station, Texas, USA). 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 heart failure, 1251 (14.9%) died from a cardiovascular cause, and 1546 (18.4%) died from any cause. Among all randomized patients, 763 (9.1%) died from a cardiovascular cause without prior worsening heart failure hospitalization, ED visit or intensification of therapy.

Examining *first* non-fatal events, 361 patients (4.3%) had intensification of therapy without a subsequent ED visit, hospital admission for heart failure or cardiovascular death within 30 days; 78 (1.0%) had an ED visit but no prior intensification of therapy or subsequent hospital admission for worsening heart failure or cardiovascular death within 30 days; and 1107 patients (13.2%) had worsening heart failure requiring hospitalization without a preceding ED visit or intensification of therapy.

Examining *mutually exclusive* first non-fatal 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 non-fatal heart failure event during the trial period or die from a CV cause. The numbers not experiencing a non-fatal heart failure event or dying from *any cause* were 203 (56% of 361) and 48 (62% of 78) for those having intensification of therapy and ED visit respectively. Therefore, these two outcomes added 278 unique events (13.7%) to the 2031 primary composite endpoints (cardiovascular death or heart failure hospitalization) accrued in PARADIGM-HF.

Baseline characteristics

The baseline characteristics of patients with the different first manifestations of heart failure 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, worse NYHA functional class, were more commonly treated with diuretics, digoxin, a defibrillating device and cardiac resynchronization therapy and more frequently had a history of pre-randomization heart failure hospitalization.

Different manifestations of worsening and subsequent survival

Figure 1 shows the rate of death and Table 2 the unadjusted and adjusted risks of death subsequent to intensification of therapy, an ED visit or a heart failure hospitalization, compared 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 heart failure. Most deaths were attributed to cardiovascular causes.

The risk of death (compared with "no event" patients after adjustment for treatment and region only) was similar after each of the three manifestations of worsening - intensification of therapy: HR 5.2 (95% CI, 4.2-6.3); ED visit: 4.5 (3.0-6.7); hospitalization for worsening heart failure: 6.1 (5.4-6.8). Even after adjustment, the risk of death remained three to five times higher in patients experiencing some manifestation of worsening, compared with those who did not. When those patients who had only either a hospitalization for heart failure, ED

visit or intensification of therapy were analyzed i.e. they experienced that event type only, the associations between each of the event types and mortality were unchanged (Table 2). Using a seven day rather than thirty day interval between events (to define separate events) did not change the results (Appendix).

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%) compared to 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 <40mg of furosemide at baseline was 16.4% and in those taking e40mg 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. (Supplemental Table 1). Of those who experienced an intensification of heart failure therapy that was due to an increase in diuretic dose for over one month, the risk of death was higher in those who had an increase in dose that was e40mg of furosemide equivalent compared to <40mg furosemide equivalent (Supplemental Table 2).

We also examined which medications were added for the treatment of worsening heart failure (N=62). This was a diuretic in 23 (37%), a MRA in 17 (27%), a beta-blocker in 9 (15%), an ACEI/ARB in 8 (13%) and other drugs (digoxin in 2; unspecified in 3) in 5(8%).

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 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 heart failure hospitalization) of PARADIGM-HF. As can be seen at one, two and three years of follow-up, an additional 177, 248 and 269 patients, respectively, had experienced a *first* event contributing to the expanded composite outcome compared with the primary endpoint, an increment in events of around 14% overall. The one and two year Kaplan-Meier event rates for the primary endpoint were 14.2% and 24.0%, respectively, compared with 16.5% and 27.5%, respectively, for the expanded composite. The time taken to accrue 1000 patients with an event using the primary endpoint was 11 months (338 days) compared with 9 months (280 days) for the expanded composite.

Effect of sacubitril/valsartan on primary composite outcome and expanded composite

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

Sacubitril/valsartan was superior to enalapril in reducing the risk of the primary composite outcome (HR 0.80, 0.73-0.87), death from cardiovascular causes (HR 0.80, 0.71-0.89), and hospitalization for heart failure (HR 0.79, 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, 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 e.g. age, sex, race, region, medical history (data not shown).

DISCUSSION

Our findings are relevant to both clinical practice and the conduct of future clinical trials in HF-REF.

Firstly, as expected, we found that worsening leading to outpatient intensification of medical therapy is common in patients with HF-REF but more surprisingly was associated with an elevation in the risk of subsequent death similar to that seen following hospital admission. Focusing only on heart failure 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 heart failure, 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 endpoints 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 endpoint 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 heart failure, we have 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 heart failure hospitalization within 30 days. However, it should be noted that the majority of patients in PARADIGM-HF were in NYHA 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 four-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 (e.g. as part of a composite "worsening" endpoint). 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 endpoint (see below).

By contrast, ED visits were uncommonly reported (in 3% of patients) and were also frequently followed by heart failure 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 (as admission was itself an endpoint). In most countries the vast majority of ED attendances with heart failure 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 four to five-fold higher subsequent mortality (compared 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 two important messages from our findings. Firstly, 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 (e.g. could a mineralocorticoid receptor antagonist or digoxin be added)? Have all life-saving devices been considered (e.g. CRT and an ICD)? 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 heart failure hospitalization within 30 days, around one third were not. Therefore, expanding the primary composite outcome (heart failure hospitalization or cardiovascular death) used in PARADIGM-HF and other recent studies to include these additional components has two consequences. Firstly, doing so adds unique events (an additional 14% overall). Secondly 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 heart failure 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 heart failure 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 as 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 hospital for heart failure in the USA (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, as event rates have declined as a result of the cumulative benefit of effective treatments, trials in HF-REF 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 higher costs and less precision due to treatment discontinuation and patient loss to follow-up. Our findings suggest that 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 heart failure and a reduced ejection fraction which used non-hospitalized events as part of their primary endpoint 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 four hours or more without hospitalization was a component of the composite co-primary outcome.[19] Of the 1524 first events, there were only 10 non-hospitalized treatment events compared with 801 heart failure 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 out-patient events, 331 in-patient treatment events and 78 were deaths. The smaller proportion of out-patient events in these trials presumably reflects the requirement for intravenous therapy

(as opposed to augment or oral or intravenous therapy) and, perhaps, changing practice since publication of Val-HeFT. The individual contribution of non-hospitalized 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 pre-specified. The ED visits and intensification of oral therapy were not adjudicated (whereas heart failure hospitalizations and deaths were) and we do not have details of the drugs added to treat worsening heart failure. For the increase in diuretic dose component of the "intensification of therapy" endpoint, we required the increased to be sustained for at least a month, making this a relatively stringent component.

In conclusion, focusing only on heart failure 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 systematic approach in clinical practice to document episodes of non-hospitalized 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 heart failure, 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 endpoints 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

P.S.J., J.L.R., S.D.S., K.S., M.R.Z. and M.P. have consulted for Novartis. A.R.R., M.P.L., J.G and V.C.S. are employees of Novartis. M.R.Z. and K.S. have received honoraria from Novartis for sponsored lectures. J.J.V.M.s. employer, the University of Glasgow, was/is being paid for his time spent as Executive Committee member/co-chair of PARADIGM-HF. N.O. none.

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LEGENDS

Figure 1

Mortality (%) after a first event or in patients with no event.

Figure 2

Impact of adding emergency department visits and outpatient intensification therapy as additional components of a composite heart failure outcome.

Figure 3

Kaplan-Meier curves for primary endpoint (A) and expanded composite (B), according to treatment group.

Figure 4

Effect of sacubitril/valsartan versus enalapril for each outcome.

Table 1

The baseline characteristics of patients with different first manifestations of heart failure worsening, or none, or experiencing cardiovascular death

	None of event	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) (%)	1410 (23%)	212 (19%)	16 (21%)	56 (16%)	138 (18%)	<0.001
Race (%)						
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 (%)						
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 (mmHg)	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 (%)						
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 (%)	3593 (59%)	669 (60%)	44 (56%)	227 (63%)	503 (66%)	0.004

Medical history (%)						
Hypertension	4252 (70%)	824 (74%)	59 (76%)	268 (74%)	537 (70%)	0.012
Diabetes	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
Prior 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						
Prior use of ACE inhibitor	4744 (78%)	853 (77%)	60 (77%)	288 (80%)	587 (77%)	0.814
Prior 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
Beta-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

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

	None of the events	Hospitalization for HF	Emergency department visit for HF	Intensification of HF therapy
Each event as the 1st 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)

* 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.

Figure 1 Rate of death per 100 patient years after a first event or in patients with no event

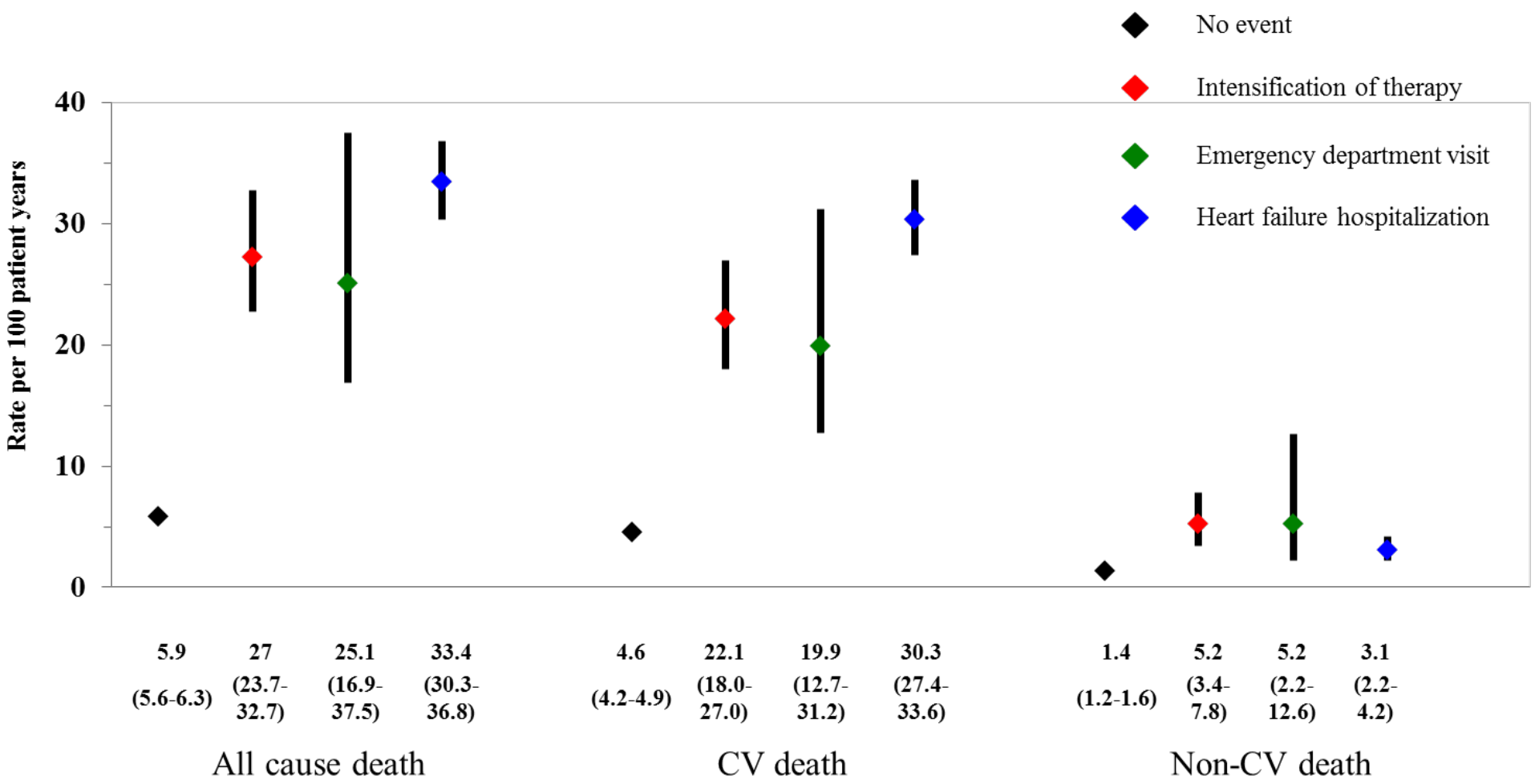
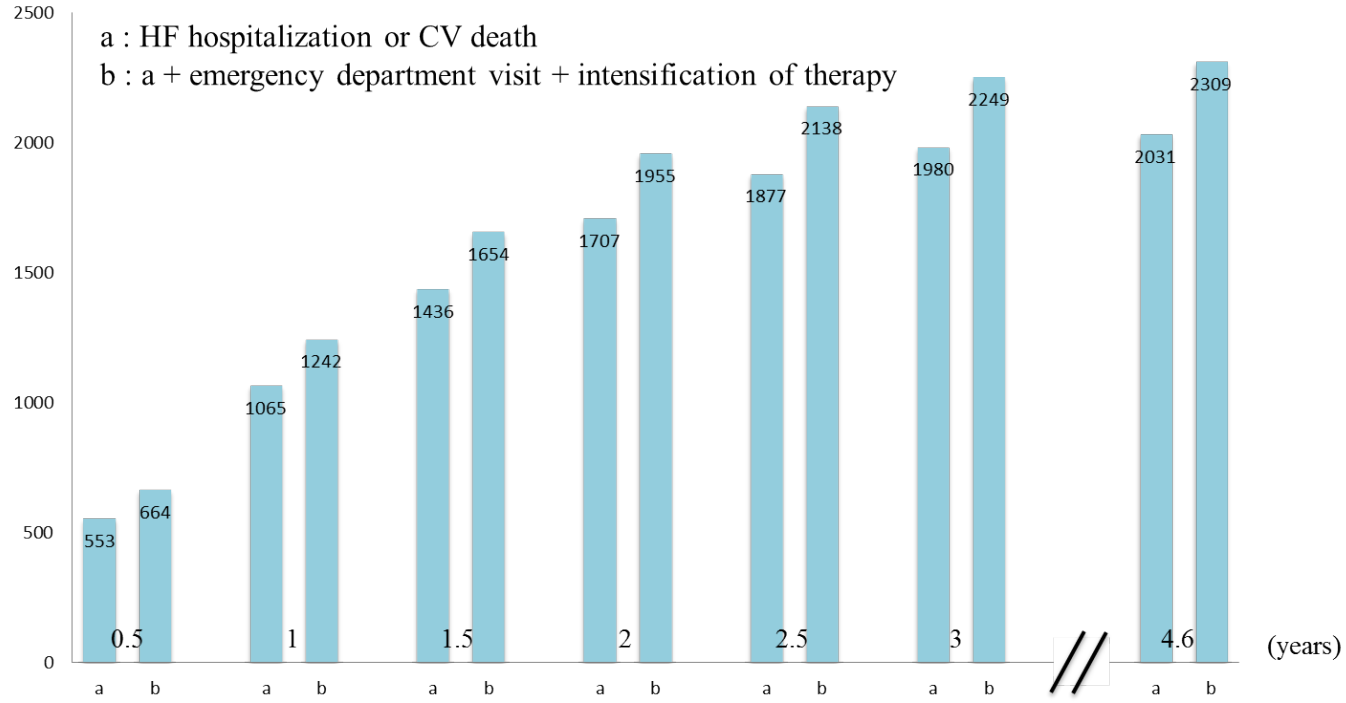


Figure 2

Impact of adding "outpatient intensification therapy" and "emergency department visits" as extra components to the primary composite outcome of cardiovascular death or heart failure hospitalization



Additional events*							
N	111	177	218	248	261	269	278
(%)	20.1	16.6	15.2	14.5	13.9	13.6	13.7

* Expanded composite compared with primary composite

Figure 3

Kaplan-Meier curves for the primary composite endpoint (A) and the expanded composite (B), according to treatment group.

(HR and corresponding p value are from the Cox model adjusted for region)

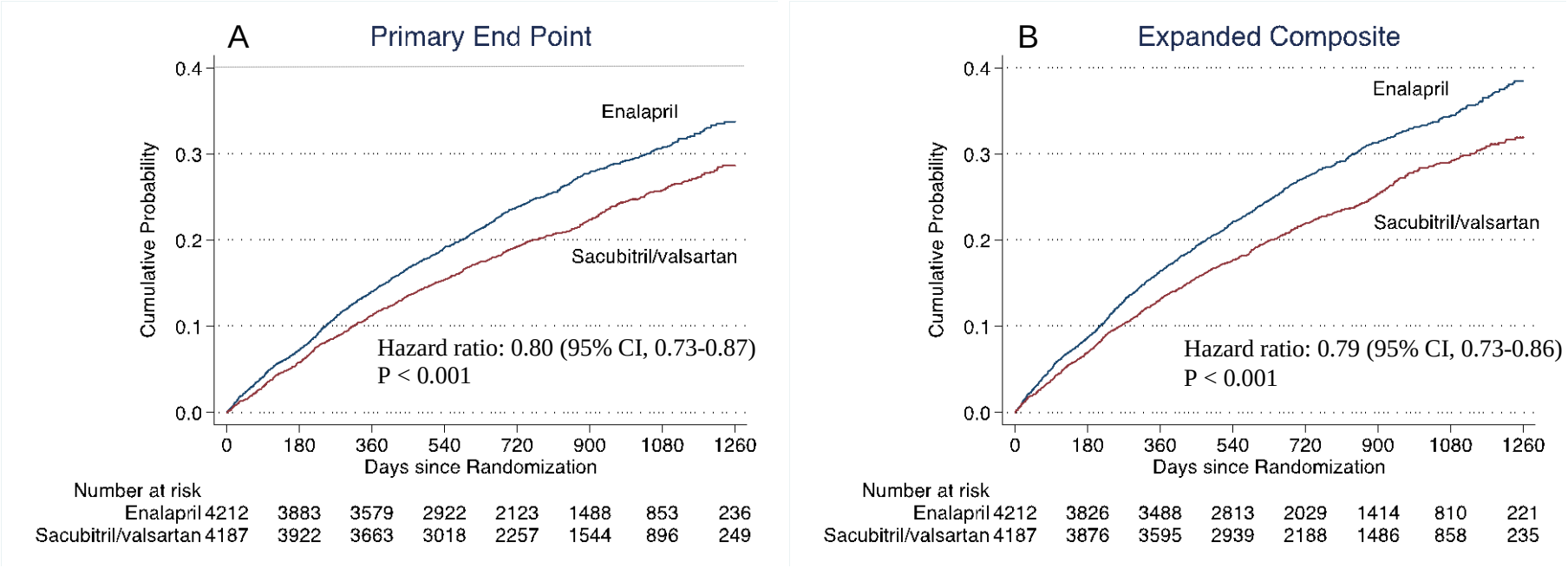
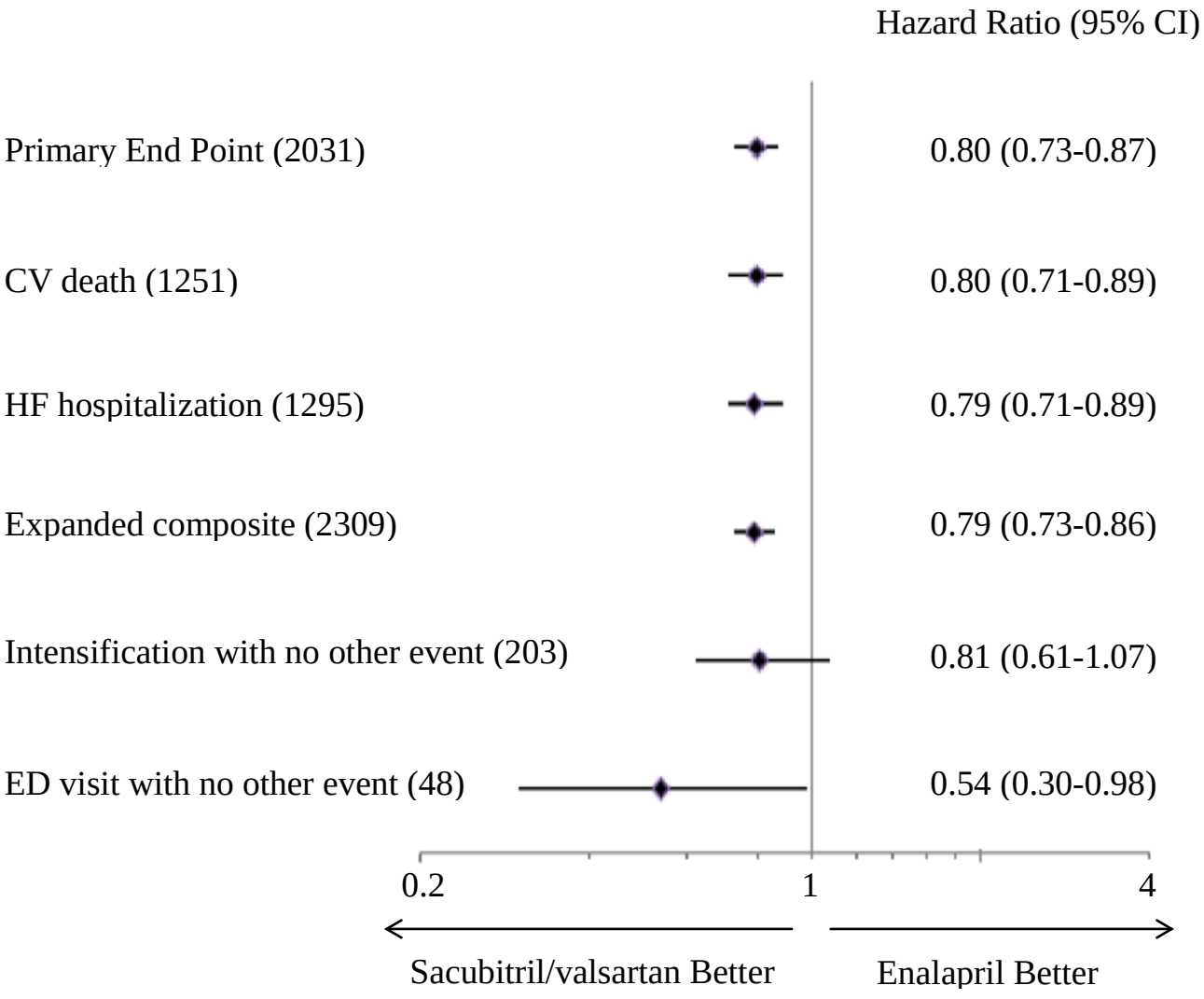
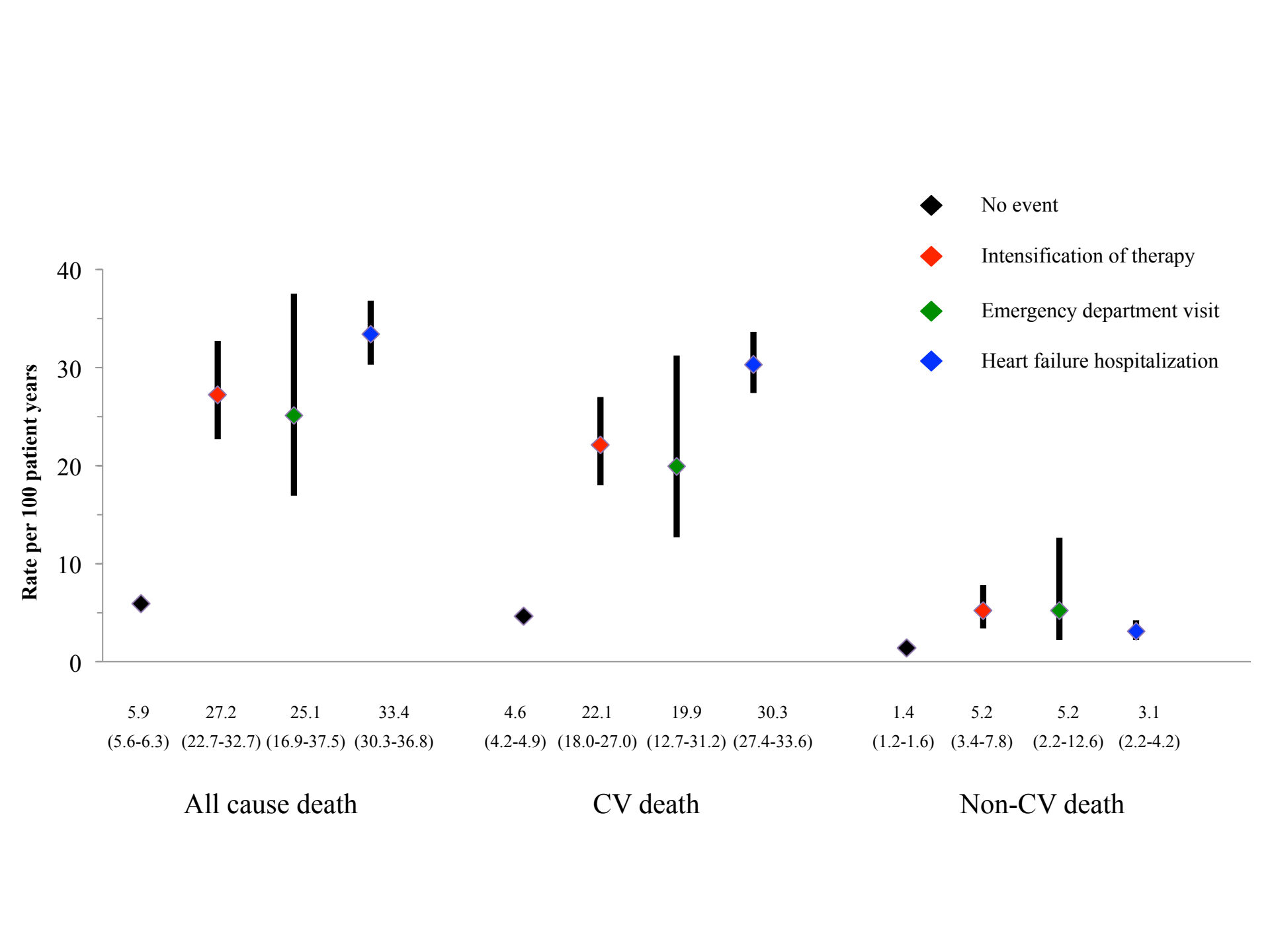
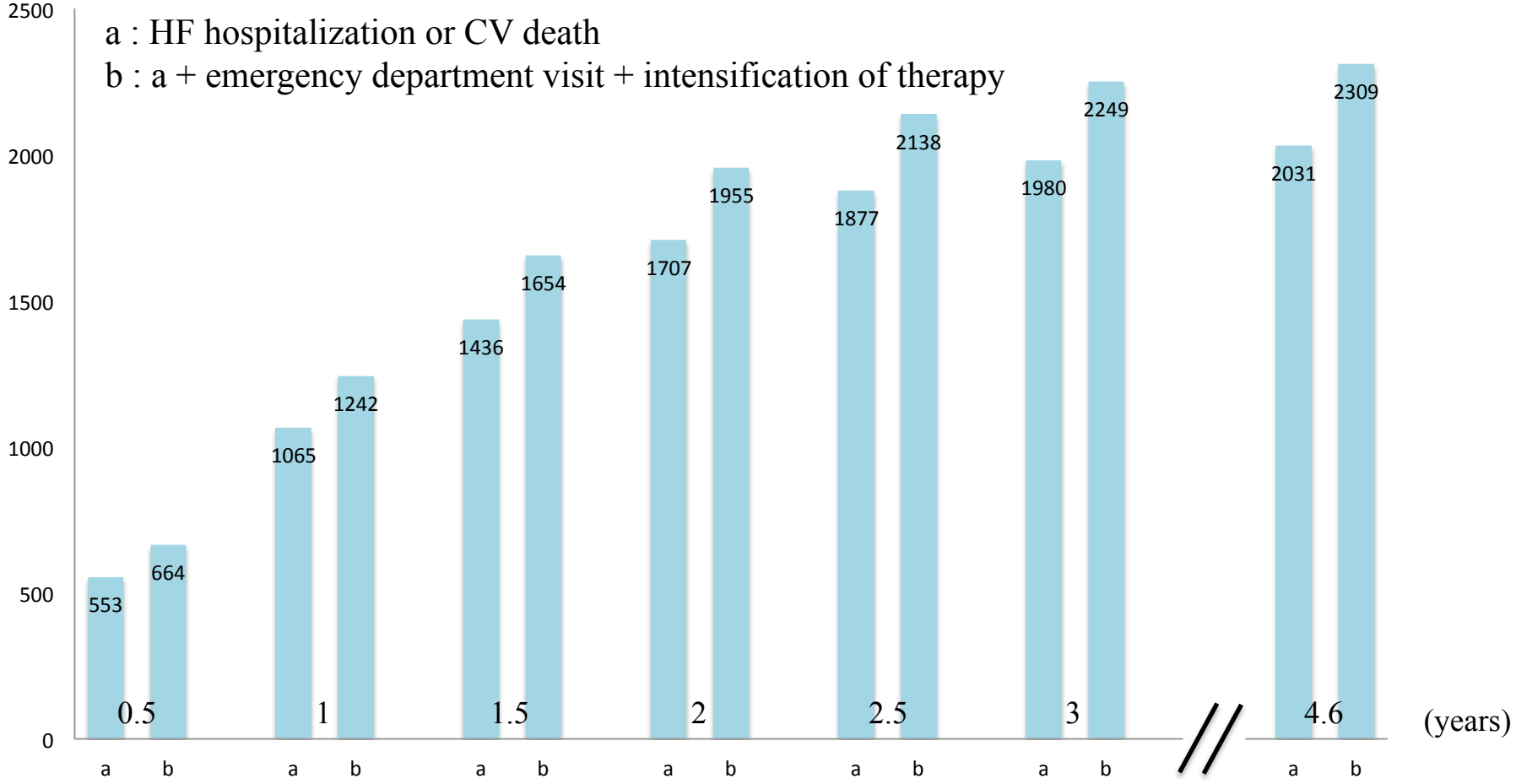


Figure 4

Effect of sacubitril/valsartan versus enalapril for different outcomes

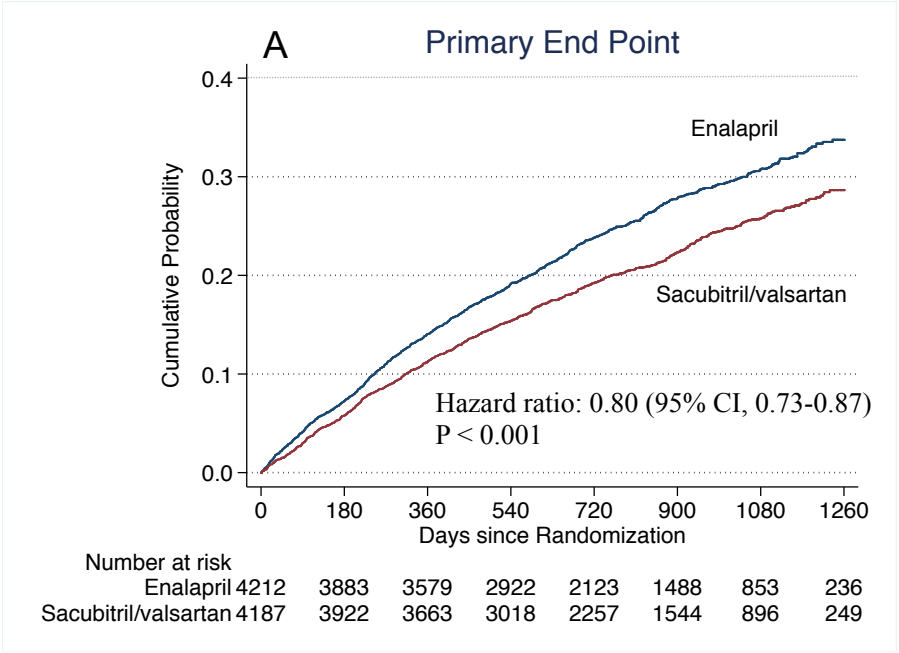


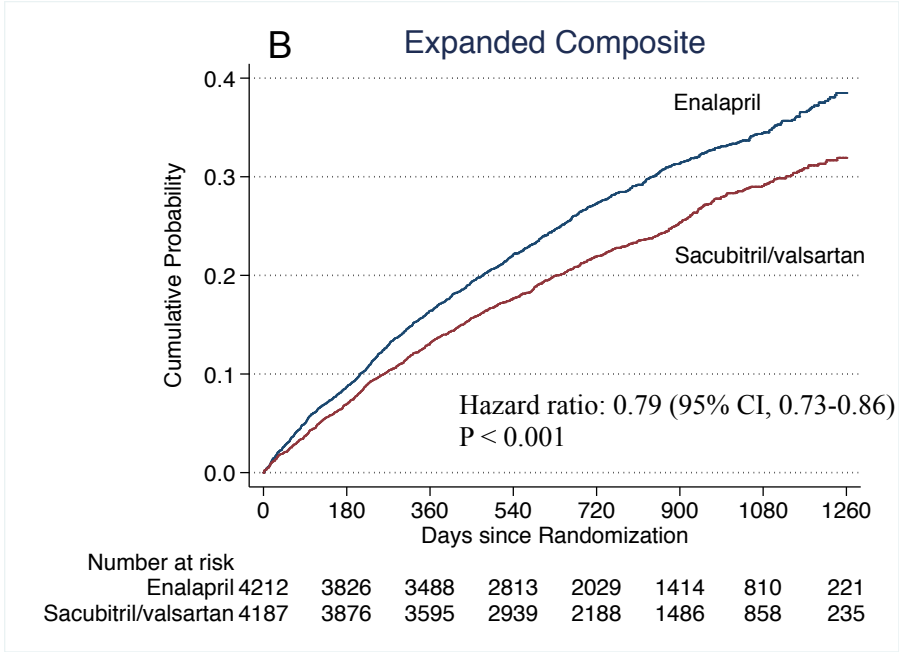

No event
Intensification of therapy
Emergency department visit
Heart failure hospitalization
Rate per 100 patient years
40
30
20
10
0
5.9 (5.6-6.3)
27.2 (22.7-32.7)
25.1 (16.9-37.5)
33.4 (30.3-36.8)
4.6 (4.2-4.9)
22.1 (18.0-27.0)
19.9 (12.7-31.2)
30.3 (27.4-33.6)
1.4 (1.2-1.6)
5.2 (3.4-7.8)
5.2 (2.2-12.6)
3.1 (2.2-4.2)
All cause death
CV death
Non-CV death

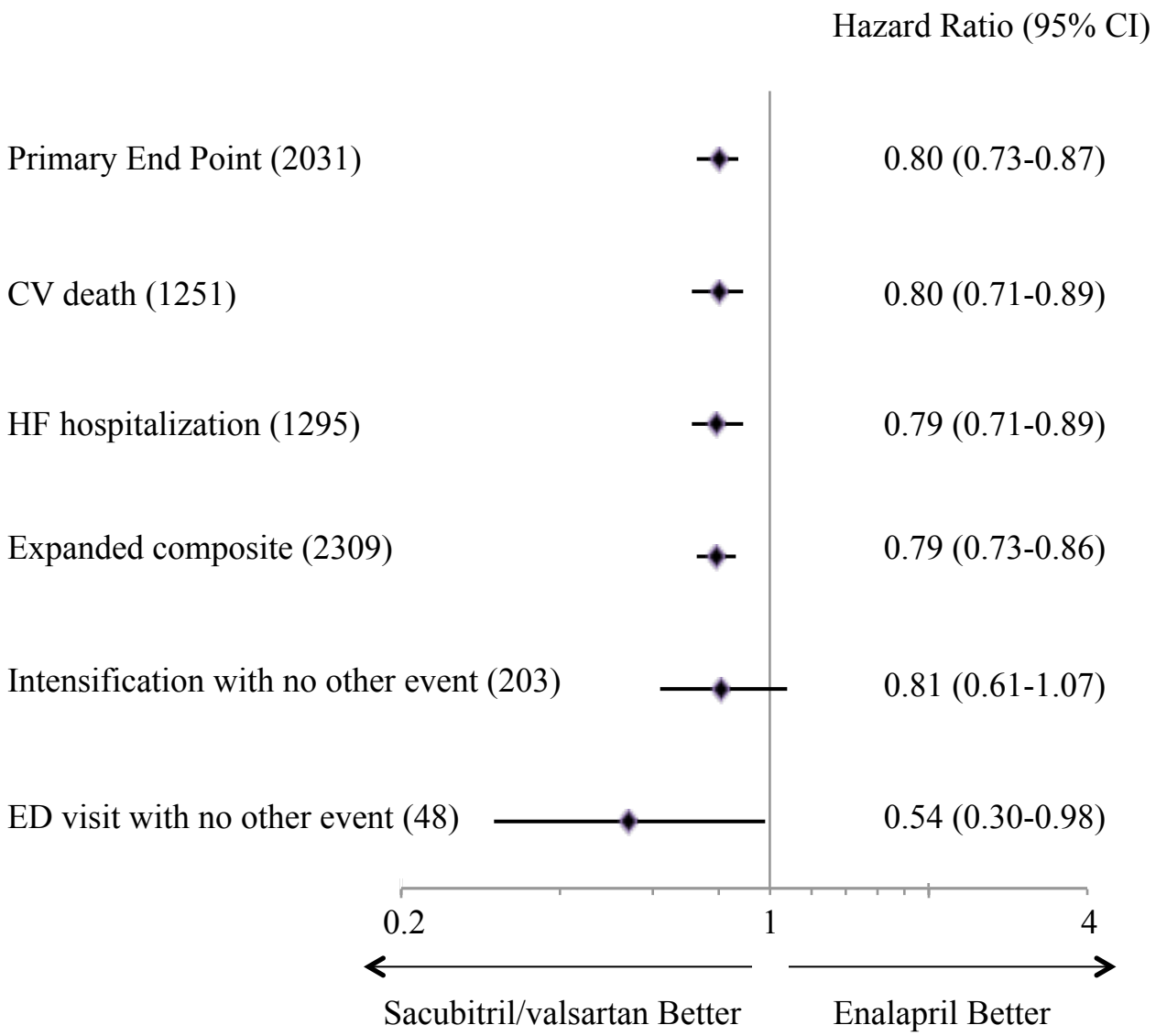


Additional events*							
N	111	177	218	248	261	269	278
(%)	20.1	16.6	15.2	14.5	13.9	13.6	13.7

* Expanded composite compared with primary composite


A
Primary End Point
Cumulative Probability
0.0
0.1
0.2
0.3
0.4
Enalapril
Sacubitril/valsartan
Hazard ratio: 0.80 (95% CI, 0.73-0.87)
P < 0.001
0
180
360
540
720
900
1080
1260
Days since Randomization
Number at risk
Enalapril 4212 3883 3579 2922 2123 1488 853 236
Sacubitril/valsartan 4187 3922 3663 3018 2257 1544 896 249


B
Expanded Composite
Cumulative Probability
0.0
0.1
0.2
0.3
0.4
Enalapril
Sacubitril/valsartan
Hazard ratio: 0.79 (95% CI, 0.73-0.86)
P < 0.001
0
180
360
540
720
900
1080
1260
Days since Randomization
Number at risk
Enalapril 4212 3826 3488 2813 2029 1414 810 221
Sacubitril/valsartan 4187 3876 3595 2939 2188 1486 858 235


Hazard Ratio (95% CI)
Primary End Point (2031)
0.80 (0.73-0.87)
CV death (1251)
0.80 (0.71-0.89)
HF hospitalization (1295)
0.79 (0.71-0.89)
Expanded composite (2309)
0.79 (0.73-0.86)
Intensification with no other event (203)
0.81 (0.61-1.07)
ED visit with no other event (48)
0.54 (0.30-0.98)
0.2
1
4
Sacubitril/valsartan Better
Enalapril Better

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

PARADIGM-HF Investigators

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