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ORIGINAL INVESTIGATIONS

Comparing LCZ696 With Enalapril According to Baseline Risk Using the MAGGIC and EMPHASIS-HF Risk Scores

An Analysis of Mortality and Morbidity in PARADIGM-HF

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ABSTRACT

BACKGROUND Although most patients in the PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial had mild symptoms, there is a poor correlation between reported functional limitation and prognosis in heart failure.

OBJECTIVES The aim of this study was to examine the spectrum of risk in PARADIGM-HF and the effect of LCZ696 across that spectrum.

METHODS This study analyzed rates of the primary composite outcome of cardiovascular death or heart failure hospitalization, its components, and all-cause mortality using the MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) and EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) risk scores to categorize patients. The authors determined whether risk, on the basis of these scores, modified the treatment effect of LCZ696.

RESULTS The complete MAGGIC risk score was available for 8,375 of the 8,399 patients in PARADIGM-HF. The median MAGGIC score was 20 (IQR: 16 to 24). An increase of 1 point was associated with a 6% increased risk for the primary endpoint ($p < 0.001$) and a 7% increased risk for cardiovascular death ($p < 0.001$). The benefit of LCZ696 over enalapril for the primary endpoint was similar across the spectrum of risk ($p = 0.159$). Treating 100 patients for 2 years with LCZ696 instead of enalapril led to 7 fewer patients in the highest quintile of risk experiencing primary outcomes, compared with 3 in the lowest quintile. Analyses using the EMPHASIS-HF risk score gave similar findings.

CONCLUSIONS Although most PARADIGM-HF patients had mild symptoms, many were at high risk for adverse outcomes and obtained a large absolute benefit from LCZ696, compared with enalapril, over a relatively short treatment period. LCZ696's benefit was consistent across the spectrum of risk. (PARADIGM-HF trial [Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure]; NCT01035255)
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ABBREVIATIONS AND ACRONYMS

ACEI = angiotensin-converting enzyme inhibitor

AF = atrial fibrillation

ARB = angiotensin receptor blocker

BMI = body mass index

BNP = B-type natriuretic peptide

eGFR = estimated glomerular filtration rate

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

LVEF = left ventricular ejection fraction

NYHA = New York Heart Association

SBP = systolic blood pressure

Although well-treated patients with heart failure (HF) may have few symptoms and little functional limitation, many remain at substantial risk for death and other adverse outcomes. This is due in part to the limited correlation between powerful prognostic variables, such as left ventricular ejection fraction (LVEF), and comorbidities, symptoms, and functional capacity. The New York Heart Association (NYHA) classification encompasses a wide and overlapping range of risks, as was recently illustrated in EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) (1). Although all patients were in NYHA functional class II at entry, when categorized into low-, medium-, and high-risk groups using a predictive score, the rate of the primary endpoint (cardiovascular death or HF hospitalization) ranged from 7.6 to 39.4 per 100 person-years in the placebo-treated patients (the rate in the medium-risk group was 19.0 per 100 person-years) (2).

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Most patients in the PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial also had mild symptoms (5% were in NYHA functional class I and 70% in class II), although 24% and 0.7% were in NYHA functional classes III and IV, respectively, at randomization (3). We therefore calculated the baseline risk of patients in PARADIGM-HF using the MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) risk score, which was derived and validated in patients with a broad spectrum of symptoms and functional limitations (4). We also analyzed risk using the EMPHASIS-HF score in PARADIGM-HF patients in NYHA functional classes I and II only (2). Additionally, we examined the effect of the angiotensin receptor neprilysin inhibitor LCZ696 compared with enalapril, according to baseline risk calculated using these scores.

METHODS

The study design, patient characteristics, and key results of the PARADIGM-HF trial have been described in detail (3,5–7). The ethics committee of each of the 1,043 participating institutions (in 47 countries) approved the protocol, and all patients gave written, informed consent.

PATIENTS AND PROCEDURES

Patients had NYHA functional class II through IV symptoms, LVEF ≤40% (changed to ≤35% by amendment), and plasma B-type natriuretic peptide (BNP) levels ≥150 pg/ml (or N-terminal pro-BNP levels ≥600 pg/ml). Patients who had been hospitalized for HF within 12 months were eligible for enrollment with lower natriuretic peptide concentrations (BNP ≥100 pg/ml or N-terminal pro-BNP ≥400 pg/ml). Patients also were required to be taking angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) in doses equivalent to enalapril 10 mg/day for at least 4 weeks before screening, along with stable doses of beta-blockers (unless contraindicated or not tolerated) and mineralocorticoid receptor antagonists, if

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indicated. The exclusion criteria were history of intolerance of an ACEI or ARB, symptomatic hypotension (or systolic blood pressure [SBP] <100 mm Hg at screening or <95 mm Hg at randomization), estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2 at screening or at randomization (or a decrease in eGFR >25% [amended to 35%] between screening and randomization), serum potassium concentration >5.2 mmol/l at screening (>5.4 mmol/l at randomization), recent acute coronary syndrome, cardiovascular procedure or surgery, anticipated cardiac transplantation, and the presence of any other disease with a life expectancy <5 years. On trial entry, existing treatment with an ACEI or ARB was stopped, but other HF treatments were continued. Patients started enalapril 10 mg twice daily for 2 weeks, then took LCZ696 (both single blind) for an additional 4 to 6 weeks, initially at 100 mg twice daily, then 200 mg twice daily. Patients tolerating both drugs at the target doses were randomly assigned to double-blind treatment with either enalapril 10 mg twice daily or LCZ696 200 mg twice daily (in a 1:1 ratio). LCZ696 200 mg twice daily delivers the equivalent of valsartan 160 mg twice daily and significant and sustained neprilysin inhibition.

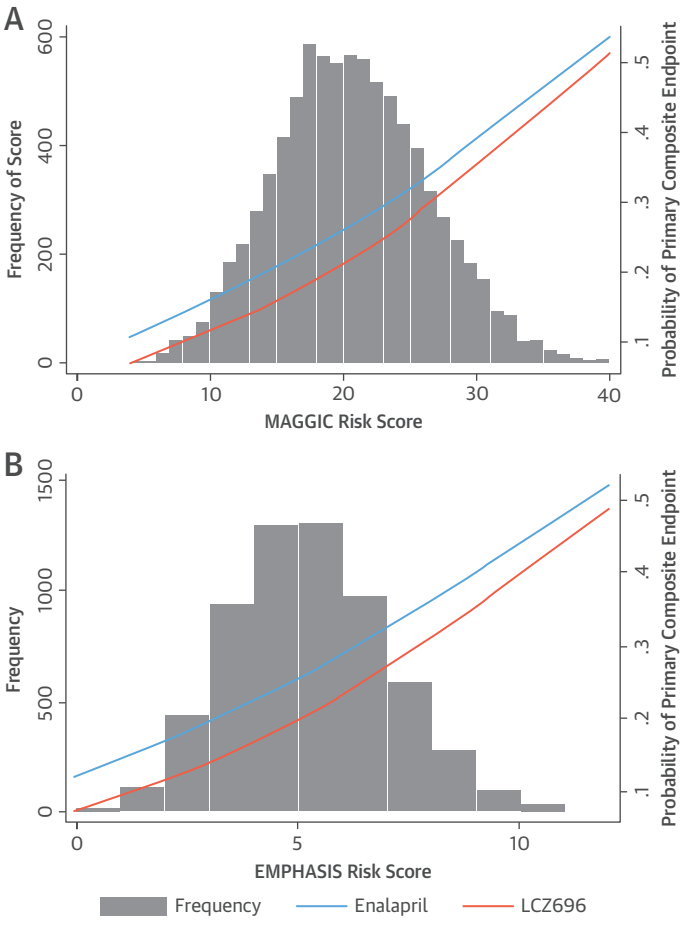
STUDY OUTCOMES. The primary outcome was a composite of death of cardiovascular causes or a first hospitalization for HF. Secondary outcomes were time to death of any cause, change from baseline to 8 months in the clinical summary score on the Kansas City Cardiomyopathy Questionnaire (on a scale of 0 to 100, with higher scores indicating fewer HF-related symptoms and physical limitations), time to new-onset atrial fibrillation (AF), and time to first occurrence of a decline in renal function. The focus of the present analyses was on the primary composite outcome, its components, and all-cause mortality.

RISK SCORES. The baseline risk for each patient in PARADIGM-HF was calculated using the MAGGIC score, the derivation and validation of which have been published (4,8). Briefly, a multivariate risk model was built after examination of 31 candidate variables in 39,372 patients enrolled in 30 clinical trials and cohort studies. Thirteen independent predictors of all-cause mortality were identified: age (per 10 years), male sex, body mass index (BMI) (per 1 kg/m^2 increase up to 30 kg/m^2), current smoking, diabetes, SBP (per 10 mm Hg increase), NYHA functional class, LVEF (per 5% increase up to 40%), chronic obstructive pulmonary disease, HF duration >18 months, creatinine (per 10 μmol/l up to 350 μmol/l), ACEI or ARB use, and beta-blocker use (significant interactions between both LVEF and age and between LVEF and SBP were also identified). A simple integer score was derived. The maximum score is 57, and an online risk calculator is available.

EMPHASIS-HF enrolled only patients with HF with reduced ejection fraction (HFrEF) and NYHA functional class II symptoms. The EMPHASIS-HF risk score, developed for the primary composite outcome of cardiovascular death or HF hospitalization (as well as all-cause mortality), uses a similar approach to that used in MAGGIC (2) and is the only risk score specifically developed in patients with mild symptoms. The risk model was validated in a subset of patients from CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity Programme) (2). More variables (including routine hematologic and biochemical variables) were available in the EMPHASIS-HF dataset than for the MAGGIC population, and 10 were identified as strong independent risk factors for the primary outcome, namely, age, sex, SBP, eGFR, diabetes, BMI, hemoglobin, prior HF hospitalization, prior myocardial infarction or coronary artery bypass grafting, and heart rate. However, this risk model does not take into account NYHA functional class (all patients in EMPHASIS-HF were in NYHA functional class II) or treatment (93% of patients were treated with ACEIs or ARBs and 87% with beta-blockers). To calculate a patient's risk score, for each binary variable, 1 point was added. For continuous variables, a binary categorization adequately explained the variation in risk, and 1 point was added for age ≥75 years, SBP <130 mm Hg, BMI <25 kg/m^2, and heart rate >80 beats/min. For eGFR and hemoglobin, 3 level categorizations better explained variation in risk, and therefore 2 points were added for eGFR <60 ml/min/1.73 m^2 or hemoglobin <11 g/dl and 1 point for eGFR 60 to 69 ml/min/1.73 m^2 or hemoglobin 11 to 12.9 g/dl. The maximum possible score was 12 (range: 0 to 12).

STATISTICAL ANALYSIS. Patients were divided into 5 quintiles of MAGGIC risk score (4 to 15, 16 to 18, 19 to 21, 22 to 25, and 26 to 40). The relationship between MAGGIC risk score category and baseline characteristics was examined using a trend test for continuous variables. For normally distributed variables, this was a regression test; for skewed variables, the Cuzick nonparametric trend test was used. Categorical variables were tested using chi-square test. The primary composite outcome, its components, and all-cause mortality were analyzed for each category. The effect of LCZ696 versus enalapril on each outcome across the spectrum of risk was examined in a Cox regression model. The interaction between risk and treatment on the occurrence of the pre-specified outcomes was tested in a logistic regression model with an interaction term between risk and treatment.

FIGURE 1 Distribution of Risk Scores and Probability of Reaching Primary Composite Endpoint



As shown by histogram, distribution of patients by **(A)** MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) risk score (n = 8,375) and **(B)** EMPHASIS (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) risk score (n = 6,112) and the association of each with reaching the primary composite endpoint of cardiovascular death or heart failure hospitalization shown by treatment.

The interaction between treatment and risk score was conducted with the risk score as a continuous variable. Pre-specified adverse events according to risk score category were also examined.

The MAGGIC risk score assigns 1 point to patients with a duration of HF of 18 months or longer. However, HF duration in PARADIGM-HF was recorded in the categories 0 to 3 months, 3 to 6 months, 6 to 12 months, 1 to 2 years, 2 to 5 years, and >5 years. For the main analysis, we added 1 point to a patient's score for HF duration ≥1 year and in a sensitivity analysis (Online Tables 1 and 2, Online Figures 1 and 2) for patients with HF for ≥2 years. Sensitivity analyses were also carried out for clinical outcomes related to MAGGIC risk score according to presence or absence of AF and geographic region (North America vs. the rest of the world) and (Online Tables 3 to 10).

An identical approach was taken in the analysis of the EMPHASIS-HF risk score, although it was applied only to patients in NYHA functional class I or II. Patients were split into 5 categories of approximately equal size: those with scores of 0 to 3, 4, 5, 6, or 7 to 12 points.

All analyses were conducted using Stata version 12.1 (StataCorp LP, College Station, Texas) and SAS version 9.4 (SAS Institute Inc., Cary, North Carolina). A p value <0.05 was considered to indicate statistical significance.

RESULTS

Overall, 8,399 patients aged 18 to 96 years were validly randomized, 8,375 of which had complete data across all 13 variables required for MAGGIC risk score calculation. The mean age was 64 years, 78% were men, and 70% of participants were in NYHA functional class II and 24% in class III. **Figure 1A** shows the distribution of MAGGIC risk scores in PARADIGM-HF. The median score was 20 points (IQR: 16 to 24 points; range: 4 to 40 points). **Table 1** shows the numbers and proportions of patients in the different MAGGIC risk-score categories analyzed.

Compared with patients with lower scores, those with higher scores were older and more often male, white, and enrolled in Western Europe and North America (**Table 1**). Patients with higher risk scores also had a lower mean SBP, LVEF, and BMI but higher mean creatinine and natriuretic peptide levels and were more likely to be in NYHA functional class III or IV than I or II and to have worse Kansas City Cardiomyopathy Questionnaire score, ischemic etiology (and other evidence of coronary heart disease), and additional comorbidities. With respect to background treatment of HF, beta-blocker use was less, but diuretic therapy, digoxin use, and device therapy were greater in patients with high scores.

OUTCOMES. When examined as a continuous variable, each 1-point increase in score was associated with a 6% (95% confidence interval: 5% to 7%) higher risk for the primary composite outcome of cardiovascular death or HF hospitalization ($p < 0.001$) (**Figure 1A**).

The unadjusted incidence of the primary outcome according to baseline risk category and randomized treatment is shown in **Table 2** and the **Central Illustration** (as a rate per 100 patient-years of

TABLE 1 MAGGIC Risk Score: Baseline Characteristics and Treatment

	Risk Score Category (Points)					
	4–15 (n = 1,762)	16–18 (n = 1,637)	19–21 (n = 1,675)	22–25 (n = 1,842)	26–40 (n = 1,459)	p Value for Trend
Age, yrs	53.9 ± 9.2	59.5 ± 9.0	63.5 ± 9.4	68.6 ± 8.8	74.9 ± 7.4	<0.0001
Female	492 (27.9)	381 (23.3)	358 (21.4)	368 (20.0)	230 (15.8)	<0.0001
Race						<0.0001
White	1,040 (59.0)	1,020 (62.3)	1,076 (64.2)	1,303 (70.7)	1,088 (74.6)	
Black	139 (7.9)	104 (6.4)	77 (4.6)	56 (3.0)	50 (3.4)	
Asian	366 (20.8)	332 (20.3)	327 (19.5)	305 (16.6)	175 (12.0)	
Other	217 (12.3)	181 (11.1)	195 (11.6)	178 (9.7)	146 (10.0)	
Region						<0.0001
North America	84 (4.8)	91 (5.6)	106 (6.3)	155 (8.4)	164 (11.2)	
Latin America	352 (20.0)	291 (17.8)	315 (18.8)	269 (14.6)	202 (13.8)	
Western Europe and other	324 (18.4)	380 (23.2)	388 (23.2)	489 (26.5)	459 (31.5)	
Central Europe	636 (36.1)	544 (33.2)	547 (32.7)	631 (34.3)	465 (31.9)	
Asia-Pacific	366 (20.8)	331 (20.2)	319 (19.0)	298 (16.2)	169 (11.6)	
SBP, mm Hg	124.9 ± 15.1	122.4 ± 15.9	120.7 ± 15.5	120.3 ± 15.0	118.2 ± 14.1	<0.0001
DBP, mm Hg	77.4 ± 10.0	74.6 ± 9.7	73.2 ± 9.8	72.3 ± 9.7	69.9 ± 9.7	<0.0001
Heart rate, beats/min	73.6 ± 12.2	72.4 ± 11.9	72.3 ± 12.4	71.7 ± 11.9	71.6 ± 11.7	<0.0001
BMI, kg/m^2	30.3 ± 6.0	28.9 ± 5.4	27.8 ± 5.3	27.4 ± 5.3	26.5 ± 4.6	<0.0001
Creatinine, μmol/l	86.8 ± 18.9	92.5 ± 21.0	97.7 ± 23.7	104.0 ± 26.6	117.8 ± 29.8	<0.0001
eGFR, ml/min/1.73m^2	78.9 ± 20.9	72.7 ± 18.1	68.2 ± 18.6	62.6 ± 17.0	54.4 ± 16.4	<0.0001
Hemoglobin, g/l	141.9 ± 15.6	141.1 ± 15.7	140.1 ± 16.2	137.4 ± 16.1	136.0 ± 15.7	<0.0001
BNP, pg/ml	209.6 (127.0–378.2)	277.6 (146.0–434.5)	256.2 (155.5–476.0)	275.1 (168.0–489.7)	317.5 (182.4–592.9)	<0.0001
NT-proBNP, pg/ml	1,198 (724–2,220)	1,379 (785–2,580)	1,625 (890–3,136)	1,846 (1,066–3,719)	2,435 (1,254–4,998)	<0.0001
Ischemic etiology	837 (47.5)	895 (54.7)	1,019 (60.8)	1,232 (66.9)	1,036 (71.0)	<0.0001
Ejection fraction, %	32.0 (4.9)	29.7 (5.9)	29.2 (6.1)	28.7 (6.4)	27.7 (6.8)	<0.0001
NYHA functional class						<0.0001
I	141 (8.0)	95 (5.8)	72 (4.3)	62 (3.4)	18 (1.2)	
II	1,514 (85.9)	1,311 (80.1)	1,242 (74.1)	1,154 (62.6)	689 (47.2)	
III	107 (6.1)	224 (13.7)	352 (21.0)	609 (33.1)	725 (49.7)	
IV	0 (0)	7 (0.4)	9 (0.5)	17 (0.9)	27 (1.9)	
KCCQ score	84.4 (68.8–93.8)	82.8 (67.7–93.8)	81.3 (65.1–92.7)	78.1 (60.4–89.6)	72.9 (55.2–87.0)	<0.0001
Medical history						
Hypertension	1,205 (68.4)	1,119 (68.4)	1,174 (70.1)	1,333 (72.4)	1,094 (75.0)	<0.0001
Diabetes	310 (17.6)	481 (29.4)	586 (35.0)	775 (42.1)	749 (51.3)	<0.0001
Atrial fibrillation	507 (28.8)	530 (32.4)	588 (35.1)	750 (40.7)	704 (48.3)	<0.0001
Hospitalization for heart failure	1,130 (64.1)	995 (60.8)	1,024 (61.1)	1,158 (62.9)	953 (65.3)	0.0663
Myocardial infarction	574 (32.6)	652 (39.8)	738 (44.1)	904 (49.1)	754 (51.7)	<0.0001
Stroke	101 (5.7)	115 (7.0)	153 (9.1)	163 (8.8)	193 (13.2)	<0.0001
Coronary artery bypass surgery	163 (9.3)	217 (13.3)	244 (14.6)	328 (17.8)	346 (23.7)	<0.0001
Percutaneous coronary intervention	299 (17.0)	334 (20.4)	372 (22.2)	457 (24.8)	335 (23.0)	<0.0001
Treatment						
Diuretic agent	1,365 (77.5)	1,287 (78.6)	1,310 (78.2)	1,493 (81.1)	1,265 (86.7)	<0.0001
Digoxin	495 (28.1)	487 (29.7)	504 (30.1)	553 (30.0)	495 (33.9)	0.009
Beta-blocker	1,721 (97.7)	1,583 (96.7)	1,579 (94.3)	1,674 (90.9)	1,232 (84.4)	<0.0001
Mineralocorticoid receptor antagonist	1,016 (57.7)	932 (56.9)	971 (58.0)	995 (54.0)	745 (51.1)	0.0002
Oral anticoagulant agent	469 (26.6)	522 (31.9)	549 (32.8)	608 (33.0)	529 (36.3)	<0.0001
Antiplatelet agent	921 (52.3)	915 (55.9)	962 (57.4)	1,082 (58.7)	844 (57.8)	0.001
Lipid-lowering agent	901 (51.1)	891 (54.4)	963 (57.5)	1,099 (59.7)	866 (59.4)	<0.0001
Implantable cardioverter-defibrillator	151 (8.6)	221 (13.5)	244 (14.6)	324 (17.6)	299 (20.5)	<0.0001
Cardiac resynchronization therapy	52 (3.0)	75 (4.6)	119 (7.1)	164 (8.9)	162 (11.1)	<0.0001

Values are mean ± SD, n (%), or median (interquartile range).

BMI = body mass index; BNP = B-type natriuretic peptide; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; KCCQ = Kansas City Cardiomyopathy Questionnaire; MAGGIC = Meta-Analysis Global Group in Chronic Heart Failure; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; SBP = systolic blood pressure.

TABLE 2 Clinical Outcomes According to MAGGIC Risk Score Category

Outcome		Risk Score Category (Points)											
		4-15 (n = 1,762)		16-18 (n = 1,637)		19-21 (n = 1,675)		22-25 (n = 1,842)		26-40 (n = 1,459)			
		Enalapril (n = 859)	LCZ696 (n = 903)	Enalapril (n = 823)	LCZ696 (n = 814)	Enalapril (n = 865)	LCZ696 (n = 810)	Enalapril (n = 937)	LCZ696 (n = 905)	Enalapril (n = 717)	LCZ696 (n = 742)		
CV death or HF hospitalization	n	143	123	203	145	234	171	263	230	273	243		
	Rate* (95% CI)	7.6 (6.4–8.9)	6.1 (5.1–7.3)	12.0 (10.5–13.8)	8.3 (7.0–9.7)	13.6 (11.9–15.4)	10.2 (8.8–11.8)	14.2 (12.6–16.34)	12.5 (11.0–14.3)	20.6 (18.3–23.2)	17.2 (15.2–19.5)		
	HR (95% CI)	0.80 (0.63–1.02)		0.69 (0.56–0.86)		0.75 (0.62–0.92)		0.89 (0.74–1.06)		0.84 (0.71–1.00)			
CV death	n	79	75	111	91	146	94	174	145	182	153		
	Rate* (95% CI)	4.0 (3.2–5.0)	3.6 (2.9–4.5)	6.0 (5.0–7.3)	5.0 (4.0–6.1)	7.7 (6.6–9.1)	5.3 (4.3–6.4)	8.7 (7.5–10.1)	7.3 (6.2–8.6)	12.2 (10.5–14.1)	9.7 (8.3–11.4)		
	HR (95% CI)	0.90 (0.65–1.23)		0.82 (0.62–1.09)		0.68 (0.52–0.88)		0.84 (0.67–1.05)		0.80 (0.65–0.99)			
HF hospitalization	n	83	66	128	70	134	102	146	139	167	158		
	Rate* (95% CI)	4.4 (3.6–5.5)	3.3 (2.6–4.2)	7.6 (6.4–9.0)	4.0 (3.2–5.1)	7.8 (6.6–9.2)	6.1 (5.0–7.4)	7.9 (6.7–9.3)	7.6 (6.4–8.9)	12.6 (10.8–14.7)	11.1 (9.6–13.1)		
	HR (95% CI)	0.74 (0.53–1.02)		0.53 (0.40–0.71)		0.78 (0.61–1.02)		0.97 (0.77–1.22)		0.89 (0.72–1.11)			
All-cause death	n	105	95	124	104	168	126	207	190	230	194		
	Rate* (95% CI)	5.3 (4.4–6.4)	4.5 (3.7–5.5)	6.7 (5.6–8.0)	5.7 (4.7–6.9)	8.9 (7.7–10.4)	7.1 (5.9–8.4)	10.3 (9.0–11.8)	9.5 (8.3–11.0)	15.4 (13.5–17.5)	12.3 (10.7–14.2)		
	HR (95% CI)	0.86 (0.65–1.13)		0.84 (0.65–1.09)		0.79 (0.63–1.00)		0.92 (0.76–1.12)		0.80 (0.66–0.97)			

*Rate per 100 patient-years.
CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; MAGGIC = Meta-Analysis Global Group in Chronic Heart Failure.

follow-up). The incidence of this endpoint in the enalapril (control) group increased incrementally with increasing score.

The effect of LCZ696 compared with enalapril was consistent across the range of risk scores examined as a categorical variable (**Table 2**, **Central Illustration**). As a result, the absolute treatment effect was greater in patients with higher risk scores. For example, applying the overall proportional risk reduction (20%) with LCZ696 (compared with enalapril) in PARADIGM-HF to patients with risk scores of 26 to 40 points would lead to 8 fewer patients per 100 treated for 2 years experiencing events compared with 4 in the category with 4 to 15 points.

The rates of both cardiovascular death and HF hospitalization, individually, in the enalapril group increased stepwise with increasing score (**Table 2**, **Central Illustration**). When the score was examined as a continuous variable, each 1-point increase in score was associated with a 7% (95% confidence interval: 6% to 8%) higher risk for cardiovascular death ($p < 0.001$).

The effect of LCZ696 compared with enalapril was consistent across the spectrum of risk examined as a categorical variable (**Table 2**, **Central Illustration**) or continuous variable. The p values for the interaction between risk score and treatment effect were 0.88 for cardiovascular death and 0.02 for HF hospitalization.

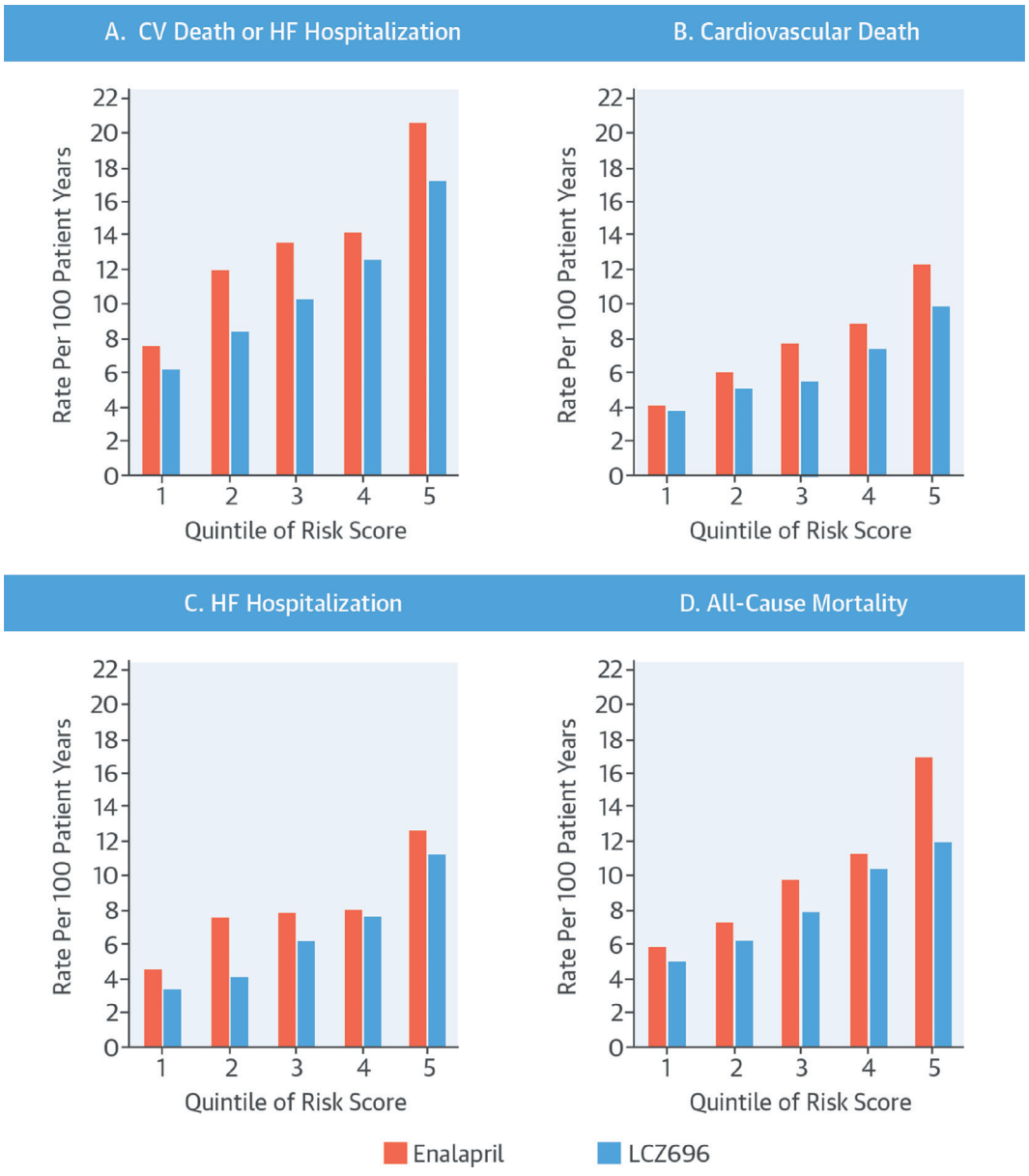
The rate of death from any cause increased stepwise with increasing risk category (**Table 2**, **Central Illustration**). When examined as a continuous variable, each 1-point increase in score was associated with a 7% (95% confidence interval: 6% to 8%) higher risk for cardiovascular death ($p < 0.001$).

The effect of LCZ696 compared with enalapril was consistent across the spectrum of risk examined as a categorical variable (**Table 2**, **Central Illustration**) or continuous variable (**Figure 1A**). The absolute treatment effect was greater in patients with higher risk scores; for example, applying the overall proportional risk reduction (20%) with LCZ696 (compared with enalapril) in PARADIGM-HF would lead to 6 fewer patients per 100 treated for 2 years experiencing events with risk scores of 26 to 40 points (compared with 2 in the category with 4 to 15 points).

As described in "Methods," further analyses were conducted to assess for the misclassification of HF duration. The findings were consistent with the main analyses (Online Tables 1 and 2, Online Figures 1 and 2).

Two further sensitivity analyses were conducted, one according to history of AF and the other by region (Europe and North America vs. the rest of the world). Generally, patients with AF had higher absolute rates

CENTRAL ILLUSTRATION **Effect of Angiotensin Receptor Neprilysin Inhibitor on Clinical Outcomes: The MAGGIC Risk Score Category**



Simpson, J. et al. J Am Coll Cardiol. 2015; 66(19):2059–71.

After categorizing patients into quintiles on the basis of the Meta-Analysis Global Group in Chronic Heart Failure risk score, the rate per 100 patient-years of follow-up was determined for **(A)** the primary composite endpoint, **(B)** cardiovascular (CV) death, **(C)** heart failure (HF) hospitalization, and **(D)** all-cause mortality according to baseline risk category and randomized treatment. The incidence of all endpoints increased incrementally with increasing risk score. The effect of LCZ696 compared with enalapril was consistent across the range of risk scores examined as a categorical variable for all endpoints. MAGGIC = Meta-Analysis Global Group in Chronic Heart Failure.

of the primary composite endpoint, its components, and all-cause death. However, event rates increased with increasing risk score in each rhythm subgroup. Moreover, the benefit of LCZ696 over enalapril was consistent across risk categories in both rhythm subgroups (Online Tables 3 to 6).

Regionally, the rate of death tended to be lower and that of HF hospitalization higher in Europe and North America compared with the rest of the world, but the rate of the primary composite outcome did not vary markedly between regions. Event rates increased with increasing risk score in each region, and the benefit of LCZ696 over enalapril was consistent across risk categories in both regions (Online Tables 7 to 10).

ADVERSE EVENTS. Among pre-specified safety outcomes in PARADIGM-HF by MAGGIC risk score category (Table 3), hyperkalemia (serum potassium >5.5 mmol/l) was the most common event. In patients randomized to enalapril (the control group), hyperkalemia occurred in 13.3% of patients in the lowest risk score category and 22.2% in the highest risk score category. The next most common adverse effect, symptomatic hypotension, occurred in 7.0% of patients in the lowest and 14.2% in the highest risk score category; 1.1% of patients in the lowest risk score category had renal dysfunction (a serum creatinine ≥2.5 mg/dl) compared with 10.5% in the highest risk score category. All 3 of these adverse events showed a trend to be more common in higher risk patients. The frequency of cough did not vary across risk score categories, and the frequency of angioedema was too low to analyze. The differential effect of LCZ696 compared with enalapril (e.g., more hypotension with LCZ696 than enalapril) was generally maintained across risk score categories (Table 3).

EMPHASIS-HF RISK SCORE ANALYSES. Overall, 6,112 patients were in NYHA functional class I or II and had complete data across all 10 variables required for calculation of the EMPHASIS-HF risk score. The mean age was 63 years, and 79.6% of participants were men. Figure 1B shows the distribution of EMPHASIS-HF risk scores in this subset of patients in PARADIGM-HF. The median score was 5 points (IQR: 4 to 6 points; range: 0 to 12 points). Table 4 shows the number and proportion of patients in the different EMPHASIS-HF risk-score categories analyzed.

The differences between those with lower and higher EMPHASIS-HF risk scores exactly mirrored those reported for the MAGGIC risk score. Similar to the

TABLE 3 Occurrence of Pre-Specified Adverse Events by MAGGIC Risk Score Category

	Risk Score Category (Points)									
	4–15		16–18		19–21		22–25		26–40	
	Enalapril (n = 859)	LCZ696 (n = 903)	Enalapril (n = 823)	LCZ696 (n = 814)	Enalapril (n = 865)	LCZ696 (n = 810)	Enalapril (n = 937)	LCZ696 (n = 905)	Enalapril (n = 717)	LCZ696 (n = 742)
Hypotension										
Symptomatic hypotension	60 (7.0)	88 (9.7)	77 (9.4)	83 (10.2)	68 (7.9)	117 (14.4)	81 (8.6)	149 (16.5)	102 (14.2)	150 (20.2)
Symptomatic hypotension with SBP <90 mm Hg	6 (0.7)	15 (1.7)	10 (1.2)	13 (1.6)	12 (1.4)	24 (3.0)	11 (1.2)	24 (2.7)	20 (2.8)	36 (4.9)
Leading to discontinuation	3 (0.3)	6 (0.7)	5 (0.6)	4 (0.5)	0 (0.0)	6 (0.7)	11 (1.2)	8 (0.9)	10 (1.4)	11 (1.5)
Renal impairment										
Serum creatinine ≥2.5 mg/dl	11 (1.1)	8 (0.9)	20 (2.4)	17 (2.1)	33 (3.8)	21 (2.6)	49 (5.2)	39 (4.3)	75 (10.5)	53 (7.1)
Serum creatinine ≥3.0 mg/dl	3 (0.3)	4 (0.4)	13 (1.6)	10 (1.2)	15 (1.7)	11 (1.4)	19 (2.0)	15 (1.7)	33 (4.6)	23 (3.1)
Leading to discontinuation	6 (0.7)	3 (0.3)	10 (1.2)	5 (0.6)	8 (0.9)	4 (0.5)	16 (1.7)	10 (1.1)	19 (2.6)	7 (0.9)
Hyperkalemia										
Serum potassium >5.5 mmol/l	114 (13.3)	125 (13.8)	135 (16.4)	93 (11.4)	135 (15.6)	143 (17.7)	182 (19.4)	156 (17.2)	159 (22.2)	154 (20.8)
Serum potassium >6.0 mmol/l	29 (3.4)	34 (3.8)	41 (5.0)	27 (3.3)	42 (4.9)	41 (5.1)	59 (6.3)	39 (4.3)	65 (9.1)	40 (5.4)
Leading to discontinuation	2 (0.2)	1 (0.1)	2 (0.2)	1 (0.1)	4 (0.5)	1 (0.1)	1 (0.1)	4 (0.4)	6 (0.8)	4 (0.5)
Cough										
Any cough	125 (14.6)	79 (8.7)	126 (15.3)	93 (11.4)	124 (14.3)	100 (12.3)	127 (13.6)	114 (12.6)	98 (13.7)	87 (11.7)
Leading to discontinuation	8 (0.9)	1 (0.1)	7 (0.9)	2 (0.2)	4 (0.5)	1 (0.1)	6 (0.6)	3 (0.3)	5 (0.7)	1 (0.1)
Angioedema										
No treatment/antihistamines only	2 (0.2)	2 (0.2)	2 (0.2)	5 (0.6)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.2)	2 (0.3)	1 (0.1)
Catecholamines/corticosteroids without hospitalization	0 (0.0)	2 (0.2)	1 (0.1)	2 (0.2)	3 (0.3)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Hospitalized/no airway compromise	1 (0.1)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Any adverse event leading to study drug discontinuation	19 (2.2)	9 (1.0)	22 (2.7)	12 (1.5)	15 (1.7)	12 (1.5)	34 (3.6)	24 (2.7)	39 (5.4)	21 (2.8)

Values are n (%).
MAGGIC = Meta-Analysis Global Group in Chronic Heart Failure.

TABLE 4 EMPHASIS-HF Risk Score: Baseline Characteristics and Treatment

	Risk Score Category (Points)					
	0–3 (n = 1,499)	4 (n = 1,314)	5 (n = 1,325)	6 (n = 987)	7–12 (n = 987)	p Value for Trend
Age, yrs	58.7 ± 11.2	60.7 ± 11.2	63.0 ± 10.8	65.9 ± 10.8	69.9 ± 10.1	<0.0001
Female	450 (30.0)	285 (21.7)	229 (17.3)	158 (16.0)	126 (12.8)	<0.0001
Race						<0.0001
White	901 (60.1)	776 (59.1)	830 (62.6)	600 (60.8)	611 (61.9)	
Black	135 (9.0)	81 (6.2)	65 (4.9)	38 (3.9)	37 (3.7)	
Asian	245 (16.3)	282 (21.5)	263 (19.8)	244 (24.7)	258 (26.1)	
Other	218 (14.5)	175 (13.3)	167 (12.6)	105 (10.6)	81 (8.2)	
Region						<0.0001
North America	68 (4.5)	76 (5.8)	106 (8.0)	85 (8.6)	131 (13.3)	
Latin America	370 (24.7)	283 (21.5)	272 (20.5)	177 (17.9)	136 (13.8)	
Western Europe and other	369 (24.6)	321 (24.4)	342 (25.8)	265 (26.8)	287 (29.1)	
Central Europe	442 (29.5)	357 (27.2)	344 (26.0)	221 (22.4)	183 (18.5)	
Asia-Pacific	250 (16.7)	2,797 (21.1)	261 (19.7)	239 (24.2)	250 (25.3)	
SBP, mm Hg	126.2 ± 16.5	121.2 ± 15.8	118.8 ± 14.8	118.5 ± 14.2	116.7 ± 13.0	<0.0001
DBP, mm Hg	76.5 ± 10.0	73.9 ± 10.1	72.5 ± 9.6	71.8 ± 9.9	69.3 ± 9.4	<0.0001
Heart rate, beats/min	70.0 ± 10.3	71.4 ± 11.6	72.2 ± 12.4	73.0 ± 12.2	73.5 ± 12.5	<0.0001
BMI, kg/m^2	29.4 ± 5.34	27.9 ± 5.2	27.7 ± 5.3	27.19 ± 5.4	26.1 ± 4.9	<0.0001
Creatinine, μmol/l	82.1 ± 15.1	90.3 ± 18.9	100.4 ± 23.5	111.4 ± 25.6	121.5 ± 26.1	<0.0001
eGFR, ml/min/1.73 m^2	81.0 ± 16.4	74.6 ± 18.9	67.0 ± 20.0	58.9 ± 16.6	51.9 ± 14.4	<0.0001
Hemoglobin, g/l	144.1 ± 13.0	142.4 ± 14.6	140.2 ± 15.6	137.7 ± 16.4	128.9 ± 16.6	<0.0001
BNP, pg/ml	224.1 (139.9–400.2)	234.8 (144.9–406.4)	239.8 (144.7–435.6)	258.5 (158.0–487.2)	291.6 (168.5–552.0)	<0.0001
NT-proBNP, pg/ml	1,277 (771–2,373)	1,420 (808–2,684)	1,521 (881–2,981)	1,728 (989–3,460)	2,099 (1,084–4,124)	<0.0001
Ischemic etiology	526 (35.1)	681 (51.8)	799 (60.3)	683 (69.2)	812 (82.3)	<0.0001
Ejection fraction, %	29.8 ± 6.1	29.0 ± 6.3	29.3 ± 6.3	29.1 ± 6.0	28.9 ± 6.5	0.01
NYHA functional class						
I	110 (7.3)	79 (6.0)	77 (5.8)	65 (6.6)	49 (5.0)	
II	1,389 (92.7)	1,235 (94.0)	1,248 (94.2)	922 (93.4)	938 (95.0)	
KCCQ score	86.3 (71.9–94.8)	87.0 (72.9–95.3)	83.9 (70.8–93.8)	83.3 (69.3–93.8)	81.3 (66.7–91.7)	<0.0001
Medical history						
Hypertension	992 (66.2)	830 (63.2)	912 (68.8)	705 (71.4)	701 (71.0)	<0.0001
Diabetes	192 (12.8)	347 (26.4)	489 (36.9)	443 (44.9)	577 (58.5)	<0.0001
Atrial fibrillation	480 (32.0)	358 (27.2)	430 (32.5)	351 (35.6)	364 (36.9)	<0.0001
Hospitalization for heart failure	616 (41.1)	769 (58.5)	821 (62.0)	692 (70.1)	781 (79.1)	<0.0001
Myocardial infarction	268 (17.9)	473 (36.0)	601 (45.4)	550 (55.7)	684 (69.3)	<0.0001
Stroke	88 (5.9)	92 (7.0)	114 (8.6)	70 (7.1)	106 (10.7)	0.001
Coronary artery bypass grafting	87 (5.8)	141 (10.7)	215 (16.2)	215 (21.8)	302 (30.6)	<0.0001
Percutaneous coronary intervention	165 (11.0)	266 (20.2)	313 (23.6)	281 (28.5)	328 (33.2)	<0.0001
Treatment						
Diuretic agent	1,136 (75.8)	1,011 (76.9)	1,031 (77.8)	765 (77.5)	832 (84.3)	<0.0001
Digoxin	442 (29.5)	396 (30.1)	384 (29.0)	269 (27.3)	277 (28.1)	0.58
Beta-blocker	1,405 (93.7)	1,238 (94.2)	1,242 (93.7)	915 (92.7)	893 (90.5)	0.0043
Mineralocorticoid receptor antagonist	791 (52.8)	749 (57.0)	751 (56.7)	509 (51.6)	496 (50.3)	0.0016
Oral anticoagulant agent	428 (28.6)	394 (30.0)	428 (32.3)	289 (29.3)	301 (30.5)	0.272
Antiplatelet agent	722 (48.2)	732 (55.7)	766 (57.8)	628 (63.6)	663 (67.2)	<0.0001
Lipid-lowering agent	690 (46.0)	704 (53.6)	798 (60.2)	630 (63.8)	716 (72.5)	<0.0001
Implantable cardioverter-defibrillator	164 (10.9)	179 (13.6)	206 (15.5)	186 (18.8)	206 (20.9)	<0.0001
Cardiac resynchronization therapy	51 (3.4)	84 (6.4)	95 (7.2)	82 (8.3)	110 (11.1)	<0.0001

Values are mean ± SD, n (%), or median (interquartile range).

EMPHASIS-HF = Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; other abbreviation as in Table 1.

MAGGIC analysis, there was an approximately 2-fold increase in the rate of all outcomes examined comparing the highest with the lowest EMPHASIS-HF risk score category (Table 5). Likewise, the effect of LCZ696 compared with enalapril was consistent across the range of risk scores examined as a categorical (Figure 2) or continuous (Figure 1B) variable, with the greatest absolute benefit in those at highest risk.

TABLE 5 Clinical Outcomes in PARADIGM-HF Patients* According to EMPHASIS-HF Risk Score

Outcome		Risk Category (Points)									
		0-3 (n = 1,499)		4 (n = 1,314)		5 (n = 1,325)		6 (n = 987)		7-12 (n = 987)	
		Enalapril (n = 747)	LCZ696 (n = 752)	Enalapril (n = 665)	LCZ696 (n = 649)	Enalapril (n = 642)	LCZ696 (n = 683)	Enalapril (n = 490)	LCZ696 (n = 497)	Enalapril (n = 491)	LCZ696 (n = 496)
CV death or HF hospitalization	n	146	91	140	114	152	136	145	118	175	137
	Rate† (95% CI)	9.3 (7.9–10.9)	5.4 (4.4–6.6)	9.7 (8.2–11.4)	8.3 (6.9–9.9)	11.5 (9.8–13.4)	9.3 (7.9–11.0)	15.1 (12.9–17.8)	11.8 (9.9–14.1)	19.0 (16.4–22.0)	14.1 (12.0–16.7)
	HR (95% CI)	0.58 (0.45–0.76)		0.85 (0.67–1.09)		0.81 (0.65–1.03)		0.78 (0.61–0.99)		0.74 (0.59–0.93)	
CV death	n	90	59	80	66	89	84	90	67	104	90
	Rate† (95% CI)	5.4 (4.4–6.6)	3.4 (2.6–4.4)	5.2 (4.2–6.5)	4.6 (3.6–5.8)	6.3 (5.1–7.7)	5.4 (4.4–6.8)	8.5 (6.9–10.5)	6.2 (4.9–7.9)	9.9 (8.2–12.0)	8.6 (7.0–10.6)
	HR (95% CI)	0.63 (0.45–0.87)		0.88 (0.63–1.21)		0.87 (0.65–1.18)		0.72 (0.53–0.99)		0.86 (0.65–1.15)	
HF hospitalization	n	82	46	78	66	95	75	86	77	125	77
	Rate† (95% CI)	5.2 (4.2–6.5)	2.7 (2.0–3.6)	5.4 (4.3–6.7)	4.8 (3.8–6.1)	7.2 (5.9–8.8)	5.1 (4.1–6.4)	9.0 (7.3–11.1)	7.7 (6.1–9.6)	13.5 (11.4–16.1)	7.9 (6.4–9.9)
	HR (95% CI)	0.53 (0.37–0.76)		0.89 (0.64–1.24)		0.72 (0.53–0.97)		0.86 (0.63–1.17)		0.59 (0.44–0.78)	
All-cause death	n	109	76	97	83	116	107	107	86	124	124
	Rate† (95% CI)	6.5 (5.4–7.9)	4.4 (3.5–5.5)	6.3 (5.2–7.7)	5.7 (4.6–7.1)	8.2 (6.8–9.8)	6.9 (5.7–8.4)	10.1 (8.4–12.3)	8.0 (6.4–9.8)	11.8 (9.9–14.1)	11.8 (9.9–14.1)
	HR (95% CI)	0.67 (0.50–0.89)		0.91 (0.68–1.22)		0.85 (0.66–1.11)		0.78 (0.59–1.04)		1.00 (0.78–1.28)	

*With NYHA functional class I or II heart failure. †Rate per 100 patient-years.
Abbreviations as in Tables 1 and 2.

DISCUSSION

This study's main findings demonstrate that there was a broad spectrum of risk among the patients with HFrEF randomized in PARADIGM-HF and that the benefits of LCZ696 over enalapril were consistent across this spectrum of risk.

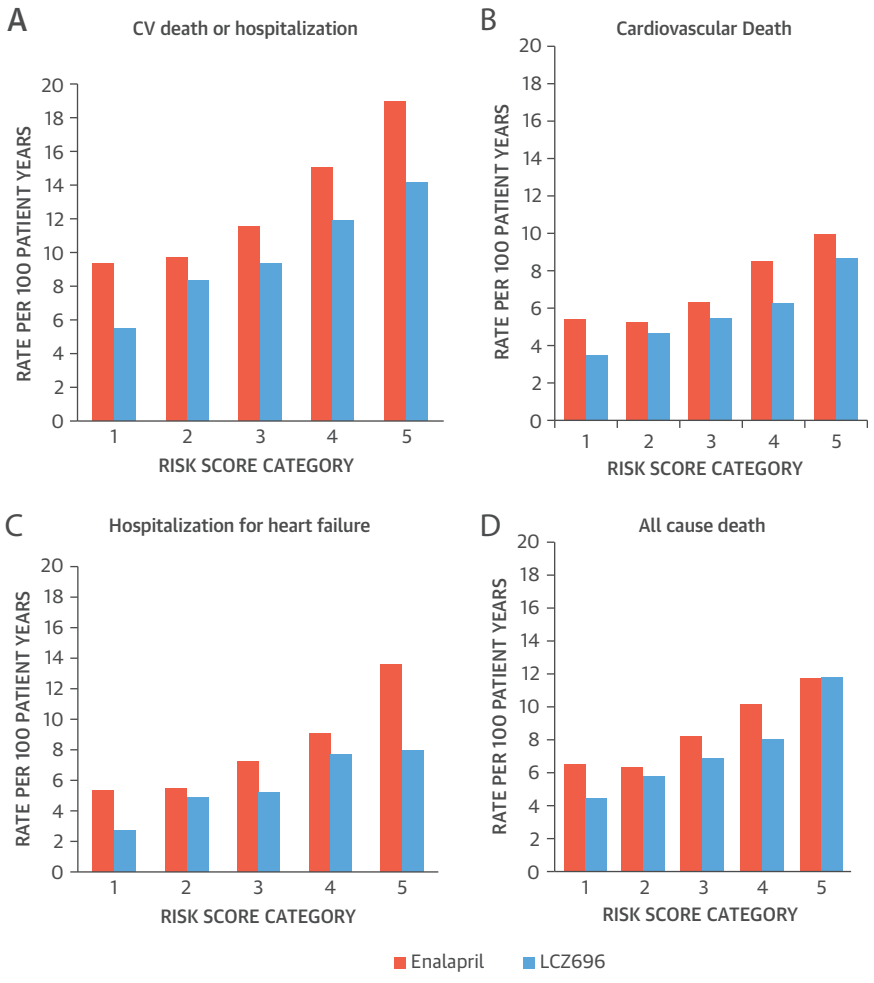
ANALYSIS BY RISK SCORE. The MAGGIC risk score was derived from an analysis of 39,372 patients enrolled in 30 clinical trials and cohort studies and validated in 51,043 patients in a large Swedish HF registry (4,8).

In the MAGGIC derivation cohort, the median risk score was 23 points (range: 0 to 52 points) (4), whereas in PARDIGM-HF, the median score was 20 points (range: 4 to 40 points). The lower median score (and range) in PARADIGM-HF reflects the exclusion of patients with a low SBP and/or low eGFR and the high use of beta-blockers, all prognostic variables in the MAGGIC risk score. Patients in CHARM with HFrEF also had a higher median risk score (26 points; range: 10 to 46 points) than in PARADIGM-HF because of the lower use of beta-blockers (55%) and greater proportion of patients in NYHA functional class III (52.4% vs. ~24% in PARADIGM-HF) (9). In EMPHASIS-HF, in which all patients were in NYHA functional class II and 87% were treated with beta-blockers, the median MAGGIC risk score of 21 points was similar to that in PARADIGM-HF, although the range of 7 to 38 points was narrower (1).

Despite the majority of patients in PARADIGM-HF being in NYHA functional class II at baseline, the incidence of the primary outcome ranged from 7.6 to 20.6 per 100 patient-years of follow-up in the lowest (4 to 15 points) and highest (26 to 40 points) quintiles, respectively, emphasizing the limited relationship between symptoms and risk of hospitalization and death. In other words, although most patients in PARADIGM-HF had "mild" symptoms, many were not at low risk. There was a similar 2- to 3-fold difference in risk for cardiovascular and all-cause death, as well as HF hospitalization, when comparing the highest and lowest quintiles of score.

The value of a multivariate score, such as MAGGIC, in discriminating risk is further illustrated by comparison with the published univariate subgroups. Those in the highest quintile of the MAGGIC risk score were at higher risk than patients in any of the prespecified subgroups of PARADIGM-HF; for instance, in patients ages 75 years and older, the rate of the primary outcome was 14.8 per 100 patient-years in the enalapril group (vs. 20.7 per 100 patient-years in

FIGURE 2 Clinical Outcomes (Expressed as a Rate per 100 Patient-Years of Treatment) by EMPHASIS Risk-Score Quintile



The rate of each outcome is expressed as per 100 patient-years of treatment for **(A)** the primary composite endpoint, **(B)** cardiovascular (CV) death, **(C)** heart failure (HF) hospitalization, and **(D)** all-cause mortality according to baseline risk category and randomized treatment. Risk groups 1 through 5 are the quintiles of risk (integer scores: 0 to 3, 4, 5, 6, and 7 to 12 points, respectively). The incidence of all endpoints increased incrementally with increasing risk score. Generally, the effect of LCZ696 compared with enalapril was consistent across the range of risk scores. EMPHASIS-HF = Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure.

the highest risk score quintile) (4). Moreover, the MAGGIC risk score represents a more comprehensive measure of risk than any of the individual univariate measures of risk.

The EMPHASIS-HF risk score was developed for the primary composite outcome of cardiovascular death or HF hospitalization using a similar approach to that used in MAGGIC and validated in a subset of patients from CHARM (2). However, unlike MAGGIC, hematologic and biochemical variables were available in the EMPHASIS-HF dataset. Additionally, the EMPHASIS-HF risk model does not take account of NYHA functional class (as all patients were in NYHA functional class II) or treatment (as the vast majority of patients were treated with ACEIs or ARBs and beta-blockers). The maximum possible score is 12 points (range: 0 to 12 points). The median score (5 points) in PARADIGM-HF patients in NYHA functional class I or II was identical to that in EMPHASIS-HF, although the range was wider in PARADIGM-HF (0 to 12 points; quartile 1 to quartile 3: 4 to 6 points) than in EMPHASIS-HF (0 to 11 points; quartile 1 to quartile 3: 3 to 6 points).

The benefit of LCZ696 over enalapril was apparent across the spectrum of risk, with no evidence of an interaction between risk score and treatment effect for the primary composite outcome, cardiovascular death, and all-cause mortality. There was a

statistically significant interaction between treatment effect and score for HF hospitalization. Although the magnitude of the effect varied, the direction of effect, i.e., benefit of LCZ696, was consistent. The greatest absolute benefit of LCZ696 versus enalapril was obtained in patients at highest absolute risk. For instance, if the overall proportional risk reduction for treatment with LCZ696 compared with enalapril is applied to the highest quintile of MAGGIC risk score, approximately 7 fewer patients per 100 treated for 2 years would experience a first occurrence of the primary composite outcome; in the lowest risk category, approximately 3 fewer patients would experience this outcome. For deaths, these numbers would be approximately 6 versus 2. This indicates that within the overall PARADIGM-HF population, with mainly mild symptoms and little functional limitation, there is a substantial subset not just at high risk but also with much to gain from angiotensin receptor neprilysin inhibitor therapy over a relatively short period of time. The number needed to treat in the high-risk category over 2 years to avoid 1 primary outcome is 15 and to avoid 1 death is 16. Even those in the lowest risk category have clinically worthwhile benefits: the number needed to treat over 2 years to avoid 1 primary outcome among these patients is 33 and to avoid 1 death is 63.

The benefit of LCZ696 over enalapril was apparent across the spectrum of risk defined by the EMPHASIS-HF risk score, and even within this subset of patients in NYHA functional classes I and II, the spread of risk for the primary composite outcome in the enalapril group was from 9.3 events per 100 patient-years (score 0 to 3 points) to 19.0 events per 100 patient-years (score 7 to 12 points). The equivalent rates for death were 6.50 and 11.52 per 100 patient-years, respectively. This means that even among patients with mild symptoms, treating 100 patients in the highest risk category for 2 years with LCZ696 instead of enalapril could postpone or prevent 3 or 4 primary outcomes and 2 deaths (applying the overall proportional risk reduction with LCZ696).

STUDY LIMITATIONS. Although the MAGGIC risk score was derived from a very large cohort of patients, the studies included were recruited between 1980 and 2006, and routine blood tests and natriuretic peptide concentrations were not available in the majority. However, although natriuretic peptides are powerful predictors of outcomes, they are still not available routinely at many sites and in many countries. Therefore, alternative means of risk stratification on the basis of readily available clinical information remain valuable. The MAGGIC risk score includes 1 point for a diagnosis of HF of 18 months or longer. The duration of HF in PARADIGM-HF was recorded as >1 to 2 years or >2 to 5 years, so for our main analysis, we assigned 1 point to patients with diagnoses of HF for 1 year or longer. However, we conducted a sensitivity analysis using a duration of HF of ≥2 years, with consistent findings.

Limitations inherent to secondary analyses must also be considered when interpreting these results; in particular, the analyses were not powered for this purpose. The MAGGIC score was developed to estimate the risk for all-cause mortality, whereas we have used this score to stratify patients in relation to risk for several other outcomes. However, as shown earlier, the MAGGIC score seemed to discriminate risk for these other outcomes. Moreover, we used an alternative score, the EMPHASIS-HF risk score, which was developed for the composite of cardiovascular death or HF hospitalization and which was specifically derived in patients with mild symptoms (NYHA functional class II only). This score does incorporate routine blood tests (hemoglobin and eGFR). Analysis of this score gave qualitatively similar findings to the MAGGIC score. Many other risk scores exist, each with strengths and weaknesses (10). Patients enrolled in the studies included in the MAGGIC meta-analyses did not require an elevated natriuretic peptide level, whereas patients enrolled in PARADIGM-HF did. However, we believe that there were many "PARADIGM-HF-like" patients among the broad spectrum of 39,372 patients included in the 30 studies used in the MAGGIC meta-analysis, and our analyses show that the MAGGIC score was predictive of outcomes in PARADIGM-HF patients. Our findings also apply only to selected patients with HFrEF able to tolerate an ACEI or ARB and without marked renal dysfunction, hypotension, or hyperkalemia.

CONCLUSIONS

Although most patients in the overall PARADIGM-HF population had mild symptoms, many were at high risk for adverse outcomes and obtained a large absolute benefit from the angiotensin receptor neprilysin inhibitor LCZ696, compared with enalapril, over a relatively short period of time. However, even patients at lower risk benefited from LCZ69.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients with HF may have minimal symptoms and little functional limitation when optimally treated yet remain at risk for adverse outcomes, including death. Prognostic variables such LVEF and comorbidities only weakly correlate with symptoms and functional capacity.

TRANSLATIONAL OUTLOOK: Additional research is needed to identify more consistent predictors of outcomes in patients with HF to inform assessments of the impact of treatment.

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APPENDIX For supplemental tables and figures, please see the online version of this article.