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CLINICAL RESEARCH

Outcomes and Effect of Treatment According to Etiology in HFrEF

An Analysis of PARADIGM-HF

Craig Balmforth, MBChB,[a] Joanne Simpson, MBChB, PhD,[a] Li Shen, MBChB, PhD,[a] Pardeep S. Jhund, MBChB, MSc, PhD,[a] Martin Lefkowitz, MD,[b] Adel R. Rizkala, PharmD,[b] Jean L. Rouleau, MD,[c] Victor Shi, MD,[b] Scott D. Solomon, MD,[d] Karl Swedberg, MD, PhD,[e] Michael R. Zile, MD,[f] Milton Packer, MD,[g] John J.V. McMurray, MBChB, MD[a]

ABSTRACT

OBJECTIVES The purpose of this study was to compare outcomes (and the effect of sacubitril/valsartan) according to etiology in the PARADIGM-HF (Prospective comparison of angiotensin-receptor-neprilysin inhibitor [ARNI] with angiotensin-converting-enzyme inhibitor [ACEI] to Determine Impact on Global Mortality and morbidity in Heart Failure) trial.

BACKGROUND Etiology of heart failure (HF) has changed over time in more developed countries and is also evolving in non-Western societies. Outcomes may vary according to etiology, as may the effects of therapy.

METHODS We examined outcomes and the effect of sacubtril/valsartan according to investigator-reported etiology in PARADIGM-HF. The outcomes analyzed were the primary composite of cardiovascular death or HF hospitalization, and components, and death from any cause. Outcomes were adjusted for known prognostic variables including N terminal pro-B type natriuretic peptide.

RESULTS Among the 8,399 patients randomized, 5,036 patients (60.0%) had an ischemic etiology. Among the 3,363 patients (40.0%) with a nonischemic etiology, 1,595 (19.0% of all patients; 47% of nonischemic patients) had idiopathic dilated cardiomyopathy, 968 (11.5% of all patients; 28.8% of nonischemic patients) had a hypertensive cause, and 800 (9.5% of all patients, 23.8% of nonischemic patients) another cause (185 infective/viral, 158 alcoholic, 110 valvular, 66 diabetes, 30 drug-related, 14 peripartum-related, and 237 other). Whereas the unadjusted rates of all outcomes were highest in patients with an ischemic etiology, the adjusted hazard ratios (HRs) were not different from patients in the 2 major nonischemic etiology categories; for example, for the primary outcome, compared with ischemic (HR: 1.00), hypertensive 0.87 (95% confidence interval [CI]: 0.75 to 1.02), idiopathic 0.92 (95% CI: 0.82 to 1.04) and other 1.00 (95% CI: 0.85 to 1.17). The benefit of sacubitril/valsartan over enalapril was consistent across etiologic categories (interaction for primary outcome; $p = 0.11$).

CONCLUSIONS Just under one-half of patients in this global trial had nonischemic HF with reduced ejection fraction, with idiopathic and hypertensive the most commonly ascribed etiologies. Adjusted outcomes were similar across etiologic categories, as was the benefit of sacubitril/valsartan over enalapril. (Efficacy and Safety of LCZ696 Compared to Enalapril on Morbidity and Mortality of Patients With Chronic Heart Failure; NCT01035255) (J Am Coll Cardiol HF 2019;7:457–65)

From the [a]BHF Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom; [b]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey; [c]Montreal Heart Institute and University of Montreal, Montreal, Quebec, Canada; [d]Brigham and Women's Hospital, Boston, Massachusetts; [e]University of Gothenburg, Gothenburg, Sweden; [f]Medical University of South Carolina and Ralph H. Johnson Veterans Administration Medical Center, Charleston, South Carolina; and the [g]Baylor University Medical Center, Dallas, Texas. Dr. Jhund has received personal fees from Novartis. Drs. Lefkowitz and Rizkala are employees of Novartis Pharmaceuticals. Dr. Rizkala owns Novartis stock. Dr. Rouleau has received personal fees from Novartis

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ABBREVIATIONS AND ACRONYMS

ACEI = angiotensin-converting enzyme inhibitor

AF = atrial fibrillation

CV = cardiovascular

EF = ejection fraction

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

LVEF = left ventricular ejection fraction

The etiology of heart failure (HF) has changed over time in more developed countries and is also evolving in less developed and other non-Western societies (1–9). In the first report from the Framingham Heart Study, initiated in 1949 and published in 1971, hypertension was the most common etiology in patients recruited in the United States, although in that report HF was not subclassified by ejection fraction (EF) phenotype (1). More recently, in most reports, coronary heart disease has become the predominant cause of HF with reduced EF (HFrEF) (1–11). An epidemiologic transition has also occurred in Eastern Europe, Asia, and Africa from hypertension and rheumatic valvular disease to coronary heart disease (1–11).

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Etiology is important for a number of reasons. First, outcome may vary according to etiology with nonischemic causes purported to carry a better prognosis than HF of ischemic origin (12,13). Second, specific etiologies may be an indication for specific therapies (e.g., bypass surgery for coronary artery disease) (14). Third, and more controversially, it has been suggested that the effectiveness of certain treatments for HFrEF may be modified by etiology (e.g., implantable cardiac defibrillator therapy in nonischemic cardiomyopathy and cardiac resynchronization therapy in ischemic compared with nonischemic HFrEF) (15,16).

To examine etiology in a contemporary and globally representative sample of patients with HFrEF, we examined investigator-reported cause of HF in the PARADIGM-HF (Prospective Comparison of angiotensin-receptor-neprilysin inhibitor [ARNI] With angiotensin-converting-enzyme inhibitor [ACEI] to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial which enrolled 8399 patients in 47 countries on 6 continents (17–19). We also examined outcomes according to etiology, adjusting for a more extensive range of other prognostic variables, including natriuretic peptides, than in prior studies. Lastly, we also examined the effect of the angiotensin-receptor-neprilysin inhibitor sacubitril/valsartan compared with the ACEI enalapril, according to etiology.

METHODS

PATIENTS AND PROCEDURES. The design and primary results of PARADIGM-HF have been reported (17–19). Briefly, PARADIGM-HF was a randomized, double-blind comparison of sacubitril/valsartan with enalapril in patients with chronic HF and HFrEF. Eligibility criteria at screening included New York Heart Association (NYHA) functional class II to IV, left ventricular ejection fraction (LVEF) ≤40 [changed to ≤35 by amendment], and elevated natriuretic peptides. Exclusion criteria at screening included symptomatic hypotension or systolic blood pressure <100 mm Hg, estimated glomerular filtration rate <30 ml/min/1.73 m^2, and potassium >5.2 mmol/l.

At trial entry, ongoing treatment with ACEI or angiotensin receptor blocker (ARB) was stopped and patients entered 2 sequential run-in periods, first receiving enalapril 10 mg twice daily for 2 weeks followed by sacubitril/valsartan for an additional 4 to 6 weeks, uptitrated from 49/51 mg to 97/103 mg twice daily. Patients tolerating both drugs at these target doses were randomly assigned to double-blind therapy with sacubitril/valsartan or enalapril in a 1:1 ratio.

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The trial was approved by the ethics committees at each participating institution and all patients provided written informed consent.

INVESTIGATOR-REPORTED ETIOLOGY. The etiology of HF was collected by means of structured questions on the trial case report form. Investigators were first asked whether the primary etiology was ischemic or nonischemic. If the answer nonischemic was checked, investigators were then asked to specify from a number of options (listed in the following order): primary valvular (specify valve and surgery), alcoholic, hypertensive, idiopathic, peripartum, infectious cardiomyopathy, viral cardiomyopathy, diabetic, drug induced (specify type of drug), and "other" (please specify). For the purposes of this analysis, patients were categorized as ischemic or nonischemic, with nonischemic etiology further subcategorized into idiopathic, hypertensive and other, because the numbers of cases in "other" were individually too few to allow robust analysis.

OUTCOMES. The primary endpoint in PARADIGM-HF was a composite of cardiovascular (CV) death or HF hospitalization. In this study, we investigated the association between etiology and the risk of the primary outcome, each of its components, and all-cause mortality. All endpoints were adjudicated by a clinical endpoint committee in a blinded fashion. We also compared the effects of the randomized treatment on these outcomes, according to etiology, as described below.

Statistical analyses. Baseline characteristics are presented as frequencies and percentages for categorical variables and means with SD or medians with interquartile range for continuous variables. Differences in baseline characteristics were tested using chi-square test for categorical variables and analysis of variance or Kruskal-Wallis test for continuous variables.

Incidence rates for each outcome of interest are presented per 100 person-years of follow-up. Event rates in each etiologic category were estimated by the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazards regression models were used to compare hazard ratios (HRs) with 95% confidence intervals according to etiology. In multivariable models, the HR was adjusted for the following baseline characteristics: age, sex, race, region, systolic blood pressure, heart rate, EF, NYHA functional class, history of HF hospitalization, duration of HF, atrial fibrillation (AF), body mass index, prior stroke, creatinine, randomized treatment (sacubitril/valsartan or enalapril), and log N terminal pro-B-type natriuretic peptide.

Analyses were performed using Stata version 13 (Stata Corp., College Station, Texas) and SAS version 9.4 (SAS Institute Inc., Cary, North Carolina). All p values are 2-sided, and a $p < 0.05$ was considered significant.

RESULTS

Of the total 8,399 patients randomized, 5,036 patients (60.0%) had an ischemic etiology and 3,363 patients (40.0%) had a nonischemic etiology. Among those with a nonischemic etiology, 1,595 patients (19.0% of all patients; 47% of nonischemic patients) were reported to have an idiopathic dilated cardiomyopathy, 968 (11.5% of all patients; 28.8% of nonischemic patients) a hypertensive cause and 800 (9.5% of all patients, 23.8% of nonischemic patients) another cause (185 infective/viral, 158 alcoholic, 110 valvular, 66 diabetes, 30 drug-related, 14 peripartum related, and 237 "other").

BASELINE CHARACTERISTICS. The clinical characteristics of the patients categorized by etiology are shown in Table 1. Patients with an ischemic (and hypertensive) etiology were older than those in the other nonischemic categories. Patients with an ischemic etiology were also more likely to be male and Caucasian. Nonischemic idiopathic patients were more frequently female and Asian (and nonischemic hypertensive patients were also more frequently female and black and less often Asian) than ischemic patients. Nonischemic patients were more often from Latin American and Asia, compared with ischemic patients.

LVEF was slightly but significantly lower in patients with idiopathic dilated cardiomyopathy compared to patients with an ischemic etiology and a hypertensive cause; however, natriuretic peptide concentrations did not differ meaningfully among the various etiologic categories.

History of myocardial infarction was more frequent in the ischemic group and hypertension and AF were each more common in the hypertensive etiology category. Conversely, history of diabetes was less frequent in the idiopathic group.

Investigator-reported etiology seemed to vary by geographic region. Ischemic etiology was most frequent in Central/Eastern Europe (70%) and least common in Latin America (43%) (Online Table 1). Among the nonischemic etiologies, hypertensive etiology was most common in Latin America (21% of all cases of HFrEF) and least common in the Asia-Pacific Region (6%), whereas idiopathic etiology was most common in the Asia Pacific Region (28%) and least common in Central/Eastern Europe and North

TABLE 1 Baseline Characteristics According to Investigator-Reported Heart Failure Etiology

		Nonischemic (N = 3,363)			
	Ischemic (n = 5,036)	Hypertensive (n = 968)	Idiopathic (n = 1,595)	Other (n = 800)	p Value
Age, yrs	65.7 ± 10.2	64.7 ± 11.5	60.0 ± 12.3	58.3 ± 12.6	<0.001
Female	969 (19.2)	283 (29.2)	373 (29.2)	207 (25.9)	<0.001
Race or ethnic group					
White	3,586 (71.2)	607 (62.7)	878 (55.1)	473 (59.1)	<0.001
Black	110 (2.2)	117 (12.1)	97 (6.1)	104 (13.0)	
Asian	891 (17.7)	89 (9.2)	416 (26.1)	113 (14.1)	
Other	449 (8.9)	155 (16.0)	204 (12.8)	110 (13.8)	
Region					
North America	381 (7.6)	65 (6.7)	82 (5.1)	74 (9.3)	<0.001
Latin America	617 (12.3)	301 (31.1)	308 (19.3)	207 (25.9)	
Western Europe and other	1,188 (23.6)	231 (23.9)	384 (24.1)	248 (31.0)	
Central Europe	1,987 (39.5)	282 (29.1)	399 (25.0)	158 (19.8)	
Asia-Pacific	863 (17.1)	89 (9.19)	422 (26.46)	113 (14.12)	
SBP, mm Hg	121.9 ± 15.2	126.6 ± 15.1	118.4 ± 15.0	117.6 ± 14.9	<0.001
HR, beats/min	71.6 ± 11.8	74.3 ± 12.3	73.1 ± 11.8	73.1 ± 13.3	<0.001
BMI	28.1 ± 5.3	29.4 ± 5.8	27.6 ± 5.9	28.2 ± 5.6	<0.001
Serum creatinine, mg/dl	1.15 ± 0.3	1.10 ± 0.3	1.08 ± 0.3	1.10 ± 0.3	<0.001
Clinical features of HF					
EF, %	30 ± 6.1	30.4 ± 6.0	28.0 ± 6.2	28.3 ± 6.5	<0.001
BNP, pg/ml	254 (159–458)	242 (146–463)	251 (142–533)	257 (139–481)	
NT-pro-BNP, pg/ml	1,543 (850–2,981)	1,793 (1,027–3,702)	1,682 (910–3,595)	1,791 (933–3,502)	
NYHA functional class					<0.001
I	201 (4.0)	53 (5.5)	82 (5.1)	53 (6.6)	
II	3,426 (68.0)	686 (70.9)	1,210 (75.9)	597 (74.6)	
III	1,359 (27.0)	220 (22.7)	295 (18.5)	144 (18.0)	
IV	41 (0.8)	8 (0.8)	7 (0.4)	4 (0.5)	
Missing data	9 (0.2)	1 (0.1)	1 (0.1)	2 (0.25)	
Medical history					
Hypertension	3,784 (75.1)	955 (98.66)	744 (48.5)	427 (53.4)	<0.001
Diabetes	1,980 (39.3)	307 (31.7)	392 (24.6)	228 (28.5)	<0.001
Atrial fibrillation	1,746 (34.7)	439 (45.4)	561 (35.2)	345 (43.1)	<0.001
Hospitalization for HF	3,111 (61.8)	586 (60.5)	1,040 (65.2)	537 (67.1)	0.002
Myocardial infarction	3,537 (70.2)	40 (4.1)	31 (1.9)	26 (3.3)	<0.001
Stroke	515 (10.2)	82 (8.5)	82 (5.1)	46 (5.8)	<0.001
Pre-trial use of ACE inhibitor	3,964 (78.7)	695 (71.8)	1,227 (76.9)	646 (80.8)	<0.001
Pre-trial use of ARB	1,089 (21.6)	277 (28.6)	371 (23.3)	155 (19.4)	<0.001
Prior PCI	1,674 (33.2)	34 (3.5)	55 (3.5)	38 (4.8)	<0.001
Prior CABG	1,274 (25.3)	7 (0.7)	8 (0.5)	14 (1.8)	<0.001
Treatments at randomization					
Diuretic	3,932 (78.1)	803 (83.0)	1,339 (84.0)	664 (83.0)	<0.001
Digitalis	1,252 (24.9)	309 (31.9)	653 (40.9)	325 (40.6)	<0.001
Beta-blocker	4,695 (93.2)	882 (91.1)	1,502 (94.2)	727 (91.50)	0.008
Mineralocorticoid antagonist	2,643 (52.5)	522 (53.9)	1,002 (62.8)	504 (63.0)	<0.001
Statin	3,560 (70.7)	369 (38.1)	556 (34.9)	238 (29.8)	<0.001
Antiplatelet	3,476 (69.0)	388 (40.1)	587 (36.8)	285 (35.6)	<0.001
ICD	832 (16.5)	71 (7.33)	222 (13.9)	118 (14.8)	<0.001
CRT	324 (6.4)	33 (3.4)	146 (9.2)	71 (8.9)	<0.001

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

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; BNP = B-type natriuretic peptide; CABG = coronary artery bypass graft; CRT = cardiac resynchronization therapy; EF = ejection fraction; HF = heart failure; HR = heart rate; ICD = implantable cardioverter-defibrillator; NT-proBNP = N terminal-pro-B-type natriuretic peptide; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; SBP = systolic blood pressure.

TABLE 2 Event Rates and Risks of the Primary Composite Endpoint of CV Mortality or HF Hospitalization, CV Mortality, HF Hospitalization, and All-Cause Mortality According to HF Etiology

	N	Events	Crude Rate per 100 Patient-Years	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	p Value
Primary composite outcome						
Ischemic	5,036	1,272	12.31 (11.66–13.01)	1.00 (reference)	1.00 (reference)	
Nonischemic						
Hypertensive	968	211	10.41 (9.09–11.91)	0.85 (0.73–0.98)	0.87 (0.75–1.02)	0.082
Idiopathic	1,595	357	10.95 (9.87–12.15)	0.89 (0.79–1.00)	0.92 (0.82–1.04)	0.207
Other	800	191	11.96 (10.37–13.78)	0.97 (0.83–1.13)	1.00 (0.85–1.17)	0.973
CV mortality						
Ischemic	5,036	789	7.07 (6.60–7.58)	1.00 (reference)	1.00 (reference)	
Nonischemic						
Hypertensive	968	127	5.86 (4.92–6.97)	0.83 (0.68–1.00)	0.87 (0.72–1.06)	0.168
Idiopathic	1,595	228	6.57 (5.77–7.48)	0.93 (0.80–1.07)	0.96 (0.82–1.12)	0.616
Other	800	107	6.16 (5.10–7.44)	0.87 (0.71–1.07)	0.94 (0.76–1.16)	0.581
HF hospitalization						
Ischemic	5,036	725	7.02 (6.53–7.55)	1.00 (reference)	1.00 (reference)	
Nonischemic						
Hypertensive	968	122	6.02 (5.04–7.19)	0.86 (0.71–1.04)	0.91 (0.74–1.11)	0.343
Idiopathic	1,595	221	6.78 (5.94–7.73)	0.96 (0.83–1.12)	1.02 (0.87–1.20)	0.770
Other	800	127	7.95 (6.68–9.46)	1.13 (0.93–1.36)	1.13 (0.93–1.39)	0.205
All-cause mortality						
Ischemic	5,036	982	8.79 (8.26–9.36)	1.00 (reference)	1.00 (reference)	
Nonischemic						
Hypertensive	968	163	7.51 (6.44–8.76)	0.85 (0.72–1.01)	0.89 (0.75–1.06)	0.186
Idiopathic	1,595	268	7.72 (6.85–8.71)	0.88 (0.77–1.01)	0.93 (0.81–1.08)	0.349
Other	800	133	7.66 (6.46–9.07)	0.87 (0.73–1.05)	0.95 (0.79–1.15)	0.623

*Adjusted for age, sex, race, region, systolic blood pressure, heart rate, ejection fraction, NYHA functional class, history of HF hospitalization, duration of HF, atrial fibrillation, body mass index, prior stroke, creatinine, randomized treatment, and log NT-proBNP.

CI = confidence interval; CV = cardiovascular; other abbreviations as in Table 1.

America (both 14%). However, because the numbers in some of these subgroups were small, these analyses may not be robust, and the apparent variation reported requires further investigation in other datasets.

Treatment at baseline varied by etiology with digoxin use much more common in idiopathic patients (40.9%) compared to those with an ischemic etiology (24.9%).

Statin and antiplatelet therapy was used much more commonly in those with an ischemic etiology compared to all other etiologic categories.

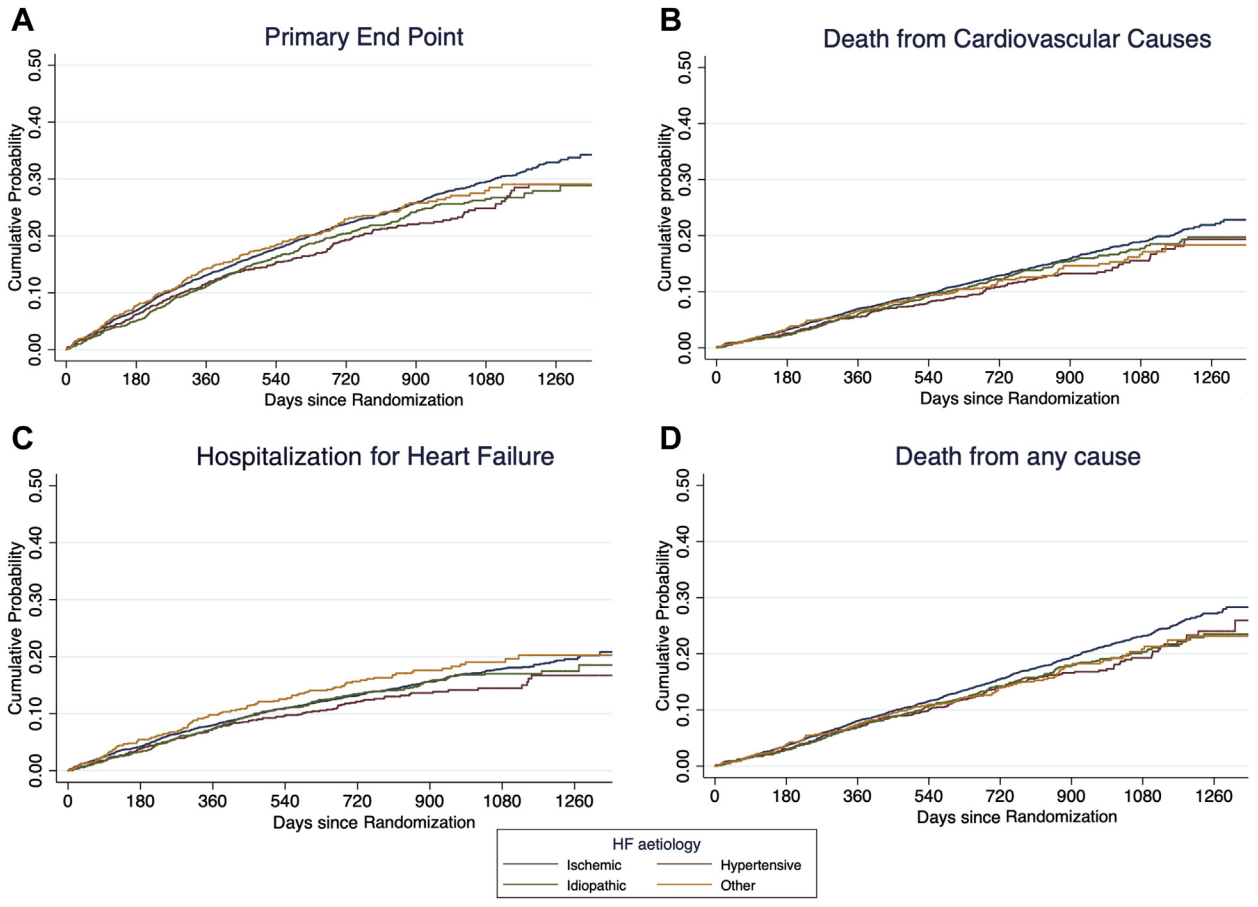
OUTCOMES ACCORDING TO ETIOLOGY. The rate of the primary composite outcome, its components and all-cause mortality are shown in **Table 2 and Figure 1**. Although, the rate of all of these events was highest in patients with an ischemic etiology, the adjusted HR was not different from patients in the 2 major nonischemic etiology categories (idiopathic and hypertensive). Repeating the analysis using any of history of myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, unstable angina, or angina to define the ischemic subgroup, instead of investigator-reported ischemic etiology, gave almost identical results (Online Table 2).

EFFECT OF SACUBITRIL/VALSARTAN ACCORDING TO ETIOLOGY. The effect of sacubitril/valsartan, compared to enalapril, on the primary composite endpoint and CV death is shown in the **Central Illustration**. The benefit of sacubitril/valsartan was consistent across the etiologic categories (interaction p value for primary endpoint = 0.11; for CV death = 0.55).

DISCUSSION

In the largest and most globally representative trial to date in patients with HFrEF, we found that the most common etiology was ischemic heart disease (in 60% of participants), although this varied with sex, race, and geographic region. Gheorghiade et al. (20) reported in a review of 24 trials published between 1986 and 2005 that 62% of patients had an investigator-reported ischemic etiology and this coronary disease and in more recent trials the proportion has varied between 65% and 70% in studies with a high

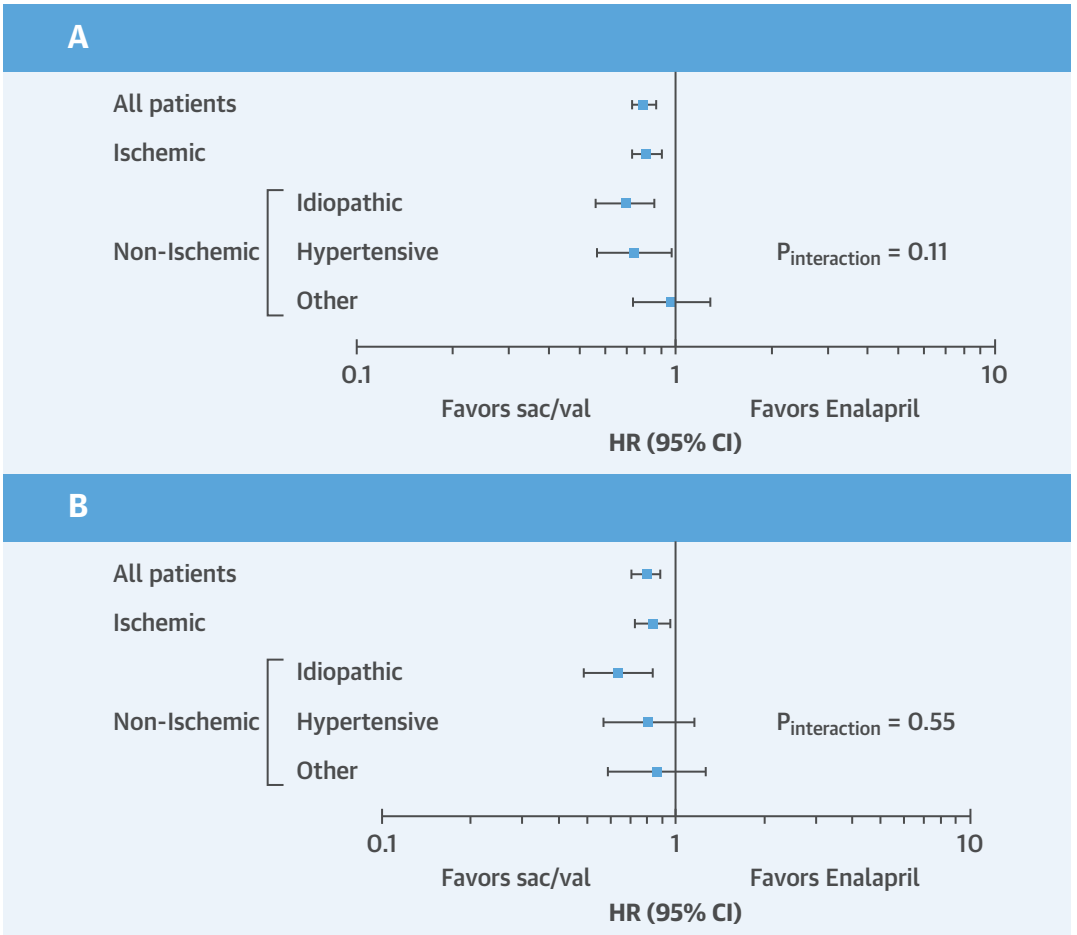
FIGURE 1 Cumulative Incidence of Outcome According to Etiology (Ischemic, Idiopathic, Hypertensive, and Other)



(A) Cumulative incidence of primary composite outcome, **(B)** cardiovascular mortality, **(C)** heart failure hospitalization, and **(D)** all-cause mortality according to etiology (ischemic, idiopathic, hypertensive, and other).

proportion of European patients (especially from Central/Eastern Europe) to 56% in another large global trial with significant numbers of patients from Asia and Latin America (19-23). Of the nonischemic etiologies reported, by far the largest category was idiopathic (47% of nonischemic cases) and another 29% of cases were ascribed a hypertensive etiology. Few prior studies have subcategorized etiology beyond ischemic and nonischemic. Felker et al. (24) studied 1,230 patients who underwent endomyocardial biopsy between December 1982 and December 1997 at Johns Hopkins Hospital, as part of an evaluation for HF due to unexplained cardiomyopathy. In that highly selected cohort, 616 patients were diagnosed with an idiopathic cardiomyopathy (24) and other etiologies were identified in much smaller number of patients including myocarditis (n = 111), HIV infection (n = 45), hypertension (n = 49), peripartum cardiomyopathy (n = 51), infiltrative myocardial disease (n = 59), connective tissue disease (n = 39), substance abuse (n = 37), doxorubicin therapy (n = 15), and other (n = 117); in addition, 91 patients had (unexpected) ischemic heart disease. In a more representative study, Pecini et al. (25) examined data from 3,078 hospitalized patients screened between 2001 and 2002 for inclusion in a clinical trial in Denmark. Overall, 1,924 (63%) of these patients had an LVEF <45%. Six major etiologic groups were identified by investigators: ischemic heart disease (n = 925; 48.1%), idiopathic dilated cardiomyopathy (n = 223; 11.6%), hypertension (n = 204; 10.6%), valvular heart disease (n = 165; 8.6%), other (n = 183; 9.5%), and unknown/mixed (n = 224; 11.6%). Our findings are broadly in keeping with these Danish

CENTRAL ILLUSTRATION **Effect of Sacubitril/Valsartan According to Etiology of Heart Failure**



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Effect of randomized therapy with sacubitril/valsartan (sac/val) or enalapril on the primary composite outcome **(A),** or cardiovascular mortality **(B)** according to etiology (ischemic, idiopathic, hypertensive, and other). There was no significant treatment by etiology interaction. CI = confidence interval; HR = hazard ratio.

data, although an ischemic etiology was more common, overall, and valvular etiology less frequent, in participants in PARADIGM-HF.

In keeping with prior reports, patients in PARADIGM-HF with an ischemic etiology had a higher crude incidence of adverse outcomes (12,13,25). However, in contrast to previous findings, when adjusted for other prognostic variables, including we believe for the first time natriuretic peptides, outcomes in PARADIGM-HF did not differ by etiology (at least for the 3 largest categories—ischemic, idiopathic, and hypertensive). In the 2 earlier studies mentioned above, the multivariable models used adjusted for few variables and did not include natriuretic peptides in either case. Moreover, evidence-based life-saving therapies were not reported (Felker et al. [24]) or underused (Pecini et al. [25]) in the aforementioned studies, which were conducted before or at the beginning of the beta-blocker era in management of HFrEF. Consequently, it would appear that in contemporary practice, mortality and morbidity are broadly similar across the most common HFrEF etiologies when other prognostic variables are adjusted for. We cannot be certain whether this is also true for the less common etiologies and it remains possible that

among patients labelled as having an idiopathic dilated cardiomyopathy there may be subgroups of patients defined by genetic or other variables that fare better or worse than the rest.

In a developing era of precision medicine, more detailed phenotyping (and genotyping) of patients has been advocated to target treatments to patients more likely to benefit (26). Etiology is one aspect of phenotyping which may help determine choice of therapy. Surgical revascularization improves outcomes in selected patients with coronary artery disease and implantable cardioverter therapy may be less effective in patients with nonischemic dilated cardiomyopathy (14,15). Other biomarkers and comorbidities may identify patients more or less likely to benefit from specific drug therapies; for example, ivabradine is effective in patients with a higher heart rate and beta-blockers may be less effective in patients in AF (23,27). In the acute setting, the efficacy and safety of intravenous milrinone appeared to be modified by etiology– with worse treatment-related outcomes in patients with an ischemic etiology and better outcomes in nonischemic patients (28). On the other hand, other treatments such as ACEIs, ARBs and mineralocorticoid receptor antagonists appear equally effective across all phenotypic subgroups examined. We have previously reported that sacubitril/valsartan is similarly effective in subgroups defined by comorbidity and biomarkers (blood pressure, heart rate, natriuretic peptides, and estimated glomerular filtration rate) (19,29-32). Here we show a benefit irrespective of etiology (at least across the major etiologic categories identified by investigators).

STUDY LIMITATIONS. As with any study of this type, there are limitations. The analyses conducted were not pre-planned and the patients analyzed were those enrolled on a clinical trial rather than an unselected community cohort. Etiology was investigator-reported and no specific instructions were provided as to how to identify etiology. Patients may not have been exhaustively investigated for specific causes of HF, and some degree of etiologic misclassification will have occurred. The difficulties of ascribing a coronary etiology, even with angiography, have been discussed (33). It was not possible to examine outcomes in nonischemic etiologic categories other than the idiopathic and hypertensive groups because of small numbers. Similarly, it would have been of interest to study subcategories of CV mortality according to etiology, but this was also impossible because of the small numbers of events.

CONCLUSIONS

In summary, in PARADIGM-HF, the most common HFrEF etiology was ischemic heart disease (in 60% of participants). Of the nonischemic etiologies reported, the largest category was idiopathic (47% of nonischemic cases) and another 29% of patients were ascribed a hypertensive etiology. When adjusted for other prognostic variables, including natriuretic peptides, outcomes were similar across etiologic categories. The benefit of sacubitril/valsartan over enalapril was not modified by etiology.

ADDRESS FOR CORRESPONDENCE: Dr. John J.V. McMurray, British Heart Foundation Cardiovascular Research Centre, University of Glasgow, 126 University Place, Glasgow G12 8TA, United Kingdom. E-mail: john.mcmurray@glasgow.ac.uk.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Although globally an ischemic etiology is the most commonly reported cause of HFrEF, approximately 40% of cases have a nonischemic etiology. How outcomes vary according to etiology in contemporary cohorts and whether etiology modifies response to therapy in HFrEF is of interest. Although patients with an investigator-reported ischemic etiology had worse outcomes than those with a nonischemic etiology, neither the unadjusted nor adjusted risk was significantly different between these 2 groups. Outcomes did not differ, either, between the 2 major nonischemic subgroups; those being hypertensive and idiopathic etiology. The benefit of sacubitril/valsartan, compared with enalapril, was consistent across etiologic category.

TRANSLATIONAL OUTLOOK: Although there may be some misclassification of cause of HF in studies using investigator-reported etiology, the present analysis suggests no major difference in outcomes according to etiology in patients treated with contemporary therapies and that etiology does not modify the response to sacubitril/valsartan. Once HFrEF is established, left ventricular systolic dysfunction and the resultant maladaptive compensatory responses, rather than underlying cause, may become the main determinants of outcome in patients. Treatments targeted at these pathophysiologic abnormalities may also be equally effective, irrespective of etiology.

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KEY WORDS angiotensin receptor blocker, angiotensin-converting enzyme inhibitor, etiology, heart failure, natriuretic peptides, neprilysin, treatment

APPENDIX For supplemental tables, please see the online version of this paper.