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ORIGINAL RESEARCH

Lactate Dehydrogenase and Outcomes in Patients With HF and Reduced Ejection Fraction

Insights From GALACTIC-HF

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ABSTRACT

BACKGROUND Lactate dehydrogenase (LDH) is a cytoplasmic enzyme found in most cells. Increased LDH levels are a nonspecific measure of cellular injury and may be prognostically important in heart failure (HF).

OBJECTIVES This study aims to assess the relationship between LDH and clinical characteristics and outcomes in heart failure with reduced ejection fraction (HFrEF).

METHODS Using data from GALACTIC-HF, a phase 3, randomized, placebo-controlled trial evaluating the efficacy and safety of omecamtiv mecarbil (OM) in patients with HFrEF, the relationship between LDH and clinical outcomes was analyzed. The incremental value of LDH added to a validated prognostic model (PREDICT-HF) was also calculated using Harrell's C statistic, integrated discrimination index (IDI), and net reclassification index (NRI).

RESULTS In GALACTIC-HF, baseline LDH data were available for 8,179 patients, including 6,138 outpatients. Patients with higher LDH were more frequently female and had worse HF status. They were also more likely to have elevated serum creatinine, liver enzymes, creatine kinase, NT-proBNP, and high-sensitivity troponin I. Compared with patients in the lowest LDH (Q1: 155 U/L [25th-75th percentile: 144-163 U/L]), the HRs for the primary outcome (first HF event or cardiovascular death) were Q2: 183 U/L (25th-75th percentile: 177-188 U/L); HR: 1.15 [95% CI: 1.02-1.31 Hazard ratio does not have unit]; Q3: 207 U/L (25th-75th percentile: 201-215 U/L); HR: 1.39 [95% CI: 1.23-1.58]; and Q4: 253 U/L (25th-75th percentile: 236-280 U/L); HR: 1.84 [95% CI: 1.62-2.08], respectively. Even after adjustment, elevated LDH remained independently associated with higher HR. When added to the PREDICT-HF risk model, baseline LDH improved Harrell's C statistic, IDI, and NRI for the primary outcome.

CONCLUSIONS In GALACTIC-HF, higher LDH levels were independently associated with a higher risk of clinical outcomes in HFrEF. (Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure [GALACTIC-HF]; NCT02929329; EudraCT number: 2016-002299-28) (JACC Heart Fail. 2026;■:102900)

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ABBREVIATIONS AND ACRONYMS

eGFR = estimated glomerular filtration rate

HF = heart failure

HFrEF = heart failure and reduced ejection fraction

hs-TnI = high-sensitivity troponin I

IDI = integrated discrimination improvement

LDH = lactate dehydrogenase

LVEF = left ventricular ejection fraction

NRI = net reclassification index

NT-proBNP = N-terminal pro-B-type natriuretic peptide

OM = omecamtiv mecarbil

Lactate dehydrogenase (LDH), a cytoplasmic enzyme found in most cells, catalyzes the forward and backward conversion of pyruvate to lactate.[1] Tissue LDH concentrations are hundreds of times higher than those in plasma, and loss of cellular integrity results in elevated circulating concentrations of LDH.[2] Consequently, increased LDH levels have historically been used to diagnose specific organ damage, such as myocardial infarction (before the introduction of more cardiac-specific biomarkers), due to the release of intracellular enzymes into the bloodstream after tissue injury.[3,4] LDH has also been recognized as a nonspecific but valuable marker of cellular injury in critically ill patients and a poor prognostic finding in these individuals.[5-7] LDH concentrations in body cavity fluids such as pleural, pericardial, and peritoneal effusions increase in response to inflammation or infection,[8,9] and in oncology LDH is an established surrogate of tumor burden, hypoxic metabolism, and proliferation.[10-12] These examples collectively highlight the utility of LDH as a widely available, inexpensive biomarker that reflects the extent of tissue injury and breakdown, systemic inflammation, and cell turnover in diverse clinical contexts.

Patients with heart failure and reduced ejection fraction (HFrEF) often exhibit concurrent hepatic and pulmonary congestion, kidney dysfunction, systemic inflammation, and skeletal muscle wasting, as well as cardiac dysfunction, all of which may contribute to elevated LDH levels, suggesting LDH may serve as an integrative biomarker of cumulative tissue injury and organ dysfunction in heart failure (HF). Previous studies have mainly focused on LDH levels in the context of acute HF, suggesting that elevated LDH reflects tissue hypoperfusion and organ congestion.[13,14] However, to date, no large-scale clinical trial has directly evaluated the prognostic or diagnostic value of LDH in patients with chronic HF. Therefore, we hypothesized that LDH concentration would be associated with fatal and nonfatal outcomes in patients with HFrEF. We tested this hypothesis in the GALACTIC-HF (Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure; NCT02929329) trial, one of the largest contemporary studies of patients with symptomatic HFrEF.[15-17] We also examined the association of LDH with hypoperfusion/preshock in these patients (consistent with stage C2D).[18]

METHODS

GALACTIC-HF STUDY DESIGN. The design and results of GALACTIC-HF, a global, phase 3, double-blind, placebo-controlled, randomized clinical trial, have been published.[15-17] In brief, the efficacy and safety of omecamtiv mecarbil (OM) vs placebo were evaluated in 8,232 patients with symptomatic HFrEF (NYHA functional class II-IV and left ventricular ejection fraction [LVEF] ≤35%). The study included both hospitalized patients and outpatients with a recent HF-related hospitalization or emergency department visit.

All participants were required to be on guideline-directed medical therapy and to have elevated natriuretic peptide levels: N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥400 pg/mL or ≥1,200 pg/mL in atrial fibrillation; B-type natriuretic peptide ≥125 pg/mL or ≥375 pg/mL in atrial fibrillation. Key exclusion criteria included hemodynamic or clinical instability requiring mechanical or intravenous therapy, systolic blood pressure <85 mm Hg or >140 mm Hg, diastolic blood pressure >90 mm Hg, and an estimated glomerular filtration rate (eGFR) <20 mL/min/1.73 m^2.

All participants provided written informed consent, and the study was approved by relevant ethics committees. A total of 24 patients were excluded from the primary analysis due to protocol violations, resulting in 8,232 patients in the final analysis set.

LDH Measurements. LDH levels were measured at randomization, at 48 weeks, and then every 48 weeks

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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until the completion of the study. All samples were analyzed at a central laboratory. The upper limit of normal was 250 U/L.

Definition of hypoperfusion/preshock. To evaluate the association between LDH and "hypoperfusion/preshock" in patients with HFrEF (consistent with stage C2D),[18,19] the following hypoperfusion/preshock score was used (with 1 point for each item, and hypoperfusion/preshock defined as a total score of ≥2 points): 1) Hypotension (systolic blood pressure <90 mm Hg or mean arterial pressure <65 mm Hg); 2) severe functional limitation (NYHA functional class III or IV); 3) elevated creatinine level (serum creatinine >1.5 mg/dL); and 4) elevated liver enzymes (aspartate aminotransferase >2 × upper normal limit [31 U/L] or alanine aminotransferase >2 × upper normal limit [33 U/L] or total bilirubin >2 × upper normal limit [1.23 mg/dL]).

TRIAL OUTCOMES. The primary outcome of this study was a composite of time to a first HF event or cardiovascular death. Secondary outcomes included a first HF event, cardiovascular death, and all-cause death. A HF event was defined as an urgent clinic visit, emergency department visit, or hospitalization for worsening HF requiring treatment intensification beyond an adjustment in oral diuretic therapy.

All clinical events were adjudicated by an independent external Clinical Events Committee (Duke Clinical Research Institute) using standardized definitions as specified in the publication of the primary results. In the present analysis, we also examined the composite of HF hospitalization and cardiovascular death because this was the outcome previously validated in the prognostic models used PREDICT-HF (PARADIGM Risk of Events and Death in the Contemporary Treatment of Heart Failure).

STATISTICAL ANALYSIS. Baseline characteristics were summarized as mean ± SD, median (25th-75th percentile), or counts with percentages. Differences in baseline characteristics were assessed using the Cochran-Armitage trend test for binary variables, the Cochran-Mantel-Haenszel test for categorical variables, and the Jonckheere-Terpstra test for continuous variables. The incidence rates for each outcome were reported per 100 patient-years.

The associations between LDH and clinical outcomes were evaluated using Kaplan-Meier estimates and Cox proportional hazards models, with the lowest LDH quartile (Q1) serving as the reference. The models were stratified according to geographic region (and randomization setting in the overall population), and adjusted for trial group, age, sex, NYHA functional class III or IV, systolic blood pressure, body mass index, LVEF, history of myocardial infarction, type 2 diabetes, atrial fibrillation or flutter at screening, race, log-transformed NT-proBNP, log-transformed hemoglobin, log-transformed high-sensitivity troponin I (hs-TnI), log-transformed total bilirubin, log-transformed serum creatinine, and log-transformed creatine kinase.

Proportional hazards assumptions were evaluated using Schoenfeld residuals and log-log survival plots, which showed no meaningful violation for LDH quartiles. Competing-risks regression with the Fine-Gray method was also used to assess outcomes other than all-cause death in the overall population and outpatients. The primary outcome and cardiovascular death were tested accounting for the competing risk of noncardiovascular death, and the HF event endpoint was tested accounting for the competing risk of all-cause death. The incidence rates for each outcome were reported per 100 patient-years. As a sensitivity analysis, patients with eGFR ≥60 mL/min/1.73 m^2 were analyzed with adjustment for the same covariates as in the main model except for log-transformed serum creatinine.

The association between the LDH as a continuous variable and the risk of each major clinical outcome was modeled using restricted cubic splines with median population LDH as reference. We compared the linear specification of log-LDH with spline models using 3-5 knots. Because the 3-knot model provided similar Akaike information criterion to the linear specification while avoiding the increased complexity and higher Bayesian information criterion of models with more knots, the 3-knot model was selected as the most parsimonious flexible form.

The baseline model was stratified according to the geographic region and adjusted for the trial group. Additional models included further adjustment for age, sex, NYHA functional class III or IV, systolic blood pressure, body mass index, LVEF, history of myocardial infarction, diabetes mellitus, atrial fibrillation/flutter at screening, race, log-transformed NT-proBNP, log-transformed hemoglobin, log-transformed hs-TnI, log-transformed total bilirubin, log-transformed serum creatinine, and log-transformed creatine kinase. To reduce the visual influence of extreme outliers, patients with LDH values outside the 1st to 99th percentile range were included in the model but not displayed in the graphs. The 3 knots were placed at default positions (10th, 50th, and 90th percentiles) of LDH.

For patients with both baseline and 48-week LDH values, 4 groups were defined according to LDH levels at these 2 time points to compare the trajectory between those with normal and elevated LDH values.

TABLE 1 Baseline Characteristics According to Quartile of Baseline LDH Levels in Outpatients With HFrEF

	Q1 (n = 1,561)	Q2 (n = 1,508)	Q3 (n = 1,551)	Q4 (n = 1,518)	*P* for Trend
Age, y	63.3 ± 11.5	64.4 ± 11.3	65.1 ± 11.2	64.6 ± 11.4	<0.001
Male	1,305 (83.6)	1,192 (79.1)	1,187 (76.5)	1,117 (73.6)	<0.001
Region					<0.001
Asia	168 (10.8)	120 (8.0)	106 (6.8)	98 (6.5)	
Eastern Europe	401 (25.7)	457 (30.3)	480 (31.0)	423 (27.9)	
Latin America	378 (24.2)	323 (21.4)	284 (18.3)	263 (17.3)	
North America	297 (19.0)	272 (18.0)	286 (18.4)	351 (23.1)	
Western Europe, Oceania, other	317 (20.3)	336 (22.3)	395 (25.5)	383 (25.2)	
Race					0.058
White	1,163 (74.5)	1,177 (78.1)	1,208 (77.9)	1,135 (74.8)	
Black	94 (6.0)	89 (5.9)	114 (7.4)	160 (10.5)	
Asian	172 (11.0)	127 (8.4)	113 (7.3)	113 (7.4)	
Other	132 (8.5)	115 (7.6)	116 (7.5)	110 (7.3)	
Clinical characteristics					
NYHA functional classification					<0.001
II	1,008 (64.6)	941 (62.4)	892 (57.5)	754 (49.7)	
III	531 (34.0)	537 (35.6)	627 (40.4)	726 (47.8)	
IV	22 (1.4)	30 (2.0)	32 (2.1)	38 (2.5)	
KCCQ total symptom score	79.2 (60.4-92.7)	79.2 (60.4-93.8)	72.9 (54.2-89.6)	66.7 (46.9-85.4)	<0.001
Physiological and laboratory measurements					
Body mass index, kg/m^2	28.4 ± 5.9	28.7 ± 6.2	28.5 ± 6.2	28.9 ± 6.6	0.25
Heart rate, beats/min	70.9 ± 11.8	71.3 ± 11.6	72.3 ± 12.4	74.0 ± 13.2	<0.001
Systolic blood pressure, mm Hg	117.2 ± 15.1	118.1 ± 15.6	117.2 ± 15.9	116.9 ± 15.7	0.27
Diastolic blood pressure, mm Hg	71.2 ± 10.2	71.9 ± 10.4	71.8 ± 10.2	72.2 ± 10.6	0.018
LVEF, %	27.0 ± 6.1	26.9 ± 6.1	26.4 ± 6.3	26.1 ± 6.4	<0.001
LDH, U/L	155 (144-163)	183 (177-188)	207 (201-215)	253 (236-280)	
Aspartate amino transferase, U/L	18 (15-21)	20 (17-24)	21 (18-26)	25 (20-31)	<0.001
Alanine amino transferase, U/L	17 (13-22)	18 (14-25)	19 (14-26)	21 (16-29)	<0.001
Total bilirubin, μmol/L	9.0 (6.0-12.0)	9.0 (6.0-14.0)	10.0 (7.0-14.0)	11.0 (8.0-17.0)	<0.001
Direct bilirubin, μmol/L	3.0 (2.0-4.0)	3.0 (2.0-4.0)	3.0 (2.0-4.0)	4.0 (3.0-6.0)	<0.001
Alkaline phosphatase, U/L	75 (61-94)	78 (63-99)	82 (67-102)	90 (71-117)	<0.001
White blood cells, 10^9/L	7.1 (6.0-8.5)	7.1 (5.9-8.3)	7.0 (5.8-8.4)	7.3 (6.0-8.7)	0.067
Hemoglobin, g/dL	13.8 (12.6-14.8)	13.8 (12.6-14.9)	13.7 (12.5-14.8)	13.6 (12.3-14.8)	0.009
NT-proBNP, pg/mL	1,410 (738-2,646)	1,701 (859-3,483)	2,032 (1,062-3,907)	2,613 (1,300-5,258)	<0.001
AF/flutter on ECG	2,132 (1,422-3,735)	2,404 (1,574-4,332)	2,780 (1,705-4,845)	3,459 (1,996-6,319)	<0.001
Without AF/flutter on ECG	1,201 (646-2,318)	1,436 (740-3,102)	1,696 (855-3,466)	2,244 (1,030-4,826)	<0.001
Creatine kinase, U/L	67 (48-95)	80 (57-111)	87 (62-127)	100 (65-161)	<0.001
Creatine kinase-isozyme MB, ng/mL	1.4 (0.9-2.1)	1.8 (1.2-2.6)	2.1 (1.4-3.0)	2.5 (1.6-3.8)	<0.001
High-sensitivity TnI, ng/L	20 (10-34)	21 (11-40)	25 (14-49)	36 (20-64)	<0.001
Serum creatinine, μmol/L	99 (82-124)	102 (85-126)	105 (87-131)	111 (91-139)	<0.001
eGFR, mL/min/1.73 m^2	64.3 (49.7-79.8)	61.6 (47.5-75.9)	58.5 (44.2-73.5)	55.0 (41.6-69.7)	<0.001
Potassium, mmol/L	4.6 ± 0.5	4.6 ± 0.5	4.6 ± 0.5	4.6 ± 0.6	<0.001

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In the GALACTIC-HF trial, the upper limit of normal for LDH was defined as 250 U/L; therefore, patients were classified as "normal" (LDH ≤250 U/L) or "high" (LDH >250 U/L) at each time point, resulting in the following 4 categories: Normal to normal, Normal to high, High to normal, and High to high. Delta LDH was defined as (LDH at 48 weeks − baseline LDH)/baseline LDH. Based on these classifications, a landmark analysis was conducted at week 48 to generate Kaplan-Meier curves and estimate HRs.

To evaluate the association between LDH and other potentially related biomarkers, including NT-proBNP, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, hs-TnI, hemoglobin, creatine kinase, and creatinine, all variables were natural log-transformed

TABLE 1 Continued

	Q1 (n = 1,561)	Q2 (n = 1,508)	Q3 (n = 1,551)	Q4 (n = 1,518)	*P* for Trend
Medical history					
Type 2 diabetes mellitus	690 (44.2)	558 (37.0)	611 (39.4)	577 (38.0)	0.003
Hypertension	1,076 (68.9)	1,083 (71.8)	1,050 (67.7)	1,075 (70.8)	0.77
Myocardial infarction	616 (39.5)	610 (40.5)	653 (42.1)	660 (43.5)	0.015
AF or flutter at screening	332 (20.6)	355 (23.5)	402 (25.9)	440 (29.0)	<0.001
Stroke	147 (9.4)	130 (8.6)	127 (8.2)	150 (9.8)	0.78
COPD	242 (15.5)	246 (16.3)	253 (16.3)	247 (16.3)	0.58
Ischemic HF etiology	807 (51.7)	776 (51.5)	867 (55.9)	816 (53.8)	0.061
Smoking status	220 (14.1)	184 (12.3)	171 (11.1)	128 (8.5)	<0.001
Treatments					
ACEI, ARB, or ARNI	1,431 (91.7)	1,352 (89.7)	1,350 (87.0)	1,273 (83.9)	<0.001
ARNI	342 (21.9)	308 (20.4)	323 (20.8)	294 (19.4)	0.12
Beta-blocker	1,487 (95.3)	1,441 (95.6)	1,475 (95.1)	1,413 (93.1)	0.007
SGLT2 inhibitor	48 (3.1)	41 (2.7)	46 (3.0)	28 (1.8)	0.062
MRA	1,211 (77.6)	1,172 (77.7)	1,188 (76.6)	1,109 (73.1)	0.003
CRT	123 (7.9)	167 (11.1)	279 (18.0)	320 (21.1)	<0.001
ICD	349 (22.4)	440 (29.2)	588 (37.9)	636 (41.9)	<0.001

Values are mean ± SD, n (%), or median (25th-75th percentile), unless otherwise indicated.

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HF = heart failure; HFrEF = heart failure and reduced ejection fraction; ICD = implantable cardioverter-defibrillator; KCCQ = Kansas City Cardiomyopathy Questionnaire; LDH = lactate dehydrogenase; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro–B-type natriuretic peptide; SGLT2 = sodium-glucose cotransporter 2; TnI = troponin I.

due to their skewed distributions. Scatterplots were generated, and Pearson's correlation coefficients were calculated.

Furthermore, to evaluate the effect of OM compared with placebo on clinical outcomes in the overall population, we performed time-to-event analyses using Cox proportional hazards models, stratified by region and randomization setting and adjusted for baseline eGFR. Potential effect modification by baseline LDH was assessed using a likelihood ratio test comparing models with and without an interaction term between treatment assignment and LDH quartiles.

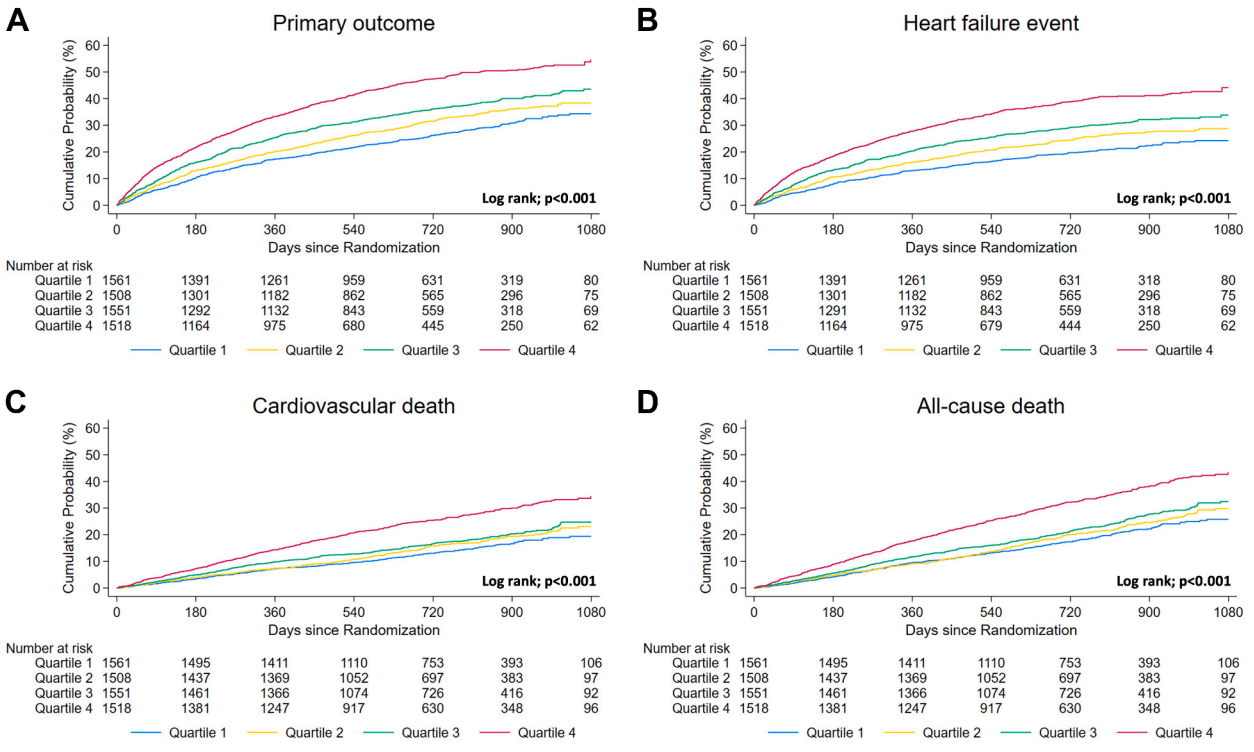
The incremental value of LDH added to a clinical model was tested using the PREDICT-HF risk models.[20] Because these models had been built in outpatient populations, only outpatients enrolled in GALACTIC-HF were included in the present analysis. PREDICT-HF models had been built for the outcomes of a composite of HF hospitalization or cardiovascular death, cardiovascular death, and all-cause death in outpatients. The value of adding was examined using Harrell's C statistic, a continuous net reclassification index (NRI), and the integrated discrimination improvement (IDI) metric. PREDICT-HF Scores were calculated from the sum of the multiplication of each variable in the models by the beta coefficient obtained in the derivation study using the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine impact on Global Mortality and Morbidity in Heart Failure) trial. LDH was included as a continuous variable. Variables required for the PREDICT-HF models that were not collected in GALACTIC were imputed using the median value from the PARADIGM-HF derivation cohort as described elsewhere.[20] The extent of missingness for these models is presented in Supplemental Table 1.

All statistical analyses were performed using Stata/SE version 18.0 (Stata Corp). To calculate NRI and IDI (95% CI), we used survIDINRI package of R software version 4.5.0 (R Project for Statistical Computing). A significance level of 0.05 was used to define statistical significance.

RESULTS

Among the 8,232 patients analyzed in GALACTIC-HF, a baseline serum LDH was available in 8,179 patients, including 6,138 outpatients who were the focus of the present study. The distribution of LDH at baseline is shown in Supplemental Figure 1. For the present analysis, outpatients were divided into the following 4 groups according to LDH quartile (Q1-Q4): Q1: 50-170 U/L; Q2: 171-194 U/L; Q3: 195-224 U/L; and

FIGURE 1 Kaplan-Meier Curves for Clinical Outcomes According to the Baseline Lactate Dehydrogenase Level in Outpatients With HFrEF



Kaplan-Meier curves illustrating the association between baseline lactate dehydrogenase level and the following clinical outcomes: primary outcome of heart failure event or cardiovascular death (A), first heart failure event (B), cardiovascular death (C), and all-cause death (D). HFrEF = heart failure and reduced ejection fraction; Q1 = blue line; Q2 = yellow line; Q3 = green line; Q4 = red line.

Q4: 225-854 U/L. The median of each quartile for serum LDH was Q1: 155 U/L (25th-75th percentile: 144-163 U/L); Q2: 183 U/L (25th-75th percentile: 177-188 U/L); Q3: 207 U/L (25th-75th percentile: 201-215 U/L); and Q4: 253 U/L (25th-75th percentile: 236-280 U/L).

PATIENT CHARACTERISTICS ACCORDING TO LDH LEVELS AT BASELINE. The baseline characteristics of outpatients, according to LDH quartile, are shown in **Table 1**. Compared with the patients who had lower LDH concentrations, those with higher LDH concentrations were more frequently female and had worse HF status: higher NYHA functional class, lower Kansas City Cardiomyopathy Questionnaire total symptom scores, higher concentrations of NT-proBNP, and a lower mean LVEF. Patients with higher LDH levels were more likely to have a history of myocardial infarction and atrial fibrillation/flutter, and to have worse kidney function and a lower hemoglobin concentration. Patients with higher LDH levels also had higher concentrations of hs-TnI, liver transaminases, bilirubin, and alkaline phosphatase.

The baseline characteristics of the overall population, including both inpatients and outpatients, are summarized in Supplemental Table 2. Similar trends were observed to those seen in outpatients alone, although the inpatients had higher median LDH levels than the outpatients (204 U/L vs 194.5 U/L; $P < 0.001$).

ASSOCIATION BETWEEN LDH AND OTHER BIOMARKERS. Except for hemoglobin, log-transformed LDH levels showed only weak associations with the other biomarkers measured (NT-proBNP, hs-TnI, creatine kinase, creatinine, transaminases, bilirubin, alkaline phosphatase), with correlation coefficients ranging from 0.123 to 0.376 (all $P < 0.001$) (Supplemental Figure 2).

CLINICAL OUTCOMES ACCORDING TO LDH LEVELS AT BASELINE. Clinical outcomes in outpatients according to LDH quartile are shown in **Figure 1** and **Table 2**. Patients with higher LDH had a greater risk of all outcomes assessed, and similar trends were apparent in the overall population (Supplemental

TABLE 2 Clinical Outcomes in Outpatients With HFrEF According to Quartile of LDH Level at Baseline

	Q1 (n = 1,561)	Q2 (n = 1,508)	Q3 (n = 1,551)	Q4 (n = 1,518)
LDH, U/L	155 (144-163)	183 (177-188)	207 (201-215)	253 (236-280)
HF event or CV death				
Number of events	418 (26.8)	474 (31.4)	564 (36.4)	705 (46.4)
Event rate	15.7 (14.3-17.3)	19.2 (17.5-21.0)	23.1 (21.3-25.1)	33.4 (31.0-35.9)
Adjusted HR[a]	Ref.	1.18 (1.03-1.35)	1.24 (1.09-1.42)	1.48 (1.29-1.69)
SHR[b]	Ref.	1.17 (1.02-1.34)	1.25 (1.09-1.43)	1.46 (1.27-1.68)
HF event				
Number of events	296 (19.0)	352 (23.3)	431 (27.8)	546 (36.0)
Event rate	11.1 (9.9-12.5)	14.2 (12.8-15.8)	17.6 (16.1-19.4)	25.8 (23.8-28.1)
Adjusted HR[a]	Ref.	1.23 (1.04-1.44)	1.33 (1.14-1.56)	1.58 (1.34-1.85)
SHR[b]	Ref.	1.22 (1.04-1.44)	1.32 (1.13-1.56)	1.52 (1.29-1.79)
CV death				
Number of events	214 (13.7)	240 (15.9)	274 (17.7)	395 (26.0)
Event rate	7.2 (6.3-8.2)	8.4 (7.4-9.6)	9.4 (8.4-10.6)	14.9 (13.5-16.4)
Adjusted HR[a]	Ref.	1.15 (0.95-1.40)	1.12 (0.93-1.35)	1.49 (1.23-1.81)
SHR[b]	Ref.	1.12 (0.92-1.36)	1.13 (0.93-1.36)	1.46 (1.20-1.78)
All-cause death				
Number of events	296 (19.0)	317 (21.0)	368 (23.7)	518 (34.1)
Event rate	9.9 (8.9-11.2)	11.1 (10.0-12.4)	12.6 (11.4-14.0)	19.5 (17.9-21.3)
Adjusted HR[a]	Ref.	1.12 (0.95-1.32)	1.13 (0.96-1.33)	1.52 (1.29-1.79)

Values are median (25th-75th percentile), n (%), event rate (95% CI), or HR (95% CI), unless otherwise indicated. Event rate is the number of events per 100 person-years. [a]Models were stratified by region, and adjusted for baseline treatment assignment, age, sex, NYHA functional class III or IV, systolic blood pressure, body mass index, left ventricular ejection fraction, history of myocardial infarction, diabetes mellitus, atrial fibrillation/flutter at screening, race, log-transformed NT-proBNP, log-transformed hemoglobin, log-transformed high-sensitivity troponin I, log-transformed total bilirubin, log-transformed serum creatinine, and log-transformed creatine kinase. [b]Competing-risks regression with the Fine-Gray method was used to assess outcomes other than all-cause death. The primary outcome (HF event or cardiovascular death) and cardiovascular death were tested accounting for the competing risk of noncardiovascular death. The HF event endpoint was tested accounting for the competing risk of all-cause death. Models were adjusted for region, treatment assignment, age, sex, NYHA functional class III or IV, systolic blood pressure, body mass index, left ventricular ejection fraction, history of myocardial infarction, diabetes mellitus, atrial fibrillation/flutter at screening, race, log-transformed NT-proBNP, log-transformed hemoglobin, log-transformed high-sensitivity troponin I, log-transformed total bilirubin, log-transformed serum creatinine, and log-transformed creatine kinase.

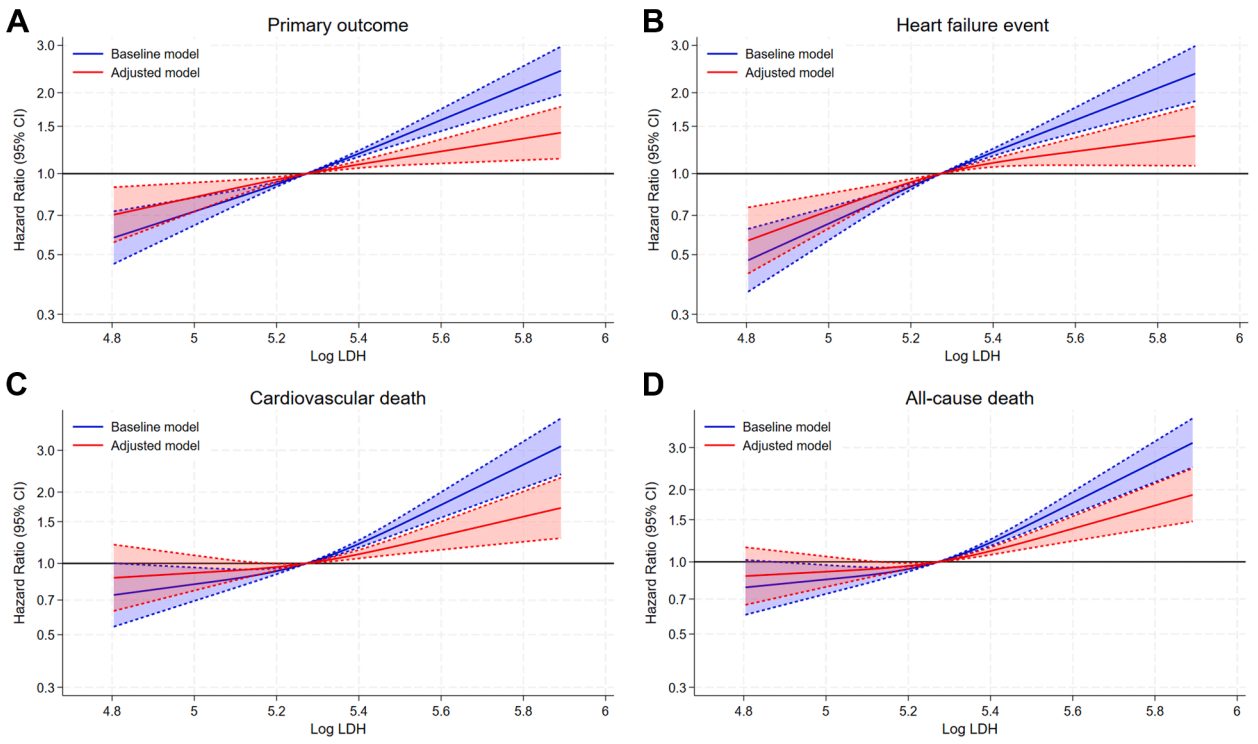
CV = cardiovascular; Ref. = Reference; SHR = subdistribution HR; other abbreviations as in Table 1.

Figure 3, Supplemental Table 3). The incidence rates for the primary composite endpoint (time-to-first occurrence of worsening HF or cardiovascular death), from the lowest to the highest LDH quartiles (Q1-Q4), were 15.7 (95% CI: 14.3-17.3), 19.2 (95% CI: 17.5-21.0), 23.1 (95% CI: 21.3-25.1), and 33.4 (95% CI: 31.0-35.9) per 100 person-years, respectively. Similar trends were observed for other clinical outcomes, including a first HF event, cardiovascular death, and all-cause death.

Although individual HRs were partially attenuated after adjustment for recognized prognostic variables and biomarkers specific to certain organs/tissues (NT-proBNP, hs-TnI, total bilirubin, creatinine, and creatine kinase), higher LDH remained significantly associated with worse outcomes (**Table 2**). The sensitivity analysis in patients with preserved eGFR showed similar trends (Supplemental Table 4). HRs for each clinical outcome, analyzing LDH as a continuous variable using the median value as the reference, are shown in **Figure 2**. A linear relationship was observed between increasing log-transformed LDH and worsening outcomes.

ASSOCIATION BETWEEN LDH LEVELS AND HYPOPERFUSION/PRESHOCK. Among 6,138 outpatients, 851 patients (13.9%) were classified as having hypoperfusion/preshock (Supplemental Table 5). Elevated LDH levels were associated with higher hypoperfusion/preshock scores, and the presence of hypoperfusion/preshock was defined as a score of ≥2 points (Supplemental Figure 4). The adjusted odds ratio for hypoperfusion/preshock was 1.44 (95% CI: 1.13-1.84) in the highest (Q4) compared with the lowest quartile (Q1), and 1.45 (95% CI: 1.17-1.79) in the high LDH group (≥250 U/L) compared with the normal group (<250 U/L) (Supplemental Table 6). Both the presence of hypoperfusion/preshock and elevated LDH levels (>250 U/L) were associated with a worse prognosis, with hypoperfusion/preshock

FIGURE 2 **HRs for Each Clinical Outcome According to Baseline Log-Transformed LDH Level in Outpatients With HFrEF**



Spline curves illustrating the association between baseline log-transformed LDH level (restricted to 99th percentile) and the clinical outcomes: primary outcome of heart failure event or cardiovascular death (A), first heart failure event (B), cardiovascular death (C), and all-cause death (D). The baseline model (blue) is stratified according to the geographic region and adjusted for the trial group. The adjusted model (red) included additional adjustment for age, sex, NYHA functional class III or IV, systolic blood pressure, body mass index, left ventricular ejection fraction, history of myocardial infarction, diabetes mellitus, atrial fibrillation/flutter at screening, hemoglobin, race, NT-proBNP (log-transformed), high-sensitivity troponin I (log-transformed), total bilirubin (log-transformed), creatinine (log-transformed), and creatine kinase (log-transformed). The shaded area represents the 95% CI. LDH = lactate dehydrogenase; NT-proBNP = N-terminal pro-B-type natriuretic peptide; other abbreviation as in **Figure 1**.

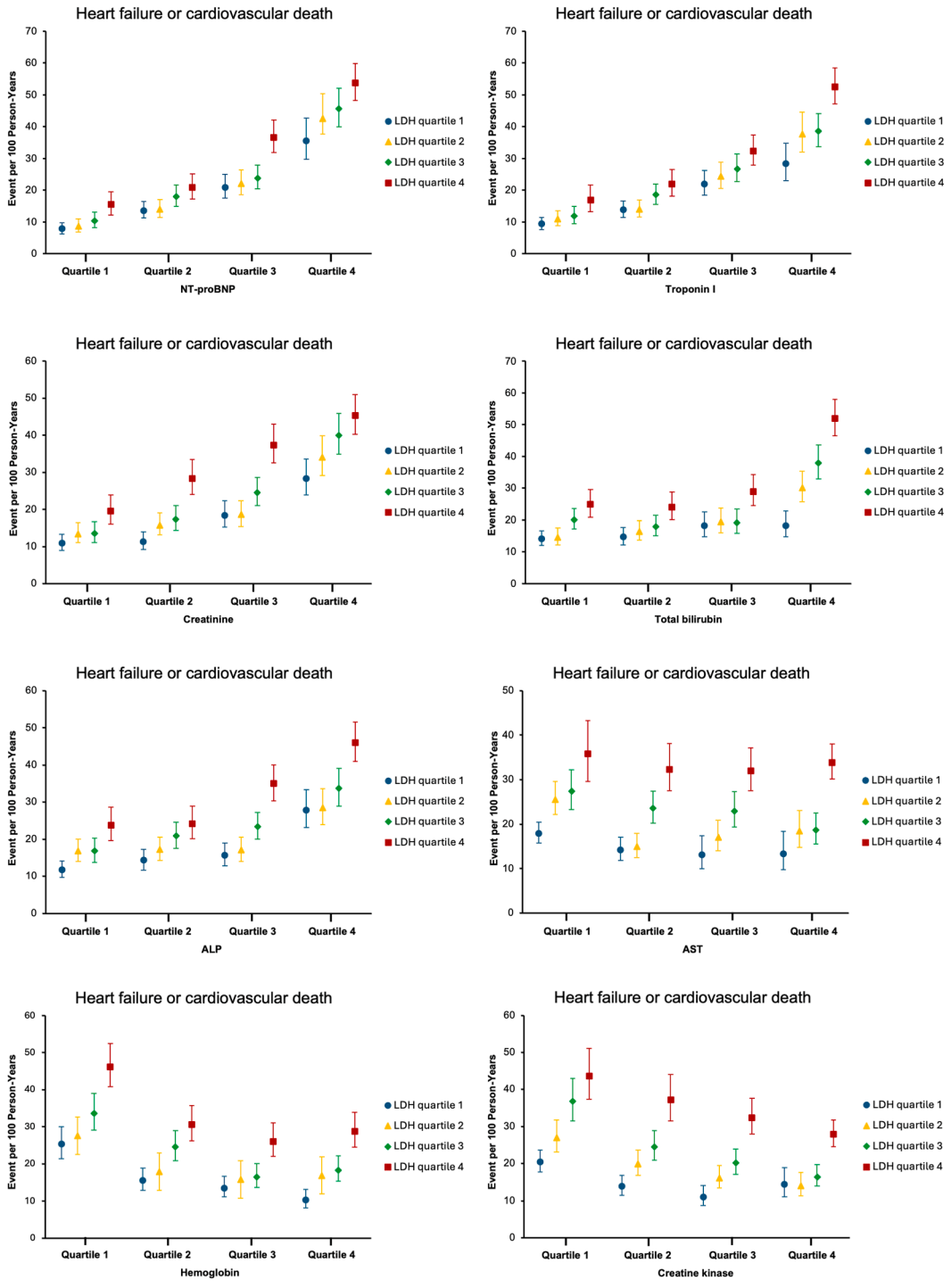
showing a stronger association with adverse outcomes than LDH alone (Supplemental Figure 5).

LDH CHANGE AND OUTCOMES. A total of 4,879 patients had both baseline and 48-week LDH measurements available. Regarding the evolution of LDH levels from baseline to 48 weeks, the median LDH values were 192 U/L (25th-75th percentile: 168-221 U/L) at baseline and 195 U/L (25th-75th percentile: 170-229 U/L) at 48 weeks. The mean change was 10.0 (95% CI: 7.6-12.3) in women and 3.7 (95% CI: 2.5-5.0) in men, and 7.5 (95% CI: 5.9-9.1) in the OM group and 2.6 (95% CI: 1.2-4.3) in the placebo group, respectively (Supplemental Table 7).

In the trajectory-based landmark analysis, the normal (baseline) to normal (48 weeks of follow-up) and high to normal groups had the lowest event rates and the normal to high and high to high groups experienced the worst outcomes (Supplemental Figure 6, Supplemental Table 8). An increase in LDH from baseline to 48 weeks was associated with a higher HR for the primary outcome, with a positive linear relationship between percentage delta LDH and this outcome (Supplemental Figure 7).

PREDICTIVE VALUE OF LDH ADDED TO OTHER PROGNOSTIC BIOMARKERS. **Figure 3** shows the additional prognostic information provided when LDH was added to other recognized prognostic biomarkers. Each panel shows the rate of the primary endpoint according to quartile of the established biomarker stratified by LDH, demonstrating the incremental prognostic value of LDH. For example, among patients in the lowest quartiles of both LDH and NT-proBNP, the rate of the primary outcome was 7.9 per 100 person-years whereas in participants in the highest quartiles for both these biomarkers the rate was almost 7-fold higher at 53.8 per 100 person-years.

FIGURE 3 Rates of the Primary Endpoint According to Quartile of LDH Concentration Combined With Other Biomarkers



Rate of the primary composite endpoint (heart failure event or cardiovascular death) per 100 person-years, according to quartile of concentration at baseline of a range of prognostic biomarkers stratified by quartile of quartile of LDH concentration at baseline. ALP = alkaline phosphatase; AST = aspartate aminotransferase; other abbreviations as in Figure 2.

TABLE 3 Comparison of Harrell's C Statistic, NRI, and IDI For PREDICT-HF Score With and Without LDH in Outpatients

	PREDICT-HF	PREDICT-HF + LDH	*P* Value for Difference	IDI	NRI
First HF hospitalization or CV death					
Overall	0.680 (0.669-0.691)	0.688 (0.677-0.699)	<0.001		
1 y	0.694 (0.681-0.708)	0.701 (0.688-0.714)	<0.001	0.009 (0.004-0.013) $P < 0.001$	0.080 (0.049-0.109) $P < 0.001$
2 y	0.681 (0.669-0.692)	0.689 (0.678-0.701)	<0.001	0.009 (0.005-0.014) $P < 0.001$	0.072 (0.033-0.102) $P < 0.001$
CV death					
Overall	0.716 (0.701-0.731)	0.724 (0.709-0.739)	<0.001		
1 y	0.734 (0.715-0.754)	0.741 (0.721-0.760)	0.011	0.007 (0.003-0.013) $P < 0.001$	0.071 (0.018-0.120) $P < 0.001$
2 y	0.718 (0.702-0.733)	0.726 (0.710-0.742)	<0.001	0.006 (0.002-0.012) $P < 0.001$	0.063 (0.021-0.094) $P < 0.001$
All-cause death					
Overall	0.717 (0.704-0.731)	0.723 (0.709-0.736)	<0.001		
1 y	0.737 (0.719-0.755)	0.741 (0.723-0.759)	0.011	0.002 (−0.001-0.006) $P = 0.21$	0.021 (−0.099-0.066) $P = 0.19$
2 y	0.719 (0.705-0.733)	0.725 (0.711-0.739)	<0.001	0.002 (−0.001-0.006) $P = 0.17$	0.013 (−0.076-0.051) $P = 0.52$

IDI = integrated discrimination improvement; NRI = net reclassification index; PREDICT-HF = PARADIGM Risk of Events and Death in the Contemporary Treatment of Heart Failure; other abbreviations as in Tables 1 and 2.

PREDICTIVE VALUE OF LDH ADDED TO A COMPREHENSIVE PROGNOSTIC MODEL. When added to the PREDICT-HF risk model for the composite of HF hospitalization or cardiovascular death, LDH at baseline improved Harrell's C statistic from 0.694 (95% CI: 0.681-0.708) to 0.701 (95% CI: 0.688-0.714) at 1 year ($P < 0.001$) (Table 3). IDI and NRI increased by 0.009 (95% CI: 0.004-0.013) and 0.080 (95% CI: 0.049-0.109), respectively (both $P < 0.001$). This was also true for additional models for cardiovascular death. Regarding all-cause death, Harrell's C statistic was improved from 0.737 (95% CI: 0.719-0.755) to 0.741 (95% CI: 0.723-0.759) at 1 year ($P = 0.011$), but no significant increase of IDI and NRI was observed. Similar trends were also observed for all the measurements across all the outcomes at 2 years (Table 3).

EFFECT OF OMECAMTIV MECARBIL ACCORDING TO LDH LEVELS. The effect of OM on clinical outcomes across LDH quartiles is summarized in Supplemental Table 9. Baseline LDH levels did not modify the effect of OM compared with placebo on the other clinical outcomes. Specifically, compared with placebo, the HRs for the effect of OM on the primary composite outcome were 0.80 (95% CI: 0.68-0.94), 1.03 (95% CI: 0.88-1.19), 1.00 (95% CI: 0.87-1.15), and 0.88 (95% CI: 0.78-1.00) across LDH Q1-Q4, respectively (P for interaction = 0.10).

DISCUSSION

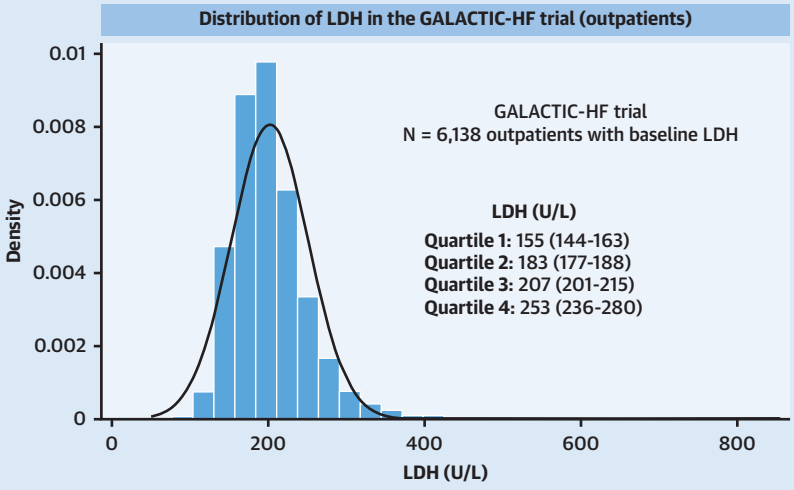
In this large, well-characterized, cohort of patients with HFrEF from the GALACTIC-HF trial, we found that higher serum LDH levels were independently associated with worse clinical outcomes, including HF hospitalization, cardiovascular death, and all-cause mortality (Central Illustration). These findings persisted even after adjustment for established prognostic variables and an extensive panel of biomarkers reflecting multiorgan dysfunction. Furthermore, higher LDH levels were associated with a higher prevalence of a hypoperfusion/preshock state. Moreover, LDH demonstrated incremental prognostic value when added to a validated risk prediction model (PREDICT-HF), suggesting that it may have a useful adjunctive role in clinical risk stratification for patients with HFrEF.

Our findings are consistent with 2 prior studies in patients with acute decompensated HF, in which elevated LDH was linked to increased short- and mid-term mortality.[13,14] However, our analysis extends this association to outpatients and a wider range of outcomes and, as mentioned earlier, shows it persists after adjustment for other prognostic variables.

Given that LDH reflects tissue injury and dysfunction across multiple organs, we further explored whether LDH could serve as a marker of a state of hypoperfusion/preshock in patients with

CENTRAL ILLUSTRATION Lactate Dehydrogenase and Outcomes in Patients With HFrEF: Insights from GALACTIC-HF

Is LDH Concentration Independently Associated With Adverse Clinical Outcomes in Patients With HFrEF?



GALACTIC-HF trial

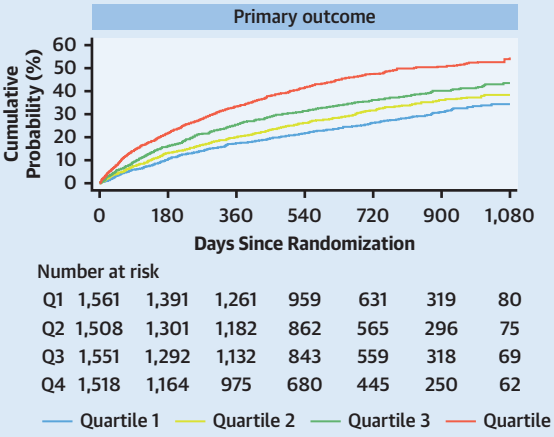
- A global, phase III, double-blind, placebo-controlled randomized clinical trial
- Efficacy and safety of omecamtiv mecarbil vs placebo

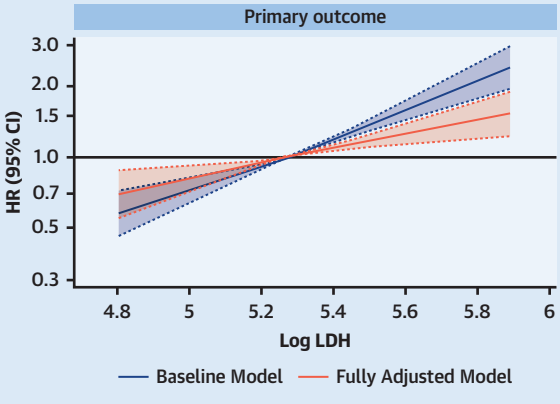
Key inclusion criteria

- LVEF≤35%
- NYHA functional class II-IV
- Elevated natriuretic peptide level
- Inpatients or outpatients with urgent visit or hospitalization for HF within 1 year

Primary outcome

- Composite of time to a first HF event or cardiovascular death





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In the HR graph, the baseline model (blue) is stratified by geographic region and adjusted for the trial group. The fully adjusted model (red) included additional adjustments for age, sex, NYHA functional class III or IV, systolic blood pressure, body mass index, left ventricular ejection fraction, history of myocardial infarction, diabetes mellitus, atrial fibrillation/flutter at screening, hemoglobin, race, NT-proBNP (log-transformed), high-sensitivity troponin I (log-transformed), total bilirubin (log-transformed), creatinine (log-transformed), and creatine kinase (log-transformed). The shaded area represents 95% CI. GALACTIC-HF = Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure; HF = heart failure; HFrEF = heart failure and reduced ejection fraction; LDH = lactate dehydrogenase; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

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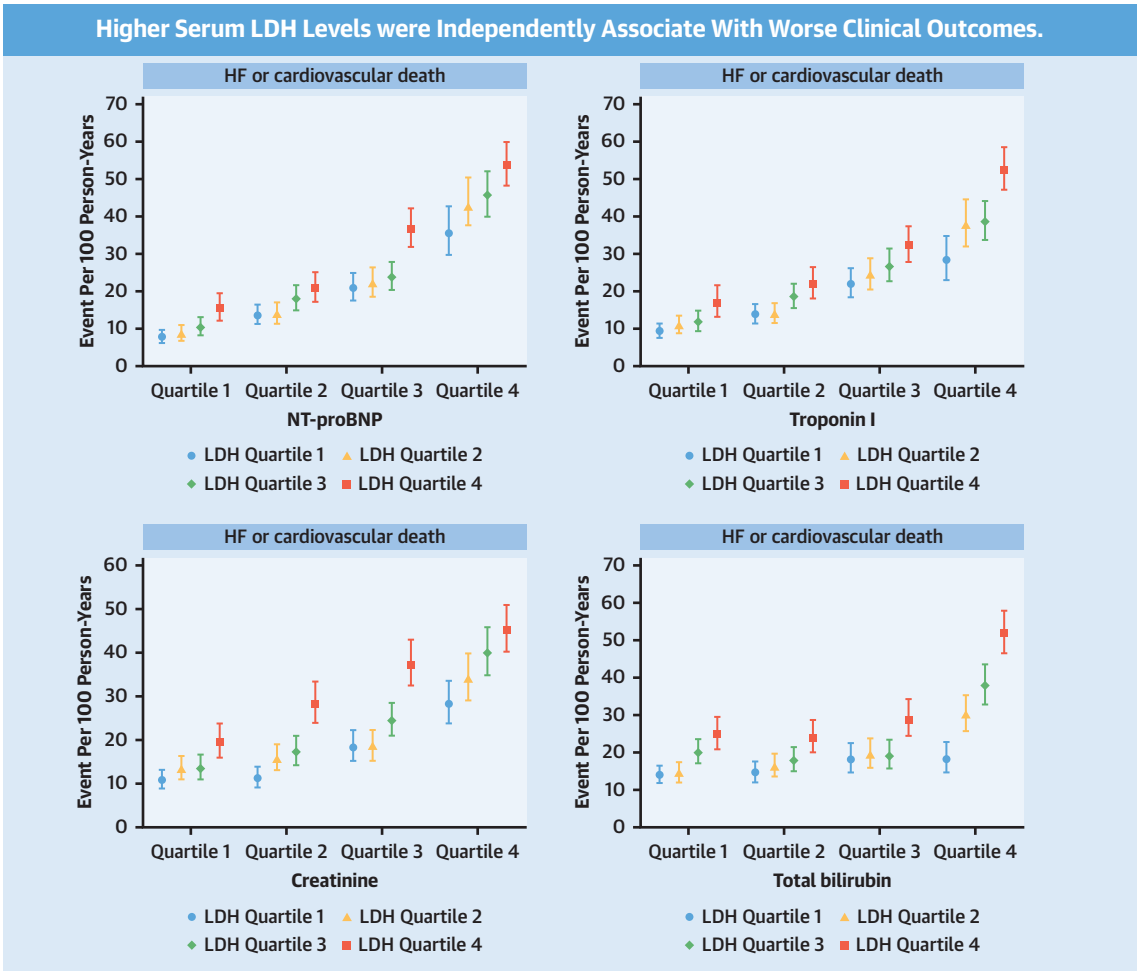
CENTRAL ILLUSTRATION Continued



Primary endpoint rates across quartiles of established prognostic biomarkers and LDH strata, illustrating the incremental prognostic value of LDH.

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HFrEF (consistent with stage C2D).[18] Higher LDH levels were indeed significantly associated with both the presence and severity of hypoperfusion/pre-shock, even after multivariable adjustment. These findings suggest that LDH may serve as a practical biomarker for low-output states in patients with HFrEF, particularly in situations where clinicians may have become accustomed to chronically elevated creatinine, hepatic enzymes, or natriuretic peptides.

We also found that changes in LDH were positively associated with worse outcomes, and patients who exhibited greater increases in LDH or joined the high LDH (>250 U/L) group during the follow-up period experienced worse subsequent outcomes. However, because this was a landmark analysis, potential selection bias may have influenced the findings, and the results should therefore be interpreted with caution.

Because of its widespread distribution in the body, serum LDH levels are increased by many tissue insults, including ischemia, sepsis, poisoning, dehydration, and extremes of temperature.[2,4-7] As a result, total serum LDH is a sensitive but nonspecific marker of cellular damage. Normal reference values for LDH vary by laboratory, but typically values of >190-220 U/L are considered elevated.[21] Using a threshold of 190 U/L, we found that 54% of outpatients in GALACTIC-HF had an elevated LDH concentration, consistent with the

idea that HFrEF is a syndrome of multiorgan dysfunction. Indeed, the linear relationship between LDH and adverse outcomes suggests that LDH may function as a marker of cumulative systemic abnormalities rather than serving as a binary indicator with a specific cutoff value.

Concentrations of LDH vary by tissue type, with values (in U/g wet weight) of 25,000 in heart, 15,000 in kidney, 9,500 in lung, 9,000 in liver, and 9,000 in skeletal muscle reported.[22] Several pathophysiologic mechanisms may underlie the association between LDH elevation and adverse outcomes in HF.[23] First, systemic hypoperfusion and tissue hypoxia in advanced HF can shift cellular metabolism toward anaerobic glycolysis, resulting in increased LDH activity and release. Additionally, elevated central venous pressure and hepatic congestion may cause hepatocellular injury and impaired hepatic perfusion.[24] Furthermore, skeletal muscle hypoperfusion and catabolism, common in chronic HF and cachexia, may also contribute to increased circulating LDH despite reduced muscle mass.[25] Isoenzyme analysis can help localize the source of an increase in LDH level, but we measured total LDH concentration and therefore do not know which isoenzymes and tissues contributed to the elevation detected in the patients in the present study. However, the associations with other circulating biomarkers indicative of cardiac (troponin and NT-proBNP), liver (bilirubin), kidney (creatinine), and muscle injury (creatine kinase) in the present study are consistent with the hypothesis that LDH may be an integrative marker of systemic organ/tissue dysfunction. Importantly, LDH remained associated with worse outcomes after multivariable adjustment for these other biomarkers.

Finally, LDH significantly enhanced the prognostic performance of the PREDICT-HF models. These models, to the best of our knowledge, represent the most comprehensive tools for risk prediction in outpatients with HFrEF.[18,26,27] Their ability to accurately predict morbidity and mortality at 1 and 2 years in ambulatory patients with chronic HFrEF has been externally validated in large clinical trials and population-based cohorts.[8,26,27] When LDH was incorporated into the PREDICT-HF models, it significantly improved Harrell's C statistics at both 1 and 2 years, both for the composite outcome of HF hospitalization or cardiovascular death and for cardiovascular death alone. In addition, LDH significantly improved the NRI and IDI, indicating enhanced risk stratification beyond the established prognostic markers. Although the improvement in discrimination was modest and may not contribute to clinical decision-making, our results support that LDH serves as a complementary biomarker for refining existing risk prediction models.

STUDY LIMITATIONS. Several limitations should be considered. First, this study is a post hoc analysis of the GALACTIC-HF trial. Second, the patients analyzed were selected according to specific trial inclusion and exclusion criteria, so the findings may not be generalizable to all patients with HFrEF. We did not study patients with HFpEF. Third, residual confounding may persist despite multivariable adjustment because LDH may be influenced by comorbidities not fully captured, such as malignancy or infection. Fourth, LDH comprises 5 isoenzymes (LDH1-LDH5)[2] that are variably expressed across different tissues, and we did not have measurements of the specific LDH isoforms. LDH levels can be affected by hemolysis, and although centralized laboratory processing was used in the GALACTIC-HF trial, we cannot completely exclude the possibility of measurement error due to phlebotomy-related hemolysis. Finally, we did not validate these findings in a second cohort.

CONCLUSIONS

LDH is an independent predictor of adverse outcomes in patients with HFrEF. It provides incremental prognostic value beyond traditional risk factors and established biomarkers, improving the performance of validated risk models.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

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director GCTP Ltd. Dr Yang has received a Global CardioVascular Clinical Trialists (CVCT) Young Trialist Grant and travel grants from AstraZeneca and Bayer. Dr Henderson has received personal fees from Bayer outside the submitted work. Dr Metra has received funding to his institution from Amgen and Cytokinetics as participant in the executive committee during the trial and for patients' enrollment; has received consulting fees for participation to advisory boards from AstraZeneca, Bayer, Boehringer-Ingelheim, Novo-Nordisk, and Roche Diagnostics; and has received speaker fees from Boehringer-Ingelheim. Drs Liu, Divanji, Heitner, Kupfer, and Malik are employees and shareholders of Cytokinetics. Dr Felker has received grant funding to his institution from American Heart Association, Amgen, Bayer, Bristol Myers Squibb, CSL-Behring, Cytokinetics, Merck, Myokardia, and the National Institutes of Health; has received consulting fees from Abbott, American Regent, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Cardionomic, Cytokinetics, Medtronic, Myovant, Novartis, Reprieve, Sequana, Windtree Therapeutics, and WhiteSwell; and has participated on data safety monitoring boards or advisory boards for EBR Systems, LivaNova, Medtronic, Siemens, Rocket Pharma, and V-Wave. Dr Solomon has received research grants from Actelion, Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, Bristol Myers Squibb, Celladon, Cytokinetics, Eidos, Gilead, GlaxoSmithKline, Ionis, Lilly, Mesoblast, MyoKardia, the National Institutes of Health/NHLBI, Neurotronik, Novartis, Novo Nordisk, Respicardia, Sanofi Pasteur, Theracos, and S2.AI; and has consulted for Abbott, Action, Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GlaxoSmithKline, Lilly, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellPro-Thera, Moderna, American Regent, and Sarepta. Dr Teerlink has received personal fees as chairperson of the GALACTIC-HF Executive Committee from Amgen and Cytokinetics; has received personal fees for research contracts from 3ive Labs, Amgen, AskBio, AstraZeneca, Bayer, Boehringer-Ingelheim, Cardiac Dimensions, Cytokinetics, EBR Systems, Edgewise Therapeutics, Edwards, Endotronix, Impulse Dynamics, LivaNova, Medtronic, Myovant, PCORI, RECARDIO, Tectonic, and V-Wave; has received fees as a consultant from 3ive Labs, AOP Medical, Arena, AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol Myers-Squibb, Cardiac Dimensions, CorHepta, Cytokinetics, Daiichi-Sankyo, EBR Systems, Edwards, Impulse Dynamics, JuvLabs, Kaiser Permanente, Lilly, LivaNova, Medtronic, Myovant, Novartis, PCORI, Pfizer, RECARDIO, ReCor Medical, Regeneron, Reprieve, Stealth, Tectonic, V-Wave, Verily, ViCardia, Windtree Therapeutics; has served on data monitoring committees for Angitia, Cardurion, Kaiser Permanente, and Medtronic; and has served as secretary, treasurer and president of the Heart Failure Society of America. Dr McMurray has received payments to Glasgow University for clinical trials and other research projects from the British Heart Foundation, National Institutes of Health-National Heart Lung and Blood Institute, Alnylam Pharmaceuticals, AstraZeneca, Bayer, Cardurion, Cytokinetics, Novartis, and Roche Diagnostics; has received personal consultancy fees from Alnylam Pharmaceuticals, AnaCardio, AstraZeneca, Bayer, Cardurion, Cytokinetics, Novartis, River BioMedics, Biohaven Pharmaceuticals, and DalCor Pharmaceuticals; has received personal lecture fees from Alkem Metabolics, AstraZeneca, Canadian Medical and Surgical Knowledge, Centrix Healthcare, Emcure Pharmaceuticals, Eris Lifesciences, Hikma Pharmaceuticals, Imagica Health, Intas Pharmaceuticals, J.B. Chemicals and Pharmaceuticals, Lupin Pharmaceuticals, Medscape/Heart.Org, ProAdWise Communications, Radcliffe Cardiology, Sun Pharmaceuticals, Translational Medicine Academy, Regeneron, MCI India, Hilton Pharmaceuticals, IMEDIC Pharmaceuticals Micro Labs Ltd, At the Limits Ltd, and ARMGO Pharmaceuticals; has served on data safety monitoring boards for WCG Clinical Services; and is a director of Global Clinical Trial Partners Ltd, which provides clinical trial services such as endpoint committees and educational programs.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In GALACTIC-HF, higher LDH levels were independently associated with a higher risk of fatal and nonfatal outcomes in patients with HFrEF, consistent with this biomarker reflecting multiorgan dysfunction.

TRANSLATIONAL OUTLOOK: LDH is a widely available and inexpensive biomarker reflecting nonspecific cellular injury. In GALACTIC-HF, elevated LDH levels were independently associated with worse outcomes in patients with HFrEF, and its inclusion improved established risk prediction models. These findings suggest that LDH, despite being a nonspecific marker, may provide incremental prognostic value in routine clinical practice and could help refine risk stratification in HFrEF.

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