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CLINICAL RESEARCH

Prognostic Value of Estimated Plasma Volume in Heart Failure

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ABSTRACT

OBJECTIVES The purpose of this study was to assess the prognostic value of the estimation of plasma volume or of its variation beyond clinical examination in a post-hoc analysis of EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study).

BACKGROUND Assessing congestion after discharge is challenging but of paramount importance to optimize patient management and to prevent hospital readmissions.

METHODS The present analysis was performed in a subset of 4,957 patients with available data (within a full dataset of 6,632 patients). The study endpoint was cardiovascular death or hospitalization for heart failure (HF) between months 1 and 3 after post-acute myocardial infarction HF. Estimated plasma volume variation (ΔePVS) between baseline and month 1 was estimated by the Strauss formula, which includes hemoglobin and hematocrit ratios. Other potential predictors, including congestion surrogates, hemodynamic and renal variables, and medical history variables, were tested. An instantaneous estimation of plasma volume at month 1 was defined and also tested.

RESULTS Multivariate analysis was performed with stepwise logistic regression. ΔePVS was selected in the model (odds ratio: 1.01; $p = 0.004$). The corresponding prognostic gain measured by integrated discrimination improvement was significant (7.57%; $p = 0.01$). Nevertheless, instantaneous estimation of plasma volume at month 1 was found to be a better predictor than ΔePVS.

CONCLUSIONS In HF complicating myocardial infarction, congestion as assessed by the Strauss formula and an instantaneous derived measurement of plasma volume provided a predictive value of early cardiovascular events beyond routine clinical assessment. Prospective trials to assess congestion management guided by this simple tool to monitor plasma volume are warranted. (J Am Coll Cardiol HF 2015;3:886–93) © 2015 by the American College of Cardiology Foundation.

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Congestion is the major cause for heart failure (HF) hospitalization; however, many HF patients are discharged with persistent signs and symptoms of congestion, high left ventricular filling pressures (1), and evidence of hypervolemia (2). Available data suggest that a pre-discharge clinical assessment of congestion is often not performed, and even if performed is not done systematically (1).

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The same issue arises after discharge and may contribute to the burden of rehospitalizations. Careful evaluation of all physical findings, laboratory variables, weight change, and net fluid change is warranted before discharge, as suggested by guidelines (3). Among readily available data at discharge, biological surrogates of plasma volume (PV) and therefore of congestion have been shown to be associated with post-discharge outcomes (4–8). PV may be assessed indirectly by several published methods. Whether these various methods of PV measurement beyond clinical examination have different prognostic value is unknown and was therefore investigated in this study using data from EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study).

METHODS

POPULATION. The design and results of the trial have been reported previously (9). The EPHESUS study enrolled 6,632 patients with HF after acute myocardial infarction (AMI) complicated by left ventricular systolic dysfunction (ejection fraction ≤40%). HF had to be documented by at least 1 of the following: presence of pulmonary rales, chest radiography showing pulmonary venous congestion, or the presence of a third heart sound. Clinical signs of pulmonary congestion were not required at inclusion in patients with diabetes mellitus. Patients were entered into the study from 3 to 14 days after infarction (with inclusion [M0] performed before discharge from the hospital in 80% of patients). All patients were randomly assigned to treatment with eplerenone 25 mg/day or placebo. EPHESUS was an event-driven study with a mean duration of follow-up of 16 months. Clinical assessments were made at inclusion (M0), at month 1 (M1), at month 3 (M3), and every 3 months thereafter. Among the 6,632 patients included in the EPHESUS study, 1,675 were excluded from the analysis because of unavailable data at baseline or at month 1 (259 died before 5 weeks, and 1,416 did not have the clinical or biological data required for all of the analyses conducted in the present study). The present analysis was therefore performed on the 4,957 remaining patients.

STUDY ENDPOINTS. The aim of the present study was to predict early cardiovascular events, that is, cardiovascular death or hospitalization for HF (the primary endpoint of the study, adjudicated by a blinded critical event committee, as per trial protocol [9]) between 1 and 3 months after AMI with HF (including a sensitivity analysis performed at 6 months in the study population with available hemoglobin and hematocrit data at M0).

ESTIMATION OF CHANGE IN PV. To estimate relative changes in PV between M0 and M1,

ABBREVIATIONS AND ACRONYMS

AMI = acute myocardial infarction

AUC = area under the receiver operating characteristic curve

eGFR = estimated glomerular filtration rate

ePVS = estimated plasma volume

ΔePVS = estimated plasma volume variation (Strauss formula)

HF = heart failure

LVEF = left ventricular ejection fraction

PV = plasma volume

TABLE 1 Baseline Characteristics Between Included and Nonincluded Patients

	Included (n = 4,957)	Nonincluded (n = 1,675)	p Value
NYHA functional class			
≥2	70	71 (n = 1,326)	0.53
≥3	17	22 (n = 1,326)	<0.0001
Killip class			
≥2	85	83 (n = 1,634)	0.067
≥3	19	22 (n = 1,634)	0.030
Weight, kg	77 (68-87)	76 (68-86) (n = 1,671)	0.19
eGFR, ml/min/1.73 m^2	68 (56-81)	65 (52-80) (n = 1,406)	0.0008
Blood pressure, mm Hg			
Systolic	120 (110-130)	115 (106-130) (n = 1,673)	<0.0001
Diastolic	70 (65-80)	70 (62-80) (n = 1,673)	0.0003
Hemoglobin, g/dl	13.4 (12.3-14.5)	13.2 (11.9-14.4) (n = 1,599)	<0.0001
Hematocrit, %	40 (37-43)	39 (36-43) (n = 1,534)	0.0004
Sodium, mmol/l	140 (137-142)	139 (136-142) (n = 1,637)	<0.0001
LVEF, %	35 (30-38)	34 (29-37) (n = 1,660)	<0.0001
Medical history			
Age, yrs	65 (55-72)	65 (55-74)	0.36
Male	71	72	0.16
Caucasian	91	89	0.016
Hospitalization for HF	7	9	0.12
Reperfusion therapy	46	44	0.19
Previous AMI	27	28	0.29
Diabetes mellitus	31	36	0.0001
Prior episodes of HF	14	15	0.35
Hypertension	61	58	0.011
Medications			
Eplerenone	50	50	0.90
ACEI/ARB	86	88	0.14
Beta-blockers	76	72	0.001
Loop diuretic drugs	54	59	0.0001

Values are n, median (interquartile range), or proportion (%).

ACEI = angiotensin-converting enzyme inhibitor; AMI = acute myocardial infarction; ARB = angiotensin receptor blocker; BP = blood pressure; eGFR = estimated glomerular filtration rate; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association functional class.

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