Prognostic Value of Estimated Plasma Volume in Heart Failure

Kévin Duarte, MSC,* Jean-Marie Monnez, PhD,* Eliane Albuisson, MD, PhD,*# Bertram Pitt, MD,# Faiez Zannad, MD, PhD,** Patrick Rossignol, MD, PhD***

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 ($\Delta$ePVS) 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. $\Delta$ePVS 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 $\Delta$ePVS.

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.
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).

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, biologic 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 beyond 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,
was the Strauss formula (Online Table 1), defined as follows:

$$\Delta ePVS = 100 \times \frac{\text{hemoglobin}(M0) - \text{hemoglobin}(M1)}{\text{hematocrit}(M1) - \text{hematocrit}(M0)}$$

This formula can be interpreted as the relative change in estimated PV between M0 and M1. For this reason, ePVS was defined as being proportional to this value.

The instantaneous formula for estimating PV, derived from $\Delta ePVS$, is as follows:

$$ePVS = \frac{1 - \text{hematocrit}(M1)}{\text{hematocrit}(M0)} \times 0.01$$

**VARIABLES.** Measurements at M0 and M1 included ePVS, New York Heart Association (NYHA) functional class, Killip class (available at M0 only), weight, estimated glomerular filtration rate (eGFR) assessed by the MDRD (Modification of Diet in Renal Disease) formula, blood pressure, hemoglobin and hematocrit concentrations, serum sodium, and left ventricular ejection fraction (LVEF) (available at M0 only). $\Delta ePVS$ and change in the continuous variables between M0 and M1 were also considered together with medical history (age, sex, race, previous hospitalization for HF, reperfusion therapy, previous AMI, diabetes mellitus, prior episodes of HF, and hypertension). Because of the number of missing values for albumin and serum protein at M0 and M1 (25%), those variables were not considered in the present analysis. Albumin and serum protein at M0 and M1 as well as albumin variation between M0 and M1 were also considered with outcomes but not the change in serum protein in univariate analysis (data not shown).

**CONCISE STATISTICAL ANALYSIS SECTION.** A complete description of the statistical methods used is provided in the Online Appendix. All analyses were performed with SAS version 9.1.3 (SAS Institute, Cary, North Carolina) and R software (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are described as median and interquartile range and categorical data as proportions. The chi-square test or Fisher exact test was used for categorical variables and the nonparametric Kruskal-Wallis test for continuous variables. Correlations were obtained with Spearman’s rho. The 2-tailed significance level was set to $p \leq 0.05$.

To select a set of predictors for multivariate analysis, a univariate analysis was performed to test the existence of a significant dependence between each of the initial variables and the 2-class variable “event/nonevent.” A variable was retained if the corresponding p value was smaller than 0.15, which is

---

**TABLE 2** Characteristics of Patients With and Without Events

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nonevent (n = 4,697)</th>
<th>Event (n = 260)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA functional class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0 ≥ 2</td>
<td>70</td>
<td>77</td>
<td>0.013</td>
</tr>
<tr>
<td>M0 ≥ 3</td>
<td>16</td>
<td>34</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>M1 ≥ 2</td>
<td>66</td>
<td>81</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>M1 ≥ 3</td>
<td>13</td>
<td>37</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Killip class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0 ≥ 2</td>
<td>85</td>
<td>91</td>
<td>0.008</td>
</tr>
<tr>
<td>M0 ≥ 3</td>
<td>18</td>
<td>34</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Weight, kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>78 (68 to 87)</td>
<td>74 (67 to 84)</td>
<td>0.003</td>
</tr>
<tr>
<td>M1</td>
<td>77 (68 to 87)</td>
<td>74 (66 to 83)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Δ weight*</td>
<td>0 (–2 to 1)</td>
<td>–1 (–2 to 1)</td>
<td>0.014</td>
</tr>
<tr>
<td>ePVS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>4.478 (3.931 to 5.120)</td>
<td>4.701 (4.152 to 5.428)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>M1</td>
<td>4.348 (3.904 to 4.882)</td>
<td>4.711 (4.152 to 5.485)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ΔePVS, %</td>
<td>–2 (–12 to 8)</td>
<td>0 (–9 to 12)</td>
<td>0.0009</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73 m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>68 (56 to 82)</td>
<td>62 (49 to 75)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>M1</td>
<td>67 (55 to 80)</td>
<td>57 (46 to 73)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Δ eGFR*</td>
<td>0 (–9 to 8)</td>
<td>–3 (–12 to 6)</td>
<td>0.015</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic M0</td>
<td>120 (110 to 130)</td>
<td>118 (106 to 130)</td>
<td>0.22</td>
</tr>
<tr>
<td>Systolic M1</td>
<td>120 (110 to 140)</td>
<td>120 (108 to 136)</td>
<td>0.022</td>
</tr>
<tr>
<td>Δ systolic BP*</td>
<td>5 (–7 to 15)</td>
<td>3 (–10 to 10)</td>
<td>0.14</td>
</tr>
<tr>
<td>Diastolic M0</td>
<td>70 (65 to 80)</td>
<td>70 (64 to 80)</td>
<td>0.042</td>
</tr>
<tr>
<td>Diastolic M1</td>
<td>76 (70 to 80)</td>
<td>75 (68 to 80)</td>
<td>0.061</td>
</tr>
<tr>
<td>Δ diastolic BP*</td>
<td>0 (–5 to 10)</td>
<td>0 (–5 to 10)</td>
<td>0.75</td>
</tr>
<tr>
<td>Hemoglobin, g/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>13.4 (12.3 to 14.5)</td>
<td>12.9 (11.8 to 13.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>M1</td>
<td>13.6 (12.6 to 14.5)</td>
<td>12.9 (11.8 to 14)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Δ hemoglobin*</td>
<td>0.2 (–0.6 to 1)</td>
<td>0 (–1.1 to 0.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>40 (37 to 43)</td>
<td>39 (36 to 42)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>M1</td>
<td>41 (38 to 43)</td>
<td>39 (36 to 42)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Δ hematocrit*</td>
<td>1 (–2 to 3)</td>
<td>0 (–3 to 2)</td>
<td>0.002</td>
</tr>
<tr>
<td>Sodium (mmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>140 (137 to 142)</td>
<td>139 (136 to 141)</td>
<td>0.018</td>
</tr>
<tr>
<td>M1</td>
<td>141 (139 to 143)</td>
<td>141 (138 to 143)</td>
<td>0.32</td>
</tr>
<tr>
<td>Δ sodium*</td>
<td>1 (–1 to 4)</td>
<td>1 (–1 to 4)</td>
<td>0.29</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>35 (30 to 38)</td>
<td>34 (28 to 37)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>64 (55 to 72)</td>
<td>70 (61 to 76)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male</td>
<td>71</td>
<td>64</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Continued on the next page
commonly used in such approaches. Moreover, any variable highly correlated with another variable and with a less significant p value was not retained.

To examine association with an event, a stepwise logistic regression based on the remaining variables was performed by using the likelihood ratio test at a threshold of 0.05. This analysis automatically excluded insufficiently predictive variables. Prognostic gain of $\Delta$ePVS or ePVS was assessed by the integrated discrimination improvement (IDI), the continuous net reclassification improvement (NRI), and the increased area under the receiver-operating characteristic curve (IAUC). Stepwise discriminant analysis and linear discriminant analysis were also performed to verify the stability of the set of retained variables (Online Table 2). Furthermore, the quality and stability of all models were tested by cross-validation (Online Table 3). Finally, subgroup analyses were performed by a stepwise logistic regression: with and without anemia, anticoagulant agents, antithrombotic therapy, and reperfusion therapy at baseline. Anemia was defined according to the World Health Organization criteria as a baseline hemoglobin $<13$ g/dl for men and $<12$ g/dl for women.

RESULTS

Comparison of the characteristics at baseline between included and nonincluded patients showed that the 1,675 nonincluded patients generally had more severe HF (Table 1).

BASELINE, 1-MONTH, AND IN-BETWEEN FEATURES ASSOCIATED WITH CARDIOVASCULAR EVENTS IN UNIVARIATE ANALYSIS. Patients with events (Table 2) were older and had a lower LVEF, weight, and eGFR at baseline and M1, as well as higher NYHA and Killip classes and lower hemoglobin and hematocrit concentrations. $\Delta$ePVS was significantly associated with early cardiovascular events ($p = 0.0009$). Of note, ePVS at baseline and M1 were also significantly associated with cardiovascular events ($p < 0.0001$). Patients who lost weight experienced more frequent events. Of note, $\Delta$ePVS and changes in body weight were not significantly correlated ($\rho = 0.02$; $p = 0.093$).

MULTIVARIATE ANALYSIS INCLUDING $\Delta$ePVS. $\Delta$ePVS was retained in the logistic regression model (odds ratio [OR]: 1.01; $p = 0.004$) (Table 3): if plasma volume increased, the probability of a cardiovascular event also increased. With regard to the added predictive ability of $\Delta$ePVS in the model beyond that of clinical variables, both NRI and IAUC measures were positive but not significant (NRI: $0.09$ [p = 0.18], IAUC: $0.0012$ [p = 0.39]). $\Delta$ePVS significantly improved the IDI by 7.57% ($p = 0.01$). Of note, in a sensitivity analysis in the subgroups with and without anemia, $\Delta$ePVS was also retained in the models (Online Table 4).

MULTIVARIATE ANALYSIS INCLUDING INSTANTANEOUS ePVS. ePVS at M1 was retained in the logistic regression model (OR: 1.38; $p < 0.0001$) (Table 4). The 3 measures of added predictive ability of ePVS at M1 were positive and significant: relative IDI = 15.06% ($p = 0.004$), NRI = 0.18 ($p = 0.004$), and IAUC = 0.01 ($p = 0.035$).

With regard to sensitivity analyses, we found the following results: 1) ePVS M1 was a better predictor of early cardiovascular events than $\Delta$ePVS (Online Appendix); 2) in the subgroups with and without anemia at baseline, ePVS M1 was retained in the models, as was the case in the subgroups with and without anticoagulant agents, antithrombotic drugs, and reperfusion therapy at baseline (Online Table 4); 3) in a larger EPHESUS dataset (i.e., that included 5,845 or 5,880 patients with available hemoglobin or hematocrit measurements at M0), ePVS M0 was only marginally associated with event occurrence at M1 ($p = 0.051$), whereas it was significantly associated with 90-day events (OR: 1.12, $p = 0.007$; NRI: $p = 0.027$; IDI: $p = 0.075$) and 180-day events (OR: 1.14, $p = 0.0006$; NRI: $p = 0.0003$; IDI: $p = 0.002$). Of note, when ePVS M1 was considered in lieu of ePVS M0, it was retained in the model ($p < 0.0001$) and significantly increased the predictive capacity of the model (data not shown); and 4) in a subset of the EPHESUS population with available brain natriuretic peptide (BNP) measurements, we previously reported significant positive

---

**TABLE 2 Continued**

<table>
<thead>
<tr>
<th></th>
<th>Nonevent (n = 4,697)</th>
<th>Event (n = 260)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>91</td>
<td>89</td>
<td>0.39</td>
</tr>
<tr>
<td>Previous hospitalization for HF</td>
<td>7</td>
<td>16</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Reperfusion therapy</td>
<td>46</td>
<td>37</td>
<td>0.002</td>
</tr>
<tr>
<td>Previous AMI</td>
<td>26</td>
<td>37</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>31</td>
<td>39</td>
<td>0.005</td>
</tr>
<tr>
<td>Prior episodes of HF</td>
<td>14</td>
<td>26</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Hypertension</td>
<td>61</td>
<td>71</td>
<td>0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medications</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Eplerenone</td>
<td>51</td>
<td>42</td>
<td>0.007</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>86</td>
<td>89</td>
<td>0.17</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>76</td>
<td>70</td>
<td>0.017</td>
</tr>
<tr>
<td>Loop diuretic drugs</td>
<td>52</td>
<td>79</td>
<td>$&lt;0.0001$</td>
</tr>
</tbody>
</table>

Values are median (interquartile range) or proportion (%). *Absolute change between month 1 and baseline. Events considered between months 1 and 3 after AMI were cardiovascular death or hospitalization for HF.

M0 = baseline measurement; M1 = measurement at month 1; $\Delta$ePVS = estimated plasma volume variation (Strauss formula); other abbreviations as in Table 1.
correlations between changes in BNP and PV, as assessed by the Strauss formula between baseline and month 1 (5). Present analysis of this subset of 346 patients showed that BNP and instantaneous ePVS at M0 and M1 were significantly but weakly correlated (rho = 0.23, p < 0.0001 at M0; rho = 0.25, p < 0.0001 at M1). Among this subset, 14 patients experienced a cardiovascular event. BNP M1 (area under the ROC curve [AUC] = 0.88) and ePVS M1 (AUC = 0.78) were good predictors of cardiovascular events in univariate analysis, although the model had an even greater discriminative ability when both variables were combined (AUC = 0.90) (Figure 1). With regard to the added predictive ability of ePVS M1 in the model that included both variables, the 3 measures were positive, and only IAUC was not significant (relative IDI = 129.9%, p = 0.029; NRI = 0.89, p = 0.0006; and IAUC = 0.02, p = 0.36). However, because of the small number of cardiovascular events, these last results should be interpreted with caution.

**DISCUSSION**

To the best of our knowledge, the results of this analysis show for the first time that in patients with HF and left ventricular systolic dysfunction complicating AMI, a short-term (1 month) decrease in ePVS using the Strauss formula (i.e., decongestion) was associated with better cardiovascular outcomes independent of the clinical variables used in routine practice (e.g., NYHA functional class, Killip class, body weight, blood pressure, LVEF, and eGFR). Moreover, we found that an instantaneous estimation of PV directly derived from the Strauss formula displayed greater prognostic value. An instantaneous PV estimation should enable physicians to immediately and reliably assess a patient’s congestive status beyond usual routine clinical assessment and natriuretic peptide measurement.

The noninvasive assessment of PV is important in the management of HF patients to tailor diuretic doses to the needs of the individual patient, as recommended by all current guidelines (3,16) but often not achieved because of the unreliability of clinical signs and symptoms. In the present study, a majority of patients received loop diuretic drugs at baseline, with these patients experiencing more events. Of note, observational studies have shown an association between high-dose loop diuretic drugs and adverse outcomes; however, these studies are confounded by the fact that patients receiving higher doses of diuretic

![Table 3](image)

**TABLE 3** Stepwise Logistic Regression With ΔePVS

<table>
<thead>
<tr>
<th>Variables Retained by the Model</th>
<th>Coefficient</th>
<th>OR (95% CI)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA functional class M1 ≥3</td>
<td>1.07</td>
<td>2.92 (2.21-3.86)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>eGFR M1</td>
<td>-0.02</td>
<td>0.98 (0.98-0.99)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Killip class M0 ≥3</td>
<td>0.47</td>
<td>1.60 (1.21-2.12)</td>
<td>0.001</td>
</tr>
<tr>
<td>ΔePVS</td>
<td>0.01</td>
<td>1.01 (1.00-1.02)</td>
<td>0.004</td>
</tr>
<tr>
<td>LVEF M0</td>
<td>-0.02</td>
<td>0.98 (0.96-1.00)</td>
<td>0.031</td>
</tr>
<tr>
<td>Previous hospitalization for HF</td>
<td>0.44</td>
<td>1.55 (1.07-2.25)</td>
<td>0.025</td>
</tr>
<tr>
<td>Systolic BP M1</td>
<td>-0.01</td>
<td>0.99 (0.98-1.00)</td>
<td>0.005</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.43</td>
<td>1.54 (1.15-2.07)</td>
<td>0.003</td>
</tr>
<tr>
<td>Weight M1</td>
<td>-0.01</td>
<td>0.99 (0.98-1.00)</td>
<td>0.043</td>
</tr>
</tbody>
</table>

*p value associated with the likelihood ratio test.

CI = confidence interval; OR = odds ratio; other abbreviations as in Tables 1 and 2.

![Table 4](image)

**TABLE 4** Stepwise Logistic Regression With ePVS at M1

<table>
<thead>
<tr>
<th>Variables Retained</th>
<th>Coefficient</th>
<th>OR (95% CI)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA functional class M1 ≥3</td>
<td>1.00</td>
<td>2.72 (2.05-3.61)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ePVS M1</td>
<td>0.32</td>
<td>1.38 (1.21-1.59)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>eGFR M1</td>
<td>-0.01</td>
<td>0.99 (0.98-0.99)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Killip class M0 ≥3</td>
<td>0.46</td>
<td>1.58 (1.19-2.10)</td>
<td>0.002</td>
</tr>
<tr>
<td>LVEF M0</td>
<td>-0.02</td>
<td>0.98 (0.96-1.00)</td>
<td>0.030</td>
</tr>
<tr>
<td>Previous hospitalization for HF</td>
<td>0.43</td>
<td>1.53 (1.06-2.22)</td>
<td>0.030</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.39</td>
<td>1.47 (1.10-1.97)</td>
<td>0.009</td>
</tr>
<tr>
<td>Systolic BP M1</td>
<td>-0.01</td>
<td>0.99 (0.98-1.00)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

*p value associated with the likelihood ratio test.

CI = confidence interval; OR = odds ratio; other abbreviations as in Tables 1 and 2.
drugs tend to have greater disease severity or comorbidity (17). In the present series, decongestion between baseline and at 1 month, as assessed by a decrease in ePVS, was found to be associated with better clinical outcomes. This finding corroborates and extends data derived from 3 randomized trials in acute decompensated HF that reported an association between decongestion (as assessed by biological surrogates of PV) during index hospitalization and better outcomes. An analysis of the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial investigated baseline-to-discharge increases in hematocrit, albumin, and total protein values. Patients with 2 or more of the 3 aforementioned variables with values in the top tertile were considered to have evidence of hemoconcentration, which was associated with greater net weight or fluid loss and greater reductions in right atrial pressure and pulmonary capillary wedge pressure, along with a substantially lower risk of mortality (4). In an analysis of the PROTECT (Placebo-Controlled Randomized Study of the Selective Adenosine A1 Receptor Antagonist Rolofylline for Patients Hospitalized With Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function), hemoconcentration was defined as an increase in hemoglobin levels between baseline and day 7 in patients presenting with acute decompensated HF. A rapid increase in hemoglobin during hospitalization was related to improved 180-day survival (6). In the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan), analysis of the absolute in-hospital hematocrit changes calculated between baseline and discharge or day 7 (whichever occurred first) showed that patients with hemoconcentration (i.e., ≥3% absolute increase in hematocrit) were less likely to have clinical congestion at discharge, whereas every 5% increase in in-hospital hematocrit change was associated with decreased cardiovascular mortality or HF hospitalization at ≥100 days after randomization (7).

The present study, EPHESUS, provided an opportunity to monitor decongestion using both clinical and biological variables after hospital discharge between baseline and 1 month, a critical time frame in terms of rehospitalization burden. Several formulas were used to estimate instantaneous PV and respective changes between baseline and 1-month post-myocardial infarction in patients with HF. In a head-to-head comparison during univariate analysis, only the Strauss formula (to assess variations) and its instantaneous derivation were associated with 3-month outcomes. This formula contains hemoglobin ratios and therefore includes both hemoglobin changes, which may be relevant in HF patients with cardiorenal anemia syndrome (18), and multifactorial changes, involving medications as well as bone marrow dysfunction associated with kidney dysfunction, inflammation, and malnutrition. Although both hematocrit and hemoglobin and their respective changes were also associated with outcomes under univariate analysis, they were not considered in the multivariate analysis because of the collinearity with PV estimation and the uncertainty related to the relative contribution of congestion and anemia in these variables. Hemoconcentration, as evidenced by a rising hemoglobin, is an appropriate surrogate that indicates that the plasma refill rate has been exceeded by the rate of fluid removal, which can be measured easily and continuously by use of an in-line hematocrit sensor during ultrafiltration therapy (19).

Importantly, however, in the subgroups with and without anemia at baseline, ΔePVS or ePVS at M1 was always retained in the multivariate models. The fact that neither the Kaplan nor Hakim formulas were associated with outcomes may arise from the integration of body weight in both formulas. Indeed, both Kaplan and Hakim ePVS increase when hematocrit decreases and conversely decrease when weight decreases, whereas patients with events displayed lower weight and hemoglobin. Ideally, dry weight (i.e., the body weight measured in noncongested patients), which was not assessed in the present study and is difficult to estimate in routine practice because of frequently persisting edema in HF patients, should have been used to run these 2 formulas. Moreover, body weight loss, which was found to be associated with worse outcomes, may rather be associated with cachexia (20–22) as opposed to decongestion and therefore may be misleading for use in monitoring congestive status.

**STUDY LIMITATIONS.** First, the analysis in the EPHESUS patient population was performed in myocardial infarction patients with HF and altered ejection fraction, and thus, the external validity of these results remains to be assessed in other patient populations. In any event, the present results are hypothesis generating, stemming from a post-hoc analysis, and should be confirmed by further prospective investigations. Of importance, we believe that the statistical results are robust, considering that 2 different methods of discrimination (logistic regression and linear discriminant analysis) were used to create an event prediction model to verify the consistency of the results. Finally, the stability of the
models was tested by performing cross-validations, with ΔePVS or ePVS being selected consistently in the models.

Second, changes in PV, as estimated by the Strauss formula, were assessed by a proposed (10) indirect estimation of PV changes. This is a validated (on comparison with a radiolabeled gold standard) method that integrates hematocrit changes and is used routinely to estimate PV in patients with scheduled plasma exchanges (23,24), or even ultrafiltration in the HF setting (25), whereas notably, no specific validation has been reported to date in the HF setting. Interestingly, a sensitivity analysis showed that BNP (as a surrogate of cardiac congestion) measured in 346 patients and instantaneous ePVS were significantly but weakly correlated and that the coexistence of both elevated BNP and elevated instantaneous ePVS at month 1 predicted worse outcomes than either alone, which further strengthens the pathophysiological relevance of PV estimation beyond the usual tools.

CONCLUSIONS

In the setting of HF complicating AMI, our data provide important insights related to congestion assessment and its post-discharge prognostic value using a simple estimation of PV (with the Strauss formula or its instantaneous derivate) beyond usual clinical variables, which may therefore have major clinical implications for patient management. We suggest that monitoring plasma changes in volume may be useful to guide therapy optimization in patients after discharge from an HF hospitalization, which remains an important unmet need. Dedicated prospective outcome studies evaluating the role of the Strauss formula to estimate changes in PV are warranted.

ACKNOWLEDGMENT The authors thank Mr. Pierre Pothier for editing this manuscript.

REFERENCES


**KEY WORDS** congestion, heart failure, plasma volume

**APPENDIX** For an expanded Methods section, please see the online version of this article.