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Plasma Volume Status and its Association with In-Hospital and Post-Discharge Outcomes in Decompensated Heart Failure

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Abstract

Background: Prior analyses suggest an association between formula-based plasma volume (PV) estimates and outcomes in heart failure (HF). We assessed the association between estimated PV-status by the Duarte-ePV and Kaplan Hakim (KH-ePVS) formulas, and in-hospital and post-discharge clinical outcomes, in the ASCEND-HF trial.

Methods and Results: KH-ePVS and Duarte-ePV were calculated on admission. We assessed associations with in-hospital worsening HF, 30-day composite cardiovascular mortality or HF rehospitalization and 180-day all-cause mortality. 6,373 (89.2%), and 6,354 (89.0%), patients had necessary characteristics to calculate KH-ePVS and Duarte-ePV, respectively. There was no association between PV by either formula with in-hospital worsening HF. KH-ePVS showed a weak correlation with NT-proBNP, and with measures of decongestion such as body weight change and urine output ($r < 0.3$ for all). Duarte-ePV was trending towards an association with worse 30-day (adjusted-OR 1.07, 95%CI 1.00-1.15, $p = 0.058$), but not 180-day outcomes (adjusted-HR 1.03, 95%CI 0.97-1.09, $p = 0.289$). Continuous KH-ePVS > 0 (per 10 unit increase) was associated with improved 30-day outcomes (adjusted-OR 0.75, 95%CI 0.62-0.91, $p = 0.004$). Continuous KH-ePVS was not associated with 180-day outcomes (adjusted-HR 1.05, 95%CI 0.98-1.12, $p = 0.139$).

Conclusions: Baseline PV estimates had a weak association with in-hospital measures of decongestion. Duarte-ePV, trended towards an association with early clinical outcomes in decompensated HF, and may improve risk stratification in HF.

Key Words: Heart Failure, Plasma Volume, Congestion

Abbreviations: Kaplan-Hakim estimated plasma volume status (KH ePVS), Duarte estimated plasma volume (Duarte ePV), HF (heart failure), Plasma Volume (PV), actual calculated plasma volume (aPV), ideal plasma volume (iPV)

INTRODUCTION

Although cardiovascular congestion is a hallmark of decompensated heart failure (HF), clinical assessment of total volume status by physical exam and biomarkers such as brain natriuretic peptides has marked variability.¹⁻³ The direct quantification of total plasma volume (PV) by the indicator dilution method provides precise measurements of PV excesses and deficits and early evidence suggests that it could be of clinical utility in patients with decompensated HF.⁴⁻⁷ However, such direct quantification is only rarely performed due to cost and logistic constraints. As such, calculated estimates of total PV have been developed which incorporate venous hemoglobin and/or hematocrit, and body weight parameters. Though recent work suggests that these calculated PV estimates are weakly correlated with directly measured PV in HF patients⁸, multiple prior analyses have suggested that calculated PV estimates are associated with biomarkers of (de)congestion and with morbidity and mortality in HF.⁹⁻¹⁷ We thus sought to evaluate the association between two calculated estimates of PV and post-discharge clinical outcomes in a large cohort of patients hospitalized for acute decompensated HF enrolled in the global, Effect of Nesiritide in Patients with Acute Decompensated Heart Failure (ASCEND-HF) Trial.¹⁸ We hypothesized that greater estimated PV would be associated with both increased measurements of decongestion, and with worse post-discharge clinical outcomes.

MATERIAL AND METHODS

Study Design

The design¹⁹ and primary results¹⁸ of ASCEND-HF have been reported previously. In brief, ASCEND-HF was a multinational, prospective, randomized, double-blind, placebo-controlled trial designed to examine the safety and efficacy of nesiritide, an intravenous recombinant B-type natriuretic peptide with vasodilatory properties, in patients with decompensated HF. Patients were eligible for trial enrollment if they were hospitalized for acute HF occurring within 24 hours since they received their first IV HF treatment, or if they received a

diagnosis of acute HF < 48 hours after admission for another cause. At the time of randomization, patients were required to have dyspnea either at rest or with minimal activity, as well as one additional symptom and one objective sign of acute HF. On a background of standard guideline-recommended HF therapy, patients were randomized to either nesiritide or placebo. The co-primary endpoints of ASCEND-HF were change in self-reported dyspnea at 6 and 24 hours after drug initiation, and a composite endpoint of either 30-day HF readmission or 30-day all-cause mortality. In our analysis we evaluated the following clinical outcomes: in-hospital worsening HF, composite of 30-day cardiovascular mortality or HF readmission, and 180-day all-cause mortality. Patients provided written informed consent, and each site's institutional review board or local ethics committee approved the study.

Calculation of Plasma Volume

Our analysis used baseline patient data to calculate estimates of PV at time of randomization to nesiritide or placebo. As such, we combined nesiritide and placebo arms for the current analysis. Two separate, validated estimates of PV status were calculated using baseline patient data. Estimated PV as assessed by the Duarte Formula (modified Strauss formula)^{9,20} was used to compute a point estimate of baseline PV (Duarte ePV), calculated as: Duarte ePV = [(1-hematocrit)/(Hemoglobin)] x 100, measured in the unit of dL/g.²¹

Additionally, estimated PV status as assessed by the Kaplan-Hakim formula²² (KH ePVS) was developed as an index of the degree to which a patient's actual calculated PV (aPV) has deviated from their ideal PV (iPV), calculated as: KH ePVS= [(aPV-iPV)/iPV] x 100%. aPV is computed with the following equation which was derived by curve-fitting techniques using subjects' hematocrit and dry body weight, as has been previously reported²³: aPV= (1-hematocrit) x [a + (b x weight in kg)] where adjustment factors were a = 1,530 in males and 864 in females, and b=41 in males and 47.9 in females. The iPV was calculated from a formula based on body weight: iPV= c x weight (kg) where the adjustment factor for c was 39 in males and 40 in females.²⁴

Multiple imputation by chained equations was used to impute missing covariates for the regression models, which were aggregated across 10 imputed datasets. Imputation models included demographic variables, baseline vitals, baseline labs, baseline medications, and outcome variables. For adjustment variables we utilize existing imputation datasets that have been used in previously published ASCEND secondary manuscripts and ran separate imputation models for the two plasma volume measurements.

Statistical Analysis

Continuous variables are expressed as median (Q1-Q3) and categorical variables are reported as number and percentage. For descriptive purposes, baseline characteristics and endpoint analyses are presented by quartiles of both baseline Duarte ePV and KH ePVS, using one-way analysis of variance, Kruskal-Wallis tests, and chi-square tests, as appropriate.

Univariable and multivariable logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals for the 30-day composite outcome. Univariable and multivariable Cox proportional-hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for calculated PVS, analyzed as a continuous variable (per 10% increase in KH ePVS and 1 unit increase in Duarte ePV) and by quartiles for 180-day all-cause mortality. The linearity of relationships between the 30-day and 180-day outcomes and continuous variables was evaluated and proportional-hazards assumptions were tested using Kolmogorov-type supremum tests. Departures from proportional hazards were modeled using stratification. C-indices were calculated for the individual models. Kaplan-Meier curves were constructed for calculated PVS quartiles, and time-to-first event was compared using log-rank tests.

Eight preselected baseline covariates, consistent with prior analyses²⁵, were included in final multivariable models: age, baseline BUN (log), dyspnea, hospitalization in prior year, baseline sodium (high), JVP, baseline systolic blood pressure (high), and baseline NT-proBNP. Knot selection for adjustment variables was based on previously published work; additionally we

used graphical methods to confirm the cut points for this analysis. For the PVS measurements, we evaluated the linearity test and spline plots to determine the appropriate functional form for each PVS measurement. For the 30 day outcome, we determined a linear spline adequately modeled the relationship between Kaplan-Hakim PVS measurement and the outcome; additionally a linear spline provides easier interpretation than a restricted cubic spline.

Age was modeled using a piecewise linear spline with a single knot at 55. Baseline sodium was modeled using a piecewise linear spline up to 140. Baseline systolic blood pressure (high) was modeled using a piecewise linear spline up to 140. Treatment with nesiritide and a treatment X PV interaction term were added to the models but neither were significant so they were dropped from the final models.

In the subset of patients with LVEF, an interaction term between type of heart failure (defined as LVEF \leq 40% and >40%) and the estimated PVS variable was added to the adjusted models described above. All statistical analyses were performed using SAS version 9.4, and $p < 0.05$ were considered to be statistically significant.

RESULTS

Baseline Characteristics

ASCEND-HF included 7,141 patients, of whom 6,373 (89.2%), and 6,354 (90.7%), had necessary baseline characteristics to calculate PV using Duarte ePV and KH ePVS, respectively. Admission estimated PV by both formulas was wide-ranging and showed marked heterogeneity (Duarte ePV: range 0.38 to 11.1, mean 5.0 ± 1.2 . KH ePVS: range -78.3% to 67.2%, mean $-5.9 \pm 11.6\%$) (**Figures 1.1, 1.2**). Duarte ePV and KH ePVS were strongly correlated ($r=0.738$, $p < 0.001$) (**Supplemental Figure 1/Table 1**). Duarte ePV ($r=0.160$, <0.001) and KH ePVS ($r=0.275$, $p < 0.001$) were also correlated with baseline NT-proBNP.

Patient baseline characteristics are presented, as stratified by quartiles of Duarte ePV (**Table 1.1**) and KH ePVS (**Table 1.2**). There were statistically significant differences by Duarte ePV quartiles. Those in higher quartile tended to be older, female, had higher rates of prior myocardial infarction and diabetes mellitus, and had greater baseline NT-proBNP levels and creatinine. They were also more likely to have rales and peripheral edema. KH ePVS quartiles also revealed significant differences. Patients in the higher quartiles tended to be older, female, higher LVEF, lower BMI, higher rates of NYHA class IV disease and prior myocardial infarction, lower use of ACEi/ARB, beta-blocker, and aldosterone antagonist therapies, higher baseline natriuretic peptide levels and creatinine, and lower baseline sodium. Patients in higher quartiles were also more likely to have rales, but less likely to have peripheral edema.

Correlation of ePVS with markers of clinical decongestion

Spearman rank correlation revealed that baseline Duarte ePV was not significantly correlated with either in-hospital weight change, or with 24-hour urine output (**Supplementary Table 1**). Baseline KH ePVS was weakly, positively correlated with in-hospital weight change ($r=0.147$, $p<0.001$), and weakly inversely correlated with 24-hour urine output ($r=-0.129$, $p<0.001$).

Association between Plasma Volume Formulas and Clinical Outcomes

Incidence of in hospital worsening HF events, 30- day outcomes, and incidence rates of 180-day outcomes are reported (**Tables 2.1, 2.2**). In-hospital worsening HF events did not differ across quartiles of Duarte ePV ($p=0.052$) or KH ePVS ($p=0.797$).

The risk of 30-day composite outcomes (**Table 3.1**) differed significantly by Duarte ePV quartiles ($p<0.001$), with event rates increasing from the lowest quartile to the highest quartile. However, such differences did not persist beyond covariate adjustment (OR 1.13, 95% CI 0.98-1.31, $p=0.114$) (**Table 3.1**). When represented as a continuous variable, a 1-unit increase in Duarte ePV was associated with the 30-day composite outcome in both unadjusted (OR 1.17,

95% CI 1.10-1.25), $P < 0.001$) and fully adjusted (OR 1.07, 95% CI 1.00-1.15, $p = 0.058$) logistic regression models (**Table 3.1**).

30-day composite outcome also differed across KH ePVS quartiles ($p = 0.008$) (**Table 2.2**), but such differences did not retain significance in logistic regression modeling (adjusted OR 0.87, 95% CI 0.75-1.01, $p = 0.229$) (**Table 3.1**). A 10% increase in KH ePVS was non-linearly associated with the 30-day composite outcome (**Supplementary Figure 3**). As such, this relationship was modeled using a piecewise linear spline, with results reported separately for patients with KH ePVS $> 0\%$ (top 29% of the population), and for those with KH ePVS $< 0\%$. In patients above $> 0\%$ KH ePVS, each 10% increase was associated with a significant decrease in risk of 30-day composite outcome in fully adjusted models (OR 0.75, 95% CI 0.62-0.91, $p = 0.004$) (**Table 3.1**).

180-day all-cause mortality was significantly different across Duarte ePV quartiles, with event rates increasing from the lowest quartile to the highest quartile (**Table 2.1, Figure 2**). Using Cox proportional hazard models to compare the lowest and highest quartiles (**Table 3.2**), such differences did not persist beyond covariate adjustment (adjusted HR 1.18, 95% CI 0.95-1.45 $p = 0.226$). Continuous Duarte ePV was associated with 180-day all-cause mortality, in unadjusted (HR 1.18, 95% CI (1.12-1.24), $p < 0.001$), but not fully adjusted (HR 1.03, 95% CI 0.97-1.10, $p = 0.273$), Cox regression models (**Table 3.2**).

180-day all-cause mortality also differed significantly by KH ePVS quartiles (**Table 2/Figure 2**), with quartile four demonstrating higher all-cause mortality as compared to quartile one in unadjusted, but not in fully adjusted models (adjusted HR 1.23, 95% CI 0.97 - 1.56, $p = 0.365$) (**Table 3.2**). Continuously valued KH ePVS (10% increase) was significantly associated with 180-day all-cause mortality in unadjusted (HR 1.25, 95% CI 1.19 - 1.32, $p < 0.001$), but not adjusted analysis (HR 1.05, 95% CI 0.98-1.12, $p = 0.139$).

In a sensitivity analysis, the association with the 30 days / 180 days outcomes and individual components of the estimated PV formulas was evaluated (**Supplementary Table 2.1**

and 2.2). For Duarte PV no individual component of the formula was independently associated with the clinical outcomes. In the KH ePVS the weight was independently associated with 30 but not 180 days outcome.

HFpEF vs HFrEF

In the subset of patients with available LVEF, we investigated whether the associations between ePVS and both 30-day composite outcome and 180-day all-cause mortality were modified by HF type, HFpEF versus HFrEF (LVEF > 40, or LVEF ≤ 40%, respectively) (**Supplementary Table 3**). No significant interactions were found ($p > 0.05$ for all).

DISCUSSION

The present study has several key findings: 1) In the largest analysis of estimated PV to date, irrespective of the formula used, estimated PV on admission ranged widely, suggesting vast heterogeneity. 2) Despite good correlation between formulas, estimates of PV were poorly correlated with surrogates of clinical decongestion during the hospitalization. 3) Continuous Duarte ePV had a trend towards an association with 30-day composite cardiovascular mortality or HF readmission, but not with 180-day all cause mortality, beyond adjustment for multiple risk factors. KH ePVS had no consistent association with 30-day or 180-day outcomes. 4) In all instances the prognostic utility of estimated PV did not differ between HFrEF versus HFpEF. In sum, in a large population of decompensated HFrEF the relationships between formula based estimates of PV status and clinical outcomes were inconsistent, perhaps suggestive of limited clinical utility.

In decompensated HF, the degree of intravascular congestion is closely correlated with adverse clinical outcomes.^{26,27} As such, the centerpiece of decompensated HF care involves symptomatic relief with therapies targeting decongestion, most commonly, loop diuretics. However, the extent to which decongestion is achieved is highly variable and often less than clinically suspected.⁴ The assessment of vascular congestion on clinical exam,^{1,2} increase in

body weight,^{28,29} natriuretic peptide levels,³ as well as invasive hemodynamic measurements,^{30,31} lack sufficient sensitivity and specificity to accurately assess a patient's volume status. Precise measurement of intravascular PV can be achieved through indicator-dilution techniques. Studies using these methods have demonstrated marked heterogeneity in volume status in patients with chronic^{32,33} and decompensated HF³⁴, providing the ability to uncover clinically unrecognized hypervolemia even in non-edematous patients.⁴ However, this method of PV quantification is not universally available in a clinical setting.

Clinically accessible calculated estimates of total PV were initially developed for use in patients with renal disease and incorporated venous hemoglobin or hematocrit, and body weight parameters. Recent work suggests that in compensated HF, these calculated PV estimates have a variable association with directly quantified PV measurements.⁸ Nevertheless, several prior analyses have suggested that such calculated PV estimates are associated with biomarkers of (de)congestion and with short and long-term morbidity and mortality in HF.⁹⁻¹⁷

To our knowledge, this is the largest analysis to date to assess the clinical prognostic utility of two calculated point estimates of baseline PV in patients with decompensated HF. In our cohort, estimated PV by the Duarte formula (Duarte ePV) was trending towards an association with early clinical outcomes in HF, beyond adjustment for multiple measures of risk and congestive status. This finding extends prior analysis by Duarte et al,⁹ which showed that in 4,957 patients in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), estimated PV by Duarte ePV was associated with the combined endpoint of cardiovascular death or HF hospitalization between 1 and 3 months post-acute myocardial infarction. Our findings suggest that admission Duarte ePV, an easily calculated, formula based estimate of PV, may aid in achieving earlier identification of patients at risk for early poor outcomes in decompensated HF syndromes. Notably, the weak association with adverse outcomes was not present at 180 days. The disconnect between the association of

Duarte ePV with early HF/cardiovascular related outcomes and late all-cause death further underlines the prognostic utility of ePV as a marker of congestion.

Of interest, our study found an inverse relationship between increase in KH ePVS > 0 and 30-day composite outcomes, suggesting that a greater degree of estimated vascular congestion by KH ePVS was associated with an improved clinical status at 30 days. KH ePVS requires the use of dry weight to ensure maximum accuracy of estimated PVS. As dry weight is often unknown in the context of an acute decompensation, the use of baseline weight (as performed in our study), or admission hospital weight (as might be used in a clinical context), it may introduce inaccuracy to the formula, and may explain the results of our analysis. Nevertheless, such finding casts doubt on whether KH ePVS has clinical applications for the early management of decompensated HF. Though, we found KH ePVS was associated with long-term, 180 day outcomes in unadjusted analyses, this relationship did not persist beyond adjustment. This contrasts analyses from Grodin et al., which demonstrated that KH ePVS was associated with long-term risk of HF hospitalization in a subset of 3,414 patients with stable chronic HFpEF (EF >45%) from the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial (TOPCAT).³⁵ It also contradicts prior analysis from Ling et al. who found an association between KH ePVS and late clinical outcomes in a cohort of 5,002 patients with stable chronic HFrEF from the Valsartan in Heart Failure (Val-HeFT) trial.¹² Taken together, our findings may suggest limited clinical applications for the assessment of Duarte ePV and KH ePVS in acute decompensated HF.

Finally, this analysis is the first to evaluate the prognostic utility of Duarte ePV and KH ePVS in HFrEF versus HFpEF. There were significant differences in LVEF across quartiles of estimated PV, with patients in higher quartiles having greater baseline LVEF. Adjusted analyses identified no significant interactions between either KH ePVS or Duarte ePV and HF type in 30-day or 180-day clinical outcomes. This finding is important, since patients with HFpEF are suggested to be more sensitive to fluid loading,^{36,37} implying that a smaller increase in PV might

result in more pronounced intra-cardiac pressure increases and symptom onset. Yet, our study suggests that HF type had no impact on the association between estimated PV and clinical outcomes.

The importance of vascular decongestion during HF hospitalization is well established.³⁸ Besides clinical judgment, a number of non-invasive, biomarker-driven methods have been suggested to guide the decongestive process.³⁹ Greater degrees of hemoconcentration,^{15,40} greater hemoglobin,⁴¹ and larger changes in calculated PV^{9,11,42} during a hospitalization have been associated with improved in-hospital and post-discharge outcomes. The value of an instantaneous and simple point estimate, Duarte ePV, as shown here is that it may provide an index impacting and predicting short-term clinical outcomes and thus inform management decisions at an earlier time point in a patient's hospitalization. Thus, the simple formula-derived value obtained on admission may help clinicians risk stratify the patient beyond routinely available clinical factors. To what degree a change in this formula-derived index at the time of hospital discharge can enhance clinical decision-making remains to be further evaluated.

Limitations

There are several limitations to the present study. The *post hoc* retrospective design of this analysis does not allow for analysis of a causal relationship between calculated PV and measured outcomes. Despite multivariable accounting, residual confounding from unmeasured variables may influence the results. The results of study cannot be generalized beyond the specific inclusion and exclusion criteria detailed in the ASCEND-HF trial. Furthermore, patient enrollment was permitted by study protocol ≤ 48 hours after admission, and this study cannot unequivocally rule out the possibility that an association between PV and post-discharge outcomes may have differed if PVS was assessed immediately upon hospital admission in all patients. Finally, PV formulas were validated in historic non HF cohorts at a dry state, which limits applicability to a population with acute HF and could explain some of the variability in association with outcomes.

Conclusions

Our analysis suggests that a calculated estimate of total plasma volume during early hospitalization, Duarte ePV, trended towards an association with early post-discharge clinical outcomes in patients with decompensated HF beyond adjustment for traditional clinical markers of risk. Given the variable association with outcomes and lack of prospective data, dedicated trials are warranted to evaluate the use of prospectively estimated PV-guided therapy in patients with decompensated HF. The benefit may lie in identifying patients with (residual) congestion and further risk stratify them for adverse clinical outcomes.

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Tables:

Table 1.1 Baseline characteristics stratified by quartiles of estimated plasma volume (ePV) defined by the Duarte Formula

Table 1.2 Baseline characteristics stratified by quartiles of plasma volume status (PVS) defined by the Kaplan-Hakim Formula

Table 2.1 Outcomes stratified by quartiles of estimated plasma volume (ePV) defined by the Duarte Formula

Table 2.2 Outcomes stratified by quartiles of estimated plasma volume status by Kaplan- Hakim Formula (KH ePVS).

Table 3.1 Association between calculated PVS and 30 day CV Mortality and Rehospitalization for HF

Table 3.2 Association between calculated PVS and 180 day all-cause mortality

Figures

Figure 1 Distribution of PV estimates with KH ePVS and Duarte ePV

Figure 2 Kaplan-Meier Event Curves for 180 Day All-Cause Death by individual PV estimates.

Table 1.1 Baseline characteristics stratified by quartiles of estimated plasma volume (ePV) defined by the Duarte Formula

Characteristic	Q1 (0.4, 4.1) N=1586	Q2 (0.4, 4.9) N=1588	Q3 (4.9, 5.8) N=1586	Q4 (5.8, 11.1) N=1587	P-Value
Demographics					
Age, yrs	62(53 - 72)	67(56 - 76)	69(58 - 78)	70(60 - 79)	<.001
Female	328 (20.7%)	500 (31.5%)	634 (40.0%)	747 (47.1%)	<.001
Race Groups					<.001
White	942 (59.4%)	903 (56.9%)	891 (56.2%)	882 (55.6%)	
Black or African American	191 (12.1%)	268 (16.9%)	279 (17.6%)	290 (18.3%)	
Asian	364 (23.0%)	338 (21.3%)	358 (22.6%)	361 (22.7%)	
Other	88 (5.6%)	79 (5.0%)	58 (3.7%)	54 (3.4%)	
Geographic Region					<.001
Asia-Pacific	365 (23.0%)	341 (21.5%)	357 (22.5%)	349 (22.0%)	
Central Europe	316 (19.9%)	254 (16.0%)	187 (11.8%)	93 (5.9%)	
Latin America	190 (12.0%)	158 (9.9%)	119 (7.5%)	103 (6.5%)	
North America	604 (38.1%)	715 (45.0%)	810 (51.1%)	943 (59.4%)	
Western Europe	111 (7.0%)	120 (7.6%)	113 (7.1%)	99 (6.2%)	
Baseline Weight, kg	82(69 - 99)	79(66 - 96)	77(63 - 94)	77(63 - 94)	<.001
Baseline BMI	28(24 - 33)[1572]	28(24 - 33)[1577]	27(24 - 32)[1577]	28(24 - 33)[1567]	0.020
Baseline Systolic BP	122(110 - 140)	121(110 - 139)	123(110 - 140)	126(112 - 140)	<.001
Baseline Diastolic BP	78(70 - 88)[1586]	75(68 - 84)[1587]	74(65 - 82)[1586]	70(62 - 80)[1587]	<.001
Baseline Heart Rate, bpm	85(74 - 98)[1585]	83(72 - 95)[1588]	80(70 - 94)[1586]	80(70 - 92)[1587]	<.001
Left Ventricular Ejection Fraction, previous 12 months	25(20 - 35)[1092]	27(20 - 35)[1120]	30(20 - 35)[1147]	30(25 - 42)[1165]	<.001
Clinical Profile					
NYHA Classification					<.001
NYHA Class not assessed	265 (16.7%)	268 (16.9%)	271 (17.1%)	346 (21.8%)	
I	68 (4.3%)	66 (4.2%)	58 (3.7%)	35 (2.2%)	
II	235 (14.8%)	255 (16.1%)	265 (16.7%)	239 (15.1%)	
III	635 (40.0%)	642 (40.4%)	676 (42.6%)	617 (38.9%)	
IV	383 (24.1%)	357 (22.5%)	316 (19.9%)	350 (22.1%)	
Rales					0.003
No Pulmonary Congestion	242 (15.3%)	215 (13.5%)	182 (11.5%)	189 (11.9%)	
Less than 1/3 up lung fields	553 (34.9%)	553 (34.8%)	522 (32.9%)	519 (32.7%)	
Greater than or eq to 1/3 up lung fields	791 (49.9%)	820 (51.6%)	882 (55.6%)	879 (55.4%)	
Peripheral Edema	1166 (73.5%)	1177 (74.1%)	1197 (75.5%)	1292 (81.4%)	<.001
Medical History					

Characteristic	Q1 (0.4, 4.1) N=1586	Q2 (0.4, 4.9) N=1588	Q3 (4.9, 5.8) N=1586	Q4 (5.8, 11.1) N=1587	P-Value
History of Myocardial Infarction	497 (31.3%)	531 (33.5%)	575 (36.3%)	596 (37.6%)	<.001
History of Atrial Fibrillation/Flutter	632 (39.8%)	612 (38.5%)	591 (37.3%)	607 (38.2%)	0.515
History of Hypertension	1088 (68.6%)	1125 (70.8%)	1206 (76.0%)	1245 (78.4%)	<.001
History of Diabetes Mellitus	534 (33.7%)	614 (38.7%)	702 (44.3%)	877 (55.3%)	<.001
Medications at Baseline					
ACEi or ARB	958 (60.4%)	963 (60.6%)	998 (62.9%)	936 (59.0%)	0.155
Beta Blockers	909 (57.3%)	943 (59.4%)	973 (61.3%)	978 (61.7%)	0.045
Aldosterone Antagonists	495 (31.2%)	467 (29.4%)	430 (27.1%)	363 (22.9%)	<.001
Calcium Channel Blockers	140 (8.8%)	188 (11.8%)	211 (13.3%)	305 (19.2%)	<.001
Nitrates	296 (18.7%)	331 (20.8%)	391 (24.7%)	444 (28.0%)	<.001
Digoxin	473 (29.8%)	418 (26.3%)	425 (26.8%)	341 (21.5%)	<.001
Laboratory Values					
Baseline Creatinine, mg/dL	1.2(1.0 - 1.4)[1504]	1.2(1.0 - 1.5)[1517]	1.2(1.0 - 1.6)[1509]	1.4(1.1 - 1.9)[1523]	<.001
Baseline sodium, mmol/L	139(136 - 142)[1484]	139(136 - 141)[1497]	139(136 - 141)[1491]	139(136 - 141)[1510]	0.001
Baseline BUN, mg/dL	23(17 - 35)[1454]	23(17 - 35)[1475]	26(18 - 38)[1465]	30(20 - 46)[1503]	<.001
Baseline NT-proBNP, pg/mL	3750(1746 - 7197)[929]	4298(2084 - 8628)[854]	4964(2466 - 9882)[785]	5972(2708 - 12639)[733]	<.001
Baseline BNP, pg/mL	942(514 - 1800)[500]	1018(528 - 1897)[587]	996(552 - 1919)[669]	988(576 - 1794)[716]	0.384
Baseline hemoglobin, g/dl	15(14 - 16)[1586]	13(13 - 14)[1588]	12(12 - 12)[1586]	11(10 - 11)[1587]	<.001
Clinical Course					
Change in Weight (Baseline to Discharge/Day 10), kg	-2(-5 - -1)[952]	-2(-5 - -1)[936]	-2(-4 - 0)[1008]	-3(-5 - -1)[982]	0.006
Change in SBP (Baseline to 24Hrs), mmHg	-10(-21 - 0)[1465]	-10(-20 - 0)[1461]	-10(-21 - 0)[1470]	-9(-20 - 1)[1453]	0.758
Change in DBP (Baseline to 24Hrs), mmHg	-6(-15 - 0)[1465]	-6(-14 - 1)[1461]	-6(-15 - 1)[1470]	-5(-13 - 2)[1453]	0.018
Change in Creatinine (Baseline to 24Hrs), mg/dL	0.00(-0.10 - 0.15)[1406]	0.01(-0.10 - 0.15)[1427]	0.02(-0.10 - 0.15)[1415]	0.01(-0.10 - 0.20)[1432]	0.414
Urine Volume (Baseline to 24Hrs), mL	2250(1600 - 3355)[1412]	2300(1580 - 3300)[1382]	2300(1575 - 3300)[1379]	2300(1525 - 3325)[1352]	0.745
Length of Hospital Stay, days	6(4 - 10)[1586]	6(4 - 9)[1588]	5(3 - 9)[1586]	6(4 - 9)[1587]	0.010

Table 1.2 Baseline characteristics stratified by quartiles of plasma volume status (PVS) defined by the Kaplan-Hakim Formula

Characteristic	Q1 (-78%, -14%) N=1593	Q2 (-14%, -6%) N=1593	Q3 (-6%, 1%) N=1594	Q4 (1%, 67%) N=1593	P-Value
Demographics					
Age, yrs	61(50 - 71)	67(57 - 76)	70(59 - 78)	71(61 - 80)	<.001
Female	381 (23.9%)	613 (38.5%)	636 (39.9%)	585 (36.7%)	<.001
Race Groups					<.001
White	1021 (64.1%)	978 (61.4%)	909 (57.0%)	733 (46.0%)	
Black or African American	325 (20.4%)	297 (18.6%)	256 (16.1%)	153 (9.6%)	
Asian	171 (10.7%)	247 (15.5%)	367 (23.0%)	636 (39.9%)	
Other	75 (4.7%)	71 (4.5%)	62 (3.9%)	71 (4.5%)	
Geographic Region					<.001
Asia-Pacific	179 (11.2%)	251 (15.8%)	361 (22.6%)	621 (39.0%)	
Central Europe	320 (20.1%)	264 (16.6%)	176 (11.0%)	92 (5.8%)	
Latin America	162 (10.2%)	139 (8.7%)	147 (9.2%)	137 (8.6%)	
North America	820 (51.5%)	814 (51.1%)	807 (50.6%)	640 (40.2%)	
Western Europe	112 (7.0%)	125 (7.8%)	103 (6.5%)	103 (6.5%)	
Baseline Weight, kg	100(84 - 117)	84(72 - 98)	76(65 - 88)	63(54 - 73)	<.001
Baseline BMI	33(29 - 38)[1587]	29(26 - 34)[1581]	27(24 - 31)[1574]	23(21 - 26)[1579]	<.001
Baseline Systolic BP	126(112 - 140)	123(110 - 140)	123(110 - 139)	121(110 - 138)	<.001
Baseline Diastolic BP	79(70 - 89)[1592]	75(68 - 84)[1593]	72(65 - 81)[1594]	70(64 - 80)[1593]	<.001
Baseline Heart Rate, bpm	85(74 - 98)[1592]	82(72 - 95)[1593]	80(70 - 93)[1594]	81(70 - 94)[1593]	<.001
Left Ventricular Ejection Fraction, previous 12 months	26(20 - 35)[1079]	28(20 - 35)[1089]	30(20 - 38)[1160]	30(20 - 37)[1207]	<.001
Clinical Profile					
NYHA Classification					0.027
NYHA Class not assessed	301 (18.9%)	312 (19.6%)	292 (18.3%)	248 (15.6%)	
I	69 (4.3%)	59 (3.7%)	56 (3.5%)	48 (3.0%)	
II	242 (15.2%)	252 (15.8%)	248 (15.6%)	260 (16.3%)	
III	653 (41.0%)	627 (39.4%)	660 (41.4%)	636 (39.9%)	
IV	328 (20.6%)	343 (21.5%)	338 (21.2%)	401 (25.2%)	
Rales					<.001
No Pulmonary Congestion	277 (17.4%)	206 (12.9%)	184 (11.5%)	164 (10.3%)	
Less than 1/3 up lung fields	567 (35.6%)	580 (36.4%)	537 (33.7%)	476 (29.9%)	
Greater than or eq to 1/3 up lung fields	749 (47.0%)	807 (50.7%)	873 (54.8%)	953 (59.8%)	
Peripheral Edema	1332 (83.6%)	1226 (77.0%)	1180 (74.0%)	1115 (70.0%)	<.001

Characteristic	Q1 (-78%,- 14%) N=1593	Q2 (-14%, - 6%) N=1593	Q3 (-6%, 1%) N=1594	Q4 (1%, 67%) N=1593	P-Value
Medical History					
History of Myocardial Infarction	439 (27.6%)	563 (35.3%)	619 (38.8%)	584 (36.7%)	<.001
History of Atrial Fibrillation/Flutter	670 (42.1%)	640 (40.2%)	644 (40.4%)	501 (31.5%)	<.001
History of Hypertension	1197 (75.1%)	1194 (75.0%)	1209 (75.8%)	1085 (68.1%)	<.001
History of Diabetes Mellitus	667 (41.9%)	663 (41.6%)	718 (45.0%)	684 (42.9%)	0.191
Medications at Baseline					
ACEi or ARB	1023 (64.2%)	1005 (63.1%)	957 (60.0%)	885 (55.6%)	<.001
Beta Blockers	977 (61.3%)	1011 (63.5%)	989 (62.0%)	841 (52.8%)	<.001
Aldosterone Antagonists	501 (31.5%)	470 (29.5%)	428 (26.9%)	359 (22.5%)	<.001
Calcium Channel Blockers	187 (11.7%)	200 (12.6%)	227 (14.2%)	234 (14.7%)	0.046
Nitrates	278 (17.5%)	371 (23.3%)	406 (25.5%)	411 (25.8%)	<.001
Digoxin	441 (27.7%)	414 (26.0%)	405 (25.4%)	403 (25.3%)	0.391
Laboratory Values					
Baseline Creatinine, mg/dL	1.2(1.0 - 1.4)[1520]	1.2(1.0 - 1.5)[1518]	1.3(1.0 - 1.7)[1517]	1.3(1.0 - 1.8)[1524]	<.001
Baseline sodium, mmol/L	139(137 - 142)[1504]	139(137 - 142)[1490]	139(136 - 141)[1508]	138(135 - 141)[1506]	<.001
Baseline BUN, mg/dL	22(17 - 33)[1474]	24(17 - 35)[1468]	27(18 - 40)[1482]	29(20 - 45)[1499]	<.001
Baseline NT-proBNP, pg/mL	3095(1473 - 6002)[837]	4073(2061 - 7954)[820]	5135(2566 - 10180)[796]	6858(3072 - 13709)[868]	<.001
Baseline BNP, pg/mL	804(488 - 1372)[606]	1018(555 - 1891)[653]	1020(582 - 1980)[649]	1216(628 - 2280)[568]	<.001
Baseline hemoglobin, g/dl	15(14 - 16)[1585]	13(12 - 14)[1590]	12(11 - 13)[1591]	11(10 - 12)[1592]	<.001
Clinical Course					
Change in Weight (Baseline to Discharge/Day 10), kg	-3(-7 - -1)[949]	-2(-5 - -1)[944]	-2(-5 - 0)[981]	-2(-4 - 0)[1017]	<.001
Change in SBP (Baseline to 24Hrs), mmHg	-10(-22 - 0)[1473]	-10(-21 - 0)[1472]	-10(-21 - 1)[1476]	-10(-20 - 0)[1452]	0.646
Change in DBP (Baseline to 24Hrs), mmHg	-6(-15 - 0)[1473]	-5(-14 - 1)[1472]	-5(-14 - 2)[1476]	-5(-12 - 2)[1452]	0.037
Change in Creatinine (Baseline to 24Hrs), mg/dL	0.00(-0.10 - 0.16)[1427]	0.02(-0.10 - 0.17)[1428]	0.00(-0.10 - 0.17)[1426]	0.02(-0.10 - 0.15)[1425]	0.619
Urine Volume (Baseline to 24Hrs), mL	2550(1750 - 3650)[1408]	2400(1600 - 3475)[1393]	2175(1500 - 3140)[1377]	2100(1500 - 3000)[1375]	<.001
Length of Hospital Stay, days	6(4 - 10)[1593]	6(4 - 10)[1593]	6(4 - 9)[1594]	5(3 - 9)[1593]	<.001

Table 2.1: Outcomes stratified by quartiles of estimated plasma volume (ePV) defined by the Duarte Formula

Characteristic	Q1 N=1586	Q2 N=1588	Q3 N=1586	Q4 N=1587	P-Value
In hospital outcomes					
Worsening HF at discharge/day 10-- N (%) ⁺	88 (5.5%)	63 (4.0%)	68 (4.3%)	90 (5.7%)	0.052
Adverse Outcomes					
30 day CV death/HF hosp-- N (%) ⁺	114 (7.2%)	134 (8.4%)	160 (10.1%)	188 (11.8%)	<.001
180 day All-cause mortality [†]	9.7%	10.9%	13.4%	16.9%	<.001
⁺ Associated p-value is from a chi-square test.					
[†] Kaplan Meier event rate reported. Associated p-value is from a log-rank test.					

Table 2.2: Outcomes stratified by quartiles of estimated plasma volume status by Kaplan- Hakim Formula (KH ePVS).

Characteristic	Q1 N=1593	Q2 N=1593	Q3 N=1594	Q4 N=1593	P-Value
In hospital outcomes					
Worsening HF at discharge/day 10-- N (%) ⁺	84 (5.3%)	73 (4.6%)	78 (4.9%)	74 (4.6%)	0.797
Adverse Outcomes					
30 day CV death/HF hosp-- N (%) ⁺	122 (7.7%)	141 (8.9%)	176 (11.0%)	158 (9.9%)	0.008
180 day All-cause mortality [†]	8.3%	11.3%	13.7%	17.6%	<.001
⁺ Associated p-value is from a chi-square test.					
[†] Kaplan Meier event rate reported. Associated p-value is from a log-rank test.					

Table 3.1: Association between calculated PVS and 30 day CV Mortality and Rehospitalization for HF

	Unadjusted		Adjusted [†]		
	OR (95% CI)	P-value	OR (95% CI)	P-value	C-index
30 day CV Mortality and Rehospitalization for HF					
Continuous Duarte					
Duarte ePV (per 1 unit increase)	1.17 (1.10, 1.25)	<.001	1.07 (1.00, 1.15)	0.058	0.701
Quartile-based Duarte					
Q1	Reference	<.001	Reference	0.114	0.702
Q2	0.91 (0.78, 1.05)	0.192	0.95 (0.82, 1.11)		
Q3	1.10 (0.95, 1.28)	0.216	1.09 (0.93, 1.27)		
Q4	1.32 (1.15, 1.52)	<.001	1.13 (0.98, 1.31)		
Continuous KH[‡]					0.701
KH ePVS ≤ 0 (per 10 unit increase)	1.25 (1.10, 1.41)	<.001	1.08 (0.95, 1.23)	0.254	
KH ePVS > 0 (per 10 unit increase)	0.85 (0.71, 1.02)	0.083	0.75 (0.62, 0.91)	0.004	
Quartile-based KH					
Q1	Reference	0.021	Reference	0.229	0.701
Q2	0.95 (0.82, 1.11)		1.02 (0.88, 1.20)		
Q3	1.18 (1.03, 1.36)		1.12 (0.97, 1.30)		
Q4	1.08 (0.94, 1.24)		0.87 (0.75, 1.01)		
[†] Adjustment variables include: Age (low/high), baseline BUN (log), dyspnea, hospitalization in prior year, baseline sodium (high), JVP, baseline systolic blood pressure (high), NT-proBNP. [‡] Segments from a piecewise linear spline We reported the p-values from the joint test rather than the individual tests comparing each group to the reference group. The p-values represent the probability of seeing as much or more variation in our data under the null hypothesis that there is no variation in the population. We selected the joint test since it is robust against the choice of reference group.					

Table 3.2: Association between calculated PVS and 180 day all-cause mortality

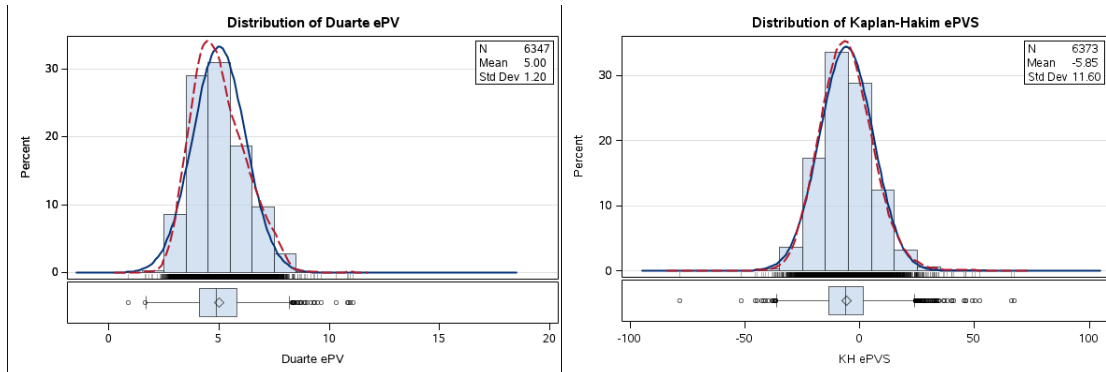
	Unadjusted		Adjusted [†]		
	HR (95% CI)	P-value	HR (95% CI)	P-value	C-index
180 day All-cause mortality					
Continuous Duarte					
Duarte ePV (per 1 unit increase)	1.18 (1.12, 1.25)	<.001	1.03 (0.97, 1.10)	0.273	0.709
Quartile-based Duarte					
Q1	Reference	<.001	Reference	0.226	0.710
Q2	1.13 (0.91, 1.40)		0.98 (0.78, 1.22)		
Q3	1.43 (1.16, 1.76)		1.14 (0.92, 1.41)		
Q4	1.79 (1.47, 2.18)		1.18 (0.95, 1.45)		
Continuous KH					
per 10 unit increase	1.25 (1.19, 1.32)	<.001	1.05 (0.98, 1.12)	0.139	0.709
Quartile-based KH					
Q1	Reference	<.001	Reference	0.365	0.709
Q2	1.38 (1.08, 1.77)		1.11 (0.86, 1.43)		
Q3	1.67 (1.33, 2.11)		1.15 (0.90, 1.47)		
Q4	2.19 (1.77, 2.71)		1.23 (0.97, 1.56)		

[†] Adjustment variables include: Age (low/high), baseline BUN (log), dyspnea, hospitalization in prior year, baseline sodium (high), JVP, baseline systolic blood pressure (high), NT-proBNP.

We reported the p-values from the joint test rather than the individual tests comparing each group to the reference group. The p-values represent the probability of seeing as much or more variation in our data under the null hypothesis that there is no variation in the population. We selected the joint test since it is robust against the choice of reference group.

Figures

Figure 1: Distribution of PV estimates with KH ePVS and Duarte ePV

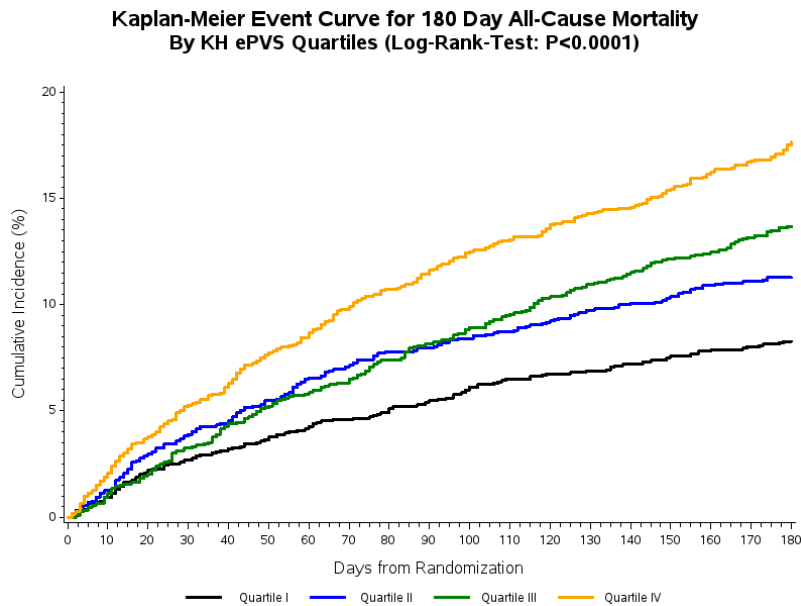
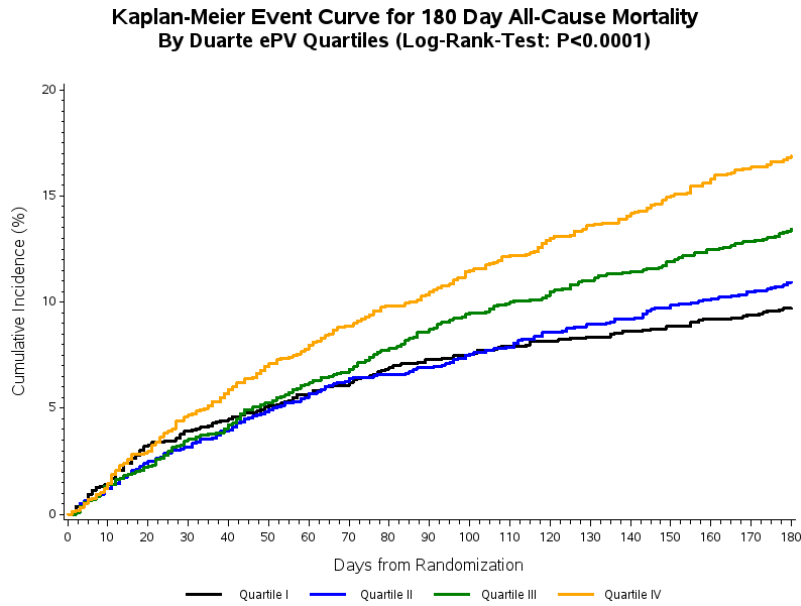


Rank for Variable Duarte ePV	N	Minimum (dL/g)	Maximum (dL/g)
Quartile I	1586	0.88235	4.1304
Quartile II	1588	4.13139	4.8571
Quartile III	1586	4.85827	5.7895
Quartile IV	1587	5.79091	11.0816

Rank for Variable KH ePVS	N	Minimum (%)	Maximum (%)
Quartile I	1594	-78.32	-13.65
Quartile II	1595	-13.65	-6.23
Quartile III	1595	-6.23	1.44
Quartile IV	1595	1.45	67.16

Caption: Distribution of Duarte ePV and KH ePVS demonstrate marked heterogeneity in baseline estimated plasma volume status.

Figure 2: Kaplan-Meier Event Curves for 180 Day All-Cause Death by individual PV estimates.



Caption: Kaplan-Meier event curves for 180-Day all cause mortality demonstrate significant differences as stratified by quartiles of Duarte ePV (top) and KH ePVS (bottom), with greater events occurring in higher quartiles.