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Decongestion Models and Metrics in Acute Heart Failure: ESCAPE Data in the Age of the Implantable Cardiac Pressure Monitor

David Paniagua, MD[1,2]; Glenn N. Levine, MD[1]; Lorraine D. Cornwell, MD[4]; Ernesto Jimenez, MD[4]; Biswajit Kar, MD[1,3]; Hani Jneid, MD[1]; Ali E. Denktas, MD[1]; Tony S. Ma, MD, PhD[1]

[1] Section of Cardiology, Baylor College of Medicine and Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas
[2] Department of Adult Cardiology, Texas Heart Institute, Houston, Texas
[3] The University of Texas Health Science Center at Houston, Houston, Texas
[4] Section of Thoracic Surgery, Baylor College of Medicine and Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas

The United States Food and Drug Administration restricts the use of implantable cardiac pressure monitors to patients with New York Heart Association (NYHA) class III heart failure (HF). We investigated whether single-pressure monitoring could predict survival in HF patients as part of a model constructed using data from the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial.

We validated survival models in 204 patients, using all-cause 180-day mortality. Two levels of model complexity were tested: 1) a simplified 1-pressure model based on pulmonary artery mean pressure ([PAM]1P) (information obtainable from an implanted intracardiac monitor alone), and 2) a pair of 5-variable risk score models based on right atrial pressure (RAP) + pulmonary capillary wedge pressure (PCWP) ([RAP+PCWP]5V) and on RAP + PAM ([RAP+PAM]5V). The more complex models used 5 dichotomous variables: a congestion index above a certain threshold value, baseline systolic blood pressure of <100 mmHg, baseline blood urea nitrogen level of ≥34 mg/dL, need for cardiopulmonary resuscitation or mechanical ventilation, and posttreatment NYHA class IV status. The congestion index was defined as posttreatment RAP+PCWP or posttreatment RAP+PAM, with congestion thresholds of 34 and 42 mmHg, respectively (median pulmonary catheter indwelling time, 1.9 d).

The 5-variable models predicted survival with areas under the curve of 0.868 for the (RAP+PCWP)5V model and 0.827 for the (RAP+PAM)5V model, whereas the 1-pressure model predicted survival with an area under the curve of 0.718. We conclude that decongestion as determined by hemodynamic assessment predicts survival in HF patients and that it may be the final pathway for treatment benefit despite improvements in pharmacologic intervention since the ESCAPE trial. ***(Tex Heart Inst J 2022;49(4):e217587)***

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Corresponding author:
Tony S. Ma, MD, PhD, Section of Cardiology, Michael E. DeBakey Veterans Affairs Medical Center, 2002 Holcombe Blvd., Houston, Texas 77030

E-mail:
Ma.TonyS@VA.gov

Decongestion is the mainstay of acute heart failure (HF) treatment, yet the 2022 American College of Cardiology Foundation/American Heart Association guidelines suggest no specific decongestion metric.[1] The use of an intracardiac pressure monitor in patients with New York Heart Association (NYHA) class III HF is discussed in the 2016 European Society of Cardiology Heart Failure Management Guidelines[2] and in the 2022 ACCF/AHA Guidelines.[1] However, neither the guidelines nor the studies cited therein[3,4] specify any validated decongestion metrics.

In the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial,[5] investigators recorded complete sets of hemodynamic measurements before and after patient treatment. The trial had 2 stated goals: 1) to improve symptoms of congestion, either by clinical management or targeted treatment, to a pulmonary capillary wedge pressure (PCWP) of 15 mmHg and a right atrial pressure (RAP) of 8 mmHg; and 2) to evaluate the benefit of using a pulmonary artery catheter (PAC). The main conclusion drawn from the ESCAPE trial was that PAC use did not confer a benefit in terms of composite survival or rehospitalization during the first 6 months after enrollment; however, the clinical and

prognostic value of decongestion was not specifically tested as a primary or secondary target.

We previously developed a congestion index—the sum of PCWP and RAP—and showed its usefulness in risk-stratifying patients according to the endpoints of death, death or heart transplant, and death or rehospitalization.[6] Recognizing that decongestion might not only relieve symptoms but also promote survival, and finding no randomized controlled trial that tested decongestion metrics as prognosticators of survival, we set out to develop a survival model related to decongestion. Given the broad-based trends of decreasing use of Swan-Ganz catheter-based management in the treatment of acute HF and increasing use of implanted cardiac pressure sensors in the long-term management of HF, our specific aim was to use the established and detailed pre- and postdecongestion data obtained in the ESCAPE trial to construct multivariable risk models that could be of value in evaluating the usefulness of decongestion for improving survival in HF patients.

Patients and Methods

The ESCAPE trial data were obtained from the National Heart, Lung, and Blood Institute (NHLBI) under the auspices of Baylor College of Medicine. The study cohort comprised 433 patients, including 204 who had hemodynamic data collected with use of a PAC. (Of note, 3 of the 433 patients had no available data for NYHA class IV status at admission.) The dependent variable in all analyses was all-cause 180-day mortality. Any missing data were replaced according to the methods detailed in Supplemental Table I. The Cox proportional hazard method, the receiver operating characteristic (ROC) plot,[7] and the area under the curve (AUC) were used to analyze the data. StatView version 5.01 (SAS Institute, Inc.) on a Windows 7 platform was used to perform statistical tests, including Cox univariable, Cox multivariable proportional hazards, and Kaplan-Meier survival analyses. The R program version 3.2.3 (https://cran.r-project.org) with the EpiR, DescTools, and Manipulate packages was used to calculate odds ratios (ORs) and their 95% CIs. The R program version 4.0.2 with the Survival, pROC,[8] and dynpred packages was used to calculate the CI of the ROC through bootstrapping (2,000 iterations) and to perform 2-ROC tests. The R program version 4.1.2 with the Survival and Survminer packages was used to perform the log-minus-log test to confirm the constancy of the hazard ratio (HR) across the study period.

Univariable Cox regression analysis was used to identify significant risk factors for death (P <0.05) (Supplemental Table II). Multivariable Cox regression analysis was then used to restrict (to a minimum) the number of independent predictors of death, starting with the univariable variable with the highest χ^2 value (namely, the posttreatment congestion index represented by the sum of RAP and PCWP [RAP+PCWP]). Using ESCAPE trial design and terminology, we defined posttreatment data as data collected after approximately 3 days of active treatment (the PAC was in place for a median of 1.9 d). Ultimately, 5 independent variables were found to be sufficient and highly predictive of 180-day mortality, as signified by a 5-variable model, called (RAP+PCWP)5V, that used the congestion index of RAP+PCWP. An equivalent congestion index (RAP+PAM) was also tested and used to construct a second 5-variable model, called (RAP+PAM)5V. (The rationale for the second model was that the intracardiac pressure monitor measures PAM but not PCWP). All pressure data used to construct the models were from the ESCAPE trial. A risk score was calculated for each patient with use of the weighted regression coefficient (Coef), which is arguably more mathematically appropriate than the weighted OR for use in assigning risk score[9] in the multivariable Cox regression analysis. Here, the Exp(Coef) = HR in the Cox regression model. We weighted the Coef by using the multivariable Cox regression analysis described above, but normalizing the model to have a maximum possible sum of 100 for the 5 variables (Table I). Each patient's risk score was calculated by multiplying the patient's score for each dichotomous variable (0 or 1) by the assigned variable-specific normalized risk score and then summing the 5 resulting numbers. Kaplan-Meier analysis with the patients partitioned into tertiles produced survival plots of high risk (score, 67–100), medium risk (score, 33–66), and low risk (score, 0–32) for the (RAP+PCWP)5V (Fig. 1A) and (RAP+PAM)5V (Fig. 1B) models. For the 1-pressure model, the risk pressure (PAM) was adjusted, with the maximum cohort pressure normalized to a score of 100 and other cohort pressures proportionally multiplied, so that the same tertile partitions could be used and the results (Fig. 1C) could be compared among models.

We compared the different models (Table II) according to 3 criteria: the relative ORs of high-risk mortality to low-risk mortality, the associated 95% CIs, and the difference of 2 AUCs by the 2-ROC test of each model as compared with the (RAP+PCWP)5V model. The OR comparisons were made with the patients separated into 3 risk groups by each model; the ROC and AUC were characteristics of the model before the patients were separated into 2 groups by a threshold risk score (the score identified as providing the best balance of sensitivity and specificity). We introduced a new inclusiveness index (I-index) for the comparison of different HF risk-prediction models. This I-index was defined as the sum percentage of patients in the total cohort who were categorized as either high or low risk (a high I-index indicating a model more useful for clinical decision-making).

TABLE I. Five-Variable Congestion Risk Models

Variable	**Model Cox Regression Coefficient** (Risk Score)[a]	
	(RAP+PCWP)5V	**(RAP+PAM)5V**
Baseline SBP <100 mmHg	0.702 (11)	0.951 (16)
Baseline BUN ≥34 mg/dL	0.811 (13)	0.751 (12)
CPR or mechanical ventilation	1.663 (26)	1.952 (32)
NYHA class IV at hospital discharge	1.358 (21)	1.247 (20)
Congestion index threshold[b]	1.803 (29)	1.216 (20)

BUN = blood urea nitrogen; CPR = cardiopulmonary resuscitation; NYHA = New York Heart Association; PAM = pulmonary artery mean pressure; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; SBP = systolic blood pressure

The (RAP+PCWP)5V model included the congestion index variable RAP+PCWP. All variables were dichotomous, with values of either 0 or 1. All intracardiac pressures were posttreatment pressures.

[a] A Cox regression coefficient (Coef) was used for risk score calculation, where Exp(Coef) = hazard ratio (HR) in the Cox regression model. Total risk scores were normalized to 100 for the sum of all Coefs in the model. Risk scores for the (RAP+PCWP)5V model were calculated for each patient as follows: 1) sum all Coefs: 0.702 + 0.811 + 1.663 + 1.358 + 1.803 = 6.337; 2) normalize the sum to 100: 100/6.337 = 15.78; and 3) calculate risk score for each variable: 0.702 × 15.78 = 11.

[b] The (RAP+PCWP) congestion threshold was 34 mmHg; the (RAP+PAM) threshold was 42 mmHg.

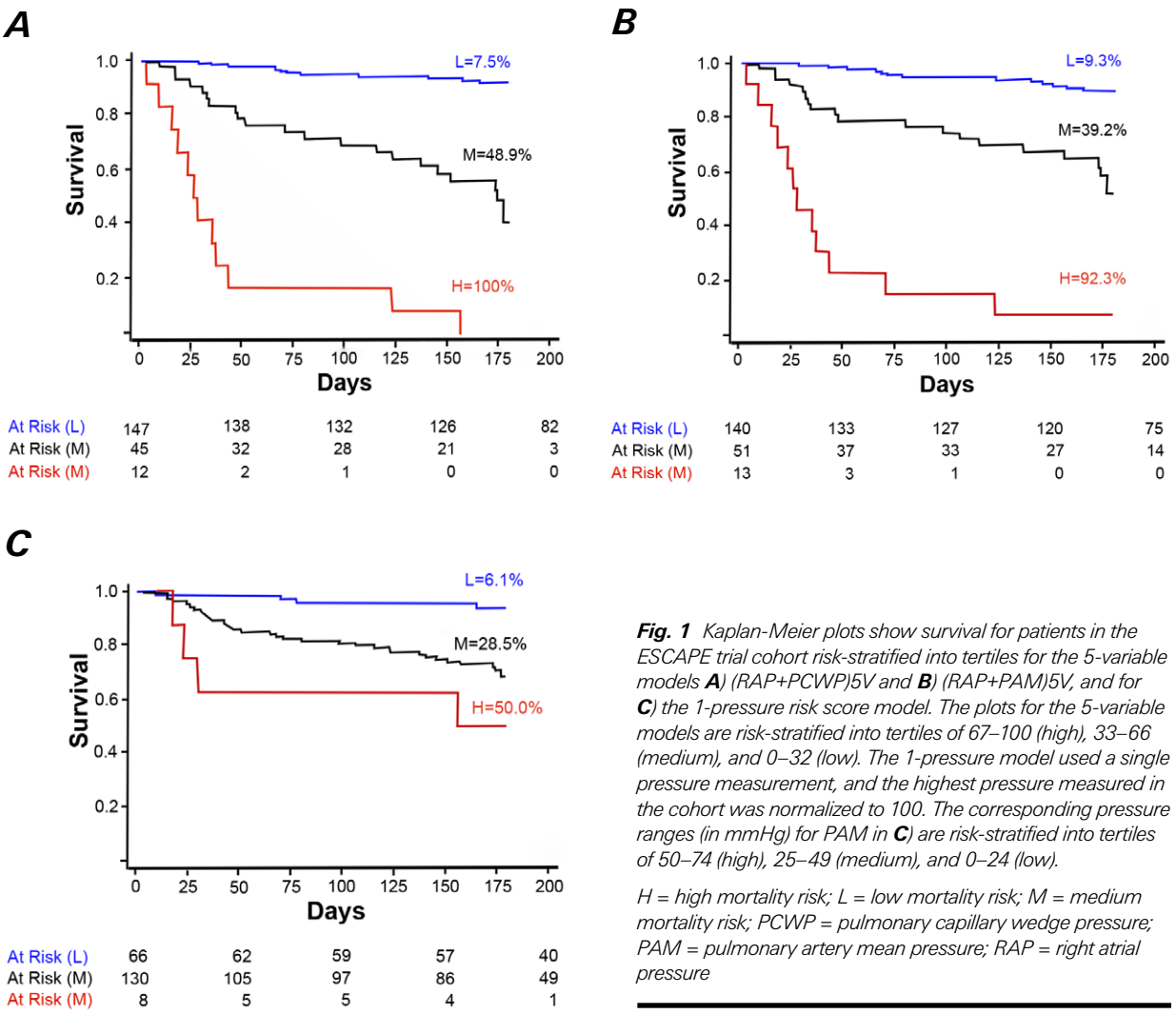

Fig. 1 *Kaplan-Meier plots show survival for patients in the ESCAPE trial cohort risk-stratified into tertiles for the 5-variable models **A**) (RAP+PCWP)5V and **B**) (RAP+PAM)5V, and for **C**) the 1-pressure risk score model. The plots for the 5-variable models are risk-stratified into tertiles of 67–100 (high), 33–66 (medium), and 0–32 (low). The 1-pressure model used a single pressure measurement, and the highest pressure measured in the cohort was normalized to 100. The corresponding pressure ranges (in mmHg) for PAM in **C**) are risk-stratified into tertiles of 50–74 (high), 25–49 (medium), and 0–24 (low).*

H = high mortality risk; L = low mortality risk; M = medium mortality risk; PCWP = pulmonary capillary wedge pressure; PAM = pulmonary artery mean pressure; RAP = right atrial pressure

TABLE II. Comparison of 5-Variable and 1-Pressure Heart Failure Models in the ESCAPE Cohort

	5-Variable Models		
	(RAP+PCWP)5V	(RAP+PAM)5V	**1-Pressure Model[a] (PAM)1P**
AUC (95% CI)	0.868 (0.786–0.913)	0.827 (0.750–0.889)	0.718 (0.627–0.780)
Risk stratification			
High-risk Mortality (% cohort)	100% (5.9)	92.3% (6.4)	50.0% (3.9)
Medium-risk Mortality (% cohort)	48.9% (22.0)	39.2% (25.0)	28.5% (63.7)
Low-risk Mortality (% cohort)	7.5% (72.1)	9.3% (68.6)	6.1% (32.4)
I-index	78.0%	75.0%	36.3%
OR (H to L) (95% CI)	296.7 (approx.)[b] (0.1–5,340)	117.2 (14.1–975.0)	15.5 (2.8–86.2)
P of 2-ROC[c]	—	0.40	0.004134

AUC = area under the curve; H = high-risk; I-index = sum percentage of patients in total cohort categorized as either high or low risk; L = low-risk; OR = odds ratio; PAM = pulmonary artery mean pressure; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; ROC = receiver operating characteristic

The 5-variable models (RAP+PCWP)5V and (RAP+PAM)5V are described in Table I. The 1-pressure model (PAM)1P used posttreatment pressure (in mmHg) as defined.

[a] Patients in the 5-variable models were stratified by risk score into tertiles of 67–100 (high), 33–66 (medium), and 0–32 (low), as described in Patients and Methods. The 1-pressure model was scaled to 100 on the basis of the highest reading in the cohort, and the patients were stratified on the basis of PAM (mmHg) into tertiles of 50–74 (high), 25–49 (medium), and 0–24 (low).

[b] OR (H to L) for (RAP+PCWP)5V was approximated by adding 0.5 to each cell because of a zero value in 1 cell (100% mortality in High-risk; therefore, zero value for the "Alive" cell in the 2 × 2 table). The lower and upper 95% CIs were less meaningful but can be calculated as 0.1 and 5,340.

[c] P of 2-ROC = paired receiver operating characteristic test in the R program version 4.0.2. For comparisons, models were paired with (RAP+PCWP)5V.

The (RAP+PCWP)5V risk score model was validated by using the Breslow-Day homogeneity test (Supplemental Table III) after first performing both random and sequential partitioning of the total cohort to produce a model generation cohort and a validation cohort (each comprising half of the total cohort). This was done as follows: First, patients from the ESCAPE trial who had PAC data were randomly separated into 2 groups of approximately equal size. The first of these 2 groups was used as the derivation cohort to generate an ROC curve and its threshold value for separating patients into high- and low-risk groups. Kaplan-Meier analysis was used to produce a 2 × 2 table of "High- and Low-Risk" versus "Dead and Alive." The threshold value for the 2-group partition derived from the first group's data was then used with data from the second group in another Kaplan-Meier survival analysis to produce a second 2 × 2 table. A Breslow-Day homogeneity test was then performed on the 2 × 2 × 2 distribution. The same process was repeated with sequential patient partition of the same cohort, in which the first 102 patients enrolled in the ESCAPE trial who had PAC data served as the derivation group and the second 102 served as the validation group. We considered the model validated only when the random and sequential partitionings both resulted in homogeneity between the derivation and validation cohorts, as verified by the Breslow-Day comparison.

To validate the hypothesis that the HR remained constant throughout the study and observational period, we analyzed a data file containing the deidentified ESCAPE risk scores (provided in a Supplemental Data File). Each patient was assigned an identification number (ID) by the following algorithm: ESCAPE ID + Rand()*1000. The data were entered into the R program by the statement X5V.raw <-read.csv(file.choose(),header=T), which was executed thereafter for the Kaplan-Meier (km), Cox proportion hazard model (cph), and log-minus-log (cloglog) functions, according to scripts provided by In and colleagues,[10] using the Survival and Survminer packages.

Results

At admission, 86.3% (371/430) of patients in the ESCAPE cohort (Supplemental Table II) had NYHA class IV HF; at discharge, 19.4% (84/433) remained in NYHA class IV. Univariable Cox regression analysis showed that NYHA class IV status at admission was not a predictor of mortality (χ^2 score, 0.19; P=0.67), whereas posttreatment NYHA class IV status was a strong predictor of mortality (χ^2 score, 26.54; P <0.0001). Heart failure treatment resulted in an average decrease of one NYHA functional class (paired difference, 1.03; n=394; P <0.0001).

We did not perform a complete-case analysis (including only patients with complete data) because a substantial number of patients had missing data (for example, there were 204 patients in the PAC group, but posttreatment PCWP and PCWP+RAP data were available for only 159 and 145 of them, respectively). Our approach to addressing missing data and our justification for it are detailed in a footnote to Supplemental Table II. The PAC group (n=204) had 45 deaths (22%). In the univariable Cox regression analysis, the posttreatment congestion index (RAP+PCWP) had a high χ^2 score of 55.68 and an HR of 1.09. In comparison, the baseline (admission) congestion index (RAP+PCWP) had a lower χ^2 score of 10.21 and HR of 1.03. The change in the congestion index in response to treatment was not a significant indicator of death (n=142; P=0.10), and neither was the change in patient body weight after treatment (n=433; P=0.89). When the posttreatment congestion index (RAP+PCWP) was treated as a dichotomous variable, it had more predictive power when the threshold value was 34 mmHg (χ^2 score, 50.12) than when that value was 30 mmHg (χ^2 score, 31.32). A posttreatment or discharge brain natriuretic peptide level (BNP_DL) of >500 pg/mL was a significant but less strong predictor of death (χ^2 score, 14.50; HR=2.895; n=283) than was a baseline blood urea nitrogen level (BUN_B) of ≥34 mg/dL (χ^2 score, 23.85; HR=3.011; n=433). Given the argument that BNP might be a surrogate marker of congestion, we used regression analysis to examine the relationship between BNP and our congestion index. We found that neither BNP_DL (R^2=0.017; n=146; P >0.05) nor log(BNP_DL) (R^2=0.022; n=142; P >0.05) was significantly correlated with the posttreatment congestion index (RAP+PCWP)_L.

The validated ESCAPE 5-variable congestion risk model (RAP+PCWP)5V (see Supplemental Table III) had a survival curve with an AUC of 0.868 (95% CI, 0.789–0.911) (Table II). The equivalent 5-variable model (RAP+PAM)5V had a survival curve with an AUC of 0.827 (Table II). The 5-variable models were not significantly different from each other with respect to AUC according to the 2-ROC test; however, the 1-pressure model, (PAM)1P, was statistically inferior to the (RAP+PCWP)5V model (Table II). The I-indices of the 5-variable models—78.0% for (RAP+PCWP)5V and 75.0% for (RAP+PAM)5V—were higher than the I-index of the 1-pressure model (36.3%).

An ROC analysis indicated that the optimal separation of the 5-variable models occurred at a risk score of 40. Therefore, patients were separated into 2 groups: those with a risk score of <40, and those with a score of ≥40. A Kaplan-Meier plot (Supplemental Fig. 1) and a log-minus-log plot of the Kaplan-Meier estimates (Supplemental Fig. 2) were then made for the 2 risk groups, and a log-rank test was performed to compare them. The 2 curves did not meet during the observation period (Supplemental Fig. 2), indicating satisfaction of the proportional hazard assumption. This Cox proportional hazard analysis used a single covariate (risk score) and showed that the incidence of death was 14.74-fold higher (95% CI, 7.427–29.27; P <0.0001) in the high-risk group than in the low-risk group.

Discussion

Current guidelines for acute HF management do not favor routine invasive hemodynamic monitoring with a PAC, instead relegating its use to guiding therapy in selected patients whose hemodynamic stability is in question.[1] Physical diagnosis has been proposed as an adequate surrogate,[11] but no randomized controlled trial has yet been performed to validate this. Limited observational studies[12-15] and a post hoc analysis of the placebo group of a vasopressin-2 receptor antagonist trial[16] have supported the clinical value of decongestion. More recently, the DOSE (Diuretic Optimization Strategies Evaluation),[17] ROSE (Renal Optimization Strategies Evaluation),[18] and CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure)[19] trials tested the usefulness of specific diuresis or decongestion treatment modalities; however, none of these trials included direct volume (hemodynamic) assessment or examined the effects of associated target-related diuresis on survival.

Congestion surrogates including BNP (AUC=0.665) and N-terminal pro-B-type (NT-proBNP) (AUC=0.679) predicted all-cause mortality in a population of 3,916 patients enrolled in the Val-HeFT (Valsartan Heart Failure Trial) study.[20] However, multiple and extensive trials have not shown that biomarker-guided treatment improves survival.[21-27] In a recent report of a study in patients with acute HF,[28] sacubitril-valsartan (at a combined targeted dose of 97 mg sacubitril and 103 mg valsartan twice daily) reduced follow-up NT-proBNP levels more effectively than did enalapril (at a targeted dose of 10 mg twice daily) after an 8-week targeted dose-titration treatment regimen. Of the patients in the study, 8.9% in the sacubitril-valsartan group and 8.2% in the enalapril group were in NYHA class IV at baseline. It

is important to note, however, that mortality was not included as an endpoint in the study.

Previously, using mathematical modeling of the circulation, we found that the systemic volume can be represented by RAP and that pulmonary volume can be represented by left atrial pressure.[29] Expanding on this conceptual foundation, we developed a congestion index (RAP+PCWP) and showed its clinical usefulness by applying it to the ESCAPE data.[6]

During the time frame of the ESCAPE study, implantable pressure and impedance monitors were introduced into clinical practice. This in turn enabled the replacement of static invasive monitoring of pulmonary arterial pressure with continuous monitoring of the intrathoracic blood volume (impedance) or intracardiac pressure. Initial studies involved use of the Medtronic Chronicle hemodynamic monitor. The COMPASS-HF (Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure) study,[30] reported in 2008, was a single-blind, parallel-controlled trial in 274 patients with NYHA class III (85%) or IV (15%) function at baseline. The study revealed that acute decompensated HF developed together with a rise in the lowest nighttime pulmonary artery diastolic pressure (PAD) measurement from 17 to 22 mmHg in patients with diastolic HF and from 21 to 24 mmHg in patients with systolic HF.[30] No changes in average body weight were noted; however, paired comparison in individual patients was not performed. Furthermore, at 6 months, the total number of HF-related events did not differ significantly between the treatment group and the group that received optimal medical management.[31] Mortality alone, although not an endpoint in the study, was 9.7% (13 of 134 patients) in the implant-monitored group and 7.9% (11 of 140 patients) in the implanted but nonmonitored group.

The REDUCEhf (Reducing Decompensation Events Utilizing Intracardiac Pressures in Patients With Chronic Heart Failure) trial,[32] reported in 2010, also used the Medtronic Chronicle monitor. Four hundred patients with NYHA class II or III HF were randomly assigned to receive or not receive monitoring for HF management. Although the trial was prematurely terminated because of device defects and limited device availability, the available data showed no difference in HF outcome (a combined endpoint of HF hospitalizations, emergency department visits, and urgent clinic visits) between the 2 groups at 12 months.[32]

Zile and colleagues,[33] in a combined retrospective analysis of 3 cohorts comprising 790 patients—from the Chronicle phase II (n=116), COMPASS-HF (n=274), and REDUCEhf (n=400) trials—with a median follow-up of 2.9 years, showed that when baseline PAD exceeded the median value of 23 mmHg, mortality was significantly greater throughout the observation period. The Medtronic Chronicle implanted monitor was not approved by the United States Food and Drug Administration (FDA), and the phase II trial data were not in the public domain at the time of the writing of this report (https://ichgcp.net/clinical-trials-registry/NCT00991120).

Because including patients with NYHA class IV HF may have led to negative outcomes in previous studies, the single-blind CHAMPION trial[34] enrolled 550 patients who had NYHA class III HF and either reduced or preserved left ventricular ejection fraction. Half of the patients had their data masked (unavailable to physicians), and half were being monitored with use of the CardioMEMS system (Abbott). The optimized hemodynamic target values were a PAD of 8 to 20 mmHg and a PAM of 10 to 25 mmHg.[35] For the treatment arm, the baseline PAD and PAM were 18.6 mmHg and 28.9 mmHg, respectively; for the control arm, they were 19.3 mmHg and 29.9 mmHg, respectively.[3] At 6 months, HF-related hospitalization was less frequent in the treatment arm (reported HR, 0.72; 95% CI, 0.60–0.85; P=0.0002). The 6-month mortality rates in the CHAMPION study were 5.6% (15/270) in the treatment arm and 7.1% (20/280) in the control arm, a difference that was not reported as significant. The investigators chose the pulmonary artery pressure AUC (mmHg × days) for analysis. Use of an implanted cardiac monitor for HF management is mentioned in the 2016 European Society of Cardiology Heart Failure Management Guidelines.[2] The FDA approved the CardioMEMS system in 2014 for use in patients with class III HF and a hospitalization for chronic HF in the year before device implantation.

A follow-up study of the patients in the CHAMPION trial after 6 months of masking, when all patients and physicians were given access to the PA data, showed sustained reduction of hospitalizations among patients in the original treatment arm (monitoring data available throughout) and new reductions in hospitalizations among patients in the original control arm (monitoring data absent for the first 6 months).[3] Again, because of the study design, mortality itself was not an endpoint. Over a 19-month follow-up period, the mortality rates were 30.0% (81/270) in the original treatment group and 30.4% (85/280) in the original control group, thus showing no difference in either 6-month or 19-month mortality. A post hoc subgroup analysis of the CHAMPION trial data in patients receiving either angiotensin-converting enzyme inhibitor/angiotensin-receptor blockers (ACE-I/ARBs) or β-blockers (n=445) or both types of drugs (n=337) showed lower mortality (OR) in the 6-month monitored group than in the control group.[36] This comparison was not prespecified in the original trial's protocol.

In the MEMS-HF (CardioMEMS European Monitoring Study for Heart Failure) trial, 234 patients with NYHA class III HF were followed up for 1 year, with the cohort patients' preimplantation data serving as their

own control. Between the pre- and postimplantation periods, HF hospitalizations were reduced by 62%.[37] A similar conclusion was reached in another nonrandomized, single-arm observational trial of 1,200 patients with NYHA class III HF (CardioMEMS Post-Approval Study)[38] and a baseline mean PAD of 20 mmHg; these patients had a rehospitalization risk reduction of 57% between the pre- and postimplantation periods.

In contrast, the intrathoracic impedance monitoring associated with an implantable cardioverter-defibrillator in 335 patients with NYHA class II or III HF did not reduce the composite rate of all-cause mortality and HF hospitalization, but actually increased it. This counterintuitive finding was attributed to increased alarms for hospitalization (namely, more frequent impedance alarms may have increased patients' likelihood of being hospitalized).[39]

Our models are the first risk-score models to show that hemodynamic data can be significantly prognostic in HF, extending our previous work and showing that decongestion (reducing hemodynamic load) could be beneficial, just as decongestion was the stated goal in the ESCAPE trial. The threshold value of 34 mmHg (RAP+PCWP) was determined by Cox regression analysis (Supplemental Table II), whereas the 30-mmHg threshold that we published previously[6] was equivalent to the ESCAPE trial's stated clinical targets. A notable finding in this study was that PAM, not normally considered an index of pulmonary blood volume (in contrast with PCWP and PAD[29]), was found to be just such an index, possibly due in part to an absence of patients with significant intrinsic pulmonary vascular disease in the ESCAPE cohort. Finally, although the CHAMPION trial consisted of patients with NYHA class III HF, the observed reduction in rehospitalization rates and empirically stated treatment goals (the optimized hemodynamic targets were a PAD of 8 to 20 mmHg and a PAM of 10 to 25 mmHg)[35] are similar to the outcomes of our model's low-risk group pertaining to (RAP+PAM)5V and (PAM)1P (Fig. 1 and Table II), and they were the same for a model with congestion index using posttreatment RAP+PAD (at 40 mmHg) (not included in this writing for reasons of clarity; see Supplemental Table II). This supports the validity of our models of decongestion in general. However, because of their nonrandomized designs, none of the current intracardiac pressure monitor trials can address the question of whether monitoring reduces mortality,[34,37,38] or the usefulness of applying such monitoring to patients with NYHA class IV HF.

One of the ESCAPE trial's inclusion criteria was a depressed left ventricular ejection fraction of 30% or less at baseline,[5] which could be perceived as a limitation of our study. However, the CHAMPION trial[34] included patients with either depressed or preserved ejection fraction, which suggests that HF patients presented with similarly elevated intracardiac pressure and volume congestion. The ESCAPE trial's hemodynamic cohort of 204 patients is small, but 2 measures strengthened our models: First, there were 45 deaths in the cohort, and our models each had 5 variables, so that there were 9 outcome events per variable (EPV), with EPV=10 being the number appropriate for a risk model.[40] Second, we internally validated our model (Supplemental Table III).

Some may contend that our models identified only the patients at risk. Of the 5 variables for each model, 2 of them are immutable patient characteristics (blood pressure and BUN level at admission), and one (cardiopulmonary resuscitation or mechanical ventilation) reflects the severity of current decompensation. However, the other 2 variables—the posttreatment congestion variable and posttreatment NYHA functional status—are clinically actionable targets changeable by intervention (decongestion), thereby potentially improving survival. We compared our models by using tertile stratification, with the intention of removing bias related to arbitrary partition to fit selected cohort data, which can exaggerate prognostic efficacy (for example, by overestimating the OR and the I-index because of the arbitrary boundaries of each risk group).

Since publication of the ESCAPE results, additional advances in HF pharmacological management have been made, not least the use of sacubitril-valsartan[41] and empagliflozin.[42]

Our 5-variable models do not include treatment variables such as the use of ACE-I/ARBs or β-blockers, because these variables, despite being associated with a statistically significant HR of <1.0 in univariable analysis (Supplemental Table II), were not found to be independent predictors of death in the multivariable analysis of the ESCAPE cohort. Similarly, the furosemide dose—a positive predictor of death in univariable analysis—was also found not to be an independent predictor in our study beyond the 5 variables already chosen. The BNP data were not found to be as strong a predictor of death in ESCAPE as our congestion index (χ^2 score, 14.50 vs 55.68) (Supplemental Table II). Furthermore, BNP was not an independent predictor of death in the multivariable analysis after the abovementioned 5 variables were in place, nor could BNP replace the congestion index as a surrogate congestion marker in a variant 5-variable model (data not shown).

Cox regression survival analysis assumes a constant HR throughout the study period. We validated this assumption by using the log-minus-log test (Supplemental Figs. 1 and 2).[10,43]

We chose and limited our model to 5 variables and maintained a rigid inclusion criterion (P <0.050) in the multivariable model, with the following 3 objectives: First and foremost, the model had to achieve a high ROC value: our (RAP+PCWP)5V model's ROC was 0.868. Second, we aimed to include as few variables as

possible in the model to make it simple and generally applicable in other clinical settings (for example, we chose not to include 6-min walk time, which is included in the ESCAPE data but is not available in many settings). We also tried to keep the EPV as close to 10 as possible (our EPV was 9) to make the model generally applicable to other populations. Third, the inclusion of additional variables was intended to substantially improve the ROC's clinical impact.[44] To this end, we added 2 separate high-impact univariable variables (Supplemental Table II)—any ACE-I or ARB use at discharge (ACE-I/ARB_D), and any β-blocker use at discharge (β-blocker_D)—to produce a 7-variable model (data not shown), and we used 2-ROC in the R program to evaluate any statistical improvement in ROC fitting. The new 7-variable model caused 3 variables to have a *P* value >0.05 (but still <0.10); nevertheless, it improved the ROC to 0.8692 from the 0.8682 obtained with the 5-variable model. The 2-ROC test showed that this difference was not significant (*P*=0.9831). The 7-variable model risk scores for the 7 variables were as follows: 17, 14, 36, 24, 38, –14, and –15; the 2 negative scores represented the salutary value of ACE-I/ARB_D and β-blocker_D, respectively, whereas the order of the first 5 risk scores corresponds to the order of variables listed in Table I for the 5-variable model. To avoid the computational problems associated with using negative risk scores, we added 30 points to the final (sum) score for each patient before data analysis. We concluded that our 5-variable model is adequate and useful.

Although our 5-variable congestion models are not meant to compete with any other model that includes other selected variables, our results clearly indicate their feasibility, simplicity, and high predictive value. These models may be particularly useful in the current era of implantable cardiac pressure sensors, whose implantation also generally involves a baseline Swan-Ganz catheter examination.

Conclusions

Evidence suggests that the current strategy of using implantable cardiac pressure monitors and associated decongestion interventions reduces the risk of rehospitalization. Yet, the FDA has restricted the use of these monitoring devices in patients with NYHA class III HF,[34] and patients with NYHA class IV HF have generally been excluded because of the hesitancy of investigators to address presumably "advanced" HF.[45]

By reanalyzing data from the ESCAPE study, we draw 2 important conclusions: First, patients with NYHA class IV HF who are optimally treated can recover to a better functional class and have better survival. Second, a simple multivariable model can accurately categorize patients (ie, high AUC) as being at high, medium, and low risk of death when the model comprises 3 static, dichotomous clinical variables (worse prognosis if the patient has one or more of the following: baseline systolic blood pressure <100 mmHg, baseline BUN of ≥34 mg/dL, or need for cardiac resuscitation or mechanical ventilation during decompensation) and 2 actionable variables (improved prognosis if the patient is in a posttreatment NYHA class <IV, has a posttreatment congestion index of <34 mmHg, or both).

Our models suggest the advantage of including RAP as part of the congestion index and therefore require an accurate RAP measurement; this could be achieved by in-office ultrasonographic estimation of jugular venous pressure rather than bedside physical diagnosis. Our analysis leads to the hypothesis, supported by the ESCAPE data but contrary to the current HF guidelines,[1] that posttreatment PAC has clinical predictive value for most, if not all, patients admitted with acute HF. A single static posttreatment measurement obtained early in the index hospitalization (in the ESCAPE trial, the median PAC indwelling time after randomization was 1.9 d)[5] provides prognostic information regarding 6-month survival and identifies high-risk patients (those with a 6-month mortality risk of >90%) who may need more aggressive strategies then those commonly adopted.

Finally, the practice of using the AUC of pressure over time (mmHg × days) in the pressure monitor may not be necessary or more informative than using the static or mean value. The decongestion metric we propose showed that a better prognosis does not necessarily require reaching normal physiologic values: the sum of 2 posttreatment intracardiac pressures of the left (PCWP) and right (RAP) circulation below a threshold (34 mmHg) is sufficient (the normal sum range being 6–20 mmHg).

It would be valuable if the ESCAPE investigators were to test these proposed models in predicting 1-year survival (the ESCAPE trial examined 6-month outcomes only, so 1-year outcomes data are not currently available in the public domain). Nevertheless, the value of the current models and analysis rests on the means of identifying the population at risk for 6-month mortality early in the index admission, whereas maintenance of decongestion status might still be needed to achieve a longer-term survival benefit.

A major limitation of our models is that pharmacologic therapies for HF have advanced since the ESCAPE trial was completed; therefore, our models might be outdated. Nonetheless, our results suggest that decongestion as evaluated hemodynamically predicts survival in HF patients and may be the final pathway to a treatment benefit despite improvements in pharmacologic intervention. This supposition is made more compelling by our finding that, despite the known benefits of ACE-I (HR=0.337; n=432), ACE-I/ARB (HR=0.208; n=433), and β-blocker use (HR=0.457; n=433) in the

ESCAPE trial patients (where HR <1.0 indicates a salutatory effect on risk of death) (Supplemental Table II), these medications were not identified as independent predictors of survival in our multivariable model when our rigid inclusion criteria (P <0.05) were used and tested for any statistically significant improvement of ROC with the 2-ROC test. This suggests that the survival benefit of treatment depended on decongestion alone, and not on the specific treatment modalities that produced it. This finding further emphasizes that the ability to evaluate otherwise unrecognized residual congestion at the time of discharge will continue to be of paramount importance for survival. Still, external validation of our models with more exact risk-score boundaries would be necessary. Finally, our models can provide metrics for decongestion in the current era of implantable intracardiac pressure sensors (RAP+PCWP, 34 mmHg; RAP+PAM, 42 mmHg), even though the use of inpatient hemodynamic monitoring to evaluate decongestion has been decreasing since the publication of the ESCAPE trial data.

As a final note added here is the recognition of the recent randomized controlled Hemodynamic-guided management of heart failure (Guide-HF) trial, using the CardioMEMS implanted pressure sensor.[46,47] In this trial, 1,000 patients with NYHA class II (29%–30%), III (65%), and IV (5%–6%) HF, with a target PAM of 10 to 25 mmHg in the hemodynamic monitoring arm, were followed for 1 year (395 d). No difference was found in the primary endpoint (death or HF exacerbation) or in mortality. This trial result does not contradict our thesis in that the study population had a low percentage of NYHA class IV patients, the patients did not have acute HF, posttreatment congestion parameters were not assessed as part of the metrics for outcomes, and a single pressure parameter (PAM) was used.

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Supplemental Material

Supplemental data for this article are available at 10.14503/THIJ-21-7587.s1.pdf.

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