ORIGINAL RESEARCH

External Validation of the ELAN-HF Score, Predicting 6-Month All-Cause Mortality in Patients Hospitalized for Acute Decompensated Heart Failure

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***Background*—**Our aim was to calibrate and externally revalidate the ELAN-HF (European Collaboration on Acute Decompensated Heart Failure) score, to confirm and improve on a previous external validation of the risk score.

***Methods and Results*—**The ELAN-HF score predicts 6-month all-cause mortality in patients hospitalized for acute decompensated heart failure using absolute and percentage change of NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels in addition to clinical variables. For the external validation, we used the PRIMA II (Can NT-proBNP–Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?) trial. For both data sets, observed versus predicted mortality was compared for the 4 risk categories; and the mean predicted mortality was plotted against the observed mortality with calculation of a correlation coefficient and SEE. The model discriminant ability was determined by comparing the C-statistics for both data sets. The predicted versus actual 6-month mortality values in the derivation cohort were 3.7% versus 3.6% for the low-risk category, 9.4% versus 9.2% for the intermediate-risk category, 24.2% versus 23.5% for the high-risk category, and 54.2% versus 51.1% for the very-high-risk category. The correlation between predicted and observed mortality by deciles was 0.92, with an SEE of ±4%. In the validation cohort, predicted versus actual 6-month mortality values were 3.0% versus 2.2% for the low-risk category, 9.4% versus 8.2% for the intermediate-risk category, 25.0% versus 22.9% for the high-risk category, and 56.8% versus 53.6% for the very-high-risk category. The correlation between predicted and actual mortality by quintiles was 0.99, with an SEE of ±2%. There was no significant difference in C-statistic between the derivation cohort (0.78; 95% CI, 0.74–0.82) and the validation cohort (0.77; 95% CI, 0.69–0.84; *P*=0.693).

***Conclusions*—**Our study confirms that the ELAN-HF score predicts accurately 6-month mortality in patients hospitalized for acute decompensated heart failure with the use of easily obtained characteristics. **(*J Am Heart Assoc*. 2019;8:e010309. DOI: 10.1161/JAHA.118.010309.)**

Key Words: acute heart failure • external validation • NT-proBNP • prognosis • risk score

Patients admitted for acute decompensated heart failure (ADHF) are diverse in age, type of heart disease, comorbidities, and patterns of disease progression, which creates important challenges in patient management.[1–4] A common denominator of treatment success is decongestion; however, decongestion is not the only prognostic factor,

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An accompanying Table S1 is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.010309

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Received December 9, 2018; accepted May 20, 2019.

Clinical Perspective

What Is New?

- This external validation study of the ELAN-HF (European Collaboration on Acute Decompensated Heart Failure) score confirms the excellent predictive proportional value of the risk score and shows that 6-month mortality increases with increasing score.

What Are the Clinical Implications?

- The ELAN-HF score is a statistically robust risk score predicting 6-month all-cause mortality in patients after hospitalization for acute decompensated heart failure, using NT-proBNP (N-terminal pro-B-type natriuretic peptide) values in addition to easily obtained clinical and laboratory characteristics, making it an easy to use and reliable bedside score to be used in the clinic practice.

and it is well established that patients with ADHF differ from one another substantially on their risk estimate.[5–7] A reliable risk stratification before discharge from the hospital may be used to further intensify therapies or intensify follow-up of those patients at higher risk and, in addition, provides extra information to the clinician as a performance measure.[7] To be usefully applied in the clinic, prognostic scores/models must be robust, simply applicable, and generalizable.

The ELAN-HF (European Collaboration on Acute Decompensated Heart Failure) score is such a bedside score, predicting 6-month all-cause mortality in patients after hospitalization for ADHF.[8] This easy-to-use score offers several promising applications for clinical use as it does not exclude any particular ADHF population.[8] The 2017 American College of Cardiology/American Heart Association/Heart Failure Society of America focused update of the 2013 guideline for heart failure recommends that "during a HF hospitalization, a predischarge natriuretic peptide level can be useful to establish a postdischarge prognosis," for which the ELAN-HF score has been cited.[9]

The score has been validated previously in an external cohort,[10] which confirmed the predictive proportionality of the model.[8] However, in the original article, we did not calibrate the score and there were limitations about the validation cohort.[8] First, although discharge NT-proBNP (N-terminal pro-B-type natriuretic peptide) values were available in all patients, the NT-proBNP values at admission were not available; therefore, NT-proBNP values obtained 3 days before discharge were used as a proxy to calculate the change of NT-proBNP during hospitalization.[8,10] Second, assuming similar hazard ratios for NT-proBNP categories and other variables for shorter and longer follow-up durations, the follow-up duration of the validation cohort was extended to 1 year because of the small sample size, whereas the follow-up in the derivation cohort was 6 months after discharge.[8,10]

Therefore, the purpose of this study was to calibrate and revalidate the ELAN-HF score[8] in the recently published PRIMA II (Can NT-proBNP–Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?) trial cohort, a multicenter, international, randomized, controlled, 2-arm trial that aimed to study the effect of in-hospital guidance of ADHF treatment by a predefined NT-proBNP target.[11] Results of the PRIMA II trial were not different between the 2 treatment arms, and both treatment arms were included in the validation cohort.

Methods

Source/Study Populations

The ELAN-HF score was developed from 7 prospective cohorts of patients hospitalized for ADHF. The selection of the risk markers and construction of the model has been published previously.[8] Briefly, the score was developed using the multivariable Cox regression model, and variables were selected on the basis of the strongest predicting value for 6-month mortality after discharge. Thereafter, a simplified model was constructed by assigning weights to individual risk markers proportional to their regression coefficients.[8] The ELAN-HF score consisted of the following variables: absolute NT-proBNP levels at discharge of 1500 to 5000 pg/mL (1 point), 5001 to 15 000 pg/mL (3 points), and >15 000 pg/mL (4 points). Other risk markers (1 point each) were as follows: NT-proBNP reduction of ≤30% from admission to discharge, aged ≥75 years at admission, presence of peripheral edema at admission, systolic blood pressure ≤115 mm Hg at admission, hyponatremia (sodium <135 mmol/L) at admission, serum urea of ≥15 mmol/L at discharge, and New York Heart Association class III or IV at discharge. The risk groups were categorized in the following manner: low (≤2 points), intermediate (3–4 points), high (5–7 points), and very high (≥8 points).[8]

To perform an external validation, we used the cohort of the PRIMA II trial, an investigator-initiated, multicenter, randomized, prospective, 2-arm trial with either NT-proBNP–guided therapy or conventional therapy for patients with ADHF.[11] The design and study population and the primary outcomes of the trial were reported previously.[11,12] Briefly, patients admitted for ADHF (either de novo or acute-on-chronic HF) and with NT-proBNP levels of ≥1700 pg/mL measured within 24 hours of hospital admission were eligible for the PRIMA II trial.[11,12] From NT-proBNP measurements that were performed during hospitalization, we used only

admission and discharge NT-proBNP measurements. Follow-up visits for event registration were performed after discharge at 1 week and at 1, 3, and 6 months, where event registration was performed. The primary end point was a composite end point of all-cause mortality and readmission for HF at 6 months.[11,12] Results of the PRIMA-II trial were not different between the 2 treatment arms, and both treatment arms were included in the validation cohort.

Both trials (ELAN-HF and PRIMA-II) were approved by the institutional review committees in their respective centers, and all subjects gave informed consent.[8,11,12] The data that support the findings of this study are available from the corresponding author to other researchers for purposes of reproducing the results or replicating the procedure on reasonable request, ensuring data deidentification.

Statistical Analysis

The primary end point for model calibration and discrimination was all-cause mortality at 6 months. Demographic characteristics were published previously.[8,11] We compared the baseline demographics and clinical characteristics between the derivation and validation cohorts using the Fisher exact test to make a comparison for categorical data and the independent *t* test to make a comparison for normally distributed continuous variables; the independent-sample Mann-Whitney *U* test was used to make a comparison for all other continuous variables. The distribution of ELAN-HF score predictors in the derivation and validation data sets is presented as frequencies and percentages.

To assess the discriminatory accuracy of our model, we calculated 6-month mortality in the validation cohort (PRIMA II) by the Kaplan-Meier method (Kaplan-Meier curves) with log-rank test for each of the 4 categories of the ELAN-HF risk score. To calculate the ELAN-HF score, each variable in the multivariate model was multiplied by its regression coefficient[8]; and the products were summed and prospectively applied to each patient in both the derivation cohort as well as in the validation cohort to provide individual estimates of survival at 6 months.[13,14]

First, the baseline survival function (B_0) was estimated at the observed time of 6 months in the derivation cohort (B_0=0.983). For a given value of the ELAN-HF score, we calculated the predicted mortality function (M_{pred}) in the derivation and validation data sets by the following equation[13]: $M_{pred}(t)=1-[B_0(t)^{exp(ELAN\text{-}HF)}]$.

Thereafter, calibration was assessed by calculating the actual mortality using Kaplan-Meier curves and the expected mortality in each risk group by calculating the mean predicted mortality at 6 months over all members of each aforementioned risk group in both the derivation (ELAN-HF) and the validation (PRIMA II) cohorts. Moreover, to further asses the accuracy of the calibration of our model, we also plotted the mean predicted mortality against the observed mortality (Kaplan-Meier) by deciles of predicted mortality for the derivation cohort and by quintiles (because of the smaller sample size) of predicted mortality for the validation cohort.[14] Calibration was assessed by a correlation coefficient and SEE. The model discriminant ability was determined by the 6-month receiver-operating characteristic area under the curve for both data sets, using the categorized model. We used the method of Hanley and MacNeil to compare the C-statistics.[15]

To accommodate for the different cohorts, separate baseline hazard functions were used to adjust for between-study differences. For the multivariable model, we performed multiple imputation pooling algorithms (n=10) to correct for missing values using predictive mean matching. All patient, medical history, and treatment variables (including outcome variables) were used when creating the multiple imputation data sets. All probability values were 2 sided and considered significant if $P<0.05$. Statistical analyses were conducted using SPSS 24.0.0.0 (SPSS IBM, New York, NY).

Results

Demographic Characteristics

The detailed demographics table for both the derivation cohort as well as for the validation cohort has been reported previously in the original articles.[8,11] Briefly (Table S1), the patients in the PRIMA II (validation) cohort were older than those in the ELAN-HF (derivation) cohort (77 versus 74 years; $P<0.001$), with more female patients (51% versus 40%; $P<0.001$) and patients more frequently with hypertension (64% versus 51%; $P<0.001$), peripheral edema (73% versus 62%; $P<0.001$), and a higher mean systolic blood pressure at admission (137 versus 133 mm Hg; $P=0.028$) and fewer patients admitted with New York Heart Association class III/IV (79% versus 96%; $P<0.001$). For routine laboratory measurements, patients in the validation cohort had significantly lower mean levels of urea nitrogen at admission (12 versus 13 mmol/L; $P=0.024$), lower serum sodium levels at admission (138 versus 139 mmol/L; $P=0.005$), and lower estimated glomerular filtration rate levels at admission (52 versus 57 mL/min per 1.73 m^2; $P=0.002$). There was no significant difference between validation and derivation cohorts for median NT-proBNP level at admission (6182 versus 6447 pg/mL; $P=0.433$) as well as at discharge (2910 versus 3252 pg/mL; $P=0.096$). The median NT-proBNP reduction percentage during hospitalization was significantly higher for the validation cohort compared with the derivation cohort (47% versus 43%; $P=0.007$). At discharge, significantly fewer patients in the validation cohort received diuretics compared with patients in the derivation cohort (92% versus

95%; P=0.010), but more patients received β blockers (75% versus 57%; P<0.001).

The Distribution Predictors

The distribution of the predictors between the derivation and validation cohorts is shown in Table 1. The distributions happen to be broadly similar between the derivation and validation data sets, although this is not a requirement for successful validation.[13]

Adverse Events

In both studies, no patients were lost to follow-up, and follow-up data were 100% complete. In the PRIMA II trial, 74 died of any cause within 6 months, which was equal to an all-cause mortality of 18%. In the ELAN-HF trial, 195 died of any cause within 6 months, which was equal to an all-cause mortality of 15% (P=0.118).

Calibration and Validation of the ELAN-HF Score

Figure 1 shows Kaplan-Meier curves for 6-month all-cause mortality in the validation cohort, according to the 4 risk groups. The figure shows that the curves are increasing significantly in a stepwise manner across the risk groups, confirming our earlier conclusion that the model has excellent discriminatory ability.[8] The predicted and observed mortality rates in the derivation and the validation cohorts are presented in tabular (Table 2) form for the 4 risk groups. The stepwise increase in all-cause mortality for the 4 risk groups for the derivation cohort increased with a rate of 3.6%

Table 1. Distribution of Predictors in the Derivation and Validation Data Sets

Predictors	ELAN-HF Cohort		PRIMA II Cohort		*P* Value
NT-proBNP value at discharge, pg/mL					0.509
1500–5000	471	(37)	171	(48)	
5001–15 000	334	(26)	80	(22)	
>15 000	132	(10)	27	(8)	
NT-proBNP reduction ≤30%	494	(39)	102	(29)	<0.001
Aged ≥75 y at admission	575	(44)	244	(60)	<0.001
Peripheral edema at admission	674	(62)	285	(73)	<0.001
Systolic blood pressure ≤115 mm Hg at admission	411	(32)	103	(26)	0.018
Hyponatremia (sodium <135 mmol/L) at admission	204	(17)	77	(19)	0.287
Serum urea ≥15 mmol/L at discharge	377	(33)	78	(25)	0.019
NYHA class III/IV at discharge	216	(18)	81	(21)	0.215

Data are given as number (percentage) of each group. ELAN-HF indicates European Collaboration on Acute Decompensated Heart Failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PRIMA II, Can NT-proBNP–Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?

Table 2. Observed Mortality and Expected Mortality in the Derivation (ELAN-HF) and Validation (PRIMA II) Cohorts

Demographics	ELAN-HF Cohort		PRIMA II Cohort	
Follow-up, d	180		180	
Death, n (%)	195 (15)		74 (18)	
Risk Categories	Actual, %	Predicted, %	Actual, %	Predicted, %
Low (≤2)	3.6	3.7	2.2	3.0
Intermediate (3–4)	9.2	9.4	8.2	9.4
High (5–7)	23.5	24.2	22.9	25.0
Very high (≥8)	51.1	54.2	53.6	56.8

ELAN-HF indicates European Collaboration on Acute Decompensated Heart Failure; PRIMA II, Can NT-proBNP (N-terminal Pro-B-Type Natriuretic Peptide)–Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?

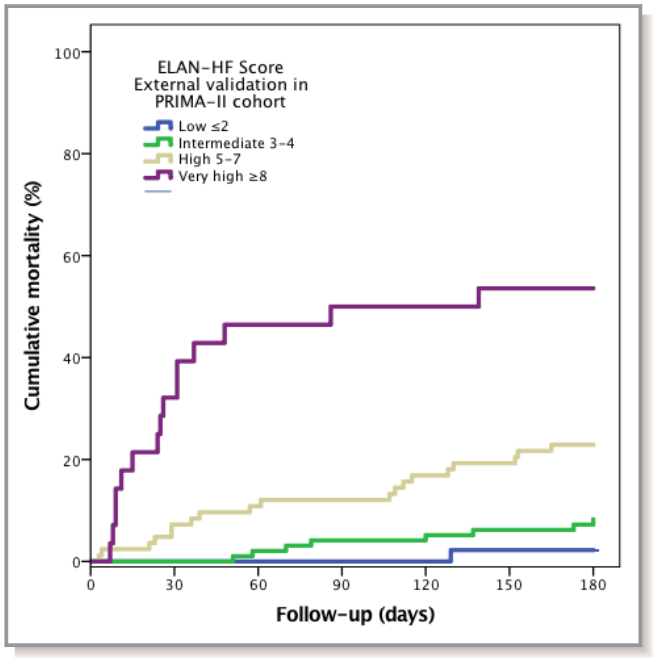

Figure 1. Kaplan-Meier curve of ELAN-HF (European Collaboration on Acute Decompensated Heart Failure) score in the external validation (PRIMA II [Can NT-proBNP {N-terminal Pro-B-Type Natriuretic Peptide}-Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?]) cohort.

for the low-risk patients, 9.2% for the patients with an intermediate risk, 23.5% for the patients with a high risk, and 51.1% for the very-high-risk patients.[8] This was in complete agreement with the results in the validation cohort, after the ELAN-HF model was applied prospectively to the validation cohort, with mortality rates in the 4 risk categories of 2.2%, 8.2%, 22.9%, and 53.6%, respectively.

In the derivation cohort, the predicted 6-month mortality rates, according to the risk categories, were 3.6% for the low-risk category, 9.4% for the intermediate-risk category, 24.2% for the high-risk category, and 54.2% for the very-high-risk category; there was a correlation coefficient of 0.92, with a SEE of ±4%, between predicted and observed mortality by decile (Figure 2). In the validation cohort, predicted 6-month mortality rates, according to the risk categories, were 3.0%, 9.4%, 25.0%, and 56.8%, respectively; there was a correlation coefficient of 0.99, with a SEE of ±2%, between predicted and observed mortality by quintiles.

ELAN-HF Score Discriminant Ability

Table 3 shows the 6-month receiver-operating characteristic for the derivation cohort was 0.78 (95% CI, 0.74–0.82). In the validation cohort, the 6-month receiver-operating characteristic was 0.77 (95% CI, 0.69–0.84), not different from the C-statistic of the derivation cohort (P=0.693).

Discussion

The ELAN-HF score is a bedside score predicting 6-month all-cause mortality in patients after hospitalization for ADHF, for patients with both preserved ejection fraction and reduced ejection fraction, with a wide range of heart failure symptoms at discharge (New York Heart Association class I to IV).[8] The ELAN-HF score was previously validated in an external cohort.[8,10] However, because of limitations of the validation data set, we set out to calibrate and revalidate the ELAN-HF score prospectively in the PRIMA II cohort.[11] Our data show that the score is statistically robust in that both the calibration and external validity of the risk score were confirmed in the validation cohort using 4 risk categories. The model shows an excellent predictive proportional value and confirms the increasing 6-month mortality with increasing score using NT-proBNP values in addition to easily obtained clinical and laboratory characteristics.

Revalidating the ELAN-HF Score

External validation is a crucial step toward acceptance of a risk score into clinical practice. If a prognostic model predicts outcome well on a derivation cohort, but weakly on an independent cohort, it is clearly not fit for use. There are 2 fundamental aspects of validating model performance: discrimination and calibration.[13] Discrimination is the ability

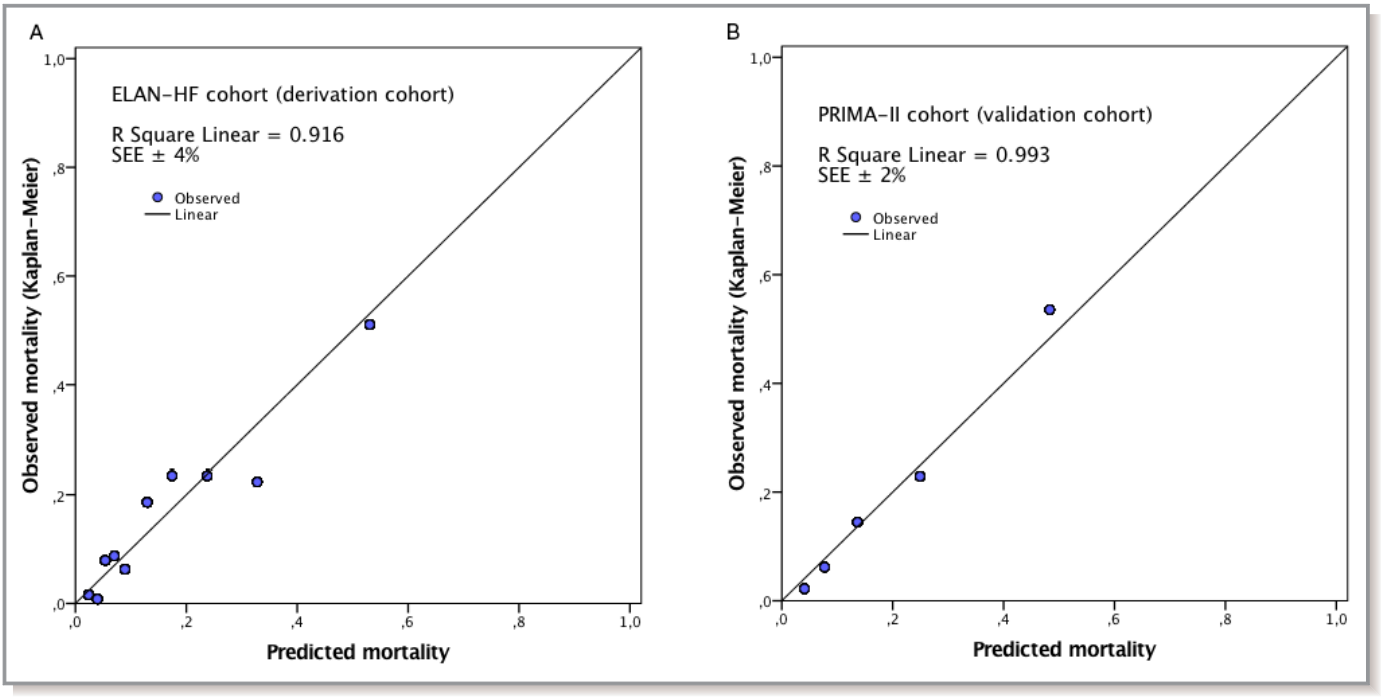

Figure 2. Calibration plots of mean predicted mortality vs observed mortality (Kaplan-Meier) by deciles of predicted mortality for the derivation cohort (ELAN-HF [European Collaboration on Acute Decompensated Heart Failure] cohort; **A**) and by quintiles of predicted mortality for the validation cohort (PRIMA II [Can NT-proBNP {N-terminal Pro-B-Type Natriuretic Peptide}–Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?] cohort; **B**).

Table 3. Comparison of C-Statistics Between the Derivation (ELAN-HF) Cohort and the Validation (PRIMA II) Cohort

	C-Statistic for the Simplified ELAN-HF Score	
Cohort	AUC (95% CI)	*P* Value*
ELAN-HF	0.78 (0.74–0.82)	0.693
PRIMA II	0.77 (0.69–0.84)	. . .

AUC indicates area under the curve; ELAN-HF, European Collaboration on Acute Decompensated Heart Failure; PRIMA II, Can NT-proBNP (N-terminal Pro-B-Type Natriuretic Peptide)–Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?
*AUCs were compared using the method of Hanley and MacNeil.[15]

of a model to predict that patients at higher risk should exhibit higher event rates than those at lower risk. Calibration reflects the prediction accuracy, where the correct event probability is assigned at all levels of predicted risk, without underpredicting or overpredicting the event probability.[13] The ELAN-HF score performs excellent on both departments. The model shows an excellent discriminative proportional value and confirms the increasing 6-month mortality with increasing score. Furthermore, our data showed that the calibration is excellent for the 4 risk categories for both data sets. The observed and predicted all-cause mortality rates in the 2 data sets are almost identical, reflecting the similarity in the distributions of the ELAN-HF score in each risk group across the data sets. In our previous study,[8] we only performed the external validation with level 2 information available.[13] With this study, we were able to externally validate the risk score with level 3 information available,[13] which shows that it is a reliable risk score to be used in the clinic practice.

Discriminative Ability

The risk score performed as well in the derivation cohort (ELAN-HF) as in the validation cohort (PRIMA II), as evidenced by the C-statistics. There was no difference between the C-statistics, with values of the C-statistic of 0.76 (95% CI, 0.71–0.80) and 0.77 (95% CI, 0.69–0.84) for the derivation and validation cohorts, respectively. The strength of the ELAN-HF model is its broad applicability and its easy calculation. Moreover, variables in the model can be easily ascertained when a patient has been hospitalized for ADHF.

Other Risk-Predicting Models for Patients With ADHF, Using Natriuretic Peptide Levels

The OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) study showed that a model using clinical variables plus discharge BNP appropriately reclassifies risk in tertiles of 1-year mortality in a mixed population of patients with ADHF, aged ≥65 years, and improves discrimination compared with a model with clinical variables alone, with a final C-statistic of 0.69.[16] Calibration of the model was done; however, the model was not externally validated.[16] ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) was used to derive a clinical model, including natriuretic peptides (BNP) at discharge, with a C-index of 0.76 for predicting 6-month mortality.[17] The patient population consisted of patients with severe left systolic heart failure. The model was externally validated with clinical variables only, although BNP levels were the most important prognostic variable.[17] The COACH (Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure) risk engine was previously published, using clinical and laboratory variables and discharge NT-proBNP levels, in a mixed population with ADHF, similar to our populations with ADHF. From a multistate model, the COACH risk engine predicts 18-month mortality and/or hospital readmissions for heart failure.[18] Their C-index for mortality was 0.73 in the derivation cohort and (with 48-hour NT-proBNP levels in place of discharge levels) was 0.70 in the validation cohort.[18] The prediction is for 18 months, which may make it less useful for earlier assessments, as risk weans off with time and other risk predictors may come into play. The program can be downloaded from the internet, which makes its clinical use more convenient. The ADHF/NT-proBNP risk score for 1-year mortality, heart transplantation, or left ventricular assist device implantation, in patients with ADHF with left ventricular ejection fraction ≤40% well treated with an implantable cardioverter defibrillator and a cardiac resynchronization therapy defibrillator, performs well, with a C-statistic of 0.84 in the derivation cohort and 0.77 in the validation cohort.[19] Apart from its selected population, a critique may be the use of admission NT-proBNP levels, which have lower predictive ability than discharge NT-proBNP levels, although their contribution to the final risk assessment was high in this particular score.[19] The more recent risk models, such as the BIOSTAT-CHF (A Systems Biology Study to Tailored Treatment in Chronic Heart Failure), include patients after discharge as well as patients at the outpatient clinic, necessitating the incorporation of having been hospitalized for heart failure as an added risk variable, which was also externally validated.[20] However, the C-statistic for the compact model was lower compared with the C-statistic of our simple bedside model (0.69 versus 0.76), possibly because of the interference of the outpatient population.

Limitations

The derivation cohort was an individual patient data analysis of 7 cohorts, which was conceived after publication of the

original studies.[8] Apart from some variation in NT-proBNP assays used, treatment and inclusion criteria in the different centers should be considered. Nevertheless, the range in markers and therapeutic approach of patients, as observed, reflects the day-to-day clinical practice. Missing data should be considered as a limitation in our study. However, we did correct for the bias from data missing at random by using multiple imputation pooling algorithms. Furthermore, the use of all-cause mortality instead of cardiovascular mortality as the primary outcome is a limitation. It is, however, clear that cardiovascular mortality explains 63% to 87% of mortality after ADHF.[21,22]

Conclusions

External validation of the ELAN-HF risk score in the PRIMA II cohort confirms its excellent accuracy and discriminative ability. The score allows accurate prediction of 6-month mortality of patients hospitalized for ADHF with the use of easily obtained clinical and laboratory characteristics, including absolute natriuretic peptide levels at discharge and a relative change in natriuretic peptide of ≤30% from admission values. The risk stratification, as predicted in our bedside model, is in complete agreement with that in the external validation cohort, which shows that it is a reliable score to be used in the clinic practice.

Author Contributions

Drs Salah and Kok had the idea for the project, designed the collaborative analysis, and undertook searches of published work. Drs Salah and Stienen collected the individual patient data and prepared for analysis. Statistical analysis and elaboration of figures was done by Drs Salah, Kok, and Tijssen. Dr Salah wrote the article, with important contribution from Drs Kok and Tijssen and input from Drs Pinto, Stienen, Ferreira, and Moons, who provided valuable comments on the article. All coauthors had an opportunity to contribute to the interpretation of results and to the redrafting of the article. All authors reviewed and revised the article and approved the final version.

Sources of Funding

The PRIMA II (Can NT-proBNP–Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?) trial was funded by a grant (2010B97) from the Netherlands Heart Foundation and by the University of Amsterdam (Amsterdams Universiteitsfonds). NT-proBNP (N-terminal pro-B-type natriuretic peptide) laboratory kits were kindly supplied by Roche Diagnostics. Drs Salah, Stienen, Tijssen, Kok, and Pinto had full access to all data in the study and had final responsibility for the study design, data analysis, data interpretation, and the decision to submit the article for publication. The study was conducted and analyzed independently.

Disclosures

Pinto received research funding for their original study from the Dutch Heart Foundation, Dutch Organization for Scientific Research, the Royal Dutch Academy of Arts and Sciences–Interuniversity Cardiology Institute of the Netherlands, Pfizer, Astra-Zeneca, Medtronic, and Roche Diagnostics. Dr Pinto is a recipient of payments for lectures, including service on speakers' bureaus, and research grants from Roche Diagnostics. Dr Pinto has an unrelated biomarker patent and stocks in a university spinoff company. Dr Kok received a grant from the Dutch Heart Foundation for the PRIMA II (Can NT-proBNP–Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?) trial (grant 2010B97) and has participated in advisory board meetings of Roche Diagnostics and Novartis. Dr Ferreira reports receiving modest board fees from Novartis and modest speaker fees from Roche Diagnostics. Dr Marques reports receiving modest honoraria and expert witness fees. Dr Bayes-Genis reports receiving significant research grants, significant research support, and modest honoraria from Roche Diagnostics. The remaining authors have no disclosures to report.

References

1. Alba AC, Agoritsas T, Jankowski M, Courvoisier D, Walter SD, Guyatt GH, Ross HJ. Risk prediction models for mortality in ambulatory patients with heart failure: a systematic review. *Circ Heart Fail*. 2013;6:881–889.
2. Cleland JG, Swedberg K, Cohen-Solal A, Cosin-Aguilar J, Dietz R, Follath F, Gavazzi A, Hobbs R, Korewicki J, Madeira HC, Preda I, van Gilst WH, Widimsky J, Mareev V, Mason J, Freemantle N, Eastaugh J. The Euro Heart Failure Survey of the EUROHEART survey programme: a survey on the quality of care among patients with heart failure in Europe: the Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology: the Medicines Evaluation Group Centre for Health Economics University of York. *Eur J Heart Fail*. 2000;2:123–132.
3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; Authors/Task Force Members; Document Reviewers. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC): developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2016;18:891–975.
4. Logeart D, Isnard R, Resche-Rigon M, Seronde M-F, de Groote P, Jondeau G, Galinier M, Mulak G, Donal E, Delahaye F, Juilliere Y, Damy T, Jourdain P, Bauer F, Eicher J-C, Neuder Y, Trochu J-N; on behalf of the working group on Heart Failure of the French Society of Cardiology. Current aspects of the spectrum of acute heart failure syndromes in a real-life setting: the OFICA study. *Eur J Heart Fail*. 2013;15:465–476.
5. Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JEA, Cleland JG, Dickstein K, Drazner MH, Fonarow GC, Jaarsma T, Jondeau G, Sendon JL,

Mebazaa A, Metra M, Nieminen M, Pang PS, Seferovic P, Stevenson LW, van Veldhuisen DJ, Zannad F, Anker SD, Rhodes A, McMurray JJV, Filippatos G. Assessing and grading congestion in acute heart failure: a scientific statement from the acute heart failure committee of the heart failure association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. *Eur J Heart Fail*. 2010;12:423–433.

6. Nohria A, Lewis E, Stevenson LW. Medical management of advanced heart failure. *JAMA*. 2002;287:628–640.
7. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, O'Connor CM, Pieper K, Sun JL, Yancy C, Young JB; OPTIMIZE-HF Investigators and Hospitals. Association between performance measures and clinical outcomes for patients hospitalized with heart failure. *JAMA*. 2007;297:61.
8. Salah K, Kok WE, Eurlings LW, Bettencourt P, Pimenta JM, Metra M, Bayes-Genis A, Verdiani V, Bettari L, Lazzarini V, Damman P, Tijssen JG, Pinto YM. A novel discharge risk model for patients hospitalised for acute decompensated heart failure incorporating N-terminal pro-B-type natriuretic peptide levels: a European coLlaboration on Acute decompeNsated Heart Failure: ÉLAN-HF Score. *Heart*. 2014;100:115–125.
9. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017;136:e137–e161.
10. Carubelli V, Lombardi C, Lazzarini V, Bonadei I, Castrini AI, Gorga E, Richards AM, Metra M. N-terminal pro-B-type natriuretic peptide-guided therapy in patients hospitalized for acute heart failure. *J Cardiovasc Med (Hagerstown)*. 2016;17:828–839.
11. Stienen S, Salah K, Moons AH, Bakx AL, van Pol P, Kortz M, Ferreira JP, Marques I, Schroeder-Tanka JM, Keijer JT, Bayés-Genis A, Tijssen JGP, Pinto YM, Kok WE. NT-proBNP-guided therapy in acute decompensated heart failure: the PRIMA II randomized controlled trial. *Circulation*. 2018;137:1671–1683.
12. Stienen S, Salah K, Moons AHM, Bakx ALM, van Pol PE, Schroeder-Tanka JM, Voogel AJ, Keijer JT, Kortz RAM, Dickhoff C, Meregalli PG, Tijssen JG, Pinto YM, Kok WE. Rationale and design of PRIMA II: a multicenter, randomized clinical trial to study the impact of in-hospital guidance for acute decompensated heart failure treatment by a predefined NT-PRoBNP target on the reduction of readmIssion and Mortality rAtes. *Am Heart J*. 2014;168:30–36.
13. Royston P, Altman DG. External validation of a Cox prognostic model: principles and methods. *BMC Med Res Methodol*. 2013;13:33.
14. Levy WC. The Seattle Heart Failure Model: prediction of survival in heart failure. *Circulation*. 2006;113:1424–1433.
15. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology*. 1982;143:29–36.
16. Kociol RD, Horton JR, Fonarow GC, Reyes EM, Shaw LK, O'Connor CM, Felker GM, Hernandez AF. Admission, discharge, or change in B-type natriuretic peptide and long-term outcomes: data from organized program to initiate lifesaving treatment in hospitalized patients with heart failure (OPTIMIZE-HF) linked to Medicare claims. *Circ Heart Fail*. 2011;4:628–636.
17. O'Connor CM, Hasselblad V, Mehta RH, Tasissa G, Califf RM, Fiuzat M, Rogers JG, Leier CV, Stevenson LW. Triage after hospitalization with advanced heart failure. *J Am Coll Cardiol*. 2010;55:872–878.
18. Postmus D, van Veldhuisen DJ, Jaarsma T, Luttik ML, Lassus J, Mebazaa A, Nieminen MS, Harjola V-P, Lewsey J, Buskens E, Hillege HL. The COACH risk engine: a multistate model for predicting survival and hospitalization in patients with heart failure. *Eur J Heart Fail*. 2012;14:168–175.
19. Scrutinio D, Ammirati E, Guida P, Passantino A, Raimondo R, Guida V, Braga SS, Pedretti RF, Lagioia R, Frigerio M, Catanzaro R, Oliva F. Clinical utility of N-terminal pro-B-type natriuretic peptide for risk stratification of patients with acute decompensated heart failure: derivation and validation of the ADHF/NT-proBNP risk score. *Int J Cardiol*. 2013;168:2120–2126.
20. Voors AA, Ouwerkerk W, Zannad F, van Veldhuisen DJ, Samani NJ, Ponikowski P, Ng LL, Metra M, ter Maaten JM, Lang CC, Hillege HL, van der Harst P, Filippatos G, Dickstein K, Cleland JG, Anker SD, Zwinderman AH. Development and validation of multivariable models to predict mortality and hospitalization in patients with heart failure: mortality and hospitalization models in heart failure. *Eur J Heart Fail*. 2017;19:627–634.
21. Hamaguchi S, Kinugawa S, Sobirin MA, Goto D, Tsuchihashi-Makaya M, Yamada S, Yokoshiki H, Tsutsui H; JCARE-CARD Investigators. Mode of death in patients with heart failure and reduced vs. preserved ejection fraction: report from the registry of hospitalized heart failure patients. *Circ J*. 2012;76:1662–1669.
22. O'Connor CM, Miller AB, Blair JEA, Konstam MA, Wedge P, Bahit MC, Carson P, Haass M, Hauptman PJ, Metra M, Oren RM, Patten R, Piña I, Roth S, Sackner-Bernstein JD, Traver B, Cook T, Gheorghiade M. Causes of death and rehospitalization in patients hospitalized with worsening heart failure and reduced left ventricular ejection fraction: results from efficacy of vasopressin antagonism in heart failure outcome study with tolvaptan (EVEREST) program. *Am Heart J*. 2010;159:841–849.e1.

SUPPLEMENTAL MATERIAL

Table S1. Baseline demographics.

	ELAN-HF cohort N=1301	PRIMA II cohort N=404
Variables		
Age, years, median (IQR)	74 (64-80)	77 (69-85)
Male sex, n (%)	775 (60)	198 (49)
History of DM, n (%)	422 (33)	138 (34)
History of Hypertension, n (%)	661 (51)	254 (64)
History of COPD, n (%)	209 (18)	79 (20)
Ischemic etiology, n (%)	631 (51)	102 (43)
LVEF, %, mean ± SD	35 ± 16	36 ± 15
JVP distended at admission, n (%)	635 (62)	142 (57)
Pulmonary rales at admission, n (%)	821 (76)	302 (77)
Peripheral edema at admission, n (%)	674 (62)	285 (73)
SBP at admission, mmHg, median (IQR)	133 ± 32	137 ± 30
DBP at admission, mmHg, mean ± SD	81 ± 20	81 ± 22
Heart rate at admission, bpm, mean ± SD	93 ± 25	94 ± 28
Atrial fibrillation (AF) at admission, n (%)	513 (43)	154 (39)
NYHA class at admission, n (%)		
I/II	48 (4)	81 (21)
III/ IV	1134 (96)	310 (79)
Laboratory findings, mean ± SD		
Hemoglobin at admission, mmol/L	7.9 ± 1.3	7.7 ± 1.2
Serum urea nitrogen at admission, mmol/l	13 ± 7.8	12 ± 6.8
Serum sodium at admission, mmol/l	139 ± 4.8	138 ± 4.8
eGFR at admission, ml/min/1.73m²	57 ± 33	52 ± 25
NT-proBNP at admission, pg/ml, median (IQR)	6447 (3057-12632)	6182 (3945-11146)
NT-proBNP at discharge, pg/ml, median (IQR)	3252 (1419-7291)	2910 (1643-5779)
NT-proBNP reduction during hospitalization, median (IQR)	43 (13-67)	47 (22-66)
Duration admission, days, median (IQR)	9 (6-14)	9 (6-15)

Medication at discharge, n (%)		
Diuretics	1156 (95)	370 (92)
ACE-inhibitors or ARB	806 (66)	287 (71)
Beta-blocker	685 (57)	304 (75)