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ORIGINAL INVESTIGATIONS

N-Terminal Pro–B-Type Natriuretic Peptide in the Emergency Department

The ICON-RELOADED Study

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ABSTRACT

BACKGROUND Contemporary reconsideration of diagnostic N-terminal pro–B-type natriuretic peptide (NT-proBNP) cutoffs for diagnosis of heart failure (HF) is needed.

OBJECTIVES This study sought to evaluate the diagnostic performance of NT-proBNP for acute HF in patients with dyspnea in the emergency department (ED) setting.

METHODS Dyspneic patients presenting to 19 EDs in North America were enrolled and had blood drawn for subsequent NT-proBNP measurement. Primary endpoints were positive predictive values of age-stratified cutoffs (450, 900, and 1,800 pg/ml) for diagnosis of acute HF and negative predictive value of the rule-out cutoff to exclude acute HF. Secondary endpoints included sensitivity, specificity, and positive (+) and negative (−) likelihood ratios (LRs) for acute HF.

RESULTS Of 1,461 subjects, 277 (19%) were adjudicated as having acute HF. The area under the receiver-operating characteristic curve for diagnosis of acute HF was 0.91 (95% confidence interval [CI]: 0.90 to 0.93; $p < 0.001$). Sensitivity for age stratified cutoffs of 450, 900, and 1,800 pg/ml was 85.7%, 79.3%, and 75.9%, respectively; specificity was 93.9%, 84.0%, and 75.0%, respectively. Positive predictive values were 53.6%, 58.4%, and 62.0%, respectively. Overall LR+ across age-dependent cutoffs was 5.99 (95% CI: 5.05 to 6.93); individual LR+ for age-dependent cutoffs was 14.08, 4.95, and 3.03, respectively. The sensitivity and negative predictive value for the rule-out cutoff of 300 pg/ml were 93.9% and 98.0%, respectively; LR− was 0.09 (95% CI: 0.05 to 0.13).

CONCLUSIONS In acutely dyspneic patients seen in the ED setting, age-stratified NT-proBNP cutpoints may aid in the diagnosis of acute HF. An NT-proBNP <300 pg/ml strongly excludes the presence of acute HF. (J Am Coll Cardiol 2018;71:1191–200) © 2018 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

ED = emergency department

FDA = Food and Drug Administration

HF = heart failure

LR− = negative likelihood ratio

LR+ = positive likelihood ratio

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

NPV = negative predictive value

PPV = positive predictive value

ROC = receiver-operating characteristic

Natriuretic peptide testing (B-type natriuretic peptide [BNP] and its amino-terminal pro-peptide cleavage equivalent, N-terminal pro-B-type natriuretic peptide [NT-proBNP]) aids in the diagnosis of acute heart failure (HF) (1–4). These biomarkers are now embedded as Class I, Level of Evidence: A in clinical practice guidelines (5). Understanding the optimal means to interpret natriuretic peptide tests has evolved, and recent changes in certain characteristics of patients affected by HF suggest the need to reassess the current natriuretic peptide diagnostic cutoffs. Such changes include shifting HF demographics (6,7), including more prevalent renal disease and atrial fibrillation, which possibly contributes to higher biomarker concentrations (8). Conversely, increasing incidence and prevalence of HF with preserved ejection fraction and patient obesity, both of which may result in lower natriuretic peptide concentrations, may require lower BNP or NT-proBNP cutoffs. Similarly, the growing use of HF medications influencing BNP or NT-proBNP values (such as neprilysin inhibition) may also change optimal cutoffs for diagnosis of acute exacerbation of HF.

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Data from the PRIDE (N-Terminal Pro-BNP Investigation of Dyspnea in the Emergency Department) and ICON (International Collaborative of NT-proBNP) studies suggested optimal diagnostic cutoffs of 450, 900, and 1,800 pg/ml for age categories of <50, 50 to 75, and >75 years, respectively, for the identification of acute HF (9), along with an age-independent cutoff of 300 pg/ml to exclude acute HF. These cutoffs have been widely endorsed (1,5,10); however, they differ substantially from the Food and Drug Administration (FDA)-approved cutoffs for NT-proBNP (125 and 450 pg/ml for <75 and ≥75 years of age) (11), which are optimized for outpatient exclusion of ambulatory HF. Thus, there is a need to reconsider which cutoffs should be used, as continued reliance on current, approved cutoffs has the potential for diagnostic inaccuracy, particularly for test specificity.

In light of these current gaps, the aim of the ICON-RELOADED (ICON: Re-evaluation of Acute Diagnostic Cut-Offs in the Emergency Department) study is to validate the age-specific NT-proBNP cutoffs identified in the first ICON study in a contemporary cohort. We hypothesized that the original ICON strategy for NT-proBNP interpretation would remain useful for diagnostic evaluation of HF in an all-comer population of patients with dyspnea.

METHODS

STUDY DESIGN. The rationale and design of the ICON-RELOADED study has been previously described (12). The study was a prospective, multicenter clinical trial conducted at 19 sites in the United States and Canada. Briefly, subjects 22 years of age or older presenting to emergency departments (EDs) with complaints of dyspnea (defined as a subjective feeling of shortness of breath, difficult or labored

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breathing) were enrolled, and were blindly and independently assessed for the presence of acute HF. A blood sample was taken at enrollment.

A clinical events adjudication committee, blinded to NT-proBNP results (obtained either by the hospital or by the study), independently reviewed and adjudicated the diagnosis of acute HF. The institutional review board at each participating institution approved the study, and all patients provided written, informed consent before enrollment. Patients provided additional written, informed consent prior to giving the biorepository blood sample.

STUDY OBJECTIVES. The primary objective of this study was to externally validate the use of Elecsys proBNP II (Roche Diagnostics, Indianapolis, Indiana) concentrations to aid in the diagnosis or exclusion of acute HF in patients presenting emergently through use of the ICON cutpoint strategy (9).

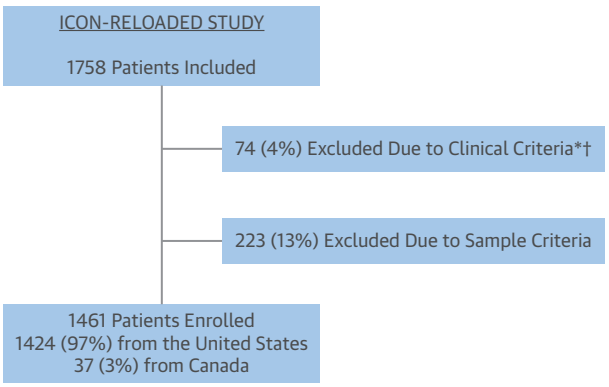
STUDY ENDPOINTS. The primary efficacy endpoints for this study were the positive predictive value (PPV) of age-specific rule-in cutoffs of 450, 900, and 1,800 pg/ml for ages <50, 50 to 75, and >75 years, respectively, for the diagnosis of acute HF, and the negative predictive value (NPV) of the rule-out cutoff of 300 pg/ml to exclude the adjudicated diagnosis of acute HF. Secondary endpoints included the NPV, positive likelihood ratio (LR+), sensitivity, and specificity for the age-specific rule-in cutoffs, as well as the negative likelihood ratio (LR−), sensitivity, and specificity for the rule-out cutoff. Other secondary endpoints included the PPV of all age-based rule-in cutoffs combined for the adjudicated diagnosis of acute HF by region (United States and Canada), and the NPV of the rule-out cutoff by region.

NT-proBNP MEASUREMENTS. A cobase 601 analyzer (Roche Diagnostics) was used for all NT-proBNP measurements.

STATISTICAL ANALYSES. The study was designed to include 1,765 patients to ensure a sample size of at least 1,500 analyzable patients, assuming 15% attrition.

Receiver-operating characteristic (ROC) curves for performance of NT-proBNP for diagnosis of acute HF were constructed. Operating characteristics for each cutoff for rule-in and the proposed cutoff for rule-out relative to the gold-standard diagnosis were evaluated, including sensitivity, specificity, PPV, NPV, LR+, and LR−. Estimates and 95% confidence intervals (CIs) were determined for the NPV and PPV parameters (13), and separately for LR+ and LR− using a nonlinear mixed-effects model. The significance of an elevated age-adjusted NT-proBNP value was further assessed by multivariable logistic regression analyses using backward elimination. Variables entered into the model were pre-specified as: history of diabetes mellitus, hypertension, or prior HF; history including a chief complaint of orthopnea; physical examination findings of pulmonary rales or peripheral edema; and testing results including estimated glomerular filtration rate, chest radiography revealing interstitial edema, as well as an elevated age-adjusted NT-proBNP. Variables were retained in the final model with an alpha level of 0.2; odds ratios (ORs) with 95% CIs were generated along with estimation of an overall C-statistic for the model.

FIGURE 1 CONSORT Diagram



Patients were included in the study only if both clinical and sample criteria were met. *Data are presented nonhierarchically; 2 subjects also had sample exclusion criteria but are only counted in this box. †57 subjects included in this box met the clinical criteria but did not have a baseline blood sample. ICON-RELOADED = ICON: Re-evaluation of Acute Diagnostic Cut-Offs in the Emergency Department.

Based on data generated in the ICON study (9), overall sensitivity and specificity of the proposed age-dependent cutoffs were expected to be 90.0% and 84.0%, respectively. The expected prevalence of acute HF was 50% with a PPV of 85.0%, and the LR+ was expected to be 5.62. This expectation was based on the prevalence observed in the original ICON study (9).

With 1,500 analyzable patients and an assumed HF prevalence of 50% (9), the anticipated lower bounds of a 95% 2-sided CI for the hypothesized PPV and LR+ were 86.2% and 4.77, respectively (14). With 1,275 analyzable patients from the United States, the lower bounds were anticipated to be 82.5% and 4.6 for PPV and LR+, respectively.

The expected sensitivity and specificity values of the rule-out cutoff of 300 pg/ml were 99.0% and 60.0%, respectively (9). Thus, the expected NPV was 98.5% (96.7% lower bound of the 95% CI) and the expected LR− was 0.017 (0.034 upper bound of the

TABLE 1 Baseline Characteristics of Enrolled Patients

	All Patients (N = 1,461)	Patients With Acute HF (n = 277)	Patients Without Acute HF (n = 1,184)	p Value
Age, yrs	56.4 ± 15.7	63.9 ± 13.4	54.6 ± 15.6	<0.001
Female	49.1 (718/1,461)	39.0 (108/277)	51.5 (610/1,184)	<0.001
Body mass index, kg/m^2	(N = 1,346)	(n = 267)	(n = 1,079)	<0.001
	32.0 ± 9.2	33.8 ± 9.9	31.5 ± 9.0	
Race				0.01
American Indian or Alaska Native	0.3 (4/1,432)	0.4 (1/271)	0.3 (3/1,161)	
Asian	1.5 (21/1,432)	1.8 (5/271)	1.4 (16/1,161)	
Black or African American	36.6 (524/1,432)	27.3 (74/271)	38.8 (450/1,161)	
Native Hawaiian or other Pacific Islander	0.6 (9/1,432)	0.7 (2/271)	0.6 (7/1,161)	
White	59.6 (853/1,432)	69.0 (187/271)	57.4 (666/1,161)	
Other	1.5 (21/1,432)	0.7 (2/271)	1.6 (19/1,161)	
Hispanic or Latino	13.6 (191/1,406)	8.9 (24/270)	14.7 (167/1,136)	0.01
Medical history				
Diabetes mellitus	28.9 (420/1,454)	45.3 (125/276)	25.0 (295/1,178)	<0.001
Hypertension	63.3 (921/1,455)	86.2 (237/275)	58.0 (684/1,180)	<0.001
Heart failure	24.9 (356/1,431)	68.2 (182/267)	14.9 (174/1,164)	<0.001
Peripheral arterial disease	4.3 (61/1,434)	9.1 (24/265)	3.2 (37/1,169)	<0.001
Implantable cardioverter-defibrillator	5.9 (86/1,452)	15.6 (43/276)	3.7 (43/1,176)	<0.001
Cardiac resynchronization therapy	1.7 (24/1,442)	4.4 (12/270)	1.0 (12/1,172)	<0.001
Coronary artery bypass graft	6.6 (96/1,451)	15.4 (42/272)	4.6 (54/1,179)	<0.001
Prior coronary artery disease	21.2 (307/1,445)	37.5 (103/275)	17.4 (204/1,170)	<0.001
Prior myocardial infarction	13.2 (188/1,428)	24.3 (65/268)	10.6 (123/1,160)	<0.001
Prior percutaneous coronary intervention	8.9 (128/1,431)	16.3 (44/270)	7.2 (84/1,161)	<0.001
Renal insufficiency/failure	7.8 (114/1,455)	19.6 (54/275)	5.1 (60/1,180)	<0.001
eGFR CKD-EPI, ml/min/1.73 m^2	(N = 1,323)	(n = 269)	(n = 1,054)	<0.001
	81.7 ± 27.9	64.3 ± 27.0	86.2 ± 26.4	
Most recent LVEF prior to enrollment	(N =405)	(n = 143)	(n = 262)	<0.001
	51.0 ± 17.1	41.7 ± 18.2	56.1 ± 14.2	
LVEF				<0.001
<50%	33.6 (136/405)	58.7 (84/143)	19.8 (52/262)	
≥50%	66.4 (269/405)	41.3 (59/143)	80.2 (210/262)	
Atrial fibrillation	14.9 (216/1,453)	34.3 (94/274)	10.3 (122/1,179)	<0.001
Significant mitral valve disease	4.2 (57/1,372)	11.6 (30/259)	2.4 (27/1,113)	<0.001
Significant aortic valve disease	2.3 (31/1,338)	6.1 (15/247)	1.5 (16/1,091)	<0.001
Asthma	30.1 (437/1,450)	15.9 (44/276)	33.5 (393/1,174)	<0.001
COPD	27.5 (399/1,449)	24.4 (67/275)	28.3 (332/1,174)	0.19
History/lung cancer	2.8 (40/1,454)	1.8 (5/276)	3.0 (35/1,178)	0.41
Alcohol history				0.30
Never	36.6 (514/1,404)	36.6 (94/257)	36.6 (420/1,147)	
Former	16.4 (230/1,404)	19.5 (50/257)	15.7 (180/1,147)	
Current	47.0 (660/1,404)	44.0 (113/257)	47.7 (547/1,147)	
Tobacco history				<0.001
Never	41.5 (591/1,423)	39.9 (107/268)	41.9 (484/1,155)	
Former	36.7 (522/1,423)	45.9 (123/268)	34.5 (399/1,155)	
Current	21.8 (310/1,423)	14.2 (38/268)	23.5 (272/1,155)	
Cocaine history				0.03
Never	89.0 (1,227/1,379)	84.6 (214/253)	90.0 (1,013/1,126)	
Former	10.4 (144/1,379)	14.6 (37/253)	9.5 (107/1,126)	
Current	0.6 (8/1,379)	0.8 (2/253)	0.5 (6/1,126)	

Values are mean ± SD or % (n/N).

COPD = chronic obstructive pulmonary disease; eGFR CKD-EPI = estimated glomerular filtration rate chronic kidney disease epidemiology collaboration equation; HF = heart failure; LVEF = left ventricular ejection fraction.

95% CI) (14). Additionally, as described previously (12), analyses were performed in pre-specified diagnostic subgroups. Baseline characteristics were compared between subjects with and without acute HF, using the Student's *t* test for continuous variables, the Pearson chi-square test for categorical variables, and the Fisher exact test for categorical variables with small counts.

RESULTS

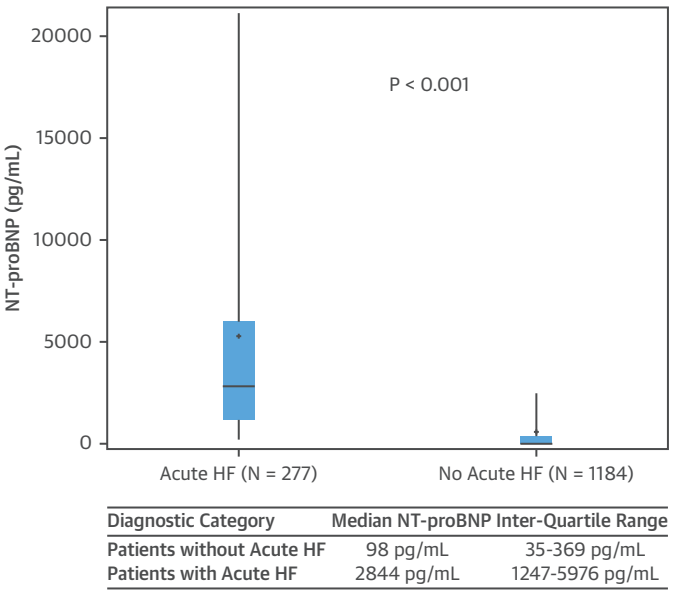
A total of 1,758 patients were enrolled from October 30, 2015, to October 15, 2016. Of these, 297 were excluded due to clinical or sample exclusion criteria, leaving 1,461 enrolled, of which 1,424 were from the United States and 37 were from Canada (**Figure 1**) (12).

DEMOGRAPHICS, DIAGNOSIS, AND MEDICAL HISTORY. As demonstrated in **Table 1**, 277 (19%) patients were diagnosed with acute HF and 1,184 (81%) did not have acute HF after adjudication (site diagnoses for these 1,184 patients are displayed in Online Table 1). This prevalence of 19% is significantly less than the 50% prevalence that was assumed at the outset of the trial, which had a significant effect on the expected predictive values described earlier. Overall, the mean patient age was 56.4 ± 15.7 years, 49.1% were female, and 36.6% were black; 63.3% had hypertension, and 24.9% had a history of prior HF. The most recent left ventricular ejection fraction (LVEF) measurement before enrollment, available in 28% of the patients (405 of 1,461), was mean 51 ± 17%. Asthma, chronic obstructive pulmonary disease, and a history of lung cancer were present in 30.1%, 27.5%, and 2.8% of the enrolled cohort, respectively; 58.5% of patients reported being current or former smokers. Subjects with acute HF were older and were more likely to have diabetes, hypertension, prior HF, prior coronary artery disease, chronic kidney disease, and atrial fibrillation compared with those without acute HF (all $p < 0.001$). Not surprisingly, those with acute HF were more likely to have lower mean LVEF at the most recent evaluation before enrollment. Additionally, most patients (58.7%) with acute HF had LVEF <50%.

Baseline characteristics of the subgroup of patients with acute HF, comparing those with reduced versus preserved ejection fraction, are presented in Online Table 2.

NT-proBNP CONCENTRATIONS. The results of NT-proBNP testing between those with and without acute HF are shown in **Figure 2**. The median NT-proBNP concentration of patients with acute HF (2,844 pg/ml; interquartile range: 1,247 to 5,976 pg/ml) was substantially higher than those without acute HF (98 pg/ml; interquartile range: 35 to 369 pg/ml; $p < 0.001$ for difference).

FIGURE 2 NT-proBNP Values Between Diagnostic Groups



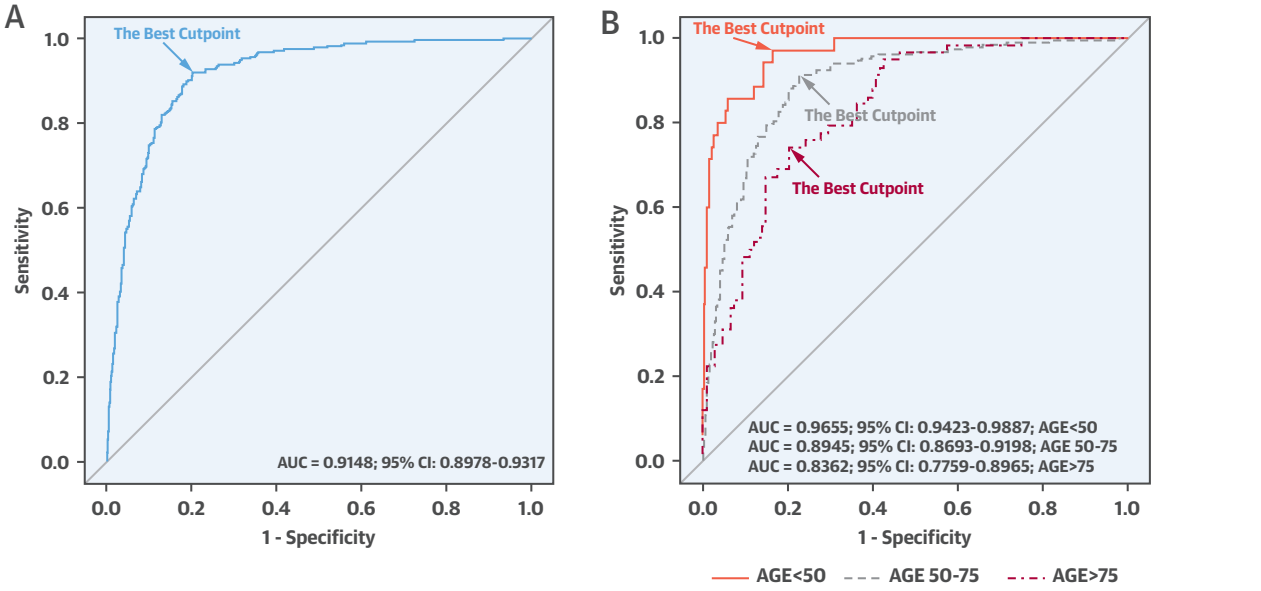
Diagnostic Category	Median NT-proBNP	Inter-Quartile Range
Patients without Acute HF	98 pg/mL	35-369 pg/mL
Patients with Acute HF	2844 pg/mL	1247-5976 pg/mL

Concentrations of NT-proBNP were considerably higher in those patients with acute HF ($p < 0.001$). HF = heart failure; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

The ROC curve for all patients (**Central Illustration**, panel A) demonstrated an area under the curve (AUC) of 0.91 (95% CI: 0.90 to 0.93; $p < 0.001$). The AUCs derived from the age categories are depicted in the **Central Illustration**, panel B. Among patients <50 (n = 462), 50 to 75 (n = 833), and >75 years of age (n = 166), NT-proBNP had AUCs of 0.97 (95% CI: 0.94 to 0.99), 0.89 (95% CI: 0.87 to 0.92), and 0.84 (95% CI: 0.78 to 0.90), respectively, for the diagnosis of acute HF (all $p < 0.001$).

CUTPOINT ANALYSIS: IDENTIFICATION OF ACUTE HF. The diagnostic sensitivities, specificities, PPV and NPV, and likelihood ratios for age-stratified diagnostic cutpoints in the study population are depicted in **Table 2**. This cutpoint strategy was associated with PPVs (primary endpoint) of 53.6% (95% CI: 43.7% to 63.2%), 58.4% (95% CI: 53.7% to 63.0%), and 62.0% (95% CI: 53.3% to 70.0%) for the age-dependent cutoffs of 450, 900, and 1,800 pg/ml, respectively. The corresponding sensitivities for each cutoff were 85.7% (95% CI: 74.1% to 97.3%), 79.3% (95% CI: 73.5% to 85.2%), and 75.9% (95% CI: 64.8% to 86.9%), respectively. Results using the FDA-approved NT-proBNP cutpoints (125 and 450 pg/ml) are presented in Online Table 3. The 125- and 450-pg/ml

CENTRAL ILLUSTRATION **NT-proBNP–Based Diagnosis of Acute HF: ROC Curves**



Sensitivity	92.1% (95% CI 88.9%-95.2%)
Specificity	79.6% (95% CI 77.4%-81.9%)
PPV	51.4% (95% CI 48.5%-54.3%)
NPV	97.7% (95% CI 96.6%-98.5%)
Accuracy	82.0% (95% CI 80.0%-84.0%)

	Age <50	Age 50-75	Age ≥75
Sensitivity	97.1% (95% CI 91.6%-100.0%)	91.3% (95% CI 87.2%-95.4%)	74.1% (95% CI 62.9%-85.4%)
Specificity	83.6% (95% CI 80.1%-87.1%)	77.0% (95% CI 73.8%-80.3%)	79.6% (95% CI 72.0%-87.2%)
PPV	32.7% (95% CI 28.0%-37.7%)	53.0% (95% CI 49.3%-56.7%)	66.2% (95% CI 56.6%-74.5%)
NPV	99.7% (95% CI 98.1%-100.0%)	96.9% (95% CI 95.1%-98.0%)	85.1% (95% CI 78.6%-90.0%)
Accuracy	84.6% (95% CI 81.3%-87.9%)	80.2% (95% CI 77.5%-82.9%)	77.7% (95% CI 71.4%-84.0%)

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The receiver-operating characteristic curves for the NT-proBNP–based diagnosis of acute heart failure are presented for **(A)** all patients (n = 1,461), and **(B)** across the 3 age groups: <50 years of age (n = 462); 50 to 75 years of age (n = 833); and >75 years of age (n = 166). The sensitivity, specificity, PPV, NPV, and accuracy are presented for the Youden index **(A)** for all patients, and **(B)** for each age group. AUC = area under the curve; HF = heart failure; NPV = negative predictive value; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PPV = positive predictive value; ROC = receiver-operating characteristic.

cutoffs were respectively associated with PPVs of 33.5% (95% CI: 31.7% to 35.3%) and 43.7% (95% CI: 40.5% to 46.8%); sensitivity of 96.7% (95% CI: 94.3% to 99.1%) and 98.4% (95% CI: 95.3% to 100.0%).

Given a lower prevalence (19%) (Online Figure 1) of acute HF than projected (which affects predictive values), it is worthwhile to emphasize that the overall LR+ for the age-stratified cutpoint strategy was as predicted at 5.99 (95% CI: 5.05 to 6.93); LR+ values for each cutoff were 14.08 (95% CI: 8.48 to 19.67), 4.95 (95% CI: 4.00 to 5.90), and 3.03 (95% CI: 1.94 to 4.13), respectively.

In multivariable logistic regression, an elevated age-adjusted NT-proBNP had the highest OR of all variables retained (OR: 11.80; 95% CI: 7.66 to 18.18; $p < 0.001$). Other variables significantly predictive of acute HF included prior HF (OR: 2.67; 95% CI: 1.76 to 4.07; $p < 0.001$), interstitial edema on chest radiography (OR: 4.70; 95% CI: 2.67 to 8.27; $p < 0.001$), rales on lung examination (OR: 2.56; 95% CI: 1.35 to 4.87; $p = 0.004$), and presence of peripheral edema on physical examination (OR: 3.95; 95% CI: 2.56 to 6.09; $p < 0.001$). The overall model C-statistic with these variables was 0.933.

CUTPOINT ANALYSIS: EXCLUSION OF ACUTE HF. The age-independent approach for ruling out acute HF using the single cutpoint of 300 pg/ml exhibited an NPV (primary endpoint) of 98.0% (95% CI: 96.9% to 98.8%), and a specificity of 71.7% (95% CI: 69.1% to 74.3%). The LR− was 0.09 (95% CI: 0.05 to 0.13) in our patient population (**Table 2**).

SUBGROUP FINDING. Subgroup analyses assessing the AUC of the optimal NT-proBNP cutpoints for the diagnosis or exclusion of acute HF are presented in **Table 3**. AUCs were generally similar to previous descriptions in men and women, or black versus nonblack patients (15), with no significant differences between groups in AUC. Additionally, in certain populations with conditions affecting the accuracy of

TABLE 2 NT-proBNP Cutpoints for the Diagnosis or Exclusion of Acute Decompensated HF

	Acute HF +	Acute HF −	Total
Confirmatory ("rule-in") cutpoints			
<50 yrs			
Test +	30	26	56
Test −	5	401	406
Total	35	427	462
50-75 yrs			
Test +	146	104	250
Test −	38	545	583
Total	184	649	833
>75 yrs			
Test +	44	27	71
Test −	14	81	95
Total	58	108	166
Rule-in, overall			
Test +	220	157	377
Test −	57	1,027	1,084
Total	277	1,184	1,461
Exclusionary ("rule-out") cutpoint			
All patients			
Test +	260	335	595
Test −	17	849	866
Total	277	1,184	1,461

Category	Cutpoint, pg/ml	Sensitivity	Specificity	PPV	NPV	LR+	LR−
Confirmatory ("rule-in") cutpoints							
<50 yrs (n = 462)	450	85.7 (74.1-97.3)	93.9 (91.6-96.2)	53.6 (43.7-63.2)	98.8 (97.3-99.4)	14.08 (8.48-19.67)	0.15 (0.03-0.28)
50-75 yrs (n = 833)	900	79.3 (73.5-85.2)	84.0 (81.2-86.8)	58.4 (53.7-63.0)	93.5 (91.5-95.0)	4.95 (4.00-5.90)	0.25 (0.18-0.32)
>75 yrs (n = 166)	1,800	75.9 (64.8-86.9)	75.0 (66.8-83.2)	62.0 (53.3-70.0)	85.3 (78.4-90.2)	3.03 (1.94-4.13)	0.32 (0.17-0.47)
Rule-in, overall (n = 1,461)		79.4 (74.7-84.2)	86.7 (84.8-88.7)	58.4 (54.5-62.1)	94.7 (93.5-95.8)	5.99 (5.05-6.93)	0.24 (0.18-0.29)
Exclusionary ("rule-out") cutpoint							
All patients (n = 1,461)	300	93.9 (91.0-96.7)	71.7 (69.1-74.3)	43.7 (41.4-46.1)	98.0 (96.9-98.8)	3.32 (3.00-3.63)	0.09 (0.05-0.13)

The sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios are presented as % (95% confidence interval) for the age-dependent rule-in cutoffs of 450, 900, and 1,800 pg/ml for ages <50, 50-75, >75 years, and for the rule-out cutoff of 300 pg/ml, in all enrolled subjects.

HF = heart failure; LR+ = positive likelihood ratio; LR− = negative likelihood ratio; NPV = negative predictive value; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PPV = positive predictive value.

NT-proBNP, we saw generally similar effects of comorbidities to those previously reported, with the expected effect of reduced/preserved ejection fraction, abnormal renal function (16), obesity (17), and atrial fibrillation (18). Similar results were seen in subgroup analyses assessing the AUC of the FDA-approved NT-proBNP cutpoints (125 and 450 pg/ml), as demonstrated in Online Table 4.

DISCUSSION

Although widely used in U.S. clinical practice, the age-stratified NT-proBNP rule-in cutpoint strategy for diagnosis of acute HF and age-independent rule-out cutpoint to exclude acute HF have not been prospectively validated in a North American cohort. Our results provide contemporary information about NT-proBNP cutpoints to aid in the diagnosis and exclusion of acute HF in a cohort of all-comer patients with acute dyspnea presenting to EDs. Our study represents a diverse range of patient groups, with approximately 50% women and more than 40% nonwhite patients. Results of the study indicate excellent performance of NT-proBNP to identify or exclude acute HF, and support the utility of the widely-used age-stratified diagnostic approach for its use, while also verifying high NPV of 300 pg/ml to exclude acute HF.

Notably, the overall age of the patients diagnosed with acute HF was relatively young in comparison to other cohorts (2). The characteristics of participants in this study are consistent with data suggesting that the demographics of ED patients with acute HF, as well as those of patients with measurable NT-proBNP, have changed compared with the last major evaluation 12 years ago (6,7). It is also noteworthy that the prevalence of acute HF in this study of all-comers with acute dyspnea (n = 277; 19%) was considerably

TABLE 3 Comparison of ROC Curves for NT-proBNP-Based Diagnosis of Acute HF Across Patient Subgroups

	Sensitivity	Specificity	PPV	NPV	AUC	p Value for Difference in AUC
Patients with eGFR <60.0 ml/min/1.73 m^2	89.3 (84.0–94.6)	68.3 (61.6–75.0)	66.5 (61.4–71.2)	97.3 (90.1–99.3)	0.872	0.12
Patients with eGFR ≥60.0 ml/min/1.73 m^2	70.3 (62.7–77.9)	89.6 (87.6–91.7)	51.9 (46.3–57.4)	98.1 (96.8–98.8)	0.907	
Patients with body mass index <30.0 kg/m^2	90.3 (84.8–95.7)	85.0 (81.9–88.0)	56.4 (51.1–61.5)	100.0 (–)	0.946	0.001
Patients with body mass index ≥30.0 kg/m^2	72.1 (65.0–79.2)	87.0 (84.2–89.8)	60.7 (54.9–66.1)	96.2 (94.1–97.6)	0.896	
Male	80.5 (74.5–86.4)	84.8 (81.9–87.8)	61.0 (56.0–65.8)	97.5 (95.5–98.6)	0.908	0.44
Female	77.8 (69.9–85.6)	88.5 (86.0–91.1)	54.5 (48.5–60.5)	98.5 (97.0–99.3)	0.922	
Black	82.4 (73.8–91.1)	90.4 (87.7–93.2)	58.7 (51.2–65.8)	98.7 (97.0–99.4)	0.933	0.16
Nonblack	78.7 (73.0–84.4)	84.5 (81.9–87.2)	58.5 (53.9–62.9)	97.9 (96.2–98.8)	0.908	
Presence of atrial fibrillation	87.2 (80.5–94.0)	56.6 (47.8–65.4)	60.7 (55.5–65.8)	100.0 (–)	0.807	<0.001
Absence of atrial fibrillation	75.6 (69.3–81.8)	90.4 (88.6–92.1)	57.1 (52.1–62.0)	98.0 (96.8–98.7)	0.918	
Patients with HFrEF	90.8 (85.1–96.5)	38.6 (24.2–53.0)	76.7 (72.1–80.8)	75.0 (38.7–93.5)	0.646	0.11
Patients with HFpEF	72.6 (61.5–83.7)	68.6 (58.8–78.4)	62.5 (54.1–70.2)	80.4 (68.2–88.7)	0.758	

Values are % (95% confidence interval). Performed with the Elecsys proBNP II Assay in all enrolled subjects. Sensitivity, specificity, and PPV refer to results for age-adjusted triple cutoff, whereas NPV refers to results for the age-independent rule-out cutoff of 300 pg/ml.

AUC = area under the curve; eGFR = estimated glomerular filtration rate; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; ROC = receiver-operating characteristic; other abbreviations as in Table 2.

lower than projected (vs. 50%); in comparison, a recent report from Singapore and New Zealand confirms reduced prevalence of HF in dyspneic patients (36% and 24%, respectively) (19). This may suggest use of the ED by patients with acute HF may be declining, despite a rise in overall prevalence of the diagnosis. These trends may be caused by the increasing use of programs aimed at reducing ED HF visits, HF hospitalization, and HF rehospitalization (20). Despite differences in demographics compared with older studies and lower prevalence, NT-proBNP had excellent sensitivity, specificity, and area under the ROC for diagnosis of acute HF, and the age-adjusted cutoff had an OR >10 for the diagnosis of HF, substantially stronger than traditional variables from history, physical examination, or other forms of laboratory testing. Importantly, we noted lower than expected PPV, which is explainable by the lower prevalence of acute HF in this population; given the lower-than-expected prevalence of acute HF (which affects the stability of the statistical predictive value), using LR+ and LR− may be a better approach for assessing the performance of the test than PPV and NPV.

TABLE 4 Comparisons of Area Under the ROC Curve Along With LR+ and LR− for BNP or NT-proBNP Assays to Diagnose or Exclude Acute HF in Various Large Trials of Acute Dyspnea

First Author/Study, Year (Ref. #)	Biomarker	N	AUC	Overall LR+ for "Rule In"	Overall LR− for "Rule Out"
Maisel et al., 2002 (4)	BNP	1,586	0.91	2.60	0.05
Januzzi et al., 2005 (2)	NT-proBNP	600	0.94	4.27	0.11
Maisel et al., 2010 (27)	NT-proBNP	1,641	0.91	2.51	0.07
ICON-RELOADED	NT-proBNP	1,461	0.91	5.99	0.09

BNP = B-type natriuretic peptide; NT-proBNP = N-terminal pro-B-type natriuretic peptide; other abbreviations as in Tables 2 and 3.

Taken in context, the performance of NT-proBNP in ICON-RELOADED compares favorably with other large, pivotal trials of BNP and NT-proBNP testing (Table 4). In this regard, compared with the first ICON study, we found slightly higher overall LR+ (5.99 vs. 4.27) and slightly lower overall LR− (0.09 vs. 0.11). In the balance, the LR results in the present study confirm that elevated age-stratified cutoff results may be used as an aid in the diagnosis of acute HF, whereas an NT-proBNP concentration <300 pg/ml provides a substantial ability to exclude the presence of acute HF. Despite not being on the package insert, the age-stratified approach has been incorporated in clinical practice guidelines (5) and textbooks, and is used globally at present. The FDA-approved cutoffs are for outpatient application, in particular, for excluding the presence of chronic HF on the basis of their high NPV. In contrast, among a more acutely dyspneic population, where natriuretic peptide assays are more widely used, these cutoffs deliver reasonable NPV, but their PPV is undermined by the lack of specificity. Clinicians should consider the venue in which they are using NT-proBNP, and select cutoffs accordingly. Having consistency in FDA-approved cutoffs, as well as clinical practice guidelines, would ease the confusion surrounding the different cutoffs.

Analysis of pre-specified subgroups with demographics or comorbidities that could potentially

confound the performance of NT-proBNP demonstrated that the diagnostic and exclusionary performance of the test remained accurate in these patient subgroups, with consistent effects of sex and race (15), abnormal renal function (16), obesity (17), and atrial fibrillation (18) on sensitivity or specificity of NT-proBNP.

Early and accurate diagnosis of patients with acute dyspnea in the ED is essential, as delayed treatment for acute HF is associated with increased mortality (21). Studies from PRIDE (22,23), the Canadian-based IMPROVE-CHF (Improved Management of Patients with Congestive Heart Failure) study (24), the ADHERE (Acute Decompensated Heart Failure National Registry) analysis (25), and others (21) suggest that prompt, accurate diagnosis reduces indecision, potentially improves outcomes, and leads to a reduction in health care expenditures. Validation of the ICON diagnostic cutoffs in an all-comers, contemporary cohort may thus aid in enhancing diagnosis of acute HF in the ED.

STUDY LIMITATIONS. The clearest limitation of the study is that fewer than expected patients with acute HF were enrolled, which is reflected in the lower PPV result, as PPV is largely dependent on the prevalence of the disease. For example, the same assay tested here would have a PPV of 80% to 90% if the prevalence of acute HF was 50%. As a matter of fact, the PPV noted in this study was exactly as projected based on the lower prevalence of acute HF (Online Figure 1). In this regard, the use of LR+ to express the performance of a test is arguably a more reliable approach when comparing tests from 2 different studies with different disease prevalence, and the results confirm the expected performance of the age-adjusted cutoff approach studied in this analysis. Similarly, in the BNP (Breathing Not Properly) multinational study (4), which had a higher prevalence of patients with HF (47%), the PPV was indeed higher (71% to 83%, depending upon the BNP level), but the LR+ was lower (3.4) when evaluating BNP ≥100 pg/ml (26). As with BNP, certain clinical factors, such as impaired renal function, can increase NT-proBNP levels in the absence of HF and deliver a lower specificity as well as PPV. However, age stratification largely addresses the effects of renal function (16). As seen in the AUC curve, using a higher NT-proBNP cutpoint would result in better specificity and better PPV, as was the case of BNP in the Breathing Not Properly Study (4). Lower prevalence of acute HF in this study likely reflects the evolution in practices surrounding ED use for HF over the last decade, in favor of urgent care and office-based practice. It is important to note that despite the lower prevalence of acute HF in the study cohort, the performance of the cutoffs for exclusion of acute HF was great. Lastly, because this study was conducted in the United States and Canada, the generalizability of the findings outside of this geographic region may be limited.

CONCLUSIONS

The ICON-RELOADED study demonstrates that the NT-proBNP cutoffs proposed in the first ICON study perform consistently in a current, multicenter cohort of all-comer patients. As in all prior studies of BNP or NT-proBNP, our results confirm that elevated NT-proBNP may aid in identification of acute HF, whereas an NT-proBNP <300 pg/ml provides a strong ability to exclude acute HF. Despite changes in prevalence, demographics, comorbidities, and management of patients with HF nearly 15 years after NT-proBNP was first developed as a biomarker test, the utility of the assay for both the diagnosis and exclusion of acute HF in the ED setting endures.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: For patients presenting to the ED with acute dyspnea categorized by age <50, 50 to 75, and ≥75 years, accurate diagnosis of HF may be based on ICON NT-proBNP cutoff levels of 450, 900, and 1,800 pg/ml, respectively, and acute HF is largely excluded when the level is below 300 pg/ml.

TRANSLATIONAL OUTLOOK: Future studies should assess the generalizability of these thresholds in patients evaluated in other care settings and with manifestations of HF other than dyspnea.

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APPENDIX For supplemental tables and a figure, please see the online version of this paper.