

# Left Ventricular Ejection Fraction and Clinically Defined Heart Failure to Predict 90-Day Functional Outcome After Ischemic Stroke

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*Background:* Heart failure (HF) is a risk factor for atrial fibrillation (AF), stroke, and post-stroke disability. However, differing definitions and application of HF-criteria may impact model prediction. We compared the predictive ability of left ventricular ejection fraction (LVEF), a readily available objective echocardiographic index, with clinical HF definitions for functional disability and AF in stroke patients. *Methods:* We retrospectively analyzed ischemic stroke patients evaluated between January 2013 and May 2015. Outcomes of interest were: (a) 90-day functional disability (modified Rankin score 3-6) and (b) AF. We compared: (1) LVEF (continuous variable), (2) left ventricular systolic dysfunction (LVSD)-categories (absent to severe), (3) clinical history of HF, and (4) HF/LVSD-categories: (i) HF absent without LVSD, (ii) HF absent with LVSD, (iii) HF with preserved ejection fraction (HFpEF), and (iv) HF with reduced ejection fraction (HFrEF). Multivariable logistic regression was used to determine the predictive ability for 90-day disability and AF, respectively. *Results:* Six hundred eighty five consecutive patients (44.5% female) fulfilled the study criteria and were included. After adjustment, the LVEF was independently associated with 90-day disability (OR .98, 95% CI .96-.99,  $P = .011$ ) with similar predictive ability (area under the curve [AUC] = .85) to models including the LVSD-categories (AUC = .85), clinically define HF (AUC = .86), and HF/LVSD-categories (AUC = .86). The LVEF, HF, LVSD-, and HF/LVSD-categories were independently associated with AF ( $P < .01$ , each) with similar predictive ability (AUC = .74, .74, .73, and .75, respectively). *Conclusions:* Compared to commonly defined HF definitions, the objectively

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Received August 3, 2018; revision received October 1, 2018; accepted October 6, 2018.

Sources of funding: Dr. Henninger is supported by [K08NS091499](#) from the National Institute of Neurological Disorders and Stroke of the National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Dr. McManus is supported through [R01HL126911-01A1](#) and NSF award #1522052.

Author contributions: Y.L. and T.P.F. acquired the data. Y.L., T.P.F., and N.H. were involved in the study design. Y.L. and N.H. conducted statistical analyses and drafted the article. Y.L., T.P.F., D.D.M., and N.H. were involved in data interpretation. All authors commented on the manuscript for important intellectual content.

Competing interests: Dr. Henninger serves on the advisory board of Omnix, Inc. Dr. McManus has received consultation or research funding from Samsung Electronics, Philips Healthcare, FlexCon, Biotronik, Bristol Myers Squibb, Pfizer, Care Evolution; Inventor/Equity Stake: Mobile-Sense Technologies, LLC ([NIH SBIR R43 HL135961](#)). Dr. Silver has received funding from his service as surveyor for the Joint Commission, adjudicating stroke outcomes for the Women's Health Initiative, study section reviewer for the NIH, medicolegal malpractice reviews, and he received honoraria for chapters in Ebix, Medlink, and Medscape. All other authors declare no competing interests.

Ethical approval: Our investigation was approved by our Institutional Review Board, and we were granted a Health Insurance Portability and Accountability Act waiver of informed consent.

Data sharing: The investigators will share anonymized data (with associated coding library) used in developing the results presented in this manuscript upon reasonable request to investigators who have received ethical clearance from their host institution.

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1052-3057/\$ - see front matter

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<https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.10.002>

determined LVEF possesses comparable predictive ability for 90-day disability and AF in stroke patients.

**Key Words:** Atrial fibrillation—cardioembolism—disability—heart failure—HFpEF—HFrfEF—outcome—TOAST

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## Introduction

Heart failure (HF) is a recognized risk factor for near and long-term risk of stroke that may be useful to predict post stroke functional disability, death, and atrial fibrillation given the shared underlying risk factors.<sup>1-5</sup> However, the definition and physician application of HF criteria have been shown to vary substantially.<sup>6-8</sup> For example, the functional classification based on the widely-used New York Heart Association (NYHA) definition relies on subjective and self-reported criteria. Although this classification has been validated,<sup>9</sup> it has nevertheless been shown to suffer suboptimal reproducibility and lack of sensitivity.<sup>10,11</sup> This increases the risk for bias, particularly in studies that rely on medical record review or when information is difficult to extract such as in subjects with aphasia or cognitive impairment.

Accordingly, it may be advantageous to define the severity of HF based on objective indices such as the echocardiographically defined left ventricular ejection fraction (LVEF) when investigating the association of HF and stroke. Indeed, the severity of left ventricular systolic dysfunction (LVSD), as determined by a reduced LVEF, has been found to inversely correlate with the 3-month functional outcome after stroke.<sup>2</sup> Furthermore, several lines of data suggest that a reduced LVEF represents the greatest stroke risk factor when multiple definitions of HF are used.<sup>8</sup> This is an important observation because an increasing proportion of HF patients are diagnosed with HF and preserved left ventricular ejection fraction (HFpEF).<sup>12</sup> Yet, there is a striking paucity of contemporary studies that systematically explored the potential relation of different HF definitions with post-stroke disability.<sup>2,4,13,14</sup> Understanding this issue is important because there is increasing interest to use established stroke scales that incorporate HF (such as the CHA<sub>2</sub>DS<sub>2</sub>-VASc score) to stratify stroke risk and outcome as well as AF.<sup>15-18</sup>

To elucidate this issue, we sought to determine whether the use of different HF definitions impact outcome prediction and AF in ischemic stroke. Given the complexity of defining HF based on clinical grounds we used the echocardiographically defined LVEF both as continuous variable as well as stratified according to LVSD-category. We hypothesized that the LVEF may serve as objective HF-index to predict the 90-day functional outcome as well as AF among patients with ischemic stroke as compared to commonly used clinical HF definitions.

## Materials and Methods

### *Study Cohort*

We retrospectively analyzed 685 patients with acute ischemic stroke that were consecutively included in the University of Massachusetts Memorial Medical Center Stroke registry between January 2013 and May 2015.

Our investigation was approved by our Institutional Review Board (#H00006964) and Health Insurance Portability and Accountability Act waiver of informed consent granted. We adhere to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines ([www.strobe-statement.org](http://www.strobe-statement.org)).

### *Clinical Characteristics, Stroke Etiology, and Stroke Severity*

At baseline, all study participants underwent a standardized clinical history, physical examination, head CT or 1.5 T brain MRI (typically obtained within 24-48 hours after the symptoms onset) per institutional protocol. Patient demographics, laboratory data, co-morbidities, and pre-admission medications were abstracted from the medical record by trained physician abstractors. Members of the stroke team certified in NIHSS scoring graded the severity of stroke at presentation. The stroke etiology was determined based on the Trial of ORG-10172 in Acute Stroke Treatment (TOAST) classification after completion of the stroke workup.<sup>19</sup> In addition, we defined embolic stroke of undetermined source (ESUS) according to the criteria proposed by the Cryptogenic Stroke/ESUS International Working Group as a visualized non-lacunar brain infarct in the absence of the following: (1) extracranial or intracranial atherosclerosis causing  $\geq 50\%$  luminal stenosis in arteries supplying the area of ischemia, (2) major-risk cardioembolic source, and (3) any other specific cause of stroke (eg, arterial dissection).<sup>20</sup> We trichotomized the stroke cause according to the presumed mechanism to cardioembolic stroke (CES), non-embolic stroke (non-ES; ie, large vessel disease, small vessel disease, and other determined etiology), and ESUS for statistical purposes.

### *Risk Factor Definitions*

We determined the presence of hypertension (use of antihypertensive medications, or systolic blood pressure of  $\geq 140$  mm Hg or diastolic blood pressure of  $\geq 90$  mm Hg on 2 separate occasions), hypercholesterolemia (use of

lipid-lowering agents, or fasting blood total cholesterol level of  $\geq 200$  mg/dL, or low density lipoprotein cholesterol [LDLc] of  $\geq 130$  mg/dL, and diabetes mellitus (history of fasting glucose  $\geq 126$  mg/dL or current use of hypoglycemic drugs) as defined according to the National Diabetes Data Group and World Health Organization.<sup>21</sup>

#### *Clinically Defined Heart Failure and Left Ventricular Dysfunction*

All patients underwent cardiac workup including a transthoracic echocardiogram (TTE) or transesophageal echocardiogram (TEE) with evaluation of the LVEF. For the purpose of this study we used the following definitions of heart failure.

First, we clinically defined HF based on the patients' subjective report or as documented in the incident admission records as well as primary care physician and cardiologist notes ("clinical HF"). Of note, the NYHA classification was not used because the required information to define the specific categories was not reliably available in the medical records.

Second, we determined the LVEF from 2D images using Simpson's biplane method of discs as previously described<sup>22</sup> and as adjudicated by a board-certified cardiologist (TPF) masked to clinical data and study outcomes to avoid biased interpretation. In addition to using the LVEF as continuous variable ("LVEF") in analyses, we also stratified patients according to the degree of LVSD ("LVSD categories") to (i) absent (LVEF of 53%-73%), (ii) mild LVSD (LVEF of 41%-52%), (iii) moderate (LVEF of 30%-40%), or (iv) severe LVSD (LVEF  $< 30\%$ ).<sup>2,22,23</sup>

Third, we stratified subjects based on the presence of clinical HF (absent versus present) and LVSD (ie, presence versus absence of a reduced LVEF of  $< 53\%$ ) to the following "HF/EF" categories: (i) clinical HF absent without LVSD, (ii) clinical HF absent with LVSD, (iii) clinical HF present with LVSD (ie, HF with preserved ejection fraction; HFpEF), and (iv) clinical HF present with LVSD (ie, HF with reduced ejection fraction; HFrEF).<sup>6,24</sup>

#### *Atrial Fibrillation*

All participants were screened for incident AF with 12-lead electrocardiogram (ECG) at presentation and 24-hour in-patient cardiac telemetry with automated arrhythmia detection per institutional protocol. Additional long-term rhythm monitoring was done at the treating physician's discretion. AF was defined according to the American Heart Association Atrial Fibrillation Management Guidelines.<sup>25</sup> Patients with AF in the setting of rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve repair (valvular AF) were included in this study.<sup>25,26</sup> Given our study design it was not possible to reliably determine the AF duration and AF burden. Thus, for the purposes of our analyses, we considered AF present if AF

of any duration was documented in the admission history, or if present on an admission 12-lead ECG. In addition, abstractors reviewed all clinical notes, 30-day non-invasive monitor reports, implantable device reports (including pacemaker and implantable loop recorders), as well as all 12-lead ECGs obtained for any reason for newly diagnosed AF of any duration during hospitalization and within 90 days of index hospital discharge.

The CHA<sub>2</sub>DS<sub>2</sub>-VASc score (range 0 to 9) was calculated based on data available in the medical record (HF, hypertension, age  $\geq 75$  years (doubled), diabetes mellitus, prior stroke/TIA (doubled), vascular disease, age 65-74 years, sex category [female]). The qualifying stroke/TIA was counted towards the CHA<sub>2</sub>DS<sub>2</sub>-VASc-score; hence the minimal possible score in our cohort was 2.

#### *Functional Outcome*

The modified Rankin Scale (mRS) score was assessed at discharge and 90 days after admission by a stroke-trained physician or stroke study nurse certified in mRS via in-person or telephone interview. When the mRS was unavailable, the same observers reconstructed the score from the case description according to the mRS criteria. The 90-day outcome was dichotomized to good (mRS score 0-2; disability free) versus poor (mRS score 3-6; disabled or dead).

#### *Statistics*

Unless otherwise stated, continuous variables are reported as mean  $\pm$ SD or median (25th-75th percentile). Categorical variables are reported as proportions. Between-group comparisons for continuous and ordinal variables were made with Mann-Whitney U test and Kruskal-Wallis one-way ANOVA on ranks with post hoc Dunn's test as appropriate. Categorical variables were compared using the  $\chi^2$ -test. Bonferroni method was used to correct for multiple comparisons.

We created separate multivariable logistic regression models to determine whether (i) clinical HF, (ii) HF/EF, (iii) LVEF, and (iv) LVSD-categories predicted 90-day disability (dependent variable, primary analyses). Models were adjusted for the stroke severity (as assessed by the admission NIHSS), treatment with recombinant tissue-type plasminogen activator (rtPA), and the trichotomized stroke cause. In addition, we adjusted all models for risk factors included in the CHA<sub>2</sub>DS<sub>2</sub>-VASc risk score, which is increasingly used to predict stroke and atrial fibrillation risk as well as post-stroke outcome.<sup>3,15,17</sup> For secondary analyses we created separate multivariable logistic regression models to determine whether the (i) clinical HF, (ii) HF/EF, (iii) LVEF, and (iv) LVSD-categories predicted the presence of AF (dependent variable). These models were adjusted for risk factors included in the CHA<sub>2</sub>DS<sub>2</sub>-VASc risk score.

To obtain better comparability of odds ratio (OR) strengths with other studies based on the CHA<sub>2</sub>DS<sub>2</sub>-VASc we transformed metric measures into the same categorical variables according to CHA<sub>2</sub>DS<sub>2</sub>-VASc score determination. To avoid model overfitting, variables were sequentially removed (likelihood ratio) from the models at a significance level of .1. Collinearity diagnostics were performed (and its presence rejected) for all multivariable regression models. The Hosmer-Lemeshow goodness-of-fit statistic was used to assess model fit. To determine the diagnostic accuracy of the different HF definitions for functional outcome and AF, we calculated the area under receiver-operator curves (AUC; c-statistics) with corresponding 95% CIs. Two-sided significance tests were used throughout and unless stated otherwise a two-sided  $P < .05$  was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics Version 22 (IBM-Armonk, NY).

## Results

### Study Cohort

Over the study period a total of 827 adult ischemic stroke patients were evaluated by our stroke team. After

independent chart review we excluded 24 (.3%) patients as they had no imaging confirmed stroke or because they represented duplicate entries. One hundred eighteen (14.2%) subjects had no TTE or TEE available for review, leaving 685 patients for analysis (Fig 1). Data was complete for all variables except for the 90-day mRS because 69 (10.1%) subjects were lost to follow up. For these subjects, we imputed the 90-day mRS by carrying forward the discharge mRS.

Compared to included patients, excluded patients were older ( $P = .001$ ), had a higher admission NIHSS ( $P = .002$ ), and had more often goals of care shifted to comfort measures only (CMO;  $P < .001$ ). However, there was no difference in sex ( $P = .27$ ) and history of HF ( $P = .53$ ).

Overall, 240 (35.0%) of the studied patients had a poor 90-day functional outcome. On average, these patients were older (76 versus 67 years,  $P < .001$ ), more frequently female (54.6% versus 39.1%,  $P < .001$ ), had worse neurological deficits at admission (NIHSS 13 versus 3,  $P < .001$ ), and had more vascular risk factors, when compared to patients with a good functional outcome (Table 1). The stroke mechanism was CES in 151 (22.0%), ESUS in 128 (18.7%), and non-ES in 406 (59.3%) patients. Non-ES causes related to large artery atherosclerosis in 175

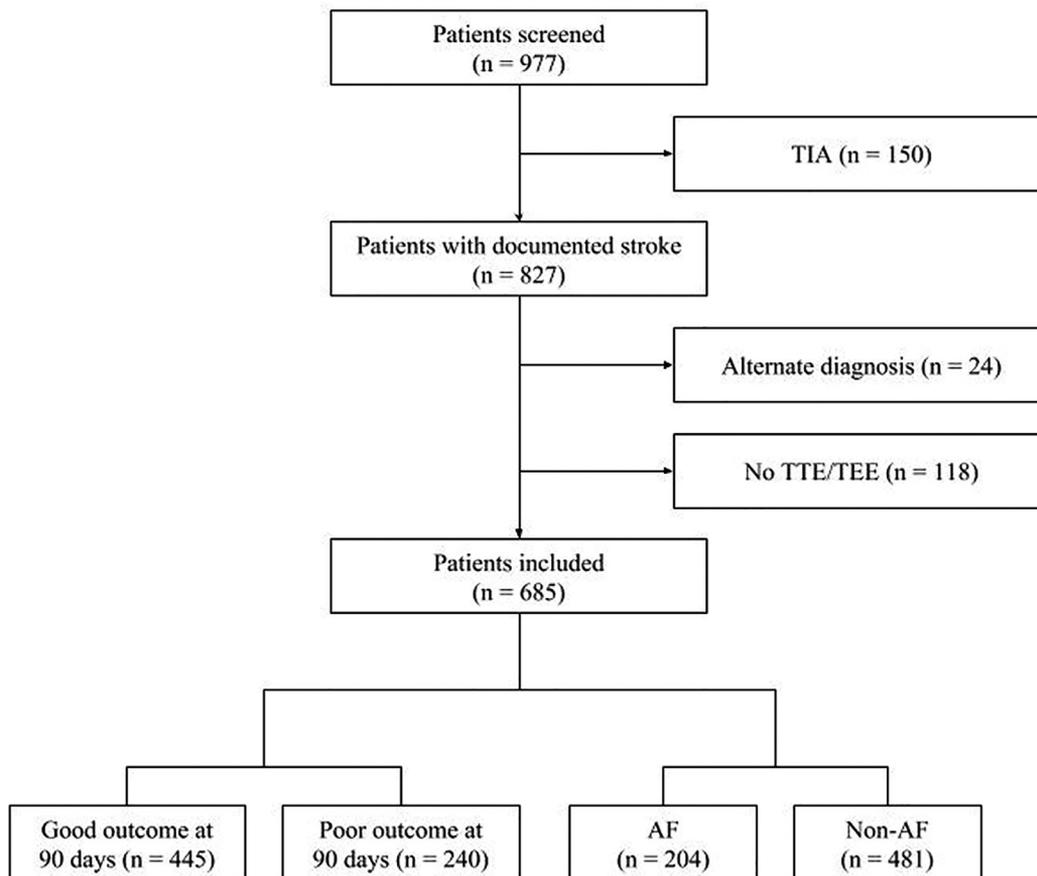


Figure 1. Flow chart.

**Table 1.** Baseline characteristics (unadjusted) of the studied patient population as stratified by the 90-day outcome

Characteristics	All patients	Good outcome	Poor outcome	P-value
	(n = 685)	(n = 445)	(n = 240)	
Age, years	70 (60-80)	67(59-78)	76 (63-86)	<.001
Female sex	305 (44.5)	174 (39.1)	131 (54.6)	<.001
Admission NIHSS	5 (2-12)	3 (1-7)	13 (6-19)	<.001
<i>Stroke mechanism</i>				<.001
Non-embolic*	406 (59.3)	273 (61.3)	133 (55.4)	
Cardioembolic	151 (22.0)	75 (16.9)	76 (31.7)	
ESUS	128 (18.7)	97 (21.8)	31 (12.9)	
<i>Preexisting risk factors</i>				
Hypertension	535 (78.1)	334 (75.1)	201 (83.8)	.009
Diabetes	195 (28.5)	113 (25.4)	82 (34.2)	.017
Prior stroke or TIA	161 (23.5)	92 (20.7)	69 (28.8)	.018
Peripheral artery disease	199 (29.1)	117 (26.3)	82 (34.2)	.034
Hyperlipidemia	378 (55.2)	246 (55.3)	132 (55.0)	1.000
Atrial fibrillation	204 (29.8)	108 (24.3)	96 (40.0)	<.001
CHA <sub>2</sub> DS <sub>2</sub> -VASc score	5 (4-6)	4 (3-5.5)	6 (4-6)	<.001
Left ventricular ejection fraction (LVEF), %	65 (65-65)	62 (65-65)	60 (65-65)	.004
Clinical HF	80 (11.7%)	35 (7.9)	45 (18.8)	<.001
<i>LVSD-categories**</i>				.023
Absent LVSD (LVEF >52)	599 (87.4)	401 (90.1)	198 (82.5)	
Mild LVSD (LVEF 41-52)	31 (4.5)	18 (4.0)	13 (5.4)	
Moderate LVSD (LVEF 30-40)	34 (5.0)	15 (3.4)	19 (7.9)	
Severe LVSD (LVEF <30)	21 (3.1)	11 (2.5)	10 (4.2)	
<i>HF/EF-categories**</i>				<.001
Clinical HF absent without LVSD	553 (80.7)	382 (85.8)	171 (71.3)	
Clinical HF absent with LVSD	52 (7.6)	28 (6.3)	24 (10.0)	
Clinical HF present with preserved LVEF	46 (6.7)	19 (4.3)	27 (11.3)	
Clinical HF present with reduced LVEF	34 (5.0)	16 (3.6)	18 (7.5)	
<i>Preadmission medications</i>				
Statin	326 (47.6)	210 (47.2)	116 (48.3)	.810
Antihypertensive	476 (69.5)	290 (65.2)	186 (77.5)	.001
Antiglycemic	140 (20.4)	83 (18.7)	57 (23.8)	.136
Antiplatelets	359 (52.4)	216 (48.5)	143 (59.6)	.006
Oral anticoagulants	65 (9.5)	33 (7.4)	32 (13.3)	.014
Thrombolysis with rtPA	141 (20.6)	85 (19.1)	56 (23.3)	.199

Data are n (%) or median (25th-75th quartile), ESUS = embolic stroke of undetermined source, TIA = transient ischemic attack, NIHSS = National Institutes of Health Stroke Scale, rtPA = recombinant tissue-type plasminogen activator.

\*Includes large artery atherosclerosis, small vessel disease, other determined, and undetermined [not ESUS].

\*\*LVEF of <53% denoted a reduced LVEF and the presence of LVSD.

(25.5%), small vessel disease in 85 (12.4%), multiple coexisting causes in 96 (14.0%), and other determined causes in 50 (7.3%) subjects.

With respect to cardiac workup for AF, 98.7% patients in the entire cohort underwent ECG at admission in addition to routine 24-hour in-patient cardiac telemetry. Two hundred thirty four (34.2%) patients underwent 30-day event monitoring, and 52 (7.6%) patients had implantable loop recorder or ICD data available for review. Among ESUS patients, 98.4% had an admission ECG, 10.2% underwent TEE in addition to TTE, and 76.6% underwent long-term rhythm monitoring.

Based on the used HF definitions, 80 (11.7%) subjects were diagnosed with clinical HF, 86 (12.6%) had LVSD,

and 132 (19.3%) were deemed to have either HFpEF ( $n = 46$ ), HFrEF ( $n = 34$ ), or absent HF with reduced LVEF ( $n = 52$ ) (Table 1). The association of clinical variables with the HF/EF categories and LVSD categories is summarized in Table 2 and Supplemental Table 1, respectively. Notably, while HFpEF subjects had a (by definition) significantly lower LVEF than subjects with HFrEF ( $P < .05$ ), there was no significant difference between these categories for any other clinical variable as well as the 90-day functional outcome after adjustment for multiple comparisons ( $P > .05$ , each).

One hundred fifty one (22%) patients had a known history of AF and an additional 53 (7.7%) were newly diagnosed with AF either during admission ( $n = 23$  [3.4%]) or

**Table 2.** Baseline characteristics of the studied patient population as stratified by HF/EF categories

Characteristics	Absent clinical HF without LVSD (n = 553)	Absent clinical HF with LVSD (n = 52)	Clinical HF with preserved LVEF (HFpEF) (n = 46)	Clinical HF with reduced LVEF (HFrEF) (n = 34)	P value
Age, years	68 (59-79)	73 (65-82)	80 (71-86)	75 (64-88)	<.001
Female sex	251 (45.4)	18 (34.6)	26 (56.5)	10 (29.4)	.045
Admission NIHSS	5 (2-11)	5 (2-13)	9 (3-21)	6 (3-12)	.034
Thrombolysis with rtPA	107 (19.3)	7 (13.5)	15 (32.6)	12 (35.3)	.016
Good 90-day outcome	382 (69.1)	28 (53.2)	19 (41.3)	16 (47.1)	<.001
<i>Stroke mechanism</i>					
Non-embolic*	350 (63.3)	22 (42.3)	21 (45.7)	13 (38.2)	<.001
Cardioembolic	98 (17.7)	20 (38.5)	20 (43.5)	13 (38.2)	
ESUS	105 (19.0)	10 (19.2)	5 (10.9)	8 (23.5)	
<i>Preexisting risk factors</i>					
Hypertension	419 (75.8)	44 (84.6)	42 (91.3)	30 (88.2)	.019
Diabetes	150 (27.1)	19 (36.5)	12 (26.1)	14 (41.2)	.170
Prior stroke or TIA	124 (22.4)	13 (25.0)	11 (23.9)	13 (38.2)	.217
Peripheral artery disease	115 (20.8)	25 (48.1)	31 (67.4)	28 (82.4)	<.001
Hyperlipidemia	292 (52.8)	31 (59.6)	30 (65.2)	25 (73.5)	.042
Atrial fibrillation	138 (25.0)	22 (42.3)	27 (58.7)	17 (50.0)	<.001
CHA <sub>2</sub> DS <sub>2</sub> -VASc score	5 (3-6)	6 (5-7)	6 (5-6)	6 (5-7)	<.001
LVEF, %	65 (65-65)	40 (35-45)	65 (65-65)	30 (25-41)	<.001
<i>Preadmission medications</i>					
Statin	244 (44.1)	29 (55.8)	31 (67.4)	22 (64.7)	.002
Antihypertensive	369 (66.7)	34 (65.4)	42 (91.3)	31 (91.2)	<.001
Antiglycemic	113 (20.4)	9 (17.3)	10 (21.7)	8 (23.5)	.891
Antiplatelets	279 (50.5)	26 (50.0)	27 (58.7)	27 (79.4)	.007
Oral anticoagulants	38 (6.9)	9 (17.3)	12 (26.1)	6 (17.6)	<.001

Data are *n* (%) or median (25th-75th quartile), ESUS = embolic stroke of undetermined source, HF = heart failure, LVEF = left ventricular ejection fraction, LVSD = left ventricular dysfunction, TIA = transient ischemic attack, NIHSS = National Institutes of Health Stroke Scale, rtPA = recombinant tissue-type plasminogen activator.

\*Includes large artery atherosclerosis, small vessel disease, other determined, and undetermined [not ESUS]).

during the 90 days of follow up (*n* = 30 [4.4%]). On average, patients with a poor outcome more frequently had AF than patients with a good outcome (40% versus 24.3%, *P* < .001). Among patients without a known history of AF, there was no significant difference in the proportion of newly diagnosed AF between patients with a good (39/376 [10.7%]) versus poor outcome (14/158 [8.9%]; *P* = .638).

#### Association of HF With the 90-Day Functional Outcome

In unadjusted analysis, clinical HF, HF/EF, LVEF, and LVSD-categories were associated with poor stroke 90-day outcome, respectively (*P* < .05 each, Tables 1–3 and Supplemental Table 1). After adjustment, for variables included in the CHA<sub>2</sub>DS<sub>2</sub>-VASc, AF, stroke mechanism, and stroke severity all HF definitions were independently associated with a poor 90-day outcome (Table 3). Examination of the *c*-statistics (AUC) indicated that there was no significant difference in the predictive ability of the models using the different HF definitions for the 90-day functional outcome (Fig 2A).

#### Association of HF With AF

Patients with AF had a significantly lower LVEF than subjects without AF (59.5 ± 12.0 versus 62.1 ± 9.0, *P* = .002). In unadjusted analyses, AF was significantly more common among subjects with clinical HF than those without HF (55.0% versus 26.4%, *P* < .001). AF was significantly less common in subjects without LVSD as compared to patients with LVSD (*P* = .009, Supplemental Table 1) without significant difference between mild, moderate, and severe LVSD after adjustment for multiple comparisons (*P* > .05, each). Lastly, AF was significantly less common in subjects with no HF and without LVSD as compared to all other HF/EF categories (*P* < .001, Table 2) without difference between absent HF with LVSD, HFpEF, and HFrEF after adjustment for multiple comparisons (*P* > .05, each).

The respective associations of clinical HF, HF/EF, LVEF, and LVSD-categories with AF remained after adjustment for pertinent covariates (*P* < .05 each; Table 4). Examination of the *c*-statistics (AUC) indicated that there was no significant difference in the predictive ability

**Table 3.** Multivariable logistic regression analysis for factors independently associated with a poor 90-day outcome

Independent variable	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Cardioembolic stroke cause	Reference		Reference	
Non-embolic stroke cause	.48 (.33-.70)	<.001	0.76 (0.4.6-1.26)	.290
ESUS	.32 (.19-.53)	<.001	0.41 (0.21-0.80)	.008
LVEF*	.98 (.96-.99)	.004	0.98 (0.96-0.99)	.011
Hypertension	1.713 (1.143-2.567)	.009	—	—
Age ≤64 years	Reference		Reference	
Age 65-74 years	.88 (1.04-1.60)	.876	.90 (.53-1.55)	.709
Age ≥75 years	2.63 (1.82-3.81)	<.001	2.11 (1.30-3.44)	.003
Diabetes mellitus	1.53 (1.08-2.15)	.016	2.11 (1.37-3.26)	.001
Prior stroke/TIA	1.55 (1.08-2.22)	.018	1.79 (1.14-2.81)	.012
Vascular disease	1.46 (1.04-2.04)	.031	1.56 (1.21-2.02)	.001
Female sex	1.87 (1.36-2.57)	<.001	1.52 (1.01-2.30)	.047
Atrial fibrillation	2.08 (1.49-2.91)	<.001	—	—
Admission NIHSS	1.20 (1.16-1.23)	<.001	1.23 (1.18-1.27)	<.001
iv rtPA treatment	1.29 (.88-1.89)	.192	.50 (.30-.84)	.008

Numbers of patients in each category are shown in Table 1. Odds ratios indicate the increased or decreased odds of the clinical factor being present, for a 1% increase in the left ventricular ejection fraction (LVEF), or a 1 point increase in the admission National Institutes of Health Stroke Scale (NIHSS) score. We used  $P \leq .05$  as criteria for backward steps. Blank cells represent variables that were dropped as non-significant during stepwise selection. EF and NIHSS score were entered into the model as continuous variables; thus the odds ratio for ejection fraction represents the estimated change in odds of the outcome for a 1% increase in the ejection fraction, with all other variables unchanged. The units for NIHSS score are points on a scale from 0 to 40 (maximum observed in this study). Hosmer-Lemeshow goodness of fit  $\chi^2$  13.887,  $P = .085$ . ESUS indicates embolic stroke of undetermined source; iv rtPA, intravenous recombinant tissue-type plasminogen activator; TIA, transient ischemic attack.

\*Note that entering the clinically defined heart failure, left ventricular systolic dysfunction, and heart failure with or without reduced ejection fraction instead of the LVEF did not meaningfully change the results and are thus not shown. Also, when age was entered as continuous variable, the association of the LVEF with the 90-day outcome was not substantially affected (OR .98, 95% CI .96 to .99,  $P = .011$ ).

of the models using the different HF definitions for the presence of AF, respectively (Fig 2B).

## Discussion

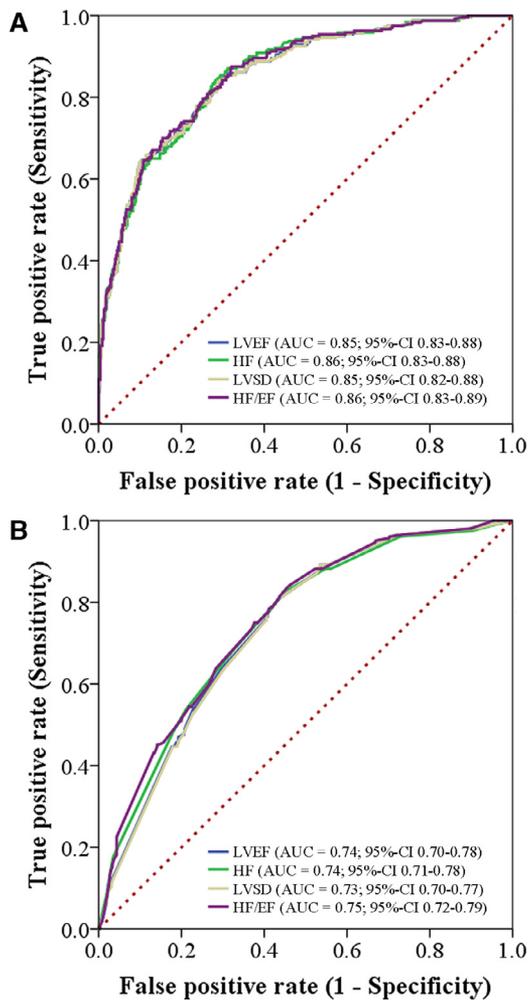
HF has been associated with both a worse outcome after ischemic stroke as well as AF.<sup>2-4,27</sup> Because commonly used clinical definitions of HF may suffer suboptimal reproducibility and lack of sensitivity, particularly in retrospective studies, we sought to determine whether the echocardiographically defined LVEF may serve as objective HF-index to predict functional disability after ischemic stroke. The most important finding of our study was that the predictive ability of the LVEF for a poor 90-day outcome as well as AF was similar to all clinically defined HF definitions.

This finding suggests equipoise for using the LVEF and frequently used clinical HF-definitions to predict outcome, results that may facilitate research as it provides the rationale for researchers to choose a HF definition that they can most reliably obtain. In this respect the LVEF is of particular interest because it is a readily available and easy to interpret echocardiographic metric that does not require detailed clinical information for diagnosing HF.

Several prior studies investigated the potential association between HF and the LVEF with post-stroke

functional outcome;<sup>13,28-31</sup> however, none directly compared the possible impact of different HF definition for predicting outcome, which impairs comparison of results across studies. In this respect it is noteworthy that the prevalence of HF in our cohort is consistent with prior studies indicating generalizability of our results.<sup>29,30,32,33</sup> Depending of the definition used in our study the prevalence of HF ranged from 11.7% to 19.3%—a difference driven by the classification of subjects to have asymptomatic LVSD (ie, absent HF with reduced LVSD). This is a striking observation as it suggests that asymptomatic LVSD, which was graded as moderate-to-severe LVSD in our cohort and represents a precursor for symptomatic HF,<sup>24</sup> is an equally strong predictor for poor functional status after ischemic stroke as HFpEF and HFrEF.<sup>33</sup>

Patients with HF are at high risk for developing AF, which frequently complicates HF, affecting approximately one-third of all adults with HF,<sup>4</sup> as well as presents a major risk factor for subsequent ischemic stroke.<sup>1</sup> Accordingly, it is important to understand the association between HF and AF in stroke patients. However, relatively few contemporaneous studies have sought to determine the impact of different HF definition on AF prediction.<sup>5</sup> Similar to the 90-day functional outcome we found equipoise for the models incorporating the LVEF and the different used HF definitions for predicting AF in



**Figure 2.** Area under the receiver operating characteristic curves (AUC) for outcome and atrial fibrillation (AF) prediction. Multivariable models using the LVEF and different HF definitions showed similar predictive ability for the (A) 90-day functional outcome and (B) diagnosis of AF in the entire cohort. LVEF, indicates left ventricular ejection fraction, HF = clinical heart failure, LVSD = left ventricular dysfunction (defined as reduced LVEF of <53%), HF/EF = clinical heart failure with or without reduced ejection fraction.

our cohort. These results are not dissimilar to data reported from a larger population based study in approximately 24,000 adults with a history of HF that found similar odds ratios for HFpEF and HFrEF to predict AF. Hence, our data indicates that the LVEF may serve as a predictor for AF in stroke patients and may serve as the impetus for conducting further studies to confirm this hypothesis. It would be particularly interesting to assess whether the LVEF and clinically defined HF can be used to predict AF in patients with ESUS (ie, subjects with presumed, but unknown, AF diagnosis)—and issue that we could not address in our study due to the overall low number of subjects with both new onset AF and HF (<5%) rendering analyses underpowered.

Strengths of our study relate to the investigation of a well-characterized patient population with collection of pertinent clinical variables, definition of HF based on several frequently used schemes, as well as rigorous adjustment of all analyses. This study is subject to the limitations inherent to its retrospective design. With respect to our exploratory analyses, not all ESUS patients underwent long-term rhythm monitoring for covert AF, the approach to rhythm monitoring after discharge was at the discretion of the treating physician, and the overall number of included subjects was modest. Accordingly, new onset AF may have been missed in a subset of patients and further study in a larger ESUS cohort with standardized rhythm monitoring is required to clarify the association between HF and AF in this subset of patients. Nevertheless, the overall monitoring strategy in our cohort is consistent with current clinical practice and more than 80% of subjects had some form of long term monitoring assuaging concerns of major bias. Finally, our primary outcome of interest was the presence of functional disability at 90 days. Although this approach is consistent with contemporaneous stroke studies, future studies may include assessment of long-term stroke recurrence and survival.

**Table 4.** Multivariable logistic regression analysis for factors independently associated with atrial fibrillation in the entire cohort

Independent variable	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
LVEF*	.98 (.96-.99)	.003	.98 (.96-.99)	.009
Hypertension	2.51 (1.58-4.00)	<.001	1.73 (1.04-2.87)	.036
Age ≤64 years	Reference		Reference	
Age 65-74 years	3.55 (2.13-5.90)	<.001	3.47 (2.06-5.85)	<.001
Age ≥75 years	7.27 (4.58-11.54)	<.001	6.54 (2.06-10.54)	<.001
Diabetes mellitus	.70 (.48-1.02)	.063	.54 (.36-.81)	.001
Prior stroke/TIA	1.17 (.80-1.71)	.425	—	—
Vascular disease	1.29 (.91-1.84)	.155	—	—
Female sex	1.30 (.93-1.80)	.124	—	—

Hosmer-Lemeshow goodness of fit  $\chi^2$  1.163,  $P = .979$ . TIA indicates transient ischemic attack. We used  $P < .05$  as criteria for backward steps. Blank cells represent variables that were dropped as non-significant during stepwise selection.

\*Note that entering the clinically defined heart failure, left ventricular systolic dysfunction, and heart failure with or without reduced ejection fraction instead of the LVEF did not meaningfully change the results and are thus not shown. Also, when age was entered as continuous variable, the association of the LVEF with atrial fibrillation was not substantially affected ( $P = .008$ ).

## Conclusion

We found that the LVEF and different HF definitions equally relate to the 90-day functional outcome as well as diagnosis of AF in patients with acute ischemic stroke. These results are useful for researchers conducting outcome studies based on HF metrics in stroke populations.

## Supplementary Materials

Supplementary data to this article can be found online at [doi:10.1016/j.jstrokecerebrovasdis.2018.10.002](https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.10.002).

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