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Original article

The first prognostic model for stroke and death in patients with systolic heart failure

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ABSTRACT

Background: Patients with systolic heart failure (HF) are at increased risk of both ischemic stroke and death. Currently, no risk scores are available to identify HF patients at high risk of stroke or death. The Warfarin vs. Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial studied 2305 HF patients, in sinus rhythm, followed for up to 6 years (3.5 ± 1.5 years). This trial showed no overall difference in those treated with warfarin vs aspirin with regard to death or stroke. The present study develops the first prognostic model to identify patients at higher risk of stroke or death based on their overall risk profile.

Methods and results: A scoring algorithm using 8 readily obtainable clinical characteristics as predictors, age, gender, hemoglobin, blood urea nitrogen, ejection fraction, diastolic blood pressure, diabetes status, and prior stroke or transient ischemic attack (C-index = 0.65, 95% CI: 0.613–0.681), was developed. It was validated internally using a bootstrap method. In predicting 1-year survival for death alone, our 8-predictor model had an AUC of 0.63 (95% CI: 0.579–0.678) while the 14-predictor Seattle model had an AUC of 0.72. The Seattle model did not report stroke.

Conclusions: This novel prognostic model predicts the overall risk of ischemic stroke or death for HF patients. This model compares favorably for death with the Seattle model and has the added utility of including stroke as an endpoint. Use of this model will help identify those patients in need of more intensive monitoring and therapy and may help identify appropriate populations for trials of new therapies.

Clinical Trial Registration: http://www.Clinicatrials.gov NCT00041938.

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Background

Chronic heart failure is a major cause of morbidity and mortality. Heart failure (HF) is associated with stasis, hypercoagulable state, left ventricular (LV) thrombus formation, and embolic phenomena [1,2]. It is also associated with both sudden death and deaths resulting from progressive heart failure that may be caused by unrecognized atheroembolic events [3]. HF ranks second as a cause of cardiogenic stroke after atrial fibrillation. Decreased ejection fraction was found to be strongly associated with ischemic stroke even after adjusting for other stroke risk factors [4].

The risk of death in patients with HF is not homogenous and several risk factors have been identified to help stratify patients into high, medium, and low risk of death. Little work to date has been done to identify those HF patients who are also at risk of the most feared major morbidity, ischemic stroke. Quantifying the likelihood of a patient's stroke-free survival may help identify those in need of more intensive monitoring and therapy, and may also help target appropriate patient populations for trials of new therapies.

Several models predicting mortality in patients with HF have been published [5–8]. Most of these studies have features that limit their applicability. To date, no studies predicting mortality also include predictors of stroke in HF patients. Our goal in this analysis was to develop a convenient and accurate model to predict the risk of stroke-free survival in patients with systolic HF and an ejection fraction of 35% or less.

Methods and results

Details of the Warfarin Reduced Cardiac Ejection fraction (WARCEF) trial (http://clinicaltrials.gov No. NCT00041938) have been published previously [9]. In this randomized, double-blind trial, patients with left ventricular ejection fraction (LVEF) ≤35% in sinus rhythm were randomly assigned to warfarin (target international normalized ratio 2.75, with acceptable target range of 2.0–3.5) or aspirin (325 mg per day). Patients were enrolled at 168 centers in 11 countries between October 2002 and January 2010. The median follow-up time was 3.4 years (IQR 2.0–5.0). Patients who had a clear indication for warfarin or aspirin were not eligible. Additional eligibility criteria were modified Rankin score of 4 or less (on a scale of 0 to 6, with higher scores indicating more severe disability), and planned treatment with a beta-blocker, an angiotensin-converting enzyme (ACE) inhibitor (or, if the side-effect profile with ACE inhibitors was unacceptable, with an angiotensin-receptor blocker), or hydralazine and nitrates. Patients were ineligible if they had a condition that conferred a high risk of cardiac embolism, such as atrial fibrillation, a mechanical cardiac valve, endocarditis, or an intracardiac mobile or pedunculated thrombus.

The prognostic model

We developed and compared two prognostic models for time to ischemic stroke or death, using Cox proportional hazards modeling, stratification by clinical center, and stepwise regression for variable selection, with $p < 0.05$ as the entry and stay criterion. The variables prior stroke or transient ischemic attack (TIA) were forced to stay in the models because the clinical investigators considered it essential, given that they are established major risk factors.

The first "full" model used all of the predictors and interactions considered reasonable on the basis of previous research and clinical judgment that were available in the WARCEF dataset. The second "practical" model was a simpler version of the full model that excluded terms considered difficult to measure or interpret. We used standard techniques to evaluate both models, and to assess whether, compared to the full model, the practical model retained adequate predictive capacity. These were the Grambsch–Therneau test to assess the validity of the proportional hazards assumption [10]; the C-index to measure discriminating ability (this gives the probability that a model correctly identifies which of two individuals will have a longer survival time based on their risk scores) [11]; and a bootstrap method for internal validation [12]. We also evaluated the performance of our two models in predicting death alone by comparing their performance to that of the existing Seattle model, using the WARCEF data and the 1-year area under the curve (AUC). Appendix provides more details of the evaluation procedures.

We generated a risk score and a probability of stroke-free survival for individual patients by refitting a parametric model assuming constant risk using the predictors in the practical model.

We used SAS version 9.2 for the modeling and R version 2.8 for the C-index and internal validation. A p-value <0.05 was considered statistically significant.

For the full model we included 30 candidate predictors (12 continuous and 18 categorical), and their interactions with age, gender, and device (Table 1). Treatment was not included,

Table 1
Estimated hazard ratios, 95% confidence intervals, and p-values for the full model.

Variable	Hazard ratio	95% hazard ratio confidence limits		p-value
BUN	1.018	1.010	1.027	<0.0001
EF	0.975	0.963	0.988	0.0001
Hemoglobin	0.893	0.836	0.955	0.0009
Six-minute walk	0.998	0.998	0.999	0.0001
DBP	0.988	0.980	0.997	0.0093
Age (≥60 years vs <60 years)	1.351	1.100	1.659	0.0041
Already on warfarin	0.487	0.256	0.928	0.0288
BMI (low vs normal)	1.230	0.995	1.521	0.0554
BMI (high vs normal)	0.819	0.659	1.017	0.0709
On device	0.700	0.534	0.916	0.0094
Diabetes mellitus	1.387	1.144	1.681	0.0009
Gender	0.569	0.443	0.731	<0.0001
Prior stroke or TIA	1.114	0.773	1.605	0.5639
Already on warfarin * Age	3.215	1.529	6.760	0.0021
On device * Prior stroke TIA	1.993	1.074	3.701	0.0289

Candidate variables: BUN, DBP, SBP, EF, estimated glomerular filtration rate, hematocrit, hemoglobin, sodium, mini-mental state examination, six-minute walk, white blood cell count, age, alcohol consumption, already on warfarin, atrial fibrillation, BMI, country, on device, diabetes mellitus, education, gender, hypertension, ischemic cardiomyopathy, myocardial infarction, New York Heart Association class, prior stroke/TIA, race-ethnicity, smoking, statin, aspirin/antiplatelet.
BUN, blood urea nitrogen; EF, ejection fraction; DBP, diastolic blood pressure; SBP, systolic blood pressure; BMI, body mass index category; Device, defibrillator and/or pacemaker; TIA, transient ischemic attack.