Validation of the Health ABC Heart Failure Model for Incident Heart Failure Risk Prediction

The Cardiovascular Health Study

Andreas Kalogeropoulos, MD; Bruce M. Psaty, MD, PhD; Ramachandran S. Vasan, MD; Vasiliki Georgiopoulou, MD; Andrew L. Smith, MD; Nicholas L. Smith, PhD; Stephen B. Kritchevsky, PhD; Peter W.F. Wilson, MD; Anne B. Newman, MD, MPH; Tamara B. Harris, MD, MS; Javed Butler, MD, MPH; for the Cardiovascular Health Study

Background—The recently developed and internally validated Health ABC HF model uses 9 routinely available clinical variables to determine incident heart failure risk. In this study, we sought to externally validate the Health ABC HF model.

Methods and Results—Observed 5-year incidence of heart failure, defined as first hospitalization for new-onset heart failure, was compared with 5-year risk estimates derived from the Health ABC HF model among participants without heart failure at baseline in the Cardiovascular Health Study. During follow-up, 400 of 5335 (7.5%) participants developed heart failure over 5 years versus 364 (6.8%) predicted by the Health ABC HF model (predicted-to-observed ratio, 0.90). Observed versus predicted 5-year heart failure probabilities were 3.2% versus 2.8%, 9.0% versus 7.0%, 15.9% versus 13.7%, and 24.6% versus 30.8% for the <5%, 5% to 10%, 10% to 20%, and >20% 5-year risk categories, respectively. The Hosmer-Lemeshow $\chi^2$ was 14.72 (degrees of freedom, 10; $P=0.14$), and the C index was 0.74 (95% CI, 0.72 to 0.76). Calibration and discrimination demonstrated adequate performance across sex and race overall; however, risk was underestimated in white men, especially in the 5% to 10% risk category. Model performance was optimal when participants with normal left ventricular function at baseline were assessed separately. Performance was consistent across age groups. Analyses with death as a competing risk yielded similar results.

Conclusions—The Health ABC HF model adequately predicted 5-year heart failure risk in a large community-based study, providing support for the external validity of the model. This tool may be used to identify individuals to whom to target heart failure prevention efforts. 

(Circ Heart Fail. 2010;3:495-502.)

Key Words: heart failure ■ epidemiology ■ elderly

Heart failure prevalence continues to rise globally, with the majority of affected individuals being elderly.1–3 Unless effective prevention strategies are implemented, this trend is likely to worsen as the proportion of elderly people increases in the population.4 However, to implement cost-effective prevention strategies, risk stratification for incident heart failure at the population level is important. Such risk prediction schemes have to be applicable across major demographic groups. Moreover, to enhance community dissemination, these prediction schemes preferably should be based on parameters that are widely available and obtained at no or minimal cost.

Clinical Perspective on p 502

We recently developed and internally validated the Health ABC HF model,5 which uses 9 routinely available clinical variables to provide 5-year incident heart failure risk estimates in older adults. The model performed well in the overall cohort and in the 4 gender and race subgroups. Although internal validation by bootstrapping is a valid statistical method,6 it does not obviate the need for external validation because bootstrapping cannot overcome the limitations related to the specific characteristics of the derivation population, which may be biased in some respects. Specifically, the Health ABC HF model was derived from data on...
Blood chemistries were assessed after a 12-hour overnight fast. and tests, including ECG and echocardiogram, were performed.

women). Interviews and questionnaires were used to obtain information.

An original cohort of 5201 persons was recruited in 1989 to 1990, and a second cohort of 687 black persons was recruited in 1992 to 1993, yielding a total of 5888 participants (2495 men and 3393 women). The CHS design, rationale, and details of CHS have been published previously.11 Briefly, in CHS, potential clinical events were identified through the following: (1) the regular surveillance process (every 6 months), which included clinic visits and surveillance calls by the field centers; during this process, participants were asked to provide information on all hospitalizations and outpatient end point diagnoses since the last CHS contact; (2) participant-initiated reports, in which participants or proxies contacted the local site to report an event; and (3) secondary sources of events, including unreported earlier hospitalizations or end point diagnoses during review of medical records for a reported event, and Medicare hospitalization data.

The CHS events committee adjudicated heart failure by reviewing all pertinent data, including history, physical examination, chest radiograph report, and medication use.12 A heart failure event was confirmed if in addition to a physician diagnosis there was (1) documentation in the medical record of a constellation of symptoms (eg, shortness of breath, fatigue, orthopnea, paroxysmal nocturnal dyspnea) and physical signs (eg, edema, pulmonary rales, gallop rhythm, displaced left ventricular apical impulse); (2) supporting clinical findings, such as evidence of pulmonary edema on chest radiograph; or (3) a record of medical therapy for heart failure, including diuretics, digitalis, angiotensin-converting enzyme inhibitors, or β-blockers. All potential incident cardiovascular events in CHS were adjudicated by the events committee. To be consistent with the definition in the derivation cohort (Health ABC Study), incident heart failure in the current analysis was defined as adjudicated first hospitalization for heart failure.

LVEF at the time of incident heart failure was not assessed systematically in CHS. Therefore, data on LVEF post-heart failure development are based on reviews of the available echocardiographic reports by the CHS investigators.13

Statistical Analysis

Application and Validation of the Health ABC HF Model

In the Health ABC HF model, heart failure risk prediction for each participant is based on the prognostic index (PI) of the model (ie, the weighted sum of the 9 covariates [age; history of coronary heart disease; smoking status; systolic blood pressure; heart rate; serum cholesterol; diabetes; angina pectoris]. To align definitions with those used in the Health ABC Study, definite coronary heart disease was defined as a history of coronary artery bypass graft surgery, percutaneous coronary intervention, myocardial infarction, or angina accompanied by antianginal medication use (calcium channel blockers, β-blockers, or nitrates). Probable coronary heart disease was defined as a history of angina without use of antianginal medications (or missing data on medications) and missing or negative information about coronary revascularization or myocardial infarction. Smoking status was classified as current, past, or never. ECG left ventricular hypertrophy was classified with Minnesota code 3.1 criteria.9 Heart rate was recorded from the ECG. Blood pressure was calculated as the average of two sitting measurements. The core laboratory at the University of Vermont (Colchester, Vt) performed the analyses of fasting serum chemistry.

Baseline Echocardiographic Assessment in CHS

The design for the echocardiographic study in CHS has been published previously.10 Two-dimensional echocardiography was performed at baseline for the original cohort (n=5201); for the second cohort consisting of 687 black participants, echocardiography was performed at the year 2 visit. Global left ventricular systolic function could be assessed qualitatively in 99% of the cohort and was classified as normal, borderline, or impaired, corresponding to a left ventricular ejection fraction (LVEF) of ≥0.55, 0.45 to 0.54, and <0.45, respectively.

Methods

Study Population

The design, rationale, and details of CHS have been published previously.7 Eligible participants (noninstitutionalized persons aged 65 to 100 years expected to remain in the defined geographic area for ≥3 years) were recruited from Medicare eligibility lists and examined at the 4 field centers in Forsyth County, NC; Sacramento County, Calif; Allegheny County, Pa; and Washington County, Md. An original cohort of 5201 persons was recruited in 1989 to 1990, and a second cohort of 687 black persons was recruited in 1992 to 1993, yielding a total of 5888 participants (2495 men and 3393 women). Interviews and questionnaires were used to obtain information on medical history and medications. Physical examinations and tests, including ECG and echocardiogram, were performed. Blood chemistries were assessed after a 12-hour overnight fast.

The Health ABC HF model was developed for 5-year heart failure risk prediction; therefore, the model performance was evaluated for events during the first 5 years of follow-up in CHS participants without heart failure at baseline.8 Figure 1 presents the flow diagram for selection of CHS participants for the current analysis.

Definition of Risk Factors

Classification of prevalent coronary heart disease was based on self-report of coronary revascularization, myocardial infarction, or angina pectoris.8 To align definitions with those used in the Health ABC Study, definite coronary heart disease was defined as a history of coronary artery bypass graft surgery, percutaneous coronary intervention, myocardial infarction, or angina accompanied by antianginal medication use (calcium channel blockers, β-blockers, or nitrates). Probable coronary heart disease was defined as a history of angina without use of antianginal medications (or missing data on medications) and missing or negative information about coronary revascularization or myocardial infarction. Smoking status was classified as current, past, or never. ECG left ventricular hypertrophy was classified with Minnesota code 3.1 criteria.9 Heart rate was recorded from the ECG. Blood pressure was calculated as the average of two sitting measurements. The core laboratory at the University of Vermont (Colchester, Vt) performed the analyses of fasting serum chemistry.
Table 1. Baseline Participant Characteristics in the CHS and Health ABC Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CHS (n=5335)</th>
<th>Health ABC Study (n=2935)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>72.7±5.5 (65–100)</td>
<td>73.6±2.9 (68–80)</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>42.4</td>
<td>47.9</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, %</td>
<td>84.7</td>
<td>58.6</td>
</tr>
<tr>
<td>Black, %</td>
<td>14.7</td>
<td>41.4</td>
</tr>
<tr>
<td>Other, %</td>
<td>0.6</td>
<td>...</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.6±4.5 (14.7–45.8)</td>
<td>27.3±4.8 (14.6–47.5)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>136±21 (79–227)</td>
<td>136±21 (77–224)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>71±11 (40–116)</td>
<td>71±12 (30–120)</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>65±11 (30–113)</td>
<td>65±11 (38–113)</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>46.3</td>
<td>43.4</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>11.2</td>
<td>14.8</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current, %</td>
<td>11.8</td>
<td>10.5</td>
</tr>
<tr>
<td>Past, %</td>
<td>41.7</td>
<td>45.0</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite, %</td>
<td>15.5</td>
<td>16.5</td>
</tr>
<tr>
<td>Probable, %</td>
<td>1.7</td>
<td>3.1</td>
</tr>
<tr>
<td>Peripheral vascular disease, %</td>
<td>2.1</td>
<td>4.7</td>
</tr>
<tr>
<td>Cerebrovascular disease, %</td>
<td>6.8</td>
<td>6.8</td>
</tr>
<tr>
<td>Left ventricular hypertrophy, %</td>
<td>4.4</td>
<td>11.9</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>2.1</td>
<td>1.4</td>
</tr>
<tr>
<td>Hematocrit, % units</td>
<td>41.8±3.8 (25.3–56.7)</td>
<td>...†</td>
</tr>
<tr>
<td>White blood count, ×10³/mm³</td>
<td>6.2±1.6 (1.3, 13.4)</td>
<td>...†</td>
</tr>
<tr>
<td>Platelet count, ×10³/mm³</td>
<td>249±69 (48–543)</td>
<td>...†</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL*</td>
<td>101 (94, 111) (53–448)</td>
<td>94 (87, 105) (47–449)</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.05±0.30 (0.4–10.0)</td>
<td>1.05±0.41 (0.5–10.6)</td>
</tr>
<tr>
<td>Uric acid, mg/dL</td>
<td>5.7±1.5 (0.5–12.2)</td>
<td>...†</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>4.00±0.29 (2.8–5.2)</td>
<td>3.98±0.31 (2.8–5.0)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>212±39 (59–370)</td>
<td>203±38 (76–372)</td>
</tr>
<tr>
<td>High-density lipoprotein, mg/dL</td>
<td>54±15 (18–123)</td>
<td>54±17 (13–124)</td>
</tr>
<tr>
<td>Low-density lipoprotein, mg/dL</td>
<td>130±35 (25–277)</td>
<td>122±35 (6–270)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL*</td>
<td>120 (92, 164) (24–710)</td>
<td>118 (88, 162) (26–871)</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>92.4</td>
<td>...†</td>
</tr>
<tr>
<td>Normal</td>
<td>5.0</td>
<td>...</td>
</tr>
<tr>
<td>Borderline</td>
<td>2.6</td>
<td>...</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD (range), unless otherwise stated.
*Expressed as median (25th, 75th percentile) because of skewed distributions.
†Data not available at baseline in Health ABC Study.

Kalogeropoulos et al Validation of the Health ABC HF Model 497

glucose, creatinine, and albumin levels; and left ventricular hypertrophy by ECG):5

\[ PI = 1.104 \text{ (if definite coronary heart disease)} + 0.435 \text{ (if probable coronary heart disease)} + 0.826 \text{ (if current-smoker)} + 0.115 \text{ (if former-smoker)} + 0.433 \text{ (if left ventricular hypertrophy)} + 0.0635 \text{ (age [years] minus 73.6) – 0.750 (albumin [g/dL] minus 4.0) + 0.0046 (fasting glucose [mg/dL] minus 104.1) + 0.0217 (heart rate [bpm] minus 65.3) + 0.0173 (systolic blood pressure [mm Hg] minus 136.0) + 0.0952 (in[creatinine [mg/dL]] plus 0.0256).} \]

During internal validation,5 we estimated that predictions should be moderated by a linear factor of 0.95 (shrinkage factor) to obtain more realistic risk estimates.14 Thus, we used the moderated prognostic index (\( PI_{mod} \)) for all subsequent calculations:

\[ PI_{mod} = 0.95PI \]

The estimated heart failure risk \( P \) over 5 years then becomes:

\[ P = 1 - S_0 \exp(PI_{mod}) \]

where \( S_0 \) is the event-free Kaplan–Meier estimate at 5 years (\( S_0 = 0.9658 \)) as observed in the Health ABC Study, for a reference person with a 0 sum of covariates (\( PI = 0 \)).

We assessed calibration by comparing observed versus predicted probabilities of incident heart failure. In the total cohort, we compared probabilities across deciles of risk, obtained the Hosmer-Lemeshow goodness of fit \( \chi^2 \) (H-L \( \chi^2 \)), and plotted smoothed calibration plots. We also compared probabilities across categories of 5-year predicted risk (<5%, 5% to 10%, >10%) and calculated the predicted-to-observed ratio. In subgroup analyses, we only considered calibration across categories of risk because of small numbers of events within deciles of risk. Discrimination was evaluated using the Harrell C index for survival models,14 which is equivalent in interpretation to the area under the receiver operating characteristic curve.

In subgroup analyses, we evaluated model performance in sex and race subgroups. Because CHS included participants aged 65 to 100 years at baseline, whereas the Health ABC HF model was derived in a population of 70 to 79 years, we also examined performance in age groups by 5-year increments. Due to small numbers of participants and events in those ≥80 years, the corresponding groups were combined into a single category. In the derivation cohort (Health ABC Study), data on baseline left ventricular systolic function were not available, raising the possibility that participants with asymptomatic systolic dysfunction (stage B heart failure) may have been inadvertently included in the analysis. Although the model performance is still valid from a clinical perspective, as it is designed to assess the risk of clinical (stage C) heart failure irrespectively of baseline asymptomatic stage A or B, to further clarify this issue, we examined model performance in the subset of participants with normal left ventricular systolic function at baseline.

**Competing Risks Analysis**

Mortality in the derivation and validation cohorts was higher than heart failure incidence, raising concerns about the validity of absolute risk estimates.15,16 Therefore, we repeated the validation analyses using the competing risks extension of the Cox proportional hazards model, as proposed by Fine and Gray,17 to estimate the baseline cumulative subhazard function of incident heart failure (ie, the cumulative hazard of heart failure considering death as competing event) in the Health ABC Study. We then obtained predictions for cumulative heart failure incidence at 5 years in the CHS, using the baseline cumulative subhazard function and the \( PI \) of the Health ABC HF model.16 Further details for this analysis are provided in the online-only Data Supplement.

**Missing Value Analysis**

To evaluate for possible bias introduced by the omission of participants with incomplete data on model covariates (5.0%), we repeated the process in 5 imputed data sets that included all participants who were free of prevalent heart failure at baseline. For missing values, we used imputation by chained equations as de-
scribed by van Buuren et al.17 All statistical analyses were carried out in STATA version 10.1.

Results

Baseline Characteristics and Heart Failure Incidence

There were 5613 CHS participants without prevalent heart failure at baseline. Of these, 278 (5.0%) had incomplete data on Health ABC HF model variables and were excluded from the main analysis, leaving 5335 participants in the validation cohort (Figure 1). Mean ± SD age was 72.7 ± 5.5 years, 57.6% were women, and 84.7% were white (96.2% of nonwhite participants were black). The characteristics of the derivation (Health ABC Study) and validation (CHS) cohorts are presented in Table 1. There were 400 (7.5%) of 5335 incident heart failure events at 5 years, corresponding to 16.2 events per 1000 person-years (95% CI, 14.7 to 17.9), and 651 (12.2%) deaths, corresponding to a 2.6% (95% CI, 2.4% to 2.8%) annual mortality. There was no loss to follow-up during the 5-year period.

Data on left ventricular systolic function at baseline were available in 4720 (88.5%) of 5335 participants in the validation cohort; of these, 4363 (92.4%) had normal systolic function, 235 (5.0%) had borderline systolic function, and 122 (2.6%) had impaired systolic function. The 357 participants with diminished left ventricular systolic function contributed 62 (15.5%) of the total 400 incident heart failure cases.

Data on LVEF at the time of incident heart failure were available in 228 (57.0%) of the 400 heart failure cases. The average LVEF at the time of incident heart failure in those cases was 43.4 ± 16.1% (median, 43%; interquartile range, 30% to 55%); 109 (57.3%) of 228 cases presented with an LVEF ≤ 45%.

Performance of the Health ABC HF Model

Table 2 presents the observed 5-year heart failure incidence compared to the Health ABC HF model predicted probability across categories of predicted risk. The total number of expected events was 364; 36 fewer cases than the observed 400 (predicted versus observed 5-year heart failure probability, 6.8% versus 7.5%, respectively; ratio, 0.90). Observed 5-year heart failure incidence was within the predicted 5-year probability range in all risk categories. Figure 2 shows the calibration of the model across deciles of predicted risk. The H-L $\chi^2$ did not reach significance ($\chi^2$, 14.72; degrees of freedom, 10; $P = 0.14$), indicating adequate model fit. The C index was 0.74 (95% CI, 0.72 to 0.76), which is comparable to the moderated estimate (C index, 0.72) obtained during development of the Health ABC HF model.5

Among participants with normal left ventricular systolic function (n = 4363), there were 275 (6.3%) incident heart failure events at 5 years versus 271.4 (6.2%) predicted with the model (predicted-to-observed ratio, 0.99). Observed versus predicted 5-year heart failure probabilities were 3.5% versus 3.1%, 7.7% versus 7.8%, 14.9% versus 15.0%, and 28.0% versus 33.3% for the <5%, 5% to 10%, 10% to 20%, and >20% 5-year risk categories, respectively. The H-L $\chi^2$ was 8.02 (degrees of freedom, 10; $P = 0.63$) and the C index was 0.73 (95% CI, 0.70 to 0.76).

Model Performance in Subgroups

Figure 3 and Table 3 summarize the predictions of the Health ABC HF model in the sex- and race-based subgroups. Overall risk was underestimated in white men (predicted versus observed 5-year heart failure probability, 7.7% versus 9.6%, respectively; ratio, 0.80); this was primarily due to underestimation of risk in the 5% to 10% risk category (Figure 3).
Predicted 5-year heart failure probability was concordant with the observed heart failure incidence in the remaining subgroups (Figure 3 and Table 3). Black men and women represented small subgroups, with only 26 and 40 events, respectively. Therefore, assessment of calibration in these subgroups should be interpreted with caution. Discrimination (C index) was adequate in the sex- and race-based subgroups (Table 3). Figure 4 summarizes the age-specific performance of the model; observed and predicted heart failure probabilities were concordant across age groups.

**Competing Risks Analysis**

When predictions were obtained using the 5-year cumulative subhazard estimate for incident heart failure (with death as a competing event) as the basis of predictions, results were very similar to those obtained using the Kaplan–Meier estimate (standard Cox approach). The model predicted a total of 365 events in the validation cohort (predicted-to-observed ratio, 0.91). Observed versus predicted 5-year heart failure probabilities were 3.2% versus 2.8%, 8.9% versus 7.0%, 15.9% versus 13.7%, and 24.7% versus 30.8% for the <5%, 5% to 10%, 10% to 20%, and >20% 5-year risk categories, respectively. The corresponding H-L $\chi^2$ was 14.42 (degrees of freedom, 10; $P=0.15$). The calibration plot for this analysis is provided in the online supplement.

**Missing Value Analysis**

In analyses performed on 5 imputed data sets, including all participants without heart failure at baseline ($n=5613$), the increased number of participants and events led to higher values of the H-L $\chi^2$ statistic, suggesting relatively more marginal model fit. However, predictions were not materially affected from a clinical perspective. The predicted-to-observed ratio was 0.91 to 0.92 across imputed data sets, and the C index was 0.74. The performance summaries for these data sets are provided in the online supplement.

**Discussion**

In this study, we examined the external validity of the Health ABC HF model in the CHS cohort. The model showed clinically adequate properties in this independent cohort and performed well in sex- and race-based subgroups. These data support the potential use of this model to determine heart failure risk in elderly persons and possibly identify those who would benefit the most from preventive interventions.

The Health ABC HF model was developed based on a well-functioning, well-characterized elderly population and

---

**Table 3. Model Performance in Major Demographic Groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>Persons at Risk</th>
<th>Predicted 5-Year Events</th>
<th>n</th>
<th>% (95% CI)</th>
<th>Ratio*</th>
<th>C Index (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White men</td>
<td>1951</td>
<td>150 (7.7)</td>
<td>187</td>
<td>9.6 (8.3–11.0)</td>
<td>0.80</td>
<td>0.71 (0.68–0.75)</td>
</tr>
<tr>
<td>White women</td>
<td>2570</td>
<td>144 (5.6)</td>
<td>143</td>
<td>5.6 (4.7–6.5)</td>
<td>1.00</td>
<td>0.75 (0.70–0.79)</td>
</tr>
<tr>
<td>Black men</td>
<td>299</td>
<td>27 (9.0)</td>
<td>26</td>
<td>8.7 (5.8–12.5)</td>
<td>1.04</td>
<td>0.74 (0.65–0.83)</td>
</tr>
<tr>
<td>Black women</td>
<td>484</td>
<td>41 (8.4)</td>
<td>40</td>
<td>8.3 (6.0–11.1)</td>
<td>1.02</td>
<td>0.72 (0.65–0.79)</td>
</tr>
</tbody>
</table>

*Predicted to observed event ratio.
showed good performance on internal validation. However, internal validation takes into account only sampling variability; thus, external validation is necessary in order to assess generalizability of a model.\(^{18,19}\) Moreover, baseline echocardiographic assessment was not performed in the Health ABC Study, raising the possibility that individuals with asymptomatic systolic dysfunction (stage B heart failure) may have been inadvertently included in the analysis. The CHS was designed to assess the development and progression of cardiovascular disease in elderly persons and was ideally suited for external validation of the Health ABC HF model. The enrollment criteria provided an opportunity for a broader group of elderly persons to be studied. In contrast to the Health ABC Study, all participants in the original CHS cohort had a baseline echocardiogram performed. The performance of the model in this independent cohort supports heart failure risk prediction with this tool. Moreover, model performance remained stable when assessed in the subset of individuals with normal left ventricular systolic function, alleviating concerns about the validity of the original results due to the potential influence of including participants with baseline asymptomatic ventricular dysfunction (ie, in transition from stage B to stage C heart failure). It is important to note, however, that although assessment of ventricular function is not recommended for screening purposes, impaired left ventricular systolic function increases risk for heart failure and, when known, probably adds to risk stratification. Thus, although assessment of ventricular function is not a cost-effective screening procedure in the general population, the practical applicability may be significantly limited. The Health ABC HF model was the first attempt to systematically stratify heart failure risk in these major demographic subgroups.\(^5\) In this external validation study, the model had adequate performance in white women; however, risk was underestimated among white men in the intermediate risk category. The cause of this deviation is not obvious and may represent a more prominent role of nontraditional risk factors, necessitating assessment of other risk markers for further risk classification in the intermediate-risk male population. On the other hand, we did not observe systematic effects of race on model performance; however, the overall number of participants and events was low in black men and black women; thus, these results need to be interpreted with caution.

Considering the increasing proportion of elderly individuals in the population, the already worsening heart failure epidemic is likely to be accentuated\(^{22-26}\) with major clinical, quality-of-life, and economic consequences. For many other common, lethal, and costly diseases (eg, breast or colon cancer, coronary heart disease), specific tools exist either to risk stratify individuals or to detect high-risk individuals.\(^{27-29}\) Heart failure is an exception where there are no targeted risk stratification tools,\(^30\) an issue partly rooted in the belief that treating individual risk factors like hypertension or diabetes would reduce the risk for heart failure. Although largely true, such an approach misses many details and opportunities. For example, there is growing support in the literature that treating blood pressure with different agents leads to a differential reduction in cardiovascular risk\(^31\) and that for other risk factors like diabetes, intensive control may have no impact on certain clinical outcomes.\(^32\) Treatment of individual risk factors is a disease-based and not a patient-based approach. Many subjects have multiple risk factors that act in concert to determine risk. Therefore, patients may need differential control of risk factors if multiple risk factors coexist (eg, hypertension control in patients with both hypertension and diabetes is different from that in patients with hypertension alone).\(^33\) Moreover, evidence suggests that among agents used to control a risk factor (eg, hypertension), there may be differential preventive effects regarding development of heart failure. For example, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial,\(^34\) there was a significantly higher risk of new-onset heart failure with doxazosin-based therapy. Similarly, there were quantitative differences in incident heart failure between chlorthalidone-based versus lisinopril- or amlodipine-based therapy.\(^34\) These data suggest that careful therapeutic consideration needs to be given when attempting
to treat risk factors for heart failure in order to achieve maximum benefit. Additionally, the Health ABC HF model could serve as a tool to identify individuals who might require intensified control of individual risk factors based on the overall heart failure risk profile; however, this concept is speculative and needs further study. It is also likely, though not proven, that nonpharmacologic lifestyle interventions might reduce heart failure risk in high-risk individuals. The Health ABC HF model therefore puts the risk for incident heart failure development in a comprehensive perspective and may potentially be used both for individual risk assessment and for intervention evaluation in research settings.

Both the Health ABC Study and CHS enrolled older adults. However, as the risk factor profile for cardiovascular diseases, including obesity and metabolic syndrome, increases in society, it is possible that a higher proportion of younger individuals may develop heart failure. How the Health ABC HF model will perform for risk assessment in younger individuals needs further study. Neither the Health ABC Study nor the CHS had left ventricular function systematically assessed after heart failure development, and thus, the differential properties of the model for prediction of heart failure with reduced versus preserved left ventricular systolic function need further investigation. Prevalence of risk factors and their impact on developing disease may vary by race; for example, risk for coronary heart disease in subjects of Asian descent tends to be lower at the same levels of risk factors, such as body mass index or cholesterol levels. The performance of the model in individuals not of white or black race needs further study. In addition, risk calculation is based on accurate identification of prevalent risk factors in a population; although variability in risk factor ascertainment is less of a concern for physical examination (eg, blood pressure), laboratory (eg, serum creatinine), and behavioral (eg, smoking) parameters, ascertainment of coronary heart disease may be challenging. Despite the vigorous study design of CHS, documentation of coronary imaging or revascularization is not always present, and history of myocardial infarction, and even more so angina, can be subject to interpretation. This can adversely affect the model estimates because presence of coronary heart disease may be overdiagnosed (eg, subjective chest pain and use of β-blockers or calcium channel blockers for other indications such as hypertension) or underdiagnosed (eg, recall bias or suboptimal therapy). Additionally, it is important to note that the Health ABC HF model is based on inpatient incident heart failure and therefore provides only an estimate of the risk of hospitalization for incident heart failure among elderly persons. Finally, in the development of the Health ABC HF model, we specifically focused on commonly available clinical variables that may be suitable for screening purposes. Imaging modalities and biomarkers also may help to classify risk further, especially in the intermediate-risk group, but the cost-effectiveness of these more expensive tests needs further study.

In conclusion, the Health ABC HF model demonstrated adequate performance for heart failure risk assessment in a large prospective cohort. Whether determination of heart failure risk in the community with this tool and subsequent lifestyle or other interventions will help to reduce heart failure incidence needs further study. Considering the epidemiological trends in both the societal demographics and the cardiovascular risk factor profile, such efforts are essential.

Sources of Funding

The research reported in this article was supported by contract numbers N01-HC-85079 through N01-HC-85086, N01-HC-35129, N01-HC-15103, N01-HC-55222, N01-HC-75150, N01-HC-45133, and grant number U01-HLO80925 from the National Heart, Lung, and Blood Institute, with additional contributions from the National Institute of Neurological Disorders and Stroke. A full list of the CHS investigators and institutions can be found at http://www.chs-nhlbi.org/pi.htm. This project also was partially funded by an Emory University Heart and Vascular Board grant entitled “Novel Risk Markers and Prognosis Determination in Heart Failure” and Public Health Service grant UI-R0025008 from the Clinical and Translational Science Award program, National Institutes of Health, National Center for Research Resources.

Disclosures

None.

References

We compared the 5-year heart failure incidence in the Cardiovascular Health Study with predicted 5-year risk estimates derived with the Health ABC HF model, a clinically oriented prediction model that uses 9 routinely available variables to determine heart failure risk in elderly persons. Among 5335 participants without heart failure at baseline, 400 (7.5%) developed heart failure over 5 years compared to the 364 (6.8%) predicted by the model. Observed versus predicted 5-year heart failure probabilities were 3.2% versus 2.8%, 9.0% versus 7.0%, 15.9% versus 13.7%, and 24.6% versus 30.8% for the <5%, 5% to 10%, 10% to 20%, and >20% 5-year risk categories, respectively. Calibration and discrimination were adequate in this external validation cohort (Hosmer-Lemeshow $\chi^2=14.72$; degrees of freedom, 10; $P=0.14$; C index, 0.74; 95% CI, 0.72 to 0.76). Performance was consistent across sex-, race-, and age-based subgroups overall; however, risk was underestimated in white men with predicted 5% to 10% 5-year risk. Analyses with death as a competing risk yielded similar results. Similarly, the results were not materially affected when analysis was restricted to participants with normal left ventricular systolic function at baseline. The adequate performance of the Health ABC HF model in this large community-based cohort provides support for the external validity of the model as a heart failure risk assessment. However, the Health ABC HF model was developed and validated in older adults; therefore, its utility in younger populations needs to be studied. This clinical tool may be used to identify elderly individuals who might benefit from targeted heart failure prevention efforts.
Validation of the Health ABC Heart Failure Model for Incident Heart Failure Risk Prediction: The Cardiovascular Health Study
Andreas Kalogeropoulous, Bruce M. Psaty, Ramachandran S. Vasan, Vasiliki Georgiopoulou, Andrew L. Smith, Nicholas L. Smith, Stephen B. Kritchevsky, Peter W.F. Wilson, Anne B. Newman, Tamara B. Harris, Javed Butler and for the Cardiovascular Health Study

Circ Heart Fail. 2010;3:495-502; originally published online April 28, 2010;
doi: 10.1161/CIRCHEARTFAILURE.109.904300
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circheartfailure.ahajournals.org/content/3/4/495

Data Supplement (unedited) at:
http://circheartfailure.ahajournals.org/content/suppl/2010/04/28/CIRCHEARTFAILURE.109.904300.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Heart Failure can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Heart Failure is online at:
http://circheartfailure.ahajournals.org//subscriptions/
SUPPLEMENTAL MATERIAL

Supplemental Methods

Analysis considering death as competing risk (Fine and Gray model)

The cumulative incidence function of the event of interest $CIF(t)$ in the Fine and Gray competing-risks regression model, which keeps subjects who experience competing events “at risk” so that they can be adequately counted as not having any chance of failing, is given by the formula:

$$CIF(t) = 1 - e^{-H(t)}$$

where $H(t)$ is the cumulative hazard for the event of interest (“subhazard”) at time $t$. It can be shown that the cumulative subhazard $H(t)$, similarly to the cumulative hazard in standard Cox regression, is a function of the baseline cumulative subhazard $H_0(t)$ (that for covariates set to zero) and the prognostic index $PI$ (assuming proportional hazards):

$$H(t) = H_0(t)e^{PI}$$

In the Health ABC Study, we estimated that the baseline cumulative subhazard at 5 years for a participant with zero sum of covariates ($PI=0$) was 0.03492 (which is close to the Kaplan-Meier failure estimate at 5 years, 1-0.9658=0.0342). In turn, the predicted cumulative incidence of heart failure over 5 years becomes:

$$CIF = 1 - e^{-0.03492\exp(PI)}$$

Missing Value Analysis

The Supplemental Table 1 summarizes the performance of the model in the 5 imputed datasets. In this analysis, number of participants at risk is 5613 (all CHS participants without heart failure at baseline; the number of observed 5-year heart failure events is 426, and the observed 5-year incidence is 7.6%. Not surprisingly, the H-L statistic yields higher values now because of the increased sample size and number of events.\(^1\) However, predictions were not materially affected from a clinical perspective; the predicted to observed ratio was 0.91-0.92 and the C index was 0.74. Predicted risk was within the pre-specified range across risk categories in all datasets (data not shown).
Supplemental Tables

**Supplemental Table 1.** Model performance summary in imputed datasets

<table>
<thead>
<tr>
<th>Imputation</th>
<th>Predicted events, n (%)</th>
<th>Ratio*</th>
<th>H-L $\chi^2$</th>
<th>P</th>
<th>C (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>389.6 (6.9)</td>
<td>0.92</td>
<td>18.22</td>
<td>0.051</td>
<td>0.74 (0.72-0.76)</td>
</tr>
<tr>
<td>#2</td>
<td>389.1 (6.9)</td>
<td>0.91</td>
<td>17.41</td>
<td>0.066</td>
<td>0.74 (0.72-0.76)</td>
</tr>
<tr>
<td>#3</td>
<td>389.3 (6.9)</td>
<td>0.91</td>
<td>19.75</td>
<td>0.032</td>
<td>0.74 (0.72-0.76)</td>
</tr>
<tr>
<td>#4</td>
<td>390.3 (7.0)</td>
<td>0.92</td>
<td>16.94</td>
<td>0.076</td>
<td>0.74 (0.72-0.76)</td>
</tr>
<tr>
<td>#5</td>
<td>389.4 (6.9)</td>
<td>0.91</td>
<td>19.43</td>
<td>0.035</td>
<td>0.74 (0.72-0.76)</td>
</tr>
</tbody>
</table>

* Predicted to observed ratio. Number of persons at risk is 5613; number of observed 5-year events is 426; observed 5-year event incidence is 7.6%.
Supplemental Figure 1

H-L $\chi^2 = 14.42$; d.f.=10; $P=0.15$
Supplemental Figure Legends

Supplemental Figure 1. Calibration of the Health ABC HF model with death as a competing event. Upper panel: Predicted and observed 5-year heart failure probabilities across deciles of predicted risk. The numbers below each decile represent predicted (first row) and observed (second row) 5-year probabilities for each decile. Lower panel: smoothed plot of observed against predicted probabilities; the dashed 45º line represents optimal calibration.

Supplemental References