Population Risk Prediction Models for Incident Heart Failure:
A Systematic Review

Echouffo-Tcheugui et al: Incident Heart Failure Risk Prediction Models

Justin B. Echouffo-Tcheugui, MD1; Stephen J. Greene, MD2;
Lampros Papadimitriou, MD3; Faiez Zannad, MD, PhD4; Clyde W. Yancy, MD, MSc5;
Mihai Gheorghiade, MD2; Javed Butler, MD MPH3

From 1Rollins School of Public Health, Emory University, Atlanta, GA; 2Center for Cardiovascular Innovation, Northwestern Feinberg School of Medicine, Chicago, IL; 3Stony Brook University, Stony Brook, NY; 4School of CHU Nancy, Institute of Lorraine Heart and Blood Vessels, Nancy, France; 5Cardiology Division, Northwestern Feinberg School of Medicine, Chicago, IL

Correspondence to
Javed Butler MD MPH
Division of Cardiology, Stony Brook University, Health Sciences Center, T-16, Room 080, SUNY at Stony Brook, NY 11794
Email: javed.butler@stonybrookmedicine.edu
Tel: 631 444 1066
Fax: 631 444 1054

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Abstract

Background—The prevalence of heart failure (HF) is expected to significantly rise unless high-risk patients are effectively screened and appropriate, cost-effective prevention interventions are implemented.

Methods and Results—We performed a systematic review to evaluate the prediction characteristics of the published HF risk prediction models as of August 2014 using MEDLINE and EMBASE databases. Eligible studies reported the development, validation, or impact assessment of a model. Two investigators performed independent review to extract data on study design and characteristics, risk predictors, discrimination, calibration, and reclassification ability of models, as well as validation and impact analysis. We included 13 publications reporting on 28 HF risk prediction models. Models had acceptable-to-good discriminatory ability (c-statistics >0.70) in the derivation sample. Calibration was less commonly assessed, but was acceptable when it was. Only two models were externally validated more than once, displaying modest-to-acceptable discrimination (c-statistics 0.61-0.79). When assessed, novel blood and imaging markers modestly improved risk prediction. One model assessed the prediction properties in race-based subgroups while two models evaluated gender-based subgroups. Impact analysis found none of the models recommended for use in any clinical practice guideline.

Conclusions—Incident HF risk prediction remains at an early stage. The discrimination ability of current models is acceptable in derivation datasets but most models have not been externally validated. It remains unclear which models are cost-effective and best suit population screening needs. The attendant effects of models on clinical and preventative care requires further study.

Key Words: heart failure, prevention, risk prediction, discrimination, calibration
Heart failure (HF) affects over 5 million Americans.\(^1\) Unless effective preventive interventions are implemented, it is estimated that by 2030, HF prevalence will grow by 25% and annual costs of care from $21 to $53 billion.\(^2\) The prognosis of patients with HF remains poor with a projected 50% five year mortality, underscoring the importance of prevention.\(^3\) Prevention interventions however, are unlikely to be cost-effective unless targeted towards reliably identified high-risk populations. Due to the epidemiologic paradox, more HF cases occur in patients with the absence of any given individual risk factor, which makes it important to develop a more comprehensive risk assessment scheme than to rely solely on individual risk factors. Unfortunately, the best approach for quantifying overall incident HF risk in individuals remains unclear. In this study, we sought to systematically assess the performance characteristics and the utility of the available HF risk models for predicting incident HF in the general population.

**Methods**

**Data Sources**

We searched PubMed and EMBASE databases from January 1990 to August 2014 for HF risk prediction models published in English language. We used search terms related to HF and disease prediction (Supplemental Appendix A) and reviewed the reference lists of studies and identified their citations through the ISI Web of Science for additional data. Eligible studies had to report a risk assessment model in a cohort study either by an equation and/or a score. Two evaluators (JBE, JB) independently identified articles and screened them for the inclusion criteria (Figure) by reviewing text and supplemental materials. Disagreements were solved by consensus. We excluded studies for models developed in specific population (e.g. post-operative
patients, patients already diagnosed with HF, studies that reported measures of risk without information on model characteristics, and simulation studies). We extracted information on the area under the receiver operating characteristic curve (AUC) or C-statistic, reclassification percentage, net reclassification improvement (NRI), and integrated discrimination improvement index (IDI).4

**Bias, Clinical Usefulness and External Validity**

Risk for bias in models was assessed per Hayden et al. recommendations5, including seven categories; participation (sampling bias), attrition (attrition bias), prognostic factor selection, prognostic factor measurement, outcome measurement (ascertainment bias), statistical analysis, and reporting model performance. Extent and methods of dealing with missing data, (Supplemental Table), appropriateness of statistical methods, and clinical usefulness as a combination of clinical utility and usability were assessed. Clinical utility was assessed as whether predictive models proposed clinical scenarios or decision nodes linked to a risk category or threshold where the model may be useful for guiding diagnostic or therapeutic interventions. For usability, we noted whether a calculator or nomogram that enables easier knowledge translation was added. To examine generalizability and external validity, we evaluated whether models had been validated in an independent population in the original or a subsequent publication.

**Data Extraction and Quality Assessment**

Two reviewers (JBE and JB) performed quality assessment and extracted information regarding design, setting, population characteristics, number of patients in the derivation and validation
 cohorts, number of outcomes of interest, number of candidate predictor variables and the type of regression model used. For predictors, we specifically assessed for age, gender, hypertension, left ventricular hypertrophy (LVH), myocardial infarction, diabetes, valvular disease, and overweight/obesity, based on previously reported association of these factors with HF. For discriminative ability, information on the C-statistic, and for calibration, the difference between the observed and predicted rates, as well as the P value of the corresponding test statistic, were extracted. Data relevant to reclassification included NRI and IDI values, as well as their respective 95% confidence intervals (CI) and P values, when available. Given the heterogeneity in the type and number of metrics, the number and nature of risk factors included, and the study designs used, our analysis consisted mainly of a narrative synthesis of the evidence.

**Impact of Heart Failure Risk Models**

Impact of studies was identified through scanning the references of all publications and applying search strategies for impact studies proposed by Reilly and Evans, which combines the model’s acronym or name of the cohort or first author with specific search term combination (Supplemental Appendix B). We searched relevant practice guidelines to assess the implementation of HF prediction models in countries or regions in which such models were developed. We also targeted English-language guidelines compiled by a selection of professional organizations known to regularly issue recommendations for the management of HF, including the American College of Cardiology (ACC), the American Heart Association (AHA), Heart Failure Society of America (HFSA), and the European Society of Cardiology (ESC).
Results

Prediction Models

We screened 413 abstracts, retrieved 48 citations for full-text review, and selected 13 studies that described 28 HF prediction risk models (Figure 1). The characteristics of the risk prediction models are presented in Table 1.

Populations, Risk Factors and Outcomes

Eleven models were developed from US cohorts, 1 in Sweden, 1 in Britain, and 2 multicenter cohorts (19 European countries in one and 38 countries from America, Europe, Asia and Africa in another study). Models were mostly developed in Caucasians; the models based on US populations included non-Caucasian participants, mainly Blacks. The number of participants ranged from 725 to 359,947 and age from 18 to 99 years. The length of follow-up ranged from 2.9 to 14 years. Three models were developed in specific populations, including diabetes, impaired glucose tolerance, and atrial fibrillation. The method of HF identification varied, but was mainly based on clinical presentation, hospital discharge records, and cause of death. One study defined HF using outpatient records in addition to hospital and death record and one study included an echocardiographic-based definition of HF. None of the studies assessed HF with preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF) separately.

One study published the numbers of variables tested for inclusion, thus for most studies, the number of outcomes of interest per candidate variable could not be assessed. The predictors most commonly included in the final models were age, sex, body mass index, diabetes, systolic blood pressure, creatinine, serum albumin or total protein, LVH, and coronary artery disease (CAD). Biomarkers were evaluated in several studies, including B-type natriuretic peptide.
(BNP) or N-terminal pro-BNP (NT-proBNP), mid-regional pro-atrial natriuretic peptide (MR-
proANP), interleukin 6 (IL-6), tumor necrosis factor (TNF) -alpha, C-reactive protein (CRP),
soluble interleukin-2 receptor (sST2), growth differentiation factor-15 (GDF-15), high-sensitivity
troponin I (hsTnI) and urinary albumin to creatinine ratio.

All models were developed using a Cox regression model with reporting of the model
with beta coefficients, with two studies providing additional point-based scoring systems.10, 11

Performance of the Models

Table 1 shows the model performance. The AUC ranged from 0.71 to 0.87, indicating a modest-
to-good discrimination. Risk scores were internally validated through bootstrapping in 411, 17, 20, 22
and jackknife in 1 study.13 Five models had calibration estimated with the Hosmer-Lemeshow
test. Most studies did not test for sex,10-13, 16-18, 21, 22 or race10-13, 15-19, 21, 22 based specific
performance, except the Health ABC HF score that predicted HF risk similarly in both genders
and in white/black race in development cohort,11 but the risk was underestimated in white men,
especially in the 5% to 10% risk category, in the validation cohort.24 The AUCs were 0.71, 0.75,
0.74, and 0.72 in White men, White women, Black men and Black women respectively.24

Model Improvement

In the Framingham Study, BNP and the urinary albumin to creatinine ratio increased the AUC
from 0.84 to 0.8613 and 13% of subjects were appropriately reclassified. In the Health ABC
study, the addition of IL6, TNF-alpha, and CRP increased AUC from 0.717 to 0.737, mainly due
to IL-6 that improved AUC to 0.734 (P=0.001).16 In the Cardiovascular Health Study, NT-
proBNP increased AUC from 0.667 to 0.719 (P<0.001), but discrimination remained moderate.25
In the Malmö Diet and Cancer study, MR-proANP, NT-proBNP, and CRP together improved AUC from 0.815 to 0.842 with an IDI of 0.05 (P<0.001) and a NRI of 22% (P<0.001).\textsuperscript{15} In the Atherosclerosis Risk in Communities study, adding NT-proBNP increased the AUC by 0.032, NRI by 13%, and IDI 0.057; NRI was higher in women (17.9%) than men (14.4%).\textsuperscript{20}

Echocardiographic score (left ventricular [LV] ejection fraction and mass, E/A ratio, and left atrium), and NT-proBNP improved AUC (echocardiography 0.031, NT-proBNP 0.027, combined 0.043; all P<0.01), and yielded robust IDI (echocardiography 43.3%, NT-proBNP 42.2%, combined 61.7%; all P<0.001), and NRI (echocardiography 11.3%; NT-proBNP 10.6%, combined 16.3%; all P<0.01), when added to the Health ABC model.\textsuperscript{18} Participants at intermediate risk (5% to 20% 5-yr risk; 35.7% of the cohort) derived the most reclassification benefit. Echocardiography yielded modest reclassification when used sequentially after NT-proBNP.

A multimarker score with sST2, GDF-15, hsTnI, hsCRP, and BNP increased AUC (0.846 to 0.870), NRI (0.39); and IDI (0.04) in the Framingham study.\textsuperscript{19} In the Atherosclerosis Risk in Communities study, cTnT and NT-proBNP improved AUC by 0.040 and 0.057; and NRIs 50.7% and 54.7% in women and men, respectively.\textsuperscript{26} In the Multi-Ethnic Study of Atherosclerosis cohort, NT-proBNP and LV mass index change AUC from 0.81 to 0.89; IDI by 0.046; NRI 6-year risk probability categorized by <3%, 3–10%, >10% of 0.175, P=0.019 and category-less NRI by 561, P<0.001).\textsuperscript{27} In the Framingham cohort, a composite of LVH and LV dysfunction increased AUC from 0.765 to 0.770. With GDF-15 and hsTnI, the NRI was 0.212 (P<0.0001).\textsuperscript{28} In the British Heart Regional Study, the addition of NT-proBNP to the Health ABC model improved AUC from 0.706 to 0.764 (P<0.0001).\textsuperscript{23} In the Prevention of Vascular and Renal End stage Disease (PREVEND) study, NT-proBNP, MR-proANP, hs-TnT, hs-CRP, Cystatin-C and...
urinary albumin excretion, individually modestly improved the AUC of 0.826 by 4.7%, 2.2%, 2.5%, 1.9%, 1.0%, and 1.6%, respectively.29

External Validity

Five models were externally validated (Table 2). Of these, the Framingham10 and Health ABC models11 were externally validated more than once. The AUC in validation studies were generally lower and with a poorer calibration, though the latter was not assessed in most of validation studies.

Single Biomarker or Imaging Data

In the Cardiovascular Health Study, a comparison of the Health ABC score, NT-proBNP, and echocardiographic data for detecting LV dysfunction indicated >5% risk of HF at 5 years in 44% of the cohort and identified 76% of those who developed HF by 5 years.24, 25 An abnormal NT-proBNP was present in 29.5% of the cohort and identified 45% of those who developed HF by 10 years; and baseline echocardiography identified reduced ejection fraction in 7.2% of the population, but identified only 12% of those who developed HF by 10 years.

Depending upon the method of indexing LV mass (body surface area, fat-free mass, or height), the AUC for the Health ABC HF score (0.73, 0.75, and 0.64, respectively) was greater than that for BNP (0.62, 0.70, and 0.57, respectively) and NT-pro-BNP (0.62, 0.69, and 0.56, respectively) (P<0.01 for all). Similar results were seen in the Framingham score except when LV mass was indexed to fat-free mass (0.65, 0.69 and 0.66, and 0.64, respectively). Addition of BNP resulted in an improvement in discrimination of stage B HF (difference in AUC, 0.01-
In an elderly at high risk, NT-proBNP (AUC 0.74) was superior to the Framingham HF score (AUC 0.63) in predicting asymptomatic LV systolic dysfunction.31

**Model Impact**

There were no recommendations for using any risk prediction model to estimate the risk of incident HF in either the clinical or community settings in any of the existing guidelines. There were no studies assessing the impact of adopting HF risk models in clinical practice on the process of care and outcomes of patients.

**Discussion**

This systematic review demonstrates the feasibility of global HF risk prediction in the general population. Compared to CAD and stroke, prediction of incident HF risk is at an early stage and is not incorporated into contemporary clinical or public health practice. Defining risk can be reliably done using a combination of common variables with an acceptable-to-good discrimination, though correcting for over-fitting (internal validation) or testing in new population (external validation) may attenuate discrimination. Implementation of prediction models may identify a wider segment of at-risk population compared to single risk factors. Additionally, biomarkers may be used to further categorize patients into different risk strata in concert with the clinical variables.

HF guidelines advocate prevention of progression from at-risk HF stages (A and B) to symptomatic stages (C and D), thus requiring identification of susceptible patients likely to benefit from interventions,7 including lifestyle changes or more intense risk factor modification. Risk communication to patients may motivate adherence; indeed healthy lifestyle is associated
with a lower lifetime risk of HF. Furthermore, risk scores can be incorporated into electronic medical records, allowing continual passive screening of high-risk subjects with alerts for patients entering higher-risk strata. HF risk models may also circumvent uncertainties surrounding the stage B HF definition that is dictated by limitations in what can be measured with imaging rather than a complete understanding of the risk. In stepwise screening with models as the first step followed by imaging or biomarkers, those with stage B HF may be more reliably referred for interventions known to halt and possibly reverse structural changes that precede clinical HF. With increasing HF risk, LV mass and concentric remodeling increases, supporting the traditional belief that HF risk correlates with structural heart disease. HF models may be useful in assessing the utility of novel biomarkers for risk prediction or for selecting patients for inclusion in clinical trials. Indeed, investigating novel markers is warranted, especially given the relatively modest additional discriminative ability of natriuretic peptides (BNP or NT-proBNP) beyond that of clinical variables. This finding is not surprising as factors included in models (e.g. plasma creatinine, female sex, and age) may increase these biomarkers independently of left ventricular ejection fraction and filling pressures. Moreover, a number of screening studies have found use of natriuretic peptide level as standalone test to lack discriminative ability for detecting structural abnormalities among healthy young adults.

Some of the existing models have been statistically underpowered, especially as consideration was not given to the ratio of outcomes to predictors. Models with an inappropriate ratio (<10 events per variable) are less robust, with a performance that shrinks when applied to other populations. While the overall study size and the prognostic ability of individual predictors is important, a key driver of statistical power is the number of events. These performance metrics mostly originated from the derivation sample, which are optimistic. Some models were internally
validated (bootstrap or jackknife validation), providing an idea about their potential performance when applied to a new population. Calibration was not always assessed. A poorly calibrated model may have the same discrimination as a well calibrated model, necessitating both of these characteristics to be assessed in concert. Attempts to update models by extra variables have focused on discrimination,\textsuperscript{13, 15, 16, 18-20, 25} and none of the studies reported change in the calibration. Lastly, validation is an important step before it can be recommended for widespread use. This was limited to only three models in US populations. Hence, further validations of existing models are needed to guarantee their generalizability.

HF models have mainly been published as mathematical equations. Complex formulas may not be suitable for clinical application. Indeed, previous research suggests that many clinicians find risk calculation too time consuming and are not convinced of the value of information derived from these models.\textsuperscript{36} Additional translation efforts are needed to convert predictions equations into user-friendly tools to improve uptake.\textsuperscript{15} Efforts are needed to derive the appropriate context for defining high-risk status to facilitate their use. It is also important to study whether implementing HF risk prediction affects the behavior of healthcare providers and improves clinical outcomes. Few studies examined the incremental predictive value of novel biomarkers (e.g. collagen matrix\textsuperscript{37, 38} and ‘omic’ markers) that may be useful for risk stratification. Clinical risk models provide good basis to assess the incremental value of new discoveries.

Misclassification of HF events may have occurred as there are no universally agreed specific criteria for diagnosing HF, thus affecting the performance of the models. HF is a heterogeneous syndrome, representing a spectrum of etiologies, as well as normal to depressed ejection fraction. Existing studies use multiple criteria to define HF\textsuperscript{39} with little agreement.\textsuperscript{40}
Inconsistencies were indeed observed in the presently reviewed studies, which may have impacted model performance. In most studies, diagnosis did not rely on imaging. Consequently specific forms of HF such as HFrEF and HFpEF, were not considered. Although there is an overlap between predictors of HFrEF and HFpEF, there are differences that merit consideration. Moreover, HFrEF and HFpEF are regarded as distinct pathophysiologic entities, as exemplified by the lack of evidence-based disease modifying therapies for the later. Accordingly, it stands to reason that differing preventative strategies and interventions may exist. Furthermore, the majority of participants included were Caucasians. However, HF risk is known to be heightened in specific groups (e.g. Blacks), thus supporting the need to incorporate more patients of different ethnic backgrounds.

Although existing models may lead to implementation of prevention interventions, such efforts may be premature, particularly in the absence of external validation studies and impact analysis. The lack of studies evaluating the impact of model utilization on outcomes should be addressed in future studies. Such an undertaking could potentially strengthen the case for their use in routine clinical or public health practice. The absence of existing studies may simply be an indication of the embryonic nature of the HF prediction field, and of HF prevention in general. This limitation is not specific to HF and does not in itself invalidate the future utility of the models. Indeed, even with coronary heart disease, for which prediction models have been in existence since the early nineties, only a limited number of studies have assessed the impact of their implementation, though their use has been consistently recommended in guidelines. We did not explicitly rank or categorize the quality of existing HF models, as there is no agreed-on scientific system for rating risk prediction model quality. Some argue minimizing risk for potential bias is of critical importance, while others contend that a risk score should be judged on
ability to perform accurately across diverse settings. Finally, our ability to assess publication bias was limited.

In conclusion, risk models for predicting incident HF have acceptable-to-good discriminative ability. These tools need to be better calibrated and externally validated, and the impact of their use on outcomes assessed before incorporation into clinical practice guidelines. With advancement of our understanding of systemic conditions and cardiac and non-cardiac structural and functional abnormalities that predispose to HF risk, better approaches for HF prevention are needed. HF prevention extends beyond simply addressing risk factors or precursors such as diabetes, hypertension and CAD, especially as the latter is not a sine qua non for the development of HF. HF scores may be viewed as a means for selecting a targeted population that would undergo imaging for detection of asymptomatic structural disease (e.g. left ventricular systolic dysfunction), a potential therapeutic target in itself. Successful prevention approaches mandate the correct identification of the target population, underscoring the importance of further research in the performance and use of incident HF risk models.

Disclosures

None.

References


## Table 1. Overview of heart failure risk prediction model

<table>
<thead>
<tr>
<th>Reference &amp; cohort</th>
<th>Population</th>
<th>Risk factors</th>
<th>N Outcome Follow-up (years)</th>
<th>Definition</th>
<th>Discrimination</th>
<th>Calibration</th>
<th>Validation</th>
<th>Reclassification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kannel et al., 1999&lt;sup&gt;10&lt;/sup&gt;</td>
<td>USA - Caucasian</td>
<td>age, LVH, HR, SBP, vital capacity, CHD, valve disease, DM, cardiomegaly</td>
<td>15,267 486 4</td>
<td>Framingham criteria</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Butler et al., 2008&lt;sup&gt;11&lt;/sup&gt;</td>
<td>USA / Caucasian and blacks</td>
<td>age, CHD, smoking, SBP, HR, glucose, creatinine, albumin and LVH</td>
<td>2935 258 4-9</td>
<td>Physician diagnosis and treatment for HF</td>
<td>0.73 (0.72 after bootstrapping)</td>
<td>HL $\chi^2 = 6.24$, ($p=0.621$)</td>
<td>Apparent Bootstrapping</td>
<td>NR</td>
</tr>
<tr>
<td>deFilippi, et al., 2010&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Mainly Caucasian</td>
<td>age, sex, race, SBP, ECG, glucose, CHD, smoking, creatinine, albumin, HR</td>
<td>4221 1279</td>
<td>Diagnosis + symptoms/signs + HF therapy</td>
<td>0.752</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>deFilippi, et al., 2010&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Mainly Caucasian</td>
<td>age, sex, race, SBP, ECG, glucose, CHD, status, creatinine, albumin, HR</td>
<td>4221 1279</td>
<td>Diagnosis + symptoms/signs + HF therapy</td>
<td>0.767</td>
<td>NR</td>
<td>NR</td>
<td>0.043 0.026</td>
</tr>
<tr>
<td>Smith et al., 2010&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Sweden – mainly Caucasian</td>
<td>Age, gender, SBP, DBP, LDL, MI antihypertensives,</td>
<td>5,187 112 14</td>
<td>ICD 8.9 and 10 codes</td>
<td>0.815</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Notes:**
- USA- Mixed but mainly Caucasian
- USA - Mainly Caucasian
- USA - Mixed but mainly Caucasian
- USA - Mainly Caucasian
- USA - Mainly Caucasian
- USA / Caucasian and blacks
- USA - Mainly Caucasian
- USA - Mainly Caucasian
- USA - Mainly Caucasian
- USA - Mixed but mainly Caucasian
- USA - Mainly Caucasian
- USA - Mainly Caucasian
<table>
<thead>
<tr>
<th>Study</th>
<th>Country and Race</th>
<th>Variables</th>
<th>Sample Size</th>
<th>Area Under the ROC Curve</th>
<th>C-statistic</th>
<th>p-value</th>
<th>p-value Adjusted</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
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<tbody>
<tr>
<td>Smith et al, 2010&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Sweden – mainly Caucasian</td>
<td>Age, gender, SBP, DBP, LDL, MI, antihypertensives, MR-proANP</td>
<td>5,187</td>
<td>0.824</td>
<td>NR NR</td>
<td>14 % (p=0.005)</td>
<td>0.03 (p&lt;0.001)</td>
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<tr>
<td>Smith et al, 2010&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Sweden – mainly Caucasian</td>
<td>Age, gender, SBP, DBP, LDL, MI, antihypertensives, NT-proBNP</td>
<td>5,187</td>
<td>0.837</td>
<td>NR NR</td>
<td>16 % (p=0.003)</td>
<td>0.03 (p&lt;0.001)</td>
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<tr>
<td>Smith et al, 2010&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Sweden – mainly Caucasian</td>
<td>Age, gender, SBP, DBP, LDL, MI, antihypertensives, CRP</td>
<td>5,187</td>
<td>0.823</td>
<td>NR NR</td>
<td>7 % (p=0.10)</td>
<td>0.01 (p=0.02)</td>
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<tr>
<td>Smith et al, 2010&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Sweden – mainly Caucasian</td>
<td>Age, gender, SBP, DBP, LDL, MI, antihypertensives, MR-proANP, NT-proBNP</td>
<td>5,187</td>
<td>0.838</td>
<td>NR NR</td>
<td>17 % (p=0.002)</td>
<td>0.03 (p&lt;0.001)</td>
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<tr>
<td>Smith et al, 2010&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Sweden – mainly Caucasian</td>
<td>Age, gender, SBP, DBP, LDL, MI, antihypertensives, NT-proBNP, CRP</td>
<td>5,187</td>
<td>0.842</td>
<td>NR NR</td>
<td>19 % (p=0.003)</td>
<td>0.04</td>
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<td>Kalogeropoulos et al, 2010&lt;sup&gt;16&lt;/sup&gt; Health ABC score 2</td>
<td>USA / Caucasian and blacks</td>
<td>age, CHD, smoking, SBP, HR, glucose, LVH, creatinine, albumin, IL-6</td>
<td>2610</td>
<td>0.734 (0.706–0.763)</td>
<td>NR NR</td>
<td>NR NR</td>
<td>0.084</td>
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<td>Kalogeropoulos et al, 2010&lt;sup&gt;16&lt;/sup&gt; Health ABC score 2</td>
<td>USA / Caucasian and blacks</td>
<td>age, CHD, smoking, SBP, HR, glucose, LVH, creatinine, albumin, IL-6, TNF-α, CRP</td>
<td>2610</td>
<td>0.737 (0.709–0.765)</td>
<td>NR NR</td>
<td>NR NR</td>
<td>0.084</td>
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<tr>
<td>Pfister et al, 2013&lt;sup&gt;17&lt;/sup&gt; PROactive trial score</td>
<td>19 European countries - Caucasian</td>
<td>Age, CKD, diuretic, MI use, HbA1c, DM, LDL, HR, R/LBBB, pioglitazone, microalbuminuria</td>
<td>4951</td>
<td>0.75 (0.751 after bootstrapping correction)</td>
<td>NR Apparent</td>
<td>NR NR</td>
<td>0.084</td>
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<tr>
<td>Study</td>
<td>Population</td>
<td>Variables</td>
<td>Sample Size</td>
<td>Diagnosis Criteria</td>
<td>AUC</td>
<td>NR</td>
<td>NR</td>
<td>p-Value</td>
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<td>Kalogeropoulos et al, 2012</td>
<td>USA/Mixed but 86.5% white</td>
<td>age, CHD, smoking, SBP, HR, glucose, creatinine, albumin LVH, echo score (EF, LA, and E/A) and NT-proBNP</td>
<td>3,752</td>
<td>Diagnosis + clinical or echo findings + medical therapy</td>
<td>0.777</td>
<td>NR</td>
<td>NR</td>
<td>10.6%</td>
<td>0.044</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kalogeropoulos et al, 2012</td>
<td>USA/Mixed but 86.5% white</td>
<td>age, CHD, smoking, SBP, HR, glucose, creatinine, albumin LVH, echo score (EF, LA, and E/A) and NT-proBNP</td>
<td>3,752</td>
<td>Diagnosis + clinical or echo findings + medical therapy</td>
<td>0.773</td>
<td>NR</td>
<td>NR</td>
<td>11.3%</td>
<td>0.045</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kalogeropoulos et al, 2012</td>
<td>USA/Mixed but 86.5% white</td>
<td>age, CHD, smoking, SBP, HR, glucose, creatinine, albumin LVH, echo score (EF, left atrium, and E/A Ratio) and NT-proBNP</td>
<td>3,752</td>
<td>Diagnosis + clinical or echo findings + medical therapy</td>
<td>0.789</td>
<td>NR</td>
<td>NR</td>
<td>16.3%</td>
<td>0.064</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang et al, 2012</td>
<td>FHS - mainly Caucasian</td>
<td>age, sex, BMI, SBP, HTN, DM, smoking, total and HDL-cholesterol, AF, CVD, EKG- LVH, murmur</td>
<td>3428</td>
<td>Framingham criteria</td>
<td>0.846</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang et al, 2012</td>
<td>FHS - mainly Caucasian</td>
<td>age, sex, BMI, SBP, HTN, DM, smoking, total and HDL-cholesterol, AF, CVD, EKG- LVH, murmur, and sST2, GDF-15, hsTnI, hsCRP, and BNP</td>
<td>3428</td>
<td>Framingham criteria</td>
<td>0.870</td>
<td>NR</td>
<td>NR</td>
<td>0.39</td>
<td>0.04 (0.21–0.57)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agarwal et al, 2012</td>
<td>ARIC-biethnic – Caucasian and Blacks</td>
<td>age, race, sex, prevalent CHD, SBP, antihypertensives, DM, smoking, HR, BMI</td>
<td>13555</td>
<td>HF hospitalization or ICD-9 code on the death certificate</td>
<td>NR</td>
<td>0.7937 after bootstrap</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Agarwal et al, 2012</td>
<td>ARIC - Caucasian and Blacks</td>
<td>age, race, sex, NT-proBNP</td>
<td>13555</td>
<td>HF admission or ICD-9 code on death certificate</td>
<td>NR</td>
<td>0.745</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Schnabel et al, 2013</td>
<td>FHS - Caucasian</td>
<td>Age, BMI, EKG LVH, DM, MI significant murmur</td>
<td>725</td>
<td>Framingham criteria</td>
<td>0.71 (0.67–0.75)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>HL $\chi^2 = 7.29$, (p=0.61).</td>
<td></td>
</tr>
</tbody>
</table>

**Framingham criteria**<br>0.846 NR NR NR NR 0.793 NR NR NR NR 0.745 NR NR NR NR 0.71 0.67 0.75 NR NR NR NR NR 7.29 (p=0.61).
<table>
<thead>
<tr>
<th>Study</th>
<th>Countries/Participants</th>
<th>Age, Risk Factors</th>
<th>Follow-Up</th>
<th>Endpoint</th>
<th>AUC</th>
<th>Method</th>
<th>p-Value</th>
<th>Method</th>
<th>Hazard Ratio</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wong et al, 201322 NAVIGATOR study</td>
<td>38 Countries Mixed</td>
<td>Age, CHD, EKG,</td>
<td>8975</td>
<td>HF hospitalization</td>
<td>0.864 (0.79 after bootstrapping)</td>
<td>NR</td>
<td>Apparent</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>waist SBP, AF,</td>
<td>124</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>COPD, urine albumin: creatinine ratio, hemoglobin</td>
<td>6.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wannamethee et al, 201423 British Regional Heart Study</td>
<td>Mainly Caucasian</td>
<td>age obesity, HTN, DM, MI, and angina</td>
<td>3870</td>
<td>Physician diagnosis</td>
<td>0.708 (0.676–0.741)</td>
<td>NR</td>
<td>Apparent</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>254</td>
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<tr>
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<td></td>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author, Reference</th>
<th>Validated risk score</th>
<th>Validation population / Country</th>
<th>Ethnicity</th>
<th>Design</th>
<th>Sample Size</th>
<th>Age (years)</th>
<th>Time-horizon (years)</th>
<th>Discrimination</th>
<th>Calibration</th>
<th>Reclassification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butler et al, 2008&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Framingham HF risk score</td>
<td>USA/Health ABC study</td>
<td>Mainly Caucasian</td>
<td>Prospective cohort</td>
<td>Males (n=1315) and female (n=1364)</td>
<td>70 to 79</td>
<td>5-year</td>
<td>0.735 in males and 0.684 in females</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Kalogeropoulos et al, 2010&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Health ABC score</td>
<td>Cardiovascular Health Study</td>
<td>Mainly Caucasian</td>
<td>Prospective cohort</td>
<td>5335 (400 events)</td>
<td>Mean 72.7 (SD: 5.5)</td>
<td>5</td>
<td>0.74 (95% CI, 0.72 to 0.76).</td>
<td>HL Chi square = 14.72 (P=0.14),</td>
<td>NA</td>
</tr>
<tr>
<td>Gupta et al, 2010&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Health ABC Composition HF risk score</td>
<td>Dallas Heart study</td>
<td>Caucasians and Blacks</td>
<td>Prospective cohort</td>
<td>2,540</td>
<td>30 to 65</td>
<td>stage B HF-BSA, - 0.73 stage B HF-FFM- 0.75 stage B HF-height - 0.64</td>
<td>NR</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Agarwal et al, 2012&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Framingham-published score</td>
<td>ARIC cohort / USA</td>
<td>Mixed</td>
<td>Prospective cohort</td>
<td>12,038</td>
<td></td>
<td></td>
<td>0.610</td>
<td>NR</td>
<td>NA</td>
</tr>
<tr>
<td>Agarwal et al, 2012&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Framingham-recalibrated score</td>
<td>ARIC cohort / USA</td>
<td>Mixed</td>
<td>Prospective cohort</td>
<td>4298 for NHANES and 21, 221 for ARIC/CHS</td>
<td>5 (ARIC/CHS cohort)</td>
<td></td>
<td>0.762</td>
<td>NR</td>
<td>NA</td>
</tr>
<tr>
<td>Agarwal et al 2012&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Health ABC HF recalibrated score</td>
<td>ARIC cohort / USA</td>
<td>Mixed/ Mainly Caucasian</td>
<td>Prospective cohort</td>
<td>2145 for ENRICHD and 3640 for VISP</td>
<td>NA</td>
<td></td>
<td>0.783</td>
<td>NR</td>
<td>NA</td>
</tr>
<tr>
<td>Agarwal et al 2012&lt;sup&gt;20&lt;/sup&gt;</td>
<td>ARIC risk score validation 1</td>
<td>ARIC cohort / USA</td>
<td>Mixed/ Mainly Caucasian</td>
<td>Prospective cohort</td>
<td>5168</td>
<td></td>
<td></td>
<td>0.785</td>
<td>NR</td>
<td>NA</td>
</tr>
<tr>
<td>Agarwal et al 2012&lt;sup&gt;20&lt;/sup&gt;</td>
<td>ARIC risk score validation 2</td>
<td>ARIC cohort / USA</td>
<td>Mixed/ Mainly Caucasian</td>
<td>Prospective cohort</td>
<td>5168</td>
<td></td>
<td>Mean: 51.2 (SD10.5)</td>
<td>0.797</td>
<td>NR</td>
<td>NA</td>
</tr>
<tr>
<td>Study</td>
<td>Risk Score</td>
<td>British Heart Regional Study</td>
<td>Mainly Caucasian</td>
<td>Prospective cohort</td>
<td>N</td>
<td>40-59</td>
<td>11</td>
<td>0.706</td>
<td>NR</td>
<td>-</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>------------</td>
<td>-------------------------------</td>
<td>------------------</td>
<td>--------------------</td>
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<td>-------</td>
<td>----</td>
<td>---</td>
</tr>
</tbody>
</table>

Figure Legend

Figure. Study selection process
Flowchart showing literature search strategy and selection process for inclusion of studies in the systematic review.
1067 MEDLINE Citations identified through PubMed and 12314 identified through EMBASE

4550 duplicates excluded

8831 titles examined

8418 citations excluded on the basis of title

413 abstracts closely examined

365 Articles excluded:
- 220 studies of causal associations
- 109 studies focusing on the predictive value of a single marker, not on a combination of risk factors

48 full-text articles read

35 articles excluded:
- 25 did not report a risk prediction equation or score

13 Articles reporting on 28 heart failure prediction models studies included
Population Risk Prediction Models for Incident Heart Failure: A Systematic Review
Justin B. Echouffo-Tcheugui, Stephen J. Greene, Lampros Papadimitriou, Faiez Zannad, Clyde W. Yancy, Mihai Gheorghiade and Javed Butler

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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/early/2015/03/03/CIRCHEARTFAILURE.114.001896

Data Supplement (unedited) at:
http://circheartfailure.ahajournals.org/content/suppl/2015/03/03/CIRCHEARTFAILURE.114.001896.DC1
http://circheartfailure.ahajournals.org/content/suppl/2016/12/26/CIRCHEARTFAILURE.114.001896.DC2

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## Supplemental Material

### Supplemental Table. Reporting and management of missing data

<table>
<thead>
<tr>
<th>Author, Reference</th>
<th>Name of the risk score</th>
<th>Outcome(s)</th>
<th>Variables included in risk models</th>
<th>Missing data</th>
<th>Management of missing data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kannel et al, 1999&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Framingham Heart Study failure risk score</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Value carried forward from previous examinations</td>
</tr>
<tr>
<td>Butler et al, 2008&lt;sup&gt;2&lt;/sup&gt;</td>
<td>The Health ABC (Aging, and Body Composition) Heart Failure Score</td>
<td>Reported</td>
<td>82 had missing data on HF status at baseline; these participants were excluded</td>
<td>Reported</td>
<td>Participants were excluded</td>
</tr>
<tr>
<td>Goyal et al, 2010&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Kaiser Permanente Georgia risk score</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Velagaleti et al, 2010&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Framingham Heart Study Risk score 2</td>
<td>Reported</td>
<td>Participants were excluded</td>
<td>Reported</td>
<td>Participants were excluded</td>
</tr>
<tr>
<td>deFilippi, et al, 2010&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Cardiovascular Health Study score 1</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Smith et al, 2010&lt;sup&gt;5&lt;/sup&gt;</td>
<td>The Malmö Diet and Cancer Study (MDCS) risk score 6</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Kalogeropoulos et al, 2010&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Health ABC (Aging, and Body Composition) Study score 3</td>
<td>Reported</td>
<td>Missing values of covariates were imputed using the multiple imputation by chained equations procedure</td>
<td>Reported</td>
<td>Participants excluded</td>
</tr>
<tr>
<td>Pfister et al, 2013&lt;sup&gt;8&lt;/sup&gt;</td>
<td>PRoactive trial score</td>
<td>NR</td>
<td>Participants excluded</td>
<td>NR</td>
<td>Participants excluded</td>
</tr>
<tr>
<td>Kalogeropoulos et al, 2012&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Cardiovascular Health Study</td>
<td>NR</td>
<td>Patients were excluded from the study</td>
<td>NR</td>
<td>Patients were excluded from the study</td>
</tr>
<tr>
<td>Authors</td>
<td>Study Description</td>
<td>Exclusion Status</td>
<td>Exclusion Status</td>
<td></td>
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</tr>
<tr>
<td>--------------------------</td>
<td>------------------------------------------------------------------------------------</td>
<td>------------------</td>
<td>------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang et al, 2012&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Framingham Heart Study</td>
<td>Reported</td>
<td>Patients were excluded from the study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agarwal et al, 2012&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Atherosclerosis Risk in Communities (ARIC) Study cohort</td>
<td>NR</td>
<td>Patients were excluded from the study</td>
<td></td>
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</tr>
<tr>
<td>Schnabel et al, 2012&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Framingham Heart Study.</td>
<td>NR</td>
<td>Patients were excluded from the study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wong et al, 2013&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research Study (NAVIGATOR) British Heart Regional Study</td>
<td>NR</td>
<td>Patients were excluded from the study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wannamethe et al, 2014&lt;sup&gt;14&lt;/sup&gt;</td>
<td></td>
<td>NR</td>
<td>Patients were excluded from the study</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NR: Not reported
## Appendix A: Search terms

**Database: PubMed (January 1990 until August 2014)**

<table>
<thead>
<tr>
<th>Search Term 1</th>
<th>Search Term 2</th>
<th>Search Term 3</th>
<th>Search Term 4</th>
<th>Search Term 5</th>
<th>Search Term 6</th>
<th>Search Term 7</th>
<th>Limits: age&gt;19 years, English language</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1 &quot;heart failure&quot; OR &quot;congestive heart failure&quot; OR &quot;cardiac insufficiency&quot; OR &quot;cardiac failure&quot;</td>
<td>#2 &quot;decompensation&quot; OR &quot;progression&quot;</td>
<td>#3 #1 NOT #2</td>
<td>#4 (validat* OR predict*[tiab] OR rule*) OR (predict* AND (outcome* OR risk* OR model*)) OR ((history OR variable* OR criteria OR scor* OR characteristic* OR finding* OR factor*) AND (predict* OR model* OR decision* OR identif* OR prognos*)) OR (decision* AND (model* OR clinical* OR logistic models)) OR (prognostic AND (history OR variable* OR criteria OR scor* OR characteristic* OR finding* OR factor* OR model*)) OR &quot;stratification&quot; OR &quot;ROC Curve&quot;[MeSH] OR &quot;discrimination&quot; OR &quot;discriminate&quot; OR &quot;c statistic&quot; OR &quot;area under the curve&quot; OR &quot;Calibration&quot; OR &quot;Indices&quot; OR &quot;algorithm&quot; OR &quot;Multivariable&quot;)</td>
<td>#5 &quot;cohort&quot; OR &quot;observational&quot; OR &quot;prospective&quot; OR &quot;trial&quot; OR &quot;epidemiology&quot;</td>
<td>#6 #3 AND #4 AND #5</td>
<td>#7 (Animals[MeSH] NOT Humans[MeSH])</td>
<td>#8 #6 NOT #7</td>
</tr>
</tbody>
</table>

**Database: EMBASE (January 1990 until August 2014)**
#1 "heart failure " OR "congestive heart failure" OR "cardiac insufficiency" OR "cardiac failure"
#2 "decompensation" OR "progression"
#3  #1 NOT #2
#4 (validat* OR predict* OR rule*) OR (predict* AND (outcome* OR risk* OR model*)) OR ((history OR variable* OR criteria OR scor* OR characteristic* OR finding* OR factor*) AND (predict* OR model* OR decision* OR identif* OR prognos*)) OR (decision* AND (model* OR clinical* OR logistic models)) OR (prognostic AND (history OR variable* OR criteria OR scor* OR characteristic* OR finding* OR factor* OR model*)) OR ("stratification" OR "ROC Curve" OR "discrimination" OR "discriminate" OR "c statistic" OR "area under the curve" OR "Calibration" OR "Indices" OR "algorithm" OR "Multivariable")
#5 “cohort analysis” OR “observational study” OR “prospective study” OR “clinical trial” OR “randomized controlled trial” OR “epidemiology”
#6 #3 AND #4 AND #5 AND #6 AND ([adult]/lim OR [aged]/lim) AND [humans]/lim AND [english]/lim AND [1-1-1990]/sd NOT [23-8-2014]/sd
Appendix B – Search terms for impact studies

Search terms used to identify all impact studies, which are combined with each specific risk scores acronym, or if not applicable the name of the cohort in which the score was developed or first author:


EMBASE: (Effectiveness:ti,ab OR Comparing:ti,ab OR Compared:ti,ab OR Evaluate:ti,ab) AND (Algorithm:ti,ab OR Strategy:ti,ab OR Managed:ti,ab OR Management:ti,ab OR Decision:ti,ab) AND (heart failure " OR "congestive heart failure" OR "cardiac insufficiency" OR "cardiac failure") AND [humans]/lim AND [1-1-1990]/sd NOT [8-23-2014]/sd
Supplemental References


일반인에서의 심부전 발생 위험 예측 모델
A Systematic Review

유 병수 교수 · 원주세브란스 기독병원 심장내과

초록
배경
고위험군 환자들을 효율적으로 선별하여, 적절하면서도 비용 효율이 높은(cost-effective) 예방적 조치를 시행한다면, 심부전의 유병률을 낮출 수 있을 것이다.

방법 및 결과
연구진은 발표된 심부전 위험 예측 모델들의 특성을 평가하기 위해, 2014년 8월 현재의 MEDLINE과 EMBASE 데이터베이스를 이용하여 체계적인 문헌 검색과 검토를 수행하였다. 연구에 적합한 논문들은 예측 모델의 개발, 적합성, 영향 평가 등을 보고하였다. 연구진은 적합성과 영향 분석뿐만 아니라, 데이터를 추출하기 위해 연구의 설계 및 특성, 위험 예측인자, 식별, 계측, 재분류 능력 등을 독립적으로 검토하였다. 최종적으로 28가지의 심부전 예측 모델에 대해 언급한 13개의 발표 연구가 포함되었는데, 모델들은 용인될 만큼 좋은(acceptable-to-good) 식별력을 갖추고 있었다(c-statistics, >0.70). 그리고 계측은 흔하지 않게 평가되었다. 모델들은 용인할 만큼 좋은(acceptable-to-good) 식별력을 갖추고 있었다(c-statistics, >0.70). 그리고 계측은 흔하지 않게 평가되어도, 용인할 만큼은 되었다. 2개의 모델만이 외부에서 한 번 이상 검증되었으며, 적당하게 용인할 만한(modest-to-acceptable) 식별력을 보여주었다(c-statistics, 0.61-0.79).

평가가 진행되는 동안, 새로운 혈액 및 영상 표지자들은 경미하게 위험 예측을 개선시켰다. 한 개의 모델이 인종을 기초로 하위 그룹에서 예측 특성을 평가한 반면, 두 개의 모델은 성별을 기초로 하위 그룹에서 예측 특성을 평가하였다. 영향 분석에서는 어떠한 모델도 임상 진료지침에서의 사용이 추천되지 않을음을 확인하였다.

결론
심부전 위험의 예측은 초기 단계에 머물러 있다. 현존 모델의 예측 능력은 주어진 자료에서는 효과적이었으나, 타집단을 대상으로는 검증되지 않았다. 또한, 어떤 모델이 비용 효율적이 고 일반 검진에 필요한지는 명확하지 않다. 모델들의 임상적, 예방적 조치에 대한 효과는 앞으로 추가적인 연구가 필요하다.