Predicting new-onset HF in patients undergoing coronary or peripheral angiography: results from the Catheter Sampled Blood Archive in Cardiovascular Diseases (CASABLANCA) study

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Abstract

Aims Methods to identify patients at risk for incident HF would be welcome as such patients might benefit from earlier interventions.

Methods and results From a registry of 1251 patients referred for coronary and/or peripheral angiography, we sought to identify independent predictors of incident HF during follow-up and develop a clinical and biomarker strategy to predict this outcome. There were 991 patients free of prevalent HF at baseline. Cox proportional hazard models were developed to predict adjudicated diagnosis of incident HF. Model discrimination and reclassification were evaluated. At follow-up, 177 (18%) developed new-onset HF. Independent predictors of new-onset HF included five clinical variables (age, male sex, heart rate, history of atrial fibrillation/flutter, and history of hypertension) and two biomarkers (amino-terminal pro-B type natriuretic peptide and ST2). The c-statistic for the model without biomarkers was 0.69; including biomarkers increased the c-statistic to 0.76 (P < 0.001). A score was developed from the model. Patients in the highest score quintile had shortest time to incident HF compared with lower quintiles (log-rank P < 0.001). Following 100 bootstrap iterations, internal validation was confirmed with Harrell’s c-statistic of 0.77. Use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta-blockers at enrollment was associated with substantial attenuation of predictive value of the risk score.

Conclusions Patients undergoing coronary/peripheral angiographic procedures are a population at high risk for incident HF. We describe an accurate clinical and biomarker strategy for predicting incident HF and possibly intervening in such patients (NCT00842868).

Keywords HF; Biomarker; Diagnosis; Score

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Introduction

HF is a complex disease process growing in prevalence, despite ongoing efforts to curb its expansion. This rise in HF is partially attributable to an aging population, improved care of other forms of acute heart disease, and increasing prevalence of risk factors that contribute to the development of HF.¹ Despite advancements in treatment of those with established HF, the impact of the diagnosis has continued to increase with unacceptably high morbidity, mortality, and cost.²–⁴ It is clear that a change in the approach to HF management is needed. One such change might be attempts to better predict the onset of the diagnosis, with an eye towards therapeutic interventions to reduce its incidence. Indeed, in
comparison with efforts towards treating symptomatic forms of HF, prevention of the diagnosis in at-risk patients remains largely under-explored.

The American College of Cardiology and the American Heart Association identify two groups of patients without symptomatic HF but at risk for progression to symptoms;\textsuperscript{5} such patients with so-called Stage A or B HF (at-risk and asymptomatic structural heart disease, respectively) appear to benefit from risk factor modification to prevent progression to overt HF. However, the number of patients in these stages of HF is massive, with broad heterogeneity in terms of absolute risk for HF onset. Accordingly, researchers have sought to develop tools to better refine the ability to predict new-onset HF in at-risk subjects;\textsuperscript{6,7} however, drawbacks to these models include potential lack of portability and limitation in variables incorporated, including concentrations of cardiac biomarkers such as amino-terminal pro-B type natriuretic peptide (NT-proBNP); incorporating such markers may also allow for greater parsimony of included variables.\textsuperscript{8}

As well, feasibility of general population screening with these tools remains uncertain. Thus, identifying patient populations at highest risk for incident HF in whom targeted therapeutic intervention would be expected to reduce such risk would be welcome.

In contrast to challenges in screening general populations for risk of incident HF, it may be possible to identify patient groups at particularly high risk for incident HF. Horne and colleagues described value of a risk score for predicting incident HF in patients undergoing coronary angiography;\textsuperscript{9} however, this score lacked specific cardiac biomarkers. Subsequently, Kleber and colleagues demonstrated that von Willebrand factor and NT-proBNP improved risk prediction in patients with HF with preserved ejection fraction undergoing coronary angiography.\textsuperscript{10} Similarly, Koller and colleagues found C-reactive protein to be an independent predictor of mortality in patients with HF with preserved ejection fraction undergoing coronary angiography.\textsuperscript{11} Accordingly, in the present post hoc analysis, we sought to identify clinical and biomarker predictors of new-onset HF in patients undergoing coronary and/or peripheral angiography enrolled in the Catheter Sampled Blood Archive in Cardiovascular Diseases (CASABLANCA; clinical trials.gov NCT00842868) study.\textsuperscript{12} We hypothesized that the combination of clinical and circulating plasma biomarkers would provide accuracy of predicting new-onset HF and therapeutic interventions might be useful to reduce such risk.

**Methods**

All study procedures were approved by the Partners Healthcare Institutional Review Board and carried out in accordance with the Declaration of Helsinki.

**Study design and participants**

The design of the CASABLANCA study has been described previously.\textsuperscript{12} Briefly, 1251 patients undergoing coronary and/or peripheral angiography with or without intervention between 2008 and 2011 were prospectively enrolled at the Massachusetts General Hospital in Boston, MA. Patients were referred for angiography for various acute and non-acute indications including acute coronary syndromes, HF, abnormal stress tests, stable chest pain, claudication, and routine pre-operative evaluation. Of the 1251 patients enrolled, 991 patients were free of prevalent HF as identified by the combination of past medical history and hospital records taken at the time of study enrolment. Prevalent HF was identified on the basis of self-report, and/or clinician identified diagnosis using standard diagnostic criteria as outlined in HF management guidelines.\textsuperscript{13}

**Data acquisition**

After informed consent was obtained, detailed clinical and historical variables and reason for referral for coronary and/or peripheral angiography were recorded using a standardized case report form at the time of the angiographic procedure.

**Follow-up**

Medical record review from time of enrolment to end of follow-up was performed. Median follow-up was 3.8 years with a maximum follow-up of 8 years. For identification of clinical endpoints, review of medical records as well as phone follow-up with patients and/or managing physicians was performed. The Social Security Death Index and/or postings of death announcements were used to confirm vital status. A detailed definition of endpoints for CASABLANCA was previously published.\textsuperscript{12} Specific to this analysis, new-onset HF was defined as signs and symptoms of HF in a patient without a previous diagnosis of chronic HF and at least one of the following: (i) initiation or increase in dosage of diuretic or (ii) radiographic evidence for pulmonary congestion or (iii) structural heart disease with documentation of left ventricular ejection fraction $<40\%$ or (iv) diastolic dysfunction or (v) BNP $\geq 400$ pg/mL or NT-proBNP according to age $<50$ years, $\geq 500$ pg/mL; 50–75 years, $\geq 900$ pg/mL; $>75$ years, $\geq 1800$ pg/mL.\textsuperscript{14} For any recurring events, each discrete event was recorded.

**Biomarker testing**

A total of 15 mL of blood was obtained immediately before the angiographic procedure through a centrally placed vascular access sheath. The blood was immediately centrifuged for 15 min, serum and plasma aliquoted on ice, and frozen at
−80 °C until biomarker measurement. The samples for this study were analysed after the first freeze–thaw cycle for baseline biomarker values only. Testing for NT-proBNP was performed on an automated platform (Dimension VISTA; coefficient of variation = 1.7% at 120 ng/L, 1.1% at 438 ng/L, 1.8% at 5075 ng/L; limit of detection, 0.8 ng/L), while ST2 was measured using a research assay (Presage ST2, Critical Diagnostics, San Diego, CA, USA) on an automated enzyme-linked immunosorbent assay platform. This assay has a coefficient of variation of 2.0%, with values <35 pg/mL considered normal.15

**Statistical analysis**

The CASABLANCA patients selected for this analysis consisted of 991 patients free of prevalent HF at baseline assessment. These patients were referred for coronary and/or peripheral angiography for various acute and non-acute indications. Baseline characteristics between those with and without new-onset HF were compared; dichotomous variables were compared using χ² or Fisher’s exact test, while continuous variables were compared using Kruskal–Wallis test.

We first used Cox proportional hazards model to assess the relationship between each individual predictor and adjudicated diagnosis of new-onset HF from a list of pre-selected covariates. We then included the covariates significant at α level of 0.10 into stepwise Cox proportional hazard models (using α level of 0.10 for both entry and retain) to develop a prediction model. Model discrimination and reclassification (categorical net reclassification improvement and integrated discrimination improvement) with and without biomarkers were evaluated. The final model included heart rate, history of atrial fibrillation/flutter, history of hypertension, and NT-proBNP and ST2 concentrations; age and sex were forced into the model. We then used the final model to develop a risk score for the new-onset HF.16 NT-proBNP was log-transformed for the Cox model but dichotomized at 1000 pg/mL for the HF risk score; ST2 was dichotomized at 35 ng/mL. Age and heart rate were considered in deciles in the scoring system.

Cox proportional hazard models were used to predict the risk of new-onset HF as a function of the HF risk score divided into quintiles. Patients who did not experience an event were censored at the time of last contact or at the time of death. Comparison between time-to-event curves was made using the log-rank test.

Cox models by the quintile of HF risk score was stratified by guideline-directed medical therapy (GDMT) including angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), and beta-blocker. The number of patients on aldosterone antagonists was small, and therefore, we were unable to run the model stratified by treatment with aldosterone antagonists.

For the purpose of internal validation, the observed vs. predicted risk deciles for the HF risk model was tested using the Hosmer–Lemeshow χ² test. Additionally, bootstrapping was used to internally validate the performance of the HF risk model.17

In all statistical analyses, a two-tailed P value of <0.05 was considered statistically significant. All analyses were performed using the SAS Version 9.4.

**Results**

A study flow for the present analysis is detailed in Figure 1. Following the removal of patients with prevalent HF at the time of enrolment, the study sample was 991 patients. Of these, 177 (17.9%) developed new-onset HF following enrolment.

**Baseline characteristics**

Baseline characteristics as a function of patients who developed incident HF and those who did not are detailed in Table 1. Patients with new-onset HF not surprisingly had prevalent risk factors for the diagnosis; they were more likely to be older and to have a history of arrhythmia, hypertension, coronary artery disease, diabetes mellitus, and chronic kidney disease.
Table 1 Baseline characteristics dichotomized by development of new-onset HF during follow-up

| Characteristics                                      | Subjects with new-onset HF (N = 177) | Subjects without HF (N = 814) | P-value |
|------------------------------------------------------|--------------------------------------|-------------------------------|---------|
| **Demographic**                                      |                                      |                               |         |
| Age—mean ± SD                                        | 69.9 ± 11.9                          | 65.3 ± 11.2                   | <0.001  |
| Male sex                                             | 74.6% (132)                          | 69.8% (568)                   | 0.20    |
| Caucasian                                            | 91.5% (162)                          | 93.2% (759)                   | 0.44    |
| **Vital signs**                                      |                                      |                               |         |
| Heart rate (beats per min)                           | 71.1 ± 14.5 (173)                    | 67.8 ± 12.7 (786)             | 0.006   |
| Systolic blood pressure (mmHg)                       | 140.7 ± 23.4 (174)                   | 138.2 ± 22.6 (792)            | 0.19    |
| Diastolic blood pressure (mmHg)                      | 73.3 ± 12.2 (174)                    | 72.8 ± 11.3 (792)             | 0.58    |
| **Medical history**                                  |                                      |                               |         |
| Smoker                                               | 14.8% (26/176)                       | 15.7% (126/805)               | 0.77    |
| Atrial fibrillation/flutter                           | 24.3% (43)                           | 10.1% (82)                    | <0.001  |
| Hypertension                                         | 86.4% (153)                          | 72.5% (590)                   | <0.001  |
| Coronary artery disease                              | 58.2% (103)                          | 48.2% (392)                   | 0.02    |
| Prior myocardial infarction                          | 24.3% (43)                           | 18.8% (153)                   | 0.10    |
| Peripheral artery disease                            | 36.2% (64)                           | 22.7% (185)                   | <0.001  |
| COPD                                                 | 25.6% (45/176)                       | 14.1% (115)                   | <0.001  |
| Diabetes type I/type II                              | 37.3% (66)                           | 22.6% (184)                   | <0.001  |
| CVA/TIA                                              | 15.3% (27)                           | 9.2% (75)                     | 0.02    |
| CKD                                                  | 22.6% (40)                           | 8.0% (65)                     | <0.001  |
| Renal replacement therapy                            | 7.3% (13)                            | 1.9% (15)                     | <0.001  |
| Prior angioplasty                                     | 17.5% (31)                           | 11.8% (96)                    | 0.04    |
| Prior stent                                           | 36.2% (64)                           | 30.2% (246)                   | 0.12    |
| Prior CABG                                            | 28.3% (50)                           | 17.9% (146)                   | 0.002   |
| **Medications**                                      |                                      |                               |         |
| ACEi/ARB                                             | 60.8% (107/176)                      | 49.6% (402/811)               | 0.007   |
| Beta-blocker                                         | 76.3% (135)                          | 66.9% (543/811)               | 0.02    |
| Aldosterone antagonist                               | 3.9% (7)                             | 3.1% (25/811)                 | 0.55    |
| Loop diuretics                                       | 24.9% (44)                           | 8.3% (67/811)                 | <0.001  |
| Nitrates                                             | 24.9% (44)                           | 17.4% (141/810)               | 0.02    |
| CCB                                                  | 37.9% (67)                           | 23.8% (193/811)               | <0.001  |
| Statin                                               | 76.3% (135)                          | 72.5% (587/810)               | 0.30    |
| Aspirin                                              | 78.0% (138)                          | 80.3% (651/811)               | 0.49    |
| Warfarin                                             | 15.9% (28/176)                       | 8.1% (66/811)                 | 0.001   |
| Clopidogrel                                          | 21.6% (38/176)                       | 25.4% (206/811)               | 0.29    |
| **Cardiac tests**                                    |                                      |                               |         |
| LVEF (%)                                              | 56.8 ± 14.2 (107)                    | 61.2 ± 11.7 (309)             | 0.005   |
| Stress test—mean ± SD                               | 56.4 ± 11.7 (33)                     | 59.9 ± 12.0 (195)             | 0.12    |
| RVSP by echo (mmHg)—mean ± SD                        | 43.0 ± 12.3 (68)                     | 38.4 ± 10.2 (150)             | 0.004   |
| Mitral regurgitation                                 | <0.001                               |                               |         |
| Trace                                                | 33.8% (24/71)                        | 54.5% (110/202)               |         |
| Mild                                                 | 42.3% (30/71)                        | 28.2% (57/202)                |         |
| Moderate                                             | 19.7% (14/71)                        | 6.9% (14/202)                 |         |
| Severe                                               | 1.4% (1/71)                          | 2.5% (5/202)                  |         |
| Aortic insufficiency                                 | 0.07                                 |                               |         |
| Trace                                                | 49.3% (34/69)                        | 41.5% (78/188)                |         |
| Mild                                                 | 13.0% (9/69)                         | 7.5% (14/188)                 |         |
| Moderate                                             | 2.9% (2/69)                          | 1.6% (3/188)                  |         |
| Severe                                               | 1.5% (1/69)                          | 0.0% (0/188)                  |         |
| Aortic valve area <1.0 cm                            | 25.0% (11/44)                        | 25.2% (27/107)                | 0.98    |
| Tricuspid regurgitation                               | <0.001                               |                               |         |
| Trace                                                | 72.2% (52/72)                        | 83.4% (161/193)               |         |
| Mild                                                 | 25.0% (18/72)                        | 8.3% (16/193)                 |         |
| Moderate                                             | 2.8% (2/72)                          | 1.0% (2/193)                  |         |
| **Angiography results**                              |                                      |                               |         |
| ≥30% coronary stenosis ≥2 vessels                    | 67.8% (101/149)                      | 59.1% (424/717)               | 0.05    |
| ≥30% coronary stenosis ≥3 vessels                    | 50.7% (85/149)                       | 41.7% (259/717)               | <0.001  |
| ≥50% coronary stenosis ≥2 vessels                    | 57.7% (86/149)                       | 46.9% (336/717)               | 0.02    |
| ≥60% coronary stenosis ≥3 vessels                    | 41.6% (62/149)                       | 25.9% (186/717)               | <0.001  |
| ≥70% coronary stenosis ≥2 vessels                    | 47.6% (71/149)                       | 34.0% (244/717)               | 0.002   |
| ≥70% coronary stenosis ≥3 vessels                    | 24.8% (37/149)                       | 15.8% (113/717)               | 0.008   |
| **Lab measures**                                     |                                      |                               | <0.001  |
| Creatinine (mg/dL)—mean ± SD (N)                     | 1.7 ± 1.7 (158)                      | 1.2 ± 0.7 (675)               |         |

(Continues)
disease (CKD). Patients who developed new-onset HF were more likely to be taking GDMT for HF, including ACEi/ARB, beta-blocker, and loop diuretic, compared with those who did not develop HF. The indications for diagnostic coronary angiography were similar between both groups; however, more patients who developed new-onset HF had a primary indication of shortness of breath for coronary angiography, and more patients who had a primary indication of an abnormal stress test for coronary angiography did not go on to develop new-onset HF (Table 1).

Among those with echocardiographic data at presentation, those with new-onset HF were more likely to have a lower left ventricular ejection fraction when assessed by echocardiography (56.8 ± 14.2% vs. 61.2 ± 11.7%, P = 0.005). Baseline aortic valve disease was similar in the two groups, Presence of mitral and tricuspid valve disease did not consistently predict development of new-onset HF (Table 1). Baseline blood pressure was not different between the two groups, but those who developed new-onset HF had a higher baseline heart rate (71.1 ± 14.5 vs. 67.8 ± 12.7, P = 0.006). Those with new-onset HF were also more likely to have an elevated right ventricular systolic pressure compared with those without HF (43.0 ± 12.3 mmHg vs. 38.4 ± 10.2 mmHg, P = 0.004). Additionally, they had worse renal function compared with those without HF. Multiple prognostic biomarkers were abnormal at baseline in those with new-onset HF, including higher concentrations of highly sensitive troponin I, NT-proBNP, cystatin C, myeloperoxidase, and ST2.

### Predicting incident HF

Starting with 16 variables in univariate analyses, we then performed multivariable modelling to identify independent predictors of incident HF. These included clinical variables (heart rate, history of atrial fibrillation/flutter, and history of hypertension) and concentrations of two biomarkers (NT-proBNP and ST2). Age and sex were forced into the final multivariable HF risk prediction model (Table 2). In development of the HF risk score, age and heart rate were considered in deciles and weighed accordingly; NT-proBNP was dichotomized at 1000 pg/mL18 and ST2 was dichotomized at 35 ng/mL19 (Table 3).

The c-statistic for the HF risk score model without biomarkers was 0.69; including biomarkers significantly increased the c-statistic to 0.76 (P < 0.0001). Biomarkers also significantly reclassified risk for new-onset HF beyond clinical

| Variables | Hazard ratio (95% CI) | P-value |
|-----------|-----------------------|---------|
| Age       | 1.01 (1.00, 1.03)     | 0.11    |
| Sex       | 1.79 (1.20, 2.68)     | 0.005   |
| Heart rate| 1.01 (1.00, 1.03)     | 0.045   |
| History of atrial fibrillation/flutter | 1.59 (1.06, 2.37) | 0.02 |
| History of hypertension | 1.77 (1.09, 2.85) | 0.02 |
| Log-transformed NT-proBNP | 1.55 (1.39, 1.73) | <0.0001 |
| ST2 ≥ 35 ng/mL | 1.46 (1.01, 2.13) | 0.046 |

Cl, confidence interval; NT-proBNP, N-terminal pro B-type natriuretic peptide.

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**Table 1** Characteristics (continued)

| Characteristics | Subjects with new-onset HF (N = 177) | Subjects without HF (N = 814) | P-value |
|-----------------|-------------------------------------|-------------------------------|---------|
| CKD-EPI eGFR—mean ± SD (N) | 75.7 ± 30.2 (173) | 96.2 ± 25.5 (802) | <0.001 |
| Haemoglobin (g/dL)—median (Q1, Q3) | 12.8 (11.5, 14.1) | 13.4 (12.3, 14.5) | <0.001 |

Baseline biomarkers

- MPO (pmol/L)—median (Q1, Q3) | 459.3 (334.2, 640.0) | 405.1 (309.3, 580.1) | 0.01 |
- hsTnI (pg/mL)—median (Q1, Q3) | 11.7 (5.6, 40.8) | 5.7 (2.9, 18.2) | <0.001 |
- NT-ProBNP (pg/mL)—median (Q1, Q3) | 955.0 (299.0, 2514.0) | 199.0 (79.0, 560.0) | <0.001 |
- Cystatin C (mg/L)—median (Q1, Q3) | 1.0 (0.8, 1.2) | 0.8 (0.7, 0.9) | <0.001 |
- ST2 (ng/mL)—median (Q1, Q3) | 41.5 (31.1, 58.1) | 34.9 (26.8, 46.4) | <0.0001 |

Indications for catheter: presenting symptoms

- Shortness of breath | 32.2% (57/177) | 15.4% (125/814) | <0.001 |
- AMI | 6.2% (11/177) | 8.7% (71/814) | 0.27 |
- UAP | 8.5% (15/177) | 12.4% (101/814) | 0.14 |
- Symptoms with positive imaging/stress test | 31.07% (55/177) | 41.2% (335/814) | 0.01 |
- Chest pain without or with negative imaging | 15.3% (27/177) | 17.8% (145/814) | 0.42 |
- Arrhythmia evaluation | 6.2% (11/177) | 3.9% (32/812) | 0.18 |
- Transplant coronary evaluation | 0.6% (1/177) | 0.6% (5/814) | 0.94 |
- Claudication | 10.2% (18/177) | 8.7% (71/812) | 0.55 |
- Hypertension | 3.4% (6/177) | 2.6% (21/814) | 0.55 |
- Carotid stenosis with TIA/CVA | 0.6% (1/177) | 0.3% (2/814) | 0.48 |
- Carotid stenosis without TIA/CVA | 0.6% (1/177) | 1.1% (9/812) | 0.51 |
- Other PAD without claudication | 2.8% (5/177) | 2.7% (22/813) | 0.93 |
- Pre-operative evaluation | 10.2% (18/177) | 10.9% (89/814) | 0.77 |

ACEi, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CCb, calcium channel blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate; EPI, epidemiology; hsTnI, high sensitivity troponin I; LVEF, left ventricular ejection fraction; MPO, myeloperoxidase; NT-proBNP, N-terminal pro B-type natriuretic peptide; PAD, peripheral artery disease; RVSP, right ventricular systolic pressure; SD, standard deviation; TIA, transient ischaemic attack; UAP, unstable angina pectoris.

Patients developing incident HF showed numerous differences at baseline.
variables (net reclassification improvement 0.26; integrated discrimination improvement 0.10; both \( P < 0.0001 \)).

As shown in the Supporting Information, Table S1, we found direct association between risk for incident HF and higher risk scores. When the HF risk score was divided into quintiles, patients in the highest quintile had the highest incidence of development of new-onset HF compared with those with scores in lower quintiles (Figure 2).

Comparison of the observed vs. predicted risk deciles for the HF risk score model using Hosmer–Lemeshow testing indicates good model calibration \( (P = 0.12) \). We then internally validated the modelling using 100 bootstrap iterations, which yielded a Harrell’s c-statistic of 0.77.

### Guideline-directed medical therapy, risk scores, and incident HF

Cox models by the quintile of HF risk score were stratified by GDMT with ACEi/ARB and beta-blocker. Patients in the highest quintiles had the highest risk of development of new-onset HF, and those not taking an ACEi/ARB or a beta-blocker had a higher risk of developing new-onset HF compared with those taking an ACEi/ARB or a beta-blocker (Table 4). The number of patients on aldosterone antagonists was small, and therefore, we were unable to run the model stratified by aldosterone antagonists.

### Discussion

In the CASABLANCA study of patients without prevalent HF undergoing coronary and/or peripheral angiography for both acute and non-acute indications, we found a high risk for progression on to development of symptomatic HF with nearly 20% of those without prevalent HF developing the

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**Table 3 Components of the HF risk score**

| Variable                  | Category | Points |
|---------------------------|----------|--------|
| Age                       | 20–29    | −4     |
|                           | 30–39    | −3     |
|                           | 40–49    | −2     |
|                           | 50–59    | −1     |
|                           | 60–69a   | 0      |
|                           | 70–79    | 1      |
|                           | 80–89    | 2      |
|                           | 90–99    | 3      |
| Sex                       | Male     | 1      |
|                           | Femalea  | 0      |
| Heart rate                | 30–39    | −3     |
|                           | 40–49    | −2     |
|                           | 50–59    | −1     |
|                           | 60–69a   | 0      |
|                           | 70–79    | 0      |
|                           | 80–89    | 1      |
|                           | 90–99    | 2      |
|                           | 100–109  | 3      |
|                           | 110–119  | 4      |
|                           | 120–129  | 4      |
| History of atrial fibrillation | Yes | 3     |
|                           | Noa      | 0      |
| History of hypertension   | Yes      | 4      |
|                           | Noa      | 0      |
| NT-proBNP \( \geq 1000 \) pg/mL | Yes | 6     |
|                           | Noa      | 0      |
| ST2 \( \geq 35 \) ng/mL    | Yes      | 3      |
|                           | Noa      | 0      |

NT-proBNP, N-terminal pro B-type natriuretic peptide. Relative weight for each category is shown.

aReference category.

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**Figure 2** Time to first HF event based on quintiles of risk score. Patients in the highest score quintile had the shortest time to development of incident HF.
Table 4 Predicting new-onset HF as a function of quintiles of HF risk score stratified by guideline-directed medical therapies

A

| Quintiles of risk score | Hazard ratio (95% CI) Taking ACEi/ARB | P-value | Hazard ratio (95% CI) Not taking ACEi/ARB | P-value |
|-------------------------|----------------------------------------|---------|------------------------------------------|---------|
| Quintile 1               | Reference                               |         | Reference                                 |         |
| Quintile 2               | 0.62 (0.17, 2.30)                       | 0.47    | 2.31 (0.82, 6.49)                        | 0.11    |
| Quintile 3               | 2.58 (0.88, 7.54)                       | 0.08    | 2.51 (0.77, 8.23)                        | 0.13    |
| Quintile 4               | 2.32 (0.79, 6.80)                       | 0.12    | 3.50 (1.31, 9.33)                        | 0.01    |
| Quintile 5               | 7.24 (2.62, 20.04)                      | 0.0001  | 11.44 (4.75, 27.59)                      | <0.0001 |

B

| Quintiles of risk score | Taking beta-blocker Hazard ratio (95% CI) | P-value | Not taking beta-blocker Hazard ratio (95% CI) | P-value |
|-------------------------|-------------------------------------------|---------|-----------------------------------------------|---------|
| Quintile 1               | Reference                                 |         | Reference                                     |         |
| Quintile 2               | 1.05 (0.40, 2.77)                        | 0.91    | 2.20 (0.49, 9.81)                            | 0.30    |
| Quintile 3               | 2.77 (1.16, 6.59)                        | 0.02    | 4.08 (1.02, 16.30)                           | 0.05    |
| Quintile 4               | 2.52 (1.08, 5.87)                        | 0.03    | 5.33 (1.47, 19.36)                           | 0.01    |
| Quintile 5               | 7.52 (3.44, 16.40)                       | <0.0001 | 19.02 (5.52, 65.47)                          | <0.0001 |

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval.

It is a noteworthy hazard for incident HF was higher in those not taking (A) ACEi/ARB or (B) beta-blockers.

Adjudicated diagnosis within 4 years after index procedure. Following, we identified predictors of incident HF during this follow-up period; from this, we developed a novel scoring system to predict new-onset HF that consisted of a combination of clinical variables (age, sex, heart rate, history of atrial fibrillation/flutter, and history of hypertension) and concentrations of two pathophysiologically distinct and important biomarkers (NT-proBNP and ST2). Higher scores correlated with a higher risk of development of new-onset HF. Notably, those in the highest quintiles not prescribed GDMT with ACEi/ARB or beta-blocker at the time of assessment had a higher risk of development of new-onset HF compared with those taking these medications. While most studies of risk scores in disease processes are undermined by lack of actionable therapeutic information, this non-randomized observation suggests our risk model may not only identify risk for HF onset, but it may also predict benefit from aggressive application of therapies to reduce such risk.

Prior studies have shown value of combining clinical variables with biomarkers to more accurately discriminate risk for future HF. Agarwal and colleagues added NT-proBNP to a pre-existing 10 year new-onset HF risk prediction score in the Atherosclerosis Risk in Communities study, improving the performance of the score; a model restricted to age, sex, race, and NT-proBNP alone was comparable with scores with a greater number of variables. In a study by Brouwers and colleagues, 8569 patients without HF were categorized into high and low risk on the basis of cardiovascular history, and the prognostic value of 13 biomarkers reflecting diverse pathophysiologic pathways was evaluated; risk stratification increased the incremental value per biomarker to predict new-onset HF, especially in patients with HF with reduced ejection fraction. In another study by Wannamethee and colleagues of 3870 men aged 60–79 years not diagnosed with HF, NT-proBNP was associated with HF in those with and without established cardiovascular disease. Such findings illustrate that perhaps biomarkers would improve discrimination, calibration, and portability of new-onset HF risk prediction scores.

We found that concentrations of two biomarkers with a broad knowledge base in those with established HF (NT-proBNP and ST2) added considerably to clinical variables to predict incident HF. The importance of biomarkers in the diagnosis and prognostication of prevalent HF is widely recognized; however, the potential role of biomarkers to supplement clinical variables to predict onset of HF in those without prevalent HF is less widely accepted. Our data suggest in this particularly at-risk population that the combination of both NT-proBNP (a biomarker reflecting cardiomyocyte strain) and ST2 (a member of the interleukin-1 receptor family released under conditions of cardiovascular stress) adds independent prognostic value. The addition of biomarkers to clinical factors substantially improved model discrimination and reclassified risk for new-onset HF beyond clinical variables alone. Although both markers have been shown to predict HF events in those with established HF syndromes, their role in patients such as those in CASABLANCA is not as well determined. As well, several other relevant biomarkers were not predictive of incident HF, including highly sensitive troponin I, myeloperoxidase, and measures of renal function (cystatin C and estimated glomerular filtration rate). More patients who developed new-onset HF had CKD or were on renal replacement therapy at baseline (22.6% vs. 8.0% and 7.3% vs. 1.9%, P < 0.001 for both, respectively), and while underlying CKD is a well-known risk factor for the development of HF, not all patients with CKD developed new-onset HF. Furthermore, our HF score model was vigorously adjusted to account for underlying renal dysfunction, and while NT-proBNP concentrations may be affected by underlying CKD, data suggest that when elevated in patients with CKD, NT-proBNP is more (rather than less) prognostic.

A major advantage of our cohort is its detailed characterization and our experience working with this particular cohort of patients. Our score is also clinically relevant and easily...
applicable. Although in the development of this HF risk score our approach was methodical, limitations to our study exist. The CASABLANCA cohort was predominantly male, Caucasian, and representative of patients in a tertiary care referral centre. Data regarding pre-existing underlying diastolic dysfunction are lacking as are data regarding whether atrial fibrillation is persistent, both of which can predispose patients to development of HF. More patients who developed new-onset HF were on diuretics, and while there are several indications for use of loop diuretics other than HF, we, unfortunately, do not have data regarding the indication for treatment with loop diuretics. We concede that we possibly detected a forme fruste of HF in some patients.

We did not have an external cohort to validate our score, but internal validation testing returned consistent results; we presently have plans to externally validate this score in a distinct patient cohort. Additionally, because the patients in our study were referred for coronary and/or peripheral angiography, the pre-test probability for development of new-onset HF was higher than if a community-based cohort without indications for invasive angiography was studied; we do not feel this is a limitation, however, as such patients have a substantial risk for HF onset, the very patients where therapeutic intervention might be well expected to reduce hazard substantially, as we found. Lastly, while therapies appear to interact with our risk score—implying potential value from intervention in those at highest risk—we lack data regarding doses of GDMT applied, and we do not have serial measurement of clinical variables, medication therapy, or biomarkers to see if changes in treatment over time modify risk score results and/or influence subsequent predicted risk for HF onset.

Appropriate attention has been given to the identification and optimal management of patients at high risk for symptomatic HF (i.e. those with Stages A and B HF). Study participants in CASABLANCA indeed reflect such patients, and our data suggest the ability to accurately detect those at highest risk for onset of HF. This is of some interest, and such data might be useful to inform clinical trial design or even be applied as inclusion criteria in trials of therapies that might reduce HF risk. On a clinical utility level, however, as most risk scores do not have a therapeutic imperative, we felt it important to further explore how GDMT for HF might influence subsequent onset of HF in those judged at highest risk. In this, we found lower observed HF onset in those predicted as higher risk treated with GDMT. This finding is a substantial difference from many studies describing risk scores, which tend to lack guidance regarding how results might be used to optimize patient management. More data regarding interaction between our score and other HF GDMT options, including sacubitril/valsartan, are warranted.

In conclusion, we have developed a clinical and biomarker score to predict incident HF in an at-risk population. This strategy, using traditional variables available at the bedside together with biomarker concentrations, is likely to provide a cost-effective and widely available method to predict risk for incident HF in patients commonly treated in cardiovascular medicine. The potential to prevent HF onset through application of therapies triggered/guided by this score deserves further exploration.

Conflict of interest

H.K.G. has received grant support from Roche and Portola; consulting income from Roche Diagnostics, American Regent, Amgen, Boston Heart Diagnostics, and Critical Diagnostics; and research payments for clinical endpoint committees for EchoSense. J.L.J. has received grant support from Siemens, Singulex, and Prevencio and consulting income from Roche Diagnostics, Critical Diagnostics, Sphingotec, Philips, and Novartis and participates in clinical endpoint committees/data safety monitoring boards for Novartis, Amgen, Janssen, and Boehringer Ingelheim. Siemens Diagnostics, Inc., had no involvement in the present study design, collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. The remaining authors have nothing to disclose.

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Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article.

Table S1. Risk for development of new-onset HF increased as HF risk score increased.

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