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# The WAP Four-Disulfide Core Domain Protein HE4: A Novel Biomarker for Heart Failure

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**Objectives** This study investigated clinical determinants and added prognostic value of HE4 as a biomarker not previously described in heart failure (HF).

**Background** Identification of plasma biomarkers that help to risk stratify HF patients may help to improve treatment.

**Methods** Plasma HE4 levels were determined in 567 participants of the COACH (Coordinating study evaluating outcomes of Advising and Counseling in Heart failure). Patients had been hospitalized for HF and were followed for 18 months. The primary endpoint of this study was a composite of all-cause mortality and HF hospitalization.

**Results** HE4 showed a strong correlation with HF severity, according to New York Heart Association functional class and brain natriuretic peptide (BNP) levels ($p < 0.001$). HE4 also showed a positive correlation with GDF15 ($p < 0.001$) and, in addition, correlated with kidney function (estimated glomerular filtration rate [eGFR]; $p < 0.001$). Cox regression analysis revealed that a doubling of HE4 levels was associated with a hazard ratio (HR) of 1.73 (95% confidence interval [CI]: 1.53 to 1.95) for the primary outcome ($p < 0.001$). After correction for age, gender, BNP, and eGFR, the HR was 1.46 (95% CI: 1.23 to 1.72; $p < 0.001$), and after additional adjustment for GDF15, the HR lowered to 1.30 (95% CI: 1.07 to 1.59; $p = 0.009$). The area under the curve in the receiver-operating characteristic curve analysis increased from 0.727 to 0.752 when HE4 was included in the clinical evaluation ($p = 0.051$). The integrated discrimination improvement and net reclassification index for reclassification showed significant improvements when HE4 was added to the clinical model, and this remained significant after BNP inclusion in the model.

**Conclusions** HE4 plasma levels are correlated with markers of HF severity, show prognostic value, and can improve risk assessment in HF. (J Am Coll Cardiol HF 2013;1:164–9) © 2013 by the American College of Cardiology Foundation

Heart failure (HF) is the final common syndrome of most cardiovascular diseases, including myocardial infarction, hypertension, valvular disease, cardiomyopathy, and others. Once HF ensues, it is associated with high morbidity and mortality, especially because HF often is diagnosed after it has already progressed (1–3). The number of HF patients is estimated to be between 1% and 2% of the total population (2) and is expected to increase dramatically in the next decade because of the ageing population.

There is not a single diagnostic or prognostic test for HF, reflecting the heterogeneous background of HF. Prognosis is estimated using several key patient characteristics such as age, comorbidity, and severity of disease (New York Heart Association [NYHA] class, left ventricular ejection fraction [LVEF]). Natriuretic peptides have clearly enhanced management of patients with HF, and current guidelines mention brain natriuretic peptide (BNP), its precursor N-terminal pro-brain natriuretic peptide (NT-prBNP), and N-terminal pro-atrial natriuretic peptide (NT-proANP) as diagnostic biomarkers (2,3). With the increasing availability of therapeutic strategies and novel treatment modalities, decision making in the care of the patient, however, has become more difficult. The demand for patient-tailored therapeutic strategies requires a careful risk stratification of patients with HF and requires identification of new biomarkers that may fulfill these purposes.

A number of potential new biomarkers for HF have recently been described, including galectin-3, ST2, and GDF15 (4–7), but none has come into standard clinical

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use so far. This underscores the fact that despite impressive technical developments in genomics and proteomics, identification of useful biomarkers is still a daunting task. Plasma HE4 (also termed WFDC-2) is currently in use for monitoring recurrence of progression of epithelial ovarian cancer (8), but its biomarker potential has not been investigated in other diseases. During standard specificity testing, a strong correlation was observed between HE4 and severity of heart failure (NYHA functional class) (Alere Company, unpublished results, March 2012), which prompted the present investigation.

Here we aimed to evaluate whether or not HE4 could constitute a potential new HF biomarker. Plasma samples of the COACH (Coordinating study evaluating Outcomes of Advising and Counseling in Heart failure) trial were analyzed.

## Methods

**Study design and outcome parameters.** This is a substudy of the COACH trial. The design and outcomes of the COACH trial (NCT 98675639) have been published (9,10). Plasma (for determination of HE4 and of other biomarkers) was available from 567 patients during the index admission, and these patients formed the cohort for the present substudy. This study complies with the Declaration of Helsinki and local medical ethics committees approval, and all patients provided written informed consent. Detailed information and further methods can be found in the Online Methods section.

**Statistical analysis.** HE4 levels (ng/ml) were divided into quartiles (first quartile 0.7 to 3.5; second quartile 3.5 to 5.6; third quartile 5.6 to 10.1; fourth quartile 10.1 to 63.3). Baseline demographic values are mean ± SD or median (interquartile ranges [IQR]) when variables were non-normally distributed. Detailed statistical analysis is described in the Online Methods section.

**Abbreviations and Acronyms**

ACE = angiotensin-converting enzyme
ARB = angiotensin receptor blockers
AUC = area under the curve
BNP = brain natriuretic peptide
CRP = C-reactive protein
eGFR = estimated glomerular filtration rate
HF = heart failure
HR = hazard ratio
IDI = integrated discrimination improvement
IQR = interquartile range
LVEF = left ventricular ejection fraction
NRI = net reclassification index
NYHA = New York Heart Association
WFDC-2 = WAP four-disulfide core domain protein 2

## Results

**Study population.** Baseline characteristics of the 567 patients in this subanalysis (Table 1) were comparable to those of the total COACH cohort (n = 1,023; data not shown) (10). Mean age of the study population was 71 ± 11 years, and 62% of patients were male. Approximately one-half of the patients were NYHA class II, and the other half was class III, and 3% were class IV. LVEF was measured predominantly by echocardiography, and the mean LVEF was 33 ± 14%. Mean eGFR was 54 ml/min/1.73 $m^2$, median BNP value was 456

**Table 1** Baseline Parameters According to Plasma HE4 Levels

| Variable | Quartiles of HE4 (ng/ml) Quartile 1 (0.7–3.5) | Quartile 2 (3.5–5.6) | Quartile 3 (5.6–10.1) | Quartile 4 (10.1–63.3) | Overall Sample | p Value |
|---|---|---|---|---|---|---|
| N | 142 | 141 | 142 | 142 | 567 | |
| Age (yrs) | 66 ± 12 | 70 ± 11 | 74 ± 9 | 75 ± 9 | 71 ± 11 | <0.001 |
| Gender (% male) | 56 | 60 | 63 | 69 | 62 | 0.13 |
| NYHA functional class II/III/IV (%) | 66/32/2 | 51/48/1 | 40/54/6 | 30/65/5 | 47/50/3* | <0.001 |
| BMI (kg/$m^2$) | 28 ± 5 | 27 ± 5 | 27 ± 6 | 26 ± 5 | 27 ± 5† | 0.050 |
| LVEF (%) | 33 ± 14 | 33 ± 16 | 32 ± 13 | 34 ± 13 | 33 ± 14‡ | 0.82 |
| LVEF ≥40% | 35 | 31 | 28 | 30 | 31‡ | 0.70 |
| LVEF ≥55% | 10 | 13 | 9 | 11 | 11‡ | 0.75 |
| Medical history (%) | | | | | | |
| Hypertension | 39 | 39 | 44 | 47 | 42 | 0.46 |
| Myocardial infarction | 33 | 41 | 41 | 49 | 41 | 0.070 |
| Diabetes | 25 | 28 | 31 | 38 | 30 | 0.093 |
| Atrial fibrillation | 35 | 42 | 52 | 55 | 46 | 0.002 |
| COPD | 23 | 21 | 32 | 36 | 28 | 0.018 |
| CVA | 8 | 9 | 11 | 13 | 10 | 0.56 |
| Medication (%) | | | | | | |
| ACE inhibitors + ARB | 87 | 87 | 82 | 73 | 82 | 0.005 |
| Beta-blocker | 73 | 72 | 53 | 69 | 67 | 0.001 |
| Diuretics | 93 | 95 | 98 | 96 | 96 | 0.21 |

Values are n, mean ± SD, or %. *N = 564, †N = 539, ‡N = 515.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CVA = cardiovascular accident; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.