ORIGINAL RESEARCH

# Prohormones in the Early Diagnosis of Cardiac Syncope

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***Background*—**The early detection of cardiac syncope is challenging. We aimed to evaluate the diagnostic value of 4 novel prohormones, quantifying different neurohumoral pathways, possibly involved in the pathophysiological features of cardiac syncope: midregional–pro-A-type natriuretic peptide (MRproANP), C-terminal proendothelin 1, copeptin, and midregional-proadrenomedullin.

***Methods and Results*—**We prospectively enrolled unselected patients presenting with syncope to the emergency department (ED) in a diagnostic multicenter study. ED probability of cardiac syncope was quantified by the treating ED physician using a visual analogue scale. Prohormones were measured in a blinded manner. Two independent cardiologists adjudicated the final diagnosis on the basis of all clinical information, including 1-year follow-up. Among 689 patients, cardiac syncope was the adjudicated final diagnosis in 125 (18%). Plasma concentrations of MRproANP, C-terminal proendothelin 1, copeptin, and midregional-proadrenomedullin were all significantly higher in patients with cardiac syncope compared with patients with other causes ($P<0.001$). The diagnostic accuracies for cardiac syncope, as quantified by the area under the curve, were 0.80 (95% confidence interval [CI], 0.76–0.84), 0.69 (95% CI, 0.64–0.74), 0.58 (95% CI, 0.52–0.63), and 0.68 (95% CI, 0.63–0.73), respectively. In conjunction with the ED probability (0.86; 95% CI, 0.82–0.90), MRproANP, but not the other prohormone, improved the area under the curve to 0.90 (95% CI, 0.87–0.93), which was significantly higher than for the ED probability alone ($P=0.003$). An algorithm to rule out cardiac syncope combining an MRproANP level of <77 pmol/L and an ED probability of <20% had a sensitivity and a negative predictive value of 99%.

***Conclusions*—**The use of MRproANP significantly improves the early detection of cardiac syncope among unselected patients presenting to the ED with syncope.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT01548352. **(*J Am Heart Assoc*. 2017;6: e006592. DOI: 10.1161/JAHA.117.006592.)**

**Key Words:** arrhythmia • biomarker • diagnosis • syncope (fainting)

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Accompanying Data S1, Tables S1 through S5, and Figure S1 are available at http://jaha.ahajournals.org/content/6/12/e006592/DC1/embed/inline-supplementary-material-1.pdf

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## Clinical Perspective

### What Is New?

- This is the first prospective analysis assessing the diagnostic role of 4 novel prohormones in patients presenting with syncope to the emergency department.
- Diagnostic accuracy of midregional–pro-A-type natriuretic peptide for cardiac origin among unselected patients presenting with syncope to the emergency department is high and provides significantly incremental diagnostic value on top of clinical judgement and a recommended risk stratification tool.

### What Are the Clinical Implications?

- An algorithm based on the combination of midregional–pro-A-type natriuretic peptide and clinical judgement allowed us to rule out the presence of cardiac syncope with a sensitivity of 99% and a negative predictive value of 99% and may, therefore, improve patient care and logistics.
- Although this study represents an important step towards the integration of biomarkers into the clinical management of patients presenting with syncope to the emergency department, external validation in a large diagnostic study of comparable methodological scrutiny is required.

Syncope is a transient loss of consciousness associated with an inability to maintain postural tone attributable to global cerebral hypoperfusion.[1,2] Syncope is common and represents 1% to 2% of all emergency department (ED) visits.[3] Establishing the cause is challenging and, therefore, generally time and resource consuming. In the United States, 30% to 40% of such patients are subsequently admitted for further investigation at an annual cost of $2.4 billion, according to the Medicare database.[4] The risk of death is doubled among patients with cardiac syncope in comparison to other causes.[5,6] Identification of these patients is, therefore, crucial. Several risk scores,[7–9] and the establishment of specialized syncope units[10,11] in the ED, were proposed to improve the diagnostic yield to identify patients at risk of an adverse outcome. However, these tools have not been implemented in most institutions, at least in part because of their perceived complexity. Therefore, the rapid and accurate detection of cardiac syncope in the ED remains an unmet clinical need.

We hypothesized that blood biomarkers might provide incremental diagnostic value in the rapid and accurate detection of cardiac syncope in the ED, similar to the contribution that they have made for other common presenting symptoms, such as acute chest pain[12–15] and acute dyspnea.[16–18]

It is challenging to find a biomarker that could represent the "memory of the cardiac or arrhythmic event" at ED presentation, when the patient has again become asymptomatic and hemodynamically stable. The recent development and clinical introduction of assays that reliably quantify stable prohormone fragments, rather than the more unstable active hormone, have provided a new and unique diagnostic window.[19,20] Using this concept, immunoassays targeting 4 prohormone fragments, including midregional–pro-A-type natriuretic peptide (MRproANP), C-terminal proendothelin 1 (CTproET1), copeptin, and midregional-proadrenomedullin (MRproADM), were developed and applied in several clinical settings.[18–23] These prohormones allow us to quantify the activation of 4 distinct cardiovascular and biochemical pathways possibly involved in either the pathophysiological features of syncope or the endogenous response to it.[18–24] As a first hint about the possible role of these prohormones in syncope, CTproET1 plasma concentrations were associated with malignant arrhythmias in patients with chronic heart failure.[25]

We, therefore, performed a large international study evaluating the diagnostic utility of MRproANP, CTproET1, copeptin, and MRproADM in patients presenting with syncope to the ED.

## Methods

### Study Design, Setting, and Selection of Participants

BASEL IX (Basel Syncope Evaluation Study) is an ongoing, prospective, international, diagnostic, multicenter study enrolling unselected patients in 13 hospitals in 8 countries (Switzerland, Spain, Germany, Italy, Poland, New Zealand, Australia, and the United States) on 3 continents (Europe, Australia, and North America; Table S1). The study is designed to contribute to improving the management of patients presenting with syncope. Patients aged >40 years presenting to the ED with syncope within the past 12 hours were recruited, after written informed consent was obtained.

For this analysis, the exclusion criteria included patients with missing prohormone fragment measurements, patients with a final diagnosis of a nonsyncopal loss of consciousness, and those in whom the final diagnosis remained unclear even after central adjudication. The study was performed according to the principles of the Declaration of Helsinki preregistered and was approved by the local ethics committees. The authors designed the study, gathered and analyzed the data according to the Standards for the Reporting of Diagnostic Accuracy Studies guidelines for studies of diagnostic accuracy (Data S1), vouch for the data and analysis, wrote the article, and made the decision to submit the article for publication.

### Routine Clinical Assessment

Two sets of data were obtained: (1) by the treating ED physician as part of routine clinical care, according to local

standard operating procedures; and (2) by an experienced research fellow, using standardized case report forms uniformly collecting predefined details of patient history, the circumstances of syncope, and physical examination findings. A digital 12-lead ECG was recorded at presentation and stored electronically. Clinical judgment by the ED physician about the presence of cardiac syncope was quantified using a visual analogue scale ranging from 0% to 100%. The treating ED physician estimated cardiac origin probability on the basis of all information available in the individual patient 90 minutes after presentation, including clinical assessment, the 12-lead ECG, and the routine laboratory test results (but not the ones assessed for the study). To also provide a comparison with a recommended standard, the "Evaluation of Guidelines in Syncope Study" (EGSYS) risk score was calculated (Data S1).[1,2] Clinical decisions were absolutely independent of the present study. All participating centers were using standardized operating procedures for the diagnostic workup of patients presenting with syncope to the ED, according to current European Society of Cardiology Guidelines.[2]

## Biochemical Measurements

Immediately after informed consent was obtained, venous blood was obtained in EDTA plastic tubes, centrifuged, and stored at −80°C. Measurement of MRproANP, CTproET1, copeptin, and MRproADM was performed in a blinded manner in a dedicated core laboratory using validated sandwich immunoassays (Brahms, Hennigsdorf/Berlin, Germany).[26–29] In a subgroup of patients, B-type natriuretic peptide (BNP) was measured as part of the local clinical standardized operating procedures for patients with syncope from fresh plasma using the Architect system (Abbott, Chicago, IL).

## Follow-Up and Adjudicated Final Diagnosis

Patients were contacted 12 and 24 months after discharge by telephone or in written form. Information about recurrent syncope, hospitalization, and cardiac events during follow-up was further obtained from the patient's hospital notes, the family physician's records, and national registries on mortality, where possible. To determine the final diagnosis of the index syncopal event in each patient, 2 independent cardiologists reviewed all available medical records from both data sets: the clinical data set and the study-specific data set after at least 12 months of follow-up. The clinical data set included the clinical history, findings on physical examination, results of routine laboratory tests, radiologic testing results, ECG findings, and, if available, Holter-ECG, external and implantable loop device, echocardiography, cardiac exercise test, Schellong test, tilt table testing, coronary angiography, electrophysiological examination, pacemaker control, and further investigation findings during recurrent hospitalizations or ambulatory treatment. A detailed overview of all performed diagnostic tests is given in Table S2. Study-specific data included standardized forms uniformly collecting predefined details of patient history, the circumstances of syncope, the physical examination findings, and at least 12 months of follow-up data. In situations of adjudicator disagreement about the diagnosis, cases were reviewed and adjudicated in conjunction with a third cardiologist. Predefined categories for the adjudication included cardiac syncope, reflex syncope, orthostatic syncope, other noncardiac syncope, and unknown cause of syncope (Table S3). According to guidelines,[2] cardiac causes of syncope were defined as supraventricular or ventricular arrhythmias, severe structural heart diseases (eg, hypertrophic cardiomyopathy or valvular diseases), pericardial tamponade, congenital myocardial or valvular anomalies, aortic dissection, or acute pulmonary hypertension (eg, attributable to pulmonary embolism), leading to a transient loss of consciousness. It is important to highlight that the presence of cardiac disease (eg, coronary artery disease) was not at all sufficient for the adjudication to a cardiac cause of syncope. The detailed reconstruction of the syncopal event with the study-specific data set and third-party anamnesis, and long-term follow-up on cardiovascular events and/or recurrent syncope, were critical pillars of the adjudication. Further details on the adjudication are given in Data S1.

## Statistical Analysis

Continuous variables are presented as mean±SD when normally distributed and median with 25th and 75th percentiles when nonnormally distributed. Categorical variables are expressed as numbers and percentages. The Mann-Whitney *U* test was applied for comparison of continuous variables between cardiac and noncardiac syncope, and categorical variables were compared by Pearson $\chi^2$ test and Fisher exact test, as appropriate. We calculated the sample size on the basis of our previous experiences with studies on the diagnosis of acute myocardial infarction in patients presenting with chest pain to the ED[12–15,30,31] and aimed to enroll a total of 120 patients with cardiac syncope. Using the nomogram of Carley et al and Jones et al,[32,33] the targeted sample size ranged from 660 to 940 patients, estimating a sensitivity of 90% with a 2-sided 95% confidence interval (CI) of 5% to detect cardiac syncope. To evaluate diagnostic accuracy for the diagnosis of cardiac syncope, receiver-operating characteristic curves were constructed to assess the sensitivity and specificity of the ED physician's clinical judgment and the EGSYS risk score for cardiac origin probability, alone and in combination with MRproANP, CTproET1, copeptin, and MRproADM. The comparison of

areas under the receiver-operating characteristic curves (AUCs) was performed according to DeLong et al.[34] In addition, reclassification tables for net reclassification improvement were used to assess the incremental yield of the additional use of MRproANP at presentation to predict cardiac syncope.[35] Logistic regression was used to combine clinical judgement with prohormone plasma concentrations in predicting the final adjudicated diagnosis, generating a graphic displayed as a cardiac syncope diagnosis nomogram. Glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[36]

All hypothesis testing was 2 tailed, and $P<0.05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (SPSS Inc, Chicago, IL) and R 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

# Results

## Characteristics of Study Subjects

Eight-hundred eighty-six consecutive patients were enrolled in the BASEL IX study (Figure S1) from May18th, 2010 until July 25th, 2014. A complete screening log was not kept in all participating sites. In those sites with a screening log, 14% of presenting patients were excluded because they presented to the ED >12 hours after the syncopal event. For this analysis, patients with missing prohormone fragment measurements (n=3), those with a final diagnosis of a nonsyncopal loss of consciousness (n=117), and individuals in whom the final diagnosis remained unclear even after central adjudication (n=77) were excluded, leaving 689 patients for the analysis. A complete follow-up at 12 months was available in 99% of patients and at 24 months in 89% of patients.

Patients with cardiac syncope were significantly older, more often had a history of coronary artery disease, arrhythmia, or valvular heart disease, and more often experienced syncope during exertion. Further details on patient demographics are provided within Table 1.

## Adjudicated Final Diagnosis of Syncope

The overall patient population had the following adjudicated syncope causes: 125 (18%) cardiac, 320 (46%) reflex (neurally mediated), 181 (26%) orthostatic hypotension, and 63 (9%) other noncardiac causes. Among patients with cardiac syncope, most (90 [13%]) experienced arrhythmias, of which 58 (8.4%) were bradyarrhythmias and 27 (3.9%) were tachyarrhythmias. Twenty-eight patients (4.1%) had structural heart disease, including acute myocardial infarction in 13 (1.9%); in 7 patients (1%), other cardiac origin triggered syncope (eg, pulmonary embolism). All final adjudicated diagnoses are listed in Table S3.

## Prohormone Plasma Concentrations According to Adjudicated Diagnosis

Plasma concentrations of MRproANP, CTproET1, copeptin, and MRproADM were all significantly higher among patients with cardiac syncope compared with patients with other adjudicated causes of syncope (Table 2, Figure 1).

## Diagnostic Performance

The diagnostic accuracy of MRproANP levels for determining a cardiac syncope cause, as quantified by the AUC curve, was 0.80 (95% CI, 0.76–0.84; Figure 2). Diagnostic performance measures of receiver-operating characteristic curve–derived cutoff points achieving predefined target sensitivities for rule out and rule in are summarized in Tables 3 and 4. At a threshold of <77 pmol/L, MRproANP ruled out 30% of individuals (n=211), with a sensitivity of 95% and a negative predictive value of 97%. An algorithm to rule out cardiac syncope, combining an MRproANP level of <77 pmol/L and an ED probability of <20%, had a sensitivity of 99% and a negative predictive value of 99% and allowed us to triage 18% of patients toward rule out. At a threshold of >181 pmol/L, MRproANP ruled in 28% of individuals (n=192), with a specificity of 80% and a positive predictive value of 41%. An algorithm to rule in cardiac syncope, combining an MRproANP level of >181 pmol/L and an ED probability of >80%, had a specificity of 98% and a positive predictive value of 81% and allowed us to triage 8% of patients toward rule in.

The diagnostic accuracy for the other prohormone markers for detecting cardiac syncope, presented as AUC, was 0.69 (95% CI, 0.64–0.74) for CTproET1, 0.58 (95% CI, 0.52–0.63) for copeptin, and 0.68 (95% CI, 0.63–0.73) for MRproADM. The combination of CTproET1 and MRproANP did not improve diagnostic accuracy compared with that of MRproANP alone ($P=0.90$).

## Combination of Overall Clinical Judgement With MRproANP

The AUC for the combination of ED probability with MRproANP was significantly higher (0.90; 95% CI, 0.87–0.93) than for the ED probability alone (AUC, 0.86; 95% CI, 0.82–0.90; $P=0.003$). The net reclassification improvement of MRproANP was calculated at 0.216 ($P<0.001$). Integrated discriminatory improvement was 0.035 ($P=0.001$; Table S4). The combination of the other prohormones with ED probability did not provide a significant improvement in diagnostic accuracy when compared with ED probability alone

**Table 1.** Baseline Characteristics of the Patients

| Characteristics | All Patients (n=689) | Patients With Cardiac Syncope (n=125) | Patients Without Cardiac Syncope (n=564) | *P* Value |
|---|---|---|---|---|
| Age, y | 70 (57–80) | 77 (68–84) | 68 (54–78) | <0.001 |
| Time to presentation, min | 75 (50–127) | 81 (52–150) | 75 (50–122) | 0.379 |
| Time to blood draw since presentation, min | 107 (70–159) | 109 (75–162) | 107 (70–159) | 0.682 |
| Time to blood draw since syncopal event, min | 190 (140–290) | 187 (156–298) | 190 (137–289) | 0.464 |
| Male sex | 404 (58.6) | 76 (60.8) | 328 (58.2) | 0.658 |
| Inpatient treatment | 368 (53.4) | 106 (84.8) | 262 (46.5) | <0.001 |
| Time hospitalized, d | 4 (1–8) | 6 (2–9) | 3 (1–7) | <0.001 |
| Risk factors | | | | |
| Hypertension | 393 (57.1) | 79 (63.7) | 314 (55.7) | 0.124 |
| Hypercholesterolemia | 262 (39.3) | 57 (47.9) | 205 (37.5) | 0.045 |
| Diabetes mellitus | 98 (14.2) | 25 (20.2) | 73 (12.9) | 0.052 |
| Current smoking | 130 (19.0) | 15 (12.3) | 115 (20.4) | 0.051 |
| History of smoking | 218 (31.8) | 43 (35.2) | 175 (31.1) | 0.431 |
| History | | | | |
| Coronary artery disease | 149 (21.9) | 45 (37.2) | 104 (18.6) | <0.001 |
| Previous MI | 92 (13.4) | 28 (22.4) | 64 (11.3) | 0.002 |
| Arrhythmia* | 138 (20.5) | 43 (35.5) | 95 (17.2) | <0.001 |
| Valvular heart disease | 63 (9.3) | 22 (18.0) | 41 (7.4) | <0.001 |
| Previous stroke | 48 (7.0) | 9 (7.3) | 39 (7.0) | 1 |
| Epilepsy | 19 (2.8) | 2 (1.6) | 17 (3.0) | 0.551 |
| Previous syncope | 413 (61.4) | 74 (59.7) | 339 (61.7) | 0.745 |
| Syncope situation | | | | |
| Orthostatic | 83 (12.3) | 8 (6.5) | 75 (13.6) | 0.043 |
| While standing | 271 (40.2) | 50 (40.7) | 221 (40.1) | 0.993 |
| Exertion | 76 (11.3) | 32 (26.2) | 44 (8.0) | <0.001 |
| While sitting | 256 (37.9) | 41 (33.6) | 215 (38.9) | 0.325 |
| While lying down | 22 (3.3) | 3 (2.5) | 19 (3.4) | 0.781 |
| Presence of injury | 97 (14.5) | 18 (15.0) | 79 (14.4) | 0.983 |
| Vital parameters | | | | |
| Heart rate | 72 (64–84) | 73 (60–92) | 72 (64–82) | 0.509 |
| Systolic BP | 129 (114–145) | 131 (117–152) | 128 (114–144) | 0.062 |
| Diastolic BP | 73 (62–82) | 73 (60–84) | 73 (63–81) | 0.972 |
| Pathological ECG† | 240 (34.8) | 72 (57.6) | 168 (29.8) | <0.001 |
| Long-term medication | | | | |
| Aspirin | 242 (32) | 52 (41) | 190 (29.5) | 0.013 |
| Vitamin K antagonists | 92 (12) | 26 (21) | 66 (10.3) | 0.002 |
| β-Blockers | 256 (33) | 54 (43) | 202 (31.4) | 0.017 |
| Antiarrhythmics | 26 (3.4) | 7 (5.6) | 19 (3.0) | 0.227 |
| ACEIs/ARBs | 333 (43) | 66 (52) | 267 (41.5) | 0.031 |

Continued

**Table 1.** Continued

| Characteristics | All Patients (n=689) | Patients With Cardiac Syncope (n=125) | Patients Without Cardiac Syncope (n=564) | *P* Value |
|---|---|---|---|---|
| Calcium antagonists | 130 (17) | 23 (18) | 107 (16.6) | 0.755 |
| Diuretics | 222 (29) | 56 (44) | 166 (25.8) | <0.001 |
| Nitroglycerine | 44 (5.7) | 14 (11) | 30 (4.7) | 0.008 |

Data are presented as median (25th–75th percentile) or number (percentage). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; and MI, myocardial infarction.

*Arrhythmia indicates history of supraventricular or ventricular tachycardia.

†Pathological ECG was defined as meeting at least one of the following criteria: bifascicular block (left bundle branch block or right bundle branch block [RBBB] combined with left anterior fascicular block), second- or third-degree AV block, asymptomatic inappropriate sinus bradycardia (<50 beats/min) in the absence of negatively chronotropic medications, nonsustained ventricular tachycardia, preexcited QRS complexes, long or short QT intervals (men, >450 ms; women, >470 ms), RBBB pattern with ST elevation in leads V1 to V3 (Brugada syndrome), early repolarization, Q waves suggesting myocardial infarction, negative T waves in right precordial leads, and ε waves and ventricular late potentials suggestive of arrhythmogenic right ventricular dysplasia.[2]

(CTproET1, *P*=0.05; copeptin, *P*=0.09; and MRproADM, *P*=0.08, for the comparisons of ED probability plus biomarker versus ED probability alone).

## Cardiac Syncope Using the Fagan Nomogram

Figure 3 is a Fagan nomogram for cardiac syncope to visualize the additive value of MRproANP to clinical judgement. As indicated by the nomogram, MRproANP has the greatest value as a diagnostic test in patients with intermediate pretest probability. In this category (visual analogue scale score ≥10% and ≤60%), 34 of 424 patients (8%) experienced cardiac syncope. MRproANP ≥175 pmol/L correctly classified 77% of all patients as having cardiac syncope or not having cardiac syncope. In 358 patients with a low ED probability of cardiac syncope (≤20%), 12 of 358 (3.4%) had a final adjudicated diagnosis of cardiac syncope. Of these 12 individuals, 11 (99.3%) could have had the misdiagnosis corrected if the additional information of MRproANP ≥77 pmol/L had been available. Specific patient characteristics of these 11 patients are provided in Table S5. A diagnosis other than cardiac syncope was initially suspected in the ED in the presence of prodromal symptoms (8 of 11 patients) and a normal ECG at presentation (7 of 11 patients) or in the absence of cardiac risk factors, such as diabetes mellitus (2 of 11 patients) or hypertension (3 of 11 patients).

## Combination of MRproANP With EGSYS Risk Score

The diagnostic accuracy of MRproANP levels in combination with the EGSYS risk score in detecting cardiac syncope is shown in Figure 2. The AUC for the combination of MRproANP and the EGSYS risk score was significantly higher (0.81; 95% CI, 0.77–0.85) than for the EGSYS risk score alone (AUC, 0.67; 95% CI, 0.63–0.72; *P*<0.001).

## Prediction of Cardiac Syncope

Logistic regression analysis confirmed MRproANP as a predictor of cardiac syncope in both univariate and multivariate analyses (Table 5). In multivariable analysis, only a pathological ECG (according to the European Society of Cardiology Guidelines), impaired renal function, and

**Table 2.** Plasma Concentration of Prohormones According to Adjudicated Diagnosis

| Prohormones | Cardiac (n=125) | Reflex (n=320) | Orthostatic (n=181) | Other, Noncardiac (n=63) | *P* Value* |
|---|---|---|---|---|---|
| MRproANP, pmol/L | 246 (141–355) | 91 (59–146) | 122 (72–197) | 111 (62–189) | <0.001 |
| CTproET1, pmol/L | 89 (65–118) | 61 (53–75) | 80 (59–104) | 65 (52–83) | <0.001 |
| Copeptin, pmol/L | 45 (20–78) | 32 (14–64) | 33 (14–72) | 18 (10–52) | 0.01 |
| MRproADM, nmol/L | 1.0 (0.7–1.4) | 0.6 (0.5–0.9) | 0.9 (0.7–1.2) | 0.7 (0.6–1.0) | <0.001 |

Data are given as median ($25^{th}$–$75^{th}$ percentile). MRproANP: In healthy individuals, the range of MRproANP concentrations was from 9.6 to 313 pmol/L. The median was 45 pmol/L. The 99th percentile was 197.5 pmol/L.[26] CTproET1: In healthy individuals, the range of CTproET1 concentrations was from 10.5 to 77.4 pmol/L, and the mean (SD) was 44.3 (10.6) pmol/L. The 99th percentile was 72.8 pmol/L.[27] Copeptin: In healthy individuals, the range of copeptin concentrations was from 1 to 13.8 pmol/L. The median was 4.2 pmol/L. The 99th percentile was 13.5 pmol/L.[29] MRproADM: In healthy individuals, the range of MRproADM concentrations was from 0.10 to 0.64 nmol/L, and the mean (SD) was 0.33 (0.07) nmol/L. The 99th percentile was 0.52 nmol/L.[28] CTproET1 indicates C-terminal proendothelin 1; MRproADM, midregional-proadrenomedullin; and MRproANP, midregional–pro-A-type natriuretic peptide.

*The *P* values were tested for the comparison across the 4 categories in the table. The Kruskal-Wallis test was used to conduct this test.

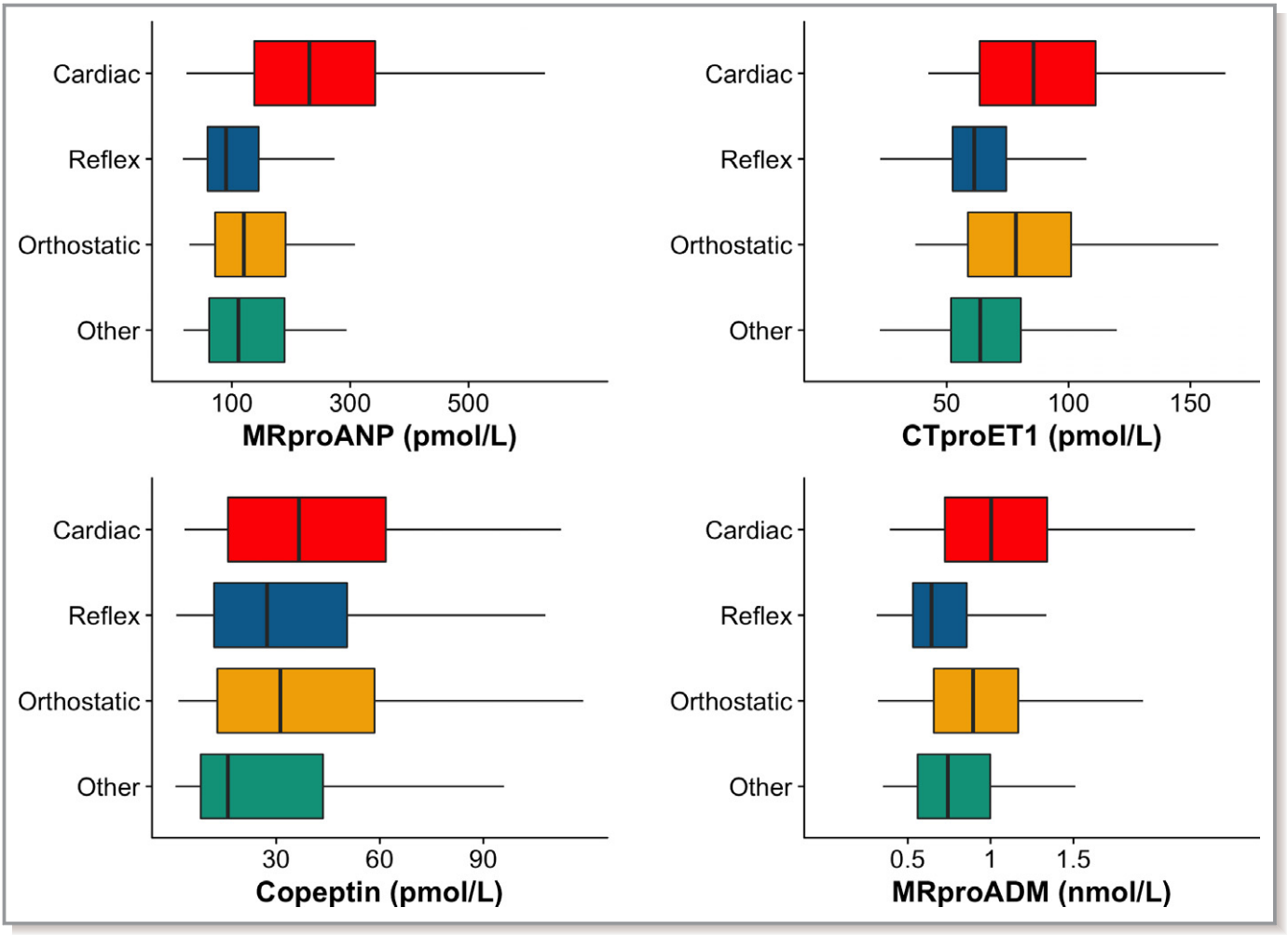


**Figure 1.** Box plots for all assessed prohormones in patients with a different origin of syncope. The ends of the whisker were defined so that the maximum length of each whisker is 1.5 times the interquartile range. Midregional–pro-A-type natriuretic peptide (MRproANP): In healthy individuals, the range of MRproANP concentrations was from 9.6 to 313 pmol/L. The median was 45 pmol/L. The 99th percentile was 197.5 pmol/L.[26] C-terminal proendothelin 1 (CTproET1): In healthy individuals, the range of CTproET1 was from 10.5 to 77.4 pmol/L, and the mean (SD) was 44.3 (10.6) pmol/L. The 99th percentile was 72.8 pmol/L.[27] Copeptin: In healthy individuals, the range of copeptin concentrations was from 1 to 13.8 pmol/L. The median was 4.2 pmol/L. The 99th percentile was 13.5 pmol/L.[29] Midregional-proadrenomedullin (MRproADM): In healthy individuals, the range of MRproADM was from 0.10 to 0.64 nmol/L, and the mean (SD) was 0.33 (0.07) nmol/L. The 99th percentile was 0.52 nmol/L.[28]

MRproANP (odds ratio, 4.51; 95% CI, 2.84–7.16) were independent predictors of cardiac syncope.

## Direct Comparison of MRproANP With BNP

In the subgroup of patients with both biochemical signals available (n=393 [57%]), the AUC was 0.77 (95% CI, 0.71–0.83) for MRproANP and 0.74 (95% CI, 0.68–0.81) for BNP ($P$=0.278) for detecting cardiac syncope.

## Discussion

This prospective multicenter study using long-term follow-up and central adjudication aimed to contribute to advancing the rapid and accurate diagnosis of patients presenting with syncope to the ED. The study evaluated the diagnostic utility of prohormones quantifying 4 different neurohumoral pathways possibly involved in the pathophysiological characteristics of cardiac syncope. Prohormones were selected on the basis of the hypothesis that they could represent the "memory of the cardiac and in fact often arrhythmic event" at ED presentation and because commonly they are more stable analytically compared with active hormones.[16–18]

We report 7 major findings: First, in patients with an adjudicated diagnosis of cardiac syncope, prohormone plasma levels (MRproANP, CTproET1, copeptin, and MRproADM) were significantly higher than in patients with noncardiac causes of syncope. Second, although MRproANP

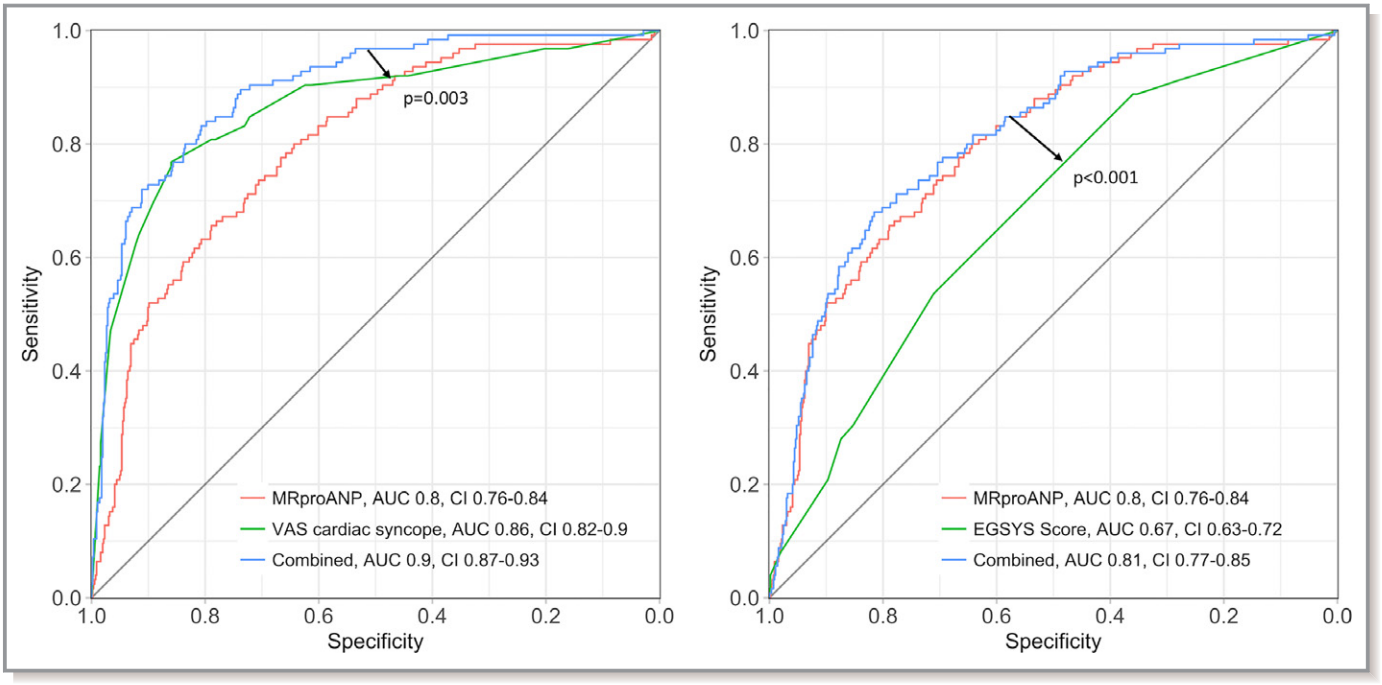


**Figure 2.** Receiver-operating characteristic (ROC) curves for detection of cardiac syncope for midregional–pro-A-type natriuretic peptide (MRproANP), alone and in combination with either clinical judgement (left) or Evaluation of Guidelines in Syncope Study (EGSYS) risk score (right). ROC curves for the diagnostic performance of MRproANP, alone and in combination with either clinical judgment (left) or EGSYS risk score (right), for diagnosing cardiac syncope. The red curve displays the biomarker alone; the green curve, emergency department (ED) probability (visual analogue scale [VAS]; left) or EGSYS risk score (right) for detecting cardiac syncope; and the blue curve, the combination of the biomarker and ED probability (left) or EGSYS risk score (right). The black arrows show the comparison of areas under the ROC curves (AUCs) for the combination of ED probability with MRproANP against ED probability alone (left) and for the combination of EGSYS risk score with MRproANP against the EGSYS risk score alone (right). CI indicates confidence interval.

levels were nearly exclusively elevated in patients with cardiac syncope, CTproET1 and MRproADM levels were also elevated in patients with syncope attributable to orthostatic hypotension. Third, diagnostic accuracy for cardiac syncope of prohormones, as quantified by the AUC curve, was high for MRproANP, moderate for CTproET1 and MRproADM, and poor for copeptin. Fourth, MRproANP provided significant incremental value when combined with clinical judgment in the ED, which was mainly based on the clinical assessment and the 12-lead ECG. Diagnostic accuracy for the combination of MRproANP and ED probability was high (AUC, 0.90; 95% CI, 0.87–0.93) and significantly higher than for ED probability alone. Although the 0.04 higher C-statistic represents a modest increase, a confirmed diagnosis in a population fraught with diagnostic uncertainty suggests important potential clinical utility. MRproANP concentrations might add information of a more objective and more specific marker of heart disease than a subjective clinical history or examination alone. An algorithm incorporating MRproANP levels seems to perform better than existing protocols based on international syncope guidelines[1,2] (eg, the substantial incremental value of MRproANP was confirmed using the EGSYS risk score as an alternative method of reflecting the standard of care). The magnitude of the increase in diagnostic accuracy provided by MRproANP was identical compared with the increase in diagnostic accuracy in the diagnosis of myocardial infarction provided by high-sensitivity cardiac troponin compared with sensitive cardiac troponin.[37] None of the other biochemical signals provided incremental value on top of clinical judgment. Fifth, increased MRproANP levels were independently associated with cardiac causes of syncope (odds ratio, 4.51; 95% CI, 2.84–7.16) and were a stronger predictor than clinical features. Sixth, an algorithm based on the combination of MRproANP and clinical judgement allowed use to rule out the presence of cardiac syncope, with a sensitivity of 99% and a negative predictive value of 99%. Seventh, subgroup analysis in patients in whom BNP was measured as part of the clinical standardized operating procedures documented comparable diagnostic accuracy of MRproANP and BNP. This suggests that our findings about the incremental diagnostic value of MRproANP likely can be extrapolated to BNP. Further studies are warranted to appropriately test this hypothesis.

These findings extend and corroborate previous pilot data on the possible clinical utility of biomarkers quantifying neurohormonal pathways.[22,38–42] Several studies have demonstrated that ANP and BNP plasma concentrations are increased in heart failure and cardiac arrhythmias.[43–45] For example, in a pilot study of 18 patients, a significant increase

**Table 3.** Diagnostic Test Characteristics of Prespecified Cut Point Values for Rule Out of Cardiac Syncope

| Target Sensitivity, % | No. (%) of Patients | Cut Point for MRproANP, pmol/L | Sensitivity, % | Specificity, % | NPV, % | PPV, % | Accuracy, % |
|---|---|---|---|---|---|---|---|
| 70 | 450 (65) | <159 | 70 (62–78) | 73 (69–77) | 92 (90–94) | 37 (33–41) | 72 (69–76) |
| 80 | 380 (55) | <130 | 80 (73–87) | 63 (59–67) | 94 (91–96) | 33 (30–36) | 63 (63–70) |
| 90 | 289 (42) | <98 | 90 (85–94) | 49 (45–53) | 96 (93–98) | 28 (26–30) | 56 (53–60) |
| 95 | 211 (31) | <77 | 95 (91–98) | 36 (32–40) | 97 (95–99) | 25 (24–26) | 47 (44–50) |
| Combination | 124 (18) | <77 (VAS score, <20%) | 99 (96–100) | 22 (19–26) | 99 (96–100) | 22 (19–25) | 36 (32–39) |

Numbers represent percentage (95% confidence interval) unless otherwise indicated. MRproANP indicates midregional–pro-A-type natriuretic peptide; NPV, negative predictive value; PPV, positive predictive value; and VAS, visual analogue scale.

of BNP and NT-proBNP (N-terminal pro-B-type natriuretic peptide) plasma concentrations was observed after the induction of ventricular fibrillation in patients with an implantable cardioverter defibrillator.[45] Accordingly, BNP and NT-proBNP have been proposed to help identify patients with syncope of cardiac origin and to be good markers for risk stratification in this population.[8,39,46–48] Finally, retrospective single-center studies reported higher BNP and NT-pro-BNP levels in patients admitted for syncope to a cardiology department in whom a cardiac cause was found during in-hospital workup compared with other causes.[31,45]

Detection of cardiac syncope has immediate consequences for patient management and, in general, triggers hospital admission, ECG-rhythm monitoring, and cardiology consultation.[1,2] ECG-rhythm monitoring is mandatory because the next episode of bradyarrhythmia or tachyarrhythmia may be fatal if undetected and untreated.[1,2] Cardiology consultation is necessary for the rapid initiation of the appropriate further diagnostic and therapeutic measures. These include implantation of a pacemaker in patients with documented symptomatic bradycardia (eg, high-degree AV block) and transthoracic echocardiography in patients with suspected severe aortic stenosis, followed by coronary angiography and computed tomography–angiography once severe aortic stenosis is confirmed in the preparation of aortic valve replacement. They also include implantation of a cardioverter-defibrillator in patients with coronary artery disease and severely impaired left ventricular ejection fraction or further risk stratification by an electrophysiological study for the assessment of ventricular arrhythmias. Moreover, if the risk of recurrence of a cardiac syncope is estimated to be high (eg, in patients with intermittent high-degree AV block), bed rest would seem prudent to avoid the possible harm of injuries related to falls in case of recurrence.

Our findings suggest that plasma levels of MRproANP can be considered a marker of cardiac syncope. Therefore, MRproANP can possibly offer diagnostic information that would improve management of syncopal patients in the ED. As demonstrated by the nomogram, and by proposing an algorithm implementing the combination of a low ED probability and low plasma levels of MRproANP (with sensitivity and negative predictive values of 99% for cardiac syncope), the benefits of MRproANP application may be predominately in ruling out a cardiac cause of syncope and defining low-risk patients suitable for outpatient management. Avoiding unnecessary hospital admissions and extensive cardiac workup by a more accurate diagnosis likely will result in cost savings. This approach mirrors the use of D-dimers in the rule out of venous thromboembolism.[49] Further studies specifically addressing cost-effectiveness of MRproANP are warranted to evaluate whether the cost savings of the biomarker-guided approach are similar to cost savings observed with the use of natriuretic peptides in patients presenting with acute dyspnea.[50,51]

**Table 4.** Diagnostic Test Characteristics of Prespecified Cut Point Values for Rule In of Cardiac Syncope

| Target Specificity, % | No. (%) of Patients | Cut Point for MRproANP, pmol/L | Sensitivity, % | Specificity, % | NPV, % | PPV, % | Accuracy, % |
|---|---|---|---|---|---|---|---|
| 70 | 262 (38) | >147 | 74 (66–82) | 70 (66–74) | 92 (90–94) | 35 (31–39) | 71 (67–74) |
| 80 | 192 (28) | >181 | 63 (54–71) | 80 (77–83) | 91 (89–93) | 41 (36–47) | 77 (74–80) |
| 90 | 121 (18) | >243 | 51 (42–60) | 90 (88–93) | 89 (88–91) | 53 (46–62) | 83 (81–86) |
| 95 | 55 (8) | >373 | 22 (14–29) | 95 (93–97) | 85 (83–86) | 49 (37–62) | 82 (80–84) |
| Combination | 53 (8) | >181 (VAS score, >80%) | 34 (27–43) | 98 (97–99) | 81 (69–90) | 87 (84–90) | 87 (84–89) |

Numbers represent percentage (95% confidence interval) unless otherwise indicated. MRproANP indicates midregional–pro-A-type natriuretic peptide; NPV, negative predictive value; PPV, positive predictive value; and VAS, visual analogue scale.

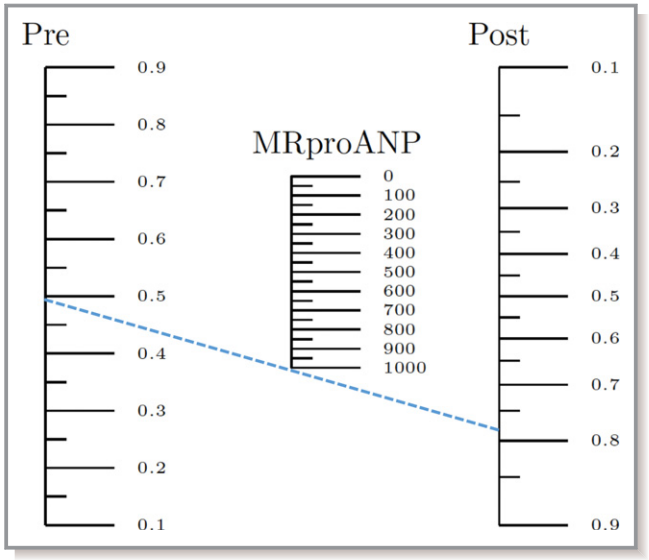


**Figure 3.** Cardiac syncope diagnosis nomogram. Clinical judgment by the emergency department (ED) physician about the presence of cardiac syncope is displayed as "Pre." The treating ED physician estimated cardiac origin probability on the basis of all information available in the individual patient 90 minutes after presentation, including clinical assessment, the 12-lead ECG, and the routine laboratory test results. The middle line represents midregional–pro-A-type natriuretic peptide (MRproANP) level (in pmol/L) at presentation. When a straight line is drawn through the pretest probability and MRproANP level, the posttest probability is found on the right line ("Post"). For example, an ED probability of 50% with an MRproANP level of 1000 pmol/L yields an ≈78% probability of cardiac syncope on the basis of these 2 predictors (blue-dotted line).

Further studies are also necessary to decipher the exact pathophysiological link between the vasoconstrictor prohormone CTproET1 and the vasodilator prohormone MRproADM and orthostatic hypotension.

Most patients presenting with syncope to the ED had mildly elevated plasma concentrations of copeptin, a stable peptide derived from the precursor of vasopressin, irrespective of the cause of syncope. This suggests that the arginine-vasopressin system may be activated to a similar extent by several mechanisms leading to syncope. Accordingly, copeptin does not seem to have a role as a diagnostic biomarker in this setting.[41,52]

This study has 3 important methodological strengths that differentiate it from previous studies on syncope: global representation of patients attributable to enrollment in 8 countries on 3 continents, long-term follow-up, and central adjudication by 2 independent cardiologists to maximize the accuracy of the reference standard diagnosis of cardiac versus noncardiac syncope.

Although this study represents an important step towards the integration of biomarkers into the clinical management of patients presenting with syncope to the ED, external validation in a large diagnostic study of comparable methodological scrutiny is required.

This applies to the diagnostic accuracy of MRproANP in general and the suggested cutoff levels for early rule out in particular. Because patients with syncope show a wide age range (44–94 years in this study), an even larger data set may allow derivation of age-optimized cutoff levels to further improve the sensitivity and/or the effectiveness of the biomarker-based rule-out approach.[53] Also, additional studies are warranted to evaluate other biochemical and/or electrocardiographic signatures, in combination with clinical judgment, to improve the early diagnosis of cardiac syncope. These studies are needed because diagnostic uncertainties in patients presenting to the ED with syncope have become the focus of debate about inappropriate use of resources,

**Table 5.** Logistic Regression

| | Univariable Logistic Regression | | | | Multivariable Logistic Regression | | | |
|---|---|---|---|---|---|---|---|---|
| Variable | Odds Ratio | 95% CI (Lower-Upper) | | *P* Value | Odds Ratio | 95% CI (Lower-Upper) | | *P* Value |
| Age* | 1663 | 1412 | 1958 | <0.001 | 1293 | 1012 | 1654 | 0.040 |
| Male sex | 1124 | 757 | 1669 | 0.535 | | | | |
| Valvular disease | 2747 | 1569 | 4809 | <0.001 | 1726 | 901 | 3307 | 0.01 |
| Charlson comorbidity index | 1252 | 1164 | 1347 | <0.001 | | | | |
| Palpitations | 1025 | 502 | 2093 | 0.945 | | | | |
| ECG pathological | 3236 | 2176 | 4812 | <0.001 | 2020 | 1268 | 3218 | 0.003 |
| GFR, CKD-EPI | 981 | 973 | 989 | <0.001 | 1023 | 1008 | 1038 | 0.002 |
| MRproANP (ln transformed) | 4569 | 3329 | 6271 | <0.001 | 4506 | 2837 | 7156 | <0.001 |
| CTproET1 (ln transformed) | 5522 | 3380 | 9022 | <0.001 | 1700 | 765 | 3744 | 0.193 |

CI indicates confidence interval; CKD-EPI indicates Chronic Kidney Disease Epidemiology Collaboration; CTproET1, C-terminal proendothelin 1; GFR, glomerular filtration rate; ln, natural log; and MRproANP, midregional–pro-A-type natriuretic peptide.
*Per 10-year increase.

increasing healthcare costs, and, most important, patient safety.[54,55]

Potential limitations of the present study merit consideration. First, this diagnostic study using central adjudication required informed consent. This may have introduced a small, but unavoidable, selection bias. Because this study enrolled all patients presenting with syncope to the ED, irrespective of the pretest probability for a cardiac cause, any selection bias should have been minimized. Second, we recruited patients presenting to the ED. Therefore, it is unknown whether our findings can be extrapolated to patients presenting to primary care. Third, we cannot comment on patients who present >12 hours after symptom onset because these patients were excluded from our study. However, only a few patients presented >12 hours after the syncopal event. Fourth, prohormone levels were measured once. Further studies are warranted to evaluate whether serial sampling would allow a further increase in diagnostic accuracy. Fifth, despite using the most stringent and unprecedented method of central adjudication of the final diagnosis by 2 independent cardiologists who had access to the whole clinical workup and the study-specific data set, third-party anamnesis, and long-term follow-up of cardiovascular events and/or recurrent syncope, a few patients may still have been misclassified. This invariably may lead to a slight underestimation of the true accuracy of the prohormones tested.

In conclusion, this large multicenter diagnostic study suggests that the plasma level of MRproANP may be a quantitative marker of cardiac syncope. Using it in conjunction with the ED probability, summarizing all information commonly available at 90 minutes in the ED, including the 12-lead ECG, improves the early rule out and/or rule in of cardiac syncope. In contrast, the other prohormones tested did not seem to have diagnostic utility.

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# SUPPLEMENTAL MATERIAL

**Data S1.**

## SUPPLEMENTAL METHODS

### Adjudication of the final diagnosis

The first step in the adjudication process was to decide whether there was syncope or not. If the criteria for a true syncope were not fulfilled, a distinction between the following non-syncopal disorders was made: pre-syncope; falls; stroke/TIA; epilepsy; metabolic disorders: e.g. hypoglycaemia, hypoxia, hyperventilation; intoxication: e.g. alcohol, benzodiazepines, opiates; functional (psychogenic pseudosyncope); others. The classification of syncope is based on pathophysiological considerations. The following predefined differential diagnoses were used:[1,2]

1) Cardiac syncope: We distinguished between:
    a. Arrhythmia as primary cause: Arrhythmias are the most common cause of syncope; *Bradycardia:* sinus node dysfunction, atrioventricular conduction system disease, implanted device malfunction or drug-induced; *Tachycardia:* supraventricular or ventricular.
    b. *Structural heart disease:* structural heart diseases can cause syncope when circulatory demands outweigh the impaired ability of the heart to increase output. However, in some cases syncope may not solely be the result of restricted cardiac output, but be in part due to an inappropriate reflex. However, when a structural heart disease was the primary cause or contributed most to syncope, it was classified as cardiovascular syncope.
    c. *Others:* pulmonary embolism, acute aortic dissection, pulmonary hypertension or any other cause for a cardiovascular syncope.

2) Reflex (neutrally-mediated) syncope: This syncope is characterized by cardiovascular reflexes which are normally useful in controlling circulation but become intermittently inappropriate in response to a trigger. The reflex results in vasodilation and/or bradycardia which lead to a fall in arterial blood pressure and consequently to cerebral hypoperfusion. Identifying a trigger is central when diagnosing a reflex syncope. Typically symptoms as light-headedness, nausea, sweating, weakness or visual disturbances precede reflex syncope. We distinguished between:
    a. Vasovagal: “common faint”, triggered by emotional distress/ pain or mediated by orthostatic stress.
    b. Situational: refers to reflex syncope associated with some specific circumstances, e.g. post-micturition, post-prandial, gastrointestinal stimulation, cough.
    c. Carotid sinus syncope: triggered by mechanical manipulation of the carotid sinus. It can be diagnosed by carotid sinus massage.
    d. Atypical forms: reflex syncope occurring with uncertain or apparently absent triggers.

3) Syncope due to orthostatic hypotension: Orthostatic hypotension is defined as an abnormal decrease in systolic blood pressure after changing from supine to standing position. Key can be syncope immediately after standing up or a pathological Schellong test. We distinguished between:
    a. Primary autonomic failure: There is an autonomic failure which is clearly a primary part of Parkinson syndrome as idiopathic Parkinson disease or atypical Parkinson syndrome (multiple system

atrophy, progressive supranucleair oculomotoric paresis, corticobasal degeneration or lewy body dementia).

b. Secondary autonomic failure: autonomic failure may be due to circumstances such as diabetes, uraemia, amyloidosis or spinal cord injuries
c. Drug-induced orthostatic hypotension: orthostatic hypotension is due to drugs which can lead to orthostatic hypotension such as diuretics, antidepressants, vasodilators, alcohol
d. Volume depletion: orthostatic hypotension is caused by a hypovolemia due to haemorrhage, diarrhoea, vomiting or fever
e. Others: sometimes the pathophysiology remains unclear.

4) Others, non-cardiac syncope: Sometimes the underlying pathophysiological mechanism of syncope remains unclear, but a cardiac syncope is ruled-out.
5) Syncope of unknown etiology (cardiac syncope possible): the etiology of syncope still remained unknown and a cardiac syncope was considered to be a possible cause.

**EGSYS risk score – Multivariate**[2,1]

The point score is found as the sum of the following risk factors:

- Palpitations: 4
- Abnormal ECG/Cardiopathy: 3
- Effort Syncope: 3
- Syncope in supine position: 2
- Neurovegetative prodromes: -1
- Precipitating and predisposive factors: -1

A score greater than 2 implies an increased risk for cardiac syncope.

## STARD Checklist for studies of diagnostic accuracy

| Section & Topic | No | Item | Reported on page # |
|---|---|---|---|
| **TITLE OR ABSTRACT** | | | |
| | **1** | Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC) | 2 |
| **ABSTRACT** | | | |
| | **2** | Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts) | 2 |
| **INTRODUCTION** | | | |
| | **3** | Scientific and clinical background, including the intended use and clinical role of the index test | 3 |
| | **4** | Study objectives and hypotheses | 3-4 |
| **METHODS** | | | |
| *Study design* | **5** | Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study) | 5 |
| *Participants* | **6** | Eligibility criteria | 5 |
| | **7** | On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry) | 5 |
| | **8** | Where and when potentially eligible participants were identified (setting, location and dates) | 5 |
| | **9** | Whether participants formed a consecutive, random or convenience series | **5** |
| *Test methods* | **10** | Index test, in sufficient detail to allow replication | **6-7** |
| | **11** | Reference standard, in sufficient detail to allow replication | **6-7** |
| | **12** | Rationale for choosing the reference standard (if alternatives exist) | **6-7** |
| | **13** | Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory | **6-7** |
| | **14** | Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory | **6-7** |
| | **15** | Whether clinical information and reference standard results were available to the performers/readers of the index test | **6-7** |
| | **16** | Whether clinical information and index test results were available to the assessors of the reference standard | **6-7** |
| *Analysis* | **17** | Methods for estimating or comparing measures of diagnostic accuracy | **7** |
| | **18** | How indeterminate index test or reference standard results were handled | **5** |
| | **19** | How missing data on the index test and reference standard were handled | **5** |
| | **20** | Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory | **7** |
| | **21** | Intended sample size and how it was determined | **5** |
| **RESULTS** | | | |
| *Participants* | **22** | Flow of participants, using a diagram | **Supplemental** |
| | **23** | Baseline demographic and clinical characteristics of participants | **24** |
| | **24** | Distribution of severity of disease in those with the target condition | **24** |
| | **25** | Distribution of alternative diagnoses in those without the target condition | **24** |
| | **26** | Time interval and any clinical interventions between index test and reference standard | **24** |
| *Test results* | **27** | Cross tabulation of the index test results (or their distribution) by the results of the reference standard | **26** |
| | **28** | Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals) | **28** |
| | **29** | Any adverse events from performing the index test or the reference standard | **26** |
| **DISCUSSION** | | | |

| | | | |
|---|---|---|---|
| | **30** | Study limitations, including sources of potential bias, statistical uncertainty, and generalizability | **15** |
| | **31** | Implications for practice, including the intended use and clinical role of the index test | **15** |
| **OTHER INFORMATION** | | | |
| | **32** | Registration number and name of registry | **5** |
| | **33** | Where the full study protocol can be accessed | **5** |
| | **34** | Sources of funding and other support; role of funders | **17** |

**Table S1.** Enrollment across regions

| | |
|---|---|
| Switzerland: | 59% |
| Germany: | 6% |
| Spain: | 22% |
| Italy: | 2% |
| Poland: | 2% |
| USA: | 1% |
| Australia: | 2% |
| New Zealand: | 6% |

**Table S2.** Performed diagnostic tests at admission or during long-term follow-up in all 689 patients

| Investigation | Test done (%) |
|---|---|
| ECG | 666 (97) |
| Carotid Duplex | 50 (7) |
| Cranial CT | 208 (30) |
| TTE | 229 (33) |
| X-Ray Chest | 322 (47) |
| EEG | 46 (7) |
| Ergometry | 23 (3) |
| Holter-ECG | 111 (16) |
| Telemetry | 131 (19) |
| Loop Recorder | 7 (1) |
| Coronary Angiography | 33 (5) |
| MPI | 9 (1) |
| Schellong | 290 (43) |

*ECG = Electrocardiogram; Cranial CT = Cranial computed tomography; TTE = Transthoracic echocardiography; EEG = Electroencephalogram; MPI = Myocardial perfusion imaging.

**Table S3.** All final adjudicated diagnoses, n (%)

| | | |
|---|---|---|
| **Cardiac Syncope** | | 125 (18.1) |
| Arrhythmia as primary cause | | 90 (13.1) |
| Bradycardia | | 58 (8.4) |
| | Sinus node dysfunction | 30 (4.4) |
| | AV conduction system disease | 27 (3.9) |
| | Implanted device malfunction | 1 (0.1) |
| | Drug induced | 5 (0.7) |
| Tachycardia | | 27 (3.9) |
| | Supraventricular | 15 (2.2) |
| | Drug-induced | 2 (0.3) |
| | Ventricular | 10 (1.5) |
| | Idiopathic | 1 (0.1) |
| | Channelopathies | 1 (0.1) |
| | Secondary to structural heart disease | 8 (1.2) |
| | Drug-induced | 0 (0) |
| Unknown | | 5 (0.7) |
| Structural Heart Disease | | 28 (4.1) |
| | Cardiac valvular disease | 12 (1.7) |
| | Acute myocardial infarction/ischaemia | 13 (1.9) |
| | Hypertrophic cardiomyopathy | 1 (0.1) |
| | Congenital anomalies of coronary arteries | 0 (0) |
| | Prosthetic valves dysfunction | 0 (0) |
| | Cardiac masses | 0 (0) |
| | Pericardial disease | 0 (0) |
| | Others | 2 (0.3) |
| Others | | 7 (1.0) |
| | Pulmonary embolism | 6 (0.9) |
| | Acute aortic dissection | 0 (0) |
| | Pulmonary hypertension | 1 (0.1) |
| | Others | 0 (0) |
| Total | | 689 (100%) |
| **Reflex (neurally-mediated) syncope** | | 320 (46.4) |
| Vasovagal | | 157 (22.8) |
| | Mediated by emotional distress/pain | 104 (15.1) |
| | Mediated by orthostatic stress | 53 (7.7) |
| Situational | | 116 (16.8) |
| | Cough, Sneeze | 6 (0.9) |
| | Gastrointestinal stimulation | 63 (9.1) |
| | Post-prandial | 28 (4.1) |
| | Post-micturition | 10 (1.5) |
| | Others | 9 (1.3) |
| Carotid sinus syncope | | 2 (0.3) |
| Atypical forms (without apparent triggers or atypical presentation) | | 45 (6.5) |
| **Syncope due to orthostatic hypotension** | | 181 (26.3) |

| | | |
|---|---|---|
| Primary autonomic failure | | 6 (0.9) |
| | Pure autonomic failure | 0 (0) |
| | Multiple system atrophy | 0 (0) |
| | Lewy body dementia | 0 (0) |
| | Parkinson's disease with autonomic failure | 6 (0.9) |
| | Others | 0 (0) |
| Secondary autonomic failure | | 6 (0.9) |
| | Diabetes mellitus | 2 (0.3) |
| | Amyloidosis | 0 (0) |
| | Uraemia | 0 (0) |
| | Spinal Cord Injuries | 0 (0) |
| | Others | 4 (0.6) |
| Drug-induced orthostatic hypotension | | 66 (9.6) |
| | Alcohol | 8 (1.2) |
| | Phenothiazines | 2 (0.3) |
| | Vasodilators | 23 (3.3) |
| | Diuretics | 15 (2.2) |
| | Antidepressants | 6 (0.9) |
| | Others | 20 (2.9) |
| Volume Depletion | | 72 (10.4) |
| | Haemorrhage | 6 (0.9) |
| | Diarrhoea | 6 (0.9) |
| | Vomiting | 2 (0.3) |
| | Fever/SIRS | 40 (5.8) |
| | Others | 18 (2.6) |
| Others | | 31 (4.5) |
| **Others (but no cardiac syncope)** | | 63 (9.1) |

**Table S4.** Reclassification by means of MRproANP

| | Patients with non-cardiac syncope | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *VAS & MRproANP* | | | | | | | | | | |
| *VAS* | 0-10% | 11-20% | 21-30% | 31-40% | 41-50% | 51-60% | 61-70% | 71-80% | 81-90% | 91-100% | % |
| 0-10% | 225 | 21 | 1 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 10 |
| 11-20% | 3 | 68 | 17 | 3 | 1 | 3 | 0 | 0 | 0 | 1 | 29 |
| 21-30% | 0 | 3 | 44 | 10 | 2 | 2 | 0 | 0 | 0 | 0 | 28 |
| 31-40% | 0 | 0 | 3 | 28 | 1 | 2 | 0 | 0 | 0 | 0 | 16 |
| 41-50% | 0 | 0 | 0 | 8 | 25 | 9 | 1 | 1 | 0 | 0 | 75 |
| 51-60% | 0 | 0 | 0 | 0 | 5 | 10 | 2 | 1 | 0 | 0 | 44 |
| 61-70% | 0 | 0 | 0 | 0 | 0 | 2 | 10 | 1 | 0 | 1 | 29 |
| 71-80% | 0 | 0 | 0 | 0 | 0 | 0 | 10 | 13 | 3 | 2 | 54 |
| 81-90% | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 5 | 4 | 50 |
| 91-100% | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 6 | 33 |
| | Patients with cardiac syncope | | | | | | | | | | |
| | *VAS & MRproANP* | | | | | | | | | | |
| *VAS* | 0-10% | 11-20% | 21-30% | 31-40% | 41-50% | 51-60% | 61-70% | 71-80% | 81-90% | 91-100% | % |
| 0-10% | 6 | 2 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 40 |
| 11-20% | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 100 |
| 21-30% | 0 | 0 | 4 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 43 |
| 31-40% | 0 | 0 | 0 | 1 | 3 | 0 | 1 | 0 | 0 | 0 | 60 |
| 41-50% | 0 | 0 | 0 | 0 | 1 | 2 | 1 | 0 | 0 | 1 | 80 |
| 51-60% | 0 | 0 | 0 | 0 | 0 | 7 | 1 | 1 | 0 | 0 | 22 |
| 61-70% | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 2 | 0 | 1 | 43 |
| 71-80% | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 9 | 8 | 2 | 57 |
| 81-90% | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 8 | 15 | 68 |
| 91-100% | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 30 | 12 |

**Net reclassification improvement** focuses on reclassification tables constructed separately for participants without events (non-cardiac syncope) and patients with events (cardiac syncope), and quantifies the balance between correct movements in categories (upwards for events and downwards for non-events) and incorrect movements (downwards for events and upwards for non-events)

The biggest incremental value of MRproANP is seen in patients with intermediate risk of cardiac syncope, determined by the

ED-physician with a visual analogue score (VAS) ranging between 21%-80%. In patients with non-cardiac syncope, 31 (5.5%) correctly moved downward in the classification and 38 patients (6.7%) incorrectly moved upward. In patients with cardiac syncope, 26 patients (21%) correctly moved upwards and 2 (1.6%) incorrectly moved downward in the classification.

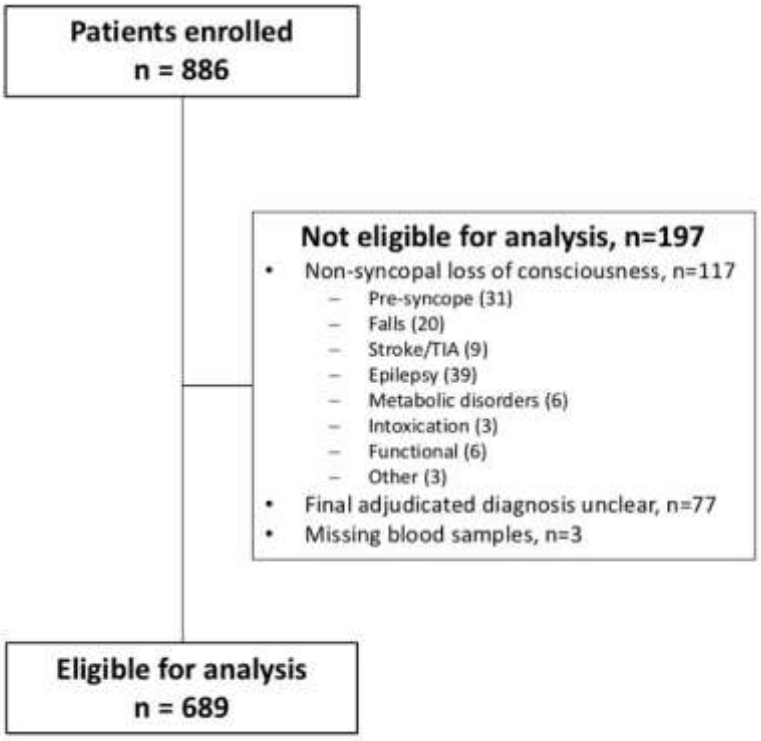
The net reclassification improvement was calculated at 0.216 ($p<0.001$). Integrated discriminatory improvement (IDI) was 0.035 ($p=0.001$).

**Table S5.** Overview of patients with low initial ED-probability (VAS-Score ≤20%) and a final diagnosis of cardiac syncope

| Age | Sex | VAS (%) | Prodromi | Situation | ECG | MRproANP (ng/L) | Diabetes | HT | HC | Smoking | ARRH | History of MI | Valvular | Epilepsy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 77 | male | 10 | No | Sitting | normal | 106 | No | No | Yes | No | Yes | No | No | No |
| 44 | female | 10 | Yes | Standing | normal | 121 | No | No | No | No | No | No | No | No |
| 79 | male | 10 | Yes | Standing | normal | 187 | No | No | Yes | No | Yes | No | No | No |
| 86 | female | 0 | Yes | Sitting | normal | 196 | Yes | No | Yes | No | No | No | No | No |
| 70 | male | 20 | No | Exertion | abnormal | 256 | No | No | No | No | No | No | No | No |
| 80 | female | 10 | Yes | Sitting | abnormal | 262 | No | No | Yes | No | No | No | No | No |
| 61 | male | 0 | No | Standing | normal | 275 | No | Yes | No | Yes | No | Yes | No | No |
| 76 | male | 0 | Yes | Standing | abnormal | 295 | No | Yes | Yes | Yes | No | Yes | No | No |
| 85 | female | 10 | No | Standing | abnormal | 451 | No | No | No | No | Yes | No | No | No |
| 80 | male | 0 | Yes | Standing | abnormal | 682 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No |
| 71 | female | 20 | Yes | Standing | normal | 1142 | No | No | Yes | Yes | No | No | No | No |

VAS = Visual analogue scale; Prodromi = Blurred Vision, Sweating or Dizziness; ECG = Electrocardiogram; HT = Hypertension; HC = Hypercholesterolemia; ARRH = Arrhythmia; MI = Myocardial Infarction; Valvular: Valvular heart disease.

**Figure S1. Patient flow diagram for all patients.**



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