Circulation

ORIGINAL RESEARCH ARTICLE

B-Type Natriuretic Peptides and Cardiac Troponins for Diagnosis and Risk-Stratification of Syncope

Editorial, see p 2419

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et al

BACKGROUND: The utility of BNP (B-type natriuretic peptide), NT-proBNP (N-terminal proBNP), and hs-cTn (high-sensitivity cardiac troponin) concentrations for diagnosis and risk-stratification of syncope is incompletely understood.

METHODS: We evaluated the diagnostic and prognostic accuracy of BNP, NT-proBNP, hs-cTnT, and hs-cTnI concentrations, alone and against those of clinical assessments, in patients >45-years old presenting with syncope to the emergency department in a prospective diagnostic multicenter study. BNP, NT-proBNP, hs-cTnT and hs-cTnI concentrations were measured in a blinded fashion. Cardiac syncope, as adjudicated by 2 physicians based on all information available including cardiac work-up and 1-year follow-up, was the diagnostic end point. EGSYS (Evaluation of Guidelines in Syncope Study), a syncope-specific diagnostic score, served as the diagnostic comparator. Death and major adverse cardiac events at 30 and 720 days were the prognostic end points. Major adverse cardiac events were defined as death, cardiopulmonary resuscitation, life-threatening arrhythmia, implantation of pacemaker/implantable cardioverter defibrillator, acute myocardial infarction, pulmonary embolism, stroke/transient ischemic attack, intracranial bleeding, or valvular surgery. ROSE (Risk Stratification of Syncope in the Emergency Department), OESIL (Osservatorio Epidemiologico della Sincope nel Lazio), SFSR (San Fransisco Syncope Rule), and CSRS (Canadian Syncope Risk Score) served as the prognostic comparators.

RESULTS: Among 1538 patients eligible for diagnostic assessment, cardiac syncope was the adjudicated diagnosis in 234 patients (15.2%). BNP, NT-proBNP, hs-cTnT, and hs-cTnI were significantly higher in cardiac syncope versus other causes (P<0.01). The diagnostic accuracy for cardiac syncope, as quantified by the area under the curve, was 0.77 to 0.78 (95% CI, 0.74–0.81) for all 4 biomarkers, and superior to EGSYS (area under the curve, 0.68 [95%-CI 0.65–0.71], P<0.001). Combining BNP/NT-proBNP with hs-cTnT/hs-cTnI further improved diagnostic accuracy to an area under the curve of 0.81 (P<0.01). BNP, NT-proBNP, hs-cTnT, and hs-cTnI cut-offs, achieving predefined thresholds for sensitivity and specificity (95%), allowed for rule-in or rule-out of ≈30% of all patients. A total of 450 major adverse cardiac events occurred during follow-up. The prognostic accuracy of BNP, NT-proBNP, hs-cTnI, and hs-cTnT for major adverse cardiac events was moderate-to-good (area under the curve, 0.75–0.79), superior to ROSE, OESIL, and SFSR, and inferior to CSRS.

CONCLUSIONS: BNP, NT-proBNP, hs-cTnT, and hs-cTnI concentrations provide useful diagnostic and prognostic information in emergency department patients with syncope.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT01548352.

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Full author list is available on page 2416.

Key Words: brain natriuretic peptide ■ emergency service, hospital ■ NT-proBNP ■ syncope ■ troponin

Sources of Funding, see page 2416

https://www.ahajournals.org/journal/circ

Clinical Perspective

What Is New?

- This large international multicenter study using central adjudication shows that BNP (B-type natriuretic peptide), NT-proBNP (N-terminal proBNP), and hs-cTn (high-sensitivity cardiac troponin) T and I concentrations display moderate-to-good diagnostic and prognostic accuracy in patients with syncope presenting to the emergency department.
- Their performance is superior to most established diagnostic and prognostic syncope scores.

What Are the Clinical Implications?

- BNP, NT-proBNP, hs-cTnT, and hs-cTnI seem useful tools for the early rule-out and rule-in of cardiac syncope in the emergency department.
- BNP, NT-proBNP, hs-cTnT, and hs-cTnI seem helpful in the triage toward hospitalization versus outpatient management in patients with syncope.

Syncope is a transient loss of consciousness associated with an inability to maintain postural tone caused by global cerebral hypoperfusion[1]. This symptom is commonly reported by patients presenting to the emergency department (ED).[2] Establishing the cause of syncope is often challenging as well as time and resource consuming. The risk of death or other adverse events is substantially higher in patients with a cardiac cause of syncope compared with those with vasovagal or orthostatic etiologies.[1,3,4] Accordingly, the diagnosis of cardiac syncope and the risk-stratification for short- and long-time major adverse cardiac events (MACE) are related.[3,4]

In contrast to other common symptoms in the ED such as acute chest pain or acute dyspnea,[5–7] the possible clinical utility of cardiovascular biomarkers including BNP (B-type natriuretic peptide), NT-proBNP (N-terminal proBNP), and hs-cTn (high-sensitivity cardiac troponin) T and I has not been thoroughly evaluated in large multicenter diagnostic studies adjudicating the final diagnosis. BNP and NT-proBNP are considered quantitative markers of hemodynamic cardiac stress and are released from the heart in response to increased intracardiac volume and pressure.[8,9] Their concentration reliably detects functionally relevant cardiac disease and predicts future cardiac events, including arrhythmias and death in both presumably healthy individuals as well as patients with known cardiac disease.[7,10–12] On the other hand, cardiomyocyte injury, as quantified by hs-cTnT and hs-cTnI concentrations, seems to be associated with the risk of death, heart failure, and arrhythmias in many cardiovascular disorders[13–15] and could also provide clinical utility in patients with syncope.

Encouraged by promising data from pilot studies in patients with syncope,[16–22] we assessed the clinical utility of BNP, NT-proBNP, hs-cTnT, and hs-cTnI in a large multicenter study, namely the diagnostic accuracy for an adjudicated diagnosis of cardiac syncope, and the prognostic accuracy for MACE and death at 30 and 720 days. In addition, we aimed at comparing the diagnostic and prognostic utility of these biomarkers with established syncope scores present in current guidelines.[1,21,23–25] We further characterized the clinical utility of BNP, NT-proBNP, hs-cTnT, and hs-cTnI in a predefined subgroup of patients in whom no obvious syncope etiology was present following initial ED evaluation.

METHODS

Study Design, Setting and Selection of Participants

The BASEL IX study (Basel Syncope Evaluation) is an ongoing prospective international diagnostic multicenter study enrolling patients from thirteen hospitals in 8 countries (Switzerland, Spain, Germany, Italy, Poland, New Zealand, Australia, and the USA). The study is designed to contribute to improving the management of patients presenting with syncope (URL: https://www.clinicaltrials.gov. Unique identifier: NCT01548352). Patients aged ≥40 years, and presenting to the ED with syncope within the last 12 hours, were recruited after written informed consent was obtained. Those with the final diagnosis of a nonsyncopal loss of consciousness (eg, epilepsy, fall, alcohol intoxication), or in whom BNP, NT-proBNP, hs-cTnT, or hs-cTnI measurement were missing, were excluded. Patients in whom a possible cardiac etiology of the index event could neither be clearly documented nor reliably excluded during central adjudication were excluded from all diagnostic analyses but remained in the prognostic analyses for death and MACE during follow-up. Patients with no obvious syncope etiology following initial ED evaluation (excluding patients presenting with atrioventricular block II type II Mobitz, atrioventricular block III, heart rate <40 bpm, life-threatening arrhythmia at presentation, central pulmonary embolism, symptomatic orthostatic dysregulation, and relevant aortic stenosis) were analyzed as a predefined subgroup to inform the need for hospitalization based on BNP, NT-proBNP, hs-cTnT, and hs-cTnI concentrations and events in the follow-up.

The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees. All patients gave their consent before participation. The authors designed the study, gathered, and analyzed the data according to the TRIPOD statement (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis; Table I in the online-only Data Supplement), [26] wrote the paper, and decided to submit. This study was conducted before data sharing processes were in place, and thus individual data, analytic methods, and study material will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Clinical Assessment, Follow-Up and Adjudicated Final Diagnosis

All patients underwent a clinical assessment as described in the Methods in the online-only Data Supplement. Patients

were contacted 6, 12, and 24 months after discharge by telephone or in written form and information regarding recurrent syncope, hospitalization and cardiac events during follow up was obtained.

To determine the final diagnosis for the index syncope in each patient, 2 independent physicians, blinded to the study-specific natriuretic peptides concentrations, reviewed all available medical records from the clinical data set and the study-specific data set (Methods in the online-only Data Supplement). 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. According to guidelines,[1] cardiac causes of syncope were defined as supraventricular or ventricular arrhythmia, severe structural heart disease, pericardial tamponade, congenital myocardial or valvular anomaly, aortic dissection, or acute pulmonary hypertension. It is important to highlight that the presence of cardiac disease (eg, coronary artery disease) alone was insufficient for the adjudication as cardiac syncope. The detailed reconstruction of the syncopal event with the study-specific data set and third-party anamnesis, as well as long-term follow-up regarding cardiovascular events or recurrent syncope, were critical pillars of the adjudication. Further details on the adjudication are given in the Methods in the online-only Data Supplement.

Blood Sampling and Laboratory Methods

Venous blood samples were drawn via a peripheral intravenous line on ED arrival. EDTA plasma was then immediately processed and frozen at –80°C until it was assayed. BNP measurements were performed using the Architect BNP assay,[27] NT-proBNP using the Elecsys proBNP (Roche Diagnostics) ,[28] hs-cTnT using the hs-cTnT Elecsys 2010 assay (Roche Diagnostics),[29] and hs-cTnI using the ARCHITECT High Sensitive STAT Troponin I assay (Abbott Laboratories).[30] To possibly further extrapolate the findings generated for BNP and NT-proBNP, also the third natriuretic peptide assay becoming available for clinical practice (MR-proANP [midregional proatrial natriuretic peptide]) was measured in a subgroup using a validated sandwich immunoassay.[31] The laboratory team who measured biomarkers were blinded to patient, clinical and diagnostic assessment, discharge, and adjudicated diagnosis.

End Points

The primary diagnostic end point was the diagnostic accuracy of BNP, NT-proBNP, hs-cTnT, and hs-cTnI for cardiac syncope. The coprimary prognostic end points were the accuracy of BNP, NT-proBNP, hs-cTnT, and hs-cTnI to predict either death or overall MACE at 30 and 720 days of follow-up.

Secondary end points were the prognostic accuracies of BNP, NT-proBNP, hs-cTnT, and hs-cTnI for ischemic and arrhythmic MACE at similar time points. Arrhythmic MACE were defined as a composite of death, resuscitated cardiac arrest, life-threatening arrhythmia, implantation of a pacemaker or implantable cardioverter defibrillator (ICD). Ischemic MACE were defined as a composite of death or acute myocardial infarction. Life-threatening arrhythmia was defined as ventricular fibrillation, sustained ventricular tachycardia >120 beats/min, ventricular pause >3 s,ventricular standstill, or asystole, consistent with the definition given in previous syncope research[16]. Acute myocardial infarction was defined according to the Third Universal Definition[9]. Overall MACE included pulmonary embolism, stroke/transient ischemic attack, intracranial bleeding and valvular surgery in addition to arrhythmic and ischemic MACE. pulmonary embolism, stroke/transient ischemic attack, intracranial bleeding and valvular surgery in addition to arrhythmic and ischemic MACE.

Accuracies of BNP, NT-proBNP, hs-cTnT, hs-cTnI, MR-proANP, Established Syncope Scores and a Combination of Predefined Clinical Variables

To further characterize the clinical utility of BNP, NT-proBNP, hs-cTnT, and hs-cTnI, we performed a direct comparison of their diagnostic and prognostic accuracies with other biomarkers, namely MR-proANP and clinically available cTn (because various conventional assays were used in the different centers, cTn values were normalized to their 99th percentile). Further comparisons were performed with established syncope scores or a combination of clinical variables. The scores are designed to inform the diagnosis of syncope in the ED[1,21,23–25]: This included the EGSYS diagnostic score, which was designed to differentiate between cardiac and noncardiac causes of syncope;[32] the OESIL risk score, which was designed to identify patients at higher risk of mortality within the first 12 months;[25] the ROSE rule and CSRS (Canadian Syncope Risk Score), both predicting 1-month serious outcome and all-cause death[16,21]; and SFSR (San Francisco Syncope Rule),[24] which predicts 7-day adverse events. We used these scores for their respective end points and compared their predictive accuracy with those of BNP, NT-proBNP, hs-cTnT, and hs-cTnI (Methods in the online-only Data Supplement). Moreover, we compared the diagnostic accuracy of BNP, NT-proBNP and hs-cTn with a combination of several clinically relevant variables known as relevant confounders in the evaluation of syncope,[3] as listed in the Methods in the online-only Data Supplement.

Need for Hospitalization in Patients With No Obvious Syncope Etiology on ED Evaluation

In the predefined subgroup of patients with no obvious syncope etiology on ED evaluation, BNP, NT-proBNP, hs-cTnT, and hs-cTnI concentrations were analyzed depending on whether the patients had a MACE within 30 days of the ED presentation in order to inform the possibility to avoid hospitalization without risking 30-day readmission in these patients.

Statistical Analyses

Continuous variables were presented as mean±SD or median with interquartile ranges. Categorical variables were expressed as numbers and percentages. Mann-Whitney-U test was applied for comparison of continuous variables and Pearson Chi-square test or Fisher exact test for comparison of categorical variables. Areas under the receiver operating characteristic curve (AUC) were constructed to assess the diagnostic accuracy. Comparisons of AUCs were performed according to Delong et al.[33]

To assess the possible presence and effect of verification bias, sensitivity analysis was performed in the subgroups of patients in whom BNP, NT-proBNP, or cTn concentrations were measured as part of routine clinical care.

Optimal cut-offs for given sensitivities/specificities for the diagnosis of cardiac syncope using BNP, NT-proBNP, hs-cTnT, and hs-cTnI were derived. We predefined a sensitivity of ≥95% for possible use as rule-out and a specificity of ≥95% for rule-in for cardiac syncope. Confidence intervals for these measures were computed according to Agresti and Caffo.[34] Univariable and multivariable logistic regressions were used to assess the predictive accuracy of log-transformed BNP, NT-proBNP, hs-cTnT, and hs-cTnI concentrations to diagnose cardiac syncope (Methods in the online-only Data Supplement).

As different cardiac disorders may lead to cardiac syncope, the diagnostic accuracy of BNP and NT-proBNP was assessed specifically for the predefined cardiac syncope phenotypes of ventricular tachycardia or valvular heart disease and bradycardia.

Because BNP and NT-proBNP may provide lower diagnostic accuracy for bradycardia,[10,35] their diagnostic accuracy was also assessed in combination with an ECG score derived in this dataset.

Time-dependent receiver operating characteristic[36] curves were computed using the "time receiver operating characteristic" package to assess the accuracy of BNP, NT-proBNP, hs-cTnT, and hs-cTnI to predict death, MACE, and ischemic and arrhythmic MACE during the whole follow-up length. A time-dependent receiver operating characteristic curve varies as a function of time and accommodates censored data.

The Cox proportional hazard model was used to assess log-transformed BNP, NT-proBNP, hs-cTnT, and hs-cTnI concentrations in the prediction of these outcomes when correcting for predefined important covariates (Methods in the online-only Data Supplement). Kaplan-Meier curves were used to represent event-free survival. Comparison of Kaplan-Meier curves was performed according to the log-rank test. All hypothesis testing was 2-tailed, and $P<0.05$ was considered statistically significant. Statistical analyses were performed using the R statistical package (Vienna, Austria).

RESULTS

Characteristics of Patients

From May 2010 to March 2017, 1913 patients were enrolled (Figure I in the online-only Data Supplement), of which 1472 and 1338 patients were eligible for the analysis of prognostic and diagnostic end points, respectively.

Mean age was 71 years, 40% of patients were women, and approximately half had a history of cardiovascular disease (Table 1). Patients with a final adjudicated diagnosis of cardiac syncope (n=221, 15.0%) were significantly older, had more often a history of cardiovascular diseases, and were more likely to be on long-term cardiovascular medications versus those with other adjudicated diagnoses. Distribution of patients with cardiac syncope among the predefined cardiac subcategories are shown in Table II in the online-only Data Supplement. Other adjudicated diagnoses included reflex (n=588, 39.9%), orthostatic (n=403, 27.3%), other noncardiac (n=126, 8.6%), and syncope of unknown etiology (n=134, 9.1%).

Concentrations of BNP, NT-proBNP, hs-cTnT, and hs-cTnI and Syncope Etiology

BNP, NT-proBNP, hs-cTnT, and hs-cTnI plasma concentrations were significantly higher in patients adjudicated to have cardiac syncope compared with patients with reflex, orthostatic, or other noncardiac syncope (Figure 1, $P<0.001$ for each comparison).

Diagnostic Accuracy of BNP, NT-proBNP, hs-cTnT, and hs-cTnI for the Diagnosis of Cardiac Syncope

The diagnostic accuracies of the biomarkers and clinical scores alone or in combination are presented in Figure 2 and Table 2. The diagnostic accuracies of BNP, NT-proBNP, hs-cTnT, and hs-cTnI for cardiac syncope were moderate-to-good (all AUCs, 0.77–0.78; 95% CI, 0.74–0.81; *P* for comparison=NS), superior to EGSYS ($P<0.001$) and to a combination of clinical variables ($P\leq0.01$), and similar to MR-proANP (Figure II in the online-only Data Supplement). When added to the EGSYS score or to a combination of clinical variables, BNP, NT-proBNP, hs-cTnT, and hs-cTnI significantly improved the diagnostic accuracy of these clinical models. When combined, BNP or NT-proBNP with hs-cTnT or hs-cTnI, these performed significantly better than either biomarker alone and provided high diagnostic accuracy (AUC, 0.81).

Sensitivity Analysis

In some patients, BNP (n=168, 11.4%), NT-proBNP (n=137, 9.3%), or cTn (n=1036, 70.4%, mostly using a conventional and not hs-cTn assay) were measured as part of clinical routine.

Sensitivity analysis in the subgroups of patients with at least one of these biomarkers measured as part of clinical routine revealed similar AUCs compared with the overall cohort for the diagnosis of cardiac syncope (Figure III in the online-only Data Supplement).

In the subgroup of patients with cTn measured as part of clinical routine, BNP and NT-proBNP provided higher AUC compared with clinical cTn (Figure IV in the online-only Data Supplement).

Derivation of Optimal BNP, NT-proBNP, hs-cTnT, and hs-cTnI Cut-Offs for the Diagnosis of Cardiac Syncope

The biomarkers cut-offs associated with a predefined specificity of ≥95% for rule-in of patients with car-

Table 1. Patient Characteristics

	All Patients	Cardiac	Noncardiac	Unknown	*P* Value
Number of patients	1472	221	1117	134	
Age-years (median [IQR])	71.0 [57.0, 80.0]	77.0 [66.0, 83.0]	68.0 [55.0, 78.0]	79.0 [69.2, 84.0]	<0.001
Female, n (%)	591 (40)	79 (36)	458 (41)	54 (40)	0.167
Characteristics of the syncope, n (%)					
Nausea or vomiting	426 (29)	42 (19)	364 (33)	20 (15)	<0.001
Sweating	452 (31)	47 (22)	386 (35)	19 (15)	<0.001
Pallor	401 (44)	45 (35)	330 (47)	26 (32)	0.014
Palpitations	100 (7)	22 (10)	71 (7)	7 (5)	0.075
Angina	85 (6)	23 (11)	56 (5)	6 (5)	0.004
Caused injury	211 (15)	35 (16)	146 (13)	30 (23)	0.305
Position of the syncope, n (%)					
While lying	38 (3)	5 (2)	30 (3)	3 (2)	0.899
While sitting	584 (40)	75 (34)	457 (41)	52 (39)	0.056
Orthostatic	176 (12)	18 (8)	148 (13)	10 (8)	0.044
While standing	656 (45)	121 (55)	466 (42)	69 (52)	0.001
Exertion	124 (9)	40 (18)	68 (6)	16 (12)	<0.001
Risk factors, n (%)					
Hypertension	881 (60)	153 (70)	626 (56)	102 (77)	<0.001
Hypercholesterolemia	610 (43)	107 (50)	440 (41)	63 (50)	0.011
Diabetes	210 (14)	44 (20)	142 (13)	24 (18)	0.007
Smoking	753 (52)	106 (49)	574 (52)	73 (56)	0.425
History, n (%)					
Previous stroke	116 (8)	16 (7)	81 (7)	19 (14)	1.000
Chronic heart failure (NYHA II–IV)	108 (7)	35 (16)	60 (5)	13 (10)	<0.001
History of arrhythmia	299 (21)	83 (38)	184 (17)	32 (24)	<0.001
Pacemaker	66 (5)	21 (10)	44 (4)	1 (1)	0.001
ICD or CRT	39 (3)	17 (8)	20 (2)	2 (2)	<0.001
Coronary artery disease	310 (21)	77 (36)	197 (18)	36 (27)	<0.001
Previous DVT or PE	102 (7)	15 (7)	71 (6)	16 (12)	0.929
Previous MI	184 (12)	48 (22)	116 (10)	20 (15)	<0.001
Chronic medication, n (%)					
ACEIs/ARBs	669 (45)	121 (55)	474 (42)	74 (55)	0.001
α-Blockers	115 (8)	17 (8)	84 (8)	14 (10)	1.000
Antiarrhythmics class I	55 (4)	15 (7)	32 (3)	8 (6)	0.007
Aspirin	428 (29)	80 (36)	297 (27)	51 (38)	0.005
β-Blockers	468 (32)	99 (45)	314 (28)	55 (41)	<0.001
Calcium antagonists	245 (17)	41 (19)	171 (15)	33 (25)	0.269
Digitalis	25 (2)	11 (5)	13 (1)	1 (1)	<0.001
Diuretics	443 (30)	100 (45)	295 (26)	48 (36)	<0.001

P values are given for the comparison cardiac versus noncardiac syncope. A history of arrhythmia was defined as any symptomatic supraventricular or ventricular arrhythmia present in the patient's history.

ACEI indicates angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; DVT, deep venous thrombosis; ICD, intracardiac defibrillator; IQR, interquartile range; MI, myocardial infarction; NYHA, New York Heart Association; and PE, pulmonary embolism.

diac syncope (for BNP 302 pg/mL, NT-proBNP 1966 pg/mL, hs-cTnT 42 ng/L, and hs-cTnI 31.1 ng/L) allowed for a rule-in rate of ≈9% of patients, whereas the cut-off for a predefined sensitivity of ≥95% (for BNP 14.9 pg/mL, NT-proBNP 69 pg/mL, hs-cTnT 5 ng/L, and hs-cTnI 2.2 ng/L) for rule-out allowed a rule-out rate of ≈21% of patients (Table III in the online-only Data Supplement). Accordingly, these

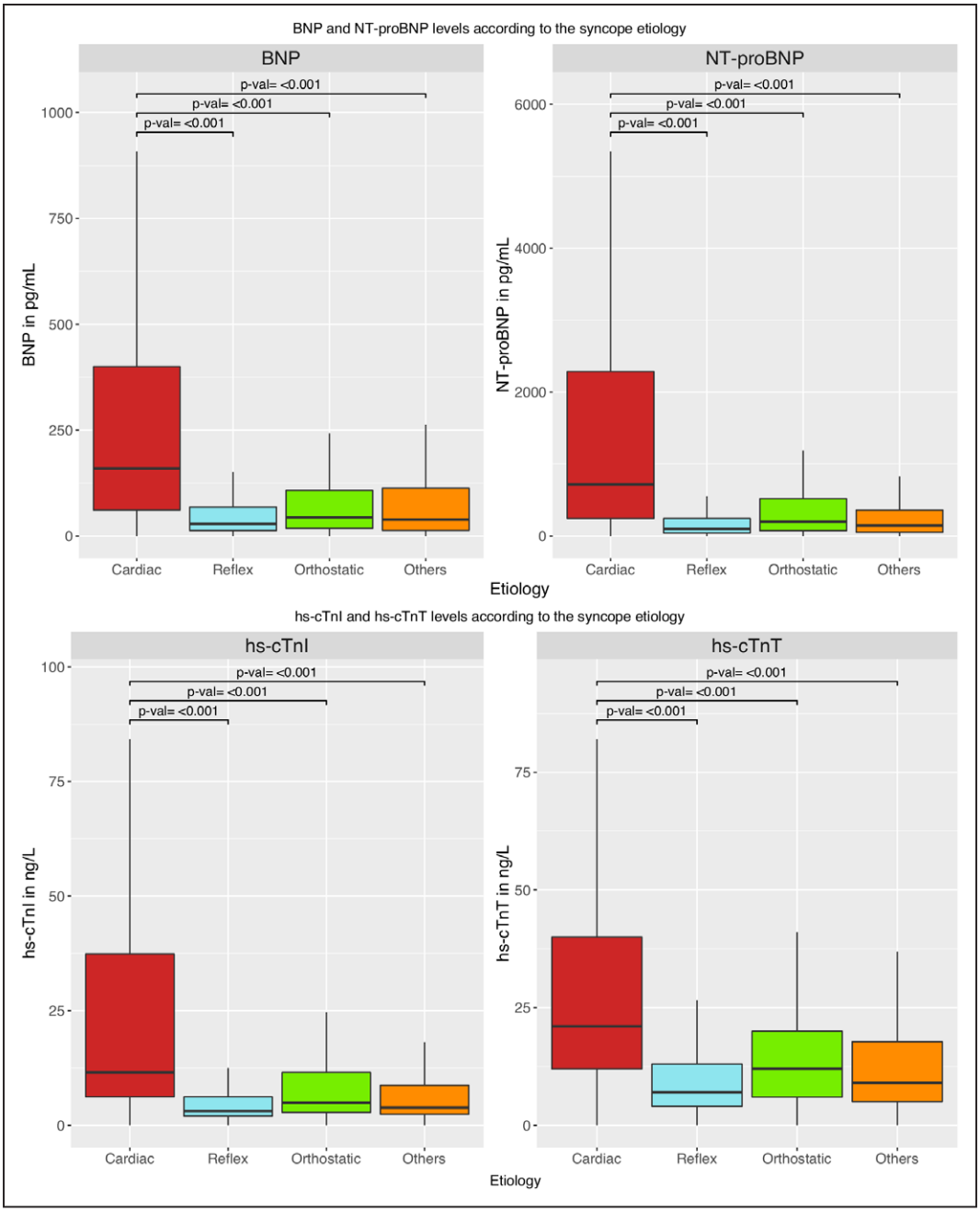

Figure 1. Box plots representing the BNP/NT-proBNP and hs-cTnT/I concentrations according to the syncope etiology (cardiac syncope n=234, reflex syncope n=617, orthostatic syncope n=417, other noncardiac syncope n=130).
The box plots represent the median with the interquartile range, whiskers represent ±1.5 × the interquartile range. *P* values were calculated based on a Wilcoxon-rank-sum test. Syncope was defined as of "other, noncardiac" etiology when the underlying pathophysiological mechanism of syncope remained unclear but a cardiac syncope was ruled-out. BNP indicates B-type natriuretic peptide; hs-cTn, high-sensitivity cardiac troponin; and NT-proBNP, N-terminal proBNP.

cut-offs allowed for the rule-in or rule-out of ≈30% of all patients.

Likelihood Ratios

The positive and negative likelihood ratios for adding BNP, NT-proBNP, hs-cTnT, or hs-cTnI to the recommended cut-off of the EGSYS score (≥3) and the resulting posterior probability for cardiac syncope are shown in Figure 3. Table IV in the online-only Data Supplement shows the negative predictive value, positive predictive value, and incidence of criteria (% of patients classified as rule-in or rule-out) when a stratification using EGSYS≥3 is applied first or when only predefined 95%-sensitivity/specificity BNP, NT-proBNP, hs-cTnT, and hs-cTnI cut-offs are used. MACE rates at 30 days in the rule-out groups were very low and similar when EGSYS<3 was first used for risk-stratification or when only predefined 95%-cut-offs were used (Table V in the online-only Data Supplement).

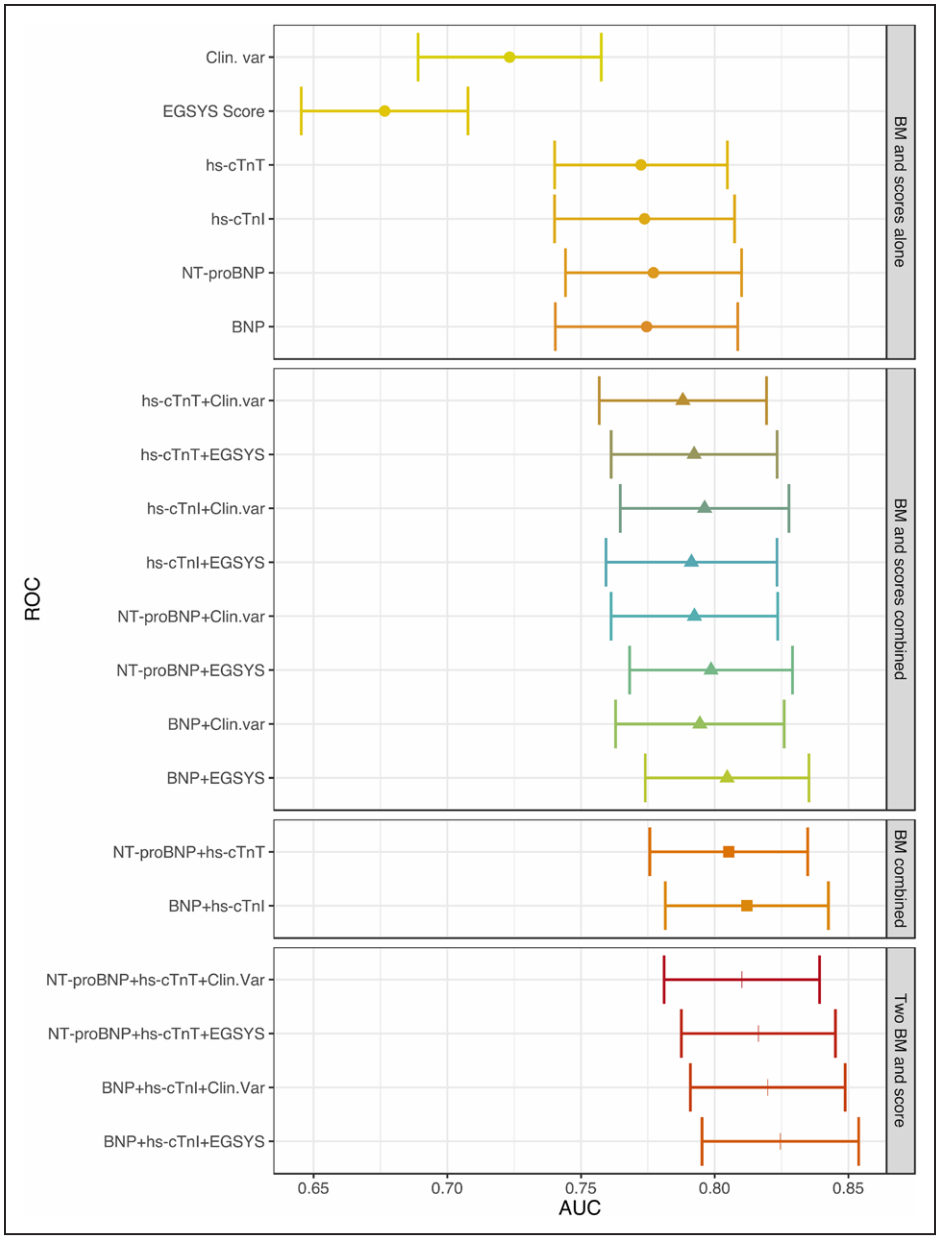

Figure 2. Forest plot representing the accuracies, as defined by the AUC, of BNP, NT-proBNP, hs-cTnT, and hs-cTnI and clinical scores alone, biomarkers and scores combined, or biomarkers combined.
The combinations of BNP with hs-cTnI (both on Architect) and NT-proBNP with hs-cTnT (both on Elecsys) are represented as these pairs of assays were available on the same laboratory platform and therefore more easily available to clinicians. Points represent the AUC; whiskers represent 95% confidence interval. AUC indicates area under the curve; BM,biomarker; BNP, B-type natriuretic peptide; Clin. var, clinical variables; EGSYS, Evaluation of Guidelines in Syncope Study score; hs-cTn, high-sensitivity cardiac troponin; and NT-proBNP, N-terminal proBNP.

Natriuretic Peptides Diagnostic Accuracy Among Cardiac Syncope Etiologies

Among cardiac syncope, patients adjudicated to have ventricular tachycardia or valvular heart disease had higher BNP and NT-proBNP than the patients adjudicated to have bradycardia-induced syncope.

Accordingly, the AUC of BNP and NT-proBNP to diagnose ventricular tachycardia or valvular heart disease was higher compared with the AUC to diagnose bradycardia-induced syncope (Figure V in the online-only Data Supplement).

Combining BNP or NT-proBNP with an ECG risk score derived in this data set improved the diagnostic accuracy for bradycardia (Table VI and Figure VI in the online-only Data Supplement).

Multivariable Analysis

In multivariable analysis, BNP, NT-proBNP, hs-cTnT, and hs-cTnI concentrations and an abnormal ECG were significant predictors of a cardiac etiology (Tables VII and VIII in the online-only Data Supplement).

Table 2. Comparison of AUCs

First AUC	Second AUC	Comparison by DeLong: *P* Value
BNP, 0.77 [0.74, 0.81]	NT-proBNP, 0.78 [0.74, 0.81]	0.73
BNP, 0.77 [0.74, 0.81]	hs-cTnI, 0.77 [0.74, 0.81]	0.967
BNP, 0.77 [0.74, 0.81]	hs-cTnT, 0.77 [0.74, 0.8]	0.912
BNP, 0.77 [0.74, 0.81]	EGSYS score, 0.68 [0.65, 0.71]	<0.001
BNP, 0.77 [0.74, 0.81]	Clin var, 0.72 [0.69, 0.76]	0.01
BNP, 0.77 [0.74, 0.81]	BNP+EGSYS, 0.80 [0.77, 0.84]	<0.001
BNP, 0.77 [0.74, 0.81]	BNP+Clin var, 0.79 [0.76, 0.83]	0.008
BNP, 0.77 [0.74, 0.81]	BNP+hs-cTnI, 0.81 [0.78, 0.84]	<0.001
BNP, 0.77 [0.74, 0.81]	BNP+hs-cTnI+EGSYS, 0.82 [0.8, 0.85]	<0.001
BNP, 0.77 [0.74, 0.81]	BNP+hs-cTnI+Clin var, 0.82 [0.79, 0.85]	<0.001
NT-proBNP, 0.78 [0.74, 0.81]	NT-proBNP+EGSYS, 0.80 [0.77, 0.83]	0.004
NT-proBNP, 0.78 [0.74, 0.81]	NT-proBNP+Clin var, 0.79 [0.76, 0.82]	0.022
NT-proBNP, 0.78 [0.74, 0.81]	NT-proBNP+hs-cTnT, 0.81 [0.78, 0.83]	0.002
NT-proBNP, 0.78 [0.74, 0.81]	NT-proBNP+hs-cTnT+EGSYS, 0.82 [0.79, 0.85]	<0.001
NT-proBNP, 0.78 [0.74, 0.81]	NT-proBNP+hs-cTnT+Clin var, 0.81 [0.78, 0.84]	0.001
hs-cTnI, 0.77 [0.74, 0.81]	hs-cTnI+EGSYS, 0.79 [0.76, 0.82]	0.035
hs-cTnI, 0.77 [0.74, 0.81]	BNP+hs-cTnI, 0.81 [0.78, 0.84]	<0.001
hs-cTnI, 0.77 [0.74, 0.81]	BNP+hs-cTnI+EGSYS, 0.82 [0.8, 0.85]	<0.001
hs-cTnI, 0.77 [0.74, 0.81]	BNP+hs-cTnI+Clin.Var, 0.82 [0.79, 0.85]	<0.001
hs-cTnT, 0.77 [0.74, 0.8]	hs-cTnT+EGSYS, 0.79 [0.76, 0.82]	0.005
hs-cTnT, 0.77 [0.74, 0.8]	hs-cTnT+Clin.var, 0.79 [0.76, 0.82]	0.008
hs-cTnT, 0.77 [0.74, 0.8]	NT-proBNP+hs-cTnT, 0.81 [0.78, 0.83]	<0.001
hs-cTnT, 0.77 [0.74, 0.8]	NT-proBNP+hs-cTnT+EGSYS, 0.82 [0.79, 0.85]	<0.001
hs-cTnT, 0.77 [0.74, 0.8]	NT-proBNP+hs-cTnT+Clin var, 0.81 [0.78, 0.84]	<0.001
EGSYS score, 0.68 [0.65, 0.71]	BNP+EGSYS, 0.80 [0.77, 0.84]	<0.001
EGSYS score, 0.68 [0.65, 0.71]	NT-proBNP+EGSYS, 0.8 [0.77, 0.83]	<0.001
EGSYS score, 0.68 [0.65, 0.71]	hs-cTnI+EGSYS, 0.79 [0.76, 0.82]	<0.001
EGSYS score, 0.68 [0.65, 0.71]	hs-cTnT+EGSYS, 0.79 [0.76, 0.82]	<0.001
EGSYS score, 0.68 [0.65, 0.71]	BNP+hs-cTnI+EGSYS, 0.82 [0.8, 0.85]	<0.001
EGSYS score, 0.68 [0.65, 0.71]	NT-proBNP+hs-cTnT+EGSYS, 0.82 [0.79, 0.85]	<0.001
Clin var, 0.72 [0.69, 0.76]	BNP+Clin var, 0.79 [0.76, 0.83]	<0.001
Clin var, 0.72 [0.69, 0.76]	NT-proBNP+Clin var, 0.79 [0.76, 0.82]	<0.001
Clin var, 0.72 [0.69, 0.76]	hs-cTnI+Clin var, 0.80 [0.76, 0.83]	<0.001
Clin var, 0.72 [0.69, 0.76]	hs-cTnT+Clin var, 0.79 [0.76, 0.82]	<0.001
Clin var, 0.72 [0.69, 0.76]	BNP+hs-cTnI+Clin var, 0.82 [0.79, 0.85]	<0.001
Clin var, 0.72 [0.69, 0.76]	NT-proBNP+hs-cTnT+Clin var, 0.81 [0.78, 0.84]	<0.001

95% CI are given in brackets. The clinical variables are described in the Appendix in the online-only Data Supplement. All comparisons with the EGSYS score have been conducted only in patients with an available EGSYS score. AUC indicates area under the curve; BNP, B-type natriuretic peptide; Clin var,clinical variables; EGSYS, Evaluation of Guidelines in Syncope Study score; Hs-cTnT/I, high-sensitivity cardiac troponin T/I; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Prognostic Accuracy of BNP, NT-proBNP, hs-cTnT, and hs-cTnI

Follow-up was complete in 100% of patients at 30 days, in 99.7% of patients at 360 days, and in 83.2% of patients at 720 days. During follow-up, 209 patients (14.2%) died and 425 (28.8%) had at least 1 MACE. During follow-up, an ischemic MACE occurred in 259 patients (17.6%), and an arrhythmic MACE in 332 patients (22.6%).

The prognostic accuracy of BNP, NT-proBNP, hs-cTnT, and hs-cTnI was moderate-to-good for death and MACE (Figure 4; Figure VII in the online-only Data Supplement). For death and MACE, all biomarkers performed similarly in the short-term but NT-proBNP and hs-cTnT showed sig-

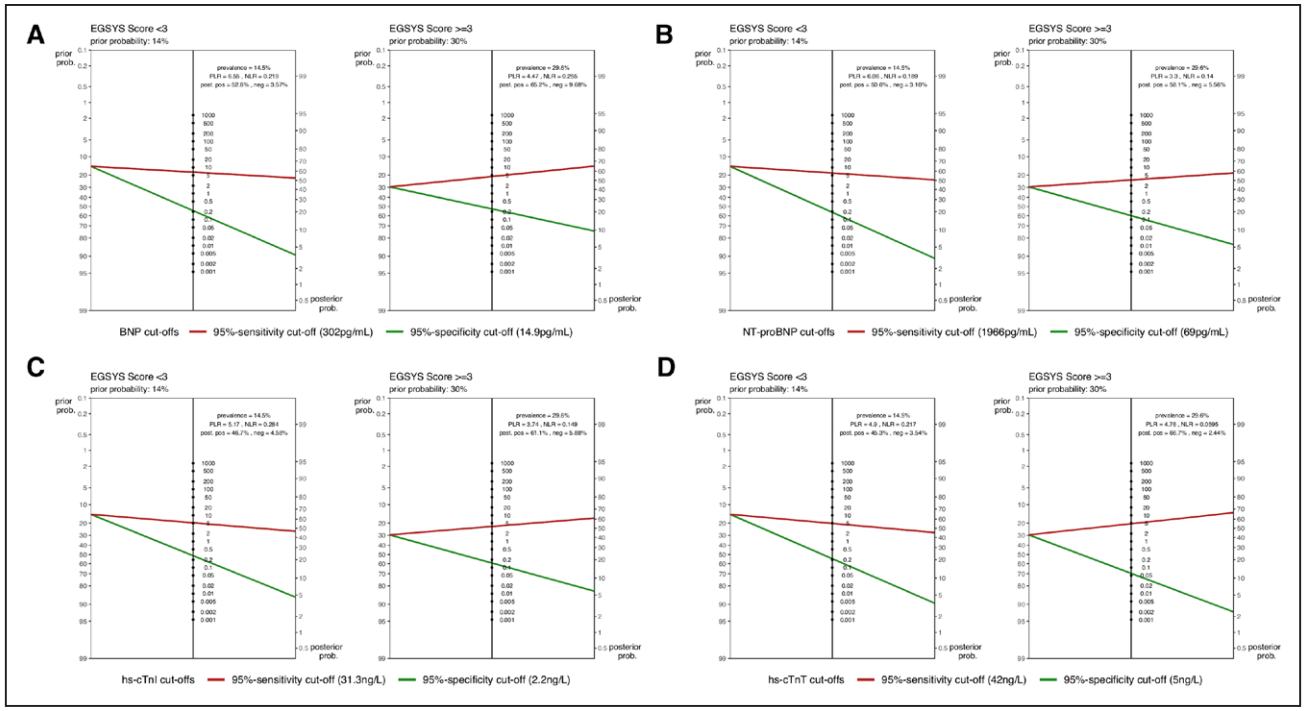

Figure 3. Prior probability, likelihood ratios (on the middle line), and posterior probability given by the EGSYS score and the adjunction of 1 biomarker. The tested biomarkers are BNP (**A**), NT-proBNP (**B**), hs-cTnI (**C**), and hs-cTnT (**D**). EGSYS indicates Evaluation of Guidelines in Syncope Study score; hs-cTn, high-sensitivity cardiac troponin; NLR,negative likelihood ratio; PLR, positive likelihood ratio; post. Pos, positive posterior probability; and post. Neg, posterior negative probability.

nificantly better performance at 720 days (for instance, NT-proBNP versus BNP at 720 days, $P<0.001$ for death and $P=0.007$ for MACE; Figure 4). In the short-term, hs-cTnT and hs-cTnI performed better for ischemic MACE, whereas BNP and NT-proBNP performed better for arrhythmic MACE (Figure VII in the online-only Data Supplement). In the long-term, NT-proBNP performed better in the prediction of arrhythmic MACE than hs-cTnI (NT-proBNP versus hs-cTnI at 720 days $P=0.007$ for arrhythmic MACE), but similarly to BNP and hs-cTnT ($P\geq0.05$).

In the 693 patients eligible for the direct comparison of BNP and MR-proANP, both assays displayed similar prognostic accuracy for MACE (for all comparisons at 30 and 720 days, P=NS; Figure VIII in the online-only Data Supplement).

Direct Comparison of BNP, NT-proBNP, hs-cTnT, and hs-cTnI With Established Prognostic Risk Scores

During the first 7 days, 75 patients (5.3%) experienced an adverse event as defined by the original derivation of SFSR. During the first month of follow-up, 160 patients (11.2%) experienced an adverse event as defined by the original derivation of the ROSE rule and 182 (12.8%) experienced an adverse event as defined by the original derivation of CSRS. During the first year of follow-up, 87 (5.9%) patients died. The prognostic accuracy of BNP, NT-proBNP, hs-cTnI, and hs-cTnT for MACE was moderate-to-good (AUC, 0.75–0.79), superior to ROSE, OESIL, and SFSR, and inferior to CSRS (Figure IX, Table IX in the online-only Data Supplement) All biomarkers significantly improved the scores.

Multivariable Analysis for Death and MACE at 30 and 720 Days

Log-transformed BNP and NT-proBNP concentrations were significant predictors in the multivariable Cox proportional hazard model for all long-term prognostic end points (death, overall MACE, ischemic MACE, and arrhythmic MACE at 720 days). Short-term, BNP, and NT-proBNP concentrations were significant predictors for death, BNP for arrhythmic MACE and NT-proBNP for overall MACE. (Tables X through XIII in the online-only Data Supplement).

Need for Hospitalization in Patients With No Obvious Syncope Etiology on ED Evaluation

Among patients with no obvious etiology for their syncope on ED evaluation, 10 died within 30 days and 146 experienced a MACE.

Patients experiencing a MACE during follow-up had significantly higher BNP, NT-proBNP, hs-cTnT, and hs-cTnI concentrations compared with patients without events (Figure 5). The lowest 90%-sensitivity cut-offs

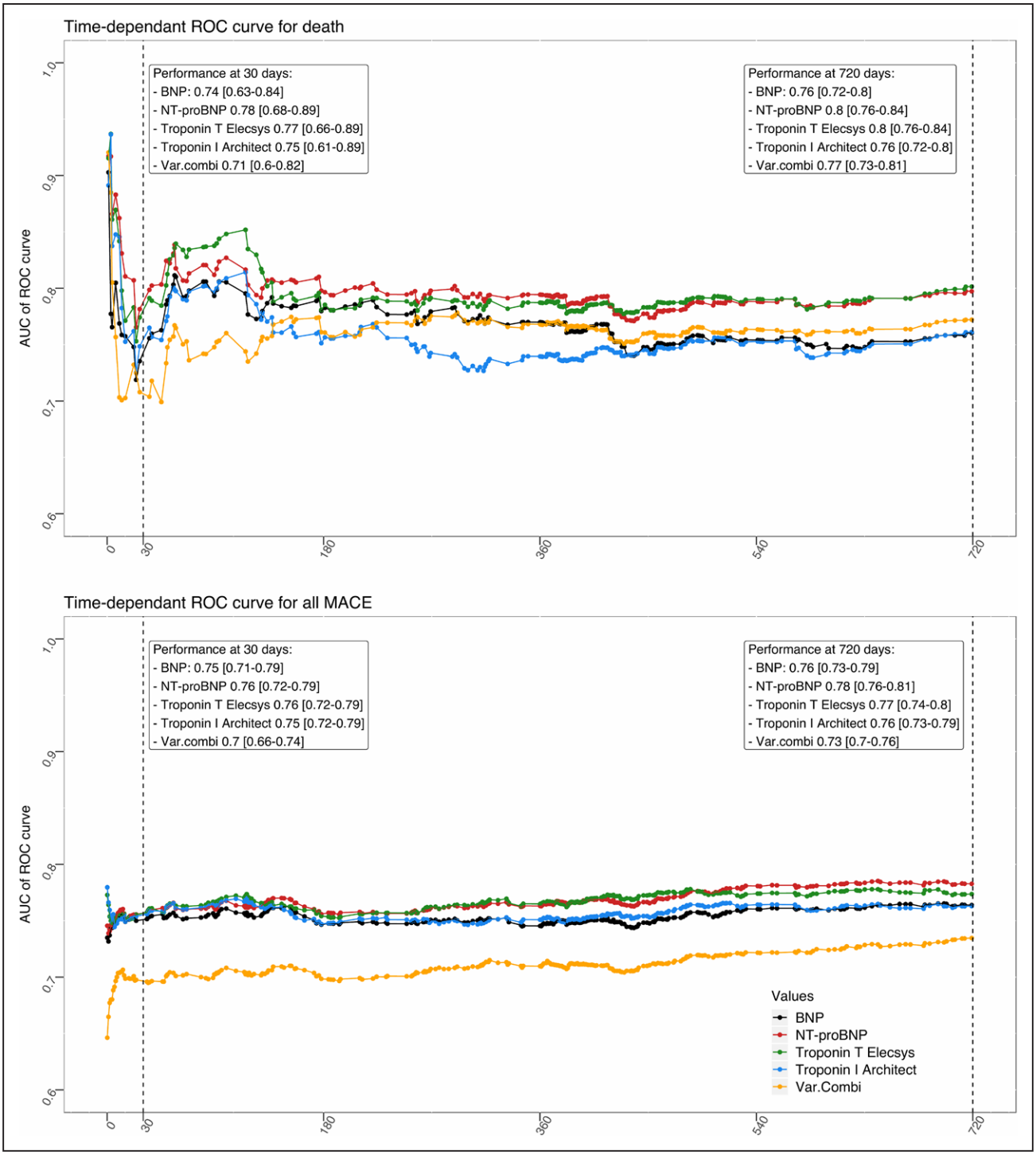

Figure 4. Time-dependent receiver operating characteristic curves for the accuracy of BNP and NT-proBNP for the prognosis of death and overall MACE.

95% confidence intervals are given in brackets. AUC indicates area under the curve; BNP, B-type natriuretic peptide; MACE, major cardiovascular events; NT-proBNP, N-terminal proBNP; ROC, receiver operating characteristic; and Var. combi, combination of clinical variables.

to rule out both death and MACE up to 30-day follow-up (as highlighted in Table XIV in the online-only Data Supplement) allowed for a safe rule-out of ≈30% of patients (Figure 6). Among the patients ruled out by the respective 90%-sensitivity cut-offs, ≈25% had been hospitalized for a median of 3 days (Table XV in the online-only Data Supplement).

DISCUSSION

This large prospective, multicentre study using central diagnostic adjudication and long-term follow-up aimed to advance the rapid and accurate diagnosis and risk stratification of patients presenting with syncope to the ED. We report 3 major findings.

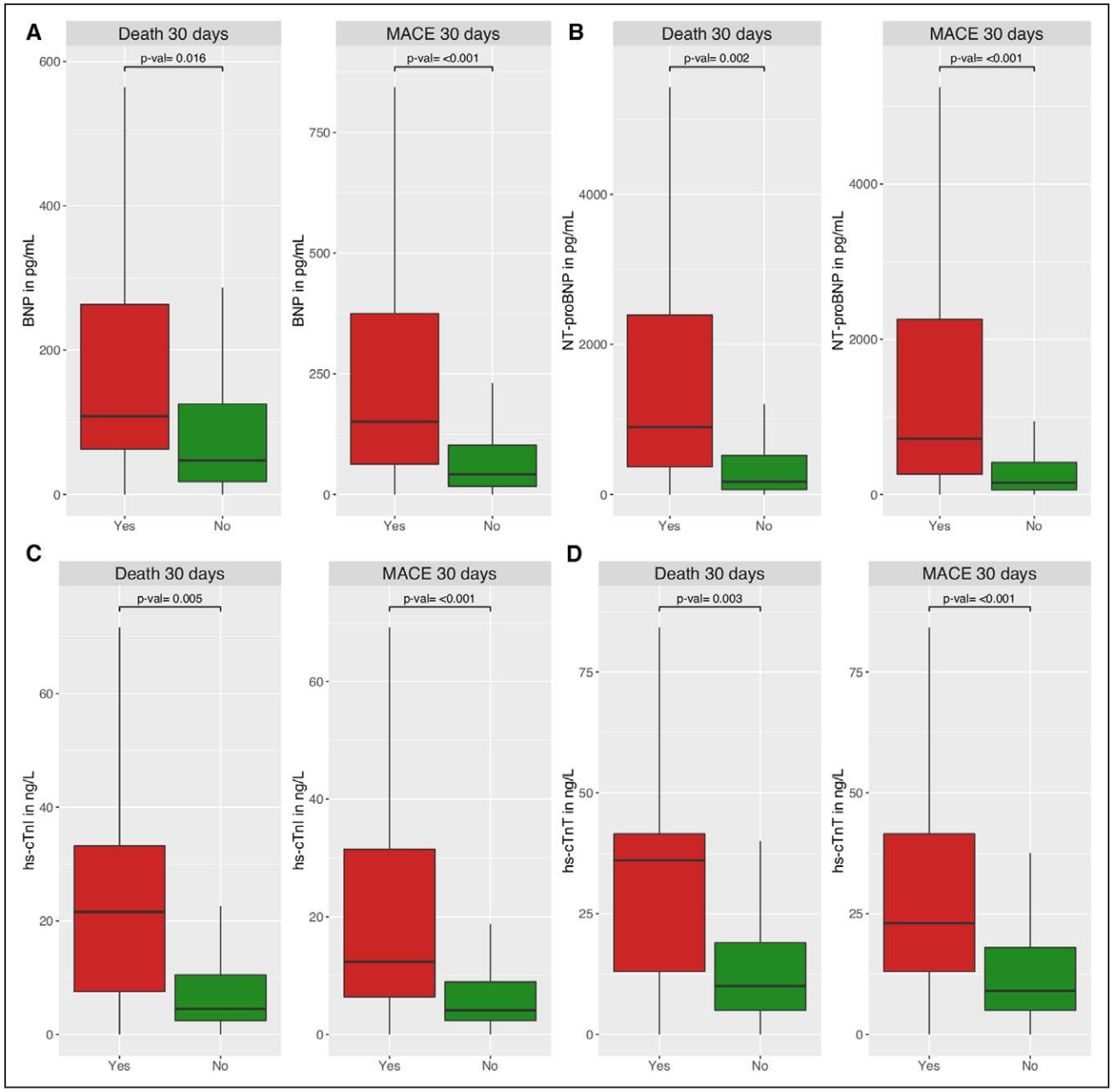

Figure 5. Box plots representing the biomarker concentrations according to whether patients experienced a clinical event during the 30-day follow-up. BNP (**A**), NT-proBNP (**B**), hs-cTnI (**C**), and hs-cTnT (**D**). The box plots represent the median with the interquartile range, whiskers represent ±1.5 × the interquartile range. *P* values were calculated based on a Wilcoxon-rank-sum test. BNP indicates B-type natriuretic peptide; hs-cTn, high-sensitivity cardiac troponin; MACE, major cardiovascular events; and NT-proBNP, N-terminal proBNP.

First, BNP, NT-proBNP, hs-cTnT, and hs-cTnI concentrations were significantly higher in patients adjudicated to have cardiac syncope compared with other causes of syncope and provided moderate-to-high accuracy for the diagnosis of cardiac syncope. All 4 biomarkers were superior to clinical diagnostic models, and their combination even further increased diagnostic accuracy.

Second, if applied as a triage tool on the whole study population of patients >45 years presenting to the ED with syncope, BNP, NT-proBNP, hs-cTnT, and hs-cTnI concentrations allowed the rule-out and rule-in of cardiac syncope with the predefined 95% sensitivity and 95% specificity criteria in about 30% of patients.

Third, BNP, NT-proBNP, hs-cTnT, and hs-cTnI provided high accuracy for the prediction of short- and long-term death and MACE and performed better than a combination of clinical variables or several established syncope-specific risk scores. The clinical utility of these biomarkers is likely highest in the subgroup of patients in whom the ED diagnosis remains unclear after the standard diagnostic processes available in the ED (ECG, history of severe aortic stenosis, Schellong test for orthostatic hypotension), where they could provide

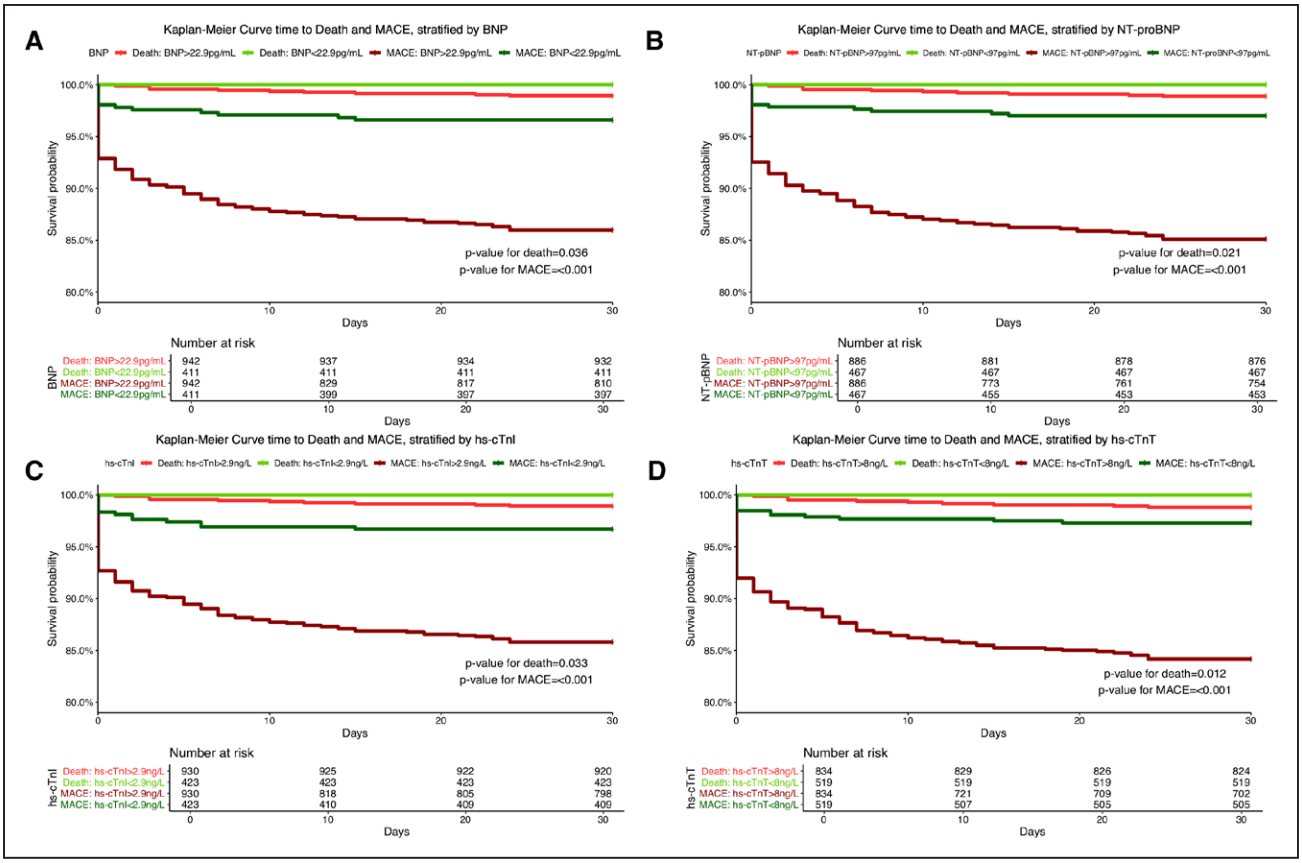

Figure 6. Kaplan Meier Curves representing event-free survival for death and MACE according to a cut-offs for each biomarker.
BNP (cut-off 22.9 pg/mL) (**A**), NT-proBNP (cut-off 97 pg/mL) (**B**), hs-cTnI (cut-off 2.9 ng/L) (**C**), and hs-cTnT (cut-off 8 ng/L) (**D**). These cut-offs allow for a safe rule out of ≈30% of patients (411/1353 for BNP, 467/1353 for NT-proBNP, 423/1353 for hs-cTnI and 519/1353 for hs-cTnT), none of whom died within 30 days. *P* values were calculated with a log-rank test. BNP indicates B-type natriuretic peptide; hs-cTn, high-sensitivity cardiac troponin; MACE, major cardiovascular events; and NT-proBNP, N-terminal proBNP.

guidance regarding the decision for ED discharge and outpatient management by identifying patients with a very low risk of death and MACE within 30 days. Cut-offs of <22.9 pg/mL for BNP, <97 pg/mL for NT-proBNP, <8 ng/L for hs-cTnT, and <2.9 ng/L for hs-cTnI allowed the identification of ≈30% of eligible patients with a mortality risk at 30 days of 0% (95%-CI, 0.0–1.1%).

Our findings extend and corroborate previous single-center studies on the clinical utility of biomarkers for diagnosis and risk-stratification of patients presenting to the ED following syncope.[16–18,20,21] To the best of our knowledge, this was the first multicenter study centrally adjudicating the cause of syncope by 2 independent physicians, incorporating initial cardiac work-up and long-term follow-up, and comparing the 4 most commonly used cardiac biomarkers: BNP, NT-proBNP, hs-cTnT, and hs-cTnI. The clinical value of BNP, NT-proBNP, hs-cTnT, and hs-cTnI for diagnosis of cardiac syncope observed in this study seems promising, particularly when combining either BNP or NT-proBNP with hs-cTnT or hs-cTnI. BNP with hs-cTnI and NT-proBNP with hs-cTnT concentrations remained predictive of cardiac syncope in multivariable models, their discriminative power, as given by the AUCs, was higher than that of a commonly used syncope score, and their combination further increased the diagnostic accuracy to an AUC of 0.81.

The pathophysiological link between BNP and NT-proBNP as a quantitative marker for the presence and severity of cardiac disease, as single markers, and cardiac syncope was weaker than we had hypothesized. This may be explained by the high prevalence of bradycardia-induced syncope, which may often be related to degenerative processes not directly related to the hemodynamic severity of cardiac disease and intracardiac filling pressures. In contrast, cardiac syncope because of severe aortic stenosis or ventricular tachycardia seems more closely related to the hemodynamic severity of cardiac disease[10,35,37] and therefore better predictable using BNP or NT-proBNP. Complementing BNP and NT-proBNP with a derived ECG score again provided high diagnostic accuracy for bradycardia.

An additional finding was that hs-cTnT and hs-cTnI provided comparable diagnostic accuracy for cardiac syncope as compared to BNP and NT-proBNP. This extends and corroborates multiple recent studies highlighting hs-cTnT and hs-cTnI as quantitative markers of cardiomyocytes injury and biochemical signatures of disease severity in many cardiac disorders.[20,38,39]

The assessment of biomarkers and scores using AUCs leads to a cut-off independent unbiased comparison of their accuracy. However, ultimately cut-offs are essential for the implementation of scores and biomarkers into ED decision-making. The findings of this study suggest that a strategy based solely on a 95%-sensitivity/specificity natriuretic peptides cut-off for rule-in and rule-out of cardiac syncope as a preliminary patient assessment, followed by biomarkers measurements, is as efficient and safe as using first the EGSYS score for risk-stratification or directly proceeding to triage using biomarkers, which led to similar negative predictive value and incidence of criteria. This further emphasizes the possibility for a direct triage based on biomarkers concentrations if biomarker-specific 95%-sensitivity/specificity cut-offs are used.

In contrast to other common ED symptoms such as chest pain, no clinical consensus has been quantified regarding the acceptable metrics for safe ED discharge and outpatient management in patients with syncope.[40] We hypothesize, that particularly given the extensive list of adverse events included in the MACE composite used in this study, the very low 30-day MACE-rates seen in the respective biomarker-defined rule-out groups would be attractive and acceptable for the ED community.

Although the diagnostic accuracy quantified in this analysis was comparable among the 3 natriuretic peptides examined[16–18,41], and the cost of ordering it in most countries is comparable and low (≈25 USD[42]), it is important to highlight that their availabilities in the ED differ substantially. Although most hospitals in developed countries have implemented BNP or NT-proBNP testing[43], MR-proANP is used only in a very small number of institutions.[44,45] Similarly, hs-cTnT and hs-cTnI assays are widely available at very low cost (≈5 USD).

The usefulness of BNP, NT-proBNP, hs-cTnT, and hs-cTnI for risk-stratification has previously been established in a range of cardiovascular diseases[13–15,46,47] and in the context of syncope.[16,18–21] Our results showed that, even after correcting for the etiology of syncope, age and important baseline characteristics, BNP, NT-proBNP, hs-cTnT, and hs-cTnI all remained strong predictors of MACE including death during long-term follow-up. The better performance of BNP and NT-proBNP to predict arrhythmic MACE over ischemic MACE reinforces previously suggested associations of these biomarkers with arrhythmia[10,35,37,48] whereas hs-cTnT and hs-cTnI had a stronger association with ischemic events.[13–15]

BNP/NT-proBNP and hs-cTnT/hs-cTnI performed better than 2 previously derived prognostic scores, ROSE and SFSR, showing that the 4 cardiac biomarkers allow for a more precise risk-stratification than tree-based algorithms considering few components of patient history, ECG, or details of the syncope event. BNP, NT-proBNP, and hs-cTnT, but not hs-cTnI, also outperformed the OESIL score in the prediction of death within 360 days. The lower predictive accuracy of hs-cTnI for death is supported by similar findings in patients presenting with acute chest pain to the ED.[49] On the other hand, the multivariable CSRS, which combines hs-cTnI with the ED discharge diagnosis based on extensive information acquired during ED evaluation, outperformed all 4 biomarkers as single variables.

As BNP, NT-proBNP, hs-cTnT, and hs-cTnI were more accurate than several syncope-specific risk scores, the simple use of these biomarkers for early risk-stratification in patients presenting to the ED seems to render them appealing, rapid and easy triage tools, especially if their use would lead to numerically fewer or shorter hospitalizations. Considering the well-documented value of BNP, NT-proBNP, hs-cTnT, and hs-cTnI as screening tools for cardiovascular disease in the community in general and in persons at increased cardiovascular risk, our findings may justify the inclusion of these biomarkers in the work-up of patients >45 years old presenting with syncope to the ED.

Several limitations of the present study merit consideration. First, patients with syncope who do not present to the ED were not included. Therefore, it is unknown whether our findings can be extrapolated to patients presenting to primary care. Second, we cannot comment on the possible clinical utility of BNP, NT-proBNP, hs-cTnT, and hs-cTnI in patients presenting >12 hours after their syncope or patients <45 years old, as these were excluded from the present study. As the incidence of cardiac syncope is considerably lower in patients <45 years old, the clinical utility of BNP, NT-proBNP, hs-cTnT, and hs-cTnI in young patients presenting with syncope may be lower. Further studies seem warranted to explore the possible utility of biomarkers in settings with lower incidence of cardiac syncope including younger patients in general and patients presenting with syncope to the general practitioner. Third, BNP, NT-proBNP, hs-cTnT, and hs-cTnI concentrations were only obtained once and no serial measurements were available. Further studies are needed to evaluate the possible value of serial biomarker sampling. Fourth, despite using a very stringent method of central adjudication of the final diagnosis by 2 independent physicians, we cannot exclude the possibility that a few patients might have been misclassified. This invariably would have led to an underestimation of the true diagnostic accuracy of the biomarkers examined. Fifth, BNP, NT-proBNP, and cTn were measured as part of clinical care in some patients. A sensitivity analysis evaluating the diagnostic accuracy of BNP, NT-proBNP, and cTn in the subgroup of patients in whom these biomarkers were measured as part of clinical routine revealed similar diagnostic accuracy as compared with the overall cohort. Thus, we consider the extent of verification bias small.

In conclusion, BNP, NT-proBNP, hs-cTnT, and hs-cTnI seem to be promising biomarkers, both for the diagnosis of cardiac syncope etiologies and for the risk-stratification for MACE, including death. Further studies are needed to determine which components of the patients' history, comorbidities, the physical examination and ECG could further increase the diagnostic and prognostic yield of these biomarkers.

ARTICLE INFORMATION

Received October 11, 2018; accepted February 6, 2019.

The online-only Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/circulationaha.118.038358.

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Acknowledgments

The authors designed the study, gathered and analyzed the data, vouch for the data and analysis, wrote the paper, and decided to publish. Drs du Fay de Lavallaz, Badertscher, Zimmermann, Nestelberger, and Mueller had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors have read and approved the manuscript. The sponsors had no role in designing or conducting the study and no role in gathering or analyzing the data or writing the manuscript. The manuscript and its contents have not been published previously and are not being considered for publications elsewhere in whole or in part in any language, including publicly accessible web sites or e-print servers.

We are indebted to the patients who participated in the study and to the ED staff as well as the laboratory technicians of all participating sites for their most valuable efforts. In addition, we wish to thank Melanie Wieland, RN, Irina Klimmeck, and RN, Fausta Chiaverio, RN (University Hospital Basel, Switzerland); Esther Garrido, MD, Isabel Campodarve, MD, and Joachim Gea, MD (Hospital del Mar, IMIM, Barcelona, Spain); Helena Mañé Cruz, Sofia Calderon, and Carolina Isabel Fuenzalida Inostroza (Hospital Clinic, Barcelona, Spain); and Miguel Angel García Briñón and María Suárez Cadenas (Hospital Clínico San Carlos, Madrid, Spain).

Sources of Funding

This work was supported by research grants from the Swiss National Science Foundation, the Swiss Heart Foundation, the Cardiovascular Research Foundation Basel (Switzerland), the University Basel (Switzerland), Brahms Diagnostica, Singulex, the University Hospital Basel (Switzerland), and the Emergency Medicine Foundation (Australia) and the Emergency Care Foundation (New Zealand).

Disclosures

Dr Mueller has received research support from the Swiss National Science Foundation, the Swiss Heart Foundation, the European Union, the Kommission für Technologie und Innovation (KTI), the Cardiovascular Research Foundation Basel, Abbott, Astra Zeneca, Biomerieux, Beckman Coulter, BG Medicine, Brahms, Critical Diagnostics, Radiometer, Roche, Siemens, and Singulex, as well as speaker/consulting honoraria or travel support from Abbott, Alere, Bayer, BMS, Boehringer Ingelheim, Brahms, Cardiorentis, Daiichi Sankyo, Novartis, Roche, Sanofi, Siemens, and Singulex. Dr Badertscher has received research funding from the University of Basel, from the "Stiftung für Herzschrittmacher und Elektrophysiologie" and from the "Freiwillige Akademische Gesellschaft Basel," outside the submitted work. Dr Twerenbold reports grants from the Swiss National Science Foundation (Grant No P300PB_167803), the University Hospital Basel, the University of Basel and the Cardiovascular Research Foundation Basel, personal fees from Roche Diagnostics, Abbott Diagnostics, Siemens, Singulex and Brahms, outside the submitted work. Dr Than reports grants and personal fees from Abbott, grants and personal fees from Alere, grants from Beckman, grants and personal fees from Roche, outside the submitted work. Dr Cullen reports grants and personal fees from Abbott Diagnostics, personal fees from Beckman Coulter, grants and personal fees from Siemens, outside the submitted work. Dr Kühne reports personal fees from Bayer, personal fees from Daiichi-Sankyo, personal fees from Pfizer-BMS, personal fees from Böhringer-Ingelheim, outside the submitted work. Dr Peacock reports research grants from Abbott, Braincheck, Immunarray, Janssen, Roche, and ZS Pharma, having served as a consultant for Abbott, Astra-Zeneca, Bayer, Beckman, Boehrhinger-Ingelheim, Ischemia Care, Dx, Immunarray, Instrument Labs, Janssen, Ortho Clinical Diagnostics, Relypsa, Roche, and Siemens, having provided expert testimony for Johnson and Johnson, and having ownership interests in Comprehensive Research Associates LLC, and Emergencies in Medicine LLC, Ischemia DX, LLC, outside the submitted work. Dr Martin-Sanchez received speaker, advisory or consulting fees from Novartis, MSD, Bristol-Myers Squibb, Pfizer, The Medicine Company, Otsuka, Thermo Fisher, Cardiorentis, Sanofi, and research grants from the Spanish Ministry of Health and FEDER, Mapfre, Novartis, Bayer, MSD, Abbot, and Orion-Pharma, outside the submitted work. Dr Koechlin received a research grant from the "Freiwillige Akademische Geselleschaft Basel" outside of the submitted work. The other authors report no conflicts.

APPENDIX

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