B-Type natriuretic peptides and cardiac troponins for diagnosis and risk-stratification of syncope

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Abstract:

Background: The utility of B-type Natriuretic Peptide (BNP), N-terminal proBNP (NT-proBNP), and high-sensitivity cardiac troponin (hs-cTn) 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 the ones of clinical assessments, in patients >45years presenting with syncope to the emergency department (ED) 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 two physicians based on all information available including cardiac work-up and 1-year follow-up, was the diagnostic endpoint. The EGSYS, a syncope-specific diagnostic score, served as the diagnostic comparator. Death and MACE at 30 and 720 days were the prognostic endpoints. MACE 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. The ROSE, OESIL, San Fransisco Syncope Rule (SFSR) and Canadian Syncope Risk Score (CSRS) 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 vs. other causes ($p<0.01$). The diagnostic accuracy for cardiac syncope, as quantified by the area under the curve (AUC), was 0.77-0.78 (95% confidence interval (CI) 0.74-0.81) for all four biomarkers, and superior to the one of EGSYS (AUC 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 AUC of 0.81 ($p<0.01$).

BNP, NT-proBNP, hs-cTnT, and hs-cTnI cut-offs, achieving pre-defined thresholds for sensitivity and specificity (95%), allowed for rule-in or rule-out of ~30% of all patients.

A total of 450 MACE occurred during follow-up. 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 the CSRS.

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

Clinical Trial Registration: NCT01548352, https://clinicaltrials.gov/ct2/show/NCT01548352

Keywords: Syncope; brain natriuretic peptide; troponin; NT-proBNP; emergency department

Clinical Perspective (93 words):

1. **What is new?**

    - This large international multi-center study using central adjudication shows that BNP, NT-proBNP, hs-cTnT, and hs-cTnI concentrations display moderate-to-good diagnostic and prognostic accuracy in syncope patients presenting to the ED.
    - Their performance is superior to most established diagnostic and prognostic syncope scores.

2. **What are the clinical implications?**

    - BNP, NT-proBNP, hs-cTnT, and hs-cTnI seem useful tools for the early rule-out and/or rule-in of cardiac syncope in the ED.
    - BNP, NT-proBNP, hs-cTnT, and hs-cTnI seem helpful in the triage towards hospitalization versus out-patient management in patients with syncope.

Introduction:

Syncope is a transient loss of consciousness associated with an inability to maintain postural tone due to 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 in comparison to 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 B-type natriuretic peptide (BNP), N-Terminal (NT)-proBNP, high-sensitivity cardiac Troponin (hs-cTn) T and hs-cTnI 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 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 to 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 pre-defined subgroup of patients in whom no obvious syncope etiology was present following initial ED evaluation.

METHODS

Study design, setting and selection of participants

BAsel Syncope EvaLuation Study (BASEL IX) is an ongoing prospective international diagnostic multicenter study enrolling patients from thirteen hospitals in eight countries (Switzerland, Spain, Germany, Italy, Poland, New Zealand, Australia and the United States of America). The study is designed to contribute to improving the management of patients presenting with syncope (ClinicalTrials.gov registry, number NCT01548352). Patients aged 40 years or older, and presenting to the ED with syncope within the last twelve hours, were recruited after written informed consent was obtained. Those with the final diagnosis of a non-syncopal loss of consciousness (e.g. 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 (AV) block II Type II Mobitz, AV-Block III, heart rate < 40bpm, life-threatening arrhythmia at presentation, central pulmonary embolism, symptomatic orthostatic dysregulation and relevant aortic stenosis) were analyzed as a pre-defined 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[26] (Supplemental table 1), 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 supplemental methods. 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, two 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 (Supplemental methods for details). 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 and/or recurrent syncope, were critical pillars of the adjudication. Further details on the adjudication are given in the supplemental material.

Blood sampling and laboratory methods

Venous blood samples were drawn via a peripheral intravenous line upon 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], 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 (Mid-regional pro-atrial natriuretic peptide (MR-proANP)) 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.

Endpoints

The primary diagnostic endpoint was the diagnostic accuracy of BNP, NT-proBNP, hs-cTnT, and hs-cTnI for cardiac syncope. The co-primary prognostic endpoints 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 endpoints 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 (VT) [>120 beats/min], ventricular pause [>3s], 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 (TIA), intracranial bleeding and valvular surgery in addition to arrhythmic and ischemic MACE. pulmonary

embolism, stroke/transient ischemic attack (TIA), 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, 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, 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 "Evaluation of Guidelines in Syncope Study" (EGSYS) diagnostic score, which was designed to differentiate between cardiac and non-cardiac 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 Canadian Syncope Risk Score (CSRS), both predicting 1-month serious outcome and all-cause death[16,21] and the San Francisco Syncope Rule (SFSR)[24], which predicts 7-day adverse events. We used these scores for their respective endpoints and compared their predictive accuracy to the one of BNP, NT-proBNP, hs-cTnT, and hs-cTnI (Supp. methods for details). 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 supplemental methods.

Need for hospitalization in patients with no obvious syncope etiology upon ED evaluation

In the pre-defined subgroup of patients with no obvious syncope etiology upon 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 analysis

Continuous variables are presented as mean ± standard deviation (SD) or median with interquartile ranges (IQR). Categorical variables are expressed as numbers and percentages. Mann-Whitney-U test was applied for comparison of continuous variables and Pearson Chi-square test or Fisher's exact test for comparison of categorical variables. Areas under the receiver operating characteristic (ROC) curve (AUC) were constructed to assess the diagnostic accuracy. Comparisons of AUCs were performed according to DeLong[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 at least 95% for possible use as rule-out and a specificity of at least 95% for rule-in for cardiac syncope. Confidence intervals for these measures were computed according to Agresti and Coull[34]. Univariable/Multivariable logistic regression was used to assess the predictive accuracy of log-transformed BNP, NT-proBNP, hs-cTnT, and hs-cTnI concentrations to diagnose cardiac syncope (Supp. Methods).

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

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

Time-dependent ROC[36] curves were computed using the "timeROC" package to assess the accuracy of BNP, NT-proBNP, hs-cTnT, and hs-cTnI to predict death, MACE, ischemic and

arrhythmic MACE during the whole follow-up length. A time-dependent ROC varies as a function of time and accommodates censored data.

Cox proportional hazard (CPH) 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 pre-defined important co-variates (Supp. Methods). Kaplan Meier curves were used to represent event-free survival. Comparison of KM curves was performed according to the log-rank test. All hypothesis testing was two-tailed, p-values <0.05 were 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 (Supplemental figure 1) of which 1472 and 1338 patients were eligible for the analysis of prognostic and diagnostic endpoints, respectively.

Mean age was 71 years, 40% of patients were women, and about 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, more often had 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 pre-defined cardiac subcategories are shown in Supplemental table 2. Other adjudicated diagnoses included reflex (n=588, 39.9%), orthostatic (n=403, 27.3%), other non-cardiac (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 as compared to patients with reflex, orthostatic, or other non-cardiac 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% confidence interval (CI) 0.74-0.81), p for comparison=ns), superior to EGSYS ($p<0.001$) and to a combination of clinical variables ($p=<0.01$), and similar to the one of MR-proANP (Supplemental figure 2). 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/NT-proBNP plus hs-cTnI/T 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 as compared to the overall cohort for the diagnosis of cardiac syncope (Supplemental figure 3).

In the subgroup of patients with cTn measured as part of clinical routine, BNP and NT-proBNP provided higher AUC as compared to clinical cTn (Supplemental figure 4).

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 cardiac 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, while 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 (Supplemental table 3). Accordingly, overall these 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. Supplemental table 4 shows the negative predictive value (NPV), positive predictive value (PPV) and incidence of criteria (% of patient classified as rule-in

or rule-out) when a stratification using EGSYS≥3 is applied first or when only pre-defined 95%-sensitivity/specificity BNP, NT-proBNP, hs-cTnT, and hs-cTnI cut-offs are used. MACE rates at 30d in the rule-out groups were very low and similar when EGSYS<3 was first used for risk-stratification or when only pre-defined 95%-cut-offs were used (Supplemental table 5).

Natriuretic peptides diagnostic accuracy among cardiac syncope etiologies

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

Accordingly, the AUC of BNP and NT-proBNP to diagnose VT or valvular heart disease was higher as the AUC to diagnose bradycardia-induced syncope (Supplemental figure 5).

Combining BNP or NT-proBNP with an ECG risk score derived in this data set improved the diagnostic accuracy for bradycardia (Supplemental table 6, Supplemental figure 6).

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 (Supplemental table 7 and 8).

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% at 360 days and in 83.2% of patients at 720 days. During follow-up, 209 patients (14.2%) died, 425 (28.8%) had at least one MACE. An ischemic MACE occurred in 259 patients (17.6%) and an arrhythmic MACE in 332 (22.6%) during follow-up.

The prognostic accuracy of BNP, NT-proBNP, hs-cTnT, and hs-cTnI was moderate-to-good for death and MACE (Figure 4, Supplemental figure 7). For death and MACE, all biomarkers performed similarly in the short-term but NT-proBNP and hs-cTnT showed a significant better performance at 720 days (for instance, NT-proBNP vs BNP at 720d $p<0.001$ for death and $p=0.007$ for MACE, Figure 4). In the short-term, hs-cTnT and hs-cTnI performed better for

ischemic MACE, while BNP and NT-proBNP performed better for arrhythmic MACE (Supplemental figure 7). In the long-term, NT-proBNP performed better in the prediction of arrhythmic MACE than hs-cTnI (NT-proBNP vs hs-cTnI at 720d p=0.007 for arrhythmic MACE), but similarly to BNP and hs-cTnT (p=>0.05).

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 720d p=ns) (Supplemental figure 8).

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%) suffered an adverse event as defined by the original derivation of the SFSR. During the first month of follow-up, 160 patients (11.2%) suffered an adverse event as defined by the original derivation of the ROSE rule and 182 (12.8%) suffered an adverse event as defined by the original derivation of the 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 the CSRS (Supplemental figure 9, supplemental table 9) All the 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 CPH model for all long-term prognostic endpoints (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. (Supplemental tables 10-13).

Need for hospitalization in patients with no obvious syncope etiology upon ED evaluation

Among patients with no obvious etiology for their syncope upon ED evaluation, 10 died within 30 days and 146 suffered from MACE.

Patients experiencing a MACE during follow-up had significantly higher BNP, NT-proBNP, hs-cTnT, and hs-cTnI concentrations as compared to patients without events (Figure 5). The lowest 90%-sensitivity cut-offs to rule-out both death and MACE up to 30-day follow-up (as highlighted in Supplemental table 14) allowed for a safe rule-out of ~30% of patients (Figure 6). Among the patients ruled-out by the respective 90%-sensitivity cut-offs, around 25% had been hospitalized for a median of 3 days (Supplemental table 15).

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 **three** major findings.

First, BNP, NT-proBNP, hs-cTnT and hs-cTnI concentrations were significantly higher in patients adjudicated to have cardiac syncope as compared to other syncope etiologies and provided moderate-to-high accuracy for the diagnosis of cardiac syncope. Moreover, all four 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 >45years presenting to the ED with syncope, BNP, NT-proBNP, hs-cTnT, and hs-cTnI concentrations allowed to rule-out and rule-in 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 also 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 likely is highest in the subgroup of patients in whom the ED diagnosis remains unclear after standard the diagnostic process available in the ED (ECG, history of severe aortic stenosis, Schellong test for orthostatic hypotension), where they could provide guidance regarding the decision for ED discharge and out-patient management by identifying patients with a very low risk of death and MACE within 30 days. For instance, 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 to identify ~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 two independent physicians, incorporating initial cardiac work-up and long-term follow-up and comparing the four 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 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 due to 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. Interestingly, complementing BNP and NT-proBNP with a derived ECG score again provided high diagnostic accuracy also for bradycardia.

An additional surprising finding was the fact 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 signature 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 is as efficient and safe as a preliminary patient assessment followed by biomarkers measurements, as using first the EGSYS score for risk-stratification or directly proceeding to triage using biomarkers only led to similar NPV 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 syncope patients.[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 three natriuretic peptides examined[16–18,41], and also the cost of ordering it in most countries is comparable and low (about 25 USD[42]), it is important to highlight that their availabilities in the ED differ substantially. While the vast majority of hospitals in developed countries meanwhile 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 (about 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] while hs-cTnT and hs-cTnI had a stronger association with ischemic events.[13–15]

BNP/NT-proBNP and hs-cTn performed better than two previously derived prognostic scores, ROSE and SFSR, showing that the four 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 four 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 also 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 younger than 45 years of age, as these were excluded from the present

study. As the incidence of cardiac syncope is considerably lower in patients <45 years of age, the clinical utility of BNP, NT-proBNP, hs-cTnT, and hs-cTnI in young patients presenting with syncope may be lower. likely is substantially lower. Still, further studies seem warranted to also explore the possible utility of biomarkers in settings with lower incidence of cardiac syncope included 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 two 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.

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Appendix

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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.

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Table 1

	All patients	Cardiac	Non cardiac	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 - counts (%)	591 (40)	79 (36)	458 (41)	54 (40)	0.167
Characteristics of the syncope - counts (%)					
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 - counts (%)					
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 - counts (%)					
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 - counts (%)					
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

	All patients	Cardiac	Non cardiac	Unknown	P value
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 - counts (%)					
ACEIs/ARBs	669 (45)	121 (55)	474 (42)	74 (55)	0.001
Alphablocker	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
Beta-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

Table 1 – Patients characteristics. IQR = Interquartile Range, DVT=Deep venous thrombosis, PE= Pulmonary embolism, MI= Myocardial infarction, ACEI =Angiotensin converting enzyme inhibitors , ARB= Angiotensin receptor blockers, NYHA = New York Heart Association. P-values are given for the comparison cardiac versus non-cardiac syncope. A history of arrhythmia was defined as any symptomatic supraventricular or ventricular arrhythmia present in the patient's history.

Table 2

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.vars, 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.vars, 0.72 [0.69, 0.76]	BNP+Clin.var, 0.79 [0.76, 0.83]	<0.001
Clin.vars, 0.72 [0.69, 0.76]	NT-proBNP+Clin.var, 0.79 [0.76, 0.82]	<0.001
Clin.vars, 0.72 [0.69, 0.76]	hs-cTnI+Clin.var, 0.80 [0.76, 0.83]	<0.001
Clin.vars, 0.72 [0.69, 0.76]	hs-cTnT+Clin.var, 0.79 [0.76, 0.82]	<0.001
Clin.vars, 0.72 [0.69, 0.76]	BNP+hs-cTnI+Clin.Var, 0.82 [0.79, 0.85]	<0.001
Clin.vars, 0.72 [0.69, 0.76]	NT-proBNP+hs-cTnT+Clin.Var, 0.81 [0.78, 0.84]	<0.001

Table 2 – Comparison of AUCs. 95%-CI are given in brackets. The clinical variables (Clin. Vars) are described in the supplemental appendix. All comparisons with the EGSYS score have been conducted only in patients with an available EGSYS score. Hs-cTnT/I = high-sensitivity cardiac troponin T/I, BNP = B-type natriuretic peptide, NT-proBNP = N-terminal pro-B-type natriuretic peptide.

Figure legends:

Figure 1 - Boxplots 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 non-cardiac syncope n=130). The boxplots represent the median with the interquartile range (IQR), whiskers represent ± 1.5 x the IQR. P-values were calculated based on a Wilcoxon-rank-sum test. Syncope was defined as of "other, non-cardiac" etiology when the underlying pathophysiological mechanism of syncope remained unclear, but a cardiac syncope was ruled-out

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 (upper panel), biomarkers and scores combined (middle panel) or biomarkers combined (lower panel). We represented the combinations of BNP with hs-cTnI (both on Architect) and NT-proBNP with hs-cTnT (both on Elecsys), 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. BM = Biomarker.

Figure 3 – Prior probability, Likelihood ratios (on the middle line) and posterior probability given by the EGSYS score and the adjunction of A) BNP, B) NT-proBNP, C) hs-cTnI and D) hs-cTnT. PLR = positive likelihood ratio, NLR = negative likelihood ratio, post. Pos = positive posterior probability, post. Neg = posterior negative probability.

Figure 4 – Time-dependent ROC curves for the accuracy of BNP and NT-proBNP for the prognosis of death and overall MACE. 95%-confidence intervals are given in brackets.

Figure 5 – Boxplots representing the A) BNP, B) NT-proBNP, C) hs-cTnI and D) hs-cTnT concentrations according to whether or not patients experienced a clinical event during the 30-day follow-up. The boxplots represent the median with the interquartile range (IQR), whiskers represent ± 1.5 x the IQR. P-values were calculated based on a Wilcoxon-rank-sum test.

Figure 6 – Kaplan Meier representing event-free survival for death and MACE according to a cut-offs of A) BNP 22.9 pg/mL, B) NT-proBNP 97 pg/mL, C) hs-cTnI 2.9 ng/L and D) hs-cTnT 8 ng/L. 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.

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