Early Diagnosis and Risk Stratification of Patients with Syncope

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Summary of the project

Background: Syncope is a common and challenging problem in the Emergency Department (ED), representing about 1-2% of patients visits. Early detection of the underlying cause is critical as it defines treatment and prognosis. Cardiac syncope is associated with the highest mortality of all syncope etiologies and requires specific interventions such as implantation of a pacemaker or defibrillator. ED clinicians struggle to rapidly identify the underlying cause and the threat of a possible serious cardiac origin which leads to numerous diagnostics and high hospitalisation rates. In an attempt to improve diagnosis and risk-stratification in syncope patients in the ED, several rules and scores were derived, mostly of mono-centric and rather small studies. Additionally, their external validity has never been assessed and their complexity represent a problem for a rapid and efficient implementation in the ED. Similarly, the diagnostic and prognostic value of some readily available cardiac biomarkers (such as cardiac troponins or B-type Natriuretic peptides) has been investigated in some pilot studies but the small number of patients assessed and the use of poorly sensitive assays resulted in varying results and did not allow for any definitive conclusions.

Aim and Hypothesis: The aim of this thesis is to assess the accuracy of diagnostic and prognostic accuracy of scores and biomarkers in a large international cohort of syncope patients presenting to the ED. First, the accuracy of existing syncope-specific diagnostic and risk-stratification rules will be compared and their complexity put in perspective through a comparison with the $CHADS_2$ score. Second, the diagnostic and prognostic performance of cardiac troponins, as assessed by three different assays, and BNP will be investigated. We hypothesize that complex syncope-specific scores might not reliably diagnose or risk-stratify syncope patients and that both assessed biomarkers, at least in certain subgroups of patients for which the determination of a precise etiology appears particularly difficult, could be of specific interest to improve the diagnosis and risk stratification of patients presenting with syncope to the ED.

Patients and Methods: BASEL IX is an ongoing prospective international multicenter diagnostic cohort study coordinated by the University Hospital Basel. Patients >40y presenting to the ED with a syncope within the 12 last hours are enrolled and blood is drawn for the blinded analysis of the investigational biomarkers. All patients underwent clinical assessment that included standardized and detailed assessment of predefined details of the medical history and syncopal event. The adjudication of the final diagnosis is performed by two independent cardiologists based on all available information after diagnostic work-up of patients as well as the clinical follow-up at 12 months. Patients are followed up to 5 years. The diagnostic endpoint is the diagnostic accuracy for cardiac syncope, the prognostic endpoints are the accuracy to predict death or major cardiovascular events (MACE).

Results: Syncope diagnostic and risk stratification rules showed a moderate accuracy in patients presenting with syncope to the ED (with Area Under The Receiver Operating Curve (AUC) between 0.67 and 0.75 for diagnostic endpoints and between 0.57 and 0.79 for prognostic endpoints) and most of them were, not superior to a readily calculable $CHADS_2$ score. Both assessed biomarkers performed with a moderate-to-good accuracy for the diagnosis and risk stratification of the overall cohort (AUC for diagnostic endpoints between 0.76 and 0.77, AUC for prognostic endpoints between 0.73 and 0.8 depending on the chosen time-point). When assessed in patients for whom the diagnosis stayed

unclear despite initial ED evaluation, these biomarkers could provide guidance to the ED physician regarding his decision for hospitalization and further testing.

Conclusion: Diagnosis and risk-stratification of patients with syncope is a challenging task and currently available structured clinical assessments scores do not sufficiently help with initial ED evaluation. Common and readily available cardiac biomarkers seem to represent a valuable tool, especially in patients for whom a first evaluation did not lead to a satisfactory diagnosis.

Introduction

Syncope in the Emergency Department

Syncope is defined as a "transient loss of consciousness due to cerebral hypoperfusion, characterized by a rapid onset, short duration and spontaneous complete recovery"[1]. It is a common and challenging problem in the Emergency Department (ED), representing about 1-2% of patients visits[2–4],[5].

The ability of ED clinicians to rapidly identify the underlying cause is often limited by scant patient recall, absence of witnesses, the paroxysmal nature of cardiac arrhythmias, and time pressure[6]. Moreover, as the opportunity to capture a spontaneous event during initial evaluation is very rare, the exact syncope etiology remains unclear in a relevant number of patients[7,8].

Early detection and exact definition of the underlying cause is critical as it defines treatment and prognosis. For instance, reflex syncope requires lifestyle measures including education and reassurance as well as physical counterpressure manoeuvres, and has a very low risk of death[1]. In contrast, cardiac syncope requires specific cardiac interventions and has a high risk of death[1,9,10]. According to current European Guidelines[1] the evaluation of syncope in the ED should answer the following three questions :

1. Is there a serious underlying cause that can be identified?
2. If the cause is uncertain, what is the risk of a serious outcome?
3. Should the patient be admitted to the hospital?

These same guidelines[1] further recommend three main components for the initial evaluation of syncope in the ED: first a careful history taking, second a thorough physical examination and third an electrocardiogram (ECG). Depending on the results of these examinations, further investigations should be initiated.

As the threat of a possible serious cardiac origin currently leads to consequent unnecessary admissions, diagnostic procedures and costs, ongoing research aims at improving pathways and organizational issues by focusing on these three initial components and subsequent diagnostic measures[1,6,8].

Cardiac syncope

After reflex syncope, cardiac syncope represents the second most common cause of syncope[1]. A cardiac cause is found in about 5 to 30% of patients presenting to the ED with syncope. The spectrum of heart conditions likely to cause syncope is wide and can be

summarized as all cardiovascular pathologies leading to a temporary cardiac output impairment.

Arrhythmias are the most common cause of cardiac syncope: they include pathologic bradycardia and pauses, as found in a sick sinus syndrome, high grade atrioventricular (AV) heart blocks (Mobitz II and complete AV blocks), tachycardia (ventricular as well as supraventricular) or drug-induced arrhythmias. The dysfunction of an implanted pacemaker can also lead to haemodynamic compromise and fainting.

A variety of cardiac structural diseases (valvular, ischemic, congenital, neoplastic)[1,11] are known to cause syncope as well.

Other cardiovascular pathologies, such as pulmonary embolism, acute aortic dissection or pulmonary hypertension, can lead to an increase in the afterload and consequently a decrease in the cardiac output, inducing syncope[1,9].

Syncope caused by one of these pathologies shows an increased one-year mortality compared to non-cardiac syncope (about 18-33% for cardiac syncope[9,10] versus 0-12% for the other etiologies[9,12]). Short-term morbidity is also not negligible in patients with an underlying cardiac etiology: Around 15% of syncope patients will experience a MACE within 30 days of the initial event, with about half of these manifesting only during subsequent hospitalization or after discharge at home.[13,14]

Both high mortality and morbidity emphasize the importance of recognizing the heart as the cause of the problem in order to initiate an effective mechanism-specific treatment (such as for example the implantation of a pacemaker or defibrillator, an electrophysiologic ablation therapy or a percutaneous coronary intervention) and improve the prognosis of the patient[1].

Despite many efforts to improve the systematic evaluation of syncope patients, a high percentage remains undiagnosed after ED evaluation (17 to 33%[7,8]). This diagnostic uncertainty leads to unnecessary hospitalizations: depending on the country[15] 12 to 86% of ED syncope referrals are treated in an inpatient setting[1,3] but only 25% of these admissions are considered appropriate.[16] Moreover, patients with syncope are exposed to numerous diagnostic tests often irrelevant to the cause of syncope and at times associated with relevant risks and costs.[1]

Therefore, research currently still focuses on designing and validating structured and standardized approaches using numerous components of the patient history, physical evaluation, electrocardiographic and laboratory data to provide guidance to ED physicians to

reduce unnecessary diagnostic procedures, superfluous admissions, misdiagnoses and costs.[1,6,8]

Syncope-specific scores and structured ED evaluation

In an attempt to identify patients at risk of cardiac syncope and adverse outcome, numerous syncope-specific diagnostic and risk-stratification scores have been developed. [5,17–22] These rules and scores incorporate important predictors for the diagnosis or outcome stemming from the past medical history, details of the syncopal event, physical examination, and basic diagnostic tests.

Most of these scores focus on short-term serious outcomes, reflecting the largely unmet clinical need of reducing 30-day readmissions in syncope patients.[5,6,8,16,19,21,22] Less importance was attributed to long term outcome and fewer scores address adverse events occurring after 30 days.[18,20,22]

The use of these tools in the ED is debated[1]. On the one hand, several of these scores were successfully validated in small cohorts[23–26] and they could represent cheap tools to reduce unnecessary admissions and help with diagnosis and risk stratification. On the other hand, their poor methodological quality, their complexity and the impractical parameters some of them take into account (as for instance some rarely conducted examinations[5]) cast doubt upon their usefulness in the ED, so that current guidelines do not recommend their implementation. [4,8]

However, both American and European guidelines[1,4] recognize the need to focus on standardized tools to guide the evaluation by healthcare teams, both for the diagnosis and short- or long-term outcome in follow-up and score derivation stays on top of their research agenda.

Biomarkers

Blood biomarkers contributed greatly to the diagnostic and prognostic evaluation of other common presenting symptoms (including acute chest pain and acute dyspnea[27–29]). Given the near universal use of blood sampling at ED presentation, biomarkers linked to the pathophysiology of cardiac syncope (Figure a) could provide an incremental value in the detection of cardiac syncope but their utility in ED syncope evaluation remains unclear.[30]

Previous pilot studies provided initial insights regarding a possible role of natriuretic peptides as quantitative markers of hemodynamic cardiac stress and high-sensitivity cardiac troponin (hs-cTn) as quantitative marker of cardiomyocyte injury.[31]

Cardiac troponins are regulatory proteins controlling the interaction between actin, myosin and calcium. Cardiac troponin I and T are released in the blood when the permeability of myocyte membranes increases, like during demand ischemia due to hypotension or supraventricular tachycardia, or myocardial strain due to pulmonary embolism.[32] Troponin release is therefore consistent with numerous underlying mechanisms linked to cardiac syncope (Figure a). In three single-center studies plasma concentrations of hs-cTn at ED presentation overall displayed a moderate-to-high diagnostic accuracy for the detection of cardiac syncope and were associated with adverse outcomes.[33–35]

BNP and N-terminal pro-BNP (NT-proBNP) derive from the same precursor, which is mainly secreted by cardiac myocytes in response to volume and pressure overload [36–38], summarizing and quantifying left ventricular and right ventricular dysfunction[28,36]. This biomarker has led to improvement in the diagnosis and risk-stratification of heart failure and has a prognostic predictive value in diverse cardiac and non-cardiac conditions[28,39] (as for example in myocardial infarction or pulmonary embolism). Elevated levels of BNP have been found in arrhythmias, as for instance in tachycardia or atrial fibrillation, as the result of the induced hemodynamic wall stress[38,40]. Arrhythmias being the most common cause of cardiac syncope[41], this peptide could thus represent a promising marker in their diagnosis.[42,43]

As the measurement of these biomarkers is already well implemented in the everyday clinical practice[39], their use could increase the efficiency of the initial classification of the type of syncope and facilitate final diagnosis and risk estimation. However, previous studies assessing these biomarkers were rather small and some of them used clinically required biomarker measurements or assays whose sensitivity is nowadays obsolete. Accordingly, guidelines and clinicians remain skeptical about the role of biomarkers in the evaluation of syncope[4].

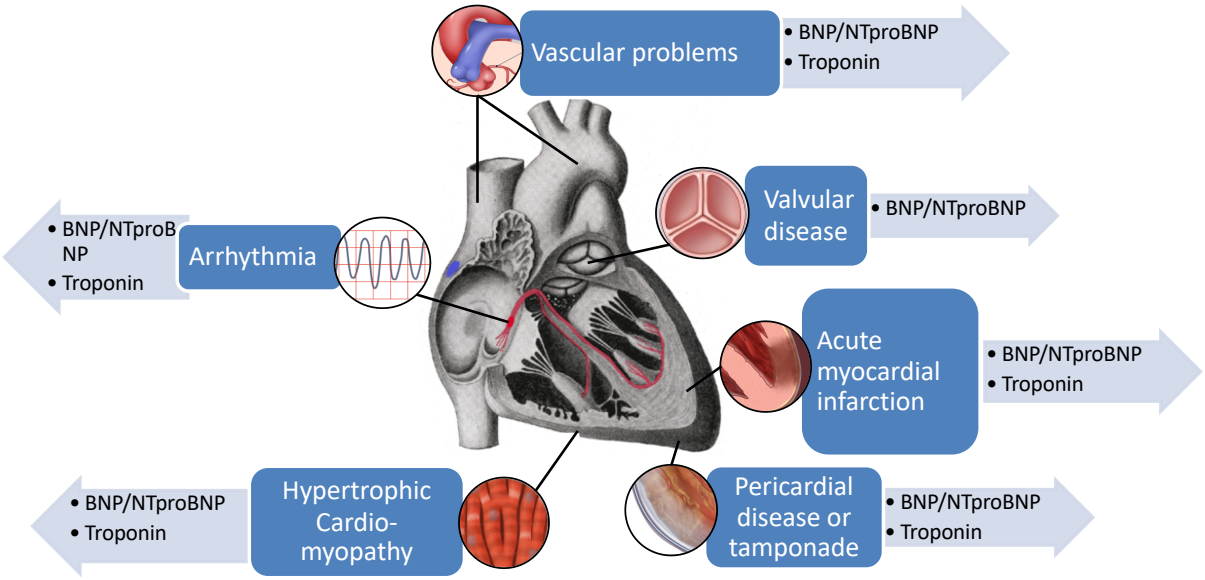

Figure a - Main etiologies of cardiovascular syncope and their association with elevated plasma levels of BNP or cardiac troponin[32,38,44–49]

The BASEL IX Syncope Study

BASEL IX is a prospective ongoing international multicenter diagnostic cohort study coordinated by the University Hospital Basel enrolling unselected patients in fourteen hospitals in nine countries (Switzerland, Spain, Germany, Italy, Poland, New Zealand, Australia, the United States of America and Argentina) on four continents. Patients more than 40 years old presenting to the ED with a syncope within the 12 last hours are enrolled after providing informed consent. A blood draw is performed for the blinded analysis of the investigational biomarkers signals. Furthermore, a questionnaire is done using a clinical report form, and the patient's medical history is recorded. Patients are contacted after 12 and 24 months to assess recurrence of syncope and occurrence of major adverse cardiac events (especially death, myocardial infarction, life-threatening arrhythmia, , ischemic and hemorrhagic stroke). The exact etiology of the index syncope is determined by two independent cardiologists blinded to investigational biomarker signals according to the newest ESC-Guidelines.[1] Cardiovascular causes of syncope are defined as supraventricular or ventricular arrhythmias, severe structural heart disease like hypertrophic cardiomyopathy or valvular diseases, pericardial tamponade or congenital myocardial or valvular anomalies, or other structural diseases as pulmonary embolus or acute aortic dissection, leading to a transient loss of consciousness. Non-cardiac syncope includes reflex syncope or syncope due to orthostatic hypotension.

The adjudication of the final diagnosis is performed based on all clinical information available after diagnostic work-up of patients as well as the clinical follow-up. In cases of disagreement, a third reviewer determined the final diagnosis.

Thesis aim and hypotheses

The aim of this thesis is to assess various aspects of the diagnosis and risk-stratification of syncope patients presenting in the ED through the assessment of the accuracy of scores and biomarkers in a large, international cohort. First, the accuracy of existing syncope diagnostic and risk-stratification rules will be compared and their complexity put into perspective by comparing them with the easily-calculable $CHADS_2$ score. Second, the diagnostic and prognostic accuracy of cardiac troponin, as assessed by three different assays, and BNP will be investigated. We hypothesize that the complex scores might not reliably diagnose or risk-stratify syncope patients and that both assessed biomarkers, at least in certain subgroup of patients for which the determination of a precise etiology appears particularly difficult, could be of strong interest to improve the diagnosis and risk stratification of patients presenting with syncope to the ED.

I - Prospective Validation of Prognostic and Diagnostic Syncope Scores in the Emergency Department

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Key questions

- What is already known about this subject: The diagnosis and risk-stratification of syncope patients in the ED is difficult. Several scores have been derived to fill this gap.
- What does this study add? In a large cohort of syncope patients presenting to the ED, several syncope-specific scores performed poorly in the diagnosis of cardiac syncope. A simple $CHADS_2$ score showed similar accuracy to predict death or major cardiovascular events than more complicated syncope-specific risk-stratification scores.
- How might this impact on clinical practice? Complicated and time-consuming syncope-specific risk scores could be replace with a simple $CHADS_2$-score. There is a need for better diagnostic and risk-stratification tools incorporating novel biochemical and electrocardiographic markers for syncope patients in the ED.

Abstract

Background: Various scores have been derived for the assessment of syncope patients in the emergency department (ED) but stay inconsistently validated. We aim to compare their performance to the one of a common, easy-to-use $CHADS_2$ score.

Methods: We prospectively enrolled patients ≥ 40 years old presenting with syncope to the ED in a multicenter study. Early clinical judgment (ECJ) of the treating ED-physician regarding the probability of cardiac syncope was quantified. Two independent physicians adjudicated the final diagnosis after 1-year follow-up. Major cardiovascular events (MACE) and death were recorded during 2 years of follow-up. Nine scores were compared by their area under the receiver-operator characteristics curve (AUC) for death, MACE or the diagnosis of cardiac syncope.

Results: 1490 patients were available for score validation. The $CHADS_2$-score presented a higher or equally high accuracy for death in the long- and short-term follow-up than other syncope-specific risk scores. This score also performed well for the prediction of MACE in the long- and short-term evaluation and stratified patients with accuracy comparative to OESIL, one of the best performing syncope-specific risk score. All scores performed poorly for diagnosing cardiac syncope when compared to the ECJ.

Conclusions: The $CHADS_2$-score performed comparably to more complicated syncope-specific risk scores in the prediction of death and MACE in ED syncope patients. While better tools incorporating biochemical and electrocardiographic markers are needed, this study suggests that the $CHADS_2$-score is currently a good option to stratify risk in syncope patients in the ED.

Introduction

Syncope is a transient loss of consciousness (T-LOC) associated with an inability to maintain postural tone due global cerebral hypoperfusion.[50] It is frequent and represents 1-2% of all Emergency Department (ED) visits.[2] The underlying etiologies range from benign conditions, such as vasovagal reactions, to life-threatening cardiac diseases.[50–52] Early risk stratification during initial evaluation is important to guide decisions regarding treatment and disposition and prevent long-term morbidity and mortality[50]. Syncope outcomes are mainly linked to the underlying etiology and the associated comorbidities. In the ED, the rapid identification of the underlying cause and associated risks are challenging, thus leading to a high hospitalization rate. However, only 25% of these hospitalizations have been considered appropriate[53] and, despite extensive cardiovascular investigations, 75% of patients in whom the cause of the syncope remains unexplained after initial clinical assessment will not receive a final diagnosis of causality[17].

In an attempt to improve the identification of patients at risk of adverse outcomes, numerous syncope-specific risk scores[5,18,23] have been derived. However, as highlighted in the recent ACC/AHA/HRS “Guideline for the Evaluation and Management of Patients With Syncope”,[54] these scores were derived in only a few centers, are based on inconsistent definitions of outcomes, time frames and predictors, and have been subject to limited external validation.[10] Furthermore, these tools have not been implemented in most institutions, partly due to their perceived complexity. The $CHADS_2$ score is widely known and used for prediction of thromboembolic episodes and initiation of treatment with anticoagulants in patients with atrial fibrillation[55]. In addition, it has recently been applied as a risk stratification tool for predicting mortality after an episode of syncope and was recommended in current guidelines[54,56]. However, a prospective validation in a multicenter study is lacking. Our study aims to validate syncope-specific risk scores[5,18,23] and compare their performance to the one of a common, easy-to-use $CHADS_2$ score in a large, multicenter cohort of prospectively enrolled patients presenting following a syncopal episode to the ED and provide a valid overview of the diagnostic and prognostic accuracy of these tools.

Methods

Study design, setting and selection of participants

BAsel Syncope EvaLuation Study (BASEL IX) is an ongoing prospective international diagnostic multicenter study enrolling patients in 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 and improve the management of patients presenting with syncope (ClinicalTrials.gov registry, number NCT01548352). Patients aged more than 40 years presenting to the ED with syncope within the last twelve hours were recruited, after written informed consent was obtained.

Patients with the final diagnosis of a non-syncopal loss of consciousness (e.g. epilepsy, fall, alcohol intoxication) were excluded of the analysis. As the majority of scores requested ECG data for their correct computation, patients who did not undergo electrocardiographic testing upon arrival to the ED were excluded as well. Patients in whom the final diagnosis remained unclear even after central adjudication were excluded for the validation of diagnostic scores (Supp. Figure I).

The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees. The authors designed the study, gathered, and analysed the data according to the STARD guidelines for studies of diagnostic accuracy, vouched for the data and analysis, wrote the paper, and decided to publish.

Clinical assessment

All patients underwent a clinical assessment that included standardized and detailed assessment of predefined details of medical history, including previous syncope events and circumstances of current syncope, vital signs, physical examination, routine laboratory tests, radiologic testing, and a 12-lead ECG. Additionally, patients may have also undergone 24-hour ECG, external or implantable loop device, cardiac exercise test, Shellong test, tilt table testing, coronary angiography, continuous rhythm monitoring, pulse oximetry, echocardiography, results from device controls

(e.g. pacemaker) or electrophysiological examinations, and recording of findings of further investigations during recurrent hospitalization or ambulant treatment. Additional tests and treatment of patients were left to discretion of the attending physician.

Clinical judgment by the ED physician regarding the presence of cardiac syncope was quantified using a visual analogue scale within 90 minutes after presentation and following initial patients' assessment encompassing patient history and status as conducted by the ED physician, first standard laboratory values and the ECG.

Follow-up and adjudicated final diagnosis

Patients were contacted 6, 12 and 24 months after discharge by telephone or in written form. Information regarding recurrent syncope, hospitalization and cardiac events during follow up was furthermore obtained from the patient's hospital notes, the family physician's records and national mortality registries, where available. To determine the final diagnosis for the index syncope in each patient, two independent physicians reviewed all available medical records from the clinical data set and the study-specific data set. The clinical data set included data from the clinical assessment, while study-specific data included standardized forms uniformly collecting predefined details of patient history, the circumstances of syncope, and physical examination, as well as at least 12 months follow-up. In situations of disagreement between adjudicators, cases were reviewed and adjudicated in conjunction with a third physician. Further details regarding the adjudicated diagnosis are available in the supplemental material.

Score selection and computation

The scores listed in the recent AHA/ACC/HRS Guidelines,[54] for which our study contained appropriate data to allow their validation, were computed according to the original score definition (Supplemental table I). In total, seven syncope-specific scores mentioned in these guidelines were computed in all patients for this analysis: The score by Martin[20], the OESIL[18] score, the SFSR[19] score, the Boston Syncope[21], the STePS[22] score (for long- and short-term risk prediction) and the EGSYS[17] score. As these same guidelines mentioned the $CHADS_2$ score as a long-term risk factor, this score and its extension, the CHA_2DS_2VASc score, were

analyzed as well. The computed scores were not available to the Emergency Physician at the time of admission.

Table I summarizes the different scores, their individual components, the recommended cut-off values and their performance as reported in the original publications.

Outcome measures

As the definitions of clinical endpoints or serious outcomes and the time frame for predictions varied strongly between studies (Table I), we decided to validate all scores for clinically relevant endpoints. The co-primary prognostic endpoints were all-cause death and major adverse cardiovascular events (MACE, defined as a combined endpoint of all-cause death, life-threatening arrhythmia, pacemaker/implantable Cardioverter Defibrillator implantation, stroke, acute myocardial infarction (AMI) and pulmonary embolism) during 2 years of follow-up[50,54] and the primary diagnostic endpoint was cardiac syncope. The co-secondary prognostic endpoints were all-cause death and MACE at 30 days.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) when normally distributed and median with interquartile ranges (IQR) when non-normally distributed. Categorical variables are expressed as numbers and percentages. Mann-Whitney-U test was applied for comparison of continuous variables between cardiac and non-cardiac syncope. Categorical variables were compared by Pearson Chi-square test and Fisher's exact test, respectively.

Receiver-operating characteristic (ROC) curves were constructed to assess the sensitivity (SE) and specificity (SP) of each score regarding their prognostic and diagnostic accuracy for the predefined endpoints. SE and SP of the early clinical judgment of the ED physician for the diagnosis of cardiac syncope were assessed in a similar way. The comparison of areas under the independent ROC curves (AUC) was performed according to DeLong.

We assessed the performance of each score to predict cardiac syncope, death or MACE when either the recommended cut-off or any other possible cut-off was applied.

Survival analysis was conducted using graphical representation of Kaplan-Meier curves. Difference in time-to-event stratification was tested by the use of the log-rank test.

All hypothesis testing was two-tailed and p-values <0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (SPSS Inc, Chicago, IL) and the R statistical package (MathSoft, Seattle, WA, packages “foreign”, “haven”, “tableone”, “reshape2”, “ggplot2”, “gridExtra”, “survival”, “survminer”).

Results

Characteristics of study subjects

From May 2010 to August 2016, a total of 1753 patients were enrolled in the BASEL IX study (Supplemental Figure I).

Patients with a non-syncopal loss of consciousness (n=214) or missing ECG's (n=61) were excluded for both analyses, while patients in whom the final diagnosis remained unclear even after central adjudication (n=145) were excluded from analyses of diagnostic endpoints, leaving a total of 1490 and 1345 patients available for the analysis of diagnostic and prognostic endpoints, respectively.

The characteristics of patients who suffered a cardiac syncope (n=216), a non-cardiac syncope (n=1129) and a syncope of unknown etiology (n=145) are presented in Table II. Patients diagnosed with a cardiac syncope were significantly older, had more cardiovascular comorbidities and were taking more chronic medications.

Prognostic accuracy of the scores

During a median follow-up duration of 739 days (IQR 720-835) in survivors, 227 patients (15.2%) died and 319 patients (21.4%) suffered from MACE.

The prognostic accuracies of all analyzed scores for the prediction of death and MACE for the entire follow-up length are represented in Figure I. For the prediction of death, the $CHADS_2$, CHA_2DS_2VASc, and STEPS long scores (all three AUC 0.71, 95%CI 0.68-0.74) displayed the highest prognostic accuracy (p for comparison=ns).

For the risk prediction of MACE, the OESIL, $CHADS_2$, CHA_2DS_2VASc, Martin, Boston and STEPS long-term scores provided comparable prognostic accuracy (p=ns for comparison).

The prognostic accuracies of the scores for death and MACE for a limited time span of 30 days following the initial syncope are presented in supplemental Figure II. The results were consistent with the long-term prognostic accuracy, with the $CHADS_2$ and CHA_2DS_2VASc-Scores performing best for the short-term prediction of death (AUC 0.79, 95%CI 0.72-0.87 and AUC 0.76, 95%CI 0.65-0.82 respectively, p=ns). The

Martin and the OESIL score again performed best for the prediction of MACE in the short term (AUC 0.72, 95%CI 0.68-0.75 and AUC 0.70, 95%CI 0.66-0.74 respectively, p=ns).

The percentage of patients ruled in and out and the sensitivity, specificity, negative predictive value and positive predictive value of the individual scores to predict death or MACE during the entire follow-up using the recommended cut-off levels of each individual score are presented in Supplemental Table IIA and IIB. The performance of the best performing scores at alternative cut-off points is presented in the supplemental Table IIIA and IIIB.

Survival and survival free of MACE up to 2 years of follow-up according to the $CHADS_2$ and OESIL score are shown in Figure II. Both scores allowed for an efficient and comparable risk stratification

Diagnostic accuracy of the scores for cardiac syncope

The diagnostic accuracy of all analyzed scores as well as the one of the Early Clinical Judgment of the ED physician for a syncope of cardiac etiology is represented in Figure I. Of all analyzed scores, the one by Martin and the OESIL score displayed the highest accuracy (AUC 0.75, 95%CI 0.72-0.78 and AUC 0.72, 95%CI 0.68-0.75 respectively, p=ns). However, it performed poorly compared with the Early Clinical judgment of the ED physician (AUC 0.87, 95%CI 0.84-0.9, p=<0.001 for the comparison with the Martin score).

Details regarding the performance of recommended or alternative cut-off points of each individual score to predict cardiac syncope are presented in Supplemental Table IIC and supplemental Table IIIC, respectively.

When added to the early clinical judgment of the ED physician, the OESIL, Martin, CHA_2DS_2VASc and $CHADS_2$ score did not lead to any improvement of the diagnostic accuracy of the Emergency Physician (Supplemental Table IV).

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 by evaluating the prognostic and diagnostic utility of various clinical risk scores potentially implementable in the ED and compare their performance to the one of a common, easy-to-use $CHADS_2$ score.

We report four major findings. First, all validated syncope risk-stratification scores showed only moderate performance for the prediction of death and MACE on the long- and on the short-term. Second, the syncope-specific risk scores were less or equally accurate than a simpler $CHADS_2$ score for the prediction of death and MACE over two years of follow-up and for a 30-days period following the index event. Third, all syncope-specific diagnostic scores performed poorly compared with the early clinical judgment of the ED physician. Fourth, none of the evaluated score added any diagnostic value to the early clinical judgment of the emergency physician.

These findings corroborate and extend previous studies which tried to establish the most appropriate diagnostic and prognostic clinical use of various scores possibly implementable in the ED.[17–22,57] To the best of our knowledge, this is the first observational study using prospectively collected data to validate seven syncope-specific scores in the same patient data set. We observed a strong overlap between several scores, most of them taking into account signs of the acute presentation, age, prior history of heart disease or electrocardiographic abnormalities. However, as highlighted in previous studies[58], the exact definition of the overlapping components was heterogeneous between scores, contributing to their variability in diagnostic and prognostic accuracy.

Our study demonstrated that syncope-specific risk scores did not perform better than a simple $CHADS_2$ or CHA_2DS_2VASc score. These scores has been validated in several cardiovascular diseases[59–63] and are widely used prediction tools for thromboembolic episodes and initiation of treatment with anticoagulants in patients with atrial fibrillation[55,64,65]. Our results discourage the unnecessary use of complicated and time-consuming syncope-specific scores for long- and short-term risk stratification, as comparable accuracy can be obtained through a simple, quick

and widespread score. However, the $CHADS_2$ score is known to be a general indicator of morbidity and, as shown by Ruwald et al.[56], it stratifies a syncope population just as well as a general population not suffering any syncopal events. The performance of this score to predict adverse outcome better than or equally to syncope-specific scores highlights that syncope-related adverse prognostic factors are not reliably established.

The diagnostic accuracy of all scores was poor and inferior to the early clinical judgment of the ED physician. Moreover, in conjunction with this judgment, none of the scores brought a clinically relevant improvement. This inferiority has been observed in previous studies[17] and reflects the difficulty of diagnostic models to capture the clinical synthesis made by a physician. Previous research tried to reproduce this complex process of physicians' reflection using neural networks and could accurately predict short-term adverse outcome in patients presenting with syncope to the ED[66]. While the use of such sophisticated non-linear models is certainly promising, clinical validation of this approach is pending.

We rated the different scores by analyzing and comparing their AUC for different endpoints (Figure I and Supplemental Figure II), leading to a cut-off-independent comparison of their accuracy. While the comparison of these AUCs reflects the relevance of the scores components, it only partly represents the real clinical value in the settings where the scores were developed and where they will be used. During score derivations, most of the authors accompanied their publication with a recommended cut-off [4,17–19,21,56], which is essential for the implementation of these scores into ED decision making. Our analysis reveals important differences in the sensitivity of the scores when the recommended cut-off was applied. For instance, the EGSYS and its recommended cut-off of ≥3 points led to a much lower sensitivity than other scores. A cut-off adaptation to ≥1 point would have significantly raised its sensitivity to detect cardiac syncope or stratify risk in our patient collective. Acknowledging that this score was derived in a study involving centers exclusively in Italy, the recommended cut-off does not seem to be generalizable to a more international setting. This again highlights the importance of validation studies to insure not only the relevance of the score components but also the suitability of the recommended cut-offs in other populations.

Furthermore, a single cut-off strategy was recommended for all the scores in the derivation studies. Recently, strategies using different cut-offs for rule-in and rule-out were proven useful for the diagnostic stratification of other cardiovascular diseases in clinical practice, mainly acute myocardial infarction[67–69]. Most of the validated syncope-specific scores already show very good safety, but classifying patients into “high-risk”, “low-risk” and “observe” cohorts could allow for clinical efficacy optimization and improvement of resource utilization.

Some limitations merit considerations when interpreting our findings. First, despite using the most stringent methodology to adjudicate the etiology of the underlying syncope event, we still may have misclassified a small number of patients. Second, the underlying etiology of the syncopal events stayed unclear in 11% our patients. However, this percentage is much lower than reported by other studies[51] and highlight our strong methodology. Third, we did not validate three further syncope-specific scores present in the literature due to the lack of systematic measurements of troponin and BNP in all of our patients. Fourth, we are aware that the validated scores have been originally derived to ease either diagnosis or risk-stratification and thus the definition of the endpoints and timeframes were heterogeneous. Nevertheless, to allow for comparison, we assessed all scores regarding their diagnostic and prognostic accuracy for death and MACE, which were endpoints we considered as clinically relevant.

In conclusion, all currently available clinical scores perform only moderately in the prognosis and diagnosis of cardiac syncope. None of the scores bring a relevant improvement to the early judgment of the clinician. Syncope-specific risk-stratification scores were less or equally accurate than a simpler $CHADS_2$ score for the prediction of death and MACE in the short- and long-term follow-up. Our analysis underlines the need for improved tools for diagnosis and risk stratification, potentially including novel biochemical and electrocardiographic markers.

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Conflict of interest and disclosures

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 and Mueller had full access to all the data in the study and take

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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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All other authors declare that they have no conflict of interest with this study.

Figures

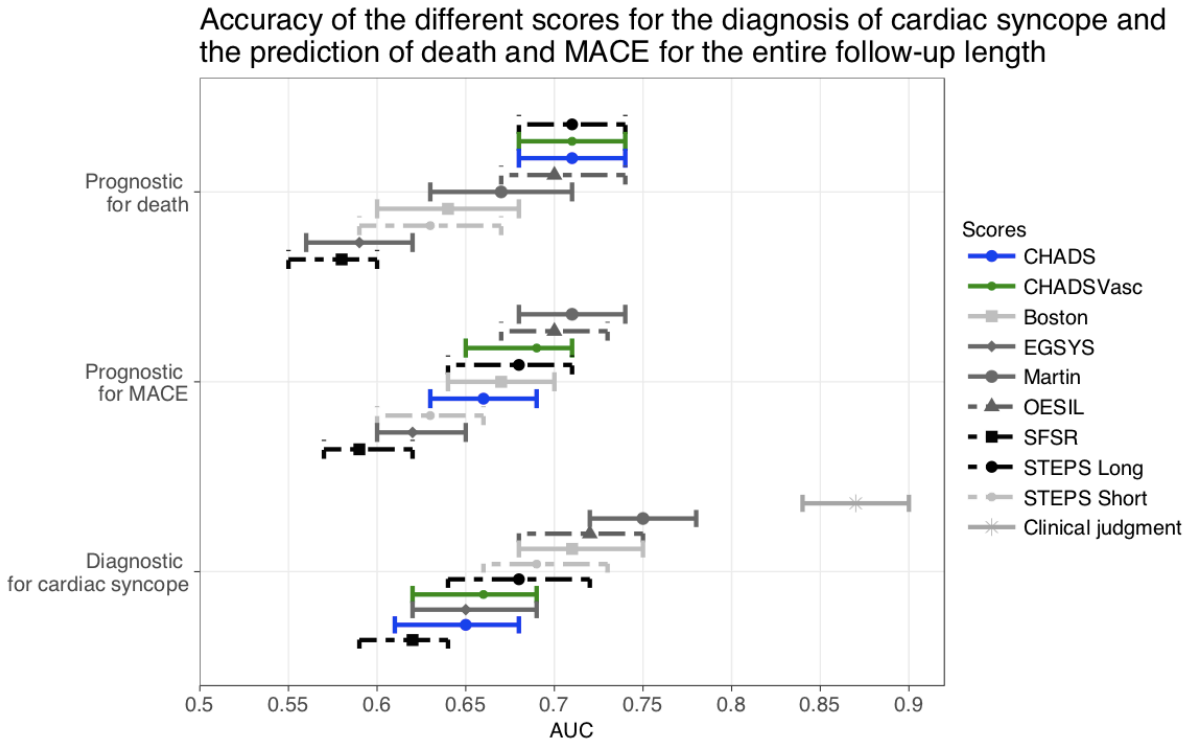


Figure I: Accuracy of the analyzed scores for the prediction of death and MACE (for a median follow-up of 739 days) and for the diagnosis of cardiac syncope, as given by value of the Area Under the Curve.

Whiskers represent the 95%-confidence intervals.

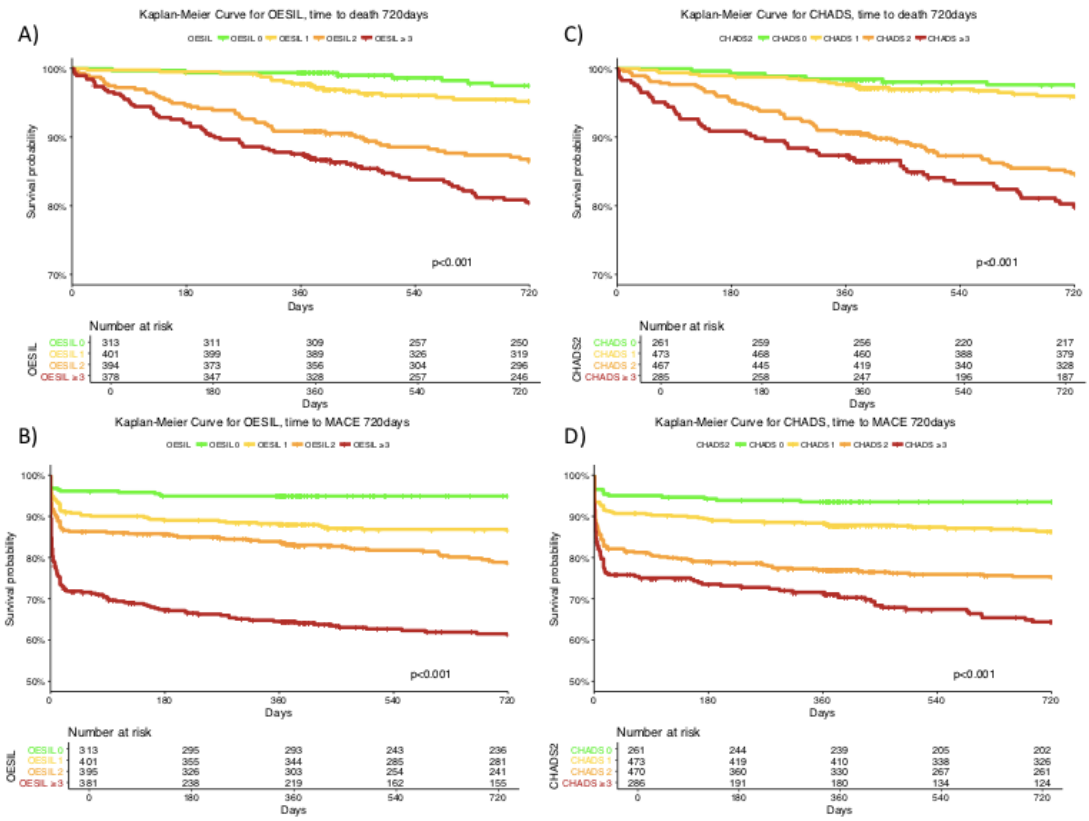


Figure II: Survival analysis using the OESIL- (A and B) or $CHADS_2$-score (C and D) for time-to-death and time-to-first MACE until 720 days.

p-values calculated according to the log-rank test.

Tables

Table I: Summary of the scores and their performance according to the literature.

Score	Range	Components	Recommended cut-off	Original endpoint	Original accuracy
Martin	0-4	Abnormal ECG, >45y of age, history of ventricular arrhythmias, history of CHF	≥1[a]	1-y death or arrhythmia	AUC=0.80 NPV = 93%*
OESIL	0-4	Abnormal ECG, >65y of age, no prodromi, cardiac history	≥2	1-y death	AUC=0.89 NPV= 99% PPV=32% SE=97% SP =73%
SFSR	0-1	Abnormal ECG, dyspnea, hematocrit, systolic BP<90mmHg, history of CHF	≥1	7-d serious events	NPV= 99% PPV=25% SE =96% SP =62%
Boston Syncope Rule	0-8	Symptoms of acute coronary syndrome, worrisome cardiac history, family history of SCD, valvular disease, signs of conduction disease, volume depletion, persistent abnormal vital signs, primary central nervous event	≥1	30-d serious events	NPV=100% PPV=44% SE = 97% SP=62%
EGSYS	-2-12	Abnormal ECG, cardiac history, palpitations, exertional, supine, precipitants, autonomic prodromi	≥3	Cardiac etiology	AUC=0.90 NPV= 99% PPV=33% SE =95% SP = 61%

[a] As mentioned in the AHA/ACC Guidelines[4]

STePS (short term)	0-14[a]	Abnormal ECG, trauma, no prodromi, male sex	n.a.	10-d serious events	n.a.
STePS (long term)	0-15[†]	Age >65, neoplasms, cerebrovascular diseases, structural heart disease, ventricular arrhythmias	n.a.	1-y serious events	n.a.
$CHADS_2$	0-6	CHF, hypertension, Age>75, Diabetes, prior Stroke/TIA	≥1	Cardiovascular death	NPV = 93% PPV = 41% SE =82% SP = 67%
CHA_2DS_2 VASc	0-10	CHF, hypertension, Age>75, Diabetes, prior Stroke/TIA, Vascular disease, Age 65-74y, female sex	n.a.	n.a.	n.a.

Table I: Comparison of the analysed scores according to the data provided in the literature. AUC = Area Under the Curve, BP= Blood pressure, NPV = Negative predictive value, PPV = Positive Predictive Value, CHF = Congestive Heart Failure, ECG = Electrocardiogram, SE = Sensitivity, SP = Specificity, SCD = Sudden Cardiac Death, TIA = Transient Ischemic Attack, n.a. = not applicable

[a] Derived from the odds ratios of the original publication

Table II	Baseline characteristics				
	All patients N= 1490	Not cardiac N= 892	Cardiac N= 175	Unknown N= 128	p
Age - years [IQR]	71.0 [58.0, 80.0]	68.0 [55.0, 78.0]	77.0 [66.0, 84.0]	79.0 [71.0, 84.0]	<0.001
Women gender – no. (%)	593 (40)	458 (41)	78 (36)	57 (39)	0.468
Characteristics of the syncope – no (%)					
Nausea/Vomiting	430 (29)	362 (33)	44 (21)	24 (17)	<0.001
Sweating	452 (31)	389 (35)	42 (20)	21 (15)	<0.001
Pallor	398 (44)	323 (46)	47 (37)	28 (33)	0.013
Palpitations	101 (7)	77 (7)	18 (9)	6 (4)	0.293
Angina	91 (6)	63 (6)	20 (9)	8 (6)	0.118
Caused injury	214 (15)	150 (14)	33 (16)	31 (22)	0.027
Position of the syncope – no (%)					
While lying	36 (2)	27 (2)	6 (3)	3 (2)	0.901
While sitting	596 (40)	460 (41)	81 (38)	55 (38)	0.569
Orthostatic	181 (12)	152 (14)	16 (7)	13 (9)	0.020
While standing	656 (44)	473 (42)	111 (52)	72 (50)	0.016
Exertion	127 (9)	75 (7)	35 (16)	17 (12)	<0.001
Risk factors – no (%)					
Hypertension	897 (60)	640 (57)	147 (69)	110 (76)	<0.001
Hypercholesterolemia	626 (44)	449 (41)	106 (50)	71 (53)	0.003
Diabetes	228 (15)	155 (14)	44 (20)	29 (20)	0.011
Smoking	756 (51)	580 (52)	99 (47)	77 (55)	0.283
History – no (%)					
Previous stroke	124 (8)	87 (8)	18 (8)	19 (13)	0.091
Chronic heart failure (NYHA II – IV)	117 (8)	68 (6)	33 (16)	16 (11)	<0.001
Arrhythmia	318 (22)	197 (18)	83 (39)	38 (27)	<0.001

Pacemaker	72 (5)	50 (4)	17 (8)	5 (4)	0.073
Coronary artery disease	325 (22)	207 (19)	73 (35)	45 (31)	<0.001
Previous DVT or PE	103 (7)	71 (6)	14 (7)	18 (13)	0.020
Previous MI	192 (13)	125 (11)	43 (20)	24 (17)	0.001
Epilepsy	43 (3)	33 (3)	2 (1)	8 (6)	0.039
Chronic medication – no (%)					
ACEIs/ARBs	667 (45)	475 (42)	113 (52)	79 (54)	0.001
Alphablocker	117 (8)	83 (7)	19 (9)	15 (10)	0.386
Antiarrhythmics Class I	54 (4)	34 (3)	13 (6)	7 (5)	0.069
Aspirin	451 (30)	313 (28)	80 (37)	58 (40)	0.001
Beta-blockers	482 (32)	324 (29)	93 (43)	65 (45)	<0.001
Calcium antagonists	253 (17)	176 (16)	42 (19)	35 (24)	0.021
Digitalis	26 (2)	13 (1)	11 (5)	2 (1)	<0.001
Diuretics	456 (31)	303 (27)	98 (45)	55 (38)	<0.001

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

Supplemental material

Supplemental Methods:

Adjudication of the final diagnosis

The first step in the adjudication process was to decide whether there was syncope or not. If the criteria for a true syncope were not fulfilled, a distinction between the following non-syncopal disorders was made: pre-syncope; falls; stroke/TIA; epilepsy; metabolic disorders: e.g. hypoglycaemia, hypoxia, hyperventilation; intoxication: e.g. alcohol, benzodiazepines, opiates; functional (psychogenic pseudosyncope); others.

The classification of syncope is based on pathophysiological considerations. The following predefined differential diagnoses were used:

1) Cardiac syncope: We distinguished between:
    a. Arrhythmia as primary cause: Arrhythmias are the most common cause of syncope; Bradycardia: sinus node dysfunction, atrioventricular conduction system disease, implanted device malfunction or drug-induced; Tachycardia: supraventricular or ventricular.
    b. Structural heart disease: structural heart diseases can cause syncope when circulatory demands outweigh the impaired ability of the heart to increase output. However, in some cases syncope may not solely be the result of restricted cardiac output, but be in part due to an inappropriate reflex. However, when a structural heart disease was the primary cause or contributed most to syncope, it was classified as cardiovascular syncope.
    c. Others: pulmonary embolism, acute aortic dissection, pulmonary hypertension or any other cause for a cardiovascular syncope.
2) Reflex (neutrally-mediated) syncope: This syncope is characterized by cardiovascular reflexes which are normally useful in controlling circulation but become intermittently inappropriate in response to a trigger. The reflex results in vasodilation and/or bradycardia which lead to a fall in arterial blood pressure and consequently to cerebral hypoperfusion. Identifying a trigger is central when diagnosing a reflex syncope. Typically symptoms as lightheadedness,

nausea, sweating, weakness or visual disturbances precede reflex syncope. We distinguished between:

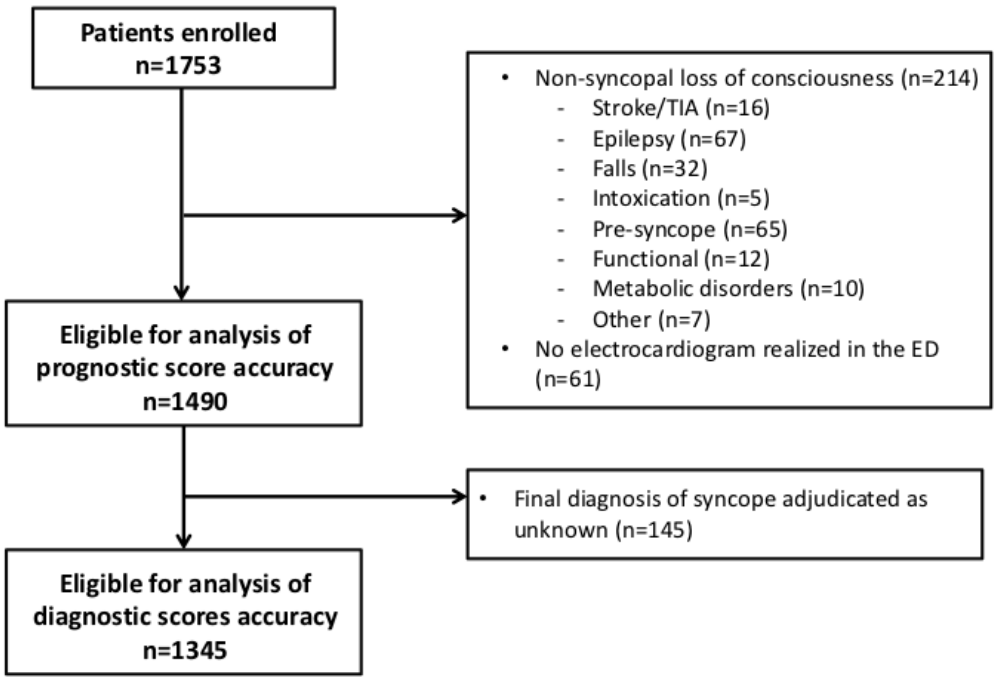
   a. Vasovagal: “common faint”, triggered by emotional distress/ pain or mediated by orthostatic stress.
   b. Situational: refers to reflex syncope associated with some specific circumstances, e.g. post-micturition, post-prandial, gastrointestinal stimulation, cough.
   c. Carotid sinus syncope: triggered by mechanical manipulation of the carotid sinus. It can be diagnosed by carotid sinus massage.
   d. Atypical forms: reflex syncope occurring with uncertain or apparently absent triggers.

3) Syncope due to orthostatic hypotension: Orthostatic hypotension is defined as an abnormal decrease in systolic blood pressure after changing from supine to standing position. Key can be syncope immediately after standing up or a pathological Schellong test. We distinguished between:
   a. Primary autonomic failure: There is an autonomic failure which is clearly a primary part of Parkinson syndrome as idiopathic Parkinson disease or atypical Parkinson syndrome (multiple system atrophy, progressive supranuclear oculomotoric paresis, corticobasal degeneration or lewy body dementia).
   b. Secondary autonomic failure: autonomic failure may be due to circumstances such as diabetes, uraemia, amyloidosis or spinal cord injuries
   c. Drug-induced orthostatic hypotension: orthostatic hypotension is due to drugs which can lead to orthostatic hypotension such as diuretics, antidepressants, vasodilators, alcohol
   d. Volume depletion: orthostatic hypotension is caused by a hypovolemia due to haemorrhage, diarrhoea, vomiting or fever
   e. Others: sometimes the pathophysiology remains unclear.
4) Others, non-cardiac syncope: Sometimes the underlying pathophysiological mechanism of syncope remains unclear, but a cardiac syncope is ruled-out.
5) Syncope of unknown etiology (cardiac syncope possible): the etiology of syncope still remained unknown and a cardiac syncope was considered to be a possible cause.

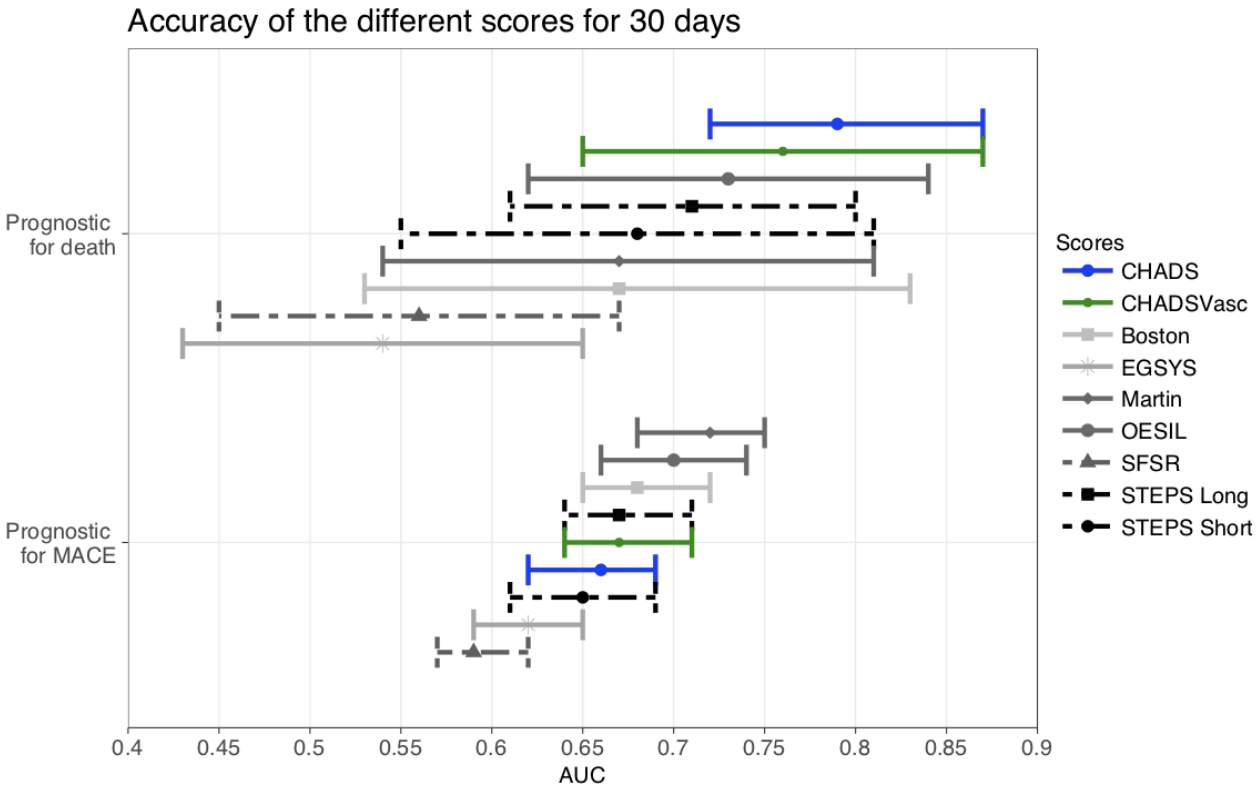
Supplemental Figures:

Supplemental figure I : Patient flow-chart.

ED = Emergency Department.



Supplemental figure II: Accuracy of the analyzed scores for the prediction of death or MACE at 30 days, as given by value the Area Under the Curve.



Whiskers represent the 95%-confidence intervals.

Supplemental Tables :

Supplemental table I : Details of the score computation

Score	Variable	Definition of the variable	Computation with our data	Computation oft he score
$CHADS_2$	Congestive heart failure	Patients with clinical diagnostic of heart failure or LVEF<40% or NYHA Class II-IV	If the patient had a clinical history of heart failure (NYHA II-IV) or an EF of <40% on the TTE	+1
	Hypertension	BPSys>140 or BPdiast>90 or 1 anti-hypertensive med.	If the patient had a history of hypertension or if he was under a chronic treatment of at least one alphablocker and/or one diuretic and/or one ACE-inhibitor and/or one AT-II blocker and/or one betablocker and/or one calcium antagonist.	+1
	Age > 75yo		If age >75yo	+1
	DM	Previous diagnosis or use of antidiabetic medications	If the patient had a diagnosis of diabetes or was using antidiabetics, including insulin.	+1
	History of Stroke or TIA		If the patient had a previous diagnosis of stroke or TIA	+2
CHA_2DS_2VASc	Age >65yo		Age>65yo.	+1
	Vascular disease	History of myocardial infarction, peripheral artery disease or vascular plaques, including previous surgery for vessels or previous arterial and venous thrombosis.	If the patient had a diagnosis of peripheral artery disease, a history of a previous myocardial infarction, deep vein thrombosis, a coronary artery bypass or a percutaneous coronary revascularisation.	+1
	Sex	Female	If the patient was a woman	+1
OESIL score	Cardiovascular disease	1. Previous clinical or laboratory diagnosis of any form of structural heart disease, including ischemic heart disease, valvular dysfunction and primary myocardial disease,	If the patient had a history of congestive heart failure (NYHA II-IV), a known valvular disease, a previous history of stroke or TIA, myocardial infarction, bypass operation, percutaneous	+1

		2. Previous diagnosis or clinical evidence of congestive heart failure, 3. Previous diagnosis or clinical evidence of peripheral arterial disease, 4. Previous diagnosis of stroke or transient ischemic attack.	coronary revascularisation or a diagnosis of peripheral artery disease.	
	No prodromi	No prodromal symptoms such as light-headedness, nausea, diaphoresis, weakness, and visual disturbances	If the patients had no prodromal symptoms such as light-headedness, nausea, vomiting, diaphoresis, weakness, and visual disturbances.	+1
	Abnormales EKG	The tracings were considered abnormal in the following cases: 1. Rhythm abnormalities (atrial fibrillation or flutter, supraventricular tachycardia, multi- focal atrial tachycardia, frequent or repetitive premature supraventricular or ventricular com- plexes, sustained or non-sustained ventricular tachycardia, paced rhythms), 2. Atrioventricular or intraventricular conduction disorders (complete atrioventricular block, Mobitz I or Mobitz II atrioventricular block, bundle branch block or intraventricular conduction delay), 3. Left or right ventricular hypertrophy, 4. Left axis deviation, 5. Old myocardial infarction, 6. ST segment and T wave abnormalities consistent with or possibly related to myocardial ischemia. Electrocardiographic recordings showing non- specific repolarization abnormalities were not considered as abnormal.	The tracings were considered abnormal in the following cases: 1. Rhythm abnormalities : Atrial fibrillation, atrial flutter, atrial ectopic rhythm, ventricular ectopic rhythm 2. Atrioventricular block Mobitz I and II, complete atrioventricular block or higher atrioventricular blocks, right, left left-anterior hemi- and bundle branch block 3. Left ventricular hypertrophy 4. Left axis deviation 5. Presence of significant Q-waves 6. ST segments modification and T wave abnormalities possibly related to myocardial ischemia	+1

EGSYS score	Age >65yo		Age >65yo	
	Palpitation preceding syncope		If the patient reported palpitations preceding the event.	+4
	History of Heart disease or abnormal ECG in the ED	ECG abnormality was considered as the presence of one or more of the following abnormalities: bradycardia (<40 beat/minute), ST changes (>1 mm elevation or depression), QT prolongation (440ms), ventricular tachycardia, atrioventricular block (second or third degree), sick sinus syndrome, ventricular and rapid paroxysmal supraventricular arrhythmias, sinus pauses, and pace malfunction. No precisions given regarding the “history of heart disease” component.	The tracings were considered abnormal in the following cases: 1. Bradycardia <40bpm 2. Rhythm abnormalities : Atrial fibrillation, atrial flutter, atrial ectopic rhythm, ventricular ectopic rhythm and pacemaker rhythm 3. Sicksinus syndrome 4. Atrioventricular block Mobitz I and II, complete atrioventricular block or higher atrioventricular blocks 5. ST segments modification and T wave abnormalities possibly related to myocardial ischemia 6. QT prolongation (440ms) A history of heart disease was positive if the patient had a diagnosis of congestive heart failure (NYHA II-IV), of valve disease, a previous history of myocardial infarction, bypass surgery, percutaneous coronary intervention.	+3
	Syncope during effort		If the patient reported syncope during effort.	+3
	Syncope while supine		If the patient reported syncope while supine.	+2
	Precipitating or predisposing factor	Predisposing or precipitating factors were considered as the presence of one or more of the following abnormalities: Warm-crowded place/prolonged orthostasis/fear–pain–emotion	If the patient reported syncope while standing, sitting, while standing up or accompanied by weakness.	-1

	Autonomic prodromi	Prodromal symptoms and signs were considered as the presence of one or more of the following abnormalities: nausea/vomiting	If the patients had no prodromal symptoms such as light-headedness, nausea, vomiting, diaphoresis, weakness, and visual disturbances.	-1
Martin Score	Age >45		Age >45yo	1
	History of congestive heart failure		If the patient had a known history of congestive heart failure (NYHA II-IV)	1
	Arrhythmia	Definition of arrhythmia: ventricular tachycardia (VT) of three or more beats; sinus pauses of 2 seconds or longer and those pauses that were symptomatic; symptomatic sinus bradycardia ("symptomatic" for the purposes of this study refers to the simultaneous occurrence of dizziness, lightheadedness, or syncope and an arrhythmia on ECG monitoring); supra-ventricular tachycardia (SVT) with symptoms or associated with hypotension (systolic blood pressure less than 90 mm Hg); atrial fibrillation with slow ventricular response (RR interval longer than 3 seconds); complete atrioventricular block; Mobitz II atrioventricular block; and evidence of pacemaker malfunction. Isolated, asymptomatic premature ventricular contractions (PVCs), couplets, asymptomatic premature atrial contractions, brief asymptomatic runs of SVT, chronic atrial fibrillation, and atrial flutter were not included in the definition of arrhythmias unless they were associated with symptoms (dizziness, lightheadedness, or syncope).	If the patient had any known history of arrhythmia.	1
	Abnormal ECG:	ECG reports and tracings (from ED ECG, Holter monitoring, or bedside ECG monitoring in the CCU) were reviewed for identification and verification of arrhythmias. Two definitions of clinically important arrhythmias were considered. It was not required that these arrhythmias were the cause of the syncope.	ECG reports from the ED ECG, Holter monitoring and telemetry monitoring data were review. Abnormal parameters on the ECG were considered to be : 1. Rhythm abnormalities : Atrial fibrillation, atrial flutter, atrial ectopic rhythm, ventricular ectopic rhythm	1

		Rhythm abnormalities were : atrial fibrillation or flutter, multifocal atrial tachycardia, junctional or paced rhythms; frequent or repetitive PVCs (including VT), conduction disorders (ie, left axis deviation, bundle branch block, intraventricular conduction delay), left or right ventricular hypertrophy (LVHor RVH), short PRinterval (less than 0.10sec), old myocardialinfarction, and atrioventricular block (ie, complete atrioventricular block, Mobitz II, or Mobitz I with other abnormalities present). Not abnormal: normal (including patients with only sinus bradycardia or sinus tachycardia); nonspecific ST- and T-wave abnormalities (NST) for patients with NST as the only abnormality	2. Atrioventricular block Mobitz I and II, complete atrioventricular block or higher atrioventricular blocks, right, left left-anterior hemi- and bundle branch block or a PQ-time <0.10sec 3. Left ventricular hypertrophy 4. Left axis deviation 5. Presence of significant Q-waves 6. ST segments modification and T wave abnormalities possibly related to myocardial ischemia 7. Presence of nonsustained ventricular tachycardia Abnormal parameters on the Holter analysis were considered to be: 1. Rhythm abnormalities : Atrial fibrillation, atrial flutter, atrial ectopic rhythm, ventricular ectopic rhythm 2. Atrioventricular block Mobitz I and II, complete atrioventricular block or higher atrioventricular blocks 3. Incomplete and complete right, left blocks or combinations. 4. Any pause >2.5 sec The telemetry monitoring data were considered abnormal if any pause of >2.5sec occurred.	
SFSR	Abnormal ECG	New abnormal ECG	All ECGs upon arrival in the ED were compared with previously realized ECGs (anytime). A new pathology was considered when the ECG upon arrival but not the previous ECG displayed at least one of: 1. Atrioventricular block Mobitz I and II, complete atrioventricular block or higher atrioventricular blocks, right, left left-anterior hemi- and bundle branch block 2. Left ventricular hypertrophy 3. Left axis deviation 4. Presence of significant Q-waves 5. ST segments modification and T wave abnormalities possibly related to myocardial ischemia 6. Presence of nonsustained ventricular tachycardia 7. QTc time >440 8. Sick sinus syndrome	Made the rule positive

			Any rhythm abnormality (Atrial fibrillation, atrial flutter, atrial ectopic rhythm, ventricular ectopic rhythm), even already present on the previous ECG, was considered abnormal.	
	Dyspnea		If the patient reported dyspnea before or after the event.	Made the rule positive
	Hematocrit <30		If the haematocrit upon arrival was <30	Made the rule positive
	Systolic BP <90		If the systolic BP upon arrival was <90	Made the rule positive
	HF		If the patient had a clinical history of heart failure (NYHA II-IV) or an EF of <40% on the TTE	Made the rule positive
STEPS short term	Abnormal ECG	Electrocardiogram (ECG) was defined as abnormal in the presence of any of the following: 1) atrial fibrillation or tachycardia; 2) sinus pause >2 s; 3) sinus bradycardia with heart rate ranging between 35 and 45 beats/min; 4) conduction disorders (i.e., bundle branch block, second-degree Mobitz I atrioventricular block); 5) ECG signs of previous myocardial infarction or ventricular hypertrophy; and 6) multiple premature ventricular beats.	If any of: 1. Rhythm abnormalities : Atrial fibrillation, atrial flutter or heart rate >100 bpm or <45bpm 2. Atrioventricular block Mobitz I, complete atrioventricular block or higher atrioventricular blocks, right, left left-anterior hemi- and bundle branch block 3. Left ventricular hypertrophy 4. Left axis deviation 5. Presence of significant Q-waves 6. ST segments modification and T wave abnormalities possibly related to myocardial ischemia 7. Presence of nonsustained ventricular tachycardia	6.9
	Trauma		If the patient reported any injury	2.9
	No prodrome		If the patients had no prodromal symptoms such as light-headedness, nausea, vomiting, diaphoresis, weakness, and visual disturbances.	2.4
	Male Sex		Male sex	2.2

STEPS Long term	Age >65 yrs		Age >65yo	3.4
	Coexistence at presentation of neoplasms		If the patient displayed any diagnosis of leucemia, malignant lymphoma or malignant solid tumor.	3.2
	Hx of Cerebrovascular diseases		If the patient had any history of stroke or TIA	2.5
	Structural heart disease		A history of heart disease was positive if the patient had a diagnosis of congestive heart failure (NYHA II-IV), of valve disease, a previous history of myocardial infarction, bypass surgery, percutaneous coronary intervention.	2.3
	Ventricular arrhythmias		If the patient reported any diagnosis of arrhythmia	3.9
Boston	Signs and symptoms of ACS	Complaint of CP Ischemic ECG changes (ST elevation or deep ST depression) Other ECG changes : VT, VF, SVT, rapid AF or new ST/T wave change Complaint of SOB	If the patient reported any complain of chest pain/dyspnea before or after the syncope, if the ECG upon arrival to the ED was showing Q-waves, ST elevation or deep ST depression, VT, VF or AF.	Made the rule positive
	Worrisome cardiac history	Hx of CAD, cardiomyopathy Hx of congestive HF or LV dysfunction Hx of Ventricular tachycardia or VF Hx of PM, ICD Prehosp use of antidysrhythmic meds but not BB or Ca-blockers	If the patient reported any history of arrhythmia, diagnosis of CHF (NYHA II-IV), showed a LV dysfunction in the TTE, had a Pacemaker, ICD or CRT, had a history of AMI, bypass, PCI, were taking antiarrhythmic class I medication or digitalis.	Made the rule positive

	FaHX SCD		If the patient reported any familial history of SCD	Made the rule positive
	Valvular heart disease	Heart murmur noted on examination or in history	If the patient reported any diagnosis of valvular disease or if a systolic or diastolic murmur was noticed during physical examination.	Made the rule positive
	Signs of conduction disease	Multiple syncopal episodes within the last 6 mo Rapid heart beat by patient history Syncope during exercise QT interval >500 2^{nd} or 3^{rd} degree AV block or intraventricular block	If the patient reported syncope during exercise, any history of palpitations or more than 2 previous syncopal events. If the QTc interval was >500, if the ECG showed any of : 1. Atrioventricular block Mobitz I, complete atrioventricular block or higher atrioventricular blocks, right, left left-anterior hemi- and bundle branch block 2. QTc>500ms	Made the rule positive
	Volume depletion	GI bleeding by haemoccult or history Hct<30 Dehydration not corrected in the ED by physician	If the patient reported any GI bleeding during the last week, if there were signs of GI bleeding upon arrival to the ED or if haematocrit was lower than 30.	Made the rule positive
	Persistent (>15min) abnormal vital signs in the ED	Respiratory rate >24/min O_2 saturation <90% SR <50bpm or >100bpm BP <90mmHg	If respiratory rate >24/min O_2 saturation <90% SR <50bpm or >100bpm BP <90mmHg	Made the rule positive
	Primary CNS event	SAH or stroke	If a bleeding or acute ischemia was present on the cranial CT or if the patients received a discharge diagnosis of stroke or TIA.	Made the rule positive

Supplemental table II: Effectiveness of the different scores for the risk stratification for death (B) and MACE (C) and for the diagnosis of cardiac syncope (C) when the recommended cut-off is used:

Percentage of patients ruled in and out, sensitivity (SE), specificity (SP), negative predictive value (NPV) and positive predictive value (PPV). There is no recommended cut-off for the CHADSVasc and both STEPS scores.

IIA) Effectiveness for the risk stratification for death

Score	Recommended cut-off	% of patients ruled in	% of patients ruled out	SE	SP	NPV	PPV
CHADS	≥1	82,5	17,5	96,8	20,0	97,3	17,2
OESIL	≥2	52,1	47,9	79,9	52,7	93,8	22,6
EGSYS	≥3	14,2	85,8	18,3	86,5	86,0	18,9
Boston	≥1	99,4	0,6	100,0	0,7	100,0	14,8
SFSR	≥1	71,0	29,0	84,0	31,2	91,9	17,4
Martin	≥1	95,8	4,2	100,0	4,9	100,0	15,3

IIB) Effectiveness for the risk stratification for MACE

Score	Recommended cut-off	% of patients ruled in	% of patients ruled out	SE	SP	NPV	PPV
CHADS	≥1	82,5	17,5	94,1	20,5	93,1	23,5
OESIL	≥2	52,1	47,9	75,6	54,0	89,5	29,9
EGSYS	≥3	14,2	85,8	18,9	87,0	80,5	27,4
Boston	≥1	99,4	0,6	99,7	0,7	88,9	20,7
SFSR	≥1	71,0	29,0	85,7	32,8	89,8	24,9
Martin	≥1	95,8	4,2	99,7	5,2	98,4	21,4

IIC) Effectiveness for the diagnosis of cardiac syncope

Score	Recommended cut-off	% of patients ruled in	% of patients ruled out	SE	SP	NPV	PPV
CHADS	≥1	81,0	19,0	93,1	21,3	94,1	18,4
OESIL	≥2	49,4	50,6	74,5	55,4	91,9	24,2
EGSYS	≥3	14,3	85,7	23,6	87,4	85,7	26,4
Boston	≥1	99,3	0,7	100,0	0,8	100,0	16,2
SFSR	≥1	70,0	30,0	89,4	33,7	94,3	20,5
Martin	≥1	95,5	4,5	100,0	5,3	100,0	16,8

Supplemental table III: Details of the performance for $CHADS_2$, OESIL, EGSYS and Martin when different cut-offs are assessed.

A) Characteristics of the scores for the prediction of death

CHADS								
Cutoff	**% ruled-in**	**% ruled-out**	**SE**	**SP**	**NPV**	**PPV**	**% with events in rule-in**	**% with events in rule-out**
≥0	82,5	17,5	96,8	20	97,3	17,2	14,2	0,5
≥1	50,7	49,3	84	55	95,2	24,3	12,3	2,3
≥2	19,2	80,8	34,7	83,5	88,1	26,6	5,1	9,6
≥3	7,5	92,5	11,4	93,2	85,9	22,3	1,7	13
≥4	1,7	98,3	1,8	98,3	85,3	15,4	0,3	14,4
≥5	0,2	99,8	0,5	99,8	85,3	33,3	0,1	14,6
≥6	0	100	0	100	85,3	#N/A	0	14,7

OESIL								
Cutoff	**% ruled-in**	**% ruled-out**	**SE**	**SP**	**NPV**	**PPV**	**% with events in rule-in**	**% with events in rule-out**
≥0	100	0	100	0	#N/A	14,7	14,7	0
≥1	79	21	95,9	23,9	97,1	17,8	14,1	0,6
≥2	52,1	47,9	79,9	52,7	93,8	22,6	11,7	3
≥3	25,6	74,4	46,6	78	89,4	26,8	6,8	7,9
≥4	5,6	94,4	13,7	95,8	86,6	36,1	2	12,7

EGSYS

Cutoff	% ruled-in	% ruled-out	SE	SP	NPV	PPV	% with events in rule-in	% with events in rule-out
≥-2	100	0	100	0	#N/A	14,7	14,7	0
≥-1	100	0	100	0	#N/A	14,7	14,7	0
≥0	69,2	30,8	84	33,4	92,4	17,8	12,3	2,3
≥1	69,1	30,9	84	33,4	92,4	17,9	12,3	2,3
≥2	68,7	31,3	83,6	33,9	92,3	17,9	12,3	2,4
≥3	14,2	85,8	18,3	86,5	86	18,9	2,7	12
≥4	11,5	88,5	16	89,3	86,1	20,5	2,3	12,3
≥5	10,3	89,7	13,7	90,3	85,9	19,6	2	12,7
≥6	4,5	95,5	4,6	95,5	85,3	14,9	0,7	14
≥8	0,4	99,6	0,9	99,7	85,4	33,3	0,1	14,6
≥9	0,4	99,6	0,9	99,7	85,4	33,3	0,1	14,6
≥10	0	100	0	100	85,3	#N/A	0	14,7
Martin								
Cutoff	% ruled-in	% ruled-out	SE	SP	NPV	PPV	% with events in rule-in	% with events in rule-out
≥0	95,8	4,2	100	4,9	100	15,3	14,7	0
≥1	56,8	43,2	78,1	46,8	92,5	20,2	11,5	3,2
≥2	22,8	77,2	42,5	80,6	89,1	27,4	6,2	8,5
≥3	4,1	95,9	9,6	96,9	86,1	34,4	1,4	13,3
≥4	0	100	0	100	85,3	#N/A	0	14,7

B) Characteristics of the scores for the prediction of MACE

CHADS

Cutoff	% ruled-in	% ruled-out	SE	SP	NPV	PPV	% with events in rule-in	% with events in rule-out
≥0	82,5	17,5	96,8	20	97,3	17,2	14,2	0,5
≥1	50,7	49,3	84	55	95,2	24,3	12,3	2,3
≥2	19,2	80,8	34,7	83,5	88,1	26,6	5,1	9,6
≥3	7,5	92,5	11,4	93,2	85,9	22,3	1,7	13
≥4	1,7	98,3	1,8	98,3	85,3	15,4	0,3	14,4
≥5	0,2	99,8	0,5	99,8	85,3	33,3	0,1	14,6
≥6	0	100	0	100	85,3	#N/A	0	14,7

OESIL								
Cutoff	% ruled-in	% ruled-out	SE	SP	NPV	PPV	% with events in rule-in	% with events in rule-out
≥0	100	0	100	0	#N/A	20,6	20,6	0
≥1	79	21	94,5	25	94,6	24,6	19,5	1,1
≥2	52,1	47,9	75,6	54	89,5	29,9	15,6	5
≥3	25,6	74,4	46,9	80	85,3	37,8	9,7	10,9
≥4	5,6	94,4	11,7	96	80,7	43,4	2,4	18,2

EGSYS								
Cutoff	% ruled-in	% ruled-out	SE	SP	NPV	PPV	% with events in rule-in	% with events in rule-out
≥-2	100	0	100	0	#N/A	14,7	14,7	0
≥-1	100	0	100	0	#N/A	14,7	14,7	0
≥0	69,2	30,8	84	33,4	92,4	17,8	12,3	2,3
≥1	69,1	30,9	84	33,4	92,4	17,9	12,3	2,3
≥2	68,7	31,3	83,6	33,9	92,3	17,9	12,3	2,4
≥3	14,2	85,8	18,3	86,5	86	18,9	2,7	12

≥4	11,5	88,5	16	89,3	86,1	20,5	2,3	12,3
≥5	10,3	89,7	13,7	90,3	85,9	19,6	2	12,7
≥6	4,5	95,5	4,6	95,5	85,3	14,9	0,7	14
≥8	0,4	99,6	0,9	99,7	85,4	33,3	0,1	14,6
≥9	0,4	99,6	0,9	99,7	85,4	33,3	0,1	14,6
≥10	0	100	0	100	85,3	#N/A	0	14,7

Martin								
Cutoff	**% ruled-in**	**% ruled-out**	**SE**	**SP**	**NPV**	**PPV**	**% with events in rule-in**	**% with events in rule-out**
≥0	100	0	100	0	#N/A	20,6	20,6	0
≥1	95,8	4,2	99,7	5,2	98,4	21,4	20,5	0,1
≥2	56,8	43,2	84,4	50,3	92,5	30,6	17,4	3,2
≥3	22,8	77,2	43,6	82,7	85	39,5	9	11,6
≥4	4,1	95,9	8,5	97	80,3	42,6	1,7	18,9

C) Characteristics of the scores for the diagnosis of cardiac syncope

CHADS								
Cutoff	**% ruled-in**	**% ruled-out**	**SE**	**SP**	**NPV**	**PPV**	**% with events in rule-in**	**% with events in rule-out**
≥0	100	0	100	0	#N/A	16,1	16,1	0
≥1	81	19	93,1	21,3	94,1	18,4	14,9	1,1
≥2	48	52	69,4	56,1	90,6	23,2	11,2	4,9
≥3	17,7	82,3	27,3	84,1	85,8	24,8	4,4	11,7
≥4	6,9	93,1	11,1	93,9	84,7	25,8	1,8	14,3
≥5	1,6	98,4	3,2	98,7	84,2	31,8	0,5	15,5
≥6	0,2	99,8	0,5	99,8	84	33,3	0,1	16

OESIL								
Cutoff	**% ruled-in**	**% ruled-out**	**SE**	**SP**	**NPV**	**PPV**	**% with events in rule-in**	**% with events in rule-out**
≥0	100	0	100	0	#N/A	16,1	16,1	0
≥1	77,2	22,8	93,1	25,8	95,1	19,3	14,9	1,1
≥2	49,4	50,6	74,5	55,4	91,9	24,2	12	4,1
≥3	23,8	76,2	53,7	81,9	90,2	36,2	8,6	7,4
≥4	5,1	94,9	13	96,5	85,3	41,2	2,1	14

EGSYS								
Cutoff	**% ruled-in**	**% ruled-out**	**SE**	**SP**	**NPV**	**PPV**	**% with events in rule-in**	**% with events in rule-out**
≥-2	100	0	100	0	#N/A	16,1	16,1	0
≥-1	100	0	100	0	#N/A	16,1	16,1	0
≥0	67,7	32,3	90,3	36,6	95,2	21,4	14,5	1,6
≥1	67,7	32,3	90,3	36,7	95,2	21,4	14,5	1,6
≥2	67,3	32,7	89,8	37	95	21,4	14,4	1,6
≥3	14,3	85,7	23,6	87,4	85,7	26,4	3,8	12,3
≥4	11,4	88,6	21,8	90,5	85,8	30,5	3,5	12,6
≥5	10,2	89,8	19,9	91,7	85,7	31,4	3,2	12,9
≥6	4,6	95,4	6,9	95,8	84,3	24,2	1,1	14,9
≥8	0,4	99,6	0,9	99,6	84	33,3	0,1	15,9
≥9	0,4	99,6	0,9	99,6	84	33,3	0,1	15,9
≥10	0	100	0	100	83,9	#N/A	0	16,1

Martin								
Cutoff	**% ruled-in**	**% ruled-out**	**SE**	**SP**	**NPV**	**PPV**	**% with events in rule-in**	**% with events in rule-out**

≥0	100	0	100	0	#N/A	16,1	16,1	0
≥1	95,5	4,5	100	5,3	100	16,8	16,1	0
≥2	55,3	44,7	89,4	51,2	96,2	25,9	14,3	1,7
≥3	21,9	78,1	48,1	83,1	89,3	35,3	7,7	8,3
≥4	3,9	96,1	8,3	97	84,7	34,6	1,3	14,7

#N/A = not applicable

Supplemental Table IV: Comparison of the added value of different scores on top of the Clinical judgement of the ED physician for the prediction of cardiac syncope.

Score	AUC
Clinical judgment	0.868 (95%-CI 0.840-0.897)
Clinical judgment +CHADS	0.871 (95%-CI 0.845-0.898) (p=0.89)
Clinical judgment + CHADSVasc	0.874 (95%-CI 0.848-0.899) (p=0.79)
Clinical judgment +OESIL	0.880 (95%-CI 0.855-0.905) (p=0.54)
Clinical judgment +Martin	0.880 (95%-CI 0.855-0.905) (p=0.54)

* p are given for the comparison with the clinical judgment alone.

II - B-Type natriuretic peptide for diagnosis and risk-stratification of syncope

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Abstract

Background: The clinical utility of B-type Natriuretic Peptide (BNP) for diagnosis and risk-stratification of syncope is incompletely understood.

Objective : We aim at investigating BNP utility for the diagnosis of cardiac syncope and for the short/long-term prognostic of major cardiovascular events (MACE) or death.

Methods: We evaluated the diagnostic and prognostic accuracy of BNP in patients presenting with syncope to the emergency department (ED) in a prospective diagnostic multicenter study. BNP was measured in a blinded fashion. Cardiac syncope, as adjudicated by two physicians based on all information available including 1-year follow-up, was the diagnostic endpoint. MACE were defined as death, resuscitation, life-threatening arrhythmia, implantation of pacemaker/implantable cardioverter defibrillator, acute myocardial infarction, pulmonary embolism, stroke/transient ischemic attack, intracranial bleeding or valvular surgery.

Results: Among 1561 patients available for diagnostic assessment, cardiac syncope was the adjudicated diagnosis in 239 patients (15.3%). BNP was significantly higher in cardiac syncope vs. other causes ($p<0.01$), and remained independent predictor of cardiac syncope in multivariable models. The diagnostic accuracy for cardiac syncope, as quantified by the Area Under the Curve (AUC), was 0.77 (95%CI 0.73-0.80). A total of 463 MACE occurred during follow-up. The prognostic accuracy for MACE was moderate (AUC 0.70-0.77). BNP performed better than the OESIL, EGSYS, and ROSE syncope scores for both diagnostic and prognostic endpoints. When no obvious etiology is present on the ED, BNP could provide guidance for hospitalization.

Conclusion: BNP provides useful diagnostic and prognostic information in ED 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.[1,51,52] Accordingly, the diagnosis of cardiac syncope and the risk-stratification for short- and long-time major adverse cardiac events (MACE) are related.[51,52]

In contrast to other common symptoms in the ED such as acute chest pain or acute dyspnea,[70–72] the possible clinical utility of cardiovascular biomarkers including B-type natriuretic peptide (BNP) has not been thoroughly evaluated in large multicenter diagnostic studies adjudicating the final diagnosis. BNP is considered a quantitative marker of hemodynamic cardiac stress and released from the heart in response to increased intracardiac volume and pressure.[29,73] Its 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.[74–78]

Encouraged by promising data from pilot studies in patients with syncope[5,79–81] we aim at exploring the clinical utility of BNP 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 5, 30, 180 and 720 days, In addition we evaluate the diagnostic and prognostic accuracy of BNP with midregional pro-A-type natriuretic peptide (MR-proANP),[82] and compare the diagnostic and prognostic accuracy of BNP with established syncope scores recommended in current guidelines[1,5,17,18]. We further characterize the clinical utility of BNP 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 of age 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 measurement was missing, were excluded. Patients in whom the final diagnosis remained unclear even after central adjudication were excluded from diagnostic analyses, but remained in the prognostic analyses. Patients with no obvious syncope etiology following initial ED evaluation (excluding patients presenting with as 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 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. The authors designed the study, gathered, and analysed the data according to the STARD guidelines for studies of diagnostic accuracy, vouch for the data and analysis, wrote the paper, and decided to submit for publication.

Clinical assessment

All patients underwent a clinical assessment that included standardized and detailed assessment of predefined details of medical history, including previous syncope events and circumstances of current syncope, vital signs, physical examination, routine laboratory tests, radiologic testing, and a 12-lead ECG. Additionally, patients may have also undergone 24-hour ECG, external or implantable loop device, cardiac exercise test, Schellong test, tilt table testing, coronary angiography, continuous

rhythm monitoring, pulse oximetry, echocardiography, implanted cardiac device interrogation or electrophysiological examinations, and recording of findings of further investigations during recurrent hospitalization or ambulant treatment. Additional tests and treatment of patients were left to discretion of the clinically responsible physician.

Follow-up and adjudicated final diagnosis

Patients were contacted 6, 12 and 24 months after discharge by telephone or in written form. Information regarding recurrent syncope, hospitalization and cardiac events during follow up was furthermore obtained from the patient's hospital notes, the family physician's records and national mortality registries, where available. To determine the final diagnosis for the index syncope in each patient, two independent physicians, blinded to the BNP results, reviewed all available medical records from the clinical data set and the study-specific data set. The clinical data set included data from the clinical assessment, while study-specific data included standardized forms uniformly collecting predefined details of patient history, the circumstances of syncope, physical examination results, and at least 12 months follow-up. 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 (eg, hypertrophic cardiomyopathy or valvular disease), pericardial tamponade, congenital myocardial or valvular anomaly, aortic dissection, or acute pulmonary hypertension (eg, attributable to pulmonary embolism). 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 by use of the Architect BNP assay[83]. The assay's LoB is 0.6 ng/l, LoD is 1.4 ng/l, and LoQ is 3.4 ng/l at 20% CV. There is no hook effect up to 100,000 ng/l. Total imprecision is < 10% for concentrations 4.5 ng/l and higher. In this study, controls run on each assay plate provided inter-assay precision of 8.3% at 4.5 ng/l and 4.1% at 218 ng/l. Measurement of MRproANP was performed using an validated sandwich immunoassays.[84] The laboratory team who measured BNP and/or MR-proANP were blinded to patient, clinical and diagnostic assessment, discharge and adjudicated diagnosis.

Endpoints

The primary diagnostic endpoint was the diagnostic accuracy of BNP concentrations for cardiac syncope. The co-primary prognostic endpoints were the accuracy of BNP concentrations to predict either death or overall MACE at 5 days, 30 days, 180 days and 720 days of follow-up.

Secondary endpoints were the prognostic accuracies of BNP concentrations for ischemic and arrhythmic MACE at similar time points. Arrhythmic MACE were defined as a composite of death, reanimation, 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 [>3s], ventricular standstill, or asystole, consistent with the definition given in previous syncope research[5]. Acute myocardial infarction was defined according to the Third Universal Definition[85]. 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

Direct comparison with syncope scores and a combination of clinical variables

To further characterize the clinical utility of BNP, we performed a direct comparison of its diagnostic and prognostic accuracy with established syncope scores designed to inform the diagnosis of syncope in the ED[1,5,17,18]: 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;[17] the OESIL risk score, which was designed to identify patients at higher risk of mortality within the first 12 months;[18] and the ROSE rule, which is a clinical decision rule to predict 1-month serious outcome and all-cause death.[5] We validated these scores for their respective endpoints and compared their predictive accuracy to the one of a BNP concentration as a quantitative variable. (Supp. methods for details). Moreover, we compared the diagnostic accuracy of BNP with a combination of several clinically relevant variables known as relevant confounders in the evaluation of syncope[51], 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 concentrations were analyzed depending on whether the patients had an adverse event (defined as death or 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 of BNP concentrations , for a combination of clinical variables or the EGSYS risk score[57] (Supp. methods). Comparisons of AUCs were performed according to DeLong[86]. Optimal cut-offs for given sensitivities/specificities for the diagnosis of cardiac syncope using BNP were derived. Confidence intervals for these measures were computed according to Agresti and Coull[87]. Univariable/Multivariable logistic regression was used to assess the predictive accuracy of log-transformed BNP concentrations to diagnose cardiac syncope (Supp. Methods). Confidence intervals for these measures were computed according to Agresti and Coull[87].

Time-dependent ROC[88] curves were computed using the “timeROC” package to assess the accuracy of BNP 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 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 and a Bonferroni correction conducted when there was a concern for multiple testing.

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 A), of which 1575 and 1430 patients were eligible for the analysis of prognostic and diagnostic endpoints, respectively.

Mean age was 71 years, 41% of patients were women, and about half had a history of cardiovascular disease (Table A). Patients with a final adjudicated diagnosis of cardiac syncope (n=239, 15.3%) were significantly older, more often had a history of cardiovascular diseases and were more likely to be on long-term cardiovascular medications.

Concentrations of BNP and syncope etiology

BNP 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 B, Bonferroni corrected $p<0.001$ for each comparison).

Diagnostic accuracy of BNP for the diagnosis of cardiac syncope

The diagnostic accuracy of BNP for cardiac syncope was moderate (AUC 0.77, 95%-CI 0.74-0.80; Figure C) in the whole patient collective. The BNP cut-off associated with a specificity of ≥95% for rule-in of patients with cardiac syncope (344ng/L) allowed for a rule-in rate of ~9% of patients, while the cut-off for a sensitivity of ≥95% (15.4ng/L) for rule-out allowed a rule-out rate of ~21% of patients (Supplemental table A). Among cardiac syncope, patients with bradycardia-induced syncope had lower BNP concentrations in comparison to those with syncope due to ventricular tachycardia or valvular heart disease (suppl. Figure A.A). There was a non-significant trend for a higher accuracy of BNP to diagnose ventricular tachycardia or valvular disease (AUC 0.8, 95%-CI 0.75-0.86) over bradycardia (AUC 0.75, 95%-CI 0.71-0.8, $p=0.13$).

The diagnostic accuracy of BNP for cardiac syncope was higher than that of the EGSYS score (AUC 0.67, 95%CI 0.64-0.70, $p<0.001$) and than a combination of clinical variables (AUC 0.7, 95%-CI 0.67-0.74, $p=0.004$).

Prediction of cardiac syncope

Logistic regression analysis confirmed BNP concentrations as predictors of cardiac syncope in both univariate and multivariable analyses (Supplemental table B). In multivariable analysis, only BNP concentrations and an abnormal ECG were significant predictors of a cardiac etiology.

Direct comparison of BNP and MR-proANP for the diagnosis of cardiac syncope

In the 688 patients eligible for the direct comparison of BNP and MR-proANP, both assays displayed similar diagnostic accuracy (AUC for BNP 0.77 (95%-CI 0.73-0.82) versus AUC for MR-proANP 0.80 (95%-CI 0.75-0.84), p = 0.16, Suppl. Figure B).

Prognostic accuracy of BNP

Follow-up was complete in 100% of patients at 5 days and 30 days, and in 84.3% of patients at 720 days. During follow-up 228 patients (14.4%) died, 459 (29.1%) suffered first a MACE, 282 (17.9%) suffered first from an ischemic MACE and 359 (22.8%) suffered first from an arrhythmic MACE.

The prognostic accuracy of BNP up to 720 days was moderate to good for all four endpoints with AUCs ranging between 0.70 and 0.77 (Figure D).

Prediction of death and MACE at 30 and 720 days

Log-transformed BNP 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 concentrations were significant predictors for all MACE endpoints but not for death (Supplemental Table C).

Direct comparison of BNP and MR-proANP for risk-stratification

In the 762 patients eligible for the direct comparison of BNP and MR-proANP, both assays displayed similar prognostic accuracy for MACE (Suppl. Figure C).

Direct comparison of BNP with established risk scores

During the first month of follow-up, 183 patients (11.6%) suffered an adverse event as defined by the original derivation of the ROSE rule. The prevalence of each component of the rule is given in Supplemental table D. The rule displayed an AUC of 0.62 (95%-

CI 0.58-0.66) for the prediction of these adverse outcomes while BNP alone displayed an AUC of 0.75 (95%-CI 0.71-0.79, p<0.001)) for the same outcomes. Details on the sensitivity, specificity, NPV, PPV and incidence of criteria of the ROSE rule, and comparison with a BNP cut-off of 300pg/L alone, are given in Supplemental table E.

The EGSYS score showed an AUC of 0.67 (95%-CI 0.64-0.70) while BNP alone displayed an AUC of 0.77 (95%-CI 0.73-0.80, p<0.001) to predict a diagnosis of cardiac syncope. During the first year of follow-up, 90 patients died. The OESIL score displayed an AUC of 0.72 (95%-CI 0.67-0.76) for the prediction of one-year death while BNP alone displayed an AUC of 0.77 (95%-CI 0.72-0.82, p=0.017) for this same outcome. BNP was significantly superior to all scores in the validation of their respective endpoints.

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, 159 suffered from MACE, 41 suffered from ischemic MACE and 105 from arrhythmic MACE.

Patients experiencing an event in the follow-up had significantly high BNP concentrations (Figure E). The lowest 90%-sensitivity cut-off to rule-out both death or MACE up to 30-day follow-up was 22ng/L (Supp. Table F) and allowed for a safe rule-out of 430 (30%) patients (Figure F). Among these patients, 122 patients (28%) had been hospitalized for a mean of 4.7 days.

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 **seven** major findings.

First, BNP concentrations were significantly higher in patients adjudicated to have cardiac syncope as compared to other syncope etiologies. **Second**, BNP concentrations showed comparable and moderate accuracy for the diagnosis of cardiac syncope and BNP concentrations remained an independent predictor of a cardiac syncope after multivariable adjustments. **Third**, if applied as a triage tool on the whole syncope population, BNP concentrations allowed to rule-out and rule-in cardiac syncope with 95% sensitivity and 95% specificity in about 30% of patients. **Fourth**, in the subgroup that also had MR-proANP measurements available, the natriuretic pro-hormone fragment recently shown to have the highest diagnostic accuracy among several pro-hormones quantifying different pathophysiological processes[82], BNP and MR-proANP had comparable AUCs. **Fifth**, BNP performed well for the prediction of short- and long-term MACE. **Sixth**, as a single variable, BNP had higher diagnostic and prognostic accuracy as compared to OESIL, EGSYS, and ROSE syncope risk scores currently mentioned in clinical practice guidelines[1]. **Seventh,** in the subgroup of patients with no obvious syncope etiology upon ED evaluation, BNP could inform the decision for hospitalization by identifying patients with a very low risk of death and MACE within 30 days. For instance, a BNP cut-off of <22pg/L allowed to identify 30% of eligible patients with a mortality risk at 30-days of 0%.

Our findings extend and corroborate previous single-center studies on the clinical utility of BNP for diagnosis and risk-stratification of patients presenting to the ED following syncope[5,79,80,89]. To the best of our knowledge, this was the first multicenter study centrally adjudicating the cause of syncope by two independent physicians and incorporating long-term follow-up. The clinical value of the diagnostic utility of BNP for cardiac syncope observed in this study seems debatable. Although BNP concentrations remained predictive of cardiac syncope in multivariable models, and the AUC was higher than that of a commonly used syncope score, the performance of

BNP to diagnose cardiac syncope is only moderate. This suggests that the pathophysiological link between BNP as a quantitative marker for the presence and severity of cardiac disease and cardiac syncope is 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. In contrast, cardiac syncope due to conditions, such as severe aortic stenosis or ventricular tachycardia, seems more closely related to the hemodynamic severity of cardiac disease.[72,74,90–92].

In conjunction with previous work our data suggest that BNP and MR-proANP provide comparable clinical utility in the early management of patients with syncope.[5,79,80,82,89] This is of major clinical importance as usually only one of these natriuretic peptides is made available to clinicians by the laboratory of the respective institution.

The usefulness of BNP for risk-stratification has previously been established in a range of cardiovascular diseases[90] and in the context of syncope[5,80]. Our results showed that, even after correcting for the etiology of syncope, age and important baseline characteristics, BNP stayed a strong predictor of MACE including death in the long-term follow-up. The better performance of this biomarker to predict arrhythmic MACE over ischemic MACE again reinforces previously suggested associations of BNP with arrhythmia[74,91,92].

A pioneering study by Reed et al.[5] investigated the value of BNP for risk-stratification by integrating the biomarker as a dichotomized variable within a rule utilising additional clinical characteristics. This rule was derived and validated in the same study and performed with an AUC of 0.76 (95% CI: 0.70 to 0.83), a sensitivity of 87.2%, and a specificity of 65.5%. The poorer performance of the ROSE rule in this contemporary cohort may at least be in part explained by the current widespread use of gastroprotectant drugs and the related reductions in hemodynamically relevant acute gastrointestinal bleedings as a possible cause of syncope,[93] which weakened the importance of some of the prognostic components of the ROSE rule. In our study, BNP as a single quantitative variable was a more accurate prognosticator as compared to the multivariable ROSE score, as well as several other multivariable scores recommended in current clinical practice guidelines. Therefore, the simple use of this

biomarker alone as early risk-stratification tool in patients presenting to the ED seems to provide an appealing, rapid and easy triage tool, especially when this could lead to numerically fewer or shorter hospitalizations.

Given the high rates of MACE associated with syncope and the well-documented value of BNP as a screening tool for cardiovascular disease in the community and in persons at increased risk,[77] our findings may justify the inclusion of BNP, a widely available and inexpensive biomarker, in the work-up of patients presenting with syncope to the ED.

Some limitations of the present study merit consideration. First, only patients presenting to the ED were recruited. 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 in patients presenting >12 hours after their syncope or patients younger than 40 years of age, as these were excluded from the present study. Third, BNP concentrations were only obtained once and no serial measurements were available. Further studies are needed to evaluate the possible value of serial BNP sampling. Fourth, despite using the most 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 may have led to a slight underestimation of the true diagnostic accuracy of BNP.

In conclusion, BNP seems to be a promising biomarker, 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, ECG or elements of the physical examination could further increase the diagnostic and prognostic yield of this marker.

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Conflict of interest and disclosures

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 and Mueller had full access to all the data in the study and take

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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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All other authors declare that they have no conflict of interest with this study.

Figures

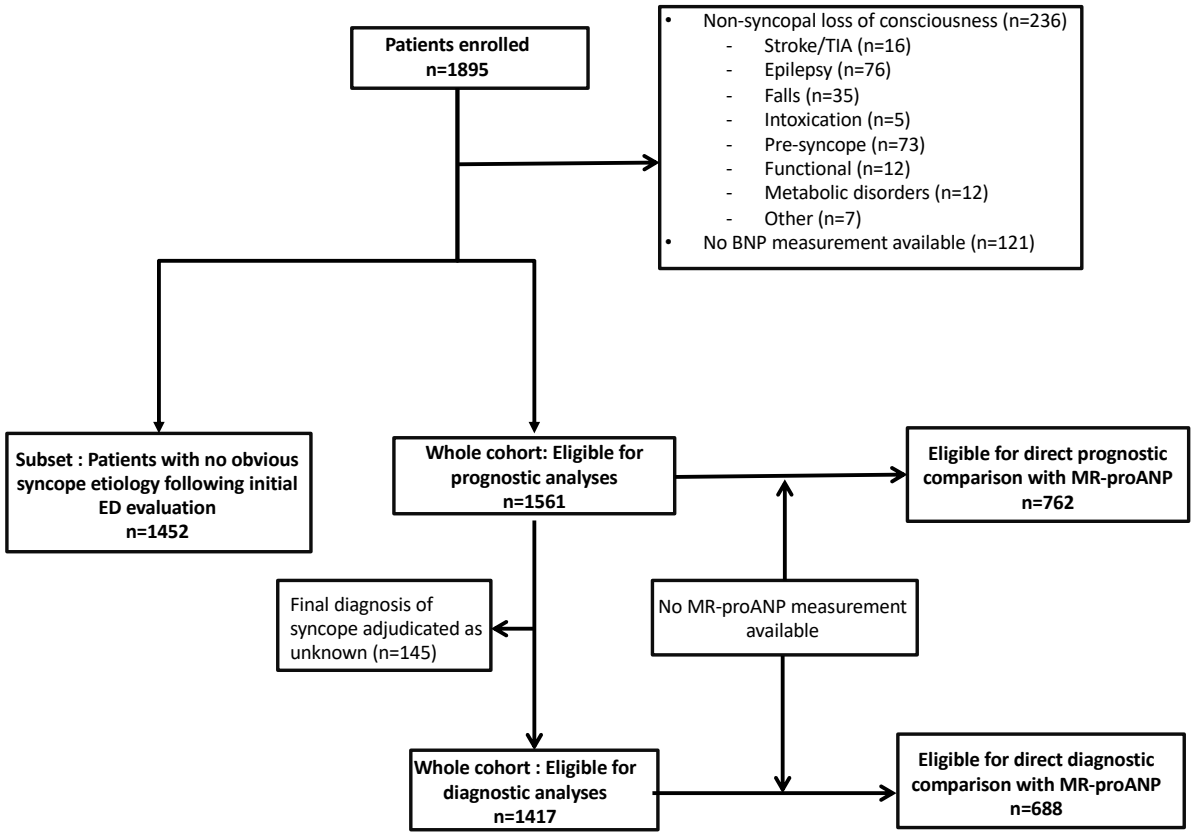


Figure A - Patient flow.

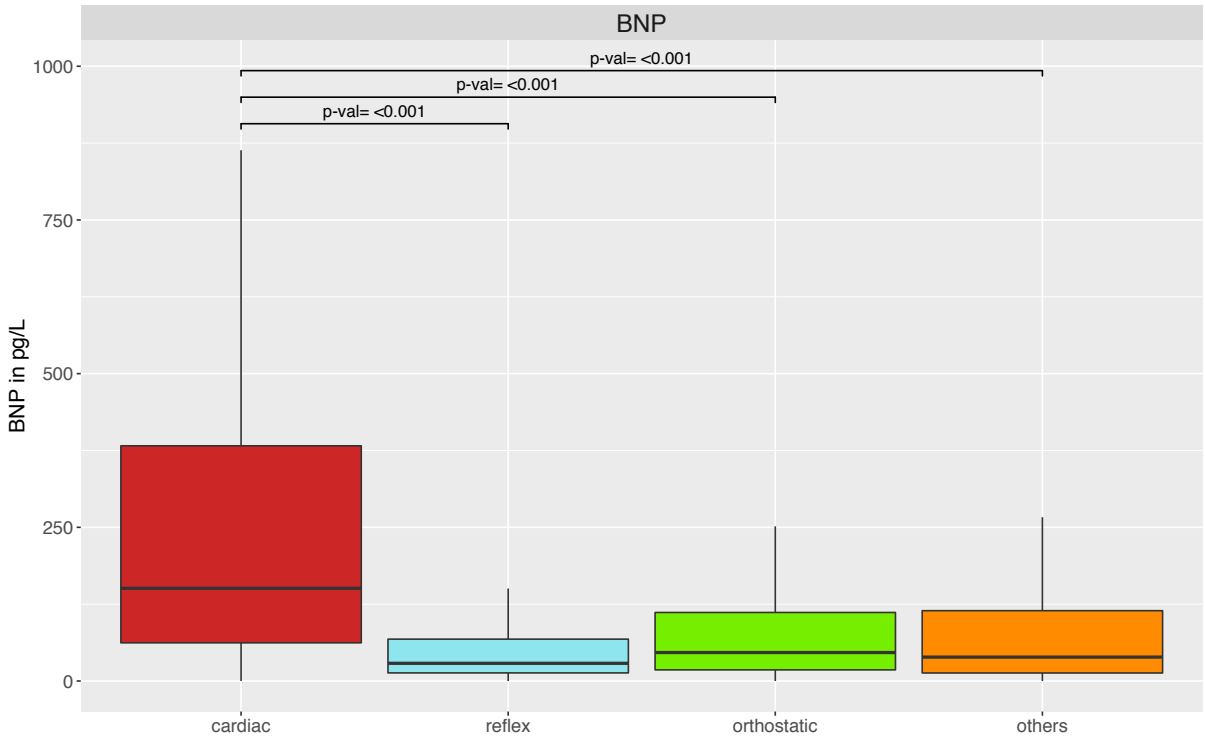


Figure B – Boxplots representing the BNP concentrations according to the syncope etiology. The boxplots represent the median with the interquartile range (IQR), whiskers represent ± 1.5 x the IQR. P-values are calculated based on a Wilcoxon-rang-sum test and corrected for multiple testing according to Bonferroni.

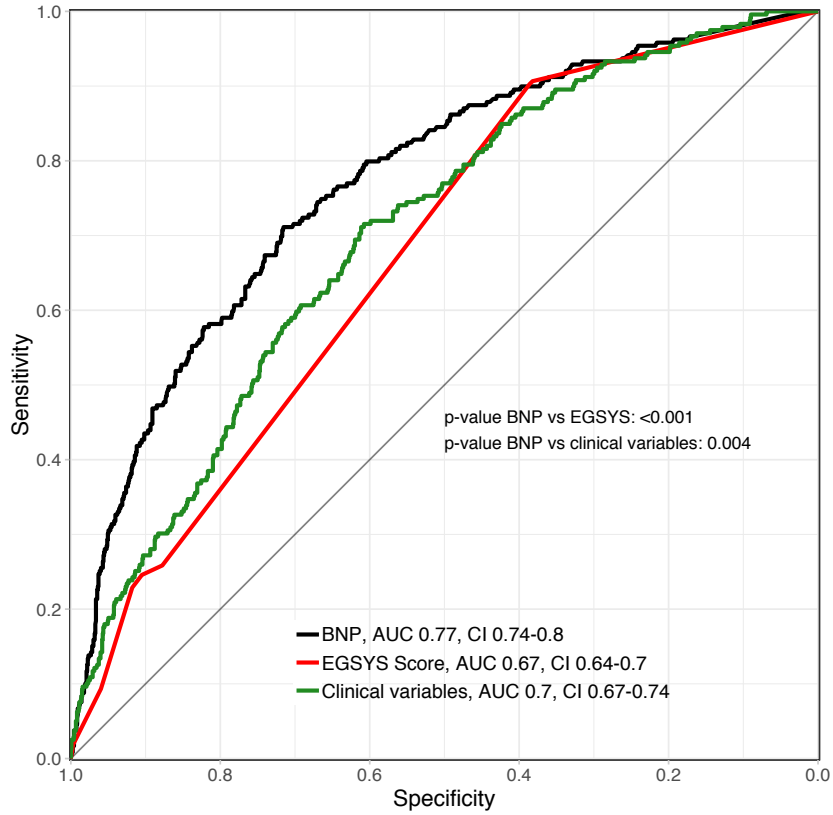


Figure C – Accuracy of BNP alone, the EGSYS score and a combination of clinically relevant variables for the diagnosis of cardiac syncope.

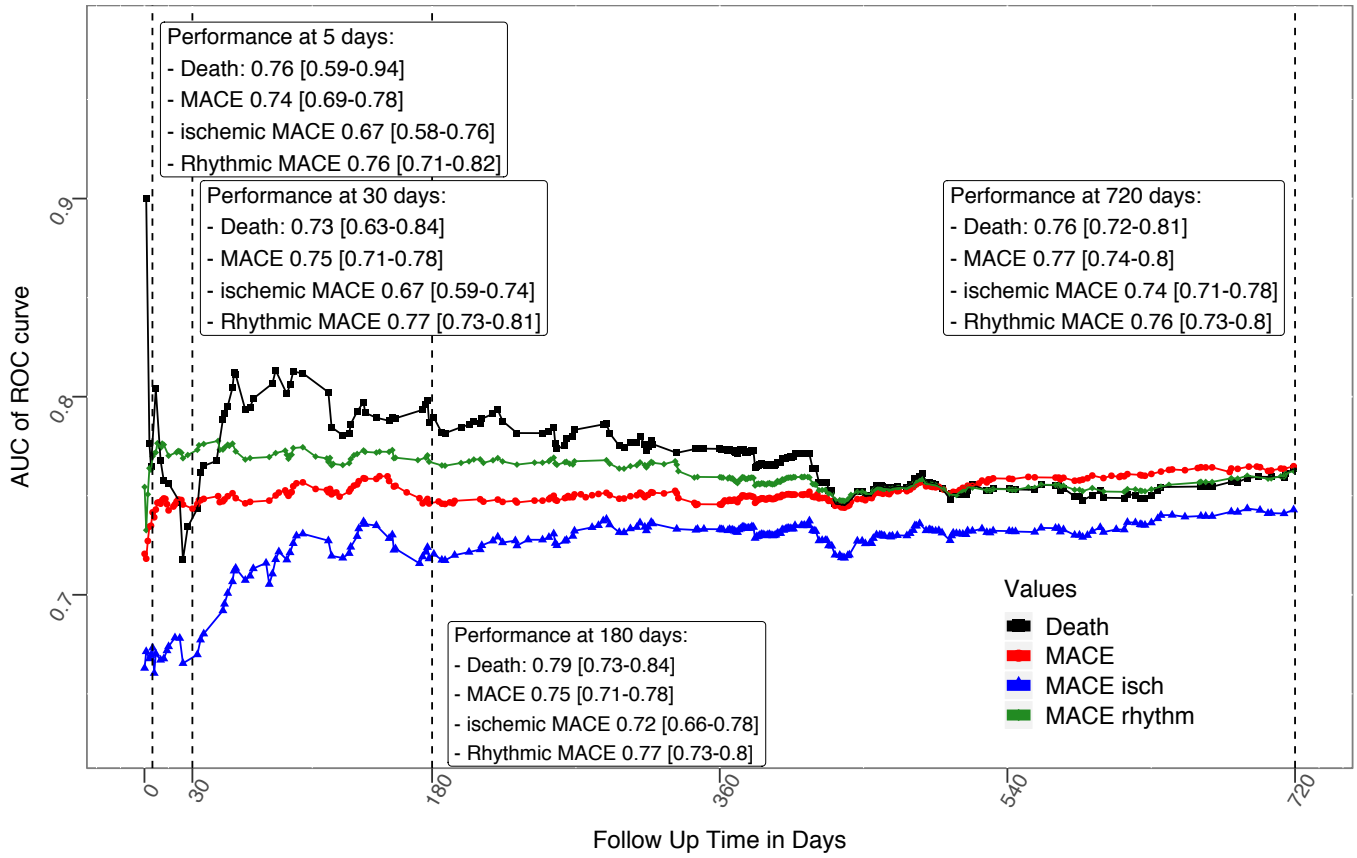


Figure D – Time-dependant ROC curves for the accuracy of BNP for the prognosis of death and several type of MACE.

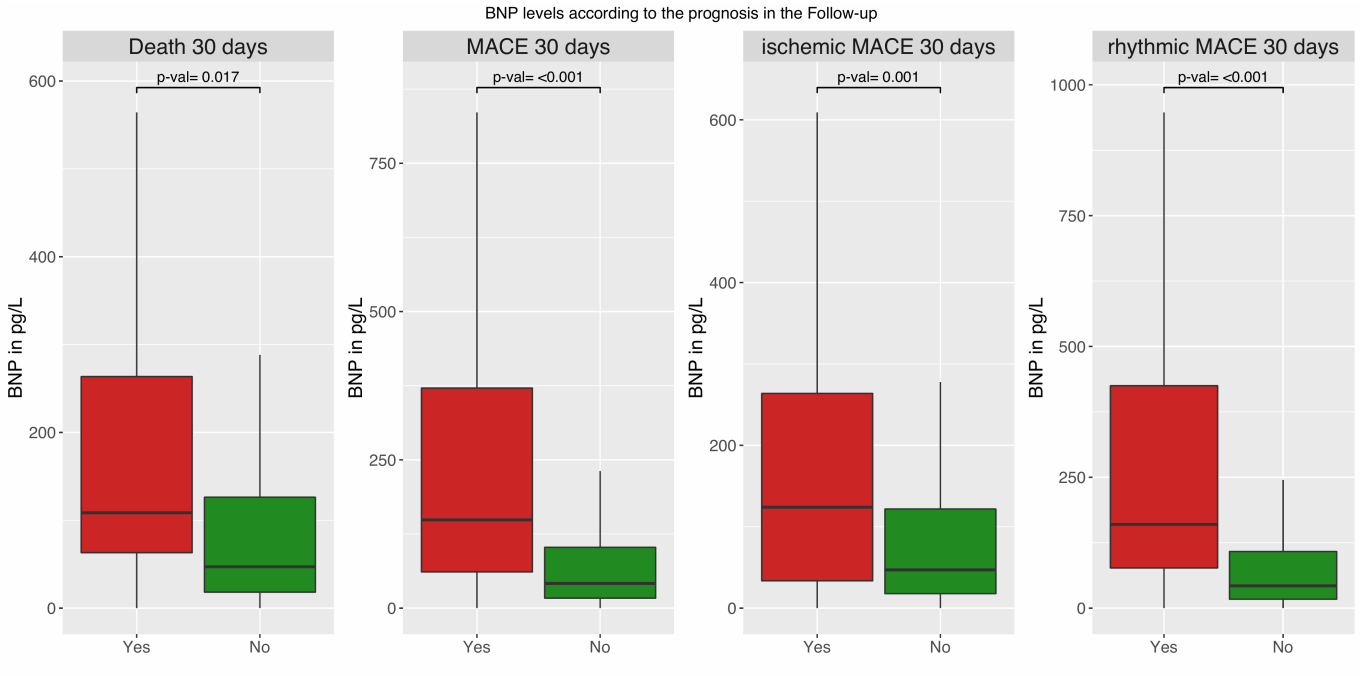


Figure E – Boxplots representing the BNP concentrations according to whether or not patients experienced the event during the 30-day follow-up. The boxplots represent the median with the interquartile range (IQR), whiskers represent ± 1.5 x the IQR. P-values are calculated based on a Wilcoxon-rang-sum test.

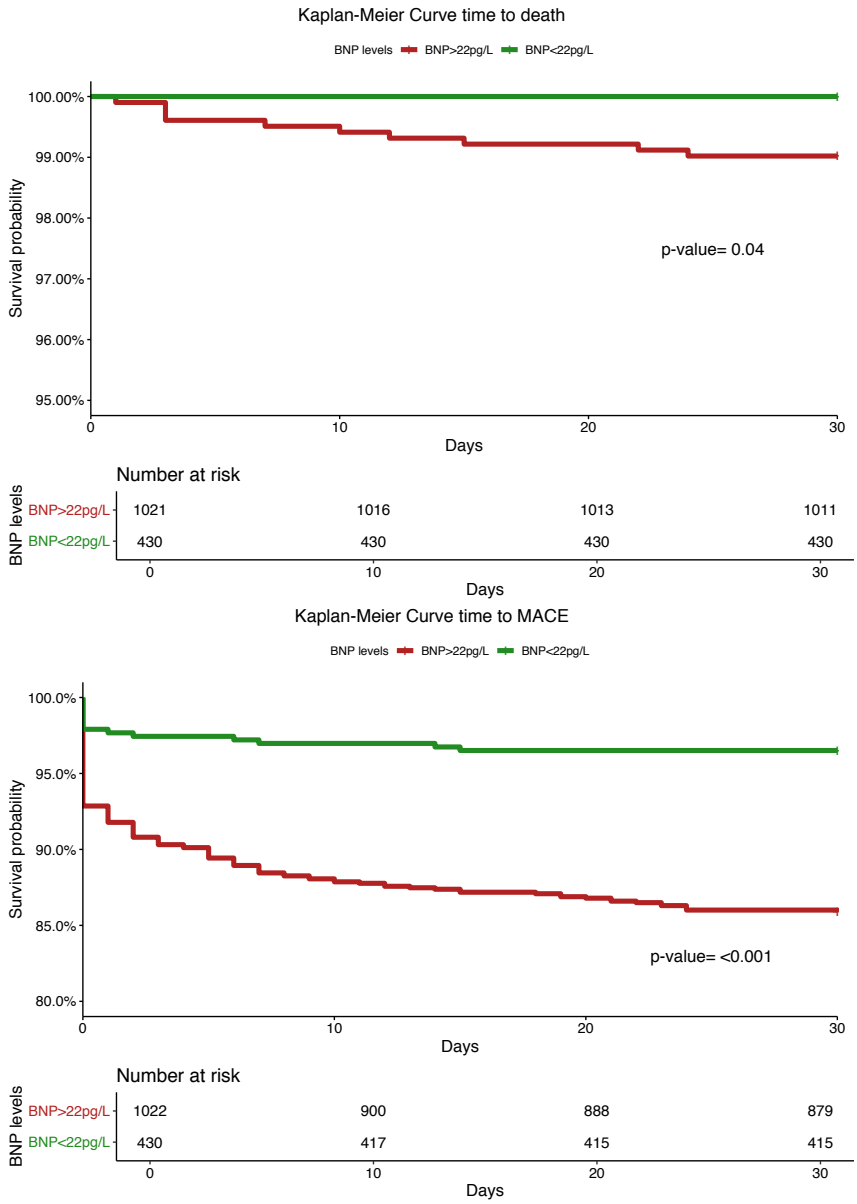


Figure F – Kaplan Meier representing event-free survival for death and MACE according to a BNP cut-off of 22pg/L. P-values are calculated with a log-rank test.

Tables

Table A	Patients characteristics				
	All patients	**Cardiac**	**Non cardiac**	**Unknown**	**P value**
Number of patients	1575	239	1191	145	
Age-years (median [IQR])	71.0 [57.0, 80.0]	77.0 [66.5, 83.0]	68.0 [55.0, 78.0]	78.0 [69.0, 84.0]	<0.001
Female - no. (%)	643 (41)	84 (35)	499 (42)	60 (41)	0.151
Characteristics of the syncope - no. (%)					
Nausea or vomiting	463 (30)	48 (21)	393 (33)	22 (15)	<0.001
Sweating	482 (31)	51 (22)	409 (35)	22 (15)	<0.001
Pallor	427 (45)	49 (36)	351 (48)	27 (32)	0.002
Palpitations	108 (7)	24 (10)	77 (7)	7 (5)	0.077
Angina	93 (6)	25 (11)	61 (5)	7 (5)	0.006
Caused injury	232 (15)	39 (17)	160 (14)	33 (23)	0.010
Position of the syncope - no. (%)					
While lying	41 (3)	6 (3)	32 (3)	3 (2)	0.907
While sitting	627 (40)	85 (36)	487 (41)	55 (38)	0.265
Orthostatic	187 (12)	18 (8)	158 (13)	11 (8)	0.010
While standing	698 (45)	127 (53)	497 (42)	74 (52)	0.002
Exertion	137 (9)	43 (18)	77 (7)	17 (12)	<0.001
Risk factors - no. (%)					
Hypertension	936 (60)	165 (70)	662 (56)	109 (76)	<0.001
Hypercholesterolemia	643 (42)	116 (50)	456 (39)	71 (52)	<0.001
Diabetes	219 (14)	47 (20)	145 (12)	27 (19)	0.002
Smoking	797 (51)	114 (49)	606 (51)	77 (55)	0.511
History - no. (%)					

Table A	Patients characteristics				
	All patients	**Cardiac**	**Non cardiac**	**Unknown**	**P value**
Previous stroke	125 (8)	18 (8)	87 (7)	20 (14)	0.023
Chronic heart failure (NYHA II-IV)	120 (8)	38 (16)	66 (6)	16 (11)	<0.001
Arrhythmia	329 (21)	90 (38)	201 (17)	38 (27)	<0.001
Pacemaker	72 (5)	21 (9)	49 (4)	2 (1)	0.001
ICD or CRT	41 (3)	17 (7)	21 (2)	3 (2)	<0.001
Coronary artery disease	338 (22)	87 (38)	210 (18)	41 (29)	<0.001
Previous DVT or PE	111 (7)	15 (6)	80 (7)	16 (11)	0.140
Previous MI	201 (13)	53 (22)	125 (10)	23 (16)	<0.001
Chronic medication - no. (%)					
ACEIs/ARBs	706 (45)	128 (54)	498 (42)	80 (55)	<0.001
Alphablocker	118 (7)	19 (8)	85 (7)	14 (10)	0.530
Antiarrhythmics Class I	57 (4)	16 (7)	33 (3)	8 (6)	0.005
Aspirin	458 (29)	90 (38)	314 (26)	54 (37)	<0.001
Beta-blockers	501 (32)	104 (44)	336 (28)	61 (42)	<0.001
Calcium antagonists	262 (17)	46 (19)	180 (15)	36 (25)	0.006
Digitalis	27 (2)	12 (5)	13 (1)	2 (1)	<0.001
Diuretics	471 (30)	107 (45)	311 (26)	53 (37)	<0.001

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.

Supplemental material

Supplemental methods

Clinical assessment and follow-up

All patients underwent a clinical assessment that included standardized and detailed assessment of predefined details of medical history, including previous syncope events and circumstances of current syncope, vital signs, physical examination, routine laboratory tests, radiologic testing, and a 12-lead ECG. Additionally, patients may have also undergone 24-hour ECG, external or implantable loop device, cardiac exercise test, Shellong test, tilt table testing, coronary angiography, continuous rhythm monitoring, pulse oximetry, echocardiography, results from device controls (e.g. pacemaker) or electrophysiological examinations, and recording of findings of further investigations during recurrent hospitalization or ambulant treatment.

During the follow-up, information regarding recurrent syncope, hospitalization and cardiac events during follow up was furthermore obtained from the patient's hospital notes, the family physician's records and national mortality registries, where available.

Adjudication of the final syncope diagnosis

The first step in the adjudication process was to decide whether there was syncope or not. The clinical data set included data from the clinical assessment, while study-specific data included standardized forms uniformly collecting predefined details of patient history, the circumstances of syncope, and physical examination, as well as at least 12 months follow-up. If the criteria for a true syncope were not fulfilled, a distinction between the following non-syncopal disorders was made: pre-syncope; falls; stroke/TIA; epilepsy; metabolic disorders: e.g. hypoglycaemia, hypoxia, hyperventilation; intoxication: e.g. alcohol, benzodiazepines, opiates; functional (psychogenic pseudosyncope); others.

The classification of syncope is based on pathophysiological considerations. The following predefined differential diagnoses were used:

6) Cardiac syncope: We distinguished between:

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

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

a. Primary autonomic failure: There is an autonomic failure which is clearly a primary part of Parkinson syndrome as idiopathic Parkinson disease or atypical Parkinson syndrome (multiple system atrophy, progressive supranuclear oculomotoric paresis, corticobasal degeneration or lewy body dementia).
b. Secondary autonomic failure: autonomic failure may be due to circumstances such as diabetes, uraemia, amyloidosis or spinal cord injuries
c. Drug-induced orthostatic hypotension: orthostatic hypotension is due to drugs which can lead to orthostatic hypotension such as diuretics, antidepressants, vasodilators, alcohol
d. Volume depletion: orthostatic hypotension is caused by a hypovolemia due to haemorrhage, diarrhoea, vomiting or fever
e. Others: sometimes the pathophysiology remains unclear.

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

Evaluation of Guidelines in Syncope Study (EGSYS)[17] diagnostic score components

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

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

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

Osservatorio Epidemiologico sulla Sincope nel Lazio (OESIL)[18] risk score components

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

- age >65 years: + 1
- cardiovascular disease in clinical history +1
- syncope without prodromes: +1
- abnormal electrocardiogram +1

The primary end point was death from any cause within 12 months of the initial evaluation in the ED.

Patients were considered to have cardiovascular disease in their clinical history in the following cases:

- Previous clinical or laboratory diagnosis of any form of structural heart disease, including ischemic heart disease, valvular dysfunction and primary myocardial disease,
- Previous diagnosis or clinical evidence of congestive heart failure,
- Previous diagnosis or clinical evidence of peripheral arterial disease,
- Previous diagnosis of stroke or transient ischemic attack.

Electrocardiographic tracings were considered abnormal in the following cases:

- Rhythm abnormalities (atrial fibrillation or flutter, supraventricular tachycardia, multifocal atrial tachycardia, frequent or repetitive premature supraventricular or ventricular complexes, sustained or non-sustained ventricular tachycardia, paced rhythms),
- Atrioventricular or intraventricular conduction disorders (complete atrioventricular block, Mobitz I or Mobitz II atrioventricular block, bundle branch block or intraventricular conduction delay),
- Left or right ventricular hypertrophy,

- Left axis deviation,
- Old myocardial infarction,
- ST segment and T wave abnormalities consistent with or possibly related to myocardial ischemia.

Electrocardiographic recordings showing non-specific repolarization abnormalities were not considered as abnormal.

Combination of clinically relevant variables

The diagnostic accuracy for cardiac syncope of a combination of clinically relevant variables was tested against the one of BNP. The combination of clinically relevant variables for the diagnosis of syncope were: age, sex, presence or absence of a history of cardiovascular disease (myocardial infarction, coronary heart disease, stroke or transient ischemic attack, congestive heart failure, atrial fibrillation, and intermittent claudication), smoking status, presence or absence of hypertension, systolic blood pressure, presence or absence of diabetes, presence of hypercholesterolemia, heart rate, and use or nonuse of cardiac medication, including antihypertensive medications. These variables were characterized as important confounders in the evaluation of syncope in previous research.[51]

Validation of the ROSE rule

The ROSE rule is defined as positive if any of the following component is present : BNP level ≥ 300pg/mL, bradycardia ≤50 in the ED or pre-hospital, a rectal examination showing fecal occult blood (if suspicion of gastrointestinal bleeding), a hemoglobin level ≤90g/L, chest pain associated with the syncope, ECG showing Q-wave, oxygen saturation ≤94% on room air. The rule was designed to predict a composite outcome at 1 month after ED presentation of all-cause death, AMI, life-threatening arrhythmia (similarly defined as in our study), decision to implant a pacemaker or ICD, a pulmonary embolus, a cerebrovascular accident, an intracranial or subarachnoid hemorrhage, a hemorrhage requiring a blood transfusion an acute surgical procedure or endoscopic intervention. In the current analysis, we validated the ROSE rule and compared the performance of the structured rule to the one of a BNP cut-off of ≥300pg/mL alone for this same composite outcome.

Predictive accuracy of BNP to predict cardiac syncope: Multivariable model

Logistic regression was used to assess the predictive accuracy of log-transformed BNP concentrations to diagnose cardiac syncope, first in an univariable model and second in a multivariable model correcting for pre-defined baseline characteristics as recommended in previous literature[94]. The multivariable models were adjusted for age, sex, presence or absence of a history of cardiovascular disease (myocardial infarction, coronary heart disease, stroke or transient ischemic attack, congestive heart failure, atrial fibrillation, and intermittent claudication), smoking status, presence or absence of hypertension, systolic blood pressure, presence or absence of diabetes, presence of hypercholesterolemia, heart rate, and use or nonuse of cardiac medication, including antihypertensive medications.

Hypertension was a dichotomous variable defined as a systolic blood pressure of at least 140 mm Hg, a diastolic blood pressure of at least 90 mm Hg, or current use of antihypertensive medication.

The presence or absence of a history of cardiovascular disease, smoking status, presence or absence of diabetes, use or nonuse of cardiac medication and the presence of hypercholesterolemia were also included in the model as dichotomous variables. Age, systolic blood pressure, and heart rate were included as continuous variables.

The same variables were used to predict the risk of cardiac syncope in all patients, risk therefore predicted solely by clinical variables. The performance of these variables was then compared to the one of BNP alone.

Accuracy of BNP to predict adverse outcome: Cox proportional model

Cox proportional hazard model was used to assess the importance of log-transformed BNP concentrations for the prediction of these outcomes in a multivariable model accounting for pre-defined important co-variables. We allowed for the correction of one variable for every ten events[94]. Accordingly, the prediction of death at 720 days, overall MACE and arrhythmic MACE at 30 and 720 days was corrected for age, sex, history of cardiovascular disease, smoking status, hypertension, diabetes or hypercholesterolemia, systolic blood pressure, heart rate, cardiac medication and the adjudicated syncope etiology. The prediction of ischemic MACE at 30 and 720 days

was corrected for age, sex, history of cardiovascular disease and the adjudicated syncope etiology. The prediction of death at 30 days was corrected for age only.

Supplemental table A – BNP cut-offs for specific sensitivities/specificities

Cut-offs for BNP	**Target Sensitivity**	**Cut-off (pg/mL)**	**Sensitivity (95%-CI)**	**Specificity (95% CI)**	**NPV (95%-CI)**	**Incidence of criteria % (95%-CI)**
	80	48	80.3 (74.8, 84.9)	58.7 (55.9, 61.5)	93.7 (91.7, 95.2)	52.2 (49.6, 54.7)
	85	34.8	85.4 (80.3, 89.3)	49.6 (46.8, 52.5)	94.4 (92.3, 96)	43.8 (41.2, 46.4)
	90	22.9	90.4 (86, 93.5)	37.1 (34.4, 39.9)	95.1 (92.7, 96.7)	32.5 (30.1, 35)
	95	14.2	95.4 (91.9, 97.4)	24.1 (21.8, 26.6)	96.3 (93.5, 97.9)	20.8 (18.8, 23)
	98	9.9	99.6 (97.7, 99.9)	3.8 (2.8, 5)	97.8 (88.7, 99.6)	3.2 (2.4, 4.3)
	Target Specificity	**Cut-off (pg/mL)**	**Specificity (95%-CI)**	**Sensitivity (95% CI)**	**PPV (95%-CI)**	**Incidence of criteria % (95%-CI)**
	80	115.6	81.5 (79.2, 83.6)	58.2 (51.8, 64.2)	38.7 (33.8, 43.9)	25.1 (22.9, 27.4)
	85	139.4	85.2 (83.1, 87.1)	52.7 (46.4, 59)	41.7 (36.3, 47.4)	21.1 (19.1, 23.3)
	90	199.7	90.2 (88.4, 91.7)	43.5 (37.4, 49.9)	47.1 (40.6, 53.6)	15.5 (13.7, 17.4)
	95	308.9	95 (93.7, 96.1)	30.1 (24.7, 36.2)	55 (46.4, 63.2)	9.2 (7.8, 10.8)
	98	757.5	98.1 (97.1, 98.7)	10 (6.8, 14.5)	51.1 (37.2, 64.7)	3.3 (2.5, 4.4)

Supplemental table B – Predictors for a diagnostic of cardiac syncope

Supplemental table B	Logistic Regression: Predictors for a diagnostic of cardiac syncope							
	Univariable logistic regression				**Multivariable logistic regression**			
	OR	**95% CI (Lower-Upper)**		**p-val**	**OR**	**95% CI (Lower-Upper)**		**p-val**
BNP concentrations, per 10ng/L increase	2,27	2,01	2,59	<0.001	2,059	1,767	2,412	<0.001
Age, each year increase	1,05	1,03	1,06	<0.001	1,007	0,992	1,022	0.372
Sex (Women)	0,76	0,57	1,01	0.061				
Known CV disease	2,61	1,85	3,76	<0.001	1,301	0,661	2,525	0.440
Smoking status	0,88	0,67	1,17	0.383				
Hypertension	1,8	1,34	2,44	<0.001	0,84	0,511	1,41	0.498
Hypercholesterolemia	1,53	1,15	2,04	0.003	1,012	0,719	1,424	0.943
Diabetes	1,76	1,21	2,51	0.002	1,103	0,706	1,697	0.660
Heart rate, per 5 bpm increase	1	0,98	1,02	0.647				
Systolic BP, per 5mmHg increase	1,03	1	1,06	0.044	1,017	0,987	1,047	0.279
Any cardiac medication	2,53	1,81	3,6	<0.001	0,858	0,487	1,522	0.598
Abnormal ECG	2,76	2,03	3,8	<0.001	1,645	1,168	2,333	0.005

Bpm = beats per minute, mmHg= milimeter mercury. Variables were used to correct the multivariable model only if they were significant in the univariable regression.

Supp Table C.A)	Death 720d		Overall MACE 720d		Arrhythmic MACE 720d		Ischemic MACE 720d	
	HR [95%CI]	p-val	HR [95%CI]	p-val	HR [95%CI]	p-val	HR [95%CI]	p-val
log BNP, per 10pg/mL increase	1.61 [1.36,1.90]	<0.001	1.29 [1.15,1.45]	<0.001	1.19 [1.01,1.39]	0.033	1.43 [1.17,1.74]	0.001
Age	1.04 [1.02,1.06]	<0.001	1.00 [0.99,1.02]	0.372	0.99 [0.97,1.01]	0.226	1.00 [0.98,1.01]	0.668
Sex	0.68 [0.45,1.02]	0.064	1.16 [0.89,1.51]	0.280	1.04 [0.72,1.51]	0.825	0.80 [0.51,1.25]	0.330
Known CV disease	0.88 [0.36,2.17]	0.779	1.28 [0.74,2.20]	0.377	1.50 [0.70,3.21]	0.297	2.26 [1.10,4.64]	0.026
Smoking status	1.48 [1.00,2.19]	0.048	1.54 [1.19,1.99]	0.001	1.27 [0.90,1.81]	0.176		
Hypertension	1.62 [0.89,2.95]	0.112	0.67 [0.48,0.94]	0.022	0.62 [0.39,0.98]	0.039		
Hypercholesterolemia	0.65 [0.45,0.95]	0.024	1.22 [0.94,1.57]	0.136	1.02 [0.71,1.46]	0.933		
Diabetes	1.44 [0.95,2.19]	0.089	1.25 [0.94,1.67]	0.131	1.00 [0.66,1.52]	1.000		
Heart rate, per 5 bpm increase	1.00 [0.98,1.03]	0.730	0.94 [0.91,0.97]	<0.001	0.91 [0.87,0.95]	<0.001		
Systolic BP, per 5mmHg increase	0.94 [0.91,0.98]	0.001	1.01 [0.99,1.04]	0.233	1.03 [1.00,1.07]	0.054		
Any cardiac medication	0.94 [0.44,1.98]	0.863	1.34 [0.82,2.18]	0.242	1.27 [0.65,2.51]	0.483		
Etiology:Reflex	0.42 [0.22,0.79]	0.007	0.06 [0.04,0.08]	<0.001	0.01 [0.01,0.03]	<0.001	0.22 [0.12,0.41]	<0.001
Etiology:Orthostatic	1.04 [0.65,1.67]	0.860	0.07 [0.05,0.10]	<0.001	0.04 [0.02,0.07]	<0.001	0.18 [0.09,0.35]	<0.001
Etiology:Others	1.14 [0.57,2.29]	0.716	0.07 [0.04,0.13]	<0.001	0.02 [0.01,0.10]	<0.001	0.22 [0.08,0.63]	0.005

Etiology:Unknown	1.75 [1.04,2.95]	0.036	0.15 [0.10,0.23]	<0.001	0.17 [0.10,0.29]	<0.001	0.39 [0.19,0.79]	0.009
Abnormal ECG	1.41 [0.94,2.12]	0.094	1.29 [1.15,1.45]	<0.001	1.40 [0.95,2.06]	0.091	0.53 [0.34,0.84]	0.006

Supplemental table C – Cox proportional Hazards analysis for several short- and long-term outcomes

Supp Table C.B)	Death 30d		Overall MACE 30d		Arrhythmic MACE 30d		Ischemic MACE 30d	
	HR [95%CI]	p-val	HR [95%CI]	p-val	HR [95%CI]	p-val	HR [95%CI]	p-val
log BNP, per 10pg/mL increase	1.37 [0.78,2.40]	0.269	1.22 [1.06,1.40]	0.005	1.25 [1.05,1.48]	0.011	1.39 [1.10,1.74]	0.005
Age	1.05 [0.99,1.12]	0.131	1.00 [0.99,1.01]	0.869	0.99 [0.98,1.01]	0.435	0.99 [0.97,1.01]	0.364
Sex			1.43 [1.04,1.97]	0.027	1.18 [0.80,1.73]	0.414	0.83 [0.49,1.41]	0.501
Known CV disease			1.10 [0.57,2.12]	0.782	1.32 [0.60,2.91]	0.495	1.98 [0.88,4.48]	0.100
Smoking status			1.43 [1.05,1.95]	0.023	1.39 [0.95,2.02]	0.089		
Hypertension			0.70 [0.47,1.06]	0.092	0.61 [0.38,1.00]	0.050		
Hypercholesterolemia			1.28 [0.94,1.76]	0.122	0.97 [0.66,1.42]	0.866		
Diabetes			1.07 [0.74,1.53]	0.719	1.07 [0.69,1.66]	0.762		
Heart rate, per 5 bpm increase			0.95 [0.92,0.98]	0.004	0.91 [0.87,0.95]	<0.001		
Systolic BP, per 5mmHg increase			1.02 [0.99,1.04]	0.245	1.04 [1.01,1.08]	0.015		

Any cardiac medication		1.26 [0.70,2.27]	0.439	1.26 [0.62,2.54]	0.525		
Etiology:Reflex		0.03 [0.02,0.05]	<0.001	0.01 [0.00,0.03]	<0.001	0.16 [0.07,0.34]	<0.001
Etiology:Orthostatic		0.04 [0.02,0.06]	<0.001	0.03 [0.01,0.07]	<0.001	0.11 [0.04,0.26]	<0.001
Etiology:Others		0.05 [0.02,0.12]	<0.001	0.01 [0.00,0.10]	<0.001	0.19 [0.06,0.64]	0.007
Etiology:Unknown		0.13 [0.08,0.21]	<0.001	0.15 [0.09,0.28]	<0.001	0.38 [0.17,0.83]	0.015
Abnormal ECG		1.02 [0.74,1.42]	0.888	1.15 [0.77,1.71]	0.498	0.67 [0.40,1.14]	0.140

Supplemental table D – Prevalence of each component of the ROSE rule in the cohort

Component	Number of patients	Prevalence
BNP ≥300pg/mL	147	10.1%
Positive fecal occult blood	7	0.48%
Hemoglobin ≤90g/dL	118	8.1%
Oxygen saturation ≤94%	187	12.8%
Q waves in the ECG	88	6.0%

Supplemental table E – Performance of the ROSE rule versus a BNP cut-off of 300pg/L alone.

	% ruled-in (95%-CI)	% ruled-out (95%-CI)	SE (95%-CI)	SP (95%-CI)	NPV (95%-CI)	PPV (95%-CI)	AUC (95%-CI)
BNP cut-off 300pg/L alone	9.9 (8.5, 11.5)	90.1 (88.5, 91.5)	0.3 (0.24, 0.37)	0.93 (0.91, 0.94)	0.91 (0.89, 0.93)	0.35 (0.27, 0.43)	0.74 (0.7, 0.78)
ROSE rule	32 (29.8, 34.4)	68 (65.6, 70.2)	0.51 (0.44, 0.59)	0.7 (0.68, 0.73)	0.92 (0.9, 0.93)	0.18 (0.15, 0.22)	0.63 (0.59, 0.68)

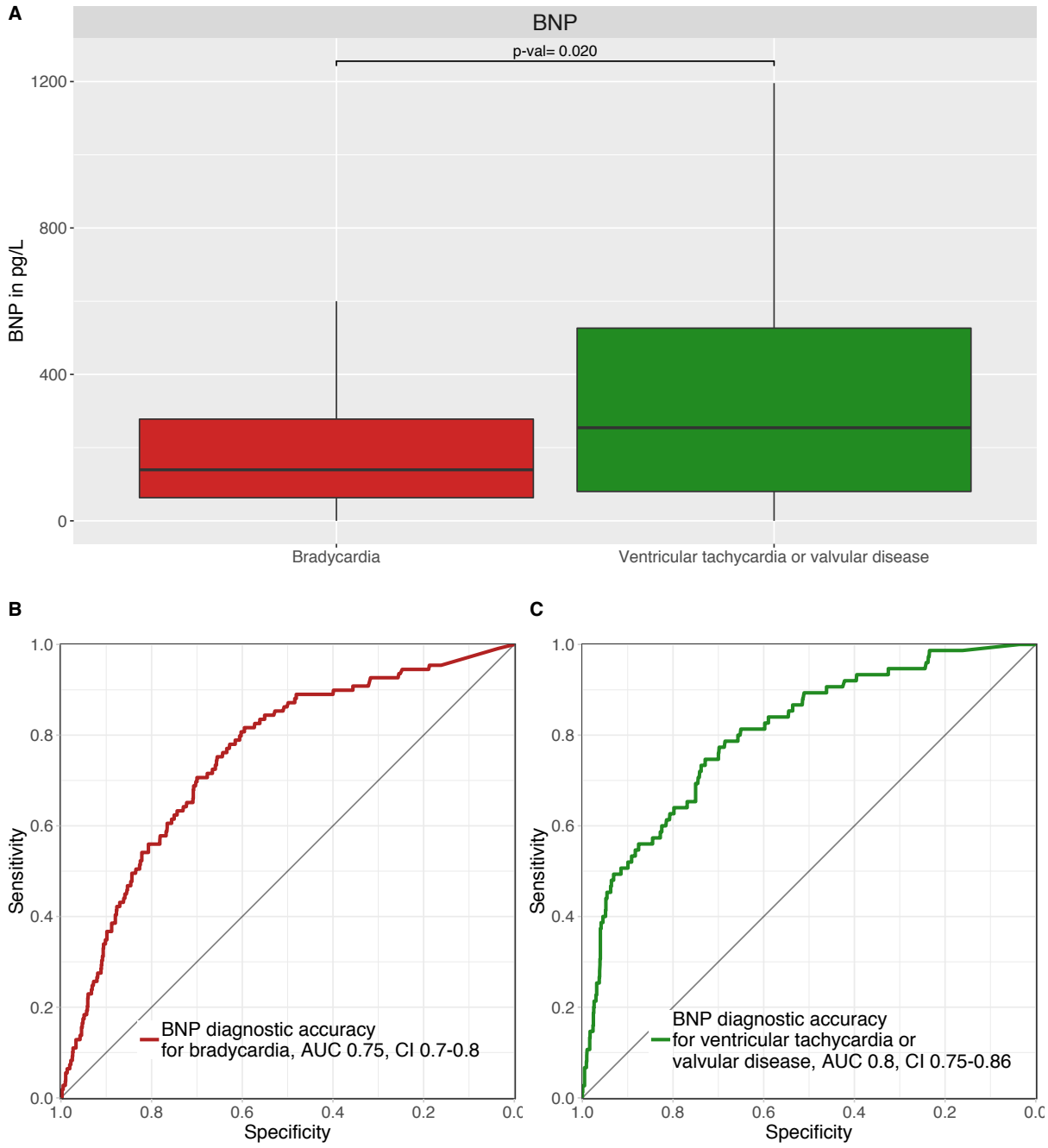
Supplemental table F – Optimal cut-offs to rule-out/rule-in events in the 30-day follow-up of patients with no obvious syncope cause in the ED.

	Target Sensitivity	Cut-off (pg/mL)	Sensitivity (95%-CI)	Specificity (95% CI)	NPV (95%-CI)	Incidence of criteria % (95%-CI)
Cut-offs for BNP for 30-day death	80	56.4	80 (49, 94.3)	55.3 (52.7, 57.8)	99.7 (99.1, 99.9)	55 (52.5, 57.6)
	85	36	90 (59.6, 98.2)	42.8 (40.3, 45.4)	99.8 (99.1, 100)	42.6 (40, 45.1)
	90	36	90 (59.6, 98.2)	42.8 (40.3, 45.4)	99.8 (99.1, 100)	42.6 (40, 45.1)
	95	33.6	100 (72.2, 100)	41.1 (38.5, 43.6)	100 (99.4, 100)	40.8 (38.3, 43.3)
	98	33.6	100 (72.2, 100)	41.1 (38.5, 43.6)	100 (99.4, 100)	40.8 (38.3, 43.3)
	Target Specificity	**Cut-off (pg/mL)**	**Specificity (95%-CI)**	**Sensitivity (95% CI)**	**PPV (95%-CI)**	**Incidence of criteria % (95%-CI)**
	80	171.4	81.6 (79.5, 83.5)	40 (16.8, 68.7)	1.5 (0.6, 3.7)	18.6 (16.7, 20.7)
	85	294.3	90.2 (88.6, 91.6)	30 (10.8, 60.3)	2.1 (0.7, 5.9)	9.9 (8.5, 11.6)
	90	294.3	90.2 (88.6, 91.6)	30 (10.8, 60.3)	2.1 (0.7, 5.9)	9.9 (8.5, 11.6)
	95	975.2	98.3 (97.5, 98.8)	20 (5.7, 51)	7.4 (2.1, 23.4)	1.9 (1.3, 2.7)
	98	975.2	98.3 (97.5, 98.8)	20 (5.7, 51)	7.4 (2.1, 23.4)	1.9 (1.3, 2.7)

	Target Sensitivity	Cut-off (pg/mL)	Sensitivity (95%-CI)	Specificity (95% CI)	NPV (95%-CI)	Incidence of criteria % (95%-CI)
Cut-offs for BNP for 30-day MACE	80	41	80.5 (73.7, 85.9)	49.8 (47.1, 52.5)	95.4 (93.6, 96.7)	46.5 (43.9, 49.1)
	85	31.1	85.5 (79.2, 90.2)	41.8 (39.2, 44.5)	95.9 (94, 97.3)	38.8 (36.4, 41.4)

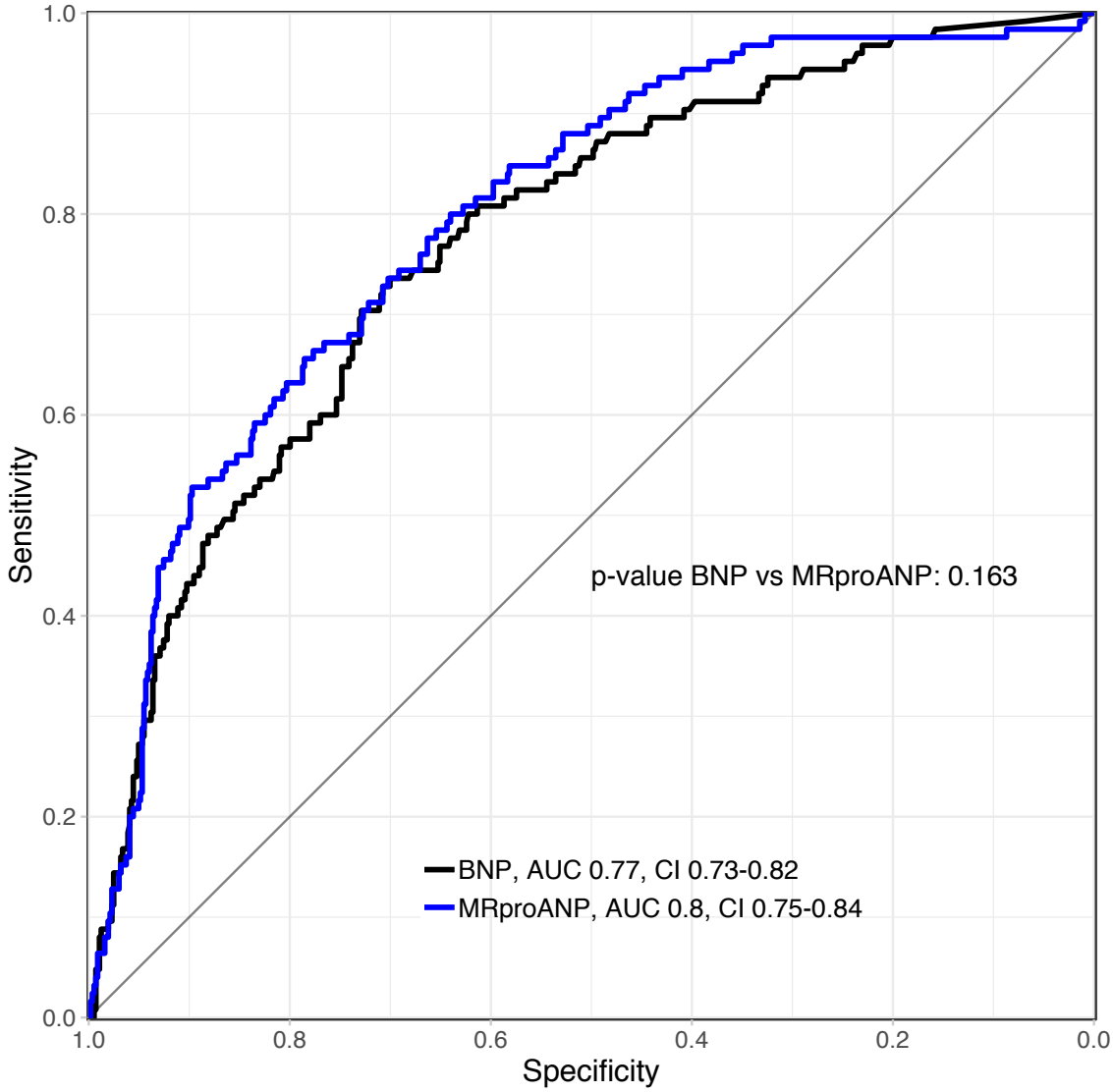
	90	22.6	90.6 (85, 94.2)	32.6 (30.1, 35.2)	96.6 (94.4, 97.9)	30.1 (27.8, 32.5)
	95	11.8	95.6 (91.2, 97.9)	16.9 (14.9, 19)	96.9 (93.7, 98.5)	15.5 (13.7, 17.5)
	98	9.9	98.7 (95.5, 99.7)	3 (2.2, 4.1)	95.1 (83.9, 98.7)	2.8 (2.1, 3.8)
	Target Specificity	**Cut-off (pg/mL)**	**Specificity (95%-CI)**	**Sensitivity (95% CI)**	**PPV (95%-CI)**	**Incidence of criteria % (95%-CI)**
	80	132.8	80.1 (77.9, 82.2)	54.1 (46.3, 61.6)	25.1 (20.8, 29.9)	23.6 (21.5, 25.9)
	85	172.6	85.1 (83, 86.9)	45.3 (37.7, 53)	27.2 (22.2, 32.8)	18.3 (16.4, 20.3)
	90	254	90.2 (88.4, 91.7)	35.2 (28.2, 42.9)	30.6 (24.4, 37.6)	12.6 (11, 14.4)
	95	409.9	95.1 (93.7, 96.1)	24.5 (18.5, 31.8)	37.9 (29.1, 47.5)	7.1 (5.9, 8.5)
	98	836.6	98.2 (97.3, 98.8)	10.1 (6.3, 15.7)	41 (27.1, 56.6)	2.7 (2, 3.7)

Supplemental Figure A : BNP concentrations depending on the subtype of cardiac syncope.



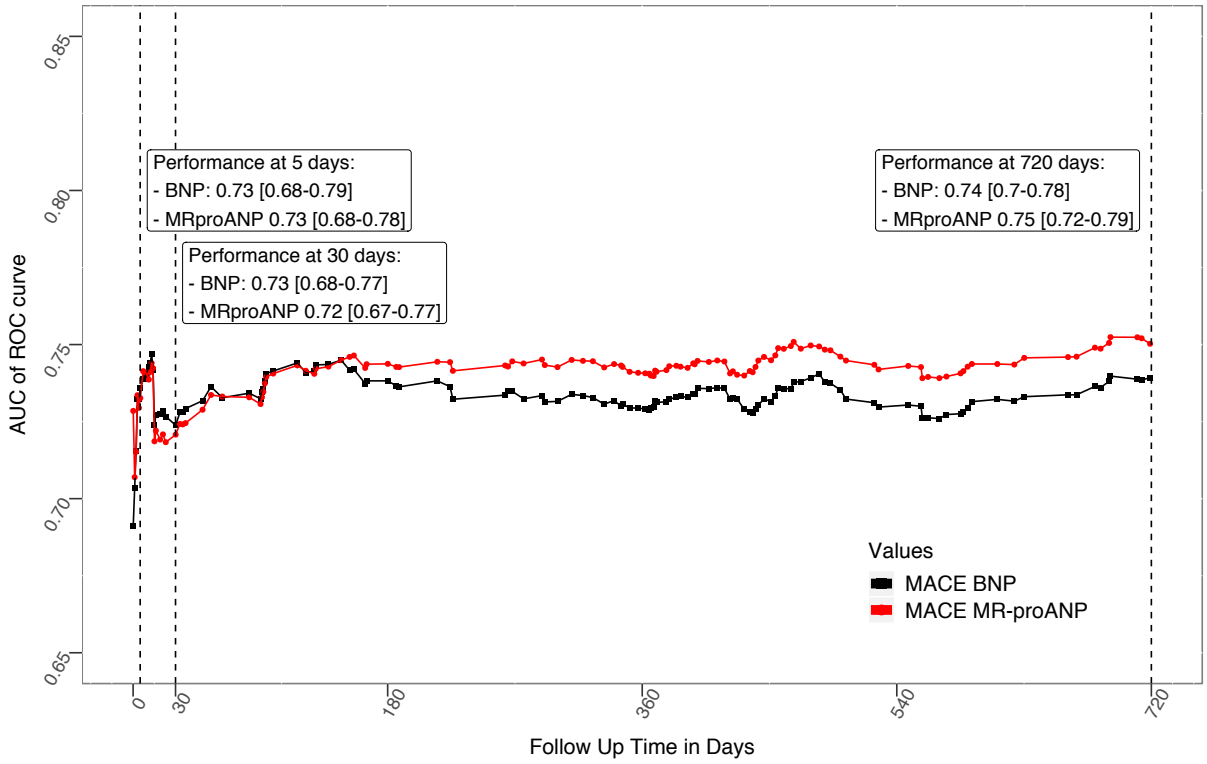
Supp. Figure A – A) Boxplots representing the BNP concentrations according to the cardiac etiology of the syncope. The boxplots represent the median with the interquartile range (IQR), whiskers represent ± 1.5 x the IQR. P-values are calculated based on a Wilcoxon-rang-sum test. B) and C) ROC curves of the performance of BNP for the diagnosis of bradycardia or ventricular tachycardia/valvular disease.

Supplemental Figure B : Direct comparison of the accuracy of BNP versus MRproANP



Supp Fig. B – Direct comparison of the accuracy of BNP versus MRproANP.

Supplemental Figure C : Direct comparison of BNP and MR-proANP for risk-stratification



Supp Fig. C – Time-dependent ROC curves for direct comparison of the accuracy of BNP and MR-proANP for risk-stratification of major adverse cardiac events including death.

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III - High-sensitivity cardiac troponin for diagnosis and risk-stratification of syncope

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Abstract

Background: It is unknown, whether high-sensitivity cardiac troponin I (hs-cTnI) or hs-cTnT provide higher accuracy for the diagnosis and risk-stratification of patients with syncope.

Methods: We directly compared the diagnostic and prognostic accuracy of hs-cTnI and hs-cTnT in a prospective international multicenter study enrolling patients >40y presenting with syncope to the emergency department (ED). Hs-cTnI/T concentrations were measured in a blinded fashion using three assays (hs-cTnI-Architect, hs-cTnI-Erenna, hs-cTnT-Elecsys). Cardiac syncope, as adjudicated by two physicians using all available information including 1-year follow-up, was the diagnostic endpoint. Death and major adverse cardiovascular events (MACE) at 5, 30 and 720 days were the prognostic endpoints.

Results: Among 1213 patients, cardiac syncope was the adjudicated diagnosis in 198 (16.3%). Hs-cTnI (both assays) and hs-cTnT concentrations were higher in patients with cardiac syncope compared to patients with other causes (all $p<0.01$) and remained independent predictors of cardiac syncope in multivariable models. Hs-cTnI/T diagnostic accuracy for cardiac syncope was moderate-to-good and similar for the three assays, with an area under the curve (AUC) of 0.76-0.77 (95%CI, 0.73-0.80, p=ns for all direct comparisons). Hs-cTnI/T prognostic accuracy was comparable among the assays and very high for imminent (within 5 days) death (AUC 0.93-0.94), and high for 30 and 720-day death (AUC 0.74-0.8), as well as MACE (AUC 0.72-0.76). When no obvious etiology is present on the ED, hs-cTn could provide guidance for hospitalization.

Conclusion: Hs-cTnI/T concentrations may have clinical utility in patients presenting with syncope as they provide diagnostic as well as prognostic information.

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 common in the emergency department (ED), representing 1% to 2% of all ED visits[2]. In contrast to other common ED presenting symptoms, e.g., acute chest pain or acute dyspnea,[71,72] improvements in the early diagnosis and risk-stratification are limited for patients presenting with syncope.[1,51] The risk of an adverse outcome is substantially higher in patients with a cardiac cause of syncope as compared to vasovagal or orthostatic causes.[1,51] Accordingly, the diagnosis of cardiac syncope and the risk-stratification for short- and long-time major adverse cardiac events (MACE) are essential, yet challenging tasks in the ED.[51]

In contrast to other common ED presenting symptoms, the clinical utility of high-sensitivity cardiac troponin (hs-cTn) in syncope has not been thoroughly evaluated in large multicenter diagnostic studies adjudicating the final diagnosis. Cardiomyocyte injury, as quantified by hs-cTnT and hs-cTnI concentrations, seems to identify risk in most, if not all, cardiovascular disorders.[95–97] Thus, we hypothesized that hs-cTnT and hs-cTnI may provide clinical utility in patients with syncope. This hypothesis is supported by pilot data mostly using less sensitive cTn assays.[5,98–100] Further, recent research suggests there may be relevant pathophysiological differences between hs-cTnT and hs-cTnI. These include a circadian rhythm for hs-cTnT, a stronger association with death for hs-cTnT, a slightly earlier cardiomyocyte release of hs-cTnI, and a stronger association of hs-cTnT and renal dysfunction.[101,102] Therefore, our primary aim was to directly compare hs-cTnT and hs-cTnI against each other, as well as against a previously derived risk-score[1], in the early diagnosis and risk-stratification of syncope. As cardiac syncope may be associated with only tiny amounts of cardiomyocyte injury, rendering the sensitivity and precision of hs-cTn assays in the normal range of possible importance, our secondary aim was to directly compare the best validated hs-cTnI assay with an experimental hs-cTnI assay using single-molecule counting technology and providing even 8-times higher sensitivity (as quantified by the limit of detection).[103]

Methods

Study design, setting and selection of participants

BAsel Syncope EvaLuation Study (BASEL IX) is an ongoing prospective international diagnostic multicenter study enrolling patients in fourteen hospitals in nine countries (Switzerland, Spain, Germany, Italy, Poland, New Zealand, Australia, the United States of America and Argentina). The study is designed to contribute to and improve the management of patients presenting with syncope (ClinicalTrials.gov registry, number NCT01548352). Patients more than 40 years old, and presenting to the ED with syncope within the last twelve hours, were recruited after written informed consent was obtained.

Patients with the final diagnosis of a non-syncopal loss of consciousness (e.g. epilepsy, fall, alcohol intoxication) or in whom at least one hs-cTnT/I measurement was missing were excluded for all analyses. Patients in whom the final diagnosis remained unclear, even after central adjudication, were excluded for analyses concerning the diagnostic endpoints (Figure 1). Patients in whom the final diagnosis remained unclear were still included in all survival analyses.

Patients with no obvious syncope etiology following initial ED evaluation (excluding patients presenting with as 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 hs-cTn 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. The authors designed the study, gathered, and analysed the data according to the STROBE guidelines (Supplemental table 1) for studies of diagnostic accuracy, vouched for the data and analysis, wrote the paper, and decided to publish.

Clinical assessment

All patients underwent clinical assessment that included standardized and detailed assessment of predefined details of medical history as listed in the Supplemental.

During patient enrolment, most participating sites (8/14) used a conventional less sensitive cTn assay clinically. In the remaining centers (6/14), a hs-cTn assay was used.

As a comparator for diagnostic and prognostic accuracy, the “Evaluation of Guidelines in Syncope Study” (EGSYS) risk score was used (Supplemental), as well as a combination of several predefined clinically relevant confounders in the evaluation of syncope[51].

Follow-up and adjudicated final diagnosis

Patients were contacted 6, 12 and 24 months after discharge, all information was collected as described in the supplemental. To determine the final diagnosis for the index syncope in each patient, two independent physicians, blinded to hs-cTn results, reviewed all available medical records as detailed in the supplemental. In case of adjudicator disagreement, cases were reviewed and adjudicated in conjunction with a third physician. Predefined categories for the adjudication included cardiac syncope, reflex syncope, orthostatic syncope, other noncardiac syncope, and unknown cause of syncope, as defined by the guidelines[1]. The presence of cardiac disease (eg, coronary artery disease) was not, in isolation, sufficient for the adjudication of a cardiac cause of syncope. The detailed reconstruction of the syncopal event with the study-specific data set and third-party anamnesis, and long-term follow-up on cardiovascular events and/or recurrent syncope, were critical pillars of the adjudication.

Blood sampling and laboratory methods

Venous blood samples were drawn via a peripheral venous line upon arrival on the ED. Blood was then immediately processed and frozen at -80°C until analysis. Details to the assays assessed (Hs-cTnI Architect, Hs-cTnI Erenna, Hs-cTnT Elecsys) are available in the supplemental.

The laboratory team who measured hs-cTnI/T concentrations were blinded to all clinical information and the adjudicated diagnosis.

The possible incremental value of serial sampling was evaluated in the subgroup of patients that had two consecutive cTn measurements as part of their routine clinical care (study blood was ascertained only at a single time point). As the recruiting centers used different cTn assays, analyses were standardized to the respective 99th of the respective assay.[71]

Outcome measures

The primary diagnostic endpoint was the diagnostic accuracy for cardiac syncope. The primary objective was to compare the diagnostic accuracy of the hs-cTnI versus hs-cTnT concentrations for cardiac syncope. The co-primary prognostic endpoints were the accuracy of hs-cTnI/T concentrations to predict either death or overall MACE at 5 days, 30 days and 2 years of follow-up. Secondary endpoints were the comparative prognostic accuracies of hs-cTnI/T concentrations for ischemic and arrhythmic MACE at similar time points. Details to outcome definition are given in the Supplemental.

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, hs-cTn concentrations were analyzed depending on whether the patients had an adverse event (defined as death or MACE) within 30 days of the ED presentation in order to inform the possibility to safely avoid hospitalization 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/Fisher's exact test for comparison of categorical variables.

Areas under the receiver operating characteristic curve (AUC) were constructed to quantify diagnostic accuracy. Comparisons of AUCs were performed according to DeLong. Univariable/Multivariable logistic regression was used to assess the predictive accuracy of log-transformed cTn concentrations to diagnose cardiac syncope. Optimized cut-offs for given sensitivities/specificities for the diagnosis of cardiac syncope using the three cTn assays were derived. Confidence intervals for these measures were computed according to Agresti and Coull.

To address the possible confounding effect of exclusion of patients with unclear diagnosis even after final adjudication for the diagnostic analyses, a sensitivity analysis was conducted with all syncope patients (Sup.fig.1).

Time-dependent ROC[88] curves were computed using the "timeROC" package to assess the accuracy of the three cTn assays to predict death, MACE, ischemic and rhythmic MACE

during the whole follow-up length. For comparison, the prognostic accuracy of a series of clinically relevant variables known as relevant confounders in the evaluation of syncope were assessed as well.

Cox proportional hazard (CPH) model was used to assess log-transformed cTn concentrations in the prediction of these outcomes when correcting for pre-defined important co-variates. Kaplan Meier curves were used to represent survival at 30 days or 1 year, to compare stratification with a given hs-cTnT/I cut-off (hs-cTn tertiles or with a given cut-off for safe discharge). Differences were assessed through a log-rank test.

All hypothesis testing was two-tailed, p-values <0.05 were considered statistically significant and a Bonferroni correction conducted to control for multiple testing. Statistical analyses were performed using the R statistical package (Vienna, Austria). Details are given in the Supplemental.

Results

Characteristics of the patients

From May 2010 to February 2017, 1894 patients were enrolled (Figure 1), of which 1213 and 1099 were eligible for the analysis of prognostic and diagnostic endpoints, respectively. Mean patient age was 71 years, 39% were women, and about half had a history of cardiovascular disease (Table 1). Patients with a final adjudicated cardiac diagnosis (n=198) were significantly older, more often had a history of cardiovascular diseases and were more often on long-term cardiovascular medications.

Concentrations of hs-cTnI/T and syncope etiology

Hs-cTnI/T concentrations were significantly higher in patients adjudicated to have cardiac syncope as compared to patients with reflex, orthostatic, or other non-cardiac syncope (Figure 2, Bonferroni corrected $p<0.001$ for each comparison). While intra-assay comparisons showed similar differences between cardiac and non-cardiac syncope and the correlation among all three hs-cTn assays was high, relevant inter-assay discrepancies emerged relative to the approved 99th percentile of each hs-cTnT/I assay (Sup.fig.2). E.g. 361 patients classified as having elevated hs-cTnT concentrations according to the approved 99th-percentile, representing 73.5% of syncope patients with elevated hs-cTnT concentrations, would be classified as having normal hs-cTnI (Architect) concentrations according to the approved 99th-percentile.

Diagnostic accuracy of hs-cTnI/T for cardiac syncope

The diagnostic accuracy of hs-cTnI/T concentrations was moderate-to-good (AUC 0.76-0.77, 95%-CI 0.73-0.80) and comparable for all three hs-cTnI/T assays (p=ns for direct comparisons, Fig.3). Results were consistent in a sensitivity analysis including patients with an unknown final diagnosis (Sup.fig.1). Hs-cTnI/T cut-offs achieving a specificity of 95% for rule-in of patients with cardiac syncope, identified ~8% of patients. Cut-offs achieving a sensitivity of 95% ruled out ~20% (Sup.Table.2). The proportion of patients ruled-in and ruled-out were comparable between the three assays.

The diagnostic accuracy of hs-cTnI/T for cardiac syncope was higher than that of the EGSYS score (AUC 0.67, 95%-CI 0.63-0.70, p for comparison with all hs-cTnI/T assays alone $p<0.001$), and significantly higher than the performance of a combination of clinically

meaningful variables. Adding one of the three hs-cTn assay to these clinical variables also significantly improved their prediction for cardiac syncope (Sup.fig.3, p-value always <0.05). Combining hs-cTnI and hs-cTnT concentrations did not lead to any further improvement (AUC Abbott-Erenna 0.77, 95%-CI 0.73-0.81, AUC Abbott-Elecsys 0.77, 95%-CI 0.73-0.80, AUC Elecsys-Erenna 0.78, 95%-CI 0.74-0.81, p=ns for comparison with all assays alone).

In the subgroup of patients with serial clinical cTn measurements (368/1099 patients) (Sup.Table.3), absolute and relative changes provided incremental value to the first measurement, the second measurement had higher accuracy as compared to the first measurement, but all clinical cTn measurements had lower accuracy as compared to hs-cTnT/I (Sup.fig.4).

Prediction of cardiac syncope

Logistic regression analysis confirmed hs-cTnI/T concentrations as significant predictors of cardiac syncope in both univariable and multivariable analyses (Table 2).

Prognostic accuracy of hs-cTnI/T concentrations

The follow-up was completed up to 360 days in 100% and up to 720 days in 85% of patients. During the whole follow-up 182 (15.0%) died, 368 (30.3%) suffered MACE, 221 (18.2%) had an ischemic MACE and 293 (24.1%) were diagnosed with an arrhythmic MACE (Sup.table.4). The prognostic accuracies of hs-cTnI/T concentrations and of the combination of several clinically relevant variables for the four endpoints up to 720 days are represented using time-dependent ROCs in Figure 4. The performance in predicting death, MACE, ischemic MACE and arrhythmic MACE was good and comparable among the three hs-cTnI/T assays and all three assays performed similarly to the combination of clinical variables during the whole follow-up. The prognostic accuracy for imminent death (within 5 days) was very high (AUC 0.93-0.94, 95%-CI [0.90-0.97]). Hs-cTnI/T identified 100% of all deaths within 5 days with 89% specificity (cut-offs: hs-cTnT 38 ng/L, hs-cTnI-Architect 25.6 ng/L, hs-cTnI-Erenna 13.76 ng/L). Table 3 summarizes the clinical details of all patients dying within 5 days. Sup.fig.5 showed a risk-stratification based on hs-cTnT/I tertiles.

Prediction of death and MACE at 5, 30 and 720 days

Log-transformed hs-cTnI/T concentrations were significant predictors in the multivariable CPH model for death and MACE at all time points (Sup.table.5).

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, 9 died within 30 days and 167 suffered from MACE.

Patients experiencing an event in the follow-up had significantly higher hs-cTnT/I concentrations (Sup.fig.6). Figure 5 shows the assay-specific lowest 95%-sensitivity cut-off to rule-out both death or MACE up to 30 days, the rule-out allowed by these cut-offs and the number of hospitalization days that would have been spared.

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 by evaluating and comparing the diagnostic and prognostic accuracy of three hs-cTnI/T assays.

We report **seven** major findings. **First**, concentrations of hs-cTnI/T were significantly higher in patients adjudicated to have cardiac syncope as compared to other syncope etiologies. **Second**, hs-cTnI/T concentrations showed comparable and moderate-to-good accuracy for the diagnosis of cardiac syncope, which was higher than that of a currently recommended multivariable risk score.[17] **Third**, if applied as a triage tool, hs-cTnI/T concentrations allowed to rule-out and rule-in cardiac syncope with 95% sensitivity and 95% specificity in 25-30% of patients. **Fourth**, while intra-assay comparisons showed similar differences between cardiac and non-cardiac syncope and high correlation, relevant inter-assay discrepancies emerged relative to the approved 99th percentile of each hs-cTnT/I assay. Analysing the distribution of high-senstivitiy cardiac troponin I (Architect and Erenna) and hs-cTnT (Elecsys) concentrations from the same patients obtained at the same time point showed that the currently approved clinical decision values (99th percentiles) are not biologically equivalent in this cohort of patients with syncope. This finding extend and corroborates prior studies in patients with suspected AMI[104] and population based-analysis[97], showing that biological equivalent concentrations differ more than 100% from the corresponding 99th percentile. The clinical implications of these discrepancies are enormous. E.g. 361 patients classified as having elevated hs-cTnT concentrations according to the approved 99th-percentile, representing 73.5% of all syncope patients with elevated hs-cTnT concentrations, would be classified as having normal hs-cTnI (Architect) concentrations according to the approved 99th-percentile. **Fifth**, hs-cTnI/T concentrations remained an independent predictor of a cardiac syncope after multivariable adjustments. **Sixth**, hs-cTnI/T concentrations had very high and unprecedented accuracy to predict imminent death (AUC 0.93-0.94), as well as high accuracy to predict MACE during long-term follow-up. **Seventh,** in the subgroup of patients with no obvious syncope etiology upon ED evaluation, hs-cTn could inform the decision for hospitalization by identifying patients with a very low risk of death and MACE within 30 days. The respective assay-specific hs-cTnI/T cut-offs we highlighted would allow to identify about 18% of eligible patients with a

mortality risk at 30-days of 0% and therefore spare between 145 and 200 cumulative hospitalization days.

Our findings extend previous diagnostic studies on cTn in patients with syncope.[98,99,105,106] Despite relevant emerging pathophysiological differences between hs-cTnI and hs-cTnT,[97,107] as well as substantial differences in analytical sensitivity among the hs-cTnI/T assays used, this study did not show clinically relevant differences in their diagnostic or prognostic accuracy. Given the large number of patients enrolled, and their high incidence of cardiac syncope and MACE during follow-up, a type II error is unlikely.

Our findings corroborate previous prognostic single-center studies using less-sensitive cTn assays, as well as a recent metaanalysis[13,100,108]. Hs-cTnI/T is a powerful predictor of death, however they are less accurate in the prediction of the non-fatal ischemic or arrhythmic endpoints captured in the various composite endpoints used. The very high accuracy of hs-cTnI/T to predict death within 5 days may have important clinical utility. Irrespective of the adjudicated syncope etiology, substantial amounts of cardiomyocyte injury, as quantified by hs-cTnI/T, seems to be a universally available and inexpensive biochemical signature to rapidly identify syncope patients at very high risk of dying within the next 5 days. It is important to highlight that while organ-specific, hs-cTnT/I are not disease-specific and may therefore be substantially elevated in several acute cardiovascular conditions associated with syncope including AMI, myocarditis, ventricular tachycardia, severe aortic stenosis, or central pulmonary embolism. For all of these patients, immediate hospitalization in a monitored unit and rapid diagnostic and therapeutic assessment will be the direct consequence of this information. In some of these patients (for instance patient 1 and 3), early pacemaker or defibrillator implantation may have been beneficial. Acknowledging the low number of patients dying within the first five days, these results need to be further validated and any hypothesis regarding the possible benefit of more precise risk assessment proven in an intervention study.

To the best of our knowledge, this is the first multicenter, centrally adjudicated, long-term follow up study performed in syncope. It provides precise and reliable estimates for the clinical utility of hs-cTnI/T. Although hs-cTnI/T concentrations remained predictive of cardiac syncope in multivariable models, and the AUC was higher as compared to that of a commonly used syncope score, it was only moderate-to-good. While AMI may have very

atypical symptoms, and syncope may be the sole manifestation of AMI, the diagnostic yield in this setting is low.[98,99] Also, some amount of cardiomyocyte injury as quantified by hs-cTnI/T concentrations seems common also in patients developing orthostatic or other non-cardiac syncope, and correlates with the extent of atherosclerosis, ventricular hypertrophy and vascular stiffness. Accordingly, this biomarker flags patients with a higher burden of often subclinical cardiac pathologies, who are at higher risk for long-term cardiac events including death.[109]

Some limitations of the present study merit consideration. First, only patients presenting to the ED were recruited. 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 hs-cTnI/T in patients presenting >12 hours after their syncope, or patients younger than 40 years of age, as these were excluded from our study. Third, hs-cTnI/T concentrations were only obtained once at ED presentation and no serial study-specific measurements were available. Based on the findings regarding serial measurements of cTn performed as part of clinical care available in a selected subgroup of 368 patients in this study, it seems unlikely that serial measurements of hs-cTnT/I would provide substantially higher diagnostic and prognostic accuracy as compared to that of a single measurement. However, further studies seem warranted to evaluate the possible utility of serial hs-cTnI/T sampling in unselected syncope patients presenting to the ED. Fourth, despite using one of the most stringent methods of final diagnosis adjudication, we cannot exclude the possibility that a few patients might have been misclassified by our central adjudication process. This could potentially have resulted in an underestimation of the true diagnostic accuracy of hs-cTnI/T.

In conclusion, hs-cTnI/T concentrations seem to have some clinical utility in patients presenting with syncope as they combine both diagnostic and prognostic information. Despite relevant emerging differences between hs-cTnI and hs-cTnT, as well as substantial analytical differences among the hs-cTnI/T assays investigated, overall diagnostic and prognostic accuracy were comparable.

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Conflict of interest and disclosures

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 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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Tables

Table 1	Baseline characteristics				
	All patients N= 1213	Cardiac N= 198	Non cardiac N= 901	Unknown N= 114	p
Age-years (median [IQR])	71.0 [58.0, 80.0]	76.0 [66.0, 83.0]	68.0 [55.0, 79.0]	79.0 [70.2, 85.8]	<0.001
Female - no. (%)	468 (39)	68 (34)	354 (39)	46 (40)	0.398
Characteristics of the syncope - no. (%)					
Nausea or vomiting	338 (28)	36 (19)	287 (32)	15 (13)	<0.001
Sweating	350 (30)	39 (20)	294 (33)	17 (15)	<0.001
Pallor	284 (39)	37 (33)	230 (42)	17 (27)	0.021
Palpitations	84 (7)	18 (9)	59 (7)	7 (6)	0.423
Angina	75 (6)	21 (11)	48 (5)	6 (5)	0.022
Caused injury	163 (14)	26 (14)	118 (13)	19 (17)	0.623
Position of the syncope - no. (%)					
While lying	33 (3)	4 (2)	26 (3)	3 (3)	0.791
While sitting	453 (38)	64 (32)	344 (39)	45 (39)	0.257
Orthostatic	149 (12)	14 (7)	125 (14)	10 (9)	0.013
While standing	563 (47)	115 (58)	393 (44)	55 (49)	0.002
Exertion	101 (8)	37 (19)	52 (6)	12 (11)	<0.001
Risk factors - no. (%)					
Hypertension	744 (62)	139 (71)	517 (58)	88 (78)	<0.001
Hypercholesterolemia	488 (42)	90 (47)	348 (40)	50 (48)	0.068
Diabetes	175 (15)	42 (21)	113 (13)	20 (18)	0.004
Smoking	640 (54)	98 (50)	477 (54)	65 (59)	0.332
History - no. (%)					
Previous stroke	97 (8)	14 (7)	64 (7)	19 (17)	0.002
Chronic heart failure (NYHA II-IV)	94 (8)	30 (16)	54 (6)	10 (9)	<0.001
Arrhythmia	269 (23)	78 (40)	162 (18)	29 (26)	<0.001
Pacemaker	63 (5)	18 (9)	44 (5)	1 (1)	0.005

Coronary artery disease	257 (22)	67 (35)	160 (18)	30 (27)	<0.001
Previous DVT or PE	89 (7)	13 (7)	60 (7)	16 (14)	0.016
Previous MI	159 (13)	44 (22)	98 (11)	17 (15)	<0.001
Epilepsy	38 (3)	2 (1)	27 (3)	9 (8)	0.003
Chronic medication - no. (%)					
ACEIs/ARBs	561 (46)	110 (56)	385 (43)	66 (58)	<0.001
Alphablocker	101 (8)	16 (8)	73 (8)	12 (11)	0.671
Antiarrhythmics Class I	49 (4)	13 (7)	29 (3)	7 (6)	0.047
Aspirin	356 (29)	71 (36)	243 (27)	42 (37)	0.008
Beta-blockers	391 (32)	86 (43)	260 (29)	45 (39)	<0.001
Calcium antagonists	208 (17)	37 (19)	142 (16)	29 (25)	0.029
Digitalis	18 (1)	9 (5)	8 (1)	1 (1)	0.001
Diuretics	378 (31)	93 (47)	243 (27)	42 (37)	<0.001

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.

Table 2		Logistic Regression: Predictors for cardiac syncope														
		Univariable logistic regression				**Multivariable logistic regression**										
						Hs-cTnI Architect			**Hs-cTnI Erenna**			**Hs-cTnT Elecsys**				
		OR	**95% CI (Lower-Upper)**		**p-val**	**OR**	**95% CI (Lower-Upper)**		**p-val**	**OR**	**95% CI (Lower-Upper)**		**p-val**	**OR**	**95% CI (Lower-Upper)**		**p-val**
cTn concentrations, per 5ng/L increase	Hs-cTnI Architect	2,63	2,22	3,14	<0.001	2,25	1,87	2,73	<0.001								
	Hs-cTnI Erenna	3,01	2,44	3,74	<0.001					2,49	1,99	3,14	<0.001				
	Hs-cTnT Elecsys	3,38	2,73	4,22	<0.001									2,88	2,24	3,75	<0.001
Age, each year increase		1,04	1,03	1,06	<0.001	1,02	1,01	1,04	0.003	1,03	1,01	1,04	0.001	1,01	0,99	1,03	0.255
Sex (Women)		0,81	0,58	1,11	0.196												
Known CV disease		2,51	1,71	3,77	<0.001	1,36	0,62	2,90	0.438	1,48	0,69	3,12	0.313	1,46	0,70	3,04	0.311
Smoking status		0,88	0,64	1,2	0.406												
Hypertension		1,8	1,29	2,54	0.001	0,72	0,41	1,29	0.255	0,69	0,39	1,22	0.190	0,61	0,35	1,09	0.088
Hypercholesterolemia		1,36	0,99	1,87	0.054												

Diabetes	1,88	1,26	2,77	0.002	1,30	0,81	2,06	0.270	1,31	0,82	2,07	0.254	1,16	0,72	1,82	0.541
Heart rate, per 5 bpm increase	1	0,98	1,03	0.634												
Systolic BP, per 5mmHg increase	1,04	1,01	1,07	0.022	1,03	1,00	1,07	0.061	1,03	1,00	1,07	0.081	1,04	1,00	1,07	0.031
Any cardiac medication	2,41	1,67	3,56	<0.001	1,11	0,59	2,12	0.752	1,19	0,64	2,26	0.587	1,13	0,61	2,09	0.705
Abnormal ECG	3,04	2,14	4,38	<0.001	1,82	1,22	2,75	0.004	1,93	1,30	2,91	0.001	1,88	1,26	2,84	0.002
Chest pain before the event	2,08	1,19	3,51	0.008	1,87	0,96	3,55	0.060	1,96	1,01	3,70	0.041	1,95	1,00	3,69	0.043

Bpm = beats per minute, mmHg= millimeter mercury, ECG = electrocardiogram, CV = cardiovascular, BP = blood pressure.

Nr	Age	Sex	Syst. BP upon ED arrival	Diast. BP upon ED arrival	HR upon ED arrival	Diagnosis	Syncope etiology	Immediate cause of death	Previous AMI
1	78	man	115	75	125	Supraventr. tachycardia	Cardiac	Asystolie	no
2	84	man	155	83	40	Drug-induced sick-sinus syndrom	Cardiac	Stroke	no
3	82	woman	76	44	74	Sick-sinus syndrome	Cardiac	Asystolie	yes
4	79	man	167	74	87	Syncope etiology unknown	Unknown	Rapidly progressive shock (unclear etiology)	no

Nr	Days of hospitalization	Hours in ICU	Days until death	hs-cTnI Architect (ng/L)	hs-cTnI Erenna (ng/L)	hs-cTnT Elecsys (ng/L)	Unexpected death	Preventable death
1	1	17	1	25,6	13,76	42	yes	Likely
2	3	7	3	35,4	18,54	50	yes	No
3	3	24	3	75,3	42,45	38	yes	Likely
4	3	0	3	78,9	76,97	132	yes	Likely

Table 3 – Characteristics of the 4 patients dead by the 5th day post-syncope. BP = blood pressure, ICU = intensive care unit.

Figures

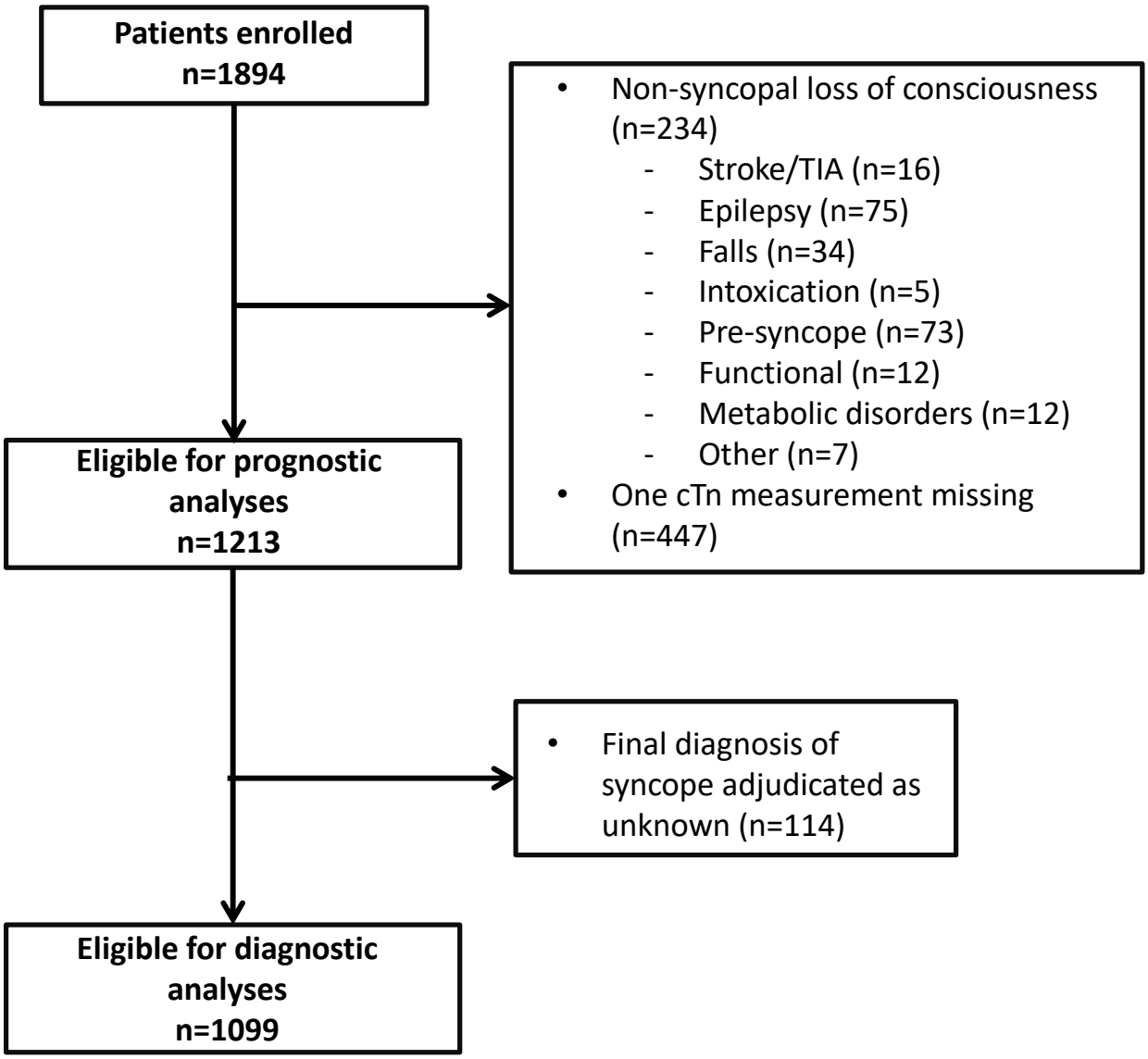


Figure 1 - Patient flow

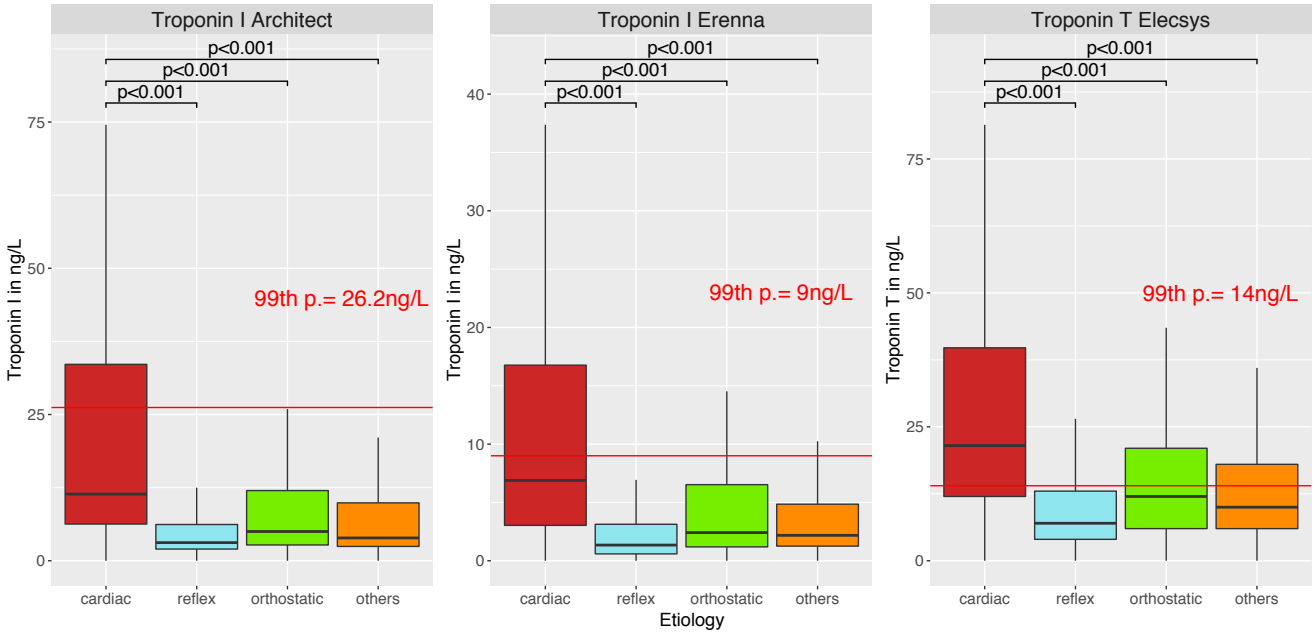


Figure 2 – Boxplots representing the high-sensitivity cardiac troponin I/T (hs-cTnI/T) concentrations according to the syncope etiology. The boxplots represent the median with the interquartile range (IQR), whiskers represent ± 1.5 x the IQR. P-values are calculated based on a Wilcoxon-rang-sum test and corrected for multiple testing according to Bonferroni. The red lines indicate the respective 99th percentile (99th p.) for each assay, as provided by the manufacturer.

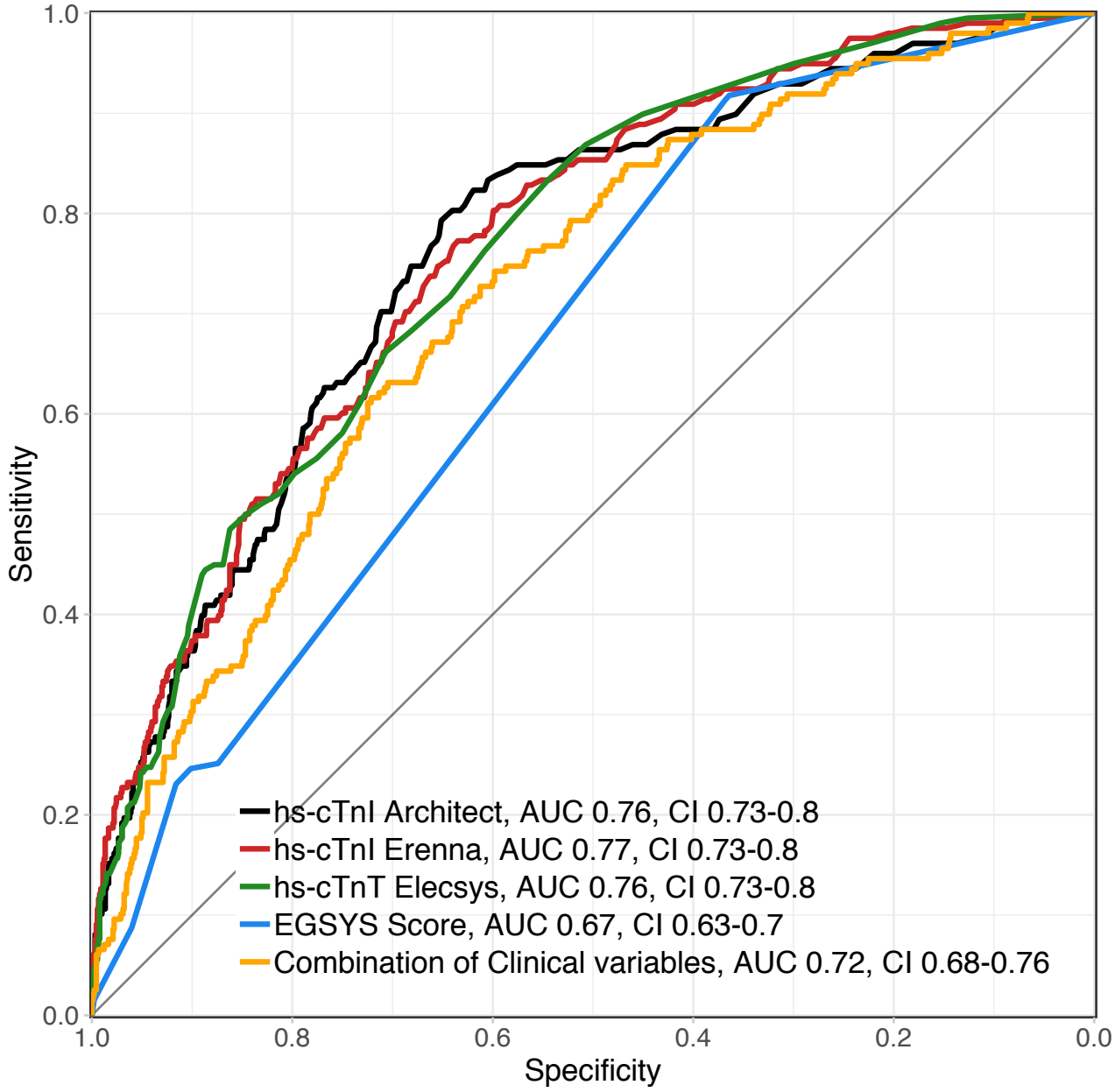


Figure 3 – Accuracy of the three cTn assays, separately, and as comparison of the EGSYS score and of a set of clinically relevant variables (Supplemental) for the diagnosis of cardiac syncope.

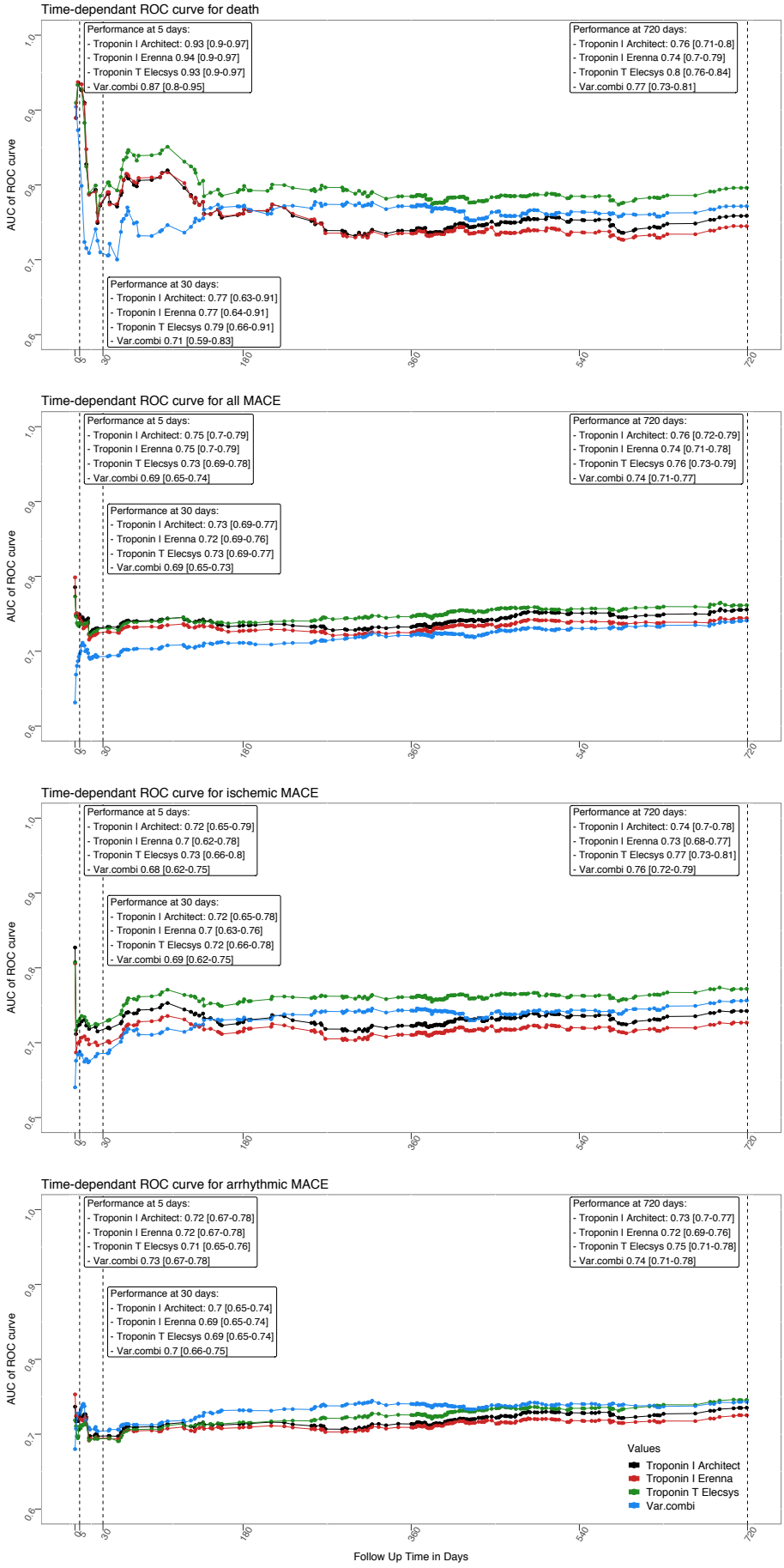


Figure 4 – Time-dependent ROC curves for the accuracy of the three cTn assays and of a set of clinically relevant variables (Supplemental) for the prognosis of death, all MACE, ischemic MACE and arrhythmic MACE.

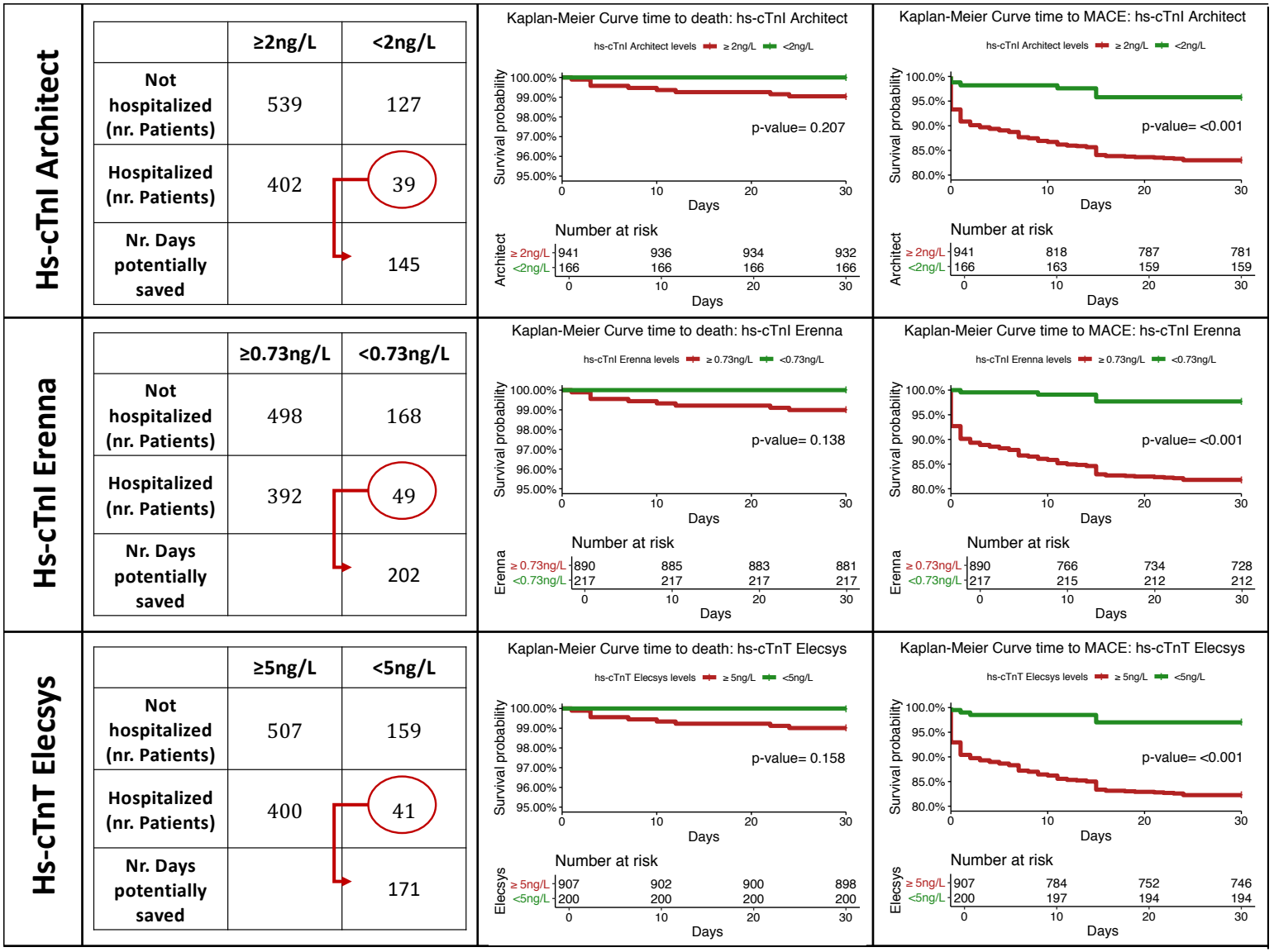


Figure 5 – Hospitalization and potential rule-out pattern and survival curves for death and MACE using the lowest 95%-sensitivity cut-off to rule-out both outcomes up to 30 days for each assay.

Supplemental material

Supplemental methods

Clinical assessment

All patients underwent clinical assessment that included standardized and detailed assessment of predefined details of medical history including previous syncope events and circumstances of current syncope, vital signs, physical examination, routine laboratory tests, radiologic testing, and a 12-lead ECG. Additional tests and treatment of patients were left to discretion of the attending physician. Additional tests included 24-hour ECG, external or implantable loop device, cardiac exercise test, Schellong test, tilt table testing, coronary angiography, continuous rhythm monitoring, pulse oximetry, echocardiography, interrogation of implanted devices (e.g. pacemaker) or electrophysiological examinations, and recording of findings of further investigations during recurrent hospitalization or ambulant treatment.

Follow-up and Adjudication of the final syncope diagnosis

Patients were contacted 6, 12 and 24 months after discharge by telephone or in written form. Information regarding recurrent syncope, hospitalization and cardiac events during follow up was obtained from the patient's hospital notes, the family physician's records and national mortality registries, where available.

To determine the final diagnosis for the index syncope in each patient, two independent physicians, blinded to hs-cTn results, reviewed all available medical records from clinical and study-specific datasets. Clinical data included information from the clinical assessment, while study-specific data included standardized forms uniformly collecting predefined details of patient history, the circumstances of syncope, and physical examination, as well as at least 12 months follow-up.

According to guidelines,[1] cardiac causes of syncope were defined as supraventricular or ventricular arrhythmias, severe structural heart diseases (eg, hypertrophic cardiomyopathy or valvular diseases), pericardial tamponade, congenital myocardial or valvular anomalies, aortic dissection, or acute pulmonary hypertension (eg, attributable to pulmonary embolism), leading to a transient loss of consciousness.

The first step in the adjudication process was to decide whether there was syncope or not. If the criteria for a true syncope were not fulfilled, a distinction between the following non-syncopal disorders was made: pre-syncope; falls; stroke/TIA; epilepsy; metabolic disorders: e.g. hypoglycaemia, hypoxia, hyperventilation; intoxication: e.g. alcohol, benzodiazepines, opiates; functional (psychogenic pseudosyncope); others.

The classification of syncope is based on pathophysiological considerations. The following predefined differential diagnoses were used:

11) Cardiac syncope: We distinguished between:
    a. Arrhythmia as primary cause: Arrhythmias are the most common cause of syncope; Bradycardia: sinus node dysfunction, atrioventricular conduction system disease, implanted device malfunction or drug-induced; Tachycardia: supraventricular or ventricular.
    b. Structural heart disease: structural heart diseases can cause syncope when circulatory demands outweigh the impaired ability of the heart to increase output. However, in some cases syncope may not solely be the result of restricted cardiac output, but be in part due to an inappropriate reflex. However, when a structural heart disease was the primary cause or contributed most to syncope, it was classified as cardiovascular syncope.
    c. Others: pulmonary embolism, acute aortic dissection, pulmonary hypertension or any other cause for a cardiovascular syncope.
12) Reflex (neutrally-mediated) syncope: This syncope is characterized by cardiovascular reflexes which are normally useful in controlling circulation but become intermittently inappropriate in response to a trigger. The reflex results in vasodilation and/or bradycardia which lead to a fall in arterial blood pressure and consequently to cerebral hypoperfusion. Identifying a trigger is central when diagnosing a reflex syncope. Typically symptoms as lightheadedness, nausea, sweating, weakness or visual disturbances precede reflex syncope. We distinguished between:
    a. Vasovagal: “common faint”, triggered by emotional distress/ pain or mediated by orthostatic stress.

b. Situational: refers to reflex syncope associated with some specific circumstances, e.g. post-micturition, post-prandial, gastrointestinal stimulation, cough.
c. Carotid sinus syncope: triggered by mechanical manipulation of the carotid sinus. It can be diagnosed by carotid sinus massage.
d. Atypical forms: reflex syncope occurring with uncertain or apparently absent triggers.

13) Syncope due to orthostatic hypotension: Orthostatic hypotension is defined as an abnormal decrease in systolic blood pressure after changing from supine to standing position. Key can be syncope immediately after standing up or a pathological Schellong test. We distinguished between:
    a. Primary autonomic failure: There is an autonomic failure which is clearly a primary part of Parkinson syndrome as idiopathic Parkinson disease or atypical Parkinson syndrome (multiple system atrophy, progressive supranuclear oculomotoric paresis, corticobasal degeneration or lewy body dementia).
    b. Secondary autonomic failure: autonomic failure may be due to circumstances such as diabetes, uraemia, amyloidosis or spinal cord injuries
    c. Drug-induced orthostatic hypotension: orthostatic hypotension is due to drugs which can lead to orthostatic hypotension such as diuretics, antidepressants, vasodilators, alcohol
    d. Volume depletion: orthostatic hypotension is caused by a hypovolemia due to haemorrhage, diarrhoea, vomiting or fever
    e. Others: sometimes the pathophysiology remains unclear.
14) Others, non-cardiac syncope: Sometimes the underlying pathophysiological mechanism of syncope remains unclear, but a cardiac syncope is ruled-out.
15) Syncope of unknown etiology (cardiac syncope possible): the etiology of syncope still remained unknown and a cardiac syncope was considered to be a possible cause.

Evaluation of Guidelines in Syncope Study (EGSYS)[17] *diagnostic score components*

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

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

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

Blood sampling and laboratory methods

Hs-cTnI Architect measurements were performed at the University Hospital of Basel using the ARCHITECT High Sensitive STAT Troponin I assay (Abbott Laboratories, Abbott Park, IL). This assay has a 99th percentile concentration of 26.2 ng/L with a corresponding CV of <5% and an LoD of 1.9 ng/L[110]. Hs-cTnI Erenna measurements were performed at Singulex, Inc. (Alameda, CA, USA) using the experimental Erenna system, a single-molecule counting technology. The Erenna Immunoassay System reports an LOD of 0.2 ng/L, a 10% CV between 0.78 and 1.6 ng/L, and a 99th percentile of 9 ng/L[111].

Hs-cTnT measurements were performed at the University Hospital of Basel on the Elecsys 2010 (Roche Diagnostics). The limit of blank and LOD have been determined to be 3 ng/L and 5 ng/L. An imprecision corresponding to 10% CV was reported at 13 ng/L and the 99th-percentile of a healthy reference population at 14 ng/L.[112]

Outcome definition

Arrhythmic MACE were defined as a composite of death, resuscitation, 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. Overall MACE included all of the above as well as pulmonary embolism, stroke/transient ischemic attack (TIA), intracranial bleeding and valvular surgery. 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[5]. Acute myocardial infarction was defined according to the Fourth Universal Definition.

Statistical analysis

Predictive accuracy of Troponin to predict cardiac syncope: Multivariable model and diagnostic ROC curve incorporating important co-variables.

We assessed the predictive accuracy of log-transformed hs-cTnI concentrations to diagnose cardiac syncope first in an univariable model and second in a multivariable model correcting for pre-defined baseline characteristics (age, sex, history of cardiovascular disease, smoking status, hypertension, diabetes or hypercholesterolemia, systolic blood pressure, heart rate, and cardiac medication, as recommended in previous literature[51]).

When assessing the diagnostic accuracy of hs-cTnI for the diagnosis of cardiac syncope, multivariable models were adjusted for age, sex, presence or absence of a history of cardiovascular disease (myocardial infarction, coronary heart disease, stroke or transient ischemic attack, congestive heart failure, atrial fibrillation, and intermittent claudication), smoking status, presence or absence of hypertension, systolic blood pressure, presence or absence of diabetes, presence of hypercholesterolemia, heart rate, and use or nonuse of cardiac medication, including antihypertensive medications.

Hypertension was a dichotomous variable defined as a systolic blood pressure of at least 140 mmHg, a diastolic blood pressure of at least 90 mmHg, or current use of antihypertensive medication.

The presence or absence of a history of cardiovascular disease, smoking status, presence or absence of diabetes, use or nonuse of cardiac medication and the presence of hypercholesterolemia were also included in the model as dichotomous variables. Age, systolic blood pressure, and heart rate were included as continuous variables.

The same variables were used to predict the risk of cardiac syncope in all patients, risk therefore predicted solely by clinical variables. The performance of these variables was then compared to the one of cardiac troponins alone.

Cox proportional hazard model:

We allowed for the correction of one variable for every ten events[94].

Accordingly:

- Overall MACE at 720 days and arrhythmic MACE at 720 days were corrected for age, sex, history of cardiovascular disease, smoking status, hypertension, diabetes or hypercholesterolemia, systolic blood pressure, heart rate, cardiac medication, the adjudicated syncope etiology, an abnormal ECG and the presence of chest pain before the event.
- Death at 720 days, ischemic MACE at 720 days, overall MACE at 30d, arrhythmic MACE at 30d, overall MACE at 5d were corrected for age, sex, history of cardiovascular disease, smoking status, hypertension, diabetes, cardiac medication, the adjudicated syncope etiology, and an abnormal ECG.
- Ischemic MACE at 30d and ischemic MACE at 5d were corrected for age, sex, history of cardiovascular disease and the adjudicated syncope etiology.
- Death at 30d and arrhythmic MACE at 5d were corrected for age.
- Death at 5d was not corrected

Time dependent ROC curves:

To compare the performance of cardiac troponins with the predictive accuracy of a combination of clinically relevant variables, known as potential confounders in the evaluation of syncope[51], we computed a time-dependent ROC curve incorporating following variables : age, sex, presence or absence of a history of cardiovascular disease (myocardial infarction, coronary heart disease, stroke or transient ischemic attack, congestive heart failure, atrial fibrillation, and intermittent claudication), smoking status, presence or absence of hypertension, systolic blood pressure, presence or absence of diabetes, presence of hypercholesterolemia, heart rate, and use or nonuse of cardiac medication, including antihypertensive medications.

Supplemental information to the figures:

The set of clinically relevant variables for the diagnosis of syncope were: age, sex, presence or absence of a history of cardiovascular disease (myocardial infarction, coronary heart disease, stroke or transient ischemic attack, congestive heart failure, atrial fibrillation, and intermittent claudication), smoking status, presence or absence of hypertension, systolic blood pressure, presence or absence of diabetes, presence of hypercholesterolemia, heart rate, and use or nonuse of cardiac medication, including antihypertensive medications.

Supplemental table 1 – STROBE Statement

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **(page 2 and title)**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **(page 2)**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **(page 3-4)**
Objectives	3	State specific objectives, including any prespecified hypotheses **(page 3-4)**
Methods		
Study design	4	Present key elements of study design early in the paper **(page 5)**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **(page 6-7)**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **(page 6-7)** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **(page 5-8)**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **(page 5-10)**
Bias	9	Describe any efforts to address potential sources of bias **(page 5-10)**
Study size	10	Explain how the study size was arrived at **(page 5-10)**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **(page 6-10)**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **(page 9-10)**
		(*b*) Describe any methods used to examine subgroups and interactions **(page 6-10)**
		(*c*) Explain how missing data were addressed

		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses **(page 5)**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **(page 11)**
		(b) Give reasons for non-participation at each stage **(page 11, Figure 1)**
		(c) Consider use of a flow diagram **(Figure 1)**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **(page 11, Table 1)**
		(b) Indicate number of participants with missing data for each variable of interest **(Table 1)**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **(page 12)**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **(page 12)**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **(page 11-13)**
		(*b*) Report category boundaries when continuous variables were categorized **(page 11-13)**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **(page 11-13)**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **(page 11-13)**
Discussion		
Key results	18	Summarise key results with reference to study objectives **(page 14)**

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **(page 16)**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **(page 15-16)**
Generalisability	21	Discuss the generalisability (external validity) of the study results **(page 14-16)**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **(Page 17)**

Supplemental table 2 – hs-cTnI/T cut-offs for specific sensitivities/specificities

1A) hs-cTnI Architect					
Target Sensitivity	**Cut-off (ng/L)**	**Sensitivity (95%-CI)**	**Specificity (95% CI)**	**NPV (95%-CI)**	**Incidence of criteria % (95%-CI)**
80	5.6	80.3 (74.1, 85.3)	64.1 (60.9, 67.2)	93.8 (91.6, 95.4)	56.2 (53.2, 59.1)
85	3.9	86 (80.4, 90.2)	51.4 (48.1, 54.7)	94.4 (92, 96.1)	44.7 (41.8, 47.7)
90	2.7	91.7 (87, 94.8)	33.9 (30.9, 37.1)	95 (92, 96.9)	29.3 (26.7, 32.1)
95	2.2	95.9 (92, 97.9)	21.9 (19.3, 24.7)	96.1 (92.4, 98)	18.7 (16.5, 21.2)
98	1.6	98.4 (95.5, 99.5)	9.9 (8.1, 12)	96.7 (90.8, 98.9)	8.4 (6.9, 10.2)
Target Specificity	**Cut-off (ng/L)**	**Specificity (95%-CI)**	**Sensitivity (95% CI)**	**PPV (95%-CI)**	**Incidence of criteria % (95%-CI)**
80	10.9	80.5 (77.7, 82.9)	53.9 (46.8, 60.8)	37.4 (31.9, 43.2)	25.6 (23.1, 28.3)
85	14.1	85.9 (83.4, 88)	44.6 (37.7, 51.6)	40.6 (34.2, 47.3)	19.6 (17.3, 22)
90	19.5	90.5 (88.4, 92.2)	36.3 (29.8, 43.3)	45.2 (37.5, 53)	14.3 (12.3, 16.5)
95	34.2	95.1 (93.4, 96.3)	24.9 (19.3, 31.4)	52.2 (42.1, 62.1)	8.5 (7, 10.3)
98	73.9	98.3 (97.2, 99)	15 (10.7, 20.7)	65.9 (51.1, 78.1)	4.1 (3, 5.4)

Supp 1B) hs-cTnI Erenna					
Target Sensitivity	**Cut-off (ng/L)**	**Sensitivity (95%-CI)**	**Specificity (95% CI)**	**NPV (95%-CI)**	**Incidence of criteria % (95%-CI)**
80	2.46	80.3 (74.1, 85.3)	59.9 (56.7, 63.1)	93.4 (91, 95.1)	52.8 (49.8, 55.7)
85	1.92	85.5 (79.8, 89.8)	51.4 (48.1, 54.7)	94.2 (91.8, 96)	44.8 (41.9, 47.8)
90	1.46	90.2 (85.1, 93.6)	41.8 (38.6, 45)	95.1 (92.5, 96.9)	36.1 (33.3, 39)
95	0.78	95.3 (91.4, 97.5)	25.8 (23, 28.8)	96.2 (93, 98)	22 (19.7, 24.6)
98	0.59	98.4 (95.5, 99.5)	18.2 (15.8, 20.8)	98.2 (94.8, 99.4)	15.2 (13.2, 17.5)
Target Specificity	**Cut-off (ng/L)**	**Specificity (95%-CI)**	**Sensitivity (95% CI)**	**PPV (95%-CI)**	**Incidence of criteria % (95%-CI)**
80	5.47	80.2 (77.5, 82.7)	54.9 (47.9, 61.8)	37.6 (32.1, 43.4)	26 (23.5, 28.7)
85	7.16	85.2 (82.7, 87.4)	49.7 (42.8, 56.7)	42.1 (35.9, 48.6)	21 (18.7, 23.6)
90	10.21	90 (87.9, 91.8)	36.8 (30.3, 43.8)	44.4 (36.9, 52.1)	14.8 (12.8, 17)
95	18.54	95.3 (93.7, 96.5)	24.4 (18.8, 30.9)	52.8 (42.5, 62.8)	8.2 (6.7, 10)
98	30.73	98.3 (97.2, 99)	18.1 (13.3, 24.2)	70 (56.2, 80.9)	4.6 (3.5, 6)

Supp 1C) hs-cTnT Elecsys					
Target Sensitivity	**Cut-off (ng/L)**	**Sensitivity (95%-CI)**	**Specificity (95% CI)**	**NPV (95%-CI)**	**Incidence of criteria % (95%-CI)**

80	10	83.4 (77.5, 88)	54.4 (51.2, 57.7)	93.8 (91.4, 95.6)	47.7 (44.7, 50.7)
85	9	87 (81.6, 91.1)	50.7 (47.5, 54)	94.8 (92.4, 96.4)	44 (41.1, 47)
90	8	90.2 (85.1, 93.6)	45.1 (41.9, 48.4)	95.5 (93.1, 97.1)	38.8 (36, 41.8)
95	5	96.9 (93.4, 98.6)	22.3 (19.7, 25.2)	97.1 (93.8, 98.7)	18.9 (16.7, 21.4)
98	4	99 (96.3, 99.7)	15.3 (13.1, 17.8)	98.6 (94.9, 99.6)	12.7 (10.9, 14.9)
Target Specificity	**Cut-off (ng/L)**	**Specificity (95%-CI)**	**Sensitivity (95% CI)**	**PPV (95%-CI)**	**Incidence of criteria % (95%-CI)**
80	20	81.1 (78.4, 83.6)	51.8 (44.8, 58.8)	37.3 (31.7, 43.2)	24.7 (22.2, 27.4)
85	23	86.1 (83.7, 88.2)	48.2 (41.2, 55.2)	42.9 (36.5, 49.5)	20 (17.7, 22.5)
90	29	90.2 (88.1, 92)	38.3 (31.8, 45.4)	46 (38.4, 53.7)	14.9 (12.9, 17.1)
95	44	95.1 (93.4, 96.3)	24.4 (18.8, 30.9)	51.6 (41.5, 61.6)	8.4 (6.9, 10.2)
98	62	98.5 (97.5, 99.1)	14.5 (10.2, 20.2)	68.3 (53, 80.4)	3.8 (2.8, 5.1)

Supplemental table 3 – Baseline characteristics and adjudicated diagnosis of the patients for whom serial troponin measurements were or were not clinically ordered.

	No serial measurements ordered	Serial measurements ordered	P value
Number of patients	731	368	
Age-years (median [IQR])	69.0 [56.0, 79.0]	73.0 [58.8, 81.0]	0.002
Female - no. (%)	329 (45)	93 (25)	<0.001
Characteristics of the syncope - no. (%)			
Nausea or vomiting	233 (32)	90 (25)	0.016
Sweating	227 (32)	106 (29)	0.483
Pallor	162 (38)	105 (44)	0.135
Palpitations	47 (7)	30 (8)	0.369
Angina	30 (4)	39 (11)	<0.001
Caused injury	107 (15)	37 (10)	0.036
Position of the syncope - no. (%)			
While lying	19 (3)	11 (3)	0.873
While sitting	257 (36)	151 (41)	0.085
Orthostatic	107 (15)	32 (9)	0.005
While standing	339 (47)	169 (46)	0.796
Exertion	54 (8)	35 (10)	0.286
Risk factors - no. (%)			
Hypertension	406 (56)	250 (68)	<0.001
Hypercholesterolemia	261 (37)	177 (50)	<0.001
Diabetes	80 (11)	75 (20)	<0.001
Smoking	360 (50)	215 (59)	0.009
History - no. (%)			
Previous stroke	47 (7)	31 (8)	0.303
Chronic heart failure (NYHA II-IV)	42 (6)	42 (12)	0.001

	No serial measurements ordered	Serial measurements ordered	P value
Arrhythmia	145 (20)	95 (26)	0.028
Pacemaker	34 (5)	28 (8)	0.065
Coronary artery disease	118 (17)	109 (30)	<0.001
Previous DVT or PE	47 (6)	26 (7)	0.786
Previous MI	66 (9)	76 (21)	<0.001
Epilepsy	19 (3)	10 (3)	1.000
Chronic medication - no. (%)			
ACEIs/ARBs	295 (40)	200 (54)	<0.001
Alphablocker	56 (8)	33 (9)	0.527
Antiarrhythmics Class I	26 (4)	16 (4)	0.632
Aspirin	185 (25)	129 (35)	0.001
Beta-blockers	211 (29)	135 (37)	0.010
Calcium antagonists	106 (15)	73 (20)	0.030
Digitalis	9 (1)	8 (2)	0.349
Diuretics	198 (27)	138 (38)	0.001
Syncope etiology as by adjudicated diagnosis - no. (%)			
Reflex syncope	325 (44)	135 (37)	0.016
Orthostatic syncope	220 (30)	110 (30)	1.000
Cardiac syncope	101 (14)	97 (26)	<0.001
Cardiac syncope: Arrhythmia	84 (11)	54 (15)	0.160
Cardiac syncope: Structural disease	10 (1)	31 (8)	<0.001
Cardiac syncope: Structural disease - AMI	4 (1)	19 (5)	<0.001

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.

Supplemental table 4 – Number of events in each of the composite endpoints

Outcome : Overall MACE (first event)	Number with event (%)
Death	125 (10.3 %)
Non-fatal Life-threatening arrhythmia	48 (4.0 %)
Pacemaker implantation	69 (5.7 %)
Survived cardiac arrest	7 (0.6 %)
ICD implantation	9 (0.7 %)
Valvular surgery	11 (0.9 %)
Non-fatal ACS	51 (4.2 %)
Non-fatal Stroke or TIA	21 (1.7 %)
Non-fatal pulmonary embolism	21 (1.7 %)
Non-fatal intracranial bleeding	6 (0.5 %)

Outcome : Arrhythmic MACE (first event)	Number with event (%)
Death	151 (12.4 %)
Non-fatal life-threatening arrhythmia	51 (4.2 %)
Pacemaker implantation	73 (6.0 %)
Survived cardiac arrest	9 (0.7 %)
ICD implantation	9 (0.7 %)

Outcome : Ischemic MACE (first event)	Number with event (%)
Death	164 (13.5 %)
Non-fatal ACS	57 (4.7 %)

Supplemental table 4 – Number of events within the three composite outcomes. Listed are the numbers and percentages of patients who experienced the outcomes as their first event during follow-up. ICD = Implantable Cardioverter Defibrillator , ACS = Acute coronary syndrome, TIA = transient ischemic attack.

Supplemental table 5 – Cox proportional Hazards analysis for several short- and long-term outcomes

Supp Table 2A1) hs-cTnI Architect	Death 720d		Overall MACE 720d		Arrhythmic MACE 720d		Ischemic MACE 720d	
	HR [95%CI]	p-val	HR [95%CI]	p-val	HR [95%CI]	p-val	HR [95%CI]	p-val
log hs-TnI, per 5ng/L increase	1.58 [1.32,1.90]	<0.001	1.32 [1.17,1.48]	<0.001	1.12 [0.98,1.29]	0.094	1.46 [1.25,1.71]	<0.001
Age	1.05 [1.03,1.07]	<0.001	1.02 [1.01,1.03]	<0.001	1.01 [1.00,1.03]	0.032	1.04 [1.03,1.06]	<0.001
Sex	0.57 [0.36,0.92]	0.022	1.07 [0.81,1.42]	0.609	0.91 [0.66,1.25]	0.562	0.78 [0.53,1.14]	0.201
Known CV disease	1.08 [0.38,3.08]	0.879	1.24 [0.69,2.23]	0.471	1.39 [0.69,2.83]	0.361	1.57 [0.67,3.68]	0.298
Smoking status	1.35 [0.88,2.07]	0.175	1.35 [1.04,1.76]	0.025	1.24 [0.92,1.68]	0.160	1.76 [1.22,2.55]	0.003
Hypertension	1.13 [0.60,2.13]	0.714	0.72 [0.50,1.04]	0.083	0.77 [0.50,1.18]	0.223	1.13 [0.66,1.95]	0.652
Hypercholesterolemia			0.95 [0.73,1.23]	0.680	0.81 [0.60,1.09]	0.164		
Diabetes	1.40 [0.89,2.20]	0.142	1.38 [1.02,1.87]	0.036	1.21 [0.85,1.73]	0.293	1.61 [1.11,2.33]	0.012
Heart rate, per 5 bpm increase			0.96 [0.93,0.99]	0.005	0.93 [0.90,0.97]	<0.001		
Systolic BP, per 5mmHg increase			0.99 [0.97,1.02]	0.466	0.99 [0.96,1.02]	0.540		
Any cardiac medication	1.22 [0.51,2.91]	0.659	1.67 [0.99,2.81]	0.056	2.25 [1.19,4.28]	0.013	0.84 [0.43,1.64]	0.612
Etiology:Reflex	0.50 [0.26,0.97]	0.042	0.06 [0.04,0.09]	<0.001	0.05 [0.03,0.09]	<0.001	0.35 [0.20,0.59]	<0.001
Etiology:Orthostatic	1.04 [0.62,1.75]	0.868	0.10 [0.07,0.15]	<0.001	0.12 [0.08,0.18]	<0.001	0.55 [0.35,0.85]	0.008
Etiology:Others	0.94 [0.44,2.00]	0.873	0.09 [0.05,0.16]	<0.001	0.10 [0.05,0.19]	<0.001	0.60 [0.32,1.15]	0.126
Etiology:Unknown	1.38 [0.76,2.50]	0.294	0.21 [0.14,0.31]	<0.001	0.28 [0.18,0.44]	<0.001	0.78 [0.47,1.30]	0.340
Abnormal ECG	1.23 [0.77,1.95]	0.384	0.89 [0.67,1.19]	0.434	1.42 [1.00,2.00]	0.047	0.78 [0.54,1.13]	0.192
Chest pain before the event			1.40 [0.90,2.17]	0.136	0.69 [0.38,1.23]	0.205		

Supp Table 2A1) hs-cTnI Architect	Death 30d		Overall MACE 30d		Arrhythmic MACE 30d		Ischemic MACE 30d	
	HR [95%CI]	p-val	HR [95%CI]	p-val	HR [95%CI]	p-val	HR [95%CI]	p-val
log hs-TnI, per 5ng/L increase	2.13 [1.41,3.21]	<0.001	1.18 [1.03,1.35]	0.020	0.92 [0.77,1.09]	0.338	1.31 [1.03,1.66]	0.027
Age	1.04 [0.99,1.10]	0.114	1.01 [1.00,1.02]	0.137	1.00 [0.99,1.02]	0.522	1.01 [0.98,1.03]	0.559
Sex			1.42 [1.03,1.98]	0.034	1.31 [0.89,1.93]	0.173		
Known CV disease			1.53 [0.75,3.10]	0.242	1.74 [0.74,4.10]	0.207	2.26 [0.92,5.58]	0.075
Smoking status			1.42 [1.02,1.97]	0.035	1.21 [0.82,1.77]	0.333		
Hypertension			0.59 [0.39,0.91]	0.017	0.54 [0.33,0.88]	0.013		
Hypercholesterolemia								
Diabetes			1.36 [0.95,1.96]	0.097	1.27 [0.83,1.96]	0.274		
Heart rate, per 5 bpm increase								
Systolic BP, per 5mmHg increase								
Any cardiac medication			1.63 [0.84,3.13]	0.146	2.58 [1.13,5.89]	0.024		
Etiology:Reflex			0.03 [0.02,0.06]	<0.001	0.01 [0.01,0.04]	<0.001	0.22 [0.10,0.49]	<0.001
Etiology:Orthostatic			0.04 [0.02,0.07]	<0.001	0.04 [0.02,0.08]	<0.001	0.14 [0.06,0.36]	<0.001
Etiology:Others			0.04 [0.01,0.10]	<0.001	0.01 [0.00,0.10]	<0.001	0.23 [0.07,0.78]	0.018
Etiology:Unknown			0.13 [0.08,0.22]	<0.001	0.15 [0.08,0.28]	<0.001	0.43 [0.19,1.00]	0.051
Abnormal ECG			0.81 [0.56,1.16]	0.239	1.26 [0.81,1.97]	0.297		
Chest pain before the event								

Supp Table 2A1) hs-cTnI Architect	Death 5d		Overall MACE 5d		Arrhythmic MACE 5d		Ischemic MACE 5d	
	HR [95%CI]	p-val	HR [95%CI]	p-val	HR [95%CI]	p-val	HR [95%CI]	p-val
log hs-TnI, per 5ng/L increase	2.65 [1.49,4.72]	0.001	1.24 [1.05,1.46]	0.011	1.75 [1.47,2.08]	<0.001	1.33 [1.04,1.70]	0.025
Age			1.01 [0.99,1.03]	0.277	1.03 [1.01,1.05]	<0.001	1.00 [0.98,1.03]	0.756
Sex			1.35 [0.90,2.03]	0.147				
Known CV disease			1.84 [0.73,4.63]	0.193			2.42 [0.90,6.47]	0.079
Smoking status			1.46 [0.97,2.19]	0.069				
Hypertension			0.73 [0.42,1.24]	0.240				
Hypercholesterolemia								
Diabetes			1.41 [0.92,2.17]	0.120				
Heart rate, per 5 bpm increase								
Systolic BP, per 5mmHg increase								
Any cardiac medication			1.23 [0.55,2.76]	0.623				
Etiology:Reflex			0.02 [0.01,0.05]	<0.001			0.20 [0.09,0.46]	<0.001
Etiology:Orthostatic			0.03 [0.01,0.07]	<0.001			0.07 [0.02,0.24]	<0.001
Etiology:Others			0.02 [0.00,0.12]	<0.001			0.16 [0.04,0.67]	0.012
Etiology:Unknown			0.11 [0.05,0.22]	<0.001			0.25 [0.09,0.73]	0.011
Abnormal ECG			0.70 [0.45,1.10]	0.124				
Chest pain before the event								

Supp Table 2A2) hs-cTnI Erenna	Death 720d		Overall MACE 720d		Arrhythmic MACE 720d		Ischemic MACE 720d	
	HR [95%CI]	p-val	HR [95%CI]	p-val	HR [95%CI]	p-val	HR [95%CI]	p-val
log hs-TnI, per 5ng/L increase	1.52 [1.23,1.88]	<0.001	1.30 [1.13,1.50]	<0.001	1.06 [0.90,1.24]	0.488	1.36 [1.13,1.63]	0.001
Age	1.05 [1.03,1.07]	<0.001	1.02 [1.01,1.03]	<0.001	1.02 [1.00,1.03]	0.024	1.05 [1.03,1.07]	<0.001
Sex	0.53 [0.33,0.86]	0.010	1.07 [0.81,1.41]	0.641	0.90 [0.65,1.25]	0.545	0.74 [0.50,1.09]	0.127
Known CV disease	1.18 [0.42,3.30]	0.747	1.27 [0.71,2.27]	0.416	1.40 [0.69,2.84]	0.348	1.68 [0.72,3.88]	0.228
Smoking status	1.34 [0.87,2.06]	0.180	1.34 [1.03,1.75]	0.029	1.24 [0.92,1.69]	0.160	1.76 [1.22,2.55]	0.003
Hypertension	1.05 [0.56,1.98]	0.877	0.71 [0.49,1.03]	0.069	0.77 [0.50,1.17]	0.221	1.07 [0.62,1.83]	0.814
Hypercholesterolemia			0.94 [0.72,1.23]	0.668	0.80 [0.59,1.08]	0.148		
Diabetes	1.37 [0.87,2.16]	0.176	1.42 [1.05,1.92]	0.025	1.24 [0.87,1.78]	0.237	1.61 [1.11,2.35]	0.012
Heart rate, per 5 bpm increase			0.96 [0.93,0.99]	0.006	0.94 [0.90,0.97]	<0.001		
Systolic BP, per 5mmHg increase			0.99 [0.97,1.02]	0.493	0.99 [0.96,1.02]	0.491		
Any cardiac medication	1.21 [0.51,2.86]	0.664	1.70 [1.01,2.86]	0.045	2.25 [1.19,4.24]	0.012	0.86 [0.44,1.66]	0.644
Etiology:Reflex	0.47 [0.24,0.92]	0.026	0.06 [0.04,0.09]	<0.001	0.05 [0.03,0.08]	<0.001	0.32 [0.19,0.54]	<0.001
Etiology:Orthostatic	1.03 [0.61,1.75]	0.897	0.10 [0.07,0.14]	<0.001	0.12 [0.08,0.18]	<0.001	0.53 [0.34,0.83]	0.005
Etiology:Others	0.94 [0.44,2.02]	0.877	0.09 [0.05,0.16]	<0.001	0.09 [0.05,0.19]	<0.001	0.59 [0.31,1.12]	0.107
Etiology:Unknown	1.32 [0.73,2.40]	0.356	0.20 [0.14,0.30]	<0.001	0.28 [0.18,0.43]	<0.001	0.74 [0.44,1.23]	0.240
Abnormal ECG	1.28 [0.81,2.04]	0.291	0.94 [0.70,1.24]	0.641	1.46 [1.04,2.06]	0.029	0.82 [0.57,1.19]	0.299
Chest pain before the event			1.48 [0.95,2.30]	0.080	0.71 [0.40,1.28]	0.255		

Supp Table 2A2) hs-cTnI Erenna	Death 30d		Overall MACE 30d		Arrhythmic MACE 30d		Ischemic MACE 30d	
	HR [95%CI]	p-val	HR [95%CI]	p-val	HR [95%CI]	p-val	HR [95%CI]	p-val
log hs-TnI, per 5ng/L increase	1.98 [1.15,3.42]	0.014	1.18 [1.01,1.38]	0.035	0.89 [0.73,1.09]	0.259	1.16 [0.87,1.55]	0.302
Age	1.06 [1.00,1.12]	0.059	1.01 [1.00,1.02]	0.122	1.01 [0.99,1.02]	0.509	1.01 [0.99,1.03]	0.398
Sex			1.40 [1.01,1.94]	0.046	1.29 [0.87,1.91]	0.200		
Known CV disease			1.55 [0.77,3.15]	0.220	1.72 [0.73,4.05]	0.215	2.25 [0.92,5.55]	0.077
Smoking status			1.40 [1.01,1.95]	0.044	1.19 [0.81,1.75]	0.372		
Hypertension			0.58 [0.38,0.89]	0.012	0.54 [0.33,0.89]	0.014		
Hypercholesterolemia								
Diabetes			1.37 [0.95,1.97]	0.095	1.25 [0.81,1.93]	0.310		
Heart rate, per 5 bpm increase								
Systolic BP, per 5mmHg increase								
Any cardiac medication			1.66 [0.86,3.18]	0.130	2.56 [1.12,5.83]	0.026		
Etiology:Reflex			0.03 [0.02,0.06]	<0.001	0.01 [0.01,0.04]	<0.001	0.20 [0.09,0.43]	<0.001
Etiology:Orthostatic			0.04 [0.02,0.07]	<0.001	0.04 [0.02,0.08]	<0.001	0.14 [0.06,0.34]	<0.001
Etiology:Others			0.04 [0.01,0.10]	<0.001	0.01 [0.00,0.10]	<0.001	0.21 [0.06,0.72]	0.013
Etiology:Unknown			0.13 [0.08,0.22]	<0.001	0.15 [0.08,0.28]	<0.001	0.41 [0.17,0.94]	0.036
Abnormal ECG			0.83 [0.58,1.19]	0.308	1.24 [0.80,1.91]	0.341		
Chest pain before the event								

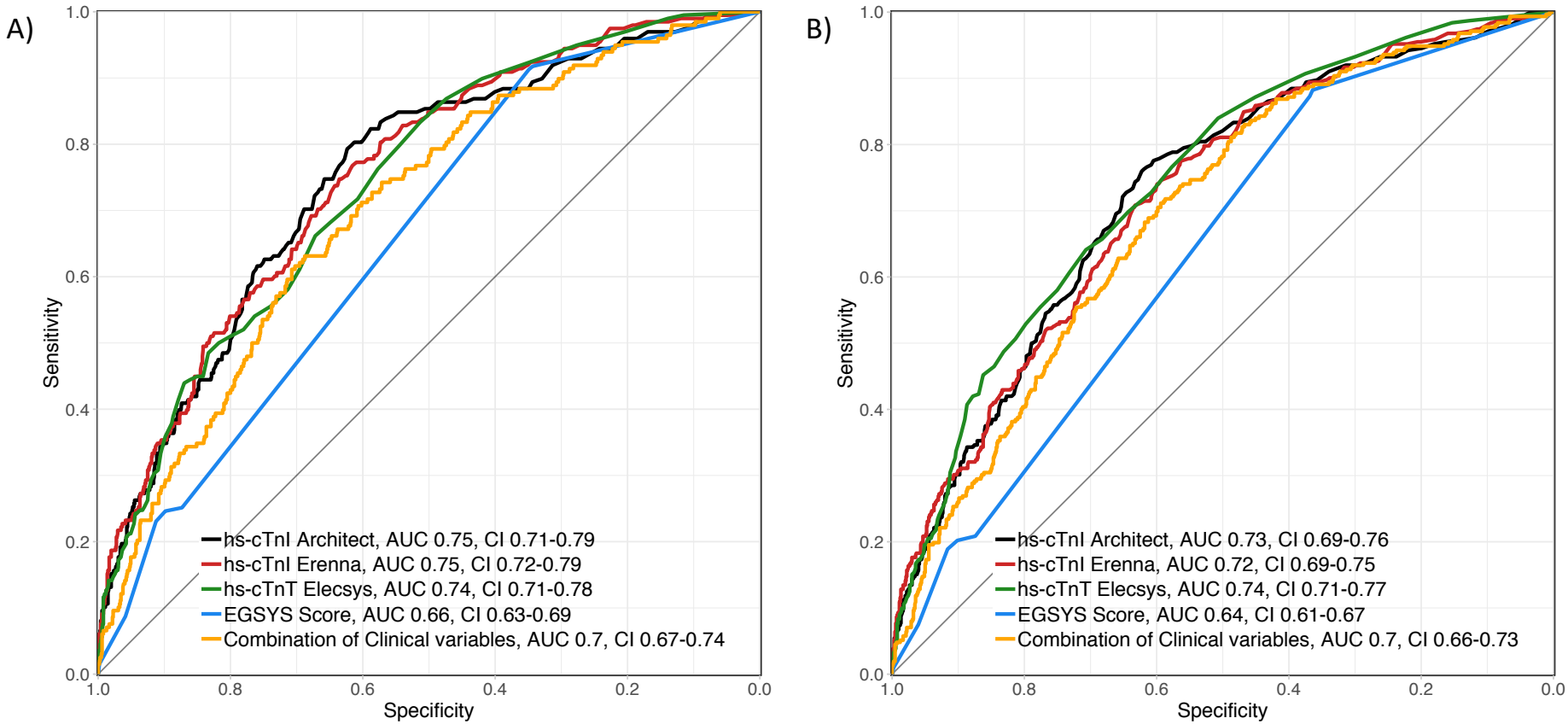
Supp Table 2A2) hs-cTnI Erenna	Death 5d		Overall MACE 5d		Arrhythmic MACE 5d		Ischemic MACE 5d	
	HR [95%CI]	p-val	HR [95%CI]	p-val	HR [95%CI]	p-val	HR [95%CI]	p-val
log hs-TnI, per 5ng/L increase	3.36 [1.68,6.75]	0.001	1.22 [1.01,1.47]	0.035	1.79 [1.44,2.22]	<0.001	1.17 [0.86,1.57]	0.318
Age			1.01 [0.99,1.03]	0.252	1.04 [1.02,1.06]	<0.001	1.01 [0.98,1.03]	0.570
Sex			1.33 [0.88,2.01]	0.170				
Known CV disease			1.91 [0.76,4.75]	0.167			2.38 [0.89,6.38]	0.084
Smoking status			1.43 [0.95,2.15]	0.083				
Hypertension			0.70 [0.41,1.19]	0.186				
Hypercholesterolemia								
Diabetes			1.42 [0.92,2.20]	0.110				
Heart rate, per 5 bpm increase								
Systolic BP, per 5mmHg increase								
Any cardiac medication			1.25 [0.56,2.80]	0.586				
Etiology:Reflex			0.02 [0.01,0.05]	<0.001			0.18 [0.08,0.40]	<0.001
Etiology:Orthostatic			0.03 [0.01,0.07]	<0.001			0.07 [0.02,0.23]	<0.001
Etiology:Others			0.02 [0.00,0.11]	<0.001			0.14 [0.03,0.61]	0.009
Etiology:Unknown			0.10 [0.05,0.22]	<0.001			0.23 [0.08,0.67]	0.007
Abnormal ECG			0.74 [0.47,1.14]	0.174				
Chest pain before the event								

Supp Table 2A3) hs-cTnT Elecsys	Death 720d		Overall MACE 720d		Arrhythmic MACE 720d		Ischemic MACE 720d	
	HR [95%CI]	p-val	HR [95%CI]	p-val	HR [95%CI]	p-val	HR [95%CI]	p-val
log hs-TnT, per 5ng/L increase	2.21 [1.72,2.83]	<0.001	1.57 [1.32,1.87]	<0.001	1.16 [0.96,1.40]	0.112	1.91 [1.54,2.36]	<0.001
Age	1.04 [1.02,1.06]	<0.001	1.02 [1.00,1.03]	0.008	1.01 [1.00,1.03]	0.071	1.03 [1.02,1.05]	<0.001
Sex	0.64 [0.40,1.03]	0.065	1.15 [0.87,1.51]	0.316	0.92 [0.66,1.27]	0.592	0.85 [0.58,1.25]	0.408
Known CV disease	1.13 [0.41,3.12]	0.813	1.18 [0.66,2.09]	0.583	1.39 [0.69,2.82]	0.359	1.57 [0.68,3.63]	0.287
Smoking status	1.38 [0.90,2.12]	0.146	1.32 [1.01,1.72]	0.039	1.25 [0.93,1.70]	0.145	1.79 [1.24,2.59]	0.002
Hypertension	0.98 [0.52,1.85]	0.952	0.70 [0.49,1.01]	0.060	0.75 [0.49,1.15]	0.191	1.00 [0.58,1.72]	0.993
Hypercholesterolemia			0.99 [0.76,1.29]	0.951	0.79 [0.59,1.07]	0.132		
Diabetes	1.30 [0.83,2.05]	0.248	1.28 [0.94,1.74]	0.112	1.21 [0.85,1.74]	0.290	1.50 [1.03,2.18]	0.032
Heart rate, per 5 bpm increase			0.96 [0.93,0.99]	0.007	0.93 [0.90,0.97]	<0.001		
Systolic BP, per 5mmHg increase			1.00 [0.97,1.02]	0.772	0.99 [0.96,1.02]	0.664		
Any cardiac medication	1.27 [0.54,2.96]	0.585	1.73 [1.04,2.88]	0.034	2.27 [1.20,4.29]	0.011	0.91 [0.47,1.75]	0.775
Etiology:Reflex	0.56 [0.29,1.08]	0.083	0.06 [0.04,0.10]	<0.001	0.05 [0.03,0.09]	<0.001	0.37 [0.22,0.63]	<0.001
Etiology:Orthostatic	1.08 [0.65,1.80]	0.776	0.10 [0.07,0.15]	<0.001	0.12 [0.08,0.18]	<0.001	0.55 [0.35,0.85]	0.008
Etiology:Others	1.03 [0.48,2.22]	0.931	0.10 [0.06,0.17]	<0.001	0.10 [0.05,0.19]	<0.001	0.64 [0.34,1.22]	0.177
Etiology:Unknown	1.38 [0.76,2.51]	0.285	0.20 [0.13,0.29]	<0.001	0.28 [0.18,0.43]	<0.001	0.76 [0.46,1.27]	0.295
Abnormal ECG	1.20 [0.76,1.91]	0.433	0.88 [0.66,1.17]	0.393	1.42 [1.00,2.00]	0.047	0.77 [0.53,1.11]	0.161
Chest pain before the event			1.41 [0.91,2.18]	0.122	0.62 [0.34,1.11]	0.108		

Supp Table 2A3) hs-cTnT Elecsys	Death 30d		Overall MACE 30d		Arrhythmic MACE 30d		Ischemic MACE 30d	
	HR [95%CI]	p-val	HR [95%CI]	p-val	HR [95%CI]	p-val	HR [95%CI]	p-val
log hs-TnT, per 5ng/L increase	3.02 [1.70,5.34]	<0.001	1.45 [1.19,1.78]	<0.001	0.89 [0.70,1.13]	0.325	1.62 [1.18,2.22]	0.003
Age	1.03 [0.97,1.08]	0.332	1.01 [0.99,1.02]	0.281	1.01 [0.99,1.02]	0.482	1.00 [0.98,1.02]	0.986
Sex			1.52 [1.10,2.10]	0.011	1.26 [0.85,1.85]	0.244		
Known CV disease			1.46 [0.72,2.94]	0.296	1.76 [0.74,4.18]	0.200	2.18 [0.89,5.38]	0.089
Smoking status			1.40 [1.01,1.94]	0.044	1.22 [0.83,1.79]	0.306		
Hypertension			0.57 [0.37,0.87]	0.009	0.55 [0.34,0.89]	0.014		
Hypercholesterolemia								
Diabetes			1.25 [0.86,1.80]	0.244	1.30 [0.84,2.01]	0.237		
Heart rate, per 5 bpm increase								
Systolic BP, per 5mmHg increase								
Any cardiac medication			1.75 [0.92,3.34]	0.090	2.54 [1.11,5.84]	0.028		
Etiology:Reflex			0.04 [0.02,0.07]	<0.001	0.01 [0.01,0.04]	<0.001	0.25 [0.11,0.54]	0.001
Etiology:Orthostatic			0.04 [0.02,0.07]	<0.001	0.04 [0.02,0.08]	<0.001	0.15 [0.06,0.37]	<0.001
Etiology:Others			0.04 [0.01,0.11]	<0.001	0.01 [0.00,0.10]	<0.001	0.25 [0.07,0.84]	0.026
Etiology:Unknown			0.13 [0.07,0.22]	<0.001	0.15 [0.08,0.29]	<0.001	0.44 [0.19,1.01]	0.054
Abnormal ECG			0.79 [0.55,1.13]	0.191	1.25 [0.81,1.94]	0.320		
Chest pain before the event								

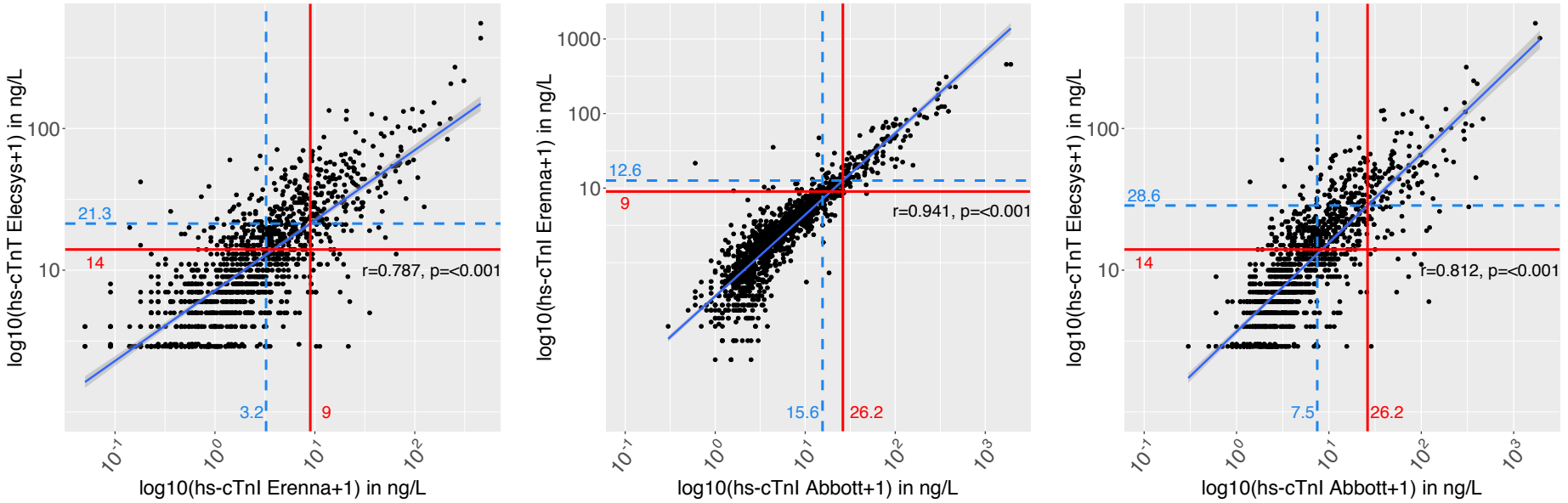
Supp Table 2A3) hs-cTnT Elecsys	Death 5d		Overall MACE 5d		Arrhythmic MACE 5d		Ischemic MACE 5d	
	HR [95%CI]	p-val	HR [95%CI]	p-val	HR [95%CI]	p-val	HR [95%CI]	p-val
log hs-TnT, per 5ng/L increase	4.35 [1.91,9.88]	<0.001	1.51 [1.19,1.91]	0.001	2.00 [1.55,2.58]	<0.001	1.62 [1.16,2.26]	0.005
Age			1.01 [0.99,1.02]	0.448	1.02 [1.00,1.04]	0.017	1.00 [0.97,1.02]	0.855
Sex			1.44 [0.96,2.16]	0.075				
Known CV disease			1.73 [0.69,4.30]	0.242			2.33 [0.87,6.23]	0.093
Smoking status			1.42 [0.95,2.14]	0.088				
Hypertension			0.69 [0.41,1.17]	0.168				
Hypercholesterolemia								
Diabetes			1.29 [0.84,2.00]	0.246				
Heart rate, per 5 bpm increase								
Systolic BP, per 5mmHg increase								
Any cardiac medication			1.37 [0.61,3.05]	0.443				
Etiology:Reflex			0.02 [0.01,0.06]	<0.001			0.22 [0.10,0.51]	<0.001
Etiology:Orthostatic			0.03 [0.01,0.07]	<0.001			0.08 [0.02,0.25]	<0.001
Etiology:Others			0.02 [0.00,0.12]	<0.001			0.17 [0.04,0.72]	0.016
Etiology:Unknown			0.10 [0.05,0.21]	<0.001			0.25 [0.09,0.73]	0.011
Abnormal ECG			0.70 [0.45,1.09]	0.112				
Chest pain before the event								

Supplemental figure 1



Supplemental Figure 1 – Sensitivity analysis for the diagnostic accuracy of the three cardiac troponin assays to detect cardiac syncope when A) all syncope adjudicated as unknown are classified as being of non-cardiac origin or B) when all syncope adjudicated as unknown are classified as being of cardiac origin.

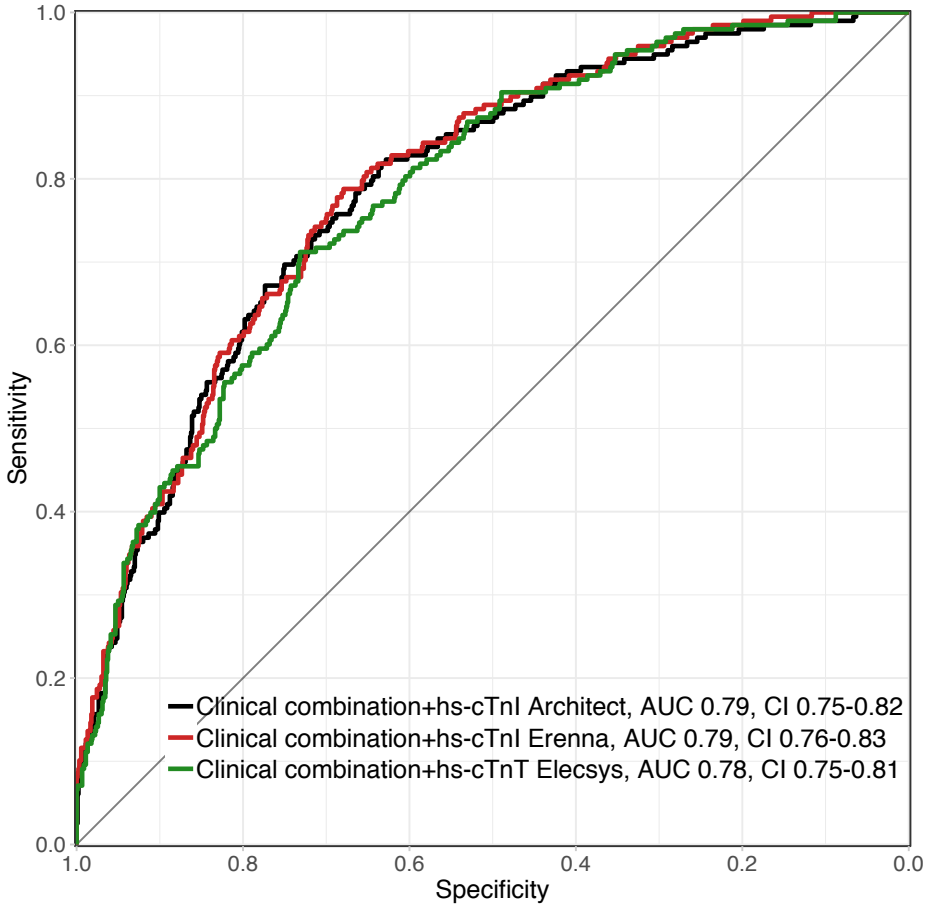
Supplemental figure 2



Supplemental figure 2 – Pearson correlations between the three logged troponin assays and the bioequivalent value of the 99th percentile (dotted blue line) for each assay, as predicted by the 99th percentile of one of the two other assays (red line).

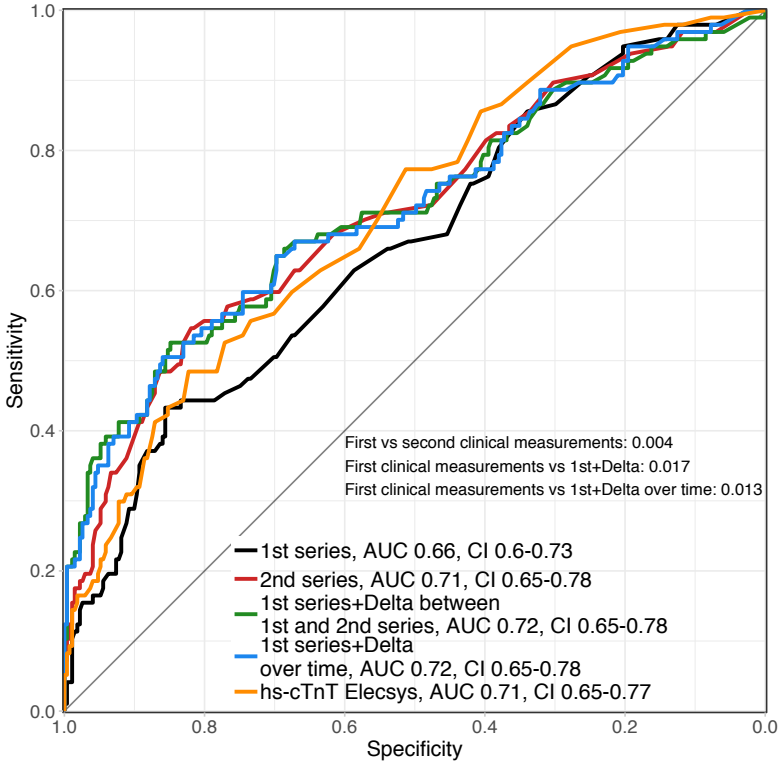
For instance, 7.5ng/L as given by the Architect hs-cTnI assay would be bioequivalent to 14ng/L for the Elecsys hs-cTnT assay (99th percentile for this assay) and 26.2ng/L of the Architect hs-cTnI assay (99th percentile for this assay) would be bioequivalent to 26.6ng/L of the Elecsys hs-cTnI assay.

Supplemental figure 3



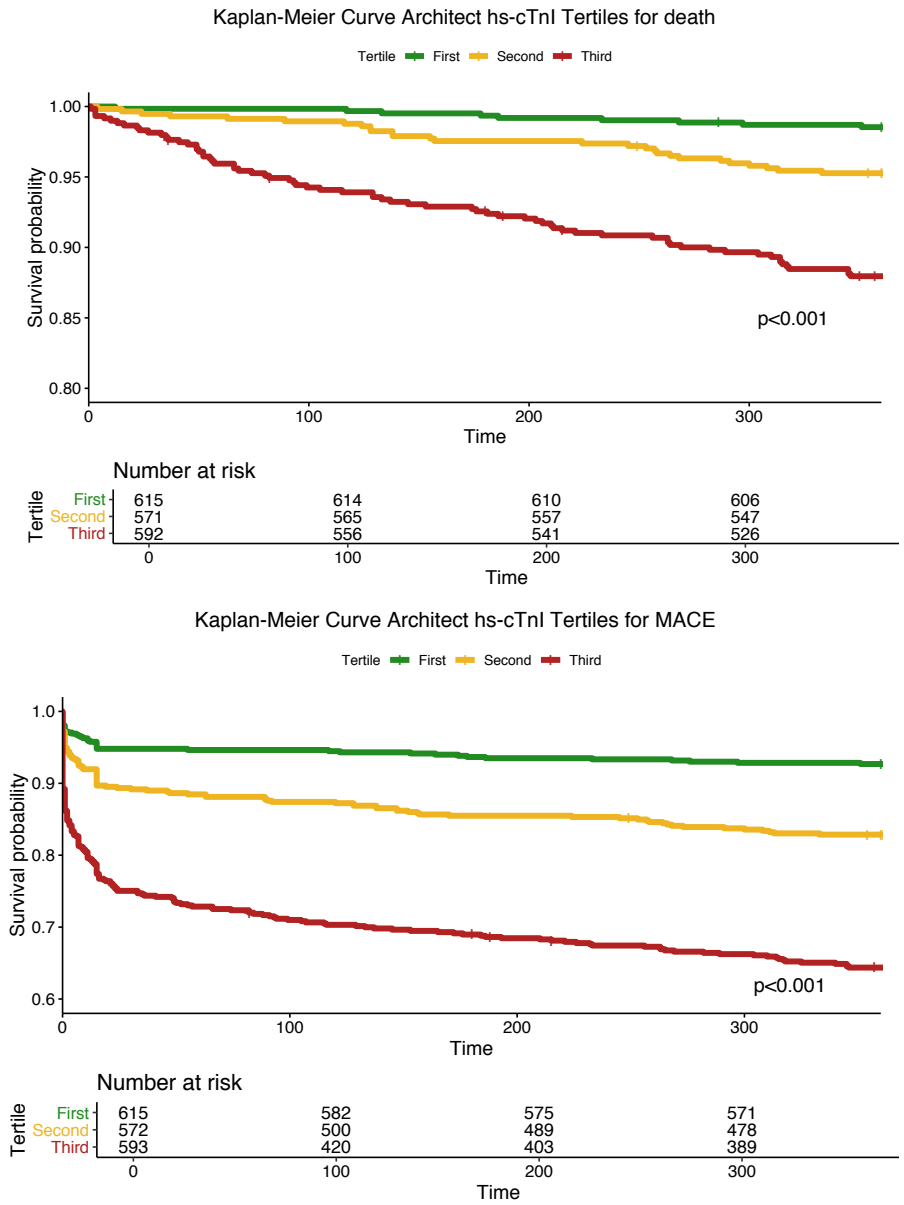
Supplemental Figure 3 – Diagnostic accuracy of the three hs-cTn assays in combination with a set of clinical variables to detect cardiac syncope. The clinical variables added to the model were : age, sex, presence or absence of a history of cardiovascular disease (myocardial infarction, coronary heart disease, stroke or transient ischemic attack, congestive heart failure, atrial fibrillation, and intermittent claudication), smoking status, presence or absence of hypertension, systolic blood pressure, presence or absence of diabetes, presence of hypercholesterolemia, heart rate, and use or nonuse of cardiac medication, including antihypertensive medications.

Supplemental figure 4



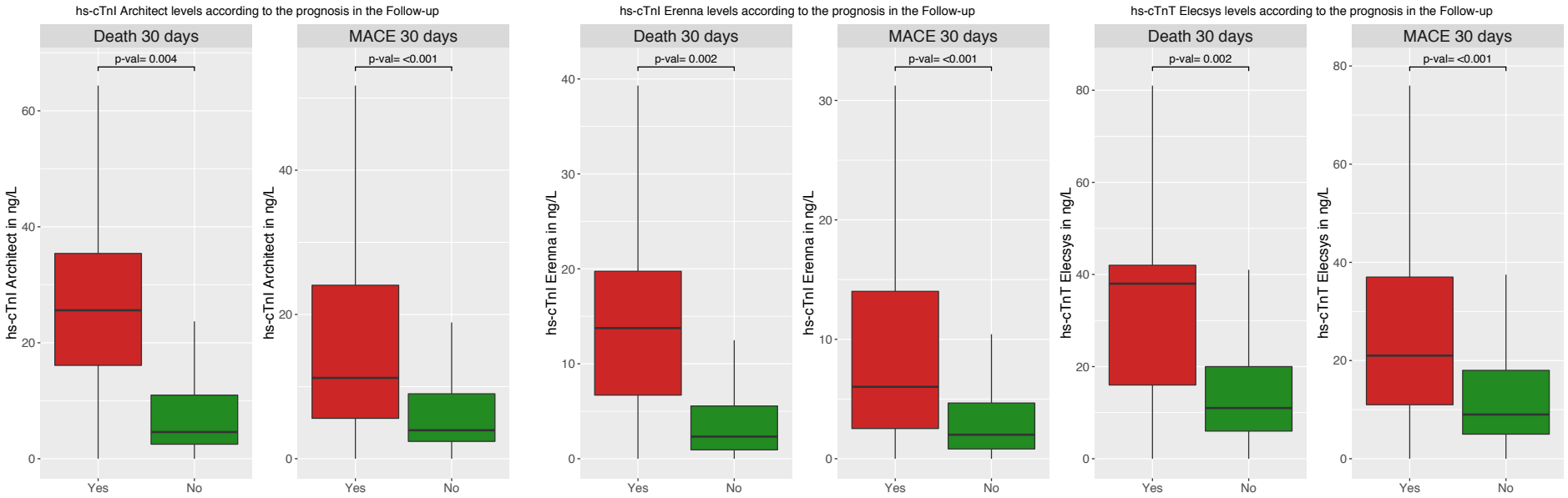
Supplemental figure 4 – Accuracy of the first and second clinical series of measurement of cTn, of the delta between the first and second series of measurement (Delta between the 1st and 2nd measurements) and of the delta over time for the diagnosis of cardiac syncope. Serial clinical cTn measurements were available in 368/1099 patients. As comparison, the accuracy of the Elecsys hs-cTnT assay in these patients is represented as well.

Supplemental figure 5



Supplemental figure 5 – Kaplan Meier representing the survival of patients for death and MACE according to Architect hs-cTnI tertiles (assay chosen as example).

Supplemental figure 6



Supplemental figure 6 – Boxplots representing the hs-cTn concentrations for each assay at 30-days depending on whether or not patients died or experienced MACE.

Discussion and outlook

The aim of this PhD Thesis was to contribute to the improvement of the diagnosis and risk-stratification of patients presenting to the ED following a syncopal event by assessing and validating important components of the initial ED evaluation in a large cohort study.

For more than ten years, several scores have been derived[5,17–22] to improve the evaluation of syncope on the ED but our cohort is the first one to assess the validity of all these scores in comparison.

Similarly, several small studies assessed the usefulness of BNP[5,79–81] or cardiac troponins[34,98,99] in syncope patients in the ED. Thanks to our stringent methodology, large sample size and the use of the most modern assays, we are able to contribute important novel insights to this topic.

Novel insights in the diagnosis of cardiac syncope in the emergency department.

Syncope Guidelines[1,4] emphasize the need for a detailed clinical history taking, a physical examination and the conduction of an ECG during initial patient evaluation. These components have been the cornerstones for the derivation of the several scores currently available for the diagnosis and risk stratification of syncope patients in the ED, which attempted to link important variables in their respective cohort to a diagnosis of cardiac syncope or an adverse outcome[5,17–22]. In our validation, most of these scores did not perform with the same accuracy than the one reached during original derivation and some non syncope-specific, readily calculable markers of morbidity (the $CHADS_2$ or CHA_2DS_2VASc Scores) performed equivalently for the prediction of death or MACE.

The poor performance of these scores in our cohort probably is explained by several issues. First, the monocentric character and lack of internationality of most of the original cohorts seems to be detrimental to the external validity of the derived scores. Indeed, assessment procedures but also patients' understanding of symptoms[113,114] are likely to be hospital and country-specific and do not seem to translate well across borders. Second, the small size of these cohorts and the possibly resulting lack of power could have led to incorrect inferences regarding the respective importance of the selected score components. Third, despite targeting similar important variables (such as past medical history or electrocardiographic abnormalities), the exact definition of these components was heterogenous between scores[58], which contributed to their varying diagnostic and prognostic accuracy. Further research on each specific step of the patient evaluation seems warranted to accurately define when these components have to be considered "abnormal".

Some of the underlying complexity associated with syncope evaluation is also linked with the partly subjective components assessed by the ED physician, the strong overlap of these components between syncope etiologies and the hospitals' specific assessment procedures. For instance, the patients' description and clinicians' understanding of prodromi strongly varies between individuals[113,114], hospitals and countries and moreover, their presence or absence is not pathognomonic for either cardiac or reflex syncope[115]. Similarly, physician education greatly varies between hospital and departments and leads to different diagnostic strategies.[8]

However, as highlighted in an Editorial[116] on the first manuscript of this thesis, all these scores targeted important and available variables: A thorough history of the syncopal event, the underlying comorbidities and a good physical examination undoubtedly provide valuable information about the underlying etiology and prognosis of syncope.

All available syncope-specific scores were based on an attempt to accurately model and then efficiently simplify the clinical evaluation for the emergency physician and to provide a structured and homogenous initial evaluation of syncope patients, a currently clearly unmet clinical need[1,4]. Despite the appeal of using a simple score to assess patients and the success of such an approach for other diseases in the ED (such as triage algorithms for myocardial infarctions[68]), reducing the complex evaluation of syncope patients to a sum of points appears to be an invalid oversimplification and current scores fail at providing important clues to the initial patient evaluation[116].

More developed statistical techniques and larger sample size seem to be required to accurately model an optimal assessment strategy for syncope in the ED. American guidelines already recognized the importance of emerging technologies, which imperatively need to be integrated in diagnostic and prognostic strategies.[4] Machine learning procedures for instance, were tentatively introduced in the diagnostic evaluation of syncope in the ED.[66] Despite the complexity of such models, they could easily be integrated in computer- or phone-based applications to efficiently function in an ED setting.

In order to rely on assessor-, structure- and patient-independent measures, more objective parameters such as biomarkers could play an essential role in the early evaluation of syncope patients on the ED. Indeed, cardiac biomarkers such as several cardiac troponin or BNP assays are currently readily available on many EDs and reflect important components of the patient's cardiac health, providing precious hints for diagnosis. Moreover, as observed in several other cardiac diseases or population-wide studies[74–76,109,117], blood concentrations of these biomarkers seem to be linked with short- and long-time prognosis in syncope patients.[5,13,34,79,80] The promising potential of these biomarkers in syncope has already been largely acknowledged[8,116] but whether these biomarkers should be used as screening tools or as guidance in specific patient populations has to be further investigated. Nevertheless, a definitive clinical utility of cardiac troponin and BNP is present in patients with no obvious syncope etiology following initial ED evaluation, where assay-specific cut-offs could inform the decision to admit patients and have a large impact on hospitalization reductions and cost savings.[8]

However, biomarkers still present some important drawbacks which need to be taken into account. First, as biomarkers gained in importance during the last years, pharmaceutical companies developed several different assays to measure the same molecule, with an increasing sensitivity coming along with each new assay. In an attempt to simplify diagnosis and care delivery, a binary notion of "normal" and "abnormal" was introduced for each of these assays. For cardiac troponins for instance, a 99th percentile cut-off, reflecting the upper reference limit of a normal, healthy reference population as well as the decision level for the diagnosis of myocardial infarction, was defined for each of the assay currently available. Debates have emerged on how this cut-off was defined, as lack of attention to this question might result in misleading medical decisions.[104,118] We effectively observed large differences in patients' classification when this

99th percentile was applied to our cohort, emphasizing the need for more homogenous definitions of abnormality. Second, false-positive cases could again lead to unnecessary diagnostic measures and the several non-cardiac diseases potentially leading to increased cardiac troponin concentrations[119] (such as chronic obstructive pulmonary diseases, endogenous antibodies, chronic muscle disorders or chronic renal failure) need to be taken into account and integrated in physicians' education.

Directions for future research

Both American[4] and European[1] Guidelines as well as previous expert consensus[58,120] emphasize the need for structured and accurate evaluation tools in the ED, thriving for the improvement of the diagnostic accuracy for cardiac syncope, correct prognostic prediction and reduction of unnecessary hospitalization.

The BASEL IX Syncope study displays several unique strengths: First, the adjudication used to determine the final diagnosis is extremely stringent and allows to reduce the rate of unknown syncope to a much lower rate than the one observed in other observational studies.[51] Second, the study design includes a follow-up up to five years, which will allow for important long-term inferences regarding prognosis. Third, all included patients underwent venous puncture and frozen blood samples are available for the measurements of potentially promising future biomarkers. Finally, this study displays an impressive international character, bolstering its external validity.

Syncope is a complex and heterogenous symptom and its successful evaluation can most likely only be achieved by models of equal complexity. The development of currently available diagnostic and risk-stratification tools has been subject to many flaws[8] (overfitting, mono-centric studies with lack of external validity, too small sample size, wrong modelling assumptions), which need to be addressed in future research. The idea of summarizing the most important data and variables to structure, simplify and accelerate the diagnostic process (and its prognostic implications) in the ED has been shown very efficient for other cardiovascular diseases[68] and stay an attractive and efficient option to achieve accurate and rapid care. Despite the recognized importance of patients history, results from the physical examination and electrocardiographic data, these components do not seem to have been modelled with sufficient precision for the correct assessment of syncope patients. Similarly, both biomarkers assessed in this thesis do not, on their own, have the accuracy to reliably rule-in or rule-out cardiac syncope or accurately predict prognosis. Moreover, summarizing continuous data in binary responses (such as "normal" or "abnormal" for biomarkers) might be an unreasonable simplification, which needs to be addressed by developing continuous estimates based on a large number of syncope patients. Therefore, new approaches based on more flexible models need to be developed and eventually integrated into readily-available technologies.

Contributions by the PhD student

I had the chance to be part of the BASEL IX Syncope Team for the whole time of my MD-PhD and contributed to data collection, patient recruitment, international study management, synchronisation of the adjudication of final diagnoses, ethics amendments, grants submissions, data management, database updates, computation of masterfiles and data analysis.

I benefited from the large infrastructure of the Cardiovascular Research Institute Basel (CRIB) and its incredible manpower, which both contributed to the large number of patients included in the database.

At the beginning of my PhD, I first learned about the project by recruiting patients in the ED, entering these data in the dedicated database and conducting follow-up. This very practical hands-on experience allowed me to later manage the team working for the study. Indeed, to insure a constant and excellent data quality, I could then efficiently train several team member in these tasks.

The multi-centric character of the study required a great amount of coordination work: Not only in Switzerland but also in our participating centers distributed over nine countries, several patients were enrolled each week. This led to several shipments of patient data and blood samples, asking for a collaborative synchronisation effort from our whole team.

All recruited patients received at least two (and sometimes three) adjudications of their final diagnosis by a seasoned team of physicians in our external centers and in the department of internal medicine and cardiology at the University Hospital of Basel, for which I ensured a timely coordination.

We quickly noticed that one of the main strength of the BASEL IX study could be emphasized by prolonging the follow-up. Such a modification in the protocol and in patients consent required me to submit an amendment not only to the respective Swiss ethics boards, but also internationally and separately for each external center.

I wrote and submitted several grants to participate in the financing of the Syncope Study during my time, such as grants for the PPHS and the Swiss Heart Foundation. I also participated to the submission of a large and approved SNF-grant. Writing grants provided me with supplementary skills in study planning, budgeting and project development.

Data management and database updates also represented an important part of my work at the CRIB. External centers use similar databases, and require regular synchronisation with the main database in Basel. For the purpose of specific projects or data cleaning, variables had to be updated and reprogrammed regularly. To allow for analyses, data needed to be cleaned and extracted from the main database to create a Masterfile. I developed an exhaustive computing code to allow for automatic and rapid generation of these files.

Last but not least, I learned essential components of data analysis: Writing a data-analysis plan, conducting and computing statistical analyses, presenting results in tables and graphics, summarizing and discussing them. Thanks to the precious help and patience of several collaborators inside (Patrick Badertscher, Christian Puelacher, Ivo Strebel, Joan Walter, Tobias Zimmermann) and outside of the CRIB (Michael Coslovsky, Clara Sailer), my computing and statistical abilities rapidly improved and allowed for the timely redaction of the three manuscript submitted in this work.

Teaching is an important component of our everyday life at the CRIB. I could particularly benefit from teaching by other PhD students and post-docs upon my arrival and have later transmitted my knowledge to subsequent colleagues, post-docs, doctoral and master students.

A second important project marked my time at the CRIB : I designed, with the help of Professor Müller and collaborators of the department of Neurology and Rheumatology, a prospective study assessing cardiac troponin levels in patients with musculoskeletal diseases, which is currently enrolling patients. Starting a study from the very beginning brought me further valuable and essential insights in study design, database development, team leading and the importance of interdisciplinary projects.

Conclusion and closing remarks

This MD-PhD Thesis represents a part of the large effort of our group to improve the diagnosis of syncope on the ED, a currently recognized unmet clinical need. In our large cohort, we could observe that the diagnosis and risk-stratification of these patients is challenging and is hardly well modelled by comprehensive summaries of clinical variables. With growing utilization of biomarkers in the ED, a better assessment using BNP or cardiac troponins could be reached in patients with no obvious syncope etiology upon ED admission. Future research needs to investigate new assessment strategies englobing more variables and making best use of new technologies for their practical implementation.

References

[1] Brignole M, Moya A, de Lange FJ, Deharo J-C, Elliott PM, Fanciulli A, et al. 2018 ESC Guidelines for the diagnosis and management of syncope. Eur Heart J 2018:1–69. doi:10.1093/eurheartj/ehy037.

[2] Baron-Esquivias G, Martínez-Alday J, Martín A, Moya A, García-Civera R, Paz López-Chicharro M, et al. Epidemiological characteristics and diagnostic approach in patients admitted to the emergency room for transient loss of consciousness: Group for Syncope Study in the Emergency Room (GESINUR) study. Europace 2010;12:869–876. doi:10.1093/europace/euq018.

[3] Hatoum T, Sheldon R. A practical approach to investigation of syncope. Can J Cardiol 2014;30:671–674. doi:10.1016/j.cjca.2014.03.043.

[4] Shen W-K, Sheldon RS, Benditt DG, Cohen MI, Forman DE, Goldberger ZD, et al. 2017 ACC/AHA/HRS Guideline for the Evaluation and Management of Patients With Syncope: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation 2017;136:e60–e122. doi:10.1161/CIR.0000000000000499.

[5] Reed MJ, Newby DE, Coull AJ, Prescott RJ, Jacques KG, Gray AJ. The ROSE (Risk Stratification of Syncope in the Emergency Department) Study. J Am Coll Cardiol 2010;55:713–721. doi:10.1016/j.jacc.2009.09.049.

[6] Sun BC, Costantino G, Barbic F, Bossi I, Casazza G, Dipaola F, et al. Priorities for Emergency Department Syncope Research. Ann Emerg Med 2014;64:649–655.e2. doi:10.1016/j.annemergmed.2014.04.014.

[7] Thiruganasambandamoorthy V, Stiell IG, Sivilotti ML a, Murray H, Rowe BH, Lang E, et al. Risk stratification of adult emergency department syncope patients to predict short-term serious outcomes after discharge (RiSEDS) study. BMC Emerg Med 2014;14:8. doi:10.1186/1471-227X-14-8.

[8] Numeroso F, Mossini G, Lippi G, Cervellin G. Syncope: current knowledge, uncertainties and strategies for management optimisation in the emergency department. Acta Cardiol 2018;73:215–221. doi:10.1080/00015385.2017.1362146.

[9] da Silva RMFL. Syncope: epidemiology, etiology, and prognosis. Front Physiol 2014;5:471. doi:10.3389/fphys.2014.00471.

[10] Yasa E, Ricci F, Magnusson M, Sutton R, Gallina S, De Caterina R, et al. Cardiovascular risk after hospitalisation for unexplained syncope and orthostatic hypotension. Heart 2018;104:487–493. doi:10.1136/heartjnl-2017-311857.

[11] D'Ascenzo F, Biondi-Zoccai G, Reed MJ, Gabayan GZ, Suzuki M, Costantino G, et al. Incidence, etiology and predictors of adverse outcomes in 43,315 patients presenting to the Emergency Department with syncope: An international meta-analysis. Int J Cardiol 2013;167:57–62. doi:10.1016/j.ijcard.2011.11.083.

[12] Rosanio S, Schwarz ER, Ware DL, Vitarelli A. Syncope in adults: Systematic review and proposal of a diagnostic and therapeutic algorithm. Int J Cardiol 2013;162:149–157. doi:10.1016/j.ijcard.2011.11.021.

[13] Thiruganasambandamoorthy V, Kwong K, Wells GA, Sivilotti MLA, Mukarram M, Mph M, et al. Development of the Canadian Syncope Risk Score to predict serious adverse events after emergency department assessment of syncope. Can J Emerg Med 2016;188:1–10. doi:10.1503/cmaj.151469/-/DC1.

[14] Quinn J, McDermott D, Kramer N, Yeh C, Kohn MA, Stiell I, et al. Death After Emergency Department Visits for Syncope: How Common and Can It Be Predicted? Ann Emerg Med 2008;51:585–590. doi:10.1016/j.annemergmed.2007.08.005.

[15] Abulhamayel A, Savu A, Sheldon RS, Kaul P, Sandhu RK. Geographical Differences in Comorbidity Burden and Outcomes in Adults With Syncope Hospitalizations in Canada. Can J Cardiol 2018;34:937–940. doi:10.1016/j.cjca.2018.04.011.

[16] Bartoletti A, Fabiani P, Adriani P, Baccetti F, Bagnoli L, Buffini G, et al. Hospital admission of patients referred to the Emergency Department for syncope: a single-hospital prospective study based on the application of the European Society of Cardiology Guidelines on syncope. Eur Heart J 2006;27:83–88. doi:10.1093/eurheartj/ehi474.

[17] Del Rosso A, Ungar A, Maggi R, Giada F, Petix NR, De Santo T, et al. Clinical predictors of cardiac syncope at initial evaluation in patients referred urgently to a general hospital: the EGSYS score. Heart 2008;94:1620–1626. doi:10.1136/hrt.2008.143123.

[18] Colivicchi F, Ammirati F, Melina D, Guido V, Imperoli G, Santini M. Development and prospective validation of a risk stratification system for patients with syncope in the emergency department: The OESIL risk score. Eur Heart J 2003;24:811–819. doi:10.1016/S0195-668X(02)00827-8.

[19] Quinn J V, Stiell IG, McDermott DA, Sellers KL, Kohn MA, Wells GA. Derivation of the San Francisco Syncope Rule to predict patients with short-term serious outcomes. Ann Emerg Med 2004;43:224–232. doi:10.1016/S0196064403008230.

[20] Martin TP, Hanusa BH, Kapoor WN. Risk Stratification of Patients With Syncope. Ann Emerg Med 1997;29:459–466. doi:10.1016/S0196-0644(97)70217-8.

[21] Shamai A. Grossman, Fischer C, Lipsitz LA, Mottley L, Sands K, Thompson S, et al. Predicting adverse outcomes in Syncope. J Emerg Med 2007. doi:10.1016/j.jemermed.2007.04.001.PREDICTING.

[22] Costantino G, Perego F, Dipaola F, Borella M, Galli A, Cantoni G, et al. Short- and Long-Term Prognosis of Syncope, Risk Factors, and Role of Hospital Admission. Results From the STePS (Short-Term Prognosis of Syncope) Study. J Am Coll Cardiol 2008;51:276–283. doi:10.1016/j.jacc.2007.08.059.

[23] Quinn J, McDermott D, Stiell I, Kohn M, Wells G. Prospective Validation of the San Francisco Syncope Rule to Predict Patients With Serious Outcomes. Ann Emerg Med 2006;47:448–454. doi:10.1016/j.annemergmed.2005.11.019.

[24] Kariman H, Harati S, Safari S, Baratloo A, Pishgahi M. Validation of EGSYS Score in Prediction of Cardiogenic Syncope. Emerg Med Int 2015;2015:2–7. doi:10.1155/2015/515370.

[25] Numeroso F, Mossini G, Spaggiari E, Cervellin G. Syncope in the emergency department of a large northern Italian hospital: Incidence, efficacy of a short-stay observation ward and validation of the OESIL risk score. Emerg Med J 2010;27:653–658. doi:10.1136/emj.2009.077701.

[26] Sun BC, Mangione CM, Merchant G, Weiss T, Shlamovitz GZ, Zargaraff G, et al. External validation of the San Francisco Syncope Rule. Ann Emerg Med 2007;49:420–427, 427.e1-4. doi:10.1016/j.annemergmed.2006.11.012.

[27] Twerenbold R, Boeddinghaus J, Nestelberger T, Wildi K, Rubini Gimenez M, Badertscher P, et al. Clinical Use of High-Sensitivity Cardiac Troponin in Patients With Suspected Myocardial Infarction. J Am Coll Cardiol 2017;70:996–1012. doi:10.1016/j.jacc.2017.07.718.

[28] Mueller C. Happy birthday BNP. Eur Hear J Acute Cardiovasc Care 2012;1:109–110. doi:10.1177/2048872612447143.

[29] Maisel A, Mueller C, Adams K, Anker SD, Aspromonte N, Cleland JGF, et al. State of the art: Using natriuretic peptide levels in clinical practice. Eur J Heart Fail 2008;10:824–839. doi:10.1016/j.ejheart.2008.07.014.

[30] Peeters S., Hoek A., Mollink S. HJ. Syncope : Risk Stratification And Clinical Decision Making. EB Med 2014:1–24.

[31] Thygesen K, Mair J, Mueller C, Huber K, Weber M, Plebani M, et al. Recommendations for the use of natriuretic peptides in acute cardiac care: A position statement from the Study Group on Biomarkers in Cardiology of the ESC Working Group on Acute Cardiac Care. Eur Heart J 2012;33:2001–2006. doi:10.1093/eurheartj/ehq509.

[32] Jeremias A, Gibson CM. Alternative Causes for Elevated Cardiac Troponin. Ann Intern Med 2005;142:786–791.

[33] Reed MJ, Newby DE, Coull AJ, Prescott RJ, Gray AJ. Diagnostic and prognostic utility of troponin estimation in patients presenting with syncope: a prospective cohort study. Emerg Med J 2010;27:272–276. doi:10.1136/emj.2008.068635.

[34] Sun BC, Derose SF, Liang LJ, Gabayan GZ, Hoffman JR, Moore AA, et al. Predictors of 30-Day Serious Events in

Older Patients With Syncope. Ann Emerg Med 2009;54:769–778.e5. doi:10.1016/j.annemergmed.2009.07.027.

[35] Reed MJ, Mills NL, Weir CJ. Sensitive troponin assay predicts outcome in syncope. Emerg Med J 2012;17:1001–1003. doi:10.1136/emermed-2012-201332.

[36] Thygesen K, Mair J, Mueller C, Huber K, Weber M, Plebani M, et al. Recommendations for the use of natriuretic peptides in acute cardiac care: A position statement from the Study Group on Biomarkers in Cardiology of the ESC Working Group on Acute Cardiac Care. Eur Heart J 2010;33:2001–2006. doi:10.1093/eurheartj/ehq509.

[37] Hall C. Essential biochemistry and physiology of (NT-pro)BNP. Eur J Heart Fail 2004;6:257–260. doi:10.1016/j.ejheart.2003.12.015.

[38] Zakynthinos E, Kiropoulos T, Gourgoulianis K, Filippatos G. Diagnostic and prognostic impact of brain natriuretic peptide in cardiac and noncardiac diseases. Heart Lung 2008;37:275–285. doi:10.1016/j.hrtlng.2007.05.010.

[39] Thygesen K, Mair J, Mueller C, Huber K, Weber M, Plebani M, et al. Recommendations for the use of natriuretic peptides in acute cardiac care: A position statement from the Study Group on Biomarkers in Cardiology of the ESC Working Group on Acute Cardiac Care. Eur Heart J 2012;33:2001–2006. doi:10.1093/eurheartj/ehq509.

[40] Vanderheyden M, Bartunek J, Goethals M. Brain and other natriuretic peptides: molecular aspects. Eur J Heart Fail 2004;6:261–268. doi:10.1016/j.ejheart.2004.01.004.

[41] Stryjewski PJ, Nessler B, Kuczaj A, Matusik P, Gilowski W, Nowak J, et al. The role of NT-proBNP in the diagnostics and differentiation of cardiac and reflex syncope in adults: relative importance to clinical presentation and medical examinations. J Interv Card Electrophysiol 2014;41:1–8. doi:10.1007/s10840-014-9923-x.

[42] Pfister R, Hagemeister J, Esser S, Hellmich M, Erdmann E, Schneider C a. NT-pro-BNP for diagnostic and prognostic evaluation in patients hospitalized for syncope. Int J Cardiol 2012;155:268–272. doi:10.1016/j.ijcard.2010.10.013.

[43] Costantino G, Solbiati M, Casazza G, Bonzi M, Vago T, Montano N, et al. Usefulness of N-Terminal Pro-B-Type natriuretic peptide increase as a marker for cardiac arrhythmia in patients with syncope. Am J Cardiol 2014;113:98–102. doi:10.1016/j.amjcard.2013.08.044.

[44] Geske JB, McKie PM, Ommen SR, Sorajja P. B-type natriuretic peptide and survival in hypertrophic cardiomyopathy. J Am Coll Cardiol 2013;61:2456–2460. doi:10.1016/j.jacc.2013.04.004.

[45] Ishimitsu T, Ono H, Minami J, Matsuoka H. Pathophysiologic and therapeutic implications of adrenomedullin in cardiovascular disorders. Pharmacol Ther 2006;111:909–927. doi:10.1016/j.pharmthera.2006.02.004.

[46] Behnes M, Papassotiriou J, Walter T, Fiedler E, Sauer T, Lang S, et al. Long-term prognostic value of mid-regional pro-adrenomedullin and C-terminal pro-endothelin-1 in patients with acute myocardial infarction. Clin Chem Lab Med 2008;46:204–211. doi:10.1515/CCLM.2008.040.

[47] Pedowska-Włoszek J, Kostrubiec M, Kurnicka K, Ciurzynski M, Palczewski P, Pruszczyk P. Midregional proadrenomedullin (MR-proADM) in the risk stratification of patients with acute pulmonary embolism. Thromb Res 2013;132:506–510. doi:10.1016/j.thromres.2013.08.008.

[48] Elmas E, Doesch C, Fluechter S, Freundt M, Weiss C, Lang S, et al. Midregional pro-atrial natriuretic peptide: a novel marker of myocardial fibrosis in patients with hypertrophic cardiomyopathy. Int J Cardiovasc Imaging 2011;27:547–556. doi:10.1007/s10554-010-9704-2.

[49] Vass a., Süveges G, Érces D, Nógrády M, Varga G, Földesi I, et al. Inflammatory activation after experimental cardiac tamponade. Eur Surg Res 2013;51:1–13. doi:10.1159/000352089.

[50] Moya A, Sutton R, Ammirati F, Blanc JJ, Brignole M, Dahm JB, et al. Guidelines for the diagnosis and management of syncope (version 2009). Eur Heart J 2009;30:2631–2671. doi:10.1093/eurheartj/ehp298.

[51] Soteriades ES, Evans JC, Larson MG, Chen MH, Chen L, Benjamin EJ, et al. Incidence and prognosis of syncope. N Engl J Med 2002;347:878–885. doi:10.1056/NEJMoa012407.

[52] Kapoor WN, Karpf M, Wieand S, Peterson JR, Levey GS. A prospective evaluation and follow-up of patients with syncope. N Engl J Med 1983;309:197–204. doi:10.1056/NEJM198307283090401.

[53] Brignole M, Menozzi C, Bartoletti A, Giada F, Lagi A, Ungar A, et al. A new management of syncope: Prospective systematic guideline-based evaluation of patients referred urgently to general hospitals. Eur Heart J 2006;27:76–82. doi:10.1093/eurheartj/ehi647.

[54] Shen W-K, Sheldon RS, Benditt DG, Cohen MI, Forman DE, Goldberger ZD, et al. 2017 ACC/AHA/HRS Guideline for the Evaluation and Management of Patients With Syncope: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, and the Heart Rhythm Society. Circulation 2017:CIR.0000000000000499. doi:10.1161/CIR.0000000000000499.

[55] Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of Clinical Classification Schemes Results From the National Registry of Atrial Fibrillation. Jama 2001;285:2864–2870.

[56] Ruwald MH, Ruwald AC, Jons C, Lamberts M, Hansen ML, Vinther M, et al. Evaluation of the CHADS2 risk score on short- and long-term all-cause and cardiovascular mortality after syncope. Clin Cardiol 2013;36:262–268. doi:10.1002/clc.22102.

[57] Costantino G, Casazza G, Reed M, Bossi I, Sun B, Del Rosso A, et al. Syncope risk stratification tools vs clinical judgment: an individual patient data meta-analysis. Am J Med 2014;127:1126.e13-25. doi:10.1016/j.amjmed.2014.05.022.

[58] Costantino G, Sun BC, Barbic F, Bossi I, Casazza G, Dipaola F, et al. Syncope clinical management in the emergency department: a consensus from the first international workshop on syncope risk stratification in the emergency department. Eur Heart J 2015:ehv378. doi:10.1093/eurheartj/ehv378.

[59] Ruwald AC, Gang U, Thomsen PEB, J??rgensen RM, Ruwald MH, Huikuri H V., et al. The predictive value of CHADS2 risk score in post myocardial infarction arrhythmias - A Cardiac Arrhythmias and RIsk Stratification after Myocardial infArction (CARISMA) substudy. Int J Cardiol 2014;173:441–446. doi:10.1016/j.ijcard.2014.03.010.

[60] Lu D-Y, Huang C-C, Huang P-H, Chen J-W, Chen T-J, Lin S-J, et al. Usefulness of the CHADS2 Score for Prognostic Stratification in Patients With Coronary Artery Disease Having Coronary Artery Bypass Grafting. Am J Cardiol 2017;119:839–844. doi:10.1016/j.amjcard.2016.11.035.

[61] Huang F-Y, Huang B-T, Pu X-B, Yang Y, Chen S-J, Xia T-L, et al. CHADS2, CHA2DS2-VASc and R2CHADS2 scores predict mortality in patients with coronary artery disease. Intern Emerg Med 2017;12:479–486. doi:10.1007/s11739-017-1608-x.

[62] Huang SS, Chen YH, Chan WL, Huang PH, Chen JW, Lin SJ. Usefulness of the CHADS2 score for prognostic stratification of patients with acute myocardial infarction. Am J Cardiol 2014;114:1309–1314. doi:10.1016/j.amjcard.2014.07.063.

[63] Cetin M, Cakici M, Zencir C, Tasolar H, Baysal E, Balli M, et al. Prediction of coronary artery disease severity using CHADS2 and CHA2DS2-VASc scores and a newly defined CHA 2DS2-VASc-HS score. Am J Cardiol 2014;113:950–956. doi:10.1016/j.amjcard.2013.11.056.

[64] Richardson S, Khan S, McCullagh L, Kline M, Mann D, McGinn T. Healthcare provider perceptions of clinical prediction rules. BMJ Open 2015;5:e008461. doi:10.1136/bmjopen-2015-008461.

[65] Sarazin M, Chiappe SG, Kasprzyk M, Mismetti P, Lasserre A. A survey of French general practitioners and a qualitative study on their use and assessment of predictive clinical scores. Int J Gen Med 2013;6:419–426. doi:10.2147/IJGM.S39022.

[66] Costantino G, Falavigna G, Solbiati M, Casagranda I, Sun BC, Grossman SA, et al. Neural networks as a tool to predict syncope risk in the Emergency Department. Europace 2017;19:1891–1895. doi:10.1093/europace/euw336.

[67] Reichlin T, Cullen L, Parsonage W a, Greenslade J, Twerenbold R, Moehring B, et al. Two-hour Algorithm for Triage Toward Rule-out and Rule-in of Acute Myocardial Infarction Using High-sensitivity Cardiac Troponin T. Am J Med 2014. doi:10.1016/j.amjmed.2014.10.032.

[68] Rubini Gimenez M, Twerenbold R, Jaeger C, Schindler C, Puelacher C, Wildi K, et al. One-hour Rule-in and Rule-out of Acute Myocardial Infarction Using High-sensitivity Cardiac Troponin I. Am J Med 2015. doi:10.1016/j.amjmed.2015.01.046.

[69] Reichlin T, Twerenbold R, Wildi K, Rubini Gimenez M, Bergsma N, Haaf P, et al. Prospective validation of a 1-hour algorithm to rule-out and rule-in acute myocardial infarction using a high-sensitivity cardiac troponin T assay. CMAJ 2015;187:E243–E252. doi:10.1503/cmaj.141349.

[70] Chapman AR, Lee KK, McAllister DA, Cullen L, Greenslade JH, Parsonage W, et al. Association of high-sensitivity cardiac troponin I concentration with cardiac outcomes in patients with suspected acute coronary syndrome. JAMA - J Am Med Assoc 2017;318:1913–1924. doi:10.1001/jama.2017.17488.

[71] Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, et al. Early Diagnosis of Myocardial Infarction with Sensitive Cardiac Troponin Assays. N Engl J Med 2009;361:858–867. doi:10.1056/NEJMoa0900428.

[72] Mueller C, Scholer A, Laule-Kilian K, Martina B, Schindler C, Buser P, et al. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. N Engl J Med 2004;350:647–654. doi:10.1056/NEJMoa031681.

[73] Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Eur Heart J 2012;33:2551–2567. doi:10.1093/eurheartj/ehs184.

[74] Levine YC, Rosenberg MA, Mittleman M, Samuel M, Methachittiphan N, Link M, et al. B-type natriuretic peptide is a major predictor of ventricular tachyarrhythmias. Hear Rhythm 2014;11:1109–1116. doi:10.1016/j.hrthm.2014.04.024.

[75] Simon T, Becker R, Voss F, Bikou O, Hauck M, Licka M, et al. Elevated B-type natriuretic peptide levels in patients with nonischemic cardiomyopathy predict occurrence of arrhythmic events. Clin Res Cardiol 2008;97:306–309. doi:10.1007/s00392-007-0629-2.

[76] Christ M, Laule-Kilian K, Hochholzer W, Klima T, Breidthardt T, Perruchoud AP, et al. Gender-Specific Risk Stratification With B-Type Natriuretic Peptide Levels in Patients With Acute Dyspnea. Insights From the B-type Natriuretic Peptide for Acute Shortness of Breath Evaluation Study. J Am Coll Cardiol 2006;48:1808–1812. doi:10.1016/j.jacc.2006.07.037.

[77] Wang K, Asinger RW, Marriott HJL. ST-Segment Elevation in Conditions Other Than Acute Myocardial Infarction. N Engl J Med 2003;349:2128–2135. doi:10.1056/NEJMra022580.

[78] Mueller C, Scholer A, Laule-Kilian K, Martina B, Schindler C, Buser P, et al. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. N Engl J Med 2004;350:647–654. doi:10.1056/NEJMoa031681.

[79] Tanimoto K, Yukiiri K, Mizushige K, Takagi Y, Masugata H, Shinomiya K, et al. Usefulness of brain natriuretic peptide as a marker for separating cardiac and noncardiac causes of syncope. Am J Cardiol 2004;93:228–230. doi:10.1016/j.amjcard.2003.09.048.

[80] Isbitan A, Hawatmeh A, Elnahar Y, Patel K, Altheeb Z, Debari V, et al. Utility of brain natriuretic peptide assay as a predictor of short term outcomes in patients presenting with syncope to the emergency department. Cardiovasc Diagn Ther 2016;6:234–240. doi:10.21037/cdt.2016.03.06.

[81] Pfister R, Diedrichs H, Larbig R, Erdmann E, Schneider CA. NT-pro-BNP for differential diagnosis in patients with syncope. Int J Cardiol 2009;133:51–54. doi:10.1016/j.ijcard.2007.11.082.

[82] Badertscher P, Nestelberger T, de Lavallaz JF, Than M, Morawiec B, Kawecki D, et al. Prohormones in the early diagnosis of cardiac syncope. J Am Heart Assoc 2017;6. doi:10.1161/JAHA.117.006592.

[83] Tamm NN, Seferian KR, Semenov AG, Mukharyamova KS, Koshkina E V., Krasnoselsky MI, et al. Novel

immunoassay for quantification of brain natriuretic peptide and its precursor in human blood. Clin Chem 2008;54:1511–1518. doi:10.1373/clinchem.2007.100545.

[84] Morgenthaler NG, Struck J, Thomas B, Bergmann A. Immunoluminometric Assay for the Midregion of Pro-Atrial Natriuretic Peptide in Human Plasma. Clin Chem 2004;50:234–236. doi:10.1373/clinchem.2003.021204.

[85] Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Circulation 2012;126:2020–2035. doi:10.1161/CIR.0b013e31826e1058.

[86] Delong ER, Delong DM, Clarke-pearson DL, Carolina N. Comparing the Areas under Two or More Correlated Receiver Operating Characteristic Curves : A Nonparametric Approach Published by : International Biometric Society Stable URL : http://www.jstor.org/stable/2531595 REFERENCES Linked references are available 2016;44:837–845.

[87] Agresti A, Caffo B. Simple and Effective Confidence Intervals for Proportions and Differences of Proportions Result from Adding Two Successes and Two Failures. Am Stat 2000;54:280–288.

[88] Blanche P, Dartigues JF, Jacqmin-Gadda H. Estimating and comparing time-dependent areas under receiver operating characteristic curves for censored event times with competing risks. Stat Med 2013;32:5381–5397. doi:10.1002/sim.5958.

[89] Reed MJ, Gibson L. The effect of syncope on brain natriuretic peptide. Emerg Med J 2011;28:1066–1067. doi:10.1136/emj.2010.106955.

[90] Clavel MA, Malouf J, Michelena HI, Suri RM, Jaffe AS, Mahoney DW, et al. B-type natriuretic peptide clinical activation in aortic stenosis: Impact on long-term survival. J Am Coll Cardiol 2014;63:2016–2025. doi:10.1016/j.jacc.2014.02.581.

[91] Richards M, Di Somma S, Mueller C, Nowak R, Peacock WF, Ponikowski P, et al. Atrial fibrillation impairs the diagnostic performance of cardiac natriuretic peptides in dyspneic patients: Results from the BACH study (Biomarkers in ACute Heart Failure). JACC Hear Fail 2013;1:192–199. doi:10.1016/j.jchf.2013.02.004.

[92] Scott PA, Barry J, Roberts PR, Morgan JM. Brain natriuretic peptide for the prediction of sudden cardiac death and ventricular arrhythmias: A meta-analysis. Eur J Heart Fail 2009;11:958–966. doi:10.1093/eurjhf/hfp123.

[93] Scally B, Emberson JR, Spata E, Reith C, Davies K, Halls H, et al. Effects of gastroprotectant drugs for the prevention and treatment of peptic ulcer disease and its complications: a meta-analysis of randomised trials. Lancet Gastroenterol Hepatol 2018;3:231–241. doi:10.1016/S2468-1253(18)30037-2.

[94] Peduzzi P, Concato J, Kemper E, Holford TR, Feinstem AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 1996;49:1373–1379. doi:10.1016/S0895-4356(96)00236-3.

[95] Aimo A, Januzzi JL, Vergaro G, Ripoli A, Latini R, Masson S, et al. Prognostic Value of High-Sensitivity Troponin T in Chronic Heart Failure. Circulation 2018;137:286–297. doi:10.1161/CIRCULATIONAHA.117.031560.

[96] Puelacher C, Lurati Buse G, Seeberger D, Sazgary L, Marbot S, Lampart A, et al. Perioperative Myocardial Injury After Noncardiac Surgery: Incidence, Mortality, and Characterization. Circulation 2017:CIRCULATIONAHA.117.030114. doi:10.1161/CIRCULATIONAHA.117.030114.

[97] van der Linden N, Klinkenberg LJJ, Bekers O, Loon LJC van, Dieijen-Visser MP van, Zeegers MP, et al. Prognostic value of basal high-sensitive cardiac troponin levels on mortality in the general population: A meta-analysis. Medicine (Baltimore) 2016;95:e5703. doi:10.1097/MD.0000000000005703.

[98] Christ M, Geier F, Popp S, Singler K, Smolarsky A, Bertsch T, et al. Diagnostic and prognostic value of high-sensitivity cardiac troponin T in patients with syncope. Am J Med 2015;128:161–170.e1. doi:10.1016/j.amjmed.2014.09.021.

[99] Lindner G, Pfortmueller C a., Funk GC, Leichtle AB, Fiedler GM, Exadaktylos AK. High-Sensitive Troponin Measurement in Emergency Department Patients Presenting with Syncope: A Retrospective Analysis. PLoS One 2013;8:8–11. doi:10.1371/journal.pone.0066470.

[100] Sun B, Derose S, Liang L, Gabayan G. Predictors of 30-day serious events in older patients with syncope. Ann

Emerg 2009;54:769–778. doi:10.1016/j.annemergmed.2009.07.027.Predictors.

[101] Gimenez MR, Reiter M, Twerenbold R, Reichlin T, Wildi K, Haaf P, et al. Sex-specific chest pain characteristics in the early diagnosis of acute myocardial infarction. JAMA Intern Med 2014;174:241–249. doi:10.1001/jamainternmed.2013.12199.

[102] Klinkenberg LJJ, Wildi K, Van Der Linden N, Kouw IWK, Niens M, Twerenbold R, et al. Diurnal rhythm of cardiac troponin: Consequences for the diagnosis of acute myocardial infarction. Clin Chem 2016;62:1602–1611. doi:10.1373/clinchem.2016.257485.

[103] Walter JE, Honegger U, Puelacher C, Mueller D, Wagener M, Schaerli N, et al. Prospective validation of a biomarker-based rule out strategy for functionally relevant coronary artery disease. Clin Chem 2018;64:386–395. doi:10.1373/clinchem.2017.277210.

[104] Wildi K, Gimenez MR, Twerenbold R, Reichlin T, Jaeger C, Heinzelmann A, et al. Misdiagnosis of Myocardial Infarction Related to Limitations of the Current Regulatory Approach to Define Clinical Decision Values for Cardiac Troponin. Circulation 2015;131:2032–2040. doi:10.1161/CIRCULATIONAHA.114.014129.

[105] Thiruganasambandamoorthy V, Perry JJ. High-sensitivity cardiac troponin T in isolation has limited diagnostic utility in identifying cardiac causes of syncope. Evid Based Med 2015;20:146. doi:10.1136/ebmed-2015-110191.

[106] Reed MJ, Newby DE, Coull AJ, Prescott RJ, Gray AJ. Diagnostic and prognostic utility of troponin estimation in patients presenting with syncope: A prospective cohort study. Emerg Med J 2010;27:272–276. doi:10.1136/emj.2008.068635.

[107] Rubini Gimenez M, Twerenbold R, Reichlin T, Wildi K, Haaf P, Schaefer M, et al. Direct comparison of high-sensitivity-cardiac troponin I vs. T for the early diagnosis of acute myocardial infarction. Eur Heart J 2014;35:2303–2311. doi:10.1093/eurheartj/ehu188.

[108] Thiruganasambandamoorthy V, Perry JJ. High-sensitivity cardiac troponin T in isolation has limited diagnostic utility in identifying cardiac causes of syncope. Evid Based Med 2015;20:146. doi:10.1136/ebmed-2015-110191.

[109] Blankenberg S, Salomaa V, Makarova N, Ojeda F, Wild P, Lackner KJ, et al. Troponin I and cardiovascular risk prediction in the general population : the BiomarCaRE consortium 2016:2428–2437. doi:10.1093/eurheartj/ehw172.

[110] Krintus M, Kozinski M, Boudry P, Capell NE, Köller U, Lackner K, et al. European multicenter analytical evaluation of the Abbott ARCHITECT STAT high sensitive troponin i immunoassay. Clin Chem Lab Med 2014;52:1657–1665. doi:10.1515/cclm-2014-0107.

[111] Todd J, Freese B, Lu A, Held D, Morey J, Livingston R, et al. Ultrasensitive flow-based immunoassays using single-molecule counting. Clin Chem 2007;53:1990–1995. doi:10.1373/clinchem.2007.091181.

[112] Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical validation of a high-sensitivity cardiac troponin T assay. Clin Chem 2010;56:254–261. doi:10.1373/clinchem.2009.132654.

[113] Lichtman JH, Leifheit EC, Safdar B, Bao H, Krumholz HM, Lorenze NP, et al. Sex differences in the presentation and perception of symptoms among young patients with myocardial infarction. Circulation 2018;137:781–790. doi:10.1161/CIRCULATIONAHA.117.031650.

[114] Tan MP, Parry SW. Vasovagal Syncope in the Older Patient. J Am Coll Cardiol 2008;51:599–606. doi:10.1016/j.jacc.2007.11.025.

[115] Oh JH, Hanusa BH, Kapoor WN. Do symptoms predict cardiac arrhythmias and mortality in patients with syncope? Arch Intern Med 1999;159:375–380.

[116] Palaniswamy C, Aronow WS. Risk prediction tools for Syncope: The quest for the holy grail. Int J Cardiol 2018;269:192–193. doi:10.1016/j.ijcard.2018.07.127.

[117] Mueller C, Laule-Kilian K, Scholer A, Frana B, Rodriguez D, Schindler C, et al. Use of B-type natriuretic peptide for the management of women with dyspnea. Am J Cardiol 2004;94:1510–1514.

doi:10.1016/j.amjcard.2004.08.029.

[118] Sandoval Y, Apple FS. The global need to define normality: The 99th percentile value of cardiac troponin. Clin Chem 2014;60:455–462. doi:10.1373/clinchem.2013.211706.

[119] Tanindi A, Cemri M. Troponin elevation in conditions other than acute coronary syndromes. Vasc Health Risk Manag 2011;7:597–603. doi:10.2147/VHRM.S24509.

[120] Probst MA, Sun BC. How can we improve management of syncope in the Emergency Department? Cardiol J 2014;21:643–650. doi:10.5603/CJ.a2014.0074.

Curriculum Vitae

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Education

University of Basel, Basel (CH), PhD Clinical Research **2016-2019**
- Title of the project: Improving the Early Diagnosis and Risk Stratification of Patients with Syncope.

Educational Commission for Foreign Medical Graduates, United States Medical Licencing Exam **2014-2016**
- Step 1: Score 242; Step 2Clinical Skills: Pass; Step 2Clinical Knowledge: Score 252

Swiss Medical Licensing Examination, Top 10th percentile nationwide **2016**

University of Basel, Basel (CH), Master of Human Medicine. Grade average: 5.8/6 **2013-2016**

University of Fribourg, Fribourg (CH), Bachelor of Human Medicine. Grade average: 5.7/6 **2010-2013**
- Special award for the best Bachelor final grade of the class of 2010

Secondary School of Burier, Burier (CH), Baccalaureate. Grade average : 5.3/6 **2007-2010**
- Bilingual maturity French/German with 1 year at Kantonsschule Wettingen, Aargau, Switzerland
- Special award for the best grade average in Biochemistry

Further education

Harvard Medical School/University of Zürich, Summer School Clinical Investigation **2018**

Dresden International University, Master of Clinical Research **2017-2019**

Harvard T.H. CHAN School of Public Health, Principles and Practice of Clinical Research **2017**
- Online interactive course (5h/week) with 1-week immersion course in Brazil

Swiss Distance Learning University, Bachelor of Science in Economics and Management **2014-2018**
- Grade average: 5.5/6

Clinical Internships

Cleveland Clinic, Cleveland (USA), *Cardiothoracic Intensive Care Unit* **03/2016**

Brigham and Women's Hospital, Boston (USA), *Cardiology* **02/2016**

Clinic of Neurology, Aarau Canton Hospital (CH), *Neurology* **01/2016**

Claraspital, Basel (CH), *General Surgery* **11–12/2015**

University Hospital, Lausanne (CH), *Gynecology* **10/2015**

Basel University Hospital, Basel (CH), *Internal Medicine* **07–08/2015**

Ospedale Regionale, Bellinzona (CH), *Radiology* **06/2015**

Cardiocentro Ticino, Lugano (CH), *Cardiology* **04–05/2015**

Cantonal Hospital, Fribourg (CH), *Abdominal surgery* **09/2012**

Research experience

University of Basel (CH) *Cardiology, Clinical Research*, Prof. C. Mueller **09/2015**

University of Basel (CH) *Myocardial Research Laboratory*, PD Dr. G. Kuster **02–03/2015**

University of Fribourg (CH), *Tumor Microenvironment Biology Laboratory*, Prof. C. Rüegg **06–08/2013**

University of Alberta, Edmonton (Canada), *Cardiac Transplantation Group*, Prof. L. J. West **07/2012**

Weizmann Institute, Rehovot (Israel)**,** *Dr. B. F. L. International Summer Science Institute* (ISSI) **07/2009**

Scientific awards and grants

Young Investigator Award (820 USD) **2018**
Global Research on Acute Conditions Team Congress, Venice, Italy, July 6-8, 2018

Research Grant from the Swiss Heart Foundation (100'500 USD) **2017**
- Received as first applicant to fund own study (Heart&Muscle Study)

Integrated Management of Acute and Chronic CV Disease, Best Poster Price (340 USD) **2017**
Innsbruck, Austria, January 21-24, 2017

Personal grant from the Goldschmidt-Jacobson Stiftung, Basel (56'200 USD) **2016**

Scholarly activities

Swiss Study Foundation **2010-2019**

- Scholarship holder and participant in lectures and weekend seminars, e.g., on Information Technology, Conflict Resolution, and Self Management

Teaching activities

PPHS (PhD Program Health Sciences), Basel (CH) **2017-2019**

- Organisation of the Science Club (Monthly meeting to discuss statistical and scientific topics)

Medical Faculty, University of Basel, Basel (CH) **2016**

- Tutor to the 3rd year medical students

Computer skills and language

Language: French (native language), German (fluent/C2 level), English (fluent, TOEFL score: 111/120, C2 level), Italian (fluent/C1 level), Spanish (basics)

Computer skills: Advanced programming skills in the "R"-language and SPSS (both statistical softwares), excellent knowledge in Microsoft Office (especially Excel and Powerpoint), excellent knowledge in electronic data capture systems RedCap and Microsoft Access.

Oral presentations(*) and posters(#) presented at congresses

European Society of Cardiology Congress# Munich (DE) **2018**
GREAT (Global REsearch on Acute Conditions Team) Meeting* Venice (IT) **2018**
Integrated Management of Acute and Chronic Cardiovascular Disease# Innsbruck (AT) **2018**
European Society of Cardiology Congress# Barcelona (ES), **2017**
GREAT (Global REsearch on Acute Conditions Team) Meeting* Barcelona (ES) **2017**
Integrated Management of Acute and Chronic Cardiovascular Disease# Innsbruck (AT) **2017**