Supplemental Material

Supplemental Appendix – Utility of brain natriuretic peptide and cardiac troponins in the diagnosis and risk-stratification of patients presenting with syncope to the emergency department

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. Additional tests and treatment of patients were left to discretion of the clinically responsible physician.

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:

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.

Laboratory methods

BNP measurements were performed by use of the Architect BNP assay[1]. 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.
NT-proBNP measurements were performed by use of the Elecsys proBNP assay (Roche Diagnostics, Zug, Switzerland)[2], a quantitative electrochemiluminescence immunoassay. The analytical detection limit of the assay was 5 pg/mL. The intra-assay coefficient of variation was 2.4% at 355 pg/mL and 1.8% at 4962 pg/mL; the inter-assay coefficients of variation were 2.9% at 355 pg/mL and 2.3% at 4962 pg/mL
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[3].

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.[4]
Measurement of MR-proANP was performed using an validated sandwich immunoassays.[5]

Evaluation of Guidelines in Syncope Study (EGSYS)[6] 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 or equal 3 implies an increased risk for cardiac syncope.

Osservatorio Epidemiologico sulla Sincope nel Lazio (OESIL)[7] 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.

Canadian Syncope Risk score[8]

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

- Vasovagal predisposition: -1
- History of heart disease : +1
- Any ED systolic blood pressure (BP) <90 or >180mmHg : +2
- Troponin elevated (>99thpercentile normal population) +2
- Abnormal QRS Axis (<-30 or >100) : +1
- QRS duration >130 milliseconds : +1
- Corrected QT interval >480miliseconds: +2
- Diagnosis in the ED : Vasovagal syncope : -2
- Diagnosis in the ED : Cardiac syncope : +2

The BASEL IX study only recorded systolic blood pressure measured upon admission.
The primary end point was death or MACE (as defined in the BASEL IX study) within 30 days of the initial evaluation in the ED.

SFSR Rule[9]

The San Fransisco Syncope Rule was found positive if any of the following factor was present:

- Congestive heart failure history
- Hematocrit <30%
- Abnormal ECG (ECG changed or any non-sinus rhythm on ECG or monitoring)
- Shortness of breath
- Systolic BP<90mmHg at triage

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.[10]

Predictive accuracy of BNP, NT-proBNP and hs-cTn to predict cardiac syncope: Multivariable model

Logistic regression was used to assess the predictive accuracy of log-transformed BNP, NT-proBNP and hs-cTn 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[11]. 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, NT-proBNP and hs-cTn alone.

Accuracy of BNP, NTpro-BNP and hs-cTn to predict adverse outcome: Cox proportional model

Cox proportional hazard model was used to assess the importance of log-transformed BNP, NT-proBNP and hs-cTn 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[11]. 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 1

Section/Topic			Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	Title
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	Abstract
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	5
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	5-6
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	6
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	12
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	6
	5b	D;V	Describe eligibility criteria for participants.	6
	5c	D;V	Give details of treatments received, if relevant.	-
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	7
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	-
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	10-11 + Supplemental
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	-
Sample size	8	D;V	Explain how the study size was arrived at.	-
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	10-11
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	10-11+ Supplemental
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	11-12 + Supplemental
	10c	V	For validation, describe how the predictions were calculated.	11-12 + Supplemental
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	11-12 + Supplemental
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	-
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	11-12 + Supplemental
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	11-12 + Supplemental
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	Supplemental
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Table 1, page 12, 14
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Supplemental
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	Supp. Table 1
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	Supp. Table 6
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Supp. Table 6, Supp. Table 8
	15b	D	Explain how to the use the prediction model.	12-16
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	Table 2, Supp. Table 7
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	Supp. Table 4
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	20-21

Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	17-20
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	17-20
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	17-20
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	Supplemental
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	24

Supplemental table 1 – TRIPOD Statement

Supplemental table 2

			All
Number of patients			1472
Arrhythmia			158 (11)
	Bradycardia		99 (7)
		Atrioventricular conduction system disease	48 (3)
		Implanted device malfunction	4 (0)
		Drug-induced	4 (0)
		Sinus node dysfunction	42 (3)
	Tachycardia		53 (4)
		Supraventricular	25 (2)
		Supraventricular: Drug-induced	1 (0)
		Ventricular: Channelopathies	2 (0)
		Ventricular: Drug-induced	4 (0)
		Ventricular : Idiopathic	1 (0)
		Ventricular : Secondary to structural heart disease	20 (1)
	Unknown		6 (0)
Structural disease			46 (3)
	Acute myocardial infarction/ischemia		24 (2)
	Congenital anomalies of coronary arteria		0 (0)
	Hypertrophic cardiomyopathy		2 (0)
	Cardiac masses		0 (0)
	Others		2 (0)
	Pericardial disease/tamponade		0 (0)
	Valvular disease		18 (1)
	Prosthetic valve dysfunction		0 (0)
Other cardiac			17 (1)

		All
	Pulmonary embolism	16 (1)
	Pulmonary hypertension	0 (0)
	Acute aortic dissection	0 (0)
	Others	1 (0)

Supplemental Table 2 - Distribution of patients with cardiac syncope among the pre-defined cardiac subcategories Details of the adjudicated cardiac etiologies.

Supplemental table 3

Cut-offs for BNP	**Target Sensitivity**	**Cut-off (pg/mL)**	**Sensitivity (95%-CI)**	**Specificity (95% CI)**	**NPV (95%-CI)**	**Negative Likelihood ratio (95%-CI)**	**Incidence of criteria % (95%-CI)**
	80	48	80.1 (74.3, 84.8)	58.5 (55.6, 61.4)	93.7 (91.6, 95.3)	0.3 (0.3, 0.4)	52.2 (49.5, 54.8)
	85	35	85.1 (79.8, 89.2)	49.6 (46.7, 52.5)	94.4 (92.2, 96)	0.3 (0.2, 0.4)	43.9 (41.2, 46.5)
	90	24.8	90 (85.4, 93.3)	39.6 (36.7, 42.5)	95.3 (92.9, 96.8)	0.3 (0.2, 0.4)	34.7 (32.2, 37.3)
	95	**14.9**	95 (91.3, 97.2)	24.8 (22.4, 27.4)	96.2 (93.3, 97.9)	0.2 (0.1, 0.4)	**21.5 (19.4, 23.8)**
	98	9.9	99.5 (97.5, 99.9)	3.9 (2.9, 5.2)	97.8 (88.4, 99.6)	0.1 (0, 0.8)	3.4 (2.5, 4.5)
	Target Specificity	**Cut-off (pg/mL)**	**Specificity (95%-CI)**	**Sensitivity (95% CI)**	**PPV (95%-CI)**	**Positive Likelihood ratio (95%-CI)**	**Incidence of criteria % (95%-CI)**
	80	107	80 (77.6, 82.3)	59.3 (52.7, 65.5)	37 (32.1, 42.1)	3 (2.5, 3.5)	26.5 (24.2, 28.9)
	85	139.4	85.4 (83.2, 87.4)	53.8 (47.3, 60.3)	42.2 (36.6, 48)	3.7 (3.1, 4.4)	21.1 (19, 23.3)
	90	199.7	90.4 (88.6, 92)	44.3 (37.9, 50.9)	47.8 (41.1, 54.6)	4.6 (3.7, 5.8)	15.3 (13.5, 17.4)
	95	**302**	95.1 (93.6, 96.2)	31.2 (25.5, 37.6)	55.6 (46.9, 64.1)	6.3 (4.6, 8.8)	**9.3 (7.8, 10.9)**
	98	666	98 (97, 98.7)	11.3 (7.8, 16.2)	53.2 (39.2, 66.7)	5.7 (3.3, 10)	3.5 (2.6, 4.7)

Cut-offs for NT-proBNP	**Target Sensitivity**	**Cut-off (pg/mL)**	**Sensitivity (95%-CI)**	**Specificity (95% CI)**	**NPV (95%-CI)**	**Negative Likelihood ratio (95%-CI)**	**Incidence of criteria % (95%-CI)**
	80	172	80.1 (74.3, 84.8)	57.7 (54.8, 60.6)	93.6 (91.5, 95.2)	0.3 (0.3, 0.5)	51.5 (48.8, 54.2)
	85	125	85.5 (80.3, 89.6)	49.5 (46.6, 52.4)	94.5 (92.4, 96.1)	0.3 (0.2, 0.4)	43.7 (41.1, 46.4)
	90	101	90 (85.4, 93.3)	43.9 (41, 46.8)	95.7 (93.6, 97.1)	0.2 (0.2, 0.3)	38.3 (35.7, 40.9)
	95	**69**	95 (91.3, 97.2)	31.8 (29.1, 34.6)	97 (94.7, 98.3)	0.2 (0.1, 0.3)	**27.4 (25, 29.8)**
	98	29	98.6 (96.1, 99.5)	12.8 (11, 14.9)	97.9 (94.1, 99.3)	0.1 (0, 0.3)	10.9 (9.4, 12.7)
	Target Specificity	**Cut-off (pg/mL)**	**Specificity (95%-CI)**	**Sensitivity (95% CI)**	**PPV (95%-CI)**	**Positive Likelihood ratio (95%-CI)**	**Incidence of criteria % (95%-CI)**
	80	445	80 (77.6, 82.3)	62.9 (56.4, 69)	38.4 (33.5, 43.5)	3.2 (2.7, 3.7)	27.1 (24.7, 29.5)
	85	670	85 (82.8, 87)	52.5 (45.9, 59)	41 (35.4, 46.8)	3.5 (2.9, 4.2)	21.2 (19, 23.4)
	90	1201	90.1 (88.2, 91.7)	39.8 (33.6, 46.4)	44.2 (37.5, 51.2)	4 (3.2, 5.1)	14.9 (13.1, 16.9)
	95	**1966**	95.2 (93.7, 96.3)	28.1 (22.5, 34.3)	53.4 (44.4, 62.3)	5.8 (4.2, 8.1)	**8.7 (7.3, 10.3)**
	98	4134	98 (97, 98.7)	14.9 (10.8, 20.2)	60 (46.8, 71.9)	7.6 (4.5, 12.7)	4.1 (3.2, 5.3)

Cut-offs for hs-cTnI	**Target Sensitivity**	**Cut-off (pg/mL)**	**Sensitivity (95%-CI)**	**Specificity (95% CI)**	**NPV (95%-CI)**	**Negative Likelihood ratio (95%-CI)**	**Incidence of criteria % (95%-CI)**
	80	5.3	80.5 (74.8, 85.2)	63.8 (61, 66.6)	94.3 (92.4, 95.8)	0.3 (0.2, 0.4)	56.5 (53.8, 59.1)

	85	4.5	85.1 (79.8, 89.2)	57.9 (55, 60.8)	95.1 (93.3, 96.5)	0.3 (0.2, 0.4)	50.8 (48.1, 53.5)
	90	2.8	90.5 (85.9, 93.7)	35.5 (32.8, 38.4)	95 (92.4, 96.7)	0.3 (0.2, 0.4)	31.2 (28.8, 33.8)
	95	**2.2**	95.9 (92.4, 97.8)	22.6 (20.3, 25.2)	96.6 (93.6, 98.2)	0.2 (0.1, 0.3)	**19.6 (17.5, 21.8)**
	98	1.6	98.6 (96.1, 99.5)	10.7 (9, 12.6)	97.5 (93, 99.2)	0.1 (0, 0.4)	9.1 (7.7, 10.8)
	Target Specificity	**Cut-off (pg/mL)**	**Specificity (95%-CI)**	**Sensitivity (95% CI)**	**PPV (95%-CI)**	**Positive Likelihood ratio (95%-CI)**	**Incidence of criteria % (95%-CI)**
	80	9.8	80 (77.6, 82.3)	60.2 (53.6, 66.4)	37.4 (32.5, 42.5)	3 (2.6, 3.5)	26.6 (24.3, 29)
	85	12.8	85.3 (83.1, 87.3)	47.1 (40.6, 53.6)	38.8 (33.2, 44.8)	3.2 (2.6, 3.9)	20 (18, 22.3)
	90	18.1	90.3 (88.5, 91.9)	40.3 (34, 46.9)	45.2 (38.4, 52.2)	4.2 (3.3, 5.3)	14.7 (12.9, 16.7)
	95	**31.3**	95.1 (93.6, 96.2)	26.7 (21.3, 32.9)	51.8 (42.7, 60.7)	5.4 (3.9, 7.6)	**8.5 (7.1, 10.1)**
	98	63.4	98.1 (97.1, 98.8)	16.3 (12, 21.7)	63.2 (50.2, 74.5)	8.7 (5.2, 14.6)	4.3 (3.3, 5.5)

Cut-offs for hs-cTnT	**Target Sensitivity**	**Cut-off (pg/mL)**	**Sensitivity (95%-CI)**	**Specificity (95% CI)**	**NPV (95%-CI)**	**Negative Likelihood ratio (95%-CI)**	**Incidence of criteria % (95%-CI)**
	80	11	80.1 (74.3, 84.8)	59.1 (56.2, 61.9)	93.8 (91.7, 95.3)	0.3 (0.3, 0.4)	52.6 (49.9, 55.3)
	85	9	87.3 (82.3, 91.1)	51.7 (48.7, 54.6)	95.4 (93.4, 96.8)	0.2 (0.2, 0.3)	45.2 (42.6, 47.9)
	90	8	90.5 (85.9, 93.7)	46.2 (43.3, 49.1)	96.1 (94.1, 97.4)	0.2 (0.1, 0.3)	40.1 (37.5, 42.8)
	95	**5**	96.4 (93, 98.2)	23.6 (21.2, 26.2)	97.1 (94.3, 98.5)	0.2 (0.1, 0.3)	**20.3 (18.3, 22.6)**
	98	4	98.6 (96.1, 99.5)	16.3 (14.2, 18.6)	98.4 (95.3, 99.4)	0.1 (0, 0.3)	13.8 (12.1, 15.8)
	Target Specificity	**Cut-off (pg/mL)**	**Specificity (95%-CI)**	**Sensitivity (95% CI)**	**PPV (95%-CI)**	**Positive Likelihood ratio (95%-CI)**	**Incidence of criteria % (95%-CI)**
	80	19	80.9 (78.5, 83.1)	53.8 (47.3, 60.3)	35.8 (30.9, 41.1)	2.8 (2.4, 3.4)	24.8 (22.6, 27.2)
	85	22	85.2 (83, 87.2)	49.8 (43.2, 56.3)	40 (34.4, 45.9)	3.4 (2.8, 4.1)	20.6 (18.5, 22.8)
	90	29	90.6 (88.7, 92.2)	38.9 (32.7, 45.5)	45 (38.1, 52.1)	4.1 (3.2, 5.3)	14.3 (12.5, 16.3)
	95	**42**	95.1 (93.6, 96.2)	24.9 (19.6, 31)	50 (40.8, 59.2)	5.1 (3.6, 7.1)	**8.2 (6.9, 9.8)**
	98	59	98.1 (97.1, 98.8)	15.4 (11.2, 20.7)	61.8 (48.6, 73.5)	8.2 (4.8, 13.8)	4.1 (3.2, 5.3)

Supplemental table 3 – BNP, NT-proBNP, hs-cTnT and hs-cTnI cut-offs for specific sensitivities/specificities. BNP, NT-proBNP, hs-cTnT and hs-cTnI cut-offs for specific sensitivities and specificities. For instance, a 95%-sensitivity cut-off allows for the rule-out of ~20% of patients with syncope (highlighted in green) while a 95%-specificity cut-off allows for the rule-in of ~9% of syncope patients (highlighted in red), allowing for an overall classification of ~30% of the cohort

Supplemental table 4

Strategy	EGSYS<3			EGSYS≥3	No score		
	Below 95%-specificity biomarker-cut-off : Rule-out	Between cut-offs : Observe	Above 95%-sensitivity biomarker-cut-off : Rule-in		Below 95%-specificity biomarker-cut-off : Rule-out	Between cut-offs : Observe	Above 95%-sensitivity biomarker-cut-off : Rule-in
BNP	248	1036	23	BNP	279	908	120
	NPV: 0.97				NPV: 0.96		
	PPV: 0.65				PPV: 0.55		
	Incidence of criteria: 21%				Incidence of criteria: 30%		
NT-proBNP	319	958	31	NT-proBNP	354	840	112
	NPV: 0.97				NPV: 0.97		
	PPV: 0.58				PPV: 0.53		
	Incidence of criteria: 27%				Incidence of criteria: 36%		
Hs-cTnI	224	1035	36	Hs-cTnI	252	926	111
	NPV: 0.96				NPV: 0.96		
	PPV: 0.61				PPV: 0.51		
	Incidence of criteria: 20%				Incidence of criteria: 28%		
Hs-cTnT	234	973	27	Hs-cTnT	260	853	102
	NPV: 0.97				NPV: 0.97		
	PPV: 0.67				PPV: 0.51		
	Incidence of criteria: 20%				Incidence of criteria: 28%		

Supplemental table 4 : Negative and positive predictive values and incidence of criteria when the population is first stratified using EGSYS≥3 or when predefined 95%-sensitivity/specificity biomarkers cut-offs are directly used. NPV = Negative predictive value, PPV = Positive predictive value, Incidence of criteria is defined as the percentage of patients classified as rule-in or rule-out.

Supplemental table 5

Biomarker	First stratifying with EGSYS<3	Directly using 95%-sensitivity BM cut-offs
BNP	2.82%	2.87%
NT-proBNP	2.51%	2.26%
hs-cTnI	2.68%	2.78%
hs-cTnT	2.14%	1.92%

Supplemental Table 5 – MACE rates at 30d in the rule-out group when the population is first stratified using EGSYS≥3 or when predefined 95%-sensitivity/specificity biomarkers cut-offs are directly used. BM = Biomarker.

Supplemental table 6

	Nr of patients (%)	Attributed points
Patients for whom an ECG was recorded in the Emergency Department	1299	
Heart rate		
- Normocard	1151 (89)	0
- Bradycard ≤45bpm	28 (2)	17
- Bradycard 46-50bpm	44 (3)	2
- Bradycard 51-55bpm	76 (6)	2
Atrioventricular conduction block (AVB)		
- No AVB	1087 (84)	0
- AVB 1st degree and PQ-time 200-300ms	191 (15)	3
- AVB 1st degree and PQ-time >300ms or AVB 2nd degree Wenckebach	9 (1)	19
- AVB 2nd degree Mobitz or AVB 3rd degree	12 (1)	14
Bradycardia score		
- 0 points	981 (76)	
- 2 points	94 (7)	
- 3 points	161 (12)	
- 5 points	23 (2)	
- 14 points	2 (0)	
- 16 points	1 (0)	
- 17 points	12 (1)	
- 19 points	7 (1)	
- 20 points	7 (1)	
- 21 points	2 (0)	
- 31 points	9 (1)	

Supplemental table 6 – Components of an ECG risk-score aiming at the diagnosis of bradycardia-induced cardiac syncope. The prevalence are given for all patients of the BASEL IX cohort for whom an ECG was recorded upon arrival in the ED. The components were chosen based on their clinical relevance. The points of the score

are based on the rounded coefficients obtained through logistic regression aiming at explaining a diagnosis of bradycardia-induced cardiac syncope.

Supplemental table 7

Supplemental table 7 – BNP and hs-cTnI	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 10 ng/L increase	2.34	2.06	2.69	<0.001	1.812	1.525	2.164	<0.001
log-transformed hs-cTnI, per 10 ng/L increase	3.01	2.47	3.69	<0.001	1.913	1.53	2.404	<0.001
Age, each year increase	1.05	1.03	1.06	<0.001	1.006	0.99	1.023	0.432
Sex (Women)	0.8	0.59	1.08	0.146				
Known CV disease	2.62	1.84	3.83	<0.001	1.273	0.611	2.596	0.513
Smoking status	0.88	0.66	1.18	0.384				
Hypertension	1.81	1.33	2.48	<0.001	0.809	0.469	1.429	0.454
Hypercholesterolemia	1.48	1.1	1.99	0.009	0.952	0.657	1.377	0.794
Diabetes	1.71	1.16	2.47	0.005	1.072	0.664	1.7	0.770
Heart rate, per 5 bpm increase	1	0.98	1.02	0.734				
Systolic BP, per 5mmHg increase	1.03	1	1.06	0.036	1.031	0.999	1.064	0.058
Any cardiac medication	2.48	1.75	3.57	<0.001	0.851	0.462	1.579	0.607
Abnormal ECG	3.23	2.34	4.54	<0.001	1.738	1.197	2.542	0.004

Supplemental table 7 - Predictors for a diagnostic of cardiac syncope : BNP and hs-cTnI . Bpm = beats per minute, mmHg= milimeter mercury. Variables were used to correct the multivariable model only if they were significant in the univariable regression. CI = Confidence interval. We combined BNP with hs-cTnI as these two assays are from the same manufacturer (Abbott) and therefore more likely to be available together in the EDs.

Supplemental table 8

Supplemental table 8 – NT-proBNP and hs-cTnT	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**
NT-proBNP concentrations, per 50	2.09	1.87	2.34	<0.001	1.619	1.375	1.913	<0.001

ng/L increase								
log-transformed hs-cTnT, per 10 ng/L increase	3.48	2.79	4.39	<0.001	2.025	1.517	2.714	<0.001
Age, each year increase	1.05	1.03	1.06	<0.001	0.996	0.98	1.013	0.667
Sex (Women)	0.8	0.59	1.08	0.146				
Known CV disease	2.62	1.84	3.83	<0.001	1.152	0.562	2.321	0.695
Smoking status	0.88	0.66	1.18	0.384				
Hypertension	1.81	1.33	2.48	<0.001	0.763	0.444	1.342	0.336
Hypercholesterolemia	1.48	1.1	1.99	0.009	1.029	0.711	1.488	0.880
Diabetes	1.71	1.16	2.47	0.005	0.854	0.529	1.351	0.509
Heart rate, per 5 bpm increase	1	0.98	1.02	0.734				
Systolic BP, per 5mmHg increase	1.03	1	1.06	0.036	1.037	1.005	1.071	0.024
Any cardiac medication	2.48	1.75	3.57	<0.001	0.833	0.458	1.524	0.552
Abnormal ECG	3.23	2.34	4.54	<0.001	1.67	1.145	2.457	0.008

Supplemental table 8 - Predictors for a diagnostic of cardiac syncope : NT-proBNP and hs-cTnT. Bpm = beats per minute, mmHg= milimeter mercury. Variables were used to correct the multivariable model only if they were significant in the univariable regression. CI = Confidence interval. We combined NT-proBNP with hs-cTnT as these two assays are from the same manufacturer (Roche) and therefore more likely to be available together in the EDs.

Supplemental table 9

AUC 1	AUC 2	P-value for comparison according to DeLong
CSRS, AUC 0.88 [0.85, 0.9]	BNP, AUC 0.76 [0.73, 0.8]	<0.001
CSRS, AUC 0.88 [0.85, 0.9]	NT-proBNP, AUC 0.78 [0.74, 0.81]	<0.001
CSRS, AUC 0.88 [0.85, 0.9]	hs-cTnI, AUC 0.79 [0.75, 0.82]	<0.001
CSRS, AUC 0.88 [0.85, 0.9]	hs-cTnT, AUC 0.78 [0.74, 0.81]	<0.001
CSRS, AUC 0.88 [0.85, 0.9]	CSRS+BNP, AUC 0.88 [0.86, 0.91]	0.044
CSRS, AUC 0.88 [0.85, 0.9]	CSRS+NT-proBNP, AUC 0.88 [0.86, 0.91]	0.043
CSRS, AUC 0.88 [0.85, 0.9]	CSRS+hs-cTnI, AUC 0.89 [0.86, 0.91]	0.005
CSRS, AUC 0.88 [0.85, 0.9]	CSRS+hs-cTnT, AUC 0.89 [0.86, 0.91]	0.01
OESIL, AUC 0.71 [0.67, 0.76]	BNP, AUC 0.77 [0.72, 0.82]	0.019
OESIL, AUC 0.71 [0.67, 0.76]	NT-proBNP, AUC 0.8 [0.75, 0.84]	0.001
OESIL, AUC 0.71 [0.67, 0.76]	hs-cTnI, AUC 0.74 [0.68, 0.79]	0.366
OESIL, AUC 0.71 [0.67, 0.76]	hs-cTnT, AUC 0.79 [0.74, 0.83]	0.005
OESIL, AUC 0.71 [0.67, 0.76]	OESIL+BNP, AUC 0.78 [0.73, 0.82]	<0.001
OESIL, AUC 0.71 [0.67, 0.76]	OESIL+NT-proBNP, AUC 0.8 [0.76, 0.84]	<0.001
OESIL, AUC 0.71 [0.67, 0.76]	OESIL+hs-cTnI, AUC 0.77 [0.72, 0.82]	<0.001
OESIL, AUC 0.71 [0.67, 0.76]	OESIL+hs-cTnT, AUC 0.8 [0.75, 0.85]	<0.001
ROSE, AUC 0.61 [0.57, 0.65]	BNP, AUC 0.75 [0.71, 0.79]	<0.001
ROSE, AUC 0.61 [0.57, 0.65]	NT-proBNP, AUC 0.76 [0.72, 0.79]	<0.001
ROSE, AUC 0.61 [0.57, 0.65]	hs-cTnI, AUC 0.76 [0.72, 0.8]	<0.001
ROSE, AUC 0.61 [0.57, 0.65]	hs-cTnT, AUC 0.76 [0.72, 0.8]	<0.001
ROSE, AUC 0.61 [0.57, 0.65]	ROSE+BNP, AUC 0.75 [0.71, 0.79]	<0.001
ROSE, AUC 0.61 [0.57, 0.65]	ROSE+NT-proBNP, AUC 0.76 [0.72, 0.8]	<0.001
ROSE, AUC 0.61 [0.57, 0.65]	ROSE+hs-cTnI, AUC 0.76 [0.73, 0.8]	<0.001
ROSE, AUC 0.61 [0.57, 0.65]	ROSE+hs-cTnT, AUC 0.77 [0.73, 0.8]	<0.001
SFSR, AUC 0.64 [0.6, 0.68]	BNP, AUC 0.74 [0.69, 0.8]	0.001
SFSR, AUC 0.64 [0.6, 0.68]	NT-proBNP, AUC 0.74 [0.69, 0.79]	<0.001
SFSR, AUC 0.64 [0.6, 0.68]	hs-cTnI, AUC 0.73 [0.68, 0.78]	<0.001
SFSR, AUC 0.64 [0.6, 0.68]	hs-cTnT, AUC 0.72 [0.68, 0.77]	0.002

SFSR, AUC 0.64 [0.6, 0.68]	SFSR+BNP, AUC 0.75 [0.7, 0.8]	<0.001
SFSR, AUC 0.64 [0.6, 0.68]	SFSR+NT-proBNP, AUC 0.75 [0.7, 0.8]	<0.001
SFSR, AUC 0.64 [0.6, 0.68]	SFSR+hs-cTnI, AUC 0.74 [0.69, 0.79]	<0.001
SFSR, AUC 0.64 [0.6, 0.68]	SFSR+hs-cTnT, AUC 0.73 [0.68, 0.78]	<0.001

Supplemental table 9 – P-values for comparison of prognostic scores and biomarkers. CSRS Canadian Syncope Risk score, SFSR San Francisco Syncope Rule.

Supplemental table 10

	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 10 pg/mL increase	1.64 [1.40,1.93]	<0.001	1.38 [1.24,1.53]	<0.001	1.37 [1.22,1.55]	<0.001	1.55 [1.35,1.77]	<0.001
Age	1.04 [1.02,1.06]	<0.001	1.02 [1.01,1.03]	0.003	1.01 [1.00,1.03]	0.024	1.02 [1.01,1.03]	0.006
Sex	0.67 [0.44,1.02]	0.061	0.86 [0.67,1.11]	0.247	0.76 [0.56,1.02]	0.067	0.60 [0.44,0.82]	0.001
Known CV disease	0.98 [0.39,2.47]	0.967	1.18 [0.71,1.96]	0.534	1.24 [0.68,2.27]	0.489	1.37 [0.85,2.20]	0.197
Smoking status	1.48 [1.00,2.19]	0.050	1.33 [1.05,1.69]	0.018	1.17 [0.88,1.53]	0.278		
Hypertension	1.52 [0.84,2.76]	0.164	0.73 [0.53,1.01]	0.055	0.80 [0.54,1.17]	0.253		
Hypercholesterolemia	0.64 [0.44,0.94]	0.022	0.96 [0.76,1.21]	0.715	0.74 [0.57,0.97]	0.032		
Diabetes	1.36 [0.90,2.08]	0.148	1.48 [1.13,1.94]	0.004	1.17 [0.85,1.61]	0.336		
Heart rate, per 5 bpm increase	1.00 [0.98,1.03]	0.833	0.97 [0.94,0.99]	0.010	0.94 [0.91,0.97]	<0.001		
Systolic BP, per 5mmHg increase	0.95 [0.92,0.98]	0.004	0.99 [0.97,1.01]	0.469	0.99 [0.96,1.01]	0.365		
Any cardiac medication	0.99 [0.46,2.13]	0.971	1.14 [0.73,1.78]	0.571	1.55 [0.91,2.63]	0.106		
Etiology:Reflex	0.44 [0.24,0.83]	0.010	0.05 [0.04,0.08]	<0.001	0.06 [0.04,0.10]	<0.001	0.25 [0.15,0.42]	<0.001
Etiology:Orthostatic	1.14 [0.72,1.80]	0.581	0.12 [0.09,0.16]	<0.001	0.17 [0.12,0.24]	<0.001	0.67 [0.46,0.98]	0.037
Etiology:Others	1.21 [0.60,2.43]	0.595	0.12 [0.07,0.19]	<0.001	0.16 [0.09,0.29]	<0.001	0.66 [0.36,1.20]	0.172

Etiology:Unknown	1.60 [0.93,2.74]	0.088	0.20 [0.14,0.29]	<0.001	0.33 [0.22,0.48]	<0.001	0.87 [0.56,1.36]	0.550
Abnormal ECG	1.32 [0.89,1.97]	0.173	1.00 [0.79,1.28]	0.984	1.47 [1.09,1.97]	0.010	0.91 [0.66,1.24]	0.536

	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 10 pg/mL increase	1.70 [1.06,2.72]	0.027	1.15 [0.99,1.34]	0.065	1.31 [1.09,1.58]	0.005	0.99 [0.74,1.32]	0.951
Age	1.03 [0.98,1.09]	0.263	1.00 [0.99,1.02]	0.543	1.00 [0.98,1.02]	0.809	1.00 [0.97,1.03]	0.882
Sex			1.23 [0.85,1.78]	0.268	1.23 [0.79,1.90]	0.365	0.99 [0.51,1.92]	0.983
Known CV disease			1.53 [0.75,3.09]	0.241	1.91 [0.78,4.69]	0.158	1.55 [0.61,3.95]	0.358
Smoking status			1.31 [0.92,1.86]	0.140	1.21 [0.79,1.85]	0.389		
Hypertension			0.57 [0.36,0.89]	0.014	0.43 [0.26,0.73]	0.002		
Hypercholesterolemia			1.03 [0.72,1.47]	0.886	0.72 [0.48,1.09]	0.126		
Diabetes			1.33 [0.89,2.01]	0.169	1.08 [0.66,1.76]	0.767		
Heart rate, per 5 bpm increase			0.96 [0.92,0.99]	0.020	0.90 [0.86,0.95]	<0.001		
Systolic BP, per 5mmHg increase			1.02 [0.99,1.05]	0.258	1.03 [1.00,1.07]	0.072		
Any cardiac medication			0.97 [0.52,1.80]	0.922	1.68 [0.73,3.87]	0.224		
Etiology:Reflex			0.01 [0.00,0.02]	<0.001	0.01 [0.00,0.04]	<0.001	0.01 [0.00,0.08]	<0.001
Etiology:Orthostatic			0.03 [0.01,0.05]	<0.001	0.04 [0.01,0.08]	<0.001	0.09 [0.04,0.23]	<0.001
Etiology:Others			0.02 [0.01,0.08]	<0.001	-	-	0.05 [0.01,0.39]	0.004
Etiology:Unknown			0.05 [0.02,0.12]	<0.001	0.08 [0.03,0.21]	<0.001	0.15 [0.04,0.49]	0.002
Abnormal ECG			0.95 [0.66,1.38]	0.796	1.34 [0.84,2.15]	0.219	0.53 [0.28,1.02]	0.059

Supplemental table 10 - Cox proportional Hazards analysis for BNP on several short- and long-term outcomes
BP= blood pressure, CV = cardiovascular, MACE = Major Adverse Cardiovascular Events, 95%-confidence intervals are given in brackets.

Supplemental table 11

	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 NT-proBNP, per 50 pg/mL increase	1.77 [1.53,2.04]	<0.001	1.42 [1.29,1.56]	<0.001	1.34 [1.21,1.49]	<0.001	1.63 [1.44,1.83]	<0.001
Age	1.03 [1.01,1.05]	0.001	1.01 [1.00,1.03]	0.014	1.01 [1.00,1.03]	0.036	1.02 [1.00,1.03]	0.012
Sex	0.64 [0.42,0.97]	0.036	0.85 [0.66,1.10]	0.218	0.75 [0.56,1.01]	0.060	0.59 [0.43,0.81]	0.001
Known CV disease	0.90 [0.36,2.28]	0.826	1.07 [0.64,1.78]	0.804	1.20 [0.65,2.20]	0.560	1.20 [0.74,1.95]	0.452
Smoking status	1.42 [0.96,2.09]	0.080	1.29 [1.01,1.64]	0.040	1.13 [0.86,1.49]	0.392		
Hypertension	1.50 [0.83,2.70]	0.182	0.74 [0.54,1.03]	0.071	0.79 [0.54,1.15]	0.218		
Hypercholesterolemia	0.67 [0.46,0.97]	0.032	1.03 [0.81,1.30]	0.803	0.78 [0.59,1.02]	0.065		
Diabetes	1.30 [0.85,1.98]	0.228	1.40 [1.06,1.83]	0.016	1.10 [0.79,1.52]	0.575		
Heart rate, per 5 bpm increase	0.99 [0.96,1.03]	0.772	0.96 [0.93,0.99]	0.003	0.93 [0.90,0.96]	<0.001		
Systolic BP, per 5mmHg increase	0.96 [0.93,0.99]	0.017	1.00 [0.98,1.02]	0.897	0.99 [0.97,1.02]	0.573		
Any cardiac medication	0.90 [0.41,1.98]	0.797	1.11 [0.71,1.74]	0.657	1.51 [0.89,2.57]	0.129		
Etiology:Reflex	0.51 [0.27,0.96]	0.038	0.06 [0.04,0.08]	<0.001	0.06 [0.04,0.10]	<0.001	0.28 [0.17,0.47]	<0.001
Etiology:Orthostatic	1.14 [0.72,1.80]	0.574	0.12 [0.09,0.15]	<0.001	0.17 [0.12,0.24]	<0.001	0.66 [0.45,0.95]	0.026
Etiology:Others	1.37 [0.68,2.75]	0.382	0.12	<0.001	0.17 [0.10,0.31]	<0.001	0.74 [0.41,1.35]	0.328

			[0.08,0.21]					
Etiology:Unknown	1.60 [0.93,2.74]	0.088	0.20 [0.14,0.29]	<0.001	0.34 [0.23,0.49]	<0.001	0.89 [0.57,1.39]	0.616
Abnormal ECG	1.19 [0.80,1.78]	0.393	0.96 [0.76,1.23]	0.769	1.45 [1.08,1.94]	0.013	0.83 [0.61,1.15]	0.264

	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 NT-proBNP, per 50 pg/mL increase	1.70 [1.13,2.57]	0.012	1.17 [1.02,1.34]	0.028	1.15 [0.97,1.35]	0.104	1.09 [0.85,1.40]	0.505
Age	1.03 [0.97,1.09]	0.325	1.00 [0.99,1.02]	0.604	1.01 [0.99,1.03]	0.553	0.99 [0.97,1.02]	0.715
Sex			1.22 [0.84,1.76]	0.298	1.27 [0.81,1.97]	0.294	0.96 [0.50,1.87]	0.915
Known CV disease			1.43 [0.70,2.91]	0.329	1.92 [0.78,4.74]	0.158	1.47 [0.57,3.77]	0.426
Smoking status			1.29 [0.90,1.84]	0.160	1.19 [0.78,1.82]	0.425		
Hypertension			0.58 [0.37,0.90]	0.016	0.43 [0.26,0.72]	0.001		
Hypercholesterolemia			1.06 [0.74,1.51]	0.757	0.76 [0.50,1.14]	0.188		
Diabetes			1.27 [0.83,1.92]	0.266	1.07 [0.64,1.77]	0.799		
Heart rate, per 5 bpm increase			0.95 [0.92,0.99]	0.013	0.90 [0.85,0.94]	<0.001		
Systolic BP, per 5mmHg increase			1.02 [0.99,1.05]	0.179	1.03 [0.99,1.07]	0.089		
Any cardiac medication			0.97 [0.52,1.79]	0.918	1.69 [0.73,3.94]	0.221		
Etiology:Reflex			0.01 [0.00,0.02]	<0.001	0.01 [0.00,0.04]	<0.001	0.01 [0.00,0.09]	<0.001
Etiology:Orthostatic			0.03 [0.01,0.05]	<0.001	0.03 [0.01,0.08]	<0.001	0.10 [0.04,0.25]	<0.001
Etiology:Others			0.02 [0.01,0.08]	<0.001	-	-	0.06 [0.01,0.43]	0.006
Etiology:Unknown			0.05 [0.02,0.12]	<0.001	0.08 [0.03,0.20]	<0.001	0.15 [0.05,0.51]	0.002
Abnormal ECG			0.94 [0.65,1.36]	0.735	1.41 [0.88,2.25]	0.154	0.52 [0.27,0.99]	0.047

Supplemental table 11 - Cox proportional Hazards analysis for NT-proBNP on several short- and long-term outcomes. BP= blood pressure, CV = cardiovascular, MACE = Major Adverse Cardiovascular Events, 95%-confidence intervals are given in brackets.

Supplemental table 12

	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-cTnI, per 10 ng/L increase	1.62 [1.36,1.93]	<0.001	1.46 [1.29,1.65]	<0.001	1.09 [0.94,1.26]	0.259	1.52 [1.31,1.76]	<0.001
Age	1.05 [1.03,1.07]	<0.001	1.03 [1.02,1.04]	<0.001	1.03 [1.01,1.04]	<0.001	1.04 [1.02,1.05]	<0.001
Sex	0.62 [0.40,0.97]	0.035	0.89 [0.69,1.15]	0.364	0.79 [0.59,1.07]	0.125	0.57 [0.41,0.79]	0.001
Known CV disease	1.10 [0.43,2.84]	0.842	1.20 [0.70,2.05]	0.506	1.19 [0.64,2.21]	0.584	1.58 [0.97,2.56]	0.064
Smoking status	1.50 [1.00,2.24]	0.049	1.47 [1.15,1.88]	0.002	1.24 [0.94,1.64]	0.134		
Hypertension	1.25 [0.69,2.24]	0.466	0.70 [0.50,0.97]	0.034	0.76 [0.51,1.12]	0.168		
Hypercholesterolemia	0.68 [0.46,0.99]	0.046	0.92 [0.72,1.17]	0.490	0.70 [0.53,0.93]	0.014		
Diabetes	1.54 [1.00,2.38]	0.050	1.49 [1.13,1.96]	0.004	1.29 [0.93,1.78]	0.128		
Heart rate, per 5 bpm increase	1.00 [0.97,1.04]	0.972	0.97 [0.94,0.99]	0.020	0.94 [0.90,0.97]	<0.001		
Systolic BP, per 5mmHg increase	0.95 [0.92,0.98]	0.004	0.99 [0.97,1.01]	0.317	0.98 [0.95,1.01]	0.128		
Any cardiac medication	1.12 [0.50,2.48]	0.784	1.36 [0.85,2.17]	0.195	1.95 [1.13,3.37]	0.017		
Etiology:Reflex	0.40 [0.21,0.76]	0.005	0.05 [0.04,0.08]	<0.001	0.05 [0.03,0.08]	<0.001	0.23 [0.14,0.38]	<0.001
Etiology:Orthostatic	1.02 [0.63,1.65]	0.941	0.11 [0.08,0.14]	<0.001	0.14 [0.10,0.20]	<0.001	0.57 [0.39,0.84]	0.004
Etiology:Others	0.85 [0.40,1.81]	0.682	0.10 [0.06,0.16]	<0.001	0.12 [0.06,0.21]	<0.001	0.49 [0.26,0.92]	0.026

Etiology:Unknown	1.34 [0.76,2.38]	0.313	0.19 [0.13,0.27]	<0.001	0.28 [0.18,0.42]	<0.001	0.74 [0.47,1.18]	0.210
Abnormal ECG	1.35 [0.90,2.04]	0.149	1.04 [0.81,1.33]	0.781	1.75 [1.29,2.37]	<0.001	0.88 [0.63,1.22]	0.432

	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-cTnI, per 10 ng/L increase	2.15 [1.42,3.26]	<0.001	1.25 [1.05,1.47]	0.011	0.89 [0.72,1.11]	0.307	1.32 [0.97,1.80]	0.079
Age	1.05 [1.00,1.10]	0.062	1.01 [1.00,1.03]	0.101	1.01 [0.99,1.03]	0.346	1.00 [0.97,1.03]	0.940
Sex			1.28 [0.88,1.86]	0.202	1.44 [0.92,2.26]	0.110	0.98 [0.51,1.90]	0.950
Known CV disease			1.46 [0.69,3.12]	0.326	1.90 [0.77,4.73]	0.166	1.86 [0.69,5.04]	0.223
Smoking status			1.42 [0.98,2.06]	0.064	1.36 [0.87,2.11]	0.174		
Hypertension			0.56 [0.35,0.89]	0.015	0.41 [0.24,0.70]	0.001		
Hypercholesterolemia			1.00 [0.69,1.45]	0.994	0.71 [0.46,1.10]	0.123		
Diabetes			1.32 [0.87,2.01]	0.190	1.29 [0.78,2.13]	0.328		
Heart rate, per 5 bpm increase			0.96 [0.93,1.00]	0.055	0.91 [0.86,0.96]	<0.001		
Systolic BP, per 5mmHg increase			1.01 [0.98,1.05]	0.347	1.02 [0.98,1.06]	0.274		
Any cardiac medication			1.17 [0.60,2.27]	0.644	2.09 [0.86,5.09]	0.104		
Etiology:Reflex			0.01 [0.00,0.02]	<0.001	0.01 [0.00,0.03]	<0.001	0.01 [0.00,0.10]	<0.001
Etiology:Orthostatic			0.03 [0.01,0.06]	<0.001	0.03 [0.01,0.07]	<0.001	0.10 [0.04,0.26]	<0.001
Etiology:Others			0.02 [0.01,0.09]	<0.001	0.00 [0.00,Inf]	0.994	0.06 [0.01,0.46]	0.007
Etiology:Unknown			0.06 [0.03,0.13]	<0.001	0.08 [0.03,0.19]	<0.001	0.16 [0.05,0.53]	0.003
Abnormal ECG			0.99 [0.67,1.48]	0.961	1.79 [1.07,2.98]	0.025	0.46 [0.23,0.90]	0.024

Supplemental table 12 – Cox proportional Hazards analysis for hs-cTnI on several short- and long-term outcomes. BP= blood pressure, CV = cardiovascular, MACE = Major Adverse Cardiovascular Events, 95%-confidence intervals are given in brackets.

Supplemental table 13

	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-cTnT, per 10 ng/L increase	1.96 [1.54,2.50]	<0.001	1.73 [1.48,2.04]	<0.001	1.13 [0.94,1.35]	0.195	1.91 [1.57,2.31]	<0.001
Age	1.04 [1.02,1.06]	<0.001	1.02 [1.01,1.03]	<0.001	1.02 [1.01,1.04]	0.001	1.03 [1.01,1.04]	0.001
Sex	0.65 [0.41,1.02]	0.063	0.96 [0.74,1.25]	0.776	0.78 [0.57,1.06]	0.107	0.62 [0.44,0.87]	0.006
Known CV disease	1.16 [0.46,2.94]	0.759	1.24 [0.73,2.11]	0.428	1.32 [0.70,2.49]	0.389	1.53 [0.94,2.50]	0.085
Smoking status	1.49 [0.99,2.23]	0.054	1.47 [1.15,1.89]	0.002	1.27 [0.95,1.69]	0.104		
Hypertension	1.09 [0.60,1.96]	0.781	0.65 [0.47,0.91]	0.011	0.74 [0.50,1.09]	0.126		
Hypercholesterolemia	0.70 [0.47,1.03]	0.070	0.96 [0.75,1.23]	0.744	0.69 [0.52,0.92]	0.012		
Diabetes	1.33 [0.86,2.07]	0.197	1.30 [0.98,1.72]	0.069	1.27 [0.91,1.76]	0.160		
Heart rate, per 5 bpm increase	1.00 [0.96,1.05]	0.964	0.96 [0.94,0.99]	0.010	0.93 [0.90,0.97]	<0.001		
Systolic BP, per 5mmHg increase	0.96 [0.92,0.99]	0.025	0.99 [0.97,1.02]	0.586	0.98 [0.96,1.01]	0.239		
Any cardiac medication	1.17 [0.54,2.56]	0.689	1.37 [0.87,2.17]	0.178	1.91 [1.09,3.33]	0.023		
Etiology:Reflex	0.44 [0.23,0.84]	0.013	0.05 [0.04,0.08]	<0.001	0.05 [0.03,0.09]	<0.001	0.25 [0.15,0.42]	<0.001
Etiology:Orthostatic	1.10 [0.68,1.79]	0.697	0.11 [0.08,0.15]	<0.001	0.15 [0.10,0.21]	<0.001	0.60 [0.41,0.88]	0.009
Etiology:Others	0.99 [0.47,2.12]	0.985	0.11 [0.06,0.18]	<0.001	0.12 [0.07,0.23]	<0.001	0.57 [0.30,1.07]	0.079

Etiology:Unknown	1.34 [0.76,2.36]	0.315	0.18 [0.12,0.26]	<0.001	0.28 [0.18,0.41]	<0.001	0.74 [0.46,1.17]	0.194
Abnormal ECG	1.29 [0.85,1.96]	0.233	0.99 [0.77,1.28]	0.963	1.75 [1.28,2.38]	<0.001	0.80 [0.57,1.12]	0.196

	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-cTnT, per 10 ng/L increase	1.78 [0.83,3.83]	0.139	1.52 [1.21,1.90]	<0.001	0.89 [0.66,1.21]	0.450	1.46 [0.97,2.20]	0.069
Age	1.05 [0.99,1.11]	0.114	1.01 [1.00,1.03]	0.147	1.01 [0.99,1.03]	0.333	1.00 [0.97,1.02]	0.768
Sex			1.26 [0.86,1.85]	0.239	1.39 [0.87,2.22]	0.163	0.99 [0.50,1.96]	0.971
Known CV disease			1.30 [0.61,2.81]	0.496	2.15 [0.82,5.66]	0.119	1.73 [0.64,4.68]	0.285
Smoking status			1.50 [1.03,2.19]	0.036	1.40 [0.89,2.21]	0.145		
Hypertension			0.54 [0.34,0.87]	0.011	0.39 [0.23,0.68]	0.001		
Hypercholesterolemia			1.07 [0.74,1.56]	0.717	0.68 [0.44,1.05]	0.084		
Diabetes			1.19 [0.77,1.82]	0.434	1.35 [0.80,2.29]	0.259		
Heart rate, per 5 bpm increase			0.96 [0.93,1.00]	0.046	0.91 [0.87,0.96]	<0.001		
Systolic BP, per 5mmHg increase			1.02 [0.99,1.05]	0.204	1.02 [0.99,1.07]	0.214		
Any cardiac medication			1.35 [0.69,2.64]	0.386	2.40 [0.92,6.29]	0.074		
Etiology:Reflex			0.01 [0.00,0.03]	<0.001	0.01 [0.00,0.04]	<0.001	0.02 [0.00,0.12]	<0.001
Etiology:Orthostatic			0.03 [0.01,0.06]	<0.001	0.03 [0.01,0.08]	<0.001	0.11 [0.04,0.28]	<0.001
Etiology:Others			0.03 [0.01,0.10]	<0.001			0.07 [0.01,0.53]	0.010
Etiology:Unknown			0.06 [0.03,0.13]	<0.001	0.08 [0.03,0.20]	<0.001	0.16 [0.05,0.53]	0.003
Abnormal ECG			0.96 [0.64,1.44]	0.838	1.69 [1.01,2.83]	0.047	0.42 [0.21,0.83]	0.012

Supplemental table 13 - Cox proportional Hazards analysis for hs-cTnI on several short- and long-term outcomes. BP= blood pressure, CV = cardiovascular, MACE = Major Adverse Cardiovascular Events, 95%-confidence intervals are given in brackets.

Supplemental table 14

Cut-offs for BNP for 30-day death	**Target Sensitivity**	**Cut-off (pg/mL)**	**Sensitivity (95%-CI)**	**Specificity (95% CI)**	**NPV (95%-CI)**	**Incidence of criteria % (95%-CI)**
	80	56.4	80 (49, 94.3)	55 (52.4, 57.6)	99.7 (99.1, 99.9)	54.8 (52.2, 57.3)
	85	36	90 (59.6, 98.2)	42.6 (40, 45.2)	99.8 (99.1, 100)	42.3 (39.8, 44.9)
	90	36	90 (59.6, 98.2)	42.6 (40, 45.2)	99.8 (99.1, 100)	42.3 (39.8, 44.9)
	95	33.6	100 (72.2, 100)	40.8 (38.3, 43.4)	100 (99.3, 100)	40.5 (38, 43.1)
	98	33.6	100 (72.2, 100)	40.8 (38.3, 43.4)	100 (99.3, 100)	40.5 (38, 43.1)
	Target Specificity	**Cut-off (pg/mL)**	**Specificity (95%-CI)**	**Sensitivity (95% CI)**	**PPV (95%-CI)**	**Incidence of criteria % (95%-CI)**
	80	171.4	81.7 (79.6, 83.7)	40 (16.8, 68.7)	1.5 (0.6, 3.9)	18.4 (16.5, 20.5)
	85	294.3	90.5 (88.8, 91.9)	30 (10.8, 60.3)	2.2 (0.7, 6.2)	9.7 (8.2, 11.3)
	90	294.3	90.5 (88.8, 91.9)	30 (10.8, 60.3)	2.2 (0.7, 6.2)	9.7 (8.2, 11.3)
	95	975.2	98.3 (97.5, 98.9)	20 (5.7, 51)	7.7 (2.1, 24.1)	1.8 (1.2, 2.7)
	98	975.2	98.3 (97.5, 98.9)	20 (5.7, 51)	7.7 (2.1, 24.1)	1.8 (1.2, 2.7)

Cut-offs for BNP for 30-day MACE	**Target Sensitivity**	**Cut-off (pg/mL)**	**Sensitivity (95%-CI)**	**Specificity (95% CI)**	**NPV (95%-CI)**	**Incidence of criteria % (95%-CI)**
	80	41	80.5 (73.6, 86)	49.5 (46.7, 52.2)	95.4 (93.5, 96.8)	46.2 (43.6, 48.8)
	85	32.1	85.1 (78.6, 89.8)	42.6 (39.9, 45.3)	95.9 (93.9, 97.3)	39.6 (37.1, 42.2)
	90	**22.9**	90.3 (84.6, 94)	32.5 (29.9, 35.1)	96.5 (94.3, 97.8)	**30 (27.7, 32.4)**
	95	13.1	95.5 (90.9, 97.8)	18.7 (16.6, 20.9)	97.1 (94.2, 98.6)	17.1 (15.3, 19.2)
	98	9.9	98.7 (95.4, 99.6)	3.1 (2.3, 4.2)	95.1 (83.9, 98.7)	2.9 (2.1, 3.9)
	Target Specificity	**Cut-off (pg/mL)**	**Specificity (95%-CI)**	**Sensitivity (95% CI)**	**PPV (95%-CI)**	**Incidence of criteria % (95%-CI)**
	80	132.8	80.3 (78, 82.4)	54.5 (46.7, 62.2)	25.2 (20.9, 30.2)	23.5 (21.4, 25.8)
	85	172.6	85.3 (83.2, 87.1)	45.5 (37.8, 53.3)	27.3 (22.2, 33.1)	18.1 (16.2, 20.2)
	90	254	90.3 (88.6, 91.8)	35.1 (28, 42.9)	30.7 (24.3, 37.8)	12.4 (10.8, 14.2)
	95	409.9	95.2 (93.9, 96.3)	24 (18, 31.4)	38.1 (29.1, 48.1)	6.8 (5.6, 8.3)
	98	766.3	98 (97.1, 98.7)	12.3 (8, 18.5)	43.2 (29.7, 57.8)	3.1 (2.3, 4.2)

Cut-offs for NT-proBNP for 30-day death	**Target Sensitivity**	**Cut-off (pg/mL)**	**Sensitivity (95%-CI)**	**Specificity (95% CI)**	**NPV (95%-CI)**	**Incidence of criteria % (95%-CI)**
	80	327	80 (49, 94.3)	65.4 (62.9, 67.8)	99.8 (99.2, 99.9)	65.1 (62.5, 67.5)
	85	280	90 (59.6, 98.2)	62 (59.4, 64.5)	99.9 (99.4, 100)	61.6 (59, 64.1)
	90	280	90 (59.6, 98.2)	62 (59.4, 64.5)	99.9 (99.4, 100)	61.6 (59, 64.1)
	95	97	100 (72.2, 100)	34.6 (32.2, 37.1)	100 (99.2, 100)	34.4 (31.9, 36.9)
	98	97	100 (72.2, 100)	34.6 (32.2, 37.1)	100 (99.2, 100)	34.4 (31.9, 36.9)
	Target Specificity	**Cut-off (pg/mL)**	**Specificity (95%-CI)**	**Sensitivity (95% CI)**	**PPV (95%-CI)**	**Incidence of criteria % (95%-CI)**
	80	1137	84.4 (82.4, 86.2)	50 (23.7, 76.3)	2.2 (1, 5.1)	15.8 (14, 17.8)
	85	2251	91.9 (90.4, 93.2)	40 (16.8, 68.7)	3.4 (1.3, 8.4)	8.3 (7, 9.9)
	90	2251	91.9 (90.4, 93.2)	40 (16.8, 68.7)	3.4 (1.3, 8.4)	8.3 (7, 9.9)
	95	4436	96.6 (95.5, 97.4)	20 (5.7, 51)	4 (1.1, 13.5)	3.5 (2.7, 4.6)
	98	6470	98.4 (97.6, 98.9)	10 (1.8, 40.4)	4.2 (0.7, 20.2)	1.7 (1.1, 2.5)

Cut-offs for NT-proBNP for 30-day MACE	**Target Sensitivity**	**Cut-off (pg/mL)**	**Sensitivity (95%-CI)**	**Specificity (95% CI)**	**NPV (95%-CI)**	**Incidence of criteria % (95%-CI)**
	80	169	80.5 (73.6, 86)	53 (50.3, 55.8)	95.7 (93.9, 97)	49.4 (46.8, 52)
	85	123	85.1 (78.6, 89.8)	44.4 (41.7, 47.2)	96.1 (94.2, 97.4)	41.2 (38.7, 43.8)
	90	**97**	90.3 (84.6, 94)	37.4 (34.7, 40.1)	96.9 (95, 98.1)	**34.4 (31.9, 36.9)**
	95	65	95.5 (90.9, 97.8)	26.4 (24.1, 28.9)	97.9 (95.8, 99)	24.1 (21.9, 26.4)
	98	29	98.1 (94.4, 99.3)	11.2 (9.5, 13)	97.9 (94.1, 99.3)	10.2 (8.7, 11.9)
	Target Specificity	**Cut-off (pg/mL)**	**Specificity (95%-CI)**	**Sensitivity (95% CI)**	**PPV (95%-CI)**	**Incidence of criteria %**

						(95%-CI)
	80	622	80.4 (78.1, 82.5)	52.6 (44.7, 60.3)	24.6 (20.3, 29.6)	23.2 (21.1, 25.5)
	85	1010	85.7 (83.6, 87.5)	43.5 (35.9, 51.4)	27 (21.9, 32.9)	17.5 (15.6, 19.6)
	90	1423	90.1 (88.3, 91.6)	31.2 (24.4, 38.9)	27.7 (21.6, 34.8)	12.2 (10.6, 14)
	95	2995	95.6 (94.3, 96.6)	20.1 (14.6, 27.2)	35.6 (26.4, 46.1)	6.1 (5, 7.5)
	98	5173	98.1 (97.2, 98.7)	11 (7, 17)	41.5 (27.8, 56.6)	2.9 (2.1, 3.9)

	Target Sensitivity	**Cut-off (ng/L)**	**Sensitivity (95%-CI)**	**Specificity (95% CI)**	**NPV (95%-CI)**	**Incidence of criteria % (95%-CI)**
Cut-offs for hs-cTnI for 30-day death	80	4.7	80 (49, 94.3)	51.5 (48.8, 54.1)	99.7 (99, 99.9)	51.2 (48.6, 53.9)
	85	3.2	90 (59.6, 98.2)	35.7 (33.1, 38.3)	99.8 (98.8, 100)	35.5 (33, 38.1)
	90	3.2	90 (59.6, 98.2)	35.7 (33.1, 38.3)	99.8 (98.8, 100)	35.5 (33, 38.1)
	95	3.1	100 (72.2, 100)	33.7 (31.3, 36.3)	100 (99.2, 100)	33.5 (31, 36)
	98	3.1	100 (72.2, 100)	33.7 (31.3, 36.3)	100 (99.2, 100)	33.5 (31, 36)
	Target Specificity	**Cut-off (ng/L)**	**Specificity (95%-CI)**	**Sensitivity (95% CI)**	**PPV (95%-CI)**	**Incidence of criteria % (95%-CI)**
	80	16.1	83 (80.9, 84.9)	70 (39.7, 89.2)	3 (1.5, 6)	17.4 (15.4, 19.5)
	85	25.6	89.4 (87.6, 90.9)	50 (23.7, 76.3)	3.4 (1.5, 7.7)	10.9 (9.4, 12.7)
	90	35.4	92.1 (90.5, 93.4)	30 (10.8, 60.3)	2.8 (0.9, 7.8)	8.1 (6.7, 9.6)
	95	75.3	96.5 (95.4, 97.4)	20 (5.7, 51)	4.1 (1.1, 13.7)	3.6 (2.7, 4.8)
	98	1922.1	99.9 (99.6, 100)	0 (0, 27.8)	0 (0, 79.3)	0.1 (0, 0.5)

	Target Sensitivity	**Cut-off (ng/L)**	**Sensitivity (95%-CI)**	**Specificity (95% CI)**	**NPV (95%-CI)**	**Incidence of criteria % (95%-CI)**
Cut-offs for hs-cTnI for 30-day MACE	80	5.4	80.1 (72.9, 85.8)	59.6 (56.8, 62.3)	96.1 (94.5, 97.3)	55.3 (52.6, 57.9)
	85	4.6	85.6 (79, 90.4)	54.5 (51.7, 57.3)	96.9 (95.3, 98)	50.2 (47.5, 52.8)
	90	**2.9**	90.4 (84.5, 94.2)	33.9 (31.3, 36.6)	96.7 (94.5, 98)	**31.3 (28.9, 33.8)**
	95	2	96.6 (92.2, 98.5)	17.2 (15.2, 19.5)	97.7 (94.6, 99)	15.7 (13.9, 17.8)
	98	1.6	99.3 (96.2, 99.9)	9.7 (8.1, 11.5)	99.2 (95.4, 99.9)	8.7 (7.3, 10.4)
	Target Specificity	**Cut-off (ng/L)**	**Specificity (95%-CI)**	**Sensitivity (95% CI)**	**PPV (95%-CI)**	**Incidence of criteria % (95%-CI)**
	80	11.5	80 (77.7, 82.2)	52.7 (44.7, 60.7)	24.2 (19.8, 29.2)	23.5 (21.3, 25.8)
	85	15.1	85.3 (83.2, 87.2)	45.9 (38, 54)	27.5 (22.2, 33.4)	18 (16.1, 20.2)
	90	23.7	90.1 (88.3, 91.7)	32.2 (25.2, 40.1)	28.3 (22, 35.6)	12.3 (10.6, 14.1)
	95	43.2	95 (93.7, 96.1)	20.5 (14.8, 27.8)	33.3 (24.5, 43.6)	6.7 (5.4, 8.1)
	98	91.6	98.2 (97.3, 98.8)	11 (6.9, 17.1)	42.1 (27.9, 57.8)	2.8 (2, 3.8)

	Target Sensitivity	**Cut-off (ng/L)**	**Sensitivity (95%-CI)**	**Specificity (95% CI)**	**NPV (95%-CI)**	**Incidence of criteria % (95%-CI)**
Cut-offs for hs-cTnT for 30-day death	80	12	80 (49, 94.3)	54.1 (51.5, 56.8)	99.7 (99, 99.9)	53.9 (51.2, 56.5)
	85	10	90 (59.6, 98.2)	47.9 (45.2, 50.6)	99.8 (99.1, 100)	47.6 (44.9, 50.3)
	90	10	90 (59.6, 98.2)	47.9 (45.2, 50.6)	99.8 (99.1, 100)	47.6 (44.9, 50.3)
	95	9	100 (72.2, 100)	43.7 (41.1, 46.4)	100 (99.3, 100)	43.4 (40.8, 46)
	98	9	100 (72.2, 100)	43.7 (41.1, 46.4)	100 (99.3, 100)	43.4 (40.8, 46)
	Target Specificity	**Cut-off (ng/L)**	**Specificity (95%-CI)**	**Sensitivity (95% CI)**	**PPV (95%-CI)**	**Incidence of criteria % (95%-CI)**
	80	34	88.9 (87.1, 90.5)	60 (31.3, 83.2)	3.9 (1.8, 8.2)	11.5 (9.9, 13.3)
	85	34	88.9 (87.1, 90.5)	60 (31.3, 83.2)	3.9 (1.8, 8.2)	11.5 (9.9, 13.3)
	90	38	90.5 (88.9, 92)	50 (23.7, 76.3)	3.8 (1.6, 8.6)	9.8 (8.3, 11.5)
	95	132	99.3 (98.7, 99.6)	10 (1.8, 40.4)	10 (1.8, 40.4)	0.7 (0.4, 1.4)
	98	132	99.3 (98.7, 99.6)	10 (1.8, 40.4)	10 (1.8, 40.4)	0.7 (0.4, 1.4)

Cut-offs for hs-cTnT for	**Target Sensitivity**	**Cut-off (ng/L)**	**Sensitivity (95%-CI)**	**Specificity (95% CI)**	**NPV (95%-CI)**	**Incidence of criteria %**

30-day MACE						**(95%-CI)**
	80	11	81.5 (74.4, 87)	54.8 (52, 57.6)	96.1 (94.4, 97.3)	50.9 (48.3, 53.6)
	85	9	89 (82.9, 93.1)	47.3 (44.5, 50.1)	97.3 (95.6, 98.3)	43.4 (40.8, 46)
	90	**8**	90.4 (84.5, 94.2)	41.8 (39.1, 44.6)	97.3 (95.5, 98.4)	**38.4 (35.8, 41)**
	95	6	95.2 (90.4, 97.7)	28.3 (25.9, 30.9)	98 (95.9, 99)	25.8 (23.5, 28.2)
	98	2.9	100 (97.4, 100)	28.3 (25.9, 30.9)	98 (95.9, 99)	25.8 (23.5, 28.2)
	Target Specificity	**Cut-off (ng/L)**	**Specificity (95%-CI)**	**Sensitivity (95% CI)**	**PPV (95%-CI)**	**Incidence of criteria % (95%-CI)**
	80	21	80.2 (77.9, 82.3)	54.1 (46, 62)	24.8 (20.4, 29.9)	23.5 (21.3, 25.8)
	85	26	85.7 (83.7, 87.6)	45.9 (38, 54)	28 (22.7, 34)	17.7 (15.7, 19.8)
	90	32	90.2 (88.4, 91.8)	36.3 (28.9, 44.4)	31 (24.5, 38.3)	12.6 (11, 14.5)
	95	47	95 (93.7, 96.1)	21.9 (16, 29.3)	34.8 (25.8, 44.9)	6.8 (5.6, 8.3)
	98	62	98 (97.1, 98.7)	15.1 (10.2, 21.8)	47.8 (34.1, 61.9)	3.4 (2.6, 4.5)

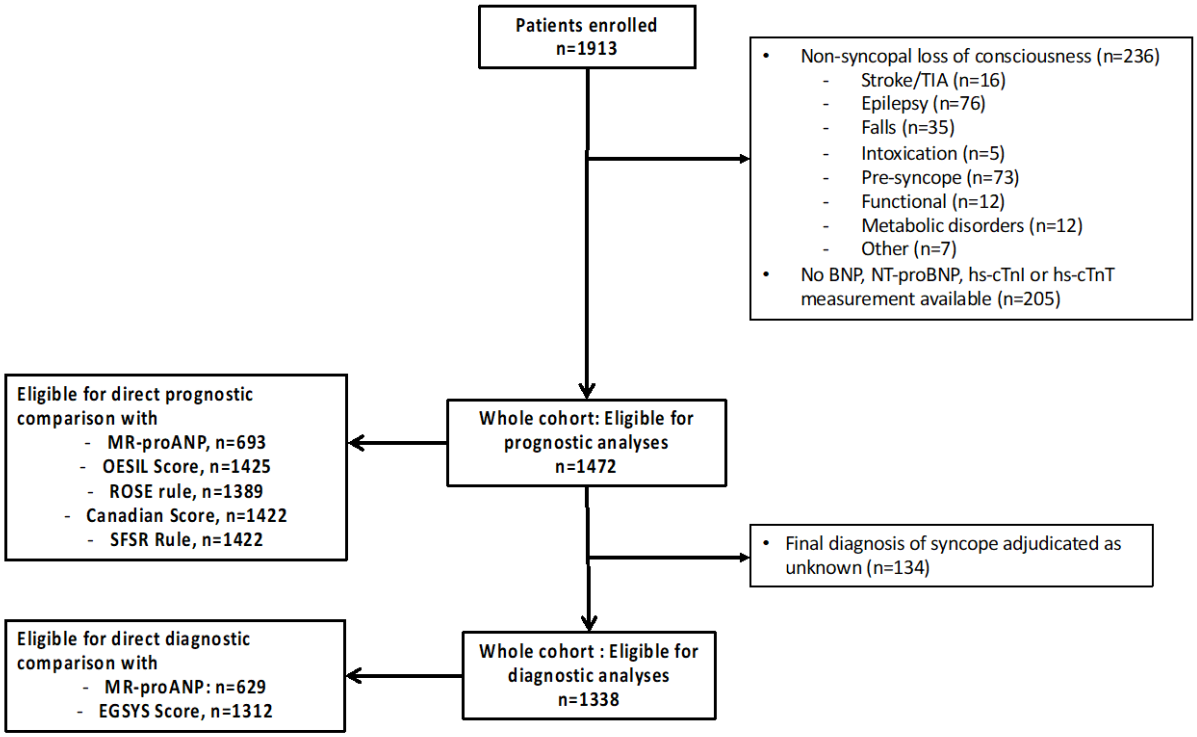
Supplemental table 14 - Optimal cut-offs to rule-out/rule-in events in the 30-day follow-up of patients with no obvious syncope cause in the ED. Highlighted in green are the BNP, NT-proBNP and hs-cTnT/I cut-offs that allowed for an at least 90%-sensitivity rule-out of death and MACE at 30 days, therefore classifying ~30% of the cohort as rule-out for these events. CI = Confidence interval.

Supplemental table 15

	BNP>22.9	BNP<22.9
Not hospitalized	508 (53.93%)	298 (72.51%)
Hospitalized	434 (46.07%)	113 (27.49%)
	NT-proBNP>97	**NT-proBNP<97**
Not hospitalized	456 (51.47%)	350 (74.95%)
Hospitalized	430 (48.53%)	117 (25.05%)
	Hs-cTnI>2.9	**Hs-cTnI<2.9**
Not hospitalized	484 (52.04%)	322 (76.12%)
Hospitalized	446 (47.96%)	101 (23.88%)
	Hs-TnT>8	**Hs-cTnT<8**
Not hospitalized	412 (49.4%)	394 (75.92%)
Hospitalized	422 (50.6%)	125 (24.08%)

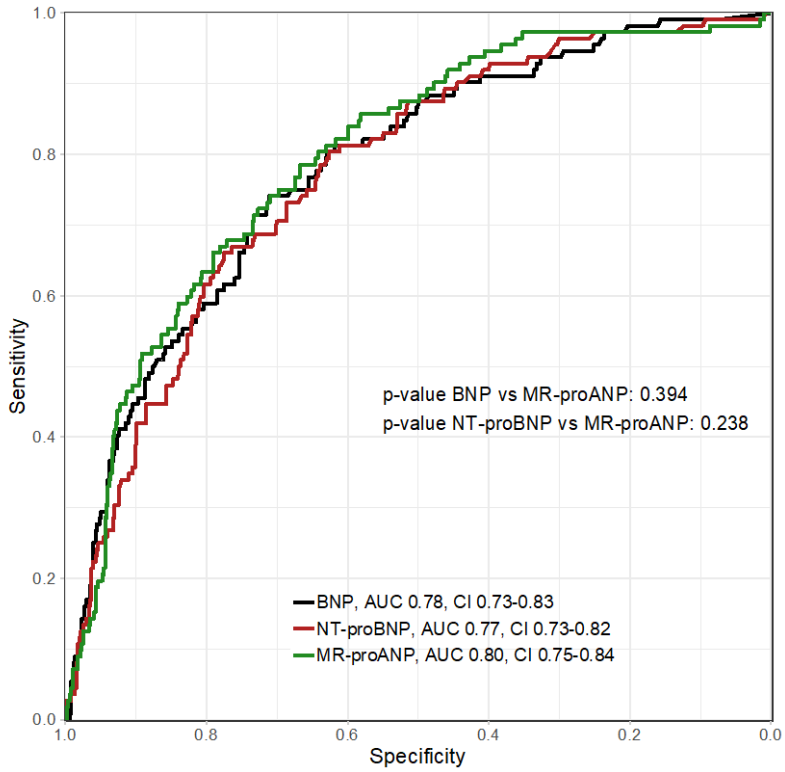
Supplemental table 15 - Number and percentage of hospitalizations among patients with no obvious syncope etiology upon admission and above/below the 90%-sensitivity cut-off to rule-out both death and MACE in a 30-day follow-up

Supplemental Figure 1



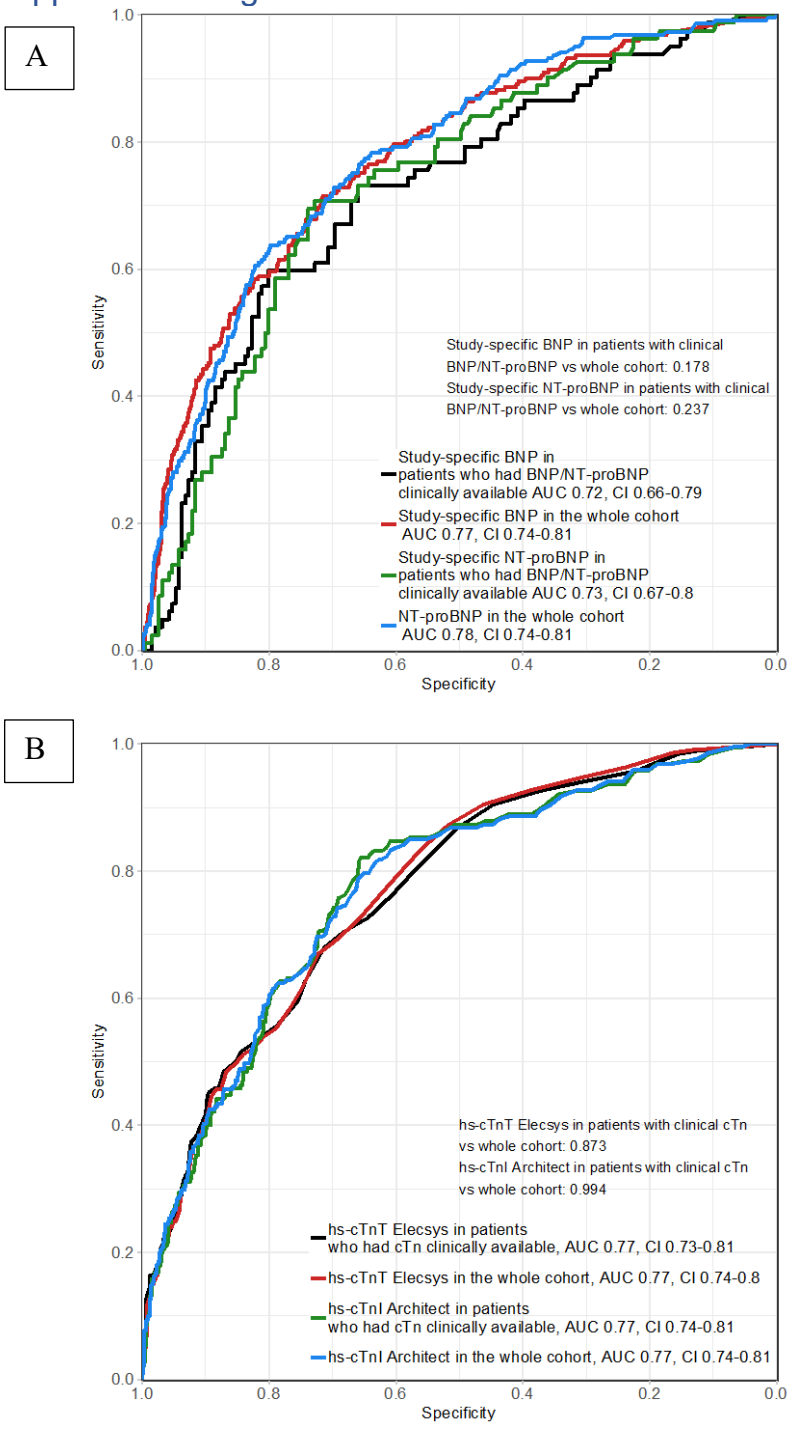
Supplemental figure 1 – Patient chartflow

Supplemental Figure 2



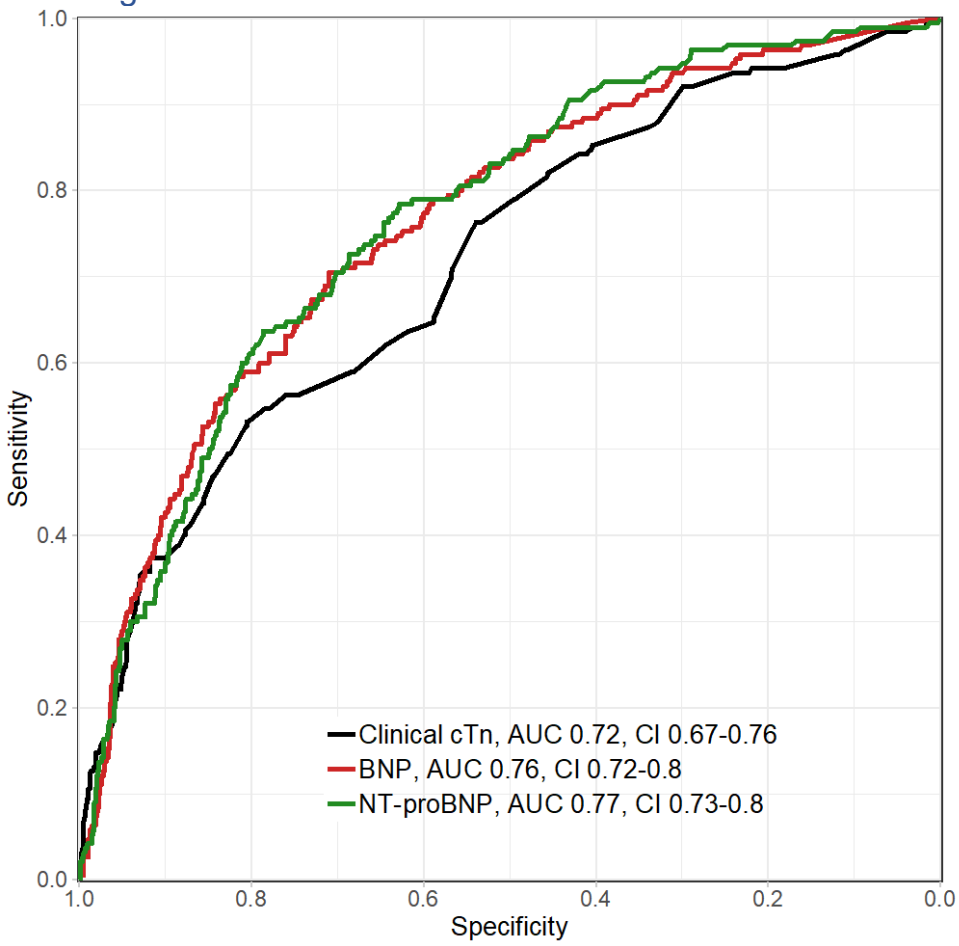
Supplemental figure 2 – Direct comparison of the accuracy of BNP and NT-proBNP versus MR-proANP. P-values were calculated according to DeLong. CI = 95%-confidence interval

Supplemental Figure 3



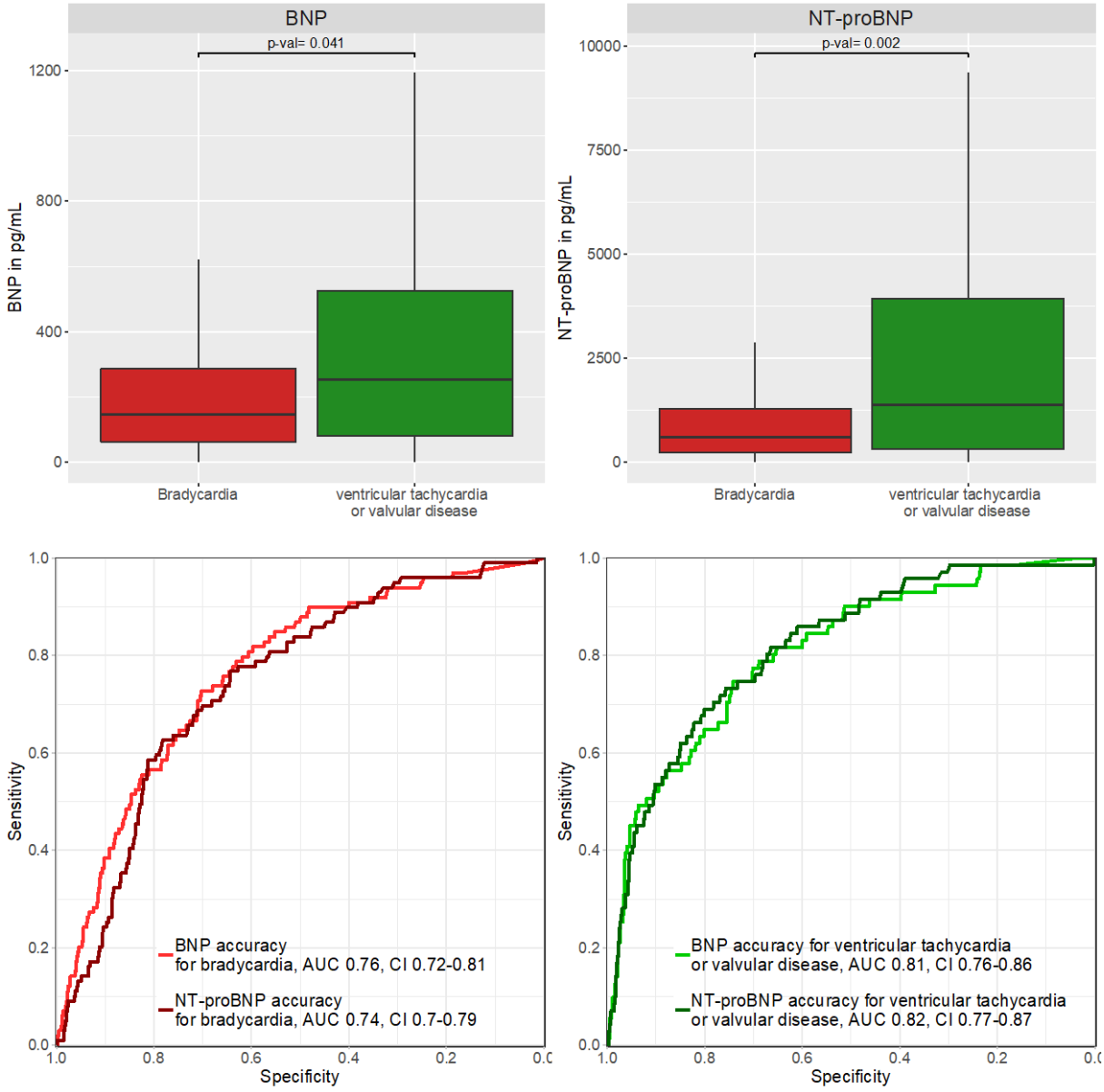
Supplemental figure 3 – Sensitivity analysis : Comparison of the performance of the biomarkers in the subgroup of patients in whom the biomarkers were clinically assessed versus the performance of the biomarkers in the overall cohort for the diagnosis of cardiac syncope. A) for BNP and NT-proBNP, B) for hs-cTnT Elecsys and hs-cTnI Architect. P-values were calculated according to DeLong.CI = 95%-confidence interval

Supplemental Figure 4



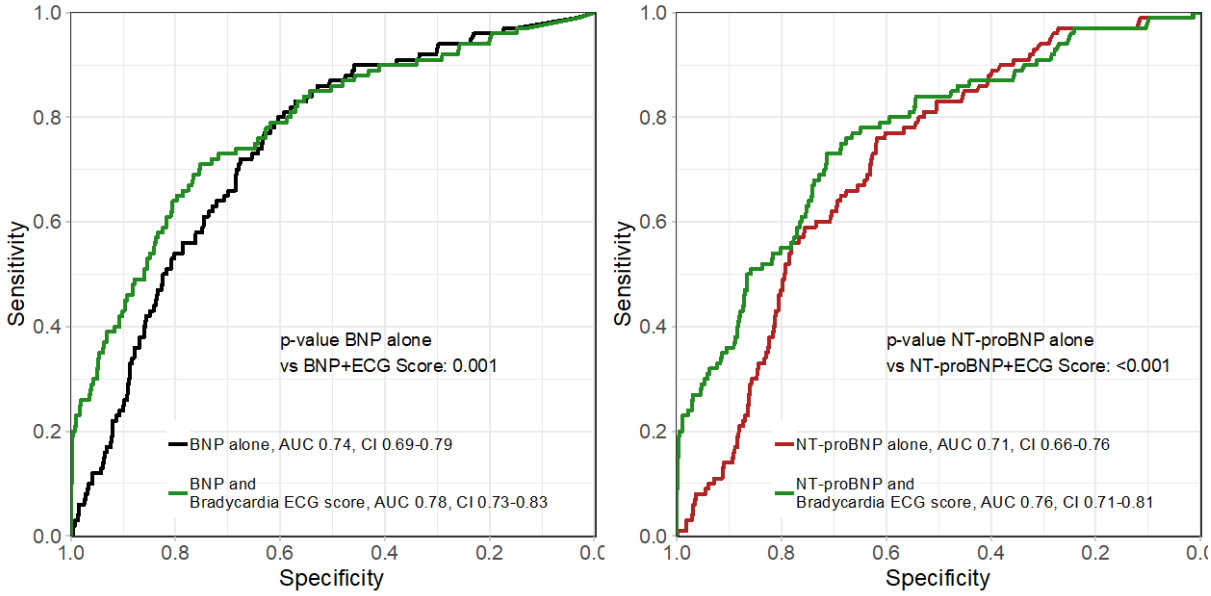
Supplemental figure 4 – Direct comparison of the diagnostic accuracy of BNP and NT-proBNP versus clinically ordered cardiac troponins for the diagnosis of cardiac syncope. CI = 95%-confidence interval

Supplemental Figure 5



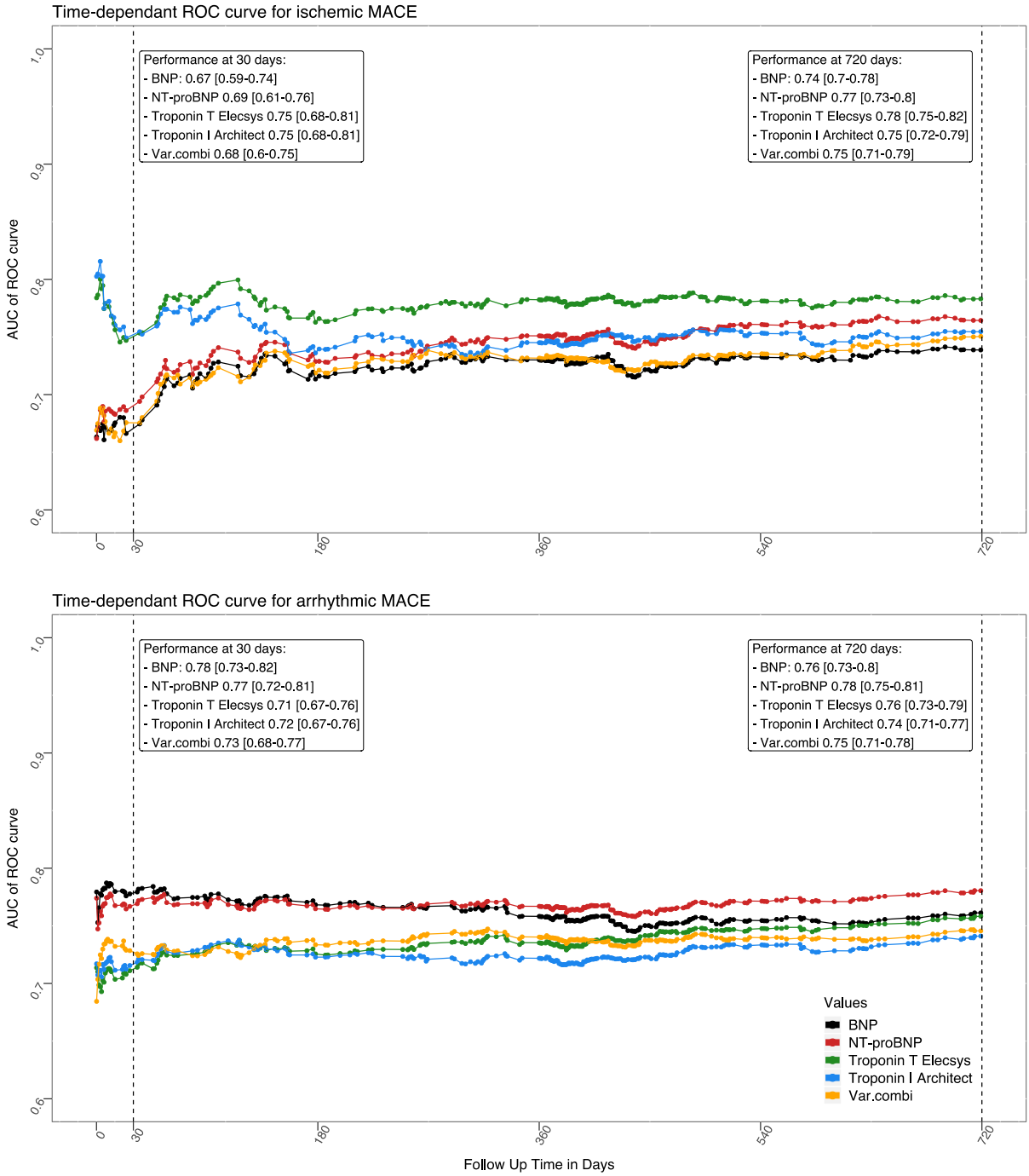
Supplemental Figure 5 –
Up: Boxplots representing the BNP concentrations according to the cardiac etiology of the syncope. The boxplots represent the median with the interquartile range (IQR), whiskers represent ± 1.5 x the IQR. P-values are calculated based on a Wilcoxon-rang-sum test.
Down: ROC curves of the performance of BNP for the diagnosis of bradycardia or ventricular tachycardia/valvular disease.

Supplemental Figure 6



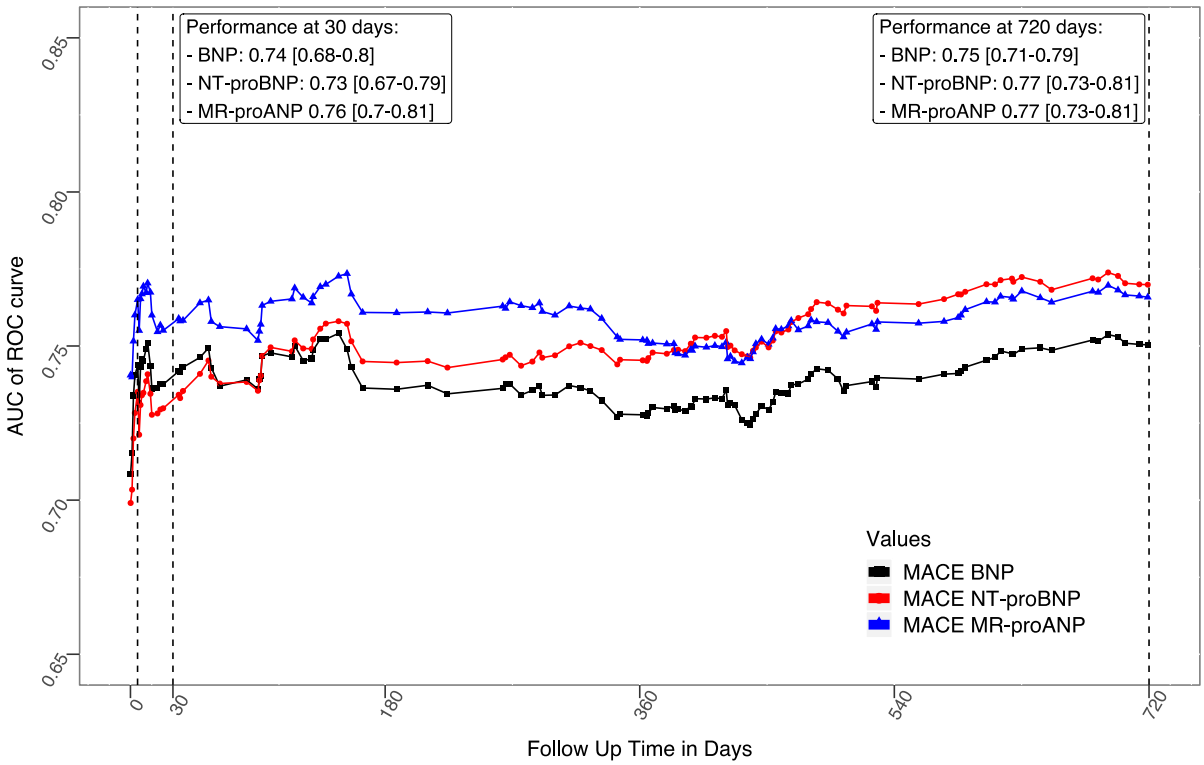
Supplemental figure 6 – Performance of natriuretic peptides alone versus in conjunction with a score based on bradycardia-related baseline ECG findings. P-values were calculated according to DeLong. CI = 95%-Confidence intervals.

Supplemental Figure 7



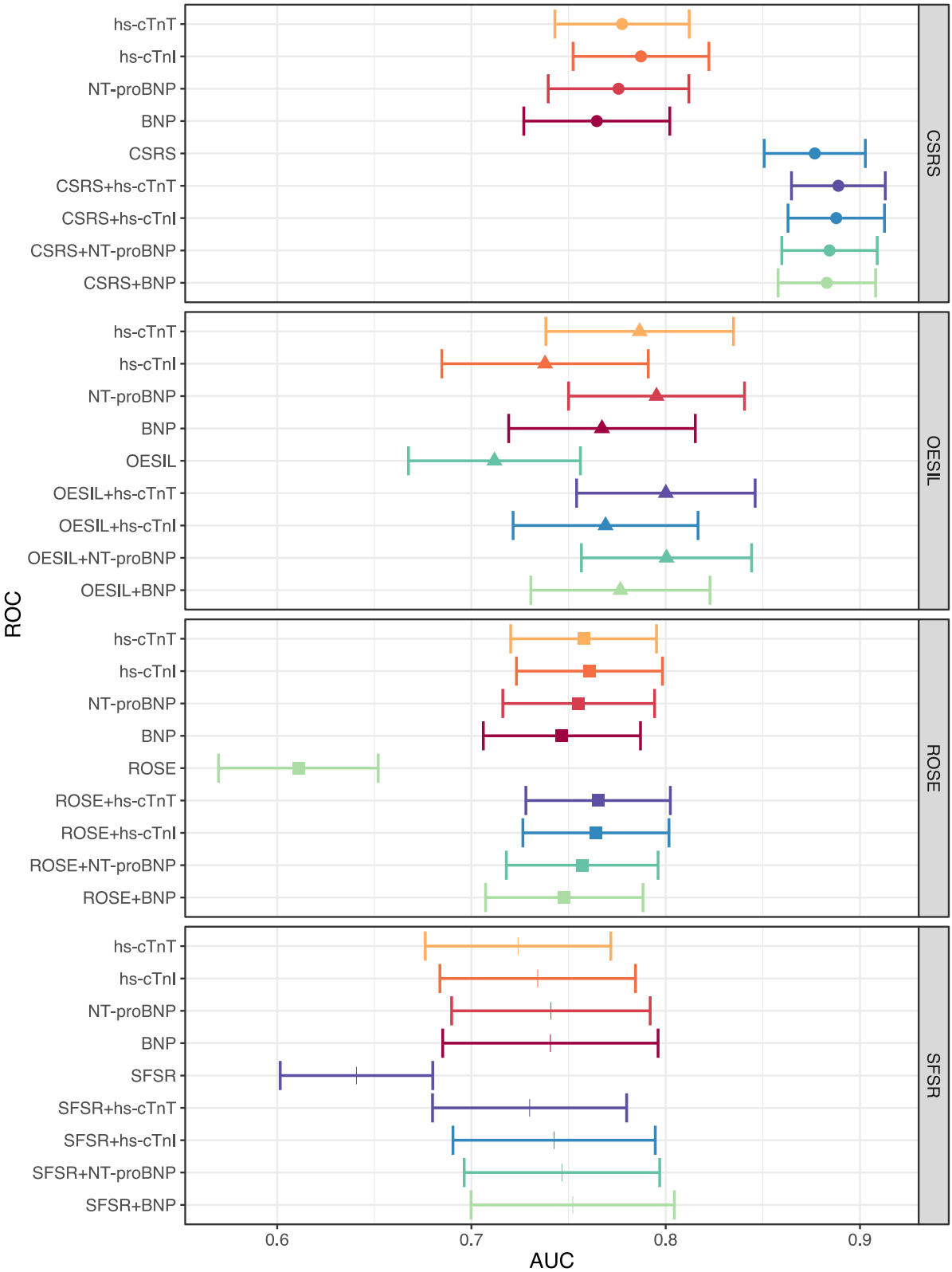
Supplemental figure 7 – Prognostic accuracy of natriuretic peptides for ischemic and arrhythmic MACE. The combination of clinical variables is detailed in the supplemental methods. 95%-confidence intervals are given in brackets.

Supplemental Figure 8



Supplemental figure 8 – Time-dependent ROC curves for direct comparison of the accuracy of BNP, NT-proBNP and MR-proANP for risk-stratification of major adverse cardiac events including death. 95%-confidence intervals are given in brackets.

Supplemental figure 9



Supplemental figure 9 – Direct comparison of natriuretic peptides and cardiac troponins with established prognostic risk scores: the Canadian Syncope Risk Score (CSRS), the OESIL Score, the ROSE rule, and the San Francisco Rule (SFSR). All scores and rules are validated for their respective endpoint.

Appendix

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