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.

INTRODUCTION

Syncope is a transient loss of consciousness (T-LOC) associated with an inability to maintain postural tone due global cerebral hypoperfusion.[1] 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.[1,3,4] Early risk stratification during initial evaluation is important to guide decisions regarding treatment and disposition and prevent long-term morbidity and mortality[1]. 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[5] 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[6].

In an attempt to improve the identification of patients at risk of adverse outcomes, numerous syncope-specific risk scores[7–9] have been derived. However, as highlighted in the recent ACC/AHA/HRS “Guideline for the Evaluation and Management of Patients With Syncope”,[10] 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[11]. 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[10,12]. However, a prospective validation in a multicenter study is lacking. Our study aims to validate syncope-specific risk scores[7–9] 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 1).

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,[10] for which our study contained appropriate data to allow their validation, were computed according to the original score definition (Supplemental table 1). In total, seven syncope-specific scores mentioned in these guidelines were computed in all patients for this analysis: The score by Martin[13], the OESIL[9] score, the SFSR[14] score, the Boston Syncope[15], the STePS[16] score (for long- and short-term risk prediction) and the EGSYS[6] 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 1 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 1), 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[1,10] 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 1).

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 2. 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 1. 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 2. 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 2A and 2B. The performance of the best performing scores at alternative cut-off points is presented in the supplemental Table 3A and 3B.

Survival and survival free of MACE up to 2 years of follow-up according to the $CHADS_2$ and OESIL score are shown in Figures 2. 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 1. 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 2C and supplemental Table 3C, 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 4).

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.[6,9,13–17] 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[18], 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[19–23] and are widely used prediction tools for thromboembolic episodes and initiation of treatment with anticoagulants in patients with atrial fibrillation[11,24,25]. 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.[12], 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[6] 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[26]. 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 1 and Supplemental Figure 2), 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 [6,9,12,14,15,27], 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[28–30]. 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[3] 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 INTERESTS 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

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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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Figures

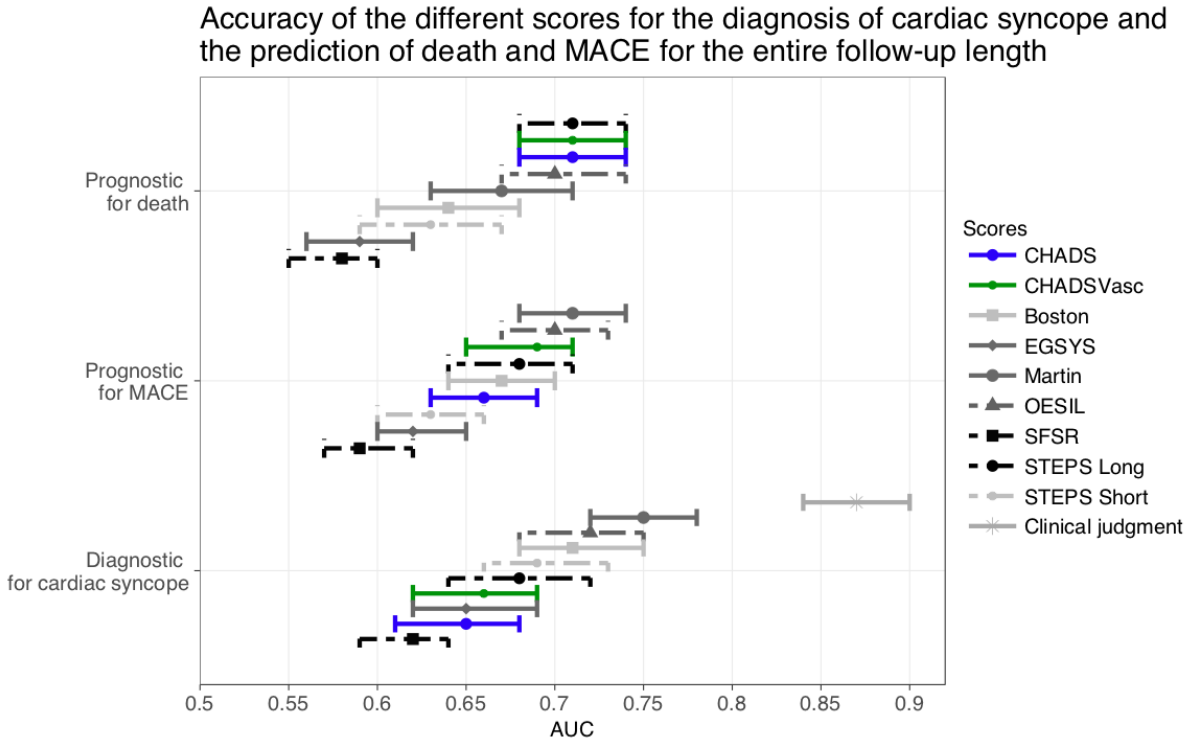

Figure 1: Accuracy of the analyzed scores for the prediction of death and MACE (for a median follow-up of 739 days) and for the diagnosis of cardiac syncope, as given by value of the Area Under the Curve.

Whiskers represent the 95%-confidence intervals.

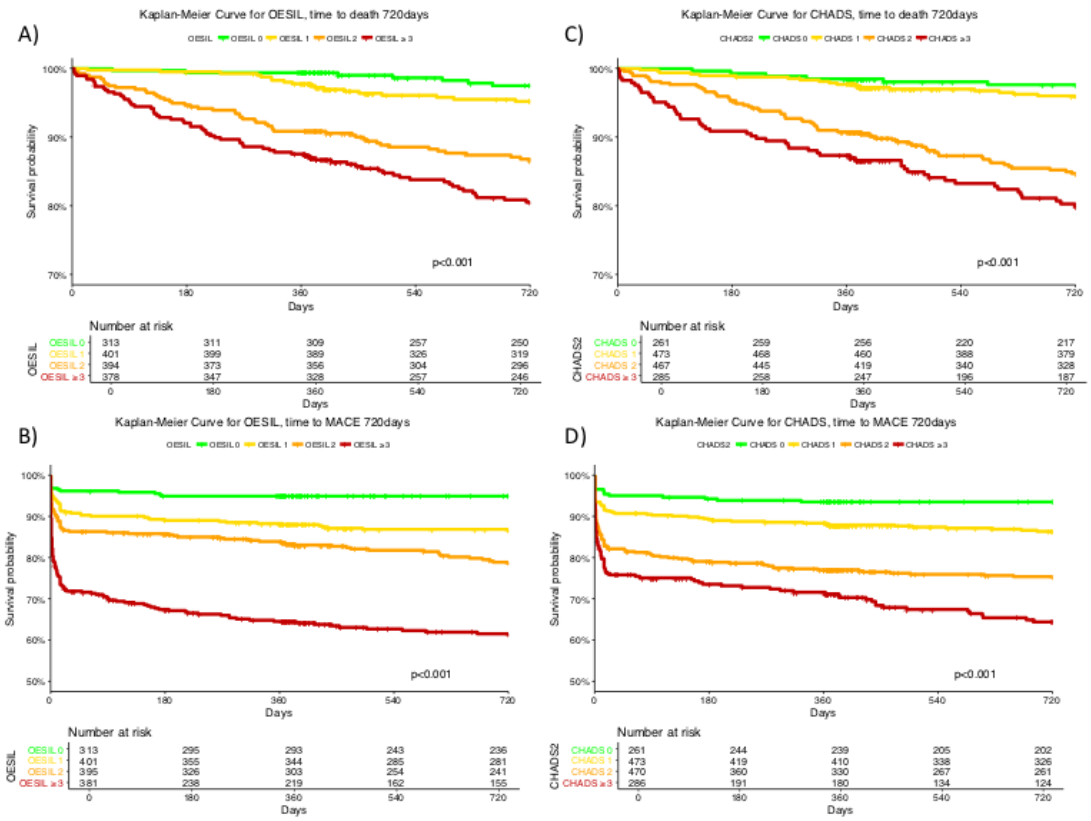

Figure 2: Survival analysis using the OESIL- (A and B) or $CHADS_2$-score (C and D) for time-to-death and time-to-first MACE until 720 days.

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

Tables

Table 1: 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	≥1	30-d serious events	NPV=100% PPV=44% SE = 97% SP=62%

[a] As mentioned in the AHA/ACC Guidelines[27]

		abnormal vital signs, primary central nervous event			
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%
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.

1

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

Table 1: 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

Table 2	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