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:¹,²

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 light-headedness, 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.
EGSYS risk score – Multivariate

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.
## STARD Checklist for studies of diagnostic accuracy

| Section & Topic | No | Item                                                                 | Reported on page # |
|-----------------|----|----------------------------------------------------------------------|-------------------|
| **TITLE OR ABSTRACT** |    | Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC) | 2                 |
| **ABSTRACT** |    | Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts) | 2                 |
| **INTRODUCTION** |    | Scientific and clinical background, including the intended use and clinical role of the index test | 3                 |
| **METHODS** |    | Study objectives and hypotheses | 3-4               |
| **Study design** |    | Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study) | 5                 |
| **Participants** |    | Eligibility criteria | 5                 |
| |    | On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry) | 5                 |
| |    | Where and when potentially eligible participants were identified (setting, location and dates) | 5                 |
| |    | Whether participants formed a consecutive, random or convenience series | 5                 |
| **Test methods** |    | Index test, in sufficient detail to allow replication | 6-7               |
| |    | Reference standard, in sufficient detail to allow replication | 6-7               |
| |    | Rationale for choosing the reference standard (if alternatives exist) | 6-7               |
| |    | Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory | 6-7               |
| |    | Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory | 6-7               |
| |    | Whether clinical information and reference standard results were available to the performers/readers of the index test | 6-7               |
| |    | Whether clinical information and index test results were available to the assessors of the reference standard | 6-7               |
| **Analysis** |    | Methods for estimating or comparing measures of diagnostic accuracy | 7                 |
| |    | How indeterminate index test or reference standard results were handled | 5                 |
| |    | How missing data on the index test and reference standard were handled | 5                 |
| |    | Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory | 7                 |
| |    | Intended sample size and how it was determined | 5                 |
| **RESULTS** |    | Flow of participants, using a diagram | Supplemental      |
| **Participants** |    | Baseline demographic and clinical characteristics of participants | 24                |
| |    | Distribution of severity of disease in those with the target condition | 24                |
| |    | Distribution of alternative diagnoses in those without the target condition | 24                |
| |    | Time interval and any clinical interventions between index test and reference standard | 24                |
| **Test results** |    | Cross tabulation of the index test results (or their distribution) by the results of the reference standard | 26                |
| |    | Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals) | 28                |
| |    | Any adverse events from performing the index test or the reference standard | 26                |

**DISCUSSION**
|   | Study limitations, including sources of potential bias, statistical uncertainty, and generalizability | 15 |
|---|--------------------------------------------------------------------------------------------------|----|
|   | Implications for practice, including the intended use and clinical role of the index test         | 15 |
| **OTHER INFORMATION**                  |                                               |    |
| 32 | Registration number and name of registry                                                          | 5  |
| 33 | Where the full study protocol can be accessed                                                    | 5  |
| 34 | Sources of funding and other support; role of funders                                            | 17 |
**Table S1. Enrollment across regions**

| Region       | Enrollment |
|--------------|------------|
| Switzerland  | 59%        |
| Germany      | 6%         |
| Spain        | 22%        |
| Italy        | 2%         |
| Poland       | 2%         |
| USA          | 1%         |
| Australia    | 2%         |
| New Zealand  | 6%         |
Table S2. Performed diagnostic tests at admission or during long-term follow-up in all 689 patients

| Investigation             | Test done (%) |
|---------------------------|---------------|
| ECG                       | 666 (97)      |
| Carotid Duplex            | 50 (7)        |
| Cranial CT                | 208 (30)      |
| TTE                       | 229 (33)      |
| X-Ray Chest               | 322 (47)      |
| EEG                       | 46 (7)        |
| Ergometry                 | 23 (3)        |
| Holter-ECG                | 111 (16)      |
| Telemetry                 | 131 (19)      |
| Loop Recorder             | 7 (1)         |
| Coronary Angiography      | 33 (5)        |
| MPI                       | 9 (1)         |
| Schellong                 | 290 (43)      |

*ECG = Electrocardiogram; Cranial CT = Cranial computed tomography; TTE = Transthoracic echocardiography; EEG = Electroencephalogram; MPI = Myocardial perfusion imaging.
| Table S3. All final adjudicated diagnoses, n (%) |
|-----------------------------------------------|
| **Cardiac Syncope**                           |
| Arrhythmia as primary cause                   |
| Bradycardia                                   |
| Sinus node dysfunction                        | 30 (4.4) |
| AV conduction system disease                  | 27 (3.9) |
| Implanted device malfunction                  | 1 (0.1)  |
| Drug induced                                  | 5 (0.7)  |
| Tachycardia                                   |
| Supraventricular                              | 15 (2.2) |
| Drug-induced                                  | 2 (0.3)  |
| Ventricular                                   | 10 (1.5) |
| Idiopathic                                    | 1 (0.1)  |
| Channelopathies                                | 1 (0.1)  |
| Secondary to structural heart disease          | 8 (1.2)  |
| Drug-induced                                  | 0 (0)    |
| Unknown                                       |
| Structural Heart Disease                       |
| Cardiac valvular disease                      | 12 (1.7) |
| Acute myocardial infarction/ischaemia         | 13 (1.9) |
| Hypertrophic cardiomyopathy                   | 1 (0.1)  |
| Congenital anomalies of coronary arteries      | 0 (0)    |
| Prosthetic valves dysfunction                 | 0 (0)    |
| Cardiac masses                                 | 0 (0)    |
| Pericardial disease                           | 0 (0)    |
| Others                                        | 0 (0)    |
| Others                                        | 2 (0.3)  |
| Reflex (neurally-mediated) syncpe              |
| Vasovagal                                     |
| Mediated by emotional distress/pain           | 157 (22.8)|
| Mediated by orthostatic stress                | 104 (15.1)|
| Situational                                   |
| Cough, Sneeze                                 | 6 (0.9)  |
| Gastrointestinal stimulation                  | 63 (9.1) |
| Post-prandial                                 | 28 (4.1) |
| Post-micturition                              | 10 (1.5) |
| Others                                        | 9 (1.3)  |
| Carotid sinus syncope                         | 2 (0.3)  |
| Atypical forms (without apparent triggers or atypical presentation) | 45 (6.5)|
| Syncope due to orthostatic hypotension        | 181 (26.3)|

Total 689 (100%)
| Category                                                                 | Count (Percentage) |
|-------------------------------------------------------------------------|--------------------|
| Primary autonomic failure                                                |                    |
| Pure autonomic failure                                                   | 6 (0.9)            |
| Multiple system atrophy                                                 | 0 (0)              |
| Lewy body dementia                                                      | 0 (0)              |
| Parkinson's disease with autonomic failure                              | 6 (0.9)            |
| Others                                                                   | 0 (0)              |
| Secondary autonomic failure                                             |                    |
| Diabetes mellitus                                                        | 2 (0.3)            |
| Amyloidosis                                                              | 0 (0)              |
| Uraemia                                                                  | 0 (0)              |
| Spinal Cord Injuries                                                    | 0 (0)              |
| Others                                                                   | 4 (0.6)            |
| Drug-induced orthostatic hypotension                                    |                    |
| Alcohol                                                                 | 8 (1.2)            |
| Phenothiazines                                                          | 2 (0.3)            |
| Vasodilators                                                            | 23 (3.3)           |
| Diuretics                                                               | 15 (2.2)           |
| Antidepressants                                                          | 6 (0.9)            |
| Others                                                                   | 20 (2.9)           |
| Volume Depletion                                                        |                    |
| Haemorrhage                                                             | 6 (0.9)            |
| Diarrhoea                                                               | 6 (0.9)            |
| Vomiting                                                                | 2 (0.3)            |
| Fever/SIRS                                                              | 40 (5.8)           |
| Others                                                                   | 18 (2.6)           |
| Others                                                                   |                    |
| Others (but no cardiac syncope)                                         | 63 (9.1)           |
Table S4. Reclassification by means of MRproANP

| VAS | Patients with non-cardiac syncope | VAS & MRproANP |
|-----|----------------------------------|----------------|
|     | 0-10%                            | 11-20%         | 21-30% | 31-40% | 41-50% | 51-60% | 61-70% | 71-80% | 81-90% | 91-100% | %   |
| 0-10% | 225 | 21 | 1 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 10 |
| 11-20% | 3 | 68 | 17 | 3 | 1 | 3 | 0 | 0 | 0 | 1 | 29 |
| 21-30% | 0 | 3 | 44 | 10 | 2 | 2 | 0 | 0 | 0 | 0 | 28 |
| 31-40% | 0 | 0 | 3 | 28 | 1 | 2 | 0 | 0 | 0 | 0 | 16 |
| 41-50% | 0 | 0 | 0 | 8 | 25 | 9 | 1 | 1 | 0 | 0 | 75 |
| 51-60% | 0 | 0 | 0 | 0 | 5 | 10 | 2 | 1 | 0 | 0 | 44 |
| 61-70% | 0 | 0 | 0 | 0 | 0 | 2 | 10 | 1 | 0 | 1 | 29 |
| 71-80% | 0 | 0 | 0 | 0 | 0 | 10 | 13 | 3 | 2 | 54 |
| 81-90% | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 5 | 4 | 50 |
| 91-100% | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 6 | 33 |   |

| VAS | Patients with cardiac syncope | VAS & MRproANP |
|-----|---------------------------------|----------------|
|     | 0-10%                           | 11-20%         | 21-30% | 31-40% | 41-50% | 51-60% | 61-70% | 71-80% | 81-90% | 91-100% | %   |
| 0-10% | 6 | 2 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 40 |
| 11-20% | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 100 |
| 21-30% | 0 | 0 | 4 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 43 |
| 31-40% | 0 | 0 | 0 | 1 | 3 | 0 | 1 | 0 | 0 | 0 | 60 |
| 41-50% | 0 | 0 | 0 | 0 | 1 | 2 | 1 | 0 | 0 | 1 | 80 |
| 51-60% | 0 | 0 | 0 | 0 | 0 | 7 | 1 | 1 | 0 | 0 | 22 |
| 61-70% | 0 | 0 | 0 | 0 | 0 | 4 | 2 | 0 | 1 | 43 |
| 71-80% | 0 | 0 | 0 | 0 | 0 | 2 | 9 | 8 | 2 | 57 |
| 81-90% | 0 | 0 | 0 | 0 | 0 | 2 | 8 | 15 | 68 |
| 91-100% | 0 | 0 | 0 | 0 | 0 | 4 | 30 | 12 |   |   |
**Net reclassification improvement** focuses on reclassification tables constructed separately for participants without events (non-cardiac syncope) and patients with events (cardiac syncope), and quantifies the balance between correct movements in categories (upwards for events and downwards for non-events) and incorrect movements (downwards for events and upwards for non-events)

The biggest incremental value of MRproANP is seen in patients with intermediate risk of cardiac syncope, determined by the ED-physician with a visual analogue score (VAS) ranging between 21%-80%. In patients with non-cardiac syncope, 31 (5.5%) correctly moved downward in the classification and 38 patients (6.7%) incorrectly moved upward. In patients with cardiac syncope, 26 patients (21%) correctly moved upwards and 2 (1.6%) incorrectly moved downward in the classification.

The net reclassification improvement was calculated at 0.216 (p<0.001). Integrated discriminatory improvement (IDI) was 0.035 (p=0.001).
Table S5. Overview of patients with low initial ED-probability (VAS-Score ≤20%) and a final diagnosis of cardiac syncope

| Age | Sex | VAS (%) | Prodromi | Situation | ECG     | MRproANP (ng/L) | Diabetes | HT | HC | Smoking | ARRH | History of MI | Valvular | Epilepsy |
|-----|-----|---------|----------|-----------|---------|----------------|----------|----|----|---------|------|---------------|----------|----------|
| 77  | male| 10      | No       | Sitting   | normal  | 106           | No       | No | Yes| No      | Yes  | No            | No       | No       |
| 44  | female | 10     | Yes      | Standing | normal  | 121           | No       | No | No | No      | No   | No            | No       | No       |
| 79  | male| 10      | Yes      | Standing | normal  | 187           | No       | No | Yes| No      | Yes  | No            | No       | No       |
| 86  | female | 0      | Yes      | Sitting  | normal  | 196           | Yes      | No | Yes| No      | No   | No            | No       | No       |
| 70  | male| 20      | No       | Exertion | abnormal| 256           | No       | No | No | No      | No   | No            | No       | No       |
| 80  | female | 10     | Yes      | Sittin   | abnormal| 262           | No       | No | No | No      | No   | No            | No       | No       |
| 61  | male| 0       | No       | Standing | normal  | 275           | No       | Yes| No | Yes     | Yes  | No            | No       | No       |
| 76  | male| 0       | Yes      | Standing | abnormal| 295           | No       | Yes| Yes| Yes     | No   | Yes           | No       | No       |
| 85  | female | 10     | Yes      | Standing | abnormal| 451           | No       | No | No | No      | Yes  | No            | No       | No       |
| 80  | male| 0       | Yes      | Standing | abnormal| 682           | Yes      | Yes| Yes| Yes     | Yes  | No            | Yes      | No       |
| 71  | female | 20     | Yes      | Standing | normal  | 1142          | No       | No | Yes| Yes     | Yes  | No            | No       | No       |

VAS = Visual analogue scale; Prodromi = Blurred Vision, Sweating or Dizziness; ECG = Electrocardiogram; HT = Hypertension; HC = Hypercholesterolemia; ARRH = Arrhythmia; MI = Myocardial Infarction; Valvular: Valvular heart disease.
Figure S1. Patient flow diagram for all patients.

Patients enrolled  
\( n = 886 \)

Not eligible for analysis, \( n = 197 \)

- Non-syncopal loss of consciousness, \( n = 117 \)
  - Pre-syncpe (31)
  - Falls (20)
  - Stroke/TIA (9)
  - Epilepsy (39)
  - Metabolic disorders (6)
  - Intoxication (3)
  - Functional (6)
  - Other (3)
- Final adjudicated diagnosis unclear, \( n = 77 \)
- Missing blood samples, \( n = 3 \)

Eligible for analysis  
\( n = 689 \)
Supplemental References:

1. Shen WK, Sheldon RS, Benditt DG, Cohen MI, Forman DE, Goldberger ZD, Grubb BP, Hamdan MH, Krahn AD, Link MS, Olshansky B, Raj SR, Sandhu RK, Sorajja D, Sun BC, Yancy CW. 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. J Am Coll Cardiol. 2017;70:620-663.

2. Task Force for the Diagnosis and Management of Syncope; European Society of Cardiology (ESC); European Heart Rhythm Association (EHRA); Heart Failure Association (HFA); Heart Rhythm Society (HRS), Moya A, Sutton R, Ammirati F, Blanc JJ, Brignole M, Dahm JB, Deharo JC, Gajek J, Gjesdal K, Krahn A, Massin M, Pepi M, Pezawas T, Ruiz Granell R, Sarasin F, Ungar A, van Dijk JG, Walma EP, Wieling W. Guidelines for the diagnosis and management of syncope (version 2009). Eur Heart J. 2009;30:2631-2671.