Evidence-based evaluation of unexplained severe syncope in a modern syncope unit: an observational study

Acronym: Diamond Study

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1. KEY STUDY CONTACTS

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2. STUDY SUMMARY

Title	Diamond Study
Document and Version Date	V.1, 14-04-2026
Clinical Study Type	Observational Pilot Study
Investigation Purpose	To evaluate the clinical practice in the diagnosis of severe unexplained syncope among European Syncope Units (or equivalent) adhering to the standards set forth by the ESC guidelines.
Objectives	Primary endpoint: Rate and type of final diagnoses and the number of tests utilized to reach them. Secondary endpoints: 1-Adherence of the clinical practices to a standardized diagnostic pathway 2- Assessment of resource utilization associated to the clinical practices.
Sites	Up to 15 sites across Europe

3. BACKGROUND

The diagnostic pathway for patients with severely symptomatic, recurrent, unexplained syncope is standardized according to current syncope guidelines (1,2,3) and is widely accepted by syncope specialists in modern syncope units (or equivalent).

Despite the existence of recommended diagnostic flow charts, their real-world implementation remains inconsistent, leading to variable adherence to international guidelines. The complexity of the syncope diagnostic process – often requiring multiple tests performed by different physicians in various centres, over extended periods due to long outpatient waiting lists

- contributes significantly to this low adherence. The absence of a systematic approach to syncope management is associated with increased healthcare and social costs, unnecessary hospitalizations and diagnostic procedures, prolonged hospital stays, lower diagnostic rates, and higher incidences of symptom recurrence (4). To maximize guidelines implementation in clinical practice, standardized, evidence-based pathways for syncope assessment and management are essential. Over the past 20 years, the establishment of syncope units (5,6,7,8,9,10,11) and the utilization of standardized pathways implemented via digital tools (6,12,13) have proven effective in increasing diagnostic yield, reducing inappropriate tests, and decreasing hospitalizations.

An example is provided by the Syncope Unit Project (SUP) study (13), which enrolled 941 outpatients from 9 syncope units in Italy. All units followed the 2004 ESC guidelines (14) and utilized a web-based interactive software based on guidelines recommendations to standardize the syncope diagnosis pathway. A diagnosis was reached at initial evaluation in 21% of cases and after early testing in 61%. A likely reflex cause was identified in 67%, orthostatic hypotension in 4%, a cardiac cause in 6%, and a non-syncopal cause in 5%. In 18% of patients, the cause of syncope remained unexplained despite further testing.

Since then, knowledge on syncope evaluation has continued to advance, thanks to the latest syncope guidelines (1,2). The diagnostic work-up for autonomic syncope has recently been standardized and validated (15,16). This three-phase diagnostic approach begins with the initial evaluation of the patient; if this is inconclusive, the second phase consists in performing 24-hour ambulatory blood pressure monitoring (ABPM) and cardiovascular autonomic function test (SCAFA). If the mechanism remains unclear, long-term ECG monitoring using an implantable cardiac monitor (ICM) is recommended (15).

The aim of the present study is to evaluate clinical practice in the diagnosis of severe unexplained syncope among European Syncope Units (or equivalent) adhering to the standards set forth by the ESC guidelines.

4. STUDY DESIGN

The Diamond study is an investigator-initiated, prospective, international, multicenter study, coordinated by the non-profit organization Gruppo Italiano Studio Sincope (GIMSI), conducted within European Syncope Units (or equivalent) that fulfill the personnel and equipment criteria recommended by the European Heart Rhythm Association (EHRA) (4) and the (GIMSI) (https://www.gimsi.it/modello-organizzativo/).

Eligibility of each center is certified by the head of the syncope unit (or equivalent), who completes a questionnaire confirming compliance with the required standards (see Appendix 1). Additionally, the head of the syncope unit attests that the current clinical practice within their Syncope Unit (or equivalent) aligns with the standardized, guidelines-based diagnostic pathway outlined in the following recommendations:

1. A dedicated outpatient facility (even if part-time) for the evaluation and management of syncope

2. Formally assigned medical, nursing and technical staff specifically dedicated to syncope care
3. One or more physicians with recognized expertise in syncope overseeing the facility
4. Continuous, non-invasive, beat-to-beat blood pressure monitoring during autonomic testing, with recording capabilities for subsequent analysis
5. Continuous ECG monitoring during autonomic testing, with recording capabilities for subsequent analysis.
6. Head-up tilt testing
7. Availability of 24-hour ambulatory blood pressure monitoring (ABPM)
8. Capability to perform carotid sinus massage (CSM), both in the supine position and upright on a tilt table
9. Access to comprehensive arrhythmia assessment and therapeutic interventions, including Holter ECG, external loop recorders, implantable loop recorders, electrophysiological studies, pacemaker and ICM implantation, and catheter ablation of arrhythmias.

4.1 Web-based Clinical Report Form (CRF)

To allow uniform clinical data collection from participating centres, a web-based CRF was designed.

Accessible via laptop, tablet, and smartphone, this provides clinicians consistent and structured data collection throughout the diagnostic workflow. In parallel, it enables quick access to guideline-based recommendations, standardized definitions, and curated learning materials on syncope evaluation and management.

Within the application, clinicians can review evidence-based diagnostic steps while documenting patient information such as demographic details (e.g., date of birth, age, medical history), diagnostic tests performed, classify results as normal or abnormal according to current guideline criteria. This tool is not intended to constrain physician decision-making, but rather to support reflective learning and understanding of practice variation.

Reference materials, including guidelines and supporting evidence for recommended diagnostic procedures, are available within the tool for consultation.

Printable patient reports can be generated directly within the application, summarizing all data entered for the patient up to the current stage of the diagnostic workflow.

Importantly, the web application is not a medical device (MD), and it is not designed for the management or care of individual patients. The web application is exclusively a digital tool designed to support real-world data collection. Physicians are expected to exercise their own clinical judgment in accordance with their standard practice in compliance with the required standards of the center. The web application is not intended for decision-making; instead, it functions only as an educational tool providing standardized definitions according to guidelines, consulting educational materials, guideline recommendations and collect data on diagnostic pathway adherence.

Data collection concludes upon reaching an exit point, which may correspond to a confirmed diagnosis of syncope (cardiac or autonomic), an alternative outcome such as the exclusion of syncope, or the absence of a definitive diagnosis.

4.2 Diagnostic flow chart and definitions.

In order to evaluate the secondary objectives, an ideal diagnostic syncope flow chart with the definitions of the diagnostic tests, based on ESC guidelines (1,2) and on the recent evidence (15,16) was designed (see Appendix 3).

4.3 Inclusion criteria: severe unexplained syncope or unexplained fall

Consecutive outpatients aged ≥16 years referred to the Syncope Unit (or equivalent) due to severe, unexplained syncope and/or unexplained fall requiring comprehensive evaluation to identify the most appropriate mechanism-specific therapy.

Unexplained syncope is defined as unexplained etiology or unexplained syncope mechanism.

Severe syncope is defined by the presence of one or more among the following:

1) Suspected life-threatening arrhythmias
2) Substantial impact on patient's quality of life (QoL)
    - Frequent episodes
    - Restriction of educational or occupational activities (including, but not limited to, unemployment)
    - Restriction of social or daily-life activities, e.g. when syncope occurs while driving
3) High risk of clinically significant outcomes
    - Syncope associated with major injuries/trauma, i.e. head injury or fractures
    - Unpredictable syncope, i.e. without prodrome or identifiable triggers
4) Presence of serious comorbidities, such as concomitant heart disease, neurologic disease, diabetes or renal failure
5) Suspected Autonomic syncope overlapping with suspected psychogenic pseudosyncope

In these patients, identification of the hemodynamic mechanism of syncope, i.e., syncope phenotype, is essential to guide therapeutic interventions and prevent syncope recurrences.

4.4 Exclusion criteria: non-severe syncope

Non-severe syncope is defined by the presence of one or more among the following:

1) Sporadic (isolated) episodes without major impact on patient's QoL
2) Predictable syncope, i.e. syncope preceded by prodrome and/or occurring in association with identifiable triggers, with low risk of injuries

In these patients, identification of the hemodynamic mechanism of syncope, i.e., syncope phenotype, may not be necessary as the explanation of syncope mechanism, patient education,

reassurance and appropriate lifestyle adaptations may suffice to prevent recurrences. This should be performed directly after the initial evaluation in the emergency department, outpatient clinic or primary care when there is a certain or highly likely diagnosis of non-severe autonomic syncope. Further diagnostic investigation and additional interventions may be considered if syncope recurs.

4.5 Study workflow

Following documented patient consent, clinical personnel at the site -trained in the use of the web-app- will access the digital tool to enter the patient's I/E criteria assessment, personal information and medical history. From that point forward, data will be entered into the web-app on an ongoing basis, in accordance with the site's routine clinical practice, until the patient reaches a defined exit point (such as diagnosis of cardiac syncope, diagnosis of autonomic syncope, no syncope, no diagnosis), or drop-out (e.g., patient death, patient unable to comply with diagnostic pathway, etc.).

4.6 Objectives

To evaluate the clinical practice in the diagnosis of severe unexplained syncope among European Syncope Units (or equivalent) adhering to the standards set forth by the ESC guidelines.

4.7 Endpoints

Primary endpoint

Primary endpoint will be the rate and type of final diagnoses and the number of tests utilized to reach them.

The primary endpoint includes the diagnostic yield of the standardized digital diagnostic pathway, measured by the rate of final diagnoses (such as cardiac syncope, autonomic syncope, or no syncope diagnosis) and test utilization. These outcomes will be assessed in patients who fully adhere to the pathway (effectiveness study) as well as those who do not.

Secondary endpoint:

1. Adherence of the clinical practices to a standardized diagnostic pathway shown in the appendix 3.

   The results obtained from the clinical practices will be used to assess the adherence of the clinical practice to the standardized diagnostic pathway, called Diamond Syncope Pathway (see Appendix 3).

2. Assessment of resource utilization associated to the clinical practices (Efficiency study). The economic analysis will focus on direct medical costs, specifically the costs of diagnostic examinations included in the pathway, and on time-related operational metrics. The analysis will adopt the hospital/provider perspective.

5. STATISTICAL ANALYSIS, SAMPLE SIZE AND TIMELINES

5.1 Sample size and study termination

A formal sample size calculation was not performed, as the primary objective of the study is exploratory rather than hypothesis-driven efficacy evaluation. The planned sample size will be determined pragmatically, based on operational considerations and expected availability of eligible participants during the study period.

An interim analysis will be conducted upon Steering Committee indication. This preliminary review will verify whether any refinements to the digitalized clinical pathway are necessary.

A maximum of 15 sites will be activated in this study.

5.2 Statistical Analysis

This pilot study is primarily designed to assess feasibility outcomes rather than to formally test hypotheses on clinical effectiveness. Therefore, all analyses will be mainly descriptive in nature. No formal hypothesis testing is planned. Any exploratory analyses will be purely descriptive and interpreted with caution, given the limited sample size and the exploratory nature of the study.

Descriptive statistics will be used to summarize baseline characteristics, diagnostic pathway adherence, and diagnosis rate. Categorical variables will be presented as frequencies and percentages, while continuous variables will be reported using means and standard deviations or medians and interquartile ranges, depending on distributional assumptions

The secondary analysis will assess the association between adherence to the Diamond Syncope Pathway and the likelihood of receiving a final diagnosis. A binary logistic regression model will be used, where the dependent variable is the occurrence of a final diagnosis (1 = yes, 0 = no) and the covariate of interest is adherence status (Yes vs No).

The economic evaluation will be conducted from the hospital/provider perspective and will focus on direct medical costs only. Specifically, the analysis will include the costs of all diagnostic tests performed by the centres according to their clinical practices.

All analysis will be conducted using a two-sided significance level of 0.05.

Interim analyses will be descriptive in nature and primarily aimed at assessing study feasibility and overall data quality. These analyses will include all patients enrolled irrespective of whether a final diagnostic outcome has been reached at the time of the interim assessment. The objective of the interim evaluation is to provide an early characterization of emerging data patterns and pathway performance.

6.STUDY SITES REQUIREMENTS AND ADMINISTRATION

6.1 Study Sites Requirements

Sites interested in participating in the study, specifically through their head of the syncope unit (or equivalent), are required to fill out a checklist that will be submitted to the steering committee, to determine their eligibility (Appendix 1). The checklist will assess whether each site meets the inclusion and exclusion criteria necessary for participation in the study, basically the confirmation that the Syncope Unit (or equivalent) of the site is following clinical practice in accordance with the European Heart Rhythm Association guidelines for the diagnostic pathway (4). For sites selected, prior to the initiation of any study-related activities, protocol, informed consent forms, and supporting materials must be submitted to the local Ethics Committee (EC) for review and approval following local specific requirements.

Then a Training Form will be created and completed by the sponsor once the site's training has been conducted. After the training is finalized, the sponsor will send a confirmation letter to the participating sites, indicating their involvement in the study and clarifying that there is no profit associated with participation in this specific study. The sponsor will fill out also a Center Activation Form, which will include the necessary information for activating users at each center. This process ensures that only appropriately trained and eligible sites and users are activated for participation in the study.

During the study execution, each site is responsible for their own data integrity.

The list of identified sites can be found in Appendix 2. Participation in the study will be confirmed only after all criteria outlined in the checklist (Appendix 1) have been met.

6.2 Study Administration

Study closure is defined as closure of a study that occurs when the requirements described in the protocol have been satisfied, sponsor is responsible for the study closure.

Early Termination is the closure of a study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single study site. Suspension is a temporary postponement of study activities related to enrollment or web-app issues. This is possible for the whole study or a single study site.

7. DATA COLLECTION AND DATA MANAGEMENT

Study data will be collected through the dedicated web-based Clinical Report Form (CRF), a mobile user-friendly application requiring only a browser and internet access to be used.
Data collection will start after documented patient consent and will continue until the subject exits. Participants who are enrolled in the study as minors will be required to provide their own informed consent upon reaching the age of majority in order to continue participation in the study. Once consent is obtained, the investigator will enroll patients by creating a profile in the

web app, from that moment the collection of the real-world data relevant to evidence-based diagnostic pathways will begin.

Upon exiting the study, no further study data will be collected. All data available through the time of the subject's exit will be used for analysis.

Subjects are urged to remain in the study as long as possible in order to complete the diagnostic pathway but may be exited from the study for any of the following situations:

- Subject death
- Subject chooses to withdraw the consent
- Subject unable to comply with diagnostic pathway (e.g., relocation to other geography, lost to follow up, investigator deems withdrawal necessary due to medical reasons…)

Data collected via the study web-app will be stored in a protected database; to ensure security, all information will be encrypted on transit and at rest with state-of-the-art algorithm.

To facilitate the data collection and reduce potential mismatches between data and individual, the system will let physician collect patient first and last names, then the system will automatically and immediately associate a unique identifier as pseudonym.

Furthermore, there will be multiple backups per day stored in a different building and in a different geography providing a reliable disaster recovery.

At the end of the study, the data will be retained by GIMSI as the sponsor in accordance with applicable regulations. The aggregated data and the results of the analyses will be made available also to Medtronic.

To ensure high quality, data will be reviewed using programmed and manual data checks, additionally, there will also be management reports with relevant information to monitor the study progress.

8. ETHICS

8.1 Risk and Benefits Considerations

This study will document diagnostic assessments and tests conducted according to each center's routine clinical practice since the aim of the study is to collect real-world data, all assessments and procedures will be conducted according to routine clinical practice in hospitals equipped with a syncope unit (or equivalent). The web application does not pose any potential serious risk to the health, safety, or welfare of participants, as it solely functions as a digital tool for collecting non-interventional data, along with a minimal set of patient information required for the syncope diagnostic workflow (i.e., diagnostic tests performed and their results classification as normal or abnormal).

Although participation in the Diamond study may not provide a direct benefit to individual patient, the insights gained from this study could contribute to the development of a more standardized clinical pathway for the diagnosis of unexplained syncope.

8.2 Safety Considerations

There is no study objectives related to the evaluation of device safety and the web-application used as basis for the study conduct is not a medical device, thus adverse events will not be collected through the study. If new risks arise, including those involving patient data security, participants will be notified promptly.

The reporting of adverse events for any devices used by enrolled patients, and potentially affected during the conduct of the trial, will follow the manufacturer's procedures as well as the applicable national regulations and requirements.

8.3 Regulatory rules

This trial will be conducted in accordance with the latest version of the Declaration of Helsinki, ICH Guidelines for Good Clinical Practice (GCP), the Medical Research Involving Human Subjects Act (WMO) and other relevant Italian and international laws, regulations and codes of conduct. To avoid publication bias and duplicate studies, the trial will be registered on http://clinicaltrials.gov.

8.4 Informed consent

The informed consent is defined as a legally effective documented confirmation of a patient's voluntary agreement to participate in a particular clinical study after information has been given to the patient on all aspects of the clinical study that are relevant to the patient's decision to participate. The patient must have ample time and opportunity to read and understand the Informed Consent Form, to inquire about details of the study. Participants who are enrolled in the study as minors will be required to provide their own informed consent upon reaching the age of majority in order to continue participation in the study.

Eligible patients' data will be stored in the web-app only after the subjects have signed-the informed consent to confirm their participation in the Diamond study. The informed consent will be obtained the same day the subject is eligible to begin participating in this study in accordance with local applicable regulatory requirements and ethical guidelines. The Informed Consent Form will be provided in a language understandable to the participant.

A copy of the consent will be stored by each participating hospital.

8.5 Management of data

All information and data sent to parties involved in study conduct concerning subjects or their participation in this study will be considered confidential.

For approved data sources, data will be collected through the application on an ongoing basis, and all the information will be administered at variable timepoints to meet study needs.

Study sites will have the possibility to collect patient contact details. Additionally, there will be a unique study specific subject identifier as pseudonym for each subject. All data shall be secured against unauthorized access. The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data.

All data will be encrypted on transit and at rest with state-of-the-art algorithm.

9. STUDY ADMINISTRATION

9.1 Data collection

To develop the web-app, a secure and reliable data collection system was implemented, with a strong emphasis on user experience for healthcare professionals. The solution complies with recognized standards such as ISO 27001 and GAMP 5, and regular quality audits are conducted to maintain high standards. Data is securely stored on servers within the European Union and is not shared with external parties. Robust security measures and comprehensive staff training are in place to safeguard all clinical data.

9.2 Property of the data

The study is entirely designed and owned in terms of IP by Michele Brignole and Fabrizio Ammirati. The web-app tool, including the design of related data collection forms, is owned by Medtronic.

9.3 Steering Committee

A Steering Committee, composed of key opinion leaders from the European countries participating in the study, will be established. The committee will be responsible for:

- Evaluating analysis proposals
- Drive evidence dissemination study
- Confirming the web-app functionality and providing feedback to optimize it
- Reviewing the inclusion and exclusion criteria for centers to determine their eligibility for participation in the study
- All analyses and publications

9.4 Publication rules

Results will be published in scientific presentations, peer-reviewed journals, and a Clinical Study Report. Decisions on data analysis will be taken exclusively by the Steering Committee. GIMSI

and Medtronic will be consulted for technical input and will support the agreed analyses and related activities, as necessary.

Results from this study could be disseminated through peer-reviewed publications, presentations at national and international conferences, and patient and public engagement events.

Authors must at a minimum meet all of the conditions below:

- Substantial contributions to the acquisition, analysis, or interpretation of data for the work;
- Drafting the work or revising it critically for important intellectual content;
- Final approval of the version to be published;
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Decisions regarding authorship and contributor-ship will be made by Steering Committee. The selected authors will be responsible for drafting the publication. All selected authors must fulfill the authorship conditions stated above to be listed as authors.

10. FUTURE DIRECTIONS

Following the study completion, it will be evaluated to initiate a large international study. In addition to its educational value, the study data will help define standardized characteristics for future therapeutic trials and provide valuable support for future innovative initiatives.

11. REFERENCES

1) Brignole M, Moya A, De Lange FJ, Deharo J, Elliott PM, Fanciulli A, et al. 2018 ESC Guidelines for the diagnosis and management of syncope. European Heart Journal. 2018 -08-13;39(21):1883.
2) Brignole M, Moya A, De Lange FJ, Deharo J, Elliott PM, Fanciulli A, et al. Practical Instructions for the 2018 ESC Guidelines for the diagnosis and management of syncope. European Heart Journal. 2018 -06-17;39(21):e43.
3) Shen WK, Sheldon RS, Benditt DG, Cohen MI, Forman DE, Goldberger ZD, et al. 2017 ACC/AHA/HRS Guideline for the Evaluation and Management of Patients With Syncope. Circulation. 2017 Aug 1;136(5):e60-e122.
4) Kenny RA, Brignole M, Dan G, Deharo JC, Van Dijk JG, Doherty C, et al. Syncope Unit: rationale and requirement – the European Heart Rhythm Association position statement endorsed by the Heart Rhythm Society. Europace. 2015 -06-24;17(9):1325.
5) Brignole M, Disertori M, Menozzi C, Raviele A, Alboni P, Pitzalis MV, et al. Evaluation of Guidelines in Syncope Study group. Management of syncope referred urgently to general hospitals with and without syncope units. Europace. 2003 Jul;5(3):293-8.
6) Brignole M, Ungar A, Bartoletti A, Ponassi I, Lagi A, Mussi C, Ribani MA, et al Standardized-care pathway vs. usual management of syncope patients presenting as emergencies at general hospitals. Europace. 2006 Aug;8(8):644-50
7) Shen WK, DeckerWW, Smars PA, Goyal DG, Walker AE, Hodge DO et al. Syncope Evaluation in the Emergency Department Study (SEEDS): a multidisciplinary approach to syncope management. Circulation 2004;110:3636–45.
8) Sun BC, McCreath H, Liang LJ, Bohan S, Baugh C, Ragsdale L et al. Randomized clinical trial of an emergency department observation syncope protocol versus routine inpatient admission. Ann Emerg Med 2014;64:167–75
9) Kenny RA, O'Shea D,Walker HF. Impact of a dedicated syncope and falls facility for older adults on emergency beds. Age Ageing 2002;31:272–5.
10) Ammirati F, Colaceci R, Cesario A, Strano S, Della Scala A, Colangelo I et al. Management of syncope: clinical and economic impact of a Syncope Unit. Europace 2008;10: 471–6.
11) Farwell DJ, Sulke AN. Does the use of a syncope diagnostic protocol improve the investigation and management of syncope? Heart 2004;90:52–8.
12) Sanders NA, Jetter TL, Brignole M, Hamdan MH. Standardized care pathway versus conventional approach in the management of patients presenting with faint at the University of Utah. Pacing Clin Electrophysiol 2013;36:152–62.
13) Brignole M, Ungar A, Casagranda I, Gulizia M, Lunati M, Ammirati F, et al. Prospective multicentre systematic guideline-based management of patients referred to the Syncope Units of general hospitals. Europace. 2010 Jan;12(1):109-18.
14) Brignole M, Rivasi G, Fedorowski A. Mechanism-based therapy of non-cardiac syncope: a practical guide. Europace. 2024 -03-26;26(4).
15) Groppelli A, Russo V, Parente E, Comune A, De Lange FJ, Rivasi G, et al. Mechanism of syncope: role of ambulatory blood pressure monitoring and cardiovascular autonomic function assessment. European Heart Journal. 2025; 46: 827-835

12. APPENDIX 1

Syncope Facility Resource Assessment Questionnaire

A) Resources

1. Is there an outpatient clinic/facility at your hospital dedicated (even part-time) to the study of syncope?
2. Is there a formalized pathway/procedure at your hospital from the Emergency Room/ED Observation Unit to the outpatient facility for the management of the syncope patient?
3. Are there formally dedicated medical/nursing/technical staff?

B) Diagnostic investigations and therapy

Can the above tests or procedure be performed directly or indirectly by the syncope facility after the initial evaluation, i.e., history taking, physical examination including active standing test and standard 12-lead ECG:

1. Head-up tilt test according to the Italian protocol (passive phase + active phase with nitroglycerin)
2. Continuous (beat-to-beat) non-invasive blood pressure monitoring during autonomic tests (Finapres®, Task Force®, or similar)
3. Continuous ECG monitoring during autonomic tests
4. 24-hour ambulatory blood pressure monitoring (ABPM)
5. Carotid sinus massage supine and upright on tilt table
6. 24-hour Holter ECG monitoring
7. Prolonged external ECG monitoring (external loop recorder)
8. Implantable loop recorder
9. Intracavitary electrophysiological study
10. Pacemaker and ICD implant
11. Catheter ablation of arrhythmias

The underlined dr ..... head of the Syncope Unit of the hospital of .....

certifies

that the above requisites are met and that the current clinical practice is in accordance with the standardized guideline-based diagnostic pathway described in the study protocol.

Date Signature

13. APPENDIX 2

Study Sites

The following sites have been currently identified by the sponsor and will be evaluated as described above to be part of this study:

Site Name	PI Name	Location
Auxologico	Michele Brignole	Milano, IT
Ospedale Careggi	Andrea Ungar	Firenze, IT
Monaldi	Vincenzo Russo	Napoli, IT
Ospedale di Bolzano	Marco Tomaino	Bolzano, IT
UMC Heart Center	De Lange Frederik	Amsterdam, NL
Karolinska University Hospital	Artur Fedorowski	Stockholm, SE
Hannover Medical School	David Dunker	Hannover, DE
Vall d'Hebron Hospital	Jaume Francisco Pasqual	Barcelona, ES
Hospital Timone	Jean-Claude Deharo	Marseille, FR
Trinity College Dublin	Rose Anne Kenny	Dublin, IE
Queen Elizabeth University Hospital	Lara Mitchell	Glasgow, UK

14. APPENDIX 3

Diamond Syncope Pathway

The following flow-chart (figure 1) and the definitions used are based on the recommendations of the ESC guidelines on syncope (1,2). The diagnostic work-up for autonomic syncope has recently been assessed and validated (15,16).

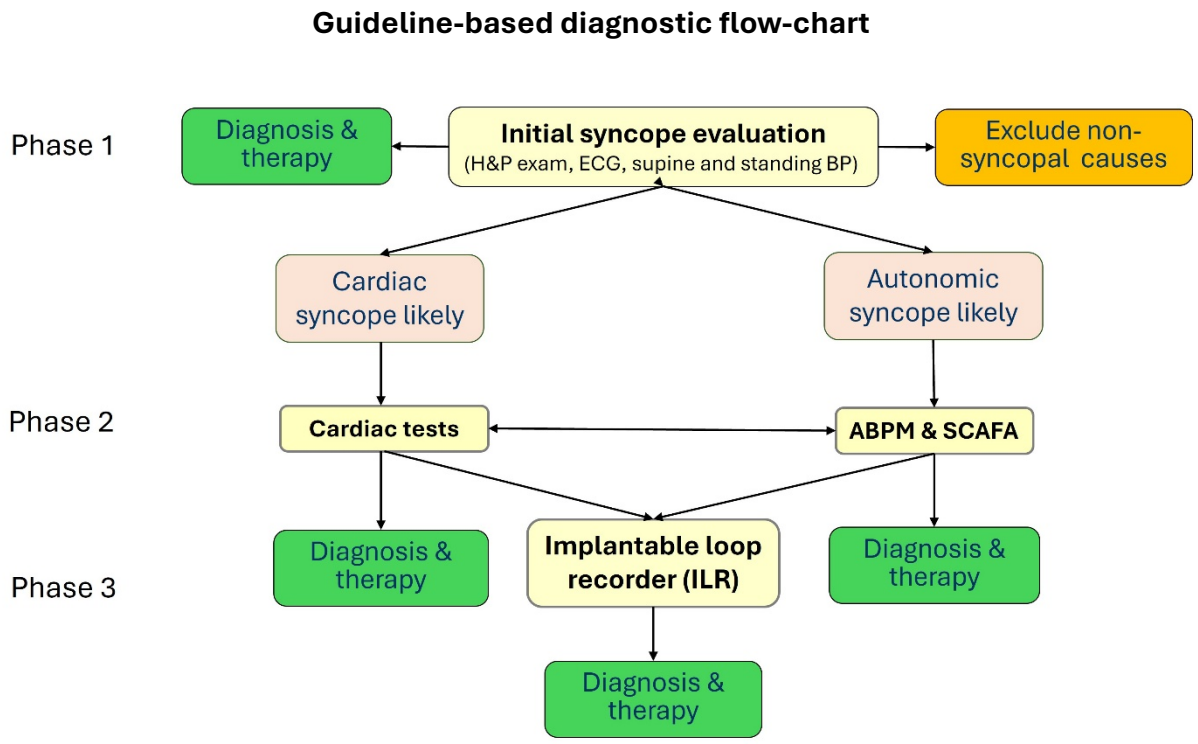

Figure 1. Standardized guideline-based diagnostic flow-chart
Abbreviations: TLOC=transient loss of consciousness; ABPM= 24-hourambulatory blood pressure monitoring; SCAFA=short cardiovascular autonomic function assessment

At the initial evaluation, it is essential to exclude non-syncopal causes of transient loss of consciousness (TLOC) - such as epilepsy, psychogenic pseudosyncope, and other conditions of apparent loss of consciousness that may be incorrectly diagnosed as syncope. Once non-syncopal causes have been excluded and the loss of consciousness is determined to be syncopal in nature, the primary objective of the diagnostic work-up is to identify cases of cardiac syncope. Cardiac syncope is characterized by loss of consciousness due to a primary cardiac disorder, such as arrhythmias or structural heart disease, and requires prompt recognition and appropriate treatment due to its association with higher morbidity and mortality. When both cardiac syncope and non-syncopal causes of TLOC are reasonably ruled out, the diagnosis of autonomic syncope becomes likely. Autonomic syncope encompasses both reflex (neurally mediated) syncope and orthostatic hypotension and represents the most frequent cause of syncope.

Definitions

Phase 1 – Initial evaluation

Cardiac syncope established - Arrhythmic syncope:

- Persistent sinus bradycardia <40 b.p.m. or sinus pause >3 s
- Mobitz II second- and third-degree AV block
- Alternating left and right BBB
- VT or rapid paroxysmal SVT
- Non-sustained episodes of polymorphic VT and long or short QT interval
- Pacemaker or ICD malfunction with cardiac pauses
- Cardiac ischaemia-related syncope when syncope presents with evidence of acute myocardial ischaemia
- Syncope due to structural cardiopulmonary disorders when syncope presents in patients with prolapsing atrial myxoma, left atrial ball thrombus, severe aortic stenosis, pulmonary embolus, or acute aortic dissection

Autonomic syncope established - Syncope due to orthostatic hypotension

- Syncope due to OH is confirmed when there is a fall in systolic BP from baseline value ≥20 mmHg or a decrease in systolic BP to <90 mmHg that reproduces spontaneous symptoms.
- VVS is highly probable if syncope is precipitated by pain or fear or standing, and is associated with typical progressive prodrome (pallor, sweating, nausea).
- Situational reflex syncope is highly probable if syncope occurs during or immediately after specific triggers.

3-min active standing test

Abnormal result: Syncope due to orthostatic hypotension (OH) is confirmed when there is a fall in systolic BP from baseline value ≥20 mmHg (≥30 mmHg in hypertensive patients) or diastolic BP >_10 mmHg, or a decrease in systolic BP to <90 mmHg that reproduces spontaneous symptoms.

Phase 2 – Laboratory tests

1) 24-h ABPM

Abnormal diagnosis conditions

Diagnosis	Definition	Blood pressure cut-offs
Drug-unrelated persistent hypotension (constitutional hypotension)	Persistently low BP in the absence of hypotensive medications	Males: 24h SBP <105 mm Hg; Daytime SBP <115 mm Hg Females: 24h SBP <98 mm Hg; Daytime SBP <105 mm Hg
Drug-related persistent hypotension	SBP values persistently below the recommended target in patients receiving hypotensive medications	24h SBP <120 mm Hg
Hypotensive (intermittent) episodes	Hypotensive drops	≥1 episodes of daytime SBP <90 mm Hg ≥2 episodes of daytime SBP <100 mm Hg

2) Carotid sinus massage (supine and standing)

Diagnosis	Definition	Cut-off values
☐ VD-CSS	Reproduction of (pre)syncope during carotid sinus massage (method of symptoms)	Reproduction of spontaneous (pre)syncope, recognized by the patient itself, with fall in SBP >50 mmHg or below 85 mmHg and absence of asystolic pause/s >3 s
☐ CI CSS	Reproduction of spontaneous symptoms during CSM (method of symptoms)	Reproduction of spontaneous (pre)syncope, recognized by the patient itself, with fall in SBP >50 mmHg and asystolic pause/s >3 s.
☐ CSH	No symptoms	Pause >3 sec and/or fall in SBP >50 mmHg or below 85 mmHg

3) Passive standing test

Syncope due to orthostatic hypotension (OH) is confirmed when there is a fall in systolic BP from baseline value ≥20 mmHg (≥30 mmHg in hypertensive pts) or diastolic BP ≥10 mmHg, or a decrease in systolic BP to <90 mmHg that reproduces spontaneous symptoms

4) Tilt testing.

Diagnosis	Definition	Blood pressure cut-offs
☐ Hypotensive reflex syncope	Induction of syncope during tilt table test	Typical haemodynamic pattern of mixed or vasodepressor vasovagal syncope with hypotension and bradycardia but without asystolic pauses >3 s. Delayed orthostatic hypotension: prolonged (>3 min) hypotensive prodromes that may be followed by reflex syncope in absence of fall in heart rate
☐ Cardioinhibitory reflex syncope	Induction of syncope during tilt table test	Typical ECG pattern of vasovagal syncope during hypotension and asystolic pause >3 s)

5) Hypotensive phenotype: diagnostic criteria (ref 15)

Diagnosis	Definition	Test	Blood pressure cut-offs
Drug-unrelated persistent hypotension (constitutional hypotension)	Persistently low BP in the absence of hypotensive medications	24-hour ABPM (1)	*Males* 24 h SBP <105 mm Hg Daytime SBP <115 mm Hg *Females* 24h SBP <98 mm Hg Daytime SBP <105 mm Hg
Drug-related persistent hypotension	SBP values persistently below the recommended target in patients receiving hypotensive medications	24-hour ABPM (2)	24h SBP <120 mmHg
Hypotensive (intermittent) episodes	Orthostatic hypotension (classical form)	Active and passive standing	Symptomatic SBP fall ≥20mmHg or standing SBP <90mmHg within 3 min of active standing during the initial evaluation or during passive standing while performing SCAFA
	Orthostatic hypotension (initial form)	Active standing	Initial OH is characterized by a BP decrease on standing of >40 mmHg for systolic BP and/or >20 mmHg for diastolic BP within 15 s of standing. BP then spontaneously and rapidly returns to normal, so the period of hypotension and symptoms is short (<40 s) but may still cause syncope. A beat-to-beat BP monitoring is preferable.
	Hypotensive drops	24-hour ABPM (3)	≥1 episodes of daytime SBP <90 mmHg ≥2 episodes of daytime SBP <100 mmHg
Hypotensive reflex syncope	1) Induction of syncope during tilt table test	Tilt table test (4)	Typical haemodynamic pattern of mixed or vasodepressor vasovagal syncope with hypotension and bradycardia but without asystolic pauses >3 s. Delayed orthostatic hypotension: prolonged (>3 min) hypotensive prodromes that may be followed by reflex syncope in absence of fall in heart rate
	2) Reproduction of (pre)syncope during carotid sinus massage (method of symptoms)	Carotid sinus massage	Reproduction of spontaneous (pre)syncope, recognized by the patient itself, with fall in SBP >50 mmHg or below 85 mmHg and absence of asystolic pause/s >3 s

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure

6) Bradycardic phenotype: diagnostic criteria (ref 15)

Diagnosis	Definition	Test	CI cut-offs
CI reflex syncope	1)Reproduction of spontaneous symptoms during CSM (method of symptoms)	Supine and standing CSM	Reproduction of spontaneous (pre)syncope, recognized by the patient itself, with fall in SBP >50 mmHg and asystolic pause/s >3 s.
	2)Reproduction of spontaneous syncope during tilt table test	Tilt table test (4)	Typical ECG pattern of vasovagal syncope during hypotension and asystolic pause >3 s)
	3)Asystolic pauses of likely reflex origin during prolonged ECG monitoring (ILR)	Prolonged ECG monitoring (ILR)	Typical ECG pattern of asystolic (>3 s) vasovagal syncope or documentation of asymptomatic asystolic pause >6 s of likely reflex origin

CI = cardioinhibitory; CSM = carotid sinus massage; SBP= systolic blood pressure; ILR = implantable loop recorder

7) Echocardiogram

Diagnostic criteria: Aortic stenosis, obstructive cardiac tumours or thrombi, pericardial tamponade, and aortic dissection are the most probable causes of syncope when the ECG shows the typical features of these conditions

8) Elettrocardiographic monitoring

Diagnostic criteria:

- Arrhythmic syncope is confirmed when a correlation between syncope and an arrhythmia (bradyarrhythmia or tachyarrhythmia) is detected
- In the absence of syncope, arrhythmic syncope should be considered likely when periods of Mobitz II second- or third degree AV block or a ventricular pause >3 s (with the possible exception of young trained persons, during sleep or rate controlled atrial fibrillation), or rapid prolonged paroxysmal SVT or VT are detected

9) Electrophysiological study

Diagnostic criteria:

- In patients with unexplained syncope and bifascicular BBB, a pacemaker is indicated in the presence of either a baseline H-V interval of >_70 ms, second- or third-degree His-Purkinje block during incremental atrial pacing, or with pharmacological challenge.I B
- In patients with unexplained syncope and previous myocardial infarction, or other scar-related conditions, it is recommended that induction of sustained monomorphic VT is managed according to the current ESC Guidelines for VA.
- In patients without structural heart disease with syncope preceded by sudden and brief palpitations, it is recommended that the induction of rapid SVT or VT, which reproduce

hypotensive or spontaneous symptoms, is managed with appropriate therapy according to the current ESC Guidelines.I C

- In patients with syncope and asymptomatic sinus bradycardia, a pacemaker should be considered if a prolonged corrected SNRT is present.

10) Stress test

Diagnostic criteria:

- Syncope due to second- or third-degree AV block is confirmed when the AV block develops during exercise, even without syncope.

- Reflex syncope is confirmed when syncope is reproduced immediately after exercise in the presence of severe hypotension

11) Coronary angiography

Diagnostic criteria: Angiography alone is not diagnostic of the cause of syncope

Phase 3 – Implantable Cardiac Monitors (ICM)

Diagnostic criteria:

- Arrhythmic syncope is confirmed when a correlation between syncope and an arrhythmia (bradyarrhythmia or tachyarrhythmia) is detected
- In the absence of syncope, arrhythmic syncope should be considered likely when periods of Mobitz II second- or third degree AV block or a ventricular pause >3 s (with the possible exception of young trained persons, during sleep or rate controlled atrial fibrillation), or rapid prolonged paroxysmal SVT or VT are detected

Classification of ECG diagnoses:

- Type 1. Asystole (R-R pause >_3 seconds):
    - Type 1A. Sinus arrest: progressive sinus bradycardia or initial sinus tachycardia followed by progressive sinus bradycardia until sinus arrest (see Web Figure 27)
    - Type 1B. Sinus bradycardia plus AV block: progressive sinus bradycardia followed by AV block (and ventricular pause/s) with concomitant decrease in sinus rate
    - Type 1C. AV block: sudden onset AV block (and ventricular pause/s) with concomitant increase in sinus rate (see Web Figures 29 and 30)
- Type 2. Bradycardia Decrease in HR >30% or <40 b.p.m. for >10 seconds (see Web Figure 31)
- Type 3. No (type 3A) or slight (type 3B) rhythm variations. Variations in HR <30% and HR >40 b.p.m
- Type 4. Tachycardia. Increase in HR >30% or >120 b.p.m:

- Type 4A. Progressive sinus tachycardia
- Type 4B. Atrial fibrillation
- Type 4C. SVT (except sinus)
- Type 4D. Ventricular tachycardia

Flow Chart structure of the Diamond Syncope Pathway