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CLINICAL RESEARCH

Diagnostic yield and accuracy in a tertiary referral syncope unit validating the ESC guideline on syncope: a prospective cohort study

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Aims To assess in patients with transient loss of consciousness the diagnostic yield, accuracy, and safety of the structured approach as described in the ESC guidelines in a tertiary referral syncope unit.

Methods and results Prospective cohort study including 264 consecutive patients (≥18 years) referred with at least one self-reported episode of transient loss of consciousness and presenting to the syncope unit between October 2012 and February 2015. The study consisted of three phases: history taking (Phase 1), autonomic function tests (AFTs) (Phase 2), and after 1.5-year follow-up with assessment by a multidisciplinary committee (Phase 3). Diagnostic yield was assessed after Phases 1 and 2. Empirical diagnostic accuracy was measured for diagnoses according to the ESC guidelines after Phase 3. The diagnostic yield after Phase 1 (history taking) was 94.7% (95% CI: 91.1–97.0%, 250/264 patients) and increased to 97.0% (93.9–98.6%, 256/264 patients) after Phase 2. The overall diagnostic accuracy (as established in Phase 3) of the Phases 1 and 2 diagnoses was 90.6% (95% CI: 86.2–93.8%, 232/256 patients). No life-threatening conditions were missed. Three patients died, two unrelated to the cause of transient loss of consciousness, and one whom remained undiagnosed.

Conclusion A clinical work-up at a tertiary syncope unit using the ESC guidelines has a high diagnostic yield, accuracy, and safety. History taking (Phase 1) is the most important diagnostic tool. Autonomic function tests never changed the Phase 1 diagnosis but helped to increase the certainty of the Phase 1 diagnosis in many patients and yield additional diagnoses in patients who remained undiagnosed after Phase 1. Diagnoses were inaccurate in 9.4%, but no serious conditions were missed. This is adequate for clinical practice.

Keywords Syncope • Diagnostic accuracy • Diagnostic yield • Transient loss of consciousness

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What's new?

- A standardized method of assessment of patients with syncope based on the ESC guidelines (as is performed in syncope units), with history taking playing a mayor role, results in a high diagnostic yield.
- The patients had previously consulted several specialists and had multiple tests, which were inconclusive. Unfortunately, detailed history taking is not part of common medical practice anymore. Thus, this study reinforces the need of specialized syncope units.
- The study was able to measure the diagnostic accuracy of diagnoses according to the ESC definitions (recommendations).
- For diagnostic purposes, autonomic function tests are not needed in patients with a certain, highly likely, or possible diagnosis, but are still indicated in such cases for therapeutic purposes and reassurance of both the physician and the patient.
- Patients with psychogenic pseudosyncope often remain undiagnosed in secondary care despite multiple tests and consultations with specialists.

Introduction

Transient loss of consciousness (T-LOC) occurs frequently and can be caused by multiple mechanisms ranging from benign conditions, such as reflex syncope, to life-threatening conditions, such as ventricular tachyarrhythmias and heart block.[1,2] After work up for the diagnosis leading to T-LOC and after the exclusion of life-threatening conditions, as well as obvious causes of reflex syncope, many patients remain undiagnosed and subsequently, untreated.[3] As the cumulative lifetime incidence of syncope is high, the number of undiagnosed cases is substantial.[4]

The diagnostic yield of the initial evaluation and the prevalence of causes of T-LOC in primary care[3] and outpatient departments have been described in several studies.[1,2] These studies were conducted in hospitals within the departments of Cardiology, Neurology, Internal Medicine, and Emergency Medicine, both with and without syncope units.[2,3]

Dedicated syncope units with specific expertise on the various causes of syncope could enhance the number of diagnosed patients with complex presentations.[5] The diagnostic yield in patients referred to a *tertiary* dedicated syncope unit with a structured approach (i.e. with second opinion referrals from primary and secondary care) has never been assessed, despite the call for such studies by the 2018 ESC Syncope Guidelines and the 2017 ACC/AHA/HRS Syncope Guidelines.[1,6]

Hence, this gap in data on the effectiveness of tertiary referral syncope units remains. We, therefore, assessed the diagnostic yield of a structured diagnostic approach of T-LOC within a tertiary referral syncope unit where the diagnostic recommendations of the ESC guidelines on syncope are applied in daily practice. In addition, a multidisciplinary panel evaluated patients after long-term follow-up in order to determine the diagnostic accuracy and safety of the diagnosis established in the syncope unit.[2,7,8]

Methods

Patients

This is a prospective cohort study. All consecutive patients older than 18 years old and referred by a remote specialist with at least one self-reported episode of T-LOC to the tertiary referral syncope unit of Amsterdam University Medical Centres, location Academic Medical Centre, from October 2012 to February 2015 were eligible for inclusion. Patients were referred in order to confirm or exclude an initial suspicion of reflex syncope or orthostatic hypotension or for diagnosis of unexplained syncope after one or more consultations by specialists. As the collected data are routine data, the local ethics committee (in accordance with national law and the declaration of Helsinki) issued a waiver for obtaining informed consent.

Patients were evaluated in line with the recommendations of the ESC Guidelines on syncope,[1] in order to confirm or exclude the initial suspicion of syncope. The study consisted of three phases, the first two phases were part of the consultation at the syncope unit, the third phase consisted of dedicated follow-up.

Phase 1: initial evaluation

Consultation started with the initial evaluation, consisting of history taking, physical examination, and electrocardiography (ECG). History taking consisted of carefully listening to the patient, while sitting face-to-face.[9–11] Historical clues were collected while asking open questions and physiological reasoning was applied.[12,13] Every episode of T-LOC was reconstructed and timelines of symptoms were determined. Prior diagnostic tests including outcomes were reported. The suggested diagnosis of the referring physician prior to consultation in the syncope unit was included. The patient was asked if he/she could recall this diagnosis during the consultation. At the end of Phase 1, a diagnosis and certainty of diagnosis was made according to the diagnostic criteria (*Table 1*).

Phase 2: autonomic function testing

After Phase 1, the consultation reached Phase 2, which consisted of autonomic function tests (AFTs). A physician was present throughout this phase. Criteria for performing AFTs and the interpretation of test results were identical to the ESC guidelines of 2018.[1,12] AFTs were performed with continuous blood pressure and heart rate measurements (Finapres Nova, Amsterdam, The Netherlands) and, based on history taking, could include: (i) an active stand test, (ii) Valsalva manoeuvres, a deep breathing test, a cold pressor test, a sustained hand grip test, and a mental stress test, (iii) carotid sinus massage in supine and upright position when older than 40 years, and (iv) a head-up tilt according to the Italian protocol.[1] When specific triggers were identified during history taking (e.g. arising from squatting, coughing, swallowing, or exercise), these were reproduced during AFTs to assess blood pressure and heart rate response. After AFTs, physical counter-pressure manoeuvres were practiced when syncope was caused by a blood pressure regulation disorder.[14] At the end of Phase 2, a diagnosis was made again, along with certainty (*Table 1*).

Diagnostic criteria and level of certainty: certain, highly likely, and likely

The diagnostic criteria were derived to the ESC Guidelines on syncope and, more specific, the historical clues in the practical instructions.[1,12] Diagnoses were classified by the physician as either 'certain', 'highly likely', or 'possible'[15] and are specified in *Table 1*.

In patients with multiple T-LOC episodes, more than one diagnosis was allowed.

Table 1 **Diagnostic criteria defined per diagnosis and subjective probability level derived from the ESC guideline on syncope**[1,12,19]

Reflex syncope	Certain	Highly likely	Possible
Vasovagal syncope	Syncope precipitated by pain, fear, or standing, and associated with progressive prodrome (pallor, sweating, and/or nausea)	1. Features that suggest VVS are present but not consistent over all episodes with recognition during a positive tilt test 2. 'Possible' criteria with recognition during a positive tilt test	In the presence of any features that might suggest VVS and the following observations are excluded: cardiac syncope, cOH non-syncopal LOC, and subclavian steal syndrome
Carotid sinus syndrome	Carotid sinus massage caused bradycardia (asystole) and/or hypotension that reproduced spontaneous symptoms and patients had clinical features compatible with a reflex mechanism of syncope and with specific triggers	Syncope consistent with specific triggers like head-turning but no carotid sinus massage is performed yet	Sudden syncope of unknown origin compatible with a reflex mechanism, >40 years old, and the following observations are excluded: cardiac syncope, cOH non-syncopal LOC and subclavian steal syndrome
Orthostatic hypotension	*Symptomatic* abnormal BP fall and History *highly suggestive for OH*: syncope and presyncope are present during standing, absent while lying, and less severe or absent while sitting; a predilection for the morning; sitting or lying down must help; complaints may get worse immediately after exercise, after meals or in high temperatures; no 'autonomic activation'	1. *Symptomatic* abnormal BP fall and history of syncope and orthostatic complaints are *possibly due to OH:* not all of the features highly suggestive of OH are present 2. *Asymptomatic* abnormal BP fall and history of syncope and orthostatic complaints are *highly suggestive of OH*: syncope and presyncope are present during standing, absent while lying, and less severe or absent while sitting; a predilection for the morning; sitting or lying down must help; complaints may get worse immediately after exercise, after meals or in high temperatures; no 'autonomic activation'	Orthostatic intolerance: *asymptomatic* fall in systolic BP and history of syncope and orthostatic complaints *possibly due to OH:* not all of the features syncope always while standing but without fall in blood pressure during orthostatic standing test, features suggesting autonomic reflex absent
Initial OH	Frequent complaints of light-headedness, seeing black spots or (near)syncope <10 s upon active standing with disappearance of symptoms <30 s *and* IOH positive on active stand test	1. Frequent complaints of light-headedness, seeing black spots, or (near)syncope <10 s upon active standing with disappearance of symptoms <30 s *and* IOH negative on active stand test 2. ('Possible' criteria and IOH on active stand test	History inconsistent but presence of light-headedness, seeing black spots or (near)syncope <10 s upon active standing with disappearance of symptoms <30 s, no IOH on active stand test
Cardiac syncope	Cardiac syncope was certain when a correlation between syncope and an arrhythmia (bradyarrhythmia or tachyarrhythmia) was detected in the presence of syncope	1. All features from history are suggestive for arrhythmic syncope and 2. ECG shows high-risk major features as stated by the ESC guideline	1. Not all features from history suggestive for arrhythmic syncope and 2. ECG shows minor criteria of high risk of cardiac syncope
Psychogenic pseudosyncope	History suggestive for PPS and recording of spontaneous attacks with a video by an eyewitness and/or witnessed or witness an attack during AFT's	History suggestive for PPS but no attack occurred during AFTs and no video recording of spontaneous attacks available	History inconsistent but some features for PPS are present, no attack occurred during AFTs, and no video recording of spontaneous attacks available

BP, blood pressure; cOH, classic orthostatic hypotension; ECG, electrocardiogram; IOH, initial orthostatic hypotension, LOC, loss of consciousness; OH, orthostatic hypotension; VVS, vasovagal syncope.

Phase 1 and Phase 2 diagnosis

After both the initial evaluation (Phase 1) and after AFTs (Phase 2), a diagnosis and certainty level (certain, highly likely, possible) were established. This physician-reported level of certainty is the *subjective probability* of a diagnosis being correct and was recorded at the end of both Phases 1 and 2. The guidelines mention these levels of subjective probability but do not specify what these levels reflect in terms of accuracy. The AFTs could confirm or change the Phase 1 diagnosis and/or the level of certainty.

Patient explanation and clarification

After Phase 2, the physician explained the diagnosis and treatment options. The most likely diagnosis was always specifically communicated. Results of AFTs were used for further clarification. Also, the patient was informed if no diagnosis was made or if a psychogenic cause was suspected and referred for guidance if possible.[4,16]

Additional diagnostic testing

Patients with suspected cardiac syncope or a structural cardiopulmonary cause were monitored with an implantable loop recorder (ILR), echocardiogram, Holter monitor, or exercise-ECG.

Patients with epileptic seizures were referred to an epileptologist.[1] If the diagnosis remained unknown after the consultation, either an ILR was implanted, or a fourth opinion was requested, to the discretion of the treating physician.

Phase 3: follow-up and reference standard multidisciplinary committee

Phase 3 consisted of a follow-up procedure to assess the diagnostic accuracy of the Phase 2 diagnoses as recommended by the ESC guidelines.[2,7]

All patients received two follow-up questionnaires: 3–6 months and 1 to 1.5 years after first consultation. The questions regarded recurrences, additional diagnostic testing, and received treatments. If the questionnaire was not returned, patients were contacted by telephone to answer questions regarding recurrences, consultations with specialists, diagnostic tests, and quality of life (data will be reported elsewhere). When patients could not be contacted, the primary care physician or the patient's insurance company was contacted to confirm if the patient was alive. When patients answered that additional tests had been performed or that they had consulted a specialist other than their general practitioner, their medical records were retrieved.

The information collected during follow-up was used as input for the reference standard.[2,7] Diagnoses were considered accurate by default. If patients did not experience a reduction of yearly T-LOC episodes of >50% during follow-up, if they underwent further diagnostic testing or treatment incompatible with the Phase 2 diagnosis during follow-up, or if patients had died, a review by a multidisciplinary committee was performed.

The Phase 2 diagnosis was reviewed by a multidisciplinary committee, which consisted of a neurologist, an internist, and a cardiologist. The committee first independently reviewed all available anonymized information per patient, including the data at presentation and the follow-up information and made a diagnosis for each patient according to the ESC guidelines on syncope. When there was unanimous agreement, or when two experts agreed and a third made no diagnosis, the adjudicated diagnosis was established. In the presence of any disagreement, the patient's case was discussed in a face-to-face expert consensus meeting. T-LOC was deemed unexplained if no consensus was reached. Patients with unexplained T-LOC after Phase 2 could still be diagnosed by the expert committee.

Table 2 Baseline patient characteristics

	Patients
N	264
Male, *n* (%)	121 (46)
Age, median (IQR)	51 (34–64)
Age of first T-LOC episode, median (IQR)	41 (17–60)
Number of T-LOC episodes life-time, median (IQR)	6 (3–20)
Number of T-LOC episodes last year, median (IQR)	3 (1–6)
Previous diagnostic tests at least once, *n* (%)	259 (98)
ECG, *n* (%)	241 (91)
Holter monitor, *n* (%)	207 (78)
Echocardiogram, *n* (%)	206 (78)
Exercise-ECG, *n* (%)	198 (75)
EEG, *n* (%)	160 (61)
X-Thorax, *n* (%)	129 (49)
CT-brain, *n* (%)	97 (37)
24-h blood pressure measurement, *n* (%)	96 (36)
Cardiac MRI, *n* (%)	40 (15)
Implantable loop recorder, *n* (%)	35 (13)
Carotid echo duplex, *n* (%)	35 (13)
Head-up tilt test, *n* (%)	22 (8)
Myocardial perfusion scan, *n* (%)	8 (3)
Previous specialist consultations at least once, *n* (%)	264 (100)
Cardiologist, *n* (%)	234 (89)
Neurologist, *n* (%)	187 (71)
Internist, *n* (%)	95 (36)

CT, computed tomography; ECG, electrocardiogram; EEG, electroencephalogram; IQR, interquartile range; MRI, magnetic resonance imaging; T-LOC, transient loss of consciousness; X, X-ray.

Unexpected diagnosis of cardiac syncope (tachyarrhythmia, heart block, or structural heart disease), and death due to T-LOC episodes were considered for the safety outcome.

The committee was not involved in the data collection in Phases 1 and 2 and follow-up data of this study.

Statistical analysis

Shapiro–Wilk tests were performed to check for skewed data. Continuous variables are expressed as mean with standard deviation or median with interquartile range (IQR), where appropriate. Wilson's method was used to calculate confidence intervals (CIs) of proportions.

Diagnostic yield was defined as the percentage of patients that received a Phase 2 diagnosis. Diagnostic accuracy was defined as the proportion of the correct adjudicated diagnoses that conformed to the Phase 2 diagnoses.

A follow-up duration was defined as the weeks between syncope unit consultation and return of the last questionnaire.

Results

Patient characteristics

A total of 264 patients were included in this study. The baseline clinical characteristics are displayed in *Table 2*. The most frequently referring physicians were cardiologists (67.0%), general practitioners

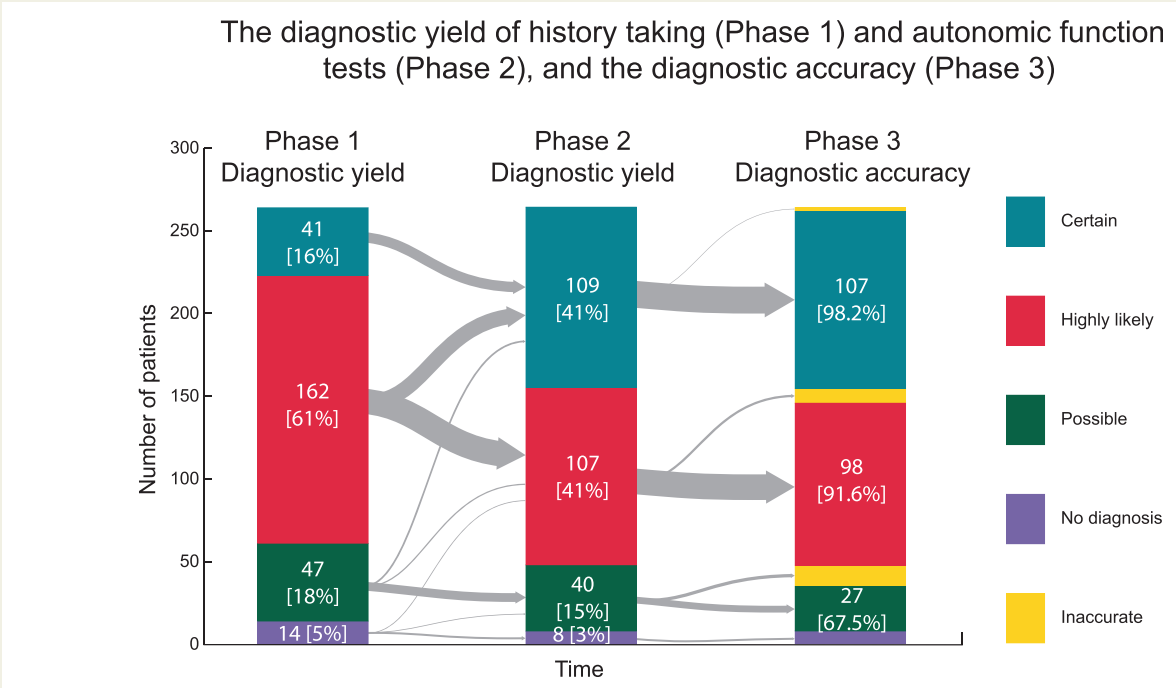

Figure 1 The diagnostic yield and accuracy of Phase 1 (history taking) and Phase 2 (autonomic function testing) in a tertiary syncope unit sorted by physician's certainty of the diagnosis (level of subjective probability). The levels of certainty are certain, highly likely, and possible. Left to right: the Phase 1 diagnosis after history taking sorted by subjective probability level; the Phase 2 diagnosis after autonomic testing sorted by subjective probability level; diagnostic accuracy after Phase 3 (follow-up with expert committee). Gray arrows indicate patient flow from different certainty groups. Thickness of arrows indicate relative number of patients.

(12.1%), neurologists (9.8%), and internists (7.2%). All patients who were referred by general practitioners had previously undergone evaluation by specialists. Prior to the consultation, 234 patients (88.6%) had been seen at least once by a cardiologist, 187 (70.8%) by a neurologist, and 95 (36.0%) by an internist, with a median of 6.5 specialist consultations per patient (IQR: 4.0–11.0) prior to the consultation in the syncope unit.

At the time of syncope unit consultation, patients had undergone a median of 11.0 diagnostic tests (IQR: 7.0–15.0) (*Table 2*). The referring physician suggested no diagnosis in 134/264 (50.8%) of patients. In the other 130 104 patients (80.0%) could not recall this diagnosis at the time of the syncope unit consultation.

In Phase 1, all patients underwent history taking, physical examination, and an ECG. *Figure 2* displays the use of AFTs during Phase 2.

Median follow-up duration was 61.4 weeks (IQR: 56.0–69.9 weeks). Questionnaires were returned, either by mail or phone, by 241/264 (91.3%) of the patients.

Diagnostic yield

After Phase 1, the Phase 1 diagnosis was considered certain in 41 patients (15.5%, 95% CI: 11.5–20.6%), highly likely in 162 patients (61.4%, 95% CI: 55.2–67.2%), and possible in 47 patients (17.8%) (95% CI: 13.5–23.1%) (*Figure 1*). A Phase 1 diagnosis was thus made in 250/264 patients, resulting in a diagnostic yield of 94.7% (95% CI: 91.1–97.0%).

After AFTs, the Phase 2 diagnosis was considered certain in 109 patients (41.3%, 95% CI: 35.3–47.5%), highly likely in 107 patients (40.5%, 95% CI: 34.6–46.7%), and possible in 40 patients (15.2%, 95% CI: 11.1–20.2%). The resulting diagnostic yield of Phases 1 and 2 together was 97.0% (95% CI: 93.9–98.6%, 256/264 patients). Autonomic function tests did not result in change of the Phase 1 diagnosis but resulted in an overall higher subjective probability level, and in six additional diagnoses of the remaining 14 undiagnosed patients (reduction of 43% of undiagnosed patients).

Diagnostic accuracy

The follow-up procedure required adjudication due to diagnostic or treatment failure as prescribed per protocol by the multidisciplinary committee in 63/264 patients. The committee changed the Phase 2 diagnosis after evaluation of all the available information (including additional follow-up information that was not available during Phases 1 and 2) in 24/63 patients, which resulted in an overall diagnostic accuracy (based on accurate by default and adjudicated diagnoses) of 90.6% (232/256 patients, 95% CI: 86.2–93.8%).

Of Phase 2 diagnoses considered certain ($n = 109$), 2/12 that were presented were changed by the committee. This resulted in an accuracy of 98.2% (95% CI: 92.9–99.7%) of the patients with a certain diagnosis (*Figure 1*). However, the changes in diagnoses did not affect the treatment of the patients (see *Appendix*).

Of Phase 2 diagnoses considered highly likely ($n = 107$), 9/17 that were presented were changed by the committee. The diagnostic

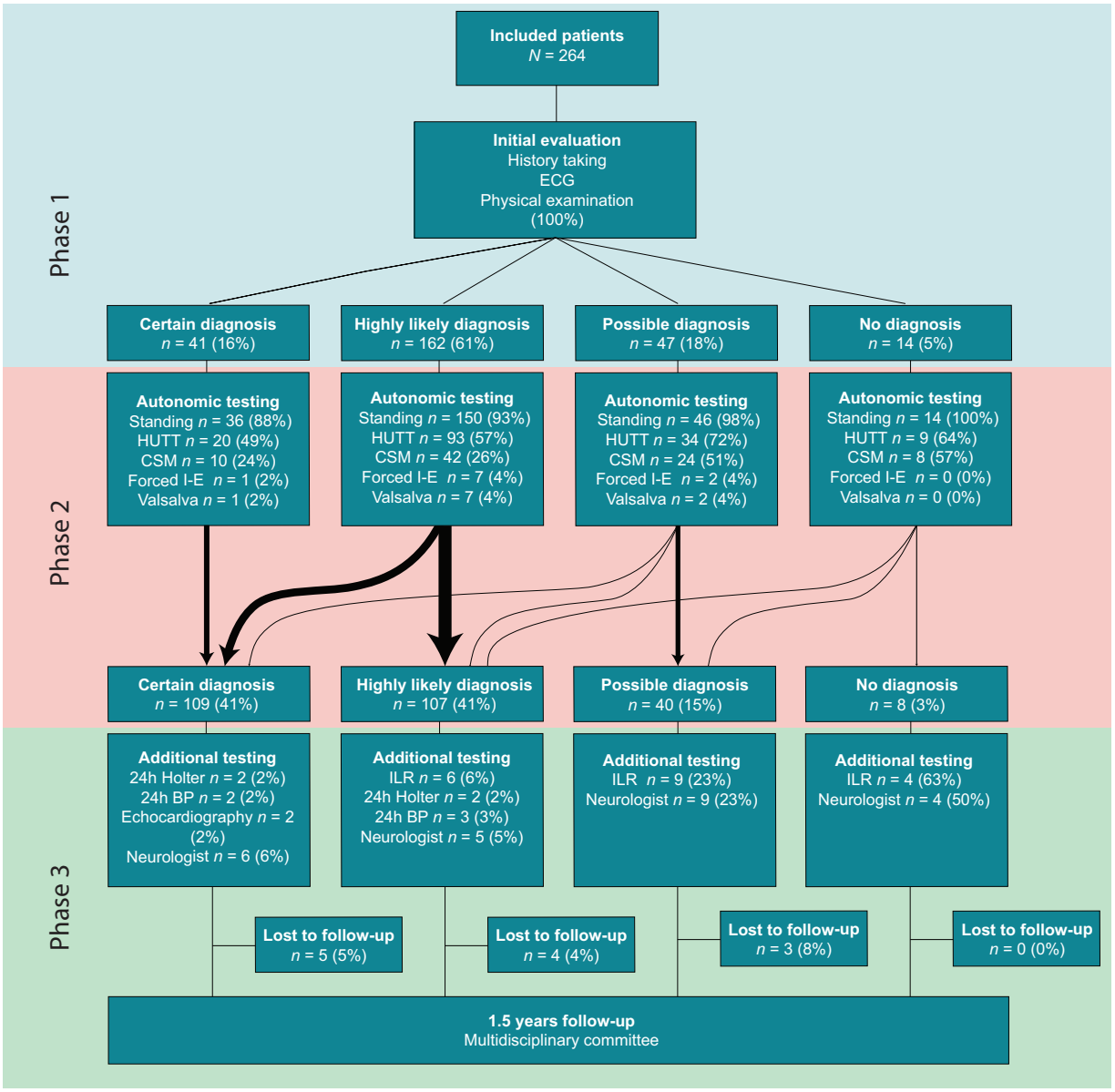

Figure 2 A flowchart of patients through study. Percentage of patients in whom tests were performed, percentage of patients in different groups of certainty and follow-up are shown. Rates of patients in different certainty groups are shown. BP, blood pressure; ECG, electrocardiography; h, hour; ILR, implantable loop recorder.

accuracy of a highly likely diagnosis was thus 91.6% (95% CI: 84.2–95.8%).

Of Phase 2 diagnoses considered possible ($n = 40$), 13/26 that were presented were changed. The diagnostic accuracy of patients with a possible diagnosis was 67.5% (95% CI: 50.8–80.9%).

Diagnostic safety

A total of 39 (14.8%) patients were considered at risk of cardiac syncope (risk >5%). Seven of these patients received a Phase 3 diagnosis of cardiac syncope (17.9%; in two patients this was the second diagnosis). Six out of seven patients were correctly diagnosed after Phase 2; one patient was diagnosed with vasovagal syncope (VVS) after Phase 2 but with cardiac syncope not sufficiently excluded. An ILR was implanted and proved cardiac arrhythmia during an episode.

Three patients were diagnosed with an epileptic seizure after Phase 3 by the committee, although this diagnosis had not been made after Phase 2. The first patient did not receive a final diagnosis after Phase 2 but was referred to an epileptologist who established a definite diagnosis of epilepsy. The second patient was diagnosed with *possible* VVS after Phase 2, but this diagnosis appeared inaccurate during follow-up yielding a final diagnosis of epileptic seizures due to a cerebral glioma. The third patient was diagnosed with *possible* VVS but was referred for a fourth opinion to an epileptologist who subsequently diagnosed epileptic seizures.

Table 3 Patient characteristics sorted by adjudicated diagnosis

	Reflex syncope	Orthostatic hypotension	Cardiac syncope	Psychogenic pseudosyncope	Epileptic seizure	Other	Unexplained T-LOC
N (%)	175 (66)	65 (25)	11 (4)	39 (15)	8 (3)	5 (2)	8 (3)
Male, *n* (%)	79 (45)	34 (52)	7 (64)	10 (26)	6 (75)	2 (40)	2 (25)
Age (years) (IQR)	48 (31–63)	56 (39–69)	74 (69–79)	36 (26–49)	59 (55–63)	59 (54–63)	61 (53–69)
Age of first T-LOC episode (IQR)	32 (15–56)	53 (27–67)	73 (65–75)	25 (15–39)	56 (43–61)	56 (49–57)	61 (52–68)
T-LOC episodes life-time, *n* (IQR)	6 (3–19)	4 (2–10)	4 (4–6)	50 (14–73)	11 (4–21)	3 (2–4)	4 (1–12)
T-LOC episodes last year, *n* (IQR)	3 (1–5)	2 (1–5)	3 (2–4)	12 (5–50)	6 (4–8)	1 (1–1)	2 (1–6)

Patients could be diagnosed with more than one cause of transient loss of consciousness if multiple episodes had occurred. This results in a sum of >100% of diagnoses.
Arrh, cardiac arrhythmia; BP, blood pressure; CSS, carotid sinus syncope; Delayed OH, delayed orthostatic hypotension; DI-OH, drug-induced orthostatic hypotension; IOH, initial orthostatic hypotension; IQR, interquartile range; NOH, neurogenic orthostatic hypotension; PPS, psychogenic pseudosyncope; SHD, structural heart disease; situ-VVS, situational vasovagal syncope; T-LOC, transient loss of consciousness; VVS, vasovagal syncope.

Three patients died during follow-up. For two of those patients, the committee deemed that the cause of death was unrelated to the cause of T-LOC. In the third patient, the T-LOC episode remained unexplained after Phase 3. No cause of death could therefore be determined as no autopsy was performed.

Diagnostic tests

During Phase 3, no additional echocardiograms and exercise-ECGs were performed. Twenty-four-hour blood pressure measurements were taken in six patients (*Figure 2* for tests used). In all patients with unexplained T-LOC ILRs were implanted or patients were referred for a fourth opinion (*Figure 2*). If an ILR had been previously implanted the results were already known at the consultation.

Nineteen ILRs (7.2%) were implanted during Phase 3, of which five demonstrated cardiac arrhythmias (26.3%; 95% CI: 10.1–51.4%). During follow-up, ILRs were implanted by remote cardiologists outside the protocol of this study in another five patients; none of these provided a diagnosis during the follow-up period.

Adjudicated diagnoses

Most patients were diagnosed with VVS (43.9%), followed by psychogenic pseudosyncope (PPS) (14.8%), and initial orthostatic hypotension (14.0%). *Table 3* displays an overview of adjudicated diagnoses.

Sixty (22.7%) patients were diagnosed with multiple causes of T-LOC. The combinations of PPS and VVS ($n = 26$) and initial orthostatic hypotension and VVS ($n = 15$) accounted for 65.1% of these patients.

Discussion

This study provides solid evidence for the effectiveness of a tertiary referral syncope unit with a structured approach according to the ESC Guidelines on syncope, with a remarkably high diagnostic yield (97.0%) with high accuracy (90.6%). The vast majority of the diagnoses (94.7%) were made after Phase 1, consisting of the initial evaluation, but most importantly history taking. Thus, in a tertiary setting, history taking is the most important diagnostic test, combining high diagnostic yield with only a few additional tests during follow-up. This emphasizes the application of the ESC guidelines on syncope also in a tertiary setting with sufficient time for history taking (Phase 1) with basic knowledge of physiology and *building* a history rather than *taking* history,[9] which results in expert history taking. We might conclude that taking/appointing time for a good complete medical history (including collateral history) is not part of common medical practice anymore and unfortunately seems to belong to the medical practice of tertiary care. AFTs only contributed diagnostic value in complex patients who remained undiagnosed after the initial evaluation (Phase 1), since AFTs yielded six additional diagnoses, thereby increased the diagnostic yield by only 2.3%.

There was a unidirectional change (either no change or increased) in the level of certainty of the diagnosis in many patients (*Figure 1*), but AFTs never changed the diagnosis made after the initial evaluation. Moreover, a negative AFT did not downgrade the diagnosis after the initial evaluation. Thus, even in a tertiary setting the use of AFTs can be avoided for diagnostic purposes in a large proportion of patients. AFTs tailored to the patient's history, however, remain very useful for reassuring the patients and physicians when symptoms have been witnessed and correctly interpreted, explained, and clarified. Hypothetically, this may lead to better compliance and/or increased quality of life, although a false negative tilt test could also result in the opposite. More research is needed to test this hypothesis. Another important indication for AFTs in the tertiary setting is selection of therapies (e.g. physical counter-pressure manoeuvres and characterization of the vasovagal reflex). Thus, AFTs continue to play an important role in the work up of patients in a tertiary syncope unit.[17]

The safety of the syncope unit was high in our study. No potentially life-threatening conditions were missed. The high safety of this study may in part have been caused by the distribution of the causes of T-LOC. Although a large consecutive group of patients was included, there was a remarkably low prevalence of cardiac syncope and structural cardiopulmonary causes, and a high rate of PPS and initial orthostatic hypotension. Of note, all patients were referred by other physicians and specialists, who may have already recognized and not referred the cases of cardiac syncope. The low rate of life-threatening causes indicates that these are identified in primary and secondary care. Another cause for the low rate of cardiac syncope could be that the patients that were referred were relatively young (median 51 years old). We found a higher prevalence of PPS than in

any other study.[1,2] A possible explanation could be that patients presenting to a tertiary syncope unit are more severely affected than other patients with T-LOC.[2] Also, PPS is often under recognized in primary and secondary care,[18] which may have resulted in some of these patients in the population being referred to a tertiary centre. Additionally, it could indicate a large gap in the knowledge of this cause of T-LOC. Our cohort is thus not representative for emergency care, or patients first consulting a specialist.

We used long-term critical follow-up after Phase 2 as a gold standard to demonstrate that diagnoses considered to be 'certain' were accurate in 92.9–99.7%. For diagnoses considered 'highly likely' they were accurate 84.2–95.8%, and for 'possible' this was 50.8–80.9%. These percentages resemble the statistically *objective probability* of accuracy. Moreover, Van Dijk *et al.*[2] found an accuracy of 87–97% for 'certain' diagnoses and 80–89% for 'highly likely' diagnoses hospital wide. The subjective probability of 'certain' in the guidelines thus seem to reflect an objective probability of accuracy of 90–100%, for 'highly likely' diagnoses this is 80–90%, and for 'possible' diagnoses this is 50–80%.

We used adjudicated diagnosis by a multidisciplinary committee during long-term follow-up as a reference standard to test the accuracy of the initial diagnosis. To the best of our knowledge, such approach is only rarely applied in studies on the diagnostic yield of syncope.[2] This could imply that in the other studies assessing diagnostic yield a significant amount of diagnoses might be inaccurate, depending on the certainty of the diagnoses. We believe that inclusion of long-term follow-up using a multidisciplinary committee is critical to avoid inaccurate diagnoses.

Our study is a single-centre study with a specific design and organization of the syncope unit; that meets the ESC/EHRA criteria for tertiary referral syncope unit as proposed in Kenny *et al.*[5] Larger multicentre studies including tertiary referral centres with the same structural approach need to be performed to examine to what extent these results are applicable to other tertiary referral syncope units, and to evaluate the generalizability of these results.

As with all second or third opinion, including this study, knowledge of the diagnostic tests that were performed prior to consultation affected the diagnostic yield of the initial evaluation. The diagnostic yield of the initial evaluation could thus be different in primary and secondary care, where fewer tests have been performed before history taking, although the likelihood of reflex syncope is very high in these contexts.[2] Based on the many consultations and many diagnostic tests prior to the consultation in the syncope unit, we consider the included patients as complex and therefore typical tertiary referrals.

We emphasize that very few of the referred patients (80%) could reproduce the possible aetiology of syncope assessed by the referring physician. This indicates a major gap in syncope management and shows the important role of dedicated syncope units for these patients, where explanation and clarification of the diagnosis is a vital part of the consultation.[4]

We demonstrate that the structured approach including application of the ESC guidelines on syncope in a tertiary referral syncope unit results in a high diagnostic yield of 97.0% with 90.6% accuracy and is safe.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Appendix

Table A1 Individual patients with changed final diagnosis after follow-up

Patient	Phase 2 diagnosis	Phase 3 diagnosis	Certainty after phase 2
1	VVS and PPS	Only VVS	Certain
2	VVS and delayed OH	Drug-induced OH & delayed OH	Certain
3	Epileptic seizure	Unexplained T-LOC	Highly likely
4	VVS	Unexplained T-LOC	Highly likely
5	PPS	PPS and VVS	Highly likely
6	VVS	VVS and initial OH	Highly likely
7	VVS	Unexplained T-LOC	Highly likely
8	Initial OH	PPS	Highly likely
9	Arrhythmia and VVS	only VVS	Highly likely
10	Arrhythmia	CSS	Highly likely
11	VVS	VVS and arrhythmia	Highly likely
12	PPS	Unexplained T-LOC	Possible
13	Epileptic seizure and VVS	Only VVS	Possible
14	Delayed OH	Unexplained T-LOC	Possible
15	VVS	Unexplained T-LOC	Possible
16	Epileptic seizure	VVS	Possible
17	VVS	Epileptic seizure	Possible
18	VVS	Epileptic seizure and VVS	Possible
19	Arrhythmia and VVS	only VVS	Possible
20	Arrhythmia	CSS	Possible
21	Initial OH	VVS and initial OH	Possible
22	Arrhythmia	VVS and arrhythmia	Possible
23	Arrhythmia and epileptic seizure	Only epileptic seizures	Possible
24	Arrhythmia	Situational syncope	Possible

CSS, carotid sinus syndrome; OH, orthostatic hypotension; PPS, psychogenic pseudosyncope; T-LOC, transient loss of consciousness; VVS, vasovagal syncope.