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Prospective multicentre systematic guideline-based management of patients referred to the Syncope Units of general hospitals†

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Aims Although an organizational model for syncope management facilities was proposed in the 2004 guidelines of the European Society of Cardiology (ESC), its implementation in clinical practice and its effectiveness are largely unknown.

Methods and results This prospective study enrolled 941 consecutive patients referred to the Syncope Units of nine general hospitals from 15 March 2008 to 15 September 2008. A median of 15 patients per month were examined in each unit, but the five older units had a two-fold higher volume of activity than the four newer ones (instituted <1 year before): 23 vs. 12, $P = 0.02$. These figures give an estimated volume of 163 and 60 patients per 100 000 inhabitants per year, respectively. Referrals: 60% from out-of-hospital services, 11% immediate and 13% delayed referrals from the Emergency Department, and 16% hospitalized patients. A diagnosis was established on initial evaluation in 191 (21%) patients and early by means of 2.9 ± 1.6 tests in 541 (61%) patients. A likely reflex cause was established in 67%, orthostatic hypotension in 4%, cardiac in 6% and non-syncopal in 5% of the cases. The cause of syncope remained unexplained in 159 (18%) patients, despite a mean of 3.5 ± 1.8 tests per patient. These latter patients were older, more frequently had structural heart disease or electrocardiographic abnormalities, unpredictable onset of syncope due to the lack of prodromes, and higher OESIL and EGSIS risk scores than the other groups of patients. The mean costs of diagnostic evaluation was €209 per outpatient and €1073 per inpatient. The median cost of hospital stay was €2990 per patient.

Conclusion We documented the current practice of syncope management in specialized facilities that have adopted the management model proposed by the ESC. The results are useful for those who wish to replicate this model in other hospitals. Syncope remains unexplained during in-hospital evaluation in more complex cases at higher risk.

Keywords Syncope • Syncope Unit • Diagnostic pathway • Guidelines

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Introduction

Although an organizational model for syncope management facilities was proposed in the 2004 guidelines of the European Society of Cardiology (ESC)[1,2] in order to optimize service delivery, its implementation in clinical practice and its effectiveness in syncope management are largely unknown.

A nationwide census taken in 2006 in Italy showed that there were 86 hospitals equipped with dedicated syncope facilities which partly or completely met the ESC requisites.[3] The model proposed by the ESC guidelines has been endorsed by the Associazione Italiana di Aritmologia e Cardiostimolazione (AIAC)[3] and several hospitals in Italy have adopted similar systems to that proposed by the ESC. Finally, 21 Syncope Units have been certified as meeting the ESC and AIAC requisites by a multidisciplinary organization nominated by the national societies of arrhythmias, internal and emergency medicine, and geriatrics.[4]

In the present study, we wanted to document the organizational model of Syncope Units in Italy and the effectiveness in clinical practice of the current standard of syncope management (diagnosis and treatment) proposed by the ESC guidelines.

Methods

This prospective study was conducted by nine certified Syncope Units in Italy. The characteristics of the Syncope Units and the criteria required for certification are described in the Appendix section. The protocol was approved by the Ethics Committees of all participating hospitals and all participants gave written informed consent to the anonymous treatment of their personal data.

Patient recruitment

We enrolled 941 consecutive patients from 15 March 2008 to 15 September 2008 either because they were affected by unexplained transient loss of consciousness (T-LOC) which, on initial evaluation, was attributed to a syncopal condition or because a syncopal condition could not be excluded (non-syncopal T-LOC), or there was a need to evaluate the precise mechanism of syncope in order to administer the proper specific treatment.

Patients aged <18 years and those with a definite cause of syncope on initial evaluation were excluded. Specifically, patients with arrhythmia-related syncope diagnosed by 12-lead standard electrocardiogram (ECG) (i.e. sinus bradycardia <40 bpm or repetitive sinoatrial blocks or sinus pauses >3 s; second-degree Mobitz II or third-degree atrioventricular block; rapid paroxysmal supraventricular tachycardia or ventricular tachycardia; and pacemaker malfunction) were excluded because, in these cases, the diagnosis is already certain and the proper therapy can be administered immediately.

Diagnostic pathway and management strategy

Each Syncope Unit adopted the diagnostic pathway proposed by the ESC guidelines.[1,2] Moreover, in order to maximize the standardization of syncope management according to ESC guidelines, each enrolling unit was provided with web-based on-line interactive decision-making software (Syncope Web, version 1.0). This web-based software helped physicians to collect data on patient's history and diagnostic work-up in a logical standardized format and also acted as the database for analysis of results. Drop-out criteria (incomplete or incorrect evaluation, patient's record missing) were pre-defined.

Definitions

A Definition Committee reviewed all the records after the end of the recruitment period in order to assign a uniform final diagnosis in accordance with the ESC classification.[1,2] Consistency with the original diagnosis was evaluated. The definitions that were used are reported in the Appendix section.

Sample size and statistics

A 6-month recruitment period was deemed able to achieve a balance between the need for representativeness of the general population referred to Syncope Units and the risk of changes in clinical practice if longer periods were considered.

The average incidence rate of patients evaluated per month was calculated by dividing the number of patients by the number of months of recruitment; the yearly volume per centre rate was normalized with regard to the total population of the district of referral.

Comparison between multiple continuous variables which had a non-Gaussian distribution was performed by means of the Kruskal–Wallis test (non-parametric ANOVA); a post-test was performed only if $P < 0.05$; the pairs of columns were compared by means of Dunn's multiple comparison test. Comparison between two continuous variables which had a non-Gaussian distribution was performed by applying the Mann–Whitney non-parametric test. Comparison between multiple proportions was made by means of the χ^2 test for multiple contingency tables (GrapfPad software, CA, USA).

An economic evaluation was conducted to estimate the total cost per patient. The cost of the tests was calculated on the basis of the tariffs set by the schedule of tariffs of the Italian National Health Service updated to the year 2008. The average total daily cost of hospitalization (sum of direct and indirect costs, excluding the cost of tests and treatments) was calculated by using the hospital accounting reports separately for the departments of cardiology, internal medicine, geriatrics, neurology, and emergency; the total cost of hospitalization for each patient was estimated by multiplying the average daily cost of the department concerned by the number of days of hospitalization.

Results

Volume of activity

A median of 15 (inter-quartile range, 12–23) patients per month were evaluated in each Syncope Unit during the 6 months of observation (*Table 1*). The five older Syncope Units had a two-fold higher volume of activity than the four newer units (instituted <1 year before): median 23 (20–28) vs. 12 (11–14), $P = 0.02$. This difference was mainly due to higher rate of out-of-hospital referrals for the older than for the newer: 16 (13–18) vs. 7 (6–8), $P = 0.04$ (the data from the Syncope Unit located inside the Emergency Department were not considered for this analysis). These figures give an estimated volume of 163 (132–181) and 60 (54–65) patients per 100 000 inhabitants per year, respectively ($P = 0.03$).

Management of the patients

Of the 941 eligible patients, 891 (95%) were able to be analysed (*Table 2*).

Table 1 Volume of activity

	Median	Inter-quartile range	Range
Patients evaluated per month per centre	15	12–23	9–28
Inhabitants per district of referral	220 000	150 000–250 000	150 000–300 000
Estimated volume per centre (patients per 100 000 inhabitants per year)	71	63–163	43–220

Table 2 Characteristics of the 891 analysed patients with T-LOC

	Total population (n = 891)	Diagnosis at initial evaluation (n = 191)	Early diagnosis with investigations (n = 541)	No diagnosis or waiting for diagnosis (n = 159)	P-value
Median age (inter-quartile range)	66 (46–76)	52 (36–69)[a]	67 (46–76)	73 (65–80)	0.001
Male gender (%)	476 (53%)	103 (54%)	275 (51%)	98 (62%)[a]	0.05
History of T-LOCs					
First episode (%)	245 (27%)	66 (35%)[a]	143 (26%)	36 (23%)	0.03
Recurrent T-LOCs	646 (73%)	125 (65%)[a]	398 (74%)	123 (77%)	0.03
Median number (inter-quartile range)	3 (2–5)	3 (2–6)	3 (2–5)	3 (2–6)	0.12
Duration, years (inter-quartile range)	3 (1–10)	5 (2–20)	3 (1–10)	2 (1–5)[a]	0.001
No warning at the onset of the attack (%)	250 (28%)	18 (9%)[a]	104 (30%)[a]	68 (43%)[a]	0.001
Structural heart disease (%)	177 (20%)	15 (8%)[a]	86 (16%)[a]	76 (48%)[a]	0.001
coronary artery disease	88 (10%)	10	39	39	
Hypertensive cardiopathy (%)	36 (4%)	2	20	14	
Valvular (%)	26 (3%)	2	16	8	
Others (%)	27 (3%)	1	11	4	
Electrocardiographic abnormalities (%)	208 (23%)	17 (9%)[a]	116 (21%)[a]	75 (47%)[a]	0.001
Sinus bradycardia <50 bpm	26 (3%)	2	10	14	
Bundle branch block	84 (9%)	5	38	41	
ST-T abnormalities and/or ischaemia	41 (5%)	5	26	10	
Atrial fibrillation/flutter	43 (5%)	5	28	10	
Others	27 (2%)	0	14	10	
OESIL risk score, median (inter-quartile range)	1 (0–2)	0 (0–1)[a]	1 (0–3)[a]	2 (1–3)[a]	0.001
EGSYS risk score, median (inter-quartile range)	0 (−1 to 2)	−1 (−1 to 0)[a]	0 (−1 to 2)[a]	2 (0–3)[a]	0.001

[a]Field with significant differences from the other/s.

The majority of the patients (60%) were referred from out-of-hospital services (general practitioners, other specialists, primary care, and patients themselves), 11% had immediate referral and 13% delayed referral (so-called 'protected discharge' with an appointment for early assessment) from the Emergency Department, and 16% were hospitalized patients. Excluding the data from the Syncope Unit located inside the Emergency Department, referrals to the other eight units were: 66% outpatient, 15% delayed from the Emergency Department, and 19% hospitalization. Referral from out-of-hospitals was higher for the older than for the newer Syncope Units: 73 vs. 58%, $P = 0.001$.

The diagnostic flow is shown in *Figure 1*. A diagnosis was established on initial evaluation in 191 (21%) patients, early (within 45 days) through diagnostic tests is 541 (61%) patients, and remained unexplained in 159 (18%) patients (*Table 3*). In 102 (11%) patients, a different diagnosis was assigned by the Definition Committee. Among these, 60 patients were reclassified as having unexplained syncope because they did not fully meet diagnostic criteria or

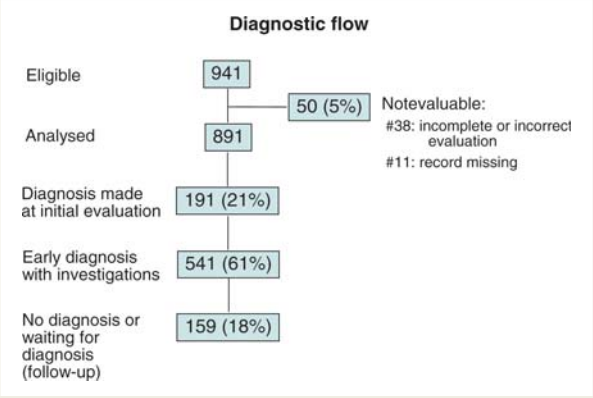

Figure 1 Diagnostic flow of 941 patients referred to the syncope units.

had multiple possible causes of syncope and 33 patients were reclassified as having likely reflex rather than unexplained syncope (*Figure 2*).

Table 4 lists the tests performed and their diagnostic value. The patients referred to the newer Syncope Units performed more tests than those referred to the older, with few exceptions (*Figure 3*). However, the final diagnosis mix was fairly very similar: reflex 68 vs. 68%, cardiac 8 vs. 5%, and unexplained 20 vs. 17%.

The patients with unexplained syncope were older, more frequently had structural heart disease or ECG abnormalities, and unpredictable onset of syncope due to the lack of prodromes than the other groups of patients (*Table 2*). Contrasting features suggesting competing diagnoses were present in 72 of these. The patients with unexplained syncope were at higher risk of death and cardiac syncope than the others, as predicted by their significantly higher OESIL[5] and EGSIS[6] risk scores. Despite a

Table 3 Causes of loss of consciousness in 891 patients (according to ESC classification)

Causes of loss of consciousness	Initial evaluation	Investigations	Total
Reflex (neurally mediated) (%)	169 (19)	292 (33)	461 (52)
Vasovagal (fear, pain, emotion, instrumentation, prolonged standing + typical prodromal symptoms) (%)	131 (15)	–	131 (15)
Atypical form: tilt-positive (%)	–	231 (26)	231 (26)
Carotid sinus syncope (%)	–	61 (7)	61 (7)
Situational [micturition, gastrointestinal stimulation (swallowing, defecation, visceral pain), coughing] (%)	38 (4)	–	38 (4)
Likely reflex (neurally mediated) (%)		139 (15)	139 (15)
Likely reflex, after exclusion of other causes and absence of heart disease (%)	–	62 (7)	62 (7)
Single/rare syncope, no heart disease (%)	–	77 (8)	77 (8)
Orthostatic hypotension (%)	18 (2)	14 (2)	32 (4)
Cardiac arrhythmia as primary cause (%)	–[a]	50 (5)	50 (5)
Sinus node dysfunction (%)	–	10 (1)	10 (1)
Atrioventricular conduction system disease (%)	–	23 (3)	23 (3)
Paroxysmal supraventricular tachycardias (%)	–	3 (0)	3 (0)
Paroxysmal ventricular tachycardias (%)	–	13 (1)	13 (1)
Permanent pacemaker dysfunction (%)	–	1 (0)	1 (0)
Structural cardiac or cardiopulmonary disease (%)	–	8 (1)	8 (1)
Pulmonary embolism	–	3 (0)	3 (0)
Aortic stenosis	–	2 (0)	2 (0)
Acute coronary syndrome	–	2 (0)	2 (0)
Atrial myxoma	–	1 (0)	1 (0)
Unexplained (%)	–	–	159 (18)
Non-syncopal attacks (initially misdiagnosed as syncope) (%)	4 (0)	38 (4)	42 (5)
Metabolic disorders (hypoxia, hypoglycaemia) (%)	–	9 (1)	9 (1)
Epilepsy (%)	–	10 (1)	10 (1)
Intoxication (%)	2	1 (0)	3 (0)
Vertebro-basilar transient ischemic attack (%)	–	3 (0)	3 (0)
Accidental falls (%)	–	9 (1)	9 (1)
Psychogenic pseudo-syncope (%)	2	6 (1)	8 (1)

[a]The patients in whom the diagnosis of arrhythmic syncope was made by means standard electrocardiogram (initial evaluation) were excluded as per protocol.

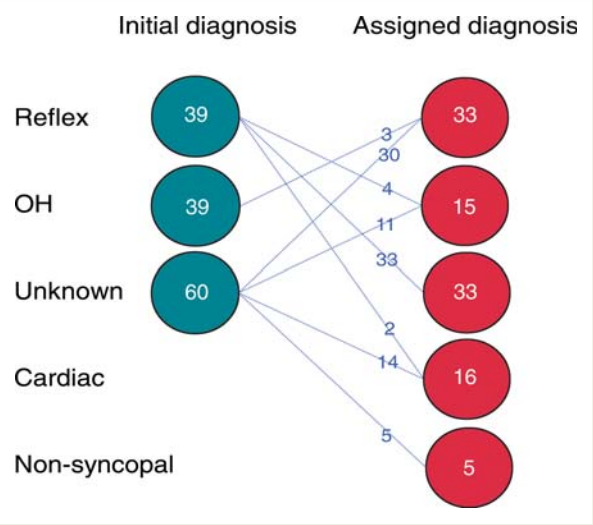

Figure 2 Distribution of contrasting diagnoses among 102 (11%) of the 891 patients.

non-diagnostic work-up, several patients were suspected of having cardiac syncope because of the presence of bundle branch block (#41 patients), moderate bradycardia (#14 patients), or an EGSYS score $\geq$3 (#71 patients).

The treatment assigned at the end of the work-up is summarized in *Table 5*. Physical counterpressure manoeuvres were the most frequently used specific treatments for reflex syncope and orthostatic hypotension; vasoconstrictor drugs were only seldom used in these situations. Most patients with a diagnosis of cardiac syncope received a specific treatment. Overall, 100 patients received cardiac pacing therapy: 61 for asystolic reflex syncope, 29 for established primary arrhythmia, and 10 with unexplained syncope and bundle branch block. A cardioverter-defibrillator was implanted in nine patients.

Hospitalization and cost analysis

The mean cost of the diagnostic tests and examinations (excluding treatment) of the 720 patients evaluated on an outpatient basis was €209 $\pm$ 140 per patient.

A total of 171 (19%) patients needed to be hospitalized: of these, 144 had already been hospitalized before referral to the Syncope Unit, whereas 27 were hospitalized upon request of the syncope expert in order to perform invasive tests; the median in-hospital stay was 7 days (inter-quartile range, 5–10). The median cost per hospital stay (excluding the costs of tests and treatments) was €2990 (inter-quartile range, 2004–4497). In addition, 71 (8%) patients stayed a total of 119 days in the observation unit of the Emergency Department. The mean cost was €502 per patient. The mean cost of the diagnostic tests for hospitalized patients was €1073 $\pm$ 716.

The total cost of evaluating the study population was €1 034 511, which corresponds to a cost per patient of €1161.

Discussion

This study documented the current practice of management of syncope in specialized facilities that have adopted the management model proposed by the ESC.[1,2] These results are useful for those who wish to replicate this model in other hospitals and provide all stakeholders (physicians, hospital and clinical governance managers, future research planners, etc.) with a frame of reference for their daily activity when dealing with syncope.

After the pivotal experience in Newcastle,[7] different models of care have been developed in single centres[8,9] or special settings[10] in order to improve the management of syncope. Guidelines have also been assessed in emergency settings in a multicentre experimental study, the results of which are difficult to reproduce in everyday clinical practice due to its special design.[11] In general, these studies have shown that a considerable improvement in diagnostic yield and cost effectiveness (i.e. cost per reliable diagnosis) can be achieved in comparison to the usual practice. Nevertheless, these models have not been widely adopted. Two recent single-centre studies[12,13] have evaluated the impact of introducing ESC guideline-based syncope facilities on the management of patients referred to the Emergency Department with special emphasis on hospitalization rates. The organizational principle of these two studies, i.e. the adoption of the ESC model of the syncope management facility, was similar to that of the present study, but referrals were restricted to those from the Emergency Department.

Contrary to the ESC guidelines which recommend a multidisciplinary approach and evaluation, in our model, the 'Syncope Expert' leads the process of comprehensive management of the patient from risk stratification to diagnosis, therapy, and follow-up. We believe that the appointment of the syncope expert/s characterizes this organizational model and facilitates the development of standardized internal organizational protocols. Conversely, the lack of someone who takes such responsibility is the main determinant of the inappropriate use of diagnostic tests and therapies and of many misdiagnosed and/or unexplained episodes. Many general hospitals provided by a department of cardiology actually have already the equipment necessary for the management of syncope. Thus, it is the creation of a well-identifiable facility and the appointment of the syncope leader/s—i.e. in essence, an organization—that characterizes our model of syncope management unit.

Some other considerations from this study are worth mentioning. The Syncope Units assessed in this study are low-volume units. The preferred model seems to be that of 'one hospital one unit' rather than that of larger 'hub' unit serving several hospitals. It seems to take at least 1 year for the volume of activity to grow and stabilize. The new units have lower outpatient referrals and utilize more tests for making a diagnosis. If investigations are appropriately selected, few of these (in general, not very expensive) are needed for diagnosis and their diagnostic value is in general good. In this study as in others, hospitalization costs *per se* (excluding tests) accounted for >75% of the total costs.[7,14,15] The logical conclusion is that reducing the need for hospitalization would result in a substantial cost saving.

Table 4 **Tests: diagnostic yield in 700 patients who did not have a diagnosis on initial evaluation**

	Performed (% of total patients)	Abnormal (% of performed)	Diagnostic (% of performed)	Note
Tilt testing (%)	443 (63)	265 (60)	237 (53)[a]	CI = 37; M = 85; VD = 115
Carotid sinus massage (%)	509 (73)	92 (18)	62 (12)[b]	CI = 46; M = 14; VD = 2
24 h Holter monitoring (%)	166 (24)	34 (20)	15 (9)	Brady, 14; tachy, 1
In-hospital ECG monitoring (%)	80 (11)	18 (22)	14 (17)	Brady, 9; tachy, 5
Electrophysiological study (%)	40 (6)	15 (37)	14 (35)	Brady, 9; tachy, 5
Echocardiography (%)	269 (38)	71 (26)	8 (3)	Depressed syst. function, 5; aortic stenosis, 2; atrial myxoma, 1
Blood tests (%)	298 (43)	25 (8)	5 (2)	Hypoglycaemia, 1; pulmonary embolism, 3; myocardial ischaemia, 1
Brain computed tomography/resonance imaging (%)	73 (10)	20 (27)	5 (7)	Epilepsy, 4; vertebro-basilar TIA, 1
Electroencephalography (%)	34 (5)	4 (12)	2 (6)	Epilepsy, 2
Exercise test (%)	41 (6)	5 (12)	1 (2)	AV block, 1
Coronary angiography (%)	14 (2)	ND	1 (7)	Acute coronary syndrome, 1
External loop recorder (%)	9 (1)	1 (11)	0 (0)	
Implantable loop recorder (%)	30 (4)	ND	ND	
Total number of tests (%)	2006	550 (27)	370 (18)[c]	
Mean (SD) tests per patient	2.9 ± 1.8	0.8 ± 0.8		

CI, cardio-inhibitory form; M, mixed form; VD, vasodepressor form.
[a]Vasodepressor response with syncope served to confirm the diagnosis of orthostatic hypotension in six patients with asymptomatic non-diagnostic orthostatic hypotension during standing.
[b]Vasodepressor response with syncope served to confirm the diagnosis of orthostatic hypotension in a patient with asymptomatic non-diagnostic orthostatic hypotension during standing.
[c]In four patients the diagnostic test is not listed in the table: syncope due to ventricular tachyarrhythmia was diagnosed in two patients by means of interrogation of their implanted ICD; syncope due to pulmonary embolism was diagnosed in two patients by computed tomography of the lung.

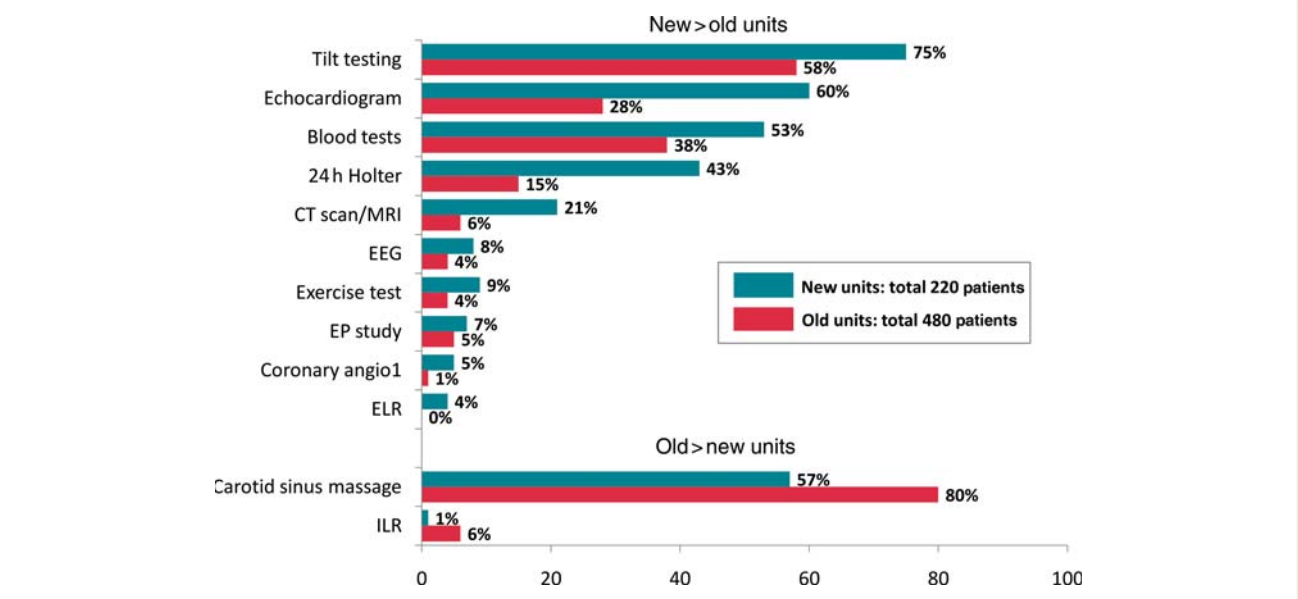

Figure 3 Test performed (% of total patients) in the new and in the old syncope units. Except for carotid sinus massage and implantable loop recorder, the patients referred to the newer performed more tests than those referred to the older syncope units (on average 3.5 ± 1.8 vs. 2.6 ± 1.7 tests per patient). All the differences were statistically significant, with the exception of electrophysiological study. CT, brain computed tomography; MRI, magnetic resonance imaging; EEG, electroencephalography; ELR, external loop recorder; ILR, implantable loop recorder.

Limits of the current guideline-based management

Finally, the present study suggests some limitations and pitfalls of the current strategy of evaluation of the syncope patient, even if it is performed according to the standard provided by the guidelines.

It is well known that patients are typically asymptomatic at the time of evaluation; the causal relationship between a diagnostic abnormality and syncope in a given patient is therefore often presumptive. This necessarily leads to uncertainty in establishing a cause. Thus, it is not surprising that we observed an 11% rate of contrasting diagnoses between the initial local diagnosis and that resulting from strict application of the definitions of the ESC classification (see Appendix). The most commonly observed inconsistency was between reflex and unexplained syncope (*Figure 2*); in other cases, an initially unexplained syncope was reassigned to orthostatic hypotension or to cardiac causes. This finding, which is original, underlines the difficulty of reaching a diagnosis based mainly on pathophysiological reasoning and testifies the need for careful adoption of well-accepted standardized diagnostic criteria. Uncertainty regarding diagnostic definitions hampers comparison between different studies and the evaluation of treatments.

It seems that the most complex (i.e. with competing possible causes) and potentially severe cases—which therefore would require more specific treatment—remain undiagnosed by means of in-hospital investigations. Indeed, our patients with unexplained syncope were older, more frequently had structural heart disease or ECG abnormalities, and unpredictable onset of syncope due to the lack of prodromes than the other groups of patients (*Table 2*). Many of these were suspected of having cardiac syncope, although this was not demonstrated; they were at higher risk of death and cardiac syncope than the others, as predicted by the significantly higher OESIL[5] and EGSYS[6] risk scores. Conversely, a diagnosis was more easily obtained in healthy young patients without structural heart disease, who are known to have a favourable outcome. The paradox seems to be that the more we need a precise diagnosis the more difficult is to obtain one. Apart from the issue of different definitions, as discussed above, the patients with unexplained syncope in Syncope Units are probably different from those with unexplained syncope in epidemiological studies[16] or in other settings,[17–19] who show a relatively good outcome. The patients referred to the Syncope Unit are *per se* the most difficult cases because they have been selected from many others. Although we could not obtain a formal screening log in this study, we know from the literature that only a quarter of the patients with syncope seek medical advice,[16,20] that a minority are referred to an Emergency Department,[20] and that about a half of the patients referred urgently to an emergency department[11,13] require further investigations, if possible in a specialized facility. The finding that 18% of the patients potentially at high risk remain without a diagnosis cannot be considered satisfactory for a specialized facility and indicates the need for new management strategies. Whether a strategy of extensive utilization of prolonged ECG monitoring, i.e. implantable loop recorders, could be helpful is a matter of future researches. In this study, implantable loop recorder was performed in only a minority of patients and is therefore unlikely to change these results substantially during follow-up. By evidencing the limitations and pitfalls of the current standard of evaluation represented by the ESC guidelines, the present study promotes future research aimed at improving diagnostic accuracy in patients with syncope.

Table 5 Treatment and measures prescribed according to the final diagnosis

Reflex (neurally mediated) and likely reflex[a]	600
Education, reassurance, and avoidance of triggers alone (%)	253 (42)
Physical manoeuvres (counterpressure manoeuvres) (%)	247 (41)
Tilt training	69 (11)
Cardiac pacing (%)	61 (10)
Modification or discontinuation of hypotensive drugs (%)	53 (9)
Implantable loop recorder (%)	2 (0)
Vasoconstrictor drugs (%)	9 (1)
Orthostatic hypotension[a]	32
Modification or discontinuation of hypotensive drugs (%)	21 (66)
Education and avoidance of triggers (%)	20 (62)
Physical manoeuvres (counterpressure manoeuvres, elastic stockings) (%)	18 (56)
Volume expansion (%)	15 (47)
Vasoconstrictor drugs (%)	1 (3)
None	1 (3)
Cardiac arrhythmias as primary cause[a]	50
Cardiac pacing (%)	29 (58)
Cardioverter-defibrillator implantation (%)	8 (16)
Modification or discontinuation of antiarrhythmic/ hypotensive drugs (%)	5 (10)
Antiarrhythmic drug therapy (%)	5 (10)
Catheter ablation (%)	1 (1)
Not specified	9 (18)
Structural cardiac or cardiopulmonary disease	8
Cardiac surgery (%)	3 (37)
Coronary revascularization (%)	2 (25)
Antithrombotic drug therapy (%)	3 (37)
Syncope of unknown origin	159
Implantable loop recorder (%)	28 (18)
Physical manoeuvres (counterpressure manoeuvres) (%)	14(9)
Modification or discontinuation of hypotensive drugs (%)	4 (3)
Cardiac pacing (%)	10 (6)
Tilt training	4 (2)
None of the above (%)	109 (68)
Non-syncopal attacks	42
Anti-epileptic drugs (%)	6 (14)
Antidepressant drugs (%)	2 (5)
No therapy or referred to specialist (%)	36 (81)

[a]More than one treatment was assigned to some patients of this group.

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Appendix

Characteristics of the Syncope Units

The nine recruiting Syncope Units are located in public general hospitals in referral districts with a median of 220 000 inhabitants (inter-quartile range, 150 000–250 000). Together, they serve a population of 1 870 000 inhabitants, a figure which accounts for 3.2% of the total population of Italy.

In accordance with the certification document by GIMSI,[4] the Syncope Unit is intended as a functional facility located inside a general hospital endowed with 24 h emergency department and a cardiology ward with a coronary care unit. Patients are referred from the emergency room and from in-hospital and out-of-hospital services. Hospitalized patients are directly managed by the Syncope Unit during hospitalization. Patients at low risk admitted to the emergency room have a delayed referral (so-called 'protected discharge' with an appointment for early assessment), in order to reduce hospitalization rate. The patients evaluated in the syncope facility benefit by formalized procedures for a preferential access to other investigations, therapies, and specialists' consultancies that are needed.

In brief, the certified requisites include equipment and appointment of one or more syncope leader/s.

Each Unit is provided with: (i) a core equipment for syncope evaluation (i.e. phasic blood pressure monitoring, tilt table testing, external and implantable loop recorders, 24 h ambulatory blood pressure monitoring, 24 h ambulatory ECG monitoring, and autonomic function testing); (ii) on-site access to the usual investigations (echocardiography, invasive electrophysiological testing, stress testing, cardiac imaging, computed tomography or magnetic resonance imaging, and electroencephalography) and on-site access to any therapy that may be required for syncope [i.e. pacemaker and implantable cardioverter-defibrillator (ICD) implantation, catheter ablation of arrhythmias, etc.]; (iii) dedicated rooms for ambulatory examinations and a dedicated laboratory for the execution of core tests, keeps a separated waiting list and schedules follow-up visits.

The Unit is led by the *syncope expert/s*, formally appointed by the director of the department or by the director of the hospital. The syncope expert is a single physician (in four Units) or a team of physicians (two to four each in the other five Units who lead the unit in turn) who lead/s the comprehensive management of the patient from risk stratification to diagnosis, therapy, and follow-up.

The syncope team includes part-time trained technical personnel. The syncope team usually performs the core laboratory tests and the administrative issues.

Seven syncope units are located inside the Cardiology Department; their activity (and personnel and resources) is part of the daily non-invasive arrhythmologic activity of the department. One syncope unit is located in dedicated rooms inside the

Observation Unit of the Emergency Department and is run by an emergency physician; triage and initial evaluation of patients referred in emergency are performed by different physicians; referral of the patient to the Syncope Unit, if necessary, may be either immediate or delayed ('protected discharge'), according to the initial risk stratification. Finally, one Syncope Unit is located inside a Geriatric Department. Formalized multidisciplinary cooperation in diagnostic/therapeutic procedures are established with neurologist/s in eight cases, with psychiatrist/s in three cases, and with cardiologist/s in the two cases in which the Syncope Unit is located outside that Cardiology Department.

Definitions

The following definitions were used and patients were accordingly classified.

(i) *Reflex (neurally mediated), classical vasovagal syncope* if the syncope was precipitated by emotional distress (fear, severe pain, and instrumentation) or prolonged standing and was associated with typical prodromes.

(ii) *Reflex (neurally mediated), atypical form* if the syncope occurred without apparent triggers and/or had an atypical presentation and the diagnosis was based on the reproduction of similar symptoms by means of tilt testing and on the exclusion of other causes of syncope (absence of structural heart disease).

(iii) *Reflex (neurally mediated), carotid sinus syncope* if the syncope was reproduced by carotid sinus massage in the presence of asystole >3 s and/or fall in systolic blood pressure >50 mmHg and in the absence of competing diagnoses.

(iv) *Reflex (neurally mediated), situational syncope* if the syncope occurred during or immediately after urination, defecation, coughing, laughing, or swallowing.

(v) *Likely reflex (neurally mediated)* if the history suggested a reflex cause, unconfirmed by tests, structural heart disease was absent and other causes could reasonably be excluded; or syncope was the first (or rare) episode, structural heart disease was absent, and other causes could reasonably be excluded.

(vi) *Orthostatic hypotension* if syncope occurred after standing up and symptomatic orthostatic hypotension was documented. The *Classical form* was diagnosed if orthostatic hypotension occurred within 3 min after active standing up, whereas *Progressive (delayed) form* was diagnosed—usually by means of tilt testing—if progressive orthostatic hypotension occurred >3 min after standing up.

(vii) *Cardiac arrhythmia* if the Class I diagnostic criteria of the ESC guidelines[1,2] were met during prolonged ECG monitoring or by means of electrophysiological study; cardiac arrhythmia also included the case of patients with severely depressed ejection fraction who had a definite indication for ICD regardless of the mechanism of syncope.

(viii) *Structural cardiac or cardiopulmonary disease* if the patient was affected by acute cardiac ischaemia or other acute cardiopulmonary diseases or prolapsing atrial myxoma or severe aortic stenosis.

(ix) *Non-syncopal attacks* if the episode of T-LOC was initially attributed to a syncopal condition but the subsequent evaluation demonstrated a non-syncopal mechanism [i.e. metabolic disorders (hypoxia and hypoglycaemia), epilepsy, intoxication, vertebro-basilar ischaemic attack, accidental fall, or psychogenic (functional) pseudo-syncope].

(x) *Unexplained* in those patients without any of the above diagnosis.

Investigators and participating centres

The following persons participated in the SUP study.

Steering Committee: M.B., Lavagna (chairman); F.A., Ostia (co-chairman); A. Castro, Rome; A.D.R., Empoli; G. Demarchi, Alessandria; F.G., Mestre; M.G., Catania; M.L., Milano; M.S., Rome; A.U., Florence.

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Definition Committee: M.B., R.M., A.D.R., and F.G.

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