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CLINICAL RESEARCH

Early and late outcome of treated patients referred for syncope to emergency department: the EGSYS 2 follow-up study

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Aims We evaluated the early (1 month) and late (2 years) death rate and syncopal relapses of patients referred for syncope to 11 general hospitals emergency departments. Patients were enrolled in the Evaluation of Guidelines in SYncope Study 2 (EGSYS 2) study. The guidelines of the European Society of Cardiology were strictly followed in the management of patients.

Methods and results Out of the 465 patients enrolled in the EGSYS 2 study, 398 (86%) underwent a complete follow-up. We excluded 18 patients with non-syncopal attacks. Among the remaining 380 patients, death of any cause occurred in 35 (9.2%). The mean follow-up was 614 $\pm$ 73 days. Six deaths (17% of total) occurred during the first month of follow-up. Patients who died were older, had a higher incidence of structural heart disease and/or abnormal ECG, had injuries related to syncope and higher EGSYS score. Syncope recurred in 63 (16.5%) patients. Syncopal relapses occurred in only one patient during the first month of follow-up. The incidence of syncopal recurrences was unrelated to the mechanism of syncope. No clinical differences were found between patients with or without syncopal recurrence and in patients with EGSYS score $<$ or $\geq$3.

Conclusion A peak of cardiovascular mortality but not of syncopal recurrences was observed in patients attending to the emergency department for syncope within the first month. Late unfavourable outcomes were caused by associated cardiovascular diseases rather than by the mechanism of syncope. The causes of syncope did not determine the recurrence rate.

Keywords Syncope • Emergency department • Diagnosis • Prognosis • Therapy

Introduction

There are two main reasons to evaluate a patient with syncope: diagnosis and prognosis.[1–3] That is to say: to stratify the risk of future clinical events to which the patient is subjected, either directly related to syncope or, more generally, related to the underlying disease of which syncope is only an ominous finding or one of the clinical manifestations. The risk of life-threatening

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conditions immediately following the Emergency Department (ED) referral is the main reason for an immediate hospital admission and an exhaustive evaluation. However, few studies directly evaluated the short-term risk of syncope.[4–6]

The Guidelines on Management of Syncope of European Society of Cardiology[1] define the current standard management of patients with syncope.[7]

The main aim of the present study was to evaluate the early and late clinical event rate (death and syncopal relapses) in a population of patients who were referred to an ED and were managed according to the current standard strategy. Secondary aim was the identification of early and late clinical predictors of clinically serious adverse events.

Methods

We performed a prospective study evaluating the clinical outcome of patients referred for syncope to ED. Patients were managed according to the recommendation of the Guidelines on Management of Syncope of the European Society of Cardiology for the diagnosis.[1] The follow-up protocol was predefined at the time of enrolment. The study includes consecutive patients attending to ED of 11 general hospitals in Italy from the 4 of October 2004 to the 5 of November 2004. They were selected because of their transient loss of consciousness which, during the initial evaluation, was ascribed to a syncopal condition. The patients were the same as those who were enrolled in the Evaluation of Guidelines in SYncope Study 2 (EGSYS 2).[7] Patients with a definite non-syncopal cause of loss of consciousness on the initial evaluation, those aged <18 years, and those referred >24 h after their episode were excluded. A decision-making software (EGSYS software version 1.0) was used to maximize the guideline application in the diagnostic phase. Data were collected on precipitating and predisposing factors, prodromal and recovery symptoms, and physical signs during loss of consciousness and recovery phase. These variables were pre-specified in the EGSY-2 protocol.

Of the 541 patients initially enrolled in the EGSYS 2 study, 76 dropped-out during the first phase of the study.[7] Of the remaining 465 patients, the follow-up was completed in 398 patients (86%). We excluded 18 patients with non-syncopal attacks and the remaining 380 patients were considered for inclusion in the follow-up study. The decision on when and how to treat patients was left to the clinical practice of any individual physician. The follow-up data were collected by the family physician, through telephone calls, through outpatients visits, after 21–24 months (actual average follow-up length of 614 ± 73 days, range 0–782 days), on the basis of a predefined structured questionnaire. Events were confirmed by death certificate, hospital chart, and/or physician's records. The primary endpoint was death from any cause or syncope recurrence. The study was approved by the local Ethics Committees. All subjects agreed to take part in the study at enrolment time.

The EGSYS score, a risk stratification system for cardiac syncope, was calculated as already described.[8] Briefly, a seven item score was calculated assigning positive or negative values to: palpitations preceding syncope, heart disease &/or abnormal ECG, syncope during effort, syncope while supine, precipitating and/or predisposing factors (i.e. warm-crowded place, prolonged orthostasis, fear/pain emotion), autonomic prodrome such as nausea and vomiting.

Patients were considered to suffer from heart disease whenever the following criteria were fulfilled: (i) previous clinical or laboratory diagnosis of any form of structural heart disease including ischaemic heart disease, valvular heart disease, cardiomyophaties, and congenital heart disease; (ii) previous diagnosis or clinical evidence of congestive heart failure; (iii) physical signs of structural heart disease. Electrocardiogram was evaluated by the ED physician and subsequently reviewed by a cardiologist and was considered abnormal in the following cases: sinus bradycardia, second and third degree atrioventricular block, bundle branch block, acute or old myocardial infarction, supraventricular or ventricular tachycardia, left or right ventricular hypertrophy, ventricular-pre-excitation, long QT interval, Brugada syndrome pattern. The actual average follow-up length was 614 ± 73 days.

Statistical analysis

Continuous and categorical variables were compared between groups by Students' *t*-test and χ^2 or Fisher test, respectively. The False Discovery Rate (FDR) was used to control the expected proportion of incorrectly rejected null hypotheses (type I errors) in multiple comparisons.[9] The FDR represents the expected false positive rate and the adjusted *P*-value implies the percentage of significant test will result in false positives. The Cox Regression Model was used to perform univariate analysis of the outcome. Hazard functions were assessed for proportionality by Schoenfeld residuals test. Hazard ratio (HR) is provided with its 95% confidence interval (CI). χ^2 test was used to assess linearity of continuous variables. Events occurring within 1 month of enrolment were used to analyse the short-term outcome. All the enrolled patients were included in the syncopal recurrence analysis. Dead patients were considered with or without recurrence according to the occurrence of the syncopal relapse before their death. Event-free survival was assessed by Kaplan–Meier method. Survival free of recurring syncope was analysed by means of the cumulative incidence estimation, considering death as competing risk. A two-tailed *P*-value <0.05 was considered significant. All analyses were performed with Statistica 7.0 (StatSoft Italia, Padua, Italy), SPSS 12.2 (SPSS, Inc., Chicago, IL, USA) and StataSE 9.2 (StataCorp, TX, USA) statistical packages.

Results

Patient demographic and clinical characteristics are reported in *Table 1*. One hundred and fifty-seven patients (39%) were hospitalized for diagnosis of syncope and/or management of comorbidities.

Mortality

Death of any cause occurred in 35 (9.2%) patients. Death was considered cardiovascular in 9 patients (26%), non-cardiovascular in 10 (29%), and of unknown origin in the other 16 (46%). Among the patients who died, 82% had an abnormal ECG and/or heart disease; on the contrary, only six (3%) deaths occurred in patients without abnormal ECG and/or heart disease, indicating a negative predictive value of 97%. During the first month, six patients died (17% of all deaths): all these deaths were due to cardiovascular causes (four cardiac and two vascular), but no patient died suddenly. In these patients diagnosis of syncope was neurally mediated in two, cardiac in two, and orthostatic in two. All six patients had abnormal ECGs and structural heart disease. Moreover all patients who died in the first month of follow-up had an EGSYS score ≥ 3.

Table 1 Demographic and clinical characteristics of the 380 patients

Variable	
Age, years, means ± SD	66 ± 20 (20–100)
Male, *n* (%)	220 (58)
Structural heart disease, *n* (%)	138 (36)
Abnormal ECG, *n* (%)	154 (41)
Number of syncopal episodes, *n*	3 ± 5
Injures related to syncope, *n* (%)	111 (29)
Presyncope history, *n* (%)	79 (21)
Final diagnosis	
Cardiac syncope, *n* (%)	57 (15)
Arrhythmic, *n* (%)	41 (11)
Structural cardiac or cardiopulmonary diseases, *n* (%)	16 (4)
Neurally mediated, *n* (%)	243 (64)
Orthostatic hypotension, *n* (%)	66 (17)
Unexplained, *n* (%)	14 (4)

Table 2 Mortality predictors in univariate analyses

Variable	Univariate		
	P-value	HR	CI
Age	<0.0001	1.07	1.04–1.11
Trauma	0.018	2.24	1.15–4.35
Heart disease and/or abnormal ECG	<0.0001	5.57	2.31–13.41
Sex (male)	0.030	2.25	1.08–4.68
Hypertension	0.002	2.97	1.48–5.96
Diabetes	0.808	1.16	0.36–3.78
Presyncope	0.180	0.49	0.17–1.39
Number of previous syncope[a]	0.041	0.73	0.54–0.99
Specific syncope treatment	0.030	2.25	1.08–4.69
Absence of prodrome	0.411	1.34	0.67–2.69
Palpitations before syncope	0.908	1.13	0.15–8.22
Supine syncope	0.209	2.50	0.60–10.42

[a] χ^2 for linear trend <0.05.

On the univariate analysis the predictors of mortality were age, the presence of heart disease and/or abnormal ECG, the presence of trauma and decreasing number of previous syncopes (*Table 2*).

Kaplan–Meier's survival curves showed a significantly worse mortality in patients with structural cardiac or cardiopulmonary cause of syncope compared with patients with other causes of syncope (*Figure 1*). Indeed, mortality for structural cardiac or cardiopulmonary syncope occurred in 37% cases: 11% by orthostatic syncope, 10% by syncope due to primary cardiac arrhythmia, 7% by unexplained syncope, and 7% by neurally mediated syncope (log rank $P = 0.0012$).

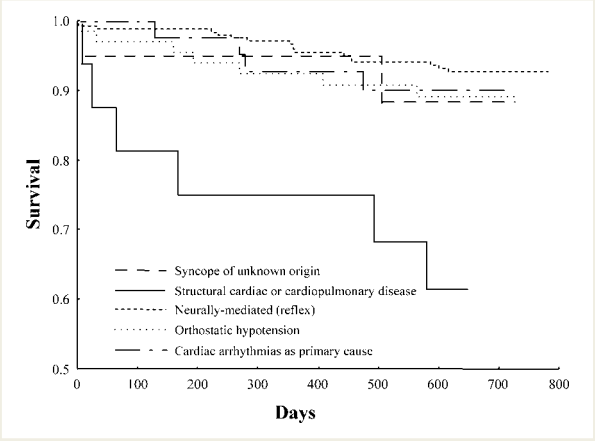

Figure 1 Kaplan–Meier's survival curves in the different syncope forms. Log rank $P = 0.0012$.

Syncopal recurrence

The actual syncope treatment prescribed at discharge is summarized in *Table 3*. Syncope recurred in 63 (16.5%) patients. Syncopal relapse occurred only in one patient during the first month of follow-up. The recurrence rate was 0.3% in the first month, 0.8% per month during the first year, and 0.5% per month during the second year ($P = 0.125$, ns). In six patients (9.5% of all patients with syncope recurrence) the cause of syncopal recurrence was different from that of index loss of consciousness. Incidence of syncope recurrence was similar in all syncope forms (*Figure 2*). On the univariate analysis the predictors of recurrence were male gender, absence of palpitations, and presence of prodrome (*Table 4*). Syncope rate was 12.5 per 100 patient-years in patients with syncope due to primary cardiac arrhythmia. Among these, the syncope rate was 9.1 per 100 patient years in those who received some specific treatment (pace-maker, ablation, or ICD) and 20.0 per 100 patient years in those who did not ($P = 0.286$). Syncope rate was 14.9 per 100 patient years in patients with structural cardiac or cardiopulmonary syncope; among these, syncope recurred in 2 out of 12 patients who received some specific treatment (by-pass or aortic valve replacement) and 1 out of 4 patients who did not. Finally, syncope recurred in 9.8 per 100 patient years in patients with neurally mediated syncope, in 8.8 per 100 patient years in patients with orthostatic syncope, and 4.1 per 100 patient years in patients with unexplained syncope.

Discussion

This study was not intended to describe the natural history of patients referred for syncope to ED. Instead, it was planned to address the outcome of patients managed on the basis of the best available guideline-based evidence.

Early outcome

We observed a peak of mortality within the first month, which accounted for 17% of all deaths. Indeed, mortality during the first month was four-fold higher than that expected (6 deaths

Table 3 Prescribed treatment and measures

Neurally-mediated (reflex)[a], *n*	243
Education, reassurance, and avoidance of triggers alone, *n* (%)	190 (78)
Modification or discontinuation of hypotensive drugs, *n* (%)	27 (11)
Physical manoeuvres (tilt training or counterpressure manoeuvres), *n* (%)	5 (2)
Vasoconstrictor drugs, *n* (%)	2 (1)
Pacemaker, *n* (%)	11 (5)
Orthostatic hypotension[a], *n*	66
Education and avoidance triggers, *n* (%)	30 (45
Modification or discontinuation of hypotensive drugs, *n* (%)	25 (40)
Physical manoeuvres (counterpressure manœuvres, elastic stockings), *n* (%)	2 (3)
Volume expansion, *n* (%)	9 (14)
Vasoconstrictor drugs, *n* (%)	2 (3)
Cardiac arrhythmias as primary cause[a], *n*	41
Cardiac pacing, *n* (%)	27 (66)
Antiarrhythmic drug therapy, *n* (%)	8 (20)
Cardioverter-defibrillator implant, *n* (%)	2 (5)
Catheter ablation, *n* (%)	2 (5)
Structural cardiac or cardiopulmonary disease, *n*	16
Coronary revascularization (angioplasty, by-pass), *n* (%)	5 (31)
Valvular surgery, *n* (%)	2 (12)
Drug therapy, *n* (%)	5 (31)
Syncope of unknown origin, *n*	14
No specific therapy, *n* (%)	3 (21)

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

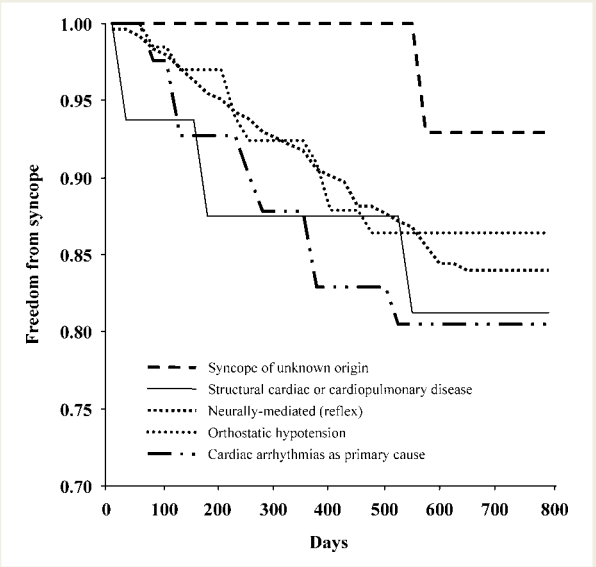

Figure 2 Actual freedom from syncope recurrence curves in the different syncope forms (P = ns).

Table 4 Recurrence predictors in univariate analysis

Variable	Univariate		
	P-value	HR	CI
Age	0.430	0.99	0.98–1.01
Trauma	0.454	1.23	0.71–2.12
Heart disease and/or abnormal ECG	0.783	0.93	0.56–1.55
Sex (male)	0.026	1.84	1.08–3.16
Hypertension	0.810	0.94	0.56–1.58
Diabetes	0.148	1.79	0.81–3.94
Presyncope	0.582	0.83	0.43–1.60
Number of previous syncope	0.870	1.00	0.95–1.05
Specific syncope treatment	0.648	0.84	0.40–1.77
Absence of prodromes	0.018	0.42	0.21–0.86
Palpitations before syncope	0.018	3.41	1.23–9.40
Supine syncope	0.598	1.46	0.36–5.99

instead of 1.5, calculated according to total observed death rate). Mortality was mainly due to the severity of underlying cardiovascular disease and was unrelated to the mechanism of syncope. Moreover, no patient died suddenly, reinforcing the lack of correlation between death and cause of syncope. The San Francisco Syncope Rule[6] showed that patients with an abnormal ECG, a complaint of shortness of breath, haematocrit <30%, systolic blood pressure <90 mmHg, or a history of congestive heart failure had a worse short-term prognosis. In agreement with our result, among high-risk patients, the risk of death and of adverse outcome is high in the few days following the index syncopal episode. Accordingly, in the STePS study,[4] four out of five deaths happened within 48 h of medical evaluation in the ED. Taken together, these observations justify prompt identification of high-risk patients, their hospitalization, and intensive clinical management.

Importantly, during the month following syncope, we did not observe a peak in syncope recurrence. Even if our data do not explain the low recurrence rate of syncope in the short term, we can hypothesize that an efficient early diagnosis and treatment may ultimately result in such a positive clinical effect. The observed short-term low syncopal recurrence rate also suggests that at least patients with unexplained syncope, after initial evaluation, can be safely managed in the outpatient clinic thus avoiding immediate hospitalization.

Late outcome

Like in short-term outcome, structural heart disease together with abnormal ECG were the main death predictors during the subsequent 2 years. It is important to underline that few previous syncope episodes was a mortality predictor during the long-term follow up, possibly because a higher rate of syncope is suggestive of a neuromediated mechanism.

Of interest, despite these patients undergoing specific therapy, the type of syncope was unrelated to the mechanism of death.

This finding may be related to different aspects. First, the population included in our study was elderly and had significant comorbidities. It may simply be that syncope is nothing else that a marker of frailty or progression of underling disease that may lead to the death of patients. In fact the markers of risk are also markers of frailty in the elderly as injuries and cardiovascular disease. An exception was syncope caused by structural cardiac or cardiopulmonary disease. This finding is relevant, since little is known about the effects of specific therapy in patients with syncope caused by structural cardiac or cardiopulmonary disease. In addition, it is unknown if the mechanisms of death and syncope were the same, although both were indirectly related to common underlying heart disease. Whatever the reason, syncope in those with structural heart disease triples probability of death [35 vs. 15%, $P = 0.05$, OR 3.0 (95% CI 1–10)]. The outcome of arrhythmic syncope, instead, is more favourable and not different from the syncope forms usually considered as benign such as neurally mediated and orthostatic hypotension.[10] We can hypothesize that the specific arrhythmic syncope therapy might have favourably influenced the outcome. In long term follow-up, Martin *et al.*[11] demonstrated that arrhythmia predictors or 1 year mortality in the validation cohort are abnormal ECG, history of ventricular arrhythmia, history of congestive heart failure, and age higher than 45 years. The event rate (clinically significant arrhythmia or death) after 1 year ranged from 0% for those with none of the four risk factors to 27% for those with three or four risk factors. In the OESIL risk score[12] mortality significantly increased within 1 year in patients with age $>$ 65 years, cardiovascular disease history, lack of prodrome, and abnormal electrocardiogram (0% for no factor, 0.8% for 1 factor; 19.6% for 2 factors; 34.7% for 3 factors; 57.1% for 4 factors). Soteriades *et al.*[10] showed that in the Framingham population, during an average follow-up of 17 years, there was no increased risk of cardiovascular morbidity or mortality associated with vasovagal syncope, while patients with cardiac syncope were at increased risk of death from any cause and cardiovascular events.

The syncopal recurrence rate observed in this study is consistent with previous literature data.[13–17] In some studies, ~35% of patients suffered from syncope recurrences after 3 years of follow-up.[13,14] In a prospective study of patients with syncope referred to ED, ambulatory clinics or admitted in hospital, Kapoor and Hanusa[15] observed a 20.2% recurrence rate in 1 year. In a 5 year follow-up study of patients hospitalized for syncope, Racco[16] observed a syncope recurrence in 25% of all patients. In a population of 611 patients referred to ED for unexplained syncope, syncope recurrence was observed in 15% cases,[17] a very similar percentage to that observed in the present study. The recurrence rate increased progressively during the follow-up and a long period of time frequently elapses before patients had their first recurrence. For this reason, syncopal recurrence should not be evaluated in the short term, but a careful prolonged follow-up is recommended. Predictors of syncope recurrence include a high number of syncope during lifetime. In the study of Rose *et al.*,[18] indeed, patients who already had had more than five episodes, had a 50% recurrence chance in the following year. In the Grimm's study about half patients with a history of $\geq$2 syncopal episodes suffered from recurrent syncope and, thus, they might undergo appropriate prophylactic medical therapy.[19] On the contrary, in our study the syncopal recurrence rate was the same in patients with isolated or recurrent syncope. Also, the EGSYS score could not predict syncope recurrences, whereas it proved to be suitable for predicting mortality and the cause of syncope.[8] These different results may be explained as follows: in the above-mentioned studies all patients were affected by neurally mediated syncope, while in the present study all syncope causes were included. It is possible that the number of previous syncopes is a valuable predictor only for neurally mediated syncope and not for the other causes of loss of consciousness. Moreover, many patients in our study received a therapy which, obviously, favourably influenced the outcome. Finally, the event rate may be too small to show any difference.

Little is available in literature about therapy effects in population studies of syncope patients. Overall, despite a definite diagnosis being obtained in 96% of patients and therapy being administered in 74% of patients, the syncopal recurrence was relevant. Syncopal relapse rate was about the same in treated patients and in the non-treated ones. Even if no comparison can be drawn between these two groups because of their different characteristics, a recurrence rate, shifting from 13 to 20%, in treated patients cannot be considered satisfying and prompts a different diagnosis and treatment methodology. Therapy was unrewarding unsatisfying in all patient subgroups. The only favourable therapy trend was found in the subgroup of those patients suffering from arrhythmic syncope but without any statistical differences.

Limitation of this study

We obtained treatment data at discharge time and not during follow-up. For this reason, it is not possible to evaluate the effect of possible treatment changes during the follow-up. In addition, we were unable to define the cause of death in 40% of patients. Thus, the correlation between death and syncope mechanism could not be fully evaluated.

Conclusion

In patients attending to the ED for syncope, a peak of cardiovascular mortality but not of syncopal relapses was observed within the first month after the sentinel event. Late outcome was unfavourably affected by associated cardiovascular diseases rather than the sheer mechanism of syncope. The mechanism of syncope does not affect its recurrence rate. An unsatisfactory high recurrence rate of syncope was observed despite the specific guideline based therapy. EGSYS score can predict the long-term mortality but not the syncope recurrence.

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Internisti (FADOI), and Società Italiana di Medicina Interna (SIMI). A. Scivales and D.S.T. are employees of Medtronic fundation.

Conflict of interest: none declared.

Appendix

The following persons participated in the EGSYS-2 study.

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Notes

Contributors: Andrea Ungar, Attilio Del Rosso, Angelo Bartoletti, and Raffaello Furlan: study concept and design, acquisition of subjects and data, interpretation of data. Fabio Quartieri, Chiara Mussi, and Giuseppe De Marchi: acquisition of subjects, analysis, and interpretation of data. Alessandro Morrione: acquisition of subjects and data, preparation of manuscript. Franco Giada, Alfonso Lagi, Maurizio Lunati: study concept and design, interpretation of data. Niccolò Marchionni and Michele Brignole: analysis and interpretation of data, preparation, and revision of manuscript.

References

1. Brignole M, Alboni P, Benditt DG, Bergfeldt L, Blanc JJ, Thomsen PE, Gert van Dijk J, Fitzpatrick A, Hohnloser S, Janousek J, Kapoor W, Kenny RA, Kulakowski P, Masotti G, Moya A, Raviele A, Sutton R, Theodorakis G, Ungar A, Wieling W, Priori SG, Garcia MA, Budaj A, Cowie M, Deckers J, Burgos EF, Lekakis J, Lindhal B, Mazzotta G, Morais J, Oto A, Smiseth O, Menozzi C, Ector H, Vardas P, Task Force on Syncope, European Society of Cardiology. Guidelines on management (diagnosis and treatment) of syncope-update 2004. *Europace* 2004;**6**:467–537.
2. Huff JS, Decker WW, Quinn JV, Perron AD, Napoli AM, Peeters S, Jagoda AS, American College of Emergency Physicians. Clinical policy: critical issues in the evaluation and management of adult patients presenting to the emergency department with syncope. *Ann Emerg Med* 2007;**49**:431–444.
3. Strickberger SA, Benson DW, Biaggioni I, Callans DJ, Cohen MI, Ellenbogen KA, Epstein AE, Friedman P, Goldberger J, Heidenreich PA, Klein GJ, Knight BP, Morillo CA, Myerburg RJ, Sila CA. AHA/ACCF Scientific Statement on the evaluation of syncope. *Circulation* 2006;**113**:316–327.
4. Costantino G, Perego F, Dipaola F, Borella M, Galli A, Cantoni G, Dell'Orto S, Dessi S, Filardo N, Duca PG, Montano N, Furlan R. Short and long-term prognosis of syncope, risk factors and role of hospital admission. Results from the STePS (Short-Term Prognosis of Syncope) Study. *J Am Coll Cardiol* 2008;**51**:276–283.
5. Grossman SA, Fischer C, Lipsitz LA, Mottley L, Sands K, Thompson S, Zimetbaum P, Shapiro NI. Predicting adverse outcomes in syncope. *J Emerg Med* 2007;**33**:233–239.
6. Quinn J, McDermott D, Stiell I, Kohn M, Wells G. Prospective validation of the San Francisco Syncope Rule to predict patients with serious outcomes. *Ann Emerg Med* 2006;**47**:448–454.
7. Brignole M, Bartoletti A, Giada F, Lagi A, Ungar A, Ponassi I, Mussi C, Maggi R, Re G, Furlan R, Rovelli G, Ponzi P, Scivales A. A new management of syncope: prospective systematic guideline-based evaluation of patients referred urgently to general hospitals. *Eur Heart J* 2006;**27**:76–82.
8. Del Rosso A, Ungar A, Maggi R, Giada F, Petix NR, De Santo T, Menozzi C, Brignole M. Clinical predictors of cardiac syncope at initial evaluation in patients referred urgently to general hospital: the EGSYS score. *Heart* 2008;**94**:1620–1626.
9. Curran-Everett D. Multiple comparisons: philosophies and illustrations. *Am J Physiol Regulatory Integrative Comp Physiol* 2000;**279**:1–8.
10. Soteriades ES, Evans JC, Larson MG, Chen MH, Chen L, Benjamin EJ, Levy D. Incidence and prognosis of syncope. *New Engl J Med* 2002;**347**:878–885.
11. Martin TP, Hanusa BH, Kapoor WN. Risk stratification of patients with syncope. *Ann Emerg Med* 1997;**29**:459–466.
12. Colivicchi F, Ammirati F, Melina D, Guido V, Imperoli G, Santini M. Development and prospective validation of a risk stratification system for patients with syncope in the emergency department: the OESIL risk score. *Eur Heart J* 2003;**24**:811–819.
13. Kapoor WN. Evaluation and outcome of patients with syncope. *Medicine* 1990;**69**:169–175.
14. Kapoor WN, Peterson J, Wieand HS, Karpf M. Diagnostic and prognostic implications of recurrences in patients with syncope. *Am J Med* 1987;**83**:700–708.
15. Kapoor WN, Hanusa BH. Is syncope a risk factor for poor outcomes? Comparison of patients with and without syncope. *Am J Med* 1996;**100**:646–655.
16. Racco F, Sconocchini C, Alesi C, Zappelli L, Pratillo G. Long-term follow-up after syncope. A group of 183 patients observed for 5 years. *Minerva Cardioangiol* 2000;**48**:69–78.
17. Sarasin FP, Louis-Simonet M, Carballo D, Slama S, Rajeswaran A, Metzger JT, Lovis C, Unger PF, Junod AF. Prospective evaluation of patients with syncope: a population-based study. *Am J Med* 2001;**111**:177–184.
18. Rose MS, Koshman ML, Spreng S, Sheldon R. The relationship between health-related quality of life and frequency of spells in patients with syncope. *J Clin Epidemiol* 2000;**53**:1209–1216.
19. Grimm W, Degenhardt M, Hoffmann J, Menz V, Maisch WB. Syncope recurrence can better be predicted by history than by head-up tilt testing in untreated patients with suspected neurally mediated syncope. *Eur Heart J* 1997;**18**:1465–1469.