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Syncope recurrence and mortality: a systematic review

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Aims Data on adverse events and death rates following syncope are heterogeneous among studies, and knowledge of syncope prognosis could help to better define the correct management of patients.

Methods and results We performed a systematic review of literature by searching for prospective observational studies enrolling consecutive patients presenting to the Emergency Department because of syncope. The outcomes considered were syncope recurrence and short- and long-term mortality. Morbidity and a composite of morbidity and mortality were also assessed. Pooled event rates and 95% confidence intervals (CI) were calculated for each outcome using the random effects model. Twenty-five studies (11 158 patients) were included. The incidence of syncope relapse linearly increased from 0.3% at 30 days to 22% at 2 years follow-up. One-year mortality rate varied between 5.7 and 15.5%; the pooled estimate was 8.4% (95% CI: 6.7–10.2%). The incidence of adverse events (morbidity) varied between 6.1 and 25.2% at 10 days and 2 years, respectively. The short-term (10 days) pooled incidence of the composite of morbidity and mortality was 9.1% (95% CI: 6.6–12.5%). We found a high statistical heterogeneity between studies.

Conclusion This meta-analysis of prospective observational studies shows that the chance of being asymptomatic linearly progressively decreased over time after the first syncope. Short-term (10–30 days) mortality after syncope was $<2\%$ and that the overall 10-day rate of the composite endpoint of death and major events was $\sim 9\%$. The knowledge of syncope prognosis could help clinicians to understand syncope patients' prognosis and researchers to design future studies.

Keywords Syncope • Systematic review • Meta-analysis • Prognosis • Mortality • Recurrence

Introduction

Syncope, defined as a transient loss of consciousness (TLOC) due to transient global cerebral hypoperfusion and associated with the inability to maintain postural tone, is a common symptom accounting for 1–3% of emergency department (ED) visits[1,2] and involving about 40% of people at least once in their lifetime.[3] It may be the final common presentation of a number of clinical conditions spanning from benign to life-threatening diseases, but its aetiology is not always easy to be determined. A recent systematic review showed that about one-third of patients were discharged without a diagnosis from the ED.[4] For this reason many studies on syncope risk stratification and management have been conducted so far. Nonetheless, there are still unresolved questions. First, even a low-risk syncope from a clinical standpoint might lead to an adverse outcome if the TLOC happens in a high-risk setting, such as employment or driving.[5,6] In this regard, knowing the risk of syncope recurrence is of primary importance. However, being a relatively low-risk condition, data on syncope recurrence are usually collected only in highly specialized centres, in which patients with a higher burden of symptoms tend to converge. Therefore, the risk of recurrence of unselected patients with low-risk or unexplained syncope is currently unknown.

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What's new?

- Data on adverse events and death rates following syncope are heterogeneous among studies.
- We performed a systematic review of prospective observational studies enrolling patients presenting to the Emergency Department because of syncope.
- Our data show that the chance of being asymptomatic linearly progressively decreased over time after the first syncope. Indeed, the incidence of syncope relapse linearly increased from 0.3% at 30 days to 22% at 2 years follow-up.
- Short-term syncope mortality is <2 and $<8.4\%$ at 10 days and 1-year follow-up, respectively.
- The short-term (10 days) pooled incidence of the composite of morbidity and mortality was 9.1%.
- The knowledge of syncope prognosis could help clinicians to understand syncope patients' prognosis and researchers to design future studies.

Moreover, the studies that have focused on syncope risk stratification have failed to provide helpful tools to predict mortality, mainly because of a low rate of events and a lack of an adequate sample size. Given the low risk of death after syncope, a high number of patients should be enrolled to obtain a precise death rate estimate. Unfortunately, no study enrolled such a number of patients so far. Furthermore, an adequate sample size calculation is affected by the high heterogeneity in syncope mortality rate among studies. Different study design (prospective/retrospective), diverse clinical setting (emergency department/non-emergency department), and different health system organizations could have led to this heterogeneity.

The aim of our systematic review was to summarize the current evidence on short- and long-term risk of mortality and syncope recurrence.

Methods

Data sources and searches

We attempted to identify all relevant published articles that considered consecutive adult patients presenting for syncope in the emergency department ED. We searched Medline and Embase using the following search terms: ('syncope' OR 'loss of consciousness' OR 'unconscious*' OR 'faint*' OR 'drop attack' OR 'dizziness' OR 'lipothymia') AND ('follow' OR 'cohort' OR 'mortality' OR 'prognosis' OR 'outcome' OR 'recurrence'). The search was completed in November 2012. We manually searched the references of retrieved publications and guidelines to look for additional studies. No language restrictions were applied. Couple of investigators (A.M.R. and M.S.; F.D. and G.Co.) independently evaluated the studies for inclusion, and disagreements were resolved by consensus.

Study selection

In order to be included in this systematic review, the published studies had to meet the following criteria: (i) *patients*: investigations had to have enrolled consecutive adult patients presenting to the ED because of syncope; (ii) *study design*: prospective observational studies; and (iii) *outcomes*: availability of data on syncope recurrence, mortality, or morbidity at least in the short-term period (7 days). We accepted the definition of syncope of the original studies.

Exclusion criteria were: (i) having enrolled only patients with a history of recurrent syncope; (ii) having enrolled only patients with a defined aetiology of syncope; and (iii) having assessed the response to a treatment.

Quality assessment

To evaluate the quality of the included studies, we used the criteria of Hayden *et al.*,[7] which take into account study participation, study attrition, prognostic factor measurement, outcome measurement, confounding measurement, and account and statistical analysis. We did not assess confounding measurement because it cannot be applied to the included studies.

Each of five domains is based on two or three items assessing quality criteria's satisfaction. Items were scored as 'yes', 'no', 'partially', and 'unclear'. The quality criteria for each domain were defined as follows: (i) criteria satisfied (good quality): all items scored 'yes'; (ii) criteria unsatisfied (poor quality): at least one item scored 'no'; and (iii) criteria partially satisfied (moderate quality): the remaining. The overall quality for each study was defined as: (i) *good*: good quality in at least three domains out of five; (ii) *poor*: poor quality in at least three domains out of five; and (iii) *moderate*: the remaining possibilities.

Outcomes

The outcomes considered were mortality and syncope recurrence. Morbidity and a composite of morbidity and mortality were also retrieved. As the definition of adverse events was heterogeneous among studies, we collected as morbidity any major adverse event not resulting in death as specified in each study.

Since primary studies considered different time ranges, we pre-defined to pool outcomes at 10 and 30 days, 6 months, 1, 1.5, and 2 years. If a study had reported outcomes at different times, they were considered in the closest pre-defined time range.

Data extraction

Couple of investigators (A.M.R. and F.D.; M.S. and G.Co.) independently extracted the data on study characteristics, study quality, mortality, morbidity, and risk of recurrence at different time intervals. The data extracted for each study were confirmed by consensus between the two reviewers.

Statistical methods

For each included primary study, an event rate with its 95% confidence interval (CI) was calculated for every pre-defined outcome. Event rate was computed as the ratio between the number of events and the number of patients at risk.

Due to expected clinical and methodological differences between the primary studies, all meta-analyses were performed using the Der Simonian and Laird random effects model on the logit transformed rates. Pooled rates were calculated for each outcome at each pre-defined time point.

However, statistical heterogeneity was formally assessed by a χ^2 test, and was quantified using the inconsistency index (I^2) statistic, which ranges from 0 to 100% and is defined as the percentage of the observed between-trial variability that is due to heterogeneity rather than chance. To investigate heterogeneity among the primary studies, subgroup analyses and simple meta-regression analyses were performed. The predefined potential sources of heterogeneity considered were: (i) the publication year, (ii) the mean age, (iii) the percentage of males of included

patients, (iv) the overall number of patients included in the study, and (v) the country in which the study was performed.

Finally, a graphical representation of the pooled results obtained at each time point was provided to show the trend of the outcomes considered over time.

All analyses were performed using SAS (release 9.2) and STATA (release 11) statistical software.

Results

Study selection

Figure 1 shows the process of study selection. We identified 45 770 articles (17 505 from Medline and 28 265 from Embase); 5436 of these studies were duplicates and were therefore eliminated, leaving 40 334 articles for consideration. After the exclusion of irrelevant studies, which were identified by reviewing the titles and abstracts of all retrieved articles, 73 publications remained for analysis. Forty eight of them were subsequently excluded after reading the full-length paper. The review of the references of original studies and guidelines identified no additional study.

Twenty-five studies were included in the meta-analysis (see Supplementary material online, *Appendix S1*), containing 11 158 patients enrolled between 1978 and 2009. The studies were published from 1982 to 2012. Most of them were conducted in Europe, nine in the USA, two in Oceania, and one in Singapore. All but four were single-centre studies. The percentage of males in each study varied between 38 and 58 (mean 46) and the mean age of the population recruited varied between 41 and 74 years (mean 60). The number of patients enrolled in each study varied between 69 and 1474 (mean 446) and the mean follow-up between 7 and 810 days. *Table 1* describes the main characteristics of the included studies.

Assessment of study quality

We completed quality assessment according to the criteria developed by Hayden *et al.*[7] Six studies were considered of good quality in all five domains. Fifteen studies were considered of good quality, nine were moderate and only one was of poor quality (see Supplementary material online, *Figure S1*). The overall quality was good in 60%, moderate in 36%, and poor in 4% of the domains (see Supplementary material online, *Figure S2*).

Data synthesis

Table 2 shows the pooled incidence of mortality, syncope relapse, morbidity, and overall serious outcomes at different time intervals.

Mortality

One-year mortality rate varied between 5.7 and 15.5% in the nine considered studies. Pooled estimate of 1-year death rate was 8.4% (95% CI: 6.7–10.2%) (*Figure 2*). *Figure 3A* shows that the pooled estimate of survival progressively decreased through time.

Syncope relapse

Figure 3B shows the pooled relapse-free probabilities after the first ED admission for syncope. The chance of being asymptomatic linearly progressively decreased over time after the first syncope (*Figure 4*). There was no significant heterogeneity between studies.

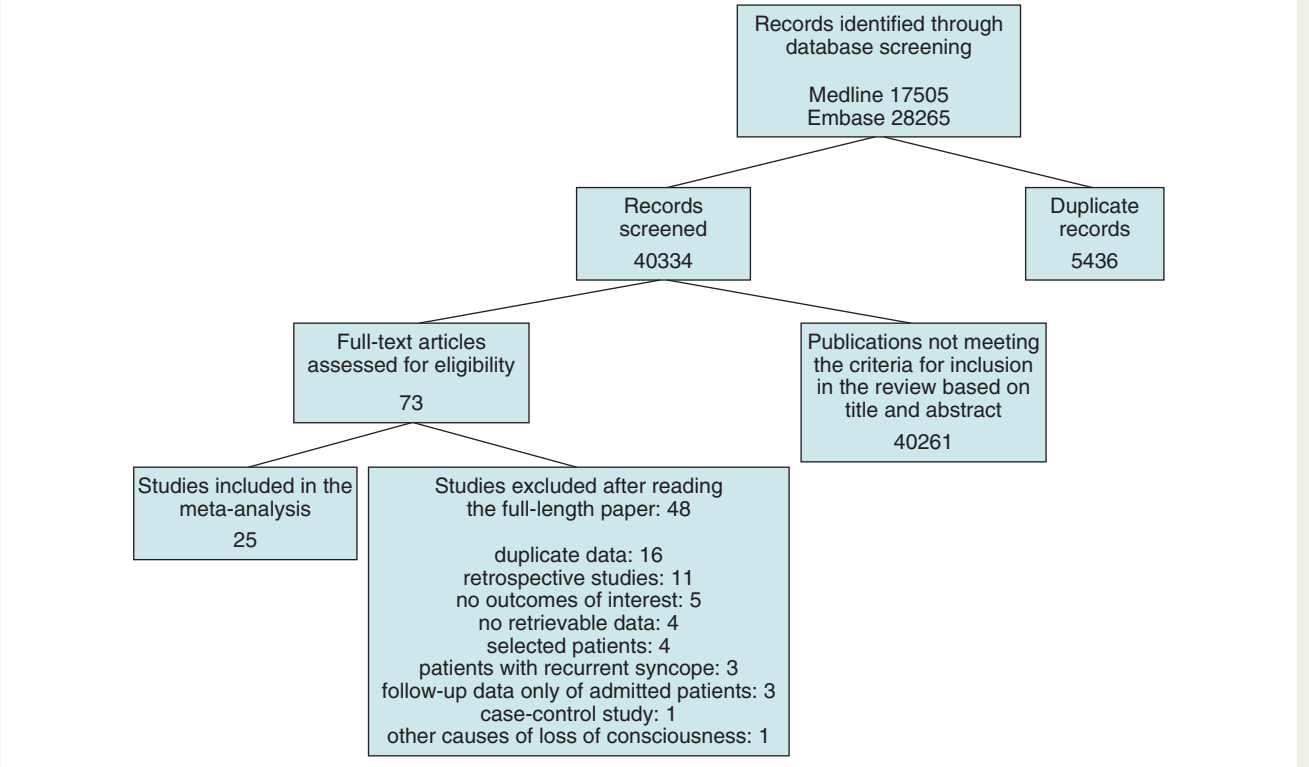

Figure 1 Study selection progression.

Table I Characteristics of the included studies

Author and publication year	Journal	Nation	Year of study begin	Multicentre study	Aim of the study	Number of patients	Mean age (years)	Percentage of males	Mean follow-up
Day (1982)	Am J Med	USA	1978	No	Diagnostic strategy and prognosis	198	44	44	330 days
Martin (1984)	Ann Emerg Med	USA	1982	No	Diagnosis	151	41	n.r.	6.2 months
Eagle (1985)	Am J Med	USA	1981	No	Prognosis	176	54	49	11.7 months
Racco (1993)	Minerva Med	Italy	1990	No	Prognosis	194	57	56	660 days
Martin (1997)	Ann Emerg Med	USA	1981	No	Derivation of Martin risk score	626	57	46	365 days
Wagner (2000)	Eur J Int Med	Switzerland	n.r.	No	Identification of hospitalization predictors	87	64	42	27 months
Sarasin (2001)	Am J Med	Switzerland	1997	No	Diagnostic strategy and prognosis	611	60	48	18 months
Crane (2002)	Emerg Med J	UK	1998	No	Prognosis according to ACP classification	189	55	39	365 days
Colivicchi (2003)	Eur Heart J	Italy	1997	Yes	Derivation of OESIL risk score	598	58	46	365 days
Cosgriff (2007)	Can J Emerg Med	Oceania	2005	No	Validation of SFSR	89	74	42	7 days
Grossman (2007)	J Emerg Med	USA	2003	No	Prognosis	293	58	42	30 days
Reed (2007)	Emerg Med J	UK	2005	No	Prognosis and validation of SFSR and OESIL risk score	99	71	48	n.r.
Birnbaum (2008)	Ann Emerg Med	USA	2005	No	Validation of SFSR	713	61	38	7 days
Costantino (2008)	JACC	Italy	2004	Yes	Prognosis	670	59	44	365 days
Quinn (2008)	Ann Emerg Med	USA	2000	No	Long term prognosis of SFSR	1474	62	44	365 days
Rodriguez-Entem (2008)	Rev Esp Cardiol	Spain	2005	No	Diagnostic strategy	199	67	54	237 days
Agarwal (2009)	Ann Emerg Med	USA	n.r.	No	Prognosis according to ECG presentation	282	61	44	365 days
Han (2010)	Heart, Lung and Circulation	Oceania	n.r.	No	Prognosis	69	n.r.	n.r.	18 months
Reed (2010)	JACC	UK	2007	No	Derivation and validation of ROSE rule	1067	63	45	1 month
Romero-Rodriguez (2010)	Rev Clin Esp	Spain	2005	No	High risk syncope prognosis	77	74	56	2.1 years
Ungar (2010)	Eur Heart J	Italy	2004	Yes	EGSYS patients prognosis	380	66	58	614 days
Long (2011)	Ann Emerg Med	USA	2009	No	Prognosis	447	62	50	30 days
Reed (2011)	Ann Emerg Med	UK	2007	No	1-year follow-up of ROSE rule	1043	63	45	365 days
Kayayurt (2012)	Int J Emerg Med	Turkey	2009	No	Validation of existing rules and derivation of the Anatolic Syncope Rule	231	n.r.	n.r.	7 days
Tan (2012)	Acad Emerg Med	Singapore	n.r.	Yes	Prospective validation of SFRS	1195	n.r.	n.r.	7 days

n.r., not reported; OESIL, Osservatorio Epidemiologico della Sincope nel Lazio; SFSR, San Francisco Syncope Rule; ECG, electrocardiogram; ROSE, Risk Stratification of Syncope in the Emergency Department; EGSYS, European Guidelines in Syncope Study.

Table 2 Pooled incidence of mortality, syncope relapse, major events, and overall serious outcomes at different times

Outcome	Time	Number of studies	Number of patients	Number of events	Pooled rate (%)	95% CI (%)	I^2 (%)[b]	Heterogeneity *P*-value[c]
Mortality	10 days	3 (S2; S4; S5)	1472	10	0.7	0.4–1.3	0	0.8015
	30 days	4 (S9; S15; S18; S24)	3214	50	1.6	1.2–2.1	0	0.6851
	6 months	4 (S13; S15; S17; S20)	1923	75	3.7	2.5–5.4	29.2	0.2372
	1 year	9 (S1; S3; S5–S8; S14; S15; S19)	4879	387	8.4	6.7–10.2	77.2	<0.0001
	1.5 years	4 (S10; S16; S22; S24)	1254	111	8.9	7.4–10.6	0	0.8345
	2 years	2 (S21; S25)	164	18	11.0	7–16.8	0	0.7836
Syncope recurrence	30 days	1 (S24)	380	1	0.3	0–1.8[a]	0	–
	6 months	2 (S13; S20)	350	18	5.2	3.3–8.2	0	0.3915
	1 year	2 (S7; S22)	797	72	9.0	7.2–11.3	0	0.5987
	1.5 years	4 (S10; S16; S22; S24)	1254	202	16.1	14.2–18.3	0	0.9582
	2 years	2 (S21; S25)	164	36	22.0	16.3–29.1	0	0.4727
Morbidity	10 days	2 (S4; S5)	759	45	6.9	3.7–12.6	67.3	0.0804
	30 days	3 (S9; S12; S18)	1807	179	11.4	5.7–21.5	96.6	<0.0001
	6 months	1 (S17)	99	6	6.1	2.7–12.8[a]	0	–
	1 year	4[d] (S5; S14; S19)	2336	262	11.3	5.8–20.9	96.3	<0.0001
	1.5 years	2 (S10; S16)	263	58	25.2	11–47.8	90.5	0.0012
Overall serious outcomes	10 days	7 (S2; S4; S5; S11; S17; S19; S23)	4040	357	9.1	6.6–12.5	88.5	<0.0001
	30 days	3 (S9; S17; S18)	1459	155	11.6	4.5–26.4	96.4	<0.0001
	6 months	2 (S17; S19)	1142	118	10.3	8.7–12.2	0	0.79012
	1 year	4 (S1; S5; S14; S19)	2244	363	17.3	8.6–31.6	97.6	<0.0001
	1.5 years	2 (S10; S16)	263	79	32.9	19.3–50.2	84.1	0.01227

[a]CI were calculated on the basis of a single study.
[b]Variation in the pooled rate not attributable to chance.
[c]Assessed using a χ^2 test.
[d]In one study,[19] two different cohorts (derivation and validation) have been analysed separately.

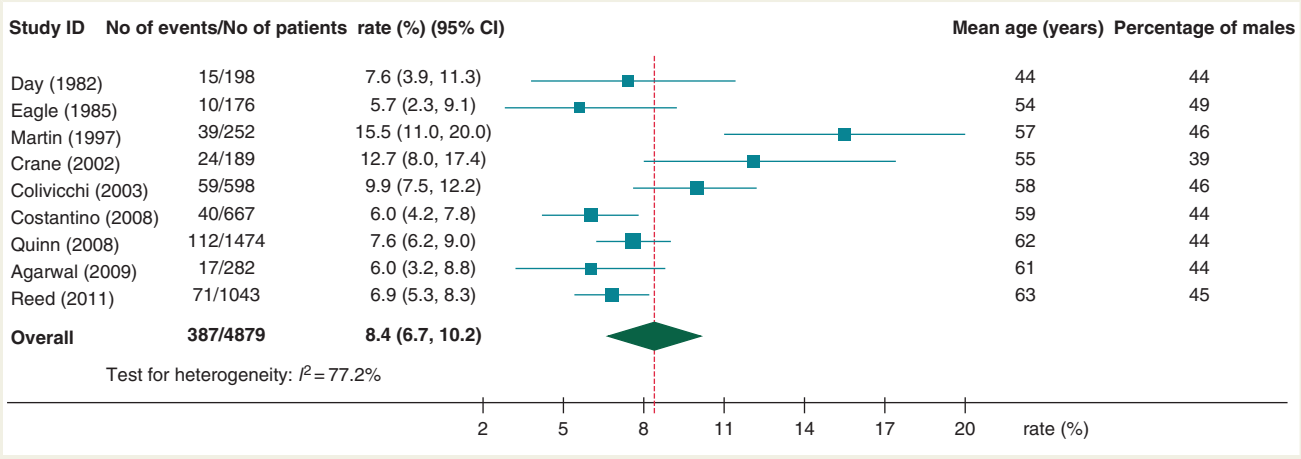

Figure 2 Pooled estimate of 1-year mortality.

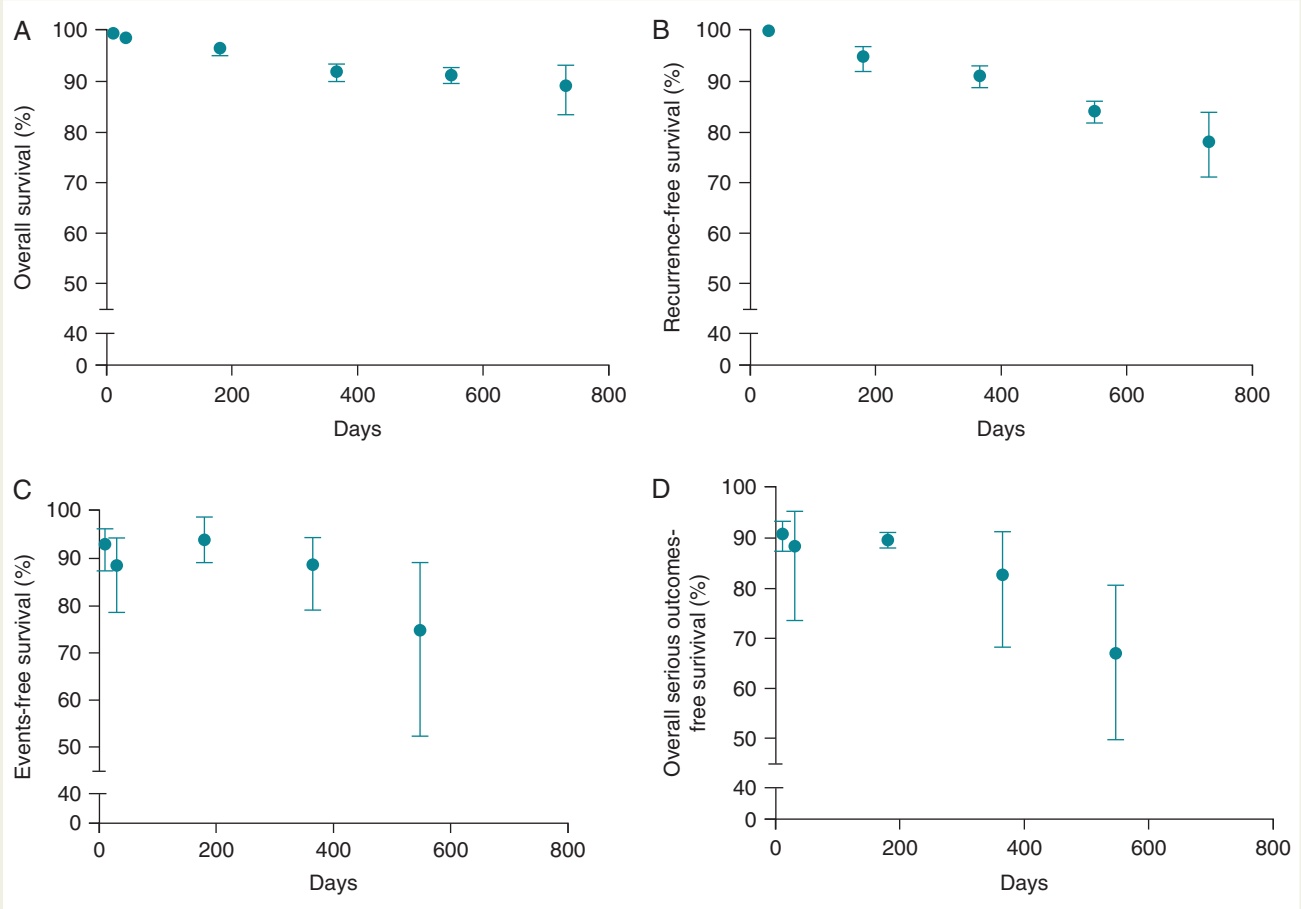

Figure 3 (*A*) Overall survival; (*B*) syncope recurrence-free survival; (*C*) adverse events-free survival; and (*D*) overall serious outcomes-free survival (pooled estimates from meta-analyses).

Morbidity

Few studies reported data on morbidity at different time points. As the definition of adverse events was heterogeneous among studies, we collected as morbidity any major adverse event not resulting in death, as specified in each study. The adverse events considered in each included study are reported in the Appendix (see

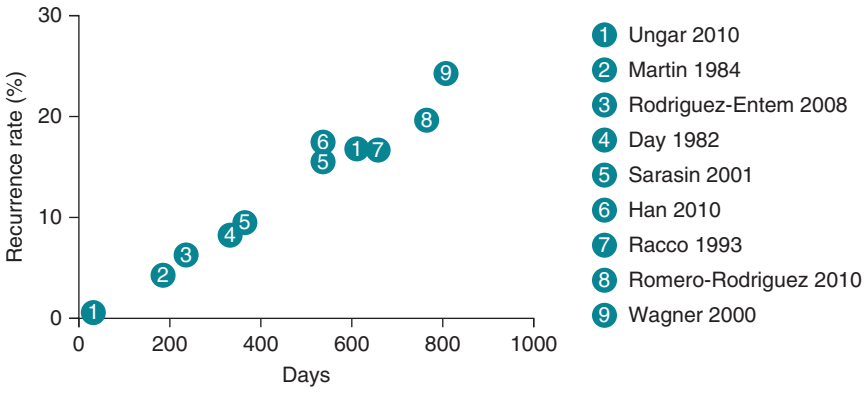

Figure 4 Syncope recurrence rate for every study at each time point.

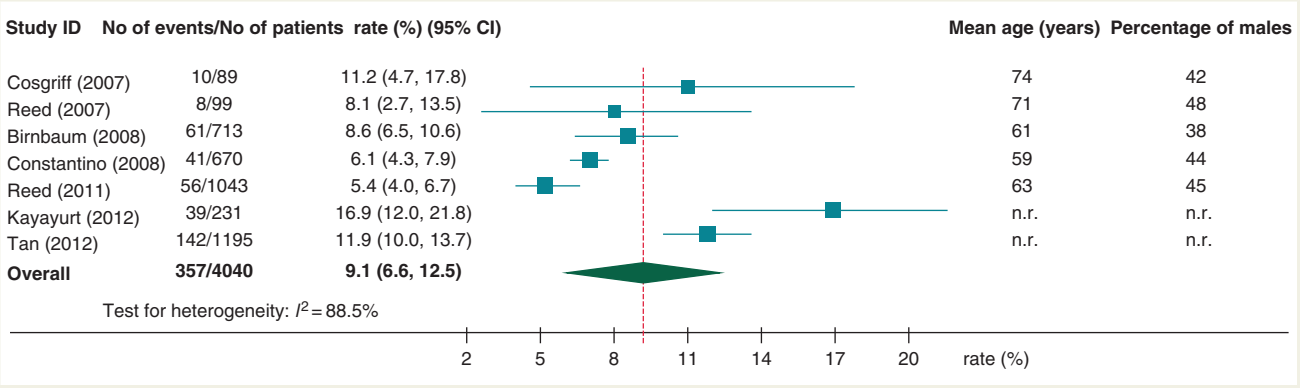

Figure 5 Pooled estimate of 10 days incidence of adverse events and death.

Supplementary material online, *Table S1*). The pooled rates of morbidity varied between 6.9 and 25.2% at 10 days and 2 years, respectively, without evidence of any progressive increase over time (*Figure 3C*).

Overall serious outcomes

Most of the studies' primary outcomes were composites of mortality and major adverse events (as defined above). Since it is likely that the patient's prognosis is mostly affected by syncope in the short-term period, we analysed the short-term (10 days) pooled incidence of serious outcomes as defined in the different studies. Short-term incidence of serious outcomes varied between 5.4 and 16.9%; the pooled (seven studies, 4040 patients) rate was 9.1% (95% CI: 6.6–12.5%) (*Figure 5*). *Figure 3D* shows the pooled overall serious outcomes-free probabilities after the first ED admission for syncope.

Heterogeneity

As expected, we found a high statistical heterogeneity between studies (*Table 2*).

Some exploratory pre-specified analyses were performed to investigate the heterogeneous mortality retrieved among the studies. Due to the small number of included studies, a meta-regression analysis was performed only on the following outcomes: 1-year mortality (see Supplementary material online, *Figure S3*) and morbidity (see Supplementary material online, *Figure S4*), 10-day and 1-year overall serious outcomes (see Supplementary material online, *Figure S5* and *S6*, respectively). We found no influence of the predefined sources of heterogeneity (publication year, mean age and percentage of males of included patients, overall number of patients included in the study, and country in which the study was performed).

Discussion

The aim of our systematic review was to assess syncope mortality and risk of recurrence. We found that the short-term mortality rate after syncope was <1% at 10 days and <1.6% at 30 days of follow-up. Major adverse events occurred in ~7 and 11% of patients at 10 and 30 days of follow-up, respectively. The overall 10-day rate of the composite endpoint of death and major adverse events was about 9%.

Our data showed that patients presenting to the ED because of syncope have a short-term mortality rate of <2% and an overall

10-day adverse outcomes rate of <10%. The paucity of adverse events might explain why all previous attempts to derive clinical scores or decision rules to identify high-risk patients have failed.[8] To overcome this problem, most of the studies have used composite endpoints[9,10] or prolonged follow-up (i.e. 1-year events, which are not definitely related to syncope).[11] It is likely that much larger sample sizes are necessary to derive risk stratification tools able to recognize even low-incidence events. Our results might help to calculate adequate sample size for future studies by giving a more accurate estimate of short-term events.

In ED patients, syncope seems to recur almost linearly over time, increasing from 0.3% at 30 days to 22% at 2 years follow-up. This observation is consistent with a Danish registry study, in which all Danish residents aged 50 years and over with a first-time discharge for syncope from all public hospital departments showed a progressive syncope recurrence, with a 22% rate at 3 years follow-up.[12] The same population showed similar results in terms of mortality, with a progressive increase over time and a 1-year death risk of <10%.[13] Should these data be confirmed in future studies, this observation could help improving patients' everyday management. Indeed, despite its benign prognosis, even recurrent vasovagal and unexplained syncope may lead to a significant decrease in quality-of-life because of trauma and psychological, driving, employment, and financial implications. Therefore, the knowledge of syncope recurrence risk might help to decide how to manage patients which are at low risk of adverse events from a clinical point of view, but whose everyday risk of adverse events is not negligible if syncope happens while driving or while performing risky jobs.[6,14] Our data showed that the risk of recurrence progressively increases, thus excluding the feasibility of an 'observation period' after which the risk of relapse may be negligible. This observation seems to be in contrast with that reported by previous studies, which suggested a higher incidence of recurrence in the first 6 months after syncope.[15,16] The same nonlinear recurrence rate was observed in the ISSUE study, in which patients with recurrent syncope and a negative diagnostic workup underwent implantable loop recorder (ILR) placement.[17] The authors observed a higher syncope recurrence within 6 months after ILR implant. However, the ISSUE patients might differ from the ED population, because they represent a highly selected population of patients with a high burden of syncope. Even with the limitation of having matched different dataset and different patients, the strength of our study is to represent a wide and unselected population. Moreover, although the absence of information on diagnosis may be confusing, this reflects usual clinical practice, as most of syncope patients are discharged from the ED with a diagnosis of vasovagal or unexplained syncope.[4] Conversely, cardiac syncope, which is much more worrisome from a clinical point of view, is probably less relevant in the assessment of recurrence risk because its diagnosis leads usually to an effective treatment.

While mortality and recurrences seem to increase over time, the incidence of major adverse events did not show a progressively growing trend. This unexpected finding might be due to both heterogeneity in defining adverse events and difficulty in collecting data about long-term outcomes. Moreover, if a life-threatening condition was the cause of syncope, it would result in a poor outcome in the short-time period, and consequently, it would be easily captured as a major adverse event. Conversely, long-term prognosis was previously found to be related more to the patient's frailty than to syncope itself.[15] This might explain the progressive increase in mortality in the absence of a similar increase in syncope-related major adverse events. In keeping with this hypothesis, Kapoor and Hanusa[18] found that patients with a history of cardiac disease had the same 1-year prognosis whether or not they previously suffered from syncope. Therefore, syncope itself did not affect patients' long-term prognosis. Conversely, Ruwald *et al.*[19] found that patients without previous co-morbidities were characterized by a higher risk of all-cause mortality, stroke, cardiovascular hospitalization, device implantation, and syncope recurrence after the first hospital or ED admission for syncope as compared to matching controls. The authors hypothesized that syncope itself could be the first symptom of an unrecognized underlying cardiovascular disease. The results of Ruwald and colleagues' study[20] must be interpreted carefully, as their investigation was a retrospective case–control analysis of registries data. Instead, our study was aimed instead to assess mortality, morbidity, and risk of recurrence of syncope patients and not to compare them to a control group's prognosis.

Study limitations

A limitation of our work is the high heterogeneity, although we have tried to limit it by enrolling only studies carried out in the Emergency Departments. Yet, besides the country of origin and the year in which they were performed, studies differed in terms of patient's characteristics, diagnostic strategies, admission rates, and outcomes considered. Unfortunately, because of the relatively small number of studies, we could not perform a formal heterogeneity analysis.

Moreover, we considered data from different studies as a continuum over time so that the endpoints at different time intervals appear as progressive observations of the same population, while they are actually coming each time from different pooled studies.

As already mentioned, the absence of data on prognosis according to syncope diagnosis might be considered a limitation. However, we believe that evaluating an unselected population is a pragmatic approach, as most of the syncope patients in the ED require risk stratification and prognostic assessment rather than diagnosis.

Finally, as in every meta-analysis of observational studies, the quality of the individual studies may largely influence the results of the review.

Conclusions

Our systematic review showed that short-term mortality was <1% at 10 days and <1.6% at 30 days of follow-up in patients presenting to the ED because of syncope. While the risk of mortality and syncope recurrence seems to increase almost linearly over time, the incidence of major adverse events did not parallel such an increase.

Our results could help both clinicians to understand patients' prognosis and researchers to better estimate events in order to design future syncope studies.

Supplementary material

Supplementary material is available at *Europace* online.

Conflict of interest: none declared.

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