

Prognosis Among Healthy Individuals Discharged With a Primary Diagnosis of Syncope

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CME Objective for This Article: At the conclusion of this activity, the learner should be able to examine the risk of major adverse events and death in a nationwide cohort of patients without previous comorbidity admitted for syncope.

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Prognosis Among Healthy Individuals Discharged With a Primary Diagnosis of Syncope

Objectives	This study sought to examine the risk of major cardiac adverse events and death in a nationwide cohort of patients without previous comorbidity admitted for syncope.
Background	Syncope is a common clinical event, but knowledge of prognosis is not fully elucidated in healthy individuals.
Methods	Patients without previous comorbidity admitted for syncope in Denmark from 2001 to 2009 were identified in nationwide administrative registries and matched by sex and age with 5 control subjects from the Danish population. The risk of death or recurrent syncope, implantation of pacemaker or implantable cardioverter-defibrillator, and cardiovascular hospitalization were analyzed with multivariable Cox proportional hazard models.
Results	We identified 37,017 patients with a first-time diagnosis of syncope and 185,085 control subjects; their median age was 47 years (interquartile range, 32 to 63 years) and 47% were male. A total of 3,023 (8.2%) and 14,251 (7.1%) deaths occurred in the syncope and the control population, respectively, yielding an event rate of 14.3 per 1,000 person-years (PY) in the syncope population. Multivariable Cox regression analysis demonstrated a significantly increased risk of all-cause mortality (hazard ratio [HR]: 1.06; 95% confidence interval [CI]: 1.02 to 1.10), cardiovascular hospitalization event rate of 26.5 per 1,000 PY (HR: 1.74; 95% CI: 1.68 to 1.80), recurrent syncope event rate of 45.1 per 1,000, stroke event rate of 6.8 per 1,000 PY (HR: 1.35; 95% CI: 1.27 to 1.44), and pacemaker or implantable cardioverter-defibrillator event rate of 4.2 per 1,000 PY (HR: 5.52; 95% CI: 4.67 to 5.73; $p < 0.0001$).
Conclusions	The first admission for syncope among healthy individuals significantly predicts the risk of all-cause mortality, stroke, cardiovascular hospitalization, device implantation, and recurrent syncope. (J Am Coll Cardiol 2013;61:325–32) © 2013 by the American College of Cardiology Foundation

Syncope is a common medical problem (1–4) that is difficult to evaluate and is associated with a high mortality rate in selected subgroups of patients (5–11).

The primary purpose of the evaluation of the patient with syncope is to determine whether the patient is at increased risk and implement preventive measures. Previous studies have shown conflicting results regarding the risk of death, and no data reflect the risk in syncope patients who are otherwise healthy (i.e., no known cardiovascular disease or comorbidity). The prognosis given in the different studies varies significantly and depends on the setting and whether it is the prognosis in the general population, in patients examined in the emergency department (ED), or in patients admitted to hospital with syncope (5,8–10,12–20).

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In addition, all studies had 1 thing in common: there was a very high rate of unexplained syncope, which questions the reliability of the true outcomes of syncope when dividing into categories of etiology.

There is still a lack of evidence concerning the risk of patients with syncope and no known comorbidity. To our knowledge, no study has estimated mortality in a (pre)defined subset of otherwise healthy syncope patients discharged from hospital or sent home from the ED and compared this with a representative background population. We investigated nationwide registries of supposedly healthy syncope patients and estimated their prognosis and time to future cardiac events.

Methods

A personal and unique civil registration number (CPR number) is assigned to all residents in Denmark that enables linkage of nationwide administrative registries on the individual level. Information on all dispensed prescriptions from Danish pharmacies since 1995 is registered according to the Anatomical Therapeutic Chemical system in the Danish Register of Medicinal Products (21). We obtained information on hospitalization and comorbidities from the Danish National Patient Register, where information on all hospital admissions in Denmark has been stored since 1978 (22). At discharge, each hospital admission is coded with 1 primary diagnosis and, if appropriate, 1 or more secondary diagnoses according to the International Classification of Diseases (ICD), before 1994, the 8th revision, and from 1994 to date, the 10th revision (ICD-10). Demographic information on date of birth, age, sex, and vital status were obtained from the Danish Civil Register.

Study population. From the Danish National Patient Register, we identified all Danish residents with a first-time admission to hospital or ED visit for syncope when classified as the primary discharge diagnosis (ICD-10 code R55.9) between January 1, 2001, and December 31, 2009. All hospital admissions, ED contacts, and nonacute referrals (i.e., outpatients were included but each unique patient was only recorded once). R55.9 refers to “syncope and collapse.” Patients seen in the ED, given the discharge diagnosis of R55.9, and immediately hospitalized were included if they

retained the diagnosis of R55.9 during the hospital admission and were discharged with that diagnosis. All secondary diagnoses given at the same index hospitalization were recorded. After identification, every syncope patient was matched by age and sex with 5 random control subjects from the Danish population. The control subjects were assigned the same date of syncope as the case with which they were matched (risk set matching). The “greedy macro match” algorithm was used to identify the matched control population (23).

Comorbidity and pharmacotherapy. Identification and information on major comorbidities related to syncope up to 5 years before the index date for syncope admission or ED visit were based on hospital discharge diagnosis codes according to a modified Charlson Comorbidity Index (24,25). We obtained information through the Danish National Patient Register based on the primary or secondary diagnosis for the following ICD-10 codes: cerebral vascular disease (I60 through I69), ischemic heart disease (I20 through I25), previous myocardial infarction (I21, I22), cardiac conduction disorders (I44, I45), atrial fibrillation (I48, I49), other cardiac arrhythmias (I46, I47), heart failure (I42, I50), chronic renal failure (N18, I12, I13), acute renal failure (N17, N19, R34), pulmonary edema (J81), shock (R57, A41), chronic obstructive pulmonary disease (J42 through J44), and cancer (C00 through C97). Hypertension was defined as treatment. We identified patients with hypertension from combination treatment with at least 2 of the classes of antihypertensive drugs as defined in the Online Appendix. This definition of hypertension was validated in a previously described, randomly selected cohort 16 years of age and older from the Danish population (26). We defined diabetes mellitus as a claimed prescription for a glucose-lowering drug (A10) or admission for diabetes with or without complications (E10 through E14).

Information on concomitant drug use up to 6 months before syncope was provided through the Register of Medicinal Product Statistics using the following Anatomical Therapeutic Chemical system codes: statins (C10A), beta-blockers (C07), angiotensin-converting enzyme inhibitors (C09), loop diuretics (C03C), spironolactone (C03D), thiazides (C03A), calcium channel blockers (C08), digoxin (C01A), class I antiarrhythmic drugs (C01BC), class III antiarrhythmic drugs (C01BD and C07AA), class IV antiarrhythmic drugs (C08DA), morphine (N02AA), glucose-lowering medication (A10), clopidogrel (B01AC04), acetylsalicylic acid (B01AA0), vitamin K antagonists (B01AA0), sedative and anxiolytic agents (N05B, N05C), antipsychotic agents (N05A), and bronchodilators (R04).

To define the population of patients with no comorbidity, we therefore excluded all patients who had been hospitalized previously with any of the comorbidities listed in Table 1 and who had claimed prescription of selected pharmacotherapy within 180 days as defined in the Online Appendix.

Validation population. We previously validated the discharge diagnosis of R55.9 and found a positive predictive value of 95% and a sensitivity of 61% (27).

Outcome measures. Survival status (whether patient is dead or alive) is obtained from the National Person Register. Cause of death is obtained from the National Danish Registry of Causes

of Death. The primary outcomes are long-term all-cause mortality and within 1 year. Secondary outcomes are insertion of an implantable cardioverter-defibrillator or pacemaker, admission for stroke, or cardiovascular hospitalization and admission for recurrent syncope. These outcomes are gathered from the Danish Patient Registry according to ICD-10 discharge diagnosis and procedural codes.

Statistical analyses. Data are presented as number and percentage or mean and SD. Data not normal distributed are presented as the median and interquartile range. Differences between categorical variables were analyzed with the chi-square test and differences between continuous variables with the Wilcoxon rank sum test or the Kruskal-Wallis test.

Events and outcomes were individually evaluated and then analyzed by Cox regression analysis, competing model analysis, and cumulative incidence calculations. All models were tested for linearity of continuous variables. All analyses were done using SAS statistical software, version 9.2 (SAS Institute Inc., Cary, North Carolina).

Ethics. The study was accepted by the Danish Data Protection Agency (ref. 2007-58-0015, int. ref: GEH-2010-001). Ethical approval is not required for registry-based studies in Denmark, and all data are anonymous and encrypted.

Results

We identified 88,335 patients with syncope, of whom 37,017 patients had no known previous hospitalization for comorbidities and no concomitant use of selected pharmacotherapy as listed in Table 1. The mean follow-up was 4.5 years. The complete sex- and age-matched control population comprised 185,085 individuals. The control group or background population was likewise a low-risk population with a generally low rate of comorbidity. The matching was unable to reach 100% due to the lack of control population in the very high age groups. The complete matching reached 99.73%. The median age was 47 years (interquartile range, 32 to 63 years), and 53% of the population were women.

1-year mortality. The 1-year overall mortality rate was 1.9% (696 deaths) in the syncope population and 2.0% (3,694 deaths) in the control population ($p = 0.1358$). The 1-year mortality rate was significantly increased in the age groups between 25 and 75 years, as depicted by the hazard

Abbreviations and Acronyms

- CI = confidence interval
- ED = emergency department
- HR = hazard ratio
- ICD = International Classification of Diseases
- PY = person-years

Table 1 Baseline Characteristics

Characteristic	Syncope	Controls	Age (yrs), p Value
N	37,017	185,085	48.5 ± 19.8, 47.0 (32-63)
Men	17,304 (46.8)	98,565 (46.8)	50.1 ± 18.2, 50.0 (36-63)
Women	19,713 (53.2)	86,520 (53.2)	47.1 ± 21.0, 45 (28-63)
Comorbidity			
Hypertension	0	17,584 (9.5)	<0.0001
Ischemic heart disease	0	4,137 (2.2)	<0.0001
Cerebral vascular disease	0	2,995 (1.6)	<0.0001
Previous myocardial infarction	0	1,575 (0.9)	<0.0001
Cardiac conduction disorder	0	418 (0.2)	<0.0001
Cardiac arrhythmia	0	3,505 (1.9)	<0.0001
Previous atrial fibrillation	0	2,805 (1.5)	<0.0001
Heart failure or pulmonary edema	0	1,973 (1.1)	<0.0001
Diabetes	0	5,644 (3.1)	<0.0001
Acute or chronic renal failure	0	654 (0.4)	<0.0001
COPD	0	1,947 (1.1)	<0.0001
Cancer	0	2,233 (1.2)	<0.0001
Liver disease, mild to severe	0	436 (0.2)	<0.0001
Concomitant pharmacotherapy			
Statins	887 (2.4)	11,143 (6.0)	<0.0001
Beta-blockers	0	11,842 (5.3)	<0.0001
ACEI/ARB	0	16,424 (7.4)	<0.0001
Loop diuretics	0	7,251 (3.9)	<0.0001
Spirolactone	0	1,733 (0.9)	<0.0001
Thiazide	0	10,966 (5.9)	<0.0001
Calcium channel blockers	0	10,126 (5.5)	<0.0001
Antianginal agents	0	2,825 (1.5)	<0.0001
Digoxin	0	2,718 (1.5)	<0.0001
Class I antiarrhythmic	0	147 (0.1)	<0.0001
Class III antiarrhythmic	0	204 (0.1)	<0.0001
Class IV antiarrhythmic	0	1,216 (0.7)	<0.0001
Clopidogrel	0	730 (0.4)	<0.0001
ASA	1,053 (2.8)	11,092 (6.0)	<0.0001
VKA	0	2,681 (1.5)	<0.0001
Glucose-lowering drugs	0	5,644 (3.1)	<0.0001
Antipsychotic drugs	0	3,825 (2.1)	<0.0001
Anxiolytic drugs	3,754 (10.1)	19,026 (10.3)	0.4233
Bronchodilators	0	10,533 (5.7)	<0.0001
Morphine	728 (2.0)	3,442 (1.9)	0.1663

Values are N, n (%), mean ± SD, median (interquartile range), or p value.

ACEI/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ASA = acetylsalicylic acid; COPD = chronic obstructive pulmonary disease; IQR = interquartile range; VKA = vitamin K antagonist.

ratios (HRs) in Table 2. The youngest age group in the syncope population only accounted for 1 death (0.0%), whereas 26 deaths (0.2%) occurred in those between 25 and

44 years of age and 268 deaths (1.7%) occurred in those between 45 and 75 years of age. There were 401 deaths (8.8%) within 1 year in the oldest age group. The event rates of all-cause mortality within the first year were 15.3 per 1,000 person-years (PY) in the syncope population and 16.3 per 1,000 PY in the control group.

Long-term mortality. The overall mortality was 8.2% (3,023 deaths) in the syncope population and 7.7% (14,251 deaths) in the control population, with an HR of 1.06 (95% confidence interval [CI]: 1.02 to 1.10) and a p value of 0.0033. The event rate for all-cause mortality was 14.3 per 1,000 PY for the syncope patients compared with 13.3 per 1,000 PY for the control subjects, and the mortality was increased in the syncope population across all age groups

Table 2 One-Year Mortality HRs Stratified by Age Groups Adjusted for Sex, Age, Comorbidity, and Pharmacotherapy

Age Group, yrs	HR	95% CI	p Value
<25	0.36	0.05-2.72	0.3201
26-44	2.02	1.27-3.21	<0.0001
45-74	1.29	1.13-1.48	<0.0001
>75	0.89	0.83-0.96	0.0012
All age groups	0.94	0.87-1.02	0.1358

CI = confidence interval; HR = hazard ratio.

Table 3 Long-Term Mortality HRs Stratified by Age Groups Adjusted for Sex, Age, Comorbidity, and Pharmacotherapy			
Age Group	HR	95% CI	p Value
<25	1.60	1.03-2.68	0.0197
26-44	2.29	1.87-2.80	<0.0001
45-74	1.23	1.15-1.31	<0.0001
>75	0.98	0.94-1.01	0.2063
All age groups	1.06	1.10-1.17	0.0033

Abbreviations as in Table 2.

younger than 75 years of age. The HR was 1.6 (95% CI: 1.03 to 2.68) in the youngest age group (younger than 25 years of age) (Table 3). The HR in the age group ranging from 25 to 44 years of age was 2.29 (95% CI: 1.87 to 2.80). In the middle-aged population (45 to 74 years of age), the HR was 1.23 (95% CI: 1.15 to 1.31) and 0.98 (95% CI: 0.94 to 1.01) in the elderly. We found no significant difference in long-term cardiovascular mortality between the 2 groups (event rate: 11.1 and 11.2 per 1,000 PY, $p = 0.4204$). The cumulative incidence plot in Figure 1 shows long-term mortality across age groups, and Figure 2 shows the cumulative incidence plot for the selected age group of 45 to 74 years of age.

The development of cardiovascular comorbidity, stroke, and the risk of device implantation after presentation of first syncopal event in a healthy population. A total of 4,183 patients in the syncope population were hospitalized for cardiovascular reasons. The event rate of cardiovascular hospitalization was found significantly increased in the syncope population, with an event rate of 26.5 per 1,000 PY

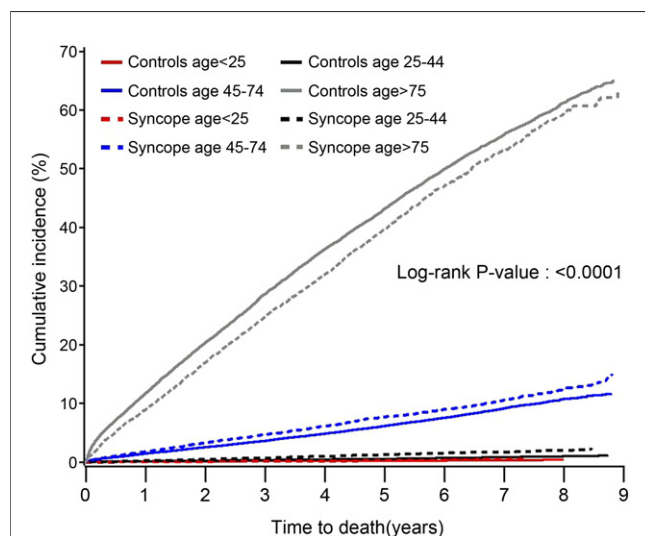


Figure 1

Cumulative Incidence Plot of Long-Term All-Cause Mortality According to Age Groups in Those With Syncope Compared With Control Subjects

No significant difference in the risk of all-cause mortality was found in the age groups older than 75 years and younger than 25 years of age. A significant difference in the risk of all-cause mortality was found in the age groups 25 to 44 years and 45 to 74 years.

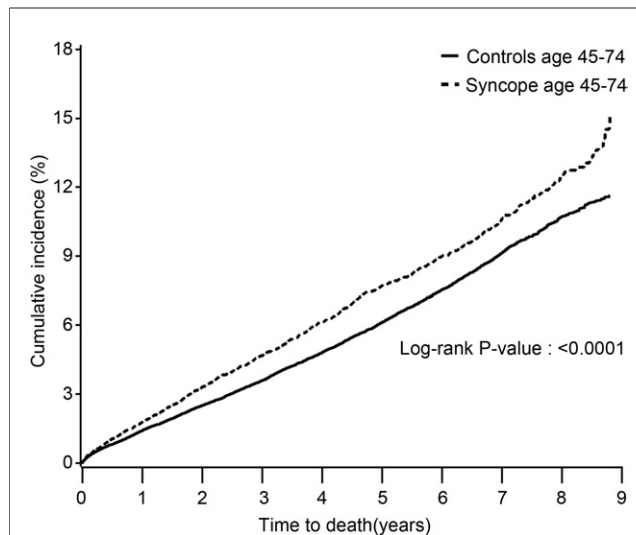


Figure 2

Cumulative Incidence Plot of Long-Term All-Cause Mortality in the Age Group 45 to 74 Years: Syncope Versus Control Group

A significant difference in the risk of all-cause mortality in the age group 45 to 74 years indicates that this age group may have syncope as a first symptom of future cardiovascular disease and adverse outcome.

versus 15.3 per 1,000 PY, respectively (HR: 1.74; 95% CI: 1.68 to 1.80; $p < 0.0001$). Similarly, we found an increased risk of device implantation with an event rate of 4.2 per 1,000 PY versus 0.8 per 1,000 PY, respectively (HR: 5.52; 95% CI: 4.67 to 5.73; $p < 0.0001$). The total amount of implanted devices in the syncope population was 698. A total of 1,131 patients experienced a stroke in the syncope population, and the event rate of strokes was 6.8 versus 5.0 in the control population (HR: 1.35; 95% CI: 1.27 to 1.44; $p > 0.0001$). Data are presented in Figures 3 to 5.

Recurrent syncope. The event rate of recurrent syncope was 45.1 per 1,000 PY. We saw an inverse relationship between increasing event rates and decreasing HRs with increasing age groups, as depicted in Table 4.

Discussion

This nationwide retrospective cohort study reveals novel insights into the patterns of short- and long-term mortality after an ED visit or admission for syncope in supposedly healthy patients. First, we found a short-term increased risk of death in the age groups between 25 and 74 years; however measured in all age groups, only borderline significance was noted between the 2 groups. Second, we found a significantly increased risk of all-cause long-term mortality across all age groups, and, finally, in our subgroup analysis, we found a higher risk of death in those 44 to 75 years of age, representing a group at especially increased risk. Furthermore, our results showed that syncope as a first symptom significantly predicted several adverse outcomes such as an increased risk of stroke, device implantation, and cardiovascular hospitalization.

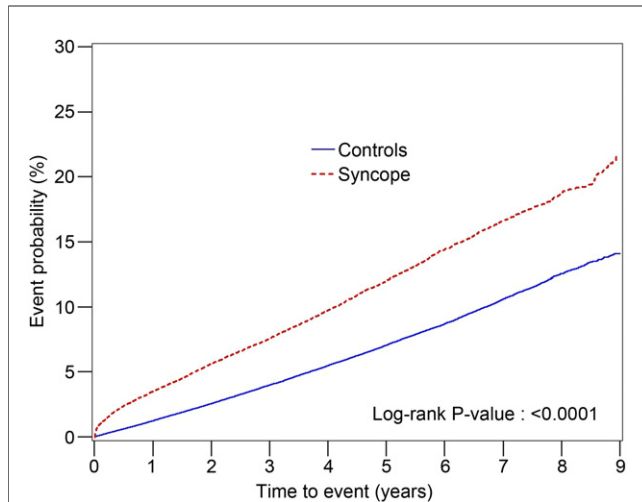


Figure 3 Competing Risk Model of Patients With Syncope Compared With Control Subjects and the Cumulative Incidence of Cardiovascular Hospitalization

A significant difference in the risk of future cardiovascular hospitalization across all age groups indicates that syncope in healthy individuals may be the first symptom of future cardiovascular disease and increased hospitalization compared with the background population.

Not surprisingly, we found a very high event rate of recurrent syncope that was also confirmed in the multivariable adjusted Cox regression analysis. However, the event rate, in numbers not previously seen, describes very well what is observed by clinicians—that the syncope patient is seen in hospital several times and most likely is submitted to

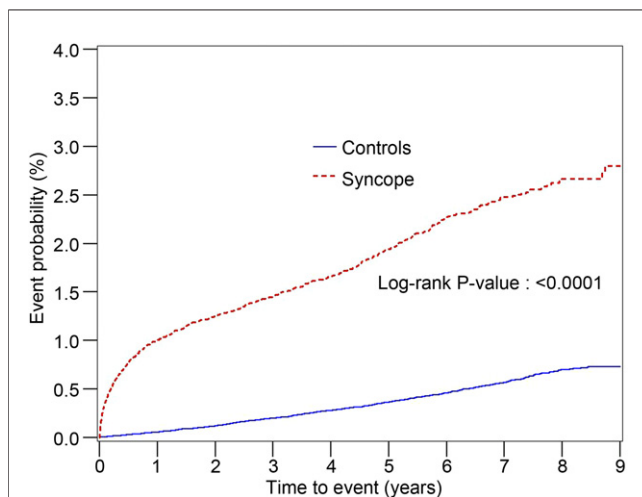


Figure 4 Competing Risk Model of Patients With Syncope Compared With Control Subjects and the Cumulative Incidence of Implantation of a Pacemaker or ICD

There was a significant difference in the risk of insertion of a pacemaker (PM) or implantable cardioverter-defibrillator (ICD) when comparing syncope patients and control subjects. The increase in risk was particularly dramatic within the first year after discharge for syncope, after which the curves became parallel.

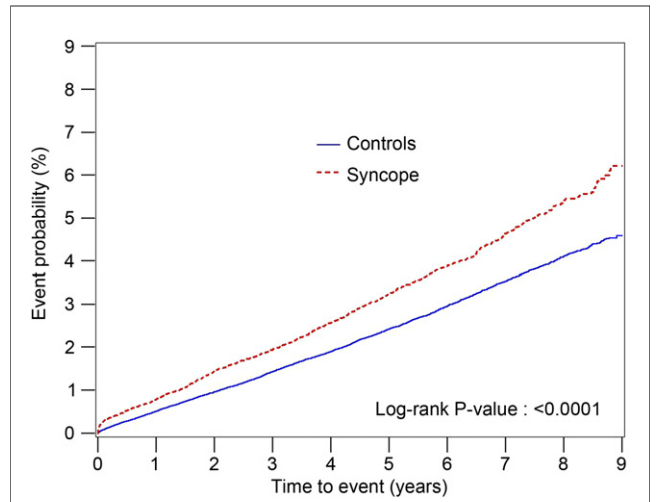


Figure 5 Competing Risk Model of Patients With Syncope Compared With Control Subjects and the Cumulative Incidence of Stroke

Stroke as an indicator of future cardiovascular disease was significantly increased across all age groups in the healthy syncope population compared with the control population.

several tests, which have low diagnostic yield. Furthermore, previous studies have shown that recurrent syncope increases the risk of fractures and diminishes quality of life markedly to levels of patients with rheumatoid arthritis and epilepsy (16,17,28).

We defined the syncope population with no comorbidities according to their lack of hospitalizations in the previous 5 years combined with no use of selected prescription drugs. The use of other prescription drugs in the syncope group was low and did not exceed that by the control group on any points. The increased rate of syncope among patients with psychiatric disease was described previously, and anti-psychotics in particular are associated with syncope, so we chose to include this as a selected pharmacotherapy to exclude from the study population (29-31). With regard to the other types of drugs, we found significantly lower use than in the control population. This supports that our syncope population can be recognized as a presumably “healthy” group. Generally, the use of prescription drugs in the control population was likewise low, indicating that this

Table 4 Event Rates and HRs of Recurrent Syncope Stratified by Age Groups Adjusted for Sex, Age, Comorbidity, and Pharmacotherapy

Age Group, yrs	Event Rates per 1,000 PY	HR	95% CI	p Value
<25	35.4	312.37	187.49-520.42	<0.0001
26-44	38.7	545.70	343.10-867.94	<0.0001
45-74	46.9	135.13	111.86-163.23	<0.0001
>75	74.7	37.75	31.94-44.63	<0.0001
All age groups	45.1	118.27	105.38-132.73	<0.0001

PY = patient year; other abbreviations as in Table 2.

is representative of the background population and comparison between the 2 groups is justified. Furthermore, we assessed the secondary discharge diagnoses, and in only one sixth of the syncope patients was there a secondary diagnosis, indicating that, as suspected, syncope was the primary reason for admission and the prominent symptom during the hospitalization. Important secondary diagnoses in terms of mortality and relevancy to syncope relates to heart failure, aortic stenosis, cerebral infarction, and ischemic heart disease. These secondary diagnoses are, in our data, very limited in terms of absolute and relative numbers, and relevant cardiovascular disease discovered during the actual and first hospitalization, represented by secondary discharge diagnoses, is low. The secondary diagnoses are given in Online Table.

Syncope as a predictor of mortality in the young and the elderly. We found a significantly increased risk of death in the 25- to 44-year age group. This is important new information not previously shown in larger studies. We hypothesize that this group of patients may be underdiagnosed in terms of unrecognized cardiovascular disease revealing a worse prognosis.

We found no significant association of increased all-cause mortality or cardiovascular death in the elderly, but this may largely be due to our control population. Therefore, it is reasonable to assume that the true HR ratio of this subgroup of our population would be higher if compared with a control population of no comorbidity.

Mortality due to cardiovascular disease. Soteriades et al. (5) followed 7,814 patients in the general population with syncope for 17 years and found a higher mortality rate for patients with cardiac syncope compared with noncardiac syncope. Suzuki et al. (18) studied 912 patients with syncope for an average of 3 years and found the same result. A retrospective study of 1,516 patients showed, however, no difference in the survival after syncope between causes of syncope (divided into groups of unexplained, cardiovascular, and noncardiovascular) (8). Our study fills a gap in knowledge, and the interpretation of the increased risk in mortality in certain age groups deserves extra attention. It may not be safe to rely on a history of no comorbidity when evaluating a patient with syncope, as some studies suggest.

A study comparing patients with and without syncope matched for cardiovascular disease and other important clinical variables found that cardiac syncope (per se) was not a significant predictor of overall or cardiac 1-year survival (10). Rather, underlying heart disease, particularly heart failure, was found to be the significant survival predictor. Likewise, a study of hospitalized syncope patients (8) found that the risk of death was not associated with a cardiac cause but correlated with age and comorbidity, which also included cardiovascular diseases. In a study of patients with advanced heart failure, poor left ventricular function was associated with a high risk of sudden death, regardless of the cause of syncope (19). Overall, there are discrepancies

regarding the mortality of syncope. Our study clearly indicates that syncope as a first symptom in healthy people represents an increased risk of death and may be the first symptom of underlying cardiovascular disease.

This study is important to the clinician when evaluating the prognosis of otherwise healthy individuals who have experienced syncope. More studies, however, are needed and, more importantly, proper risk stratification. Our study particularly fills a gap in the evaluation of the healthy younger and elderly who seem at the same risk as the background population, where, however, more studies are needed to clarify the much higher risk associated with the middle age groups in terms of mortality and development of cardiovascular disease.

Important strengths of the study include the long follow-up period, the large size of our study sample, and the fact that it was based on a nationwide unselected cohort of patients with syncope in a clinical setting. The Danish National Patient Register is the only nationally representative dataset that provides descriptive information about Danish ED visits. By including information from nationwide registries, we minimize the risk of selection bias. This study included patients independent of sex, socioeconomic status, age, ethnicity and participation in insurance or health programs and, importantly, included patients independent of participation in the labor market. Validation of the accuracy of a very similar ICD-9 (780.2) code in the United States was performed by Gabayan et al. (32) ($n = 100$), demonstrating a positive predictive value of 92% and a negative predictive value of 100%. In a substudy, we validated 750 charts with the diagnosis R559 and found a positive predictive value of 95% and 5,652 randomly selected medical patients and found the sensitivity of syncope to be 61%. This means that at least one third of the patients hospitalized for syncope in the Danish registries are not coded as syncope in the discharge diagnosis, which may create a bias toward a more benign outcome as some cardiovascular syncope cases are coded as specific cardiac causes (i.e., aortic stenosis or ventricular tachycardia).

Study limitations. The main limitation is inherent in the observational nature of the study and the lack of clinical data, particularly, electrocardiographic data. The assumption that the patients were without comorbidity was based on the lack of hospital contact for comorbidities and on the lack of use of selected pharmacotherapy. However, considering the fact that the patients did not take more medications for other conditions than the control group, we must assume that they at least had no more comorbidities than the control group. Our case ascertainment strategy could not identify individuals with syncope who had an alternative discharge diagnosis and did not have syncope coded as the principal ICD-10 discharge diagnosis. Furthermore, it is an inherent weakness that our outcome is based on hospital discharge diagnosis rather than adjudicated events.

Conclusions

First admission for syncope in a population without previous comorbidity significantly predicts the risk of all-cause mortality, stroke, cardiovascular hospitalization, device implantation, and recurrent syncope. The study suggests that syncope in seemingly healthy persons may be a first symptom of a more severe underlying cardiovascular disease.

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REFERENCES

1. Sarasin FP, Louis-Simonet M, Carballo D, et al. Prospective evaluation of patients with syncope: a population-based study. *Am J Med* 2001;111:177-84.
2. Quinn J, McDermott D, Kramer N, et al. Death after emergency department visits for syncope: how common and can it be predicted? *Ann Emerg Med* 2008;51:585-90.
3. Ruwald MH, Hansen ML, Lamberts M, et al. The relation between age, sex, comorbidity, and pharmacotherapy and the risk of syncope: a Danish nationwide study. *Europace* 2012;14:1506-14.
4. Sun BC, Emond JA, Camargo CA Jr. Characteristics and admission patterns of patients presenting with syncope to U.S. emergency departments, 1992-2000. *Acad Emerg Med* 2004;11:1029-34.
5. Soteriades ES, Evans JC, Larson MG, et al. Incidence and prognosis of syncope. *N Engl J Med* 2002;347:878-85.
6. Alshekhlee A, Shen WK, Mackall J, Chelimsky TC. Incidence and mortality rates of syncope in the United States. *Am J Med* 2009;122:181-8.
7. Lipsitz LA, Wei JY, Rowe JW. Syncope in an elderly, institutionalised population: prevalence, incidence, and associated risk. *Q J Med* 1985;55:45-54.
8. Getchell WS, Larsen GC, Morris CD, McAnulty JH. Epidemiology of syncope in hospitalized patients. *J Gen Intern Med* 1999;14:677-87.
9. Kapoor WN. Evaluation and outcome of patients with syncope. *Medicine (Baltimore)* 1990;69:160-75.
10. Kapoor WN, Hanusa BH. Is syncope a risk factor for poor outcomes? Comparison of patients with and without syncope. *Am J Med* 1996;100:646-55.
11. Kapoor W, Snustad D, Peterson J, et al. Syncope in the elderly. *Am J Med* 1986;80:419-28.
12. Savage DD, Corwin L, McGee DL, Kannel WB, Wolf PA. Epidemiologic features of isolated syncope: the Framingham Study. *Stroke* 1985;16:626-9.
13. Moya A, Sutton R, Ammirati F, et al. Guidelines for the diagnosis and management of syncope (version 2009). *Eur Heart J* 2009;30:2631-71.
14. Costantino G, Perego F, Dipaola F, et al. 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;51:276-83.
15. Ungar A, Mussi C, Del Rosso A, et al. Diagnosis and characteristics of syncope in older patients referred to geriatric departments. *J Am Geriatr Soc* 2006;54:1531-6.
16. Linzer M, Pontinen M, Gold DT, et al. Impairment of physical and psychosocial function in recurrent syncope. *J Clin Epidemiol* 1991;44:1037-43.
17. van Dijk N, Sprangers MA, Colman N, et al. Clinical factors associated with quality of life in patients with transient loss of consciousness. *J Cardiovasc Electrophysiol* 2006;17:998-1003.
18. Suzuki M, Hori S, Aikawa N. Application of the recent American practice resources for risk stratification system for patients presenting to a Japanese emergency department because of syncope. *Int Heart J* 2007;48:513-22.
19. Middlekauff HR, Stevenson WG, Stevenson LW, Saxon LA. Syncope in advanced heart failure: high risk of sudden death regardless of origin of syncope. *J Am Coll Cardiol* 1993;21:110-6.
20. Roussanov O, Estacio G, Capuno M, et al. Outcomes of unexplained syncope in the elderly. *Am J Geriatr Cardiol* 2007;16:249-54.
21. Gaist D, Sorensen HT, Hallas J. The Danish prescription registries. *Dan Med Bull* 1997;44:445-8.
22. Andersen TF, Madsen M, Jorgensen J, Mellemejkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999;46:263-8.
23. Parsons LS. Reducing Bias in a Propensity Score Matched-Pair Sample Using Greedy Matching Techniques. Available at: <http://www2.sas.com/proceedings/sugi26/p214-26.pdf>. Accessed November 27, 2012.
24. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373-83.
25. Nuttall M, van der Meulen J, Emberton M. Charlson scores based on ICD-10 administrative data were valid in assessing comorbidity in patients undergoing urological cancer surgery. *J Clin Epidemiol* 2006;59:265-73.
26. Ekholm O, Hesse U, Davidsen M, Kjoller M. The study design and characteristics of the Danish national health interview surveys. *Scand J Public Health* 2009;37:758-65.
27. Ruwald MH, Hansen ML, Lamberts M, et al. Accuracy of the ICD-10 discharge diagnosis for syncope. *Europace* 2012 Nov 4 [E-pub ahead of print].
28. Santhouse J, Carrier C, Arya S, Fowler H, Duncan S. A comparison of self-reported quality of life between patients with epilepsy and neurocardiogenic syncope. *Epilepsia* 2007;48:1019-22.
29. Ziemssen T, Reichmann H. Cardiovascular autonomic dysfunction in Parkinson's disease. *J Neurol Sci* 2010;289:74-80.
30. Vieweg WV, Wood MA, Fernandez A, et al. Proarrhythmic risk with antipsychotic and antidepressant drugs: implications in the elderly. *Drugs Aging* 2009;26:997-1012.
31. Weeke P, Folke F, Gislason GH, et al. Hospital admissions and pharmacotherapy before out-of-hospital cardiac arrest according to age. *Resuscitation* 2012;83:584-90.
32. Gabayan GZ, Derose SF, Asch SM, et al. Predictors of short-term (seven-day) cardiac outcomes after emergency department visit for syncope. *Am J Cardiol* 2010;105:82-6.

Key Words: cardiovascular events ■ epidemiology ■ prognosis ■ syncope.

APPENDIX

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