Incidence and Influence of Hospitalization for Recurrent Syncope and Its Effect on Short- and Long-Term All-Cause and Cardiovascular Mortality

Martin H. Ruwald, MD, PhD[a,b,*], Anna-Karin Numé, MB[a], Morten Lamberts, MD[a], Carolina M. Hansen, MD[a], Morten L. Hansen, MD, PhD[a], Michael Vinther, MD, PhD[a], Lars Kober, MD, DMSc[c], Christian Torp-Pedersen, MD, DMSc[d], Jim Hansen, MD, DMSc[a], and Gunnar H. Gislason, MD, PhD[a,e,f]

Recurrence of syncope is a common event, but the influence of recurrent syncope on the risk of death has not previously been investigated on a large scale. We examined the prognostic impact of recurrent syncope in a nationwide cohort of patients with syncope. All patients (n = 70,819) hospitalized from 2001 to 2009 in Denmark with a first-time diagnosis of syncope aged from 15 to 90 years were identified from national registries. Recurrence of syncope was incorporated as a time-dependent variable in multivariable-adjusted Cox models on the outcomes of 30-day, 1-year, and long-term all-cause mortality and cardiovascular death. During a mean follow-up of 3.9 ± 2.6 years, a total of 11,621 patients (16.4%) had at least 1 hospitalization for recurrent syncope, with a median time to recurrence of 251 days (33 to 364). A total of 14,270 patients died, and 3,204 deaths were preceded by a hospitalization for recurrent syncope. The long-term risk of all-cause death was significantly associated with recurrent syncope (hazard ratio 2.64, 95% confidence interval 2.54 to 2.75) compared with those with no recurrence. On 1-year mortality, recurrent syncope was associated with a 3.2-fold increase in risk and on 30-day mortality associated with a threefold increase. The increased mortality risk was consistent over age groups 15 to 39, 40 to 59, and 60 to 89 years, and a similar pattern of increase in both long-term and short-term risk of cardiovascular death was evident. In conclusion, recurrent syncope is independently associated with all-cause and cardiovascular mortality across all age groups exhibiting a high prognostic influence. Increased awareness on high short- and long-term risk of adverse events in subjects with recurrent syncope is warranted for future risk stratification. **(Am J Cardiol 2014;■:■−■)**

Syncope is a common symptom in the general population and a frequent cause of hospitalization and emergency department visit.[1,2] Many patients experience recurrence, and it has recently been shown that in patients aged >50 years, at least 20% are rehospitalized for recurrent syncope within 3.5 years,[3] while studies with implantable loop recorders in patients with multiple recurrences have shown even higher frequencies and short-term risk of recurrences.[4−8] Recurrences have been associated with increased risk of fractures, low quality of life, and greater chance of subsequent recurrent syncope,[9,10] but it is unknown if recurrence in itself is a cause for concern as a marker for increased risk of mortality and should be acknowledged in risk stratification. Naturally, the prognosis of syncope is determined by the underlying cause and/or co-morbidity.[2,11−15] However, recent hospitalization for first syncope was associated with adverse prognosis even in otherwise healthy subjects suggesting that either syncope could be the first sign of unrecognized cardiovascular disease or that syncope per se (maybe due to recurrences, fractures, or traumatic accidents) was responsible for the increased risk.[16] Studies on specific cardiac conditions such as Brugada syndrome and long QT syndrome have shown that the number of recurrences is directly correlated with increased risk of death,[17,18] but the impact of recurrent syncope in an unselected cohort of patients hospitalized for syncope has never been examined. We aimed to investigate the overall prognosis of syncope and the incidence and effect of recurrent syncope in a large cohort of unselected patients hospitalized for first-time syncope.

Methods

In Denmark, all residents have a unique and permanent civil registration number that enables linkage on an individual level among nationwide administrative registries. We identified all patients aged 15 to 90 years who had

[a]Department of Cardiology, Gentofte Hospital, Hellerup, Denmark; [b]Division of Cardiology, Heart Research Follow-up Program, University of Rochester Medical Center, Rochester, New York; [c]Department of Cardiology, The Heart Centre, Rigshospitalet, Copenhagen, Denmark; [d]Department of Health Science and Technology, University of Aalborg, Aalborg, Denmark; [e]National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark; and [f]Faculty of Health and Medical Sciences, University of Copenhagen, Denmark. Manuscript received January 9, 2014; revised manuscript received and accepted February 18, 2014.

See page 6 for disclosure information.

*Corresponding author: Tel: (+45) 2991 5585; fax: (+45) 3977 7642.
E-mail address: mruwald@hotmail.com (M.H. Ruwald).

0002-9149/14/$ - see front matter
http://dx.doi.org/10.1016/j.amjcard.2014.02.035

Table 1
Baseline characteristics of the study population

Variable	Total Patients (n = 70,819)	Recurrent Syncope	
		Yes (n = 11,621 [16.4%])	No (n = 59,198 [83.6%])
Men	34,692 (49.0)	5,982 (51.5)	28,710 (48.5)*
Women	36,127 (51.0)	5,639 (48.5)	30,488 (51.5)*
Age, yrs (mean ± SD)	60.4 ± 19.7	63.7 ± 18.5	59.7 ± 19.9*
15–39	13,161 (18.6)	1,592 (13.7)	11,569 (19.5)*
40–59	17,053 (24.1)	2,333 (20.1)	14,270 (24.9)*
60–89	40,605 (57.3)	7,696 (66.2)	32,909 (55.6)*
<60	30,214 (42.7)	3,925 (33.8)	26,289 (44.4)
ED as first syncope contact	36,268 (51.2)	4,983 (42.9)	31,285 (52.9)*
Admitted at first syncope	34,551 (48.8)	6,638 (57.1)	27,913 (47.2)*
Cardiovascular disease	27,117 (38.4)	5,427 (46.7)	21,750 (36.7)*
Hypertension	19,075 (26.9)	3,772 (32.5)	15,303 (25.9)*
Coronary heart disease	7,565 (10.7)	1,696 (14.6)	5,869 (9.9)*
Myocardial infarction	2.638 (3.7)	537 (4.6)	2,101 (3.6)*
Heart failure	4,430 (6.3)	904 (7.8)	3,526 (6.0)*
Cerebral vascular disease	5,502 (7.8)	1,045 (9.0)	4,457 (7.5)*
Peripheral artery disease	948 (1.3)	209 (1.8)	739 (1.3)
Atrioventricular block	1,378 (1.9)	318 (2.7)	1,060 (1.8)*
Atrial fibrillation	5,273 (7.5)	1,119 (9.6)	4,154 (7.0)*
Diabetes mellitus	5,679 (8.0)	1,106 (9.5)	4,573 (7.7)*
Renal disease	961 (1.4)	216 (1.9)	745 (1.3)*
Liver disease	657 (0.9)	115 (1.0)	542 (0.9)
Chronic obstructive pulmonary disorder	6,970 (9.9)	1,265 (10.9)	5,714 (9.7)*
Cancer	2,264 (3.2)	389 (3.4)	1,875 (3.2)
Implanted pacemaker	725 (1.0)	139 (1.2)	586 (1.0)
Implanted cardioverter-defibrillator	201 (0.3)	41 (0.4)	160 (0.3)
Concomitant pharmacotherapy			
β Blockers	12,329 (17.4)	2,450 (21.1)	9,979 (16.7)*
ACEi/ARB	16,931 (23.9)	3,375 (29.0)	13,556 (22.9)*
Loop diuretics	8,718 (12.3)	1,802 (15.5)	6,916 (11.7)*
Thiazide	9,642 (13.6)	1,874 (16.1)	7,768 (13.1)*
Nitrates	4,871 (6.9)	1,131 (9.7)	3,740 (6.3)*
Antipsychotics	3,582 (5.1)	590 (5.1)	2,992 (5.1)
Anxiolytics	16,561 (23.4)	3,090 (26.6)	13,471 (22.8)*

Data are presented as n (%), unless otherwise specified.
ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ED = emergency department.
* p Value for comparison <0.05.

a first-time diagnosis of syncope (International Classification of Diseases, tenth revision [ICD-10] discharge diagnosis R55.9) from all public hospitals and emergency departments in the period 2001 to 2009. The patients were censored at the end of follow-up (December 31, 2009) or on the date of turning 90 years. Validation of the syncope diagnosis (R55.9) carried out in 2012 revealed a positive predictive value of 95% and a sensitivity of 63%.[19,20] Validation and chart review also showed that the syncope discharge diagnosis contained most common forms of etiological causes of syncope, such as reflex syncope, orthostatic hypotension syncope, and cardiac syncope, and that approximately 50% are of unknown or undetermined etiology at the end of follow-up.[19] Etiological data are not available in the registries on the individual level, because they are not registered as such in the ICD-10 system.

Information on previous hospitalizations and co-morbidities were gathered from the Danish National Patient Register[21] in a 5-year period before first-time hospitalization for syncope. The diagnoses were based on primary or secondary discharge diagnoses according to the ICD-10 system. Cardiovascular disease was categorized as presence of one of the following co-morbidities: hypertension, previous stroke, ischemic heart disease or previous myocardial infarction, heart failure, atrial fibrillation, previous atrioventricular block, peripheral vascular disease, or a previous implantation with implantable cardioverter-defibrillator or pacemaker.

Baseline medications were obtained from the Register of Medicinal Products Statistics[22] in a 180-day period up to first-time hospitalization for syncope. This register holds information on all dispensed prescriptions from all Danish pharmacies and is based on the Anatomical Therapeutic Chemical system. Cause and date of death, date of birth, and vital status were obtained from the Danish Register of Causes of Death[23] and the Central Personal Registry.

Recurrent syncope was defined as a discharge diagnosis of syncope (ICD-10 R55.9) from either an admission or visit to an emergency department (hospital contact) at any time after discharge of initial first-time syncope until end of follow-up or until time of censoring. Outpatient or ambulatory diagnoses were not considered as events. Primary