

Warning Symptoms Are Associated With Survival From Sudden Cardiac Arrest

Eloi Marijon, MD, PhD*; Audrey Uy-Evanado, MD*; Florence Dumas, MD, PhD; Nicole Karam, MD, MPH; Kyndaron Reinier, MPH, PhD; Carmen Teodorescu, MD, PhD; Kumar Narayanan, MD; Karen Gunson, MD; Jonathan Jui, MD; Xavier Jouven, MD, PhD; and Sumeet S. Chugh, MD

Background: Survival after sudden cardiac arrest (SCA) remains low, and tools for improved prediction of patients at long-term risk for SCA are lacking. Alternative short-term approaches aimed at preemptive risk stratification and prevention are needed.

Objective: To assess characteristics of symptoms in the 4 weeks before SCA and whether response to these symptoms is associated with better outcomes.

Design: Ongoing prospective population-based study.

Setting: Northwestern United States (2002 to 2012).

Patients: Residents aged 35 to 65 years with SCA.

Measurement: Assessment of symptoms in the 4 weeks preceding SCA and association with survival to hospital discharge.

Results: Of 839 patients with SCA and comprehensive assessment of symptoms (mean age [SD], 52.6 [8] years; 75% men), 430 patients (51%) had warning symptoms (50% of men vs. 53% of women; $P = 0.59$), mainly chest pain and dyspnea. In most symptomatic patients (93%), symptoms recurred within the 24 hours preceding SCA. Only 81 patients (19%) called emergency

medical services (911) to report symptoms before SCA; these persons were more likely to be patients with a history of heart disease ($P < 0.001$) or continuous chest pain ($P < 0.001$). Survival when 911 was called in response to symptoms was 32.1% (95% CI, 21.8% to 42.4%) compared with 6.0% (CI, 3.5% to 8.5%) in those who did not call ($P < 0.001$).

Limitation: Potential for recall and response bias, symptom assessment not available in 24% of patients, and missing data for some patients and SCA characteristics.

Conclusion: Warning symptoms frequently occur before SCA, but most are ignored. Emergent medical care was associated with survival in patients with symptoms, so new approaches are needed for short-term prevention of SCA.

Primary Funding Source: National Heart, Lung, and Blood Institute.

Ann Intern Med. doi:10.7326/M14-2342 www.annals.org
For author affiliations, see end of text.
This article was published online first at www.annals.org on 22 December 2015.
* Drs. Marijon and Uy-Evanado contributed equally to this work.

Sudden cardiac arrest (SCA) is commonly perceived by the lay and medical communities as a sudden unexpected collapse. With more than 550 000 U.S. patients having out-of-hospital and in-hospital SCA annually, SCA accounts for more than half of cardiovascular deaths and is a major public health issue (1, 2).

Survival after SCA remains very low and stable (approximately 7%), despite major investments by the medical and research communities in SCA over the past decades (3). Further, methods to improve prediction of patients at long-term risk for SCA are lacking; therefore, alternative approaches aimed at preemptive risk stratification and prevention are needed (1, 4, 5). Sentinel events preceding SCA may be of special interest in light of recent advances in communication and remote transmission technologies (6, 7). We hypothesized that “warning events” in the hours, days, and weeks before SCA might identify a subgroup of patients with SCA in whom timely and early intervention could affect outcomes.

Investigation of SCA remains particularly challenging because most patients die in the field, so the information collected by emergency medical services (EMS) is often restricted to data about the resuscitation process. Details of the medical history of patients with SCA (especially those who cannot be resuscitated) are thus usually sparse and very rarely considered systematically. In the Oregon SUDS (Sudden Unexpected Death

Study), we collected information on symptoms and clinical history for all patients with SCA, including those who died before reaching the hospital.

We therefore conducted a comprehensive assessment of warning symptoms in the 4 weeks before SCA in a large prospective community-based study of deceased and surviving patients with SCA in the Portland, Oregon, metropolitan area. We hypothesized that the presence of and response to warning symptoms may be associated with better survival from SCA.

METHODS

Setting, Definitions, and Survey Methods

Oregon SUDS is an ongoing community-based prospective study of out-of-hospital SCA. Detailed methods have been published previously (8–11). Briefly, since 1 February 2002, cases of SCA in the Portland area were identified using several sources that included a 2-tiered EMS system, the medical examiner’s office, and emergency departments of all local hospitals. This study was approved by the relevant institutional review boards of Cedars-Sinai Medical Center,

See also:
Summary for Patients 1

EDITORS' NOTES**Context**

Because many persons do not survive sudden cardiac arrest (SCA), we need better ways to prevent it.

Contribution

The researchers collected information about the 4 weeks before SCA from survivors, family members, friends, medical records, and emergency response records. About one half of patients with information had warning symptoms in those 4 weeks that often recurred during the 24 hours before SCA. Most patients ignored their symptoms.

Caution

Information was not available for about one quarter of patients.

Implication

Warning symptoms may provide an opportunity to prevent SCA.

Los Angeles, California, and Oregon Health & Science University, Portland, Oregon.

We defined SCA as an unexpected loss of pulse, without obvious extracardiac cause, and rapid collapse with specific resuscitation records available. We excluded SCAs occurring in a patient with a prior terminal condition, such as cancer that was not in remission or end-stage chronic obstructive lung disease. At the time of adjudication, 3 physicians had access to lifetime medical history with all available hospital and outpatient medical records, including information on prior symptoms.

Variables considered in the present analysis included demographics, circumstances of occurrence, and resuscitation data according to the revised Utstein style (12). In addition to the data from EMS and the medical examiner, an Oregon SUDS working group collected and assessed the lifetime medical history for deceased patients and survivors, including symptom assessment before SCA, by reviewing records of all inpatient and outpatient visits from the Portland area hospitals. The principal outcome was survival to hospital discharge; such data were available for all decedents and survivors.

Assessment of Symptoms Before SCA

Symptoms and their frequency were characterized during the 4 weeks before SCA among patients aged 35 to 65 years, and adjudicated from February 2002 to February 2012. The data on symptoms were collected by the Oregon SUDS investigators based on information documented by the EMS team (in the field), intensivists or cardiologists (at 16 hospitals), and physicians (in the community). Symptom assessment recorded on the EMS prehospital care report was derived from several sources, including information provided by family

at the scene, witnesses, and survivors of SCA. In addition, available hospital and outpatient medical records for all patients were systematically analyzed for information about symptoms.

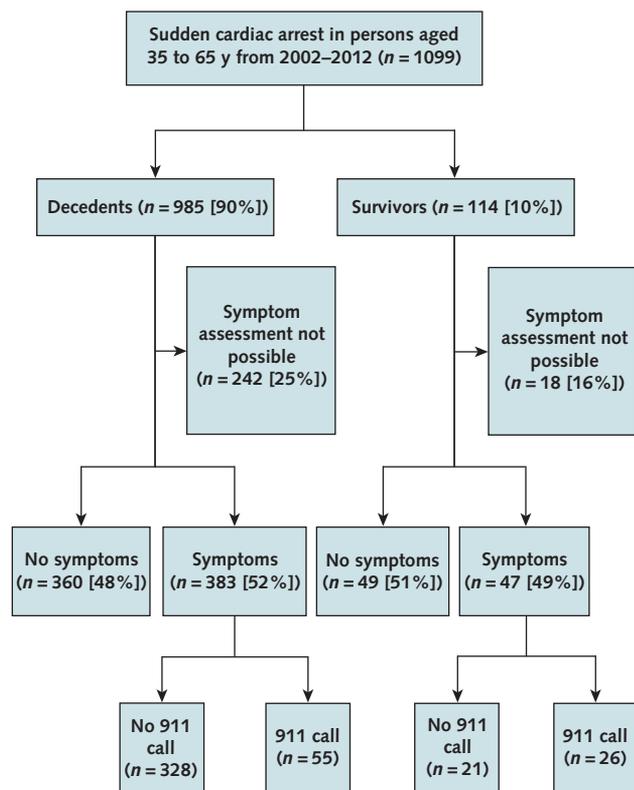
Symptoms were categorized as absent, present, or not evaluable based on the extent of information available and the agreement of investigators. Symptoms were considered "absent" when there was no record of any medical consultation during the 4 weeks preceding SCA, at least 1 of the other sources specifically ascertained the absence of any symptoms, and none of the other sources reported any symptoms. Symptoms were considered "present" if they were documented by at least 1 of the sources. Of note, symptoms starting immediately before SCA (symptoms with instantaneous collapse) were considered "no symptoms" because they would have been unlikely to lead to any early intervention.

Symptoms were classified as chest pain (subclassified as typical and atypical), dyspnea, palpitations, syncope, and other (including abdominal pain, nausea or vomiting, back pain, and miscellaneous symptoms). Finally, the presence of ongoing typical influenza-like symptoms was also evaluated. In cases of multiple symptoms (combined symptoms), chest pain was designated as the principal symptom when present. Time intervals from the onset of a symptom to SCA were categorized into 4 groups where possible (98%): within the first hour, 24 hours or less, 7 days or less, and 4 weeks or less before SCA.

Symptoms were considered "not acted on" if patients, relatives, or witnesses did not attempt to contact EMS (911) in response to symptoms that occurred before SCA.

Statistical Analysis

This report was prepared in compliance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist for observational studies (13, 14). The characteristics of SCA were reported as means (SDs), proportions, medians, and interquartile ranges as appropriate. Comparisons between groups used the chi-square test for categorical variables and the *t* test for continuous variables. A logistic regression model was used to compare survival to hospital discharge by 911 call in patients with symptoms. Covariates included age, sex, and meaningful independent variables according to Utstein guidelines (12). Missing values for covariates were accounted for using multiple imputations (*mi impute* command in Stata, version 11.0 [StataCorp]) by chained equations. Imputation models included terms for age, sex, location, witnessed and cardiopulmonary resuscitation status, initial rhythm, timing, onset, diabetes, dyslipidemia, body mass index, hypertension, current smoking, coronary artery disease, time to intervention, and the outcome. We used 10 imputations and Rubin rules to combine the results (15, 16). The results were similar to those from a complete-case analysis, so only results using multiply imputed data are presented as primary results. Sensitivity analyses were done to assess the rela-

Figure 1. Study flow diagram.

tionship between survival and a 911 call, with additional adjustment for possible confounding due to the hospital or period (before and after 2005). Differences were assumed to be statistically significant for a 2-tailed probability ($P \leq 0.05$). We calculated 95% CIs when appropriate. All data were analyzed using STATA software.

Role of Funding Source

The National Heart, Lung, and Blood Institute provided funding for the study. The funding source had no role in the design, conduct, and analysis of the study or in the decision to submit the manuscript for publication.

RESULTS

Frequency of Warning Signs and Associated Characteristics

Sixteen hospitals in the Portland area were included, with the median number of patients per hospital of 71 (IQR, 56 to 81). Overall, symptom data were not available for analysis in 260 patients (24%) because of insufficient or conflicting documentation (Figure 1 and Appendix Table 1, available at www.annals.org). Reasons for not having symptom data included the absence of witnesses and relatives before and at the time of SCA and no medical report recorded in the area during the previous 4 weeks (166 patients); witnesses

or relatives could not provide clear information in the absence of a specific medical record (69 patients); information on symptoms provided by patients, witnesses, or relatives considered as being too nonspecific to make definite conclusions (23 patients); and brain injury with significant cognitive dysfunction (2 patients). Patients without symptom assessment were more likely to not have a witness (65.4% vs. 43.3%) (Appendix Table 2, available at www.annals.org). The most common source for symptom information was the Oregon EMS personnel, in 766 patients (91%) overall (Appendix Table 1), who were trained to gather important information in the field.

Of the 839 patients with symptom assessment, 430 patients (51%) presented with at least 1 symptom within the 4 weeks before SCA (Figure 1), with similar frequency in men and women (50% vs. 53%; $P = 0.59$). Of the 430 patients with symptoms, 51 had consulted a family or specialist physician during the 4 weeks before SCA.

Patient characteristics according to the presence or absence of warning symptoms are described in Table 1. Overall, characteristics of patients with and without symptoms before SCA were similar, including medical history. Patients with symptoms (vs. no symptoms) were more likely to be at home at the time of SCA (76% vs. 64%; $P < 0.001$). Response times (between 911 call and EMS arrival) were similar in both groups (mean [SD], 6.9 [4.1] minutes vs. 7.0 [3.2] minutes; $P = 0.73$), without a significant difference in the proportion with initial shockable rhythm (49% vs. 52%; $P = 0.40$).

Characteristics of Symptoms and Temporal Pattern

The onset of cardiovascular symptoms is summarized in Figure 2. In 334 patients (80%), symptoms started more than 1 hour before SCA, including 147 with onset more than 24 hours before SCA. Among those, 136 (93%) had recurrent new episodes of symptoms during the 24 hours preceding SCA.

The main symptom was chest pain, documented in 199 patients (46%), 151 (76%) of whom had intermittent typical angina. Coronary heart disease was previously identified in 28% of those with chest pain. Dyspnea was present in 78 patients (18%). Of these, 32% previously had congestive heart failure or pulmonary conditions. Syncope or palpitations were found in 22 patients (5%), with the first episode homogeneously distributed during the 4-week period. In 86 patients (20%), symptoms were related to abdominal or other complaints. Finally, typical ongoing influenza-like symptoms were reported in 41 patients (10%). A significant overlap of symptoms was observed, notably chest pain and dyspnea; 65 patients (33%) with chest pain developed concomitant acute dyspnea before SCA. Among those without chest pain, none presented with more than 1 symptom.

The pattern of symptoms significantly differed between men and women (Table 2); men had more chest pain and women had more dyspnea ($P < 0.001$). When the analysis was restricted to cases of SCA with docu-

Table 1. Characteristics of Patients With SCA Based on Presence or Absence of Symptoms Before the Event*

Characteristic	Absence of Symptoms (n = 409)	Presence of Symptoms (n = 430)	P Value
Demographic data			
Mean age (SD), y	52.5 (8)	52.6 (8)	0.84
Male	298 (76.0)	320 (74.4)	0.59
Timing of SCA			
Night (midnight-5:59 a.m.)	21 (11.2)	40 (17.2)	0.120†
Morning (6:00-11:59 a.m.)	52 (27.8)	71 (30.4)	
Afternoon (noon-5:59 p.m.)	57 (30.5)	62 (26.6)	
Evening (6:00-11:59 p.m.)	57 (30.5)	60 (25.8)	
Missing	222	197	
Type of symptoms			
Chest pain	-	199 (46.3)	
Dyspnea	-	78 (18.1)	
Syncope/palpitation	-	22 (5.6)	
Others	-	127 (29.5)	
Missing	-	4	
≥2 known cardiovascular risk factors			
Diabetes mellitus	108 (27.5)	95 (23.0)	0.170†
Missing	16	16	
Dyslipidemia	115 (29.3)	117 (28.3)	0.75†
Missing	16	16	
Systemic hypertension	192 (48.9)	196 (47.3)	0.72†
Missing	16	16	
Mean body mass index, kg/m ²	31.2 (8)	31.7 (9)	0.69†
Missing	105	105	
Current smoker	148 (53.6)	204 (64.1)	0.010†
Missing	133	112	
Known heart disease			
CAD	82 (29.4)	105 (24.4)	0.31
Heart failure	61 (21.9)	63 (19.9)	0.56
Atrial fibrillation	36 (12.9)	32 (10.2)	0.29
Pacemaker	6 (2.1)	2 (0.7)	0.110
≥2 known cardiovascular risk factors and/or heart disease			
	246 (60.2)	280 (65.1)	0.140
CAD-related SCA			
Missing	145	134	0.160†

CAD = coronary artery disease; SCA = sudden cardiac arrest.

* Values are numbers (percentages) unless otherwise indicated. Percentages were calculated on the basis of the total number of known events.

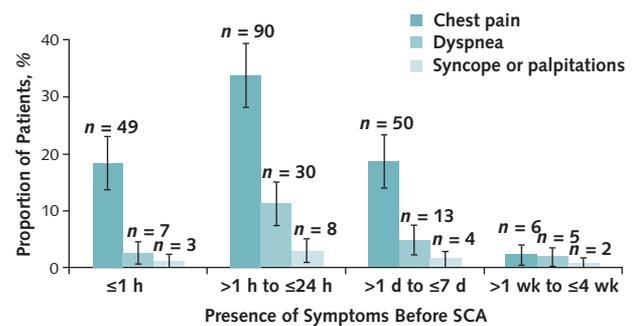
† Obtained by using multiple imputation to account for missing data.

mented coronary artery disease, women still had a lower frequency of chest pain (32% vs. 58%; *P* = 0.001).

Response to Symptoms and Relationship With Survival Outcome

Among the 430 patients with symptoms, 81 (19%) called EMS before SCA (Figure 1). Characteristics of patients based on their decision to call 911 are summarized in Table 3. Older age (*P* = 0.020) and a history of heart disease (*P* = 0.001) were associated with 911 calls. Symptoms suggestive of cardiovascular conditions, especially continuous chest pain, were more likely to be associated with 911 calls than all other symptoms (69% vs. 15%; *P* < 0.001).

Figure 2. Warning symptoms in patients with SCA based on period between onset of symptoms and occurrence of SCA.



Information about the timing of symptom onset was available in 267 of 299 patients with chest pain, dyspnea, or syncope or palpitations. Error bars correspond to 95% CIs. SCA = sudden cardiac arrest.

Among the 81 patients with symptoms who made a 911 call, 63 (78%) developed SCA before the arrival of emergency medical responders, whereas 18 (22%) had SCA in the ambulance on the way to the hospital. Compared with patients who did not call 911 before SCA, those who called had witnesses more often (*P* = 0.001), a higher proportion of bystander cardiopulmonary resuscitation (*P* = 0.001), and a higher rate of initially shockable rhythm (*P* = 0.02).

Survival to hospital discharge was 32.1% (95% CI, 21.8% to 42.4%) compared with 6.0% (CI, 3.5% to 8.5%) in patients who did not call 911 (*P* < 0.001). After adjustment for differences in patients and resuscitation variables, and multiple imputation for missing data, a 911 call remained significantly associated with survival to hospital discharge (odds ratio [OR], 4.82 [CI, 2.23 to 10.43]; *P* < 0.001) (Appendix Table 3, available at www.annals.org). A sensitivity analysis using complete-case analysis found a significant association (OR, 3.27 [CI, 1.37 to 7.79]; *P* = 0.008) as did analyses that controlled for potential confounding due to the hospital (OR, 3.35 [CI, 1.47 to 7.65]; *P* = 0.004) and periods before and after 2005 (OR, 5.64 [CI, 2.59 to 12.43]; *P* = 0.001).

DISCUSSION

To our knowledge, this study is the first comprehensive evaluation of symptoms in the 4 weeks preced-

Table 2. Warning Symptoms Among Patients With SCA, by Sex*

Symptom	Men (n = 320)	Women (n = 110)	Total
Chest pain	173 (54)	26 (24)	199
Dyspnea	45 (14)	33 (31)	78
Syncope or palpitation	14 (4)	8 (7)	22
Other	58 (18)	28 (25)	86
Influenza-like symptoms	28 (9)	13 (12)	41

SCA = sudden cardiac arrest.

* Values are numbers (percentages). Data were missing (specific types of symptoms were not assessable) in 4 patients (2 men and 2 women).

Table 3. Characteristics and Circumstances of SCA Based on Whether 911 Was Called in Response to Symptoms*

Variable	911 Call (n = 81)	No 911 Call (n = 349)	P Value
Study period			0.41
2002-2005	52 (64.2)	198 (56.7)	
2006-2009	18 (22.2)	103 (29.5)	
2010-2012	11 (13.6)	48 (13.8)	
Demographic data			
Mean age (SD), y	54.2 (7)	52.2 (8)	0.020
Male	61 (75.3)	259 (74.2)	0.84
Timing of SCA			0.90†
Night (midnight-5:59 a.m.)	11 (17.7)	29 (17.0)	
Morning (6:00-11:59 a.m.)	16 (25.8)	55 (32.1)	
Afternoon (noon-5:59 p.m.)	20 (32.3)	42 (24.6)	
Evening (6:00-11:59 p.m.)	15 (24.2)	45 (26.3)	
Missing	19	178	
Known heart disease			
CAD	45 (55.6)	114 (32.7)	<0.001
	28 (34.8)	77 (22.1)	0.010
Type of symptoms			<0.001
Chest pain	45 (55.6)	154 (44.6)	
Dyspnea	23 (28.4)	55 (15.9)	
Syncope/palpitation	6 (7.4)	16 (4.6)	
Others	7 (8.6)	120 (34.8)	
Missing	0	4	
Onset of symptoms			0.56†
≤1 h	21 (28.8)	57 (17.9)	
≤1 d	32 (43.8)	142 (44.5)	
≤1 wk	17 (23.3)	108 (33.8)	
≤1 mo	3 (4.1)	12 (3.8)	
Missing	8	30	
Home occurrence			<0.001†
Missing	0	2	
Witnessed status			<0.001†
No witness	7 (8.6)	164 (47.4)	
Witnessed without CPR	43 (53.1)	135 (39.0)	
Witnessed with CPR	31 (38.3)	47 (13.6)	
Missing	0	3	
Mean time from call to EMS arrival (SD), min			0.67†
Missing	16	133	
Rhythm			0.020†
Ventricular fibrillation/tachycardia	42 (58.4)	112 (45.7)	
Pulseless electrical activity	25 (34.7)	60 (24.5)	
Asystole	5 (6.9)	73 (29.8)	
Missing	10	103	

CAD = coronary artery disease; CPR = cardiopulmonary resuscitation; EMS = emergency medical services; SCA = sudden cardiac arrest.

* Values are numbers (percentages) unless otherwise indicated. Percentages were calculated on the basis of the total number of known events.

† Obtained by using multiple imputation to account for missing data.

ing SCA. The findings can be summarized as several key points. First, there is a relatively high frequency of warning signs in middle-aged persons when evaluation is extended to the 4 weeks preceding SCA. Second, these symptoms seem to be frequently ignored or minimized by patients in the community, with at least two thirds of affected patients not seeking urgent medical care, given that most symptoms recurred during the

24-hour period before SCA. Finally, our findings suggest that an early 911 call among patients with symptoms is associated with better survival because in most patients, symptoms recurred in the hours immediately preceding SCA. These findings suggest the potential to enhance short-term prevention of SCA in the future.

The term “sudden” has classically suggested that collapse occurred without warning. Although previous community-based studies that investigated the circumstances before SCA have documented the early warning symptoms in some patients (17, 18), they were mainly focused on symptoms occurring very shortly before SCA was witnessed. Further, findings were limited to those collected in the field by EMS providers and probably underestimated the potential window for timely intervention. Of note, most of our patients with symptoms who eventually developed SCA did not call 911. This is a noteworthy finding because most patients (>90%) who had symptoms during the days and weeks before SCA also had recurrent symptoms in the hours before the event. Not surprisingly, patients with continuous symptoms or with known heart disease seem more likely to call 911, probably because of a better awareness of warning signs. However, two thirds of such patients did not call 911, so there is room for improvement (19).

Our findings emphasize the need to encourage efforts that target public awareness of SCA as a largely fatal event. It is important to reinforce knowledge of prodromal symptoms of SCA in the general public and in patients affected by heart disease and their family members. The recent impressive advances in mobile telecommunication technologies could help improve the management of patients with SCA who have warning symptoms, potentially affording a unique opportunity for early intervention (6). This may be particularly helpful in patients with known heart disease because instant transmission of point-of-care electrocardiograms and the development of automated algorithms could enable comparison with baseline recordings stored in a mobile device (6, 7). Further, using immediate geolocalization to find the closest automatic external defibrillator is technically feasible and potentially beneficial in this setting. Thus, targeted public education to enhance timely reporting of symptoms and develop appropriate response strategies may lead to new paradigms for short-term prevention of SCA. Our results also show that 12% of patients had consulted a physician within the 30 days before SCA and received a systematic work-up. These results show the intrinsic difficulty in estimating the risk for SCA, even in symptomatic patients, and should motivate more focused investigation.

Unlike what has been previously suggested about women (20, 21), a significant proportion of women in our study had cardiac symptoms in the weeks before SCA. The overall frequency of symptoms was similar between men and women, which challenges to some extent the traditional concept that SCA may be more difficult to predict or prevent in women. The pattern of symptoms differed significantly, however, with chest

pain occurring less often in women, even when our analysis was restricted to cases with definite coronary artery disease. These results seem consistent with recent findings about sex differences in sentinel symptoms before myocardial infarction (22-24).

Although the concept that an early call to EMS improves survival seems intuitive, our findings emphasize that patients who called 911 before SCA had witnesses more often (22% had SCA in front of EMS personnel), a higher rate of cardiopulmonary resuscitation, and a higher rate of initially shockable rhythm. All of these factors have been associated with better survival (3). An early 911 call remains associated with better survival after multiple adjustments on patient characteristics and the circumstances of SCA, so the mechanisms of this association need further investigation.

Preexisting symptoms correlate with a higher chance of initially shockable rhythms (ventricular fibrillation or tachycardia vs. pulseless electrical activity or asystole), and there are 3 possible factors. Studies (25) suggest that the patterns of prodromal symptoms we observed before sudden death (out of hospital) are similar to symptoms observed before nonfatal myocardial infarction; therefore, a high proportion of patients probably had coronary ischemia. We and others (26) have previously reported a higher likelihood of shockable rhythms in patients with coronary disease. Finally, the higher frequency of witnessed events and bystander cardiopulmonary resuscitation, especially in the group that called 911, probably contributed to the higher prevalence of shockable rhythms in patients with preexisting symptoms (27).

Although our results are derived from a unique and comprehensive survey of survivors of SCA and decedents, several limitations warrant consideration. First, because symptom ascertainment was not possible for 24% of our population, there is a potential for bias. In addition, data for many potential confounders were missing. Multiple imputation was used to handle data that were missing for the covariates. Second, our population comprised patients who eventually developed SCA, so the benefit of any early symptom alerts on outcomes may be underestimated because many patients with symptoms and timely and appropriate medical management may not have developed SCA. Third, the specificity of identified symptoms, possibly in combination with other factors, to predict imminent SCA needs further evaluation to improve short-term risk stratification. The ultimate goal would be to optimize triage by EMS or other health care providers. In this regard, our preliminary findings suggest that chest pain and dyspnea may frequently occur together; this seems to agree with previous reports indicating that acute heart failure and myocardial ischemia increases the risk for ventricular arrhythmias (28). Fourth, although EMS remain the most important source of information collected on site, and EMS personnel of the Portland area have systematically received specialized training for information gathering in the setting of SCA since the early 1990s, our results on the proportion of patients with symptoms may be subject to some recall and re-

sponse bias. However, the influence of this potential response bias is probably low because in the setting of SCA both in general and in this evaluation, the proportion of survivors included in the symptom assessment is small (5.6% in our study). Further, the influence of symptoms (leading to an earlier 911 call) on survival is unlikely to be significantly affected by this bias because information on 911 calls was directly ascertained from the EMS system and did not rely on patient or family recall. Finally, this observational study cannot establish a causal association between an early 911 call and survival. The underlying mechanisms behind this association need further investigation.

In summary, a high proportion of middle-aged men and women in the community had warning symptoms before SCA, but most symptoms were ignored. Because a timely response to such symptoms was associated with an increase in survival, our results highlight the potential importance of developing new community-based strategies for short-term prevention of SCA. Further studies are needed to improve risk stratification among patients with symptoms as well as investigations of whether early intervention based on symptoms may improve outcomes or even prevent SCA.

From Cedars-Sinai Medical Center, Los Angeles, California; Paris Descartes University and European Georges Pompidou Hospital, Paris, France; and Oregon Health & Science University, Portland, Oregon.

Acknowledgment: The authors thank all EMS personnel (American Medical Response and Portland and Gresham fire departments), the Oregon State Medical Examiner's Office, and hospitals in the Portland metropolitan area for their assistance; and Dr. Wulfran Bougouin (Paris Sudden Death Expertise Center, Paris, France) and Prof. David S. Celermajer (Sydney Medical School, Sydney, Australia) for their critical review of the manuscript.

Grant Support: In part by the National Heart, Lung, and Blood Institute (grants R01HL105170 and R01HL122492; Dr. Chugh). Dr. Marijon was a visiting faculty scientist at the Cedars-Sinai Heart Institute funded by research grant support from the Philip Foundation, Bettencourt Schueller Foundation, French Society of Cardiology, Foundation for Medical Research, and French National Institute of Health and Medical Research.

Disclosures: Dr. Chugh reports grants from the National Heart, Lung, and Blood Institute. Dr. Marijon reports grants from the Philip Foundation, Bettencourt Schueller Foundation, French Society of Cardiology, Foundation for Medical Research, Fondation Coeur et Artères, and French National Institute of Health and Medical Research outside the submitted work. Authors not named here have disclosed no conflicts of interest. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M15-2342.

Reproducible Research Statement: *Study protocol:* Available from Dr. Chugh (e-mail, sumeet.chugh@cshs.org). *Statistical code and data set:* Not available.

Warning Symptoms and Sudden Cardiac Arrest

Requests for Single Reprints: Sumeet S. Chugh, MD, Cedars-Sinai Medical Center, Heart Institute, Advanced Health Sciences Pavilion, Suite A3100, 127 South Vicente Boulevard, Los Angeles, CA 90048; e-mail, sumeet.chugh@cshs.org.

Current author addresses and author contributions are available at www.annals.org.

References

- Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2014 update: a report from the American Heart Association. *Circulation*. 2014;129:e28-e292. [PMID: 24352519]
- Adabag AS, Luepker RV, Roger VL, Gersh BJ. Sudden cardiac death: epidemiology and risk factors. *Nat Rev Cardiol*. 2010;7:216-25. [PMID: 20142817]
- Sasson C, Rogers MA, Dahl J, Kellermann AL. Predictors of survival from out-of-hospital cardiac arrest: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes*. 2010;3:63-81. [PMID: 20123673]
- Pauker SG, Estes NA, Salem DN. Preventing sudden cardiac death: can we afford the benefit? [Editorial]. *Ann Intern Med*. 2005;142:664-6. [PMID: 15838073]
- Achtelik M. Preventing sudden cardiac death [Letter]. *Ann Intern Med*. 2005;143:756; author reply 756. [PMID: 16287802]
- Steinhubl SR, Muse ED, Topol EJ. Can mobile health technologies transform health care? *JAMA*. 2013;310:2395-6. [PMID: 24158428]
- Topol EJ. Transforming medicine via digital innovation. *Sci Transl Med*. 2010;2:16cm4. [PMID: 20371472]
- Noheria A, Teodorescu C, Uy-Evanado A, Reinier K, Mariani R, Gunson K, et al. Distinctive profile of sudden cardiac arrest in middle-aged vs. older adults: a community-based study. *Int J Cardiol*. 2013;168:3495-9. [PMID: 23684602]
- Chugh SS, Jui J, Gunson K, Stecker EC, John BT, Thompson B, et al. Current burden of sudden cardiac death: multiple source surveillance versus retrospective death certificate-based review in a large U.S. community. *J Am Coll Cardiol*. 2004;44:1268-75. [PMID: 15364331]
- Narayanan K, Reinier K, Uy-Evanado A, Teodorescu C, Chugh H, Marijon E, et al. Frequency and determinants of implantable cardioverter defibrillator deployment among primary prevention candidates with subsequent sudden cardiac arrest in the community. *Circulation*. 2013;128:1733-8. [PMID: 24048201]
- Teodorescu C, Reinier K, Uy-Evanado A, Ayala J, Mariani R, Wittwer L, et al. Survival advantage from ventricular fibrillation and pulseless electrical activity in women compared to men: the Oregon Sudden Unexpected Death Study. *J Interv Card Electrophysiol*. 2012;34:219-25. [PMID: 22406930]
- Jacobs I, Nadkarni V, Bahr J, Berg RA, Billi JE, Bossaert L, et al; International Liaison Committee on Resuscitation. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries. A statement for healthcare professionals from a task force of the international liaison committee on resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa). *Resuscitation*. 2004;63:233-49. [PMID: 15582757]
- Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al; STROBE initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Ann Intern Med*. 2007;147:W163-94. [PMID: 17938389]
- Vandenbroucke JP. The making of STROBE. *Epidemiology*. 2007;18:797-9. [PMID: 18049193]
- White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med*. 2011;30:377-99. [PMID: 21225900]
- Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009;338:b2393. [PMID: 19564179]
- Nishiyama C, Iwami T, Kawamura T, Kitamura T, Tanigawa K, Sakai T, et al. Prodromal symptoms of out-of-hospital cardiac arrests: a report from a large-scale population-based cohort study. *Resuscitation*. 2013;84:558-63. [PMID: 23069588]
- Müller D, Agrawal R, Arntz HR. How sudden is sudden cardiac death? *Circulation*. 2006;114:1146-50. [PMID: 16952983]
- Meischke H, Dulberg EM, Schaeffer SS, Henwood DK, Larsen MP, Eisenberg MS. 'Call fast, Call 911': a direct mail campaign to reduce patient delay in acute myocardial infarction. *Am J Public Health*. 1997;87:1705-9. [PMID: 9357360]
- Kannel WB, Wilson PW, D'Agostino RB, Cobb J. Sudden coronary death in women. *Am Heart J*. 1998;136:205-12. [PMID: 9704680]
- Albert CM, Chae CU, Grodstein F, Rose LM, Rexrode KM, Ruskin JN, et al. Prospective study of sudden cardiac death among women in the United States. *Circulation*. 2003;107:2096-101. [PMID: 12695299]
- Graham MM, Westerhout CM, Kaul P, Norris CM, Armstrong PW. Sex differences in patients seeking medical attention for prodromal symptoms before an acute coronary event. *Am Heart J*. 2008;156:1210-1216.e1. [PMID: 19033022]
- Moriel M, Gavrielov-Yusim N, Gottlieb S. Cardiac symptoms in women and men [Letter]. *JAMA Intern Med*. 2013;173:1929. [PMID: 24217383]
- Khan NA, Daskalopoulou SS, Karp I, Eisenberg MJ, Pelletier R, Tsadok MA, et al; GENESIS PRAXY Team. Sex differences in acute coronary syndrome symptom presentation in young patients. *JAMA Intern Med*. 2013;173:1863-71. [PMID: 24043208]
- Alonzo AA, Simon AB, Feinleib M. Prodromata of myocardial infarction and sudden death. *Circulation*. 1975;52:1056-62. [PMID: 1182949]
- Teodorescu C, Reinier K, Dervan C, Uy-Evanado A, Samara M, Mariani R, et al. Factors associated with pulseless electric activity versus ventricular fibrillation: the Oregon sudden unexpected death study. *Circulation*. 2010;122:2116-22. [PMID: 21060069]
- Cobb LA, Weaver WD, Fahrenbruch CE, Hallstrom AP, Copass MK. Community-based interventions for sudden cardiac death. Impact, limitations, and changes. *Circulation*. 1992;85:198-102. [PMID: 1728511]
- Bouguin W, Marijon E, Puymirat E, Defaye P, Celermajer DS, Le Heuzey JY, et al; FAST-MI Registry Investigators. Incidence of sudden cardiac death after ventricular fibrillation complicating acute myocardial infarction: a 5-year cause-of-death analysis of the FAST-MI 2005 registry. *Eur Heart J*. 2014;35:116-22. [PMID: 24258072] doi:10.1093/eurheartj/eh453

Current Author Addresses: Drs. Marijon, Dumas, Karam, and Jouven: Cardiology Department, European Georges Pompidou Hospital, 20-40 rue Leblanc, 75908 Paris Cedex 15, France.

Drs. Uy-Evanado, Reinier, Teodorescu, Narayanan, and Chugh: Cedars-Sinai Medical Center, Heart Institute, Advanced Health Sciences Pavilion, Suite A3100, 127 South Vicente Boulevard, Los Angeles, CA 90048.

Dr Dumas: Departement of Emergency Medicine, Cochin Hospital, 27 Rue du Faubourg Saint-Jacques, 75014 Paris, France.

Dr. Gunson: Department of Pathology, Oregon Health & Science University, 3181 Southwest Sam Jackson Park Road, Portland, OR 97239.

Dr. Jui: Department of Emergency Medicine, Oregon Health & Science University, 3181 Southwest Sam Jackson Park Road, Portland, OR 97239.

Author Contributions: Conception and design: E. Marijon, J. Jui, S.S. Chugh.

Analysis and interpretation of the data: E. Marijon, F. Dumas, N. Karam, K. Narayanan, S.S. Chugh.

Drafting of the article: E. Marijon, N. Karam, S.S. Chugh.

Critical revision of the article for important intellectual content: E. Marijon, N. Karam, K. Reinier, K. Narayanan, J. Jui, X. Jouven, S.S. Chugh.

Final approval of the article: E. Marijon, F. Dumas, N. Karam, K. Reinier, S.S. Chugh.

Provision of study materials or patients: K. Gunson, J. Jui, S.S. Chugh.

Statistical expertise: E. Marijon, F. Dumas, N. Karam, K. Reinier, X. Jouven.

Obtaining of funding: S.S. Chugh.

Administrative, technical, or logistic support: J. Jui.

Collection and assembly of data: A. Uy-Evanado, C. Teodorescu, J. Jui, S.S. Chugh.

Appendix Table 1. Primary Sources for SCA Symptom Information*

Variable	Value, n (%)
Patients with 1 source	602 (72)
EMS	549
ICU	39
Cardiology	8
Physician consult	6
Patients with 2 sources	137 (17)
EMS + ICU	80
EMS + physician consult	45
Cardiology + ICU	12
Patients with > 2 sources	92 (11)
EMS + ICU + cardiology	92

EMS = emergency medical services; ICU = intensive care unit; SCA = sudden cardiac arrest.

* Identification of sources of information was possible in 831 (out of 839).

Appendix Table 2. Patient Characteristics and Circumstances of SCA, by Symptom Assessment*

Variable	Patients Without Symptom Assessment (n = 260)	Patients With Symptom Assessment (n = 839)	P Value
Demographic data			
Mean age (SD), y	54.1 (7)	52.6 (8)	0.04
Male	194 (74.6)	631 (75.2)	0.85
Timing of SCA			
Night (midnight to 5:59 a.m.)	14 (14.3)	61 (14.5)	0.15
Morning (6:00-11:59 a.m.)	25 (25.5)	123 (29.3)	
Afternoon (noon-5:59 p.m.)	39 (39.8)	119 (28.3)	
Evening (6:00-11:59 p.m.)	20 (20.4)	117 (25.9)	
Missing	162	419	
≥2 known cardiovascular risk factors			
Missing	7	4	0.39
Known heart disease			
CAD	95 (36.5)	301 (35.9)	0.85
	53 (20.4)	198 (23.6)	0.28
≥2 known cardiovascular risk factors and/or heart disease			
	167 (64.2)	526 (62.7)	0.65
CAD-related SCA			
Missing	111 (79.9)	458 (80.5)	0.08
	121	279	
Home occurrence			
Missing	162 (62.8)	586 (70.2)	0.03
	2	4	
Witnessed status			
No witness	168 (65.4)	361 (43.3)	<0.001
Witnessed without CPR	58 (22.6)	301 (36.1)	
Witnessed with CPR	31 (12.1)	172 (20.6)	
Missing	3	5	
Mean time from call to EMS arrival (SD), min			
Missing	6.9 (3)	6.9 (4)	0.80
	91	296	
Rhythm			
Ventricular fibrillation/tachycardia	78 (44.1)	312 (50.2)	0.56
Missing	83	218	0.15

CAD = coronary artery disease; CPR = cardiopulmonary resuscitation; EMS = emergency medical services; SCA = sudden cardiac arrest.

* Values are numbers (percentages) unless otherwise indicated.

Appendix Table 3. Independent Factors Associated With Survival to Hospital Discharge*

Variable	OR (95% CI)	P Value
Age (per 1-y increase)	1.06 (1.0-1.12)	0.04
Male sex	0.31 (0.14-0.76)	0.01
Time of intervention (per 1-min increase)	0.98 (0.88-1.09)	0.68
Witnessed status		
Not witnessed	1.00	
Witnessed	3.28 (0.90-11.90)	0.07
Witnessed and bystander CPR	4.28 (1.32-13.77)	0.02
Public location	1.62 (0.95-2.78)	0.08
Shockable rhythm	16.21 (5.48-47.90)	<0.001
911 call before SCA	4.82 (2.23-10.44)	<0.001

CPR = cardiopulmonary resuscitation; OR = odds ratio; SCA = sudden cardiac arrest.

* Missing values (time to intervention, witnessed status, public location, and shockable rhythm) were imputed using multiple imputations by chained equations.