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Prospective Countywide Surveillance and Autopsy Characterization of Sudden Cardiac Death: The San Francisco POstmortem Systematic InvesTigation of Sudden Cardiac Death (POST SCD) Study

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Abstract

Background—Studies of out-of-hospital cardiac arrest (OHCA) and sudden cardiac death (SCD) use emergency medical systems (EMS) records, death certificates, or definitions that infer cause of death, thus its true incidence is unknown. Over 90% of SCDs occur out-of-hospital; non-forensic autopsies are rarely performed therefore causes of death are presumed. We conducted a medical examiner (ME)-based investigation to determine the precise incidence and autopsy-defined causes

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of all SCDs in an entire metropolitan area. We hypothesized that postmortem investigation would identify actual sudden arrhythmic deaths (SADs) among presumed SCDs.

Methods—Between 2/1/2011-3/1/2014 we prospectively identified all incident deaths due to OHCA (EMS primary impression cardiac arrest) ages 18-90 in San Francisco County for autopsy, toxicology, and histology via ME surveillance of consecutive out-of-hospital deaths, all reported by law. We obtained comprehensive records to determine whether OHCA deaths met World Health Organization (WHO) criteria for SCD. We reviewed death certificates filed quarterly for missed SCDs. Autopsy-defined SADs had no extra-cardiac cause of death or acute heart failure. A multidisciplinary committee adjudicated final cause.

Results—All 20,440 deaths were reviewed; 12,671 were unattended and reported to the ME. From these, we identified 912 OHCA deaths; 541 (59%) met WHO SCD criteria (mean 62.8 years, 69% male) and 525 (97%) were autopsied. Eighty-nine additional WHO-defined SCDs occurred within 3 weeks of active medical care with death certificate signed by attending physician, ineligible for autopsy but included in countywide WHO-defined SCD incidence of 29.6/100,000 person-years, highest in Black men ($P<.0001$). Of 525 WHO-defined SCDs, 301 (57%) had no cardiac history. Leading causes of death were coronary disease (32%), occult overdose (13.5%), cardiomyopathy (10%), cardiac hypertrophy (8%), and neurologic (5.5%). Autopsy-defined SADs were 55.8% (293/525) of overall, 65% (78/120) of witnessed, and 53% (215/405) of unwitnessed WHO-defined SCDs ($P=.024$); 286 of 293 (98%) had structural cardiac disease.

Conclusion—Forty percent of deaths due to stated cardiac arrest were not sudden or unexpected and nearly half of presumed SCDs were not arrhythmic. These findings have implications for the accuracy of SCDs as defined by death certificates or EMS records in aggregate mortality data, clinical trials, and cohort studies.

Keywords

Epidemiology; Sudden Cardiac Death; cardiac arrest; sudden cardiac death; arrhythmia; autopsy; pathology

Introduction

Sudden cardiac death (SCD) is considered a major cause of worldwide mortality, yet incidence estimates vary widely because of variable data sources and definitions.[1, 2] Studies based on death certificate review are known to overestimate incidence due to inaccuracies in stated causes of death,[3] and investigations relying on emergency medical system (EMS) records[4] and epidemiologic definitions[5-7] presume cardiac etiology or infer cardiac cause of death. Expert panels have advocated for the use of precise and uniform definitions of SCD and to integrate multiple sources of ascertainment,[8] but non-cardiac and non-arrhythmic conditions leading to sudden death cannot be excluded without a complete autopsy.[9]

The large majority of SCDs occur out of hospital,[10] therefore are unattended and in the jurisdiction of the coroner or medical examiner. Postmortem investigation after these natural deaths is not routine coroner or medical examiner practice, due to limited local resources that are focused on accidental or possible criminal deaths. Therefore autopsy rates for out of

hospital natural deaths range from 10% in the United States[11] to 23% in some European countries.[12] Moreover, three-quarters of the 82 sudden arrhythmic deaths (SADs) that were the basis for the original Hinkle-Thaler definition did not have autopsy confirmation.[6] Exemplar autopsy studies demonstrating coronary artery disease (CAD) as the cause of approximately 80% of SCDs[13, 14] are thus limited by referral bias of the minority of total SCDs that underwent postmortem investigation. We sought to determine the precise incidence and underlying causes of all incident SCDs in San Francisco County, California via prospective medical examiner surveillance and comprehensive postmortem investigation as part of the San Francisco POstmortem Systematic invesTigation of Sudden Cardiac Death (POST SCD) Study.

Methods

The authors declare that all supporting data and analytic methods are available within the manuscript and supplemental material.

Setting

The study population included all residents and inhabitants of San Francisco County, California (population: 805,235, 46.9 sq miles).[15] Ten adult hospitals, 3 emergency medical services (EMS) agencies (with the San Francisco Fire Department responding to >85% of all 911 activations), and a single Office of the Chief Medical Examiner serve the County. All out of hospital and unattended deaths must be reported to the medical examiner by California state law. The study was approved by the UCSF IRB and had additional IRB approval at all 10 San Francisco County adult hospitals and 3 EMS agencies to obtain medical records.

Inclusion Criteria

SCD was defined by World Health Organization (WHO) criteria (WHO-defined SCD): sudden unexpected death either within 1 hour of symptom onset (event witnessed), or within 24 hours of having been observed alive and symptom free (unwitnessed).[7] Subjects otherwise meeting WHO criteria who had recent admission for myocardial infarction were included. Out of hospital cardiac arrest (OHCA) required an EMS primary impression of cardiac arrest, consistent with the Cardiac Arrest Registry to Enhance Survival (CARES).[4] OHCA Deaths were defined as (1) OHCA victims who died in the field or emergency department (ED) if the event was witnessed and/or active resuscitation was performed; or (2) unwitnessed natural deaths if the victim was last observed alive and symptom free within 24 hours, with no active resuscitation but primary EMS impression of cardiac arrest. Resuscitated OHCA victims surviving to hospital admission, whether they subsequently died as an inpatient or survived, were considered OHCA survivors rather than SCDs.

The following deaths were excluded: (1) subjects with severe non-cardiac chronic and terminal illness in which imminent death was not unexpected, including terminal cancer; (2) end-stage renal disease on dialysis; (3) hospice residents; (4) subjects with an identifiable non-cardiac etiology of death at presentation, including evidence of drug abuse/overdose at the scene (e.g., intravenous needIes, empty pill bottles), clear life-threatening trauma,

homicide, or suicide; (5) subjects who had hospital admission within the prior 30 days for non-cardiac illness or surgical procedure.

Prospective Surveillance and Identification of WHO-Defined SCDs

From February 1, 2011, to March 1, 2014, we performed daily surveillance of all consecutive San Francisco County out of hospital deaths. Each morning, EMS records and medical examiner investigator scene reports of all unattended (not under the care of a physician within 3 weeks for an active medical condition) out of hospital deaths from the previous day were reviewed by a cardiac electrophysiologist (Z.H.T.) and the Assistant ME (E.M.) to identify all OHCA deaths, ages 18-90 years for detailed autopsy, including toxicology and histology. All OHCA deaths underwent a full autopsy (described below), except in rare cases where the family objected to full autopsy. We obtained comprehensive medical records from the 10 San Francisco County adult hospitals and EMS records for all cases. Out-of-county medical records were also obtained.

Subjects under the care of a physician within 3 weeks of death (i.e., office visit for active medical condition or inpatient care) are considered “attended” by the medical examiner. Under these circumstances, the attending physician is contacted by the forensic investigator and asked to infer cause of death in order to sign the death certificate; once the death certificate is signed, these attended deaths are no longer in the jurisdiction of the medical examiner and are therefore ineligible for autopsy. We interviewed each attending physician who signed a death certificate and reviewed EMS and complete medical records to determine whether any such attended deaths met criteria for WHO-defined SCDs; those meeting criteria were included in WHO-defined SCD incidence calculations but not autopsied. To determine total San Francisco County mortality and to ascertain for any WHO-defined SCDs missed, we retrieved and reviewed all county death certificates quarterly for location, death certificate-stated cause of death, and circumstances of death by forensic investigator reports to cross-check with cases obtained via medical examiner surveillance.

Postmortem Investigation

All identified OHCA deaths, except the rare cases that did not receive next-of-kin agreement, underwent complete external and internal postmortem examination performed by a single board-certified forensic pathologist (Assistant ME E.M.) according to a prospectively developed protocol for examining all cavities and tissues including thorough heart and brain examinations.[16] Every autopsy was further reviewed in full by a cardiac pathologist and the chief of the UCSF Autopsy Service (P.C.U.).

Cardiac Examinations—Hearts were excised, weighed, and dissected systematically before careful examination for gross evidence of cardiovascular pathology including acute myocardial infarct (MI) or scar denoting healed MI. The major extramural coronary arteries were cut in cross section every 5 mm to identify atherosclerotic plaques, thrombi, dissecting hematomas, or other stenoses. In addition to samples of coronary artery lesions, samples of myocardium for histology were taken from 5 standard locations: septum, posterobasal, lateral, mid-anterior left ventricular free wall, and right ventricular free wall. An extra

section of the high septum was also taken for histologic examination of the conduction system. Histologic sections were stained with H & E and trichrome and independently examined by two pathologists (E.M. and P.C.U.).

Examination of Other Organs and Tissues—A comprehensive examination of the internal organs of the thorax, abdomen, and cranial vault were performed according to established autopsy methods.[17] Complete details of the autopsy procedure are provided in Supplemental Appendix.

Postmortem vitreous chemistries (electrolytes, creatinine, urea nitrogen, and glucose) were obtained for all subjects. Toxicology (blood and urine) was obtained for all subjects ≤ 75 years and for subjects ≥ 75 years without obvious cause of death (e.g., acute MI, intracranial hemorrhage, saddle pulmonary embolus) on gross examination at autopsy. Cardiac implantable electronic device (CIED) interrogation was performed on all cases with a permanent pacemaker (PPM) or implantable cardioverter-defibrillator (ICD). Terminal rhythm was determined from device interrogation, correlating events stored on the device with the timing of the arrest from EMS documentation and medical examiner scene investigation.[18]

Adjudication of Inclusion and Cause of Death

A multidisciplinary committee including the Assistant Medical Examiner (E.M.), a cardiac pathologist (P.C.U.), a neurologist (A.S.K.), and two cardiologists/cardiac electrophysiologists (J.E.O. and Z.H.T.) reviewed comprehensive pre-mortem medical records, forensic investigator reports (including scene investigations, and witness and next-of-kin interviews), EMS records, medication prescriptions, as well as detailed autopsy, toxicology and histology findings for all OHCA deaths to determine whether they met criteria for a WHO-defined SCD and to adjudicate a single final cause of death. Autopsy-defined SAD was a death for which no identifiable non-arrhythmic cause of death was found (e.g., acute cerebrovascular accident, viscus perforation, tamponade, vascular rupture, pulmonary embolism, hemorrhage, lethal toxicology/occult overdose, acute heart failure with pulmonary edema), but may have had underlying or associated cardiac disease. Per usual forensic toxicology protocol, lethal serum or tissue levels (i.e., ethanol levels >0.5 mg/L, opiates >0.3 mg/L) were used in the absence of other pathologic findings that could explain sudden death as evidence for occult overdose as the cause of death.[19, 20] For WHO-defined SCDs with pathologic evidence of chronic ethanol or opiate/heroin use (i.e., hepatic findings, needle track marks), higher lethal thresholds (ethanol >0.7 mg/L, opiates >0.5 mg/L) were used.

Statistical Analysis

The characteristics of the study sample were summarized using proportions. For between-group comparisons, we used chi-square and Fisher's exact tests as appropriate. To make the 525 WHO-defined SCDs with autopsy representative of the demographic and risk factor distribution of the overall set of 630 WHO-defined SCDs, we used inverse probability weights, based on a logistic model using demographics and risk factors to predict having an autopsy. The resulting weights were used to estimate the proportion of autopsy-defined SAD

among all SCD cases, with or without autopsy. Incidence of autopsy-defined SAD was estimated using person-time methods, and compared across demographic subgroups using Poisson models. Analyses used Stata Version 14.2 (StataCorp LP, College Park, TX). A two-tailed P < .05 was considered statistically significant.

Results

A total of 20,440 deaths occurred in San Francisco County during the 37-month study period (Figure I). Of these, 12,671 out of hospital, ED, and unexpected inpatient deaths were reported to the medical examiner: 2,021 were due to non-natural (e.g., trauma, homicide) causes, 2,012 did not meet age criteria, 3,862 were inpatient, nursing home, or hospice deaths (Supplemental Table I). The medical examiner considered 1,120 reported out of hospital deaths as attended deaths due to active medical care within 3 weeks, thus out of medical examiner jurisdiction and ineligible for autopsy. Of these, 89 (7.9%) met criteria for WHO-defined SCD after comprehensive records review and interviews with the attending or treating physicians who signed the death certificate. Via prospective daily surveillance of the remaining 3,656 unattended out of hospital deaths, we identified 912 deaths due to OHCA with primary EMS impression of cardiac arrest. Next-of-kin of 16 (2%) OHCA deaths declined autopsy for religious reasons; thus 896 (98%) OHCA deaths underwent the protocol autopsy. At adjudication, of the 896 OHCA deaths, 371 (41%) did not meet WHO criteria for SCD (i.e., were not sudden or unexpected, Supplemental Table I), leaving 525 adjudicated autopsied WHO-defined SCDs during the study period. Thus we identified 630 (525 autopsied + 16 declined autopsy + 89 under recent medical care) WHO-defined SCDs over 37 months for a countywide WHO SCD incidence of 29.6/100,000 person-years, accounting for 3.4% (630/18,443) of total adult mortality. Autopsy rates were 98.2% (896/912) for OHCA deaths and 83.3% (525/630) for WHO-defined SCDs.

Mean age of the 525 autopsied WHO-defined SCDs was 62.8 years, 69% were male and reflected the diverse population of San Francisco County; half were in the lowest income tertile (Table I [21]). WHO-defined SCDs without autopsy (*N*=105, most of whom had received recent medical care) were a decade older (mean age 73.1 years) and more likely to be Asian (*P*=.0013).

Autopsy-Defined Causes of Death

Autopsy-defined SADs that in 98% of patients occurred in the setting of structural heart disease accounted for 55.8% (293/525), non-arrhythmic cardiac causes of death 4.2% (22/525), and non-cardiac causes of death 40% (210/525) of all WHO-defined SCDs (Figure IIA). Leading autopsy-defined cause of death for WHO-defined SCDs were coronary artery disease (CAD, 32%), occult overdose (13.5%), cardiomyopathy (10%), cardiac hypertrophy (8%), and neurologic (5.5%). Of 168 cases with CAD causes, one-third (52 cases) had postmortem findings of acute CAD (35 with acute coronary lesion, 17 with histologic evidence of acute MI). Of 17 cases with pacemaker or ICD; 4 were adjudicated to have device concern (3: undersensing, software error, inappropriate device selection) or hardware failure (1). Occult overdose (*N*=71) was the leading non-cardiac cause of death for WHO-defined SCDs. Lethal toxicological levels of opiates were found in 61% (43/71) of the occult

overdoses; all of these SCDs had a primary EMS impression of cardiac arrest and none had evidence or suspicion of drug use at the scene. The second largest group of non-cardiac cause of death for WHO-defined SCDs was sudden neurologic deaths, which included acute cerebrovascular accident, intracranial hemorrhage, and sudden unexplained death in epilepsy (SUDEP).[15]

Of the 371 OHCA deaths excluded as non-sudden at adjudication, 142 were autopsy-defined SAD (Supplemental Figure I), therefore less than half of 896 deaths with EMS primary impression of cardiac arrest in the study period were autopsy-defined SAD ([142 non-sudden + 293 meeting WHO criteria])/896=48.6%).

The proportion of total WHO-defined SCDs due to autopsy-defined SAD was significantly greater in witnessed (78/120=65.0%) vs. unwitnessed cases (215/405=53.1%, *P*=.024; Figure IIB), and in men (220/362=60.8%) compared to women (73/163=44.8%, *P*=.0006). Autopsy-defined SADs accounted for a similar proportion of WHO-Defined SCDs Age 18-39 (19 of 32, 59%) vs. Age ≥ 40 (274 of 493, 56%, P=.68, Figure IIC). Presumed cause of death as stated by the attending or treating physicians on death certificate was cardiac for 101 of the 105 WHO-defined SCDs that did not undergo autopsy (Supplemental Table II).

Incidence of Autopsy-Defined SAD

Countywide incidence of autopsy-defined SAD, weighted to account for the 105 (16.7%) WHO-defined SCDs not autopsied, was 17/100,000 person-years (Figure III). Incidence rates for WHO-defined SCD and autopsy-defined SAD were over 2- and 3-fold higher in men vs. women, respectively (*P*<.0001), highest in Blacks (P>.0001), and lowest in Hispanics (*P*=.0018). Blacks and Hispanics had the lowest proportion of autopsy-defined SADs, at 44.6% and 54.8% respectively.

Impact of Prior Medical History

Comprehensive past medical records were obtained for 94% (492/525) of all WHO-defined SCDs; 24 WHO-defined SCDs (5%) were known to be previously healthy with no medical conditions, with similar proportions in autopsy-defined SAD and non-SAD groups (Table II). Less than half of WHO-defined SCDs (224/525, 43%) had prior cardiac history, with a similar proportion in autopsy-defined SADs (131/293, 45%) and non-SADs (93/232, 40%); therefore, sudden death was the first manifestation of cardiac disease for more than half of all adult WHO-defined SCDs (301/525, 57%) and autopsy-defined SADs (162/293, 55%) in San Francisco County. History of hypertension, dyslipidemia, and congestive heart failure (CHF) was more common in autopsy-defined SADs, while history of seizure disorder, psychiatric disorder, alcohol abuse, and illicit drug use was more common in non-SADs (Table II).

Presenting Rhythm and Symptoms

Initial rhythm at EMS arrival was asystole for nearly all 405 unwitnessed WHO-defined SCDs, while ventricular fibrillation (VF) and asystole each accounted for one-third and pulseless electrical activity (PEA) 13% of the 120 witnessed WHO-defined SCDs (Supplemental Figure II). For the witnessed WHO-defined SCDs, mean time to EMS arrival

was similar for all rhythms (P=.34, Supplemental Figure III). VT/VF predicted autopsy-defined SAD (39 of 43, 91%) and PEA non-SAD (13 of 15, 87%, P<.0001 for both, Supplemental Table III). The proportions of autopsy-defined SAD vs. non-SAD were similar for all other rhythms. Two-thirds of WHO-defined SCDs and autopsy-defined SCDs presented suddenly with no known symptoms. (Supplemental Table IV).

Discussion

In the POST SCD study, capturing nearly all deaths due to stated OHCA and presumed SCDs in an entire ethnically diverse metropolitan area over 37 months, 40% of OHCA deaths were not sudden and only half (55.8%) of SCDs defined by conventional epidemiologic criteria were proven to be SAD after postmortem investigation. We leveraged the medico-legal authority of the county medical examiner for complete prospective surveillance of all out of hospital deaths, which are reported as mandated by state law, to initially identify OHCA deaths as defined by CARES criteria for comprehensive autopsy. We then obtained EMS and comprehensive medical records to refine these to WHO-defined SCDs and adjudicate their causes of death with pre- and postmortem data. Although we have previously demonstrated the high fidelity of medical examiner surveillance for WHO-defined SCDs in San Francisco,[16] in this investigation we further cross-checked all death certificates filed in the county to ensure that we did not miss any cases during the study period.

Estimates of the annual incidence of OHCA and SCD vary widely depending on data sources for case ascertainment, definitions used, and methods employed. Indeed, SCD incidence rates in San Francisco would be >50% higher if CARES OHCA criteria rather than the WHO definition were used. Restricted to WHO-defined cases, SCD incidence in San Francisco is notably lower than contemporaneous estimates,[8] which may be due to the exclusion of OHCA survivors and the diverse source population. Postmortem investigation then allowed us to further refine SCD incidence to autopsy-defined SAD incidence, approximately half that using the WHO definition.

Death certificates are known to overestimate SCD rates,[3] and cause of death on death certificates are often unreliable[22] because non-forensic autopsies are rarely performed[11] and protocols and guidelines for autopsies in suspected SCDs vary widely. Non-cardiac conditions that occur rapidly such as vascular or viscus rupture, hemorrhage, or pulmonary embolism cannot be excluded without a full autopsy, and the recent AHA/ACC/HRS guideline on SCD prevention includes recommendations on postmortem evaluation of SCD.[23] Autopsy rates of SCDs in community-based cohorts and clinical trials range from 11-27%,[3, 6, 24] reflecting typical forensic practice of low priority for natural deaths. A recent medical examiner-based study in Hennepin County, MN reported an apparent 62% autopsy rate of 71 SCDs aged 25-59 over 3 years; however, 580 potential sudden deaths with existing illness that did not undergo autopsy were excluded, thus the calculated SCD incidence was only 15% of expected.[25] If these uninvestigated sudden deaths were included, the actual autopsy rate was 10%. In San Francisco County prior to the prospective POST SCD study, the prevailing medical examiner autopsy rate was 43% of WHO-defined SCDs;[16] in the

present study, autopsy rates were doubled to 83% of WHO-defined SCDs and 98% of OHCA deaths ages 18-90.

We performed vitreous chemistries in all subjects, and blood and urine toxicology for subjects < 75 years or ≥ 75 years that did not have an obvious cause of death on gross examination. Lethal levels of opiates were the culprit in over half of the 71 WHO-defined SCDs found to be due to occult overdose, a reflection of the ongoing U.S. opioid epidemic – urban, suburban, and rural alike.[26] Because none of the WHO-defined SCDs found to be due to occult overdose had evidence or suspicion of drug use at the scene and all had a primary EMS impression of cardiac arrest, overdoses and other metabolic emergencies may be under-recognized as underlying causes of sudden death.

Our results confirm substantial racial and sex differences in contemporary SCD epidemiology. Rates of WHO-defined SCD and autopsy-defined SAD were highest in Blacks and lowest in Hispanics, while the proportion of WHO-defined SCD due to autopsy-defined SAD in both populations was significantly lower than for Whites. We found significant differences in the distribution of non-cardiac causes and marked sex differences: autopsy-defined SAD accounted for 61% of WHO-defined SCDs in men but only 45% in women. These findings reinforce the importance of SCD investigations in women and diverse populations.

While a central tenet of SCD epidemiology is that CAD accounts for ~80% of SCDs,[9, 27] autopsy studies supporting this premise were limited by referral bias of the minority of community sudden deaths referred for postmortem investigation.[13] In contrast, our study reflects the contemporary epidemiology and underlying causes of nearly every incident SCD in San Francisco, and confirms recent secular trends of the decreasing prevalence of CAD[28] and increasing prevalence of non-ischemic causes. Indeed, the “classic” presentation of acute coronary lesion and/or pathologic evidence of acute myocardial infarction leading to arrhythmic death was found in only 10% of WHO-defined SCDs overall and 18% of autopsy-defined SADs. A third of autopsy-defined SADs were due to non-ischemic cardiomyopathies and cardiac hypertrophy without histologic evidence of hypertrophic cardiomyopathy. We have recently reported on sudden neurologic deaths[15] and CIED concerns[18] as previously unrecognized causes of SCD. Cardiac non-arrhythmic causes (e.g., heart failure with pulmonary edema, tamponade) also accounted for 4% of SCDs. Therefore, since SAD is the only phenotype of SCD rescued by AEDs and ICDs and the intended focus of genetic association and risk studies of SCD, it is essential to distinguish SAD from non-arrhythmic causes of SCD.

Although many of the SCDs initially found in asystole may have started as VT/VF, mean EMS response times for witnessed cases were similar across all rhythms. An initial rhythm of VT/VF was highly specific (91%) yet not perfectly predictive for autopsy-defined SAD. For example, ICD documentation and treatment of VF did not always represent definitive evidence of SAD: a 59 year-old-man with heart failure, ICD, and unwitnessed SCD was found to have a large subarachnoid hemorrhage which caused neuro-cardiogenic VF.[15] PEA was found in 13% of witnessed cases, and a 2013 NHLBI workshop identified this condition as an SCD research priority, in part due to it slower survival vs. VT/VF.[29] This may be

explained by the fact that 87% of cases presenting with PEA were due to non-arrhythmic and non-cardiac causes of death, therefore further inroads into reducing the public health burden of sudden death requires investigation and earlier recognition of non-arrhythmic causes.

Prior studies have typically identified SCD outcomes retrospectively, relying on death certificates or *ex post facto* retrieval of event and medical records and application of WHO or Hinkle-Thaler criteria to determine underlying cause.[3, 30-32] The WHO-defined SCDs and autopsy-defined SADs in this report represent the entirety of these deaths in the community over a 3-year period. The positive predictive value of WHO SCD criteria for autopsy-defined SAD was 55.8% in the POST SCD Study. Because approximately half of deaths due to OHCA and WHO-defined SCDs were found to be non-arrhythmic after postmortem examination, it is difficult to identify sudden "cardiac" deaths with a high degree of accuracy using conventional methods; therefore one may consider deaths meeting WHO criteria "sudden deaths" rather than "sudden *cardiac* deaths." While comprehensive autopsies are not practical in most clinical trials and population, observational, or genetic association studies, understanding the limits of current criteria used to define SCD is important for interpreting the results.

This study has several limitations. Standardized investigations and prospective pre-mortem data collection as done in cohort studies were not possible in the population-based POST SCD study. However, we collected all available pre-mortem data for nearly every WHO-defined SCD; therefore, these records reflect typical population medical care in the entire metropolitan area. Although the population of the United States is rapidly diversifying with no majority ethnicity projected by the U.S. Census Bureau by 2043,[33] our findings in a diverse area such as San Francisco may not be entirely generalizable to other populations. Despite evaluating more comprehensive data per SCD than any other study to date, the exact cause of death sometimes remains unclear and is subject to interpretation. Similar to many other SCD cohorts and studies, we included unwitnessed sudden deaths, for which the timeline of "suddenness" is less certain. Conversely, an unknown number of solitary deaths that may have been sudden could have been missed by our criteria because no witnesses were available to verify that the victim had been alive and well within 24 hours. Therefore, although we have demonstrated the limited specificity and positive predictive value of WHO criteria for autopsy-defined SAD, the sensitivity of WHO criteria for all SADs in San Francisco is unknown. While some studies may include resuscitated OHCA victims with substantial hemodynamic or neurologic sequelae as SCDs, these cases were considered OHCA survivors rather than SCDs in POST SCD. Because the medical examiner considered a patient who died within 3 weeks of physician care "attended," OHCAs in such patients may have been missed, although we confirmed that > 90% of these deaths were not sudden. Lastly, our protocol did not include genetic testing which may be helpful for unexplained SCDs with negative autopsy, accounting for up to 40% of SCDs in pediatric/young adult populations.[34] However, nearly all adult SCDs in POST SCD had an identifiable gross, histologic, or toxicologic cause of death, therefore genetic testing may have helped identify underlying cause for only the 7 cases (1.3%) that may be considered unexplained (primary electrical disease with negative autopsy).

In conclusion, in this prospective postmortem investigation of nearly all out of hospital WHO-defined SCDs in an entire ethnically diverse metropolitan area, just over half of presumed SCDs were actually autopsy-defined SAD. These data provide an unbiased, real-world picture of the contemporary epidemiology, burden, and underlying causes of sudden death in the community, and have implications for the accuracy of SCDs and aggregate mortality data as defined by death certificates, in clinical trials, and by cohort studies. Our methods may also provide an outline for medical examiner or coroner protocols for the systematic examination of these out of hospital natural deaths, which are rarely investigated in the community

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Perspective

What is new?

- In this prospective countywide autopsy study of all deaths due to stated cardiac arrest and presumed sudden cardiac deaths over 37 months, 40% were found to have a non-sudden, non-cardiac cause of death
- Only half (55.8%) of “sudden cardiac deaths” defined by conventional criteria were autopsy-defined sudden arrhythmic deaths
- Sudden death was the first manifestation of cardiac disease for over half of all autopsy-defined sudden arrhythmic deaths
- Leading causes of presumed sudden cardiac deaths were coronary disease (32%), occult overdose (13.5%), cardiomyopathy (10%), cardiac hypertrophy (8%), and neurologic (5.5%)
- 98% of sudden arrhythmic deaths had structural heart disease at autopsy

What are the clinical implications?

- Cardiac arrests defined by paramedic criteria and sudden cardiac deaths defined by conventional and/or retrospective methods, as in most cohort studies or clinical trials, have limited accuracy for actual arrhythmic deaths
- These data reflect the decreasing prevalence of coronary disease and increasing prevalence of non-ischemic causes, therefore further inroads into reducing the overall burden of sudden death requires investigation and earlier recognition of non-ischemic and non-arrhythmic causes
- In contrast to sudden death in the young, the vast majority of sudden arrhythmic death in adults is associated with structural heart disease

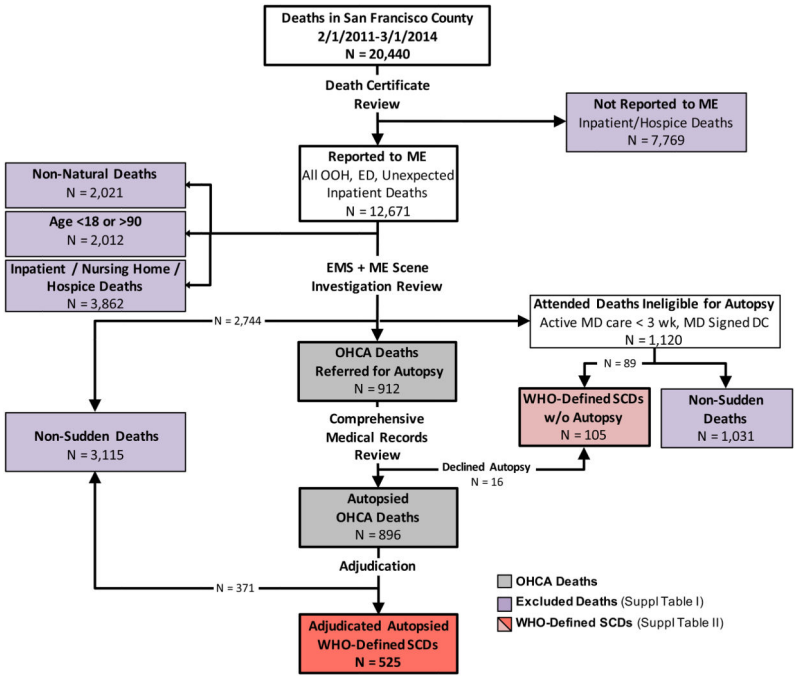


Figure I. Identification of WHO-Defined SCDs in the San Francisco Postmortem Systematic invesTigation of Sudden Cardiac Death (POST SCD) Study, February 1, 2011-March 1, 2014

Identification of WHO-defined SCDs via active Medical Examiner surveillance of all out-of-hosptial deaths in San Francisco County 1 February 2011 to 1 March 2014. County death certificates for every death were reviewed for location, circumstances, and cause of death. EMS records and forensic investigator reports were reviewed for all out-of-hospital natural deaths between ages 18-90 years. All OHCA deaths referred for autopsy underwent comprehensive review of medical records and medical examiner records, and those meeting WHO criteria underwent full adjudication. A total of 20,440 deaths occurred in San Francisco County during the 37-month study period (Figure I). Of these, 12,671 out of hospital, ED, and unexpected inpatient deaths were reported to the medical examiner: 2,021 were due to non-natural (e.g., trauma, homicide) causes, 2,012 did not meet age criteria, 3,862 were inpatient, nursing home, or hospice deaths (Supplemental Table I). The medical examiner considered 1,120 reported out of hospital deaths as attended deaths due to active medical care within 3 weeks, thus out of medical examiner jurisdiction and ineligible for autopsy. Of these, 89 (7.9%) met criteria for WHO-defined SCD after comprehensive records review and interviews with the attending or treating physicians who signed the death certificate (Supplemental Table II). Via prospective daily surveillance of the remaining 3,656 unattended out of hospital deaths, we identified 912 OHCA deaths with primary EMS impression of cardiac arrest. Next-of-kin of 16 (2%) OHCA deaths declined autopsy for religious reasons, thus 896 (98%) OHCA deaths underwent the protocol autopsy. At adjudication, 371 OHCA deaths did not meet WHO criteria for SCD, leaving 525 adjudicated autopsied WHO-defined SCDs during the study period. Thus we identified 630 (525 autopsied + 16 declined autopsy + 89 under recent medical care) WHO-defined SCDs over 37, accounting for 3.4% (630/18,443) of total adult mortality. Autopsy rates were 98.2% (896/912) for OHCA deaths and 83.3% (525/630) for WHO-defined SCDs.

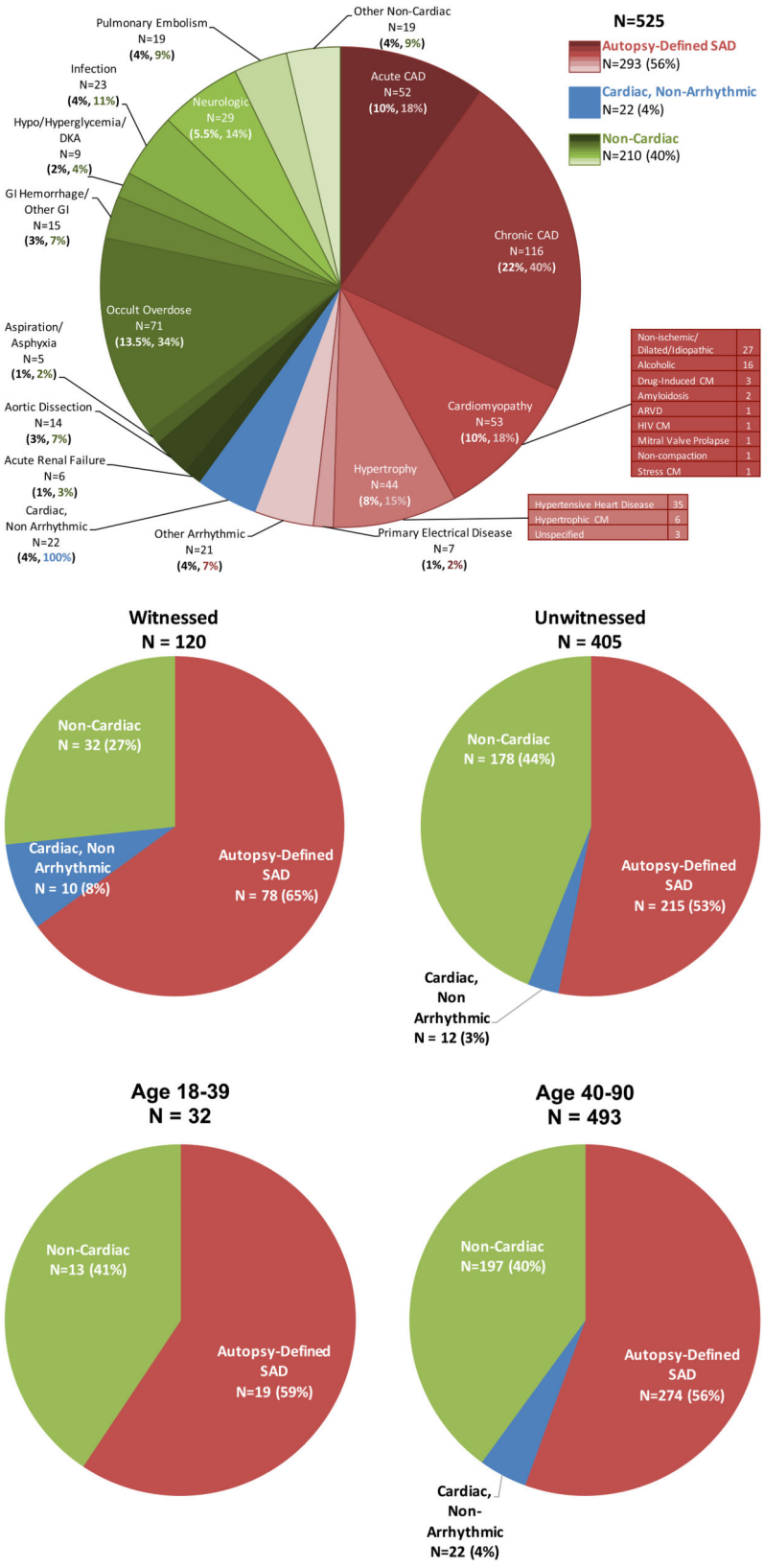


Figure II. Adjudicated Etiologies of Autopsied WHO-Defined SCDs

IIA: Adjudicated Etiologies of All Autopsied WHO-Defined SCDs, Adjudicated Etiologies of Autopsied WHO-defined SCDs after review of comprehensive medical records, EMS records, complete autopsy, toxicology, and postmortem chemistries. Autopsy-defined SADs had no identifiable extra-cardiac (e.g., pulmonary embolism, hemorrhage, lethal toxicology) or non-arrhythmic (tamponade, acute HF) cause of death. First % is of total WHO-defined SCDs, second % is of cause of death category. Overall autopsy-defined SADs accounted for 56% of all WHO-defined SCDs, 4% were cardiac non-arrhythmic cause of death, and 40% were non-cardiac cause of death.

Autopsy-Defined SAD N = 293

Acute CAD N = 52

Acute Coronary Lesions N = 35; Acute MI N = 17

Chronic CAD N = 116

Chronic Coronary Lesions 41; Healed MI 45; Hypertensive CAD 16; Ischemic CM 14,

Cardiomyopathy N = 53, Alcoholic N = 16; Amyloidosis N = 2; ARVD N = 1; Drug-Induced CM N = 3; HIV Cardiomyopathy N = 1; CM w/ Valve Prolapse N = 1; Non-compaction N = 1; Non-ischemic/Dilated/Idiopathic N = 27; Stress CM N = 1

Hypertrophy (Incuding HCM) N = 44

Hypertensive Heart Disease N = 35; HCM N = 6; Unspecified Hypertrophy N = 3

Primary Electrical Disease N = 7

Complete Heart Block N = 1; Short QT Syndrome N = 1; Unspecified N = 5

Other Arrhythmic N = 21, Acquired Long QT Syndrome N = 1; Bicupid Aortic Valve N = 1; MINOCA – Acute N = 4; MINOCA - Healed N = 4; CIED Concern N = 3; CIED Failure N = 1; Myocarditis N = 2; Acute AVR Failure N = 1; Mitral Valve Prolapse N = 2; Critical Aortic Stenosis N = 3

Cardiac, Non Arrhythmic N = 22

Acute MI w/ Pump Failure N = 4; Acute MI w/ Rupture + Tamponade N = 12; Acute on Chronic Heart Failure N = 5; Pericarditis N = 1

Non-Cardiac N = 210

Acute Renal Failure N = 6

Aortic Dissection N = 14

Aspiration/Asphyxia N = 5

Chemical Overdose N = 71

Opiates N = 40, Non-Opiates N = 31

GI N = 15

GI Hemorrhage N = 7; Incarcerated/strangulated hernia N = 4; Bowel Obstruction N = 2; Hepatorenal failure / pancreatitis N = 1; Liver Failure N = 1

Hyperglycemia/DKA N = 9

Infection N = 23

Pneumonia N = 12; Sepsis N = 6; Other Infection N = 5

Neurologic N = 29

Intracranial Hemorrhage N = 18; SUDEP N = 7; Aneurysm Rupture N = 2; Acute CVA N = 1; Other Neuro (Huntington disease) N = 1

Pulmonary Embolism N = 19

Other Non-Cardiac N = 19

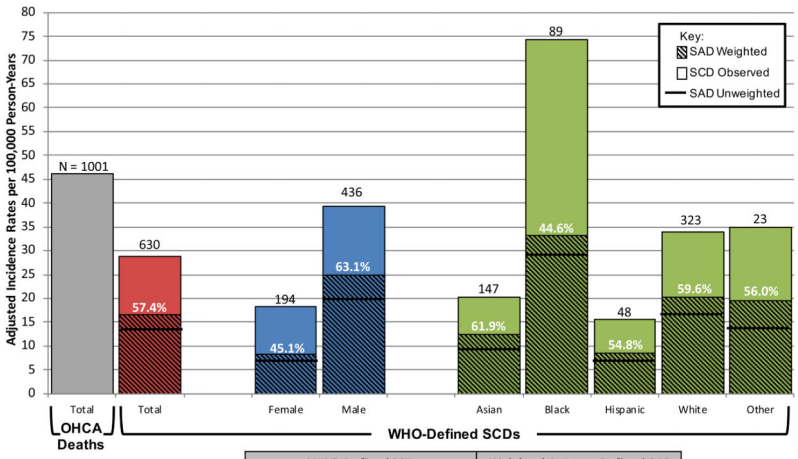
Acute Alcohol Withdrawal N = 1; Disseminated Cancer N = 1; Hypothermia N = 1; Other Hemorrhage N = 2; Other Trauma N = 4; End-stage COPD N = 4; Obstructive Sleep Apnea N = 1; Aortic Aneurysm Rupture N = 2; Renal Artery Dissection N = 1; Iliac Arterial Dissection N = 1; Pulmonary Artery Dissection N = 1

IIB: Adjudicated Etiologies of Witnessed vs. Unwitnessed WHO-Defined SCDs

Adjudicated Etiologies of Witnessed vs Unwitnessed WHO-defined SCDs after review of comprehensive medical records, EMS records, complete autopsy, toxicology, and postmortem chemistries. Autopsy-defined SADs accounted for 65% of witnessed and 53% of unwitnessed WHO-defined SCDs, (OR=1.62, 95% CI: 1.06 to 2.48; P=.024). Witnessed: Autopsy-Defined SAD N = 78 (Acute CAD N=16 [20%], Chronic CAD N=35 [45%], Cardiomyopathy N=9 [11%], Hypertrophy N=10 [13%], Primary Electrical Disease N=2 [3%], Other Arrhythmic N=6 [8%]). Unwitnessed: Autopsy-Defined SAD N = 215 (Acute CAD N=36 [17%], Chronic CAD N=81 [38%], Cardiomyopathy N=44 [20%], Hypertrophy N=34 [16%], Primary Electrical Disease N=5 [2%], Other Arrhythmic N=15 [7%]).

IIC: Adjudicated Etiologies of WHO-Defined SCDs Age 18-39 vs. Age ≥ 40

Autopsy-defined SADs accounted for a similar proportion of WHO-Defined SCDs Age 18-39 (19 of 32, 59%) vs. Age ≥ 40 (274 of 493, 56%), P=.68.Age 18-39: Autopsy-Defined SADs N = 19 (Acute CAD N=1 [5%], Chronic CAD N=3 [16%], Cardiomyopathy N=8 [42%], Hypertrophy N=4 [21%], Primary Electrical Disease N=3 [16%]). Age ≥ 40: Autopsy-Defined SADs N = 274 (Acute CAD N=51 [19%], Chronic CAD N=113 [41%], Cardiomyopathy N=45 [16%], Hypertrophy N=40 [15%], Primary Electrical Disease N=4 [1%], Other Arrhythmic N=21 [8%]).



	WHO-Defined SCD		Weighted Autopsy-Defined SAD	
	IRR	P-value	IRR	P-value
Male vs. Female	2.26	**<.0001**	3.18	**<.0001**
Asian vs. White	.51	**<.0001**	.55	**.0001**
Black vs. White	1.81	**.0001**	1.37	.07
Hispanic vs. White	.60	**.0018**	.56	**.0046**
Other vs. White	1.68	**.0149**	1.58	.09

Figure III. Adjusted Incidence rates for OHCA Deaths, WHO-defined SCDs, and Autopsy-defined SADs in San Francisco County 1 February 2011 to 1 March 2014

Adjusted incidence rates per 100,000 person-years for all observed OHCA deaths, WHO-defined SCDs, and Autopsy-defined SADs in San Francisco County 1 February 2011 to 1 March 2014. Adult countywide incidence of OHCA death and WHO-defined SCD over 37 months were 46/100,000 and 29.6/100,000 person-years, respectively. OHCA death and WHO-defined SCD incidence rates both include the 89 identified WHO-defined SCDs that were considered attended by the medical examiner (due to recent medical care < 3 weeks prior to death) and 16 OHCA deaths that did not undergo autopsy. After comprehensive records review and adjudication, 371 OHCA deaths initially identified by CARES OHCA criteria were excluded as not meeting WHO SCD criteria at presentation. Sex- and race-specific incidence rate ratios (IRR) for all WHO-defined SCD and weighted autopsy-defined SAD are shown. Weighted countywide incidence of autopsy-defined SAD was 17/100,000 person-years, accounting for the 89 WHO-defined SCDs without autopsy. Autopsy-defined SAD accounted for a weighted proportion of 57.4% all WHO SCDs. Incidence rate ratios for WHO SCD and autopsy-defined SAD were over 2- and 3-fold higher in men vs. women, respectively (P<.0001), and highest in Blacks (P>.0001), lowest in Hispanics (P=.0018). Blacks (45%) and Hispanics (54.6%) had the lowest proportion of WHO-defined SCDs that were autopsy-defined SADs. Other race includes American Indian/Alaskan Natives, Native Hawaiians, and other Pacific Islanders.

Table I

Demographic Characteristics of WHO-Defined SCDs and Reference Populations

	WHO-Defined SCDs with Autopsy	WHO-Defined SCDs without Autopsy	*P* Value WHO-Defined SCDs w/ Autopsy vs. w/o Autopsy*	SF Adult Population 2011[21]	US Adult Population 2011[21]
N	525	105	-	705,364	232,556,019
Age, mean ± SD	62.8 ± 14.5	73.1 ± 11.6	**<.0001**	-	-
	18-90	37-89	-	-	-
Male, n (%)	362 (69%)	74 (70%)	.82	358,410 (51%)	112,848,136 (49%)
Race (%)					
Asian	110 (21%)	37 (35%)		235,089 (33%)	11,299,490 (5%)
Black	81 (15%)	8 (8%)		39,383 (6%)	27,630,124 (12%)
Hispanic	40 (8%)	8 (8%)	**.0001**	99,337 (14%)	32,478,615 (14%)
White	279 (53%)	44 (42%)		310,496 (44%)	156,622,672 (67%)
Other†	15 (3%)	8 (8%)		21,059 (3%)	4,525,118 (2%)
Median Income‡	N = 460	N = 97			
Tertile 1	231 (50%)	42 (43%)		275,092 (39%)	184,288,905 (79%)
Tertile 2	136 (30%)	28 (29%)	.35	232,770 (33%)	16,631,720 (7%)
Tertile 3	93 (20%)	27 (28%)		197,502 (28%)	31,635,394 (14%)

*For age, t-test assuming unequal variance; for categorical, Fisher's exact test

†Includes American Indians, Alaskan Natives, and Native Hawaiians

‡Median Income analysis restricted to SF residents

Table II
Pre-Mortem Conditions in WHO-Defined SCDs, Autopsy-Defined SADs, and Non-SADs

	WHO-Defined SCD	Autopsy-Defined SAD	Non-SAD	*P* Value Autopsy-Defined SAD vs. Non-SAD
N	525	293	232	-
Medical Records Unobtainable	33 (6%)	15 (5%)	18 (8%)	
Confirmed No Medical History	24 (5%)	15 (5%)	9 (4%)	
History of:				
HTN	290 (55%)	175 (60%)	115 (50%)	**.023**
DM	117 (22%)	72 (25%)	45 (19%)	.14
Dyslipidemia	157 (30%)	108 (37%)	49 (21%)	**<.0004**
Any cardiac history *	224 (43%)	131 (45%)	93 (40%)	.34
MI	76 (14%)	49 (17%)	27 (12%)	.07
CHF	68 (13%)	47 (16%)	21 (9%)	**.022**
AF/AFL	50 (10%)	27 (9%)	23 (10%)	.39
Aortic stenosis (mod or severe)	6 (1%)	3 (1%)	3 (1%)	*>.99*
Mitral valve prolapse	8 (2%)	5 (2%)	3 (1%)	>.99
CKD (non ESRD)	58 (11%)	33 (11%)	25 (11%)	.72
Seizure Disorder	39 (7%)	14 (5%)	25 (11%)	**.029**
CVA	33 (6%)	18 (6%)	15 (6%)	.99
Psychiatric Disorder †	143 (27%)	61 (21%)	82 (35%)	**.005**
COPD	64 (12%)	32 (11%)	32 (14%)	.41
Non-Metastatic Cancer	63 (12%)	40 (14%)	23 (10%)	.26
Tobacco Use	211 (40%)	115 (39%)	96 (41%)	.72
Alcohol Abuse	122 (23%)	57 (19%)	65 (28%)	**.014**
Illicit Drug Use	79 (15%)	27 (9%)	52 (22%)	**.001**

*Includes prior diagnosis of CAD, Cardiomyopathy, A-fib, A-flutter, PPM, ICD, Considered for Device, Brugada Syndrome, WPW Syndrome, LBBB, LVH, Ischemia, MI, V-Tach, 3rd Degree Heart Block, Acute Coronary Syndrome, Valvular Disease (not including aortic sclerosis), Endocarditis, Angina, Coronary Vasospasm, Arrhythmia NOS, Cardiomegaly, Congenital cardiac anomaly, A-tach, Pericardial Effusion, Mitral Prolapse, 2nd Degree Heart Block, IVCD, SVT, Early Repolarization, and moderate or severe: Aortic or Mitral Stenosis, Aortic, Mitral, Tricuspid, or Pulmonary Regurgitation.

†Includes a prior diagnosis of Anxiety, Bipolar, Depression, Schizophrenia, PTSD, Mood Disorders, Psychosis, Borderline Personality Disorder, Obsessive Compulsive Disorder, and Insomnia.