

The Changing Epidemiology of Ventricular Arrhythmias

Kelley P. Anderson, MD, FHRS, FACC, FACP

*University of Wisconsin Medical School, Department of Cardiology, Marshfield Clinic,
1000 North Oak Avenue, Marshfield, WI 54449-5777, USA*

... it is probable that fatal syncope often differs from non-fatal syncope in the supervention in the former case of fibrillar contraction (or delirium) in the ventricular muscle; this seals the fate of the depressed heart by arresting the circulation and by causing a rapid exhaustion of the ventricular energy in consequence of the violent and continued excitement of the contractile tissues. In the great majority of cases where sudden death is caused by cardiac failure, there is, no doubt, an altered and impaired state of nutrition in the cardiac tissues, sometimes rendered palpable by degenerative changes recognizable with the microscope or pointed to by the presence of disease in the coronary arteries.

—James MacWilliam, 1889 [1]

More than a century ago James MacWilliam [1] related findings from epidemiology, pathology, and the experimental laboratory when he proposed that ventricular fibrillation (VF), rather than cardiac standstill, is the mechanism of sudden cardiac death in most cases. Moreover, he recognized that death due to VF was associated with pathologic abnormalities attributable to coronary heart disease (CHD) along with other conditions, including some without evident structural heart disease [1]. Today, death caused by ventricular tachyarrhythmias (VTA) remains a problem of epidemic proportions. The incidence of VTA death is not precisely known and is estimated by the incidence of various forms of cardiac arrest or various definitions of sudden cardiac death (SCD), each of which has significant potential for error. Nevertheless, the impact of death caused by VTA can be gaged by considering statistics reported by the American

Heart Association Statistics Committee [2]: (1) In 2004, 310,000 SCD (defined as CHD deaths that occurred out of hospital or in hospital emergency departments) occurred in the United States. (2) In North America the annual incidence of out-of-hospital cardiac arrest is about 55 per 100,000 population, which implies that about 166,200 out-of-hospital cardiac arrests occur annually in the United States, assuming a population of 302,196,872. (3) About two thirds of unexpected cardiac deaths occur without previous recognition of cardiac disease. (4) In a population 20 years of age or older, the incidence of out-of-hospital cardiac arrest treated by emergency medical services (EMS) is from 36 to 81 per 100,000. Of these, 20% to 38% have VTA as the first recorded rhythms (see later discussion) [2–8]. Surveys suggest that the incidence of deaths caused by VTA have been declining for several decades. Recent trends indicate a slowing of this beneficial trend, however, and a possible reversal in some groups of younger people.

Ventricular ectopic activity

Observations of accidental events and experiments performed by several teams of investigators between 1900 and 1940 led Wiggers [9] to conclude that brief, localized electrical stimuli could initiate VTA when they occurred late in systole or on the T wave during an interval that he called the “vulnerable phase”. Smirk [10] noted that R waves appearing on the downslope of T waves (R-on-T) were observed in experimental studies and clinical cases to precede the onset of VTA and were associated with sudden death. These and other observations prompted clinicians and scientists to

E-mail address: kpand@att.net

postulate that ventricular ectopic activity (VEA), which refers to premature ventricular complexes (PVCs), ventricular pairs, and nonsustained ventricular tachycardia (NSVT), cause or predict VTA death. Epidemiologic studies have shown that asymptomatic ventricular arrhythmias (VA) are not unusual in healthy people, however. Hiss and Lamb [11] reported findings of resting 12-lead ECGs from 122,043 relatively young, healthy individuals entering flight training in the US Air Force from age 16 to older than 50 years. PVCs were identified in 0.78% of the subjects. In a more representative population, Chiang and colleagues [12] performed 12-lead ECGs in 5129 people composing 85% of the population of a small town in the United States, and detected PVCs in 3.6%. Longer recording durations result in detection of VEA in more subjects. In a study from the Framingham sample, Bikkina and colleagues [13] identified PVCs in 33% of subjects who did not have known CHD using 1-hour recordings. In a study of middle-aged men, both with and without known heart disease, a 6-hour monitor sampling technique identified a 62% incidence of asymptomatic VEA [14].

The prevalence of VEA is strongly related to age and sex. In healthy flight training recruits Hiss and Lamb [11] reported a prevalence of 0.47% in 16- to 19-year-olds and 1.91% in 45- to 49-year-olds. In the Tecumseh study of Chiang and colleagues [12], the prevalence rose from 1.4% in 16- to 29-year-olds to 10.7% in 60- to 69-year-olds. PVCs were recorded in 2.9% of women compared with 4.4% of men. The differences between men and women were not evident until the age of 50, however [12]. It is noteworthy that the prevalence of premature supraventricular complexes (PSVCs) was also age dependent (0.7% in 16- to 29-year-olds to 4.8% in 60- to 69-year-olds), but not different between sexes. Chiang and colleagues [12] and Hinkle and colleagues [14] found an association between VEA and CHD and subsequent SCD. In the Framingham population, Bikkina and colleagues [13] reported an association between frequent PVCs (> 30 per hour) or complex VEA (multiform PVCs, couplets, NSVT, or R-on-T PVCs) and CHD. Multivariate analysis showed that men who did not have CHD who had complex VEA or frequent PVCs were at increased risk for all-cause mortality and increased risk for myocardial infarction (MI) or death attributable to CHD. In contrast, Kennedy and colleagues [15] found that healthy subjects who had frequent or complex asymptomatic VEA had a similar mortality to that of the healthy United States population.

Coronary heart disease and ventricular ectopic activity

VA and CHD are related in many ways. PVCs are more prevalent in patients who have CHD. In the Framingham population, Bikkina and colleagues [13] reported a prevalence of 58% in men who had CHD compared with 33% in those who did not have CHD. The Tecumseh study showed a strong association between PVCs and CHD. In people older than 30 years, 15.8% of those who had PVCs had CHD, whereas only 5% of patients who did not have PVCs had CHD. Coronary risk factor levels (blood pressure, cholesterol, weight, smoking status) were no higher in people who had PVCs than in the total Tecumseh population. During follow-up, 45 people died suddenly (death within 1 hour of onset of symptoms outside the hospital). Of these, 10 had PVCs at the initial examination. Among these, only 5 had pre-existing CHD. Of those who had PVCs at the initial examination, 6.1% died suddenly compared with 1.0% of those who did not have PVCs [12]. Chiang and colleagues [12] also evaluated PSVCs. In both sexes PSVCs increased with age, similar to the trend observed with PVCs. PVCs were more frequent in men, however, a pattern that seems to become more prominent with increasing age. Moreover, in contrast to the pattern observed in subjects who had PVCs, there was no significant difference in the prevalence of CHD among people with and without PSVCs. Also, there was only 1 SCD among 78 people who had PSVCs.

In the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico study (GISSI), the frequency and complexity of VEA were prospectively examined in 8624 patients who had acute MI treated with thrombolytic agents [16]. Arrhythmias were present in 64% of the patients, which was somewhat lower than in studies published a decade earlier in the prethrombolytic era, such as the Multicenter Post-Infarction Research Group (MPIP) study (86%) [17] and the placebo group of the Beta-Blocker Heart Attack Trial study (84%) [18]. The prevalence of NSVT was 6.8% in the GISSI database, lower than that observed by Cats and colleagues (19.5%) [19] and the MPIP investigators (11.3%) [17]. Conversely, the 19.7% prevalence of frequent PVCs (> 10 PVCs per hour) was within the range of values reported by earlier studies, such as the MPIP (21.2%) [17], the Multicenter Investigation of the Limitation of Infarct Size (14.6%) [20], and

the Beta-Blocker Heart Attack Trial study (12.9%) [18].

The mortality rate at 6 months after MI among the patients in GISSI who had 24-hour ECG recordings was 3.0%. The rate of SCD was 0.98%, or 32.8% of all deaths. The SCD rate was 0.6% in patients who did not have VA, 0.8% in those who had 1 to 10 PVCs per hour (odds ratio [OR] 1.50; 95% CI 0.85–2.64), and 2.1% in those who had 10 or more PVCs per hour (OR 4.07; 95% CI 2.30–7.20). Complex VEA was associated with an SCD rate of 1.7% (OR 3.29; 95% CI 2.08–5.19). All-cause mortality rates were 2.01% in patients who did not have VA, 2.7% in patients who had 1 to 10 PVCs per hour, 5.5% in those who had more than 10 PVCs per hour, and 4.8% in those who had complex VEA. In the multivariate Cox analysis, frequent (≥ 10 per hour) PVCs and complex VEA were predictors of total mortality (relative risk [RR] 1.62; 95% CI 1.16–2.26 and RR 1.64; 95% CI 1.27–2.12, respectively) and SCD (RR 2.24; 95% CI 1.22–4.08 and RR 2.11; 95% CI 1.34–3.17, respectively). NSVT was associated with increased mortality and SCD in univariate but not multivariate analysis (RR 1.20; 95% CI 0.80–1.79 for total mortality and RR 1.42; 95% CI 0.74–2.74 for SCD). Sustained ventricular tachycardia was identified on the 24-hour ECG monitoring at predischarge in 12 patients (0.1% of the total population). At 6 months, 2 of the 12 patients had died (16.7%), whereas the mortality rate in patients who did not have sustained ventricular tachycardia was 3.0% (254 of 8540).

Death caused by ventricular tachyarrhythmias

Prevention of VTA-related deaths is one of the highest priorities of the medical community not only because it is a frequent cause of death but also because if the arrhythmia is terminated quickly, the victim may survive and live for many more years. In addition, VTA deaths are usually unexpected, often occurring in the absence of known cardiac disease and often in people in their most productive years, enhancing the disruption in the lives of family, friends, and associates of victims, and enhancing the grief and suffering. There is a profound and urgent need to better understand deaths caused by VTA to delineate the extent of the problem, to identify areas in need of research, and eventually to reduce mortality attributable to VTA. Unfortunately, barriers interfere with population studies of this

phenomenon because proof of death caused by VTA requires physiologic recordings of the onset of the events leading to death in a large, representative sample of the population. Instead, the incidence of death attributable to VTA must be based on a surrogate event in the target population. Although several surrogates for VTA deaths have been used, each has strengths and weaknesses.

A person who has cardiac arrest in whom the initial rhythm is ventricular tachycardia or VF is a possible surrogate for death caused by VTA. Cobb and colleagues [8] estimated the incidence of death due to VTA based on occurrence of VF as the initial rhythm recorded at the time of cardiac arrest in the city of Seattle and extrapolated this to the United States population. Using 2000 US Census data, the estimated age-adjusted incidence was 38 per 100,000. Extrapolation of the 2000 incidence rates of cardiac arrest for people aged 20 years or older in Seattle to a national level suggests that approximately 184,000 treated cardiac arrests could be anticipated in the United States annually. Of these, about 76,000 would have VF as the initially recorded rhythm. Cobb and colleagues observed that the age- and sex-adjusted annual incidence of VF extrapolated to the United States declined by 56% during the 20-year span between 1980 and 2000. Reductions in VF incidence rates occurred in men and women (57% and 51%, respectively) and were present in most age strata. The incidence of VF in men (60 per 100,000) far exceeded that of women (17 per 100,000), and the ratio of male/female incidence rates decreased only from 4.0 to 3.5 in 20 years. The incidence of VF cardiac arrests decreased significantly in blacks and whites but not in Asians/Pacific Islanders over the study interval. Whites experienced a decrease of 53%, from 85 to 40 per 100,000. Blacks had a 54% decrease in VF incidence. The incidence of asystole and pulseless electrical activity as the first recorded rhythms did not decrease significantly over the same period of time (Fig. 1) [8]. Decreases in the incidence of VF cardiac arrests have been observed in European cities. Kuisma and colleagues [21] reported that the incidence of out-of-hospital VF of cardiac origin decreased by 48% from 1994 to 1999 ($P = .0036$) in Helsinki, Finland. Herlitz and colleagues [22] observed a more modest decline in the proportion of patients who had VF as the initial rhythm at the time of cardiac arrest, from 39% in 1981 to 32% in 1997, whereas the number who had cardiac arrest

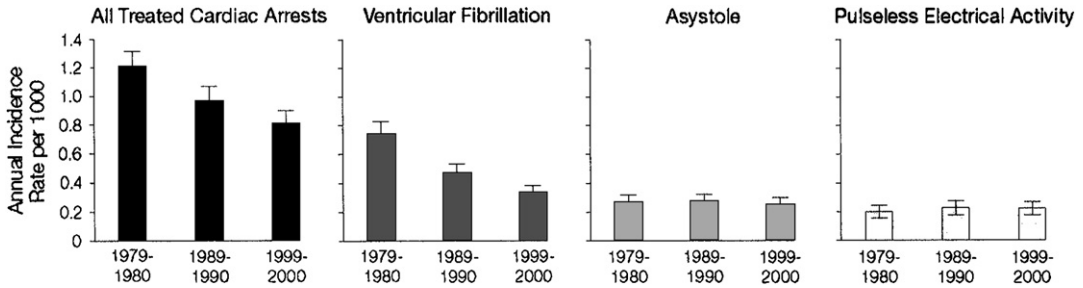


Fig. 1. Incidence rates of treated out-of-hospital cardiac arrest over a 20-year span adjusted for age and sex to the Seattle, Washington population of 2000. Error bars represent 95% CIs. Most of the reduced incidence was because of fewer cases who had ventricular fibrillation as the first identified rhythm. The proportion of cases who had ventricular fibrillation decreased from 61% in 1980 to 41% in 2000. (From Cobb LA, Fahrenbruch CE, Olsufka M, et al. Changing incidence of out-of-hospital ventricular fibrillation, 1980–2000. *JAMA* 2002;288(23):3011; with permission.)

was unchanged in Göteborg, Sweden. More striking reductions would have been identified, however, if the incidences were adjusted for the increase in number of city residents and aging of the population.

Because fatal VF often degenerates into asystole or pulseless electrical activity, using the initial recording of VF as an estimate of death due to VTA may miss episodes recorded too late to document the original rhythm. Holmberg and colleagues [23] examined the first recorded rhythm at the time of cardiac arrest in relation to the time to the first ECG recording and extrapolated backward to estimate the incidence of VF at the time of cardiac arrest. The first ECG showed VF in 43% of all patients. The investigators estimated that VF was the initial rhythm in 60% to 70% of all patients and 80% to 85% of cases who had probable heart disease.

Cardiac arrest, therefore, is a reasonable alternative event that could be used to estimate the incidence of death attributable to VTA. Several studies have prospectively examined the community incidence of primary cardiac arrest using data collected by first responders. From several studies, the annual incidence of treated primary cardiac arrest has ranged between 41 and 91 of 100,000 [8,24–27]. Cobb and colleagues [8] estimated the incidence of cardiac arrest in the United States to be 91 per 100,000 in 2000. This figure represented a significant decline of 34% since 1980.

Chugh and colleagues [28] exposed reasons that use of data from EMS could underestimate VTA-associated deaths as manifested by SCD or cardiac arrest. They identified victims of SCD or cardiac arrest in a prospectively designed study

with data from sources in addition to the EMS, including the county medical examiner's office, area hospitals, and health care providers. SCD was defined as sudden unexpected death either within 1 hour of symptom onset (event witnessed), or within 24 hours of having been observed alive and symptom-free. Available medical records were obtained and evaluated for each case. In this study, the annual incidence of SCD was 53 per 100,000 residents, well within the range of cardiac arrests noted above. At ages older than 35 years, the lowest incidence was observed in the 35- to 44-year-old age group (17 per 100,000) and the highest incidence was observed in the 75- to 84-year-old age group (346 per 100,000). Women composed 43% of cases.

The estimation of deaths by adjudicated SCD as a representation of deaths due to VTA could be questioned. Evidence favoring a close relationship between SCD and death due to VTA has come from implantable cardioverter defibrillator (ICD) trials. In these trials the mode of each death has been determined by committees based on review of medical records and other data. In some trials committee members were blind to ICD assignment. In most trials, ICD therapy has been associated with a marked reduction in SCD in contrast to nonsudden and noncardiac deaths. This finding supports the concept that most SCD are mediated by VTA [29–32]. Although ICDs could prevent bradyarrhythmic deaths, these have been shown to represent a small component of death mechanisms in ICD trials [33].

Chugh and colleagues [28] exposed potential inaccuracies of other approaches for identifying SCD. Of all cases that met SCD criteria in their

study, 64% had rhythms recorded at the time of the EMS arrival. Of these, 44% had VTA, whereas the others had pulseless electrical activity or asystole, similar to what has been reported in other trials. Some 26% of cases presenting to the EMS did not meet criteria for SCD, however. Moreover, 21% of the SCD victims were identified from sources other than EMS, including the medical examiner's office, medical providers, and hospitals, implying that accurate estimation of deaths attributable to VTA requires prospective surveillance from multiple sources and adjudication based on appropriate clinical data. Nevertheless, despite meticulous care in case ascertainment, there are chances for both underestimation and overestimation of the incidence of deaths due to VTA. Overestimation is possible because SCD attributable to bradyarrhythmias, pulseless electrical activity, or "mechanical" disorders (cardiac tamponade, aortic dissection, pulmonary embolism, and so forth) might not be distinguishable from death due to VTA. Underestimation is possible because unwitnessed deaths due to VTA that were discovered more than 24 hours after they were last seen alive have not been included. Also, county residents who suffered SCD while traveling out of state would be missed.

The methods used by Chugh and colleagues [28] could be a model for providing a reliable estimate of SCD and deaths due to VTA, but the data acquired apply only to a single year and only to a single county. The extent to which it pertains to the rest of the United States or other countries can only be assumed. To examine national trends, the US Centers for Disease Control (CDC) used national and state mortality statistics for 1999 based on data from death certificates with cardiac disease death defined as one for which the underlying cause of death was classified and coded using the International Classification of Diseases, Tenth Revision for diseases of the heart (codes I00–I09, I11, I13, and I20–I51) or congenital malformations of the heart (Q20–Q24) [34]. SCD was defined as death from cardiac disease that occurred out of hospital, in an emergency department, or one in which the decedent was reported to be "dead on arrival" at a hospital. Among 728,743 cardiac disease deaths that occurred during 1999, a total of 462,340 (63.4%) were SCDs; 120,244 (16.5%) occurred in an emergency department or were dead on arrival, and 341,780 (46.9%) occurred out of hospital. Women had a higher total number of cardiac deaths (375,243) and a higher proportion of out-of-hospital cardiac deaths

(51.9%) than men (41.7% of 353,500 deaths). Women had a lower proportion of cardiac deaths that occurred in an emergency department or were dead on arrival (12.0%) compared with men (21.2%). SCDs accounted for 10,460 (75.4%) of all 13,873 cardiac disease deaths in people aged 35 to 44 years, and the proportion of cardiac deaths that occurred out of hospital increased with age, from 5.8% in people aged 0 to 4 years to 61.0% in people aged greater than 85 years. SCDs accounted for 63.7% of all cardiac deaths among whites, 62.3% among blacks, 59.8% among American Indians/Alaska Natives, 55.8% among Asians/Pacific Islanders, and 54.2% among Hispanics. Whites had the highest proportion of cardiac deaths out of hospital, and blacks had the highest proportion of cardiac deaths in an emergency department or dead on arrival.

The SCD rate (per 100,000) was strongly related to age (3.0 in age range 0–34 years, 75.4 in 35–65 years, 1099.8 in age range 85 years or older). The overall age-adjusted rate was 175.4 per 100,000. The age-adjusted SCD rate was 47.0% higher among men than women (206.5 versus 140.7 per 100,000 population). Blacks had the highest age-adjusted rates (253.6 in men and 175.3 in women) followed by whites (204.5 in men and 138.4 in women), American Indians/Alaska Natives (132.7 in men and 76.6 in women), and Asians/Pacific Islanders (111.5 in men and 66.5 in women). Non-Hispanics (217.8 in men and 147.3 in women) had higher age-adjusted SCD rates than Hispanics (118.5 in men and 147.3 in women). In 1999, the state-specific proportion of all cardiac deaths that was SCD ranged relatively narrowly from 57.2% (Hawaii) to 72.9% (Wisconsin). In contrast, age-adjusted SCD rates in 1999 ranged widely from 114.6 (Hawaii) to 212.2 per 100,000 (Mississippi).

The death certificate data analyzed by CDC produced an age-adjusted SCD rate (175 per 100,000) more than three times greater than reported by Chugh and colleagues (55 per 100,000) [28,34]. The state with the lowest incidence of SCD was still more than twice that detected by Chugh and colleagues. To examine reasons for the differences in results based on the death certificate method, Chugh and colleagues compared results from their SCD registry to a retrospective death certificate-based analysis using methods similar to those used by the CDC. The death certificate method yielded almost three times more cases (incidence 153 per 100,000) than the prospective method and was therefore of

similar magnitude to the national estimate of 175 per 100,000 reported by the CDC. Subjects identified as having SCD by retrospective death certificate review were older and more often female than subjects identified by prospective, community-based methods. Only 59% of the SCD nonsurvivors identified by prospective methods were correctly identified by retrospective review. The remaining 41% were missed by the death certificate review for several reasons, specifically inpatient location of death (25%), diabetes as cause of death (15%), and miscellaneous other noncardiac causes of death (60%). The death certificate method identified 82% non-SCDs correctly, resulting in a specificity of 86%. Of the cases designated as SCD by the death certificate method, only 19% were identified correctly. By this analysis, the death certificate method had a sensitivity of 59%, a specificity of 86%, and a positive predictive value of only 19%.

This analysis underscores the high potential for error of death certificate data for estimating VTA deaths. The accuracy of cause of death depends on the correctness of the diagnosis by the physician, medical examiner, or coroner. Furthermore, time of onset of disease symptoms and time of death are often not recorded on death certificates. Despite significant limitations, death certificate data are the only data source presently available to assess national trends in VTA-related mortality that allow comparison between states and other community units provided that the false-positive rate remains relatively constant. These methods were used by Zheng and colleagues [35] to examine mortality trends from 1989 to 1998. SCD, the VTA death surrogate, was defined as deaths occurring out of the hospital, in the emergency room, or as dead on arrival with an underlying cause of death reported as a cardiac disease (International Classification of Diseases, Ninth Revision code 390–398, 402, or 404–429). Death rates were calculated for residents of the United States aged 35 years or older and standardized to the 2000 United States population. The investigators showed that SCD rates declined between 1989 and 1998. This decline was observed in all race groups among men (Fig. 2A) and in all but American Indian/Alaska Native women, who experienced declining SCD rates until 1996, with an increase in SCD rate in 1997 and 1998 (Fig. 2B).

Overall, age-adjusted SCD rates declined 8.3% (11.7% in men and 5.8% in women) during the 10 years. The decline was less among men aged

35 to 44 years (−2.8%) compared with all other male age groups (−5.7% to −18.1%). In women, the SCD rates declined but the decrement was less than observed in the corresponding male age groups. Women aged 35 to 44 years demonstrated an increase in SCD rate of 21.1%, however. The proportion of cardiac deaths that occurred in the hospital, in the emergency room, or were dead on arrival at the emergency room declined, whereas the proportion that never made it to the hospital increased. This trend probably reflects aging of the United States population and the later onset of sudden, fatal cardiac events in the elderly, who experienced 83% of SCDs as defined in this investigation.

Death due to ventricular tachyarrhythmias related to coronary heart disease

Most VTA-related deaths are probably due to CHD. This theory is supported by retrospective death certificate data from the CDC that indicate about 70% of SCDs are attributable to CHD [34]. Chugh and colleagues [28] used a prospectively designed, multiple-source method of identification and found autopsy evidence of CHD in 76% of SCD victims. Bunch and White [36] have shown not only that a large proportion of out-of-hospital VF arrests encountered by EMS are due to CHD but also that the decline in the incidence of out-of-hospital VF is due to a decrease in VF events related to CHD (Fig. 3). Specifically, the incidence (per 100,000) of EMS-treated out-of-hospital VF in their community decreased significantly between 1991 and 2004 (1991–1994: 18.2; 1995–1999: 11.8; 2000–2004: 8.7). The incidence of out-of-hospital VF due to CHD paralleled this decline (1991–1994: 13.4; 1995–1999: 11.1; 2000–2004: 5.5). In contrast, the incidence of out-of-hospital VF not attributable to CHD increased slightly but significantly (1991–1994: 2.1; 1995–1999: 2.3; 2000–2004: 2.9) (Fig. 4) [36].

Evidence that VTA-related death due to CHD has declined has been provided by analysis from the Framingham population [37]. This sample provided advantages for studying long-term trends in CHD death and SCD because risk factors and other data were prospectively collected in uniform fashion during 50 years of observation. In particular, the mode of death was evaluated using multiple sources and adjudicated by a physician panel using prespecified criteria. SCD was defined as a CHD death that occurred within 1 hour of the onset of symptoms. This definition was

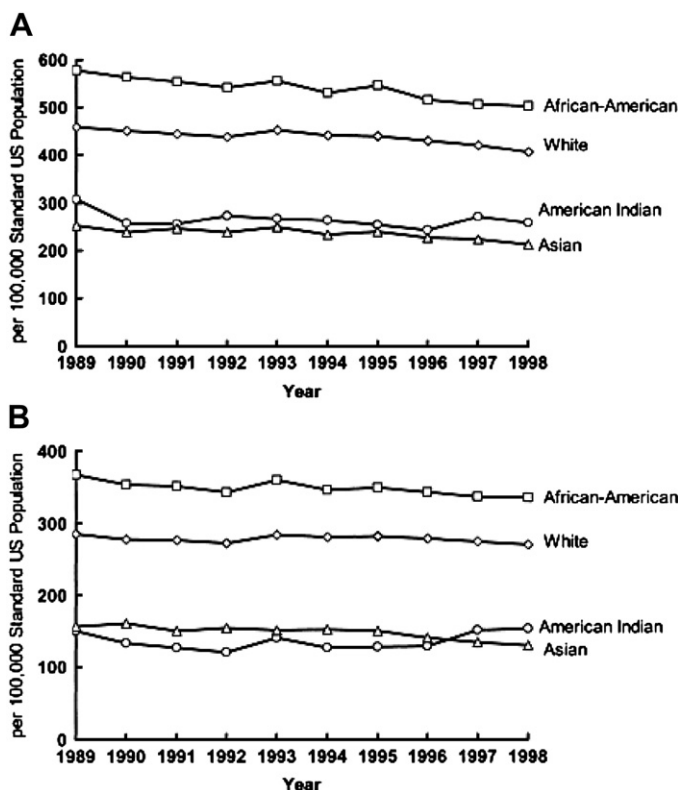


Fig. 2. Age-adjusted death rates for sudden cardiac death among men (A) and women (B) aged 35 years and older by race in the United States from 1989 to 1999. (From Zheng ZJ, Croft JB, Giles WH, et al. Sudden cardiac death in the United States, 1989 to 1998. *Circulation* 2001;104(18):2161; with permission.)

distinctive in that unwitnessed deaths were excluded unless it could be shown that the victim had been alive within the hour of discovery. Although some would be missed, deaths meeting this definition were probably dominated by fatal VTA.

Subjects between ages 40 and 79 years were analyzed in four time periods: 1950 to 1969, 1970 to 1979, 1980 to 1989, and 1990 to 1999. From 1950 to 1969 through 1990 to 1999, the overall CHD death rate decreased by 59%, SCD rates decreased by 49%, and nonsudden CHD death decreased by 64% (Fig. 5). Approximately half of the SCDs occurred in subjects who did not have a clinical history of CHD or CHF. This proportion did not change between 1950 and 1999. In subjects who did not have a prior history of CHD or CHF, the SCD risk was 39% lower in 1990 to 1999, suggesting that primary prevention participated in reductions in VTA deaths. Evidence that secondary prevention also plays a role in the reduction in deaths due to

VTA is the 57% decline in SCD victims who had a prior history of CHD or CHF during the same periods.

The decline in VTA deaths was associated with changes in the risk profile of the overall Framingham sample from the 1950 to 1969 to the 1990 to 1999 groups. Specifically, systolic blood pressure declined from 140 to 130 mm Hg, hypertension prevalence decreased from 48% to 38%, hypertension treatment increased from 7% to 20%, cholesterol declined from 241 to 207 mg/dL, and smoking prevalence declined from 44% to 27%. These findings suggest that improvements in risk factors contributed to the decrease in VTA deaths. The prevalence of diabetes increased from 3% to 8%, body mass index (BMI) increased from 26.1 to 26.9 kg/m², age increased from 56 to 60 years, and the proportions of male sex increased from 44% to 47%. A possible interpretation of these observations is that reduction in hypertension, cholesterol, and smoking resulted in a reduction of fatal VTA related to CHD and other types of

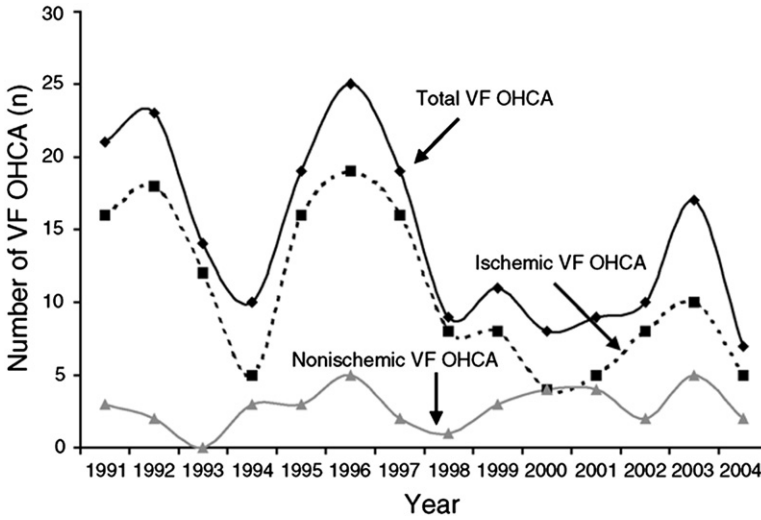


Fig. 3. The number of ventricular fibrillation out-of-hospital cardiac arrests (VF OHCA) per year from 1991 to 2004 are shown as total (solid line with diamonds), ischemic (broken line with squares), and nonischemic (thin solid line with triangles). (From Bunch TJ, White RD. Trends in treated ventricular fibrillation in out-of-hospital cardiac arrest: ischemic compared with non-ischemic heart disease. Resuscitation 2005;67(1):52; with permission.)

CHD deaths, and that reduction in these factors outweighed adverse effects of more diabetes, obesity, and older age.

The risk profile of the SCD victims differed substantially from that of the overall population

in initial and final values and the magnitude of change. Comparing groups from the same two time periods (1950–1969 and 1990–1999), mean age increased from 62 to 72 years, the percentage of males decreased from 80% to 79%, systolic

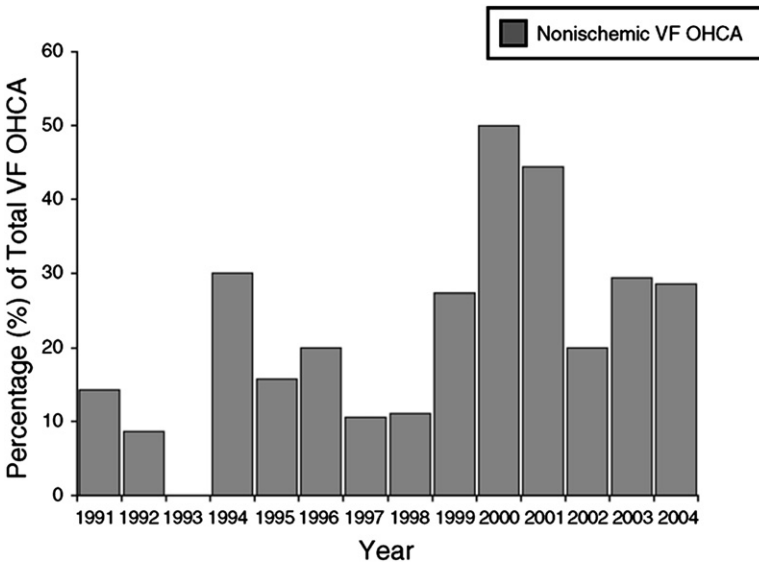


Fig. 4. The percentages of ventricular fibrillation out-of-hospital cardiac arrests (VF OHCA) per year from 1991 to 2004 attributed to nonischemic heart disease per year. (From Bunch TJ, White RD. Trends in treated ventricular fibrillation in out-of-hospital cardiac arrest: ischemic compared with non-ischemic heart disease. Resuscitation 2005;67(1):52; with permission.)

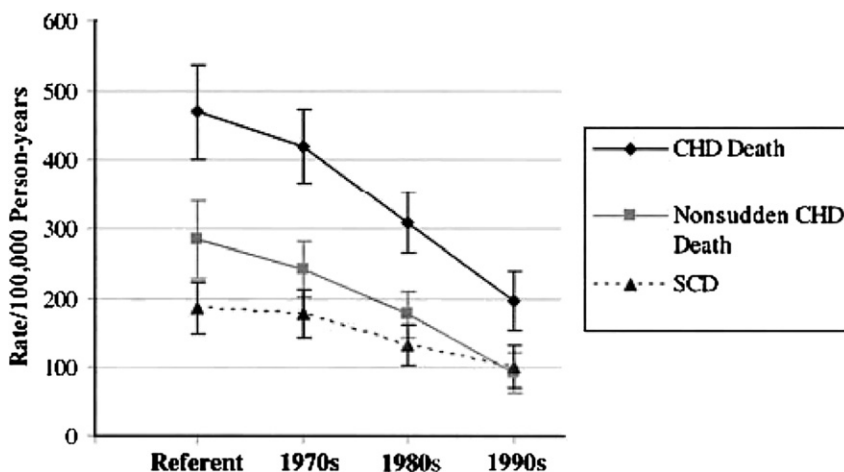


Fig. 5. Incidence rates adjusted for age and sex per 100,000 person-years for overall CHD mortality (solid black diamonds), nonsudden CHD death (squares), and SCD (triangles) from 1950 to 1969 (Referent) to 1990 to 1999 (1990s). Error bars represent 95% CIs. (From Fox CS, Evans JC, Larson MG, et al. Temporal trends in coronary heart disease mortality and sudden cardiac death from 1950 to 1999: the Framingham Heart Study. *Circulation* 2004;110(5):523; with permission.)

blood pressure decreased from 149 to 144 mm Hg, hypertension prevalence decreased from 67% to 63%, hypertension treatment increased from 8% to 36%, cholesterol decreased from 263 to 246 mg/dL, and smoking decreased from 52% to 26%. Diabetes increased from 9% to 19%, however, and BMI increased from 26.4 to 27.8 kg/m². Compared with the overall Framingham population, as might be expected, SCD victims had worse risk factors in the early (1950–1969) group (greater age, more males, higher mean blood pressure, higher cholesterol, more smokers, more diabetes, higher BMI). The changes that occurred by the time of the 1990 to 1999 cohort paralleled the changes that occurred in the overall Framingham population, but with greater risk value. Age, percentage of diabetics, and BMI increased more in the SCD victims from the 1950 to 1969 to the 1990 to 1999 groups compared with the overall Framingham sample. Mean blood pressure, prevalence of hypertension, mean cholesterol level, and percent smokers declined in the SCD victims but, with the exception of smoking, in 1990 to 1999 were still higher than in the overall Framingham sample. Although the proportion of diabetics and BMI increased in the whole Framingham sample, the SCD values were greater in the 1950 to 1969 years and increased more by 1990 to 1999. The risk profiles in the VTA death surrogate group therefore improved less with respect to hypertension and

cholesterol and worsened more with respect to age, diabetes, and BMI over the years compared with the entire Framingham sample. A possible interpretation of these risk profiles is that victims of fatal VTA were distinguished from the Framingham population as a whole as having worse risk factors at all periods of observation, as one would expect. Over time, however, as the incidence of SCD declined, deviation in risk profile seems to have increased, possibly because improved treatments have increased the intensity of certain risk factors necessary to result in VTA.

The risk profile of the nonsudden CHD victims over the course of the observation period differs little from that of the SCD victims. Specifically, age increased from 64 to 73 years, systolic blood pressure decreased from 154 to 141 mm Hg, hypertension prevalence increased slightly from 75% to 79%, hypertension treatment increased from 20% to 56%, cholesterol decreased from 268 to 240 mg/dL, and smoking decreased from 49% to 25%. Diabetes increased from 17% to 22% and BMI increased from 26.2 to 28.1 kg/m². The major difference was that the proportion of males was lower (62% in the 1950–1969 group to 67% in the 1990–1999 cohort) for the nonsudden CHD compared with the SCD group (see values given previously). A possible interpretation of these findings is that risk factors have similar influences on VTA-related CHD deaths and other CHD deaths.

Fox and colleagues [37] repeated the trend analyses after including 12 cases from 1990 to 1999 of participants who were resuscitated after a cardiovascular collapse and survived 1 hour or longer. These 12 cases would likely have resulted in SCD were it not for attempted resuscitation. The reduction in SCD plus resuscitated cardiovascular collapse in 1990 to 1999 compared with 1950 to 1969 was 38%, less than the reduction of 49% obtained when SCDs alone were considered. These findings suggest that measures leading to more effective resuscitation have contributed to the reduction in VTA-related deaths.

Contributors of the decline in incidence of death due to ventricular tachyarrhythmias

Elucidation of the factors that led to the decline in deaths due to VTA could provide important insights into specific treatments and direction for efficient use of health care resources. Studies discussed earlier indicate that most VTA deaths are related to CHD and that most of the decline in VTA deaths results from a decline of CHD deaths. The study of CHD deaths in the Framingham population showed that the decrease in VTA-related deaths reflects the decline in all CHD mortality over the past 50 years. Because the decrease in mortality was seen in subjects who did not have previously known CHD and subjects who had known CHD, the reduction in deaths is probably related to both primary prevention and secondary prevention. This theory was supported by a decline in several important risk factors. Conversely, other risk factors worsened and some did not seem to change. Of greater potential significance are risk factors that were not analyzed and treatments developed since the 1950s that have been shown to influence CHD mortality.

To determine the possible contributors to the decline in CHD deaths in the United States, Ford and colleagues [38] used a mortality model that incorporated risk factors and medical and surgical treatments. Their analysis included a wide array of treatments for several manifestations of CHD, including acute MI, unstable angina, secondary prevention after MI, secondary prevention after revascularization, chronic angina, and heart failure. Treatments related to acute MI, for example, included resuscitation, thrombolysis, primary angioplasty, primary coronary artery bypass grafting, beta-blocker, angiotensin-converting enzyme inhibitor, and aspirin. Inputs for each treatment included the prevalence of CHD conditions (eg,

number of people who had acute MI), the frequency of use of specific treatments (eg, aspirin), the case fatality rate, and the risk reduction due to treatment, all stratified by age and sex. The number of deaths prevented or postponed as a result of each intervention in each group of patients in the year 2000 was calculated by multiplying the number of people in each CHD condition by the proportion of those patients who received a particular treatment, by the case fatality rate over a period of 1 year, and by the relative reduction in the 1-year case fatality rate that was accounted for by the treatment.

Using United States vital statistics, Ford and colleagues [38] found that from 1980 through 2000, the age-adjusted death rate for CHD decreased from 542.9 to 266.8 deaths per 100,000 population among men and from 263.3 to 134.4 deaths per 100,000 population among women, resulting in 341,745 fewer deaths from CHD in 2000. Using their model of risk factor and treatment effects they determined that approximately 47% of this decrease in deaths could be attributed to treatments, including reductions attributable to secondary preventive therapies after MI or revascularization (11%), initial treatments for acute MI or unstable angina (10%), treatments for heart failure (9%), revascularization for chronic angina (5%), and other therapies (12%). Another 44% of the reduction in CHD deaths was attributed to changes in risk factors, including reductions in total cholesterol (24%), systolic blood pressure (20%), smoking prevalence (12%), and physical inactivity (5%), although these reductions were partially offset by increases in the BMI and the prevalence of diabetes, which accounted for an increased number of deaths (8% and 10%, respectively). Although this study did not specifically address VTA-related deaths, the evidence suggests that factors that reduce CHD deaths also reduce deaths due to VTA. This analysis implies that reduction of traditional CHD risk factors and evidence-based therapies of CHD complications have resulted in reductions in fatal VTA.

Disturbing trends

Unfortunately, there is evidence of a lessening of the decades-long decline in deaths due to VTA. Zheng and colleagues [35] reported that SCD rates decreased 8.3% (11.7% in men and 5.8% in women) during the 10-year period from 1989 to 1999. The decline was less among men aged

35 to 44 years (-2.8%) compared with all other male age groups (-5.7% to -18.1%). More alarming was the demonstrated increase in SCD rate of 21.1% among women aged 35 to 44 years.

Ford and Capewell [39] also found a lessening of the decline in CHD mortality from 1980 to 2002 in younger people. Between 1980 and 2002 they determined that the age-adjusted mortality rate declined 52% in men and 49% in women. The average annual rate of decline for men was 2.9% during the 1980s and 2.6% during the 1990s. For women, it was 2.6% and 2.4% , respectively. From 2000 through 2002, the average annual rate of decline was 4.4% for both men and women. The investigators derived the estimated annual percentage change in mortality (EAPCM), which allowed delineation and statistical evaluation of changes in slopes of time plots of CHD death incidence. Among men aged 35 to 54 years, the investigators found that EAPCM declined significantly from -6.2% during 1980 to 1989 to -2.3% during 1989 to 2000). This undesirable trend continued during 2000 to 2002 (EAPCM -0.5%). By contrast, among men 55 years and older, mortality rates improved in recent years. The investigators found that EAPCM was -2.6 between 1980 and 1990, declined significantly to -1.9 (1990–1996), but improved to -3.7 (1996–2002). The changes in CHD mortality rates were much more dramatically different between age groups in women. Among women 35 to 54 years, the EAPCM was -5.4% during 1980 to 1989, -1.2% during 1989 to 2000, and turned positive, 1.5% during 2000 to 2002. But among women 55 years and older the EAPCM increased significantly from -1.5 (1980–1999) to -4.8 (1999–2002).

Ford and Capewell [39] emphasize that the unfavorable trends in CHD mortality among young adults coincides with deterioration in several risk factors for CHD, including obesity, diabetes, and hypertension in younger adults compounded by stasis in cholesterol concentrations. The adverse trends in mortality have occurred despite continued decline in the prevalence of smoking and increasing use of evidence-based therapies, such as angioplasty, thrombolysis, angiotensin-converting enzyme inhibitors, statins, and antiplatelet agents.

Summary

Investigations of the impact of VA in populations have focused primarily on two aspects,

asymptomatic VEA and SCD. Despite a wealth of evidence that spontaneous VEA can cause fatal VTA and early reports that VEA identifies people at high risk for SCD, well-conducted studies have shown that VEA is an ambiguous signal. In people who do not have known heart disease, VEA is associated with undetected cardiac disease and as such is a risk factor for adverse events. The presence of VEA does not have an adverse prognosis in most people who do not have an identifiable cardiac disorder, however. In patients who have known heart disease, the presence of VEA is associated with more severe underlying disease and worse outcome but it is not specific for death due to VTA.

In contrast, MacWilliam's [1] speculation that SCD is caused by VTA continues to receive empiric support nearly 130 years later. MacWilliam's observation that CHD is an important background of death due to VTA remains the dominant belief today and this is supported by the observation that the decline in surrogates for fatal VTA during the past several decades parallels the decrease in CHD deaths. The reasons for the decline in fatal VTA are most likely reductions in CHD incidence and case fatality rate. There is no persuasive evidence that any specific antiarrhythmic treatment accounts for more than a small proportion of the reduced incidence of VTA deaths, and no risk factor is known to affect deaths due to VTA more than other modes of CHD deaths. Instead, the evidence supports the principle that reduction of deaths due to VTA is multifactorial and results from improved primary prevention (risk factor reduction before manifest CHD), treatment of CHD complications, and secondary prevention (risk factor control and other evidence-based treatments after manifest CHD).

Recent evidence for unfavorable trends for SCD and CHD mortality raises the specter of a reversal in the gains made against fatal VTA in recent decades. These adverse trends are all the more worrisome because they are occurring despite significant advances and wider use of preventive therapy and interventions. These dark clouds may nevertheless have a silver lining because the adverse CHD mortality trends have occurred in the context of worse control of potent risk factors and could be considered an affirmation that CHD risk factors have a crucial impact on mortality related to VTA and they provide clear targets for intervention. There is no time for complacency because there is a need to reverse the increasing incidence of risk factors, such as

obesity, diabetes, and metabolic syndrome, and there is a need to interrupt the strong influence of these risk factors on fatal VTA. The demonstration that basic and clinical research and public education have contributed to large reductions in fatal VTA, along with reductions in other forms of morbidity and mortality, is an achievement that should not be discounted at this critical time, because it illuminates the path to be followed to address the new challenges.

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