Sudden Cardiac Death in Patients with Diabetes

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Current Diabetes Reports 2004, **4**:187–193
Current Science Inc. ISSN 1534–4827

Sudden cardiac death (SCD) affects over 450,000 people in the United States annually. The mechanisms involved are poorly understood. The predictors currently known include traditional coronary heart disease risk factors, electrocardiographic abnormalities, cardiac autonomic neuropathy, left ventricular hypertrophy, cardiomyopathy, and conduction abnormalities. Diabetes mellitus and impaired glucose tolerance are of special importance due to their increased prevalence reaching epidemic proportions and the elevated risk of SCD in people with these disorders. This article reviews the current predictors of SCD with a focus on people with diabetes, hoping to offer physicians and researchers a better understanding of and a solid ground for further needed research on this important cause of premature death.

Introduction

Sudden cardiac death (SCD) is a major problem in industrialized nations [1••,2–14]. In 1999, there were over 450,000 cases of SCD, constituting approximately 63.4% of all coronary heart disease (CHD) deaths in the United States for that year, according to the Centers for Disease Control *Morbidity and Mortality Weekly Report* (CDC *MMWR*) [1••]. Traditional CHD risk factors, such as dyslipidemia, smoking, hypertension, age, vital capacity, obesity, heavy alcohol consumption, and diabetes mellitus (DM), are also predictive of SCD [2,3]. In particular, DM and impaired glucose tolerance (IGT) have been shown to increase the risk of cardiovascular disease (CVD) mortality and SCD [3–6].

Several mechanisms have been postulated to explain this increased predisposition to SCD in people with these disorders. Coronary thrombosis [7], as well as noncoronary microvascular and neural pathologies, have been implicated, including dysautonomia, prolonged QT, QT and QTc dispersion, left ventricular hypertrophy (LVH), diabetic cardiomyopathy, and ventricular arrhythmias [8–11]. Because three fifths of coronary fatalities occur outside the hospital with approximately half dying suddenly, prevention of SCD is a major component of reduction of CHD deaths [1••,4]. Further, with the increased prevalence of DM reaching epidemic proportions [12] and in the absence of specific predictors for SCD, targeting people with DM, especially through population-based approaches, may have a significant beneficial impact on SCD.

Definition and Epidemiology

Most studies define SCD as death occurring suddenly or unexpectedly within 1 hour of onset of symptoms, although some extend this period to 24 hours after onset of symptoms [4]. Around 44% of men and 63% of women with SCD have no previous history of CHD [2,6]. Current estimates of SCD in the United States, as of the February 15, 2002, CDC *MMWR* issue [1••], indicate that of the 728,743 cardiac disease deaths that occurred during 1999, a total of 462,340 (63.4%) were due to SCD. A total of 120,244 (16.5%) of these deaths occurred in an emergency department (ED) or were dead on arrival, and 341,780 (46.9%) occurred out of hospital. Further, in this report, when SCD was subclassified by age, gender, and ethnicity, men had a higher proportion of cardiac deaths that occurred in an ED or were dead on arrival compared with women (21.2% of 353,500 vs 12% of 375,243, respectively), whereas women had a higher total number of cardiac deaths and higher proportion of out-of-hospital cardiac deaths than men (51.9% of 375,243 and 41.7% of 353,500, respectively). SCDs accounted for 75.4% of the 13,873 cardiac disease deaths in persons aged 35 to 44 years, and the proportion of cardiac deaths that occurred out of hospital increased with age, from 5.8% in persons aged 0 to 4 years to 61.0% in persons aged ≥ 85 years. SCDs accounted for 63.7% of all cardiac deaths among white persons, 62.3% among black persons, 59.8% among American Indians or Alaska Natives, 55.8% among Asians or Pacific Islanders, and 54.2% among Hispanics [1••]. Thus, the fraction of cardiac deaths that are sudden are the same in white persons, black persons, and American

Indians and lower in Asians and Hispanics. Whites had the highest proportion of cardiac deaths out of hospital, and blacks had the highest proportion of cardiac deaths in an ED or dead on arrival.

It is important to note that death certificates are notoriously unreliable and are often at odds with the medical record. Thus, the figures just discussed are estimates of the real numbers. However, they still provide an idea of the overall impact of SCD as well as the difference of predisposition by ethnicity, age, and gender.

Despite the previously mentioned high crude incidence figures, the overall incidence of SCD is only 0.1% per year. In other words, 1000 people need to be targeted in prevention strategies to avoid one case of SCD [15]. This emphasizes the importance of safe, low-cost, population-based prevention approaches in the management of SCD.

Risk Factors

Diabetes as a risk factor for SCD

Diabetes mellitus and IGT have been associated with increased CVD mortality [5,16–20] and SCD [3,4,6,21,22]. For example, after 23-year follow-up on 8006 participants in the Honolulu Heart Program, those with DM or IGT were found to be at increased risk for SCD [4]. This relation was graded with a relative risk reaching 2.76 in those with DM versus those with normal sugar values [4]. This association held true for those who died within 1 hour as well as 24 hours after the onset of symptoms. The relation between DM and SCD was stronger in patients with DM who died suddenly due to unknown causes (53%) versus CHD-related (43%) total number of SCDs. This strengthens the hypothesis that a major contribution of DM to SCD may be through microvascular noncoronary complications, especially cardiac autonomic neuropathy (CAN), while recognizing the possible role of macrovascular complications, particularly coronary atherosclerosis. The Framingham study revealed a strong association between DM and SCD in women over 26 years of follow-up [21]. Further, in the PPSI (Paris Prospective Study I), DM was an independent risk factor for SCD even after adjusting for other known risk factors [22].

The increased predisposition to SCD in people with DM may be due to a combination of atherosclerosis, thrombosis, and neural factors. Diabetes-associated CAN and microvascular disease affecting the electrical conduction system of the heart may enhance the propensity to SCD in people with CHD. This is suggested by the relatively strong relationship between prolonged QT intervals and decreased RR variability (RRV), among other changes, and SCD in diabetic patients.

Impact of autonomic neuropathy and other cardiovascular abnormalities on SCD in people with diabetes

Dysglycemic subjects are prone to earlier development of microvascular and macrovascular abnormalities, leading to CAN [23••]. CAN confers high mortality in people with DM and IGT [24,25] and is associated with increased heart rate (HR), decreased RRV and baroreflex sensitivity (BRS), QT abnormalities, and ventricular arrhythmias.

Valsalva, deep breathing, and HR change between lying and standing are three of the cardiac autonomic function tests performed to objectively assess CAN (Table 1) [26]. RR-interval variations are used to reflect the results of these tests. With the patient seated, the Valsalva test consists of forcing exhalation and maintaining a pressure of 40 mm Hg for 15 seconds. The result is expressed as the ratio of RR maximum to RR minimum. The deep breathing test consists of taking six deep breaths for 1 minute in a lying position. The result is expressed as the mean ratio of maximal HR to minimal HR. In the lying-to-standing test, HR variation is determined again by calculating the maximal-to-minimal HR ratio; the maximal HR was approximately the fifteenth beat, and the minimal HR was approximately the thirtieth beat. The specificity of these measurements to sympathetic nervous system (SNS) or parasympathetic nervous system (PNS) function remains to be clarified [26].

Elevated basal HR and decreased heart rate variability (HRV) secondary to abnormalities of SNS and PNS have been shown to predict SCD [27,28]. In the PPSI, after 23-year follow-up of a cohort of 7746 subjects, elevated basal HR was confirmed as an independent risk factor for SCD in middle-aged men free of CHD. This relationship persisted even after adjusting for DM status, which was also found to be an independent SCD predictor [27]. Similar results on basal HR were obtained from Chicago [29], Framingham [30], and British Regional Heart [31] studies. Suggested mechanisms include increased myocardial oxygen consumption, decreased coronary blood supply secondary to decreased diastolic filling, overall poor health status, and possible associated ischemic or nonischemic cardiomyopathy [27]. However, the use of basal HR as a predictor of SCD is limited by the inherent variability such that no one threshold level of elevated HR can be considered abnormal for a given subject. Conversely, HRV is free of such limitation and, therefore, a more practical means to assess CAN.

Decreased HRV, defined as HRV on deep breathing of less than 10 bpm in a supine position, is a manifestation of CAN, especially decreased vagal modulation, in diabetic subjects [23••]. It was proven as an independent risk factor for SCD in a prospective study of 843 type 2 diabetic Veterans Affairs patients [23••]. The Framingham Heart Study [32], and an analysis from the Pittsburgh Epidemiology of Diabetes Complications Study [33], had similar findings. Also, in post-acute myocardial infarction (MI) patients, the prospective study ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) confirmed that decreased HRV and BRS, which is another tool to assess vagal tone, are strong predictors of cardiac and arrhythmic death, especially in people with low left ventricular ejection fraction (LVEF) [34].

Table 1. Reflex tests for CAN

Reflex tests for CAN	Terms of expression
Valsalva	Maximal-to-minimal RR ratio
Deep breathing	Maximal-to-minimal heart rate ratio
Lying-to-standing	Maximal-to-minimal heart rate ratio

CAN—cardiac autonomic neuropathy.

Other electrocardiographic (ECG) abnormalities have been reported useful in the prediction of SCD. QT prolongation was noticed in diabetic subjects with versus without CAN, predisposing them to an elevated SCD [8]. Also, QT dispersion (QTd), which is a measure of electrical inhomogeneity, reflecting on several cardiac abnormalities predisposing to SCD, including ischemic and nonischemic cardiomyopathy, cardiac fibrosis, and CAN, has been suggested as a screening tool and an early alert for SCD, especially in people with diabetes [9,10]. However, the predictive value of QTd and QTc has been quite inconsistent in a large number of studies, limiting the efficacy of these measurements as screening tools for SCD risk. Also, ventricular late potentials (VLPs) have been suggested to be helpful in predicting SCD because the duration of VLPs has been linked to fatal arrhythmias and SCD [11]. Moreover, a recent multicenter longitudinal observational study by Whang and Bigger [35] confirmed that reduced RRV is associated with increased long-term cardiac and arrhythmic mortality in post-MI patients. In diabetic patients, this association was at least as strong as in nondiabetic subjects [35]. As such, this study suggests that RRV is a promising valuable predictor of SCD in post-MI patients and emphasizes the role of CAN in elevated cardiac death, including SCD.

A possible common pathway through which CVD abnormalities, including advanced and subclinical CAN [36], lead to SCD in diabetes is by promoting ventricular arrhythmias, such as ventricular tachycardia and fibrillation [37]. In people with diabetes and dysautonomia, there is decreased vagal tone, probably due to parasympathetic arch damage [36]. This weakens the protective role of PNS for malignant ventricular arrhythmias, which are enhanced by the unopposed SNS activity. SNS activity predisposes to these arrhythmias through decreasing the refractoriness and increasing the excitability of the ventricles [28]. Other comorbidities, frequently present in people with DM, need to be examined in further studies to clarify whether this effect of altered PNS is causative, or just reflective, of abnormalities predisposing to SCD. Also, hyperadrenergic tone has been suggested by other studies as another contributory mechanism to increased SCD risk in people with DM [27].

About 60% of SCDs have CHD. However, in addition to thrombosis and ischemia-related conduction defects, autonomic neuropathy may enhance the propensity to SCD in those with CHD, through ventricular arrhythmias. In those without CHD, confounding effects of CHD-related comorbidities are lessened and, as such, one may speculate that CAN may play a more important role in the etiology of sudden death.

Role of coronary thrombosis in SCD among people with diabetes

Coronary causes constitute around 80% of SCDs [7]. The presence of DM seems to have a different effect on men versus women with CHD [7,38]. In women with CHD, especially older women, DM is associated with increased SCD risk in those with stable plaque and healed myocardium in the chronically ischemic heart with LVH [7]. However, no such association exists in those with plaque rupture or erosion, suggesting a more important role of noncoronary complications of DM in predisposing to SCD [7]. Conversely, in men with CHD one study failed to find an association between DM and SCD risk [38].

However, several studies have revealed that more severe coronary atherosclerosis is associated with SCD [39,40]. In a study of 1085 autopsies from Japanese-American men in Hawaii, 71% of SCDs had more severe coronary atherosclerosis in at least one out of the three main coronaries [39]. Similar results were presented by Davies and Thomas [40]. Because people with DM are prone to earlier development of macrovascular complications, including coronary atherosclerosis, it seems reasonable to think that DM increases SCD risk in those with CHD, in part through enhancing early coronary atherosclerosis and thrombosis, in addition to microvascular and neural complications, including CAN and subsequent arrhythmias.

Effect of silent ischemia on SCD risk in people with diabetes

Altered perception of pain may have an important, underestimated, and less well-studied role in the higher prevalence of SCD in diabetic individuals. The decreased sensation of ischemic cardiac pain and angina in this high-risk population may prevent or at least delay seeking medical attention for serious acute coronary syndromes. Further, it may lead to wrong triaging in the emergency room with subsequent delay in treatment, including defibrillation, elevating SCD risk [41]. Also, this decreased perception of angina may contribute to the elevated SCD secondary to exercise-induced arrhythmias by masking the anginal signal to stop. Additional research is needed in this area to quantify the prevalence of silent myocardial ischemia in DM and its relationship to SCD.

Effect of metabolic and vascular abnormalities associated with diabetes on SCD risk

Dysglycemia is increasingly being recognized as a part of a wider array of maladaptive cardiometabolic responses to obesity referred to as cardiometabolic syndrome, which is currently recognized as a disease entity [42•]. Dysglycemia, as well as several other associated disorders in the cardiometabolic syndrome, including dyslipidemia, elevated blood

pressure (BP), obesity, fibrinolytic and inflammatory disorders, have been associated with the elevated risk of SCD [2,6,7,38,43•]. Dyslipidemia, DM, and hypertension seem to be relevant in men, whereas dyslipidemia (*eg,* elevated total cholesterol, decreased high-density lipoprotein cholesterol, and hypertriglyceridemia) and diabetes are particularly significant in women as it relates to SCD risk [7,38].

The contribution of dysglycemia to SCD risk has been discussed in other sections of this article. Elevated cholesterol levels are associated with increased SCD risk, probably due to excessive plaque vulnerability [38]. Similar reasoning applies to the effect of the fibrinolytic and inflammatory abnormalities, associated with the cardiometabolic syndrome, through increased predisposition to plaque fragility and rupture leading to fatal MI [42•].

Also, elevated BPs were shown to be significantly associated with increased SCD risk [7,44,45]. The use of antihypertensive agents, predominantly high-dose diuretics [2,15] and potassium-wasting diuretics [2,46,47], may contribute to this risk, especially if hypokalemia or hypomagnesemia occur.

The Framingham multivariate risk index combined several of these metabolic abnormalities (*eg,* systolic BP, total cholesterol, and relative weight, which are also CHD risk factors), with other CHD risk factors (*eg,* age, smoking, HR, vital capacity, and ECG abnormalities, including LVH, intraventricular conduction delay, and nonspecific ST-T abnormalities), to predict the risk for SCD [2]. Risk of SCD increased steeply with each decile of multivariate risk. However, after 15-year follow-up, the actual number of SCDs was significantly lower than that predicted through the risk index. This does not negate the SCD risk attributed to these CHD risk factors and ECG abnormalities included in the risk index; rather, it emphasizes the need for more specific predictors of SCD. Nevertheless, a majority of SCDs are due to CHD, and the control of CHD risk factors has been repeatedly shown to decrease CHD deaths, including SCDs.

Other risk factors for SCD

Male gender carries three to four times the higher risk for SCD than female gender, outweighing the CHD risk factor differences [6,44]. However, with advancing age and increased burden of CHD risk factors, this difference decreases [6,13]. Cardiac protection against fatal arrhythmias has been hypothesized in premenopausal women [6].

Also, African-American ethnicity carries a higher risk for SCD than white persons [14]. It has been postulated that this is partially due to lower socioeconomic status as well as genetic factors [14]. In fact, parental SCD was shown to increase the risk of SCD in the PPSI [3], whereas a history of MI or cardiac arrest in a first-degree relative carried a higher risk for SCD in the case-control King County study [48]. Further, psychosocial stressors, including anxiety, depression, mental stressors, and social isolation, may add to the risk of SCD, presumably due to increased SNS activity with subsequently decreased HRV [49,50].

Management

Coronary heart disease deaths constitute up to 80% of SCDs. Thus, control of traditional CHD risk factors, which has been associated with a substantial decrease in CHD deaths, indirectly reduces SCDs. Currently, in the absence of specific predictors of SCD, control of CHD risk factors, including DM, seems to be an acceptable safe, low-cost SCD prevention strategy, especially through population-based approaches. This would include weight reduction, increased physical activity, cholesterol and BP lowering, and perhaps intensive glycemic control [51–71]. Although there is no definitive evidence for glycemic control preventing SCD, the evidence for improved survivorship in type 2 diabetes with treatment of low-density lipoprotein cholesterol and BP is much stronger and some consider it definitive.

Although no survival benefit could be detected, intensive glycemic control was shown by the DCCT (Diabetes Control and Complications Trial) in patients with type 1 DM to slow the development and progression of CAN in this high-risk population [51]. This beneficial effect of glycemic control is yet to be demonstrated in patients with type 2 DM. Nevertheless, the control of dysglycemia and associated CVD risk factors remains suboptimal [52]. Therefore, diabetes prevention is gaining momentum to reduce the burden of DM-related cardiovascular complications and elevated SCD risk [53]. In addition, this helps curb the rising prevalence of diabetes, which is reaching epidemic proportions [53]. This may be possible through lifestyle modifications and the use of metformin, acarbose, and glitazones, which have been confirmed in prospective randomized trials to lessen the development of DM [53]. Other ongoing large, prospective, randomized studies are investigating the potential of other agents, such as angiotensin-converting enzyme (ACE) inhibitors and other thiazolidinediones, in DM prevention [53].

Also, regular physical activity, in sufficient intensity, frequency, and duration, is encouraged because it helps condition the patients through physiologic changes consisting of increased vagal and decreased adrenergic tones. This reduces the risk of malignant arrhythmias and, subsequently, long-term SCD [42•,45,54,55], although during or shortly after vigorous exercise SCD risk increases transiently [56].

Additionally, nutritional factors have been associated with the risk of SCD [43•]. Two observational studies and one randomized study revealed beneficial effects of n-3 polyunsaturated fatty acids (PUFAs), derived primarily from fish, on SCD risk reaching 50% reduction, presumably through antiarrhythmic properties [57–59]. This is believed to operate through the modulation of sodium, potassium, and calcium channels [60,61]. Several prospective cohort studies revealed decreased cardiovascular mortality from amounts of fish, as small as one meal per week [62–65]. Eicosapentaenoic acid and docosahexaenoic acid are the main sources of n-3 PUFAs in fish.

α-Linoleic acid is another source in foods of plant origin, including tofu, soybean, canola oil, and nuts [43•], although there are no randomized studies yet on the effect of α-linoleic acid on SCD risk. Light to moderate alcohol intake may also have beneficial impact on SCD risk [66], whereas heavy intake worsens this risk [67]. Vitamin E and magnesium intake has also been reported to help reduce the SCD risk [43•].

As for pharmacologic interventions, β blockers have been reported to increase HRV by increasing vagal tone, and thus leading to decreased rate of ventricular arrhythmias, especially in post-MI patients [32,54,68]. Also, similar beneficial effects of ACE inhibitors include increasing HRV [69,70] and decreasing basal HR in subjects with congestive heart failure [71]. In addition, cholesterol-lowering therapy may be helpful in preventing SCD in men and women with dyslipidemia, especially those with DM [38]. This is believed to be via plaque stabilization rather than regression.

A few parameters, including decreased BRS, have been confirmed as specific predictors for SCD and may help in identifying high SCD risk patients who may then benefit from implantable cardioverter-defibrillator (ICD) therapy cost effectively in depressed LVEF setting. Therefore, until further studies identify more common and specific predictors of SCD, invasive cardiac interventions, including ICD therapy, do not seem cost-effective enough as population-based prevention strategies.

Conclusions

Sudden cardiac death remains a major health burden in industrialized nations and worldwide. People with DM and IGT are at increased risk of cardiovascular mortality and SCD. They are prone to earlier development of macrovascular complications, particularly coronary atherosclerosis and thrombosis and microvascular neural complications. Both of these are believed to play a role in the etiology of SCD in this high-risk population. Diabetes-associated CAN is of particular importance and may predispose people with and without coronary atherosclerosis to premature death via enhancing fatal ventricular arrhythmias. Although no specific SCD predictors are yet available, evidence suggests that some ECG abnormalities, including QT alterations and VLPs, are promising. Therefore, until more specific and cost-effective markers for SCD are discovered and because CHD deaths constitute a majority of SCDs, prevention and control of traditional CHD risk factors (especially in patients with type 2 DM, which is increasing in epidemic proportions), seems to be among the safest and most cost-effective strategies to prevent SCD, especially through population-based approaches.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1.•• **Center for Disease Control and Prevention: state-specific mortality from sudden cardiac death—United States, 1999 [no authors listed].** *MMWR Morb Mortal Wkly Rep* 2002, **51:**123–126.

This CDC *MMWR* issue provides the best current estimates of SCDs in the United States. It breaks down SCD by age, gender, and state where the death occurred. In many respects, the 1999 data are similar to the 1995 reference on 1993 data. The 1999 data show that the fraction of cardiac deaths that are sudden are the same in white persons, black persons, and American Indians, and lower in Asians and Hispanics.

2. Kannel WB, Schatzkin A: **Sudden death: lessons from subsets in population studies.** *J Am Coll Cardiol* 1985, **5:**141B–149B.
3. Jouven X, Desnos M, Guerot C, Ducimetiere P: **Predicting sudden death in the population: the Paris Prospective Study I.** *Circulation* 1999, **99:**1978–1983.
4. Curb JD, Rodriguez BL, Burchfiel CM, *et al.*: **Sudden death, impaired glucose tolerance, and diabetes in Japanese American men.** *Circulation* 1995, **91:**2591–2595.
5. Kannel WB, McGee DL: **Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham Study.** *Diabetes Care* 1979, **2:**120–126.
6. Kannel WB, Wilson PW, D'Agostino RB, Cobb J: **Sudden coronary death in women.** *Am Heart J* 1998, **136:**205–212.
7. Burke AP, Farb A, Malcom GT, *et al.*: **Effect of risk factors on the mechanism of acute thrombosis and sudden coronary death in women.** *Circulation* 1998, **97:**2110–2116.
8. Ewing DJ, Boland O, Neilson JM, *et al.*: **Autonomic neuropathy, QT interval lengthening, and unexpected deaths in male diabetic patients.** *Diabetologia* 1991, **34:**182–185.
9. Naas AA, Davidson NC, Thompson C, *et al.*: **QT and QTc dispersion are accurate predictors of cardiac death in newly diagnosed non-insulin dependent diabetes: cohort study.** *BMJ* 1998, **316:**745–746.
10. Elming H, Brendorp B, Kober L, *et al.*: **QTc interval in the assessment of cardiac risk.** *Card Electrophysiol Rev* 2002, **6:**289–294.
11. Tong NW, Yang TG, Liang JZ: **Ventricular late potentials in patients with diabetes mellitus.** *Zhonghua Nei Ke Za Zhi* 1993, **32:**464–466.
12. El-Atat F, McFarlane SI, Sowers JR: **Diabetes, hypertension and cardiovascular derangements: pathophysiology and management.** *Curr Hypertens Rep* 2004, **6:**215–223.
13. Kannel WB, Thomas HE Jr: **Sudden coronary death: the Framingham Study.** *Ann N Y Acad Sci* 1982, **382:**3–21.
14. Becker LB, Han BH, Meyer PM, *et al.*: **The CPR Chicago Project. Racial differences in the incidence of cardiac arrest and subsequent survival.** *N Engl J Med* 1993, **329:**600–606.
15. Myerburg RJ, Kessler KM, Castellanos A: **Sudden cardiac death: epidemiology, transient risk, and intervention assessment.** *Ann Intern Med* 1993, **119:**1187–1197.
16. Sowers JR: **Recommendations for special populations: diabetes mellitus and the metabolic syndrome.** *Am J Hypertens* 2003, **16(11 suppl):**41–45.
17. Schumacher MC, Smith KR: **Diabetes in Utah among adults: interaction between diabetes and other risk factors for microvascular and macrovascular complications.** *Am J Public Health* 1988, **78:**1195–1201.
18. Butler WJ, Ostrander LD, Carman WJ, Lamphiear DE: **Mortality from coronary heart disease in the Tecumseh Study: long-term effect of diabetes mellitus, glucose intolerance and other risk factors.** *Am J Epidemiol* 1985, **121:**541–547.
19. Morrish NJ, Stevens LK, Fuller JH, *et al.*: **Incidence of macrovascular disease in diabetes mellitus: the London cohort of the WHO Multinational Study of Vascular Disease in Diabetics.** *Diabetologia* 1991, **34:**584–589.

20. Mihara T, Oohashi H, Hirata Y: **Mortality of Japanese diabetics in a seven-year follow-up study.** *Diabetes Res Clin Pract* 1986, **2:**139–144.
21. Kannel WB, McGee DL: **Epidemiology of sudden death: insights from the Framingham Study.** In *Sudden Cardiac Death.* Edited by Josephson ME. Philadelphia, PA: FA Davis Co.; 1985:93–104.
22. Balkau B, Jouven X, Ducimetiere P, Eschwege E: **Diabetes as a risk factor for sudden death.** *Lancet* 1999, **354:**1968–1969.
23.•• Wheeler SG, Ahroni JH, Boyko EJ: **Prospective study of autonomic neuropathy as a predictor of mortality in patients with diabetes.** *Diabetes Res Clin Pract* 2002, **58:**131–138.

This study tackled a very promising and novel concept in the prediction of SCD, which is to discover a more specific marker for the prediction of SCD. This marker was autonomic neuropathy as reflected by HRV. The study confirmed an independent significance of decreased HRV in the prediction of SCD in diabetic subjects.

24. Rathman W, Ziegler D, Jahnke M, *et al.*: **Mortality in diabetic patients with cardiovascular autonomic neuropathy.** *Diabet Med* 1993, **10:**820–824.
25. Ewing DJ, Campbell IW, Clarke BF: **The natural history of diabetic autonomic neuropathy.** *Q J Med* 1980, **49:**95–108.
26. Valensi P,Huard JP,Giroux C,Attali JR:**Factors involved in cardiac autonomic neuropathy in diabetic patients.** *J Diabetes Complications* 1997,**11:**180–187.
27. Jouven X, Zureik M, Desnos M, *et al.*: **Resting heart rate as a predictive risk factor for sudden death in middle-aged men.** *Cardiovasc Res* 2001, **50:**373–378.
28. Zipes DP, Levy MN, Cobb LA, *et al.*: **Sudden cardiac death: neural-cardiac interactions.** *Circulation* 1987, **76:**1202–1207.
29. Dyer AR, Persky V, Stamler J *et al.*: **Heart rate as a pronostic factor for coronary heart disease and mortality: findings in three Chicago epidemiologic study.** *Am J Epidemiol* 1980, **112:**736–749.
30. Kannel WB, Kannel C, Paffenbarger RS, *et al.*: **Heart rate and cardiovascular mortality: the Framingham study.** *Am Heart J* 1987, **113:**1489–1494.
31. Shaper AG, Wannamethee G, Macfarlane PW, *et al.*: **Heart rate, ischaemic heart disease, and sudden cardiac death in middle-aged British men.** *Br Heart J* 1993, **70:**49–55.
32. Cook JR, Bigger JT, Kleiger RE, *et al.*: **Effect of atenolol and diltiazem on heart rate variability in normal persons.** *J Am Coll Cardiol* 1991, **17:**480–484.
33. Orchard TJ, Lloyd CE, Maser RE, Kuller LH: **Why does diabetic autonomic neuropathy predict IDDM mortality? An analysis from the Pittsburgh Epidemiology of Diabetes Complications Study.** *Diabetes Res Clin Pract* 1996, **34(suppl):**S165–S171.
34. La Rovere MT, Pinna GD, Hohnloser SH, *et al.*: **Autonomic tone and reflexes after myocardial infarction. Baroreflex sensitivity and heart rate variability in the identification of patients at risk for life-threatening arrhythmias: implications for clinical trials.** *Circulation* 2001, **103:**2072–2077.
35. Whang W, Bigger JT Jr: **Comparison of the prognostic value of RR-interval variability after acute myocardial infarction in patients with versus those without diabetes mellitus.** *Am J Cardiol* 2003, **92:**247–251.
36. Wirta O, Pasternack A, Mustonen J, Laippala P: **Renal and cardiovascular predictors of 9-year total and sudden cardiac mortality in non-insulin-dependent diabetic subjects.** *Nephrol Dial Transplant* 1997, **12:**2612–2617.
37. Bigger JT Jr: **Spectral analysis of R-R variability to evaluate autonomic physiology and pharmacology and to predict cardiovascular outcomes in humans.** In *Cardiac Electrophysiology from Cell to Bedside,* edn 2. Edited by Zipes DP, Jalife J. Philadelphia, PA: WB Saunders; 1995:1151–1170.
38. Burke AP, Farb A, Malcom GT, *et al.*: **Coronary risk factors and plaque morphology in men with coronary disease who died suddenly.** *N Engl J Med* 1997, **336:**1276–1282.
39. Yano K, McCarthy LJ, Reed DM, Kagan A: **Postmortem findings in sudden and non-sudden deaths among Japanese-American men in Hawaii.** *Am J Med* 1987, **83:**1037–1044.
40. Davies MJ, Thomas A: **Thrombosis and acute coronary-artery lesions in sudden cardiac death.** *N Engl J Med* 1984, **310:**1137–1140.
41. Timmis AD: **Diabetic heart disease: clinical considerations.** *Heart* 2001, **85:**463–469.
42.• El-Atat F, Aneja A, Mcfarlane SI, Sowers JR: **Obesity and hypertension.** *Endocrinol Metab Clin North Am* 2003, **32:**823–854.

A thorough review of the maladaptive cardiovascular and metabolic responses to obesity in the cardiometabolic syndrome, with a focus on obesity-related cardiovascular derangements and an overview of the associated fibrinolytic and inflammatory disorders contributing to plaque vulnerability.

43.• Albert CM, Ruskin JN: **Risk stratifiers for sudden cardiac death (SCD) in the community: primary prevention of SCD.** *Cardiovasc Res* 2001, **50:**186–196.

This is a valuable review of the available predictors of SCD. It also sheds light on the mounting evidence on the beneficial effect of some nutritional elements and other nonpharmacologic approaches on SCD risk.

44. Albert CM, McGovern BA, Newell JB, Ruskin JN: **Sex differences in cardiac arrest survivors.** *Circulation* 1996, **93:**1170–1176.
45. **Multiple risk factor intervention trial. Risk factor changes and mortality results. Multiple Risk Factor Intervention Trial Research Group [no authors listed].** *JAMA* 1982, **248:**1465–1477.
46. Siscovick DS, Raghunathan TE, Psaty BM, *et al.*: **Diuretic therapy for hypertension and the risk of primary cardiac arrest.** *N Engl J Med* 1994, **330:**1852–1857.
47. **Baseline rest electrocardiographic abnormalities, antihypertensive treatment, and mortality in the Multiple Risk Factor Intervention Trial. Multiple Risk Factor Intervention Trial Research Group [no authors listed].** *Am J Cardiol* 1985, **55:**1–15.
48. Friedlander Y, Siscovick DS, Weinmann S, *et al.*: **Family history as a risk factor for primary cardiac arrest.** *Circulation* 1998, **97:**155–160.
49. Rozanski A, Blumenthal JA, Kaplan J: **Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy.** *Circulation* 1999, **99:**2192–2217.
50. Januzzi JL, Stern TA, Pasternak RC, DeSanctis RW: **The influence of anxiety and depression on outcomes of patients with coronary artery disease.** *Arch Intern Med* 2000, **160:**1913–1921.
51. **The effect of intensive diabetes therapy on measures of autonomic nervous system function in the Diabetes Control and Complications Trial (DCCT) [no authors listed].** *Diabetologia* 1998, **41:**416–423.
52. McFarlane SI, Jacober SJ, Winer N, *et al.*: **Control of cardiovascular risk factors in patients with diabetes and hypertension at urban academic medical centers.** *Diabetes Care* 2002, **25:**718–723.
53. McFarlane SI, Shin JJ, Rundek T, Bigger JT: **Prevention of type 2 diabetes.** *Curr Diabetes Rep* 2003, **3:**235–241.
54. Schwartz PJ, Randall WC, Anderson EA, *et al.*: **Sudden cardiac death. Nonpharmacologic interventions.** *Circulation* 1987, **76(1 Pt 2):**I215–I219.
55. Wannamethee G, Shaper AG, Macfarlane PW, Walker M: **Risk factors for sudden cardiac death in middle-aged British men.** *Circulation* 1995, **91:**1749–1756.
56. Albert CM, Mittleman MA, Chae CU, *et al.*: **Triggering of sudden cardiac death by vigorous exertion.** *N Engl J Med* 2000, **343:**1351–1361.
57. Siscovick DS, Raghunathan TE, King I, *et al.*: **Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest.** *JAMA* 1995, **274:**1363–1367.
58. Albert CM, Hennekens CH, O'Donnell CJ, *et al.*: **Fish consumption and decreased risk of sudden cardiac death.** *JAMA* 1998, **279:**23–28.
59. **Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico [no authors listed].** *Lancet* 1999, **354:**447–455.

60. Kang JX, Leaf A: **Antiarrhythmic effects of polyunsaturated fatty acids: recent studies.** *Circulation* 1996, **94:**1774–1780.
61. Billman GE, Kang JX, Leaf A: **Prevention of sudden cardiac death by dietary pure omega-3 polyunsaturated fatty acids in dogs.** *Circulation* 1999, **99:**2452–2457.
62. Kromhout D, Bosschieter EB, de Lezenne Coulander C: **The inverse relation between fish consumption and 20-year mortality from coronary heart disease.** *N Engl J Med* 1985, **312:**1205–1209.
63. Norell SE, Ahlbom A, Feychting M, Pederson NL: **Fish consumption and mortality from coronary heart disease.** *BMJ* 1986, **293:**426.
64. **Fish consumption and mortality from coronary heart disease [no authors listed].** *N Engl J Med* 1985, **313:**820–824.
65. Daviglus ML, Stamler J, Orencia AJ, *et al.*: **Fish consumption and the 30-year risk of fatal myocardial infarction.** *N Engl J Med* 1997, **333:**1046–1053.
66. Albert CM, Manson JE, Cook NR, *et al.*: **Moderate alcohol consumption and the risk of sudden cardiac death among US male physicians.** *Circulation* 1999, **100:**944–950.
67. Wannamethee G, Shaper AG: **Alcohol and sudden cardiac death.** *Br Heart J* 1992, **68:**443–448.
68. Yusuf S, Peto R, Lewis J, *et al.*: **Beta blockade during and after myocardial infarction an overview of the randomized trials.** *Prog Cardiovasc Dis* 1985, **27:**335–371.
69. Kontopoulos AG, Athyros VG, Papageorgiou AA, *et al.*: **Effect of angiotensin-converting enzyme inhibitors on the power spectrum of heart rate variability in post-myocardial infarction patients.** *Coron Artery Dis* 1997, **8:**517–524.
70. Binkley PF, Haas GJ, Starling RC, *et al.*: **Sustained augmentation of parasympathetic tone with angiotensin-converting enzyme inhibition in patients with congestive heart failure.** *J Am Coll Cardiol* 1993, **21:**655–661.
71. **Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators [no authors listed].** *Lancet* 1993, **342:**821–828.