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Type 2 diabetes mellitus and the risk of sudden cardiac arrest in the community

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Abstract

The reduction of mortality from sudden cardiac arrest (SCA) in the setting of coronary heart disease (CHD) remains a major challenge, especially among patients with type 2 diabetes. Diabetes is associated with an increased risk of SCA, at least in part, from an increased presence and extent of coronary atherosclerosis (macrovascular disease). Diabetes also is associated with microvascular disease and autonomic neuropathy; and, these non-coronary atherosclerotic pathophysiologic processes also have the potential to increase the risk of SCA. In this report, we review the absolute and relative risk of SCA associated with diabetes. We summarize recent evidence that suggests that the increase in risk in patients with diabetes is not specific for SCA, as diabetes also is associated with a similar increase in risk for non-SCA CHD death and non-fatal myocardial infarction. These data are consistent with prior observations that coronary atherosclerosis is a major contributor to the increased SCA risk associated with diabetes. We also present previously published and unpublished data that demonstrates that both clinically-recognized microvascular and autonomic neuropathy also are associated with the risk of SCA among treated patients with diabetes, after taking into account prior clinically-recognized heart disease and other risk factors for SCA. We then discuss how these data might inform research and clinical efforts to prevent SCA. Although the prediction of SCA in this “high” risk population is likely to remain a challenge, as it is in other “high” risk clinical populations, we suggest that current recommendations for the prevention of SCA in the community, related to both lifestyle prescriptions and risk factor reduction, are likely to reduce mortality from SCA among patients with diabetes.

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Keywords

Diabetes mellitus; Sudden cardiac death; Cardiac arrest; Coronary heart disease; Autonomic dysfunction; Microvascular disease

1 Introduction

The reduction of mortality from sudden cardiac arrest (SCA) in the setting of coronary heart disease (CHD) remains a major challenge, especially among patients with type 2 diabetes [1–3]. There is mounting evidence that type 2 diabetes is associated with an increased risk of mortality from coronary heart disease and SCA [4–13]. The increased risk of CHD mortality and SCA among patients with diabetes likely results, at least in part, from the increased presence and extent of coronary atherosclerosis (macrovascular disease) due to abnormalities of glucose/insulin homeostasis and/or other risk factors, such as dyslipidemia, high blood pressure, and renal disease. Diabetes also is associated with micro-vascular disease and autonomic neuropathy; and, these non-coronary atherosclerotic pathophysiologic processes also have the potential to influence CHD mortality and SCA among patients with diabetes [14–17]. However, few prior studies have assessed the risk of CHD mortality and SCA associated with clinically-recognized and subclinical micro-vascular disease or diabetic autonomic neuropathy.

In this review, we provide estimates of the absolute and relative risk of SCA associated with diabetes, examine whether the increase in risk is specific for sudden (coronary heart disease) cardiac arrest and not other forms of fatal and non-fatal CHD, and provide previously unpublished evidence that both clinically-recognized microvascular disease and diabetic autonomic neuropathy are associated with the risk of SCA in treated diabetic patients, after taking into account other risk factors for SCA. We then discuss efforts to prevent SCA and we put these findings into a clinical context. We note that while several factors have been identified that are associated with the risk of SCA in patients with diabetes, the prediction of SCA in this “high risk” population is likely to remain a challenge, as it has for other “high risk” clinical populations, such as patients with a prior myocardial infarction or congestive heart failure. Nevertheless, several clinical recommendations have the potential to reduce mortality from SCA among patients with diabetes.

2 Sudden cardiac arrest

SCA, also known as out-of-hospital cardiac arrest due to a cardiac etiology, remains a major cause of mortality among the general population and especially among patients with Type 2 diabetes. In the general population, SCA accounts for approximately 10% of total mortality and 40% of mortality from coronary heart disease (CHD), the major cause of mortality in Western populations [18, 19]. SCA is typically viewed as a heterogeneous condition: a variety of pathologic conditions, electrophysiologic characteristics, and molecular pathways can influence risk of SCA. However, clinical and autopsy studies have consistently demonstrated a predominant, common pathophysiology: the most common pathologic substrate for SCA in adults is atherosclerotic CHD (85%) and the most common electro-physiologic mechanism for SCA is ventricular fibrillation (VF). SCA frequently occurs in the setting of prior MI or heart failure, but it also commonly occurs among those without overt heart disease. For all these substrates, a final common mechanism may be the susceptibility of the myocardium to VF. In the absence of resuscitation and return of spontaneous circulation, SCA is uniformly fatal.

While the exact molecular mechanism(s) of SCA due to VF is poorly understood, two conditions appear to be important for the initiation of VF that results in SCA: (1) an abnormal substrate leading to aberrant electrogenesis and propagation, and (2) a transient triggering event. The effect of a transient disturbance on a susceptible substrate is thought to lead to electrical instability. The proximal molecular determinants of normal electrogenesis involve ion channel function. However, pathways that influence ion channels, e.g. neurohumoral modulator pathways and intermediary signaling pathways, also have the potential to influence SCA. Disturbances in any of these biologic processes can lead to VF. The complexity of potential molecular mechanisms of SCA means that there are a variety of factors, both genetic and environmental, that need to be examined to explore more fully potential determinants of SCA.

Epidemiologic studies have identified demographic and clinical characteristics associated with SCA. Despite differences in populations, study designs, the availability of clinical data, and the operational definitions used to classify SCA, the results of prior epidemiologic studies generally have been consistent. The risk of SCA has been consistently associated with older age, male gender, and black race, as well as coronary heart disease risk factors, markers of subclinical disease, and clinical disease.

3 Diabetes and SCA

SCA occurs in the setting of abnormalities of the coronary arteries, myocardium, and electrogenesis and propagation in the heart. Of particular relevance to this review, type 2 diabetes is associated with a set of interrelated determinants of SCA risk, including: 1) the presence and extent of atherosclerotic coronary artery disease that results in clinical CHD; 2) patchy areas of myocardial fibrosis that results in impaired left ventricular (LV) filling (diastolic dysfunction) and/or LV systolic heart failure; and, 3) abnormalities of electrical propagation in the myocardium that is reflected in electrocardiographic repolarization and conduction abnormalities, e.g. prolongation of the QT—interval and QRS—interval. These characteristics are known to be associated with an increased risk of SCA in the community.

In a prior study conducted in a large HMO in Western Washington State, we estimated the incidence of SCA and confirmed that the absolute risk of SCA was associated with older age, male gender, risk factors (treated hypertension, treated diabetes, active smoking) and clinical cardiovascular disease (particularly CHF and prior MI) [20] We identified all of the cases of SCA (1,275 events) in a defined population (675,910 person years of observation) occurring from 1986 to 1994 among persons 50–79 years of age. The incidence rate of SCA was 0.82 (95% CI 0.74–0.90) per 1000 patient-years among those without clinically-recognized heart disease (e.g. CHD, CHF, atrial or ventricular arrhythmias, or congenital or valvular heart disease); and, the incident rate was 5.98 (95% CI 5.59–6.40) per 1000 patient-years among those with clinically-recognized heart disease. Approximately 5% of the HMO enrollees in this age range had treated diabetes during the study period. The incidence rate of SCA was 3.15 (95% CI 2.39–4.08) per 1000 patient-years among patients with diabetes without prior clinically-recognized heart disease; and, the incident rate was 13.80 (95% CI 11.96–15.84) per 1000 patient-years among patients with diabetes with clinically-recognized heart disease.

Type 2 diabetes is associated with a 2–4 fold increase in the risk of SCA [9–13]. Most but not all risk factors for SCA are known risk factors for other manifestations of CHD, including fatal (non SCA) CHD and non-fatal MI. For this reason, some argue that SCA is not a disease but a common mechanism of CHD death, given the importance of coronary atherosclerosis in all of the clinical manifestations of CHD. However, there is mounting evidence that both myocardial and electrical abnormalities that are independent of coronary

atherosclerosis also likely influence the risk of SCA. Several studies have sought to identify factors related to SCA specifically and not to other manifestations of CHD.

In a report from the Paris Prospective Study, there was a suggestion that diabetes might specifically increase the risk of SCA but not non-SCA CHD mortality [12]. However, the proportion of subjects with diabetes (combined diagnosed and screened based upon an oral glucose tolerance test) in this cohort of middle-aged men at baseline was 5%. As a result of the small number of subjects with clinical and screened diabetes, there were few events over the 20 year follow-up among those with diabetes, limiting the statistical power to detect differences in the associations of diabetes with these CHD related outcomes.

In contrast, a recent report from the Atherosclerosis Risk in Communities Study (ARIC), based upon a substantially larger number of patients with diabetes followed for 12 years with a larger number of events, demonstrated that the magnitude of the relative increase in risk associated with diabetes was similar for SCA, non SCA cardiac death, and non-fatal myocardial infarction [21]. The presence of diabetes at baseline was associated with a 2.6 fold increase in SCA (95% CI 1.9–3.5), a 2.6 fold increase in non-SCA death (95% CI 1.7–3.9) and a 2.2 fold increase in non-fatal MI (95% CI 1.9–2.8), after adjustment for age, gender, race, site, smoking, blood pressure, anti-hypertensive medication use and HDL-cholesterol. Of note, adjustment for lipids and blood pressure attenuated the associations for all three outcomes; but, further adjustment for smoking, creatinine, hemostatic and inflammatory markers did not attenuate the associations. In this large, bi-racial cohort, diabetes was not specifically associated with SCA, pointing to a common underlying pathophysiology for these CHD events, such as atherosclerotic coronary heart disease.

Importantly, the report from ARIC assessed both the relative risk and absolute risk of CHD/SCA associated with diabetes among demographically-defined subsets of the study population. There was no evidence that the associations, reflected by estimates of relative risk, differed by race or gender, although the absolute risk of each of the outcomes were higher among blacks and men than whites and women respectively. Of note, the absolute incident rates, of both SCA and non-SCA death were similar in diabetic men and women, although the incidence rates were higher in non-diabetic men than women. This was not true for non-fatal MI, where the incident rates were higher for both diabetic men and non-diabetic men than in diabetic women and non-diabetic women respectively. In short, the presence of diabetes attenuated the gender difference in absolute risk for both SCA and non-SCA CHD death but not for non-fatal MI.

4 Diabetes complications and SCA

Type 2 diabetes also is a heterogeneous condition, with abnormalities of insulin resistance and insulin secretion; and, these abnormalities can impact multiple pathways involved in the development of macrovascular and micro-vascular diseases, conditions that have the potential to influence the risk of SCA. Few epidemiologic studies have taken into account the heterogeneity of type 2 diabetes and with few exceptions the studies have focused on the role of macrovascular and not the role of microvascular abnormalities in contributing to clinical cardiovascular diseases, such as SCA.

We examined the associations of glycemia/diabetes and microvascular disease, defined by the presence of a physician-diagnosis of retinopathy and/or urine protein, with SCA, among those with and without impaired glucose tolerance and diabetes in the setting of an HMO in Western Washington State [13]. Compared to a referent group with no diabetes (defined as plasma glucose<7.7 mmol/L and without physician diagnosis of diabetes), the risk of SCA was progressively higher among enrollees with borderline diabetes (OR=1.24; 95% CI 0.98–1.57), diabetes without microvascular disease (OR=1.73, 95% CI 1.28–2.34), and diabetes

with microvascular disease (OR 2.66, 95% CI 1.84–3.85), after adjustment for smoking, systolic blood pressure, anti-diabetic treatment, prior myocardial infarction and congestive heart failure (P-value for trend < .001) [13]. The increase in SCA risk across these categories was seen both among those with and without prior clinically-recognized heart disease and among men and women. However, microvascular complications in the absence of elevated glucose (< 7.7 mmol/L) were not associated with an increased risk of SCA.

We also examined the associations of both clinically-recognized microvascular disease and diabetic autonomic neuropathy with SCA among pharmacologically-treated patients with diabetes in the HMO in Washington State using a nested case-control study design. Since these findings have not been published previously, we briefly describe the methods, findings, and implications below. We included treated diabetic patients 18–79 years who were enrolled for at least 1 year or had four or more clinic visits in the prior year, and had physician-diagnosed diabetes noted in their ambulatory care medical record and were treated with oral hypoglycemics or insulin. In this analysis, we included patients with and without prior physician-diagnosed heart disease. SCA cases were enrollees in the HMO with treated diabetes who experienced a sudden pulseless condition without a known non-cardiac cause between January 1980 and December 1994. Others, including the American College of Cardiology, the American Heart Association, and the Heart Rhythm Society, recently have proposed similar definitions [22].

We identified potential cases from Seattle and suburban King County emergency medical service incident reports and the HMO death records. Potential controls were a stratified random sample of enrollees with treated diabetes, frequency matched to cases within strata defined by age in decades, sex, and index year. We used information from ambulatory care medical records, EMS incident reports, medical examiner and autopsy reports (when available) to exclude cases with prior, non-cardiac, life-threatening conditions. We used the date of SCA as the index date for each case, and we randomly assigned an index date for each subject from the distribution of case index dates. Clinical characteristics, such as prior myocardial infarction and congestive heart failure, stroke, hypertension (blood pressure), physician-diagnosed diabetes, duration of diabetes, glucose levels, presence of microvascular disease, e.g. retinopathy and protein in the urine, and diabetic autonomic neuropathy, e.g. orthostatic hypotension, syncope, gastroparesis, diabetic diarrhea, were determined by a review of ambulatory care medical records for the period prior to the index date. ECGs from the medical record prior to the index date were read in a standardized fashion, blinded to case-control status. Treatment with medications at the index date was determined using an HMO computerized pharmacy database.

While the presence and extent of prior heart disease is a major determinant of SCA, it was not the focus of our research. For this reason, we stratified the sampling of controls in this study by pharmacologic markers of heart disease, so they would be more similar to the cases in the presence of prior heart disease. As a result, the proportion of controls with prior myocardial infarction and congestive heart failure and severe angina was substantially greater than in a random sample of the diabetic patient population within the HMO. We note, therefore, that comparisons of the prevalences of specific forms of heart disease across case-control groups may underestimate the association of these conditions with SCA. The data on the presence and extent of prior heart disease included in Table 1 are primarily for descriptive purposes and to indicate the rationale for further adjustment for prior forms of heart disease in our analyses. The residual differences observed in these prior physician-diagnosed clinical cardiovascular conditions reflects the fact that cases of SCA had more severe manifestations of heart disease than the controls, after applying the frequency matching for any form of heart disease in the design. To minimize the impact of these

residual differences, we further adjusted for each specific form of heart disease in our analyses as noted below.

The characteristics of the SCA cases and controls with treated diabetes included in the analysis are presented in Table 1. As expected, age and gender were not related to case-control status, given the matching on the characteristics in the study design. In bi-variate unadjusted analyses, the prevalence of current smoking, and the mean values for heart rate, serum total cholesterol, and serum creatinine were higher among SCA cases with diabetes compared to controls with diabetes. Even after matching on the presence of any form of heart disease in the design and sampling of controls, noted above, the prevalences of both myocardial infarction and congestive heart failure were higher among the cases than controls: more severe manifestations of prior heart disease than stable angina, for example, were more common among SCA cases than controls.

The means of non-fasting glucose levels and duration of diabetes and the prevalence of insulin treatment, a marker of severity of type 2 diabetes, were higher among cases than controls. Of note, markers of microvascular disease and autonomic neuropathy also were more common among cases than controls. When examined simultaneously in a conditional logistic regression model that adjusted for congestive heart failure, myocardial infarction, systolic blood pressure, current smoking, and treatment with insulin, both clinically-recognized microvascular disease and autonomic neuropathy were associated with a 50% increase in the risk of SCA (for microvascular disease, OR=1.56; 95% CI 1.15–2.11; and, for diabetic autonomic neuropathy, OR=1.51; 95% CI 1.02–2.24). Further adjustment of other factors included in Table 1, such as serum creatinine, duration of diabetes, heart rate, and the QT interval altered these estimates of risk only slightly (Table 2). There also was little evidence to suggest that the associations of both microvascular disease and autonomic neuropathy with SCA among treated patients with diabetes differed among those with and without prior clinically-recognized heart disease, although the statistical power to detect these interactions was limited.

Numerous epidemiologic studies have demonstrated associations of blood glucose level with CHD among those without diabetes; and, several studies have demonstrated similar associations with SCA. In our population-based case-control study in the HMO, higher glucose levels were associated with the risk of SCA both in the absence and in the presence of microvascular disease [13]. In contrast, glucose levels within the pre-diabetic range (fasting serum glucose level of 100–126 mg/dl among those not meeting criteria for diabetes) were not associated with an increased risk of CHD and SCA, when compared to fasting serum glucose level <100 mg/dl in the ARIC Study [21, 23].

Diabetes is the major determinant of microvascular disease processes, and microvascular disease also can lead to ischemia and/or electrophysiologic abnormalities that predispose to arrhythmia. At autopsy, the hearts of patients with diabetes commonly are found to have small, patchy, areas of myocardial fibrosis, most likely due to microvascular disease. It is possible that these pathologic abnormalities account, at least in part, for resting ECG abnormalities, such as non-specific ST-T wave changes and QT prolongation; and, these ECG abnormalities (or their determinants) may lead to an increased risk of SCA. Additionally, the myocardial abnormalities associated with microvascular disease may contribute to impairment of LV filling (e.g. diastolic dysfunction) in patients with Type 2 diabetes.

Diabetes also is associated with autonomic neuropathy due to nerve damage and results in abnormal cardiac reflexes. Diabetic autonomic neuropathy is associated with an increase in sympathetic and decrease in parasympathetic tone. Prior studies have sought to determine

whether these autonomic nervous system changes have the potential to influence SCA, but these studies have been limited by the number of SCA events [24]. For this reason, several studies have focused on the association of glucose levels with subclinical markers of autonomic neuropathy, such as heart rate variability. In the Framingham Study, higher plasma glucose levels were associated lower heart rate variability [25]. In the ARIC Study, glucose levels within both the diabetic and pre-diabetic range also were associated with altered heart rate variability [26]. However, whether reduced heart rate variability in diabetic patients is associated with SCA after taking into account other risk factors remains unknown.

Several studies have demonstrated that diabetes is associated with cardiac repolarization abnormalities, characterized by prolongation of the QT-interval, a known risk factor for SCA [27–29]. In our population-based study in the HMO in Western Washington State, among patients with type 2 diabetes and without prior physician-diagnosed heart disease, we found that the risk of SCA was associated with QT prolongation, after taking into account age, race, clinical characteristics (smoking, hypertension, diastolic blood pressure, body mass index, diabetes type, diabetes duration, metabolic complications, cerebrovascular disease, peripheral vascular disease, glucose, creatinitine, protein-uria, diabetic medications, and ACE inhibitors), other ECG abnormalities (T-wave negativity score, ST-segment depression score, and Q-wave score), markers of autonomic function (history of symptomatic dysautonomia, treatment with beta-blockers and tricyclic antidepressants, heart rate, and RR variation) and microvascular disease (retinopathy and protein in the urine) [30]. Patients with diabetes and a QT interval in the upper quartile (QTI > 107%) had a 2.8 fold increase in risk of SCA, compared to patients with diabetes in the lowest QTI quartile. There was no evidence of an increase in SCA risk among patients with diabetes in the second and third quartile of the QT interval.

5 Prevention of sudden cardiac arrest in type 2 diabetes

There are several limitations of the available data that provide the evidence base for prevention of SCA in type 2 diabetes. Epidemiologic studies are useful for identifying characteristics, e.g. genes, biomarkers, markers of subclinical disease, associated with various clinical outcomes, e.g. risk factors, subclinical, and clinical disease. For most established CHD and SCA risk factors, the strength of the association observed typically is moderate, with a relative risk of 2 to 4-fold. While these observations provide clues to etiology and potential targets for preventive interventions, the findings typically have less utility for prediction of events over a short period of time. Furthermore, clinical trials are needed, when possible, to demonstrate that altering risk factor levels reduces the incidence of events.

The challenge of prediction of SCA is the result of the following: 1) the low incidence rates over a short (5–10 year) period; 2) the modest relative risk estimates associated with demographic and clinical characteristics; 3) the likely interaction of coronary, myocardial, and electrical component causes of SCA; 4) the importance of genetics, lifestyle, treatments, and 5) the role of triggers, transient, time-varying exposures, in influencing susceptibility to VF. For these reasons, the importance of the findings presented in this review relates to the clues provided regarding potential determinants of SCA in patients with diabetes. While the goal remains the reduction of mortality from SCA, the clinical application of these findings relate to potential targets for clinical prevention of SCA, rather than screening to identify patients at risk. Additionally, the findings point to areas that merit further research needed to extend available knowledge and develop novel approaches to reduce further the occurrence of SCA in this “high risk” population.

The prevention of SCA among patients with diabetes, a “high” risk population, is particularly important, but there is little evidence to suggest that the approach to prevention should differ in patients with and without diabetes. When associations are examined separately among patients with diabetes and non-diabetes, the direction and strength of the risk factor associations for CHD and SCA typically are similar among those with and without diabetes. We note that most studies to identify risk factors have been conducted in the general population, where the prevalence of diabetes in middle-aged populations is modest. Few observational studies have focused on the identification of risk factors for CHD and SCA among patients with diabetes; and, most of these studies have been of small to modest size populations, limiting the statistical power to examine associations with SCA, a subset of CHD death.

The recommendations for the prevention of SCA in the community also are appropriate for patients with type 2 diabetes [31]. We recommend 1–2 servings (3–6 oz) of fatty fish per week, regular and moderate intensity physical activity, smoking cessation, and treatment of high blood cholesterol (e.g. use of statins to lower LDL-cholesterol), and hypertension (e.g. use low-dose thiazide diuretic therapy for hypertension) to reduce mortality from coronary heart disease and SCA. Recently, a joint statement on the primary prevention of cardiovascular diseases in people with diabetes mellitus sought to harmonize the recommendations of the ADA and the AHA related to risk assessment, lifestyle and risk factor management, use of anti-platelet agents and glucose management [32]. Additionally, guidelines on diabetes, pre-diabetes, and cardiovascular diseases were suggested by a joint task force of the ESC and the EASD [33].

In short, SCA is a major cause of mortality among patients with diabetes. While there are some SCA risk factors that may be specifically related to diabetes, such as microvascular disease and autonomic neuropathy, for now, the focus of clinical and public health interventions should be on the primary prevention of diabetes, atherosclerosis, coronary heart disease and the secondary prevention of the cardiovascular consequences of these common conditions. Further research is needed to identify the mechanisms of SCA among patients with diabetes and to develop targeted interventions to reduce mortality from SCA.

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References

1. Sotoodehnia N, Zivin A, Bardy GH, Siscovick DS. Reducing mortality from sudden cardiac death in the community: lessons from epidemiology and clinical applications research. Cardiovasc Res. 2001; 50(2):197–209. [PubMed: 11334823]
2. Spooner PM. Sudden cardiac death: influence of diabetes. Diabetes Obes Metab. 2008; 10(7):523–32. [PubMed: 17451424]
3. El-Atat FA, McFarlane SI, Sowers JR, Bigger JT. Sudden cardiac death in patients with diabetes. Curr Diab Rep. 2004; 4(3):187–93.
4. Fox CS, Coady S, Sorlie PD, Levy D, Meigs JB, D'Agostino RB Sr, et al. Trends in cardiovascular complications of diabetes. JAMA. 2004; 292(20):2495–9. [PubMed: 15562129]
5. Lee CD, Folsom AR, Pankow JS, Brancati FL. Cardiovascular events in diabetic and nondiabetic adults with or without history of myocardial infarction. Circulation. 2004; 109(7):855–60. [PubMed: 14757692]
6. Hu FB, Stampfer MJ, Solomon CG, Liu S, Willett WC, Speizer FE, et al. The impact of diabetes mellitus on mortality from all causes and coronary heart disease in women: 20 years of follow-up. Arch Intern Med. 2001; 161(14):1717–23. [PubMed: 11485504]

7. Lotufo PA, Gaziano JM, Chae CU, Ajani UA, Moreno-John G, Buring JE, et al. Diabetes and all-cause and coronary heart disease mortality among US male physicians. Arch Intern Med. 2001; 161(2):242–7. [PubMed: 11176738]
8. Cho E, Rimm EB, Stampfer MJ, Willett WC, Hu FB. The impact of diabetes mellitus and prior myocardial infarction on mortality from all causes and from coronary heart disease in men. J Am Coll Cardiol. 2002; 40(5):954–60. [PubMed: 12225722]
9. Kannel WB, Wilson PW, D'Agostino RB, Cobb J. Sudden coronary death in women. Am Heart J. 1998; 136(2):205–12. [PubMed: 9704680]
10. Albert CM, Chae CU, Grodstein F, Rose LM, Rexrode KM, Ruskin JN, et al. Prospective study of sudden cardiac death among women in the United States. Circulation. 2003; 107(16):2096–101. [PubMed: 12695299]
11. Curb JD, Rodriguez BL, Burchfiel CM, Abbott RD, Chiu D, Yano K. Sudden death, impaired glucose tolerance, and diabetes in Japanese American men. Circulation. 1995; 91(10):2591–5. [PubMed: 7743621]
12. Balkau B, Jouven X, Ducimetiere P, Eschwege E. Diabetes as a risk factor for sudden death. Lancet. 1999; 354(9194):1968–9. [PubMed: 10622302]
13. Jouven X, Lemaitre RN, Rea TD, Sotoodehnia N, Empana JP, Siscovick DS. Diabetes, glucose level, and risk of sudden cardiac death. Eur Heart J. 2005; 26(20):2142–7. [PubMed: 15980034]
14. Targher G, Bertolini L, Zenari L, Lippi G, Pichiri I, Zoppini G, et al. Diabetic retinopathy is associated with an increased incidence of cardiovascular events in Type 2 diabetic patients. Diabet Med. 2008; 25(1):45–50. [PubMed: 18199131]
15. 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(2):131–8. [PubMed: 12213355]
16. Rathmann W, Ziegler D, Jahnke M, Haastert B, Gries FA. Mortality in diabetic patients with cardiovascular autonomic neuropathy. Diabet Med. 1993; 10(9):820–4. [PubMed: 8281726]
17. Ewing D, Campbell I, Clarke B. The natural history of diabetic autonomic neuropathy. Q J Med. 1980; 49:95–108. [PubMed: 7433630]
18. Demirovic J, Myerburg RJ. Epidemiology of sudden coronary death: an overview. Prog Cardiovasc Dis. 1994; 37(1):39–48. [PubMed: 8022985]
19. Zheng ZJ, Croft JB, Giles WH, Mensah GA. Sudden cardiac death in the United States, 1989 to 1998. Circulation. 2001; 104(18):2158–63. [PubMed: 11684624]
20. Rea TD, Pearce RM, Raghunathan TE, Lemaitre RN, Sotoodehnia N, Jouven X, et al. Incidence of out-of-hospital cardiac arrest. Am J Cardiol. 2004; 93(12):1455–60. [PubMed: 15194012]
21. Kucharska-Newton AM, Couper DJ, Pankow JS, Prineas RJ, Rea TD, Sotoodehnia N, et al. Diabetes and the risk of sudden cardiac death, the Atherosclerosis Risk in Communities study. Acta Diabetol. 2009
22. Buxton AE, Calkins H, Callans DJ, DiMarco JP, Fisher JD, Greene HL, et al. ACC/AHA/HRS 2006 key data elements and definitions for electrophysiological studies and procedures: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (ACC/AHA/ HRS Writing Committee to Develop Data Standards on Electro-physiology). Circulation. 2006; 114(23):2534–70. [PubMed: 17130345]
23. Pankow JS, Kwan DK, Duncan BB, Schmidt MI, Couper DJ, Golden S, et al. Cardiometabolic risk in impaired fasting glucose and impaired glucose tolerance: the Atherosclerosis Risk in Communities Study. Diabetes Care. 2007; 30(2):325–31. [PubMed: 17259502]
24. Suarez GA, Clark VM, Norell JE, Kottke TE, Callahan MJ, O'Brien PC, et al. Sudden cardiac death in diabetes mellitus: risk factors in the Rochester diabetic neuropathy study. J Neurol Neurosurg Psychiatry. 2005; 76(2):240–5. [PubMed: 15654040]
25. Singh JP, Larson MG, O'Donnell CJ, Wilson PF, Tsuji H, Lloyd-Jones DM, et al. Association of hyperglycemia with reduced heart rate variability (The Framingham Heart Study). Am J Cardiol. 2000; 86(3):309–12. [PubMed: 10922439]
26. Schroeder EB, Chambless LE, Liao D, Prineas RJ, Evans GW, Rosamond WD, et al. Diabetes, glucose, insulin, and heart rate variability: the Atherosclerosis Risk in Communities (ARIC) study. Diabetes Care. 2005; 28(3):668–74. [PubMed: 15735206]

27. Kahn JK, Sisson JC, Vinik AI. QT interval prolongation and sudden cardiac death in diabetic autonomic neuropathy. J Clin Endocrinol Metab. 1987; 64(4):751–4. [PubMed: 3818902]

28. Bellavere F, Ferri M, Guarini L, Bax G, Piccoli A, Cardone C, et al. Prolonged QT period in diabetic autonomic neuropathy: a possible role in sudden cardiac death? Br Heart J. 1988; 59(3): 379–83. [PubMed: 3355728]

29. Ewing DJ, Boland O, Neilson JM, Cho CG, Clarke BF. Autonomic neuropathy, QT interval lengthening, and unexpected deaths in male diabetic patients. Diabetologia. 1991; 34(3):182–5. [PubMed: 1884890]

30. Whitsel EA, Boyko EJ, Rautaharju PM, Raghunathan TE, Lin D, Pearce RM, et al. Electrocardiographic QT interval prolongation and risk of primary cardiac arrest in diabetic patients. Diabetes Care. 2005; 28(8):2045–7. [PubMed: 16043757]

31. Siscovick, DS.; Podrid, PJ. Olshansky, B.; Manaker, S., editors. Overview of sudden cardiac arrest and sudden cardiac death.. UpToDate. 2009.

32. Buse JB, Ginsberg HN, Bakris GL, Clark NG, Costa F, Eckel R, et al. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. Circulation. 2007; 115(1):114–26. [PubMed: 17192512]

33. Ryden L, Standl E, Bartnik M, Van den Berghe G, Betteridge J, de Boer MJ, et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). Eur Heart J. 2007; 28(1):88–136. [PubMed: 17220161]

Table 1

Characteristics of drug-treated diabetic SCA cases and age, gender, and index year matched diabetic controls in a large HMO: 1980–1994

	Cases (*N*=342)	Controls (*N*=667)	p-value
Age (years)	67.7 (8.1)	67.4 (8.1)	
Male	62.6	62.1	
Current smoker	21.1	13.5	.002
Myocardial infarction	40.9	25.2	
Congestive heart failure	47.7	21.7	
Body mass index (kg/m^2)	28.0 (5.7)	29.0 (5.7)	.007
Pulse at rest (b.p.m.)	79.1 (14.1)	76.9 (12.9)	.01
QT interval	108.6 (0.8)	103.7 (0.4)	< .0001
Systolic blood pressure (mm Hg)	134.5 (24.1)	143.0 (20.1)	<.0001
Total cholesterol (mg/dL)	238.4 (56.6)	228.7 (51.7)	.01
Creatinine (g/L)	1.48 (0.78)	1.26 (.62)	<.0001
Duration of diabetes (years)	10.4 (8.2)	8.3 (7.2)	.0001
Insulin treatment	52.9	36.7	<.0001
Oral hypoglycemic agent treatment	50.9	66.0	<.0001
Non-fasting plasma glucose (mmol/L)	12.6 (5.6)	11.9 (5.3)	.05
Microvascular disease	47.1	33.3	<.0001
Diabetic autonomic neuropathy	19.9	11.8	0.001

Values are mean (SD) and per cent for continuous and categorical variables, respectively.

Microvascular disease defined as clinical evidence of protein in urine and/or retinopathy (either non-proliferative or proliferative retinopathy).

Autonomic neuropathy was defined as the presence of any of the following: clinically recognized orthostatic hypotension, gastroparesis, diabetic diarrhea, atonic bladder or syncope.

Table 2

Associations of microvascular disease and autonomic complications with risk of sudden cardiac arrest among treated diabetic patients

	Odds ratio[a] (95% confidence interval)	
	Model 1	**Model 2**
Microvascular disease	1.56 (1.15–2.11)	1.56 (1.12–2.16)
Autonomic neuropathy	1.51 (1.02–2.24)	1.52 (1.02–2.27)

[a]From conditional logistic regression, adjusted for age, congestive heart failure, myocardial infarction, systolic blood pressure, current smoking, and treatment with insulin (Model 1), and further adjusted for serum creatinine, duration of diabetes, heart rate, and the QT interval (Model 2).