Journal of the American College of Cardiology Vol. 47, No. 2, 2006

Published by Elsevier Inc.
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2005.08.067

Prolonged QTc Interval and Risk of Sudden Cardiac Death in a Population of Older Adults

Sabine M. J. M. Straus, MD, PHD,*†‡ Jan A. Kors, PHD,† Marie L. De Bruin, PHD,§ Cornelis S. van der Hooft, MD,†‖ Albert Hofman, MD, PHD,* Jan Heeringa, MD,* Jaap W. Deckers, MD, PHD,* J. Herre Kingma, MD, PHD,‖¶ Miriam C. J. M. Sturkenboom, PHD,*† Bruno H. Ch. Stricker, PHD,*‖ Jacqueline C. M. Witteman, PHD*

Rotterdam, the Hague, Utrecht, and Groningen, the Netherlands

OBJECTIVES This study sought to investigate whether prolongation of the heart rate-corrected QT (QTc) interval is a risk factor for sudden cardiac death in the general population.

BACKGROUND In developed countries, sudden cardiac death is a major cause of cardiovascular mortality. Prolongation of the QTc interval has been associated with ventricular arrhythmias, but in most population-based studies no consistent association was found between QTc prolongation and total or cardiovascular mortality. Only very few of these studies specifically addressed sudden cardiac death.

METHODS This study was conducted as part of the Rotterdam Study, a prospective population-based cohort study that comprises 3,105 men and 4,878 women aged 55 years and older. The QTc interval on the electrocardiogram was determined during the baseline visit (1990 to 1993) and the first follow-up examination (1993 to 1995). The association between a prolonged QTc interval and sudden cardiac death was estimated using Cox proportional hazards analysis.

RESULTS During an average follow-up period of 6.7 years (standard deviation, 2.3 years) 125 patients died of sudden cardiac death. An abnormally prolonged QTc interval (>450 ms in men, >470 ms in women) was associated with a three-fold increased risk of sudden cardiac death (hazard ratio, 2.5; 95% confidence interval, 1.3 to 4.7), after adjustment for age, gender, body mass index, hypertension, cholesterol/high-density lipoprotein ratio, diabetes mellitus, myocardial infarction, heart failure, and heart rate. In patients with an age below the median of 68 years, the corresponding relative risk was 8.0 (95% confidence interval 2.1 to 31.3).

CONCLUSIONS Abnormal QTc prolongation on the electrocardiogram should be viewed as an independent risk factor for sudden cardiac death. (J Am Coll Cardiol 2006;47:362–7) © 2006 by the American College of Cardiology Foundation

In developed countries, sudden cardiac death is one of the major causes of cardiovascular mortality. Sudden cardiac death accounts for almost half of all coronary heart disease deaths and is often the first and only manifestation of coronary heart disease (1–3). According to the most recent definition, sudden cardiac death is a natural death attributable to cardiac causes, heralded by abrupt loss of consciousness, within one hour after the onset of acute symptoms, or an unwitnessed, unexpected death of someone seen in a stable medical condition <24 h previously with no evidence of a non-cardiac cause (2,3). Much of this mortality is assumed to be caused by ventricular tachyarrhythmias, and evaluation of risk factors is a major challenge when searching for treatments to reduce this risk (4). In the search for non-invasive risk factors to predict mortality, the heart rate corrected QT (QTc) interval has been studied extensively (4–14). The QT interval on the surface electrocardiogram (ECG) represents the time from onset of ventricular depolarization to completion of repolarization, and prolongation has been associated with ventricular arrhythmias that may trigger ventricular fibrillation and sudden cardiac death (15). There is an ongoing debate on the clinical significance of a prolonged QTc interval (14,16,17). Several large population-based studies evaluating the association between QTc interval and mortality did not find a consistent association between QTc prolongation and total or cardiovascular mortality (4,7–9,11,12,18). Only a few specifically addressed sudden cardiac death, and when they did, the number of cases was often too small to detect significant differences (5,8,10).

We investigated whether prolongation of the QTc interval is an independent risk factor for sudden cardiac death in a population of older adults.

See page 368

From the *Department of Epidemiology and Biostatistics, Erasmus Medical Center, Rotterdam; †Department of Medical Informatics, Erasmus Medical Center, Rotterdam; ‡Medicines Evaluation Board, the Hague, §Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences, Utrecht; ‖Inspectorate for Healthcare, the Hague; and the ¶Department of Clinical Pharmacology, University of Groningen, Groningen, the Netherlands.

Manuscript received May 22, 2005; revised manuscript received July 11, 2005, accepted August 1, 2005.

Abbreviations and Acronyms

AAI	= ankle-arm index
CI	= confidence interval
HR	= hazard ratio
LBBB	= left bundle branch block
SD	= standard deviation
QTc interval	= heart rate-corrected QT interval

METHODS

Setting, study population, and baseline data collection. The study is embedded in the Rotterdam Study, a prospective population-based cohort study, which started between 1990 and 1993. All inhabitants of a suburb in Rotterdam, Ommoord, aged 55 years and over (10,275), were invited to participate. Of these, 7,983 (78%) gave written informed consent and took part in the baseline examination. Objectives and methods have been described in detail elsewhere (19). All participants were visited at home for a standardized questionnaire, and 7,151 were subsequently examined at the research center. A second visit took place between 1993 through 1995. For the present study, follow-up started at baseline and lasted until January 1, 2000.

Information on smoking was obtained during the home interview of the Rotterdam Study. During the research center visit, non-fasting blood samples were obtained, serum total cholesterol was determined by an enzymatic procedure, and high-density lipoprotein was measured similarly after precipitation of the non–high-density lipoprotein fraction (20). Body mass index was computed as weight divided by height squared. Hypertension was defined as the use of antihypertensive medication for high blood pressure, or a systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥100 mm Hg (21). Diabetes mellitus was defined as the use of blood glucose-lowering medication and/or non-fasting or post-load serum glucose level of ≥11.1 mmol/l (22). A history of myocardial infarction was assessed by self-report checked with records from general practitioners or cardiologists and/or electrocardiographic evidence. All reported myocardial infarctions were verified, and assessment has been described in detail earlier (23). Assessment of heart failure has also been described in detail earlier. Briefly, prevalent cases were assessed by screening all medical records for at least two signs and symptoms suggestive of heart failure or use of medication for heart failure and review of all hospital discharge letters. Cases of incident heart failure were obtained by continuous monitoring (24,25). The ankle-arm index (AAI) is the ratio of systolic blood pressure at the ankle to systolic blood pressure in the arm (26).

The Medical Ethics Committee of the Erasmus Medical Center, Rotterdam approved the study.

Outcomes assessment. Participants in the Rotterdam Study are continuously monitored for major events, including heart failure, myocardial infarction, and death. Information on vital status is obtained from municipal health authorities in Rotterdam and general practitioners. In case of a fatal event, general practitioners filled in a questionnaire relating to the circumstances of the death, including time since first symptoms until death, most likely cause of death, and time and place of death. Subsequently, research assistants gathered information about these events at the general practitioners' offices. Questionnaires and a copy of the medical records were used to assess whether death could be classified as sudden cardiac death using the most recent definition: natural death attributable to cardiac causes, heralded by abrupt loss of consciousness, within one hour after onset of acute symptoms, or an unwitnessed, unexpected death of someone seen in a stable medical condition <24 h previously with no evidence of a non-cardiac cause (2,3). If death was witnessed and occurred within one hour after the start of symptoms, we assumed it to be a sudden cardiac death, without additional review of medical records. In case of an unwitnessed death, evidence of cardiac causes was searched for, using all available information. Two research physicians coded all events independently according to the International Classification of Diseases-10th edition (sudden cardiac death: I.46 [27]). In case of disagreement, consensus was sought. Finally, a cardiologist, whose judgment was considered decisive, reviewed all events.

ECG interpretation and measurement. A 10-s 12-lead resting ECG (on average, 8 to 10 beats) was recorded with an ACTA electrocardiograph (ESAOTE, Florence, Italy) at a sampling frequency of 500 Hz and stored digitally. All ECGs were processed by the Modular ECG Analysis System (MEANS) to obtain ECG measurements. The MEANS determines common onsets and offsets for all 12 leads together on one representative averaged beat, with the use of template matching techniques, and has been evaluated extensively (28–30). The MEANS program determines the QT interval from the start of the QRS complex until the end of the T-wave. To adjust for heart rate, the Bazett formula ($QTc = QT/\sqrt{RR}$) was used (31).

The most recent European regulatory guideline document, based on the opinion of an ad-hoc expert group, was used to categorize QTc prolongation into three gender-specific categories. For women, the cutoff points were ≤450 ms (normal), 451 to 470 ms (borderline), and >470 ms (prolonged), and for men ≤430 ms (normal), 431 to 450 ms (borderline), and >450 ms (prolonged) (32). In addition, we used different QTc thresholds varying from 440 to 470 ms, based on literature (4,5,7–10,12,13,18,33,34).

Digitally stored ECGs of 6,134 participants (86% of the participants who visited the research center) were available at the first visit. At the second visit, 4,415 (70%) digitally stored ECGs were available. Missing ECGs were mainly attributable to temporary technical problems with ECG recording. The diagnosis of left bundle branch block (LBBB) was based on established criteria (35).

Table 1. Baseline Characteristics of the Study Population Stratified by Category of QTc Prolongation at Baseline*

Characteristic	All (n = 6,134)	Normal (n = 4,344)	Borderline (n = 1,109)	Abnormal (n = 681)	p
Age	69.2 (9)	68.4 (8.9)	70.1 (8.8)	73.5 (9.0)	<0.001
Female gender	59.6%	64.9%	49.4%	42.4%	<0.001
Smoking	22.7%	21.5%	27.1%	22.8%	<0.001
Total/HDL cholesterol ratio	5.2	5.2	5.3	5.4	0.01
Body mass index (SD)	26.3 (3.7)	26.2 (3.6)	26.4 (3.8)	26.7 (3.8)	ns
Blood pressure					
Systolic (mm Hg)	139.4 (22.3)	137.8 (21.9)	142.2 (22.2)	145.1 (23.4)	<0.001
Diastolic (mm Hg)	73.5 (11.6)	72.9 (11.3)	75.3 (12.1)	75.0 (12.1)	<0.001
Hypertension	33.6%	30.6%	39%	44.9%	<0.001
Diabetes mellitus	10.5%	8.5%	14%	17.8%	<0.001
Myocardial infarction	6.3%	5.2%	6.6%	12.9%	<0.001
Heart failure	3.2%	2.1%	3.6%	9.5%	<0.001

Values are means (SD) for continuous variables and percentages for dichotomous variables. *Classification of QTc prolongation: normal men ≤430 ms; women ≤450 ms; borderline men 431–450 ms; women 451–470 ms; abnormal men ≥451 ms; women ≥471 ms.

HDL = high-density lipoprotein; SD = standard deviation; QTc = heart rate corrected QT interval.

Statistical analysis. Differences in baseline characteristics between participants with normal (male, ≤430 ms; female, ≤450 ms), borderline (male, 431 to 450 ms; female, 451 to 470 ms), and abnormal (male, ≥451 ms; female, ≥471 ms) QTc interval prolongation were examined with analysis of covariance. The hazard ratio (HR) (95% confidence interval [CI]) of the association between prolonged QTc interval and sudden cardiac death was estimated using a Cox proportional hazards analysis. The QTc interval at the time of the first visit was taken as the independent variable. For those participants who also had a second ECG at the follow-up visit, the results of follow-up QTc interval measurements were included in the analyses. All information concerning co-morbidities (hypertension, diabetes mellitus, myocardial infarction, heart failure) was also updated at that time. Potential confounders were included in the multivariate model: age, gender, body mass index, hypertension, cholesterol/high-density lipoprotein ratio, diabetes mellitus, myocardial infarction, heart failure, AAI. Because the Bazett formula tends to undercorrect for lower heart rates and overcorrect for higher heart rates, we also included heart rate in the model. Sensitivity analyses were performed using different QTc cutoff points. Because LBBB can cause secondary repolarization changes and atrial fibrillation can cause difficulties in measuring the QT interval, analyses also were performed after exclusion of patients with LBBB and atrial fibrillation at baseline. We also assessed the risk of sudden cardiac death in participants with at least one cardiovascular risk factor at baseline. We added interaction terms of QTc with age, hypertension, smoking, diabetes mellitus, myocardial infarction, and heart failure in the model. Finally, we calculated the attributable risk percent as: $(HR - 1/HR \times 100)$ (36).

RESULTS

The mean follow-up time was 6.7 years (standard deviation [SD], 2.3 years). During follow-up, 1,407 (22.8%) participants died and 67 were lost to follow-up. We identified 125 sudden cardiac deaths, yielding an incidence rate of approximately 3 per 1,000 person-years. Table 1 shows baseline characteristics of all participants with a normal, borderline, and abnormal QTc interval. The prevalence of cardiovascular comorbidity increased with an increasing QTc interval. Women had a significantly longer QTc interval (435 ms; SD, 26) than men (426 ms; SD, 28). The characteristics of the cases and non-cases are presented in Table 2. Cases had a significantly longer mean QTc interval (441.9 ms; SD, 33.0) compared with the non-cases (431.3 ms; SD, 27.1). In our population we identified 118 patients (1.9%) with LBBB and 168 (2.7%) with atrial fibrillation.

Abnormal QTc prolongation was associated with a more than two-fold increase in the risk of sudden cardiac death compared with reference QTc values in the fully adjusted model. The relative risk was most pronounced in the lower age group (ages 55 to 68 years) (Table 3). In Figure 1, the Kaplan-Meier log survival plot of the risk of sudden cardiac death in relation to the QTc interval is shown.

In patients with at least one cardiovascular risk factor at baseline, abnormal QTc prolongation was associated with a four-fold increase in the risk of sudden cardiac death (HR, 4.3; 95% CI, 2.2 to 8.6). After exclusion of patients with LBBB or atrial fibrillation, the risk of sudden cardiac death was significantly increased in both patients with borderline prolonged QTc interval (HR, 1.9; 95% CI, 1.0 to 3.7) as well as in patients with an abnormally prolonged QTc interval (HR, 2.7; 95% CI, 1.3 to 5.4). Because many studies used QTc interval classifications into two categories, we also analyzed QTc prolongation using cutoff points varying from 440 ms to 470 ms (Fig. 2). Using 440 ms as a cutoff point of QTc interval prolongation, we observed a significant increase in the risk of sudden cardiac death after adjustment for age and gender (HR, 2.3; 95% CI, 1.4 to 3.8), and this risk remained increased in the fully adjusted model (HR, 1.3; 95% CI, 0.9 to 1.9). None of the

Table 2. Baseline Characteristics of Non-Cases and Cases of Sudden Cardiac Death

Characteristics at Baseline	Non-Cases (n = 6,009)	SCD Cases (n = 125)	HR* (95% CI)	p
Age	69.1 (9)	74.3 (8)	1.1 (1.0–1.1)	<0.000
Female gender	59.9%	44.8%	0.4 (0.3–0.6)	<0.000
Smoking	22.7%	17.6%	1.4 (0.9–2.7)	0.2
Cholesterol/HDL ratio	5.2	5.5	1.1 (1.0–1.2)	0.04
Body mass index	26.3	26.1	0.9 (0.9–1.0)	0.7
Hypertension	33.2%	56.0%	2.4 (1.7–3.5)	<0.000
Diabetes mellitus	10.3%	23.2%	2.4 (1.6–3.4)	<0.000
Myocardial infarction	5.8%	28%	4.6 (3.1–6.9)	<0.000
Heart failure	2.9%	15.2%	4.5 (2.7–7.5)	<0.000
QTc interval	431.25 (27.1)	441.9 (33.0)	1.01 (1.00–1.02)	<0.000

Values are means (SD) for continuous variables and percentages for dichotomous variables. QTc interval in ms. *HR adjusted for age and gender (age: gender-adjusted and gender: age-adjusted)

CI = confidence interval; HDL = high-density lipoprotein (mmol/l); HR = hazard ratio; SCD = sudden cardiac death; SD = standard deviation.

interactions we tested for were statistically significant. The increase in risk of sudden cardiac death corresponded with an attributable risk proportion of 0.6, meaning that in our study 60% of all cases of sudden cardiac death were associated with an abnormally prolonged QTc interval.

DISCUSSION

In this population-based study, an abnormally prolonged QTc interval was associated with a more than two-fold increased risk of sudden cardiac death. In patients below the median age of 68 years, a prolonged QTc interval was associated with an eight-fold increased risk. Risk estimates were independent of cardiovascular risk factors. In our analyses, we used European regulatory guidelines to classify QTc prolongation in three gender-specific categories (32). If we classified the QTc interval according to previously used cutoff levels, we observed an increased risk of sudden cardiac death starting at a cutoff point of 440 ms. The AAI is considered a marker of atherosclerosis influenced not only by the presence of plaques but also by hemodynamic factors and vascular factors (37). Because subclinical atherosclerotic disease can influence the QTc interval, we analyzed the effect of AAI on the risk of sudden cardiac death. The adjustment did not change the point estimates.

Results of several epidemiologic studies evaluating total and cardiovascular mortality in relation to QTc prolongation have yielded conflicting results (4,7–12,18,38), and only a few specifically addressed sudden cardiac death (5,8). In patients referred for Holter monitoring, a QTc interval of more than 440 ms doubled the risk of sudden cardiac death (5). In the Zutphen study, QTc prolongation of 420 ms or more was associated with a three-fold increased risk of sudden cardiac death (HR, 3.0; 95% CI, 1.0 to 8.9) in elderly men (ages 65 to 85 years), but not in men ages 40 to

Table 3. QTc Prolongation and Risk of Sudden Cardiac Death

QTc Prolongation	HR (95% CI)*	HR (95% CI)†
Normal (n = 4,344)	1 (reference)	1 (reference)
Borderline (n = 1,109)	2.3 (1.3–4.2)	1.6 (0.9–3.1)
Abnormal (n = 681)	3.7 (2.0–6.9)	2.5 (1.3–4.7)
<Median age (55–68 yrs)		
Normal (n = 2,341)	1 (reference)	1 (reference)
Borderline (n = 514)	5.0 (1.5–16.8)	3.7 (1.1–14.0)
Abnormal (n = 212)	9.8 (2.7–35.1)	8.0 (2.1–31.3)
≥Median age (>68 yrs)		
Normal (n = 2,003)	1 (reference)	1 (reference)
Borderline (n = 595)	1.7 (0.9–3.6)	1.3 (0.6–2.7)
Abnormal (n = 469)	2.8 (1.4–5.9)	2.1 (1.0–4.4)
Men		
Normal (n = 1,523)	1 (reference)	1 (reference)
Borderline (n = 561)	2.4 (1.0–5.3)	1.8 (0.8–4.1)
Abnormal (n = 392)	3.9 (1.8–8.4)	2.6 (1.1–5.8)
Women		
Normal (n = 2,821)	1 (reference)	1 (reference)
Borderline (n = 548)	2.3 (0.9–5.9)	1.3 (0.5–3.7)
Abnormal (n = 289)	3.5 (1.3–9.8)	2.5 (1.0–7.1)

*Adjusted for age and gender (adjusted for age in gender-stratified analyses and for gender in age-stratified analyses). †Adjusted for age, gender, smoking, cholesterol/HDL ratio, body mass index, hypertension, diabetes mellitus, myocardial infarction, heart failure, and heart rate.

Reference = reference value; other abbreviations as in Table 2.

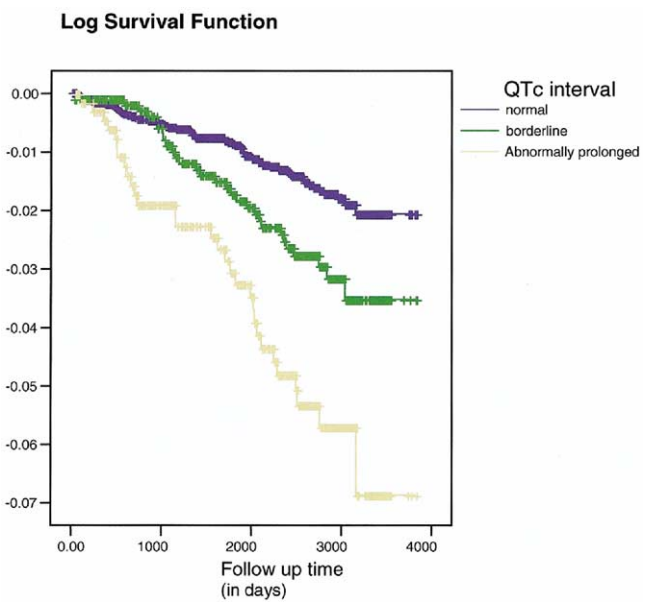

Figure 1. Kaplan-Meier log survival plot of heart rate corrected QT (QTc) interval prolongation and sudden cardiac death.

JACC Vol. 47, No. 2, 2006
January 17, 2006:362–7

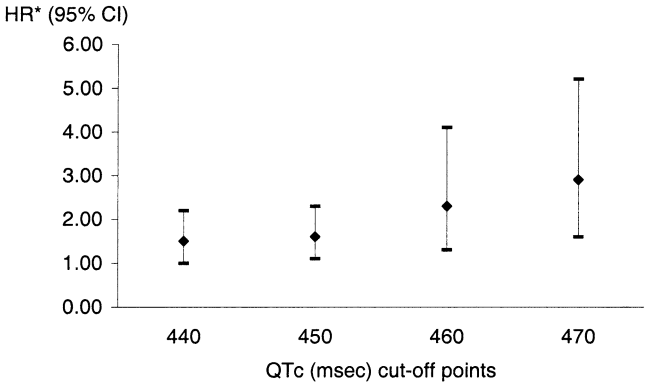

Figure 2. Risk of sudden cardiac death (SCD) at different heart rate corrected QT (QTc) interval cutoff points. *Adjusted for age, gender, body mass index, cholesterol/high-density lipoprotein ratio, smoking, hypertension, diabetes, myocardial infarction, and heart rate. CI = confidence interval; HR = hazard ratio.

60 years (8). The Framingham study failed to show an association of baseline QTc prolongation with total mortality, sudden death, or coronary mortality (9). The Cardiovascular Health Study, on the other hand, showed an association between a QTc interval of >450 ms and total mortality, and in the Strong Heart Study, a QTc interval of ≥460 ms was associated with a two-fold increased risk of cardiac and total mortality (12). In the Rotterdam Study, we previously found that QTc prolongation (>440 ms) was associated with an increased risk of total and cardiovascular mortality (7). In this study, however, shorter follow-up and one baseline ECG were used, and the relationship with sudden cardiac death was not specifically evaluated. The risk of sudden cardiac death in the present study was higher in the younger population. This may be partly explained by depletion of susceptible patients at an older age. The proportion of sudden cardiac deaths attributable to a prolonged QTc interval is larger in the younger age category. The absolute risk of sudden cardiac death, however, increases with age (39,40).

The strength of our study lies in the fact that data were available on a large group of patients. The relatively long follow-up period enabled us to take advantage of the fact that a large part of the participants underwent two ECGs. There was little loss to follow-up and detailed information on cardiovascular risk factors. Conflicting results in earlier studies may be partly explained by differences in definition of sudden cardiac death, differences in populations, classification of QTc prolongation, or use of general rather than gender-specific QTc cutoff points. To our knowledge, this study is the first to use gender-specific classification based on a European guideline in a population-based study (32). In addition, in all studies QTc prolongation was based on one baseline ECG and related to outcomes that usually occurred many years later.

Nevertheless, our study also has some limitations. First, we cannot exclude that misclassification of outcomes occurred. We were, however, able to take advantage of the fact that in most cases complete information regarding the facts surrounding death was available, including a detailed questionnaire and in many cases the time between start of symptoms and death. Second, misclassification of exposure may have occurred because we related sudden cardiac death to QTc prolongation measured before the event, and the QTc interval could have changed in the meantime. Finally, our study population consisted of patients aged 55 years and older. Whether our findings also apply to other age groups requires further study.

In conclusion, the results of our study show that abnormal QTc prolongation on the ECG should be viewed as an independent risk factor for sudden cardiac death. Two-thirds of the cases of sudden cardiac death are associated with an abnormal prolongation of the QTc interval.

Reprint requests and correspondence: Dr. Bruno H. Ch. Stricker, Department of Epidemiology and Biostatistics, Erasmus Medical Center, P.O. Box 1738, 3000 DR Rotterdam, the Netherlands. E-mail: b.stricker@erasmusmc.nl.

REFERENCES

1. Fox CS, Evans JC, Larson MG, Kannel WB, Levy D. Temporal trends in coronary heart disease mortality and sudden cardiac death from 1950 to 1999: the Framingham Heart Study. Circulation 2004;110:522–7.
2. Myerburg RJ. Cardiac arrest and sudden cardiac death. In: Braunwald E, editor. Heart Disease: A Text Book of Cardiovascular Medicine. New York, NY: Saunders, 1997:742–79.
3. Priori SG, Aliot E, Blomstrom-Lundqvist C, et al. Task Force on Sudden Cardiac Death of the European Society of Cardiology. Eur Heart J 2001;22:1374–450.
4. Elming H, Holm E, Jun L, et al. The prognostic value of the QT interval and QT interval dispersion in all-cause and cardiac mortality and morbidity in a population of Danish citizens. Eur Heart J 1998;19:1391–400.
5. Algra A, Tijssen JG, Roelandt JR, Pool J, Lubsen J. QTc prolongation measured by standard 12-lead electrocardiography is an independent risk factor for sudden death due to cardiac arrest. Circulation 1991; 83:1888–94.
6. de Bruyne MC, Hoes AW, Kors JA, et al. Prolonged QT interval: a tricky diagnosis? Am J Cardiol 1997;80:1300–4.
7. de Bruyne MC, Hoes AW, Kors JA, Hofman A, van Bemmel JH, Grobbee DE. Prolonged QT interval predicts cardiac and all-cause mortality in the elderly. The Rotterdam Study. Eur Heart J 1999;20: 278–84.
8. Dekker JM, Schouten EG, Klootwijk P, Pool J, Kromhout D. Association between QT interval and coronary heart disease in middle-aged and elderly men. The Zutphen Study. Circulation 1994; 90:779–85.
9. Goldberg RJ, Bengtson J, Chen ZY, Anderson KM, Locati E, Levy D. Duration of the QT interval and total and cardiovascular mortality in healthy persons (the Framingham Heart Study experience). Am J Cardiol 1991;67:55–8.
10. Karjalainen J, Reunanen A, Ristola P, Viitasalo M. QT interval as a cardiac risk factor in a middle aged population. Heart 1997;77:543–8.
11. Montanez A, Ruskin JN, Hebert PR, Lamas GA, Hennekens CH. Prolonged QTc interval and risks of total and cardiovascular mortality and sudden death in the general population: a review and qualitative overview of the prospective cohort studies. Arch Intern Med 2004; 164:943–8.
12. Okin PM, Devereux RB, Howard BV, Fabsitz RR, Lee ET, Welty TK. Assessment of QT interval and QT dispersion for prediction of all-cause and cardiovascular mortality in American Indians: the Strong Heart Study. Circulation 2000;101:61–6.

13. Schouten EG, Dekker JM, Meppelink P, Kok FJ, Vandenbroucke JP, Pool J. QT interval prolongation predicts cardiovascular mortality in an apparently healthy population. Circulation 1991;84:1516–23.
14. Schwartz PJ. QT prolongation, sudden death, and sympathetic imbalance: the pendulum swings. J Cardiovasc Electrophysiol 2001;12: 1074–7.
15. Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. Heart 2003;89:1363–72.
16. Davey P. QT interval and mortality from coronary artery disease. Prog Cardiovasc Dis 2000;42:359–84.
17. Al-Khatib SM, LaPointe NM, Kramer JM, Califf RM. What clinicians should know about the QT interval. JAMA 2003;289:2120–7.
18. Robbins J, Nelson JC, Rautaharju PM, Gottdiener JS. The association between the length of the QT interval and mortality in the cardiovascular health study. Am J Med 2003;115:689–94.
19. Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. Eur J Epidemiol 1991;7:403–22.
20. van Gent CM, van der Voort HA, de Bruyn AM, Klein F. Cholesterol determinations. A comparative study of methods with special reference to enzymatic procedures. Clin Chim Acta 1977;75:243–51.
21. Guidelines Subcommittee. 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. J Hypertens 1999;17:151–83.
22. Diabetes Mellitus. Technical Reports series 894. Geneva: World Health Organization, 1985.
23. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. Circulation 1997;96: 1432–7.
24. Mosterd A, Hoes AW, de Bruyne MC, et al. Prevalence of heart failure and left ventricular dysfunction in the general population; the Rotterdam Study. Eur Heart J 1999;20:447–55.
25. Bleumink GS, Knetsch AM, Sturkenboom MC, et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure, the Rotterdam Study. Eur Heart J 2004;25: 1614–9.
26. Meijer WT, Hoes AW, Rutgers D, Bots ML, Hofman A, Grobbee DE. Peripheral arterial disease in the elderly: the Rotterdam Study. Arterioscler Thromb Vasc Biol 1998;18:185–92.
27. International Classification of Diseases and Health Related Problems. Geneva: World Health Organization, 1992.
28. Willems JL, Abreu-Lima C, Arnaud P, et al. The diagnostic performance of computer programs for the interpretation of electrocardiograms. N Engl J Med 1991;325:1767–73.
29. de Bruyne MC, Kors JA, Hoes AW, et al. Diagnostic interpretation of electrocardiograms in population-based research: computer program research physicians, or cardiologists? J Clin Epidemiol 1997;50:947–52.
30. van Bemmel JH, Kors JA, van Herpen G. Methodology of the modular ECG analysis system MEANS. Methods Inf Med 1990;29: 346–53.
31. Bazett H. An analysis of time relations of the electrocardiogram. Heart 1920;7:353–70.
32. Committee for Proprietary Medicinal Products. The assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products. London: Committee for Proprietary Medicinal Products, 1997.
33. Kardys I, Kors JA, van der Meer IM, Hofman A, van der Kuip DA, Witteman JC. Spatial QRS-T angle predicts cardiac death in a general population. Eur Heart J 2003;24:1357–64.
34. Molnar J, Zhang F, Weiss J, Ehlert FA, Rosenthal JE. Diurnal pattern of QTc interval: how long is prolonged? Possible relation to circadian triggers of cardiovascular events. J Am Coll Cardiol 1996;27:76–83.
35. Willems JL, Robles-deMedina EO, Bernard R, et al. Criteria for intraventricular conduction disturbances and pre-excitation. World Health Organizational/International Society and Federation for Cardiology Task Force Ad Hoc. J Am Coll Cardiol 1985;5:1261–75.
36. Hennekens CH, Buring JE. Epidemiology in Medicine. Philadelphia, PA: Lippincott-Raven, 1987.
37. Oei HH, Vliegenthart R, Hak AE, et al. The association between coronary calcification assessed by electron beam computed tomography and measures of extracoronary atherosclerosis: the Rotterdam Coronary Calcification Study. J Am Coll Cardiol 2002;39:1745–51.
38. Algra A. Elektrocardiographic risk factors for sudden death. Thesis Cardiology. Rotterdam: Erasmus Medical Center, 1990.
39. Zipes DP, Wellens HJ. Sudden cardiac death. Circulation 1998;98: 2334–51.
40. Krahn AD, Connolly SJ, Roberts RS, Gent M. Diminishing proportional risk of sudden death with advancing age: implications for prevention of sudden death. Am Heart J 2004;147:837–40.