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Electrocardiographic QT interval and mortality: a meta-analysis

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Abstract

Background—Extremely abnormal prolongation of the electrocardiographic QT interval is associated with malignant ventricular arrhythmias and sudden cardiac death. However, the implications of variations in QT-interval length within normal limits for mortality in the general population are still unclear.

Methods—We performed a meta-analysis to investigate the relation of QT interval with mortality endpoints. Inverse-variance weighted random-effects models were used to summarize the relative risks across studies. Twenty-three observational studies were included.

Results—The pooled relative risk estimates comparing the highest with the lowest categories of QT-interval length were 1.35 (95% confidence interval = 1.24–1.46) for total mortality, 1.51 (1.29–1.78) for cardiovascular mortality, 1.71 (1.36–2.15) for coronary heart disease mortality, and 1.44 (1.01–2.04) for sudden cardiac death. A 50 msec increase in QT interval was associated with a relative risk of 1.20 (1.15–1.26) for total mortality, 1.29 (1.15–1.46) for cardiovascular mortality, 1.49 (1.25–1.76) for coronary heart disease mortality, and 1.24 (0.97–1.60) for sudden cardiac death.

Conclusions—We found consistent associations between prolonged QT interval and increased risk of total, cardiovascular, coronary, and sudden cardiac death. QT-interval length is a determinant of mortality in the general population.

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The studies were: 1) Schouten, 1991 (men)¹⁸; 2) Schouten, 1991 (women)¹⁸; 3) Algra, 1993³; 4) Dekker, 1994 (middle-aged)⁸; 5) Dekker, 1994 (elderly)⁸; 6) Bernstein, 1997⁵; 7) Elming, 1998⁹; 8) Pytlak, 2000 (men)¹⁵; 9) Pytlak, 2000 (women)¹⁵; 10) Perkiomaki, 2001¹⁴; 11) Nikitin, 2002²⁵; 12) Robbins, 2003¹⁷; 13) Dekker, 2004⁷; 14) Nakanishi, 2004¹¹; 15) Straus, 2006²²; 16) Anttonen, 2007⁴; 17) Sohaib, 2008²¹; and 18) Cuddy, 2009.⁶

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Abnormal prolongation of the electrocardiographic QT interval (whether genetically determined or acquired) predisposes to malignant ventricular arrhythmias and sudden cardiac death.¹⁻² While the association of extremely abnormal QT intervals with sudden cardiac death is well established, the mortality implications of variations in QT interval length in the general population are unclear. Indeed, a qualitative review of 7 major prospective cohort studies (total n = 36,031) published in 2004 concluded that there was no consistent evidence of an association between QT-interval prolongation and risk of total mortality, cardiovascular mortality, or sudden cardiac death in the general population.² However, that review did not quantitatively synthesize results from the various studies. Several additional population-based studies investigating the association between prolonged QT interval and mortality endpoints have been published since then,³⁻²⁵ and this evidence has not been summarized systematically.

The objective of this meta-analysis was to quantitatively synthesize the available literature on the association of QT-interval length with the risk of total, cardiovascular, and coronary heart disease mortality, and with sudden cardiac death in the general population.

METHODS

Data Sources and Searches

We searched MEDLINE and EMBASE for observational studies investigating the relation of QT interval with mortality endpoints using the free text and key words “QT”, “QT interval”, “mortality”, and “death”. The search period was January 1966 through April 2009, with no language restrictions.

Study Selection

We aimed to identify all observational studies that assessed the association of QT interval with mortality in general population settings. The exclusion criteria were the following: (1) no original research (reviews, editorials, or letters); (2) case reports or case series; (3) studies not conducted in humans; (4) studies conducted in population samples comprised only of patients with established cardiovascular disease at baseline (e.g., studies conducted in post-myocardial infarction patients); (5) studies not reporting mortality outcomes; and (6) studies not using QT interval as an exposure. For populations described in several reports, we selected the publication with the longest follow-up. One study reported only mean QT interval, without standard error or any other estimate of variability²⁶; this study was included in the review but was excluded from the combined analysis.

Data Extraction

Two investigators (Y.Z. and E.B.-C.) independently reviewed all search results applying the inclusion/exclusion criteria stated above, and abstracted eligible articles. Discrepancies between reviewers were solved by consensus.

Data Synthesis and Analysis

The study endpoints were total, cardiovascular and coronary heart disease mortality and sudden cardiac death. None of the studies identified used non-cardiovascular mortality as the outcome. The endpoint definitions used in each study are presented in the eTable (<http://links.lww.com>). We used as many endpoints as reported in each study, and we conducted separate meta-analyses for each endpoint. Measures of association (hazard ratios, odds ratios, or relative risks) and their 95% confidence intervals (CIs) were abstracted or derived from published data. When several measures of association for a given endpoint were reported in the same study, we selected the measure according to the following hierarchy: (1) model using Bazett's equation corrected QT interval (QTc); (2) model using

mean QT interval (if mean QT was not available, then we chose maximum QT); (3) model with the highest number of categories for QT interval; and (4) model adjusted for most covariates. For studies reporting results separately for men and women,¹⁵ middle-aged and elderly men,⁸ and diabetics and non-diabetics,²⁴ we used these groups as two independent results for the meta-analyses. For studies reporting risk estimates for both the full cohort and the subgroup free of cardiovascular disease, we used estimates from the subgroup free of cardiovascular disease.^{9,16–17}

For evaluating the risk associated with QT prolongation, we compared the risk of mortality endpoints comparing the highest vs. the lowest QT-interval length category reported in each study. For studies that did not use the lowest QT-interval length category as the reference category,^{3–4,21} we recalculated the relative risk comparing the highest vs. the lowest categories and its 95% confidence intervals using the method of Greenland and Longnecker.²⁷ We also used this method to calculate the 95% confidence interval for the adjusted relative risk in a study that did not report it.¹⁸ For studies that reported the association of QT interval only as a continuous variable,^{5,14–15} we calculated the relative risk associated with a 50 ms increase in QT-interval length.

We used DerSimonian and Laird's random-effects models to calculate summary relative risks across studies. Between-study heterogeneity was quantified using the I^2 statistic, which describes the proportion of total variation in study estimates due to heterogeneity. We also assessed the relative influence of each study by omitting one study at a time from the pooled analysis. Publication bias was evaluated using funnel plots and Egger's test.²⁸

Studies presenting 3 or more categories of QT interval and those presenting QT intervals as continuous exposures were also combined using a random-effects dose-response meta-analysis.²⁷ In this analysis we estimated the increase in risk associated with absolute changes in QT-interval lengths above the reference category for each study and pooled the estimates across studies. Departure from a linear trend was evaluated by testing for a quadratic term in the dose-response meta-analysis.²⁷ All statistical analyses were conducted with Stata version 10 (STATA Corp, College Station, TX).

RESULTS

Prolonged QT interval and mortality

Sixteen prospective cohort studies, 3 retrospective cohort studies, 2 case-cohort studies, and 2 nested case-control studies met our inclusion criteria (Table 1, Figure 1). Thirteen studies were performed in Europe, 8 in the US, 1 in Japan, and 1 in Canada. The prevalence of cardiovascular disease at baseline among study participants ranged from 0% to 38%. Sixteen studies (reporting 19 comparisons) presented relative risks for total mortality, 10 studies (13 comparisons) for cardiovascular mortality, 9 studies (12 comparisons) for coronary heart disease mortality, and 5 studies (6 comparisons) for sudden cardiac death.

Ten studies measured mean QT interval from 12-lead ECGs, while a few studies measured maximum or median QT interval and one study measured mean QT interval from 24-hour Holter monitoring (Figure 2).³ Bazett's formula was the most common method used to adjust for heart rate. The average QTc intervals of the study populations ranged from 385 to 461 ms, and the studies differed widely in the cutpoint selection for categorizing QTc intervals (Figure 2).

Virtually all studies reported an increased risk of mortality comparing the highest with the lowest QT categories for all study endpoints (Figure 3), although the associations were not always statistically significant. The pooled relative risk estimates comparing the highest

with the lowest category of QT interval length were 1.35 (95% CI = 1.24–1.46; $I^2 = 33.4\%$) for total mortality, 1.51 (1.29–1.78; 52.2%) for cardiovascular mortality, 1.71 (1.36–2.15; 35.3%) for coronary heart disease mortality, and 1.44 (1.01–2.04; 30.9%) for sudden cardiac death.

Excluding individual studies did not substantially affect the estimates. The pooled estimates after leaving out one study at a time ranged from 1.32 to 1.36 for total mortality, 1.50 to 1.57 for cardiovascular mortality, 1.66 to 1.81 for coronary heart disease mortality, and 1.33 to 1.61 for sudden cardiac death. Egger's tests for publication bias were not statistically significant. Funnel plots, however, suggested that small studies were reporting stronger associations compared with larger studies, but even large studies reported positive associations. The pooled relative risks for the largest 50% of the studies were 1.32 (95% CI = 1.22–1.44) for total mortality, 1.82 (1.39–2.38) for cardiovascular mortality, 1.51 (1.10–2.08) for coronary heart disease mortality, and 1.86 (1.17–2.98) for sudden cardiac death.

For the dose-response analysis, we combined studies that presented data using 3 or more categories of QT-interval length, or that reported QT as a continuous exposure. The dose-response meta-analyses also evidenced increasing trends of mortality risk with increasing QT interval (Figure 4). The pooled relative risk associated with a 50 msec increase in QT interval length was 1.20 (1.15–1.26) for total mortality, 1.29 (1.15–1.46) for cardiovascular mortality, 1.49 (1.25–1.76) for coronary heart disease mortality, and 1.24 (0.97–1.60) for sudden cardiac death. Adding a quadratic term to the dose-response models did not significantly improve model fit. The p-values for the quadratic terms were ≥ 0.75 for all study outcomes.

In addition, we pooled 6 studies^{6,9–11,16–17} with participants free of cardiovascular diseases (i.e., they either specified excluding participants with cardiovascular diseases at baseline, or reported estimates in a cardiovascular-disease-free subgroup). The pooled relative risk estimates comparing the highest with the lowest categories of QT-interval length were very similar to the main analyses: 1.29 (1.12–1.49, 4 studies) for total mortality, 1.59 (1.02–2.47, 4 studies) for coronary heart disease mortality, and 1.14 (0.75–1.74, 2 studies) for sudden cardiac death. Only one study assessed cardiovascular disease mortality.¹¹

DISCUSSION

In this meta-analysis, we found consistent associations between prolonged QT-interval length and increased risk of total, cardiovascular, coronary, and sudden cardiac death mortality. At the population level, these associations are substantial and comparable in magnitude to the effect of other traditional cardiovascular risk factors.²⁹ While smaller studies were possibly affected by publication bias, the associations remained when the analyses were restricted to the largest studies in the meta-analysis, which are less prone to publication and other sources of selection bias.

The electrocardiographic QT interval corrected for heart rate (QTc) is approximately normally distributed in the general population.^{4,30–34} Normal values for QTc range from 350 to 450 ms for adult men, and 360 to 460 ms for adult women.^{4,30,32,35–36} but up to 10–20% of otherwise healthy persons may have QTc values outside of this range.^{35,37} Marked prolongations of the QT interval may be caused by genetic disorders (e.g., long QT syndrome), pharmacologic agents (e.g., antiarrhythmics, antipsychotics, antibiotics), electrolyte abnormalities (e.g., hypokalemia and hypomagnesemia), and their interactions.² Other factors associated with QT interval length variability in the population include age, sex, hypertension, BMI, medication usage, low-calorie diets, serum potassium levels,^{38–39}

and common genetic variants.³² Finally, within-person variability and measurement error are additional sources of variability in QT-interval length.

Several mechanisms may explain an increased risk of mortality with prolonged QTc. In animal models, prolongation of the QT interval is associated with the occurrence of early afterdepolarization, in which abnormal depolarization occurs during phases 2 or 3 of the action potential before repolarization is completed.⁴⁰ These premature or triggered action potentials can generate cardiac arrhythmias such as torsade de pointes, which may progress to ventricular fibrillation and sudden cardiac death.^{41–42} In general, longer QT intervals driven by longer ventricular action potentials tend to be more spatially and temporally heterogeneous because of a reduction in repolarizing reserve.⁴³ This allows for the development of functional reentry, in which still-activated regions of ventricular myocardium reenter and reactivate regions with shorter action potentials, producing polymorphic ventricular tachycardias such as torsade de pointes.

QT-interval prolongation may also be associated with conditions affecting autonomic tone or left ventricular structure, including left ventricular hypertrophy or myocardial infarction.⁴¹ While it has been speculated that the QT interval may simply be a marker for the severity of underlying clinical or subclinical cardiac disease,⁴⁴ most studies in our meta-analysis adjusted for blood pressure levels or for the presence of hypertension, and either excluded or adjusted for the presence of pre-existing coronary heart disease. Furthermore, the direct link established between genetic variations in QT-interval length and sudden cardiac death indicates that QT prolongation is a direct causal contributor to mortality risk. Indeed, common genetic polymorphisms that partly explain population variability in QTc, such as *NOS1AP*, may also explain a significant fraction of the risk in sudden cardiac death.⁴⁵

Our meta-analysis provides evidence of substantial heterogeneity in the methodology used to study QT- and mortality relationships across studies. This heterogeneity has likely complicated the elucidation of the role of an increase in QT-interval length as a risk factor for mortality in the general population. Some factors contributing to this heterogeneity were the lack of uniform criteria for choosing the ECG leads to measure the QT interval, differences in the method for determining the end of the T wave, and differences in the method for correcting for heart rate.⁴⁶ The 12-lead ECG was the most frequently used technique for measuring the QT interval. However, some studies averaged the intervals across all 12 leads, while others used the single longest QT across all leads. The longest QT interval may be related to QT dispersion, which may represent the heterogeneity of ventricular repolarization,^{41,47} and may carry different implications than mean QT in terms of arrhythmogenesis. The mean and the longest QT are not very well related to each other and may not be used interchangeably.⁴¹ 24-hour Holter monitoring was also used in one study.³ Holter methodology is more often employed to detect infrequent extreme QT intervals and diurnal variations, and QT interval measured using the Holter monitoring may not correspond directly to those from standard 12-lead ECG.^{37,46}

Bazett's formula was the most commonly used method for adjustment of heart rate, although it tends to underestimate the duration of repolarization when heart rate is particularly slow (or overestimate when heart rate is fast).³⁷ Other methods, such as Hodge's or Rautaharju's linear equations,^{12,16,21} may provide a more uniform correction over a wide range of heart rates, but may report discordant results as compared with the Bazett's formula.^{4,12} Reassuringly, in resting conditions with heart rates 60–90 beats/min, different formulae tend to provide equivalent results for detecting QT prolongation, and so the impact of the method of correction may have been relatively minor in population studies.⁴⁶

In addition, studies varied substantially in the cutoffs used to present the associations between QT-interval length and mortality. We selected the comparisons of the highest vs the lowest reported categories for our meta-analysis. This is likely to result in between-study heterogeneity, as the cut-points for the highest category ranged from 420 to 470 ms and those for the lowest category from 360 to 460 ms. However, even with this degree of heterogeneity, virtually all studies reported a positive association. More uniform reporting standards in this area would facilitate comparison across studies and should therefore be a priority in future studies.

Other limitations of our meta-analysis need to be considered. Most studies included in this meta-analysis measured QT interval at a single point in time. Given the large degree of within-person variability in QT-interval length,⁴⁸ it is likely that the relative risks obtained in these studies underestimated the association between QT interval and mortality. Repeated measurements under uniform conditions would more reliably estimate the associations.² Furthermore, subjects at the extremes of normal QT distribution may have been eliminated by previous ECGs showing an abnormal interval, or by selective mortality. Also, there was large variability in the prevalence of cardiovascular disease at baseline across studies. However, half of the studies adjusted for previous cardiovascular disease in their models, which may help reduce potential confounding due to preexisting disease. In addition, there was substantial variability in the measures of association and the adjustment factors used in each study, adding to the heterogeneity of the results. It is also possible that some individual studies failed to adjust for key risk factors or electrocardiographic parameters that may account for the observed association of QT interval duration and mortality endpoints.

Finally, not all mortality endpoints were reported consistently across all studies, and only 5 studies specifically reported sudden cardiac death. Lack of data on this outcome in most studies was likely caused by the substantial difficulty in assigning sudden cardiac death in population study settings due to the unpredictable nature of this event and the lack of standard definition.⁴⁹ Indeed, estimates of the incidence of sudden cardiac death in the US vary from less than 200,000 to 450,000 per year, depending on the source.⁵⁰ Epidemiologic studies of sudden cardiac death are plagued by difficulties in phenotyping and case definition. Conventional estimates, such as those from the National Center for Health Statistics, use death certificate adjudication, which overestimates sudden cardiac death rates. Prospective, multisource identification of sudden cardiac death, such as in the Seattle Emergency Rescue data and the Oregon Sudden Unexpected Death study, are more likely to provide accurate estimates.⁵¹

In spite of methodological heterogeneity across studies, our meta-analysis identified consistent increases in mortality associated with a prolonged QT interval. In combination with genetic findings relating to genetic variability in QT-interval length and mortality, our findings indicate that QT-interval length is a determinant of mortality in the general population. Our analysis calls for more standardized methods for measuring and reporting QT-interval measurements, population characteristics, and sudden cardiac death, in order to estimate more precisely the magnitude of the increase in risk associated with QT prolongation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Flow diagram of study selection process

Figure 2. QT metric and interval cutpoints used in the original studies

Solid lines represent studies reporting categorical QT intervals. The triangles represent the cutpoints used in the original studies, and the bold segments represent the reference category originally used in each study. (In this meta-analysis we recalculated the results so that the reference category used in the meta-analysis was the lowest QT interval category). Dotted lines represent studies using QT-interval length as a continuous variable. Stars represent median QTc intervals instead of mean intervals.

Figure 3. Meta-analysis of the association of increased QT-interval length with mortality endpoints

Relative risks (RRs) correspond to comparisons of the highest vs. the lowest reported category of QT-interval length in studies that categorized QT interval or to the RR for mortality associated with an increase in 50 ms in QT interval length in studies that used QT interval length as a continuous variable. The area of each square is proportional to the inverse of the variance of the log RR. Horizontal lines represent 95% CIs. Diamonds represent pooled estimated from inverse-variance weighted random effects models.

Figure 4. Dose-response meta-analysis of QT-interval length and mortality endpoints
 Circle areas are inversely proportional to the variance of the log relative risks from studies using categorical QT intervals. Dashed lines correspond to studies that used QT-interval length as a continuous variable. The pooled linear risk trend (thick solid line) and its 95% confidence band (shaded region) were obtained using a random-effects dose-response meta-analysis.

Table

s of QT interval and mortality endpoints

author, year, and reference number	Country	Population	Exclusion criteria	Study design	Follow-up (year)	Sample size	Age (years): mean or range	% Female	% CVD at baseline	Mortality endpoints (number)
erg, 1991 ¹⁰	USA	Framingham Heart Study	CHD, taking medications that may affect the QT interval	Prospective cohort	30	5,125	30–62	53.9	0.0	Total (NR) SCD (NR) CHD (NR)
en, 1991 (men) ¹⁸	Netherlands	Civil servants and spouses	NR	Nested case cohort	28	1,564	52.6	0.0	13.0	Total (1205) CVD (953) CHD (854)
en, 1991 (women) ¹⁸	Netherlands	Civil servants and spouses	NR	Nested case cohort	28	1,496	51.9	100.0	7.6	Total (839) CVD (650) CHD (558)
1993 ³	Netherlands	Rotterdam QT project	Intraventricular conduction defect, evidence of cardiac dysfunction	Nested case cohort	2	104 cases; 201 random cohort	78% >60 y in cases; 49% >60 y in random cohort	27% in cases; 42% in random cohort	NR	SCD (104)
; 1994 (middle-aged) ⁸	Netherlands	Zurphen Study	Previous MI	Prospective cohort	25	851	49.9	0.0	NR	CHD (132) SCD (106)
; 1994 (elderly) ⁸	Netherlands	Zurphen Study	Previous MI	Prospective cohort	5	720	71.9	0.0	NR	CHD (24) SCD (22)
ein, 1997 ⁵	USA	Bronx Aging Study	Terminal illness, CHF, dementia, missing baseline ECG, poor quality tracings, or mechanical or wandering pacemaker rhythm, right ventricular pacing, AF or flutter, advanced degrees of heart block, or >3 premature beats on baseline ECG	Prospective cohort	7–10	391	75–85	64.5	NR	Total (117) CVD (52) CHD (20)
; 1998 ⁹	Denmark	Danish Study	BBB, AF, patients not in sinus rhythm, <9 leads	Retrospective cohort	11–13	2,269	44	48.0	0.0	Total (140)
1998 ¹⁹	USA	Honolulu Heart Program	NR	Prospective cohort	3.5	3,056	77.19754581	0.0	16.2	Total (NR)
2000 ¹³	USA	Strong Heart Study	Digital ECG unavailable	Prospective cohort	3.7	1,839	55.4	56.4	18.4	Total (188) CVD (55)
2000 (men) ¹⁵	Poland	Warsaw Pol-MONICA Project	BBB, AF, delta wave, frequent premature beats	Retrospective cohort	11.6	1,309	50.1	0.0	38.1	Total (309) CVD (162) CHD (59)

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Author, year, and reference number	Country	Population	Exclusion criteria	Study design	Follow-up (year)	Sample size	Age (years): mean or range	% Female	% CVD at baseline	Mortality endpoints (number)
2000 (women) ¹⁵	Poland	Warsaw Pol-MONICA Project	BBB, AF, delta wave, frequent premature beats	Retrospective cohort	11.6	1,337	50	100.0	37.1	Total (150) CVD (64) CHD (22)
Imaki, 2001 ¹⁴	Finland	General community population	NR	Prospective cohort	10	330	74	47.3	7.9	Total (180) CVD (78)
2002 ²⁵	Russia	MONICA project	NR	Prospective cohort	9.5	777	25-64	0.0	NR	Total (84)
2003 ¹⁷	USA	Cardiovascular Health Study (CHS)	No ECG, QRS>120, AF	Prospective cohort	11	4,129	72.6	59.9	0.0	Total (1236) CHD (256)
2004 ²⁰	England	Caerphilly Heart Study	BBB, interference on ECGs	Nested case-control	7.1	207 cases; 215 age-matched controls	53.7	0.0	10.7 (MI)	CHD (207)
2004 ⁷	USA	ARIC	Self-reported heart attack, cardiovascular surgery, coronary angioplasty, ECG evidence of prior MI, missing data on QT	Prospective cohort	4-6	14,548	53.9	56.6	NR	Total (514) CVD (178)
2004 ¹¹	Japan	Adult Health Study (AHS)	Exclusion: CHD, AF, atrial flutter, or BBB; taking medications that could cause the prolongation of QT duration at baseline	Prospective cohort	8.8	3,543	65	66.6	0.0	Total (593) CVD (117) CHD (42)
2006 ¹²	Sweden	Vasteras Study	Locomotor impairment, treatment for heart disease, other diseases, drugs associated QT interval prolongation	Prospective cohort	6.4	433	75	51.5	9.5	Total (81)
2006 ¹⁶	USA	Women's Health Initiative (WHI)	QRS>=120, inadequate quality or missing ECG data	Prospective cohort	6.2	35,715	62.1	100.0	0.0	CHD (112)
2006 ²²	Netherlands	Rotterdam Study	NR	Prospective cohort	6.7	6,134	69.2	59.6	6.3 (MI)	SCD (125)
2007 ⁴	Finland	Finnish study	NR	Prospective cohort	29	10,822	44	47.7	8.0	Total (5,635)
2008 ²¹	England	British Regional Heart Study	ECG abnormalities associated with prolonged QTc (i.e., BBB, WPW, intermittent aberrant AV conduction, artificial pacemaker)	Prospective cohort	7	3,596	60-79	0.0	18.4	Total (689) CVD (290)
2008 ²³	USA	Male veterans	Death within 1 week of the ECG recording,	Retrospective cohort	7.5	24,270	56.7	0.0	NR	CVD (1859)

author, year, and reference number	Country	Population	Exclusion criteria	Study design	Follow-up (year)	Sample size	Age (years): mean or range	% Female	% CVD at baseline	Mortality endpoints (number)
, 2008 ²⁴ (diabetics)	Germany	MONICA/KORA	women, AF, BBB, paced rhythms, WPW syndrome	Prospective cohort	9	151	65.2	48.8	12.5	Total (49) CVD (18)
			AF, atrial flutter, BBB, second- and third- degree AV or SA block, antiarrhythmic use, QT- prolonging medication use, multiple supraventricular or ventricular extra- systoles, pacemaker therapy, or missing data							
, 2008 ²⁴ (non-diabetics)	Germany	MONICA/KORA	AF, atrial flutter, BBB, second- and third- degree AV or SA block, antiarrhythmic use, QT- prolonging medication use, multiple supraventricular or ventricular extra- systoles, pacemaker therapy, or missing data	Prospective cohort	9	1,496	63.7	48.7	5.8	Total (164) CVD (50)
2009 ⁶	Canada	Manitoba Follow-up Study (MFUS)	ECG $\leq$ 8 leads	Case-control	58	135 cases; 261 age- matched controls	31	0.0	0.0	SCD (135)