Clinical interpretation of changes in the QT interval is of growing interest. In 1984, Surawicz and Knoehel stated in an extensive review that it is still “difficult to judge when a prolonged QT interval is good, bad or indifferent.” Recently, Algra et al published a study in Circulation entitled “QT Prolongation Measured in a Standard 12-Lead Electrocardiogram Is an Independent Risk Factor for Sudden Death.” In the present issue of Circulation, Schouten et al present the study, “QT-Interval Prolongation Predicts Cardiovascular Mortality in an Apparently Healthy Population.” The titles include no question marks. Should they, and how strong a predictor is QT interval prolongation for cardiac death?

The Rotterdam QT project included 6,693 consecutive candidates for 24-hour ECG recording. In patients without intraventricular conduction, defect QT interval was measured once by one investigator from standard ECG leads I, II, and III and corrected for heart rate with Bazett’s formula (QTc). During the ensuing 2 years, 176 patients died suddenly. QTc prolongation (>440 msec) doubled the risk for sudden death. Patients with a history of pump failure or left ventricular ejection fraction less than 0.40 had 4.5 times higher relative risk for sudden death than those without cardiac dysfunction. In patients with dysfunction QTc prolongation did not further increase the risk for sudden death (1.0), whereas among those without dysfunction QTc prolongation bore a 2.3 times higher risk for sudden death. These relative risks were not altered when analyses were adjusted for age, sex, history of angina, or myocardial infarction (MI), arrhythmias, heart rate, and use of drugs (digitalis, β-blockers, or antiarrhythmic class I, III, or IV drugs). Overall, these results are in accordance with studies of patients with ischemic heart disease, although differences in study design are quite apparent. In this study Algra et al studied a very large number of heterogenous patients and, since the results were stable in many subgroup analyses, they may well apply to a broad patient population.

Does QTc prolongation also predict cardiac mortality in healthy individuals? Somewhat conflicting results have recently been published in two epidemiological studies addressing this question. Schouten et al related QTc, registered in 1953–1954 and measured as in the study by Algra et al, to mortality during 28-year follow-up in 3,091 apparently healthy subjects, aged 40–65 years. They found moderate (420<QTc<440 msec) and extensive (QTc>440 msec) QTc prolongation to significantly predict overall mortality during the first 15 years both for men (adjusted relative risk, 1.5 and 1.7, respectively) and women (1.7 and 1.6, respectively). In men, but not in women, this relation was due to cardiovascular and ischemic heart disease mortality (relative risks, 1.6, 1.8, and 2.1, respectively). After 28 years, some of these relations were still significant although weaker. As part of the Framingham Heart Study experience, Goldberg et al have related the longest QTc recorded from any lead in 1948 to 30-year mortality in 5,125 subjects. This study failed to demonstrate an association between quintiles of QTc (≤360, 360–380, 390–400, 410–430, and ≥440 msec) and overall mortality, and deaths due to sudden cardiac events or coronary artery disease. If they had also presented detailed calculations for 15-year mortality it would have been easier to compare these two epidemiological studies, as the significant relation between QTc and outcome decreased over 28 years in the study from the Netherlands. However, if there really is a difference here in the prognostic importance of QT, this could be due to several factors.

The QT interval represents the time registered for depolarization and repolarization of the ventricles, that is, the algebraic summation of action potentials of both ventricles. Factors that influence action potentials generate changes in the QT interval. QT duration is highly dependent on heart rate, and therefore is corrected for heart rate, and the formula most often used, as in the studies here reviewed, is the one by Bazett. As this formula (QTc=QT/square root of RR) may overcorrect at high heart rates, several other formulas have been proposed. However, it is always possible to calculate a formula for the QT–heart rate relation from every study group being evaluated, and until
studies with an extremely large quantity of high-quality data suggest a formula that can be applied universally, Bazett’s formula must be recommended.5,30,31

In the study by Schouten et al32 9.5% of the subjects had QTc values exceeding 440 msec compared to 5.4% in the one by Goldberg et al.23 Although the number and types of errors in RR and QT interval measurements may vary between readers, and sometimes with difference in lead selection,32-34 in the studies here reviewed these errors should be of no importance for outcome since a very large number of subjects were studied.33

Not only will QT interval be influenced by heart rate and by errors in measurement, in addition electrolyte abnormalities must be considered. Hypercalcemia will generate narrowing and peaking of the T wave through increased velocity of the rapid repolarization phase, phase 3. During hypocalcemia phase 2 of the action potential shortens and may even disappear, while phase 3 lengthens. Thus a slight increase of the QRS duration, a shortening and depression of the ST segment, a decrease in amplitude and change in shape of the T wave, and an increase in the U wave amplitude will be seen. Hypocalcemia prolongs ST segment and QT interval, whereas hypercalcemia may generate opposite changes. Most often, serum electrolytes are regularly checked and abnormal values corrected by supplementation. However, local cellular electrolyte changes may be of importance in this context. Damaged myocardial cells take up calcium in the mitochondria; thus, phase 2 of the action potential and consequently the QT interval will be prolonged. Local electrolyte disturbances will affect neurogenic impulses generated from ischemic and infarcted zones, which in turn will influence the efferent neurogenic impulses and blood catecholamine levels. During acute MI the myocardium will also be influenced by metabolic substrates and local temperature changes, lengthening the QT interval. This is accompanied by a reduction in baroreflex sensitivity, a marker of increased risk for sudden death.35

The influence of autonomic tone on the QT interval has been demonstrated when fixed heart rate has been achieved by pacing.36-47 Imbalance of this tone can influence QT in patients with central nervous system diseases and especially in those with the idiopathic long QT syndromes in which neurally mediated noncoronary sudden cardiac death can occur. Consequently these patients are treated with betablockers or even left cardiac sympathetic denervation.48 However, the occurrence of long QT syndromes is extremely low and it causes death at younger ages (<40 years), so that this disease did not influence outcome in the studies reviewed here.

In 194823 and 1953–1954,3 most drugs that influence QT were not used except for digitalis, which shortens QTc. However, nowadays drug induced QTc prolongation exists that may have a proarrhythmic or an antiarrhythmic effect. Prolonged QT associated with increased dispersion of refractoriness may induce ventricular arrhythmias, especially torsade de pointes,49–51 whereas prolongation associated with increased repolarization homogeneity decreases the likelihood of such arrhythmias.

Influenced by so many factors, is it then realistic to consider QTc to be a predictor for cardiac or overall mortality during short or long time follow-up periods. As QTc is generated from the heart, its strength should be evaluated together with other cardiac risk factors. Among cardiac variables different “groups” can be separated for prognostication purposes, although these to a greater or lesser extent may be interrelated. They include age, sex, primary risk factors, patient history, variables reflecting the pumping status (e.g., left ventricular ejection fraction, use of digitalis), and those reflecting the electrical status of the heart, for example, QT interval, ST-T changes, arrhythmias, and anatomic findings on coronary angiography. In multivariate analysis of post-MI patients, variables reflecting the mechanical status of the left ventricle most often will be a stronger predictor for cardiac mortality than those reflecting the electrical status of the heart.52–55 This was true also in the study by Algra et al.2

However, not only can high-risk patients be identified (e.g., with left ventricular ejection fraction determination) but also low risk patients, especially if left ventricular ejection fraction is considered together with age.56,57 As stressed by Algra et al.,2 low risk patients usually have no cardiac dysfunction. In addition, they seldom have severe ventricular arrhythmias and consequently these patients are usually not treated with digitalis, β-blockers or antiarrhythmic drugs that will influence QT. In a prospective collaborative study among low-risk acute MI patients without drug and pacemaker therapy, we have previously found that patients who died within 90, 180, and 365 days tended to have longer uncorrected QT at hospital discharge than survivors. This tendency reach highly significant levels for QTc. A QTc of 440 msec was the optimal discriminant value, and it yielded 77% sensitivity and 84% specificity for 1-year cardiac mortality.17 Subsequent stepwise linear discriminant analyses to evaluate the independent importance of prognostic hospital discharge variables for 1-year cardiac death ranked QTc as number one followed by basal rates and QRS duration (unpublished data). During MI QTc prolongation will be most pronounced during the very acute phase, especially in patients with non-Q wave MI.1,16,58 Among these patients extension of MI is a strong univariate predictor for 1-year cardiac mortality,59 and furthermore in these non–Q wave MI patients the presence of complex ventricular arrhythmias on 24-hour monitoring at hospital discharge is an important predictor of 1-year cardiac mortality as well.60

The two excellent studies by Algra et al.2 and Schouten and associates3 have expanded our knowledge about the prognostic importance of QTc for mortality. The size (6,693 subjects) and the hetero-
geneity of the study by Algra et al\(^2\) (31% had had an MI, 15% cardiac dysfunction, 16% transient ischemic attack or stroke, and 80% use of drugs) gave an opportunity for relevant subgroup analyses. Schouten et al\(^3\) studied a large number (3,091) of healthy middle-aged and low-risk subjects during a long period and found QT\(_{c}\) to be a predictor for 15-year outcome. Most likely, QT\(_{c}\) prolongation here is linked to subsequent development of coronary artery disease. Whether QT\(_{c}\) prolongation was related to silent myocardial ischemia at the time was not possible to evaluate, as the only other ECG at study baseline was registered after a low-level Master two-step exercise test. The relation between QT\(_{c}\) and silent ischemia, especially in relation to changes in the autonomic nervous tone, needs further investigation in larger study groups.

Although QT\(_{c}\) is quite stable over time in MI patients\(^5\) the pioneering case-control study by Schwartz and Wolf\(^6\) of 55 post-MI patients showed that those with repeatedly prolonged QT\(_{c}\) measured every 2 months over 7 years and with high variability were more likely to die suddenly. In addition, not only QT\(_{c}\) variability over time needs to be studied but also in different areas of the heart, that is, variability between ECG leads.

Variables reflecting cardiac electrical instability and abnormality are predictors for mortality. How strong these univariate predictors, including QT interval, are in different groups will depend on whether high- or low-risk subjects are considered, which other variables are taken into account, and on the time over which this prediction is to be made. It is beyond question that QT\(_{c}\) prolongation (>440 msec) is a predictor for cardiac death in low risk patients. Naturally, as a single measurement its prognostic strength will decrease over a long time period.

To obtain information about QT is inexpensive and does not require sophisticated equipment. Nevertheless, electrophysiological testing and computerized ECGs permitting time expansion and use of filtering techniques to exclude noise will make it even easier for us to reduce errors in QT measurement and recognize QT abnormalities, including delayed after potentials or other diastolic waves that may be markers of dispersion of the repolarization process associated with ventricular arrhythmias and cardiac death.

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