Using the electrocardiogram as a crystal ball for cardiovascular and all-cause mortality

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This editorial refers to ‘Risk prediction of cardiovascular death based on the QTc interval: evaluating age and gender differences in a large primary care population’, by J.B. Nielsen et al., on page 1335.

Imagine a 55-year-old man with no medical history or previous cardiac symptoms who presents to his general practitioner with complaints of fatigue. His resting electrocardiogram (ECG) and ensuing cardiac symptoms who presents to his general practitioner with complaints of fatigue. His resting electrocardiogram (ECG) and ensuing physical examination are unremarkable, except for a slightly prolonged heart rate-corrected QT (QTc) interval of 470 ms. And then you wonder: what would be the clinical relevance of this finding?

In 1950, Wolff stated: ‘The QT interval is measured from the beginning of the QRS complex to the end of the T wave, but it is not often necessary to determine this value’.1 However, nowadays we are well aware of its importance as a marker of a risk for sudden cardiac death in patients affected with the congenital long and short QT syndromes and, to a lesser extent, with acquired long QT syndrome. In addition, > 20 studies have demonstrated an association between the QTc interval and all-cause and cardiovascular mortality in large samples from the general population, with dose–effect responses even within the normal QTc interval range.2

The meticulously performed study by Nielsen and co-workers now presents data to predict the 5-year risk of all-cause, cardiovascular, and non-cardiovascular mortality based on the QTc interval in 72 subgroups from 173 529 Danish primary care patients aged 50–90 years.3 In line with previous studies, prolongation of the QTc interval was associated with a worse prognosis. In addition, shorter QTc intervals (< 379 ms) were also associated with an increased mortality, especially in women. When added to a conventional risk model for cardiovascular mortality, the QTc interval increased the accuracy of this model in several subgroups, particularly in elderly women (70–90 years of age).

When interpreting the data of this study, several important issues, also acknowledged by the authors, need to be considered. First, this large middle-aged and elderly primary care population had an ECG recorded on behalf of their general practitioner for unknown indications. During the study period, this occurred in 29% of the Copenhagen population, and 51% of these patients met the inclusion criteria of this study. Some form of selection bias will thus be inevitable. Secondly, all ECGs were recorded digitally and stored in the MUSE® Cardiology Information System (GE Healthcare, Wauwatosa, WI, USA) and were later processed using version 21 of the Marquette 12SL algorithm. A total of 150 ECGs were sampled for manual evaluation without further details on the method of the assessment of the end of the QT interval. We know from previous studies that the 12SL algorithm may lack a prolonged QTc interval diagnostic statement and that QT experts prefer manual measurements. There was only a 1.3 ms mean difference in the manual and automated QTc interval measurements in the study of Nielsen and co-workers. However, outliers reached differences > 90 ms (their Supplementary figure 5). So, ideally, the automated measurements should be manually confirmed, in daily clinical practice and for scientific purposes—also for such large data sets.

Thirdly, heart rate correction of the QT interval is fraught with problems. Historically, Bazett’s correction has been used most commonly and is still recommended for making the diagnosis of congenital long and short QT syndrome. Framingham’s linear correction is often rather comparable, but many efforts have been made to improve this matter. There are several excellent papers on this issue, e.g. by Luo et al.8

Fourthly, it is intuitive also to consider geographic factors in the determination of risk assessment models. Previous studies showed that normal values for ECG indices may differ between individuals from different ethnic backgrounds.9 So the translatability of the study by Nielsen et al. will be confined to predominantly white European populations.

Still, the most important question remains of how the QTc interval-based predicted risk of mortality can affect patient management. In addition to the QTc interval, other resting conduction and repolarization ECG indices such as heart rate, P-wave duration,11 and frontal T-wave angle12 are increasingly being associated with all-cause and cardiovascular mortality and morbidity in the general population (Figure 1). Studies reporting these associations have...
analysed only one or a few markers at the same time. It is, however, conceivable that ‘mortality calculators’ based on multivariate models including all recently reported ECG indices associated with mortality will be developed in the near future, with similar efforts that have been made in the past as an example.13 These calculators may remind us of SCORE14 or other cardiovascular disease risk models that are frequently used in patient management. Yet, the obvious difference is that ECG indices may not be causally related to mortality and that, if a causal relationship would be assumed, evidence-based interventions to improve a patient’s prognosis are not available.

According to the Nielsen study, our imaginary 55-year-old male with a QTc interval of 470 ms has a 5-year risk of death, cardiovascular death, and non-cardiovascular death of 8, 2, and 6%, respectively. Nielsen and co-workers point out that they sought to analyse the value of the QTc interval in long-term prediction of cardiovascular death, ‘because cardiovascular death is potentially preventable and identifying high risk subpopulations is thus warranted.’ Although this statement is intuitive, in our imaginary patient the prolonged QTc interval seems to be an indicator of an increased risk for non-cardiovascular death in particular. In addition, even the predicted increased risk for cardiovascular death in this patient cannot, in the absence of known modifiable risk factors for cardiovascular disease, be influenced. So what should we advise this patient, in view of his mildly prolonged QTc interval, regarding his complaint.

**Figure 1** Association of conduction and repolarization indices on a normal resting ECG with (arrhythmic and non-arrhythmic) cardiovascular mortality in individuals without known cardiovascular disease from the general population. This figure depicts indices that, even within the normal range, have been associated with cardiovascular mortality. In indices with a consistent association with cardiovascular mortality, multivariate-adjusted hazard ratios or relative risk (RR) estimates from a meta-analysis1 or recent representable study10–12 are shown to indicate the strength of the association. *Pooled relative risk estimate of 16 studies including 0–38% of individuals with known cardiovascular disease. Pooled relative risk estimates for all-cause mortality, coronary heart disease mortality, and sudden cardiac death of six studies including apparently healthy individuals only were similar to those including individuals with known cardiovascular disease.† Multivariate adjusted relative risk estimates of sudden arrhythmic death in apparently healthy individuals and of non-arrhythmic cardiac mortality in the entire population, including a small proportion with known cardiovascular disease.12
of fatigue or his general health? From a cardiological point of view, we could postulate that he might be developing a cardiomyopathy associated with both fatigue and QTc interval prolongation, but it is probably more likely that his prolonged QTc interval is just a bystander. We could of course advise further cardiological examinations, particularly echocardiography and familial screening. Also we should be aware of the risk potential of cardiovascular and non-cardiovascular drugs that may further lengthen his QTc interval (www.QTdrugs.org). However, as already said, influencing non-cardiovascular mortality risks based on a lengthened QTc interval seems otherwise impossible.

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References