Prognostic significance of electrocardiographic Q-waves in a low-risk population

Peter Godsk1,2*, Jan Skov Jensen1,2,3, Steen Z. Abildstrøm4, Merete Appleyard1, Sune Pedersen2, and Rasmus Mogelvang1,5

1The Copenhagen City Heart Study, Bispebjerg Hospital, Copenhagen, Denmark; 2Department of Cardiology, Gentofte Hospital, Niels Andersens vej 65, DK-2900 Hellerup, Denmark; 3Faculty of Health Sciences, Clinical Institute of Surgery and Internal Medicine, University of Copenhagen, Copenhagen, Denmark; 4Department of Cardiology, Bispebjerg Hospital, Copenhagen, Denmark; and 5Department of Medicine, Holbæk Hospital, Holbæk, Denmark

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Aims In individuals without known heart disease, electrocardiographic Q-waves predict a poor prognosis. We aimed to examine whether prognostic information can be derived from the size and location of Q-waves in persons from the general population without known ischaemic heart disease (IHD) or heart failure (HF).

Methods and results Electrocardiograms (ECGs) of 5381 persons without known IHD or HF from the 4th Copenhagen City Heart Study were reviewed and Q-waves were classified according to their size and location. Multivariate Cox proportional hazards regression models were used to examine the associations of Q-waves adjusted for age, hypertension, diabetes, and estimated glomerular filtration rate with the risk of the combined endpoint of death and hospitalization for IHD. During a median of 7.8 years of follow-up, 1003 persons reached the combined endpoint. One hundred fourteen (2.1%) had pathological Q-waves, of whom 44% suffered from an event compared with 18% from the control group, $P = 0.001$. Persons with hypertension, diabetes, and impaired renal function were more likely to have Q-waves. Even small Q-waves (i.e. Minnesota code 1.2.x-1.3.x) were associated with a poor prognosis, hazard ratio (HR) 1.4 (95% confidence interval (CI): 1.0–2.0; $P = 0.05$), though not as grave as large Q-waves (i.e. Minnesota code 1.1.x) HR 2.8 (95%CI: 1.6–5.0; $P < 0.001$). Conversely, there was no difference in the outcome of patients with anteriorly HR 1.6 (95%CI: 1.1–2.4) vs. posteriorly HR 1.5 (95%CI: 0.9–2.4) located Q-waves ($P = 0.85$).

Conclusion In the general population without known IHD or HF, even small Q-waves in the ECG are associated with a poor prognosis.

Keywords Myocardial infarction • Silent myocardial infarction • Unrecognized myocardial infarction • Q-waves • Cohort study

Introduction Myocardial infarction (MI) is not always associated with classical chest pain. In fact, previous studies1–13 have shown that 20–43% of all MIs are not diagnosed—either because there are no symptoms (silent MI) or because the symptoms are so mild or diffuse that neither patient nor doctor consider the diagnosis. Silent MI might even be more prevalent, since the reported prevalences are based on the occurrence of pathological Q-waves in the electrocardiogram (ECG) thus omitting the probably substantial percentage of MIs that does not (or only briefly) display Q-waves in the ECG.14,15

Previous cohort studies show conflicting results with regard to long-term prognosis of these silent or unrecognized MIs compared with that of recognized MIs. Some6,7,8,11 find a similar mortality while others find a better prognosis of unrecognized MIs3,10 or recognized MIs,6 respectively. This discrepancy might to some extent be explained by large differences in baseline populations. Moreover, Ammar et al.16 have shown that the variation in prevalence of unrecognized MIs might be due to differences in the electrocardiographic criteria used in cohort studies for diagnosing prior MI. This could also explain the differences in long-term prognosis since some
studies with more strict ECG criteria would include only larger MIs compared with those with less strict ECG criteria.

However, since previous studies have used the ECG to determine whether or not there were signs of former MI, it is not known whether all electrocardiographic signs of MI are equally important concerning prognostic significance. Furthermore, this information would be of higher interest for the clinician, than the academic discussion of whether a Q-wave represents a former MI or not.

Therefore, we aimed to examine the ECGs from the clinician’s point of view in order to see if prognostic information resides within the ECG, in which case it would enable us to identify high- and/or low-risk electrocardiographic changes. This was done using the data from a random selection of the general population without known ischaemic heart disease (IHD) or heart failure (HF) and using information obtained solely from the ECG with focus on Q-waves. We hypothesized that prognosis was not only dependent on the presence but also on the size and location of the Q-waves.

**Methods**

**Study population**

The Copenhagen City Heart Study is a longitudinal cohort study of cardiovascular disease and risk factors.\(^{17,18}\) The first examination took place in 1976–78 where a random sample of 19 329 predominantly white Caucasians living within a well-defined area of the inner Copenhagen City Boundary was drawn from the Central Office of Civil Registration and invited to participate. The sample was stratified by gender and age (5-year age strata starting from the age of 20 years), ensuring most people in the age groups 40–60 years.

The fourth examination was conducted in 2001–03 where 12 600 randomly chosen individuals were invited. The group consisted of participants from the previous studies (n = 11 600) supplemented by persons from the younger strata (n = 1000). Of these 6237 persons chose to participate (49.5%).

All subjects gave informed consent to participate, and the study was performed in accordance with the Second Helsinki Declaration and approved by the regional ethics committee.

**Health examination**

Body mass index (BMI) was weight in kilograms divided by the square of the height in metres. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or use of antihypertensive medication.\(^{19}\) Diabetes mellitus was defined as plasma glucose concentration ≥11.1 mmol/L, use of insulin or other anti-diabetic medicine, self-reported disease, or HbA\(_1c\) level >7.0%.\(^{20,21}\) Smoking status was self-reported and individuals were defined as smokers if they were current or former smokers. Estimated glomerular filtration rate (eGFR) was calculated by Cockcroft-Gault formula:

\[
(140 - \text{age (years)}) \times \text{[weight (kg)]} \\
\times (1.23 \text{ if male; } 1.04 \text{ if female}) / \text{[serum creatinine (µmol/L)]}.
\]

Known IHD was defined as either a history of hospital admission due to acute coronary artery occlusion, percutaneous coronary intervention, or coronary artery bypass grafting and known HF was defined as prior hospitalization for HF.

**Electrocardiogram**

At inclusion an ECG was obtained on all individuals and coded according to the Minnesota Code Classification system.\(^{22,23}\) The Minnesota classification system divides evidence of prior MI into three groups: 1.1.x, 1.2.x, or 1.3.x—all codes (except one) reflecting the duration, amplitude and for some codes the location and extent of Q-waves. The code 1.1.x reflects large and 1.2.x to 1.3.x reflect smaller Q-waves (Figure 1) with the only exception of 1.2.8 that describes loss of R-wave progression in the precordial leads.\(^{22}\) Two independent reviewers reviewed all ECGs and in case of disagreement a third reviewer settled the case. Furthermore, all ECG with codes 1.1.x to 1.3.x were reviewed to determine location of Q-waves. Q-waves in leads II, III, and aVF were defined as posterior and Q-waves in V\(_1\)–V\(_6\), I, aVL, and loss R-wave progression in V\(_1\)–V\(_6\) were defined as anterior.

**Endpoints and follow-up**

The primary study endpoint was total mortality and hospitalization for IHD. Follow-up was performed on a yearly basis for a median of 7.8 years. Data on mortality were obtained using the unique personal identification number in the Central Office of Civil Registration and
hospitalization for IHD were obtained from the highly validated Danish National Board of Health’s National Patient Registry, using ICD-10 codes: I20–I25.

**Statistics**
Comparisons between groups were performed by Student’s t-test and Fisher’s exact test. Values in parentheses are 95% confidence intervals (CIs), unless otherwise stated. Multivariable Cox proportional hazards regression models were used to examine the associations of Q-waves and age, hypertension, diabetes, and eGFR with the risk of the combined endpoint of death and hospitalization for IHD. Misspecification of the functional form of the covariates and the assumption of proportional hazards were evaluated by plots of the cumulative martingale residuals.

Cumulative survival curves were established by the Kaplan–Meier method, and the curves were compared using the log-rank test. P values <5% on two-sided tests were considered significant. All analyses were performed by SAS software (SAS System for Windows, release 9.2, SAS Institute Inc., Cary, NC, USA).

**Results**
Of a randomly chosen population of 6237 individuals from the fourth Copenhagen City Heart Study a total of 5381 with no history of IHD or HF were identified. Of these 114 (2.1%) had Q-waves according to the Minnesota Code Classification. This group was significantly older, had a higher prevalence of hypertension, diabetes, and impaired renal function compared with controls without Q-waves (Table 1). During follow-up of a median of 7.8 years, 1003 persons reached the combined endpoint of total mortality and hospitalization for IHD. There were significantly more events in the group with Q-waves compared with controls (44 vs. 18%; P < 0.001) (Figure 2). The difference persisted after adjusting for age, hypertension, diabetes, and eGFR [hazard ratio (HR): 1.6, 95%CI: 1.2–2.1; P < 0.002].

Of the 114 persons with Q-waves, 22 had large and 92 had small Q-waves. The risk of reaching the combined endpoint increased with larger Q-waves, thus 59% of the persons with large Q-waves and 40% with small Q-waves reached the endpoint, compared with 18% among controls (P < 0.001) (Figure 3). This pattern remained significant after adjusting for age, hypertension, diabetes, and eGFR: large Q-waves HR 2.8 (95%CI: 1.6–5.0; P < 0.001) and small Q-waves HR 1.4 (95%CI: 1.0–2.0; P < 0.05).

Anterior location of the Q-waves was found in 72 cases and posterior location in 40. In only two cases there were both anterior and posterior Q-waves present in the ECG and they were excluded from the subsequent analyses. Similar proportions of the two groups reached the combined endpoint (anterior: 41% vs. posterior: 46%; P = 0.60) (Figure 4) and there was no significant difference (P = 0.85) between their HRs after adjusting for age, hypertension, diabetes, and eGFR [anterior: HR 1.6 (95%CI: 1.1–2.4) vs. posterior: HR 1.5 (95%CI: 0.9–2.4)].

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<th>Table 1 Baseline characteristics</th>
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<td>No Q-waves (n = 5267)</td>
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<td>Q-waves (n = 114)</td>
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<td><strong>P value</strong></td>
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<td><strong>Age (years)</strong></td>
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<td><strong>Male gender (%)</strong></td>
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<td><strong>BMI (kg/m²)</strong></td>
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<td><strong>Total cholesterol (mmol/L)</strong></td>
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<td><strong>eGFR (mL/min)</strong></td>
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<td>Continuous traits are reported as mean (± standard deviations).</td>
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<td>*Estimated glomerular filtration rate.</td>
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Figure 2 Cumulative probability of event-free survival according to the presence of Q-waves in persons without known ischaemic heart disease and heart failure. Events were defined as death and hospitalization for ischaemic heart disease. P < 0.001 by log-rank test.

Figure 3 Cumulative probability of event-free survival according to size of Q-waves in persons without known ischaemic heart disease and heart failure. Events were defined as death and hospitalization for ischaemic heart disease. P < 0.001 by log-rank test.
Discussion

We found that in the general population without known heart disease, Q-waves in the ECG is a strong predictor of death or hospitalization for IHD regardless of age, hypertension, diabetes, and renal function. Moreover, though large Q-waves carry the worst prognosis even small Q-waves are associated with an increased risk. Conversely, no difference in outcome was found between anterior and posterior location of Q-waves, and both locations were associated with equally poor prognoses.

Presence of Q-waves

In recognized MIs, Q-waves were traditionally thought to represent transmural infarctions. This view was based primarily on animal studies conducted >50 years ago. The advent of magnetic resonance imaging (MRI) has enabled researchers to perform studies of electrocardiographic changes in vivo, and have revealed that Q-waves represent larger infarctions rather than transmural extent. From this point of view, the persons with Q-waves, who did not have a history of heart disease, have supposedly suffered from a larger MI without noticing it. Hence, it is not surprising that these persons have substantially increased risk of dying or being hospitalized for IHD regardless of age, gender, hypertension, diabetes, and renal function.

The grave prognosis of unrecognized MI was also found in the follow-up of the Framingham population. This study was initiated in 1948 and reported a 10-year mortality of 45%. This was in common with the results from the Reykjavik study, that was initiated in the 1960s but continued enrolment until the 1980s. So, despite the technological and medical advances obtained during those decades, unrecognized MI has remained a substantial health problem. Furthermore, the Framingham study reported that 30% of all MIs were unrecognized. The ARIC study that enrolled patients from 1987 to 1989 and was published in 2002 found an equal distribution of recognized and unrecognized MIs. Thus, during the 40 years between these two studies, apparently, there has been no improvement in diagnosing MIs with vague or without symptoms. Our study was not designed to assess the distribution of recognized and unrecognized MIs, which in this context is unfortunate, since that would have allowed us to evaluate the effect of the primary prophylactic efforts made during the last decades to put focus on symptoms of heart disease.

Q-wave size

It is well established, that both short-term and long-term prognosis of patients suffering from MI is dependent on the extent of myocardium involved and subsequently the amount of damage inflicted on cardiac structure and function. Furthermore, based on autopsy reports, the extent of MIs can be assessed by judging size, location and extent of Q-waves as well as R-wave abnormalities. This has also been confirmed in vivo with MRI. In concordance, we found that larger Q-waves carry a worse prognosis than small Q-waves supporting the conception, that the size of Q-waves reflects the extent of myocardial damage, loss of cardiac function and, consequently, prognosis.

This is to our knowledge the first study to describe that the extent of the necrotic area of infarction determines prognosis also in the case of unrecognized MI. Even more, not only large Q-waves are important, and yet interpreters of ECGs might be inclined not to take notice of small, incidental Q-waves, our results show that this is not a recommendable approach because of a significantly higher IHD morbidity and mortality in this group of patients.

Large Q-waves

Large Q-waves were defined according to the Minnesota Code Classification System that was introduced in 1960 in Circulation. It is an epidemiological tool often used in cohort studies to identify individuals with prior MI based only on electrocardiographic abnormalities. It was developed as an expert consensus and validated according to inter- and intra-observer reliability and diagnostic validity.

Unfortunately, the Minnesota Code Classification System is complicated and requires very frequent use to acquire and maintain routine. Therefore, to be able to identify the high-risk population with large Q-waves (i.e. Minnesota Codes 1.1.x) we have reformulated the Minnesota codes 1.1.x to make criteria, which in this context is unfortunate, since that would have been easier to remember in daily clinical practice (Table 2). It is worth noting that any Q-wave ≥0.04 s (except III and aVF)...

Table 2: Large Q-waves according to rewritten Minnesota criteria

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<th>Large Q-waves:</th>
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<td>(1) All Q-waves ≥0.04 s (aVL R amplitude ≥3 mm) or ≥0.03 s if Q/R ≥1/3 (not V1)</td>
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<td>Except: III or aVF ≥0.05 s (Q amplitude ≥1 mm in most beats in III)</td>
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<td>(2) QS in one of V2–V6 if preceding lead has a R-wave or QS in all leads V1–V6</td>
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Figure 4: Cumulative probability of event-free survival according to location of Q-waves in persons without known ischaemic heart disease and heart failure. Events were defined as death and hospitalization for ischaemic heart disease.
and that any QS-wave that does not respect the normal progression of R-waves in the precordial leads predicts a particularly poor prognosis.

**Q-wave location**
The impact on prognosis of anterior vs. posterior location of recognized MIs has been studied extensively. Most studies, including data from the Framingham Study and a follow-up of 872 patients submitted to a coronary care unit, show that anterior infarctions are associated with a worse prognosis than posterior infarctions. This is caused by a higher frequency of arrhythmias, cardiogenic shock, and damage to cardiac function and thus reflecting infarct size. A few others have shown no or only short-term difference in prognosis. To our knowledge, this study is the first to assess the differences of anterior and posterior unrecognized MIs. We found, that location of Q-waves does not affect prognosis, suggesting that unrecognized posterior infarctions are equally as serious as unrecognized anterior infarctions.

Moreover, we found that electrocardiographic unrecognized anterior infarctions are almost twice as frequent as posterior infarctions. This raises the question of whether anterior infarctions present with more vague symptoms making them more susceptible to being misinterpreted by the patient. This is partially supported by an older review of 26 patients that were diagnosed with MI with atypical symptoms (i.e. no chest pain) where 50% had anterior and only 27% had posterior MIs (no data on P-value). However, this review also found anterior infarctions (48%) more common than posterior (37%) among typical infarctions. A larger study of 1546 patients with recognized MI showed a difference in symptoms accompanying chest pain according to location of infarction. For instance, anterior infarctions were more often associated with complaints of left arm and left shoulder, headache, weakness, and dyspnoea, whereas posterior infarctions more often occurred in conjunction with epigastric, neck and jaw pain, sweating, nausea, and vomiting. Intuitively, this ought to result in a larger proportion of unrecognized posterior infarctions, since their accompanying symptoms would be more likely to be misinterpreted as non-cardiac.

This is not the case in our study, however, and the explanation might be that because the ECG covers the anterior wall with more leads (I, aVL, V1–V4) than the posterior (II, III, aVF), each anterior lead represents a smaller area of the left ventricle. Therefore, it is reasonable to argue that smaller MIs are detected in the anterior wall than in the posterior wall, which in turn could explain the larger number of anterior infarctions. In addition, it would explain why we found that unrecognized anterior MIs apparently carry a better prognosis than recognized anterior MIs compared with their posterior counterparts.

**Risk factors**
In the Cardiovascular Health Study, factors associated with unrecognized MI were among others: female gender, increasing age and blood pressure. Absence of angina was also associated with higher risk of unrecognized MI, suggesting that myocardial ischaemia in these patients is silent, atypical, or not perceived as a significant health problem by the patient. While silent ischaemia is seen more often in diabetes patients, there is no consistency in evidence supporting increased numbers of unrecognized MI among diabetes patients in the former cohort studies. Only the ARIC study comprising a cohort of both Whites and African-Americans reports of an increased incidence.

In this random sample of the general population, however, there was a higher risk of unrecognized MI among the elderly and individuals with diabetes, hypertension, or impaired renal function. On the other hand, whereas smoking, plasma cholesterol levels, and BMI are known risk factors for IHD, in our study there were no significant correlations between these conditions and unrecognized MI, although there was a tendency towards a higher prevalence of all known risk factors among all persons with Q-waves. The fact that age, diabetes, hypertension, and impaired renal function are significantly associated with unrecognized MI suggests that these conditions can blur the normal symptoms of MI and thus increase its risk of passing by unnoticed.

**Strengths and limitations**
The strength of the present study is the complete randomness of the baseline population, which limits bias to a minimum. Whereas former studies regarding prevalence and incidence of unrecognized MI are based on populations of either only women or men this population consists of a random sample of the general population of both gender and all age groups >20 years, enabling us to draw consequences of our study in a larger scale.

Abnormal Q-waves in the ECG may be produced by conditions other than MI such as: pre-excitation of the ventricles; hypertrophic cardiomyopathy; other types of cardiomyopathy including the myocardial disease of Friedreich's ataxia; myotonia atrophica; amyloid heart disease; and dilated cardiomyopathy of any cause; systolic or diastolic pressure overload of the left ventricle; acute pulmonary embolism; and several types of severe congenital heart disease. Although this consideration is of interest to the academic discussion of whether an abnormal Q-wave represents an MI or not, it has only little importance for our purpose, since we are interested in the diagnostic rather than the prognostic implications of Q-waves.

A limitation to the study is the relatively small number of persons with large Q-waves. A larger number would have been preferable. However, a very large proportion of this group reached an endpoint in the follow-up period, so even though it consisted of only 22 persons we were able to obtain significant results. Another limitation is the fact that in 15 cases (13%) an abnormal Q-wave was present in only one lead. Although this is not a limitation according to the Minnesota criteria, it raises the question of whether or not these Q-waves are pathological.

**Conclusion**
Even small—and in particular large—Q-waves in the ECG of individuals without known IHD or HF are associated with a substantial risk of IHD and death, and any such Q-wave may indicate the need for further investigation in order to detect asymptomatic cardiovascular disease and institute proper medical and potentially invasive or surgical treatment.
Conflict of interest: none declared.

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References