

PAPER II

Electrocardiographic Unrecognized Myocardial Infarction Does Not Improve Prediction of Cardiovascular Events Beyond Traditional Risk Factors, The Tromsø Study.

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Abstract

Background: Unrecognized myocardial infarction (MI) is a frequent and intriguing entity associated with a similar risk of death as recognized MI. Previous studies have not fully addressed if the poor prognosis is explained by traditional cardiovascular risk factors. We investigated if electrocardiographically detected unrecognized MI was independently associated with cardiovascular events and death and whether it improved prediction for future MI in a general population.

Design: Prospective cohort study.

Methods: We studied 5,686 women and men without clinically recognized MI at baseline in 2007-08. We assessed the risk of future MI, stroke and all-cause mortality in persons with unrecognized MI compared to persons with no MI during 31,051 person-years of follow-up.

Results: In the unadjusted analyses, unrecognized MI was associated with increased risk of future recognized MI (HR 1.84 95% CI 1.15-2.96) and all-cause mortality (HR 1.78 95% CI 1.21-2.61), but not stroke (HR 1.09, 95 % CI: 0.56-2.17). The associations did not remain significant after adjustment for traditional risk factors (HR 1.25, 95% CI: 0.76-2.06 and HR 1.38, 95% CI: 0.93-2.05) for MI and all-cause mortality respectively. Unrecognized MI did not improve risk prediction for future recognized MI using the Framingham Risk Score ($p=0.96$) or the European SCORE ($p=0.65$). There was no significant sex interaction regarding any of the endpoints.

Conclusion: Electrocardiographic unrecognized MI was not significantly associated with future risk of MI, stroke or all-cause mortality in the general population after adjustment for the traditional cardiovascular risk factors, and it did not improve prediction of future MI.

Key words: Myocardial infarction, Asymptomatic conditions, Risk factors, Epidemiology, Cardiovascular diseases, Electrocardiography (ECG)

Introduction

A substantial proportion of all myocardial infarctions (MI's) are unrecognized¹⁻⁴, often due to the lack of chest pain. Several large cohort studies have found that electrocardiographically detected unrecognized MI confers similar risk of death and recurrent MI as recognized MI¹⁻⁶. Most of these studies were conducted before the era of widespread coronary angiography and have not fully addressed whether the risk of future adverse events is explained by the traditional cardiovascular risk factors. However, one recent publication with contemporary data from a general population reported an independently increased mortality risk associated with unrecognized MI⁷. Previous studies of risk scores have not shown utility in persons with known cardiovascular disease⁸. Persons with unrecognized MI are embedded within the population targeted for primary prevention, and the effect of unrecognized MI on risk prediction in this group has not been studied before. We investigated if presence of electrocardiographic unrecognized MI was independently associated with increased risk of MI, stroke, and all-cause death in a general population without clinically recognized MI at baseline, and whether the risk differed with sex and age. We also examined if addition of unrecognized MI to existing risk scores improved risk prediction for future MI.

Subjects and Methods

Study population

The Tromsø Study is a population-based cohort study conducted in the municipality of Tromsø, Norway, initiated in 1974. Seven waves of data collection have been carried out 6-7 years apart, referred to as Tromsø 1-7. All surveys comprise the collection of questionnaire data, the sampling of biological specimens and clinical measurements. The population consists of predominantly Caucasians⁹. The sixth survey took place in 2007-2008 and consisted of two visits. Total birth cohorts and random samples of birth cohorts were invited to the first visit, and a 12,981 attended (attendance rate 66%)⁹. Those eligible for the second visit were first-visit participants in the age groups 50-62 years and 75-84 years, a 20% random sample in the age

group 63-74 and those who had attended the second visit of Tromsø 4 if aged <75 years in 1994⁹. A total of 7,307 (91.8%) participated, of whom 6,199 were examined with resting 12-lead ECG. Due to capacity limitations, not all participants had their ECG recorded. All participants gave informed, written consent to research. The Tromsø Study was approved by the Norwegian Data Protection Authority and the Regional Committee of Medical and Health Research Ethics, North Norway¹⁰.

Data collection and the endpoint registry

Baseline information on the traditional cardiovascular risk factors and use of medication was obtained by self-reported questionnaires and physical examinations. Blood pressure was measured using an automated device (Dinamap, GE Healthcare, USA). The cuff was adjusted according to arm circumference, and the blood pressure was measured 3 times in a seated position at 1-min intervals and after a 2-min rest¹⁰. Total cholesterol and high density lipoproteins were measured non-fasting at baseline. We defined hypertension as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or use of blood pressure lowering medication. We defined diabetes as HbA1c $\geq 6.5\%$ or use of insulin or oral diabetes medication, current smoking as self-reported current daily smoking, and family history of premature MI as self-reported MI in parents or siblings before 60 years of age.

Information on first-ever MI is retrospectively registered for all participants of the Tromsø Study, identified by linkage to the diagnosis registry of the University Hospital of North Norway. Participants were followed prospectively for future recognized MI, stroke and all-cause mortality until December 31st, 2013 (mean follow-up time 5.5 years). All first-ever cases of these events were reviewed and adjudicated by an independent endpoint committee with medical expertise based on the local hospital records and the Cause of Death Registry for deaths outside the hospital⁹.

The ECG

A 12-lead resting ECG was recorded in 2007-08, using a computer-based electrocardiograph (Cardiovit AT-104 PC, Schiller AG, Baar, Switzerland). We used a computer-based algorithm to

extract all ECGs with a Q-wave of amplitude ≤ -0.1 mV and duration ≥ 0.02 s in any lead among the 5,686 participants. Two trained medical doctors (A.M.Ø and H.L.) independently assessed the 2,040 extracted ECGs. There were discrepancies in the assessment in 140 (6.9%) of the ECGs. Disagreement was resolved after discussion with an expert cardiologist (H.S.). We used the Third universal definition of MI¹¹ to identify prior MI on the ECG as i) any Q wave in leads V2-V3 ≥ 0.02 sec or QS complex in leads V2 and V3; ii) Q wave ≥ 0.03 sec or QS complex in any two leads of a contiguous lead grouping (I, aVL; V1-V6; II, III, aVF); or iii) R wave ≥ 0.04 sec in V1-V2 and R/S ≥ 1 with a concordant positive T wave in absence of conduction defect. We defined a Q wave as a negative deflection on the ECG with amplitude ≥ 0.1 mV without any initial positive QRS deflection. We defined a QS wave as a negative deflection on the ECG with amplitude ≥ 0.1 mV without any positive deflection in the QRS complex.

Unrecognized MI

We defined participants with “unrecognized MI” as those with findings of prior MI on the ECG in Tromsø 6 without a registered MI in the endpoint registry or self-reported MI.

Inclusion and exclusion criteria

A total of 6,199 participants were examined with ECG in the Tromsø 6 survey. We excluded 513 participants: 334 participants due to validated prior recognized MI in the endpoint registry upon attendance; 97 due to self-reported prior MI; 19 due to a diagnosed “silent” MI in the endpoint registry at baseline (diagnosed by ECG, echocardiography or radionuclide angiography incidentally or during work up for symptoms such as dyspnea or swollen ankles); 22 due to pathologic non-infarct Q waves because of altered conduction (e.g. left bundle branch block and Wolff-Parkinson-White syndrome) or ventricular enlargement; 17 due to uncodable ECGs (e.g. pacemaker rhythm or missing leads) and 24 due to missing ECG files. This left 5,236 with no history of MI and 450 persons with unrecognized MI available for analyses. The total population at baseline without recognized MI was 5,686 participants. Figure 1 shows extraction and assesment of Q-wave ECGs in the population without recognized MI.

Statistical analyses and data management

We calculated descriptive statistics for persons with unrecognized MI and No MI. We used Pearson's chi-square test to compare categorical variables and t test to compare continuous variables between unrecognized and no MI. We used Cox proportional hazard model to examine the association between unrecognized MI on the ECG and future events (MI, stroke and all-cause mortality). Hazard ratios (HRs) were calculated with 95% confidence intervals (CI), unadjusted and adjusted for traditional cardiovascular risk factors. We also performed analyses stratified on sex and age \geq / $<$ 65 years. Evaluation of Schoenfeld residuals and inspection of log-log survival plots did not indicate that the proportional hazards assumption was violated. We calculated Receiver Operating Characteristic curves for future MI using Framingham Risk Score and the Systematic COronary Risk Evaluation (SCORE). We compared area under the curves (AUC) for the standard models to models where we also included unrecognized MI to examine whether addition of unrecognized MI improved prediction of future MI during the follow-up period. We examined interactions by adding cross product terms of unrecognized MI and the potential effect modifying variables to the fully adjusted models. All data were analyzed using STATA, version 13 (StataCorp, Texas, USA). All analyses used 5% two-sided level of significance.

Results

Unrecognized MI was present in 450 (7.9%) of the 5,686 participants at baseline. Participant characteristics are shown in Table 1. Participants with prior unrecognized MI were significantly older ($p < 0.01$), had higher blood pressure (< 0.01) and cardiovascular risk scores ($p < 0.01$) compared to those with no MI. Total cholesterol ($p = 0.028$), diabetes ($p = 0.051$), family history of premature MI ($p = 0.26$) and smoking habits overall ($p = 0.34$) did not differ significantly, although participants with unrecognized MI were more often former smokers. Statins ($p < 0.01$), angiotensin-converting-enzyme inhibitors ($p < 0.01$) and antiplatelet drugs ($p < 0.01$) were used more frequently in participants with unrecognized MI).

Incidence of MI, stroke and all-cause mortality

Figure 2 shows failure curves for MI, stroke and all-cause mortality in persons with no MI and unrecognized MI on the ECG. 148 MI's, 229 all-cause deaths and 106 strokes were observed during 31,152 person-years follow-up. In persons with unrecognized MI, the incidence of future

recognized MI was 8.2 (95% CI 5.3-12.8), incidence of stroke was 3.6 (95% CI 1.9-7.1) and the all-cause mortality was 12.2 (95% CI 8.5–17.4) per 1000 person-years. In participants with no MI, the incidence of recognized MI was 4.5 (95% CI 3.8-5.3), incidence of stroke was 3.4 (95% CI 2.8-4.1) and the all-cause mortality was 6.9 (95% CI 6.0-7.9) per 1000 person-years.

Unrecognized MI as a risk factor for MI, stroke and all-cause mortality

Table 2 shows HRs for MI, stroke and all-cause mortality for participants with unrecognized MI compared to participants with no MI. In the unadjusted analyses, unrecognized MI was associated with an increased risk of MI (HR 1.84 95% CI 1.15-2.96), all-cause mortality (HR 1.78 95% CI 1.21-2.61). The associations did not remain significant after adjustment for traditional risk factors (HR 1.25, 95% CI: 0.76-2.06 and HR 1.38, 95% CI: 0.93-2.05 for MI and all-cause mortality, respectively) Unrecognized MI was not significantly associated with the risk of stroke (unadjusted HR 1.09, 95 % CI: 0.56-2.17).

Unrecognized MI and cardiovascular risk assessment

Figure 3 shows receiver operating characteristic curves for predicting myocardial infarction using the Framingham Risk Score and European SCORE with and without unrecognized MI on the ECG. Addition of unrecognized MI on the ECG did not improve risk prediction for future recognized MI using the Framingham Risk Score (area under the curves 0.68 vs. 0.68, $p=0.96$) or the European SCORE (area under the curves 0.63 vs. 0.63, $p=0.65$).

Sex and age differences

There was no significant interaction between sex and unrecognized myocardial infarction for the risk of future recognized MI ($p=0.81$), stroke ($p=0.75$) or all-cause mortality ($p=0.42$). There was no significant interaction between age as a continuous variable and unrecognized MI with respect to the incident recognized MI ($p=0.19$), all-cause mortality ($p=0.30$) or stroke ($p=0.53$). The interactions terms with age as a dichotomous variable (\geq / $<$ 65 years) were $p=0.15$, $p=0.29$ and $p=0.56$ respectively. There was a tendency towards a higher risk of future MI in middle aged persons (<65 years) with unrecognized MI, and significant in women only (HR women 3.92, 95% CI 1.12-13.68 and HR men: 1.64, 95% CI 0.72-3.74). Analyses stratified by sex and

age <65 and \geq 65 years old are presented in the supplemental table. Addition of unrecognized MI to the Framingham Risk Score and the European SCORE did not affect the predictive ability differently in men and women, nor when stratified by age \geq / $<$ 65 years (data not shown).

Discussion

In the unadjusted analyses, unrecognized MI was associated with future risk of MI and all-cause mortality in the general population without clinically recognized MI. However, the associations were not significant after adjustment for the traditional cardiovascular risk factors apart from in women younger than 65 years, and unrecognized MI did not improve prediction of future MI during the follow-up period.

Four previous population-based cohort studies have studied the association of electrocardiographic unrecognized MI with future adverse events in the general population^{5-7,12}. The ARIC Study⁵ from 1987-89 found an almost identical risk of all-cause mortality associated with unrecognized MI as in our study adjusted for the cardiovascular risk factors (HR 1.34 95% CI 1.09-1.65), although they included persons aged 45-64 only. In the Rotterdam Study from 1990-93⁶, unrecognized MI was associated with increased risk of all-cause mortality in women (HR 1.33, 95% CI 1.11-1.58) and men (HR 1.57, 95% CI 1.30-1.89), adjusted for the cardiovascular risk factors. Both studies had longer follow-up and more events compared to our study, this may explain the statistically significant multivariable adjusted risk estimates compared to our results. In contrast to the two studies, we conducted our study more recently and in the era of widely available angiography and widespread statin therapy, which may have contributed to a lower risk of death and MI. Our results show more use of cardioprotective medication in participants with unrecognized MI, which supports this. In the Copenhagen City Heart Study from 2001¹², unrecognized MI was associated with increased risk of death or hospitalization for coronary heart disease (HR 1.6, 95% CI 1.2- 2.1), adjusted for the selected confounders age, hypertension, diabetes and estimated glomerular filtration rate. They included hospitalization for coronary heart disease in the end-point and did not adjust for all cardiovascular risk factors. The recently published article from the Lifeline Cohort Study (2006-2013)⁷ reports an independent risk of mortality associated with unrecognized MI (OR 2.21 95% CI 1.12-4.37), adjusted for age, sex, diabetes and heart rate. Unrecognized MI was reported to be

a stronger predictor for mortality in persons < 65 years. This may partly explain the independent mortality risk in the Lifeline Cohort study and the ARIC study compared to our findings as they studied a younger population.

Although unrecognized MI was associated with a 1.8-fold-higher risk of both MI and all-cause mortality, given that these associations did not remain significant after adjustment for traditional risk factors, our data seem to indicate that the prognostic role of unrecognized MI could be largely explained by the cardiovascular risk of the patients. This underlines the importance of a continued focus on the traditional cardiovascular risk factors, and support the notion that discovery of unrecognized MI should lead to careful work-up of cardiovascular risk factors. Treatment of these in line with guidelines for established cardiovascular disease^{13,14} should be considered. Our findings also add to the literature by showing that unrecognized MI does not add incremental value to the prediction of future MI in a population without known recognized MI at baseline.

Prevalence of unrecognized MI

The prevalence of unrecognized MI in our study was 7.9%. In comparison, previous studies have found prevalence of unrecognized MI from 0.2%-6.4%⁴⁻⁷. There are three possible explanations for this difference. First, there are differences in ECG criteria for prior MI between the different studies. We used the Third universal definition of MI which includes smaller Q waves compared to the Minnesota code or NOVA-CODE¹¹, used in other studies. A recently published study, however, reports that small- and large Q-wave unrecognized MI are confirmed by imaging techniques with comparable frequencies¹⁵. Second, age structure of the populations differs, and the highest prevalence is reported in the elderly. The Lifeline Cohort Study⁷ also used the Third universal definition of MI but the prevalence of unrecognized MI was only 0.23%. This is probably largely explained by the younger population. Also, the initial ECG extraction may have contributed to the differences as they used the automatic software of the ECG recorder whereas we used an algorithm based on smaller Q waves. Third, the true prevalence of unrecognized MI may be higher in our study population as the incidence of cardiovascular disease in North Norway used to be among the highest in Europe¹⁶ and the Norwegian population see their doctor less frequent compared to the rest of the European population¹⁷.

The specificity of ECG in detecting prior MI is considered to lie in the range 76%-97%^{18,19}, although some studies indicate a lower specificity, especially in inferior leads²⁰. The sensitivity, however, is low^{18,19}. The prevalence of unrecognized MI in the general population may therefore be underestimated, as most epidemiological studies have used ECG to detect unrecognized MI. Although imaging techniques such as cardiac magnetic resonance have shown increased sensitivity in the detection of unrecognized MI, we believe ECG is of interest due to its lower cost and better availability. Also, accidental discovery of unrecognized MI by ECG is common, and consensus on additional work-up or treatment is warranted.

Sex differences

Some previous studies have found that unrecognized MI confers a lower risk of death and cardiovascular events for women compared to men^{6,21}. In contrast to this, we found that the highest risk of future MI, was in women < 65 years, and significant in this group only, and implies an independent unexplained risk in this group. Prognosis did not differ significantly with sex and age group (>/< 65 years, p for interaction <0.1), and the number of events was low, so it is possible that the results of the age-and sex stratified analyses were due to chance because of multiple comparisons. The finding is, however, in line with the ARIC study⁵ reporting a higher risk associated with unrecognized MI in women. It is of interest because middle-aged women are often classified as low/moderate risk by traditional risk scores and the potential of unrecognized MI in risk prediction of middle-aged women should be further investigated in studies with longer follow-up.

Limitations

Some important limitations should be acknowledged. First, it is possible that false positive and false negative ECGs have diluted our findings; we did not use imaging techniques to confirm the presence of unrecognized MI, and ECG is a method with low sensitivity. Second, direct comparison with other epidemiological studies is difficult as the ECG criteria for MI differ between the studies. Last, the study population consisted of middle-aged and elderly Caucasians and may not be generalizable to other groups.

Conclusion

Electrocardiographic unrecognized MI was not significantly associated with future risk of MI, stroke or all-cause mortality in the general population after adjustment for the traditional cardiovascular risk factors. It did not improve prediction of future MI during the follow-up period.

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Conflict of Interest Disclosures

None

Authorship

AØ, HS and HL contributed to the conception or design of the work. All authors contributed to the acquisition, analysis, or interpretation of data for the work. AØ drafted the manuscript. All authors critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Table 1. Baseline characteristics of the study population by MI status. The Tromsø Study 2007-2008

	Unrecognized MI (n=450)	No MI(i) (n=5,236)	p-value
Age (years)	64.4 ±8.8	62.6 ±9.1	<0.01
Women	178 (40%)	3179 (60%)	<0.01
Blood pressure			
Mean systolic blood (mmHg)	143.5 ±23.8	139.7 ±22.8	<0.01
Mean diastolic blood (mmHg)	80.2 ±11.2	78.3 ±10.5	<0.01
Hypertension(ii),	282 (63%)	3,008 (57%)	<0.03
Diabetes (iii),	43 (9.5%)	370 (7%)	0.051
Smoking habits (iv)			0.34
Current daily smoker	79 (18%)	992 (19%)	
Former daily smoker	215 (48%)	2,347 (45%)	
Never daily smoker	144 (32%)	1,827(35%)	
Lipids			
Total cholesterol (mmol/L)	5.8 ±1.1	5.8 ±1.1	0.28
HDL (mmol/L)	1.6 ±0.5	1.5 ±0.4	<0.01
Medication use			
Statins	74 (16%)	634 (12%)	<0.01
Beta- blockers	56 (12%)	556 (11%)	0.23
ACEIs (v)	86 (19%)	759 (15%)	<0.01
Antiplatelet drugs	72 (16%)	534 (11%)	<0.01
Anticoagulants	16 (3.6%)	127 (2.4%)	0.14
Family history of premature MI(vi)	75 (17%)	984 (19%)	0.26
Cardiovascular risk score			
European SCORE 10-year risk of fatal cardiovascular event	4.3% ±3.9	2.9% ±2.9	<0.01
Framingham 10-year risk of fatal and non-fatal cardiovascular event	23.4% ±16.1	18.3% ±14.0	<0.01

MI; Myocardial Infarction. All values are means \pm SD or number (%). ACEIs indicates angiotensin-converting enzyme inhibitors

(i) No history of recognized MI *or* unrecognized MI at baseline

(ii) Defined as mean systolic blood pressure ≥ 140 or mean diastolic blood pressure ≥ 90 or use of blood pressure lowering medication

(iii) Defined as use of insulin, oral diabetes medication or HbA1c ≥ 6.5 .

(iv) Self-reported

(v) Angiotensin-converting-enzyme inhibitor

(vi) Defined as myocardial infarction in parents or siblings before 60 years of age.

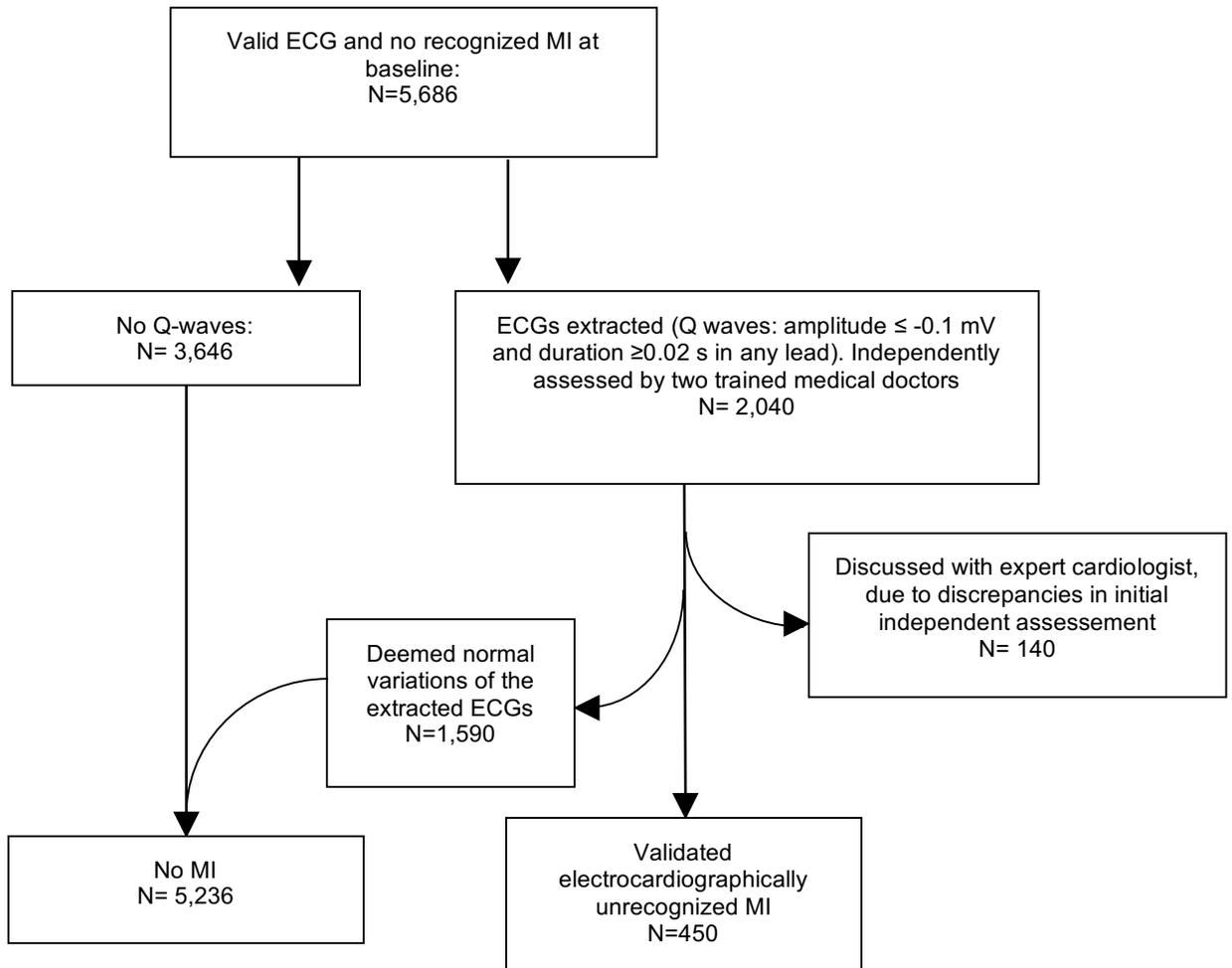
Table 2. Hazard ratios for MI, stroke and all-cause mortality a in participants with unrecognized MI compared to no MI. The Tromsø Study 2007-2008

	Number (events)	Unadjusted		Multivariable adjusted(i)	
		HR	95% CI	HR	95% CI
MI					
No MI	5,236 (128)	1.00	-	1.00	-
Unrecognized	450(20)	1.84	1.15-2.96	1.25	0.76-2.06
MI					
Stroke					
No MI	5,236 (97)	1.00	-	1.00	-
Unrecognized	469 (9)	1.09	0.56-2.17	0.90	0.45-1.79
MI					
All-cause mortality					
No MI	5,236 (199)	1.00	-	1.00	-
Unrecognized	450 (30)	1.78	1.21-2.61	1.38	0.93-2.05
MI					

MI; Myocardial
Infarction

(i)Adjusted for sex, age, hypertension, diabetes, daily smoking, total serum cholesterol, high-density cholesterol, use of cholesterol lowering medication, and family history of premature MI.

Figure 1: Flow diagram demonstrating extraction and assesement of Q-wave ECGs. The Tromsø Study 2007-2008



MI; Myocardial Infarction

Figure 2. Kaplan-Meier failure plots for MI, stroke and all-cause death in participants with unrecognized MI and no MI. The Tromsø Study 2007-2008

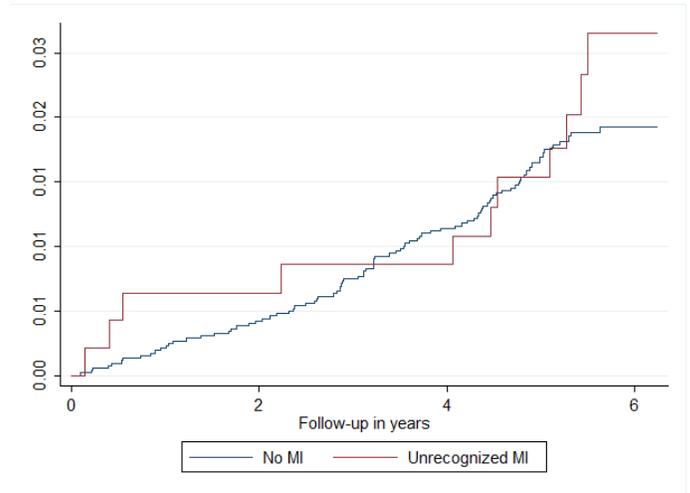
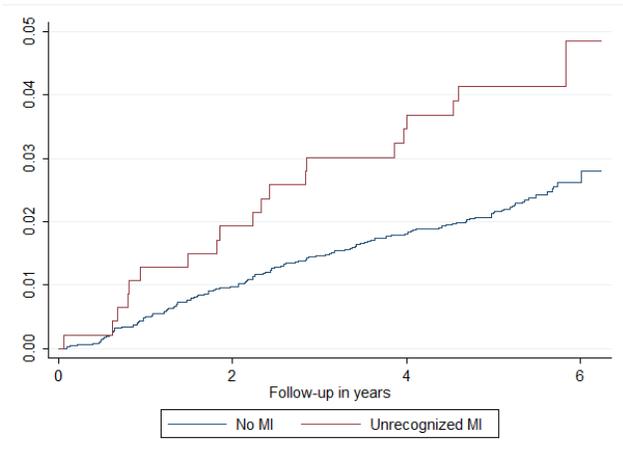


Figure 2a. MI

Figure 2b. Stroke

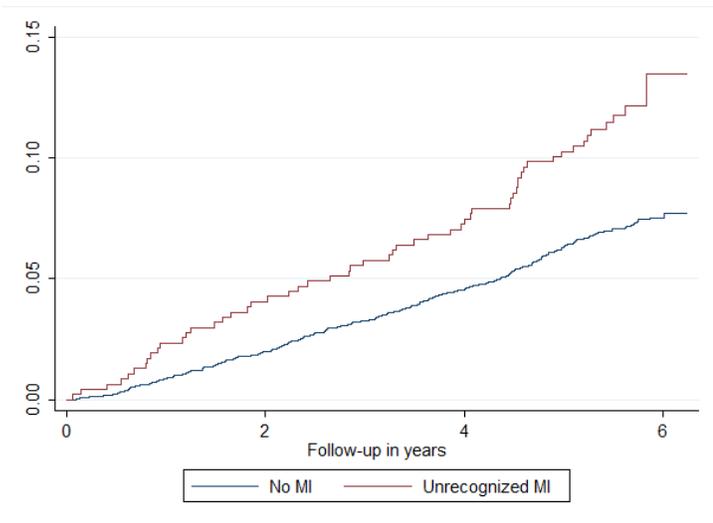


Figure 2c. All-cause mortality

Figure 3. Receiver Operating Characteristic (ROC) curves for prediction of future MI using the Framingham Risk Score and Systematic COronary Risk Evaluation (SCORE), with standard model (blue line) and standard model+ unrecognized MI (red line). The Tromsø Study 2007-2008

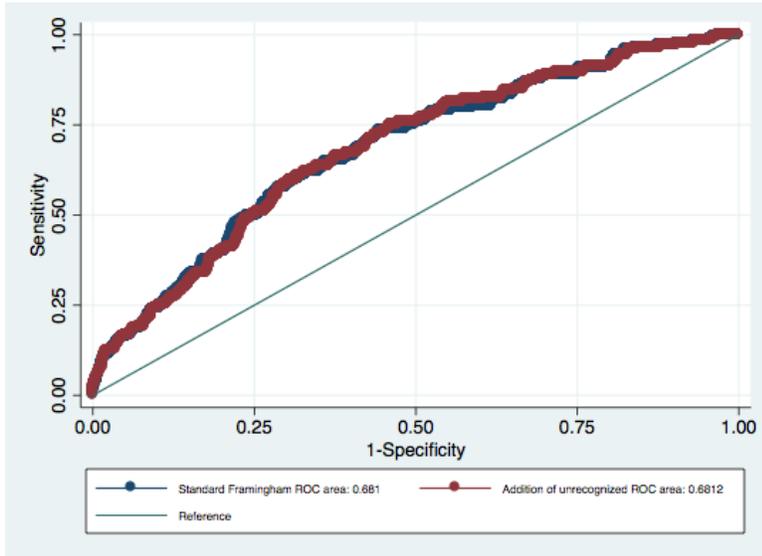


Figure 3a. Framingham Risk Score

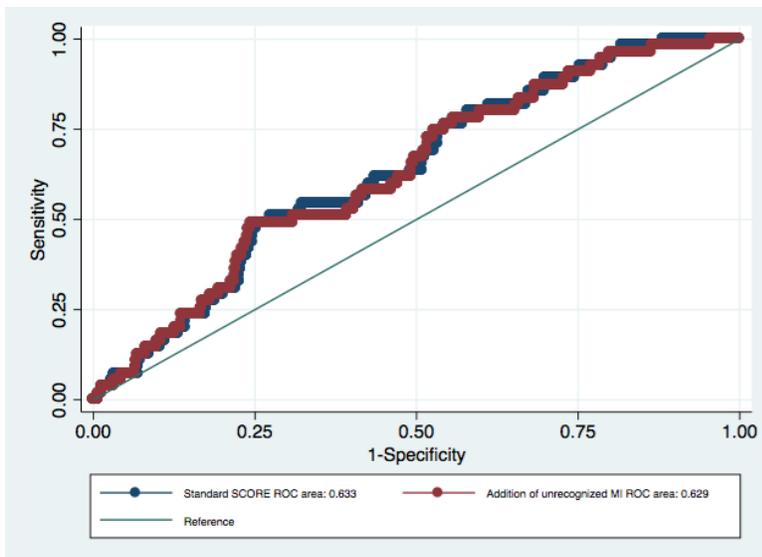


Figure 3b. European SCORE

Supplemental table. Hazard ratios for MI, all-cause mortality and stroke in participants with unrecognized MI compared to no MI, stratified on sex and age \geq / $<$ 65 years. The Tromsø Study 2007-2008

	Number (events)	< 65 years Women(i)	Number (events)	\geq 65 years Women(i)	Number (events)	<65 years Men(i)	Number (events)	\geq 65 year Men(i)
MI								
No MI (ref)	2,081 (16)	1.00	1,098 (36)	1.00	1,376 (34)	1.00	681 (42)	1.00
Unrecognized MI	99 (3)	3.92(1.12-13.68)	79 (3)	0.63(0.15-2.67)	171 (8)	1.64(0.72-3.74)	101 (6)	0.98(0.42-2
All-cause mortality								
No MI (ref)	2,081 (32)	1.00	1,098 (75)	1.00	1,376 (28)	1.00	681 (64)	1.00
Unrecognized MI	99 (2)	1.17(0.28-4.92)	79 (3)	0.98(0.42-2.28)	171 (4)	0.99 (0.35-2.88)	101 (17)	1.78(1.00-3
Stroke								
No MI (ref)	2,081 (16)	-	1,098 (39)	1.00	1,376 (16)	1.00	681 (26)	1.00
Unrecognized MI	99 (0)	Too few cases	99 (4)	1.35(0.47-3.86)	171 (3)	1.23(0.35-4.29)	101 (2)	0.50(0.12-2

MI; Myocardial Infarction

(i) All analyses are adjusted for age, hypertension, diabetes, daily smoking, total serum cholesterol, high-density cholesterol, use of cholesterol lowering medication, and family history of premature MI.