ISMO JAAKKO TAPANI ANTTILA

The Relation between Resting Electrocardiogram Changes and Prognosis in the Health 2000 Survey

A population-Based study on Adult Finns

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ACADEMIC DISSERTATION
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UNIVERSITY OF TAMPERE

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Painotuote

To my family – Petra, Aamos, Luukas and Martta.

"And when he saw him, he had compassion. So he went to him and bandaged his wounds, pouring on oil and wine; and set him on his own animal, brought him to an inn, and took care of him. On the next day, when he departed, he took out two denarii, gave them to the innkeeper, and said to him, 'Take care of him; and whatever more you spend, when I come again, I will repay you'."

Luke, A.D.60-62,
Physician, referring Christ´s answer to who is my neighbour

Contents

List of Original Communications

Anttila I, Nikus K, Nieminen T, Jula A, Reunanen A, Salomaa V, Kattainen A, Nieminen MS, Lehtimäki T, Virtanen V, Sclarovsky S and Kähönen M (2010): Prevalence and prognostic value of poor R-wave progression in standard resting electrocardiogram in general adult population. The Health 2000 Survey. Annals of Medicine 42:123-130.*

Anttila I, Nikus K, Kähönen M, Jula A, Reunanen A, Salomaa V, Nieminen MS, Lehtimäki T, Virtanen V, Verrier RL, Varis J, Sclarovsky S and Nieminen T (2010): Prognostic implications of quantitative ST-segment characteristics and T-wave amplitude for cardiovascular mortality in a general population from the Health 2000 Survey. Annals of Medicine 42:502-511.*

Anttila I, Nikus K, Nieminen T, Jula A, Salomaa V, Reunanen A, Nieminen MS, Lehtimäki T, Virtanen V and Kähönen M (2011): Relation of Positive T wave in lead aVR to risk of Cardiovascular Mortality. The American Journal of Cardiology 108:1735-1740.**

Haataja P, Anttila I, Nikus K, Nieminen T, Jula A, Salomaa V, Reunanen A, Nieminen M, Lehtimäki T, Eskola M and Kähönen M (submitted): Prognostic implications of ventricular conduction defect for cardiovascular mortality in a general population from the Health 2000 Survey.

In addition, the study contains unpublished data.

Abbreviations

ACEI	angiotensin-converting enzyme inhibitor
ACS	acute coronary syndrome
AF	atrial fibrillation
AP	angina pectoris
ARB	angiotensin II receptor antagonist
aVRT	T wave amplitude in the lead aVR
BMI	body mass index
BP	blood pressure
CCB	calcium channel blocker
CV	cardiovascular
CHD	coronary heart disease
CMR	cardiac magnetic resonance imaging
COPD	chronic obstructive pulmonary disease
ECG	electrocardiogram
HDL	high-density lipoprotein
HR	hazard ratio
IVCD	intraventricular conduction delay
LAH	left anterior hemiblock
LBBB	left bundle branch block
LDL	low-density lipoprotein
LVH	left ventricular hypertrophy
MC	Minnesota code
MI	myocardial infarction
NQWMI	non-Q-wave myocardial infarction
PRWP	poor R wave progression
QWMI	Q-wave myocardial infarction
RBBB	right bundle branch block
RMI	recognised myocardial infarction
RR	relative risk
SD	standard deviation
STD	ST segment depression
STEMI	ST elevation MI
UMI	Unrecognised myocardial infarction
WHO	World Health Organization

Abstract

The resting electrocardiogram (ECG) provides valuable diagnostic and prognostic information on the heart. Many pathological changes seen in the ECG increase mortality in population-based studies. These abnormalities, such as Q waves as a sign of a prior MI, are usually presented as categorical variables like those defined in Minnesota Coding System. However, many ECG abnormalities are not included in these classification systems.

A prior myocardial infarction (MI) may be detected as pathological Q waves. Over time, MI-related Q waves may disappear and only low-amplitude R waves or poor R wave progression (PRWP) are seen. There is no population-based data on the prevalence and prognosis of PRWP.

The magnitude of ST segment depression and type of slope (descending, ascending or horizontal) may represent various degrees of ongoing ischaemia. These changes may accompany T wave inversion, which is seen frequently and transiently alone without other ECG abnormalities or with left ventricular hypertrophy (LVH). However, there is no population-based data on the prognosis of ST segment depression, slope and T waves as combined continuous variables.

The electrical axis of lead aVR is opposite to the normal conduction pathway. Therefore, the P wave, QRS complex and T wave normally have a negative deflection. There is limited data on lead aVR in population studies and no data on a positive T wave in lead aVR (aVRT+).

A wide QRS as seen in left and right bundle branch block (LBBB, RBBB) has different prognostic implications depending on the population and clinical settings of the study. There is limited population-based data on comparing different intraventricular conduction delays (IVCD) in terms of CV and total mortality.

The aims of the present study were to examine the prevalence and mortality of PRWP in a population-based cohort (**I).** We studied the cardiovascular (CV) mortality of ST segment depression, slope and T waves as continuous variables in a population-based cohort **(II).** We examined the prevalence and prognosis of aVRT+ in a population-based cohort **(III).** Furthermore, we established the prognostic significance of eight different IVCDs in a population-based study **(IV).**

This study is based on the Health 2000 Survey, which is a randomised population study carried out in Finland. The study consisted of 6,354 subjects (2,876

men, 3,478 women) aged 30 years or more who participated in a health examination in 2000–2001. Data on mortality and the National Hospital Discharge Register were linked to the Health 2000 Survey data. Follow-up data is available for up to 8 years.

PRWP was more common in women (7.0%) than in men (2.7%, p<0.001). The adjusted total mortality for PRWP was 1.89 for men (95% CI 1.00–3.59, p = 0.051) and 2.22 for women (95% CI 1.42–3.46, p=0.001). Adjusted CV mortality for PRWP was 2.28 for men (95% CI 0.91-5.68, p = 0.08) and 3.47 for women (95% CI 1.78–6.76, p < 0.001); the finding was significant only among women.

Among all women, ST segment depression in the lateral lead group as well as lead V5 showed particularly uniform and highly significant predictivity at all four measurement points in the adjusted analyses. However, this significance was lost in women aged at least 55 years when those with LVH were excluded. The effect of LVH on the prognostic value of ST segment depression was also present in men, but in an opposite direction and to a lesser degree than among women. Our study showed the highest hazard ratios for cardiovascular mortality for low ST segments in the lateral leads V5, V6, I and aVL compared to other lead groups. This effect was markedly stratified by the polarity of the T waves.

The prevalence of aVRT+ was 2.2% (n = 138, 69 women and 69 men), with no difference between men and women. In Cox regression analysis after adjustment for age and sex, the relative risk of CV mortality for aVRT+ was 3.24 (95% CI 2.32–4.54, p < 0.001) and that of total mortality 1.91 (95% CI 1.47–2.49, p < 0.001) when compared to those with aVRT-.

After adjustment for age and sex, the relative risk of all-cause and CV mortality for non-specific IVCD was 2.46 (95% CI 1.27–4.77, p = 0.008) and 4.29 (95% CI 2.01–9.16, p < 0.0001), respectively; for LBBB 1.61 (95% CI 1.12–2.33, p = 0,011) and 2.11 (95% CI 1.31-3.41, p = 0.002), respectively; and for IRBBB 1.98 (95% CI 1.18–3.3, p = 0.009) and 2.24 (95% CI 1.06-4.77, p = 0.036), respectively. The other types of IVCD did not have sn impact on prognosis.

In conclusion, PRWP is relatively common in women and increases CV and total mortality in women but not in men. We observed that ST segment depression has prognostic significance for cardiovascular death in a general adult population, consisting of individuals both with and without CHD, and that this predictivity is strongly dependent on ECG signs of increased left ventricular mass. The prevalence of aVRT+ is 2% in a general population. The total mortality associated with aVRT+ is twofold and CV mortality threefold when compared to those with aVRT-. IVCD was associated with increased CV mortality but did not increase total mortality. The risk of total and CV mortality for non-specific IVCD was twofold and fourfold, respectively. LBBB and incomplete RBBB increased mortality to a lesser extent than non-specific IVCD. RBBB did not increase mortality.

Tiivistelmä

Levossa otettava sydänfilmi (elektrokardiogrammi, EKG) tarjoaa tärkeää diagnostista ja ennusteeseen liittyvää tietoa sydämestä. Monet EKG:ssä todetut patologiset muutokset lisäävät kuolleisuutta väestötutkimuksissa. Tavallisesti nämä EKG poikkeamat esitetään luokiteltuina muuttujina esimerkiksi Minnesota koodauksen mukaisesti. Luokittelujärjestelmät eivät kuitenkaan sisällä kaikkia EKG poikkeavuuksia.

Aikaisempi sydäninfarkti (MI) voidaan tunnistaa patologisen Q-aallon avulla. Infarktiin liittyvät Q-aallot voivat hävitä kokonaan niin, että Q-aaltojen sijasta nähdään matala amplitudinen R-aalto tai huono R-aallon progressio (PRWP). Väestötason tietoa PRWP löydöksen esiintyvyydestä tai ennusteesta ei ole saatavilla.

ST-segmentin laskun (STD) suuruus sekä laskun suunta (laskeva, nouseva tai horisontaalinen) voi edustaa eriasteista hapenpuutetta sydämessä. Näihin muutoksiin voi liittyä myös T-aallon invertoituminen, joka voi esiintyä ajoittain ja ohimenevänä yksinkin, ilman muita patologisia EKG muutoksia tai vasemman kammion hypertrofiaa (LVH). Väestötason tietoa ST-segmentin laskun, laskun suunnan ja T-aallon yhdistelmien vaikutuksesta ennusteeseen, jatkuvina muuttujina, ei ole.

aVR-kytkennän sähköinen akseli on vastakkainen verrattuna normaaliin johtumisjärjestelmään. Siksi P-aalto, QRS-kompleksi, ja T-aalto ovat normaalisti negatiivisia aVR-kytkennässä. aVR-kytkentää koskevaa väestötason tietoa on vain vähän saatavilla eikä tietoa ole lainkaan positiivisesta T-aallosta kytkennässä aVR (aVRT+).

Leveään QRS-kompleksiin, kuten vasen ja oikea haarakatkos (LBBB, RBBB), liittyvä ennuste riippuu tutkittavasta populaatiosta sekä tutkimusasetelmasta. Vertailevaa väestötason tutkimusta erilaisten kammionsisäisten johtumishäiriöiden (IVCD) kardiovaskulaari- (CV) ja kokonaiskuolleisuudesta on vähänlaisesti.

Tämän tutkimuksen tavoite oli selvittää huonon R-progression esiintyvyys ja vaikutus kuolleisuuteen väestö tasolla (I). Selvitimme ST-segmentin laskun, laskusuunnan ja T-aallon vaikutusta CV- ja kokonaiskuolleisuuteen väestötasolla (II). Tutkimme aVRT+ esiintyvyyttä ja ennustevaikutusta väestötasolla (III). Lisäksi määritimme kahdeksan IVCDn vaikutusta ennusteeseen väestötasolla (IV).

Tutkimuksemme perustuu Suomessa satunnaisotannalla tehtyyn Terveys 2000 väestötutkimukseen. Tutkimukseen osallistui 6354 yli 30 vuotista henkilöä (2876 miestä, 3478 naista) vuosina 2000–2001. Tiedot sairaaloiden hoitojaksoista sekä kuolin tiedot liitettiin Terveys 2000 aineistoon. Seuranta-aika oli kahdeksan vuotta.

PRWP esiintyvyys oli suurempi naisilla (7.0 %) kuin miehillä (2.7 %, p<0.001). PRWP liittyvä vakioitu kokonaiskuolleisuus oli miehillä 1.89 (95 % CI 1.00–3.59, p = 0.051) ja naisilla 2.22 (95 % CI 1.42–3.46, p=0.001). PRWP liittyvä vakioitu sydän- ja verisuonitautikuolleisuus oli miehillä 2.28 (95 % CI 0.91–5.68, p = 0.08) ja naisilla 3.47 (95 % CI 1.78–6.76, p < 0.001); löydös oli merkittävä vain naisilla.

ST-segmentin lasku lateraalikytkennöissä ja V5-kytkennässä oli kaikissa neljässä mittauskohdassa ennustava ja merkittävä naisilla. Tämä merkittävyys hävisi yli 55 vuotiailla naisilla, jos LVH poissuljettiin. Miehillä LVH vaikutti ST-laskun ennustemerkitykseen vähemmän ja eri suuntaan kuin naisilla. Tutkimuksemme osoitti, että korkein CV-kuolleisuus liittyi matalaan ST-segmenttiin lateraalikytkennöissä V5, V6, I ja aVL verrattuna muihin kytkentöihin. Löydöksen merkitys korostui T-aallon polariteetin mukaan.

aVRT+ esiintyvyys oli 2.2 % (n=138, 69 miestä ja naista) eikä eroja miesten ja naisten välillä ollut. Sukupuolen ja iän suhteen vakioidussa Coxin regressioanalyysissä aVRT+ liittyvä CV-kuoleman suhteellinen riski oli 3.24 (95 % CI 2.32–4.54, p < 0.001) ja kokonaiskuolleisuuteen liittyvä riski 1.91 (95 % CI 1.47–2.49, p < 0.001) verrattuna niihin joilla oli aVRT-.

Sukupuolen ja iän suhteen vakioidussa Coxin regressioanalyysissä epäspesifiseen IVCD liittyvä suhteellinen kokonaiskuolleisuuden riski oli 2.46 (95% CI 1.27–4.77, p = 0.008) ja kardiovaskulaari riski 4.29 (95% CI 2.01–9.16, p < 0.0001); LBBB liittyvä riksi oli 1.61 (95% CI 1.12–2.33, p = 0,011) ja 2.11 (95% CI 1.31-3.41, p = 0.002); IRBBB liittyvä riski 1.98 (95% CI 1.18–3.3, p = 0.009) ja 2.24 (95% CI 1.06-4.77, p = 0.036). Muilla IVCD tyypeillä ei ollut merkittävää vaikutusta ennusteeseen.

Yhteenvetona todetaan, että PRWP on verrattain tavallinen löydös sekä miehillä että naisilla ja löydös lisää CV- ja kokonaiskuolleisuutta naisilla mutta ei miehillä. ST segmentin laskulla on merkitystä kokonais- ja CV-kuoleman ennustamisessa aikuisväestössä niin sepelvaltimopotilailla kuin niillä, joilla ei ole koronaaritautia. aVRT+ esiintyvyys on 2 % väestössä ja siihen liittyvä kokonaiskuolleisuus on kaksinkertainen ja CV-kuolema kolminkertainen verrattuna niihin, joilla ei ole aVRT+. IVCD liittyy CV-kuolleisuuteen mutta ei kokonaiskuolleisuuteen. Epäspesifiseen IVCD liittyvä kokonaiskuolleisuus oli kaksinkertainen ja CV-kuolleisuus nelinkertainen. LBBB ja epätäydellinen RBBB lisäsivät kuolleisuutta jonkin verran. RBBB ei liittynyt kuolleisuuden lisääntymistä.

Introduction

Cardiovascular (CV) diseases are the leading cause of death in the developed countries (WHO 2013). The diagnostics and therapeutic possibilities have evolved enormously since the first human electrocardiogram (ECG) was obtained in 1903 (Einthoven 1924). Currently, cardiac catheterisation and coronary angiography are widely available, and they provide fundamental instruments to the study of normal and abnormal functions of the heart. Invasive cardiology with advances in coronary instrumentation techniques and devices enables the treatment of conventional coronary stenosis as well as challenging lesions such as total occlusions. Coronary bypass grafting surgery and other open-heart operations are carried out with the assistance of a heart-lung machine.

The 20th century was also triumphant for unfolding coronary risk factors such as hypertension, smoking and diabetes, but also in terms of discovering therapeutic drugs such as the angiotensin-converting enzyme inhibitor, beta blockers and statins. The invention of echocardiography and the pacemaker are examples of great successes in cardiology and electronic engineering (Altman 2002). The cardiac echo allows the non-invasive evaluation of the heart, and pacemakers and implantable cardioverter-defibrillators are accompanied by cardiac resynchronising devices in treating electrical abnormalities of the heart.

In emergency situations, the ECG provides information on two main pathological heart conditions, arrhythmias and ischaemia. First, in life-threatening arrhythmias, ECG is the only way to obtain the correct diagnosis. The rapid detection and treatment of ventricular arrhythmias in the cardiac control unit was the main reason behind the halving of the in-hospital mortality of myocardial infarction. Second, the urgency of treatment in acute coronary syndrome is based on abnormalities seen in the ECG: the choice is made between urgent primary percutaneous coronary intervention and a less urgent strategy.

In non-urgent situations, the resting ECG may reveal previous damage to the heart and significant information on the CV risk. A very typical observation is atrial fibrillation (AF), which may not cause symptoms at all. However, as proved by the original Framingham Heart Study, AF increases the mortality rate remarkably over 40 years of follow-up. (Benjamin et al. 1998.)

The Framingham Heart Study was a pioneer epidemiological study leading to the discovery that CV mortality was five times greater among subjects with newly

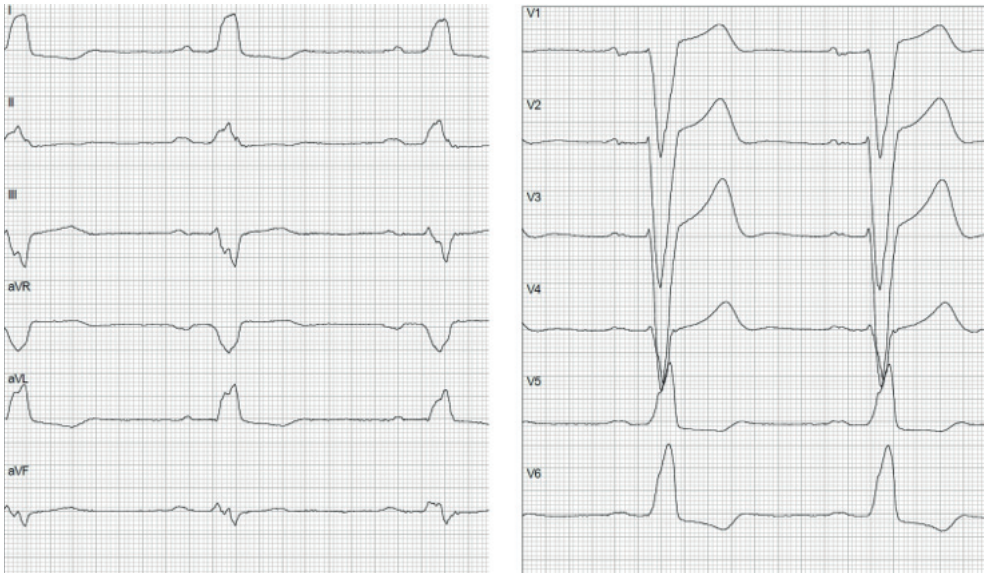


Figure 1
Left bundle branch block with wide QRS complex (146ms) in a 57-year old man with normal coronary arteries. Cardiac magnetic resonance (CMR) imaging and echocardiography revealed moderate dilated cardiomyopathy (DCMP). ECG obtained 6 days after sudden cardiac arrest (VF). Minnesota Code 7.1.1.

acquired left bundle branch block (LBBB) when compared to control subjects (Figure 1). Fifty percent of the subjects with LBBB died of CV disease within 10 years of the onset of LBBB (Schneider et al. 1979). Interestingly, at the same time, LBBB was not linked to excess mortality among an extremely healthy American population – LBBB did not increase CV death or CV morbidity when compared to RBBB among pilots of the United States Air Force over 10 years of follow-up (Rotman and Triebwasser 1975).

A broken QRS configuration in subjects with intraventricular conduction delays (IVCD) denotes that a diagnosis of a previous MI may not be possible. In acute settings, subjects with new onset LBBB and angina pectoris (AP) might be treated as those with an ST-elevation MI, whereas with other IVCD patients, the treatment strategy depends on a possible identifiable ST segment abnormality.

Amongst the many ECG abnormalities, the presence of pathologic Q waves, alone or with T wave inversions, is suggestive of a prior MI. The pioneer era of Q wave studies included autopsies confirming the association between myocardial necrosis and the Q wave. However, this correlation was not absolute because not all MIs caused Q waves. Furthermore, experimentally produced Q waves disappeared as the coronary circulation was returned in animal works (Bayley and

LaDue 1944). In real life, some of the MI-associated Q waves may disappear over time (Wasserman et al. 1982). Sometimes, an MI-related Q wave is substituted by a new low-amplitude R wave. At this point, a decrease in R wave amplitude, or poor R wave progression (PRWP), is the only evidence of prior anterior-wall MI (Zema et al. 1981).

Identifying subjects with a prior MI is important, since they die prematurely. One of the major challenges in the diagnostics is the fact that more than 25% of the MIs occur without symptoms. Unfortunately, these subjects share the same risk as those with a symptomatic MI (Kannel and Abbot 1984, Sheifer et al. 2001).

Transient T-wave inversions are seen frequently among healthy persons (Hiss et al. 1962). The prevalence of inverted T waves, defined as negative T wave amplitude of 1 mm or more in any lead except lead aVR, in the general population is 3% for men and 5.5% for women in Finland (Reunanen et al. 1983) and 6.1% for men and 9.6% for women in Belgium (De Bacquer et al. 1998). ST segment depression without concomitant T wave abnormality is a rare phenomenon, but ischaemic T wave inversion appears frequently alone (De Bacquer et al. 1998). Minor ST segment and/or T wave changes increase the risk of CV mortality (Greenland et al. 2003, Ström Moller et al. 2007). Men with T wave inversion in lead aVR have been found to have a fivefold risk of CV mortality (Tan et al. 2008).

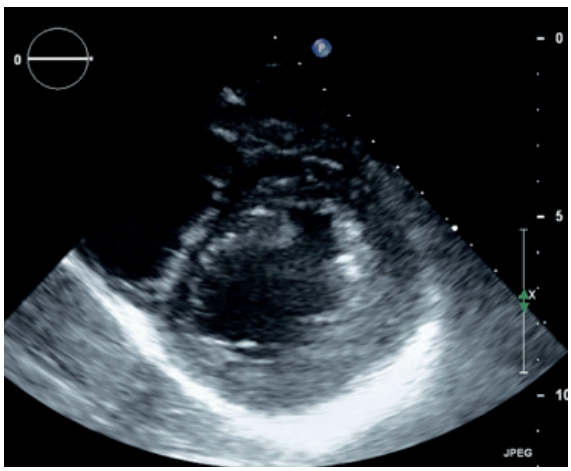
Left ventricular hypertrophy (LVH) may produce excessive electrical voltages in the resting ECG with or without T wave inversions (Figure 2). These electrical changes bear a remarkable risk of MI, stroke and congestive heart failure. After more than 30 years of follow-up, the risk of all-cause mortality associated with LVH was fourfold and that of CV mortality more than six times higher than in subjects without LVH. Sudden death is also more likely in subjects with LVH than in those without LVH (Kannel and Cobb 1992, Levy et al. 1994).

At the beginning of the 21st century, thrombolytic therapy without primary percutaneous coronary intervention, was available for the majority of ST-elevation MI patients in Finland. The prognosis for this thrombolytic reperfusion-era population or, at least for CV patients, may be very different when compared to those who suffered an MI in the late 1970s. The introduction of a wide range of new CV area drugs (diabetes and antithrombotic drugs), the restrictions on the use of tobacco products, the availability of guidelines and even existence of new catheterisation laboratories may have unforeseen effects on the population level in terms on morbidity and, perhaps, even mortality. If any morbidity or mortality chance is to happen, it would probably be noticeable in a population-based ECG study (Haim et al. 1998, Furman et al. 2001).

There is no information on the prevalence and prognosis of PRWP in a general population. The prognostic value of the quality of ST segment depression and

T wave amplitude with or without LVH has not been studied. The prevalence and prognosis of T wave amplitude abnormalities in lead aVR are not known in the population level. The impact of various IVCDs on long-term prognosis in the Finnish general population has not been studied.

Therefore, the focus of this thesis was to study the association between PRWP, ST depression, T wave inversion and IVCDs with total and CV mortality among a Finnish general population aged 30 years or more.



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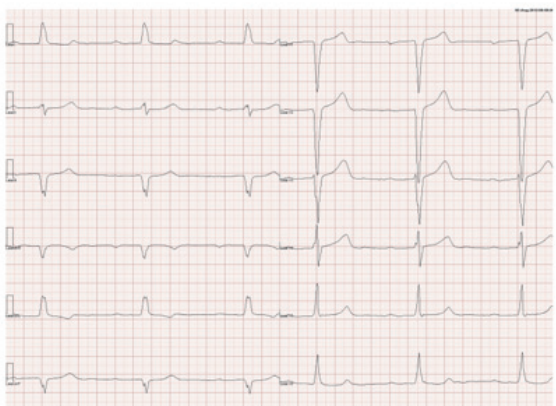


B

Figure 2.
A, Left ventricular noncompaction cardiomyopathy in a 21-year man with had atypical chest pain. In echocardiography left ventricular septum was abnormally thin (6-7mm) and postelateral wall remarkably thick (17-25mm). Position/visibility of pulmonary and aortic valve was altered and computed tomography (CT) revealed incomplete rotation of great arteries. Magnetic resonance imagining revealed no infiltrative process but noncompactation of left ventricle.
B, The ECG was recorded during routine follow-up visit and shows rather typical LVH but no strain pattern. The QS deflections in lead III and aVF suggest inferior wall myocardial damage. (Images courtesy of Essi Ryödi, MD, Seinäjoki Central Hospital.)

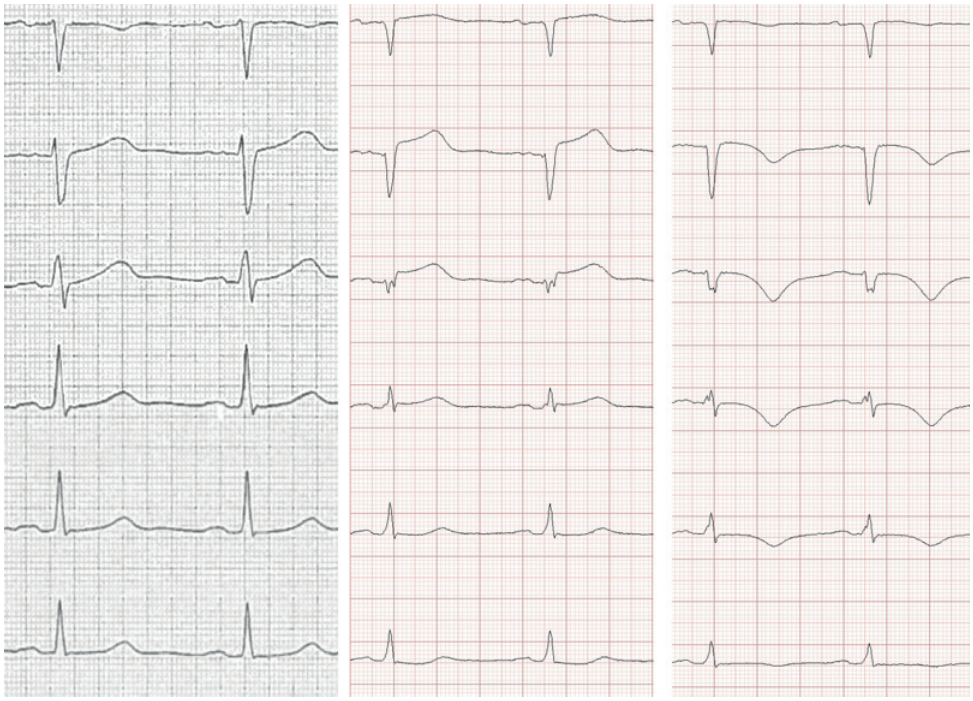
Review of the Literature

Resting ECG

The resting ECG is the most widely used cardiovascular diagnostic test. For a hundred years, up until today, the ECG has been used across the world to diagnose heart diseases. The foundations for this single most important cardiologic instrument were laid by the work of physicians and physiologist at the end of 19th century. The first ECG was obtained by British physiologist Augustus D. Waller (1856–1922; Waller 1887). The Nobel Prize in Physiology or Medicine 1924 was awarded to Dutch physiologist and physician Willem Einthoven (1860–1927) "for his discovery of the mechanism of the electrocardiogram" (Johansson 1924). The letters used to identify atrial depolarisation (P), ventricular depolarisation (Q, R, and S) and ventricular repolarisation (T) were denoted by Einthoven (Hurst 1998).

Myocardial Infarction in ECG

The hallmark of a prior MI, Q waves, builds up when the normally positive initial deflection of ventricular depolarisation, the R wave, is replaced by a negative deflection, namely a Q wave (Figure 3 and 5). By using animal experiments, Wilson and associates demonstrated that it was possible to localise an infarct lesion with multiple epicardial leads (Wilson et al. 1935). The correlation, accuracy and limitations of the ECG in localising and detecting myocardial infarction in humans were studied further after World War II. The earliest study was that of Myers and colleagues examining data on 161 subjects in whom an ECG was recorded while the subject was living and a myocardial infarction was accurately located at autopsy. Myers and colleagues were able to verify the relationship of QS and QR deflections in infarct-related leads (Myers et al. 1948). The extent of the infarct (transmural or subendocardial) correlated with a pathological ECG. However, 16% of the transmural infarctions in the anterior wall did not show a QS or QR deflection in V3 and/or V4, and 16% of the transmural infarctions in the lateral wall did not show a QS or QR deflection in lead V5 or V5 and V6. Myers et al. found that subjects with a subendocardial infarct had fewer QS/QR deflections than those with a transmural infarction.



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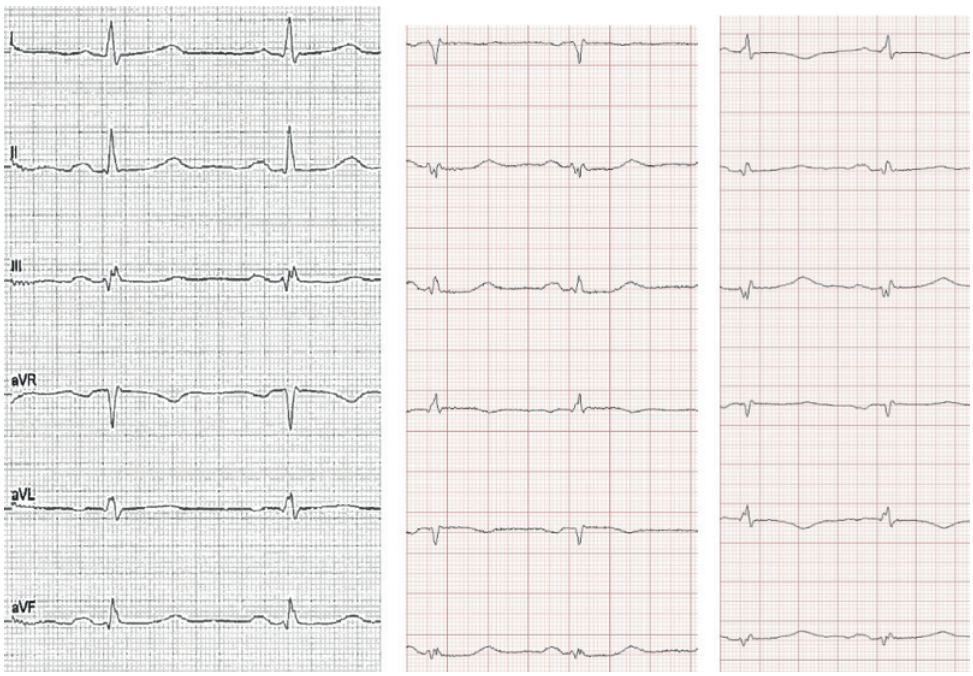


D E F

The correlation of a left ventricular contractile pattern and resting ECG abnormalities was first evaluated in 123 coronary angiographically verified CHD patients. Cineangiography revealed dyssynergy in 95% (73/77) of the patients with Q waves in contrast to 24% (11/46; P<0.01) of those without Q waves. Of the 11 patients with hypokinesis, akinesis or dyskinesia in the absence of Q waves, 10 had non-specific ST-T wave changes, leaving only one patient with asynergy in the presence of a normal ECG (Miller et al. 1974).

The results were similar in a cineangiographic study of 265 patients, 61 with normal coronary arteries and 204 with coronary artery disease. Asynergy of the specific wall segment and Q waves in the corresponding ECG leads correlated well, but asynergy was also found in other segments. There was a significant ($p < 0.001$) correlation between the number of leads with Q waves and the degree of the extension of asynergy. Q waves had better predictive value for segmental asynergy than did the loss of R wave voltage in the same lead (Bär et al. 1984).

The relationship between two-dimensional echocardiographic wall motion abnormalities and morphologic evidence of myocardial infarction was initially demonstrated in 20 autopsied patients. Out of 15 infarcts, 14 were detected by regional akinesis, dyskinesis or hypokinesis. The relationship between abnormal segmental wall motion and morphologic evidence of myocardial necrosis or fibrosis was significant. Seventy-nine out of 88 (90%) infarcted segments showed abnormal wall motion, although 38 out of 82 (46%) morphologically normal segments also demonstrated wall motion abnormalities. Fifty-eight out of the 65 segments that showed regional akinesis or dyskinesis were transmurally infarcted. Twenty-five out of 38 pathologically normal segments observed in two-dimensional echocardiography as akinetic or dyskinetic were adjacent to a scar. Hypokinesis was nonspecific (31 segments normal, 21 sub-

Figure 3.
ECG of a 33-year old woman with history of smoking. ECG 24 hours before (A, D), on the acute settings (B, E) and 2 days after (C, F) anterior ST-elevation myocardial infarction (STEMI). Primary percutaneous coronary intervention (PCI) revealed critical proximal stenosis of left anterior descending artery (LAD). Extensive anteroseptal and apical wall motion abnormality (WMA) was detected. New Q waves appeared in leads V1-V2, and lead II. Loss of R wave amplitude is evident throughout leads V3-V6, I and aVF(C, F). Symmetric infarct related T inversions are visible (C). Misplacement of cables is suspected as the electrical axis of QRS is opposite in leads aVR, aVL and I (E).

endocardial infarction). Normal wall motion excluded transmural infarction (0 out of 46 segments), but was associated in one patient with subendocardial injury (9/42 segments). Accordingly, it was considered that two-dimensional echocardiography is sensitive in detecting and localising segmental pathologic myocardial lesions but may overestimate their extent (Weiss et al. 1981).

The relation between echocardiographic wall motion abnormality and resting ECG Q waves was studied among 365 patients with the first MI. The reliability of the ECG in identifying the presence of an anterior or inferior myocardial infarct was confirmed. However, the real localisation and extent of the necrotic area may be unseen in the ECG (Giannuzzi et al. 1987).

The frequency and significance of left ventricular wall motion abnormalities was evaluated among 252 patients without ECG evidence of an MI and who subsequently underwent coronary angiography. Seventy-seven patients (31%) had one or more segmental wall motion abnormalities. Sixty-six of these 77 patients (86%) had significant CHD (≥50% luminal diameter stenosis). Thirty-two patients underwent coronary artery bypass surgery or percutaneous transluminal coronary angioplasty. Wall motion improved in 17 out of 20 regions (85%) and returned to normal in 15 regions (75%) (Lewis et al. 1991). Later studies in cardiac magnetic resonance (CMR) imaging demonstrated that a Q/non-Q distinction is useful but that it is determined by the total size rather than the transmural extent of the underlying MI. Using cardiac magnetic resonance imaging as a reference, it was discovered that an ECG is not capable of differentiating a transmural MI from a non-transmural MI (Sievers et al. 2004). One CMR imaging study showed that the Q wave was present in more than 25% of both the subendocardial and transmural MIs (Moon et al. 2004).

The need to standardise ECG classification produced a set of criteria for epidemiologic studies. One of the criteria is the Minnesota Code (MC) system developed in 1950s and 1960s (Blackburn et al. 1960). The accuracy of MC Q and QS criteria for detection of prior MI has been evaluated by Uusitupa et al. in a large (n=1,100) Finnish autopsy study (Uusitupa et al. 1983). The study showed a high specificity of the MC Q-QS abnormalities in the diagnosis of a MI. However, the sensitivity of MC criteria for detection of prior MI was, at best, modest. Another study (n=214) compared data of resting myocardial scintigraphy and MC Q and QS criteria in localising MI. The study indicated that sensitivity of MC in detecting MI is relatively modest and specificity is reasonable, but not good (Sandler et al. 2004)

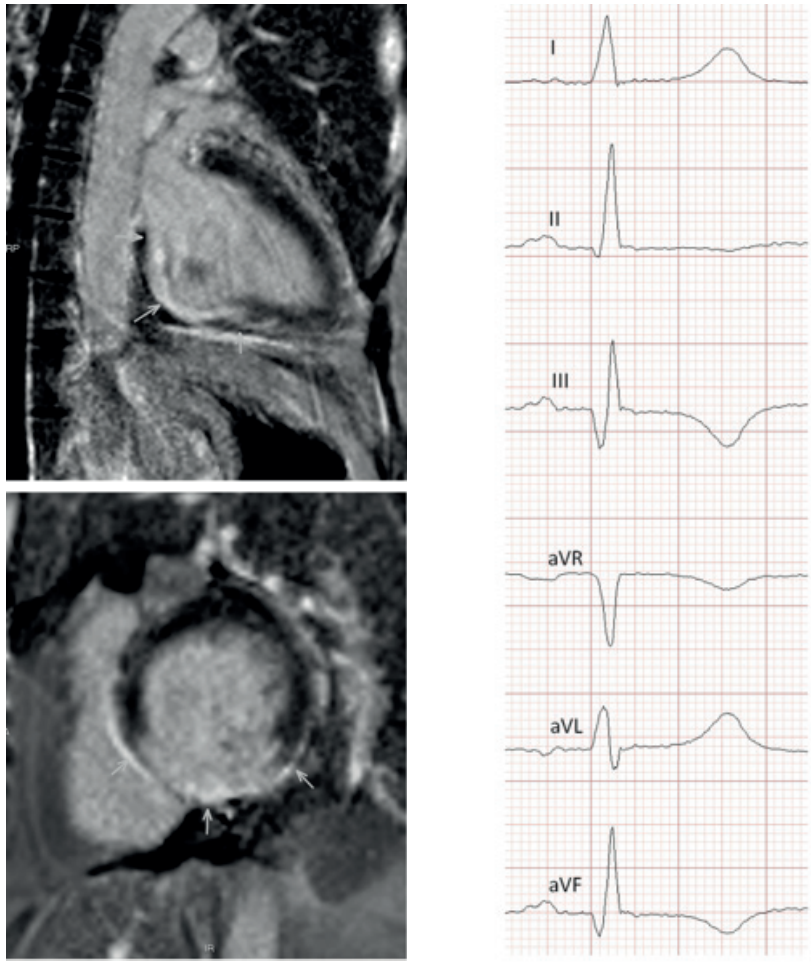


Figure 4.
Cardiac sarcoidosis in a 44-year women. (A) Cardiac magnetic resonance (CMR) imaging reveals late gadolinium enhancement (LGE) in basal inferoposterior wall of the left ventriculum (white arrows = LGE); (B) The ECG is abnormal as Q wave in lead III (Q > 0.04ms) and in lead aVF (Q ≥1.0mm) shows (Minnesota code 1.2.4.). (Image courtesy of Pekka Linden, MD. Hospital district of South Ostrobotnia, Seinäjoki Central Hospital)

Prior MI – a Diagnostic Challenge

At some point over time, infarct-related Q waves may disappear so that a diagnostic Q wave may be present in less than 30% of the subjects with a prior, confirmed and recognised MI (Ammar et al. 2006). For example, in a study of more than 4,000 MI patients, the disappearance of the Q waves during 2-year follow up was discovered in 20.4% of subjects with a lateral MI, in 19.1% of subjects with an inferior wall MI, and in 18.0% of subjects with an anterior wall MI. If subjects had Q waves involving multiple ECG sites, the loss of the Q wave occurred in 3.9% over time ($p<0.01$) (Wasserman et al. 1982).

A study with autopsy-derived data concluded that not all transmural or subendocardial infarcts show a typical QS/QR deflection. Some of the large subendocardial or transmural anterolateral infarctions cause an initial R in leads V1–V4 (Myers at al 1948, p 874). The causes of the registration of an initial R wave rather than a Q wave after an MI was proposed as follows: 1) displacement of the transitional zone to the left, 2) LBBB, 3) early registration of the ECG after the onset of symptoms and 4) a patchy infarction with a viable island of muscle within the myocardial wall (Myers et al. 1948).

In the AMIS (Aspirin Myocardial Infarction Study), the disappearance of a previously documented diagnostic Q wave occurred in 14.2% of participants. Mortality among patients who lost Q waves (6.5%) was not significantly different from that among those with persistent Q waves in a single infarct location (8.7%). The AMIS report agrees with earlier publications concerning patients in whom significant Q waves were lost (Wasserman et al. 1982). The lack of prognostic benefit is in contrast with the information that greater improvement in R-wave voltage is associated with unobstructed coronary flow during 4 weeks after onset of MI (Isobe et al. 2002).

Echocardiographic regional wall movement abnormalities associated with local myocardial infarctions will disappear in more than 50% of subjects even in recognised MIs (Ammar et al. 2006).

When 259 randomly chosen 70-year-old subjects of the PIVUS (Prospective Investigation of the Vasculature in Uppsala Seniors) study were evaluated with CMR, MI scars were found in 60 subjects (24.2%), in 49 of whom (19.8%) they were unrecognized MIs (UMI). Only 3 out of these 49 CMR-revealed UMIs had Q waves in their ECG. No suggestions of the possible clinical impact or prognosis were made regarding these UMIs (Barbier et al. 2006).

A study of 195 patients with no known prior MI showed that the extent of late gadolinium enhancement in CMR imaging independently associated with major adverse cardiac events. The lowest tertile of late-gadolinium-enhancement-involved myocardium experienced a >7-fold increased risk (Kwong et al. 2006).

Table 1. Prognosis of NQWMI and QWMI and Q waves in selected studies

Study	study period	n	women (%)	age	post mi	exlusio	follow-up	Definition of QWMI	Definition of NQWMI	Proportion of QWMI	Loss of Q waves during follow-up	Mortality difference QWMI vs. NQWMI	Other
The Social Insurance Institutions (SII) Study (Reunanen et al 1983)	1966-1972	906	0	40-59 yrs (men)	na	na	5 yrs	na	na	na	na	CV mortality 22.7% if large Q wave (MC 1.1), mortality 1.7% if no CHD findings in ECG	
The Aspirin Myocardial Infarction Study (AMIS)	1975-1979	4524	11.5%	30-69 yrs	8 wk to 60 mo	NYHA III-IV, LBBB	3 yrs	Symptoms, enzymes, MC 1.1 (=major MI), 1.2 (=moderte), 1.3 (=minor)	Symptoms, enzymes, ECG "no codable location"	18.9%	14.2%	No mortality difference: lateral 11.8%, inferior 8.0, anterior 9.4%, multisite q waves 14.6%, p<0.0002) nonqwmi 7.1%, total 10.1	
Data 1979-1984 (Nicod et al 1989)	1979-1984	2024	24% QWMI, 30% NQWMI (p<0.05)	18-95 yrs	0-24 h	Subsequent CABG, Symtoms >24 h	12 mos	New Q waves and typical chest pain / CK elevation	STD/T wave inversion and CK elevation	78%	na	No mortality difference in 1 year follow up. 19.5% vs 20.4%.	
Data of 5 trials 1981-1992 (Goodman et al 2002)	1981-1992	5005	na	na	1 day	non STEMI	1 year	Initial STEMI, symtoms, Selvester criteria for Q wave	Initial STEMI, symptoms, no Q wave	86.3%	na	Trombolysis treated: Inhospital and 1 year mortality lower in NQWMI than QWMI	Receiving trombolysis more often developed NQWMI
The Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT) (Behar et al 1996)	1981-1992	4037	25% QWMI, 34% NQWMI (p<0.0001)	61.4 yrs (mean)	1 day	No first MI	10 yrs	Symptoms, enzymes, MC 1.1-3	Symptoms, enzymes, ST segment or/and T wave changes	86%	na	In hospital mortality: QWMI 10%, NQWMI 7% (p<0.05), 5 and 10 year mortality: QWMI 22% and 44%, NQWMI 20% and 40%.	Proportion of NQWMI 14% in 1983 and 32% in 1994-
The Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT) (Haim et al 1998)	1981-1983, 1994	835 (1994 n=225)	0,35	63 yrs (mean)	1 day	No first MI	1 year	na	Symptoms, enzymes, ST segment or/and T wave changes	na	na	7- and 30-day total mortality rates significantly lower in 1994 compared with the early 1980s (5% vs 9% and 5% vs 13%, respectively, (P < .05 for both) 1 year mortality of NQWMI in 1981-1983 19%, 1994 15%, p=0.13)	Confirmed MI and death within minutes arrival at hospital without Q wave considered NQWMI
Worcester Heart Attack Study 1975-1997 (Furman et al 2001)	1975-1997	5832	37% QWMI, 46% NQWMI (p<0.001)	65 yrs (mean)	1 day	Perioperative MI, secondary non cardiac related MI	up to 22 years	New Q wave (≥0.04ms, amplitude ≥25% of R wave) with dynamic ST-T and chest pain / enzymes	STD ≥1mm / T wave inversion and chest pain / enzymes	58%	na	During 22 yrs: Incidence of QWMI and in-hospital mortality decreased. Incidence of NQWMI increased with no change in in-hospital mortality.	
MI Register Study in Spain 1992-1998 (Marrugat et al 2004)	1992-1998	20834	24.8%	23-94 yrs	1 day	na	28 days	Abnormal Q waves	Symptoms and enzymes	81.9%	na	28d mortality significantly higher in ALL settings in women compared to men, (p<0.001): in first QWMI 24.3% vs 10.9%, in recurrent QWMI 32.8% vs 22.5% and in NQWMI 15.8% vs. 10.1%.	
The Copenhagen City Heart Study (Godsk et al 2012)	1976-1978, 2001-2003	5381	58%	58 (no Q), 68 (Q)	na	Known CHD or CHF (Hospital data only)	7.8 yrs	Large Q wave MC 1.1, Small Q wave MC 1.2-3	na	2.1%	na	Mortality or hospialization for CHD: large Q waves 59% , small Q waves 44%, no Q waves 18%.	No interview of subjects. These Q waves may reflect either RMI or UMI

NYHA, New York Heart Association; CABG, Cardiac bypass grafting; CK, Creatine kinasis

Characteristics of non-Q-Wave MI and Q Wave MI

Several differences characterise NQWMI as opposed to QWMI. Data from real-life registers are somehow conflicting. Subjects with NQWMI are older and have recurrent AP more often than QWMI subjects (Nicod et al. 1989). Furthermore, according to a Spanish STEMI register, individuals with NQWMI are older and more likely to suffer from AP. In addition, NQWMI patients were found to have DM, a stroke and hypertension more often than those with QWMI. NQWMI subjects more frequently used aspirin, b-blockers and calcium-channel blockers, and they were less often treated with thrombolytic therapy in the acute phase of STEMI (Marrugat et al. 2004). Moreover, according to Israelis, NQWMI patients are more likely to suffer from AP and use more b-blockers, calcium-channel blockers and digoxin when compared to QWMI patients. However, there were no differences in the history of DM, ASO or stroke between NQWMI and QWMI (Behar et al. 1996). Individuals with NQWMI have been found to have lower cardiac enzyme leakage in the acute phase of MI than those with QWMI. NQWMI patients tend to more often have a history of MI and CHF but are less likely to suffer LV failure during the index hospitalisation than QWMI patients (Nicod et al. 1989).

There are some differences in mortality between NQWMI and QWMI. Some of the studies summarising the prognostic aspect of NQWMI and QWMI are presented in Table 1. In general, in-hospital mortality is higher among QWMI patients, but after one year from the infarction, there is no difference in mortality between NQWMI and QWMI (Behar et al. 1996, Haim et al. 1998, Nicod et al. 1989).

The prognostic difference between QWMI and NQWMI in stable coronary disease was studied in 4,524 subjects of the AMIS study. The subjects had suffered an MI 2 months to 5 years prior to the study initiation. During the follow up of three years, no mortality difference between subjects with any QWMI location and NQWMI were found (lateral 11.8%, inferior 8.0%, anterior 9.4%, non-Q 7.1%). Only subjects who had multiple QWMI locations had a significant increase of 14.6% in mortality in comparison to the overall study population of 10.1% ($p < 0.0002$) (Wasserman et al. 1982). In another study, subjects who suffered a recurrent QWMI had higher mortality compared to those with first QWMI (Marrugat et al. 2004).

Long-time-span prognosis was studied in Israel in 1981–1992 among 4,037 subjects followed for 10 years. In this notable study, 518 (14%) subjects had a NQWMI and 3,457 (86%) a QWMI. The in-hospital mortality was significantly higher in patients with a Q wave MI (10%) in comparison to patients with a non-Q wave MI (7%) ($p<0.05$). The one-year out-of-hospital recurrence

and mortality rates were similar among QWMI and NQWMI patients (4% and 7%). Similarly, 5- and 10-year post-discharge mortality rates were equally high in patients with a non-Q-wave (26% and 44%) as in those with a first episode of a Q-wave myocardial infarction (22% and 40%, respectively) (Behar et al. 1996)

In a study by Goodman et al., thrombolytic treatment for ST elevation MI (STEMI) reduced the overall mortality of MI patients. Compared to standard therapy (which, at the time, did not include thrombolysis), patients receiving thrombolysis more often developed a NQWMI instead of a QWMI. If thrombolytic treatment was delivered, those with a NQWMI had a better prognosis than QWMI (Goodman et al. 2002).

The proportion of women in MI studies has been relatively small (Table 1). However, the reported mortality has been higher among women than men in both QWMI and NQWMI (Marrugat et al. 2004).

During the past decades, the incidence and in-hospital mortality of QWMI have decreased. Simultaneously, the incidence of NQWMI has increased, while the in-hospital mortality has not changed (Furman et al. 2001, Kattainen et al. 2006).

All in all, Q waves in acute settings of MI associate with greater total mortality than in NQWMI. This is partially due to the greater extent of MI in QWMI in comparison to NQWMI. However, the difference in mortality diminishes after one year from discharge and finally disappears after many years of follow-up. In stable settings of a previous MI, the annual mortality is approximately 4% in patients both with and without Q waves.

Unrecognized MI (UMI)

There is no universal criteria for UMI. Usually UMI is diagnosed if patient with prior MI had no recognised clinical MI event. Diagnosis of MI is based on the presence of pathological Q waves or loss of R waves. However, some studies use CMR or cardiac echo in diagnosing MI (Table 2). Historically, in the Framingham Heart Study, more than 25% of the evolved MIs were discovered only by the appearance of new diagnostic evidence during a routine ECG examination (Kannel 1987). However, not all Q waves are related to CHD or previous MI as other mechanism may produce myocardial necrosis as well (Figure 4). In addition to minimal short Q waves which are met frequently in the inferior leads II, III and aVF, and in leads I and aVL due to the more vertical or horizontal heart position, Q waves are met in IVCD and ventricular hypertrophy (Figure 2).

Previous studies of UMI report that up to 25%–40% of the MIs are clinically unrecognised (Sheifer et al. 2001). A study on 2,042 Olmsted County residents found that 44% (81/182) of the MIs were UMIs (Ammar et al. 2006). The diagnosis of an UMI is based on Q waves, generally Minnesota Code (MC) 1.1-1.3.

In a study with 1,316 Greenland Inuits aged 18 or more (mean age 44.2 years), the prevalence of UMI was 3.5% in men and 7.5% in women. In this study, MC 1.1-2 was used to diagnose an old MI. The participation rate was only 67%, and 56% of the participants were women (Jorgensen et al. 2007).

In the Social Insurance Institution's (SII) Coronary Heart Disease Study consisting of 10,962 Finnish individuals, 20% of the men and 38% of the women with large or moderate Q waves (MC 1.1-2) had no history of chest pain (Reunanen et al. 1983). This finding is in concordance with the outcome of 5,127 subjects followed for 30 years in the Framingham Heart Study where the proportion of UMIs was 28% in men and 35% in women (Kannel 1987).

In the Reykjavik study of 9,141 men, at least one third of all individuals with MIs had no history or symptoms of MI (Sigurdsson et al. 1995).

The investigators of the West of Scotland Study (WOSCOPS) with 6,595 men reported that an ECG detected 96/355 (27%) definitely UMIs. Of the 355 incident MIs in WOSCOPS, 47.3% were silent or unrecognised (Macfarlane and Norrie 2007).

The Cardiovascular Health Study (CHS) included 5,888 subjects aged 65 and over, among whom 22.3% (201/901) of those with an MI had suffered an UMI (Sheifer et al. 2000).

The prevalence of UMI and silent myocardial ischaemia was 23% and 28%, respectively, in a cohort of 1,092 elective patients undergoing preoperative dobutamine stress echocardiography prior to non-cardiac vascular surgery (Feringa et al. 2007).

In a search for optimal screening tool, six different ECG criteria were tested to recognise UMIs among 2,024 subjects. The UMI proportion estimates varied from 32% to 61% due to variation in the ECG-MI criteria (Ammar et al. 2005). In a study of 970 subjects aged 67–93 years, the prevalence of UMI detected by cardiac CMR imaging was 17%. Meanwhile, the prevalence of UMI detected by ECG (MC 1.1.1 -1.2.8) was only 5%. The prevalence of recognised MI was 9.7%, which is 36% of all MIs if the UMI was diagnosed by CMR imaging or 64% if the UMI was diagnosed by means of ECG (Schelbert et al. 2012).

In a retrospective analysis of 669 type 2 diabetic individuals, the prevalence of unrecognised Q-wave MI at baseline was 1.9% (n = 13). The incidence of unrecognised Q-wave myocardial infarction at the end of 2 years of follow-up was 1.5/1,000 person years (n = 2). One third (13 of 39) of prevalent and one in

four (2 of 8) incident myocardial infarctions were unrecognised. Unfortunately, the ECG of one third (335/1004) of the original study cohort was not available (Macdonald et al. 2011).

A far lower incidence of UMI (4.1%) was reported for 2,763 postmenopausal (<80 years) women with a history of CHD during a mean follow-up of 4.1 years (Shlipak et al. 2001).

The relation between resting ECG abnormalities and subclinical coronary atherosclerosis was studied among a general population of 4,814 subjects aged 45–75 years (50% females). The prevalence of UMI was 5.8% and consisted of 46% (278/605) of the subjects with a history of MI, coronary revascularisation or UMI. Coronary artery calcification scores were calculated for subjects with no history of MI or coronary revascularisation (4,487). Coronary artery calcification scores were much higher in subjects with a UMI than in those with normal ECG (Möhlenkamp et al. 2008).

In a study on 259 subjects aged 70 years or more, CMR imaging detected MI scars in 60 subjects (24.2%), in 49 of whom (19.8%) the MIs were UMIs (Barbier et al. 2006).

In summary, the prevalence of UMI in the general population is roughly 5% to 9% if the diagnosis is based on resting ECG. UMI is slightly more frequent in women than in men. The proportion of UMI is 20%–40% of all MIs. However, the prevalence of UMI is remarkably higher if diagnosed with CMR imaging.

Clinical Aspects of UMI

The evidence of the Framingham Heart Study stretching over more than 30 years indicates that, out of all MIs, UMI is more common in women (35%) than in men (28%) and subjects with a UMI tend to visit physicians less often, suggesting an element of denial. The electrocardiographic location of the infarction was no different than in symptomatic infarctions. Furthermore, the proportion of MIs that occurred unrecognised increased with the severity of hypertension (Kannel 1987).

Compared to individuals with no MI, those suffering a UMI have a statistically significantly higher incidence of diabetes, heart failure and hypertension. They have higher B-type natriuretic peptide levels, more diastolic dysfunction, a larger left atrium dimension, lower ejection fraction and more regional wall movement abnormalities than individuals without MI. Forced expiratory volume 1 (FEV1) and forced vital capacity (FVC) are also lower in UMI patients. The most common echocardiographic abnormality in those with an unrecognised QWMI has been observed to be diastolic dysfunction, which was seen in 57% of individuals. However, these variables will not distinguish UMI and RMI as subjects with an

RMI have categorically more profound abnormalities in these variables (Ammar et al. 2006).

Scheifer et al. (2000) characterised factors associating with UMI. They found that female sex, increasing age and blood pressure along with the absence of common CV diagnoses – including angina, congestive heart failure and claudication – predicted that an MI would be unrecognised. The absence of a family history of CHD, low FEV1, increasing Factor VII level and good or excellent self-assessed health status were additional factors that associated with UMI. In accordance with the Olmsted County subjects, there were no differences between subjects with UMI and RMI in current smoking or body mass index. Former smoking was associated with recognised infarction (Sheifer et al. 2000).

It is thought that women are more prone to silent MI, but in a trial with 2,763 postmenopausal women with known CHD, the proportion of UMI out of all nonfatal MIs was only 4.3% (11/256)(95% CI, 2.2%–7.6%)(Shlipak et al. 2001).

Both diabetes and heart failure have been observed to be important predictors of unrecognised MI and silent myocardial ischaemia in subjects referred to preoperative dobutamine stress echocardiography (Feringa et al. 2007).

In a study with 70-year-old subjects, the volumes of the UMIs as assessed with CMR were significantly smaller than those of the RMIs. No differences between risk factors (hypertension, hypercholesterolemia, diabetes, current smoking) were reported. UMIs were more frequently located in the inferior and inferolateral segments of the LV, whereas RMIs seemed to be more evenly distributed between the segments (Barbier et al. 2006).

In summary subjects with a UMI tend to have more co-morbidies such as diabetes mellitus, hypertension and heart failure. Women may also have more UMIs than men.

Prognosis of UMI

The prognosis of individuals with an ECG-based UMI is no better than individuals with RMI. Less than 10 years ago the reported mortality of first MI survivors was 51.5% (305/597) in women and 40.7% (393/966) in men during a median follow-up of just 3.4 years (Griffith et al. 2005). According to large population register, Finnish National Cardiovascular Disease Register (CVDR), the 1-year mortality of MI was 55% (17,583/31,936) among men and 62 % (17,360/28,103) in women (Lehto et al. 2011). Several population-based studies suggest that the mortality associated with UMI is equal or even greater than RMI-related mortality. Studies containing prognostic information regarding UMI, with a combined more than 80,000 subjects and up to 30 years of follow–up, are

summarised in the table 2. In almost all the studies, mortality in subjects with a UMI has been greater than in those with no MI. Generally, the reported annual mortality related to UMI or RMI is 4%–5%, which is at least twice that of subjects with no MI. In one study, consisting type II DM patients, there was no difference in mortality between individuals with a UMI and those with no CHD/non-Q-wave MI (Davis et al. 2004).

Some of the earliest works have reported greater mortality among UMI than RMI patients. Studies launched later confirmed great but equal mortality for UMI and RMI. The Copenhagen City Heart Study reported that death or CHD-related hospitalisation was significantly more common with UMI than with RMI (Godsk et al. 2012).

The definition of UMI in these studies is usually based on diagnostic ECG changes in conjugation with no history of AP symptoms. ECG criteria for UMI are largely based on the categorical Minnesota Code Classification system for electrocardiographic findings (Prineas et al. 1982). Studies not relying solely on MC classifications have defined UMI not only as the presence of a pathologic Q wave, but as the loss of an initial R wave as well. Interestingly, it is precisely these earliest studies, the Framingham Heart Study (Kannel and Abbot 1984) and The Honolulu Heart Program (Yano et al. 1989) that reported greater mortality among UMI patients as opposed to RMI patients. In two studies, the proportion of a prior anterior location of UMI (loss of anterior forces) was the highest (Medalie and Goldbourt 1976, Kehl et al. 2011)

Some studies, like the Reykjavik Study, have reported prognostic information only for men but not for women (personal remark by Professor Vilmundur Guðnason, the Icelandic Heart Association and the University of Iceland).

Unlike other studies, the study on Israeli men reports lower mortality for UMI in comparison to RMI. This may be due to the fact that the MC criteria were not used in defining UMI and the subjects worked for the government (Medalie and Goldbourt 1976).

In the CHS Study, total mortality for UMI and RMI was equal. However, there were significantly more CV related deaths among RMI patients than UMI patients. Therefore, it may be suggested that in the presence of UMI, the possibility of other underlying CV diseases may be severely unrecognised as well (Scheifer et al. 2000).

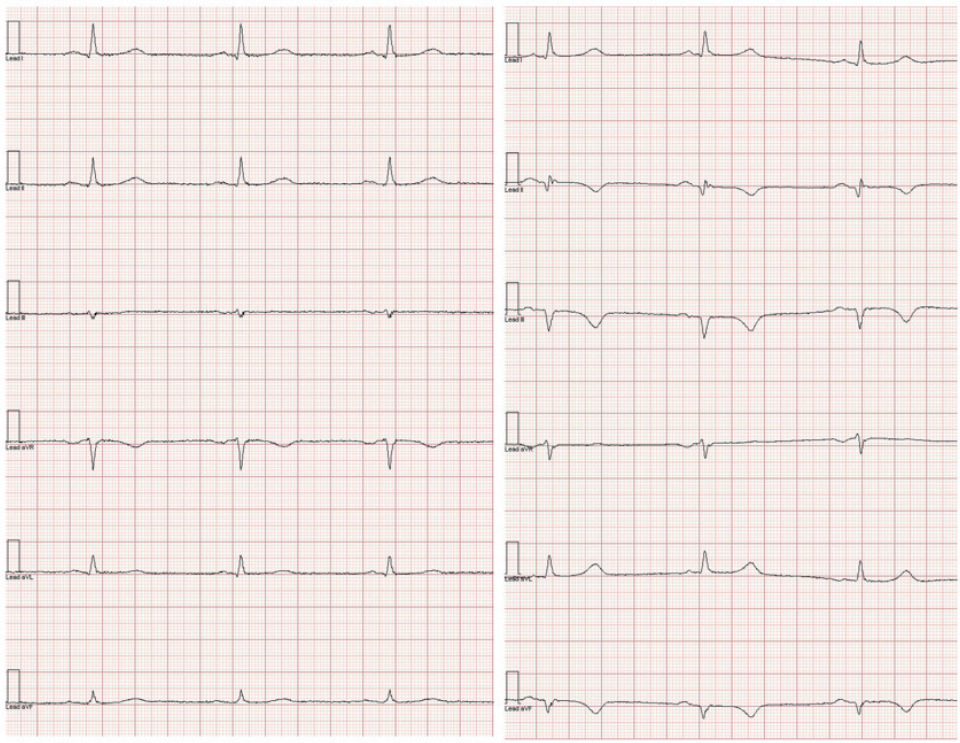
In the Reykjavik Study, symptomatic UMI (HR 16.9; 95% CI 9.4–30.3) was a greater risk for CHD death than symptomatic RMI (HR 8.5; 95% CI 5.8–12.6) (Sigurdsson et al. 1995). Furthermore, among the Olmsted County residents, UMI with symptoms (dyspnea on exertion, orthopnea, palpitations or history of fluid overload) was associated with increased mortality (risk ratios ranging from 2.3 to 9.1). In this study, if any echocardiographic abnormality was present (left atrium enlargement, systolic dysfunction, ejection fraction 50% or less, diastolic

Table 2. Studies with available data on the prognosis of UMI

Study	Period	n (women %)	Age	Follow-up	Definition of UMI *	Mortality	Main results	Observation
The Framingham Heart Study, USA (Kannel and Abbot 1984)	1948-1978	5127 (55%)	30-62 yrs	30 yrs	Pathologic Q wave duration ≥0.04s, or loss of initial R wave	10 -year mortality 45% in UMI and 39% in RMI	First population based data of detrimental effect of UMI	proportion of UMI (130/469) 28% in men and (83/239)35% in women
Data from Israel (Medalie and Goldbourt 1976)	1963-1968	9509, (-)	≥ 40 yrs	5 yrs	ECG evidence of MI, automatic screening and specialist acceptance	UMI 17.3/1000, RMI 36.3/1000, no MI 4.6/1000	Death was lower in UMI than RMI	All men worked for goverment. Proportion of prior anterior UMI highest
The Honolulu Heart Program, USA/japanese (Yano and MacLean 1985)	1965-1968	7331 (-)	45-68 yrs	10 yrs	Loss of initial R waves or new abnormal Q waves	10 -year mortality 45% in UMI and 35% in RMI	Death rate was equal in RMI and UMI	
The Social Insurance Intitution´s Coronary Heart Diease Study, Finland (Reunanen et al 1984)	1966-1972	10962 (48%)	30-59 yrs	5 yrs	MC 1.1-2 and no history of AP	In men: MC 1.1 (40-59y) mortality 27.5% and age adjuted risk ratio for CHD mortality 13.4 compared to subjects without Q waves.	Major Q waves increase CHD mortality significatly in middle aged me	
The Reykjavik Study, (Sigurdsson et al 1995)	1967-1987	9141 (-)	59 yrs (mean)	4-20 yrs	MC 1.1.1-1.2.8	10- and 15 yrs CHD mortality for UMI 51% and 55%, for RMI 38% and 52%	Death rate was equal in RMI and UMI	Prognostic data of women not available
The Copenhagen City Heart Study (Godsk et al 2012)	1976-1978, 2001-2003	6237 (58%)	≥20 yrs, mean > 58 yrs	7.8 yrs	MC 1.1-3 (HF and CHD exluded)	Death or CHD hospitalization: UMI 44% , RMI 18% (p<0.0001)	Death or symptomatic CHD was more common in UMI than in RMI. HR 1.6 (95% CI 1.2-2.1; p<0.002)	51% of the invited 12600 subjects declined participation
The Atherosclerosis Risk in Communities (ARIC) Study, USA (Machado et al 2006)	1987-1989	15792 (57%)	45-64 yrs	11.6 yrs (mean)	Major Q waves exluded; only those with minor Q waves (MC 1.2.6, 1.2.8 and 1.3) included	HR ratio for MI or CHD death 1.85, (95% CI, 1.27-2.7; adjusted race, gender, education) and 1.59 (multiadjusted)	Small Q waves associated with MI and CHD mortality	Subject had no history of CHD. Only small Q waves
The Cardiovascular Health (CHS) Study, USA (Scheifer et al 2000)	1989-	5888 (58%)	≥65 yrs	5.4 yrs (median), 4.8 (mean)	Major Q wave (MC 1.1-2, exept 1.2.8) or minor Q wave (MC 1.2.8 or 1.3) with ST-T abnormality (4.1-3, 5.2-3)	UMI 21.4%, RMI 25.4%, no MI 12%	No mortality difference between UMI and RMI (p=0.24)	Difference in CV death among UMI and RMI (9% vs 16-1%, p=0.01). Unrecognized until death?
Data of patients undergoing major vascular surgery, Netherlands (Feringa et al 2007)	1990-2004	1092 (22%)	64 yrs (mean)	6 yrs (mean)	Rest wall motion abnormality	HR for mortality in UMI 1.86 and in RM 1.99 compared to no MI (p<0.001).	UMI and RMI had similar, poor prognosis.	
The Fremantle Diabetes Study (Davis et al 2004)	1993-1996	1269 (51%)	64 yrs (mean)	7 yrs, mean (range 0.1 - 9.2 yrs)	MC 1.1-2 and no history or typical symptoms of CHD.	UMI 26%, CHD no Q wave 42%, CHD + Q wave 42%, no CHD no Q wave 18.2%	Prognosis of UMI in DM type II similar to those with no CHD/Q waves	UMI prevalence 3.9%, 44% of all Q-wave myocardial infarctions
The Olmsted County Heart Function Study, USA (Ammar et al 2006)	1997-	2042 (54%)	≥ 45 yrs	5 yrs	Major Q waves MC 1.1-1.2.7 and also minor Q waves 1.2.8-1.3	HR for mortality 3.5 in UMI compared to no MI	Stepwise increase of non-AP symtoms (and poor prognosis) MI/ UMI/RMI	
The Heart and Soul Study, USA (Kehl et al 2011)	2000-2002	1024, (21%)	67 yrs (mean)	6.3 yrs (mean)	Significant Q wave if duration >40ms, propable if 30-40ms	Q wave 29%, no Q wave 23%	No difference in mortality (Q wave vs no Q wave) Only combined CV events (all cause death, MI, stroke) were more common with Q waves (p=0.05)	Subjets had stable CHD. Proportion of prior anterior UMI highest
Iceland MI Study (Shelbert et al 2012)	2004-2007	936 (52%)	67-93 yrs, 76 yrs (median)	6.4 yrs (median)	ECG-UMI: (Minnesota codes 1.1.1-1.2.8). CMR-UMI: Late gadolium encahcement in a coronary distribution	no MI 17%, UMI 28%, RMI 33%	CMR-UMI associated with incresed mortality while ECG-UMI not. See text for details.	Patients were not asked if they had AP or non- anginal symtoms. Only records used
Data from REGARDS Study, USA (Rizk et al 2011)	2004-2010	18864, (62%)	≥ 45 yrs	4 yrs (median)	Major Q wave (MC 1.1-2) alone or minor Q wave with ST-T abnormality (MC 1.3 and 4.1-2 or 5.1/5.2)	Adjusted HR for mortality with UMI 1.65 and RMI 1.65 compared to no MI.	No mortality difference between UMI and RMI	Subjects at predialysis phase
The the Multi-Ethnic Study of Atherosclerosis (MESA)(Li et al 2013)	2000-2002	6551 (53%)	45-84 yrs	7.8 yrs	MC 1.3	Rate of all CV events (fatal and non fatal) was higher with UMI than no-MI (1.55; 95% CI 1.1-2.17).	Subanalysis: Result significant only among hispanic, not among white, black or chinese.	All subjects with CV diseases, major Q waves and FA exluded.

* Without exception If criteria for prior MI were met but subject had no recognized clinical MI event, as defined by spesific study, then UMI status was assigned

dysfunction or left ventricular enlargement), the risk of all-cause mortality for UMI was 4.22 (95% CI, 2.05–7.75, p=0.0003). Interestingly, it was diastolic dysfunction and other echocardiographic abnormalities, not regional wall motion abnormality that associated with UMI-related symptoms and mortality. Finally, in the small subset of patients (n = 20) with a clinical UMI and no echocardiographic abnormality, the hazard was not increased (HR = 0.99, P =0.99). However, the number of subjects with no echocardiographic abnormality is too small to draw robust conclusions (Ammar et al. 2006).



A B

Figure 5.
Limb leads of the ECG of the 64-year old man with hemochromatose. (A) ECG 8 months before, and (B) 1 month after inferior STEMI. Coronary angiography revealed proximal total occlusion in right coronary artery (RCA) and 50% stenosis in left anterior descending artery (LAD). QS complexes in lead aVF and III as well as Q wave in lead II show infarct related T wave inversions.

The excess mortality of UMI is not related only to ECG-based diagnostics but also to other modalities capable of diagnosing UMI. UMI defined by a resting wall motion abnormality seen in cardiac echocardiography had a similar poor prognosis to RMI (Feringa et al. 2007).

Investigators in the ICELAND MI, a cohort study of 936 (266 with DM) participants aged 67–93 years, used late gadolinium enhancement of CMR imaging to detect and define UMI (Schelbert et al. 2012). MCR imaging detected more UMIs (17%) than did ECG (5%). In this study, the reported UMI mortality is comparable to other ECG-defined UMI studies. Over the median follow-up of 6.4 years, the mortality was similar for recognised MI (33%) and UMI (28%), with significantly higher rates than for subjects with no MI (17%). Surprisingly, and unlike in other studies, ECG-detected UMIs did not associate with higher mortality (HR 0.95, 95% CI, 0.49–1.87).

There are several limitations concerning the ICELAND MI study. The final cohort was 936 individuals, representing 74% of the 1,260 individuals invited, which may influence the analysis. The information regarding ECG status in the UMI group detected by CMR is not reported. Possible MI-related changes may not be detected in the resting ECG in conjugation with LVH (Figure 2), right ventricular hypertrophy (RVH) or ventricular conduction delays (VCD), while these electrical abnormalities do not limit CMR-imaging-based MI detection. However, the presence of LVH increases mortality among MI patients (Behar et al. 1992). Furthermore, the report includes no statements concerning previous ECG recordings. The minor ischaemic ECG changes over time predict future CV mortality, but we do not know if there was a change in the Minnesota Coded Q waves over time (Crow et al. 1997). Furthermore, only hospital records and surveillance data were used to judge whether a patient had an RMI or UMI. At no point were subjects asked if they had a history of AP or non-anginal symptoms (personal remark from Andrew E. Arai MD, National Institutes of Health, Bethesda, Maryland, USA). Thus, there may have been subjects in the UMI group who had symptoms and, accordingly, should have been allocated to the RMI group. Finally, CHD is more than just the Q waves studied in the ICELAND MI study. The ST segment depression or T wave inversions (MC 4.1-3, MC 5.1-2) may represent ongoing ischaemia with a similar prognosis as Q waves (MC 1.1.-3) (Reunanen et al. 1983), but these were not included in the ICELAND MI study or in any study dealing with UMI (Table 2).

Changes in Minnesota Coding over time and their association with CHD mortality were studied in the Multiple Risk Factor Intervention trial (MRFIT). During the follow-up of 16 years with consisting 12,866 male subjects, the CHD mortality rate increased by a factor of 4 with an evolving Q pattern when compared to men without progress. Out of the evolving Q patterns, 195/394 (49%) occurred in the absence of a clinical myocardial infarction (Crow et al. 1997).

As a whole, the prognosis of individuals with an ECG-based UMI is similar (10-year mortality of 45%) or even worse when compared to those with RMI. The risk of mortality is roughly twofold in UMI patients compared to those without MI. UMI with symptoms has an even more detrimental prognosis.

Anterior MI and Poor R Wave Progression

The loss of anterior depolarisation forces due to anterior MI has long been established clinically and experimentally to produce the abnormally low R wave amplitude extending from the right into the mid- or left precordial leads (DePace et al. 1983, Zema and Kligfield 1979a, Zema and Kligfield 1979b). This ECG phenomenon, termed poor R wave progression (PRWP), is a troublesome clinical finding. Although in many cases indicating MI of the anterior wall, the finding is often seen in patients with a variety of cardiac disorders and not infrequently in apparently normal subjects.

MI of the anterior wall is independently associated with an adverse outcome when compared to MI of the lateral or inferior wall (Stone et al. 1988). MI-related large Q waves in the anterior wall may disappear or regress to minor Q waves in 4 weeks and in 10%–20% of patients over a 1–2-year period (Pyörälä and Kentala 1974, Isobe et al. 2006, Dwyer 1990, Okada et al. 1999). Many criteria have been proposed for a better diagnosis of an old anterior MI. Warner et al. (1983) defined old anterior MI as a Q wave of any magnitude or an initial R wave in lead V2 < 20ms. This straight-forward criterion, derived from angiographic data (N=199), has a sensitivity of 83% and a specificity of 99% (Warner et al. 1983). In a much larger study, angiographic data (N=1,102) was combined with definite ECG criteria and 12-lead vectorcardiogram criteria. This method, albeit not clinically practical for today's purposes, showed a sensitivity of 80% and specificity of 96.4% in diagnosing a healed anterior MI (Pettersson et al. 1995).

In 265 patients examined by means of ventriculography because of chest pain (mean age 50 years), a loss of the R wave in lead V2 was a more precise indicator of segmental wall motion abnormalities than was the presence of this finding in lead V3 or V4. In contrast to Q waves in the precordial leads, the loss of R waves or, in effect, the presence of a small R wave, suggests the presence of viable tissue in the left ventricle in the anterior segments (Bär et al. 1984).

In practice, 12-lead ECG and Q/QS criteria are used instead of a vectorcardiogram. However, this everyday tool lacks accuracy to evaluate the presence of a former MI.

An increase in myocardial fibrosis has been suggested to result in decreased R wave amplitudes in ECG (Figure 4). In a study by Takatsu et al., a myocardial biopsy was taken from 79 patients during a coronary bypass grafting operation.

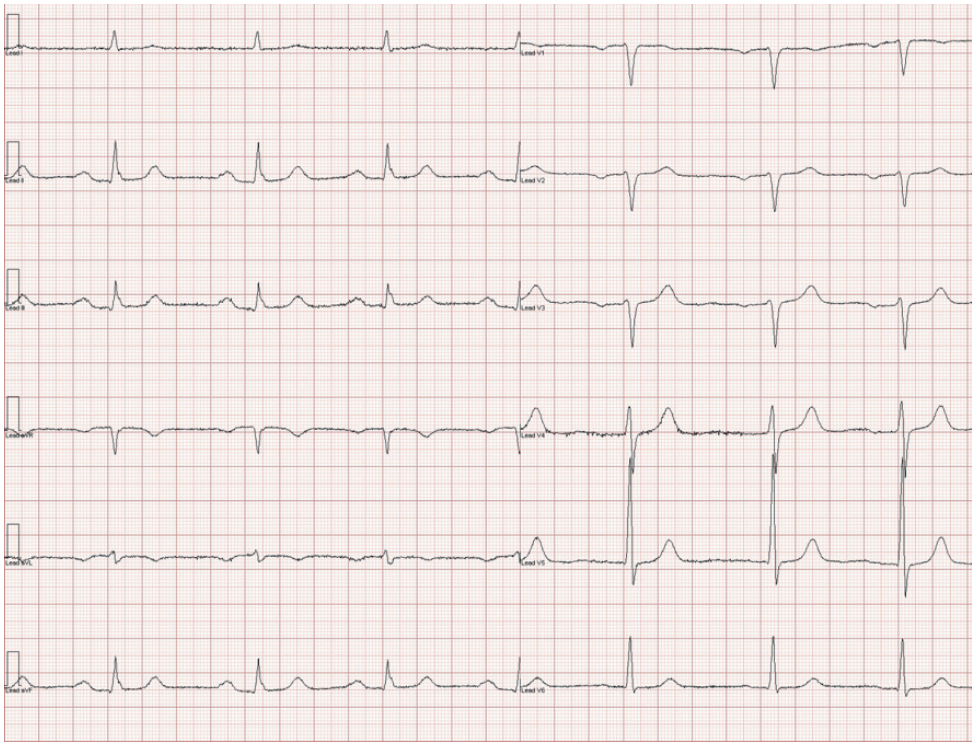


Figure 6.
ECG of an 82-year-old man with severe chronic obstructive pulmonary disease (COPD), emphysema and history of spontaneous pneumothorax. Poor R-wave progression is evident.

Patients with Q waves had more (38%–100%) myocardial fibrosis than patients without Q waves or decreased R wave amplitudes (20%–45%). Patients with normal ECG had only slight fibrosis (3-27%) (Takatsu et al. 1993).

In a retrospective sample of 146 subjects, one third of the largest myocardial scars were not detected with ECG, whereas the necrosis was visible in cardiac magnetic resonance imaging. The study used Minnesota coded Q/QS criteria which had a low negative predictive value for MI (64%). The sensitivity of Q/QS criteria in detecting scars localised to the anterior or inferior walls was approximately 50% (Asch et al. 2006).

PRWP (Figure 6) or reverse R wave progression may appear in the presence of incomplete or complete LBBB, LVH, left anterior hemiblock (LAH), a pseudo-Q wave caused by perpendicular orientation of the initial QRS deflection to the lead axis, mitral valve prolapse and an abnormally low diaphragm position in pulmonary emphysema (Mittal et al. 1986, Zema et al. 1980, Surawicz et al. 2008). In normal subjects with no evident cardiac or pulmonary disease, the ECG pattern may be caused by a shift of the transitional zone to the left or by an abnormally high placement of the mid-precordial chest leads (Garcia-Niebla 2009).

PRWP was observed in 19% of adult women and 11% of adult men who were hospitalised (Colaco et al. 2000). In a university hospital setting with adult patients, the prevalence of PRWP and reverse R wave progression was 7%–10% and 1%–2%, respectively (Zema and Kligfield 1982). PRWP is a frequent abnormal ECG pattern faced in insurance medicine (MacKenzie 2005). In 1,250 symptomatic patients evaluated for suspected angina pectoris, PRWP was present in 8% with an equal distribution among the sexes (DePace et al. 1983). However, the prevalence and clinical significance of the ECG finding in the general population is not well known (Gami et al. 2004).

In summary, MI-related large Q waves in the anterior wall may disappear over time. PRWP is frequently met in hospital settings and may signify prior anterior MI.

T Waves

Repolarisation of the ventricles of the heart generates the T wave recorded by the ECG. Because the normal T wave vector is directed leftward and inferiorly in the frontal plane, the T wave is inverted in lead aVR, the positive pole of which is oriented to the right upper side of the heart. T wave abnormalities are among the most frequently encountered pathological ECG findings in an apparently healthy population (Hiss and Lamb 1962). It is thought that in ischaemic heart disease, Q waves represent prior MI while T wave and ST segment changes represent myocardial ischaemia. Changes in the ST segment and T wave are the most typical ECG abnormalities in patients with acute coronary syndromes (ACS), but changes may develop gradually by advancing CHD (Burch 1957). Ischaemic ECG findings also increase with advancing age (Jacobsen et al. 2005, Armstrong et al. 1982, Ström Möller 2006).

ST-T abnormalities are common in clinical settings and population studies. Although ST segment and T wave findings were once routinely considered benign and nonspecific, Bursch reported in the 1950s that ST-T abnormalities could reflect early signs of CHD (Bursch 1957). Increased fatal coronary events and morbidity were associated with ST depression with or without T abnormalities over a period of 30 years. Flattened T waves showed strong independent prognostic power (Kannel 1986). Thereafter, many studies have demonstrated the negative impact of small deviations in the ST segment and T wave. Almost all of these studies have classified the abnormalities according to the Minnesota Code, and none of the studies have handled these abnormalities as continuous variables using a population-based approach. Even minor ST-T abnormalities are associated with increased long-term cardiovascular (CV) and total mortality (Greenland et al. 2003). Minnesota Code T wave abnormalities at age 50 were an independent

risk factor for development of major Q/QS abnormality and ST-segment depression (STD) 20 years later (Ström Möller 2006). Persistent ST-T abnormalities signify doubled mortality risk when compared with new or reverted abnormalities (Ström Möller et al. 2006).

In a Belgian general population study with 4,797 men and 4,320 women with no history of MI or major (MC 1.1-1.2) Q waves in the ECG, the prevalence of ischaemic ECG findings was 8.4% in men and 10.6% in women. The prevalence of isolated T wave inversions in this context was 4.5% in men and 6.4% in women. The majority of these ischaemic findings were T wave inversions, either alone (53.5% in men, and 60.5% in women) or together with STD (19.1% in men and 22.5% in women). The proportion of isolated STD among all ischaemic findings was 0.3% in men and 0% in women. STD together with T wave inversion was seen in 19.1% of men and 22.5% of women. The risk ratio for CV mortality in subjects with major ischaemic ECG changes (MC 4.1-2, 5.1-2 and 7) was 4.21 for men (95% CI 2.6–6.8) and 4.72 for women (95%CI 2.49–8.96) (DeBacquer et al. 1998).

In the Finnish SII Coronary Heart Disease Study with 5,738 men and 5,224 women, the prevalence of T wave inversion (at least 1mm, MC 5.1-2) was 5.5% in women and 3.0% in men. Large (at least 5mm) negative T waves (MC 5.1) were rare, occurring in 0.2% of the women and 0.2% of the men. An isoelectric T wave (MC 5.3) was present in 7.8% of women and 3.0% of men. If an isoelectric T wave appearing only in aVF was taken into account, the prevalence rates were 16.6% in women and 7.5% in men (Reunanen et al. 1983).

Subjects without MI but T wave inversion during the ischaemic phase had an increased risk of subsequent ischaemic events ($p<0.002$) (acute myocardial infarction, acute ischaemic syndrome, angina pectoris, silent ischaemia), inducible ischaemia (during treadmill test) and wall-motion abnormalities (demonstrated by echocardiography) compared to subjects with no T wave inversion during the ischaemic phase. The resolving of T waves occurred within 3–21 days of presentation (Simon et al. 1994).

Persistent negative T waves in infarct-related leads predict poor long-term prognosis after MI (Lancellotti et al. 2002). Sex-related differences in ECG after MI were studied among 838 subjects, with 216 women and 622 men. Women had significantly more T wave inversions in the anterior (38% vs 29%, $p=0.0012$) and lateral (63% vs 52%, $p=0.004$) locations, with no difference in regard to the inferior location when compared to men (Mieszczanska et al. 2008).

Left ventricular wall motion assessment was performed in a study of 265 patients, 61 with normal coronary arteries and 204 with CHD. The majority of the patients with ST segment depression or negative T waves had asynergy in ventriculography (Bär et al. 1984).

T wave abnormalities accompanying major or minor ST segment depressions in individuals with no evidence of MI have been found to be even better predictors of CV mortality than STD. In a study with 31,074 men (mean age 55 years) and a follow-up of six years, the combination of major abnormalities in ST segments and T waves carried the greatest hazard compared to subjects with no ST segment or T wave abnormalities (3.2 [CI 2.7–3.8]). Minor ST depression combined with more severe T wave abnormalities carried a hazard of 3.1 (CI 2.5–3.7), whereas minor T wave abnormalities combined with more severe ST depression carried a hazard of only 1.9 (CI 1.6–2.3)(Beckerman et al. 2005).

In a study consisting of retrospectively obtained ECGs from inpatient and outpatient men (n=41,997), the significance of the T wave was studied not as a categorical variable but as a continuous variable. CV mortality increased with decreasing T wave amplitude in limb lead I. This ECG parameter outperformed commonly used ECG indicators, including QRS duration, pathological Q waves, left ventricular hypertrophy and STD (Yamazaki et al. 2005).

In a retrospective study of 24,270 male patients, Tan et al. reported a 7.3% prevalence of positive T waves in lead aVR (aVRT+), indicating a relative risk (RR) of 5.0 for CV deaths. In the subset of 2,250 patients with clinical data available, the polarity of the T wave in lead aVR was independently associated with CV mortality after adjusting for other potential confounding variables, including LVH, STD, Long QT syndrome and Q waves. (Tan et al. 2008). Yet, no prospective population-based study of this topic is reported.

The prevalence of T wave abnormalities was studied among 1,710 adolescent athletes and 400 healthy controls aged 14–18 years. Subjects with T wave inversions underwent intensive cardiac investigations to identify a potential cause, but no cardiac abnormalities were found. There was no significant difference in the overall prevalence of T wave inversions between athletes and controls (4 vs. 3%; P = 0.46) (Papadakis et al. 2009).

ST depression with or without T wave abnormalities has been observed to associate with increased fatal coronary events and morbidity over a period of 30 years. Flattened T waves showed strong independent prognostic power. Despite the many possible causes and variable appearance of ST and T wave aberrations, their unexplained occurrence in asymptomatic persons often seems to imply a compromised coronary circulation (Kannel 1986).

In the Finnish SII Coronary Heart Disease Study including 136 men aged 40–59 years with negative T waves (MC 5.1-2), 37 (27.2%) men died within 5 years of follow-up, 20 of whom from CHD. The CHD mortality risk was highest in men with large negative T waves (risk ratio 23.0), but it was also high in men with 1–5mm negative T waves (MC 5.2; risk ratio 10.7). There was no basis for a reasonable analysis in women because only one with MC 5.2 died from CHD within 5 years of follow-up (Reunanen et al. 1983).

In summary, T wave abnormalities are the most common ischaemic changes alone or alongside STD in resting ECG. The reported prevalence of T wave inversion or isoelectric T waves is 5%–8% in women and 3–3.5% in men. There is an at least threefold adjusted mortality associated with T wave inversion. Among middle aged Finnish men with negative T wave, annual mortality is 5%. However, data from population-based studies analysing changes in T wave as a continuous, quantifiable variable is limited. Furthermore, there is no population-based data on the prevalence and prognosis of T inversion in lead aVR, aVRT+.

ST Segment

The ECG ST segment corresponds to the plateau of the ventricular action potential, representing the repolarisation phase of the myocardial cells. ST segment depression with or without associated T wave abnormalities is frequently encountered in various clinical situations and in the community (De Bacquer et al. 1998, Greenland et al. 2003, Strom Moller et al. 2007, Lauer et al. 2007). The prevalence of ST segment changes (MC 4.1-3) was 2.2% in men and 4.3% in women in the Finnish SII Coronary Heart Disease Study (Reunanen et al. 1983). While Q waves represent permanent damage to the myocardium, ST segment deviation and T wave inversions are thought to represent viable myocardium in jeopardy.

Increased fatal coronary events and morbidity have been associated with ST depression with or without T wave abnormalities over the follow-up period of 30 years. Flattened T waves have demonstrated strong independent prognostic power. Despite the many possible causes and variable appearance of ST and T wave aberrations, their unexplained occurrence in asymptomatic persons often seems to imply a compromised coronary circulation (Kannel 1986). In the SII Coronary Heart Disease Study, 33% of the men with ischaemic ST segment depressions died within 5 years of follow-up. Men with Q/QS changes included in the same study had a mortality of 22.7% in 5 years. Age-adjusted mean annual total and CHD death rates in men aged 40–59 years with ST changes were 6.2% and 3.3%, respectively. Among men with STD, the risk ratio for all-cause mortality was 6.0 and for CHD deaths 11.4 when compared to men without these changes. There was no basis for a reasonable analysis in women because only one woman with MC 4.1 died from CHD in 5 years of follow-up (Reunanen et al. 1983).

Sex-related differences in the diagnosis, treatment and prognosis of cardiovascular disease have received attention in preventive cardiology. In a study of 838 post-MI subjects (216 women, 622 men), ST segment depression (36% vs 19%, $p<0.001$) in the lateral leads (V5, V6, I and aVL) was significantly more common among women than among men (Mieszczanska et al. 2008). Minnesota codes indicating slightly "ischaemic ECG" (mainly minor ST segment depression and

T wave changes) have demonstrated a similarly increased risk for mortality in both women and men in population studies (De Bacquer et al. 1998, Greenland et al. 2003, Kumar et al. 2008), including the elderly (Rautaharju et al. 2006). However, none of the population-based studies have analysed changes in the ST segment as a continuous, quantifiable variable.

In addition to myocardial ischaemia and acute coronary syndrome, when the detrimental impact of even minor ST segment depression or T wave abnormality has been well documented (Jacobsen et al. 2005, Atar et al. 2007, Barrabes et al. 2000), the most common causes of ST segment depression are tachycardia due to the overlap with atrial repolarisation and delayed repolarisation secondary to slow depolarisation (e.g. ventricular hypertrophy, bundle branch block, pre-excitation) (Nikus et al. 2010). Regarding population-based studies, an association of major (Liao et al. 1987) or categorically defined minor (De Bacquer et al. 1998, Greenland et al. 2003, Kumar et al. 2008, Daviglus et al. 1999, Beckerman et al. 2005) abnormalities of the ST segment and T wave with a heightened risk of mortality or cardiovascular events have been reported.

The classic strain pattern, defined as a downward-sloping convex ST segment with inverted asymmetrical T waves opposite to the QRS axis in leads V5 and/or V6 on the ECG, is a well-recognised marker of the presence and severity of anatomic LVH. The strain pattern has been associated with an adverse prognosis in a variety of populations (Kannel 1983, Okin et al. 2004, Verdecchia et al. 1998), including hypertensive patients (Okin et al. 2004), and it has been designated as the primary marker of untoward outcomes when ECG LVH criteria are used for risk stratification (Okin et al. 2004, Verdecchia et al. 2007). Furthermore, the development of a new ECG strain was associated with an increased risk of cardiovascular morbidity and mortality in the setting of antihypertensive therapy and regression of ECG left ventricular hypertrophy in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study (Okin et al. 2009).

Despite the well-defined impact of LVH on the ST segment and mortality, none of the previous population-based studies have compared the association between minor ST segment changes and mortality in separate analyses for the entire study population and for those without LVH.

In summary, STD is associated with even higher mortality rates than Q waves. STD often appears with T wave inversion.

Ventricular Conduction Block (VCB)

In the early days of ECG, it was noticed that subjects with wide a QRS complex could live decades without remarkable symptoms (Einthoven 1924). Published data regarding the clinical and prognostic significance of intraventricular conduc-

Table 3.
Outcomes in subjects and patients with left bundle-branch block (LBBB)

Reference	n	Mean age (yrs)	Sample	Outcome
Rotman and Triebwasser 1975	237000	35	USAF pilots	No increased mortality for LBBB
Scheiner et al 1979	5209	50	Framingham	Increased mortality for LBBB
Östör et al 1981	19662	> 20	Copenhagen, population	Increased 4 -year mortality for LBBB
Freedman et al 1987	15609	55	Chronic CAD	Increased mortality for LBBB
Fahy et al 1996	100000	44	Screening	Increased prevalence of cardiovascular disease at follow-up, Increased cardiac mortality for LBBB+CAD, No differences in all-cause mortality for LBBB
Gil et al 1998	69	59	Normal dipyridamole thallium-201 scintigraphy	Very good prognosis (no MI, no death) during 2 year follow up
Eriksson et al 1998	855	70	Randon sample men, b. 1913	Increased mortality for LBBB only in conjunction with CAD
Hesse et al 2001	7073	60	Sterss testing	Increased all-cause mortality for LBBB
Brilakis et al 2001	894	76	Acute MI	Lower pre-discharge ejection fraction, Higher in-hospital and long term-unadjusted mortality
Baldasseroni et al 2002	5517	63	CHF	Increased 1-year mortality and sudden death
Stenestarnd et al 2004	88026	77	Acute MI	Increased unadjusted 1-year mortality
Guerrero et al 2005	3053	69	Acute MI	Increased in-hospital death for LBBB
Wong et al 2006	17073	68	Acute MI	Increased 30-day mortality for LBBB
Imanishi et al 2006	17361	69	Routine Screening/ Case-Control	No increased all-cause mortality for LBBB, Increased CHF mortality for LBBB
Tabritzini et al 2007	21685	75	Hospitalized CHF	Increased all-cause 1-, 5-, and 10 year mortality for LBBB. No increased mortality after adjusting for LFEF.
Barsheshet et al 2008	4102		Hospitalized CHF	Increased 1-year mortality on univariate analysis for LBBB and RBBB, Adjusting for multiple risk factors, only RBBB increased mortality.
Huvelle et al 2010	403		Hospitalized severe CHF	Increased 1-year mortality for LBBB with 4wk survivors
Lewinter et al 2011	6676		Acute MI	Increased multivariate adjusted all-cause mortality for LBBB and RBBB. Increased all-cause mortality for LBBB in patients with preserved LV systolic function.

CAD, coronary artery disease; MI, myocardial infarction; CHF, congestive heart failure; USAF, United States Air Force; LVEF, left ventricular ejection fraction.

tion delays (IVCD) are highly varied. The epidemiological data have mostly been derived from hospitalised patients with findings partly dependent on the characteristics of the patient cohort (McAnulty et al. 1978). In studies performed with healthy populations, findings concerning future cardiovascular (CV) events have not been consistent.

In the Framingham Heart Study, a newly acquired LBBB associated with five times greater CV mortality when compared to subjects without a LBBB. The CV mortality of the subjects with LBBB was 50% within 10 years of the onset of LBBB (Schneider et al. 1979). Meanwhile, LBBB did not increase CV death or CV morbidity when compared to RBBB among healthy subjects over 10 years' follow up (Rotman and Triebwasser 1975).

Accordingly, the prognostic implications of IVCDs depend on the category of conduction disturbance and on the population studied (Table 3).

In several studies on chronic and acute coronary artery disease, left bundle branch block (LBBB) was found to be an excellent predictor of mortality and future clinical events (Freedman et al. 1987, Guerrero et al. 2005, table 3). LBBB may also be a marker of structural heart disease, especially dilated cardiomyopathy (Dec et Fuster 1994, Miller et al. 2008). However, there is no consensus on LBBB-related prognosis in general populations (Francia et al. 2007). In a recent population study, right bundle branch block (RBBB) was associated with increased CV risk and all-cause mortality, whereas incomplete RBBB (IRBBB) was not (Bussink et al. 2013). Previous authors found no increased overall mortality in RBBB in the absence of clinically overt cardiac disease (Fahy et al. 1996).

In one population study, left anterior hemiblock (LAHB) was associated with cardiac morbidity and mortality (Miller et al. 2008), while other authors have considered LAHB in a healthy population as an incidental ECG finding (Elizari et al. 2007). In a population study on ECGs recorded 1966 –1972, a prolonged duration of the QRS complex in a 12-lead ECG and nonspecific IVCD was a predictor of mortality (Aro et al. 2011). Regarding the prognostic impact of incomplete LBBB (ILBBB), left posterior hemiblock (LPHB) or the R-R´ pattern in the general population, data is scarce or non-existent.

In general, the fact that the increasing number of heart failure patients who are potential candidates for cardiac resynchronisation therapy (CRT) is increasing has resulted in growing interest in IVCDs among clinicians (Dickstein et al. 2010). Interestingly, a wide QRS complex (>150ms) associated with LBBB is the most important selection criteria for CRT therapy in advanced heart failure (Brignole et al. 2013). In a recently published study, heart failure subjects with a narrow QRS complex and echocardiographically defined asynchrony did not benefit from CRT therapy (Ruschitzka et al. 2013).

Despite the negative result of the EchoCRT Study (Ruschitzka et al. 2013), Professor Carlo Pappone (Department of Arrhythmology, Villa Maria Cecilia Hospital, Cotignola, Italy) suggested that the goal width of the QRS complex obtained with CRT therapy should be much narrower, namely below 100ms. The proposed basis of the potential benefit related to very narrow QRS is the inhibition of re-entrytachycardia (Prof. Pappone's suggestion was made on Monday, 30 September 2013 at the Future of CRT congress in Prague, the Chech Republic).

Aims of the Thesis

One of the goals of the Health 2000 Survey was to gain updated data on cardiovascular diseases. As the manifestation of CHD has changed over time, it may have an influence on the penetration of ischaemic variables in resting ECG or other measurable parameters such as mean T wave amplitudes in a population (Kattainen et al. 2006). Treatment modalities have changed tremendously, which may reflect on the clinical manifestations and prognosis of diseases.

The aim of this thesis was to provide contemporary knowledge regarding the prevalence and prognostic value of certain abnormal ECG findings in a Finnish general population aged ≥30 years.

1. We examined the prevalence of PRWP in a general population as it has not been reported earlier. We studied the prognostic impact of PRWP in standard resting ECG in a Finnish general population separately for men and women in relation to the risk of all-cause and cardiovascular mortality. We studied the significance of PRWP among other risk factors **(I).**

2. We determined the sex-specific prognostic impact of quantitative measures of ST segment characteristics as well as ST slope and T wave amplitude in a population-based cohort **(II).**

3. We studied the prevalence of aVRT+ in the general population as it has not been reported in earlier works. We investigated the impact of aVRT+ on all cause and CV mortality. The significance of aVRT+ in relation to other risk factors was analysed **(III).**

4. We investigated the prognostic significance of eight different VCBs in a population-based cohort **(IV).**

Materials and Methods

The Health 2000 Survey

A random sample of the Finnish population was examined in 2000–2001 by comprehensive methods. After the field work, sub-populations were invited to attend several in-depth studies. This major collaborative effort was led by the National Public Health Institute of Finland (THL, previously KTL).

Study Population

The target population of the Health 2000 Survey consisted of individuals aged 18 or over and living in mainland Finland. In addition to the household population, people living in institutions were included. Geographically, the Autonomous Territory of Åland Islands was excluded, as were people living on islands not accessible by road. The Health 2000 involved two separate surveys: the main survey was carried out in the population aged 30 years or over, and the study of young adults focused on people aged 18–29. In order to obtain a sufficient number of observations from the oldest age cohorts in the main survey, people aged 80 or over were oversampled with a double sampling fraction. In other respects, the sampling design was similar in both studies. The sample was drawn at KELA, the Social Insurance Institution of Finland, using the population-wide insurance database as a sampling frame.

The main survey of the Health 2000 comprised 8,028 individuals (3,637 men and 4,391 women) aged 30+, 79% of whom (6,354 individuals, 2,876 men and 3,478 women) participated in the health examination including a resting ECG recording. The different aspects of data collection are clarified in Table 4. A detailed description of the materials and methods is available online (http://www.terveys2000.fi/doc/methodologyrep.pdf).

Table 4.
Different stages of data collection in the Health 2000 Survey. Adapted from Heistaro et al (2008).

	Number	%
Sample	8028	
deceased before field work	49	
Final sample	7979	100
Partipicants in home-visit interview	6986	87.6
Partipicants in health examination	6354	79.6
Symptoms interview	6238	78.2
measurements (including weight, height, ECG)	6351	79.6
laboratory	6354	79.6
clinical examination	6326	79.3
ECG obtained succesfully	6318	100
lost of ECG data	19	
ECG available for the study	6299	99.6

Blood Pressure and Heart Rate

Blood pressure was measured after the subjects had been seated quietly in the measurement room for at least five minutes (Heistaro 2008, p.60-61). Blood pressure was always measured from the right arm if possible. Prior to the measurement, a proper level of systolic pressure was determined by palpating the wrist artery. At the same time, heart rate was measured by counting the number of pulses from the artery in the wrist during 30 seconds. Measurements were taken with a standard mercury manometer (Mercuro 300; Speidel & Keller, Jungingen, Germany). The width of the rubber cuff was 12 cm and its length 35 cm. If the proximal circumference of the upper arm measured at a height of 5 cm from the crook of the aim was in excess of 35 cm, a larger cuff (width 15, length 43 cm) was used. Current instructions (Rose et al. 1982, Finnish Hypertension Society working group 2002) were followed in wrapping the cuff around the upper arm, positioning the bend of the elbow at the level of the heart and listening to the Korotkoff sounds.

For the proper blood pressure measurements, the mercury column was raised either to the level of 180 mmHg or 30 mmHg above that level at which the pulse disappeared, if the systolic pressure measured at the wrist was higher than

150 mmHg. The pressure was then steadily released at 2–3 mmHg per second. Systolic pressure was recorded at the appearance of the first Korotkoff sounds to an accuracy of 2 mmHg. Diastolic pressure was also recorded to an accuracy of 2 mmHg at the fifth phase of the Korotkoff sounds, when the latter of two consecutive sounds was no longer audible. The same instructions were followed when a second set of readings was taken two minutes after the first measurement. The average of the two measurements was used in the analysis. The quality of blood pressure and heart rate measurements was constantly monitored during the field examinations and in connection with separate quality control checks during which measurements were taken from people who were not included in the study population.

Height, Weight, BMI and Waist Circumference

Height was measured using a wall-mounted stadiometer (Person-Check, Medizintechnik, KaWe, Kirchner & Wilhelm, Germany). The subjects stood upright with the feet together, head up and back against the wall. Height was preferably measured without socks, but thin socks were allowed depending on the circumstances. Height was recorded to an accuracy of 0.5 cm. Weight (in under pants) was measured to the nearest 0.1 kg. Body mass index (BMI) was calculated as weight (kg) divided by height (meters) squared.

Waist circumference was measured in a standing position, with the legs slightly apart. The recommendations for anthropometric measurements in population studies were observed (Seidell et al. 2001). The horizontal waist position was determined as the mid-point between the lowest rib bones and the high point of the iliac crest, i.e. strictly on the basis of bony points of reference. Circumference measurements were recorded to an accuracy of 0.5 cm.

Resting ECG

Among 6,354 subjects attending the health examination, there were 36 for whom an ECG was not possible to obtain. The reasons for not succeeding were recorded by the investigators with entries such as “difficult to move,” “wheelchair”, “denial”, “leg/hand amputated”, “in geriatric chair”, “massive hernia”, “plaster in leg/hand”. 6,318 ECGs were obtained successfully (99% of the individuals attending the health examination). In the further process, 19 ECGs were lost (diskette lost 9, coupling error 4, data reading failure 5, unspecific reason 1), leaving 6,299 ECG recordings for the analysis (Table 4).

Standard 12-lead ECGs were recorded in the resting supine position using recommended standardised procedures (Rose et al. 1982). Recordings were taken using a MAC 5000 recorder (by Marquette Hellige, Freiburg, Germany and Milwaukee, WI, USA). ECG was recorded, stored on 2HD diskettes and printed using a paper speed of 50 mm/sec. The maximal filter setting of the system (150 Hz) was used.

Heavy skin hair especially on the chest was shaved if necessary, but as a general rule no other procedures were applied to the skin. Disposable electrodes were used as far as possible throughout the examination, but on a few occasions these ran out and reusable electrodes had to be used. If the subject had a fully or partly amputated limb, the limb electrode was attached to the amputated stub. If the technical quality of the ECG recording was not satisfactory, a new recording was taken, possibly after checking the attachment of the electrodes.

ECG data were stored electronically and transmitted in dispatches of approximately 100 ECGs per transmission to the National Institute for Health and Welfare for further analysis and for storage in a local network server system (MUSE CV, Marquette Electronics Inc., Milwaukee, WI, USA). This digital data was re-analysed with Magellan program (Marquette Electronics Inc. Milwaukee, WI, USA) and measure points suggested by the program were checked and manually corrected if needed.

As opposed to human ECG reader, which may inspect the QRS duration in any single lead of the ECG, the computer measures the QRS duration as a global interval. This way the computer programme defines the earliest depolarisation in any lead (QRS onset) and as a result the isoelectric point. Measurements by Magellan program (Marquette Electronics Inc. Milwaukee, WI, USA) yielded excel-data from every ECG-recording with amplitudes and time intervals.

Minnesota Coding classifications were obtained by two researchers at the Institute of Cardiology, Kaunas Medical Academy, Lithuania. The researchers were also blinded to the clinical data of the patient. Abnormalities identified visually in the ECG strips were coded in accordance with the Minnesota coding scheme (Prineas et al. 1982). Accordingly repeatability of ECG coding was examined and no systematical intra- or interindividual coding differences were observed.

The Minnesota coding was accepted if the individual ECG strip got two identical coding. Discrepancies were solved by consensus decisions by the researchers.

ECG Classifications

The ECG variables are summarised in Table 5.

Table 5.
Summary and definition of used ECG variables.

Variable	Abbreviation	Definition	Paper
Poor R wave progression	PRWP	RV3 ≤ 3 mm and RV2 ≤ RV3 *	I
Left bundle branch block	LBBB	Minnesota code 7.1	I, II, III, IV
Right bundle branch block	RBBB	Minnesota code 7.2	I, II, III, IV
Incomplete RBBB	IRBBB	Minnesota code 7.3	I, II, IV
Incomplete LBBB	ILBBB	Minnesota code 7.6	I, II, IV
Left anterior hemiblock	LAHB	Minnesota code 7.7	I, II, III
Left anterior hemiblock	LAHB	Frontal QRS axis between -30° and -90° , rS configuration in II, III and aVF, and qR configuration in aVL, with a QRS duration less than 120ms **	IV
Q waves		Minnesota code 1.1-1.3	I, II, III
Wolff-Parkinson-White	WPW	Minnesota code 6.4	I, II, III
Pacemaker		Minnesota code 6.8	I
Left ventricular hypertrophy	LVH	Minnesota code 3.1, 3.3-3.4	I, II
Right ventricular hypertrophy	RVH	Minnesota code 3.2-3.4	I, II
Anterior group		Leads V1-V4	II
Lateral group		Leads V5-V6, I, aVL	II
Inferior group		Leads I, II, III	II
Positive T wave in lead aVR	aVRT+	T wave amplitude in lead aVR ≥0 mm (isoelectric or positive deflection)	III
Negative T wave in lead aVR	aVRT-	T wave amplitude in lead aVR <0 mm (negative deflection)	III
Atrial fibrillation	AF	Minnesota code 8.3	III
Non-spesific ventricular block		Minnesota code 7.4	IV
R-R`-pattern		R-R´ pattern in either of the leads V1-V2 with R´>R, Minnesota code 7.5	IV
Left posterior hemiblock	LPHB	Frontal QRS axis >120°, lead I rS configuration, leads II, III and aVF qR configuration, and no pathological Q-waves in leads II, III, avF **	IV

* Zema et al. 1980, ** Castellanos and Lemberg 1971

Spirometry

In population studies, spirometry has been used for the purposes of monitoring respiratory inadequacies and measuring respiratory function (Aromaa et al. 1985). Spirometry tests are essential in the assessment of asthma and chronic obstructive pulmonary disease and they are fundamental part of the routine differential diagnostics arsenal in AP related symptoms (Rekiaro 1997). Flow-volume spirometry is a sensitive method that may allow the early detection of changes in the respiratory tract caused by smoking. Measurements for the Health 2000 Survey were taken with a Vitalograph 2150 bellow spirometer. The key measurements taken were: forced vital capacity (FVC), forced expiratory volume in one second (FEV1) and forced expiratory volume in one second percentage (FEV%).

Laboratory tests

Venous blood samples were drawn from the antecubital vein. Serum high-density lipoprotein (HDL) cholesterol, total cholesterol, triglyceride and plasma glucose concentrations were determined enzymatically (Roche Diagnostics, GmbH, Mannheim, Germany for HDL; Olympus System Reagent, Hamburg, Germany, for total cholesterol, triglycerides, and glucose) from venous blood with a clinical chemistry analyser (Olympus, AU400, Hamburg, Germany). Low-density lipoprotein (LDL) cholesterol was calculated with the Friedewald formula.

The serum uric acid concentration was determined enzymatically (Urikaasi PAP, Konelab, Thermo Electron Oy, Vantaa, Finland). High-sensitivity C-reactive protein concentrations were determined using a chemiluminescent immunometric assay (Immulite, Diagnostic Products Corporation, Los Angeles, California). The gamma-glutamyltransferase activity concentration was determined enzymatically according to the International Federation of Clinical Chemistry (Gamma-GT, Konelab, Thermo Electron Oy, Vantaa, Finland).

The determinations were made from frozen samples within six months of sampling. The quality of the results of the analysis series was ascertained by using controls, which were used to determine interassay coefficients of variation. The laboratories took part in Labquality's External Quality Assessment schemes. The accuracy of the methods (bias%) was calculated as the mean of the Short-term programme organised by Labquality.

Smoking

Smoking was defined as the daily use of tobacco products.

Classification of CHD MI and UMI

The classification of CHD required at least ≥1 of the following: diagnosis of MI and/or AP during the field health examination by a physician, large Q waves in ECG at rest, hospitalisation for CHD (*International Classification of Diseases, Eighth Revision* [ICD-8] or *Ninth Revision* [ICD-9] codes 410 to 414 or *Tenth Revision* [ICD-10] codes I20 to I25), history of a coronary revascularisation procedure, right to drug reimbursements for CHD, or use of nitroglycerin combined with an anticoagulant, acetyl salicylic acid or β-blocker.

The classification of MI required a clinical diagnosis of an old MI by the examining physician, large Q waves in ECG at rest or a previous discharge diagnosis of MI (ICD-8 or ICD-9 code 410 or ICD-10 codes I21 to I22). MI was defined as a positive history of the condition in medical records, an old MI in ECG or a typical self-reported history of MI treated in a hospital. Large Q waves indicating a probable previous MI included Minnesota Codes 1.1 to 1.3.

The classification of RMI required a previous discharge diagnosis of MI (ICD-8 or ICD-9 code 410 or ICD-10 codes I21 to I22) or a typical self-reported history of MI or severe AP lasting 30 minutes or longer (Rose and Blackburn 1966) and diagnosis of old MI by the examining physician. The classification of UMI required classification of MI with large Q waves indicating MI (MC 1.1 or 1.2 with MC 5.1-2) in conjugation with no history of hospitalization because of MI, no self-reported history of MI and no history of severe AP lasting 30 minutes or longer (Table 7).

Classification of Heart Failure, Stroke and Peripheral Arterial Disease

A heart failure classification required a clinical diagnosis by the examining physician and a previous discharge diagnosis of heart failure (ICD-8 code 4270, ICD-9 code 428, or ICD-10 code I50) or the right to drug reimbursements for heart failure. Almost without exception, the classification for stroke required ≥1 discharge diagnosis of stroke (ICD-8 codes 430 to 431, 433 to 434, ICD-9 codes 430 to 434, or ICD-10 codes I60, I61, I63). The classification of peripheral arterial disease required a clinical diagnosis by the examining physician or a previous hospitalisation for peripheral arterial disease.

Definition of Diabetes Mellitus and Chronic Obstructive Pulmonary Disease

Diabetes mellitus was defined as a serum glucose level of ≥ 7.0 mmol/L or a history of use of oral hypoglycaemic agents or insulin injections. A chronic obstructive pulmonary disease classification required a clinical diagnosis by the examining physician including bronchial obstruction in lung function tests (forced expiratory volume <70%) or previous hospitalisation for chronic obstructive pulmonary disease (ICD-8or ICD-9 codes 490 to 492 or ICD-10 code J44).

Table 6.
Diseases causing cardiovascular death in Health 2000 Survey

Diagnosis	ICD-10 code	n = 277	%
Hypertension	I10 - I11	4	1.5
Acute myocardial infarction	I21 - I22	75	27
Other form of coronary heart disease	I25	90	32.5
Pulmonal embolism and deep venous trombosis	I26, I80	5	1.8
Mitral regurgitation	I34	3	1.1
Aortic valve disease	I35	9	3.4
Tricuspid valve regurgitation	I36	1	0.3
Cardiomyopathy and other heart diseases	I40 -I42, I51	15	5.5
Arytmia	I46 - I48	3	1.1
Heart failure	I50	3	1.1
Stroke and other cerebrovascular diseases	I60 - I61, I63 - I69	53	19.1
Other forms of atherosclerosis and aortic aneurysm/dissection	I70 - I71	16	5.8

Follow-up 98.5 months (interquartile range 96.6 to 99.6). Unpublished data.

Data Protection and Ethical Approval

A major consideration at all stages of the Health 2000 Survey was the provision of data protection and the appropriate handling and storage of all data and materials collected. Every possible precaution was taken to prevent unauthorised access. In the examination files, personal data were replaced by examination codes; even the researchers analysing the final data no longer have access to any personal data. However, since these data will be needed for follow-up purposes as well as for linking with other data, they are accessible to a small number of authorised personnel for these specific purposes. The plans and protocols for the Health 2000 Survey

were submitted for approval to the relevant ethical committees. The application was first reviewed by the National Public Health Institute's Ethical Committee in September 1999. Following changes in legislation, the more detailed project plan was submitted to the Ethical Committee for Research in Epidemiology and Public Health at the Hospital District of Helsinki and Uusimaa (HUS) in May 2000. At both these stages, the plans received favourable opinions. An information letter was handed out to the subjects in connection with the home interviews by Statistics Finland staff and later in connection with the health examinations. Trained staff were available in both situations to answer any questions. Once the subjects had read the information letter, they were asked to sign the informed consent form.

Data Obtained from Registers

Data were extracted from various register sources to complement the main body of data collected in the field examinations. At all stages of the register data process, special attention was given to data protection. This was ensured by close adherence to the relevant legislation, the rules of the National Public Health Institute and the bodies maintaining the registers, and the guidelines of good research practice. The linking of register data was designed and carried out in close co-operation between the project organisation and the bodies maintaining the registers concerned. The most important data items linked to the field materials concern causes of death, hospital treatments, entitlements to special medication reimbursements and certain other illness-related benefits, purchases of prescribed medicines, cancers, work disability and employment as well as housing. The validity of the data obtained from the Finnish Hospital Discharge Register and the Causes of Death Register are adequate for study purposes (Pajunen et al. 2005).

Study of PRWP and Quantitative ST Segment Analysis

The ECG analysis was based on 5,613 participants comprising 3,151 female and 2,462 male subjects. Patients with ventricular conduction defects, mainly LBBB, RBBB or LAH, were excluded (MC 7) as was one individual with ECG signs of Wolff-Parkinson-White syndrome. Prognostic analysis was performed with and without patients with suspected pathological Q/QS in ECG MC 1.1-1.3. The definition of PRWP was based on the criterion first adopted by Zema et al. (1980) as an R wave in the precordial lead V3≤3mm and R in lead V2≤ R in lead V3.

The lead groups used in the quantitative ST segment analysis were anterior (V1–V4), lateral (V5, V6, I, aVL) and inferior (II, III, aVF). V5 as a single lead

is shown for comparison. Automated computer analysis using Magellan software (Marquette Electronics Inc., Millwaukee, WI, USA) was used to determine measurement points. The software uses information of the all ECG leads to determine QRS onset point and QRS offset point in a single lead in order to determine isoelectric baseline. Four measurement points along the ST segment were used for the determination of ST segment deviation: the J point as well as 40 and 80 ms thereafter, and, additionally, the lower of the deviations at J point and J + 80 ms. ST slope was defined as the difference between the ST segment deviation at J + 80 ms and J point. The ST segments with a maximum shift of less than 0.5 mm were labelled as horizontal, those with a positive change of > 0.5 mm as having a positive slope (ascending), and those with a negative change of > 0.5 mm as having a negative slope (descending).

Study of aVRT+

Subjects with atrial fibrillation, a cardiac pacemaker, pre-excitation and RBBB or LBBB were excluded (Minnesota Codes 6.4, 6.8, 7.1 to 7.2, 7.8, 8.3). The final analysis was performed with 6,063 subjects (3,330 women and 2,733 men). T wave amplitude was automatically measured using Magellan software (Marquette Electronics Inc., Millwaukee, WI, USA). Isolectric baseline was determined asa line between QRS onset point and QRS offset point. The maximum positive amplitude of the T wave was measured and considered as a T wave amplitude. We defined aVRT+ as aVRT ≥0 mm (isoelectric or positive deflection). Negative aVRT (aVRT-) was defined as aVRT <0 mm. Data were categorised into 2 groups according to aVRT: the aVRT+ group (aVRT ≥0 mm) and the aVRT- group (aVRT <0 mm).

Study of VCD

No subjects were excluded based on ECG findings. Individuals with a cardiac pacemaker (N=4) were also included. The final analysis was performed with 6,299 subjects: 3,442 women and 2,857 men.

For the identification of different ventricular conduction blocks, both Minnesota codes (Prineas et al. 1982) and measurements based on the Magellan software programme were used. Six of the conduction blocks were classified according to the respective Minnesota classes: LBBB (code 7-1), RBBB (code 7-2), IRBBB (code 7-3), non-specific IVCD (code 7-4), the R-R' pattern in either of the leads V1 or V2 with an R' amplitude of ≥ R (R-R' pattern; code 7-5) and ILBBB (code 7-6). For left anterior hemiblock (LAHB), we used the following definition:

frontal QRS axis between -30° and -90°; an rS configuration in II, III and aVF; and a qR configuration in aVL, with a QRS duration of less than 120ms (Castellanos and Lemberg 1971). Left posterior hemiblock (LPHB) was defined as a frontal QRS axis of >120°; rS configuration in lead I; qR configuration in leads II, III and aVF; and no pathological Q waves in leads II, III and avF (Castellanos and Lemberg 1971).

The accuracy of the classification of LAHB, LPHB, non-specific ventricular block, partial RBBB and the R-R' pattern was checked by means of a manual ECG analysis by two of the investigators (PH, KN). The classifications proved to be accurate.

Data was categorised into two groups according to the presence of IVCD: the IVCD- group (no ventricular conduction delay) and the IVCD+ group (subjects with ventricular conduction delay).

End Points and Follow-Up Data

Mortality data was gathered by linking the personal identity code from the Health 2000 Survey database to the Causes of Death Register maintained by Statistic Finland, which records 100% of the deaths of Finnish citizens who die in Finland and nearly 100% of those occurring abroad. In studies I and II, mortality data was available until October 2006 and the follow-up period was 72.4 months (interquartile range 70.8–73.2 months). In studies **III** and **IV**, the follow-up period was 98.5 months (interquartile range 96.6–99.6) and mortality information was available until January 2009. The cause of death was classified as cardiovascular death if one of the following ICD-10 codes was registered as the cause of death: I00–I99 (Table 6).

Statistical Methods

For the analyses of prevalence, the data were weighted to reduce the bias due to non-response and to correct for the over-sampling in the age group of 80 years and older. The complex sampling design was taken into account by using SUDAAN procedures version 10.0 (SUDAAN Language Manual; RTI International, Research Triangle Park, NC). The rest of the statistical analyses were performed with SPSS releases 15.0 to 19.0 for Windows (SPSS Inc., Chicago, Illinois) and SAS version 9.1 (SAS Institute, Inc., Cary, NC). Statistical significance was based on $P < 0.05$.

The difference in the prevalence of PRWP **(I)** between the sexes was determined with logistic regression using PRWP as a dependent and sex as an independent variable. The same method was used with aVRT+ **(III)**.

Comparisons between variables were calculated with either the *t* test for independent samples or the chi-square test for dichotomous variables. Receiver operating characteristic curve analysis was used to determine the ability of aVRT+ to distinguish between subjects with and without CV mortality during follow-up **(III)**.

Cox proportional hazards models were constructed for the variables PRWP **(I)**, maximum ST segment depression, minimum T wave amplitude and ST slope **(II),** aVRT+ **(III)** and VCBs **(IV)**. The end-point was all-cause death or cardiovascular death, and the models included the following covariates: age and CHD **(I, II, III, IV)**, MI **(I, II, IV)**, hypertension and diabetes mellitus **(I, III, IV),** sex, smoking, heart failure, total cholesterol, HDL cholesterol, LDL cholesterol and body mass index **(III, IV)**, left or right ventricular hypertrophy, Q waves, ST segment depression in lead V5 and heart rate **(III)**, and triglycerides **(IV)**.

Analyses and power calculations for ST segment depression and slope as well as T wave amplitude **(II)** and PRWP **(I)** were performed for Cox regression separately for men and women. With a two-sided alpha of 0.05, the standard deviation of ST segment depression as well as the number of subjects and cardiovascular deaths, the power to reach a clinically meaningful relative risk of 1.5 was 100% for both sexes. For PRWP, the power to reach a clinically meaningful relative risk of 1.5 was 90% for men and 100% for women.

Results

General Results

The proportion of UMI was higher in women (11.8.5%) than in men (6.5%). Q waves were present in 19.4%% of the men and 10.4% of the women with RMI (Table 7).

Table 7.
Prevalence of UMI and RMI in the Health 2000 Survey

	Men (n=2857) n (%)	Women (n=3442) n (%)
All MIs	124	68
RMI	96 (77.4)	48(70.6)
– QWMI (MC1.1-2)	18(14.5)	5(7.4)
– NQWMI (by MC1.1-2)	78(62.9)	43(63.2)
UMI	8(6.5)	8(11.8)

RMI = recognized myocardial infarction; UMI = unrecognized myocrdial infarction; QWMI = Q wave infarction; NQWMI = non Q-wave infarction. Unpublished data.

A summary of mortality data based on the ECG variables used in this study is seen in Table 8. During the follow-up of 98.5 months (Study **I** and **II** had 71 months), 640 subjects died (10.2%); 277 (4.4%) of these deaths were cardiovascular deaths (Table 8). After 8 years, almost 40% of the subjects with RMI had died mainly due to CV diseases. Half of the women and the men with UMI died during the follow-up. As a group, those with LBBB, RBBB, FA, ST segment depression and aVRT+ had a significant all-cause mortality rate ranging from 30% to 70%. Mortality in the FA group was 70% among women and 53% among men.

Table 8.
Mortality according to baseline ECG in the Health 2000 survey

	men (n=2857)		women (n=3442)	
	CV mortality n (%)	total mortality n (%)	CV mortality n (%)	total mortality n (%)
All included	143 (5)	313 (11)	134 (3.9)	327 (9.5)
MI	34 (27.4)	54 (43.5)	19 (27.9)	29 (42.6)
RMI	28 (29.2)	39 (40.6)	12 (25.0)	18 (37.5)
– QWMI (MC 1.1-2)	3 (16.7)	7 (38.9)	2 (40)	4 (80)
– QWMI (MC1.1-3)	7 (25.9)	12 (30.8)	2 (28.6)	4 (57.1)
– NQWMI (MC1.1-2 excluded)	25 (32.1)	32 (41)	10 (23.3)	14 (32.6)
UMI (by MC 1.1-2)	2 (25.0)	4 (50.0)	4 (50.0)	5(62.5)
aVRT+	25 (36.2)	31 (44.9)	21 (25.0)	35 (41.7)
FA	12 (25.5)	25 (53.2)	22 (46.8)	33 (70.2)
PRWP	8 (11.6)	14 (20.3)	16 (7.3)	30 (13.8)
LBBB	9 (30.0)	12 (40.0)	10 (26.3)	19 (50.0)
RBBB	9 (19.1)	16 (34.0)	4 (14.3)	9 (32.1)
STD (MC 4)	21 (27.6)	33 (43.4)	39 (31.7)	59 (48.0)
LVH (MC 3.1-3)	34 (5.8)	59 (10.1)	31 (9.2)	53 (15.8)

Follow-up 8.2 years (interquartile range 8.1 to 8.3). See text for abbreviations and classifications. Unpublished data.

Poor R Wave Progression (Study I)

Prevalence

PRWP was more frequent in women than in men for all the age groups. Altogether, there were 287 subjects with PRWP in their resting ECG, representing 2.7% of the men and 7.0% of the women ($P < 0.001$ for difference between men and women). Women were significantly more prone to have PRWP than men (odds ratio 2.58, $P < 0.001$ in logistic regression, figure 7).

Men and women with PRWP were older and had more diabetes, CHD and previous MIs than did those without PRWP, while for hypertension such a difference between the groups only applied to females (Table 9). A total of 787 persons

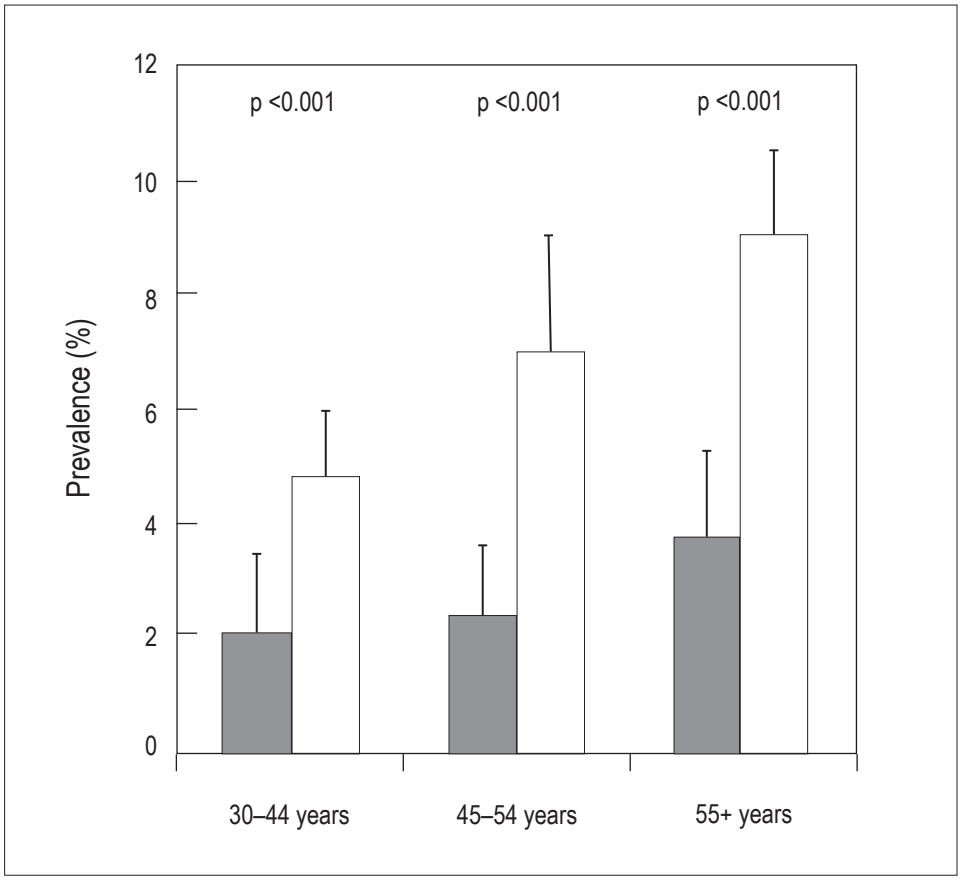


Figure 7.
Prevalence of PRWP in the three age groups among men (black bars) and women (white bars); the upper 95% confidence interval limits and the significance of the difference between genders are shown (chi-square test) (I). Anttila I, Nikus K, Nieminen T et al., Annals of Medicine, 2010; 42:135-142, copyright © 2010, Informa Healthcare. Reproduced with permission of Informa Healthcare.

Table 9.
Clinical characteristics and mortality of the study population (I)

	Men			Women		
	PRWP- n (%)	PRWP+ n (%)	p	PRWP- n (%)	PRWP+ n (%)	p
Regular smoking	658 (27.6)	25 (36.2)	0.13	490 (16.8)	41 (18.9)	0.45
COPD	35 (1.5	2 (2.9)	0,28	33 (1.1)	4 (1.8)	0.32
Hypertension	713 (29.9)	23 (33.3)	0.59	851 (29.1)	88 (40.6)	<0.01
Diabetes	122 (5.1)	8 (11.6)	0,03	141 (4.8)	25 (11.5)	<0.001
LVH/RVH	503 (21.1)	11 (15.9)	0.07	284 (9.7)	22 (10.1)	0.16
CHD						
– No	2159 (90.2)	52 (75.4)		2652 (90.4)	188 (86.2)	
– Possible	35 (1.5)	0 (0)	<0.001	72 (2.5)	6 (2.8)	0.10
– Yes	199 (8.3)	17 (24.6)		209 (7.1)	24 (11.0)	
MI						
– No	2304 (96.3)	60 (87)		2876 (98.1)	207 (95)	
– Possible	18 (0.8)	2 (2.9)	<0.001	12 (0.4)	3 (1.4)	<0.01
– Yes	71 (3)	7 (10.1)		45 (1.5)	8 (3.7)	
Medication						
– Beta-blocker	258 (10.8)	16 (23.2)	<0.01	426 (14.5)	46 (21.1)	0.01
– Ccb	121 (5.1)	4 (5.8)	0.78	177 (6.0)	19 (8.7)	0.14
– ACI/ARB	188 (7.9)	8 (11.6)	0.26	227 (7.7)	20 (9.2)	0.43
Death, all-cause	149 (6.2)	10 (14.5)	0,01	135 (4.6)	23 (10.6)	<0.01
Death, cardiovascular	60 (2.5)	5 (7.2)	0.03	44 (1.5)	11 (5)	<0.01

Follow-up of 6.0 years (interquartile range 5.9-6.1 years). PRWP- = no poor R wave progression; PRWP+ = poor R wave progression; COPD = chronic obstructive pulmonary disease; LVH = left ventricular hypertrophy; RVH = right ventricular hypertrophy; CHD = coronary heart disease; MI = myocardial infarction; Ccb = calcium channel blocker; ACI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor antagonist. Anttila I, Nikus K, Nieminen T et al., Annals of Medicine, 2010; 42:135-142, copyright © 2010, Informa Healthcare. Reproduced with permission of Informa Healthcare.

(14.0%) fulfilled the Minnesota criteria for left or right ventricular hypertrophy (Minnesota code 3.1 and/or 3.3). Thirty-three (4%) individuals with and 254 (5.3%) without ECG markers of ventricular hypertrophy fulfilled the criteria for PRWP. A negative P wave in leads V2 and/or V3 was observed in 65 individuals (1.2%), wit 36 women and 29 men.

Prognosis

Both all-cause and cardiovascular mortality was higher in the group with PRWP than in those without PRWP in both women and men (Table 9).

In Cox regression analysis after adjustment for age, the relative risk of all-cause mortality for PRWP was 1.89 (95% CI 1.00–3.59, P = 0.051) for men and 2.22 (95% CI 1.42–3.46, P = 0.001) for women. For cardiovascular mortality, the relative risk for individuals with PRWP was 2.28 (0.91–5.68, P = 0.08) for men and 3.47 (1.78–6.76, P = 0.001) for women. When individuals with previous MI (n = 166) were excluded, the results remained essentially similar: the relative risk for all-cause mortality for PRWP was 1.78 (95% CI 0.83–3.80, P = 0.14) for men and 2.44 (95% CI 1.54–3.89, P = 0.001) for women; for cardiovascular mortality, the relative risk was 1.33 (0.32–5.49, P = 0.69) for men and 3.57 (95% CI 1.71–7.42, P = 0.001) for women. When individuals with ventricular hypertrophy were excluded from the analyses, the relative risk for all-cause mortality was 1.78 (95% CI 0.87–3.64, P = 0.12) for men and 2.31 (1.42–3.76, P = 0.001) for women.

In Cox regression analysis after adjustment for age, hypertension, diabetes, previous MI and CHD, the relative risk of all-cause mortality for PRWP was 1.69 (95% CI 0.89–3.22, P = 0.112) for men and 2.00 (95% CI 1.28–3.13, P = 0.002) for women. For cardiovascular mortality, the relative risk for individuals with PRWP was 1.85 (0.74– 4.65, P = 0.19) for men and 3.02 (1.54–5.93, P = 0.001) for women.

Quantitative ST Segment Changes and T Wave Amplitude (Study II)

Participant characteristics are given in Tables 10 and 11. The minimum ST segment levels and T wave amplitudes for men and women within all the three age groups, separately, are reported in Table 12. Women presented slightly lower ST segment levels than men in most lead groups. T wave amplitude was clearly decreased in women in comparison to men in the anterior leads and, to a lesser degree, in the lateral leads, while men had somewhat lower amplitudes in the inferior leads. Most of the differences were statistically significant in our large study

Table 10.
Patient characteristics for continuous parameters (II).

	Men					Women				
	No CV death (n=2397)		CV death (n=65)			No CV death (n=3096)		CV death (n=55)		
	Mean	SD	Mean	SD	P	Mean	SD	Mean	SD	P
Age	50	13	68	13	0.000	52	15	77	9	0.000
Height (cm)	176	7	171	8	0.000	162	7	156	7	0.000
Weight (kg)	84	14	78	12	0.000	70	14	69	16	0.268
BMI	27.1	4.1	26.5	3.6	0.145	26.8	5.1	28.1	5.2	0.073
fS-Gluk (mmol/l)	5.7	1.3	6.6	3.1	0.000	5.4	1.1	6.6	2.2	0.000
fS-Kol (mmol/l)	6.0	1.1	6.0	1.1	0.731	5.9	1.1	6.4	1.2	0.016
fS-Kol-HDL (mmol/l)	1.2	0.3	1.1	0.3	0.019	1.4	0.4	1.4	0.4	0.008
fS-Kol-LDL (mmol/l)	3.9	1.0	3.9	1.1	0.793	3.6	1.0	3.9	1.2	0.072
fS-Trigly (mmol/l)	1.8	1.2	2.0	1.4	0.239	1.4	0.7	2.0	1.1	0.000

SD, standard deviation; BMI, body mass index; fS-Gluk, fasting serum glucose; fS-Kol, fasting serum cholesterol; fS-Kol-HDL, fasting serum high density lipoprotein cholesterol; fS-Kol-LDL, fasting serum low density lipoprotein cholesterol

population, even though several of the margins would not be clinically discernible. Among individuals < 55 years old, a negative ST slope was infrequent (< 1%) except in inferior leads.

ST Segment and T Wave Amplitude in Relation to Cardiovascular Mortality

The median follow-up period was 72.4 months (interquartile range 70.8–73.2 months). A total of 317 deaths (5.6% of the population) were registered, and 120 (2.1%) of those were of cardiovascular causes. Cardiovascular mortality was 0.37%/year. The diseases causing cardiovascular deaths were acute myocardial infarction (ICD-10 codes I21–I22), 37 patients; other manifestations of CHD (I25), 35; heart failure (I50), 1; other forms of heart disease (I10, I34–I42), 12; cerebrovascular diseases (I60, I61, I63–I69), 26; other forms of atherosclerosis and aortic aneurysm/dissection (I70-I71), 7; and deep vein thrombosis/pulmonary embolism (I26, I80), 2.

Among women, ST segment deviation in lateral leads as well as the single lead V5 yielded uniform and highly significant (P < 0.01) predictivity for all four

measurement points, and all lead groups had at least one prognostic measurement point (Figure 8). None of the lead groups and measurement points for ST segment deviation were a significant predictor among men (Figure 8a). Minimum T wave amplitude in lateral leads and lead V5 bore prognostic information among women but not among men (Figure 8b).

In unadjusted analyses, a high incidence of cardiovascular deaths characterised the patient group with the lowest ST segment tertile and horizontal or negative

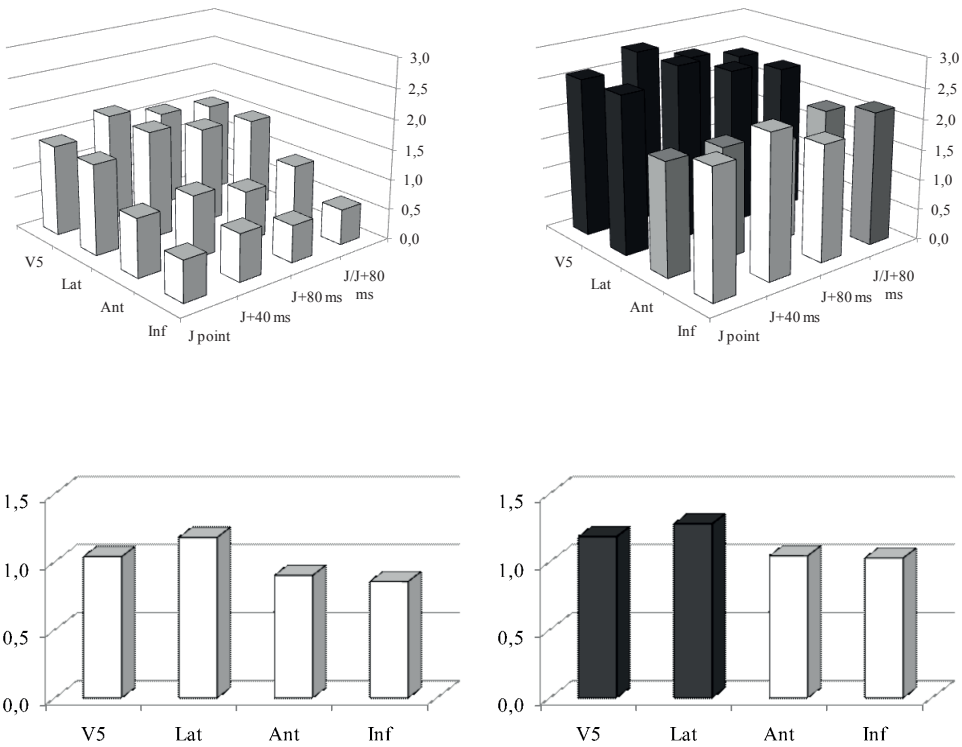


Figure 8.
Left: men, right: women.

Upper (a): Adjusted Cox-regression hazard ratios for ST-segment deviation divided by the lead group and measurement point. Three different bar colors are used: the darkest for p<0.01, gray for p<0.05 and the lightest for non-significant hazard ratios. Hazard ratios are scaled for a change of 1 mm.
Lower (b): Adjusted Cox-regression hazard ratios for minimum T-wave amplitude in separate lead groups (II).
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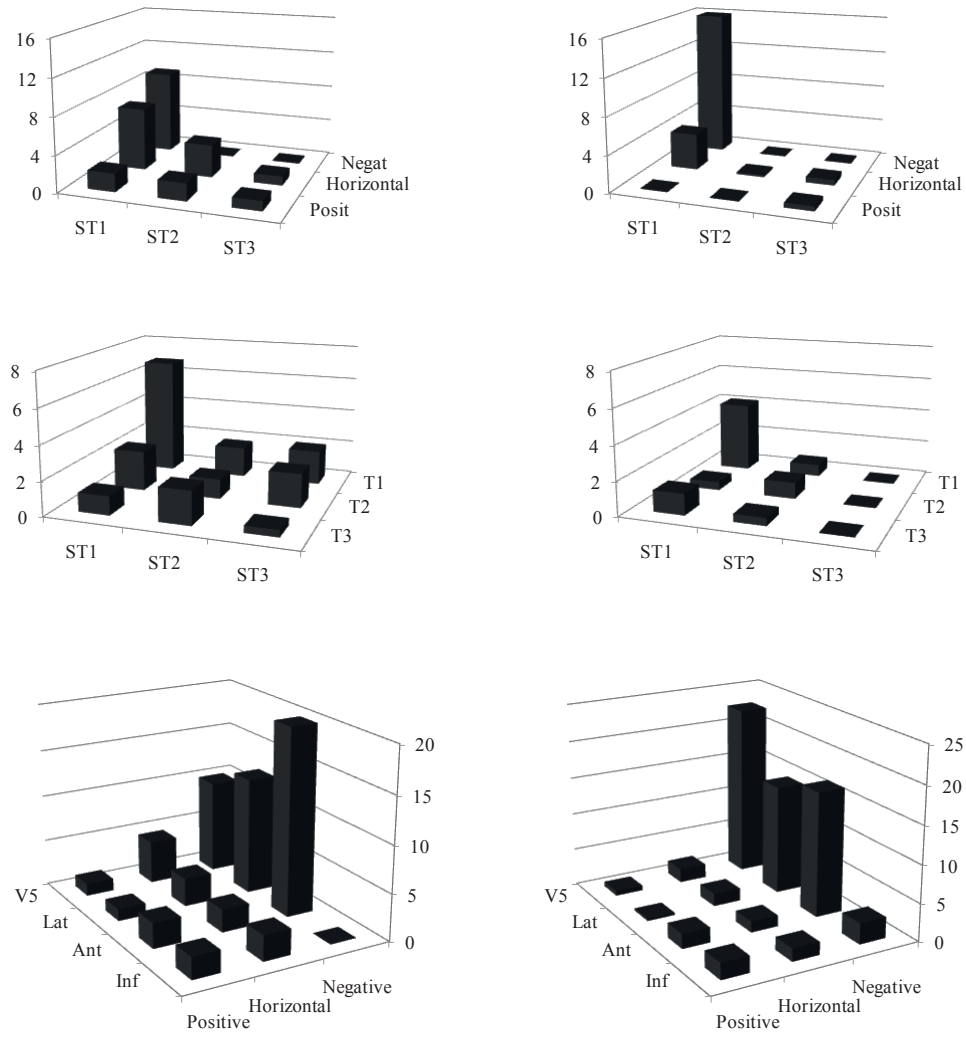

Figure 9.
Left: men, right: women.

Upper (a): Unadjusted cardiovascular mortality percentage divided by combinations of ST-slope and tertiles of ST-segment deviation at J+80 ms using lateral leads. Ranges for tertiles are given in mm.
Middle (b): Unadjusted cardiovascular mortality percentage for combinations of tertiles of ST-segment deviation (lower value at J and J+80 ms) and minimum T-wave amplitude using the lateral leads.
Lower (c): Unadjusted cardiovascular mortality percentage according to ST slope in the different lead groups (II).
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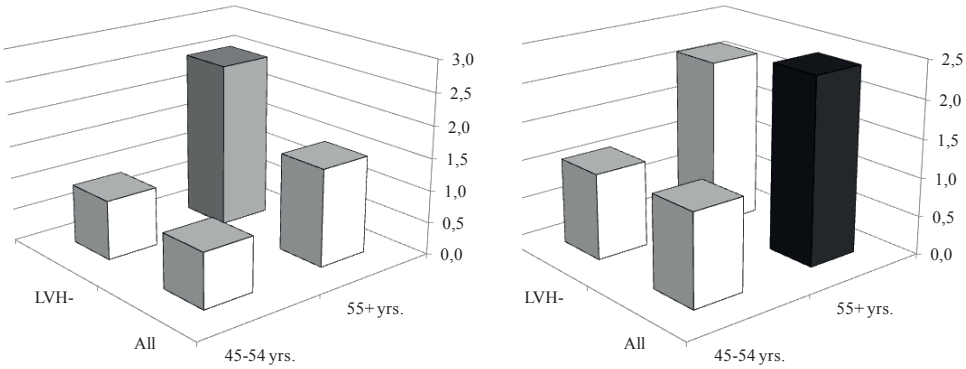

Figure 10.
Left (10a), men; right (10b), women.

Adjusted Cox-regression hazard ratios for ST-segment deviation (the lower of J point and J point + 80 ms) using lateral lead group divided by LVH status and age groups. Three different bar colors are used: the darkest for p<0.01, gray for p<0.05 and the lightest for non-significant hazard ratios. Hazard ratios are scaled for a change of 1 mm (II).

ST slope, particularly among women (Figure 9a). Similarly, the tertile with both low ST segment and low T wave amplitude was associated with a high incidence of cardiovascular mortality (Figure 9b). The infrequent finding of negative ST slope in any lead except the inferior leads was strongly linked to a high incidence of cardiovascular mortality among both men and women (Figure 9c). The unadjusted hazard ratios from the Cox regression analysis were as high as 53 for women based on ST slope in lateral leads ($P < 0.001$). However, ST slope was not significant in Cox analysis when ST segment depression was used as a covariate (data not shown).

ST Segment Deviation with/without Ventricular Hypertrophy and Age Group Considerations

A total of 820 individuals presented with LVH. Only two men and no women without LVH died of cardiovascular causes among those < 45 years old, and that age group was excluded from this sub-analysis. Women ≥ 55 years of age had clearly significant results when all the participants were included, but the significance was lost when those with LVH were excluded (Figure 10).

Table 11.
Patient characteristics for dichotomous parameters **(II)**.

	Men			Women		
	No CV death N (%)	CV death N (%)	P	No CV death N (%)	CV death N (%)	P
Regular smoking	662 (28.1)	21 (34.3)	0.248	527 (17.3)	4 (9.5)	0.032
COPD	34 (1.4)	3 (5.3)	0.073	34 (1.1)	3 (7.6)	0.026
Hypertension	708 (29.6)	28 (43.2)	0.016	909 (29.6)	30 (56.5)	0.000
Diabetes	118 (4.8)	12 (20.4)	0.000	151 (4.7)	15 (26.1)	0.000
LVH	496 (20.7)	18 (26.4)	0.369	292 (9.3)	14 (30.0)	0.000
CHD						
– No	2172 (90.6)	39 (60.0)		2813 (90.9)	27 (49.1)	
– Possible	33 (1.4)	2 (3.1)	0.000	70 (2.3)	8 (14.5)	0.000
– Yes	192 (8.0)	24 (36.9)		213 (6.9)	20 (36.4)	
Myocardial infarction						
– No	2316 (96.6)	48 (73.8)		3038 (98.1)	45 (81.8)	
– Possible	17 (0.7)	3 (4.6)	0.000	13 (0.4)	2 (3.6)	0.000
– Yes	64 (2.7)	14 (21.5)		45 (1.5)	8 (14.5)	
Medication						
– Beta-blocker	254 (10.2)	20 (31.4)	0.000	452 (14.6)	20 (36.5)	0.000
– CCB	115 (4.7)	10 (15.7)	0.001	184 (5.9)	12 (21.1)	0.000
– Digitalis	22 (0.8)	9 (9.5)	0.000	40 (1.1)	11 (17.3)	0.000
– ACEI/ARB	181 (7.4)	15 (22.0)	0.000	233 (7.4)	14 (24.9)	0.000

COPD, chronic obstructive pulmonary disease; LVH, left ventricular hypertrophy; CHD, coronary heart disease; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor antagonist.

ST deviation did not bear prognostic value among all men (Figure 10). When those with LVH were excluded, men aged ≥ 55 years showed borderline significance.

Table 12.
ST-segment and T-wave characteristics for each age group. ST-segment level is the lower of values at J point and J point +80 ms. ST-slope percentages are for positive/horizontal/negative slopes **(II).**

	30–44 years			45–54 years			≥55 years		
	Men (n=885)	Women (n=1061)	P	Men (n=712)	Women (n=777)	P	Men (n=867)	Women (n=1313)	P
ST segment (mm), mean (SD)									
Anterior	0.08 (0.30)	-0.10 (0.26)	0.000	-0.02 (0.77)	-0.09 (0.25)	0.027	-0.09 (0.41)	-0.23 (0.35)	0.000
Lateral	0.00 (0.23)	-0.06 (0.18)	0.000	-0.05 (0.26)	-0.10 (0.18)	0.000	-0.16 (0.32)	-0.24 (0.31)	0.000
Inferior	-0.05 (0.31)	-0.07 (0.24)	0.146	-0.13 (0.39)	-0.07 (0.23)	0.001	-0.17 (0.29)	-0.14 (0.28)	0.030
V5	0.32 (0.34)	0.09 (0.24)	0.000	0.15 (0.37)	0.02 (0.25)	0.000	-0.02 (0.40)	-0.14 (0.36)	0.000
T-wave amplitude (mm), mean (SD)									
Anterior	0.94 (1.48)	-0.44 (1.09)	0.000	1.00 (1.46)	-0.22 (1.1)	0.000	1.06 (1.61)	0.04 (1.44)	0.000
Lateral	1.40 (1.02)	1.11 (0.72)	0.000	1.33 (1.01)	1.09 (0.78)	0.000	0.91 (1.23)	0.75 (1.13)	0.000
Inferior	0.31 (1.36)	0.37 (1.07)	0.262	0.02 (1.28)	0.24 (1.08)	0.000	0.10 (1.21)	0.23 (1.06)	0.012
V5	5.42 (2.17)	3.90 (1.52)	0.000	4.73 (2.15)	3.61 (1.55)	0.000	3.89 (2.43)	3.01 (2.00)	0.000
ST slope, %									
Anterior	58.1 / 41.8 / 0.1	40.2 / 59.8 / 0.0	0.000	58.7 / 41.2 / 0.1	49.3 / 50.7 / 0.0	0.000	62.4 / 37.2 / 0.3	50.2 / 49.4 / 0.5	0.001
Lateral	25.8 / 73.7 / 0.6	10.9 / 88.8 / 0.3	0.000	27.2 / 72.6 / 0.1	10.7 / 89.1 / 0.3	0.000	23.8 / 75 / 1.2	9.9 / 86.8 / 3.3	0.000
Inferior	4.7 / 91.8 / 3.5	3.4 / 95.1 / 1.5	0.005	5.1 / 91.7 / 3.2	3.6 / 96 / 0.4	0.000	5.8 / 93.1 / 1.2	5.6 / 93.1 / 1.3	0.939
V5	74.6 / 25.1 / 0.3	24.2 / 75.8 / 0.0	0.000	61.2 / 38.6 / 0.1	20.8 / 79.2 / 0.0	0.000	43.0 / 56.3 / 0.7	14.9 / 83.5 / 1.7	0.000

aVRT+ (Study III)

In the entire population, the mean aVRT was - 2.55 ± 1.02 mm (mean ± SD). The mean T wave amplitudes were -2.69 ±1.09 mm in men and -2.44 ± 0.94 mm in women (t = - 9.54, degrees of freedom 6.061, p < 0.001 for difference). There was a significant correlation of the T wave amplitude and ST segment depression measurements between lead V5 and lead aVR (Table 13). There were 176 (2.9%) subjects with isoelectric or negative T waves in lead V5. Of these 176 subjects, 94 (53%) also had aVRT+. On the other hand, only 68% of the subjects with aVRT+ had isoelectric or negative T waves in lead V5.

Table 13.
Relationship of the ST segment and T wave amplitudes of the 6299 subjects of Health 2000 Survey

Variable	lead V5	lead aVR	Pearson correlation
ST segment amplitude (mm) J + 60ms	0.373	-0.253	-0.824 **
T wave amplitude (mm)	3.92	-2.50	-0.819 **

** Correlation is significant at the 0.01 level (2-tailed). Previously unpublished data.

Prevalence

The prevalence of aVRT+ was 2.2% (n = 138, 69 women and 69 men), with no difference between men and women (Figure 11). Subjects with aVRT+ were older and more often had a history of CV disease and risk factors than subjects with aVRT- (Tables 1 and 2 in **III**). The prevalence of aVRT+ was 5.2% in subjects ≥ 55 years of age and 0.4% in subjects < 55 years of age (Figure 11).

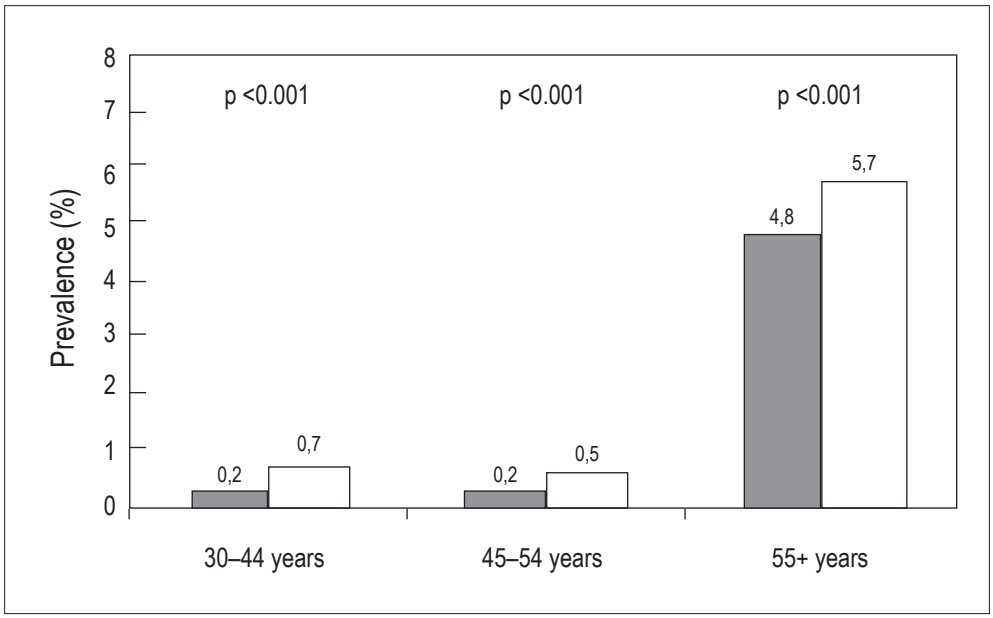

Figure 11.
Prevalence of aVRT+ for the three age groups among women (black bars) and men (white bars) (III).

aVRT+, T-wave amplitude in lead aVR equal or more than 0mm (=isoelectric or positive deflection).
The significances of the difference between age groups are shown (chi-square test).

Prognosis

During the first five years of follow-up, there were 354 deaths (5.8% of the population) and 135 of those were CV deaths (2.2% of the population). Among subjects with aVRT+, CV mortality was 17.6% (women 14.3%, men 21.7%), while the mortality of those with a T wave amplitude of ≤ -2.00mm was 1.1% (women 0.8%, men 1.6%). This means that CV death was 16 times more prob-

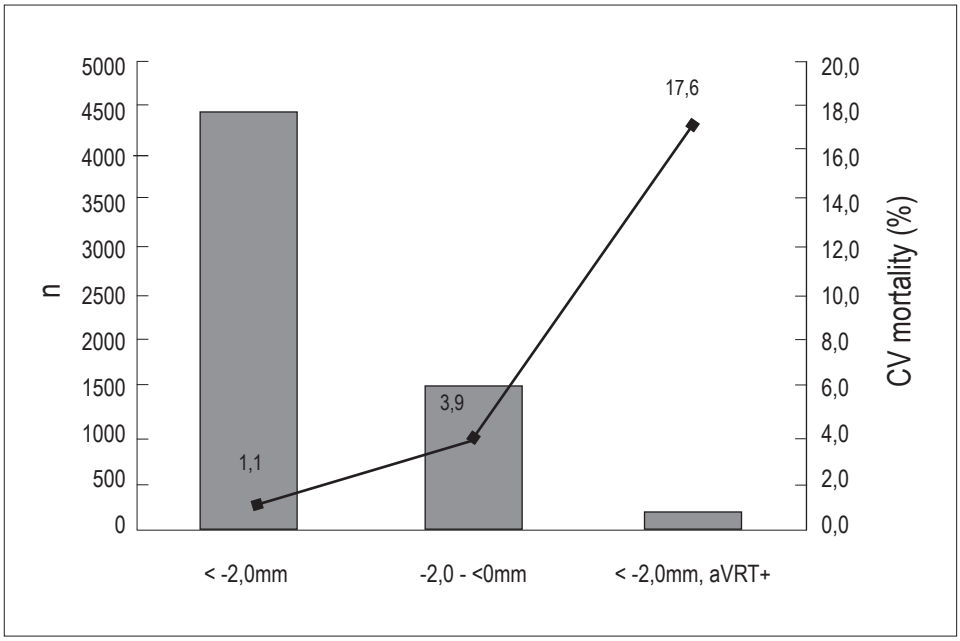

Figure 12.
Cardiovascular mortality within 5 years of follow –up in the three groups based on T wave amplitude in lead aVR (III).

aVRT+, T-wave amplitude in lead aVR equal or more than 0mm (=isoelectric or positive deflection).

able in the aVRT+ category when compared with the group with the most negative T waves (Figure 12).

The receiver operating characteristic curve analysis demonstrated that age and sex alone were able to distinguish between patients with and without subsequent CV deaths at the 98-month follow-up (area under the curve 0.89, 95% confidence interval [CI] 0.87–0.91, p <0.001). Adding classic risk factors or aVRT+ in this simple model did not improve the area under the curve.

In Cox regression analysis after adjustment for age and sex, the relative risk of CV mortality for aVRT+ was 3.24 (95% CI 2.32 to 4.54, p <0.001) and that of total mortality 1.91 (95% CI 1.47–2.49, p <0.001) as compared to those with aVRT- (Figure 1 in **III**). An angle between the QRS axis and the T axis >90° in lead aVR or menopausal status had no influence on the results. In Cox regression analysis after adjustment for age, sex and pathologic ECG parameters (ST-segment depression in lead V5, left or right ventricular hypertrophy, and Q waves), aVRT+ was the strongest predictor of CV mortality when compared to those with

normal T waves (hazard ratio 3.24, 0.95% CI 2.32–4.54, p <0.001). This result remained when women and men were analysed separately. When Cox regression analysis was performed using a wide range of confounding factors (age, sex, left or right ventricular hypertrophy, Q waves, ST segment depression in lead V5, heart rate, history of angina pectoris, diabetes mellitus, hypertension, smoking, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and body mass index), the relative risk of CV mortality for aVRT+ was 2.94 (95% CI 2.07–4.18, p <0.001) in comparison to those with aVRT- (Table 3 in **III**). In Cox regression analysis of subjects (n = 4,932) with no history of heart disease (angina pectoris, MI, heart failure, medically treated hypertension) and adjusted for age and sex, the relative risk of CV mortality for aVRT+ was 3.78 (CI 2.45–5.83, p < 0.001) when compared to those with aVRT-. When the analysis was performed with subjects (n = 4,834) with no pathologic ECG parameters (ST segment depression in lead V5, left or right ventricular hypertrophy and Q waves), the relative risk for aVRT+ was 3.81 (CI 2.46–5.89, p <0.001).

IVCD (Study IV)

The baseline characteristics of the study population are presented in Table 14 and clinical characteristics as well as outcome in Table 15. Both regarding men and women, patients with IVCDs were older than those without. Individuals with IVCD had a higher prevalence of heart failure, CHD and MI, and a higher rate of all-cause and CV mortality than those without conduction delay.

During the follow-up of 8.2 years (interquartile range 8.1–8.3), 640 subjects died (10.2%), and 277 (4.4%) of the deaths were of CV causes.

Table 14.
Baseline characteristics of the subjects in IVCD study of the Health 2000 Survey **(IV).**

Variable	Men					Women				
	IVCD+		IVCD-			IVCD+		IVCD-		
	Mean	SD	Mean	SD	p value	Mean	SD	Mean	SD	p value
Age	57	16	51	13	< 0.001	63	17	53	15	<0.001
Height (cm)	176	7.6	176	7.0	0.992	161	8	162	7	0.001
Weight (kg)	84	15	84	14	0.691	68	13	70	14	0.014
BMI (kg/m^2)	27.0	4.2	27.1	4.1	0.621	26.5	4.6	26.8	5.1	0.235
Waist circumference (cm)	98	12	98	11	0.934	88	13	88	13	0.813
Glucose (mmol/L)	5.8	1.4	5.7	1.3	0.172	5.7	1.3	5.4	1.1	<0.001
Total cholesterol (mmol/L)	5.89	1.14	5.97	1.11	0.251	6.19	1.21	5.90	1.11	<0.001
High-density lipoprotein cholesterol (mmol/L)	1.21	0.34	1.20	0.33	0.509	1.43	0.37	1.45	0.41	0.545
Low-density lipoprotein cholesterol (mmol/L)	3.77	1.23	3.79	1.29	0.797	3.90	1.26	3.79	1.08	0.109
Triglycerides (mmol/L)	1.8	1.4	1.8	1.2	0.466	1.6	0.8	1.4	0.7	0.003
C-reactive protein (mg/L)	2.1	5.0	2.3	7.3	0.579	2.7	8.8	1.4	5.1	0.177
g-Glutamyltransferase (U/L)	51	90	46	53	0.170	30.2	30	26.8	31	0.060
Uric acid (µmol/L)	340	75	340	72	0.748	288	86	269	73	<0.001

IVCD= intra-ventricular conduction delay, SD=standard deviation , BMI=body mass index. Previously unpublished data.

Table 15.
Clinical characteristics and mortality of the study population according to presence of intra-ventricular conduction delay at 8,2 year's mean follow-up (IV).

	Men			Women		
	IVCD+ n (%)	IVCD- n (%)	p value	IVCD+ n (%)	IVCD- n (%)	p value
Regular smoking	84 (23.6)	718 (28.5)	0.051	38 (13.9)	567 (17.9)	0.098
Heart failure	27 (7.6)	70 (2.8)	<0.001	39 (14.4)	131 (4.1)	<0.001
Chronic obstructive pulmonary disease	5 (1.4)	38 (1.5)	0.860	3 (1.1)	37 (1.2)	0.920
Hypertension	120 (33.7)	750 (30.1)	0.168	100 (36.8)	959 (30.3)	0.028
Stroke	13 (3.7)	67 (2.7)	0.300	12 (4.4)	62 (2.0)	0.007
Peripheral artery disease	13 (3.7)	52 (2.1)	0.063	7 (2.6)	41 (1.3)	0.082
Diabetes mellitus	25 (7.0)	135 (5.4)	0.221	18 (6.6)	172 (5.4)	0.416
Left or right ventricular hypertrophy	40 (11.2)	268 (10.7)	0.767	40 (14.7)	371 (11.7)	0.150
Coronary heart disease						
No	273 (76.7)	2206 (88.2)	<0.001	210 (76.9)	2840 (89.6)	<0.001
Possible	21 (5.9)	90 (3.6)		20 (7.3)	114 (3.6)	
Yes	62 (17.4)	205 (8.2)		43 (15.8)	215 (6.8)	
Myocardial infarction						
No	310 (87.1)	2365 (94.6)	<0.001	252 (92.3)	3086 (97.4)	<0.001
Possible	12 (3.4)	46 (1.8)		9 (3.2)	27 (0.8)	
Yes	34 (9.6)	90 (3.6)		12 (4.4)	56 (1.8)	
Medication						
Beta adrenergic blockers	83 (23.3)	303 (12.1)	<0.001	58 (21.2)	489 (15.4)	0.012
Calcium channel blockers	28 (7.9)	121 (4.8)	0.016	25 (9.2)	192 (6.1)	0.43
Digitalis	20 (5.6)	30 (1.2)	<0.001	25 (9.2)	52 (1.6)	<0.001
ACEI/ARB	41 (11.5)	201 8.0)	0.027	31 (11.4)	252 (8.0)	0.050
Statin	30 (8.4)	167 (6.7))	0.223	12 (4.4)	179 (5.2)	0.386
Aspirin	49 (13.8)	168 (6.7)	<0.001	33 (12.1)	218 (6.9)	0.001
Clopidogrel	6 (1.7)	26 (1.0)	0.279	8 (2.9)	45 (1.4)	0.052
Death						
all-cause	64 (18.0)	249 (10.0)	<0.001	61 (22.3)	266 (8.4)	<0.001
cardiovascular	36 (10.1)	107 (4.3)	<0.001	32 (11.7)	102 (3.2)	<0.001

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor antagonist. Previously unpublished data.

Prognosis

In Cox regression analysis after adjustment for age and sex, the relative risk of all-cause mortality for IVCD was 1.14 (95% CI 0.93–1.39, p = 0.202) and that of CV mortality 1.38 (95% CI 1.04–1.82, p = 0.023) as compared to subjects with no IVCD. After adjustment for age and sex, the relative risk of all-cause and CV mortality for non-specific IVCD was 2.46 (95% CI 1.27–4.77, p = 0.008) and 4.29 (95% CI 2.01–9.16, p < 0.0001), respectively; for LBBB 1.61 (95% CI 1.12–2.33, p = 0,011) and 2.11 (95% CI 1.31–3.41, p = 0.002), respectively; and for IRBBB 1.98 (95% CI 1.18–3.3, p = 0.009) and 2.24 (95% CI 1.06-4.77, p = 0.036), respectively. The other types of IVCD did not have an impact on the prognosis (Table 16).

The relative age- and sex-adjusted risk of CV mortality for individuals with LBBB and AP was 2.41 (95% CI 1.46–4.00, p = 0.001) and for individuals with LBBB and a history of MI 2.55 (95% CI 1.36–4.77, p = 0.003). The corresponding risk for individuals with non-specific IVCD and heart failure was 3.80 (95% CI 1.18–12.25, p = 0.001). RBBB did not have an impact on CV mortality in subjects either with or without previous heart disease (Table 17a-c).

In subjects without BBB or fascicular block (n = 5952) and no history of CHD, after adjustment for age and sex, the relative risk of CV mortality for QRS ≥120ms (n= 67) was 0.506 (95% CI 0.07–3.66, p = 0.500) as compared to subjects with QRS <120ms. When the corresponding analysis was performed for subjects with CHD, the relative risk of CV death for QRS≥120ms was 2.35 (95% CI 1.13–4.9, p = 0.023) when compared to subjects with QRS<120ms.

Table 16.
Adjusted Cox proportional hazard analysis for cardiovascular mortality according to intra-ventricular conduction block (IV).

Variable	Prevalence n (%)	Hazard Ratio (95% CI)	p value
Age and gender adjusted			
LAHB	69 (1.1)	0.84 (0.40-1.80)	0.660
LPHP	8 (0.1)	No events	
LBBB	68 (1.1)	2.11 (1.31-3.4)	0.002
RBBB	75 (1.2)	1.15 (0.65-2.02)	0.640
Incomplete LBBB	66 (1.0)	1.14 (0.42-3.07)	0.790
Incomplete RBBB	61 (1.0)	2.24 (1.06-4.77)	0.036
R-R'	249 (4.0)	0.90 (0.50-1.65)	0.731
NSIVCD	33 (0.5)	4.29 (2.01-9.16)	<0.001
Multivariate adjusted*			
LBBB	68 (1.1)	1.44 (0.88-2.35)	0.143
Incomplete RBBB	61 (1.0)	2.00 (0.94-4.27)	0.730
NSIVCD	33 (0.5)	4.25 (1.95-9.26)	<0.001

CI=confidence interval; LAHB=left anterior hemiblock; LPHB=left posterior hemiblock; LBBB=left bundle branch block; RBBB=right bundle branch block; NSIVCD=non-specific intra-ventricular conduction delay

***** Adjusted for gender, age angina pectoris, myocardial infarction, heart failure, hypertension, diabetes, smoking, body mass index, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides. Chi-square test was used for testing difference of prevalence between age groups (p<0.001). Unpublished data.

Table 17a.
Age and gender adjusted Cox proportional hazard analysis for cardiovascular mortality **(IV).**

	No angina pectoris		Angina pectoris	
Variable	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
LAHB	0.97 (0.36-2.64)	0.951	0.72 (0.23-2.27)	0.572
LPHB	0.003 (NA)	0.971	0	0.959
LBBB	0.36 (0.05-2.61)	0.313	2.41 (1.46-4.00)	0.001
RBBB	0.58 (0.18-1.84)	0.353	1.55 (0.81-3.00)	0.189
Incomplete LBBB	0.62 (0.09-4.42)	0.629	1.47 (0.47-4.65)	0.509
Incomplete RBBB	2.81 (1.03-7.64)	0.043	1.74 (0.55-5.45)	0.345
R-R´	0.84 (0.34-2.06)	0.701	1.07 (0.46-2.48)	0.874
NSIVCD	2.49 (0.35-18.0)	0.365	3.98 (1.73-9.13)	0.001

Table 17b.
Age and gender adjusted Cox proportional hazard analysis for cardiovascular mortality.

	No myocardial infarction		Myocardial infarction	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
LAHB	0.923 (0.41-2.09)	0.847	0.61 (0.08-4.41)	0.621
LPHB	0.003 (NA)	0.847	0 (NA)	0.989
LBBB	1.10 (0.48-2.50)	0.827	2.55 (1.36-4.77)	0.003
RBBB	1.12 (0.59-2.14)	0.726	1.65 (0.50-5.39)	0.411
Incomplete LBBB	1.56 (0.50-4.91)	0.445	0.51 (0.07-3.70)	0.503
Incomplete RBBB	3.11 (1.46-6.64)	0.003	0 (NA)	0.974
R-R´	0.70 (0.31-1.58)	0.387	1.38 (0.53-3.60)	0.507
NSIVCD	1.52 (0.21-10.88)	0.675	3.43 (1.44-8.20)	0.005

Table 17c.
Age and gender adjusted Cox proportional hazard analysis for cardiovascular mortality.

	No heart failure		Heart failure	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
LAHB	0.75 (0.28-2.04)	0.577	0.67 (0.21-2.13)	0.491
LPHB	NA	NA	NA	NA
LBBB	1.98 (1.00-3.89)	0.048	1.61 (0.81-3.19)	0.171
RBBB	1.08 (0.55-2.14)	0.817	1.09 (0.39-3.02)	0.872
Incomplete LBBB	1.13 (0.36-3.54)	0.840	0.83 (0.12-6.03)	0.855
Incomplete RBBB	2.09 (0.77-5.67)	0.146	1.86 (0.57-6.07)	0.301
R-R´	0.87 (0.41-1.86)	0.725	0.95 (0.34-2.66)	0.922
NSIVCD	5.40 (1.98-14.73)	0.001	3.80 (1.18-12.25)	0.025

Discussion

General Observations

In this study, certain abnormalities in the resting ECG signified a tremendous risk of death during follow-up. Alarmingly, seven out of ten women and half of the men with AF at baseline died within 8 years of follow-up (Table 8). Out of those subjects with a history of MI, 40% were dead by that time. A similar result, 39% mortality over 10 years, was reported in the Framingham Heart Study (Kannel 1987).

Generally, subjects with LBBB, RBBB, FA, ST segment depression and aVRT+ had a significant all-cause mortality ranging from 19% to 70% (Table 8). The mortality data over selected ECG variables is seen in Table 8.

The proportion of UMI out of all MIs was 6.5% in men and 11.8% in women if the categorical code MC 1.1-2 was used. In the Framingham Heart Study the proportion of UMI was substantially higher (28% in men, 35% in women) than in our study (Kannel 1987). This may reflect the differences in determining the concept of UMI.

Q waves were present in 14.5% of the men and 7.4% of the women with RMI (Table 7). Subjects with asymptomatic MI had an equal or worse prognosis than subjects with RMI. Sixty percent of the women and fifty percent of the men with UMI died during follow-up (Table 7). This finding is also in concert with a previous report where 50% mortality for women and 34% mortality for men was observed over 10 years of follow-up among subject with UMI (Kannel and Abbott 1984, Table 2).

Main findings

PRWP is more frequent in women than in men in all age groups. PRWP increases total and CV mortality in women but not in men.

In all measurement points (J point, J+40ms, J+80ms, J/J+80ms) ST segment deviation in lateral leads and in lead V5 significantly increased CV mortality in women but not in men. The infrequently met negative ST slope in the lateral and anterior lead groups and lead V5 is strongly linked to a high incidence of cardiovascular mortality among both men and women.

aVRT+ increases total and CV mortality in both women and men with or without prior heart disease.

Non-specific IVCD, LBBB and IRBBB are associated with increased CV and total mortality. RBBB is not associated with CV mortality.

All-cause mortality related to patients with MI was 43% in 8 years follow-up both in men and women. Mortality was equally high among patients with STD, aVRT+ and LBBB. The highest total mortality was among patients with FA, 53% in men and 70% in women (Table 8.)

PRWP

The present study is, to our knowledge, the first to demonstrate the prevalence of PRWP in a general adult population. In our study population, PRWP proved to be a common ECG finding. Additionally, this ECG phenomenon was more frequent in women than in men in all three age groups of 30 years or older. Importantly, PRWP predicted total and cardiovascular mortality in women.

The findings of the present study could be helpful in screening general populations for the risk of total and cardiovascular mortality.

Differences in the reported prevalence of PRWP in non-population-based materials are partly explained by different criteria for the ECG finding. DePace et al. reviewed the resting ECGs of 1,250 consecutive patients who underwent thallium-201 scintigraphy (Depace et al. 1983). Using the same inclusion criteria but slightly different exclusion criteria as in the present study, they reported an 8% prevalence of PRWP in their patients, who all had chest pain or were evaluated for suspected AP. At the Glasgow Royal Infirmary, the prevalence of PRWP was estimated by reviewing all electrocardiograms (n=1315) recorded over a 2-week period. As in the present study, PRWP was more frequent in women (19% vs. 11%) than in men (Colaco et al. 2000). The authors also found that the positioning of electrodes beneath rather than on top of the breast was not responsible for the increased prevalence of poor R wave progression in women with a variety of clinical problems.

We found a very low prevalence of negative P waves in leads V2 and/or V3 (n=65, 1.2%), a possible sign of high electrode placement (Garcia-Niebla 2009), which could cause PRWP as an artefact. Excluding those patients did not confer a major impact on the study results.

In the present study, both men and women with PRWP had an increased unadjusted total and cardiovascular mortality during an average follow-up of 5.8 years. In Cox regression analysis after adjustment for age, hypertension, diabetes, previous MI and CHD, PRWP was an independent determinant of both all-cause and cardiovascular mortality in women, but not in men (for cardiovascular

mortality the relative risk was 3.02 [p=0.001] for women and 1.85 [p=0.19] for men). Interestingly, the risk increase is in the same range as that reported with the presence of major or minor Q waves and higher than the risk associated with minor ST segment and/or T wave abnormalities (Ashley et al. 2000, Greenland et al. 2003). The explanation for the finding that PRWP predicted mortality independently of CHD and MI in women but not in men is not fully evident in the present findings. A lack of power was studied further because there were only 69 men with PRWP as compared to the 218 women. However, power calculations showed that there was enough power to reach a clinically meaningful relative risk of 1.5 for men as well. The difference could be explained by the fact that PRWP was more often associated with known CHD and MI in men than in women (Table 9). In accordance, PRWP strongly predicted mortality in women after excluding subjects with previous myocardial infarction from the analysis in the present study.

Furthermore, earlier reports support the view that PRWP is strongly associated with CHD and MI and that this association appears to be more often visible in men than in women. In a retrospective study, men with PRWP had a higher probability of anterior wall motion abnormality in echocardiography than women (Stuglin et al. 2004). In the study by DePace et al., men with PRWP had a higher probability of anterior scars than women as detected in thallium scintigraphy. Zema et al. showed that the relative risk of autopsy-documented anterior MI was increased sixfold in patients meeting PRWP criteria (Zema and Kligfield 1979, Zema et al. 1980). In another study, wall motion abnormalities were associated with PRWP in patients with left ventricular end-diastolic diameters of 5 cm or more, but not in patients with smaller ventricular diameters (Yape et al. 2002). Another explanation for the CHD- and MI-independent predictive power of PRWP in women could be that women had more undiagnosed CHDs or MIs than men in the present general population. Altogether, these findings support the view that PRWP could be a useful screening tool for cardiovascular morbidity and mortality in general populations of women.

Clinical and experimental studies have shown that sex-related differences exist in cardiac electrophysiology in various animal species as well as humans. Sex-related differences in repolarisation have been well described, although the basis for the differences is still debated (Surawicz et al. 2002, Bidoggia et al. 2000, James et al. 2007).

The QRS complexes, representing projections of the QRS vectors in the ventricular depolarisation, generally show larger amplitudes in men than in women. With advancing age, the amplitude of the QRS complex, and also of the R wave, decreases (Surawicz et al. 2008). In age groups of 30 years and older, women have slightly lower R wave amplitudes than men.

One major aetiology for the loss of electrotonic forces in the anteroposterior axis, mainly in the ECG leads V2 and V3, is fibrotic tissue replacing muscular tissue. Structural remodelling of the ventricular walls, with a potential for worsened patient outcome, takes place in several cardiac disorders including acute MI, cardiomyopathy and hypertensive heart disease. Ventricular remodelling is characterised by structural rearrangement involving cardiomyocyte hypertrophy, the proliferation of cardiac fibroblasts, fibrosis and cell death. Animal studies have shown that sex can influence the development of fibrotic phenotypes (Du 2004). Oestrogen and its various bioactive metabolites can attenuate cardiac fibrosis (Watanabe et al. 2003). In comparison with premenopausal women, men and postmenopausal women are at a higher risk of cardiovascular diseases, suggestive of the possible protective role of oestrogen (Lekgabe et al. 2006). In our study, the prevalence of PRWP increased with age. In women, this could, to some extent, be due to the loss of the protective effect of oestrogen, with increased fibrotic tissue replacing the myocardium and resulting in the ECG phenomenon of PRWP. In hypertensive heart disease, pressure overload induces increased extracellular matrix remodelling with eventual myocardial fibrosis, which in turn is directly associated with increased myocardial stiffness, diastolic dysfunction and heart failure (Spinale 2007). Our observation that the association between PRWP and hypertension is stronger in female than in male individuals could support the role for fibrosis as a possible pathophysiologic explanation for the adverse prognostic significance of PRWP, especially in women. If this hypothesis is correct, it raises the question whether there would be a role for the use of aldosterone and angiotensin 1 receptor blockers – which have been shown to prevent increases in collagen types I and III messenger ribonucleic acid (mRNA) and fibrosis in rats – in patients with PRWP (Robert et al. 1999).

In our study, men with PRWP had a more than two times higher probability of CHD or MI than women. However, in the vast majority of individuals of both sexes, PRWP was not associated with known CHD or a history of MI. In post-MI left ventricular remodelling, the infarct area undergoes proliferation and differentiation of fibroblasts and other interstitial cells as well as the elaboration of bioactive molecules which contribute to a robust synthesis of ECM for the purposes of scar formation (Spinale et al. 2007). The reappearance of R waves in anterior MI have been associated with a larger extent of stunned, but viable, myocardium, and a trend towards a smaller amount of necrotic myocardium, when compared to patients with persisting Q waves (Nagase et al. 1998). Magnetic resonance imaging has shown that MI size is associated with Q waves after an ST elevation MI (Moon et al. 2004). The fact that we excluded individuals with pathological Q waves may have resulted in the selection of a relatively low-risk post-MI subpopulation of individuals in our study. This, in turn, could be one explanation for the ECG phenomenon not being associated with poor outcome in males.

It is well-known that patients with LVH represent a subgroup of PRWP. To make our study results applicable to a large patient group, we decided not to exclude patients with ECG criteria for LVH from our main analyses. However, excluding individuals with LVH (Minnesota Code 3.1, 3.3 or 3.4) had no major impact on the study results.

ST-T

Main Findings

We observed that ST segment depression has prognostic significance for cardiovascular death in a general adult population consisting of individuals both with and without CHD and that this predictability is strongly dependent on ECG signs of increased left ventricular mass. Among all women, ST segment depression in the lateral lead group as well as lead V5 showed particularly uniform and highly significant predictability at all four measurement points in adjusted analyses (Figure 8). However, this significance was lost in women aged at least 55 years when those with LVH were excluded (Figure 10). The effect of LVH on the prognostic value of ST segment depression was also present in men, but in an opposite direction and to a lesser degree as among women (Figure 10).

Even though prediction based on ST segment depression in the male population without LVH was only marginally significant (p=0.039) in this study with a large number of analyses, it is possible that the different direction of effect of LVH between the sexes is due to different pathophysiologies. This surmise is supported by our finding that there is a sex-specific difference in the mortality risk based on T wave amplitudes (Figure 9b). Both ST segment depression and LVH are strongly associated with structural heart disease. Consequently, LVH has been linked to an increased risk of cardiovascular diseases including angina pectoris, myocardial infarction, congestive heart failure, arrhythmia and sudden death (Kannel 1983, Okin et al. 2004, Verdeccia et al. 1998). In population studies, myocardial ischaemia, left ventricular remodelling and bundle branch block represent the most important clinical entities with potential for increased cardiovascular mortality in individuals with ST segment depression. We excluded individuals with ECG signs of old Q-wave myocardial infarction or bundle branch block, and ischaemia and remodelling remain the main culprits in cardiovascular demise. From an ECG point of view, these two entities differ with respect to LVH: CHD per se is not associated with LVH, while there is a strong association between left ventricular remodelling and LVH. The present population also showed a clear sex-specific association between myocardial infarction and death. For patients with a history of myocardial infarction, cardiovascular mortality during follow-up was higher in

men (17.3%) than in women (14.7%, p<0.001). It may be speculated that the predictive power of low ST segments related to CHD in men was more evident after individuals with LVH were excluded. In women, other mechanisms may be involved. For example, in the Strong Heart Study, women more often than men developed new-onset heart failure (Levy et al. 1990), an untoward effect of left ventricular remodelling.

Lead Groups and T Wave Polarity

Our study indicated the highest cardiovascular mortality hazard ratios for low ST segments in the lateral leads V5, V6, I and aVL when compared to other lead groups (Figure 8a). This effect was markedly stratified by the polarity of T waves (Figure 9b). In a GUSTO IIb substudy of patients with non-ST-elevation acute coronary syndrome, ST segment depression with inverted T waves in lateral leads V4–V6 was associated with increased one-year mortality (Atar et al. 2007). The authors suggested elevation of left ventricular end-diastolic pressure with subendocardial ischaemia and diastolic dysfunction as a possible pathophysiologic background (Atar et al. 2007). The present observational study does not reveal whether similar mechanisms may be operating in our general population.

Measurement Point

No recommendation has been provided for the measurement point of ST segment depression in the case of STD. Due to differences in the stage of repolarisation between individual myocardial fibres, some ST segment deviation may normally be present at the J point. However, it is customary to measure ST segment deviation at 60 to 80 ms after the end of the QRS complex, when all ventricular fibres are expected to be depolarised to the same level of membrane potential. In clinical trials, investigators have measured the ST segment deviations from different points along the ST segment. According to the universal definition of myocardial infarction, ST elevation should be measured from the J point (Thygesen et al. 2007). We found no major differences in hazard ratios between different ST segment depression measurement points.

ST Slope

Data on the prognostic significance of ST segment slope in resting ECGs are limited. A horizontal or down-sloping ST segment depression during an exercise stress test indicates CHD (Gianrossi et al. 1989). A more negative ST segment

slope was associated with increased mortality risk during follow-up in a routine preoperative ECG in patients who underwent bypass surgery (Lauer et al. 2007). This was not the case in the present study, where statistical significance was lost when ST segment depression was introduced as a covariate. Accordingly, the predictive value of ST slope may be different in patients with CHD when compared to individuals without CHD. However, the combination of a descending STD with LVH – the strain pattern – is a well-documented prognostic marker.

AVRT+

This study showed, for the first time, that a positive T wave in lead aVR (aVRT+) independently predicts the risk of CV mortality both in women and men of a nationally representative population. As expected, the 2.2% prevalence of aVRT+ in the general adult population is lower than for study populations including patients only where rates of 7.3% to 11% have been reported (Tan et al. 2008, Verma et al. 2003). Our finding that aVRT+ patients are older than aVRT- patients is in accordance with the findings of Tan et al., and also with the fact that the prevalence of T wave abnormalities in general increases by advancing age, being 5.6% at age 50 and 15.9% at age 70 (Stöm-Möller et al. 2006).

Previous Studies on the Value of Lead aVR

In ACS, ST segment elevation in lead aVR signifies severe multivessel coronary disease and can be a marker of acute left main or proximal left anterior descending coronary artery occlusion (Atar et al. 2006, Sakai et al. 2003). In non-ST-segment elevation MI patients, the existence and severity of ST segment elevation in lead aVR on admission predicts poor outcome (Barrabes et al. 2003, Szymanski et al. 2008, Kosuge et al. 2006).

Distinct ECG abnormalities in lead aVR have been reported in acute pericarditis (Spodick 1973, Williamson et al. 2006, Brady 2006), tricyclic antidepressant intoxication (Williamson et al. 2006), pre-excitation-related narrow complex tachycardia and pulmonary embolism (Williamson et al. 2006, Van Mieghem et al. 2004). During supraventricular tachycardia, lead aVR is helpful in determining the site of origin of the tachycardia or the tachycardia pathway (Verecei et al. 2008, Gorgels et al. 2001). Incorrect electrode cable connections can be recognised by unusual P-QRS patterns in lead aVR (Batcharov et al. 2007). In spite of the clinical relevance of lead aVR, ECG interpreters tend to neglect this lead, especially when presented with the classical display method (Pahlm et al. 1996).

The direction of the repolarisation process in the ventricles determines the direction of the T wave in lead aVR. The mean values of the T wave in lead aVR in age groups between 12 and 60 years reported by Lepeschkin varied between -2.0 and -2.9 mm, with ranges from -0.1 to -5.2 mm (Lepeschkin 1971). In the present study, extending the age range above the age of 60, the mean T wave amplitude in lead aVR, namely -2.6 mm, was in the same range.

In the present study, aVRT+ was associated with a threefold CV mortality risk during the follow-up. This is in concordance with the findings by Tan et al. – in their retrospective study, upward pointing T waves in lead aVR were associated with increased CV mortality (24% vs. 7.7% for the whole study population) and a fivefold increased relative risk during the 7.5-year follow-up (Tan et al. 2008). These findings are also in agreement with the fact that abnormal T waves in leads I, V6, aVL, II, aVF and V2-V6 are associated with a relative risk of 2.4–2.7 for CV death in the general population (DeBecquer et al. 1998).

The negative impact of inverted T waves on patient outcome in cardiac diseases has been known for a long time. In 1921, Willius showed that in patients with hypertension, those with significantly inverted T waves in lead I or in leads I and II had double or threefold mortality compared to those without inverted T waves (Willius 1921, Willius 1924). Interestingly, inverted lead aVR points at +30 degrees in the frontal plane, falling between leads I and II. Accordingly, inverted T waves in leads I and II are accompanied by a positive T wave in lead aVR. Furthermore, patients with aortic insufficiency and inverted T waves showed twice the mortality present in patients without T wave inversion (Willius 1921). In 1929, Barnes and Whitten proposed that the heart muscle has the capacity to adapt to fatigue or "overstrain" to a certain degree, and when the fatigue or strain reaches a certain limit, uncompensated metabolic disturbances occur which are capable of modifying the electrical forces produced by the ventricular muscle cells and thus bring about significant inversions of the T waves (Barnes and Whitten 1929). Based on a large autopsy series of different cardiac pathology, they reported inversion of the T wave in lead I or lead I and II in disease primarily affecting the left ventricle.

Due to the fact that lead aVR is electrically opposite to the lateral precordial leads, STD in leads V5–V6 is often accompanied by ST elevation in lead aVR (Scarovsky et al. 2002). Moreover, the present study indicated an inverse relationship between ST-T changes in leads aVR and V5 (Table 13). Assuming that negative T waves in the lateral precordial leads in general are accompanied by a positive T wave in lead aVR, one may find a tempting explanation for the negative prognostic impact of aVRT+ shown in the present study. Disease states that

induce secondary repolarisation ST-T changes in the ECG have been associated with ventricular remodelling and, hence, with an unfavourable outcome. Strain defined as an inverted asymmetrical T wave opposite to the QRS axis in leads V5 and/or V6 accompanied by a down-sloping convex ST segment was associated with greater indexed LV mass in patients with and without CAD in the LIFE study (Okin et al. 2001). Strain was associated with an increased risk of anatomic LVH in patients with and without CAD and in the overall population. In addition, ECG strain was associated with concentric LVH, lower myocardial contractility and higher estimated myocardial oxygen demand. Previously, the strain pattern has been associated with greater LV mass in patients with isolated aortic regurgitation (Roman et al. 1987). Experimental evidence suggests that the increased risk of sudden death in hypertension may be mediated by LVH-induced arrhythmogenic repolarisation abnormalities (Kowey et al. 1991, Ben-David et al. 1992, Yan et al. 2001, Kozhevnikov et al. 2002). In a multicentre study with hypertension and ECG-LVH, serial changes in repolarisation significantly predicted the prognosis, independent of voltage changes (Verdeccia et al. 2007). The persistence or new development of ST-T alterations identified subjects with a high risk of cardiovascular events. In addition, persistent negative T waves after MI correspond to extensive necrosis or a non-revascularised, jeopardised myocardium (Maeda et al. 1996, Pierard et al. 2005).

IVCD

Our study showed clinically important prognostic differences between the categories of IVCD. Of the eight studied IVCDs, three were associated with an increased relative risk for all-cause and CV mortality, namely LBBB, IRBBB and non-specific IVCD, the last-mentioned of which proved to carry the highest risk. In subgroup analyses, LBBB and IRBBB demonstrated increased CV mortality only in individuals with CHD. RBBB in the general population carried no increased risk for all-cause or CV mortality.

One of the main findings of the present study was the strong association between non-specific IVCD and increased CV mortality. A broad QRS, in our study defined according to the Minnesota code system as ≥120 ms, may be caused by complex delays in the conduction system, regional conduction slowing in the myocardium, or a combination of the two (Surawicz 2008). Accordingly, structural heart disease with the potential for an inferior outcome may result in ECG changes falling into this category. Non-specific IVCD is probably an under-recognised entity both as an ECG diagnosis and as a negative prognostic factor. The negative prognostic impact of this ECG finding in conjunction with CHD is not surprising. Regions with myocardial scarring may alter the conduction sequence

in the left ventricle, thereby slowing conduction and inducing the fragmentation of the QRS complex, resulting in a broadened QRS not typical of RBBB or LBBB (Das et al. 2011). In a Finnish population study of 10,899 middle-aged subjects, prolonged QRS duration in ECGs recorded between 1966 and 1972 without the criteria for complete or partial BBB predicted mortality and was strongly associated with arrhythmic death (Aro et al. 2011).

In the Multicenter Automatic Defibrillator Implantation Trial – CRT (MADIT-CRT), the poor response of patients with non-specific IVCD to cardiac resynchronisation therapy has been speculated to stem from generalised slow conduction within the left ventricle, which in turn is related to ischaemic endocardial damage rather than discrete bundle-branch disease (Zareba et al. 2011). The negative prognostic outcome associated with non-specific IVCD in our study may be largely explained by unrecognised ischaemic or non-ischaemic structural heart disease.

In the Finnish cohorts of individuals aged ≥65 years (n=697) included in the Seven Countries study (Tervahauta et al. 1996), 5-year mortality was 25% (2/8 subjects) for non-specific IVCD. The data were collected during the 1980s and, in general, the mortality figures were high.

In selected patient populations, as in myocardial infarction patients, both LBBB and RBBB have proven to be independent predictors of mortality (Newby et al. 1996, Widimsky et al. 2012). Previous investigators have come to varied conclusions regarding the impact of LBBB and RBBB on CV morbidity and mortality in the general population. The Framingham Study (n=5,209) demonstrated a clear association between LBBB and the main CV diseases, such as hypertension, cardiac enlargement and CHD (Schneider et al. 1979). Within 10 years of LBBB detection, CV mortality was 50%. Imanishi et al. studied 17,361 Japanese individuals who underwent health examinations between 1958 and 2002, including echocardiography; LBBB predicted heart-failure-related but not all-cause mortality (Imanishi et al. 2006). In the present study, LBBB was associated with an increased relative risk of all-cause and CV mortality. The increased risk was seen only in individuals with coronary heart disease. As an aggregate, LBBB as an incidental finding in subjects with risk factors for CHD should result in a thorough clinical evaluation and echocardiography (Francia et al. 2007). The presence of LBBB has no adverse prognostic significance for subjects without evidence of structural heart disease. Such patients fall into the category of older patients with primary disease of the conducting system.

In the present study, after age and sex adjustment, LBBB was not associated with worse outcome in subjects with HF. On the contrary, in individuals without HF, there was a trend towards an increased relative risk of CV mortality with LBBB. This somewhat contradictory finding could be explained by the fact

that subjects with undiagnosed left ventricular dysfunction have a worse outcome than those with known disease who are given proper medical and device therapy known to influence the outcome positively.

In the Copenhagen City Heart Study (n=18,441), in subjects without a previous MI or chronic heart failure, RBBB but not IRBBB was associated with significantly increased all-cause and CV mortality in both sexes (Fahy et al. 1996). The findings are opposite to those of our study. We found no increased mortality for RBBB, while IRBBB was associated with increased CV mortality. The increased risk was observed only in subjects who were free from coronary heart disease. Differences in study populations may, to some extent, explain the diverging results from the two studies. The Danish study did not include subjects with known CAD or heart failure. Older population studies indicated no adverse outcome in otherwise healthy (young) subjects with RBBB (Schneider et al. 1981, Smith et al. 1979).

Surprisingly, in the present study, IRBBB was associated with increased CV mortality among subjects with no previous coronary heart disease. IRBBB may be present in normal subjects, but it may also be a marker of acute or chronic right ventricular pressure or volume load, such as pulmonary embolism, congenital heart disease or arrhythmogenic right ventricular cardiomyopathy. Discrimination between IRBBB and Brugada type 2 and 3 may be troublesome, although this fact does not necessarily explain the differences in outcome between population studies (Chevallier et al. 2011).

IRBBB has not been extensively studied in previous population studies. Disparate findings were reported from the Chicago Western Electric Company study of white middle-aged men (n=1,960), 6.8% of whom had IRRRB at study entry (Liao et al. 1986). Although IRBBB was not related to an increased risk of CV death during 20-year follow-up, this particular IVCD was frequently a manifestation of primary abnormality in heart's conduction system; individuals with IRBBB had an increased risk of complete RBBB.

ILBBB was not associated with adverse outcome in the present general population. This conduction block is probably associated with the slowing of conduction in the left bundle branch. However, a differential diagnosis from LVH with QRS widening is not straightforward, and the ECG diagnosis is even somewhat controversial. This may be the reason behind the lack of earlier population studies related to the prognostic significance of this ECG pattern.

Studies related to the prognostic impact of LAHB have shown somewhat disparate results, probably in part due to differences in the definition of this conduction disorder. Some overlap between left axis deviation due to, for example, horizontal heart or inferolateral myocardial infarction and left axis deviation due to LAHB is unavoidable (Elizari et al. 2007). The prognosis of LAHB is basically

dependent on the associated pathology. Coronary and hypertensive heart disease are the most common causes of LAHB. In a study of 1,187 patients with suspected coronary artery disease referred for stress testing, LAHB (n=159) was associated with an increased risk of cardiac death during 6-year follow-up (p=0.004) (Biagini et al. 2005). Most population studies have not found any association between the presence of LAHB and increased risk of cardiac death. In a community population of 8000 Japanese-American men aged 45 to 69 years, the incidence of fatal or nonfatal coronary heart disease and stroke during observation periods of 3 to 6 years among men with LAHB was not significantly different from that of control men (Yano et al. 1975). Left axis deviation or LAHB was a quite common finding in centenarians without prognostic implications (Basile et al. 2011). Our results support the notion of LAHB being a benign incidental ECG finding in the general population.

Isolated LPHB is extremely rare, as it is almost invariably associated with RBBB (Rosenbaum 1968). In a study form the 1970s, LPHB plus RBBB in acute MI was associated with a high mortality rate (80% to 87%) during the first weeks after the acute event (Rizzon et al. 1975). Likewise, the risk of progression towards complete AV block was considerable (42%), and 75% of these patients died from pump failure (Roos and Dunning 1978). In the present study as well, LPHB was a rare finding and was not associated with mortality increase.

Very little data on the R-R´ pattern is available. It has sometimes been classified as a part of a fragmented QRS complex which is associated with myocardial scarring and increased mortality in CAD patients (Das et al. 2008). In non-ischaemic dilated cardiomyopathy patients, fragmented QRS was associated with an increased number of cardiac events but not with cardiac fibrosis measured with contrast-enhanced myocardial resonance imaging (Ahn et al. 2013). In our study, the R-R´-pattern was not associated with the diseases studied or increased mortality, and we therefore consider this ECG finding benign.

Limitations

The validity of the results of our study is dependent on the representativeness of the study sample. The study was based on a large, nationally representative observational study of the ethnically homogeneous Finnish population. An observational study cannot, by definition, give conclusive information about causality. Our analysis contained a relatively high number of statistical comparisons, which may produce false positive results. Our results may not be transferable to other populations.

The participation rate in the health examination survey was high (79%), especially when the home interviews were taken into account (91%). Since non-participation is selective with regard to morbidity and disability, high participation rates are essential in examining the prevalence of a chronic disabling disease. It is possible that persons with the most severe disease were not selected for the health examinations.

The prevalence of ECG signs of LVH depends on which criteria are chosen for analysis. In this study, only Minnesota criteria (including clinically widely used Sokolow-Lyon criteria) were used to define LVH. We do not have follow-up data on changes in medications potentially affecting left ventricular mass. ECGs were recorded only once and no data on the progression or regression of ECG changes are available. We did not have echocardiography data for the population.

In the study (**II**) we describe a sophisticated technique for analysis of ST/T changes. Implementing this technique may be impractical, to say the least, for the average cardiologist whereas there is no such limitations related to measuring PRWP (**I**), aVRT+ (**III**) or IVCD (**IV**).

The number of patients with QWMI and UMI may be too small to draw strong conclusion.

The prognostic information presented herein is based on data obtained from the resting ECG. Data from the ECG obtained in urgent situations should not be considered resting ECG.

Strengths

The Health 2000 Survey is an example of fruitful collaboration among different organisations in Finland. As a result of the vast combined databases of the organizations, the researchers have excellent data and maximum coverage within the chosen cohort. Due to well organized Finnish social security system and society, the follow-up information providing mortality data and causes of death information reaches virtually all study patients. Practically all ECGs were successfully recorded and analysed.

Earlier studies of PRWP have been about patients in hospital settings or patients with limited clinical data. There is no information available on the prognosis of PRWP in a population. This is first population wide prospective study reporting prevalence and prognostic information of PRWP both in women and men. PRWP is easy to recognize and it may be another simple ECG tool for clinicians.

Previous population-based studies assessing the prognostic importance of minor ST segment changes have used different classifications schemes for ST segment depression (DeBacquer et al. 1998, Greenland et al. 2003, Kumar et al. 2008, Daviglus et al. 1999, Beckerman et al. 2005). A particular strength of our study, in addition to separating the population according to LVH status, is the quantitative assessment of ST segment depression and T wave amplitude, which enabled the analysis of these parameters as continuous variables. This approach should be preferred, as dichotomisation may lead to a considerable loss of power and residual confounding (Roylston et al. 2006). However, this is a follow-up study of a large population cohort with well-defined baseline parameters.

This is the first population based study reporting prevalence and mortality information of aVRT+ both in men and women. Identifying aVRT+ is as simple as basic ECG interpretation.

This prospective study revealed important prognostic differences between different categories of IVCD in a homogenous population based cohort.

Conclusion

PRWP is a common ECG finding and predicts the risk of total and cardiovascular mortality in women in a general population. This finding could aid in screening general populations at risk of total and cardiovascular mortality.

ST segment depression, regardless of the measurement point, is a robust predictor of cardiovascular death in women in a general population. However, the effect disappears as those with LVH are excluded. This observation highlights the need for the consideration of LVH status when depressed ST segments are observed clinically.

In resting ECG, aVRT+ predicts the risk of CV mortality in both women and men in the general population. T wave positivity in lead aVR is a rather infrequent ECG finding in the general population, but the abnormality is easily recognised and has the potential to represent an efficient screening tool.

IVCD was associated with increased CV mortality but did not increase total mortality. The risk of total and CV mortality associated with non-specific IVCD was twofold and fourfold, respectively. LBBB and incomplete RBBB increased mortality to a lesser extent than non-specific IVCD. RBBB did not increase mortality.

Finally, well-known ECG abnormality FA signified a vast increase in mortality within the Health 2000 population exceeding the very high mortality numbers of both RMI and UMI patients.

Clinical implications

In some individuals, PRWP may be the only sign of a prior MI. In women, PRWP may signify underlying CV disease with increased mortality. Proper treatment of hypertension may be essential, as the adverse influence of PRWP may be linked to hypertension.

Among women, ST segment depression in the lateral leads and lead V5 denotes an increased risk of CV mortality, and possible other CV diseases should be diagnosed.

The presence of aVRT+ independently increases the risk of CV and total mortality even in a general population and among subject with prior MI or CV disease. The adverse influence of aVRT+ is independent of T wave inversion in lead V5. aVRT+ is also related to many CV risk factors which should be taken into consideration.

Non-specific IVCD increases total and CV mortality more than does LBBB. The underlying mechanism of CHF and CHD should be taken into consideration whenever non-specific IVCD is encountered.

The poor prognosis of prior MI should courage clinicians to implement a full arsenal of secondary preventive measures. Finally, this study acts as a reminder of the strong relationship of FA with all-cause mortality.

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ORIGINAL ARTICLE

Prevalence and prognostic value of poor R-wave progression in standard resting electrocardiogram in a general adult population. The Health 2000 Survey

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Abstract

Aims. We examined the prevalence and prognostic impact of poor R-wave progression (PRWP) in a standard electrocardiogram (ECG) in a general population.

Methods. Data and standard resting ECG recording were collected from a large nationally representative (random sample) health examination survey conducted in Finland in 2000–2001. The final study population consisted of 5613 individuals.

Results. The prevalence of PRWP (defined as RV3 ≤ 3 mm and RV2 ≤ RV3) was 7.0% in women and 2.7% in men ($P < 0.001$ for difference). During follow-up of 70 ± 9 months (mean ± SD), 317 patients died (5.6%). Both all-cause and cardiovascular mortality was higher in the group with PRWP than in those without PRWP in both women and men. In Cox regression analysis after adjustment for age, hypertension, diabetes, previous myocardial infarction, and coronary heart disease, the relative risk for all-cause mortality for PRWP was 1.69 (95% CI 0.89–3.22, $P = 0.112$) for men and 2.00 (95% CI 1.28–3.13, $P = 0.002$) for women. For cardiovascular mortality the relative risk for individuals with PRWP was 1.85 (0.74–4.65, $P = 0.19$) for men and 3.02 (1.54–5.93, $P = 0.001$) for women.

Conclusions. PRWP is a common ECG finding and predicts risk for total and cardiovascular mortality in women in a general population.

Key words: *Electrocardiography, mortality, outcome, poor R-wave progression*

Introduction

Electrocardiogram (ECG) changes in the acute setting of a myocardial infarction (MI) are usually characteristic enough to allow confirmation of the diagnosis together with elevated biochemical markers of myocardial injury. Recognition of healed MI is more difficult. Once the ST-T changes stabilize or resolve, only abnormal Q-waves remain (1,2). In some patients, MI-related Q-waves may regress or

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Key messages

- Poor R-wave progression is a common electrocardiogram finding and predicts risk for total and cardiovascular mortality in women in a general population.

Abbreviations

AP	angina pectoris
BMI	body mass index
BP	blood pressure
CHD	coronary heart disease
ECG	electrocardiogram
HDL	high-density lipoprotein
IL	Illinois
LAH	left anterior hemiblock
LBBB	left bundle branch block
LDL	low-density lipoprotein
LVH	left ventricular hypertrophy
MI	myocardial infarction
mRNA	messenger ribonucleic acid
NC	North Carolina
PRWP	poor R-wave progression
RBBB	right bundle branch block
RRWP	reverse R-wave progression
WHO	World Health Organization
WI	Wisconsin

disappear in 4 weeks and in 10%–20% of patients over a 1–2 year period (2–4). Moreover, loss of anterior depolarization forces due to anterior myocardial infarction has long been established clinically and experimentally to produce the abnormally low R-wave amplitude extending from the right into the mid or left precordial leads (5–7). This ECG phenomenon, termed poor R-wave progression (PRWP), is a troublesome clinical finding. Although in many cases indicating myocardial infarction of the anterior wall, the finding is often seen in patients with a variety of cardiac disorders and not infrequently in apparently normal subjects. PRWP or reverse R-wave progression (RRWP) may appear in the presence of incomplete or complete left bundle branch block (LBBB), right bundle branch block (RBBB), left ventricular hypertrophy (LVH), left anterior hemiblock (LAH), pseudo-Q-wave caused by perpendicular orientation of the initial QRS deflection to the lead axis, mitral valve prolapse, and abnormally low diaphragm position in pulmonary emphysema (8). In normal subjects without evident cardiac or pulmonary disease, the ECG pattern may be caused by a shift of the transitional zone to the left or by an abnormally high placement of the mid-precordial chest leads.

PRWP was observed in 19% of women and 11% of men who were hospitalized adult patients (9). In a university hospital setting with adult patients, the prevalence of PRWP and RRWP was 7%–10% and 1%–2%, respectively (10). PRWP is a frequent abnormal ECG pattern faced in insurance medicine (11). In 1250 symptomatic patients who were evaluated for suspected angina pectoris, PRWP was present in 8%, with equal distribution in both sexes (5). However, the prevalence and clinical significance of the ECG finding in the general population is not well known (12).

Therefore, the aim of the present study was to examine the prevalence and prognostic impact of PRWP in standard resting ECG in a general population. In addition, we tested separately for men and women whether PRWP increases the risk of all-cause and cardiovascular mortality.

Materials and methods

This study is based on the Health 2000 Survey, a major Finnish population study. It was carried out in 2000–2001, and a representative stratified random cluster sample of the Finnish population was examined. For the population aged $\geqslant$80 years, the sampling probability was twice as high as among those $<$80. After a home interview, a comprehensive health examination, including questionnaires, measurements (e.g. blood pressure, resting ECG), and physician's physical examination, was performed. The implementation of the survey is described in detail elsewhere (13). One of the goals of the Health 2000 Survey was to obtain contemporary information about major diseases in Finland.

The Health 2000 sample comprised 8028 individuals (3637 men and 4391 women) aged 30+, of whom 79% (6354 individuals; 2876 men and 3478 women) participated in the health examination. The National Hospital Discharge Register and the national register on rights to reimbursements for medication costs were linked to the Health 2000 Survey data. The study protocol of the Health 2000 survey was approved by the Epidemiology Ethics Committee of the Helsinki and Uusimaa Hospital District. The participants in the survey signed an informed consent both before the health interview and at the beginning of the health examination.

Laboratory tests

Venous blood samples were drawn from the antecubital vein. High-density lipoprotein (HDL) cholesterol, total cholesterol, triglyceride, and plasma glucose concentrations were determined enzymatically (Roche Diagnostics, GmbH, Mannheim, Germany

for HDL; Olympus System Reagent, Hamburg, Germany for total cholesterol, triglycerides, and glucose) with a clinical chemistry analyzer (Olympus, AU400, Hamburg, Germany). Low-density lipoprotein (LDL) cholesterol was calculated with the Friedewald formula.

ECG registration and analysis

Standard 12-lead ECGs were recorded in the resting supine position using recommended standardized procedures and MAC 5000 recorder (by Marquette Hellige, Freiburg, Germany and Milwaukee, WI, USA). ECG was recorded and printed using the paper speed of 50 mm/sec. The maximal filter setting of the system (150 Hz) was used. The ECG analyses were performed by a Health 2000 investigator blinded to the clinical data of the patient. The Minnesota coding was performed at the Institute of Cardiology, Kaunas Medical Academy, Lithuania by two investigators, who also were blinded to the clinical data of the patient. ECGs were obtained successfully in 6318 individuals (99%) who attended the health examination. ECG data were stored electronically and transmitted in dispatches of approximately 100 ECGs per transmission to the National Institute for Health and Welfare for further analysis. Abnormalities identified visually in the ECG strips were coded in accordance with the Minnesota coding scheme (14). The electrical recordings were analyzed by means of Magellan software program (Marquette Electronics Inc., Milwaukee, WI, USA). At this phase, the measurement points were checked and corrected if needed. Nineteen ECGs were rejected owing to data lost in further process, leaving 6299 ECGs for analysis.

Definition of coronary heart disease

The examining physicians followed detailed written instructions and applied uniform diagnostic criteria in accordance with good clinical practice. The examining physician critically assessed history and available documents and performed a structured physical examination. Diagnostic assessments were recorded on structured forms. Information on the rights for drug reimbursements was obtained from the national register. All persons with coronary heart disease (CHD) in Finland are entitled to special reimbursement for medication costs. To obtain that right, they have to apply for it and append a medical certificate by their physician to show that the objective criteria of CHD are fulfilled. The study participants were asked whether they used any medications, and the names and doses of these medications were recorded. Persons with typical angina pectoris (AP) symptoms were identified by the World Health Organization (WHO) chest pain questionnaire. Also, history of coronary by-pass surgery or percutaneous coronary intervention was checked during the interview.

Information on previous hospitalization for MI or CHD was obtained from hospital discharge summaries that study participants brought along or from the National Hospital Discharge Register. The Finnish hospital discharge register has been shown to be valid in identifying major CHD events (15).

Classification as CHD required at least one of the following: diagnosis of MI and/or AP during the field health examination by a physician, large Q-waves in resting ECG, hospitalization for CHD (International Classification of Diseases (ICD)-8 or ICD-9 codes 410–414, or ICD-10 codes I20–I25), a history of coronary revascularization procedure, the right to drug reimbursements for CHD, or the use of nitroglycerine combined with an anticoagulant, acetyl salicylic acid, or beta-blocker. Typical AP symptoms identified by the WHO chest pain questionnaire only were not considered to be an indicator of CHD.

Myocardial infarction (MI)

Classification for MI required either a clinical diagnosis of old MI by the examining physician, large Q-waves in resting ECG, or a previous discharge diagnosis of MI (ICD-8 or ICD-9 code 410, or ICD-10 codes I21–I22). MI was defined as a positive history of the condition in the medical records or old MI on ECG or typical self-reported history of MI treated in hospital. Large Q-waves indicating probable previous MI included Minnesota codes 1.1–1.3.

Other measurements and definitions

Height and weight were measured and body mass index (BMI) calculated. Blood pressure was measured with a mercury sphygmomanometer (Mercuro 300, Speidel & Keller, Juningen, Germany) from the right arm. The first measurement was carried out after at least 5 minutes of rest in the sitting position. Korotkoff's first phase was used as the sign of systolic blood pressure, and the fifth phase as the sign of diastolic pressure. The measurement was repeated 2 minutes after the first measurement. The average of the two measurements was used in the analysis. Clinic hypertension was defined as a clinic blood pressure (BP) $\geq$140/90 mmHg. Diabetes mellitus was defined as a serum glucose level of 7.0 mmol/L or greater or a history of the use of oral hypoglycemic agents or insulin injections. Smoking was defined as the daily use of tobacco products.

Exclusion criteria

Patients with suspected pathological Q/QS in ECG were excluded using Minnesota codes (MC) 1.1-1.3. All the patients with ventricular conduction defects, mainly LBBB or right bundle branch block (RBBB) or LAH, were excluded (MC 7). Also, one individual with ECG signs of the Wolff-Parkinson-White syndrome was excluded. Finally, 5613 ECGs were used for analysis, 3151 from female and 2462 from male individuals.

Definition of PRWP

We defined PRWP as an R-wave in the precordial lead V3 $\leq$ 3 mm and R in lead V2 $\leq$ R in lead V3 (16) (Figure 1). This criterion was first adopted by Zema et al. (in 1980) and has been used commonly in studies concerning PRWP (5,12,16,17). We did not include RRWP, used in some studies (5), in our definition.

Follow-up

The information about deaths was obtained from the Statistic Finland after follow-up of 70 $\pm$ 9 months.

Statistical analyses

For the analyses of prevalence, the data were weighted to reduce the bias due to non-response and to correct for the over-sampling in the age group of 80 years and older. The prevalence of PRWP was determined within the sexes and various age groups. The complex sampling design was taken into account by using SUDAAN procedures version 10.0 (SUDAAN Language Manual; RTI International, Research Triangle Park, NC). The rest of the statistical analyses were performed with the SPSS release 15.0 for Windows (SPSS Inc., Chicago, IL) and SAS version 9.1 (SAS Institute, Inc., Cary, NC). The difference in PRWP prevalence between sexes was determined with logistic regression using PRWP as a dependent and sex as an independent variable. Thereafter, women and men were analyzed in their own groups. Continuous subject characteristics were compared between those with and without PRWP using the *t* test for independent samples and the chi-square test for dichotomous variables, including mortality. The relative risks of PRWP for all-cause and cardiovascular death were estimated with a Cox proportional hazards model using the following covariates: age, hypertension, diabetes, previous MI, and CHD. $P < 0.05$ was considered statistically significant in all the analyses.

Power calculation was performed for Cox regression separately for men and women. Given two-sided alpha of 0.05, standard deviation of PRWP as well as the number of subjects and cardiovascular deaths, the power to reach clinically meaningful relative risk of 1.5 is 90% for men and 100% for women.

Results

The prevalence of PRWP for three age groups among men and women is shown in Figure 2. The ECG finding was more frequent in women than in men for all the age groups. Altogether there were 287 subjects with PRWP in their resting ECG (Table I), 2.7% of men and 7.0% of women ($P < 0.001$ for difference between men and women). Women were significantly more prone to have PRWP than men (odds ratio 2.58, $P < 0.001$ in logistic regression).

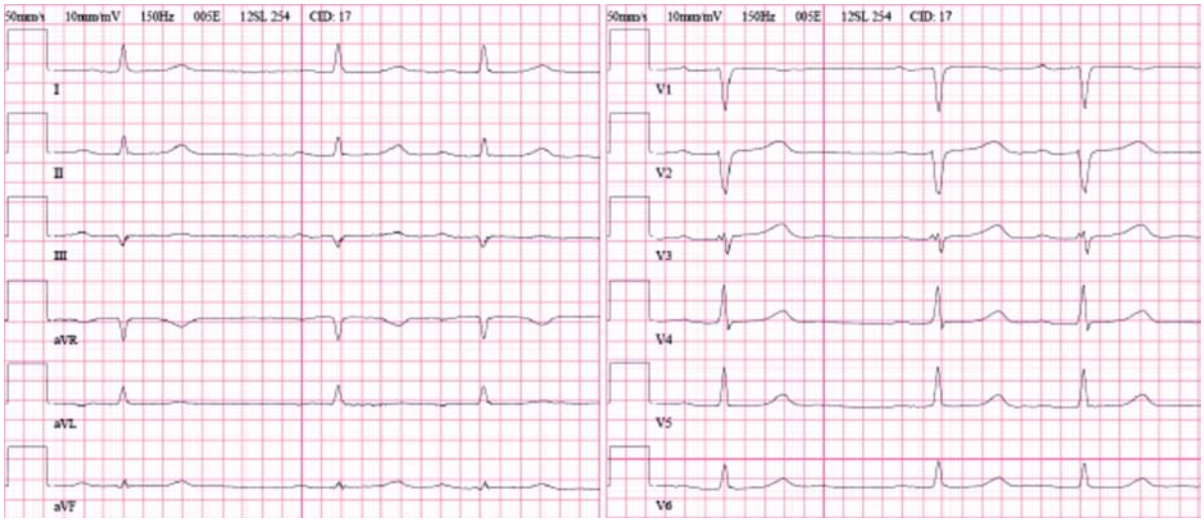

Figure 1. Electrocardiogram of 62-year-old woman with poor R-wave progression (PRWP) without organic heart disease.

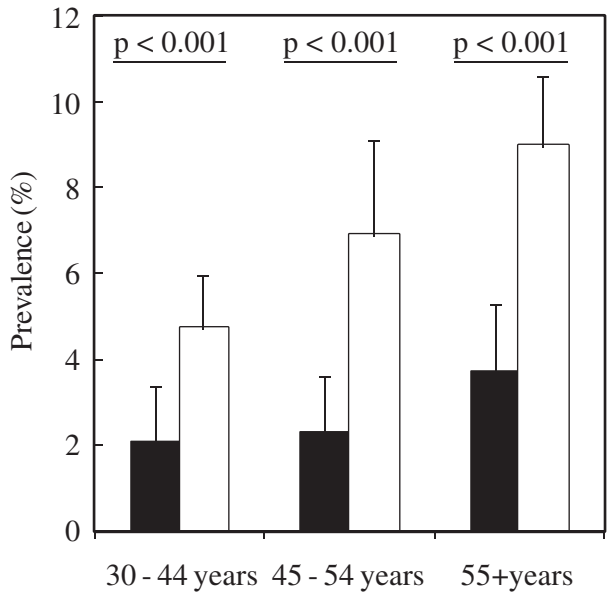

Figure 2. Prevalence of poor R-wave progression for the three age groups among men (black bars) and women (white bars); the upper 95% confidence interval limits and the significances of the difference between the sexes are shown (chi-square test).

Men and women with PRWP were older, had more diabetes, CHD, and previous MIs, than did those without PRWP, while for hypertension there was a difference between the groups that only concerned females (Tables I and II).

During follow-up of 70 ± 9 months (mean ± SD), 317 patients died (5.6%); 120 (2.1%) were cardiovascular deaths. Both all-cause and cardiovascular mortality were higher in the group with PRWP than in those without PRWP in both women and men (Table II).

A total of 787 persons (14.0%) fulfilled Minnesota criteria for left or right ventricular hypertrophy (Minnesota code 3.1 and/or 3.3). Thirty-three (4%) individuals with and 254 (5.3%) without ECG markers of ventricular hypertrophy fulfilled criteria for PRWP. A negative P-wave in leads V2 and/or V3 was observed in 65 individuals (1.2%), 36 women and 29 men.

In Cox regression analysis after adjustment for age, the relative risk for all-cause mortality for PRWP was 1.89 (95% CI 1.00–3.59, $P = 0.051$) for men and 2.22 (95% CI 1.42–3.46, $P < 0.001$) for women. For cardiovascular mortality, the relative risk for individuals with PRWP was 2.28 (0.91–5.68, $P = 0.08$) for men and 3.47 (1.78–6.76, $P < 0.001$) for women. When individuals with previous MI ($n = 166$) were excluded, the results remained essentially similar: the relative risk for all-cause mortality for PRWP was 1.78 (95% CI 0.83–3.80, $P = 0.14$) for men and 2.44 (95% CI 1.54–3.89, $P < 0.001$) for women; for cardiovascular mortality the relative risk was 1.33 (0.32–5.49, $P = 0.69$) for men and 3.57 (95% CI 1.71–7.42, $P = 0.001$) for women. When individuals with ventricular hypertrophy were excluded from the analyses, the relative risk for all-cause mortality was 1.78 (95% CI 0.87–3.64, $P = 0.12$) for men and 2.31 (1.42–3.76, $P < 0.001$) for women.

In Cox regression analysis after adjustment for age, hypertension, diabetes, previous MI, and CHD, the relative risk for all-cause mortality for PRWP was 1.69 (95% CI 0.89–3.22, $P = 0.112$) for men and 2.00 (95% CI 1.28–3.13, $P = 0.002$) for women, respectively. For cardiovascular mortality, the relative risk for individuals with PRWP was 1.85 (0.74–4.65, $P = 0.19$) for men and 3.02 (1.54–5.93, $P = 0.001$) for women. When also subjects with inferior and anterior Q-waves were included in the analyses, the relative risk for all-cause mortality for PRWP was 1.86 (95% CI 1.12–3.09, $P = 0.017$) for men and 2.17 (95% CI 1.45–3.24, $P < 0.001$) for women.

Table I. Baseline characteristics of The Health 2000 Survey participants.

	Men					Women				
	PRWP− ($n = 2393$)		PRWP+ ($n = 69$)			PRWP− ($n = 2933$)		PRWP+ ($n = 218$)		
	Mean	SD	Mean	SD	*P*	Mean	SD	Mean	SD	*P*
Age	50	13	56	15	<0.001	53	15	57	15	<0.001
Height	176	7	173	7	<0.01	162	7	162	6	0.88
Weight	84	14	82	14	0.21	70	14	72	14	0.07
BMI	27.1	4.1	27.2	4.2	0.84	26.8	5.0	27.5	5.3	0.05
fS-Gluk (mmol/L)	5.7	1.3	5.9	2.1	0.14	5.4	1.1	5.6	1.4	0.02
fS-Chol (mmol/L)	6.0	1.1	5.9	1.0	0.40	5.9	1.1	6.0	1.1	0.28
fS-Chol-HDL (mmol/L)	1.2	0.3	1.2	0.4	0.30	1.4	0.4	1.4	0.4	0.83
fS-Chol-LDL (mmol/L)	3.9	1.0	3.7	1.0	0.13	3.6	1.0	3.7	1.1	0.47
fS-Trigly (mmol/L)	1.8	1.2	2.0	1.5	0.22	1.4	0.7	1.5	0.7	0.37

PRWP− = no poor R-wave progression; PRWP+ = poor R-wave progression; SD = standard deviation; BMI = body mass index; fS-Gluk = fasting serum glucose; fS-Chol = fasting serum cholesterol; fS-Chol-HDL = fasting serum high-density lipoprotein cholesterol; fS-Chol-LDL = fasting serum low-density lipoprotein cholesterol; fS-Trigly = fasting serum triglyceride.

Table II. Clinical characteristics and mortality of the study population.

	Men			Women		
	PRWP− *n* (%)	PRWP+ *n* (%)	*P*	PRWP− *n* (%)	PRWP+ *n* (%)	*P*
Regular smoking	658 (27.6)	25 (36.2)	0.13	490 (16.8)	41 (18.9)	0.45
COPD	35 (1.5)	2 (2.9)	0.28	33 (1.1)	4 (1.8)	0.32
Hypertension	713 (29.9)	23 (33.3)	0.59	851 (29.1)	88 (40.6)	<0.01
Diabetes	122 (5.1)	8 (11.6)	0.03	141 (4.8)	25 (11.5)	<0.001
LVH/RVH	503 (21.1)	11 (15.9)	0.07	284 (9.7)	22 (10.1)	0.16
CHD						
No	2159 (90.2)	52 (75.4)		2652 (90.4)	188 (86.2)	
Possible	35 (1.5)	0 (0)	<0.001	72 (2.5)	6 (2.8)	0.10
Yes	199 (8.3)	17 (24.6)		209 (7.1)	24 (11.0)	
MI						
No	2304 (96.3)	60 (87)		2876 (98.1)	207 (95)	
Possible	18 (0.8)	2 (2.9)	<0.001	12 (0.4)	3 (1.4)	<0.01
Yes	71 (3)	7 (10.1)		45 (1.5)	8 (3.7)	
Death, all-cause	149 (6.2)	10 (14.5)	0.01	135 (4.6)	23 (10.6)	<0.01
Death, cardiovascular	60 (2.5)	5 (7.2)	0.03	44 (1.5)	11 (5)	<0.01
Medication						
Beta-blocker	258 (10.8)	16 (23.2)	<0.01	426 (14.5)	46 (21.1)	0.01
Ccb	121 (5.1)	4 (5.8)	0.78	177 (6.0)	19 (8.7)	0.14
ACI/ARB	188 (7.9)	8 (11.6)	0.26	227 (7.7)	20 (9.2)	0.43

Follow-up of 70 ± 9 months (mean ± SD).
PRWP− = no poor R-wave progression; PRWP+ = poor R-wave progression; COPD = chronic obstructive pulmonary disease; LVH = left ventricular hypertrophy; RVH = right ventricular hypertrophy; CHD = coronary heart disease; MI = myocardial infarction; Ccb = calcium channel blocker; ACI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor antagonist.

For cardiovascular mortality, the relative risk for individuals with PRWP was 2.09 (95% CI 1.02–4.26, $P = 0.043$) for men and 2.88 (95% CI 1.56–5.30, $P = 0.001$) for women.

Discussion

This is, to our knowledge, the first study to show the prevalence of PRWP in a general adult population. In our study population, PRWP proved to be a common ECG finding. Additionally, this ECG phenomenon was more frequent in women than in men in three age groups 30 years or older. Importantly, PRWP predicted risk for total and cardiovascular mortality in women. The findings of the present study could be helpful in screening general populations for risk of total and cardiovascular mortality.

Differences in the reported prevalence of PRWP in non-population-based materials are partly explained by different criteria for the ECG finding. DePace et al. reviewed the resting ECGs in 1250 consecutive patients who underwent thallium-201 scintigraphy (5). Using the same inclusion criteria but slightly different exclusion criteria as in the present study, they reported an 8% prevalence of PRWP in their patients, who all had chest pain or were evaluated for suspected AP. At Glasgow Royal Infirmary, the prevalence of PRWP was estimated by reviewing all electrocardiograms ($n = 1315$) recorded over a 2-week period. As in the present study, PRWP was more frequent in women (19% versus 11%) than in men (9). The authors also found that the positioning of electrodes beneath rather than above the breast was not responsible for the increased prevalence of poor R-wave progression in women with a variety of clinical problems. Negative P-waves in leads V2 and/or V3, a possible sign of high electrode placement (18), was found with a very low prevalence ($n = 65$, 1.2%) and without major impact on the study results.

In the present study, both men and women with PRWP had increased unadjusted total and cardiovascular mortality during an average follow-up of 5.8 years. In Cox regression analysis after adjustment for age, hypertension, diabetes, previous MI, and CHD, PRWP was an independent determinant of both all-cause and cardiovascular mortality in women, but not in men (for cardiovascular mortality the relative risk was 3.02 ($P = 0.001$) for women and 1.85 ($P = 0.19$) for men). When also subjects with inferior and anterior Q-waves were included in the analysis, PRWP independently predicted all-cause and cardiovascular mortality in both sexes. This is not surprising as Q-wave MI is a well documented etiology of PRWP.

Interestingly, the risk increase is in the same range as that reported with the presence of major or minor Q-waves, and higher than the risk

associated with minor ST-segment and/or T-wave abnormalities (19,20). The explanation for the finding that PRWP predicted mortality independently of CHD and MI in women but not in men is not fully evident from the present findings, but an explanation could be provided by the fact that PRWP was more often associated with CHD and MI in men than in women (Table II). In accordance, PRWP strongly predicted mortality in women after excluding subjects with previous myocardial infarction from the analysis in the present study. Also, earlier reports support the view that PRWP is strongly associated with CHD and MI and that this association appears to be more often visible in men than in women: in a retrospective study, men with PRWP had a higher probability than did women for anterior wall motion abnormality on echocardiography (21). In the study by DePace et al. (5), men with PRWP had a higher probability for anterior scar than did women by thallium scintigraphy. Zema et al. showed that the relative risk of autopsy-documented anterior MI was 6-fold increased in patients meeting PRWP criteria (22). In another study, wall motion abnormalities were associated with PRWP in patients with left ventricular end-diastolic diameters 5 cm or more, but not in patients with smaller ventricular diameters (23). Another explanation for CHD- and MI-independent predictive power of PRWP in women could be that women had more undiagnosed CHD or MI than did men in the present general population. Altogether, these findings support the view that PRWP could be a useful screening tool for cardiovascular morbidity and mortality in general populations of women.

In our study, men with PRWP had more than two times higher probability for CHD or MI than did women. However, in the vast majority of individuals from both sexes, PRWP was not associated with known CHD or a history of MI. In post-MI left ventricular remodeling, the infarct area undergoes proliferation and differentiation of fibroblasts and other interstitial cells and the elaboration of bioactive molecules which contribute to a robust synthesis of extracellular matrix (ECM) for the purposes of scar formation (24). Reappearance of R-waves in anterior MI was associated with a larger extent of stunned but viable myocardium and a trend towards a smaller amount of necrotic myocardium, compared to patients with persisting Q-waves (25). Magnetic resonance imaging has shown that MI size is associated with Q-waves after ST-elevation MI (26). The fact that we excluded individuals with pathological Q-waves may have resulted in the selection of a relatively low-risk post-MI sub-population of individuals in our study. This in turn could be one explanation for the ECG phenomenon not being associated with poor outcome in males.

It is well known that patients with LVH represent a subgroup of PRWP. To make our study results applicable to a large patient group, we decided not to exclude patients with ECG criteria for LVH from our main analyses. However, excluding individuals with LVH had no major impact on the study results. The prevalence of LVH in the ECG depends on which criteria are chosen for analysis. In this study, Minnesota criteria (including clinically widely used Sokolow-Lyon criteria) were used to define LVH, which may be considered as a study limitation. Another limitation is the fact that echocardiographic data on left ventricular function or LVH were not available in the present study.

The validity of the results of our study is dependent on the representativeness of the study sample. The study was based on a large nationally representative health examination survey conducted in Finland. Participation rate in the health examination survey was high (79%), especially when the home interviews were taken into account (91%). Since non-participation is selective with regard to morbidity and disability, high participation rates are essential in examining the prevalence of a chronic disabling disease. It is possible that persons with the most severe disease were not selected for the health examinations.

In conclusion, PRWP is a common ECG finding and predicts risk for total and cardiovascular mortality in women in a general population. This finding could aid in screening general populations for risk of total and cardiovascular mortality.

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ORIGINAL ARTICLE

Prognostic implications of quantitative ST-segment characteristics and T-wave amplitude for cardiovascular mortality in a general population from the Health 2000 Survey

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Abstract

Aims. We determined the gender-specific prognostic importance of quantitative measures of the ST segment and T wave in a community cohort. *Methods.* Data were collected from 5613 Finnish individuals. Four electrocardiogram (ECG) lead groups were used: anterior, lateral, inferior, and lead V5. ST-segment depression, determined at four points along the ST segment, and T-wave amplitude were treated as continuous variables in Cox regression analyses. *Results.* During a median follow-up period of 72.4 months, 120 cardiovascular deaths were registered. Among women, lateral lead group as well as lead V5 showed highly significant adjusted hazard ratios at all four ST-depression assessment points. This significance was lost in women ≥ 55 years when those with ECG-based criteria of left ventricular hypertrophy (LVH) were excluded. Results for ST-segment depression were not significant among men. As those with LVH were excluded, men ≥ 55 years showed borderline significance. T-wave amplitude did not reach significance among men, while lateral leads and lead V5 bore prognostic information among women. *Conclusion.* Quantitative ST-segment depression, regardless of the measurement point, allows prediction of cardiovascular death in women within a general population. However, the effect disappears as those with LVH are excluded. This observation highlights the need for consideration of LVH when depressed ST segments are clinically observed.

Key words: *Prognostics, quantitative, ST-segment depression, ST slope, T-wave amplitude*

Introduction

ST-segment depression with or without associated T-wave abnormalities is frequently encountered in various clinical situations and in the community (1–4). In addition to myocardial ischemia and acute coronary syndrome, in which the detrimental impact of even minor ST-segment depression or T-wave abnormality has been well documented (5–7), the most common causes of ST-segment depression are tachycardia because of the overlap with atrial

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Key messages

- Quantitative ST-segment depression, regardless of the measurement point along the ST segment, allows prediction of cardiovascular death in women within a general population.
- The predictivity among women disappears as those with left ventricular hypertrophy are excluded. This observation highlights the need for consideration of left ventricular hypertrophy when depressed ST segments are clinically observed.

Abbreviations

BMI	body mass index
CHD	coronary heart disease
ECG	electrocardiogram
HDL	high-density lipoprotein
LDL	low-density lipoprotein
LVH	left ventricular hypertrophy
WHO	World Health Organization

repolarization and delayed repolarization secondary to slow depolarization (e.g. ventricular hypertrophy, bundle branch block, pre-excitation) (8). Regarding population-based studies, an association of major (9) or categorically defined minor (1,2,10–12) abnormalities of the ST segment and T wave with heightened risk of mortality or cardiovascular events has been reported.

Gender differences in diagnosis, treatment, and prognosis of cardiovascular disease have received attention in preventive cardiology. Minnesota codes indicating slightly 'ischemic electrocardiogram (ECG)' (mainly minor ST-segment depression and T-wave changes) have shown similarly increased risk for mortality in both women and men in population studies (1,2,10), including the elderly (13). However, none of the population-based studies analyzed changes in the ST segment and T wave as continuous, quantifiable variables.

The classic strain pattern, defined as downsloping convex ST segment with inverted asymmetrical T waves opposite to the QRS axis in leads V5 and/or V6 on the ECG, is a well recognized marker of the presence and severity of anatomic left ventricular hypertrophy (LVH). The strain pattern has been associated with adverse prognosis in a variety of populations (14–16), including hypertensive patients (15), and it has been designated as the primary marker of untoward outcomes when ECG LVH criteria are used for risk stratification (15,16). Despite the well defined impact of LVH on ST segment and mortality, none of the previous population-based studies has compared the association between minor ST-segment changes and mortality in separate analyses for the entire study population and those without LVH.

The aim of the present study was to determine the gender-specific prognostic impact of quantitative measures of ST-segment characteristics and T-wave amplitude in a population-based cohort, with and without known coronary heart disease (CHD), taking possible LVH into account.

Materials

This study is based on the Health 2000 Survey (17), a major Finnish population study designed to obtain contemporary information about major diseases in Finland. A representative stratified random cluster sample of the Finnish population was examined in 2000–2001. For the group aged ≥ 80 years, the sampling probability was twice as high as among those < 80. After a home interview, a comprehensive health examination including questionnaires, measurements (e.g. blood pressure, resting ECG), and physician's physical examination was performed.

The Health 2000 Survey sample comprised 8028 individuals (3637 men and 4391 women) aged 30+, of whom 79% (6354 individuals, 2876 men and 3478 women) participated in the health examination. The National Hospital Discharge Register and the national register on rights to drug reimbursements were linked to the Health 2000 Survey data. The study protocol of the Health 2000 Survey was approved by the Epidemiology Ethics Committee of the Helsinki and Uusimaa Hospital District. The participants in the survey signed an informed consent both before the health interview and at the beginning of the health examination.

Laboratory tests

Serum high-density lipoprotein (HDL) cholesterol, total cholesterol, triglyceride, and plasma glucose concentrations were determined enzymatically (Roche Diagnostics, GmbH, Mannheim, Germany for HDL; Olympus System Reagent, Hamburg, Germany, for total cholesterol, triglycerides, and glucose) from venous blood samples with a clinical chemistry analyzer (Olympus, AU400, Hamburg, Germany). Low-density lipoprotein (LDL) cholesterol was calculated with the Friedewald formula.

ECG registration and analysis

During the health examination, standard 12-lead ECGs were recorded in the resting supine position using recommended standardized procedures and MAC 5000 recorder (by Marquette Hellige, Freiburg, Germany, and Milwaukee, WI, USA). ECGs were recorded at maximal low-pass filter setting (150 Hz), stored electronically, and printed at paper speed of 50 mm/s. ECGs were obtained successfully in 6318 individuals (99%) and transmitted to the National Institute for Health and Welfare for further analysis. The ECG analyses were performed by a Health 2000 Survey investigator blinded to clinical status. The electronic recordings were analyzed with Magellan software (Marquette Electronics Inc., Milwaukee, WI, USA), and measurements were checked and corrected if needed. The Minnesota coding (18) was performed at the Institute of Cardiology, Kaunas Medical Academy, Lithuania, by two investigators blinded to clinical status. Nineteen ECGs were rejected from further processing due to loss of data, with 6299 ECGs remaining for analysis.

The lead groups used in the present analysis were anterior (V1–V4), lateral (V5, V6, I, aVL), and inferior (II, III, aVF). V5 as a single lead is shown for comparison. Four measurement points along the ST segment were used for determination of ST-segment deviation: J point as well as 40 and 80 ms thereafter, and, additionally, the lower of the deviations at J point and J + 80 ms. ST slope was defined as the difference between ST-segment deviation at J + 80 ms and J point. The ST segments with a shift of ≤ 0.5 mm were labeled as horizontal, those with a positive change > 0.5 mm as having a positive slope (ascending), and those with a negative change > 0.5 mm as having a negative slope (descending).

Definition of coronary heart disease

The examining physicians followed detailed written instructions and applied uniform diagnostic criteria. They critically assessed history and available documents including records of coronary bypass surgery or percutaneous coronary intervention and performed a structured physical examination. Diagnostic assessments were recorded on structured forms. Information on patients' rights for drug reimbursements, which mandate a medical certificate confirming objective criteria of CHD, was obtained from the national register. Names and dosages of subject-reported medications were recorded. Patients with typical angina pectoris symptoms were identified by World Health Organization (WHO) chest pain questionnaire, but angina pectoris alone was not considered a sufficient indicator of CHD. Information on previous hospitalization for myocardial infarction or CHD was obtained from hospital discharge summaries provided by study participants or obtained from the National Hospital Discharge Register. The Finnish hospital discharge register has been shown to be valid in identifying major CHD events (19).

Classification as CHD required at least one of the following: diagnosis of myocardial infarction and/or angina pectoris during the field health examination by a physician, large Q waves in resting ECG, hospitalization for CHD (ICD-8 or ICD-9 codes 410–414 or ICD-10 codes I20–I25), a history of coronary revascularization, the right to drug reimbursement for CHD, or the use of nitroglycerine combined with an anticoagulant, acetyl salicylic acid, or beta-blocker.

Myocardial infarction

Classification of myocardial infarction required either a clinical diagnosis of old myocardial infarction by the examining physician, large Q waves in resting ECG, or a previous discharge diagnosis of myocardial infarction (ICD-8 or ICD-9 code 410 or ICD-10 codes I21–I22), or typical self-reported history of myocardial infarction treated in hospital.

Other measurements and definitions

Height and weight were measured, and body mass index (BMI) was calculated. Blood pressure was measured with a mercury sphygmomanometer (Mercuro 300, Speidel & Keller, Juningen, Germany) from the right arm. An average of two measurements was used, the first measurement taken after at least 5 minutes of rest in the sitting position and the second at 2 minutes thereafter. Hypertension was defined as blood pressure $\geq$ 140/90 mmHg. Diabetes mellitus was defined as a serum glucose level $\geq$ 7.0 mmol/L or a history of use of oral hypoglycemic agents or insulin injections. Smoking was defined as the daily use of tobacco products.

Exclusion criteria

Patients with suspected pathological Q/QS waves in ECG were excluded using Minnesota codes 1.1–1.3. All patients with ventricular conduction defects, mainly left or right bundle branch block or left anterior hemiblock, were excluded (Minnesota code 7). One individual with ECG signs of Wolff-Parkinson-White syndrome was excluded. The total ECG analysis was based on 5613 participants comprised of 3151 female and 2462 male subjects (Tables I and II).

Follow-up

Mortality information until October 2006 was gathered by linking the personal identity code from the Health 2000 Survey database to the Causes of Death Register, maintained by Statistics Finland, which records 100% of deaths of Finnish citizens at home and nearly 100% abroad.

Statistical analyses

Comparisons in variables were calculated with either the *t* test for independent samples or the chi-square test as applicable (Tables I–III). Cox proportional hazards models were constructed separately for maximum ST-segment depression, minimum T-wave amplitude, and ST slope based on the four different lead groups (anterior, lateral, inferior, and V5). The endpoint was cardiovascular death, and models used the following covariates: age, previous myocardial infarction, and CHD. ST-segment depression and T-wave amplitude were handled as continuous variables, and hazard ratios were scaled for a change of 1 mm. The proportionality assumption was checked for the main analyses based on correlations of survival rankings with Schoenfeld residuals; all the covariates fulfilled this criterion. Age group analyses (for 30–44, 45–54, and ≥ 55 years) were performed for participants according to LVH status (Minnesota codes 3.1, 3.3, or 3.4, which are based on voltage criteria) (Table III). The complex sampling design was taken into account by correcting for the oversampling of subjects ≥ 80 years of age. All analyses were performed with the SPSS release 16.0 for Windows (SPSS Inc., Chicago, Illinois). Statistical significance was based on $P < 0.05$. Analyses and power calculations for ST-segment depression and slope and T-wave amplitude were performed for Cox regression separately for men and women. With two-sided alpha of 0.05, the standard deviation of ST-segment depression, as well as the number of subjects and cardiovascular deaths, the power to reach clinically meaningful relative risk of 1.5 was 100% for both sexes.

Results

Participant characteristics are given in Tables I and II. The minimum ST-segment levels and T-wave amplitudes for men and women within all the three age groups, separately, are reported in Table III. Women presented with slightly lower ST-segment levels than men in most lead groups. T-wave amplitude was clearly decreased in women in comparison to men in the anterior leads and, to a lesser degree, in the lateral leads, while men had somewhat lower amplitudes in the inferior leads. Most of the differences were statistically significant in our large study population, even though several of the margins would not be clinically discernable. Among individuals < 55 years old, negative ST slope was infrequent (< 1%) except in inferior leads.

ST segment and T-wave amplitude in relation to cardiovascular mortality

The median follow-up period was 72.4 months (interquartile range 70.8–73.2 months). A total of 317 deaths (5.6% of the population) were registered, and 120 (2.1%) of those were of cardiovascular causes. Cardiovascular mortality was 0.37%/year. The diseases causing cardiovascular deaths were acute myocardial infarction (ICD-10 codes I21–I22), 37 patients; other manifestations of CHD (I25), 35;

Table I. Patient characteristics for continuous parameters.

	Men					Women				
	No CV death (n = 2397)		CV death (n = 65)			No CV death (n = 3096)		CV death (n = 55)		
	Mean	SD	Mean	SD	P	Mean	SD	Mean	SD	P
Age	50	13	68	13	0.000	52	15	77	9	0.000
Height (cm)	176	7	171	8	0.000	162	7	156	7	0.000
Weight (kg)	84	14	78	12	0.000	70	14	69	16	0.268
BMI	27.1	4.1	26.5	3.6	0.145	26.8	5.1	28.1	5.2	0.073
fS-Gluk (mmol/L)	5.7	1.3	6.6	3.1	0.000	5.4	1.1	6.6	2.2	0.000
fS-Kol (mmol/L)	6.0	1.1	6.0	1.1	0.731	5.9	1.1	6.4	1.2	0.016
fS-Kol-HDL (mmol/L)	1.2	0.3	1.1	0.3	0.019	1.4	0.4	1.4	0.4	0.008
fS-Kol-LDL (mmol/L)	3.9	1.0	3.9	1.1	0.793	3.6	1.0	3.9	1.2	0.072
fS-Trigly (mmol/L)	1.8	1.2	2.0	1.4	0.239	1.4	0.7	2.0	1.1	0.000

BMI = body mass index; CV = cardiovascular; fS-Gluk = fasting serum glucose; fS-Kol = fasting serum cholesterol; fS-Kol-HDL = fasting serum high-density lipoprotein cholesterol; fS-Kol-LDL = fasting serum low-density lipoprotein cholesterol; fS-Trigly = fasting serum triglyceride; SD = standard deviation.

Table II. Patient characteristics for dichotomous parameters.

	Men			Women		
	No CV death *n* (%)	CV death *n* (%)	*P*	No CV death *n* (%)	CV death *n* (%)	*P*
Regular smoking	662 (28.1)	21 (34.3)	0.248	527 (17.3)	4 (9.5)	0.032
COPD	34 (1.4)	3 (5.3)	0.073	34 (1.1)	3 (7.6)	0.026
Hypertension	708 (29.6)	28 (43.2)	0.016	909 (29.6)	30 (56.5)	0.000
Diabetes	118 (4.8)	12 (20.4)	0.000	151 (4.7)	15 (26.1)	0.000
LVH	496 (20.7)	18 (26.4)	0.369	292 (9.3)	14 (30.0)	0.000
CHD						
No	2172 (90.6)	39 (60.0)		2813 (90.9)	27 (49.1)	
Possible	33 (1.4)	2 (3.1)	0.000	70 (2.3)	8 (14.5)	0.000
Yes	192 (8.0)	24 (36.9)		213 (6.9)	20 (36.4)	
Myocardial infarction						
No	2316 (96.6)	48 (73.8)		3038 (98.1)	45 (81.8)	
Possible	17 (0.7)	3 (4.6)	0.000	13 (0.4)	2 (3.6)	0.000
Yes	64 (2.7)	14 (21.5)		45 (1.5)	8 (14.5)	
Medication						
Beta-blocker	254 (10.2)	20 (31.4)	0.000	452 (14.6)	20 (36.5)	0.000
CCB	115 (4.7)	10 (15.7)	0.001	184 (5.9)	12 (21.1)	0.000
Digitalis	22 (0.8)	9 (9.5)	0.000	40 (1.1)	11 (17.3)	0.000
ACEI/ARB	181 (7.4)	15 (22.0)	0.000	233 (7.4)	14 (24.9)	0.000

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor antagonist; CCB = calcium channel blocker; CHD = coronary heart disease; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; LVH = left ventricular hypertrophy.

heart failure (I50), 1; other forms of heart disease (I10, I34–I42), 12; cerebrovascular diseases (I60, I61, I63–I69), 26; other forms of atherosclerosis and aortic aneurysm/dissection (I70-I71), 7; and deep vein thrombosis/pulmonary embolism (I26, I80), 2.

Among women, ST-segment deviation in lateral leads as well as single lead V5 yielded uniform and highly significant ($P < 0.01$) predictivity for all four measurement points, and all lead groups had at least one prognostic measurement point (Figure 1a). None of the lead groups and measurement points for ST-segment deviation was a significant predictor among men (Figure 1a). Minimum T-wave amplitude in lateral leads and lead V5 bore prognostic information among women but not among men (Figure 1b).

In unadjusted analyses, a high incidence of cardiovascular death characterized the patient group with the lowest ST-segment tertile and horizontal or negative ST slope, particularly among women (Figure 2a). Similarly, the tertile with both low ST segment and low T-wave amplitude was associated

Table III. ST-segment and T-wave characteristics for each age group. ST-segment level is the lower of values at J point and J point + 80 ms. ST-slope percentages are for positive/horizontal/negative slopes.

	30–44 years			45–54 years			≥ 55 years		
	Men (*n* = 885)	Women (*n* = 1061)	*P*	Men (*n* = 712)	Women (*n* = 777)	*P*	Men (*n* = 867)	Women (*n* = 1313)	*P*
ST segment (mm), mean (SD)									
Anterior	0.08 (0.30)	–0.10 (0.26)	0.000	–0.02 (0.77)	–0.09 (0.25)	0.027	–0.09 (0.41)	–0.23 (0.35)	0.000
Lateral	0.00 (0.23)	–0.06 (0.18)	0.000	–0.05 (0.26)	–0.10 (0.18)	0.000	–0.16 (0.32)	–0.24 (0.31)	0.000
Inferior	–0.05 (0.31)	–0.07 (0.24)	0.146	–0.13 (0.39)	–0.07 (0.23)	0.001	–0.17 (0.29)	–0.14 (0.28)	0.030
V5	0.32 (0.34)	0.09 (0.24)	0.000	0.15 (0.37)	0.02 (0.25)	0.000	–0.02 (0.40)	–0.14 (0.36)	0.000
T-wave amplitude (mm), mean (SD)									
Anterior	0.94 (1.48)	–0.44 (1.09)	0.000	1.00 (1.46)	–0.22 (1.1)	0.000	1.06 (1.61)	0.04 (1.44)	0.000
Lateral	1.40 (1.02)	1.11 (0.72)	0.000	1.33 (1.01)	1.09 (0.78)	0.000	0.91 (1.23)	0.75 (1.13)	0.000
Inferior	0.31 (1.36)	0.37 (1.07)	0.262	0.02 (1.28)	0.24 (1.08)	0.000	0.10 (1.21)	0.23 (1.06)	0.012
V5	5.42 (2.17)	3.90 (1.52)	0.000	4.73 (2.15)	3.61 (1.55)	0.000	3.89 (2.43)	3.01 (2.00)	0.000
ST slope, %									
Anterior	58.1 / 41.8 / 0.1	40.2 / 59.8 / 0.0	0.000	58.7 / 41.2 / 0.1	49.3 / 50.7 / 0.0	0.000	62.4 / 37.2 / 0.3	50.2 / 49.4 / 0.5	0.001
Lateral	25.8 / 73.7 / 0.6	10.9 / 88.8 / 0.3	0.000	27.2 / 72.6 / 0.1	10.7 / 89.1 / 0.3	0.000	23.8 / 75 / 1.2	9.9 / 86.8 / 3.3	0.000
Inferior	4.7 / 91.8 / 3.5	3.4 / 95.1 / 1.5	0.005	5.1 / 91.7 / 3.2	3.6 / 96 / 0.4	0.000	5.8 / 93.1 / 1.2	5.6 / 93.1 / 1.3	0.939
V5	74.6 / 25.1 / 0.3	24.2 / 75.8 / 0.0	0.000	61.2 / 38.6 / 0.1	20.8 / 79.2 / 0.0	0.000	43.0 / 56.3 / 0.7	14.9 / 83.5 / 1.7	0.000

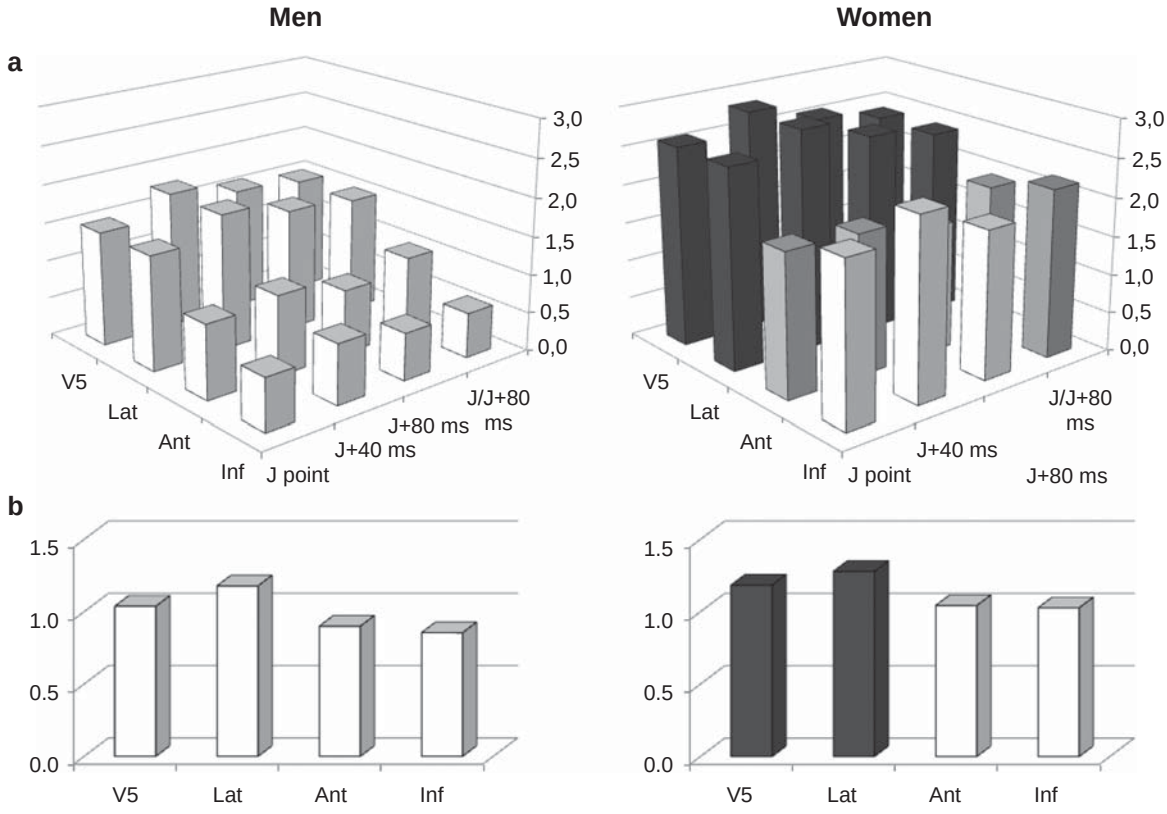

Figure 1. Among women (right) but not among men (left), ST-segment depression and low T-wave amplitude in lateral leads and V5 provided highly prognostic information in adjusted Cox analyses. Upper (a): Hazard ratios, scaled for a change of 1 mm, for ST-segment deviation separated according to the lead group and measurement point. Three different bar shades are used: the darkest for $P < 0.01$, gray for $P < 0.05$, and the lightest for non-significant hazard ratios. Lower (b): Hazard ratios for minimum T-wave amplitude in separate lead groups.

with a high incidence of cardiovascular mortality (Figure 2b). The infrequent finding of negative ST slope in any lead except inferior leads was strongly linked to high incidence of cardiovascular mortality among both men and women (Figure 2c). The unadjusted hazard ratios from Cox regression analysis were as high as 53 for women based on ST slope in lateral leads ($P < 0.001$). However, ST slope was not significant in Cox analysis when ST-segment depression was used as a covariate (data not shown).

ST-segment deviation with/without ventricular hypertrophy and age group considerations

A total of 820 individuals presented with LVH. Only two men and no women without LVH died of cardiovascular causes among those < 45 years old, and that age group was excluded from this subanalysis. Women ≥ 55 years of age had clearly significant results when all the participants were included, but the significance was lost when those with LVH were excluded (Figure 3). ST deviation did not bear prognostic value among the group of all men (Figure 3). As those with LVH were excluded, men ≥ 55 years showed border-line significance.

Discussion

Main findings

We observed that ST-segment depression has prognostic significance for cardiovascular death in a general adult population, consisting of individuals both with and without CHD, and that this predictivity is strongly dependent on ECG signs of increased left ventricular mass. Among all women, ST-segment depression in the lateral lead group as well as lead V5 showed particularly uniform and highly significant predictivity at all the four measurement points in adjusted analyses (Figure 1a). However, this significance was lost in women at least 55 years when those with LVH were excluded (Figure 3). While specificity of the ECG criteria of LVH is high in the range of 90%, sensitivity is poorer (20). Therefore, the group without LVH actually also includes some hypertrophy cases not detected by ECG. This consideration does not change our results, as excluding

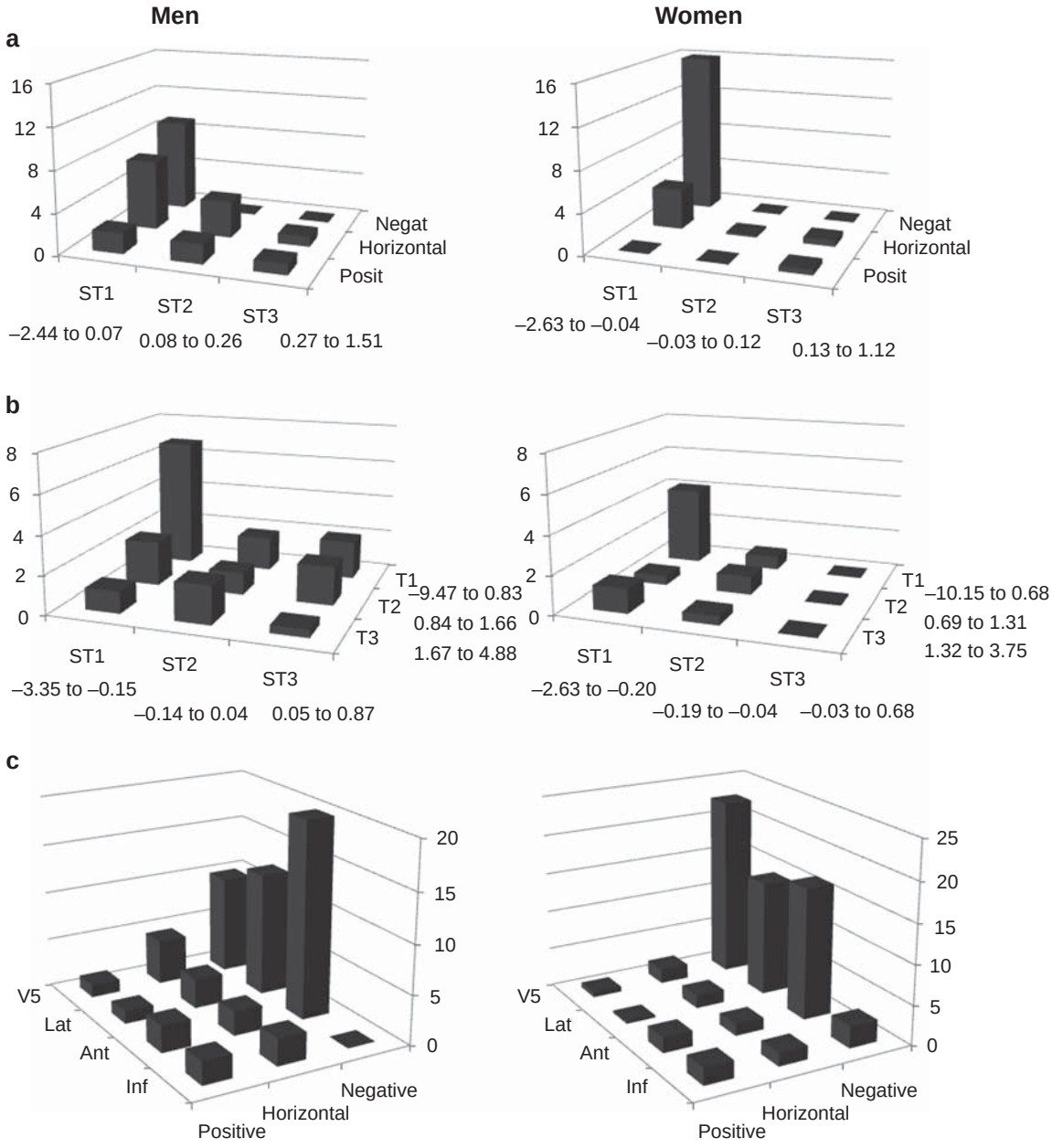

Figure 2. A high incidence of cardiovascular death characterized men (left) and women (right) in the lowest ST-segment tertile with either negative ST slope or low T-wave amplitude. Upper (a): Unadjusted cardiovascular mortality percentage separated by ST slope and tertiles of ST-segment deviation at J + 80 ms in lateral leads. Ranges for tertiles are given in mm. Middle (b): Unadjusted cardiovascular mortality for tertiles of ST-segment deviation (the lower of J and J + 80 ms) and minimum T-wave amplitude in the lateral leads. Lower (c): Unadjusted cardiovascular mortality according to ST slope in the different lead groups.

a portion of the LVH cases already turned the results to negative among women. The effect of LVH on the prognostic value of ST-segment depression was also present in men, but in an opposite direction and to a lesser degree compared to women (Figure 3).

Even though prediction based on ST-segment depression in the male population without LVH was only marginally significant ($P = 0.039$) in this study with a large number of analyses, it is possible that the different direction of effect for LVH between sexes is due to different pathophysiologies. This surmise is supported by our finding that there is a gender difference in the mortality risk based on T-wave amplitudes (Figure 1b). Both ST-segment depression and LVH are strongly associated with structural heart disease. Consequently, LVH has been linked to increased risk for cardiovascular diseases including angina pectoris, myocardial infarction, congestive heart failure, arrhythmia, and sudden death (14–16). In population studies, myocardial ischemia,

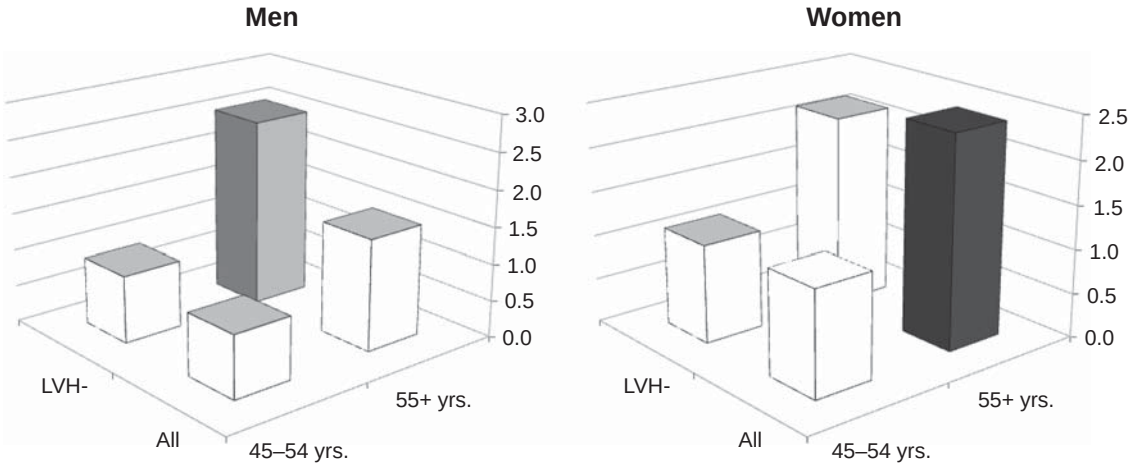

Figure 3. ST-segment deviation provided significant adjusted Cox regression hazard ratios for women (right) ≥ 55 years, but not when those with LVH were excluded (LVH-), and for men (left) when patients with LVH were excluded. ST-segment deviation is the lower of the values at the J point and J point + 80 ms in the lateral lead group. Three different bar shades are used: the darkest for $P < 0.01$, gray for $P < 0.05$, and the lightest for non-significant hazard ratios. Hazard ratios are scaled for a change of 1 mm.

left ventricular remodeling, and bundle branch block represent the most important clinical entities with potential for increased cardiovascular mortality in individuals with ST-segment depression. We excluded individuals with ECG signs of old Q-wave myocardial infarction or bundle branch block, and ischemia and remodeling remain the main culprits in cardiovascular demise. From an ECG point of view, these two entities differ with respect to LVH: CHD per se is not associated with LVH, while there is a strong association between left ventricular remodeling and LVH. The present population also showed a clear sex-specific association between myocardial infarction and death. For patients with a history of myocardial infarction, cardiovascular mortality during follow-up was higher in men (17.3%) than in women (14.7%, $P < 0.001$). It may be speculated that the predictive power of low ST segments related to CHD in men was more evident after individuals with LVH were excluded. In women, other mechanisms may be involved. For example, in the Strong Heart Study, women more often than men developed new-onset heart failure (21), an untoward effect of left ventricular remodeling.

Lead groups and T-wave polarity

Our study showed the highest hazard ratios for cardiovascular mortality for low ST segments in the lateral leads V5, V6, I, and aVL compared to other lead groups (Figure 1a). This effect was markedly stratified by the polarity of T waves (Figure 2b). In a GUSTO IIb substudy of patients with non-ST elevation acute coronary syndrome, ST-segment depression with inverted T waves in lateral leads V4–V6 was associated with increased 1-year mortality (6). The authors suggested elevation of left ventricular end-diastolic pressure with subendocardial ischemia and diastolic dysfunction as a possible pathophysiological background (6). The present observational study does not reveal whether similar mechanisms may be operating in our general population.

Measurement point

No recommendation has been provided for the measurement point of ST-segment depression (22), but it is customary to measure ST-segment deviation at 60 to 80 ms after the end of the QRS complex. We found no major differences in hazard ratios between different ST-segment depression measurement points.

ST slope

Data on the prognostic significance of ST-segment slope in resting ECGs are limited. Horizontal or downsloping ST-segment depression during an exercise stress test indicates CHD (23). More negative ST-segment slope was associated with increased mortality risk during follow-up in a routine preoperative ECG in patients who underwent bypass surgery (4). This was not the case in the present study, where statistical significance was lost when ST-segment depression was introduced as a covariate. Accordingly, the predictive value of ST slope may be different in patients with CHD compared to individuals without CHD.

Study limitations and strengths

We did not have echocardiographic data on LVH. The prevalence of ECG signs of LVH depends on

which criteria are chosen for analysis. In this study, only Minnesota criteria (including clinically widely used Sokolow-Lyon criteria) were used to define LVH. We do not have follow-up data on changes in medications potentially affecting left ventricular mass. A CHD criterion of using nitroglycerine combined with an anticoagulant, acetyl salicylic acid, or beta-blocker is not rigorous and could potentially dilute the results. Health 2000 Survey is a representative observational study of the racially homogeneous Finnish population. Our results may not be transferable to other populations. Our analysis contained a relatively high number of statistical comparisons, which may produce false positive results. Data with borderline significance (gray bars in Figures 1 and 3) should be interpreted with caution. An observational study cannot, by definition, give conclusive information about causality. The present results should be confirmed in other populations, and a clinically applicable algorithm should be constructed before more widespread use of the findings.

Previous population-based studies assessing the prognostic importance of minor ST-segment changes used different classification schemes for ST-segment depression (1,2,10–12). A particular strength of our study, in addition to separating the population according to the LVH status, is the quantitative assessment of ST-segment depression and T-wave amplitude, which enabled analysis of these parameters as continuous variables. This approach should be preferred, as dichotomization may lead to a considerable loss of power and residual confounding (24).

Conclusions

ST-segment depression, regardless of the measurement point, is a robust predictor of cardiovascular death in $\geq$ 55 year-old women of a general population. However, the effect disappears as those with LVH are excluded. This observation highlights the need for consideration of LVH status when depressed ST segments are observed clinically. Simultaneous downward slope of the ST segment or flatness/negativity of T wave clearly potentiates the deleterious effects of ST-segment depression. Overall, our study highlights the importance of even minor but quantifiable repolarization changes in a resting ECG, which is a widely available and relatively inexpensive ancillary modality for assessment of cardiovascular patients.

Acknowledgements

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Declaration of interest: The authors state no conflict of interest.

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Relation of Positive T Wave in Lead aVR to Risk of Cardiovascular Mortality

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We examined the prevalence and prognostic impact of a positive T wave in lead aVR (aVRT+) on a standard electrocardiogram in the general population. Data were collected from a large nationally representative (random sample) health examination survey conducted in Finland from 2000 through 2001. The survey consisted of 6,354 subjects (2,876 men and 3,478 women) ≥30 years who participated in the field health examination including standard electrocardiographic (ECG) recording at rest. The prevalence of aVRT+ (defined as positive or isoelectric T wave in lead aVR) was 2.2%. During the median follow-up of 98.5 months (interquartile range 96.6 to 99.6), there were 214 (3.5%) cardiovascular (CV) deaths. In Cox regression analysis after adjustment for age and gender, relative risks for CV and total mortalities associated with aVRT+ were 3.24 (95% confidence interval [CI] 2.32 to 4.54, p <0.001) and 1.91 (95% CI 1.47 to 2.49, p <0.001), respectively. In the fully adjusted model controlling for other risk factors, CV morbidity, and ECG findings, the relative risk for CV mortality for aVRT+ was 2.94 (95% CI 2.07 to 4.18, p <0.001). In conclusion, aVRT+, an easily recognized ECG finding, predicts risk for CV mortality in the general population. This finding could aid in screening for risk of total and CV mortalities. **(Am J Cardiol 2011;108:1735–1740)**

T-wave abnormalities are among the most frequently encountered pathologic electrocardiographic (ECG) findings in apparently healthy population.[1] Even minor ST-T abnormalities are associated with increased long-term cardiovascular (CV) and total mortalities.[2] Prevalence of a positive T wave in lead aVR (aVRT+) in the general population is not known. Neither is it known whether there are differences in prevalence between women and men. There is no population-based data on the impact of aVRT+ on mortality. Therefore, the aim of the present study was to determine the prevalence and prognostic impact of aVRT+ on standard electrocardiogram at rest in a population-based cohort.

Methods

This study is based on the Health 2000 Study, which is a major Finnish health examination survey. It was carried out from 2000 through 2001, and a representative stratified random cluster sample of the Finnish population was examined. For the population ≥80 years of age, the sampling probability was 2 times as high as in those <80 years. Implementation of the survey is described in detail elsewhere.[3] One of the goals of the Health 2000 Survey was to obtain contemporary information about major diseases in Finland.

The Health 2000 Survey sample consisted of 8,028 subjects (3,637 men and 4,391 women) ≥30 years old, of whom 79% (6,354 subjects, 2,876 men and 3,478 women) participated in the health examination. The national hospital discharge register and the national register on rights to reimbursements for medication costs were linked to the Health 2000 Survey data. The study protocol of the Health 2000 Survey was approved by the epidemiology ethics committee of the Helsinki and Uusimaa hospital district. Participants in the survey signed an informed consent before the health interview and at the beginning of the health examination.

Examining physicians followed detailed written instructions and applied uniform diagnostic criteria in accordance with good clinical practice. Information on rights for drug reimbursements was obtained from the national register. Study participants were asked whether they used any medications and the names and doses of these medications were recorded. Subjects with typical angina pectoris symptoms were identified by the World Health Organization chest pain questionnaire. Also, a history of coronary bypass surgery or

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Table 1
Baseline characteristics of the Health 2000 Survey participants

Variable	Women			Men		
	aVRT− (n = 3,246)	aVRT+ (n = 84)	p Value	aVRT− (n = 2,669)	aVRT+ (n = 69)	p Value
Age (years)	52.6 ± 73.7		<0.001	50.3 ± 66.8		<0.001
Height (cm)	162.4 ± 156.8		<0.001	176.0 ± 171		<0.001
Weight (kg)	70.2 ± 73.1		0.054	83.9 ± 83.2		0.692
Body mass index (kg/m^2)	26.7 ± 2.7		<0.001	27.0 ± 28.4		0.006
Waist circumference (cm)	88.1 ± 93.0		<0.001	97.5 ± 102.1		0.001
Glucose (mg/dl)	97 ± 114		<0.001	103 ± 112		<0.001
Total cholesterol			0.001			0.56
mg/dl	228 ± 243			232 ± 228		
mmol/L	5.9 ± 6.3			6.0 ± 5.9		
High-density lipoprotein cholesterol			<0.001			0.002
mg/dl	54 ± 46			46 ± 42		
mmol/L	1.4 ± 1.2			1.2 ± 1.1		
Low-density lipoprotein cholesterol			0.314			0.328
mg/dl	147 ± 151			147 ± 143		
mmol/L	3.8 ± 3.9			3.8 ± 3.7		
Triglycerides			<0.001			0.031
mg/dl	124 ± 177			159 ± 186		
mmol/L	1.4 ± 2.0			1.8 ± 2.1		
C-reactive protein (mg/L)	2.1 ± 3.0		0.126	2.2 ± 4.3		0.017
γ-Glutamyltransferase (U/L)	26.7 ± 30.7		0.234	46.1 ± 53.3		0.284
Uric acid (mg/dl)	4.5 ± 5.7		<0.001	5.7 ± 6.3		<0.001

Values are presented as mean ± SD.

percutaneous coronary intervention was checked during the interview.

Information on previous hospitalization for myocardial infarction (MI) or coronary heart disease was obtained from hospital discharge summaries that study participants brought along or from the national hospital discharge register. The Finnish hospital discharge register has been shown to be valid in identifying major coronary heart disease events.[4]

Classification of coronary heart disease required ≥1 of the following: diagnosis of MI and/or angina pectoris during the field health examination by a physician, large Q waves on electrocardiogram at rest, hospitalization for coronary heart disease (*International Classification of Diseases, Eighth Revision* [ICD-8] or *Ninth Revision* [ICD-9] codes 410 to 414 or *Tenth Revision* [ICD-10] codes I20 to I25), history of a coronary revascularization procedure, right to drug reimbursements for coronary heart disease, or use of nitroglycerin combined with an anticoagulant, acetyl salicylic acid, or β blocker.

Classification for MI required a clinical diagnosis of old MI by the examining physician, large Q waves on electrocardiogram at rest, or previous discharge diagnosis of MI (ICD-8 or ICD-9 code 410 or ICD-10 codes I21 to I22). MI was defined as a positive history of the condition in medical records or old MI on electrocardiogram or typical self-reported history of MI treated in a hospital. Large Q waves indicating probable previous MI included Minnesota Codes 1.1 to 1.3.

Heart failure classification required a clinical diagnosis by the examining physician and a previous discharge diagnosis of heart failure (ICD-8 code 4270, ICD-9 code 428, or ICD-10 code I50) or right to drug reimbursements for heart failure. Almost without exception the classification for stroke required ≥1 discharge diagnosis of stroke (ICD-8 codes 430 to 431, 433 to 434, ICD-9 codes 430 to 434, or ICD-10 codes I60, I61, I63). Classification for peripheral arterial disease required a clinical diagnosis by the examining physician or previous hospitalization for peripheral arterial disease. Chronic obstructive pulmonary disease classification required a clinical diagnosis by the examining physician including bronchial obstruction in lung function tests (forced expiratory volume <70%) or previous hospitalization for chronic obstructive pulmonary disease (ICD-8 or ICD-9 codes 490 to 492 or ICD-10 code J44).

Height and weight were measured and body mass index calculated. Waist circumference was measured in the standing position using standards created for population health studies.[5] Blood pressure was measured with a mercury sphygmomanometer (Mercuro 300, Speidel and Keller, Juningen, Germany) from the right arm. The first measurement was carried out after ≥5 minutes of rest in the sitting position. Korotkoff first phase was used as the sign of systolic blood pressure and the fifth phase as the sign of diastolic pressure. Measurement was repeated 2 minutes after the first measurement. The average of the 2 measurements was used in the analysis. Clinic hypertension was defined as a clinic blood pressure ≥140/90 mm Hg. Diabetes mellitus was defined as a serum glucose level ≥7.0 mmol/L or a history of use of oral hypoglycemic agents or insulin therapy. Smoking was defined as daily use of tobacco products.

Venous blood samples were drawn from the antecubital vein. High-density lipoprotein cholesterol, total cholesterol, triglyceride, and serum glucose concentrations were determined enzymatically (high-density lipoprotein: Roche Di-

Table 2
Clinical characteristics and mortality of the study population according to presence of T-wave amplitude ≥0 mm in lead aVR

	Men			Women		
	aVRT−	aVRT+	p Value	aVRT−	aVRT+	p Value
Regular smoking	740 (27.8%)	14 (20.3%)	0.169	556 (17.1%)	9 (10.7%)	0.122
Heart failure	60 (2.3%)	10 (14.5%)	<0.001	106 (3.3%)	16 (13.1%)	<0.001
Chronic obstructive pulmonary disease	39 (1.5%)	1 (1.4%)	0.988	35 (1.1%)	3 (3.6%)	0.034
Hypertension	792 (29.8%)	27 (39.1%)	0.097	950 (29.1%)	49 (59.0%)	<0.001
Stroke	57 (2.1%)	10 (14.5%)	<0.001	58 (1.8%)	5 (6.1%)	0.005
Peripheral artery disease	48 (1.8%)	2 (2.9%)	0.506	38 (1.2%)	4 (4.9%)	0.003
Diabetes mellitus	133 (5.0%)	10 (14.5%)	<0.001	158 (4.9%)	14 (16.9%)	<0.001
Left ventricular hypertrophy/right ventricular hypertrophy	342 (12.8%)	6 (8.7%)	0.308	407 (12.5%)	13 (15.5%)	0.423
Coronary heart disease						
No	2,437 (91.5%)	62 (89.9%)	0.634	2,922 (90.0%)	74 (88.1%)	0.562
Yes	227 (8.5%)	7 (10.1%)		327 (10.0%)	10 (11.9%)	
Myocardial infarction						
No	2,556 (95.9%)	69 (100%)	0.088	3,087 (95.1%)	78 (92.9%)	0.349
Yes	108 (4.1%)	0 (0%)		159 (4.9%)	6 (7.1%)	
Death						
All-cause	231 (8.7%)	31 (44.9%)	<0.001	232 (7.1%)	35 (41.7%)	<0.001
Cardiovascular	90 (3.4%)	25 (36.2%)	<0.001	78 (2.4%)	21 (25.0%)	<0.001
Medication						
β Blockers	310 (11.6%)	10 (14.5%)	0.466	459 (14.1%)	10 (11.9%)	0.561
Calcium channel blockers	128 (4.8%)	6 (8.7%)	0.139	182 (5.6%)	2 (2.4%)	0.201
Angiotensin-converting enzyme inhibitors/ angiotensin receptor antagonists	203 (7.6%)	7 (10.1%)	0.437	255 (7.9%)	7 (8.3%)	0.872
Statins	136 (5.1%)	6 (8.7%)	0.185	157 (4.8%)	2 (2.4%)	0.565
Aspirin	179 (6.7%)	3 (4.3%)	0.435	237 (7.3%)	5 (6.0%)	0.860

Follow-up 98.5 months (interquartile range 96.6 to 99.6).

agnostics, GmbH, Mannheim, Germany; total cholesterol, triglycerides, and glucose: Olympus System Reagent, Olympus, Hamburg, Germany) with a clinical chemistry analyzer (AU400, Olympus). Low-density lipoprotein cholesterol was calculated with the Friedewald formula. Serum uric acid concentration was determined enzymatically (Urikaasi PAP, Konelab, Thermo Electron Oy, Vantaa, Finland). High-sensitivity C-reactive protein concentrations were determined using a chemiluminescent immunometric assay (Immulite, Diagnostic Products Corporation, Los Angeles, California). Gamma-glutamyltransferase activity concentration was determined enzymatically according to the International Federation of Clinical Chemistry (Gamma-GT, Konelab, Thermo Electron Oy, Vantaa, Finland).

Standard 12-lead electrocardiograms were recorded at rest in the supine position using recommended standardized procedures and MAC 5000 recorders (Marquette Hellige, Freiburg, Germany/Milwaukee, Wisconsin). Electrocardiogram was recorded and printed using a paper speed of 50 mm/s. The maximal filter setting of the system (150 Hz) was used. ECG analyses were performed by a Health 2000 Survey investigator blinded to patients' clinical data. Minnesota coding was performed at the Institute of Cardiology, Kaunas Medical Academy, Kaunas, Lithuania by 2 investigators who were also blinded to patients' clinical data. Electrocardiograms were obtained successfully in 6,318 subjects (99%) who attended the health examination. Abnormalities identified visually on the ECG strips were coded in accordance with the Minnesota coding scheme.[6] Electrical recordings were analyzed using Magellan software (Marquette Electronics, Inc., Milwaukee, Wisconsin). Nineteen electrocardiograms were rejected owing to data lost in further processes, leaving 6,299 electrocardiograms for analysis.

Mortality information until January 2009 was gathered by linking the personal identity code from the Health 2000 Survey database to the causes of death register, maintained by Statistic Finland, which records 100% of deaths of Finnish citizens at home and nearly 100% abroad.

Subjects with atrial fibrillation (n = 94), cardiac pacemaker (n = 4), preexcitation (n = 1), and right or left bundle branch block (n = 143) were excluded (Minnesota Codes 6.4, 6.8, 7.1 to 7.2, 7.8, 8.3). Final analysis was performed with 6,063 subjects (3,330 women and 2,733 men).

We defined aVRT+ as aVRT ≥0 mm (isoelectric or positive deflection). Negative aVRT (aVRT−) was defined as aVRT <0 mm.

Prevalence of aVRT+ was defined for the total study population and by gender and 3 age groups. Chi-square test was applied to confirm the significance of differences between groups. Data were categorized into 2 groups according to aVRT: "aVRT− group" (aVRT <0 mm) and "aVRT+ group" (aVRT ≥0.00 m). To evaluate prevalence, cross tabs with aVRT+, gender, and age groups were used.

Comparisons between groups were calculated with *t* test for independent samples or with chi-square test as applicable (Table 1).

Receiver operating characteristic curve analysis was used to determine the ability of aVRT+ to distinguish

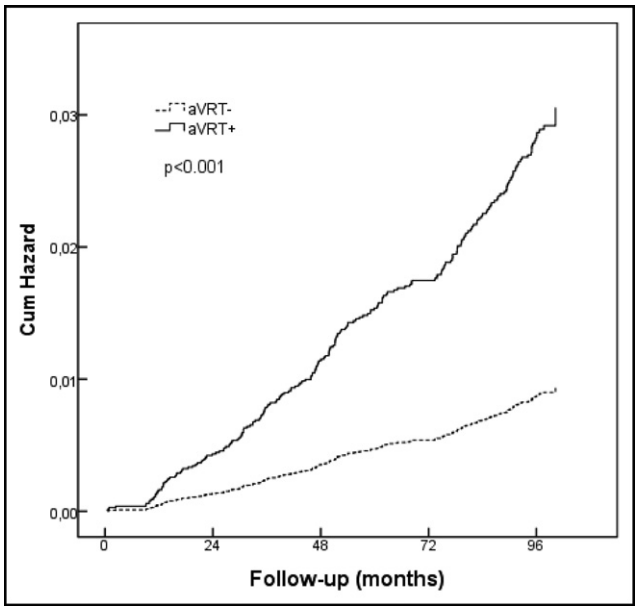

Figure 1. Age- and gender-adjusted cardiovascular mortality for positive T-wave amplitude in lead aVR in the Health 2000 Survey using Cox regression analysis for comparison of curves.

between subjects with and without CV mortality during follow-up.

In Cox proportional hazards models the aVRT+ was used. The proportionality assumption was checked for the main analyses based on correlations of survival rankings with Schoenfeld residuals; all covariates fulfilled this criterion. The end point was CV death and models used the following covariates: age, gender, left or right ventricular hypertrophy, Q waves, ST-segment depression in lead V_5, heart rate, angina pectoris, diabetes mellitus, hypertension, smoking, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and body mass index.

Age group analyses (30 to 44, 45 to 54, and ≥55 years) were performed. The complex sampling design was taken into account by correcting for the oversampling of subjects ≥80 years of age. All analyses were performed with SPSS 17.0 for Windows (SPSS, Inc., Chicago, Illinois). Statistical significance was based on a p value <0.05.

Results

Prevalence of aVRT+ was 2.2% (n = 138, 69 women and 69 men) with no difference between men and women. Subjects with aVRT+ were older and more often had a history of CV disease and risk factors than subjects with aVRT− (Tables 1 and 2). Prevalence of aVRT+ was 5.2% in subjects ≥55 years of age and 0.4% in subjects <55 years of age.

In the entire population mean aVRT was −2.55 ± 1.02 mm (mean ± SD). Mean T-wave amplitudes were −2.69 ± 1.09 mm in men and −2.44 ± 0.94 mm in women (t = −9.54, degrees of freedom 6.061, p <0.001 for difference).

Receiver operating characteristic curve analysis demonstrated that age and gender alone were able to distinguish between patients with and without subsequent CV death at 98-month follow-up (area under the curve 0.89, 95% confidence interval [CI] 0.87 to 0.91, p <0.001). Adding classic risk factors or aVRT+ to this simple model did not improve the area under curve.

Table 3
Adjusted Cox proportional hazard analysis for cardiovascular mortality according to electrocardiographic findings in participants of the Health 2000 Survey

Variable	Hazard Ratio (95% CI)	p Value
Age and gender adjusted		
Positive T-wave amplitude in lead aVR	3.24 (2.32–4.54)	<0.001
ST-segment depression	0.40 (0.10–1.62)	0.200
Left ventricular hypertrophy/right ventricular hypertrophy	1.34 (0.91–1.98)	0.135
Q waves	1.18 (0.48–2.86)	0.721
Multivariate adjusted*		
Positive T-wave amplitude in lead aVR	2.94 (2.07–4.18)	<0.001
ST-segment depression	1.40 (0.56–3.49)	0.477
Left ventricular hypertrophy/right ventricular hypertrophy	1.32 (0.89–1.95)	0.164
Q waves	1.40 (0.56–3.49)	0.477

* Adjusted for gender, age, heart rate, angina pectoris, diabetes mellitus, smoking, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, body mass index, heart failure, and hypertension.

In Cox regression analysis after adjustment for age and gender, relative risk for CV mortality for aVRT+ was 3.24 (95% CI 2.32 to 4.54, p <0.001) and for total mortality was 1.91 (95% CI 1.47 to 2.49, p <0.001) compared to those with aVRT− (Figure 1). An angle between the QRS axis and the T axis >90° in lead aVR or menopausal status had no influence on the results.

In Cox regression analysis after adjustment for age, gender, and pathologic ECG parameters (ST-segment depression in lead V_5, left or right ventricular hypertrophy, and Q waves), aVRT+ was the strongest predictor of CV mortality compared to those with normal T wave (hazard ratio 3.24, 0.95% CI 2.32 to 4.54, p <0.001). This result remained when women and men were separately analyzed.

When Cox regression analysis was performed using a wide range of confounding factors (age, gender, left or right ventricular hypertrophy, Q waves, ST-segment depression in lead V_5, heart rate, history of angina pectoris, diabetes mellitus, hypertension, smoking, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and body mass index), relative risk for CV mortality for aVRT+ was 2.94 (95% CI 2.07 to 4.18, p <0.001) compared to those with aVRT− (Table 3).

In Cox regression analysis of subjects (n = 4,932) with no history of heart disease (angina pectoris, MI, heart failure, medically treated hypertension) and adjusted for age and gender, relative risk for CV mortality for aVRT+ was 3.78 (CI 2.45 to 5.83, p <0.001) compared to those with aVRT−. When analysis was performed with subjects (n = 4,834) with no pathologic ECG parameters (ST-segment depression in lead V_5, left or right ventricular hypertrophy, and Q waves), relative risk for aVRT+ was 3.81 (CI 2.46 to 5.89, p <0.001).

Discussion

This study showed for the first time that aVRT+ independently predicted risk for CV mortality in women and men of a nationally representative population. As expected, prevalence of aVRT+ in the general adult population (2.2%) was lower than for study populations including patients in whom rates of 7.3% to 11% have been reported.[7,8] Our finding that patients with aVRT+ are older than those with aVRT− is in accordance with the findings of Tan et al[7] and with the fact that the prevalence of T-wave abnormalities in general increases by advancing age, being 5.9% at 50 years of age and 16% at 70 years of age.[9]

Direction of the repolarization process in the ventricles determines the direction of aVRT. Mean values of aVRT in age groups 12 to 60 years reported by Lepeschkin[10] varied from −2.0 to −2.9 mm (range −0.1 to −5.2). In the present study, when extending the age range to >60 years, the mean aVRT, −2.6 mm, was in the same range.

In the present study, aVRT+ was associated with a threefold risk for CV mortality during follow-up. This is in concordance with the findings by Tan et al[7]; in their retrospective study, upward pointing aVRTs were associated with increased CV mortality (24% vs 7.7% for entire study population) and a fivefold increased relative risk during 7.5-year follow-up. These findings also agree with the fact that abnormal T waves in leads I, V_6, aVL, II, aVF, and V_2 to V_6 are associated with a relative risk of 2.4 to 2.7 for CV death in the general population.[11]

The negative impact on patient outcome of "inverted" T waves in cardiac diseases has been known for a long time. In 1921, Willius[12,13] showed that in patients with hypertension, those with significantly inverted T waves in lead I or in leads I and II had 2 or 3 times the mortality compared to those without inverted T waves. Also, patients with aortic insufficiency and inverted T waves showed 2 times the mortality present in patients without T-wave inversion.[12]

Because lead aVR is electrically opposite to the lateral precordial leads, ST-segment depression in leads V_5 to V_6 is often accompanied by ST-segment elevation in lead aVR.[14] Also, the present study indicated an inverse relation between ST-T changes in leads aVR and V_5 (data not shown). Assuming that negative T waves in the lateral precordial leads in general are accompanied by a positive T wave in lead aVR, the reader may find a tempting explanation for the negative prognostic impact of aVRT+ showed in this study. Disease states, which induce secondary repolarization ST-T changes on electrocardiogram, have been associated with ventricular remodeling and, hence, with an unfavorable outcome. Strain defined as inverted asymmetrical T wave opposite the QRS axis in leads V_5 and/or V_6 accompanied by a downsloping convex ST segment, was associated with greater indexed left ventricular mass in patients with and without coronary artery disease in the Losartan Intervention For End Point (LIFE) study.[15] Strain was associated with an increased risk of anatomic left ventricular hypertrophy in patients with and without coronary artery disease and in the overall population. Experimental evidence suggests that the increased risk for sudden death in hypertension may be mediated by left ventricular hypertrophy–induced arrhythmogenic repolarization abnormalities.[16–19] In a multicenter study with hypertension and ECG left ventricular hypertrophy, serial changes in repolarization significantly predicted the prognosis independent of voltage changes.[20]

Absence of echocardiographic data on left ventricular hypertrophy is a study limitation. Also, lack of data related to possible changes in medication during follow-up could be considered a limitation. However, we do not believe that these limitations weaken the main messages from our study. Although the validity of the results of our study stems from the fact that this represents a large prospective nationally representative health examination survey, we cannot exclude the possibility that subjects selected for the home health examinations differ in risk factor profile or disease severity from the general population. However, the participation rate in the survey was high. Because nonparticipation is selective for morbidity and disability, high participation rates are essential in examining the prevalence of a chronic disabling disease. Because populations may differ in many aspects, the results may not be applicable on a universal basis.

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CLINICAL RESEARCH STUDY

Prognostic implications of intraventricular conduction delays in a general population: the Health 2000 Survey

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Abstract and Keywords

Aims: We examined the prognostic impact of eight different intra-ventricular conduction delays (IVCD) in the standard electrocardiogram (ECG) in a community cohort.

Methods and results: Data were collected from 6299 Finnish individuals. During a mean 8,2 years (interquartile range 8,1 to 8,3) follow-up 640 subjects died (10.2%); 277 (4.4%) were cardiovascular deaths. For both sexes, all-cause and cardiovascular mortality was higher in subjects with IVCD than in those without. In Cox regression analysis after adjustment for age and gender, the hazard ratio for cardiovascular mortality for non-specific IVCD was 4.25 (95% confidence interval [CI] 1.95–9.26, $p < 0.0001$) and for left bundle branch block (LBBB) 2.11 (95% CI 1.31–3.41, $p = 0.002$). Right bundle branch block (RBBB) was not related to additional mortality, while incomplete RBBB (IRBBB) presented a hazard ratio of 2.24 (95% CI 1.064–4.77, $p = 0.036$).

Conclusions: In the general population, non-specific IVCD, LBBB and IRBBB were associated with increased relative risk for all-cause and cardiovascular mortality. RBBB did not have impact on cardiovascular mortality either in subjects with or without previous heart disease

Keywords: Bundle branch block, ventricular conduction disturbance, electrocardiography, prognosis.

Introduction

In the early days of electrocardiography (ECG), it was noticed that subjects with wide QRS could live decades without remarkable symptoms (1). Published data regarding the clinical and prognostic significance of intraventricular conduction delays (IVCD) are highly varied. The epidemiological data have mostly been derived from hospitalized patients with findings partly dependent on the characteristics of the patient cohort (2). In studies performed in healthy populations, findings about future cardiovascular (CV) events have not been consistent (3,4). Accordingly, the prognostic implications of IVCDs depend on the category of conduction disturbance and on the population studied.

In several studies on chronic and acute coronary artery disease, left bundle branch block (LBBB) was found to be an excellent predictor of mortality and future clinical events (5,6). LBBB may also be a marker of structural heart disease, especially dilated cardiomyopathy (7,8). However, there is no consensus on LBBB-related prognosis in general populations (9). In a recent population study, right bundle branch block (RBBB) was associated with increased CV risk and all-cause mortality, whereas incomplete RBBB (IRBBB) was not (10). Previous authors found no increased overall mortality in RBBB in the absence of clinically overt cardiac disease (11).

In a population study, left anterior hemiblock (LAHB) was associated with cardiac morbidity and mortality (8) while other authors consider LAHB in a healthy population as an incidental ECG finding (12). In a population study from ECG´s taken between 1966–1972 prolonged duration of the QRS complex in a 12-lead ECG and nonspecific IVCD was a predictor of mortality (13). Regarding the prognostic impact of incomplete LBBB (ILBBB), left posterior hemiblock (LPHB) or the R-R´-pattern in the general population, data is scarce or non-existent.

The fact that the number of heart failure patients, who are potential candidates for cardiac resynchronization therapy (CRT), is increasing, has resulted in growing interest in IVCDs among clinicians (14). The ECG is an important tool for the prediction of positive response to this relatively new treatment modality.

The aim of the present study was to establish the prognostic significance of eight different IVCDs in a population-based cohort.

Materials and Methods

This study is based on the Health 2000 Study, which is a major Finnish health

examination survey. The survey was carried out in 2000–2001, and a representative stratified random cluster sample of the Finnish population was examined. For the population aged ≥80 years, the sampling probability was twice as high as among those <80 years. The implementation of the survey is described in detail elsewhere (15,16).

The Health 2000 sample comprised 8028 individuals (3637 men and 4391 women) aged 30+, of whom 79% (6354 individuals, 2876 men and 3478 women) participated in the health examination. The National Hospital Discharge Register and the national register on rights to reimbursements for medication costs were linked to the Health 2000 Survey data. The study protocol of the Health 2000 survey was approved by the Epidemiology Ethics Committee of the Helsinki and Uusimaa Hospital District. The participants in the survey signed an informed consent both before the health interview and at the beginning of the health examination.

Definition of coronary heart disease

Classification as coronary heart disease (CHD) required at least one of the following: diagnosis of myocardial infarction (MI) and/or angina pectoris (AP) during the field health examination by a physician, large Q waves in resting ECG, hospitalization for CHD (International Classification of Diseases (ICD)-8 or ICD-9 codes 410–414 or ICD-10 codes I20–I25), a history of coronary revascularization procedure, the right to drug reimbursements for CHD, or the use of nitroglycerine combined with an anticoagulant, acetyl salicylic acid or beta-blocker.

Myocardial infarction

Classification for myocardial infarction (MI) required either a clinical diagnosis of old MI by the examining physician, large Q waves in resting ECG, or a previous discharge diagnosis of MI (ICD-8 or ICD-9 code 410 or ICD-10 codes I21–I22). MI was defined as a positive history of the condition in the medical records or old MI on ECG, or typical self-reported history of MI treated in a hospital. Large Q waves indicating probable previous MI included Minnesota codes 1.1.–1.3.

Heart failure, stroke, peripheral artery disease and chronic obstructive pulmonary disease

Heart failure (HF) classification required a clinical diagnosis by the examining physician and either a previous discharge diagnosis of HF (ICD-8 code 4270, ICD-9 code 428 or ICD-10 code I50) or the right to drug reimbursements for HF. Almost without exception the classification for stroke required one or more discharge diagnoses of stroke (ICD-8 codes 430–431, 433–434, ICD-9 codes 430–434 or ICD-10 codes I60, I61, I63). Classification for peripheral arterial disease (PAD) required a clinical diagnosis by the examining physician or previous hospitalization for PAD. Chronic obstructive pulmonary disease (COPD) classification required a clinical diagnosis by the examining physician, including bronchial obstruction in lung function

tests (forced expiratory volume, FEV% < 70), or previous hospitalisation for COPD (ICD-8 or ICD-9 codes 490–492 or ICD-10 code J44).

Other measurements and definitions

The health examination included measurements of height, weight, body mass index and waist circumference. Blood pressure (BP) was measured with a mercury sphygmomanometer (Mercuro 300, Speidel & Keller, Juningen, Germany) from the right arm. Clinic hypertension was defined as a clinic BP ≥ 140/90 mmHg. Diabetes mellitus was defined as a serum glucose level of 7.0 mmol/l or greater or a history of the use of oral hypoglycemic agents or insulin therapy. Smoking was defined as the daily use of tobacco products.

Laboratory tests

Laboratory tests included measurements for high density lipoprotein cholesterol, total cholesterol, triglyceride and serum glucose. Low density lipoprotein cholesterol was calculated with the Friedewald formula.

ECG registration and analysis

Standard 12-lead ECGs were recorded in the resting supine position by MAC 5000 recorders (Marquette Hellige, Freiburg, Germany and Milwaukee, Wisconsin, USA) and stored as digital data on a Marquette MUSE CV 5B system (Marquette Hellige, Milwaukee, WI). All ECGs were overread, and the computerized diagnoses and measurements corrected if needed, by a single physician experienced with ECG before being stored into the database. ECG was recorded and printed using the paper speed of 50mm/sec. The maximal filter setting of the system (150Hertz) was used. The Minnesota coding was performed at the Institute of Cardiology, Kaunas Medical Academy, Lithuania, by two investigators, who were blinded to the clinical data of the patient. ECGs were obtained successfully in 6318 individuals (99%) who attended the health examination. Abnormalities identified visually in the ECG strips were coded in accordance with the Minnesota coding (MC) scheme (17). The electrical recordings were analysed by means of Magellan software programme (Marquette Electronics Inc, Milwaukee, WI, USA). Nineteen ECGs were rejected owing to data lost in further process, leaving 6299 ECGs for analysis.

Follow-up

Mortality information until January 2009 was gathered by linking the personal identity code from the Health 2000 Survey database to Causes of Death register, maintained by Statistic Finland, which records 100% of deaths of Finnish citizens at home and nearly 100% abroad.

Exclusion criteria

There was no exclusion of subjects based on ECG findings. Final analysis was performed with 6299 subjects: 3442 women and 2857 men.

Definition of different VCDs

For the identification of different ventricular conduction delays, both Minnesota codes (18) and measurements based on the Magellan software program were used. Six of the conduction delays were classified according to the respective Minnesota classes: LBBB (code 7-1), RBBB (code 722), IRBBB (code 7-3), non-specific IVCD (code 7-4), the R-R' pattern in either of leads V1, V2 with R' amplitude ≥ R (R-R' pattern) (code 7-5) and ILBBB (code 7-6). For left anterior hemiblock (LAHB) we used the following definition: frontal QRS axis between -30° and -90° , rS configuration in II, III and aVF, and qR configuration in aVL, with a QRS duration less than 120ms (19). Left posterior hemiblock (LPHB) was defined as frontal QRS axis >120°, lead I rS configuration, leads II, III and aVF qR configuration, and no pathological Q-waves in leads II, III, avF (19). The accuracy of the classification of LAHB, LPHB, non-specific ventricular block, partial RBBB and the R-R' pattern was checked by manual ECG analysis by two of the investigators (PH, KN). The classifications proved to be accurate.

Statistical analyses

The prevalence of IVCDs was defined for the total study population as well as by sex and three age groups. χ^2 test was applied to confirm significance of the differences between groups. Data was categorised into two groups according to the presence of IVCD: "IVCD- group" (no ventricular conduction delay) and "IVCD+ group" (subjects with ventricular delay).To evaluate prevalence, crosstabs with IVCD+, gender, and age groups were used.

Comparisons between the groups were calculated either with the t test for independent samples or with the χ^2 test as applicable.

The proportionality assumption was checked for the main analyses based on correlations of survival rankings with Schoenfeld residuals; all the covariates fulfilled this criterion. The endpoint was CV death and models used the following covariates: age, gender, smoking, AP, MI, HF, diabetes mellitus, hypertension, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides and body mass index.

Age group analyses (for 30–50, 51–70 and ≥71 years) were performed. The complex sampling design was taken into account by correcting for the oversampling of subjects ≥80 years of age. All analyses were performed with the SPSS release 19.0 for Windows (SPSS Inc, Chicago, Illinois). Statistical significance was based on $p<0.05$.

Results

The baseline characteristics of the study population are presented in Table 1 and clinical characteristics and outcome in Table 2. Both regarding men and women, patients with IVCDs were older than those without. Individuals with IVCD had a higher prevalence of heart failure, CHD, and MI, and a higher rate of all-cause and CV mortality than those without conduction delay.

During the follow-up of 8.2 years (interquartile range 8.1 to 8.3) 640 sub-

Table 1.
Baseline characteristics of the subjects in IVCD study of the Health 2000 Survey **(IV).**

Variable	Men					Women				
	IVCD+		IVCD-			IVCD+		IVCD-		
	Mean	SD	Mean	SD	p value	Mean	SD	Mean	SD	p value
Age	57	16	51	13	< 0.001	63	17	53	15	<0.001
Height (cm)	176	7.6	176	7.0	0.992	161	8	162	7	0.001
Weight (kg)	84	15	84	14	0.691	68	13	70	14	0.014
BMI (kg/m^2)	27.0	4.2	27.1	4.1	0.621	26.5	4.6	26.8	5.1	0.235
Waist circumference (cm)	98	12	98	11	0.934	88	13	88	13	0.813
Glucose (mmol/L)	5.8	1.4	5.7	1.3	0.172	5.7	1.3	5.4	1.1	<0.001
Total cholesterol (mmol/L)	5.89	1.14	5.97	1.11	0.251	6.19	1.21	5.90	1.11	<0.001
High-density lipoprotein cholesterol (mmol/L)	1.21	0.34	1.20	0.33	0.509	1.43	0.37	1.45	0.41	0.545
Low-density lipoprotein cholesterol (mmol/L)	3.77	1.23	3.79	1.29	0.797	3.90	1.26	3.79	1.08	0.109
Triglycerides (mmol/L)	1.8	1.4	1.8	1.2	0.466	1.6	0.8	1.4	0.7	0.003
C-reactive protein (mg/L)	2.1	5.0	2.3	7.3	0.579	2.7	8.8	1.4	5.1	0.177
g-Glutamyltransferase (U/L)	51	90	46	53	0.170	30.2	30	26.8	31	0.060
Uric acid (µmol/L)	340	75	340	72	0.748	288	86	269	73	<0.001

IVCD= intra-ventricular conduction delay, SD=standard deviation , BMI=body mass index. Previously unpublished data.

Table 2.
Clinical characteristics and mortality of the study population according to presence of intra-ventricular conduction delay at 8,2 year's mean follow-up (IV).

	Men			Women		
	IVCD+ n (%)	IVCD- n (%)	p value	IVCD+ n (%)	IVCD- n (%)	p value
Regular smoking	84 (23.6)	718 (28.5)	0.051	38 (13.9)	567 (17.9)	0.098
Heart failure	27 (7.6)	70 (2.8)	<0.001	39 (14.4)	131 (4.1)	<0.001
Chronic obstructive pulmonary disease	5 (1.4)	38 (1.5)	0.860	3 (1.1)	37 (1.2)	0.920
Hypertension	120 (33.7)	750 (30.1)	0.168	100 (36.8)	959 (30.3)	0.028
Stroke	13 (3.7)	67 (2.7)	0.300	12 (4.4)	62 (2.0)	0.007
Peripheral artery disease	13 (3.7)	52 (2.1)	0.063	7 (2.6)	41 (1.3)	0.082
Diabetes mellitus	25 (7.0)	135 (5.4)	0.221	18 (6.6)	172 (5.4)	0.416
Left or right ventricular hypertrophy	40 (11.2)	268 (10.7)	0.767	40 (14.7)	371 (11.7)	0.150
Coronary heart disease						
No	273 (76.7)	2206 (88.2)	<0.001	210 (76.9)	2840 (89.6)	<0.001
Possible	21 (5.9)	90 (3.6)		20 (7.3)	114 (3.6)	
Yes	62 (17.4)	205 (8.2)		43 (15.8)	215 (6.8)	
Myocardial infarction						
No	310 (87.1)	2365 (94.6)	<0.001	252 (92.3)	3086 (97.4)	<0.001
Possible	12 (3.4)	46 (1.8)		9 (3.2)	27 (0.8)	
Yes	34 (9.6)	90 (3.6)		12 (4.4)	56 (1.8)	
Medication						
Beta adrenergic blockers	83 (23.3)	303 (12.1)	<0.001	58 (21.2)	489 (15.4)	0.012
Calcium channel blockers	28 (7.9)	121 (4.8)	0.016	25 (9.2)	192 (6.1)	0.43
Digitalis	20 (5.6)	30 (1.2)	<0.001	25 (9.2)	52 (1.6)	<0.001
ACEI/ARB	41 (11.5)	201 8.0)	0.027	31 (11.4)	252 (8.0)	0.050
Statin	30 (8.4)	167 (6.7))	0.223	12 (4.4)	179 (5.2)	0.386
Aspirin	49 (13.8)	168 (6.7)	<0.001	33 (12.1)	218 (6.9)	0.001
Clopidogrel	6 (1.7)	26 (1.0)	0.279	8 (2.9)	45 (1.4)	0.052
Death						
all-cause	64 (18.0)	249 (10.0)	<0.001	61 (22.3)	266 (8.4)	<0.001
cardiovascular	36 (10.1)	107 (4.3)	<0.001	32 (11.7)	102 (3.2)	<0.001

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor antagonist. Previously unpublished data.

jects died (10.2%); 277 (4.4%) were CV deaths.

Cox regression analysis

In Cox regression analysis after adjustment for age and gender, the relative risk for all-cause mortality for IVCD was 1.14 (95% CI 0.93–1.39, p = 0.202) and for CV mortality 1.38 (95% CI 1.04–1.82, p = 0.023) as compared to subjects with no IVCD. After adjustment for age and gender, the relative risk for all-cause and CV mortality for non-specific IVCD was 2.46 (95% CI 1.27– 4.77, p = 0.008) and 4.29 (95% CI 2.01–9.16, p < 0.0001), for LBBB 1.61 (95% CI 1.12–2.33, p = 0,011) and 2.11 (95% CI 1.31–3.41, p = 0.002) and for IRBBB 1.98 (95% CI 1.18–3.3, p = 0.009) and 2.24 (95% CI 1.06–4.77, p = 0.036), respectively. The other types of IVCD did not have impact on prognosis (Table 3).

The relative age and gender adjusted risk for CV mortality for individuals with LBBB and AP was 2.41 (95% CI 1.46–4.00, p = 0.001) and for LBBB and a history of MI 2.55 (95% CI 1.36–4.77, p = 0.003). The corresponding risk for individuals with non-specific IVCD and heart failure was 3.80 (95% CI 1.18–12.25, p = 0.001). RBBB did not have impact on CV mortality either in subjects with or without previous heart disease (Table 4a–c).

In the subjects without BBB or fascicular block (n = 5952) and no history of CHD, after adjustment for age and gender, the relative risk for CV mortality for QRS ≥120ms (n= 67) was 0.506 (95% CI 0.07–3.66, p = 0.500) compared to subjects with QRS <120ms. When the corresponding analysis was performed for subjects with CHD, the relative risk for CV death for QRS≥120ms was 2.35 (95% CI 1.13–4.9, p = 0.023) compared to subjects with QRS<120ms.

Discussion

Our study showed clinically important prognostic differences between the categories of IVCD. Of the eight studied IVCDs, three were associated with increased relative risk for all-cause and CV mortality, namely LBBB, IRBBB and non-specific IVCD, of which the last one proved to carry the highest risk. In subgroup analyses, LBBB and IRBBB demonstrated increased CV mortality only in individuals with CHD. RBBB in the general population carried no increased risk for all-cause or CV mortality.

One of the main findings of the present study was the strong association between non-specific IVCD and increased CV mortality. A broad QRS, in our study defined according to the Minnesota code system as ≥120 ms, may be caused by complex delays in the conduction system, regional conduction slowing in the myocardium, or a combination of the two (20) . Accordingly, structural heart disease with potential for inferior outcome may result in ECG changes falling into this category. Non-specific IVCD is probably an under-recognized entity both as an ECG diagnosis and as a negative prognostic factor. The negative prognostic impact of this ECG finding in conjunction with CHD is not surprising. Regions with myocardial scar may alter the conduction sequence in the left ventricle thereby slowing conduction and inducing fragmentation of the QRS complex, resulting in a broadened QRS

Table 3.
Adjusted Cox proportional hazard analysis for cardiovascular mortality according to intra-ventricular conduction block (IV).

Variable	Prevalence n (%)	Hazard Ratio (95% CI)	p value
Age and gender adjusted			
LAHB	69 (1.1)	0.84 (0.40-1.80)	0.660
LPHP	8 (0.1)	No events	
LBBB	68 (1.1)	2.11 (1.31-3.4)	0.002
RBBB	75 (1.2)	1.15 (0.65-2.02)	0.640
Incomplete LBBB	66 (1.0)	1.14 (0.42-3.07)	0.790
Incomplete RBBB	61 (1.0)	2.24 (1.06-4.77)	0.036
R-R'	249 (4.0)	0.90 (0.50-1.65)	0.731
NSIVCD	33 (0.5)	4.29 (2.01-9.16)	<0.001
Multivariate adjusted*			
LBBB	68 (1.1)	1.44 (0.88-2.35)	0.143
Incomplete RBBB	61 (1.0)	2.00 (0.94-4.27)	0.730
NSIVCD	33 (0.5)	4.25 (1.95-9.26)	<0.001

CI=confidence interval; LAHB=left anterior hemiblock; LPHB=left posterior hemiblock; LBBB=left bundle branch block; RBBB=right bundle branch block; NSIVCD=non-specific intra-ventricular conduction delay

* Adjusted for gender, age angina pectoris, myocardial infarction, heart failure, hypertension, diabetes, smoking, body mass index, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides.
Chi-square test was used for testing difference of prevalence between age groups (p<0.001). Unpublished data.

Table 4a.
Age and gender adjusted Cox proportional hazard analysis for cardiovascular mortality **(IV).**

	No angina pectoris		Angina pectoris	
Variable	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
LAHB	0.97 (0.36-2.64)	0.951	0.72 (0.23-2.27)	0.572
LPHB	0.003 (NA)	0.971	0	0.959
LBBB	0.36 (0.05-2.61)	0.313	2.41 (1.46-4.00)	0.001
RBBB	0.58 (0.18-1.84)	0.353	1.55 (0.81-3.00)	0.189
Incomplete LBBB	0.62 (0.09-4.42)	0.629	1.47 (0.47-4.65)	0.509
Incomplete RBBB	2.81 (1.03-7.64)	0.043	1.74 (0.55-5.45)	0.345
R-R´	0.84 (0.34-2.06)	0.701	1.07 (0.46-2.48)	0.874
NSIVCD	2.49 (0.35-18.0)	0.365	3.98 (1.73-9.13)	0.001

Table 4b.
Age and gender adjusted Cox proportional hazard analysis for cardiovascular mortality.

	No myocardial infarction		Myocardial infarction	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
LAHB	0.923 (0.41-2.09)	0.847	0.61 (0.08-4.41)	0.621
LPHB	0.003 (NA)	0.847	0 (NA)	0.989
LBBB	1.10 (0.48-2.50)	0.827	2.55 (1.36-4.77)	0.003
RBBB	1.12 (0.59-2.14)	0.726	1.65 (0.50-5.39)	0.411
Incomplete LBBB	1.56 (0.50-4.91)	0.445	0.51 (0.07-3.70)	0.503
Incomplete RBBB	3.11 (1.46-6.64)	0.003	0 (NA)	0.974
R-R´	0.70 (0.31-1.58)	0.387	1.38 (0.53-3.60)	0.507
NSIVCD	1.52 (0.21-10.88)	0.675	3.43 (1.44-8.20)	0.005

Table 4c.
Age and gender adjusted Cox proportional hazard analysis for cardiovascular mortality.

	No heart failure		Heart failure	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
LAHB	0.75 (0.28-2.04)	0.577	0.67 (0.21-2.13)	0.491
LPHB	NA	NA	NA	NA
LBBB	1.98 (1.00-3.89)	0.048	1.61 (0.81-3.19)	0.171
RBBB	1.08 (0.55-2.14)	0.817	1.09 (0.39-3.02)	0.872
Incomplete LBBB	1.13 (0.36-3.54)	0.840	0.83 (0.12-6.03)	0.855
Incomplete RBBB	2.09 (0.77-5.67)	0.146	1.86 (0.57-6.07)	0.301
R-R´	0.87 (0.41-1.86)	0.725	0.95 (0.34-2.66)	0.922
NSIVCD	5.40 (1.98-14.73)	0.001	3.80 (1.18-12.25)	0.025

not typical for RBBB or LBBB (21). In a Finnish population study of 10 899 middle-aged subjects, prolonged QRS duration in ECGs recorded between 1966 and 1972 without the criteria for complete or partial BBB predicted mortality and was strongly associated with arrhythmic death (13).

In the Multicenter Automatic Defibrillator Implantation Trial – CRT (MADIT-CRT), poor response of patients with non-specific IVCD to cardiac resynchronization therapy has been speculated to stem from generalized slow conduction within the left ventricle, which in turn is related to ischemic endocardial damage rather than to discrete bundle-branch disease (22). The negative prognostic outcome associated with non-specific IVCD in our study may be largely explained by unrecognized ischemic or non-ischemic structural heart disease.

In the Finnish cohorts of ≥65 year old subjects (n=697) of the Seven Countries study (23), 5-year mortality was 25% (2/8 subjects) for non-specific IVCD. Data were collected during the 1980's and, in general, mortality figures were high.

In selected patient populations, as in myocardial infarction patients, both LBBB and RBBB have proven to be independent predictors of mortality (24)(25). Previous investigators have come to varied conclusions regarding the impact of LBBB and RBBB on CV morbidity and mortality in the general population. The Framingham Study, (n=5,209), showed a clear association between LBBB and main CV diseases, such as hypertension, cardiac enlargement and CHD (26). Within 10 years from LBBB detection, CV mortality was 50%. Imanishi et al. studied 17,361 subjects from Japan who underwent health examinations from 1958 to 2002, including echocardiography; LBBB predicted heart failure-related but not all-cause mortality (27).In the present study LBBB was associated with increased relative risk for all-cause and CV mortality. The increased risk was seen only in individuals with coronary heart disease. As an aggregate, LBBB as an incidental finding in subjects with risk factors for CHD should result in a thorough clinical evaluation and echocardiography (9). The presence of LBBB has no adverse prognostic significance in subjects without evidence of structural heart disease. Such patients fall into the category of older patients with primary disease of the conducting system.

In this study, after age and gender adjustment, LBBB was not associated with worse outcome in subjects with HF. On the contrary, in individuals without HF there was a trend for increased relative risk for CV mortality with LBBB. This somewhat contradictory finding could be explained by the fact that subjects with undiagnosed left ventricular dysfunction have worse outcome than those with known disease, who are given proper medical and device therapy known to influence outcome positively.

In the Copenhagen City Heart Study (n=18,441), in subjects without previous MI or chronic heart failure, RBBB but not IRBBB was associated with significantly increased all-cause and CV mortality in both genders (10). The findings are opposite to the findings from our study. We found no increased mortality for RBBB, while IRBBB was associated with increased CV mortality. The increased risk was observed only in subjects who were free from coronary heart disease. Differences in study populations

may to some extent explain the diverging results from the two studies. The Danish study did not include subjects with known CAD or heart failure. Older population studies indicated no adverse outcome in otherwise healthy (young) subjects with RBBB (3,28).

Surprisingly, in the present study, IRBBB was associated with increased CV mortality among subjects with no previous coronary heart disease. IRBBB may be present in normal subjects, but it may also be a marker of acute or chronic right ventricular pressure or volume load, such as pulmonary embolism, congenital heart disease or arrhythmogenic right ventricular cardiomyopathy. Discrimination between IRBBB and Brugada type 2 and 3 may be troublesome, although this fact does not necessarily explain differences in outcome between population studies (29).

IRBBB has not been extensively studied in previous population studies. Disparate findings were reported from the Chicago Western Electric Company study of white middle-aged men (n=1,960), of whom 6.8% had IRRRB at study entry (30).Although IRBBB was not related to an increased risk of CV death during 20-year follow-up, this particular IVCD was frequently a manifestation of primary abnormality of the conduction system of the heart; individuals with IRBBB had increased risk for complete RBBB.

ILBBB was not associated with adverse outcome in the present general population. This conduction block is probably associated with slowing of conduction in the left bundle branch. However, differential diagnosis from LVH with QRS widening is not straightforward, and the ECG diagnosis is even somewhat controversial. This may be the reason to the lack of earlier population studies related to the prognostic significance of this ECG pattern.

Studies related to the prognostic impact of LAHB have shown somewhat disparate results, probably in part due to differences in definition of this conduction disorder. Some overlap between left axis deviation e.g. due to horizontal heart or inferolateral myocardial infarction and left axis deviation due to LAHB is unavoidable (12). The prognosis of LAHB is basically dependent on the associated pathology. Coronary and hypertensive heart disease are the most common causes of LAHB. In a study of 1,187 patients with suspected coronary artery disease referred for stress testing, LAHB (n=159) was associated with increased risk of cardiac death during 6-year follow-up (p=0.004) (31). Most population studies have not found any association between the presence of LAHB and increased risk of cardiac death. In a community population of 8,000 Japanese-American men aged 45 to 69 years, the incidence of fatal or nonfatal coronary heart disease and stroke during observation periods of 3 to 6 years was not significantly different from that of control normal men (32). Left axis deviation or LAHB was a quite common finding in centenarians without prognostic implications (33). Our results support the notion of LAHB being a benign incidental ECG finding in the general population.

Isolated LPHB is extremely rare, as it is almost invariably associated with RBBB (34). In a study form the 1970,s, LPHB plus RBBB in acute MI was associated with a high mortality rate (80% to 87%) during the first weeks after the acute event (35). Likewise, the risk of progression toward complete AV block

was considerable (42%), and 75% of these patients died from pump failure (36). Also in the present study, LPHB was a rare finding and was not associated with mortality increase.

Very little data on R-R´-pattern is available. It has sometimes been classified as a part of fragmented QRS complex which is associated with myocardial scar and increased mortality in CAD patients (21). In non-ischemic dilated cardiomyopathy patients, fragmented QRS was associated with increased number of cardiac events but not with cardiac fibrosis measured with contrast enhanced myocardial resonance imaging (37). In our study R-R´-pattern was not associated with the diseases studied or increased mortality and we consider this ECG finding benign.

Limitations

Only participants 30 years or older were included in the study. ECGs were recorded only once and no data on progression or regression of ECG changes are available. We did not have echocardiography data for the population. However, this is a follow-up study of a large population cohort with well-defined baseline parameters.

In conclusion: In the general population, non-specific IVCD, LBBB and IRBBB were associated with increased relative risk for all-cause and CV mortality. For LBBB, and non-specific IVCD, CV mortality was increased only in individuals with angina pectoris/MI and for IRBBB only in subjects with no coronary heart disease. RBBB in the general population carried no increased risk for all-cause or CV mortality.

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Declaration of interest

No conflicts of interest declared.

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