The Resting Electrocardiogram and Risk for Cardiovascular Disease

A Population-Based Study in Middle-Aged Men with up to 32 Years of Follow-Up

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Dissertation presented at Uppsala University to be publicly examined in Auditorium Minus, Museum Gustavianum, Akademigatan 3, 75310 Uppsala, Friday, December 8, 2006 at 09:15 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in Swedish.

Abstract

The aim was to contribute to the optimal use of the resting ECG by exploring, in middle-aged and elderly men, the development and regression of ECG abnormalities; the prognostic value of the ECG for cardiovascular disease compared to conventional risk factors; and the impact of age at baseline and follow-up time for prediction of cardiovascular disease.

It was based on the Uppsala Study of Adult Men cohort that was started in 1970. Participants were examined at ages 50, 70, 77, and 82, with annual updates on mortality and in-hospital morbidity using national registries.

The studies indicated that the prevalence of silent MI and frequency of regression of major Q/QS patterns may be higher than previously believed. Considering that persistent T wave abnormalities and ST segment depression carried twice as high a risk for future cardiovascular disease (CVD) mortality as new or reverted abnormalities, the results suggested that serial electrocardiograms (ECG) would contribute to proper risk assessment. Also, the inclusion of ischemic ECG findings significantly increased the predictive power of the Framingham score at age 70 for CVD.

While hypertension and dyslipidemia were consistent long-term risk factors for myocardial infarction at ages 50 and 70, the length of follow-up period and age at baseline affected the predictive power of ECG abnormalities, fasting insulin, BMI, and smoking.

For stroke, midlife values for blood pressure and ECG abnormalities retained prognostic value over long follow-up periods, even though they improved when re-measured in elderly participants. ApoB/apoA1 ratio, driven by apoA1, was associated with stroke in elderly but not middle-aged men. Hyperinsulinemia and diabetes mellitus were more specifically associated with ischemic stroke than with any-cause stroke.

In summary, the resting ECG carried prognostic information beyond conventional risk factors. Even though the low prevalence of ECG abnormalities at the age of 50 calls into question the role of the ECG as a screening tool, the additional risk information it carries with it justifies its regular and repeated registration above the age of 50.

Keywords: electrocardiogram, risk factors, epidemiology, population-based studies, cardiovascular mortality, apolipoproteins

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<th>Description</th>
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<tbody>
<tr>
<td>AF</td>
<td>AF</td>
</tr>
<tr>
<td>AIS</td>
<td>acute ischemic stroke</td>
</tr>
<tr>
<td>Apo(a)</td>
<td>apolipoprotein (a)</td>
</tr>
<tr>
<td>ApoA1</td>
<td>apolipoprotein A1</td>
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<td>ApoB</td>
<td>apolipoprotein B</td>
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<tr>
<td>BP</td>
<td>blood pressure</td>
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<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>CDR</td>
<td>Cause of Death Registry</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>CAD</td>
<td>coronary artery disease</td>
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<tr>
<td>CHF</td>
<td>cardiac heart failure</td>
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<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
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<tr>
<td>DBP</td>
<td>diastolic blood pressure</td>
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<tr>
<td>ECG</td>
<td>electrocardiography/electrocardiogram</td>
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<tr>
<td>ECG-LVH</td>
<td>electrocardiographic left ventricular hypertrophy</td>
</tr>
<tr>
<td>HDL</td>
<td>high density lipoprotein</td>
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<tr>
<td>HR</td>
<td>hazard ratio</td>
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<tr>
<td>ICD</td>
<td>International Classification of Disease</td>
</tr>
<tr>
<td>ICH</td>
<td>intracerebral hemorrhage</td>
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<tr>
<td>IPR</td>
<td>In-Patient Registries</td>
</tr>
<tr>
<td>IRS</td>
<td>Insulin Resistance Syndrome</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>lipoprotein(a)</td>
</tr>
<tr>
<td>LBBB</td>
<td>left bundle branch block</td>
</tr>
<tr>
<td>LDL</td>
<td>low density lipoprotein</td>
</tr>
<tr>
<td>LVH</td>
<td>left ventricular hypertrophy</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
</tr>
<tr>
<td>PRO</td>
<td>pooled repeated observations</td>
</tr>
<tr>
<td>RR</td>
<td>relative risk</td>
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<tr>
<td>RBBB</td>
<td>right bundle branch block</td>
</tr>
<tr>
<td>SAH</td>
<td>subarachnoidal hemorrhage</td>
</tr>
<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
</tr>
<tr>
<td>ULSAM</td>
<td>Uppsala Longitudinal Study of Adult Men</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</table>
Introduction

Cardiovascular disease
The common pathological background to cardiovascular disease (CVD) is atherosclerosis. An intact vascular endothelium prevents the migration of lipids and inflammatory cells into the intima of arteries, while the risk factors for coronary artery disease (CAD), such as hypercholesterolemia, hypertension, and cigarette smoking lead through different mechanisms to endothelial injury, with thickening of the intima and subsequent formation of a plaque with lipid core and fibrous cap. Atherosclerosis starts early in life, followed by a long asymptomatic phase before clinical manifestations become apparent in mid- or late life. The terminal events, such as myocardial infarction (MI) or cerebral infarction, are usually derived from secondary changes within the fibrous plaque that lead to the formation of occlusive thrombus. The term “vulnerable plaque” has been used to designate a thrombosis-prone plaque with high probability for undergoing progression.

Clinical evidence of atherosclerosis in one vascular bed is believed to reflect a more widespread atheromatous disease. Prospective studies have indicated that the risk-factor pattern for the complications of atherosclerosis is different in the different parts of the cardiovascular tree (e.g., for stroke, hypertension is quantitatively the most important risk factor whereas for intermittent claudication, smoking appears to be the most important factor). There are still questions as to the relative importance of different risk factors in the prediction of different cardiovascular disease such as MI and stroke.

Cardiovascular risk factors
Hypertension is a strong and common risk factor for CVD and was one of the first risk factors to be identified. The Framingham Heart Study has played a key role in establishing cigarette smoking, physical inactivity, cholesterol, and obesity as risk factors for CVD, and it has also secured the link between hypertension and stroke.

Today, it is believed that hypertension, along with metabolic aberrations (metabolic syndrome or insulin resistance syndrome (IRS)) contributes to
cardiovascular target organ damage. The metabolic syndrome includes hypertension, obesity, Type 2 diabetes, impaired glucose tolerance, and central obesity. The IRS predict CAD events in elderly Type II-diabetic men, however, the independent role of fasting insulin, a surrogate marker for insulin sensitivity, has been under some debate. In previous studies in UL-SAM, the amount of insulin resistance measured by the euglycemic insulin clamp, predicted subsequent CAD in elderly men; proinsulin provided a better prediction of CAD than insulin.

Recent studies have shown that the apolipoprotein B/apolipoprotein A1 (apoB/apoA1) ratio, which indicates the balance between atherogenic apoB-containing and atheroprotective apoA1 containing particles, may be a better predictor for cardiovascular disease than the more traditional markers for dyslipidemia such as total cholesterol, low density lipoprotein (LDL) cholesterol and triglycerides.

Moderate increase in body weight has also been associated with an increased risk of coronary death and non-fatal MI. Other risk factors discussed in the literature include smoking, leucocyte counts, lipoprotein (a), plasma fibrinogen, homocysteinemia, sleep disorders, C-reactive protein, and renal dysfunction.

As evidence accumulates on the multifactor pathogenesis of vascular disease there is an increasing trend toward multimodal vascular prevention.

Despite major advances in the treatment of patients with CAD, a large number of subjects die suddenly, without previous symptoms, and available screening methods are insufficient to identify victims before the events occur.

**Risk scores and risk assessment strategies**

Since the risk of developing CVD depends on a number of different risk factors that interact and act synergistically, it may be difficult to assess the exact impact and role of each risk factor. Investigators have developed CAD risk equations, based on regression equations derived from observational studies, for use by clinicians in predicting the development of coronary disease.

Current recommendations on the prevention of CVD in clinical practice stress the need to base intervention on an assessment of the individual’s total burden of risk, rather than on the level of any particular risk factor. Different scoring systems have been developed that take several risk factors into account. Scoring systems include the Framingham score, the Prospective Cardiovascular Münster Study (PROCAM), the European scoring system developed by the SCORE Project and the BMJ risk score. A risk prediction score including the more recently identified variables proinsulin and the apoB/apoA1 ratio was applied to ULSAM data, and was at least as good as the Framingham and the PROCAM scores.
Previous versions of the Framingham score, included presence or absence of ECG-LVH but this has been excluded from more recent versions due to lack of standard universally accepted ECG criteria for ECG-LVH and its high association to hypertension. The BMJ risk score includes LVH but the definition of LVH is unclear.

All above-mentioned risk scores are based on established conventional risk factors known to contribute to chronic development of atherosclerosis. Even though they have been shown to predict long-term outcome in large populations they may not be as efficient in predicting near future events in individual clinical practice. A new risk assessment strategy that has been proposed is the Cumulative Vulnerability Index, a score based on vulnerable plaque/artery, vulnerable blood (prone to thrombosis) and vulnerable myocardium (prone to life-threatening arrhythmia).

Myocardial infarction

Introduction

Myocardial infarction (MI) reflects the necrosis of cardiac myocytes caused by prolonged ischemia, due to perfusion-dependent imbalance between supply and demand. The primary event is acute, partial, or complete obstruction to coronary flow, with a thrombus forming on severe preexisting atherosclerotic coronary artery disease. Typical symptoms are: chest pain and epigastric, arm, wrist, or jaw discomfort. Other possible accompanying symptoms are: nausea, vomiting, shortness of breath, left ventricular failure, weakness, dizziness, or syncope. After myocardial ischemia, cell death will occur after 20 to 60 minutes if there is little or no collateral flow, while it may take up to six hours if collateral flow is higher. Cell death spreads through the myocardial wall, often starting in the sub-endocardium, which is the most vulnerable part. Silent myocardial necrosis is clinically unrecognized MI, occurring without symptoms.

Myocardial necrosis can be recognized by various proteins released into the circulation due to the damage of myocytes (e.g. cardiac troponins T and I, MB fraction of creatinine kinase (CK-MB), and lactate dehydrogenase (LDH)); and by characteristic Q/QS patterns and ST-T changes on the ECG. Not all patients who develop myocardial necrosis exhibit ECG changes. Thus, a normal ECG does not rule out the diagnosis of MI. On the other hand, clinically unrecognized MI also occurs. Prevalence of unrecognized MI varies among studies, with an average of 30% Clinically unrecognized MI is believed to be associated with the same risk as recognized symptomatic MI, although a lower risk for unrecognized MI has also been described. Shortly after a transmural MI has occurred, a typical Q/QS pattern develops that has been considered an indicator of myocardial necrosis. Q
wave loss may occur in 11-25% of patients after transmural MI\textsuperscript{36,37} and can be expected to vary according to length of follow-up period after Q wave MI. In the Framingham Study, a year after a Q wave MI, the Q wave persisted in 73% of cases and those with a persistent Q had a worse prognosis compared to subjects where the ECG reverted to normal\textsuperscript{38}. The clinical significance of such an ECG phenomenon has not been fully clarified. Functional recovery of stunned and/or hibernating myocardium\textsuperscript{39} and regeneration of myocytes\textsuperscript{40} have been proposed as possible mechanisms. While permanent negative T waves in the post-MI phase have indicated the presence of transmural infarction\textsuperscript{41}, transient T waves in a post-MI phase have been associated with the presence of viable myocardium at jeopardy\textsuperscript{42}.

Definition of myocardial infarction

In the past, there was a general consensus that the clinical entity “acute MI” should be defined using a combination of two out of three typical findings: chest discomfort, enzyme rise, and a typical ECG pattern involving the development of Q waves\textsuperscript{43}.

However, the advent of sensitive and specific serologic biomarkers and precise imaging techniques has led to a reevaluation of established definitions of MI\textsuperscript{44}. The recent introduction of the biomarkers cardiac troponins T and I into routine daily practice allows for highly accurate, sensitive and specific determination of myocardial injury.

The application of new, more sensitive diagnostic criteria will cause an increase in incidence of MI.

Incidence

The incidence of coronary events varies among countries and few studies provide information on non-fatal events\textsuperscript{45}.

In the Copenhagen City Heart Study, the age standardized incidence per 1000 male patients of combined non-fatal and fatal MI during 7 and 21 years of follow-up was 7.5 and 10.0, respectively\textsuperscript{46}.

Etiology and established risk factors

Most publications refer to risk factors for MI in the broader context of atherosclerosis, CAD or CVD. Ischemic heart disease varies in its clinical presentation, from stable angina, to unstable angina or acute myocardial infarction (MI)\textsuperscript{47}. Rupture of an atherosclerotic plaque with subsequent thrombosis formation may be an important mechanism behind acute coronary events\textsuperscript{48} and risk factors of acute coronary events may differ from risk factors for stable angina.
Stroke

Introduction

Stroke is a term used to designate the sudden and dramatic development of a focal neurological deficit. The clinical manifestations of stroke are variable and depend on the complex anatomy of the brain and its vasculature. Cerebral ischemia is caused by a reduction in blood flow that lasts longer than several seconds. Neurological symptoms are manifest within seconds, but when blood flow is quickly restored, brain tissue can fully recover and the patient's symptoms will only be transient.

Acute stroke is divided into two main types: acute ischemic stroke (AIS) and hemorrhagic stroke. In AIS, the blood flow to the brain is compromised or blocked. This may be due to atherothrombosis (40-50%); cardiac emboli from AF or prosthetic heart valve (25-30%); or small vessel disease (25-30%). In hemorrhagic stroke, there is a rupture of a blood vessel within the brain (intracerebral hemorrhage) or in the subarachnoid space on the surface of the brain (subarachnoidal hemorrhage). The distribution of AIS, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH) in Caucasian populations is approximately 72% to 86%, 8% to 15%, and 1% to 5%, respectively.49

Approximately 20% of stroke patients do not survive longer than 1 month, and a third of those who are alive after 6 months are dependent on others.50

Definition of stroke

Stroke is not a single disease but a clinical syndrome with several different pathologies49. According to the WHO definition, stroke has occurred if the neurological signs and symptoms last for more than 24 hours51. Neurological signs and symptoms lasting less than 24 hours are called transient ischemic attacks (TIA). The diagnosis of stroke is clinical, but today brain imaging is, in most cases, used to support the diagnosis and to further establish the type of stroke.

Incidence

Even though there is a trend toward decreasing mortality from stroke in many countries, the number of stroke victims is on the rise due to changes in age structure of the Western population52.

Based on a stroke register, the incidence of non-fatal and fatal stroke in Göteborg, Sweden in 1970 was estimated at 150/100,000 population and year53. However, incidences may vary greatly among countries and regions. According to the International Stroke Incidence Collaboration, the annual
incidence rate of fatal and non-fatal stroke for subjects aged 45 to 84 has been estimated to vary between 300/100,000 and 500/100,000 subjects in most places.

Etiology and established risk factors

In the Göteborg population-based study, blood pressure, smoking, diabetes mellitus, atrial fibrillation, severe psychological stress, previous transient ischemic attacks, and intermittent claudication were associated with future stroke in middle-aged men, while high cholesterol was not. Impairment of renal function has also been associated with increased risk of stroke.

The association between risk factors and any-cause stroke may vary between different types of stroke. Even though the different types share many of the risk factors, there is some evidence that total cholesterol may be inversely associated with the risk of hemorrhagic stroke.

Risk factors for stroke in the elderly may differ from younger subjects, with congestive heart failure (CHF), AF and chronic nephropathy becoming more important in the elderly.

The resting electrocardiogram (ECG)

Introduction

The resting ECG is the registration on the surface of the body of the heart’s electrical activity. It is through perturbation in the normal electrical patterns that many different cardiac disorders, including myocardial infarction, cardiac ischemia, and arrhythmias, are diagnosed. Even though the ECG is one of the oldest diagnostic medical tools, it continues to be the most commonly used cardiovascular laboratory procedure. It is noninvasive, cheap, simple to record, highly reproducible and can be applied serially.

Two major landmarks in the century-old history of electrocardiography were the introduction of electrocardiography as a noninvasive investigative technique on humans by Augustus Waller in 1887 and Wilhelm Einthoven's electrocardiograph from 1901. The first ECG machine was a simple string galvanometer, capable of measuring small changes in electrical potential as the heart contracted and relaxed. The recording of the light reflected from the string galvanometer was projected on a moving glass photographic plate. The signals were obtained from the two arms and left leg (modern Lead I). To enhance conduction, hands and left foot were bathed in saline solution with the tubs wired to the input of the electrocardiograph. The string galvanometer for electrocardiography was soon superseded by direct writing equipment.
Einthoven was awarded the Nobel Prize in Medicine in 1924 for his “discovery of the mechanism of the electrocardiogram” 58. Also, Lewis and Wilson made very important contributions to the development of the ECG and its standardization. Lewis carried out a large amount of work on cardiac arrhythmias; Wilson contributed with analyses of ECG waveform patterns in conduction defects and other cardiac disorders and promoted standardization and uniformity in ECG methodology 59.

The ECG has been widely used in epidemiological studies designed to determine the prevalence of ischemic heart disease and to identify latent heart disease. However, the resting ECG has also been considered unspecific and its prognostic value as independent marker has been much debated 59. Also, the diagnostic and prognostic implication of a given ECG abnormality has been considered to differ depending on the population studied and the reason for the ECG recording 59, 60.

The large volume of tracings and the shortage of properly trained personnel have stimulated search for alternative approaches to interpretation, processing, storage and retrieval of ECG 59. A large international project, sponsored by the European Commission, was launched in 1980 to develop “Common Standards for Quantitative Electrocardiography (CSE).” The actions performed by this project have become internationally recognized milestones in the standardization of quantitative electrocardiography 61.

The ECG in population studies and ECG classification systems

Population studies with ECG registration
A number of epidemiological studies have been identified where ECGs have been taken at baseline and where follow-up with respect to CVD has been carried out at different time points. Major population studies where ECGs have been assessed and evaluated have been summarized in Table 4 62-64. Only a small number of studies focused particularly on the elderly population. Some cohorts excluded subjects with symptomatic heart disease and ECG abnormalities at baseline, while others did not. Participation rates in most studies were generally greater than 70%.

Variation in the method of calculating risk and varying length of follow-up periods, end-points, age at baseline, sample size, gender, and exclusion criteria (e.g. symptoms of CAD or ECG indicating ischemia, excluded or not at baseline) have occurred among studies 62. Some studies have followed up, after screening, with vital status checks, using registries or directly contacting subjects, while others have carried out extensive, frequent, and regular examinations of the subjects. Most studies were longitudinal with CAD, CVD, or any-cause mortality as end-points.
Population studies in the elderly.

The Cardiovascular Health Study is a population-based, longitudinal study of CAD and stroke in adults over 65 years of age. The aim was to confirm the importance of CVD risk factors in the elderly and to identify new risk factors. The prevalence of any major ECG abnormality in those with no previous history of CAD or hypertension increased with age, with the prevalence of ECG abnormalities among participants older than 85 years being three times higher than those in the age group 65 to 69. There are very few studies that have specifically looked at ECG abnormalities and their associated prognostic value in the very old. In subjects 85 years old or older, ECG abnormalities suggesting ischemia were associated with significant increased mortality. The greatest mortality rate was found in subjects with AF or first-degree atrioventricular block. Left bundle branch block (LBBB) or right bundle branch block (RBBB), supra-ventricular premature beats and ventricular premature beats were not associated with an increased risk of death. ST segment depression, T wave inversion, ventricular premature complexes, and AF were related statistically to clinical CHF, as were ST segment depression and T wave inversion to clinical CAD. A study of serial ECGs in elderly people suggests that the voltage changes of ECG-LVH may disappear, and that ST-T patterns may change to Q/QS patterns or LVH patterns.

Population studies in Sweden.

Before ULSAM, the Study of Men Born in 1913, a prospective cohort study had been started in Göteborg in 1963. One-third of the 50-year-old men living in Göteborg were invited. ULSAM itself was started in 1970, with the Primary Preventive Trial also being started in Göteborg. All men in Göteborg born between 1915 and 1925 participated, and among measured variables at the screening examination were: blood pressure, total cholesterol, weight and ECGs. The Malmö Preventive Project, started in 1974, aimed at examining large strata of the adult population to identify high-risk individuals for preventive intervention on cardiovascular risk factors, alcohol abuse, impaired glucose tolerance, and breast cancer. Between 1974 and 1992, a total of 21,911 men and 8,676 women participated with an overall attendance rate of 71.2%. A Myocardial Infarction Register has also been in operation in Göteborg since 1968 and a stroke register since 1970. A stroke registry was also set up more recently, in 1989, in Malmö.

Population studies in women.

Even if epidemiological trials now include women in their cohorts, historically many of the epidemiological studies included only middle-aged men. A population study of women was set up in Göteborg in 1968.

16
The Women’s Health Initiative Study \(^77\) has studied the incidence of CAD and all-cause mortality in postmenopausal women. Several re-polarization variables were found to be as important predictors of CAD and all-cause mortality as old MI by ECG criteria \(^64\).

**ECG classification systems**

The “Minnesota code” (MC) was developed by cardiovascular epidemiologists as a tool to aid consistency and comparison of ECGs in large clinical studies. The rules for its application were defined in 1960 \(^78\) and a modified version was published in 1982 \(^79\). It rapidly became the standard for the classification of ECGs in clinical trials and has been used in most epidemiological studies.

The initial code was designed for visual manual morphologic categorization of ECG waveform features and for estimation of the prevalence of ECG abnormalities \(^80\). Computerized Minnesota coding has also been available for many years \(^81\) and some authors claim that it outperforms visual manual coding \(^82\), \(^83\) by reducing the intra- and inter-observer variability. It also reduces cost by reducing the times spent by physicians on coding \(^84\).

One criticism of the Minnesota code has been its limited ability to deal with serial changes. The NOVACODE system is a computer coding ECG classification system \(^80\) based on a different coding sequence and logical structure, better designed for classification of serial ECGs changes.

The Cardiac Infarction Injury Score (CIIS) is an ECG based measure, originally constructed as a visual coding diagnostic tool to improve accuracy and stability of ECG classification in ischemic heart disease \(^85\). The classification of ECGs by means of the CIIS seems to be equivalent to classification by a combination of MC items, and some authors considered it to be an efficient alternative for MC in epidemiological studies \(^86\). CIIS has been associated with risk of both coronary morbidity and mortality in middle-aged and elderly men, the association being the strongest for mortality \(^87\).

An alternative to descriptor codes in health surveys could be diagnostic ECG interpretation performed by computer programs \(^84\). Basically, there are two methods for diagnostic classification of ECGs, one that is heuristic one and one that is statistical \(^88\). The heuristic approach attempts to simulate the reasoning of the cardiologist, while statistical approaches are less intuitive and use multivariate statistical techniques \(^88\). Diagnostic ECG interpretation by computers has been shown to be at least as good as ECG interpretation by a trained research physician \(^84\). Even though the percentage of ECGs correctly classified by the computer programs has been shown to be lower than that of cardiologists in some studies, some computer programs perform almost as well as cardiologists in identifying the major cardiac disorders \(^89\).

Variability of ECG measurements and MCs is to be expected in population-based studies \(^90\). One important source is intra- and inter-observer variability among physicians interpreting ECGs, which does not apply to ECGs
analysed by computer programs. Variability has been shown to be highest for ST segment depression (7.1% in a year-to-year comparison)\(^90\). Part of the variability observed for ECG coding may be explained by the all-or-non criteria and single threshold, used by most classification systems\(^90\).

Other sources of variability are differences in recording technique, especially electrode placement, random physiologic fluctuations (e.g. respiratory movements, fluctuations in autonomic balance, and changes in body position), signal-analysis errors in the computer program; and true clinical and sub-clinical changes in health status\(^90\).

Computerized ECG classification will most certainly improve in the future. New directions for research include: using information from all available beats; combining knowledge contained in different programs; incorporating knowledge gained in body surface mapping and modeling using information from non-ECG data; and collecting large ECG datasets for assessment of ECG programs\(^91\). New ECG variables, reflecting ventricular repolarization applied in recent studies are spatial angle between QRS and T vectors, T wave roundness index, ST gradient, rate-adjusted QT as a linear function of RR interval, and T wave nondipolar voltage\(^64\).

**ECG as a risk factor**

Initially ECGs were used mainly for the purpose of clinical diagnosis, and doctors were familiar with the significance of findings as they occurred in patients with specific cardiac diseases. In recent years ECGs are increasingly being recorded in apparently healthy people of different ages in order to assess occupational fitness, screening services or epidemiological surveys. This requires reassessment and reinterpretation of ECG findings as they arise in different settings.

The validity of using 12-lead ECG as a screening test for cardiovascular disease (CVD) has been questioned and debated in the literature\(^60, 62, 92-94\).

The value of any screening test depends critically on four key principles: its cost; the prevalence of the abnormalities detected in the population assessed; the link of the abnormalities to morbidity and mortality; and the possibility of reducing or avoiding future morbidity or mortality given the information provided by the test. In particular, to be worth the additional expense, the ECG must add significantly to the ability of standard risk factors in identifying asymptomatic persons with sub-clinical disease\(^62\). Ashley et al.\(^62\) carried out a literature review and attempted to identify subjects, where a randomly selected population of asymptomatic patients, with no history of ischemic heart disease, underwent ECG before a follow-up of at least 5 years, with respect to mortality. However, since very few studies fulfilled these criteria, the review included studies with different end-points, where subjects had not been randomly selected and where symptomatic subjects
may have been included. Their conclusion was that in symptomatic patients with ischemic heart disease, CAD, diabetes, hypertension, or with high cardiovascular risk scores, the ECG could help to identify subjects with the highest risk, and that the threshold for performing ECG should decrease in elderly subjects.

Impact of follow-up time and re-measurement of risk factors

For longitudinal population-based studies, the hazard of developing disease depends on age at baseline, time-on-study, birth cohort effects, as well as risk factors and covariates. In following up a healthy population, age has been considered the most appropriate time-scale for most outcomes. Since this does not take into consideration calendar effects that may be caused by advances in medical management, stratification on birth cohort may be necessary.

Mid-life values are more likely to represent lifelong exposure, which in turn constitutes the main contribution to the development of atherosclerosis. A substantial redistribution of major CVD risk factor values has been observed to take place between mid-life and old age, and caution is advised when using modifiable risk factor values measured late in life as the only method of assessing risk. However, most epidemiological knowledge of risk factors for cardiovascular disease has been based on studies of middle-aged populations, ignoring the fact that changes in predictive power may take place during prolonged follow-up periods.

The risk period may be the same as the exposed period but it does not have to be. In some studies, the follow-up period has been split into shorter follow-up periods, to identify risk factors with short-term effect or long-term effect. Some risk factors may carry long-term significance and be less important in the short-term, while some risk factors may only be important in the short-term. If current risk depends mainly on recent risk factors, the prognostic utility of a baseline value will decrease over time. However, each risk factor may have its own “optimal” time lag between measurement and outcome.

The Framingham Heart Study has collected repeated measurements for many risk factors prospectively every two years since 1948. Studies based on the Framingham data have compared baseline versus repeated measure covariate techniques. One approach is to ignore repeated measurements and evaluate only measures with long-term disease outcome. An alternative method is the pooling of repeated observation (PRO) technique, where each 2-year examination is treated as a mini follow-up study, and observations are pooled over all intervals to examine the short-term development of disease.
This method follows traits over time, rather than individuals over time, and takes into account the changing risk profile over time, without taking secular trends into consideration. PRO technique can be considered equivalent to Cox regression, with time-dependent covariates.

Because of fluctuations in the measured values of risk factors, comparisons generally tend to underestimate the real association between risk factors and disease rates. This regression dilution effect may be caused by measurement error, short term biological variability (such as diurnal or seasonal variability), or long-term fluctuations in risk factor values (related to age, treatment, or disease) \textsuperscript{101}. Pairs of measurement of the risk factors made in the same individual, on different occasions, separated by an appropriate interval, can be used to estimate the magnitude of the regression dilution ratio with a particular exposure, and correction can be made for it \textsuperscript{101}. Apparent decline with increasing age in relatively importance of specific risk factors in prospective studies may be due to regression dilution. Failure to correct for within-person variability can substantially dilute associations between risk factors and disease rates in prospective studies \textsuperscript{101, 102}. 

\textsuperscript{101}

\textsuperscript{102}
Aims of the thesis

The aim of this thesis was to provide further knowledge regarding the prognostic value of abnormal ECG findings for CVD, in relation to conventional risk factors, thereby contributing to the optimization of one of the most useful medical tools in the global assessment of cardiovascular risk.

The specific aims were:

I To determine how new, persistent, or reverted ischemic ECG abnormalities at age 50 and 70 affect the risk of subsequent cardiovascular disease. To investigate the added value of including ischemic ECG findings in the Framingham score.

II To investigate if different ECG characteristics, observed in a sample of men from the general population followed over a 20-year period, have different impact at age 50 compared to age 70 with regard to the predictive power for future fatal and non-fatal MI. To investigate if traditional cardiovascular risk factors are as strong predictors for myocardial infarction at age 70 as at age 50.

III To investigate if different ECG characteristics, observed in a sample of men from the general population followed over a 20-year period, have different impact at age 50 compared to age 70 with regard to the predictive power for future fatal and non-fatal stroke. To investigate if traditional cardiovascular risk factors are as strong predictors for stroke at age 70 as at age 50.

IV To identify predictors for the development of abnormal major Q/QS patterns, as a marker for MI, irrespective of chest pain. To determine predictors for ST segment depression and T wave abnormalities.
Methods

Participants

The ULSAM study

ULSAM is a population-based study aimed at identifying risk factors for CVD. Between 1970 and 1973, all 50-year-old men born during the period 1920 to 1924 and resident in the municipality of Uppsala, Sweden, were invited to participate in a health survey. 2322 out of the 2841 invited men participate (82%) \textsuperscript{103}.

All eligible participants investigated in the first survey at age 50, traced by their ten-digit social security number, were invited to re-investigation at age 60, 70, and 77. Eligible participants investigated either in the survey at age 70 or age 77, were invited to a re-examination at age 82 (figure 1a).

The examinations at age 60 were more limited and ECGs were not registered. The re-examination at age 70, 77 and 82 were carried out during the periods 1991 to 1995, 1997 to 2001, and 2003 to 2005, respectively. The participation rate at the different re-examinations was 73%, 60%, and 56% for the 70-, 77-, and 82-year survey, respectively. Further details on deaths, eligibility and participation are presented in figure 1b.

The screening data has been updated annually, with mortality and in-hospital morbidity data using national registries.
THE ULSAM COHORT

Figure 1a. Study design. Age of subjects invited for re-investigation.

Figure 1b. The ULSAM study population. All eligible participants investigated at age 50, were invited to re-investigation at age 70 and 77; and, all eligible participants investigated either in the survey at age 70 or age 77, were invited to a re-examination at age 82.
Study populations

**Paper I**
The risk analyses section was based on the 2322 subjects examined at age 50, and the 1221 subjects re-examined at age 70. Subjects that had been hospitalized for MI before the examination at age 50 (n=7) and at age 70 (n=99) were excluded, when assessing the association of ECG findings at age 50 and 70 to future MI morbidity.

**Papers II and III**
The study population was based on the 2322 subjects examined at age 50, and the 1221 subjects re-examined at age 70.

For Paper II, only subjects free from MI at the baseline for the 50-year examination, were included for Part I and Part IIa. For Part IIb, subjects with pacemaker (n=6) and subjects with MI before the 70-year examination were excluded from the final study population (n=1118).

For Paper III, only subjects free from stroke at baseline age 50 (n=2320) were included for Part I and Part IIa. For Part IIb subjects with pacemaker (n=6) and subjects with stroke before the 70-year examination (n=67), were excluded from the study population (n=1148). Sub-analyses were also carried out excluding subjects with transitory ischemic attack (TIA) (n=57) and non-ischemic stroke (n=65).

**Paper IV**
The study population was based on the 2322 subjects examined at age 50, and the 1221 subjects re-examined at age 70. A total of 19 subjects were excluded from further analyses due to: acute MI before the 50-year examination, major Q wave (1.1), or LBBB (7.1) on ECG at age 50; resulting in a study population of 2303 men at age 50, of which 1131 men were re-investigated also with ECG at age 70. Development of ST segment depression and isolated T wave abnormality on ECG at age 70, were investigated in subgroups of 1006 men (additional exclusion of men with MCs 4.1-4.2 at age 50) and 858 men (additional exclusion of men with MCs 4.1-4.2 at age 50 and/or 70, and 5.1-5.4 at age 50), respectively.

**Investigations at age 50**
These measurements have extensively been described elsewhere.^{103}
ECG
A 12-lead resting ECG was recorded, including standard leads I, II and III, unipolar leads aVR, aVL and aVF and V₁₋₆. The conventional amplification 1 mV=10 mm was used with a paper speed of 50 mm per second. The ECG was a direct-writing Minograf 61 (Siemens-Elema Ltd, Solna, Sweden).

The ECGs were classified according to the MC 78 by two experienced physicians of the Department of Physiology. The coding of pathological ECGs was done separately by the two physicians. The final coding was not accepted until full agreement was achieved. ECG status was classified as abnormal based on presence of one or more of the ECG diagnoses listed below:

<table>
<thead>
<tr>
<th>ECG diagnosis</th>
<th>Minnesota code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Q or QS pattern</td>
<td>1.1</td>
</tr>
<tr>
<td>Minor Q or QS pattern</td>
<td>1.2 or 1.3</td>
</tr>
<tr>
<td>High amplitude R waves</td>
<td>3.1 or 3.3</td>
</tr>
<tr>
<td>ST segment depression</td>
<td>4.1 or 4.2</td>
</tr>
<tr>
<td>T wave abnormalities</td>
<td>5.1, 5.2 or 5.3</td>
</tr>
<tr>
<td>AV block I</td>
<td>6.3</td>
</tr>
<tr>
<td>Left bundle branch block</td>
<td>7.1</td>
</tr>
<tr>
<td>Right bundle branch block</td>
<td>7.2</td>
</tr>
<tr>
<td>AF or flutter</td>
<td>8.3</td>
</tr>
<tr>
<td>Artificial pacemaker</td>
<td>6.8</td>
</tr>
</tbody>
</table>

Criteria for the different MCs are based on duration and amplitude of ECG complexes (table 1).
<table>
<thead>
<tr>
<th>ECG abnormalities</th>
<th>Minnesota Code</th>
<th>Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q or QS pattern</td>
<td>1.1</td>
<td>Q duration ≥ 0.04s in I, II, V2-V6.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q duration ≥ 0.05s in both aVF and III.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>QS pattern through V1-V6, V5 and V6.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>QS pattern when R wave is present in adjacent precordial lead to the right of V2-V6.</td>
</tr>
<tr>
<td>ST segment</td>
<td>4.1-4.2</td>
<td>4.1: ST-depression ≥ 1 mm in I, II, aVL, aVF, V1-V6.</td>
</tr>
<tr>
<td>depression</td>
<td></td>
<td>4.2: ST depression 0.5-0.9 mm in I, II, aVL, aVF, V1-V6.</td>
</tr>
<tr>
<td>T wave items</td>
<td>5.1-5.3</td>
<td>5.1: T amplitude ≥ 5 mm in I, II, V2-V6 when R amplitude ≥ 5 mm in aVL when QRS mainly upright in aVF.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.2: T amplitude = -1 to -5 in I, II, V2-V6 when R amplitude ≥ 5 mm in aVL when QRS mainly upright in aVF.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.3: T wave flat or small biphasic in I, II, V2-V6 when R amplitude ≥ in aVL when QRS mainly upright in aVF.</td>
</tr>
<tr>
<td>High R wave</td>
<td>3.1/3.3</td>
<td>3.1: R amplitude &gt; 26 mm in either V5 or V6 or R amplitude &gt; 20 mm in I, II, III, aVF, or R amplitude &gt; 12 mm in aVL.</td>
</tr>
<tr>
<td>amplitude</td>
<td></td>
<td>3.3 (when 3.1 is not present): R amplitude in V5 or V6 plus S amplitude in V1 &gt; 35 mm.</td>
</tr>
<tr>
<td>LBBB</td>
<td>7.1</td>
<td>QRS duration ≥ 0.12s, plus R peak duration ≥ 0.06.</td>
</tr>
<tr>
<td>RBBB</td>
<td>7.2</td>
<td>QRS duration ≥ 0.12s, plus R' &gt; R in V1.</td>
</tr>
<tr>
<td>AF/flutter</td>
<td>8.3</td>
<td>Persistent AF or AF pattern.</td>
</tr>
<tr>
<td>AV block I</td>
<td>6.3</td>
<td>PQ interval ≥ 0.22s.</td>
</tr>
</tbody>
</table>

LBBB = left bundle branch block; RBBB = right bundle branch block.
Anthropometry

Height (without shoes) was measured to the nearest whole cm and the weight (in under shorts) to the nearest whole kg. Body mass index (BMI) was calculated as weight (in kg) divided by height (in meters) squared.

Blood pressure

The blood pressure (BP) was measured on the right arm, with mercury manometer (Kifa Ercameter; Speidel & Keller, Jungingen, Germany; width 12.5 cm; length, 35 cm) after 10 minutes’ rest in the recumbent position. Systolic (SBP) and diastolic blood pressure (DBP) were read to the nearest 5 mmHg. The DBP was recorded at the disappearance of the Korotkoff sounds (phase five).

Glucose and insulin

Blood-glucose was measured by spectrophotometry using the glucose oxidase method.

Blood-glucose concentrations at age 50 were multiplied by a conversion factor of 1.11 to be comparable to plasma, according to IFCC recommendations.

The serum insulin was determined with the Phadebas Insulin Test (Pharmacia AB, Uppsala, Sweden), based upon the radioimmunosorbent technique.

Lipids and apolipoproteins

Determinations of serum cholesterol and triglyceride concentrations were performed on a Technicon Auto Analyzer type II in 1981-82 on serum samples that had been stored since sampling, initially in liquid nitrogen and later in freezers. HDL was assayed in the supernatant after precipitation with a C Grin/manganese-chloride solution. LDL cholesterol was calculated using Friedewald’s formula: LDL=serum cholesterol-HDL-(0.42·* serum triglycerides).

Apolipoprotein (a) (apo(a)) and apoB were determined by a two-site immuno-radiometric assay, and apoA1 by a competitive radioimmunoassay in 1988, with use of commercial kits from Pharmacia (Uppsala, Sweden). Lipoprotein (a) (Lp(a)) consists of an LDL-like particle to which apo(a) is linked by a disulfide bond.
Smoking

Smoking habits were collected through interview. At the 50-year examination, 51% were smokers. The number of ex-smokers (stopped smoking at least one month ago) was 23.8% and 25.2% had never smoked.

Investigations at age 70, 77, and 82

The cohort was reinvestigated at age 70, 77, and 82, at which time all investigations performed at age 50, including standard resting ECG, were repeated. At age 70, the apoB/apoA1 ratio was determined in a random sample of 551 subjects.

The ECGs were classified according to the MC by two different experienced physicians. One physician coded all ECGs from the 70-year examination and another physician coded all ECGs from the 77- and 82-year examinations. ECGs from the 77- and 82-year examination were coded during the same time period.

Prevalence of ECGs in ULSAM

Prevalence of ECG findings at age 50, 70, 77, and 82 was determined using all available ECGs from the different examinations, except ECGs from subjects with pacemaker. A resting ECG was not recorded in the first 44 participants of the 77-year examination, or in the 15 men of the 82-year examination who did not participate in the hospital examinations, but were visited by nurses in their homes.

The prevalence of “ECG indicating ischemia” abnormalities increased from 7% at age 50 to 43% at age 77. At age 82 the prevalence was 39%, probably due to death of some subjects with ECG abnormalities (figure 2a). When considering only subjects attending all four surveys, the prevalence of most ECG abnormalities was similar at age 77 and 82, except for a slight increase in major Q/QS patterns, LBBB, AV-block I and AF (figure 2b).
Figure 2a. Prevalence of ECG abnormalities by age (all subjects included)

Figure 2b. Prevalence of ECG abnormalities by age (only subjects attending all surveys included)

Definitions

ECG dummy variables
ECG dummy variables were generated and used in the different papers (table 2).
Table 2. ECG dummy variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Definition</th>
<th>Paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Abnormal Q/QS pattern&quot;</td>
<td>Q/QS patterns with a certain precision according to MC 1.1, 1.2 or 1.3</td>
<td>II and III</td>
</tr>
<tr>
<td>&quot;ECG-LVH&quot;</td>
<td>High R-wave amplitude (3.1/3.3) accompanied by ST segment depression (4.1-4.2)</td>
<td>I, II and III</td>
</tr>
<tr>
<td>&quot;ECG indicating ischemia&quot;</td>
<td>ECG with the following MC: major Q/QS patterns (1.1), minor Q/QS patterns (1.2-1.3), LBBB (7.1) and ST-T abnormalities (4.1-4.2 and 5.1-5.3)</td>
<td>I</td>
</tr>
<tr>
<td>&quot;Normal ECG&quot;</td>
<td>ECGs without the following MC: major and minor Q/QS patterns (1.1-1.3), high R-wave amplitude (3.1/3.3), ST-T abnormalities (4.1-4.2 and 5.1-5.3), 6.3, 7.1, 7.2 and 8.3.</td>
<td>I</td>
</tr>
</tbody>
</table>

MC = Minnesota code

Definition of diabetes mellitus

At the 50-year examination, fasting blood-glucose concentration was analyzed, and diabetes mellitus was defined as a fasting blood glucose concentration ≥6.1 mmol/L and/or pharmacological treatment for diabetes mellitus.

At the 70-year examination, fasting plasma-glucose was analyzed and diabetes mellitus was defined as fasting plasma glucose concentration ≥7.0 mmol/L and/or pharmacological treatment for diabetes mellitus.

Framingham score

The Framingham score, based on: age, smoking habits, diabetes mellitus, blood pressure, and levels of LDL/HDL, was determined for each subject.

Follow-up periods and outcomes

Follow-up periods

Outcome and survival-time variables were defined using registry data. For Paper I the maximum follow-up period was 33.7 (censored date 31 December...
ber 2003). For Papers II and III the maximum follow-up period was 31.7 years (censored data 31 December, 2001).

The two baselines considered for Paper I were the examination dates of the 50- and 70-year survey. All men were followed for the first occurrence of fatal or non-fatal MI, CVD mortality and any-cause mortality.

Papers II and III were divided into 2 parts. In Part I of the study, the follow-up period was divided into three consecutive periods, between ages: 50-60 years, 60-70 years, and 70-80 years. Part II of the study was divided into 2 follow-up periods. Part IIa, with a maximum follow-up time of 23.8 years, covered the period from date of the first examination at age 50 (n=2322) to date of first non-fatal or fatal MI event, or second examination at age 70; and Part IIb, with a maximum follow-up time of 10.4 years, covered the period from baseline at age 70 (n=1221), until event date or censored date.

For Paper IV, the follow-up period was 20 years, from the 50-year examination date to the 70-year examination date.
Figure 3. Study design (Papers II and III)
BL=baseline
Outcomes:
  i) Fatal or non-fatal MI (Paper II)
  ii) Fatal or non-fatal any-cause stroke/ischemic stroke (Paper III)

Outcome definitions
Information concerning mortality and morbidity from incident disease was collected from the official Swedish registries: Cause of Death (CDR) and In-Patient (IPR) Registries held by The Centre for Epidemiology, National Board of Health and Welfare in Sweden. Mortality was defined as death recorded in the CDR, and morbidity as first time hospitalized recorded in the IPR.

Paper I
MI was defined according to International classification of disease, $9^\text{th}$ revision (ICD-9), as code 410 or according to $10^\text{th}$ revision (ICD-10), as code I21; and CVD as code 390-459 (ICD-9) or I00-I99 (ICD-10).

Paper II
MI was defined according to International classification of disease, $9^\text{th}$ revision (ICD-9), as code 410 or according to $10^\text{th}$ revision (ICD-10), as code I21.
Paper III

Stroke was defined according to *International classification of disease*, 9th revision (ICD-9), as codes 431 and 433-436 or according to 10th revision (ICD-10), as codes I61 and I63-I66, thereby including both ischemic (81%) and hemorrhagic stroke (19%). Transitory stroke events were included among ischemic stroke. Separate analyses were also carried out for ischemic stroke alone, code 434 (ICD-9) or I63 (ICD-10).

Statistical analysis

The statistical analyses were carried out using Stata 8.0 (Stata Corporation, College Station, TX, USA). All tests were two-tailed and a p-value <0.05 was considered statistically significant.

Distribution

The distribution of a continuous variable was tested for normality using Shapiro Wilk’s test. Skewed variables were logarithmically transformed to reach normal distribution (w>0.95 assessed using Shapiro Wilk’s test). Logarithmically transformed variables were used in logistic regression analyses (Paper IV).

Standardization

Continuous variables were standardized to one SD, with the mean value being given the value of zero (mean=0), and one SD being given the value of one (1 SD=1).

Group comparisons

Univariate regression analyses were performed on the list of candidate predictor variables at age 50, comparing those with and without ECG abnormalities at age 70 using χ² or ANOVA (Paper IV).

Logistic regression analysis

All candidate predictors with a univariate p<0.15 were evaluated for independent association in a backward stepwise logistic regression model. Standardized continuous variables were used. The robustness of the final model was checked by including previously removed variables. The final model was adjusted for age at baseline (Paper IV).
Cox’s proportional hazard regression analysis

Univariate Cox’s proportional hazard regression analyses were used to determine the relationship of various risk factors and subsequent end-points, first MI (Paper II) or first stroke (Paper III) in different follow-up periods. Results were presented as hazard ratios (HRs) with 95% confidence interval. The magnitude and the statistical significance of the relationships between the predictors were determined for each of the defined outcome variables. Main analyses were made excluding the cardiovascular outcome being studied if present at baseline (Paper II and III).

All factors with p value of <0.15, in the different follow-up periods in part I and II, were evaluated for independency in a backward stepwise multiple model. In multivariate analyses, hazard ratios were adjusted for age at entry. A p value of < 0.05 was considered to be statistically significant.

The proportional hazard assumption was checked for each of the variables for the whole follow-up period (0-30 years) and for each of the follow-up periods using the test for Schoenfeld’s residuals. Also, to test for proportionality within each of the follow-up periods, time dependent covariates were generated by creating interactions of the predictors and a function of survival time, and time dependent covariates were included in all multivariate models and tested for significance using likelihood-ratio test (Papers II and III). Also, inspection of log-log survival curves was used to confirm proportional hazard assumption (Paper IV).

Receiver-operating characteristic (ROC) curves

Comparison of areas under ROC curves was used to test the hypothesis that Framingham score plus “ECG indicating ischemia” predicted CVD mortality better that Framingham score alone (paper IV) (C-statistics).

Approval of Ethics Committee

The Ethics Committee of the Faculty of Medicine, Uppsala University has approved the study on several occasions. All subjects have given informed consent.
Discussion of methods

Epidemiological and statistical methods

The studies in this thesis are epidemiological in character. In prospective, observational, longitudinal studies such as those in this thesis, it is possible to demonstrate if a characteristic measured at baseline can predict future disease. However, it is possible that the association is not a direct causal relationship but that it is confounded by other factors. Age is one possible confounding factor that has been adjusted for in all analyses. However, since all subjects have approximately the same age at the time of examination, age adjustment had very little impact on the results.

By using continuous variables standardized to 1SD, the impact of traditional risk factors could be compared to each other, and to categorical ECG and smoking variables in the same statistical model. By using backward stepwise selection multiple models, the most significant, independently associated risk factors could be identified. The robustness of the model was tested by re-inserting previously excluded variables.

The two statistical methods typically employed for examining the relationship between a set of singly-measured baseline risk factors and outcome data are the logistic and proportional hazard regression models. For Papers I, II and III, the proportional hazard model was chosen since it is the model that best accounts for subjects lost to follow-up during the observation period.

The design of the ULSAM study, with all participants having the same age at baseline and at re-examination, permitted the evaluation of the effect of time both as age at baseline, and time since baseline. The hazard function is based on the person’s age at two baselines (age 50 and age 70) and on different observation periods.

For Paper I, a multivariate risk scores, was used as confounding score, providing a means of simultaneously correcting for the effect of several CVD risk factors. The usefulness of applying multivariate risk scores in research has previously been pointed out by Karp et al. 98.

As recommended, the proportional hazard assumption was tested using three different approaches 108 based on: i) graphical techniques comparing log-log survival curves (Paper I), ii) goodness-of-fit test based on Schoenfelder residuals (Paper II and III), and iii) time-dependent variables, where Cox model was extended to contain product terms, involving the time-independent variable being assessed and a function of time (Papers II and III).
Participation and selection bias

The participation rates were 82%, 73%, 60%, and 56% at the examinations at age 50, 70, 77, and 82, respectively. Participation rates for the 50- and 70-year surveys are similar to the participation rate in another Swedish prevention trial in Göteborg\textsuperscript{109} and to other international population trials (see table 4).

Subjects participating in the 50-year examination, but who did not participate in the 70-year examination were still invited to the 77-year survey. A possible explanation to the low participation rate at the 77-year examination could be the extension of the invitation to participate in the 77-year survey, to subjects who attended the 50- but not the 70-year survey. Non-participants in cohort studies generally have more social and alcoholic problems and tend to have higher mortality rated due to CAD\textsuperscript{109}. The estimated risk for MI, stroke, and CVD may therefore be underestimated.

This cohort has been followed for more than 30 years and may therefore be healthier than the general population. Subjects attending both the 50- and 70-year examination tended to have fewer ECG abnormalities, and lower blood pressure and glucose values. Among those attending both surveys, there were fewer smokers and less subjects with diabetes mellitus (Paper III).

Mortality and morbidity analyses

The precision of the diagnosis of MI and stroke, defined by combining data from the Swedish CDR and IPR has been shown to be high\textsuperscript{110,111} and therefore a validation of the outcome detection system was not considered to be necessary.

Even though both non-fatal and fatal cardiovascular outcomes are interesting from the patients and public health perspectives, most epidemiological studies have only fatal cardiovascular end-points, since non-fatal events are more dependent on definitions and methods used in their ascertainment\textsuperscript{26}. In the SCORE project, where sixty-nine cohorts were pooled, only 6 studies had non-fatal and fatal MI as end-point and even fewer had non-fatal and fatal stroke as end-point\textsuperscript{26}. Non-fatal and fatal MIs and strokes were therefore chosen as end-points in these studies since that would give a complementary picture to other reported studies with only fatal outcomes.

Apolipoprotein analyses

Storage of samples has allowed the analyses of apoA1 and apoB at a later stage when these analysis techniques became more readily available. At age 70, the apoB/apoA1 ratio was determined in a random sample of 551 sub-
jects. Technical problems with one of the freezers lead to a random loss of samples.

To determine if this loss of samples introduced any selection bias, the incidence of MI and stroke after 70-year examination was compared between subjects where samples were available to subjects where samples were not available. The incidence rate for MI was 1.03 and 0.95 per 100 patient-years, respectively for those with apolipoproteins available, compared to those without; and for stroke it was 1.35 versus 1.10 per 100 patient-years, respectively. Since the incidence rates were very similar it was assumed that this random loss of samples had not introduced a selection bias.

ECG coding and inter-observer variability

Overall four observers have coded and recoded ECGs from the four surveys. Inter-observer agreement on classification has been carried out on samples (n=50) of ECGs randomly selected from each of the three ECG sets coded at different time points (i.e., ECGs from 50-, 70- and 77/82-year surveys). The observer who coded ECGs from the 77- and 82-year surveys recoded samples of ECGs from the 50-year and 70-year surveys and the observer who coded ECGs from the 70-year survey recoded samples from the 77- and 82-year surveys. The percentage agreement for coding was 92 percent or more for all variables except for right bundle branch block (RBBB) in the subset of ECGs from the 77/82-year survey, where 89 percent agreement was obtained (table 3).

Today computer processing and blinded ECG readings using core laboratories are available techniques, however, visual manual coding was used to allow for comparison with historical data.

Table 3: Validation of Minnesota coding

<table>
<thead>
<tr>
<th>ECG abnormality</th>
<th>Coding agreement (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50-y examination</td>
</tr>
<tr>
<td>Major Q/QS pattern (1.1)</td>
<td>100</td>
</tr>
<tr>
<td>Minor Q/QS pattern (1.2-1.3)</td>
<td>100</td>
</tr>
<tr>
<td>ST depression (4.1-4.2)</td>
<td>100</td>
</tr>
<tr>
<td>T wave abnormality (5.1-5.3)</td>
<td>100</td>
</tr>
<tr>
<td>LBBB (7.1)</td>
<td>100</td>
</tr>
<tr>
<td>RBBB (7.2)</td>
<td>96</td>
</tr>
<tr>
<td>AV-block (6.3)</td>
<td>100</td>
</tr>
<tr>
<td>AF/flutter (8.3)</td>
<td>100</td>
</tr>
</tbody>
</table>

LBBB = left bundle branch block    RBBB = right bundle branch block
Results

Paper I

At age 50, even after adjusting for established conventional risk factors, T wave abnormalities, ST segment depression, major Q/QS pattern, ECG-LVH, and "ECG indicating ischemia" were all independent risk factors for the first MI (fatal and non-fatal) event, CVD mortality, and all-cause mortality. These ECG variables were also independent risk factors for CVD and all-cause mortality at age 70 but lost in significance regarding MI. Also, subjects with pathological ECG findings at the 70-year examination had higher mortality rates for CVD and all-cause mortality, while the incidence rate for MI was not affected by the ECG findings.

Some of the ischemic ECG abnormalities observed at age 50 and 70 were transient and reverted to normal. At the 70-year examination, 29% had received new "ECG indicating ischemia", 3.5% had persistent ECG abnormalities, while 1% had lost the ischemic pattern observed at previous examination. As many as 69% of new major Q/QS patterns observed at age 70 had reverted at age 77.

In general it was more dangerous to have a persistent T wave abnormality, ST segment depression, or "ECG indicating ischemia" compared to a new or reverted abnormality between age 50 and age 70. Regarding mortality, it was twice as dangerous to have persistent T wave abnormalities (HR, 4.63; 95% CI, 2.18-9.83) or ST segment depression (HR, 5.66; 95% CI, 1.77-18.1), compared to new T wave abnormalities (HR, 2.20; 95% CI, 1.48-3.29) or ST segment depression (HR, 2.55; 95% CI, 1.74-3.75), developing between ages 50 and 70 (figure 4).
Figure 4. Kaplan-Meier plots of the effects of “ECG indicating ischemia” at age 70 for all-cause mortality and CVD mortality during 12 years of follow-up. Note: There was only one ECG with reversible ischemia for CVD mortality.

The addition of “ECG indicating ischemia” significantly increased the predictive power of the Framingham score (areas under ROC curves: 0.58 versus 0.67; p<0.001) (Figure 5).
Conclusion

It is worthwhile to obtain serial ECGs for proper risk assessment, since persistent T wave and ST segment depression carry twice as high risk for future mortality as new or reverted abnormalities, and since inclusion of ECG indicating ischemia significantly increased the predictive power of the Framingham score.

Paper II

During the total follow-up period of up to 31.7 years, 43.7% (n=1012) had died and 470 had either been hospitalized or died due to MI. 41% of the MIs were fatal (n=195). Between age 50 and 70, mean systemic blood pressure (SBP), BMI, and fasting blood glucose had increased slightly, while the value for all lipid variables had decreased slightly. Smoking habits had decrease markedly from 51% to 21%. The prevalence of ECG abnormalities was five-fold more frequent at age 70 compared with age 50.
Part I: Predictive value of midlife risk factors for MI over three different follow-up periods

All variables tested in univariate analyses, including abnormal Q/QS patterns, ST segment depression, T wave abnormalities and ECG-LVH, were significant risk factors for MI over the total follow-up period of 30 years. ECG-LVH had the strongest predictive power, but only over the first decade while ST segment depression and T wave abnormalities retained their prognostic value for MI for the first two decades, even though it decreased over time. Abnormal Q/QS patterns only predicted MI over the second decade.

Blood pressure, dyslipidemia variables, and smoking were significant predictors in the three follow-up periods. Fasting insulin was a predictor in the second decade, while fasting glucose was only a predictor over the first decade.

In multivariate analyses, ECG-LVH was the strongest independent risk factor for MI, but only over the first decade. Diastolic blood pressure (DBP), smoking, and apoB/apoA1 ratio, were independent risk factors for MI over the whole follow-up period, retaining their predictive power up to 30 years later.

Part IIa and Part IIb: Comparison between risk factors for MI in midlife and at age 70

In the univariate analysis, the same predictors for MI were found between age 50 and 70, as observed for the total follow-up period in part I. When re-measured at age 70, in subjects free from previous MI, all variables except for BMI, Lp(a) and ECG abnormalities, were still significant predictors for MI for the next 10 years. Even though still significant, the predictive power of many of the dyslipidemia variables was reduced at age 70 compared to the measurements at age 50, while apoB/apoA1 ratio retained its predictive power when re-measured (figure 6). Fasting glucose and fasting insulin regained importance when re-measured in elderly.
Figure 6. Hazard ratios from univariate analyses for MI according to risk factors measured at two different baselines, at age 50 and age 70, respectively.

In multivariate analysis at the age of 50, ST segment depression, smoking, high BMI, high DBP, high apoB/apoA1 ratio, high Lp(a) and high fasting glucose were independent risk factors for MI. In multivariate analysis at age of 70, smoking, high fasting insulin, and high apoB/apoA1 ratio were the only independent risk factors for MI.

Conclusion

Despite increase in prevalence of ECG abnormalities and increase in BMI with age, they showed predictive value in mid-life only. Mid-life values of BP, dyslipidemia variables, such as apoB/apoA1 ratio, and smoking retained predictive value for MI over long follow-up periods and when re-measured in elderly, suggesting that they are important for long-term risk. Fasting glucose and insulin, on the other hand, need to be measured repeatedly since they loose predictive power over time.
Paper III
During the total follow-up period of up to 30 years, 43.9 percent (n=1,019) had died and 343 had either been hospitalized or died due to any-cause stroke and of these, 221 due to ischemic stroke. Thirteen percent of the stroke events were fatal (n=45). Between age 50 and 70, there was a statistically significant increase in SBP, DBP, BMI and fasting glucose, while there was a statistically significant decrease for all lipid variables. Smoking habits had decrease markedly from 51 percent to 21 percent and diabetes mellitus had increased from 5.4% to 9.8%.

Part I: Predictive value of midlife risk factors for stroke over three different follow-up periods

a) Any-cause stroke
The ECG abnormalities (except AF), smoking and diabetes, were significant predictors during the first two decades of follow-up, while blood pressure was a significant predictor for all three decades in univariate analyses (figure 7). Fasting insulin and glucose were predictors for the first decade and diabetes mellitus for the first two first decades. None of the lipid variables was associated with stroke.

In multivariate analyses, SBP was an independent predictor during all follow-up periods, even though the impact of middle-aged measured SBP decreased with time. The presence of ST segment depression, T wave abnormality, and smoking were significant independent predictors during the first two decades, while the only variable that still had a predictive value for events occurring between the age of 70 and 80, was SBP.
Figure 7. Association of systolic blood pressure and ECG characteristics at age 50 to stroke, during 3 different follow-up periods, according to univariate analyses. Hazard ratios for SBP, was based on 1SD of the continuous variable.

b) Ischemic stroke
Similar results were found for ischemic stroke as for any-cause stroke. However, ST segment depression and BMI were predictors over the three decades. The results for ischemic stroke compared to any-cause stroke were also similar for multivariate analyses except that diabetes mellitus (HR 3.20; 95% CI, 1.01-10.8) and AF (HR 15.07, 95% CI 1.77-128) were independent predictors for ischemic stroke during the first decade of follow-up after the 50-year examination.

Part II a and Part II b: Comparison between risk factors for stroke in midlife and at age 70

a) Any-cause stroke
In the univariate analysis for any-cause stroke, all ECG variables (except AF) were significant predictors for stroke both when evaluated at age 50 and age 70, even though the impact of ECG abnormalities was higher at age 50 than age 70 (figure 8). AF was a significant predictor at age 70 only. None of the lipid variables measured at age 50 predicted stroke in any of the follow-up periods, however, when measured at age 70, both LDL cholesterol and ApoB/ApoA1 predicted development of future stroke. The ApoB/ApoA1 in elderly was driven by the protective role of ApoA1, suggesting that ApoA1 may be especially important in protecting from stroke in the elderly. Fasting
glucose, fasting insulin, and diabetes mellitus were only associated with any-cause stroke when evaluated at age 50.

In multivariate analysis for variables measured at age 50, SBP, ST segment depression, T wave abnormality, and smoking were independent predictors for any-cause stroke when measured at age 50, while AF and LDL-cholesterol were independent risk factors at age 70. ApoA1 protected from stroke in elderly.

b) Ischemic stroke
In univariate analyses, the results for ischemic stroke were similar to any-cause stroke, except that glucose, insulin and diabetes mellitus were also associated with ischemic stroke at age 70.

In multivariate analyses, diabetes mellitus and AF were also independent predictors at age 50, in addition to SBP, ST segment depression, T wave abnormality, and smoking.
Conclusion
Mid-life values for ECG and BP abnormalities retained their predictive value over long follow-up periods even though they improved in predictive power when re-measured in elderly. Despite lower prevalence, ECG abnormalities had greater impact at age 50 compared to age 70. ApoB/apoA1 ratio, driven the apoA1, was associated with any-cause stroke in elderly, while apoA1 protected from any-cause and ischemic stroke at age 70. Similar results were obtained when considering only ischemic stroke as outcome, but fasting glucose, fasting insulin and diabetes mellitus appeared to be more strongly associated with ischemic stroke than any-cause stroke.

Paper IV
After having excluded subjects with MI prior to the 50-year examination, at the age of 70, 9% (n=102) had developed a major abnormal Q/QS pattern but 63% (n=64) of these subjects had not been hospitalized due to MI. Among the 89 men that had been hospitalized due to MI at any time-point during the 20 years follow-up, 57% (n=51) had no major Q/QS pattern on ECG at the age of 70.

T wave abnormalities (Odds ratio 3.11, 95% CI, 1.18-8.17), Lp(a) levels, high body mass index (BMI) and smoking were identified as significant independent predictors for the development of abnormal major Q/QS patterns. T wave abnormalities and high fasting glucose levels were significant independent predictors for the development of ST segment depression without abnormal Q/QS pattern.

Of the 1006 men free of ST segment depression at age 50, 13% had developed ST segment depression at the age of 70. In multiple logistic regression analysis, T wave abnormalities (OR=3.94; 95% CI 1.58-9.82, p=0.003) and high fasting blood glucose levels (OR=1.25; 95% CI 1.02-1.54, p=0.035), were independent predictor for ST segment depression.

Of the 858 men without ST segment depression (at age 50 and/or 70) and T wave abnormality at age 50, 9% had developed an isolated T wave abnormality at the age of 70. An increase in BMI by 1SD increased the risk of having a T wave abnormality at the age of 70 by 50% (OR=1.48; 95% CI 1.14-1.92). None of the other variables tested predicted future development of a T wave abnormality.

Independent predictors for MI mortality were, besides T wave abnormality, high BMI, and smoking; also DM, high BP, and apoB/apoA1 ratio. However, Lp(a) was only an independent predictor for major Q/QS pattern, and not for MI mortality.
Conclusion:
The prevalence of silent MI and frequency of regression of major Q/QS patterns may be higher than reported in previous studies. Previous studies have reported an average of 30% unrecognized MI and 10-20% of Q wave regression. T wave abnormalities on resting ECG should be given special attention. Risk factors for major Q/QS patterns need not be the same as traditional risk factors for clinically recognized CAD. High Lp(a) levels may be a stronger risk factor for silent MI compared to clinically recognized MI.
General Discussion

Prevalence and regression of pathological ECG findings

In general, ECG abnormalities increase with age, some being more prevalent in men (Q waves, RBBB, ECG-LVH) and some more prevalent in women (ST-T abnormalities, LBBB) \(^{62,112}\). Therefore, the prevalence of ECG findings in ULSAM cannot be generalized to women. Also, the prevalence of ECG abnormalities varies depending on the population being studied. This difference can be explained by factors such as different ECG classification systems, definitions of ECG abnormalities, and exclusions at baseline. It should also be remembered that different medications may affect ECG patterns, which may confound our comprehension of the true nature of ECG abnormalities, especially in elderly.

Especially when comparing prevalence of ECG-LVH, it is important to consider that over the years there has been no consensus on how ECG-LVH should be defined, even though in more recent publications, ECG-LVH usually refers to high R-voltage criteria associated with ST segment depression, ST-T abnormalities or “strain pattern” \(^{46,62}\). It should be emphasized, however, that the ECG is a poor screening test for echocardiographic LVH, identifying only a small fraction of subjects with echocardiographic hypertrophy, even though specificity is high \(^{113}\).

The prevalence of major Q/QS patterns, ST segment depression and AF in ULSAM is consistent with other population studies \(^{62,114}\). However, since ULSAM only record the presence of AF on one ECG, there is probably an overall underreporting of AF since up to one-third of patients may have intermittent AF \(^{115}\). In ULSAM, the prevalence of T wave abnormalities and ECG-LVH (based on voltage criteria associated with ST segment depression) at age 50 was consistent with the Copenhagen City Heart Study. However, at age 70, the prevalence of T wave abnormalities and ECG-LVH in ULSAM, were slightly higher with 16.0 % and 6.5% compared to 11.8% and 3.5%, respectively, in the Copenhagen study \(^{46}\).

The prevalence of 3.42% for AV-block found at the 70-year examination in ULSAM appears to be slightly lower compared to 8.1% reported by Furberg et al \(^{65}\) for subjects above 65 years of age. However, the prevalence of AV-block increases steeply with age, reaching 15% in ULSAM at the age of 77.
Regression of some of the ECG abnormalities was observed between the
surveys (Paper I). Part of these ECG abnormalities regressions may be
associated with reversibility of other disease states or conditions not associated
with atherosclerotic disease, since the presence of ST-T abnormalities occur
not only with myocardial ischemia and infarction, but also with cardiomyopathy
and pulmonary embolism, electrolyte abnormalities, and drugs,
such as cardiac glycosides. Furthermore, non-infarction Q waves may be
carried by myocarditis, cardiac amyloidosis, cardiomyopathy or displace-
ment of diaphragm due to chronic obstructive lung disease. ECG abnor-
mality regressions can, however, be attributed to an improvement of the
underlying myocardial ischemic disorder. Q wave regression has been re-
ported to occur in 11-25% of MI cases. Functional recovery of stunned
and/or hibernating myocardium has been suggested as an explanation
for regression of Q waves; and reversible T waves post-infarction have been
associated with the presence of viable myocardium at jeopardy. T wave
normalization has been associated with excellent outcome, in contrast to
persistent T waves. Regression of echocardiographic LVH has been ob-
erved after anti-hypertensive treatment and reduction of BP, suggesting
that this may also be applicable for ECG-LVH.

Risks associated with ECG abnormalities

The existing literature has consistently shown that the resting ECG carries
important independent prognostic information for future cardiac events.
ECG indicating ischemia, Q/QS patterns, and ST-T abnormalities, including minor ST-T abnormalities, have all consistently been associated with an increased risk of CVD events with most studies reporting a doubled relative risk (RR). Also ECG-LVH, usually based on voltage criteria accompanied by ST segment depression or characteristic “strain” pattern, has been associated with increased risk for CVD morbidity and mortality.

Consistently with other studies, Paper I showed that, even after adjusting
for conventional risk factors, “ECG indicating ischemia” was associated
with a two-fold increased of CVD and any-cause mortality, at both age 50
and age 70. The association with future CVD and any-cause mortality ap-
plied also to ECG-LVH and ST-T wave abnormalities. As also shown in
Paper I, major Q/QS pattern at age 50 and 70 was also associated with an
increased risk of CVD and any-cause mortality, even though the risk associ-
ated with major Q/QS pattern at age 50 was much stronger than at age 70.

Even, though all ECG variables were associated with the outcome MI at
age 50, none of the ECG variables were specifically associated with MI at
age 70. A possible explanation to this unexpected finding could be that the
extent of atherosclerosis, reflected by “ECG indicating ischemia” is less
important for development of unheralded MI in elderly, compared to factors leading to plaque rupture. Ischemic heart disease varies in its clinical presentation from stable angina to unstable angina and acute MI. Rupture of an atherosclerotic plaque with subsequent thrombosis formation, is an important mechanism behind acute coronary events. On the other hand, all ECG findings indicating ischemia at both age 50 and 70 were associated with ischemic stroke, strengthening the hypothesis that the ECG findings may be a reflection of myocardial ischemia and advanced stage of atherosclerosis in different cardiovascular beds.

As suggested by Levy et al. for left ventricular mass, it is possible that ECG-LVH and “ECG indicating ischemia” reflect cumulative life-long exposure to cardiovascular insults such as hypertension and obesity; and ECG abnormalities may therefore provide a better estimate of the extent of cardiac end-organ damage than is provided by casual measurement of blood pressure, body weight or other established conventional risk factors.

Information on the prognostic significance of persistent versus reversible ECG findings from longitudinal studies with serial ECG tracings is limited. ULSAM, being a longitudinal population study with 32 years of follow-up and repeated ECG examination, provided a unique opportunity for exploring the development and reversibility of ECG abnormalities. In general, as shown in Paper I, persistent T wave abnormalities, ST depression, or "ECG indicating ischemia” carried with them twice the risk of developing future CVD or all-cause mortality compared to new T wave abnormalities, ST segment depression, or "ECG indicating ischemia”. Regression of the ECG abnormality improved the prognosis considerably. The findings in Paper I suggest that ECG-LVH and “ECG indicating ischemia” may be sensitive indicators of cardiac damage, in both middle-aged and elderly men, resulting from cumulative exposure to established conventional risk factors. Repeated examinations of ECG after the age of 50 could contribute to the identification of high risk groups for cardiovascular events. The prognostic role of the resting ECG should be strengthened, with serial ECG assessments for proper risk assessment.

Impact of follow-up time and re-measurement of the electrocardiogram and conventional cardiovascular risk factors on their predictive value for myocardial infarction and stroke (Paper II and III)

Mid-life values of BP retained their predictive value for both MI and stroke over long follow-up periods and when re-measured in elderly. However, fasting glucose and insulin as predictor for MI and ischemic stroke need to be measured repeatedly since they lose predictive power over time. Also,
BMI lost predictive power for MI and stroke over long follow-up periods. Similar results, with regard to BP and BMI, were found in a study comparing the risk of coronary events predicted by baseline factors during 28 years of follow-up divided in three different follow-up periods, where diabetes, elevated blood pressure, and serum cholesterol were independently associated with increased risk of coronary events for each of the periods, while smoking and BMI lost some power during the latest follow-up period. Cholesterol and other lipid variables retained their prognostic value for MI over long follow-up periods also in the ULSAM studies, but they were not predictors for stroke at the age of 50.

The strongest predictor for development of MI and stroke tested at age 50 was ECG-LVH, retaining its predictive value for MI and stroke for 10 and 20 years, respectively. Although not as strong predictors as ECG-LVH, ST-T abnormalities at age 50 also predicted both MI and stroke over the next 20 years. ECG-LVH, ST depression and T wave abnormalities at age 70 were also predictors of future development of stroke but not of MI. AF, a known predictor of stroke in all ages, only became a strong significant predictor in elderly, probably due to the low number of cases at age 50.

Re-measurement of SBP at age 70 increased the predictive value for stroke but not for MI. For stroke, a SBP increase of 18 mmHg at the 50-year examination was associated with a 50% increased risk of stroke during the first decade of follow-up, and a 20% increase during the third decade of follow-up. The decrease in risk with follow-up time could also be explained by regression dilution to the mean of the SBP measurement. The analyses in Paper II and III did not take into account regression dilution bias and its effect on long-term risk. The effect of SBP during 15-25 years of follow-up is believed to be underestimated by about one-half when results are not corrected for regression dilution bias. Re-measurement of SBP at the age of 70 showed that the risk for stroke increased by 50%.

Regression dilution bias varies between different risk factors and its effect on categorical ECG variables, manually coded according to MC, is not known.

All lipid variables were predictors for MI in all follow-up periods. However, apoB/apoA1 appeared to be the most sensitive and consistent predictor of MI compared to other lipid variables over all follow-up periods. This indicates that the apoB/apoA1 ratio carries both short- and long-term predictive power. None of the lipid variables measured at age 50 predicted stroke in any of the follow-up periods; however, when measured at age 70, both LDL cholesterol and apoB/apoA1 ratio predicted development of future any-cause stroke. The apoB/apoA1 in the elderly was driven by the protective role of apoA1 suggesting that apoA1 may be especially important in protecting from any-cause stroke and ischemic stroke in the elderly.
Smoking predicted both MI and stroke in all follow-up periods except for stroke in the elderly. When re-measured in the elderly, smoking was a predictor for MI but not for stroke. Since stroke usually occurs later in life than coronary heart disease, some participants may have died from CAD before reaching the age of stroke, thereby reducing the impact of some traditional risk factors. This could explain why risk factors such as smoking, DM, and BMI were predictors of stroke in mid-life but not at 70.

The utilization of updated cardiovascular risk factors may improve risk assessment and it has been shown that change in some risk factors such as cholesterol, blood pressure, and smoking may lead to changes in coronary risk within the next 2 to 5 years. However, considering that there is a 20-year interval between the ECG measurements at age 50 and age 70, using a statistical model with updated risk factors was not considered to be a correct approach in this case. However, the estimated RRs for ECG abnormalities in the papers included in this thesis are probably slightly underestimated since the prevalence of abnormal ECGs increases with age, and some of the subjects classified as normal may have developed an ECG abnormality during the long follow-up periods before the occurrence of MI or stroke.

As described by Cupples et al., the strong short-term prediction of ECG abnormalities for sudden death compared to SBP suggests that some ECG abnormalities may reflect a late stage in the causal pathway of CVD.

Predictors of pathological ECG findings

Paper IV is unique in that it uses ECG variables as outcomes, instead of clinical outcomes. By choosing ECG abnormalities as end-points, asymptomatic subjects, including those with silent MI, and subjects in early stages of myocardial ischemia were included in the analyses.

Conventional risk factors such as DM, high BP, and apoB/apoA1, were predictors for MI mortality, but they were not associated with the development of major abnormal Q/QS patterns. Lp(a) was associated with major Q/QS but not with MI mortality. This suggests that predictors of major abnormal Q/QS patterns may be different from those predicting symptomatic MI, a possibility that has also been raised by other authors. A previous nested case-control study carried out in ULSAM by Dunder et al., also showed that high proinsulin and BP levels were only independent predictors of unheralded MI, but not of angina pectoris. The prognostic ability of Lp(a) has been under debate, and it has been associated with silent CHD in diabetic patients.

ST segment depression is seen both in LVH and myocardial ischemia. In ULSAM (Paper IV), both T wave abnormality and fasting glucose were associated with future ST segment depression. Impaired glucose metabolism
could be a predictor for ST segment depression due to LVH\textsuperscript{137, 138}. On the other hand, patients with DM and high fasting glucose have an increased risk of developing arteriosclerosis\textsuperscript{139}.

T wave abnormalities were predictors for both major Q/QS patterns and ST segment depression, and should therefore be given special attention. Even though there may be alternative explanations to its presence besides myocardial ischemia, due to its strong predictive role also for MI and CVD mortality, it should be considered as an early warning sign for myocardial ischemia until an alternative explanation has been found or repeated ECG has shown its regression.

Many studies have suggested that clinically unrecognized MI is associated with the same risk as recognized symptomatic MI\textsuperscript{34, 62, 140} although a lower risk for unrecognized MI has also been described\textsuperscript{141}. A previous study in ULSAM\textsuperscript{142} demonstrated that a new Q/QS pattern was an independent predictor of any-cause and CAD mortality, irrespective of clinical symptoms.

**The role of the resting ECG and the global assessment of cardiovascular risk**

As also suggested by other authors\textsuperscript{63, 100}, Papers II and III showed that the prognostic value of ischemic ECG findings for MI and stroke were more powerful than conventional established risk factors. Paper I, II, and III, as well as existing literature, have clearly demonstrated that “ECG indicating ischemia” and ECG-LVH are associated with a significant increased risk of CVD and stroke both in middle-aged and elderly men. Consistently with the Framingham findings\textsuperscript{143}, Papers II and III have shown that ECG abnormalities carry a short-time risk, while many of the established conventional risk factors carry a long-term risk. Despite the recognized prognostic value of the resting ECG, many authors have questioned the practical role of the ECG in screening asymptomatic populations\textsuperscript{62}, claiming that there is no evidence that early detection of ECG abnormalities leads to clinical intervention that improves health outcomes [Sox, 1989 #481.

Effective measures to prevent long-term modifiable risk factors with high prevalence in the general asymptomatic population\textsuperscript{144}, such as lipids, hypertension, and smoking, would probably prevent many premature cases of myocardial infarction. However, it seems that the ECG carries short-term information beyond the traditional risk factors that should be taken into consideration. Paper I suggests that it is worthwhile to obtain serial ECGs for proper risk assessment, since persistent T wave and ST segment depression carry twice as high a risk for future mortality as new or reverted abnormalities, even though the optimal time between ECG assessments has yet to be
established. Also, adding “ECG indicating ischemia” to the Framingham score significantly increased its prognostic ability (Paper I).

Strength and limitations

Strengths of the ULSAM Study include its large study population, its long follow-up period, the detailed characterization of its cohort and the fact that relatively few subjects have been lost to follow-up. However, since the study has only examined men of the same age with a similar ethnic background, the findings can only be generalized to other Caucasian men. On the other hand, since it is known that there are gender differences in the prevalence and prognostic values of ECG abnormalities, there is no need for stratification and adjustment for gender in these studies.

As population characteristics change, so do CAD incidence and mortality. Secular trends can be expected to occur with regard to CAD and CVD. In ULSAM, all men in the community were invited to participate and all men were recruited at the same age. Therefore, bias due to secular trends has been kept at a minimum. The prevalence of ECG abnormalities has been found to be lower in later born cohorts, which needs to be taken into consideration when comparing prevalence of ECG abnormalities between studies.

A standard, simple method of visual coding has been used in order to allow comparison with historical data. Coding results can be affected by inter-reader variability; however, coding differences due to inter-reader variability are believed to be low in ULSAM, since all coding has been done by three readers only. Consistency in electrode placement is also expected to be high since the same staff made the registration of the ECGs at all four examinations.

A limitation of long-term cohort studies is that it is not possible to correctly relate the cardiovascular risk factors to treatment of diabetes, hypertension, and hyperlipidemia, since these may differ and change over the long follow-up period.

The long follow-up period and repeated measurements have allowed for the determination of cardiovascular risk factors and ECG abnormalities at two different baselines. However, since stroke usually occurs later in life than coronary heart disease, some of the participants in the cohort studies will have died from coronary heart disease before reaching the age of stroke, thereby reducing the impact of some traditional cardiovascular risk factors on future development of stroke.
Conclusions

I  It is worthwhile to obtain serial ECGs for proper risk assessment, since persistent T wave and ST segment depression carry twice as high a risk for future mortality as new or reverted abnormalities. Inclusion of “ECG indicating ischemia” significantly increased the predictive power of the Framingham score.

II  Despite the increase in prevalence of ECG abnormalities and increase in BMI with age, they showed prognostic value for MI in mid-life only. Mid-life values of BP, dyslipidemia variables such as apoB/apoA1 ratio, and smoking retained prognostic value for MI over long follow-up periods and when re-measured in elderly. Fasting glucose and fasting insulin needs to be measured repeatedly since they lose predictive power for MI over time.

III  Mid-life values for ECG and BP abnormalities retained their prognostic value for stroke over long follow-up periods, even though they improved in predictive power when re-measured in the elderly. Despite lower prevalence, ECG abnormalities had greater impact at age 50 compared to age 70. ApoB/apoA1 ratio, driven by the apoA1, was associated with any-cause stroke in the elderly, while apoA1 protected from any-cause and ischemic stroke at age 70. Similar results were obtained when considering only ischemic stroke as outcome, but fasting glucose, fasting insulin and diabetes mellitus, were more strongly associated with ischemic stroke than any-cause stroke.

IV  The prevalence of silent MI and frequency of regression of major Q/QS patterns may be higher than reported in previous studies. T wave abnormalities on resting ECG should be given special attention. Risk factors for major Q/QS patterns need not be the same as traditional risk factors for clinically recognized CAD. High Lp(a) levels may be a stronger risk factor for silent MI compared to clinically recognized MI.
What this thesis contributes

The thesis confirmed previous findings regarding the increased risk associated with ECG indicating ischemia for future cardiovascular morbidity and mortality. It also confirmed the long-term prognostic value of the recently identified risk factor, apoB/apoA1 ratio for future myocardial infarction and stroke.

The findings of the thesis indicate that the prevalence of silent MI and the frequency of regression of ECG abnormalities may be higher than reported in previous studies, and contributes the new information that persistent T wave and ST segment depression carry twice as high a risk for future cardiovascular disease mortality as new or reverted abnormalities.

The long follow-up period and study design made it possible to study and compare, in the same cohort, the impact of age at baseline and follow-up time on the prognostic value of the resting ECG in relation to conventional risk factors for future stroke and myocardial infarction. This is an original and new approach, and the results of these studies, contribute to the discussion regarding the meaningfulness of repeated measurements of different risk factors.

The thesis also confirms the hypothesis that different risk factors may have different lag times, and that “ECG indicating ischemia” is a short-term predictor in comparison to long-term predictors like high blood-pressure and hyperlipidemia. A new major finding in the thesis is that it is worthwhile to re-measure the ECG at the age of 70 since it increased the predictive power for stroke; and even if re-measurement of the ECG at age 70 did not increase the predictive power for MI, “ECG indicating ischemia” retained predictive power for CVD mortality and overall mortality. In addition, this thesis contributes with new information regarding the significant contribution of the ECG to the Framingham score.

The thesis also contributes new information regarding risk factors, including ECG abnormalities, that predict future major Q/QS pattern and ST-T abnormalities, irrespective of clinical symptoms. A T wave abnormality was an
independent predictor for both major Q/QS pattern and ST segment depression, indicating that T waves should be given special attention.

In conclusion: the thesis brings new and valuable information to the discussion of the role of the resting ECG in the global risk assessment for CVD by pointing out that the additional risk information carried by the resting ECG justifies its regular and repeated registration above the age of 50.
Future perspectives

Much remains to be investigated concerning the prognostic value of the resting ECG. Confirmation of the importance of ECG as a risk factor should be obtained using updated risk factors, and taking into consideration symptoms and treatments. Issue under debate include: the ECG’s screening role in asymptomatic populations, effect of treatment on ECG abnormalities, and the possibilities of making better use of computer technology in interpreting ECG abnormalities. The use of different statistical methods to analyze risk factors in populations with long follow-up is also under debate.

With computer processing, exact ECG intervals can be obtained, waveforms can be analyzed, and new ECG variables can be derived. Future studies can be expected to investigate the correlation between cardiac disease and new repolarization variables such as QRS/T angle and waveform amplitudes. Quantitative ECG measurements would be easier to register, to follow over time, and to include in risk scores.

Even though the studies in this thesis are epidemiological in their character and therefore not conclusive, they indicate that the resting ECG should be an important tool in the identification of the subjects most in need of therapeutic interventions. The results of this thesis suggest that there could be a role for ECG abnormalities in future risk scoring systems for CVD.
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Table 4. Demographics and follow-up of studies that have looked at prognostic significance of ECG abnormalities \(^{62-64}\) (fu=follow-up)

<table>
<thead>
<tr>
<th>Studies</th>
<th>Size and Age</th>
<th>Study period Follow-up (fu)</th>
<th>ECGs</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framingham Heart Study</td>
<td>5209 men and women 5124 men and women  Age 30-62 years</td>
<td>1948, 1(^{st}) generation 1971, 2(^{nd}) generation Examination every 2 years</td>
<td></td>
<td>Mortality study. Subjects with CAD excluded at baseline. End-points: All-cause mortality and CAD mortality.</td>
</tr>
<tr>
<td>Seven Countries Study (Italy, US, Japan, Yugoslavia, Finland, Greece and The Netherlands)</td>
<td>13737 subjects</td>
<td>1959-1989 5 years fu</td>
<td>ECGs were coded according to MC and CIIS</td>
<td>Mortality study. 96% participation rate. No exclusions at baseline. End-points: All-cause mortality, CAD mortality and CVD mortality.</td>
</tr>
<tr>
<td>The US Pooling Project</td>
<td></td>
<td>1964-1972 8 years of fu</td>
<td></td>
<td>Mortality study. 78% participation rate. Subjects with history of angina pectoris /MI or ECG evidence of MI were excluded at baseline.</td>
</tr>
<tr>
<td>Studies</td>
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<tr>
<td>Reykjavik Study</td>
<td>9328 men and 10062 women, 33-87 years</td>
<td>1967-1996</td>
<td></td>
<td>Mortality study. End-points: All-cause mortality, CVD mortality and first MI.</td>
</tr>
<tr>
<td>Manitoba Study</td>
<td>3983 men at age of 30</td>
<td>1946 30 years of fu</td>
<td>ECGs were followed initially at 5 and later at 3 yearly intervals.</td>
<td>Mortality study. The original stimulus was the study of long-term predictive value of ECGs recorded on initially young and healthy persons.</td>
</tr>
<tr>
<td>The Busselton Health Studies</td>
<td>3331 men and women aged 21 and over</td>
<td>1966-1972 5-13 years of fu</td>
<td></td>
<td>Mortality study. 91% participation rate.</td>
</tr>
<tr>
<td>Chicago Heart Association</td>
<td></td>
<td></td>
<td></td>
<td>Mortality study. ECG evidence of MI at baseline was exclusion criteria. End-points: All-cause mortality, CAD mortality, CVD mortality and sudden death.</td>
</tr>
<tr>
<td>Detection Project in Industry</td>
<td></td>
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<tr>
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<tr>
<td>Chicago Western Electric Study</td>
<td>2107 middle-aged men</td>
<td>1957</td>
<td>Extensive baseline examinations were carried out annually for 11 years.</td>
<td>Prevalence study.</td>
</tr>
<tr>
<td>White Hall Study</td>
<td>18403 men aged 40 to 64</td>
<td>Early 1970’s 5 years of fu</td>
<td>Assessed ECG abnormalities and mortality.</td>
<td>Mortality study. Symptomatic and asymptomatic subjects were analysed separately. End-point: CAD mortality.</td>
</tr>
<tr>
<td>British Regional Heart Study</td>
<td>3 different parts. ECGs were studied in a selected group of 7735 men aged 40 to 59 years.</td>
<td>1969-1973 1978-1980 9.5 years of fu</td>
<td>Relationship between resting ECG abnormalities and CAD was studied.</td>
<td>Mortality study. Symptomatic and asymptomatic subjects were analysed separately. End-points: All-cause mortality and CAD mortality.</td>
</tr>
<tr>
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<tr>
<td>Italian Risk Factors and Expectancy Pooling Project</td>
<td>Exact number of subjects not available.</td>
<td>1978-1987 6 years of fu</td>
<td>ECGs were recorded in 12,180 men and 10,373 women from 30 to 69 years.</td>
<td>Mortality study. Participation rate 65-70%. Symptomatic subjects excluded at baseline.</td>
</tr>
<tr>
<td>The Tecumseh Community Health Study</td>
<td>8641 men and women over 16 years</td>
<td>1959-1960</td>
<td>ECGs were recorded on 5129 people.</td>
<td>Prevalence study. No exclusion for CV disease at baseline.</td>
</tr>
<tr>
<td>Belgian Interuniversity Research on Nutrition and Health</td>
<td>More than 11,000 people were studied, men and women aged 25 to 74.</td>
<td>1979 1981-1984 10 years of fu</td>
<td>ECG findings were related to CVD mortality in 5,208 men and 4,746 women .</td>
<td>Cross-sectional survey with multiple objectives. For ECG evaluation subjects with CVD at baseline were excluded. End-points: All-cause, CAD and CVD mortality.</td>
</tr>
<tr>
<td>The World Health Organization European Study (Belgium, Denmark, Italy,</td>
<td>4522 subjects. 40-59-year-old-men</td>
<td></td>
<td></td>
<td>Mortality study. 86-95% participation rate</td>
</tr>
<tr>
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<tr>
<td>Multiple Risk Factor Interventional Trial</td>
<td>12866 men with high risk for CAD. 35-57 years old</td>
<td>1973-1976 6 years of fu</td>
<td></td>
<td>Mortality study. Subjects with CAD by history, physical examination or ECG at baseline were excluded.</td>
</tr>
<tr>
<td>The Honolulu Heart Program</td>
<td>7682 men born 1900-1919</td>
<td>1965-1968 12y</td>
<td></td>
<td>Mortality study. ECG evidence of MI or chest pain compatible with angina pectoris or MI were excluded at baseline.</td>
</tr>
<tr>
<td>Evans Country Study</td>
<td>308 black and 511 white men</td>
<td>1960-1962 20y of fu</td>
<td></td>
<td>Mortality study. 92% participation rate. Subjects with major Q waves on ECG and history of MI or AP were excluded.</td>
</tr>
<tr>
<td>Charleston Heart Study</td>
<td>1394 white and 787 black men and women.</td>
<td>1960 30 years of fu</td>
<td></td>
<td>Key aim was to determine racial differences in prevalence of ECG findings.</td>
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<td></td>
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<td>Mortality. 84% participation rate. Endpoints: All-cause mortality and CAD mortality.</td>
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<tr>
<td>The Cardiovascular Health Study</td>
<td>1250 men and women above 65y</td>
<td></td>
<td></td>
<td>End-point: CAD mortality.</td>
</tr>
<tr>
<td>The ECG and Survival in the Very Old</td>
<td>559 subjects above 85 years of age.</td>
<td>5y of fu</td>
<td>Specifically studies ECG abnormalities in very old. More than 96% of subjects had ECG abnormalities.</td>
<td>Mortality study. 83% of the total population 85 years of age or over in the city of Tampere, Finland were evaluated.</td>
</tr>
<tr>
<td>Rotterdam⁰,¹⁴⁹</td>
<td>7983 men and women above 55 years of age</td>
<td>1990-1993</td>
<td>12-lead ECGs were collected. Year-to-year, day-to-day and minute-to-minute variability was studied in a subset of subjects.</td>
<td>78% participation rate.</td>
</tr>
<tr>
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<tr>
<td>Women’s Health Initiative Study</td>
<td>65000 women aged 50 to 79 planned for clinical trial (CT) and 100000 for observational study (OS).</td>
<td>1992-2007</td>
<td>ECGs were evaluated from more than 40000 women participating in the dietary modification part of the study. ECGs were computer processed.</td>
<td>Most common causes of morbidity and mortality including coronary heart disease. Studies were stratified for CVD at baseline. End-points were fatal and non-fatal CAD and CAD mortality.</td>
</tr>
</tbody>
</table>
A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine”.)