Assessment of clinically silent atherosclerotic disease and established and novel risk factors for predicting myocardial infarction and cardiac death in healthy middle-aged subjects: Rationale and design of the Heinz Nixdorf RECALL Study

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Background In view of consistently high cardiovascular morbidity and mortality rates, international efforts are aimed at developing tools for more precise risk prediction to allow preventive treatment targeted at high-risk individuals. Direct visualization of anatomic, preclinical atherosclerotic disease has the potential for individualized risk discrimination. Further, a variety of risk factors are actively evaluated, including markers of the activity of atherosclerotic disease, thrombogenic risk, and genetic polymorphisms.

Methods The Heinz Nixdorf RECALL (Risk Factors, Evaluation of Coronary Calcium and Lifestyle) study is a population-based, prospective cohort study of the comparative value of modern risk stratification techniques for “hard” cardiac events. It is designed and powered to define the relative risk associated with the specific extent of coronary atherosclerosis measured by means of electron-beam computed tomography (EBCT)-derived coronary calcium quantities for myocardial infarction and cardiac death in 5 years in 4200 males and females aged 45 to 75 years in an unselected urban population from the large, heavily industrialized Ruhr area. Additionally, the predictive values of conventional cardiovascular risk factors, new candidate and socioeconomic risk factors, certain genetic polymorphisms, and direct signs of subclinical disease are examined with the ankle-brachial index, resting and stress electrocardiograms, and determination of carotid artery intima-media thickness. Prospective clinical risk-benefit and health economic analyses are an inherent part of the study. Study findings with established clinical significance are reported to the participants, but the EBCT findings are withheld until the conclusion of the study.

Conclusions The Heinz Nixdorf RECALL study will define appropriate methods for identifying high-risk subgroups in the general urban population who may derive the greatest benefit from preventive treatment. (Am Heart J 2002;144:212-8.)

In industrialized nations, approximately 50% of patients with acute myocardial infarction die within the first month of the event.1 Two thirds of these patients do not reach the hospital.1 The decline in cardiovascular mortality in the last decades is caused by improved survival rate of patients with clinical events rather than by a declining incidence of these events.2,3 As a result, an increased prevalence of chronic ischemic heart disease and especially congestive heart failure has been described in patients who have survived acute events.4 On the basis of these data, there is worldwide agreement on the importance of prevention. The relative effectiveness of prevention on the community level versus prevention targeting high-risk individuals re-

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Trial Design
A number of new technologies have become available for noninvasive visualization and quantification of atherosclerotic disease in the peripheral and coronary arteries. The American Heart Association Prevention Conference 5 saw an established value for the ankle-brachial index and ultrasound scanning of the carotid artery intima-media thickness measurements. The use of electron-beam computed tomography (EBCT) as a means of quantifying coronary calcium was initially judged to require more data before broad application. A recent update, however, embraced EBCT more strongly as a promising method for directly visualizing coronary atherosclerosis.

The Heinz Nixdorf RECALL (Risk Factors, Evaluation of Coronary Calcium and Lifestyle) project aims to determine whether direct visualization of coronary atherosclerosis provides more independent and incremental information than traditional risk factor analysis. Further, factors that influence the functional consequences of a given amount of atherosclerotic plaque disease, such as markers of the activity of coronary atherosclerosis, thrombogenic risk factors, socioeconomic aspects, and certain genetic polymorphisms, are analyzed.

Participant recruitment was started in December 2000. A more detailed description of the epidemiologic field work, statistics, and biometry is given in a separate report. This report focuses on the clinical rationale (background) of the study and the methods being evaluated.

**Methods**

**Overview**

The overall study group is randomly selected from mandatory registries of residence of the cities of Bochum, Essen, and Mülheim, Germany. These cities belong to the Ruhr area, which can be seen as a conglomeration of large, industrial cities. The presence of overt cardiovascular disease (expected in 12% of the 4200 participants) leads to exclusion from the primary analysis, but not from the study. A targeted assessment of medical history and physical examination are performed in all participants, as are all tests explained herein and shown in Figure 1. These tests are performed during the initial visit. The only exception is that some participants, for whom scheduling of the EBCT is not possible on the same day, undergo EBCT within 1 week of the other baseline tests. Questionnaires with comprehensive risk-assessment, in particular for socioeconomic aspects, are filled in with the help of a computerized system. Blood is drawn for comprehensive laboratory tests. Fifty-three aliquots of plasma and serum samples are stored at -80°C for future analysis. Blood pressure measurements, resting and exercise electrocardiograms (ECGs), determination of the ankle-brachial index, ultrasound scanning measurement of the carotid intima-media thickness, and a noncontrast-enhanced EBCT examination are performed. All findings except the EBCT results and experimental findings, such as some novel risk factors or genetic polymorphisms, are reported to the participants and, when they agree, their primary physicians, to whose discretion further evaluation and treatment are left.

Follow-up is obtained by sending out questionnaires about study end points in 12-month intervals. Additionally, 5 years after entry, the participants are seen again for a repeat assessment of medical history, physical and risk factor status, and resting ECG. A loss to follow-up of 15% is expected, so of the initial cohort of participants who are free of overt cardiovascular disease, approximately 3150 constitute the final sample. Figure 2 gives an overview of the study.

**End points**

The primary end points are the first occurrence of nonfatal myocardial infarction or cardiac death. Primary and secondary end points are listed in Table 1. All end points are adjudicated by a blinded end point committee, consisting of 5 independent cardiologists and an epidemiologist.
Study hypothesis and aims

The underlying hypothesis is that extensive subclinical coronary atherosclerosis, as determined by means of the EBCT-derived coronary calcium score, predicts the risk of myocardial infarction and death in the general population with a relative risk ratio in the upper calcium score quartile ≥3. The specific study aims are listed in Table II.

Exclusion criteria

Because this is a study of the general population, only a few exclusion criteria apply. They include an inability or unwillingness to give informed consent to participate in the study, conditions (medical or other) that preclude follow-up for 5 years, severe psychiatric disorders or illegal substance abuse, and pregnancy.

Sample size

Earlier reports on the relative risks associated with increased amounts of coronary calcium detected by means of EBCT in persons who have no symptoms vary substantially and are limited by study participants not being completely unselected.10-13 For sample size calculations in the current study, the relative risk of sustaining a subsequent myocardial infarction or cardiac death was conservatively estimated to be 2.5 in the upper quartiles, compared with the lower quartiles of the coronary calcium quantity distribution. The incidence of cardiac events was estimated with the results of the MONICA (German centers) and Münster Heart (PROCAM) studies because of their geographic proximity.14,15 After appropriate stratification for age and sex, the event rate (primary end points) for the current study population was—again conservatively—estimated to be 300 to 500 per 100,000 subjects per year. Accepting a probability of type I and II errors of 5% and 10%, respectively, a final cohort of 3150 was calculated (Figure 2).

Questionnaires

Behavioral risk factors (such as smoking, nutrition, and physical activity), medical history (such as a family history of ischemic heart disease and medication use), angina complaints, and sociodemographics are assessed. In addition, psychosocial risk factors are evaluated.
Social gradients in cardiovascular morbidity and mortality have been consistently demonstrated in economically developed countries, with increasing cardiovascular risk associated with declining socioeconomic status. Health damaging lifestyle factors are an important reason, but they account for only approximately one third of the social gradient. Chronic psychosocial stress, as specified by means of theoretical models, is believed to have a considerable impact on enhanced cardiovascular morbidity and mortality through sustained activation of the autonomic nervous system. It is therefore actively investigated as an additional explaining factor in the association between socioeconomic status and health.

One such model of psychosocial stress, the model of effort-reward imbalance at work, is examined in the study. It focuses on violations of norms of reciprocity and fairness in work-related exchanges. Imbalance between high effort and low reward has been demonstrated to be a means of predicting cardiovascular risk and disease. Further assessment of the psychosocial environment includes measurements of protective psychosocial conditions, such as social support and optimism. Negative affectivity is assessed as a possible confounder.

### Laboratory tests

General health
- Blood cell count
- Serum electrolytes and minerals
- Liver enzymes
- Lactate dehydrogenase
- Creatinine kinase
- Serum proteins
- Serum creatinine, urea, and uric acid

Causal risk factors
- Cholesterol subfractions with direct measurement of low- and high-density lipoprotein cholesterol, apolipoproteins A1 and B
- Blood glucose and hemoglobin A1c
- General health
  - Blood cell count
  - Serum electrolytes and minerals
  - Liver enzymes
  - Lactate dehydrogenase
  - Creatinine kinase
  - Serum proteins
  - Serum creatinine, urea, and uric acid

Causal risk factors
- Lipoprotein(a)
- Triglycerides
- Fibrinogen
- Homocysteine

Markers of inflammatory activity
- C-reactive protein (high-sensitive)

Genes encoding for
- Endothelial nitric oxide synthase
- G protein β3 subunit
- Angiotensinogen
- Angiotensin-converting enzyme
- Apolipoprotein E
- Plasminogen activator inhibitor type 1

### Blood pressure measurements, resting, and exercise electrocardiogram

Valid measurements of systemic blood pressure and recording of resting and exercise ECGs are obtained, as described in detail in a separate method-oriented report.

Exercise stress testing is widely used as a means of predicting cardiovascular events in subjects with no symptoms, but its performance has been criticized. The American College of Cardiology/American Heart Association guidelines for exercise testing state that it is not useful for screening subjects with no symptoms because of the high number of false-positive and false-negative test results. However, the exercise stress test offers information apart from the traditional ECG. A growing body of evidence suggests that cardiovascular and all-cause mortality are independently predicted by means of exercise capacity measured with treadmill exercise testing. It has been estimated that approximately 20% of cardiovascular deaths can be attributed to a low fitness level detected by means of treadmill exercise testing. The largest reduction in overall mortality appears to occur on moving from the lowest to the next lowest quintile of physical fitness.
population setting, the achieved treadmill workload, a measure of exercise capacity, exhibited the strongest association with mortality of all tested variables (eg, ECG variables and exercise-induced angina). An increase in 1 metabolic equivalent in workload was associated with a 20% risk reduction in males and a 25% risk reduction in females.

The study participants exercise upright on an electrically braked cycle calibrated to watts. Stress testing is done in a strictly symptom-limited fashion to optimize the test results.

Ankle-brachial index

Risk factor exposure affects the complete arterial system. Elevated cholesterol levels, for example, are not only associated with coronary dysfunction, but also peripheral arterial endothelial dysfunction. One of the earliest signs of systemic hypertension and atherosclerosis is the decrease in aortic compliance, resulting in increased pulse wave velocity. The ankle-brachial index has been defined as the ratio of the ankle systolic blood pressure to the arm systolic blood pressure, which is usually >1.0 in healthy adults. Values of the index <0.9 are quite sensitive and specific for the presence of peripheral arterial disease.

The ankle-brachial index is determined by means of the relationship of posterior tibial to brachial artery blood pressure on both the right and the left side. Blood pressure is measured with a pressure cuff and continuous wave Doppler ultrasound scanning analysis.

Carotid intima-media thickness

Carotid intima-media thickness is a reliable marker for atherosclerotic vascular injury. A mean intima-media thickness >1 mm in the common carotid and internal carotid arteries has been demonstrated to indicate a substantially enhanced risk of ischemic heart disease in subjects aged 45 to 65 years with no symptoms. Increases in intima-media thickness are associated with continuous increases in ischemic heart disease risk. Although intima-media thickness is—as might be expected— influenced by the causal risk factors, its measurement provides incremental prognostic information. After adjusting for the influence of causal risk factors, the relative risk of elderly subjects with no symptoms sustaining an acute myocardial infarction was 3.6 when intima-media thickness was in the highest quintile, compared with the lowest quintile.

Intima-media thickness is determined at the far wall of the left and right common carotid arteries.

Electron-beam computed tomography

EBCT is the current standard technique for quantitative assessment of coronary calcium. Coronary calcium has been established as a specific expression of underlying atherosclerotic disease in pathologic-anatomic studies. It represents an active, regulated process which can be found in stages of atherogenesis seen in young adults. The extent of coronary calcium is related to the extent of coronary atherosclerotic plaque formation. A number of studies have addressed the potential prognostic information derived from EBCT-derived quantification of coronary calcium in subjects with no symptoms. In the heterogeneous populations in these studies, the relative risk associated with increased amounts of coronary calcium ranged from 2.7 to >22 for “hard” cardiac events (myocardial infarction and cardiac death) and also including revascularization. In most studies, but not all, the information provided by means of EBCT was incremental over the causal risk factors. Accordingly, further evaluation of this technique has been mandated.

The study participants are examined with an Imatron “Ultrafast CT” scanner (Imatron, South San Francisco, Calif). The study protocol and data analysis adhere to the suggestions of Agatston et al. Apart from the “Agatston score,” which has been used by most laboratories, a more recently developed volumetric score is computed. This facilitates comparison of the results with those of other CT methods for quantification of coronary calcium, in particular 4-slice multi-detector spiral CT.

Discussion

The Heinz Nixdorf RECALL study provides a large database on the prognostic power of various modern tests in predicting cardiovascular events in the general population. An important focus is the noninvasive determination of the extent of coronary atherosclerosis by means of quantification of coronary calcium with EBCT. It is hypothesized that by directly measuring the anatomic extent of coronary atherosclerosis, EBCT provides a link between coronary risk factors and ischemic heart disease and facilitates individualized risk discrimination. The independent and incremental value of this measure is analyzed for alternative, established, and novel methods of risk assessment. The aim is to improve the accuracy of risk assessment over what can be achieved with traditional risk factor analysis, thus improving public health while avoiding unnecessary treatment and use of resources.

At present, the value of quantification of coronary calcium by means of EBCT for prognostication in subjects with no symptoms remains controversial. Indeed, the first prognostic studies have yielded results that are quite diverse. These studies were done in heterogeneous populations as part of the early initial evaluation of the new technique. Further studies, such as this one, will have to provide more definitive data as part of an ongoing process of evaluation. Two large projects are currently being undertaken in parallel, the Multiethnic Study of Atherosclerosis (MESA) and the Dallas Heart Disease Prevention Project. The Epidemiology of Coronary Calcification Study in Olmsted County, Minnesota, and the Prospective Army Coronary Calcium Project in Washington, DC, are further epidemiologic projects examining the relationship between coronary calcium and cardiovascular events. Thus, studies in Europe and the United States will yield an aggregate of data.

Two theoretical limitations should be considered. First, the most common mechanism of acute coronary
syndromes is rupture or erosion of “vulnerable” atherosclerotic plaques. Visualization of coronary calcium does not allow the identification of such vulnerable plaques. However, subjects sustaining acute coronary syndromes have much more extensive and severe coronary atherosclerosis than age- and sex-matched control subjects. This is true even in young age groups, with sudden death being the first manifestation of ischemic heart disease. The importance of identifying localized vulnerable or complicated plaques needs to be weighed against assessing the extent of atherosclerotic plaque disease as the underlying substrate of “vulnerability.” Second, EBCT is a complex technology associated with considerable costs. Atherosclerotic plaque formation is influenced by systemic mechanisms of disease affecting all vascular territories. Competing techniques that evaluate the peripheral vasculature, in particular measurements of the ankle-brachial index, are less expensive. However, they may be less effective in younger age groups because of the low prevalence of the disease. It is therefore an integral part of the study to perform economic analyses and comparisons among different strategies for identifying high-risk individuals.

Quantifying preclinical atherosclerosis may in itself be limited, because the functional consequences of the same amount of anatomical disease may vary substantially between individuals. However, results from investigations with EBCT concur with reports on the predictive power of intima-media thickness and ankle-brachial index measurements, indicating the potential for incremental value over traditional risk factor analysis.

Clinical implications

The results of the Heinz Nixdorf RECALL study will help to define in the general population whether new methods such as the assessment of coronary calcium, novel risk factors, and psychosocial environment allow improved risk prediction over traditional risk factor analysis. An individual classified as “intermediate risk” on the basis of established methods might benefit from further risk stratification with the methods evaluated in this project. Only large studies such as this one can yield reliable data on the performance of a new technique and, at the same time, place it in the context of competing methods and economic considerations. In contrast to earlier epidemiological studies conducted in more rural districts, the current study is being conducted in a large, industrialized urban area.

References