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Coronary Risk Stratification, Discrimination, and Reclassification Improvement Based on Quantification of Subclinical Coronary Atherosclerosis

The Heinz Nixdorf Recall Study

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Objectives The purpose of this study was to determine net reclassification improvement (NRI) and improved risk prediction based on coronary artery calcification (CAC) scoring in comparison with traditional risk factors.

Background CAC as a sign of subclinical coronary atherosclerosis can noninvasively be detected by CT and has been suggested to predict coronary events.

Methods In 4,129 subjects from the HNR (Heinz Nixdorf Recall) study (age 45 to 75 years, 53% female) without overt coronary artery disease at baseline, traditional risk factors and CAC scores were measured. Their risk was categorized into low, intermediate, and high according to the Framingham Risk Score (FRS) and National Cholesterol Education Panel Adult Treatment Panel (ATP) III guidelines, and the reclassification rate based on CAC results was calculated.

Results After 5 years of follow-up, 93 coronary deaths and nonfatal myocardial infarctions occurred (cumulative risk 2.3%; 95% confidence interval: 1.8% to 2.8%). Reclassifying intermediate (defined as 10% to 20% and 6% to 20%) risk subjects with CAC <100 to the low-risk category and with CAC ≥ 400 to the high-risk category yielded an NRI of 21.7% ($p = 0.0002$) and 30.6% ($p < 0.0001$) for the FRS, respectively. Integrated discrimination improvement using FRS variables and CAC was 1.52% ($p < 0.0001$). Adding CAC scores to the FRS and National Cholesterol Education Panel ATP III categories improved the area under the curve from 0.681 to 0.749 ($p < 0.003$) and from 0.653 to 0.755 ($p = 0.0001$), respectively.

Conclusions CAC scoring results in a high reclassification rate in the intermediate-risk cohort, demonstrating the benefit of imaging of subclinical coronary atherosclerosis. Our study supports its application, especially in carefully selected individuals with intermediate risk. (J Am Coll Cardiol 2010;56:1397–406) © 2010 by the American College of Cardiology Foundation

Coronary artery disease (CAD) risk prediction in asymptomatic individuals represents a major challenge. Currently, risk stratification algorithms are applied, allowing global risk assessment rather than focusing on single risk factors (1,2). The widely used Framingham algorithm is based on traditional CAD risk factors, including age, sex, smoking, total cholesterol or low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, blood pressure, and diabetes. The lifetime prognostic power of these risk

See page 1415

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Abbreviations and Acronyms

ATP = Adult Treatment Panel
AUC = area under the curve
CAC = coronary artery calcification
CAD = coronary artery disease
FRS = Framingham Risk Score
HDL = high-density lipoprotein
IDI = integrated discrimination improvement
LDL = low-density lipoprotein
NRI = net reclassification improvement
ROC = receiver-operator characteristic
RR = relative risk

factors is well established. However, their prognostic effects depend on the duration of exposure and on the magnitude of the deviation of the risk factors from normal, which may vary over time (3).

Atherosclerotic plaque formation can be regarded as the intermediate between risk factor exposure and clinical events and can be imaged at a pre-clinical stage. The quantity of coronary artery calcification (CAC), a specific marker of coronary atherosclerosis, is correlated with coronary atherosclerotic plaque burden and seems to reflect the cumulative effects of risk factors and vascular aging (4). Clinical studies have demonstrated its ability to predict cardiovascular risk (5), but methodological shortcomings include selective recruitment, lack of sex-specific analysis, use of soft end points (i.e., revascularization or angina), and nonblinded assessment of results and outcome (6). In order to overcome these shortcomings, the HNR (Heinz Nixdorf Recall) study was initiated (7). Meanwhile, the MESA (Multi-Ethnic Study of Atherosclerosis) could demonstrate an incremental prognostic value of CAC over traditional risk factors in a representative U.S.-American population (8,9). Similarly, biomarkers and other parameters are used for improvements in risk prediction. The clinical value is expressed as their ability to reclassify individual risk (10,11). We hypothesized that CAC testing can be used for reclassification and improved risk prediction of hard events (i.e., nonfatal myocardial infarction and coronary death) beyond traditional risk factors.

Methods

Study design and population. The Heinz Nixdorf Recall Study is a population-based cohort study with subjects randomly selected from mandatory lists of residence. Study methods have been described in detail (7,12,13). Briefly, 4,814 participants 45 to 75 years of age were enrolled between 2000 and 2003 in the metropolitan Ruhr area in Germany. Of these, 327 (6.8%) reported a history of CAD at baseline and were excluded from this analysis (Fig. 1). The CAC scores were not reported to participants. All participants gave their written informed consent, and the study was approved by the institutional local ethical committees.

Cardiovascular risk factors. The risk factor assessment has previously been described (Online Appendix) (13).

Risk stratification algorithms. We assessed 2 different algorithms for coronary risk stratification: 1) the Framingham Risk Score (FRS) was defined as published using LDL cholesterol charts (1); and 2) in order to estimate the effect of the high-risk variables symptomatic carotid stenosis, stroke, peripheral artery disease, or diabetes, we allocated these subjects to the high-risk category following the National Cholesterol Education Program Adult Treatment Panel (ATP) III algorithm (14).

In both algorithms, participants were categorized into low (<10% or <6% in 10 years), intermediate (10% to 20% or 6% to 20%) and high (>20%) risk categories (9–11,15).

Electron-beam computed tomography. Nonenhanced electron-beam computed tomography scans were performed with a C-100 or C-150 scanner (GE Imatron, San Francisco, California) in 2 radiology institutions (D.G. and R.S.), as outlined in the Online Appendix.

Follow-up. Annual postal questionnaires and a second medical examination assessed the morbidity status during follow-up (i.e., hospital admissions, outpatient diagnoses of cardiovascular disease). Participants were followed for a median of 5 years (mean 5.1 ± 0.3 years). Exclusion of subjects is shown in Figure 1, leaving 4,129 participants (53% women) for the present analysis.

Study end points and verification of study end points. Primary end points for this study were based on unequivocally documented incident coronary events that met predefined study criteria (7). We considered a myocardial infarction event based on symptoms, signs of electrocardiography, and enzymes (levels of creatine kinase), as well as troponin T or I, and necropsy as nonfatal acute myocardial infarction and coronary death (16).

For all primary study end points, hospital and nursing home records, including electrocardiograms, laboratory

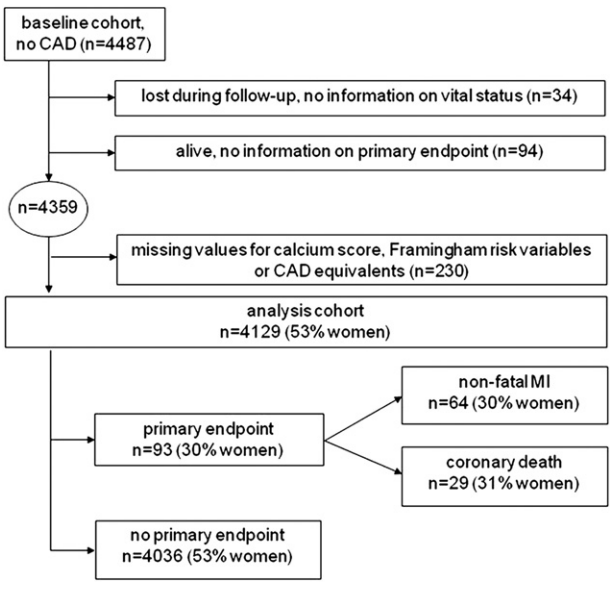

Figure 1 Flow Chart of the HNR Study Cohort

Study cohort includes 4,487 participants 45 to 75 years of age without coronary artery disease (CAD). MI = myocardial infarction.