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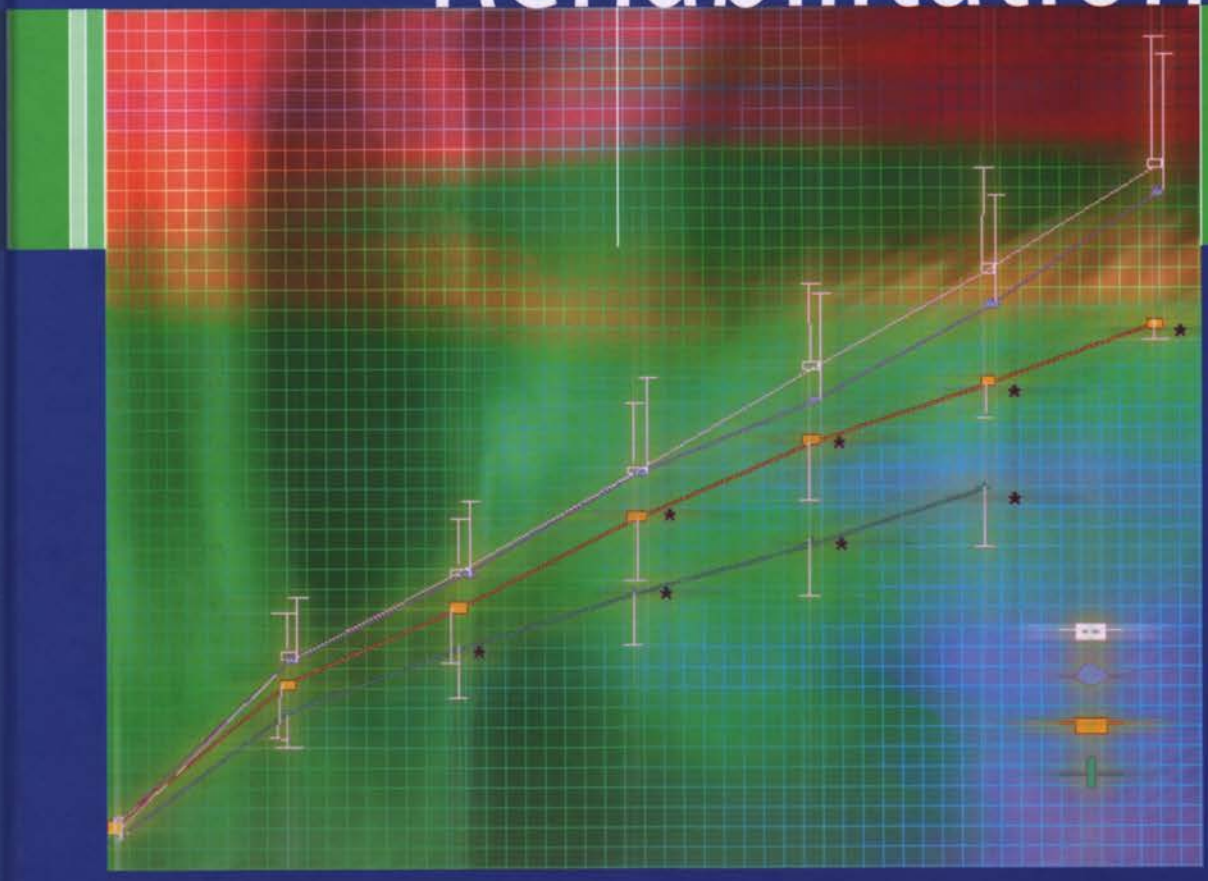
Cardiovascular Prevention and Rehabilitation



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New Concepts for Early Diagnosis of Coronary Artery Disease

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Background and Problem

Cardiovascular diseases are still the number one killer in developed countries. The term "death from cardiovascular disease," however, includes not only acute myocardial infarction, but also death from chronic ischemic heart disease, stroke, peripheral artery disease, and pulmonary embolism. A more detailed analysis shows that only approximately 18% of the cardiovascular deaths arise from *acute* myocardial infarction, while a continuously increasing percentage result from *chronic* ischemic heart disease. Although modern medicine significantly improved the short-term outcome of acute myocardial infarction, it shifted the problem from a decrease in mortality to an increase in morbidity. Therefore, the challenge of modern medicine is not only to further reduce the already declining cardiovascular mortality,[1,2] but also to reduce cardiovascular morbidity. The major goal is to thus prevent the first acute myocardial infarction to ensure not only a long life but also a life without cardiovascular events. This is even more important, since 31% to 72% of coronary occlusions developed from a previously "insignificant" coronary lesion by sudden and "unexpected" plaque rupture leading to a nonfatal or fatal coronary event.[3] To achieve this goal it is not only important to detect "atherosclerosis" per se, but also to identify the asymptomatic high-risk individual, then initiate intensive risk factor modification at this preclinical stage.[4,5]

Noninvasive Detection of the Presence of Atherosclerotic Disease

Asymptomatic atherosclerotic disease is defined as the presence of abnormal function or structure of the vessel wall due to atherosclerosis. In this early stage, patients cannot be warned by ischemic chest pain (angina pectoris). Also, functional tests, like exercise ECG, stress echocardiography, perfusion scintigraphy, or perfusion magnetic resonance imaging (MRI), will be negative, because there is not yet a critical lumen narrowing leading to inducible perfusion abnormalities or myocardial ischemia. Intravascular (intracoronary) ultrasound (IVUS) is an excellent tool to diagnose and follow up preclinical atherosclerosis.[6] It is, however, an invasive tool requiring arterial access (cardiac catheterization).

Pathology studies have documented that levels of traditional risk factors are associated with the extent and severity of atherosclerosis. However, at every level of risk factor exposure, there is substantial variation in the amount of atherosclerosis. This variation in disease is probably due to genetic susceptibility, combinations and interactions with other risk factors, including life habits, duration of exposure to the specific level of the risk factors and such factors as biological and laboratory variability. Therefore, no blood test exists that "proves" the presence of atherosclerotic disease. All the known traditional (e.g. hypercholesterolemia) and modern (e.g. elevated C-reactive protein) risk factors increase the likelihood of

atherosclerosis, but they do not prove its existence in an individual person. Therefore functional and imaging techniques have to be used for diagnosing atherosclerosis at this early stage. A variety of noninvasive tests are available for determining the presence of asymptomatic atherosclerosis in various vascular beds.

Functional Tests for Early Detection of Atherosclerotic Disease

Endothelial Dysfunction and Forearm Blood Flow Testing

Endothelial cells play a central role in inhibiting the development of atherosclerosis and its thrombotic consequences. Endothelial dysfunction is secondary to the long-term impact of risk factors on endothelial cells. Conventional risk factors increase the oxidative stress in vascular tissue, giving oxidative stress a crucial role in endothelial dysfunction.[7] In patients undergoing either routine diagnostic catheterization for the evaluation of chest pain or percutaneous transluminal coronary angioplasty (PCI), a significantly increased vasoconstrictor response to acetylcholine predicted long-term atherosclerotic disease progression and cardiovascular event rates.[8] Noninvasive endothelial function testing is emerging as a biomarker of vascular disease.[9] The most frequently used endothelial-directed vasodilator stimulus is an increase in blood flow (brachial artery flow-mediated vasodilation, FMD). This is assessed by changes in brachial artery diameter (7–12 MHz linear array probe) after 5-minute blood pressure cuff arterial occlusion. Vasodilation is usually measured 1 minute after cuff release. To assess endothelium-independent vasodilation, the subject is given a single dose of nitroglycerin. Patients with risk factors for coronary heart disease (CHD) have impaired vasodilator responses.[10] Investigators are still seeking to improve the methods for ultrasonographic analysis of brachial artery vasomotion. More precise analysis techniques are now available in the form of automated continuous estimation of brachial artery responses. There is, however, significant biologic variability in measurement, greatly varying in response to factors such as size of the blood pressure cuff, baseline arterial diameter, a high-fat meal, and a women's menstrual cycle. The technique is skill- and labor-intensive and not yet easily used in routine clinical practice.[10]

Ankle–Brachial Index (ABI)

The measurement of the ankle–brachial blood pressure index (ABI) is an easy-to-perform, inexpensive, and reproducible noninvasive test to detect asymptomatic atherosclerotic disease. Technical requirements are a regular blood pressure cuff and a Doppler ultrasound device to measure the systolic blood pressures in left and right brachial arteries as well as both posterior tibial and dorsalis pedis arteries.[10] Usually, the highest systolic ankle pressure is used for calculation. Because of its high sensitivity and specificity (>90% respectively), an ABI <0.90 is considered a reliable sign of peripheral arterial disease (PAD). Its high specificity is partially explained by the fact that the ABI may paradoxically be elevated with age-dependent increased arterial stiffness, including arterial calcification. Therefore, an ABI >1.5 may be difficult to interpret.[11] ABI reflecting significant PAD adds additional validity to medical history, because 50% to 89% of patients with an ABI <0.9 do not have typical claudication.[12] The history of claudication alone "dramatically underestimates" the presence of large-vessel PAD.[13]

The presence of PAD is strongly related to a high incidence of coronary events and stroke. Therefore, ABI also correlates with further development of angina, myocardial infarction, congestive heart failure, coronary artery bypass graft surgery, stroke, or carotid surgery. However, ABI should not be considered as a continuous measure of generalized atherosclerosis.[11] In asymptomatic individuals over 55 years of age, an ABI < 0.9 may be found in 12% to 27%. Even in an elderly population (71–93 years), a low ABI further identifies a higher-risk CHD subgroup.[14] However, a normal ABI does not predict the absence of severe coronary artery disease (CAD).[15]

Imaging for Early Detection of Atherosclerotic Disease

Carotid Ultrasound

Sonography of superficial arteries is a relatively inexpensive means of noninvasively visualizing

the lumen and walls of arteries which are involved in the ubiquitous process of atherosclerosis. Risk assessment using carotid ultrasound focuses on measurement of the intima–media thickness (IMT) and plaque characteristics.

Intima–Media Thickness (IMT)

Intima–media thickness is an integrated measurement of the involvement of both the intima and the media in the atherosclerotic process. Current ultrasound instrumentation with transducers ≥8 MHz is capable of identifying the borders between the vessel lumen and the intima as well as between the media and the adventitia. Although there is no uniformly accepted methodology, the common carotid IMT is determined as the average of 12 measurements (6 measurements each from the near and far wall of each of the three segments in both sides). As there is a graded increase of cardiovascular risk with increasing IMT, no cut-off value to distinguish between normal and abnormal has been defined. In young and healthy individuals with multiple traditional risk factors from the Bogalusa Heart Study, IMT increased significantly with the number of risk factors for both common carotid and carotid bulb segments, but not for the internal carotid segment.[16] Persons without known cardiovascular disease with higher IMT values (those in the highest quintile or ≥1 mm) are at increased risk for cardiac events and stroke.[17] When IMT is used to predict the incidence of subsequent stroke, the risk is graded but nonlinear, with hazards increasing more rapidly at lower IMTs than at higher IMTs.[18] Therefore, precision of measurements is of greatest importance in the submillimeter range, which poses high requirements on instruments and physicians. The risk of cardiac events in 4–7 years of follow-up in patients free of clinical coronary artery disease at baseline is also nonlinearly related to IMT.[19]

Plaque Characteristics

Plaque characteristics as assessed by carotid ultrasound were found to be predictive of subsequent cerebral ischemic[20] and coronary[21] events. Patients with echolucent stenotic plaques had a higher risk of cerebrovascular and coronary events than subjects with other plaque types. On B-mode ultrasound assessments, lipids, thrombi, and hemorrhage will all appear as echolucent structures. As the Rotterdam Study showed, noninvasive measures of extracoronary atherosclerosis are predictors of myocardial infarction (MI).[22] The relatively crude measures directly assessing plaques in the carotid artery (and abdominal aorta) predicted MI equally well as the more precisely measured carotid IMT.[22]

Magnetic Resonance Imaging (MRI)

MRI offers direct visualization of the atherosclerotic plaque, allowing identification of plaque components such as the fibrous cap, lipid core, hemorrhage, and thrombosis. It has been evaluated as a means of in vivo imaging of the arterial wall by noninvasively depicting coronary plaques.[23,24] Using optimized three-dimensional (3D) imaging sequences to improve contrast between lumen and vessel wall, a spatial resolution of $0.66 \times 0.66 \times 2$ mm can be obtained. However, longer acquisition times are still a limitation. Regression of the lipid component of atherosclerotic plaques induced in animal models can now be demonstrated by serial in vivo MR examinations.[25] The current fast technical improvement has led to 3D black-blood vessel wall imaging which permits in vivo distinction between "normal" and diseased vessel walls.[26] MRI may identify the fibrous cap in the atherosclerotic aorta.[27] Carotid, aortic, and even coronary plaque assessment with MRI may lead to its use as a scanning tool for quantifying subclinical disease, predicting future cardiovascular events, and evaluating therapeutic interventions. For the present, MRI is a promising research tool, but its use is limited to only a small number of research laboratories. Further advances are needed to reduce the problems from cardiac and respiratory motion and the nonlinear course of the coronary arteries. Thus, MRI is not yet appropriate for use in identifying patients at high risk for CAD in clinical practice.

Ultrafast CT Imaging (EBCT, MSCT)

For cardiac CT imaging, ultrafast techniques are necessary: In Europe, predominantly very fast

rotating mechanical CTs are used (MSCT with 16 or more slices simultaneously acquiring the data), while in the US, electron beam CT (EBCT, no mechanically moving parts) is the prevailing technology. Besides the considerably lower costs of MSCT, the spatial resolution of MSCT is superior to EBCT with the temporal resolution still a matter of debate using the "sector technology" for MSCT. In contrast to cardio-MR, cardio-CT easily depicts the presence of calcified plaques of more than 1 mg. In general, there is clinically good agreement between the calcium scores measured by EBCT and MSCT.[28–30] As regards radiation exposure, the effective dose for calcium scoring is 0.7 mSv for EBCT and 1.0 mSv for (prospectively triggered) MSCT.[31] For a practical comparison, the German government allows a radiation dose of 1.0 mSv during pregnancy for an unborn child.

The presence of coronary calcium is identical with "disease" – there is no "normal" calcium in the coronary vessel wall.[3,32] In an international multicenter study of 5345 individuals with no signs or history of CAD, calcified atherosclerotic plaques were present in 63% of men and in 41% of women.[33] The amount of calcified coronary plaques reflects the *total* coronary plaque burden, that is, the more calcified plaques are present, the higher is the amount of non-calcified plaques.[34] In an autopsy study of sudden-death coronary victims, all hearts of age >50 years showed some calcification.[35] A calcified plaque is not necessarily stable; stable and vulnerable plaques contain the same amount of calcium.[35,36]

The use of contrast media for the cardio-CT examination enables non-calcified plaques to be visualized and characterized. The density measurements of non-calcified plaques reflect echogenicity and plaque composition and may allow differentiation between soft and fibrous plaques.[37–39] Cardio-CT may one day be considered a "noninvasive IVUS." At the present time, the clinical role of non-calcified plaques, especially in persons without any calcified plaques, has not yet been determined. Nevertheless, the demonstration of coronary calcium for the first time offers the opportunity to *directly* and *noninvasively* visualize coronary atherosclerosis.

Modern Identification of the High-Risk Individual

In the RECALL Study "any form of atherosclerosis" was present in 53% of the individuals investigated (4814 persons, age 45–74 years), so atherosclerosis is a common finding in people over 45 years.[40,41] Although population-based, general recommendations for risk factor modification make sense, they have not been as successful as expected.[42] In recent years, there has been a shift of paradigm regarding the detection of early atherosclerotic disease. Whereas in the previous versions of the European and US guidelines the detection of "any atherosclerosis" was essential for decision making in further treatment,[43–45] the newer guidelines focus specifically on the assessment of the *individual* risk, particularly on detection of the "high-risk" individual.[4,5,46] The determination of a high "absolute" individual risk has been increasingly recognized as a critical determinant for making decisions about instituting pharmacological therapy for risk reduction in prevention of cardiovascular disease in the US[47] and in Europe.[48,49]

Today, there are two concepts for the definition of a "high-risk" individual, one based on morbidity *and* mortality, and the other on mortality only: For the combination of morbidity and mortality, traditionally the Framingham score[46] or, predominantly in Germany, the PROCAM score[50] are used. Both scores (based on approximately 5000 individuals each, from Framingham/US or industrial workers from Münster/Germany) have determined a "high risk" if the likelihood for a cardiovascular event is >20% per 10 years, that is, 2% per year. The question remains whether data from the US can be extrapolated to Europe.[51] The Framingham and PROCAM scores overestimated the absolute CHD risk of middle-aged men in Belfast and France.[52] These regional differences were considered when introducing the European SCORE system (based on more than 200,000 individuals), focusing only on the hard endpoint "cardiovascular death."[53] Thus, the "SCORE score" has defined "high risk" as a likelihood of >5% to die from cardiovascular disease within the next 10 years.

The Dilemma of Traditional Identification of High-Risk Patients

Two large cohort studies revealed that 80% to 90% of the patients with CHD had at least one of four traditional risk factors (cigarette smoking, hyperlipidemia, arterial hypertension, or diabetes).[54,55] In the clinical practice of prevention, however, we have the opposite problem: of course we treat arterial hypertension and diabetes anyway, but which asymptomatic patient without demonstrable myocardial ischemia with which risk factors is at high risk for developing a cardiovascular event? The identification of high-risk individuals based on a single laboratory parameter may be misleading: for example, only about 50% of patients having an MI demonstrated hypercholesterolemia.[56] Thus, predicting a heart attack based on hypercholesterolemia alone may be like flipping a coin. The diagnosis of a "metabolic syndrome" has not been shown to be of additional value in predicting events as compared to the Framingham score.[57] Adding abdominal obesity, triglycerides, and fasting glucose to these equations provides little or no increase in power of prediction.[57]

The usefulness of newer blood-laboratory parameters to identify high-risk patients is not yet established: There are newer promising data for plasma natriuretic peptide levels predicting cardiovascular events and death.[58] Elevated homocysteine has been shown to be an independent risk factor for MI in middle-aged women.[59] Among older adults, an elevated level of Lp(a) lipoprotein is an independent predictor of stroke, death from vascular disease, and death from any cause in men but not in women.[60] ApoB, apoB/apoA-I and apoA-I were also regarded as highly predictive in evaluation of cardiac risk.[61] The value of C-reactive protein (CRP) in identifying high-risk individuals is a matter of ongoing controversy, with reports describing CRP levels as a marker of atheromatous plaque vulnerability,[62,63] enhancing global risk assessment.[64] A recent study, however, questioned its predictive value and recommended a review of its use for predicting coronary events.[65] Measurement of CRP in elderly people has no additional value in coronary disease prediction when traditional cardiovascular risk factors are already present.[66] Thus, the clinical relevance of CRP measurements in the prediction of the risk of CHD remains unproven.[67] Although CRP, Lp(a), homocysteine, apoB, apoA-I, and fibrinogen may be associated with vascular disease risk, their optimal use in routine screening remains to be determined.[68] At the present time it is not clear how to integrate all these blood tests into an evidence-based risk score.

High-risk patients are traditionally identified using one of the three major risk scores, derived from the parameters listed in Table 11-1.

There is, however, one inherent problem in identifying individuals at high risk related to the prevalence. This is explained for the PROCAM score as follows: Figure 11-1 shows the actually observed 10-year coronary events based on the PROCAM score.[50] Taking the prevalence into consideration, the following calculations can be made: A score >61 was observed in 2% of the population with an event rate of 43.2%. Thus, out of 1000 persons, 20 persons (2%) would have a score >61, leading in 9 persons (43.2% of 20 persons) to an event. On the other hand, a score of 45–53 was observed in 15% of the population with an event rate of 14.8%. Thus, out of 1000 persons, 150 persons (15%) would have a score of 45–53, leading in 22 persons (14.8% of 150 persons) to an event. Thus, twice as many patients with a heart attack (62%) come from the "medium-risk" group as from the "high-risk" group (31%) (Figure 11-2). A similar problem has been shown for the Framingham score. Thus, the dilemma is that the guidelines primarily focus on the "high-risk" patients,

Table 11-1. Comparison of the parameters used for calculating the individual "absolute" risk according to the three major risk scores

Parameter	Framingham score	PROCAM score	SCORE score
Age	+	+	+
Gender	+	– (men only)	+
Systolic blood pressure	+	+	+
Smoking	+	+	+
Diabetes mellitus	–	+	–
Total cholesterol	+	–	+
HDL cholesterol	+	+	+
LDL cholesterol	–	+	–
Triglycerides	–	+	–
Positive family history	–	+	–

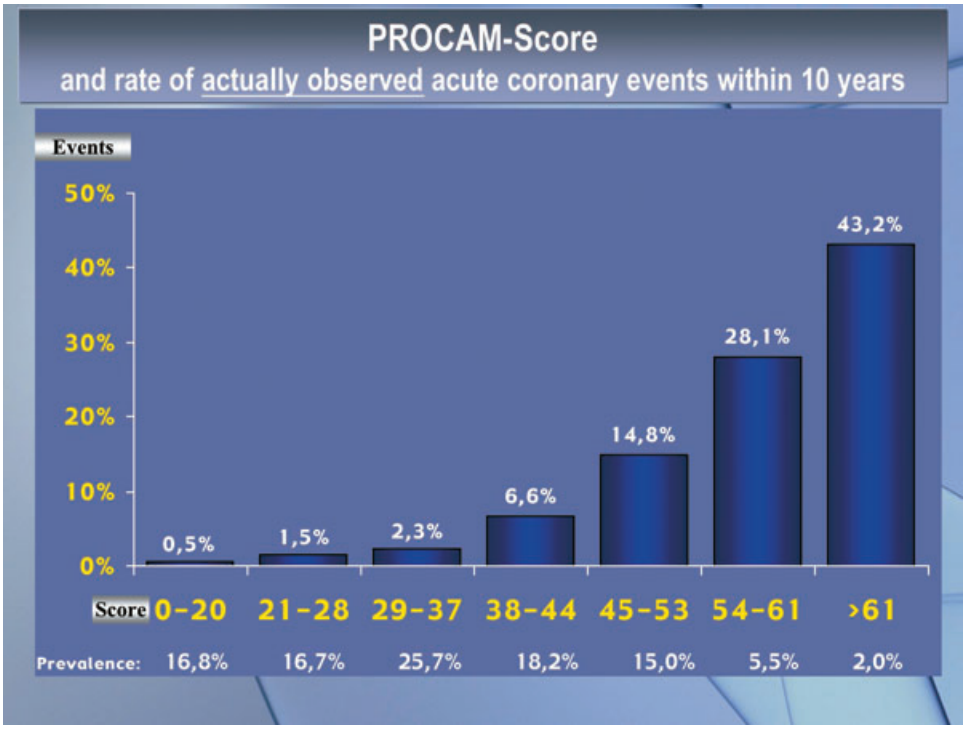

Figure 11-1. The PROCAM score, its prevalence, and the percentage of observed acute coronary events within each risk group.

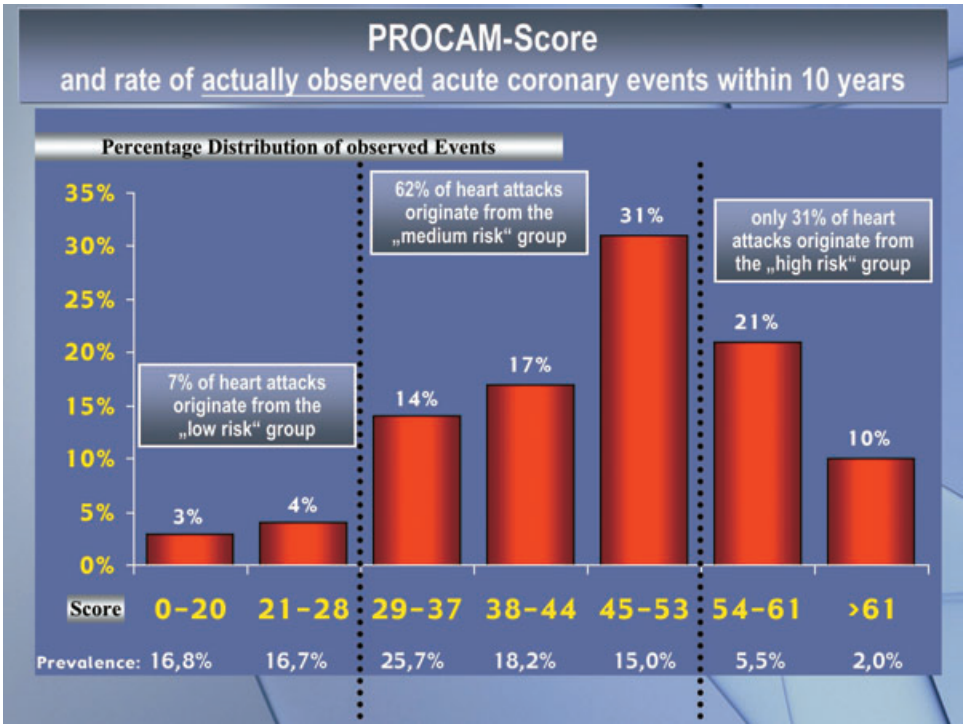

Figure 11-2. The PROCAM score, its prevalence, and the percentage of the number of patients with an observed acute coronary event within each risk group.

but most events occur in the large intermediate-risk group. Therefore, an additional method is needed to identify the "true high-risk" individuals hidden in the medium-risk group.

Imaging Methods for the Detection of High-Risk Individuals

An ideal valuable additional tool should meet the following requirements:

- proven independent risk factor (= independent from the risk factors in Table 11.1)
- proven information additional to the traditional risk factors
- no inherent risk
- widely available.

Although MRI is a valuable research tool for assessing plaques in asymptomatic atherosclerotic disease (see above), there are no data proving that this imaging method delivers clinically important, independent, and additional information. Atherosclerosis of the carotid artery as detected by ultrasound (see above) is related to an increased hazard ratio. But neither for MRI nor for carotid ultrasound does data exist regarding how to additionally identify patients at high risk for cardiovascular events, that is, a risk of >2%/year.

Calcium Scoring for the Detection of High-Risk Patients

For the identification of high-risk individuals, the absolute calcium score has to be interpreted within the context of age and gender. Thus each interpretation of the calcium score (e.g. the Agatston score) should describe the percentile allocated to the score.[28,69,70] An overwhelming number of studies have shown that a calcium score, especially in the upper (usually >75%) percentile range, is a predictor of coronary/cardiovascular events, *independent* of the traditional risk factors.[70–81] There is in particular no correlation between the calcium score and LDL or HDL cholesterol,[82] nor any correlation with CRP,[83,84] even after adjusting for traditional risk factors.[85] In an unselected population of subjects older than 55 years, 30% of the men and 15% of the women without risk factors had extensive coronary calcification.[86] There is no or only a weak correlation between calcium scoring and the Framingham risk estimate[87,88] as well as the PROCAM risk factor model.[89]

Three studies have shown that coronary calcium provides independent incremental information in addition to the Framingham score in the prediction of cardiovascular events.[71,76,90] Mortality data from 10,377 asymptomatic individuals with cardiac risk factors showed that when considering the receiver operating curve, the concordance index alone for cardiac risk factors increased from 0.72 to 0.78 ($P < 0.001$) when the calcium score was added to a multivariable model for prediction of death.[76] Another study including 1461 asymptomatic adults has shown that across all Framingham risk categories, calcium scoring was predictive of risk among patients with a Framingham score higher than 10%.[71] All three studies concluded that calcium scoring offers the most additional information among individuals in the Framingham intermediate-risk category. Therefore, the ESC guidelines recommended calcium scoring (with either EBCT or MSCT) as an independent method of incremental information for detecting a subset of high-risk patients.[4,5] Although calcium scoring does not identify an individual vulnerable plaque, it identifies the vulnerable individual.

According to the NCEP guidelines, diabetic patients are already a "CAD equivalent" and should therefore be treated like patients with established CAD.[46] An ABI <0.9 always represents an individual at high risk (see above). Chronic kidney disease is a risk factor for the development of cardiovascular disease. It has been recommended that chronic kidney disease be regarded as a high risk in the full prevention and treatment of CVD risk factors.[91] The role of carotid plaque imaging in ruling out high-risk coronary patients is not yet clear: In the RECALL Study, 52% of 1526 individuals (mean age 58 ± 8 years) with no carotid plaque did have coronary calcified plaques.[40]

The indications for calcium scoring in asymptomatic patients without evidence of myocardial ischemia are listed in Table 11-2.

If high-risk strategies are to have a major impact on CVD in the population, they need to be more widely used than previously envisaged.[49] Combining the two approaches – conventional

Table 11-2. Indications for calcium scoring in asymptomatic patients with no demonstrable myocardial ischemia. The highest additional information is obtained in individuals classified as "intermediate risk" according to conventional risk factor scoring

Conventional risk scoring (e.g. Framingham score, PROCAM score)	Calcium scoring
Low-risk patients	Not indicated (no screening method, radiation, not cost-effective)
Intermediate-risk patients:	Indicated (additional information, identification of individuals actually at high risk)
High-risk patients	Not indicated (not necessary, no additional information)
Diabetic patients, ABI < 0.9, chronic kidney disease (carotid plaques?)	Not indicated (not necessary, no additional information, because already at high risk)

risk estimation and calcification measurement – should enable clinicians to better assess the management of asymptomatic individuals.[92]

Once an individual patient has been detected as at "high-risk," an intensive risk factor modification including lifestyle changes and medical therapy should be initiated. An intensive nurse-based educational program, however, was not successful.[93] Obviously, more than patient education is necessary to reach these goals.[94] Fortunately, calcium scoring is helpful in patients' motivation.[95]

Summary and Conclusions

Although modern medicine significantly improved the short-term outcome of acute myocardial infarction, it shifted the problem from a decrease in mortality to an increase in morbidity. Therefore, the challenge of modern medicine is to reduce the cardiovascular morbidity, that is, to prevent the first event.

Asymptomatic atherosclerotic disease is defined as the presence of abnormal function or structure of the vessel wall without angina pectoris or demonstrable myocardial ischemia. Functional tests for early detection of asymptomatic atherosclerotic disease are forearm blood flow measurements (not yet clinically established) and the ankle–brachial index (ABI). An ABI <0.9 identifies patients with (even asymptomatic) peripheral artery disease. Carotid ultrasound detects increased intima–media thickness (IMT) and plaque characteristics. The relatively crude measures directly assessing plaques in the carotid artery (and abdominal aorta) predicted myocardial infarction equally well as the more precisely measured carotid IMT. Magnetic resonance imaging (MRI) has been evaluated as a means of in vivo imaging of the arterial wall by noninvasively visualizing coronary plaques, but MRI is not yet appropriate for use in additionally identifying patients at high risk for CAD in clinical practice.

In contrast, cardio-CT easily depicts the presence of calcified plaques. The presence of coronary calcium is identical with "disease" – there is no "normal" calcium in the coronary vessel wall. The amount of calcified coronary plaques reflects the *total* coronary plaque burden; that is, the more calcified plaques are present, the higher the amount of non-calcified plaques. The demonstration of coronary calcium offers for the first time the opportunity to directly visualize coronary atherosclerosis by noninvasive means.

In recent years, there has been a paradigm shift from the detection of "any atherosclerosis" to the assessment of the individual risk, particularly detecting the "high-risk" individual, defined as a risk of >2%/year. High-risk patients can be identified using the Framingham, PROCAM, or SCORE score. There is, however, one inherent problem in identifying individuals at high-risk related to the prevalence: twice as many patients with a heart attack (62%) arise from the "medium-risk" group as from the "high-risk" group. The dilemma is that the guidelines primarily focus on "high-risk" patients, but most events occur in the large intermediate-risk group. Therefore, an additional method is needed to identify the "true high-risk" individuals hidden in the medium-risk group:

An ideal and valuable additional tool should be a proven independent risk factor, provide additional information to the traditional risk factors with no inherent risk, and be widely available. An overwhelming number of studies have shown that a high (percentile) calcium score is a predictor of coronary/cardiovascular events, *independent* of the traditional risk factors. Three studies showed that coronary calcium provides independent

incremental information in addition to the Framingham score in the prediction of cardiovascular events. Thus, in asymptomatic individuals with no demonstrable myocardial ischemia, the highest additional information from calcium scoring is obtained in individuals classified as "intermediate risk" according to conventional risk factor scoring. Combining the two approaches – conventional risk estimation and calcification measurement – should enable clinicians to better assess the management of asymptomatic individuals.

References

1. Cooper R, Cutler J, Desvigne-Nickens P, et al. Trends and disparities in coronary heart disease, stroke, and other cardiovascular diseases in the United States: findings of the national conference on cardiovascular disease prevention. Circulation 2000; 102:3137–3147.
2. Unal B, Critchley JA, Capewell S. Explaining the decline in coronary heart disease mortality in England and Wales between 1981 and 2000. Circulation 2004;109:1101–1107.
3. Silber S. Quantification of coronary artery calcifications in the risk stratification of cardiac events. Dtsch Med Wochenschr 2002;127:2575–2578.
4. De Backer G, Ambrosioni E, Borch-Johnsen K, et al. Executive Summary: European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (executive summary). Eur Heart J 2003;24:1601–1610.
5. De Backer G, Ambrosioni E, Borch-Johnsen K, et al. Full Version: European guidelines on cardiovascular disease prevention in clinical practice: third joint task force of European and other societies on cardiovascular disease prevention in clinical practice (full version). Eur J Cardiovasc Prev Rehabil 2003;10:S1–S10.
6. Nissen SE, Tsunoda T, Tuzcu EM, et al. Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. JAMA 2003;290:2292–2300.
7. Heitzer T, Schlinzig T, Krohn K, Meinertz T, Münzel T. Endothelial dysfunction, oxidative stress, and risk of cardiovascular events in patients with coronary artery disease. Circulation 2001;104:2673–2678.
8. Schächinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. Circulation 2000;101:1899–1906.
9. Verma S, Buchanan MR, Anderson TJ. Endothelial function testing as a biomarker of vascular disease. Circulation 2003;108:2054–2059.
10. Smith SC Jr, Greenland P, Grundy SM. AHA Conference Proceedings. Prevention conference V: Beyond secondary prevention: Identifying the high-risk patient for primary prevention: executive summary and full version. Circulation 2000;101: 111–116 (full version: e116–e122).
11. Oei HH, Vliegenthart R, Hak AE, et al. The association between coronary calcification assessed by electron beam computed tomography and measures of extracoronary atherosclerosis: the Rotterdam Coronary Calcification Study. J Am Coll Cardiol 2002;39:1745–1751.
12. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA 2001;286: 1317–1324.
13. Criqui MH, Fronek A, Barrett-Connor E, Klauber MR, Gabriel S, Goodman D. The prevalence of peripheral arterial disease in a defined population. Circulation 1985;71:510–515.
14. Abbott RD, Petrovitch H, Rodriguez BL, et al. Ankle/brachial blood pressure in men > 70 years of age and the risk of coronary heart disease. Am J Cardiol 2000;86:280–284.
15. Otah KE, Madan A, Otah E, Badero O, Clark LT, Salifu MO. Usefulness of an abnormal ankle-brachial index to predict presence of coronary artery disease in African-Americans. Am J Cardiol 2004;93:481–483.
16. Urbina EM, Srinivasan SR, Tang R, Bond MG, Kieltyka L, Berenson GS. Impact of multiple coronary risk factors on the intima-media thickness of different segments of carotid artery in healthy young adults (The Bogalusa Heart Study). Am J Cardiol 2002;90:953–958.
17. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK, Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med 1999;340:14–22.
18. Chambless LE, Folsom AR, Clegg LX, et al. Carotid wall thickness is predictive of incident clinical stroke: the Atherosclerosis Risk in Communities (ARIC) study. Am J Epidemiol 2000;151:478–487.
19. Chambless LE, Heiss G, Folsom AR, et al. Association of coronary heart disease incidence with

carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987–1993. Am J Epidemiol 1997;146: 483–494.
20. Mathiesen EB, Bonaa KH, Joakimsen O. Echolucent plaques are associated with high risk of ischemic cerebrovascular events in carotid stenosis: the Tromso study. Circulation 2001;103:2171–2175.
21. Honda O, Sugiyama S, Kugiyama K, et al. Echolucent carotid plaques predict future coronary events in patients with coronary artery disease. J Am Coll Cardiol 2004;43:1177–1184.
22. van der Meer IM, Bots ML, Hofman A, del Sol AI, van der Kuip DA, Witteman JC. Predictive value of noninvasive measures of atherosclerosis for incident myocardial infarction: the Rotterdam Study. Circulation 2004;109:1089–1094.
23. Botnar RM, Stuber M, Kissinger KV, Kim WY, Spuentrup E, Manning WJ. Noninvasive coronary vessel wall and plaque imaging with magnetic resonance imaging. Circulation 2000;102:2582–2587.
24. Fayad ZA, Fuster V, Fallon JT, et al. Noninvasive in vivo human coronary artery lumen and wall imaging using black-blood magnetic resonance imaging. Circulation 2000;102:506–510.
25. Helft G, Worthley SG, Fuster V, et al. Progression and regression of atherosclerotic lesions: monitoring with serial noninvasive magnetic resonance imaging. Circulation 2002;105:993–998.
26. Kim WY, Stuber M, Bornert P, Kissinger KV, Manning WJ, Botnar RM. Three-dimensional black-blood cardiac magnetic resonance coronary vessel wall imaging detects positive arterial remodeling in patients with nonsignificant coronary artery disease. Circulation 2002;106:296–299.
27. Kramer CM, Cerilli LA, Hagspiel K, DiMaria JM, Epstein FH, Kern JA. Magnetic resonance imaging identifies the fibrous cap in atherosclerotic abdominal aortic aneurysm. Circulation 2004;109:1016–1021.
28. Schmermund A, Erbel R, Silber S. Age and gender distribution of coronary artery calcium measured by four-slice computed tomography in 2,030 persons with no symptoms of coronary artery disease. The MUNICH registry. Am J Cardiol 2002;90:168–173.
29. Stanford W, Thompson BH, Burns TL, Heery SD, Burr MC. Coronary artery calcium quantification at multi-detector row helical CT versus electron-beam CT. Radiology 2004;230:397–402.
30. Becker CR, Jakobs TF, Aydemir S, et al. Helical and single-slice conventional CT versus electron beam CT for the quantification of coronary artery calcification. AJR Am J Roentgenol 2000;174:543–547.
31. Morin RL, Gerber TC, McCollough CH. Radiation dose in computed tomography of the heart. Circulation 2003;107:917–922.
32. Sangiorgi G, Rumberger JA, Severson A, et al. Arterial calcification and not lumen stenosis is highly correlated with atherosclerotic plaque burden in humans: a histologic study of 723 coronary artery segments using nondecalcifying methodology. J Am Coll Cardiol 1998;31:126–133.
33. Silber S, Shemesh J, Weg N, Yoon HC. Multicentre age and gender distribution of coronary artery calcification as measured by four-slice computed tomography in 5,345 people. Eur Heart J 2003; 24(Suppl):570.
34. Rumberger JA, Simons DB, Fitzpatrick LA, Sheedy PF, Schwartz RS. Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study. Circulation 1995;92:2157–2162.
35. Burke AP, Taylor A, Farb A, Malcom GT, Virmani R. Coronary calcification: insights from sudden coronary death victims. Z Kardiol 2000;89(Suppl 2):49–53.
36. Schmermund A, Erbel R. Unstable coronary plaque and its relation to coronary calcium. Circulation 2001;104:1682–1687.
37. Leber AW, Knez A, Becker A, et al. Accuracy of multidetector spiral computed tomography in identifying and differentiating the composition of coronary atherosclerotic plaques: a comparative study with intracoronary ultrasound. J Am Coll Cardiol 2004;43:1241–1247.
38. Achenbach S, Moselewski F, Ropers D, et al. Detection of calcified and noncalcified coronary atherosclerotic plaque by contrast-enhanced, submillimeter multidetector spiral computed tomography: a segment-based comparison with intravascular ultrasound. Circulation 2004;109:14–17.
39. Schroeder S, Kopp AF, Baumbach A, et al. Noninvasive detection and evaluation of atherosclerotic coronary plaques with multislice computed tomography. J Am Coll Cardiol 2001;37:1430–1435.
40. Erbel R, Schmermund A, Stang A, et al. The "Heinz Nixdorf RECALL Study": Improvement of prediction of risk for myocardial infarction based on known and newer risk factors as well on modern imaging and non-imaging methods. Z Kardiol 2004;93(Suppl. 3):III/244.
41. Schmermund A, Möhlenkamp S, Stang A, et al. 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. Risk

Factors, Evaluation of Coronary Calcium and Lifestyle. Am Heart J 2002;144:212–218.
42. The EUROASPIRE I and II Group, Clinical reality of coronary prevention guidelines: a comparison of EUROASPIRE I and II in nine countries. EUROASPIRE I and II Group. European Action on Secondary Prevention by Intervention to Reduce Events. Lancet 2001;357:995–1001.
43. The NCEP Expert Panel, Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). JAMA 1993;269:3015–3023.
44. The NCEP Expert Panel, National Cholesterol Education Program. Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). Circulation 1994;89:1333–1445.
45. Wood D, De Backer G, Faergeman O, Graham I, Mancia G, Pyorala K. Prevention of coronary heart disease in clinical practice. Summary of recommendations of the Second Joint Task Force of European and other Societies on Coronary Prevention. Eur Heart J 1998;19:1434–1503.
46. The NCEP Expert Panel, Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486–2497.
47. Grundy SM, Bazzarre T, Cleeman J, et al. Prevention Conference V: Beyond secondary prevention: identifying the high-risk patient for primary prevention: medical office assessment: Writing Group I. Circulation 2000;101:e3–e11.
48. Hennekens CH, D'Agostino RB. Global risk assessment for cardiovascular disease and astute clinical judgement. Eur Heart J 2003;24:1899–1900.
49. Emberson J, Whincup P, Morris R, Walker M, Ebrahim S. Evaluating the impact of population and high-risk strategies for the primary prevention of cardiovascular disease. Eur Heart J 2004;25: 484–491.
50. Assmann G, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Munster (PROCAM) study. Circulation 2002;105:310–315.
51. Brindle P, Emberson J, Lampe F, et al. Predictive accuracy of the Framingham coronary risk score in British men: prospective cohort study. BMJ 2003; 327:1267.
52. Empana JP, Ducimetiere P, Arveiler D, et al. Are the Framingham and PROCAM coronary heart disease risk functions applicable to different European populations? The PRIME Study. Eur Heart J 2003;24:1903–1911.
53. Conroy RM, Pyorala K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003;24:987–1003.
54. Greenland P, Knoll MD, Stamler J, et al. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. JAMA 2003;290:891–897.
55. Khot UN, Khot MB, Bajzer CT, et al. Prevalence of conventional risk factors in patients with coronary heart disease. JAMA 2003;290:898–904.
56. Böger GI, Hoopmann M, Busse R, Budinger M, Welte T, Böger RH, Drug therapy of coronary heart disease – are therapeutic guidelines being paid attention to? Z Kardiol 2003;92:466–475.
57. Grundy SM, Hansen B, Smith SC Jr, Cleeman JI, Kahn RA. Clinical management of metabolic syndrome: report of the American Heart Association/ National Heart, Lung, and Blood Institute/ American Diabetes Association conference on scientific issues related to management. Circulation 2004;109:551–556.
58. Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. N Engl J Med 2004;350:655–663.
59. Zylberstein DE, Bengtsson C, Bjorkelund C, et al. 4-year follow-up of the population study of women in Gothenburg. Circulation 2004;109:601–606.
60. Ariyo AA, Thach C, Tracy R. Lp(a) lipoprotein, vascular disease, and mortality in the elderly. N Engl J Med 2003;349:2108–2115.
61. Walldius G, Jungner I, Holme I, Aastveit AH, Kolar W, Steiner E. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. Lancet 2001;358:2026–2033.
62. Arroyo-Espliguero R, Avanzas P, Cosin-Sales J, Aldama G, Pizzi C, Kaski JC. C-reactive protein elevation and disease activity in patients with coronary artery disease. Eur Heart J 2004;25:401–408.
63. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997;336:973–979.
64. Koenig W, Lowel H, Baumert J, Meisinger C. C-reactive protein modulates risk prediction based on the Framingham Score: implications for future risk assessment: results from a large cohort study in southern Germany. Circulation 2004;109:1349–1353.
65. Danesh J, Wheeler JG, Hirschfield GM, et al. C-reactive protein and other circulating markers of

inflammation in the prediction of coronary heart disease. N Engl J Med 2004;350:1387–1397.
66. van der Meer IM, de Maat MP, Kiliaan AJ, van der Kuip DA, Hofman A, Witteman JC. The value of C-reactive protein in cardiovascular risk prediction: the Rotterdam Study. Arch Intern Med 2003;163: 1323–1328.
67. Tall AR, C-reactive protein reassessed. N Engl J Med 2004;350:1450–1452.
68. Hackam DG, Anand SS. Emerging risk factors for atherosclerotic vascular disease: a critical review of the evidence. JAMA 2003;290:932–940.
69. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827–832.
70. Raggi P, Callister TQ, Cooil B, et al. Identification of patients at increased risk of first unheralded acute myocardial infarction by electron-beam computed tomography. Circulation 2000;101:850–855.
71. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA 2004;291:210–215.
72. Arad Y, Spadaro LA, Goodman K, et al. Predictive value of electron beam computed tomography of the coronary arteries. 19-month follow-up of 1173 asymptomatic subjects. Circulation 1996;93:1951–1953.
73. Arad Y, Spadaro LA, Goodman K, Newstein D, Guerci AD. Prediction of coronary events with electron beam computed tomography. J Am Coll Cardiol 2000;36:1253–1260.
74. Kondos GT, Hoff JA, Sevrukov A, et al. Electron-beam tomography coronary artery calcium and cardiac events: a 37-month follow-up of 5635 initially asymptomatic low- to intermediate-risk adults. Circulation 2003;107:2571–2576.
75. Möhlenkamp S, Lehmann N, Schmermund A, et al. Prognostic value of extensive coronary calcium quantities in symptomatic males – a 5-year follow-up study. Eur Heart J 2003;24:845–854.
76. Shaw LJ, Raggi P, Schisterman E, Berman DS, Callister TQ. Prognostic value of cardiac risk factors and coronary artery calcium screening for all-cause mortality. Radiology 2003;228:826–833.
77. Vliegenthart R, Oudkerk M, Song B, van der Kuip DA, Hofman A, Witteman JC. Coronary calcification detected by electron-beam computed tomography and myocardial infarction. The Rotterdam Coronary Calcification Study. Eur Heart J 2002;23: 1596–1603.
78. Wayhs R, Zelinger A, Raggi P. High coronary artery calcium scores pose an extremely elevated risk for hard events. J Am Coll Cardiol 2002;39:225–230.
79. Wong ND, Hsu JC, Detrano RC, Diamond G, Eisenberg H, Gardin JM. Coronary artery calcium evaluation by electron beam computed tomography and its relation to new cardiovascular events. Am J Cardiol 2000;86:495–498.
80. Taylor AJ, Burke AP, O'Malley PG, et al. A comparison of the Framingham risk index, coronary artery calcification, and culprit plaque morphology in sudden cardiac death. Circulation 2000;101:1243–1248.
81. Taylor AJ, Feuerstein I, Wong H, Barko W, Brazaitis M, O'Malley PG. Do conventional risk factors predict subclinical coronary artery disease? Results from the Prospective Army Coronary Calcium Project. Am Heart J 2001;141:463–468.
82. Hecht HS, Superko HR, Electron beam tomography and National Cholesterol Education Program guidelines in asymptomatic women. J Am Coll Cardiol 2001;37:1506–1511.
83. Hunt ME, O'Malley PG, Vernalis MN, Feuerstein IM, Taylor AJ. C-reactive protein is not associated with the presence or extent of calcified subclinical atherosclerosis. Am Heart J 2001;141:206–210.
84. Reilly MP, Wolfe ML, Localio AR, Rader DJ. C-reactive protein and coronary artery calcification: The Study of Inherited Risk of Coronary Atherosclerosis (SIRCA). Arterioscler Thromb Vasc Biol 2003;23:1851–1856.
85. Schmermund A, Stang A, Moebus S, et al. Is there an association of high-sensitive C-reactive protein with coronary calcium? The Heinz Nixdorf RECALL Study. J Am Coll Cardiol 2004;43(Suppl A): 334A.
86. Oei HH, Vliegenthart R, Hofman A, Oudkerk M, Witteman JC. Risk factors for coronary calcification in older subjects. The Rotterdam Coronary Calcification Study. Eur Heart J 2004;25:48–55.
87. Schmermund A, Lehmann N, Möhlenkamp S, et al. Independent information provided by Framingham risk algorithm and coronary calcium scores in a large German population sample: Heinz Nixdorf RECALL Study. J Am Coll Cardiol 2004;43(Suppl. A):334A.
88. Desai MY, Nasir K, Braunstein JB, et al. Framingham risk estimate is weakly correlated with coronary artery calcification in asymptomatic population. J Am Coll Cardiol 2004;43(Suppl A):363A.
89. Achenbach S, Nomayo A, Couturier G, et al. Relation between coronary calcium and 10-year risk scores in primary prevention patients. Am J Cardiol 2003;92:1471–1475.

90. Arad Y, Newstein D, Roth M, Guerci AD. Rationale and design of the St. Francis Heart Study: a randomized clinical trial of atorvastatin plus antioxidants in asymptomatic persons with elevated coronary calcification. Control Clin Trials 2001;22:553–572.
91. Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation 2003;108:2154–2169.
92. Thompson GR, Partridge J, Coronary calcification score: the coronary-risk impact factor. Lancet 2004;363:557–559.
93. Lichtman JH, Amatruda J, Yaari S, et al. Clinical trial of an educational intervention to achieve recommended cholesterol levels in patients with coronary artery disease. Am Heart J 2004;147:522–528.
94. Kline-Rogers EM, Eagle KA. It takes more than patient education to reach low-density lipoprotein cholesterol goals. Am Heart J 2004;147:381–382.
95. Kalia NK, Miller LG, Budoff MJ. Higher coronary calcification scores improve adherence to cardiac risk factor-modifying behaviors. J Am Coll Cardiol 2004.43:363A (abstract).