Deaths from diseases of the heart are decreasing. Cardiovascular diseases (CVD) will be the main cause of morbidity and mortality in 2015 according to a WHO report. The main problem is related to the long-time delay between the start of the development of atherosclerosis in young adults and the manifestation many decades later. Despite a recent decline in a CVD mortality rate in men and women, the main problem is related to the acute manifestation as the acute coronary syndrome, which leads 30–50% of subjects to sudden and fatal outcomes. In addition, about 20% of first and recurrent acute myocardial infarctions are silent. The lifetime risk of coronary artery disease after 40 years is 49% for men and 32% for women. That means, we are confronted with a major health care problem. This is even more obvious, when the rate of coronary heart disease deaths out of the hospital are taken into account which amount to 70% in 2007. These data are confirmed for Europe despite a strong decline of hospital deaths. Another problem is related to the fact that the number of sudden cardiac death amounts to >300 000 in the general US population. It is about 10 times higher than in those patients who are defined as prone to sudden death due to low ejection fraction, ventricular arrhythmias, and acute myocardial infarction. For cardiologists, this general topic becomes even more obvious, because even well-known cardiologists experienced early (≤65 years) sudden cardiac deaths such as RW Campbell, JM Isner, PA Poole-Wilson, H Drexler, and recently the paediatric cardiologist from Hannover, A Wessels. These events underline again what has been emphasized 15 years ago by the MONICA study that two-thirds of patients die outside the hospital and that we have to concentrate on primary and secondary prevention, also in memory of these colleagues. This review will demonstrate the potential value of coronary artery calcification screening which can be used as a sign of subclinical coronary arteriosclerosis for improved risk prediction, the first step to prevention. Subclinical atherosclerosis represents the vessel memory of risk factor exposure.

Keywords: Prevention • Atherosclerosis • Coronary artery calcification • Coronary imaging • Risk factors • Risk scores

Introduction
Deaths from diseases of the heart are decreasing. Cardiovascular diseases (CVD) will be the main cause of morbidity and mortality in 2015 according to a WHO report. The main problem is related to the long-time delay between the start of the development of atherosclerosis in young adults and the manifestation many decades later. Despite a recent decline in a CVD mortality rate in men and women, the main problem is related to the acute manifestation as the acute coronary syndrome (ACS), which leads 30–50% of subjects to sudden and fatal outcomes. In addition, about 20% of first and recurrent acute myocardial infarctions (MI) are silent. The lifetime risk of coronary artery disease (CAD) after the age of 40 years is 49% for men and 32% for women. That means, we are confronted with a major health care problem. This becomes even more obvious, when the rate of coronary heart disease (CHD) deaths out of the hospital are taken into account which amount to 70% in 2007. These data

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are confirmed for Europe despite a strong decline in hospital deaths.\textsuperscript{8,9} Another problem is related to the fact that the number of sudden cardiac death amounts to \(>300,000\) in the general US population. It is about 10 times higher than in those patients who are defined as prone to sudden death due to low ejection fraction, ventricular arrhythmias, and acute MI.\textsuperscript{10} For cardiologists, this gains specific interest, because even well-known cardiologists experienced early (\(\leq 65\) years) sudden cardiac deaths.\textsuperscript{11–14} These events underline what has been emphasized 15 years ago by the MONICA study that two-thirds of patients die outside the hospital and that we have to concentrate on primary and secondary prevention,\textsuperscript{15} also in memory of these colleagues.

This review will demonstrate the potential value of coronary artery calcification (CAC) screening (Figure 1) which can be used as a sign of subclinical coronary arteriosclerosis for improved risk prediction, the first step to prevention. Subclinical atherosclerosis represents the vessel memory of risk factor exposure.

**Algorithms for risk prediction**

**Framingham**

The Framingham study started in 1948 after a dramatic increase in the rate of MI in the USA, identifying traditional risk factors for MI (Table 1).\textsuperscript{16–18} Integration of these factors in the Framingham sex-specific risk score allows the estimate of the degree of risk for CHD.\textsuperscript{19} Using these data, the MRFIT study could confirm that not only for CHD, but also for all-cause mortality, the risk factors seem to play a major role.\textsuperscript{20} The latest version of the Framingham Risk Score (FRS) predicts the general cardiovascular risk as well as the risk for components of CVD like stroke, peripheral arterial disease, and heart failure.\textsuperscript{21,22} Lifetime risk assessment has been established in order to improve the value of the FRS assessment.\textsuperscript{7}

The FRS overestimates risk more than two-fold in European cohorts,\textsuperscript{23} but did better, when the FRS for CVD was used.\textsuperscript{24} In order to further improve risk prediction, the National Education Cholesterol Panel Adult Treatment Program (NCEP ATP III) used diabetes, stroke, aortic aneurysms, and peripheral artery disease for the identification of high-risk individuals.\textsuperscript{25}

**PROCAM**

Another attempt was followed in Germany using the Prospective Cardiovascular Münster (PROCAM) algorithm (Table 1).\textsuperscript{26–28} The study started in 1979 and was completed in 1985 after 10 years observing men from 52 companies and local government authorities. The risk score was redefined for the body mass index.\textsuperscript{28} For women it was extrapolated taking a calibration factor of 0.25 into account.\textsuperscript{27,28}

**HeartScore**

The HeartScore (Table 1) of the European Society of Cardiology is based on prospective studies in Europe, in order to assess the risk for fatal events including myocardial infarction, stroke, aortic rupture, and peripheral artery diseases.\textsuperscript{29} Thereby the threshold for high-risk estimates was changed.\textsuperscript{30} A big advantage is the potential for regional adjustment, which is provided for many areas in Europe.\textsuperscript{31}

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**Figure 1** Schematic drawing of the development of coronary arteriosclerosis including positive remodelling during plaque burden increase and the listing of invasive and non-invasive methods concerning their ability to detect signs of atherosclerosis starting with endothelial dysfunction and ending with signs of ischaemia in the EKG. Modified according to Erbel et al.\textsuperscript{86}
CARRISMA
For further improved risk prediction, the CARRISMA Score (Cardiovascular Risk Management) included:
(1) the body mass index (BMI),
(2) the number of cigarettes smoked daily, and
(3) the physical activity estimated in calories per week in the three mentioned risk algorithms (http://carrissma.net/information/fuer-mediziner.html).
A validation of this score will be based on recent population-based studies.

QRISK2
In order to facilitate the general practitioner work in a more accurate and reliable way for the risk assessment, the QRISK2 Score (Table 1) was developed in the UK. Predisposing risk factors such as type 2 diabetes, treated hypertension, rheumatoid arthritis, renal disease, and atrial fibrillation as well as self assignment ethnicity information were chosen.

Reynolds Risk Score
Due to the observed major differences of risk in women, a separate risk score, the Reynolds Risk Score (Table 1), was developed. Here high-sensitive C-reactive protein was used as a biomarker. Important to notice was the further analysis in men.

NHANES Score
In the recent National Health and Nutrition Examination Survey (NHANES), laboratory- and non-laboratory-based methods for the assessment of CVD were compared, again dealing with the problem of a wide spread use of risk assessment by the practitioner. For the non-laboratory method, age, systolic blood pressure, smoking, history of diabetes, treatment of blood pressure, and BMI were taken into account, whereas for the laboratory algorithm total cholesterol but not BMI was used. The NHANES system will adopt the European approach to develop specific algorithms for the different countries as others did before. The INTERHEART study, however, suggested that risk factors are similar across different countries when patient characteristics are used. Also the WHO score may be used in the future for risk assessment.

Limitation of risk score algorithm
Current risk-screening tools are not perfect and despite lasting discussions, no prospective study has been performed in order to test the hypothesis of risk stratification followed by an adjusted treatment strategy. The effect of risk factors such as atherogenic dyslipidaemia, smoking, or hypertension is related to both the magnitude and the deviation of the factors from normal and the duration of exposure. These influences may vary over time, smoking may be stopped and restarted, therapy changed, and living attitudes altered. In addition, an increasing obesity combined with the decline in low density lipoprotein (LDL) results in a new mixture of risk factors of central obesity, high waist circumference, moderate elevated LDL, low HDL, high triglycerides, and insulin resistance. Conventional risk factor assessment does not separate between the biological changes of ageing within arteries—the non-modified effect of ageing over time—and...
those produced by exposure over time to risk factors. In addition to the observed decline in CHD over the last 50 years, the marked regional differences in the baseline risk factors have to be taken into account. Calibration of risk factors may change over time, too, as has been shown for diabetes. Practitioners and even professionals will find the use of risk assessment confusing because the algorithms differ related to endpoints, thresholds, and populations studied (Table 1). Thus, risk scores in preventive medicine are not regularly used as much as possible.

To analyse the consequences of risk factor exposure on target organ damage, the detection of signs of subclinical atherosclerosis may be a better way for risk assessment. According to JG Edgren, Professor at Karolinska Institute in Stockholm, Lobstein was the first to use the term arteriosclerosis 100 years ago. He wrote that there is no way to detect atheroma during life and to reverse it. Today, more than 100 years later, we can visualize the atheroma and fibroatheroma as well as vulnerable plaques (Figure 1) and start to attenuate or reverse plaque growth.

**Refinement of risk assessment using signs of subclinical atherosclerosis**

**Risk factor association with atherosclerosis**

Based on the different risk-scoring systems, subjects can be classified in different categories, (i) with lifestyle changes for low-risk subjects with reassessment after 3–5 years and (ii) risk reduction including treatment for high-risk individuals, but (iii) for intermediate risk, the strategy has not been fully validated. Based on the ‘Bayesian’ approach, the application of further tests (Figure 2) is best applied to this cohort. Most attractive are imaging techniques which are able to demonstrate the development of atherosclerosis early, so that lesions including atheroma and fibroatheroma are already detected in the subclinical (silent) status. These signs of atherosclerosis are evidence of the CAD itself. Risk factors, measured about 1 year before a coronary event, were somewhat poor at predicting what was found at autopsy compared with those obtained earlier in life. Total cholesterol and blood pressure levels but also low-HDL-C were associated with coronary arteriosclerotic lesions and coronary artery stenosis. Also others showed that CHD is strongly associated with the presence of stenosis; cholesterol except for females in Framingham and blood pressure except for men in Framingham. None of the other risk factors such as glucose, triglycerides, uric acid, physical activity, or alcohol were associated with coronary arteriosclerosis at autopsy.

**Non-invasive imaging of coronary atherosclerosis**

For further risk stratification, imaging and non-imaging techniques (Figure 2) were suggested to be used including computed tomography (CT), ultrasound as well as hs-C-reactive protein and other biomarkers. As CT allows the direct non-invasive imaging of coronary atherosclerosis, the technique seems to be best suited for preventive cardiology. Computed tomography...
allows the visualization of CAC, which is a direct sign of atherosclerosis detected by pathology first intra-cellularly and then extracellularly.\textsuperscript{62} Comparative studies with intravascular ultrasound demonstrated that even single spots of CAC could be detected and that CAC is not a late, but an early marker of atherosclerosis.\textsuperscript{63} The CAC distribution in the coronary tree reflects the natural history of the disease, starting at the first 2 cm of the left anterior descending coronary artery, followed by the right coronary artery, left main and left circumflex coronary artery (LCX),\textsuperscript{64} thereby verifying previous pathological anatomic studies\textsuperscript{65,66} and analysis of coronary angiography.\textsuperscript{67}

Fluoroscopy was the first step in the direction of detecting CAC.\textsuperscript{68,69} But quantification of CAC was not possible, so that risk classification as well as follow-up studies were rarely performed.\textsuperscript{69} The breakthrough was the development of the electron beam CT. Now calcification could be detected, localized, and quantified due to the high temporal resolution of 50/100 ms.\textsuperscript{70} For modern MDCTs, the temporal resolution is still lower, but providing higher spatial resolution.\textsuperscript{70} The radiation exposure for EBCT is in the range of 0.8–1.3 mSv.\textsuperscript{71}

A prospective ECG triggering is done at 80\% of the RR interval and continuously 3 mm slice thickness scans down to the base of the heart are obtained. Scans can be performed even at the heart rate of up to 110 b.p.m.\textsuperscript{72} With a total scanning time of about 20 s, the total examination time is about 3–4 min with an additional 5–10 min for evaluation and quantification of CAC: an ideal screening technique.

For MDCTs, lower heart rates are recommended; usually reached by injection of beta-blocking agents.\textsuperscript{72} Currently, high-resolution 64, 256, 320, and even 640 row scanners are being used or are in development (Table 2). The temporal resolution has continuously decreased and is now 165 ms for 64 slice scanners and 83 ms for dual-source scanners.\textsuperscript{73} Modern systems have a resolution of 0.4 mm. For coronary calcium scans, a slice thickness of 3 mm is currently chosen with approximately 100–120 kV and variable mAs (ca. 150 mAs).\textsuperscript{72}

With new generations of CT systems, the X-ray exposure with MDCTs can be reduced to 0.8–1.0 mSv using prospective triggering.\textsuperscript{73,77}

For MDCTs, the tube voltage and tube current can be modified in order to adjust for body weight and other patient parameters.\textsuperscript{76} The total scanning time is <10 s for the entire chest (Table 2).\textsuperscript{72} Prospective ECG triggering has greater advantages with significant dose reductions.\textsuperscript{72,76}

During recent years, cardiac CT angiography has become very popular, because not only calcified but also non-calcified plaques can be visualized and the degree of coronary artery stenosis can be estimated.\textsuperscript{73,76} Also for CT angiography, the prospective gating is able to reduce the radiation dose significantly as a recent comparison demonstrated. Radiation reduction techniques including prospective gating reach 2.0 mSv instead of 9.6 mSv (P < 0.0001).\textsuperscript{78,77} However, no prospective studies of CT angiography have been reported in asymptomatic populations, so use for screening is currently discouraged.

The Society of Atherosclerosis Imaging and the Society of Cardiovascular Computed Tomography recently published guidelines for minimizing radiation exposure during acquisition of CAC.\textsuperscript{72} It is recommended:

- to regularly monitor the radiation exposure in the dose–length–product (DLP) and
- to measure the effective radiation dose (E). Dose–length–product should be <200 mGy cm and E should average 1–1.5 mSv and never exceed 3.0 mSv.
- to select prospective ECG triggering in an axial mode using a tube voltage of 120 kVp.
- to select tube current on the basis of patient size and topogram with the measurement at the chest.
- to limit the scans to the heart itself to protect other thoracic organs from radiation exposure.

### Quantification of coronary artery calcification

The analysis of the images became very standardized. Worldwide, the Agatston Score has been demonstrated as the most reliable algorithm providing excellent accuracy even between different studies.\textsuperscript{78} The Agatston Score includes the analysis of the calcium density multiplied with the area of the plaque using three or four pixels and the detection threshold of 130 IU Hounsfield for differentiation between calcium and surrounding tissue structures. Coronary artery calcification values range from 0 to levels as high as 8000–10 000, which represents a methodological and clinical advantage.

In comparison with the Agatston Score, also a coronary artery tree-based segmental score has been developed as well as a mass score integrating the signals of pixels for a given threshold, representing the total mineral content.\textsuperscript{79} When these parameters were used in order to estimate the accuracy for assessing outcome, the Multi-Ethnic Study of Atherosclerosis (MESA) could not confirm any improvement for sensitivity and specificity.\textsuperscript{80}

The reproducibility of CTs has been analysed and reached an inter-observer variability of about 3\%, intra-observer variability less than 1\%, and inter-scan variability of about 15\%.\textsuperscript{70} In the Heinz Nixdorf Recall (HNR) study, a group of more than 500 subjects were re-evaluated reaching a kappa-value of 0.94, suggesting minimal inter-institutional variability.\textsuperscript{81} Recently, a low absolute difference between dual-scans of only CAC 15.8 could be demonstrated.\textsuperscript{82} For the Agatston score of 100 CAC, the confidence

<table>
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</table>
limit ranged from 77 to 123. Other groups reported larger inter-scan variability. For the modern dual-CT, the reproducibility was tested for low radiation dose reaching a mean value of 1.5 ± 0.2 mSv with a kappa-value for calcified plaques of 0.93–0.94 and for non-calcified plaques 0.67–0.84 on a patient level. The mean intra-observer variability reached 2.08 with limits of agreements from 2.4.7 to 2.9. For low-radiation dosage with high pitch coronary CT-angiography, the inter-scan, inter-observer, and intra-observer variability were excellent but a high variability was shown for non-calcified plaques.

In order to estimate the difference between MDCT (dual-CT) (128 = 2 × 64 multidetector row) and standard EBCT, scan quantification of CAC was compared in 92 subjects. The Agatston score was significantly lower using the dual-CT in comparison with EBCT. The underestimation of CAC by MDCT compared with EBCT is related to the higher resolution of the new systems, so that larger blurring effects of the calcification are avoided. Using the thresholds of 100 CAC and 400 CAC, a different classification was found in 4 (7%) of 92 patients only.

For non-calcified plaques, detected by CT-angiography, a highly reproducible method for quantification is yet not available and currently more qualitative instead of quantitative analyses are provided.

### Classification of coronary artery calcification

The CAC scores show an uneven distribution in the general population (Figure 3). Previous and recent outcome studies lead to the proposal in the clinical expert consensus document of the ACCF/AHA in 2007.

1. 0 = no calcification;
2. >0–100 = mild coronary calcification;
3. >100–400 = moderate calcification;
4. >400–1000 = severe calcification;
5. >1000 = extensive calcification.

Modifications were used in the other studies. In the first MESA outcome manuscript, 300 CAC was used for the definition of the high risk. In the Rotterdam study, a CAC level of <50 was found to define the low risk and a CAC level >615 to define the high risk.

### Prevalence of coronary artery calcification

The HNR study as well as the MESA study have looked into the prevalence of CAC in a general population (Figure 4). In the HNR study (n = 4487), more than 20% of men have CAC > 100 and up to 8% CAC > 1000. The prevalence of higher degrees of CAC is much lower in women, so that a value of CAC > 100 is reached only by 10% and CAC > 400 only by 3%. Totally, 82% of men and 55% of women demonstrate CAC. However, in participants of the HNR study with known CAD at baseline (n = 327), the prevalence of CAC was 100% in men and 94% in women. In a younger group of US adults between 33 and 45 years, a prevalence in men of 17.6% and in women of 11.3% was found in whites, but only 5.2 and 4.9% in blacks. In the MESA study of US adults between 45 and 84 years, calcification

![Figure 3](https://academic.oup.com/eurheartj/article-abstract/33/10/1201/486108/43x43x319)

**Figure 3** Density estimates of log c-transformed coronary calcium scores on the bases of histogram analyses for the epidemiology of coronary artery calcification (ECAC) study based in Olmsted county in the USA and the Heinz Nixdorf Recall (HNR) study in Germany. The curved lines represent the shape function kernel (c = 0.3). ECAC epidemiology of coronary calcification study, HNR, Heinz Nixdorf Recall study, Schmermund et al.

![Figure 4](https://academic.oup.com/eurheartj/article-abstract/33/10/1201/486108/43x43x319)

**Figure 4** A prevalence of coronary artery calcification score units according to the different categories of CAC ranging from 0–9 to >1000 units based on data from the Heinz Nixdorf Recall study. Modified according to Erbel et al.
was found in 70.4% in white men and 44.6% in white women. Again, lower rates were found in black, Hispanic, and Chinese US citizens. By matching the group of MESA and HNR, the higher rate of CAC was confirmed for men and women in Europe in comparison with US citizens, which was also obvious in comparison with a different Olmsted County cohort (Figure 3).

Age- and sex-adjusted percentile distribution of coronary artery calcification

Previous studies based on selected cohorts underestimated the risk based on age- and sex-adjusted CAC distribution. This was corrected by true population-based cohorts.

Risk assessment based on percentile distribution for men and women has been published for the HNR and MESA studies. In comparison, it can be shown (Figure 5) that in Germany, the 50th or 90th percentile for men is slightly shifted to the left and for women at the age of 70 years. But the difference is very small and the concordance of the curves impressive. Both studies allow to estimate the individual degree of CAC in comparison with the general population cohorts: www.recall-studie.uni-essen.de, www.mesa-nhlbi.org.

Association of risk factors and coronary artery calcification

Smoking

In order to estimate the effect of risk factors on CAC, plots for different subgroups of the HNR study were defined. For smoking, a striking difference between current smokers, former smokers, and no smoking was found with a 10-year difference in ‘vascular age’ when the degree of calcification in no smokers and current smokers was compared. The degree of CAC in smokers at the age of 65 years reached the degree of no smokers at the age of 75 years. Despite the five-fold difference in the degree of CAC, a 10-year difference was also found in women. Recently, we were able to demonstrate that passive smoking, passive exposure to smoke, was also associated with a slightly higher CAC degree compared with those without exposure to this risk factor.

Diabetes

When compared with the degree of CAC in females with diabetes and non-diabetes, prevalent diabetes demonstrated a difference of 13 years in ‘vascular age’ which decreased to 4 years in those with pre-diabetes. But this difference could not be demonstrated in a similar way in men and was much smaller reaching only a difference between diabetes and non-diabetes of 5 years.

Low density lipoprotein-cholesterol and blood pressure

The effect of risk factors on CAC was again much more obvious in women than men when the effect of LDL-cholesterol and blood pressure was analysed. When comparing women with LDL values <100 mg/dL with those with LDL values >190 mg/dL, a difference of 17 years in ‘vascular age’ was detected.

When comparing women with normal blood pressure and hypertension stage 2, a difference of 17 years in ‘vascular age’ could again been demonstrated. Even in pre-hypertension, a difference to normative women was found. For men, as for diabetics, the difference was much smaller, possibly explained by the strong confounder smoking and ever smoked which was much more prevalent in men than in women.

Figure 5 Comparability of estimated percentiles from the Multi-Ethnic Study of Atherosclerosis (MESA) with the Heinz Nixdorf Recall (HNR) study; MESA estimates are from whites only. Estimated 50th percentile of CAC (A) and estimated 90th percentile of CAC (B). Visualized are the results for men and women in both studies. McClelland et al.
Psychosocial factors
Most important was the aspect that in addition to traditional risk factors, an association of psychosocial factors with CAC could be demonstrated. It could be shown that the higher the educational level, the lower the CAC and therefore the disease extent. This could be verified for men as well as for women. In CAC quartiles, the difference between the lowest income and highest income was 20% in men and 80% in women. However, depressed mood and poor self-perceived health status had a positive constellation with the age-standardized prevalence of cardiovascular risk factors in both sexes and a measurable value of CAC in men, but not in women. In addition, daily long siestas also had a positive association with the prevalence and severity of cardiovascular risk factors and CAC.

Air pollution and traffic exposure
The imaging of CAC as a sign of coronary atherosclerosis seems to be an excellent tool to study the residential exposure to traffic on development of coronary atherosclerosis. With multivariable logistic regression, controlling for background air pollution and risk factors, the prevalence of the CAC was 1.85 (95% CI 1.21–1.84) when compared with participants living >200 m away from the road with traffic. The effects were stronger for men and individuals younger than 60 years as well as those who had never smoked (OR 2.72, 95% CI 1.40–5.29). Compared with participants of the HNR study living 200 m away from major roads (Figure 6), participants living within 50, 51–100, and 101–200 m from these roads an odds ratio of 1.63 (95% CI 1.14–2.33), 1.34 (95% CI 1–1.79), and 1.08 (95% CI 0.85–1.39) for the prevalence of CAC could be demonstrated. The reduction in the distance between the residence and the major road by 50% was associated with a 7% increase in CAC. One possible explanation may be that the traffic exposure is also an exposure to ultrafine and fine particles which are associated with signs of systemic inflammation. In addition to other factors like traffic noise, changes of sympathetic tone blood pressure and heart rate may play an important role.

Inflammatory biomarkers in chronic inflammatory disease and coronary artery calcification
The role of inflammation, which is discussed in the pathogenesis of atherosclerosis since the work of Virchow 100 years ago, is further supported in studies using hs-C-reactive protein as an important and validated biomarker for risk prediction. However, this could not be confirmed by other analysis. The predictive value of hs-C-reactive protein to the FRS in comparison with CAC remained controversial. In the HNR study, the influence of CAC to improve discrimination and reclassification was superior to that of hs-C-reactive protein. Both CAC and hs-C-reactive protein were of similar and additive value to FRS for improved discrimination of all-cause mortality, which was shown by others too. An additional effect was found for those with CAC for coronary events, limited to subjects with low CAC. The MESA study also observed an increased risk in subjects with lower CAC, but high hs-C-reactive protein. Therefore, a combined approach has been suggested and validated to use CAC and hs-C-reactive protein for risk prediction. The strong association between HDL-cholesterol, oxidative stress, and severity of CAC in rheumatoid arthritis further supports the role of inflammation in atherosclerosis.

Role of increased coronary artery calcification in chronic kidney disease (CKD)
Cardiovascular diseases are the main limitations of renal failure due to the development of atherosclerosis but also due to the development of media sclerosis (Moenckeberg)-type atherosclerosis. Coronary artery calcification reaches the highest levels in subjects with renal failure and dialysis already in young adults. Already coronary angiography had demonstrated that CKD is an independent risk factor of CAD, but it has to be taken into account that patients with CKD demonstrate many coronary risk factors. These factors lead to intimal calcification. Medial calcification is found only in CKD.

The degree of CAC seems to be related to the estimated glomerular filtration rate (eGFR) with an OR of 1.53 (95% CI 1.07–2.20) for eGFR > 30 mL/min/1.73 m³ in a multivariate analysis.
Coronary artery calcification for risk prediction of cardiovascular disease

Previous studies using CAC for risk prediction demonstrated that the degree of CAC is strongly associated with future events. Multicentre studies and registries, mainly performed in the USA, indicated that the risk for MI during follow-up increased with CAC > 100 and >400. The threshold of CAC > 1000 was even more predictive and demonstrated event rates of more than 20% within 1 year in asymptomatic and symptomatic patients. Within 5 years, the survival rate was only about 40% in a clinical cohort and hard coronary events occurred in 12% of 149 patients. In 98 asymptomatic subjects with CAC > 1000 followed for roughly 1.5 years, 36% suffered from hard coronary events.

The HNR and MESA studies were designed as prospective observational cohort studies in the 1990s and started 1999/2000 with recruitment up to 2002/2003. The primary hypothesis of the HNR study was to prove that the assessment of CAC is able to predict hard coronary events with a relative risk of 2.5 comparing the fourth and the first quartiles of CAC. The primary endpoints were defined as fatal and non-fatal MI after a follow-up time of 5 years. In the HNR study, 30% of men and 71% of women out of 4487 participants without CAD studied in a cohort from the general population belonged to the low-risk category (<10% events in 10 years), whereas 31% and 9%, respectively, belonged to the high-risk group, and 39% and 20% to the intermediate risk category. After 5.1 ± 0.26 years, primary events occurred in 93 (2.3%) of 4137 participants (30% females). In addition, 107 (2.6%) non-coronary deaths (43% females) occurred. Diabetes was in men two times and in women nearly three times higher than in those without events.

In the HNR study, the event rates (Figure 7) using the FRS or ATP III algorithm were: for the 10–20% threshold, low risk: 1.8 and 1.7%, intermediate risk: 3.2 and 3.3%, and high risk: 5.3 and 4.8% as well as for the 6–20% threshold 0.9 and 0.9%, 2.8 and 2.8%, as well as 5.3 and 4.8%, respectively.

The event rate increased with the degree of CAC. Most importantly, the event rate in women with CAC ≥ 400 was similar to that in men (8.3% in 5 years) (Figure 8). This means that the main determinant for the risk has to be seen in the degree of plaque burden. Based on hard events, we calculated the sensitivity and specificity for the ATP III 10-year risk score thresholds of different percentile distributions of CAC scores (Table 3). For a threshold of CAC ≥ 1000, the positive predictive accuracy reached 15.8% with a negative predictive accuracy still of 99%.

In the HNR study, the FRS reached an AUC of 0.681 (Table 4) and CAC improved the c-statistics significantly to 0.749 (P = 0.0003). For all-cause mortality, the AUC curve was for FRS 0.695, increasing with CAC to 0.719.

In the MESA study (Table 4), major coronary events (MI or cardiac death) were observed in 89 (1.3%) of 6712 participants within 3.8 years. Those with CAC > 100 had a seven-fold increase in odds for developing events, and those with a CAC > 400 demonstrated a 10.3-fold increase in events (Table 6). The
Table 3  Sensitivity, specificity, positive, and negative predictive accuracy for hard events within 5 years in the Heinz Nixdorf Recall study of NECP ATP III Score, CAC percentile threshold, and absolute CAC Score Heinz Nixdorf Recall Study

<table>
<thead>
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<th>Hard events</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
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<tr>
<td>&gt; 10%</td>
<td>55/1387</td>
<td>84.6</td>
<td>30.0</td>
<td>4.0</td>
</tr>
<tr>
<td>&gt; 20%</td>
<td>30/623</td>
<td>46.2</td>
<td>68.6</td>
<td>4.8</td>
</tr>
<tr>
<td>CAC score percentile threshold</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 50th</td>
<td>51/976</td>
<td>78.5</td>
<td>51.1</td>
<td>5.2</td>
</tr>
<tr>
<td>&gt; 75th</td>
<td>30/488</td>
<td>46.2</td>
<td>75.8</td>
<td>6.2</td>
</tr>
<tr>
<td>&gt; 90th</td>
<td>16/190</td>
<td>24.6</td>
<td>90.8</td>
<td>8.4</td>
</tr>
<tr>
<td>CAC score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 0</td>
<td>62/1613</td>
<td>95.4</td>
<td>17.0</td>
<td>3.8</td>
</tr>
<tr>
<td>≥ 100</td>
<td>47/794</td>
<td>72.3</td>
<td>60.5</td>
<td>5.9</td>
</tr>
<tr>
<td>≥ 400</td>
<td>27/328</td>
<td>41.5</td>
<td>84.1</td>
<td>8.2</td>
</tr>
<tr>
<td>≥ 1000</td>
<td>18/142</td>
<td>27.7</td>
<td>93.4</td>
<td>12.7</td>
</tr>
</tbody>
</table>

CAC, coronary artery calcium; NECP s.o. ATP III, National Cholesterol Education Program Adult Treatment Panel III; NPV, negative predictive value; PPV, positive predictive value.

Table 4  Baseline data and c-statistics for MESA, HNR, Rotterdam study using Framingham or ATP III scoring, coronary artery calcium scoring or combination of risk score and coronary artery calcium

<table>
<thead>
<tr>
<th>MESA I87</th>
<th>MESA II145</th>
<th>HNR I8</th>
<th>Rotterdam I124</th>
<th>Rotterdam II88</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>White</td>
<td>Total</td>
<td>Total</td>
<td>Men</td>
</tr>
<tr>
<td>n</td>
<td>6722</td>
<td>2598</td>
<td>5878</td>
<td>4129</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62</td>
<td>63</td>
<td>62</td>
<td>59</td>
</tr>
<tr>
<td>Male (%)</td>
<td>47</td>
<td>47</td>
<td>46</td>
<td>47</td>
</tr>
<tr>
<td>FU time (years)</td>
<td>3.8</td>
<td>3.8</td>
<td>5.8</td>
<td>5.0</td>
</tr>
<tr>
<td>Major CHD events</td>
<td>89</td>
<td>–</td>
<td>122</td>
<td>93</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>72</td>
<td>–</td>
<td>96</td>
<td>64</td>
</tr>
<tr>
<td>CHD death</td>
<td>17</td>
<td>–</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>CPR</td>
<td>–</td>
<td>–</td>
<td>12</td>
<td>–</td>
</tr>
<tr>
<td>AUC ROC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRS</td>
<td>0.79</td>
<td>0.76</td>
<td>0.76</td>
<td>0.681</td>
</tr>
<tr>
<td>ATP III</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.683</td>
</tr>
<tr>
<td>RF + CAC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRS</td>
<td>0.83</td>
<td>0.79</td>
<td>0.81</td>
<td>0.749</td>
</tr>
<tr>
<td>ATP III</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.755</td>
</tr>
<tr>
<td>Δ RF + CAC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRS</td>
<td>0.04</td>
<td>0.03</td>
<td>0.15</td>
<td>0.068</td>
</tr>
<tr>
<td>ATP III</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.072</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRS</td>
<td>0.006</td>
<td>0.10</td>
<td>0.001</td>
<td>0.003</td>
</tr>
<tr>
<td>ATP III</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

*Framingham variable best fitted model.

ATP III, National Cholesterol Education Program Adult Treatment Panel III; AUC, area under the curve; CHD, coronary heart disease; CPR, cardiopulmonary resuscitation; FRS, Framingham Risk Score; FU, follow-up time; HNR, Heinz Nixdorf Recall Study; MESA, Multi Ethnic Study of Atherosclerosis; RF, risk factor; ROC, receiver operating curve; Rotterdam, Rotterdam Coronary Calcification Study.
adjusted risk for events reached 6.84 (2.93–15.99) for participants with CAC.\textsuperscript{87} Also the use of the 75th percentile as a threshold of CAC, which was recommended by NCEP ATP III, did not improve the results obtained by the Agatston method.\textsuperscript{123} In MESA, CAC was shown to be a much more robust predictor of events than C-reactive protein, carotid IMT, and ankle-brachial index, as three other tests advocated as screening tests in an asymptomatic population.

The Rotterdam study started 10 years earlier than HNR and MESA and included a prospective population based on subject age 62–85 years (Table 4). After exclusion of subjects with CAD, 1795 (49%) of 3370 asymptomatic subjects remained in the study.\textsuperscript{124} During a mean follow-up of 3.3 years, 40 (2.2%) of 1795 asymptomatic participants had a hard coronary event, including MI and cardiac death. The relative risk of events was calculated according to a CAC 0–100 as referent (Table 6) yielding for those with CAC 101–400 a value of 2.7 (1.0–7.7), for CAC 401–1000 a value of 4.1 (1.4–11.6), and for CAC > 1000 a value of 8.1 (2.9–22.3).\textsuperscript{124}

After 9.2 years, the study reported 54 CHD deaths and 81 non-fatal MI (8.7%) in this elderly population of 2028 asymptomatic subjects. Framingham Risk Score reached similar values for AUC as in the HNR and MESA.\textsuperscript{88}

**The myth of zero calcium**

Despite an excellent risk prediction related to the different levels of CAC, it has to be taken into account that coronary events rarely occur in the presence of zero CAC.\textsuperscript{125} These events may be related to different pathogenesis including coronary dissection, Tako-Tsubo syndrome, paradoxical embolization, or inflammatory diseases. However, for those with zero calcium, the 5-year event rate was 0.9% in men and 0.8% in women in the HNR study, representing an annual event rate of only 0.16% per year.\textsuperscript{4} In MESA, the event rates were similarly very low for subjects with zero scores with an overall event rate of 0.11% per year.

Other EBCT- as well as MDCT-based studies confirmed the low event rates in individuals with zero CAC.\textsuperscript{126–130}

Recently, 13 out of the 49 studies were selected for inclusion in a meta-analysis with the outcome date in 64 873 patients.\textsuperscript{129} Cardiovascular events occurred in 146 (0.56%) of 25 903 patients with zero CAC during a mean time period >4 years.\textsuperscript{129} The sensitivity reached 98% and the negative predictive accuracy 93% for detection of significant CAD by invasive coronary angiography. In 4870 individuals, even myocardial perfusion was tested and positive exams with typical signs of ischaemia were found in only 6% in the absence of CAC.\textsuperscript{129} In this analysis, the negative predictive accuracy to rule out an ACS was 99%.

The absence of CAC indicates also a very low all-cause mortality.\textsuperscript{128,129} During a follow-up time of 5.6 ± 2.6 years (1–13 years), all-cause mortality was only 0.52% corresponding to 104 events in 19,898 patients.\textsuperscript{53} The projected 10-year event rate reached only 1%.\textsuperscript{53} But those with CAC > 0–10 were at a different risk and need more attention as others also demonstrated.\textsuperscript{85,131}

**Progression of coronary artery calcification**

Zero calcium does not mean that lifelong zero calcium persists.\textsuperscript{132} Progression to the development of calcified coronary atherosclerosis has to be taken into account, which was found in 106 (25.1%) of 422 patients. The rate of conversion was 13.4% in the first 4 years and 25.1% at 5 years.\textsuperscript{132} The progression to calcified disease was non-linear, showing a slow and flat curve in the first two and more rapid increase in the next 3 years which are reflected in the sex- and age-adjusted percentile distribution of CAC.\textsuperscript{94} A repeat CT-scan after a 4-year interval may be considered.\textsuperscript{133} Prospective randomized trials have shown no effect of lipid-lowering therapy on CAC progression.\textsuperscript{134,135} In addition, a conversion to CAC > 0 is not a clinical event and the conversion is not expected to be beyond 100 within the time interval <5 years.\textsuperscript{133} Thus, cost savings in such a group of patients during a 3–5-year period could be of great magnitude.\textsuperscript{133} Stress testing in asymptomatic patients with multiple risk factors is currently a class IIb indication according to the ACC/AHA with CAC testing accruing a class IIa indication.

Physicians have to take into account that the CAC progression rate ranges from 15 to 25% per year.\textsuperscript{136} In a group with a mean age of 59 years, the mean annual relative progression of CAC was 51% and the median progression 32%.\textsuperscript{137} Other authors found a mean annual increase in the range of 24–33% \textsuperscript{137–141} (Figure 9). The risk of progression is predicted by male sex, hyperlipidaemia, smoking, and baseline CAC scores, followed by hypertension, diabetes, and older age.\textsuperscript{132} Diabetes and smoking were found to be the strongest predictors.

**Low-risk asymptomatic subjects and progression of coronary artery calcification**

Individuals with CAC > 0 and <100 are regarded to have a low plaque burden and a low event rate. This group compromised 30% of the male and 72% of the female cohort in the HNR study. The event rate reached an extrapolated 10-year risk of coronary events of 3.1% in men and 1.2% in women.\textsuperscript{6} In these individuals, lifestyle changes and non-pharmacological therapy and reassessment after 3–5 years are recommended.\textsuperscript{25,131–133} Coronary artery calcification screening can thus not be recommended because the reclassification for those with CAC > 400 is not reaching the high risk level >20% 10-year risk.\textsuperscript{142} An increase in CAC with age may change the advice concerning pharmacotherapeutic interventions when the critical level of CAC 100 is exceeded.\textsuperscript{143}

**Intermediate risk individuals and reclassification effect of coronary artery calcification**

According to the Bayesian approach, CAC scanning is most effective in intermediate risk asymptomatic subjects and recommended by the ACCF/AHA guidelines for the assessment of risk in asymptomatic adults (class IIa).\textsuperscript{144} The recommendations are particularly based on the MESA study, which demonstrated risk prediction and
risk classification using CAC during a follow-up time of 5.8 years \(^{145}\) (Table 5). The entire endpoints in 209 (3.6%) of 5878 participants consisted of coronary events with 96 MI, 14 deaths, and 12 resuscitated cardiac arrests as well as 87 probable or definite angina pectoris cases. In the intermediate risk group (3–10%), 25% were reclassified (Table 5).\(^{145}\) The net reclassification improvement was for the entire cohort 25% and for the intermediate cohort 23%. The higher risk category had an event rate of 8.7% and the lower risk group of 2.7% with a 5-year event rate for the entire cohort of 3.1%. Those who were upgraded had in 16.4% an event, and those who were downgraded had an event in 2.3%\(^ {145}\). In the intermediate risk score cohort, 16% were reclassified as high risk and 39% at low risk which resulted in a net reclassification improvement of 55%\(^ {145}\).

In the HNR study, 57% of male and 64% of female subjects in the intermediate group were reclassified as the low-risk category\(^ {91}\). Only 6.6% of the total intermediate group remained in the intermediate category and would need reassessment during follow-up or additional analysis of signs of atherosclerosis in other vascular territories. The HNR study yielded a net reclassification improvement for hard coronary events of 21.7% for the narrow (10–20%/10-year risk) and 30.6% for the wider FRS 6–20%/10-year risk thresholds, respectively.\(^ {145}\) Using the NCEP ATP III categories, the HNR study could demonstrate a reclassification improvement of 18.3% and 29%, respectively, for the different ranges of intermediate risk definitions.\(^ {9}\) The integrated discrimination improvement using FRS variables and CAC was 1.52% (\(P < 0.0001\)).

Also the Rotterdam study presented the effect of reclassification in the intermediate risk group defined as 10–20% 10-year risk.\(^ {88}\) A total of 52% of men and women were reclassified, all into more accurate categories.

In asymptomatic patients the Saint Francis Heart study demonstrated reclassification in 73% of patients.\(^ {86}\)

### High-risk individuals and reclassification effect of coronary artery calcification

Currently, there is no overall agreement that subjects in high-risk categories, showing low CAC scores, can be treated differently compared with those with high CAC scores, because there is no evidence that preventive interventions alone can safely be indicated for subjects at high risk.\(^ {142–145}\) In those with excessive CAC (>400), the reported event rates and the positive predictive accuracy seem to be so high, that in these subjects additional diagnostic work up seems to be needed, in order to detect signs of myocardial ischaemia which would classify for coronary angiography and further revascularization.\(^ {131}\)

### Limitation of CAC screening

**X-ray exposure and safety for screening**

In recent years, the EBCT has been replaced by MDCTs, increasing the question of safety according to the X-ray exposure, which was 0.8–1.3 mSv for EBCT compared with higher values in the beginning of conventional CTs.\(^ {71}\) Meanwhile, many attempts have been made to reduce the X-ray exposure by CT including prospective instead of retrospective gating, limiting the scan field, and using the flash technique.\(^ {72–74}\) Thus, the X-ray exposure could be reduced to 0.8–1.0 mSv or even less.

It was estimated that a single CT scan at the age of 55 years may lead to a lifetime excess risk of 8 and 20 cancers per 100 000 persons for men and women, respectively.\(^ {76}\) Others used a presumption of a screening scan every 5 years from the age of 45–75 years in men and 55–75 years in women.\(^ {147}\) Important to note that lifetime risk of dying from malignancy is about 21% in the USA.\(^ {147}\) A CT scan with 1 mSv would add 0.005% to this risk.

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Table 5: Reclassification rate in three predictive risk groups using coronary artery calcification defined low, intermediate and high risk thresholds

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>MESA (^{145})</th>
<th>HNR (^4)</th>
<th>Rotterdam (^{88})</th>
<th>Male/female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk (%)</td>
<td>11.6</td>
<td>15</td>
<td>12</td>
<td>15/9</td>
</tr>
<tr>
<td>Definition (%)</td>
<td>0–3</td>
<td>0–10</td>
<td>0–10</td>
<td>10–20</td>
</tr>
<tr>
<td>Intermediate risk (%)</td>
<td>54.4</td>
<td>65.0</td>
<td>52.9</td>
<td>51/53</td>
</tr>
<tr>
<td>Definition (%)</td>
<td>3–10</td>
<td>10–20</td>
<td>10–20</td>
<td>10–20</td>
</tr>
<tr>
<td>High risk (%)</td>
<td>35.8</td>
<td>15.5</td>
<td>34</td>
<td>33/39</td>
</tr>
<tr>
<td>Definition (%)</td>
<td>&gt;10</td>
<td>&gt;20</td>
<td>&gt;20</td>
<td></td>
</tr>
<tr>
<td>Total (%)</td>
<td>26.2</td>
<td>21.7/22.4(^4)</td>
<td>21.9</td>
<td>29.5/16.1</td>
</tr>
</tbody>
</table>

Total (%) means reclassification rate in the three studies. \(^6\) for FRS/ATP III.
percentage, so that the expected rate for malignancy would increase to 21.005%.

The ratio of risk and benefit of coronary artery calcification screening

Screening for risk stratification is an important issue. The risk–benefit ratio seems to be in favour of CAC quantification in asymptomatic subjects with no previous history of CAC and intermediate risk for coronary and cardiovascular events (Table 6). However, the risk of developing cancer may play only a minor role, when persons with high risk due to their profession are undergoing a check-up assessment like pilots, who have a much higher continuous X-ray exposure during flights than a scan which may be performed once at the age of 45 or 65 years, when fitness is tested. Similar important considerations can be applied for other individuals who are at the stage when they are planning a new position or face career-related decisions. Also individuals starting an extreme sport activity, which by itself may present a high risk, such as mountain biking, marathon running and other disciplines are those in whom risk–benefit consideration may change. And in addition, the knowledge of CAC may stimulate risk preventive behaviour.

Conclusion

Computed coronary tomography allows for quantification and localization of CAC as a sign of subclinical atherosclerosis. The SHAPE (Screening for Heart Attack Prevention and Education) Task Force presented a practice guideline for cardiovascular screening in the asymptomatic risk population based on signs of subclinical atherosclerosis. This practice guideline could, however, not be based on prospective observational cohort studies, which are now available and thus these aspects were further emphasized including other tasks for subclinical atherosclerosis such as ultrasound of the carotid artery and screening with biomarkers.

Coronary artery calcification can be used for risk stratification and has already received a class IIa recommendation by the ACC/AHA. Coronary artery calcification should be in the focus of cardiologists particularly for those who are interested in preventive cardiology because important and unique insights in CAD can be provided. Coronary atherosclerosis represents the memory of lifetime risk factor exposure, and has a significant short-term and intermediate term prognostic implication. Our colleagues who experienced a sudden fatal event just like thousands of other people, unaware of their risk, should stimulate us to improve primary prevention by using signs of subclinical atherosclerosis as a marker of risk.

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References

Improvement of CR prediction using coronary imaging


Stary HC. Evolution and progression of atherosclerotic lesions in coronary arteries of children and young adults: Arteriosclerosis. Klinische Studien. 47. Edgren JG.


