European Heart Journal (2014) **35**, 2960–2971
doi:10.1093/eurheartj/ehu288

Progression of coronary artery calcification seems to be inevitable, but predictable - results of the Heinz Nixdorf Recall (HNR) study†

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Received 28 January 2014; revised 3 June 2014; accepted 23 June 2014; online publish-ahead-of-print 25 July 2014

See page 2934 for the editorial comment on this article (doi:10.1093/eurheartj/ehu377)

Aim Coronary artery calcification (CAC), as a sign of atherosclerosis, can be detected and progression quantified using computed tomography (CT). We develop a tool for predicting CAC progression.

Methods and results In 3481 participants (45–74 years, 53.1% women) CAC percentiles at baseline (CAC_b) and after five years (CAC_{5y}) were evaluated, demonstrating progression along gender-specific percentiles, which showed exponentially shaped age-dependence. Using quantile regression on the log-scale ($\log(CAC_b+1)$) we developed a tool to individually predict CAC_{5y}, and compared to observed CAC_{5y}. The difference between observed and predicted CAC_{5y} (log-scale, mean $\pm$ SD) was 0.08 ± 1.11 and 0.06 ± 1.29 in men and women. Agreement reached a kappa-value of 0.746 (95% confidence interval: 0.732–0.760) and concordance correlation (log-scale) of 0.886 (0.879–0.893). Explained variance of observed by predicted $\log(CAC_{5y}+1)$ was 80.1% and 72.0% in men and women, and 81.0 and 73.6% including baseline risk factors. Evaluating the tool in 1940 individuals with $CAC_b>0$ and $CAC_b<400$ at baseline, of whom 242 (12.5%) developed $CAC_{5y}>400$, yielded a sensitivity of 59.5%, specificity 96.1%, (+) and (−) predictive values of 68.3% and 94.3%. A pre-defined acceptance range around predicted CAC_{5y} contained 68.1% of observed CAC_{5y}; only 20% were expected by chance. Age, blood pressure, lipid-lowering medication, diabetes, and smoking contributed to progression above the acceptance range in men and, excepting age, in women.

Conclusion CAC nearly inevitably progresses with limited influence of cardiovascular risk factors. This allowed the development of a mathematical tool for prediction of individual CAC progression, enabling anticipation of the age when CAC thresholds of high risk are reached.

Keywords Coronary artery calcification • Progression of atherosclerosis • CT • Imaging • Heinz Nixdorf Recall study • Epidemiology

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†The data of the manuscript will in part be presented at the ESC congress in Barcelona 2014.

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Introduction

Coronary atherosclerotic lesions often contain calcified components, which can be detected using computed tomography (CT) and quantified by the Agatston method.[1] Longitudinal assessment of coronary artery calcium (CAC) burden allows the quantification of progression of coronary artery disease.[2] An annual score increase >15% is associated with an enhanced risk of myocardial infarction,[3,4] and a higher CAC burden carries a greater risk for future coronary heart disease (CHD) events and all-cause mortality.[5]

While CAC is associated with many cardiovascular risk factors, overall explanation of variance of CAC by risk factors is limited. Major risk factors such as low-density lipoprotein cholesterol (LDL-C) and hypertension showed only weak associations with CAC, explaining a variance of <5% for a single risk factor and <25% for established risk factors.[6,7] Also risk modifying medical therapy, known to reduce risk for CV events,[8] showed no reduction or attenuation of CAC progression.[9–12]

Coronary artery calcification scores in an European unselected population were similar to an American cohort despite differences in a risk factor profile,[13] subsequently confirmed for the comparison with the multi-ethnic study of atherosclerosis (MESA).[14] This study, however, showed that the prevalence and amount of CAC are heavily influenced by ethnicity in addition to age and gender. Thus, genetic factors seem to influence CAC and even CAC progression beyond what is captured by risk factors including a family history of CHD.[15] Nevertheless, Leopold[16] pointed out recently that new experimental studies suggest that vascular calcification is not inevitable and can be ameliorated. We have previously demonstrated that the rate of CAC progression at a time is proportional to pre-existing CAC.[17] We thought, that, if this mechanism and heritable influences are the major determinants of CAC progression combined with a minor influence of the risk factor profile, than it should be possible to predict the progression of CAC based on a single CAC measurement. Therefore, the aim of this study was to measure the progression of CAC with the same CT technology over a time period of 5 years and derive a new mathematical tool for prediction of CAC progression.

Methods

Study participants

Between December 2000 and August 2003, the Heinz Nixdorf Recall (HNR) study recruited a total of 4814 Caucasians (age 45–75 years) from the three cities in the Ruhr area, Germany.[18] Subjects with prior coronary artery disease (coronary artery bypass surgery and/or interventional revascularization procedures and history of prior myocardial infarction) were excluded. In 4275 (95.3%) of 4487 participants (2027 men and 2248 women) electron beam CT was performed at baseline. Individuals were followed with a second CT after a mean of 5.1 ± 0.3 years (4.2–7.5 years) scans. A total of 3481 participants (53% women) had complete CAC data at baseline (CAC_b) and at follow-up (CAC_{5y}); 156 died before the 5-year follow-up, 47 had non -fatal myocardial infarctions, 107 coronary revascularizations, 407 cancelled , 28 had missing risk factors, 12 were out of the age range. All the participants provided written informed consent and the study had been approved by the ethical committee at the University Clinic Essen, Germany. The study was certified and recertified according to DIN EN ISO 9001:2000/2008.

Computed tomography

Computed tomography scans were performed with a C-100 and C-150 scanner (GE, Imatron, South San Francisco, CA, USA) in two radiology institution (D.G. and R.S.) at baseline.[13] The 5-year follow-up CT was performed at the Radiology Department of the Alfred Krupp-Hospital, Essen (T.B. and M.M.) also with a C-150 scanner. The CTs were operated in the single-slice mode with an image acquisition time of 100 ms. A slice thickness of 3 mm was chosen. Prospective ECG-triggering was done at 80% of the R–R interval.[13] Contiguous slices down to the apex of the heart were obtained. The CAC score was determined using the methods of Agatston *et al.*[1] At least four contiguous pixels with a CT density ≥130 Hounsfield Units were used to define an area of CAC. The total CAC score was computed, comprising all calcified lesions in the coronary system. Analyses were performed using a Virtuoso workstation (Siemens Medical Solutions, Forchheim, Germany).[13] Computed tomography scan results were not disclosed to the participants or the study centre.

Follow-up data collection

Annual postal questionnaires and a second medical examination assessed the morbidity health status during the follow-up, i.e. hospital admissions, outpatient diagnoses of cardiovascular (CV) disease.[19]

Risk factor analyses

Cardiovascular risk factors were assessed at baseline and after 5 years. The methodology has recently been published.[19] Smoking behaviour was assessed in detail.[20] The body mass index (BMI: kg/m^2) was calculated using height and weight measurements. Total cholesterol, high-density lipoprotein (HDL-C) cholesterol, and triglycerides as well as low-density lipoprotein (LDL) cholesterol were measured with the standard enzymatic methods.[7] Use of lipid-lowering medication was documented. Blood pressure was measured using an oscillometric method (Omron; Netherlands). The mean value of the second and third of three measurements taken at least 2 min apart was used.[6] Hypertension was defined as systolic or diastolic blood pressure ≥140 or ≥90 mmHg, respectively, or the use of antihypertensive medication.[6] Blood glucose was measured after overnight fasting 9.7 ± 4.9 h (median 12 h). Participants were classified as diabetics when glucose exceeded ≥126 mg/dL or reported use of insulin or oral hypoglycaemic agents.[21] From the respective risk factors, the Framingham risk equation was used to predict the 10- year probability of CHD (10-year CHD risk) at baseline and follow-up.[19] Serum creatinine was measured (Advia Clinical Chemistry Analyzer, Siemens HealthCare Diagnostics, Eschborn, Germany) and glomerular filtration rate (GFR in millilitres per minute per 1.73 m^2 of BSA) was estimated. High-sensitive C-reactive protein was determined (BN-II, Siemens HealthCare Diagnostics, Germany). Homocysteine was measured using a fluorescence polarization immunoassay (IMx, Abbott Laboratories, USA). All analyses were done within 12 h at one central laboratory (D.F.).

Statistical analysis

Continuous data were depicted as means ± SD, and in the case of substantially skewed distribution also as median (Q1, Q3); count data as frequency and percentage. Demographics and risk factors at baseline (b) and after 5 years (5y) were given in quartiles/upper deciles of CAC_b and CAC_{5y}, respectively. To evaluate the relationship between CAC groups and continuous data, we used a Spearman correlation test for trend with CAC groups, and for count data a Cochran–Armitage test for trend.

In a first step, age- and sex-related percentiles of CAC distribution for baseline and 5-year follow-up data were analysed. Previously, we had shown that the graphical presentation of percentiles such as the 50th, 75th, and 90th percentiles calculated from linear quantile regression of

log(CAC + 1) on age showed an exponential curvature during ageing.[14,17] This reflects the natural history of CAC with a progression of CAC proportional to the given CAC_b value.[17]

To prove that also the CAC progression for individual participants follow such an exponential curvature of CAC distribution, we developed a new mathematical tool (*Figure 1*). Therefore, we performed a linear quantile regression analysis from the baseline data set of the form $\log(CAC_b + 1) = I + \beta \cdot \text{age}$ in 0.05 quantile steps, starting at 0.025 up to 0.975 getting a total of 20 quantiles. Each step yields an intercept (I) and a slope parameter (β), which is demonstrated in *Figure 1* for the 50th, 75th, and 90th percentiles. To interpolate between these straight lines, both I and β were fitted as functions of quantile (Q) using quadratic equations (see Supplementary material online). In short, to determine a subject's percentile at baseline in two steps, we first identified the percentile (resolution 5%) pertaining to the straight line fit $I + \beta \cdot \text{age}$, which is closest to the subject's coordinates (determined by age, gender, and CAC_b). Second we refined, by selecting the solution of the respective quadratic equation which is closest to the first, the coarse-grained prediction.

Our hypothesis was that the individual CAC value increases with age along the given percentile at baseline. Therefore, we calculated

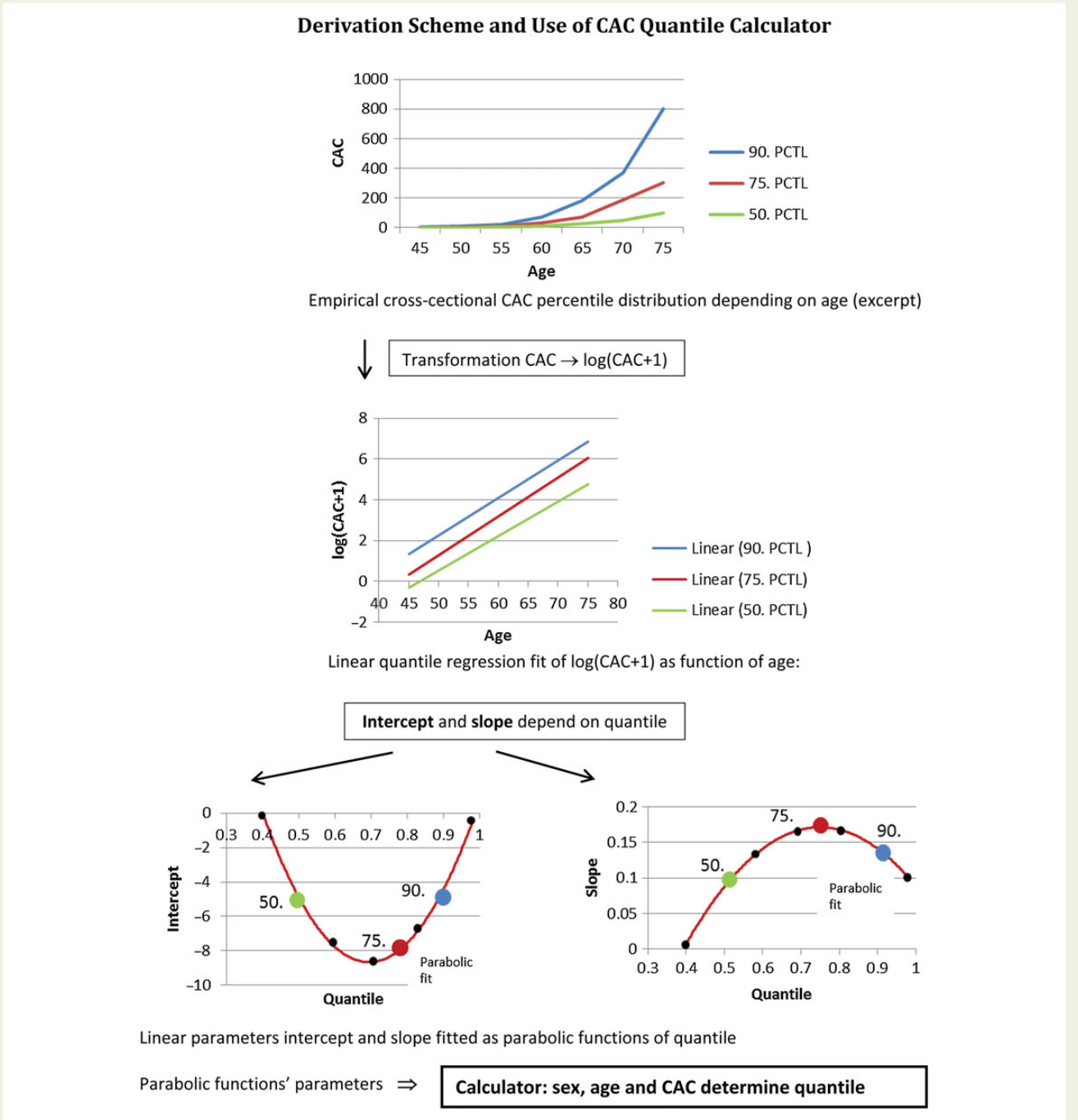

Figure 1 Derivation scheme and use of coronary artery calcification quantile calculator.

$\log(CAC_{5y}+1)$ using only the baseline CAC_b quantile Q_b, gender, and increased age by time between the two CTs (time) from $\log(CAC_{5y}+1) = l(Q_b) + \beta(Q_b)\cdot(\text{age}+\text{time})$. (see Appendix). Note that time between scans is a random variable, not necessarily equal to 5 years.

In a next step, we compared the predicted with the observed CAC_{5y} progression after the 5-year interval. First we evaluated the number of participants for the total cohort who would be correctly classified. In addition, (multivariable) linear regression analysis for $\log(CAC_{5y}+1)$ as function of the predicted value (plus risk factors) gives the percentage of explained variance (coefficient of determination). Agreement statistics (weighted kappa and concordance correlation coefficient) were calculated as well. For kappa, we used the ordinal categories of CAC 0, CAC1-9.9, CAC10-99.9, CAC100-399.9, CAC > 400. Here, a predicted value below one was counted as zero (left truncation).

We also analysed the predictive ability for exceeding the cut-point of CAC = 400 at follow-up among subjects with baseline CAC > 0 but <400. The influence of risk factors was assessed, when the observed CAC_{5y} exceeded the threshold of CAC = 400, when the predicted CAC_{5y} was <400, using multivariable logistic regression.

Furthermore, we define a 20%-acceptance range delta (Δ) for the predicted CAC values, which is skewed with respect to the quantile Q, i.e. for $Q = 0.8$ (80th percentile), the range is 0.64–0.84. The corresponding formula for calculating the Δ is given in the Appendix. We calculated the fractions of subjects with Q_{5y} below and above the accepted range. The influence of classical risk factors and the presence of CV medication on the probability to exceed the range was modelled using multivariable logistic regression analysis.

In a final step, we attempted to predict the age at which a subject on the Qth quantile would reach a clinically relevant CAC threshold (like CAC = 100 or CAC = 400). We could solve the sex-specific equations $\log(u+1) = l(Q) + \beta(Q)\cdot\text{age}(u,Q)$ for age, using the continuous coefficients given in the appendix. This resulted in a rational function (quotient of two quadratic polynomials).

Results

The baseline demographics of the cohort of 3481 participants, who underwent baseline and 5-year follow-up CTs are given in *Table 1* for men and women. The male cohort is subdivided in five categories according to the percentiles of the CAC distribution: 0–25th, 25–50th, 50–75th, 75–90th, and >90th percentiles (*Table 1*). The female cohort was subdivided in four categories, because in women CAC values were 0 up to the 40th percentile (*Table 1*). In men, all baseline risk factors showed a significant association with CAC except for HDL-C, serum creatinine and GFR. For women the association to risk factors was similar, but not significant for smoking and serum creatinine.

After 5 years, the demographics in men show a higher BMI with a higher prevalence of obesity and diabetes and higher HbA1c level (*Table 2*). Systolic blood pressure was higher and diastolic blood pressure lower despite a higher use of antihypertensive agents. On the other hand, we found a lower prevalence of smoking as well as lower LDL-C levels with a higher rate of lipid-lowering medication. The 5-year follow-up data in women showed very similar trends in comparison with men (*Table 2*).

For the male and female cohort, the CAC values for the 10th , 25th, 50th,75th, 90th, and 95th percentiles of the CAC distribution are listed for the baseline and 5-year follow-up CTs (Appendix Table A1–4). After 5 years, the graphics of the age- and gender-related percentiles of CAC distribution showed a nearly indistinguishable curvature in comparison with the baseline results except for men in the highest percentile of CAC (*Figure 2*). Based on this observation, we tested the hypothesis that not only for the total cohort, but also for individual participants the progression of CAC over time follows an exponential curvature once the calcification process has started. The derived mathematical tool was used to predict the individual CAC progression rate.

Residual and correlation analysis showed that (i) the mean differences between the observed and the predicted $\log(CAC_{5y}+1)$ were close to 0; 0.08 ± 1.11 in 1633 men and 0.06 ± 1.29 in 1848 women, (ii) the coefficient of determination between the observed and predicted $\log(CAC_{5y}+1)$ was $R^2 = 0.801$ in men and $R^2 = 0.720$ in women. This corresponds to an explained variance of log-transformed CAC_{5y} of 80.1 and 72.0% in men and women. When we adjusted for baseline risk factor including medication the values increased to $R^2 = 0.810$ for men and $R^2 = 0.736$ for women (explained variance: 81.0 and 73.6%), respectively. Overall agreement between observed and predicted CAC values reached a kappa value of 0.746 (95% CI: 0.732–0.760) and a concordance correlation on the log-scale of 0.886 (95% CI: 0.879–0.893).

To demonstrate the benefit of our approach, we plotted the predicted age (at which a CAC value is reached) vs. the percentile based on our mathematical tool for CAC = 10, CAC = 20, CAC = 50, CAC = 100, CAC = 200, CAC = 400. For CAC = 400, we also plotted the corresponding acceptance limits (*Figure 3A*). Thus, the age can be predicted at which an interesting threshold of CAC is reached. For instance, when the baseline CAC value in an individual man corresponds to the 40th percentile, CAC = 100 is reached at the age of 69.4 (64.2–73.6) years and CAC = 400 at the age of 77.7 (73.5–81.7) years. On the other hand, if it corresponds to the 80th percentile, CAC = 100 is reached at 48.3 (44.7–58.6) years and CAC = 400 at 63.3 (61.3–69.6) years. For women, predicted age at a given CAC percentile is much higher and shown in *Figure 3B*. Women with CAC values below the 50th percentile will not reach CAC = 100 until the age of 85 years and those with a level below the 70th percentile reach the CAC = 100 threshold not before the age of ~70 years. CAC = 100 is predicted to be reached by women on the 80th percentile at 65.4 (63.1–74.6) years, and CAC = 400 at 73.4 (71.5–82.9) years.

Overall, the observed CAC values were in 68.1% of the cohort (men: 67.1%; women: 69.1%) within the pre-defined 20%-acceptance range, while 19.4% of the cohort (20.0 and 18.8%, respectively) had a higher observed CAC value and 12.5% (12.9 and 12.1%) a lower CAC value than predicted. Please note that by chance assignment we expected 20% in a pre-specified acceptance range around the predicted values. However, our calculation demonstrates that more than two-thirds of observed CAC values after 5 years were included. Multivariable logistic regression analysis (*Table 3*) showed that in men, age, systolic blood pressure, diabetes, and smoking as well lipid-lowering medication contributed significantly to the probability for CAC progression above the predicted value. In women similar odds ratios were found except for the factor age in women.

To further test the accuracy of our mathematical tool, we selected 1940 participants, who had a baseline CAC between 0 and 400. Out of these 242 (12.5%) participants had a CAC score of >400 after 5 years; 163 (15.3%) of 1068 men and 79 (9.1%) of 872 women.

Table 1 **Baseline characteristics by 25th/50th/75th/90th percentiles in men and 50th/75th/90th in women of coronary artery calcification distribution 2.3/41.0/192.6/557.0 and 0/1.0/24.5/139.8, respectively**

	1633 men CAC_b percentile						1848 women CAC_b percentile				
	0–25th	25–50th	50–75th	75–90th	>90th	*P* for trend	0–50th	50–75th	75–90th	>90th	*P* for trend
n (%)	403 (24.7)	413 (25.3)	408 (25.0)	245 (15.0)	164 (10.0)	n.a.	915 (49.5)	471 (25.5)	277 (15.0)	185 (10.0)	n.a.
Age (years)	55.1 ± 7.0	57.6 ± 7.0	60.1 ± 7.1	61.1 ± 7.0	63.5 ± 6.8	<0.0001	56.7 ± 7.1	59.0 ± 7.3	62.4 ± 7.1	64.7 ± 6.6	<0.0001
BMI (kg/m^2)	26.6 ± 3.0	28.4 ± 3.6	28.3 ± 3.8	28.4 ± 3.9	28.3 ± 3.3	<0.0001	26.2 ± 4.2	28.4 ± 4.8	28.0 ± 5.8	28.9 ± 5.3	<0.0001
Obesity (BMI ≥30 kg/m^2)	43 (10.7)	115 (27.9)	116 (28.5)	69 (28.3)	50 (30.5)	<0.0001	153 (31.7)	173 (36.8)	85 (30.7)	72 (39.1)	<0.0001
Diabetes (%)	37 (9.2)	58 (14.0)	59 (14.5)	44 (18.0)	41 (25.0)	<0.0001	35 (3.8)	45 (9.6)	37 (13.4)	35 (18.9)	<0.0001
HbA1c (%)	5.4 ± 0.6	5.6 ± 0.9	5.6 ± 0.8	5.7 ± 1.1	5.7 ± 0.9	<0.0001	5.3 ± 0.7	5.4 ± 0.6	5.5 ± 0.7	5.7 ± 1.0	<0.0001
Systolic BP (mmHg)	131.9 ± 16.7	136.0 ± 18.3	138.5 ± 18.7	140.6 ± 19.3	146 ± 19.9	<0.0001	122.7 ± 19.0	129.3 ± 20.2	130.9 ± 19.4	138.4 ± 22.0	<0.0001
Diastolic BP (mmHg)	83.1 ± 9.6	84.8 ± 11.0	84.5 ± 10.3	84.8 ± 10.4	85.6 ± 10.0	0.0033	77.4 ± 10.0	80.2 ± 10.6	79.6 ± 10.3	80.5 ± 10.9	<0.0001
Hypertension (%)	169 (41.9)	219 (53.0)	269 (65.9)	166 (67.8)	135 (82.3)	<0.0001	329 (36.0)	235 (49.9)	160 (57.8)	138 (74.6)	<0.0001
Antihypertensive medication (%)	79 (19.6)	108 (26.2)	139 (34.1)	85 (34.7)	80 (48.8)	<0.0001	196 (21.4)	160 (34.0)	105 (37.9)	106 (57.3)	<0.0001
Never smoking (%)	134 (33.3)	137 (33.2)	132 (32.4)	55 (22.5)	39 (23.8)	0.023	498 (54.4)	272 (57.8)	161 (58.1)	102 (55.1)	0.18
Former smoking (%)	174 (43.2)	183 (44.3)	178 (43.6)	118 (48.2)	89 (54.3)	0.023	241 (13.0)	100 (21.2)	60 (21.7)	37 (20.0)	0.18
Present smoking (%)	95 (23.6)	93 (22.5)	98 (24.0)	72 (29.4)	36 (22.0)	0.023	176 (19.2)	99 (21.0)	56 (20.2)	46 (24.9)	0.18
LDL-C (mg/dL)	141.6 ± 36.0	146.9 ± 35.5	150.8 ± 34.6	148.8 ± 33.0	149.6 ± 36.7	0.0002	139.7 ± 34.2	147.2 ± 37.8	154.9 ± 35.7	154.7 ± 35.8	<0.0001
HDL-C (mg/dL)	53.2 ± 14.8	51.2 ± 13.7	51.5 ± 13.9	51.2 ± 13.4	51.6 ± 14.5	0.10	67.4 ± 16.8	64.9 ± 17.7	63.6 ± 15.5	64.2 ± 16.6	<0.0001
ApoB (mg/dL)	109.6 ± 26.2	116.2 ± 25.5	117.6 ± 27.0	118.4 ± 22.9	117.6 ± 26.5	<0.0001	106.1 ± 42.3	110.7 ± 31.9	117.2 ± 24.7	118.1 ± 26.6	<0.0001
Lipid-lowering medication (%)	16 (4.0)	30 (7.3)	29 (7.1)	33 (13.5)	28 (17.1)	<0.0001	46 (5.0)	53 (11.3)	35 (12.6)	40 (21.6)	<0.0001
Framingham risk score (%/10 years)	11.4 ± 7.1	13.9 ± 8.3	16.5 ± 9.2	17.4 ± 9.0	20.4 ± 10.1	<0.0001	5.9 ± 4.0	8.0 ± 5.2	9.2 ± 5.5	10.9 ± 5.6	<0.0001
High-sensitive C-reactive protein (mg/L)	2.6 ± 7.6	2.8 ± 5.6	2.7 ± 5.7	3.5 ± 9.7	2.9 ± 3.3	<0.0001	2.4 ± 6.0	4.0 ± 21.7	2.8 ± 3.4	3.4 ± 4.8	<0.0001
Serum creatinine (mg/dL)	1.0 ± 0.3	1.0 ± 0.2	1.0 ± 0.2	1.0 ± 0.2	1.0 ± 0.1	0.54	0.8 ± 0.1	0.9 ± 0.3	0.9 ± 0.2	0.9 ± 0.1	0.079
GFR (mL/min/1.73 m^2)	84.7 ± 18.0	85.3 ± 18.1	83.8 ± 20.0	82.3 ± 16.2	82.2 ± 15.9	0.0049	78.0 ± 19.5	75.9 ± 18.3	74.6 ± 14.6	73.0 ± 13.8	0.0001
GFR < 60 (mL/min/1.73 m^2)	18 (4.5)	11 (2.7)	17 (4.2)	10 (4.1)	5 (3.1)	0.77	74 (8.1)	61 (13.0)	35 (12.7)	32 (17.3)	<0.0001
Homocystein (μmol/L)	11.7 ± 3.2	12.0 ± 4.1	12.1 ± 4.3	12.5 ± 3.8	12.6 ± 3.8	<0.0001	11.5 ± 35.0	10.7 ± 3.1	11.7 ± 6.7	12.2 ± 4.0	<0.0001

apo B, apoliporotein B; BMI, body mass index; CAC, coronary artery calcification; systolic/diastolic BP, systolic/diastolic blood pressure; HbA1c, haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; GFR, glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; *n*, number of participants; b, baseline values.

Table 2 **Five-year follow-up characteristics by 25th/50th/75th/90th percentiles in men and 50th/75th/90th in women of coronary artery calcification distribution 7.2/94.9/376.0/999.2 and 1.6/68.2/291.6, respectively**

	1633 men CAC_{5y} percentile						1848 women CAC_{5y} percentile				
	0–25th	25–50th	50–75th	75–90th	>90th	*P* for trend	0–50th	50–75th	75–90th	>90th	*P* for trend
n (%)	406 (24.9)	410 (25.1)	408 (25.0)	245 (15.0)	164 (10.0)	n.a.	917 (49.6)	469 (25.4)	277 (15.0)	185 (10.0)	n.a.
Age (years)	59.6 ± 6.4	63.5 ± 7.2	65.3 ± 7.1	66.3 ± 7.0	68.2 ± 6.8	<0.0001	61.3 ± 6.8	65.3 ± 7.2	67.5 ± 7.4	69.8 ± 6.6	<0.0001
BMI (kg/m^2)	27.4 ± 3.6	28.3 ± 3.9	28.7 ± 3.8	28.6 ± 3.9	28.8 ± 3.3	<0.0001	27.4 ± 4.9	28.0 ± 5.2	28.2 ± 5.3	29.5 ± 5.6	<0.0001
Obesity (BMI ≥30 kg/m^2)	71 (17.5)	119 (29.1)	126 (31.0)	77 (31.7)	56 (34.2)	<0.0001	243 (26.5)	142 (30.4)	94 (33.9)	81 (44.0)	<0.0001
Diabetes (%)	48 (11.8)	83 (20.2)	95 (23.3)	58 (23.7)	62 (37.8)	<0.0001	80 (8.7)	63 (13.4)	46 (16.6)	54 (29.2)	<0.0001
HbA1c (%)	5.5 ± 0.6	5.7 ± 0.9	5.8 ± 0.9	5.8 ± 1.0	6.0 ± 1.0	<0.0001	5.5 ± 0.6	5.6 ± 0.6	5.8 ± 0.7	5.9 ± 0.8	<0.0001
Systolic BP (mmHg)	132.2 ± 16.7	138.3 ± 19.5	139.9 ± 19.8	142.4 ± 18.0	143.1 ± 19.7	<0.0001	126.0 ± 18.0	133.2 ± 19.3	133.5 ± 21.1	137.3 ± 21.5	<0.0001
Diastolic BP (mmHg)	81.0 ± 10.2	82.6 ± 10.8	81.9 ± 10.5	82.0 ± 10.4	79.9 ± 11.3	0.0033	77.0 ± 9.7	78.3 ± 9.5	77.7 ± 10.4	77.2 ± 10.9	0.16
Hypertension (%)	200 (49.4)	295 (72.0)	291 (71.7)	190 (77.6)	141 (86.0)	<0.0001	430 (46.9)	302 (56.0)	186 (67.2)	149 (81.0)	<0.0001
Antihypertensive medication (%)	112 (27.6)	180 (43.9)	198 (48.5)	136 (55.5)	118 (72.0)	<0.0001	313 (34.1)	220 (46.9)	146 (52.7)	129 (69.7)	<0.0001
Never smoking (%)	143 (35.2)	134 (32.8)	110 (27.0)	58 (23.7)	45 (27.4)	0.03	506 (55.2)	262 (55.2)	166 (59.9)	97 (52.4)	0.58
Former smoking (%)	191 (47.0)	202 (49.4)	211 (51.8)	132 (53.9)	94 (57.3)	0.03	275 (30.0)	118 (25.2)	66 (23.8)	54 (29.2)	0.58
Present smoking(%)	72 (17.7)	73 (17.9)	86 (21.1)	55 (22.5)	25 (15.2)	0.03	135 (14.7)	88 (18.8)	45 (16.3)	34 (18.4)	0.58
LDL-C (mg/dL)	127.6 ± 32.1	132.9 ± 35.2	134.0 ± 30.7	135.9 ± 36.5	126.4 ± 32.2	0.0002	131.0 ± 33.6	138.6 ± 36.4	140.2 ± 36.8	130.8 ± 35.8	0.006
HDL-C (mg/dL)	54.5 ± 13.8	54.0 ± 12.9	53.0 ± 12.6	54.4 ± 13.7	53.2 ± 13.2	0.10	68.3 ± 15.5	66.1 ± 16.2	65.4 ± 16.3	65.3 ± 18.0	0.0002
ApoB (mg/dL)	110.4 ± 26.3	116.0 ± 28.1	116.8 ± 24.8	119.5 ± 28.9	112.7 ± 26.2	0.007	112.1 ± 26.9	117.3 ± 28.2	121.2 ± 27.7	116.4 ± 29.4	<0.0001
Lipid-lowering medication (%)	39 (9.6)	68 (16.6)	80 (19.6)	63 (25.7)	56 (34.2)	<0.0001	90 (9.8)	85 (18.1)	68 (24.6)	69 (37.3)	<0.0001
Framingham risk score (%/10 years)[a]	11.6 ± 6.4	15.2 ± 8.2	17.0 ± 8.6	18.9 ± 9.3	18.2 ± 8.1	<0.0001	6.6 ± 4.1	8.4 ± 4.6	9.0 ± 5.3	10.8 ± 6.2	<0.0001
High-sensitive C-reactive protein (mg/L)	2.4 ± 5.7	2.4 ± 4.0	2.6 ± 4.7	2.9 ± 3.9	2.8 ± 6.1	0.71	2.4 ± 4.0	2.8 ± 4.2	3.2 ± 5.0	3.2 ± 3.6	<0.0001
Serum creatinine (mg/dL)	1.1 ± 0.1	1.2 ± 0.3	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	0.54	1.0 ± 0.1	1.0 ± 0.3	1.0 ± 0.2	1.0 ± 0.1	0.079
GFR (mL/min/1.73 m^2)	71.1 ± 10.5	68.7 ± 10.7	69.1 ± 10.5	69.0 ± 10.3	68.1 ± 10.1	0.0049	62.9 ± 9.0	61.9 ± 9.5	61.6 ± 12.0	59.8 ± 12.8	<0.0001
GFR < 60 mL/min/1.73 m^2	50 (3.1)	74 (18.1)	72 (17.7)	42 (17.2)	33 (20.1)	0.03	352 (38.7)	186 (40.0)	124 (45.1)	100 (54.6)	<0.0001
Homocysteine (μmol/L)	11.2 ± 5.2	11.9 ± 6.0	12.0 ± 3.6	12.2 ± 4.5	12.1 ± 3.6	<0.0001	10.1 ± 3.2	10.7 ± 3.8	11.6 ± 4.5	12.1 ± 4.4	<0.0001

apo B, apoliporotein B; BMI, body mass index; CAC, coronary artery calcification; systolic/diastolic BP, systolic/diastolic blood pressure; HbA1c, haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; GFR, glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; *n*, number of participants; t_1, data for 5-year follow-up values.
[a]Calculated only for subjects aged 75 or younger at follow-up.

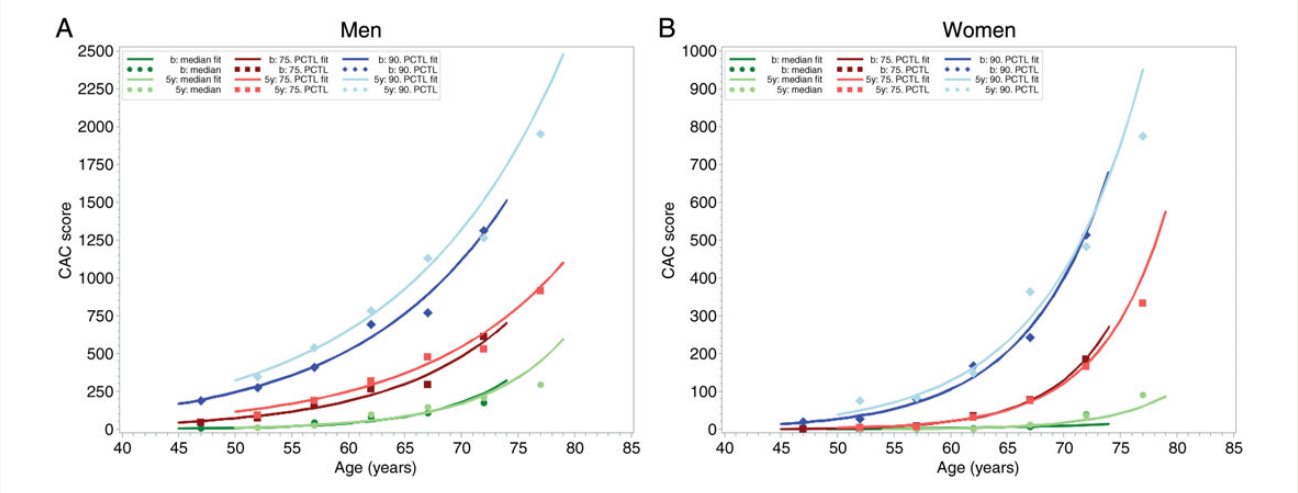

Figure 2 (*A*) Observed and fitted 50th, 75th, and 90th percentile of the coronary artery calcification distribution for men by age categories. In dark colors for the baseline values, when the participants (1633 men) were aged between 45 and 74 years, and in light colors for the 5-year follow-up data, when the cohort was aged 50–79 years. Note the exponential shape of the increase of coronary artery calcification. Dots represent observed percentile values for each 5-year age categories, lines show linear quantile regression on a log scale after retransformation. (*B*) Observed and fitted 50th, 75th, and 90th percentile of the coronary artery calcification distribution for men by age categories. In dark colors for the baseline values, when the participants (1848 women) were aged between 45 and 74 years, and in light colors for the 5-year follow-up data, when the cohort was aged 50–79 years. Note the exponential shape of the increase of coronary artery calcification. Dots represent observed percentile values for each 5-year age categories, lines show linear quantile regression on a log scale after retransformation. The *y*-axis range in *Figure 1A* and *B* differ by a factor of 2.5 in men compared with women.

Multivariable logistic regression analysis for exceeding observed CAC = 400 among those, who were predicted to stay below CAC = 400, demonstrated the importance of diabetes and present smoking for both genders and systolic blood pressure for women (*Table 4*). We used this cohort of 1940 men and women to calculate the accuracy of our mathematical tool for prediction of a progression beyond CAC = 400. The misclassification rate was only 8.5% for the total cohort (men 9.8% and women 6.9%) meaning correct classification in 91.5% (*Table 5*). The sensitivity reached 59.5% and a specificity of 96.1%, a positive-predictive accuracy of 68.3% and negative-predictive accuracy of 94.3% (*Table 5*), which means that the model was particular useful to rule out a CAC progression beyond 400. The results in men were slightly better than in women.

In terms of a sensitivity analysis, we performed a validation using a half sample design. We determine the CAC calculator from baseline values in one half and apply it to predict follow-up CAC from baseline CAC in the other half. Results support a stable prediction.

Discussion

Our study demonstrates (i) that age- and gender-related percentiles of CAC distribution follow an exponential curvature, which showed a nearly indistinguishable shift along the baseline during a follow-up period of 5 years. (ii) The progression of the coronary artery calcification seems to be nearly inevitable with a very high explained variance, which increases only slightly after adjustment for risk factors including lipid lowering and antihypertensive medication. (iii) Based on the observation of the exponential curvature of the CAC distribution for the whole cohort, we developed a mathematical tool to predict the CAC progression for individual participants of the study. (iv) The difference between observed and predicted CAC progression was very small and the coefficient of determination between both values very high. (v) The age, at which relevant CAC of enhanced coronary or CV risk, like CAC = 100 or CAC = 400 is reached can be calculated once the individual baseline CAC percentile value is available. The predictable rate of CAC progression will re-inforce the understanding of the atherosclerotic process for physicians and patients as it seems indeed to be in many aspects inevitable and heritable.[15] Physicians can use the new calculation tool, when they are interested in the progression of CAC for their patients. Further validation studies are needed in cohorts of different ethnicity and for different CT scanners. However, it is interesting to note that percentiles of CAC distribution are comparable in populations of similar ethnicity for both genders despite striking differences in risk factors.[13,14,22] In other ethnic populations, the percentile of CAC distribution and CAC progression were lower for Chinese, blacks, and Hispanic cohorts compared with Caucasians.[14,23] This view is supported by the Epidemiology of Coronary Artery Calcification (ECAC) study,[15] showing in 877 asymptomatic white adults, that risk factors and baseline CAC explained 64% of the variation in CAC progression, comparable with our study showing 81.0% in men and 73.6% in women.

Signs of atherosclerosis were found in male and female mummies and in virtually every era of Egypt.[24] When mummies of different continents were compared, covering 4000 years of human history, abdominal aortic calcification was more common in non-Hispanic-whites (97%), than Chinese (96%), Hispanics (91%), and

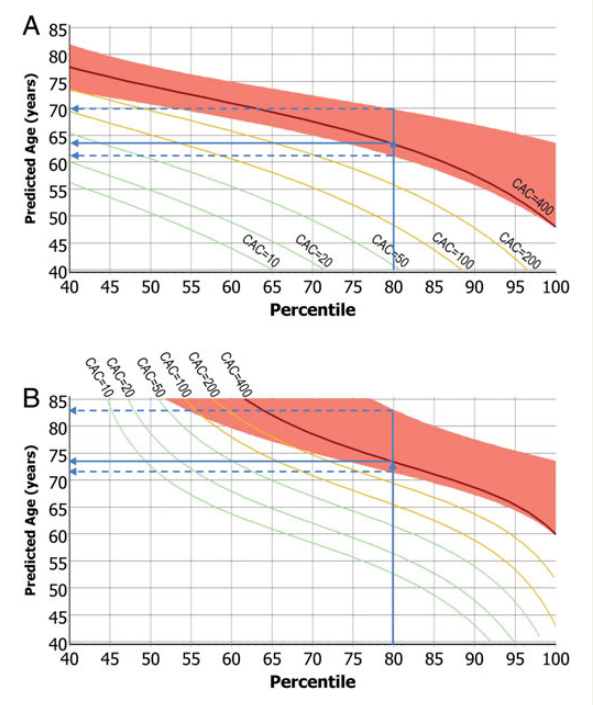

Figure 3 (*A*) Predicted age, at which a man reaches a coronary artery calcification value, as function of coronary artery calcification percentile. The red band around the curve for CAC = 400 represents respective prediction limits. A man with an observed coronary artery calcification on the 80th percentile reaches CAC = 400 at 63.3 (61.3–69.6) years. (*B*) Predicted age, at which a woman reaches a coronary artery calcification value, as function of coronary artery calcification percentile. The red band around the curve for CAC = 400 represents respective prediction limits. A woman with an observed coronary artery calcification on the 80th percentile reaches CAC = 400 at 73.4 (71.5–82.9) years, 10 years later than her male counterpart.

Afro-Americans (80%).[25] This corresponds to the observation of MESA that blacks tended to have the lowest CAC prevalence and CAC levels after adjusting for risk factors.[26] The rate of CAC progression was higher in whites compared with Chinese, Hispanics, and blacks.[23] A very similar inverse worldwide ethnic distribution was found for the β3 subunit of heterotrimeric G-protein (GNB3) subunit 825T allele associated with features of metabolic syndrome as well as stroke and CAD.[27,28] The 825T allele frequencies were highest in Africa ranging from 72 to 91%, lower in Australoids with 72%, even lower in China with 42–62%, Europe with 22–38%, and lowest in North American Musqueams with 30% as well as South America with 15–32%, but reached 72% in AfroAmericans.[28] The obvious strong genetically based heritable determination of the CAC-related atherosclerotic process may thus be related to polymorphism like the G-proteins.

Risk factors and progression of coronary artery calcification

Predictors of CAC progression are reported to be related to endothelium dysfunction, inflammation, autoantibodies to oxidized LDL-cholesterol, increased apoB100 immune complex and lipoprotein (a).[29] Association studies demonstrated very low values for the explained variance in the range of 2–3% for different lipid parameters including apo A1 and B as well as Lp(a) and risk factor ratios.[8] Including all risk factors in the model the explained variance amounted to <25%.[6,7] In our longitudinal observational study, the explained variance for log(CAC + 1) (observed vs. predicted) reached 80.1% in men and 72.0% in women. Risk factor adjustment including medication improved the explained variance to only 81.0 and 73.6%, respectively. These findings correspond to previous observations in the EBAC trial that baseline risk factors and CAC quantity explained 64% of the variation in CAC progression.[23] Our study shows that variable changes of risk factor profile and treatment occurred during the follow-up, which in part could explain the lack of CAC attenuation. Some factors such as obesity and diabetes as well as systolic blood pressure increased, whereas others like

Table 3 **Multivariable logistic regression for CAC_{5y} above the accepted range of deviation**

	Men		Women	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (per 5 years)	0.71 (0.65–0.78)	<0.0001	0.94 (0.86–1.02)	0.14
Systolic blood pressure (per 10 mmHg)	1.13 (1.06–1.21)	0.0005	1.08 (1.01–1.14)	0.02
Antihypertensive medication	1.26 (0.95–1.67)	0.11	1.15 (0.88–1.51)	0.32
LDL-cholesterol (per 10 mg/dL)	1.01 (0.98–1.05)	0.47	1.02 (0.99–1.06)	0.23
HDL-cholesterol (per 5 mg/dL)	1.04 (0.99–1.09)	0.09	1.02 (0.98–1.05)	0.43
Lipid-lowering medication	1.89 (1.24–2.89)	0.003	1.49 (1.02–2.19)	0.04
Diabetes mellitus	1.90 (1.37–2.63)	<0.0001	1.56 (1.05–2.33)	0.03
Former smoking	1.30 (0.95–1.77)	0.10	1.11 (0.82–1.50)	0.51
Present smoking	1.99 (1.42–2.80)	<0.0001	1.98 (1.47–2.67)	<0.0001

Table 4 Multivariable logistic regression for observed $CAC_{5y} \geq 400$ where predicted $CAC_{5y} < 400$[a]

	Men		Women	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (per 5 years)	0.92 (0.65–1.11)	0.38	1.16 (0.87–1.54)	0.31
Systolic blood pressure (per 10 mmHg)	1.19 (0.98–1.27)	0.13	1.38 (1.08–1.51)	0.004
LDL-cholesterol (per 10 mg/dL)	1.02 (0.95–1.09)	0.63	0.94 (0.84–1.05)	0.25
Diabetes mellitus	1.97 (1.08–3.62)	0.03	4.71 (2.1–10.55)	0.0002
Present smoking	1.73 (1.01–2.92)	0.05	4.54 (1.88–11.01)	0.0008

[a]Based on subjects with baseline CAC > 0 but <400.

Table 5 Diagnostic accuracy for the prediction of CAC ≥ 400[a]

		Both genders		Men		Women	
CAC score ≥400 at follow-up		No	Yes	No	Yes	No	Yes
Predicted CAC score ≥400	No	1631	98	867	67	764	31
	Yes	67	144	38	96	29	48
Sensitivity (%)		59.5		58.9		60.8	
Specificity (%)		96.1		95.8		96.3	
Positive-predictive value (%)		68.3		71.6		62.3	
Negative-predictive value (%)		94.3		92.8		96.1	

[a]Based on subjects with baseline CAC > 0 but <400.

LDL-C and smoking decreased. The multivariable analysis demonstrated in addition, that in men systolic blood pressure, diabetes, and smoking, in women smoking, too, were confounders which explained a higher than expected CAC progression, supporting previous studies.[23,29–31] Note that the odds ratios in men for age were <1, indicating higher variability of CAC in younger individuals, which means, that younger men were more prone to CAC progression than elderly participants. The quite small influence of risk factors including lipid-lowering medication and antihypertensive therapy can explain, why in four randomized, in both verum and placebo controlled, studies, statin treatment was unable to stop or even attenuate CAC progression.[9–12] The CAC progression seems to be quite heritable and therefore inevitable,[15] as previously suggested and supported by our results in a large observational study.[16,23]

Clinical implications

Coronary artery calcification progression follows a given exponential curvature based on the relationship between age and CAC distribution at a baseline, during a time period of 5 years. Our results demonstrate that CAC progression seems to be heritable and inevitable, but predictable. Our analysis suggest that repetitive quantification of CAC over time may not be suitable to measure the effectiveness of intensified risk factor modification, as reduction of risk profile may not transfer in attenuation of CAC progression. This opens a new interpretation for physicians and patients, which may lead to better understanding of the lack of attenuation of this process by lifestyle changes or current known medication and avoid multiple scans. This offers the opportunity to initiate re-scans after time intervals at which certain CAC-thresholds can be expected and to avoid unnecessary CT scans in between. To be able to anticipate the age, at which CAC thresholds of high risk like CAC > 300 or CAC > 400 are reached, can be regarded as a considerable advantage leading potentially to a different patient management and can be regarded as an important step forward to a personalized medicine in preventive cardiology. However, this study only addresses the progression of calcifications, but the inevitability of this process does not mean that outcome is inevitable or cannot be modified by preventive measures.

Strength and limitation of the study

The strength of our study represents a very well-defined large cohort with close follow-up over 5 years. The CT scans were repeated with the same system and protocol, so that we avoided the use of any correction factors, which otherwise would have been needed using different types of scanners.[14,25,32] A 5-year follow-up period may be too short, but may allow an extrapolation to longer time intervals based

on the exponential percentile curvature, which remained constant over time. In addition, we found for some patient, for whom we had during a 10-year follow-up multiple CT scans, that their individual CAC progression followed the age- and gender-related exponential curvature calculated form our baseline data of the total cohort.[33–35] An extrapolation to longer time intervals has, however, to be proved in larger cohorts.

We excluded those subjects with coronary events during the 5-year period, because different revascularization procedures would have disturbed the CAC score analysis. However, we did know that those with events have had higher CAC scores and different percentile of CAC distribution.[6,19,36] These observations may also explain, why a small left and upward shift to the higher percentiles of CAC distribution was found in men.

On the other hand, some subjects were not included, because we did not reach them or they refused to come. It may be that they were at a lower risk than those who attended the second study. Higher risk individuals would possibly be more interested in the second evaluation of their risk profile as they could be more concerned about their health situation. This assumption would, however, mean that inclusion of lower risk subjects with lower CAC values would outbalance the enhanced CAC score we observed in men for those with more than the 75th percentile and would not influence the results in women in whom such a difference was not seen.

Progression of CAC seems to follow a sustained, apparently inevitable and partly genetically determined heritable pathway which can be predicted over time from age- and gender-related percentile of CAC distribution once CAC level exceeds CAC $>$ 10. A web-based application offers the possibility to calculate the degree of CAC progression based on age, gender, and percentile of CAC distribution for a given time span. Our data suggest that repetitive CAC-scoring only renders limited additional information and can only to a small amount be influenced by risk factor modification, which may reduce the indication for multiple CT examinations. The demonstration of the natural history of the atherosclerotic calcification process will help the physician–patient interaction and avoid potential misinterpretation of medication efficacy on the disease process, because a profound attenuation cannot be detected. In this regard, our approach could be regarded as an important step to a more personalized medicine in preventive cardiology. However, while CAC progression may not be modified, this does not mean that outcome is inevitable or cannot be modified by preventive measures due to the different patho-anatomical pathway.

Our data explain why current approaches for attenuation of CAC progression have failed. Studies related to ameliorate vascular calcification will have to take into account these analyses. The demonstration of the natural history of the atherosclerotic calcification process will help the physician–patient interaction and avoid potential misinterpretation of medication efficacy on the disease process, because a profound attenuation cannot be expected.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Advisory Board

Criteria and endpoint committee

Acknowledgements

We acknowledge the support of the Sarstedt AG & Co. (Nümbrecht, Germany) concerning laboratory equipment. We thank Prof. K. Lauterbach (Adjunct Professor, Harvard School of Public Health, Boston, USA) for his valuable contributions in an earlier phase of the study. We are indebted to the all study participants and to the dedicated personnel of both the study center of the HNR study and the EBT-scanner facilities as well as to the investigative group, in particular to U. Slomiany, E.M. Beck, A. Öffner, S. Münkel, M. Bauer, S. Schrader, R. Peter, and H. Hirche.

Funding

We thank the Heinz Nixdorf Foundation [Chairman: Martin Nixdorf; Past Chairman: Dr Jur Gerhard Schmidt (deceased)], for their generous support of this study. This study is also supported by the German Ministry of Education and Science (BMBF), and the German Aero-space Center [Deutsches Zentrum für Luft- und Raumfahrt (DLR)], Bonn, Germany. The German Research Council Assessment supported the study (DFG project: ER 155/6-2) and funded the study of psychosocial factors and neighbourhood level information (DFG project SI 236/8-1 and SI 236/9-1). The sponsor of the study transferred the monitoring of the study to the German Ministry of Education and Science, Bonn using an international advisory board and quality control as well as event committee, but had no role concerning the study design, data collection, analysis, interpretation, or writing the report. The corresponding authors had full access to all data in the study and final responsibility for the submission of the manuscript for publication. Funding to pay the Open Access publication charges for this article was provided by the Heinz Nixdorf Recall Investigative Group.

Conflict of interest: none declared.

Appendix

(*Table A1*, *Table A2*, *Table A3*, *Table A4*).

Table A1 Baseline observed percentiles of coronary artery calcification for male participants by age category

Age groups	45–49 years	50–54 years	55–59 years	60–64 years	65–69 years	69–74 years	75–79 years
n	227	327	298	376	262	143	
CAC scores							
Percentile: of CAC distribution							
10th	0.0	0.0	0.0	0.0	1.0	1.3	
25th	0.0	0.0	4.1	8.0	16.5	36.4	
50th	2.8	8.5	43.1	74.7	104.6	173.0	
75th	45.9	76.3	166.1	270.4	298.1	614.7	
90th	184.1	272.6	393.0	692.9	770.2	1312.5	
95th	291.4	476.5	622.5	1152.1	1561.6	1745.7	
Mean CAC value	73.1	120.4	145.2	255.4	321.0	420.9	
SD	270.5	398.5	270.2	494.8	649.3	585.8	

Table A2 Five-year follow-up observed percentiles of coronary artery calcification for male participants by age category

Age groups	50–54 years	55–59 years	60–64 years	65–69 years	69–74 years	75–79 years
n	217	328	293	376	271	148
CAC scores						
Percentiles of CAC distribution						
10th	0.0	0.0	0.0	0.0	10.8	15.2
25th	0.0	0.0	7.7	23.6	53.9	90.0
50th	7.7	21.7	97.5	143.2	205.5	295.9
75th	93.1	188.1	320.5	479.5	536.3	917.3
90th	343.7	512.1	757.6	1130.2	1264.8	2042.0
95th	550.8	1223.3	1346.6	1882.9	2144.6	2519.0
Mean CAC value	131.0	218.6	270.6	419.3	513.2	669.2
SD	393.0	560.6	475.6	693.9	850.7	857.0

Table A3 Baseline observed percentiles of coronary artery calcification for female participants by age category

Age groups	45–49 years	50–54 years	55–59 years	60–64 years	65–69 years	69–74 years	75–79 years
n	257	362	333	416	288	192	
CAC scores							
Percentiles of CAC distribution							
10	0.0	0.0	0.0	0.0	0.0	0.0	
25	0.0	0.0	0.0	0.0	0.0	1.1	
50	0.0	0.0	0.0	2.3	6.4	37.8	
75	1.5	2.6	9.5	37.3	78.9	186.2	
90	18.8	25.8	79.4	166.1	242.6	513.9	
95	53.9	83.8	176.1	311.2	420.1	923.1	
Mean CAC value	8.1	19.1	28.8	68.4	105.0	171.1	
SD	30.9	97.6	84.1	211.6	398.1	329.5	

Table A4 Five-year follow-up observed percentiles of coronary artery calcification for female participants by age category

Age groups	50–54 years	55–59 years	60–64 years	65–69 years	69–74 years	75–79 years
n	230	380	332	415	293	198
CAC scores						
Percentiles of CAC distribution						
10	0.0	0.0	0.0	0.0	0.0	0.0
25	0.0	0.0	0.0	0.0	0.0	6.7
50	0.0	0.0	0.0	10.8	39.5	89.4
75	5.7	7.5	33.0	76.3	172.8	334.5
90	73.9	83.0	148.0	362.3	483.2	774.6
95	150.9	200.7	291.6	601.3	877.8	1465.7
Mean CAC value	24.5	39.1	60.8	130.9	185.7	302.4
SD	77.1	167.8	180.8	377.3	593.7	527.3

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