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Screening for cardiovascular disease risk using traditional risk factor assessment or coronary artery calcium scoring: the ROBINSCA trial

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Aims	Screening for a high cardiovascular disease (CVD) risk followed by preventive treatment can potentially reduce coronary heart disease-related morbidity and mortality. ROBINSCA (Risk Or Benefit IN Screening for CArdiovascular disease) is a population-based randomized controlled screening trial that investigates the effective- ness of CVD screening in asymptomatic participants using the Systematic COronary Risk Evaluation (SCORE) model or coronary artery calcium (CAC) scoring. This study describes the distributions in risk and treatment in the ROBINSCA trial.
Methods and results	Individuals at expected elevated CVD risk were randomized into screening arm A ($n = 14$ 478; SCORE, 10-year fatal and non-fatal risk); or screening arm B ($n = 14$ 450; CAC scoring). Preventive treatment was largely advised according to current Dutch guidelines. Risk and treatment differences between the screening arms were analysed. A total of 12 185 participants (84.2%) in arm A and 12 950 (89.6%) in arm B were screened. In total, 48.7% were women, and median age was 62 (interquartile range 10) years. SCORE screening identified 45.1% at low risk (SCORE < 10%), 26.5% at intermediate risk (SCORE 10–20%), and 28.4% at high risk (SCORE ≥ 20%). According to CAC screening, 76.0% were at low risk (Agatston < 100), 15.1% at high risk (Agatston 100–399), and 8.9% at very high risk (Agatston ≥ 400). CAC scoring significantly reduced the number of individuals indicated for preventive treatment compared to SCORE (relative reduction women: 37.2%; men: 28.8%).

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Conclusion	We showed that compared to risk stratification based on SCORE, CAC scoring classified significantly fewer men and women at increased risk, and less preventive treatment was indicated.
Trial registration number	NTR6471.
Keywords	Cardiovascular disease • Computed tomography imaging • Coronary artery calcification • Population-based screening • Risk prediction • ROBINSCA trial

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide and it is responsible for 45% of all annual deaths in Europe.^{1,2} Although various preventive measures in terms of lifestyle and timely drug treatment are known to reduce CVD burden, their application is suboptimal and unhealthy lifestyles remain frequent. Populationbased screening for cardiovascular risk aims to identify individuals at increased risk in order to stop or delay disease progression by preventive treatment. This might be an appropriate strategy to reduce CVD-related events.^{3–5} However, there is no evidence from randomized controlled trials (RCTs) on the effectiveness of screening and a reliable screening modality yet.

One potentially suitable risk assessment tool is the Dutch Systematic Coronary Risk Evaluation (SCORE) risk model, which predicts 10-year risk for developing fatal and non-fatal CVD.^{4,6,7} Although this model is easy to use and is integrated into current guidelines, it has limited accuracy in predicting the correct risk status. The indication for preventive treatment is often uncertain in intermediate-risk individuals, limiting the ability to prevent coronary heart disease (CHD) in this group.^{4,8} Another potential screening modality is quantification of coronary artery calcification (CAC), expressed as CAC score, using computed tomography (CT) scanning.^{9,10} Evidence shows that CAC scoring is a strong independent predictor of CHD events and improves classification of intermediaterisk individuals, causing a large shift in the distribution of CVD risk.^{11,12} Currently, European and American guidelines recommend considering additional CAC scoring to guide preventive therapy decisions in intermediate-risk adults.^{4,13}

In CVD screening, the expected difference in CVD risk distribution between the SCORE model and CAC scoring might cause an effective shift towards more correctly classified individuals and more accurate risk reduction. In addition, a reduction in preventive overtreatment with cardiovascular medication is expected when CAC scoring is used as the screening modality. This will not only be beneficial for participants as it reduces potential side effects, but it will also save costs.¹⁴ However, the effect of the shift in risk distribution in the setting of CVD screening in an elevated risk population is unknown.

The Risk Or Benefit IN Screening for CArdiovascular diseases (ROBINSCA) trial is a population-based randomized controlled screening trial to investigate whether screening for a high risk of CVD in asymptomatic individuals followed by early treatment will reduce CHD-related morbidity and mortality compared to

no screening.¹⁵ The SCORE model and CAC scoring are used as potential screening modalities. The aim of the present study is to present the CVD risk distributions in both screening arms and to investigate the shift in risk distribution and the potential reduction in preventive (over)treatment due to the use of different risk assessment tools.

Methods

Study population

The design, objectives and recruitment of the ROBINSCA trial have been described previously.¹⁵ In summary, 394 058 individuals, women aged 55-74 years and men aged 45-74 years from three regions in the Netherlands, were selected from the national population registry, and received an invitation to participate, including an information brochure, a baseline questionnaire, a waist circumference measuring tape and a written informed consent form. Asymptomatic individuals were subsequently selected based on at least one of the following inclusion criteria: (i) a high self-measured waist circumference (≥88 cm for women and ≥102 cm for men); (ii) a high body mass index (BMI; \geq 30 kg/m²); (iii) a family history of myocardial infarction or sudden death before the age of 65 years in firstor second-degree relatives; and/or (iv) current smoking. Exclusion criteria were: (i) previously diagnosed CVD; (ii) previous CVD surgery; (iii) prescription of a combination of cholesterol- and blood pressure-lowering medication; (iv) CAC score measurement in the past year; and/or (v) incomplete informed consent. In total, 43 447 eligible individuals were randomized (1:1:1) to either the control arm where usual care was continued, or to one of the two intervention arms where screening was offered. All participants received generic healthy lifestyle recommendations of the Dutch Heart Foundation (Figure 1). The current study focuses only on the screening arms.

Screening

Screening was performed from 2015 to 2018. In intervention arm A, the 10-year risk for fatal and non-fatal CVD was estimated using the adapted version of the SCORE model as described in the Dutch guideline for Cardiovascular Risk Management (CVRM, edition 2011) by the College of General Practitioners.⁷ Participants were invited for blood pressure and cholesterol measurement. The algorithm stratifies participants into low (SCORE <10%), intermediate (SCORE 10–20%), or high (SCORE \geq 20%) risk according to the guideline.¹⁵ In intervention arm B, participants underwent CT scanning using a second-generation dual-source CT system. The CAC imaging protocol has been described elsewhere.¹⁶ In short, images were analysed with semiautomatic identification of calcifications. A calcification was defined as an area with a density of \geq 130 Hounsfield units and \geq 2 adjacent voxels. Individual calcifications per

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Figure I Flowchart of the recruitment, inclusion, and randomization process in the ROBINSCA trial.

coronary artery could be selected for CAC scoring using dedicated CAC scoring software. We calculated CAC scores according to Agatston.^{16,17} CAC scores were stratified into low (Agatston < 100), high (Agatston 100–399), and very high (Agatston ≥400) risk, according to cut-offs from literature.¹⁸ This terminology was chosen for the screening setting for early detection of preclinical disease. We used this classification in an asymptomatic population as an indication of preventive treatment and to distinguish between SCORE and CAC score.

Study protocol for preventive treatment

Participants were notified about their risk status, as were their general practitioners (GPs). Participants with a SCORE of >10% were advised to consult the GP. GPs are asked to initiate preventive treatment according to the Dutch CVRM guideline for 'patients without CVD'.⁷ This guideline recommends lifestyle measures for all high-risk individuals (\geq 20%), and intermediate-risk individuals (\geq 10%) who have ≥ 1 risk-increasing factors. For these individuals, preventive drug treatment is recommended additionally when systolic blood pressure is >140 mmHg and/or LDL-cholesterol >2.5 mmol/L. The treatment advice for a high CAC score was designed in consultation with local cardiologists, GPs and the research team. The study advice recommended prescription of angiotensin-converting enzyme-inhibitors and statins, independent from cholesterol and blood pressure levels (except when blood pressure is too low), for participants with a CAC score \geq 100, as adapted from the CVRM guideline for 'patients with CVD'.7

Statistical analysis

Study population characteristics are expressed as percentages or medians [interquartile range (IQR)] as appropriate for men and women separately. The Pearson's χ^2 test and the Mann–Whitney U test were used to analyse differences in distributions and medians respectively between intervention arm A and B. The distributions of CVD risk in both intervention arms were analysed using the Pearson's χ^2 test and medians were analysed using the Kruskal–Wallis test. The difference in preventive treatment indications between the intervention arms was analysed to check for potential reduction in overtreatment when using CAC scoring and was tested for statistically significant difference using the Pearson's χ^2 test. The differences are presented as absolute and relative differences. A *P*-value of <0.005 was considered statistically significant after application of the Bonferroni correction. All analyses were performed using IBM SPSS Statistics version 25.0. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

Baseline characteristics

In total, 14 478 and 14 450 participants were randomized into intervention arm A and intervention arm B, respectively. Screening attendance rate was high for both intervention arms; 12 185 (84.2%) participants underwent a SCORE assessment and 12 950 (89.6%) participants underwent CT scanning for CAC quantification (P < 0.001). Supplementary data online, *Table SA* provides information on differences between screened and non-screened individuals. Baseline characteristics of the screened women and men of both intervention arms were comparable (*Table 1*). Median age of the women (12 232 out of 25 135; 48.7%) was 64.0 years (IQR 8) and of the men (12 903 out of 25 135; 51.3%) 59.0 years (IQR 13)

(P < 0.001). More men were current smokers (25.3 vs. 13.7%, P < 0.001) and men had a higher BMI compared to women (26.9 vs. 25.5 kg/m²; P < 0.001). Reported family history of CHD was comparable for men and women (P = 0.428). Slightly more women reported baseline use of antihypertensive treatment (21.9 vs. 17.1%; P < 0.001).

SCORE and **CAC** score assessment

Based on the Dutch SCORE model, 3234 out of 6009 (53.8%) women were classified as low risk, 1479 (24.6%) as intermediate, and 1296 (21.6%) as high risk. A significantly different CVD risk distribution was observed using CAC scoring: more low-risk women were identified. A zero CAC score was measured in 48.0% of the women (2984/6223). Furthermore, 35.3% (2196) had a low CAC score (Agatston 1-99), 12.1% (754) had a high CAC score (Agatston 100-399), and 4.6% (289) had a very high CAC score (Agatston \geq 400) (Table 2). Men were stratified into higher-risk categories compared to women within both intervention arms. There were 2262 out of 6176 (36.6%) men assessed as being at low risk based on the SCORE model, whereas 1751 (28.4%) and 2163 (35.0%) were classified as intermediate- and high-risk individuals, respectively. Among the 6727 men, 31.2% (2098) had a zero CAC score. Furthermore, 2561 (38.1%) men with a low CAC score were identified, followed by 1200 (17.8%) and 868 (12.9%) with a high and very high CAC score, respectively (Table 3).

In both women and men, apart from the factors included in SCORE calculation, larger waist circumference, diabetes mellitus, and use of blood pressure or cholesterol-lowering medication were associated with a higher SCORE. In addition, a higher BMI was associated with a higher SCORE in women. In contrast, BMI and waist circumference were not associated with an increase in CAC score in women (P = 0.653 and P = 0.062, respectively). A higher BMI was not associated with a higher SCORE, nor with a higher CAC score in men (P = 0.012 and P = 0.605, respectively). Waist circumference and current smoking in men were not associated with an increase in CAC score (P = 0.259 and P = 0.811, respectively; *Tables 2 and 3*).

In addition to the SCORE calculations based on the Dutch CVRM guideline, Supplementary data online, *Table SB* presents the converted SCORE risks according to the European model from the European Society of Cardiology.⁶

Difference in risk and preventive treatment

The absolute reduction in the number of increased risk individuals was 29.4% in women and 32.7% in men when CAC scoring was used as screening tool. The subsequent rate ratios (RRs) were 0.363 [95% confidence interval (CI) 0.341–0.386] for women and 0.485 (95% CI 0.466–0.505) for men. This resulted in relative reductions of increased-risk individuals of 63.7% and 51.5% in women and men, respectively.

These large differences in CVD risk distributions between the screening modalities in both women and men caused statistically significant differences in the number of individuals indicated to consult their GP for preventive drug treatment (*Figure 2*). Potential preventive drug treatment was indicated for 1604 out of 6009 (26.7%)

	Intervention arm A SCORE, n/N (%)	Intervention arm B CAC score, n/N (%)	P-value
a) Women	N = 6009	N = 6223	
Median age (IQR)	64.0 (8)	64.0 (8)	0.786
Educational level ^a			0.278
Low	2692/5987 (45.0)	2699/6200 (43.5)	
Medium	1454/5987 (24.3)	1552/6200 (25.0)	
High	1841/5987 (30.7)	1949/6200 (31.4)	
Current smoker	827/6009 (13.8)	850/6223 (13.7)	0.868
BMI, median (IQR)	25.5 (5.1)	25.5 (5.0)	0.826
Waist circumference, ^b median (IQR)	97.0 (13.5)	96.5 (13.5)	0.277
Family history of CHD ^c	2451/5437 (45.1)	2518/5614 (44.9)	0.810
Diabetes mellitus	152/6009 (2.5)	178/6223 (2.9)	0.259
Hypertension in past year	948/5864 (16.2)	1005/6080 (16.5)	0.592
Hypercholesterolaemia in past year	938/5802 (16.2)	974/5994 (16.2)	0.903
Baseline medical treatment			
Antihypertensive	1306/5989 (21.8)	1370/6203 (22.1)	0.709
Lipid-lowering	449/5987 (7.5)	490/6189 (7.9)	0.388
b) Men	N = 6176	N = 6727	
Age, median (IQR)	59.0 (13)	59.0 (13)	0.095
Educational level ^a			0.976
Low	1900/6165 (30.8)	2057/6705 (30.7)	
Medium	1840/6165 (29.8)	2012/6705 (30.0)	
High	2425/6165 (39.3)	2636/6705 (39.3)	
Current smoker	1525/6176 (24.7)	1736/6727 (25.8)	0.146
BMI, median (IQR)	26.9 (4.3)	26.9 (4.4)	0.758
Waist circumference, ^b median (IQR)	104.5 (12.0)	104.5 (12.0)	0.647
Family history of CHD ^c	2637/5718 (46.1)	2812/6262 (44.9)	0.183
Diabetes mellitus	200/6176 (3.2)	258/6727 (3.8)	0.067
Hypertension in past year	964/6020 (16.0)	1119/6561 (17.1)	0.116
Hypercholesterolaemia in past year	917/5997 (15.3)	1001/6541 (15.3)	0.985
Baseline medical treatment			
Antihypertensive	1017/6157 (16.5)	1187/6710 (17.7)	0.078
Lipid-lowering	493/6152 (8.0)	585/6709 (8.7)	0.149

Table I Baseline characteristics of the study population split for women (a) and men (b)

A P-value of <0.005 was considered statistically significant after application of the Bonferroni correction.

CAC, coronary artery calcium; CHD, coronary heart disease; IQR, interquartile range; SCORE, systematic coronary risk evaluation.

^aEducational levels: low: primary, lower secondary general, or lower vocational education; medium: intermediate vocational or higher secondary education; and high: higher vocational education or university.

^bWaist circumference in centimetres.

^cFamily history of myocardial infarction or sudden death before the age of 65 years in first and second degree relatives.

women according to the SCORE model, compared to 1043 out of 6223 (16.8%) women according to CAC scoring (P < 0.001; absolute reduction of 9.9%). The relative reduction in the number of women indicated for preventive drug treatment was estimated to be 37.2% when using CAC scoring compared to SCORE calculation (based on RR 0.628, 95% CI 0.586–0.673). Among men, 2666 out of 6176 (43.2%) were advised to start preventive drug treatment based on SCORE calculation, whereas 2068 out of 6727 (30.7%) received preventive drug treatment advice based on CAC score (P < 0.001; absolute reduction of 12.4%). Risk estimation using CAC scoring caused a relative reduction in the number of preventive drug treatment indications of 28.8% in men (based on RR 0.712, 95% CI 0.680–0.746).

Discussion

In this population-based screening RCT for the early detection and treatment of an increased risk for CVD, 25 135 asymptomatic participants were screened by means of either applying the SCORE model or CAC scoring. As expected, the CVD risk distributions differed significantly between the two screening modalities. Risk assessment through CAC scoring identified more low-risk individuals compared to the SCORE model. Follow-up analyses should establish whether the indicated high-risk individuals were treated correctly.

The associations between traditional risk factors and a higher SCORE are a natural result of the SCORE model being based on these risk factors. However, similar associations were not observed

SCORE <10%, IN (%) SCORE <10%, IN (%) SCORE <10%, IN (%) SCORE <10%, IN (%) CAC score <0-9, N (%) CAC score <00-39, IN (%) CAC score CAC s		Low risk	Intermediate	High risk	P-value	Low risk	High risk	Very high risk	P-val
3234(600) (53.8) 1479(6009 (24.6) 1266(6009 (21.6) 5180(6223 (83.2) 754(6223 (12.1) 289(6223 (4.6) Age, median (IQR) 6.00 (5) 6.70 (4) 7.1.0 (4) 6.0.001 6.30 (9) 6.6.5 (8) 6.8.0 (8) < Age, median (IQR) 5.00 (5) 6.70 (4) 7.1.0 (4) <0.001 6.30 (9) 6.6.5 (8) 6.8.0 (8) < < < < < < < 6.0 (7) 0.001 5.30 (8) < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < < <th></th> <th>SCORE <10%,ª n/N (%)</th> <th>SCORE 10-20%,^a n/N (%)</th> <th>SCORE</th> <th></th> <th>CAC score 0–99, n/N (%)</th> <th>CAC score 100–399, n/N (%)</th> <th>CAC score ≥400, n/N (%)</th> <th></th>		SCORE <10%,ª n/N (%)	SCORE 10-20%, ^a n/N (%)	SCORE		CAC score 0–99, n/N (%)	CAC score 100–399, n/N (%)	CAC score ≥400, n/N (%)	
Age median (IQR) 600 (5) 67.0 (4) 71.0 (4) <0.001 63.0 (9) 66.5 (8) 68.0 (8) < Current smoker 371/3234 (11.5) 255/1479 (17.2) 201/1296 (15.5) <0.001		3234/6009 (53.8)	1479/6009 (24.6)	1296/6009 (21.6)		5180/6223 (83.2)	754/6223 (12.1)	289/6223 (4.6)	
Current smoker $371/3234$ (11.5) $255/479$ (17.2) $201/1296$ (15.5) <0.001 $654/5190$ (12.6) $142/754$ (18.8) $54/289$ (18.7) <0.001 BMI, median (IQR) 25.3 (5.0) 25.3 (5.0) 25.5 (5.3) 25.6 (5.7) 0.0 Waist circumference, median (IQR) 96.0 (13.5) 97.0 (13.5) 97.5 (14.9) 97.5 (14.9) 0.001 Waist circumference, median (IQR) 96.0 (13.5) 97.0 (13.5) 97.5 (14.5) 0.001 25.5 (5.0) 25.5 (5.0) 25.5 (5.7) 0.0 Waist circumference, median (IQR) 96.0 (13.5) 97.0 (13.5) 97.0 (13.5) 97.5 (14.9) 97.5 (14.9) 0.0 Maist circumference, median (IQR) 25.1 (5.5) 98.5 (14.5) 0.001 95.6 (13.5) 97.0 (13.0) 97.5 (14.9) 0.0 Image and (IQR) $21/3224$ (0.6) $37/1479$ (2.5) $94/1296$ (7.3) <0.001 $114/5180$ (2.2) $49/754$ (6.5) $151/264$ (57.2) <0.001 Hypertension in past year $443/3173$ (14.0) $236/1445$ (16.3) $269/1246$ (21.6) $70/45004$ (15.5) $114/717$ (19.7) $59/273$ (21.6) 0.0 Hypertension in past year $473/3147$ (15.1) $267/1413$ (18.9) $196/1242$ (15.8) 0.0001 $1077/5166$ (2.0) $98/287$ (34.1) <0.001 In past year $57/3227$ (17.8) $360/1474$ (24.4) $373/1288$ (29.0) <0.001 $1077/5166$ (20.6) $98/287$ (34.1) <0.001 Mithypertensive $57/32227$ (17.8) $360/1474$ (24.4) $373/1288$ (10.2) <0.001 <td>Age, median (IQR)</td> <td>60.0 (5)</td> <td>67.0 (4)</td> <td>71.0 (4)</td> <td><0.001</td> <td>63.0 (9)</td> <td>66.5 (8)</td> <td>68.0 (8)</td> <td><0.0></td>	Age, median (IQR)	60.0 (5)	67.0 (4)	71.0 (4)	<0.001	63.0 (9)	66.5 (8)	68.0 (8)	<0.0>
BMI, median (IQR) 25.3 (5.0) 25.7 (5.3) 25.6 (5.7) 0. Waist circumference, 96.0 (13.5) 97.0 (13.5) 98.5 (14.5) 60.001 25.5 (5.0) 25.5 (5.3) 25.6 (5.7) 0. Waist circumference, 96.0 (13.5) 97.0 (13.5) 98.5 (14.5) 60.001 96.0 (13.5) 97.5 (14.9) 0. Waist circumference, 96.0 (13.5) 97.0 (13.5) 98.5 (14.5) 60.001 96.0 (13.5) 97.5 (14.9) 0. Median (IQR) 1352/2968 (45.6) 598/1325 (45.1) 501/1144 (43.8) 0.596 2008/4684 (42.9) 359/666 (53.9) 151/264 (57.2) 60 Diabetes mellitus 21/3234 (0.6) 37/1479 (2.5) 94/1296 (7.3) <0.001	Current smoker	371/3234 (11.5)	255/1479 (17.2)	201/1296 (15.5)	<0.001	654/5180 (12.6)	142/754 (18.8)	54/289 (18.7)	<0.0
Waist circumference, ^b 96.0 (13.5) 97.0 (13.5) 97.0 (13.5) 97.0 (13.5) 97.0 (13.0) 97.5 (14.9) 0. median (IQR) median (IQR) 96.0 (13.5) 97.0 (13.5) 97.0 (13.0) 97.5 (14.9) 0. family history of CHD ^c 1352/2968 (45.6) 598/1325 (45.1) 501/1144 (43.8) 0.596 2008/4684 (42.9) 359/666 (53.9) 151/264 (57.2) <	BMI, median (IQR)	25.3 (5.0)	25.7 (5.3)	26.0 (5.1)	<0.001	25.5 (5.0)	25.5 (5.3)	25.6 (5.7)	0.6
median (IQR) median (IQR) 598/1325 (45.1) 501/1144 (43.8) 0.596 2008/4684 (42.9) 359/666 (53.9) 151/264 (57.2) <0 Family history of CHD ^c 1352/2968 (45.6) 37/1479 (2.5) 94/1296 (7.3) 0.596 2008/4684 (42.9) 359/666 (53.9) 151/264 (57.2) <0	Waist circumference, ^b	96.0 (13.5)	97.0 (13.5)	98.5 (14.5)	<0.001	96.0 (13.5)	97.0 (13.0)	97.5 (14.9)	0.06
Family history of CHD ^c 1352/2968 (45.6) 598/1325 (45.1) 501/1144 (43.8) 0.596 2008/4684 (42.9) 359/666 (53.9) 151/264 (57.2) <c< th=""> Diabetes mellitus 21/3234 (0.6) 37/1479 (2.5) 94/1296 (7.3) <0.001</c<>	median (IQR)								
Diabetes melltus 21/3234 (0.6) 37/1479 (2.5) 94/1296 (7.3) <0.001 114/5180 (2.2) 49/754 (6.5) 15/289 (5.2) <0 Hypertension in past year 443/3173 (14.0) 236/1445 (16.3) 269/1246 (21.6) <0.001	Family history of CHD ^c	1352/2968 (45.6)	598/1325 (45.1)	501/1144 (43.8)	0.596	2008/4684 (42.9)	359/666 (53.9)	151/264 (57.2)	<0.0
Hypertension in past year 443/3173 (14.0) 236/1445 (16.3) 269/1246 (21.6) <0.001	Diabetes mellitus	21/3234 (0.6)	37/1479 (2.5)	94/1296 (7.3)	<0.001	114/5180 (2.2)	49/754 (6.5)	15/289 (5.2)	<0.(
Hypercholesterolaemia 475/3147 (15.1) 267/1413 (18.9) 196/1242 (15.8) 0.005 774/5004 (15.5) 141/717 (19.7) 59/273 (21.6) 0. in past year in past year Baseline medical treatment 573/3227 (17.8) 360/1474 (24.4) 373/1288 (29.0) <0.001	Hypertension in past year	443/3173 (14.0)	236/1445 (16.3)	269/1246 (21.6)	<0.001	786/5065 (15.5)	151/737 (20.5)	68/278 (24.5)	<0.(
in past year Baseline medical treatment Antihypertensive 573/3227 (17.8) 360/1474 (24.4) 373/1288 (29.0) <0.001 1077/5166 (20.8) 195/750 (26.0) 98/287 (34.1) <0 Lipid-lowering 186/3226 (5.8) 132/1472 (9.0) 131/1289 (10.2) <0.001 340/5153 (6.6) 1077/50 (14.3) 43/286 (15.0) <0	Hypercholesterolaemia	475/3147 (15.1)	267/1413 (18.9)	196/1242 (15.8)	0.005	774/5004 (15.5)	141/717 (19.7)	59/273 (21.6)	0.0
Baseline medical treatment Antihypertensive 573/3227 (17.8) 360/1474 (24.4) 373/1288 (29.0) <0.001 1077/5166 (20.8) 195/750 (26.0) 98/287 (34.1) <0 Lipid-lowering 186/3226 (5.8) 132/1472 (9.0) 131/1289 (10.2) <0.001 340/5153 (6.6) 1077/50 (14.3) 43/286 (15.0) <0	in past year								
Antihypertensive 573/3227 (17.8) 360/1474 (24.4) 373/1288 (29.0) <0.001 1077/5166 (20.8) 195/750 (26.0) 98/287 (34.1) <0.001 Lipid-lowering 186/3226 (5.8) 132/1472 (9.0) 131/1289 (10.2) <0.001 340/5153 (6.6) 107/750 (14.3) 43/286 (15.0) <0.000 <0.001 340/5153 (6.6) 107/750 (14.3) 43/286 (15.0) <0.000 <0.001 340/5153 (6.6) 107/750 (14.3) 43/286 (15.0) <0.000 <0.001 340/5153 (6.6) 107/750 (14.3) 43/286 (15.0) <0.000 <0.001 340/5153 (6.6) 107/750 (14.3) 43/286 (15.0) <0.000 <0.001 340/5153 (6.6) 107/750 (14.3) 43/286 (15.0) <0.000 <0.001 340/5153 (6.6) 107/750 (14.3) 43/286 (15.0) <0.000 <0.001 340/5153 (6.6) 107/750 (14.3) 43/286 (15.0) <0.000 <0.001 340/5153 (6.6) 107/750 (14.3) 43/286 (15.0) <0.000 <0.001 340/5153 (6.6) 107/750 (14.3) 107/750 (14.3) 107/750 (14.3) 107/750 (14.3) 107/750 (14.3) 107/750 (14.3) 107/750 (14.3) 107/750 (14.3) 107/750 (14.3) <td>Baseline medical treatment</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>	Baseline medical treatment								
Lipid-lowering 186/3226 (5.8) 132/1472 (9.0) 131/1289 (10.2) <0.001 340/5153 (6.6) 107/750 (14.3) 43/286 (15.0) <0	Antihypertensive	573/3227 (17.8)	360/1474 (24.4)	373/1288 (29.0)	<0.001	1077/5166 (20.8)	195/750 (26.0)	98/287 (34.1)	<0.(
	Lipid-lowering	186/3226 (5.8)	132/1472 (9.0)	131/1289 (10.2)	<0.001	340/5153 (6.6)	107/750 (14.3)	43/286 (15.0)	<0.(
-S-CURE alculation according to the 2011 edition of the Cardiovascular Kisk Management protocol of the Dutch College of General Practitioners. ^b Valat sicroundernoe in centimetres.	">CUKE calculation according to 1 bVaist circumference in centimeti ^c Family history of myocardial infari	the 2011 edition of the Car es. ction or sudden death befo	diovascular Kisk Management re the age of 65 years in first a	protocol of the Dutch Colli ind second degree relatives.	ege of General Pr	actitioners.			

Distributions of cardiovascular risks by baseline characteristics in intervention arm A (Dutch SCORE calculation) and intervention arm B (CAC Table 2

Table 3Distributions of calfication) in men	rdiovascular risk	s by baseline chara	ucteristics in inte	rvention	arm A (Dutch SC	ORE calculation) and	d intervention arm B (C	AC quanti-
	Low risk SCORE <10%, ^a n/N (%)	Intermediate risk SCORE 10–20%, ^a n/N (%)	High risk SCORE ≥20%,ª n/N (%)	P-value	Low risk CAC score 0–99, n/N (%)	High risk CAC score 100–399, n/N (%)	Very high risk CAC score ≥400, n/N (%)	P-value
Age, median (IQR) Current smoles	2262/6176 (36.6) 52.0 (6) 432/2262 (19.1)	1751/6176 (28.4) 60.0 (7) 441/1751 (75 2)	2163/6176 (35.0) 68.0 (7) 452/21453 (30.1)	<0.001	4659/6727 (69.3) 56.0 (12) 1198/4659 (75 7)	1200/6727 (17.8) 63.0 (11) 318/1700 (7.4 5)	868/6727 (12.9) 66.0 (9) 720/848 (75 3)	<0.001
BMI, median (IQR)	26.6 (4.3)	27.1 (4.3)	26.9 (4.2)	0.012	26.9 (4.3)	27.0 (4.6)	26.9 (4.4)	0.605
Waist circumference, ^b median (IQR)	104.0 (12.0)	104.5 (11.5)	105.0 (11.0)	< 0.001	104.0 (12.0)	104.5 (11.0)	104.5 (12.0)	0.259
Family history of CHD ^c	1046/2141 (48.9)	755/1640 (46.0)	836/1937 (43.2)	0.001	1880/4341 (43.3)	512/1119 (45.8)	420/802 (52.4)	<0.001
Diabetes mellitus	19/2262 (0.8)	24/1751 (1.4)	157/2163 (7.3)	< 0.001	138/4659 (3.0)	52/1200 (4.4)	67/868 (7.7)	<0.001
Hypertension in past year	264/2202 (12.0)	324/1706 (19.0)	376/2112 (17.8)	< 0.001	694/4550 (15.3)	237/1169 (20.3)	188/842 (22.3)	<0.001
Hypercholesterolaemia in past year	298/2208 (13.5)	289/1694 (17.1)	330/2095 (15.8)	0.007	648/4546 (14.3)	209/1156 (18.1)	144/839 (17.2)	0.002
Baseline medical treatment								
Antihypertensive	198/2258 (8.8)	305/1746 (17.5)	514/2153 (23.9)	< 0.001	647/4648 (13.9)	288/1196 (24.1)	252/866 (29.1)	<0.001
Lipid-lowering	124/2258 (5.5)	132/1741 (7.6)	237/2153 (11.0)	< 0.001	323/4649 (6.9)	135/1194 (11.3)	127/866 (14.7)	<0.001
A P-value of <0.005 was considered statisti The risk distribution categories in intervent BMI, body mass index; CAC, coronary arter aSCORE calculation according to the 2011 (^b Waist circumference in centimetres. ^c Family history of myocardial infarction or s	ally significant after app ion arm A are as in the L Y calcium; CHD, corona edition of the Cardiovas udden death before the	leation of the Bonferroni c Dutch Cardiovascular Risk I rry heart disease: IQR, inter cular Risk Management pro age of 65 years in first and	orrection. Management protocol. T quartile range; SCORE, i stocol of the Dutch Colle second degree relatives.	he risk distrib systematic co ege of Genera	ution categories in interv ronary risk evaluation. I Practitioners. ⁷	intion arm B are as cut-offs fro	m literature.	



Figure 2 Individuals indicated to consult their general practitioner for preventive drug treatment in intervention arm A and B based on estimated risks and the absolute and relative difference between both intervention arms. *Level of significance: P < 0.001. The difference in the number of individuals indicated for preventive treatment between the intervention arms were analysed and are presented as absolute and relative differences. CAC, coronary artery calcium; SCORE, systematic coronary risk evaluation.

in intervention arm B: higher CAC score categories were not associated with increasing waist circumference in women and men, nor with current smoking in men, nor with increasing BMI in women. In men, BMI was not associated with a higher SCORE, nor a higher CAC score. Regarding BMI, previous studies indeed reported that BMI does not predict CAC, which is largely related to the inability of BMI to differentiate between fat and muscle and the assumption that CAC scores can be underestimated in women with large chest size and large patients.^{19,20} In contrast, the lack of an association between waist circumference and CAC contradicts earlier findings indicating that waist circumference is associated with CAC beyond traditional risk factors.²¹ As there is no unambiguous evidence on this subject yet, future research should focus more on this potential association. Furthermore, the proportion of male current smokers did not increase with higher CAC score categories. This is in line with previous research that concluded that the effect of current smoking on CAC might decrease with age.²² Discrepancies in presence of CAC and absence of traditional risk factors, and vice versa, might influence the decision on whether to start preventive drug treatment or not. In particular, current preventive treatment in people with zero CAC may be considered as overtreatment, since this score represents a minimal risk.²³ Current preventive treatment decisions are largely based on traditional risk prediction models, whereas CAC scoring is thought to be better at correctly identifying individuals who would benefit the most from preventive treatment.²⁴

The SCORE model has several limitations, including the limited adaptation for different ethnic groups and age ranges, and the lack of incorporating risk modifiers that potentially reclassify CVD risk, such as socio-economic status, CVD family history and obesity, and therefore lacks discriminative power.^{4,8} CAC scoring has superior discrimination and risk reclassification as compared with other risk indicators.²⁵ Previous studies showed that asymptomatic intermediate-risk individuals were more often downgraded to a lower-risk category after adding CAC scoring to risk prediction, which is in line with our results.^{11,12} In addition, the review of

Greenland *et al.*,⁹ which summarized the results of population-based cohorts, convincingly showed the value of CAC scoring as a single predictive cardiovascular risk marker beyond traditional risk factors. Furthermore, recent literature described that shared decision making guided by CAC scoring in intermediate-risk individuals can be a cost-effective strategy to avoid years of preventive medication.^{9,14} Future analyses on CVD-related events in the ROBINSCA trial might add important evidence on the extent to which preventive treatment decisions should be based on CAC screening.

The observed reduction in the number of individuals indicated to consult their GP for preventive treatment after screening by CAC scoring compared to screening using the SCORE model will potentially influence prevention strategies. However, future analyses on CVD-related events are needed to determine whether the indicated high-risk individuals were treated correctly. Within the screening setting of the current study, the results might imply a reduction in burden for both screening participants and GPs. The improved estimate of a CAC-based CVD risk status might reduce unnecessary stress that participants may experience upon receiving an unfavourable test result, while it might increase adherence to preventive treatment.²⁶ For GPs, risk management in intervention arm B participants is less time consuming since the treatment indication in intervention arm A is not solely based on the SCORE model, but also on additional riskincreasing factors that are not known in the ROBINSCA trial. Furthermore, a potential reduction in unnecessary treatment will reduce costs. However, as CT scanning is more expensive compared to using the SCORE model, the effectiveness of CT screening should first be confirmed.^{14,27}

The strength of this study is its large study population that was randomly selected from the national population registry. The aimed sample size was reached and therefore there should be sufficient power to show a reduction in CHD events of at least 15%.¹⁵ Furthermore, screening results were consistently obtained by adequately trained research personnel. A main limitation was that the presented data analysis is cross-sectional. Therefore, conclusions on the reduction of preventive overtreatment cannot be drawn yet. Future analyses on this subject are required. Another limitation was that recall bias might have caused some inaccuracies in the population characteristics data obtained from the self-reported baseline questionnaire. However, multiple questions were used per health topic to increase the reliability of the answers. Therefore, self-reported questionnaires are the preferred and most cost-effective method for obtaining data in large study populations. Another point is that the described treatment indications in intervention arm A are not completely comparable with preventive treatment based on the SCORE model in current practice. To maintain feasibility, not all risk-increasing factors that codetermine the treatment indication were incorporated in the screening as they are not part of the SCORE calculation itself. Lastly, the final decision regarding preventive treatment was made in consultation with the GP as GPs have access to participants' medical background. The role of GPs in the risk management of increased-risk individuals is important in the feasibility of a potential CVD screening programme.

Within this first population-based RCT on screening for a high risk of CHD, CAC scoring classified significantly fewer individuals at intermediate and high risk in both women and men compared to applying the SCORE model. Subsequently, the potential expected reduction in preventive overtreatment favours the use of CAC scoring in screening. However, future analyses are required to confirm the effectiveness of CVD screening for reduction of CHD and to incorporate costs of CT scanning and preventive treatment. Should screening for a high risk of CVD be net-effective, large health gains will be achieved.

Supplementary data

Supplementary data are available at European Heart Journal - Cardiovascular Imaging online.

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