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Published in:
European Heart Journal - Cardiovascular Imaging

DOI:
10.1093/ehjci/jeac137

ESC European Society of Cardiology

European Heart Journal - Cardiovascular Imaging (2022) **00**, 1–9
https://doi.org/10.1093/ehjci/jeac137

ORIGINAL PAPER

Pre-screening to guide coronary artery calcium scoring for early identification of high-risk individuals in the general population

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Received 25 February 2022; revised 24 June 2022; accepted 2 July 2022

Aims To evaluate the ability of Systematic COronary Risk Estimation 2 (SCORE2) and other pre-screening methods to identify individuals with high coronary artery calcium score (CACS) in the general population.

Methods and results Computed tomography-based CACS quantification was performed in 6530 individuals aged 45 years or older from the general population. Various pre-screening methods to guide referral for CACS were evaluated. Miss rates for high CACS (CACS ≥300 and ≥100) were evaluated for various pre-screening methods: moderate (≥5%) and high (≥10%) SCORE2 risk, any traditional coronary artery disease (CAD) risk factor, any Risk Or Benefit IN Screening for CArdiovascular Disease (ROBINSCA) risk factor, and moderately (>3 mg/24 h) increased urine albumin excretion (UAE). Out of 6530 participants, 643 (9.8%) had CACS ≥300 and 1236 (18.9%) had CACS ≥100. For CACS ≥300 and CACS ≥100, miss rate was 32 and 41% for pre-screening by moderate (≥5%) SCORE2 risk and 81 and 87% for high (≥10%) SCORE2 risk, respectively. For CACS ≥300 and CACS ≥100, miss rate was 8 and 11% for pre-screening by at least one CAD risk factor, 24 and 25% for at least one ROBINSCA risk factor, and 67 and 67% for moderately increased UAE, respectively.

Conclusion Many individuals with high CACS in the general population are left unidentified when only performing CACS in case of at least moderate (≥5%) SCORE2, which closely resembles current clinical practice. Less stringent pre-screening by presence of at least one CAD risk factor to guide CACS identifies more individuals with high CACS and could improve CAD prevention.

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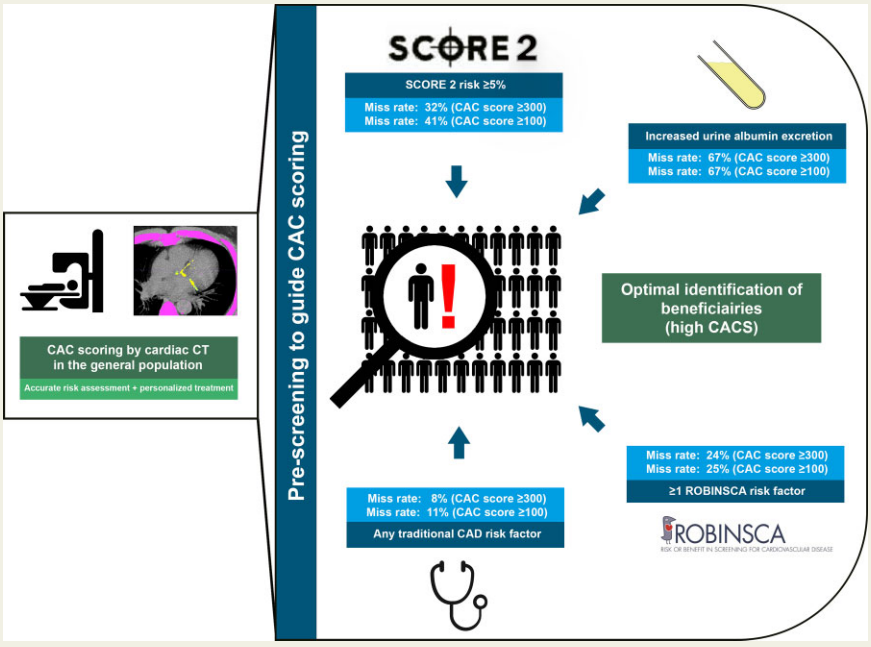
Graphical Abstract



Performance of pre-screening methods to guide CAC scoring. CAC, coronary artery calcium; CACS, coronary artery calcium score; CAD, coronary artery disease; CT, computed tomography; ROBINSCA, Risk Or Benefit IN Screening for CArdiovascular Disease.

Keywords pre-screening • screening • coronary artery calcium • cardiovascular disease • coronary artery disease • prevention

Introduction

Despite implementation of strategies to prevent coronary artery disease (CAD), CAD remains one of the main causes of death and disability.[1,2] In addition, CAD-related healthcare costs are forecasted to increase over the next decades.[3] Improved preventive strategies are warranted to further reduce CAD mortality and morbidity and to fight the increasing CAD burden for society. Professional practice guidelines recommend to initiate lifestyle and drug therapy interventions for prevention of CAD in asymptomatic individuals who are at high risk.[4,5] Recently, the Systematic COronary Risk Estimation (SCORE) was updated and SCORE2 is now recommended to estimate CAD risk and determine treatment strategy in Europe.[5] Following current guidelines, quantification of coronary artery calcium (CAC) based on non-contrast cardiac computed tomography (CT) may be considered in intermediate- or borderline-risk individuals to guide treatment decisions.[4,5] CAC reflects the cumulative lifetime effect of modifiable and non-modifiable risk factors on vulnerable tissue, whereas clinical risk scores provide only a one-time measurement of a small collection of clinical risk factors with only an indirect relationship to underlying atherosclerosis.[6] The CAC score (CACS) has emerged as an excellent tool to improve CAD risk stratification.[7] CACS-based preventive treatment was proved to be cost-effective in asymptomatic individuals at intermediate CAD risk.[8,9] In contrast, clinical CAD risk estimation scores, such as SCORE, tend to over- or underestimate risk on an individual level.[10,11] By using CACS only in a limited group of individuals selected by inaccurate risk scoring, many high-risk individuals with high CACSs remain unrecognized and untreated and many low-risk individuals with in fact low CACSs receive unnecessary treatment.[12] It remains the question whether referral for CACS only in case of borderline risk estimated by risk scores provides the most optimal strategy in the prevention of CAD on a population level. The aim of the present study was therefore to evaluate and compare the performance of the new SCORE2 and other pre-screening methods for identifying individuals with a high CACS, who are at elevated cardiovascular risk and require further therapy to prevent CAD.

Methods

Study design and participants of Lifelines and Imaging in Lifelines cohort studies

The study population consists of individuals from the general population without CAD who underwent CT-based CAC quantification as part of the Imaging in Lifelines (ImaLife) study, a population-based imaging study embedded in the Lifelines cohort. Lifelines is a population-based cohort study examining the health and health-related behaviours of three generations of inhabitants of the northern part of The Netherlands. The study design and rationale of Lifelines were previously described in

detail.[13] Written informed consent was provided by all Lifelines participants. During the baseline visit (2007–13), as well as during the second visit (2013–17), blood and urine samples of all participants were collected, and all participants underwent a physical examination including anthropometric measurements and a 12-lead electrocardiogram (ECG). Lifelines participants who had completed the second visit were additionally invited for the ImaLife study. Eligible candidates (≥45 years of age) providing additional written informed consent for ImaLife underwent a low-dose CT examination of the chest during an extra imaging visit. The ImaLife study was approved by the medical ethics committee of the University Medical Center Groningen, The Netherlands.[14] For the current study, all ImaLife participants who completed the imaging visit so far and had the CACS measured were included. Individuals with a known medical history of myocardial infarction (MI), percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), or heart failure were excluded from analyses.

Coronary artery calcium score

Non-contrast cardiac CT scanning for CAC quantification was performed with a third-generation dual-source CT system (Somatom Force, Siemens Healthineers, Germany) with prospective ECG triggering. A tube voltage of 120 kVp and tube current of 64 quality reference mAs/rot were used. Images were reconstructed with a slice thickness and increment of 3.0 and 1.5 mm. CACS was quantified using the Agatston method with dedicated software (Syngo.via VB30A, CaScoring; Siemens) by a well-trained researcher.

Definitions of cardiovascular risk factors and diseases

Cardiovascular diseases and risk factors were defined based on questionnaires, physical examination, and blood biomarkers obtained at baseline and during follow-up, as described earlier.[15] When discrepancies existed regarding the presence of risk factors between baseline and second visit, data from the second visit were used. In case of missing data at the second visit, data from the baseline visit were used. MI was defined as self-reported MI (in questionnaires during baseline or follow-up), or signs on the ECG suggestive for previous myocardial infarction.[16] History of PCI or CABG was obtained from baseline or follow-up questionnaires. A history of heart failure was considered to be present when a participant answered confirmatively on the question 'do you have heart failure?'. Hypertension was defined as a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg or the use of blood pressure–lowering drugs. Hypercholesterolaemia was defined as a total cholesterol ≥6.5 mmol/L or the use of cholesterol-lowering medication. Diabetes mellitus was considered to be present if diabetes mellitus was self-reported or if using anti-diabetic medication. Family history of CAD was defined as the presence of a parent, sibling, or child with CAD acquired before the age of 60, obtained from a questionnaire. SCORE2 risk was calculated by standardized formulas incorporating age, sex, smoking, systolic blood pressure, and total cholesterol.[17] Urinary albumin concentration was measured by nephelometry and multiplied by urine volume to obtain a value of urinary albumin excretion (UAE) in milligrams per 24 h. Thresholds of >3 and >30 mg/24 h were used in our analyses to define increased UAE. Due to missing data, SCORE and SCORE2 could not be calculated in 27 participants. Data on UAE were not available for 129 participants.

Objectives and outcome definition

The primary objective was to evaluate whether pre-screening methods can accurately identify individuals with a high CACS indicative of elevated CAD risk, who likely benefit from early preventive therapy. European guidelines do not provide exact CACS cut-offs to decide on preventive therapy initiation.[5] Given the lack of evidence on the optimal CACS threshold to initiate preventive therapy, two co-primary high CACS outcomes were defined in this study. A CACS ≥ 100 was suggested as a potential CACS cut-off above which preventive (drug) therapy could be beneficial.[12,18] CACS ≥ 300 is widely accepted as indicative of high CAD risk,[19] and intensive preventive management is indicated in individuals with CACS ≥ 300, following US guidelines.[4] Therefore, CACS ≥ 100 and CACS ≥ 300 were defined as co-primary outcomes. US guidelines recommend therapy in individuals with a CACS threshold above the 75th age- and sex-standardized percentile.[4] We therefore additionally evaluated secondary outcomes incorporating age- and sex-standardized CACS: (i) CACS ≥ 300 OR a CACS > 75th age- and sex-standardized percentile, and (ii) CACS ≥ 100 OR a CACS > 75th age- and sex-standardized percentile. CACS percentiles were defined based on pooled data from various cohorts.[20]

A secondary objective was to evaluate the proportion of the population being theoretically referred for CACS by testing positive on pre-screening.

Statistical analyses

Normally distributed continuous variables were presented with mean and standard deviation. Continuous variables not normally distributed were presented as medians with interquartile ranges and categorical variables as percentages. The χ^2 test was used to compare frequencies of risk factors in individuals with and without the primary or secondary outcome. Differences in continuous variables, not normally distributed, were ascertained by two-sample Wilcoxon rank-sum (Mann–Whitney) test. The miss rate (i.e. 1-sensitivity), which is the probability of missing individuals with high CACS by pre-screening methods, was primarily evaluated to study the performance of pre-screening methods. Secondarily, positive predictive value, negative predictive value, and specificity were evaluated. In addition, the percentage of the population theoretically being referred for CACS by pre-screening was reported ($n_{\text{positive pre-screening}}/n_{\text{total}} \times 100\%$). The following pre-screening methods were tested:

- Presence of any traditional CAD risk factor [i.e. increased body mass index (BMI) ≥30 kg/m^2, hypercholesterolaemia, hypertension, diabetes mellitus, current or former smoking, and positive family history of CAD].
- Presence of ≥1 risk factor as defined in the Risk Or Benefit IN Screening for CArdiovascular Disease (ROBINSCA) study (i.e. increased waist circumference: ≥102 cm for men; ≥88 cm for women), BMI ≥30 kg/m^2, current smoking or positive family history of CAD). ROBINSCA is a population-screening trial evaluating whether CAC-based screening to start preventive therapy provides benefit or harm compared with SCORE-based screening and no screening.[21]
- The presence of increased UAE at the lower threshold of >3 mg/24 h and the higher threshold of >30 mg/24 h.
- SCORE risk: ≥1% (moderate risk) and ≥5% (high risk).[22]
- SCORE2 risk: ≥5% (moderate risk) and ≥10% (high risk).[5] The cut-offs indicating moderate and high SCORE2 risk, which depend on

age category according to the European guideline on CAD prevention, were defined in this study based on the median age of our study population.

Two-sided *P*-values <0.05 were considered to be statistically significant. All statistical analyses were performed using Stata version IC 13 (StataCorp, College Station, TX, USA).

Results

Baseline characteristics of the study population

Data of 6763 individuals who underwent CT for CAC quantification were available. About 233 individuals were excluded from analyses due to a history of MI, PCI, CABG, or heart failure (*Figure 1*). In total, 6530 participants were included in this study, of whom 9.8% (643/6530) had CACS ≥300 and 18.9% (1236/6530) had CACS ≥ 100. CACS ≥ 300 or CACS > 75th percentile was present in 24.6% (1.605/6530) of study participants, and CACS ≥ 100 or CACS > 75th percentile in 27.8% (1820/6530). Baseline characteristics of the study population are provided in *Table 1*. In general, individuals with CACS ≥ 300 and CACS ≥ 100 were on average older, more frequently male and had higher prevalence of traditional cardiovascular risk factors compared with those without the primary outcome. For the secondary outcomes (CACS ≥300 or >75th percentile and CACS ≥100 or >75th percentile), similar patterns were observed (see Supplementary data online, *Tables S1* and *S2*).

Performance of pre-screening methods for identification of CACS ≥ 300

Performance of pre-screening methods for the detection of CACS ≥ 300 is provided in *Table 2*.

Miss rate for CACS ≥ 300 was 32% [95% confidence interval (CI): 28–36%] for pre-screening by SCORE2 risk ≥5%, and 81% (95% CI: 78–84%) for pre-screening by SCORE2 ≥ 10%. For pre-screening based on SCORE ≥1 and ≥5%, miss rate for CACS ≥ 300 was 10% (95% CI: 8–13%) and 85% (95% CI: 82–87%), respectively. Miss rate for CACS ≥ 300 was 67% (95% CI: 63–70%) for pre-screening by UAE >3 mg/24 h and 97% (95% CI: 96–98%) for pre-screening by UAE > 30 mg/24 h. For simple pre-screening based on the presence of at least one traditional CAD risk factor, miss rate for CACS ≥ 300 was 8% (95% CI: 6–11%). Miss rate for CACS ≥ 300 was 24% (95% CI: 21–28%) for pre-screening based on the presence of at least one ROBINSCA risk factor. For the secondary outcome of CACS ≥ 300 or CACS > 75th percentile, miss rates were on average higher than for the co-primary outcome of CACS ≥ 300, but showed similar patterns when mutually comparing performance of the various pre-screening methods (see Supplementary data online, *Table S3*). Miss rates were on average lower for men compared with women for all pre-screening methods (see Supplementary data online, *TablesS4A-B* and *S5A-B*).

Performance of pre-screening methods for identification of CACS ≥ 100

Performance of pre-screening methods for detection of CACS ≥ 100 is provided in *Table 3*.

Miss rate for CACS ≥ 100 was 41% (95% CI: 39–44%) for pre-screening by SCORE2 risk ≥5%, and 87% (95% CI: 85–89%) for pre-screening by SCORE2 ≥ 10%. For pre-screening based on SCORE ≥1 and ≥5%, miss rate for CACS ≥ 100 was 16% (95% CI: 14–18%) and 89% (95% CI: 88–91%), respectively. Miss rate for CACS ≥ 100 was 67% (95% CI: 64–69%) for pre-screening by UAE >3 mg/24 h and 97% (95% CI: 96–98%) for pre-screening by UAE >30 mg/24 h. For simple pre-screening based on the presence of at least one traditional CAD risk factor, miss rate for CACS ≥ 100 was 11% (95% CI: 9–13%). Miss rate for CACS ≥ 100 was 25% (95% CI: 23–28%) for pre-screening based on presence of at least one ROBINSCA risk factor. For the secondary outcome of CACS ≥ 100 or CACS > 75th percentile, miss rates were on average higher than for the co-primary outcome CACS ≥ 100, but showed similar patterns when mutually comparing the various pre-screening methods (see Supplementary data online, *Table S6*). Miss rates for CACS ≥ 100 were on average lower for men compared with women for all pre-screening methods (see Supplementary data online, *Tables S7A-B* and *S8A-B*).

Proportion of the population receiving CAC screening for various pre-screening methods

Pre-screening by SCORE2 ≥ 5% leads to CACS in 25% (95% CI: 24–26%) and SCORE ≥ 10% to CACS in 3% (95% CI: 3–4%) of the total population. For pre-screening by SCORE ≥1 and ≥5%, CAC screening theoretically leads to CACS in 49% (95% CI: 48–50%) and 3% (95% CI: 2–3%) of the population, respectively. For pre-screening by UAE >3 and >30 mg/24 h, CAC screening is performed in 31% (95% CI: 30–32%) and 2% (95% CI: 1–2%) of the population. Pre-screening by presence of ≥1 traditional CAD risk factor results in CAC screening in 73% (95% CI: 72–74%) and pre-screening by ≥1 ROBINSCA risk factor to CAC screening in 66% (95% CI: 64–67%) of the population.

Discussion

Current European professional practice guidelines recommend to perform CACS only in case of at least moderate (≥5%) or borderline risk as estimated by SCORE2. However, it remains unclear whether pre-screening by SCORE2 risk to guide CACS provides the optimal strategy for prevention of CAD. In this unselected population-based imaging study, 32–41% of all individuals with a high CACS would be missed when applying pre-screening by the moderate SCORE2 risk cut-off (≥5%) to decide on referral for CACS, which closely resembles current clinical practice. By simple pre-screening based on the presence of at least one CAD risk factor, the majority of individuals with high CACS were identified.

The findings of this study suggest that many individuals with high CACSs, who are at high risk of facing CAD, are left unidentified and untreated by the current approach to perform CACS only in case of moderate or borderline SCORE2 risk. This finding is in line with a previous study reporting that high CACS is frequently present in those with low SCORE risk.[23] In addition, acute MI frequently occurs in individuals who are classified as 'low-risk' by clinical risk prediction scores.[24] In fact, most cardiovascular events occur in low-risk individuals, because they represent the majority of the population

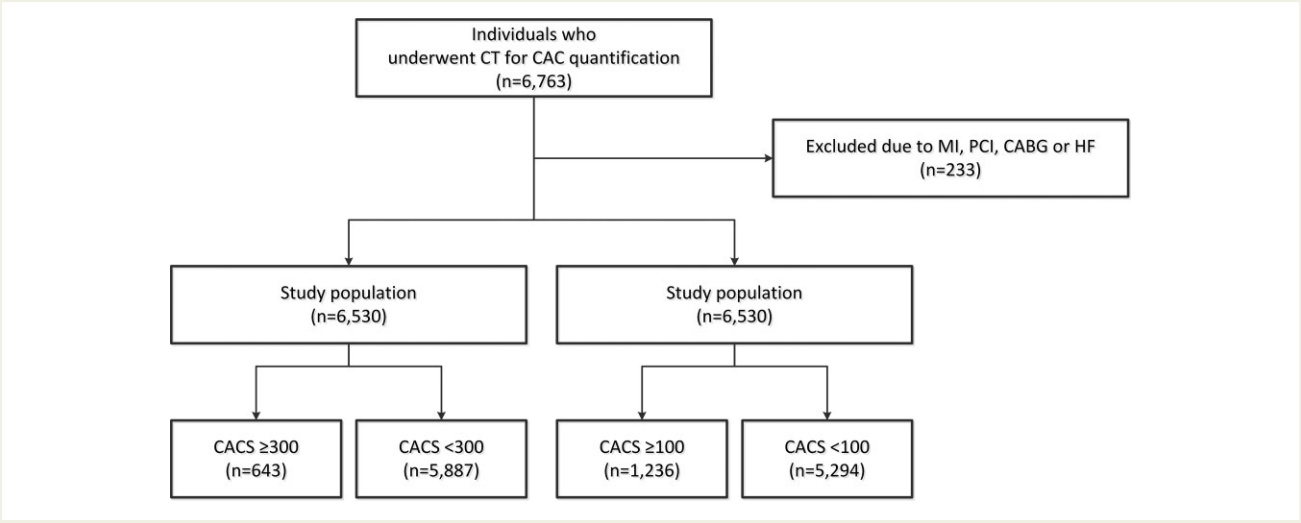


Figure 1 Flow chart of the study population. CABG, coronary artery bypass grafting; CAC, coronary artery calcium; CACS, coronary artery calcium score; CT, computed tomography; HF, heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention.

(i.e. the 'Rose paradox'). Targeting truly high-risk individuals as indicated by accurate CACS and also targeting more relatively low-risk individuals may aid in preventing more cardiovascular events and may improve health of the general population. Importantly, interference of a physician is required to determine SCORE2, which undermines accessibility to CAD preventive care. Home-based self-assessment, for instance by a digital application on phone, tablet, or personal computer, could improve accessibility to preventive care and could optimize early identification of high-risk individuals who benefit most from early CACS and early preventive therapy. Digital health self-monitoring, for instance by heart rate and rhythm monitoring via smart watches, is widely available and is more commonly implemented in routine cardiovascular care nowadays, even in the elderly.[25] We showed that simple, potentially home-based pre-screening by, for instance the presence of at least one traditional CAD risk factor, is able to identify the majority of asymptomatic individuals with a high CACS. Compared with scanning the population based on an age criterion only (e.g. all aged >45 years, as was performed in our study), pre-screening by presence of one CAD risk factor or one ROBINSCA risk factor can already substantially reduce the number of CAC screening procedures needed, at cost of missing only very few individuals with high CACS. However, wider indications for CACS will lead to more CACS procedures being performed. There is a risk of harm (both monetary and non-monetary) for more widespread CACS, although CT imaging to quantify CAC is simple, non-invasive, and low cost. In addition, CT is associated with radiation, but improved CT techniques have resulted in very low radiation doses associated with CACS and radiation burden is now comparable with, for instance, screening mammography (<1 mSv).[26] The ROBINSCA trial will provide more evidence on the benefit and risk of widespread CACS in the general population.[21] Further studies, especially cost–utility evaluations, will be needed to gain more insight in which pre-screening method allows for the most optimal selection of potential beneficiaries.

CACS-guided initiation of preventive therapy results in a reduction of CAD-related events.[27] However, no large-scale randomized-controlled clinical trials proving the benefit of CACS-guided initiation of preventive therapy have been performed and controversy exists regarding the optimal CACS cut-off to decide on initiation of preventive therapy. An absolute CACS ≥ 300 is associated with a nearly 10-fold increased risk of events compared with a CACS of zero, and is generally considered indicative of high cardiovascular risk.[19] Other absolute CACS cut-offs to decide on initiation of preventive drug therapy (e.g. CACS ≥ 100) may also be considered.[8,9] Age- and sex-standardized CACS have been proposed to improve risk stratification,[20] but absolute CACS outperforms age- and gender-standardized CACS in prediction of clinical events.[28] Clinical practice guidelines currently do not provide an unequivocal recommendation on which CAC risk-categorization method should be preferred. Therefore, we evaluated both CACS ≥ 300 and CACS ≥ 100 as co-primary outcomes and also evaluated performance of pre-screening methods for alternative CACS thresholds combining absolute and age- and sex-standardized CACS cut-offs (≥300 OR >75th percentile and ≥100 OR >75th percentile). Interestingly, performance of pre-screening methods for detection of these secondary CACS outcomes showed comparable patterns when comparing the various pre-screening methods. Miss rates of pre-screening methods were slightly higher for the outcomes including age- and sex-standardized CACS cut-offs than for CACS outcomes including absolute CACS only. This suggests that it is more difficult to identify all cases with a relatively high CACS for their sex and age by these pre-screening methods. Other non-modifiable risk factors, such as genetic predisposition, might play an important role in the presence and severity of CAC in these individuals.[29] It remains uncertain whether early treatment of individuals with a relatively high CACS for their age and sex provides additional benefit over treatment guided by absolute CACS, and whether it is worthwhile to early treat these individuals with primary preventive drug therapy.

Recently, a home-based urinalysis smartphone test was proposed as a potential tool to measure increased UAE as a marker of CAD risk.[30] We therefore evaluated whether this home-based marker of atherosclerotic disease could improve early identification of high-

Table 1 **Baseline characteristics of the study population**

	ALL *N* = 6530	CACS < 300 *N* = 5887	CACS ≥ 300 *N* = 643	*P*-value	CACS < 100 *N* = 5294	CACS ≥ 100 *N* = 1236	*P*-value
AGE (YEARS)	53.7 (8.2)	52.8 (7.7)	62.0 (8.3)	<0.001	52.2 (7.3)	60.3 (8.4)	<0.001
MEN	42.7 (2786)	39.5 (2323)	72.0 (463)	<0.001	37.5 (1987)	64.6 (799)	<0.001
ANTHROPOMETRY							
HEIGHT (CM)	174.3 (9.4)	174.2 (9.4)	175.6 (9.2)	<0.001	174.1 (9.3)	175.3 (9.4)	<0.001
WEIGHT (KG)	79.9 (14.5)	79.5 (14.3)	83.8 (15.2)	<0.001	79.2 (14.3)	83.0 (15.0)	<0.001
BMI (KG/MCSSUPSTART2CSSUPEND)	26.3 (4.0)	26.2 (4.0)	27.1 (3.9)	<0.001	26.1 (4.0)	26.9 (4.0)	<0.001
HEART RATE (B.P.M.)	67.4 (10.9)	67.4 (10.8)	67.7 (11.9)	0.563	67.3 (10.8)	67.9 (11.7)	0.104
WAIST-TO-HIP RATIO	0.91 (0.09)	0.90 (0.08)	0.96 (0.08)	<0.001	0.90 (0.08)	0.95 (0.09)	<0.001
RISK FACTORS							
DIASTOLIC BLOOD PRESSURE (MMHG)	75.3 (9.6)	75.0 (9.5)	78.5 (9.6)	<0.001	74.6 (9.4)	78.4 (9.7)	<0.001
SYSTOLIC BLOOD PRESSURE (MMHG)	129.7 (16.3)	128.9 (16.0)	137.4 (16.4)	<0.001	128.0 (15.7)	137.2 (16.8)	<0.001
HYPERTENSION	38.1 (2490)	35.3 (2080)	63.8 (410)	<0.001	32.9 (1739)	60.8 (751)	<0.001
HYPERCHOLESTEROLAEMIA	19.2 (1252)	17.3 (1080)	36.4 (234)	<0.001	15.9 (839)	33.4 (413)	<0.001
DIABETES	3.8 (251)	3.2 (190)	9.5 (61)	<0.001	2.9 (151)	8.1 (100)	<0.001
SMOKING	50.1 (2966)	48.7 (2599)	62.1 (367)	<0.001	47.2 (2267)	62.2 (699)	<0.001
SCORE RISK (%)	0 (0–1)	0 (0–1)	2 (1–4)	<0.001	0 (0–1)	2 (1–3)	<0.001
SCORE2 RISK (%)	3 (2–4)	3 (2–4)	6 (4–8)	<0.001	2 (1–4)	5 (3–7)	<0.001
UAE (MG/24 H)	1.8 (1.0–3.5)	1.8 (1.0–3.5)	1.9 (1.1–3.8)	0.045	1.8 (1.0–3.5)	1.9 (1.1–3.9)	0.002
INCREASED UAE							
>3 MG/24 H	31.2 (1998)	31.0 (1786)	33.3 (212)	0.235	30.7 (1590)	33.4 (4.0)	0.072
>30 MG/24 H	1.7 (111)	1.6 (94)	2.7 (17)	0.057	1.5 (77)	2.8 (34)	0.002

Data presented as mean ± standard deviation, median (interquartile range) or % (*n*).
BMI, body mass index; SCORE, Systematic Coronary Risk Evaluation; UAE, urine albumin excretion.

Table 2 Diagnostic performance of pre-screening criteria for CACS ≥ 300 in men and women ≥45 years

CACS ≥300:10% (*n* = 643/6530)	Miss rate (1-sensitivity)	% of population receiving CAC scan	PPV	NPV	Specificity
≥1 traditional risk factor	8% (54/643)	73% (4748/6530)	12% (589/4748)	97% (1728/1782)	29% (1728/5887)
≥1 ROBINSCA risk factor[a]	24% (156/643)	66% (4287/6530)	11% (487/4287)	93% (2087/2243)	35% (2087/5887)
Increased UAE					
Low cut-off (3 mg/24 h)	67% (425/637)	31% (1998/6401)	11% (212/1998)	90% (3978/4403)	69% (3978/5764)
High cut-off (30 mg/24 h)	97% (620/637)	2% (111/6401)	15% (17/111)	90% (5670/6290)	98% (5670/5764)
SCORE					
≥1%	10% (67/643)	49% (3199/6502)	18% (575/3199)	98% (3236/3303)	55% (3236/5860)
≥5%	85% (544/643)	3% (180/6502)	54% (98/180)	91% (5778/6322)	99% (5778/5860)
SCORE2					
≥5%	32% (202/636)	25% (1598/6502)	27% (434/1598)	96% (4702/4904)	80% (4702/5866)
≥10%	81% (517/636)	3% (205/6502)	58% (119/205)	92% (5780/6297)	99% (5780/5866)

CAC, coronary artery calcium; CACS, coronary artery calcium score; NPV, negative predictive value; PPV, positive predictive value; SCORE2, Systematic Coronary Risk Evaluation 2; UAE, urine albumin excretion.
[a]Waist circumference ≥102 cm (men) or ≥88 cm (women), body mass index ≥30 kg/m^2, current smoker and/or a family history of coronary artery disease.

Table 3 Diagnostic performance of pre-screening criteria for CACS ≥ 100 in men and women ≥45 years

CACS ≥ 100: 19% (n = 1236/6530)	Miss rate (1-sensitivity)	% of population receiving CAC scan	PPV	NPV	Specificity
≥1 TRADITIONAL RISK FACTORS	11% (132/1236)	73% (4748/6530)	23% (1104/4748)	93% (1650/1782)	31% (1650/5294)
≥1 ROBINSCA RISK FACTORSCSSUPSTARTACSSUPEND	25% (315/1236)	66% (4287/6530)	21% (921/4287)	86% (1928/2243)	36% (1928/5294)
INCREASED UAE					
Low cut-off (3 mg/24 h)	67% (815/1223)	31% (1998/6401)	20% (408/1998)	81% (3588/4403)	69% (3588/5178)
High cut-off (30 mg/24 h)	97% (1189/1223)	2% (111/6401)	31% (34/111)	81% (5101/6290)	99% (5101/5178)
SCORE					
≥1%	16% (196/1228)	49% (3199/6502)	32% (1032/3199)	94% (3107/3303)	59% (3107/5274)
≥5%	89% (1098/1228)	3% (180/6502)	72% (130/180)	83% (5224/6322)	99% (5224/5274)
SCORE2					
≥5%	41% (508/1226)	25% (1598/6502)	45% (718/1598)	90% (4396/4904)	83% (4396/5276)
≥10%	87% (1072/1226)	3% (205/6502)	75% (154/205)	83% (5225/6297)	99% (5225/5276)

CAC, coronary artery calcium; CACS, coronary artery calcium score; NPV, negative predictive value; PPV, positive predictive value; SCORE2, Systematic Coronary Risk Evaluation 2; UAE, urine albumin excretion.
[a]Waist circumference ≥102 cm (men) or ≥88 cm (women), body mass index ≥30 kg/m^2, current smoker and/or a family history of coronary artery disease.

risk individuals as indicated by an increased CACS. High miss rates were observed for both the UAE cut-offs investigated in our study. This suggests that pre-screening by increased UAE will not improve current clinical practice for referral to CACS.

Some limitations should be mentioned when interpreting the results of the present study. Since we evaluated individuals participating in a population-based study, some individuals could have already received primary preventive treatment, potentially affecting their CACS. In addition, whether intended treatment based on the CACS cut-offs used in this study would lead to over- or undertreatment, and would be accurately targeted to those actually facing CAD-related events could not be evaluated due to the lack of follow-up data at this time. Furthermore, although our findings are likely representative for the general Caucasian middle-aged and older population, one should be cautious to extrapolate these results to populations below the age of 45 years and populations of different race/ethnicity. Finally, presence of risk factors was ascertained by asking participants simple digital questions to explore the use of medication in combination with physical measurements as part of study visits (e.g. waist-to-hip ratio, blood pressure measurements). Although in theory, all of these measurements could be performed at home and the pre-screening methods applied here could be simply

implemented in a digital application that could be used at home, pre-screening was not fully conducted at home in this study. Choice for the pre-screening methods evaluated here was based on the currently most commonly applied forms of pre-screening, for instance as mentioned by professional practice guidelines. However, the choice for pre-screening methods evaluated in this study remains arbitrary.

Conclusions

In this large population-based imaging study, SCORE2 risk ≥5% and other conventional high-risk indicators (SCORE2 risk ≥10%, increased UAE >3 and >30 mg/24 h) failed to detect the majority of individuals at elevated CAD risk as indicated by a CACS ≥ 300 and CACS ≥ 100. Simple, potentially home-based pre-screening by presence of at least one traditional CAD risk factor detected the majority of individuals with a high CACS. Less stringent indications for CACS in the general population can identify more high-risk individuals and could improve CAD prevention by early appropriate therapy.

Supplementary data

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

Acknowledgements

Funding by FES (Fonds Economische Structuurversterking), SNN (Samenwerkingsverband Noord Nederland), and REP (Ruimtelijk Economisch Programma) has supported the Lifelines Biobank initiative. The ImaLife study has been made possible by an institutional research grant from Siemens Healthineers and by the Ministry of Economic Affairs and Climate Policy by means of the PPP Allowance made available by the Top Sector Life Sciences & Health to stimulate public–private partnerships. The authors are grateful to all the study participants for their contribution and acknowledge the services of the Lifelines Cohort Study and the contributing research centres delivering data to Lifelines.

Funding

This research received grants from Siemens Healthineers & the Dutch Ministry of Economic Affairs and Climate Policy.

Conflict of interest: R.V. reports receiving grant support by Siemens Healthineers and Ministry of Economic Affairs and Climate Policy and lecture fees by Siemens Healthineers and Bayer, and P.V.D.H. receiving grant support by Siemens Healthineers and Guerbet. The other authors did not report any potential conflict of interest relevant to this article.

Data availability

Data requests should be submitted to the principal investigator (P.V.D.H.) for consideration. The authors aim to share data to the maximum extent, but within specific boundaries relating to ethical approval and informed consent, contractual and legal obligations of this study, and publication timelines. All proposals will be reviewed for their scientific merit by the trial management group. Only data relevant to the purpose of the data request will be provided.

References

1. Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, *et al.* Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020;**396**:1204–22. doi:10.1016/S0140-6736(20)30925-9
2. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, *et al.* Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;**392**:1789–858. doi:10.1016/S0140-6736(18)32279-7
3. Odden MC, Coxson PG, Moran A, Lightwood JM, Goldman L, Bibbins-Domingo K. The impact of the aging population on coronary heart disease in the United States. *Am J Med* 2011;**124**:827–33. doi:10.1016/j.amjmed.2011.04.010
4. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, *et al.* 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2019;**74**:e177–232. doi:10.1016/j.jacc.2019.03.010
5. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, *et al.* 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021;**42**:3227–337. doi:10.1093/eurheartj/ehab484
6. Blaha MJ, Silverman MG, Budoff MJ. Clinical risk scores are not sufficient to define primary prevention treatment strategies among asymptomatic patients. *Circ Cardiovasc Imaging* 2014;**7**:398–408. doi:10.1161/CIRCIMAGING.113.000341
7. Hecht HS. Coronary artery calcium scanning: past, present, and future. *JACC Cardiovasc Imaging* 2015;**8**:579–96. doi:10.1016/j.jcmg.2015.02.006
8. Pletcher MJ, Pignone M, Earnshaw S, McDade C, Phillips KA, Auer R, *et al.* Using the coronary artery calcium score to guide statin therapy a cost-effectiveness analysis. *Circ Cardiovasc Qual Outcomes* 2014;**7**:276–84. doi:10.1161/CIRCOUTCOMES.113.000799
9. Hong JC, Blankstein R, Shaw LJ, Padula WV, Arrieta A, Fialkow JA, *et al.* Implications of coronary artery calcium testing for treatment decisions among statin candidates according to the ACC/AHA cholesterol management guidelines: a cost-effectiveness analysis. *JACC Cardiovasc Imaging* 2017;**10**:938–52. doi:10.1016/j.jcmg.2017.04.014
10. DeFilippis AP, Young R, Carrubba CJ, McEvoy JW, Budoff MJ, Blumenthal RS, *et al.* An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. *Ann Intern Med* 2015;**162**:266–75. doi:10.7326/M14-1281
11. Rana JS, Tabada GH, Solomon MD, Lo JC, Jaffe MG, Sung SH, *et al.* Accuracy of the atherosclerotic cardiovascular risk equation in a large contemporary, multiethnic population. *J Am Coll Cardiol* 2016;**67**:2118–30. doi:10.1016/j.jacc.2016.02.055
12. van der Aalst CM, Denissen SJAM, Vonder M, Gratama JWC, Adriaansen HJ, Kuijpers D, *et al.* Screening for cardiovascular disease risk using traditional risk factor assessment or coronary artery calcium scoring: the ROBINSCA trial. *Eur Hear J - Cardiovasc Imaging* 2020;**21**:1216–24. doi:10.1093/ehjci/jeaa168
13. Scholtens S, Smidt N, Swertz MA, Bakker SJL, Dotinga A, Vonk JM, *et al.* Cohort profile: LifeLines, a three-generation cohort study and biobank. *Int J Epidemiol* 2015;**44**:1172–80. doi:10.1093/ije/dyu229
14. Xia C, Rook M, Pelgrim GJ, Sidorenkov G, Wisselink HJ, van Bolhuis JN, *et al.* Early imaging biomarkers of lung cancer, COPD and coronary artery disease in the general population: rationale and design of the ImaLife (Imaging in Lifelines) Study. *Eur J Epidemiol* 2020;**35**:75–86. doi:10.1007/s10654-019-00519-0
15. van der Ende MY, Hartman MHT, Hagemeijer Y, Meems LMG, de Vries HS, Stolk RP, *et al.* The LifeLines Cohort Study: prevalence and treatment of cardiovascular disease and risk factors. *Int J Cardiol* 2017;**228**:495–500. doi:10.1016/j.ijcard.2016.11.061
16. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, *et al.* Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol* 2018;**72**:2231–64. doi:10.1016/j.jacc.2018.08.1038
17. Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, *et al.* Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003;**24**:987–1003. doi:10.1016/S0195-668X(03)00114-3
18. Dzaye O, Razav AC, Dardari ZA, Shaw LJ, Berman DS, Budoff MJ, *et al.* Modeling the recommended age for initiating coronary artery calcium testing among at-risk young adults. *JACC* 2021;**78**:1573–83. doi:10.1016/j.jacc.2021.08.019
19. Detrano R, Guerci AD, Carr J, Bild DE, Burke G, Folsom AR, *et al.* Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med* 2008;**358**:1336–45. doi:10.1056/NEJMoa072100
20. de Ronde MWJ, Khoshiwal A, Planken RN, Boekholdt SM, Biemond M, Budoff MJ, *et al.* A pooled-analysis of age and sex based coronary artery calcium scores percentiles. *J Cardiovasc Comput Tomogr* 2020;**14**:414–20. doi:10.1016/j.jcct.2020.01.006
21. Van Der Aalst CM, Vonder M, Gratama J, Adriaansen HJ, Kuijpers D, Denissen SJ, *et al.* Risk or benefit in screening for cardiovascular disease (ROBINSCA): the rationale and study design of a population-based randomized-controlled screening trial for cardiovascular disease. *J Clin Trials* 2019;**9**:1–8. doi:10.4172/2167-0870.1000361

22. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, *et al.* 2016 European Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2016;**37**:2315–81. doi:10.1093/eurheartj/ehw106
23. Östgren CJ, Söderberg S, Festin K, Angerås O, Bergström G, Blomberg A, *et al.* Systematic coronary risk evaluation estimated risk and prevalent subclinical atherosclerosis in coronary and carotid arteries: a population-based cohort analysis from the Swedish Cardiopulmonary Bioimage Study. *Eur J Prev Cardiol* 2020;**28**:250–9. doi:10.1177/2047487320909300
24. Lauer M. Primary prevention of atherosclerotic cardiovascular disease. *JAMA* 2007; **297**:1376–8. doi:10.1001/jama.297.12.1376
25. Liu L, Stroulia E, Nikolaidis I, Miguel-Cruz A, Rios Rincon A. Smart homes and home health monitoring technologies for older adults: a systematic review. *Int J Med Inform* 2016;**91**:44–59. doi:10.1016/j.ijmedinf.2016.04.007
26. Baron KB, Choi AD, Chen MY. Low radiation dose calcium scoring: evidence and techniques. *Curr Cardiovasc Imaging Rep* 2016;**9**:1–8. doi:10.1007/s12410-016-9373-1
27. Mitchell JD, Fergestrom N, Gage BF, Paisley R, Moon P, Novak E, *et al.* Impact of statins on cardiovascular outcomes following coronary artery calcium scoring. *J Am Coll Cardiol* 2018;**72**:3233–42. doi:10.1016/j.jacc.2018.09.051
28. Budoff MJ, Nasir K, McClelland RL, Detrano R, Wong N, Blumenthal RS, *et al.* Coronary calcium predicts events better with absolute calcium scores than age-sex-race/ethnicity percentiles. MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol* 2009;**53**:345–52. doi:10.1016/j.jacc.2008.07.072
29. Van Der Harst P, Verweij N. Identification of 64 novel genetic loci provides an expanded view on the genetic architecture of coronary artery disease. *Circ Res* 2018; **122**:433–43. doi:10.1161/CIRCRESAHA.117.312086
30. Leddy J, Green JA, Yule C, Molecavage J, Coresh J, Chang AR. Improving proteinuria screening with mailed smartphone urinalysis testing in previously unscreened patients with hypertension: a randomized controlled trial. *BMC Nephrol* 2019;**20**: 132. doi:10.1186/s12882-019-1324-z