

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

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## 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  $\geq 300$  and  $\geq 100$ ) were evaluated for various pre-screening methods: moderate ( $\geq 5\%$ ) and high ( $\geq 10\%$ ) SCORE2 risk, any traditional coronary artery disease (CAD) risk factor, any Risk Or Benefit IN Screening for Cardiovascular Disease (ROBINSICA) risk factor, and moderately ( $>3$  mg/24 h) increased urine albumin excretion (UAE). Out of 6530 participants, 643 (9.8%) had CACS  $\geq 300$  and 1236 (18.9%) had CACS  $\geq 100$ . For CACS  $\geq 300$  and CACS  $\geq 100$ , miss rate was 32 and 41% for pre-screening by moderate ( $\geq 5\%$ ) SCORE2 risk and 81 and 87% for high ( $\geq 10\%$ ) SCORE2 risk, respectively. For CACS  $\geq 300$  and CACS  $\geq 100$ , miss rate was 8 and 11% for pre-screening by at least one CAD risk factor, 24 and 25% for at least one ROBINSICA risk factor, and 67 and 67% for moderately increased UAE, respectively.

## Conclusion

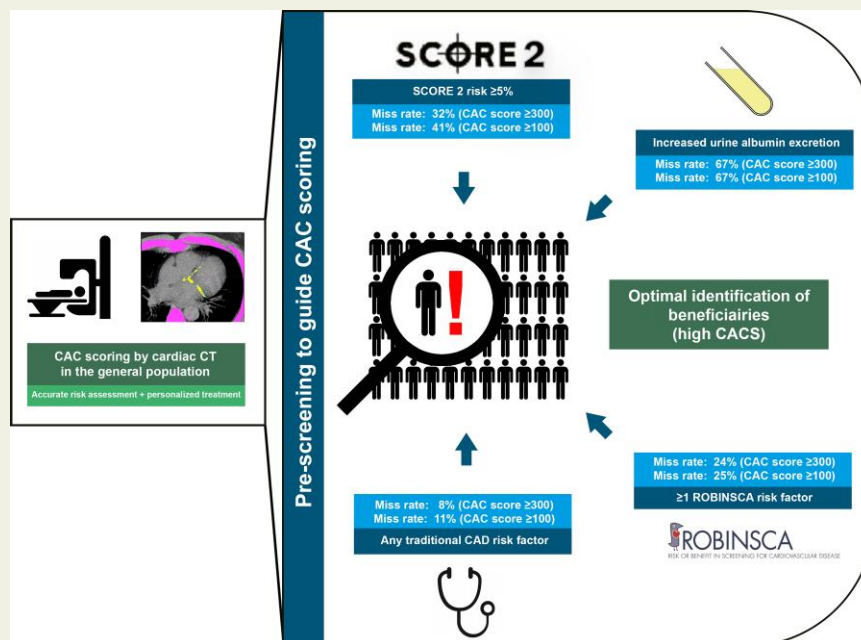
Many individuals with high CACS in the general population are left unidentified when only performing CACS in case of at least moderate ( $\geq 5\%$ ) SCORE2, which closely resembles current clinical practice. Less stringent pre-screening by presence of at least one CAD risk factor to guide CACS identifies 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; ROBINSICA, 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.<sup>1,2</sup> In addition, CAD-related healthcare costs are forecasted to increase over the next decades.<sup>3</sup> 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.<sup>4,5</sup> Recently, the Systematic COronary Risk Estimation (SCORE) was updated and SCORE2 is now recommended to estimate CAD risk and determine treatment strategy in Europe.<sup>5</sup> 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.<sup>4,5</sup> 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.<sup>6</sup> The CAC score (CACS) has emerged as an excellent tool to improve CAD risk stratification.<sup>7</sup> CACS-based preventive treatment was proved to be cost-effective in asymptomatic individuals at intermediate CAD risk.<sup>8,9</sup> In contrast, clinical CAD risk estimation scores, such

as SCORE, tend to over- or underestimate risk on an individual level.<sup>10,11</sup> By using CACS only in a limited group of individuals selected by inaccurate risk scoring, many high-risk individuals with high CACS remain unrecognized and untreated and many low-risk individuals with in fact low CACS receive unnecessary treatment.<sup>12</sup> 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.<sup>13</sup> 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 ( $\geq 45$  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.<sup>14</sup> 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.<sup>15</sup> 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.<sup>16</sup> 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 affirmatively on the question 'do you have heart failure?'. Hypertension was defined as a systolic blood pressure  $\geq 140$  mmHg or a diastolic blood pressure  $\geq 90$  mmHg or the use of blood pressure-lowering drugs. Hypercholesterolaemia was defined as a total cholesterol  $\geq 6.5$  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.<sup>17</sup> 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.<sup>5</sup> 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  $\geq 100$  was suggested as a potential CACS cut-off above which preventive (drug) therapy could be beneficial.<sup>12,18</sup> CACS  $\geq 300$  is widely accepted as indicative of high CAD risk,<sup>19</sup> and intensive preventive management is indicated in individuals with CACS  $\geq 300$ , following US guidelines.<sup>4</sup> Therefore, CACS  $\geq 100$  and CACS  $\geq 300$  were defined as co-primary outcomes. US guidelines recommend therapy in individuals with a CACS threshold above the 75th age- and sex-standardized percentile.<sup>4</sup> We therefore additionally evaluated secondary outcomes incorporating age- and sex-standardized CACS: (i) CACS  $\geq 300$  OR a CACS  $> 75$ th age- and sex-standardized percentile, and (ii) CACS  $\geq 100$  OR a CACS  $> 75$ th age- and sex-standardized percentile. CACS percentiles were defined based on pooled data from various cohorts.<sup>20</sup>

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  $\chi^2$  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. Secondly, 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)  $\geq 30$  kg/m<sup>2</sup>, hypercholesterolaemia, hypertension, diabetes mellitus, current or former smoking, and positive family history of CAD].
- Presence of  $\geq 1$  risk factor as defined in the Risk Or Benefit IN Screening for Cardiovascular Disease (ROBINSICA) study (i.e. increased waist circumference:  $\geq 102$  cm for men;  $\geq 88$  cm for women), BMI  $\geq 30$  kg/m<sup>2</sup>, current smoking or positive family history of CAD). ROBINSICA 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.<sup>21</sup>
- 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:  $\geq 1\%$  (moderate risk) and  $\geq 5\%$  (high risk).<sup>22</sup>
- SCORE2 risk:  $\geq 5\%$  (moderate risk) and  $\geq 10\%$  (high risk).<sup>5</sup> 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  $\geq$ 300 and 18.9% (1236/6530) had CACS  $\geq$ 100. CACS  $\geq$ 300 or CACS >75th percentile was present in 24.6% (1.605/6530) of study participants, and CACS  $\geq$ 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  $\geq$ 300 and CACS  $\geq$ 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  $\geq$ 300 or >75th percentile and CACS  $\geq$ 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 $\geq$ 300

Performance of pre-screening methods for the detection of CACS  $\geq$  300 is provided in Table 2.

Miss rate for CACS  $\geq$  300 was 32% [95% confidence interval (CI): 28–36%] for pre-screening by SCORE2 risk  $\geq$ 5%, and 81% (95% CI: 78–84%) for pre-screening by SCORE2  $\geq$  10%. For pre-screening based on SCORE  $\geq$ 1 and  $\geq$ 5%, miss rate for CACS  $\geq$  300 was 10% (95% CI: 8–13%) and 85% (95% CI: 82–87%), respectively. Miss rate for CACS  $\geq$  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  $\geq$  300 was 8% (95% CI: 6–11%). Miss rate for CACS  $\geq$  300 was 24% (95% CI: 21–28%) for pre-screening based on the presence of at least one ROBINSICA risk factor. For the secondary outcome of CACS  $\geq$  300 or CACS > 75th percentile, miss rates were on average higher than for the co-primary outcome of CACS  $\geq$  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, Tables S4A-B and S5A-B).

### Performance of pre-screening methods for identification of CACS $\geq$ 100

Performance of pre-screening methods for detection of CACS  $\geq$  100 is provided in Table 3.

Miss rate for CACS  $\geq$  100 was 41% (95% CI: 39–44%) for pre-screening by SCORE2 risk  $\geq$ 5%, and 87% (95% CI: 85–89%) for pre-screening by SCORE2  $\geq$  10%. For pre-screening based on SCORE  $\geq$ 1 and  $\geq$ 5%, miss rate for CACS  $\geq$  100 was 16% (95% CI: 14–18%) and 89% (95% CI: 88–91%), respectively. Miss rate for CACS  $\geq$  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  $\geq$  100 was 11% (95% CI: 9–13%). Miss rate for CACS  $\geq$  100 was 25% (95% CI: 23–28%) for pre-screening based on presence of at least one ROBINSICA risk factor. For the secondary outcome of CACS  $\geq$  100 or CACS >75th percentile, miss rates were on average higher than for the co-primary outcome CACS  $\geq$  100, but showed similar patterns when mutually comparing the various pre-screening methods (see Supplementary data online, Table S6). Miss rates for CACS  $\geq$  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

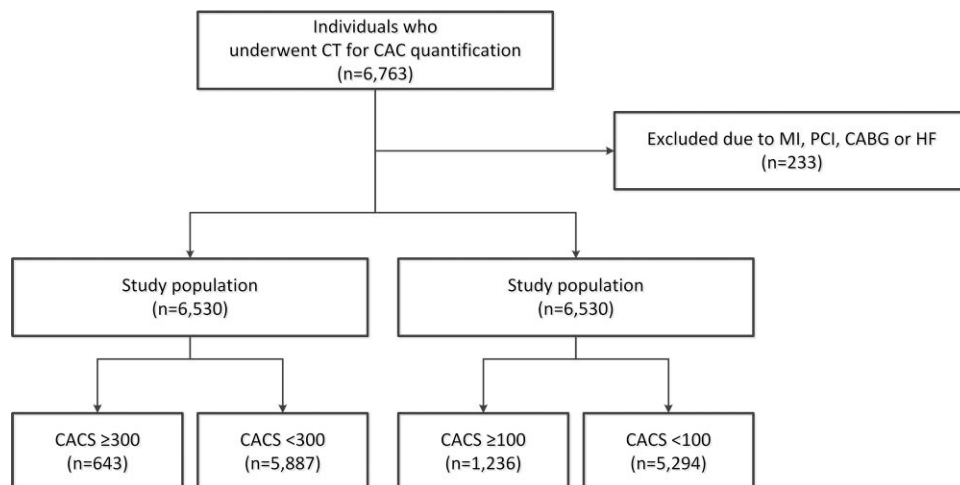
Pre-screening by SCORE2  $\geq$  5% leads to CACS in 25% (95% CI: 24–26%) and SCORE  $\geq$  10% to CACS in 3% (95% CI: 3–4%) of the total population. For pre-screening by SCORE  $\geq$ 1 and  $\geq$ 5%, CAC screening theoretically leads to CACS in 49% (95% CI: 48–50%) and 3% (95% CI: 2–3%) of the population, 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  $\geq$ 1 traditional CAD risk factor results in CAC screening in 73% (95% CI: 72–74%) and pre-screening by  $\geq$ 1 ROBINSICA 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 ( $\geq$ 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 ( $\geq$ 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.<sup>23</sup> In addition, acute MI frequently occurs in individuals who are classified as 'low-risk' by clinical risk prediction scores.<sup>24</sup> 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.<sup>25</sup> 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 ROBINSICA 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).<sup>26</sup> The ROBINSICA trial will provide more evidence on the benefit and risk of widespread CACS in the general population.<sup>21</sup> 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.<sup>27</sup> 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  $\geq 300$  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.<sup>19</sup> Other absolute CACS cut-offs to decide on initiation of preventive drug therapy (e.g. CACS  $\geq 100$ ) may also be considered.<sup>8,9</sup> Age- and sex-standardized CACS have been proposed to improve risk stratification,<sup>20</sup> but absolute CACS outperforms age- and gender-standardized CACS in prediction of clinical events.<sup>28</sup> Clinical practice guidelines currently do not provide an unequivocal recommendation on which CAC risk-categorization method should be preferred. Therefore, we evaluated both CACS  $\geq 300$  and CACS  $\geq 100$  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 ( $\geq 300$  OR  $>75$ th percentile and  $\geq 100$  OR  $>75$ th 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.<sup>29</sup> 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.<sup>30</sup> 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/MCSSUPSTARTZCSSUPEND)	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

<b>CACS ≥ 300:10% (n = 643/6530)</b>	<b>Miss rate (1-sensitivity)</b>	<b>% of population receiving CAC scan</b>	<b>PPV</b>	<b>NPV</b>	<b>Specificity</b>
≥1 traditional risk factor	8% (54/643)	73% (4748/6530)	12% (589/4748)	97% (1728/1782)	29% (1728/5887)
≥1 ROBINSKA risk factor <sup>a</sup>	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.

<sup>a</sup>Waist circumference ≥102 cm (men) or ≥88 cm (women), body mass index ≥30 kg/m<sup>2</sup>, 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

<b>CACS ≥ 100: 19% (n = 1236/6530)</b>	<b>Miss rate (1-sensitivity)</b>	<b>% of population receiving CAC scan</b>	<b>PPV</b>	<b>NPV</b>	<b>Specificity</b>
≥1 TRADITIONAL RISK FACTORS	11% (132/1236)	73% (4748/6530)	23% (1104/4748)	93% (1650/1782)	31% (1650/5294)
≥1 ROBINSKA RISK FACTORSCSSUPSTARTACSSPEND	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.

<sup>a</sup>Waist circumference ≥102 cm (men) or ≥88 cm (women), body mass index ≥30 kg/m<sup>2</sup>, 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  $\geq 5\%$  and other conventional high-risk indicators (SCORE2 risk  $\geq 10\%$ , increased UAE  $>3$  and  $>30$  mg/24 h) failed to detect the majority of individuals at elevated CAD risk as indicated by a CACS  $\geq 300$  and CACS  $\geq 100$ . 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.

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## 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.

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