

Risk or Benefit in Screening for Cardiovascular Disease (ROBINSICA): The Rationale and Study Design of a Population-Based Randomized-Controlled Screening Trial for Cardiovascular Disease

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Abstract

Objectives: This article aims to describe the rationale, study design, and the recruitment process of the Dutch Risk or Benefit in Screening for Cardiovascular Disease (ROBINSICA) trial, worldwide the first population-based randomized-controlled Computed-Tomography (CT) screening trial for cardiovascular disease, powered to detect a benefit of 15% reduced Coronary Heart Disease (CHD) morbidity and mortality.

Methods: Addresses of men (aged 45-74 years) and women (aged 55-74 years) were obtained (n=394,058) from the national population registry. All received a mailing with an information brochure, a questionnaire and waist measurement tape and an informed consent form. Asymptomatic people with an expected high-risk for developing CHD were included in this study: 1) a waist circumference of ≥ 102 cm (men) or ≥ 88 cm (women), 2) Body Mass Index of ≥ 30 kg/m², 3) current smoker and/or 4) a family history of CHD. Eligible respondents were Randomized (1:1:1) to one of the study arms: intervention arm A (screening traditional risk factors), intervention arm B (screening by Coronary Artery Calcium scoring only) or the control arm (usual care). Screened participants with a high risk for developing CHD were referred to the general practitioner for cardiovascular risk management. Linkages with national registries will be performed to measure (CHD-related) morbidity and mortality.

Results: A total of 87,866 (22.3%) people responded to the questionnaire, of which 43,447 (49.4%) were Randomized to intervention arm A (n=14,478 (33.3%)), intervention arm B (n=14,450 (33.3%)), or the control arm (n=14,519 (33.4%)). Of those who were considered to be ineligible, one had prior diagnosis of CHD (n=14,156), a medication for hypercholesterolemia and hypertension (n=13,670), no completed informed consent (n=4,490), previous cardiovascular surgery (n=4,146), and/or a CAC score within the last 12 months (n=393).

Conclusion: Evidence for net-effectiveness of population-based screening for cardiovascular risk in an asymptomatic population will possibly enable large-scale implementation with large health gains.

Keywords: Population screening; Coronary artery calcium; Imaging; Primary care; RCT; CT

Introduction

Coronary Heart Disease (CHD) remains a major cause of morbidity and mortality worldwide [1]. As stated by the European Heart Network (EHN), about 20% (1.7 million deaths) of all-cause mortality can be attributed to CHD in 2015. A further 17 million men and 13 million women suffered from CHD in 2015 and more than 35 million (14% in

males; 11% in females) disability-adjusted life years (DALY) were lost due to CHD [2,3]. The total annual costs of CHD are considerable and estimated at €59 billion annually. About 32% (€18.9 billion) is due to health care costs, 33% (€19.8 billion) due to production losses and 35% (€20 billion) due to the informal care of people with CHD [3].

Despite all medical advances last decades, one major concern is that CHD is often asymptomatic until the presentation of a serious event as myocardial infarction (MI) leading to persisting disability and/or premature death. The underlying process of (sub-clinical)

atherosclerosis has one of the longest (stable) unrecognized courses, and therefore mainly untreated. Modifying cardiovascular disease (CVD)-related risk factors can prevent the vast majority of the CVD events [4]. However, the combination of a high prevalence of unhealthy lifestyles as well as the suboptimal use of prevention measures and the ageing population remains a concern [3,5]. The rationale of screening is to halt or delay progression of the (sub-clinical) disease and thereby gain healthy life-years by offering treatment options at an earlier, yet undetected, and hopefully more efficacious stage. Although cost-effective preventive treatment options are available for cardiovascular diseases, there is no hard evidence from RCTs about whether the earlier detection of a high risk for developing CHD in the asymptomatic high-risk population indeed leads to earlier, more effective, less intensive treatment and therefore to health benefits in terms of reduced morbidity and mortality.

The identification of asymptomatic people at risk of CVD relied almost exclusively on traditional risk factors to subsequently stratify individuals into low, intermediate, and high-risk to guide treatment decisions: age, gender, smoking habits, family history of CVD, Body Mass Index (BMI), lipids, and blood pressure [6,7]. However, the observation that the majority of coronary events occur in the intermediate risk group whose members are not considered candidates for intensive treatment as their high-risk counterparts [8,9] calls for improvement in the risk stratification. Computed Tomography (CT) enables the non-invasive detection and quantification of calcifications of coronary arteries [10]. This Coronary Artery Calcium (CAC) score is argued to be useful by presenting an individualized cumulative lifetime risk exposure of (un)known risk factors, independently of traditional risk factors, but strongly related to both non-lethal major adverse cardiovascular events (such as myocardial infarction and stroke) and all-cause mortality, as shown by the Multi-Ethnic Study on Atherosclerosis (MESA) [11,12], Framingham Heart Study [13] and Heinz Nixdorf Recall Study [14-16]. Based on the total amount of coronary artery calcium (Agatston score) [17], CAC scoring seems to provide the opportunity for personalized risk assessment to identify those who might benefit most from preventive treatment. The net classification index after CAC scoring compared with traditional risk scoring implies the superiority of CAC scoring above risk factor based testing [8].

The European Guidelines on cardiovascular disease prevention in clinical practice only recommend systematic screening in those likely to be at high risk due to the presence of a family history of premature CVD, familial hypercholesterolemia, major CVD-related risk factors and/or co-morbidities (Class I recommendation; level of Evidence C) [18]. The American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology state that asymptomatic individuals at intermediate Framingham risk may be reasonable candidates for coronary calcification screening “when a risk-based decision to prescribe statins is uncertain after a patient-physician risk discussion”, whereas the American College of Preventive Medicine does not recommend routine screening in asymptomatic individuals using CT [7,18-20]. The IIb recommendation (“may be considered”) is mainly caused by the fact that data from large-scale RCTs, indicating that CAC screening for CHD will reduce CHD-related mortality and morbidity, are lacking. The EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) trial is the only small RCT among 2,137 (preferentially selected and higher educated) volunteers, comparing a group that did undergo CAC scanning before risk counselling or a control group that only had risk factor counselling [21]. Randomisation to CAC scanning

was associated with superior CAD factor control on FRS, blood pressure, lipids, and medication after four years of follow-up. Unfortunately, the study was too small to have sufficient statistical power on hard events outcomes as CHD mortality and morbidity [22].

There is an urgent need for large-scale population-based RCTs. Although this type of study requires a large amount of resources and time, it is the only way to provide evidence on the balance between potential benefits (reduction in CHD-related morbidity and mortality, reduction in overuse of statins and aspirin) and harms (radiation risk, overdiagnosis, overtreatment, and impact on quality of life) of CHD screening. The aim of this article is to describe the rationale, study design, and the recruitment process of the Dutch ROBINSICA (Risk or Benefit IN Screening for Cardiovascular disease) trial, a population-based randomized controlled screening trial for cardiovascular diseases, incorporating CAC scoring in one of the intervention arms.

Methods

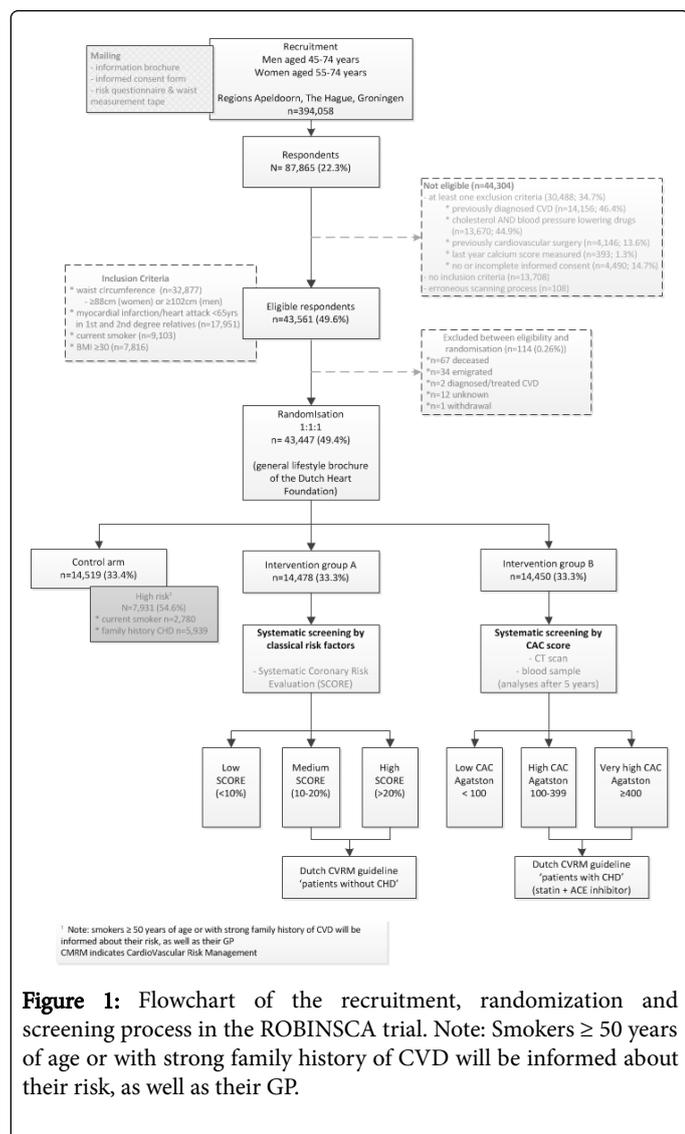
ROBINSICA study objectives

The ROBINSICA trial is a 3-arms trial, designed (1) to investigate whether population-based screening for a high risk for developing cardiovascular heart diseases by SCORE followed by risk reducing treatment can reduce coronary artery disease-related morbidity and mortality with at least 15% compared to no screening amongst asymptomatic men and women after five years of follow-up and (2) to investigate whether population-based screening for a high risk for developing cardiovascular heart diseases by CAC scoring followed by risk reducing treatment can reduce coronary artery disease-related morbidity and mortality with at least 15% compared to screening by SCORE amongst asymptomatic men and women after five years of follow-up.

Recruitment procedure

To start the study, addresses of all men (aged 45-74 years) and women (aged 55-74 years) who lived in one of the three selected regions in The Netherlands were obtained (n=394,058) after a positive advice for a linkage with the national population registry (Figure 1). All selected people received a mailing with an information brochure, a questionnaire and waist measurement tape to examine eligibility and an informed consent form. The risk questionnaire was based on validated questionnaires to assess the CVD risk [23-25]. The questionnaire contains items on age, gender, social-economic status (5-point scale), ethnicity, height, weight, waist circumference, CAC screening in the preceding year (yes/no), presence of chronic diseases and CVD (list: yes/no), surgery for CVD (list: yes/no), prescription of medication for hypertension/ hypercholesterolemia and/or diabetics (yes/no), list of prescribed medication, familial history of CVD (MI or sudden death) in first of second degree relatives before the age of 65 years (6-point scale), and current smoking behavior (smoking last week (yes/no), smoking duration (in years), smoking intensity (cigarettes/day)).

Inhabitants received the information packet in Apeldoorn region in July 2014, in The Hague in October 2014 and in Groningen in June 2016.



Selection of participants

A respondent was considered to be eligible when one or more of the inclusion criteria were fulfilled, while none of the exclusion criteria were met. The inclusion criteria for ROBINSICA are a waist circumference of ≥ 102 cm (men) or ≥ 88 cm (women) [26], Body Mass Index of ≥ 30 kg/m², current smoker and/or a family history of MI or sudden death.

Those who had already been diagnosed with cardiovascular disease (MI, heart attack, Cerebral Vascular Accident/Transient Ischemic Accident, heart failure, angina pectoris, aneurysm, stenosis of the carotid artery/femoral artery and atherosclerosis), who have had previous cardiovascular surgery (Coronary Artery Bypass Grafting, Percutaneous Coronary Intervention, or heart transplantation), who were on prescribed cholesterol lowering and blood pressure-lowering drugs, who had a CAC scoring by CT scanning in the previous year and/or no complete informed consent form were excluded for participating in this study. Eligible respondents were Randomized (1:1:1) to intervention arm A, intervention arm B or the control arm (Figure 1).

Screening

Intervention arm A: Participants were invited to one of the local screening sites to measure their risk for developing cardiovascular diseases. A blood sample was taken to determine non-fasted cholesterol levels (Total Cholesterol level, High-Density Lipid-protein (HDL) Cholesterol level; mmol/l). Mean rested blood pressure (mmHg) was measured by two automatic consecutively measurements using an electronic blood pressure device (Microlife WatchBP Office, model TWIN200 AFS).

The 10 years risk for fatal and non-fatal CVD was calculated using the SCORE risk table, as used by the Dutch College of General Practitioners [27]. Variables included in the model are age, gender, smoking status, systolic blood pressure and Total Cholesterol/HDL-Cholesterol ratio). For those participants with established diabetes mellitus, the actual age was increased with 15 years. Since data about diagnosed rheumatoid arthritis was considered to be invalid, there was no recalculation possible in these participants. A SCORE $<10\%$ indicates a low 10 years risk for developing CVD, whereas a SCORE of 10-20% were classified as a moderate risk and a SCORE of 20% or more as high risk.

Intervention arm B: All participants Randomized in intervention arm B received an invitation for a CT scan to measure the CAC Score. The scanning protocol has been published previously [28]. In brief, the CAC Score was measured using dual-source CT (DSCT) without the use of a contrast agent. According to participants' weight and size (small/slender or large) the radiation dose exposure was adjusted automatically. The DSCT calcium scoring examination followed a scout view and was performed with prospective ECG-triggering. All scans were performed by experienced technicians, who were blinded to the clinical data of the participants. Quantification of coronary calcifications was performed with using dedicated CAC scoring software and the CAC scores were determined according to Agatston method [17] by multiplying each area of interest with a factor indicating peak density within the individual area. The effective dose of CAC screening (accounting for the sensitivity of exposed tissues) is 0.7-2 mSv, depending on the technology used. CAC scores were then divided into <100 (low risk), 100-399 (high risk) and ≥ 400 (very high risk), since absolute scores better predicts the risk for CVD compared with the use of percentiles according to gender, age and ethnicity [29].

Incidental findings in the chest or abdomen with expected clinical relevance (aortic aneurysm of ≥ 50 mm, calcified pleural plaques and/or pleural fluid (≥ 2 cm thickness), large liver cyst(s) (≥ 10 cm), identifiable abdominal mass) were reported at the general practitioner after verifying that the participant gave their written informed consent (divided in serious incidental findings versus non-serious incidental findings). Incidental findings with no or limited clinical relevance (valve calcification (aortic valve, mitral valve, e.g.), valve calcification (aortic valve, mitral valve, e.g.), pericardial abnormalities (thickening, calcification, e.g.), hiatus hernia, small to medium size liver cyst(s)) were only reported at the screening site.

Control arm: Study participants who were Randomized in the control arm received usual care (no screening). However, those aged above 55 years who currently smoked and those with a family history of CHD were prompted that they can ask for a risk scoring measurement by their GP, confirm the national guidelines for general practitioners [27]. The GP was also informed about this message given to the participant.

Referral and preventive treatment

For participants of intervention group A, a SCORE of 10% and above indicated advice for referral to the GP for preventive treatment according to the Dutch guideline cardiovascular risk management for “patients without cardiovascular disease” from the Dutch College of General Practitioners [27].

Participants in intervention group B with an Agatston score above 100 were referred to the GP for further cardiovascular risk management. It was recognised that the lack of knowledge will possibly impact the clinical management of the CAC score. Information about the trial, the screening result and the recommended treatment was provided to all general practitioners. The advice for treatment was established in accordance with the current literature and in consultation of the research team and local cardiologists and GPs. The aim of the treatment study protocol was to keep it as close as possible to the current practice in primary care. Therefore, the recommended treatment comprises the prescription of ACE-inhibitors and statins. This is in line with the Dutch guideline cardiovascular risk management for “patients with CHD” from the Dutch College of General Practitioners [27].

End points

The primary outcome is to investigate whether screening for CHD in subjects at increased risk reduces CHD-events. A CHD event is defined as the first occurrence, within the follow-up period after randomization, of non-fatal or fatal coronary heart disease. These data will be collected through linkages with Causes of Death registry and National Hospital Discharge Registry at Statistics Netherlands. The underlying and contributory causes of death of participants who died will be retrieved through linkage with the Causes of Death Registry coded according to the International Classification of Deaths. In a subset of individuals, charts from the GPs and hospitals will be collected and reviewed by an independent committee to assess the validity of the official statistics, as has been done in our other RCTs [30,31].

Secondary outcomes

Secondary outcomes measures include extensions of the primary outcome measures, sensitivity of the screening test(s), the

reclassification of individuals in risk categories and corresponding change in treatments, the effects of CHD screening and cost-effectiveness.

The effects of the interventions may have an effect on stroke as well. In an extended analysis, the rate of strokes in each arm will be incorporated in additional analyses as secondary outcome measure. Since fatal coronary heart disease is a large proportion of all deaths, differences in all-cause mortality between arms will be analysed too. The sensitivity of the screen test will be evaluated using the 5-year follow-up data and equals the proportion of subjects who developed CHD and who were correctly identified as intermediate or high-risk participants by the conventional risk assessment (group 2) or by CAC score (group 3). The area under the receiver-operating-characteristic curve, reclassification ratio, integrated sensitivity and specificity will be used as criteria for the performance of the tests [32]. In the intervention arms, the change in risk estimates and distribution will be compared to the control arm. At the end of the follow-up period, questionnaires will be sent to the participants to ask for treatments received, compliance, lifestyle, risk perception, and impact of earlier diagnosis. The percentage of overtreatment and/or unnecessary treatments can be deducted.

The favourable and unfavourable effects of CVD screening (Health-Related Quality of Life and health-related behaviour) are assessed in a random subsample of 5000 participants from randomisation until 12 months after screening.

Power analysis

The expected annual average event rate was estimated at 1.38%, based on data (year: 2008) for gender and age obtained from Statistics Netherlands. Based on previous population screening trials, the compliance rate in intervention group B was set on 90%, while the contamination rate of CT screening in intervention group A was set on 15%. This might be overestimated, since coronary calcium scoring is not part of the national guidelines for general practitioners. To reach a power of 80% to detect a 15% reduction in CHD under above mentioned conditions, a sample size of 13,028 was needed (Table 1).

| CHD-event rate comparison arm (%) | CHD-event (%) | reduction | Screen compliance group 3 (%) | Contamination of CAC-screening group 2 (%) | N needed per arm |
|-----------------------------------|---------------|-----------|-------------------------------|--|------------------|
| 1.17 | 15 | 95 | 95 | 5 | 10,682 |
| 1.17 | 15 | 95 | 95 | 10 | 11,929 |
| 1.17 | 15 | 95 | 95 | 15 | 13,414 |
| 1.17 | 15 | 90 | 90 | 5 | 12,026 |
| 1.17 | 15 | 90 | 90 | 10 | 13,524 |
| 1.38 | 15 | 95 | 95 | 5 | 9,079 |
| 1.38 | 15 | 90 | 90 | 10 | 11,496 |
| 1.38 | 15 | 90 | 90 | 15 | 13,028 |
| 1.17 | 20 | 90 | 90 | 20 | 9,554 |

| | | | | |
|--------------------------------|-------------------------|------------------------------|--|------------------|
| 1.38 | 20 | 80 | 20 | 11,184 |
| CHD-event rate control arm (%) | CHD-event reduction (%) | Screen compliance group 2(%) | Contamination of classic-screening group 1 (%) | N needed per arm |
| 1.38 | 15 | 95 | 20 | 12,922 |

Table 1: Power calculations under different conditions.

Some assumptions were made. The reduction in CHD that can be showed should be at least 15% between intervention group B (CAC score) and intervention group A (SCORE). This implies that comparisons of intervention group A versus controls and intervention group B versus controls should also be possible. Reasons for a 15% reduction threshold derived from an estimated reclassification of about 35%, and the estimated higher risk categories due to screening by CAC scanning.⁸ Thereby, a population screening programme with a morbidity and mortality reduction less than 15% seems to become never cost-effective.

Ethical Approval

The study was approved by the Minister of Health, after a positive advice of the Dutch Health Council, because of the Dutch Population Screening Act. All participating centres gave their approval for conducting the study in the centres. Furthermore, the Minister of the Interior and Kingdom Relations gave permission to obtain all addresses from the Dutch population registry of men (aged 45-74 years) and women (aged 55-74 years) living in one of the three regions.

Results

Recruitment and randomization

A total of 394,058 addresses of men and women living in Apeldoorn, The Hague or Groningen were obtained from the Dutch

Population Registry of which 87,866 (22.3%) people responded to the questionnaire. Of the respondents, almost half (n=43,562; 49.6%) were considered to be eligible for participating in the ROBINSCA trial (Figure 1). In the region Apeldoorn and Groningen, 52.1% and 51.0% of the respondents were considered to be eligible respectively, whereas this was 44.4% of the respondents in the (most urban) region The Hague. Of those who were considered to be ineligible, most of them had prior diagnosis of CHD (n=14,156) and/or a prior prescription of both cholesterol as well as blood pressure lowering drugs (n=13,670). No informed consent or an incomplete informed consent form (n=14.7%), previous cardiovascular surgery (n=4,146), and/or a CAC score within the last 12 months (n=393) were reason for exclusion. A total of 114 eligibles were excluded just before randomisation due to death, emigration, diagnosed/treated CHD or withdraw/unavailability. All other eligibles (n=43,447) were Randomized (1:1:1) to intervention arm A (n=14,478 (33.3%)), intervention arm B (n=14,450 (33.3%)), or the control arm (n=14,519 (33.4%)) (Figure 1). Baseline characteristics (gender, age, educational level, region, BMI, waist circumference, family history of myocardial infarction, smoking status, and diabetes mellitus) of study participants were comparable (p>0.05) between the three study arms (Table 2), concluding an adequate randomization.

| | Control arm n/N (%) | Intervention arm A n/N (%) | Intervention arm B n/N (%) | p-value |
|---------------------------------------|---------------------|----------------------------|----------------------------|---------|
| Gender | | | | 0.866 |
| • Male | 7044/14519 (51.5%) | 7456/14478 (51.5%) | 7480/14450 (51.8%) | |
| • Female | 7475/14519 (48.5%) | 7022/14478 (48.5%) | 6970/14450 (48.2%) | |
| Age (median (IQR)) | 61 (11) | 61 (11) | 61 (11) | 0.696 |
| Educational level | | | | 0.492 |
| • Low | 2899/14469 (20.0%) | 2980/14436 (20.6%) | 3007/14399 (20.9%) | |
| • Medium | 6476/14469 (44.8%) | 6419/14436 (44.5%) | 6307/14399 (43.8%) | |
| • Higher | 5094/14469 (35.2%) | 5037/14436 (34.9%) | 5022/14399 (34.9%) | |
| Region | | | | 0.447 |
| • Apeldoorn | 5858/14519 (40.3%) | 5855/14478 (40.4%) | 5887/14450 (40.7%) | |
| • The Hague | 3594/14519 (24.8%) | 3662/14478 (25.3%) | 3526/14450 (24.4%) | |
| • Groningen | 5067/14519 (34.9%) | 4961/14478 (34.3%) | 5037/14450 (34.9%) | |
| Body Mass Index (median (IQR)) | 26.3 (5) | 26.3 (5) | 26.3 (5) | 0.702 |

| | | | | |
|---|---------------------|---------------------|---------------------|-------|
| Waist Circumference (median (IQR)) | 101.5 (14.4) | 101.5 (14.5) | 101.5 (14.5) | 0.7 |
| Family history of CHD | | | | 0.269 |
| • No | 7340/13302 | 7190/13223 | 7304/13213 | |
| • Yes | 5962/13320 | 6033/13223 | 5909/13213 | |
| Smoking status | | | | 0.218 |
| • Former smoker | 11420/14519 (78.7%) | 11503/14478 (79.5%) | 11454/14450 (79.3%) | |
| • Current smoker | 3099/14519 (21.3%) | 2975/14478 (20.5%) | 2996/14450 (20.7%) | |
| Diabetes Mellitus | | | | 0.382 |
| • No | 14055/14519 (96.8%) | 14009/14478 (96.8%) | 13949/14450 (96.5%) | |
| • Yes | 464/14519 (3.2%) | 469/ 14478 (3.2%) | 501/ 14450 (3.5%) | |

IQR=Interquartile Range, CHD=coronary heart disease

Table 2: Baseline characteristics of study participants.

Discussion

Systematic population-based screening in an asymptomatic population is not yet recommended in (inter)national guidelines, although screening for several types of cancer has become a population screening strategy, despite the much lower incidence. The European Guidelines on cardiovascular disease prevention in clinical practice only recommend systematic screening in those likely to be at high risk due to the presence of a family history of premature CVD, familial hypercholesterolemia, major CVD-related risk factors and/or comorbidities [18]. The American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology stated that asymptomatic individuals at intermediate Framingham risk may be reasonable candidates for coronary calcification screening “when a risk-based decision to prescribe statins is uncertain after a patient-physician risk discussion”, whereas the American College of Preventive Medicine does not recommend routine screening in asymptomatic individuals using CT [7,18-20]. The IIB recommendation (“may be considered”) is mainly caused by the fact that data from large-scale RCTs, indicating that CAC screening for CHD will reduce CHD-related mortality and morbidity, are lacking. Long-term RCTs that evaluate hard end-points as morbidity and mortality are needed to overcome well-known biases of screening (lead-time and length time bias and overdiagnosis) in case of using survival rates as reflection of programmes’ effectiveness. Evidence for net-effectiveness of population-based screening for cardiovascular risk in an asymptomatic population will enable large-scale implementation with possibly exceptionally large health gains. This article presented the rationale, study design, and the results of the recruitment process of the Dutch large-scale population-based randomized-controlled screening trial for cardiovascular diseases: the ROBINSCA trial.

Advantages of population-based recruitment over volunteer-based recruitment is that it is assumed that potential differences in background variables (morbidity and mortality, general health e.g.) are comparable between the study population and the target population (high-risk for developing CHD). But, self-selection might always be present. Thereby, it is well-known that less deprived are more likely to have higher risk, but they are less likely to attend screening or take part in trials, although the potentially high gain from screening [33]. Future

comparison of background characteristics between the study population (data from the questionnaire) and the general population (data from Statistics Netherlands) is warranted to estimate the representativeness of the study population.

Another advantage of the population-based recruitment strategy is that those who were approached with the question to participate in the screening trial were unaware of the in- and exclusion criteria, what limit potential response bias that should increase the risk of study participation.

Data of the ROBINSCA trial will provide more insight on the balance between the harms and benefits of screening for cardiovascular diseases.

Recently, researchers of the Multi-Ethnic Study on Atherosclerosis found that the (absence of) an elevated CAC score is also associated with and increased risk for (the absence of) non-cardiovascular disease (cancer, chronic kidney disease, chronic obstructive pulmonary disease and hip fractures), what suggest a more widespread use in risk prevention of multiple diseases [34]. Now-a-days, CAC scoring on low-dose CT for lung cancer screening participants is also recommended in current guidelines [10].

The obstruction of the coronary arteries is seldom not accompanied with an increased calcium score. In that perspective is a CAC of zero indicative for a low risk for CHD in the near future. The absence of CAC seems to be an overall marker for a process of healthy ageing due to the lower risk for not only developing cardiovascular diseases, but also other diseases as cancer and chronic lung diseases [10]. It is needed to determine whether (current) over-treatment based on traditional risk factors could be diminished in the asymptomatic population with absent CAC.

The ROBINSCA trial only performed a single screening round. The question is whether multiple CT scans might provide better individualized risk prediction. However, Radford and colleagues [35] found that the progression in CAC score provides no additional prognostic information. Nevertheless, more research is needed to further understand the impact of CAC progression on future CHD risk.

Conclusion

Evidence for net-effectiveness of population-based screening for cardiovascular risk in an asymptomatic population will possibly enable large-scale implementation with large health gains. If a population screening programme for cardiovascular risk turns out to be successful, CAC screening is estimated to prevent 100,000 CHD-related death and 500,000 CHD-related hospital admissions in Europe yearly, while considering the assumption of a 15% reduced morbidity and mortality.

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Declaration of Helsinki

The authors declare that the ROBINSCA study complies with the Declaration of Helsinki. Due to the Dutch Population Screening Act, the study was approved by the Dutch Minister of Health, Welfare and Sports after a positive advice of the Dutch Health Council. Local Medical Ethical Committees approved the execution of the study locally. All participants gave their written informed consent.

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