



Early detection of obstructive coronary artery disease in the asymptomatic high-risk population: objectives and study design of the EARLY-SYNERGY trial

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Background Coronary artery disease (CAD) burden for society is expected to steeply increase over the next decade. Improved feasibility and efficiency of preventive strategies is necessary to flatten the curve. Acute myocardial infarction (AMI) is the main determinant of CAD-related mortality and morbidity, and predominantly occurs in individuals with more advanced stages of CAD causing subclinical myocardial ischemia (obstructive CAD; OCAD). Unfortunately, OCAD can remain subclinical until its destructive presentation with AMI or sudden death. Current primary preventive strategies are not designed to differentiate between non-OCAD and OCAD and the opportunity is missed to treat individuals with OCAD more aggressively.

Methods EARLY-SYNERGY is a multicenter, randomized-controlled clinical trial in individuals with coronary artery calcium (CAC) presence to study (1.) the yield of cardiac magnetic resonance stress myocardial perfusion imaging (CMR-MPI) for early OCAD diagnosis and (2) whether early OCAD diagnosis improves outcomes. Individuals with CAC score ≥ 300 objectified in 2 population-based trials (ROBINSICA; ImaLife) are recruited for study participation. Eligible candidates are randomized 1:1 to cardiac magnetic resonance stress myocardial perfusion imaging (CMR-MPI) or no additional functional imaging. In the CMR-MPI arm, feedback on imaging results is provided to primary care provider and participant in case of guideline-based actionable findings. Participants are followed-up for clinical events, healthcare utilization and quality of life.

Conclusions EARLY-SYNERGY is the first randomized-controlled clinical trial designed to test the hypothesis that subclinical OCAD is widely present in the general at-risk population and that early differentiation of OCAD from non-OCAD followed by guideline-recommended treatment improves outcomes. (Am Heart J 2022;246:166–177.)

Background and rationale

Coronary artery disease (CAD) is one of the leading causes of mortality and morbidity globally^{1,2} and the burden for society is forecasted to increase over the next decades³. Acute myocardial infarction (AMI) is the main driver of CAD mortality and morbidity¹. AMI causes irreversible myocardial damage and leads to hospitalization, chronic heart failure, sudden cardiac death, reduced quality of life and decreased life expectancy^{4,5}.

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Submitted June 18, 2021; received in revised form December 11, 2021; accepted January 10, 2022

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0002-8703

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<https://doi.org/10.1016/j.ahj.2022.01.005>

To reduce the risk of AMI, professional practice guidelines currently recommend initiating cardiovascular risk management (CVRM) based on individual AMI risk assessment by clinical risk prediction scores. More recently, computed tomography (CT)-based coronary artery calcium (CAC) quantification has been acknowledged as a powerful risk prediction tool to advance personalized AMI prevention strategies. The on-going ROBINSICA trial compares the efficacy of primary preventive treatment in individuals identified at high risk by CAC scoring vs conventional Systematic Coronary Risk Evaluation (SCORE) risk assessment⁶. The risk assessment strategy used in ROBINSICA focuses on reducing AMI risk by initiating statin and angiotensin-converting enzyme (ACE)-inhibitor treatment and does not deploy more aggressive management in individuals with more advanced CAD stages. Substantial residual risk of AMI remains present despite optimal primary preventive treatment⁷⁻⁹. This raises the question whether further refining risk stratification and treatment based on an individual's CAD stage could further enhance the overall effectiveness of preventive strategies.

Especially individuals at the higher end of the AMI risk spectrum are prone to suffering events and might benefit from additional treatments. Individuals at the highest end of the risk spectrum are those with obstructive CAD (OCAD) resulting in substantial myocardial ischemia¹⁰⁻¹². Professional practice guidelines recommend to revascularize large areas of myocardial ischemia caused by OCAD to improve prognosis, irrespective of the presence of symptoms. Unfortunately, like non-OCAD, OCAD can remain subclinical until its presentation with AMI or sudden cardiac death. At least in theory, early diagnosis of OCAD and aggressive treatment thereof can prevent sudden cardiac death, AMI and its late consequences. To date, no dedicated population screening programs aimed at early diagnosis and treatment of OCAD exist.

CT-based CAC quantification has very high sensitivity and negative predictive value (> 95%) in OCAD assessment¹³ and is low-cost, non-invasive, fast, and can easily be performed. CAC quantification by CT is associated with only minimal radiation exposure (<1 mSv), comparable to screening mammography, and has negligible life-time risk of malignancy in middle aged or older individuals^{14,15}. Importantly, increased CAC score has been associated with increased prevalence of myocardial ischemia detected by myocardial perfusion imaging in symptomatic patients¹⁶. Cardiac magnetic resonance myocardial stress perfusion imaging (CMR-MPI) has excellent diagnostic performance to detect myocardial ischemia caused by OCAD¹⁷. CMR-MPI is non-invasive, relatively low-cost and is not associated with exposure to ionizing radiation, in contrast to single-photon emission computed tomography (SPECT) and positron emission

tomography (PET) myocardial perfusion imaging. Synergistically combining CT-based CAC quantification with CMR-MPI might open avenues to efficiently diagnose subclinical OCAD in the general population and to allow more aggressive early treatment.

EARLY-SYNERGY is the first trial designed to evaluate the yield of CMR-MPI for detection of subclinical OCAD in asymptomatic individuals derived from the general population based on an increased CAC score. Importantly, the results of EARLY-SYNERGY will contribute to determine whether utilization of CMR-MPI to early diagnose subclinical OCAD combined with guideline-based treatment in asymptomatic individuals at increased risk improves outcomes.

Methods

Study design and population

EARLY-SYNERGY is a multicenter randomized-controlled clinical trial performed in 5 hospitals in the Netherlands. An overview of the study design is provided in [Figure 1](#).

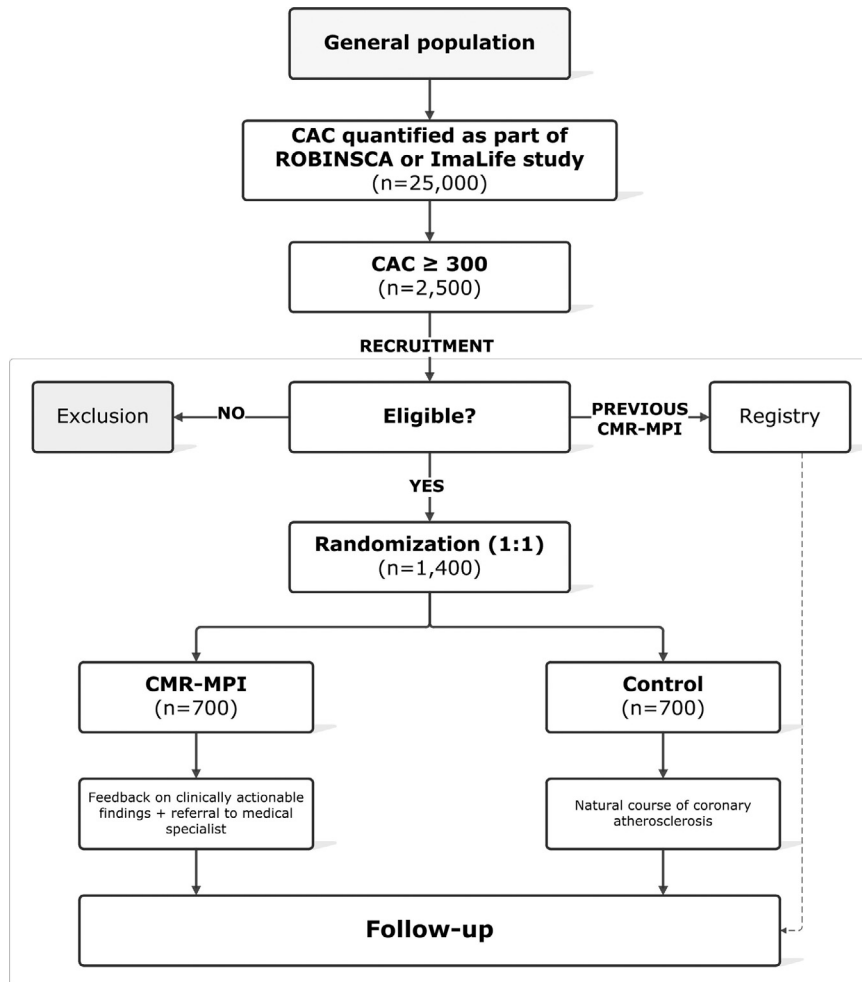
CT-based CAC quantification

Asymptomatic individuals derived from the general population who have a CAC score ≥ 300 , quantified during prior participation in either ROBINSICA⁶ or ImaLife¹⁸, are recruited. The study design of ROBINSICA and ImaLife has been described in detail before^{6,18}. In brief, ROBINSICA has randomized 43,447 individuals from the general population at increased risk but without known cardiovascular disease in 3 regions in the Netherlands 1:1:1 to either¹ SCORE- or² CAC score-based primary preventive treatment or³ no risk-based treatment (control)⁶. ImaLife is an ongoing observational study, embedded in the Lifelines Biobank¹⁹, that will recruit approximately 12,000 individuals who undergo CT, including CAC scoring, in the general population¹⁸. CT acquisition and CAC quantification methods, which were similar in both ImaLife and ROBINSICA, have been described in detail elsewhere²⁰.

In- and exclusion criteria

ROBINSICA and ImaLife participants are eligible for inclusion in EARLY-SYNERGY if they had a CAC score ≥ 300 and if they are not known to have CAD or other cardiac conditions, did not previously undergo coronary revascularization, catheter ablation or cardiac surgery and do not have a contra-indication for CMR-MPI. A detailed overview of the in- and exclusion criteria is provided in [Table I](#). EARLY-SYNERGY aims to study the yield of CMR-MPI and to study whether early OCAD detection improves clinical outcome of asymptomatic individuals. Individuals at high risk by having an increased CAC score formed the target population of EARLY-SYNERGY,

Figure 1



Study design.

Individuals who underwent CT-based CAC quantification as part of 2 population-based studies ROBINSICA and ImaLife (embedded in the Lifelines Biobank), who are at increased risk of AMI because of subclinical coronary atherosclerosis presence (CAC score ≥ 300) are recruited for EARLY-SYNERGY. If eligible, participants are randomized to either additional functional imaging with CMR-MPI or no additional functional imaging (control). Participants and their primary care provider receive a written report only in case of clinically actionable findings on CMR-MPI. Clinically actionable findings on which feedback to participant and primary care provider is provided include (1.) at least moderate myocardial ischemia (approximately $> 10\%$ of left ventricle), (2.) signs of (subclinical) myocardial infarction (MI), (3.) signs of probably severe valvular disease, (4.) signs of cardiomyopathy and/or reduced left ventricular ejection fraction (LVEF) $< 40\%$, (5.) severe aortic aneurysm and/or (6.) other extra-cardiac pathology likely to require further medical management. Participants in both arms are followed up for clinical events, healthcare utilization and quality of life, for up to 5-years. Participants who underwent CMR-MPI prior to inclusion in EARLY-SYNERGY are included in a separate follow-up registry. The numbers of participants mentioned here reflect estimates. CAC = coronary artery calcium; CMR-MPI = cardiac magnetic resonance myocardial perfusion imaging.

in order to have sufficient events occurring in both arms to study the effect of imaging on clinical outcome with sufficient statistical power. Resources allowed additional CMR-MPI procedures to be performed within EARLY-SYNERGY in a maximum of 10% of the total

ROBINSICA and ImaLife population (i.e., ≥ 90 th percentile for CAC scores). A CAC score of ≥ 300 indicated the 90th percentile cut-off in these 2 population-based imaging studies at the time of EARLY-SYNERGY set-up.

Table 1. In- and exclusion criteria of EARLY-SYNERGY participants

Inclusion criteria	Exclusion criteria
Underwent CT for CAC quantification (as part of ROBINSCA or ImaLife) CAC score \geq 300	History of angina, AMI, SCA, heart failure, severe valvular disease, cardiomyopathy or congenital heart disease Previous revascularization with CABG or PCI or coronary evaluation by ICA Previous catheter ablation or valvular surgery Other major cardiac surgery (e.g. cardiac transplantation) Contra-indication for CMR-MPI (claustrophobia, CMR incompatible device, weight > 125kg) Contra-indications for adenosine and regadenoson Known adverse reaction to contrast agents Pregnancy Severe comorbidity with life expectancy < 1 year Inability to provide informed consent

AMI, acute myocardial infarction; CABG; coronary artery bypass grafting; CAC, Coronary Artery Calcium; CAD, coronary artery disease; CMR-MPI, cardiovascular magnetic resonance myocardial stress perfusion imaging; CT, computed tomography; ICA, invasive coronary angiography; PCI, percutaneous coronary intervention; SCA, sudden cardiac arrest

Screening, enrolment and randomization

Potential candidates receive an invitation letter, information brochure, informed consent form and a questionnaire on in- and exclusion criteria, co-morbidities, presence of cardiovascular risk factors, cardiac symptoms and quality of life. Candidates returning the written informed consent form will be checked for eligibility and eligible candidates will be randomized in a 1:1 fashion to additional CMR-MPI or the control arm without additional imaging. A permuted block randomization scheme, stratified for gender, the origin of the CAC score (ROBINSCA or ImaLife) and demographic region, will be applied. Candidates who already underwent CMR-MPI for clinical reasons prior to invitation into EARLY-SYNERGY will be excluded from the randomized trial but will enroll in a separate registry. Follow-up will be obtained for participants in the CMR-MPI arm, control arm and registry.

CMR-MPI arm

Participants randomized to the CMR-MPI arm will visit 1 of the 5 participating CMR-MPI facilities. At the imaging visit, participants will undergo CMR-MPI and blood will be drawn for biobanking to allow future blood-based biomarker studies.

CMR-MPI acquisition

CMR-MPI will be performed on a 1.5-T clinical MRI system according to a standardized study protocol allowing minor deviations per local hospital to facilitate limitations in available scanning time and imaging sequences. The CMR-MPI protocol was designed adhering to CMR-MPI practice guidelines²¹. Vasodilator-induced stress perfusion imaging will be performed using either adenosine or regadenoson. Regadenoson will be used if contra-indications for adenosine (e.g., active bronchoconstrictive or bronchospastic disease) are present or if standard in local clinical practice. Hyperemia will be induced with a continuous intravenous infusion of 140 μ g/kg/min

adenosine over 4 minutes or a single intravenous bolus of 400 μ g regadenoson. In case of inadequate hemodynamic response to adenosine, adenosine dose will be increased to a maximum of 210 μ g/kg body weight/min at the attending physician's discretion. Electrocardiography (ECG) will be monitored continuously during the examination. Blood pressure and heart rate will be recorded at baseline, during vasodilator infusion, during rest perfusion and at termination of the procedure. Participants will be instructed by phone to refrain from caffeine containing beverages and (vasodilating) medication (theophylline, dipyridamole and calcium antagonists) prior to the examination to avoid potential interaction with the vasodilator agent.

After standardized axial, coronal and sagittal localizer and scout imaging, 2D balanced steady-state free precession (bSSFP) cine imaging with retrospective ECG gating of left ventricular (LV) long-axis 4-chamber, 3-chamber, 2-chamber and LV outflow tract views will be acquired. Next, basal, midventricular and apical short-axis slice positions will be defined. First-pass 2D saturation-recovery bSSFP perfusion imaging on the 3 short-axis slices will be performed either 4 minutes after start of adenosine or 1-2 minutes after regadenoson infusion, by injecting 0.1 mmol/kg gadolinium (Dotarem) at 5 mL/s, followed by a saline flush of 20 mL at 5 mL/s. After acquiring stress perfusion images, the vasodilator-effect will be reversed by stopping adenosine infusion, or intravenous administration of 100-200 mg aminophylline in case of regadenoson if in accordance with local practice. 2D gradient echo cine imaging with retrospective ECG gating of 3 planar slices parallel to the aortic valve for assessment of aortic valve structure will be acquired. Rest perfusion imaging will be performed at least 5 minutes after first-pass stress perfusion with the same slice positioning and injection characteristics as first-pass perfusion imaging, for secondary (semi-)quantitative perfusion analysis. Then, 2D bSSFP cine imaging with retrospective ECG gating on LV short axis stack will be performed for quantification of

cardiac volumes and function. At least ten minutes after the second contrast injection (administered at rest perfusion imaging), 2D Inversion-recovery bSSFP single shot late gadolinium enhancement (LGE) imaging with phase-sensitive inversion recovery (PSIR) will be performed.

CMR-MPI analysis and reporting

Clinically actionable CMR-MPI findings will be reported in writing to the participant and their primary care provider (PCP). Actionable findings are defined as pathology that likely requires (immediate) further management based on professional practice guidelines and discussion with experts in the field. These findings include:

- (1) at least moderate myocardial ischemia (approximately > 10% of left ventricle);
- (2) signs of (silent) myocardial infarction;
- (3) signs of probably severe valvular disease;
- (4) signs of cardiomyopathy and/or reduced left ventricular ejection fraction (LVEF) <40%;
- (5) severe aortic aneurysm (≥ 50 mm) and/or
- (6) other extra-cardiac pathology likely to require further medical management.

Participants in whom clinically actionable findings are detected are advised to consult their PCP. The PCP is provided with a standardized report and is advised to contact their patient to discuss the findings. Clinical consultation of the cardiologist or any other medical specialist is strongly recommended to the PCP and their patient in case of OCAD or any other incidental finding of clinical relevance. Reports to the PCP contain references to clinical practice guidelines when appropriate to emphasize the importance of this recommendation.

CMR images will be evaluated primarily locally by experienced radiologists or imaging cardiologists and secondly adjudicated centrally by an independent expert (R.N.) in the field of cardiovascular imaging (European Association of Cardiovascular Imaging CMR Imaging Certification, Level 3). Segmental classification and classification of coronary territory (left anterior descending, circumflex, right coronary artery) will be based on the standardized 16 American Heart Association segment model, excluding the apical segment²². In case of discrepancies, the central evaluation will be considered for the written report to participants and their GP and for statistical analysis.

Control arm

In the control arm, no additional functional imaging will be performed. Participants in the control arm will be followed-up to determine the natural course of occurrence of symptoms with or without self-referral to a physician for further management.

Long-term follow-up

Participants will be invited to complete questionnaires at 1, 2.5 and 5 years after randomization. To improve response, questionnaires will be provided to participants based on their preference, either online or by regular mail. Data regarding clinical outcome, health-related quality of Life (EQ-5D-5L, HeartQoL), healthcare utilization (iMTA medical consumption questionnaire [iMCQ]) and cost-productivity (iMTA productivity cost questionnaire [iPCQ]) will be collected during follow-up²³. Additional clinical information will be collected from treating physicians if a participant answers confirmatively on any question regarding visits to a doctor or the hospital for both urgent and outpatient clinical care concerning clinical endpoints during follow-up. Additionally, municipality registries and hospital registries will be checked to complete follow-up data. Clinical source documents will be stored on a secure server, separated from pseudonymous clinical research data in the online research database. An event adjudication committee (EAC) will review all clinical outcome data and decide on the occurrence of clinical events as studied in final analysis.

Ethical considerations, data management and privacy

All study procedures, except invitation of potential candidates, will be coordinated by the trial coordinating center (University Medical Center Groningen, Groningen, the Netherlands). EARLY-SYNERGY study procedures in the ROBINSCA- and ImaLife -arm are the same but will be conducted under the acronyms 'ROBINSCA-MR' and 'CardioLife', respectively, to clarify the add-on character of study procedures towards participants and supportive personnel. Study procedures, information brochures and websites with information will be tailored to the participants based on their original study participation in which CAC was quantified. To protect privacy of candidates, eligible candidates who participated in the ROBINSCA and ImaLife studies will initially be invited by ROBINSCA and Lifelines study personnel, respectively, to whom these candidates initially consented to be invited for additional research. Personal and research data will only be transferred to the EARLY-SYNERGY investigators after written informed consent for participation in the EARLY-SYNERGY trial has been secured. Personal data will be transferred and stored in accordance with the General Data Protection Regulation (GDPR). A dedicated trial management system with secured access has been developed to safely handle personal data. Pseudonymous images will be transferred to the coordinating center through a cloud-based environment provided and securely hosted by the coordinating center. Images will be downloaded by research personnel and stored on a network drive on hospital servers with secured access permissions. Research data will be

stored under study participant number in eCRFs in an electronic database builder. All research data will be handled and stored pseudonymously under participant identification number. Connection between participant identification number and personal data can only be made by the principal investigator and coordinating investigators who execute study procedures involving personal data (e.g., sending appointment letter or CMR-MPI result letter). The study was approved by the Medical Ethical Committee of the University Medical Center Groningen in Groningen, The Netherlands (METC 2018/114), and by each institutional review committee of participating centers. The study is registered at clinicaltrials.gov (NCT04680338). The study will be conducted in accordance with the medical research involving human subjects act and the Declaration of Helsinki. This study was supported by the Dutch Heart Foundation (EARLY-SYNERGY - research grant CVON2015-17) and Siemens Healthineers (PUSH - partnership IPA No.11 PUSH MRA). The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Study aims and outcomes

EARLY-SYNERGY has 2 co-primary objectives, which are investigated separately. Co-primary objectives of EARLY-SYNERGY are (1.) to study the yield of CMR-MPI for detection of subclinical OCAD in asymptomatic in-

dividuals with atherosclerosis (CAC score ≥ 300) and (2.) to evaluate the downstream effect of early diagnosis of subclinical myocardial ischemia and other clinically actionable findings by CMR-MPI on clinical outcomes (Table II), as compared to the natural course. Primary and secondary imaging and clinical outcomes are listed in Table II. Exact definitions of clinically actionable findings and primary and secondary imaging outcomes are listed in Table III and in *Supplementary Table S2*. The prevalence of subclinical OCAD in this asymptomatic population at increased risk is currently unknown. A sufficiently high yield of CMR-MPI for early detection of OCAD is important to induce fast-tracked appropriate therapy in a substantial number of individuals, in order to make an impact on cardiovascular event rates. We therefore evaluate the prevalence of OCAD and other clinically relevant incidental findings as a first co-primary objective, which is an important indicator of the ability to observe a potential effect of early OCAD detection on clinical outcome.

Important secondary objectives are to study in asymptomatic individuals with increased CAC score (1.) yield of CMR-MPI for detection of cardiomyopathy, reduced LVEF, valvular disease and aortic aneurysm, (2.) cost-utility of the synergistic imaging strategy combining CT-based CAC quantification and CMR-MPI, (3.) the association of imaging outcomes with clinical outcome and (4.) optimization of the diagnostic imaging strategy by study-

Table II. Primary and secondary imaging and clinical outcomes, specified per objective

Objective	Imaging outcome	Definition
To study the yield of CMR-MPI	<i>Primary imaging outcome</i>	I) Composite of mild-severe myocardial ischemia and/or silent myocardial infarction
	<i>Secondary imaging outcome</i>	I) Inclusion of (1) CM, (2) LVEF < 40%, (3) probably severe valvular disease, 4) aortic aneurysm ≥ 50 mm and/or severe extra-cardiac findings, in the primary imaging outcome II) Inclusion of LVEF 40%-50% in the secondary composite imaging outcome III) Individual components of the primary and secondary imaging outcomes
To study the downstream effect of early diagnosis by CMR-MPI	<i>Primary clinical outcome</i>	I) Composite of (1) cardiovascular death, (2) AMI and (3) hospitalization for unstable angina, heart failure or resuscitated cardiac arrest
	<i>Secondary clinical outcome</i>	I) Individual components of the primary clinical outcome II) All-cause mortality III) Inclusion of stroke in the primary clinical outcome IV) Cardiovascular interventions (including PCI, CABG, valvular interventions and aortic surgery), separated: - following study CMR-MPI - unplanned (not following study CMR-MPI)
	<i>Primary imaging outcome</i>	I) Composite of (1) moderate-severe myocardial ischemia, (2) subclinical AMI, (3) CM, (4) LVEF < 40%, (5) probably severe valvular disease and 6) aortic aneurysm ≥ 50 mm
	<i>Secondary imaging outcome</i>	I) Individual components of the primary imaging outcome II) Inclusion of severe extra-cardiac findings in the primary imaging outcome

AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CM, cardiomyopathy; CMR-MPI, cardiovascular magnetic resonance myocardial stress perfusion imaging; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

Table III. Definition of primary and secondary imaging outcomes

Imaging outcome	Definition	Classification
Myocardial ischemia	A perfusion defect that 1) lasts > 3 heartbeats after maximum signal intensity on first-pass perfusion imaging, and 2) is not related to LGE	<i>Moderate-severe:</i> myocardial ischemia in ≥ 2 segments that are neighbouring or in adjacent slices and are conformed to a coronary artery territory <i>Mild:</i> myocardial ischemia in 1 segment
Myocardial fibrosis	Trapping of gadolinium contrast agent on late gadolinium enhancement imaging	<i>Ischemic (silent myocardial infarction):</i> LGE with a subendocardial or transmural pattern that is conformed to a coronary artery territory <i>Non-ischemic (cardiomyopathy):</i> any midwall, subepicardial, diffuse or global LGE with a pattern judged to be indicative of cardiomyopathy.*
LVEF	(LVEDV-LVESV)/LVEDV \times 100, quantified by volumetric CMR-MPI post-processing	<i>Reduced:</i> LVEF < 40% <i>Mid-range:</i> LVEF 40-50% <i>Preserved:</i> LVEF \geq 50%
Valvular disease	Any valvular jet indicative of stenosis or regurgitation or any structurally abnormal valve	<i>Probably severe:</i> (1.) a valvular stenosis or regurgitation deemed severe by visual assessment, supported by evidence of concomitant structural cardiac abnormalities (e.g., left ventricular dilatation, left ventricular hypertrophy) or (2.) non-tricuspid aortic valve structure <i>Probably non-severe:</i> any other valvular stenosis or regurgitation or structural abnormality
Thoracic aneurysm	Any thoracic or abdominal aortic dilation	<i>Severe:</i> \geq 50 mm <i>Non-severe:</i> < 50 mm
Extra-cardiac findings		(1.) pleural fluid with \geq 2 cm thickness, (2.) lung nodules with a diameter > 0.8 cm (in accordance with Imalife protocol), (3.) abdominal mass, (4.) splenomegalia > 10 cm and (5.) ascites

* Further (suspected) differentiation is made, if possible, based on LGE pattern, tissue characterization by T1 mapping and cardiac structure, into: hypertrophic cardiomyopathy (HCM), dilating cardiomyopathy (DCM), myocarditis, sarcoidosis, amyloidosis or other/unknown type. AMI, acute myocardial infarction; CMR-MPI, cardiovascular magnetic resonance myocardial stress perfusion imaging; LGE, late gadolinium enhancement; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume.

ing relationships of clinical data, blood-based biomarkers, CAC with imaging and clinical outcomes.

Recruitment for EARLY-SYNERGY started on May 27th 2019. As of February 1, 2021, 2,081 individuals with CAC score \geq 300 were identified (83% of total projected). A total of 1,194 individuals were randomized (75% of total projected). The imaging visit was completed in 503 individuals randomized to CMR-MPI (71% of total projected).

Statistical considerations

Sample size calculation

Sample size was estimated for both co-primary objectives separately.

Yield of CMR-MPI

To date, no studies evaluating the prevalence of OCAD in asymptomatic individuals at increased risk have been performed. The prevalence of OCAD in this asymptomatic population at increased risk is therefore unknown. To calculate the required sample size to accurately describe the prevalence of OCAD, the prevalence of OCAD was estimated based on data from symptomatic patients undergoing CAC quantification and SPECT perfusion imaging. Based on aggregated data from these

studies showing a 35.2% prevalence in symptomatic patients, a slightly lower estimated prevalence of 20%-25% of the primary imaging outcome for this objective was deemed reasonable in EARLY-SYNERGY²⁴. To show a 20%-25% prevalence of the primary imaging outcome with a width of the 2-sided 95% confidence interval (95% CI) of 8%, required sample size is estimated at $n = 407$ - 473 in the CMR-MPI arm. To account for possible inconclusive or non-interpretable imaging data, yield of CMR-MPI will be reported at completion of $n = 500$ CMR-MPI examinations.

Downstream effect on clinical outcome

In the control arm (CAC \geq 300), an event rate of 10% at 5 years was projected based on a meta-analysis of 5 large studies¹⁶. A reduction of 50% of events in cases with substantial (> 10% of LV) ischemia was deemed reasonable based on a meta-analysis of several large randomized-controlled clinical trials²⁵. It was estimated that > 90% of events occur in individuals with myocardial ischemia, and < 10% in cases with no ischemia¹². To show a 50% reduction in 90% of events (45% reduction of total events) in the CMR-MPI arm, at a power of 0.80, alpha of 0.05, accrual time of 2 years and follow-up duration of 5 years, approximately $n = 700$ individuals per study

arm are required (approximately $n = 1400$ in total). Individuals in the control arm are followed-up for the natural course of coronary atherosclerosis. Cross-over to imaging in the control arm is highly unlikely since CMR-MPI is not performed in asymptomatic individuals in clinical care in the Netherlands, unless individuals in the control arm become symptomatic. Healthcare utilization due to symptoms occurring in the control arm (i.e., the natural diagnostic pathway) is an EARLY-SYNERGY endpoint and not a cross-over. Cross-overs were therefore not accounted for in the sample size calculation. Loss to follow-up is projected to be very low ($< 5\%$) due to consultation of municipal and hospital registries as part of EARLY-SYNERGY follow-up.

Analysis of the primary endpoint

For studying the yield of CMR-MPI, frequencies and percentages of primary and secondary imaging outcomes will be reported for the overall population and compared between subgroups of age, gender and CAC score. To evaluate the effect of early disease diagnosis by CMR-MPI on primary and secondary clinical outcomes, time-to-event analysis comparing the CMR-MPI arm and the control arm will be performed according to the “intention-to-image” principle. Comparison of hazard ratios as estimated by covariate-adjusted Cox proportional hazards model will be considered the primary analysis to evaluate the effect of early disease diagnosis^{26,27}. The hazard ratio as provided by the covariate-adjusted Cox model will be reported, along with its 2-sided 95% Wald-type confidence interval. Covariates included in the analysis primarily include age, gender, origin of the CAC score (ROBINSICA or ImaLife) and demographic region in the Netherlands. Secondary, Kaplan-Meier curves will be created to visualize time-to-event for the CMR-MPI and the control arm. Time-to-event curves will be compared by the logrank test. Accelerated failure time models will be constructed to estimate risk if the proportional hazards assumption is violated. Log-log survival plots and a time-dependent covariate to the Cox model will be used to test the proportionality assumption of the Cox model. The time-dependent covariate will be the interaction between early treatment by imaging and time. If this interaction is large and statistically significant, there is evidence of non-proportionality. In case of a large and statistically significant interaction, non-proportionality is likely. Cox model hazard ratios will then be cautiously interpreted, and interpretation of non-parametric event rate will be emphasized. Cumulative endpoint event rates will be estimated as a function of follow-up time in each randomization arm using Kalbfleisch & Prentice’s nonparametric estimator of the cumulative incidence function (CIF). The Kalbfleisch & Prentice CIF estimator was selected for this study in order to account for competing risks. Cumulative outcome rates for groups at yearly time points will be estimated

and differences in cumulative outcome rates will be presented along with 95% confidence intervals. Subanalyses for the impact on outcome will be focused on subgroups of age, sex, CAC score and origin of the CAC score (ROBINSICA or ImaLife). The relationship of clinical parameters, blood markers and CAC parameters with imaging and clinical outcomes is of particular interest, and will be studied using univariate and multivariable logistic regression analysis. A 2-sided alpha of 0.05 will be considered the statistical significance threshold for all statistical analyses.

Analysis of healthcare utilization, cost-utility and patient reported outcome measures

The balance between incremental costs and incremental quality-adjusted life years (QALYs) of CAC quantification and CMR-MPI will be calculated and represented as an incremental cost-utility ratio. The EQ-5D-5L and HeartQoL will be used to assess the health-related quality of life of participants, and to calculate QALYs, using the Dutch tariff^{28,29}. The iMCQ will be used to measure health resources consumed and the iPCQ will be used to measure productivity losses²³. The health economic evaluation will be performed according to Dutch national guidelines and applying 1.5% discounting for health outcomes and 4% discounting for cost outcomes³⁰. Furthermore, a willingness-to-pay threshold is applied according to the Dutch guidelines.

To estimate long-term health and cost outcomes, a patient-level simulation model will be developed to predict the future impact of early ischemia detection. This is necessary to estimate the full impact, as early detection and subsequent early treatment may prevent cardiovascular events much later in life³¹. A life-long time horizon will be used in this analysis. Bootstrapping will be applied to define distributions reflecting the uncertainty in model parameters based on this clinical data³².

Probabilistic analysis will be performed to assess uncertainty in simulation outcomes using a Monte Carlo simulation with 5000 iterations³³. Uncertainty will be visualized in an incremental cost-effectiveness plane and a cost-effectiveness acceptability curve. In addition, subgroup analysis will be performed to derive subgroup specific cost-effectiveness outcomes. The financial impact of implementing CMR-MPI in a 2-stage CAD screening strategy in daily practice will be determined in a budget impact analysis using a 5-year time horizon³⁴.

Discussion

EARLY-SYNERGY will be the first to study an innovative imaging strategy for the early diagnosis of myocardial ischemia caused by OCAD, as well as to enhance our knowledge on whether early diagnosis and intensified management of these conditions can improve clinical

cal outcomes. If proven effective and cost-efficient, synergistic imaging by CT-based CAC quantification followed by CMR-MPI in high-risk individuals could be applied in strategies to improve primary prevention of AMI and sudden cardiac death.

Professional practice guidelines recommend revascularization of large areas of myocardial ischemia (> 10% of the LV wall), irrespective of the presence of symptoms. Ischemic size mentioned in the guidelines is based on older SPECT studies^{35,36}. Recent studies evaluating minimal ischemic size for benefit of revascularization based on CMR-MPI reported a beneficial effect in case moderate-severe myocardial ischemia, defined as ≥ 2 ischemic myocardial segments detected by CMR-MPI, is present^{37,38}. Moderate-severe myocardial ischemia, defined as ≥ 2 ischemic segments indeed approximates an ischemic size of > 10% of LV and was therefore also considered a clinically actionable finding in EARLY-SYNERGY. More recently, the ISCHEMIA trial suggested that revascularization does not impact on outcome compared to optimal medical therapy (OMT) in individuals with objectified myocardial ischemia²⁶. However, the results of the ISCHEMIA trial have some limitations and important differences to consider in comparison to the EARLY-SYNERGY trial. First, a selection bias might be a relevant limitation to generalizability of ISCHEMIA results. Approximately 25,000 individuals with positive ischemia testing were required to randomize 5,179 patients. A large number of countries and centers participated and the average recruitment has been estimated to be 2 patients per center per year during an 8 year period. The strategy to detect myocardial ischemia in the ISCHEMIA trial was stress ECG testing in 25% and stress echocardiography in 20%, which have modest diagnostic performance in evaluation of OCAD, while only a small minority of 5% was based on the superior CMR-MPI technique¹⁷. Treatment of patients with false positive stress ECG or echocardiography might decrease net-benefit of revascularization and increase risk of complications. Crossovers might also have impacted the results. In the patients randomized to revascularization, approximately 20% did not undergo revascularization and approximately 20% of the patients randomized to optimal medical therapy did undergo revascularization. Also relevant was that the outcomes appeared to be driven largely by peri-procedural infarctions in the revascularization arm early in follow-up, while after 2 years the revascularization appeared to accrue a lower number of spontaneous infarctions, which are deemed to have a stronger effect on long-term outcomes. Long-term follow-up of the ISCHEMIA trial will cast more clarity on the effect of revascularization as compared to OMT in patients referred to the cardiologist for symptoms. However, in contrast to ISCHEMIA, the EARLY-SYNERGY trial does not aim to compare different treatment strategies, but is designed to study whether CMR-MPI based early myocardial

ischemia diagnosis in asymptomatic individuals impacts outcomes.

The prevalence of subclinical OCAD in the general population is low and a large number of tests will be required to identify asymptomatic individuals with subclinical OCAD in an unselected population. However, the prevalence of colorectal and breast cancer is also low and screening studies on these cancer types have provided evidence for its cost-efficacy. In contrast to cancer, studies to investigate the benefit of early subclinical OCAD diagnosis and treatment in the general population are lacking. The rapid developments in the field of cardiac imaging continues to generate novel opportunities for their application in the primary preventive setting. A synergistic imaging strategy combining CT-based CAC quantification and CMR-MPI for early OCAD diagnosis is theoretically feasible and can efficiently diagnose subclinical OCAD with high post-test probability given a positive CMR-MPI, and low total number of false negative tests in the total population (Ties et al, submitted). The unique setting of 2 population-based CAC studies in The Netherlands (ROBINSICA and ImaLife) made the conception and execution of EARLY-SYNERGY feasible, allowing EARLY-SYNERGY to study whether additional functional imaging with CMR-MPI in population-based individuals with increased CAC score will yield a sufficient number of OCAD cases to cost-efficiently reduce the rate of AMI and sudden cardiac death in the general population. To meet these cost-utility criteria, further optimization of the balance between case finding and number of tests might still be warranted. Prediction of myocardial ischemia and cardiac dysfunction on CMR-MPI by CAC parameters, clinical characteristics and blood-based biomarkers are integrated in the EARLY-SYNERGY protocol. The extent or distribution of CAC or levels of blood biomarkers like troponins or brain natriuretic peptides may provide important additional criteria to most cost-efficiently select individuals for CMR-MPI¹⁶.

The EARLY-SYNERGY trial has some inherent limitations to acknowledge. First, the time interval between CT-based CAC quantification and CMR-MPI might be sub-optimal because of dependency of previously performed CT's in already on-going ROBINSICA and ImaLife studies. Also the COVID-19 pandemic led to a temporary halt of the execution of the EARLY-SYNERGY trial, further increasing the interval. Secondary, treatment of conditions after early diagnosis by CMR-MPI performed within EARLY-SYNERGY is not part of the EARLY-SYNERGY study protocol but will be left to discretion of the GP or treating physicians and the participant. This might lead to underutilization of preventive strategies. Reference to practice guidelines is aimed to overcome this.

The main strength of EARLY-SYNERGY is its multicenter, randomized-controlled design, allowing a head-to-head comparison of clinical outcome between additional functional imaging for early myocardial ischemia diagno-

sis and the natural course of symptom onset. In addition, EARLY-SYNERGY is able to provide data on the prevalence of subclinical OCAD in the at-risk population. A dedicated CMR-MPI protocol in line with professional practice guidelines was developed, resembling modern clinical practice. Two different vasodilating drugs will be used to induce hyperemia during CMR-MPI, increasing accessibility by allowing individuals who have contraindications for traditional adenosine-induced hyperemia to undergo secondary CMR-MPI.

In conclusion, EARLY-SYNERGY will study a novel synergistic imaging strategy combining CT-based CAC quantification and CMR-MPI for early diagnosis of subclinical myocardial ischemia caused by OCAD in the general population and will provide novel evidence regarding whether early recognition of subclinical OCAD improves outcome. Primary objectives of EARLY-SYNERGY are to study the yield of CMR-MPI for detection of subclinical OCAD in asymptomatic individuals with atherosclerosis (CAC score ≥ 300) and to evaluate the downstream effect of early diagnosis of subclinical myocardial ischemia and other clinically actionable findings by CMR-MPI on clinical outcome, as compared to the natural course.

Disclosures

Dr. van der Aalst reports receiving grant support by the EU, Dr. Westenbrink receiving grant support by the Dutch Heart Foundation and Dutch CardioVascular Alliance, Dr. Išgum receiving grant support from Pie Medical Imaging BV, Dutch Technology Foundation and Dutch Cancer Foundation and travel fees from the Society of Cardiovascular Computed Tomography and Radiological Society of North America, fees as co-founder and scientific leader of Quantib-U and holding stock options in Quantib-U, Dr. Nijveldt receiving grant support by Philips Volcano and Biotronik and lecture fees from Bayer and Sanofi, Dr. de Koning receiving grant support by the EU, Dr. Vliegthart receiving grant support and lecture fees by Siemens Healthineers, Dr. Oudkerk receiving grant support by the EU, and Dr. van der Harst receiving grant support by Siemens Healthineers and Guerbet. The other authors did not report any potential conflict of interest relevant to this article.

Acknowledgements

This research was supported by the Dutch Heart Foundation (EARLY-SYNERGY - research grant [CVON2015-17](#)) and [Siemens Healthineers](#) (PUSH - partnership IPA No.11 [PUSH MRA](#)). The Lifelines Biobank initiative has been made possible by funding by FES (Fonds Economische Structuurversterking), SNN (Samenwerkingsverband Noord Nederland) and REP (Ruimtelijk Economisch Programma). The ImaLife study is supported 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 ROBINSICA trial has been made possible by funding by the EU (ROBINSICA - Advanced research grant: grantnumber 294604). The authors wish to acknowledge the services of the Lifelines Cohort Study, the contributing research centers delivering data to Lifelines, and all the study participants. The authors are grateful to all the imaging technicians and supporting personnel at the local hospitals for their contribution to conducting the study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.ahj.2022.01.005](https://doi.org/10.1016/j.ahj.2022.01.005).

CRediT authorship contribution statement

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