CARDIAC CT IN MIDDLE-AGED ATHLETES

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CARDIAC CT IN MIDDLE-AGED ATHLETES

Cardiale CT bij mannelijke sporters van middelbare leeftijd

(met een samenvatting in het Nederlands)

Proefschrift

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CHAPTER 1

General introduction and outline of this thesis

GENERAL INTRODUCTION

Report of a case

A 47-year-old endurance athlete with no cardiovascular history collapsed while climbing in the mountains during a holiday. Despite bystander resuscitation and the arrival of the emergency medical services (helicopter), he died shortly after collapsing. Two years before the event, he had undergone a routine sports medical evaluation that included a 12-lead electrocardiogram as well as exercise electrocardiography. He trained 12 hours a week (endurance running). Apart from a positive family history for cardiovascular disease and a slightly elevated LDL/HDL cholesterol ratio, the cardiovascular evaluation was unremarkable. One year before the event, he participated in a research project on magnetic resonance imaging (MRI) of the athlete's heart. The cardiac MRI and resting ECG showed no abnormalities.

At autopsy he was found to have three-vessel coronary artery disease (CAD), the culprit lesion being located in the right coronary artery. Re-evaluation of the records from both the sports medical evaluation and cardiac MRI study confirmed the absence of abnormalities. CT scanning, had it been performed, would undoubtedly have revealed the presence of a significant amount of coronary calcium and prompted further evaluation.

This tragic case exemplifies the many pitfalls of preparticipation screening: a thorough and repeated cardiovascular evaluation that included exercise electrocardiography and cardiac MRI evaluation, in addition to the routine Lausanne criteria (medical and family history, physical examination, resting ECG) revealed no abnormalities and he was considered fit for intensive sports activities. Yet, this 47-year-old endurance athlete died suddenly during moderate exercise.

Screening athletes to prevent cardiovascular events

Regular physical exercise is recommended to reduce cardiovascular morbidity and mortality and is gaining popularity among middle-aged and older persons.[1-3] Yet (vigorous) exercise is also associated with a transiently increased risk of acute cardiac events, particularly in untrained persons with unknown cardiac disease.[4] More than 90% of acute exercise related cardiac events occur in men, predominantly those aged 35 years or over.[5] Acute events in young athletes (35 years or younger) are mainly caused by inherited cardiac diseases, whereas events in older athletes are largely caused by CAD.[4] Despite the rare occurrence of cardiac events in young athletes (approx. 1 per 100.000 athletes per year) in 2005 the study group of sport cardiology of the European Society of Cardiology (ESC) recommended mandatory preparticipation screening of athletes aged 35 years or younger.[6] It would make more sense to direct screening efforts at older athletes as they have a higher risk of acute cardiac events. This would imply screening for the presence of CAD in (largely) asymptomatic athletes to identify those at a high risk of cardiovascular events.[7] Minimally invasive cardiac imaging is likely to play an important role in this group.[8]

Traditionally, risk scores (e.g. the Framingham Heart Study (FHS) score and the Systematic COronary Risk Evaluation (SCORE) of the ESC) are used to estimate the chance of cardiovascular events in asymptomatic persons, aiming to divide individuals in low, intermediate and high risk categories, corresponding to a 0-4%, 5-9% and 10% or higher 10 year CV mortality risks respectively, in case SCORE is used.[1, 9]

Non-contrast coronary CT (CCT) for the assessment of coronary artery calcium (CAC) provides a non-invasive direct measure of burden of coronary atherosclerosis and is an independent predictor of cardiovascular events.[10] Moreover, CAC is the most powerful cardiac risk prognosticator in asymptomatic persons, with consistent superiority to all risk factor-based scores.[11] Absence of CAC is associated with a very low risk of future cardiovascular events in asymptomatic as well as symptomatic individuals.[12] The amount of CAC, however, relates poorly to the degree of luminal narrowing of the coronary arteries and a low coronary artery calcium score (CACS) does not exclude CAD.[13, 14] The 'Agatston Score' remains the most commonly used measure to quantify CAC because most previous large-scale trials and cross-sectional studies used this method, so that large reference data sets exist (e.g. http://www.mesa-nhlbi.org/Calcium).[15] Coronary artery calcification is age, gender, and race dependent. Agatston scores are often classified into five groups according to severity as listed in Table 1.[16] A score <10 Agatston Units (AU) is ranked as low risk, scores between 10 and 100 as moderate, scores between 100 and 400 as moderately high risk and above 400 AU as high risk of future atherosclerotic cardiovascular events.[16] CACS is increasingly used as a tool to expand risk-stratification in asymptomatic persons with an intermediate risk of cardiovascular events.[17] The low number needed to screen (NNS) in the general population to identify an individual with moderate or severe CAC (8 and 20 respectively) seems to provide a justification for extending CAC testing to lower risk individuals,[10] as CAC is also associated with risk of cardiovascular events among individuals with little or no risk factors.

The use of traditional cardiovascular risk scores in persons who are physically active is hampered by the reduction of risk factors by regular exercise. As such, risk scores are likely to underestimate the risk of cardiovascular events by neglecting risk factor exposure in the years prior to commencing regular exercise.[18] It has been suggested that regular, intense, physical exercise (e.g. marathon running) by itself may be harmful to the heart by causing myocardial fibrosis and contributing to coronary artery plaque formation (as evidenced by coronary artery calcium scanning) with cardiovascular events occurring at an alarmingly high rate (21% percent 10 year event rate) in a group of 108 recreational German marathon runners aged 50 years or older.[18-20] Nearly all cardiovascular events occurred in those with a CACS higher than 100 AU.

Table 1. Classification of coronary artery calcium score

Absolute value (Agatston units)	Ranking	Risk of CV events
0	Absent	Very low
>0<10	Minimal	Low
≥10 <100	Mild	Moderate
≥100 <400	Moderate	Moderately high
≥400<1000	Severe	High

Classification of coronary calcium absolute content evaluated by cardiac CT and quantified by Agatston units

The 2011 ESC position paper on cardiovascular evaluation of middle-aged/senior individuals engaged in leisure time sports activities pleads the use of maximal exercise testing.[21] Adding maximal exercise testing to the cardiovascular evaluation of middle-aged/senior athletes, as advocated by the ESC, may be useful to identify some persons at high risk, by detecting ischemia caused by a significant coronary artery stenosis.[22] Numerous studies have indicated that asymptomatic men with an abnormal exercise test received the greatest benefits of interventions to reduce risk factors.[23, 24] Notwithstanding the low predictive value (high false negative rate) for CAD of both resting and exercise electrocardiography in asymptomatic individuals, exercise testing is still frequently performed in the course of a sports medical check-up.[25] This is partly attributable to the fact that the results of exercise testing will also provide information on cardio respiratory fitness relevant to recommendations for subsequent training programs.

Although the presence and amount of CAC provides additional information to conventional CV risk scores (judged to be an appropriate tool to apply to persons with an intermediate cardiovascular risk) –and carries important prognostic information,[17, 26] the use of CACS has only been evaluated sporadically in an athletic population. Importantly, coronary calcium can only be regarded as a proxy measure for CAD. Acute coronary syndromes, attributed to rupture of a so called “soft” plaque, are known to occur in patients with no coronary calcium or low calcium scores.[27] An analysis of cardiac arrests during long distance running implicated a causal role for demand ischemia in athletes with (unknown) CAD.[2]

Selective coronary angiography (CAG) is the method of choice for the evaluation of symptomatic CAD in daily clinical practice, generally reserved for symptomatic patients with documented ischemia or otherwise a high likelihood of significant CAD. Apart from costs, morbidity, mortality (in the order of 0,1% for diagnostic procedures), the radiation exposure and the invasive nature of the procedure prevent the use of CAG in the evaluation of asymptomatic persons. Low dose minimally invasive coronary CT angiography (CCTA) is becoming an increasingly realistic option to detect CAD in asymptomatic persons, both in the general population as well as in athletes.[8, 28] Apart from an assessment of coronary artery narrowing (stenosis), CCTA offers the advantage of vessel wall visualization to distinguish between calcified, non-calcified and mixed coronary plaques.[29] The vulnerable plaque paradigm states that plaque composition is a better predictor of acute coronary events than stenosis grade.[30]

CCT can be of added value by providing a minimally invasive opportunity to image the coronary arteries for CAC, total atherosclerotic burden and coronary stenosis.[31] It is conceivable that non invasive imaging of the coronary arteries of athletes will lead to a better estimation of the risk of CV events in athletes.[8] The selection of asymptomatic persons who will benefit from CCT (CACS as well CCTA) or electrocardiographic exercise testing to reduce the risk of cardiovascular events remains an area of controversy.[32] There are no published data comparing the yield of CCT with exercise testing in asymptomatic persons, let alone athletes, and no clinical trials have specifically addressed whether CT or electrocardiographic testing in asymptomatic persons improve hard CV outcomes.[33] One randomized study indicates that CACS results in a better CV risk profile at no increase of medical costs.[34]

CT radiation protection and dose reduction are important issues in the evaluation of asymptomatic persons. As they will normally have a low heart rate and BMI, athletes are suitable candidates for low radiation dose (2 milliSievert – mSv) CCTA.[28] This dose corresponds to the yearly background radiation each person receives in Europe.[35] Furthermore, a position paper that analyzed acute and long-term composite risks related to cardiovascular imaging, showed that life time risk of imaging procedures for fatal events is small compared with the general risk of fatal cardiac events by CAD in both asymptomatic and symptomatic populations.[36]

Aims of the Measuring Athlete's Risk of Cardiovascular events (MARC) study

The current cardiovascular evaluation of middle-aged recreational athletes essentially consists of a medical history, physical examination, resting and exercise electrocardiography. As most exercise related cardiac arrests in men aged 45 years or older is due to CAD, we propose that it is probably more efficient to visualize CAD directly. Low dose, minimally-invasive coronary CT imaging, with both CACS and CCTA, is becoming an increasingly realistic option to detect CAD in asymptomatic persons, both in the general population as well as in athletes. There are no published data comparing the yield of CCTA with exercise testing in asymptomatic persons and no clinical trials have specifically addressed whether CCT or electrocardiographic testing in asymptomatic persons improve hard CV outcomes. This information is pivotal to evaluate preparticipation screening strategies in middle-aged men who are or want to become physically active. The aim of this thesis was therefore to investigate the added value of CCT (non-contrast CT for CACS and contrast-enhanced CT for CCTA) to routine sports medical evaluation in asymptomatic male recreational athletes, aged ≥45 years, without known cardiovascular disease.

If, as we anticipate, coronary CT imaging will reclassify a substantial proportion of sportsmen to a higher risk of cardiovascular events, our study will pave the way for CCT based intervention studies to help reduce the occurrence of cardiovascular events. This thesis will provide guidance in the debate on the optimal preparticipation evaluation of the rapidly growing group of older sportsmen in whom CAD is the main cause of cardiovascular events.

OUTLINE OF THIS THESIS

As an introduction to this thesis, we present a scoping review of studies in **chapter 2** that have evaluated cardiac imaging to detect CAD in asymptomatic sportspersons, aged 35 years and above, and we describe both the potential of cardiac imaging and the knowledge gaps. C**hapter 3** provides the rationale and design of the MARC Study; "The role of coronary CT in the cardiovascular evaluation of middle-aged sportsmen." Increased arterial stiffness is an established marker of subclinical atherosclerosis and has been shown to be an independent predictor of cardiovascular mortality in various populations.[37-39] Arterial stiffness can easily be determined non-invasively by means of pulse wave velocity (PWV) measurement in an SME setting. If this measurement of arterial stiffness is related to CAD it could be used to select sportsmen who could benefit from CCT imaging. In **chapter 4** we investigated the additional value of increased arterial stiffness measured by means of pulse wave velocity (PWV) in a subgroup of MARC-participants to detect CAD on CCT.

Chapter 5 focuses on dose reduction. CT radiation protection and dose reduction are important issues in the evaluation of asymptomatic persons. As individuals referred for CCTA commonly undergo a separate non-contrast CT for CACS prior to CCTA, both non-contrast CT and CCTA studies add to the total radiation dose. Therefore we investigated whether CACS could be adequately quantified from CCTA with novel noise-reducing techniques on low-dose CCTA, and thereby obviating the need for an additional scan, and reducing the radiation dose. **Chapter 6** presents the main results of the MARC study by reporting the occurrence of CAD in sportsmen aged 45 years and over, reclassification rates for developing symptomatic cardiovascular disease, as well as an estimation of the number needed to screen with CCT to prevent cardiovascular events. In **chapter 7** we discuss the psychological impact of cardiovascular screening with CCT in the MARC-cohort. In **chapter 8** we describe the impact of lifelong exercise and ideal cardiovascular health on the occurrence of CAD as assessed by CCT in a subgroup of low SCORE risk participants. The main findings and implications of the studies described in this thesis are discussed in **Chapter 9. Chapter 10** provides a summary.

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CHAPTER 2

Cardiac imaging to detect coronary artery disease in athletes aged 35 years and older. Scoping review to identify gaps and challenges in research

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ABSTRACT

Sudden cardiac death (SCD) is a devastating event in athletes. Screening efforts that were first directed at athletes younger than 35 years, are now focusing on the rapidly growing group of older sportspersons. Athletes aged ≥35 years have a 10-fold increased risk of exercise-related cardiac arrest, mostly due to coronary artery disease (CAD). Although cardiac imaging is pivotal in identifying CAD, the role of imaging modalities in screening asymptomatic older sportspersons remains unclear. We performed a scoping review to identify the role of cardiac imaging to detect CAD in older sportspersons and to identify gaps in the existing literature. We searched Medline, Embase and the Cochrane library for studies reporting data on cardiac imaging of CAD in sportspersons ≥35 years. The systematic search yielded 1737 articles and 14 were included in this scoping review. Imaging modalities included 2 echocardiography, 1 unenhanced Computed Tomography (CT) for coronary artery calcium scoring (CACS), 3 CACS and contrast-enhanced CT angiography (CCTA), 2 CACS and Cardiac Magnetic Resonance (CMR), 1 CCTA with CMR and echocardiography, 2 CCTA, 2 CMR, and 1 myocardial perfusion imaging article.

The low number of relevant articles and the selection bias introduced by studying specific groups, like veteran marathon runners, indicate the need for future research. Cardiac CT (CACS and CCTA) probably has the highest potential for preparticipation screening, with high diagnostic value to detect CAD and low radiation dose. However, currently there is insufficient evidence for incorporating routine cardiac imaging in the preparticipation screening of asymptomatic sportspersons over 35 years.

INTRODUCTION

Regular physical exercise is recommended to reduce cardiovascular morbidity and mortality and is gaining popularity among middle-aged and older persons.[1-3] Yet, exercise also transiently increases the risk of cardiovascular events, particularly in those with unknown cardiac disease.[4] Over 90% of acute exercise-related cardiac events occur in athletes older than 35 years.[5, 6] Recent studies have shown that the vast majority of sports-related cardiac arrests occur in men, with a 9:1 male-female ratio,[5, 6] increasing to 20:1 in middle-aged runners.[7] The incidence is expected to rise as a growing number of middle-aged or older individuals engage in sports, for instance marathon running.[2, 3] While cardiac arrests in younger athletes are mainly caused by cardiomyopathies, electrical heart disease and coronary anomalies, coronary artery disease (CAD) is by far the most common cause of sudden cardiac death (SCD) in athletes aged 35 years and older, accounting for almost 90% of all cardiac deaths.[3-6] Even in athletes aged 25 to 35 years CAD accounted for 43% of deaths in a recent US study.[8] The traditional view that exercise-induced acute coronary events result from atherosclerotic plaque disruption and coronary thrombosis,[4, 9, 10] was recently challenged by a study of cardiac arrests during long distance running.[2] The absence of coronary plaque rupture in many victims suggests there may be a causal role for demand ischemia in athletes with (unknown) CAD.[2] Consequently, it seems wise to aim at early identification of CAD in the preparticipation evaluation of sportspersons aged 35 years and older. To date traditional cardiovascular (CV) risk scores, like the Framingham Risk Score (FRS) and European Society of Cardiology (ESC) Systematic COronary Risk Evaluation (SCORE), as well as resting and exercise electrocardiography (ECG), are used to identify athletes with a high risk of exercise related cardiac events.[11] The use of CV risk scores and (exercise) ECG in athletes has limitations. CV risk scores may underestimate the risk in athletes, as these scores were not designed for physically active people. Regular exercise favourably influences CV risk factors by reducing weight and blood pressure and improving the lipid profile, and the resulting lower CV risk scores may provide a false sense of security.[12] Maximal exercise testing for CV evaluation of middle-aged individuals engaged in leisure time sports activities is recommended by the ESC,[11] and is now frequently part of a sports medical evaluation. Although the information on cardiorespiratory fitness is relevant for subsequent training programs, both the resting and exercise ECG are of limited value to detect occult CAD because of their low sensitivity in asymptomatic subjects with low and intermediate CV risk.[13, 14] The role of imaging modalities in the prevention of sports related CV events in older sportspersons is only beginning to be addressed. This paper provides a scoping review of studies that have evaluated cardiac imaging to detect CAD in asymptomatic sportspersons aged 35 years and older and demonstrates both the potential of cardiac imaging and the knowledge gaps.

METHODS

The scoring review was guided by Aksey and O'Malley's methodological framework that was refined by Levac and colleagues: "identifying the research question, searching for relevant studies, selecting studies, charting the data and collecting and reporting the results."[15, 16] We chose to perform a scoping review because of the absence of randomized controlled trials and to summarize the breadth of available evidence with different imaging modalities in this field. A scoping study design is ideal for incorporating a range of studies, and despite several similarities to a systematic review, it does not typically involve quality assessment and therefore we report findings in a narrative format.[15, 16]

The research question

We performed unrestricted searches in Medline, Embase and the Cochrane Central Register of Controlled Trials, which identified relevant articles to answer our research question: "What imaging studies have been conducted on identification of CAD in sportspersons aged ≥35 years and what were the outcomes of these studies?" Searches were performed in February 2017 using a combination of the following terms: coronary artery disease, CV evaluation, athletes, middle-aged and imaging. We included studies of middle-aged sportspersons engaged in non-professional competitive or recreational leisure sports who were screened for CAD including all possible imaging modalities.

The search was expanded by reviewing references found in the manuscripts. The full search strategy is available in an online appendix (e-Appendix 1). Searches were performed without language or publication restrictions.

Outcome measures and definitions of CAD

Various imaging modalities can be used to identify CAD and these modalities are either modalities that visualise coronary anatomy for coronary calcification and luminal stenosis or functional tests that detect inducible myocardial ischemia perfusion abnormalities or wall motion abnormalities with exercise stress or intravenous pharmacological stress. Pharmacological agents are vasodilator stress (adenosine, dipyridamole or regadenoson) or inotropic agent dobutamine

- Echocardiography can only indirectly identify CAD by demonstrating segmental wall motion abnormalities either at rest or during exercise stress or alternatively pharmacological stress if patients are unable to exercise adequately.
- Cardiac CT provides direct information on the presence and extent of CAD:
  - CACS: the coronary calcium burden is graded according to Rumberger et al.,[17] in the following categories: Agatston score 0 (no coronary calcium), 1 – 10 (minimal), 11 – 100 (mild), 101 – 400 (moderate) and > 400 (extensive coronary calcium). Agatston scores > 100 are generally considered to indicate relevant CAD, conferring a moderately high risk of future CV events.
  - CCTA: provides additional information to coronary calcium, on the presence of non-calcified plaques and luminal narrowing, with moderate CAD, luminal narrowing >50 %, and severe CAD, luminal narrowing >75%.[18]
- On Cardiac Magnetic Resonance (CMR), wall thinning with wall motion abnormalities and subendocardial or transmural late gadolinium enhancement (LGE) are typical for myocardial infarction due to coronary artery disease. Myocardial ischemia can be detected by myocardial perfusion abnormalities with vasodilator stress (adenosine, dipyridamole or regadenoson) or ischemia-induced wall motion abnormalities with dobutamine.
- Myocardial Perfusion Scintigraphy (MPS) identifies cardiac ischemia due to significant CAD by reduced regional radioactive tracer uptake during exercise or pharmacological stress compared with preserved perfusion at rest, in combination with possible wall motion abnormalities and transient ischemic dilatation at stress.

Article selection

Electronic search results were downloaded into EndNote bibliographic software, Thomson Reuters, Philadelphia, United States. Two authors (TB and MW) independently screened titles and abstracts identified by the electronic search and applied the selection criteria to potentially relevant papers. Differences were resolved by consensus between these authors. Data, including aims, imaging modality, study populations, outcome measures and important results, were entered onto a 'data charting form' using Excel, Microsoft, Redmond, United States.

Reporting the results

Of 1737 citations identified after searching Medline, Embase and Cochrane with the above search terms, 11 papers were selected for full text reading. References of these 11 manuscripts and the personal database of one author (SS) were reviewed for potentially relevant manuscripts, identifying another 3 articles, and yielding a total of 14 articles,[12, 14, 19-30] that were included in the current review. A flowchart of study inclusions is provided in appendix 1.

RESULTS

The search identified 14 original manuscripts, the characteristics of which are summarized below. Details of individual studies are shown in table 1. Table 2 demonstrates the advantages, costs and diagnostic accuracy of the available imaging modalities compared to the non-imaging functional exercise test (X-ECG). Figure 1 demonstrates the gap in the existing literature and indicates where future research is necessary.

Study characteristics

All articles were published in peer-reviewed journals, between 1998 and beginning 2017, and sample sizes ranged from 19 to 318 subjects. Five studies related to the same German male cohort of 108 marathon runners.[12, 21-24]

Populations in the other papers were 19 Scottish veteran endurance athletes,[25] 153 marathon and long distance runners from Sweden,[19] a US combined cohort of 70 triathletes, runners, tennis players, cyclists and cross-trainers,[26] a combined cohort of 95 triathletes, long-distance runners, cyclists, and handball players from Germany,[27] another small cohort of 70 German marathon runners,[28] a small cohort of 25 Canadian marathon runners,[20] a Dutch cohort of 318 middle aged men engaged in competitive or recreational leisure sports,[14] another cohort of 50 US male marathon runners,[29] and 26 US long-term female marathon runners.[30]

The mean age of participants was above 35 years in all studies (overall mean age 55 years, range 18-83), with only 50 women included in 3 of 14 studies,[19, 26, 30] compared to a total of 884 men. Most studies (10/14) were cross-sectional. Follow-up data, ranging from 21 months to 12 years, were available for 4 studies,[12, 23-25] 3 of which were based on the German Marathon cohort.[12, 23, 24]

Table 1 demonstrates the used imaging modalities: echocardiography only (n=2), unenhanced CT for CACS (n= of 1), CACS combined with Contrast-enhanced CCTA (n=3), CACS combined with CMR imaging (n=2), CCTA only (n=2), CCTA with CMR and echocardiography (n=1), CMR alone (n=2), and MPS (n=1).

Table 1. Study characteristics and outcomes

Author (year) [reference]	N	Age: range (years) and mean ±SD	Gender	Population	Sport years	Current sport	Imaging Modality	Measure	Follow-up Mean ±SD	Outcome	Author's findings and conclusion
Mohlenkamp (2008)[12] *	108	50-72 57±6	Male	Marathon runners	Median 20 (IQR 14-42) marathons	4686 + 2285 MET/week	CACS	CACS / LGE	21.3 ±2.8 months	Coronary events	Coronary events in 4 runners, all CACS ≥100. Higher than anticipated coronary risk warranted
Kroger (2011)[21] *	100						CACS	Prevalence of CAC	-	-	Increased awareness of atherosclerosis prevalence
Nassenstein (2009)[22] *	105						CACS + CMR	CACS	-	-	Higher risk than that anticipated from conventional risk factor assessment
Breuckmann (2009)[23] *	102						CMR	LGE	21.3 ±2.8 months	Coronary event / all cause mortality	Ostensibly healthy marathon runners have an unexpected high rate of LGE
Mohlenkamp (2014)[24]*	108						CACS + CMR	CACS / LGE	6.2±1 years	Coronary event / all cause mortality	All cause mortality in marathon runners similar to that in RF-matched controls
Braber (2016)[14]	318	45-71 54.7± 6.3	Male	Competitive or recreational sportsmen		3.0 (2.25–4.75) hrs / week	CAC + CCTA	CACS / Obstructive CAD	-	-	Nearly 20% of asymptomatic middle-aged sportsmen, with a normal bicycle exercise test and predominantly low conventional cardiovascular risk scores, had occult CAD
Aagaard (2013)[19]	153	45-69 51±5	Male	Cross-country runners	-	2.4±1.9 hrs/week	Echo	Echographic abnormalities	-	-	Limited additional yield of echo
Karlstedt (2012)[20]	25	>50 years 55±4	84% Male	Marathon runners	Mean 57±8 marathons	47±7 miles/week	Echo + CMR + CCTA	LGE / obstructive CAD	-	-	Presence of myocardial fibrosis is infrequent but when present may be due to underlying occult CAD
Hood (1999)[25]	19	42-83 67±6	Male	Runners	42-83 running years	34±21 miles/week	Echo	Abnormal echo / resting and exercise ECG	12 years	All-cause morbidity / mortality	High intensity lifelong endurance exercise may be associated with altered cardiac structure and function, which rarely may be harmful
Katzel (1998)[26]	70	50-70 63±6	Male	Athletes#	Mean >20 years (no SD)	-	Combined exercise ECG and MPI	Silent ischemia on MPI and ECG	7 years	-	Prevalence of silent ischemia and coronary events on follow-up was similar in athletes and untrained men.
Mangold (2013)[27]	95	18-62 35.2±11.4	77% Male	Athletes∞	≥ 2 years	13.1±4.2 hrs/week	CMR	LGE Abnormal findings on MRI	-	-	Abnormal findings in 6.3%. Prognostic significance remains unclear. Routine CMR cannot be recommended.
Tsiflikas (2015)[28]	70	45-67 53±6	Male	Marathon runners		Mean 13.8 ± 16.2 marathons	CAC + CCTA	CACS / Obstructive CAD	-	-	Coronary atherosclerosis can be detected in almost 50% of male marathon runners aged older than 45 years.
Schwartz (2014)[29]	50	52-66 59.4 ± 6.7	Male	Marathon runners	At least 25 Marathons	-	CCTA	Plaque volume	-	-	Long-term training and competing in marathons may be paradoxically associated with accelerated coronary artery plaque formation.
Roberts (2016)[30]	26	42-82 56±10	Female	Marathon runners	At least one marathon 10 consecutive years	Mean 45 ± 36 marathons	CCTA	Plaque volume	-	-	Long term marathon training and competition in women does not appear to adversely affect the CV risk profile.

Studies as listed in References
N = number of athletes studied
* Five studies concerning the same German Marathon cohort
Athletes∞ = a combined cohort of triathletes, long-distance runners, cyclists, and handball players Athletes# = a combined cohort of triathletes, runners, tennis players, cyclists and cross-trainers
CACS = coronary artery calcium score; CMR = cardiac magnetic resonance; CCTA = coronary computed tomography angiography; IQR = interquartile range; LGE = late gadolinium enhancement; LV = left ventricle; MET = metabolic equivalent; MPI = myocardial perfusion imaging; RV = right ventricle; WMA = wall motion abnormalities.

Echocardiography

No echocardiographic study focused on detection of CAD with exercise or pharmacological stress echocardiography. The only two echocardiographic imaging studies show the limited additional value of routine echocardiography to identify CAD.

Aagaard et al. described the yield of routine echocardiography in 153 middle-aged men (mean age 51 ± 5 years) before first participation in a cross-country race.[19] Preparticipation evaluation consisted of medical history, physical examination, ECG, ESC risk SCORE and routine echocardiography. No exercise test was performed. Although the 10-year fatal CV risk was low (SCORE 1%, interquartile range 0-1%), 14 (9%) runners required further workup, of which 12 were identified by ECG and only 2 were identified by echocardiography. Echocardiography revealed a tumour attached to the tricuspid leaflet, which was a lipoma on surgery, and mild aortic regurgitation at rest in another participant, who was cleared for participation after exercise stress echocardiography. Four runners (2%) were discouraged from vigorous exercise due to QTc-intervals >500 ms in two subjects, symptomatic atrioventricular block in one subject, and the participant with the cardiac tumour before surgery. The authors concluded that medical and physical examination with a 12-lead ECG was probably most effective in identifying those requiring additional work-up, although they also stated that detection of CAD was limited by the absence of a reliable screening tool. Routine blood testing and echocardiography had no substantial additional value.

Hood et al. examined the effect of lifelong endurance exercise on cardiac structure and function with routine echocardiography, as well as resting, exercise and 24 hours ECG in a 12-year follow-up study in 19 male veteran athletes (mean age at baseline 67 ± 6.2 years) including national champions and record holders.[25] The authors conclude that high intensity lifelong endurance exercise may be associated with altered cardiac structure and function, with 10 of 19 athletes showing evidence of left ventricular (LV) hypertrophy after 12 years of follow up. Two athletes had pacemakers implanted, one for symptomatic atrial fibrillation, and the other for pauses up to 15 seconds. Another athlete had a myocardial infarction during a competitive race, without obstructive CAD on coronary angiography. The authors stressed the difficulty in interpreting the ECG and exercise ECG in this cohort, as the only three athletes with positive exercise ECG tests all had normal thallium MPS scans.

Table 2. Characteristics of imaging modalities

Modality	Sensitivity	Specificity	Costs	Risks/benefits
Exercise ECG	45-50%	85-90%	Low	Simple, Generally safe
Echocardiography	-	-	Low	Lack of ionising radiation. Wide availability. Very limited ability to detect CAD
MPS	37-92%	63-87%	High	High radiation
CMR	79-88%	81-91%	High	Lack of radiation. Limited availablity.
CCTA	95-99%	64-83%	Reasonably low	Radiation (although declining). High image quality

Coronary artery calcium scoring

Möhlenkamp (2008 and 2014), Kroger, Nassenstein, and Breuckmann all reported on the same German Marathon study of men ≥ 50 years (mean 57 ± 6 years) without known heart disease, who had completed at least five full marathons within the last three years.[12, 21-24] Möhlenkamp et al. investigated CACS and the prevalence of LGE on CMR in this group, all with a low Framingham Risk Score (FRS), and compared them to age-matched controls and FRS matched controls from the Heinz Nixdorf Recall Study with a follow-up of 21 months. The authors concluded that although the prevalence of CAC in marathon runners was similar to age-matched controls, CACS were higher than in FRS matched controls. During the 21 months follow-up four runners experienced coronary events, with events occurring exclusively in those with a CACS higher than 100 Agatston Units (AU) although their mean FRS placed them in a low-risk category. Conventional CV risk stratification thus underestimates the CAC burden in this presumably healthy cohort, warranting increased awareness of a potentially higher than anticipated CV risk in athletes.[12] After six years of follow-up seven runners experienced a coronary event, four of which during physical exercise but not related to a marathon, and one died from an acute coronary event.[24] The event rate in runners with CACS <100, 100-399, and ≥ 400 AU was 1.5, 12.0 and 21.4%, similar to the 864 age-matched controls and 216 age- and risk-matched controls from the general population. With CV event rates similar to the general population, this event rate can still be seen as unexpectedly high if one considers most experienced marathon runners to be at low risk.[24]

Kroger et al. assessed the extra-coronary atherosclerosis plaque burden and its association with CV risk factors and coronary atherosclerosis in the German male Marathon group.[21] They concluded that the prevalence of carotid and peripheral atherosclerosis is high in marathon runners and is related to CV risk factors and the coronary atherosclerotic burden as measured with CAC.[21]

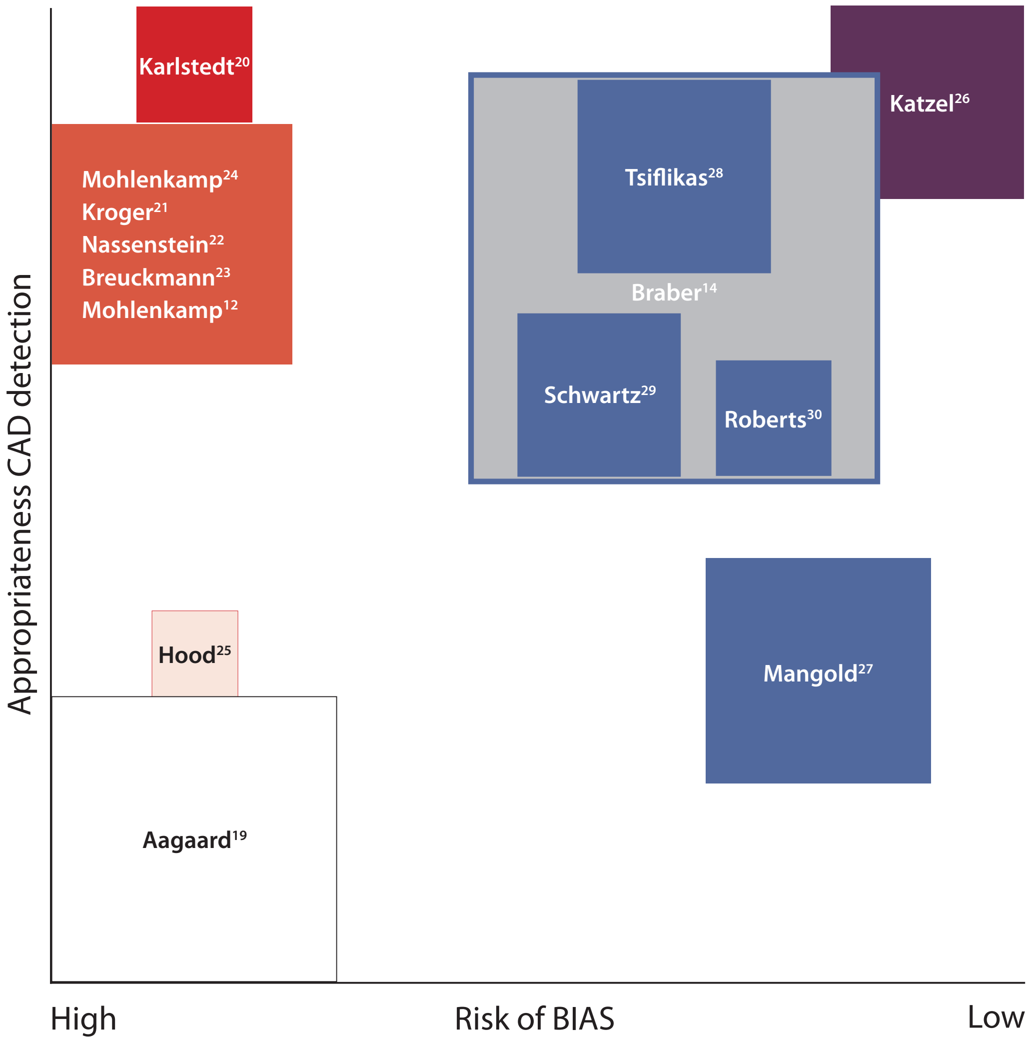

Fig 1. Gaps in existing literature

Coronary artery calcium scoring and coronary CT angiography

Tsiflikas et al. evaluated the prevalence of CAD in a relatively small group of 50 middle-aged male marathon runners (mean age 52.7 ± 5.9 years, mean PROspective CArdiovascular Munster Study (PROCAM) score 1.85 ±1.56) using CACS and CCTA.[28] Although almost 50% of the marathon runners had CAD (defined as any plaque or CACS >0), only one participant had a high-grade stenosis leading to revascularisation. The authors concluded that identifying individuals with (non-obstructive as well as obstructive) CAD might help to calculate the risk for future CV events more precisely. Although the study lacks power, the prognostic value will be evaluated during a five-year follow-up.

Braber et al. investigated the prevalence of occult CAD using CACS and CCTA in a group of 318 asymptomatic recreational sportsmen (mean age 54.7 ±6.3 years, 94% low SCORE risk) without known CV disease following a normal sports medical examination with normal resting and exercise ECG.[14] CAD as defined by Tsiflikas (any plaque or CACS >0) was seen in 63.2% of these sportsmen. Almost one in five asymptomatic sportsmen, with predominantly low conventional CV risk scores, had occult relevant CAD i.e. CACS >100 AU or >50% coronary stenosis on CCTA; and 87% of these abnormalities were detected with CACS alone.

Schwartz et al. compared coronary artery plaque volumes with CCTA in 50 male marathon runners who had run marathons for 25 consecutive years (mean age 59.4 ± 6.7 years) to a sedentary control group of 23 men with a clinical indication for CCTA (mean age 55.4 ± 10.4 years).[29] The marathon runners had significantly lower weight, BMI, lower resting heart rate, less hypertension and diabetes (none vs. 17% of the sedentary men), and significantly higher HDL cholesterol levels. Paradoxically, the marathon runners had increased total plaque volume (200 vs. 126 mm3, $p < 0.01$), calcified plaque volume (84 vs. 44 mm3, $p < 0.0001$), and non-calcified plaque volume (116 vs. 82 mm3, $p = 0.04$). The authors concluded that long-term training and competing in marathons may be associated with accelerated coronary artery plaque formation, and that larger multicentre studies are required to investigate this further. Roberts et al. compared coronary artery plaque volumes with CCTA in 26 female marathon runners who had run marathons for 10-33 consecutive years (mean age 56 ± 10 years) to a sedentary control group of 28 women (mean age 61 ± 10 years), with no known history of CV disease in either group.[30] The marathon runners had significantly lower weight, BMI, lower resting heart rate, less hypertension), less smoking history, and significantly higher HDL cholesterol levels. In contrast to the male marathon runners from the same research group, the female marathon runners had lower coronary artery plaque prevalence (19.2% vs. 50%, $p = 0.014$) and less calcified plaque volume (42.5 vs. 76.6 mm3, $p = 0.043$) than the sedentary controls.

Cardiac magnetic resonance imaging

No CMR studies administered adenosine or dobutamine for ischemia detection. Nassenstein et al. assessed left ventricular volumes (LV) and myocardial mass on CMR in the German marathon group in relation to conventional risk factors and coronary atherosclerotic burden (CACS).[22]

After initial increase of LV end-diastolic volume (LV-EDV) with age, LV-EDV decreases after 55 years of age. Although LV mass increased with increasing LV-EDV and blood pressure, runners with a LV mass ≥ 150 grams had significant higher CACS than those with LV mass < 150 grams, median CACS 110 versus 25, $p = 0.04$. They conclude that myocardial mass depends on adaptation to sport, age and blood pressure, but unbalanced increase in LV wall mass may also be a subclinical response to risk factor exposure.

Several studies reported on the role of LGE on CMR in 102 of the 108 German male marathon runners (mean age 57 ± 6 years). The extent of coronary atherosclerosis (CACS) and the number of completed marathons were both associated with myocardial fibrosis, as shown by LGE on CMR. Breuckmann et al. compared the prevalence of myocardial distribution of LGE in these male marathon runners with asymptomatic control subjects and examined the prognostic role of LGE.[23] They concluded that these seemingly healthy marathon runners have an unexpectedly high rate of myocardial LGE, 12% versus 4% in controls, $p = 0.077$, and event-free survival was lower in those with myocardial LGE compared to those without: $p < 0.0001$. Two LGE patterns emerged: a CAD pattern with subendocardial or transmural distribution and a non-CAD (non-ischemic) pattern with midmyocardial or epicardial distribution. Marathon runners with prevalent myocardial fibrosis on baseline also developed higher high-sensitive serum troponin I values during the race, but unlike CACS and LGE, higher troponin I values were not associated with future coronary events.[24]

It was unclear from the German Marathon Study whether the increased LGE occurred because of repeated marathon running or due to occult CAD. Karlstedt et al. performed a more extensive examination in a small group of 25 marathon runners (age 55 ± 4 years, 84% men) from the 2010 and 2011 Manitoba Full Marathons who had participated in at least 3 marathons in the past 2 years.[20] Extent and severity of cardiac dysfunction after a complete marathon was assessed using cardiac biomarkers and echocardiography, 1 week before, immediately after and 1 week after the marathon, CMR, before and within 24 hours after the marathon, and coronary CT angiography within 3 months of the marathon. All participants demonstrated a transiently elevated troponin T and RV dysfunction post marathon. Only two participants had a subendocardial ischemic pattern of LGE of the anterior wall of the left ventricle with evidence of a significant stenosis of the left anterior descending artery on coronary CT angiography. It is unknown if these two participants underwent subsequent ischemia testing or catheter angiography.

Mangold et al. performed CMR imaging in 95 endurance athletes aged 18-62 years (mean age 35.2 ±11.4 years, 87% male, 81% long-distance runners, cyclists or triathletes).[27] The 50-minute

CMR examination included cine images, coronary MR angiography and LGE. They reported abnormal findings in 6 (6%) athletes: two benign coronary anomalies, one dilated ascending aorta (42 mm), two patients with non-ischemic pattern of LGE, probably post myocarditis, and one patient with pericardial and pleural effusion, but no wall motion abnormalities or LGE, which was probably virus-related and resolved on follow-up. They concluded that routine implementation of CMR imaging in the context of preparticipation screening cannot be recommended since the prognostic significance of these findings remains unclear.

Myocardial perfusion scintigraphy

Katzel et al. compared prevalence of exercise-induced silent ischemia on ECG, ST-segment depression using Minnesota Code criteria, and perfusion abnormalities on thallium scintigraphy in 70 asymptomatic male athletes (aged 63 ±6 years) and in 85 healthy untrained men (aged 61 ± 7 years) with no history of CAD, hypertension or diabetes.[26] The prevalence of exercise–induced single positive test, abnormal exercise electrocardiogram or thallium scan, and silent ischemia, abnormal exercise electrocardiogram and thallium scan, was similar in athletes and untrained men: 19% vs. 18% and 16 vs. 21%, respectively, $p = 0.36$. None of these asymptomatic men with silent ischemia underwent subsequent coronary catheterization. There was also no difference in incidence of coronary events: 4 athletes with silent ischemia and 4 non-athletes with silent ischemia and 1 non-athlete with a single positive test during 7-year follow-up.

DISCUSSION

This scoping review identified 14 studies that used cardiac imaging to detect CAD in the rapidly growing group of older sportspersons. Our main findings are: (1) a low number of relevant articles were published with small sample sizes and very few women (7%); (2) the studies were predominantly cross-sectional and mostly conducted in highly selected groups (e.g. marathon runners); (3) a higher risk of coronary events in sportsmen with higher CACS and also a potentially higher coronary risk than anticipated on the basis of the (low) conventional risk scores; (4) a relatively high rate of myocardial LGE in marathon runners with a higher than anticipated risk of coronary / cardiac events in those with LGE. It should be noted that last two findings come from the same cohort.

The major goal of the preparticipation evaluation of athletes over 35 years of age should be detection of relevant CAD, the most important cause of exercise related cardiac events.[3, 5, 6] Family history of CV disease and medical history are of pivotal importance. CAD in athletes may not only present as typical angina but also as an unexplained decline in exercise performance, and one cannot base the assessment of elderly sportspersons solely on the current CV risk profile and exercise capacity. This scoping review focused on the different imaging techniques used to identify CAD in middle-aged sportspersons, and provides an overview of the gaps in literature and challenges for future research.

Gaps in research

Most studies investigate habitual master endurance athletes (figure 1), thereby ignoring the large group of middle-aged recreational sportspersons, in whom by sheer magnitude most cardiac events will occur. In addition, future studies should focus on important issues as age of presentation for screening (35-55, 55-75, >75 years), sex, the level of sports (leisure or elite sports), and the sports discipline. A lifetime sports-related risk score is necessary to assess which sportspersons require more work-up and the precise nature of this assessment. Ideally there would be a weighted score for exposure per decade for different risk factors. These risk factors include the traditional risk factors such as cholesterol, hypertension, diabetes, obesity and smoking; as well as family history and personal history for periods of regular physical exercise or sedentary lifestyle. The contrasting results between male[29] and female[30] long-term marathon runners probably have multifactorial causes, including gender and hormonal differences, differences in marathon running years (inclusion based on minimal of 10 years in women versus 25 years in men), and possibly differences in lifestyle. This requires further investigation.

Challenges

The main challenge is to provide fast, reproducible and easy to analyse information on CAD. Currently available non-invasive imaging techniques either evaluate cardiac function and anatomy (echocardiography, CMR), inducible myocardial ischemia (stress echocardiography, CMR, myocardial perfusion scintigraphy), visualize CAD indirectly (wall motion abnormalities on echo and CMR, LGE on CMR) or directly (CACS and CCTA). While these tests are relatively non-invasive compared to the reference standard (coronary catheterization), CT and MPS are also associated with radiation exposure and possible adverse effects, and costs pose a financial burden for screening asymptomatic sportspersons.

Although echocardiography is the most widely available and cheapest non-invasive imaging technique, it probably has the least additional value in the older sportspersons to detect relevant CAD. In addition, finding abnormalities in asymptomatic persons with a normal ECG in whom no murmurs are heard on physical examination is unlikely.[31] MPS, although accurate, carries the highest costs and radiation exposure, and is therefore not a realistic option for screening.

The most comprehensive imaging technique is CMR, with excellent, multi-parametric information on bi-ventricular function, volume and mass, accurate ischemia detection with adenosine stress, and myocardial fibrosis detection with LGE.[32] Myocardial fibrosis, especially with a CAD pattern, has predictive value for future events,[23] but remains an indirect sign of CAD. In addition, it remains unclear whether this predictive value in the highly selected group of marathon runners can be translated to the recreational sportspersons. Non-ischemic patterns of myocardial fibrosis, especially in the intraventricular septum and near the hinge points between the right ventricle and septum, are seen relatively often in older athletes with a lifelong history of endurance sports. This was not within the scope of this review.[33] CMR coronary angiography can detect coronary anomalies accurately, but is not yet robust enough to identify relevant CAD. The scan time, costs, limited availability of CMR for large-scale screening, and insufficient visualization of the coronaries make this a less practical screening method, especially in the field of recreational sports.

Non-contrast cardiac CT for CACS provides a direct measure of CAD. It is the strongest independent predictor of CV events in asymptomatic persons and has been recommended as a first line test over exercise testing in those with a low risk of CAD.[34, 35] Absence of coronary artery calcium (CAC) is associated with a very low risk of CV events in asymptomatic and symptomatic individuals.[36] Moreover, in a study employing both calcium scanning and stress testing in the same asymptomatic participants, the presence of calcified coronary atherosclerotic plaque conveyed increased risk for subsequent cardiac events in asymptomatics, even with a normal stress perfusion study.[37]

The radiation dose is minimal (around 1 mSv, less than half the background radiation absorbed per year) and the scan time and costs are reasonably low compared to MRI and MPS, and even echocardiography. The low number needed to screen (NNS) (20) in the general population to identify an individual with moderate CAD, a CACS ≥100 AU, seems enough justification for extending CACS to lower risk individuals in future guidelines, as CAC is also associated with risk of CV events among individuals with few or no risk factors.[34] Recent radiation dose reductions (<1-3 mSv) combined with an excellent diagnostic accuracy for CAD, regardless of risk profile, make CCTA an other viable option for screening sportspersons.[38] CCTA has additional value to CACS by visualizing the coronary lumen allowing for stenosis grading and evaluation of the total coronary atherosclerotic burden, including non-calcified plaque. This may be relevant in light of the concept that non-obstructive CAD, i.e. demand ischemia, may play an important role in exercise related cardiac events.[2]

To date, only one cross-sectional study demonstrated additional value of CACS and CCTA to exercise testing in asymptomatic sportsmen.[14] Agatston scores larger than 100 or >50% coronary stenosis were used as outcome, but whether CACS and CCTA in asymptomatic sportsmen improves management to prevent hard CV outcomes remains to be elucidated. A randomized study could investigate the hypothesis that the introduction of cardiac CT in the sports medical evaluation reduces the incidence of exercise related cardiac events in older athletes. However, being able to perform a formal randomized trial of CACS or CCTA in older sportspeople is unlikely given the costs restraints from expected low event rates. Therefore, a registry may be a more realistic goal.

Medical and family history, physical examination and (exercise) ECG in combination with conventional CV risk scores still form the cornerstone of the sports medical evaluation of older sportspersons although this approach fails to reliably identify CAD. Colleagues from Italy provided the only large-scale evaluation of exercise stress testing in preparticipation screening for competitive sports. Their study reported the results of over 30,000 referrals for screening with exercise ECG. The unselected population included a combination of well-trained athletes and non-athletes seeking to commence sport. Abnormalities were detected in 4.9% leading to disqualification from competitive sport in 0.6% of the total population. The efficacy of these exclusions in preventing SCD remains unknown.[39]

Cardiac imaging can contribute to the identification of CAD, but at this stage no firm recommendations can be made regarding the routine use of imaging studies in a sports medical evaluation setting. It is a matter of debate which steps should follow when cardiac imaging reveals asymptomatic CAD during a sports medical evaluation. Many practitioners feel that any degree of CAD on cardiac CT should be managed aggressively. The threshold for statin treatment to prevent CV events is becoming lower in recent guidelines. For example, by applying the recent ACC/AHA guideline to a European population aged 55 years or older, nearly all men (96.4%) would be eligible for statin treatment, compared to 66.1% when following the ESC guidelines.[40] One must also realize that sportspersons might suffer more from side-effects of statin treatment, such as myalgia occurring in 5-7%.[10, 41]

Perspectives

This review demonstrated the challenges and gaps in the existing literature regarding imaging to detect CAD in middle-aged sportsmen. Most of the papers investigating the role of imaging to detect CAD in older athletes have been published in highly selected groups, like long-term male marathon runners. Relatively little is known about the other sport types and training levels, including the growing group of middle-aged recreational sportsmen and few papers evaluated CAD in older female athletes, while there are clear gender differences.

This relatively low number of relevant articles indicates the need for future research on this topic, addressing the large group of recreational athletes (both men and women) rather than elite athletes. Currently there is insufficient evidence for incorporating routine cardiac imaging in the preparticipation screening of asymptomatic sportspersons over 35 years and more data is needed for different imaging modalities in this field. Therefore, prospective studies and larger observational studies with long term follow up are needed in this group to characterize the preventive value of cardiac imaging. Cardiac CT (CACS and/or CCTA) may hold the best potential for use in preparticipation screening of older athletes, especially because the diagnostic value has increased considerably and the radiation dose is declining rapidly. In the future, efforts should be made to develop a randomized design or at least a registry to investigate whether the introduction of imaging, like Cardiac CT in a sports medical evaluation setting reduces the incidence of (exercise related) cardiac events in this group and is cost-effective, compared to exercise testing.

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CHAPTER 3

Rationale and design of the Measuring Athlete's Risk of Cardiovascular events (MARC) Study. The role of coronary CT in the cardiovascular evaluation of middle-aged sportsmen

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ABSTRACT

Background More than 90% of exercise related cardiac arrests occur in men, predominantly those aged 45 years and older with coronary artery disease (CAD) as the main cause. The current sports medical evaluation (SME) of middle-aged recreational athletes consists of a medical history, physical examination, resting and exercise electrocardiography. Coronary CT (CCT) provides a minimally invasive low radiation dose opportunity to image the coronary arteries. We present the study protocol of the Measuring Athlete's Risk of Cardiovascular events (MARC) study. MARC aims to assess the additional value of CCT to a routine SME in asymptomatic sportsmen ≥45 years without known CAD.

Design MARC is a prospective study of 300 asymptomatic sportsmen ≥45 years who will undergo CCT if the SME did not reveal cardiac abnormalities. The prevalence and determinants of CAD (coronary artery calcium score ≥100 Agatston Units (AU) or ≥50% luminal stenosis) will be reported. The number needed to screen to prevent the occurrence of one cardiovascular event in the next 5 years conditional on adequate treatment will be estimated.

Discussion We aim to determine the prevalence and severity of CAD and the additional value of CCT in asymptomatic middle-aged (≥45 years) sportsmen whose routine SME revealed no cardiac abnormalities.

BACKGROUND

Screening athletes to prevent cardiovascular events

Sudden cardiac death is often the first manifestation of coronary artery disease (CAD), and is responsible for ≈ 50% of the mortality of cardiovascular disease in developed countries.[1] Regular physical exercise is recommended to reduce cardiovascular morbidity and mortality and is gaining increased popularity, especially in middle-aged and older persons.[2] Yet, exercise transiently increases the risk of cardiovascular events, particularly in those with unknown cardiac disease. More than 90% of acute exercise related cardiac events occur in men, predominantly those aged 45 years and over.[3] While sudden cardiac death in younger athletes (35 years or younger) is mainly caused by cardiomyopathies, electrical heart disease and coronary anomalies, in older athletes it is predominantly caused by CAD (80%).[4]

A recent paper on cardiac arrest during long distance running implicated a causal role for demand ischemia in athletes with (unknown) CAD.[2] Absence of coronary plaque rupture in these persons was surprising because prior data[5] and expert consensus documents[4] have suggested that exercise induced acute coronary events result from atherosclerotic plaque disruption and coronary thrombosis. It follows that early identification of CAD should be an important goal in the preparticipation evaluation of middle-aged persons.

Despite the rare occurrence of cardiac events in young athletes (<2 per 100.000 athletes per year) the study group of Sport Cardiology of the European Society of Cardiology (ESC) recommends mandatory preparticipation screening (based on medical history, physical examination and a resting electrocardiogram (ECG)) of athletes aged 35 years or younger.[6] Directing screening efforts at the rapidly growing group of older athletes that have a 10 fold higher risk of exercise related cardiac arrests[3] – mainly attributable to CAD – should be considered as well.[7]

The 2011 ESC position paper on cardiovascular evaluation of middle-aged/senior individuals engaged in leisure time sports activities advocates the use of maximal exercise testing. This is now frequently performed in the course of a sports medical examination (SME), in addition to medical history, physical examination, and the resting ECG.[8]

Cardiovascular event risk: exercise testing and cardiac imaging to detect coronary artery disease

Traditionally, risk scores such as the ESC Systematic COronary Risk Evaluation (SCORE) are used to estimate cardiovascular event risk in asymptomatic persons, aiming to divide them in low, intermediate and high risk categories. The SCORE risk categories, correspond to 0-4%, 5-9% and 10% or higher 10-year cardiovascular mortality risk.[9] Cardiovascular risk scores have not specifically been developed for persons who are physically active. As exercise favorably influences cardiovascular risk factors, e.g. by reducing weight and blood pressure and improving the lipid profile, traditional cardiovascular risk scores may underestimate CV risk in persons who exercise regularly.[10] It has also been suggested that regular, intense physical exercise (e.g. multiple marathon running) in itself may be harmful to the heart by causing myocardial fibrosis[11] and by contributing to coronary artery plaque formation with cardiovascular events occurring at an alarmingly high rate (21% percent 10 year event rate) in a group of 108 recreational German marathon runners aged 50 years or older.[10] Cardiovascular events exclusively occurred in those with a coronary calcium score (CACS) higher than 100 Agatston Units (AU).

Adding maximal exercise testing to the cardiovascular evaluation of middle-aged/senior athletes, as advocated by the ESC, may be useful to identify some persons at high risk, by detecting a physiologically significant coronary artery stenosis.[12] Several studies have indicated that asymptomatic men with an abnormal exercise test received the greatest benefits of interventions to reduce risk factors.[13] Notwithstanding the low predictive value (high false negative rate) for CAD of both resting and exercise electrocardiography in asymptomatic individuals, exercise testing is still frequently performed in the course of a sports medical check-up.[14] This is partly attributable to the fact that the results of exercise testing will also provide information on cardio respiratory fitness relevant to recommendations for subsequent training programs.

Coronary CT (CCT) can be of added value by providing a minimally invasive opportunity to image the coronary arteries for coronary artery calcium (CAC), atherosclerotic burden and coronary stenosis.[15]

Non-contrast CCT for the assessment of CAC provides a non-invasive direct measure of burden of coronary atherosclerosis and is an independent predictor of cardiovascular events.[16] The CACS is the most powerful cardiac risk prognosticator in the asymptomatic population, with consistent superiority to all risk factor-based scores.[17] Absence of CAC is associated with a very low risk of future cardiovascular events in asymptomatic as well as symptomatic individuals.[18]

The amount of CAC, however, relates poorly to the degree of luminal narrowing of the coronary arteries and a low CACS does not exclude CAD.[19, 20] The 'Agatston Score' remains the most commonly used measure to quantify CAC because most previous large-scale trials and cross-sectional studies used this method, so that large reference data sets exist (e.g. http://www.mesa-nhlbi.org/Calcium).[21] Coronary artery calcification is age, gender, and race dependent. Agatston Scores are often classified into five groups according to severity as listed in Table 1.[22] A score <100 Agatston Units (AU) is ranked as low risk, scores between 100 and 400 AU as intermediate (moderate) and above 400 AU as severe risk of future atherosclerotic cardiovascular events.[22] CACS is increasingly used as a tool to expand risk-stratification in asymptomatic persons with an intermediate risk of cardiovascular events.[23] The low number needed to screen (NNS) in the general population to identify an individual with moderate or severe CAC (8 and 20 respectively), seems to provide a justification for extending CAC testing to lower risk individuals[16] as CAC is also associated with risk of cardiovascular events among individuals with few or no risk factors. The 5-year number needed to treat (NNT) to prevent a cardiovascular event in persons with a CACS ≥ 100 AU is low (19)[24] compared to the 5-years NNT to prevent a cardiovascular event in patients with mild to moderate (140 - 160 mmHg) hypertension (122 to 135).[25]

Table 1. Classification of coronary artery calcium score

Absolute value (Agatston units)	**Ranking**
0	Absent
>0<10	Minimal
≥10 <100	Mild
≥100 <400	Moderate
≥400<1000	Severe
≥1000	Extensive

Classification of coronary calcium absolute content evaluated by cardiac CT and quantified by Agatston units

Coronary CT Angiography

Low dose coronary CT angiography (CCTA) can visualize, qualify (calcified, non-calcified, mixed plaques), and quantify (total atherosclerotic burden, degree of luminal stenosis) CAD and is increasingly used to rule out CAD in persons presenting with chest pain. The diagnostic accuracy of CCTA is high, regardless of risk profile.[26] In the near future CT fractional flow reserve is likely to provide information on the functional significance of coronary artery stenosis.[27] The vulnerable plaque paradigm states that plaque composition is a better predictor of acute coronary events than stenosis grade.[28] As athletes normally have a lower heart rate and BMI, they are suitable candidates for low radiation dose (2-3 milliSievert – mSv) CCTA to determine the presence and extent of CAD. This dose corresponds to the yearly background radiation each person receives in Europe.[29] Furthermore, a recent position paper that analyzed acute and long-term composite risks related to cardiovascular imaging, showed that life time risk of imaging procedures for fatal events is small compared with the general risk of fatal cardiac events by CAD in both asymptomatic and symptomatic populations.[30]

Aim

The aim of the Measuring Athlete's Risk of Cardiovascular events (MARC)-study is to determine the prevalence and severity of CAD and the additional value of CCT in asymptomatic middle-aged (≥ 45 years) sportsmen whose routine SME revealed no cardiac abnormalities.

METHODS/DESIGN

MARC is a prospective, cross-sectional study. Asymptomatic sportsmen aged 45 years and older, without known cardiovascular disease, engaged in competitive or recreational leisure sports or contemplating initiating regular exercise and with a normal SME (including resting and exercise electrocardiography) will be invited to undergo additional CCT. Baseline characteristics, including demography, cardiovascular risk factors, sports history, medical history and medication use, will be obtained. The results of the CCT, combined with the conventional cardiovascular risk profile, will be used to provide the participants with a tailored cardiovascular advice, based on the prevailing cardiovascular disease prevention and sports medicine guidelines.[9, 31]

Based on the number of participants (n= 108) in the only cardiac CT study of asymptomatic athletes to date and the yearly number of persons (n= 300 – 350) performing a SME at an average Dutch sports medical department that would qualify for participation in MARC we aim to include 300 asymptomatic participants to obtain estimates of the prevalence of coronary artery disease with reasonable confidence intervals and to determine the added value of CCT (CACS and CCTA) in the prevention of cardiovascular events. Given the ten to thirty fold higher incidence of exercise related cardiac arrests in men than in women we choose to enrol men only.[32]

Coronary CT imaging

Coronary CT is performed using a 256-slice CT scanner (Philips Healthcare, Best, The Netherlands). A non-contrast coronary CT is acquired first to calculate the CACS (scan parameters 120 kV, 60mAs). Participants with a heart rate >65 beats/min will receive 5 to 20 mg metoprolol (Selokeen AstraZeneca, Zoetermeer, Netherlands) intravenously before CCTA. All participants receive 2 puffs of sublingual nitroglycerine spray just before the CCTA. CCTA scan parameters will be as follows: 120 kV; 210 mAs; 90-120 ml (depending on weight) non-ionic contrast material (Iopromide, 300 mg I/ml; Ultravist, Bayer Healthcare, Berlin, Germany) will be injected at a speed of 6-6.7 ml/s followed by 30-40 ml saline injected at the same speed. The CCTA is acquired with prospective ECG triggering at a mid-diastolic phase (78%).

To determine the amount and distribution of soft and mixed coronary artery plaques CCTA will be done regardless of the CACS. In clinical practice CCTAis often withheld in patients with a CACS > 400 AU because blooming artefacts might hinder the evaluation of coronary artery stenosis.[33]

The total CCT radiation dose to which participants will be exposed is anticipated to be 3 mSv on average.[34] Participants receive extensive written and oral information prior to examination. If renal function is unknown, creatinine is measured before the scan. Participants with renal dysfunction (estimated glomerular filtration rate <60 ml/min/1.73m^2) will be excluded from the study. Blood pressure and heart rate are available from the SME and will also be measured before the CT scan.

Image analysis

CT scans are sent to a workstation (IntelliSpace Portal, Philips Healthcare) for processing by experienced technicians. All CT scans are analyzed by one of two experienced observers.

Assessment of coronary artery calcium score

CACS is measured on the non-contrast CT with the Agatston scoring method.[35] Coronary artery calcium is measurable above a density of >130 Hounsfield units (HU) in a coronary artery. Total CACS is calculated by the sum of all lesions in all four coronary arteries and their side branches. The total Agatston score will be compared with the MESA database.[21]

Assessment of Coronary CT angiography

Specialized technicians use semi-automated vessel analysis to make multiple curved multiplanar reconstructions (MPR) of all coronary arteries on the CCTA data. The radiologist views these MPR reconstructions as well as the thin-slice CCTA source images with interactive maximum intensity projection (MIP) and MPR viewing possibilities in all planes. Image quality, plaque characteristics and coronary lumen stenosis will be analyzed on a 16-segment basis according to the modified American Heart Association classification.[36]

Plaque composition will be evaluated in a qualitative matter as calcified (more than 50% of the plaque area calcified); mixed (plaques with <50% calcium) and non-calcified (plaques without calcium).[37]

Total atherosclerotic plaque burden will be measured with both the segmental involvement score (SIS) and the segment stenosis score (SSS) based on the 16-segment coronary artery model.[38] Luminal stenosis will be graded as absent, minimal (1-24%), mild (25–49%), moderate (50–69%), and severe (≥70%)[39] narrowing on the basis of diameter measurements comparing the diameters of the maximal stenosis to a reference diameter proximal and distal to the stenotic area. If severe calcifications are present and quantification of stenosis is difficult, the radiologist will refrain from stenosis quantification and score the segments involved as 'calcified, stenosis unclear'.

Outcome and consensus meetings

The primary outcome is the presence of relevant CAD that will be defined as one or more of the following on CT: a CACS ≥100 AU or luminal stenosis ≥50%. Participants with a CACS ≥100 AU will be reclassified to high risk.[24] Consensus meetings with a panel of at least two (sports) cardiologists and one radiologist will be held regularly to advise on the management of participants found to have relevant CAD. As a general rule participants with a CACS between

100 and 400 AU without obstructive CAD, will be recommended to initiate treatment with statins, in addition to lifestyle advice.[40] Participants with a CACS ≥400 AU or coronary stenosis ≥50% will be given the opportunity to consult a cardiologist for further cardiovascular workup.

Statistical analysis

Analysis of the (baseline) results from this study will be descriptive (presence and extent of CAD). Descriptive statistics will be presented as means and standard deviations for continuous variables, and frequencies and percentages for categorical data. Two tailed independent t-test will be used for comparison between groups (e.g. those with and without coronary artery disease) and analysis of variance will be used to compare means of more than two groups. The chi-square test will be used to examine the association between categorical variables. Linear regression and multivariate regression analysis will be used to study the relation between characteristics of the participants and CCT determined CAD.

The number needed to screen (NNS) to prevent one cardiovascular event (defined as coronary heart disease events -myocardial infarction, death from coronary heart disease, definite angina, probable angina resulting in revascularization or resuscitated cardiac arrest-, stroke, or other atherosclerotic death or other cardiovascular death) within 5 years will be computed based on the reciprocal of the prevalence of CAD (CACS ≥ 100 AU and / or luminal narrowing ≥50%) (multiplied by 100) multiplied by the number needed to treat (NNT) to prevent one cardiovascular event.[24]

Statistical analyses will be performed with SPSS version 22.0 (SPSS Inc., Chicago, Illinois, USA). A *p*-value of less than 0.05 will be regarded as statistically significant.

Ethical considerations

This study has been approved by the regional Medical Ethics Committee (VCMO, Nieuwegein, The Netherlands) and subsequently approved by the local ethics board committee of the University Medical Center Utrecht, The Netherlands. The study is conducted according to the principles of the Declaration of Helsinki and in accordance with the Dutch Medical Research Involving Human Subjects Act. Participants are only included in the MARC-study after written informed consent is obtained.

DISCUSSION

The MARC study will assess the additional value of low-dose coronary CCT to determine the prevalence and severity of CAD in 300 asymptomatic middle-aged (≥ 45 years) sportsmen, in whom a SME found no cardiac abnormalities. Participants of the MARC study should reflect the fast growing group of men aged 45 years or older who decide to undergo a SME that includes exercise testing. As such we anticipate to include both competitive and recreational athletes. The majority of them is likely to be engaged in high dynamic high static sports (e.g. race cycling) and high dynamic low static sports (e.g. long distance runners). The NNS with CCT to prevent the occurrence of one cardiovascular event in the next 5 years will be estimated.

Sudden cardiac death is the most devastating sport related event. Although regular exercise reduces the risk of cardiovascular disease, the risk of an acute cardiac event is transiently increased during and immediately after vigorous exercise.[4] Sports related cardiac events occur mainly in those with unknown cardiac disease, which prompts many sportsmen to undergo a SME with exercise testing. The MARC study offers the most comprehensive cardiovascular evaluation of middle-aged sportsmen to date, by adding CCT (both CACS and CCTA) to the routine SME.

CT scanning is generally considered safe, but, apart from radiation exposure (discussed in the background section: CCTA), the following considerations should be taken into account when evaluating asymptomatic persons with CCT. Potential risks of CCTA include adverse reaction to the contrast media (nausea, skin hives in 1 to 3% of participants, fatal adverse reactions in 1 in 100,000 participants) and contrast media-induced renal insufficiency (contrast nephropathy). The occurrence of contrast nephropathy is directly related to renal function; by selecting participants with a GFR higher than 60 mL/min contrast nephropathy is unlikely to occur.[41]

The result of the CCT may lead to additional diagnostic tests with extra costs and risks not covered by this study. However, the Eisner study demonstrated that CAC scanning compared with no scanning in asymptomatic volunteers can improve cardiac management without incurring a significant increase in downstream medical costs.[42] Incidental findings will be reported to the participant and his general practitioner. Pulmonary nodules are likely to be common incidental findings in our study and will be managed according to the Fleischner criteria.[43]

The results of the MARC study will give insight in the added value of CCT in the cardiovascular evaluation of asymptomatic sportsmen aged 45 years and older who have undergone a routine SME. We anticipate that our study will provide guidance in the debate on the optimal preparticipation evaluation of the rapidly growing group of older sportsmen in whom CAD is the main cause of cardiovascular events.

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CHAPTER 4

Identifying coronary artery disease in asymptomatic middle-aged sportsmen: the additional value of pulse wave velocity

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ABSTRACT

Background Cardiovascular screening may benefit middle-aged sportsmen, as coronary artery disease (CAD) is the main cause of exercise-related sudden cardiac death. Arterial stiffness, as measured by pulse wave velocity (PWV), may help identify sportsmen with subclinical CAD. We examined the additional value of PWV measurements to traditional CAD risk factors for identifying CAD.

Methods From the Measuring Athlete's Risk of Cardiovascular events (MARC) cohort of asymptomatic, middle-aged sportsmen who underwent low-dose Cardiac CT (CCT) after routine sports medical examination (SME), 193 consecutive sportsmen (aged 55±6.6 years) were included with additional PWV measurements before CCT.

Sensitivity, specificity and predictive values of PWV values (>8.3 and >7.5m/s) assessed by Arteriograph were used to identify CAD (coronary artery calcium scoring ≥100 Agatston Units or coronary CT angiography luminal stenosis ≥50%) and to assess the additional diagnostic value of PWV to established cardiovascular risk factors.

Results Forty-seven sportsmen (24%) had CAD on CCT. They were older (58.9 vs. 53.8 years, p<0.001), had more hypertension (17 vs. 4%, p=0.003), higher cholesterol levels (5.7 vs. 5.4mmol/l) p=0.048), and more often were (ever) smokers (55 vs. 34%, p=0.008). Mean PWV was higher in those with CAD (8.9 vs. 8.0 m/s, p=0.017). For PWV >8.3m/s respectively >7.5m/s sensitivity to detect CAD on CT was 43% and 74%, specificity 69% and 45%, positive predictive value 31% and 30%, and negative predictive value 79% and 84%. Adding PWV to traditional risk factor models did not change the area under the curve (from 0.78 (95% CI = 0.709-0.848)) to AUC 0.78 (95% CI 0.710-0.848, p = 0.99)) for prediction of CAD on CCT.

Conclusions Limited additional value was found for PWV on top of established risk factors to identify CAD. PWV might still have a role to identify CAD in middle-aged sportsmen if risk factors such as cholesterol are unknown.

INTRODUCTION

Regular physical activity is key in the prevention of cardiovascular disease, but vigorous exercise is also associated with a higher cardiovascular event risk, particularly in those with known or unknown cardiac disease.[1] Over 90% of exercise related cardiac arrests occur in men, predominantly in those aged 45 years and older, and the majority is attributable to coronary artery disease (CAD).[2, 3] In a group of 108 recreational German marathon runners aged 50 or more years the coronary artery calcium burden was higher in marathon runners than in Framingham Risk Score (FRS) matched controls [4]. During the six years of follow up, cardiovascular events occurred in 8 participants, 7 of whom had a CACS higher than 100 Agatston units although their mean FRS placed them in a low-risk category.[5] It seems that the conventional cardiovascular risk stratification underestimates the coronary artery calcium burden in this presumably healthy cohort and that an increased awareness of a potentially higher than anticipated coronary risk is warranted.[5] These facts indicate that early identification of subclinical CAD should be an important goal in the preparticipation sports evaluation of middle-aged persons. Preparticipation screening aims to improve the safety of exercise in the fast-growing group of middle-aged sportsmen by identifying those at increased risk of cardiovascular events. Frequently used risk scores (e.g. FRS or European Society of Cardiology SCORE) tend to underestimate cardiovascular risk in these middle-aged sportsmen, as evidenced by the results of the abovementioned Marathon study.[6] The 2011 European Society of Cardiology position paper on cardiovascular evaluation of middle-aged/senior individuals engaged in leisure time sports activities advocates the use of maximal exercise testing.[7] However, although electrocardiogram (ECG) interpretation in sportsmen can be improved using a standardized ECG criteria tool,[8] the low positive predictive value and high false positive rate for CAD of both resting and exercise electrocardiography in asymptomatic individuals remains a cause for concern.[9, 10] Although exercise ECG is not a standard part of routine preparticipation sports screening, it is still frequently performed in the sports medical evaluation (SME) of those aged 45 years and older.

Cardiac CT (CCT), including both non-contrast CT for CACS and contrast-enhanced coronary CT angiography (CCTA), provides direct, non-invasive visualization of the coronary arteries. Higher CACS independently predicts cardiovascular mortality,[11, 12] and CCTA characterizes (calcified vs. non-calcified plaque) and quantifies the extent of the total atherosclerotic burden and severity of any coronary stenosis. However, routine CCT is not routinely performed in the SME setting because of costs, radiation exposure and the need for specific equipment and expertise. Pulse wave velocity (PWV) has recently emerged as a potential new biomarker for prediction of cardiovascular mortality independent of established risk factors such as blood pressure and cholesterol,[13-15] and normal and reference values per age category based on a large European cohort have now been established.[16]

In contrast to CCT, measuring arterial stiffness is easy to perform in an outpatient setting. In addition, increased arterial stiffness measured by means of PWV has been shown to be an independent predictor of cardiovascular mortality in various populations.[17-21] Numerous studies have assessed the additional value of carotid-femoral PWV for prediction of cardiovascular events in the general population.[14, 22-24] Several carotid-femoral PWV methods (SphygmoCor™ and Complior™) are widely used to determine PWV, although both methods are observer-dependent and time-consuming.[25] The Arteriograph is a relatively new and operator-independent device, which uses oscillometric pressure curves registered by an upper arm blood pressure cuff connected to a piezo-electric sensor to determine blood pressure and PWV as validated previously.[26-28] It shows comparable results to tonometry (Complior™) in healthy controls and patients with cardiovascular disease, although systematically lower values (on average 0.8 m/s lower) are found for the Arteriograph in healthy controls.[29]

We set out to determine the value of PWV evaluated with the relatively new Arteriograph, in addition to routinely assessed cardiovascular risk factors (SCORE), to detect CAD on CCT in asymptomatic middle-aged sportsmen.

METHODS

Study population

Participants were consecutively recruited from the Measuring Athlete's Risk of Cardiovascular events (MARC) study that evaluates the additional value of CCT (both CACS and CCTA) to routine SME, including resting and exercise ECG, in asymptomatic sportsmen aged 45 years and older. Details on the MARC study design have been reported previously.[7] This study was conducted according to the principles of the Declaration of Helsinki and has been approved by the regional Medical Ethics Committee (VCMO, Nieuwegein, The Netherlands), and the local ethics committee of the University Medical Center Utrecht, The Netherlands. All participants gave written informed consent. Asymptomatic sportsmen aged 45 years and older, without known cardiovascular disease (known coronary artery disease, MI, percutaneous coronary intervention, coronary artery bypass graft surgery, stroke, transient ischemic attack or peripheral artery disease) were included if they had undergone a SME with exercise ECG that revealed no abnormalities, according to the responsible physician. Exclusion criteria were known CAD, allergy to contrast material, and renal impairment. Both competitive and recreational sportsmen were included, with the majority of them engaged in high-dynamic high-static sports (cycling) and high-dynamic low-static sports (long distance runners). Information regarding basic demographic data, cardiovascular risk factors (smoking status, cholesterol level, hypertension, diabetes, family history), medication use, as well as height, weight, body mass index (BMI) and blood pressure were obtained at the sports medical department. Two blood pressure measurements were obtained with a standard sphygmanometer. Total cholesterol and creatinine were measured on the day of the CT-scan if there were no recent values known within the last 6 months. Inclusion criteria for this specific study were arterial PWV measurement on the day of the CT-scan. The participants were asked to refrain from physical exercise and from consuming caffeine on the day of the CT-scan and PWV measurements.

Definitions

CAD was defined as a CACS ≥100 AU on non-contrast CT or a ≥50% luminal stenosis on CCTA. Smoking status was classified into two levels: ever (former and current) smoker and never smoker. Hypertension was defined as a resting blood pressure above 140/90 mm Hg or the use of blood pressure lowering medication.

Pulse wave velocity

PWV, brachial blood pressure and heart rate were measured in a supine position using a blood pressure cuff on the left arm after several minutes of rest just prior to CCT. PWV as a measure of arterial stiffness was assessed using the Arteriograph system (Tensiomed, Budapest, Hungary). One measurement was performed in each participant by one observer. The measurement was repeated in 23 (12%) cases of unsuccessful readings. Persistent unsuccessful readings did not occur. Intra-observer validation in 41 participants showed a good intra-observer agreement (Pearson's correlation 0.9, R^2 0.8). One observer performed all measurements, and inter-observer validation was beyond the scope of this study. Normal values in an age-matched population were used to identify abnormal arterial stiffness measurements as a measure for subclinical atherosclerosis.[15] We assessed both a PWV cut-off using the normal value of 8.3 m/s for the population 50-59 years old (established with carotid-femoral PWV measurements),[15] as well as a PWV cut-off value of 7.5 m/s that was corrected by 0.8 m/s for the numerical lower Arteriograph PWV measurements.[29] PWV was measured as continuous data and assessed as the percentage of participants with a higher than normal PWV, based on the established cut-off value in a population with optimal blood pressure and no identified cardiovascular risk factors,[16] and abovementioned cut-off value corrected for the systematically lower Arteriograph measurement.

Cardiac CT

Image acquisition was performed with a 256-slice CT system (Brilliance iCT, Philips Healthcare). First a non-contrast prospectively ECG-triggered CCT was acquired to calculate the CACS. Scan parameters were 120 kV, 60 mAs. Images were reconstructed at a slice thickness and increment of 3 mm. CACS was quantified as Agatston scores by identifying all regions of at least 1mm^2 with ≥130 Hounsfield units (HU) within the coronary arteries using semi-automatic software (HeartBeat-CS, Philips Healthcare).[30] CCTA scan parameters were as follows: 120 kV; 210 mAs; 95-115 ml (depending on weight < or ≥ 80 kg) non-ionic contrast material (Ultravist 300 mg I/ml, iopromide) injected at a speed of 6-6.7 ml/s followed by 30-40 ml saline injected at the same flow rate. The CCTA was acquired with prospective ECG triggering at a mid-diastolic phase (78%). Participants with a heart rate of more than 65 beats/min received 5 to 20 mg metoprolol (*Selokeen*) intravenously before CCTA. All participants received sublingual nitroglycerine (nitrolingual) immediately before CCTA. Laboratory technicians performed the coronary artery calcium score using semi-automatic software. All CT scans were assessed by one of two experienced cardiac radiologists (NP, BKV), blinded for findings at the baseline assessment. The CCTA scans were assessed for obstructive stenosis (≥50%) comparing the diameters of the maximal stenosis to a reference diameter proximal and distal to the stenotic area. The PWV measurements were collected by a different reader (TLB) who was blinded for the CAC results. All relevant findings on CCT were discussed at consensus meetings with a panel of at least two (sports) cardiologists and one radiologist.

Statistical analysis

Data are shown as mean ± SD for continuous variables where applicable, otherwise medians and 25th and 75th percentiles (interquartile range [IQR]) are given. All categorical data are reported as a percentage or absolute number. Student's t test was used for differences between groups and proportions between groups were compared by means of chi-square test. Sensitivity, specificity and positive- and negative predictive values of PWV for detecting relevant CAD for both >8.3 m/s and >7.5m/s were calculated. The additional diagnostic value of PWV measurements, compared to the SCORE parameters gender, age, systolic blood pressure, total cholesterol, and ever smokers, was quantified using multivariate logistic modelling and area under the receiver operating characteristic (ROC) curve (C-statistic) analysis. Statistical significance was defined as a two-sided p-value < 0.05. The SPSS 20.0 (SPSS Inc., Chicago, IL, USA) statistical software package was used for all calculations.

RESULTS

Arterial PWV measurements were performed in 193 consecutive participants of the MARC cohort (MARC participants 121 – 313). The characteristics of these 193 middle-aged sportsmen are summarized in Table 1. Forty-seven (24%) participants were found to have CAD on CCT. Forty-three participants had a CACS ≥100 AU. The CCTA identified a total of 12 participants with luminal narrowing ≥50%, eight of whom also had a CACS ≥100 AU. Those with CAD were older (58.9 vs. 53.8 years, p<0.001), more often had hypertension (17% vs. 4%, p=0.003), had higher total cholesterol levels (5.7 vs. 5.4 mmol/l, p<0.05) and more often were (ever) smokers (55 vs. 34% p=0.008). Mean arterial PWV was 8.25 ± 1.9 m/s with significantly higher PWV in the participants with CAD compared to those without CAD (8.9 vs. 8.0 m/s, p=0.02).

For the PWV cut-off value >8.3m/s the sensitivity to detect CAD was 43%, specificity 69%, positive predictive value 31% and negative predictive value was 79%. For the PWV cut-off value >7.5m/s the sensitivity to detect CAD was 74%, specificity 45%, positive predictive value 30% and negative predictive value was 84%. In univariate analysis, age, (ever) smoking and PWV were significantly associated with CAD with respective odds ratios (OR) of 1.15 per year (95% CI 1.08-1.21, p<0.001), 1.62 (95% CI 1.2-2.3, p=0.006) and 2.3 per m/s (1.1-4.9, p=0.01). The predictive capacity of PWV in relation to relevant CAD was characterized by a C-statistic of 0.60 (95% CI 0.50-0.69, p=0.050). The area under the curve (AUC) was 0.78 (95% CI = 0.709 to 0.848) for the SCORE parameters gender, age, systolic blood pressure, total cholesterol, and ever smokers. Adding PWV measurements to the SCORE model did not appreciably change the AUC (model 2, AUC 0.78 95% CI 0.710-0.848, p = 0.99) indicating limited additional diagnostic value of PWV assessed with a relatively new technique to SCORE parameters.

Table 1. Baseline characteristics.

Characteristic	All N = 193	CAD N = 47	No CAD N = 146	P-value
Age (years)	55.0 ± 6.6	58.9 ± 6.3	53.8 ± 6.3	<0.0001
Diabetes, n (%)	3(2)	1(2)	2(1)	0.71
Hypertension, n (%)	14 (7)	8 (17)	6(4)	0.003
BMI (kg/m2)	24.7±2.4	25.3±2.7	24.5±2.2	0.06
Ever smoked, n (%)	75(39)	26(55)	49(34)	0.008
Height (cm)	182±7.1	181±7.4	183±6.9	0.07
Weight (kg)	82±9.7	82±10.2	82±9.6	0.90
SBP (mmHg)	129±12.8	132±11.9	128±13.0	0.06
DBP (mmHg)	79±12.8	81±7.3	79±9.2	0.10
Total cholesterol (mmol/l)	5.4±0.9	5.7±0.8	5.4±0.9	0.048
PWV (m/s)	8.3±1.9	8.9±2.0	8.0±1.8	0.017
PWV >8,3 m/s, n (%)	65(34)	20(43)	45(31)	0.1
PWV >7,5 m/s, n (%)	116(60)	35(74)	81(55)	0.02
SCORE, median (IQR)	1 (1-2)	1 (1-2)	1(1-2)	0.26
Exercise tolerance (Watt)	307±47	303±46	315±51	0.2

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PWV, pulse wave velocity. Data are presented as mean ± SD, proportions (%) or median values (interquartile range i.e. 25th and 75th percentile). P-value calculated with or Pearson $\chi 2$ or Fisher's Exact Test (two sided) where appropriate, between cad and no cad groups.

DISCUSSION

In this study performed in asymptomatic sportsmen aged 45 years or older, we found that the sensitivity of Arteriograph derived PWV measurements for detecting subclinical CAD was only fair when using a cut-off of 8.3 m/s, and fairly good for 7,5 m/s with a sensitivity of 74%.
When information on established risk factors (SCORE) was available, the additional value of PWV appeared to be limited. However, as cholesterol is not always known, one might still consider implementing arterial PWV measurements with the Arteriograph in the routine SME of

middle-aged sportsmen. The diagnostic sensitivity of PWV in identifying those with a high risk of CAD is promising as 3 in 4 asymptomatic participants with subclinical CAD can be identified. This may help justify referral of asymptomatic sportsmen for CCT based on available risk factors and PWV measurements.

Early identification of CAD should be an important goal in the preparticipation sports evaluation of middle-aged persons. While sudden cardiac death in younger athletes (35 years or younger) is mainly caused by cardiomyopathies, electrical heart disease and coronary anomalies, in older individuals it is predominantly caused by CAD (80%).[3, 31] A recent paper on cardiac arrest during long distance running implicated a causal role for demand ischemia in athletes with (unknown) CAD.[32] Absence of coronary plaque rupture in these persons was surprising because prior data[33] and expert consensus documents[31] have suggested that exercise-induced acute coronary events result from atherosclerotic plaque disruption and coronary thrombosis. This means that screening for relevant CAD is perhaps more important than only performing exercise testing for a hemodynamically significant coronary stenosis. However coronary calcium can only be regarded as a proxy measure for coronary artery disease. Although it is unlikely to find someone with extensive coronary atherosclerosis who has no CAC,[34] persons with a CACS <100 AU can still suffer from a myocardial infarction.[35, 36] Although CAD has been considered the primary cause of exercise related SCD in individuals >35 years, there is evidence that diseases traditionally associated with SCD in young athletes also play a significant role in this population.[32, 37, 38] Therefore, only screening for CAD may not detect all middle-aged and older individuals at risk of SCD.

Our study is the first to evaluate the potential role of PWV to identify subclinical CAD in asymptomatic middle-aged sportsmen that have undergone a routine SME. There is substantial interest in refining cardiovascular risk prediction to better address preventative therapy among those individuals considered to be at low or moderate risk according to current guidelines.[39] Therefore, additional cardiovascular biomarkers have been identified, including the mean common carotid intima-media thickness, which has been shown to have clear additional value in prediction of CV events on top of the FRS and ESC SCORE.[40] Although PWV may have potential as a biomarker,[13-15] it remains unclear whether PWV measurements have additional clinical value in the daily practice of screening middle-aged sportsmen. Since the established risk scores tend to underestimate cardiovascular risk in middle-aged sportsmen, as demonstrated by Mohlenkamp et al.,[6] we investigated whether aortic stiffness, as measured by PWV, improved identification of sportsmen with subclinical atherosclerosis that warrants further testing. However, this study has been critiqued for a higher proportion of smokers in the self-selected study group. Our results support the association between established risk factors (including smoking), arterial stiffness and CAD on CCT in middle-aged sportsmen. Our results are comparable to a recent meta-analysis including more than 17.000 participants.[21] The authors stated that aortic PWV has value beyond conventional risk factors to predict mortality and future cardiovascular events for younger individuals at intermediate risk (improved risk prediction of 13%). Although it was still predictive for older individuals (hazard ratio 1.23 for a subgroup above 70 years of age), the addition of PWV to the adjusted cardiovascular prediction models only increased the C-statistics to a modest degree, suggesting that PWV did not add much to standard risk assessment. A possible explanation is that systolic blood pressure is a better surrogate of aortic stiffness in older people than in younger people and the authors concluded that including PWV in models already containing systolic pressure might limit the predictive value.[21] Furthermore another recent publication that was not included in the meta-analysis showed comparable results for risk prediction of CAD with PWV in a large cohort of elderly subjects.[41] The authors concluded that aortic stiffness measurement in addition to FRS resulted in only limited reclassification rates and stated that although aortic stiffness is associated with risk of CAD in elderly free of known CAD it provides no additional value in cardiovascular risk stratification. Our study must be interpreted within the context of its limitations.

First of all, we performed measurements in a relatively small group of 193 participants. Although the number of consecutive participants was considerable for a study of its kind, it remains a relatively small study of selected men (all were Caucasian with at least college education). The fact that they consented to participate after undergoing a SME may have led to additional selection bias (e.g. those with a higher chance of cardiovascular disease because of a positive family history). In order to avoid possible selection bias we compared the baseline criteria of the MARC population to a large group (n=725) of male recreational sportsmen aged ≥45 years who recently underwent a SME in the southern region of the Netherlands (Maxima Medical Centre, Veldhoven). The groups were similar in age (mean age 55.0 vs. 54.3 years) systolic blood pressure (129 vs. 129 mmHg), body mass index (24.7 vs. 25.0 kg/m^2), smoking status (current 3.1 vs. 5.1 %), and fitness level (workload 314 vs. 309 Watt), indicating that our group is representative for sportsmen that undergo a SME. Remarkably the consecutive participants who underwent additional PWV had a slightly higher incidence of CAD compared to the whole cohort (24 vs. 18%, p=0.09). However, this difference was not significant (P=0.09) and the consecutive participants who underwent additional PWV were similar in age (54.7 vs. 54.9 m/s, P= 0.4) SCORE (both 1 with IQR 1-2), systolic blood pressure (SBP 127 vs. 129 mmHg P=0.9), body mass index (BMI 24.9 vs. 24.7 kg/m^2 P=0.7) smoking status (ever smoking 37% vs 39% P=0.8) and fitness level (workload 314 vs. 307 Watt P=0.3).

Second, the Arteriograph is a relatively new device for the assessment of PWV. Although it has been validated in some studies, [26, 29, 42] to our knowledge no prospective outcome studies have been carried out with this device. Ideally, we should have performed a confirmatory study to compare our Arteriograph PWV measurements to the standard carotid-femoral PWV method, however this was beyond the scope of this study. Therefore, before the Arteriograph can be implemented, we should acquire more clinical evidence that the Arteriograph can provide additional prognostic value to the traditional CAD risk measurements, particularly in older sportsmen who have a higher risk of CAD related events.

Third, we used established cut-off values for a population with optimal or normal blood pressure and no identified CV risk factors. It is possible that the normal range however may be different in our specific (trained) population. A recent study demonstrated that high intensity aerobic interval training has the ability to reduce arterial stiffness in a cohort of treated hypertensive women after 16 weeks of follow-up.[43] However this effect has neither been demonstrated for moderate-intensity continuous exercise training nor has this been demonstrated in an asymptomatic male cohort free of known cardiovascular disease. Of note, the majority of our participants are engaged in moderate intensity continuous exercise training (cycling, long distance running).

In summary our study demonstrates that although limited additional value was found for PWV evaluated with the Arteriograph on top of established risk factors to identify CAD, PWV measurements may still have a role in the routine SME of middle-aged sportsmen to help identify those at a higher risk for relevant CAD. Larger studies of asymptomatic sportsmen in the SME setting are required to verify that functional arterial measurements can have added clinical value for cardiovascular risk stratification.

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CHAPTER 5

Assessment of coronary artery calcium on low dose coronary computed tomography angiography with iterative reconstruction

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ABSTRACT

Objective This study aims to evaluate whether coronary calcium scoring (CCS) is feasible using low-radiation-dose coronary computed tomography angiography (CCTA) in combination with iterative-reconstruction.

Methods Forty-three individuals without known coronary artery disease underwent both CCS (±1 mSv) for reference Agatston-scores and low-dose-CCTA (±3 millisievert). Raw CCTA-data were reconstructed with filtered-back-projection (FBP), hybrid-iterative-reconstruction (HIR) and model-based-iterative-reconstruction (MIR). Calcification-volumes were derived with thresholds of >351 and >600 Hounsfield units (HU) and converted to proxy Agatston-scores with linear regression analysis.

Results Intraclass correlation coefficients for Agatston scores versus CCTA volumes with FBP and iterative reconstruction were excellent (ranges 0.94-0.99 and 0.96-0.99 for >351HU and >600HU thresholds, respectively). The >351HU-threshold resulted in higher CCTA-volume-scores ranging from 65.9 (15.1-347.0) for HIR to 94.8 (42.0-423.0) for MIR (p = 0.001 and <0.001 respectively). The >600HU-threshold scores ranged from 14.1 (0.0-159.3) for HIR to 28.6 (0.0-215.6) for MIR (p = 0.003 and 0.027 respectively). At >350HU reclassification occurred in 21 individuals (49%) for FBP and HIR and 25 individuals (58%) for MIR. Reclassifications decreased with >600HU to 10 (HIR, 23%), 8 (FBP, 19%) and 4 (MIR, 9%).

Conclusion The CCS is feasible using iteratively reconstructed low-dose CCTA with a calcium threshold of >600HU. Using MIR, only 9% of individuals were reclassified.

INTRODUCTION

Coronary artery calcium (CAC) assessed on non-contrast enhanced cardiac computed tomography (CT) provides a noninvasive measure of coronary atherosclerosis and is a strong independent predictor of future cardiovascular events.[1] Moreover, CAC is the most powerful cardiac risk prognosticator in asymptomatic individuals with consistent superiority over currently used risk factor-based models.[2] Non-contrast CT for coronary calcium scoring (CCS) is increasingly used as a tool to improve risk-stratification in asymptomatic persons with low-to-intermediate and intermediate risk of cardiovascular events.[3] Elevated CAC scores are related with increased risk of cardiac events and prevalence of obstructive coronary artery disease in asymptomatic as well as symptomatic individuals.[4] The Agatston score is the most commonly used measure to quantify CAC and is often calculated as a separate nonenhanced scan prior to coronary CT angiography (CCTA).[5] Reported radiation dose for CCS ranges from 0.8 to 2.5 mSv for modern generation CT systems.[6] Recently, the use of CCTA has been advocated as a potentially valuable atherosclerosis imaging tool for risk stratification.[7] Coronary CT angiography, by virtue of contrast enhancement, has the ability to evaluate stenosis severity as well as overall coronary plaque burden.[8] In case of mild-to-moderate stenosis on CCTA, the amount of CAC provides an extensively validated quantification of future cardiovascular risk. Furthermore, current guidelines support the use of CAC screening as a guide to statin treatment decisions.[9] Moreover, based on large patient databases, the addition of CAC to CCTA adds a risk assessment component to CCTA-derived stenosis detection.[10] The development of technical refinements such as prospective or 'step and shoot' acquisition protocols with increased detector range, and iterative reconstruction have resulted in significant radiation dose reductions of (CCTA) exams without loss of imaging quality.[11] Prior studies have shown that CAC can also be quantified on CCTA exams at routine radiation dose levels (4.2 mSv to 19.1 mSv).[12-14] This means that the dedicated non-contrast acquisition for CCS that is frequently performed prior to CCTA can potentially be omitted, thus reducing the total radiation burden. However, it is currently unknown whether CAC can also be reliably quantified on low-radiation-dose CCTA examinations using standard filter back projection (FBP) techniques. Recent advances in CCTA allow for the performance of CCTA with very low radiation doses. Low dose is especially important when CT is used as a screening tool to rule out coronary heart disease. Therefore, the purpose of this study was to evaluate if adequate CCS also can be performed on low-radiation-dose CCTA using standard FBP and to assess whether the CCS performance on low dose CCTA improves with iterative reconstruction techniques.

MATERIALS AND METHODS

In this retrospective study, forty-three individuals free of known CAD underwent CCS followed by a low-radiation-dose CCTA examination, who were referred to our institution for a CCTA for exclusion of coronary artery disease between November 2012 and November 2013. Exclusion criteria included the presence of coronary stents, pacemakers, prosthetic heart valves, allergy to contrast material, and renal dysfunction. Our local ethical research board approved this study, and informed consent was waived because patient data were retrospectively analyzed.

Image acquisition

Image acquisition was performed with a 256-slice CT system (Brilliance iCT, Philips Healthcare, Best, The Netherlands) in accordance to guidelines defined by the Society of Cardiovascular Computed Tomography.[15] First a non-contrast prospectively ECG-triggered CCS CT was acquired to calculate the CAC score. Scan parameters were 120 kV (tube voltage) and a tube current of 60 mAs as standard. Images were reconstructed at a slice thickness and increment of 3 mm. Participants with a heart rate of more than 65 beats per minute received 5 to 20 mg metoprolol (Selokeen, AstraZeneca, Zoetermeer, the Netherlands) intravenously before CCTA. All participants received sublingual nitroglycerine immediately before CCTA.

Coronary CT angiography parameters were 120 kV; 210 mA, and 95 to 123 mL nonionic contrast material (iopromide, 300 mg I/mL; Ultravist, Bayer Healthcare, Berlin, Germany) injected at a speed of 6.0 to 6.7 mL/s followed by 30 to 40 mL saline injected at the same speed. The CCTA was acquired with prospective ECG-triggering in mid diastole (78% of the R-R interval). Volumetric CT dose indices ($CTDI_{vol}$) were recorded during the study and dose-length products were calculated by multiplying $CTDI_{vol}$ by scan length. Effective radiation dose estimation was calculated by multiplying the dose-length products with the conversion factor 0.0145 mSv/(mGy*cm) for chest imaging in adults [16]. Raw CCTA data were reconstructed with standard FBP, a hybrid iterative reconstruction (HIR, iDose^4 level 5, Philips Healthcare, Best, the Netherlands) and a model-based iterative reconstruction (MIR; IMR level 3; Philips Healthcare, Best, the Netherlands) technique.

Assessment of Agatston Scores

Coronary Artery Calcium was quantified as Agatston scores[17] on the CCS images with a semi-automatic software package (HeartBeat-CS, Philips Healthcare, Best, the Netherlands) For Agatston scoring, CAC was defined as regions with ≥130 Hounsfield units (HU) within coronary arteries. All regions with densities of 130 HU or more were automatically indicated by the software package. Subsequently, the observer only selected those regions located in the coronary arteries.

Assessment of CCTA Volume Scores

Calcification volumes were derived with a semi-automatic software package (QAngio CT v2; Medis Medical Imaging Systems, Leiden, the Netherlands). This semi-automated quantification software for coronary atherosclerosis has been proven to be highly reproducible between observers in previous research.[18] The software package automatically segmented the lumen and wall of the coronary arteries. Segmentations were visually examined and manually adjusted when necessary. Coronary artery calcium volumes were assessed by measuring the volume of regions with HU values above a certain threshold. As recommended by the software vendor and as previously described [13 19 20] we used calcification thresholds of >351 HU and >600 HU to separate the high-density calcium from the contrast material, respectively.

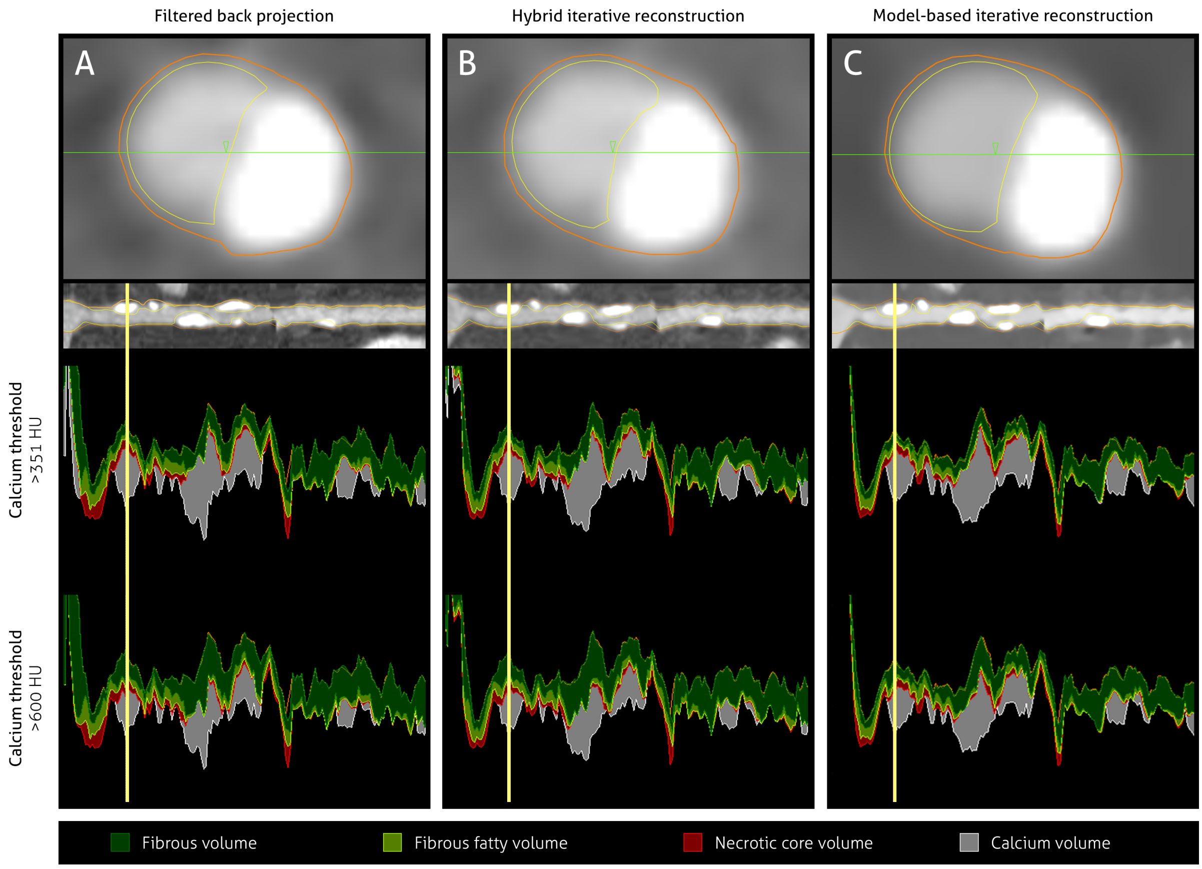

Fig. 1 Low-dose coronary computed tomography angiography images (upper two rows) and corresponding volume graphs at two calcium thresholds (>351 and >600 Hounsfield units) with larger calcium-volumes at a threshold of >351 Hounsfield units. Images were reconstructed with filtered back projection (A), hybrid iterative reconstruction (B) and model-based iterative reconstruction (C)

Volumes of regions with HU values above these thresholds were quantified as CAC volumes. Coronary CT angiography volume scores were assessed for FBP, HIR and MIR. Interobserver and intraobserver reliability has been assessed previously for FBP techniques. To assess intraobserver reliability for the iterative reconstructions, CCTA images reconstructed with HIR and MIR from 14 individuals (33%) were evaluated twice with a minimum time of four weeks between the 2 evaluations.

Statistical analysis

Linear regression with the best line of fit and y intercept set through zero was used to calculate coefficients for converting low-dose CCTA calcium volumes above pre-defined HU threshold values as a proxy for Agatston scores (CCTA volume scores) for FBP, HIR and MIR at thresholds of >351 HU and >600 HU (Fig. 1). Conversion factors were derived from the slope of the best line of fit (Fig. 2). Subsequently, CCTA results were converted to proxy Agatston scores (CCTA volume scores) by multiplying CCTA results with the conversion factors. Agatston scores and CCTA volume scores were tested for normality using the Kolmogorov–Smirnov test. Reliability for Agatston scores versus CCTA volume scores (FBP, HIR and MIR) was assessed using intra class correlation coefficients (ICCs). Intraclass correlation coefficients were also used to evaluate intraobserver reliability for HIR and MIR low-dose CCTA volume scores. Bland-Altman plots were used to assess the agreement between Agatston scores and CCTA volume scores.[21]

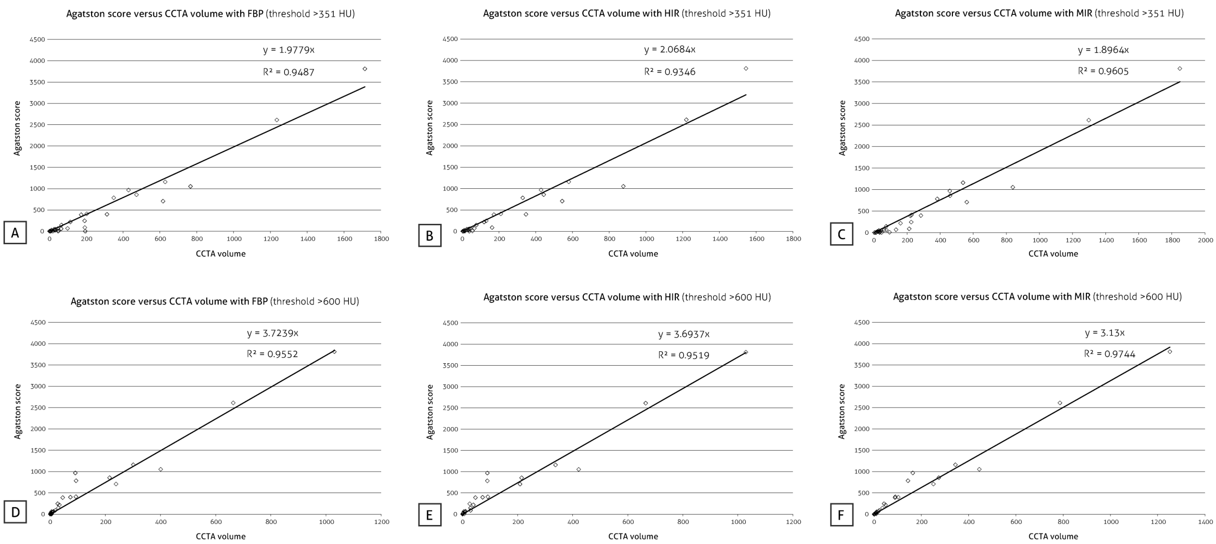

Fig. 2 Linear regression analysis for Agatston scores and CCTA volume scores for thresholds of >351 Hounsfield units (A-C) and >600 Hounsfield units (D-F) at filtered back projection (A,D), hybrid iterative reconstruction (B,E) and model-based iterative reconstruction (C,F)

Overall differences between Agatston scores and CCTA volume scores were evaluated with the Friedman test. If significance was found, a post-hoc analysis was performed with Bonferroni corrected Wilcoxon signed ranks tests.

Individuals were classified into different strata according to their Agatston scores: very low risk (0), low risk (1 - 10), moderate risk (11 - 100), moderately high risk (101 - 400), high risk (401 - 1000) and very high risk (> 1000). Subsequently, using these standard Agatston scores as the reference risk group classification, individual reclassification in risk groups was evaluated for the different CCTA volume scores (FBP, HIR and MIR). Significance level was set at $p < 0.05$. For Bonferroni corrected post-hoc analysis the significance level was set at $p < 0.008$. Normally distributed values are presented as mean (SD) and nonnormally distributed values are presented as means (first interquartile to third interquartile). Statistical analyses were performed with MedCalc version 12.7.5.0 (Mariakerke, Belgium) and SPSS version 20.0 (SPSS Inc, Chicago, Ill).

RESULTS

Forty-three individuals (age, 57.5 [8.5] years, 91% men) who underwent both nonenhanced CCS and low-dose CCTA to rule out coronary artery disease were analyzed. Patient demographics and scan characteristics are listed in Table 1. All scans were of good diagnostic quality. The median total radiation doses were 1.0 (0.9-1.1) mSv and 3.1 (3.1-3.7) mSv for nonenhanced CCS and CCTA, respectively. The median $CTDI_{vol}$ were 5.0 (4.9-5.1) mGy and 17.3 (16.8-18.0) mGy for non-enhanced CCS and CCTA, respectively. The dose length products were 72.1 (61.5-77.2) mGy*cm and 215.6 (215.5-252.6) mGy*cm for nonenhanced CSCT and CCTA, respectively. Linear regression conversion factors were 1.98, 2.07, and 1.90 for FBP, HIR and MIR at a threshold of >351 HU, respectively. At a threshold of >600 HU, conversion factors were 3.72, 3.69 and 3.13 for FBP, HIR and MIR, respectively. Figure 2 demonstrates the correlation and conversion factor for one of the comparisons. Agatston scores were 0 (N=11), 1-10 (N=8), 11-100 (N=10), 101-400 (N=5), 401-1000 (N=5) and >1000 (N=4). The median (interquartiles) reference Agatston score was 27.2 (0.3-317.3). The threshold of >351 HU for converted CCTA volumes resulted in higher CCTA volume scores ranging from 65.9 (15.1-347.0) for HIR to 94.8 (42.0-423.0) for MIR. The threshold of >600 HU resulted in median CCTA volume scores ranging from 14.1 (0.0-159.3) for HIR to 28.6 (0.0-215.6) for MIR.

Table 1. Baseline characteristics

N	**Value**
Age (years)	57.5 ± 8.5
Height (cm)	180.4 ± 6.4
Weight (kg)	81.7 ± 12.9
BMI	25.0 ± 3.9
Male (%)	39 (91)
Diabetes (%)	2 (5)
Current smoking (%)	3 (7)
Statin therapy (%)	11 (27)
Antihypertensive therapy (%)	9 (21)
Calcium scoring computed tomography	
Volumetric computed tomography dose index (mGy)	5.0 (4.9-5.1)
Dose length product, (mGy*cm)	72.1 (61.5-77.2)
Effective dose (mSv)	1.0 (0.9-1.1)
Contrast-enhanced computed tomography angiography	
Volumetric computed tomography dose index, (mGy)	17.3 (16.8-18.0)
Dose length product, (mGy*cm)	215.6 (215.5-252.6)
Effective dose (mSv)	3.1 (3.1-3.7)
Total protocol effective dose (mSv)	4.3 (4.0-4.7)

BMI, body mass index; mGy, milligray; mGy*cm, milligray-centimeter; mSv, millisievert. Data are presented as mean ± SD, proportions (%) or median values (interquartile range). The number in brackets indicate Q1-Q3, i.e. 25th and 75th percentile

Intraclass correlation coefficients for Agatston scores versus CCTA-derived volume scores with a calcification threshold of >351 HU were 0.97 (range, 0.95-0.99), 0.97 (range, 0.94-0.98) and 0.98 (range, 0.96-0.99), for FBP, HIR and MIR respectively and with >600 HU threshold 0.98 (range 0.96-0.98), 0.97 (range 0.96-0.98) and 0.99 (range 0.98-0.99) for FBP, HIR and MIR respectively. The Bland-Altman analyses comparing Agatston scores with CCTA volumes showed good agreement, especially for lower Agatston scores (Fig 3).

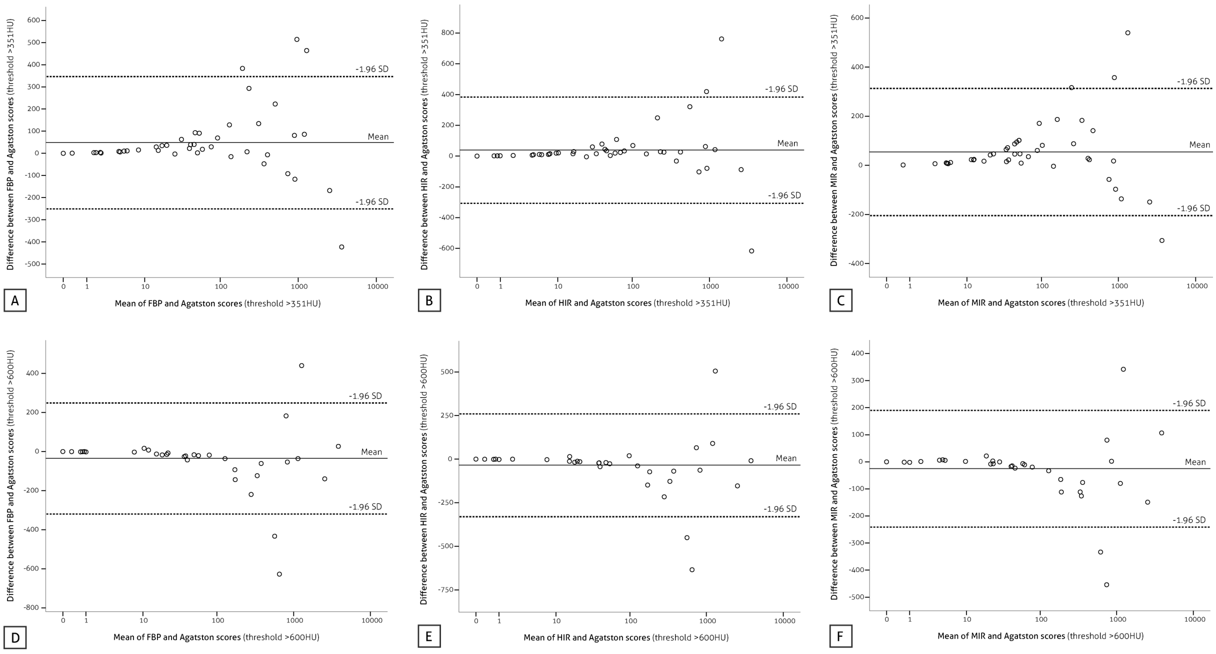

Fig. 3 Bland Altman analysis demonstrating good correlation between Agatston scores and CCTA volume scores for thresholds of >351 Hounsfield units (A-C) and >600 Hounsfield units (D-F) at filtered back projection (A,D), hybrid iterative reconstruction (B,E) and model-based iterative reconstruction (C,F)

Intraclass correlation coefficients for intraobserver reliability for HIR and MIR low-dose CCTA volume scores were 0.95 (range, 0.87-0.98) and 0.95 (range, 0.84-0.98) respectively with the >351 HU threshold and 0.99 (range, 0.99-0.99) and 0.97 (range, 0.90-0.99) with the >600 HU threshold. The overall Friedman test showed that CCTA volume scores differed significantly from reference Agatston scores (p < 0.05). Post-hoc analyses showed that all CCTA volume scores differed significantly from the reference Agatston scores (p < 0.008) except for the MIR CCTA volume scores at a threshold of >600 HU (p = 0.027).

Table 2. Coronary artery calcium scores and reclassifications

	Non-enhanced CT	CCTA					
Threshold	Reference	>351 HU			>600 HU		
Reconstruction	FBP	FBP	HIR	MIR	FBP	HIR	MIR
Agatston score[1]	27.2 (0.3-317.3)	67.9 (18.8-383.4)[2]	65.9 (15.1-347.0)[2]	94.8 (42.0-423.0)[2]	18.7 (0.0-147.7)[2]	14.1 (0.0-159.3)[2]	28.6 (0.0-215.6)[3]
Total reclassifications (% of total n)		21 (49%)	21 (49%)	25 (58%)	8 (19%)	10 (23%)	4 (9%)
Up reclassifications (% of reclassifications)		21 (100%)	21 (100%)	25 (100%)	2 (25%)	2 (20%)	2 (50%)
Down reclassifications (% of reclassifications)		0 (0%)	0 (0%)	0 (0%)	6 (75%)	8 (80%)	2 (50%)

[1] presented as medians with first and third interquartiles

[2] post-hoc analysis showed a significant difference with the reference score ($p<0.008$)

[3] post-hoc analysis showed no significant difference with the reference score ($p>0.008$)

CCTA = Coronary Computed Tomography Angiography; FBP = Filtered back projection; HIR = Hybrid iterative reconstruction; HU = Hounsfield units; MIR = Model-based iterative reconstruction

Reclassification

Reclassification analysis showed that 21 individuals (49%) for FBP and HIR to 25 individuals (58%) for MIR were wrongly reclassified using a threshold of >350 HU, and all were overestimations of the risk category. With a >600 HU threshold the number of reclassifications decreased to 10 (23%) with HIR, 8 (19%) with FBP, and 4 (9%) with MIR, with both overestimation and underestimation. Details regarding the number and type of reclassifications are listed in Table 2.

DISCUSSION

Prior studies have shown that CAC can be quantified on CCTA exams at routine radiation dose levels; however this has not yet been demonstrated for low-dose CCTA exams. We found that CAC quantification on low-radiation-dose CCTA is also feasible and shows the best results when model-based iterative reconstruction (MIR) is used to reduce noise. At a cut-off calcium threshold of >600 HU with MIR, only 9% of individuals were reclassified, as compared to 19% with FBP and 23% with HIR. Our findings imply that CCS can be obtained from CCTA using iteratively reconstructed low radiation dose CCTA without the need for an additional CCS scan. Previous studies have found that CAC can be quantified on CCTA by increasing threshold values from standard (130 HU) to 320,[12] 350,[20] or 600,[13] HU. However, the increase in attenuation thresholds resulted in underestimation,[13 20] or overestimation[19] of (proxy) CAC scores. We also found an overestimation of CCTA volume scores when a fixed threshold of >351 HU was used. Alternatively, two recent studies from Mylonas et al.[14] and Pavitt et al.[22] used a patient-specific threshold based on the average attenuation of a region of interest placed in the ascending aorta and found similar results for correlation. However, the drawback of a patient-specific threshold is that it has to be calculated individually for every patient undergoing CCTA. We used fixed thresholds because these are more easily applied in clinical routine.

A study by Rubinshtein and colleagues[23] showed similar results by using a novel fully automatic tool and demonstrated that CAC can be quantified on CCTA with good correlations for CAC values. However, they used a CCTA protocol with a radiation dose of 9.6 mSv, which is substantially higher than the median radiation dose of 3.1 mSv in the current study. Radiation doses in the other studies were also higher with CCTA doses ranging from 4.2 mSv to 19.1 mSv. [12-14]. The current study extends this prior work by demonstrating that CAC can also be quantified on CCTA at a low radiation dose, and MIR gives better results than FBP for low dose scans. Therefore, the non-contrast-enhanced CCS examination can be omitted, which would reduce the total radiation exposure with approximately 1 mSv, approximately 25% of the current combined CCS and CCTA dose.

It is already known that iterative reconstruction improves image quality for CCTA.[24-26] Furthermore, 2 studies evaluated the effect of low-dose CCTA reconstructed with HIR on quantitative coronary plaque composition.[27 28] Both studies did not find any differences between FBP and HIR; however MIR was not evaluated and quantification results were not correlated to Agatston scores. Furthermore, to our knowledge none of the previously published studies used iterative reconstruction algorithms to evaluate whether this novel technique improves CAC quantification on CCTA. We found that CAC quantification substantially improved if CCTA images were reconstructed with an MIR algorithm. The noise reducing effect of MIR algorithms is substantially stronger than for HIR algorithms.[29] Very low fluctuations in MIR image noise probably explains the improved CAC quantification.

Some limitations need to be mentioned. First, manually adjusting segmentations of the automated plaque quantification algorithm is time-consuming and could depend on operator-skills. However, we demonstrated an excellent intra-observer agreement and previous studies showed that inter-observer agreement with this semi-automated volume measurement software was excellent.[18] Second, our study was relatively small and our results were obtained using a single vendor CT scanner. Therefore our findings need to be validated in larger prospective studies. Another potential limitation is that the CCTA was performed with low iodinated contrast medium (Iopromide, 300 mg I/ml; Ultravist) and this might affect the accuracy of low-dose CCTA in the assessment of CCS. However, although some studies report that intravenous administration of contrast media with high iodine concentration yields higher intravascular attenuation than contrast media with a lower iodine concentration,[30 31] to date no consensus on the optimum contrast medium concentration has been established. Finally, the >600 HU cut-off point was based on a previous study by Glodny et al.[13] without the use of MIR. Further research is needed to explore whether this threshold value requires further refinement in combination with MIR.

To conclude, our study showed that CAC can be adequately quantified on low-radiation-dose CCTA, if iteratively reconstructed with a calcium threshold of >600 HU. With MIR, only 9% of individuals were reclassified.

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CHAPTER 6

Occult coronary artery disease in middle-aged sportsmen with a low cardiovascular risk score: the Measuring Athlete's Risk of Cardiovascular (MARC) events study

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ABSTRACT

Background Most exercise-related cardiac arrests in men aged ≥45 years are due to coronary artery disease (CAD). The current sports medical evaluation (SME) of middle-aged sportsmen includes medical history, physical examination, resting- and exercise-electrocardiography (ECG). We investigated the added value of low-dose cardiac computed tomography (CCT), both non-contrast CT for coronary artery calcium scoring (CACS) and contrast-enhanced coronary CT angiography (CCTA), to detect occult CAD in asymptomatic recreational sportsmen aged ≥45 years without known cardiovascular disease.

Methods Following a normal SME (with resting and bicycle exercise-ECG), 318 asymptomatic sportsmen underwent CCT and 300 (94%) had a low ESC score risk. Occult CAD was defined as a CACS ≥100 Agatston Units (AU) or obstructive (≥50%) luminal stenosis on CCTA. The number-needed-to-screen (NNS) to prevent one cardiovascular event within five years with statin treatment was estimated.

Results Fifty-two (16.4%, 95%CI 12.7-20.8%) of 318 participants had a CACS ≥100 AU. The CCTA identified an additional eight participants with luminal narrowing ≥50% (and a CACS <100 AU). Taken together CCT identified CAD in 60 (18.9%, 95%CI 14.9-23.5%) of 318 participants. The five-year estimated NNS was 183 (95%CI 144-236) for CACS and 159 (95%CI 128-201) for CACS combined with CCTA.

Conclusions Coronary CT detects occult CAD in almost one of five asymptomatic sportsmen ≥45 years after a normal SME that included resting- and bicycle exercise ECG. CACS reveals most relevant CAD with limited additional value of contrast-enhanced coronary CT angiography. The NNS to prevent one cardiovascular event compares favorably to that of other screening tests.

INTRODUCTION

Sudden cardiac death is often the first manifestation of coronary artery disease (CAD). Regular physical exercise is recommended to reduce cardiovascular morbidity and mortality and is gaining popularity in the middle-aged.[1-3] However, exercise transiently increases the risk of cardiovascular events, particularly in those with unknown cardiac disease.[4] More than 90% of exercise-related cardiac events occur in men, predominantly those aged 45 years and over, and are mainly attributed to CAD.[5, 6] It follows that the main goal of cardiovascular evaluation of older athletes is ruling out significant occult CAD.[2] The European Society of Cardiology (ESC) position paper on cardiovascular evaluation of middle-aged/senior individuals engaged in leisure time sports activities advocates the use of maximal exercise testing.[7] This is now frequently performed in a sports medical examination (SME), in addition to medical history, physical examination, ESC SCORE risk calculation and resting ECG, despite the low predictive value for CAD of both resting and exercise electrocardiography in asymptomatic individuals.[3, 7, 8] In addition, as exercise favorably influences cardiovascular risk factors, e.g. by reducing weight and blood pressure and improving the lipid profile, traditional cardiovascular risk scores may underestimate cardiovascular risk in persons who exercise regularly.[9] Coronary artery calcium scoring (CACS) provides a direct, non-invasive measure of CAD and is the strongest independent predictor of cardiovascular events in asymptomatic persons.[10] Absence of coronary artery calcium (CAC) is associated with a very low risk of cardiovascular events in asymptomatic and symptomatic individuals. CACS is increasingly used to expand risk-stratification in asymptomatic persons with an intermediate risk of cardiovascular events (Class IIa recommendation ESC guidelines) and has been recommended as a first-line test over exercise testing or single-photon emission computed tomography (SPECT) in asymptomatic patients and those at a low risk of for CAD.[11] Around half of the asymptomatic middle-aged persons have subclinical atherosclerosis, defined as presence of any CAC. In the absence of scientific evidence no clear recommendations are available regarding the medical management of these individuals.[12]

We aimed to evaluate the additional value of low dose cardiac computed tomography (CCT), using both CACS and coronary CT angiography (CCTA) to detect occult CAD in asymptomatic middle-aged (≥45 years) sportsmen without known cardiovascular disease (CVD), who underwent bicycle exercise testing as part of a SME. Considering the much higher incidence of exercise-related cardiac arrests in men compared to women we chose to enroll men only.[5, 6]

METHODS

Study design and population

The rationale and design of the MARC (Measuring Athlete´s Risk of Cardiovascular events) study have been published.[13] The MARC study was approved by the medical ethics committee and complies with the Declaration of Helsinki. Written informed consent was obtained from all participants. Men aged 45 years or older were eligible if they were asymptomatic, engaged in competitive or recreational leisure sports, were free of known CVD, and had undergone a SME with bicycle exercise ECG that revealed no abnormalities, according to the responsible physician. Participants underwent a SME mainly for comprehensive assessment of exercise tolerance and were recruited with the help of regional sports physicians, who provided potential participants with information, including a flyer detailing the MARC study. Exclusion criteria were known CAD, contrast allergy, and renal impairment. Baseline assessments were obtained during the SME. SME ECG´s were reassessed by a cardiologist (AM) according to the Seattle Criteria for abnormalities unrelated to athletic training.[14] In line with a recent publication, left axis deviation and atrial enlargement were considered training related normal variants.[15]

Cardiac CT (CCT)

A low dose CCT was performed using a 256-slice CT scanner (Philips Healthcare, Best, the Netherlands) with prospective electrocardiographic gating. A non-contrast coronary CT was acquired for CACS, followed by contrast-enhanced CCTA.[13] The American Heart Association 16-segment coronary artery model was used to analyse image quality, plaque characteristics and coronary lumen stenosis on CCTA.

Image analysis and definition of relevant coronary artery disease

CT scans were processed on a workstation (IntelliSpace Portal, Philips Healthcare) by experienced technicians, and assessed by one of two experienced cardiac radiologists (NP, BKV), blinded for SME findings. Presence of relevant CAD was defined as CACS ≥100 AU on non-contrast CCT and/or ≥ 50% luminal stenosis on CCTA.[16-18]

Abnormal findings on CT were reviewed by consensus with at least two (sports)cardiologists and one radiologist to provide advice on management of participants with relevant CAD or other incidental findings. In general, participants with CACS 100-400AU without obstructive CAD were given lifestyle recommendations and recommended to initiate statin treatment.[19, 20] Participants with CACS ≥400 AU or coronary artery stenosis ≥50% were offered a cardiologist consultation to discuss management options.

Number needed to screen (NNS)

The NNS to prevent one cardiovascular event within 5 years was computed based on the reciprocal of the prevalence of CAD (CACS ≥100 AU and/or stenosis ≥50%) multiplied by 100, multiplied by the number needed to treat (NNT) to prevent one cardiovascular event (angina pectoris, myocardial infarction, coronary revascularization, resuscitated cardiac arrest, stroke, or cardiovascular death) obtained from the Multi-Ethnic Study of Atherosclerosis (MESA).[21]

Statistical analysis

Differences between normally distributed variables were analysed using the Student's t-test and chi-square test. Non-normally distributed data were assessed applying Mann-Whitney U and Kruskal-Wallis tests. Reclassification rates were based on the CCT results: CACS <100, low (0-4%); CACS ≥ 100, high (≥10%) ten year risk of fatal cardiovascular events respectively.[16] After univariable analysis of the relation between participants characteristics and presence of CAD a multivariable analysis was done with stepwise logistic regression analysis. Data analysis was performed using IBM SPSS statistics for Windows (version 20.0 SPSS Inc. Chicago, Illinois). A two sided value of $p < 0.05$ was considered statistically significant.

RESULTS

A total of 318 participants (characteristics shown in table 1) underwent prospective ECG-triggered CCT between April 2012 and January 2014. Three-hundred (94.3%) participants had a low (0-4%), 14 (4.4%) had an intermediate (5-9%), and 4 participants (1.3%) with diabetes had a high (≥10%) ESC SCORE risk. The participants were fit with a mean maximal (bicycle) exercise capacity of 314 ± 48 Watt. Participants were predominantly engaged in high dynamic high static sports (45% cyclists) and high dynamic low static sports (36% long distance runners). Other sports included fitness (6%), speed/tour skating (5%), swimming/water polo (5%), rowing (1%), and tennis (1%). ECG reassessment by a cardiologist revealed abnormal findings in 4 participants (complete left bundle branch block (N=1), intraventricular conduction delay (N=1), Q waves (N=1), and QRS voltage criteria for left ventricular hypertrophy with abnormal repolarization (N=1)). The first two participants had no CAD on CCTA. The participant with Q waves underwent myocardial adenosine perfusion imaging that revealed no ischemia or infarction. The fourth participant had long-standing hypertension without CAD or hypertrophy on CCTA.

Cardiac CT

CCT results are also shown in the table 1. The total average radiation dose was 3.9 ± 0.9mSv (1.0 ± 0.4 for CACS and 3.0 ± 1.2 for CCTA). No CAC was seen in 151 participants (47.5%), 115 (36.2%) had CACS 1-99 AU, whereas 52 (16.4%) had CACS ≥100 AU. Stratification by age (45-54 (n=176), 55-64 (n=113) and 65-79 (n=29) years) revealed increasing median CACS values (0, 16AU, and 39AU, respectively, p for trend <0.001) with accordingly lower rates of zero CACS (62%, 30%, and 28%).

CCTA revealed no atherosclerosis in 117 (36.8%) and mild atherosclerosis in 184 (57.9%) participants. Seventeen (5.3%) participants had obstructive atherosclerosis (≥50% stenosis), with CACS <100 AU in eight of them. The combination of CACS and CCTA identified CAD in 60 (18.9%, 95%CI 14.9-23.5%) participants, whose exercise capacity did not differ from those without CAD (303 vs. 317 Watt, p = 0.5). In univariable analysis these 60 participants were significantly older, had higher BMIs and cholesterol levels, more frequently had hypertension or a family history of CAD, more often were former smokers, and consequently had a higher ESC score risk (data available in supplement). In a multivariable logistic regression model (see supplement) age (odds ratio (OR) 1.13, 95%CI 1.07-1.19), BMI (OR 1.19, 95%CI 1.05-1.33), total cholesterol (OR 1.75, 95% CI 1.21-2.53), and family history of CAD (OR 2.09, 95% CI 1.10-4.01) remained independent predictors of relevant CAD on CCT.

Reclassification and number needed to screen

With a CACS ≥100 AU as cut-off (found in 52 (16.4%) participants) 46 of the 300 participants with low ESC SCORE risk were reclassified to higher risk and nine of the 14 participants with intermediate ESC SCORE risk were reclassified to low risk, resulting in 55 (17.3%, 95% CI 13.5-21.8) reclassifications. CCTA reclassified another eight (2.5%) participants to higher risk, resulting in an overall reclassification of 19.8% (95% CI 15.8 – 24.5). The NNS to detect CACS ≥100 AU was 6.1 (100 x (1/16.4%)). Based on the five year NNT with a statin of 30,(21) the NNS with CACS to prevent one cardiovascular event within five years is 183 (6.1 x 30) (95%CI 144-236). Adding CCTA lowered the estimated NNS to 159 (95%CI 128-201).

Additional cardiovascular workup / management of relevant CAD

Forty-three of the 60 participants with relevant CAD were given lifestyle recommendations and suggested to contact their general practitioner to consider initiating statin treatment.

Table 1. Characteristics and CT imaging findings of MARC participants (n = 318)

Characteristics	
Age (years)	54.7 ± 6.3
Height (m)	1.82 ± 0.07
BMI (kg/m²)	24.9 ± 2.7
Systolic / Diastolic blood pressure (mmHg)	127 ± 13 / 79 ± 9
History of hypertension, n (%)	21 (6.6)
Former / current smoker, n (%)	117 (36.8) / 10 (3.1)
Diabetes mellitus, n (%)	4 (1.3)
Family history of coronary artery disease, n (%)	96 (30.2)
Total cholesterol (mmol/l)	5.4 ± 0.9
Lipid lowering medication, n (%)	18 (5.7)
ESC SCORE risk categories	
Low (0-4%) (%)	300 (94.3)
Intermediate (5-9%) (%)	14 (4.4)
High (≥10%) (%)	4 (1.3)
Abnormal ECG (Seattle criteria) (%)	4 (1.3)
Exercise tolerance: Total Watt / Watt per kg	314 ± 48 / 3.8 ± 0.6
Training volume (hours/week)	3.0 [2.25-4.75]
Cardiac CT, n (%; 95% CI)	
Coronary artery calcium score	
0 AU	151 (47.5; 42.1-53.0)
1-99 AU	115 (36.2; 31.1-41.6)
100-399 AU	29 (9.1; 6.4-12.8)
≥400 AU	23 (7.2; 4.9-10.6)
Coronary CT angiography	
No atherosclerosis	117 (36.8; 31.7-42.2)
Mild (non-obstructive) stenosis (1-49%)	184 (57.9; 52.4-63.2)
Moderate/severe (obstructive) stenosis (≥50%)	17 (5.3; 3.4-8.4)
Coronary artery disease*	60 (18.9; 14.9-23.5)

Data are presented as mean ± SD, proportions (%) or median values [IQR]AU, Agatston units; BMI, body mass index; CACS, Coronary Artery Calcium Score; ECG, electrocardiogram; Risk factors were defined by chart review, including review of medications for hypertension, lipid disorders or diabetes. Coronary artery disease defined as CACS ≥100 and / or ≥50% stenosis.

The consensus panel recommended evaluation by a cardiologist in 17 (5.3%) participants with more severe CAD (CACS ≥400 AU and/or ≥50% stenosis). Nine participants underwent myocardial adenosine perfusion imaging, with no signs of ischemia in seven, and a positive perfusion scan in two that resulted in percutaneous coronary intervention (PCI). Four other participants underwent coronary angiography, without prior myocardial perfusion imaging, which resulted in fractional flow reserve (FFR) guided PCI in two participants. The remaining four participants, after consultation with a cardiologist, opted for medical management without additional testing. In general, participants found to have relevant CAD were recommended to continue exercising but to refrain from vigorous exercise.[22]

DISCUSSION

In this predominantly low risk population (94% low ESC SCORE) of middle-aged sportsmen with a normal routine SME, CCT detected relevant CAD in almost one of every five participants. This reclassifies these persons to a higher risk of developing symptomatic CVD. Assuming a five-year NNT (with statins) of 30 to prevent one cardiovascular event in individuals at high risk, this translates into a NNS of 159 (NNS of 183 if only CACS ≥ 100 AU is used).

The results demonstrate that both traditional cardiovascular risk assessment (ESC SCORE) and ECG exercise testing fail to reliably identify sportsmen with occult CAD. The fact that a considerable proportion of coronary events are attributed to non-obstructive lesions (with a high CACS reflecting the burden of multiple subclinical plaques that can become symptomatic) and the recent concept that more exercise related cardiac arrests are caused by demand ischemia in sportsmen with CAD than by acute plaque rupture, provides a rationale for identification of occult CAD in those who are (or aim to become) physically active.[1, 23]

Comparison with other studies

Reference values for CACS are available from several population-based studies.[24, 25] Information on CCTA in asymptomatic / low cardiovascular risk persons is limited. Four studies have performed CCT in sportsmen (marathon runners).[9, 26-28]

As expected stratification by age revealed increasing median CACS in our participants, but their age related values were generally lower than that of Caucasian men free of baseline CVD in the MESA and Heinz Nixdorf Recall (HNR) studies.[24, 25] MARC participants were younger, had a more favorable CV risk profile and more frequently had zero CAC (47.4%) than the MESA and HNR study subjects (32.1%, and 18.1%, respectively). The MESA and HNR study subjects had higher BMI (28.1 and 27.9 versus 24.9kg/m²), were more often current/former smokers (11.9%/48.3% and 24.6%/45.2% versus 3.1%/36.8%), more often had diabetes (4.4% and 5.7% versus 1,3%) and hypertension (31.6% and 27.2% versus 6.6%), and were more often treated with lipid lowering medication (19.6% and 8.0% versus 5.7%).

The prevalence of obstructive (≥50% stenosis) CAD in MARC (5.3%) was appreciably lower than that reported (25%) in the CONFIRM registry (mean age 58±12 years) of persons without chest pain.[18] Apart from the higher age, the *a priori* likelihood of finding CAD was much higher in CONFIRM based on medical history and cardiovascular risk profile. In a group of 108 German marathon runners zero CACS was less common than in MARC (28.7% versus 47.5%, $p < 0.001$).[9] Cardiovascular events nearly exclusively occurred in those with a CACS≥100 AU, which was found more often than in MARC (36.1% versus 16.4%, $p < 0.001$).[29] Apart from the slightly younger age (mean 54.7±6.3 versus 57.2±5.7 years) and lower percentage former and current smokers in our group (36.8% versus 51.9%, $p = 0.004$ and 3.1% versus 4.6% $p < 0.001$ respectively), selection of participants may also play a role. The German study only enrolled persons who had run at least 5 marathons, whereas we recruited men ≥45 years from different sports disciplines with different training intensity. Two subsequent smaller studies in younger marathon runners (n=50, mean age 52.6±5.9 and n=25, mean age 55±4years) found lower numbers of CAD (10% and 8%).[26, 27] Six of forty-four (14%) asymptomatic athletes aged 30-60 years with ST-segment abnormalities during maximal exercise testing had a significant (>50%) coronary stenosis on CCTA, as compared to 5% of our sportsmen with a normal exercise test.[28]

Implications

With the increasing number of middle-aged persons engaging in sports, our CCT results may apply to a considerable segment of the population. The low NNS in the general population to identify an individual with moderate CACS (≥100 AU) seems enough justification for extending CACS to lower risk individuals in future guidelines, as CAC is also associated with risk of cardiovascular events among individuals with few or no risk factors.[10] The estimated NNS in MARC of 183 (CACS alone) or 159 (CACS combined with CCTA) to prevent one cardiovascular event in the next five years with statin treatment is low compared to other accepted screening tests such as mammography to prevent a death from breast cancer in women aged 50-59 years (NNS 2451) or a cardiovascular event in mild to moderate hypertension (140-160 mmHg)(NNS

279).[30, 31] The NNS would have been even lower if we had used the lower (21) instead of the higher (28) NNT estimate derived from the MESA study.[21]

Investigating asymptomatic persons with CCT invariably raises issues. First, prevalence of CCT detected CAD depends on CAD definitions: our cut-off values (CACS ≥100 AU and ≥ 50% luminal stenosis) are commonly used in (population based) studies.[16-18] The prevalence of any CAD (i.e. non-zero CACS or any atherosclerosis on CCTA) was 63.2% (95%CI. 57.8-68.3). Second, finding significant CAD may lead to additional diagnostic tests with extra costs and risks to asymptomatic persons. Severely calcified lesions can lead to misinterpretation of stenotic lesions and unwarranted further diagnostic testing or treatment. However, the Eisner study demonstrated that CACS compared with no scanning in asymptomatic volunteers can improve cardiac management without incurring significant downstream medical costs.[32] Third, without firm evidence-based guidelines it is debatable how to treat CAD in asymptomatic persons other than lifestyle modification. Many practitioners feel that any degree of CAD on CCT should be treated aggressively; the threshold for statin treatment to prevent cardiovascular events is becoming lower in recent guidelines. For example, by applying the recent ACC/AHA guideline to a European population aged 55 years or older, nearly all men (96.4%) would be eligible for statin treatment, compared to 66.1% when following the ESC guidelines.[33] Fourth, incidental findings, e.g. pulmonary nodules, may lead to additional investigations. We used the Fleischner Society recommendations for solid and sub-solid pulmonary nodules on CT.[34] One participant was operated for a malignant pulmonary sub-solid nodule found on CCT. Fifth, radiation is associated with a small, dose dependent increase in the risk of cancer. The mean radiation dose MARC participants received was 3.9mSv: equivalent to one to two years background radiation. Estimating the risk of cancer is difficult because there is no prospective data on the adverse events of radiation with doses used for diagnostic purposes.[35] Being aware of these limitations, and without better estimates, the International Commission on Radiological Protection estimates that the risk of a dose of 10 mSv for a member of the public translates to a fatal cancer risk of 5 per 10,000 persons.[35] Limiting the investigations to CACS reduces the dose to 1mSv, but technical developments are also lowering CCTA radiation doses substantially.

Limitations of our study require mentioning. First, although a considerable number for a study of its kind, it remains a relatively small study of 318 selected men (all were Caucasian with college education). The fact that they consented to participate after undergoing a SME may have led to additional selection bias (e.g. those with a higher chance of CVD because of a positive family history). To investigate the possibility of selection bias we compared our participants to a group of 725 unselected men aged ≥45 years who underwent a SME in 2012-2013 in another region of the Netherlands (Maxima Medical Centre, Veldhoven). The cohorts were remarkably similar (mean age 54.7 vs. 54.3 years, systolic blood pressure 127 vs. 129 mmHg, BMI 24.9 vs. 25.0 kg/m2, current smoking 3.1 vs. 5.1%, workload 314 vs. 309 Watt), indicating that our group is representative for sportsmen that undergo a SME.

Second, we used the NNT derived in the MESA cohort (estimated NNT across dyslipidemia categories, mean age 62.0±10.7 years) that is older than our group to calculate the NNS.[21] Athletes may also show less compliance with statins because of myopathy side effects.[22] For these reasons we chose the higher NNT estimate (30 rather than 23).[21]

Third, our participants did not undergo echocardiography. The MARC study focused on CAD and the probability of finding abnormalities in asymptomatic persons with a normal ECG and without heart murmurs on physical examination is low.[36] Nevertheless, careful ECG evaluation is warranted as cardiomyopathies in older sportsmen can occur. Fourth, non-invasive techniques to identify asymptomatic persons at increased risk, e.g. measurement of carotid intima media thickness, heart rate recovery after exercise and T wave-alternans analyis, were not part of this study.[37]

Our study's main strength is that it is the first to examine the additional value of CACS and CCTA to a normal SME in asymptomatic middle-aged sportsmen with a low ESC Score risk and different sport disciplines. Our results demonstrate the limited value of traditional cardiovascular risk assessment and exercise testing to detect occult CAD in older sportsmen. CCT provides a more reliable risk assessment and will give guidance to managing sportsmen found to have occult CAD to prevent (exercise related) cardiovascular events.

Currently no firm recommendations can be made regarding the routine use of CCT in preparticipation evaluation of athletes aged ≥45 years. As the additional value of CCTA is limited in this study, with extra costs, contrast use and radiation, we suggest a randomized study should investigate the hypothesis that the introduction of CACS in a SME setting reduces the incidence of (exercise related) cardiac events in older athletes and is cost-effective, compared to exercise testing.

In conclusion, almost one in five asymptomatic middle-aged sportsmen, with a normal bicycle exercise test and predominantly low conventional cardiovascular risk scores, has occult CAD, and 87% of these abnormalities can be detected with CACS alone. The five-year NNS with CCT to prevent one cardiovascular event appears to be much lower than for other screening strategies (183 for CACS and 159 for combined CACS and CCTA).

As both traditional cardiovascular risk assessment (ESC SCORE) and bicycle exercise testing do not reliably identify sportsmen with occult CAD there is a need to further investigate the role of cardiac CT in this setting.

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CHAPTER 7

No psychological distress in sportsmen aged 45 years and older after cardiovascular screening, including cardiac CT. The Measuring Athlete's Risk of Cardiovascular Events (MARC) study

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ABSTRACT

Background Psychological distress caused by cardiovascular preparticipation screening (PPS) may be a reason not to implement a PPS program. We assessed the psychological impact of PPS, including cardiac computed tomography (CT), in 318 asymptomatic sportsmen aged ≥ 45 years.

Methods Coronary artery disease (CAD) was defined as coronary artery calcium score ≥100 Agatston units and/or ≥50% luminal stenosis on contrast-enhanced cardiac CT. Psychological impact was measured with the Impact of Event Scale (IES) (seven items) on a six-point scale (grade 0-5). A sum score ≥19 indicates clinically relevant psychological distress. A Likert scale was used to assess overall experiences and impact on sports and lifestyle.

Results A total of 275 participants (86.5% response rate, 95% CI 83-90%) with a mean age of 54.5 ± 6.4 years completed the questionnaires, 48 (17.5%, 95% CI 13-22%) of whom had CAD. The median IES score was 1 (IQR 0-2, [0-23]). IES was slightly higher in those with CAD (mean rank 175 vs. 130, $p < 0.001$). One participant (with CAD) experienced clinically relevant psychological distress (IES = 23). Participants reported numerous benefits, including feeling safer exercising (58.6%, 95% CI 53-65%) and positive lifestyle changes, especially in those with CAD (17.2 vs 52.1%, $p < 0.001$). The majority was satisfied with their participation (93.8%, 95% CI 91-97%).

Conclusion Cardiovascular PPS, including cardiac CT, causes no relevant psychological distress in older sportsmen. Psychological distress should not be a reason to forego screening in sportsmen.

INTRODUCTION

Regular physical exercise reduces the risk of cardiovascular disease,[1, 2] but vigorous exertion (particularly in untrained persons) can trigger an acute cardiac event.[3, 4] This phenomenon is known as the paradox of sports. Exercise-related cardiac arrest is the leading cause of mortality during exercise.[5] Over 90% of these arrests occur in men aged ≥45 years, with coronary artery disease (CAD) as the major cause.[6, 7] In the Netherlands, the incidence of exercise related cardiac arrest in men >35 years is 5.8 per 100,000 per year, with approximately 50% surviving the event.[7] The increasing popularity of sports, especially in middle-aged and older individuals, is likely to lead to an increase in exercise-related arrests.[8, 9]

Some countries (though not the Netherlands) have adopted the policy of mandatory preparticipation screening (PPS) of young (≤35 years) competitive athletes.[10] Increasingly, older sportsmen voluntarily undergo a preventive sports medical examination.[9] Recommendations regarding sports medical examinations of senior sportsmen have been published by the European Society of Cardiology (ESC), with the main objective of ruling out significant occult CAD.[9, 11]

As the merits of PPS are still under debate,[12] recommendations vary across countries, age groups, sports disciplines and competition levels.[13] An ideal screening program meets the following six criteria: (1) the condition must have a significant impact on public health and (2) should have an asymptomatic period during which detection may be possible, (3) the outcome for a condition should improve by treatment during this asymptomatic period, (4) the screening test should be sensitive enough to detect the disease during the asymptomatic period, (5) specific enough to minimize false positive results and (6) acceptable to those undergoing the test.[14] The U.S. National Heart, Lung, and Blood Institute outlined the need to understand the psychological burden of screening in athletes, prior to widespread implementation of the PPS program.[15] Many physicians hesitate to embark on large scale PPS, citing psychological distress caused by the screening and the potential outcome as an important consideration.

To date, only two studies on the psychological impact of PPS have been performed.[16, 17] Both were carried out in relatively young persons (mean age 16 (n = 952) and 26 years (n = 441)), whose PPS included medical history and physical examination, combined with a resting electrocardiogram (ECG) (n = 917) or echocardiography (n = 441).[16, 17] Screening caused no relevant psychological distress in these groups. The psychological impact of PPS in those most frequently affected by exercise-related cardiac arrests, sportsmen aged 45 years and older, remains to be investigated. The aim of this study was to determine the psychological impact of cardiovascular screening, including cardiac computed tomography (CT), in asymptomatic recreational sportsmen aged 45 years or over.

METHODS

The design and main results of the Measuring Athlete's Risk of Cardiovascular events (MARC) study have been published.[18, 19] The study has been approved by the regional medical ethics committee. In brief, asymptomatic middle-aged (≥45 years) sportsmen whose routine sports medical examination (including medical history, physical examination, resting and bicycle exercise ECG) revealed no cardiac abnormalities were eligible to undergo additional cardiac CT imaging (mean radiation dose: 3.9 mSv). The presence of relevant CAD was defined as a coronary artery calcium score (CACS) ≥100 Agatston Units (AU) on non-contrast coronary CT and/or ≥50% luminal stenosis on contrast-enhanced coronary CT angiography (CCTA). Cardiac CT identified occult CAD in 60 (18.9%, 95% CI 14.9-23.5%) of 318 participants, resulting in a five-year estimated number-needed-to-screen of 159 (95% CI 128-201) to prevent one cardiovascular event with statin treatment.[19] All 318 MARC participants were invited by email to fill out an internet-based questionnaire to evaluate the psychological impact of participating, with an interval of 7-30 (mean 16) months after undergoing cardiac CT. A total of three reminders were sent to those who did not respond. Similar to Solberg et al.[16], we used the intrusion sub-scale of the Impact of Event Scale (IES). This scale was originally developed to measure posttraumatic stress. [20, 21] The 7 items of the IES were graded on a six-point scale (0 = never, 1 = a little, 2 = somewhat, 3 = medium, 4 = much, 5 = very much). A sum score ≥19 is generally accepted to indicate clinically relevant psychological distress. [22] In addition, the questionnaire contained items concerning global experiences and impact on sports and lifestyle, measured on a Likert scale (1 = strongly disagree, 2 = disagree, 3 = neutral, 4 = agree and 5 = strongly agree). The questionnaires were identical for all, except for one additional question (regarding advice received on sporting activities) that was added for those found to have relevant CAD (see online Supplementary Data).

Table 1. Baseline characteristics

	All N= 275	CAD N=48 (17%)	No CAD N= 227 (83%)	*p*-value
Age (years)	54.5 ± 6.4	57.9 ± 6.1	53.8 ± 6.3	<0.001*
Height (m)	1.82 ± 0.07	1.81 ± 0.07	1.83 ± 0.07	0.119
Weight (kg)	82.6 ± 10.4	84.5 ± 11.1	82.2 ± 10.2	0.163
BMI (kg/m²)	24.8 ± 2.6	25.9 ± 3.1	24.6 ± 2.5	0.003*
Systolic blood pressure (mmHg)	129 ± 13	131 ± 13	129 ± 14	0.216
Diastolic blood pressure (mmHg)	80 ± 9	82 ± 7	80 ± 9	0.122
History of hypertension, n (%)	15 (5.5)	6 (12.5)	9 (4.0)	0.018*
Current smoker, n (%)	8 (2.9)	1 (2.1)	7 (3.1)	0.709
Former smoker, n (%)	93 (33.8)	24 (50)	69 (30.4)	0.009
Diabetes mellitus, n (%)	2 (0.7)	0 (0)	2 (0.9)	0.516
Family history of CAD, n (%)	123 (44.7)	26 (54.2)	97 (42.7)	0.149
Total cholesterol (mmol/l)	5.4 ± 0.8	5.7 ± 0.9	5.3 ± 0.8	0.002*
ESC SCORE risk categories				
Low (0-4%), n (%)	264 (96)	44 (92)	220 (97)	0.092
Intermediate (5-9%), n (%)	11(4)	4 (8)	7 (3)	0.092
High (≥10%), n (%)	0	0	0	-
Exercise tolerance				
Total Watt	314 ± 48	304 ± 49	316 ± 47	0.117
Watt/kg	3.8 ± 0.7	3.6 ± 0.6	3.9 ± 0.7	0.015*
Motivation to participate, n (%)				
General screening	118 (42.9)	23 (47.9)	95 (41.8)	0.442
Contribution to science	77 (28.0)	8 (16.7)	69 (30.4)	0.055
Relatives with cardiac disease	36 (13.1)	9 (18.8)	27 (11.9)	0.202
Concerns regarding cardiac condition	12 (4.4)	3 (6.2)	9 (4.0)	0.483
Other	32 (11.6)	5 (10.4)	27 (11.9)	0.773

Data are presented as mean ± SD, proportions (%) or median values [IQR].
BMI, body mass index; CAD, coronary artery disease; ECG, electrocardiogram;
Risk factors were defined by chart review, including review of medications for hypertension, lipid disorders or diabetes. * significant difference ($p < 0.05$) between CAD and no CAD group.

Statistical analysis

The primary outcome (IES score) was calculated as median with its interquartile range (IQR). Secondary outcomes (general experiences, impact on sports and lifestyle) were dichotomized and reported in frequencies and percentages. Comparisons between those with and without CAD were conducted with the Mann-Whitney U test or Chi-square test. Data analysis was performed using SPSS statistics (version 22.0 SPSS Inc. Chicago, Illinois). A *p*-value <0.05 was considered statistically significant.

RESULTS

The questionnaire was completed by 275 of the 318 MARC participants with a mean age of 54.5 ± 6.4 years (Fig 1). Altogether 48 of 58 participants with CAD and 227 of 260 participants without CAD responded (82.8%, 95% CI 73-93 and 87.3%, 95% CI 83-91% response rate, respectively). The response rate did not differ between these groups (*p* = 0.361).

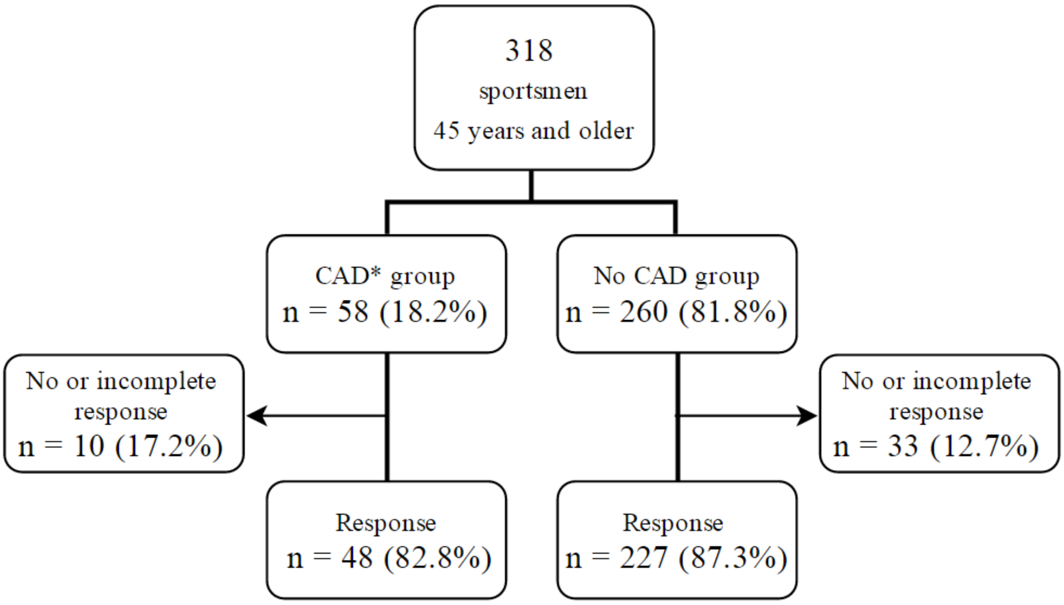

Fig. 1 Flow diagram of participants with an overall response rate of 86.5% (95% CI 83-90%) *CAD* coronary artery disease. *CAD* group* coronary artery calcium scoring (CACS) ≥100AU on non-contrast CCT and/or ≥50% luminal stenosis on contrast-enhanced CCTA.

The characteristics of the study population are shown in Table 1. Participants were asymptomatic and almost all (96%) had a low cardiovascular risk (ESC Systematic COronary Risk Evaluation (SCORE) 0-4%). All participants were Caucasian and they were fit, as evidenced by a mean maximal exercise capacity of 314 W. They were predominantly engaged in cycling (45%) and long distance running (36%). The main reason to participate in the MARC study was cardiac screening in the context of healthy and safe sports (43%). Only 4% had concerns about their own cardiac condition.

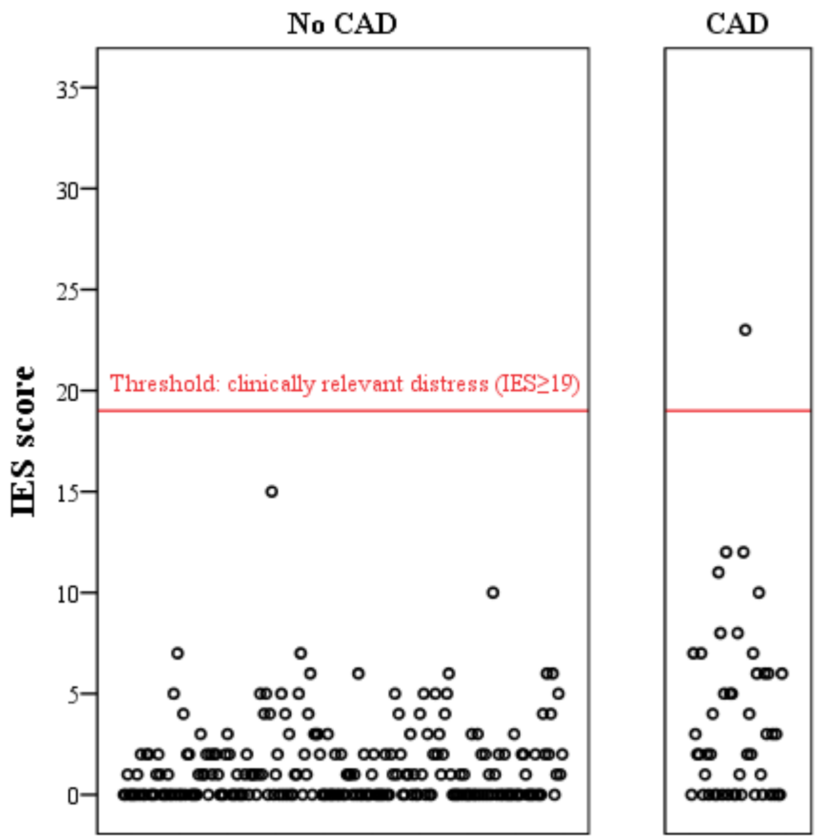

Fig. 2 Impact of event scores according to presence of coronary artery disease. (*IES score* impact of event score, *CAD* coronary artery disease. Each dot represents an individual MARC study participant.

All participants diagnosed with CAD (n = 58 of 318, 18.2%, 95% CI 14-23%) received lifestyle advice, were encouraged to continue their sports activities, but advised to avoid excessive/peak efforts, and suggested to contact their general practitioner to consider initiating statin treatment. The minority (n = 17) with severe CAD (CACS ≥400 AU and/or ≥50% coronary artery stenosis) was advised to consult a cardiologist. Thirteen participants underwent additional cardiac testing (myocardial adenosine perfusion imaging (n = 9) or coronary angiography (n = 4)), resulting in a percutaneous coronary intervention in four of them.

The median IES score of participants was 1 (IQR 0-2), obtained on average 16 months (range 7 to 30 months) post screening. The IES in participants with CAD was significantly higher than in

those without CAD (median 1 vs. 2, mean rank 175 vs. 130, $p < 0.001$). Only one participant (with CAD) experienced clinically relevant psychological distress, defined as IES ≥19 (Fig. 2).
The personal and general perspectives about PPS including cardiac CT are shown in Fig 3. Relatively few participants experienced anxiety before (8%, 95% CI 5-12%) or during (5%, 95% CI 2-8%) CT scanning, and no significant differences were seen between participants with or without CAD. Participants found to have CAD were more likely to feel anxious directly after receiving the result (27.1% vs. 3.1%, $p < 0.001$), to be afraid they would be advised to quit sports (20.8% vs. 2.6%, $p < 0.001$) and to have the opinion they were at higher risk of a cardiac condition than other sportsmen (22.9% vs. 4.0%, $p < 0.001$).

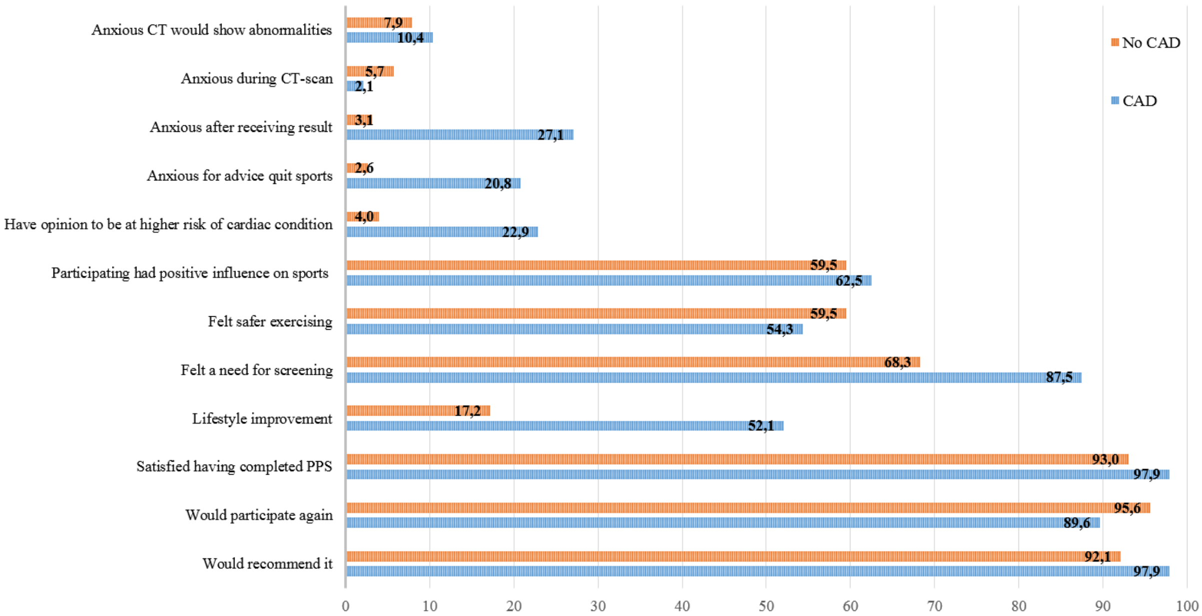

Fig. 3 Perspectives about preparticipation screening with cardiac CT (in %)

In general the screening had a positive influence on sporting activities, only 15 participants (5.5%, 95% CI 3-8%) disagreed and 34.5% (95% CI 29-40%) had a neutral opinion. The majority (58.6%, 95% CI 53-65%) felt safer exercising, whereas 32% (95% CI 26-38%) experienced no difference and a minority (9.4%, 95% CI 6-13%) felt less safe exercising. No significant differences were observed between the two groups for these two items.
Those found to have CAD more frequently felt a need for PPS screening, including CT imaging, of middle-aged sportsmen than those without CAD (87.5% vs. 68.3%, $p = 0.007$) (Fig. 3). Participating in the MARC study led to lifestyle improvement in 64 sportsmen (23.3%),

predominantly in those found to have CAD (17.2 vs. 52.1%, $p < 0.001$). The majority of these 64 participants (65.6%, 95% CI 54-77%) adjusted to a healthier diet, 46.8% (95% CI 35-59%) lost weight, 35.9% (95% CI 24-48%) increased relaxing and/or quality time and 6.2% (95% CI 0-12%) quit smoking. In the end, the vast majority was satisfied with their participation (93.8%, 95% CI 91-97%), would participate again (94.5%, 95% CI 92-97%) and would recommend participation to others (93.1%, 95% CI 90-96%). These opinions did not differ between those with and without CAD (p = 0.194, 0.096 and 0.147, respectively).

DISCUSSION

We found no relevant psychological distress in asymptomatic middle-aged recreational sportsmen who underwent cardiovascular preparticipation screening with cardiac CT, irrespective of whether they were found to have CAD or not. The median (IES) score, assessed on average sixteen months after the cardiac CT, was slightly higher in the participants with CAD, but did not reach the threshold of clinical relevance. Transient anxiety, directly after being informed about the results, was significantly more frequent in those diagnosed with CAD. Nearly all were satisfied with their participation and would recommend PPS to others. Participants reported numerous benefits, including feeling safer exercising and positive lifestyle changes, especially in those with CAD.

Our study confirms the results of two earlier studies that found no association between cardiovascular screening and psychological distress in younger athletes,[16, 17] and extends this observation to middle-aged recreational sportsmen who underwent cardiac CT (with a mean radiation dose of 3.9 mSv) in addition to the routine sports medical examination.

The psychological consequences of screening asymptomatic persons have been evaluated in other domains. A meta-analysis of 12 studies (n = 170,045, mean age varying from 41 to 69 years) documented no significant impact of screening for cancer, diabetes, abdominal aortic aneurysm, osteoporosis, peptic ulcer or coronary artery disease on anxiety, depression or quality of life, not even in those receiving positive test results.[23] A prospective investigation among 685 men aged 65 to 73 years screened for an abdominal aortic aneurysm found transient psychological stress with a small decrease in overall quality of life when offered the possibility to be screened.[24] Overall, those screened reported a better quality of life compared to controls (non-screened), although being diagnosed with an aneurysm did impair quality of life. This suggests that the results of screening rather than the procedure cause stress.[24] It follows that screening programs should have support mechanisms for individuals with a positive result.

This is the first study investigating the psychological impact of an extensive cardiovascular PPS test that included cardiac CT in asymptomatic men aged ≥45 years. Stress was measured with a frequently used and validated tool (IES questionnaire).[25] The response rate was high (86.5%, 95% CI 83-90) and the characteristics of participants were essentially similar to that of the complete MARC cohort. The percentage (17.5%) of participants with a positive result (CAD) was high compared to two former studies of psychological distress caused by PPS (5% resp. 0.7%, respectively).[16, 17]

This study has limitations. First, the psychological assessment was performed 7-30 months post screening. Although this provides insight into the long-term effects of screening, it may also have led to recall bias affecting the short-term psychological impact, because normally only extreme experiences will be remembered well.

Second, as our participants were all Caucasian men that participated on a voluntary basis, the results cannot readily be extrapolated to the larger group of older athletes. The IES score is probably lower than it would have been if participants had undergone mandatory screening. Also, the response to stress and coping mechanisms are likely to differ between men and women.[26] Third, the reassuring knowledge that the routine sports medical examination revealed no cardiac abnormalities may have blunted the psychological impact of cardiac CT. Fourth, as we did not randomise to PPS or no PPS, we have no information from a control group.

We do not advocate mandatory PPS at this stage.[27] Although the addition of cardiac CT to the sports medical examination does not have major psychological impact in older sportsmen, a randomised study is needed to investigate whether the introduction of a sports medical examination (including CT scanning) reduces the incidence of (exercise related) cardiac events in older athletes and is cost-effective.

In conclusion, PPS with cardiac CT, both coronary artery calcium scoring and coronary CT angiography, causes no relevant long-term psychological distress in recreational Caucasian sportsmen aged 45 years and older. Participants reported numerous benefits, including feeling safer exercising (58.6%, 95% CI 53-65%) and positive lifestyle changes, especially in those with CAD (17.2 vs. 52.1%, $p < 0.001$). The majority of participants was satisfied and would recommend the evaluation to others. Psychological distress should not be a reason to forego screening in older sportsmen. However, attention to transient anxiety in those with a positive result (CAD) is needed.

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CHAPTER 8

Perfect coronary arteries in sportsmen aged 45 years and older: the importance of lifelong exercise and ideal cardiovascular health

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ABSTRACT

Background Most exercise-related cardiac arrests occur in men aged ≥45 years and are caused by coronary artery disease (CAD). We determined the impact of lifelong exercise and "ideal" cardiovascular health (CVH) on the occurrence of CAD in asymptomatic sportsmen with a low European Society of Cardiology SCORE risk.

Methods Following a normal sports medical evaluation, 283 asymptomatic sportsmen ≥45 years underwent non-contrast CT and coronary CT angiography (CCTA) and self-reported their lifelong exercise. Ideal CVH was defined as fulfilling ≥5 of seven American Heart Association health metrics. Lifelong exercise was defined as minimally two hours per week training from adolescence onward. Those with a zero coronary artery calcium score and no plaques on CCTA were considered to have perfect coronaries. The relation of lifelong exercise and ideal CVH to the absence of CAD ("perfect coronaries") was determined.

Results Of the 283 sportsmen, 130 (46%) had ideal CVH, 112 (40%) were lifelong exercisers, and 104 (37%) had perfect coronaries. Ideal CVH was significantly associated with perfect coronaries (p=0.04). Among lifelong exercisers, the prevalence of perfect coronaries was 47% with ideal CVH (n=55) compared to 30% without ideal CVH (n=57). For non-lifelong exercisers with (n=75) and without (n=96) ideal CVH the prevalence was 35% and 32%, respectively. Compared to the remaining cohort, the likelihood of having perfect coronaries was 70% higher in lifelong exercisers with ideal CVH (age-adjusted OR 1.70 95%CI 1.01-2.69).

Conclusion In middle-aged sportsmen with low SCORE risk, lifelong exercisers with ideal CVH are most likely to have perfect coronaries.

INTRODUCTION

Symptomatic cardiovascular disease is the result of lifelong exposure to risk factors. Subclinical atherosclerosis
may already be present before the age of 25 years, as demonstrated in autopsy studies of young soldiers.[1] The importance of regular physical activity to prevent cardiovascular diseases (CVD) is well established,[2,3] and the rapidly growing group of middle-aged athletes testifies to the increased awareness of the benefits of exercise.[4] The overwhelmingly positive effects of exercise are questioned every now and then by the sudden demise of an athlete.[5] Most exercise-related cardiac arrests occur in men aged ≥45 years and are caused by coronary artery disease (CAD).[6-8] Identifying significant occult CAD should be the key objective of the cardiovascular evaluation of older sportsmen. Although traditional cardiovascular risk scores (e.g. the Framingham Heart Study risk score (FRS) and the European Society of Cardiology (ESC) Systematic COronary Risk Evaluation (SCORE)) and exercise testing do not reliably identify CAD in asymptomatic athletes,[9, 10] they remain the cornerstone of both the European and U.S. recommendations for the cardiovascular evaluation of middle-aged and senior sportsmen/athletes.[8, 11, 12] Risk scores aim to divide asymptomatic persons in low, intermediate and high risk categories; that correspond to 0-4%, 5-9% and 10% or higher 10-year cardiovascular mortality risks if SCORE is used.[2] Cardiovascular risk scores do not account for past exposure to risk factors and have not specifically been developed for persons who are physically active. Regular physically activity has a favourable influence on cardiovascular risk, e.g. by reduction of weight and blood pressure (BP), and improving the lipid profile.

Non-contrast cardiac CT (CCT) for the assessment of coronary artery calcium score (CACS) provides a non-invasive direct measure of coronary atherosclerosis and is an independent predictor of cardiovascular events.[13] The CACS is the most powerful cardiac risk prognosticator in the asymptomatic population, with consistent superiority to all risk factor-based scores.[14] Absence of CAC is associated with a very low risk of future cardiovascular events in asymptomatic as well as symptomatic individuals.[15] The amount of CAC, however, relates poorly to the degree of luminal narrowing of the coronary arteries and a low CACS does not exclude CAD.[16, 17]

In 2010, the American Heart Association (AHA) developed the concept of ideal CVH to promote CVD reduction. In contrast to traditional cardiovascular risk scores this concept takes into account physical activity and previous exposure to risk factors (former smoking).[18] Ideal CVH is defined as the presence of four ideal health behaviors (no current or past smoking, body mass index [BMI] <25 kg/m², physical activity at goal level, and diet consistent with current guideline recommendations) and three ideal health factors (untreated total cholesterol <5.17 mmol/l, untreated BP <120/80 mmHg and untreated fasting glucose <5.6 mmol/l) in the absence of clinical CVD: the so called "simple seven." Favourable ideal CVH metrics are associated with less CAC[19,20] and substantially lower cardiovascular disease and all-cause mortality.[21, 22]

The AHA recommends 150 minutes of moderate-intensity aerobic exercise, or 75 minutes of vigorous-intensity aerobic exercise, per week for overall cardiovascular health.[23] This is in line with the recent ESC guidelines on CVD prevention that recommend at least 30 minutes of moderate activity per day 5 days a week, or 20 minutes of intensive activity 3 days a week.[2] The World Health Organization defines sufficient physical activity as meeting or exceeding 30 minutes of moderate activity five times a week or 20 minutes of vigorous activity three times a week, or equivalent.[23] This translates to about 2 hours (120 minutes) training per week for sportsmen on top of the usual daily physical activities. We hypothesized that middle-aged men with ideal CVH who have exercised regularly (≥2 hours per week) and consistently since adolescence are more likely to have no coronary atherosclerosis ('perfect coronary arteries'). We set out to determine the impact of lifelong exercise and ideal CVH on the occurrence of CAD assessed by cardiac CT in asymptomatic sportsmen ≥45 years with a low ESC SCORE risk.

METHODS

This is a post-hoc analysis of the Measuring Athlete's Risk of Cardiovascular events (MARC) study whose rationale and results have been published.[10,24] MARC evaluated the additional value of CACS and coronary CT angiography (CCTA) to a routine Sports medical evaluation (SME), including resting and exercise electrocardiography, in asymptomatic sportsmen aged 45 years and older. Eligible participants were engaged in competitive or recreational sports, had a normal SME and no known CVD. Exclusion criteria were an abnormal SME (according to the responsible physician), contrast allergy and renal impairment. The medical ethics committee approved the study and all participants provided written informed consent before participation. The study was conducted according to the Declaration of Helsinki.

Assessment of ideal CVH and lifelong physical activity

Cardiovascular health was scored by using the seven metrics of the AHA. Information on current or past smoking, BMI, physical activity, cholesterol level and BP was obtained during the SME.

Information on dietary intake was not routinely obtained and by excluding diabetics we assumed that all participants were at goal level for blood glucose. The CVH score was scored as dichotomous variables, with a score of one indicating the AHA ideal category (versus zero for non-ideal metric). The CVH score could vary from zero to a maximum of six (excluding diet). As the presence of a maximum score of CVH in adults is rare,[20, 21, 25, 26] for the purpose of this study we considered participants with a CVH score ≥ 5 to have an ideal CVH.

MARC-participants filled in a questionnaire regarding lifelong physical activity derived from Friedenreich et al. that measures frequency and duration of each type of physical activity over a lifetime.[27] Based on the self-reported exercise history we categorized participants in two groups: lifelong exercisers (at least two hours of training per week per decade starting from 12 years of age) and non-lifelong exercisers (less than two hours per week per decade, for example participants who only started exercising on a regular basis in their thirties). Occupational and daily activity activities such as cycling to work, walking and climbing stairs were not taken into consideration.

Cardiac Computed Tomography

Participants underwent a low dose cardiac CT using a 256-slice CT scanner (Philips Healthcare, Best, The Netherlands) with prospective electrocardiographic gating as described previously.[10] A non-contrast CT was acquired to calculate the CACS (scan parameters 120 kV, 60mAs), followed by CCTA. The total average radiation dose was 3.9±0.9 mSv (1.0±0.4 mSv for CACS and 3.0±1.2 mSv for CCTA). CT scans were processed on a workstation (IntelliSpace Portal, Philips Healthcare) by experienced technicians, and assessed by two experienced cardiac radiologists who were blinded to the SME findings and exercise levels. The AHA modified 16-segment coronary artery model was used to analyse plaque and CACS characteristics per segment.[28] Those with a CACS of 0 Agatston Units (AU) and no plaques on CCTA were considered to have perfect coronary arteries.

Statistical analysis

Student's t test was used for differences between groups and proportions between groups were compared by means of chi-square test. A 2x2 contingency table was constructed to examine the frequencies and percentages of participants having ideal cardiovascular and/or were lifelong exercisers. The percentages of participants with perfect coronaries were given for each category. Logistic regression analysis with adjustment for age was performed to estimate the odds ratios of having no perfect coronaries. Statistical significance was defined as a two-sided p-value < 0.05.

The SPSS 20.0 (SPSS Inc., Chicago, IL, USA) statistical software package was used for all calculations.

RESULTS

300 (94%) of all 318 MARC participants had a low ESC SCORE risk, conferring a 10-year cardiovascular mortality risk less than 5%. These 300 MARC participants (mean age 54.3 ± 6.3 years) were fit (mean exercise capacity of 315 Watts on bicycle ergometry) and 135 (45%) had ideal CVH (i.e. fulfilling ≥ five components of the AHA simple seven).

Table 1. Characteristics of lifetime exercisers versus non-lifetime exercisers.

Characteristic	All	Lifetime exercisers	Non-lifetime exercisers	*p*-value
N	**283**	**112**	**171**	
Age (years)	54.3±6.3	54.0±5.9	54.7±6.5	0.2
Height (m)	1.83±0.07	1.83±0.06	1.82±0.07	0.9
Weight (kg)	83±10.7	84±11	83±11	0.9
BMI (kg/m2)	24.8±2.7	25.1±2.7	24.7±2.8	0.9
SBP (mmHg)	128±12	128±13	128±12	0.9
DBP (mmHg)	80±9	79±9	80±8	0.6
Hypertension, n (%)	17(6)	7(6)	10 (6)	0.9
Current smoker, n (%)	7(2)	4(4)	3(2)	0.4
Former smoker, n (%)	102(36)	42(38)	60(35)	0.5
Diabetes, n (%)	-	-	-	
Family history of CAD, n (%)	87(31)	32(29)	55(32)	0.5
Lipid lowering medication, n (%)	15(5)	4(4)	11(6)	0.3
Total cholesterol (mmol/l)	5.4±0.8	5.3±0.8	5.4±0.9	0.6
Ideal cardiovascular health, n (%)	130(46)	55(49)	75(44)	0.4
Exercise tolerance (Watt)	315±47	324±40	311±45	0.4
Current training volume (h/wk)	3.0 [2.25-4.75]	3.6[2.6-4.8]	3.0[1.75-4.00]	0.6
Perfect coronary arteries n (%)	104(37)	43(38)	61(36)	0.5
CACS >0(%)	143(51)	53(47)	90(53)	0.2
CACS ≥ 100AU	43(15)	21(19)	22(13)	0.18
Obstructive CAD n (%)	14(5)	7(6)	7(4)	0.4

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CAD, coronary artery disease; CACS, Coronary artery calcium score.
*ideal CVH defined as fulfilling at least 5 out of 7 American Heart Association (AHA) health metrics. (no current or past smoking, BMI <25 kg/m², physical activity at goal level, healthy diet, untreated total cholesterol <5.17 mmol/l, untreated blood pressure <120/80 mmHg and untreated fasting glucose <5.6 mmol/l). Data are presented as mean ± SD, proportions (%) or median values (interquartile range i.e. 25th and 75th percentile). P-value calculated with or Pearson $\chi 2$ or Fisher's Exact Test (two sided) where appropriate, (or Mann Whitney U for non-parametric) between lifetime exercisers and non lifetime exercisers groups.

Those with non-perfect coronaries were older, more likely to be (former) smokers, have hypertension, a family history of CAD, higher cholesterol levels and to be on lipid lowering medication and consequently the prevalence of ideal CVH was significantly higher in those with perfect coronaries (52% versus 41%, p = 0.04) (see appendix).

A complete lifelong physical activity questionnaire was returned by 283 (94%) of 300 participants, whose characteristics are provided in Table 1. Of these 283 sportsmen, 130 (46%) had ideal CVH, 112 (40%) were considered lifelong exercisers, and 104 (37%) had perfect coronaries. In these fit sportsmen with a low ESC SCORE risk, the cardiovascular risk profile of lifelong exercisers (n = 112) was not different from that of non-lifelong exercisers (n = 171). The prevalence of CAD was similar in both groups, whether looking at any plaque on CCTA (62% versus 64% p=0.5) or the presence of any CAC, i.e. CACS > 0 (47% versus 53% p=0.2).
Almost half (47%) of lifelong exercisers with ideal CVH (n=55) had perfect coronary arteries (i.e. a zero CACS and no plaques on CCTA), compared to 30% of lifelong exercisers without ideal CVH (n=57) (Table 2).

Table 2. Prevalence of perfect coronary arteries

Characteristic	Lifetime exercisers (n=112)	Irregular exercisers (n=171)
Ideal CVH (n=130)	47% (n=55)	35% (n=75)
Non ideal CVH (n=153)	30% (n=57)	32% (n=96)

For non-lifelong exercisers with (n=75) and without (n=96) ideal CVH the prevalence of perfect coronaries was 35% and 32%, respectively. Compared to the remainder of the cohort, the likelihood of having perfect coronary arteries was 70% higher in lifelong exercisers with ideal CVH (age-adjusted OR 1.70 95% CI 1.01-2.69).

DISCUSSION

In this study of fit middle-aged men engaged in competitive or recreational sports ideal CVH was associated with perfect coronaries, but we found no differences in the prevalence of CAD between lifelong exercisers and non-lifelong exercisers. Overall, 37% of fit sportsmen ≥45 years with a low ESC SCORE risk had perfect coronaries. Almost half of lifelong exercisers with ideal CVH had perfect coronary arteries, with a 70% higher chance of having perfect coronaries than the remainder of the group. Although the cardiovascular risk profile of lifelong exercisers was not better than that of non-lifelong exercisers, the combination of aspiring to ideal CVH and performing regular sports at an easily attainable level seems to work best for prevention of development of CAD.

Cardiovascular health and coronary artery disease

Since the publication of the simple seven, the prevalence of ideal CVH has been studied in several populations. In developed countries the presence of truly ideal CVH in adults is rare, often <1%.[25, 26] In fact, in the United States, fewer than half of all adolescents have preserved ≥ five of the seven metrics at ideal levels.[29] The same accounts for our population of fit, asymptomatic sportsmen ≥45 years in whom dietary info was not available, of whom only 45% achieved at least five out of six ideal health metrics.

Our observation that ideal CVH is associated with less subclinical CAD is consistent with previous studies among individuals of different ages and ethnicities. A strong inverse relationship between ideal CVH metrics and prevalent CAC was demonstrated in a cohort of 1731 predominantly white men and women without known CAD from the National Heart, Lung, and Blood Institute Family Heart Study.[19]

In the Cooper Center Longitudinal Cohort, the presence of subclinical CAD (assessed with CACS) in 3121 asymptomatic men and women (mean age 53.9 and 61.7 years, respectively) without known CVD was significantly lower in those with ideal CVH.[20] Notably, the percentage of no detectable CAC in those with more favourable CVH (defined as 4–7 ideal CVH metrics) in this asymptomatic population was higher than in our athletic population: 61% had no detectable CAC, compared to 49% in our athletic population.

A recent cross-sectional study in a Chinese population aged >40 years also found that those with better CVH metrics had a lower prevalence of subclinical atherosclerosis as determined by the CACS.[30] These results support the hypothesis that ideal CVH is important in the prevention of atherosclerosis in the general population. Our study extends the association between favourable CVH metrics and less CAD to the group of middle-aged sportsmen with a low SCORE risk.

Lifelong exercise and occult coronary artery disease

Lifelong exercisers in our study of asymptomatic sportsmen did not have a better cardiovascular risk profile, whether looking at traditional risk factors, ideal CVH or subclinical CAD, than those who were not lifelong exercisers. Moderate-intensity exercise is recommended to reduce the risk of CVD morbidity and mortality e.g. by favourably influencing major risk factors for CAD including BP, serum triglycerides and insulin resistance. [31-33] The optimal amount of exercise to prevent CVD is a matter of debate, given the possibility that there may be deleterious effects of extreme, prolonged exercise.[34, 35] In a recent study, although many male master endurance athletes with a low atherosclerotic risk profile had zero CACS, there was an overall increased coronary plaque burden compared to sedentary males with a similar profile. The male master athletes had more calcific plaque and higher CACS on CT, and more myocardial fibrosis as shown by late gadolinium enhancement on cardiac magnetic resonance imaging.[35]

A study of middle-aged marathon runners in Germany also found higher than expected CACS rates, 36.1% of them had CACS ≥100 AU compared to 21.8% of Framingham Heart Risk Score matched controls, even though these marathon runners generally had low levels of atherosclerotic risk factors. Surprisingly, during follow up, the CV event rates in these marathoners were equivalent to those in a population with established CAD and therefore frequent marathon running may not protect these athletes from the risk of coronary events.[9]

Similarly, American men who completed ≥1 marathon per year over the previous 25 years demonstrated higher than expected levels of CAC and coronary plaque volume.[36] In addition, the long-term marathoners had significantly more calcified plaque volume than sedentary controls.

In the MARC study we recently demonstrated that the most active sportsmen have overall more atherosclerotic plaque, including more calcified plaque, than sportsmen who train less intensively.[37] Despite this finding and inclusion of these very active sportsmen in this analysis, our results still show that sportsmen who have exercised regularly (≥2 hours per week) and consistently since adolescence and have aimed to maintain ideal CVH have less formation of any form of plaque at middle-age.

In contrast to the beneficial effect of moderate long-term exercise, intense long-term training may therefore be associated with accelerated coronary atherosclerosis. Possible mechanisms include (1) increased mechanical stress on the vessel wall altering coronary artery flow dynamics and ultimately accelerating atherosclerosis with long term (lifelong) exercise and (2) elevated parathyroid hormone levels increasing circulating calcium values, which could accelerate the process of atherosclerosis.[38, 39]

Limitations of our study included its cross-sectional design: we only recorded the CVH metrics at one time point and can therefore not fully account for changes over time. Second, we included a selected population with only Caucasian men, therefore our results are not directly generalizable to other ethnic groups or women. A recent study showed no differences in plaque morphology between athletic and sedentary women.[35] Third, we used five as a cut-off and could only measure six of the seven measures of ideal CVH. However, given the known low prevalence of meeting seven metrics of ideal CVH this seems a reasonable approach. Fourth, our study has the potential of response and recall bias as participants were asked to fill in a questionnaire regarding their lifelong exercise patterns. We expect this bias to be similar across all participants.

In conclusion, the combination of ideal CVH and regular exercise over a lifetime identifies middle-aged sportsmen with a higher chance of having perfect coronaries. Aspiring to ideal CVH and lifelong sports at an easily attainable level seems beneficial for prevention of development of CAD, and consequently a lower risk of a (sports related) cardiac event.

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CHAPTER 9

Summary and general discussion

Nederlandse samenvatting (Summary in Dutch)

SUMMARY

This thesis addresses the role of cardiac CT (CCT) imaging to identify occult coronary artery disease (CAD) in asymptomatic middle-aged sportsmen. Exercise related cardiac arrest is a devastating event with a large societal impact that invariably leads to calls for screening of sportsmen. These events occur mainly in men 35 years or older, often >45 years, and are most often caused by CAD.[1, 2] The incidence of exercise related cardiac arrests in the Netherlands in men >35 years of age is 5.8 per 100.000 per year, with approximately 50% surviving the event.[1] These infrequent events should not distract from the overwhelmingly positive effects of regular exercise.[3, 4] The growing popularity of endurance sports in an aging population will result in a large pool of older athletes.[5]

Although exercise related events in older athletes are largely caused by CAD, exercise may rarely trigger sudden cardiac events in the younger athlete (<35 years) harbouring asymptomatic cardiac disease, such as cardiomyopathy, electrical heart disease or a malignant coronary anomaly.[6-9] Despite the rare occurrence of cardiac arrests in young athletes (approx. 1 per 100.000 athletes per year) in 2005 the study group of sport cardiology of the European Society of Cardiology (ESC) recommended mandatory preparticipation screening of athletes aged 35 years or younger.[10] It would make more sense to direct screening efforts at older athletes as they have a higher risk of acute cardiac events. The 2011 ESC position paper on cardiovascular evaluation of middle-aged/senior individuals engaged in leisure time sports activities advocates the use of maximal exercise testing.[11] Adding maximal exercise testing to the cardiovascular evaluation of middle-aged/senior athletes, as advocated by the ESC, may be useful to identify some persons at high risk, by detecting a physiologically significant coronary artery stenosis.[12] Although several studies indicate that asymptomatic men with an abnormal exercise test receive the greatest benefits of interventions to reduce risk factors[13, 14] both resting and exercise electrocardiography have a low predictive value (high false negative rate) for CAD in asymptomatic individuals. Exercise testing is still frequently performed during a sports medical evaluation (SME).[13, 15] This is partly attributable to the fact that the results of exercise testing will also provide information on cardio respiratory fitness relevant to recommendations for subsequent training programs. As CAD is by far the most common cause of exercise related cardiac arrests, the main objective of preparticipation screening of the older athlete is to identify those with significant occult CAD, carrying a high risk for future cardiovascular events.[4, 16] Therefore, imaging of the coronaries has significant potential to improve risk stratification.[4]

The aim of this thesis was to investigate the added value of CCT (non-contrast CT for coronary artery calcium scoring (CACS) and contrast-enhanced CT for coronary CT angiography (CCTA)) to routine SME for detecting significant CAD in asymptomatic male sportsmen, aged ≥45 years, without known cardiovascular disease.

THESIS RESULTS

In **chapter 2** we presented a scoping review of studies that have evaluated cardiac imaging to detect CAD in asymptomatic sportspersons aged 35 years and older, and discussed the potential of cardiac imaging and the knowledge gaps. Only 14 papers investigating the role of imaging to detect CAD in middle-aged athletes have been published. These papers were often in highly selected groups such as multiple marathon runners, several papers used data from the same cohort, and few women were included. We concluded that CCT holds the highest potential for use in preparticipation screening, and that CCT will likely to lead to a more reliable risk assessment and better guidance to managing sportspersons found to have significant occult CAD to prevent (exercise related) cardiovascular events. However, no randomized studies, e.g. comparing CCT with exercise testing, have been conducted in asymptomatic athletes. We concluded that the relatively low number of relevant articles indicates a need for future research on this topic, particularly addressing the large group of recreational athletes (both men and women) rather than elite athletes.

Chapter 3 provided the rationale and design of the Measuring Athlete's Risk of Cardiovascular events (MARC) study. Our hypothesis was that CCT is likely to lead to a more reliable risk assessment and will give guidance to managing sportsmen found to have occult CAD to prevent (exercise related) cardiovascular events.

In **chapter 4** we investigated the additional value of pulse wave velocity (PWV) measurements to identify CAD in a subgroup of 193 MARC-participants. Increased arterial stiffness measured by means of PWV is an established marker of subclinical atherosclerosis and has been shown to be an independent predictor of cardiovascular mortality in various populations.[17-19] If PWV measurements correlate well with CAD on CCT, PWV measurements could serve as a readily available, low-cost test in the SME setting identifying those most likely to have CAD on CCT.

We found that the additional value of PWV evaluated with the Arteriograph device to identify CAD was limited when information on established risk factors was available.

However, PWV measurements may still have a role in the routine SME of middle-aged sportsmen to help identify those at a higher risk for relevant CAD given the fact that not all traditional risk factors such as cholesterol are always available. We concluded that larger studies of asymptomatic sportsmen in the SME setting are required to investigate if functional arterial measurements can have added clinical value for cardiovascular risk stratification.

In **chapter 5** we explored the potential for CT radiation dose reduction. CT radiation protection and dose reduction are important issues in the evaluation of asymptomatic persons. As individuals referred for CCTA commonly undergo a separate non-contrast CT for coronary artery calcium scoring (CACS) prior to CCTA, both non-contrast and CCTA studies add to the total radiation dose. A separate non-contrast CACS scan would be unnecessary if CACS could be adequately quantified from CCTA, thus reducing the radiation dose. Although prior studies have shown that CAC can be quantified on CCTA at routine radiation dose levels,[20-22] this has neither been demonstrated for low dose CCTA nor for iterative reconstruction algorithms. Iterative reconstruction is an alternative CT reconstruction method to standard filter back projection (FBP) that reduces noise without loss of spatial or contrast resolution, thereby enabling reduction in radiation dose with image quality comparable to higher dose scans.

We assessed whether CACS can be performed on low-radiation dose CCTA by determining calcification volumes, derived with a semi-automatic software package. Calcification volumes were reconstructing from the raw CCTA data using FBP, and hybrid (HIR) and model-based (MIR) iterative reconstruction techniques. In this way, we could evaluate whether these novel noise-reducing techniques improve CAC quantification on low-dose CCTA.

We found that CAC quantification on low radiation dose CCTA is feasible and shows the best results when MIR is used to reduce noise. We assessed what percentage of participants were reclassified using the following risk classification of Agatston scores: very low risk (0), low risk (1–10), moderate risk (11–100), moderately high risk (101–400), high risk (401–1000), and very high risk (>1000). At a cut-off calcium threshold of >600 HU with MIR, only 9% of individuals were reclassified, as compared to 19% with FBP and 23% with HIR. Our findings imply that CACS can be obtained from CCTA using iteratively reconstructed low radiation dose CCTA without the need for a separate non-contrast scan. However, further refinement is necessary before this can be implanted in daily routine, as the semi-automated software still required substantial manual correction. Alternatively, recent studies have shown that HIR and MIR can also be used to lower the radiation dose of the non-contrast CACS scan.[23]

In **Chapter 6** we provided the main results of the MARC study that demonstrate the superiority of CCT over exercise testing to detect occult CAD in 318 older sportsmen (mean age 54.7 ± 6.3 years) with a normal SME. In this low risk population of middle-aged sportsmen, of which 96% had a ESC score risk lower than 5%, CCT detected relevant CAD in almost one of every five participants with a normal exercise test (mean exercise tolerance 314 Watt); reclassifying these persons to a higher risk of developing symptomatic cardiovascular disease. We also demonstrated that 87% of these abnormalities can be detected with CACS alone. CACS is an established and robust indicator of the risk of cardiovascular events, even in individuals with few or no risk factors.[24 25]

The estimated number needed to screen (NNS) in the MARC population, 183 with CACS alone or 159 with CACS combined with CCTA, to prevent one cardiovascular event in the next five years conditional on statin treatment, is low compared to that of other accepted screening tests such as mammography to prevent a death from breast cancer in women aged 50-59 years (NNS 2451),[26] or to prevent a cardiovascular event in persons with mild to moderate hypertension (140 - 160 mmHg) (NNS 279).[27] We concluded that CCT is likely to lead to a more reliable risk assessment and will give guidance to managing sportsmen found to have relevant occult CAD to prevent future (exercise related) cardiovascular events.

Chapter 7 examined the psychological impact of cardiovascular screening with CCT in the MARC-cohort. Positive results on CCT, either relevant CAD or incidental findings such as a lung nodule, may lead to additional testing and possibly treatment. This may cause anxiety and psychological harm. We found no relevant psychological distress in 275 of the 318 asymptomatic middle-aged sportsmen who underwent cardiovascular preparticipation screening with CCT and returned the questionnaire, irrespective of whether they were found to have CAD or not. The mean Impact of Event Scale score (a set of 15 questions that can measure the amount of distress associated with a specific event), assessed on average sixteen months after the CCT was performed, was slightly higher in the 48 participants with CAD, but did not reach the threshold of clinical relevance. Transient anxiety, directly after being informed about the results, was significantly more frequent in those diagnosed with CAD. Nearly all (93.8%) were satisfied with their participation and would recommend pre-participation screening to others (93.1%). Participants reported numerous benefits, including feeling safer exercising and positive lifestyle changes, especially in those with CAD. Our findings confirmed the results of two earlier studies that found no association between cardiovascular screening and psychological distress in younger athletes,[28, 29] and extend this observation to middle-aged recreational sportsmen who underwent CCT in addition to the routine SME.

Recent research demonstrated that traditional cardiovascular risk scores and exercise testing do not reliably identify CAD in asymptomatic sportsmen.[30] In 2010 the American Heart Association (AHA) developed the concept of ideal cardiovascular health (CVH) to reduce mortality related to cardiovascular disease (CVD). In contrast to traditional cardiovascular risk scores this concept takes into account physical activity, diet and previous exposure to risk factors, such as former smoking.[31] Individuals with a favorable ideal CVH score have a lower prevalence of CAC and ideal CVH metrics are associated with substantially lower CVD and all-cause mortality.[32, 33]

In **chapter 8** we tested the hypothesis that middle-aged men with ideal CVH who have exercised regularly, i.e. training at least 2 hours per week since adolescence, are more likely to have no CAD ('perfect coronary arteries'). We determined the impact of lifelong exercise and ideal CVH on the occurrence of CAD assessed by CCT in 283 asymptomatic sportsmen ≥45 years with a low ESC SCORE risk (0-4%). The likelihood of having perfect coronary arteries was 70% higher in lifetime exercisers with ideal CVH, even though the cardiovascular risk profile of lifetime exercisers was not better than that of non-lifetime exercisers.

Notwithstanding the relationship of lifelong exercise and ideal CVH to the presence of perfect coronaries, 53% of lifelong exercisers with ideal CVH were found to have at least some degree of CAD (defined as CACS > 0 or any plaques on CCTA).

GENERAL DISCUSSION

Interpretation of results

The main goal of this thesis was to assess the added value of CCT to the current preparticipation strategies (routine sports medical testing, including resting- and exercise-electrocardiography (ECG), and SCORE risk) in asymptomatic older sportsmen with a low cardiovascular risk score, by determining the prevalence and severity of CAD, the leading cause of exercise related cardiac events. More than one third (36.8%) of 318 fit, asymptomatic sportsmen with a normal SME had perfect coronaries (defined as no evidence of CAD whatsoever on CACS or CCTA), while 18.9% had relevant disease (CACS ≥ 100 AU and/or ≥ 50% luminal stenosis on CCTA). It follows that occult CAD in asymptomatic middle-aged sportspersons cannot reliably be detected with the assessment of medical history, CV risk profile and (exercise) ECG. The CCT caused no relevant psychological distress to the participants, the vast majority of whom were satisfied with their participation.

In the absence of documented ischemia the management of asymptomatic (sports)persons found to have occult CAD cannot be readily based on current guidelines and thus remains a source of debate.[34] In addition to lifestyle advice and aggressive risk factor modification, including lipid lowering with statins, it appears prudent to counsel asymptomatic athletes with occult CAD with regards to their sports activities.[34-36] We recommended our participants with relevant CAD to continue sporting on a recreational level but to refrain from intense activities, such as running marathons, and to promptly search medical attention in case of symptoms or unexplained deterioration of their condition.

The main strength of our thesis is that it is the first to assess the additional value of CCT (both CACS and CCTA) in a large, relatively unselected group of asymptomatic older sportsmen, where previous imaging studies have predominantly addressed elite athletes (e.g. multiple marathon runners). A striking one in five asymptomatic middle-aged athletes with a normal SME had relevant CAD, and 87% of these abnormalities can be detected with CACS alone.

CACS is a useful tool to stratify risk in asymptomatic persons with a low CV risk by means of traditional CV risk score.[37] This was underscored by an analysis from the Multi-Ethnic Study of Atherosclerosis (MESA) that used CACS to further stratify risk in individuals eligible for the JUPITER study (low risk population, statin use for primary prevention) to identify those expected to derive either the most or the least absolute benefit from statin treatment.[38, 39]

Nearly 75% of all coronary heart disease (CHD) events occurred in the 25% of participants with CACS ≥ 100, whose event rate was 16.6 per 1000 person-years compared to <1 in persons with CAC = 0 (Hazard ratio 27.8 (95% CI: 5.97-128.8)).

Based on the results of MARC study a conservative estimate of the five-year NNS with CACS to prevent one cardiovascular event with statin treatment was 183, appreciably lower than the NNS for other accepted screening strategies.[40]

Athletes may show less compliance with statins because of myopathy side effects.[34] In the light of recent studies that found no association between statin use and exercise or tendon-, ligament-, and muscle-related injuries in runners and no effect of atorvastatin 80 mg daily on muscle strength or exercise performance over 6 months of treatment in healthy subjects, this concern seems to be unjustified [35, 36]

Future perspectives

Although a considerable proportion of asymptomatic athletes aged ≥45 years with a normal SME was found to have CAD, at this stage no firm recommendations can be made regarding the routine use of CCT in the preparticipation evaluation of older sportsmen. Introduction of new diagnostic test mandates a thorough cost-benefit analysis, particularly when used as a screening tool in asymptomatic persons. Given the limited additional value of CCTA (that involves extra time, costs, radiation exposure and the necessity of intravenous contrast) to CACS in the MARC study, the use of CACS in asymptomatic sportsmen should be the focus of future studies.

Long-term follow-up of our cohort as well as other cohorts of athletes needs to show whether the atherosclerotic burden in athletes confers a similar risk as in the general population.

There is a paucity of cardiac imaging information in older sportswomen. The little data available, showing striking differences in CAD prevalence between male (high) and female (low) long term extreme marathon runners,[41, 42] are intriguing and may provide a clue to help explain the well documented 10 fold lower incidence of exercise related cardiac arrest in women.[1, 2]

One randomized study (Early Identification of Subclinical atherosclerosis by NoninvasivE imaging Research (EISNER)) to date in 2137 asymptomatic persons (52.5% men, mean age 58.5 ± 8.4 years) demonstrated that CACS results in a better CV risk profile at no increase of medical costs.[43]

Cardiovascular outcome trials in asymptomatic persons typically involve thousands of participants (e.g. 17,802 in the Jupiter primary prevention study).[44] The costs and logistics involved preclude similar trials in asymptomatic sportspersons, even if targeting only those found to have a CACS ≥ 100 AU. A more feasible alternative would be to adapt an EISNER-like approach, randomizing a considerable amount of individuals (for instance the same number as the EISNER study) to a SME with or without CACS and assign those with a CACS above 100 to aggressive preventive treatment with a potent statin, looking at surrogate measures of hard CV outcomes and costs of downstream testing and treatment in both groups.

Exercise; can there be too much of a good thing?

The benefits of exercise are irrefutable. Individuals engaging in regular exercise have a favorable cardiovascular risk profile and reduce their risk of myocardial infarction by up to 50%.[45] Exercise promotes longevity, reduces the risk of some malignancies, retards the onset of dementia, and is considered an antidepressant. The American Heart Association (AHA) recommends 150 minutes of moderate-intensity aerobic exercise, or 75 minutes of vigorous-intensity aerobic exercise, per week for overall cardiovascular health, but the optimal amount of exercise for CVD prevention remains a matter of debate.[46]

Recent studies suggest there may also be too much of a good thing, with long-term extreme exercise coming at a price of progression of CAD, myocardial fibrosis and arrhythmias. [42, 46-48]

Studies of master endurance athletes reported adverse clinical outcomes in athletes who perform exercise volumes at the extreme upper end of the physical activity continuum.[30, 49, 50] The German marathon study found an unexpectedly high rate of relevant CAD (36.1 % had CACS ≥ 100 AU) in a group of 108 marathon runners with a low]Framingham Risk Score.[30] The results of the MARC study are consistent with the hypothesis that traditional CV risk scores underestimate the rate of CV events in the growing group of middle-aged sportsmen.[30] The impact of extreme volumes of exercise on cardiovascular health is still under debate, with speculations that the higher CACS may reflect stabilization of existing plaques which might be beneficial,[51] versus other observations that raise the possibility that high doses of exercise may have deleterious cardiac effects.[48, 52, 53]

The fact that very physically active individuals may have substantial, asymptomatic CAD and the hypothesis that high amounts of (lifelong) exercise may actually increase the risk of CV events require further examination, e.g. by looking at the dose (amount of lifetime exercise) response

(CAD on CCT) relationship and prospective CCT evaluation of large groups of middle-aged athletes in whom by sheer magnitude most cardiac events will occur.

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CHAPTER 9

Summary and general discussion

Nederlandse samenvatting (Summary in Dutch)

SAMENVATTING

Regelmatig bewegen is de beste manier om het optreden van hart- en vaatziekten voor te zijn. Dit neemt niet weg dat forse inspanning de kans op hartklachten, zoals bijvoorbeeld plotselinge hartdood, vergroot bij mensen van wie nog niet bekend is dat zij een hartaandoening hebben, bijvoorbeeld een aangeboren verdikking van de hartspier of aangedane kransslagaderen (coronarialijden).[1] Het onverwachts overlijden van (jonge) sporters leidt vaak tot ongeloof en heftige emoties. De roep om sporters preventief te screenen op een hartaandoening is na zo'n gebeurtenis nooit ver weg.

De aanbeveling uit 2005 van de European Society of Cardiology (ESC) alle sporters jonger dan 35 jaar te screenen (met anamnese, lichamelijk onderzoek en rust elektrocardiogram (ECG)) ter preventie van plotse hartdood heeft geleid tot verhitte discussies tussen voor- en tegenstanders van verplichte screening.[2-4] Plotselinge hartdood is zeldzaam bij jonge sporters (minder dan 1 per 250.000 per jaar) en mede door het negatieve advies van de gezondheidsraad is routine screening van sporters in Nederland niet ingevoerd. De recent aangepaste richtlijnen (januari 2017) zijn minder stellig in het aanbevelen van screening voor alle jonge sporters.[5]

Meer dan 90% van de sport gerelateerde hartstilstanden treedt op bij mannen: met name mannen ouder dan 45 jaar, bij wie de belangrijkste oorzaak coronarialijden is.[1, 6]

Zou men al tot screenen willen overgaan dan ligt het voor de hand de aandacht te richten op de aanwezigheid van coronarialijden in deze laatste groep. Een aanbeveling uit 2011 van de ESC richt zich op oudere sporters: naast anamnese, lichamelijk onderzoek en een rust ECG wordt voor deze groep ook ergometrie (inspannings-ECG) geadviseerd.[7] Ten aanzien van verplichte preparticipatiescreening worden geen uitspraken gedaan. De uitkomsten van het ergometrisch onderzoek zijn nuttig voor het inschatten van de conditie en het geven van trainingsadviezen, maar zijn bij klachtenvrije personen van zeer beperkte waarde voor het aantonen of uitsluiten van coronairalijden.[8, 9]

Cardiovasculaire risico-inschatting bij sporters.

Er is dan ook behoefte aan methoden om het cardiovasculaire risico van met name oudere, klachtenvrije sporters beter in te schatten. Het risico op cardiovasculaire gebeurtenissen wordt traditioneel bepaald met behulp van zogenaamde risicoscores, zoals de Framingham Risk Score (FRS) en Systematic COronary Risk Evaluation (SCORE).[10] SCORE, ontwikkeld door de ESC, gaat uit van leeftijd, geslacht, bloeddruk, cholesterolwaarde, en al dan niet roken. Het doel is een onderscheid te maken in laag, intermediair, en hoog risicogroepen: voor SCORE komt dit overeen met een geschatte 10 jaars cardiovasculaire sterfte van 0-4%, 5-9%, en 10% of hoger. Bij personen die in de hoogste risico categorie vallen is een agressief risicofactor modificerend en medicamenteus beleid geïndiceerd.

De traditionele cardiovasculaire risicoscores (FRS, SCORE) zijn mogelijk minder geschikt voor sporters: door te sporten is hun risicoprofiel waarschijnlijk verbeterd (lagere bloeddruk en gewicht, beter lipidenspectrum) en bovendien wordt de levenslange blootstelling aan risicofactoren voordat men (weer) actief werd niet meegenomen (dit is met name relevant voor oudere, herintredende sporters). In een groep van 108 recreatieve Duitse marathonlopers ouder dan 50 jaar bleek – ondanks een gunstig cardiovasculair risicoprofiel – 6,5 % een cardiovasculaire gebeurtenis te krijgen gedurende 6,5 jaar follow-up.[11] Alle gebeurtenissen traden op bij personen met een coronaire kalkscore hoger dan 100 Au.[12] Recenter Amerikaans onderzoek bij lange afstandslopers suggereert dat ischemie (zuurstofgebrek) van de hartspier door een tekortschietend aanbod (zogenaamde "demand ischemia") bij nog niet bekend coronarialijden een belangrijke oorzaak is van hartstilstanden.[13]

De risico-inschatting kan worden verbeterd door toevoeging van andere metingen, zoals bepalen van de hoeveelheid kalk in de coronairen.[14] Kalk in de coronairen is een uiting van coronarialijden en direct geassocieerd met het optreden van cardiovasculaire sterfte. Het bepalen van de hoeveelheid kalk (met de zogenaamde coronaire kalkscore - coronary artery calcium score (CACS)) wordt in toenemende mate gebruikt om personen met een intermediair cardiovasculair risico te re-classificeren naar hoog of laag risico. In het Heinz Nixdorf Recall bevolkingsonderzoek, leidde CACS in een groep van 4327 klachtenvrije personen met een intermediair cardiovasculair risico tot een "net reclassification improvement (NRI)" van 22% (P = 0.0003).[14]

The "Agatston Score" is de meest gebruikte methode om de hoeveelheid kalk te meten (zie tabel 1.). Referentiewaarden zijn ondermeer beschikbaar op http://www.mesa-nhlbi.org/Calcium. [15] Tot op heden is de toegevoegde waarde van CACS bij klachtenvrije sporters die een routine preventief sportmedisch onderzoek ondergaan niet onderzocht.

Absolute waarde (Agatston units)	*Classificatie*	*Risico op cardiovasculaire gebeurtenis*
0	Afwezig	Zeer laag
>0<10	Minimaal	Laag
≥10 <100	Mild	Gemiddeld
≥100 <400	Matig	Matig
≥400<1000	Ernstig	Hoog

Tabel 1. Coronaire calcium score (CACS).[16]

De snelle ontwikkeling van de minimaal invasieve CT beeldvorming van het hart maakt het mogelijk niet alleen de CACS te bepalen, maar ook een uitspraak te doen over de aanwezigheid, het aspect (zachte, harde of gemengde plaques) en de mate van coronarialijden (waarbij een stenose van meer dan 50% als significant wordt beschouwd).[17, 18] De stralenbelasting van dit onderzoek bedraagt zo'n 2 millisievert (mSv), vergelijkbaar met de jaarlijkse hoeveelheid achtergrondstraling in Europa.[17]

Behandeling van klachtenvrije personen met een hoog risico op cardiovasculaire gebeurtenissen.

De advisering en behandeling van klachtenvrije personen met een hoog cardiovasculair risico is gebaseerd op (inter)nationale richtlijnen.[19, 20] Alhoewel de toegevoegde waarde van CACS bij het bepalen van cardiovasculair risico bewezen is, zijn (nog) geen gerandomiseerde geneesmiddelen onderzoeken gerapporteerd die het effect van CACS op harde uitkomsten (sterfte, cardiovasculaire gebeurtenissen) hebben onderzocht.[21] Het EISNER onderzoek dat randomiseerde naar wel of geen CACS bij klachtenvrije personen heeft aangetoond dat degenen die wel een CACS kregen 4 jaar nadien een beter cardiovasculair risicoprofiel hadden, zonder dat dit ten koste ging van hogere gezondheidszorgkosten in deze groep (bijvoorbeeld door extra onderzoek naar aanleiding van de bevindingen bij CACS).[22]

Waar tot op heden een Agatston score boven 400 Au wordt gebruikt om te re-classificeren naar hoog cardiovasculair risico, gaan op grond van recentere analyses uit het MESA onderzoek stemmen op de grens om te re-classificeren te verlagen naar een Agatston score van 100 Au.[23, 24]

De geschatte 5 jaars 'number needed to treat' (NNT) om een cardiovasculaire gebeurtenis te voorkomen door behandeling met een statine (een cholesterol verlagend medicijn) van klachtenvrije deelnemers aan het MESA onderzoek met een CACS ≥100 bedraagt 19. Dit is een laag getal voor een behandeling uit primair preventief oogpunt. Deze analyse is in lijn met de recente onderzoeken die suggereren dat ook bij laag risicopatiënten behandeling met statines zinvol is.[24] Voor bloedplaatjesremmers (ascal) lijkt geen rol meer weggelegd in de primaire preventie van hart- en vaatziekten.[25]

Al met al zijn sportgerelateerde hartstilstanden mogelijk te voorkomen door de gevoeligheid van preventief sportmedisch onderzoek voor coronarialijden te vergroten.

Het voornaamste doel van dit proefschrift is bij klachtenvrije sporters de waarde van CT beeldvorming (zowel met als zonder toediening van contrastmiddel) van de kransslagaderen te onderzoeken. Enerzijds ter voorkoming van sport gerelateerde hartstilstanden bij sporters die coronarialijden blijken te hebben en anderzijds, gezien de hoge negatief voorspellende waarde van het CT onderzoek van de coronairen, of dit de deur opent naar een snelle, betrouwbare non-invasieve mogelijkheid om coronarialijden uit te sluiten. Dit is vooral van belang voor sporters bij wie, bijvoorbeeld op grond van dubieuze ("vals-positieve") bevindingen bij ergometrie, een verdenking op coronarialijden is gerezen. In deze gevallen is direct grijpen naar invasief onderzoek (een zogenaamde hartcatheterisatie) niet gewenst.

Dit proefschrift

Hoofdstuk 2 betreft een review waarin we de bestaande literatuur inzake beeldvorming van coronarialijden bij klachtenvrije sporters van 35 jaar en ouder hebben geanalyseerd. De belangrijkste conclusie is dat de weinige onderzoeken (slechts 13 manuscripten) op dit gebied meestal zijn uitgevoerd in zeer geselecteerde groepen (meer dan 95% mannen en grotendeels duursporters). Op basis van de huidige literatuur lijkt cardiale CT het meeste potentieel te hebben als beeldvormende techniek. Er zijn echter geen gerandomiseerde onderzoeken voorhanden.

Het lage aantal relevante artikelen wijst op de noodzaak voor verder onderzoek, met name gericht op de groeiende groep recreatieve sporters (zowel mannen als vrouwen).

In **hoofdstuk 3** beschrijven wij de achtergrond en rationale van het Measuring Athlete's Risk of Cardiovascular events (MARC) onderzoek. Bij klachtenvrije, mannelijk sporters van 45 jaar en ouder, die met goed gevolg een sportmedische keuring hebben ondergaan, onderzoeken wij de waarde van een CT van het hart, zowel om de CACS te meten (zonder toediening van contrastvloeistof) als de aanwezigheid, de mate en het aspect van coronairalijden te bepalen (met toediening van contrast).

In **hoofdstuk 4** hebben we onderzocht of een meting van de arteriele stijfheid met behulp van de pulse wave velocity (PWV) de aanwezigheid van coronarialijden voorspelt in een subgroep van de MARC-populatie. In tegenstelling tot CT beeldvorming is dit vaatonderzoek goed uit voeren in een poliklinische setting, bijvoorbeeld in een sportgeneeskundige praktijk.

Anders dan in eerdere onderzoeken bij klachtenvrije personen en in laag risico groepen,[26, 27] werd voor de arteriële stijfheidsmetingen bij MARC deelnemers een beperkte toegevoegde waarde gevonden (bovenop de bekende risicofactoren) om coronarialijden te identificeren. Wel toonden onze bevindingen dat, wanneer risicofactoren zoals cholesterolwaarde niet voor handen zijn, arteriële stijfheidsmetingen mogelijk toch van nut kunnen zijn.

In **hoofdstuk 5** is de mogelijkheid onderzocht de CACS te berekenen op een standaard CT scan met contrast (CCTA), met als doel de blanco CT-scan voor het meten van de CACS over te kunnen slaan en zodoende de stralingsdosis te verlagen. Zogenaamde iteratieve reconstructie (IR) technieken, een recent geïntroduceerde stralingsdosis verlagende methode, maken dit wellicht mogelijk. Filtered back projection (FBP) is de meest gebruikte techniek om afbeeldingen te maken van CT-data, met name omdat de IR techniek meer rekenkracht nodig heeft dan FBP. Dankzij verbeterde computers kan IR nu ook worden toegepast in de klinische praktijk.

In 43 proefpersonen van de MARC-studie, die zowel een CACS CT-scan (±1 mSv) als een lage dosis CCTA-scan (±3 mSv) ondergingen, concludeerden we dat CACS kan worden bepaald met lage dosis CCTA-scans als wordt gereconstrueerd met IR. Met 'model-based' IR werd maar 9% van de patiënten foutief geclassificeerd volgens de Agatston classificatie.

Hoofdstuk 6 toont de belangrijkste resultaten van het MARC onderzoek. Bij 318 klachtenvrije sporters van 45 jaar en ouder, met een lage cardiovasculaire risicoscore, bij wie een routine sportmedisch onderzoek geen afwijkingen toonde werd een CT scan van het hart gemaakt. Hun belastbaarheid bij fietsergometrie was uitstekend (314 watt gemiddeld). De CT toonde in 60 gevallen (19%) belangrijk coronarialijden, gedefinieerd als een CACS ≥ 100 Au en/of meer dan 50% stenose in de coronairen. Op grond van de resultaten van de blanco CT scan (ter bepaling van de CACS) kon 15% (46 van de 300 proefpersonen met een lage SCORE risk) worden gereclassificeerd naar een hoog cardiovasculair risico groep.

43 proefpersonen werd geadviseerd te starten met een statine. De overige 17 proefpersonen werd geadviseerd een cardioloog te consulteren (zij met een CACS > 400 Au danwel een stenose > 50%). Van deze 17 ondergingen vier proefpersonen een dotterbehandeling van de kransvaten. In het algemeen werd aan de 17 genoemde proefpersonen geadviseerd medicatie te starten en geen extreme inspanningen meer te leveren.

Behandeling van 1000 laag risicopatiënten met een statine over een periode van 5 jaar voorkomt een cardiovasculaire gebeurtenis (hartinfarct, herseninfarct, hartdood) bij 11 van hen (number needed to treat (NNT): 91).[23] De toegevoegde waarde van non-invasieve beeldvorming met CACS blijkt uit de geschatte 5 jaars NNT van statine-behandeling van klachtenvrije deelnemers aan het MESA bevolkingsonderzoek met CACS ≥ 100 Au: de NNT is 19.

In ons onderzoek werd bij 60 van de 318 deelnemers coronarialijden gevonden (19%). Bij hen zal het behandeleffect naar verwachting vergelijkbaar zijn met dat van MESA deelnemers met een CACS ≥ 100 Au. Een conservatieve schatting van het effect van ons onderzoek is de volgende: bij 60 (19%) van de 318 deelnemers werd belangrijk coronarialijden gevonden, met een NNT van 19 worden dan >3 cardiovasculaire gebeurtenissen (een hart- of herseninfarct dan wel overlijden) voorkomen. Ter vergelijking: de NNT om 1 cardiovasculaire gebeurtenis te voorkomen in een laag risico groep met een hoge bloeddruk bedraagt 81.[28] Daarnaast is uit het eerder genoemde EISNER onderzoek bekend dat klachtenvrije mensen die behandeld worden met statines zich gezonder gaan gedragen. [22]

In **hoofdstuk 7** beschrijven we de psychologische impact van screenen met cardiale CT in onze populatie. Eerder onderzoek bij jonge professionele sporters toonde aan dat geen associatie bestaat tussen cardiovasculaire screening en het ervaren van stress.[29, 30] Evenwel wordt de psychologische belasting van de sporter genoemd als een negatief aspect van screening. Het psychologische effect van screening (met CT) was nog niet onderzocht in de leeftijdscategorie die het vaakst getroffen wordt door sportgerelateerde hartdood. Onze bevindingen bij sporters van 45 jaar en ouder waren overeenkomstig die van voornoemde onderzoeken. Ook in onze populatie was geen sprake van psychologische stress op de lange termijn door een positieve CT-uitslag, in de zin van belangrijk coronairalijden.

Sterker nog, degenen bij wie coronairalijden werd vastgesteld geven aan dat zij weliswaar liever hadden vernomen dat zij geen afwijkingen hadden, maar ook sterk gemotiveerd te zijn actie te ondernemen de kans op cardiovasculaire gebeurtenissen te verkleinen.

Het doel van **hoofdstuk 8** was na te gaan of een relatie bestaat tussen levenslange lichamelijke activiteit alsook het voldoen aan tenminste vijf van de 'ideal cardiovascular health criteria' van de American Heart Association (niet roken of meer dan een jaar geleden het roken gestaakt, een body mass index [BMI] <25 kg/m^2, voldoende lichaamsbeweging (minimaal 2,5 uur per week), een gevarieerd voedingspatroon, een totaal cholesterolwaarde < 5.17 mmol/l, een bloeddruk <120/80 mmHg en een glucose <5.6 mmol/l) en het hebben van 'schone coronairen', gedefinieerd als een CACS van 0 Au tesamen met de afwezigheid van (zachte) plaques.

MARC deelnemers die hun hele leven regelmatig sporten en voldoen aan op zijn minst vijf van de ideal cardiovascular health criteria hebben de grootste kans (70%) op schone coronairen.

Toekomstige perspectieven

Op grond van ons onderzoek bij 318 klachtenvrije mannelijke sporters van 45 jaar en ouder kunnen we stellen dat het huidige sportmedische onderzoek (inclusief inspannings-ECG) het risico op hart- en vaatziekten onderschat en dat toevoeging van een CT coronairen (met name CACS) de mogelijkheid biedt de risicoinschatting te verbeteren. Een gerandomiseerd onderzoek met lange termijn follow-up zou moeten aantonen of het toevoegen van een CT-coronairen aan het huidige sportmedische onderzoek inderdaad sport-gerelateerde hartdood kan helpen voorkomen en of dit kosteneffectief kan gebeuren.

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CHAPTER 10

List of publications

List of abbreviations

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Biography

LIST OF PUBLICATIONS

Scientific publications

The relationship between lifelong exercise volume and coronary atherosclerosis in athletes.
Aengevaeren VL, Mosterd A, **Braber TL**, Prakken NHJ, Doevendans PA, Grobbee DE, Thompson PD, Eijsvogels TMH, Velthuis BK
Circulation 2017; Apr 27. [Epub ahead of print].

No psychological distress in sportsmen aged 45 years and older after cardiovascular screening, including cardiac CT: The Measuring Athlete's Risk of Cardiovascular events (MARC) study.
Braber TL, Schurink MM, Prakken NH, Doevendans PA, Backx FJ, Grobbee DE, Rienks R, Nathoe HM, Bots ML, Velthuis BK, Mosterd A
Netherlands Heart Journal 2017;25(4):271-77.

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Braber TL, Mosterd A, Prakken NH, Rienks R, Nathoe HM, Mali WP, Doevendans PA, Backx FJ, Bots ML, Grobbee DE, Velthuis BK
European Journal of Preventive Cardiology 2016;23(15):1677-84.

Assessment of Coronary Artery Calcium on Low-Dose Coronary Computed Tomography Angiography With Iterative Reconstruction.
Braber TL, Willemink MJ, Bohte EH, Mosterd A, Leiner T, Velthuis BK
Journal of Computer Assisted Tomography 2016;40(2):266-71.

Identifying Coronary Artery Disease in Asymptomatic Middle-Aged Sportsmen: The Additional Value of Pulse Wave Velocity
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PloS One 2015;10(7):e0131895.

Rationale and design of the Measuring Athlete's Risk of Cardiovascular events (MARC) study : The role of coronary CT in the cardiovascular evaluation of middle-aged sportsmen
Braber TL, Mosterd A, Prakken NH, Doevendans PA, Mali WP, Backx FJ, Grobbee DE, Rienks R, Nathoe HM, Bots ML, Velthuis BK
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Braber TL, Reitsma JB, Mosterd A, Willemink MJ, Prakken NHJ, Halle M, Sharma S, Velthuis BK
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Perfect coronary arteries in sportsmen aged 45 years and older: the importance of lifelong exercise and ideal cardiovascular health
Braber TL, Mosterd A, Aengevaeren VL, Prakken NHJ, Bots ML, Velthuis BK
Submitted

Conference proceedings

Perfect coronary arteries in sportsmen aged 45 years and older: the importance of lifelong exercise and ideal cardiovascular health. The MARC study
Braber TL, Velthuis BK, Bots ML, Grobbee DE, Nathoe HM, Doevendans PA, Rienks R, Backx FJG, Prakken NHJ, Mosterd A
European Society of Cardiology (ESC) Congress August 2015, London, United Kingdom (poster presentation)

Asymptomatic coronary artery disease in middle-aged sportsmen with a low cardiovascular risk score: the Measuring Athlete's Risk of Cardiovascular (MARC) events study.
Braber TL, Mosterd A, Prakken NH, Rienks R, Nathoe HM, Mali WP, Doevendans PA, Backx FJ, Bots ML, Grobbee DE, Velthuis BK
American College of Sports Medicine (ACSM) annual meeting, May 2015 San Diego USA (poster presentation)

Measuring athlete's risk of cardiovascular events (MARC) study: the role of coronary CT in the cardiovascular evaluation of middle-aged sportsmen
Braber TL, Velthuis BK
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Coronary Artery Disease in Asymptomatic Male Athletes Aged 45 years or Older with a Low ESC SCORE Risk: The Emerging Role of Coronary CT Angiography
Braber TL, Mosterd A, Prakken NH, Doevendans PA, Mali WP, Nathoe HM, Bots ML, Velthuis BK
Radiological Society of North America (RSNA), December 2014, Chicago, USA (poster presentation)

Voorkomen van plotselinge dood tijdens sport, van het begin tot het eind

Braber TL, Mosterd A, Prakken NH, Doevendans PA, Mali WP, Backx FJ, Grobbee DE, Rienks R, Nathoe HM, Bots ML, Velthuis BK.

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Coronary CT in the sports medical evaluation of asymptomatic male athletes aged 45 years or older

Braber TL, Mosterd A, Prakken NH, Doevendans PA, Mali WP, Backx FJ, Grobbee DE, Rienks R, Nathoe HM, Bots ML, Velthuis BK

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Coronary Artery Disease in Asymptomatic Male Athletes Aged 45 years or Older with a Low ESC SCORE Risk: The Emerging Role of Coronary CT Angiography

Braber TL, Mosterd A, Prakken NH, Doevendans PA, Mali WP, Backx FJ, Rienks R, Nathoe HM, Bots ML, Velthuis BK

European Society of Cardiology (ESC) Congress September 2014, Barcelona, Spain (oral presentation)

Coronary Artery Disease in Asymptomatic Male Athletes Aged 45 years or Older with a Low ESC SCORE Risk: The Emerging Role of Coronary CT Angiography

Braber TL, Mosterd A, Prakken NH, Doevendans PA, Mali WP, Backx FJ, Rienks R, Nathoe HM, Grobbee DE, Velthuis BK

International Academy of Cardiology annual scientific sessions, July 2014, Boston, USA (oral presentation)

Can coronary artery calcifications be quantified on low-dose coronary CTA with iterative reconstruction?

Braber TL, Willemink MJ, Bohte EH, Mosterd A, Leiner T, Velthuis BK

Society of Cardiovascular Computed Tomography (SCCT) annual meeting, July 2014, San Diego, USA (oral presentation)

Pulse wave velocity measurement for cardiovascular risk stratification in an asymptomatic athletic population: reproducibility and impact of ct scanning

Braber TL, Prakken NH, Mosterd A, Doevendans PA, Mali WP, Nathoe HM, Rienks R, Backx FJ, Velthuis BK

EuroPrevent annual congress of the European Association of Preventive Cardiology (EAPC), May 2014, Amsterdam, The Netherlands (poster presentation)

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AHA	American Heart Association
AU	Agatston units
AUC	Area under the curve
BMI	Body mass index
CAC	Coronary artery calcium
CACS	Coronary artery calcium score
CAD	Coronary artery disease
CAG	Coronary angiography
CCS	Coronary calcium scoring
CCT	Cardiac computed tomography
CCTA	Coronary coputed tomography angiography
CI	Confidence interval
CMR	Cardiac magnetic resonance
CT	Computed tomography
CTDIvol	Volumetric computed tomography dose indices
CV	Cardiovascular
CVD	Cardiovascular disease
CVH	Cardiovascular health
DBP	Diastolic blood pressure
ECG	Electrocardiogram
ESC	European Society of Cardiology
FBP	Filtered back projection

FFR	Fractional flow reserve
FHS	Framingham heart study
FRS	Framingham risk score
HIR	Hybrid iterative reconstruction
HU	Hounsfield units
ICC	Intra class correlation coefficient
IES	Impact of event scale
IQR	Interquartile range
LGE	Late gadolinium enhancement
LV	Left ventricular
MARC	Measuring athlete's risk of cardiovascular events
MESA	Multi ethnic study of atherosclerosis
MIP	Maximum intensity projection
MIR	Model based iterative reconstruction
MPR	Multiplanar reconstruction
MPS	Myocardial perfusion scintigraphy
MRI	Magnetic resonance imaging
mSv	milliSievert
NNS	Number needed to screen
NNT	Number needed to treat
OR	Odds ratio
PCI	Percutaneous coronary intervention
PPS	Preparticipation screening

PROCAM	Prospective cardiovascular Munster study
PWV	Pulse wave velocity
ROC	Receiver operating characteristic
SBP	Systolic blood pressure
SCD	Sudden cardiac death
SCORE	Systematic coronary risk evaluation
SD	Standard deviation
SME	Sports medical evaluation
SPECT	Single photon emission computed tomography
X-ECG	Exercise electrocardiography

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CHAPTER 10

BIOGRAPHY

Thijs Braber was born on the 25th of January 1986 in Nijmegen, the Netherlands. In 2004 he graduated from high school at the Stedelijk Gymnasium in Nijmegen. The same year he started Biomedical Sciences at the Radboud University in Nijmegen. After one year he decided to move to Maastricht to pursue a career as a pro cyclist and switched to medicine school at Maastricht University in 2005. Following retirement from cycling after the 2009 season, he spent the last year of his medicine school thanks to the support of the Maastricht Cardiovascular Centre (head: prof. dr. H.J.G.M. Crijns) at the cardiology department of the Meander Medical Center Amersfoort (head: dr. P.J. Senden) where he participated in a sports cardiology research project under direct supervision of dr. A. Mosterd. After obtaining his medical degree in June 2012 he started his PhD research project at the departments of Radiology and Cardiology of the University Medical Center Utrecht under supervision of prof. dr. B.K. Velthuis, prof. dr. P.A.F.M. Doevendans, prof. dr. W.P.Th.M. Mali and dr. A. Mosterd of which the results are presented in this thesis. As of May 1st 2015 he is in training to become a cardiologist under supervision of drs. T. Slagboom and dr. J.P.R. Herrman at the department of cardiology of Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands.