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**Cardiac imaging to detect coronary artery disease in athletes aged 35 years and older. A scoping review.**

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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  $\geq 35$  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

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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  $\geq 35$  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 pre-participation 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 pre-participation 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 (Kim et al., 2012; Chugh & Weiss, 2015; Piepoli et al., 2016). Yet, exercise also transiently increases the risk of cardiovascular events, particularly in those with unknown cardiac disease (Thompson et al., 2007).

The vast majority of sports-related cardiac arrests occur in men, with a 9:1 male-female ratio (Marijon et al., 2011; Berdowski et al., 2013), increasing to 20:1 in middle-aged runners (Marijon et al., 2015). The incidence is expected to rise as a growing number of middle-aged or older individuals engage in sports, for instance marathon running (Kim et al., 2012; Chugh & Weiss, 2015). 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 (Thompson et al., 2007; Marijon et al., 2011; Berdowski et al.,

2013; Chugh & Weiss, 2015). Even in athletes aged 25 to 35 years CAD accounted for 43% of deaths in a recent US study (Meyer et al., 2012).

The traditional view that exercise-induced acute coronary events result from atherosclerotic plaque disruption and coronary thrombosis (Burke et al., 1999; Giri et al., 1999; Thompson et al., 2007; Thompson, 2005) was recently challenged by a study of cardiac arrests during long distance running (Kim et al., 2012). The absence of coronary plaque rupture in many victims suggests there may be a causal role for demand ischemia in athletes with (unknown) CAD (Kim et al., 2012). 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 (Borjesson et al., 2011). 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 (Mohlenkamp et al., 2008). Maximal exercise testing for CV evaluation of middle-aged individuals engaged in leisure time sports activities is recommended by the ESC (Borjesson et al., 2011), 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 (Siscovick et al., 1991; Braber et al., 2016).

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 scoping 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" (Grant & Booth, 2009; Rumrill et al., 2010). 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 (Grant & Booth, 2009; Rumrill et al., 2010).

### *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  $\geq 35$  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. 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. Commonly used pharmacological agents are adenosine, dipyridamole or regadenoson (vasodilator stress) and dobutamine (inotropic).

- 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:
  - o CACS: the coronary calcium burden is graded according to Rumberger et al. (1999), 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, with a moderately high risk of future CV events.
  - o 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% (Raff et al., 2009).
- 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 (Katzel et al., 1998; Hood & Northcote, 1999; Mohlenkamp et al., 2008; Nassenstein et al., 2009; Breuckmann et al., 2009; Kroger et al., 2011; Karlstedt et al., 2012; Mangold et al., 2013; Aagaard et al., 2013; Mohlenkamp et al., 2014; Schwartz et al., 2014; Tsiflikas et al., 2015; Braber et al., 2016, Roberts et al., 2016), 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 (Mohlenkamp et al., 2008; Nassenstein et al., 2009; Breuckmann et al., 2009; Kroger et al., 2011; Mohlenkamp et al., 2014).

Populations in the other papers were 19 Scottish veteran endurance athletes (Hood & Northcote, 1999), 153 marathon and long distance runners from Sweden (Aagaard et al., 2013), a US combined cohort of 70 triathletes, runners, tennis players, cyclists and cross-trainers (Katzel et al., 1998), a combined cohort of 95 triathletes, long-distance runners, cyclists, and handball players from Germany (Mangold et al., 2013), another small cohort of 70 German marathon runners (Tsiflikas et al., 2015), a small cohort of 25 Canadian marathon runners (Karlstedt et al., 2012), a Dutch cohort of 318 middle aged men engaged in competitive or recreational leisure sports (Braber et al., 2016), another cohort of 50 US male marathon runners (Schwartz et al., 2014) and 26 US long-term female marathon runners (Roberts et al., 2016).

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 (Aagaard et al., 2013; Katzel et al., 1998; Roberts et al., 2016), 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 (Hood & Northcote, 1999; Mohlenkamp et al., 2008; Breuckmann et al., 2009; Mohlenkamp et al., 2014), 3 of which were based on the German Marathon cohort (Mohlenkamp et al., 2008; Breuckmann et al., 2009; Mohlenkamp et al., 2014).

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).

## *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. (2013) described the yield of routine echocardiography in 153 middle-aged men (mean age 51 ±5 years) before first participation in a cross-country race. Pre-participation 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 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 & Northcote (1999) 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. 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.

#### *Coronary artery calcium scoring*

Möhlenkamp et al., (2008 and 2014), Kroger et al., (2011) Nassenstein et al., (2009) and Breuckmann et al. (2009) all reported on the same German Marathon study of men  $\geq 50$  years (mean  $57 \pm 6$  years) without known heart disease, who had completed at least five full marathons within the last three years. Möhlenkamp et al. (2008) 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. 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 (Möhlenkamp et al., 2014). The event rate in runners with CACS  $<100$ , 100-399, and  $\geq 400$  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.

Kroger et al. (2011) assessed the extra-coronary atherosclerosis plaque burden and its association with CV risk factors and coronary atherosclerosis in the German male Marathon group. 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.

Tsiflikas et al. (2015) evaluated the prevalence of CAD in a relatively small group of 50 middle-aged male marathon runners (mean age  $52.7 \pm 5.9$  years, mean Prospective Cardiovascular Munster Study (PROCAM) score  $1.85 \pm 1.56$ ) using CACS and CCTA. 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. (2016) investigated the prevalence of occult CAD using CACS and CCTA in a group of 318 asymptomatic recreational sportsmen (mean age  $54.7 \pm 6.3$  years, 94% low SCORE risk) without known CV disease following a normal sports medical examination with normal resting and exercise ECG. 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. (2014) compared coronary artery plaque volumes with CCTA in 50 male marathon runners who had run marathons for 25 consecutive years (mean age  $59.4 \pm 6.7$  years) to a sedentary control group of 23 men with a clinical indication for CCTA (mean age  $55.4 \pm 10.4$  years). 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 mm<sup>3</sup>,  $p < 0.01$ ), calcified plaque volume (84 vs. 44 mm<sup>3</sup>,  $p < 0.0001$ ), and non-calcified plaque volume (116 vs. 82 mm<sup>3</sup>,  $p = 0.04$ ). 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. (2016) compared coronary artery plaque volumes with CCTA in 26 female marathon runners who had run marathons for 10-33 consecutive years (mean age  $56 \pm 10$  years) to a sedentary control group of 28 women (mean age  $61 \pm 10$  years), with no

known history of CV disease in either group. 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 (Schwartz et al; 2014), 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 mm<sup>3</sup>,  $p$  0.043) than the sedentary controls.

#### *Cardiac magnetic resonance imaging*

No CMR studies administered adenosine or dobutamine for ischemia detection. Nassenstein et al. (2009) 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). 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  $\geq$  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  $57 \pm 6$  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. (2009) compared the prevalence of myocardial distribution of LGE in these male marathon runners with asymptomatic control subjects and examined the prognostic role of LGE. 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 (Mohlenkamp et al., 2014)

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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. (2012) performed a more extensive examination in a small group of 25 marathon runners (age  $55 \pm 4$  years, 84% men) from the 2010 and 2011 Manitoba Full Marathons who had participated in at least 3 marathons in the past 2 years. 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. (2013) performed CMR imaging in 95 endurance athletes aged 18-62 years (mean age  $35.2 \pm 11.4$  years, 87% male, 81% long-distance runners, cyclists or triathletes). 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. (1998) 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  $63 \pm 6$  years) and in 85 healthy untrained men (aged  $61 \pm 7$  years) with no history of CAD, hypertension or diabetes. 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 cardiovascular 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 (Marijon et al., 2011; Berdowski et al., 2013; Chugh & Weiss, 2015). 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 sportspeople, 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 sportspeople 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.

Recent research (Marijon et al., 2015) confirmed the striking lower incidence of exercise related cardiac arrest in women by calculating the incidence rate of sports-related sudden death in France between 2005 and 2010 including a population of approximately 35 million inhabitants. The authors demonstrated that the overall average incidence rate in women was estimated to be 0.51 per million female sports participants vs. 10.1 in men. Although the observed sex differences may be attributed to lower sports participation rates in women, given the fact that the authors provided incidence per million participants, it is unlikely to explain such differences. Furthermore, the authors showed that the incidence rate of sports-related sudden death significantly increased with age among men, but not among women. A later onset of coronary artery disease in women could play a role, however, a greater risk of exercise-related OHCA per se in men cannot be excluded and this requires further research. Furthermore, the contrasting results between male and female long-term marathon runners (Schwartz et al., 2014; Roberts et al., 2016) 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, MPS) 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 (Corrado et al., 2005). 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 (Attili et al., 2010). Myocardial fibrosis, especially with a CAD pattern, has predictive value for future events (Breuckmann et al., 2009) 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 (Van de Schoor et al., 2016). 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 (Silverman et al., 2014; Chang et al. 2015). Absence of coronary artery calcium (CAC) is associated with a very low risk of CV events in asymptomatic and symptomatic individuals (Sarwar et al., 2009). 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 (Chang et al., 2009).

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  $\geq 100$  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 (Silverman et al., 2014).

Recent radiation dose reductions ( $<1-3$  mSv) combined with an excellent diagnostic accuracy for CAD, regardless of risk profile, make CCTA another viable option for screening sportspersons (Fuchs et al., 2014).

CCTA has additional value to CACS by visualizing the coronary lumen, and thereby enabling 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 (Kim et al., 2012) but also in the light of the concept that exercise induced acute coronary events result from plaque rupture causing myocardial infarction which was demonstrated in the study of Burke et al. (1999). They performed a study among 141 men with severe CAD, who died suddenly, and compared coronary arteries (with the aid of autopsy) between death during strenuous activity or emotional stress and death at rest. The 25 patients who died during exercise showed significantly more vulnerable plaques and plaque ruptures, compared with the 114 men who died at rest. CCTA is currently the only non-invasive diagnostic test that could establish the presence of a vulnerable plaque. As demonstrated,



positive coronary vessel remodelling, low attenuation plaques and spotty calcification are associated with subsequent occurrence of acute coronary syndrome (Motoyama et al., 2009; van Velzen et al. 2011) Therefore CCTA could be an additional screening tool for vulnerable plaque causing exercise-induced cardiac arrest.

To date, only one cross-sectional study demonstrated additional value of CACS and CCTA to exercise testing in asymptomatic sportsmen (Braber et al., 2016). Agatston scores larger than 100 or >50% coronary stenosis were used as outcome, but whether CACS and CCTA in asymptomatic sportsmen improve 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 pre-participation 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 (Sofi et al., 2008). However, Marijon et al. (2015) demonstrated in a large 12-year prospective study of sudden cardiac arrest (SCA) in a northwestern US metropolitan region that sports-associated sudden cardiac arrest in middle age represents a relatively small proportion of the overall SCA burden. In addition, their findings of a high prevalence of established cardiovascular disease and symptoms that manifested in advance of SCA highlight a prevention gap that can potentially be closed.

In addition, previous research from the Oregon region demonstrated that warning signs frequently occur in the days and weeks before a sudden cardiac arrest but are usually ignored (Marijon et al., 2016). Therefore, it appears prudent that asymptomatic athletes promptly search medical attention in case of warning symptoms such as chest pain or shortness of breath or unexplained deterioration of their condition.

In contrast to the beneficial effect of moderate long-term exercise, intense long-term training may be associated with accelerated coronary atherosclerosis. Recent research (Merghani et al., 2017) confirmed this hypothesis by demonstrating a higher prevalence of high ( $\geq 300$  AU) CAC scores in a cohort of masters athletic men without established conventional risk factors for CAD who had engaged in several decades of endurance exercise compared with sedentary men of similar age and a similarly low atherosclerotic risk profile.

Possible mechanisms include increased mechanical stress on the vessel wall altering coronary artery flow dynamics and ultimately accelerating atherosclerosis with long term (lifelong) exercise and elevated parathyroid hormone levels increasing circulating calcium values, which could accelerate the process of atherosclerosis (Chiu & Chen 2011; Hagstrom et al., 2014).

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 what 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 (Kavousi et al., 2014). One must also realize that sportspersons might suffer more from side-effects of statin treatment, such as myalgia occurring in 5-7% (Thompson, 2005; Parker et al., 2013).

## **Perspectives**

This review demonstrated the gaps and challenges 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 pre-participation 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 pre-participation 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.

## **Key words**

Middle-aged athlete, sudden cardiac death, imaging, cardiovascular screening, coronary artery disease.

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Table 1: Study characteristics and outcomes

Author (year) [reference]	N	Age: range (years) and mean $\pm$ SD	Gender	Population	Sport years	Current sport	Imaging Modality	Measure	Follow-up Mean $\pm$ SD	Outcome	Author's findings and conclusion
Mohlenkamp (2008) <sup>12</sup> *	108	50-72 57 $\pm$ 6	Male	Marathon runners	Median 20 (IQR 14-42) marathons	4686 + 2285 MET/week	CACS	CACS / LGE	21.3 $\pm$ 2.8 months	Coronary events	Coronary events in 4 runners, all CACS $\geq$ 100. Higher than anticipated coronary risk warranted
Kroger (2011) <sup>21</sup> *	100						CACS	Prevalence of CAC	-	-	Increased awareness of atherosclerosis prevalence
Nassenstein (2009) <sup>22</sup> *	105						CACS + CMR	CACS	-	-	Higher risk than that anticipated from conventional risk factor assessment
Breuckmann (2009) <sup>23</sup> *	102						CMR	LGE	21.3 $\pm$ 2.8 months	Coronary event / all cause mortality	Ostensibly healthy marathon runners have an unexpected high rate of LGE
Mohlenkamp (2014) <sup>24</sup> *	108						CACS + CMR	CACS / LGE	6.2 $\pm$ 1 years	Coronary event / all cause mortality	All cause mortality in marathon runners similar to that in RF-matched controls
Braber (2016) <sup>14</sup>	318	45-71 54.7 $\pm$ 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) <sup>19</sup>	153	45-69 51 $\pm$ 5	Male	Cross-country runners	-	2.4 $\pm$ 1.9 hrs/week	Echo	Echographic abnormalities	-	-	Limited additional yield of echo
Karlstedt (2012) <sup>20</sup>	25	>50 years 55 $\pm$ 4	84% Male	Marathon runners	Mean 57 $\pm$ 8 marathons	47 $\pm$ 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) <sup>25</sup>	19	42-83 67 $\pm$ 6	Male	Runners	42-83 running years	34 $\pm$ 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) <sup>26</sup>	70	50-70 63 $\pm$ 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) <sup>27</sup>	95	18-62 35.2 $\pm$ 11.4	77% Male	Athletes $\infty$	$\geq$ 2 years	13.1 $\pm$ 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) <sup>28</sup>	70	45-67 53 $\pm$ 6	Male	Marathon runners		Mean 13.8 $\pm$ 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) <sup>29</sup>	50	52-66 59.4 $\pm$ 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) <sup>30</sup>	26	42-82 56 $\pm$ 10	Female	Marathon runners	At least one marathon 10 consecutive years	Mean 45 $\pm$ 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<sup>∞</sup> = a combined cohort of triathletes, long-distance runners, cyclists, and handball players
- Athletes<sup>#</sup> = 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.

**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 availability.
CCTA	95-99%	64-83%	Reasonably low	Radiation (although declining). High image quality



