

Coronary Artery Disease in Athletes-Insights from Cardiac CT

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Abstract

Exercise is widely recognized for its cardiovascular benefits, including reduced mortality and a lower risk of cardiovascular events. However, recent studies suggest that athletes may exhibit a paradoxical increase in coronary artery calcium (CAC) and high-risk plaque morphology. Additionally, there is considerable conflicting evidence and numerous gaps in current research on this topic. With the growing population of athletes, particularly “Master Athletes”, understanding the implications of coronary atherosclerosis in this group is increasingly important. “Master Athletes” are typically defined as athletes aged 35 years or older who continue to engage in competitive or high-level physical activity, often participating in endurance sports. This review summarizes the prevalence of coronary artery disease (CAD) in athletes, explores the relationship between physical activity and plaque development, and examines its prognosis in this population. Furthermore, it addresses the appropriate management of athletes with CAD.

Keywords: Coronary artery calcium, Athletes, Master Athletes, Atherosclerotic cardiovascular disease

Introduction

Coronary artery disease (CAD) is the leading cause of death worldwide [1], and there is clear evidence that physical activity and exercise significantly reduce the risk of cardiovascular events [2,3]. However, recent studies suggest that athletes may have a higher prevalence and severity of coronary artery calcium (CAC), and high-risk plaque morphology detected by coronary CT angiography [4,5]. The Race Associated Cardiac Arrest Event Registry (RACER) study found that myocardial ischemia accounted for 16% of cardiac arrests during marathon and half-marathon races in the United States [6], indicating a notable prevalence of subclinical CAD in athletes. These findings challenge our understanding of how physical activity affects coronary health and underscore the importance of comprehensive cardiovascular assessments in athletes.

As the population of athletes continues to grow, including a rising number of older “Master Athletes” engaging in high-intensity activities, understanding the implications of CAD in this group is becoming increasingly important. The mechanisms behind the increased coronary atherosclerosis in athletes remain largely unknown, which complicates clinical significance and management strategies for these individuals.

Moreover, the clinical significance of CAD in athletes and the optimal strategies for managing these individuals are still unclear. This comprehensive review aims to synthesize current data on CAD in athletes, explore the relationship between physical activity and plaque development, and examine the prognosis of athletes with CAD. Additionally, it addresses the clinical management issues of athletes with CAD.

The Data of CAD in Athletes

The prevalence of CAD evaluated by CAC score in athletes has been widely studied, particularly in endurance and master athletes (**Table 1** provides a summary of the studies examining the data of CAD in athletes). One of the earliest studies investigating the prevalence of CAC in athletes was published by Möhlenkamp *et al.* in 2008 [7]. This study included 108 healthy male marathon runners who had done more than 5 marathons in the last 3 years (≥ 50 years of age) and found a prevalence of 71% for some degree of CAC, with 36% of individuals having a CAC score >100 . Another important finding in this study was that CAC score in marathon runners was higher than control group after adjusting for risk factors. The Measuring Athlete’s Risk of Cardiovascular Events (MARC) study with 318 sportsmen (≥ 45 years of age)

Table 1. Data on Coronary artery disease using cardiac CT in athletes.				
Study	Study population	Age	Results	Key Findings
Mohlenkamp <i>et al.</i> (2008) [7]	Marathon runners (n=108); Individuals who had completed >5 marathons in the last 3 years. 864 age-matched controls.	≥ 50 years	71% marathon runners had detectable CAC 36% of marathon runners had a CAC score of ≥ 100, more prevalent in marathon runners. CAC score ≥400 associated with cardiovascular events	Marathon runners had higher CAC scores than Framingham Risk Score matched control, showing a graded risk increase of all-cause mortality across CAC categories
Merghani <i>et al.</i> (2017) [4]	Masters athletes (n=152); (77% runners, 23% cyclists) and 92 age and Framingham risk-matched control. Predominantly masters athletes with low atherosclerotic risk profiles.	54.4 ± 8.5 years	60% of athletes had detectable CAC 11.3% male athletes showed a CAC ≥ 300 compared with none of the male controls Male athletes had a significantly greater proportion of calcific plaques.	Severe CAD (CAC>0) prevalence was higher in athletes. Athletes had predominantly calcified plaques compared to controls. Controls showed predominantly mixed morphology plaques.
Braber <i>et al.</i> (2017) [8]	318 asymptomatic athletes with free of known CVD and with normal sports medical evaluation (including bicycle exercise ECG). 94% of study participants had low risk scores.	54.7 ± 6.3 years	51% for any CAC with 16% of individuals having a CAC score ≥100 19% had CAD detected by CAC and coronary CTA (definition of CAD: CAC score ≥ 100 and ≥ 50% luminal stenosis)	CAC scan and Coronary CTA detects CAD in almost one in five asymptomatic athletes after sports medical evaluation.
Aengevaeren <i>et al.</i> (2017) [12]	284 men from MARC study. Athletes were categorized as exercising for <1000, 1000–2000, or >2000 MET-min/week.	55 ± 7 years	Athletes with the highest exercise dose had significantly greater CAC score and prevalence of calcified plaques.	Athletes with a high lifelong exercise volume are more likely to have coronary atherosclerosis. The most active athletes have a more benign composition of atherosclerotic plaques (less mixed and more often only calcified plaques).
De Boscher <i>et al.</i> (2023) [5]	558 individuals (176 healthy non athletes, 191 late-onset endurance athletes, and 191 lifelong endurance athletes). All participants without traditional cardiovascular risk factors (i.e., no history of hypertension, smoking, dyslipidemia, or diabetes)	56 ± 6 years	lifelong athletes exhibited: -greater coronary plaque burden -higher proportion of proximal plaques -higher proportion of obstructive lesions -higher proportion of plaques characterized by non-calcified and mixed morphology	Lifelong athletes had more coronary plaques, including more non-calcified and mixed plaques and plaques in proximal segments with significant luminal stenosis, than healthy non athletes. lower risk of cardiovascular events among athletes are not explained by plaques composition/extent

who could exercise to high workloads reported that 53% had some degree of CAC, with 16% of individuals having a CAC score >100, even though majority of participants (94%) had a low-risk profile according to the Systematic Coronary Risk Estimation (SCORE) tool [8]. Similarly, Studies by Merghani *et al.* with 152 master athletes (77% runners, 23% cyclists) and 92 controls reported that 40% of athletes (48% in male, 22% in female) had some degree of CAC, with 11% of male individuals having a CAC score >300 [4]. Importantly, all these

aforesaid studies have consistently demonstrated the high prevalence of CAD in athletes even though they have less risk factors. However, the etiology of this phenomenon remains incompletely understood and is likely multifactorial. These factors include the acute pro-inflammatory state induced by repeated prolonged bouts of intense exercise [9]. Future studies utilizing a novel CT imaging biomarker of coronary inflammation, peri-coronary adipose tissue attenuation [10], could offer valuable insights into this area. To date, one study

has reported that master athletes exhibit increased coronary inflammation evaluated by coronary CT angiography (CTA) [11]. Research by Mohlenkamp *et al.* and the MARC study indicates a higher prevalence of coronary artery calcification (CAC) in athletes than in less active individuals, challenging the assumption that athletes face lower cardiovascular risks [7,8]. This paradox shows that even athletes with healthy lifestyles can exhibit significant atherosclerosis, as evidenced by high CAC scores on CT scans. Advanced coronary CTA imaging has been crucial for in-depth plaque assessment in athletes, detecting both obstructive and non-obstructive CAD that might otherwise remain unnoticed due to their asymptomatic nature. This underscores the importance of cardiac CT in revealing critical coronary conditions, thereby guiding effective management strategies to prevent serious health outcomes.

Plaque Composition and Morphology in Athletes

Coronary CTA enables the detailed characterization of coronary atherosclerosis. Several studies have reported on the composition and morphology of plaque assessed by coronary CTA in athletes. In the study by Merghani *et al.*, calcified plaques were more common in male athletes compared with males in the control group (73% versus 31%; $P=0.0002$), whereas males in the control group had a higher prevalence of mixed morphology plaques (62% versus 23%; $P=0.0006$) [4]. No differences in plaque morphology were discovered between female athletes and females in the control group. Similarly, Aengevaeren *et al.* further examined the MARC study and reported that a lower prevalence of mixed plaques and a higher prevalence of only calcified plaques in the active athletes [12]. Since calcified plaques are more stable and less prone to rupture than mixed or non-calcified plaques, these findings were considered benign and non-alarming. Importantly, these prior studies only looked at the relative distribution of plaque type in individuals with evidence of plaque, but differences in the absolute prevalence of calcified, mixed, and non-calcified plaques were not reported. Recently, the result of Master@Heart study has been published, and has shown the absolute prevalence of different coronary plaque types [5]. This multicenter prospective cohort study included 558 individuals, including 176 healthy non athletes, 191 late-onset endurance athletes, and 191 lifelong endurance athletes. The strength of this study is that the study excluded individuals with a history of arterial hypertension, smoking, dyslipidemia, or diabetes mellitus, which can affect plaque morphology. In this study, De Bosscher *et al.* reported that the most prevalent plaque type in both athletes and non-athletes was calcified plaques, followed by mixed and non-calcified plaques. Moreover, a greater proportion of lifelong endurance athletes had proximal plaques and lesions with significant stenosis (stenosis grade of $\geq 50\%$), as well as plaques of non-calcified and mixed morphology, which are well established risk factors for ischemic heart disease. These data did not support the hypothesis that highly trained endurance athletes

have a more benign plaque composition to explain their lower risk of cardiovascular events compared to non-athletes.

Advanced coronary CTA imaging and analysis techniques allow for quantifying total plaque volume and the burden of the individual component plaque types (calcified, non-calcified, and low-attenuation plaque). Quantitative plaque imaging data, especially total plaque volume, are becoming increasingly important as novel markers for cardiovascular risk prediction [13,14]. Data on quantified coronary artery plaque volume in athletes has also been reported. A study by Schwartz, with a relatively small sample size, compared quantitative plaque volumes between athletes and controls. Male marathon runners ($n=50$), compared with sedentary male controls ($n=23$), had increased total plaque volume, calcified plaque volume, and non-calcified plaque volume, supporting the findings of the Master@Heart study [15]. Future studies with larger sample sizes using this technique are needed to explore quantitative plaque data in athletes and its association with clinical outcomes.

Recent advancements in imaging have significantly clarified the plaque composition in athletes, revealing a predominance of stable, calcified plaques less prone to rupture, alongside the critical detection of non-calcified plaques through comprehensive cardiac CT (CCTA), which traditional calcium scoring may miss. This nuanced understanding of plaque stability and associated risks necessitates routine cardiac evaluations, particularly vital for older or endurance athletes who, despite seeming low risk, may have substantial coronary plaque burdens. Such thorough cardiac assessments are crucial for tailoring treatment strategies—from lifestyle adjustments to medical interventions—ensuring proactive and precise cardiovascular management that aligns with current sports cardiology practices. CCTA could be a potential tool to offer detailed insights that guide preventive and therapeutic measures in athletes.

Physical Activity and Progression of Coronary Atherosclerosis

It is well known that plaque progression such as CAC progression is significantly associated with a higher rate of cardiovascular events [16,17]. There are several published studies on the association of physical activities with CAC progression. In the Multi-Ethnic Study of Atherosclerosis [18], individuals with pre-existing CAC who engaged in increased sedentary behavior were more likely to experience greater CAC progression. In contrast, vigorous activity was inversely associated with new incident CAC in individuals without CAC at baseline, suggesting a protective effect of physical activity on plaque progression. Similarly, the group from the Cooper Center Longitudinal Study studied whether baseline levels of physical activity are associated with CAC progression beyond a clinically meaningful threshold (CAC score ≥ 100). In this study, Shuval *et al.* reported that baseline physical activity was

not associated with CAC progression to a CAC score ≥ 100 over the follow-up period in both men and women [19]. In contrast, Sung *et al.* found a significant association between higher baseline physical activity and increased CAC progression, regardless of baseline CAC score [20].

Taken together, there appears to be discordance among these previous studies. One possible explanation lies in the limitations of CAC score calculation. Since the CAC score is based on the total area and density of calcium deposits, it may not always accurately represent plaque volume. Furthermore, some studies have shown that high calcium density is associated with plaque stability and a lower risk of cardiovascular events in population-based cohorts [21,22], highlighting the challenges in using the CAC score to assess plaque progression.

Recent advancements in coronary CTA imaging techniques have also made it possible to monitor changes in coronary artery plaque volumes and characteristics over time, providing mechanistic insights into the effects of lifestyle behavior and medical therapies noninvasively [23]. Future studies with larger sample sizes are needed to investigate the impact of physical activity on actual plaque changes through serial coronary CTA.

Physical Activity (Intensity Vs. Duration) on Coronary Atherosclerosis

The Cooper Center Longitudinal Study, a large cohort study involving 21,758 men, aimed to elucidate the association between varying levels of physical activity and CAC [24]. In this study, DeFina *et al.* reported that the adjusted risk of having a high CAC score (≥ 100) was 11% greater among individuals with exceedingly high levels of physical activity (≥ 3000 MET·minutes per week) compared to those with lower levels (<3000 MET·minutes per week). It is important to note that total physical activity reflects the product of exercise intensity and duration. The role of intensity versus duration of physical activity in relation to coronary atherosclerosis is not yet fully understood. Recently, the Cooper Center Longitudinal Study examined the association of exercise intensity and duration on CAC in a cross-sectional analysis of a large group of healthy men ($n = 23,383$) [25]. Pavlovic *et al.* reported that elevated CAC was associated with lower average intensity and longer duration of physical activity. Conversely, both mean CAC and clinically significant CAC (CAC score ≥ 100) were negatively associated with average intensity of physical activity. Higher average intensity of physical activity was related to lower mean CAC and a reduced relative risk of CAC ≥ 100 . In contrast, a higher weekly duration of physical activity was significantly associated with greater mean CAC and an increased relative risk of high CAC ≥ 100 . An opposite trend was observed in the MARC -2 (Measuring Athletes' Risk of Cardiovascular Events 2) study, a longitudinal study investigated the relationship between exercise volume and intensity and the progression of coronary atherosclerosis using both CAC and coronary

CTA [26]. Aengevaeren *et al.* reported that exercise intensity, but not volume, was associated with progression of coronary atherosclerosis during six years of follow-up. The differences between study results highlight the complex association between physical activity and coronary atherosclerosis.

Impact of Physical Activity on Prognosis

Despite the association between physical activity and coronary artery plaque, the prognosis for athletes or individuals with high physical activity appears favorable. For example, a community cohort study from Copenhagen involving 1,098 healthy joggers and 3,950 healthy non-joggers examined the association between mortality and a function of running dose [27]. Compared with sedentary non-joggers, 1 to 2.4 hours of jogging per week was associated with the lowest mortality (multivariable hazard ratio [HR]: 0.29; 95% confidence interval [CI]: 0.11 to 0.80). The beneficial effect of exercise on prognosis has also been reported in athletes with CAD (i.e., high CAC score). **Table 2** Provides a summary of key studies examining the association between physical activity and prognosis. In the Cooper Center Longitudinal Clinic Study, Defina *et al.* evaluated the relationship between CAC scores, self-reported physical activity, and both cardiac and all-cause mortality among 21,758 men followed for a mean of 10.4 years. Among the various CAC groups, a high level of self-reported physical activity was associated with lower cardiac death rates and overall mortality compared to those reporting low levels of physical activity [24]. Malik *et al.* also reported that moderate-intensity exercise, such as walking, resulted in fewer cardiovascular events in individuals with high CAC score (>400) [28]. Similarly, Radford, *et al.* observed an 11% decrease in cardiovascular event risk for each additional MET of fitness across all CAC groups [29], establishing the beneficial effect of exercise in preventing cardiovascular disease in patients with elevated CAC score. Recently, Natanzon *et al.* performed a post-hoc analysis of 9,772 patients who underwent coronary CTA at a single center [30]. Patients were divided into 4 groups according to physical activity; no physical activity, mild, moderate, and high physical activity, based on a single-item self-reported questionnaire. Authors found a stepwise inverse relationship between physical activity and mortality. Compared with the high physical activity group, the no physical activity group had a 3-fold higher mortality risk after adjustment for age, clinical risk factors, symptoms, and statin use. Another important finding of this study was that the risk of all-cause mortality was similar among the patients with obstructive stenosis with high physical activity versus those with no coronary stenosis but no physical activity, suggesting the powerful role of physical activity to impact overall cardiovascular risk. It should be noted that a limitation of previous studies is that some participants had risk factors that could have influenced the outcomes. The Master@Heart study including only subjects without risk factors is expected to clarify the unbiased association between exercise and outcome [5]. Additionally, the optimal amount of exercise remains a topic of debate because some studies imply that

Table 2. Key Data examining the association between physical activity and prognosis.			
Study	Population	Age	Key Findings
Radford <i>et al.</i> (2018) [29]	8,425 male individuals without clinical CVD who underwent assessment of both CAC and cardiorespiratory fitness	Mixed (Adults)	Each additional MET of fitness was an 11% lower risk of total cardiovascular events (HR, 0.89; 95% CI, 0.84–0.94) after adjusting for CAC level (CAC score of 0, 1–99, 100–399, and ≥ 400). Greater cardiorespiratory fitness was continuously associated with lower annual total cardiovascular events rates in all CAC groups.
Malik <i>et al.</i> (2020) [28]	270 subjects with stable CAD	Aged 37 to 80 years	Subjects with exercise capacity ≥ 10.6 MET had a 68% lower rate of cardiovascular events compared to the lowest MET group (4.0-8.1 MET). In subjects with CAC score >400, those achieving ≥ 8.2 METs had significantly better survival free of cardiovascular events.
DeFina <i>et al.</i> (2019) [24]	21,758 men	51.7 ± 8.4 years	Highly active group (≥ 3000 MET-min/week) had lower event rates compared to men with less than 1500 MET-min/week. <u>Subjects with CAC<100</u> All-cause mortality (HR 0.52; 95% CI, 0.29-0.91) Cardiovascular events (HR 0.39; 95% CI, 0.08-1.79) <u>Subjects with CAC ≥ 100</u> All-cause mortality (HR 0.77; 95% CI, 0.52-1.15) Cardiovascular events (HR 0.80; 95% CI, 0.39-1.64)
Natanzon <i>et al.</i> (2024) [30]	9,772 patients who underwent coronary CTA	62.6 ± 12.9 years (mean age 62.6)	Compared with the high activity group, the no activity group had higher mortality risk <u>All patients</u> All-cause mortality (HR 3.31; 95% CI, 1.94-5.63) <u>Obstructive CAD patients</u> All-cause mortality (HR 3.00; 95% CI, 1.29-6.92) <u>Non-obstructive patients</u> All-cause mortality (HR 1.95; 95% CI, 1.01-3.77)

extremely high levels of exercise may be harmful. For example, a J- shaped association has been reported between exercise volume and cardiac events in subjects with stable CAD with the most highly active patients having a 2.36- fold increased risk of cardiovascular mortality (95% CI, 1.05–5.34) [31]. Further research is needed to better understand these thresholds and provide clearer guidelines on exercise prescription, especially for older athletes.

Management of Athletes with Coronary Artery Disease

Given the data suggesting that athletes often exhibit significant levels of coronary atherosclerosis (i.e., high CAC score) and the growing number of master athletes, developing an appropriate management strategy for athletes with coronary artery disease is crucial. This is essential not only for preventing cardiovascular events but also for maintaining

their performance and overall well-being. Although American and European guidelines are available, it is important to manage athletes with documented CAD on a case-by-case basis, as there are still many unresolved topics in this field [32,33]. All athletes should be questioned about symptoms of myocardial ischemia, family history of atherosclerotic CAD, and current and previous risk factors. It is important to note that myocardial ischemia in athletes may present with atypical symptoms compared with non-athletes. This includes a reduction in exercise capacity, unusual tachycardia, and angina at very high exercise workloads. Symptomatic athletes should be investigated and managed in the same fashion as the general population. For asymptomatic athletes with CAD, the current European Society of Cardiology guideline recommends an aggressive management of risk factors for atherosclerosis [33]. However, we need to exercise caution when prescribing preventive medications for athletes. For example, antiplatelet therapy can be considered for

individuals especially with high CAC score, careful evaluation of the thrombotic and bleeding risks is mandatory for athletes. Additionally, when choosing an anti-ischemic or antihypertensive agent, clinicians should consider the effect on heart rate, maximum oxygen consumption, and rate of perceived exertion.

In individuals with an elevated CAC score and/or obstructive disease should consider an exercise stress test or a stress imaging test to detect evidence of ischemia. If the functional testing is positive despite adequate treatment, an invasive coronary angiogram should be performed to confirm the presence, extent, and severity of CAD. Although the data on effect of revascularization in athletes are lacking, the ESC guideline recommends revascularization in athletes with high-risk lesions such as 70% stenosis in a major coronary artery (or >50% in the left main coronary artery).

Considering the benefits of exercise on prevention of cardiovascular events, athletes with CAD should not stop exercising. In general, athletes may be advised to participate in all types of exercise if they have no evidence of inducible ischemia or arrhythmias and have a normal ejection fraction. However, given the current uncertainty about the safety threshold of volume and intensity of exercise in athletes with CAD, the intensity and length of training sessions should be determined through an individualized approach.

Mechanisms Behind the Exercise-induced Coronary Artery Calcification Paradox

Several mechanisms have been proposed to explain why athletes exhibit increased CAC. These mechanisms provide insights into how long-term, high-intensity exercise impacts the vascular system in athletes, particularly endurance athletes. Repeated mechanical stress on the coronary arteries during endurance exercise is believed to cause microvascular trauma, which can trigger calcification as part of the arterial repair process. Recent studies support this hypothesis, suggesting that the repetitive stress of endurance exercise results in a higher prevalence of calcified plaques in older athletes [34]. Additionally, chronic exercise-induced inflammation can elevate levels of inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6), both of which are associated with atherosclerosis and plaque formation [35]. The paradox in the relationship between regular exercise and favorable prognosis regardless of increased CAC might be partly explained by vascular adaptation and CAC density. Over time, the cardiovascular system of endurance athletes undergoes significant adaptations due to the demands of prolonged physical exertion [36]. These adaptations include arterial remodeling and increase coronary artery diameter, which may mitigate the functional impact of coronary artery obstruction. Compared with nonathletes, master athletes have a higher proportion of purely calcified plaque as opposed to mixed or noncalcified morphology plaques [4,12],

suggesting that long-term endurance training may confer a predisposition toward developing higher calcium density, which is more stable plaque.

Conclusions

Physical activity is fundamentally beneficial for cardiovascular health, significantly reducing the risk of cardiovascular events and mortality. However, the existence of high plaque burden in athletes with lower event rates presents a challenging paradox that is not yet fully understood. This review has introduced several hypotheses regarding the mechanisms underlying this phenomenon, suggesting that while exercise increases plaque volume, it also enhances plaque stability, thereby reducing the risk of events. Recent data suggest that athletes may be at an increased risk of developing coronary artery disease (CAD) and harmful plaque morphology. The apparent paradox of increased coronary atherosclerosis despite lower rates of cardiovascular events remains incompletely understood. Moreover, many questions in this field remain unanswered. Future research needs to address the unresolved questions about the exact nature of plaque development in athletes, the long-term effects on cardiovascular health and optimal exercise thresholds. Additionally, it is crucial to develop specific management strategies for athletes, particularly Master Athletes, to balance the benefits of high physical activity against the potential risks associated with increased coronary atherosclerosis.

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