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Coronary atherosclerosis in apparently healthy master athletes discovered during pre-PARTECIPATION screening. Role of coronary CT angiography (CCTA)

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ABSTRACT

Background: Pre-participation screening (PPS) of athletes aged over 35 years (master athletes, MA) is a major concern in Sports Cardiology. In this population, sports-related sudden cardiac death is rare but usually due to coronary atherosclerosis (CA). Coronary CT Angiography (CCTA) has changed the approach to diagnosis/management of CA, but its role in this context still needs to be assessed.

Methods and results: We retrospectively examined 167 MA who underwent CCTA in our hospital since 2006, analyzing symptoms, stress-test ECG, cardiovascular risk profiles (SCORE) and CCTA findings.

Among the whole enrolled population, 153 (91.6%) MA underwent CCTA for equivocal/positive stress-test ECG with/without symptoms, 13 (7.8%) just for clinical symptoms, 1 (0.6%) for the family history. The CCTA showed the presence of CA in 69 MA (41.3%), congenital coronary anomalies (anomalous origin or deep myocardial bridge) in 8 (4.8%), both in 7 (4.2%). A negative CCTA was observed in 83 MA (49.7%).

The risk-SCORE (age, hypertension, hypercholesterolemia, smoking) was a good indicator for the presence of moderate/severe CA on CCTA. However, mild/moderate CA was present in 17.8% of MA clinically stratified at a low risk-SCORE.

Conclusion: While coronary angiography is more indicated in athletes with positive stress-test ECG and high clinical risk, the CCTA may be useful in the evaluation of MA with an abnormal stress test ECG and/or clinical symptoms engaged in competitive sports with a high cardiovascular involvement. Age, gender, presence of symptoms and clinical risk-SCORE assessment may help sports physicians and cardiologists to decide whether to request a CCTA or not.

1. Introduction

Regular moderate physical activity reduces all-cause mortality and improves long-term cardiovascular health [1].

In contrast, strenuous efforts may increase risk of adverse cardiac events, especially in athletes over the age of 35–40 (master athletes, MA) [2].

In this population, the most frequent cause of sudden cardiac death during exertion (SCD) is coronary atherosclerosis (CA) [3,4], both as a complication of a severe obstructive disease [4,5], and due to a rupture/erosion of unstable non-obstructive plaques [2,6].

Other rarer coronary causes of SCD are congenital, such as the anomalous origin of a coronary artery (AOCA) or a myocardial bridge [4].

In recent decades, the number of MA has grown considerably [6]. This generated a debate on usefulness, feasibility and cost/effectiveness of a pre-participation screening (PPS) [7]. Several risk-stratification algorithms have been proposed, ranging from self-administered questionnaires [8] to specific examinations, including or not resting and stress-test ECG [9–13].

Furthermore, there are significant differences between European [9] and American guidelines [13,14]. Finally, some authors argue that mass

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screening of MA is by no means justified even in those participating in very demanding endurance competitions, such marathon [7].

The advent of the Coronary CT Angiography (CCTA) revolutionized the approach to CA and congenital anomalies. Despite its excellent negative predictive value [15,16], the possible role of CCTA in cardiac screening of MA has yet to be defined [17,18]. The AHA guidelines do not include it [13], while the ESC guidelines state that "*CCTA should be reserved for those athletes with symptoms or abnormalities that raise justified clinical suspicions*" [9].

In Italy, PPS is mandatory by law for all competitive athletes. This may determine problems because CA is not so rare in MA [17–20], and it is often difficult to correctly stratify the cardiovascular risk as a consequence of strenuous and repeated efforts.

2. Aim of the study

To retrospectively analyze clinical/instrumental profiles of all MA who underwent a CCTA in our Centre in the last 12-years, trying to delineate what could be the contribution of this method in the management of MA with risk factors, symptoms and/or positive/equivocal stress-test ECG.

3. Material and methods

The study population included all MA subjected to CCTA in our Sports Medicine Unit since 2006 for the following reasons: a) clinical and/or electrocardiographic abnormalities observed during a routine PPS; b) sent to us for a cardiological visit by other physicians.

The inclusion criteria were: 1) being over 35 years of age; 2) practice competitive sports; 3) having participated in competitions for at least 12 months; 4) have been subjected to stress-test ECG, in absence of left or right bundle branch block, reaching at least the 85% of theoretical maximum heart rate for age, and subsequently have been submitted to CCTA in our Centre; 5) having a CCTA fully informative of the entire coronary tree.

We utilized the CCTA as a "third level" examination in presence of: 1) clinical symptoms, as typical/atypical chest pain/discomfort or syncope during/immediately after effort; 2) abnormalities on stress-test ECG. Stress-test ECG was considered negative if there were no ST-changes or ST-depression <1 mm; equivocal with an upsloping ST-depression >1 mm; positive with horizontal/downsloping ST-depression >1 mm [14].

Furthermore, we analyzed: 1) presence/absence of symptoms; 2) cardiovascular risk factors: hypertension (blood pressure > 140/90 mm Hg); hypercholesterolemia (total cholesterol >240 mg/dL), Body Mass Index (BMI) > 25; positive family history for myocardial ischemia or SCD; diabetes; smoking habits. Risk factors were evaluated singularly and applying the European Society of Cardiology (ESC) Systematic-Coronary-Risk-Evaluation (SCORE) for low-risk Countries (Italy) [21]; 3) CCTA results, focusing on presence and severity of CA, AOCA and "deep" myocardial bridges (deeper than 2 mm and longer than 20 mm). The grading of CA was assessed as: mild (obstruction < 30%), moderate (between 30% and 70% on any vessel or between 30 and 50% on the left main trunk - LMT) and severe (>70% on any vessel or >50% on the LMT).

CCTA was performed until March 2013 by a 64-row-MDCT-scanner (Lightspeed-VCT; General Electric, Milwaukee, USA), and after this date by a second-generation Dual-Source-CT (DSCT) scanner (Definition-Flash; Siemens Healthcare, Forchheim, Germany), with standardized/optimized protocols and post-processing [22].

The whole study was conducted according the GCP and the Helsinki's declaration. Written consent was obtained from all subjects. The study design was approved from the Ethics Committee of our Institution.

3.1. Statistical analysis

Continuous variables are presented as mean ± SD or median ± IQR, depending on the shape of the distribution curve. Categorical variables are summarized with counts and percentages and were compared by X2 or Fisher's exact tests. One-way analysis of variance (ANOVA) followed by Bonferroni as a post hoc test was performed to evaluate differences between groups and age classes. A binary logistic regression analysis was performed to calculate the adjusted ORs of factors associated with the presence of atherosclerosis or multiple plaques. The following variables were included as covariates: age and BMI (as continuous variables), gender, presence of hypertension, hypercholesterolemia, symptoms and positive familiarity.

The multivariate analysis was determined including all variables that could potentially affect the subjects with presence of CA. The probability values are two-sided; a probability of <0.05 was considered to indicate statistical significance.

All computations were carried out by a biostatistician with SPSS 22.0 (SPSS Inc., Chicago, USA).

4. Results

We enrolled 167 MA (143 males, 24 females, mean age 53.8 ± 10.1 and 53.8 ± 8 years, respectively), participating at different level in competitive sports (mostly distance running and cycling). Among them, 105 (62.9%) were sent to CCTA for equivocal/positive stress-test ECG, 48 (28.7%) for equivocal/positive stress-test ECG plus symptoms, 13 (7.8%) for symptoms but negative stress-test ECG, 1 (0.6%) for the family history (30 years-old brother died during football with autopsy-proved massive CA). Details of the population's characteristics and gender differences are reported in Table 1A.

For what concerning gender, there was a statistically significant difference for: 1) risk-SCORE category, with women being more often at low risk (58.3% vs 29.4%, p = 0.011) while men at moderate risk (65.0% vs 37.5%, p = 0.012); 2) presence of any grade of CA at CCTA, with women more often free from disease (79.2% vs 50.3%, p = 0.016) while men having more frequently moderate disease (18.9% vs 0%, p = 0.006).

4.1. Presence of coronary atherosclerosis in relation to SCORE risk category (Table 2A)

Among the 167 MA, 69 (41.3%) showed CA at CCTA, 8 (4.8%) had AOCA or a deep myocardial bridge, 7 (4.2%) had both CA and AOCA or deep myocardial bridge. A completely negative CCTA was observed in 83 MA (49.7%).

Considering the SCORE risk category, none of the 56 MA with *low risk* (<1% at 10-years) had severe CA at CCTA; 5 (8.9%) had mild disease, 5 (8.9%) moderate disease (Fig. 1A), 5 (8.9%) multiple plaques. Among MA with *moderate risk* (≥1% and <5%), 35 (34.3%) showed mild CA at CCTA (Fig. 1B), 18 (17.6%) moderate CA and 4 (3.9%) severe disease (Fig. 2). All 7 MA classified at high clinical risk (≥5% and <10%) had CA at the CCTA, of which 4 were severe and 3 mild

Table 1A
Study population's characteristics and gender differences.

	M (143)	F (24)	*p value*
Age	53.8 ± 10.1	53.8 ± 8	*0.645*
BMI	25.3 ± 2.8	24.7 ± 4,1	*0.381*
Hypertension	*20.3% (29)*	*20.8% (5)*	*0.950*
Hypercholesterolemia	*21.0% (30)*	*16.7% (4)*	*0.832*
Overweight (BMI > 25)	*46.2% (66)*	*37.5% (9)*	*0.571*
Positive family history	*15.4% (22)*	*12.5% (3)*	*0.954*
Diabetes	*3.5% (5)*	*4.2% (1)*	*0.668*
Smoker	*9.1% (13)*	*12.5% (3)*	*0.880*
Symptoms	*34.3% (49)*	*50.0% (12)*	*0.210*
CV risk category (SCORE)			
Low	*29.4% (42)*	*58.3% (14)*	*0.011**
Moderate	*65.0% (93)*	*37.5% (9)*	*0.012**
High	*4.2% (6)*	*4.2% (1)*	*0.873*
Very high	*1.4% (2)*	*0*	*1*
Stress-test ECG			
Negative	*9.1% (13)*	*4.2% (1)*	*0.695*
Equivocal	*46.9% (67)*	*33.3% (8)*	*0.935*
Positive	*34.1% (63)*	*62.5% (15)*	*0.474*
Coronary atherosclerosis			
NO	*50.3% (72)*	*79.2% (19)*	*0.016**
Mild	*25.9% (37)*	*16.7% (4)*	*0.189*
Moderate	*18.9% (27)*	0	*0.006**
Severe	*4.9% (7)*	*4.2% (1)*	*0.91*
Multiple plaques	*21.7% (31)*	*12.5% (3)*	*0.448*
AOCA	*3.5% (5)*	*0*	1
Myocardial bridges			
NO	*49.7% (71)*	*54.2% (13)*	0.850
Superficial	*43.4% (62)*	*45.8% (11)*	0.877
Deep	*7.0% (10)*	*0*	0.347

() = number of subjects; * = statistically significant difference; CV = cardiovascular; AOCA = anomalous origin of a coronary artery.

or moderate. All 2 MA with very-high clinical risk (≥10% at 10 years) had moderate disease.

4.2. Presence of coronary atherosclerosis and congenital anomalies in relation to stress-test ECG (Table 2B)

None of the 14 MA with a negative stress-test ECG had severe CA at CCTA, 1 (7.1%) had moderate disease, and 4 (28.6%) mild disease. Two showed anomalous origin of the right coronary artery from the left sinus (AORCA) and one a deep myocardial bridge.

Among the 75 MA with equivocal stress-test ECG, at CCTA 24 (32.0%) showed mild, 16 (21.4%) moderate (Fig. 1) and 2 (2.6%) severe CA. Seventeen (22.7%) had multiple plaques. In addition, 2 (2.7%) had an AOCA (1 AORCA, and 1 anomalous origin of the left circumflex artery from the right sinus) and 6 (8.0%) a deep myocardial bridge.

Among the 78 MA with positive stress-test ECG, 13 (16.7%) had mild, 10 (12.8%) moderate and 6 (7.7%) severe CA (Fig. 2), 1 (1.3%) an AORCA, 3 (3.8%) a deep myocardial bridge.

Considering together MA with equivocal and positive ECG stress-test (N = 153), 76 (49,7%) had a completely negative CCTA. As regard gender differences, 14 females out of 15 (93.3%) vs 33 males out of 63 (52.4%) with positive stress-test ECG were actually false-positive (p = 0.003).

Assuming to use a PPS protocol without stress-test ECG, 29 of 167 MA (17.4%) would not have been sent to CCTA because asymptomatic, with negative family history and low risk-SCORE: of them, at CCTA, 3 (10.3%) had mild, 2 (6.9%) moderate CA, 1 (3.4%) an AORCA, and 2 (6.9%) a deep myocardial bridge. All these 8 MA with CA or congenital anomalies had equivocal (N = 6) or positive (N = 2) stress-test ECG.

4.3. Presence of coronary atherosclerosis in relation to risk factors and stress-test ECG

Analyzing *the whole population*, at the univariate analysis for presence/absence of any grade of CA, the following variables were statistically significant: sex (higher risk for males, p = 0.013, OR = 3.75-CI95% 1.33–10.58), age (higher risk for older athletes, p < 0.001, OR 1.1-CI95% 1.06–1.15), hypertension (p = 0.01, OR = 2.68-CI95% 1.22–5.87), hypercholesterolemia (p = 0.036, OR = 2.29-CI95% 1.06–4.96), BMI (higher risk for higher BMI, p = 0.003, OR = 1.19-CI95% 1.06–1.34). In the multivariate analysis, the following variables resulted statistically significant: sex (p = 0.005, OR = 5.82-CI95% 1.72–19.69), age (p < 0.001, OR 1.11-CI95% 1.06–1.15) and BMI (p = 0.013, OR = 1.17-CI95% 1.03–1.33).

In MA with *equivocal stress-test ECG*, at the univariate analysis for presence/absence of any grade of CA, the following variables were statistically significant: age (higher risk for older athletes, p = 0.001, OR 1.12-CI95% 1.05–1.19), hypertension (p = 0.046, OR = 4.00-CI95% 1.02–15.62), BMI (higher risk for higher BMI, p = 0.006, OR = 1.29-CI95% 1.08–1.55) and symptoms (p = 0.031, OR 2.93-CI95% 1.11–7.79). At the multivariate analysis, age (p = 0.005, OR 1.10-CI95% 1.03–1.18) and BMI (p = 0.033, OR = 1.23-CI95% 1.02–1.49) were statistically significant, with an increased risk of developing CA by 10% per year in subjects with the same BMI and an increased risk by 23% per point of BMI in subjects with the same age.

In MA with *positive stress-test ECG*, at the univariate analysis, the following variables resulted statistically significant: sex (higher risk for males, p = 0.02, OR = 11.2-CI95% 1.39–90.44), age (higher risk for older athletes, p < 0.01, OR 1.1-CI95% 1.05–1.18). In the multivariate analysis, sex (p = 0.015, OR 14.88-CI95% 1.66–133.06) and age (p < 0.001, OR = 1.12-CI95% 1.06–1.19) resulted statistically significant, with a risk of having CA 14.9 fold higher for males and a risk increase by 12% per-year.

Analyzing the presence of multiple plaques in the same or different coronary vessels, the logistic univariate analysis showed significant correlation (p < 0,05) with hypercholesterolemia, age, diabetes and positive family history.

Hypercholesterolemia (OR = 2.66-CI95% 1.01–6.97), positive family history (OR = 4.58-CI95% 1.58–13.23) and age (OR = 1.08-CI95%, 1.03–1.14) were statistically significant in the multivariate analysis. Concerning the age, other things being equal, every year brought an increase in risk of developing multiple plaques by 8%.

4.4. Asymptomatic vs symptomatic athletes

When analyzing asymptomatic vs symptomatic MA (Table 1B), a statistically significant difference was found for positive family history and percentage of subjects with moderate risk-SCORE (both more frequent in symptomatic MA). A significant difference was present also for percentages of equivocal and positive stress-test ECG, being paradoxically the firsts more frequent in symptomatic MA and the seconds more frequent in asymptomatic ones. No differences were found for presence and degree of CA and/or congenital coronary anomalies.

At the univariate analysis for presence/absence of any grade of CA, stratified on presence/absence of symptoms, age resulted a significant variable in both asymptomatic and symptomatic MA (OR = 1.0-CI95%, 1.04–1.15 and OR = 1.11-CI95%, 1.04–1.19, respectively), while the BMI resulted significant only in symptomatic subjects (OR = 1.34-CI95%, 1.09–1.64).

At the multivariate analysis, in symptomatic subjects the following variables resulted significant: age (OR = 1.11-CI95%, 1.03–1.19) and BMI (OR = 1.32-CI95%, 1.06–1.64).

4.5. Coronary atherosclerosis in female MA

Only 5 out of 25 (20.8%) female MA had CA at CCTA, mild in 4 cases and severe in one. All 5 were symptomatic and in post-menopausal age (mean age 63 ± 4 years). The four with mild CA had equivocal stress-test ECG and moderate risk-SCORE, while the one with severe disease had positive stress-test ECG and high risk-SCORE. As regard risk factors, 2 out of 5 had hypertension, 2 hypercholesterolemia, 4 BMI > 25, 2 positive family history and one diabetes. In 3 out of 5 cases, multiple plaques were found.

4.6. Concordance between CCTA and coronary angiography

Coronary angiography was available in 21 MA, 8 with severe, 5 with moderate, 5 with mild CA and 3 with deep myocardial bridges. Coronary angiography confirmed the degree of CA on CCTA in 15 out of 18 cases (83.3%), documented a more severe stenosis in 1 (80% vs 60% obstruction) and an overestimation of the stenosis in 2 cases (1 mild vs moderate and 1 moderate vs severe).

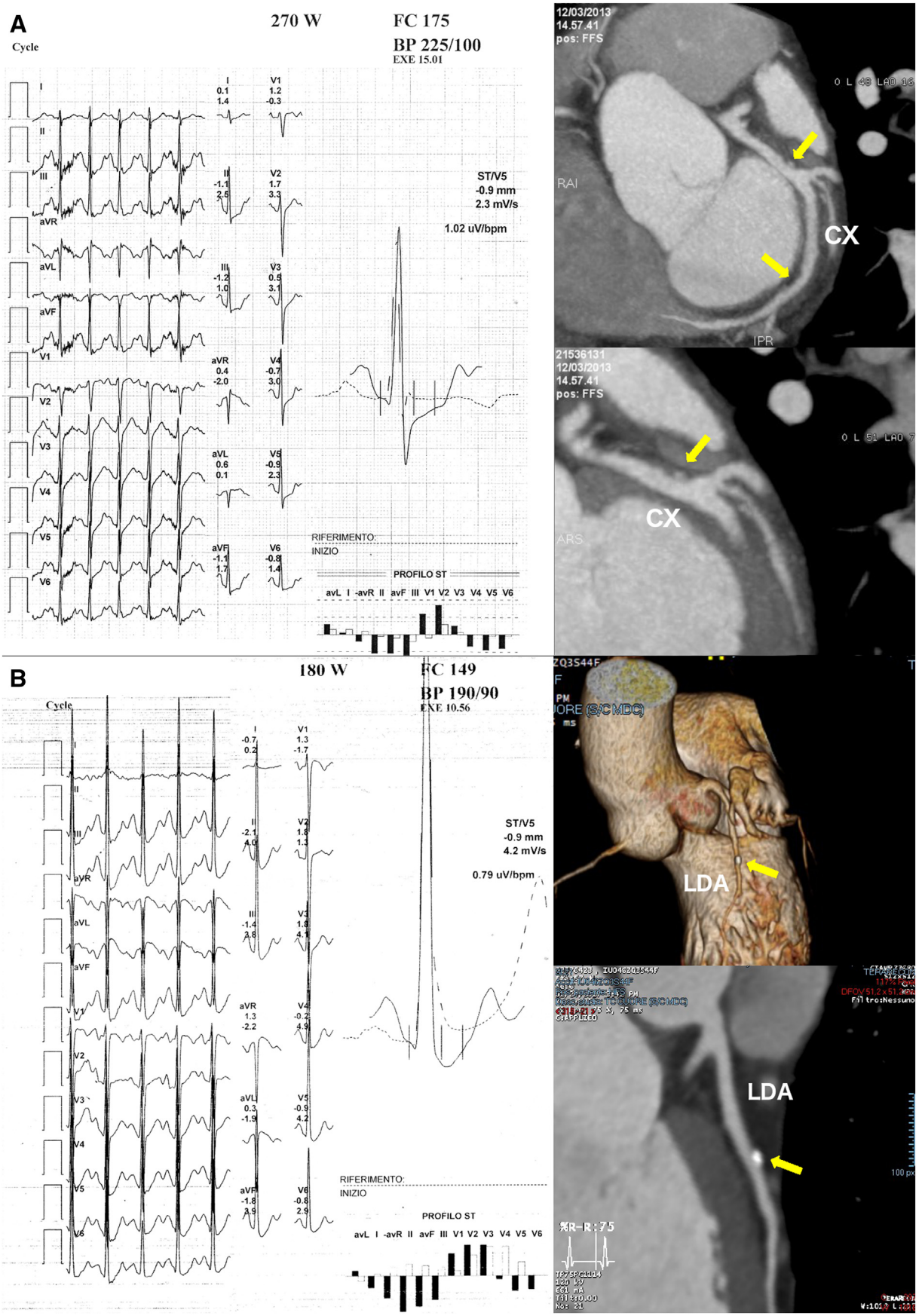
4.7. Eligibility for competitive sports

All MA with any degree of CA, AOCA or deep myocardial bridges were considered not eligible for competitive sports.

5. Discussion

Pre-participation screening (PPS) of MA involved in high-intensity competitive sports is becoming a major concern in Sports Cardiology [7]. Although sports-related sudden cardiac death (SCD) is rare in this population (0.4–2.1/100:000) [3,4], in the vast majority of cases it is related to CA [3,4], for acute rupture/erosion of small plaques [2,4] or advanced obstructive disease [4,5].

The CCTA, the only one non-invasive diagnostic tool able to rule-out or detect and grade the CA, revolutionized the approach to CA and congenital coronary anomalies, with a negative predictive value in both cases close to 100% [15,16].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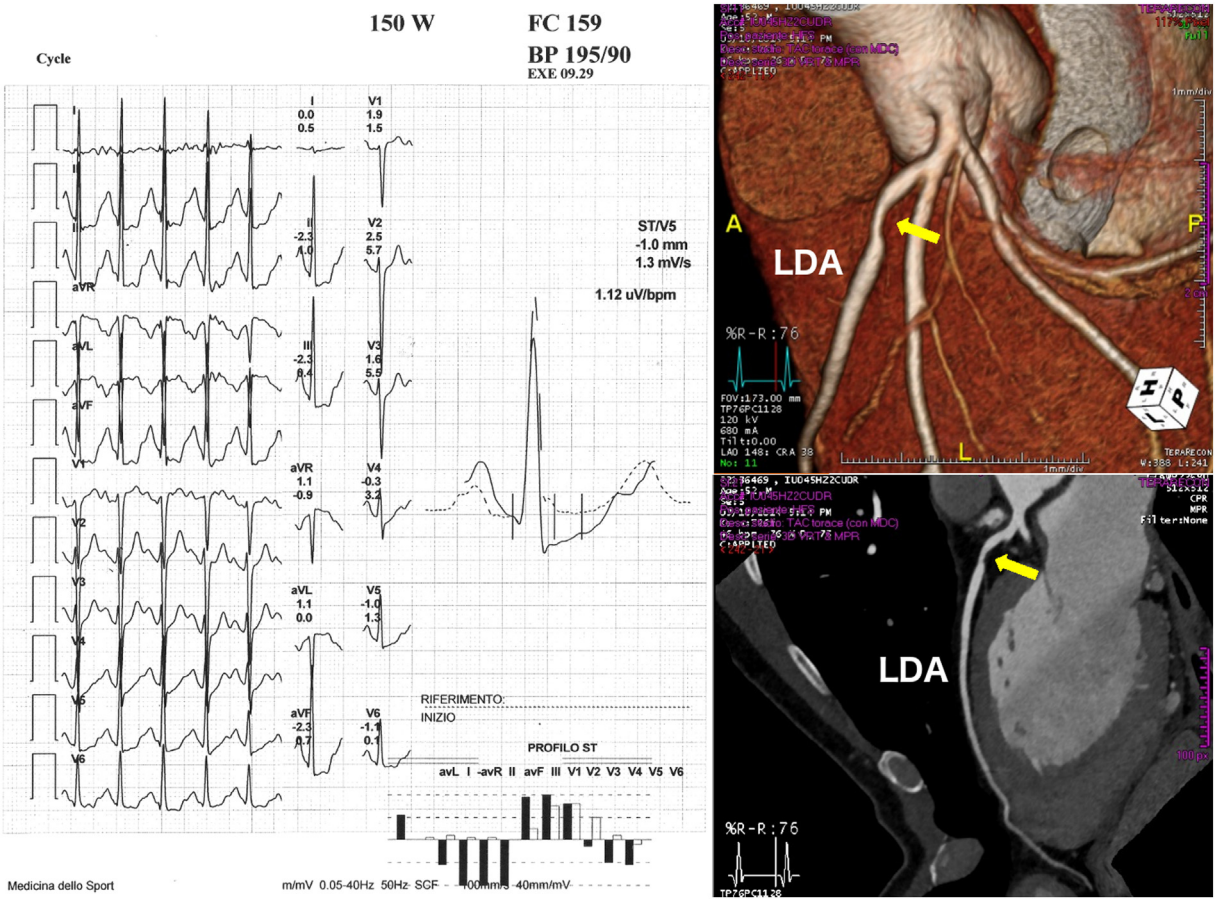

Fig. 2. 57 years-old swimmer, asymptomatic. Negative family history, moderate risk-SCORE (2% at 10 years) and positive stress-test ECG (horizontal ST-depression > 1 mm). The CCTA showed severe coronary atherosclerosis (obstruction > 70%, arrow) on the proximal tract of the left descending coronary artery (LDA).

5.1. Role of CCTA in pre-participation screening of master athletes

In our Country (Italy), PPS is mandatory by law for all competitive athletes since 1982 [23]. It includes personal/family history, physical examination, rest and stress-test ECG. The original decree did not include cardiovascular risk stratification, while current Italian Cardiological Guidelines for competitive sports [24], as well as the European and American ones [9,13,14], do include it. In the suspicion of cardiomyopathy, echocardiogram (Echo) is selected usually as first choice examination, followed by Cardiac Magnetic Resonance (CMR). On the contrary, what to do when a coronary artery disease is suspected is debated. In MA at very high risk (with positive stress-test ECG plus symptoms and/or high risk-SCORE), a coronary angiography is usually the indicated procedure. In the other cases, there is not agreement on what choosing among stress-Echocardiography (stress-Echo), stress myocardial scintigraphy (MS), stress-CMR and CCTA [25,26].

Since 2006, we have preferred the CCTA, firstly because of its excellent negative predictive value in excluding both CA and congenital anomalies [15,16]; secondly because it represented probably the best compromise regarding availability, operator independence and non-invasiveness [18,25].

The continuous improvement of the image quality and the progressive and dramatic reduction in the radiation dose, especially with the state-of-art CT scanner [27–29], has strengthened over time our choice. So, we submit to CCTA all MA with symptoms and/or electrocardiographic abnormalities suggestive of coronary artery disease.

Our results show that, in case of equivocal/positive stress-test ECG, at least half of male MA had CA at CCTA, confirming that this population is not free from coronary heart disease. Obviously, the presence of CA at CCTA is not a synonym of ischemia, since many plaques are not able to reduce enough the coronary lumen to provoke a critical drop in coronary flow at rest and/or during exertion. Conversely, a negative stress-Echo or MS do not exclude the presence of CA, as these tests become diagnostic only in presence of critical drop in the coronary flow, which in turn usually occurs if there is a significant coronary obstruction.

5.2. Role of risk-SCORE and symptoms in deciding when to perform a CCTA in master athletes

Our data suggest that, when symptoms and/or equivocal/positive stress-test ECG are present in a MA, the risk-SCORE is a good indicator

Fig. 1. A) 44 years-old runner, asymptomatic. Positive family history for myocardial ischemia, equivocal stress-test ECG (upsloping ST-depression > 1 mm), but a low risk-SCORE (<1% at 10 years). The CCTA showed moderate coronary atherosclerosis (obstruction 40–50%, arrows) on the left descending coronary artery (LDA) and the circumflex artery (CX). B) 58 years-old runner, asymptomatic. Negative family history, moderate risk-SCORE (2% at 10 years) but equivocal stress-test ECG (upsloping ST-depression > 1 mm). The CCTA showed mild coronary atherosclerosis (obstruction < 30%, arrow) on the LDA.

Table 1B
Analysis of asymptomatic vs symptomatic athletes.

	Asymptomatic (106)	Symptomatic (61)	*p value*
Age	51.8 ± 10.1	54.8 ± 9.5	*0.059*
Hypertension	*19.8% (21)*	*21.3% (13)*	*0.843*
Hypercholesterolemia	*20.8% (22)*	*19.7% (12)*	*1*
Overweight (BMI > 25)	*40.6% (43)*	*52.5% (32)*	*0.138*
Positive family history	*10.4% (11)*	*23.0% (14)*	*0.041**
Diabetes	*3.8% (4)*	*3.3% (2)*	*1*
Smoker	*11.3% (12)*	*6.6% (4)*	*0.417*
CV risk category (SCORE)			
Low	*38.7% (41)*	*24.6% (15)*	*0.091*
Moderate	*55.7% (59)*	*70.5% (43)*	*0.002**
High	*3.8% (4)*	*4.9% (3)*	*0.397*
Very high	*1.9% (2)*	*0*	*1*
Stress-test ECG			
Negative	*0.9% (1)*	*21.3% (13)*	–
Equivocal	*41.5% (44)*	*50.8% (31)*	*<0.001**
Positive	*57.5% (61)*	*27.9% (17)*	*<0.001**
Coronary atherosclerosis			
NO	*59.4% (63)*	*45.9% (28)*	*0.126*
Mild	*21.7% (23)*	*29.5% (18)*	*0.169*
Moderate	*16.0% (17)*	*16.4% (10)*	*0.640*
Severe	*2.8% (3)*	*8.2% (5)*	*0.113*
Multiple plaques	*16.0% (17)*	*27.9% (17)*	*0.075*
AOCA	*1.9% (2)*	*4.9% (3)*	0.356
Myocardial bridges			
NO	*45.3% (48)*	*59.0% (36)*	0.121
Superficial	*47.2% (50)*	*37.7% (23)*	0.186
Deep	*7.5% (8)*	*3.3% (2)*	0.194

() = number of subjects; * = statistically significant difference; CV = cardiovascular; AOCA = anomalous origin of a coronary artery.

for presence of moderate-severe CA. Conversely, the presence only of symptoms did not show significant correlation with CA and congenital anomalies.

Nevertheless, 5 out of 29 MA (17.2%) asymptomatic, with negative family history and a low risk-SCORE (<1% at 10 years), had a mild or moderate CA at the CCTA. This percentage is low but not negligible since most of the SCD occurring in MA during competitions are due to acute complications of non-obstructive plaques [2–5].

5.3. Gender differences

As expected [30,31], men showed higher risk of having CA (3.75-fold in general, up to 14.9-fold higher in case of positive stress-test ECG), while women had more often a false-positive stress-test ECG. Interestingly, none of the female MA in pre-menopausal age had CA, regardless any other factor, while in the post-menopausal age all female MA with CA were symptomatic and had at least a moderate risk-SCORE.

5.4. Role of stress-test ECG in identifying CA in MA

Although percentages of false positive (52.4% men, 93.3% women) and equivocal stress-test ECG in absence of any significant anomaly at the CCTA (37.3% men, 50% women) are high, approximately 50% of male MA with an equivocal or positive test had CA or, more rarely, congenital coronary anomalies. Interestingly, all 8 athletes with severe CA had equivocal/positive stress-test ECG, as well as 26 MA with moderate CA. In our opinion, from a theoretical point of view, both moderate and severe CA may be able to cause a significant reduction in coronary flow during extreme and maximal efforts. Moreover, in at least 2 apparently healthy athletes a moderate CA had been discovered only thanks to the stress-test ECG. Based on these data, we believe that an optimal PPS protocol for all MA should include risk-SCORE assessment and stress-test ECG. It's important to underline that the stress-test ECG should always be maximal (trying to reach at least 85% of theoretical maximum heart rate for age), since a moderate CA able to cause a significant reduction of the coronary flow probably gives electrocardiographic signs only at very high rates of effort.

Considering the whole population, in case of equivocal stress-test ECG, the most important predictors of possible presence of CA at CCTA were hypertension (OR = 4.00-CI95%, 1.02–15.62), symptoms (OR = 2.93-CI95%, 1.11–7.79), BMI (OR = 1.29-CI95%, 1.08–1.55) and age (OR = 1.12-CI95%, 1.05–1.19), while in case of positive stress-test ECG were male sex (OR = 11.2-CI95%, 1.39–90.44) and age (OR = 1.11-CI95%, 1.05–1.18).

5.5. Ultimately, when to recommend the CCTA in a master athlete?

Intentionally, we decided not to tackle a discussion on the cost-effectiveness/feasibility of PPS in MA. Our aim was only to understand what role the CCTA could have in the management of MA with suspected coronary artery disease. Our data suggest that CCTA is useful, and probably will be even more in the future. In our opinion, it should be recommended in presence of one or more of the following aspects (Fig. 3A):

1) Symptoms during/immediately after exercise like chest pain/discomfort or syncope.
2) Equivocal stress-test ECG in presence of at least one among: a) male sex or female at post-menopausal age b) risk factors (singularly or in association) as hypertension, hypercholesterolemia, BMI > 25, positive family history for myocardial ischemia or SCD; c) risk-SCORE ≥ 1% at 10 years; d) symptoms.
3) Positive stress-test ECG in asymptomatic subjects with low or intermediate risk-SCORE.
4) A very high risk-SCORE (≥10%), even in absence of electrocardiographic abnormalities and symptoms. However, this indication is

Table 2A
Presence of coronary atherosclerosis, congenital coronary anomalies and findings of the stress-test ECG in relation to class of cardiovascular risk (SCORE risk category).

		Coronary atherosclerosis					Congenital anomalies		Stress-test ECG		
		Absent	Mild	Moderate	Severe	Multiple plaques	Deep M. Bridges	AOCA	Negative	Equivocal	Positive
SCORE risk category	Low (33.5%, N = 56)	82.1% (N = 46)	8.9% (N = 5)	8.9% (N = 5)	0	8.9% (N = 5)	3.6% (N = 2)	1.8% (N = 1)	8.9% (N = 5)	33.9% (N = 19)	57.1% (N = 32)
	Moderate (61.1%, N = 102)	44.1% (N = 45)	34.3% (N = 35)	17.6% (N = 18)	3.9% (N = 4)	22.5% (N = 23)	7.8% (N = 8)	3.9% (N = 4)	8.8% (N = 9)	52.9% (N = 54)	38.2% (N = 39)
	High (4.2%, N = 7)	0	14.3% (N = 1)	28.6% (N = 2)	57.1% (N = 4)	71.4% (N = 5)	0	0	0	14.3% (N = 1)	85.7% (N = 6)
	Very high (1.2%, N = 2)	0	0	100% (N = 2)	0	50% (N = 1)	0	0	0	50.0% (N = 1)	50.0% (N = 1)

Table 2B
Presence of coronary atherosclerosis, congenital coronary anomalies and class of cardiovascular risk (SCORE risk category) in relation to stress-test ECG findings.

		Coronary atherosclerosis					Congenital anomalies		SCORE risk category			
		Absent	Mild	Moderate	Severe	Multiple plaques	Deep M. Bridges	AOCA	Low	Moderate	High	Very high
Stress-Test ECG	Negative (8.3%, N = 14)	64.3% (N = 9)	28.6% (N = 4)	7.1% (N = 1)	0	21.4% (N = 3)	7.1% (N = 1)	14.3% (N = 2)	35.7% (N = 5)	64.3% (N = 9)	0	0
	Equivocal (44.9%, N = 75)	44.0% (N = 33)	32.0% (N = 24)	21.4% (N = 16)	2.6% (N = 2)	22.7% (N = 17)	8.0% (N = 6)	2.7% (N = 2)	25.4% (N = 19)	72% (N = 54)	1.3% (N = 1)	1.3% (N = 1)
	Positive (46.7%, N = 78)	62.8% (N = 49)	16.7% (N = 13)	12.8% (N = 10)	7.7% (N = 6)	17.9% (N = 14)	3.8% (N = 3)	1.3% (N = 1)	41.0% (N = 32)	50.0% (N = 39)	7.7% (N = 6)	1.3% (N = 1)

AOCA = anomalous origin of a coronary artery; M. = myocardial; N = number of subjects.

based on the correlation between risk-SCORE and CA observed in MA with equivocal/positive ECG from stress test, and needs to be verified.

In MA with positive stress-test ECG, if symptomatic and/or with high/very high risk-SCORE, coronary angiography is more indicated.

This approach may seem "aggressive", but literature data and our experience suggest that both an advanced obstructive coronary artery disease and an acute complication of "small" unstable plaques may cause SCD during strenuous efforts [2–6].

So, from a theoretical point of view, any degree of CA can represent a problem in a MA [10]. Consequently, the crucial point is not only to investigate whether or not inducible ischemia is present, but whether or not coronary plaques are present too. This is another reason why we preferred CCTA to stress-Echo and MS.

5.6. Sport activity and management of MA with CA or congenital coronary arteries anomalies

We strongly believe that CCTA represents the future of cardiovascular prevention in MA, but we are also aware that the main problem remains how to manage and when to authorize them to participate in competitions once CCTA documents mild or moderate CA [10,26], given the difficulty in stratifying the risk of rupture/erosion of non-obstructive plaques in extreme conditions of dehydration and maximum adrenergic bursts. The same difficulty may arise in the presence of an anomalous origin of a coronary artery or a myocardial bridge [32,33].

To date, our approach is restrictive, and we considered not eligible for competitive sports all MA with any degree of CA, AOCA or deep myocardial bridge. Reasonably, non-competitive sports, preferably aerobic and "dosed" according to clinical findings and guidelines [21,34], is safer, so we allowed it (Fig. 3B).

In asymptomatic subjects with mild CA, we allowed all non-competitive sports after appropriate control/correction of risk factors, prescribing medical treatment when necessary. In MA with moderate CA and/or symptoms, we proposed further investigations: MS if they had mild CA and were symptomatic or they were asymptomatic with a coronary obstruction between 30 and 50%, a coronary angiography in the other cases. If MS excluded inducible ischemia, we allowed non-competitive sports, after appropriate control/correction of risk factors and recommending a yearly follow-up.

In case of severe CA, moderate CA plus symptoms or evidence of inducible ischemia at MS, we discouraged any physical exercise and proposed coronary angiography. If coronary angiography did not show necessity of treatment, we allowed physical exercise following the guidelines [21,34] after control/correction of risk factors, with medical treatment when appropriate and preferably under medical supervision in qualified centers, with a six-months follow up. On the contrary, if treatment was needed, we proposed a re-evaluation after the intervention following the same criteria.

In MA with AOCA or deep myocardial bridges, we allowed non-competitive sports if they were asymptomatic and no signs of inducible ischemia were present at MS and/or coronary angiography with functional tests, depending on the type of anomaly.

Probably, in most of the cases mentioned above, a shared decision-making process between physicians and athlete about competitive sports, based on accurate risk-stratification and depending on the medico-legal context, will become increasingly important in the future. A substantial aid could also derive from the almost daily progress of CCTA in the study of the composition of plaques and their vulnerability [35], in the non-invasive assessment of the fractional-flow-reserve [36], in addition to already established parameters such as the coronary artery calcium score (CACS) [20]. However, we do not yet have sufficient data to take into consideration their systematic use in this population.

5.7. Study limitations

This is a retrospective study, so it has not been possible to investigate some relevant aspects. For example, to assess the prevalence of CA in MA only on the basis of risk-SCORE, which did not constitute alone an indication for CCTA if the stress-test ECG was negative. Moreover, we did not analyze the CACS in all MA, because it was routinely calculated only in subjects with a higher risk profile, who represented a minority in our population.

Furthermore, the number of female athletes is relatively small to allow solid conclusions, although the results are rather suggestive, especially as regard the cardiovascular risk in pre- and post-menopausal age.

Another limitation is represented by the low number of available coronary angiographies, which don't allow an exhaustive evaluation of the grade of concordance with CCTA.

Finally, the medico-legal context in Italy is far different than in most of other Countries. Being eligibility for competitive sports demanded to sports physicians [23], the Italian approach has some tendency to be more "restrictive" than in other Countries, with the risk of disqualifying some athletes with cardiac abnormalities that will never have major cardiovascular events in their career. A questionable and criticized approach, but that allowed Italian cardiologists to make significant progress in detecting young athletes with cardiac diseases at risk for SCD [37,38].

In our opinion, this "philosophy of life" should also be adopted in elderly people, in which regular training at moderate intensity can add years to existence and improves its quality in the great majority of cases, while competitive sports activity always pushed to the maximum can shorten it or make it worse in some unfortunate (exasperatedly competitive) individuals.

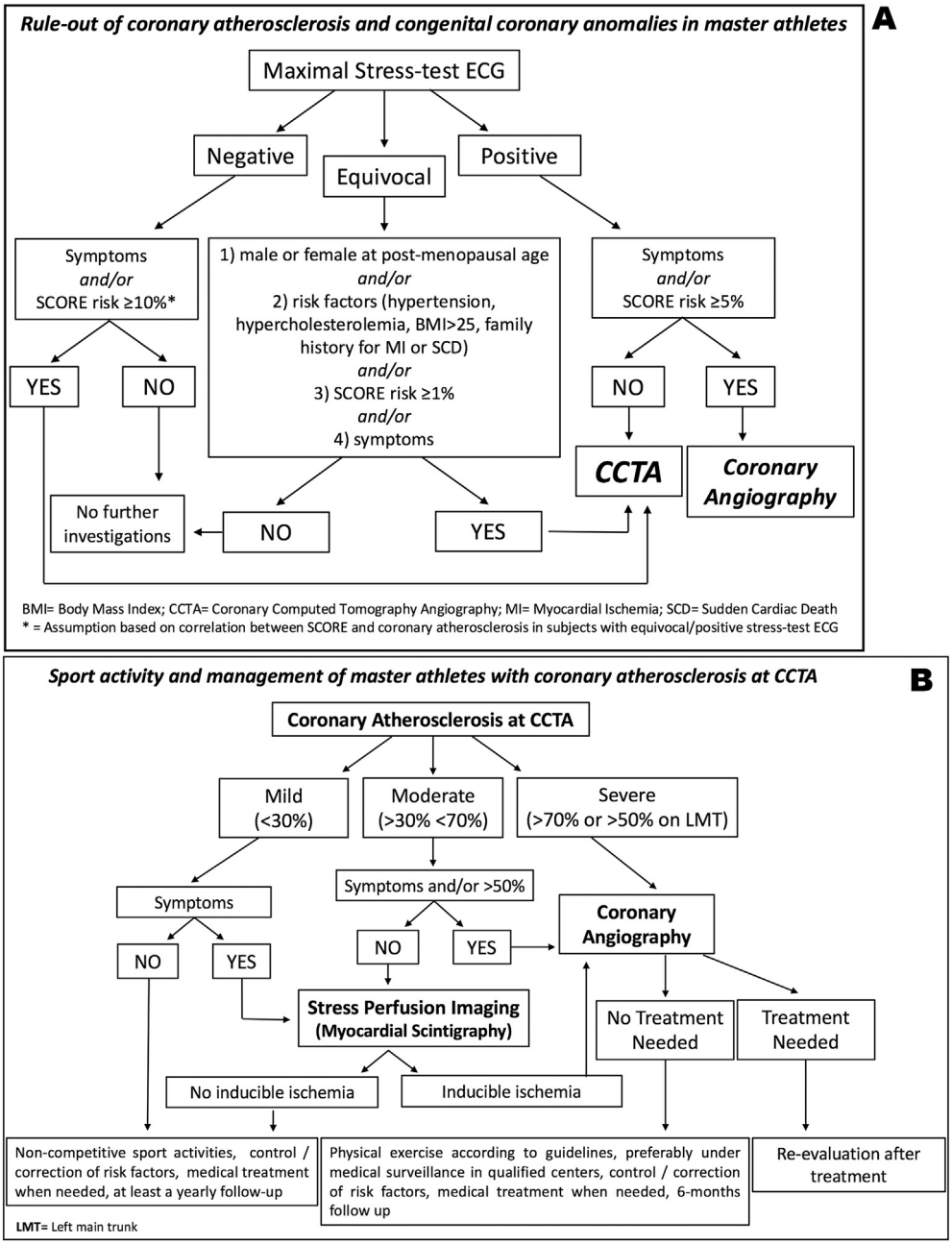

Fig. 3. Flow-charts for ruling out coronary atherosclerosis and congenital coronary anomalies in master athletes (A) and for sport activity and management of master athletes with coronary atherosclerosis at CCTA (B).

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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