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CLINICAL RESEARCH

Incidence of major adverse cardiac events in men wishing to continue competitive sport following percutaneous coronary intervention



Incidence des accidents coronariens sévères chez des patients coronariens stentés pratiquants un sport en compétition

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Abbreviations: CAD, coronary artery disease; CS, competitive sport; CVRF, cardiovascular risks factor; ILS, intensive leisure-time sport; MACE, major adverse cardiac events; MLS, moderate leisure-time sport; NCS, new coronary stenosis; PA, physical activity; SR, stent restenosis; ST, stent thrombosis.

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KEYWORDS

Coronary heart disease;
Sport;
Stent thrombosis;
Stent restenosis

Summary

Background. – The new North American guidelines for participation in competitive sport in patients with coronary artery disease (CAD) are less restrictive than previous guidelines.

Aim. – To evaluate the incidence of major adverse cardiac events (MACE) in men with CAD who practise intensive physical activity after a stenting procedure. MACE included in-stent restenosis (SR), stent thrombosis (ST), new coronary stenosis (NCS), myocardial infarction, heart failure, cardiac arrest or cardiac death.

Methods. – Asymptomatic men with CAD and a coronary stent who practised regular (>4 h/week) sport were included in this retrospective multicentre observational study. All patients presented with left ventricular ejection fraction $\geq 50\%$, no residual stenosis, and no inducible ischaemia or arrhythmias. Three groups were compared: those undertaking moderate leisure-time sport (MLS), intensive leisure-time sport (ILS) or competitive sport (CS). During follow-up, all patients had a yearly routine cardiology evaluation.

Results. – A total of 108 men with CAD (57.3 ± 9.1 years) were included: 29 MLS, 58 ILS, and 21 CS. During follow-up (57.6 ± 46.0 months) the incidence of MACE was 15.7% (SR = 5, SR + NCS = 4, ST = 4, NCS = 4) and occurred during physical exertion in 59% of patients. ST was more frequent in the CS ($n = 3$) than in the MLS ($n = 1$) or ILS ($n = 0$) groups, especially in patients with bare-metal stents.

Conclusions. – The incidence of MACE was 15.7%, and only ST was significantly more frequent in CS patients than in MLS or ILS patients. Our data support the new US guidelines for exercise eligibility in men with CAD.

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MOTS CLÉS

Coronariens ;
Sport ;
Thrombose de stent ;
Resténose de stent

Résumé

Contexte. – Les nouvelles recommandations Américaines du Nord (US 2015) sont plus permissives que les précédentes pour la pratique sportive en compétition par un coronarien.

But de l'étude. – Évaluation de l'incidence d'accidents coronariens sévères (ACS) chez des coronariens stentés qui pratiquent un sport intense. Les ACS regroupent, resténose (RS) ou thrombose de stent (TS), nouvelle sténose coronaire significative (NSC), infarctus du myocarde, insuffisance cardiaque, arrêt cardiaque, ou décès de cause cardiaque.

Méthodes. – La population concernait des hommes coronariens stentés, asymptomatiques et pratiquants au moins 4 h/semaine de sport. Tous présentaient une revascularisation complète, une fraction d'éjection $\geq 50\%$, pas d'ischémie ni d'arythmie à l'effort. Trois groupes ont été comparés, sport de loisir modéré (SLM) ou intense (SLI) et sport en compétition (SC). Ils ont eu un suivi cardiologique annuel le temps du suivi.

Résultats. – Au total 108 coronariens ($57,3 \pm 9,1$ ans), SLM ($n = 29$), SLI ($n = 58$) et SC ($n = 21$) ont été inclus. Pendant le suivi ($57,6 \pm 46,0$ mois) l'incidence globale des ACE a été de 15,7% (RS = 5, RS + NSC = 4, TS = 4, NSC = 4). Chez 59% des patients l'ACE survint pendant l'effort. Seules les TS ont été plus fréquentes dans le groupe SC ($n = 3$) que dans les groupes SLM ($n = 1$) et SLI ($n = 0$) et spécifiquement chez les patients porteurs d'un stent nu.

Conclusions. – L'incidence des ACS était de 15,7%, seuls les TS ont été plus fréquents chez les coronariens compétiteurs que dans les autres groupes. Ces données confortent les recommandations US 2015 concernant la pratique sportive chez les hommes coronariens.

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Background

For the health of the coronary circulation, physical activity can act as a "double-edged sword" [1]. Whilst it is well documented that regular, moderate physical activity supports the prevention of coronary artery disease (CAD) by controlling numerous cardiovascular risks factors (CVRFs) [2,3], vigorous physical exercise may increase the risk of acute

coronary events (5.7-fold) in middle-aged "apparently" healthy but untrained men [4]. Moreover, CAD is the leading cause of sports-related cardiovascular events in this population [5].

Some data report that habitual vigorous activity is not associated with an increased risk of myocardial infarction [6], but a recent prospective epidemiological study demonstrated that daily strenuous physical activity is associated

with increased cardiovascular mortality in patients with CAD [7]. Moreover, Merghani et al. recently examined 152 master (i.e. age > 40 years) endurance athletes and 92 controls of similar age, sex and low Framingham 10-year CAD risk scores, with echocardiograms, exercise stress tests, computed tomography coronary angiograms, cardiovascular magnetic resonance imaging (CMR) and 24-h Holter monitoring [8]. Their results showed that male athletes presented a higher prevalence of atherosclerotic plaques than sedentary men. Only male athletes (11.3%) demonstrated a coronary artery calcium score ≥ 300 Agatston units and a luminal stenosis $\geq 50\%$ (7.5%). The number of years of training was the only independent variable associated with the increased risk of coronary artery abnormalities. Lastly, male athletes (14%), but none of the controls, revealed late gadolinium enhancement on CMR; of these, seven had a pattern consistent with previous myocardial infarction.

Consequently, providing physical activity advice for patients with known CAD is difficult, as the potential risk of exercise-induced myocardial ischaemia and adverse cardiovascular events induced by vigorous physical activity are still debated [9]. Recently published Task Force eligibility and disqualification recommendations for competitive athletes with CAD note that it is reasonable for athletes with clinically concealed atherosclerotic CAD to participate in all competitive activities provided that there is good control of CVRFs, the resting left ventricular ejection fraction (LVEF) is $\geq 50\%$, and there is no inducible ischaemia or electrical instability [10]. There are, however, limited longitudinal data to ascertain if these recent Task Force 8 recommendations support this level of clearance for patients with CAD wishing to undertake competitive sport. Accordingly, the aim of this study was to evaluate the incidence of major adverse cardiac events (MACE), including stent restenosis (SR), stent thrombosis (ST), new significant coronary stenosis (NCS), myocardial infarction, heart failure, cardiac arrest or cardiac death in patients with CAD following percutaneous coronary intervention (PCI), who continued to partake in intensive physical activity (including competitive sport) after the procedure.

Methods

This retrospective study involved 19 French cardiology institutions; ethical approval was provided by the Rennes University Hospital Ethics Committee. All patients provided informed consent and gave permission for the anonymous use of their medical data for research purposes. This study was conducted according to the World Medical Association Declaration of Helsinki.

Participants

Inclusion criteria

Men with CAD who underwent PCI were eligible for inclusion in the study. Each patient had to be:

- treated with at least one coronary stent;
- present with no significant residual stenosis on the main epicardial coronary arteries;
- be asymptomatic;

- demonstrate good control of CVRFs;
- have an LVEF $\geq 50\%$;
- demonstrate no inducible ischaemia or electrical instability [10].

Each patient completed a questionnaire that documented physical activity (PA) status (activity type, regularity, frequency, duration and intensity) post-PCI procedure. Only patients who performed ≥ 4 h/week of PA 6 months after the PCI were included. Patients were divided into three groups:

- those partaking in moderate leisure-time sport (MLS), i.e. PA under the ventilatory threshold;
- intensive leisure-time sport (ILS), i.e. PA above the ventilatory threshold but not partaking in competitive sport;
- those regularly partaking in competitive sport (endurance running, including marathons, road cycling or mountain biking, swimming, basketball, football and racket sports) (CS) [11].

Importantly, at each yearly follow-up examination, the attending cardiologist verified that the patient continued to maintain their PA status and thus remained in the allocated group.

Exclusion criteria

Exclusion criteria were incomplete revascularization, coronary artery bypass grafting, abnormal LVEF, atrial fibrillation or complex ventricular arrhythmias, and irregular levels of competitive sport or physical activity (< 4 h/week) following the PCI.

Medical evaluation

Only information documented by the attending cardiologist was recorded. Indication for PCI was specified as stable or unstable angina, or myocardial infarction, in accordance with the recommendations provided by the European Society of Cardiology Task Force on the management of stable CAD [12]. Details of a post-PCI cardiovascular rehabilitation programme, together with CVRFs, were collected. The CVRFs documented were:

- cardiovascular disease history in a first-degree relative (father aged < 55 years or mother < 65 years or sibling);
- active or former (> 3 consecutive years) smoking;
- obesity;
- medical treatment for any of the following (hypertension, diabetes or cholesterol disorder).

MACE incidence and classification

All patients attended all of their yearly examinations during the follow-up period. At each appointment, clinical, 12-lead electrocardiogram, echocardiography and exercise stress test data were recorded, along with information on any MACE events. To corroborate the occurrence of MACE, each patient was contacted by telephone (by GK) to verify the occurrence or absence of any MACE between the annual follow-up examination and data capture closure. Thus, a robust MACE incidence rate could be calculated. MACE was classified as SR, ST, NCS, myocardial infarction, heart failure, cardiac arrest or cardiac death. Incidence of SR or

Table 1 Baseline characteristics of men with CAD included in the study.

Characteristic	Overall population <i>n</i> = 108	MLS <i>n</i> = 29	ILS <i>n</i> = 58	CS <i>n</i> = 21	<i>P</i>
Age (years)	57.3 ± 9.1	61.3 ± 7.5	57.1 ± 9.2	52.2 ± 8.0	< 0.01
BMI (kg/m ²)	25.1 ± 2.9	25.0 ± 3.1	24.8 ± 2.6	25.9 ± 3.4	0.39
LVEF (%)	59.9 ± 6.9	59.7 ± 7.3	59.4 ± 7.0	61.6 ± 6.2	0.56
<i>Cardiovascular risk factor</i>					
Smoking	6 (5.6)	1 (3.5)	5 (8.6)	0	0.25
Hypertension	42 (38.9)	12 (41.4)	21 (36.2)	9 (42.9)	0.88
Dyslipidaemia	52 (48.2)	18 (62.1)	25 (43.1)	9 (42.9)	0.34
Type 2 diabetes	10 (9.3)	3 (10.3)	7 (12.1)	0	0.53
Obese (BMI ≥ 30 kg/m ²)	7 (6.5)	3 (10.3)	1 (1.7)	3 (14.3)	0.21
<i>Cardiac medications</i>					
Beta-blocker	90 (83.3)	24 (82.8)	48 (82.8)	18 (85.7)	0.97
Antiplatelet ^a	107 (99.1)	29 (100)	58 (100)	20 (95.2)	0.95

Data are expressed as mean ± standard deviation or number (%). *P* values indicate the inter-group comparison. BMI: body mass index; CS: competitive sport group; ILS: intensive leisure-time sport group; LVEF: left ventricular ejection fraction; MLS: moderate leisure-time sport group.

^a For the recommended treatment duration.

definite ST confirmed by coronary angiography was recorded in accordance with classic definitions [13], together with the incidence of NCS. The incidence of MACE was calculated according to patient PA level (MLS, ILS or CS).

Statistical analysis

Quantitative values are expressed as mean ± standard deviation, with differences between groups analysed using one-way ANOVA. Qualitative values are expressed as number and/or percentages and differences between groups were tested using the χ^2 test, as appropriate. Fisher's exact test was used to compare MACE incidence between groups. Significance was set at 0.05, with all data analysed using Statistica v8 (Systat Software, Inc. Chicago, IL, USA).

Results

Participants

From 108 patients with CAD (57.3 ± 9.1 years, range 38–78 years), just over half participated in ILS (*n* = 58, 53.7%), 29 (26.9%) in MLS and 21 (19.4%) in CS. Whilst CS participants were younger than MLS and ILS participants (*P* < 0.01), no other difference was noted between the groups (Table 1).

Percutaneous coronary intervention

Between 1997 and 2013, 164 stents were inserted into 152 arteries; 97 bare-metal stents (BMS; 1997–2013) and 67 drug-eluting stents (DES; 2003–2013). More DES were implanted in ILS than in MLS or CS participants; no between-group differences were noted for BMS (Table 2). Two patients presented with myocardial infarction as the first coronary event (one MLS and one ILS, *P* = 0.76). Fifty-six patients participated in a cardiac rehabilitation programme after PCI, with no difference between groups.

CVRFs and PA status before and after PCI are shown in Table 3. Globally, smoking (*P* < 0.001) and obesity (*P* < 0.01) decreased post-PCI. However, no reduction in the prevalence of hypertension, dyslipidaemia or type 2 diabetes was observed. Twenty patients who were sedentary before PCI became physically active after the procedure (MLS *n* = 18; ILS *n* = 1; CS *n* = 1). From those patients who were physically active before their acute CAD event, the number of patients who maintained MLS did not change significantly, but ILS increased (*P* < 0.001) whilst the number of CS participants decreased (*P* < 0.05), with 21 men continuing to participate in CS following PCI intervention.

Incidence of adverse cardiac events post-PCI

During the follow-up period (57.6 ± 46.0 months, range 6–192 months), MACE occurred in 17 patients (15.7%; mean age 55.2 ± 8.3 years) (Table 4). There was no statistically significant difference in the incidence of MACE between the groups (*P* = 0.10). A MACE occurred during physical exertion in 10 of the 17 (58.8%) patients. The remaining seven events were not related to exercise, and included angina (*n* = 2), abnormal routine maximal exercise tests (*n* = 3), and during a coronary angiography investigation (*n* = 1); data were unavailable in one patient. No heart failure episodes, cardiac arrests or cardiac deaths occurred. One MLS patient had a myocardial infarction (not associated with physical activity), and underwent repeat revascularization without complication.

Globally, 4.6% of participants had isolated SR, and 3.7% each had SR plus NCS, ST or isolated NCS. In the four patients (mean age 49.2 ± 8.6 years) with ST, all had a BMS, with MACE occurring 29.2 ± 9.8 months (17–41 months) post-PCI. Stent thrombosis occurred in a greater number of CS than MLS or ILS patients (*P* ≤ 0.01) (Table 4). Nine patients (55.7 ± 8.5 years) had an SR, alone or in combination with an NCS, occurring in 11 stents (BMS *n* = 7 and DES *n* = 4) after 13.2 ± 15.6 months (1–52 months). For eight patients, an NCS was observed, with SR in four patients, and a double SR

Table 2 Coronary history and procedural data of the study cohort.

Variable	Global population (n = 108)	MLS (n = 29)	ILS (n = 58)	CS (n = 21)
<i>First coronary event</i>				
Stable angina	42 (38.9)	6 (20.7)	26 (44.8)	10 (47.6)
Unstable angina	28 (25.9)	6 (20.7)	16 (27.6)	6 (28.6)
Myocardial infarction	41 (38.0)	18 (62.1)	18 (31.0)	5 (23.8)
Mean number of stents/patient	1.5 ± 0.8	1.3 ± 0.5	1.6 ± 0.9	1.5 ± 0.8
<i>Number of stents implanted (n = 164)</i>				
One	68 (63.0)	20 (69.0)	35 (60.3)	13 (61.9)
Two	30 (27.8)	8 (27.8)	16 (27.6)	6 (28.6)
Three or more	10 (9.3)	1 (3.4)	7 (12.1)	2 (9.5)
<i>Type of stent</i>				
BMS	97	32	41	24
DES	67	7	52 ^a	8
<i>Location of stent (n = 152)</i>				
Left anterior descending artery	85/108 (78.8)	23	51	11
Circumflex artery	27/108 (19)	6	16	5
Right coronary artery	42/108 (38.9)	11	18	13
Left main artery	2/108 (1.9)	0	0	2

Data are expressed as mean ± standard deviation or number (%). BMS: bare-metal stent; DES: drug-eluting stent; MLS: moderate leisure-time sport group; ILS: intensive leisure-time sport group; CS: competitive sport group.

^a $P < 0.05$, ILS DES group compared with MLS and CS groups.

Table 3 Evolution of cardiovascular risk factors and sports practise after the stenting procedure (n = 108).

Variable	Before stenting	After stenting	P
<i>Risk factor</i>			
Smoking	41 (37.9)	6 (5.6)	< 0.001
Hypertension	30 (27.8)	42 (38.9)	0.08
Dyslipidaemia	52 (48.1)	52 (48.1)	0.77
Type 2 diabetes	6 (5.6)	10 (9.3)	0.29
Obesity	19 (17.6)	7 (6.5)	< 0.01
<i>Sports practise</i>			
No sport	20 (18.5)	0	< 0.001
MLS	22 (20.4)	29 (26.9)	0.26
ILS	31 (28.7)	58 (53.7)	< 0.001
CS	35 (32.4)	21 (19.4)	< 0.05

Data are expressed as number (%). The P values concern the inter-group comparison. CS: competitive sport; ILS: intensive leisure-time sport; MLS: moderate leisure-time sport.

Table 4 Occurrence of major adverse coronary events during a mean follow-up of 57.6 ± 46.0 months.

Event	Global population (n = 108)	MLS (n = 29)	ILS (n = 58)	CS (n = 21)	P
All MACE	17 (15.7)	5 (17.2)	7 (12.1)	5 (23.8)	0.10
Isolated SR	5 (4.6)	1 (3.5)	3 (5.2)	1 (4.8)	0.24
SR + NCS	4 (3.7)	1 (3.5)	3 (5.2)	0	0.12
ST	4 (3.7)	1 (3.5)	0	3 (14.3)	0.01
Isolated NCS	4 (3.7)	2 (6.9)	1 (1.7)	1 (4.8)	0.46

Data are expressed as number (%). The P values concern the inter-group comparison. CS: competitive sport group; ILS: intensive leisure-time sport group; MACE: major adverse cardiac events; MLS: moderate leisure-time sport group; NCS: new coronary stenosis; SR: stent restenosis; ST: stent thrombosis.

observed in two patients (ILS $n=1$; CS $n=1$); four patients (60.0 ± 4.5 years) had an NCS without associated SR, occurring after 42.5 ± 54.7 months (4–121 months). Each case required a new angioplasty.

Discussion

The aim of this study was to evaluate the incidence of MACE in CAD patients following PCI who continued to participate in intensive PA post-procedure. The main finding is that from 108 patients followed for 4 years and 9 months, MACE occurred in 15.7%, with no statistically significant difference in the incidence between PA groups. During the follow-up period, ST was significantly more frequent in CS patients than in MLS or ILS patients and no other difference was observed concerning ST and NCS. Finally, MACE occurred during physical exertion in 59% of patients; importantly, however, no heart failure episodes, cardiac arrests or cardiac deaths were documented.

To our knowledge, this is the first study to examine the incidence of MACE in patients with known CAD, in relation to their PA status. The question of how intensely a patient with CAD can exercise is a frequent conundrum faced by physicians. Until 2015, previous recommendations for intensive sports clearance in this population were extremely restrictive [11]. More recent North American recommendations, however, state that clearance for all competitive sports participation is reasonable in patients with CAD presenting with no inducible ischaemia, no electrical instability, a normal LVEF and good control of their CVRFs [10]. The population of patients with CAD who had undergone PCI in this study matched the clearance criteria set out by these recommendations and our data support the exercise eligibility proposed [10].

The prevalence of MACE was 15.7% in our study, with stent complications accounting for 77%. We observed more MACE through BMS complications than through DES complications (75% vs. 25%, respectively). This observation concurs with data from the general population [14], and underscores the increased risk of MACE with BMS versus DES [15].

In the present study, SR was the most frequent MACE (53%). It affected nine patients and 11 stents (BMS $n=7$; DES $n=4$), with two cases of two simultaneous SR. In one case, the SR (DES) was subacute (1 month). For six patients (BMS $n=5$; DES $n=1$), the SR was observed at least 12 months after the stent procedure. Intensive sport practise was associated with SR in seven cases (ILS $n=6$; CS $n=1$). For four patients, the SR was associated with an NCS. In the general population, SR is reportedly more frequently in BMS than DES (10% vs 5%, respectively) [14–16].

SR is the most feared complication after stent implantation. In the general population, the early (< 1 year) incidence of ST ranges from 0.6% to 3.4% and the incidence of early and late ST appears similar between DES and BMS [17–19]. Whilst the present study observed one patient who was non-compliant with his antiplatelet treatment, the mean time between PCI and the ST event was greater than 2 years. Data from a large registry suggested that very late ST may occur with an annual rate of 0.4–0.6% after implantation of a first-generation DES [18]. In our patients, all ST concerned BMS, with an annual rate of 0.57% for all stents. Thus, the

incidence of ST in our population appears to be similar to that in the general population. Classically, ST may be symptomatic or asymptomatic [15]. For all of our patients, ST presented with acute angina and in all cases, new PCI was successful.

The pathophysiological mechanism proposed for ST is a fast and unexplained development of in-stent neoatherosclerosis [20]. A plaque rupture associated with increased endothelial shear stress, together with neoatherosclerosis, likely accounts for most ST events [20]. Based on the predisposing factors for both early and late BMS, thrombosis due to non-compliance with antiplatelet agents and acute exercise are proposed [21]. Although the role of acute exercise in ST is not clear, exercise training during cardiac rehabilitation is safe (1.2/1000 patients or 0.8/10⁶ patient-hours of exercise) for CAD patients after PCI [22].

The risk of vigorous exercise acting as a triggering mechanism for late ST has been previously considered, but mainly in untrained patients [23]. Three mechanisms are proposed:

- the balance between coagulation and fibrinolysis;
- endothelial stress due to haemodynamic alterations;
- hormonal and dehydration changes.

During strenuous exercise, a transitory hyperreactivity of platelets is associated with a biphasic change in the fibrinolysis rate, which increases upon exercise initiation and rapidly decreases afterwards [24,25]. In healthy untrained subjects, the balance between coagulation and fibrinolysis appears to be well maintained [26]. However, in patients with CAD, the equilibrium between fibrinolysis and coagulation during peak exercise appears to be disturbed in favour of coagulation, especially during post-exercise recovery, which may favour the occurrence of stent occlusion [25]. In the present study, all cases of ST presented with symptoms after intense sport practise.

A beneficial effect of moderate endurance training on the red cell deformability during exercise is observed in sedentary people as well as in patients with CAD [24]. However, the increase in endothelial shear stress associated with intense exercise may traumatize the inner intimal vascular layer, making them prone to rupture [27]. Intense and/or long duration exercise is associated with a high concentration of catecholamines in the blood; combined with dehydration, this environment may favour vasoconstriction of coronary artery stenosis and cause endothelial injury [28]. In conclusion, a combination of coagulation perturbations, increased arterial wall stresses, dehydration and catecholergic changes due to intensive exercise, could favour ST occurrence. For the population examined in the present study, the role of collateral circulation can be considered. Indeed, the beneficial effect of physical training on coronary collateralization has been reported [29], although a subsequent meta-analysis proposed that it could be associated with an increased risk of both ST and SR [30].

Regular and moderate endurance exercise is recommended as a safe and inexpensive way to prevent and treat CAD [3]. Our study demonstrated that few athletes had additional MACE following initial PCI, despite regular PA and good control of CVRFs. We observed a significant NCS in a new arterial location in eight patients (7.2% of the whole population), with a yearly incidence of 1.8%.

This observation confirms that regular PA does not confer immunity against the development of CAD in middle-aged trained men. Indeed, compared with sedentary men of similar age and a similarly low atherosclerotic risk profile, master's athletic men present a higher prevalence of high coronary artery calcium scores and a greater number of significant atherosclerotic plaques [8].

Limitations

We note two main limitations. This was a retrospective observational study involving a relatively small number of men with CAD due to the restrictive clearance criteria set out by the US recommendations [10] and to the relatively high level (≥ 4 h/week) of PA requested for participation. However, we feel our results help support physicians when advising men with CAD who wish to undertake intensive (competitive and non-competitive) sport. No untrained CAD control cohort was studied, but the scientific literature provides enough data concerning the incidence of MACE in this population.

Conclusion

MACE occurred in 15.7% of men during follow-up, with no significant difference in the incidence of MACE between MLS, ILS or CS physical activity groups. Stent thrombosis was significantly more frequent in CS participants than in MLS or ILS participants; especially in those with a BMS. MACE occurred during physical exertion in 59% of patients, but there were no heart failure episodes, no cardiac arrests and no cardiac deaths documented. Our data supports the Task Force 8 exercise eligibility recommendations in patients with CAD with no inducible ischaemia, no electrical instability, a normal LVEF and a good control of their CVRFs, who wish to partake in intensive competitive sport.

Authors' contributions

J.M.G., L.C. and F.C. contributed to the conception or design of the work. J. M. G., F. S., L. C., S. C., J.C.V. and S.D. contributed to the acquisition and analysis of data for the work. J. M. G., G. K., and F.C. drafted the manuscript. M.W. and F.S. critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Disclosure of interest

The authors declare that they have no competing interest.

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