ESC European Society of Cardiology

European Journal of Preventive Cardiology (2022) **00**, 1–17
https://doi.org/10.1093/eurjpc/zwab198

POSITION PAPER

Cardiovascular effects of doping substances, commonly prescribed medications and ergogenic aids in relation to sports: a position statement of the sport cardiology and exercise nucleus of the European Association of Preventive Cardiology

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Received 7 September 2021; revised 30 October 2021; editorial decision 9 November 2021; accepted 9 November 2021

The use of substances and medications with potential cardiovascular effects among those practicing sports and physical activity has progressively increased in recent years. This is also connected to the promotion of physical activity and exercise as core aspects of a healthy lifestyle, which has led also to an increase in sport participation across all ages. In this context, three main users' categories can be identified, (i) professional and amateur athletes using substances to enhance their performance, (ii) people with chronic conditions, which include physical activity and sport in their therapeutic plan, in association with prescribed medications, and (iii) athletes and young individuals using supplements or ergogenic aids to integrate their diet or obtaining a cognitive enhancement effect. All the substances used for these purposes have been reported to have side effects, among whom the cardiovascular consequences are the most dangerous and could lead to cardiac events. The cardiovascular effect depends on the type of substance, the amount, the duration of use, and the individual response to the substances, considering the great variability in responses. This Position Paper reviews the recent literature and represents an update to the previously published Position Paper published in 2006. The objective is to inform physicians, athletes, coaches, and those participating in sport for a health enhancement purpose, about the adverse cardiovascular effects of doping substances, commonly prescribed medications and ergogenic aids, when associated with sport and exercise.

Keywords Cardiovascular side effects • Doping • Ergogenic aids • Energy drinks • Medications

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Introduction

Doping is defined as the use of a substance or method, which is potentially dangerous to athletes' health or capable of enhancing their performance.[1] In order to lead a collaborative worldwide movement for doping-free sport, the World Anti-Doping Agency (WADA), an international independent agency, composed and funded equally by the sport movement and governments of the world, was established in 1999. In 2004, the WADA Code was introduced (latest revision in 2021), and up to date, it has been accepted by approximately 700 sport organizations, including the International Olympic Committee (IOC), the International Paralympic Committee (IPC), International Federations (IFs), National Olympic and Paralympic Committees, as well as National and Regional Anti-Doping Organizations (NADOs and RADOs). Moreover, the WADA updates yearly the List of Prohibited Substances and Methods.[2] Nevertheless, the use of novel and unclassified agents or off-label use of prescription medications continues to pose a problem in terms of safety, equity, and regulation. This is due to the lag between the time athletes start experimenting with novel substances, to the time when authorities become aware of these agents and are able to track them.[3] Based on a recent systematic review,[4] the prevalence of doping in competitive sport ranged from 0% to 73%, with most falling under 5% and it impacts all levels of sport, from elite to amateur levels, with an increasing use in recreational athletes, who have less health surveillance.[5] Furthermore, yearly WADA reports confirm that most accredited doping control laboratories have an adverse analytical findings of approximately 2%.[6] A retrospective re-analysis of anti-doping rule violations of all samples collected at Summer Olympics Games from 1968 to 2012 revealed that the majority of positive re-tested samples contained metabolites of exogenous anabolic androgenic steroids (AAS),[7] but the list of the WADA banned drugs is extensive. The prevalence of the reported adverse analytical findings by doping category is presented in *Table 1*. Moreover, it is worthy to distinguish between the substances and methods prohibited at all times (in- and out-of-competition) and those prohibited in-competition only.

This article is an update of the 2006 adverse cardiovascular effects of doping in athletes position paper published by the European Society of Cardiology sports cardiology study group.[8] The objective of this position paper is to raise awareness and to inform cardiologists, physicians, and sport enthusiasts of the adverse cardiovascular effects of doping substances, performance-enhancing drugs, substances of abuse, and most frequently prescribed medication, with particular emphasis on their cardiovascular effects during sport participation and exercise. The authors undertook a comprehensive review of the published evidence. A critical evaluation of all substances implicated in doping, commonly prescribed medication and ergogenic aids athletes may use was performed, including assessment of pharmacological and pathophysiological mechanisms, impact on the cardiovascular system, impact on exercise performance, and the risk benefit ratio.

Doping substances

Anabolic agents

AAS are widely used not only by athletes competing in power or strength sports but also in endurance sports to aid in recovery and strength. The simultaneous use of AAS and erythropoietin is common both in strength and endurance athletes.[9] AAS act by activating androgen receptor (AR) signalling. Moreover, increased testosterone levels inhibit glucocorticoid action and protein catabolism. These mechanisms in combination with the stimulation of growth hormone and insulin-like growth factor-1 (IGF-1) axis cause muscle protein formation.[10] These effects are enhanced when combined with regular training, leading to increased muscle mass and strength and reduced fat body mass.[11–13] Significant increases in physical performance and strength have been observed in double-blinded randomized trials comparing AAS vs. placebo.[14,15]

Mortality amongst athletes doping with AAS is estimated to be 6–20 times higher than in clean athletes, and around 30% of these deaths can be attributed to cardiovascular causes.[16] Four principal mechanisms responsible for sudden cardiac death (SCD) have been proposed in AAS abusers: (i) the atherogenic model, (ii) the thrombosis model, (iii) the nitric-oxide mediated vasospasm model, and (iv) the direct myocardial injury model.[17] Attempting to study the cardiovascular side effects of AAS comes with inherent limitations as ethical and legal considerations prohibit their administration in athletes even for research purposes. Accordingly, AAS preparations, dosage and duration of AAS use are based on athlete self-reporting in most studies. Additionally, the majority of studies included a small population size and most athletes use combination of different substances, prohibited or legal, such that results cannot be solely attributed to AAS use.[18] Despite these limitations, the results of 49 studies over the last 10 years in 1467 athletes taking AAS show that the most common disorders attributable to their use include early onset of coronary heart disease, hypertension, myocardial infarction and heart failure, arrhythmias, and SCD.[19]

AAS and coronary atherosclerosis

Regarding atherosclerotic heart disease, Baggish *et al.*[20] found that there was an increase in coronary artery plaque volume in AAS users when compared with non-using weight-lifters, leading to rapidly progressive coronary artery disease. Numerous studies have shown that otherwise healthy young AAS-using athletes have elevated levels of low-density lipoprotein, markedly reduced levels of high-density lipoprotein, and increased arterial blood pressure.[16,21] Impaired coagulation leading to thrombotic complications and myocardial infarction have also been described.[19] Chang *et al.*[22] suggested that AAS use may reduce synthesis of coagulation factors, inhibitors, and fibrinolytic proteins, causing a procoagulant state that may lead to myocardial infarction and other thrombotic complications. On the contrary, Corona *et al.*[23] in a systematic review and meta-analysis, reported no increased cardiovascular risk in 1448 patients receiving testosterone over a mean duration of 34 weeks.

Table 1 Prevalence of adverse analytical findings by substance category in WADA Anti-Doping Administration and Management System (ADAMS)—(WADA, 2019 Anti-Doping Testing Figures)

Substances and methods	% of all ADAMS reported findings
Anabolic agents	43.66
Beta-2 agonists	3.66
Beta-blockers	0.48
Cannabinoids	3.11
Chemical and physical manipulation	0.05
Diuretics and other masking agents	16.20
Enhancement of oxygen transfer	0.05
Glucocorticosteroids	5.50
Hormone and metabolic modulators	8.66
Narcotics	0.72
Peptide hormones, growth factors and related substances	3.30
Stimulants	14.62

AAS and cardiomyopathies

Numerous studies have shown that AAS users are at increased risk for cardiomyopathy and left ventricular (LV) dysfunction. The existence of AAS-induced cardiomyopathy has been confirmed by data derived from post-mortem examination, echocardiography, and cardiac magnetic resonance imaging.[24–26] Indeed, AAS use has been shown to change the physiological cardiac remodelling typical of athletes to a pathophysiological cardiac hypertrophy with an increased risk of life-threatening arrhythmias. The condition shares similar characteristics with hypertrophic cardiomyopathy, showing greater cardiac mass, LV wall thickness/hypertrophy (LVH), prevalence of cardiac fibrosis, and impairment of systolic and diastolic LV function.[25,27–30] LVH was attributed to either arterial hypertension or to the direct binding of AAS to the ARs on the myocardium.[20,31] Even in cases with normal standard echocardiogram, tissue Doppler, strain, and strain rate echocardiography have been used to detect early regional myocardial dysfunction after AAS abuse. Mean dosage and duration of AAS use were found to be strongly associated with a subclinical reduction of both systolic and diastolic LV function.[29] Even past illicit AAS use was found to be associated with impaired LV global longitudinal strain, suggesting cardiac systolic dysfunction years after AAS cessation.[32] To explain early ventricular dysfunction in AAS users, it was suggested that high blood pressure may have a negative effect.[33] Montisci *et al.* supported that AAS can directly damage myocardial cells, causing a subsequent focal repair process and a disproportionate increase in the connective tissue content of the damaged area.[26] Cecchi *et al.*[34] described a direct apoptotic cardiac and endothelial change in the heart tissue in patients with heart failure who had a history of AAS abuse. Additionally, peak systolic right ventricular free wall strain and strain rate were found to be reduced in bodybuilders AAS users compared with non-users.[35] D'Andrea *et al.*[31] reported a more impaired left atrial (LA) deformation and LA systolic dysfunction with the use of speckle echocardiography in AAS users. LA enlargement has been proposed as a predictor of common cardiovascular outcomes such as atrial fibrillation, stroke, and death.[36] Many case reports described episodes of SCD in anabolic abuse, linked AAS to potentially life-threatening arrhythmias.[17,19] Hypertrophy, fibrosis, and necrosis represent a substrate for arrhythmias, especially when combined with exercise. BarbosaNeto *et al.*[37] found a marked cardiac autonomic alteration in AAS users, with a shift towards sympathetic modulation predominance and vagal attenuation. In a recent study, Kouidi *et al.*[38] found that long-term AAS in strength-trained athletes decreases baroreflex sensitivity (BRS) and short-term heart rate variability indices due to sympathetic overestimation. Moreover, a positive correlation between the reduced BRS and early LV diastolic dysfunction, which was mentioned in AAS users, was determined. An association between nandrolone use and life-threatening ventricular arrhythmias was also supported in an experimental study.[39] Moreover, Marocolo *et al.*[40] reported that anabolic administration in rats associated with cardiac autonomic dysfunction and ventricular repolarization and reflected an increase in QT interval (*Figure 1*).

Human growth hormone

Human growth hormone (hGH) is an endogenous neurohormone considered to have anabolic effects when used in supra-physiologic doses. There is little evidence that recombinant hGH improves performance although it may aid more rapid recovery from soft tissue damage.[9] Little is known about the direct cardiovascular effects of excessive hGH administration in athletes; however, excess of endogenous hGH in patients with acromegaly may result in hypertension, congestive cardiac failure, and cardiomyopathy.[9] It has been suggested that hGH causes myocardial hypertrophy due to concentric remodelling,[41] and hGH may lead to increases in myocardial collagen deposition, fibrosis, cellular inflammation, and necrosis.[8,42] These alterations may be underlying mechanisms for malignant arrhythmias and the development of heart failure.[43] Finally, limited data suggest that hGH abuse can cause dose-dependent increase in cholesterol levels.[44]

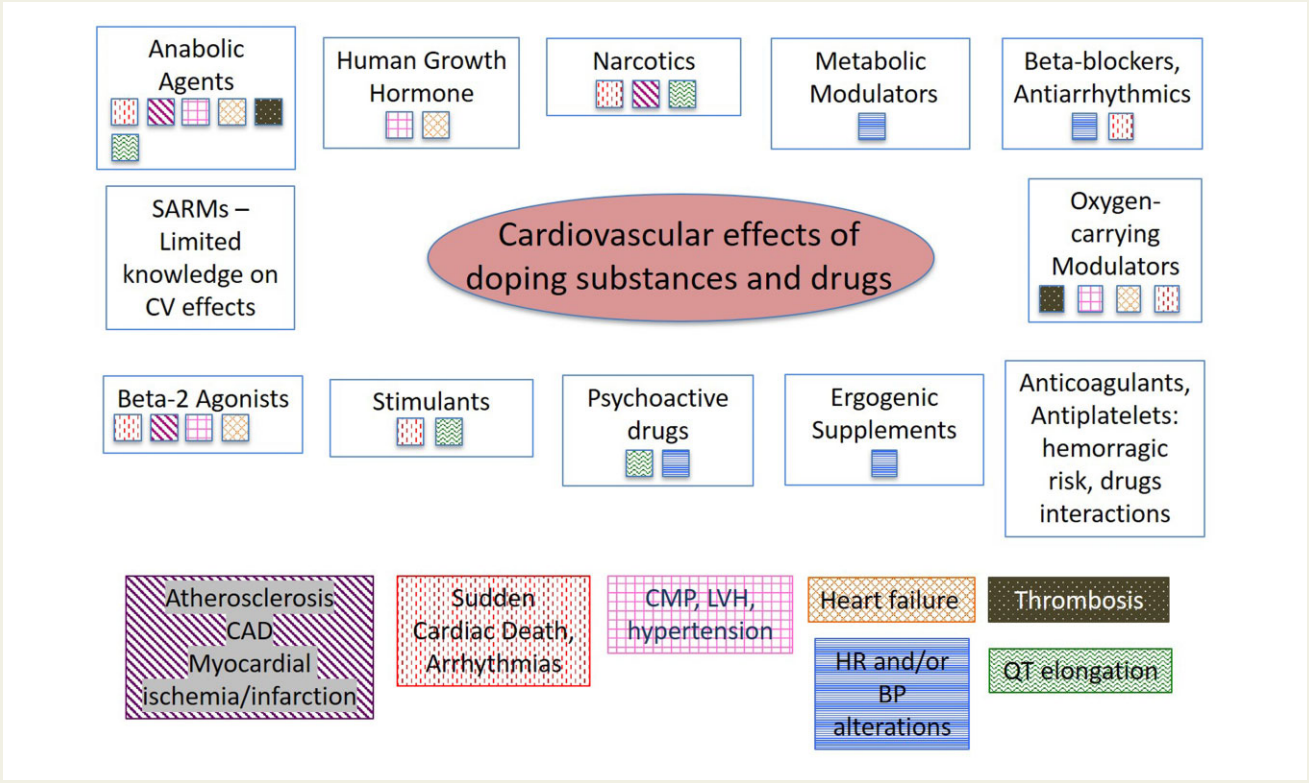

Figure 1 Cardiovascular effect of doping substances and drugs. The figure summarizes the main cardiovascular consequences of the different substance's categories. BP, blood pressure; CAD, coronary artery disease; CMP, cardiomyopathy; LVH, left ventricular hypertrophy; SARM, selective androgen receptor modulators.

Selective androgen receptor modulators

Selective androgen receptor modulators (SARMs, e.g. thymosin beta-4) are a new class of substances designed to isolate the androgenic and anabolic effects of AAS. Limited information is available on the cardiovascular side effects of the several artificially designed SARMs that are used among athletes. Experimental data suggest that thymosin beta-4 can inhibit myocardial cell death, stimulate vessel growth, and activate endogenous cardiac progenitors.[45] At present, SARMs are considered experimental in humans with potential side effects including carcinogenicity and cardiovascular problems and their performance enhancing potential incompletely understood.

Narcotics

The WADA Prohibited List includes a number of narcotic analgesic drugs including buprenorphine, dextromoramide, diamorphine (heroin), fentanyl and its derivatives, hydromorphone, methadone, morphine, nicomorphine, oxycodone, oxymorphone, pentazocine, and pethidine. Narcotics may be used in athletes for treatment of pain due to sports-related injury, and post-traumatic pain syndrome in conjunction with an approved therapeutic use exemption (TUE). Oxycodone, a strong opioid analgesic, is increasingly used among young students and athletes for non-medical and recreational use.[46] Narcotics can cause dependency, a reduction in the perception of pain and a dangerous false sense of well-being. Several narcotics such as methadone and levomethadyl can also cause QT-lengthening and increase the risk of polymorphic ventricular tachycardia.[47] Other potential adverse effects include changes in QT dispersion, Takotsubo syndrome (stress cardiomyopathy), Brugada-like syndrome, and coronary artery diseases.[48]

Stimulants

Stimulants include mainly amphetamines and methylphenidate, which are commonly prescribed for the treatment of attention-deficit hyperactivity disorder (ADHD), a common condition in athletes in some regions of the world.[49] ADHD treatment typically relies on methylphenidate or its derivatives. These substances are prohibited according to the WADA Prohibited List.[2] Amphetamine-based treatment is contraindicated in people with familial or personal history of arrhythmic diseases, in particular those with a genetic basis. The use of amphetamines and methylphenidate in athletes is only allowed upon acceptance of a TUE application. More recently, another psychoactive substance known as captagon (fenethylline), became widely popular for its addictive properties and its use as a powerful physiological and psychostimulant factor. Captagon can promote high physical performance and endurance, cognitive enhancement, and reduction of sleep and food requirements.[50]

Stimulants have profound effects on the cerebrovascular and cardiovascular system, leading to congestive heart failure, acute myocardial infarction, cardiac chambers and valvular fibrosis, pulmonary hypertension, cerebral infarction, and haemorrhage.[51,52] Additionally, a drug-induced cardiomyopathy has also been described.[53]

Pathologic mechanisms of amphetamine-related cardiomyopathy may include: direct toxic effects, neurohormonal activation, alteration of calcium homoeostasis, oxidative stress, modulation of cardiac gene expression, and apoptosis.[54] The histology of this cardiomyopathy is characterized by concentric LVH, atypical nuclei, interstitial and perivascular fibrosis, vacuolation of the cardiomyocytes, and hypertrophy of the middle layer of small intramyocardial vessels.[55] It is well known that amphetamines stimulate the release of norepinephrine affecting both alpha (α) and beta (β) adrenergic receptor sites. Alpha-adrenergic stimulation causes vasoconstriction and an increase in total peripheral resistance, while β-adrenergic receptor stimulation leads to an increase in heart rate, stroke volume, and skeletal muscle blood flow. These adverse reactions lead to tachycardia, increased body temperature, respiratory frequency and blood pressure. Furthermore, amphetamine and other nervous system stimulants lead to indirect stimulation of the autonomic nervous system through the release of catecholamines, dopamine, and serotonin in nerve terminals of the central and peripheral nervous systems, leading to cardiac arrhythmias.[56] The anatomical and functional changes derived from amphetamine abuse could act as substrates of SCD.[57] Besides the arrhythmogenic effect of amphetamine-derived substances, these drugs have also shown to increase the risk of *heat-related illnesses*. In particular, amphetamines could potentially mask or delay fatigue by slowing the exercise-induced internal temperature rise. This could also impact the thermoregulatory system potentially resulting in muscle overheating.[58] The use of dopamine reuptake inhibitors has shown to improve performance but also to cause hyperthermia without any change in the perception of effort or thermal stress, potentially increasing the risk of exertional heat injuries.[59] A similar effect is known for ephedrine-containing compounds, due to the sympathomimetic effect, impairing the body's ability to dissipate heat properly.[60] Ephedrine can be found in many over-the-counter preparations available from pharmacies.

Metabolic modulators

Meldonium (Mildronate) is licenced for clinical use in some Eastern European countries as an anti-anginal with a mechanism of action that is believed to be modulated, at least in part, by lowering of L-carnitine availability and a reduction in mitochondrial energy production.[61] Rare adverse effects were reported in athletes, including allergic reactions (redness and itchy skin, urticaria, rash, and/or angioedema), dyspepsia, tachycardia, and alterations (increase or decrease) in blood pressure.[62] After anecdotal reports of widespread use at the London 2012 Olympics, meldonium was detected in the urine of 9% of athletes at the 2015 European Games[63] and was subsequently included in the WADA Prohibited List in January 2016.

Beta-2 agonists

Beta-2 agonists such as salbutamol and clenbuterol are commonly prescribed as treatment for asthma, given their broncho-dilatory effects on the smooth muscles of the lung. In 2011, Pluim *et al.*[64] performed a meta-analysis of randomized controlled trials comparing inhaled or systemic beta-2 agonists to placebo and concluded that there are no data to support a positive effect on maximal oxygen uptake (VO_{2max}), peak power output, strength, or endurance performance with inhaled beta-2 agonists (salbutamol, albuterol, or terbutaline). There was some weak evidence in support of high dose, oral salbutamol having a positive anaerobic capacity and strength[64]; however, the doses used would be expected to produce adverse side effects such as tachycardia, ventricular ectopy, tremor, and hypokalaemia.[65] However, clenbuterol has recently emerged as a drug of misuse in both elite and recreational athletic circles, due to its effect on beta-3 receptors in adipocytes, resulting in lipolysis and weight loss, a desirable side effect in sports where being lean and/or light weight is desirable.[66] The doses required to achieve these effects are 120–160 μg daily, which is three to four times higher than the doses that are generally prescribed for the treatment of reactive airway disease.[66] Not surprisingly, side effects such as tachycardia, gastrointestinal disturbances, and tremor are common in individuals using clenbuterol in these doses.[67] Additionally, supraventricular and ventricular arrhythmias, myocardial ischaemia, sudden cardiac failure, and cardiac arrest have been reported.[68,69] The arrhythmogenic effect of the drugs is related both to their direct beta-2 stimulant action (particularly when inhaled).[70] Moreover, evidence of myocardial damage indicated by increased troponin concentrations was reported.[71] Clenbuterol is noted as an anabolic agent on the WADA Prohibited List.

Glucocorticoids

Glucocorticoids are classified as doping substances and they are prohibited in-competition when administered by oral, intravenous, intramuscular, or rectal route.[72] It has been suggested that they may increase the availability of metabolic substrates and improve the use of energy sources during exercise.[73] The major cardiovascular side effects include hypertension and dyslipidaemia. Arterial hypertension is attributed to fluid retention, increased systemic vascular resistance mainly due to reduced nitric oxide availability, and enhanced myocardial contractility.[73] Dyslipidaemia is mediated by impaired lipid metabolism and elevated levels of total plasma cholesterol, triglycerides, and low-density lipoprotein cholesterol have been reported.[18]

Methods to increase skeletal muscle oxygen delivery

Blood doping

Usually involving transfusion of autologous blood collected some time earlier to increase red blood cell mass, has been used for decades. There are small, blinded trials which support the notion that oxygen carrying capacity and hence performance are improved with blood doping.[74,75]

- Berglund *et al.*[74] performed a single blinded study on six cross-country skiers and observed a mean 6% reduction in 15 km race time both 3 and 14 days after reinfusion of 1350 mL of autologous blood.
- Similar results were observed by Brien *et al.*,[75] who performed a double blinded cross-over study on six high level amateur 10 km runners, where haematocrit increased by 5% and 10 km race time was reduced by an average of 1 min after reinfusion of 400 mL of packed red blood cells, but not after infusion of saline.

Oxygen-carrying modulators

Agents that can increase oxygen availability to the working muscles, either by

(1) increasing oxygen content in the blood,
(2) improving cardiac output, or
(3) improving peripheral oxygen extraction.

are theorized to improve endurance performance; however, the evidence for a positive effect on performance for many of these agents (e.g. perfluocarbons) is limited.[76]

Recombinant human erythropoietin

Recombinant human erythropoietin (rhEPO) triggers an increase in red blood cell mass and haemoglobin (Hb) concentration similar to that of blood doping, as well as an improvement in maximal oxygen consumption. However, systematic evidence that this translates into a positive effect on performance is limited.[77,78]

- Birkeland *et al.*[79] demonstrated an increase in both haematocrit and VO_{2max} following administration of rhEPO over 4 weeks in a double-blind placebo-controlled study with only a small cohort of trained cyclists ($n = 10$). This period was needed to demonstrate a large treatment effect [42.7 vs. 50.8% ($P < 0.0001$) and 63.6 vs. 68.1 mL/kg/min ($P < 0.0001$) for haematocrit and VO_{2max}, respectively]. Although this study did not have a direct performance measure, time to exhaustion was increased significantly in the EPO group from 12.8 to 14 min ($P < 0.0001$) as compared to 13.1 to 13.3 min ($P = 0.04$) in the control group who were exposed to the same training effect.[79]
- Similar effects on VO_{2max} have been demonstrated in other placebo-controlled, double blind studies of rhEPO administration.[78,80–82] However, in the study of Heuberger *et al.*,[78] no improvement in a cycling race to Mont Ventoux with regards to time was observed despite a 5% improvement in VO_{2max}.

Nevertheless, it is not surprising that different EPO formulations, direct EPO receptor agonists and micro-dosing techniques are used by athletes with the aim of improving performance with minimal risk of being detected.

- The potential negative cardiovascular consequences of such practices are underlined by a prospective cross-sectional study of 3000 healthy senior adults, which found that each doubling in serum EPO level was independently associated with a 25% increase in risk of incident heart failure over a mean follow-up of 10 years.[83] Cardiac side effects occurring in athletes with 'haematologic doping' (especially if they are dehydrated and exposed to strenuous exercise) are secondary to the circulatory overload, induced by the increased erythroid mass, increased blood viscosity, and altered endothelial and platelet function with possible thromboembolic events and hypertension during effort.[70,77] Additionally, it increases blood viscosity, coagulation, and platelet reactivity leading to an increased risk of thrombosis.[84] Some case reports of thromboembolic events as well as acute coronary syndrome with intraventricular thrombus in athletes following rhEpo doping have been reported.[85]

Rather than increasing the blood oxygen content (like rhEPO), theoretically, the same effect may be achieved by increasing the amount of O_2 that Hb can deliver to the surrounding tissues. A number of agents with these properties have been reportedly used by athletes to aid performance:

- *Cobalt chloride* is a water soluble compound that can stimulate erythropoiesis and angiogenesis, presumably due to activation of hypoxia-inducible factor-1 (HIF-1) signalling.[86] Although the direct cardiovascular effects in humans have not been prospectively studied, unintentional ingestion of cobalt has been associated with the development of a dilated cardiomyopathy.[87,88]
- *Efaproxiral* (right shifting reagent 13, RSR13 or Efaproxiral) is a synthetic modifier of Hb, with *in vivo* studies demonstrating a shift in the Hb/O_2 dissociation curve to the right, thereby increasing the dissociation of O_2 in the peripheral muscles. RSR13 has been shown to increase oxygen consumption in stimulated canine skeletal muscle,[89] when inspired O_2 was supplemented. However, in humans breathing sea level air, the right-shift of the O_2 curve induced by RSR13 causes significant hypoxaemia under resting conditions[90] that is likely to be further exacerbated by exercise. The side effects associated with exercising in a hypoxaemic state are not known and it is unlikely that the athletes in whom it is being used are aware of the physiology and potential risks.

There have also been attempts to improve muscle oxygen delivery by improving cardiac output. Specific pulmonary vasodilators such as *Sildenafil* are rumoured to be widely used amongst some endurance athletes. The rationale would seem that by reducing pulmonary vascular resistance it may be possible to reduce cardiac work, particularly of the right ventricle, thereby enabling the heart to maintain a high level of function for longer.[91] This is especially relevant given that exercise seems to place a disproportionate load on the pulmonary circulation and right ventricle.[92] In patients with pre-existing cardiovascular risk factors some cardiovascular, cerebrovascular, and vascular events, have been reported in the past, in temporal association with the use of sildenafil,[93] nevertheless more recent data on phosphodiesterase-5 (PDE5) inhibitors confirm the safety of the pharmacological class even in patients with cardiovascular risk factors and suggest a potential cardio-protective role of these molecules.[94] However, no complications have been reported in healthy athletes. Several studies have assessed whether pulmonary vasodilators can improve exercise performance in healthy volunteers and athletes.

- Ghofrani *et al.*[95] documented improvements in exercise capacity in a randomized, double-blind placebo-controlled trial in 14 healthy subjects during normobaric hypoxia (10% O_2) and at altitude (Mount Everest base camp, 5245 m above sea level).

However, whilst studies using both PDE5 inhibitors and endothelin antagonists have consistently demonstrated improvements in haemodynamics and exercise performance in *hypoxic* conditions, they have failed to show any benefit in *normoxia*.[96–98] These agents are thus currently not banned by the WADA.

Commonly prescribed medications

Beta-blockers and antiarrhythmics

According to the List of Prohibited Substances and Methods,[2] beta-blockers are banned drugs in certain skill-based sports such as

shooting and archery, due to the performance benefit offered by lowering heart rate and reducing anxiety and tremor. Conversely, there is a general reluctance amongst athletes and prescribers to use beta-blockers in athletes with cardiovascular disease, due to the potentially detrimental effects of lowering the heart rate during exercise and reducing performance.[99] This is particularly true for endurance athletes and those requiring high cardiac output.

- In a small group of healthy, untrained volunteers, nebivolol (a beta-1 selective beta blocker), at a dose of 5 mg daily, was found to result in no significant reduction in peak power output or VO_{2max} as compared to placebo, despite a 14% reduction in peak heart rate.[99]
- In the same study, 100 mg of atenolol (also a beta-1 selective blocker) was shown to result in a 25% reduction in maximum heart rate, and 5% reduction in both peak power output and VO_{2max}, leading the authors to conclude that the lack of impact on performance of nebivolol may have been due to the lesser impact on peak heart rate at the prescribed dose, or perhaps the vasodilatory effects of nebivolol.
- At a dose of 240 mg/day, chronic administration of propranolol (a non-selective beta blocker) in untrained healthy subjects has been shown to reduce peak heart rate by 25%, VO_{2max} by 7.5% and maximum work load by 5%.[100]
- Sotalol (non-selective beta blocker) has been shown to have a dose-dependent reduction on maximum heart rate, with the reduction ranging from a 4% at a dose of 160 mg/24 h to 25% at 640 mg/24 h.[101]
- A similar dose-dependent relationship with heart rate reduction has also been demonstrated for propranolol (another non-selective agent), with marked individual variability.[102]

Flecainide

Flecainide is a Class 1c antiarrhythmic used for the suppression of supraventricular and ventricular arrhythmias. It is commonly prescribed preferentially in athletic populations over beta-blockers due to the commonly held notion that it does not affect resting heart rate nor exercise performance, and also by the fact that it is an alternative treatment option not prohibited according to the WADA Prohibited List. Flecainide may be used regularly or as a 'pill in the pocket' for athletes with sympathetic- and vagal-mediated paroxysmal atrial fibrillation in the absence of structural heart disease.[103]

- Whilst flecainide does not lower resting heart rate, it's effect on exercise heart rate was documented in a placebo double-blinded trial of 24 non-athletes, in whom exercise heart rate was reduced even at low-intensity exercise levels on a dose of 200 mg/day, with a difference of around 15 b.p.m. (9%) at peak exercise, despite no significant reduction in exercise time.[104]

Although maximum heart rate is not a surrogate for exercise capacity, there does appear to be a threshold of around 15% heart rate reduction beyond which exercise performance would be expected to be reduced, and individual variability in the dose-heart rate response. Therefore, when prescribing beta-blockers and antiarrhythmics in athletes a TUE is needed in certain type of sports and, it is prudent to perform maximal exercise tests before prescription and during up-titration of therapy to guide exercise prescription and expectations. For more specific recommendations on anti-arrhythmic prescription and use in exercising individuals, the reader is suggested to refer to the 'Recommendations for participation in leisure-time physical activity and competitive sports of patients with arrhythmias and potentially arrhythmogenic conditions. A position statement of the Section of Sports Cardiology and Exercise from the European Association of Preventive Cardiology (EAPC) and the European Heart Rhythm Association (EHRA), both associations of the European Society of Cardiology'.[105,106]

Anti-coagulants and antiplatelets

One of the most important topics in the management of the athlete in treatment with anti-coagulants is the haemorrhagic risk during physical activity caused by traumas or collision with opponents, thus mostly in team sports and sports with a high intrinsic traumatic risk.

- It is worth reminding that in subjects treated with vitamin K antagonists (VKAs), like acenocoumarin (Sintrom®) and warfarin (Coumadin®), an increase in the training intensity or volume can affect the international normalized ratio (INR) values.

VKA achieve their anticoagulant effect by interfering with several coagulative factors like II, V, VII, and IX. Their metabolism is significantly affected by substances acting on cytochrome (CYP) P450. VKA require periodic INR control and have a delayed and prolonged effect that lasts even after suspension.

Another class of anti-coagulants is made of new oral anti-coagulants (NOACs). NOACs are thrombin selective inhibitors (Dabigratan) or of the activated X Factor (Rivaroxaban, Apixaban, and Edoxaban).

- It is still unknown if the NOAC's effect is influenced by exercise intensity and volume.
- NOACs have a short half-life and they are metabolized mostly through renal and hepatic excretion, therefore have a better and safer efficacy profile.
- Given their pharmacokinetics, bioavailability, efficacy, and safety NOACs should be preferably prescribed in physically active and exercising subjects.
- Furthermore, NOACs have very mild interactions with cardiovascular drugs, like atorvastatin, verapamil, diltiazem, quinidine, amiodarone, and dronedarone.

Having only recently been introduced, long-term therapy effects still require further investigation, in particular for the possible drug–drug interactions and the inhibiting or promoting effect on CYP3/A/4, which is directly involved in the hepatic clearance, for example, of rivaroxaban and apixaban. There is a paucity of long-term data about NOAC's risk/benefit profile in the clinical management of athletes.

The most commonly used antiplatelet drugs include aspirin, clopidogrel (Plavix®), prasugrel (Efient®), and ticagrelor (Brilique®). Just like anti-coagulants, antiplatelet medications increase the haemorrhagic risk, particularly in physically active individuals that might be involved in contact sports or sports with a higher intrinsic risk of injury.

When establishing the individual risk, it is important to consider also other age-related cardiovascular diseases that might increase the likeliness of cardiovascular events such as coronary artery disease, hypertension, and atrial fibrillation. In this group of patients, anti-coagulants and antiplatelet drugs reduce the risk of cardiovascular events but at the same time increase the risk of exercise-related and

spontaneous haemorrhagic events. Thus, when prescribing this drug category to the exercising subject, several factors need to be addressed:

(1) age,
(2) sex,
(3) coexisting cardiovascular disease (in case of atrial fibrillation the CHA_2DS_2-VASc score), and
(4) type and intensity of the physical activity practiced.

More detailed information on intensity and exercises prescription can be found in the recently published '2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease'.[107]

Psychoactive drugs

Benzodiazepines

Benzodiazepines differ among one another for kinetics, metabolic path, and active metabolites and should not be taken for a period exceeding 3–4 weeks because of the risk of tachyphylaxis and addiction. Chronic use can cause nocturnal hypoventilation, with a decrease in tissue oxygenation and clinical consequences. Particular attention should be paid to symptoms occurring after withdrawal of the agents (withdrawal syndrome):

- In drugs with a short/medium half-life (*t*1/2) like triazolam, the withdrawal syndrome is more likely to occur once the treatment is interrupted while it rarely appears after cessation of drugs with a long *t*1/2.
- Withdrawal syndrome is virtually absent with molecules such as zolpidem and zopiclone.
- Symptoms arise proportionally to *t*1/2 (e.g. 24 h for lorazepam, 3–7 days for diazepam).
- Withdrawal syndrome can cause
  - arrhythmic episodes such as
    (1) sinus tachycardia,
    (2) atrial fibrillation and atrial flutter,
    (3) supra- and ventricular cardiac ectopy, and
  - atrial pressure abnormalities such as
    (1) systolic hypertension,
    (2) orthostatic hypotension,
    (3) symptoms of sympathetic hyperactivity with diaphoresis, agitation, anxiety, tremors, and delirium.
- A beta-blocker treatment is common in case of withdrawal syndrome.[108]

Antidepressants and antipsychotics

Classic anti-depressant *tricyclics* (ADTs) are non-selective inhibitors of serotonin and noradrenaline reuptake. They can cause cardiotoxicity through different mechanisms, leading to impaired cardiac contractility and arrhythmias.[109]

- The most common effects, usually depending on the dose, are QRS enlargement, atrioventricular (AV) blocks to different extents, QT lengthening, and negative inotropic effect with a reduction in the ejection fraction.
- They can also cause, especially in older athletes, Raynaud's phenomenon, orthostatic hypotension, and sinus tachycardia and bradycardia.
- Some antidepressants and antipsychotics might cause: QT lengthening with the torsadogenic risk of producing long QT syndrome, ventricular arrhythmias, and sudden death.
- The risk is intended on the base of the single drug or attendant factors such as age, underlying pathology, hypokalaemia, and drugs coadministration.
- These drugs are ADT: amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, trimipramine, and other antidepressants such as: citalopram, fluoxetine, sertraline (see the following section on selective serotonin reuptake inhibitor), amoxapine, venlafaxine, and doxepin.

Not all antidepressants cause QT lengthening, and the torsadogenic risk increases with higher doses or when drugs are co-administered (e.g. antiarrhythmics, antihistamines, stimulants, antibiotics and antimycotics). It might be also due to familial aggregation, as in 10% of cases.[110] Typical antipsychotics (chlorpromazine, pimozide, thioridazine, perphenazine, trifluoperazine, haloperidol, and droperidol) and atypical antipsychotics (clozapine, quetiapine, risperidone, sultopride, ziprasidone, and loxapine) are more likely to cause QT lengthening and torsade des pointes. However, the group of atypical antipsychotics is actually less hazardous.

Electrocardiograms (ECGs) show that some ADTs (amitriptyline, desipramine, and nortriptyline), other antidepressants (maprotiline and lithium) and some antipsychotic drugs (trifluoperazine and loxapine), might cause even highly arrhythmic Brugada like type 1 and coved type syndrome. This is more frequent in familial aggregation cases (associated with Na channel mutation, SCN5A).[110,111]

The choice, initiation and continuation of an antidepressant and antipsychotic therapy require a careful ECG evaluation (PR, QRS, QTc, ventricular repolarization specific and non-specific alterations, bradycardia and supra- and ventricular arrhythmias).

Anti-epileptic drugs

Athletes might need prolonged anti-epileptics drug treatment and these drugs might have pharmacokinetic interactions with other drugs. The list of anti-epileptic drugs includes sodium valproate, phenytoin, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, vigabatrin, zonisamide, and carbamazepine. Treatment with anti-epileptic drugs in athletes should be always reported and plasma levels measured. Serial ECGs are necessary to verify tolerance to therapy and, as asymptomatic bradyarrhythmia and nocturnal AV block can occur, Holter monitor might be needed.

Commonly used over-the-counter medications

Anti-inflammatory drugs

The use of non-steroidal anti-inflammatories is more common in elite athletes than in non-athlete peers and this is mostly for pain and inflammation control reasons.[112,113] These drugs may cause:

(1) delayed tissue regeneration,
(2) gastrointestinal complications (gastralgia, heartburn, haemorrhage, alvus disorders),
(3) disorders of the central nervous system (fatigue, headache, decreased perception of muscle strength),

Table 2 Adverse cardiovascular effect of common legal nutritional supplements in sports[65–70,74,75,77]

Supplement	Cardiovascular side effects
Anti-cortisol supplements (glutamine, phosphatidylserine)	Unknown
Antioxidants	Unknown
β-alanine	Unknown
B-Hydroxy β-methylbutyric acid (HMB)	Unknown
Caffeine	Arrhythmias, vasoconstriction, hypertension, electrolytic disorders
Carbohydrates (sport drinks, energy bars)	Unknown
Coenzyme-Q10 (ubiquinone)	Unknown
Colostrum	Unknown
Creatine	Unknown
Dark chocolate	Unknown
Joint-supporting supplements (glucosamine, chondroitin, methylsulfonylmethane)	Unknown
L-Carnitine	Unknown
Lipotropic factors—fat burners	When contaminated with ephedra/ephedra-like compounds: arrhythmias, vasoconstriction, hypertension
Multivitamins	Unknown
Nicotine products	Arrhythmias, vasoconstriction, hypertension, coagulability, thrombogenesis
Nitrates (beetroot juice)	Unknown
Oxygenated water	Unknown
Plant supplements	
Guarana	Arrhythmias, hypertension
Ginseng	Arrhythmias, hypertension
Proteins—aminoacids	Unknown
Sodium Bicarbonate	Unknown

(4) decreased renal blood flow resulting in decreased kidney function (indomethacin, celecoxib), and
(5) cardiovascular risks (cyclooxygenase inhibitor, Cox-2). There is evidence that the cyclooxygenase-2 inhibitors may increase cardiovascular risk, like hypertension and atherosclerotic lesions. However, the mechanisms for this potentially adverse cardiovascular effect are unknown.[114,115]

Legal ergogenic supplements

The use of legal ergogenic aids is widespread in athletic populations and varies between 40% and 100% of athletes of both sexes, depending on the sport discipline and the level of competition. These supplements are intended to enhance performance and give a competitive edge. Many elite athletes consume a combination of supplements per day and various forms of sports supplements as well as vitamin/mineral supplements (VMS), which are generally the most used legal ergogenic aids.[116] Among VMS consumers, the most frequent types are multivitamins/multiminerals, vitamin C, vitamin D, and iron, with considerable variations in frequency according to countries. The reasons leading athletes to consume VMS also vary according to country, gender and the type of sports performed. The most common reasons are to optimize or enhance performance (most frequent in males) or to compensate for possible deficiencies (most frequent in females); other reasons include improvement of immune status, general health maintenance, or to reduce cold symptoms.[117]

Numerous factors may be responsible for manifestation of adverse effects in athletes using nutritional aids, such as the safety and composition of the supplement *per se* and the used protocols of intake. Often, athletes take simultaneously various products without regard to optimal dose schemes and total dosage of some ingredients or synergic and antagonistic interactions between them.[116] Thus, some commonly used nutritional aids may lead to health disorders and in limited cases to adverse cardiovascular side effects (*Table 2*).

The legal nutritional supplements which are permitted by WADA and that are supported by reliable evidence of promoting athletes' physical performance include caffeine, creatine, carbohydrate drinks/gels/bars, β-alanine, bicarbonate, nitrate (beetroot juice), and proteins.[117,118]

Caffeine

Coffee with its ergogenic ingredient caffeine, a trimethylxanthine, is probably the most often consumed beverage worldwide. Caffeine is an adenosine antagonist, acts as a non-selective PDE inhibitor and prompts the secretion of catecholamines,[18,119] Caffeine acts as a sympathetic stimulus during exercise and has been shown to attenuate autonomic recovery post-exercise. It was suggested that this effect is dose-dependent.[120]

Caffeine alone has been shown to be effective for the improvement of aerobic capacity in endurance athletes[119] but the 'more is better' philosophy, when applied to caffeine use in sports, may result in side effects that outweigh the performance benefits. Optimal performance benefits are usually achieved with intakes of 3–6 mg/kg (approximately 2–4 cups) and side effects become more common with caffeine doses over 9 mg/kg of body mass. Overdose may lead to cardiotoxicity with significant cardiovascular side effects such as tachycardia, coronary and peripheral vasoconstriction, and elevated blood pressure especially in caffeine-naive recreational athletes.[121] Hypertensive episodes, hypokalaemia, paroxysmal arrhythmias, and SCD have also been reported.[122,123] Additionally, vigorous exercise may exacerbate the known pharmacodynamic effects of caffeine.[18,121,124]

Creatine

Creatine has become the most popular non-stimulant legal ergogenic supplement in sports since early 1990s and it first gained popularity after the Barcelona Olympic Games in 1992, where medal winners in sprint and power disciplines publicly announced that they believed their performance had benefitted from its use.[125] Creatine is found predominantly (95%) in skeletal muscle tissue, and it is also synthesized in the liver, pancreas, and kidneys. It is reported that supplementation increases performance in anaerobic activities, delays muscle fatigue for short periods of time and contributes to the rapid resynthesis of adenosine triphosphate particularly in repeated short sprints of maximal intensity.[123] Creatine can be an effective legal ergogenic aid mostly when used for simple anaerobic exercise bouts of short duration and maximal effort.[119,123] Adverse effects are few and dose-dependent, including weight gain (1.6–2.4 kg), muscle cramps, gastrointestinal discomfort, and dehydration. There have been two case reports of transient renal function compromise referring to a significant loss of glomerular filtration rate and an interstitial nephritis, respectively.[125] To date, there are no well-established adverse cardiovascular effects or major cardiovascular toxicities. However, case reports have associated creatine supplementation with the presentation of deep-vein thromboses, atrial fibrillation, cardiac arrhythmia, chest pain, and even sudden death.[126] In the absence of definitive data, its use should be monitored carefully since relevant studies were mostly short-term and pertained to healthy individuals. The long-term effects of creatine supplementation, or any possible effects on other creatine-containing tissues such as the cardiac muscle have not yet been clarified.[125]

Carbohydrates

The increased total thermal load determined by the environmental temperature and evaporative power as well as by the exercise intensity and duration justify the appropriate use of fluid carbohydrate supplements for energy intake, water and electrolyte replacement in continuous efforts predominantly lasting over 1 h. Carbohydrates as supplements usually refer to multiple transportable carbohydrates (such as glucose and fructose) and are often consumed in the form of isotonic sport drinks, gels, or energy bars. Health disorders include mainly gastrointestinal discomfort and no adverse cardiovascular effects have been reported.[127] Interestingly, the excessive consumption of grapefruit juice may lead to QT prolongation, which can cause arrhythmias, especially after the simultaneous administration of drugs that cause a prolongation of repolarization.[18]

β-Alanine

β-alanine as a supplement leads to enhanced intracellular muscle-buffering capacity increasing the level of carnosine by 40–80% in skeletal muscle. Carnosine is considered as a pH regulator in sarcoplasm delaying muscle fatigue, and β-alanine is reported to present an ergogenic effect in efforts lasting 1–4 min of maximal intensity.[128]

Several studies and meta-analyses have shown that oral supplementation with β-alanine can improve human performance of high-intensity and intermittent exercise patterns.[129–131] Beta-alanine supplementation has been shown to increase carnosine levels in brain and cardiac tissue.[132] Moreover, β-alanine may increase heart rate training threshold.

Studies of adverse cardiovascular effects in humans taking oral β-alanine supplements are lacking. However, neurotoxicity, myotonia, transient paresthaesia (numbing in the skin),[133] and respiratory discomfort are clinical symptoms in humans with mitochondrial disorders associated with β-alanine plethora, and *in vitro* studies in which rat cardiomyocytes and fibroblasts were directly exposed to β-alanine, oxidative stress, and cell apoptosis were reported.[134] Therefore, it seems plausible that increased supplementation may have unfavourable cardiovascular effects.

Currently, β-alanine supplementation is legal under the WADA code and its use among athletes is widespread, with a self-reported usage of 60% in some sports.[135]

Sodium bicarbonate

Sodium bicarbonate ($NaHCO_3$) has been suggested as a performance enhancing nutritional supplement by reducing acidosis during exercise of moderate duration and high intensity. Bicarbonate may cause gastrointestinal disorders when ingested. This can impair rather than improve sports performance and may counteract the benefits of other supplements taken at the same time. No cardiovascular side effects have been reported.[136]

Nitrates

Oral supplementation with inorganic nitrate results in increased levels of nitric oxide thus promoting vasodilation and oxygen supply to the skeletal muscles and enhanced mitochondrial enzyme activity in endurance efforts. Thus, it is reported that intake of sodium nitrate or beetroot juice shows ergogenic effects on cardiorespiratory endurance that would benefit aerobic performance.[137,138] Moreover, it is noted that it may be also significantly effective in patients with cardiovascular diseases, and it should not only be addressed in healthy populations.[139] The lowering effect on blood pressure has led to the suggestion that beetroot juice could potentially be used in medical settings as an alternative to conventional anti-hypertensive drugs.[140] In sport populations, no cardiovascular side effects of nitrate supplementation have been reported although nitrates may be associated with a rapid and significant lowering of blood pressure, including syncope. Besides, further research should be conducted regarding the

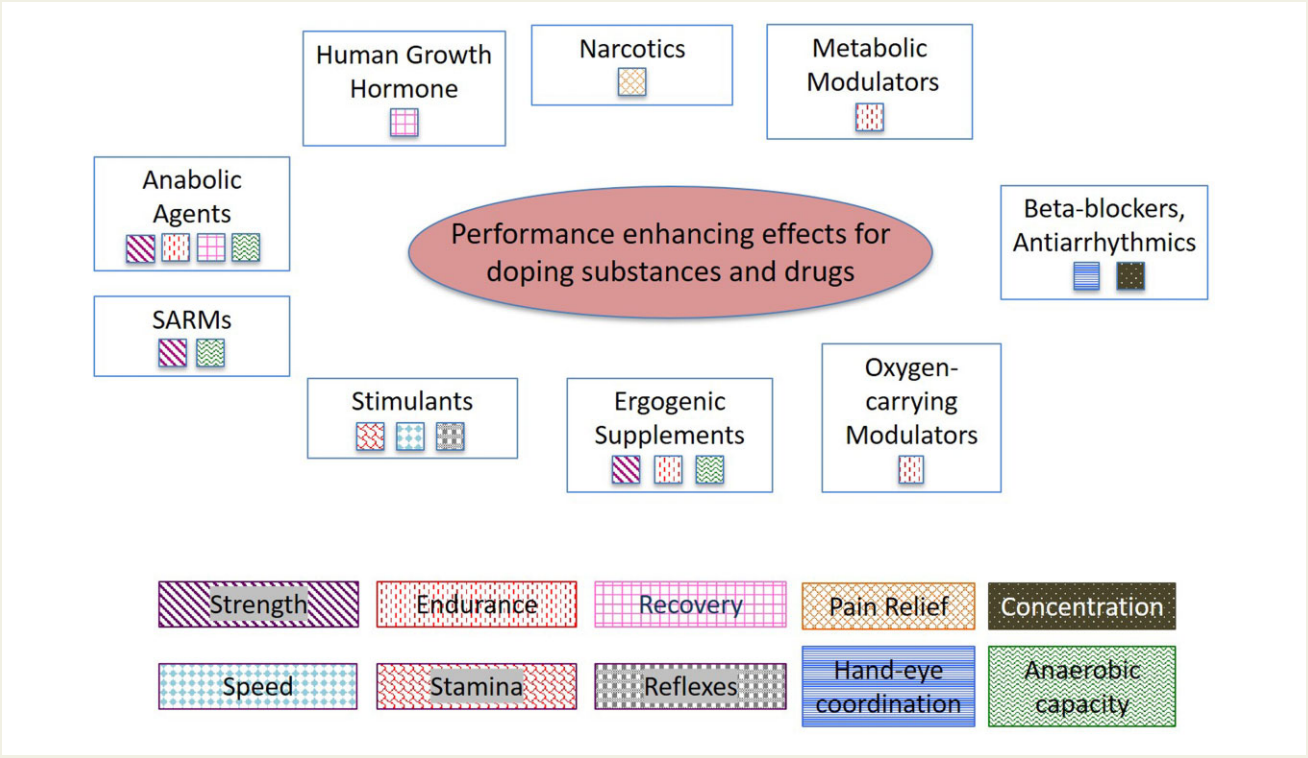

Figure 2 Performance enhancing effects for doping substances and drugs. The figure summarizes the main performance enhancing effects of the most relevant different substance's categories. SARM, selective androgen receptor modulators.

long-term effects since there are joint biochemical pathways in the metabolism of nitrates and the malignant nitrites.

Proteins

High-quality whey protein supplementation (approximately 0.4–0.5 g/kg of lean body mass) increases muscle mass and strength during resistance-type exercise training when ingested both pre-and post-exercise within about 4–6 h of each other, depending on meal size.[141,142] No cardiovascular side effects have been reported in athletes. Nevertheless, the need for appropriate water intake during periods of protein consumption should be encouraged to counteract any risk of dehydration.

Recreational drugs and energy drinks

Alcohol

Alcohol is the oldest social beverage and is unlikely to have any ergogenic effect on human performance. Therefore, it is currently not listed on the WADA Prohibited List although is banned in some sports according to the rules of the sport for safety reasons, such as in motor racing. Initially, alcohol consumption may lead to an increase of heart rate, respiratory frequency, and blood pressure as well as to minimal vasodilation with a dose–response pattern.[8] In cases of heavy drinkers, hypertension, stroke, alcoholic cardiomyopathy, coronary events, cardiac arrhythmias such as atrial fibrillation have been reported.[143] Moreover, in chronic heavy-drinking, occurrence of hypertriglyceridaemia, tachycardia, and coronary spasm can increase the risk for ischaemic heart disease and SCD (*Figure 2*).[8,143]

Nicotine and tobacco products

The use of numerous tobacco products and diverse smokeless alternatives in sports is increasing. Nicotine is a naturally occurring alkaloid and one of the most widely used psychostimulants. Athletes use nicotine either in a smokable form or during a sporting event in the form of gum (smokeless tobacco), chewable tobacco, or oral-dispersible nicotine strips or pouches, because of its psychokinetic effect.[144] Nicotine is not typically a truly ergogenic aid in terms of maximizing sports performance. However, it is reported that nicotine may improve time to exhaustion even in anaerobic bouts of exercise[144] while it seems to exert similar effects in endurance efforts as caffeine.[145] Nevertheless, it is well known that nicotine causes intense adrenergic stimulation and vasoconstriction of coronary artery segments and abuse may lead to atherosclerosis, dyslipidaemia, and cardiovascular events.[8,18,124] It also decreases cardiac contractility and output, possibly alter coronary blood flow, and may contribute to endothelial dysfunction that precipitates acute ischaemic events.[146] Moreover, nicotine has thrombogenic actions resulting in augmented coagulability.[145] Thus, tobacco use should be clearly discouraged and certainly avoided for 2 h before and after a sports event or training practice.[8]

Energy drinks

The World Health Organization has named the use of energy drinks as a public health concern.[147] Energy drinks are non-alcoholic beverages containing predominantly caffeine in combination with other presumed energy enhancing ingredients that act mainly as stimulants and they are commonly consumed particularly by adolescents and young adults.[121,148] The most common ingredients are caffeine, guarana, taurine, glucuronolactone, ginseng, and bitter orange. Energy drinks and energy shots (concentrated form of energy drink) contain higher quantities of caffeine than conventional beverages and coffee products, and their caffeine concentration can range from 9 to 250 mg/oz.[121] Consumption of a caffeine, taurine, and glucuronolactone formulation may increase arterial blood pressure, act as a platelet aggregation enhancing factor and compromise endothelial function in healthy individuals.[148] Furthermore, it is reported that *in vitro*, taurine acts as a triggering factor for enhanced haemodynamic outcomes presenting both a positive inotropic effect and potentiated caffeine-induced cardiac muscle contraction.[149] Combination with alcohol is common, with many consumers self-mixing energy drinks or energy shots with alcohol. This usage does not counteract alcohol-induced motor coordination deficits and individuals who mix energy drinks with alcohol may underestimate their true level of impairment.[150] Depending on the product and the number of units imbibed, ingested caffeine dose can easily rise over 1000 mg. In healthy adults, a caffeine intake of less than 400 mg per day is typically safe. Acute toxicity-derived effects begin at 1000 mg, and 5000–10 000 mg can be lethal.[121]

Numerous environmental, genetic, and medical settings may predispose individuals to the toxic caffeine effects of energy drinks or shots.[121] Moreover, energy shots may be more hazardous since significant increases in both systolic and diastolic blood pressure, lasting up to 6 h after intake have been noted.[151] According to the International Society of Sports Nutrition, the action and the side effects of energy drinks should be clarified since there is a variety of ingredients. The intake of more than a can may lead to side effects and patients should consume only under medical advice.[152] Energy drinks put individuals with genetic heart condition at risk and it is suggested that drinking two cans of an energy drink increases risk of cardiac arrest by 20% in people with an underlying heart condition such as in patients with long QT syndrome.[153] Cardiovascular side effects of energy drink use include increased blood pressure, coronary disease, heart failure, cardiac arrhythmias, abnormal exercise test, increased risk of atrial fibrillation, narrow complex tachycardia, prolonged QT interval, ventricular tachycardia, ventricular fibrillation, torsade des pointes, supraventricular arrhythmias, ST-segment elevation, hypokinesia with or without a reduced LV ejection fraction, and aortic dissection.[154] Furthermore, the mixture of alcohol with energy drinks may lead to severe cardiovascular disorders.[147,155,156] Children or adolescents should only consider using energy drinks with parental approval, and parents should be aware of potential adverse effects. The younger brain is more susceptible to excessive energy drink consumption and a high risk for disturbed neurodevelopment in children and adolescents has also been reported.[157] Additionally, individuals with underlying cardiovascular pathology should avoid energy drinks unless approved by their physician.

New trends of doping

Synthetic peptides

Modern performance enhancing drugs can be designer synthetic peptides triggering stimulation of natural anabolic hormone secretion. However, of possibly far greater potential risk than using AAS or other prohibited drugs is athletes' desire and consent to use experimental drugs that have not been proven safe in humans.[158] The ongoing use of SARMs like ostarine, ligandrol, andarine, and cardarine claiming anabolic to androgenic ratios high up to 90:1 or peptides like ipamorelin (growth hormone secretagogue) carry a substantial risk for long-term detrimental health consequences, which are usually understated by their promoters. Little is known about the cardiovascular side effects of the many peptides designed to modulate AR activity as it was previously reported in this paper. It is likely that side effects are less than AAS, but it is very difficult to know for certain.[3] Thus, in some respect, confirmation of biomedical side effects is always going to be one step behind use and not surprisingly, no cardiovascular side effects have been reported so far.

Furthermore, the HIF-proly hydroxylase inhibitors (i.e. cobalt, daprodustat, molidustat, roxadustat, enarodustat, vadadustat, xenon) are basically modern erythropoiesis-triggering agents and they are used in sports alternatively to injectable erythropoietin. The study of their cardiovascular effects is still ongoing mainly *in vitro*.[159] Besides, natural compounds like phytoekdysteroids or PDE5 inhibitors are also used in sports and PDE5 inhibitors are alleged to be frequently misused by healthy athletes to improve sporting performance.[160] Finally, the implementation of gene doping constitutes a great threat of major concern about the future of human performance manipulation.

Gene doping

Gene doping (WADA prohibited method) includes the use of normal or genetically modified cells as well as gene transfer, gene silencing and gene editing technologies. There are not yet any data about complications, as might be expected considering that officially there are no confirmed adverse analytical findings of gene doping in sports. Gene doping abuses the legitimate approach of gene therapy in analogue medical protocols. Over 200 genes are associated to human performance and play a role in muscle development, oxygen delivery to tissues, neuromuscular coordination, or even pain control, and are thus candidates for gene dopers.[161] The expected severe health side effects include lethal immunodeficiency and leukaemia.[162] Health risks may also result from gene overexpression, a common problem in gene therapy. IGF gene doping may be used for muscle repair and muscle performance. IGF-overexpression may cause cardiac hypertrophy, heart valve disease, and heart failure.[162–164] Additionally, increasing EPO levels may increase viscosity and the risk for heart attack.[165] Moreover, it is highly anticipated that genes for strength, analgesia, oxygen delivery, and tissue repair may be transferred simultaneously to the same athlete. Clearly, there will be hazardous side effects and probably severe gene interactions. Contrary to therapeutic gene protocols that are conducted under strict regulations and approval procedures, gene doping is expected to occur behind the scenes with limited protective actions and consequently

increased health risks. Furthermore, since 2018, the WADA list also includes gene editing as *agents designed to alter genome sequences and/or the transcriptional or epigenetic regulation of gene expression*. Gene editing with genome editing tools such as CRISPR (clustered regularly interspaced short palindromic repeats)[166] involves tweaking existing genes, rather than adding completely new ones to the athlete's body. Gene editing should make it possible to make tiny alterations to DNA in existing genes, or to just temporarily boost or switch off the activity of particular genes. Additionally, these effects could be oriented to specific tissues such as muscle, meaning the changes may not show up in blood anti-doping tests. However, it seems that there will always be the increased risk of mutation genesis and formation of malignant cells as well as unexpected side effects due to atypical regulation of cell growth and toxicity based on chronic hyper-expressions of growth factors and cytokines even affecting the cardiovascular function.[167]

Aspects for non-medics

The indiscriminate use of nutritional supplements and legal ergogenic aids in sports is a cause for concern. Nutritional supplements are commonly viewed as risk-free substances that may improve performance. Nutritional supplements, however, that have the potential to enhance human performance may also have biomedical side effects. Some nutritional supplements, including various plant and 'natural' extracts, may pose a serious health risk and athletes may even risk contravening anti-doping rules. Moreover, contamination of supplements with unknown or prohibited substances remains a significant issue, with contamination rates reported between 12% and 58%.[116,168] Supplements widely available like fat-burners or products based on plant extracts may trigger cardiovascular disorders if contaminated with ephedra or ephedra-like compounds, which is also a common cause of unintended anti-doping rule violations.

Athletes who use supplements often have no knowledge regarding their effects on sports performance and overall health. It is reported that most athletes get nutritional advice from coaches, fellow athletes, family members and friends,[169] suggesting that more wide reaching educational interventions, at an early age, are necessary. Athletes, particularly at the higher echelons of sport, should consider consulting nutritional experts who will consider the need, potential benefits, as well as side-effects of supplements and provide an individually tailored prescription.[116] Examples when nutritional supplements may be indicated include (i) specific nutrient deficiencies; (ii) clinical manifestations due to chronic inadequate nutrient intake; (iii) low-calorie diets or diets excluding a group of nutrients either voluntarily, e.g. vegetarians/vegans or due to allergies or food intolerance; (iv) regular travelling with uncertain/insufficient food supply or quality; and (v) periods of extreme training loads and increased energy expenditure.

Key points for athletes using nutritional supplements

- A natural supplement is not necessarily a safe supplement.
- Use supplements if needed for known deficiencies and recommended by nutrition experts.
- Use products by established manufacturers with known good quality standards.
- Athletes are personally responsible for any substances they consume.
- Ignorance is not accepted as an excuse in relation to a positive doping test.
- Athletes with established heart disease should be even more vigilant and consult with their physician prior to using any supplements or ergogenic aids.

Ethical considerations

The basis of using doping substances is like that of nutritional supplements used as ergogenic aids in sports, since in both cases the objective is to improve physical performance. Athletes should be aware that supplement use exposes them to a risk of ingesting prohibited substances or prohormones and precursors of prohibited substances. Supplements are regulated as food ingredients and are not subject to the stringent regulations applied to pharmaceutical products.[116] The greatest risk to athletes' health is the use of 'cocktails' and transference of effects of several substances, which might interact to the worse or the use of designer peptides produced in laboratories without rigorous safety standards. Unfortunately, it is common practice for athletes to ignore dosing recommendations and use multiple drugs simultaneously. Another aspect of consideration about ergogenic aids in sports is that when using nutritional ergogenic supplements to push physiological adaptations beyond normal under an extreme training load, supra-physiological structural and functional changes may be apparent. In this case, the induced stress reaction with high catecholamines release triggering cardiovascular response may lead to cardiovascular disorders such as atrial fibrillation or even more threatening arrhythmias.[3]

Anti-doping authorities may claim that they increase the penalties for anti-doping rule violations or have developed new anti-doping strategies based on increased number of anti-doping tests and sophisticated reliable methods for detection of doping substances. Besides, regarding the claims that underestimate the health side effects and mention that doping will always exist in sports and it could be eventually allowed, we should foresee that (i) clinical trials establishing a safe level of intake would not exist for all probable dosage schemes, and (ii) the concept of sporting fairness would be challenged due to financial burden. Furthermore, the core of sports culture should always be the athlete and not the pharmacist or the geneticist.

Prescribing physicians should familiarize themselves with the status of a prescribed medication under the WADA anti-doping code, although the majority of the supporting information sources provides information about the prohibited drugs based on the current WADA Prohibited List, but does not provide the status of nutritional substances due to the fact many are unregulated and unlicensed.[158] Usually, these tools (electronic databases and official websites) provide specific information on products sold in just a limited number of countries. Undoubtedly, it needs to be recognized that physicians should be actively part of the fight against doping and should only prescribe or recommend supplements where a clinical need can be demonstrated, such as in vitamin deficiency syndromes.[170] Moreover, physicians should always discuss with the athletes to inform them about the potential risks of taking supplements. The important role of athletic coaches, equally or even more than dieticians and physicians, in

providing nutritional information should be also noted. Therefore, there is a considerable need for well-educated coaches in collaboration with dieticians and doctors to provide an adequate nutritional support for athletes. Regarding young athletes, it should be noted that paediatricians are the primary contact for most young athletes and paediatric cardiologists are in a position to develop long-lasting relationships with their patients. Therefore, it is of great importance for paediatric physicians to be aware that drug use in sports is not only an adult problem.

An athlete guided by a strong 'will to win' may be vulnerable to cheating practices to satisfy his goals and society's expectations. Doping within this pursuit of sports success is a multi-dimensional issue and the fight against arbitrary use of ergogenic aids in professional and recreational sports should involve all stakeholders of the modern sport system: athletes, clubs, scientists, spectators, sponsors, media, family, and official authorities.[170] Physicians need to become more educated about the drugs that are being used in sports and their side effects. It is essential to have a physician who will be perceptive to the potential for drugs abuse, well informed and able to discuss openly the ergogenic and the adverse effects of nutritional supplements and drugs.[125] Athletes with established heart disease should be even more vigilant and regularly consult with their physician prior to using any supplements or ergogenic aids. More research studies on biomedical side effects and educational campaigns particularly aiming at physicians, children, and athletes of developmental ages can have a significant influence on drug use in sports and may act as the most powerful tools for an effective fight against the indiscriminate use of ergogenic aids.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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