Assessment of cardiovascular risk and physical activity: the role of cardiac-specific biomarkers in the general population and athletes

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ABSTRACT

The first part of this Inter-Society Document describes the mechanisms involved in the development of cardiovascular diseases, particularly arterial hypertension, in adults and the elderly. It will also examine how consistent physical exercise during adolescence and adulthood can help maintain blood pressure levels and prevent progression to symptomatic heart failure. The discussion will include experimental and clinical evidence on the use of specific exercise programs for preventing and controlling cardiovascular diseases in adults and the elderly. In the second part, the clinical relevance of cardiac-specific biomarkers in assessing cardiovascular risk in the general adult population will be examined, with a focus on individuals engaged in sports activities. This section will review recent studies that suggest a significant role of biomarkers in assessing cardiovascular risk, particularly the presence of cardiac damage, in athletes who participate in high-intensity sports. Finally, the document will discuss the potential of using cardiac-specific biomarkers to monitor the effectiveness of personalized physical activity programs (Adapted Physical Activity, APA). These programs are prescribed for specific situations, such as chronic diseases or physical disabilities, including cardiovascular diseases. The purposes of this Inter-Society Document are the following:

- to discuss the close pathophysiological relationship between physical activity levels (ranging from sedentary behavior to competitive sports), age categories (from adolescence to elderly age), and the development of cardiovascular diseases;
- to review in detail the experimental and clinical evidences supporting the role of cardiac biomarkers in identifying athletes and individuals of general population at higher cardiovascular risk;
- to stimulate scientific societies and organizations to develop specific multicenter studies that may take into account the role of cardiac biomarkers in subjects who follow specific exercise programs in order to monitor their cardiovascular risk

***Key words**: cardiovascular risk, cardiovascular prevention, cardiac biomarkers*

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INTERPLAY BETWEEN AGE, PHYSICAL ACTIVITY, AND CARDIOVASCULAR RISK

Cardiovascular risk assessment in the general population

Cardiovascular diseases are the leading cause of death in most industrialized countries (1-3). Data from the Italian National Institute of Statistics (ISTAT) show that mortality from cardiovascular diseases progressively increases after 55 years of age in both sexes, with a higher incidence in males up to the age of 80-85, while women are more affected in later ages (4). In recent years, especially during the COVID-19 pandemic, cardiovascular diseases have been crucial drivers of increased mortality among the older population, who present frailty and co-morbidities (4). A study published in 2017 by the Santa Fe Institute estimated that significantly reducing the negative impact of cardiovascular diseases could result in an increase in average lifespan of up to six years, at least in the most industrialized countries (3).

Arterial hypertension is considered one of the earliest manifestations of a progressive deterioration of the cardio-circulatory system, which can lead, over the course of several years, to the development of myocardial ischemia and symptomatic heart failure (HF) (5-12). HF is a progressive disease, generally divided into four stages:

- stage A, where subjects are at risk of developing HF due to the presence of predisposing factors (hypertension, atherosclerosis, diabetes, metabolic syndrome), but no structural signs of heart disease or symptoms of HF are yet evident;
- stage B, where subjects present structural alterations of heart disease (cardiac remodeling, previous myocardial infarction, alterations of the heart valves) but do not yet have symptoms of HF;
- stage C, where patients present typical signs of HF (dyspnea, fatigue, reduced exercise tolerance) but respond to pharmacological treatment;
- stage D, where patients no longer respond to standard pharmacological treatment and thus require specialized therapeutic interventions (heart transplant, mechanical circulatory support) (13).

In the first two stages (A and B), HF is at least partially reversible, so lifestyle or pharmacological interventions can postpone the development of disease symptoms for some years (13). Despite recent advances, the prognosis for patients in stage D of HF remains worse than most aggressive cancers (14). Therefore, the primary goal of the clinician is to identify patients in the reversible stages (i.e., A and B) as early as possible and treat them adequately to extend their life expectancy free from HF symptoms (14).

From the perspective of cardiovascular disease prevention, hypertension must be considered a modifiable risk factor, as its impact on morbidity and mortality can be reduced by avoiding the occurrence of major adverse cardiovascular events (MACE) (1,2,5-8). Indeed, bringing blood pressure back within “normal” limits (which are associated with low cardiovascular risk) results in a significant reduction in both mortality and the frequency of MACE. The improvement in mortality and morbidity is independent of how the reduction in blood pressure is achieved, whether through pharmacological therapy (1,2,5-22), or by lifestyle changes, particularly by implementing a specific program that includes increased physical exercise, a healthier diet, or both (21-38).

Physical activity and cardiovascular risk

Specific and personalized exercise programs not only improve the functionality of the cardiovascular system but also reduce mortality, as observed across multiple types of physical activity programs. These programs are all characterized by their ability to reduce systolic and diastolic blood pressure levels (21,28-38). Although many documents and guidelines suggest increasing the amount of aerobic physical activity (anaerobic exercise training, AET) to maintain blood pressure levels within the normal range (2,8,9), the effects of physical exercise on the cardiovascular system vary depending on baseline blood pressure levels. Higher reductions in blood pressure are achieved by following specific and personalized programs (21,31,38,39). New models of physical exercise appear to be more effective, incorporating isometric exercise types (Isometric Exercise Training, IET) (31) and high-intensity interval training (HIIT) (34). Furthermore, more recent studies suggest exercise models based on resistance training (Independent Dynamic Resistance Training, DIRT) and/or combinations of various types of exercise (21,35-37). Consequently, there is no consensus on the most suitable and effective type of physical exercise for treating hypertension in adults or the elderly (21,31,38).

The beneficial effects of physical exercise on health, particularly in the prevention and treatment of hypertension, have been emphasized by all the most recent international guidelines (2,8,9,21,40-45). However, physical exercise may be detrimental in patients with cardiovascular diseases, especially if they are sedentary or have advanced cardiac disease. Paradoxically, well-trained athletes who practice endurance sports after the age of 35 years (with a peak of events between 40 and 60 years of age) are also at risk (23,45-47). In this context, it is important to note that it is not physical exercise itself that improves health status and reduces cardiovascular risk, but rather the better physical fitness achieved through a rigorous exercise program. Fitness can be defined as the ability to perform vigorous physical activity without excessive fatigue (48,49). This explains why the level of physical activity (reported by the individual) is only moderately correlated with cardiorespiratory fitness, the parameter most closely correlated with the cardiovascular risk profile (48-50).

It is unclear if there is an upper limit to the exposure to intense endurance physical exercise (especially if prolonged over time, such as in marathons or ultra-marathons) (23). In other words, the saying “*too much of a good thing*” may or may not apply to physical exercise (51). Specifically, excessive exposure to intense physical exercise has been associated with atrial fibrillation, coronary artery calcification, and/or myocardial fibrosis (23,52). However, recent studies have shown no evidence

of increased cardiovascular risk (especially in terms of increased mortality) in former high-level athletes. On the contrary, there are data confirming a negative trend between a past of high-level athletic activity and mortality (23,53-55).

Regarding the frequency of exercise activity, the most recent documents from the Italian National Olympic Committee (CONI) (56,57) report a greater propensity to engage in significant sporting activity between the ages of 6 and 14 (especially at the school level), with a progressive decrease in the number of sports practitioners after 14 years. In the United States, only about 15% of the adult population follows guidelines suggesting vigorous physical activity at least three times a week for at least 30 minutes, while more than 60% do not engage in any regular physical activity, and about 25% of the general population is considered sedentary (58).

A 2022 study from Italy emphasizes the link between sports activity and age (59). Specifically, individuals between 6 and 24 years tend to practice sports; sports practice becomes less widespread with increasing age, while the practice of other types of physical activity increases. Unfortunately, sedentary behavior increases with age, affecting two out of ten adolescents and young people up to 24 years old and almost seven out of ten people aged 75 and over (59) (Figure 1). These Italian data align with studies from other countries confirming that the majority of the adult population does not engage in regular physical activity and tends to be sedentary (46,49,58-71).

Sedentariness and cardiovascular risk

As reported in the latest edition (2023) of the text by MacArdle et al. (58), studies published over the past 50 years conclude that inactivity leads to a constellation of problems and clinical conditions resulting in premature death. In this context, the term Sedentary Environmental Death Syndrome (SeDS) was coined to identify the progressive health deterioration in sedentary individuals with aging (58,64). Physical inactivity is recognized as a leading cause of 35 pathophysiological conditions, including metabolic syndrome, obesity, insulin resistance, pre-diabetes or type 2 diabetes, non-alcoholic fatty liver disease, cardiovascular diseases, cognitive function decline, sleep disorders, bone and connective tissue diseases, various types of cancers, as well as gastrointestinal, pulmonary, and kidney diseases (65,66). Since physical inactivity is more frequent in adulthood, especially after 65 years (58,60-63), the disorders it causes are compounded and exacerbate those typical of senescence (67-71).

The term “inflammaging” was introduced in 2000 to describe the chronic inflammation typical of elderly individuals (67). This inflammatory state is characterized by elevated levels of circulating and tissue biomarkers of inflammation, associated with a burden of comorbidities and increased risk of dysfunction or failure of the most important systems and organs, frailty, and premature death (64-70). The most significant effects are related to the activation of the Senescence Associated Secretory Phenotype (SASP) in the heart (72,73). SASP activation stimulates the production of pro-inflammatory and pro-thrombotic cytokines (such as interleukin [IL]-1, IL-6, and tumor necrosis factor-alpha), causing oxidative stress with DNA damage and reducing cellular repair and regeneration (68,69,72,73). At the cardiac level, SASP activation leads to a progressive reduction in the number of cardiomyocytes and an increase in myocardial fibrosis, which are the two signs of cardiac aging and progression toward overt, non-reversible heart failure (72,73). In line with this evidence, all international guidelines dealing with prevention strongly recommend an increase in physical activity to counteract both the deleterious effects of inactivity and senescence (1,2,8,9,40-45).

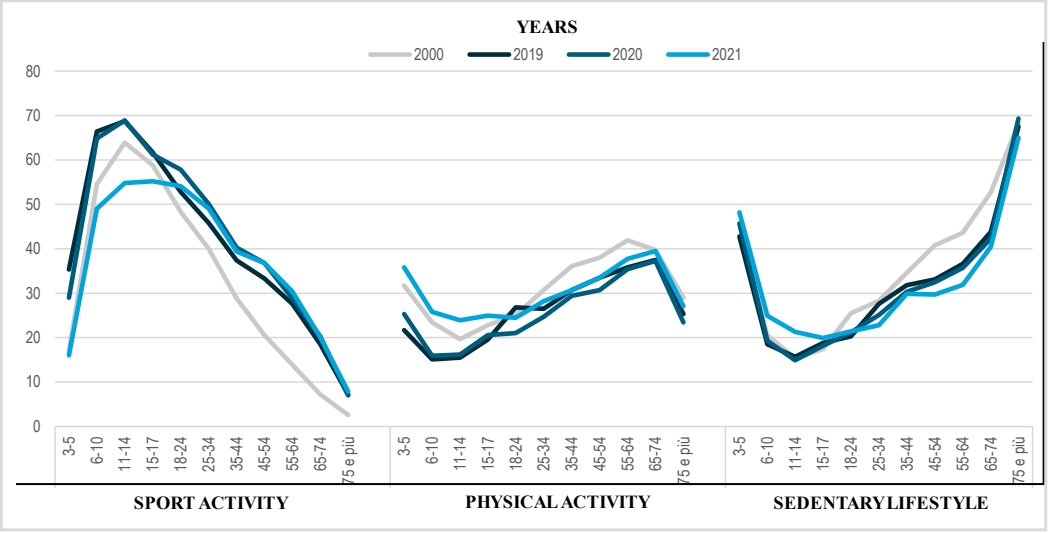

Figure 1
ISTAT data on the difference in physical and sports activity among various age groups of Italian citizens from 2000 to 2021 (59).

Objectives and outcomes of exercise programs in adults and patients with cardiovascular diseases

The primary goal of exercise programs for adults or elderly individuals is to prevent and counteract the effects of limited physical activity and senescence on health, particularly the harmful effects on the cardiovascular system (1,2,8,9,21,42,45). Assessing and monitoring the status of the cardiovascular system over time is warranted, especially for evaluating cardiovascular risk and detecting cardiac involvement and damage.

Monitoring physical performance over time in patients with heart failure (HF) symptoms is very useful for assessing the effectiveness of pharmacological treatments and outcomes, provided that relatively simple but well-standardized evaluation tests, such as the six-minute walking test (6MWT), are used (58,74). The 6MWT, which measures the distance a person can walk in six minutes on a flat surface, is a simple, safe, and reliable way to assess the functional capacity of patients with cardiopulmonary diseases (58,74). Specifically, the test predicts aerobic power (in terms of peak oxygen consumption, VO_{2max}) with reasonable accuracy (±5%) using a mathematical equation that considers weight, age, sex, walking speed, and the individual's heart rate during the test (58). The 6MWT is not a diagnostic test, as it does not provide detailed information on different systems (i.e., pulmonary, cardiovascular, or neuromuscular systems), but rather on the overall response to exercise (58). The main purpose of the 6MWT is to analyze exercise tolerance in patients with chronic respiratory diseases and HF, as well as the response to specific treatments, including pharmacological or lifestyle changes (58,74-83).

In 2016, Benda et al. (79) reported that 10 patients with stable cardiomyopathy aged 68±5 years were able to perform a prolonged test of three days (30 to 40 km of walking) without showing acute deterioration of cardiovascular and respiratory functions. Circulating levels of cardiac-specific biomarkers, B-type natriuretic peptide (BNP) and cardiac troponin I (cTnI), were measured to assess cardiac function and the presence of possible myocardial damage, demonstrating that biomarker levels did not change significantly compared to the control group matched by number, sex, and age (79). Importantly, a non-high-sensitivity analytical method was used to assess cTnI (79).

In 2017, Hua et al. studied the effect of exercise on the quality of life in 154 patients with chronic HF, randomized into two groups of 77 subjects. One group was treated according to guidelines, while the other was personally followed by nursing and technical staff to carry out an intensive and personalized lifestyle improvement project, which included a personalized physical activity program (80). After three months, the patients in the personalized program showed significant improvement in cardiac function (assessed by echocardiography), a decrease in circulating levels of N-terminal pro-BNP (NT-proBNP), and improved physical exercise tolerance, assessed with the 6MWT, compared to controls (80).

The role of cardiac-specific biomarkers in assessing cardiovascular risk has garnered significant attention in recent years, both in the general population and among patients with cardiovascular diseases. The suggestion to measure cardiac NPs (atrial and B-type NPs and related cardiac NPs) along with cTnI and cTnT reflects a shift toward a more nuanced understanding of cardiovascular risk assessment. Specifically, the emphasis on early detection of asymptomatic HF in its reversible stages (stages A and B) highlights the preventative potential of such measures (84,85).

Cardiac NPs and cardiac troponins are considered cardiac-specific biomarkers because they are exclusively (or predominantly, in the case of cardiac NPs) produced by cardiomyocytes (85-92). International guidelines endorse cardiac NPs as the biomarkers of choice for diagnosing HF (93). Moreover, these biomarkers play a critical role in risk stratification and prognosis not only for patients with HF but also for individuals with other cardiovascular conditions, including hypertension (41,85,90,94).

The relevance of measuring cTn using high-sensitivity methods (hs-cTnI and hs-cTnT) to assess cardiovascular risk in the general population has been demonstrated. These biomarkers are considered ideal, aligning with the principles of precision medicine, as circulating levels of hs-cTnI and hs-cTnT correlate with individual characteristics such as sex, age, and body composition (height and muscle mass) (91,92,95-98). The measurement of hs-cTnI and hs-cTnT has less than 10% variability for both intra-individual and analytical components, presenting a highly favorable individuality index (<0.6), comparable to creatinine (71,85,91,92,95,96). This indicates that a difference of ≥30% between values measured from different samples signifies a meaningful change (71,85,91,92,95,96).

Moderate- to high-intensity physical exercise, even among well-trained athletes, is commonly associated with an increase in levels of both types of cardio-specific biomarkers (cardiac NPs and hs-cTn) (99-101). However, significant differences between cardiac-specific biomarkers relate to the pathophysiological mechanisms responsible for their variations before and after exercise in both healthy individuals and patients with cardiovascular diseases (99-117). Thus, the interplay between biomarkers and physical exercise needs to be better detailed to clarify the importance of measuring cardiac NPs and hs-cTn in healthy individuals and, especially, in patients with cardiovascular diseases undergoing rehabilitation programs.

The interaction between physical exercise and cardiac NP levels continues to evolve with ongoing research. The increase in cardiac NP levels at the onset of physical activity, even of mild or moderate intensity in healthy adults, which returns to pre-exercise values within a relatively short time due to the biological half-life of these peptides in the bloodstream, underscores the dynamic nature of these biomarkers in response to physiological stress (89,100,101).

The fact that there are relatively few studies specifically evaluating the effects of aerobic and/or resistance exercise on the cardiac NP system in healthy

or athletic adults indicates a gap in our understanding (100,114-117). However, it is clear that the increase in cardiac NP levels during exercise is generally more influenced by the intensity and type of physical exertion rather than the duration, with younger and well-trained athletes showing smaller increases and a quicker return to baseline levels compared to less fit or older individuals, and especially compared to patients with cardiovascular diseases or comorbidities (100-106).

In young and well-trained athletes, the peak concentration of BNP/NT-proBNP during and after exercise, even of high intensity and duration, is generally below the threshold for diagnosing acute or chronic HF, and values return to pre-exercise levels within 12-24 h (100). Therefore, it is recommended that patients rest in a seated position for at least 30 minutes before blood sampling for BNP/NT-proBNP measurement to ensure accurate readings (86).

Experimental and clinical evidence suggests that the increase in circulating levels of BNP/NT-proBNP during physical exercise in healthy individuals and athletes should be viewed as a consequence of the activation of the neuro-immuno-endocrine system and myocardial stress induced by physical activity, rather than a sign of cardiovascular disease (86,100). A biomarker increase well above the threshold, with a slower return to pre-exercise levels, should prompt clinicians to consider the presence of cardiovascular system alterations, especially in subjects over 55 years of age or with comorbidities (100).

A 2015 meta-analysis reported that a BNP value ≤100 ng/L has a negative predictive value (NPV) of 0.99 [95% confidence interval (CI) 0.97-1.00], while an NT-proBNP value of 300 ng/L has an NPV of 0.98 (95%CI 0.89-1.00) (118). The 2021 European Society of Cardiology (ESC) guidelines recommend (Class I, Level B) that a diagnosis of chronic HF is unlikely if BNP <35 ng/L or NT-proBNP <125 ng/L, considering the high NPV of the biomarker (0.94-0.98) (93). This underlines the clinical utility of cardiac NP measurements for excluding the diagnosis of acute or chronic HF, rather than confirming its presence.

The measurement of BNP/NT-proBNP can also be useful for risk stratification in the general population and in patients with cardiovascular diseases (93,94,118,119). A recent meta-analysis suggested threshold NPs values for screening left ventricular systolic dysfunction in individuals at higher risk in the general population: 311 ng/L for NT-proBNP [sensitivity 0.74 (95%CI 0.53–0.88), specificity 0.85 (95%CI 0.68–0.93)] and 49 ng/L for BNP [sensitivity 0.68 (95%CI 0.45–0.85), specificity 0.81 (95%CI 0.67–0.90)].

Considering the changes in cardiac NPs during physical exercise in patients with cardiovascular diseases, studies have shown that even patients with moderately reduced ejection fraction can complete extended physical activity without significant cardiac function deterioration or pronounced BNP increase (79). Moreover, exercise programs have been shown to significantly reduce NT-proBNP levels and improve cardiovascular function in patients with chronic HF with reduced ejection fraction, underscoring the beneficial effects of tailored aerobic exercise on cardiovascular health (104). Contrasting results from studies investigating the role of cardiac NP measurements in evaluating or monitoring the effectiveness of specific preventive or therapeutic programs in symptomatic subjects or patients with HF underline the complexity of interpreting cardiac NP levels in the context of exercise (79,104,105). This highlights the need for further research to better understand the clinical implications of cardiac NP level variations during and after physical activity, particularly in relation to cardiovascular risk stratification and management.

Cardiac troponins and exercise

A recent document from the American Heart Association (103) reported not infrequent severe MACE, such as myocardial infarction, stroke, and sudden death, in athletes over 45 years old who participate in extreme sports activities like endurance races. This presents a dilemma where, on one hand, a certain degree of physical activity is essential to counteract the harmful health effects of sedentariness and aging, as all guidelines recommend. On the other hand, there is insufficient evidence to identify the best exercise programs to recommend for both the general population for prevention and to support pharmacological therapy in patients with cardiovascular disorders (2,21-25,40-42,45,93).

As discussed previously, even the strategy of using cardiac NP measurements as cardiac-specific biomarkers to select the most effective exercise programs, both in healthy individuals and in patients with HF, does not achieve significant benefits compared to the broad advice for a healthier lifestyle (79,104,105). These results suggest that more effective biomarkers are needed for assessing cardiovascular risk in both the general population and in patients with cardiovascular diseases. Cardiac troponins (cTn), measured with high-sensitivity (hs) immunometric methods (hs-cTnI and hs-cTnT), show better analytical and pathophysiological characteristics than cardiac NPs (96-98). Therefore, these biomarkers could improve risk stratification both in the general population and in patients with cardiovascular diseases, as evidenced by recent clinical studies and meta-analyses (84,85,96,98,120-131).

Many experimental and clinical studies have definitively demonstrated that in both healthy sedentary individuals and well-trained athletes, circulating levels of hs-cTnI and hs-cTnT can significantly increase during moderate or high-intensity physical exercise compared to pre-exercise values (99,107-116,132). Furthermore, circulating levels of hs-cTnI and hs-cTnT during physical exercise, even of a certain intensity and duration (marathon running, bicycle racing), return to pre-exercise values within 16-35 hours in well-trained athletes (9,110). Finally, the peak value of the biomarker is generally below the threshold value for cardiac damage (99th percentile upper reference limit [URL]), or slightly above it, in young and well-trained athletes even during strenuous effort, such as running a marathon, a long bicycle race on mountain roads, or an endurance race (99,107-116,132).

In agreement with the most recent national and international guidelines (133-136), values equal to or higher than the 99th percentile URL of hs-cTnI and hs-cTnT indicate myocardial damage. Excessive exposure to physical exercise can cause disorders to the cardiovascular system such as atrial fibrillation, coronary artery calcification, and/or myocardial fibrosis, especially in subjects over the age of 45 (23,52,58,103,111,136,137). Therefore, myocardial damage should also be diagnosed in an athlete if a value of hs-cTnI or hs-cTnT above the 99th percentile URL threshold is found during or immediately after a high-intensity and long-duration effort (133-136). The evidence that high-intensity and long-duration physical effort can cause an increase in cTnI and cTnT in circulation in athletes has prompted a debate over the last ten years on the mechanisms responsible for the release of these proteins from myocytes into the extracellular fluid of young, well-trained subjects with optimal cardiovascular function (fitness) (91,92,107,132,138-143).

In the cardiomyocyte, cTnI and cTnT, together with troponin C (cTnC), form a structural unit and a functional complex in the sarcomere, playing a fundamental physiological role in the contraction of myocytes, both at rest and during exercise (58). Considering the total content of cTnI and cTnT in the myocyte, more than 90% is present in the sarcomere, while the remainder (<10% of the total) is mainly found in the cytoplasm (107). The cTnI and cTnT present in the cytoplasm are primarily contained in cytoplasmic vesicles and have a structure different from that in the sarcomere (111-113). In the cytoplasm, the troponins have a molecular weight (MW) from 15 to 29 kDa, compared to the cTnI and cTnT proteins in the sarcomere (MW 22.5 kDa and 39.7 kDa, respectively) (111-113). This cytoplasmic form of troponins is likely in transit in the cytoplasm and about to be completely degraded with subsequent reuse of amino acids to form new proteins (111-113).

From a pathophysiological perspective, the cardiomyocyte may be subjected to either reversible or irreversible damage (107,108,110-113,139-142) (Figure 2). During an insult causing only reversible damage, a lesion of the plasma membrane may form on the myocardial cell, allowing the release of a limited amount of cytoplasm that could contain complexes or microparticles with troponins in degraded form at low MW. Otherwise, due to reversible damage, vesicles containing cytoplasm that include degraded troponins may form and then be extruded from the cell, for example in the form of circulating exosomes or membrane protrusions (blebs) (107,108,110-113,139-142). The reversible damage would then be quickly repaired by the cardiomyocyte, which would subsequently continue its normal activity (107,108,110-113,139-142).

Recent studies have shown that after intense and prolonged physical exertion (such as a marathon or bicycle race), some forms of troponins I and T can be measured, which more frequently present with reduced MW and faster plasma clearance than sarcomere-bound troponins (111-113). Unfortunately, the immunometric measurement methods for hs-cTnI and hs-cTnT are not able to directly measure and identify the circulating form of the biomarker (i.e., low or higher MW) (111-113). Therefore, these methods cannot differentiate between reversible and irreversible myocardial damage using a single biomarker measurement. Consequently, the kinetics of hs-cTnI and hs-cTnT values, measured in multiple samples, must be evaluated to ascertain the presence of acute myocardial damage (133-136).

DISCUSSION

Possible role of cardiac-specific biomarkers in assessing cardiovascular risk in the general population and athletes

In agreement with the evidence accumulated so far (84,85,96,120-131), cardiac-specific biomarkers (both cardiac NPs and cardiac troponins) should be assessed before starting a specific exercise program for prevention or to guide the therapy of cardiovascular diseases, even though the most recent international guidelines do not specify a recommendation in this regard (40-42,45). This assessment is especially indispensable in older individuals or those with comorbidities, as they may already exhibit elevated levels of one or both cardiac-specific biomarkers (i.e., BNP/NT-proBNP and hs-cTnI/hs-cTnT) (71,84,85,98). From a clinical perspective, it is always appropriate to request the combined measurement of both cardiac NPs (BNP/NT-proBNP) and troponins (hs-cTnI or hs-cTnT) in all individuals suspected of having cardiovascular disease, because these biomarkers provide additional pathophysiological and clinical information (71,84,85,98). In particular, a high level of BNP or NT-proBNP suggests the presence of an activated neuro-immuno-hormonal system due to a pathological stressor, which has caused an increase in the production and release of cardiac NPs by cardiomyocytes. If a concentration of hs-cTnI or hs-cTnT above the 99th percentile URL threshold is also found, this indicates that the stress was able to cause significant damage to the myocardial tissue with necrosis of myocytes, suggesting the diagnosis of myocardial damage in accordance with the document Fourth Universal Definition of Myocardial Infarction (133). The cause and nature of the pathological event, and the extent of anatomical and functional damage to the cardiovascular system, should be determined using functional and cardiac imaging tests in agreement with guideline recommendations (133,144).

Guideline recommendations

The World Health Organization's guidelines (145) recommended for the first time in 2020 reducing sedentary work and increasing physical activity to improve health outcomes in individuals of all ages (23-28,58,60-66,146). Accordingly, recent documents from European and North American scientific societies recommend reducing the time spent sitting during the workday to promote increased physical activity, thereby achieving a significant reduction in cardiovascular risk in the general population (42,147,148). On the other hand,

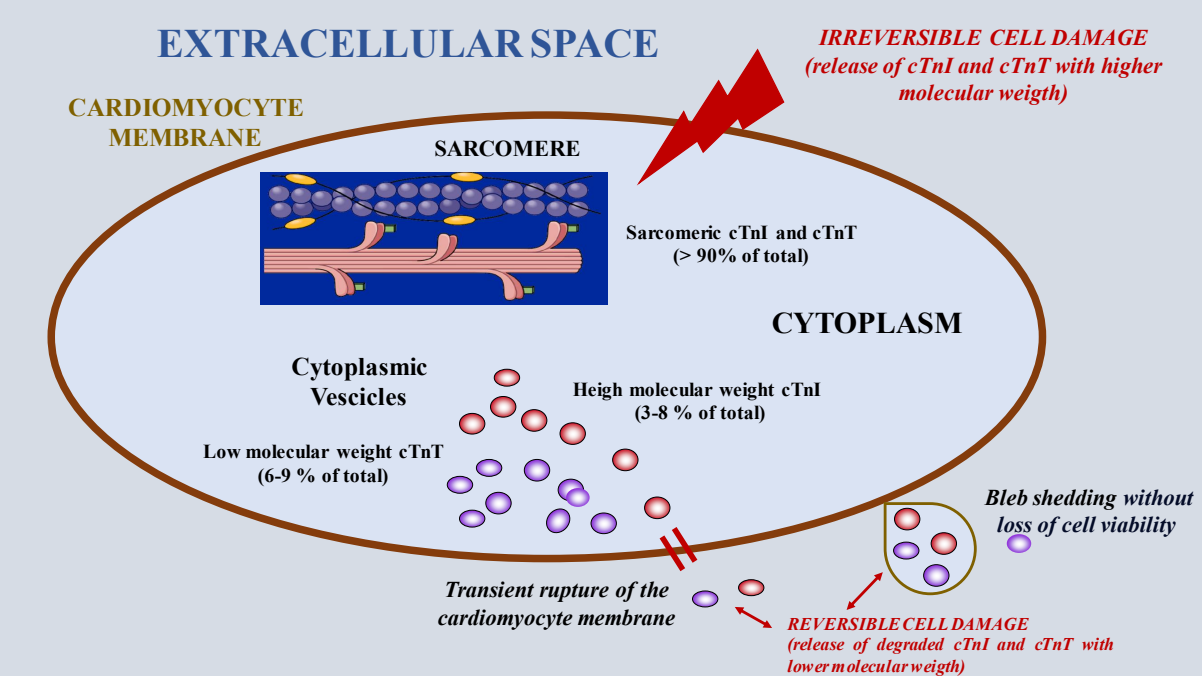

Figure 2
Distribution of troponin I and T within the cardiomyocyte and their release into the extracellular fluid due to reversible or irreversible myocardial damage (107,139,141).

the 2020 ESC guidelines on Sports Cardiology (45) report that the early recognition of potentially lethal pathologies in athletes can decrease mortality due to cardiovascular diseases through more accurate risk assessments, specific interventions depending on the diseases, and/or modifications in the training programs conducted, as reported by many experimental and clinical studies (149-154). Indeed, experimental evidence indicates that some athletes show a higher risk of sudden cardiac death due to a cardiovascular event, depending on sex (higher in males, from 3:1 to 9:1), ethnicity, and the sport practiced (45,153-160). Importantly, the incidence of SCD in competitive athletes varies greatly from 1 in 5 000 to 1 in a million athletes per year because the event is not always correctly reported and, therefore, its frequency may be underestimated (45).

In accordance with the results of many studies and guideline recommendations (161-172), the 2020 ESC guidelines (45) confirmed that current cardiovascular screening in young athletes should be based on clinical history, physical examination, and ECG, which significantly improves the diagnostic yield of clinical history and physical examination. Although echocardiographic examination may be indispensable for identifying specific structural alterations of the cardiovascular system (173), the 2020 ESC guidelines (45) report that there is currently insufficient evidence to recommend this test for routine screening in young athletes, and therefore, it should be used only in specific cases. On the other hand, the same guidelines (45) recognize that the available evidence regarding cardiovascular screening in senior athletes over the age of 35 is limited. Cardiovascular screening in athletes aged >40 years should focus on evaluating the impairment of cardiovascular function due to coronary artery disease (CAD) (45).

As is well known, a fair number of asymptomatic adult subjects test positive on the stress test but do not present myocardial ischemia (45,170-172). In agreement with these data, the ergometer stress test is generally considered of little use as a screening test in asymptomatic adult subjects (170-172), but it is recommended to evaluate symptomatic athletes at high risk of CAD based on the ESC Systematic Coronary Risk Evaluation (SCORE) system (2,45,172). The stress test can also be useful for assessing the blood pressure response to exercise, verifying the presence of exercise-induced arrhythmias, and evaluating physical performance (fitness) and the cardiovascular system's response to the modulation and implementation of the exercise program (45,168). In sedentary or older individuals who are unable to perform high-intensity physical exercises, the stress test and cardiopulmonary exercise testing (CPET) can be used to assess cardiovascular performance and overall fitness (45,58,172). Furthermore, the data obtained from these tests are useful for preparing specific exercise programs, graded for intensity and duration, depending on the physical and clinical characteristics of the individuals (45,58).

Considering physical activity in patients with cardiovascular diseases, the 2020 ESC guidelines (45) specify the different types of cardiovascular diseases (both congenital and non-congenital), their potential

impact on health, and the possibility that a personalized physical activity program can decrease cardiovascular risk. In particular, these guidelines (45) recommend specific physical activity programs for healthy adult individuals, as summarized in Table 1. Regarding the evaluation of cardio-specific biomarkers, the guidelines (45) report that high-intensity exercise, even in well-trained athletes, can cause an increase in hs-cTnI and hs-TnT, indicating the presence of myocardial damage. These guidelines (45) also report that finding elevated levels of hs-cTnI and hs-cTnT in an athlete can indicate inflammation of the myocardial tissue or pericardium.

However, despite the latest experimental and clinical evidence showing that cardio-specific biomarkers can significantly improve the assessment of cardiovascular risk in the general population (71,84,85,98), even the most recent international guidelines do not consider measuring cardiac-specific biomarkers for cardiovascular risk stratification, both in the general population engaged in recreational sports activities and in professional athletes or individuals who practice high-intensity sports continuously (45,174,175). In particular, although intense physical activity can be associated with high levels of hs-cTnI and hs-cTnT in some athletes, demonstrating the presence of myocardial damage, the mechanisms and possible clinical implications have not been analyzed in detail (45,174,175). Moreover, the utility of evaluating biomarker variations over time to follow the course of myocardial lesions and adjust the exercise program accordingly is still undefined.

FINAL REMARKS

The primary purpose of this Inter-Society Document is to promote the diffusion of personalized exercise programs in the general population, particularly among individuals who regularly engage in physical activity during their leisure time or as a sports activity. Indeed, exercise programs should be considered fundamental therapeutic tools in countering the deleterious effects of sedentary behavior and aging on health in general, and more specifically, on the cardiovascular system (2,3,8-10,21-29,41,42,62-65). Accordingly, recent documents, guidelines, and academic texts recommend personalized physical activity programs not only for the prevention of cardiovascular diseases in the general population but also as a fundamental tool for reducing cardiovascular risk and the development of myocardial infarction and MACE, both for subjects with endocrine-metabolic comorbidities and for patients who already exhibit symptoms of cardiovascular disorders (2,8,9,40-44,58,93,171,172).

Unfortunately, even the most recent expert documents and international guidelines do not recommend measuring cardiac-specific biomarkers to obtain a more accurate stratification of cardiovascular risk in individuals engaging in physical activity during leisure time or as a sports activity (42,45,171,172,174,175). Considering this deficiency, the Cardiac Biomarkers Study Group for the Italian Laboratory Medicine Societies has prepared this specific document to illustrate the mechanisms underlying the increase in circulating levels of cardiac-specific biomarkers during sports activity (91,92,99-102,107-117,132,133,138-143). Moreover, this document discusses studies demonstrating the fundamental role that hs-cTnI and hs-cTnT measurement plays in diagnosing acute cardiac damage developing during high-intensity and/or long-duration physical activity, especially in subjects with comorbidities or athletes older than 35 years (91,92,99-102,107-113,132,133,138-143).

In this context, SCD in athletes is undoubtedly the most feared adverse event, since over 80% of SCD cases occur in athletes older than 35 years who perform vigorous physical exercise. These athletes have a higher risk for myocardial infarction (42,46,176-185) because they present CAD or comorbidities (i.e., systemic arterial hypertension, obesity, diabetes mellitus) commonly associated with elevated levels of cardio-specific biomarkers (96,129,131,133-135,144). Some authors suggest that it is plausible to assume an association between elevated levels of hs-cTnI and hs-cTnT after effort and SCD (182-185), even though specific evidence from studies designed to verify this hypothesis is currently not available.

Table 1
Summary of the recommendations advised by the 2020 European Society of Cardiology guidelines concerning physical activity programs for healthy adult subjects (45).

Recommendations	Class	Level
In healthy adult subjects, aerobic exercise programs are recommended, such as: at least 150 minutes per week of moderate-intensity physical exercise, or 75 minutes per week of vigorous intensity, or a combination of these two exercise programs	I	A
To achieve additional health benefits, a gradual increase in aerobic exercise up to 300 minutes per week at moderate intensity, or 150 minutes per week at vigorous intensity, or a combination of these two exercise programs is recommended for healthy adult subjects	I	A
Regular assessment and advice by qualified personnel are recommended to encourage better adherence to the program and also to advise an increase in the volume of physical exercise over time	I	B
Multiple exercise sessions spread throughout the week are recommended, for example, spread over 4-5 days per week or preferably every day of the week	I	B

A very recent study (186) tested the hypothesis that middle-aged and older athletes with coronary atherosclerosis should demonstrate greater hs-TnI and hs-cTnT elevations following a controlled endurance exercise test compared with healthy peers. Authors enrolled 59 male athletes (mean age 61 years, interquartile range 58-68 years), stratified into three groups: group 1, control individuals (n=20); group 2, individuals with high calcium score of coronary artery (n=20); group 3, individuals with significant coronary atherosclerosis (n=19). The main results of this study (186) are that serial sampling of hs-cTnT and hs-cTnI concentrations during and following an exhaustive endurance exercise test did not reveal differences in exercise-induced cTn release among different groups of athletes with or without coronary atherosclerosis. An important clinical observation regarding this study is that all three groups of athletes showed mean hs-cTnI and hs-cTnT concentrations in the normal range before the exercise test, while only three subjects showed basal hs-cTnT and two subjects hs-cTnI concentrations >99th percentile value of the assay method (i.e., the cut-off value for myocardial injury) before the exercise test (186). The results of this recent study are contradictory to some (187), but not all previous studies (188-190). A potential explanation for these discrepant results reported in the literature may relate not only to the number and clinical characteristics of individuals enrolled in the different studies, but also to the exercise stimulus, as exercise-induced cTn release is associated with exercise intensity and duration (111,113). These experimental data taken together (187-190) seem to suggest that the standard exercise test may not be very useful to identify accurately the individuals at high risk of MACE or SCD after vigorous physical exercise among middle-aged and older athletes. The lack of evidence from experimental and/or clinical studies specifically designed to verify a close association between MACE and SCD in athletes at high cardiovascular risk, demonstrated by elevated levels of hs-cTnI and hs-cTnT, might explain why even the most recent documents and guidelines (42,45,171,172,174,175) still do not recommend measuring cardiac-specific biomarkers in senior athletes or patients with comorbidities (such as systemic arterial hypertension, hypercholesterolemia, obesity, diabetes) or cardiovascular diseases, who follow specific exercise programs to decrease cardiovascular risk and improve overall health status.

With the aim of reducing these knowledge gaps, Authors propose to initiate more specific studies on the added value of cardiac biomarkers in risk stratification of persons engaging in exercise programs. Indeed, during the last 10 years, several studies have confirmed that the evaluation at rest over time (for months or years) of variations of hs-cTnI and hs-cTnT levels is able to more accurately estimate the cardiovascular risk in subjects in the general population and, more importantly, to detect some individuals, still asymptomatic, but at high risk to develop symptomatic HF (84,85,96,98,120-131). These studies should adopt specific experimental protocols designed as the clinical studies previously reported concerning the evaluation of cardiovascular risk in the general population (84,85,96,98,120-131). The main purpose of these studies should be to demonstrate the fundamental role of measuring hs-cTnI/hs-cTnT levels in diagnosing acute cardiac damage, which may occur in some individuals or athletes during high-intensity and/or long-duration physical activity. If encouraging results is obtained by these studies, it is conceivable that some scientific societies and organizations will be stimulated to develop new guidelines that may take into account the role of cardiac biomarkers in subjects who follow specific exercise programs in order to monitor their cardiovascular risk.

KEY MESSAGES

- *Sedentary behavior produces by itself a constellation of problems and clinical conditions leading to premature death, so much so that the term Sedentary Environmental Death Syndrome (SeDS) has been coined to identify the progressive deterioration of health in sedentary individuals with advancing age (58,64).*
- *Many clinical studies and meta-analyses, as well as the recommendations of the most recent guidelines, support the use of specific and personalized exercise programs that can significantly reduce both overall mortality and mortality due to cardiovascular diseases, with the goal of improving the prospect of a healthy and worthwhile life (21,28-39,45,49,50,58).*
- *Some studies report that too intense physical activity can have negative effects on adults, especially if there are present conditions such as arterial hypertension, cardiac atherosclerosis, obesity, diabetes mellitus (23,52,58).*
- *Sudden cardiac death (SCD) in athletes is the most feared adverse event in athletes over 35 years of age, and may be promoted by vigorous physical exercise in individuals with comorbidities and elevated levels of cardiac-specific biomarkers (42,46,96,129,131,133-135,144,176-185).*
- *An association may exist between elevated levels of hs-cTnI and hs-cTnT after exercise and SCD (182-185), even though specific evidence from studies specifically designed to verify this hypothesis is not currently available.*
- *The fundamental role of measuring hs-cTnI and hs-cTnT biomarkers in diagnosing acute cardiac damage that develops during high-intensity and/or long-duration physical activity should encourage the authors of national and international guidelines to recommend the evaluation of cardio-specific biomarkers in athletes and individuals at higher cardiovascular risk following specific exercise programs.*

CONFLICT OF INTEREST

None

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