Cardiovascular conditions

Prohibited substances: beta-blockers, diuretics

1. Introduction

The purpose of these guidelines is to assist Therapeutic Use Exemption Committees (TUECs) in their assessment of applications for the use of beta-blockers in sports where this group of medications is prohibited according to WADA's Prohibited List. These guidelines are based on the World Anti-Doping Code (WADC), the International Standard for Therapeutic Use Exemptions (ISTUE), and the current evidence-based treatment of the relevant cardiovascular conditions.

IMPORTANT NOTE: When applying for a TUE for beta-blockers in precision sports, the athlete and their physician need to duly consider the implications of two recent decisions of the Court of Arbitration for Sport (CAS), both in the sport of shooting (CAS 2009/A/1948; CAS 2013/A/3437). In these cases, despite undisputed medical indications for the therapeutic use of beta-blockers, the TUE applications were rejected because the athletes could not demonstrate the absence of an enhancing effect on their individual performance.

A more recent CAS decision (2015/A/4355) reversing a TUEC's decision to deny a beta-blocker TUE turned on the Court's understanding of the physiology of the concerned athlete's rare health condition. This decision, made on narrow legal grounds, should not generally be interpreted as a shift in the CAS jurisprudence on the granting of TUEs for beta-blockers in shooting athletes (see Annex for details).

Sports in which beta-blockers are prohibited

Beta-blockers are prohibited In-competition only, in the following sports:

- Archery (WA)*
- Automobile (FIA)
- Billiards (all disciplines) (WCBS)
- Darts (WDF)
- Golf (IGF)
- Mini-golf (WMF)
- Shooting (ISSF, IPC)*
- Skiing/Snowboarding (FIS) in ski jumping, freestyle aerials/half pipe and snowboard half pipe/ big air
- Underwater sports (CMAS)* in all subdisciplines of freediving, spearfishing and target shooting.

*Prohibited both In- and Out-Of-Competition

Indications for the use of beta-blockers

For the following conditions, beta-blockers are usually recommended (alone or in combination with other medications), unless clear contraindications exist:

- Stable angina pectoris;
- Secondary prevention after myocardial infarction;
- Symptomatic heart failure (reduced ejection fraction, class II–IV);
- Supraventricular and ventricular arrhythmias;
- Long QT syndrome;
- Resistant hypertension;
- Prophylaxis of aortopathy (e.g., in the setting of connective tissue disease or systemic hypertension).

The recommended therapy with beta-blockers may only be one element of the overall treatment plan. The treating physician is responsible to make decisions based on the individual circumstances of a patient. This is, however, beyond the scope of this document. In general, it can be assumed that, for the above-mentioned conditions, the ISTUE Articles 4.2 (a) and (c) criteria will generally be fulfilled if the diagnosis is accurate and reliable.

For the following cardiovascular conditions, the use of beta-blockers is often recommended, but needs to be established in each individual case:

- Acute Coronary Syndrome (unstable angina, acute myocardial infarction)
- Hypertension with no other cardiovascular risk factors
  - Monotherapy
  - Combination therapy, with diuretics (prohibited In- and Out-of-Competition), ACE-inhibitors, Angiotensin II inhibitors or RAS inhibitors, are all considered best-practice alternatives.

Other alternative treatments may be appropriate, and the use of beta-blockers should only be considered when there are justifiable reasons as to why such alternatives should not be used in an individual athlete. Another factor for consideration may be the long-term use of beta-blockers with stable therapeutic effectiveness in an athlete who only recently has become TUE-eligible.

For all of these indications, the TUEC has to carefully consider the acceptability and the risk to the athlete of denying the TUE which could result in changing to alternative treatments. The athlete's application must include a statement by an appropriately qualified physician attesting to the necessity of the otherwise prohibited substance in the treatment of the athlete and describing why an alternative, permitted medication should not be used in the treatment of the condition. Due to international variation in medical practice, it is appropriate for any TUEC who assesses or questions such a statement to consult a cardiologist.

It is important to understand that an athlete cannot be encouraged (e.g., by a TUEC) to use a treatment that is not being advised as the treatment of choice by a responsible practitioner, in particular where the alternative carries with it greater hazards and no greater chances of success, to compete in a sport.

Administration

1. Route

   Beta-blockers are usually administered orally. Intravenous therapy is not applicable in sports and in the field, with the only exception of an acute cardiac condition.

2. Frequency

   One to four times per day depending on the substance used.

Other considerations

Beta-blockers are a highly heterogeneous group of substances with different pharmacologic properties (cardio-selectivity, blood-brain barrier passage, Intrinsic Sympathomimetic Activity (ISA), membrane-stabilizing capacity). Consequently, individual beta-blockers may either have different effects or exert certain effects to different degrees. These substance-specific effects present a considerable challenge for TUECs when assessing Article 4.2(b) of the ISTUE. TUECs must remember that the athlete has the burden of proving the performance - enhancing effects of the beta-blocker they are taking - or the absence thereof - in their case, and how these affect their performance in the concerned sport.

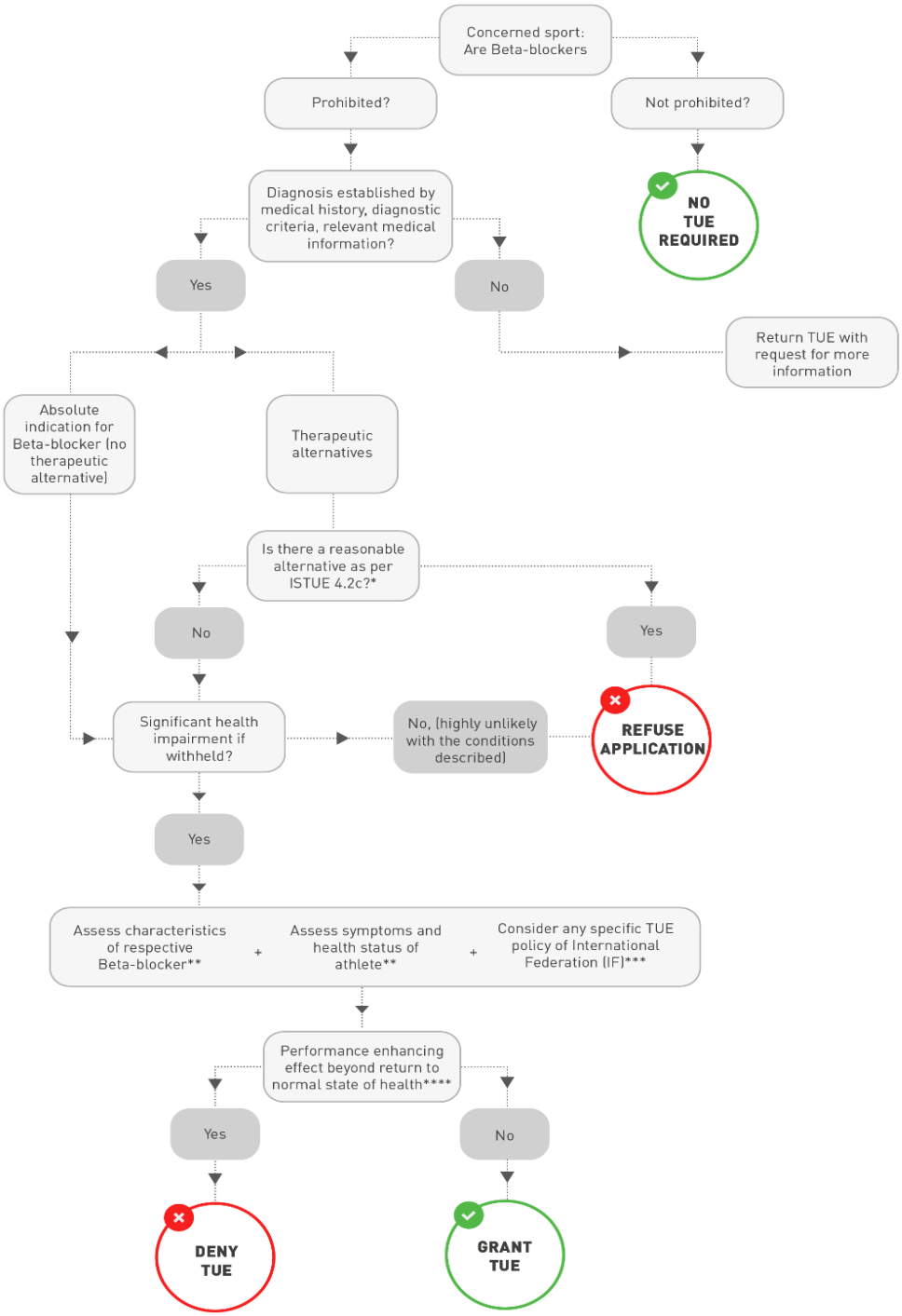
That said, an athlete is not required to determine that the potential performance-enhancing effects can be categorically excluded, just that they are highly unlikely (*CAS 2015/A/4355*). In fact, to ask the athlete for scientific evidence that cannot be provided would place an unreasonable burden on the athlete.

It should be noted that it remains for the athlete to show that they fall within the category of athletes who derive no performance-enhancing effect from the use of the substance (*CAS 2013/A/3437*). However, it is not a matter of the athlete doing everything they could do to provide evidence, but whether the evidence provided is sufficient to establish that 4.2(b) has been satisfied (*CAS 2013/A/3437*).

Conclusion

The above considerations lay the foundation for the assessment of a TUE application based on current evidence-based medicine, the relevant anti-doping regulations, and case law. As indicated, in precision sports, particularly shooting, the major challenge for the TUEC charged with making a decision on a TUE application for beta-blockers is the weighing of the symptoms and physical impairment against the effects of the medication on an individual athlete and the requirements of a specific sport. This will, however, be crucial in assessing a potential “additional enhancement of performance beyond what might be anticipated by a return to the athlete’s normal state of health” (ISTUE Article 4.2(b)). Since a number of athletes requiring beta-blocker therapy for one of the above-mentioned conditions might be significantly ill and impaired, defining the “state of normal health” in these cases represents a further challenge.

Algorithm for assessing a TUE application for beta-blockers



* As mentioned above, an athlete cannot be compelled to use a treatment that is not being advised as the treatment of choice by a responsible medical practitioner, in particular where the alternative treatment carries with it greater hazards and no greater chances of success, to compete in a sport.

**Expert opinion by a cardiologist is essential to carefully assess symptoms and health status of the athlete, including their influence on performance prior to taking beta-blockers.

***Consult with international federation to ascertain if there is a specific policy on beta-blockers.

****Important note: An athlete may have to establish that the medication does not improve their performance (e.g., by means of systematic measurements of physiological markers, tests of comparison, etc.).

2. Medical condition

2.2 Stable angina pectoris, recent myocardial infarction, and heart failure

Cardiovascular disease associated with myocardial ischemia is mainly due to atherosclerosis (coronary artery disease or CAD), but may also be due to more uncommon conditions, such as myocardial bridging or coronary artery anomaly. Myocardial ischemia is caused by an oxygen demand-supply mismatch and may be provoked by an increase in heart rate and blood pressure during exercise, typically in combination with an underlying restriction of coronary blood flow secondary to CAD. This could potentially lead to effort-related angina pectoris, acute myocardial infarction (AMI), malignant arrhythmias, and Sudden Cardiac Arrest/Death (SCA/D).

Heart failure is a complex clinical syndrome of symptoms and signs caused by an impaired pumping function of the heart. It is caused by structural or functional abnormalities. Patients with heart failure due to left ventricular systolic dysfunction have a reduced left ventricular ejection fraction, whereas other patients have a preserved ejection fraction. CAD, previous myocardial infarction, and hypertension are common causes of heart failure, but there is a multitude of cardiomyopathies of different causes that may lead to heart failure. In Paralympic sports, congestive heart failure due to muscular dystrophy may be seen.

2.3 Diagnosis

a. Medical history

The personal history should include any family history of early CAD and/or SCA/D as well as cardiovascular risk factors (e.g., hyperlipidemia, hypertension, tobacco use, and diabetes mellitus). Common symptoms range from angina, dyspnea, palpitations, light-headedness, or syncope, which are typically effort-related, to exercise intolerance in heart failure.

b. Diagnostic criteria

It is not within the scope of this document to outline the comprehensive diagnostic criteria of the presence and extent of myocardial ischemia and heart failure. The below provides only a brief overview.

Acute coronary syndrome

The diagnosis of myocardial ischemia typically relies on the presence of chest discomfort that is triggered by exertion, referred to the left arm, neck and/or jaw, and relieved by rest or the use of nitroglycerin. However, the symptoms may be more subtle, diffuse, and even atypical (e.g., right-sided chest pain).

When there is suspicion, confirmatory evidence can be derived from ECG abnormalities, typically demonstrated by ST-segment changes or relevant arrhythmias. Both the resting ECG and serum markers reflecting hypoxic damage of the myocardium may be positive. Further confirmatory studies may include cardiac imaging (magnetic resonance imaging (MRI), nuclear imaging, coronary CT, echocardiography), and coronary angiography.

The occurrence of an AMI will usually be well documented in any patient [ECG changes, biomarkers (creatine kinase, troponins (cTn, TnC, TnI, TnT), myoglobin), imaging (coronary angiography, echocardiography, MRI, nuclear imaging)], and such documentation should be included in TUE applications for beta-blocker use post-infarction.

Chronic coronary syndrome

The clinical presentation of these patients may vary considerably based on six clinical scenarios most frequently encountered based on current guidelines:

(i) patients with suspected CAD and ‘stable’ anginal symptoms, and/or dyspnea;

(ii) patients with new onset of HF or LV dysfunction and suspected CAD;

(iii) asymptomatic and symptomatic patients with stabilized symptoms <1 year after an ACS or patients with recent revascularization;

(iv) asymptomatic and symptomatic patients >1 year after initial diagnosis or revascularization;

(v) patients with angina and suspected vasospastic or microvascular disease;

(vi) asymptomatic subjects in whom CAD is detected at screening.

Non-invasive functional imaging (MRI, nuclear imaging, coronary CT, echocardiography) for myocardial ischemia or CAD is recommended as the initial test(s) in these patients. Coronary angiography is performed in high-risk patients and those with severe symptoms. Exercise testing (treadmill or ergometer cycle with ECG) may be conducted in selected patients. The resting ECG is of limited use as it has a very low sensitivity for underlying

CAD, but may be helpful in selected cases, for example, when showing evidence of earlier (unknown) myocardial infarction.

Ischemic cardiomyopathy/heart failure with reduced ejection fraction (HFrEF)

The main symptoms of heart failure are breathlessness, peripheral edema, fatigue, and exercise intolerance. In addition to routine laboratory tests, biomarkers, in particular BNP and NT-proBNP, are used to establish the presence and severity of heart failure. Markers of myocardial injury such as cardiac troponin are further used. Transthoracic echocardiogram with repeated measures of the ejection fraction and structural remodeling and MRI may be used based on the clinical status.

2.4 Treatment

Acute and chronic coronary syndrome

The management of AMI is a medical emergency and may require the use of a number of agents included on the Prohibited List. Consequently, the affected athlete should submit an application for a retroactive TUE.

In heart failure after AMI, long-term treatment with beta-blockers (bisoprolol, sustained-release metoprolol, carvedilol) can lessen symptoms, improve the patient's clinical status, and enhance the overall sense of well-being. In addition, beta-blockers can reduce the risk of death and the combined risk of death or hospitalization in patients with or without CAD if initiated early (<24 h).

The purpose of long-term beta-blockade is the prevention of adverse ventricular remodeling in and around the site of infarction, a reduction in the sympatho-responsiveness of myocytes, and heart rate and blood pressure reduction. It should be confined to the management of significant ventricular arrhythmia, anginal symptoms, and LV systolic dysfunction as defined by a reduced left ventricular ejection fraction.

Furthermore, any post-myocardial infarction efficacy of beta-blockers is most profound in the first few months during infarct healing and ventricular remodeling but becomes unlikely beyond one year. However, there are currently no evidence-based recommendations defining the optimal or minimally required duration of treatment.

Beta-blockers are a component of first-line treatment for symptomatic chronic coronary syndromes (i.e., 'stable' anginal symptoms) and in selected patients according to heart rate, blood pressure, and tolerance, and in combination with other first-line and also second-line drugs.

Ischemic cardiomyopathy/heart failure with reduced ejection fraction (HFrEF)

Beta-blockers should be prescribed to all patients with stable heart failure and reduced ejection fraction unless they have a contraindication to their use. Because of the favorable effects on survival and disease progression, a clinical trial-proven beta-blocker should be initiated upon diagnosis. Even when symptoms are mild or improve with other therapies, beta-blocker therapy is important and should not be delayed.

Supraventricular and ventricular tachyarrhythmias

Beta-blockers are effective in controlling ventricular arrhythmias related to sympathetic activation, including stress-induced arrhythmias, acute/previous myocardial infarction, ischemic heart disease, perioperatively, and heart failure. Beta-blockers might be indicated in some additional arrhythmic conditions, such as regular narrow QRS complex supraventricular tachycardia and atrial fibrillation, but the details of these indications are beyond the scope of this document.

2.5 Non-prohibited alternative treatments

In the conditions described, there are no alternatives, but only additional/complementary pharmacological treatments (salicylic acid, ACE-inhibitors, angiotensin II receptor blockers, lipid-lowering agents, nitrates, ivabradine, etc.).

2.6 Consequences to health if treatment is withheld

Withholding treatment may lead to progressive disease and a higher risk of complications, such as (further) myocardial infarction or unstable angina, accompanying malignant arrhythmias, and possibly sudden cardiac arrest/SCD.

2.7 Treatment monitoring

The requirement for medication may change, and the athlete should have regular follow-ups with a specialist. Athletes with stable angina or post-AMI should be regularly monitored for any new or developing symptoms, changes in physical examination findings, and their overall risk profile (including additional risk factors, such as hypertension, hyperlipidemia, and diabetes).

Successful atherosclerotic risk factor modification, including control of blood pressure, reduction in plasma lipids, and tobacco-use abstinence, reduces the rate of progression of atherosclerotic disease and may subsequently influence the frequency of serial examinations.

2.8 TUE duration

The maximum recommended duration of a TUE for beta-blockers in these circumstances is four years. Any changes to the therapeutic regimen should include supporting documents from the appropriate physician.

2.9 Appropriate precautionary matters

Athletes should not put their health at risk; they should always seek the most appropriate medical treatment. Contraindications to Beta-blocker use include asthma and chronic obstructive lung disease with bronchospastic activity (significant reactive airway disease), symptomatic hypotension or bradycardia and severe decompensated/unstable heart failure, AV-block, Sick Sinus Syndrome, bradycardia/tachycardia syndrome, and Wolff-Parkinson-White Syndrome. Caution is to be exerted in chronic obstructive lung disease without bronchospastic activity, diabetes mellitus, and peripheral vascular disease. These conditions are not an absolute contraindication to beta-blocker use, but benefits need to be weighed against the risk of untoward effects in the individual patient.

3. Arterial hypertension with no other cardiovascular risk factors and resistant hypertension

In hypertension, beta-blockers may be given as monotherapy or in combination with diuretics, calcium-channel blockers, ACE-inhibitors, and Angiotensin II inhibitors. It is important to consider that diuretics are also prohibited In- and Out-of-Competition as per the Prohibited List (S5. Diuretics and Masking Agents) and therefore require a TUE.

3.1 Diagnosis

a. Medical history

Hypertension may be either primary or secondary. Primary or essential hypertension constitutes the predominant form of this condition and is considered to be the result of a combination of various factors, including genetics and lifestyle behaviors (e.g., physical inactivity, poor diet (excessive salt intake), stress and negative psychosocial factors). A history of sustained elevated blood pressure is a prerequisite for the diagnosis of hypertension.

Secondary forms of hypertension are rare (5-10%) and may be due to renal parenchymal disease, reno-vascular hypertension, coarctation of the aorta, pheochromocytoma, Cushing's syndrome, primary aldosteronism, obstructive sleep apnea, or drug-induced hypertension. The treatment of secondary forms of hypertension differs and is generally directed towards the underlying cause.

b. Diagnostic criteria

Hypertension is defined by serial systolic blood pressures ≥140 mmHg and/or serial diastolic blood pressures ≥90 mmHg, measured in a sitting position, under standardized conditions. The diagnosis of hypertension must be accompanied by an appropriate clinical history, documented elevated recordings of systolic and/or diastolic blood pressure, and a report of the findings of physical examination. Investigations including ECG, echocardiography, and vascular ultrasonography may also have diagnostic

relevance. Laboratory investigations may be necessary to exclude secondary hypertension.

c. Relevant medical information

There must be a justification from a specialist physician as to why the prohibited medication is the most appropriate treatment and why a permitted alternative was not used.

3.2 Treatment

The decision to initiate antihypertensive treatment should be based on three criteria, namely the repeated measurement of elevated systolic and/or diastolic blood pressure, the degree of overall cardiovascular risk, and the presence of any target organ damage (TOD). Lifestyle modification may be the initial, sole treatment in less severe hypertension. Even when medical therapy is indicated, lifestyle modification should always be an adjunct.

The most widely used substances for hypertension in physically active individuals are vasodilators, such as calcium channel blockers, ACE-inhibitors, and Angiotensin II inhibitors (all non-prohibited and preferred choices in athletes). However, most of the sports in which beta-blockers are prohibited (e.g., shooting) do not require a high degree of physical activity.

Other medications may need to be considered to treat associated risk factors. These may include lipid-lowering agents, antiplatelet therapy, and medication for glycemic control.

3.3 Non-prohibited alternative treatments

Changes to “lifestyle” should be instituted in all patients to control blood pressure and reduce other risk factors, as far as these considerations apply to the athlete population. However, the initiation of appropriate drug treatment should not be delayed unnecessarily.

Non-prohibited medications include calcium-channel blockers, ACE-inhibitors, Angiotensin II inhibitors, alpha-adrenergic blockers, and renin inhibitors.

3.4 Consequences to health if treatment is withheld

The rationale for treating high blood pressure is to decrease the overall risk for TOD and, ultimately, for complications, such as stroke and CAD. Untreated, hypertension will lead to progressive vessel disease and atherosclerosis, affecting several organs. This may manifest early as left ventricular hypertrophy (heart) and albuminuria (kidneys) and may progress to heart failure or kidney failure. The appropriate treatment of hypertension is a fundamental standard of good medical practice. Optimal blood pressure control is even more imperative when comorbidities, such as diabetes and obesity exist.

3.5 Treatment monitoring

During the phase of drug titration, patients should be seen every two to four weeks to adjust the treatment. Individuals with a blood pressure >180/110 mmHg, or where blood pressure is uncontrolled, must be evaluated and treated pharmacologically, before starting physical training, and in extreme cases (>200/115 mmHg), exercise is contraindicated until the blood pressure is normalized and under control. Target organ damage, i.e., heart, kidney, or eye complications secondary to hypertension, should be excluded and monitored (ECG, echocardiography, urine tests, and eyes), as it could constitute a contraindication for elite sports. Additional risk factors must be monitored and treated accordingly to lower overall risk.

Once a satisfactory blood pressure level is attained, the frequency of review may be reduced to every six months. The recommended target blood pressure is below 140/90 mmHg. However, a lower blood pressure is desirable for diabetics and high-risk patients (e.g., patients with chronic kidney disease). Routine blood pressure monitoring is normally at the discretion of the primary care practitioner with specialist referral as appropriate and in accordance with the local healthcare system.

3.6 TUE duration

Any changes to the therapeutic regimen should be well documented and form the basis of a revised or new TUE. The maximum recommended duration of a TUE in these circumstances is four years.

A file containing the initial diagnostic information plus any subsequent specialist opinion is required in the case of a TUE reapplication. An application for retroactive approval would need to demonstrate urgent or emergency treatment or any of the other reasons where one may obtain a retroactive TUE – (ISTUE Article 4.1).

4. Prevention of SCD in Long QT syndrome (LQTS)

Congenital LQTS is a serious pathologic condition associated with the risk of ominous ventricular arrhythmias, including torsades de pointes and ventricular fibrillation that may result in SCD.

LQTS is one of the best-understood monogenic diseases and presents an example of a strong genotype-phenotype correlation. Following the identification of the first three genes associated with the most frequent variants, ten more genes involved in fine-tuning the cardiac action potential have been associated with LQTS. By far, KCNQ1 (LQT1), KCNH2 (LQT2), and SCN5A (LQT3) are the most common LQTS genes, accounting for about 70% of all genotype-positive cases. Two hereditary variants, the Romano-Ward (RW) syndrome and the very severe Jervell and Lange-Nielsen (JLN) syndrome, which is associated with congenital deafness, belong to the LQTS family of diseases.

4.1 Diagnosis

a. Medical history

The most typical clinical presentation in patients with LQTS is a history of cardiac events that may be triggered by exercise, swimming, or emotions, but they may also occur during night sleep. The nature of trigger events differs by genotype: a) In LQTS1, exercise, or swimming may trigger an event. Sudden exposure of the patient's face to cold water is thought to elicit a vagotonic reflex; b) In LQTS2, an emotional event, exercise or exposure to auditory stimuli (e.g., doorbell, phone) may be a trigger; c) While in LQTS3, events typically occur during sleeping at night.

b. Diagnostic criteria

Typical cases pose no diagnostic difficulty for physicians who are aware of the disease. Clinical history and analysis of repolarization duration (QTc) and morphology on the patient's ECG and on ECGs of the patient's relatives allow for proper diagnosis. In the case of a verified QTc > 500 ms on the resting ECG, in the absence of marked sinus bradycardia, the diagnostic criterion is fulfilled. However, borderline cases are more complex and require the evaluation of multiple further variables. The diagnostic criteria for LQTS are summarized in a diagnostic score, most typically the "Schwartz score", which is based on the degree of the QT prolongation and has been repeatedly updated. Patients with a score ≥ 3 should undergo molecular screening. The use of genetic testing to identify underlying causal mutations responsible for the phenotype is increasingly used in routine clinical assessment of athletes with suspected LQTS but may not be available or needed for every athlete.

c. Relevant medical information

Hearing loss or deficit in a patient and their family may indicate the possibility of Jervell and Lang-Nielsen (JLN) syndrome. A family history of cardiac arrest, unexplained sudden death, and/or unexplained cardiogenic syncope, especially at young ages, may suggest a congenital form of LQTS.

Information about what medication the patient has taken is critical for the differential diagnosis of congenital LQTS and of drug-induced QT prolongation (which may also have a genetic background).

4.2 Treatment

All patients diagnosed with LQTS, including those still asymptomatic, should be treated according to international treatment guidelines. There are three treatment options in LQTS to prevent sudden cardiac arrest due to ventricular fibrillation, all of which have clearly defined indications: beta-blockers, Left Cardiac Sympathetic Denervation (LCSD), and an Implantable Cardioverter Defibrillator (ICD).

Beta-blockers are the first-line therapy of choice in both asymptomatic and symptomatic LQTS. The initial treatment should always involve beta-blockers, with propranolol and nadolol having been shown to be the two most effective substances but alternative agents may be justifiable on an individualized basis.

In asymptomatic athletes with no history of cardiac events, variable QT intervals in serial 12-lead ECGs, and a modestly and only occasionally prolonged QTc interval, beta-blockers are the first choice as the invasiveness of the existing treatment alternatives is difficult to justify in these cases.

The indication for beta-blocker treatment may be reconsidered in individuals with a normal QT interval (silent mutation carriers) or LQTS1 males who are ≥ 25 years and never had symptoms without taking beta-blockers. It is highly unlikely that these individuals will develop cardiac events.

4.3 Non-prohibited alternative treatments

LCSD may be indicated in young patients with syncope despite beta-blocker therapy. However, this therapeutic option is only available in a few centers worldwide. Whenever syncopal episodes recur despite full-dose beta-blocker therapy, LCSD may be considered but only in centers with the relevant experience.

There is an overall consensus to immediately implant an ICD in cases where there has been a documented cardiac arrest, beta on or off therapy (exceptions are, for example, a drug-induced event in an otherwise asymptomatic patient with modest QT prolongation). An ICD is considered in patients with repeated cardiogenic syncope despite full dose beta-blocker therapy. An ICD may also be indicated in case repeated ECGs and 24-hour Holter ECG monitoring demonstrate consistent (not merely occasional) prolongation of the QTc interval above 0.50 s. A QTc interval ≥ 0.50 s is the threshold associated with a significantly higher incidence of arrhythmic complications and cardiac arrest.

4.4 Consequences to health if treatment is withheld

Individuals with LQTS are at risk of SCD at any time, irrespective of their involvement in sport. However, the mechanism of “after-depolarization” causing arrhythmias in LQTS occurs more often in states of adrenergic stimulation. Therefore, the risk of ventricular tachyarrhythmias and SCD in LQTS is greater during states of increased adrenergic tone (e.g., exercise, excitement).

Based on current evidence, withholding beta-blockers in a patient with LQTS entails accepting SCD as a consequence. The risk of SCD for an LQTS patient who is not being treated is about 12–13% in the first 40 years of life. Beta-blockers reduce the sympathetic tone and thereby the effects of adrenergic stimulation, effectively decreasing the risk of SCD in LQTS to about 1%.

4.5 Treatment monitoring

All patients on therapy require careful evaluation and follow-up care in an ambulatory setting. A cardiologist should examine asymptomatic patients with LQTS on an annual basis. Symptomatic patients require more frequent assessments and treatment reevaluations.

4.6 TUE duration

Beta-blocker treatment in case of congenital LQTS is generally lifelong unless LCSD is performed, or an ICD is implanted. TUEs may be granted for a duration of up to ten years.

5. Prevention/management of aortic disease

Diseases of the aorta (aortopathy) predispose to acute aortic dissection, which is a well-recognized cause of SCA/SCD among competitive athletes. Diseases of the aorta are most commonly caused by genetic/familial conditions that involve systemic abnormalities of connective tissue including, but are not limited to, Marfan syndrome, Loeys-Dietz syndrome, vascular Ehlers-Danlos syndrome, and Familial Thoracic Aortic Aneurysm (TAA) syndrome. A comprehensive discussion of the genetic causes of aortopathy is beyond the scope of this document. Spontaneous pathologic dilation of the aorta and/or acquired aortopathy in the context of long-standing hypertension and/or exercise-induced hypertension may also be encountered among competitive athletes.

5.1 Diagnosis

a. Medical history

The most typical clinical presentation of genetic aortopathy, aside from survival following a clinically recognized aortic dissection, is the recognition of non-cardiac stigmata of connective tissue disease. The criteria for the diagnosis of these conditions are widely accepted for clinical use, and screening for aortopathy is recommended following diagnostic confirmation of systemic connective tissue disease. Aortic aneurysms are typically clinically silent unless in the setting of a concomitant and clinically appreciable abnormality of the aortic valve (i.e., biscuspid disease with audible stenosis or regurgitation) and thus detected only during pre-participation screening with non-invasive imaging or during cardiac evaluation for another indication. Hypertensive disease of the aorta is most often detected during the evaluation of the cardiac structure and function among athletes with established hypertension.

b. Diagnostic criteria

Diagnosis of aortopathy requires non-invasive imaging which permits the measurement of the aortic root and ascending aorta. This can be accomplished with transthoracic echocardiography, but tomographic imaging with CT and/or MRI has been shown to have better accuracy and the ability to visualize the entire thoracic aorta, which includes the aortic arch and descending thoracic aorta. Quantitative cut-points for the establishment of suspected pathologic aortic enlargement have been proposed and are dependent on the biological sex of the athlete (>40 mm men, >34 mm women).

While participation in sports may lead to mild physiologic dilation of the aorta, the magnitude of adaptive remodeling is typically small and rarely leads to aortic dimensions that exceed clinical cut-points for the upper limit of normality.

c. Relevant medical information

The finding of a biscuspid aortic valve (independent of valve function), physical stigmata suggestive of and/or causal genetic mutations associated with connective tissue disease, established long-standing hypertension, particularly if sub-optimally controlled, and/or a family history of aortic dissection should prompt evaluation for a potential aortic pathology.

5.2 Treatment

All patients diagnosed with aortopathy should be risk stratified to determine the appropriateness of surgical intervention. Beta-blocker therapy may be appropriate among athletes not meeting criteria for surgical intervention, as a bridge to surgery among athletes with planned surgery, and as post-operative medical therapy. The efficacy of long-term beta-blocker therapy among athletes with a pathology that does not meet indications for surgical correction has not been established but is common clinical practice. The duration of post-operative beta-blocker therapy among competitive athletes undergoing surgical correction of aortic disease has similarly not been established.

Beta-blockers, often in combination with an ACE-inhibitor or angiotensin-receptor blockers, represent first-line therapy to prevent the development/progression of aortic pathology among athletes with connective tissue disorders. The use of beta-blockers in other causes of aortic disease is less well established but may be reasonable on an individualized basis.

5.3 Non-prohibited alternative treatments

Surgical correction of thoracic aortic aneurysms may be appropriate based on the size and physical characteristics of the aorta, the documented rate of progression of aortic growth, and the etiology of the dilation.

5.4 Consequences to health if treatment is withheld

Withholding of beta-blocker therapy among athletes with definitive aortic pathology may increase the risk of acute aortic syndromes. Concomitant physical activity restrictions, often related to limitations around the performance of isometric strength-based activities, is commonplace among athletes with established aortic pathology.

5.5 Treatment monitoring

All patients with established aortic pathology, including but not limited to those receiving beta-blocker therapy, should undergo routine surveillance imaging at a frequency dictated by the magnitude of aortic dilation and the etiology of the underlying disease. Blood pressure-lowering medical therapy to achieve normotension, including but not limited to the use of beta-blockers, is the recommended treatment. A cardiologist should examine patients with aortic disease on an annual basis (or more frequently in some cases). The development of chest pain or alternative thoracic symptoms among athletes with established aortic disease should raise a high index of suspicion for aortic dissection and should be evaluated urgently by providers with expertise in diseases of the aorta.

5.6 TUE duration

Beta-blocker treatment in cases of aortopathy must be individualized to the athlete and will be dependent on the etiology of the aortopathy, the magnitude of aortic dilation, and the timing and appropriateness of surgical intervention. Athletes with aortic dilation/aneurysm attributed to connective tissue disease may require life-long beta-blocker therapy independent of surgical intervention or aortic size and characteristics. In these instances, TUEs may be granted for a duration of up to 10 years.

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