Cardiovascular Conditions: The Therapeutic Use of Beta-Blockers in Athletes

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).

1. Sports in which Beta-blockers are prohibited

Beta-blockers are prohibited **only** in the following sports:

- Archery (WA)
- Automobile (FIA)
- Billiards (all disciplines) (WCBS)
- Darts (WDF)
- Golf (IGF)
- Shooting (ISSF, IPC)
- Skiing/Snowboarding (FIS - ski jumping, freestyle aerials/half pipe and snowboard half pipe/big air)
- Underwater sports (CMAS) - constant-weight apnoea with or without fins, dynamic apnoea with and without fins, free immersion apnoea, Jump Blue apnoea, spearfishing, static apnoea, target shooting and variable weight apnoea.[1]

[1] Please see Section P of the current Prohibited List, specifically with respect to the distinction between which sports prohibit Beta-blockers both in and out of competition.

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This Guideline is reviewed annually to determine whether revisions to the Prohibited List or new medical practices or standards warrant revisions to the document. If no changes are deemed warranted in the course of this annual review, the existing version remains in force

2. Indications for the use of Beta-blockers

For the following conditions, Beta-blockers are usually recommended 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

However, in individual patients, the recommended therapy with Beta-blockers might only be one treatment option and other alternatives may be as acceptable or even more appropriate. Furthermore, the recommendation does not overrule the responsibility of the treating physician to make decisions based on the individual circumstances of a patient. This is, however, beyond the scope of this document and in general, it can be assumed that, for the above-mentioned conditions, the ISTUE Articles 4.1 (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 has 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 as per the International Standard Prohibited List 2018: S5. Diuretics and Masking Agents), ACE-inhibitors, Angiotensin II inhibitors or RAS inhibitors - all considered best-practice alternatives.

Other alternative treatments may be appropriate and the use of Beta-blockers should only be considered when these alternatives have been tried without success or where 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 assess the acceptability of 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 cannot, or could not, be used in the treatment of the condition. Due to the international variation in medical practice, it is appropriate for any TUEC who assesses or questions such statement to consult a cardiologist.

An athlete cannot be compelled 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.

3. 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 4.1 (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 individual case, and how this affects their performance in the concerned sport.

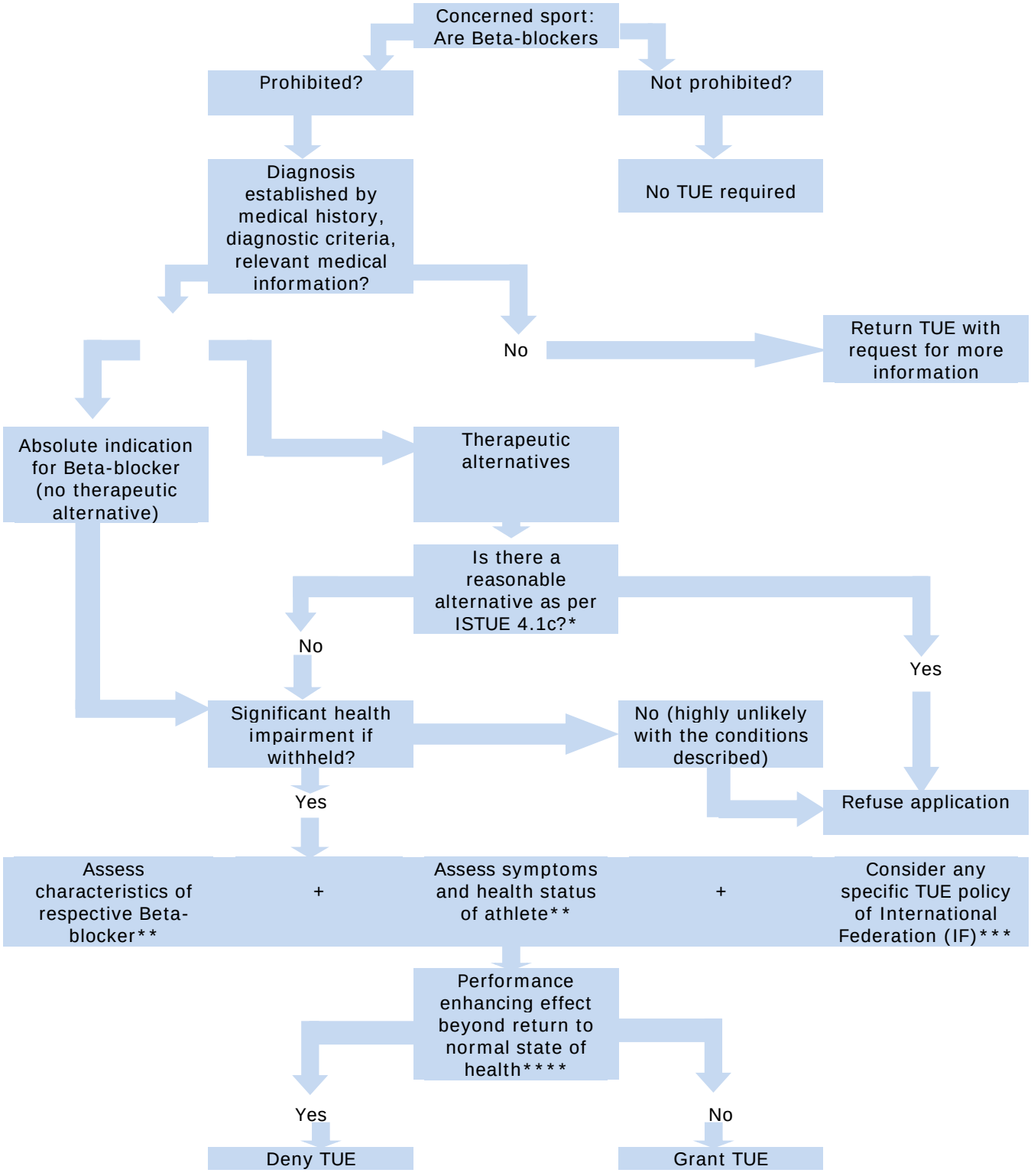
That said, an athlete is not required to determine that the potential performance enhancing effects can be categorically excluded, just that they are highly unlikely (*CAS 2015/A/4355*); in fact, to ask the athlete for scientific evidence that cannot be provided would be an impossible burden on the athlete.

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 4.1(b) has been satisfied (*CAS 2013/A/3437*).

4. Conclusion

The above considerations lay the foundation for the assessment of a TUE application based on current evidence-based medicine and the relevant anti-doping regulations and case law. As indicated, in precision sports and 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 4.1(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 cardiologist essential. Carefully assess symptoms and health status of athlete, including their influence on performance prior to taking Beta-blockers.

***Consult with IF to ascertain if there is a specific policy on Beta-blockers.

****Important note: An athlete will 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.).

Administration

- 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.

- Frequency

Several daily doses depending on the individual substance used.

Medical Conditions

1. 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 Death.

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 cause that may lead to heart failure. In Paralympic sports, congestive heart failure due to muscular dystrophy may be seen.

Most conditions where Beta-blockers are indicated are not compatible with participation in competitive sports, except the less aerobically demanding such as precision sports.

A. Medical history

The personal history should include any family history of early CAD and/or sudden cardiac death as well as cardiovascular risk factors (hyperlipidemia, hypertension, and diabetes mellitus). Common symptoms range from angina, dyspnea, palpitations, light-headedness or syncope, which all 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.

The diagnosis of myocardial ischemia typically involves chest discomfort, with referred pain to the left arm and/or jaw being described as “classic” angina pectoris. However, the symptoms may be more subtle, diffuse and even atypical (as right-sided chest pain).

When there is suspicion, confirmatory evidence is derived from ECG abnormalities typically demonstrated by T-wave and ST-segment changes during exercise testing (treadmill or ergometer cycle with ECG). 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. In the acute phase (unstable angina, myocardial infarction), however, both resting ECG and serum markers reflecting hypoxic damage of the myocardium may be positive. Further confirmatory studies may include Holter monitoring, nuclear imaging (myocardial scintigraphy), coronary CT, echocardiography and coronary angiography.

The occurrence of an AMI will usually be well documented in any patient (ECG changes, biomarkers (creatine kinase, troponin I and T, myoglobin), imaging (echocardiography, MRI)) and represent an essential part of TUE applications for Beta-blocker use post-infarction.

The main symptoms of heart failure are breathlessness, lower extremity swelling, fatigue and exercise intolerance. In addition to routine laboratory test, 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. Next to chest Xray and two-dimensional echocardiogram, repeated measures of ejection fraction and structural remodeling, radionuclide ventriculography and magnetic resonance imaging may be used based on the clinical status. There is no established role for routine or periodic invasive hemodynamic measurements in the management of heart failure.

Best practice treatment

Beta-blockers are first-line treatment for unstable angina, coronary artery disease and post-AMI. The protective effect of Beta-blockers has been shown to reduce the risk of arrhythmias, to improve survival and to prevent reinfarction and sudden cardiac death (SCD).

The management of AMI is a medical emergency and may invoke 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, 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. Long-term Beta blockade is the only pharmacologic intervention that reverses left ventricular remodeling. 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.

2. SUPRAVENTRICULAR AND VENTRICULAR TACHYARRHYTHMIAS

Beta-blockers are effective in controlling ventricular arrhythmias related to sympathetic activation including stress-induced arrhythmias, acute/previous myocardial infarction, ischaemic heart disease, perioperatively and heart failure. Beta-blockers might be indicated in some conditions with supraventricular arrhythmias and atrial fibrillations, the details of these indications are beyond the scope of this document.

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, etc.).

Consequences to health if treatment is withheld

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

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).

A success in risk factor modification influences the frequency of examinations, as it may affect the rate of progression of atherosclerotic disease.

TUE validity and recommended review process

Any changes to the therapeutic regimen should be well documented, endorsed by a cardiologist and form the basis of a revised TUE. The maximum recommended duration of a TUE for Beta-blockers 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 as per ISTUE 4.3(a) would need to demonstrate a coronary heart disease emergency.

Cautionary matters

Athletes should not put their health at risk, but 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

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.

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 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 a TUE application.

Secondary forms of hypertension are rare (5%), and may be due to renal parenchymal disease, reno-vascular hypertension, coarctation of the aorta, phaeochromocytoma, 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.

A. Diagnostic criteria

Hypertension is defined as a repeated blood pressure ≥140/≥90, 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.

B. Relevant medical information

Evidence of a sustained trial of non-prohibited agents must be included in the medical information supporting the application for therapeutic use. There must be a clear reason from a specialist physician why a prohibited agent is chosen over a permitted alternative explaining why the alternative is not reasonable to use.

Best practice 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 (non-prohibited). However, it may be possible that there are specific cases where there is a primary indication for the use of Beta-blockers and no reasonable alternative.

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.

Non-prohibited alternative treatments

Changes to "lifestyle" should be instituted in all patients to control blood pressure and reduce other risk factors, in 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.

Consequences to health if treatment is withheld

The rationale for treating a 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 fundamental standard medical practice. Optimal blood pressure control is even more imperative when comorbidities such as diabetes and obesity exist.

Treatment monitoring

During the phase of drug titration patients should be seen every 2 to 4 weeks to adjust the treatment. Individuals with a blood pressure >180/110, or where blood pressure is uncontrolled, must be evaluated and treated pharmacologically, before starting physical training, and in extreme cases (>200/115), 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, must 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, however, a lower blood pressure is desirable for diabetics and high-risk patients. 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.

TUE validity and recommended review process

Any changes to the therapeutic regimen should be well documented, endorsed by a medical specialist and form the basis of a revised 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 an acute hypertensive emergency.

4. PREVENTION OF SCD IN LONG QT SYNDROME

Congenital Long QT Syndrome (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, 10 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.

Diagnosis

A. Medical History

The most typical clinical presentation in patients with LQTS is a history of cardiac events which 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 may 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 case of a verified QTc >500ms on the resting ECG 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 summarised 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.

C. Relevant Medical Information

Hearing loss or deficit in a patient and their family may indicate possibility of Jervell and Lang-Nielsen (JLN) syndrome. A family history of cardiac arrest and/or unexplained sudden death, especially at young age, 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 genetic background however).

Best practice 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 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.

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.

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, either on or off therapy (exceptions are for example of 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 0.50s. A QTc interval ≥0.50s is the threshold associated with a significantly higher incidence of arrhythmic complications and cardiac arrest.

Importantly, competitive sports are not recommended by leading international cardiologic societies (European Society of Cardiology and American Heart Association), in cases of unequivocal LQT diagnosis. In cases of LQT treated with an ICD, contact sports are not

recommended, neither are sports where malfunction of the device may pose problems for the athlete or for someone else (e.g., driving, canoeing, etc.).

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 sudden cardiac death for a 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%.

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.

TUE validity and recommended review process

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.

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ANNEX

CAS Case law

When applying for a TUE for a beta-blocker, particularly in the sport of shooting, athletes and their physicians need to be aware of the relevant CAS case law.

In recent decisions concerning shooting, CAS has considerably limited an athlete's prospect of obtaining a TUE for beta-blockers. In two cases (CAS 2009/A/1948; CAS 2013/A/3437), the CAS Panel took this approach despite accepting expert evidence that a) it could not be definitively concluded that beta-blockers confer a performance enhancement on all shooters in all circumstances, and b) it cannot be definitively concluded that beta-blockers are uniform in their effects. CAS also indicated that it would be exceptionally difficult to demonstrate which factors exactly – for example, the use of beta-blockers, their equipment, coaching, training, competition experience or physical and physiological factors caused an observed improvement in an athlete's performance.

A more recent CAS decision (2015/A/4355) reversed a decision to deny a beta-blocker TUE, but did so on narrow grounds. The Panel considered persuasive the argument that the physiological circumstances associated with the athlete's chronic disability made an ergogenic benefit due to beta-blockers highly unlikely. This statement was not contradicted by any other evidence before the Panel. The outcome in this specific case should not be interpreted as a significant change in the CAS jurisprudence on the granting of beta-blocker TUEs in shooting sports; instead, it is important to be aware that this decision made was based on the athlete's very specific and unique individual state of health. With respect to satisfying the criteria found at ISTUE Article 4.1(b), it is worthwhile to highlight that CAS clarified that the athlete had to demonstrate that a performance enhancing effect was highly unlikely and not that potential performance enhancing effects must be categorically excluded. This decision also addressed the standard of proof for the evaluation of ISTUE 4.1 criteria, for the first time explicitly presented as the "balance of probability" and now expressly indicated in the 2016 ISTUE. This standard of proof is analogous to "more likely than not", or mathematically speaking, a probability that exceeds 50%.

Even when an athlete has little difficulty satisfying the criteria at Article 4.1 (a), (c) and (d) of the ISTUE when applying for a TUE, he/she will face a significant challenge trying to satisfy the criterion found at Article 4.1(b) of the ISTUE; that is, that the use of beta-blockers will "not enhance their performance beyond what might be anticipated by a return to the athlete's normal state of health". This includes assessment of individual impairment by a condition and a corresponding definition of "normal health".

Since the TUEC has to assess the case of the individual athlete against the requirements of their sport, it may be necessary for an athlete to go beyond clinical assessments of treatment success and include systematic measurements of physiological and performance parameters (see ISSF suggestions ISSF in CAS 2013/A/3437) before and after medication in their application. However, the TUEC has to consider that the comparison of before and after competition results is subject to diverging interpretation and always influenced by

intra- and inter-individually highly variable athletic development. Single comparators (one athlete of same gender and age performing the same sport) to prove “normal” development have been refused by CAS unless they are “materially similar”.