ARRHYTHMIAS

CHI Formulary Indication Review

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Contents

Related Documents

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- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
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Abbreviations

AAD	Antiarrhythmic Drug
ACHD	Adult Congenital Heart Disease
AF	Atrial Fibrillation
AFL	Atrial Flutter
ANP	Atrial Natriuretic Peptide
AP	Accessory Pathway
ASD	Atrial Septal Defect
AT	Atrial Tachycardia
AV	Atrioventricular
AVN	Atrioventricular Node
AVNRT	Atrioventricular Nodal Reentrant Tachycardia
AVRT	Atrioventricular Reentrant Tachycardia
BBB	Bundle Branch Block
Bpm	Beats Per Minute
CADTH	Canadian Agency for Drugs and Technologies in Health
CHI	Council of Health Insurance
CI	Confidence Interval
CL	Cycle Length
CPG	Clinical Practice Guideline
CTI	Cavo-Tricuspid Isthmus
DC	Direct Current
ECG	Electrocardiogram
EPS	Electrophysiology Study
ERP	Effective Refractory Period
FDA	Food and Drug Administration
HAS	Haute Autorité de Santé
HPS	His-Purkinje system
HR	Heart Rate
HTA	Health Technology Assessment
IDF	Insurance Drug Formulary
IQWIG	Institute for Quality and Efficiency in Health Care

IV	Intravenous
IVC	Inferior Vena Cava
LA	Left Atrium
LBBB	Left Bundle Branch Block
LV	Left Ventricle
MESA	Marshfield (Wisconsin) Epidemiologic Study Area
MRT	Macro-Reentrant Tachycardia
Ms	Milliseconds
NICE	National Institute for Health and Care Excellence
PBAC	Pharmaceutical Benefits Advisory Committee
PJRT	Permanent Junctional Reciprocating Tachycardia
POTS	Postural Orthostatic Tachycardia Syndrome
PPI	Post-Pacing Interval
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
RA	Right Atrium
RBBB	Right Bundle Branch Block
RCT	Randomized Controlled Trial
RF	Radiofrequency
RV	Right Ventricle
S	Second
SFDA	Saudi Food and Drug Authority
SR	Sinus Rhythm
SVC	Superior Vena Cava
SVT	Supraventricular Tachycardia
VA	Ventricular Arrhythmia

Executive Summary

Arrhythmias are a wide range of conditions characterized by irregularities in heart rate and rhythm. The most common way to categorize them is based on the rate of conduction as bradyarrhythmia with a heart rate of fewer than 60 beats per minute (bpm) and tachyarrhythmia with a heart rate higher than 100 bpm. Additionally, these conditions are further categorized based on their origin, transmission methods, and associated syndromes. Individuals experiencing arrhythmias may present with a diverse range of clinical symptoms, ranging from complete lack of symptoms to instances of sudden cardiac arrest.[1]

The anticipated occurrence of arrhythmias in the general population is estimated to range from 1.5% to 5%, with atrial fibrillation being the most frequently encountered type. Arrhythmias may or may not manifest noticeable symptoms and can occur intermittently, posing challenges in accurately determining their actual prevalence. The overall existence of arrhythmias is linked to increased morbidity and mortality.[1]

In Saudi Arabia, data on the epidemiology of arrhythmias is mainly focused on atrial fibrillation as it is considered as the most prevalent type of arrhythmias, and it mainly stems from single-center studies. In February 2018, a study was conducted using all medical records of patients registered in Prince Sultan Cardiac Center in Qassim, Saudi Arabia, and diagnosed with HF during the period from January 1, 2010, to June 30, 2014, to estimate the rate of atrial fibrillation (AF) among adult patients with chronic heart failure (HF) from Saudi Arabia, and to identify the clinical and the demographic characteristics. The rate of AF among chronic HF (n = 70) patients was 14.9%. The rate of AF was higher among males (15.7%) than females (12.5%). In both genders, the rate of AF rose with advancing age, and in each age stratum, it was higher in males than females.[2]

The most common types of arrhythmias include premature atrial complex, ventricular premature beats, bradycardias (including sinus bradycardia), ventricular tachycardia, atrial fibrillation (AF) and atrial flutter, supraventricular tachycardia (SVTs), AV block, nonsustained ventricular tachycardia (NSVT), follow-up of already treated VT or ventricular fibrillation (VF).[3]

This report does not detail the management of atrial fibrillation, ventricular tachycardia, supraventricular tachycardia, and bradycardia since these indications are discussed in separate documents. For more information, please refer to individual indication reports.

Symptoms caused by cardiac arrhythmias can mimic those due to other medical disorders and include palpitations, dizziness, lightheadedness, syncope, chest discomfort, neck discomfort, dyspnea, weakness, and anxiety. They can also have unusual symptomatic presentations such as tinnitus, visual changes, increased

urinary frequency, abdominal discomfort, and peripheral edema. For individuals with suspected arrhythmias, the initial diagnostic step typically involves an electrocardiogram (EKG), which often provides the diagnosis. Many patients with a suspected arrhythmia have a paroxysmal pattern, so that the ECG recorded in the absence of symptoms is either normal or does not suggest a specific arrhythmia. Four types of outpatient monitoring systems are available including: traditional Holter, event recorder, mobile continuous outpatient cardiac telemetry and insertable cardiac monitor.[3]

Consulting a specialist, such as a cardiologist or electrophysiologist is necessary when contemplating the initiation of any antiarrhythmic drug. Antiarrhythmic medications have the capacity to elevate premature ventricular contractions, induce or worsen monomorphic ventricular tachycardia (VT), torsades de pointes (TdP), ventricular fibrillation (VF), as well as cause conduction disturbances or bradycardia. This phenomenon, termed proarrhythmia, underscores the potential for significant adverse outcomes, including death. Electrophysiologists or other specialized clinicians with certification and training in device placement are usually responsible for implanting pacemakers, implantable cardioverter-defibrillators (ICDs), and biventricular devices.[3]

The Vaughan Williams classification categorizes antiarrhythmic drugs based on their primary mechanism of action. It's an established system used for several decades to classify these drugs:[4]

- **Class I** - Sodium channel blockers. This class is further subdivided into three categories based on their effect on the action potential duration:
    - **Class Ia**: Moderate sodium channel blockade. Drugs in this subclass lengthen the action potential duration. Examples include quinidine, procainamide, and disopyramide.
    - **Class Ib**: Mild sodium channel blockade. Drugs in this subclass shorten the action potential duration. Examples include lidocaine, mexiletine, and phenytoin.
    - **Class Ic**: Strong sodium channel blockade. Drugs in this subclass have minimal effect on the action potential duration. Examples include flecainide and propafenone.
- **Class II** - Beta-adrenergic blockers. These drugs slow down the heart rate and decrease the force of the heart's contraction. Examples include propranolol, metoprolol, and atenolol.
- **Class III** - Potassium channel blockers. These drugs primarily prolong the action potential duration and the refractory period. Examples include amiodarone, dronedarone, sotalol, and dofetilide.

- **Class IV** - Calcium channel blockers. These drugs slow down the conduction through the AV node. Examples include verapamil and diltiazem.
- **Class V**: Other drugs with variable mechanisms include adenosine, digoxin and magnesium sulfate.

After initiating an antiarrhythmic drug, patients should undergo regular monitoring through ECGs and laboratory tests. Additionally, given the potential for interactions with other drugs, continuous monitoring of such interactions is necessary.[3]

This report compiles all clinical and economic evidence related to arrhythmias according to the relevant sources. The ultimate objective of issuing endocarditis guidelines by the Council of Health Insurance (CHI) is to update the IDF (CHI Drug Formulary) with **the best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to patients with arrhythmias in Saudi Arabia.** The main focus of the review was on Saudi, North American and European guidelines issued within the last ten years in addition to recent systematic reviews and meta-analyses.

The management of arrhythmias involves a **multidisciplinary approach**. There are currently **multiple treatment regimen options for the management of endocarditis on the global market.** KSA has access to most of them; but a few options are not yet registered by the Saudi Food and Drug Authority (SFDA). Section 2 provides a full description of each with final statements on the placement of therapy. All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) reflecting specific drug class role in the treatment of arrhythmias. Section 3 lists the key recommendations synthesis for the management of arrhythmias.

Major recommendations for suggested drug therapies are summarized in the table below:

Table 1. SFDA-Registered Drugs for the Management of Arrhythmias

Treatment Regimen	Indication(s)	Line of therapy	Level of Evidence/Grade of Recommendation	Reference
Class I				
Lidocaine	Ventricular arrhythmias Ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT), shock-refractory (Pediatric)	2nd line	Intravenous lidocaine may be considered for the treatment of recurrent PVT/VF not responding to beta-blockers or amiodarone, or if amiodarone is contraindicated during the acute phase of ACS (Class IIb, level of evidence C).	ESC Guidelines (2022)[5]
Flecainide	Fetal tachycardia, sustained Paroxysmal atrial fibrillation/flutter and paroxysmal supraventricular tachycardias (prevention) Ventricular arrhythmias (prevention) Ventricular premature beats (off-label use) Atrial fibrillation/flutter (pharmacological cardioversion) (off-label dose) Arrhythmias (Pediatric)	1st line (symptomatic patients with idiopathic VT/PVCs from an origin other than the RVOT or the left fascicles) 2nd line (symptomatic patients with idiopathic VT/ PVCs from the RVOT or the left fascicles)	Catheter ablation or flecainide should be considered in symptomatic patients with idiopathic VT/PVCs from an origin other than the RVOT or the left fascicles (Class IIa, level of evidence C). Beta-blockers, non-DHP CCBs, or flecainide should be considered when catheter ablation is not available, desired, or is risky in symptomatic patients with	2023 HRS expert consensus[6]

			idiopathic VT/PVCs from the RVOT or the left fascicles (Class IIA, level of evidence B). In pregnant patients with recurrent VT refractory or with contraindications to beta-blockers who require additional antiarrhythmic drug therapy, treatment with flecainide, sotalol, or mexiletine is recommended with the choice of drug based on the underlying cardiac substrate. (COR 1, LOE C-LD) In fetuses with VT complicated by hydrops or ventricular dysfunction refractory or with contraindications to first-line drug options and not secondary to IAS, transplacental administration of flecainide, sotalol, or amiodarone can be beneficial, with the choice of drug according to the underlying maternal and fetal substrate. (COR 2a, LOE B-NR)	

Class II (Beta-adrenergic blockers)				
Metoprolol	Atrial fibrillation/flutter (off-label use) Atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, focal atrial tachycardia, multifocal atrial tachycardia Ventricular arrhythmias (off-label use)	N/A for atrial flutter N/A for 1st line (In pregnant individuals with ventricular arrhythmias) 1st line (in PVCs) 2nd Or 3rd line (for sinus tachycardia)	Either β-blockers or nondihydropyridine calcium channel blockers (diltiazem or verapamil) are considered first-line medicines for PVCs. IV beta blockers (metoprolol or esmolol) may be considered. (May be recommended) Metoprolol is recommended in the absence of pulmonary disease. (Is recommended) Beta-blockers and non-dihydropyridine calcium channel blockers in inappropriate sinus tachycardia are frequently ineffective or not tolerated at required doses. Therefore, may be considered as second- and third-line therapy, respectively. (May be recommended) Beta-blockers, non-DHP	AHA 2017[7] ESC Guidelines (2022)[5] European Heart Rhythm Association (EHRA) consensus (2017)[8] 2023 HRS expert consensus[6]

			CCBs, or flecainide should be considered when catheter ablation is not available, desired, or is risky in symptomatic patients with idiopathic VT/PVCs from the RVOT or the left fascicles (Class IIA, level of evidence B). In pregnant patients with idiopathic VT and hemodynamic stability, intravenous beta-blocker or adenosine for outflow tract VT and intravenous verapamil for fascicular VT are recommended as first-line options. (COR 1, LOE C-LD)	
Propranolol	Atrial fibrillation/flutter (off-label use) Atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, focal atrial tachycardia Ventricular arrhythmias (off-label use) Tachyarrhythmias (Pediatric)	1st line (In pregnant individuals with ventricular arrhythmias) 1st line (In PVCs) 2nd or 3rd line (In non-pregnant individuals with inappropriate sinus tachycardia)	Either β-blockers or nondihydropyridine calcium channel blockers (diltiazem or verapamil) are considered first-line medicines for PVCs. Beta-blockers and non-dihydropyridine calcium channel blockers are frequently ineffective or not tolerated at required doses in	ESC Guidelines (2022)[5] European Heart Rhythm Association (EHRA) consensus (2017)[8] 2023 HRS expert consensus[6]

			inappropriate sinus tachycardia. Therefore, may be considered as second- and third-line therapy, respectively. (May be recommended) Beta-blockers, non-DHP CCBs, or flecainide should be considered when catheter ablation is not available, desired, or is particular risky in symptomatic patients with idiopathic VT/PVCs from the RVOT or the left fascicles (Class IIA, level of evidence B). In pregnant patients with idiopathic VT and hemodynamic stability, intravenous beta-blocker or adenosine for outflow tract VT and intravenous verapamil for fascicular VT are recommended as first-line options. (COR 1, LOE C-LD)	
Bisoprolol	Atrial fibrillation/flutter, maintenance of ventricular rate control (off-label use)	1st line (In pregnant individuals with	Either β-blockers or nondihydropyridine calcium channel blockers (diltiazem or	ESC Guidelines (2022)[5]

	Ventricular arrhythmias (off- label use)	ventricular arrhythmias) 1st line (In PVCs) 2nd or 3rd line (In non-pregnant individuals with inappropriate sinus tachycardia)	verapamil) are considered first-line medicines for PVCs. Beta-blockers and non-dihydropyridine calcium channel blockers are frequently ineffective or not tolerated at required doses in inappropriate sinus tachycardia. Therefore, may be considered as second- and third-line therapy, respectively. (May be recommended) Beta-blockers, non-DHP CCBs, or flecainide should be considered when catheter ablation is not available, desired, or is risky in symptomatic patients with idiopathic VT/PVCs from the RVOT or the left fascicles (Class IIA, level of evidence B). In pregnant patients with idiopathic VT and hemodynamic stability, intravenous beta-blocker or	European Heart Rhythm Association (EHRA) consensus (2017)[8] 2023 HRS expert consensus[6]

			adenosine for outflow tract VT and intravenous verapamil for fascicular VT are recommended as first-line options. (COR 1, LOE C-LD)	
Carvedilol	Atrial fibrillation/flutter, maintenance of ventricular rate control (off-label use) Nonsustained ventricular tachycardia or ventricular premature beats, symptomatic (off-label use)	1st line (In pregnant individuals) 1st line (In PVCs) 2nd or 3rd line (In non-pregnant individuals with inappropriate sinus tachycardia)	Either β-blockers or nondihydropyridine calcium channel blockers (diltiazem or verapamil) are considered first-line medicines for PVCs. Beta-blockers and non-dihydropyridine calcium channel blockers are frequently ineffective or not tolerated at required doses in inappropriate sinus tachycardia. Therefore, may be considered as second- and third-line therapy, respectively. (May be recommended) Beta-blockers, non-DHP CCBs, or flecainide should be considered when catheter ablation is not available, desired, or is particular risky in symptomatic patients with	ESC Guidelines (2022)[5] European Heart Rhythm Association (EHRA) consensus (2017)[8] 2023 HRS expert consensus[6]

			idiopathic VT/PVCs from the RVOT or the left fascicles (Class IIA, level of evidence B). In pregnant patients with idiopathic VT and hemodynamic stability, intravenous beta-blocker or adenosine for outflow tract VT and intravenous verapamil for fascicular VT are recommended as first-line options. (COR 1, LOE C-LD)	
Atenolol	Atrial fibrillation/flutter, maintenance of ventricular rate control (off-label use) Atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, focal atrial tachycardia, multifactorial atrial tachycardia Ventricular arrhythmia or ventricular premature beats	1st line (In pregnant individuals with ventricular arrhythmias) 1st line (In PVCs) 2nd or 3rd line (In non-pregnant individuals with inappropriate sinus tachycardia)	Either β-blockers or non-DHP CCBs (diltiazem or verapamil) are considered first-line medicines for PVCs. Beta-blockers and non-dihydropyridine calcium channel blockers are frequently ineffective or not tolerated at required doses in inappropriate sinus tachycardia. Therefore, may be considered as second- and third-line therapy, respectively. (May be recommended)	ESC Guidelines (2022)[5] European Heart Rhythm Association (EHRA) consensus (2017)[8] 2023 HRS expert consensus[6]

			Beta-blockers, non-DHP CCBs, or flecainide should be considered when catheter ablation is not available, desired, or is particular risky in symptomatic patients with idiopathic VT/PVCs from the RVOT or the left fascicles (Class IIA, level of evidence B). In pregnant patients with idiopathic VT and hemodynamic stability, intravenous beta-blocker or adenosine for outflow tract VT and intravenous verapamil for fascicular VT are recommended as first-line options. (COR 1, LOE C-LD)	
Esmolol	Atrial fibrillation/flutter, acute ventricular rate control Sinus tachycardia, inappropriate, noncompensatory Atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, focal atrial	1st line (In pregnant individuals with ventricular arrhythmias) 1st line (In PVCs) 2nd or 3rd line (In non-pregnant individuals with	Either β-blockers or non-DHP CCBs (diltiazem or verapamil) are considered first-line medicines for PVCs. Beta-blockers and non-DHP CCBs are frequently ineffective or not tolerated at required doses in inappropriate sinus	ESC Guidelines (2022)[5] European Heart Rhythm Association (EHRA) consensus (2017)[8] 2023 HRS expert consensus[6]

	tachycardia, multifactorial atrial tachycardia	inappropriate sinus tachycardia)	tachycardia. Therefore, may be considered as second- and third-line therapy, respectively. (May be recommended) Beta-blockers, non-DHP CCBs, or flecainide should be considered when catheter ablation is not available, desired, or is risky in symptomatic patients with idiopathic VT/PVCs from the RVOT or the left fascicles (Class IIA, level of evidence B). In pregnant patients with idiopathic VT and hemodynamic stability, intravenous beta-blocker or adenosine for outflow tract VT and intravenous verapamil for fascicular VT are recommended as first-line options. (COR 1, LOE C-LD)	
Class III				
Amiodarone	Ventricular arrhythmias Atrioventricular nodal reentrant tachycardia,	2nd line (ventricular arrhythmias)	In patients with VT/VF, an indication for ICD, and no contraindication for	ESC Guidelines (2022)[5]

	atrioventricular reentrant tachycardia, focal atrial tachycardia Ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT), shock-refractory (Pediatric) Tachyarrhythmia, including junctional ectopic tachycardia (JET), paroxysmal supraventricular tachycardia (PSVT) (Pediatric)		amiodarone, amiodarone may be considered when an ICD is not available, contraindicated for concurrent medical reasons, or declined by the patient (Class IIb, level of evidence C).	
Class IV				
Verapamil	Atrial fibrillation/flutter, rate control Atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, focal atrial tachycardia, multifocal atrial tachycardia Ventricular arrhythmias	1st line (for PVCs)	Either β-blockers or non-DHP CCBs (diltiazem or verapamil) are considered first-line medicines for PVCs. Intravenous beta blockers, diltiazem, or verapamil are recommended for acute rate control in patients with AFL who are hemodynamically stable. (is recommended) IV verapamil or diltiazem may be considered for the	AHA 2017[7] European Heart Rhythm Association (EHRA) consensus document[8] ESC Guidelines (2022)[5]

			management of atrioventricular nodal reentrant tachycardia in the absence of hypotension or suspicion of VT or pre-excited AF. (May be recommended) Isoproterenol infusion, verapamil, or quinidine for acute treatment of an electrical storm or recurrent ICD discharges should be considered in idiopathic VF (Class IIa, level of evidence C).	
Diltiazem	Atrial fibrillation/flutter, rate control Atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, focal atrial tachycardia, multifocal atrial tachycardia Ventricular premature beats, symptomatic (alternative agent) (off-label use) Atrial tachyarrhythmias, rate control (Pediatric)	1st line (for PVCs)	Either β-blockers or non-DHP CCBs (diltiazem or verapamil) are considered first-line medicines for PVCs. Intravenous beta blockers, diltiazem, or verapamil are recommended for acute rate control in patients with AFL who are hemodynamically stable. (is recommended) IV verapamil or diltiazem may be considered for the management of	AHA 2017[7] European Heart Rhythm Association (EHRA) consensus document[8]

			atrioventricular nodal reentrant tachycardia in the absence of hypotension or suspicion of VT or pre-excited AF. (May be recommended)	
Others				
Adenosine	Atrioventricular Nodal Reentry Tachycardia (Adults and Pediatrics)	1st line	IV adenosine is recommended. (Is recommended)	AHA 2017[7]
Digoxin	Atrial fibrillation/flutter, rate control Fetal supraventricular tachyarrhythmia, sustained (maternal administration for transplacental transfer to the fetus) (off-label use) Atrioventricular nodal reentrant tachycardia), rate control (alternative agent) (off-label use) Tachyarrhythmias (Pediatric)	2nd line (fetal atrial tachyarrhythmias)	In immature fetuses with incessant SVT or incessant AFL complicated by hydrops that do not respond to treatment with transplacental drug therapy alone, direct fetal intramuscular injection of digoxin added to transplacental drug therapy can be effective. (COR 2a, LOE C-LD)	2023 HRS expert consensus[6]
Magnesium Sulfate	Torsade de pointes Torsade de pointes or ventricular fibrillation/pulseless ventricular tachycardia associated with torsade de pointes	1st line	Intravenous magnesium with supplementation of potassium is recommended in patients with Torsades de pointes (TdP) (Class 1, level of evidence C).	ESC Guidelines (2022)[5]

Ivabradine	Inappropriate sinus tachycardia Postural tachycardia syndrome (POTS)	N/A	Therapy is recommended mainly to control symptoms. Ivabradine is recommended for symptomatic patients. (recommended)	European Heart Rhythm Association (EHRA) consensus document (2017)[8]

Table 2. Non-SFDA-Registered Medications for the Management of Arrhythmias

Medication	Indication	Line of Therapy	Level of Evidence/Recommendation	Reference
Sotalol	Atrial fibrillation/flutter, symptomatic Fetal tachycardia, sustained (maternal/transplacental administration) (off-label use) Ventricular arrhythmias Arrhythmias (Pediatric)	2nd line (for ventricular arrhythmias and in fetuses with SVT or atrial flutter)	In patients with ischemic heart disease and recurrent VA, with significant symptoms or ICD shocks despite optimal device programming and ongoing treatment with a beta blocker, amiodarone or sotalol is useful to suppress recurrent VA. (COR 1, LOE B-R) Fetuses with incessant SVT or AFL with or without hydrops who are not considered to be mature enough for delivery should be treated trans placentally with flecainide or sotalol, alone or in combination with digoxin, with frequent monitoring of fetal well-being and maternal drug toxicity, and with drug selection according to the	2017 AHA/ACC/HRS[7] 2023 HRS[6]

			specific arrhythmia mechanism. (COR 1, LOE B-NR)	
Dofetilide	Atrial fibrillation/flutter	N/A	IV ibutilide or dofetilide, under close monitoring due to proarrhythmic risk, are recommended to cardiovert AFL. (is recommended) Oral dofetilide may be considered to cardiovert AFL in non-urgent situations but only in hospitalized patients since there is a proarrhythmic risk. (may be recommended)	European Heart Rhythm Association (EHRA) consensus document[8]
Ibutilide	Atrial fibrillation/flutter (mainly for flutter 90% success rate)	N/A	IV ibutilide or dofetilide, under close monitoring due to proarrhythmic risk, are recommended to cardiovert AFL. (is recommended) IV ibutilide may be used for pharmacologic cardioversion of micro-reentrant AT. (May be recommended)	European Heart Rhythm Association (EHRA) consensus document[8]
Quinidine	Atrial fibrillation/flutter, pharmacological conversion Paroxysmal atrial fibrillation/flutter, maintenance of sinus rhythm Ventricular arrhythmias	N/A	Quinidine should be considered for chronic therapy to suppress an electrical storm or recurrent ICD discharges in idiopathic VF (Class IIa, level of evidence B). *Has a black box warning for increased mortality; use has largely been replaced*	ESC Guidelines (2022)[5]

			by more effective/safer antiarrhythmic agents.	
Procainamide	Atrioventricular reentrant tachycardia, antidromic or orthodromic, hemodynamically stable (off-label use)	N/A	In patients presenting with a hemodynamically tolerated SMVT and known or suspected SHD, intravenous procainamide should be considered (Class IIa, level of evidence B). IV ibutilide, procainamide, propafenone or flecainide in antidromic AVRT may be considered. (May be recommended)	ESC Guidelines (2022)[5] European Heart Rhythm Association (EHRA) consensus document[8]
Mexiletine	Ventricular arrhythmias Ventricular premature beat (symptomatic) suppression (off-label use)	N/A	Mexiletine is indicated in LQT3 patients with a prolonged QT interval (Class 1, level of evidence C).	ESC Guidelines (2022)[5]
Acebutolol	Ventricular premature beats	N/A	Used in ventricular tachycardia and PVCs.	2017 AHA/ACC/HRS[7]
Propafenone	Ventricular arrhythmia	2nd line (for PVCs)	For the patient with PVCs in need of treatment who strongly prefers to avoid catheter ablation, for whom catheter ablation has failed, or who may not be a good ablation candidate (because of frailty or multifocal PVCs), additional antiarrhythmic drugs to consider include flecainide, propafenone, sotalol, and amiodarone.	2017 AHA/ACC/HRS[7]

Isoproterenol	Torsade de pointes (to reduce recurrence)	N/A	Isoproterenol infusion, verapamil, or quinidine for acute treatment of an electrical storm or recurrent ICD discharges should be considered in idiopathic VF (Class IIa, level of evidence C). Isoproterenol infusion should be considered in BrS patients suffering electrical storm (Class IIa, level of evidence C). Isoproterenol infusion should be considered for ERS patients with electrical storm (Class IIa, level of evidence B). Isoproterenol may be considered in SQTS patients with an electrical storm (Class IIb, level of evidence C).	ESC Guidelines (2022)[5]
Nadolol	Treatment of long QT syndrome	1st line	In pregnant patients with LQTS, therapy with a beta-blocker, particularly nadolol, is recommended particularly during the postpartum period, which represents a high-risk period for cardiac events. (COR 1, LOE B-NR) Beta-blockers, ideally non-selective beta-blockers (nadolol), are recommended in LQTS patients with documented QT interval prolongation, to reduce risk of arrhythmic events (Class 1, level of evidence B).	2023 HRS[6] ESC Guidelines (2022)[5]

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

1.1 KSA Guidelines

To date, no clinical guidelines have been issued by Saudi bodies for the management of arrhythmias.

1.2 North American Guidelines

1.2.1 Canadian Cardiovascular Society Clinical Practice Update on Management of the Patient with a Prolonged QT Interval (2023)

This Clinical Practice Update is a consensus document that provides practical information for the general clinician. It is not meant to replace existing literature reviews and evidence-based recommendations about long QT syndrome (LQTS). It emphasizes important diagnostic and therapeutic features of managing patients with a prolonged QT interval. It was prepared by a panel composed of cardiologists (general and subspecialty electrophysiologists) and internists with expertise in pharmacology, as well as consultants experienced in education and preparation of guideline documents.[9]

The main recommendations are detailed below:

Congenital QT prolongation treatment

Management of congenital LQTS (cLQTS):

- The cornerstone of medical therapy is b-blockade, preferably with **nadolol** or **propranolol**. Cardiac rhythm devices such as pacemakers and ICDs are rarely required.
- Tolerance of b-blockade is improved by slow up titration with the final dosage on the basis of tolerance or blunted exercise heart rate.
- Avoid QT-prolonging drugs and educate the patient.
- Most episodes of TdP are due to noncompliance with b-blockade or use of QT-prolonging medications.
- TdP and arrhythmic storm should be managed with b-blockade, cessation of QT-prolonging drugs, correction of electrolyte abnormalities, increased magnesium, lidocaine (based on the type of LQTS), and at times, transvenous pacing. Amiodarone and procainamide are contraindicated because they further prolong the QT interval and promote bradycardia.

Acquired QT prolongation treatment:

Management of acquired LQTS (aLQTS):

- aLQTS is classically due to QT-prolonging medications or electrolyte disturbances. Common drugs include antidepressants/antipsychotics, antibiotics, and antiarrhythmics. Remember the "anti's" antibiotics (macrolides and fluoroquinolones), antifungals, antiarrthymics, antipsychotics/ antidepressants, antiemetics, analgesics, (including methadone and triptans), and miscellaneous (including chloroquine). Check for complex drug interactions or potential QT prolongation before administration.
- There are important intraclass differences among QT-prolonging drugs in the risk of causing an arrhythmia (e.g., risk among macrolide antibiotics is highest with erythromycin and lowest with azithromycin), and with selective serotonin reuptake inhibitor antidepressants, risk is highest with citalopram and escitalopram and negligible with paroxetine and sertraline. Conversely, there are safe alternatives among antibiotics such as penicillins and cephalosporins, and among CNS medications; stimulants for attention deficit hyperactivity disorder are generally safe.
- Increased risk for TdP occurs when the QTc exceeds 500 ms or when a drug increases the QTc by > 60-70 ms, particularly when this increase develops rapidly.
- Women are at higher risk of aLQTS, along with elderly people and those with underlying structural heart disease.
- Consider an ECG before initiation of a QT-prolonging drug if an electrolyte disturbance is present, if already receiving a QT-prolonging drug, or when initiating a high-risk QT-prolonging drug.
- Be cautious in patients with multiple risk factors for QT prolongation (e.g., when a diuretic is used with sotalol, be mindful of the potential for hypokalemia and hypomagnesemia).
- If the QTc does not normalize after removal or correction of the inciting cause, underlying cLQTS should be ruled out.

1.2.2 Heart Rhythm Society (HRS) Expert Consensus Statement on the Management of Arrhythmias During Pregnancy (2023)

This international multidisciplinary expert consensus statement is intended to provide comprehensive guidance that can be referenced at the point of care to cardiac electrophysiologists, cardiologists, and other health care professionals, on the management of cardiac arrhythmias in pregnant patients and in fetuses.[6]

Table 3. HRS Classes (Strength) of Recommendations

Class 1 (strong)	Benefit >>> risk
Class 2a (moderate)	Benefit >> risk
Class 2b (weak)	Benefit ≥ risk
Class 3 no benefit- (moderate)	Benefit = risk
Class 3 Haram (strong)	Risk > benefit

Table 4. HRS Levels (Quality) of Evidence

Level A	High-quality evidence from more than 1 RCT Meta-analyses of high-quality RCTs One or more RCTs corroborated by high-quality registry studies
Level B-R	Moderate-quality evidence from 1 or more RCTs Meta-analyses of moderate-quality RCTs
Level B-NR	Moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies Meta-analyses of such studies
Level C-LD	Randomized or nonrandomized observational or registry studies with limitations of design or execution Meta-analyses of such studies Physiological or mechanistic studies in human subjects
Level C-EO	Consensus of expert opinion based on clinical experience

Table 5. Antiarrhythmic Drug Safety for Commonly Used Drugs in Pregnancy

	Propranolol	Metoprolol	Nadolol	Atenolol	Mexiletine	Quinidine	Sotalol
Use during pregnancy	Safe	Safe	Safe	**Risk**	**Caution**	Safe	Safe
Use when breastfeeding	Safe	Safe	**Caution**	**Risk**	**Caution**	Safe	Safe

Recommendations for the management of ventricular arrhythmias in the pregnancy not associated with inherited arrhythmia syndromes:

- In pregnant patients with sustained ventricular tachycardia (VT) and hemodynamic compromise, direct current cardioversion is recommended, with energy dosing as in the nonpregnant patient. (COR 1, LOE C-LD)

- In pregnant patients with idiopathic VT and hemodynamic stability, intravenous beta-blocker or adenosine for outflow tract VT and intravenous verapamil for fascicular VT are recommended as first-line options. (COR 1, LOE C-LD)
- In pregnant patients with hemodynamically stable VT, when pharmacological therapy is deemed necessary, intravenous procainamide is recommended for acute therapy. (COR 1, LOE C-LD)
- In pregnant patients with sustained VT refractory or with contraindications to beta-blockers and/or other antiarrhythmic drugs, synchronized cardioversion is recommended, with energy dosing as in the nonpregnant patient. (COR 1, LOE C-LD)
- In pregnant patients who meet indications for implantable cardioverter defibrillator (ICD) placement due to sustained ventricular arrhythmias or due to high risk for sudden cardiac death, device implantation is recommended with attention to and techniques for eliminating or minimizing radiation exposure to as low as reasonably achievable. (COR 1, LOE C-LD)
- In pregnant patients with ICDs prior to pregnancy, it is recommended to continue routine ICD care according to the underlying cardiac substrate. (COR 1, LOE C-LD)
- In women who are considering pregnancy and would otherwise meet indications for ICD, pacemaker, or cardiac resynchronization therapy device placement, these procedures should be performed prior to pregnancy and according to the underlying cardiac substrate. (COR 1, LOE C-LD)
- In pregnant patients with chronic or recurrent VT, beta-blockers, alone or in combination with other antiarrhythmic drugs, are recommended for arrhythmia suppression due to their overall safety profile in pregnancy. (COR 1, LOE C-LD)
- In pregnant patients with recurrent VT refractory or with contraindications to beta-blockers who require additional antiarrhythmic drug therapy, treatment with flecainide, sotalol, or mexiletine is recommended with the choice of drug based on the underlying cardiac substrate. (COR 1, LOE C-LD)
- In pregnant patients with recurrent symptomatic or hemodynamically unstable VT in whom pharmacological therapy is either ineffective or contraindicated, catheter ablation is reasonable with an experienced operator and with attention to and techniques for eliminating or minimizing radiation exposure to as low as reasonably achievable. (COR 2a, LOE C-LD)
- In pregnant patients with recurrent VT associated with hemodynamic impairment or ICD shocks, amiodarone is reasonable for arrhythmia

suppression if alternative therapies, including ablation, are contraindicated or ineffective. (COR 2a, LOE C-LD)

- In pregnant patients who meet indications for sudden death prevention due to high-risk features or VT that may be of a reversible etiology, such as peripartum cardiomyopathy, a wearable cardioverter defibrillator may be reasonable. (COR 2b, LOE C-LD)

Recommendations for fetal atrial tachyarrhythmias

- Fetuses with intermittent atrial flutter (AFL) or intermittent supraventricular tachycardia (SVT) (defined as tachycardia < 50% of the time) and no hydrops should be managed with observation, frequent fetal heart rate monitoring (auscultation), and serial biophysical testing, ideally under the guidance of a cardio-obstetrics team. (COR 1, LOE B-NR)
- Fetuses with incessant AFL or incessant SVT (defined as tachycardia 50% of the time) and/or hydrops should be referred to a cardio-obstetrics team, due to the potential for high fetal and maternal morbidity and fetal mortality. (COR 1, LOE B-NR)
- Fetuses with incessant SVT or AFL with or without hydrops who are not considered to be mature enough for delivery should be treated trans placentally with flecainide or sotalol, alone or in combination with digoxin, with frequent monitoring of fetal well-being and maternal drug toxicity, and with drug selection according to the specific arrhythmia mechanism. (COR 1, LOE B-NR)
- Fetuses with incessant AFL or incessant SVT complicated by hydrops who are close to term should be delivered. (COR 1, LOE C-LD)
- In pregnancies complicated by either fetal irregular heart rate or tachyarrhythmias, fetal echocardiography is recommended to further characterize the rhythm and to screen for structural or functional abnormalities. (COR 1, LOE C-LD)
- In pregnancies complicated by fetal PACs, serial auscultation of the fetal heart rate or serial biophysical testing (or, if these are unavailable, non-stress testing) is recommended to exclude development of fetal SVT until the arrhythmia resolves. (COR 1, LOE C-LD)
- In fetuses with incessant SVT complicated by hydrops or ventricular dysfunction refractory or with contraindications to first-line drug options, transplacental administration of oral amiodarone can be beneficial. (COR 2a, LOE C-LD)

- In immature fetuses with incessant SVT or incessant AFL complicated by hydrops that do not respond to treatment with transplacental drug therapy alone, direct fetal intramuscular injection of digoxin added to transplacental drug therapy can be effective. (COR 2a, LOE C-LD)
- In fetuses with incessant SVT or incessant AFL complicated by hydrops that do not respond to treatment with transplacental drug therapy, combination transplacental drugs, or direct injection of digoxin, direct umbilical intravenous injection or intraperitoneal injection of amiodarone may be effective as a last resort. (COR 2b, LOE C-LD)
- In fetuses with incessant SVT or incessant AFL, transplacental therapy with verapamil is potentially harmful. (COR 3, LOE C-LD)

Recommendations for fetal ventricular arrhythmias not associated with inherited arrhythmia syndromes:

- Fetuses with sustained VT with or without hydrops who are not considered to be mature enough for delivery should be treated transplacentally with either intravenous magnesium or oral propranolol, mexiletine, or lidocaine, alone or in combination, or with other antiarrhythmic agents according to the specific arrhythmia etiology, with frequent monitoring of fetal well-being and maternal drug toxicity. (COR 1, LOE B-NR)
- In fetuses with sustained VT, maternal hypomagnesemia and other correctable causes should be treated aggressively. (COR 1, LOE C-LD)
- Fetuses with VT should be referred to a cardio-obstetrics team, if available, for evaluation and treatment secondary to the high fetal morbidity and mortality. (COR 1, LOE C-EO)
- Fetuses with sustained VT with or without hydrops who are close to term or at term should be delivered. (COR 1, LOE C-EO)
- In fetuses with VT complicated by hydrops or ventricular dysfunction refractory or with contraindications to first-line drug options and not secondary to IAS, transplacental administration of flecainide, sotalol, or amiodarone can be beneficial, with the choice of drug according to the underlying maternal and fetal substrate. (COR 2a, LOE B-NR)

Recommendations for management of long QT syndrome in pregnancy

- In pregnant patients with LQTS and a preconception indication for beta-blocker therapy, beta-blockers should be continued throughout pregnancy, delivery, and the postpartum period, including breastfeeding. (COR 1, LOE B-NR)

- In pregnant patients with LQTS, therapy with a beta-blocker, particularly nadolol or propranolol, is recommended particularly during the postpartum period, which represents a high-risk period for cardiac events. (COR 1, LOE B-NR)
- In pregnant patients with LQTS who experience cardiac arrest in pregnancy or in whom cardiac syncope or ventricular arrhythmias occur despite beta-blocker use, intensification of therapy including ICD implantation, if indicated, is recommended as in the nonpregnant patient. (COR1, LOE C-LD)
- In pregnancies in which either of the parents carry a diagnosis of LQTS, fetal echocardiography is recommended to detect channelopathy-related rhythm abnormalities. (COR 1, LOE C-LD)
- In pregnant patients with LQTS who are genotype-positive but phenotype-negative, it is reasonable to treat with a beta-blocker, particularly nadolol or propranolol, after a shared decision-making discussion with the affected woman. (COR 2a, LOE B-NR)

1.2.3 American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) Guideline for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death (2017)

The purpose of this AHA/ACC/HRS document is to provide a contemporary guideline for the management of adults who have ventricular arrhythmias (VA) or who are at risk for sudden cardiac death (SCD), including diseases and syndromes associated with a risk of SCD from VA.[7]

Classes of recommendations and levels of evidence are similar to those described in tables 3 and 4 above, and the main recommendations are summarized below.

Table 6. Pharmacological Characteristics of Available Antiarrhythmic Medications for Treating Ventricular Arrhythmias

Antiarrhythmic medication (class) and dose	Uses in VA/SCA	Electrophysiological effects	Common adverse effects
Acebutolol PO: 200–1200 mg daily or up to 600 mg bid	VT, PVCs	Sinus rate slowed AV nodal refractoriness increased	Cardiac: Bradycardia, hypotension, HF, AVB Other: Dizziness, fatigue, anxiety, impotence, hyper/ hypoesthesia
Amiodarone (III) IV: 300 mg bolus for VF/pulseless VT arrest; 150-mg bolus for stable VT; 1 mg/min x 6 h, then 0.5 mg/min x 18 h PO: 400 mg* q 8 to 12 h for 1–2 wk, then 300–400 mg daily; reduce dose to 200 mg daily if possible	VT, VF, PVC	Sinus rate slowed QRS prolonged QTc prolonged AV nodal refractoriness increased; increased DFT	Cardiac: Hypotension, bradycardia, AVB, TdP, slows VT below programmed ICD detection rate, increases defibrillation threshold Other: Corneal microdeposits, thyroid abnormalities, ataxia, nausea, emesis, constipation, photosensitivity, skin discoloration, ataxia, dizziness, peripheral neuropathy, tremor, hepatitis, cirrhosis, pulmonary fibrosis, or pneumonitis
Atenolol (II) PO: 25–100 mg qd or bid	VT, PVC, ARVC, LQTS	Sinus rate slowed AV nodal refractoriness increased	Cardiac: Bradycardia, hypotension, HF, AVB Other: Dizziness, fatigue, depression, impotence
Bisoprolol (II) PO: 2.5–10 mg once daily	VT, PVC	Sinus rate slowed AV nodal refractoriness increased	Cardiac: Chest pain, bradycardia, AVB Other: Fatigue, insomnia, diarrhea

Carvedilol (II) PO: 3.125–25 mg q 12 h	VT, PVC	Sinus rate slowed AV nodal refractoriness increased	Cardiac: Bradycardia, hypotension, AVB, edema, syncope Other: Hyperglycemia, dizziness, fatigue, diarrhea
Diltiazem (IV) IV: 5–10 mg qd 15–30 min Extended release: PO: 120–360 mg/day	VT specifically RVOT, idiopathic LVT	Sinus rate slowed PR prolonged AV nodal conduction slowed	Cardiac: Hypotension, edema, HF, AVB, bradycardia, exacerbation of HFrEF Other: Headache, rash, constipation
Esmolol (II) IV: 0.5 mg/kg bolus, 0.05 mg/kg/min	VT	Sinus rate slowed AV nodal refractoriness increased	Cardiac: Bradycardia, hypotension, HF, AVB Other: Dizziness, nausea
Flecainide (IC) PO: 50–200 mg q 12 h	VT, PVC (in the absence of structural heart disease). Has a role in treating patients with CPVT	PR prolonged QRS prolonged; increased DFT	Cardiac: Sinus node dysfunction, AVB, druginduced Brugada syndrome, monomorphic VT in patients with a myocardial scar, exacerbation of HFrEF Other: Dizziness, tremor, vision disturbance, dyspnea, nausea
Lidocaine (IB) IV: 1 mg/kg bolus, 1–3 mg/min 1–1.5 mg/kg. Repeat 0.5–0.75 mg/kg bolus every 5–10 min (max cumulative dose 3 mg/kg). Maintenance infusion is 1–4 mg/min although one could start at 0.5 mg/min	VT, VF	No marked effect on most intervals; QTc can slightly shorten	Cardiac: Bradycardia, hemodynamic collapse, AVB, sinus arrest Other: Delirium, psychosis, seizure, nausea, tinnitus, dyspnea, bronchospasm

Metoprolol (II) IV: 5 mg q 5 min up to 3 doses PO: 25–100 mg Extended release qd or q 12 h	VT, PVC	Sinus rate slowed AV nodal refractoriness increased	Cardiac: Bradycardia, hypotension, AVB Other: Dizziness, fatigue, diarrhea, depression, dyspnea
Mexiletine (IB) PO: 150–300 mg q 8 h or q 12 h	VF, PVC, has a role in patients with LQT3	No marked effect on most intervals; QTc can slightly shorten	Cardiac: HF, AVB Other: Lightheaded, tremor, ataxia, paresthesias, nausea, blood dyscrasias
Nadolol (II) PO: 40–320 mg daily	VT, PVC, LQTS, CPVT	Sinus rate slowed AV nodal refractoriness increased	Cardiac: Bradycardia, hypotension, HF, AVB Other: Edema, dizziness, cold extremities, bronchospasm
Procainamide (IA) IV: loading dose 10–17 mg/kg at 20–50 mg/ min Maintenance dose: 1–4 mg/min PO (SR preparation): 500–1250 mg q 6 h	VT	QRS prolonged QTc prolonged; increased DFT	Cardiac: TdP; AVB, hypotension and exacerbation of HFrEF Other: Lupus symptoms, diarrhea, nausea, blood dyscrasias
Propafenone (IC) PO: Immediate release 150–300 mg q 8 h Extended release 225– 425 mg q 12 h	VT, PVC (in the absence of structural heart disease)	PR prolonged QRS prolonged; increased DFT	Cardiac: HF, AVB, drug-induced Brugada syndrome Other: Dizziness, fatigue, nausea, diarrhea, xerostomia, tremor, blurred vision
Propranolol (II) IV: 1–3 mg q 5 min to a total of 5 mg PO: Immediate release 10–40	VT, PVC, LQTS	Sinus rate slowed AV nodal refractoriness increased	Cardiac: Bradycardia, hypotension, HF, AVB Other: Sleep disorder, dizziness, nightmares,

mg q 6 h; Extended release 60–160 mg q 12 h			hyperglycemia, diarrhea, bronchospasm
Quinidine (IA) PO: sulfate salt 200– 600 mg q 6 h to q 12 h Gluconate salt 324– 648 mg q 8 h to q 12 h IV: loading dose: 800 mg in 50 mL infused at 50 mg/min	VF, (including short QT syndrome, Brugada)	QRS prolonged QTc prolonged; increased DFT	Cardiac: Syncope, TdP, AVB Other: Dizziness, diarrhea, nausea, esophagitis, emesis, tinnitus, blurred vision, rash, weakness, tremor; blood dyscrasias
Sotalol (III) IV: 75 mg q 12 h PO: 80–120 mg q 12 h, may increase dose every 3 d; max 320 mg/d	VT, VF, PVC	Sinus rate slowed QTc prolonged AV nodal refractoriness increased; decreased DFT	Cardiac: Bradycardia, hypotension, HF, syncope, TdP Other: Fatigue, dizziness, weakness, dyspnea, bronchitis, depression, nausea, diarrhea
Verapamil (IV) IV: 2.5–5 mg q 15–30 min Sustained release PO: 240–480 mg/d	VT (specifically RVOT, verapamil sensitive idiopathic LVT)	Sinus rate slowed PR prolonged AV nodal conduction slowed	Cardiac: Hypotension, edema, HF, AVB, bradycardia, exacerbation of HFrEF Other: Headache, rash, gingival hyperplasia, constipation, dyspepsia

Alpha indicates alpha-adrenergic receptor; ARVC, arrhythmogenic right ventricular cardiomyopathy; AV, atrioventricular; AVB, atrioventricular block; Beta, beta-adrenergic receptor; HF, heart failure; CPVT, catecholaminergic polymorphic ventricular tachycardia; DFT, defibrillation threshold; LQTS, long QT syndrome; LVT, left ventricular tachycardia; PVC, premature ventricular complex; QTc, corrected QT interval; RVOT, right ventricular outflow tract; TdP, torsades de pointes; VT, ventricular tachycardia; and VF, ventricular fibrillation.

VA in the structurally normal heart

- In patients with symptomatic PVCs in an otherwise normal heart, treatment with a beta blocker or nondihydropyridine calcium channel blocker is useful to reduce recurrent arrhythmias and improve symptoms. (COR 1, LOE B-R)
- In patients with symptomatic VA in an otherwise normal heart, treatment with an antiarrhythmic medication is reasonable to reduce recurrent symptomatic arrhythmias and improve symptoms if beta blockers and nondihydropyridine calcium channel blockers are ineffective or not tolerated. (COR 2A, LOE B-R)

Outflow Tract and Atrioventricular Annular VA

- In patients with symptomatic outflow tract VA in an otherwise normal heart for whom antiarrhythmic medications are ineffective, not tolerated, or not the patient's preference, catheter ablation is useful. (COR 1, LOE B-NR)
- In patients with symptomatic outflow tract VT in an otherwise normal heart, a beta blocker or a calcium channel blocker is useful. (COR 1, LOE B-NR)

Papillary muscle VA

- In patients with symptomatic VA arising from the papillary muscles for whom antiarrhythmic medications are ineffective, not tolerated, or not the patient's preference, catheter ablation is useful. (COR 1, LOE B-NR)

Interfascicular Reentrant VT (Belhassen Tachycardia)

- In patients with verapamil-sensitive, idiopathic LVT related to interfascicular reentry for whom antiarrhythmic medications are ineffective, not tolerated, or not the patient's preference, catheter ablation is useful. (COR 1, LOE B-NR)
- In patients with sustained hemodynamically tolerated verapamil-sensitive, idiopathic LVT related to interfascicular reentry, intravenous verapamil is recommended for VT termination. (COR 1, LOE B-NR)
- In patients with recurrent verapamil-sensitive idiopathic LVT, chronic therapy with oral verapamil can be useful. (COR 2a, LOE C-LD)

Treatment and Prevention of Recurrent VA in Patients with Ischemic Heart Disease

- In patients with ischemic heart disease and recurrent VA, with significant symptoms or ICD shocks despite optimal device programming and ongoing treatment with a beta blocker, amiodarone or sotalol is useful to suppress recurrent VA. (COR 1, LOE B-R)
- In patients with prior MI and recurrent episodes of symptomatic sustained VT, or who present with VT storm and have failed or are intolerant of amiodarone

(LOE: B-R) or other antiarrhythmic medications (LOE: B-NR), catheter ablation is recommended. (COR 1, B-R)

- In patients with ischemic heart disease and ICD shocks for sustained monomorphic VT or symptomatic sustained monomorphic VT that is recurrent, or hemodynamically tolerated, catheter ablation as first-line therapy may be considered to reduce recurrent VA. (COR 2b, LOE C-LD)
- In patients with prior MI, class IC antiarrhythmic medications (e.g., flecainide and propafenone) should not be used. (COR 3, LOE B-R)
- In patients with incessant VT or VF, an ICD should not be implanted until sufficient control of the VA is achieved to prevent repeated ICD shocks. (COR 3, LOE C-LD)

1.2.4 American Heart Association (AHA) Evaluation and Management of Premature Ventricular Complexes (2020)

This review published in 2020 by the AHA summarizes current knowledge on premature ventricular complexes (PVCs) to help provide clinically relevant guidance.[10]

The most useful contribution a physician can provide a patient with PVCs is reassurance.

In considering whether additional management beyond reassurance should be pursued, 3 key pieces of information are needed:

1. information regarding symptoms
2. the burden of the PVCs (typically reported in PVCs as a percentage of all beats)
3. the presence or absence of structural heart disease

If the burden of PVCs is low, the evaluation reveals no relevant underlying condition, and the ejection fraction is normal, reassurance alone may be reasonable and sufficient.

Determining therapy based on symptoms requires some important questions for the patient.

Treatment should not necessarily be given for symptoms alone. Often the patient is seeking evaluation because they experience a worrisome sensation with their PVCs and are concerned these symptoms may be a sign of something wrong or of some impending problem.

PVC symptoms, even in the presence of a normal LVEF, that remain bothersome to patients after reassurance are indications for treatment. Patients will often ask about lifestyle changes that might help them with their PVCs.

Medical therapy

Either **β-blockers** or **nondihydropyridine calcium channel blockers** (diltiazem or verapamil) are considered first-line medicines for PVCs. Both have a long track record of safety in structurally normal hearts, and β-blockers may have additional benefits in the setting of coronary disease or a reduced LVEF. β-Blockers are particularly effective for sympathetically mediated, triggered PVCs, with data demonstrating effectiveness specifically in outflow tract PVCs. Although better than placebo, randomized controlled clinical trials demonstrate that β-blockers result in a clinically meaningful reduction in symptomatic outflow tract PVCs in only 12% to 24%. The nondihydropyridine calcium channel blockers have similarly demonstrated effectiveness in outflow tract PVCs and are considered particularly useful for fascicular ventricular arrhythmias. In the patient with a structurally normal heart, it is reasonable to try a calcium channel blocker if a β-blocker fails (and vice versa). Failure of a drug may occur because of either insufficient effectiveness or medication intolerance. It is important to probe patients regarding side effects to medicines given the reasonable alternative of catheter ablation or other antiarrhythmic drugs.

If these initial drugs fail, catheter ablation should be considered next.

For the patient in need of treatment who strongly prefers to avoid catheter ablation, for whom catheter ablation has failed, or who may not be a good ablation candidate (because of frailty or multifocal PVCs), additional antiarrhythmic drugs to consider include flecainide, propafenone, sotalol, and amiodarone. Mexiletine may be used rarely, but its effectiveness is inferior to either other antiarrhythmic drugs or catheter ablation. Flecainide and propafenone are well-tolerated, in general, and are often efficacious.

Catheter ablation

In general, catheter ablation is more efficacious than medicines to treat PVCs given a predominately monomorphic target. Success of PVC ablation procedures range from approximately 80% to 95%. Both the American Heart Association/American College of Cardiology/Heart Rhythm Society guideline for the treatment of ventricular arrhythmias and the Heart Rhythm Society/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society/Latin American Heart Rhythm Society expert consensus statement on catheter ablation of ventricular arrhythmias generally recommend either medicines or catheter ablation as first-line therapies for PVCs that are either symptomatic or likely responsible for systolic dysfunction.

Specifically, catheter ablation is listed as a class I indication (meaning a strong recommendation where the benefit far exceeds the risk) to treat PVCs if medicines are not tolerated, not effective, or preferred by the patient.

1.3 European Guidelines

1.3.1 European Society of Cardiology (ESC) Guidelines for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death (2022)

In 2022, the European Society of Cardiology (ESC) has formed a task force to develop guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death (SCD). The guidelines were endorsed by the Association for European Pediatric and Congenital Cardiology (AEPC).[5]

Diagnostic evaluation at first presentation with ventricular arrhythmia in patients without known cardiac disease

Ventricular arrhythmia (VA) and (aborted) SCD are common first manifestations of a previously not known cardiac condition. A comprehensive diagnostic evaluation is provided for four frequently encountered scenarios:

1. Incidental finding of a non-sustained ventricular tachycardia

- In patients with newly documented VA (frequent PVCs, NSVT, SMVT), a baseline 12-lead ECG, recording of the VA on 12-lead ECG, whenever possible, and an echocardiogram are recommended as first-line evaluation **(Class 1, level of evidence C)**.
- In patients with newly documented VA (frequent PVCs, NSVT, SMVT) and suspicion of SHD other than CAD after initial evaluation, a CMR should be considered **(Class IIa, level of evidence B)**.
- In patients with an incidental finding of a NSVT, a ≥24 h Holter ECG should be considered **(Class IIa, level of evidence C)**.

2. First presentation of sustained monomorphic ventricular tachycardia

- In patients presenting with a first SMVT episode, electrophysiological study, electro anatomical mapping, and mapping-guided biopsies may be considered for etiological evaluation **(Class IIb, level of evidence C)**.

3. Sudden cardiac arrest (SCA) survivor

- The investigation of a SCA survivor without obvious extra-cardiac cause is recommended to be overseen by a multidisciplinary team **(Class 1, level of evidence B)**.

- In electrically unstable patients after SCA, with suspicion of ongoing myocardial ischemia, a coronary angiogram is indicated **(Class 1, level of evidence C)**.
- In SCA survivors, brain/chest CT scan should be considered when patient characteristics, ECG, and echocardiography are not consistent with a cardiac cause **(Class IIa, level of evidence C)**.
- In SCA survivors, collection of blood samples at presentation is recommended for potential toxicology and genetic testing **(Class 1, level of evidence B)**.
- Retrieval of recordings from CIEDs and wearable monitors is recommended for all SCA survivors **(Class 1, level of evidence B)**.
- In SCA survivors, repeated 12-lead ECGs during stable rhythm (including high precordial lead ECG), as well as continuous cardiac monitoring, are recommended **(Class 1, level of evidence B)**.
- Echocardiography is recommended for evaluation of cardiac structure and function in all SCA survivors **(Class 1, level of evidence C)**.
- Coronary imaging and CMR with LGE are recommended for evaluation of cardiac structure and function in all SCA survivors without a clear underlying cause **(Class 1, level of evidence B)**.
- Sodium channel blocker test and exercise testing is recommended in SCA survivors without a clear underlying cause **(Class 1, level of evidence B)**.
- In SCA survivors, ergonovine, acetylcholine, or hyperventilation testing may be considered for the diagnosis of coronary vasospasm **(Class IIb, level of evidence B)**.

4. <u>Relatives of sudden arrhythmic death syndrome decedents</u>

- Familial evaluation of sudden arrhythmic death syndrome (SADS) decedents is recommended for **(Class 1, level of evidence B)**:
    - First-degree relatives
    - Relatives who must carry a mutation based on analysis of the family history
    - Relatives with suspicious symptoms
    - When the decedent's age is < 50 years, or if there is other circumstantial data or family history to suggest heritable disease
- Familial evaluation of SADS decedents is recommended to include genetic testing when post-mortem genetic testing in a SADS decedent detects a pathogenic mutation **(Class 1, level of evidence B)**.

- Baseline familial evaluation of SADS decedents is recommended to include taking a medical history and performing physical examination, standard and high precordial lead ECG, echocardiography, and exercise testing **(Class 1, level of evidence B)**.
- In SADS families without a diagnosis after clinical evaluation, follow-up is recommended for children of decedents until they reach adulthood **(Class 1, level of evidence C)**.
- Pharmacological testing with a sodium channel blocker should be considered in relatives of SADS decedents who are 16 years or older when baseline testing and/or proband findings increase the suspicion of Brugada syndrome (BrS) **(Class IIa, level of evidence B)**.
- Ambulatory cardiac rhythm monitoring and cardiac magnetic resonance (CMR) may be considered in relatives of SADS decedents **(Class IIb, level of evidence C)**.
- Pharmacological testing including epinephrine challenge (if exercise testing is impractical) and sodium channel blocker challenge may be considered in first-degree relatives of SADS decedents with normal baseline testing **(Class IIb, level of evidence B)**.
- In SADS families without a diagnosis after clinical evaluation, follow-up is not recommended for asymptomatic adults who can be discharged with advice to return if they develop symptoms or if the family history changes **(Class III, level of evidence C)**.

Pharmacological therapy for the acute management of ventricular arrhythmias:

a. Acute management

Treatment of reversible causes

- Withdrawal of offending agents is recommended whenever drug-induced VAs are suspected **(Class 1, level of evidence B)**.
- Investigation for reversible causes (e.g., electrolyte imbalances, ischemia, hypoxemia, fever) is recommended in patients with VA **(Class 1, level of evidence C)**.
- Despite a possible correctable cause for the presenting VA, the need for implantable cardioverter defibrillator (ICD) implantation should be considered based on an individual evaluation of the risk of subsequent VA/SCD **(Class IIa, level of evidence C)**.

Acute management of sustained monomorphic ventricular tachycardia (SMVT)

Patients with SMVT should receive treatment based on their symptoms and the underlying cause. Those with hemodynamic instability need immediate synchronized cardioversion. If that's not achievable, an unsynchronized shock should be given. However, patients with repetitive NSVTs shouldn't undergo cardioversion. It's essential to document any wide QRS tachycardia that's hemodynamically tolerated on a 12-lead ECG. If supraventricular tachycardia (SVT) is suspected, consider administering adenosine or performing vagal maneuvers, ensuring continuous 12-lead ECG recording. IV adenosine might also halt certain VT types, hinting at a cAMP-triggered mechanism behind the VT.

The 'FBI' (fast, broad, irregular) ECG pattern signals pre-excited atrial fibrillation (AF), which can resemble VT. Avoid IV drugs like adenosine, beta-blockers, and amiodarone that slow AV conduction for these patients. Quickly ending SMVT is crucial, given the potential for fast hemodynamic decline. Termination methods include electrical cardioversion, anti-arrhythmic drugs (AADs), or pacing. AADs can cause hypotension, so one must consider the associated anesthesia/sedation risks for cardioversion.

To pharmacologically stop a hemodynamically tolerated VT with an unclear cause, use IV procainamide or amiodarone. The PROCAMIO study showed procainamide being more effective and safer than amiodarone. Yet, avoid procainamide for patients with severe heart conditions, recent heart attacks, or advanced kidney issues. Other AADs, like ajmaline, sotalol, and flecainide, might be options for patients without significant heart problems, but risks must be assessed. Some AADs, like procainamide, may not be accessible everywhere.

For patients with an ICD, manual overdrive pacing might end certain VTs. If idiopathic VT is identified, beta-blockers or verapamil can be used for acute conversion, depending on the VT type. While verapamil might halt other idiopathic VT types, it can lead to severe hypotension. If the VT's origin remains unclear, avoid administering verapamil IV.

Finally, a thorough assessment is vital for SMVT patients, especially if their heart condition is unknown or if disease progression is a concern.

Management of electrical storm and incessant ventricular tachycardia

In ICD patients, an "electrical storm" is defined as three or more sustained VA events within a day, each needing either anti-tachycardia pacing (ATP) or cardioversion/defibrillation and separated by at least 5 minutes. Experiencing such a storm makes patients more susceptible to psychological issues, worsened heart failure, and heightened mortality. Electrical storms can vary in severity, from repeated non-symptomatic VT episodes resolved by ATP to dangerous electrical

instabilities after multiple shocks. ICDs can also occasionally malfunction by delivering shocks when not needed.

In situations where the ICD inappropriately shocks the patient or provides unneeded therapy, it's advisable to turn off the ICD functions. If no specialist is available, a magnet can be placed over the device to disable it. When a patient shows signs of hemodynamic instability, immediate advanced life support (ALS) is necessary. Factors causing VA should be addressed, and subsequent treatments are based on the VA type and its root cause. Management might include ICD adjustments, anti-arrhythmic drugs, catheter ablation, sedation, and even mechanical circulatory assistance.

Addressing increased sympathetic activity is crucial. To relieve stress and lessen the risk of further arrhythmias in those with repeated ICD shocks, sedation is suggested. Common initial treatments involve beta-blockers like propranolol, which has shown superiority over metoprolol in certain studies, often paired with amiodarone. For those unresponsive to amiodarone, landiolol has shown efficacy in some cases. The choice of other anti-arrhythmic drugs is determined by the situation and VA cause. If the electrical storm is relentless and medications aren't helping, deep sedation or intubation might be necessary, possibly combined with mechanical ventilation. If beta-blockers aren't enough or are causing side effects, some patients might benefit from techniques like percutaneous ganglionic stellate blockade.

The primary arrhythmia in electrical storms is often SMVT linked to SHD, which can be treated with catheter ablation. Successful ablations have been linked to reduced recurrences of VT and better long-term survival. For continuous slow MVT, ablation is usually preferred over drugs. Mechanical support might be needed if standard treatments fail or to assist during ablation. Recent data suggests that preventative mechanical support can significantly reduce mortality in electrical storm patients. However, emergency use during ablation is linked to higher mortality. Management for recurrent PVT/VF-related electrical storms depends on the underlying cause.

<u>Acute management of sustained ventricular tachycardia and electrical storm</u>

- Direct current (DC) cardioversion is recommended as the first-line treatment for patients with hemodynamically not-tolerated SMVT **(Class 1, level of evidence B)**.
- DC cardioversion is recommended as the first-line treatment for patients presenting with tolerated SMVT provided that the anesthetic/ sedation risk is low **(Class 1, level of evidence C)**.
- In patients presenting with a hemodynamically tolerated idiopathic VT, treatment with intravenous beta-blocker (right ventricular outflow tract (RVOT VT)) or verapamil (fascicular VT) is recommended **(Class 1, level of evidence C)**.

- In patients presenting with a regular hemodynamically tolerated wide QRS complex tachycardia suspected for SVT, administration of adenosine or vagal maneuvers should be considered **(Class IIa, level of evidence C)**.
- In patients presenting with a hemodynamically tolerated SMVT and known or suspected SHD, intravenous procainamide should be considered **(Class IIa, level of evidence B)**.
- In patients presenting with a hemodynamically tolerated SMVT in the absence of an established diagnosis, intravenous amiodarone may be considered **(Class IIb, level of evidence B)**.
- Intravenous verapamil is not recommended in broad QRS complex tachycardia of unknown mechanism **(Class III, level of evidence B)**.
- Mild to moderate sedation is recommended in patients with electrical storm to alleviate psychological distress and reduce sympathetic tone **(Class 1, level of evidence C)**.
- Antiarrhythmic therapy with beta-blockers (non-selective preferred) in combination with intravenous amiodarone is recommended in patients with SHD and electrical storm unless contraindicated **(Class 1, level of evidence B)**.
- Intravenous magnesium with supplementation of potassium is recommended in patients with Torsades de pointes (TdP) **(Class 1, level of evidence C)**.
- Isoproterenol or transvenous pacing to increase heart rate is recommended in patients with acquired Long QT (LQT) syndrome and recurrent TdP despite correction of precipitating conditions and magnesium **(Class 1, level of evidence C)**.
- Catheter ablation is recommended in patients presenting with incessant VT or electrical storm due to SMVT refractory to anti-arrhythmic drug (AADs) **(Class 1, level of evidence B)**.
- Deep sedation/intubation should be considered in patients with an intractable electrical storm refractory to drug treatment **(Class IIa, level of evidence C)**.
- Catheter ablation should be considered in patients with recurrent episodes of polymorphic VT/ventricular fibrillation (PVT/VF) triggered by a similar premature ventricular complex (PVC), non-responsive to medical treatment or coronary revascularization **(Class IIa, level of evidence C)**.
- Quinidine may be considered in patients with coronary artery disease (CAD) and electrical storm due to recurrent PVT when other AAD therapy fails **(Class IIb, level of evidence C)**.

- Autonomic modulation may be considered in patients with electrical storm refractory to drug treatment and in whom catheter ablation is ineffective or not possible **(Class IIb, level of evidence C)**.
- Institution of mechanical circulatory support may be considered in the management of drug-refractory electrical storm and cardiogenic shock **(Class IIb, level of evidence C)**.

b. Long-term management

Treatment with heart failure medications

- Optimal medical treatment including ACE-I/ARB/ ARNIs, MRAs, beta-blockers, and SGLT2 inhibitors is indicated in all heart failure patients with reduced EF **(Class 1, level of evidence A)**.

Device therapy

Implantable cardioverter defibrillator (ICD)

- Implantation of a cardioverter defibrillator is only recommended in patients who have an expectation of good quality survival >1 year **(Class 1, level of evidence C)**.
- It is not recommensupded to implant an ICD in patients with incessant VAs until the VA is controlled **(Class III, level of evidence C)**.
- ICD implantation is recommended in patients with documented VF or hemodynamically not-tolerated VT in the absence of reversible causes **(Class 1, level of evidence A)**.
- In patients with VT/VF, an indication for ICD, and no contraindication for amiodarone, amiodarone may be considered when an ICD is not available, contraindicated for concurrent medical reasons, or declined by the patient **(Class IIb, level of evidence C)**.
- In patients with SMVT or SPVT/VF triggered by a PVC with similar morphology and an indication for ICD, catheter ablation may be considered when an ICD is not available, contraindicated for concurrent medical reasons, or declined by the patient **(Class IIb, level of evidence C)**.
- Subcutaneous defibrillator should be considered as an alternative to transvenous defibrillator in patients with an indication for an ICD when pacing therapy for bradycardia, cardiac resynchronization, or anti-tachycardia pacing (ATP) is not needed **(Class IIa, level of evidence B)**.
- When an ICD is indicated, it is recommended to evaluate whether the patient could benefit from cardiac resynchronization therapy (CRT)-defibrillator **(Class 1, level of evidence C)**.

Wearable cardioverter defibrillator (WCD)

- The WCD should be considered for adult patients with a secondary prevention ICD indication, who are temporarily not candidates for ICD implantation **(Class IIa, level of evidence C)**.
- The WCD may be considered in the early phase after MI in selected patients **(Class IIb, level of evidence B)**.
- Catheter ablation is recommended for ICD patients with recurrent SVT resulting in inappropriate ICD therapies **(Class 1, level of evidence C)**.
- Pharmacological treatment or catheter ablation is recommended in patients with AF-related inappropriate ICD therapies despite optimal ICD programming **(Class 1, level of evidence C)**.
- ICD implantation should be considered in left ventricular assist devices (LVAD) recipients with symptomatic sustained VAs.
- Single-chamber ICD is recommended over dual-chamber ICD in primary prevention patients without current or expected indication for atrial or AV sequential pacing due to a lower risk of device-related complications **(Class 1, level of evidence A)**.
- The use of single-coil leads over dual-coil ICD leads should be considered due to lower complication rate during transvenous lead extraction **(Class IIa, level of evidence C)**.

Interventional therapy

- Catheter ablation; **patients with structural heart disease.**

In individuals with SHD, SMVTs mainly occur due to a scar-related re-entrant mechanism. Patients with VAs linked to SHD often have a higher risk of SCD, prompting the recommendation for ICD implantation. However, ICDs don't stop VA, and many patients still face VT/VF recurrences leading to fainting or ICD shocks, necessitating further treatment. For managing VT/VF recurrences in SHD patients, the preferred anti-arrhythmic medications are usually beta-blockers, sotalol, and amiodarone, though they often come with side effects.

Over the past 30 years, catheter ablation has become a vital treatment for scar-related VTs. From the early 1990s, this method has been particularly successful for treating BBR-VT and is now the primary treatment. Catheter ablation has proven effective in managing persistent VTs and in decreasing subsequent VT instances. Several studies have noted the positive impact of VT ablation on clinical outcomes concerning VT recurrences. Furthermore, in patients with CAD, catheter ablation has been found to reduce the chances of future ICD shocks and recurrent VT episodes.

The primary focus for ablation is the 'protected VT isthmus', a significant part of re-entrant VT circuits. Identifying this area is challenging, especially in cases where the VT is not hemodynamically tolerated. Because of the complexity in locating the critical isthmuses and the high probability of multiple re-entry circuits, the ablation strategy has evolved to a more extensive ablation of the arrhythmogenic substrate.

VT circuit characteristics vary based on the specific SHD. For instance, post-infarct VTs are typically related to an endocardial VT circuit, while those with cardiomyopathies have more variability in the location of their circuits. The success of VT ablation differs based on the type of heart disease, with better outcomes in CAD.

For ablation to be effective, lasting ablation lesions on arrhythmogenic tissue are crucial. Achieving this goal remains challenging in certain cases. To enhance the creation of myocardial lesions, new catheter techniques are under evaluation. While planning for VT ablation, gathering information about the arrhythmogenic substrate is essential, especially identifying scars and determining the exit site of VAs.

The average long-term success rate of VT ablation ranges between 30% to 70%, based on the specific SHD. There are risks associated with the procedure, including potential complications like stroke, cardiac tamponade, or even death.

- Catheter ablation; **Patients without apparent structural heart disease**

‘Idiopathic VTs' refers to VTs that aren't linked to SHD or genetic arrhythmic syndromes. The majority of idiopathic VTs are caused by triggered activity, with a re-entrant mechanism involving the LV Purkinje network accounting for verapamil-sensitive fascicular VTs. Three main characteristics differentiate idiopathic VTs from those related to SHD. Firstly, idiopathic VTs typically start from one specific site and region within the heart, such as the right or left ventricular outflow tracts, along the valve annuli, papillary muscle, or the LV Purkinje network. Secondly, there's no discernible scar present in idiopathic VTs. Lastly, since idiopathic VTs generally have a favorable prognosis, ICD implantation isn't usually advised.

For treatment, the earliest activation site during VT is targeted for ablation in cases of focal sources. For left fascicular VTs, the abnormal Purkinje tissue displaying diastolic activity during VT is the ablation target. Catheter ablation is often successful in treating most idiopathic VT patients, and complications from the procedure are infrequent.

- Autonomic ablation

The influence of the autonomic nervous system in causing arrhythmias has been understood for some time, leading to the development of the concept known as Coumel’s triangle of arrhythmogenesis. Sympathetic activation is crucial in triggering VAs in certain conditions, like congenital LQTS and CPVT. Procedures

such as left cardiac sympathetic denervation have been linked to a reduction in the occurrence of arrhythmogenic syncope in congenital LQTS. Various methods, including thoracic epidural anesthesia, percutaneous stellate ganglion anesthesia, and surgical stellate ganglion resection, have demonstrated effectiveness in decreasing arrhythmia occurrences in persistent VT/VF, as observed in several small studies. More research is necessary to determine which patients might benefit from autonomic nervous system modulation to manage VT/VF more effectively.

Diagnostic evaluation, management, and risk stratification according to clinical presentation and known (likely) disease

I. Specific structural heart diseases

Treatment of VAs in acute coronary syndrome (ACS)

- Intravenous beta-blocker treatment is indicated for patients with recurrent PVT/VF during STEMI unless contraindicated **(Class 1, level of evidence B)**.
- Intravenous amiodarone treatment should be considered for patients with recurrent PVT/VF during the acute phase of ACS **(Class IIa, level of evidence C)**.
- Intravenous lidocaine may be considered for the treatment of recurrent PVT/VF not responding to beta-blockers or amiodarone, or if amiodarone is contraindicated during the acute phase of ACS **(Class IIb, level of evidence C)**.
- Prophylactic treatment with AADs (other than beta-blockers) is not recommended in ACS **(Class III, level of evidence B)**.
- In SCA survivors with coronary artery spasm, implantation of an ICD should be considered **(Class IIa, level of evidence C)**.

Treatment of VAs early after myocardial infarction (MI)

- Early (before discharge) assessment of LVEF is recommended in all patients with acute MI **(Class 1, level of evidence B)**.
- In patients with pre-discharge LVEF ≤40%, re-evaluation of LVEF 6–12 weeks after MI is recommended to assess the potential need for primary prevention ICD implantation **(Class 1, level of evidence B)**.
- Catheter ablation should be considered in patients with recurrent episodes of PVT/VF triggered by a similar PVC non-responsive to medical treatment or coronary revascularization in the subacute phase of MI **(Class IIa, level of evidence C)**.

Risk stratification, sudden cardiac death prevention, and treatment of VAs in chronic coronary artery disease (CAD)

- In patients with syncope and previous STEMI, PES is indicated when syncope remains unexplained after non-invasive evaluation **(Class 1, level of evidence C)**.
- ICD therapy is recommended in patients with CAD, symptomatic heart failure (NYHA class II–III), and LVEF ≤35% despite ≥3 months of optimal medical therapy (OMT) **(Class 1, level of evidence A)**.
- ICD therapy should be considered in patients with CAD, NYHA class I, and LVEF ≤30% despite ≥3 months of OMT **(Class IIa, level of evidence B)**.
- ICD implantation should be considered in patients with CAD, LVEF ≤40% despite ≥3 months of OMT, and non-sustained ventricular tachycardia (NSVT), if they are inducible for SMVT by programmed electrical stimulation (PES) **(Class IIa, level of evidence B)**.
- In patients with CAD, prophylactic treatment with AADs other than beta-blockers is not recommended **(Class III, level of evidence A)**.
- ICD implantation is recommended in patients without ongoing ischemia with documented VF or hemodynamically not-tolerated VT occurring later than 48 h after MI **(Class 1, level of evidence A)**.
- In patients with CAD and recurrent, symptomatic SMVT, or ICD shocks for SMVT despite chronic amiodarone therapy, catheter ablation is recommended in preference to escalating AAD therapy **(Class 1, level of evidence B)**.
- The addition of oral amiodarone or beta-blocker replacement by sotalol should be considered in patients with CAD with recurrent, symptomatic SMVT, or ICD shocks for SMVT while on beta-blocker treatment **(Class IIa, level of evidence B)**.
- In patients with CAD and hemodynamically well-tolerated SMVT and LVEF ≥40%, catheter ablation in experienced centers should be considered as an alternative to ICD therapy, provided that established endpoints have been reached **(Class IIa, level of evidence C)**.
- ICD implantation should be considered in patients with a hemodynamically tolerated SMVT and an LVEF ≥40% if VT ablation fails, is not available, or is not desired **(Class IIa, level of evidence C)**.
- Catheter ablation should be considered in patients with CAD and recurrent, symptomatic SMVT, or ICD shocks for SMVT despite beta-blockers or sotalol treatment **(Class IIa, level of evidence C)**.

- In patients with CAD eligible for ICD implantation, catheter ablation may be considered just before (or immediately after) ICD implantation to decrease subsequent VT burden and ICD shocks **(Class IIb, level of evidence B)**.

Sudden cardiac death prevention in patients with coronary anomalies

- Cardiac stress imaging during physical exercise is recommended in addition to cardiopulmonary exercise test in patients with anomalous aortic origin of a coronary artery with an interarterial course to confirm/exclude myocardial ischemia **(Class 1, level of evidence C)**.
- Cardiac stress imaging during physical exercise is recommended in addition to cardiopulmonary exercise test after surgery in patients with anomalous aortic origin of a coronary artery with a history of aborted CA **(Class 1, level of evidence C)**.
- Surgery is recommended in patients with anomalous aortic origin of a coronary artery with CA, syncope suspected to be due to VAs, or angina when other causes have been excluded **(Class 1, level of evidence C)**.
- Surgery should be considered in asymptomatic patients with anomalous aortic origin of a coronary artery and evidence of myocardial ischemia or abnormal aortic origin of the left coronary artery with high-risk anatomy **(Class IIa, level of evidence C)**.

Idiopathic premature ventricular complexes/ ventricular tachycardia and premature ventricular complex-induced cardiomyopathy

- Regular assessment of ventricular function of patients with PVC burden >10% and normal ventricular function is indicated **(Class 1, level of evidence C)**.
- In patients with PVCs/VT and a presentation not typical for an idiopathic origin (Including but not limited to older age, right bundle branch block (RBBB) morphology, SMVT consistent with re-entry) CMR should be considered, despite a normal echocardiogram **(Class IIa, level of evidence C)**.
- Catheter ablation as first-line treatment is recommended for symptomatic idiopathic VT/ PVCs from the RVOT or the left fascicles **(Class 1, level of evidence B)**.
- Beta-blockers or non-dihydropyridine CCBs are indicated in symptomatic patients with idiopathic VT/PVCs from an origin other than the RVOT or the left fascicles **(Class 1, level of evidence C)**.
- Beta-blockers, non-dihydropyridine CCBs, or flecainide should be considered when catheter ablation is not available, desired, or is particularly risky in symptomatic patients with idiopathic VT/ PVCs from the RVOT or the left fascicles **(Class IIa, level of evidence B)**.

- Catheter ablation or flecainide should be considered in symptomatic patients with idiopathic VT/PVCs from an origin other than the RVOT or the left fascicles **(Class IIa, level of evidence C)**.
- Catheter ablation may be considered for idiopathic VT/PVCs in asymptomatic patients with repeatedly more than 20% of PVCs per day at follow-up **(Class IIb, level of evidence B)**.
- Catheter ablation of idiopathic VT/PVCs is not recommended in children < 5 years of age or < 10 kg weight except when previous medical therapy fails or when VT is not hemodynamically tolerated **(Class III, level of evidence C)**.
- Amiodarone as a first-line treatment is not recommended in patients with idiopathic VTs/ PVCs **(Class III, level of evidence C)**.
- Verapamil is not recommended in children ,1 year of age with PVC/VT, particularly if they have signs of heart failure or concurrent use of other AADs **(Class III, level of evidence C)**.

Premature ventricular complex-induced or premature ventricular complex-aggravated cardiomyopathy

- In patients with an unexplained reduced EF and a PVC burden of at least 10%, PVC-induced cardiomyopathy should be considered **(Class IIa, level of evidence C)**.
- In patients with suspected PVC-induced cardiomyopathy, CMR should be considered **(Class IIa, level of evidence B)**.
- In patients with a cardiomyopathy suspected to be caused by frequent and predominately monomorphic PVCs, catheter ablation is recommended **(Class 1, level of evidence C)**.
- In patients with a cardiomyopathy suspected to be caused by frequent and predominately monomorphic PVCs, treatment with AADsc should be considered if catheter ablation is not desired, suspected to be high-risk, or unsuccessful **(Class IIa, level of evidence C)**.
- In patients with SHD in whom predominately monomorphic frequent PVCs are suspected to be contributing to the cardiomyopathy, AAD (amiodarone) treatment or catheter ablation should be considered **(Class IIa, level of evidence B)**.
- In non-responders to CRT with frequent, predominately monomorphic PVCs limiting optimal biventricular pacing despite pharmacological therapy, catheter ablation or AADs should be considered **(Class IIa, level of evidence C)**.

Risk stratification, sudden cardiac death prevention, and treatment of ventricular arrhythmias in dilated cardiomyopathy/hypokinetic non-dilated cardiomyopathy

- Genetic testing (including at least LMNA, PLN, RBM20, and FLNC genes) is recommended in patients with DCM/HNDCM and AV conduction delay at < 50 years, or who have a family history of DCM/HNDCM or SCD in a first-degree relative (at age < 50 years) **(Class 1, level of evidence B)**.
- CMR with LGE should be considered in DCM/ HNDCM patients for assessing the etiology and the risk of VA/SCD **(Class IIa, level of evidence B)**.
- Genetic testing (including at least LMNA, PLN, RBM20, and FLNC genes) should be considered for risk stratification in patients with apparently sporadic DCM/HNDCM, who present at young age, or with signs suspicious for an inherited etiology **(Class IIa, level of evidence C)**.
- Participation in high-intensity exercise including competitive sports is not recommended for individuals with DCM/HNDCM and a LMNA mutation **(Class III, level of evidence C)**.
- ICD implantation should be considered in patients with DCM/HNDCM, symptomatic heart failure (NYHA class II–III), and LVEF ≤ 35% after ≥ 3 months of OMT **(Class IIa, level of evidence A)**.
- ICD implantation should be considered in DCM/ HNDCM patients with a pathogenic mutation in LMNA gene, if the estimated 5-year risk of life-threatening VA is ≥10%c and in the presence of NSVT or LVEF, 50% or AV conduction delay **(Class IIa, level of evidence B)**.
- ICD implantation should be considered in DCM/ HNDCM patients with a LVEF < 50% and ≥ 2 risk factors (syncope, LGE on CMR, inducible SMVT at PES, pathogenic mutations in LMNA, PLN, FLNC, and RBM20 genes) **(Class IIa, level of evidence C)**.
- In DCM/HNDM patients, electrophysiological evaluation should be considered when syncope remains unexplained after non-invasive evaluation **(Class IIa, level of evidence C)**.
- ICD implantation is recommended in patients with DCM/HNDCM, who survive SCA due to VT/ VF or experience hemodynamically not-tolerated SMVT **(Class 1, level of evidence B)**.
- Catheter ablation in specialized centers should be considered in patients with DCM/HNDCM and recurrent, symptomatic SMVT or ICD shocks for SMVT, in whom AADs are ineffective, contraindicated, or not tolerated **(Class IIa, level of evidence C)**.

- The addition of oral amiodarone or replacement of beta-blockers by sotalol should be considered in patients with DCM/HNDCM and an ICD who experience recurrent, symptomatic VA despite optimal device programming and beta-blocker treatment **(Class IIa, level of evidence B)**.
- ICD implantation should be considered in patients with DCM/HNDCM and hemodynamically tolerated SMVT **(Class IIa, level of evidence C)**.
- In a first-degree relative of a DCM/HNDCM patient, an ECG and an echocardiogram are recommended if:
    - the index patient was diagnosed ,50 years of age or has clinical features suggestive of an inherited cause, or
    - there is family history of DCM/HNDCM, or premature unexpected SD **(Class 1, level of evidence C)**.
- In a first-degree relative of a patient with apparently sporadic DCM/HNDCM, an ECG and an echocardiogram may be considered **(Class IIb, level of evidence C)**.

Diagnosis, risk stratification, sudden cardiac death prevention, and treatment of ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy:

Diagnostic evaluation and general recommendations

- In patients with suspected ARVC, CMR is recommended **(Class 1, level of evidence B)**.
- In patients with a suspected or definite diagnosis of ARVC, genetic counselling and testing are recommended **(Class 1, level of evidence B)**.
- Avoidance of high-intensity exercise is recommended in patients with a definite diagnosis of ARVC **(Class 1, level of evidence B)**.
- Avoidance of high-intensity exercise may be considered in carriers of ARVC-related pathogenic mutations and no phenotype **(Class IIb, level of evidence C)**.
- Beta-blocker therapy may be considered in all patients with a definite diagnosis of ARVC **(Class IIb, level of evidence C)**.

Risk stratification and primary prevention of SCD

- ICD implantation should be considered in patients with definite ARVC and an arrhythmic syncope **(Class IIa, level of evidence B)**.
- ICD implantation should be considered in patients with definite ARVC and severe RV or LV systolic dysfunction **(Class IIa, level of evidence C)**.

- ICD implantation should be considered in symptomatic patients with definite ARVC, moderate right or left ventricular dysfunction, and either NSVT or inducibility of SMVT at PES **(Class IIa, level of evidence C)**.
- In patients with ARVC and symptoms highly suspicious for VA, PES may be considered for risk stratification **(Class IIb, level of evidence C)**.

Secondary prevention of SCD and treatment of VAs

- ICD implantation is recommended in ARVC patients with hemodynamically not-tolerated VT or VF **(Class 1, level of evidence C)**.
- In patients with ARVC and non-sustained or sustained VAs, beta-blocker therapy is recommended **(Class 1, level of evidence C)**.
- In patients with ARVC and recurrent, symptomatic SMVT or ICD shocks for SMVT despite beta-blockers, catheter ablation in specialized centers should be considered **(Class IIa, level of evidence C)**.
- In ARVC patients with indication for ICDs, a device with the capability of ATP programming for SMVT up to high rates should be considered **(Class IIa, level of evidence B)**.
- ICD implantation should be considered in ARVC patients with a hemodynamically tolerated SMVT **(Class IIa, level of evidence C)**.
- In patients with ARVC and recurrent, symptomatic VT despite beta-blockers, AAD treatment should be considered **(Class IIa, level of evidence C)**.

Management of relatives of a patient with ARVC

- In a first-degree relative of a patient with ARVC, ECG and echocardiogram are recommended **(Class 1, level of evidence C)**

Risk stratification, sudden cardiac death prevention, and treatment of ventricular arrhythmias in hypertrophic cardiomyopathy

Diagnostic evaluation and general recommendations

- CMR with LGE is recommended in HCM patients for diagnostic work-up **(Class 1, level of evidence B)**
- Genetic counselling and testing are recommended in HCM patients **(Class 1, level of evidence B)**
- Participation in high-intensity exercise may be considered for asymptomatic adult HCM patients without risk markers **(Class IIb, level of evidence C)**

Risk stratification and primary prevention of SCD

- It is recommended that the 5-year risk of SCD is assessed at first evaluation and at 1–3-year intervals, or when there is a change in clinical status (**Class 1, level of evidence C)**
- ICD implantation should be considered in patients aged 16 years or more with an estimated 5-year risk of SD ≥ 6% **(Class IIa, level of evidence B)**.
- ICD implantation should be considered in HCM patients aged 16 years or more with an intermediate 5-year risk of SCD (≥ 4 to < 6%) and with (a) significant LGE at CMR (usually ≥15% of LV mass); or (b) LVEF < 50%; or (c) abnormal blood pressure response during exercise test; or (d) LV apical aneurysm; or (e) presence of sarcomeric pathogenic mutation **(Class IIa, level of evidence B)**.
- In children less than 16 years of age with HCM and an estimated 5-year risk of SD ≥ 6% (based on HCM Risk-Kids score), ICD implantation should be considered **(Class IIa, level of evidence B)**.
- ICD implantation may be considered in HCM patients aged 16 years or more with an estimated 5-year risk of SCD of ≥ 4 to < 6% **(Class IIb, level of evidence B)**.
- ICD implantation may be considered in HCM patients aged 16 years or more with a low estimated 5-year risk of SCD (< 4%) and with (a) significant LGE at CMR (usually ≥15% of LV mass); or (b) LVEF < 50%; or (c) LV apical aneurysm **(Class IIb, level of evidence B)**.

Secondary prevention of SCD and treatment of VAs

- ICD implantation is recommended in HCM patients with hemodynamically not-tolerated VT or VF **(Class 1, level of evidence B)**.
- In patients with HCM presenting with hemodynamically tolerated SMVT, ICD implantation should be considered **(Class IIa, level of evidence C)**.
- In patients with HCM and recurrent, symptomatic VA, or recurrent ICD therapy, AAD treatment should be considered **(Class IIa, level of evidence C)**.
- Catheter ablation in specialized centers may be considered in selected patients with HCM and recurrent, symptomatic SMVT or ICD shocks for SMVT, in whom AAD are ineffective, contraindicated, or not tolerated **(Class IIb, level of evidence C)**.
- In a first-degree relative of a patient with HCM, ECG and echocardiogram are recommended **(Class 1, level of evidence C)**.

Implantable cardioverter defibrillator implantation in left ventricular non-compaction

- In patients with a LVNC cardiomyopathy phenotype based on CMR or echocardiography, implantation of an ICD for primary prevention of SCD should be considered to follow dilated cardiomyopathy (DCM)/ hypokinetic non-dilated cardiomyopathy (HNDCM) recommendations **(Class IIa, level of evidence C)**.

Implantable cardioverter defibrillator implantation in patients with cardiac amyloidosis

- An ICD should be considered in patients with light-chain amyloidosis or transthyretin-associated cardiac amyloidosis and hemodynamically not-tolerated VT **(Class IIa, level of evidence C)**.

Risk stratification, sudden cardiac death prevention, and treatment of ventricular arrhythmias in neuro- muscular diseases

General recommendations

- Annual follow-up with at least a 12-lead ECG is recommended in patients with muscular dystrophies, even in the concealed phase of the disease **(Class 1, level of evidence C)**.
- It is recommended that patients with neuromuscular disorders who have VAs or ventricular dysfunction are treated in the same way for arrhythmia as patients without neuromuscular disorders **(Class 1, level of evidence C)**.

Risk stratification, primary and secondary prevention of SCD

- Invasive electrophysiological evaluation is recommended in patients with myotonic dystrophy and palpitations or syncope suggestive of VA or surviving a CA **(Class 1, level of evidence C)**.
- ICD implantation is recommended in patients with myotonic dystrophy and SMVT or aborted CA not caused by BBR-VT **(Class 1, level of evidence C)**.
- Invasive electrophysiological evaluation should be considered in patients with myotonic dystrophy and a sudden increase in the PR interval or QRS duration **(Class IIa, level of evidence B)**.
- Invasive electrophysiological evaluation should be considered in patients with myotonic dystrophy and a PR interval ≥240 ms or QRS duration ≥120 ms or who are older than 40 years and have supraventricular arrhythmias or who are older than 40 years and have significant LGE on CMR **(Class IIa, level of evidence B)**.

- In myotonic dystrophy patients without AV conduction delay and a syncope highly suspicious for VA, ICD implantation should be considered **(Class IIa, level of evidence C)**.
- In myotonic dystrophy patients with palpitations highly suspicious for VA and induction of a non-BBR-VT, ICD implantation should be considered **(Class IIa, level of evidence C)**.
- In patients with limb–girdle type 1B or Emery– Dreifuss muscular dystrophies and indication for pacing, ICD implantation should be considered **(Class IIa, level of evidence C)**.
- Implantation of an ICD may be considered in patients with Duchenne/Becker muscular dystrophy and significant LGE at CMR **(Class IIb, level of evidence C)**.
- Implantation of an ICD over a permanent pacemaker may be considered in myotonic dystrophy patients with additional risk factors for VAs and SCD **(Class IIb, level of evidence C)**.
- In myotonic dystrophy patients, serial electrophysiological evaluation of AV conduction and arrhythmia induction is not recommended without arrhythmia suspicion or progression of ECG conduction disorders **(Class III, level of evidence C)**.

Management of VA

- In symptomatic patients with BBR-VT, catheter ablation is recommended **(Class 1, level of evidence C)**.
- In patients with myotonic dystrophy undergoing ablation for BBR-VT, pacemaker/ICD implantation is recommended **(Class 1, level of evidence C)**.

Recommendations for sudden cardiac death prevention and treatment of ventricular arrhythmias in myocarditis

General recommendations

- In confirmed or clinically suspected acute myocarditis, it is recommended that patients who present with life-threatening VAs are referred to a specialized center **(Class 1, level of evidence C)**.

Secondary prevention of SCD and treatment of VA

- In patients with hemodynamically not-tolerated SMVT occurring in the chronic phase of myocarditis, an ICD implantation is recommended **(Class 1, level of evidence C)**.

- In patients with hemodynamically not-tolerated sustained VT or VF during the acute phase of myocarditis, ICD implantation before hospital discharge should be considered **(Class IIa, level of evidence C)**.
- AADs should be considered (preferably amiodarone and beta-blockers) in patients with symptomatic non-sustained or sustained VAs during the acute phase of myocarditis **(Class IIa, level of evidence C)**.
- In post-myocarditis patients with recurrent, symptomatic VT, AAD treatment should be considered **(Class IIa, level of evidence C)**.
- Catheter ablation, performed in specialized centers, should be considered in post-myocarditis patients with recurrent, symptomatic SMVT or ICD shocks for SMVT in whom AADs are ineffective, not tolerated, or not desired **(Class IIa, level of evidence C)**.
- In patients with hemodynamically tolerated SMVT occurring in the chronic phase of myocarditis, ICD implantation should be considered **(Class IIa, level of evidence C)**.
- In patients with hemodynamically well-tolerated SMVT occurring in the chronic phase of myocarditis, preserved LV function and a limited scar amenable to ablation, catheter ablation may be considered as an alternative to ICD therapy, after discussion with the patient and provided that established endpoints have been reached **(Class IIb, level of evidence C)**.

Risk stratification, sudden cardiac death prevention, and treatment of ventricular arrhythmias in cardiac sarcoidosis

<u>Risk stratification and primary prevention of SCD</u>

- ICD implantation is recommended in patients with cardiac sarcoidosis who have a LVEF ≤35% **(Class 1, level of evidence B)**.
- In patients with cardiac sarcoidosis who have an indication for permanent cardiac pacing related to high-degree AV block, ICD implantation should be considered, regardless of LVEF **(Class IIa, level of evidence C)**.
- In patients with cardiac sarcoidosis who have a LVEF .35% but significant LGE at CMR after resolution of acute inflammation, ICD implantation should be considered **(Class IIa, level of evidence B)**.
- In patients with cardiac sarcoidosis who have a LVEF 35–50% and minor LGE at CMR, after resolution of acute inflammation, PES for risk stratification should be considered **(Class IIa, level of evidence C)**.
- In patients with cardiac sarcoidosis, LVEF 35–50% and inducible SMVT at PES, ICD implantation should be considered **(Class IIa, level of evidence C)**.

Secondary prevention of SCD and treatment of VAs

- ICD implantation is recommended in patients with cardiac sarcoidosis who (1) have documented sustained VT, or (2) aborted CA **(Class 1, level of evidence B)**.
- In patients with cardiac sarcoidosis and recurrent, symptomatic VA, AAD treatment should be considered **(Class IIa, level of evidence C)**.
- Catheter ablation, in specialized centers, may be considered in cardiac sarcoidosis ICD-recipients with recurrent, symptomatic SMVT or ICD shocks for SMVT, in whom AADs are ineffective, contraindicated, or not tolerated **(Class IIb, level of evidence C)**.

Recommendations for sudden cardiac death prevention and treatment of ventricular arrhythmias in valvular heart disease

- PES with standby catheter ablation is recommended in patients with aortic valve disease and SMVT to identify and ablate BBR-VT, especially if it occurs following a valve intervention **(Class 1, level of evidence C)**.
- In patients with valvular heart disease and persistent LV dysfunction after surgical correction, (if possible) it is recommended that ICD implantation for primary prevention follows DCM/HNDCM recommendations **(Class 1, level of evidence C)**.

Risk stratification and primary prevention of sudden cardiac death in congenital heart disease

Risk stratification and primary prevention of SCD for all CHD patients

- In adults with CHD with biventricular physiology and a left systemic ventricle presenting with symptomatic heart failure (NYHA II/III) and EF ≤35% despite ≥3 months of OMT, ICD implantation is indicated **(Class 1, level of evidence C)**.
- In patients with CHD with presumed arrhythmic syncope and with either at least moderate ventricular dysfunction or inducible SMVT on PES, ICD implantation should be considered **(Class IIa, level of evidence C)**.
- In patients with advanced single ventricle or systemic RV dysfunction with additional risk factors, ICD implantation may be considered **(Class IIb, level of evidence C)**.

Tetralogy of Fallot

- In patients after repair of TOF with arrhythmia symptoms and NSVT, electrophysiologic evaluation including PES should be considered **(Class IIa, level of evidence C)**.

- In patients after repair of TOF with arrhythmia symptoms and a positive PES, or a combination of other risk factors and a positive PES, ICD implantation should be considered **(Class IIa, level of evidence C)**.
- In patients after repair of TOF without arrhythmia symptoms, but with a combination of other risk factors, electrophysiologic evaluation, including PES, may be considered **(Class IIb, level of evidence C)**.
- In patients with repaired TOF undergoing surgical or transcutaneous pulmonary valve replacement, pre-operative catheter mapping and transection of VT-related anatomical isthmuses before or during the intervention may be considered **(Class IIb, level of evidence C)**.

Recommendations for secondary prevention of sudden cardiac death and treatment of ventricular arrhythmia in congenital heart disease

<u>All CHD patients</u>

- In patients with CHD presenting with sustained VAs, evaluation for residual lesions or new structural abnormalities is recommended **(Class 1, level of evidence B)**.
- In patients with CHD with not tolerated VT/ aborted CA due to VF, ICD implantation is indicated after exclusion of reversible causes **(Class 1, level of evidence C)**.
- In patients with CHD and recurrent, symptomatic SMVT or ICD shocks for SMVT not manageable by medical therapy or ICD reprogramming, catheter ablation performed in specialized centers should be considered **(Class IIa, level of evidence C)**.
- In selected patients with CHD (including atrial baffle repair for transposition of the great arteries, Fontan operation and Ebstein anomaly) presenting with CA, evaluation and treatment of SVT with rapid ventricular conduction should be considered **(Class IIa, level of evidence C)**.

<u>Tetralogy of Fallot</u>

- In patients with repaired TOF who present with SMVT or recurrent, symptomatic appropriate ICD therapy for SMVT, catheter ablation performed in specialized centers is recommended **(Class 1, level of evidence C)**.
- In patients with repaired TOF with SMVT who are undergoing surgical or transcutaneous pulmonary valve replacement, pre-operative catheter mapping and transection of VT-related anatomical isthmuses before or during the intervention should be considered **(Class IIa, level of evidence C)**.
- In patients with repaired TOF with a preserved biventricular function and symptomatic SMVT, catheter ablation or concomitant surgical ablation

performed in specialized centers may be considered as an alternative to ICD therapy **(Class IIb, level of evidence C)**.

II. Primary electrical diseases

Management of patients with idiopathic ventricular fibrillation

Diagnostic evaluation

- It is recommended that idiopathic VF is diagnosed in a SCA survivor, preferably with documentation of VF, after exclusion of an underlying structural, channelopathic, metabolic, or toxicological etiology **(Class 1, level of evidence B)**.
- Clinical testing (history, ECG and high precordial lead ECG, exercise test, echocardiogram) of first-degree family members of idiopathic VF patients may be considered **(Class IIb, level of evidence B)**.
- In idiopathic VF patients, genetic testing of genes related to channelopathy and cardiomyopathy may be considered **(Class IIb, level of evidence B)**.

Secondary prevention of SCD and treatment of VA

- ICD implantation is recommended in idiopathic VF **(Class 1, level of evidence B)**.
- Isoproterenol infusion, verapamil, or quinidine for acute treatment of an electrical storm or recurrent ICD discharges should be considered in idiopathic VF **(Class IIa, level of evidence C)**.
- Quinidine should be considered for chronic therapy to suppress an electrical storm or recurrent ICD discharges in idiopathic VF **(Class IIa, level of evidence B)**.
- Catheter ablation by experienced electrophysiologists should be considered in idiopathic VF patients with recurrent episodes of VF triggered by a similar PVC non-responsive to medical treatment **(Class IIa, level of evidence C)**.

Management of patients with long QT syndrome

Diagnosis

- It is recommended that LQTS is diagnosed with either QTc ≥480 ms in repeated 12-lead ECGs with or without symptoms or LQTS diagnostic score >3 **(Class 1, level of evidence C)**.
- In patients with clinically diagnosed LQTS, genetic testing and genetic counselling are recommended **(Class 1, level of evidence C)**.
- It is recommended that LQTS is diagnosed in the presence of a pathogenic mutation, irrespective of the QT duration **(Class 1, level of evidence C)**.

- The LQTS diagnosis should be considered in the presence of a QTc ≥ 460 ms and < 480 ms in repeated 12-lead ECGs in patients with an arrhythmic syncope in the absence of secondary causes for QT prolongation **(Class IIa, level of evidence C)**.
- Routine diagnostic testing with epinephrine challenge is not recommended in LQTS **(Class III, level of evidence C)**.

General recommendations to prevent SCD

- The following is recommended in LQTS:
    - Avoid QT-prolonging drugs.
    - Avoid and correct electrolyte abnormalities.
    - Avoid genotype-specific triggers for arrhythmias **(Class 1, level of evidence C).**
- Beta-blockers, ideally non-selective beta-blockers (nadolol or propranolol), are recommended in LQTS patients with documented QT interval prolongation, to reduce risk of arrhythmic events **(Class 1, level of evidence B).**
- Mexiletine is indicated in LQT3 patients with a prolonged QT interval **(Class 1, level of evidence C).**
- Beta-blockers should be considered in patients with a pathogenic mutation and a normal QTc interval **(Class IIa, level of evidence C)**.

Risk stratification, prevention of SCD and treatment of VA

- ICD implantation in addition to beta-blockers is recommended in LQTS patients with CA **(Class 1, level of evidence B).**
- ICD implantation is recommended in patients with LQTS who are symptomatic while receiving beta-blockers and genotype-specific therapies **(Class 1, level of evidence C).**
- LCSD is indicated in patients with symptomatic LQTS when: (a) ICD therapy is contraindicated or declined; (b) patient is on beta-blockers and genotype-specific drugs with an ICD and experiences multiple shocks or syncope due to VA **(Class 1, level of evidence C).**
- Either ICD implantation or LCSD should be considered in patients with symptomatic LQTS, when beta-blockers and genotype-specific therapies are not tolerated or contraindicated at the therapeutic dose **(Class IIa, level of evidence C).**
- In LQTS, it should be considered to calculate the arrhythmic risk before initiation of therapy based on the genotype and the duration of QTc interval **(Class IIa, level of evidence C).**

- ICD implantation may be considered in asymptomatic LQTS patients with high-risk profile (according to the 1-2-3 LQTS Risk calculator) in addition to genotype-specific medical therapies (mexiletine in LQT3 patients) **(Class IIb, level of evidence B).**
- Invasive electrophysiologic study is not recommended in LQTS **(Class III, level of evidence C).**

Management of patients with Andersen–Tawil syndrome

Diagnosis

- Genetic testing is recommended in patients with suspected Andersen–Tawil syndrome **(Class 1, level of evidence C).**
- Andersen–Tawil syndrome should be considered in patients without SHD who present with at least two of the following:
    - Prominent U waves with or without prolongation of the QT interval
    - Bidirectional and/or polymorphic PVCs/VT
    - Dysmorphic features
    - Periodic paralysis
    - KCNJ2 pathogenic loss of function mutation **(Class IIa, level of evidence C)**

Risk stratification, prevention of SCD and treatment of VA

- ICD implantation is recommended in patients with Andersen–Tawil syndrome after aborted CA or not-tolerated sustained VT **(Class 1, level of evidence C).**
- Beta-blockers and/or flecainide with or without acetazolamide should be considered in patients with Andersen–Tawil syndrome to treat VA **(Class IIa, level of evidence C).**
- An ILR should be considered in patients with Andersen–Tawil syndrome and unexplained syncope **(Class IIa, level of evidence C).**
- ICD implantation may be considered in patients with Andersen–Tawil syndrome who have a history of unexplained syncope or suffer from tolerated sustained VT **(Class IIb, level of evidence C)**

Management of patients with Brugada syndrome (BrS)

Diagnosis

- It is recommended that BrS is diagnosed in patients with no other heart disease and a spontaneous type 1 Brugada ECG pattern **(Class 1, level of evidence C).**

- It is recommended that BrS is diagnosed in patients with no other heart disease who have survived a CA due to VF or PVT and exhibit a type 1 Brugada ECG induced by sodium channel blocker challenge or during fever **(Class 1, level of evidence C).**
- Genetic testing for SCN5A gene is recommended for probands with BrS **(Class 1, level of evidence C).**
- BrS should be considered in patients with no other heart disease and induced type 1 Brugada pattern who have at least one of:
    - Arrhythmic syncope or nocturnal agonal respiration
    - A family history of BrS
    - A family history of SD (< 45 years old) with a negative autopsy and circumstance suspicious for BrS **(Class IIa, level of evidence C).**
- BrS may be considered as a diagnosis in patients with no other heart disease who exhibit an induced type 1 Brugada ECG **(Class IIb, level of evidence C).**
- Sodium channel blocker test is not recommended in patients with a prior type I Brugada pattern **(Class III, level of evidence C).**

<u>General recommendations</u>

- The following is recommended in all patients with BrS:
    - Avoidance of drugs that may induce ST-segment elevation in right precordial leads (http://www.brugadadrugs.org)
    - Avoidance of cocaine, cannabis, and excessive alcohol intake.
    - Treatment of fever with antipyretic drugs **(Class 1, level of evidence C).**

<u>Risk stratification, prevention of SCD and treatment of VA</u>

- ICD implantation is recommended in patients with BrS who:
    - Are survivors of an a borted CA and/or
    - Have documented spontaneous sustained VT **(Class IIb, level of evidence C)**
- ICD implantation should be considered in patients with type 1 Brugada pattern and an arrhythmic syncope **(Class IIa, level of evidence C).**
- Implantation of a loop recorder should be considered in BrS patients with an unexplained syncope **(Class IIa, level of evidence C).**
- Quinidine should be considered in patients with BrS who qualify for an ICD but have a contraindication, decline, or have recurrent ICD shocks **(Class IIa, level of evidence C).**

- Isoproterenol infusion should be considered in BrS patients suffering electrical storm **(Class IIa, level of evidence C).**
- Catheter ablation of triggering PVCs and/or RVOT epicardial substrate should be considered in BrS patients with recurrent appropriate ICD shocks refractory to drug therapy **(Class IIa, level of evidence C).**
- PES may be considered in asymptomatic patients with a spontaneous type I BrS ECG **(Class IIb, level of evidence B).**
- ICD implantation may be considered in selected asymptomatic BrS patients with inducible VF during PES using up to 2 extra stimuli **(Class IIb, level of evidence C).**
- Catheter ablation in asymptomatic BrS patients is not recommended **(Class III, level of evidence C).**

Management of patients with early repolarization pattern/syndrome

Diagnosis

- It is recommended that the ERP is diagnosed as J-point elevation of ≥1 mm in two adjacent inferior and/or lateral ECG leads **(Class 1, level of evidence C).**
- It is recommended that the ERS is diagnosed in a patient resuscitated from unexplained VF/PVT in the presence of ERP **(Class 1, level of evidence C).**
- In an SCD victim with a negative autopsy and medical chart review, and an ante-mortem ECG demonstrating the ERP, the diagnosis of ERS should be considered **(Class IIa, level of evidence C).**
- First-degree relatives of ERS patients should be considered for clinical evaluation for ERP with additional high-risk features **(Class IIa, level of evidence B).**
- Genetic testing in ERS patients may be considered **(Class IIb, level of evidence C).**
- Clinical evaluation is not recommended routinely in asymptomatic subjects with ERP. **(Class III, level of evidence C)**

Risk stratification, prevention of SCD and treatment of VA

- ICD implantation is recommended in patients with a diagnosis of ERS who have survived a CA **(Class 1, level of evidence B)**
- Isoproterenol infusion should be considered for ERS patients with electrical storm **(Class IIa, level of evidence B).**
- Quinidine in addition to an ICD should be considered for recurrent VF in ERS patients **(Class IIa, level of evidence B).**

- ILR should be considered in individuals with ERP and at least one risk featured or arrhythmic syncope **(Class IIa, level of evidence C).**
- PVC ablation should be considered in ERS patients with recurrent VF episodes triggered by a similar PVC non-responsive to medical treatment **(Class IIa, level of evidence C).**
- ICD implantation or quinidine may be considered in individuals with ERP and arrhythmic syncope and additional risk features **(Class IIb, level of evidence C).**
- ICD implantation or quinidine may be considered in asymptomatic individuals who demonstrate a high-risk ERP in the presence of a family history of unexplained juvenile SD **(Class IIb, level of evidence C).**
- ICD implantation is not recommended in asymptomatic patients with an isolated ERP **(Class III, level of evidence C).**

Management of patients with catecholaminergic polymorphic ventricular tachycardia

Diagnosis

- It is recommended that CPVT is diagnosed in the presence of a structurally normal heart, normal ECG, and exercise- or emotion-induced bidirectional, or PVT **(Class 1, level of evidence C)**
- It is recommended that CPVT is diagnosed in patients who are carriers of a mutation in disease-causing genes **(Class 1, level of evidence C)**
- Genetic testing and genetic counselling are indicated in patients with clinical suspicion or clinical diagnosis of CPVT **(Class 1, level of evidence C)**
- Epinephrine or isoproterenol challenge may be considered for the diagnosis of CPVT when an exercise test is not possible **(Class IIb, level of evidence C)**

General recommendations

- Avoidance of competitive sports, strenuous exercise, and exposure to stressful environments is recommended in all patients with CPVT **(Class 1, level of evidence C)**

Therapeutic interventions

- Beta-blockers, ideally non-selective (nadolol or propranolol) are recommended in all patients with a clinical diagnosis of CPVT **(Class 1, level of evidence C)**

- ICD implantation combined with beta-blockers and flecainide is recommended in CPVT patients after aborted CA **(Class 1, level of evidence C)**
- Therapy with beta-blockers should be considered for genetically positive CPVT patients without phenotype **(Class IIa, level of evidence C)**
- LCSD should be considered in patients with diagnosis of CPVT when the combination of beta-blockers and flecainide at therapeutic dosage are either not effective, not tolerated, or contraindicated **(Class IIa, level of evidence C)**
- ICD implantation should be considered in patients with CPVT who experience arrhythmogenic syncope and/or documented bidirectional/PVT while on highest tolerated beta-blocker dose and on flecainide **(Class IIa, level of evidence C)**
- Flecainide should be considered in patients with CPVT who experience recurrent syncope, polymorphic/bidirectional VT, or persistent exertional PVCs, while on beta-blockers at the highest tolerated dose **(Class IIa, level of evidence C)**
- PES is not recommended for stratification of SCD risk **(Class III, level of evidence C)**

Management of patients with short QT syndrome

Diagnosis

- It is recommended that SQTS is diagnosed in the presence of a QTc ≤ 360 ms and one or more of the following: (a) a pathogenic mutation, (b) a family history of SQTS, (c) survival from a VT/VF episode in the absence of heart disease **(Class 1, level of evidence C).**
- Genetic testing is indicated in patients diagnosed with SQTS **(Class 1, level of evidence C).**
- SQTS should be considered in the presence of a QTc ≤ 320 ms **(Class IIa, level of evidence C).**
- SQTS should be considered in the presence of a QTc ≥ 320 ms and ≤360 ms and arrhythmic syncope **(Class IIa, level of evidence C).**
- SQTS may be considered in the presence of a QTc ≥ 320 ms and ≤ 360 ms and a family history of SD at age < 40 years **(Class IIb, level of evidence C).**

Risk stratification, SCD prevention and treatment of VA

- ICD implantation is recommended in patients with a diagnosis of SQTS who: (a) are survivors of an aborted CA and/or (b) have documented spontaneous sustained VT **(Class 1, level of evidence C).**

- ILR should be considered in young SQTS patients **(Class IIa, level of evidence C).**
- ICD implantation should be considered in SQTS patients with arrhythmic syncope **(Class IIa, level of evidence C).**
- Quinidine may be considered in (a) SQTS patients who qualify for an ICD but present a contraindication to the ICD or refuse it, and (b) asymptomatic SQTS patients and a family history of SCD **(Class IIb, level of evidence C).**
- Isoproterenol may be considered in SQTS patients with an electrical storm **(Class IIb, level of evidence C).**
- PES is not recommended for SCD risk stratification in SQTS patients **(Class III, level of evidence C).**

Special aspects in selected populations

Prevention of sudden cardiac death and management of ventricular arrhythmia during pregnancy

Acute management of VA

- During pregnancy, electrical cardioversion is recommended for sustained VT **(Class 1, level of evidence C).**
- For acute conversion of hemodynamically tolerated SMVT during pregnancy, a beta-blocker, sotalol, flecainide, procainamide, or overdrive ventricular pacing should be considered **(Class IIa, level of evidence C).**

Long-term management of VA

- If ICD implantation is indicated during pregnancy, implantation is recommended with optimal radiation protection **(Class 1, level of evidence C).**
- Continuation of beta-blockers is recommended during pregnancy and post-partum in women with LQTS or CPVT **(Class 1, level of evidence C).**
- Continuation of beta-blockers should be considered during pregnancy in women with ARVC **(Class IIa, level of evidence C).**
- Oral metoprolol, propranolol, or verapamil should be considered for long-term management of idiopathic sustained VT during pregnancy **(Class IIa, level of evidence C).**
- Catheter ablation using non-fluoroscopic mapping systems should be considered, preferably after the first trimester, in women with highly symptomatic recurrent SMVT refractory or who are intolerant to AADs **(Class IIa, level of evidence C).**

Prevention of sudden cardiac death before and after heart transplantation

Prior to heart transplant

- In patients awaiting heart transplantation, ICD implantation for primary prevention should be considered **(Class IIa, level of evidence C).**
- In patients awaiting heart transplantation, WCD may be considered **(Class IIb, level of evidence C).**

Post heart transplant

- In selected transplanted patients with cardiac allograft vasculopathy or treated rejection, ICD implantation may be considered **(Class IIb, level of evidence C).**
- **Recommendations for risk stratification and prevention of sudden cardiac death in athletes:**
- In athletes with positive medical history, abnormal physical examination, or ECG alterations, further investigations including echocardiography and/or CMR to confirm (or exclude) an underlying disease are recommended **(Class 1, level of evidence C).**
- It is recommended that athletes diagnosed with a cardiovascular disease associated with SCD are managed according to current guidelines for sports eligibility **(Class 1, level of evidence C).**
- It is recommended that staff at sporting facilities are trained in CPR and in the use of AED **(Class 1, level of evidence C).**
- Pre-participation cardiovascular evaluation of competitive athletes should be considered **(Class IIa, level of evidence C).**
- It should be considered that cardiovascular evaluation of young (‚35 years) competitive athletes includes history, physical examination, and 12-lead ECG **(Class IIa, level of evidence C).**
- The cardiovascular risk of middle-aged and elderly individuals should be evaluated before engaging in strenuous sports through established scores such as the SCORE2 risk chart **(Class IIa, level of evidence C).**

Wolff–Parkinson–White syndrome

- In individuals diagnosed with Wolff–Parkinson–White (WPW) syndrome, AV re-entry tachycardia (AVRT) is the predominant arrhythmia, accounting for 80%. Atrial fibrillation (AF) follows at 20–30%. The most alarming concern in WPW syndrome is Sudden Cardiac Death (SCD) from pre-excited AF leading to Ventricular Fibrillation (VF). Studies suggest that the chance of Cardiac Arrest/VF in those with untreated WPW is 0.9–2.4 per 1000 person-year.

Management strategies for WPW were discussed in the 2019 ESC Guidelines for handling patients with Supraventricular Tachycardia (SVT) and were later updated in 2020 with an emphasis on athletes. For those exhibiting ventricular pre-excitation and symptoms of AVRT, the preferred treatment is catheter ablation (class I recommendation). For those without symptoms but showing ventricular pre-excitation, both invasive (class IIa) and non-invasive (class IIb) evaluations can be used for determining the risk of SCD.

- Catheter ablation is advised for pathways showing high-risk characteristics even in the absence of symptoms (class I). However, clinical monitoring (class IIa) or catheter ablations (class IIb) can be considered based on the patient's informed decision. Such choices should be influenced by the pathway's position, the proficiency in ablation procedures in the area, and the likelihood of symptomatic arrhythmias emerging over time. For young children, WPW-induced SVT can typically be treated with medications, and these accessory pathways often lose their forward conduction during early childhood. In children who have these asymptomatic accessory pathways, it's usually not advised to carry out risk assessments before they reach 8 years of age.

Implantable cardioverter defibrillator implantation in the elderly

- In elderly patients in whom a benefit from the defibrillator is not expected due to the patient's age and comorbidities, omission of ICD implantation for primary prevention may be considered **(Class IIb, level of evidence C).**

1.3.2 European Heart Rhythm Association (EHRA) Consensus Document on the Management of Supraventricular Arrhythmias, Endorsed by Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), and Sociedad Latino Americana de Estimulación Cardiaca y Electrofisiologia (SOLAECE) (2016)

The European Heart Rhythm Association (EHRA) consensus on the management of supraventricular tachycardia was endorsed by the HRS, APHRS and SOLAECE. This consensus issued the below recommendations:[8]

Table 7. EHRA Scientific Rational of Recommendations

Recommended/indicated	Scientific evidence that a treatment or procedure is beneficial and effective. Requires at least one randomized trial or is supported by strong observational evidence and authors' consensus.
May be used or recommended	General agreement and/or scientific evidence favor the usefulness/ efficacy of a treatment or procedure. May be supported by randomized trials that are, however, based on small number of patients to allow a green heart recommendation.
Should NOT be used or recommended	Scientific evidence or general agreement not to use or recommend a treatment or procedure.

Inappropriate sinus tachycardia

- Therapy is recommended mainly to control symptoms. Ivabradine is recommended for symptomatic patients. (recommended)
- Beta-blockers and non-dihydropyridine calcium channel blockers are frequently ineffective or not tolerated at required doses. Therefore, may be considered as second- and third-line therapy, respectively. (May be recommended)
- Catheter ablation should not be routinely considered in patients with inappropriate sinus tachycardia. This treatment must be restricted to the most symptomatic patients after the failure of other therapy and measures. (Is not recommended)

Sinus nodal reentrant tachycardia

- Catheter ablation may be used in patients with symptomatic sinus nodal reentrant tachycardia. (May be recommended)
- Oral beta blockers, diltiazem, or verapamil may be used in patients with symptomatic sinus nodal reentrant tachycardia. (May be recommended)

Therapy of focal atrial tachycardia

- Acute therapy
    - Synchronized DC cardioversion is recommended for hemodynamically unstable patients. (Is recommended)
    - Adenosine may be used in terminating a non-reentrant AT or diagnosing the tachycardia mechanism. (May be recommended)
    - IV beta blockers or verapamil or diltiazem may be used for pharmacologic cardioversion or rate control.
    - IV flecainide or propafenone may be used for pharmacologic cardioversion in the absence of structural or ischemic heart disease.
    - IV amiodarone may be used for pharmacologic cardioversion or rate control. (may be recommended)
    - IV ibutilide may be used for pharmacologic cardioversion of micro-reentrant AT. (May be recommended)
- Chronic therapy
    - Catheter ablation is recommended, especially for incessant AT. (Is recommended)
    - Beta blockers or verapamil or diltiazem may be considered. (May be recommended)
    - Flecainide or propafenone in the absence of structural or ischemic heart disease may be considered. (May be recommended)

Therapy of multifocal atrial tachycardia

- Metoprolol is recommended in the absence of pulmonary disease. (Is recommended)
- Verapamil or diltiazem may be considered in the presence of pulmonary disease. (may be recommended)

Therapy of atrial flutter/macro-reentrant tachycardia

- Acute therapy
    - Synchronized DC cardioversion is recommended for hemodynamically unstable patients with AFL/MRT (is recommended)
    - IV anticoagulation may be considered in case emergency cardioversion is necessary. Anticoagulation should be continued for 4 weeks after sinus rhythm is established. (may be recommended)

- Intravenous beta blockers, diltiazem, or verapamil are recommended for acute rate control in patients with AFL who are hemodynamically stable. (is recommended)
- IV ibutilide or dofetilide, under close monitoring due to proarrhythmic risk, are recommended to cardiovert AFL. (is recommended)
- Amiodarone may be considered to control ventricular rate in the acute setting. (may be recommended)
- Atrial overdrive pacing (via esophagus or endocardial) may be considered for conversion of AFL/MRT. (may be recommended)
- Oral dofetilide may be considered to cardiovert AFL in non-urgent situations but only in hospitalized patients since there is a proarrhythmic risk. (may be recommended)
- Class Ic antiarrhythmic drugs should not be used in the absence of AV blocking agents because of the risk of slowing atrial rate and leading to 1:1 AV conduction. (is not recommended)

- Chronic therapy
  - One-time or repeated cardioversion associated with AAD are recommended as a long-term alternative for patients with infrequent AFL recurrences or refusing ablation. (Is recommended)
  - In patients with recurrent or poorly tolerated typical AFL, CTI ablation is recommended for preventing recurrences with a low incidence of complications. (Is recommended)
  - In patients with depressed LV systolic function, ablation may be considered to revert dysfunction due to tachycardiomyopathy and prevent recurrences. (may be recommended)
  - Atypical AFL/MRT appearing early (3–6 months) after AF ablation may be initially treated by cardioversion and AAD, as it may not recur in the long term. (may be recommended)
  - In patients with recurrent atypical or multiple ECG AFL patterns, catheter ablation may be considered after documentation of mechanism. (may be recommended)
  - Given the high incidence of AF after CTI ablation for typical AFL, correction of ‘AF risk factors’ may be considered after ablation. (May be recommended)
  - Oral anticoagulation may be considered for patients with episodes of atrial flutter. (may be recommended)

- Stroke prevention is recommended with the same indications as in AF amongst patients with typical FL and associated episodes of AF. (Is recommended)
    - 'Low risk' AFL patients, defined as CHA2DS2-VASc 0 in males or 1 in females, do not need antithrombotic therapy.
    - Effective stroke prevention in patients with CHA2DS2-VASc score ≥ 1, is oral anticoagulation, whether with well controlled vitamin K antagonist (VKA) with a time in therapeutic range > 70%, or with a non-VKA oral anticoagulant (NOAC, either dabigatran, rivaroxaban, apixaban or edoxaban).
    - Bleeding risk should be assessed using the HAS-BLED score. Patients at high risk (score > 3) should be identified for more regular review and follow-up, and the reversible bleeding risk factors addressed. A high HAS-BLED score is not a reason to withhold anticoagulation.

Atrioventricular nodal reentrant tachycardia

Therapy of AVNRT:

- Acute therapy:
    - Valsalva maneuver, preferably in the supine position, is recommended. (Is recommended)
    - IV adenosine is recommended. (Is recommended)
    - Synchronized direct-current cardioversion is recommended for hemodynamically unstable patients in whom adenosine fails to terminate the tachycardia. (Is recommended)
    - IV verapamil or diltiazem may be considered in the absence of hypotension or suspicion of VT or pre-excited AF. (May be recommended)
    - IV beta blockers (metoprolol or esmolol) may be considered. (May be recommended)
    - IV amiodarone may be considered. (May be recommended)
    - Single oral dose of diltiazem and propranolol may be considered. (May be recommended)
- Chronic therapy
    - Catheter ablation for slow pathway modification is recommended in symptomatic patients or in patients with an ICD. (is recommended)

- Diltiazem or verapamil may be considered. (May be recommended)
- Beta blockers may be considered. (May be recommended)
- No therapy for minimally symptomatic patients with infrequent, short-lived episodes of tachycardia. (May be recommended)

Therapy of focal junctional tachycardia

- Acute therapy
  - IV propranolol with or without procainamide, verapamil or flecainide may be considered for acute therapy. (Is recommended)
- Chronic therapy
  - Beta blockers and in the absence of ischemic or structural heart disease flecainide or propafenone, may be considered for chronic therapy. (May be recommended)
  - Catheter ablation may be considered but at a risk of AV block. (May be recommended)

Therapy of atrioventricular reentrant tachycardias

- Acute therapy
  - Vagal maneuvers (Valsalva and carotid sinus massage), preferably in the supine position, are recommended as the first-line approach to achieve SVT termination. However, reversion rates range from 45.9 to 54.3%. (Is recommended)
  - Adenosine is recommended for conversion to sinus rhythm but should be used with caution because it may precipitate AF with a rapid ventricular rate and even ventricular fibrillation. (Is recommended)
  - Synchronized DC shock is recommended in hemodynamically unstable patients with AVRT if vagal maneuvers or adenosine are ineffective or not feasible. (Is recommended)
  - IV ibutilide, procainamide, propafenone or flecainide in antidromic AVRT may be considered. (May be recommended)
  - IV beta blockers, diltiazem, verapamil in orthodromic AVRT may be considered. (May be recommended)
  - IV digoxin, beta blockers, diltiazem, verapamil and, possibly, amiodarone are potentially harmful in patients with pre-excited AF. (Is not recommended)

- Chronic therapy
    - Catheter ablation of the accessory pathway is recommended in patients with symptomatic AVRT and/or pre-excited AF. (Is recommended)
    - Catheter ablation of concealed accessory pathways may be considered in symptomatic patients with frequent episodes of AVRT. (May be recommended)
    - Oral flecainide or propafenone, preferably in combination with a beta blocker, may be considered in patients with AVRT and/or pre-excited AF, and without structural or ischemic heart disease. (May be recommended)
    - Oral beta blockers, diltiazem, or verapamil may be considered for chronic management of AVRT if no pre-excitation signs on resting ECG are present. (May be recommended)
    - Oral amiodarone may be considered only among patients in whom other AADs are ineffective or contraindicated, and catheter ablation is not an option. (May be recommended).

Section 2.0 Drug Therapy

2.1 Class I Antiarrhythmic Agents

2.1.1 Lidocaine

Table 8. Lidocaine Drug Information

SCIENTIFIC NAME Lidocaine	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	I49
Drug Class	Antiarrhythmic
Drug Sub-class	Class IB
ATC Code	N01BB02
Pharmacological Class (ASHP)	24:04.04.08 Class Ib Antiarrhythmics
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Intravenous use
Dose (Adult) [DDD]*	**Sudden cardiac arrest due to ventricular fibrillation or pulseless ventricular tachycardia (unresponsive to CPR, defibrillation, epinephrine) (off-label use):** - Bolus dose: IV/intraosseous: 1 to 1.5 mg/kg; repeat with 0.5 to 0.75 mg/kg every 5 to 10 minutes as necessary; a typical dose is 50 to 100 mg. - Continuous infusion: IV/intraosseous : 1 to 4 mg/minute; if used beyond 24 hours, the rate of elimination can be prolonged and dose reduction

	may be necessary; monitor serum concentrations and signs or symptoms of toxicity to guide dose adjustment.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	**Ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT), shock-refractory: Infants, Children, and Adolescents:** IV, Intraosseous: Initial: - Loading dose: 1 mg/kg/dose; follow with continuous IV infusion; may administer second bolus if delay between initial bolus and start of infusion is >15 minutes. - Continuous IV infusion: 20 to 50 mcg/kg/minute. Per manufacturer, do not exceed 20 mcg/kg/minute in patients with shock, hepatic disease, cardiac arrest, or CHF.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Adult** **Renal Impairment:** eGFR <30 mL/minute/1.73 m2: Administer lower maintenance infusion rate with close monitoring for toxicity. **Hepatic Impairment:** Administer lower maintenance infusion rate with close monitoring for toxicity. **Pediatric** **Renal Impairment:** Infants, Children, and Adolescents: There are no dosage adjustments provided in the manufacturer's labeling; however, accumulation of metabolites may be increased in renal dysfunction. Not dialyzable (0% to 5%) by hemo- or

	peritoneal dialysis; supplemental dose is not necessary. **<u>Hepatic Impairment:</u>** Infants, Children and Adolescents: Use with caution; reduce dose. Monitor lidocaine concentrations closely and adjust infusion rate as necessary; consider alternative therapy. Maximum rate of continuous IV infusion: 20 mcg/kg/minute.
Prescribing edits*	MD, ST, QL, EU
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Should be prescribed by a cardiologist.
PA (Prior Authorization)	N/A
QL (Quantity Limit)	Maximum cumulative dose: 3 mg/kg or up to 300 mg within 1 hour.
ST (Step Therapy)	Intravenous lidocaine may be considered for the treatment of recurrent PVT/VF not responding to beta-blockers or amiodarone, or if amiodarone is contraindicated during the acute phase of ACS.
EU (Emergency Use Only)	Sudden cardiac arrest due to ventricular fibrillation or pulseless ventricular tachycardia (unresponsive to CPR, defibrillation, epinephrine) (off-label use)
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**<u>Most common:</u>** Headache, shivering, radiculopathy. **<u>Most serious</u>**: Circulatory shock, coronary artery vasospasm, edema, flushing, heart block, hypotension (including following spinal anesthesia), local thrombophlebitis, vascular insufficiency, loss of consciousness,

	peripheral neuropathy, psychosis, seizure, slurred speech, anaphylactoid reaction, respiratory depression.
Drug Interactions*	**<u>Category X:</u>** • Fexinidazole • Fusidic Acid (Systemic) • Saquinavir
Special Population	**N/A**
Pregnancy	Lidocaine and its metabolites cross the placenta and can be detected in the fetal circulation following maternal injection for anesthesia prior to delivery. Adverse reactions in the fetus/neonate may affect the CNS, heart, or peripheral vascular tone. Fetal heart monitoring is recommended by the manufacturer. Lidocaine injection is approved for obstetric analgesia (e.g., prior to epidural or spinal anesthesia). Lidocaine administered by local infiltration is used to provide analgesia prior to episiotomy and during repair of obstetric lacerations. Administration by the perineal route may result in greater absorption than administration by the epidural route. Cumulative exposure from all routes of administration should be considered. The ACOG recommends that pregnant women should not be denied medically necessary surgery regardless of trimester. If the procedure is elective, it should be delayed until after delivery. Medications used for the treatment of cardiac arrest in pregnancy are the same as in the nonpregnant woman. Doses and indications should follow current Advanced Cardiovascular Life Support guidelines. Appropriate

	medications should not be withheld due to concerns of fetal teratogenicity.
Lactation	Lidocaine is present in breast milk. The relative infant dose (RID) of lidocaine is 4.9% when calculated using the highest breast milk concentration located and compared to a weight-adjusted maternal dose of 183 mg for epidural anesthesia. In general, breastfeeding is considered acceptable when the RID of a medication is <10%. The RID of lidocaine was calculated using a mean milk concentration of 0.86 mcg/mL, providing an estimated daily infant dose via breast milk of 129 mcg/kg/day. This milk concentration was obtained following maternal administration lidocaine via local regional anesthesia to 22 women undergoing cesarean delivery. Milk was sampled 2 hours after the injection. Breast milk concentrations of lidocaine decreased over 12 hours. Lidocaine metabolites have also been detected in breast milk. Lower concentrations of lidocaine have been reported in breast milk following dental procedures, infusion for arrhythmias, and liposuction. Oral bioavailability to the breastfeeding infant is expected to be low. Available guidelines consider lidocaine to be compatible with breastfeeding when used as an antiarrhythmic or local anesthetic. Cumulative exposure from all routes of administration should be considered.
Contraindications	- Hypersensitivity to lidocaine or any component of the formulation; hypersensitivity to

	another local anesthetic of the amide type; Adam-Stokes syndrome; Wolff-Parkinson-White syndrome; severe degrees of SA, AV, or intraventricular heart block (except in patients with a functioning artificial pacemaker); premixed injection may contain corn-derived dextrose and its use is contraindicated in patients with allergy to corn or corn-related products. - Canadian labeling: Additional contraindications (not in US labeling): Hypersensitivity to ester local anesthetics (paraben-containing solutions only); supraventricular arrhythmias; severe myocardial depression; antimicrobial preservative-containing solutions should not be used intra-or retro-ocularly or for epidural or spinal anesthesia or any route that would introduce solution into the cerebrospinal fluid or in doses ≥15 mL for other types of blockades.
Monitoring Requirements	Monitor Liver function tests, lidocaine concentrations, ECG; in patients requiring drug >24 hrs, blood level monitoring recommended; consult individual institutional policies and procedures.
Precautions	**Concerns related to adverse effects:** - Intra-articular infusion related chondrolysis: Continuous intra-articular infusion of local anesthetics after arthroscopic or other surgical procedures is not an approved use; chondrolysis (primarily in the

	shoulder joint) has occurred following infusion, with some cases requiring arthroplasty or shoulder replacement. - Methemoglobinemia: Has been reported with local anesthetics; clinically significant methemoglobinemia requires immediate treatment along with discontinuation of the anesthetic and other oxidizing agents. Onset may be immediate or delayed (hours) after anesthetic exposure. Patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, exposure to oxidizing agents or their metabolites, or infants <6 months are more susceptible and should be closely monitored for signs and symptoms of methemoglobinemia (eg, cyanosis, headache, rapid pulse, shortness of breath, lightheadedness, fatigue). **Disease-related concerns:** - Hepatic dysfunction: Use extreme caution in patients with severe hepatic dysfunction; may have increased risk of lidocaine toxicity. - Pseudocholinesterase deficiency: Use caution in patients with pseudocholinesterase deficiency; may have increased risk of lidocaine toxicity. **Other warnings/precautions:**

	- CAST trial: In the Cardiac Arrhythmia Suppression Trial (CAST), recent (>6 days but <2 years ago) myocardial infarction patients with asymptomatic, non-life-threatening ventricular arrhythmias did not benefit and may have been harmed by attempts to suppress the arrhythmia with flecainide or encainide. An increased mortality or nonfatal cardiac arrest rate (7.7%) was seen in the active treatment group compared with patients in the placebo group (3%). The applicability of the CAST results to other populations is unknown. Antiarrhythmic agents should be reserved for patients with life-threatening ventricular arrhythmias.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A thorough review of various HTA bodies including NICE, CADTH, HAS, IQWIG, and PBAC yielded **no recommendations for the use of lidocaine for the treatment of arrhythmias.** Nevertheless, lidocaine has been marketed worldwide for many years, and multiple generic options are available, leading to a low cost of treatment.

CONCLUSION STATEMENT – LIDOCAINE

Intravenous lidocaine may be considered for the treatment of recurrent PVT/VF not responding to beta-blockers or amiodarone, or if amiodarone is contraindicated during the acute phase of ACS.

There are no recommendations issued by HTA bodies on the use of lidocaine in ventricular arrhythmias, however, it has been available on the market for years and multiple generics are available.

2.1.2 Flecainide

Table 9. Flecainide Drug Information

SCIENTIFIC NAME Flecainide	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	I49
Drug Class	Antiarrhythmic
Drug Sub-class	Class Ic
ATC Code	C01BC04
Pharmacological Class (ASHP)	24:04.04.12 Class Ic Antiarrhythmics
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral Use
Dose (Adult) [DDD]*	- **Fetal tachycardia sustained (maternal/transplacental administration) (off-label use): Oral:** 100 to 300 mg/day in divided doses administered every 8 to 12 hours. Adjust dose to fetal response. - **Paroxysmal atrial fibrillation/flutter and paroxysmal supraventricular tachycardias (prevention): Oral:** Initial: 50 mg every 12 hours; increase by 50 mg twice daily at 4-day intervals. - **Ventricular arrhythmias (prevention): Oral:** Initial: 50 to 100 mg every 12 hours; increase by 50 mg twice daily at 4-day intervals.

	- **Ventricular premature beats (off-label use) : Oral:** 50 to 200 mg every 12 hours. According to the prescribing information, may increase by 50 mg twice daily at 4-day intervals. - **Atrial fibrillation/flutter (pharmacological cardioversion) (off-label dose):** ✓ <70 kg: 200 mg; may not repeat in ≤24 hours. ✓ ≥70 kg: 300 mg; may not repeat in ≤24 hours.
Maximum Daily Dose Adults*	- **Fetal tachycardia (sustained):** 450 mg/day. - **Paroxysmal atrial fibrillation/flutter and paroxysmal supraventricular tachycardias (prevention):** 400 mg/day. - **Ventricular arrhythmias (prevention):** 400 mg/day. - **Ventricular premature beats:** 400 mg/day.
Dose (pediatrics)	**Arrhythmias:** BSA-directed dosing: Use caution with dose titration, as small change in dose may result in disproportionate increase in plasma concentrations. - Infants ≤6 months: Oral: Initial: 50 mg/m^2/day divided every 8 to 12 hours; may titrate dose at 4-day intervals. - Infants >6 months, Children, and Adolescents: Oral: Initial: 100 mg/m^2/day divided every 8 to 12 hours; may titrate dose at 4-day intervals; maximum daily dose. Weight-based dosing: Limited data available; dosing regimens variable:

	Infants, Children, and Adolescents: Oral: Initial: 1 to 3 mg/kg/day divided every 8 hours; may titrate dose at 4-day intervals; usual maintenance range: 3 to 6 mg/kg/day; an average effective dose of 4 mg/kg/day was reported in an expert analysis of literature and clinical experience.
Maximum Daily Dose Pediatrics*	- BSA-directed dosing: 200 mg/m^2/**day** - Weight-based dosing: 8 mg/kg/**day**
Adjustment	**Adult** **<u>Renal Impairment:</u>** o CrCl ≥60 mL/minute/1.73 m2: No dosage adjustment necessary. o CrCl >35 to <60 mL/minute/1.73 m2: Initial: No dosage adjustment necessary; consider obtaining serum trough concentrations to guide dosage adjustments in addition to the anticipated clinical response; dose increases should be made cautiously and at intervals of ~7 days. o CrCl ≤35 mL/minute/1.73 m2: Initial: Administer 50% of the usual indication-specific initial dose in 1 to 2 divided doses ; subsequent dose adjustments should preferentially be determined based on serum trough concentrations in addition to the anticipated clinical response; the manufacturer's labeling recommends not to use flecainide if monitoring of trough concentrations is not available in patients with severe impairment; dose increases should be made

	no more frequently than every 7 days. ○ **Hemodialysis, intermittent (thrice weekly) (not dialyzable) peritoneal dialysis (not dialyzable), CRRT (not significantly removed), PIRRT (not likely to be significantly removed) :** Not dialyzable: Initial: Administer 50% of the usual indication-specific initial dose in 1 to 2 divided doses; subsequent dose adjustments should preferentially be determined based on serum trough concentrations in addition to the anticipated clinical response; the manufacturer's labeling recommends not to use flecainide if monitoring of trough concentrations is not available in patients with severe kidney impairment; dose increases should be made no more frequently than every 7 days. **<u>Hepatic Impairment:</u>** There are no dosage adjustments provided in the manufacturer's labeling; however, elimination from the plasma may be slower in patients with hepatic impairment. Use with caution; obtain plasma concentrations to guide dosage adjustments. Dose increases should be made very cautiously at intervals >4 days and serum concentrations monitored frequently. Frequent plasma level monitoring is required in patients with severe hepatic impairment; if unavailable, use is not recommended. **Pediatric**

	<u>Renal Impairment:</u> There are no pediatric specific recommendations; based on experience in adult patients, dosage adjustment suggested. **<u>Hepatic Impairment:</u>** There are no dosage adjustments provided in the manufacturer's labeling; however, elimination from the plasma may be slower in patients with hepatic impairment. Use with caution; obtain plasma concentrations to guide dosage adjustments. Dose increases should be made very cautiously at intervals >4 days and serum concentrations monitored frequently. Frequent plasma level monitoring is required in patients with severe hepatic impairment; if unavailable, use is not recommended.
Prescribing edits*	MD, ST
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Should be prescribed by a cardiologist.
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	Considered as second-line therapy in symptomatic patients with idiopathic VT/ PVCs from the RVOT or the left fascicles
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**<u>Most common:</u>** Ventricular arrhythmia, dizziness, visual disturbances. **<u>Most serious</u>**: Proarrhythmic effects/conduction disturbances, 1:1 atrioventricular conduction, fatal complications associated with

	structural heart disease (SDH), sinoatrial arrest, sinus bradycardia, worsening of heart failure, complete atrioventricular block.
Drug Interactions*	**<u>Category X:</u>** • Asunaprevir • Levoketoconazole • Nirmatrelvir and Ritonavir • Pimozide • Quinidine (Non-Therapeutic) • Ritonavir • Sertindole • Tipranavir
Special Population	- Pediatric: Small changes in dose may lead to disproportionate increases in plasma concentrations in pediatric patients. Following initiation of therapy or changes in dose, obtain plasma trough concentrations and ECG once steady state has been achieved (>5 doses after initiation or change); regular monitoring of trough concentrations and ECG is recommended by the manufacturer during the first year of therapy and during major changes in dietary milk intake as milk may interfere with the absorption of flecainide in pediatric patients; consider dose reductions when milk is removed from the diet (eg, during weaning or bouts of gastroenteritis).
Pregnancy	Flecainide crosses the placenta. Placental transfer is not decreased when fetal hydrops is present. Neonatal conduction abnormalities have been reported.

	Untreated maternal arrhythmias may cause adverse events in the mother and fetus. Flecainide may be used for the ongoing management of pregnant women with highly symptomatic supraventricular tachycardia (SVT). The lowest effective dose is recommended; avoid use during the first trimester if possible. Use is also recommended for the prevention of SVT in patients with Wolff-Parkinson-White (WPW) syndrome. Until more information is available, when prevention of SVT in patients without WPW syndrome, atrial tachycardia, or atrial fibrillation is needed in pregnancy, flecainide is generally reserved for use when other agents are not effective. Flecainide (administered maternally) may be considered for the in utero management of fetal SVT or atrial flutter with hydrops or ventricular dysfunction. Flecainide may also be considered for SVT without hydrops or ventricular dysfunction if heart rate is ≥200 bpm, or other rare tachycardias with an average heart rate of ≥200 bpm. In addition, flecainide may be considered for fetal ventricular tachycardia (VT) with normal QTc with or without hydrops but is contraindicated for the treatment of fetal VT when long QT syndrome is suspected or confirmed.
Lactation	Flecainide is present in breast milk. The relative infant dose (RID) of flecainide is 8% when calculated using the highest average breast milk concentration located and compared to a weight-adjusted maternal dose of 200 mg/day.

	In general, breastfeeding is considered acceptable when the RID of a medication is <10%. The RID of flecainide was calculated using a milk concentration of 1,529 ng/mL, providing an estimated daily infant dose via breast milk of 0.23 mg/kg/day. This milk concentration was obtained following maternal administration of oral flecainide 100 mg twice daily for 5 days to 11 lactating females, beginning the first day postpartum. The average daily flecainide concentrations in breast milk, and the maternal plasma trough concentrations were variable between subjects; however, the milk/plasma ratio was consistent across the group. Concentrations of flecainide in breast milk were as high as 4 times those in the maternal serum. Based on data from this study, milk concentrations would decline at approximately the same rate as maternal serum concentrations once the medication is discontinued.
Contraindications	Hypersensitivity to flecainide or any component of the formulation; pre-existing second- or third-degree AV block or with right bundle branch block when associated with a left hemiblock (bifascicular block) (except in patients with a functioning artificial pacemaker); cardiogenic shock; concurrent use of ritonavir.
Monitoring Requirements	Monitor ECG, BP, heart rate, periodic serum trough concentrations, especially in patients with renal or hepatic impairment, concomitant administration of amiodarone and pediatric patients.

Precautions	**Disease-related concerns:** - AV block: If second- or third-degree AV block, or right bundle branch block associated with a left hemiblock occur, flecainide therapy should be discontinued unless a temporary or implanted ventricular pacemaker is in place to ensure an adequate ventricular rate. - Electrolyte imbalance: Correct electrolyte disturbances, especially hypokalemia or hypomagnesemia, prior to use and throughout therapy. - Hepatic impairment: Use with caution in patients with significant hepatic impairment; benefit should outweigh risk. Consider careful monitoring during initiation of therapy. Dose titration should occur only after steady state has been achieved (≥4 days after initiation). Frequent plasma level monitoring is required in patients with severe hepatic impairment; if unavailable, use is not recommended. - Renal impairment: Use with caution in patients with significant renal impairment. Frequent plasma level monitoring is required in patients with severe renal impairment; if unavailable, use is not recommended. - Structural or ischemic heart disease: According to the manufacturer, use with extreme caution in patients with

	structural heart disease as the risk of death and cardiac events may be increased. Avoid use in patients with structural or ischemic heart disease. **Other warnings/precautions:** - Pacemakers: Use with caution in patients with permanent pacemakers or temporary pacing wires; can increase endocardial pacing thresholds and suppress ventricular escape rhythms. Do not use in patients with existing poor thresholds or nonprogrammable pacemakers unless suitable pacing rescue is available. The pacing threshold in patients with pacemakers should be determined at baseline, 1 week after initiation and at regular intervals thereafter.
Black Box Warning	- Mortality - Ventricular proarrhythmic effects in patients with atrial fibrillation/flutter
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A thorough review of various HTA bodies including NICE, CADTH, HAS, IQWIG, and PBAC yielded **no recommendations for the use of flecainide for the treatment of arrhythmias.** Nevertheless, flecainide has been marketed worldwide for many years, and multiple generic options are available, leading to a low cost of treatment.

CONCLUSION STATEMENT – FLECAINIDE

Flecainide is an option for atrial flutter and ventricular arrhythmias. There are no recommendations issued by HTA bodies on the use of flecainide in atrial flutter and ventricular arrhythmias, however, it has been available on the market for years and multiple generics are available.

2.2 Class II Antiarrhythmic Agents

2.2.1 Metoprolol

Table 10. Metoprolol Drug Information

SCIENTIFIC NAME Metoprolol	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	No
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	I49
Drug Class	Antianginal Agent; Antihypertensive
Drug Sub-class	Beta-Blocker, Beta-1 Selective
ATC Code	C07AB02
Pharmacological Class (ASHP)	24:04.04.16 Class II Antiarrhythmics
DRUG INFORMATION	
Dosage Form	Tablet, Film-coated tablet
Route of Administration	Oral Use
Dose (Adult) [DDD]*	**Atrial fibrillation/flutter, maintenance of ventricular rate control (off-label use): Oral: Initial:** 2.5 to 5 mg once daily; increase dose gradually as tolerated to achieve ventricular rate control up to 20 mg once daily. **Ventricular arrhythmias (off- label use): Oral: Initial:** 2.5 mg once daily; titrate dose as needed based on response and tolerability up to a maximum dose of 10 mg once daily. **Atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, focal atrial tachycardia, multifocal atrial tachycardia (off-label use):** ✓ **Acute treatment:**

	○ IV: 2.5 to 5 mg over 2 minutes; repeat dose every 5 minutes as needed; maximum total dose: 15 mg. Note: Initiate cautiously in patients with concomitant heart failure. Avoid in patients with decompensated heart failure (electrical cardioversion preferred). ✓ **Maintenance therapy:** ○ Immediate release (metoprolol tartrate): Oral: Initial: 25 mg twice daily. ○ Extended release (metoprolol succinate): Oral: Initial: 50 mg once daily.
Maximum Daily Dose Adults*	**Atrial fibrillation/flutter, maintenance of ventricular rate control:** 20 mg once daily. **Ventricular arrhythmias:** 10 mg once daily. **Atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, focal atrial tachycardia, multifocal atrial tachycardia:** ○ Acute treatment: 15 mg/dose ○ Maintenance treatment: 400 mg/day
Dose (pediatrics)	**N/A**
Maximum Daily Dose Pediatrics*	**N/A**
Adjustment	**Adult** **<u>Renal Impairment:</u>** - Altered kidney function: Mild to severe impairment: No dosage adjustment necessary. - Hemodialysis, intermittent (thrice weekly): Dialyzable (metabolites): No dosage adjustment necessary.

	- Peritoneal dialysis: No dosage adjustment necessary. - CRRT: No dosage adjustment necessary. - PIRRT (eg, sustained, low-efficiency diafiltration): No dosage adjustment necessary **Hepatic Impairment:** There are no specific dosage adjustments provided in the manufacturer's labeling. Consider initiating with reduced doses and gradual dosage titration due to extensive hepatic metabolism.
Prescribing edits*	MD, ST
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Should be prescribed by a cardiologist.
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	It is considered as second-line therapy in patients with inappropriate sinus tachycardia.
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Bradycardia, hypotension. **Most serious**: Bradyarrhythmia, bronchospasm, CNS effects (fatigue, sleep disturbance, insomnia, vivid dreams, and memory impairment), withdrawal, masking of hypoglycemia, first-degree atrioventricular block, cerebrovascular accident.
Drug Interactions*	**Category X:** • Bromperidol

	• Etofylline • Fexinidazole • Rivastigmine • White Birch Allergen Extract
Special Population	N/A
Pregnancy	Metoprolol and the metabolite alpha-hydroxymetoprolol cross the placenta. Exposure to beta-blockers during pregnancy may increase the risk for adverse events in the neonate. If maternal use of a beta-blocker is needed, fetal growth should be monitored during pregnancy and the newborn should be monitored for 48 hours after delivery for bradycardia, hypoglycemia, and respiratory depression. The pharmacokinetics of metoprolol may be changed during pregnancy; the degree of changes may be dependent upon maternal CYP2D6 genotype. When treatment of hypertension in pregnancy is indicated, beta-blockers may be used. Specific recommendations vary by guideline, but use of metoprolol may be considered. Patients with preexisting hypertension may continue their medication during pregnancy unless contraindications exist. Metoprolol may be used for the treatment of maternal ventricular arrhythmias, atrial fibrillation/atrial flutter, or supraventricular tachycardia during pregnancy; consult current guidelines for specific recommendations.
Lactation	Metoprolol is present in breast milk. In general, breastfeeding is considered acceptable when the RID is <10%.

	The manufacturer recommends monitoring the breastfed infant for adverse events such as bradycardia; constipation; diarrhea; and dry mouth, skin, or eyes when metoprolol is administered to a mother who is a slow metabolizer. Use of a beta-blocker other than metoprolol may be preferred in lactating patients. In general, preventive treatment for migraine in lactating patients should be avoided. When needed, therapy should be individualized considering the available safety data and needs of the patient.
Contraindications	Hypersensitivity to metoprolol, any component of the formulation, or other beta-blockers; second- or third-degree heart block (except in patients with a functioning artificial pacemaker). - Immediate-release tablets/injectable formulation: Hypertension and angina (oral only): Sinus bradycardia; cardiogenic shock; overt heart failure; sick sinus syndrome (except in patients with a functioning artificial pacemaker); severe peripheral arterial circulatory disorders. Myocardial infarction (oral and injection): Severe sinus bradycardia (heart rate <45 beats/minute); significant first-degree heart block (P-R interval ≥0.24 seconds) (except in patients with a functioning artificial pacemaker); systolic blood pressure <100 mm Hg; moderate to severe cardiac failure.

	- Extended-release formulation: Severe bradycardia, cardiogenic shock; decompensated heart failure; sick sinus syndrome (except in patients with a functioning artificial pacemaker). Canadian labeling: Additional contraindications (not in US labeling): Cor pulmonale; untreated pheochromocytoma; asthma and other obstructive respiratory disease (injection only); concomitant use with anesthesia agents that cause myocardial depression.
Monitoring Requirements	Monitor ECG; heart rate; blood pressure; serum glucose (in patients with diabetes); mental alertness.
Precautions	**Concerns related to adverse events:** - Anaphylactic reactions: Use caution with history of severe anaphylaxis to allergens; patients taking beta-blockers may become more sensitive to repeated allergen challenges. Treatment of anaphylaxis (eg, epinephrine) in patients taking beta-blockers may be ineffective or promote undesirable effects. **Disease-related concerns:** - Diabetes: Use with caution in patients with diabetes mellitus; may potentiate hypoglycemia and/or mask signs and symptoms. - Heart failure with reduced ejection fraction: Stabilize patients on heart failure regimen prior to initiation or titration of beta-blocker. Beta-blocker therapy should be initiated at

	very low doses with gradual and careful titration. Worsening heart failure or fluid retention may occur during upward titration; dose reduction and/or slower titration may be necessary. Adjustment of other medications (angiotensin-converting enzyme inhibitors and/or diuretics) may be required. Only the ER formulation is indicated for use in heart failure. - Hepatic impairment: Use with caution in patients with hepatic impairment. - Myasthenia gravis: Use beta-blockers with caution in patients with myasthenia gravis. - Peripheral vascular disease (PVD) and Raynaud disease: May precipitate or aggravate symptoms of arterial insufficiency in patients with PVD and Raynaud disease. Use with caution and monitor for progression of arterial obstruction. - Pheochromocytoma (untreated): Adequate alpha-blockade is required prior to use of any beta-blocker. - Prinzmetal variant angina: Beta-blockers without alpha1-adrenergic receptor blocking activity should be avoided in patients with Prinzmetal variant angina because unopposed alpha1-adrenergic receptors mediate coronary vasoconstriction and can worsen anginal symptoms (Mayer 1998).

	- Psoriasis: Beta-blocker use has been associated with induction or exacerbation of psoriasis, but cause and effect have not been firmly established. - Supraventricular tachycardia (SVT): If antidromic atrioventricular reentrant tachycardia (AVRT) or pre-excited atrial fibrillation is suspected, avoid AV node-specific blocking drugs (eg, adenosine, diltiazem, verapamil, digoxin, beta-blockers). For these types of SVT enhanced antegrade conduction from atria to ventricles may occur through an accessory pathway leading to ventricular arrhythmias if the AV node is blocked. It is safe to use AV node-specific blocking drugs for orthodromic AVRT because antegrade conduction occurs through the AV node and only retrograde conduction (from ventricles to atria) occurs through the accessory pathway. - Thyroid disease: May mask signs of hyperthyroidism (eg, tachycardia). If hyperthyroidism is suspected, carefully manage and monitor; abrupt withdrawal may exacerbate symptoms of hyperthyroidism or precipitate thyroid storm. Alterations in thyroid function tests may be observed. **Other warnings/precautions:** - Abrupt withdrawal: Abrupt withdrawal may exacerbate underlying conditions, such as

	angina pectoris, sinus tachycardia, hypertension, and arrhythmias; cases of myocardial infarction have also occurred. - Major surgery: Chronic beta-blocker therapy should not be routinely withdrawn prior to major surgery.
Black Box Warning	Ischemic heart disease (metoprolol tartrate [oral])
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A thorough review of various HTA bodies including NICE, CADTH, HAS, IQWIG, and PBAC yielded **no recommendations for the use of metoprolol for the treatment of arrhythmias.** Nevertheless, metoprolol has been marketed worldwide for many years, and multiple generic options are available, leading to a low cost of treatment.

CONCLUSION STATEMENT – METOPROLOL

Metoprolol is recommended for the use in patients with atrial flutter, atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, focal atrial tachycardia, multifocal atrial tachycardia, and ventricular arrhythmias.

There are no recommendations issued by HTA bodies on the use of metoprolol in these indications, however, it has been available on the market for years and multiple generics are available.

2.2.2 Propranolol

Table 11. Propranolol Drug Information

SCIENTIFIC NAME Propranolol	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	I49

Drug Class	Antiarrhythmic
Drug Sub-class	Class Ic
ATC Code	C07AA05
Pharmacological Class (ASHP)	24:04.04.16 Class II Antiarrhythmics
DRUG INFORMATION	
Dosage Form	Tablet, Solution, Oral solution
Route of Administration	Oral Use, Intravenous use
Dose (Adult) [DDD]*	**Atrial fibrillation/flutter:** - **Acute ventricular rate control (alternative agent):** o IV: 1 mg over 1 minute; repeat as needed every 2 minutes up to a maximum of 3 doses. - **Maintenance of ventricular rate control:** o Immediate release: Oral: Initial: 10 mg 3 to 4 times daily; increase dose gradually as tolerated to achieve ventricular rate control up to 40 mg 3 to 4 times daily. o Extended release: Oral: 60 mg once daily; increase dose gradually as tolerated to achieve ventricular rate control up to 160 mg once daily. **Atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, focal atrial tachycardia):** - Acute treatment (alternative agent) (off-label dose): IV: Initial: 1 mg over 1 minute; repeat as needed every 2 minutes up to 3 doses. - Maintenance therapy (off-label use): Immediate release: Oral: Initial: 30 to 60

	mg/day in 2 or 3 divided doses titrated to effect; maximum recommended dose: 160 mg/day. **Ventricular arrhythmias** - **Nonsustained ventricular tachycardia or ventricular premature beats, symptomatic:** o Immediate release: **Oral:** Initial: 10 to 40 mg every 6 hours; adjust dose as needed based on patient response and tolerability. Some experts recommend initiating 10 mg every 8 to 12 hours; then titrate based on response and tolerability to the lowest effective dose that alleviates symptoms. o Extended release: **Oral:** Initial: 80 mg once daily; then titrate based on response and tolerability to the lowest effective dose that alleviates symptoms.
Maximum Daily Dose Adults*	- **Acute ventricular rate control:** maximum of 3 doses. - **Maintenance of ventricular rate control:** Immediate release: 160 mg once daily. - **Atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, focal atrial tachycardia): 160 mg/day** - **Ventricular arrhythmias:** 320 mg/day.

Dose (pediatrics)	**Tachyarrhythmias: Limited data available: Infants, Children, and Adolescents:** - Oral: Immediate-release formulations: Initial: 0.5 to 1 mg/kg/day in divided doses every 6 to 8 hours; titrate dosage upward every 3 to 5 days; usual daily dose: 2 to 4 mg/kg/day; higher doses may be needed; maximum daily dose: 16 mg/kg/day or 60 mg/day. - IV: 0.01 to 0.15 mg/kg/dose slow IV over 10 minutes; may repeat every 6 to 8 hours as needed;
Maximum Daily Dose Pediatrics*	Maximum dose is age-dependent: Infants: 1 mg/dose; children and adolescents: 3 mg/dose.
Adjustment	**Adult** **<u>Renal Impairment:</u>** - **Altered kidney function:** No dosage adjustment necessary for any degree of kidney dysfunction; use with caution, particularly in patients with more advanced kidney impairment, as decreased hepatic extraction has been reported and patients may be more prone to adverse effects when initiating therapy. - **Hemodialysis, intermittent (thrice weekly):** Not significantly dialyzed : No supplemental dose or dosage adjustment necessary ; use with caution. - **Peritoneal dialysis:** Unlikely to be significantly dialyzed (large Vd): No dosage adjustment necessary; use with caution. - **CRRT:** No dosage adjustment necessary.

	- **PIRRT (eg, sustained, low-efficiency diafiltration):** No dosage adjustment necessary. **<u>Hepatic Impairment:</u>** There are no dosage adjustments provided in the manufacturer's labeling. However, hepatic impairment increases systemic exposure to propranolol. Use with caution. **Pediatric** **<u>Renal Impairment:</u>** Immediate-release formulations: Not dialyzable. There are no dosage adjustments provided in the manufacturer's labeling; however, renal impairment increases systemic exposure to propranolol. Use with caution. **<u>Hepatic Impairment:</u>** Immediate-release formulations: There are no dosage adjustments provided in the manufacturer's labeling; however, propranolol is extensively metabolized by the liver; hepatic impairment increases systemic exposure to propranolol. Use with caution.
Prescribing edits*	MD, ST
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Should be prescribed by a cardiologist.
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	It is considered as second-line therapy in patients with inappropriate sinus tachycardia.
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A

SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Sleep disorder, bronchiolitis (infants), bronchitis. **Most serious**: Bradyarrhythmia, bronchospasm, CNS effects (fatigue, sleep disturbance, insomnia, vivid dreams, and memory impairment), withdrawal, masking of hypoglycemia, first-degree atrioventricular block, cerebrovascular accident.
Drug Interactions*	**Category X:** • Beta2-Agonists • Bromperidol • Etofylline • Fexinidazole • Fezolinetant • Rivastigmine • Thioridazine • White Birch Allergen Extract
Special Population	Smokers: Cigarette smoking may decrease plasma levels of propranolol by increasing metabolism. Patients should be advised to avoid smoking.
Pregnancy	Propranolol crosses the placenta. Exposure to beta-blockers during the third trimester of pregnancy may increase the risk for bradycardia, hypoglycemia, hypotension, and respiratory depression in the neonate. Newborns should be monitored and managed accordingly. If maternal use of a beta-blocker is needed, fetal growth should be monitored during pregnancy and the newborn should be monitored for 48 hours after delivery for bradycardia, hypoglycemia, and respiratory depression. The pharmacokinetics of propranolol are not significantly changed by pregnancy.

	Propranolol may be used for the treatment of maternal ventricular arrhythmias, atrial fibrillation/atrial flutter, or supraventricular tachycardia during pregnancy; consult current guidelines for specific recommendations.
Lactation	Propranolol and its inactive metabolites are present in breast milk. In general, propranolol may be compatible with breastfeeding when used at usual doses. Breastfeeding infants should be monitored for bradycardia, cyanosis, and hypoglycemia.
Contraindications	- Hypersensitivity to propranolol, beta-blockers, or any component of the formulation; uncompensated heart failure (unless the failure is due to tachyarrhythmias being treated with propranolol); cardiogenic shock; severe sinus bradycardia, sick sinus syndrome, or heart block greater than first-degree (except in patients with a functioning artificial pacemaker); bronchial asthma. - *Canadian labeling:* Additional contraindications (not in US labeling): Bronchospasm; right ventricular failure secondary to pulmonary hypertension; allergic rhinitis during pollen season; patients prone to hypoglycemia; hypotension (BP parameters not specified in labeling); metabolic acidosis; vasospastic angina (also referred to as Prinzmetal angina or variant angina); severe peripheral arterial circulatory

	disturbance; untreated pheochromocytoma; hereditary problems of galactose intolerance, glucose-galactose malabsorption, or congenital lactase deficiency (lactose-containing products only).
Monitoring Requirements	- Acute cardiac treatment: ECG, heart rate, and blood pressure. - Hypertension: Blood pressure, heart rate. - Mental alertness; signs and symptoms of bronchospasm in patients with existing bronchospastic disease; serum glucose (in patients with diabetes).
Precautions	**Concerns related to adverse events:** - Anaphylactic reactions: Use caution with history of severe anaphylaxis to allergens; patients taking beta-blockers may become more sensitive to repeated challenges. Treatment of anaphylaxis (eg, epinephrine) in patients taking beta-blockers may be ineffective or promote undesirable effects. **Disease-related concerns:** - Heart failure: Use with caution in patients with compensated heart failure and monitor for a worsening of the condition (efficacy of propranolol in heart failure has not been demonstrated). - Hepatic impairment: Use with caution in patients with hepatic impairment; dosage adjustment may be required.

	- Myasthenia gravis: Use with caution in patients with myasthenia gravis. - Peripheral vascular disease and Raynaud disease: Can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease and Raynaud disease. Use with caution and monitor for progression of arterial obstruction. - Pheochromocytoma (untreated): Adequate alpha-blockade is required prior to use of any beta-blocker. - Psoriasis: Beta-blocker use has been associated with induction or exacerbation of psoriasis, but cause and effect have not been firmly established. - Renal impairment: Use with caution in patients with advanced renal impairment during initiation of therapy, as decreased hepatic extraction may result in elevated propranolol concentrations and increase the risk of side effects. - Thyroid disease: May mask signs of hyperthyroidism (eg, tachycardia). If thyrotoxicosis is suspected, carefully manage and monitor; abrupt withdrawal may exacerbate symptoms of hyperthyroidism or precipitate thyroid storm. Alterations in thyroid function tests may be observed. - Vasospastic angina: Beta-blockers without alpha-1

	adrenergic receptor blocking activity should be avoided in patients with vasospastic angina since unopposed alpha-1 adrenergic receptors mediate coronary vasoconstriction and can worsen anginal symptoms. **Other warnings/precautions:** - Major surgery: Chronic beta-blocker therapy should not be routinely withdrawn prior to major surgery.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A thorough review of various HTA bodies including NICE, CADTH, HAS, IQWIG, and PBAC yielded **no recommendations for the use of propranolol for the treatment of arrhythmias.** Nevertheless, propranolol has been marketed worldwide for many years, and multiple generic options are available, leading to a low cost of treatment.

CONCLUSION STATEMENT – PROPRANOLOL

Propranolol is recommended for the use in patients with atrial flutter, atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, focal atrial tachycardia, multifocal atrial tachycardia, and ventricular arrhythmias.

There are no recommendations issued by HTA bodies on the use of propranolol in these indications, however, it has been available on the market for years and multiple generics are available.

2.2.3 Bisoprolol

Table 12. Bisoprolol Drug Information

SCIENTIFIC NAME **Bisoprolol**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	No

MHRA	Yes
PMDA	Yes
Indication (ICD-10)	I49
Drug Class	Antihypertensive
Drug Sub-class	Beta-blocker, Beta-1 Selective
ATC Code	C07AB07
Pharmacological Class (ASHP)	24:04.04.16 Class II Antiarrhythmics
DRUG INFORMATION	
Dosage Form	Tablet, Film-coated tablet
Route of Administration	Oral Use
Dose (Adult) [DDD]*	- **Atrial fibrillation/flutter, maintenance of ventricular rate control (off-label use):** Oral: Initial: 2.5 to 5 mg once daily; increase dose gradually as tolerated to achieve ventricular rate control up to 20 mg once daily. - **Ventricular arrhythmias (off- label use):** **Oral:** Initial: 2.5 mg once daily; titrate dose as needed based on response and tolerability up to a maximum dose of 10 mg once daily.
Maximum Daily Dose Adults*	- **Atrial fibrillation/flutter, maintenance of ventricular rate control:** 20 mg once daily. - **Ventricular arrhythmias:** 10 mg once daily.
Dose (pediatrics)	**N/A**
Maximum Daily Dose Pediatrics*	**N/A**
Adjustment	**<u>Renal Impairment:</u>** **Altered kidney function:** o CrCl ≥20 mL/minute/1.73 m2: No dosage adjustment necessary. o CrCl <20 mL/minute/1.73 m2: Start with low initial doses (eg, 1.25 to 2.5 mg daily, depending on

	indication); consider a reduced maximum dose of 10 mg daily. **Hemodialysis, intermittent (thrice weekly): Moderately dialyzable (25% to 35%):** Initial: 1.25 to 2.5 mg daily, depending on indication; consider a reduced maximum dose of 10 mg daily. When scheduled dose falls on a hemodialysis day, administer dose after hemodialysis. **Peritoneal dialysis:** Slightly dialyzable: Initial 1.25 to 2.5 mg daily, depending on indication; consider a reduced maximum dose of 10 mg daily. **CRRT:** Initial 1.25 to 2.5 mg daily, depending on indication; consider a reduced maximum dose of 10 mg daily. **PIRRT (eg, sustained, low-efficiency diafiltration):** Initial 1.25 to 2.5 mg daily, depending on indication; consider a reduced maximum dose of 10 mg daily. **Hepatic Impairment:** Hepatitis or cirrhosis: Initial: 2.5 mg once daily; increase cautiously.
Prescribing edits*	MD, AGE, ST
AGE (Age Edit)	Bisoprolol is only used in adults.
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Should be prescribed by a cardiologist.
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	It is considered as second-line therapy in patients with ventricular arrhythmias.
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Chest pain, diarrhea, vomiting, fatigue, hypoesthesia,

	dyspnea, upper respiratory tract infection. **Most serious**: Bradyarrhythmia, bronchospasm, CNS effects (fatigue, sleep disturbance, insomnia, vivid dreams, and memory impairment), withdrawal, masking of hypoglycemia, hypotension, thrombocytopenia, increased serum alanine transferase.
Drug Interactions*	**Category X:** • Bromperidol • Etofylline • Fexinidazole • Rivastigmine • White Birch Allergen Extract
Special Population	Older adult: Dosage reductions may be necessary.
Pregnancy	Outcome data following maternal use of bisoprolol during pregnancy are limited compared to other beta-1 selective beta-blockers. Exposure to beta-blockers during pregnancy may increase the risk for adverse events in the neonate. If maternal use of a beta-blocker is needed, monitor fetal growth during pregnancy; monitor the newborn for 48 hours after delivery for bradycardia, hypoglycemia, and respiratory depression.
Lactation	It is not known if bisoprolol is present in breast milk. Bisoprolol 5 mg/day was initiated in one patient 5 days postpartum. Bisoprolol was not detected in breast milk sampled 11 and 18 days later (lower limit of quantification 1 ng/mL). The manufacturer recommends that caution be exercised when administering bisoprolol to

	breastfeeding patients. Use of a beta-blocker other than bisoprolol may be preferred in lactating patients.
Contraindications	- Cardiogenic shock; overt cardiac failure; marked sinus bradycardia or heart block greater than first-degree (except in patients with a functioning artificial pacemaker). - Canadian labeling: Additional contraindications (not in US labeling): Hypersensitivity to bisoprolol or any component of the formulation; overt cardiac failure requiring IV inotropic therapy; sick sinus syndrome or sinoatrial block; hypotension (systolic BP <100 mm Hg); severe bronchial asthma or chronic obstructive pulmonary disease; peripheral arterial occlusive disease (late stages); Raynaud syndrome; pheochromocytoma (untreated); metabolic acidosis.
Monitoring Requirements	Monitor Blood pressure, heart rate, ECG; serum glucose (in patients with diabetes); signs and symptoms of bronchospasm (in patients with preexisting bronchospastic disease); mental alertness.
Precautions	**Disease-related concerns:** - Anaphylaxis reactions: Beta-blockers are unlikely to cause anaphylaxis; however, in susceptible patients, beta-blockers have been associated with an increase in the severity of anaphylaxis. Anaphylaxis in the presence of a beta-blocker may be severe, protracted, and resistant to conventional treatment. This is due to beta-2-

	adrenergic blockade and the resulting diminution of endogenous catecholamine effect. - Heart failure with reduced ejection fraction: Stabilize patients on heart failure regimen prior to initiation or titration of beta-blocker. Beta-blocker therapy should be initiated at very low doses with gradual and careful titration. Worsening heart failure or fluid retention may occur during upward titration; dose reduction and/or slower titration may be necessary. Adjustment of other medications (ACE inhibitors and/or diuretics) may be required. - Hepatic impairment: Use with caution in patients with hepatic impairment; dosage adjustment may be required. - Kidney impairment: Use with caution in patients with kidney impairment; dosage adjustment may be required. - Myasthenia gravis: Use with caution in patients with myasthenia gravis. - Peripheral vascular disease (PVD) and Raynaud disease: Can precipitate or aggravate symptoms of arterial insufficiency in patients with PVD and Raynaud disease. Use with caution and monitor for progression of arterial obstruction. - Pheochromocytoma (untreated): Adequate alpha-blockade is

	required prior to use of any beta-blocker. - Psoriasis: Beta-blocker use has been associated with induction or exacerbation of psoriasis, but cause and effect have not been firmly established. - Thyroid disease: May mask signs of hyperthyroidism (eg, tachycardia). If hyperthyroidism is suspected, carefully manage and monitor; abrupt withdrawal may precipitate thyroid storm. - Vasospastic angina: Beta-blockers without alpha1-adrenergic receptor blocking activity should be avoided in patients with vasospastic angina since unopposed alpha1-adrenergic receptors mediate coronary vasoconstriction and can worsen anginal symptoms. **Other warnings/precautions:** - Abrupt withdrawal: Beta-blocker therapy should not be withdrawn abruptly (particularly in patients with CAD), but gradually tapered to avoid acute tachycardia, hypertension, and/or ischemia. - Major surgery: Chronic beta-blocker therapy should not be routinely withdrawn prior to major surgery.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A thorough review of various HTA bodies including NICE, CADTH, HAS, IQWIG, and PBAC yielded **no recommendations for the use of bisoprolol for the treatment of**

arrhythmias. Nevertheless, bisoprolol has been marketed worldwide for many years, and multiple generic options are available, leading to a low cost of treatment.

CONCLUSION STATEMENT – BISOPROLOL

Bisoprolol is recommended for use in patients with atrial flutter and ventricular arrhythmias.

There are no recommendations issued by HTA bodies on the use of bisoprolol in these indications, however, it has been available on the market for years and multiple generics are available.

2.2.4 Carvedilol

Table 13. Carvedilol Drug Information

SCIENTIFIC NAME Carvedilol	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	No
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	I49
Drug Class	Antihypertensive
Drug Sub-class	Beta-Blocker With Alpha-Blocking Activity
ATC Code	C07AG02
Pharmacological Class (ASHP)	24:04.04.16 Class II Antiarrhythmics
DRUG INFORMATION	
Dosage Form	Tablet, Film-coated tablet
Route of Administration	Oral Use
Dose (Adult) [DDD]*	- **Atrial fibrillation/flutter, maintenance of ventricular rate control (off-label use):** Immediate release: Oral: Initial: 3.125 mg twice daily; increase dose as tolerated to achieve ventricular rate control up to 25 mg twice daily.

	- **Nonsustained ventricular tachycardia or ventricular premature beats, symptomatic (off-label use):** Immediate release: Oral: Initial: 3.125 mg twice daily; titrate as needed based on response and tolerability up to 25 mg twice daily.
Maximum Daily Dose Adults*	50 mg/day
Dose (pediatrics)	**N/A**
Maximum Daily Dose Pediatrics*	**N/A**
Adjustment	**<u>Renal Impairment:</u>** - **Mild to severe impairment:** No dosage adjustment necessary. - **Hemodialysis, intermittent (thrice weekly):** Poorly dialyzed; no supplemental dose or dosage adjustment necessary. - **Peritoneal dialysis:** Unlikely to be dialyzed; no dosage adjustment necessary (expert opinion). - **CRRT:** No dosage adjustment necessary. - **PIRRT (eg, sustained, low-efficiency diafiltration):** No dosage adjustment necessary. **<u>Hepatic Impairment:</u>** - Mild to moderate impairment: There are no dosage adjustments provided in the manufacturer's labeling; dose conservatively and interrupt therapy in the setting of hypotension (eg, mean arterial pressure [MAP] <65 mm Hg), acute kidney injury, or hyponatremia. - Severe impairment: Use is contraindicated per

	manufacturer; however, experts will use if indicated (eg, for variceal hemorrhage prophylaxis); dose conservatively and interrupt therapy in the setting of hypotension (eg, MAP <65 mm Hg), acute kidney injury, or hyponatremia.
Prescribing edits*	MD, ST
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Should be prescribed by a cardiologist.
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	It is considered as second-line therapy in patients with ventricular arrhythmias.
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Hypotension, orthostatic hypotension, hyperglycemia, weight gain, diarrhea, asthenia, dizziness, fatigue. **Most serious**: Bradyarrhythmia, bronchospasm, CNS effects (fatigue, sleep disturbance, insomnia, vivid dreams, and memory impairment), withdrawal, masking of hypoglycemia, atrioventricular block, diabetes mellitus, thrombocytopenia, increased hepatic enzymes, cerebrovascular accident, increased blood urea nitrogen, increased serum creatinine, kidney impairment.
Drug Interactions*	**Category X:** • Beta2-Agonists • Bilastine • Bromperidol

	• DOXOrubicin (Conventional) • Etofylline • Fexinidazole • PAZOPanib • Repotrectinib • Rivastigmine • Sirolimus (Protein Bound) • Topotecan • VinCRIStine (Liposomal) • White Birch Allergen Extract
Special Population	Older adult: Bradycardia may be observed more frequently in elderly patients (>65 years of age); dosage reductions may be necessary.
Pregnancy	Exposure to beta-blockers during pregnancy may increase the risk for adverse events in the neonate. If maternal use of a beta-blocker is needed, monitor fetal growth during pregnancy; monitor the newborn for 48 hours after delivery for bradycardia, hypoglycemia, and respiratory depression.
Lactation	It is not known if carvedilol is present in breast milk. According to the manufacturer, the decision to continue or discontinue breastfeeding during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother. Use of a beta-blocker other than carvedilol may be preferred in lactating patients.
Contraindications	- Serious hypersensitivity to carvedilol or any component of the formulation; decompensated cardiac failure requiring intravenous inotropic therapy; bronchial asthma or related

	bronchospastic conditions; second- or third-degree AV block, sick sinus syndrome, or severe bradycardia (except in patients with a functioning artificial pacemaker); cardiogenic shock; severe hepatic impairment - Canadian labeling: Additional contraindications (not in US labeling): Severe hypotension; primary obstructive valvular heart disease; mental incapacity (e.g., severe Alzheimer disease, alcoholism, drug abuse), unless closely supervised by an appropriate caregiver.
Monitoring Requirements	Monitor ECG, heart rate, blood pressure; kidney function; liver function; blood glucose in patients with diabetes; signs and symptoms of bronchospasm in patients with existing bronchospastic disease; mental alertness.
Precautions	**Concerns related to adverse effects:** - Anaphylactic reactions: Use caution with history of severe anaphylaxis to allergens; patients taking beta-blockers may become more sensitive to repeated challenges. Treatment of anaphylaxis (eg, epinephrine) in patients taking beta-blockers may be ineffective or promote undesirable effects. - Bradycardia: May occur; reduce dosage if heart rate drops to <55 beats/minute. - Floppy iris syndrome: Intraoperative floppy iris syndrome has been observed in cataract surgery patients who were on or were previously

	treated with alpha1-blockers; there appears to be no benefit in discontinuing alpha-blocker therapy prior to surgery. Instruct patients to inform ophthalmologist of carvedilol use when considering eye surgery. - Hypotension/syncope: Symptomatic hypotension with or without syncope may occur with carvedilol (usually within the first 30 days of therapy); close monitoring of patient is required especially with initial dosing and dosing increases; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. Initiation with a low dose, gradual up-titration, and administration with food may help to decrease the occurrence of hypotension or syncope. Advise patients to avoid driving or other hazardous tasks during initiation of therapy due to the risk of syncope. **Disease-related concerns:** - Angina: Use with caution in patients suspected of having vasospastic angina. - Bronchospastic disease: In general, patients with bronchospastic disease should not receive beta-blockers; if used at all, should be used cautiously with close monitoring. - Diabetes: Use with caution in patients with diabetes mellitus; may potentiate hypoglycemia and/or mask signs and symptoms (eg, sweating, anxiety,

	tachycardia). In patients with heart failure and diabetes, use of carvedilol may worsen hyperglycemia; may require adjustment of antidiabetic agents. - Heart failure with reduced ejection fraction: Stabilize patients on heart failure regimen prior to initiation or titration of beta-blocker. Beta-blocker therapy should be initiated at very low doses with gradual and careful titration. Worsening heart failure or fluid retention may occur during upward titration; dose reduction and/or slower titration may be necessary. Adjustment of other medications (ACE inhibitors and/or diuretics) may also be required. - Myasthenia gravis: Use with caution in patients with myasthenia gravis. - Peripheral vascular disease (PVD): May precipitate or aggravate symptoms of arterial insufficiency in patients with PVD; use with caution and monitor for progression of arterial obstruction. - Pheochromocytoma (untreated): Use with caution; adequate alpha-blockade should be initiated prior to use of any beta-blocker. - Psoriasis: Beta-blocker use has been associated with induction or exacerbation of psoriasis, but cause and effect have not been firmly established.

	- Thyroid disease: May mask signs of hyperthyroidism (eg, tachycardia). If hyperthyroidism is suspected, carefully manage and monitor; abrupt withdrawal may exacerbate symptoms of hyperthyroidism or precipitate thyroid storm. **Other warnings/precautions:** - Abrupt withdrawal: Beta-blocker therapy should not be withdrawn abruptly (particularly in patients with CAD), but gradually tapered to avoid acute tachycardia, hypertension, and/or ischemia. Severe exacerbation of angina, ventricular arrhythmias, and myocardial infarction (MI) have been reported following abrupt withdrawal of beta-blocker therapy. Temporary and prompt resumption of beta-blocker therapy may be indicated with worsening of angina or acute coronary insufficiency. - Major surgery: Chronic beta-blocker therapy should not be routinely withdrawn prior to major surgery.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A thorough review of various HTA bodies including NICE, CADTH, HAS, IQWIG, and PBAC yielded **no recommendations for the use of carvedilol for the treatment of arrhythmias.** Nevertheless, carvedilol has been marketed worldwide for many years, and multiple generic options are available, leading to a low cost of treatment.

CONCLUSION STATEMENT – CARVEDILOL

Carvedilol is recommended for use in patients with atrial flutter and ventricular arrhythmias.

There are no recommendations issued by HTA bodies on the use of carvedilol in these indications, however, it has been available on the market for years and multiple generics are available.

2.2.5 Atenolol

Table 14. Atenolol Drug Information

SCIENTIFIC NAME Atenolol	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	No
MHRA	Yes
PMDA	No
Indication (ICD-10)	I49
Drug Class	Antihypertensive; Antianginal
Drug Sub-class	Beta-Blocker, Beta-1 selective
ATC Code	C07AB03
Pharmacological Class (ASHP)	24:04.04.16 Class II Antiarrhythmics
DRUG INFORMATION	
Dosage Form	Tablet, Film-coated tablet
Route of Administration	Oral Use
Dose (Adult) [DDD]*	- **Atrial fibrillation/flutter, maintenance of ventricular rate control (off-label use):** Oral: Initial: 25 mg once daily; increase dose gradually as tolerated to achieve ventricular rate control up to 100 mg once daily. - **Atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, focal atrial tachycardia, multifactorial**

	atrial tachycardia, maintenance of ventricular rate control (off-label use): Oral: Initial: 25 to 50 mg once daily; titrate based on response and tolerability. - **Ventricular arrhythmia or ventricular premature beats (symptomatic), prevention (off-label use):** Oral: Initial: 25 mg once daily; titrate dose as needed based on response and tolerability up to a maximum dose of 200 mg/day in 1 or 2 divided doses; usual dosage range: 25 to 100 mg/day.
Maximum Daily Dose Adults*	- **Atrial fibrillation/flutter, maintenance of ventricular rate control:** 100 mg/day - **Atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, focal atrial tachycardia, multifactorial atrial tachycardia, maintenance of ventricular rate control:** 100 mg/day - **Ventricular arrhythmia or ventricular premature beats (symptomatic), prevention:** 200 mg/day
Dose (pediatrics)	**N/A**
Maximum Daily Dose Pediatrics*	**N/A**
Adjustment	**<u>Renal Impairment:</u>** **Altered kidney function:** o CrCl >30 mL/minute: No dosage adjustment necessary. o CrCl 10 to 30 mL/minute: Maximum dose: 50 mg daily. o CrCl <10 mL/minute: Maximum dose: 25 mg daily.

	Hemodialysis, intermittent (thrice weekly): Moderately dialyzable (20% to 50%): ○ Daily dosing: 25 to 50 mg daily; when scheduled dose falls on a dialysis day, administer post dialysis. ○ Three times weekly (post dialysis) dosing: Initial: 25 to 50 mg 3 times weekly administered post dialysis on dialysis days; titrate based on patient response to a maximum of 100 mg 3 times weekly administered post dialysis on dialysis days. **Peritoneal dialysis:** Not significantly dialyzed: Maximum: 25 mg daily. **Hepatic Impairment:** There are no dosage adjustments provided in the manufacturer's labeling; however, atenolol undergoes minimal hepatic metabolism.
Prescribing edits*	MD, ST
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Should be prescribed by a cardiologist.
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	It is considered as second-line therapy in patients with ventricular arrhythmias.
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Bradycardia, hypotension, supraventricular tachycardia, ventricular tachycardia. **Most serious**: Bundle branch block, heart block, bronchospasm, cardiogenic shock, renal failure syndrome.

Drug Interactions*	**<u>Category X:</u>** • Bromperidol • Etofylline • Fexinidazole • Rivastigmine • White Birch Allergen Extract
Special Population	N/A
Pregnancy	Atenolol crosses the placenta and is found in cord blood. Maternal use of atenolol may cause harm to the fetus. Adverse events, such as bradycardia, hypoglycemia, and reduced birth weight, have been observed following in utero exposure to atenolol. If maternal use of a beta-blocker is needed, fetal growth should be monitored during pregnancy and the newborn should be monitored for 48 hours after delivery for bradycardia, hypoglycemia, and respiratory depression. The maternal pharmacokinetic parameters of atenolol during the second and third trimesters are within the ranges reported in nonpregnant patients.
Lactation	Atenolol is present in breast milk. Bradycardia has been observed in some breastfeeding infants and neonates may also be at risk for hypoglycemia. Adverse events may be more likely in premature infants or infants with impaired renal function. Atenolol can be detected in the plasma of breastfeeding infants not previously exposed during pregnancy. The manufacturer recommends that caution be exercised when administering atenolol to patients who are breastfeeding. Use of a beta-blocker

	other than atenolol may be preferred in patients who are breastfeeding.
Contraindications	Hypersensitivity to atenolol or any component of the formulation; sinus bradycardia; heart block greater than first-degree (except in patients with a functioning artificial pacemaker); cardiogenic shock; uncompensated cardiac failure. Canadian labeling: Additional contraindications (not in US labeling): Bradycardia (regardless of origin); cor pulmonale; hypotension; severe peripheral arterial disorders; anesthesia with agents that produce myocardial depression; Pheochromocytoma (in the absence of alpha-blockade); metabolic acidosis.
Monitoring Requirements	Monitor BP; heart rate; mental alertness; signs and symptoms of bronchospasm in patients with existing bronchospastic disease; serum glucose (in patients with diabetes); kidney function.
Precautions	**Disease-related concerns:** - Anaphylaxis: Beta-blockers are unlikely to cause anaphylaxis; however, in susceptible patients, beta-blockers have been associated with an increase in the severity of anaphylaxis. Anaphylaxis in the presence of a beta-blocker may be severe, protracted, and resistant to conventional treatment. - Heart failure: Stabilize patients on heart failure regimen prior to initiation or titration of beta-blocker. Beta-blocker therapy should be initiated at very low doses with gradual and very careful titration. Adjustment of

	other medications (angiotensin-converting enzyme inhibitors and/or diuretics) may be required. Efficacy of atenolol in heart failure has not been demonstrated as with other beta-blockers. - Myasthenia gravis: Use with caution in patients with myasthenia gravis. - Peripheral vascular disease (PVD) and Raynaud disease: May precipitate or aggravate symptoms of arterial insufficiency in patients with PVD and Raynaud disease. Use with caution and monitor for progression of arterial obstruction. - Pheochromocytoma (untreated): Adequate alpha-blockade is required prior to use of any beta-blocker. - Psoriasis: Beta-blocker use has been associated with induction or exacerbation of psoriasis, but cause and effect have not been firmly established. - Renal impairment: Use with caution in patients with renal impairment; dosage adjustment required. - Thyroid disease: May mask signs of hyperthyroidism (e.g., tachycardia). If hyperthyroidism is suspected, carefully manage and monitor; abrupt withdrawal may precipitate thyroid storm. Alterations in thyroid function tests may be observed.

	- Vasospastic angina: Beta-blockers without alpha$_1$-adrenergic receptor blocking activity should be avoided in patients with Prinzmetal variant angina since unopposed alpha1-adrenergic receptors mediate coronary vasoconstriction and can worsen anginal symptoms. **Other warnings/precautions:** - Major surgery: Chronic beta-blocker therapy should not be routinely withdrawn prior to major surgery.
Black Box Warning	Cessation of therapy
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A thorough review of various HTA bodies including NICE, CADTH, HAS, IQWIG, and PBAC yielded **no recommendations for the use of atenolol for the treatment of arrhythmias.** Nevertheless, atenolol has been marketed worldwide for many years, and multiple generic options are available, leading to a low cost of treatment.

CONCLUSION STATEMENT – ATENOLOL

Atenolol is recommended for use in patients with atrial flutter, atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, focal atrial tachycardia, multifactorial atrial tachycardia and Ventricular arrhythmia or ventricular premature beats.

There are no recommendations issued by HTA bodies on the use of atenolol in these indications, however, it has been available on the market for years and multiple generics are available.

2.2.6 Esmolol

Table 15. Esmolol Drug Information

SCIENTIFIC NAME Esmolol	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	No
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	I49
Drug Class	Antiarrhythmic agent
Drug Sub-class	Class II, Beta-Blocker, Beta-1 Selective
ATC Code	C07AA05
Pharmacological Class (ASHP)	24:04.04.16 Class II Antiarrhythmics
DRUG INFORMATION	
Dosage Form	Solution, Solution for infusion, Solution for injection.
Route of Administration	Intravenous use
Dose (Adult) [DDD]*	**Atrial fibrillation/flutter, acute ventricular rate control:** ○ Loading doses (optional): **IV:** 500 mcg/kg over 1 minute followed by a continuous infusion; may administer repeat bolus doses of 500 mcg/kg prior to each increase in continuous infusion rate in order to achieve a more rapid response. ○ Continuous infusion: **IV:** Initial: 50 mcg/kg/minute; for inadequate response, may increase in increments of 50 mcg/kg/minute at ≥4-minute intervals up to a maximum of 300 mcg/kg/minute. To achieve a more rapid response, administer a repeat bolus before increasing the continuous

	infusion rate. In the absence of a bolus, the effects of continuous infusion rate changes may not be evident for up to 30 minutes. **Sinus tachycardia, inappropriate, noncompensatory:** ○ Loading doses (optional): **IV:** 500 mcg/kg over 1 minute followed by a continuous infusion; may administer repeat bolus doses of 500 mcg/kg prior to each increase in continuous infusion rate in order to achieve a more rapid response. ○ Continuous infusion: **IV:** Initial: 50 mcg/kg/minute; for inadequate response, may increase in increments of 50 mcg/kg/minute at ≥4-minute intervals up to a maximum of 300 mcg/kg/minute. To achieve a more rapid response, administer a repeat bolus before increasing the continuous infusion rate. In the absence of a bolus, the effects of continuous infusion rate changes may not be evident for up to 30 minutes. **Atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, ectopic atrial tachycardia, multifocal atrial tachycardia:** ○ Loading doses (optional): IV: 500 mcg/kg over 1 minute, followed by a continuous infusion; may administer repeat bolus doses of 500 mcg/kg prior to each increase in continuous infusion rate in order to achieve a more rapid response.

	○ Continuous infusion: IV: Initial: 50 mcg/kg/minute; for inadequate response, may increase in increments of 50 mcg/kg/minute at ≥4-minute intervals up to a maximum of 300 mcg/kg/minute. To achieve a more rapid response, administer a repeat bolus before increasing the continuous infusion rate. In the absence of a bolus, the effects of continuous infusion rate changes may not be evident for up to 30 minutes.
Maximum Daily Dose Adults*	**N/A**
Dose (pediatrics)	**N/A**
Maximum Daily Dose Pediatrics*	**N/A**
Adjustment	**Renal Impairment:** No dosage adjustment necessary. Not removed by hemo- or peritoneal dialysis. A supplemental dose is not necessary. **Hepatic Impairment:** No dosage adjustment necessary.
Prescribing edits*	MD, ST
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Should be prescribed by a cardiologist.
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	It is considered as second-line therapy in patients with inappropriate sinus tachycardia.
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Asymptomatic hypotension, symptomatic hypotension.

	<u>Most serious</u>: Peripheral ischemia, angioedema, coronary artery vasospasm, heart block, thrombophlebitis.
Drug Interactions*	**<u>Category X:</u>** • Bromperidol • Etofylline • Fexinidazole • Rivastigmine • White Birch Allergen Extract
Special Population	Older patients: Bradycardia may be observed more frequently in patients >65 years of age; dosage reductions may be necessary.
Pregnancy	Exposure to esmolol may cause fetal bradycardia which may continue after esmolol is discontinued. If maternal use of a beta-blocker is needed, fetal growth should be monitored during pregnancy and the newborn should be monitored for 48 hours after delivery for bradycardia, hypoglycemia, and respiratory depression. Agents other than esmolol may be preferred for the treatment of supraventricular tachycardia, atrial fibrillation, atrial flutter, and ventricular tachycardia in pregnancy.
Lactation	It is not known if esmolol is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, the manufacturer recommends a decision be made whether to discontinue breastfeeding or the drug, considering the importance of treatment to the mother. The short half-life and the fact that it is not intended for chronic use should limit any potential exposure to the breastfeeding infant.

Contraindications	- Hypersensitivity to esmolol or any component of the formulation; severe sinus bradycardia; heart block greater than first degree or sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker); cardiogenic shock; decompensated heart failure; IV administration of calcium channel blockers (eg, verapamil) in close proximity to esmolol (ie, while cardiac effects of other drug are still present); pulmonary hypertension. - Canadian labeling: Additional contraindications (not in US labeling): Patients requiring inotropic agents and/or vasopressors to maintain cardiac output and systolic blood pressure; hypotension; right ventricular failure secondary to pulmonary hypertension; untreated pheochromocytoma.
Monitoring Requirements	Monitor BP, mean arterial pressure, heart rate, continuous ECG, respiratory rate, IV site; serum potassium (especially with kidney impairment); consult individual institutional policies and procedures.
Precautions	**Concerns related to adverse effects:** - Anaphylactic reactions: Use caution with history of severe anaphylaxis to allergens; patients taking beta-blockers may become more sensitive to repeated challenges. Treatment of anaphylaxis (eg, epinephrine) in patients taking beta-blockers

	may be ineffective or promote undesirable effects. - Extravasation: Vesicant; ensure proper needle or catheter placement prior to and during infusion. Avoid extravasation. Extravasation can lead to skin necrosis and sloughing; avoid infusions into small veins or through a butterfly catheter. - Hyperkalemia: Esmolol has been associated with elevations in serum potassium and development of hyperkalemia especially in patients with risk factors (eg, kidney impairment); monitor serum potassium during therapy. - Hypotension: Can commonly occur; patients need close blood pressure monitoring. If an unacceptable drop in blood pressure occurs, reduction in dose or discontinuation may reverse hypotension (usually within 30 minutes). **Disease-related concerns:** - Bronchospastic disease: In general, patients with bronchospastic disease should not receive beta-blockers; however, esmolol, with B_1 selectivity, has been used cautiously with close monitoring. - Conduction abnormality: Can cause bradycardia including sinus pause, heart block, severe bradycardia, and cardiac arrest. Consider preexisting conditions such as first degree AV block, sick sinus syndrome, or other

	conduction disorders before initiating; use is contraindicated in patients with sick sinus syndrome or second- or third-degree AV block (except in patients with a functioning artificial ventricular pacemaker). - Diabetes: Use with caution in patients with diabetes mellitus; may potentiate hypoglycemia and/or mask signs and symptoms. - Heart failure: Use with caution in patients with compensated heart failure and monitor for a worsening of the condition. Use is contraindicated in patients with decompensated heart failure. - Kidney impairment: Use with caution in patients with kidney impairment; active metabolite retained. - Myasthenia gravis: Use with caution in patients with myasthenia gravis. - Peripheral vascular disease (PVD) and Raynaud disease: Can precipitate or aggravate symptoms of arterial insufficiency in patients with PVD and Raynaud disease. Use with caution and monitor for progression of arterial obstruction. - Pheochromocytoma (untreated): Adequate alpha-blockade is required prior to use of any beta-blocker. - Thyroid disease: May mask signs of hyperthyroidism (eg, tachycardia). If hyperthyroidism is

	suspected, carefully manage and monitor; abrupt withdrawal may exacerbate symptoms of hyperthyroidism or precipitate thyroid storm. **Other warnings/precautions:** - Abrupt withdrawal: Beta-blocker therapy should not be withdrawn abruptly (particularly in patients with CAD), but gradually tapered to avoid acute tachycardia, hypertension, and/or ischemia. Severe exacerbation of angina, ventricular arrhythmias, and myocardial infarction (MI) have been reported following abrupt withdrawal of beta-blocker therapy. Temporary but prompt resumption of beta-blocker therapy may be indicated with worsening of angina or acute coronary insufficiency. - Hypertension associated with hypothermia: Use esmolol with caution in patients with hypertension associated with hypothermia; monitor vital signs closely and titrate esmolol slowly. - Hypovolemic patients: Avoid use in patients with hypovolemia; treat hypovolemia first, otherwise, use of esmolol may attenuate reflex tachycardia and further increase the risk of hypotension.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A thorough review of various HTA bodies including NICE, CADTH, HAS, IQWIG, and PBAC yielded **no recommendations for the use of esmolol for the treatment of**

arrhythmias. Nevertheless, esmolol has been marketed worldwide for many years, and multiple generic options are available, leading to a low cost of treatment.

CONCLUSION STATEMENT – ESMOLOL

Esmolol is recommended for use in patients with atrial flutter, atrial flutter, inappropriate noncompensatory sinus tachycardia, atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, focal atrial tachycardia, and multifactorial atrial tachycardia.

There are no recommendations issued by HTA bodies on the use of esmolol in these indications, however, it has been available on the market for years and multiple generics are available.

2.3 Class III Antiarrhythmic Agents

2.3.1 Amiodarone

Table 16. Amiodarone Drug Information

SCIENTIFIC NAME Amiodarone	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	I49
Drug Class	Antiarrhythmic agent
Drug Sub-class	Class III
ATC Code	C07AA05
Pharmacological Class (ASHP)	24:04.04.20 Class III Antiarrhythmics
DRUG INFORMATION	
Dosage Form	Tablet, Solution for injection, Concentrate for solution for infusion
Route of Administration	Oral use, Intravenous use
Dose (Adult) [DDD]*	**Supraventricular tachycardia (eg, atrioventricular nodal reentrant tachycardia, atrioventricular reentrant**

	tachycardia, focal atrial tachycardia) (off-label use): ➢ **Pharmacologic cardioversion:** ○ **IV:** 150 mg over 10 minutes, followed by 1 mg/minute for 6 hours, then 0.5 mg/minute for 18 hours or transition to oral dosing. ○ **Oral :** 400 to 600 mg daily in divided doses for 2 to 4 weeks; in an inpatient monitored setting, initial oral doses up to 1.2 g daily in divided doses may be considered; administer a total loading dose of ~6 to 10 g (total of IV plus oral doses) then transition to a maintenance dose; usual maintenance dose: 100 to 200 mg once daily. **Ventricular arrhythmias:** ➢ **Electrical storm and incessant ventricular tachycardia, hemodynamically stable (off-label use):** ○ IV: 150 mg over 10 minutes (may repeat if necessary), followed by 1 mg/minute IV infusion for 6 hours, then 0.5 mg/minute for 18 additional hours or until switched to oral therapy. ○ Oral (following IV therapy): 400 mg every 8 to 12 hours for 1 to 2 weeks (loading dose of ~6 to 10 g [total of IV plus oral doses]), followed by 200 to 400 mg once daily. ➢ **Prevention of implantable cardioverter defibrillator shocks (off-label use):** ○ Oral: 400 mg twice daily for 2 weeks, followed by 400 mg once daily for 4 weeks, then 200 mg

	once daily in combination with a beta-blocker or 400 mg every 8 to 24 hours for a total loading dose of ~6 to 10 g, then 200 to 400 mg once daily. ➢ **Primary prevention of sudden cardiac death due to ventricular arrhythmias (off-label use):** o Oral: 400 mg every 8 to 24 hours for 1 to 2 weeks for a total loading dose of ~6 to 10 g, then a maintenance dose of 200 to 400 mg once daily. ➢ **Secondary prevention of sudden cardiac death due to ventricular arrhythmias (eg, ventricular fibrillation or hemodynamically unstable ventricular tachycardia):** o Oral: 400 mg every 8 to 24 hours for 1 to 2 weeks (loading dose of ~6 to 10 g [total of IV plus oral doses]), followed by a maintenance dose of 200 to 400 mg once daily. ➢ **Sudden cardiac arrest due to ventricular fibrillation or pulseless ventricular tachycardia (unresponsive to CPR, defibrillation, and epinephrine):** o IV push, Intraosseous (IO): Initial: 300 mg (undiluted) rapid bolus; if ventricular fibrillation or pulseless ventricular tachycardia continues after subsequent defibrillation attempt or reoccurs after initially achieving return of spontaneous circulation, administer supplemental dose of 150 mg.

	○ Upon return of spontaneous circulation (ROSC): Continuous IV infusion: 1 mg/minute for 6 hours, then 0.5 mg/minute for 18 hours or until switched to oral therapy for secondary prevention of sudden cardiac death due to ventricular arrhythmias. ➢ **Ventricular premature beats, symptomatic (off-label use):** ○ Oral: 400 mg every 8 to 12 hours for 1 to 2 weeks (total loading dose of ~6 to 10 g), then when adequate control is achieved, decrease to 200 to 400 mg once daily; use lowest effective dose to minimize adverse effects.
Maximum Daily Dose Adults*	**N/A**
Dose (pediatrics)	**Ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT), shock-refractory:** Infants, Children, and Adolescents: IV, Intraosseous: 5 mg/kg (maximum dose: 300 mg/dose) rapid bolus; may repeat twice up to a maximum total dose of 15 mg/kg during acute treatment. **Tachyarrhythmia, including junctional ectopic tachycardia (JET), paroxysmal supraventricular tachycardia (PSVT):** Limited data available: Infants, Children, and Adolescents: ○ Oral: Loading dose: 10 to 15 mg/kg/day in 1 to 2 divided doses/day for 4 to 14 days or until adequate control of arrhythmia or prominent adverse effects occur; dosage should then be reduced to 5 mg/kg/day given once daily for several weeks; if arrhythmia does not recur, reduce to lowest effective dosage

	possible; usual daily minimal dose: 2.5 mg/kg/day; maintenance doses may be given for 5 of 7 days/week. o IV: Loading dose: 5 mg/kg (maximum dose: 300 mg/dose) given over 60 minutes; Note: Most studies used bolus infusion time of 60 minutes to avoid hypotension; may repeat initial loading dose to a maximum total initial load: 10 mg/kg; do not exceed total daily bolus of 15 mg/kg/day. o Continuous IV infusion (if needed): ▪ Dosing based on mcg/kg/minute: Initial: 5 mcg/kg/minute; increase incrementally as clinically needed; usual required dose: 10 mcg/kg/minute; range: 5 to 15 mcg/kg/minute; maximum daily dose: 2,200 mg/day. ▪ Dosing based on mg/kg/day: Initial: 10 mg/kg/day; increase incrementally as clinically needed; range: 10 to 20 mg/kg/day; maximum daily dose: 2,200 mg/day.
Maximum Daily Dose Pediatrics*	- **Ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT), shock-refractory:** maximum dose: 300 mg/dose - **Tachyarrhythmia, including junctional ectopic tachycardia (JET), paroxysmal supraventricular tachycardia (PSVT):** maximum Continuous IV infusion dose: 2,200 mg/day.
Adjustment	**<u>Renal Impairment:</u>**

	There are no dosage adjustments provided in the manufacturer's labeling; pharmacokinetic data implies that no dosage adjustment would be necessary. o Hemodialysis: Not dialyzable; supplemental dose is not necessary. o Peritoneal dialysis: Not dialyzable; supplemental dose is not necessary. **Hepatic Impairment:** o Baseline: There are no dosage adjustments provided in the manufacturer's labeling. Although no dosage recommendations exist for adults with hepatic abnormalities, close monitoring is recommended in the elderly and those with left ventricular dysfunction. o Hepatoxicity during therapy: There are no dosage adjustments provided in the manufacturer's labeling; based on experience in adult patients, dosage adjustment or discontinuation is suggested when hepatic enzymes exceed 3 times normal or double in a patient with an elevated baseline.
Prescribing edits*	MD, ST, EU
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Should be prescribed by a cardiologist.
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	It is considered as second-line therapy in patients with ventricular arrhythmias.

EU (Emergency Use Only)	Sudden cardiac arrest due to ventricular fibrillation or pulseless ventricular tachycardia (unresponsive to CPR, defibrillation, and epinephrine)
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Hypotension, nausea, vomiting, epithelial keratopathy, pulmonary toxicity. **Most serious**: Cardiac failure, disorder of hemostatic components of blood, abnormal hepatic function tests (IV, Oral), cute respiratory distress syndrome, pulmonary fibrosis, asystole (IV), atrioventricular block (IV), cardiogenic shock (IV), ventricular tachycardia (IV, oral).
Drug Interactions*	**Category X:** • Agalsidase Alfa • Aminolevulinic Acid (Systemic) • Atazanavir • Bilastine • Bromperidol • Cimetidine • Citalopram • Clarithromycin • Daclatasvir • Domperidone • DOXOrubicin (Conventional) • Entrectinib • Erythromycin (Systemic) • Fexinidazole • Fingolimod • Flupentixol • Fusidic Acid (Systemic) • Gemifloxacin • Grapefruit Juice • Indinavir • Lefamulin

	• Levofloxacin-Containing Products (Systemic) • Levoketoconazole • Lofepramine • Moxifloxacin (Systemic) • Nelfinavir • Nilotinib • Nirmatrelvir and Ritonavir • PAZOPanib • Pimozide • Piperaquine • Posaconazole • Probucol • Propafenone • QUEtiapine • Repotrectinib • Ribociclib • Ritonavir • Saquinavir • Sertindole • Sirolimus (Protein Bound) • Sodium Iodide I131 • Sparfloxacin • Thioridazine • Tipranavir • Topotecan • VinCRIStine (Liposomal) • Voriconazole
Special Population	Surgical patients: Use caution and close perioperative monitoring in surgical patients; may enhance myocardial depressant and conduction effects of halogenated inhalational anesthetics; adult respiratory distress syndrome (ARDS) has been reported postoperatively (fatal in rare cases). Hypotension upon discontinuation of cardiopulmonary bypass during open-

	heart surgery have been reported (rare); relationship to amiodarone is unknown.
Pregnancy	Amiodarone and the active metabolite, N-desethylamiodarone, cross the placenta. In utero exposure may cause fetal harm. Reported risks include neonatal bradycardia, QT prolongation, and periodic ventricular extrasystoles; neonatal hypothyroidism (with or without goiter); neonatal hyperthyroxinemia; neurodevelopmental abnormalities independent of thyroid function; jerk nystagmus with synchronous head titubation; fetal growth retardation; and/or premature birth. Oral or IV amiodarone should be used in pregnancy only to treat arrhythmias refractory to other treatments or when other treatments are contraindicated. Amiodarone (administered either maternally or directly to the fetus) may be considered for the in utero management of fetal atrial flutter and in life-threatening cases of sustained fetal supraventricular tachycardia refractory to first and second line agents, but because of potential toxicity, risks and benefits should be assessed. If in utero exposure occurs, newborns should be monitored for thyroid disorders and cardiac arrhythmias.
Lactation	Amiodarone and its active metabolite are present in breast milk. Actual concentrations of amiodarone and the active metabolite in breast milk vary greatly. The relative infant dose (RID) of amiodarone is reported by the manufacturer to be between 3.5% and

	45% of the weight-adjusted maternal dose. In general, breastfeeding is considered acceptable when the RID of a medication is <10%; when the RID is >25% breastfeeding should generally be avoided. Hypothyroidism and bradycardia have been observed in breastfed infants. The manufacturer does not recommend breastfeeding during therapy. If the mother wishes to breastfeed, thyroid function and plasma concentrations of amiodarone in the infant should be monitored. Due to the long half-life, amiodarone and the metabolite may be present in breast milk for weeks following discontinuation of maternal therapy.
Contraindications	- Hypersensitivity to amiodarone, iodine, or any component of the formulation; sick sinus syndrome, second- or third-degree atrioventricular block, bradycardia leading to syncope without a functioning pacemaker; cardiogenic shock. - Canadian labeling (oral formulation): Additional contraindications (not in US labeling): Evidence of hepatitis; pulmonary interstitial abnormalities; thyroid dysfunction.
Monitoring Requirements	- Monitor BP, heart rate (ECG) and rhythm throughout therapy; history and physical exam every 3 to 6 months; assess patient for signs of lethargy, edema of the hands or feet, weight loss, and pulmonary toxicity (baseline

	pulmonary function tests and chest X-ray; continue monitoring chest X-ray every 3 to 6 months during therapy); LFTs (baseline and semiannually), signs or symptoms of clinical liver injury; monitor serum electrolytes, especially potassium and magnesium. Assess thyroid function tests before initiation of treatment and then periodically thereafter (some experts suggest every 3 to 6 months; particularly in elderly patients and in patients with underlying thyroid dysfunction). If signs or symptoms of thyroid disease or arrhythmia breakthrough/exacerbation occur then immediate re-evaluation is necessary. Amiodarone partially inhibits the peripheral conversion of T4 to T3; serum T4 and reverse T3 concentrations may be increased and serum T3 may be decreased; most patients remain clinically euthyroid; however, clinical hypothyroidism or hyperthyroidism may occur. - Perform regular ophthalmic exams. - Patients with implantable cardiac devices: Monitor pacing or defibrillation thresholds with initiation of amiodarone and during treatment. - Consult individual institutional policies and procedures.
Precautions	**Concerns related to adverse effects:** - Extravasation: May be a vesicant; ensure proper needle or catheter

	placement prior to infusion. Avoid extravasation. - Ocular effects: Regular ophthalmic examination (including slit lamp and fundoscopy) is recommended. May cause optic neuropathy and/or optic neuritis resulting in visual impairment (peripheral vision loss, changes in acuity) at any time during therapy; permanent blindness has occurred. If symptoms of optic neuropathy and/or optic neuritis occur, prompt ophthalmic evaluation is recommended. If diagnosis of optic neuropathy and/or optic neuritis is confirmed, reevaluate amiodarone therapy. Corneal microdeposits occur in a majority of adults and may cause visual disturbances in up to 10% of patients (blurred vision, halos); asymptomatic microdeposits may be reversible and are not generally considered a reason to discontinue treatment. Corneal refractive laser surgery is generally contraindicated in amiodarone users (from manufacturers of surgical devices). - Photosensitivity: Avoid excessive exposure to sunlight; may cause photosensitivity. During long-term treatment, a blue-gray discoloration of exposed skin may occur; risk increased in patients with fair complexion or excessive sun exposure; may be related to

	cumulative dose and duration of therapy. **Disease-related concerns:** Arrhythmias: Appropriate use: The 2015 ACLS guidelines recommend the consideration of IV amiodarone as the preferred antiarrhythmic for the treatment of pulseless ventricular tachycardia/ventricular fibrillation unresponsive to CPR, defibrillation, and vasopressor therapy (AHA [Link 2015]). In patients with non-life-threatening arrhythmias (eg, atrial fibrillation), amiodarone should be used only if the use of other antiarrhythmics has proven ineffective or are contraindicated. Cardiac devices (eg, implanted defibrillators, pacemakers): Chronic administration of antiarrhythmic drugs may affect defibrillation or pacing thresholds. Assess when initiating amiodarone and during therapy. Electrolyte imbalance: Correct electrolyte disturbances, especially hypokalemia, hypomagnesemia, or hypocalcemia, prior to use and throughout therapy. Myocardial infarction: In the setting of acute myocardial infarction (MI), beta-blocker therapy should be initiated even though concomitant amiodarone therapy provides beta-blockade. In the Cardiac Arrhythmia Suppression Trial (CAST), post-MI patients with asymptomatic, nonlife-threatening ventricular arrhythmias did not benefit and may have been harmed by attempts to suppress arrhythmia with flecainide or encainide. Although use of amiodarone post-MI was not associated with an increase in mortality in 2 trials,

	antiarrhythmic agents should be reserved for patients with life-threatening ventricular arrhythmias. Wolff-Parkinson-White (WPW) syndrome: Amiodarone should not be used in patients with WPW syndrome and preexcited atrial fibrillation/flutter since ventricular fibrillation may result. **Other warnings/precautions:** Discontinuation of therapy: Patients may still be at risk for amiodarone-related adverse reactions or drug interactions after the drug has been discontinued. The pharmacokinetics are complex (due to prolonged duration of action and half-life) and difficult to predict.
Black Box Warning	- Life-threatening arrhythmias (tablet) - Pulmonary toxicity (tablet) - Hepatotoxicity - Worsened arrhythmia (tablet)
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A thorough review of various HTA bodies including NICE, CADTH, HAS, IQWIG, and PBAC yielded **no recommendations for the use of amiodarone for the treatment of arrhythmias.** Nevertheless, amiodarone has been marketed worldwide for many years, and multiple generic options are available, leading to a low cost of treatment.

CONCLUSION STATEMENT – AMIODARONE

Amiodarone is recommended in the treatment of ventricular arrhythmias, atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, and focal atrial tachycardia.

There are no recommendations issued by HTA bodies on the use of amiodarone in ventricular arrhythmias, atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, and focal atrial tachycardia, however, it has been available on the market for years and multiple generics are available.

2.4 Class IV Antiarrhythmics Agents

2.4.1 Verapamil

Table 17. Verapamil Drug Information

SCIENTIFIC NAME Verapamil	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	I49
Drug Class	Antiarrhythmic agent
Drug Sub-class	Class IV, Calcium Channel Blocker, Nondihydropyridine
ATC Code	C08DA01
Pharmacological Class (ASHP)	24:04.04.24 Class IV Antiarrhythmics
DRUG INFORMATION	
Dosage Form	Tablet, Prolonged-release tablet, Solution for injection
Route of Administration	Oral use, Intravenous use
Dose (Adult) [DDD]*	**Atrial fibrillation/flutter, rate control (alternative agent):** Acute ventricular rate control: IV: o Bolus: Initial: 5 to 10 mg over ≥2 minutes; if there is inadequate response, dose may be repeated after 15 to 30 minutes; if there is adequate response after 1 to 2 bolus doses, then may begin a continuous infusion. o Continuous infusion: Initial: 5 mg/hour; titrate to goal heart rate up to a maximum of 20 mg/hour. Chronic ventricular rate control: oral:

	○ Immediate release: Initial: 40 mg 3 to 4 times daily; increase as needed to achieve rate control; maximum dose: 480 mg/day in 3 to 4 divided doses. ○ Extended release (off-label use): Initial: 120 or 180 mg once daily; increase as needed to achieve rate control; maximum dose: 480 mg/day in 1 to 2 divided doses. **Atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, focal atrial tachycardia, multifocal atrial tachycardia:** Acute treatment (off-label use): IV: ○ Bolus: Initial: 5 to 10 mg over ≥2 minutes; if response is insufficient after 15 to 30 minutes, a second bolus dose of 10 mg over 2 minutes may be administered. If 2 bolus doses do not terminate the arrhythmia, consider alternative therapy. Chronic maintenance: Oral: ○ Immediate release: Initial: 40 mg 3 to 4 times daily; increase as needed for heart rate control. ○ Extended release (off-label use): Initial: 120 mg once daily; increase as needed for heart rate control. **Ventricular arrhythmias** Prevention of idiopathic left ventricular arrhythmias: Oral: ○ Immediate release: 120 mg 3 times daily. ○ Extended release: 240 to 480 mg/day in 1 to 2 divided doses. Nonsustained ventricular tachycardia or ventricular premature beats, symptomatic (alternative agent) (off-label use): Oral:

	○ Immediate release: Initial: 40 or 80 mg 3 times daily; titrate as needed based on symptom control and tolerability. ○ Extended release: Initial: 120 or 180 mg once daily; titrate as needed based on symptom control and tolerability.
Maximum Daily Dose Adults*	**Atrial fibrillation/flutter, rate control (acute):** N/A **Atrial fibrillation/flutter, rate control (chronic):** ○ Immediate release: maximum dose: 480 mg/day in 3 to 4 divided doses. ○ Extended release (off-label use): maximum dose: 480 mg/day in 1 to 2 divided doses. **Atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, focal atrial tachycardia, multifocal atrial tachycardia:** N/A **Prevention of idiopathic left ventricular arrhythmias:** N/A **Nonsustained ventricular tachycardia or ventricular premature beats, symptomatic:** ○ Immediate release: maximum dose: 360 mg/day in 3 to 4 divided doses. ○ Extended release: maximum dose: 360 mg/day in 1 to 2 divided doses.
Dose (pediatrics)	**N/A**
Maximum Daily Dose Pediatrics*	**N/A**
Adjustment	**<u>Renal Impairment:</u>** - **Altered kidney function:** No dosage adjustment necessary for any degree of kidney dysfunction.

	- **Hemodialysis, intermittent (thrice weekly):** Not significantly dialyzed: No supplemental dose or dosage adjustment necessary. - **Peritoneal dialysis:** Unlikely to be significantly dialyzed (highly protein bound, large Vd): No dosage adjustment necessary. - **CRRT:** No dosage adjustment necessary. - **PIRRT (eg, sustained, low-efficiency diafiltration):** No dosage adjustment necessary. **<u>Hepatic Impairment:</u>** Oral: In cirrhosis, reduce dose to 20% of normal and monitor ECG. o Extended release: Administer 30% of the normal dose in severe hepatic impairment. o Extended release (delayed-onset/PM formulation): Initial: 100 mg once daily at bedtime. Injection: There are no dosage adjustments provided in the manufacturer's labeling; use with caution and consider additional ECG monitoring in severe impairment. In cirrhosis, reduce dose to 50% of normal and monitor ECG. Repeated injections in patients with hepatic failure may lead to accumulation. If repeated injections are essential, monitor BP and PR interval closely and use smaller doses.
Prescribing edits*	MD
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Should be prescribed by a cardiologist.
PA (Prior Authorization)	N/A

QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Headache. **Most serious**: Acute myocardial infarction, atrioventricular block, cardiac failure, cerebrovascular accident, Stevens-Johnson syndrome, increased serum transaminases, psychosis, pulmonary edema.
Drug Interactions*	**Category X:** • Aprepitant • Asunaprevir • Bilastine • Bosutinib • Bromperidol • Budesonide (Topical) • Dantrolene • Disopyramide • Dofetilide • Domperidone • DOXOrubicin (Conventional) • Elacestrant • Eletriptan • Fexinidazole • Fezolinetant • Flibanserin • Fosaprepitant • Fusidic Acid (Systemic) • Infigratinib • Ivabradine • Lemborexant • Lomitapide • Lonafarnib • Methysergide • Neratinib

	• Nirogacestat • Nisoldipine • Orelabrutinib • Pacritinib • PAZOPanib • Pimozide • Repotrectinib • Sertindole • Simeprevir • Sirolimus (Protein Bound) • Topotecan • VinCRIStine (Liposomal)
Special Population	Pediatric: In neonates and young infants, avoid IV use for supraventricular tachycardia due to severe apnea, bradycardia, hypotensive reactions, and cardiac arrest; in older children, use IV with caution as myocardial depression and hypotension may occur.
Pregnancy	Verapamil crosses the placenta. Chronic maternal hypertension is associated with adverse events in the fetus/infant. Chronic maternal hypertension may increase the risk of birth defects, low birth weight, premature delivery, stillbirth, and neonatal death. Actual fetal/neonatal risks may be related to the duration and severity of maternal hypertension. Untreated chronic hypertension may also increase the risks of adverse maternal outcomes, including gestational diabetes, preeclampsia, delivery complications, stroke, and myocardial infarction. Patients with preexisting hypertension may continue their medication during pregnancy unless contraindications exist. When treatment of hypertension

	is initiated during pregnancy, agents other than verapamil may be preferred. Patients with hypertrophic cardiomyopathy who are controlled with verapamil prior to pregnancy may continue therapy, but increased fetal monitoring is recommended. Verapamil may be used IV for the acute treatment of supraventricular tachycardia (SVT) in patients who are pregnant when adenosine or beta-blockers are ineffective or contraindicated. Verapamil may also be used for the ongoing management of SVT in highly symptomatic patients. The lowest effective dose is recommended; avoid use during the first trimester if possible. Additional guidelines are available for management of cardiovascular diseases during pregnancy. In general, preventive treatment for migraine should be avoided during pregnancy. Options for pregnant patients should be considered as part of a shared decision-making process. Nonpharmacologic interventions should be considered initially. When needed, preventive treatment should be individualized considering the available safety data, the potential for adverse maternal and fetal events, and needs of the patient. If preventive therapy is needed, verapamil may be used. Verapamil is used for the prevention of cluster headache. Verapamil may be used when prophylaxis is needed in pregnant patients; however, use should be avoided during the third trimester if possible.

Lactation	Verapamil and norverapamil are present in breast milk. Data related to the presence of verapamil in breast milk are available from multiple case reports. Following maternal use of verapamil 80 to 120 mg three times daily in patients ≤3 months postpartum, the relative infant dose (RID) of verapamil was calculated to be ≤1% of the weight-adjusted maternal dose. Adverse events were not observed in breastfed infants. In general, breastfeeding is considered acceptable when the RID of a medication is <10%. Although breastfeeding is not recommended by some manufacturers (consider the risk of infant exposure), other sources consider verapamil compatible for use in patients who are breastfeeding. In general, preventive treatment for migraine in lactating patients should be avoided. When needed, therapy should be individualized considering the available safety data and needs of the patient. If preventive therapy is needed, verapamil may be considered. Verapamil is likely compatible if prophylaxis for cluster headache is needed when breastfeeding infants are >2 months of age (limited data).
Contraindications	- Oral: Hypersensitivity to verapamil or any component of the formulation; severe left ventricular dysfunction; hypotension (systolic pressure <90 mm Hg) or cardiogenic shock; sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker); second- or third-

	degree atrioventricular (AV) block (except in patients with a functioning artificial ventricular pacemaker); atrial flutter or fibrillation and an accessory pathway (Wolff-Parkinson-White [WPW] syndrome, Lown-Ganong-Levine syndrome). o Canadian labeling: Additional contraindications (not in US labeling): Complicated myocardial infarction (MI) (ventricular failure manifested by pulmonary congestion); severe congestive heart failure and/or severe left ventricular dysfunction (eg, ejection fraction <40%) unless secondary to a supraventricular tachycardia amendable to oral verapamil; marked bradycardia; concurrent use of ivabradine or flibanserin; concurrent use with beta-blockers in patients with poor ventricular function and in the treatment of hypertension; concurrent use of grapefruit juice; breastfeeding. - IV: Hypersensitivity to verapamil or any component of the formulation; severe heart failure (unless secondary to a supraventricular tachycardia amenable to verapamil); severe hypotension or cardiogenic shock; sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker); second- or third-

	degree AV block (except in patients with a functioning artificial ventricular pacemaker); concurrent use of IV beta-blocking agents; atrial flutter or fibrillation and an accessory pathway (WPW syndrome, Lown-Ganong-Levine syndrome); ventricular tachycardia. o Canadian labeling: Additional contraindications (not in US labeling): Complicated MI (ventricular failure manifested by pulmonary congestion); severe left ventricular dysfunction; marked bradycardia; concurrent use of ivabradine or flibanserin; breastfeeding.
Monitoring Requirements	Monitor Blood pressure; heart rate; liver function; kidney function.
Precautions	**Disease-related concerns:** - Accessory pathway (eg, Wolff-Parkinson-White syndrome): During an episode of atrial fibrillation or flutter in patients with an accessory pathway or preexcitation syndrome, use has been associated with increased anterograde conduction down the accessory pathway leading to ventricular fibrillation; avoid use in such patients. - Arrhythmia: Considered contraindicated in patients with wide complex tachycardias unless known to be supraventricular in origin; severe hypotension likely to occur upon administration.

	- Attenuated neuromuscular transmission: Decreased neuromuscular transmission has been reported; use with caution in patients with attenuated neuromuscular transmission (Duchenne muscular dystrophy, myasthenia gravis); dosage reduction may be required. - Hepatic impairment: Use with caution in patients with hepatic impairment; dosage reduction may be required; monitor hemodynamics and possibly ECG in severe impairment. Avoid repeated injections of IV verapamil in patients with significant hepatic failure. - Increased intracranial pressure: IV verapamil has increased intracranial pressure in patients with supratentorial tumors at the time of anesthesia induction; use with caution in these patients. - Left ventricular dysfunction: Avoid use in patients with heart failure due to lack of benefit and/or worse outcomes with calcium channel blockers in general. - Renal impairment: Use with caution in patients with renal impairment; monitor hemodynamics and possibly ECG in severe impairment.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A thorough review of various HTA bodies including NICE, CADTH, HAS, IQWIG, and PBAC yielded **no recommendations for the use of verapamil for the treatment of arrhythmias.** Nevertheless, verapamil has been marketed worldwide for many years, and multiple generic options are available, leading to a low cost of treatment.

CONCLUSION STATEMENT – VERAPAMIL

Verapamil is recommended in the treatment of ventricular arrhythmias, atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, and focal atrial tachycardia as well as atrial fibrillation/flutter.

There are no recommendations issued by HTA bodies on the use of verapamil in ventricular arrhythmias, atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, and focal atrial tachycardia as well as atrial fibrillation/flutter however, it has been available on the market for years and multiple generics are available.

2.4.2 Diltiazem

Table 18. Diltiazem Drug Information

SCIENTIFIC NAME Diltiazem	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	I49
Drug Class	Antiarrhythmic agent
Drug Sub-class	Class IV, Calcium Channel Blocker, Nondihydropyridine
ATC Code	C08DA01
Pharmacological Class (ASHP)	24:04.04.24 Class IV Antiarrhythmics
DRUG INFORMATION	
Dosage Form	Tablet, Prolonged-release tablet, Capsule, Prolonged-release capsule, hard

Route of Administration	Oral use
Dose (Adult) [DDD]*	**Atrial fibrillation/flutter, rate control (alternative agent):** Acute ventricular rate control: IV: o Bolus: 0.25 mg/kg (actual body weight) over 2 minutes (average dose: 20 mg; if hypotension is a concern, some experts administer a lower bolus of 5 to 15 mg); if rate control is insufficient after 15 minutes, a repeat bolus dose of 0.35 mg/kg over 2 minutes may be given (average dose: 25 mg). Patients who respond after 1 or 2 bolus doses can be started on a continuous infusion. o Continuous infusion: Continuous infusion following bolus(es): Initial: 5 to 10 mg/hour; infusion rate may be increased in 5 mg/hour increments according to ventricular response, up to a maximum of 15 mg/hour. Chronic ventricular rate control: oral (off-label use): o Immediate release: Initial: 30 mg 4 times daily; increase as needed to achieve ventricular rate control; usual dose: 120 to 480 mg/day in 3 or 4 divided doses. o Extended release: Initial: 120 mg once daily or in 2 divided doses depending on formulation; increase as needed to achieve ventricular rate control; usual dose: 120 to 480 mg/day. **Atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, focal atrial tachycardia, multifocal atrial tachycardia:**

	Acute treatment: IV: ○ Bolus: 0.25 mg/kg (actual body weight) over 2 minutes (average dose: 20 mg); if response is insufficient after ≥15 minutes, a repeat bolus dose of 0.35 mg/kg over 2 minutes may be given (average dose: 25 mg). If bolus(es) do not terminate the arrhythmia, consider alternative therapy. Chronic maintenance (off-label use): Oral: ○ Immediate release: Initial: 30 mg 4 times daily; increase as needed for heart rate control; usual effective dose: 360 mg/day in divided doses. ○ Extended release (off-label use): Initial: 120 mg once daily or in 2 divided doses depending on formulation; increase as needed for heart rate control; usual effective dose: 360 mg/day. **Ventricular arrhythmias** **Nonsustained ventricular tachycardia or ventricular premature beats, symptomatic (alternative agent) (off-label use): Oral:** ○ Initial: 120 to 180 mg once daily or in divided doses depending on the drug formulation; usual effective dose: 240 to 360 mg/day.
Maximum Daily Dose Adults*	- **Atrial fibrillation/flutter, rate control:** N/A - **Atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, focal atrial tachycardia, multifocal atrial tachycardia:** N/A

	- **Nonsustained ventricular tachycardia or ventricular premature beats, symptomatic:** maximum dose: 480 mg/day.
Dose (pediatrics)	- **Atrial tachyarrhythmias, rate control (bridge to therapy):** Very limited data available: Infants ≥6 months, Children, and Adolescents: IV: Initial bolus: 0.25 mg/kg over 5 minutes (maximum dose: 20 mg/dose [average adult dose]) followed by a continuous IV infusion; reported rate range in one study was 0.05 to 0.15 mg/kg/hour.
Maximum Daily Dose Pediatrics*	**N/A**
Adjustment	**Adult** **<u>Renal Impairment:</u>** - **Altered kidney function:** Mild to severe impairment: No dosage adjustment necessary. - **Hemodialysis, intermittent (thrice weekly):** Not significantly dialyzed: No supplemental dose or dosage adjustment necessary. - **Peritoneal dialysis:** Not significantly dialyzed: No dosage adjustment necessary. - **CRRT:** No dosage adjustment necessary. - **PIRRT (eg, sustained, low-efficiency diafiltration):** No dosage adjustment necessary. **Pediatric** **<u>Renal Impairment:</u>** There are no dosage adjustments provided in the manufacturer's labeling; use with caution.

	- Dialysis: Not removed by hemo- or peritoneal dialysis; supplemental dose is not necessary. **<u>Hepatic Impairment (Adult and pediatric):</u>** There are no dosage adjustments provided in the manufacturer's labeling; use with caution; extensively metabolized by the liver; half-life is increased in patients with cirrhosis.
Prescribing edits*	MD
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Should be prescribed by a cardiologist.
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**<u>Most common:</u>** Peripheral edema. **<u>Most serious</u>**: Bundle branch block, cardiac arrhythmia, cardiac failure, complete atrioventricular block, syncope, albuminuria, increased hepatic enzymes.
Drug Interactions*	**<u>Category X:</u>** • Aprepitant • Asunaprevir • Bosutinib • Bromperidol • Budesonide (Topical) • Domperidone • DOXOrubicin (Conventional) • Elacestrant

	• Eletriptan • Fexinidazole • Flibanserin • Fosaprepitant • Fusidic Acid (Systemic) • Infigratinib • Ivabradine • Lemborexant • Lomitapide • Lonafarnib • Methysergide • Nirogacestat • Nisoldipine • Orelabrutinib • Pacritinib • Pimozide • Repotrectinib • Sertindole • Simeprevir
Special Population	N/A
Pregnancy	Adverse events have been observed in animal reproduction studies.
Lactation	Diltiazem is present in breast milk. Data related to the presence of diltiazem in breast milk are available from a case report. Oral diltiazem 60 mg four times a day was started in a mother on postpartum day 14 for arrhythmia. Four days later maternal blood and breast milk were sampled. Peak breast milk concentrations of diltiazem were 200 ng/mL, similar to those in the maternal serum. Breast milk concentrations decreased to <50 mg/mL 22 hours after the final diltiazem dose. Due to the potential for serious adverse reactions in the breastfed infant, the manufacturer recommends a decision

	be made to discontinue breastfeeding or to discontinue the drug, considering the importance of treatment to the mother; however, other sources consider diltiazem compatible for use in patients who are breastfeeding.
Contraindications	- Oral: Hypersensitivity to diltiazem or any component of the formulation; sick sinus syndrome (except in patients with a functioning artificial pacemaker); second- or third-degree AV block (except in patients with a functioning artificial pacemaker); hypotension (systolic <90 mm Hg); acute MI and pulmonary congestion - Intravenous (IV): Hypersensitivity to diltiazem or any component of the formulation; sick sinus syndrome (except in patients with a functioning artificial pacemaker); second- or third-degree AV block (except in patients with a functioning artificial pacemaker); severe hypotension; cardiogenic shock; administration concomitantly or within a few hours of the administration of IV beta-blockers; atrial fibrillation or flutter associated with accessory bypass tract (eg, Wolff-Parkinson-White syndrome, short PR syndrome); ventricular tachycardia (with wide-complex tachycardia [QRS ≥0.12 seconds], must determine whether origin is supraventricular or ventricular) - Canadian labeling: Additional contraindications (not in US

	labeling): Pregnancy; use in women of childbearing potential; breastfeeding; concurrent use with IV dantrolene, ivabradine, or lomitapide; severe bradycardia (<40 beats per minute).
Monitoring Requirements	Monitor BP; heart rate; liver function.
Precautions	**Concerns related to adverse effects:** - Hepatic effects: Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed and frequently resolve spontaneously. Significant elevations in hepatic transaminases (eg, alkaline phosphatase, LDH, AST, ALT) and signs of acute hepatic injury have also been observed 1 to 8 weeks after therapy initiation and have been reversible upon discontinuation. - Hypotension/syncope: Symptomatic hypotension with or without syncope can rarely occur; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. **Disease-related concerns:** - Accessory bypass tract (eg, Wolff-Parkinson-White [WPW] syndrome): During an episode of atrial fibrillation or flutter in patients with an accessory bypass tract or preexcitation syndrome, use has been associated with increased anterograde conduction down the accessory pathway leading to ventricular fibrillation; avoid use in such patients.

	- Hepatic impairment: Use with caution in patients with hepatic impairment. - Left ventricular dysfunction: Use with caution in left ventricular dysfunction; due to negative inotropic effects, may exacerbate condition. Avoid use in patients with heart failure due to lack of benefit and/or worse outcomes with calcium channel blockers in general. - Renal impairment: Use with caution in patients with renal impairment. **Other warnings/precautions:** - Appropriate use: IV: Unless otherwise contraindicated, appropriate vagal maneuvers should be attempted prior to administration of IV diltiazem. Use with caution in patients hemodynamically compromised; continuously monitor ECG and blood pressure during administration (especially during continuous IV infusion). Initial use should be, if possible, in a setting where monitoring and resuscitation equipment, including DC cardioversion/defibrillation, are present.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A thorough review of various HTA bodies including NICE, CADTH, HAS, IQWIG, and PBAC yielded **no recommendations for the use of diltiazem for the treatment of arrhythmias.** Nevertheless, diltiazem has been marketed worldwide for many years, and multiple generic options are available, leading to a low cost of treatment.

CONCLUSION STATEMENT – DILTIAZEM

Diltiazem is recommended in the treatment of atrial fibrillation/flutter (rate control), ventricular premature beats, atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, focal atrial tachycardia, and multifocal atrial tachycardia.

There are no recommendations issued by HTA bodies on the use of diltiazem in atrial fibrillation/flutter (rate control), ventricular premature beats, atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, focal atrial tachycardia, and multifocal atrial tachycardia, however, it has been available on the market for years and multiple generics are available.

2.5 Class V Antiarrhythmic Agents

2.5.1 Adenosine

Table 19. Adenosine Drug Information

SCIENTIFIC NAME Adenosine	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	I49
Drug Class	Antiarrhythmic agent
Drug Sub-class	Nucleoside
ATC Code	C01EB10
Pharmacological Class (ASHP)	24:04.04.24 Class V Antiarrhythmics
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Intravenous use
Dose (Adult) [DDD]*	**Atrioventricular Nodal Reentry Tachycardia: IV:** - Initial: 6 mg over 1 to 2 seconds via a peripheral line, followed immediately by an NS flush; if initial dose does not terminate

	the arrhythmia or cause AV block within 1 to 2 minutes, administer a second dose of 12 mg using the same procedures; if second dose does not terminate the arrhythmia or cause AV block, may administer a third dose of 12 or 18 mg using the same procedures. If supraventricular tachycardia terminates then recurs, may repeat the last effective dose as needed for a total of 3 doses. o Central line administration: Initial dose should be reduced to 3 mg with subsequent doses of 6 mg, then 9 mg, if needed. o Heart transplant patients: Initial dose should be reduced to 1 mg; may increase subsequent doses up to 3 mg, if needed.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	**Atrioventricular Nodal Reentry Tachycardia: IV:** ➢ **Hemodynamically unstable:** o Infants, Children, and Adolescents: Rapid IV, Intraosseous: Initial: 0.1 mg/kg (maximum initial dose: 6 mg/dose); if not effective, increase to 0.2 mg/kg (maximum dose: 12 mg/dose); follow each bolus with NS flush. ➢ **Hemodynamically stable:** o Infants, Children, and Adolescents <50 kg: Rapid IV: Initial dose: 0.05 to 0.1 mg/kg via peripheral or central line; maximum initial dose: 6 mg/dose; if not effective within 1 to 2 minutes, increase dose by 0.05 to

	0.1 mg/kg increments every 1 to 2 minutes to a maximum single dose of 0.3 mg/kg or 12 mg (whichever is less) or until termination of paroxysmal supraventricular tachycardia (PSVT); follow each bolus with NS flush. ✓ Heart transplant patients: Limited data available: Infants ≥6 months, Children, and Adolescents <50 kg: Rapid IV: Initial dose: 0.025 mg/kg; repeat dosing with gradual dose escalation has been reported. ➢ **Children and Adolescents ≥50 kg:** Rapid IV: Initial: 6 mg via peripheral line, if not effective within 1 to 2 minutes, 12 mg may be given; may repeat 12 mg bolus if needed; follow each bolus with NS flush.
Maximum Daily Dose Pediatrics*	**N/A**
Adjustment	**Renal Impairment:** There are no dosage adjustments provided in the manufacturer's labeling. Adenosine is not renally eliminated. **Hepatic Impairment:** There are no dosage adjustments provided in the manufacturer's labeling. Adenosine is not hepatically eliminated.
Prescribing edits*	MD
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Should be prescribed by a cardiologist.
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A

ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Cardiac arrhythmia, chest pressure, headache, dizziness, facial flushing, gastrointestinal distress, neck discomfort, dyspnea. **Most serious**: Atrioventricular block, Asystole (prolonged), cardiac arrest, hyperventilation, increased intracranial pressure, loss of consciousness, myocardial infarction, respiratory arrest.
Drug Interactions*	**Category X:** • Fexinidazole
Special Population	Older adult: Use with caution in older patients; may be at increased risk of hemodynamic effects, bradycardia, and/or AV block.
Pregnancy	Animal reproduction studies have not been conducted. Adenosine is an endogenous substance and adverse fetal effects would not be anticipated. Adenosine is recommended for the acute treatment of SVT in pregnant women. The usual recommended doses may be used, although higher doses may be needed in some cases. AHA guidelines suggest use is safe and effective in pregnancy.
Lactation	It is not known if adenosine is excreted in breast milk following maternal administration. Adenosine is endogenous in breast milk. Due to the potential for adverse reactions in the nursing infant, the manufacturer recommends a decision be made to interrupt nursing or not administer adenosine taking into account the importance of treatment to the mother.

Contraindications	Hypersensitivity to adenosine or any component of the formulation; second- or third-degree AV block, sick sinus syndrome, or symptomatic bradycardia (except in patients with a functioning artificial pacemaker); known or suspected bronchoconstrictive or bronchospastic lung disease, asthma (manufacturer's labeling).
Monitoring Requirements	Monitor ECG, heart rate, blood pressure; consult individual institutional policies and procedures.
Precautions	**Concerns related to adverse effects:** Atrial fibrillation/flutter: There have been reports of atrial fibrillation/flutter when administered to patients with paroxysmal supraventricular tachycardia (PSVT) and may be especially problematic in patients with PSVT and underlying Wolff-Parkinson-White syndrome; has also been reported in patients with or without a history of atrial fibrillation undergoing myocardial perfusion imaging with adenosine infusion. Cardiovascular events: Cardiac arrest (fatal and nonfatal), myocardial infarction, cerebrovascular accident (hemorrhagic and ischemic), and sustained ventricular tachycardia (requiring resuscitation) have occurred when used for pharmacologic stress testing. Avoid use in patients with signs or symptoms of unstable angina, acute myocardial ischemia, or cardiovascular instability due to possible increased risk of significant cardiovascular consequences. Appropriate measures for resuscitation should be available during use.

	Conduction disturbances: Adenosine decreases conduction through the AV node and may produce first-, second-, or third-degree heart block. Patients with preexisting SA nodal dysfunction may experience prolonged sinus pauses after adenosine; use caution in patients with first-degree atrioventricular (AV) block or bundle branch block; use is contraindicated in patients with high-grade AV block, sinus node dysfunction, or symptomatic bradycardia (unless a functional artificial pacemaker is in place). Rare, prolonged episodes of asystole have been reported, with fatal outcomes in some cases. Discontinue adenosine in any patient who develops persistent or symptomatic high-grade AV block. Hypersensitivity: Hypersensitivity reactions (including dyspnea, pharyngeal edema, erythema, flushing, rash, or chest discomfort) have been reported. Hypertension: Systolic and diastolic pressure increases have been observed. In most instances, blood pressure increases resolved spontaneously within several minutes; occasionally, hypertension lasted for several hours. Hypotension: May produce profound vasodilation with subsequent hypotension. When used as a bolus dose (PSVT), effects are generally self-limiting (due to the short half-life of adenosine). However, when used as a continuous infusion (pharmacologic stress testing), effects may be more pronounced and persistent, corresponding to continued exposure. Use infusions with caution in patients

	with autonomic dysfunction, carotid stenosis (with cerebrovascular insufficiency), hypovolemia, pericarditis, pleural effusion and/or stenotic valvular heart disease; discontinue infusion in patients who develop persistent or symptomatic hypotension. Proarrhythmic effects: Monitor for proarrhythmic effects (eg, polymorphic ventricular tachycardia) during and shortly after administration/termination of arrhythmia. The benign transient occurrence of atrial and ventricular ectopy is common upon termination of arrhythmia. Seizures: Seizures (new-onset or recurrent) have been reported; risk may be increased with concurrent use of aminophylline. Concomitant use of any methylxanthine (e.g., aminophylline, caffeine, theophylline) is not recommended. **Disease-related concerns:** • Arrhythmia (wide-complex tachycardia): Avoid use in irregular or polymorphic wide-complex tachycardias; may cause degeneration to ventricular fibrillation. • Heart transplant recipients: Use with extreme caution in heart transplant recipients; adenosine may cause prolonged asystole; reduction of initial adenosine dose is recommended; considered by some to be contraindicated in this setting. • Pulmonary artery hypertension: Acute vasodilator testing (not an approved use): Use with extreme caution in patients with

	concomitant heart failure (LV systolic dysfunction with significantly elevated left heart filling pressures) or pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis; significant decompensation has occurred with other highly selective pulmonary vasodilators resulting in acute pulmonary edema. • Respiratory disease: Avoid use in patients with bronchoconstriction or bronchospasm (eg, asthma); dyspnea, bronchoconstriction, and respiratory compromise have occurred during use. Use caution in patients with obstructive lung disease not associated with bronchoconstriction (eg, emphysema, bronchitis). Immediately discontinue therapy if severe respiratory difficulty is observed. Appropriate measures for resuscitation should be available during use. • Wolff-Parkinson-White (WPW) syndrome: Adenosine should not be used in patients with WPW syndrome and preexcited atrial fibrillation/flutter since ventricular fibrillation may result. **Concurrent drug therapy issues:** • Caffeine: Pharmacologic stress testing: Since caffeine antagonizes the activity of adenosine, withhold for 5 half-lives prior to adenosine use; avoid dietary caffeine for at least 12

	hours prior to pharmacologic stress testing. • Dipyridamole: Concomitant use potentiates the effects of adenosine; reduction of initial adenosine dose is recommended when used for SVT; withhold dipyridamole-containing medications for at least 48 hours prior to pharmacologic stress testing. • Theophylline or aminophylline: Pharmacologic stress testing: Since methylxanthines antagonizes the activity of adenosine, withhold for 5 half-lives prior to adenosine use whenever possible. **Other warnings/precautions:** • Appropriate use: ECG monitoring is required during use. Equipment for resuscitation and trained personnel experienced in handling medical emergencies should always be immediately available. Adenosine does not convert atrial fibrillation/flutter to normal sinus rhythm; however, may be used diagnostically in these settings if the underlying rhythm is not apparent.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A thorough review of various HTA bodies including NICE, CADTH, HAS, IQWIG, and PBAC yielded **no recommendations for the use of adenosine for the treatment of arrhythmias.** Nevertheless, adenosine has been marketed worldwide for many years, and multiple generic options are available, leading to a low cost of treatment.

CONCLUSION STATEMENT – ADENOSINE

Adenosine is recommended in the treatment of atrioventricular nodal reentrant tachycardia.

There are no recommendations issued by HTA bodies on the use of adenosine atrioventricular reentrant tachycardia, however, it has been available on the market for years and multiple generics are available.

2.6 Cardiac Glycosides

2.6.1 Digoxin

Table 20. Digoxin Drug Information

SCIENTIFIC NAME **Digoxin**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	No
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	I49
Drug Class	Antiarrhythmic agent
Drug Sub-class	Cardiac Glycoside
ATC Code	C01AA05
Pharmacological Class (ASHP)	24:04.04.92 Antiarrhythmics, Miscellaneous
DRUG INFORMATION	
Dosage Form	Tablet, Solution, Solution for injection
Route of Administration	Oral use, Intravenous use
Dose (Adult) [DDD]*	**Atrial fibrillation/flutter, rate control (alternative agent):** - **Total digitalizing dose (TDD):** o **Oral/IV:** 0.25 to 0.5 mg once; repeat doses of 0.25 mg every 6 hours to a maximum of 1.5 mg over 24 hours.

	or o **Oral/IV:** 8 to 12 mcg/kg (use lean body weight; not to exceed 0.75 to 1.5 **mg** over 24 hours); administer by giving 50% of TDD once, then administer the remaining 50% as 2 doses of 25% of TDD at 4- to 8-hour intervals; round doses to standard amounts. - **Maintenance dose:** Oral: 0.125 to 0.25 mg once daily. **Fetal supraventricular tachyarrhythmia, sustained (maternal administration for transplacental transfer to the fetus) (off-label use): Maternal dose:** - **Loading dose (may be given oral or IV):** o **IV:** 1.2 to 1.5 mg over 24 hours given in divided doses every 8 hours; follow with oral maintenance regimen. o **Oral:** 1 to 2 mg given over 24 to 48 hours in divided doses (eg, 0.5 mg followed by 0.25 mg, then 0.25 mg over the first 18 to 24 hours with subsequent additional doses as needed to achieve target levels); follow with an oral maintenance regimen.

	- **Maintenance dose: Oral:** 0.375 mg to 0.75 mg per day given in divided doses every 8 to 12 hours. Adjust dose to maintain a target maternal blood level between 0.7 and 2 ng/mL. **Atrioventricular nodal reentrant tachycardia, rate control (alternative agent) (off-label use):** - **Total digitalizing dose:** o **Oral:** Initial: 0.5 mg loading dose, with additional 0.125 to 0.25 mg doses administered at 6- to 8-hour intervals until evidence of adequate effect (maximum total dose over 24 hours: 8 to 12 **mcg**/kg [use lean body weight], not to exceed 0.75 to 1.5 **mg**). o **IV:** Initial: 0.25 to 0.5 mg loading dose, with additional 0.25 mg doses administered at 6- to 8-hour intervals until evidence of adequate effect (maximum total dose over 24 hours: 8 to 12 **mcg**/kg [use lean body weight], not to exceed 0.75 to 1.5 **mg**) - **Maintenance dose: Oral:** 0.125 to 0.25 mg once daily.
Maximum Daily Dose Adults*	- **Atrial flutter:** N/A - **Fetal supraventricular tachyarrhythmia:** N/A - **Atrioventricular nodal reentrant tachycardia: TDD:** maximum

	total dose over 24 hours: 8 to 12 **mcg**/kg.
Dose (pediatrics)	**Tachyarrhythmias, treatment:** Limited data available: - **Initial (digitalizing dose):** o **IV:** 10 to 12 mcg/kg/dose every 8 hours for 3 doses. o **Oral:** 13 to 17 mcg/kg/dose every 8 hours for 3 doses. - **Maintenance: Oral:** 8 to 10 mcg/kg/day divided once or twice daily (Escudero 2012); use twice daily dosing in infants and young children
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Adult** **<u>Renal Impairment:</u>** **Altered kidney function:** ➢ Loading dose: Note: Use with caution and only when rapid ventricular rate control is necessary. o CrCl >15 mL/minute: No dosage adjustment necessary. o CrCl ≤15 mL/minute: Administer 50% of usual dose. ➢ Maintenance: Note: Patients with low lean body weight may require lower doses. Doses of 0.0625 mg once daily may be given as 0.125 mg every other day. o CrCl ≥60 mL/minute: No dosage adjustment necessary. o CrCl 45 to <60 mL/minute: 0.0625 to 0.125 mg once daily. o CrCl 30 to <45 mL/minute: 0.0625 mg once daily.

	○ CrCl <30 mL/minute: 0.0625 mg every 48 hours or consider alternative agent. **Hemodialysis, intermittent (thrice weekly):** Not dialyzable: **Note:** Avoid use if possible; use in end-stage kidney disease is associated with increased mortality: ➢ **Loading dose: Oral, IV:** Use with caution and only when rapid ventricular rate control is necessary. Reduce to 50% of usual dose. ➢ **Maintenance dose: Oral, IV:** 0.0625 mg every 48 hours or 3 times/week may be considered. **Peritoneal dialysis:** Not dialyzable: **Note:** Avoid use if possible: ➢ **Loading dose: Oral, IV:** Use with caution and only when rapid rate control is necessary. Reduce to 50% of usual dose. ➢ **Maintenance dose: Oral, IV:** 0.0625 mg every 48 hours may be considered. **CRRT: Note:** Avoid use if possible: ➢ **Loading dose: Oral, IV:** Reduce to 50% of usual dose. Use with caution and only when rapid rate control is necessary. ➢ **Maintenance dose: Oral, IV:** 0.0625 to 0.125 mg every 48 hours may be considered. **PIRRT (eg, sustained, low-efficiency diafiltration): Note:** Avoid use if possible: ➢ **Loading dose: Oral, IV:** Reduce to 50% of usual dose. Use with caution and only when rapid rate control is necessary.

	➢ **Maintenance dose: Oral, IV:** 0.0625 to 0.125 mg every 48 hours may be considered. **<u>Hepatic Impairment:</u>** No dosage adjustment necessary. **Pediatric** **<u>Renal Impairment:</u>** - **Digitalizing (loading) dose:** There are no dosage adjustments provided in the manufacturer's labeling for digitalizing dose; however, 50% to 70% of a digoxin dose is excreted unchanged in the urine. The following adjustments have been recommended in adults with end-stage renal disease (ESRD): Reduce usual dose by 50%. - **Maintenance dose:** Manufacturer's labeling: Dosage reductions and close monitoring recommended; see product labeling for CrCl-specific dosage recommendation. Alternate dosing: The following adjustments have been recommended: ➢ GFR >50 mL/minute/1.73 m2: No dosage adjustment necessary ➢ GFR: 30 to 50 mL/minute/1.73 m2: Administer 75% of normal dose at normal intervals. ➢ GFR: 10 to 29 mL/minute/1.73 m2: Administer 50% of normal dose at normal intervals or administer normal dose every 36 hours. ➢ GFR: <10 mL/minute/1.73 m2: Administer 25% of normal dose at normal intervals or administer normal dose every 48 hours.

	➢ Intermittent hemodialysis: Nondialyzable (0% to 5%). Administer 25% of normal dose at normal intervals or administer normal dose every 48 hours. ➢ Peritoneal dialysis (PD): Administer 25% of normal dose at normal intervals or administer normal dose every 48 hours. ➢ Continuous renal replacement therapy (CRRT): Administer 75% of normal dose at normal intervals; titrate to desired effect; monitor serum concentrations.
Prescribing edits*	MD, ST
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Should be prescribed by a cardiologist.
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	Considered as second-line therapy in fetal tachyarrhythmias.
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Frequency of adverse reactions is not defined.** **Most serious**: Asystole, complete atrioventricular block, first degree atrioventricular block, thrombocytopenia, altered mental status, hallucination.
Drug Interactions*	**Category X:** • Disulfiram • Fexinidazole • Lasmiditan • Methotrimeprazine • MetroNIDAZOLE (Systemic)

	• Milnacipran • Ornidazole • Pacritinib • Secnidazole • Sparsentan • Taurursodiol
Special Population	Infants: Newborn infants display considerable variability to their tolerance to digoxin; premature and immature infants are particularly sensitive to the effects of digoxin.
Pregnancy	Digoxin crosses the placenta. Available guidelines note experience with digoxin in pregnancy is extensive. Based on available data, an increased risk of adverse pregnancy outcomes has not been observed. However, untreated maternal heart failure and atrial fibrillation may increase the risk of preterm birth and low birth weight, respectively. The manufacturer recommends monitoring neonates for signs and symptoms of digoxin toxicity following in utero exposure. Due to pregnancy-induced physiologic changes, some pharmacokinetic properties of digoxin may be altered. Close monitoring of maternal serum digoxin is recommended; dose adjustments may be required during pregnancy and postpartum. Heart failure and atrial fibrillation may worsen during pregnancy. Digoxin is recommended as a first-line agent for the chronic treatment of highly symptomatic supraventricular tachycardia (SVT) in pregnancy; the lowest effective dose is recommended. Digoxin may be considered for long-term rate control of maternal atrial

	tachycardia or atrial fibrillation when preferred agents fail. Monitor for an increased risk of maternal arrhythmias during labor and delivery. Digoxin may be considered for the in utero management of fetal SVT or atrial flutter with hydrops or ventricular dysfunction. Digoxin may also be considered for SVT without hydrops or ventricular dysfunction if heart rate is ≥200 bpm, atrial flutter, or other rare tachycardias with an average heart rate of ≥200 bpm.
Lactation	Digoxin is present in breast milk. The manufacturer reports the relative infant dose (RID) of digoxin to be 1% to 7% of a weight-adjusted maternal dose or ~ 0.2% to 4% of a neonatal maintenance dose. In general, breastfeeding is considered acceptable when the RID of a medication is <10%. The amount of digoxin available to the infant via breast milk is not likely to be clinically significant. The World Health Organization considers digoxin to be compatible with breastfeeding.
Contraindications	Hypersensitivity to digoxin, other forms of digitalis, or any component of the formulation; ventricular fibrillation.
Monitoring Requirements	Heart rate and rhythm should be monitored along with periodic ECGs to assess desired effects and signs of toxicity; baseline and periodic serum creatinine. Periodically monitor serum potassium, magnesium, and calcium especially if on medications where these electrolyte disturbances can occur (eg, diuretics), or if patient has a history of hypokalemia or hypomagnesemia. Observe patients for

	noncardiac signs of toxicity, confusion, and depression. When to draw serum digoxin concentrations: Digoxin serum concentrations are monitored because digoxin possesses a narrow therapeutic serum range; the therapeutic endpoint is difficult to quantify and digoxin toxicity may be life-threatening. Digoxin serum concentrations should be drawn at least 6 to 8 hours after last dose, regardless of route of administration (optimally 12 to 24 hours after a dose).
Precautions	**Concerns related to adverse effects:** - Extravasation: IV administration: Vesicant; ensure proper needle or catheter placement prior to and during administration; avoid extravasation. **Disease-related concerns:** - Accessory bypass tract (eg, Wolff-Parkinson-White [WPW] syndrome): During an episode of atrial fibrillation or flutter in patients with an accessory bypass tract or pre-excitation syndrome, use has been associated with increased anterograde conduction down the accessory pathway leading to ventricular fibrillation; avoid use in such patients. - Acute coronary syndrome: Use with caution in patients with an acute MI; may increase myocardial oxygen demand and lead to ischemia. During an acute coronary syndrome, digoxin administered IV may be used to slow a rapid ventricular response

	and improve left ventricular (LV) function in the acute treatment of atrial fibrillation associated with severe LV function and heart failure or hemodynamic instability. - Atrial fibrillation: When used for rate control in patients with atrial fibrillation, monitor serum concentrations closely; may be associated with an increased risk of mortality especially when serum concentrations are not properly controlled. - Beri beri heart disease: Patients with beri beri heart disease may fail to adequately respond to digoxin therapy; treat underlying thiamine deficiency concomitantly. - Electrolyte imbalance: Correct electrolyte disturbances, especially hypokalemia or hypomagnesemia, prior to use and throughout therapy. Hypercalcemia may increase the risk of digoxin toxicity and hypocalcemia can nullify the effects of digoxin; maintain normocalcemia. - Heart failure with reduced ejection fraction: Digoxin should be considered for use only in heart failure (HF) with reduced ejection fraction (HFrEF) when symptoms remain despite guideline-directed medical therapy. It may also be considered in patients with both HF and atrial fibrillation; however, beta blockers may offer better

	ventricular rate control than digoxin. Withdrawal of digoxin in clinically stable patients with HF may lead to recurrence of HF symptoms. Monitor serum concentrations closely; may be associated with an increased risk of mortality especially when serum concentrations are not properly controlled. - Hypermetabolic states: Atrial arrhythmias associated with hypermetabolic (eg, hyperthyroidism) or hyperdynamic (hypoxia, arteriovenous shunt) states are very difficult to treat; treat underlying condition first. If digoxin is used, ensure digoxin toxicity does not occur. - Hypertrophic cardiomyopathy with left ventricular outflow tract obstruction: Outflow obstruction may worsen due to the positive inotropic effects of digoxin; avoid use unless used to control ventricular response with atrial fibrillation. Digoxin is potentially harmful in the treatment of dyspnea in patients with HCM in the absence of atrial fibrillation. - Kidney impairment: Use with caution in patients with kidney impairment; dosage adjustment needed. - Myocarditis: In a murine model of viral myocarditis, digoxin in high doses was shown to be detrimental. If used in humans, therefore, digoxin should be used with caution and only at low

	doses. The manufacturer recommends avoiding the use of digoxin in patients with myocarditis. - Preserved left ventricular function: Decreased cardiac output may occur in patients with preserved left ventricular systolic function, including restrictive or hypertrophic cardiomyopathy, constrictive pericarditis, amyloid heart disease, and acute cor pulmonale; in general, the manufacturer recommends to avoid use unless used to control ventricular response with atrial fibrillation. - Sinus node disease and atrioventricular (AV) block: Because digoxin slows sinoatrial and AV conduction, the drug commonly prolongs the PR interval. Digoxin may cause severe sinus bradycardia or sinoatrial block particularly in patients with preexisting sinus node disease. Avoid use in patients with second- or third-degree heart block (except in patients with a functioning artificial pacemaker); incomplete AV block (eg, Stokes-Adams attacks) may progress to complete block with digoxin administration. In such patients, if treatment with digoxin is necessary, consider the insertion of a pacemaker before treatment. - Thyroid disease: Use with caution in patients with hypothyroidism,

	higher digoxin concentrations may result due to significant reduction in digoxin clearance. In patients with hyperthyroidism, lower digoxin concentrations may result due to an increase in renal clearance of digoxin. No significant differences in absorption were seen in either thyroid condition compared with those with normal thyroid function. **Other warnings/precautions:** - Elective electrical cardioversion: It is not necessary to routinely reduce or hold digoxin therapy prior to elective electrical cardioversion for atrial fibrillation; however, exclusion of digoxin toxicity (eg, clinical and ECG signs) is necessary prior to cardioversion. If signs of digoxin excess exist, withhold digoxin and delay cardioversion until toxicity subsides.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A thorough review of various HTA bodies including NICE, CADTH, HAS, IQWIG, and PBAC yielded **no recommendations for the use of digoxin for the treatment of arrhythmias.** Nevertheless, digoxin has been marketed worldwide for many years, and multiple generic options are available, leading to a low cost of treatment.

CONCLUSION STATEMENT – DIGOXIN

Digoxin is recommended in the treatment of atrial flutter, rate control, fetal supraventricular tachyarrhythmia and atrioventricular nodal reentrant tachycardia.

There are no recommendations issued by HTA bodies on the use of digoxin in these indications, however, it has been available on the market for years and multiple generics are available.

2.7 Electrolytes

2.7.1 Magnesium Sulfate

Table 21. Magnesium Sulfate Drug Information

SCIENTIFIC NAME Magnesium sulfate	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	I49
Drug Class	Electrolyte Supplement
Drug Sub-class	Magnesium Salt
ATC Code	A12CC02
Pharmacological Class (ASHP)	24:04.04 Antiarrhythmic Agents
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Parenteral use
Dose (Adult) [DDD]*	**Torsades de pointes (off-label use): Polymorphic ventricular tachycardia (with pulse) associated with QT prolongation (torsades de pointes):** ○ IV: 1 to 2 g (diluted in 50 to 100 mL D5W) over 15 minutes (range: 5 to 60 minutes). If no response or torsades de pointes recurs, may repeat dose up to a total of 4 g in 1 hour; may follow with a continuous IV infusion of 0.5 to 1 g/hour.

	Ventricular fibrillation/pulseless ventricular tachycardia associated with torsades de pointes: Note: Administer in conjunction with electrical cardioversion/defibrillation. o IV/intraosseous: 1 to 2 g (diluted in 10 mL D5W) administered as a bolus over ≥1 to 2 minutes; if ineffective, may repeat immediately; use intraosseous route if IV not available. Some experts recommend a 2 g bolus initially and repeat up to 2 additional 2 g bolus doses as needed; maximum total dose: 6 g.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	**Torsade de pointes or ventricular fibrillation/pulseless ventricular tachycardia associated with torsade de pointes:** Dose expressed as magnesium sulfate: - Infants, Children, and Adolescents: IV, Intraosseous: 25 to 50 mg/kg/dose.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Renal Impairment:** N/A. **Hepatic Impairment:** No dosage adjustment necessary.
Prescribing edits*	MD, QL, EU
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Should be prescribed by a cardiologist.
PA (Prior Authorization)	N/A
QL (Quantity Limit)	**Ventricular fibrillation/pulseless ventricular tachycardia associated**

	with torsades de pointes: maximum total dose: 6 g For pediatrics: Maximum dose: 2,000 mg/dose
ST (Step Therapy)	N/A
EU (Emergency Use Only)	***Ventricular fibrillation/pulseless ventricular tachycardia associated with torsades de pointes:*** **Note:** Administer in conjunction with electrical cardioversion/defibrillation.
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Frequency of adverse reactions is not defined.** **Most serious**: Flushing (IV; dose related), hypotension (IV; rate related), vasodilation (IV; rate related).
Drug Interactions*	**Category X:** • Baloxavir Marboxil • Calcium Polystyrene Sulfonate • Levonadifloxacin • Raltegravir • Sodium Polystyrene Sulfonate • Unithiol
Special Population	Obstetrics: Vigilant monitoring and safe administration techniques (ISMP 2005) are recommended to avoid potential for errors resulting in toxicity. Monitor mother and fetus closely. Use longer than 5 to 7 days may cause adverse fetal events.
Pregnancy	Magnesium crosses the placenta; serum concentrations in the fetus are similar to those in the mother. Continuous maternal use for >5 to 7 days (in doses such as those used for preterm labor, an off-label use) may cause fetal hypocalcemia and bone abnormalities, as well as fractures in the neonate.

Lactation	Magnesium is present in breast milk. When magnesium sulfate is used in the intrapartum management of eclampsia, breast milk concentrations are generally increased for only ~24 hours after the end of treatment. In one study, this amounted to an increase of only 1.5 mg of magnesium to the breastfed infant on the first day after maternal therapy was stopped. Magnesium is endogenous to breast milk; concentrations remain constant during the first year of lactation and are not influenced by dietary intake under normal conditions. Milk concentrations of magnesium are variable between females but are generally consistent within a given mother. Magnesium requirements are the same in breastfeeding and nonbreastfeeding females. Although the manufacturer recommends that caution be used if administered to breastfeeding females; magnesium sulfate when used for the prevention of seizures is considered compatible with breastfeeding.
Contraindications	Hypersensitivity to digoxin, other forms of digitalis, or any component of the formulation; ventricular fibrillation.
Monitoring Requirements	IV: Rapid administration: ECG monitoring, vital signs, deep tendon reflexes; magnesium concentrations if frequent or prolonged dosing required particularly in patients with renal dysfunction, calcium, and potassium concentrations; renal function. Obstetrics: Patient status including vital signs, oxygen saturation, respiration, deep tendon reflexes, level of consciousness, fetal heart rate, maternal uterine activity, renal function. Monitor

	magnesium concentrations every 4 hours in patients with renal dysfunction (every 2 hours if serum magnesium is >8 mEq/L.
Precautions	**Disease-related concerns:** - Neuromuscular disease: Use with extreme caution in patients with myasthenia gravis or other neuromuscular disease. - Renal impairment: Use with caution in patients with renal impairment; accumulation of magnesium may lead to magnesium intoxication. **Other warnings/precautions:** - Appropriate use: Unlikely to effectively terminate irregular/polymorphic VT. - Electrolyte abnormalities: Concurrent hypokalemia or hypocalcemia can accompany a magnesium deficit. Hypomagnesemia is frequently associated with hypokalemia and requires correction in order to normalize potassium. - Parenteral administration: Magnesium toxicity can lead to fatal cardiovascular arrest and/or respiratory paralysis. - Self-medication (OTC use): When used as a laxative, patients should consult a health care provider prior to use if they have: kidney disease; are on a magnesium-restricted diet; have abdominal pain, nausea, or vomiting; change in bowel habits lasting >2 weeks; have already used a laxative for >1 week.
Black Box Warning	N/A

REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A thorough review of various HTA bodies including NICE, CADTH, HAS, IQWIG, and PBAC yielded **no recommendations for the use of magnesium sulfate for the treatment of arrhythmias.** Nevertheless, magnesium sulfate has been marketed worldwide for many years, and multiple generic options are available, leading to a low cost of treatment.

CONCLUSION STATEMENT – MAGNESIUM SULFATE

Magnesium sulfate is recommended in the treatment of torsades de pointes.

There are no recommendations issued by HTA bodies on the use of magnesium sulfate in torsades de pointes indications, however, it has been available on the market for years and multiple generics are available.

2.8 Hyperpolarization-activated Cyclic Nucleotide-gated (HCN) Channel Blockers

2.8.1 Ivabradine

Table 22. Ivabradine Drug Information

SCIENTIFIC NAME Ivabradine	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	I49
Drug Class	Cardiovascular Agent
Drug Sub-class	N/A
ATC Code	C01EB17
Pharmacological Class (ASHP)	24:04.04 Antiarrhythmic Agents
DRUG INFORMATION	
Dosage Form	Film-coated tablet
Route of Administration	Oral use

Dose (Adult) [DDD]*	**Inappropriate sinus tachycardia (off-label use):** Oral: Initial: 5 mg twice daily; maintenance: 7.5 mg twice daily. May also use in combination with a beta-blocker (e.g., metoprolol) in patients who are refractory to monotherapy.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Renal Impairment:** - CrCl ≥15 mL/minute: No dosage adjustment necessary. - CrCl <15 mL/minute: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied). **Hepatic Impairment:** - Mild or moderate impairment (Child-Pugh class A or B): No dosage adjustment necessary. - Severe impairment (Child-Pugh class C): Use is contraindicated (has not been studied; increase in systemic exposure anticipated).
Prescribing edits*	MD
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Should be prescribed by a cardiologist.
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Bradycardia, hypertension, atrial fibrillation, phosphene.

	<u>Most serious</u>: Angioedema, syncope, visual impairment.
Drug Interactions*	**<u>Category X:</u>** • CYP3A4 Inducers (Moderate) • CYP3A4 Inducers (Strong) • CYP3A4 Inhibitors (Moderate) • CYP3A4 Inhibitors (Strong) • Fexinidazole • Fusidic Acid (Systemic) • Grapefruit Juice
Special Population	N/A
Pregnancy	Adverse events have been observed in animal reproduction studies, and fetal harm may occur if ivabradine is administered to pregnant women. If treatment is needed during pregnancy, closely monitor for destabilization of heart failure that could potentially result from heart rate slowing caused by ivabradine, especially during the first trimester. Pregnant women with chronic heart failure should also be monitored for preterm birth.
Lactation	It is not known if ivabradine is present in breast milk. Due to the potential risk from exposure in the breastfed infant, breastfeeding is not recommended by the manufacturer.
Contraindications	- Acute decompensated heart failure; clinically significant hypotension; sick sinus syndrome, sinoatrial block, or third-degree AV block (unless a functioning demand pacemaker is present); clinically significant bradycardia; severe hepatic impairment; pacemaker dependence (heart rate maintained exclusively by the

	pacemaker); concomitant use with strong CYP3A4 inhibitors. - Canadian labeling: Additional contraindications (not in US labeling): Hypersensitivity to ivabradine or any component of the formulation; resting heart rate <70 bpm prior to treatment; prolonged QT interval (eg, congenital long QT syndrome); cardiogenic shock; acute myocardial infarction; concomitant use of verapamil or diltiazem; pregnancy, breastfeeding, or women of child-bearing potential not using appropriate contraception; hereditary problems of galactose intolerance, glucose-galactose malabsorption, or the congenital lactase deficiency.
Monitoring Requirements	Monitor heart rate (prior to initiation, prior to increasing dose, or after decreasing dose); monitor heart rate more closely if receiving other negative chronotropes (e.g., amiodarone, beta-blockers, digoxin); blood pressure; regularly monitor cardiac rhythm (assessing for atrial fibrillation).
Precautions	**Concerns related to adverse events:** - Atrial fibrillation: Use increases the risk of atrial fibrillation; monitor cardiac rhythm. Discontinue if atrial fibrillation develops. - Bradycardia and conduction disturbances: Bradycardia, sinus arrest, and heart block may occur; monitor heart rate prior to initiation and with any dosage adjustment. Bradycardia may

	increase the risk of QT prolongation, which may lead to severe ventricular arrhythmias, including torsade de pointes, especially in patients with risk factors such as use of QTc prolonging drugs. Risk factors for bradycardia include sinus node dysfunction, conduction defects (eg, first- or second-degree AV block, bundle branch block), ventricular dyssynchrony, and use of other negative chronotropes (eg, digoxin, diltiazem, verapamil, amiodarone). Avoid concurrent use with verapamil and diltiazem. Avoid use in patients with second-degree AV block (unless a functioning demand pacemaker is present). Use is contraindicated in patients with sick sinus syndrome, sinoatrial block, third-degree AV block (unless a functioning demand pacemaker is present), or pacemaker dependence. Decrease dose or discontinue use if heart rate <50 bpm persists during therapy or signs and symptoms of bradycardia occur. Use is contraindicated in patients with clinically significant bradycardia. In patients with history of conduction defects or in whom bradycardia could lead to hemodynamic compromise, initial dosage reduction is recommended. Heart rate reduction may prolong the uncorrected QT interval while

	QTc interval remains unchanged (Camm 2003; Murat 2009). At concentrations slightly higher than that achieved with therapeutic dosing, ivabradine prolonged ventricular repolarization in perfused guinea-pig hearts. Torsades de pointes has been reported when used with other drugs that produce bradycardia or prolong the QT interval. - Visual function: Phosphenes (described as transient enhanced brightness in a limited area of the visual field, halos, image decomposition, colored bright lights, or multiple images) may occur with use. Onset is generally within the first 2 months of therapy and is reported to be of mild to moderate intensity; most cases resolve during or after treatment discontinuation.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A thorough review of various HTA bodies including NICE, CADTH, HAS, IQWIG, and PBAC yielded **no recommendations for the use of ivabradine for the treatment of arrhythmias.** Nevertheless, ivabradine has been marketed worldwide for many years, and multiple generic options are available, leading to a low cost of treatment.

CONCLUSION STATEMENT – IVABRADINE

Ivabradine is recommended in the treatment of inappropriate sinus tachycardia and postural tachycardia syndrome (POTS).

There are no recommendations issued by HTA bodies on the use of ivabradine in inappropriate sinus tachycardia, however, it has been available on the market for years and multiple generics are available.

Section 3.0 Key Recommendations Synthesis

Management of cLQTS

- The cornerstone of medical therapy is b-blockade, preferably with nadolol or propranolol. Cardiac rhythm devices such as pacemakers and ICDs are rarely required.[9]

Management of aLQTS

- aLQTS is classically due to QT-prolonging medications or electrolyte disturbances. Common drugs include antidepressants/antipsychotics, antibiotics, and antiarrhythmics. The treatment of aLQTS is mainly to stop these medications if necessary. [9]

Management of ventricular arrhythmias in the pregnancy not associated with inherited arrhythmia syndromes:

- In pregnant patients with idiopathic VT and hemodynamic stability, intravenous beta-blocker or adenosine for outflow tract VT and intravenous verapamil for fascicular VT are recommended as first-line options. (COR 1, LOE C-LD)[6]
- In pregnant patients with sustained VT refractory or with contraindications to beta-blockers and/or other antiarrhythmic drugs, synchronized cardioversion is recommended, with energy dosing as in the nonpregnant patient. (COR 1, LOE C-LD)[6]
- In pregnant patients with recurrent VT associated with hemodynamic impairment or ICD shocks, amiodarone is reasonable for arrhythmia suppression if alternative therapies, including ablation, are contraindicated or ineffective. (COR 2a, LOE C-LD)[6]

Fetal ventricular arrhythmias not associated with inherited arrhythmia syndromes:

- Fetuses with sustained VT with or without hydrops who are not considered to be mature enough for delivery should be treated trans placentally with either intravenous magnesium or oral propranolol, mexiletine, or lidocaine, alone or in combination, or with other antiarrhythmic agents according to the specific arrhythmia etiology, with frequent monitoring of fetal well-being and maternal drug toxicity. (COR 1, LOE B-NR)[6]

Management of long QT syndrome in pregnancy:

- In pregnant patients with LQTS and a preconception indication for beta-blocker therapy, beta-blockers should be continued throughout pregnancy, delivery, and the postpartum period, including breastfeeding. (COR 1, LOE B-NR)[6]

- In pregnant patients with LQTS2, therapy with a beta-blocker, particularly nadolol or propranolol, is recommended particularly during the postpartum period, which represents a high-risk period for cardiac events. (COR 1, LOE B-NR)[6]
- In pregnant patients with LQTS who experience cardiac arrest in pregnancy or in whom cardiac syncope or ventricular arrhythmias occur despite beta-blocker use, intensification of therapy including ICD implantation, if indicated, is recommended as in the nonpregnant patient. (COR1, LOE C-LD)[6]

<u>VA in the structurally normal heart</u>

- In patients with symptomatic PVCs in an otherwise normal heart, treatment with a beta blocker or nondihydropyridine calcium channel blocker is useful to reduce recurrent arrhythmias and improve symptoms. (COR 1, LOE B-R)[7]
- In patients with symptomatic VA in an otherwise normal heart, treatment with an antiarrhythmic medication is reasonable to reduce recurrent symptomatic arrhythmias and improve symptoms if beta blockers and nondihydropyridine calcium channel blockers are ineffective or not tolerated. (COR 2A, LOE B-R)[7]

<u>Outflow Tract and Atrioventricular Annular VA</u>

- In patients with symptomatic outflow tract VA in an otherwise normal heart for whom antiarrhythmic medications are ineffective, not tolerated, or not the patient's preference, catheter ablation is useful. (COR 1, LOE B-NR)[7]
- In patients with symptomatic outflow tract VT in an otherwise normal heart, a beta blocker or a calcium channel blocker is useful. (COR 1, LOE B-NR)[7]

<u>Treatment and Prevention of Recurrent VA in Patients with Ischemic Heart Disease</u>

- In patients with ischemic heart disease and recurrent VA, with significant symptoms or ICD shocks despite optimal device programming and ongoing treatment with a beta blocker, amiodarone or sotalol is useful to suppress recurrent VA. (COR 1, LOE B-R)[7]
- In patients with prior MI and recurrent episodes of symptomatic sustained VT, or who present with VT storm and have failed or are intolerant of amiodarone (LOE: B-R) or other antiarrhythmic medications (LOE: B-NR), catheter ablation is recommended. (COR 1, B-R)[7]

Inappropriate sinus tachycardia:

- Therapy is recommended mainly to control symptoms. Ivabradine is recommended for symptomatic patients. (recommended)[8]
- Beta-blockers and non-dihydropyridine calcium channel blockers are frequently ineffective or not tolerated at required doses. Therefore, may be considered as second- and third-line therapy, respectively. (May be recommended)[8]

Therapy of focal atrial tachycardia:

- Acute therapy
    - Synchronized DC cardioversion is recommended for hemodynamically unstable patients. (Is recommended)[8]
    - Adenosine may be used in terminating a non-reentrant AT or diagnosing the tachycardia mechanism. (May be recommended)[8]
    - IV beta blockers or verapamil or diltiazem may be used for pharmacologic cardioversion or rate control.[8]
- Chronic therapy
    - Catheter ablation is recommended, especially for incessant AT. (Is recommended)[8]
    - Beta blockers or verapamil or diltiazem may be considered. (May be recommended). If these options did not work, flecainide can be used.[8]

Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of arrhythmias.

These recommendations should be used to support and not supplant decisions in individual patient management.

Section 5.0 References

1. National Institutes of Health. Arrhythmias. 2023. Accessed December 18, 2023. https://www.ncbi.nlm.nih.gov/books/NBK558923/
2. *Atrial Fibrillation among Adult Saudi Patients with Chronic Heart Failure: Tertiary Center Experience*.
3. UpToDate. Arrhythmia management for the primary care clinician. Published 2021. Accessed December 18, 2023. https://www.uptodate.com/contents/arrhythmia-management-for-the-primary-care-clinician?search=arrhythmias&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H13
4. Levine E. Classifications of Antiarrhythmic Agents. Published 2019. Accessed December 18, 2023. https://emedicine.medscape.com/article/2172024-overview
5. Zeppenfeld K, Tfelt-Hansen J, De Riva M, et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2022;43(40):3997-4126. doi:10.1093/eurheartj/ehac262
6. Joglar JA, Kapa S, Saarel E V., et al. 2023 HRS expert consensus statement on the management of arrhythmias during pregnancy. *Heart Rhythm*. 2023;20(10):e175-e264. doi:10.1016/j.hrthm.2023.05.017
7. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: Executive Summary. *Circulation*. 2018;138(13):e210-e271. doi:10.1161/CIR.0000000000000548
8. Katritsis DG, Boriani G, Cosio FG, et al. European heart rhythm association (EHRA) consensus document on the management of supraventricular arrhythmias, endorsed by Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulación Cardiaca y Electrofisiologia (SOLAECE). *Europace*. 2017;19(3):465-511. doi:10.1093/europace/euw301
9. Davies RA, Ladouceur VB, Green MS, et al. The 2023 Canadian Cardiovascular Society Clinical Practice Update on Management of the Patient With a Prolonged QT Interval. *Canadian Journal of Cardiology*. 2023;39(10):1285-1301. doi:10.1016/j.cjca.2023.06.011
10. Marcus GM. Evaluation and Management of Premature Ventricular Complexes. *Circulation*. 2020;141(17):1404-1418. doi:10.1161/CIRCULATIONAHA.119.042434

Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

Appendix B. PubMed Search Methodology

Query	Filters	Search Details	Results
(((((((Arrhythmias, Cardiac[MeSH Terms]) OR (Arrhythmia, Cardiac[Title/Abstract])) OR (Cardiac Dysrhythmia[Title/Abstract])) OR (Dysrhythmia, Cardiac[Title/Abstract])) OR (Cardiac Arrhythmia[Title/Abstract])) OR (Cardiac Arrhythmias[Title/Abstract])) OR (Arrhythmia[Title/Abstract])) OR (Arrhythmia[Title/Abstract])	Guideline, in the last 5 years	("arrhythmias, cardiac"[MeSH Terms] OR "arrhythmia cardiac"[Title/Abstract] OR "cardiac dysrhythmia"[Title/Abstract] OR "dysrhythmia cardiac"[Title/Abstract] OR "cardiac arrhythmia"[Title/Abstract] OR "cardiac arrhythmias"[Title/Abstract] OR "Arrhythmia"[Title/Abstract] OR "Arrhythmia"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline [Filter]))	82

Appendix C. Treatment Algorithms

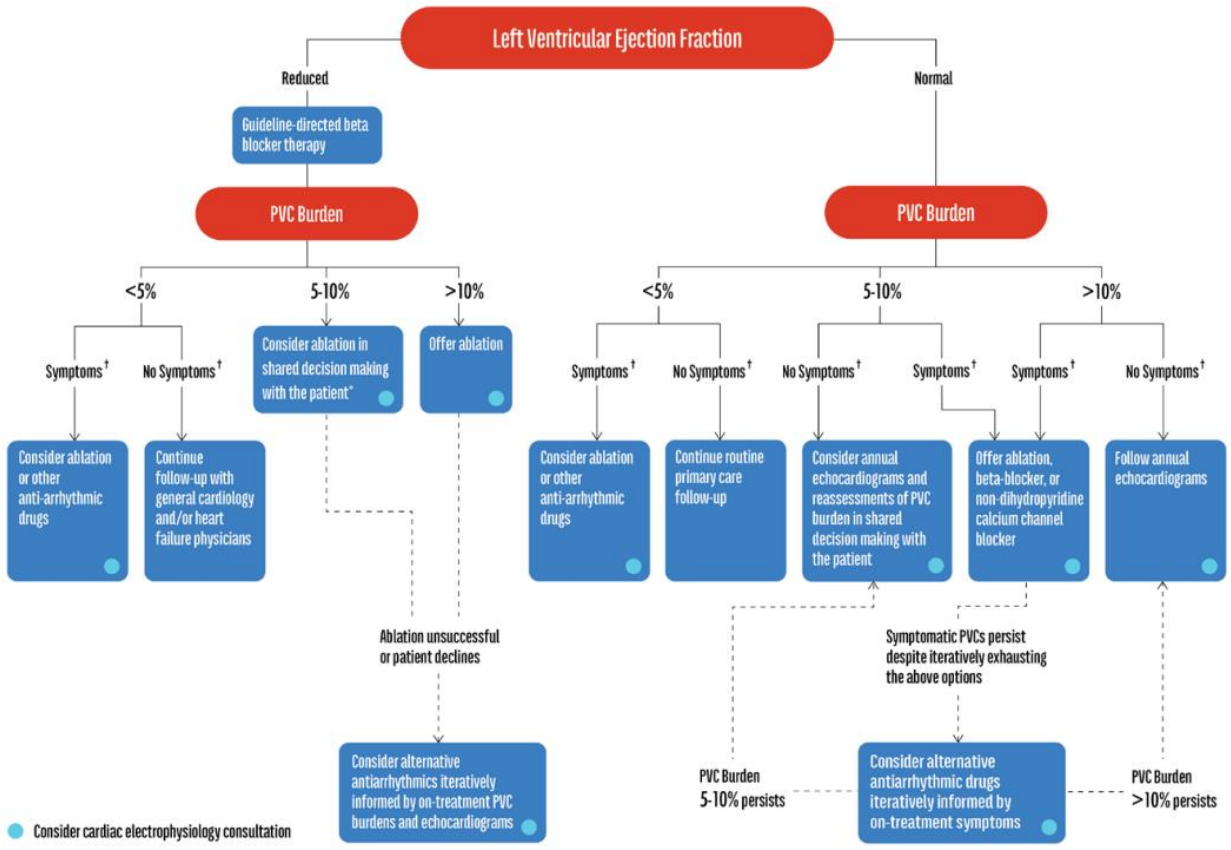

Figure 1. *Suggested workflow in considering the evaluation and management of patients with predominantly monomorphic premature ventricular complexes.*

Retrieved from the 2020 AHA recommendations.

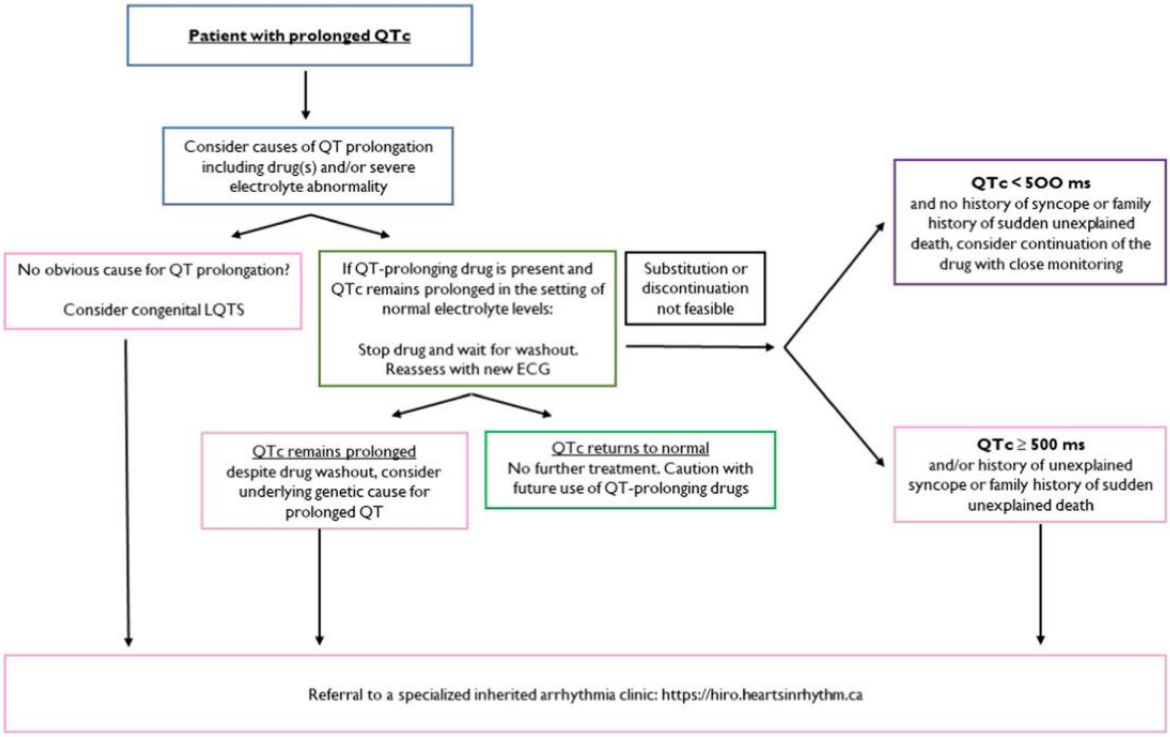

Figure 2. *Decision-making algorithm for the patient presenting with a prolonged QT interval corrected for heart rate (QTc).*

Retrieved from the 2023 Canadian cardiovascular society clinical practice guidelines.

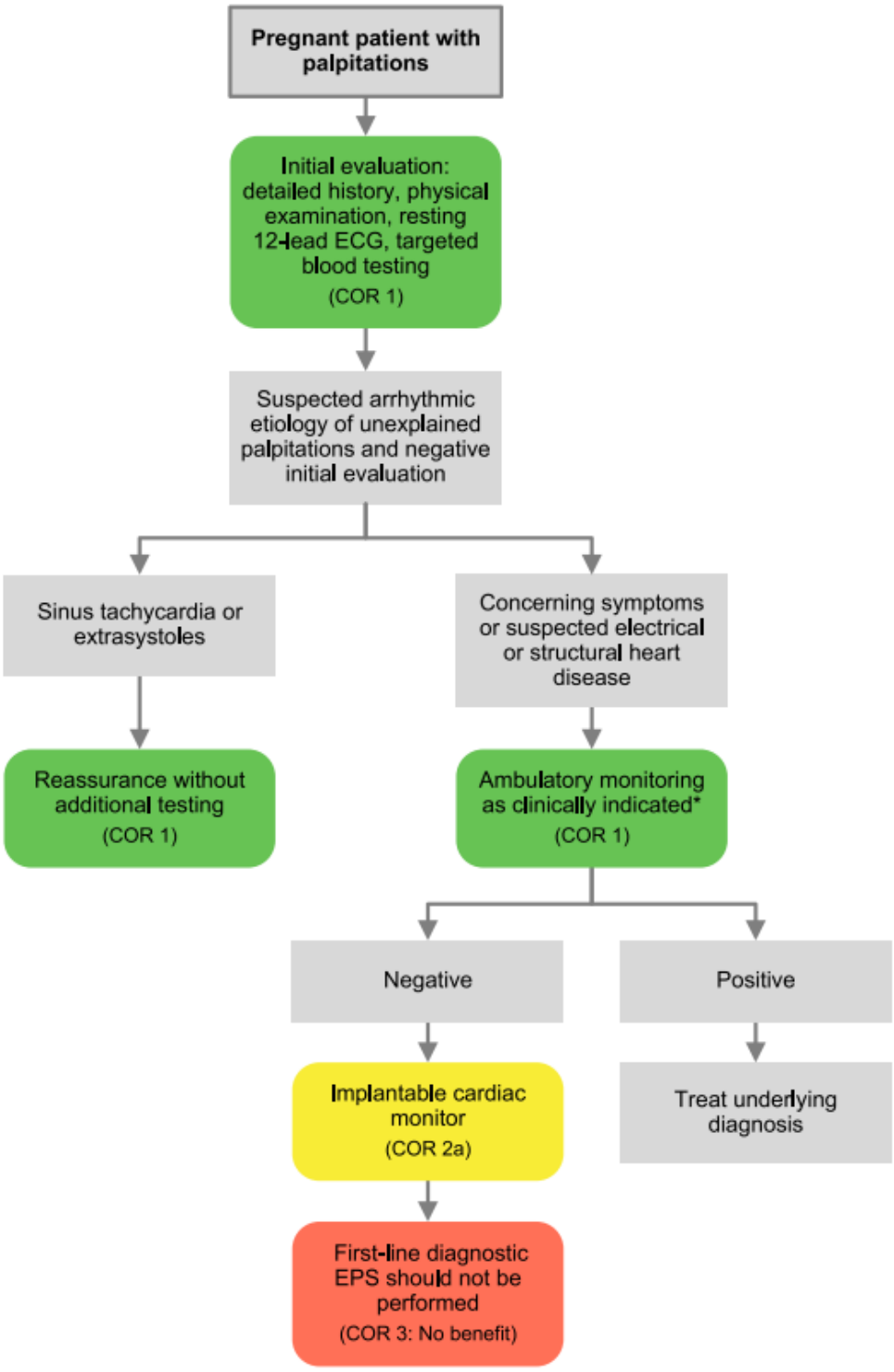

Figure 3. *Approach to the diagnosis of pregnant patients presenting with palpitations.*

Retrieved from the 2023 HRS consensus.

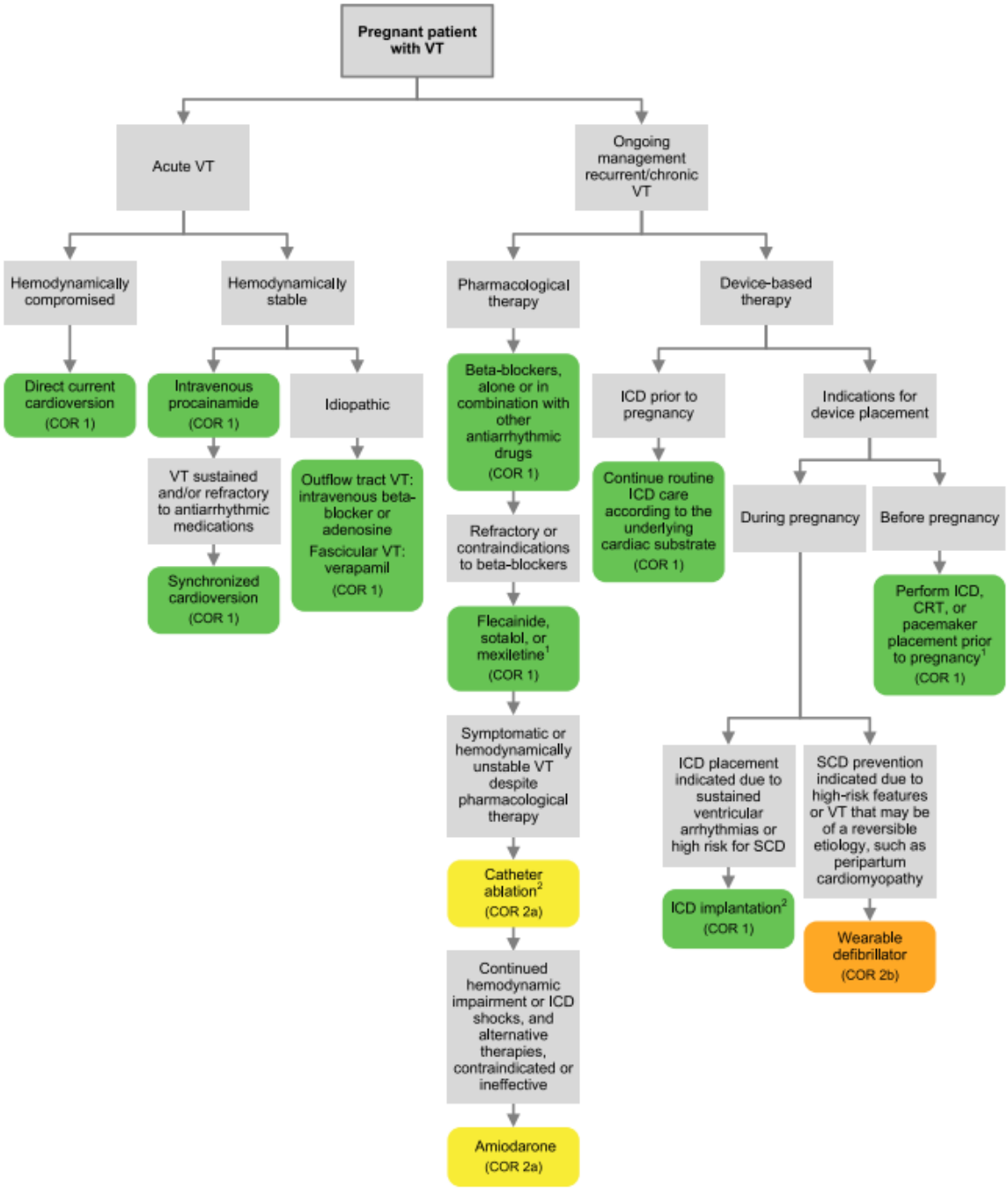

Figure 4. *Recommendations for the management of pregnant patients with ventricular arrhythmias.*

Retrieved from the 2023 HRS consensus.

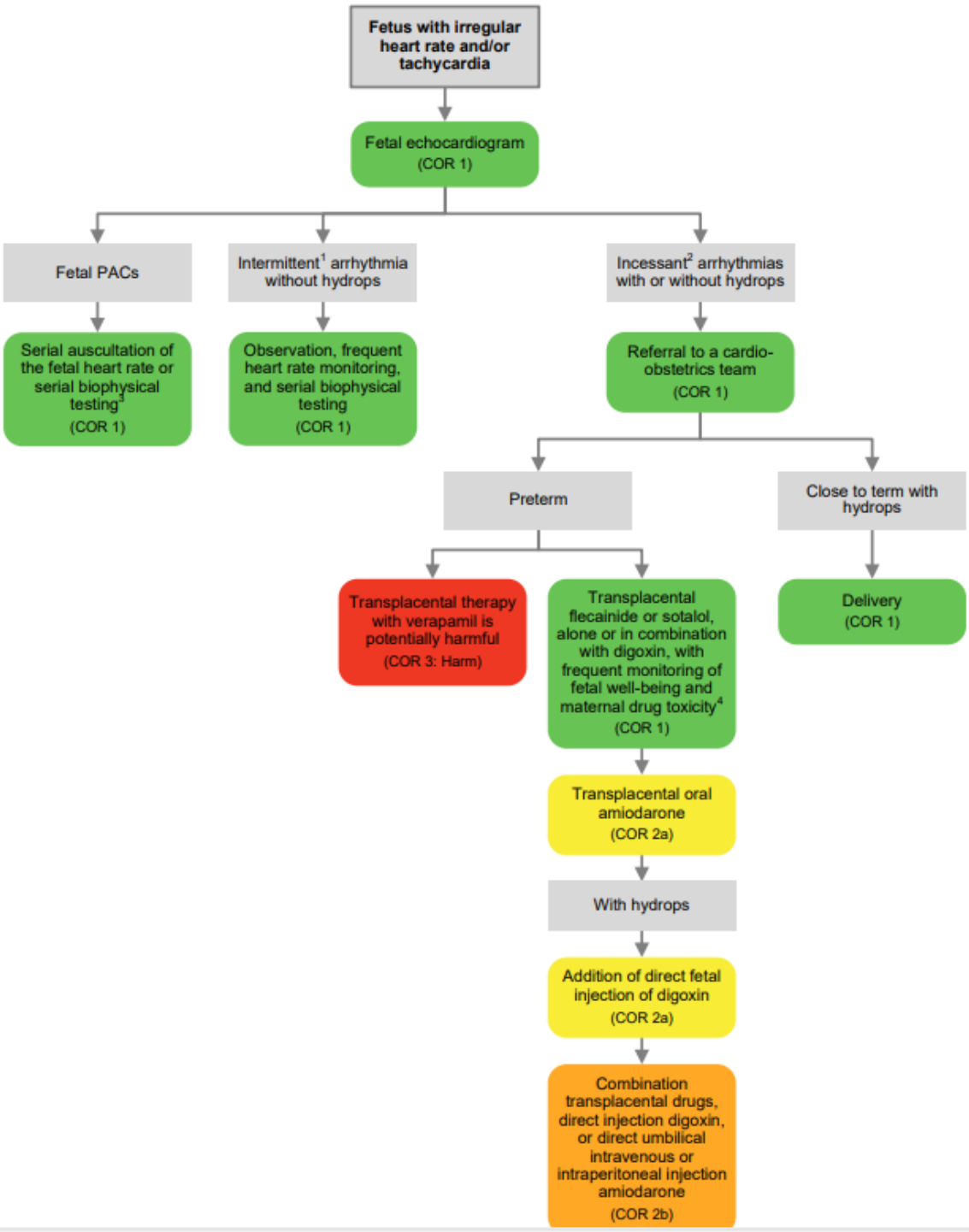

Figure 5. *Management of fetuses with irregular heart rate and tachycardia*

Retrieved from 2023 HRS consensus.

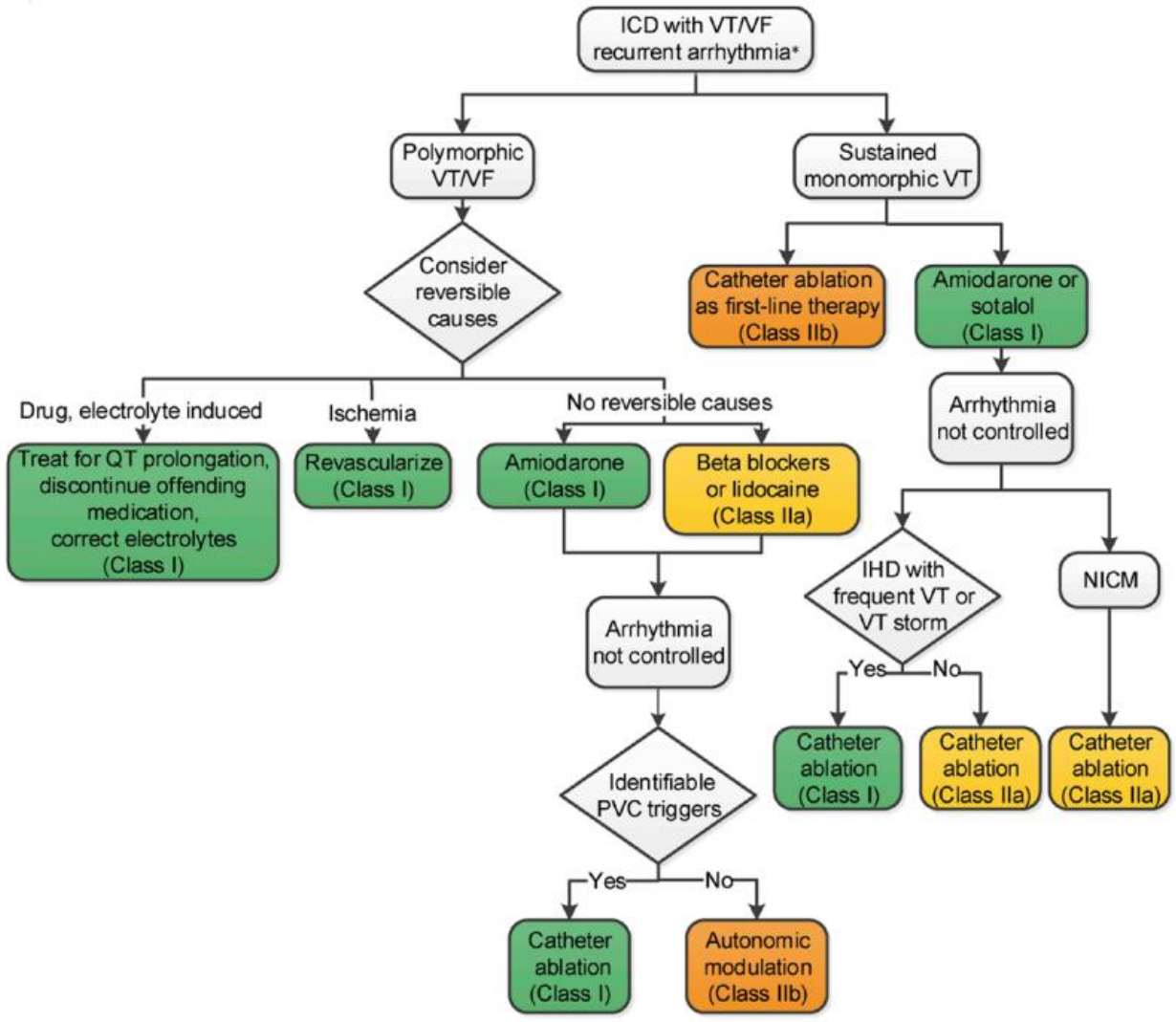

Figure 6. *Treatment of recurrent ventricular arrhythmias in patients with ischemic heart disease or nonischemic cardiomyopathy.*

Retrieved from 2017 AHA/ACC guidelines.