Heart, Lung and Circulation (2019) **28,** 49–56
1443-9506/04/$36.00
https://doi.org/10.1016/j.hlc.2018.10.002

REVIEW

Pharmacological Therapy for Ventricular Arrhythmias: A State-of-the Art Review

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While implantable cardioverter defibrillators decrease mortality in high risk groups of patients who have ventricular arrhythmias, antiarrhythmic drugs are still required to reduce the burden of both benign and life-threatening arrhythmias. This review will address the available medical therapy for ventricular arrhythmias in Australia and their use in different clinical situations.

Keywords Ventricular tachycardia • Ventricular fibrillation • Pharmacological therapy

Introduction

Ventricular arrhythmias range from benign premature ventricular contractions (PVCs) to life threatening ventricular tachycardia (VT) and ventricular fibrillation (VF).

Although implantable cardioverter defibrillators (ICDs) have been demonstrated to prevent sudden cardiac death (SCD) and decrease mortality in selected high risk groups of patients, they do not prevent recurrent VT and VF, and in up to 70% of ICD recipients, antiarrhythmic drug (AAD) therapy is required to reduce the frequency of ventricular arrhythmias, decrease ICD shocks, improve the efficacy of anti-tachycardia pacing therapies, reduce hospitalisations and improve quality of life [1].

Available Pharmacological Agents

Antiarrhythmic drugs act predominantly via blockade of one or more ion channels or via modulation of adrenoreceptors. The currently available drugs for treatment of ventricular arrhythmias in Australia are the Class IB agent lignocaine, the Class IC agent flecainide, beta blockers, the Class III agents sotalol and amiodarone, and, in certain clinical situations, the class IV agents verapamil and diltiazem. In the United States and Europe, other agents such as the class III agent dofetilide, the class IC agent propafenone and the Class I drugs mexiletine and quinidine are available. Mexiletine, quinidine and procainamide may be acquired in Australia for specific conditions via the Therapeutic Drugs Administration (TGA) Special Access Scheme. Suggested intravenous

Abbreviations: AAD, antiarrhythmic drug; ARVC, arrhythmogenic right ventricular cardiomyopathy; CPVT, catecholaminergic polymorphic ventricular tachycardia; DCCV, direct current cardioversion; ERS, early repolarisation syndrome; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrill ator; IV, intravenous [Also Class IV agent]; LV, left ventricular; NSVT, non- sustained ventricular tachycardia; PVC, premature ventricular contractions; RCT, randomised controlled trial; SCD, sudden cardiac death; TDP, Torsades de pointes; TGA, Therapeutic Drugs Administration; VF, ventricular fibrillation; VT, ventricular tachycardia; PVC, premature ventricular contractions; VT, ventricular tachycardia; VF, ventricular fibrillation

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Table 1 **Intravenous anti-arrhythmic agents.**

Medication	Usual IV dosage	Comments
Metoprolol	Initial 5 mg(1–2 mg/min)	Watch for hypotension
Flecainide	1.5–2 mg/kg total dose, at 10 mg/min	May cause metallic taste in mouth Avoid if history of CCF or AMI
Amiodarone	150–300 mg over 10–20 mins then infusion of 15 mg/kg over 24 hours	Use central venous catheter to avoid thrombophlebitis. Watch for initial hypotension
Sotalol	1–1.5 mg/kg over 5 hrs; 1–2doses/day	Monitor for QTc prolongation and Torsades de pointes Adjust dose if renal impairment
Lignocaine	1–1.5 mg/kg IV over 2–3 mins then infusion of 1–4 mg/min	Monitor for signs of neurotoxicity (early signs are paraesthesia, tinnitus, confusion then seizures) particularly if hepatic function reduced. Check serum levels if infusion continued beyond 24 hrs.

Abbreviations: CCF, congestive cardiac failure; AMI, acute myocardial infarction.

dosages for available antiarrhythmic agents are shown in Table 1.

Beta Blockers

Beta blockers, including metoprolol, bisoprolol, nadolol and carvedilol, have been shown to reduce overall mortality and sudden (presumed arrhythmic) death in patients post myocardial infarction and in those with systolic heart failure [2,3]. They represent routine, first-line therapy in these clinical situations. They are also effective, with some studies indicating increased efficacy with nadolol [4], in preventing VT, syncope and sudden death in those with the commonest forms of the Long QT Syndrome and catecholaminergic polymorphic VT (CPVT).

Flecainide

Flecainide is a potent, use-dependent sodium channel blocker and has additional blocking effects on the potassium channel IKr. It slows intraventricular and His-Purkinje conduction thereby prolonging QRS duration and the HV interval. It has mild negative inotropic effects and is contraindicated in patients with a history of ischaemic heart disease, structural heart disease or left ventricular (LV) dysfunction because of an increased risk of all-cause mortality and arrhythmic death [5]. In patients without a history of ischaemic heart disease and with normal LV function, it has low risk of pro-arrhythmia and appears safe to use. It is available in oral and intravenous preparations. The most common side effects are headache, dizziness, tremor, metallic taste, mild dyspnoea, paraesthesias and visual disturbance on lateral gaze.

Amiodarone

This iodinated benzofuran derivative is a multichannel blocker and is the most frequently used agent for acute treatment and prevention of sustained ventricular tachyarrhythmias in patients with structural heart disease and heart failure. It blocks sodium channels, potassium channels and calcium channels, as well as being a non-competitive blocker of alpha- and beta-adrenoreceptors. As the drug was originally developed as an anti-anginal agent and does not exert any significant negative inotropic effects it can be used in patients with ischaemic heart disease and heart failure. It may be used intravenously or orally. Intravenous (IV) administration should be via a central line to avoid chemical thrombophlebitis. Intravenous use can be associated with acute hypotension due to the vasodilatory effect of the drug's diluent, polysorbate 80 (Tween-80). The half-life of orally administered amiodarone is long (6–7 weeks), and a loading regimen is required. For acute suppression of VT/VF, an initial IV dose followed by a slow infusion up to a 6–10 gm total load over several days is required. The patient is then transitioned to an oral maintenance dose. Cardiac side-effects may include excessive bradycardia, hypotension and prolongation of the QT interval, although this is rarely associated with Torsades de pointes (TDP) because of the concomitant calcium channel blocking properties of the drug. Non-cardiac side effects may include: hypo- or hyperthyroidism, photosensitivity, corneal microdeposits, hepatic dysfunction, sleep disturbance, nausea, tremor, peripheral neuropathy and, rarely, pulmonary toxicity (acute alveolitis or pulmonary fibrosis). Amiodarone potentiates the effects of beta blockers, calcium channel blockers, digoxin and warfarin.

Sotalol

Sotalol has both beta blocking and potassium channel (IKr) blocking effects. It prolongs ventricular refractoriness and decreases excitability of ventricular myocardium. It produces dose-dependent prolongation of the QT interval and can result in ventricular pro-arrhythmia in the form of TDP. The drug is renally excreted and the dosage should be adjusted and the QTc interval monitored in patients with renal impairment and the elderly. It should not be used in patients with a QTc greater than 460 msec. It can be used in patients with ischaemic heart disease but should be used with caution in those with significant LV systolic dysfunction

(EF < 30%) as they are at increased risk of TDP. The maximum tolerated dose of sotalol is often lower than that required to produce significant Class III antiarrhythmic efficacy (120 mg bd) due to the side effects of fatigue, excessive symptomatic bradycardia, loss of libido, dyspnoea and gastrointestinal intolerance. Intravenous sotalol may be used for refractory VT and VF.

Lignocaine

Lignocaine is an intravenous class IB sodium channel blocking agent which can be used for acute reversion and prevention of VT generally as a second line agent to amiodarone. It does not depress cardiac contractility and is well tolerated haemodynamically. It is not associated with an increased risk of proarrhythmia or mortality. Side-effects include nausea, vomiting, confusion, headache, tremor and (in toxic doses) seizures.

Mexiletine

This drug is an oral Class IB sodium channel blocker. Although displaying relatively low efficacy as a single agent for prevention of recurrent VT, it has efficacy as an adjuvant agent with amiodarone. It is also effective in preventing TDP in patients with acquired long QT syndrome refractory to conventional therapy [6].

Quinidine

Quinidine blocks sodium channels, potassium channels and the transient outward current (Ito). It prolongs ventricular refractoriness and the QT interval, and has largely been abandoned from clinical use due to its propensity for proarrhythmia (TDP), gastro-intestinal side effect profile and evidence of an adverse effect on total mortality [7]. It has been found to have a niche role in preventing recurrent VT/VF and defibrillator shocks in patients with Brugada syndrome [8] and early repolarisation syndrome [9], possibly via its effects on Ito.

Medical Therapy in the Structurally Normal Heart

For Frequent PVCs and PVC-Induced Cardiomyopathy

Premature ventricular contractions have been considered a benign finding in the structurally normal heart. However, their presence and frequency, and possibly their morphology, may be an indicator of underlying structural heart disease so exclusion of such underlying problems is a vital part of investigation and management. Frequent PVCs have been identified as a cause of cardiomyopathy [10,11].

Management includes reassurance, and a search for correctable causes such as medication, electrolyte disturbance, systemic disturbances such as infection and thyrotoxicosis, and myocardial ischaemia.

No therapy is required for asymptomatic individuals with low frequency PVCs. In patients with symptomatic PVCs, patient education and reassurance, as well as avoidance of aggravating factors such as caffeine or sympathomimetic agents is recommended. Short-term therapy with beta blockers, flecainide or non-dihydropyridine calcium channel blockers could also be considered. Catheter ablation has been shown to be superior to antiarrhythmic drug therapy in randomised controlled trials (RCTs).

For patients with suspected PVC-induced cardiomyopathy, beta blockers and/or flecainide is reasonable to reduce recurrent arrhythmias and improve LV function although catheter ablation has proven more effective in RCTs [12,13].

For Ventricular Tachycardia

Ventricular tachycardia (VT) in the structurally normal heart (idiopathic VT) most commonly arises from the right ventricular outflow tract (RVOT) or the LV outflow tract (LVOT). RVOT VT and LVOT VT appear to be related to intracellular calcium overload and are sensitive to IV adenosine or IV verapamil, and responsive to IV flecainide. In those with recurrent symptomatic VT, longer term treatment is reasonable, with oral beta blockers or non-dihydropyridine calcium channel blockers (25–50% efficacy). If these are unsuccessful, flecainide can be considered as an alternative agent.

Fascicular VT, an uncommon form of VT due to re-entry involving a portion of the LV Purkinje system, may respond to IV verapamil. Longer term medical therapy with oral verapamil can be effective.

Idiopathic polymorphic VT/VF (IPVT) may respond to beta blockers however ICD implantation is required in those patients who have had syncope or required resuscitation.

Intravenous magnesium has little efficacy in the treatment of any form of normal heart VT unless the arrhythmia is drug-induced torsades de pointes VT [14].

In RCTs, catheter ablation for all forms of normal heart VT has proven more effective than drug therapy so this should be considered in patients who are drug-refractory or drug-intolerant, or who may choose to undergo catheter ablation as first-line therapy.

Medical Therapy in Patients With Structural Heart Disease

For VT/VF in the Setting of Cardiac Arrest

The majority of patients with an out-of-hospital cardiac arrest have a primary cardiac pathology as the underlying cause, with one third presenting with a shockable rhythm [15]. While amiodarone and lignocaine are used in shock-resistant ventricular arrhythmias, evidence for efficacy is lacking. Intravenous amiodarone has been reported to increase, cause no change in, or reduce the defibrillation threshold in humans. Two RCTs have compared amiodarone (5 mg/kg) to lignocaine (1.5 mg/kg) to placebo and found that the survival to hospital admission was higher with IV amiodarone than lignocaine [15,16]. In contrast, a similar RCT

looking at survival to hospital discharge in patients who had cardiac arrest with shock resistant VF and pulseless VT demonstrated no significant difference between amiodarone, lignocaine or placebo. In a predefined subgroup of patients with a witnessed arrest, patients who received amiodarone or lignocaine had a higher survival to hospital discharge [17]. While the positive data for the use of amiodarone is modest, in view of the limited alternative options, it remains part of the International Liaison Committee on Resuscitation (ILCOR) algorithms for acute adult cardiac arrest [18].

For VT in Ischaemic and Non-Ischaemic Cardiomyopathy

Beta blockers have been shown in ischaemic and non-ischaemic cardiomyopathy patients to decrease SCD, all-cause mortality [19], recurrent ventricular arrhythmias and increase time to first ICD shock [20]. In addition, considering the positive impact on symptoms and progression of cardiomyopathy, all such patients should be treated with beta blockers unless contraindicated.

No other medical therapy has been reliably shown to prevent SCD, thus an ICD is indicated in most patients who have sustained ventricular arrhythmias and structural heart disease [21]. Adjunctive medical therapy is targeted at terminating and preventing sustained ventricular arrhythmia requiring ICD therapies [10].

Acute management of sustained monomorphic VT is determined by its haemodynamic stability. If unconscious or having haemodynamic collapse, synchronised direct current cardioversion (DCCV) should be given immediately. If the patient is still conscious but hypotensive, IV sedation in preparation for synchronised DCCV should be given and a dose of IV lignocaine (1 mg/kg), which has limited efficacy in the terminating VT, can be given [22]. In patients with conscious VT, IV amiodarone is the most effective agent. There is limited data supporting the superiority of IV sotalol over IV lignocaine in the acute termination of sustained monomorphic VT not causing cardiac arrest, which was not seen for patients with shock-refractory ventricular arrhythmias [23,24].

The first line AADs shown to reduce the need for ICD therapy for recurrent ventricular arrhythmias are sotalol and amiodarone, with amiodarone being the more effective agent [25]. Amiodarone in combination with beta blockers was superior to sotalol or monotherapy with beta blockers in the reduction of shocks in patient with ICDs and previous ventricular arrhythmias (including induced at electrophysiology study) [26]. The poor long-term adverse effect profile of amiodarone limits its use. In contrast, the adverse reactions of sotalol are related to the daily rather than cumulative dose. This makes sotalol more attractive as first line therapy for younger patients, particularly in the presence of an ICD [27,28]. Class IC agents (flecainide [5] and propafenone [29]) should be used with caution in patients with structural heart disease and avoided in those with ischaemic cardiomyopathy as they have been associated with higher all-cause mortality. Antiarrhythmic combinations can be considered if recurrences occur despite use of first line antiarrhythmics and catheter ablation [30]. Combinations of sotalol and amiodarone with Class 1A (quinidine [31], procainamide [32], disopyramide) and Class 1B(mexiletine) [33] have shown some limited efficacy.

Escalation of AAD therapy may be less effective than proceeding to ablation. The VANISH (Ventricular Tachycardia Ablation versus Escalated Antiarrhythmic Drug Therapy in Ischemic Heart Disease) trial randomly allocated patients with ischaemic cardiomyopathy, ICD in situ and sustained monomorphic VT despite first line AAD to catheter ablation or more aggressive AAD therapy (the initiation of amiodarone, or the increase of amiodarone to 300 mg/day, or the addition of mexiletene). There was a significantly lower composite primary outcome of death, ventricular tachycardia storm, or appropriate ICD shock among patients undergoing catheter ablation than among those receiving an escalation in AADs, particularly in those who were already on amiodarone [34].There were three deaths (two from pulmonary toxicity and one from liver toxicity/multiorgan failure) attributable to amiodarone therapy.

For VT Storm

A VT storm is defined by three or more episodes of sustained VT/VF >30 s) or appropriate ICD shocks within 24 hours. Medical therapy with beta blocker and antiarrhythmic drug therapy as outlined above is instituted (Table 2) [35]; but, catheter ablation is often required. When this is ineffective or not immediately available, sedation or general anaesthesia can be used as a temporising measure to reduce arrhythmic burden and break the catecholamine driven cycle of increasing ICD shocks. Antiarrhythmic therapy to target specific aetiologies is also often required (See Figure 1).

In Specific Non-Ischaemic Cardiomyopathies

Regardless of the aetiology of cardiomyopathy, the same antiarrhythmics are generally used for all patients with ventricular arrhythmias and structural heart disease depending on other comorbidities. However, sarcoidosis and arrhythmogenic right ventricular cardiomyopathy (ARVC) do warrant special consideration. Inflammation can induce VT in sarcoidosis, triggering PVCs; and, immunosuppressive therapies can exert an antiarrhythmic effect particularly for arrhythmias that develop in the early phase prior to the onset of LV dysfunction.

In ARVC

Antiarrhythmic drugs are indicated when patients have VT. They may also be considered when there are frequent PVCs or non-sustained VT (NSVT) [36]. There are no controlled clinical trials to guide therapy. Although AADs can reduce arrhythmia burden, they have not been shown to decrease SCD. Beta blockers are indicated for ventricular arrhythmia or inappropriate shocks due to rapid supraventricular tachycardia. There is conflicting data as to the superiority of amiodarone vs sotalol as second line therapy [36]. A study

Table 2 Antiarrhythmic agents for the acute and long-term management of an electrical storm.

		Acute management	Long-term treatment
β-agonists	Isoprenaline	For management of VF storms in J wave syndromes (ERS and BrS) Initiate at 1.0 μg/min *IV*, targeting a 20% increase in heart rate or an absolute heart rate >90 bpm, titrated to haemodynamic response and suppression of recurrent ventricular arrhythmia	
β-blockers	Propranolol	Bolus: 0.15 mg/kg *IV* over 10 min	10–40 mg po three-four times a day
	Metoprolol	Bolus: 2–5 mg IV every 5 min up to 3 doses in 15 min	25 mg po twice a day up to 200 mg a day
	Esmolol	Bolus: 300 to 500 mg/kg *IV* for 1 min Infusion: 25–50 mg/kg per minute up to a maximum dose of 250 mg/kg per minute (titration every 5–10 min)	Not recommended
Class III agents	Amiodarone	Bolus: 150 mg *IV* over 10 min, up to total 2.2 g in 24 hrs Infusion: 1 mg/min for 6 hrs, then 0.5 mg/min for 18 hrs	Oral load: 800 mg po twice a day until 10 g total Maintenance dose: 200–400 mg p.o. daily
	Sotalol	Not recommended	80 mg po twice a day, up to 160 mg twice a day (serious side effects >320 mg/d)
Class I agents	Lignocaine	Bolus: 1.0 to 1.5 mg/kg *IV*, repeat dose of 0.5–0.75 mg/kg *IV* up to a total dose of 3 mg/kg Infusion: 20 mcg/kg per minute *IV*	
	*Procainamide	Bolus: 10 mg/kg *IV* over 20 min Infusion: up to 2–3 g/24 hr	3–6 g po daily fractionated in ≥ 3 administrations
	*Mexiletine	Not recommended	200 mg po three times a day, up to 400 mg po three times a day

Adapted from Muser D, Santangeli P, Liang JJ. Management of ventricular tachycardia storm in patients with structural heart disease. World journal of cardiology. 2017;9:521-30.

Abbreviations: TGA, Therapeutic Goods Administration; VF, ventricular fibrillation; ER, early repolarisation syndrome; BrS, Brugada Syndrome.

*only available via special access scheme with the TGA.

of 81 patients with ARVC showed that sotalol was more effective than other agents in suppression of arrhythmia at programmed ventricular stimulation [37]. Another small study showed addition of flecainide to metoprolol or sotalol resulted in suppression of VT in 75% of patients when followed over 3 years [38]. Amiodarone alone or with addition of beta blockers is effective in reduction of symptomatic ventricular tachycardia [36,39].

In Hypertrophic Cardiomyopathy (HCM)

Non-sustained VT has been documented in 15–31% of patients with HCM monitored with ambulatory Holter monitoring [40]. Although NSVT is a marker of SCD, this association was stronger in younger patients [41,42]. Patients with higher number of risk factors were found to have increased risk of sudden death. These risk factors were family history of SCD, NSVT, extreme septal hypertrophy (>3 cm) and unexplained syncope [43]. There is no absolute protection from sudden death by medical therapy [44]. Those with symptomatic PVCs or symptomatic NSVT and those with recurrent ventricular arrhythmia documented in ICD could be treated with beta blockers, sotalol or amiodarone [45].

Drug Therapy in Patients With Channelopathies

Patients with following conditions, in addition to pharmacological management, may require protection with ICD, especially in those with previous aborted SCD or high risk.

Long QT Syndromes

All patients with long QT syndromes should avoid QT prolonging drugs (www.qtdrugs.org) and electrolyte abnormal-

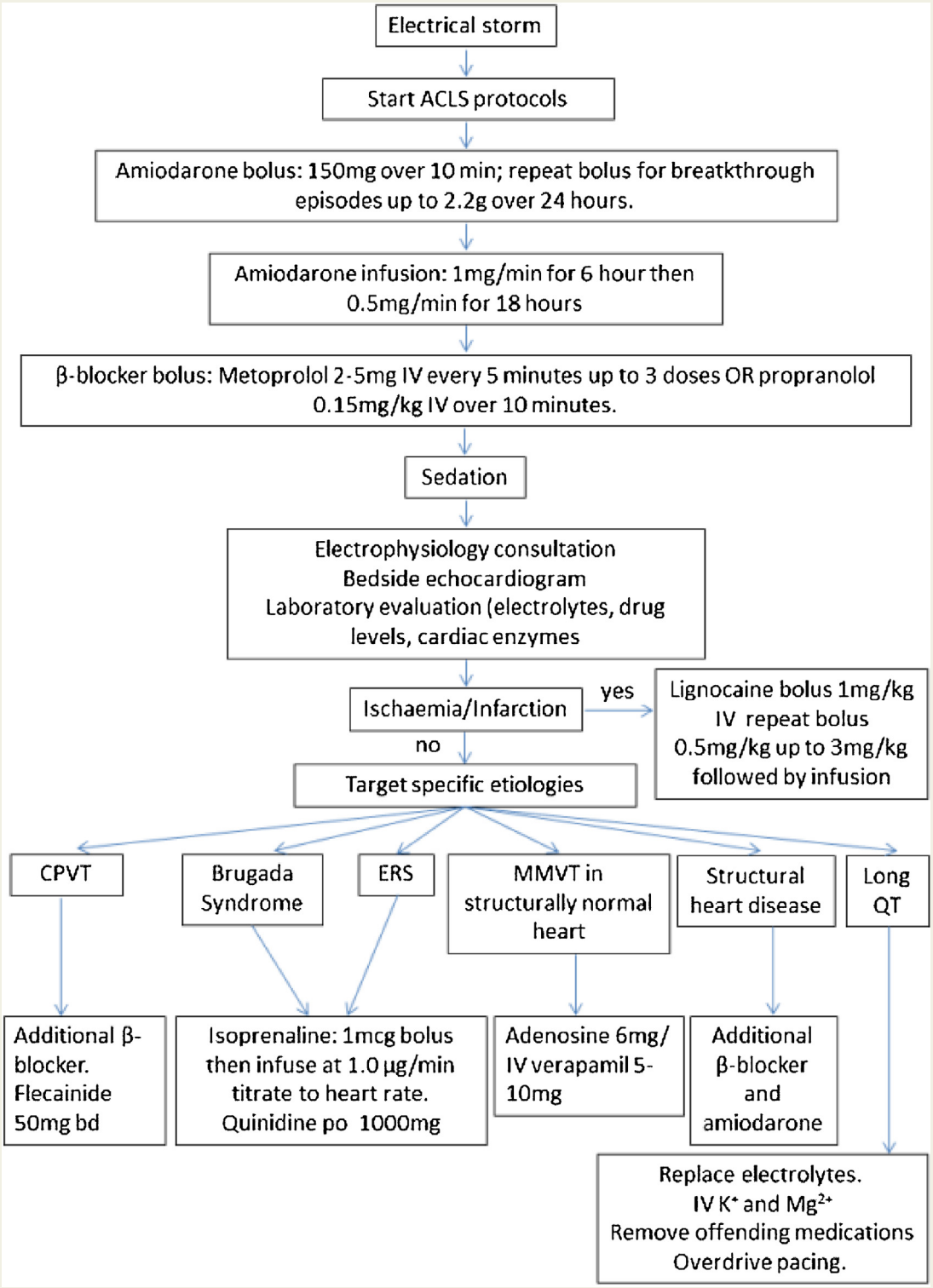

Figure 1 Management algorithm for electrical storm.
Adapted from Dan Sorajja,Thomas M. Munger,Win-Kuang Shen. Optimal antiarrhythmic drug therapy for electrical storm Journal of Biomedical Research,2015,29(1):20-34.

ities, including hypokalaemia and hypomagnesaemia. Those with documented arrhythmia symptoms, including syncope, pre-syncope and SCD and those with high risk (e.g. QTc >0.5 sec) should be considered for drug therapy. Drug selection depends on the type of channelopathy. Those with LQT1 and, to a lesser extent, LQT2 benefit from beta blocker therapy. Those with Long QT3 have low or no benefit with beta blocker therapy (but may respond to mexiletine) [46–48].

Nadolol and propranolol appear superior to metoprolol in observational studies [49]. When beta blocking agents are contra- indicated or not tolerated, cervical sympathectomy may be considered [50].

Catecholaminergic Polymorphic (CPVT)

Arrhythmias are often associated with high catecholamine states and are helped by treatment with beta blockers [51]. Some studies suggest that non-selective beta blockers like nadolol may be most effective [4]. Beta blockers should be titrated to maximum tolerable dose. Nadolol is used at 1–2 mg/kg per day and propranolol at 3–5 mg/kg per day [52]. If beta blockers are not tolerated or inadequate, treatment with verapamil or flecainide could be considered [53–56]. Flecainide has also been shown to suppress arrhythmias in ICD-induced ventricular arrhythmia storm in a patient with CPVT [57]. When beta blockers cannot be used, cervical sympathectomy has been found to be effective [58].

Brugada Syndrome (BS)

Patients should be advised to avoid sodium channel blocking agents. In a small group of patients with recurrent arrhythmias, quinidine has been shown to be beneficial [8]. In patients with BS and syncope who refuse ICD, or if ICD is contra- indicated, quinidine therapy may be considered. When patients present with arrhythmia storm, treatment with isoprenaline infusion can be helpful [59].

Conclusions

Pharmacological therapy is still needed in the management for ventricular arrhythmias in 2018–2019, even as the technology and efficacy of catheter ablation continues to improve. The antiarrhythmic actions and toxicity profiles of different agents influence their selection for the acute and chronic management of ventricular arrhythmias in different conditions.

Conflict of Interest

Karin K. M. Chia: None.

Logan Kanagaratnam- None.

Kevin Hellestrand: None.

Peter Kowey- Ad hoc consultant to Sanofi, Pfizer, Gilead, Allergan, Incarda, Milestone, Medtronic, Actelion, and Servier.

David Whalley- None.

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