Title: Multi-Faceted Approach to Ventricular Tachycardia: A Review of Management Strategies

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Abstract: Ventricular tachycardia poses a significant therapeutic challenge. It can manifest over a spectrum from minimal palpitation symptoms to sudden cardiac death. This makes large-scale trials on the treatment of ventricular tachycardia difficult to perform. The mechanism of ventricular tachycardia must also be understood before embarking on treatment. Patients with or without structural heart disease will have different mechanisms for the onset and propagation of these arrhythmias. Catheter ablation is an established management option for ventricular tachycardia; however, it is not always successful and anti-arrhythmic medications are often necessary to control these life-threatening arrhythmias. Although anti-arrhythmics can suppress ventricular tachycardias they also carry side effects. In certain substrates, some of these medications can exacerbate arrhythmias or heart failure. For these reasons, a multifaceted approach to treating ventricular tachycardia is necessary. This paper is a comprehensive review of the comprehensive management strategies for ventricular tachycardia. Anti-arrhythmic medications have an important role and their use in various cardiomyopathies and channelopathies is reviewed in detail. We also review the promising effects of gene therapy and artificial intelligence on different substrates for ventricular tachycardia.

Keywords: ventricular tachycardia; anti-arrhythmic drugs; arrhythmia; catheter ablation; gene-therapy

1. Introduction

Ventricular tachycardia (VT) stands as a formidable challenge in modern cardiology, characterized by rapid and potentially life-threatening arrhythmias originating in the ventricular myocardium. Based on decades of research, it is understood that there are differing mechanisms for VT depending on the underlying substrate such as scar from ischemic heart disease to primary cardiac channelopathies. In this non-systematic narrative review, our goal is to highlight the multi-faceted approach to VT, highlighting the importance of understanding epidemiologic data and applying pharmacologic, as well as non-pharmacologic, therapies to improve outcomes in these patients. We further synthesized some burgeoning treatment options with the promising role of gene therapy and artificial intelligence.

2. Methods

We used a non-systematic narrative review of the literature. We utilized electronic databases PubMed (NCBI), Embase (Ovid), and Google Scholar, which were searched for articles published until February 2024. We included articles that were case–control, cohort, cross-sectional, prospective randomized clinical trials, systematic reviews, and meta-analyses. We excluded non-English written articles, abstracts, and editorials. We utilized articles which varied widely in design, intervention, comparators, outcomes, and format, and therefore no formal synthesis was utilized.
3. History and Epidemiology of Ventricular Tachycardia

VT was first described by Dr. Thomas Lewis in 1909, when he observed a series of ventricularly driven extrasystole beats in a patient with recurrent episodes of dyspnea and palpitations. Using an electrogram and venous pulse recordings he was able to provide the first recorded evidence of VT [1]. Investigations by pioneers in cardiology were able to further characterize and uncover possible etiologies for this newly discovered heart rhythm. Lewis was able to recreate VT in dog models by ligating their coronary arteries, thus demonstrating a relationship between coronary occlusion and VT [2]. By the 1950s and 1960s further correlations between long QT intervals and sudden cardiac death were described [3–5]. By the late 1960s, polymorphic VT isolated on an ECG with a characteristic change in amplitudes around an isoelectric baseline which was aptly named Torsades de Pointes [6]. This landmark research early in the recognition helped pave the way for our current understanding of the disease.

Today, VT is defined as 3 or more consecutive ventricularly driven beats at a rate of 100 beats or more per minute lasting longer than 30 s. Due to its ventricular origin circumventing the conduction pathway provided by the Purkinje fibers, it causes a wide QRS complex [7]. The most common cause of VT is underlying ischemic heart disease due to the creation of arrhythmogenic scars. Other etiologies include electrolyte imbalances, illicit drug use, adverse drug reactions, cardiac channelopathies, congenital structural heart disease, non-ischemic dilated cardiomyopathy, and infiltrative cardiomyopathies.

The incidence and prevalence of VT are difficult to quantify, as this can only be identified if the patient is being actively monitored and an episode is recorded. The incidence of SCD in the US ranges anywhere between 180,000 and 450,000 cases annually. A look at the incidence of SCD across several developed nations showed an incidence of 50–100 per 100,000 people. Autopsy studies conducted in patients with SCD found approximately 75% were attributed to coronary artery disease (CAD), 15% to non-ischemic cardiomyopathy, 5% to primary electrical disease, and 5% were unknown [8,9]. While the incidence of SCD may be unreliable due to the number of confounding factors listed above, the trends provided mirror the most likely etiologies of VT.

In a retrospective study that utilized the National Inpatient Sample database it was estimated that there were 3,544,445 patients > 18 years old admitted to hospital for VT in the US between 2011 and 2019. Of this population, 33.8% were women and 66.2% were men. This discrepancy can be, in part, explained by the fact that women were found to be less likely to have CAD and ischemic cardiomyopathy than their male counterparts [10]. A similar study using the same database looked at patients between the ages of 18 and 45 who were admitted to hospital with VT from 2005 to 2018 to identify trends among this younger population. They noted similar trends across all timeframes outlined through the study, with the most recent spanning from 2015 to 2018 demonstrating a 59.97% prevalence in males versus 40.04% in females, and differences in race, with 52.29% White, 29.76% Black, 11.08% Hispanic, 2.79% Asian and Pacific Islander, 0.85% Native American, and 3.31% Other [11].

A prospective study by Aronaw et al., which monitored patients with ambulatory electrocardiograms (ECGs), estimated that the prevalence of VT in patients with CAD was approximately 15% in comparison to about 2% in the population without any known cardiovascular disease [12]. Due to continued advancements in the management of acute coronary syndrome (ACS) there has been a significant decrease in the incidence of ventricular arrhythmias associated with the condition [13,14]. Unfortunately, there has been little change in the incidence of ventricular arrhythmias in the context of non-ischemic cardiomyopathy [15].

The rarest conditions contributing to VT include channelopathies and idiopathic causes. The most common cause of SCD in patients less than 35 years of age, with structurally normal hearts, are inherited arrhythmia syndromes and channelopathies including long QT syndrome, Brugada syndrome, and catecholaminergic polymorphic VT [16].
Idiopathic VT, which is classified as VT without any identifiable etiology, accounts for approximately 10% of all VT [17]. The mechanism of idiopathic VT is thought to be due to triggered activity or abnormal automaticity, though re-entry has also been identified, for example, in interfascicular reentrant tachycardias [18].

4. Landmark Trials

The management of VT has evolved, with an increased emphasis on a multifaceted approach. This includes the use of antiarrhythmic drugs, ICDs, catheter ablation, gene therapy and artificial intelligence algorithms, as illustrated in Figure 1. To examine the effectiveness of the various components of this management approach, there have been several landmark trials.

Figure 1. Multifaceted approach to management of ventricular tachycardia.

4.1. Antiarrhythmic Drugs vs. ICD in the Management of VT

Antiarrhythmic drugs (AADs) play a pivotal role in the suppression of VT and ventricular fibrillation (VF) episodes. However, long-term use is seldom in isolation and is often an adjunct to the management offered by ICD. The Antiarrhythmics Versus Implantable Defibrillators (AVID) trial was a multicenter randomized study that examined the efficacy of ICD vs. AAD therapy for secondary prevention in 1016 patients who had been resuscitated from near-fatal VF or who required cardioversion for sustained VT [19]. The two AADs used in the study were amiodarone and sotalol. The survival of patients who underwent implantation of ICDs was better than those treated with antiarrhythmics alone over the three-year follow-up, with a relative reduction in mortality in the ICD group of 39% at 1 year, 27% at 2 years and 31% at 3 years ($p < 0.02$). Another key finding was that the use of beta blockers in the ICD group was higher than those in the AAD group (despite beta blockers having been shown to improve mortality in VT and improve left ventricular
ejection fraction) but this only resulted in a slight reduction in the benefit of ICDs when subsequent Cox regression analysis was performed.

The findings of the AVID trial have been similarly observed. The Canadian Implantable Defibrillator Study (CIDS) was a multinational trial that compared ICD to amiodarone. They found a 20% reduction in all-cause mortality when using ICD therapy. The Cardiac Arrest Study Hamburg (CASH) trial found a 23% reduction in sudden death with ICD compared to AAD therapy [20,21]. Though having been published over two decades ago, the superiority of ICDs over AADs as highlighted in these landmark trials remain convincing today. Consequently, current guidelines recommend the use of AADs for control of arrhythmias and symptomatic improvement in select patients [18,22].

4.2. Catheter Ablation

For some patients, VT episodes continue to occur despite the management of underlying VT triggers via optimal management of heart failure and ischemic heart disease, the use of evidence-based ICD programming, or AADs. In these individuals, catheter ablation has become an additional strategy.

Investigators for the VANISH trial randomly assigned patients already on AADs with ischemic cardiomyopathy and ventricular tachycardia to catheter ablation while continuing their existing dose of AADs versus escalation of AAD therapy [23]. The composite primary endpoint was death, VT storm, or appropriate ICD shocks. The composite primary endpoint was statistically lower in persons who underwent ablation, compared to those who received escalation of therapy (hazard ratio—0.72; 95% confidence interval 0.53–0.98 p = 0.04). Similarly, a meta-analysis published in 2016 which included three randomized control trials (not including the VANISH trial), with a total of 262 patients concluded that while the rate of VT was lower in persons who received catheter ablation, no difference in the rate of death across the treatment modalities was observed [24]. Current guidelines suggest that in patients with monomorphic VT refractory to antiarrhythmic medication, catheter ablation may be considered (IIb recommendation) [18].

4.3. Neuromodulation

An emerging approach to the management of VT (particularly VT storm) has been the role of neuromodulation of the sympathetic nervous system. This can be achieved via percutaneous stellate ganglion block, thoracic epidural anesthesia, or surgical stellate ganglia resection. When used as an adjunct to antiarrhythmics and ICD therapy, this strategy has been found to be most effective as a bridge to more definitive treatment [25].

5. Anti-Arrhythmic Drugs

AADs play a significant role in both the acute treatment and long-term management of VT. Among patients undergoing treatment for secondary prevention of VA, it has been observed that recurrent VA episodes requiring device therapies arise in around 20–50% of individuals within a timeframe of 5 years [26]. Overall, up to 70% of patients with an ICD receive adjuvant antiarrhythmic drug therapy for suppression of VT/VF episodes [27].

The positive results achieved with antiarrhythmic therapy in patients with ICDs are often attributed to the ability of these medications to slow VT rates and facilitate termination through anti-tachycardia pacing (ATP), rather than solely preventing fast VT-triggered shocks. Consequently, when evaluating the efficacy of concomitant antiarrhythmic therapy in patients with ICDs, it is crucial to assess its impact on the frequencies of shocks and ATP events [28].

The classification of AADs is predominantly based on the widely utilized Vaughan Williams (VW) classification system. This system serves as the most employed framework for categorizing and classifying AADs according to their mechanisms of action and electrophysiological properties. Over the last six decades, an improved understanding of pharmacologic targets and the continued development of therapeutic agents necessitated an update to the VW classification system [29]. This was introduced on the improved
understanding that many cardiac active agents have multiple actions. It now included a
class 0 for ivabradine, expanding class 1 to recognize the reduction in late Na+ channel
current by ranolazine, as well as proposing new classes V-VII, which recognize several
agents under clinical investigation. Class VII includes ACE inhibitors, ARBs, omega-3 fatty
acids, and statins, in their role of electrophysiologic and structural heart remodeling [29].

An alternative scheme known as the Sicilian Gambit was proposed in 1991 [30]. This
system was developed with the understanding that effective AAD therapy requires working
knowledge of the mechanism of the arrhythmia. While this paper provided improved
understanding of AAD action, it has not gained widespread clinical use.

The choice of AAD depends on various factors, such as the underlying cardiac condi-
tion, the presence of structural heart disease, and individual patient characteristics. The
2017 ACC/AHA guidelines emphasize a personalized approach and consider factors such
as drug efficacy, potential adverse effects, and drug-drug interactions.

5.1. Class I Medications

This class exerts effects by blocking the inward cardiac sodium current and slow con-
duction velocity in the myocardium. The Cardiac Arrhythmia Suppression Trial (CAST) [31]
trial provides evidence that by slowing conduction velocity, class I antiarrhythmic medica-
tions can potentially predispose individuals to persistent re-entry.

Class IA AADs block the rapid inward sodium current in a use-dependent manner. Addi-
tionally, they prolong depolarization by blocking the delayed rectifier potassium
channel in a reverse-use dependence fashion. Drugs in this class include procainamide,
quinidine, and disopyramide.

- **Procainamide**

PROCAMIO was the first RCT that compared procainamide and amiodarone for the
treatment of acute sustained monomorphic VT. This study showed procainamide was
associated with a higher proportion of VT termination and fewer adverse effects [32]. In
another study of 34 patients who failed to respond to standard therapy, oral procainamide
was associated with a significant decrease in ICD therapies and ventricular arrhythmias [33].
Procainamide has similar prehospital ROSC, ED ROSC, and survival, but its role in out-of-
hospital cardiac arrest remains unclear.

Side effects of procainamide include hypotension (which is secondary to its negative
inotropy), nausea, vomiting, and diarrhea. In rare cases, procainamide has been linked to
psychosis. Prolonged use of procainamide, particularly for six months or more, has been
reported to be associated with drug-induced lupus erythematosus in up to 30% of patients.

- **Quinidine**

Due to the potential risks of QT prolongation and gastrointestinal intolerance, the use
of quinidine has decreased over time, particularly with the availability of alternative thera-
pies that are better tolerated. However, there has been a recent resurgence of interest in the
use of quinidine for specific scenarios. It has found a niche role in managing patients with
Brugada syndrome [34]. It has been investigated as a treatment option for individuals with
challenging ventricular arrhythmias that have not responded to amiodarone therapy [35].

- **Disopyramide**

As with other class I AAD, disopyramide increases the action-potential duration of
cardiomyocytes. It also lowers the rate of diastolic depolarization in cells with augmented
automaticity and upstroke velocity. By doing so, disopyramide decreases myocardial
excitability and conduction velocity. Even though it has a theoretical protective effect
from re-entry in ischemic myocardium, a multi-center, double-blind, randomized study
involving over 1900 patients found that there was no decrease in mortality rate [36]. Another
effect of disopyramide is AV nodal blocking and bradycardia, as well as the effect of
anticholinergic properties that contribute to the drug’s side effects.
Class 1B medications include lidocaine and mexiletine. These AADs exert their effects by blocking sodium channels. They demonstrate preferential action in ischemic tissue. However, it is important to note that these medications can have central-nervous-system side effects. Common central-nervous-system side effects of both AADs include tinnitus (ringing in the ears), tremor, blurred vision, nausea, dysphoria (unease or dissatisfaction), and dizziness. In severe cases of toxicity, these effects can progress to seizures, altered mental status, and even coma. Close monitoring of patients receiving lidocaine or mexiletine is essential to ensure appropriate dosing and to promptly identify and manage any potential adverse effects.

Class 1C medications include flecainide and propafenone. They are the most potent inward sodium-blocking agents, resulting in markedly reduced AP conduction velocity in atrial, ventricular, and conduction tissues in a use-dependent fashion with minimal effect on overall APD or ERP. CAST [31] and CASH [21] trials have shown increased mortality in patients with structural disease treated with these agents. For patients with catecholaminergic polymorphic ventricular tachycardia (CPVT), both flecainide and propafenone can serve as second-line therapies, particularly in cases where individuals are unresponsive to beta blockers. A small, randomized trial has also demonstrated their efficacy in reduction of ventricular arrhythmias and QT interval in patients with LQT3 syndrome. Furthermore, flecainide has demonstrated a role in aiding the diagnosis of Brugada syndrome [37,38].

Based on the updated VW classification system, ranolazine is the class 1D agent. This is an antianginal medication that possesses multiple ion-channel-blocking antiarrhythmic effects, with its most significant impact observed on the late sodium current. It also prolongs APD and QT interval. These properties are sharply different from the class 1a to 1c agents; therefore, it is classified as a 1D agent in the new VW system. In the MERLIN-TIMI36 trial, it was shown to reduce NSVT episodes on ambulatory cardiac monitoring in patients with ACS. Ranolazine proved effective in reducing VT burden and ICD shocks in patients with AAD-refractory VT [15,39].

5.2. Class II Agents

In the traditional VW classification system, the class II agents are beta blockers. The updated VW classification system includes autonomic activators including isoproterenol, atropine, and adenosine [29].

- **Beta blockers**

As targets for ventricular tachycardia, the primary class II agents are beta blockers. In the CIBIS-II trial [40], Bisoprolol use demonstrated a 44% reduction in sudden cardiac death (SCD) risk among heart failure patients. Additionally, the COMMIT trial revealed that early metoprolol administration reduced the likelihood of ventricular fibrillation (VF) development. Non-selective beta blockers such as propranolol and nadolol are used in the treatment of congenital long QT syndrome and CPVT.

- **Digoxin**

Digoxin is a cardiac glycoside which inhibits plasma membrane Na⁺, K⁺-ATPase, which results in increased intracellular calcium. This ultimately results in increase force of myocardial contraction. Digoxin also has parasympathetic effects on the atrial myocardium, which result in the slowing of conduction and the prolongation of the atrioventricular-node refractory period. Under the updated VW classification system, digoxin is categorized with the class IId agents [29]. Its primary role in modern cardiology is aimed at systolic heart failure and ventricular rate control of atrial fibrillation [41]. There is no routine use for digoxin in the management of VT, due to its minimal effects on the His-Purkinje system as well as significant side effects and pharmacokinetic interaction. A sub analysis of the MADIT-CRT trial found that digoxin use was not associated with a reduction in death and resulted in a 40–65% increased risk of ventricular tachycardia [42].
5.3. Class III Medications

- **Amiodarone**

  It has the properties of all antiarrhythmic drugs in the VW classification [29]. It accumulates in various organs including adipose tissue, leading to a long half-life. It can be detected in plasma up to 6 months after discontinuation.

  Amiodarone has shown efficacy in reducing VT recurrence and improving survival in patients with various underlying heart conditions, including ischemic heart disease and non-ischemic cardiomyopathy. Amiodarone has demonstrated favorable outcomes in multiple clinical trials and is often considered as a first-line agent in the long-term management of VT. Despite its ability to prolong QT interval, Torsade de pointes occurred in <1% of patient in EMIAT [43] and CAMIAT [44] trials. Nonetheless, the long-term use of amiodarone necessitates monitoring, due to its extracardiac toxicity which includes hypo/hyperthyroidism, pulmonary toxicity, neuropathy, and vision changes.

- **Sotalol**

  A non-selective beta blocker with class III antiarrhythmic properties, Ref. [29] has also been extensively studied for its effectiveness in suppressing VT. When administered at doses below 120 mg twice daily, there seems to be a predominant beta-blocking effect for the medication. Higher doses exhibit more pronounced class III activity. Sotalol’s dual action of beta blocking and prolonging repolarization makes it a valuable option for long-term VT management. Sotalol may lead to Torsade de pointes in 2–3% of patients, particularly in women and patients with chronic kidney disease or heart failure. Other side effects include dyspnea and bronchospasm.

- **Dronedarone**

  A non-iodinated multi-channel blocker with a structure similar to amiodarone [29]. It is effective in suppressing ventricular arrhythmia in animal studies. Nevertheless, the safety of dronedarone in patients with structural heart disease has been brought into question by the ANDROMEDA [45] and PALLAS [46] trials.

- **Dofetilide**

  This agent was shown to reduce frequency of VT/VF and ICD therapies, even when other antiarrhythmic agents, including amiodarone, have previously been ineffective. In another double-blind randomized crossover study, dofetilide was as efficacious as sotalol in preventing the induction of sustained VT. In the same study, dofetilide was better tolerated during the acute phase than sotalol [47,48].

5.4. Class IV Medications

Verapamil and diltiazem are non-dihydropyridine calcium channel antagonists that primarily exert antiarrhythmic effects at the AV node by blocking the slow inward calcium current [29]. This action results in the prolongation of the effective refractory period (ERP), with minimal impact on atrial/ventricular myocytes or the His-Purkinje system. Verapamil is effective in idiopathic sustained VT originating from the left ventricle [49,50] and CPVT. There was reduction in exercise-induced ventricular ectopy and NSVT with addition of verapamil to beta blocker therapy [51].

6. Special Populations

6.1. Brugada Syndrome

Brugada syndrome (BrS) is an inherited arrhythmic syndrome characterized by pathognomonic ST-segment abnormalities first described in 1992 [52]. Despite a low prevalence of BrS in the United States, BrS appears to be a relatively common cause of sudden-cardiac-death patients reported by registries from Europe and Asia [53–55]. Multiple genes encoding sodium channels are identified as the underlying pathophysiology of BrS, with loss of SCN5A gene function as the most common associated mutation. The current pharmacologic approach of BrS focuses on re-establishing a normal epicardial–endocardial
gradient, which is the result of sodium channel dysfunction. Other ion channels including \( I_{to} \), \( I_{Ca} \), and \( I_{K-ATP} \) are also targets of AAD, as these channels are altered by abnormal repolarization [56].

Medical therapy for BrS is generally recommended for patients not qualified for ICD therapy or patients with recurrent ventricular arrhythmia after ICD implantation [18]. Risk stratification for arrhythmic events by risk score, genetic testing, or electrophysiologic study may guide the clinical decision-making to initiate the treatment [18]. Quinidine is shown to reduce ventricular arrhythmias and recurrent ICD shocks [18,57]. It upregulates the sodium channel and suppresses the outward potassium channel (\( I_{to} \)), which prolongs the action potential and restores normal epicardial–endocardial gradient. Adverse effects from quinidine require careful monitoring when used as a long-term treatment [22,56]. Quinidine has a class 1 recommendation from the AHA for management of recurrent VT or in patient who are not ICD candidates [18]. In the setting of an electrical storm in BrS, isoproterenol infusion alone or in combination with quinidine is effective during the acute phase. Isoproterenol terminates ventricular arrhythmia by augmenting the inward calcium current via beta-adrenergic stimulation, neutralizing the abnormal electrical gradient (Table 1). Milrinone, with its \( I_{Ca} \) enhancing effects, can also be used in BrS electrical storm [58]. Brugada storm triggers should be promptly addressed, and catheter ablation can be considered to prevent a recurrence [59].

Table 1. Anti-Arrhythmic Therapy in Special Populations.

<table>
<thead>
<tr>
<th>Special Population</th>
<th>Antiarrhythmic Therapy</th>
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<tbody>
<tr>
<td><strong>Primary Arrhythmia Syndromes</strong></td>
<td></td>
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<tr>
<td>Brugada Syndrome</td>
<td>Maintenance treatment:</td>
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<tr>
<td></td>
<td>- Quinidine</td>
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<td></td>
<td>Electrical storm treatment:</td>
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<td></td>
<td>- Isoproterenol</td>
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<td></td>
<td>- Quinidine</td>
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<tr>
<td></td>
<td>- Milrinone</td>
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<tr>
<td>Early Repolarization</td>
<td>Maintenance treatment:</td>
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<td></td>
<td>- Quinidine</td>
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<tr>
<td></td>
<td>- Cilostazol</td>
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<tr>
<td></td>
<td>Electrical storm treatment:</td>
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<tr>
<td></td>
<td>- Isoproterenol</td>
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<tr>
<td>Catecholaminergic Polymorphic Ventricular</td>
<td>First-line treatment:</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>- Beta blockers: nadolol or propranolol</td>
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<tr>
<td></td>
<td>Second-line treatment:</td>
</tr>
<tr>
<td></td>
<td>- Flecainide (adjunctive to beta blocker)</td>
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<tr>
<td></td>
<td>- Verapamil (adjunctive to beta blocker)</td>
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<tr>
<td>Idiopathic Ventricular Fibrillation</td>
<td>Maintenance treatment:</td>
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<tr>
<td></td>
<td>- Amiodarone</td>
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<td></td>
<td>Electrical storm treatment:</td>
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<td>- Isoproterenol</td>
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<td>- Quinidine</td>
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<td>- Verapamil</td>
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Table 1. Cont.

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<tr>
<th>Special Population</th>
<th>Antiarrhythmic Therapy</th>
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<tbody>
<tr>
<td><strong>Long QT Syndrome</strong></td>
<td>First-line treatment:</td>
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<tr>
<td></td>
<td>- Beta blockers: nadolol or propranolol (preferred over other beta blockers)</td>
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<td></td>
<td>Second-line treatment:</td>
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<tr>
<td></td>
<td>- Potassium supplement (LQT2)</td>
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<td>- Mexiletine (LQT3)</td>
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<td></td>
<td>- Flecainide (LQT3)</td>
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<td></td>
<td>- Ranolazine (LQT3)</td>
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<tr>
<td><strong>Anderson–Tawil Syndrome</strong></td>
<td>First-line treatment:</td>
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<td></td>
<td>- Beta blockers: nadolol or propranolol</td>
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<td></td>
<td>Second-line treatment:</td>
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<tr>
<td></td>
<td>- Flecainide (adjunctive to beta blocker)</td>
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<tr>
<td><strong>Short QT Syndrome</strong></td>
<td>First-line treatment:</td>
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<td></td>
<td>- Quinidine</td>
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<td>Second-line treatment:</td>
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<td>- Disopyramide</td>
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<td></td>
<td>Electrical storm treatment:</td>
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<td>- Isoproterenol</td>
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**Arrhythmogenic Cardiomyopathy**

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<th>First-line treatment:</th>
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<td>- Beta blockers</td>
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<tr>
<th>Second-line treatment:</th>
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<tbody>
<tr>
<td>- Amiodarone</td>
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<td>- Sotalol</td>
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**Hypertrophic Cardiomyopathy**

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<th>First-line treatment:</th>
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<td>- Amiodarone</td>
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<td>- Beta blockers</td>
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<th>Second-line treatment:</th>
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<tr>
<td>- Dofetilide</td>
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<td>- Mexiletine</td>
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**Cardiac Sarcoidosis**

| - Amiodarone |
| - Sotalol    |
| - Immunosuppressive therapy (in active disease) |

6.2. Early Repolarization Syndrome

As the pathophysiology between early repolarization syndrome (ERS) and BrS is similar, a parallel treatment approach is suggested. Pharmacologic treatment is recommended in symptomatic ERS patients with a history of electrical storm, cardiac arrest, or sustained VT. Medical therapy is also indicated in patients with repeated ICD shocks after insertion or those for whom an ICD therapy is not appropriate [60]. Quinidine has been used to prevent arrhythmic events, as well as during acute electrical storms, in combination with isoproterenol. Like BrS, quinidine corrects the abnormal repolarization gradient in EPS. In addition to quinidine, phosphodiesterase III (PDE-III) inhibitors such as cilostazol may have a role in the suppression of arrhythmias related to ERS, as shown in studies [61,62]. Cilostazol potentially augments $I_{Ca}$ and antagonizes $I_{to}$, which are the main dysfunctional channels in ERS. Nevertheless, the efficacy of PDE-III for arrhythmia suppression is not well-established [63]. Isoproterenol is effective in alleviating ventricular arrhythmia storms in the same fashion as BrS [60] (Table 1).
6.3. Catecholaminergic Polymorphic Ventricular Tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare familial arrhythmia syndrome, yet with a high mortality rate [64]. The two most common genetic mutations involve the cellular calcium-regulating ryanodine receptor (RYR2) and calsequestrin 2 protein (CASQ2). The result of these mutations is ventricular arrhythmia caused by delayed afterdepolarization, secondary to calcium overload [65].

Beta-adrenergic blocking agents are the backbone of medical management and should be given once the diagnosis of CPVT is made [22]. Non-selective beta blockers, nadolol and propranolol, are shown to reduce the adverse arrhythmic events in individuals with pathogenic mutation, regardless of symptoms or evidence of inducible arrhythmias [22,66] (Table 1). Nadolol and propranolol moderate the adrenergic tone and consequently decrease the intracellular calcium. In patients with prior SCD or refractory VAs with recurrent shocks after ICD implantation, recurrent syncope, or exercise-induced PVCs and VAs, despite a maximally tolerated dose of a beta-blocking agent, flecainide could be added. Flecainide (and potentially other class IC agents) suppresses ryanodine receptors, which additionally modulates the intracellular calcium. Flecainide monotherapy is not recommended as a first-line treatment, but can be considered in patients who cannot tolerate beta blockers (Table 1). Verapamil, in combination with a beta blocker, can be used in refractory cases or specific mutation variants; however, the evidence is sparse. Left cardiac sympathetic denervation and ICD therapy (if not yet performed) should be considered if symptoms or VAs cannot be controlled with medications [18,22,65].

6.4. Idiopathic Ventricular Fibrillation

Idiopathic ventricular fibrillation (IVF) is a diagnosis of exclusion from sudden-cardiac-arrest survival with documented VAs. Hereditary channelopathies and specific mutations show a modest yield [67]. ICD therapy is more effective in reducing the risk of SCD compared to amiodarone in multiple studies, and is recommended by guidelines [22,68,69]. AADs are indicated in IVF patients with recurrent ICD shocks and electrical storm. During acute arrhythmic events of electrical storms or multiple ICD discharges, isoproterenol, quinidine, and verapamil suppress VAs in studies [22,70–72]. Quinidine can also be used for the prevention of VAs as a maintenance medication [73] (Table 1).

6.5. Congenital Long QT Syndrome

Congenital long QT syndrome (LQTS) is a heterogeneous group of channelopathies with multiple clinical phenotypes. It is the most common channelopathy, with an estimated incidence of about 1 in 2534 live births with varying risks of cardiac events, depending on the exact genetic mutation acquired [74]. Since the pathophysiology of each subtype is specific to the underlying mutations, the treatment differs slightly among individuals with LQTS. Patients with either LQT1 or LQT2 have prolonged QTc secondary to potassium channel protein mutations, KCNQ1 and KCNH2, for LQT1 and LQT2, respectively. The loss of function of the voltage-gated potassium channel precipitates prolongation of the action potential during phase 3. In contrast, in LQT3, the gain-of-function mutation of the sodium channel SCN5A causes delayed repolarization and QT prolongation [75].

The most effective pharmacological treatment of LQTS available are non-selective beta blockers nadolol and propranolol. Beta blockers have class I recommendations in the management of LQTS in the 2017 AHA guidelines [18]. The adrenergic blocking effect of these agents decreases inward calcium current and subsequently prevents early afterdepolarization [76]. Other beta blockers (atenolol, bisoprolol, or metoprolol) can be considered as alternative options but should not be used as first-line agents. Beta blockers should be considered in all patients, but would benefit more the symptomatic individuals or those with high-risk features (e.g., females with LQT2, early age of onset, and LQT2 and LQT3 genotypes) [18]. Additional medications are generally recommended when symptoms are persistent after first-line treatment or recurrent VAs requiring ICD therapy. Mexiletine is shown to reduce QTc in LQT3 patients by decreasing sodium channel function.
Mexiletine therapy is not limited only to LQT3 genotypes, as the QTc shortening effect is also observed in LQT2 [77]. Less commonly, other sodium channel-blocking agents, flecainide or ranolazine, are often considered as an adjunct therapy, particularly in LQT3 (Table 1). In LQT2, a potassium supplement can be combined with a beta blocker to enhance repolarization via amplification of $\text{IK}_\text{r}$ activity [78].

A novel protein-trafficking chaperone, lumacaftor, was first approved for cystic fibrosis treatment. It has been shown to rescue the defective protein derived from mutated KCNH2 mutation in molecular models [79,80]. In another study, lumacaftor shortens the QTc in LQT2 patients effectively [81]. Further investigation to validate the clinical outcomes of this novel drug is warranted.

6.6. Anderson–Tawil Syndrome Type 1

Formerly classified as LQT7, Anderson–Tawil syndrome type 1 (ATS1) has the characteristic triad of VAs with QT prolongation, dysmorphic features, and episodic paralysis. Severe QT prolongation, prominent U-wave, polymorphic VT, and bidirectional VT are typical findings. KCNJ2 loss-of-function mutation of the $\text{IK}_\text{1}$ potassium channel in ATS1 is the proposed mechanism of QT prolongation [22].

The risk of malignant VAs in ATS1 is substantially high, and AAD is often indicated in addition to ICD therapy [82]. A combination of a beta blocker with or without flecainide effectively suppresses VAs and is recommended in ATS1 patients with significant arrhythmias [83] (Table 1).

6.7. Congenital Short QT Syndrome

Congenital short QT syndrome (SQTS) is an uncommon cause of sudden cardiac death in structurally normal hearts. Like other heritable arrhythmic syndromes, SQTS is a heterogeneous entity with multiple genetic variants. Gain-of-function mutations of genes encoding potassium channels including KCNH2, KCNQ1, and KCNJ2 are responsible for SQTS1, SQTS2, and SQTS3, respectively. Other types of SQTS are attributable to calcium channel ($\text{ICa-L}$) gene mutations. Hyperfunctioning of either the potassium or calcium channel diminishes the refractory period, which increases the risk of arrhythmia, including VAs and atrial fibrillation [84].

Broad-spectrum potassium channel-blocking agents address the pathophysiology of SQTS and, therefore, are found to be effective in prolonging the QTc and preventing VAs. Quinidine is recommended in patients with contraindications to ICD therapy or patients with a family history of SCD [85,86]. Quinidine has a class IIa recommendation in the management of short QT syndrome from the 2017 AHA guidelines [18]. Given comparable antiarrhythmic effects, disopyramide is found to lengthen QTc in an observational study, yet clinical benefit has to be verified [87]. Isoproterenol is reported to suppress electrical storms in SQTS, in a limited study [88] (Table 1). As other QTc-prolonging agents do not exhibit therapeutic benefits in prior studies, further research for alternative agents has to be explored [89].

6.8. Arrhythmogenic Cardiomyopathy

Arrhythmogenic cardiomyopathy (ACM) is a cardiomyopathy caused by fibrofatty infiltration of the myocardium. Multiple desmosome gene defects are identified as pathogenic mutations of the disease. The pathophysiology of arrhythmia of ACM is complex, and involves a combination of structural abnormalities, ion channel dysfunction, and abnormal intercellular conduction [90]. The risk of arrhythmic events varies among different genotypes and phenotypes, but the risk is considered elevated if ventricular dysfunction, syncope, frequent PVCs, non-sustained or sustained VT, or specific ECG findings are present. Apart from ICD and high-intensity-exercise avoidance, which are crucial in ACM management, AADs are used as an adjunctive treatment when suppression of ventricular arrhythmia is required [18].
Despite guideline recommendations, Refs. [18,22], beta-blockers have shown heterogeneous effect in ACM. Some studies suggest a reduction in major ventricular arrhythmias by beta blockers, [91,92] while other fail to demonstrate efficacy [93,94]. Nonetheless, the combination of a beta blocker with flecainide reduces VAs in ACM patients in recent trials [95,96]. Amiodarone is not routinely used, due to the lack of high-quality evidence on its efficacy and clinical benefit [91,93]. Long-term side effects also limit its use in younger patient populations [97]. Sotalol also has inconsistent outcomes in studies [92,98] (Table 1). The varied results of AAD performance are likely due to the heterogenous phenotype of ACM and, therefore, different responses to AADs. Targeted therapy for ACM is being developed to halt or reverse the disease process. GSK3β inhibitor (SB216763) has been shown to improve cardiomyopathy in cellular models, and will perhaps ameliorate arrhythmias in ACM [99].

6.9. Hypertrophic Cardiomyopathy

One of the most common inherited cardiomyopathy syndromes is hypertrophic cardiomyopathy (HCM). With a prevalence of at least 1:500 in the general population, [100] multiple studies have engaged in exploring VA treatment in HCM individuals. Most patients with HCM have MTBPC3 or MYH7 sarcomere protein gene mutation [101]. Increased myocardial-oxygen demand with lower myocardial blood supply and intramyocardial fibrosis leading to electrical inhomogeneity are the proposed mechanisms of VAs in HCM [102]. ICD is the mainstay of VAs as a secondary preventive strategy or as primary prevention in high-risk groups [102].

Medical therapy has a role in relieving the mechanical obstruction from myocardial hypertrophy, but no medication is shown to have clinical benefit in preventing arrhythmic events, except for amiodarone in one observational study [103,104]. Hence, amiodarone is recommended by guidelines as an alternative treatment option, should ICD therapy not be feasible [105]. Most patients will receive a beta blocker, which is often combined with amiodarone in case of recurrent, symptomatic VAs, or recurrent ICD therapy [22]. The side risk of adverse effects from amiodarone should be weighed with the benefit. There are studies showing the efficacy of dofetilide and mexiletine on reducing ventricular arrhythmic events; however, randomized trials are required for validation of efficacy [47,106] (Table 1). This may reflect the complex underlying pathophysiology of VAs in HCM. In patients with refractory VAs despite optimal device programming, or maximally tolerated AADs, catheter ablation can be considered [22].

Novel treatment with cardiac myosin inhibitors, mavacamten, and aficamten are shown to improve symptoms and LVOT obstruction [107]. The effect of these agents on VAs requires additional investigations.

6.10. Cardiac Sarcoidosis

Cardiac sarcoidosis is among the common primary inflammatory cardiomyopathies in clinical practice. VAs, which predict adverse outcomes, may occur because of active inflammation or subsequent myocardial scarring [108]. Anti-inflammatory drugs and immunosuppressive therapy are usually considered when VAs develop, due to active inflammation to stabilize disease and prevent disease progression. ICD is frequently implanted in patients with cardiac sarcoidosis, as the risk of SCD and VA is substantial [109]. Class III AADs, particularly amiodarone and sotalol, are commonly used as first-line treatment for patients with recurrent or symptomatic VAs [22,110] (Table 1). Catheter ablation is sometimes ineffective, due to the complex substrate of arrhythmias in cardiac sarcoidosis [111].

7. Gene Therapy in VT

Gene therapy has emerged as a cutting-edge and highly promising therapeutic approach for the treatment of VT, aiming to address the underlying molecular and genetic abnormalities associated with each disease. The cardiac channelopathies, with their well-
described genetic components, are of particular interest in this regard. Animal models and pluripotent stem cell-derived cardiomyocytes of CPVT, including ryanodine receptor (RYR), Ca^{2+}/calmodulin-dependent protein kinase II, and the CASQ2 gene have been studied. Using delivery mechanisms such as adeno-associated serotype 9 viral vector (AAV9), small-interfering RNA (siRNA), or CRISPR-Cas9, several studies were able to show effective suppression of ventricular arrhythmias, restoration of normal gene expression and interaction, and suppression of abnormal calcium-release events [112–116]. In human embryonic kidney cells and pluripotent stem cells, siRNA therapy can eliminate abnormal mRNA transcripts that result in faulty ion channels which result in inherited LQTS [117]. In mouse models with mutations in the SCN5A gene which results in BrS, AAV9 vectors have been utilized to enhance transportation of the cardiac sodium channel to the cell membrane. These mice showed restoration of sodium current densities and action potential durations, decreased late phase-3 early afterdepolarizations, and reversed ECG abnormalities associated with BrS [118].

Gene therapy has been studied in the treatment of certain cardiomyopathies with known genetic predisposition. ACM is associated with desmosome gene mutations, particularly plakophilin-2 (PKP2), in approximately 40–50% of cases. AAV9 vector gene-delivery technology has been studied in mouse models with severe PKP2 mutations that closely mimic classic phenotypes of ACM. The mice who received this gene therapy showed a substantial increase in cardiac PKP2 expression, double the survival rate, improved right- and left-ventricular ejection fraction on MRI, and improved suppression of ectopic beats [119]. Although the study only utilized sixteen mice, these findings suggest that gene therapy to restore PKP2 expression has the potential to halt or decelerate the advancement of ACM in later stages of life.

8. Artificial Intelligence in VT

Artificial intelligence (AI) has an evolving role in the management of arrhythmias. Technological advances in the development of large databases, electronic health records, and powerful cardiovascular-imaging techniques continue to transform the role of AI in arrhythmia management [120]. AI technology has long been applied to ECG to enhance interpretation [120]. AI, through the use of deep neural networks, has been capable of identifying concealed LQTS in those patients who were discharged from the emergency room without a diagnosis of LQTS, with nearly 80% accuracy [121]. Current risk-stratification strategies for predicting SCD have limitations, and this is one area where AI can mine information from large datasets to provide better risk-stratification variables. AI has been applied to predicting risk of SCD using clinical or demographic variables in the emergency department [122], intracardiac electrograms from ICDs [123], and using various cardiovascular imaging techniques in patients with cardiomyopathy [124]. This technology has promising potential for identifying patients who may benefit from ICD therapy.

The application of AI in the management of arrhythmias usually necessitates large datasets directed at pre-specified populations. Additionally, legal and ethical issues often arise as barriers to collecting or disclosing patient information to the AI community. Personalized computational modeling can construct a virtual heart model that is unique to the patient [125]. This model can evaluate the substrate and arrhythmic predisposition by basing it on cardiac imaging that visualizes the geometry and remodeling of the heart [126]. Computational modeling has been used as a noninvasive way to predict targets for VT ablation [127].

Some limitations of AI in the treatment of VT are due to the relatively small population size. Quality AI technology needs large datasets with heterogeneous disease states to increase accuracy and generalizability. AI can produce errors or unexpected results if there is poor generalizability of the algorithm when applied to an actual patient. To be applicable in the routine EP lab, these algorithms need high-quality input, as well as monitoring of the machine learning technology, to ensure an optimal and interpretable result. As mentioned earlier, there has been little improvement in the survival of VT in patients with
non-ischemic cardiomyopathies. Applying AI technology to the treatment of VT may be able to narrow the gap for these patients.

9. Conclusions

The therapeutic management of VT mandates a multifaceted approach. ICDs and catheter ablation play a critical role in VT management. The integration of antiarrhythmic therapy, alongside catheter ablation and ICD management, is an important consideration to minimize inappropriate shocks and improve overall patient well-being. Understanding the unique mechanisms of VT down to the molecular level helps tailor one’s approach to AAD use for special populations.

Gene therapy has emerged as a promising and targeted approach for treating VT disorders, including CPVT, LQTS, BrS, and ACM. By precisely manipulating molecular and genetic abnormalities, gene therapy interventions have demonstrated significant potential in suppressing arrhythmias, restoring normal gene expression and cellular function, and improving clinical outcomes in preclinical models. The promise of high-quality artificial intelligence algorithms will continue to expand our ability to predict sudden cardiac death, identify anomalies that present in a nonlinear fashion, and improve ablation targets for VT. Continued exploration of gene therapy interventions and artificial intelligence offers hope for personalized and precision medicine approaches in the future management of VT.

This review focused on the history and epidemiology of VT, landmark clinical trials that helped establish the role of ICD therapy, AADs, and catheter ablation on the therapeutic management of VT, as well as the role of AADs and future consideration of gene therapy and artificial intelligence.

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