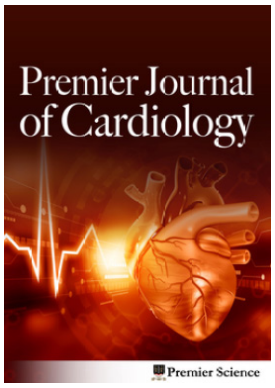

Rhythm Control and Risk Reduction: Evidence From a Narrative Review on Therapeutic Advances in Cardiac Arrhythmia Management

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ABSTRACT

With the growing prevalence of cardiac arrhythmias, effective management is crucial to improve quality of life, reduce the risk of complications, and enhance survival rates. This narrative review aimed to comprehensively provide updates regarding the clinical management of cardiac arrhythmias. Lifestyle modifications, pharmacological interventions, and procedural therapies were identified to enhance cardiac rhythm and rate control, as well as address underlying comorbid factors. Lifestyle modalities included maintaining a healthy weight, ensuring an appropriate diet, exercising regularly, managing stress, and avoiding triggers like alcohol. However, uncertainty still persists regarding the harms or benefits of these foods rich in chocolate and caffeine. While lifestyle interventions are foundational, their effectiveness depends on disease severity and individualized treatment goals. Tailored strategies, including vagal maneuvers and genetics-guided therapy, offer promise for arrhythmia management. Recent advancements in therapies have also been uncovered, including the exploration of intranasal etripamil, inhaled flecainide, and cognitive behavioral therapy, which demonstrate potential for improved disease management. Minimally invasive technologies, including wearable monitors, robotic-assisted platforms, renal denervation, and procedures like the Maze technique and cardioneuroablation, are also being explored for reshaping arrhythmia treatment and recovery timelines. These innovations reinforce a personalized and data-driven framework for cardiovascular care and underscore the importance of integrating precision-based strategies to reduce arrhythmia burden, enhance treatment efficacy, and guide future research into safer and more targeted therapies.

Keywords: Intranasal etripamil, Inhaled flecainide, Pulsed field catheter ablation, Cardioneuroablation, Wearable arrhythmia monitors

Highlights

- Lifestyle interventions are recommended as first-line management approaches for patients with cardiac arrhythmias
- Caffeine and exercise may be beneficial or harmful in patients with arrhythmia, depending on the dose
- Metformin and drugs that act on the Renin–Angiotensin–Aldosterone System can be beneficial in patients with arrhythmia
- Intranasal etripamil, inhaled flecainide, and cognitive behavioral therapy show promise in arrhythmia management
- Emerging cardioneuroablation, implantable devices, and gene editing therapies can promote precision-based management

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Introduction

Cardiac arrhythmias encompass a range of cardiovascular conditions characterized by disorders of the heart's electrical system. These abnormalities can manifest as irregular heart rate, conduction pathways, or rhythm, which could either be too slow (bradyarrhythmia: <60 beats/min) or too fast (tachyarrhythmia: >100 beats/min).[1] Although cardiac arrhythmias are broadly classified as tachyarrhythmias and bradyarrhythmias based on heart rate, they further exist as subcategories based on origin, including supraventricular arrhythmias, originating above the ventricles, and ventricular arrhythmias, originating within the ventricles. Common types of arrhythmias include atrial fibrillation (AF), atrial flutter, supraventricular tachycardia (SVT), ventricular tachycardia (VT), and ventricular fibrillation (VF).[2] While cardiac arrhythmia can occur at any age, its incidence increases with older age and is more common in individuals with underlying cardiovascular diseases such as hypertension, coronary artery disease, and heart failure. Epidemiological studies have demonstrated potential links between hypertension and the development and progression of various atrial and ventricular arrhythmias, with AF being the most common manifestation.[3,4] Although the underlying pathophysiological mechanism remains unclear, left ventricular hypertrophy resulting from chronic hypertension has been proposed to lead to progressive ventricular dysfunction and left atrial enlargement, which predisposes patients to the development of atrial and ventricular arrhythmias. Specifically, the occurrence of left ventricular hypertrophy is a strong predictor for the development of AF, ventricular ectopy, and sudden cardiac death.[5] Patients with hypertension having left ventricular hypertrophy or heart failure are therefore more susceptible to both supraventricular and ventricular arrhythmias.[6]

Cardiac arrhythmias affect millions of people worldwide, significantly contributing to the global mortality and morbidity rates. AF represents the most common manifestation of the disease, with an estimated 33 million individuals affected globally,[2] resulting in mortality, morbidity, or substantial disability-adjusted life-years.[4,6] Similarly, an increased rate of ventricular extrasystoles up to non-sustained ventricular tachycardia, and ST-depression in long-term electrocardiography (ECG) increases the risk of sudden cardiac death.[7,8]

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Owing to the growing prevalence of the disease, effective management is therefore crucial to improve quality of life, reduce the risk of complications, and enhance survival rates. This narrative review aimed to comprehensively provide updates regarding the clinical management of cardiac arrhythmias. By synthesizing current evidence, it seeks to inform clinical decision-making and support the development of targeted interventions to mitigate the global burden of arrhythmias.

Clinical Presentation

Pathophysiology and Clinical Presentation

The components of the cardiac conduction system are illustrated in Figure 1. Arrhythmias can arise from various mechanisms, primarily categorized into abnormal impulse initiation and impulse conduction, or re-entry of impulses in the heart's electrical system. The different mechanisms precipitate varying classifications of the disease, including tachyarrhythmia and bradyarrhythmia.[9] Within the subcategories of tachyarrhythmia, AF is characterized by rapid and irregular electrical signals in the atria, whereas organized electrical activity in the atria represents an atrial flutter. SVT encompasses arrhythmias originating above the ventricles, leading to a rapid heart rate, and ventricular arrhythmias, including VF, represent a more critical form of the disease. In bradyarrhythmia, an atrioventricular block may occur when conduction through the node is impaired, thereby leading to symptomatic or asymptomatic manifestations depending on the degree of the block.[2]

Multiple risk factors, such as lifestyle factors and electrolyte imbalance triggers, and underlying conditions, including viral infections, congenital heart defects, and autonomic nervous system imbalances, can predispose individuals to arrhythmogenesis.[10] In particular, degenerative electrical disease and left ventricular hypertrophy constitute a principal pathophysiological mechanism.[8] Similarly, structural heart diseases, such as coronary artery disease, cardiomyopathy, and valvular heart disease, can alter the heart's anatomy and electrical properties, increasing the likelihood of arrhythmias.

With considerable evidence linking hypertension with cardiac arrhythmias, recent reports have suggested that various antihypertensive agents prescribed for the management of hypertension in patients can also contribute to the manifestation of arrhythmias, mainly through electrolyte disturbances. It is estimated that

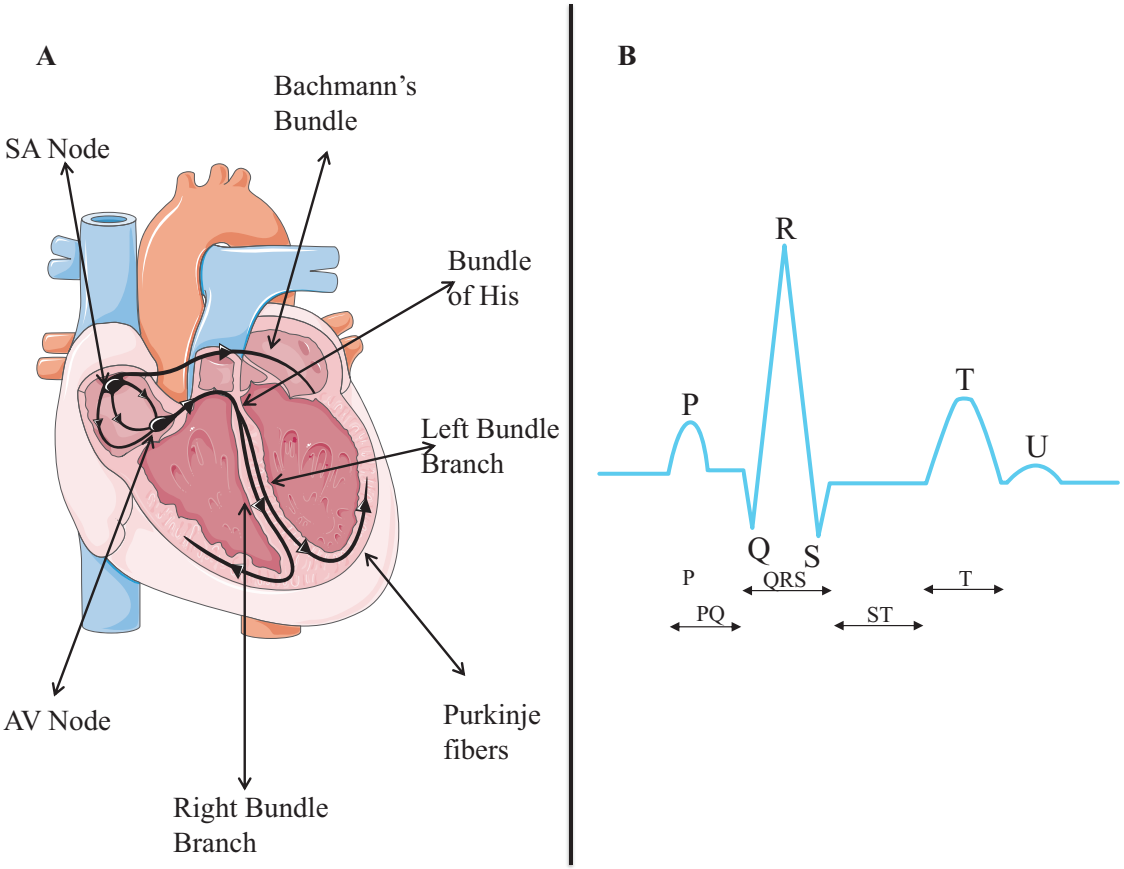

Fig 1 | Cardiac conduction system and normal electrocardiogram. (A) Schematic illustration of the cardiac conduction system, showing the sinoatrial (SA) node, atrioventricular (AV) node, bundle of His, right and left bundle branches, and Purkinje fibers. The directional arrows indicate the normal propagation of electrical impulses responsible for coordinated atrial and ventricular contraction. (B) Representative normal electrocardiogram (ECG) tracing demonstrating the characteristic P wave, QRS complex, and T wave. Illustrations adapted from Servier Medical Art (https://smart.servier.com/), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/)

people with hypertension or taking antihypertensive medication have a 73% greater likelihood of AF. According to Lip et al.,[4] caution should be exercised with the concomitant use of non-dihydropyridine calcium channel blockers and β-blockers in the management of hypertension, as this portends an increased risk of bradycardia and atrioventricular block, particularly in patients with chronic kidney disease.

Cardiac arrhythmias can present with a wide range of symptoms, which carry immediate risk depending on the type and underlying cardiac function. Symptoms may include palpitations, dizziness, lightheadedness, chest discomfort, fatigue, and anxiety.[11] However, although AF is commonly symptomatic, it remains clinically silent in up to 35% of cases, especially among individuals with minimal comorbidity, such as isolated hypertension.[4] This asymptomatic nature presents a diagnostic challenge, as untreated AF markedly increases the risk of thromboembolic events, particularly ischemic stroke, due to stasis of blood within the atria.

Other clinical manifestations of cardiac arrhythmias include irregular heartbeats, pre-syncope or syncope, chest tightness, and shortness of breath. In severe cases, arrhythmias may precipitate hemodynamic instability or sudden cardiac arrest.[12] Complications, including the development of heart failure secondary to impaired ventricular filling and output, and progression to more malignant arrhythmias, can also occur.[1] However, the prognosis of cardiac arrhythmias depends on timely diagnosis, the presence of comorbidities, and individualized therapeutic interventions.

Clinical Assessment

Early identification and management of cardiac arrhythmia is critical; if left unmanaged, it can lead to severe complications, including stroke, heart failure, and sudden cardiac death. In response to this need, techniques, including photoplethysmography and ECG signaling, have been used for the diagnosis of arrhythmias. The ECG is often the first and primary diagnostic modality performed for suspected cases of arrhythmia, as it records the heart's electrical activity. Specifically, heart rate variability and abnormal heart rhythms can be estimated from ECG signals and can reveal whether there is dysregulation of the autonomic system.[13]

Recent advances in biomedical engineering have introduced techniques such as the Holter monitoring system and event recorders, involving a portable ECG device that continuously records the heart's electrical activity for 24 to 48 h or longer, or only when the patient experiences symptoms. These modalities offer non-invasive, real-time data collection and may enhance diagnostic precision outside of clinical settings, as well as help to identify intermittent or transient arrhythmias that may not be present during a standard ECG.[14]

Beyond standard ECG diagnosis, a comprehensive arrhythmia assessment may involve a combination of other baseline clinical assessments, including the patient's medical history, physical examination, and the results of diagnostic tests. The WHO functional class and six-minute walk test are used to assess physical capacity and cardiovascular response to exertion.[15] Echocardiography and cardiac magnetic resonance imaging[16] are also being used to visualize cardiac chamber dimensions, valvular function, and systolic performance, providing insights into structural anomalies that may underlie rhythm disturbances.[17,18] These assessment modalities underscore the need for a multidisciplinary approach involving precise measurement, longitudinal monitoring, and personalized evaluation for optimizing patient outcomes.

It is therefore recommended that healthcare providers consider the specific arrhythmic symptoms, the duration and frequency of the irregular heartbeats, and underlying medical conditions to determine the most effective approaches to diagnosing and managing the varying forms of arrhythmia. The findings from this narrative review will highlight the evolving landscape of cardiac arrhythmia management, which is crucial for supporting clinicians in the development of safer regimens and informing future research directions in the management of arrhythmia.

Non-Pharmacological Management

Lifestyle modifications, which primarily involve the use of non-pharmacological approaches to address underlying cardiovascular risk factors and unhealthy habits, are a crucial aspect of controlling arrhythmias. These include maintaining a healthy weight, ensuring an appropriate diet, exercising regularly, managing stress, and avoiding triggers like alcohol.[19]

Healthy Diet

Given the impact of dietary habits on cardiac rhythm, current clinical guidelines recommend the Dietary Approaches to Stop Hypertension (DASH) plan as one of the first and particularly effective strategies for preventing and reducing cardiac arrhythmias. Diets high in potassium, magnesium, calcium, omega-3 fatty acids, dietary fiber, and lignans have demonstrated protective effects on vascular tone and cardiac excitability, thereby also contributing to arrhythmia prevention. In the FLAX-PAD trial (Table 1), a 1-year consumption of a diet supplemented with 30 g of milled flaxseed–a plant protein rich in omega-3 fatty acids, dietary fiber, and lignans–demonstrated a 2% decrease in the presence of cardiac arrhythmias without any significant change in ECG variables.[20] Additionally, coffee and other related foods such as tea, nuts, chocolates, and antioxidant vitamins have also been proposed to potentially have antiarrhythmic properties.[21] However, uncertainty still persists regarding the harms or benefits of these foods, especially meals with chocolates and caffeine. Similarly, energy drinks and meals rich in polyunsaturated and monounsaturated fatty acids, and salts, are required to be taken in limited quantities, as they may be harmful for patients with rhythm disorders.[22]

Physical Fitness

Obesity and overweight remain strong risk factors for cardiac arrhythmias, with each 5-unit increase in body

Table 1 | Overview of notable studies on cardiac arrhythmia management

S/N	Citation	Study Design	Treatment Approach	Number of Participants	Study Outcomes
1	Rodriguez-Leyva et al., 2018[20] FLAX-PAD trial	Randomized controlled trial	One-year effect of flaxseed on the prevalence of cardiac arrhythmias and exercise capacity	83	Daily consumption of a diet supplemented with 30 g of milled flaxseed decreases arrhythmia prevalence by 2% after 1 year and increases by 12% in the placebo group
2	Mostofsky et al., 2016[21]	Prospective population-based cohort study	Risk of coffee consumption on atrial fibrillation	5073	Compared with no intake, higher levels of coffee consumption were associated with a lower rate of incident atrial fibrillation
3	Pathak et al., 2015[25] LEGACY study	Cohort study	long-term impact of weight loss and weight fluctuation on rhythm control of atrial fibrillation	1415	Long-term sustained weight loss › 10% is associated with 6-fold reduction of atrial fibrillation burden and maintenance of sinus rhythm. Weight fluctuation ›5% partially offsets benefits, with a 2-fold increased risk of arrhythmia recurrence.
4	Middledorp et al., 2018[26] REVERSE-AF study	Observational study	Impact of weight and risk factor management on the progression of atrial fibrillation	1415	Weight-loss and risk factor management reverses the type and natural progression of atrial fibrillation.
5	Vedel-Larsen et al., 2016[27]	Randomized controlled trial	Effect of major rapid weight loss on cardiac repolarization	26	Average of 13.4% weight loss at 8 weeks results in increased QRS and RR intervals.
6	Pathak et al., 2015[28] CARDIO-FIT study	Observational study	Impact of cardiorespiratory fitness on atrial fibrillation recurrence in obese individuals	1415	Improvement in cardiorespiratory fitness augments the beneficial effects of weight loss in patients with atrial fibrillation.
7	Minjie et al., 2023[32]	Prospective, open, pseudo-randomized study	Effect of a 6-month behavioral therapy in atrial fibrillation	102	Cognitive behavioral therapy for 6 months effectively improves health-related quality of life in patients with atrial fibrillation.
8	Kim et al., 2021[38]	Retrospective population-based cohort study	Rhythm control vs. rate control in atrial fibrillation	22,635	Early rhythm control had a lower risk of stroke and heart failure complications
9	Soliman et al., 2020[43]	Randomized controlled trial	Effect of intensive blood pressure control on atrial fibrillation risk	8022	Intensive blood pressure lowering to ‹120 mm Hg lowers the risk of atrial fibrillation by 26%
10	Ostropolets et al., 2021[47]	Observational study	Assessment of the association between metformin and atrial fibrillation	190,180	Metformin monotherapy significantly reduced the risk of atrial arrhythmias, compared to monotherapy with DPP4 or TZD medications
11	Crijns et al., 2022[48] (INSTANT trial)	Open-label, multicenter study	Flecainide Acetate Oral Inhalation Solution	101	Oral inhalation yielded plasma concentrations sufficient to restore sinus rhythm
12	Ruskin et al., 2024[49] (INSTANT Phase 2 trial)	Phase 2 clinical trial	Flecainide Acetate Oral Inhalation Solution	98	Conversion rate: 42.6%. Median time to conversion: 14.6 min
13	Stambler et al., 2018[50] NODE-1 (phase 2) study	Multicenter, randomized, double-blind, placebo-controlled, dose-ranging study	Efficacy of etripamil nasal spray in patients with supraventricular tachycardia	104	Etripamil nasal spray rapidly terminated induced supraventricular tachycardia with a high conversion rates to sinus rhythm of 65–95%
14	Stambler et al., 2022[51] NODE-301 (phase 3) trial	Randomized, multicenter, double-blind, placebo-controlled study	Effect of self-administered intranasal etripamil for acute conversion of spontaneous paroxysmal supraventricular tachycardia	156	Etripamil treatment effectively terminates paroxysmal tachycardia within 30 minutes
15	Stambler et al., 2023[52] RAPID trial	Multicenter, randomized, placebo-controlled, event-driven trial	Safety and efficacy of 70 mg repeat dose regimen of intranasal etripamil on supraventricular tachycardia	692	Etripamil was well tolerated, safe, and superior to placebo for the rapid conversion of atrioventricular-nodal-dependent paroxysmal supraventricular tachycardia to sinus rhythm
16	Steinberg et al., 2024[53]	Observational study	Multicenter evaluation of IV sotalol in atrial arrhythmia	167	IV sotalol loading is safe and feasible for atrial arrhythmias, with low rates of adverse events, and shorter hospitalizations compared with oral sotalol
17	Lakkireddy et al., 2023[54] DASH-trial	Prospective, nonrandomized, multicenter, open-label trial	Feasibility and safety of IV sotalol in atrial fibrillation	120	IV sotalol, achieved a steady state with maximum QTc prolongation within 6 h compared with the traditional 5-dose oral titration.
18	Marrouche et al., 2018[55] (CASTLE-AF trial)	Multicenter, open-label, randomized, controlled trial	Effect of catheter ablation in atrial fibrillation	363	Lower risk of death or worsening heart failure
19	Hunter et al., 2014[56] (CAMTAF Trial)	Single-center prospective randomized controlled trial	Catheter ablation for rate control in patients with persistent AF and heart failure	55	Catheter ablation is effective in restoring sinus rhythm and can improve left ventricular function, functional capacity, and heart failure symptoms
20	Tung et al., 2025[57]	Multicenter study	Cardioneural ablation for functional bradycardia and vasovagal syncope	205	Acceleration of baseline heart rate and a significant reduction in syncope burden
21	Reinsch et al., 2024[59] PRIORI study	Retrospective, non-randomized single-center study	Pulsed field ablation vs. high-power short-duration radiofrequency ablation in paroxysmal atrial fibrillation	410	Comparable arrhythmia-free survival between Pulsed field and. high-power short-duration radiofrequency ablation.

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mass index resulting in a corresponding 19–29% increase in incident AF.[23] While obesity is linked to higher risks of atrial and ventricular arrhythmias, as well as sudden cardiac death, reports have demonstrated the effect of weight loss in mitigating arrhythmic incidence. According to reports from Abed et al.,[24] patients with symptomatic AF who underwent weight management experienced superior reductions in the disease burden, symptom severity scores, cumulative duration, and interventricular septal thickness, compared to patients who did not.

Two primary papers in this review buttressed the importance of weight loss for reduced AF incidence. First, the LEGACY study,[25] which assessed long-term outcomes, indicated that patients with weight loss of >10% exhibited lower arrhythmic burden and greater survival-free rates. Similarly, the REVERSE-AF study demonstrated that patients with the greatest degree of weight loss had the lowest rates of progression from paroxysmal to persistent AF, as well as the highest rates of reversal,[26] thereby highlighting the importance of weight loss in arrhythmia management. However, it is crucial to ensure that weight loss is gradual and nutritionally sound. Excessive or rapid weight loss, particularly from restrictive diets or malabsorptive conditions, may precipitate electrolyte imbalances, such as hypokalemia or hypomagnesemia, which can result in cardiac arrhythmias through disruption of myocardial conduction and repolarization.[27]

In line with the need for weight loss, regular physical activity is generally considered a protective intervention against arrhythmia. Reports have shown that leisure-time physical activity is associated with a lower incidence of AF in a graded manner.[28] Maintenance of proper glycemic control through structured exercise training for prediabetes and continuous positive airway pressure utilization for obstructive sleep apnea has also been correlated with reductions in AF recurrence. Moderate exercise has been shown to demonstrate greater arrhythmia-free survival and a mean reduction in the disease burden; as such, routine physical activity, including aerobic exercises, is paramount and can improve endothelial function, modulate autonomic balance, and enhance cardiac output.[29]

Behavioral Counselling Approaches and Psychological Interventions

Anxiety, depression, stress, poor quality of life, and other related aspects of psychological health significantly influence the clinical course and prognosis of both ventricular and atrial arrhythmias through their impact on autonomic activity.[30] To address these factors, interventions aimed at decreasing psychological and physiological responses have been proposed. Recently, psychologically based techniques such as biofeedback, relaxation training, meditation, hypnosis, and psychotherapy have been used in the treatment of certain patients with cardiac arrhythmias. A case report by Park and Roth[31] demonstrates the efficacy of the biofeedback system. Similarly, 6-month cognitive behavioral therapy represents a promising nonpharmacological intervention for managing arrhythmias and improving both psychological and physical quality of life.[32,33] Enacting cognitive behavioral changes using the five A's, which include patient assessment, advice, agreement, assistance, and arrangement, has been shown to significantly improve physical and emotional well-being in patients with atrial fibrillation.

Social modulators and behavioral counseling strategies have also provided favorable modifications in patients who may struggle to implement and maintain therapeutic lifestyle interventions against smoking, or excessive alcohol or caffeine intake. As smoking cessation is imperative to arrhythmia management due to its pro-arrhythmic and vasoconstrictive effects of tobacco use. Likewise, alcohol should be consumed in moderation or avoided altogether in patients with known arrhythmic predisposition. Through cognitive behavioral therapy and other modalities such as psychological stress management, mindfulness practices, and adequate sleep hygiene, patients can be motivated to overcome these predisposing risk factors and unhealthy lifestyle habits, thus modulating autonomic tone and reducing adrenergic surges that may trigger arrhythmias.[33]

Pharmacological Management

In the management of cardiac arrhythmias, modalities differ based on the disease classification. AF management is typically achieved through rate control using beta-blockers, rhythm control with antiarrhythmic drugs, and anticoagulation therapy to prevent thromboembolic events; whereas, atrial flutter, though similar in pathophysiology to AF, is often treated with electrical cardioversion, catheter ablation, and rate control medications. SVT is often managed acutely with vagal maneuvers and adenosine, a rapid-acting agent that transiently blocks atrioventricular nodal conduction.[34] For recurrent cases, non-pharmacological therapies are primarily employed.

Vaughan Williams Classification

Arrhythmic medications can be further grouped according to their electrophysiological effects at a cellular level using the Vaughan Williams classification or according to their main sites of action within the heart to maintain sinus rhythm.[35] Using the Vaughan Williams classification, antiarrhythmic therapy can be categorized into four classes: Class I, sodium channel blockers; Class II, beta blockers; Class III, potassium channel blockers; and Class IV, calcium channel blockers. Rate control involves using Class II or Class IV medications to slow the heart rate, whereas rhythm control requires the use of Class I or Class III medications for normal heart rhythm restoration.[36] Other agents include adenosine and digoxin for paroxysmal SVT and rate control in AF, respectively.[37] Figure 2 shows the Vaughan classification of antiarrhythmic drugs.

Rate Control and Rhythm Control

The choice between rate and rhythm control therapy depends on factors such as symptom severity, duration

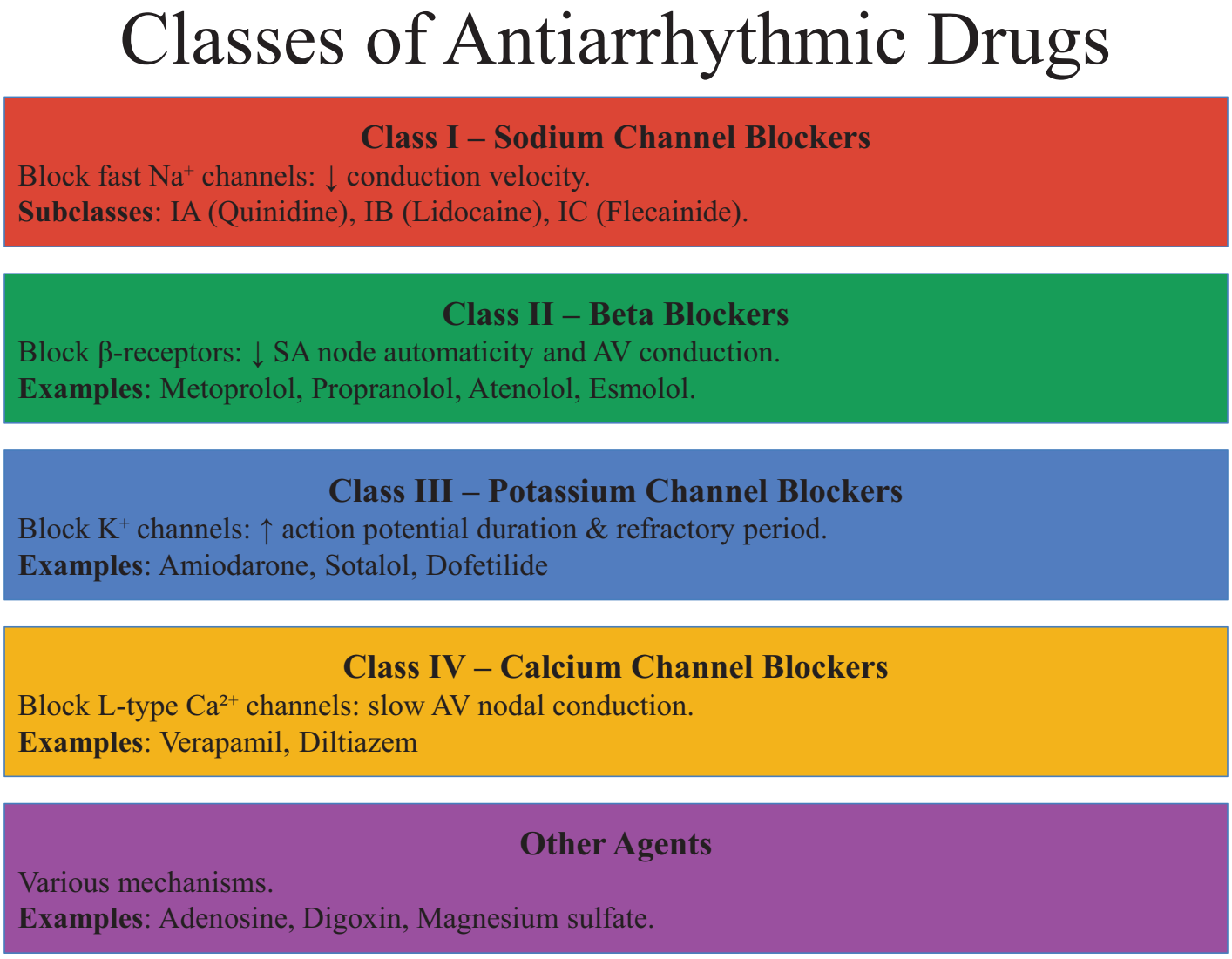

Fig 2 | Vaughan Williams' classification of antiarrhythmic drugs. The illustration depicts the four major classes of antiarrhythmic agents, their sites of action on the cardiac action potential, and representative drug examples. Other agents are grouped under "others"

of arrhythmia, and patient preferences. However, recent updates in the management of AF now report that early rhythm control should be favored over rate control in select patients, especially those with recent onset, structural heart disease, or high stroke risk.[38] Similarly, due to adverse effects such as QT prolongation and anticholinergic effects in Class IA anti-arrhythmics, and proarrhythmic and conduction blocks in Class IC drugs, these medications are contraindicated in patients with prolonged QT and prior myocardial infarction or reduced ejection fraction, respectively.[39]

Major clinical trials have shaped the management of AF and the choice between rate and rhythm control. In the AFFIRM trial,[40] patients who took rhythm-control drugs like amiodarone, sotalol, or propafenone had a 5-year mortality of 23.8%, compared with 21.3% for those on rate-control medications such as beta-blockers, calcium channel blockers, or digoxin; however, these differences were not significant (hazard ratio [HR]: 1.15; 95% confidence interval [CI]: 0.99–1.34; $p = 0.08$). Notably, hospitalizations were slightly higher in the rhythm-control group (80.1% vs. 73.0%; $p < 0.001$). Therefore, the study concluded that rhythm control using antiarrhythmic drugs offered no survival advantage over rate control.

Likewise, the RACE I trial,[41] involving over 500 patients with persistent AF, similarly found that rate control was as effective as rhythm control; the main cardiovascular events occurred in 17.2% of the rate-control group versus 22.6% in the rhythm-control group (HR: 0.73; 95% CI: 0.53–1.01). Building on findings from the previous studies, the RACE II trial[42] compared strict (resting heart rate <80 bpm) and lenient (resting heart rate <110 bpm) heart rate targets in patients with permanent AF. The study defined a primary outcome, which was a composite of death from cardiovascular causes and other complications. At 3 years, patients taking rate-controlling drugs who were allowed a lenient target demonstrated a similar incidence of the primary outcomes (12.9%) as those in the strict-control group (14.9%; $p < 0.001$). This implies that the lenient approach was just as effective as the strict

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approach, but more easily managed. Taken together, these landmark trials established rate control as a safe, effective, and often preferable strategy for the long-term management of atrial fibrillation, especially in patients with minimal symptoms or significant comorbidities.

Adjunctive Therapy

Comorbidities are significant risk factors for cardiac arrhythmias. These risks may involve poor glycemic control, renal dysfunction, congenital heart defects, autonomic nervous system imbalances, viral infections like COVID-19, and cardiovascular conditions like uncontrolled hypertension. Using data from the SPRINT trial, Soliman et al.[43] indicated the potential effect of intensive blood pressure control in reducing AF incidence in patients, reporting a 26% lower risk of developing new AF. With a particular target on the renin–angiotensin–aldosterone system, intensive treatment to a target of systolic blood pressure <120 mm Hg in patients with hypertension has been reported to lower the risk of new-onset AF and reduce the incidence of recurrence.[44] This is important, especially as uncontrolled hypertension complicates the management of cardiac arrhythmias, diminishing the effectiveness of antiarrhythmic drugs and procedures, such as catheter ablation and cardioversion.

Similarly, the impact of diabetes on the cardiac electrical conduction system has become apparent, resulting in AF and ventricular arrhythmias.[45] Type II diabetes has been closely associated with the risk of AF development; however, glucose-lowering therapies have demonstrated effects against AF.[46] An observational study by Ostropolets et al.[47] found that patients on metformin monotherapy had a significantly reduced risk of atrial arrhythmias, compared to monotherapy with sulfonylureas, thiazolidinediones, and dipeptidyl peptidase 4 inhibitors.

Recent Developments in Pharmacological Management

Recent years have witnessed significant progress in the pharmacological management of cardiac arrhythmias, driven by advances in cardiac electrophysiology and drug development. Newer antiarrhythmic agents have been designed to improve ion channel selectivity, minimize proarrhythmic risks, and enhance overall safety and efficacy.[48–54]

AF

Ongoing research into other approaches for arrhythmia management includes the development of inhaled flecainide formulations for rapid cardioversion of AF, as investigated in the INSTANT trials.[48,49] Flecainide, a Class IC antiarrhythmic, is traditionally administered orally or intravenously, but inhaled delivery aims to achieve swift and high plasma concentrations via pulmonary absorption. In a multicenter study by Crijns et al.,[48] a 120 mg inhaled dose of flecainide acetate converted approximately 48% of patients with recent-onset AF to sinus rhythm within 90 min, with a median conversion time of less than 15 min and no report of serious adverse effects. Reported side effects included mild cough, altered taste, and oropharyngeal irritation, while cardiovascular events such as bradycardia and hypotension were infrequent and self-limiting.[49] Furthermore, intravenous sotalol for acute atrial arrhythmias has been reported as efficacious and safe, with low rates of adverse events.[53] Loading of oral sotalol for AF requires 3 days; however, the DASH-AF trial reports the potential of achieving a steady state with maximum QTc prolongation within 6 h instead of the traditional oral dose duration.[54]

SVT

Additionally, increasing evidence is being recorded for arrhythmia management reports intranasal MSP-2017 (etripamil), a calcium channel antagonist, as a novel, non-invasive treatment for paroxysmal supraventricular arrhythmia. A phase I study indicates its safety at doses up to 140 mg, with PR interval prolongation observed on ECG, indicating potential efficacy. In subsequent phase II and III trials, its efficacy in rapidly terminating induced SVT with a high conversion rate to sinus rhythm was reported.[50–52] Adverse events were mostly related to local irritation or the intranasal route of administration, including nasal discomfort, nasal congestion, and rhinorrhea.[50]

Procedural Therapies

While emerging pharmacological therapies have signaled a paradigm shift toward precision-targeted, long-acting, and patient-centric solutions in cardiovascular medicine, progress has also been made to improve clinical procedures, especially in patients with refractory arrhythmias or medication intolerance. In line with this, increasing emphasis has been placed on precision medicine, minimally invasive procedures, and integration of novel technologies to improve long-term cardiovascular outcomes. Clinical procedures include interventions like renal denervation, baroreflex activation therapy, use of pacemakers and defibrillator devices, surgical and ablative therapies for cardiac arrhythmias, left atrial appendage occlusion, and other novel technologies.[55–58]

AF

CASTLE-AF[55] and CAMTAF[56] trials have reported favorable outcomes regarding catheter ablation as a standard procedural therapy for the management of cardiac arrhythmias, particularly AF. In patients with paroxysmal AF, pulmonary vein isolation represents the standard approach used with newer technologies such as pulsed field ablation, offering tissue-selective ablation with reduced collateral damage. Randomized controlled trials have demonstrated favorable safety and efficacy profiles for pulsed field ablation catheters, with reduced recurrence rates and procedural complications.[59] However, in patients undergoing concomitant cardiac surgery or those with persistent arrhythmias unresponsive to catheter-based approaches, surgical options, such as the Maze procedure for AF, are introduced.[60] Left atrial appendage occlusion is a

procedure that is also gaining traction for stroke prevention in patients with AF who cannot receive long-term anticoagulation therapy.[61]

The EAST-AFNET 4 trial[62] showed that early rhythm control in patients with recently diagnosed atrial fibrillation, using antiarrhythmic drugs and/or catheter ablation, reduced major cardiovascular events compared with usual care focused on rate control. Over a median follow-up of 5.1 years, the primary composite outcome—cardiovascular death, stroke, or hospitalization for heart failure or acute coronary syndrome—occurred at 3.9 vs 5.0 per 100 person-years (HR: 0.79; 95% CI: 0.66–0.94; p = 0.005) in patients assigned to the early rhythm control group. This highlights that early rhythm control can provide a meaningful reduction in major cardiovascular events beyond symptom management.

VT

In ventricular arrhythmias, catheter ablation guided by electroanatomic mapping and imaging modalities such as cardiac magnetic resonance imaging is increasingly used for scar-related ventricular tachycardia. Clinical trials have introduced a novel high-voltage focal pulsed field ablation catheter for VT ablation, showing promising first-in-human results.[57] Additionally, cardioneuroablation and radiofrequency ablative therapies are being explored for functional bradycardia and reflex syncope, with multicenter registry data supporting their feasibility and safety.[58]

Ablation Technologies

Exploration of different ablation technologies across major randomized trials has shown favorable outcomes, with different energy sources offering varying outcomes in terms of procedural performance and tissue selectivity. In the CABANA trial,[63] catheter ablation, compared to drug therapy, yielded a non-statistically significant reduction in the incidence of the composite of death, disabling stroke, serious bleeding, or cardiac arrest in the intention-to-treat population (8.0% vs. 9.2%; HR: 0.86; 95% CI, 0.65–1.15; p = 0.30). However, given the limitations of the study methodology, further studies are required to substantiate findings.

Trials evaluating cryothermal technology, including EARLY AF[64] and STOP AF[65] trials, demonstrated rhythm control advantages. EARLY AF[64] compared cryoablation with drug therapy as initial treatment for AF. The study reported significantly lower recurrent atrial tachyarrhythmia with first-line cryoballoon ablation within 1 year (42.9% vs. 67.8%; HR: 0.48; 95% CI: 0.35–0.66; p<0.001). Similarly, STOP AF,[65] which had a similar objective as the EARLY AF, showed 12-month freedom from symptomatic AF in 74.6% of patients in the ablation group compared with 45.0% in the drug therapy group (p < 0.001). These trials show that cryoballoon ablation delivers robust rhythm control benefits early in the treatment course and maintains safety and efficacy in broader clinical use.

Comparative evidence from the FIRE AND ICE trial[66] showed cryoballoon and radiofrequency ablation to be similar in efficacy (1-year event rate estimate: 34.6% and 35.9%, respectively; HR: 0.96; 95% CI: 0.76–1.22; p < 0.001 for noninferiority), underscoring that both thermal modalities achieve equivalent clinical outcomes despite procedural differences. The ADVENT trial[67] evaluated an emerging nonthermal ablation technology (pulsed field ablation) in comparison with conventional thermal methods for treating AF. It demonstrated that pulsed field ablation achieved noninferior acute and 12-month efficacy in maintaining sinus rhythm.

Collectively, these findings highlight how evolving ablation technologies, from radiofrequency to cryothermal to nonthermal energy sources, offer rhythm control benefits while differing in safety profiles and procedural times.

Anticoagulation Therapy

Anticoagulation therapy is essential in managing cardiac arrhythmias to prevent thromboembolic complications, particularly in atrial fibrillation. It reduces the risk of stroke by inhibiting clot formation associated with abnormal atrial activity. The choice of anticoagulant—whether a direct oral anticoagulant or warfarin—depends on patient-specific factors, including comorbidities, renal function, and contraindications.

Bleeding Risk Stratification

Effective management of cardiac arrhythmias requires balancing stroke prevention with bleeding risk. The CHA_2DS_2-VASc score estimates thromboembolic risk by considering factors such as heart failure, hypertension, age, diabetes, prior stroke, vascular disease, and sex, guiding decisions on anticoagulation.[68] Concurrently, the HAS-BLED score evaluates bleeding risk by assessing hypertension, renal or liver dysfunction, prior stroke or bleeding, labile INRs, age, and concomitant drug or alcohol use.[69] Combining these scores allows clinicians to identify patients who will benefit most from anticoagulation while addressing modifiable bleeding risk factors. Regular reassessment ensures ongoing therapy remains both safe and effective.

Left Atrial Appendage Occlusion

The PROTECT AF[70] and PREVAIL[71] trials evaluated left atrial appendage occlusion with the Watchman device as an alternative to long-term warfarin therapy for stroke prevention in nonvalvular atrial fibrillation. The PROTECT AF[70] trial showed that Watchman implantation was noninferior to warfarin for the composite of stroke, systemic embolism, and cardiovascular death, with sustained reductions in hemorrhagic stroke and cardiovascular mortality over longer-term follow-up. The PREVAIL trial,[71] designed to confirm safety and efficacy with improved operator experience, reported lower periprocedural complication rates and again demonstrated noninferiority to warfarin on key endpoints, particularly late ischemic events. Together, these trials support left atrial appendage occlusion as a viable alternative to oral anticoagulation for selected patients.

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Advances in the Management of Cardiac Arrhythmias

Emerging research also highlights the role of artificial intelligence and genetic profiling in arrhythmia management. Advances in gene therapy and molecular approaches now allow for the identification of genetic predispositions to certain arrhythmias, enabling targeted screening and personalized care for patients, particularly in underrepresented populations. This is especially important in cases of arrhythmias during pregnancy or in children, which present unique challenges and considerations, different from those in adults. Similarly, older adult patients are particularly susceptible to arrhythmias due to age-related changes in the heart's electrical system and the presence of comorbidities; as such, they require special considerations. Consequently, gene editing technologies such as CRISPR are under investigation for such cases, as well as for the management of inherited arrhythmias and lipid disorders. Similarly, minimally invasive surgical platforms, robotic-assisted procedures, remote monitoring platforms, and 3D imaging-guided interventions are also enhancing treatment precision and reducing recovery times.[72] Wearable and implantable devices for remote cardiac monitoring, continuous rhythm surveillance, and blood pressure tracking are now being enabled.[73] These are increasingly being integrated into electrophysiology laboratories for real-time decision support, arrhythmia prediction, and procedural safety enhancement to aid patient-targeted management and optimal outcomes. Moreover, integrating genetic data with electronic health records can now facilitate proactive risk stratification, thus proffering early detection and consequent adherence to therapy.

Discussion

Findings from this review highlight the current and emerging therapies for the management of cardiac arrhythmias, including lifestyle modifications, pharmacological, and procedural therapies. These modalities are critical for addressing the rising arrhythmic burden and improving quality of life, reducing the risk of complications, and enhancing survival rates. While lifestyle management is employed for ensuring the effective management of cardiac arrhythmias, pharmacological and procedural management remains critical, particularly in emergent and recurrent cases. As reported in this study, lifestyle changes for AF prevention result in fewer complications than other therapeutic interventions, and should be considered as first-line therapy.

Despite emerging evidence on lifestyle management for arrhythmia, several inconsistencies remain. Dietary interventions, such as the inclusion of coffee, tea, nuts, antioxidant vitamins, and chocolate, have been suggested to possess antiarrhythmic properties.[21] However, the role of these foods remains controversial, with reports indicating both potential benefits and risks. Evidence suggests that caffeine's impact may be dose-dependent;[74] however, most studies reporting the benefits or risks of caffeine in cardiac arrhythmia are observational, underscoring the need for controlled trials to determine optimal intake in arrhythmic patients.

Similarly, lifestyle modifications such as weight loss and physical activity have shown promise. Practices like yoga, acupuncture, and cardiorespiratory exercise have been associated with reduced symptomatic AF episodes and improved quality of life.[75] Nevertheless, excessive exercise or rapid weight loss, particularly from restrictive diets or malabsorptive conditions, may lead to electrolyte imbalances, which can disrupt myocardial conduction and repolarization. Thus, gradual, nutritionally balanced approaches for weight loss and physical activity are essential and should be further explored. Similarly, psychological interventions, including biofeedback, cognitive behavioral therapy, relaxation training, meditation, hypnosis, and psychotherapy, have also been reported for rhythm stabilization and stress reduction. However, standardized protocols are lacking, and further research is needed to validate their efficacy and facilitate integration into routine clinical care. Overall, large-scale, longitudinal studies are warranted to clarify the role of cardiorespiratory fitness, specific dietary patterns, and psychological therapies in comprehensive arrhythmia management.

To further achieve rate and rhythm control, current pharmacological management strategies are classified based on electrophysiological effects of the medications, sites of action, or type of arrhythmic manifestation. Given the different forms of the disease, varying interventions may be administered. The study indicates the importance of direct treatment using the Class I-IV arrhythmic medications or a combination of drugs, as well as adjunctive treatment stemming from addressing associated morbidities such as hypertension and diabetes. This is in correspondence with previous findings indicating the presence of comorbidities as significant risk factors for cardiac arrhythmia. In 2021, cardiac arrhythmia was reported as one of the most common cardiovascular complications caused by COVID-19.[76] Similarly, Type II diabetes and hypertension independently represent a 34% and 26% increase in the risk of cardiac arrhythmias, respectively.[77] This review, therefore, highlights the importance of managing comorbidities. However, caution should be exercised with the concomitant use of non-dihydropyridine calcium channel blockers and β-blockers in the management of hypertension for patients with cardiac arrhythmia, as this can increase the risk of bradycardia and atrioventricular block.[4] Instead, drugs targeting the renin–angiotensin–aldosterone system may be used. Furthermore, the use of metformin monotherapy has been studied in patients with comorbid diabetes.[47] Metformin was reported to be more beneficial in the reduction of arrhythmic incidence compared to other diabetic medications. However, there is a need for confirmatory trials, as evidence on the relative impact of metformin in reducing arrhythmic incidence is scarce.

Recent advances in the pharmacological management of cardiac arrhythmias have introduced novel delivery methods aimed at improving therapeutic efficacy and patient convenience. Intranasal and intravenous therapies are gaining traction for their ability

to provide rapid onset of action and reduce hospitalizations. For instance, inhaled flecainide[38,39] and intranasal etripamil have demonstrated promising results in achieving swift and high plasma concentrations via pulmonary absorption, potentially enhancing acute arrhythmia control.[51–53] These approaches offer a non-invasive alternative to traditional oral or intravenous routes, particularly in paroxysmal SVT and AF. However, further research is needed to optimize aerosol delivery systems, improve pulmonary deposition, and ensure consistent pharmacodynamic profiles across diverse patient populations.

In parallel, procedural therapies have ushered in a paradigm shift toward precision-targeted, long-acting, and patient-centric solutions, especially for individuals with refractory arrhythmias or intolerance to medications. Techniques such as renal denervation and baroreflex activation therapy are being explored for their autonomic modulation effects,[56–60] while implantable devices, including pacemakers, implantable cardioverter-defibrillators, and cardiac resynchronization therapy, remain foundational in managing bradyarrhythmias and life-threatening ventricular arrhythmias.[72,73] Catheter ablation continues to evolve with improved mapping technologies and energy delivery systems, offering curative potential in many supraventricular and ventricular arrhythmias.

Emerging technologies further emphasize the integration of artificial intelligence and gene-based therapies in arrhythmia care. As highlighted by Asatyan et al.,[78] advanced computational models and machine learning algorithms are proving valuable in the diagnosis and management of inherited arrhythmias and those with concealed or transient phenotypes. These tools can refine genotype-phenotype correlations, streamline diagnostic workflows, and reduce unnecessary testing, thereby lowering healthcare costs and enabling more targeted genetic screening.[79] Implantable biosensors and radiofrequency-based interventions also contribute to this personalized, data-driven approach, facilitating continuous monitoring and adaptive therapy. Further research is warranted to validate these innovations across broader populations, assess long-term outcomes, and ensure equitable access to emerging therapies.

Future Directions

Despite substantial advancements in clinical cardiology, the management of cardiac arrhythmias still faces significant limitations. First, disease refractoriness complicates treatment, and the diverse spectrum of arrhythmias, ranging from benign premature beats to life-threatening ventricular tachycardias, adds complexity to management and drug selection. Pharmacologic management may pose risks to the patients, including proarrhythmic potential and organ-specific toxicities. For instance, many antiarrhythmic agents can paradoxically provoke arrhythmias or cause systemic damage such as pulmonary fibrosis. Additionally, some drugs suitable for AF may be harmful in structural heart disease, such as Class IC agents, which are contraindicated following myocardial infarction.[39] This therefore suggests the need for structured guidelines following management of cardiac arrhythmias. Second, in cases involving autonomic dysfunction-driven arrhythmias, lifestyle interventions alone are insufficient. Therefore, such recommendations should be approached with caution and tailored to the individual. Finally, although procedural advances such as pulsed field ablation and robotic navigation have improved arrhythmia management, these interventions remain constrained by high costs, limited accessibility, and risks of serious complications, including vascular injury, stroke, tamponade, and device-related infections.[57–59] Novel treatment modalities are therefore needed to bridge these gaps and ensure more equitable and effective patient care.

Limitations

This study had some limitations. The study employed a narrative methodology, enabling a broad overview of recent developments in the clinical management of cardiac arrhythmias. However, due to its emphasis on descriptive synthesis rather than quantitative comparison, a meta-analysis was not performed. The included studies exhibited considerable heterogeneity in design and methodology, which posed challenges for direct comparison and limited the ability to draw definitive conclusions across the evidence base. The number of included studies was relatively small, given the broad scope of the topic, which may limit the generalizability of the findings and the comprehensiveness of the conclusions. Additionally, only studies published in English were considered, introducing the potential for language bias and the exclusion of relevant data from non-English publications. Although efforts were made to emphasize the relevance and contributions of each study, a formal assessment of risk of bias was not conducted, thereby constraining the depth of critical evaluation. These limitations should be considered when interpreting the results and highlight the need for further, more comprehensive research in this area.

Conclusion

The findings presented in this review have strong implications for informing clinical decision-making and support the development of targeted interventions to mitigate the global burden of arrhythmias through rate control, rhythm control, and appropriate lifestyle modifications. While nutritionally balanced approaches for weight loss and physical activity are essential, psychological interventions, including cognitive behavioral therapy, are also recommended as evidence-based lifestyle approaches and warrant further research to validate their efficacy and facilitate integration into routine clinical care.

Pharmacological care for cardiac arrhythmias requires a multifaceted approach, ensuring rate management, rhythm control, and addressing comorbidities. While newer therapies, including inhaled flecainide and intranasal etripamil, have been introduced, metformin for diabetes and anti-hypertensive agents

addressing the renin-angiotensin-aldosterone system have also shown efficacy in patients with arrhythmia, and further research is necessary to deepen the emergent findings.

Renal denervation, catheter ablation, baroreflex activation therapy, and implantable devices are reported procedural modalities for arrhythmia management, and emerging technologies further emphasize the integration of artificial intelligence and gene-based therapies in arrhythmia care. These modalities contribute to this personalized, data-driven care approach, facilitating continuous monitoring and adaptive therapy. Overall, the convergence of pharmacological, procedural, and digital strategies marks a transformative era in arrhythmia management for enhancing precision and patient-specific therapy.

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