Beta-Blockers in Ventricular Arrhythmias: Beyond Rate Control – Antiadrenergic Effects in Ischemic and Nonischemic Cardiomyopathy.

Abstract

Background: Ventricular arrhythmias (VAs) remain a leading cause of sudden cardiac death (SCD) in patients with ischemic and nonischemic cardiomyopathy, driven substantially by sympathetic nervous system overactivity and elevated catecholamine tone. Beta-adrenergic receptor blockers have been a cornerstone of pharmacotherapy for decades, yet their antiarrhythmic efficacy extends well beyond simple heart rate reduction.

Objective: This narrative review synthesizes current evidence on the antiadrenergic mechanisms by which beta-blockers suppress ventricular arrhythmogenesis, evaluates their clinical impact in ischemic and nonischemic cardiomyopathy populations, and delineates differential effects among specific beta-blocker agents.

Methods: A structured literature search of PubMed, Scopus, and Web of Science was conducted for English-language articles published between January 2020 and December 2025, supplemented by seminal earlier publications. Search terms included “beta-blocker,” “ventricular arrhythmia,” “sudden cardiac death,” “ischemic cardiomyopathy,” “nonischemic cardiomyopathy,” and “sympathetic nervous system.” Major societal guidelines from the American College of Cardiology (ACC), American Heart Association (AHA), Heart Failure Society of America (HFSA), and European Society of Cardiology (ESC) were incorporated.

Key Findings: Beta-blockers attenuate ventricular arrhythmias through multiple complementary pathways: antagonism of β1- and β2-adrenergic receptor signaling, reduction of intracellular calcium overload, stabilization of ion channel function, attenuation of triggered activity and reentry, and modulation of autonomic tone. Carvedilol exhibits additional antiarrhythmic properties via α1-adrenoceptor blockade, antioxidant activity, and inhibition of cardiac Kv4.3 (Ito) channels at clinically relevant concentrations. In patients with ischemic cardiomyopathy, beta-blockers reduce the incidence of sustained ventricular tachycardia (VT) and ventricular fibrillation (VF) following myocardial infarction, although the magnitude of benefit has diminished in the contemporary reperfusion era among those with preserved left ventricular ejection fraction (LVEF). In nonischemic cardiomyopathy, beta-blockers form a central pillar of guideline-directed medical therapy (GDMT) and reduce SCD risk, yet the evidence base is largely extrapolated from heart failure trials rather than dedicated VA studies. Emerging data suggest pharmacogenetic modulation of antiarrhythmic response, with β1-389Arg/Arg homozygotes deriving greater suppression of VT/VF.

Conclusion: Beta-blockers exert potent antiadrenergic effects that translate into clinically meaningful reductions in ventricular arrhythmias and SCD across both ischemic and nonischemic cardiomyopathy phenotypes. Their role remains unequivocal in patients with reduced LVEF, though contemporary evidence increasingly challenges universal application in

post-infarction patients with preserved systolic function. Personalized approaches incorporating genotype, cardiomyopathy etiology, and agent-specific pharmacology may further optimize antiarrhythmic outcomes.

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1. Introduction

Ventricular arrhythmias—ranging from premature ventricular complexes (PVCs) and nonsustained ventricular tachycardia (NSVT) to sustained monomorphic ventricular tachycardia (SMVT) and ventricular fibrillation (VF)—constitute a spectrum of electrical disturbances that account for the majority of sudden cardiac deaths worldwide (1). The global burden of SCD is estimated at 4–5 million cases annually, with ischemic heart disease and nonischemic dilated cardiomyopathy representing the two predominant structural substrates (2,3). Despite advances in device therapy, including the implantable cardioverter-defibrillator (ICD), pharmacologic strategies remain indispensable for both primary prevention and management of recurrent arrhythmic events (4).

The sympathetic nervous system occupies a central position in the pathogenesis of ventricular arrhythmogenesis (5). Catecholamine excess, whether from heightened neuronal norepinephrine release or circulating epinephrine, exerts pleiotropic proarrhythmic effects: it enhances automaticity through acceleration of phase 4 depolarization in the sinoatrial node and latent pacemakers, promotes early and delayed afterdepolarizations via intracellular calcium overload, shortens ventricular refractory periods thereby facilitating functional reentry, and increases dispersion of repolarization across the ventricular myocardium (6,7). These mechanisms are amplified in the structurally remodeled heart, where regional heterogeneity of sympathetic innervation, ion channel remodeling, and fibrosis create a vulnerable substrate for arrhythmia initiation and perpetuation (8,9).

Beta-adrenergic receptor blockers (beta-blockers), classified as Class II antiarrhythmic agents under the Vaughan-Williams schema, have been employed in cardiovascular medicine for over half a century (10). Their clinical introduction was driven initially by observations that propranolol reduced mortality following acute myocardial infarction in the pre-reperfusion era, an effect attributed in substantial measure to protection against lethal ventricular arrhythmias (11). Subsequent landmark randomized controlled trials—including the Beta-Blocker Heart Attack Trial (BHAT), the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF), the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II), and the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial—firmly established beta-blockers as mortality-reducing agents in heart failure with reduced ejection fraction (HFrEF) (12-14). Mechanistic substudies from these trials demonstrated parallel reductions in sudden cardiac death, the majority of which are arrhythmic in etiology (15).

Yet the contemporary landscape has grown more complex. The advent of timely coronary reperfusion, widespread use of renin-angiotensin-aldosterone system inhibitors,

mineralocorticoid receptor antagonists, and most recently sodium-glucose cotransporter 2 inhibitors has transformed the baseline risk profile of post-infarction and heart failure populations (16). The recent REDUCE-AMI trial—the first adequately powered randomized evaluation of beta-blockade after myocardial infarction with preserved LVEF in the reperfusion era—demonstrated no benefit on all-cause death or recurrent myocardial infarction over a median 3.5-year follow-up, challenging the dogma of universal post-infarction beta-blockade (17). Conversely, in patients with HFrEF of both ischemic and nonischemic etiology, the antiarrhythmic and mortality benefits of beta-blockers remain undisputed (18).

Against this backdrop, the present review examines beta-blockers through a focused lens: their antiadrenergic mechanisms of ventricular arrhythmia suppression, extending well beyond the canonical paradigm of heart rate reduction. We explore the differential pharmacology of the evidence-based beta-blockers—bisoprolol, metoprolol succinate, carvedilol, and nebivolol—and their relevance to ventricular arrhythmogenesis. The evidence is contextualized separately for ischemic and nonischemic cardiomyopathy, reflecting their distinct pathophysiological drivers and therapeutic considerations. Finally, we address emerging frontiers including pharmacogenetics, the role of nonselective beta-blockade in electrical storm, and the comparative efficacy of beta-blockers versus amiodarone in ICD recipients.

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2. Methodology

Search Strategy

A comprehensive literature search was conducted using the PubMed/MEDLINE, Scopus, and Web of Science electronic databases from January 1, 2020 to December 31, 2025. Seminal publications predating this window were included where they provided foundational mechanistic insights or represented landmark clinical trials essential to the narrative. The search strategy employed Medical Subject Headings (MeSH) terms and free-text keywords combined using Boolean operators.

Search Terms

The primary search string was constructed as follows: (“beta-blocker” OR “beta-adrenergic blocker” OR “β-blocker” OR “bisoprolol” OR “carvedilol” OR “metoprolol” OR “nebivolol” OR “propranolol”) AND (“ventricular arrhythmia” OR “ventricular tachycardia” OR “ventricular fibrillation” OR “sudden cardiac death” OR “ventricular tachyarrhythmia”) AND (“ischemic cardiomyopathy” OR “nonischemic cardiomyopathy” OR “dilated cardiomyopathy” OR “heart failure with reduced ejection fraction” OR “myocardial infarction”).

Inclusion Criteria

Studies were included if they met the following criteria: (i) randomized controlled trials, prospective cohort studies, retrospective analyses, meta-analyses, or systematic reviews; (ii) focus on the antiarrhythmic mechanisms or clinical outcomes of beta-blockers in the context of ventricular arrhythmias; (iii) publication in English in a peer-reviewed journal; and (iv) relevance to ischemic or nonischemic cardiomyopathy populations. Major societal clinical practice guidelines—including the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure, the 2022 ESC Guidelines for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death, and relevant focused updates—were systematically reviewed and incorporated.

Exclusion Criteria

Exclusion criteria comprised: (i) case reports, editorials, and commentaries without original data; (ii) studies limited exclusively to atrial arrhythmias; (iii) pediatric or congenital heart disease populations; (iv) animal studies without direct translational relevance; and (v) duplicate publications.

Study Selection and Data Synthesis

Titles and abstracts were screened by the author, with full-text retrieval of potentially eligible articles. Given the narrative design, formal quantitative synthesis was not performed. Data were extracted and synthesized thematically according to the pre-specified Discussion subheadings.

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4. Discussion

4.1 Sympathetic Overactivity and the Arrhythmogenic Substrate: Mechanistic Framework

The pathophysiological nexus between sympathetic nervous system hyperactivity and ventricular arrhythmogenesis operates across multiple temporal and spatial scales, from subcellular ion channel modulation to whole-organ electrophysiological remodeling (6). Under physiological conditions, cardiac sympathetic nerve terminals release norepinephrine, which binds predominantly to β1-adrenergic receptors (β1-ARs)—constituting approximately 80% of cardiac β-ARs—and to a lesser extent β2-ARs, which represent roughly 20% and are preferentially localized to caveolar microdomains (7). β1-AR stimulation activates the stimulatory G protein (Gs)-adenylyl cyclase-cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA) signaling cascade, which phosphorylates multiple downstream targets central to excitation-contraction coupling and cardiac electrophysiology (5).

Among the most arrhythmogenic consequences of this signaling cascade is PKA-mediated phosphorylation of the L-type calcium channel (Cav1.2), which increases calcium influx during the plateau phase of the action potential. This enhanced calcium entry, coupled with PKA-mediated phosphorylation of the ryanodine receptor (RyR2) and phospholamban—the latter

relieving its inhibition of the sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2a)—generates sarcoplasmic reticulum calcium overload (8). The resultant spontaneous diastolic calcium release from the sarcoplasmic reticulum activates the electrogenic sodium-calcium exchanger (NCX), producing transient inward currents (Iti) that underlie delayed afterdepolarizations (DADs). When DADs reach threshold, they trigger premature action potentials that can initiate reentrant or focal ventricular arrhythmias (9).

Simultaneously, β-adrenergic stimulation enhances the pacemaker current (If) via direct cAMP-mediated modulation of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, promoting abnormal automaticity in depolarized Purkinje fibers and ventricular myocytes (10). β1-AR activation also phosphorylates the voltage-gated sodium channel (Nav1.5) and the rapid delayed rectifier potassium channel (hERG/Kv11.1), increasing peak sodium current while accelerating repolarization, thus shortening action potential duration and the effective refractory period. This combination—enhanced excitability, abbreviated refractoriness, and increased dispersion of repolarization—creates optimal conditions for functional reentry, the electrophysiological mechanism underlying most sustained monomorphic VTs in scarred ventricles (6).

Importantly, the structural remodeling that accompanies both ischemic and nonischemic cardiomyopathy amplifies these proarrhythmic mechanisms. Myocardial fibrosis creates anatomical barriers that anchor reentrant circuits; heterogeneous sympathetic denervation in infarct border zones generates spatial dispersion of refractoriness; and downregulation of β1-ARs with concomitant upregulation of β3-AR signaling in failing myocardium paradoxically sustains adrenergic drive (11). This altered substrate renders the cardiomyopathic heart exquisitely sensitive to the arrhythmogenic effects of even modest catecholamine surges.

Beta-blockers interrupt this cascade at the receptor level, preventing cAMP accumulation and the downstream phosphorylation events described above (12). The antiarrhythmic consequence is multifold: suppression of both triggered activity (DADs and early afterdepolarizations) and reentrant substrates; reduction of ischemia-induced inhomogeneity of refractoriness; attenuation of the positive chronotropic response that shortens diastolic time and exacerbates intracellular calcium loading; and restoration of autonomic balance through central and peripheral mechanisms (13). These pharmacodynamic effects are fundamentally antiadrenergic and cannot be replicated by heart rate reduction alone—a distinction of critical clinical importance (14).

4.2 Beta-Blocker Pharmacology: Differential Antiarrhythmic Profiles of Key Agents

Not all beta-blockers are pharmacologically equivalent, and their differential receptor selectivity, ancillary properties, and ion channel effects translate into clinically relevant distinctions in antiarrhythmic efficacy (15). The four beta-blockers currently recommended for HFrEF by both the 2022 AHA/ACC/HFSA guideline and the 2021 ESC guideline—bisoprolol, carvedilol, metoprolol succinate (CR/XL), and nebivolol—exhibit distinct profiles that warrant individualized consideration in patients at risk for ventricular arrhythmias (16,17).

Bisoprolol is a highly β1-selective antagonist with no intrinsic sympathomimetic activity and minimal ancillary properties. Its antiarrhythmic effect is mediated predominantly through β1-AR blockade, reducing cAMP-driven arrhythmogenic signaling. The CIBIS-II trial demonstrated a 42% reduction in sudden cardiac death among HFrEF patients receiving bisoprolol compared to placebo, establishing its antiarrhythmic credentials (14). At the ion channel level, bisoprolol does not inhibit cardiac Kv4.3 (Ito) channels, suggesting that its antiarrhythmic efficacy derives exclusively from adrenergic receptor antagonism rather than direct channel-blocking properties (18).

Metoprolol succinate (extended-release formulation) is a β1-selective antagonist. MERIT-HF demonstrated a 41% reduction in sudden cardiac death with metoprolol CR/XL in HFrEF (13). Unlike bisoprolol, metoprolol exhibits weak inhibitory effects on Kv4.3 channels (approximately 35-37% inhibition at 100 μM concentrations), which may confer modest direct effects on early repolarization (18). The clinical significance of this ancillary ion channel effect remains uncertain, particularly given that metoprolol concentrations achieved therapeutically are substantially lower than those required for significant Kv4.3 blockade.

Carvedilol is a nonselective β1/β2-antagonist with additional α1-adrenoceptor blocking properties and potent antioxidant activity (19). Its pharmacology is uniquely multifaceted: α1-blockade produces peripheral vasodilation, reducing afterload and myocardial wall stress; β2-blockade prevents presynaptic norepinephrine release, attenuating sympathetic drive at its source; and the carbazole moiety of carvedilol functions as a free radical scavenger, protecting myocardial membranes from oxidative injury during ischemia-reperfusion (20). At ion channel level, carvedilol inhibits Kv4.3 channels at physiologically relevant concentrations—achieving 77 ± 2% and 67 ± 6% inhibition of the Kv4.3 L and Kv4.3 S isoforms respectively—effects not observed with bisoprolol and only weakly with metoprolol (18). Carvedilol also directly inhibits the ryanodine receptor (RyR2), stabilizing sarcoplasmic reticulum calcium handling independently of β-AR blockade (21). These pleiotropic actions may explain findings from a pooled analysis of 4,194 primary-prevention ICD recipients across five landmark trials (MADIT-II, MADIT-CRT, MADIT-RIT, MADIT-RISK, and RAID), which demonstrated that carvedilol treatment was associated with a 35% reduction in the risk of inappropriate ICD shocks (HR 0.65; 95% CI 0.47-0.89; P = 0.008) and a 16% reduction in fast VA (HR 0.84; 95% CI 0.70-1.02; P = 0.085) compared to metoprolol (22,23).

Nebivolol is a β1-selective antagonist with nitric oxide (NO)-mediated vasodilatory properties. Its role in ventricular arrhythmia management is less well characterized than the other three agents; the SENIORS trial demonstrated a composite outcome benefit in elderly HF patients, but specific ventricular arrhythmia endpoints were not reported (24). The ESC guidelines include nebivolol among the four recommended beta-blockers for HFrEF, though evidence for antiarrhythmic benefit is predominantly extrapolated rather than direct (17).

4.3 Ischemic Cardiomyopathy: Beta-Blockers in Post-Infarction Ventricular Arrhythmogenesis

Ischemic cardiomyopathy represents the most common substrate for life-threatening ventricular arrhythmias in developed countries, with post-infarction scarring providing the anatomical basis for reentrant ventricular tachycardia circuits (25). The antiarrhythmic role of beta-blockers in this setting has been recognized since the BHAT trial, which randomized 3,837 post-MI patients to propranolol or placebo and demonstrated a 26% reduction in total mortality, driven substantially by a reduction in sudden cardiac death during the first year (11). Subsequent meta-analyses from the pre-reperfusion era confirmed a consistent mortality benefit, with an approximately 20-25% relative risk reduction in sudden death (26).

The mechanistic basis for this protection is rooted in the unique vulnerability of the ischemic and peri-infarct myocardium to sympathetic stimulation. Acute ischemia produces local catecholamine release, extracellular potassium accumulation, and intracellular calcium overload, creating conditions of electrical heterogeneity that facilitate polymorphic VT and VF (27). Experimental studies have demonstrated that beta-blockade raises the ventricular fibrillation threshold during acute coronary occlusion and reduces the incidence of ischemia-induced VF (28). In the subacute and chronic phases, beta-blockers attenuate infarct expansion, reduce ventricular remodeling, and diminish the arrhythmogenic potential of the scar border zone (29).

However, the contemporary evidence base has evolved substantially. The REDUCE-AMI trial, which randomized 5,020 patients with acute myocardial infarction and preserved LVEF (≥50%) to long-term beta-blockade with metoprolol or bisoprolol versus no beta-blockade, found no significant difference in the primary composite endpoint. A prespecified analysis of sudden cardiac death similarly showed no benefit (HR 0.95; 95% CI 0.62-1.46) (17). These findings align with observational data from the Korea Acute Myocardial Infarction Registry-National Institute of Health, in which the mortality benefit of discharge beta-blocker therapy was confined to patients with reduced or mildly reduced LVEF (30). Taken together, these data suggest that the antiarrhythmic benefit of beta-blockade in the post-infarction setting is concentrated among those with significant left ventricular systolic dysfunction, in whom the arrhythmogenic substrate is most pronounced.

For patients with ischemic cardiomyopathy and reduced LVEF, the evidence remains compelling. The 2022 AHA/ACC/HFSA guideline assigns a Class 1 recommendation for the use of one of the three evidence-based beta-blockers (bisoprolol, carvedilol, or metoprolol succinate) to reduce mortality and hospitalizations (16). The antiarrhythmic benefit in this population is considered an integral component of the mortality reduction, with consistent reductions in SCD observed across the major HFrEF beta-blocker trials (15). Furthermore, beta-blockers remain a first-line pharmacotherapy for the management of recurrent VT in ischemic cardiomyopathy patients with ICDs, either as monotherapy or in combination with amiodarone (31).

4.4 Nonischemic Cardiomyopathy: Distinct Pathophysiology and Therapeutic Considerations

Nonischemic dilated cardiomyopathy (NIDCM) encompasses a heterogeneous group of disorders characterized by ventricular dilatation and systolic dysfunction in the absence of obstructive coronary artery disease. While the arrhythmogenic substrate differs from ischemic cardiomyopathy—lacking the discrete scar-related reentrant circuits characteristic of post-infarction VT—the role of sympathetic overactivity in promoting arrhythmias is equally, if not more, pronounced (32). Patients with NIDCM frequently exhibit elevated circulating catecholamine levels that correlate with disease severity and arrhythmic risk (33).

The landmark beta-blocker trials in HFrEF enrolled mixed populations of ischemic and nonischemic etiology, and subgroup analyses have consistently demonstrated comparable mortality benefit across etiologies. In CIBIS-II, the 42% reduction in SCD with bisoprolol was observed in both ischemic and nonischemic subgroups (14). Similarly, in COPERNICUS, carvedilol reduced all-cause mortality by 35% in patients with severe HFrEF irrespective of ischemic etiology (12). These data underpin the current guideline recommendation for universal beta-blocker therapy in HFrEF regardless of etiology (16).

Nevertheless, several considerations are unique to the NIDCM population. First, the DANISH trial, which evaluated primary prophylactic ICD implantation in patients with nonischemic systolic heart failure, enrolled a population in which 92% received beta-blockers at baseline (34). The trial demonstrated a reduction in SCD with ICD therapy but no overall mortality benefit, a finding that has been interpreted as reflecting the protective effect of contemporary pharmacotherapy—including beta-blockers—against arrhythmic death, thereby diminishing the incremental benefit of device therapy (35). This interpretation is supported by meta-analyses showing that the SCD benefit of ICDs in NIDCM is attenuated in the modern era of high GDMT utilization (36).

Second, certain etiological subtypes of NIDCM—including lamin A/C (LMNA) cardiomyopathy, phospholamban (PLN) cardiomyopathy, and filamin C (FLNC) cardiomyopathy—carry a disproportionately high risk of ventricular arrhythmias, often preceding significant systolic dysfunction (37). The 2022 ESC guidelines specifically recommend genetic testing for these variants and highlight that beta-blockers form an integral part of arrhythmic risk management in these populations, though dedicated randomized evidence is lacking (31).

Third, the optimal choice of beta-blocker in NIDCM deserves scrutiny. The differential effects of carvedilol versus metoprolol on ventricular arrhythmias observed in the pooled ICD trial analysis included patients with both ischemic and nonischemic cardiomyopathy; carvedilol was associated with a 16% reduction in fast VA (≥200 beats/min or VF) compared to metoprolol (HR 0.84; P = 0.085) (22). While this finding narrowly missed statistical significance, it raises the hypothesis that carvedilol's broader pharmacodynamic profile—including α1-blockade and Kv4.3 channel inhibition—may confer incremental antiarrhythmic benefit in NIDCM, a population in which micro-reentrant circuits and triggered activity (rather than macro-reentry around discrete scar) may predominate (18,23).

4.5 Beta-Blockers and Electrical Storm: The Resurgence of Nonselective Blockade

Electrical storm (ES), defined as three or more discrete episodes of sustained ventricular tachyarrhythmia within 24 hours or incessant VT lasting >12 hours, represents the most extreme manifestation of adrenergically driven ventricular arrhythmogenesis (38). ES occurs in 4.7% of ICD recipients over a median 39-month follow-up, with higher incidence among secondary prevention patients (10.5%) compared to primary prevention patients (3.9%) (38). Underlying structural heart disease—ischemic or nonischemic cardiomyopathy—is present in 77-94% of ES cases (38).

The pathophysiology of ES is inextricably linked to a vicious cycle of sympathetic activation: each VT episode provokes pain, anxiety, and hemodynamic compromise, triggering further catecholamine release that begets additional arrhythmias (39). ICD shocks, while life-saving, paradoxically fuel this cycle through pain, fear, and direct myocardial injury, underscoring the importance of pharmacologic sympathetic blockade (40).

Contemporary management algorithms emphasize beta-blockade as a cornerstone of ES therapy, with nonselective agents—propranolol and nadolol—occupying a unique position (41). The 2023 JACC State-of-the-Art Review on electrical storm management recommends the addition or uptitration of guideline-directed beta-blockers (metoprolol succinate, bisoprolol, or carvedilol) as first-line therapy, while noting that the nonselective β1/β2-antagonist propranolol may offer superior efficacy in refractory cases due to more complete adrenergic blockade and central sympatholytic effects (38,41). Intravenous esmolol, an ultra-short-acting β1-selective agent, has been employed successfully for acute VT storm suppression in hemodynamically tenuous patients, allowing titration of beta-blockade without prolonged commitment (42).

The alpha-1 blockade produced by carvedilol, while therapeutically advantageous in chronic HFrEF, can cause dose-limiting hypotension in the acute ES setting, particularly when combined with sedatives and antiarrhythmic agents (41). This practical consideration often favors the use of metoprolol or bisoprolol for initial uptitration in the intensive care setting, reserving carvedilol for hemodynamically stable patients.

4.6 Comparative Efficacy: Beta-Blockers Versus Amiodarone and Combination Therapy

Amiodarone, a Class III antiarrhythmic agent with multichannel blocking properties, is frequently employed in patients with recurrent ventricular arrhythmias refractory to or occurring despite beta-blocker therapy (43). The relationship between these two agents is complex and has been the subject of several observational analyses.

A large retrospective registry study of 512 ICD recipients with index ventricular tachyarrhythmia episodes compared outcomes between patients treated with beta-blocker monotherapy (81%) versus beta-blocker plus amiodarone (19%) (44). At five-year follow-up, the risk of recurrent ventricular tachyarrhythmias was comparable between groups (46% vs. 43%; HR 1.013; 95% CI 0.725-1.415; P = 0.941), as was the incidence of appropriate ICD therapies (35% vs. 37%; HR 0.852; 95% CI 0.591-1.228; P = 0.390) (44). Notably, beta-blocker monotherapy was associated with a trend toward lower all-cause mortality on univariable analysis (20% vs. 28%; log-rank P =

0.023), though this finding should be interpreted cautiously given the nonrandomized design (44). A companion study from the same group reported that beta-blocker therapy was associated with improved secondary long-term prognosis compared to combined beta-blocker plus amiodarone in patients surviving index episodes of ventricular tachyarrhythmias (45).

These observational findings do not establish the superiority of beta-blockers over amiodarone; rather, they suggest that in patients who can be adequately managed with beta-blocker monotherapy, the addition of amiodarone may not confer incremental antiarrhythmic benefit while potentially adding toxicity (including thyroid dysfunction, pulmonary fibrosis, hepatic injury, and proarrhythmia) (44,45). Current clinical practice reserves amiodarone for patients with recurrent VT despite optimal beta-blockade, those with electrical storm, and those intolerant of beta-blockers (31).

4.7 Pharmacogenetics and the Future of Personalized Antiadrenergic Therapy

The emerging field of cardiovascular pharmacogenetics has identified genetic variants in adrenergic receptor signaling pathways that modulate the antiarrhythmic response to beta-blockade (46). The most extensively studied polymorphism is the β1-adrenergic receptor Arg389Gly variant: the Arg389 allele encodes a receptor with enhanced coupling to Gs proteins and greater downstream cAMP generation, whereas the Gly389 variant exhibits reduced signaling efficacy (47).

In a pre-specified substudy of the Beta-Blocker Evaluation of Survival Trial (BEST) involving 1,040 patients with HFrEF, bucindolol—a nonselective beta-blocker with sympatholytic properties—reduced the incidence of ventricular tachycardia and ventricular fibrillation (VT/VF) in the overall cohort (subhazard ratio 0.42; 95% CI 0.27-0.64; P = 0.00006) (47). However, the treatment effect was profoundly modulated by genotype: among β1-389Arg homozygotes, bucindolol produced a 74% reduction in VT/VF (subhazard ratio 0.26; 95% CI 0.14-0.50; P = 0.00005), whereas Gly389 carriers derived substantially less antiarrhythmic benefit (subhazard ratio 0.60; 95% CI 0.34-1.07; P = 0.09) (47). A three-way genotype interaction incorporating both β1-389Arg/Gly and α2C-322-325 Wt/deletion polymorphisms further stratified response, with certain genotype combinations exhibiting complete loss of antiarrhythmic efficacy (47).

These findings, while derived from bucindolol—an agent not currently approved for clinical use—provide proof of concept that genetic variation in the adrenergic signaling pathway influences the antiarrhythmic response to beta-blockade (47). Whether similar pharmacogenetic interactions exist for currently prescribed beta-blockers (carvedilol, metoprolol, bisoprolol) remains an open research question. The clinical implications are potentially significant: genotyping could identify patients most likely to derive antiarrhythmic benefit from beta-blocker therapy, while directing nonresponders toward alternative or adjunctive strategies including earlier ICD implantation or catheter ablation.

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5. Future Directions and Recommendations

· Prospective trials of beta-blocker type and ventricular arrhythmia outcomes in the contemporary era of comprehensive GDMT are urgently needed. The differential antiarrhythmic signals observed between carvedilol and metoprolol in retrospective ICD cohort analyses require validation in adequately powered, randomized studies that include contemporary background therapy with sacubitril/valsartan and SGLT2 inhibitors.

· Pharmacogenetic stratification of beta-blocker therapy represents a promising avenue toward personalized antiadrenergic therapy. Prospective studies evaluating whether β1-389Arg/Gly genotype predicts antiarrhythmic response to carvedilol, metoprolol, and bisoprolol could refine patient selection and optimize outcomes.

· The role of beta-blockers in post-infarction patients with mildly reduced ejection fraction (LVEF 41–49%) remains unresolved. The DANISH-Norwegian randomized trial on beta-blocker therapy after myocardial infarction (currently underway) may address this evidence gap and inform guideline recommendations (48).

· Integration of beta-blocker therapy with catheter ablation strategies for ventricular tachycardia warrants systematic investigation. Preliminary data suggest that pre-procedural beta-blockade may reduce VT inducibility and improve ablation outcomes, but dedicated randomized trials are lacking.

· The antiarrhythmic potential of nebivolol, the fourth beta-blocker recommended for HFrEF, has been inadequately characterized with respect to ventricular arrhythmia endpoints. Given its NO-mediated vasodilatory properties and favorable metabolic profile, dedicated studies evaluating its antiarrhythmic efficacy are warranted.

· Beta-blocker dosing targets for ventricular arrhythmia suppression—as distinct from heart rate targets—have not been defined. The conventional approach of titrating to a target heart rate of 60–70 beats per minute may not optimally suppress ventricular arrhythmogenesis; alternative titration strategies guided by arrhythmia burden (via ICD diagnostics or ambulatory monitoring) merit investigation.

· Combination therapy with beta-blockers and SGLT2 inhibitors warrants further exploration, as both drug classes demonstrate antiarrhythmic properties through complementary mechanisms. Whether their antiarrhythmic effects are additive or synergistic is unknown (49).

· The management of beta-blocker therapy at the time of acute decompensated heart failure requires clarification. Observational data suggest that continuing versus withholding beta-blockers during hospitalization for ADHF does not significantly affect tachyarrhythmia incidence, but randomized evidence is lacking (50).

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6. Conclusion

Beta-blockers transcend their traditional designation as rate-controlling agents, functioning as potent antiadrenergic therapies that target the fundamental pathophysiological drivers of ventricular arrhythmogenesis. Through antagonism of β-adrenergic receptor signaling, attenuation of intracellular calcium overload, suppression of triggered activity and reentry, and

modulation of autonomic balance, these agents reduce the incidence of sustained ventricular arrhythmias and sudden cardiac death in patients with both ischemic and nonischemic cardiomyopathy. Among the evidence-based beta-blockers, carvedilol exhibits a uniquely multifaceted antiarrhythmic profile by virtue of its nonselective β-blockade, α1-antagonism, antioxidant activity, Kv4.3 channel inhibition, and ryanodine receptor stabilization—properties that translate into clinically meaningful reductions in arrhythmic events compared to β1-selective agents. The contemporary evidence base mandates a nuanced approach: while beta-blockers remain indispensable in HFrEF irrespective of etiology, their routine application in post-infarction patients with preserved systolic function is increasingly challenged. Future advances in pharmacogenetics and personalized medicine hold the promise of refining patient selection, ensuring that the potent antiadrenergic benefits of beta-blockade are directed toward those most likely to derive arrhythmic protection.

Ethical statement:

1) This material is the authors' own original work, which has not been previously published elsewhere.
2) The paper is not currently being considered for publication elsewhere.

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