Jana Nexus: Journal of Health and Medicine

RESEARCH ARTICLE

Article DOI: 10.21474/JNHM01/130
DOI URL: http://dx.doi.org/10.21474/JNHM01/130

BETA-BLOCKERS IN VENTRICULAR ARRHYTHMIAS: BEYOND RATE CONTROL – ANTIADRENERGIC EFFECTS IN ISCHEMIC AND NONISCHEMIC CARDIOMYOPATHY

Priyanka Hayre[1], Fnu Ritik[2], Yousuf Sohail[3] , Hira Raza Satti[4], Umar Awan[5], Fnu Prejna[6], Akwue Anthony Tochukwu[7], Alabi Damilola[8], Siffat Ullah[9], Tanzeel Ur Rehman[10], Shah Syed Noman Ali [10], Munir Shumaiem[10] and Muhammad Absar Khan[10]

1. University of Health Sciences Antigua.
2. Dow University of Health Sciences, karachi, Sindh, PK.
3. Abbasi Shaheed hospital, Karachi, Pakistan.
4. Al Nafees Medical College , Isra University , Islamabad Pakistan.
5. Windsor University School of Medicine.
6. Department of Medicine, Ghulam Muhammad Mahar Medical College, Sukkur, Pakistan .
7. Louisiana State University in Shreveport , USA .
8. Independent Researcher, Rochester New York. USA.
9. Nanchang university china.
10. Southwest Medical University , China .

Manuscript Info

Manuscript History
Received: 08 March 2026
Final Accepted:10 April 2026
Published: May 2026

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, delineates differential effects among specific beta-blocker agents, and details their safety profiles and clinical limitations.

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 ACC, AHA, HFSA, and ESC were incorporated.

Key Findings: Beta-blockers attenuate ventricular arrhythmias through multiple complementary pathways: antagonism of \beta_1- and \beta_2-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 \alpha_1-adrenoceptor blockade, antioxidant activity, and inhibition of cardiac K_v4.3 (I_{to}) 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 \beta_1-389Arg/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, safety constraints, cardiomyopathy etiology, and agent-specific pharmacology may further optimize antiarrhythmic outcomes.

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 (24). 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 (1,15). 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 (18).The sympathetic nervous system occupies a central position in the pathogenesis of ventricular arrhythmogenesis (8). 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 (7,14). 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 (11,26).

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 (9). 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 (2). 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) (3,5,16,17). Mechanistic substudies from these trials demonstrated parallel reductions in sudden cardiac death, the majority of which are arrhythmic in etiology (19).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 (10). 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 (12). Conversely, in patients with HFrEF of both ischemic and nonischemic etiology, the antiarrhythmic and mortality benefits of beta-blockers remain undisputed (10).

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 safety and toxicity profiles, emerging frontiers including pharmacogenetics, the role of nonselective beta-blockade in electrical storm, and the comparative efficacy of beta-blockers versus amiodarone.

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:

1. Randomized controlled trials, prospective cohort studies, retrospective analyses, meta-analyses, or systematic reviews;
2. Focus on the antiarrhythmic mechanisms or clinical outcomes of beta-blockers in the context of ventricular arrhythmias;
3. Publication in English in a peer-reviewed journal; and
4. 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:

1. Case reports, editorials, and commentaries without original data;
2. Studies limited exclusively to atrial arrhythmias;
3. Pediatric or congenital heart disease populations;
4. Animal studies without direct translational relevance; and
5. 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.

Discussion:-

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 (7). Under physiological conditions, cardiac sympathetic nerve terminals release

norepinephrine, which binds predominantly to \beta_1-adrenergic receptors (\beta_1-ARs)—constituting approximately 80% of cardiac \beta-ARs—and to a lesser extent \beta_2-ARs, which represent roughly 20% and are preferentially localized to caveolar microdomains (25).\beta_1-AR stimulation activates the stimulatory G protein (G_s)-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 (8).Among the most arrhythmogenic consequences of this signaling cascade is PKA-mediated phosphorylation of the L-type calcium channel (C_{av}1.2), 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 (11). The resultant spontaneous diastolic calcium release from the sarcoplasmic reticulum activates the electrogenic sodium-calcium exchanger (NCX), producing transient inward currents (I_{ti}) that underlie delayed afterdepolarizations (DADs). When DADs reach threshold, they trigger premature action potentials that can initiate reentrant or focal ventricular arrhythmias (14).

Simultaneously, \beta-adrenergic stimulation enhances the pacemaker current (I_f) via direct cAMP-mediated modulation of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, promoting abnormal automaticity in depolarized Purkinje fibers and ventricular myocytes (9). \beta_1-AR activation also phosphorylates the voltage-gated sodium channel (N_{av}1.5) and the rapid delayed rectifier potassium channel (hERG/K_v11.1), 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 (7).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 \beta_1-ARs with concomitant upregulation of \beta_3-AR signaling in failing myocardium paradoxically sustains adrenergic drive (9). 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 downstream phosphorylation events (3). 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 (5).

These pharmacodynamic effects are fundamentally antiadrenergic and cannot be replicated by heart rate reduction alone—a distinction of critical clinical importance (5).

Beta-Blocker Pharmacology: Differential Antiarrhythmic Profiles of Key Agents

Not all beta-blockers are pharmacologically equivalent. Their differential receptor selectivity, ancillary properties, and ion channel effects translate into clinically relevant distinctions in antiarrhythmic efficacy (16). The four beta-blockers currently recommended for HFrEF by major guidelines—bisoprolol, carvedilol, metoprolol succinate (CR/XL), and nebivolol—exhibit distinct profiles that warrant individualized consideration in patients at risk for ventricular arrhythmias (10,30).

Bisoprolol is a highly \beta_1-selective antagonist with no intrinsic sympathomimetic activity and minimal ancillary properties. Its antiarrhythmic effect is mediated predominantly through \beta_1-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 (5). At the ion channel level, bisoprolol does not inhibit cardiac K_v4.3 (I_{to}) channels, suggesting that its antiarrhythmic efficacy derives exclusively from adrenergic receptor antagonism rather than direct channel-blocking properties (20).

Metoprolol succinate (extended-release formulation) is a \beta_1-selective antagonist. MERIT-HF demonstrated a 41% reduction in sudden cardiac death with metoprolol CR/XL in HFrEF (16). Unlike bisoprolol, metoprolol exhibits weak inhibitory effects on K_v4.3 channels (approximately 35-37% inhibition at 100 μM concentrations), which may confer modest direct effects on early repolarization (20). 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 K_v4.3 blockade.

Carvedilol is a nonselective \beta_1/\beta_2-antagonist with additional \alpha_1-adrenoceptor blocking properties and potent antioxidant activity (6). Its pharmacology is uniquely multifaceted: \alpha_1-blockade produces peripheral vasodilation, reducing afterload and myocardial wall stress; \beta_2-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 (27). At the ion channel level, carvedilol inhibits K_v4.3 channels at physiologically relevant concentrations—achieving 77 \pm 2\% and 67 \pm 6\% inhibition of the K_v4.3\text{ L} and K_v4.3\text{ S} isoforms respectively—effects not observed with bisoprolol and only weakly with metoprolol (20). Carvedilol also directly inhibits the ryanodine receptor (RyR2), stabilizing sarcoplasmic reticulum calcium handling independently of \beta-AR blockade (28).

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 (4,21).

Nebivolol is a \beta_1-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 (23). The ESC guidelines include nebivolol among the four recommended beta-blockers for HFrEF, though evidence for antiarrhythmic benefit is predominantly extrapolated rather than direct (30).

To facilitate a quick, comprehensive clinical understanding of these pharmacological variances, Table 1 delineates their precise receptor interactions, auxiliary characteristics, and direct electrophysiological impacts.

Table 1: Comparative Pharmacological and Antiarrhythmic Profiles of Key Beta-Blockers

Property	Bisoprolol	Metoprolol Succinate	Carvedilol	Nebivolol	Propranolol
Receptor Selectivity	Highly \beta_1-selective	\beta_1-selective	Nonselective (\beta_1/\beta_2)	Highly \beta_1-selective	Nonselective (\beta_1/\beta_2)
\alpha_1-Adrenergic Blockade	None	None	Yes (promotes vasodilation)	None	None
Intrinsic Sympathomimetic Activity	None	None	None	None	None
Direct Ion Channel Inhibition	None	Weak K_v4.3 (I_{to}) inhibition	Potent K_v4.3 (I_{to}) inhibition	None known	Sodium channel blockade (high doses)
Ancillary Mechanisms	Minimal	Minimal	RyR2 stabilizer, antioxidant	NO-mediated vasodilation	Central nervous system sympatholysis
Impact on Inappropriate Shocks	Not established	Baseline comparator	35% risk reduction vs. Metoprolol	Not established	N/A (acute use primary)

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 (22). 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 (2). Subsequent meta-analyses from the pre-reperfusion era confirmed a consistent mortality benefit, with an approximately 20-25%

relative risk reduction in sudden death (24).

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. Experimental studies have demonstrated that beta-blockade raises the ventricular fibrillation threshold during acute coronary occlusion and reduces the incidence of ischemia-induced VF (13). In the subacute and chronic phases, beta-blockers attenuate infarct expansion, reduce ventricular remodeling, and diminish the arrhythmogenic potential of the scar border zone (14).

However, the contemporary evidence base has evolved substantially. The REDUCE-AMI trial, which randomized 5,020 patients with acute myocardial infarction and preserved LVEF (\ge50\%) 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) (12). 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 (15).

Taken together, these data suggest that the antiarrhythmic benefit of beta-blocker therapy in the post-infarction setting is heavily 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 (10). 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 (19). 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 (30).

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 (26). Patients with NIDCM frequently exhibit elevated circulating catecholamine levels that correlate with disease severity and arrhythmic risk (1).

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 (5). Similarly, in COPERNICUS, carvedilol reduced all-cause mortality by 35% in patients with severe HFrEF irrespective of ischemic etiology (17). These data underpin the current guideline recommendation for universal beta-blocker therapy in HFrEF regardless of etiology (10).

Nevertheless, several considerations are unique to the NIDCM population.

- **The Paradigm Shift of the DANISH Trial:** 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 (7). 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 (18). 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 (11).
- **High-Risk Genotypic Subtypes:** 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 (29). 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 (30).

- **Agent Optimization:** 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 (\ge200\text{ beats/min} or VF) compared to metoprolol (4). While this finding narrowly missed statistical significance, it raises the hypothesis that carvedilol's broader pharmacodynamic profile—including \alpha_1-blockade and K_v4.3 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 (4,20).

To contextualize the landmark historical foundations underpinning sections 4.3 and 4.4, Table 2 maps out the definitive clinical trials evaluating beta-blockade and their respective impacts on sudden cardiac mortality.

Table 2: Summary of Landmark Clinical Trials Evaluating Beta-Blockade and Sudden Cardiac Death (SCD)

Trial	Population	Primary Agent	Key Clinical Outcomes & Impact on SCD
BHAT	Post-Myocardial Infarction	Propranolol	26% reduction in total mortality, heavily driven by early reductions in SCD.
MERIT-HF	HFrEF (Ischemic & Nonischemic)	Metoprolol Succinate	41% relative risk reduction in sudden cardiac death.
CIBIS-II	HFrEF (Ischemic & Nonischemic)	Bisoprolol	42% reduction in SCD across both etiology subgroups.
COPERNICUS	Severe HFrEF	Carvedilol	35% reduction in all-cause mortality regardless of ischemic background.
DANISH	Nonischemic Systolic Heart Failure	Mixed (92% baseline \beta-blocker)	No overall mortality benefit for primary ICDs, indicating strong protective background pharmacotherapy.
REDUCE-AMI	Post-MI with Preserved LVEF (\ge50\%)	Metoprolol or Bisoprolol	No significant impact on primary composite endpoints or sudden cardiac death.

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\text{ hours}, represents the most extreme manifestation of adrenergically driven ventricular arrhythmogenesis (15). ES occurs in 4.7% of ICD recipients over a median 39-month follow-up, with a significantly higher incidence among secondary prevention patients (10.5%) compared to primary prevention patients (3.9%). Underlying structural heart disease—ischemic or nonischemic cardiomyopathy—is present in 77–94% of ES cases (15).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 (24). ICD shocks, while life-saving, paradoxically fuel this cycle through pain, fear, and direct myocardial injury, underscoring the vital importance of immediate pharmacologic sympathetic blockade (19).Contemporary management algorithms emphasize beta-blockade as a cornerstone of ES therapy, with nonselective agents—propranolol and nadolol—occupying a unique position (31). 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 \beta_1/\beta_2-antagonist propranolol may offer superior efficacy in refractory cases due to more complete adrenergic blockade and central sympatholytic effects (15,31).

Intravenous esmolol, an ultra-short-acting \beta_1-selective agent, has been employed successfully for acute VT storm suppression in hemodynamically tenuous patients, allowing precise titration of beta-blockade without a prolonged pharmacokinetic commitment (24). 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 other antiarrhythmic agents (31). 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.

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 (31). 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%) (32). At a five-year follow-up, the risk of recurrent ventricular tachyarrhythmias was comparable between groups (46\%\text{ vs. }43\%; HR 1.013; 95% CI 0.725-1.415; P = 0.941), as was the incidence of appropriate ICD therapies (35\%\text{ vs. }37\%; HR 0.852; 95% CI 0.591-1.228; P = 0.390). Notably, beta-blocker monotherapy was associated with a trend toward lower all-cause mortality on univariable analysis (20\%\text{ vs. }28\%; log-rank P = 0.023), though this finding should be interpreted cautiously given the nonrandomized design. 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 (33).

These observational findings do not establish the mechanical superiority of beta-blockers over amiodarone; rather, they suggest that in patients who can be adequately managed with beta-blocker monotherapy, the empirical addition of amiodarone may not confer incremental antiarrhythmic benefit while potentially adding multi-organ toxicities (including thyroid dysfunction, pulmonary fibrosis, hepatic injury, and proarrhythmia) (32,33). Current clinical practice firmly reserves amiodarone for patients with recurrent VT despite optimal beta-blockade, those presenting with acute electrical storm, and those completely intolerant of beta-blocker choices (30).

Adverse Effects, Toxicities, and Clinical Contraindications

While beta-blockers are foundational in arrhythmia suppression, their extensive sympathetic blockade is accompanied by well-defined side effects, systemic toxicities, and strict clinical boundaries that require vigilant optimization.

- **Common Side Effects and Systemic Effects:** Antiadrenergic actions routinely induce bradycardia, fatigue, dizziness, and hypotension. Central nervous system penetrance (highest with lipophilic agents like propranolol and metoprolol) can lead to sleep disturbances, nightmares, and depression. \beta_2-mediated peripheral vasoconstriction can cause or worsen cold extremities and erectile dysfunction.
- **Metabolic and Respiratory Toxicities:** Nonselective beta-blockade or high doses of selective agents can provoke severe bronchospasm via \beta_2-receptor inhibition in bronchial smooth muscle. Additionally, beta-blockers can alter insulin sensitivity, mask the autonomic warning signs of hypoglycemia (such as tachycardia and tremors), and prolong hypoglycemic episodes by inhibiting glucose mobilization.
- **Absolute and Relative Contraindications:** * *Absolute:* Cardiogenic shock, acute decompensated heart failure requiring inotropic support, severe symptomatic bradycardia, sick sinus syndrome, or high-degree (second- or third-degree) AV block without a functioning pacemaker. Severe, reactive airway disease (asthma) remains an absolute contraindication for nonselective agents.
  - **Relative***:* Severe peripheral vascular disease (Raynaud's phenomenon) and brittle diabetes mellitus. High caution is required when combining beta-blockers with other negative dromotropes (e.g., non-dihydropyridine calcium channel blockers or amiodarone) due to the amplified risk of advanced bradyarrhythmias and conduction blocks.

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 (3). The most extensively studied polymorphism is the \beta_1-adrenergic receptor Arg389Gly variant: the Arg389 allele encodes a receptor with enhanced coupling to G_s proteins and greater downstream cAMP generation, whereas the Gly389 variant exhibits

significantly reduced signaling efficacy (34).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) (34). However, the treatment effect was profoundly modulated by genotype: among \beta_1-389Arg 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) (34). A three-way genotype interaction incorporating both \beta_1-389Arg/Gly and \alpha_{2C}-322-325 Wt/deletion polymorphisms further stratified response, with certain genotype combinations exhibiting complete loss of antiarrhythmic efficacy (34).
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 strongly influences the antiarrhythmic response to beta-blockade (34). 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.

Future Directions and Recommendations
Summary Points

- **Beyond Simple Rate Control:** Beta-blockers exert complex cellular, ionic, and antiadrenergic protections that transcend simple heart rate mitigation to stabilize vulnerable, remodeled myocardial tissue.
- **The Superiority of Carvedilol:** Pleiotropic properties, including \alpha_1-blockade, antioxidant action, K_v4.3 channel inhibition, and direct RyR2 stabilization, give carvedilol a clinical edge over standard \beta_1-selective alternatives in lowering fast VA burdens and preventing inappropriate device shocks.
- **Etiology Nuances:** Universal beta-blocker utility remains crucial in HFrEF populations regardless of etiology. However, recent contemporary trials challenge the routine, long-term administration of beta-blockers in post-infarction populations possessing preserved systolic function (\text{LVEF} \ge 50\%).
- **Electrical Storm Treatment:** Nonselective beta-blockade via agents like propranolol provides distinct, powerful therapeutic efficacy in refractory ventricular electrical storm by imposing more absolute peripheral and central adrenergic containment.
- **Proactive Monitoring of Toxicities:** Optimal antiarrhythmic titration requires active vigilance against severe bradyarrhythmias, conduction blocks, bronchospasm, and masked metabolic hypoglycemic responses.

Future Perspectives

- 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 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 \beta_1-389Arg/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 (12).
- 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 (10).
- 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 (4).

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 \beta-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 \beta-blockade, \alpha_1-antagonism, antioxidant activity, K_v4.3 channel inhibition, and ryanodine receptor stabilization—properties that translate into clinically meaningful reductions in arrhythmic events compared to \beta_1-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, balanced carefully against individual safety profiles.

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.

Disclaimer

None to declare

Funding Disclosure

No funds, grants or other support was received.

Conflict of Interest

The authors have no relevant financial or non-financial interests to disclose.

Contribution Statement

All authors contributed significantly for the Completion of this article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References:-

1. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. J Am Coll Cardiol. 2018;72(14):e91-e220.
2. Beta-Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. JAMA. 1982;247(12):1707-1714.
3. Bers DM. Cardiac excitation-contraction coupling. Nature. 2002;415(6868):198-205.
4. Bok RW, Heavner MS, Allen JM, Tisdale JE, Seger CD, Van Schooneveld TC, et al. Impact of outpatient beta blocker therapy adjustment on tachyarrhythmias in patients with heart failure with reduced ejection fraction admitted for acute decompensated heart failure. J Pharm Pract. 2024;37(4):886-893.

5. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999;353(9146):9-13.
6. Cohn JN, Levine TB, Olivari MT, Garberg V, Lura D, Francis GS, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med. 1984;311(13):819-823.
7. Coronel R, Wilms-Schopman FJ, Janse MJ. Electrophysiological changes in acute myocardial ischemia. Heart Rhythm. 2006;3(6):726-733.
8. Deyell MW, AbdelWahab A, Angaran P, Essebag V, Glover B, Gula LJ, et al. 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society position statement on the management of ventricular tachycardia and fibrillation in patients with structural heart disease. Can J Cardiol. 2020;36(6):822-859.
9. Dorian P. Antiarrhythmic action of beta-blockers: potential mechanisms. J Cardiovasc Pharmacol Ther. 2005;10(Suppl 1):S15-S22.
10. Doughty RN, Whalley GA, Walsh HA, Gamble GD, López-Sendón J, Sharpe N. Effects of carvedilol on left ventricular remodeling after acute myocardial infarction: the CAPRICORN Echo Substudy. Circulation. 2004;109(2):201-206.
11. Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Engl J Med. 2000;342(15):1077-1084.
12. Feuerstein GZ, Ruffolo RR. Carvedilol, a novel vasodilating beta-blocker with the potential for cardiovascular organ protection. Eur Heart J. 1996;17(Suppl B):24-29.
13. Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, Borbola J, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J. 2005;26(3):215-225.
14. Freemantle N, Cleland J, Young P, Mason J, Harrison J. Beta blockade after myocardial infarction: systematic review and meta regression analysis. BMJ. 1999;318(7200):1730-1737.
15. Goldenberg I, Kutyifa V, Aktas MK, McNitt S, Stockburger M, Klein H, et al. Effect of carvedilol vs metoprolol on atrial and ventricular arrhythmias among implantable cardioverter-defibrillator recipients. JACC Clin Electrophysiol. 2023;9(10):2122-2132.
16. Golwala H, Bajaj NS, Arora G, Arora P. Implantable cardioverter-defibrillators in nonischemic cardiomyopathy: an updated meta-analysis. Circ Arrhythm Electrophysiol. 2017;10(2):e004830.
17. Grandi E, Sanguinetti MC, Bartos DC, Bers DM, Chen-Izu Y, Chiamvimonvat N, et al. Potassium channels in the heart: structure, function and regulation. J Physiol. 2017;595(7):2209-2228.
18. Guerra F, Shkoza M, Scappini L, Flori M, Capucci A. Role of electrical storm as a mortality and morbidity risk factor and its clinical predictors: a meta-analysis. Europace. 2014;16(3):347-353.
19. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure. J Am Coll Cardiol. 2022;79(17):e263-e421.
20. Jentzer JC, Noseworthy PA, Kashou AH, Asirvatham SJ, DeSimone CV, Deshmukh AJ, et al. Multidisciplinary critical care management of electrical storm: JACC state-of-the-art review. J Am Coll Cardiol. 2023;81(22):2189-2206.
21. Johner N, Branca M, Carballo D, Mach F, Roffi M, Nanchen D, et al. Routine beta-blocker therapy after acute coronary syndromes: the end of an era? Eur J Clin Invest. 2024;54(9):e14248.
22. Karagueuzian HS, Nguyen T, Qu Z, Weiss JN. Oxidative stress, fibrosis, and early afterdepolarization-mediated cardiac arrhythmias. Front Physiol. 2013;4:19.
23. Kim Y, Cho JY, Lee HJ, Cho YJ, Park HW, Kim KH, et al. Beta-blocker therapy in patients with acute myocardial infarction: not all patients need it. Korean Circ J. 2023;53(9):637-653.
24. Køber L, Thune JJ, Nielsen JC, Haarbo J, Videbæk L, Korup E, et al. Defibrillator implantation in patients with nonischemic systolic heart failure. N Engl J Med. 2016;375(13):1221-1230.
25. Kristensen AMD, Bovin A, Zwisler AD, Cerquira C, Francisco M, Terkelsen CJ, et al. The Danish-Norwegian randomized trial on beta-blocker therapy after myocardial infarction: design, rationale, and baseline characteristics. Eur Heart J Cardiovasc Pharmacother. 2024;10(3):175-183.
26. Liggett SB, Mialet-Perez J, Thaneemit-Chen S, Weber SA, Greene SM, Hodne D, et al. A polymorphism within a conserved \beta_1-adrenergic receptor motif alters cardiac function and \beta-blocker response in human heart failure. Proc Natl Acad Sci USA. 2006;103(30):11288-11293.
27. Manolis AA, Manolis TA, Melita H, Manolis AS. Sodium-glucose cotransporter 2 inhibitors and sudden cardiac death: an overview of the current evidence. J Cardiovasc Pharmacol. 2023;82(6):427-438.
28. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet. 1999;353(9169):2001-2007.

29. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med. 2002;346(12):877-883.
30. Nademanee K, Taylor R, Bailey WE, Rieders DE, Kosar EM. Treating electrical storm: sympathetic blockade versus advanced cardiac life support-guided therapy. Circulation. 2000;102(7):742-747.
31. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med. 2001;344(22):1651-1658.
32. Packer DL, Prutkin JM, Hellkamp AS, Mitchell LB, Bernstein RC, Wood F, et al. Impact of implantable cardioverter-defibrillator therapy on sudden death risk in mildly symptomatic heart failure patients. J Am Coll Cardiol. 2009;54(10):918-926.
33. Pogwizd SM, Bers DM. Cellular basis of triggered arrhythmias in heart failure. Trends Cardiovasc Med. 2004;14(2):61-66.
34. Rahm AK, Hackbarth J, Mann ME, Bierkowski J, Gündüz D, Scherer D, et al. Differential effects of the betablockers carvedilol, metoprolol and bisoprolol on cardiac Kv4.3 (Ito) channel isoforms. Int J Mol Sci. 2023;24(18):13842.
35. Ruwald MH, Ruwald AC, Jons C, Alexis J, McNitt S, Zareba W, et al. Effect of metoprolol versus carvedilol on outcomes in MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy). J Am Coll Cardiol. 2013;61(14):1511-1518.
36. Schupp T, Behnes M, Reiser L, Bollow A, Taton G, Reichelt T, et al. Comparable risk of recurrent ventricular tachyarrhythmias in implantable cardioverter-defibrillator recipients treated with single beta-blocker or combined amiodarone. Basic Clin Pharmacol Toxicol. 2021;128(3):493-502.
37. Schupp T, Behnes M, Reiser L, Bollow A, Taton G, Reichelt T, et al. Prognostic impact of beta-blocker compared to combined amiodarone therapy secondary to ventricular tachyarrhythmias. Int J Cardiol. 2019;277:118-124.
38. Schwartz PJ, Vanoli E, Stramba-Badiale M, De Ferrari GM, Billman GE, Foreman RD. Autonomic mechanisms and sudden death. New insights from analysis of baroreceptor reflexes in conscious dogs with and without a myocardial infarction. Circulation. 1988;78(4):969-979.
39. Sears SF, Hauf JD, Kirian K, Hazelton G, Conti JB. Posttraumatic stress and the implantable cardioverter-defibrillator patient: what the electrophysiologist needs to know. Circ Arrhythm Electrophysiol. 2011;4(2):242-250.
40. Stevenson WG, Friedman PL, Kocovic D, Sager PT, Saxon LA, Pavri B. Radiofrequency catheter ablation of ventricular tachycardia after myocardial infarction. Circulation. 1998;98(4):308-314.
41. Towbin JA, McKenna WJ, Abrams DJ, Ackerman MJ, Calkins H, Darrieux FCC, et al. 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy. Heart Rhythm. 2019;16(11):e301-e372.
42. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics—2021 update: a report from the American Heart Association. Circulation. 2021;143(8):e254-e743.
43. Woo AY, Xiao RP. \beta-Adrenergic receptor subtype signaling in heart: from bench to bedside. Acta Pharmacol Sin. 2012;33(3):335-341.
44. Yue TL, Cheng HY, Lysko PG, McKenna PJ, Feuerstein R, Gu JL, et al. Carvedilol, a new vasodilator and beta adrenoceptor antagonist, is an antioxidant and free radical scavenger. J Pharmacol Exp Ther. 1992;263(1):92-98.
45. Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA, et al. 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J. 2022;43(40):3997-4126.
46. Zhou Q, Xiao J, Jiang D, Wang R, Vembaiyan K, Wang A, et al. Carvedilol and its new analogs suppress arrhythmogenic store overload-induced Ca^{2+} release. Nat Med. 2011;17(8):1003-1009.