

Review

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Recent developments in nanoparticle-based treatment for atrial fibrillation and other human cardiac arrhythmias

Jared Gabriel L. Dela Rosa¹, Nathan Ross B. Bantayan¹, Ourlad Alzeus G. Tantengco^{2,3}

¹College of Medicine, University of the Philippines Manila, Ermita, Manila, Philippines.

²Department of Physiology, College of Medicine, University of the Philippines Manila, Ermita, Manila 1000, Philippines.

³Department of Biology, College of Science, De La Salle University Manila, Manila 1004, Philippines.

Correspondence to: Ourlad Alzeus G. Tantengco, Department of Physiology, College of Medicine, University of the Philippines Manila, College of Medicine Main Building, Pedro Gil Street, Taft Avenue, Ermita, Manila 1000, Philippines. E-mail: ogtantengco@up.edu.ph

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Abstract

This review aims to summarize the current landscape of cardiac arrhythmia therapeutics and highlight recent advances in nanoparticle-based strategies for the treatment of various human cardiac arrhythmias. A comprehensive literature review was conducted to curate and synthesize recent preclinical developments in nanoparticle-mediated therapies targeting cardiac arrhythmias. Cardiac arrhythmias represent one of the most prevalent and challenging forms of cardiovascular disease worldwide. Conventional treatments, including antiarrhythmic drugs, are often limited by suboptimal efficacy, high recurrence rates, and significant off-target toxicities. While catheter-based ablation techniques have emerged as alternative interventions, their long-term success remains inconsistent, as highlighted by outcomes from large trials such as the CABANA trial. In response to these limitations, nanoparticle-based interventions have emerged as a promising class of therapeutics. These strategies offer potential advantages, including site-specific drug delivery, reduced systemic toxicity, and novel approaches to both pharmacologic and ablative therapy. This review presents an overview of the emerging nanoparticle-based strategies for the treatment of atrial fibrillation and other cardiac arrhythmias. It also discusses recent proof-of-concept studies, evaluates the benefits and limitations of various nanoparticle formulations, and outlines key challenges and future directions for translating these technologies into clinical practice.



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Keywords: Nanoparticle, cardiac arrhythmia, atrial fibrillation, therapy

INTRODUCTION

Cardiac arrhythmias are a spectrum of cardiovascular diseases (CVDs) characterized by disruptions in cardiac excitation patterns and rhythm abnormalities^[1]. These disorders are among the most prevalent types of CVDs, affecting an estimated 1%-4% of the global population^[2]. Atrial fibrillation (AF), the most common rhythm disorder, impacts over 37 million individuals worldwide^[3]. In addition to atrial fibrillation, other types of cardiac arrhythmias include supraventricular tachycardias, bradyarrhythmias, ventricular tachycardia/ventricular fibrillation, and atrioventricular block^[4,5]. The prevalence of cardiac arrhythmias increases with age, making age a significant risk factor for the development of these conditions. Specifically, the prevalence of AF rises from less than 0.5% in individuals under 40 years to more than 5% in those over 60 and approximately 10%-17% in those aged 80 and older^[6]. Older adults are particularly vulnerable to arrhythmias due to age-related structural and electrical changes in the heart, including fibrosis, diminished pacemaker cell function, and slower conduction, all of which contribute to the increased incidence of arrhythmias in this population^[7]. The presence of cardiac arrhythmias can significantly reduce quality of life due to the heightened risk of disability and cardiovascular complications, including sudden death^[8]. Notably, about 80% of sudden cardiac deaths were linked to ventricular arrhythmias^[2]. As the global population ages, the incidence of cardiac arrhythmias is expected to increase significantly, rising from 8.8 million in 2010 to an estimated 17.9 million by 2060^[9]. This rise will place additional strain on healthcare systems and economic resources, driven by frequent emergency room visits for acute episodes, thus positioning cardiac arrhythmias as a major public health challenge^[10].

Antiarrhythmic drug therapy (e.g., amiodarone, beta-blockers, and calcium channel blockers) remains one of the cornerstone management strategies for cardiac arrhythmias^[11]. However, prolonged use of these medications is associated with toxic side effects. For example, prolonged amiodarone treatment for AF has off-target effects on the liver, lungs, and thyroid^[12,13]. In addition to these adverse effects, antiarrhythmic drugs exhibit limited efficacy and high rates of recurrence^[14]. The CABANA trial, the largest study to compare catheter ablation with drug therapy for AF, revealed that 36.4% and 18.4% of patients undergoing catheter ablation experienced AF recurrence within 12 months and developed symptomatic AF during follow-up, respectively^[15]. These suboptimal outcomes highlight the urgent need to further explore alternative therapies to traditional antiarrhythmic drug treatments. Nanoparticle-based therapeutics offer a promising solution to mitigate the toxic effects of conventional pharmacotherapies, given their unique physicochemical properties that enhance bioavailability and enable targeted delivery^[16]. The novel characteristics of nanoparticle-based treatments have spurred significant research into their application in cardiovascular diseases, particularly in cardiac arrhythmias [Figure 1]^[17].

This review aims to present preclinical studies on nanoparticle-based interventions for various cardiac arrhythmias, emphasizing their advantages and limitations [Tables 1 and 2]. Additionally, we include proof-of-concept studies on innovative drug and ablation therapies. Finally, we discuss future research directions and key challenges associated with the translation and clinical application of nanoparticle-based interventions for cardiac arrhythmias, with particular attention to their applicability in an aging population.

NANOPARTICLE-BASED TREATMENTS FOR ATRIAL FIBRILLATION

AF is the most common cardiac arrhythmia, accounting for nearly one-third of rhythm-related hospitalizations^[18]. It significantly increases the risk of stroke, heart failure, and sudden cardiac death^[19]. Management typically involves antiarrhythmic drugs or catheter ablation^[20].

Table 1. In-vitro studies on nanoparticle-based therapies for cardiac arrhythmia treatment

Nanoparticle	Drug (mechanism of action)	Disorder	In-vitro experiments	Advantages	Limitations	References
Lipid nanocapsules (LNCs)	Amiodarone (potassium channel blocker)	Cardiac arrhythmias (Atrial Fibrillation)	Particle size Zeta potential Drug release kinetics Solubility Partitioning Differential scanning calorimetry (DSC)	Mono-disperse Submicron-size Biocompatible excipients	Dependence on acceptor phase interfaces	[30]
TAT-conjugated polymeric liposomes	Lidocaine(sodium channel blocker)	Cardiac ventricular arrhythmias	Particle profiling Skin permeation	Facile uptake across cell membrane No considerable toxicity	Low solubility Short half-life Leakage Oxidation and hydrolysis of phospholipids	[85]
Niosomes (with Gellan gum)	Dronedrone (potassium channel blocker)	Cardiac arrhythmias (Atrial Fibrillation)	Particle size Size distribution Zeta potential Entrapment efficiency Drug release kinetics DSC	Nano- and narrow size High zeta potential High drug encapsulation Enhanced drug release	Aggregation Sedimentation Fusion Drug leakage	[38]
Niosomes	Diltiazem (calcium channel blocker)	Cardiac arrhythmias	Particle size Entrapment efficiency Drug release kinetics DSC	Controlled and prolonged drug release	Aggregation Sedimentation Fusion Drug leakage	[39]
Niosomes (Bile salt-enriched; Bilosomes)	Carvedilol (beta blocker)	Cardiac arrhythmias	Particle size Zeta potential Entrapment efficiency Drug release kinetics Stability	Prevents instability, insolubility and rapid drug degradation	Aggregation Fusion Hydrolysis	[41]
Exosomes (derived from adipose tissue-derived mesenchymal stem cells)	microRNA-320d	Atrial Fibrillation	MTT [3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide] assay TUNEL assay Cell viability assay	Widely applied to deliver functional molecules, e.g., microRNAs	Difficulty in purification and drug loading	[43]

Exosomes (derived from bone marrow mesenchymal stem cells)	microRNA-148a	Atrial Fibrillation	Cell apoptosis assay TUNEL assay	Widely applied to deliver functional molecules, e.g., microRNAs	Difficulty in purification and drug loading	[44]
Solid lipid nanoparticles (composed of lecithin, Compritol, poloxamer & modified with PEG stearate and chitosan oligosaccharide lactate)	Nebivolol (beta blocker)	Hypertension-related cardiac arrhythmias	Drug release kinetics Calcium carbonate-cells permeation ability	Slower drug release in intestinal media	Relatively high water content Inadequate loading capacity Drug leakage	[92]
Solid lipid nanoparticles	Carvedilol (beta blocker)	Cardiac arrhythmias	Calcium carbonate-cells permeation ability Absorption test	Avoidance of the first-pass metabolism Higher drug bioavailability Prolonged drug release Protection from gastric acid	Unwanted burst release (from particle growth and agglomeration)	[48]
Chitosan-based polymeric nanoparticles (modified with cyclodextrin)	Amiodarone (potassium channel blocker)	Cardiac arrhythmias	Particle size Size distribution Zeta potential Entrapment efficiency Drug release kinetics DSC X-ray diffraction	Slow and controlled drug release (long-term therapy)	High degradability rate	[64]

Nanoparticle-based antiarrhythmic drug therapy for atrial fibrillation

Amiodarone, a Class III antiarrhythmic, is the most effective and widely recommended drug for managing atrial fibrillation (AF), particularly in patients with heart failure^[21-23]. However, its use is limited by significant side effects (i.e., pulmonary, hepatic, and thyroid toxicity) due to poor solubility, long half-life, and nonspecific tissue accumulation, as reported from clinical experience and real-world data. To address these challenges, novel drug delivery systems [Figure 1] are being developed to improve its safety and therapeutic efficacy^[24-26].

(*Top Panel*) Nanoparticle-mediated drug delivery platforms - including lipid nanocapsules, liposomes, niosomes, exosomes, solid lipid nanoparticles, cyclic nanoparticles, and polymeric nanoparticles - facilitate the targeted and controlled release of antiarrhythmic agents such as amiodarone, enhancing therapeutic efficacy while minimizing systemic toxicity. (*Middle Panel*) Magnetic nanoparticle-based ablation strategies utilize externally applied magnetic fields to guide particles to sympathetic ganglia (e.g., left stellate ganglion), where localized neuromodulation or photothermal ablation may be achieved. (*Bottom Panel*) Non-magnetic nanoparticle-based ablation involves the direct injection of bioactive particles (e.g., those carrying botulinum or tetanus toxin) to modulate autonomic input to the heart.

Table 2. *In-vivo* studies on nanoparticle-based therapies for cardiac arrhythmia treatment

Nanoparticle	Drug (mechanism of action)	Mode of administration	Disorder	<i>In-vivo</i> experiments (animal model)	Advantages	Limitations	References
Liposomes	Amiodarone (potassium channel blocker)	Intravenous	Ablation-related cardiac arrhythmias	Cardiac radiofrequency ablation rat model	Sustained, stable drug release Increased circulation time	Instability High production cost Unwanted oxidation and hydrolysis	[35]
Liposomes	Amiodarone (potassium channel blocker)	Intravenous	Lethal cardiac arrhythmias	Ischemia-reperfusion (I/R) injury rat model	Reduced mortality	Instability High production cost Unwanted oxidation and hydrolysis	[34]
Liposomes	Phenytoin (sodium channel blocker)	Intravenous	Cardiac arrhythmias	I/R injury rat model	Shorter drug distribution and elimination half-life	Instability High production cost Unwanted oxidation and hydrolysis	[88]
TAT-conjugated polymeric liposomes	Lidocaine (sodium channel blocker)	Transdermal	Cardiac ventricular arrhythmias	Kunming mice	Facile uptake across the cell membrane No considerable toxicity	Low solubility Short half-life Drug Leakage Unwanted oxidation and hydrolysis	[85]
Bile salt-enriched niosomes (Bilosomes)	Carvedilol (beta blocker)	Oral	Cardiac arrhythmias	Pharmacokinetics on Wistar rats Chylomicron-blocked rat model	Improved intestinal absorption Increased peak plasma concentration	Aggregation Fusion Hydrolysis	[41]
Niosomes	Diltiazem (calcium channel blocker)	Nasal delivery	Cardiac arrhythmias	Pharmacokinetics on Wistar rats	Rapid delivery Avoidance of first-pass metabolism	Aggregation Sedimentation Fusion Drug leakage	[39]
Niosomes (with Gellan gum)	Dronedarone (potassium channel blocker)	Nasal delivery	Cardiac arrhythmias (Atrial Fibrillation)	Pharmacokinetics on male New Zealand white rabbits	Nano- and narrow size High zeta potential High drug encapsulation Enhanced drug release	Aggregation Sedimentation Fusion Drug leakage	[38]
Solid lipid nanoparticles (composed of lecithin, Compritol, poloxamer and modified with Polyethylene glycol (PEG) stearate and chitosan oligosaccharide lactate)	Nebivolol (beta blocker)	Oral	Hypertension-related cardiac arrhythmias	Pharmacokinetics on Wistar rats	Slower drug release in intestinal media	Relatively high water content Inadequate loading capacity Drug leakage	[92]
Solid lipid nanoparticles	Carvedilol (beta blocker)	Intranasal	Cardiac arrhythmias	Pharmacokinetics on	Mucous membrane	Unwanted burst release	[49]

				rabbits	adhesion Permeation of large quantities of drug to nasal mucosa	(from particle growth and agglomeration)	
Cyclodextrin nanoparticles	Amiodarone (potassium channel blocker)	Intravenous	Atrial fibrillation	MerTK ^{GFP/+} reporter mouse	Decreased effect on off-target tissues (e.g., lung, liver, and thyroid)	No evidence of anti-Afib activity (only AVN-specific targeting)	[55]
Tannic acid and cyclodextrin-derived polyphenol nanoparticles (TPTN)	TPTN (ROS scavenging ability)	Intravenous injection	Ventricular fibrillation	Male Sprague-Dawley rats	Protection from hypoxic-ischemic injury Good safety profile on i. v. route	Long-term effects and toxicological profile not evaluated	[90]
Polymeric nanoparticles	Amiodarone (potassium channel blocker)	Oral	Atrial Fibrillation	Male Sprague-Dawley rats	Controlled release Slow biodegradation Low energy fabrication	Limited biodistribution and toxicological profile	[61]
Magnetic nanoparticles	N-isopropyl acrylamide monomer (NIPA-M)	Circumflex coronary artery infusion	Atrial fibrillation	Mongrel dogs	Targeted and controlled therapy Minimal systemic side-effects	Mobilization kinetics to epicardium not measured <i>In vivo</i> payload release kinetics not measured	[74]
Magnetic nanoparticles	CaCl ₂ payload (suppression of ganglionic plexi)	Microinjection into ganglionic plexi	Atrial fibrillation	Mongrel dogs	Endogenous components Performed during cardiac catheterization	Minimal targeting time not measured	[76]
N-isopropyl acrylamide-coated Magnetic Nanoparticles (NIPA-co-MN)	N-isopropyl acrylamide	Intracardiac injection	Atrial fibrillation	Beagle dogs	Minimally-invasive and low-cost therapy	Small sample size Stimulus factors not considered Short medication time	[75]
Magnetic nanoparticles (with L-glutamate)	CaCl ₂ payload (suppression of ganglionic plexi)	Microinjection into ganglionic plexi	Postoperative atrial fibrillation	Mongrel dogs	Short burst and sustained drug release Target site concentration and stabilization	Long-term effects not evaluated	[66]
Connexin 43 (Cx43)-loaded magnetic nanoparticles	Cx43-expressing cardiac fibroblasts (cellular cardiomyoplasty)	Intramyocardial transplantation	Post-infarct ventricular tachycardia	CD-1® wild-type mice	Significant reduction of postinfraction arrhythmias	No improvement of cardiac pump function	[83]
PEG-coated gold nanorods (PEG-AuNRs)	PEG-AuNRs and near-infrared (NIR) light (left stellate ganglion inhibition)	Intraganglionic injection and irradiation	Acute ischemia-induced ventricular arrhythmias	Canines	Ameliorates acute ischemia-induced VAs	High production cost Off-target organ toxicity	[82]
Near-infrared sensitive (NIRS) gold nanoshells (GNS)	NIRS GNS (cardiac ablation)	Photothermal ablation	Medically refractory ventricular tachycardia	Porcine cardiac tissue (<i>Ex vivo</i>)	NIR light can penetrate tissue depths > 1 cm Biocompatibility and	Wavelength close to maximal absorption of hemoglobin	[89]

Botulinum toxin-chitosan nanoparticles	Botulinum toxin (autonomic block)	Subepicardial injection	Atrial fibrillation	Wistar rats	oxidation resistant Prolongs botulinum effect	High degradability rate	[80]
Tetanus toxin C (TTC)-conjugated nanoparticles	TTC and N-isopropylacrylamide (left cardiac sympathetic denervation)	Intravenous injection	Ventricular arrhythmia	Canines	Decreases toxicity Improved cardiac function Reduced ventricular arrhythmia inducibility	Biodistribution, long-term effects and toxicological profile not evaluated	[81]
Nanoparticle-encapsulated superoxide dismutase (NP-SOD)	Superoxide dismutase (antioxidant)	Intramyocardial injection	Myocardial ischemia-reperfusion injury	Wistar rats	Improves retention Protects against I/R injury Attenuates ventricular remodeling	Biodistribution, long-term effects and toxicological profile not evaluated Electrophysiological effects not assessed	[84]

TAT: transactivator peptide; ROS: reactive oxygen species; VA: ventricular arrhythmia; IR: infrared; GFP: green fluorescent protein; AVN: atrioventricular nodal.

Lipid nanocapsules

One of the earliest novel delivery systems for amiodarone in preclinical studies was the lipid nanocapsules (LNCs). LNCs are nanoscale carriers, typically ranging from 20 to 100 nm in diameter, composed of three primary components: (1) a nonionic surfactant forming the capsule membrane; (2) an aqueous phase of sodium chloride solution; and (3) an oily core consisting of medium-chain triglycerides, such as capric and caprylic acid derivatives^[27-29]. In preclinical formulations, amiodarone was successfully encapsulated within LNCs utilizing polyethylene glycol-660 hydroxystearate as the surfactant, with soybean lecithin added to enhance capsule stability^[30].

These amiodarone-loaded LNCs demonstrated a low polydispersity index and pH-sensitive drug release, thereby addressing the significant burst release commonly observed in earlier nanoparticle systems designed for low molecular weight compounds^[31,32]. The use of biocompatible excipients and the physicochemical properties of the formulation suggest potential suitability for intravenous or intraperitoneal administration^[30]. However, these findings are currently limited to preclinical evaluations and require further investigation in clinical settings to confirm their safety and therapeutic efficacy in humans.

Liposomes

Liposomes have also been explored in preclinical studies as a novel delivery system for amiodarone. These spherical vesicles, ranging in size from approximately 30 nm to several micrometers, are composed of one or more phospholipid bilayers formed from natural, non-toxic phospholipids and cholesterol^[33]. The lipophilic character of the bilayer facilitates the encapsulation and solubilization of amphiphilic and lipophilic drugs, such as amiodarone. Additionally, liposomes are generally considered non-immunogenic following both systemic and non-systemic administration^[16,33]. In animal models,

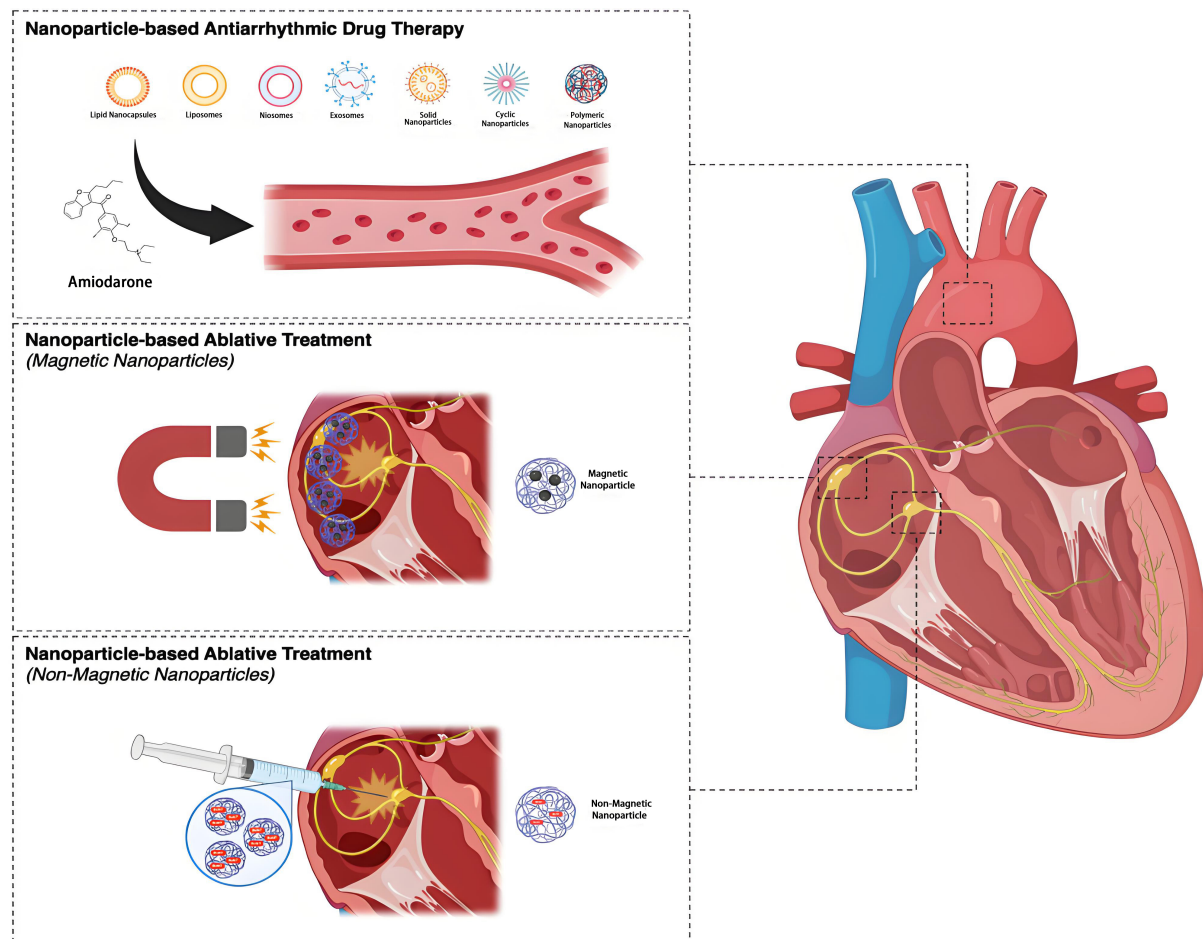


Figure 1. Schematic overview of nanoparticle-based therapeutic strategies for cardiac arrhythmias. Figure created with Microsoft PowerPoint and BioRender. Created in BioRender. <https://biorender.com/463e7en>

amiodarone-loaded liposomes have demonstrated improved therapeutic profiles compared to free amiodarone. In a rat model of ischemia/reperfusion (I/R) injury, intravenous administration of liposomal amiodarone at 3 mg/kg in Wistar rats significantly reduced the duration of ventricular tachycardia and ventricular fibrillation (VT/VF), as well as mortality from these arrhythmias, compared to a higher dose (10 mg/kg) of free amiodarone^[34]. Liposomal amiodarone was also associated with a reduced incidence of bradycardia and hypotension in the same I/R model^[34]. Furthermore, in Sprague-Dawley rats subjected to cardiac radiofrequency (RF) ablation, liposomal amiodarone exhibited more sustained and stable drug release compared to its free form^[35]. These properties contributed to enhanced antiarrhythmic efficacy at lower doses, potentially reducing dose-dependent side effects such as bradycardia and hypotension.

Biodistribution studies further revealed that liposomal amiodarone preferentially accumulates in the myocardium of rats following cardiac I/R injury and RF ablation, likely due to increased vascular permeability in inflamed cardiac tissues^[34,35]. This targeted accumulation underscores the potential utility of liposomal amiodarone in the treatment of arrhythmias associated with ischemic heart disease or post-catheter ablation interventions. However, despite reduced drug concentrations in the lungs and kidneys, potentially minimizing pulmonary and renal toxicity, liposomal delivery was associated with increased amiodarone accumulation in the liver and spleen. This effect is likely due to passive uptake by these macrophage-rich organs (i.e., organs with a high concentration of macrophages), raising concerns about

potential hepatic and splenic toxicity with long-term use^[35].

Collectively, these findings from preclinical studies suggest that liposomal delivery of amiodarone holds promise for targeted cardiac therapy, but further investigation is required to evaluate its safety and efficacy in clinical settings.

Niosomes

Niosomes have emerged in preclinical research as a promising alternative to liposomes for drug delivery. Structurally like liposomes, niosomes are spherical vesicles comprising at least one bilayer but are formed using nonionic surfactants rather than phospholipids. This substitution imparts greater stability, resulting in improved shelf life and resistance to photodegradation compared to liposomal formulations^[36]. Moreover, the simpler preparation methods make niosomes more cost-effective for large-scale production^[37].

In preclinical studies, niosomes have been employed to enhance the bioavailability of antiarrhythmic agents. Dronedarone - a non-iodinated benzofuran analog of amiodarone - was successfully encapsulated in niosomes composed of Span® 80 and cholesterol (1:1), with Gellan gum used as a mucoadhesive agent (i.e., able to stick to mucosal surfaces). When administered intranasally to male New Zealand rabbits, this formulation resulted in significantly increased maximum plasma concentration (C_{max}), the area under the concentration-time curve from 0 to 72 h (AUC_{0-72}), and total drug exposure ($AUC_{0-\infty}$) compared to an orally administered dronedarone suspension^[38].

Similarly, in a preclinical model involving male Wistar rats, the calcium channel blocker diltiazem - another drug used in atrial fibrillation management - was encapsulated in niosomes formulated with Span® 60 and cholesterol (1:1). Intranasal administration of this formulation led to enhanced pharmacokinetic parameters, including increased mean residence time (MRT), elimination half-life ($t_{1/2}$), and AUC, along with a reduced elimination rate constant (K_e), compared to an aqueous diltiazem solution in phosphate-buffered saline^[39].

Niosomes have also shown potential for improving the oral bioavailability of drugs. Although the precise mechanisms remain under investigation, previous studies have demonstrated that incorporating bile salts into vesicular systems can increase their resistance to bile salt-induced disruption in the gastrointestinal (GI) tract^[40]. This approach has been applied in a preclinical context to enhance the oral delivery of carvedilol, a third-generation β -blocker used in the prevention and treatment of atrial fibrillation. In male Wistar rats, oral administration of carvedilol-loaded niosomes with bile salts significantly increased intestinal absorption and systemic bioavailability - as indicated by higher $AUC_{0-\infty}$ - compared to carvedilol suspended in 0.5% sodium carboxymethyl cellulose^[41].

These preclinical findings underscore the versatility and promise of niosomal drug delivery systems for improving the pharmacokinetics of antiarrhythmic agents. However, further studies, including clinical trials, are necessary to validate their translational potential.

Exosomes

Exosomes are another class of nanoscale vesicles currently being investigated in preclinical studies for drug delivery applications. These endogenous, spherical vesicles range from approximately 40 to 200 nm in diameter and can transport a diverse array of signaling biomolecules, including proteins, nucleic acids, and non-coding RNAs such as microRNAs (miR)^[42].

In preclinical experiments, exosomes derived from adipose tissue-derived mesenchymal stem cells (AMSCs) and loaded with miR-320d demonstrated anti-apoptotic effects when applied to isolated cardiomyocytes obtained from a murine model of AF^[43]. Similarly, bone marrow mesenchymal stem cell (BMSC)-derived exosomes loaded with miR-148a showed protective effects in HL-1 mouse cardiomyocyte cells subjected to electrical stimulation to induce an AF-like phenotype. Treatment with these engineered exosomes significantly inhibited apoptosis in the stimulated cardiomyocytes^[44].

While these findings highlight the potential of exosome-based therapies for AF, it is important to note that all current evidence is limited to preclinical models. Significant challenges remain before clinical translation can be realized, including the development of reproducible, high-purity isolation techniques and efficient, scalable methods for exosome loading^[45].

Solid lipid nanoparticles

In contrast to the aqueous or semi-aqueous core vesicles discussed so far, solid lipid nanoparticles (SLNs) represent a distinct class of drug delivery systems characterized by a solid lipid core surrounded by a monolayer of surfactant^[46]. This rigid lipid matrix enhances the encapsulation efficiency and stability of hydrophobic drugs relative to liposomes and polymeric nanoparticles^[47].

Carvedilol, a third-generation β -blocker commonly used in the management of atrial fibrillation, exhibits poor oral bioavailability (~ 25%) due to extensive first-pass hepatic metabolism^[48]. In preclinical studies, encapsulating carvedilol in SLNs significantly improved its cellular uptake. Specifically, SLN-encapsulated carvedilol demonstrated superior absorption in Caco-2 cells (a human colorectal adenocarcinoma cell line commonly used to model intestinal epithelium) compared to carvedilol physically mixed with SLNs or carvedilol alone, suggesting the potential for overcoming its limited oral bioavailability^[48].

Additional preclinical investigations have evaluated the intranasal delivery of carvedilol-loaded SLNs. In an ex vivo study using sheep nasal mucosa, SLN formulations achieved enhanced mucosal penetration compared to carvedilol solution alone. Furthermore, in vivo administration of carvedilol-loaded SLNs incorporated into an in situ gelling system resulted in significantly higher absolute bioavailability following intranasal delivery in rabbits compared to conventional oral administration^[49].

These preclinical findings underscore the potential of SLNs as a promising platform for improving the bioavailability of poorly absorbed cardiovascular drugs. However, further studies are needed to optimize formulation parameters and assess safety and efficacy in clinical contexts.

Cyclic nanoparticles

Cyclodextrins are cyclic oligosaccharide-based nanoparticles composed of α -1,4-linked α -D-glucopyranose units^[50]. These molecules possess a hydrophobic, bucket-shaped cavity capable of forming supramolecular host-guest inclusion complexes with lipophilic compounds, such as amiodarone^[51]. In drug delivery applications, cyclodextrins offer several advantages, including enhanced solubility of hydrophobic drugs, improved encapsulation efficiency, protection from chemical degradation, and superior drug stability compared to liposomal systems^[52].

Recent preclinical studies have explored the use of cyclodextrin nanoparticles (CDNPs) for targeted antiarrhythmic drug delivery. Macrophages, which exhibit high phagocytic activity toward CDNPs, are abundant in the atrioventricular nodal (AVN) region of the heart, making this cell population an attractive target for localized drug delivery within the cardiac conduction system^[53,54]. In a murine model, intravenous

administration of amiodarone-loaded CDNPs in C57BL/6 mice resulted in selective accumulation of nanoparticles in the myocardium, particularly within the AVN, 24 h post-injection^[55]. Additional accumulation was observed in macrophage-rich organs such as the liver and spleen, whereas a relatively lower distribution was detected in the lungs and skeletal muscle^[55]. Correspondingly, tissue analysis confirmed elevated amiodarone concentrations in the heart, liver, and spleen, suggesting the potential for reduced pulmonary toxicity but raising the possibility of hepatic and splenic adverse effects.

Although these findings underscore the potential of CDNPs for site-specific delivery of amiodarone and reduction of off-target effects, it is important to note that the current evidence remains limited to preclinical models. Demonstration of therapeutic efficacy - specifically, arrhythmia prevention or suppression such as in atrial fibrillation - has yet to be established. Rigorous evaluation in disease-relevant models and eventual clinical studies will be essential to determine the translational applicability of this approach.

Polymeric nanoparticles

Polymeric nanoparticles represent a versatile class of nanocarriers for drug delivery, typically classified as nanocapsules - comprising a polymeric shell surrounding an oily core - or nanospheres, in which the drug is uniformly dispersed within a polymeric matrix^[56]. These systems can either adsorb therapeutic agents onto their surface or encapsulate them within the core or matrix, offering several pharmacokinetic advantages, including enhanced bioavailability, sustained release, and protection from premature degradation^[57,58].

Polymeric nanoparticles may be synthesized from either synthetic or natural biodegradable polymers. Synthetic polymers can be chemically modified to tailor drug release profiles, improve targeting specificity, and reduce systemic toxicity^[59,60]. Among these, poly(lactic-co-glycolic acid) (PLGA) is a well-characterized biodegradable polymer with demonstrated biocompatibility and controlled degradation properties. In preclinical studies, oral administration of PLGA-encapsulated amiodarone in Sprague-Dawley rats resulted in significantly reduced drug-related toxicities. Animals receiving the PLGA formulation exhibited lower serum levels of hepatic enzymes (alanine aminotransferase and aspartate aminotransferase), attenuated pulmonary capillary congestion and inflammatory infiltration, and preserved thyroid function (normal T4 and thyroid stimulating hormone levels) compared to those administered with free amiodarone^[61].

Natural polymers offer distinct advantages due to their inherent biocompatibility, low immunogenicity, and additional properties such as antimicrobial activity^[62]. Chitosan, a cationic natural polymer, has garnered significant attention for drug delivery applications due to its mucoadhesive properties, capacity to enhance epithelial permeability, and affinity for negatively charged cellular membranes^[63]. In a preclinical formulation, amiodarone was first modified with cyclodextrin to enhance its solubility and then encapsulated into chitosan-based nanoparticles. This system demonstrated sustained release of amiodarone over 14 days, suggesting strong potential for use in controlled-release antiarrhythmic therapy^[64].

Although these findings are currently limited to preclinical models, they collectively underscore the potential of polymeric nanoparticle systems to improve the safety and efficacy of amiodarone and other antiarrhythmic drugs. Further investigation is needed to evaluate their clinical translatability and therapeutic benefit in human subjects.

Nanoparticle-based ablative treatment for atrial fibrillation

Refractory AF is often treated with radiofrequency (RF) catheter ablation via circumferential pulmonary vein isolation (CPVI), but its non-selective nature can cause collateral tissue damage and new arrhythmogenic substrates, limiting long-term success rates to below 50% at five years^[65,66]. Targeted

ganglionated plexi (GP) ablation within the cardiac autonomic nervous system has emerged as a more precise alternative, modulating autonomic input while minimizing myocardial injury. Building on this, nanoparticle-based systems are being explored for precise, non-destructive neuromodulation of autonomic pathways^[66-70] [Figure 1]. Although still in preclinical stages, early studies suggest these platforms could offer reversible, site-specific alternatives to conventional ablation for AF treatment.

Magnetic nanoparticles

Magnetic nanoparticles (MNPs) have garnered significant interest in preclinical research for their capacity to enable the targeted delivery of therapeutic agents under the guidance of an external magnetic field^[71]. While MNP-based strategies have been explored in a variety of disease models, including oncology and neurodegenerative disorders, their application in the context of GP ablation for AF remains entirely preclinical at this stage^[72,73].

One of the earliest MNP-based formulations for GP modulation featured a magnetite core surrounded by a thermoresponsive hydrogel matrix capable of delivering a neurotoxic payload^[74]. In a preclinical canine study, MNPs loaded with the neurotoxin N-isopropyl acrylamide monomer (NIPA-M) were infused into the circumflex coronary artery of adult mongrel dogs. Within two hours, electrophysiological measurements indicated functional suppression of the inferior right GP (IRGP), with histological analysis confirming the accumulation of the nanoparticles within the IRGP^[74]. In addition to serving as a neurotoxic payload, N-isopropyl acrylamide (NIPA) can be integrated into the hydrogel matrix itself to exploit its thermoresponsive properties. In another preclinical study, MNPs coated with NIPA were administered via the circumflex coronary artery in beagle dogs and similarly suppressed IRGP activity^[75].

A distinct MNP formulation employed a PLGA matrix shell with a magnetite core and calcium chloride as the active agent^[76]. Although calcium is a physiological ion, excessive intracellular calcium in neurons can induce neuroapoptosis, thereby achieving a form of chemical GP ablation^[77]. In a preclinical canine model, calcium chloride-loaded MNPs were infused into the left circumflex artery (LCX) under an externally applied magnetic gradient, leading to marked suppression of both IRGP and superior left GP (SLGP) activity^[76].

To further enhance neurotoxicity, L-glutamate was added to a similar MNP formulation to potentiate calcium influx through NMDA receptor activation. This enhanced formulation was tested in a preclinical model of postoperative atrial fibrillation (POAF), created via sequential survival thoracotomies in mongrel dogs^[66]. Targeted injection of the MNPs into the left atrial GPs suppressed AF inducibility and reversed POAF-associated shortening of the atrial effective refractory period. Notably, this treatment preserved circadian heart rate variability and exercise-induced chronotropic response, suggesting modulation rather than complete ablation of cardiac autonomic function^[66].

These findings underscore the preclinical promise of MNP-based strategies for selective neuromodulation of cardiac autonomic inputs in AF. However, translation to clinical application will require substantial validation, including long-term safety profiling, precise magnetic targeting techniques, and robust demonstration of efficacy in larger and more heterogeneous animal models.

Non-magnetic nanoparticles

Non-magnetic nanoparticle formulations have also been investigated in preclinical studies as a potential strategy for GP ablation. Botulinum toxin has previously demonstrated efficacy in suppressing AF inducibility and delaying its progression when directly injected into atrial GPs, although these findings

remain limited to animal models^[78,79]. Building on this concept, a preclinical study recently evaluated a chitosan-based nanoparticle formulation encapsulating botulinum toxin for neuromodulation. In this study, epicardial administration of the botulinum toxin-loaded chitosan nanoparticles significantly reduced the incidence of cardiac arrhythmias - specifically ventricular fibrillation - in rat models^[80].

While these findings are promising, particularly about localized and sustained neurotoxin delivery, further preclinical investigations using validated animal models of AF are essential to determine whether this formulation can effectively modulate atrial GPs to treat or prevent atrial fibrillation specifically. Translation to clinical application will also require a comprehensive evaluation of safety, specificity of GP targeting, and long-term outcomes.

NANOPARTICLE-BASED TREATMENTS FOR OTHER CARDIAC ARRHYTHMIAS

Ventricular arrhythmias

Current research into nanoparticle-based therapies for ventricular arrhythmias (VAs) is primarily focused on the prevention of post-infarction VA and the preservation or improvement of ventricular function, all within preclinical settings. One strategy to prevent post-infarction VA involves left cardiac sympathetic denervation (LCSD), which has been shown to modulate arrhythmic risk. In a preclinical canine model of heart failure, LCSD combined with tetanus toxin C (TTC)-conjugated nanoparticles significantly improved cardiac function and reduced the inducibility of VAs^[81]. Similarly, in an acute ischemia-induced canine model, polyethylene glycol-coated gold nanorods (PEG-AuNRs) were used in combination with near-infrared (NIR) light to achieve photothermal inhibition of left stellate ganglion (LSG) activity. This preclinical intervention resulted in a marked decrease in VA occurrence^[82].

Other preclinical approaches involve reparative strategies following myocardial infarction. For instance, connexin 43 (Cx43)-loaded magnetic nanoparticles have been used in murine models of cellular cardiomyoplasty to enhance intercellular coupling and reduce post-infarction arrhythmias^[83]. In addition, superoxide dismutase (SOD), a potent antioxidant with poor myocardial retention, has been encapsulated into nanoparticles (NP-SOD) for preclinical evaluation in rat models. Intramyocardial administration of NP-SOD before reperfusion was found to reduce reperfusion injury and prevent adverse ventricular remodeling, suggesting a protective role against ischemia-reperfusion injury^[84].

In contrast, some nanoparticle formulations for VA remain at an even earlier in vitro stage of investigation. Lidocaine, a class IB antiarrhythmic agent, was previously incorporated into polymeric liposomes conjugated with a transcriptional transactivator peptide (TAT) to facilitate transdermal delivery^[85]. However, this formulation has only been evaluated in preclinical in vitro studies and, to date, has not been tested in any animal model of cardiac arrhythmia.

Ventricular tachycardia

VT can be pharmacologically managed using class IB antiarrhythmic agents such as phenytoin^[86]. Phenytoin acts by reducing calcium-dependent depolarization and prolonging the cardiac action potential refractory period, thereby inhibiting early afterdepolarizations (EADs) and suppressing ventricular tachyarrhythmias^[87]. In a preclinical study using a rat model of myocardial ischemia/reperfusion (I/R) injury, administration of liposome-encapsulated phenytoin significantly improved left ventricular function and attenuated adverse post-infarction remodeling - evidenced by reduced infarct size and decreased fibrotic area - compared to treatment with empty liposomes^[88]. These beneficial effects were partially attributed to the preferential uptake of liposome-encapsulated phenytoin by CD43⁺ inflammatory monocytes, which play a critical role in post-injury inflammation^[88]. While these results highlight the

potential of nanoparticle-mediated phenytoin delivery in post-infarction cardiac repair, the specific antiarrhythmic efficacy of this formulation remains to be demonstrated in preclinical animal models of cardiac arrhythmia.

Nanoparticle-based systems are also being explored to enhance the precision and efficacy of ablative therapies for VT. Radiofrequency (RF) ablation remains the clinical standard for treating medically refractory VT; however, it is limited by shallow lesion depth and the need for consistent tissue contact. To address these limitations, near-infrared-sensitive (NIRS) nanoparticles have been developed to facilitate site-specific, photothermal ablation through externally applied NIR light. In a preclinical ex vivo porcine model, NIRS nanoparticle-mediated ablation was shown to create deeper, transmural lesions compared to RF, offering the potential for improved therapeutic outcomes and reduced procedural complications^[89]. This approach also enables lesion formation using conventional catheters equipped with fiber optic guidance, bypassing the need for continuous tissue contact inherent to RF systems. While promising, these findings remain at the preclinical stage, and further in vivo studies are needed to evaluate the safety, specificity, and functional outcomes of NIRS-based VT ablation.

Ventricular fibrillation

Polyphenol-functionalized nanoparticles (NPs) have emerged as a promising platform for targeted therapy in cardiovascular diseases due to their high affinity for various cells and tissues. Among these, tannic acid (TA)-derived functional nanoparticles demonstrate notable accumulation in injured cardiac tissue following intravenous administration. By integrating TA with a bioactive cyclodextrin-based material (TPCD), a nanoparticle formulation known as TPTN was developed, characterized by favorable physicochemical properties and robust reactive oxygen species (ROS)-scavenging activity. In a preclinical study using a murine model of VF, intravenous administration of TPTN significantly improved survival rates, particularly when used in conjunction with therapeutic hypothermia, a standard adjunctive therapy following cardiac arrest^[90]. TPTN was found to localize effectively to the site of myocardial injury in resuscitated rats and contributed to improvements in myocardial function, reduction of oxidative stress, and attenuation of cardiac tissue damage - all under preclinical conditions^[90].

In another preclinical development, nebivolol - a third-generation β -blocker known to reduce the incidence of ventricular arrhythmias by increasing the ventricular fibrillation threshold^[91] - was incorporated into SLNs to improve its pharmacokinetic profile. These SLNs were surface-modified with chitosan oligosaccharide lactate to enhance permeability across Caco-2 cell monolayers and with polyethylene glycol (PEG) to increase systemic bioavailability^[92]. In a rat model, oral administration of PEG-modified, nebivolol-loaded SLNs resulted in a higher peak plasma concentration compared to conventional nebivolol formulations^[92]. However, it is important to note that while these delivery systems enhanced drug absorption in preclinical pharmacokinetic studies, they have not yet been tested in any animal models of cardiac arrhythmia, and their antiarrhythmic potential remains to be established.

LIMITATIONS AND CHALLENGES OF NANOPARTICLE-BASED TREATMENTS FOR CARDIAC ARRHYTHMIAS

Nanoparticle-based therapeutics represent a novel and promising approach to the treatment of cardiac arrhythmias. However, as presented in the preceding sections, nearly all investigations into their application remain in the preclinical stage, encompassing in vitro experiments and animal models. While early findings are encouraging, several critical challenges must be addressed before these novel therapeutics can advance to clinical translation.

One of the primary limitations is the incomplete understanding of cardiovascular toxicity associated with nanoparticle-based therapies, particularly concerning their impact on the cardiac conduction system^[93]. Although limited in number, existing preclinical studies examining the cardiovascular toxicities of various nanomaterials suggest that they may induce pro-thrombotic states, inflammation, apoptosis, and oxidative stress in cardiac tissues^[93,94]. Among these, inflammation and oxidative stress are believed to be the predominant contributors to nanoparticle-induced cardiovascular damage, which could potentially precipitate hypertension, myocardial infarction, or myocarditis^[93,95]. Furthermore, the off-target accumulation of nanoparticles, particularly in the liver and spleen, raises concerns regarding long-term toxicity with repeated or chronic use. Comprehensive safety evaluations - including dose-response, biodistribution, and toxicity studies - are therefore essential before human application.

Another major area of focus is the enhancement of targeting precision, particularly for MNP-mediated ablation techniques. Improved control over lesion localization is essential to avoid off-target effects that could result in inadvertent damage to critical cardiac structures such as valvular tissue, coronary vasculature, or components of the conduction system, all of which could lead to serious complications. In addition, the long-term biocompatibility of MNPs must be carefully investigated, with particular attention to the potential for iron accumulation from the magnetite core and its implications for myocardial and systemic health.

Beyond biological safety, another major hurdle is the manufacturing challenges associated with nanoparticle-based formulations. To be viable for clinical use, nanoparticles must be produced at a large scale with high throughput, reproducibility, and batch-to-batch consistency. Currently, many nanoparticle synthesis protocols yield small quantities of products with variable chemical composition, inconsistent physical properties, and limited stability^[93]. For instance, the scalable production of exosomes remains hampered by the lack of robust high-purity isolation and purification techniques^[45]. In contrast, synthetic vesicles such as niosomes offer a more straightforward and cost-effective production process compared to liposomes and represent a step in the right direction toward scalable manufacturing^[37].

Another underexplored area is the application of nanoparticle-based therapeutics in aging populations. Although no studies have directly evaluated nanoparticle toxicity in the aging heart, age-related physiological changes are known to alter the pharmacokinetics of drugs and may similarly affect nanoparticles^[96]. Aging is associated with reduced mesenteric blood flow, which may impair oral drug and nanoparticle absorption^[97]. Alterations in body composition - specifically increased fat mass and decreased total body water - can affect the distribution of lipophilic and hydrophilic nanoparticles^[98]. Furthermore, age-related declines in hepatic and renal clearance may lead to increased bioavailability of nanoparticles, necessitating careful dose adjustments in older populations^[99]. These factors underscore the importance of age-specific design and dosing strategies for nanoparticle-based therapies targeting older adults with cardiac arrhythmias.

Collectively, these scientific and technical barriers must be addressed to enable the safe and effective clinical translation of nanoparticle-based antiarrhythmic therapies. Future research should focus on comprehensive toxicological evaluation, refinement of large-scale synthesis techniques, and standardization of characterization and quality control protocols. These efforts will be instrumental in ensuring the safety, efficacy, and regulatory compliance necessary for clinical translation.

CONCLUSION

Nanoparticle-based therapies are emerging as innovative tools to advance the treatment landscape of cardiac arrhythmias, offering the potential to improve efficacy while minimizing the side effects of conventional pharmacologic and interventional approaches. However, their clinical translation hinges on overcoming several key challenges through ongoing preclinical and translational efforts.

A critical priority is enhancing targeting precision, particularly for MNP-mediated ablation. Precise lesion localization is essential to avoid collateral damage to vital cardiac structures. Additionally, the long-term biocompatibility of MNPs must be evaluated, including risks of iron accumulation from magnetite cores and associated systemic effects. For other platforms, such as liposomal, polymeric, and cyclic nanoparticles, improving targeting efficiency is equally important. Reducing off-target accumulation, especially in the liver and spleen, remains a major obstacle. Enhancing nanoparticle delivery to arrhythmogenic sites while sparing healthy tissue will be key to improving safety and therapeutic efficacy.

Future studies using large animal models will help test nanoparticle-based treatments for cardiac arrhythmias. Large animal studies, including canines (atrial fibrillation, ventricular arrhythmias), swine (ventricular tachycardia, atrial fibrillation), ovine (chronic AF), and non-human primates, offer more clinically relevant physiology than rodent models and are essential for assessing dosing, safety, and efficacy before human trials.

Finally, scalable and reproducible manufacturing remains a significant barrier. Clinical and commercial viability will depend on the ability to produce nanoparticles with consistent physicochemical properties, stability, and batch-to-batch uniformity at an industrial scale.

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Authors' contributions

Conceived and designed research, synthesized and interpreted data, drafted, edited, revised and approved the final manuscript: Dela Rosa JGL, Bantayan NRN, Tantengco OAG

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