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REVIEW

Potential Antiarrhythmic Mechanisms of Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RAs)

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Abstract: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a novel class of glucose-lowering agents that offer benefits beyond glycemic control and weight loss and are increasingly recognized for their cardioprotective benefits, including protective effects against hypertension, heart failure, myocardial infarction, and arrhythmias. Notably, GLP-1RAs have demonstrated a significant capacity to reduce arrhythmia risk not only in animal models but also in large-scale clinical trials. However, the antiarrhythmic mechanisms of GLP-1RAs remain incompletely understood. This mechanistic review synthesizes current preclinical and clinical evidence to delineate the key pathways through which GLP-1RAs may exert their antiarrhythmic effects. The primary mechanisms discussed include the attenuation of cardiomyocyte death, improvement of myocardial metabolism, and inhibition of the inflammatory response. Additional mechanisms, such as the promotion of autophagy, maintenance of ion homeostasis in cardiomyocytes, and modulation of the autonomic nervous system, are also examined. By clarifying these mechanisms, this review aims to offer novel therapeutic strategies for arrhythmia prevention, especially in the high-risk population with cardiometabolic diseases.

Keywords: glucagon-like peptide-1 receptor agonists, antiarrhythmic, liraglutide, exendin-4, semaglutide

Introduction

The therapeutic paradigm for antihyperglycemic agents has profoundly shifted from a primary focus on glycemic control to an appreciation of their distinct cardioprotective properties. This evolution, championed by metformin and solidified by SGLT2 inhibitors (eg, empagliflozin), now extends to glucagon-like peptide-1 receptor agonists (GLP-1RAs).[1–5] This raises a central question: what are the pleiotropic mechanisms through which the GLP-1RAs, beyond influencing glucose metabolism, protect the myocardium?

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by intestinal epithelial endocrine L-cells located in the distal ileum and colon.[6,7] The GLP-1 receptor (GLP-1R), a G-protein-coupled receptor (GPCR) widely expressed throughout the human body, is present in multiple tissues and organs, including the pancreas, heart, central and peripheral nervous systems, lungs, kidneys, gastrointestinal tract, and skin.[8] Specifically, GLP-1R is expressed not only in atrial and ventricular myocytes as well as sinoatrial node cells of the heart but also in various types of cardiovascular cells such as mononuclear macrophages, smooth muscle cells, and endothelial cells.[8,9]

GLP-1RAs are a new class of hypoglycemic agents, primarily including Liraglutide, Exendin-4, Semaglutide, Exenatide and Dulaglutide.[9–11] Due to their glucose-lowering and weight-reducing properties, GLP-1RAs are predominantly used in the management of type 2 diabetes mellitus (T2DM) and obesity.[11,12] However, as research

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into GLP-1RAs continues to evolve, accumulating evidence indicates that these agents confer protective effects on the cardiovascular system. These benefits encompass heart failure, myocardial infarction, arrhythmias, hypertension, dilated cardiomyopathy, and hypertrophic cardiomyopathy.[8,9,11,13–15] Currently, numerous studies have reported on the antiarrhythmic potential of GLP-1RAs.[13–17] For example, Zhong et al showed that GLP-1RAs can reduce the incidence of atrial fibrillation by regulating myocardial metabolism.[13] Ang et al revealed that GLP-1RAs exert antiarrhythmic effects by modulating β-adrenergic receptor-mediated ventricular electrophysiological remodeling.[16] Previous reviews have summarized the existing literature on the cardioprotective effects of GLP-1RAs, confirming their cardiovascular benefits.[5,18,19] However, the precise antiarrhythmic mechanisms of GLP-1RAs remain incompletely understood, and a comprehensive systematic review elucidating these mechanisms is currently lacking in the literature. Therefore, this review aims to provide an in-depth understanding of the potential antiarrhythmic mechanisms of GLP-1RAs, establish a theoretical foundation for the development of novel antiarrhythmic agents, and offer new insights and strategies for the clinical prevention and treatment of arrhythmias.

Potential Antiarrhythmic Mechanisms of GLP-1RAs

Attenuating Cardiomyocyte Death

Cardiomyocyte death, encompassing apoptosis, necroptosis, pyroptosis, and ferroptosis, plays a pivotal role in the pathogenesis of cardiac arrhythmias.[20] Accumulating evidence demonstrates that these distinct forms of programmed cell death contribute to arrhythmia development through both direct electrophysiological disturbances and structural remodeling of cardiac tissue.[20] James et al suggest that apoptosis may lead to progressive degeneration of the cardiac conduction system, ultimately resulting in complete heart block and life-threatening ventricular arrhythmias.[21] Necroptosis has been shown to be mechanistically linked to atrial fibrillation initiation and maintenance, primarily through its dual effects on promoting electrophysiological instability and facilitating structural remodeling in experimental models.[22] Pyroptosis, characterized by its highly inflammatory nature, exacerbates arrhythmogenic substrates through both acute and chronic inflammatory responses that drive myocardial fibrosis and adverse electrical remodeling.[23,24] Ferroptosis primarily promotes arrhythmogenesis through iron-dependent lipid peroxidation, which disrupts calcium homeostasis, impairs mitochondrial function, and induces oxidative stress-related electrical disturbances.[25–27]

Emerging preclinical evidence suggests that GLP-1RAs may indirectly reduce arrhythmia susceptibility through their pleiotropic actions on cell death pathways. This potential mechanism warrants careful consideration based on the following observations. Apoptosis and necroptosis are recognized as key pathophysiological features following myocardial injury.[28] Zhu et al demonstrated that Semaglutide attenuates myocardial ischemia/reperfusion (I/R)-induced cardiomyocyte apoptosis by activating the PKG/PKCε/ERK1/2 signaling pathway, resulting in notable reductions in infarct size and improvements in cardiac remodeling.[29] Given the established relationship between apoptotic cell death and conduction system impairment,[21] this antiapoptotic effect may theoretically preserve conduction system integrity. Yan et al showed that Semaglutide alleviates oxidative stress and apoptosis in the diabetic heart via Sirt1/AMPK pathway activation and Connexin 43 (Cx43) restoration, thereby improving cardiac function and electrophysiological remodeling in a diabetic cardiomyopathy (DCM) model.[30] Similarly, Zhou et al demonstrated that Liraglutide suppresses necroptosis through the GLP-1R/PI3K/Akt signaling cascade, subsequently reducing infarct size and improving cardiac remodeling.[31] Pyroptosis has emerged as a potential therapeutic target for preventing adverse cardiac remodeling.[32] As necroptosis contributes to atrial fibrillation substrates,[22] this mechanism may indirectly reduce atrial arrhythmia susceptibility. In a streptozotocin-induced diabetic rat model, four weeks of Liraglutide treatment significantly reduced the myocardial expression of NOD-like receptor family pyrin domain-containing 3 (NLRP3), a key marker of pyroptosis, suggesting that GLP-1RAs may inhibit pyroptosis and thereby prevent diabetic cardiomyopathy.[33] Multiple studies have documented the ability of GLP-1RAs to normalize oxidative stress markers characteristic of ferroptosis, including reductions in malondialdehyde (MDA), reactive oxygen species (ROS), and oxidized glutathione (GSSG), while restoring superoxide dismutase (SOD) activity and glutathione (GSH) content.[34–36] Through PI3K/Akt pathway activation, Exenatide has been shown to ameliorate ferroptosis-mediated injury in I/R mouse models,[35,36] potentially reducing

ferroptosis-related electrophysiological disturbances[25–27] (Table 1). The collective actions of GLP-1RAs on cell death pathways-through oxidative stress mitigation, inflammatory cytokine suppression, and adverse remodeling prevention-present a compelling, though not yet conclusively proven, mechanism that may contribute to arrhythmia risk reduction. While direct electrophysiological evidence remains to be established, the pathophysiological links between specific cell death modalities and arrhythmogenesis provide strong theoretical support for this hypothesis.

Improve Myocardial Metabolism

In cardiomyocytes, approximately 95% of ATP is generated via mitochondrial oxidative phosphorylation, while the remaining 5% is derived from glycolysis. Fatty acid oxidation accounts for roughly 60–90% of the energy required to sustain normal cardiac function, with the remainder being supplied by lactic acid, glucose, ketone bodies, and amino acids.[55] An imbalance in myocardial metabolic homeostasis is a key pathological basis for electrical and structural remodeling.[13,37,56,57] GLP-1RAs can modulate the myocardial metabolic network and influence the onset and progression of arrhythmias, either directly through effects on myocardial energy substrates and mitochondrial activity or indirectly through impacts on lipid deposition, as shown in Figure 1.

Firstly, GLP-1RAs exert direct antiarrhythmic effects by improving myocardial energy metabolism. This direct effect is achieved, on one hand, by optimizing the metabolic coupling between fatty acids and glucose. Ling et al showed that treatment with a GLP-1RA increased the Bcl-2/Bax ratio and reduced apoptosis in hypoxia-reoxygenated cardiomyocytes, as assessed by CCK-8 and Western blot assays. This protective effect was attenuated by PI3K inhibitors, highlighting the importance of the PI3K/AKT signaling pathway.[58] Subsequently, Rui et al reported that GLP-1RAs enhance glucose uptake in cardiomyocytes by promoting the translocation of glucose transporter 4 (GLUT4) via activation of the PI3K/AKT signaling pathway.[59] Semaglutide ameliorates cardiac remodeling in male mice by optimizing energy substrate utilization such as free fatty acids, glucose, and lipid through the Creb5/NR4a1 axis in the PI3K/AKT pathway.[52] These findings have been corroborated in experimental studies involving classical GLP-1RAs such as Liraglutide, Dulaglutide, and Semaglutide, as well as multi-target agonists like tirzepatide and retatrutide.[8,52,59] Zhong et al further indicated that GLP-1RAs not only enhance glucose oxidation but also decrease free fatty acid (FFA) uptake, thereby optimizing myocardial energy substrate utilization.[13] This leads to reduced lipotoxicity-induced myocardial injury and abnormal electrical activity, improved myocardial metabolic efficiency, and consequently mitigates lipotoxicity-related myocardial damage and electrophysiological disturbances.[13] Liraglutide has been shown to reduce triglycerides by 30.4 mg/dL, decrease visceral fat accumulation, and improve lipid profiles.[60] At the molecular level, GLP-1RAs, by activating the GLP-1R, modulate lipid metabolism through pathways including the suppression of hepatic lipogenesis via the AMPK/SIRT1/SREBP-1c axis and promoting macrophage cholesterol efflux through the LXRα-ABCA1 pathway, collectively improving plasma lipid profiles.[61] Recent studies have revealed that tirzepatide can lower LDL-C levels by 5–8% and elevate HDL-C levels, potentially mediated through Gastric inhibitory polypeptide (GIP) receptor-dependent lipolysis.[62–64] Additionally, clinical evidence suggests a positive correlation between serum vitamin D levels and endogenous GLP-1 activity, and the study inferred that the protective effects of GLP-1 on bone structure and metabolism are similar to those of vitamin D.[54] Dulaglutide has been found to ameliorate mitochondrial fragmentation in cardiac muscle cells and restore mitochondrial morphology and function in diabetic hearts, thus alleviating myocardial metabolic remodeling.[54] These metabolic corrections directly alleviate key arrhythmogenic substrates. By reducing systemic and ectopic cardiac lipid accumulation, GLP-1RAs mitigate lipotoxicity, decrease associated myocardial inflammation, and ameliorate fibrosis-each being a critical metabolic driver of structural and electrical remodeling that predisposes to arrhythmias.[13,65,66] Thus, beyond improving plasma lipid parameters, GLP-1RAs exert antiarrhythmic benefits by targeting the fundamental metabolic disturbances that underlie the development of arrhythmogenic substrates.

Further research has indicated that GLP-1RAs not only influence energy substrate utilization but also directly affect arrhythmogenesis by modulating mitochondrial respiratory chain activity. Batran et al demonstrated that GLP-1RAs activate AMPK signaling, inhibit the accumulation of harmful metabolites-such as long-chain acylcarnitines-generated during fatty acid β-oxidation, improve mitochondrial dysfunction caused by lipid toxicity, optimize mitochondrial respiratory chain activity, maintain stable ATP production, and reduce oxidative stress-induced arrhythmias associated with ROS overload.[56,57]

Table 1 Potential Mechanisms of Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RAs) on Arrhythmias: Animal Studies

GLP-1 RAs	Year	Test Models	Study Design	Targets or Signal Pathway	Effect	Outcomes	Refs.
Liraglutide	2023	T2DM Mice	0.25 mg/kg/d i.h.for 4 weeks	/	↑ atrial CV ↓ AF durations	Reduced AF and prevented atrial remodeling	[13]
	2023	Myocardial I/R injury rats	140 μg/kg/day i.p. for 7 days	GLP-1R/PI3K/Akt	↑cardiomyocytes ↓ cardiac enzyme	Inhibited necroptosis and reduced infarct size	[31]
	2021	Male Wistar rats with streptozotocin-induced diabetes	200 μg/kg/12 h i.p. for 4 weeks	/	↓ NLRP3 ↓ TNF-α ↓ IL-1 ↓ apoptosis	Attenuated apoptosis and myocardial fibrosis	[33]
	2016	Microvascular endothelial cells	1–100 nmol/L	GLP-1R/PI3K/Akt/survivin	↓ ROS ↑ SERCA2a	Suppress CMECs oxidative damage	[37]
	2023	Aged rats (24-month-old)	300 μg/kg/day for 4 weeks	IRS1-eNOS-PKG	↓ APD ↓ QRS ↓ ROS ↑I NCX	Recovered mitochondrial dysfunction and oxidative stress in aging hearts	[38]
	2021	Polymicrobial sepsis model mice	200 μg/kg/day i.p.for 3 days	/	↓ IL-6	Reduced vascular inflammation and ameliorates sepsis-induced endothelial dysfunction	[39]
	2022	The atrial fibroblasts of C57BL/6 mice (AngII pre-treatment for 24 h)	10 nmol/L, 50 nmol/L, 100 nmol/L in medium and continue incubation for 1 h	miR-21/PTEN/PI3K	↓ ECM deposition ↓cardiac fibroblasts	Reduced inflammation and inhibited remodeling	[40]
	2019	HFD -induced atherosclerotic mice	300 μg/kg/day i.h. for 4 weeks	/	↓ TNF-α ↓ IL-6	Reduced inflammation and attenuated atherosclerosis	[41]
	2023	Myocardial I/R diabetes mice	200 μg/kg/day i.h.for 4 weeks	AMPK/mTOR	↓ p-mTOR ↓ p62	Reduced infarct size and enhanced cardiac function	[42]
	2017	The Zucker diabetic fatty rat model	200 μg/kg/day i.h.for 8 weeks	AMPK/mTOR	↑ p-AMPK ↓ p-mTOR ↑ autophagy	Improved left ventricular functional status and alleviated myocardial fibrosis	[43]
	2020	Abdominal aortic constriction male SD rats	0.3 mg/kg/12 h i.h.for 16 weeks	mTOR/p70S6K	↓ LC3-II/LC3-I ↑ Beclin-1 ↓ p62 ↑ autophagy	Inhibited cardiac fibrosis and dysfunction	[44]
	2021	Pressure overload induced cardiac hypertrophy rats	0.3 mg/kg/twice day	K_{ATP} channels	↑ BCL-2 ↑ ATP	Ameliorated cardiac hypertrophy and apoptosis	[45]
	2022	High-carbohydrate induced MetS rats	0.3 mg/kg/day for 4 weeks	↑ K+ ↑ Ca^{2+}	↓ APD ↓ long-QT interval ↑ INCX	Mitigated electrical abnormalities, maintained Ca^{2+}-homeostasis in ventricular cardiomyocytes.	[46]
	2021	HFD-induced diabetes rats	200 μg/kg/12 h i.h.	↓ Ito	↓ QTc	Improved myocardial electrical remodeling and inhibited myocardial hypertrophy and fibrosis	[47]

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Exendin-4	2018	Adult male SD rats	In isolated perfused hearts (3 nmol/L)	/	↑ APD ↑ cardiac parasympathetic	Reduced ventricular arrhythmia susceptibility	[16]
	2021	Myocardial I/R injury rats	(0.140 μg/kg, i.v.), 10 min after LAD artery occlusion	↑ SIRT1 ↑ SIRT3	↑ MnSOD ↓ ROS ↓ ferroptosis	Reduced infarct size and preserved the function and structure of the left ventricle	[35]
	2021	Acute MI rats	10 μg/day i.p. for 7 days	Wnt1/β-catenin	↓ inflammatory cytokines ↓ ROS	Mitigated cardiac fibrosis, and ventricular remodeling	[48]
	2020		25 nmol/kg/day i.p. for 6 weeks	PARP1/NF-κB Axis in A SIRT1-Dependent Mechanism	↓ TNF-α ↓ IL-6 ↓ ROS	Inhibited structural remodeling and improved left ventricle function	[49]
	2017	HF rat model after MI	10 μg/kg/day i.p. for 4 weeks	↑ eNOS/cGMP/PKG ↓ CaMKII	↑ SERCA2a ↓ phosphorylated RyR ↑ICa-L	Improved cardiac remodeling and maintained Ca^{2+}-homeostasis	[50]
	2021	HFD-induced obese rats	Intrapelvic injection (1 μg)	Renal nerve–neprilysin–GLP-1 pathway	↓ renal sympathetic nerve ↑ urine excretion	Reduced cardiac volumetric load and reduced risk factors for arrhythmias	[51]
	2018	Adult male SD rats	In vivo (5 μg/kg intravenously) and isolated perfused hearts (3 nmol/L)	Acetylcholine and nitric oxide	↓ cardiac parasympathetic ↑ APD ↑HR	Opposed the effects of β-adrenoceptor stimulation on cardiac ventricular excitability and reduced ventricular arrhythmic potential via stimulation of cardiac parasympathetic	[16]
Semaglutide	2023	Myocardial I/R rats	0.3 mg/kg	PKG/PKCε/ERK1/2	↓ apoptosis	Suppressed cardiomyocyte apoptosis and reduced infarct size	[29]
	2024	Pressure overload-induced HF male mice	60 μg/kg	Creb5/NR4a1	↑ FA oxidation ↑ ATP	Improved cardiac function and reduced hypertrophy and fibrosis	[52]
	2024	DCM mice	0.15 mg/kg/week i.h. for 8 weeks	Sirt1/AMPK ↑ Cx43	↓ oxidative stress ↓ apoptosis ↓ RR ↓ QRS ↓ QT ↓ QTc	Improved cardiac function and electrophysiological remodelling	[30]
	2025	Mice with diabetes induced by HFD/streptozotocin	100μg·kg/day i.h. for 8 weeks	Sirt3-dependent RKIP pathway TBK1-NF-κB signalling pathway	↓ TNF-α ↓ IL-6 ↓ ROS ↓ apoptosis	Ameliorated myocardial fibrosis and improved cardiac function	[53]
GLP-1 (7–36) amide	2023	PV and SAN tissue from Male New Zealand white rabbits	(1, 10, and 100 nM) of GLP-1 (7–36) amide in normal Tyrode's solution for 20 min	PKA CaMKII NCX	↓ $I_{Na\text{-}Late}$ ↓ I_{NCX} ↓ $I_{Ca\text{-}L}$	Regulated Ca^{2+}-homeostasis and reduced PV arrhythmogenesis	[14]
Exenatide	2013	Myocardial I/R rats	10 μg/kg/day i.p. for 2 weeks	PI3K/Akt	↓ ROS ↓ ferroptosis	Reduced infarct size and enhanced cardiac function	[36]
Dulaglutide	2022	Mice with HFD/streptozotocin-induced T2DM	0.6 mg·kg−1·week−1 i.h. for 8 weeks	/	↓ hyperlipidemia ↓ mitochondria fragmentation	Improved myocardial metabolic remodeling	[54]

Notes: A black upward arrow indicates an increase, while a black downward arrow indicates a decrease.

Abbreviations: T2DM, Type 2 Diabetes Mellitus; i.h., subcutaneous injections; CV, Conduction Velocity; AF, Atrial fibrillation; I/R, ischemia/reperfusion; i.p., Intraperitoneal injection; GLP-1R, Glucagon-like peptide-1 receptor; PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B; NLRP3, nod-like receptor family pyrin domain containing 3; TNF-α, tumor necrosis factor-α; IL-1, interleukin-1; ROS, reactive oxygen species; SERCA2a, Sarcoplasmic/Endoplasmic Reticulum Calcium ATPase 2a; CMECs, Microvascular endothelial cells; IRS1, Insulin Receptor Substrate 1; eNOS, endothelial nitric oxide synthase; PKG, Protein kinase G; APD, Action potential duration; I_{NCX}, Na^+/Ca^{2+} exchanger currents; IL-6, interleukin-6; AngII, Angiotensin II; miR-21, microRNA-21; PTEN, Phosphatase and tensin homolog; ECM, Extracellular Matrix; HFD, high-fat diet; AMPK, Adenosine 5′-monophosphate (AMP)-activated protein kinase; mTOR, Mammalian Target of Rapamycin; p-mTOR, Phosphorylated mammalian target of rapamycin; p62, Sequestosome 1; p-AMPK, Phosphorylated AMP-activated protein kinase; SD, Sprague-Dawley; p70S6K, p70 Ribosomal Protein S6 Kinase; LC3-II, Microtubule-associated protein 1A/1B-light chain 3-phosphatidylethanolamine conjugate; LC3-I, Microtubule-associated protein 1A/1B-light chain 3; K_{ATP} ATP-sensitive potassium channel; BCL-2, B-cell lymphoma-2; ATP, adenosine triphosphate; MetS, metabolic syndrome; Ito, Transient outward potassium current; QTc, Corrected QT interval; i.v., intravenous injection; LAD, Left Anterior Descending artery; SIRT1, silent information regulator 1; SIRT3, silent information regulator 3; MnSOD, Manganese Superoxide Dismutase; MI, myocardial infarction; PARP1, poly (ADP-ribose) polymerase-1; NF-κB, Nuclear factor kappa-B; cGMP, Cyclic Guanosine Monophosphate; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; RyR, Ryanodine receptor; HR, heart rate; PKCε, Protein kinase C epsilon; ERK1/2, Extracellular regulated protein kinases 1/2; HF, heart failure; Creb5, cAMP Responsive Element Binding Protein 5; NR4a1, Nuclear Receptor Subfamily 4 Group A Member 1; FA, fatty acid; DCM, diabetic cardiomyopathy; Cx43, Connexin 43; RR, R wave to R wave interval; RKIP, Raf kinase inhibitor protein; TBK1, TANK-binding kinase 1; PV, pulmonary vein; SAN, Sinoatrial node; PKA, Protein Kinase A; NCX, Na^+/Ca^{2+} exchanger; $I_{Na\text{-}Late}$, Late Sodium Current; $I_{Ca\text{-}L}$, L-type calcium current.

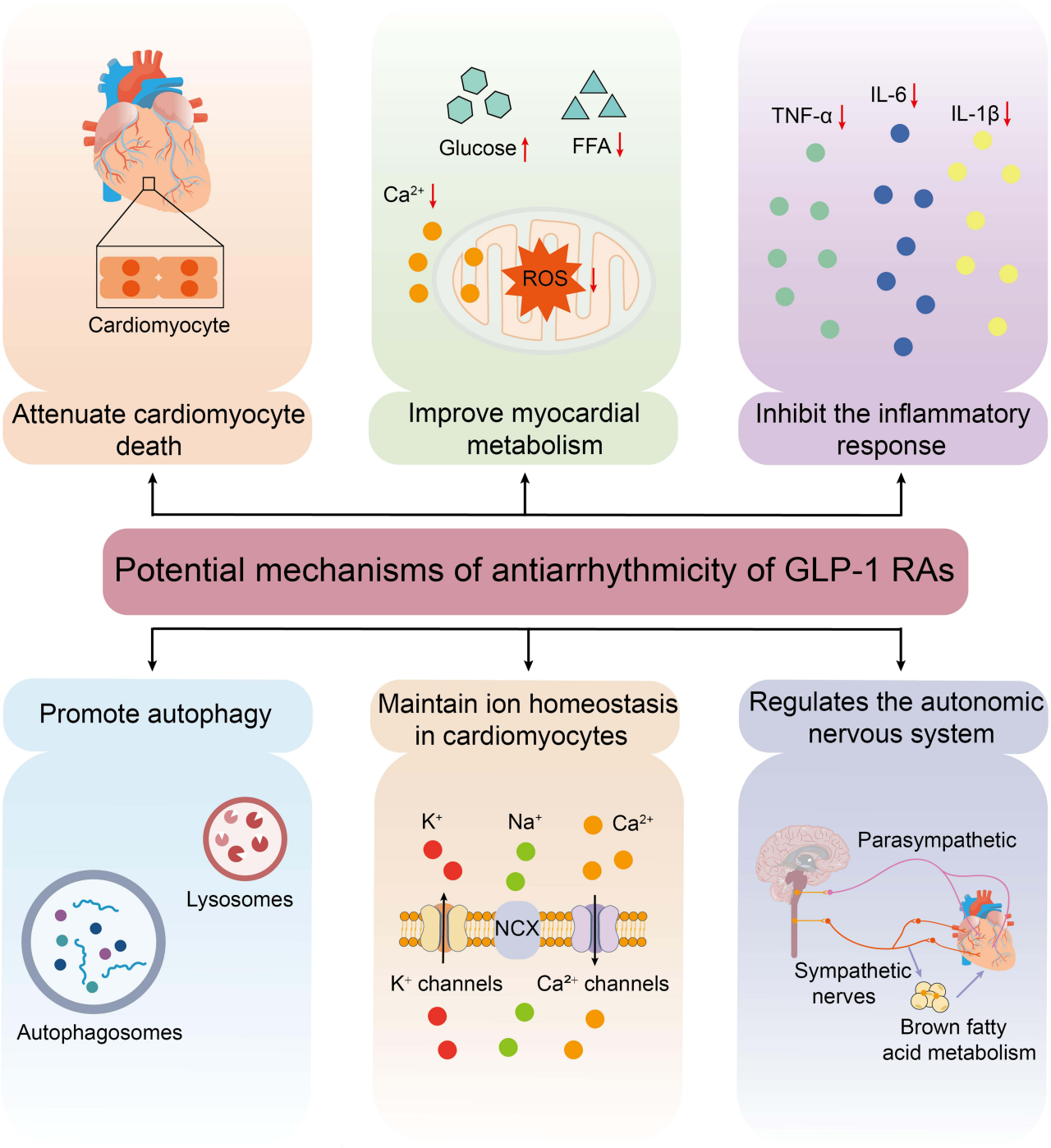

Figure 1 Potential mechanisms of antiarrhythmicity of GLP-1RAs. Mechanisms mainly include attenuating cardiomyocyte death, improving myocardial metabolism, inhibiting the inflammatory response, promoting autophagy, maintaining ion homeostasis in cardiomyocytes and regulating the autonomic nervous system. A red upward arrow indicates an increase, while a red downward arrow indicates a decrease. A black upward arrow indicates the outflow of potassium ions, while a black downward arrow indicates the inflow of calcium ions.

Abbreviations: GLP-1RAs, Glucagon-like peptide-1 receptor agonists; FFA, free fatty acid; ROS, reactive oxygen species; IL-1β, interleukin 1β; IL-6, interleukin 6; TNF-α, Tumor necrosis factor-α; NCX, Na^+/Ca^{2+} exchanger.

Liraglutide activates the GLP-1R/PI3K/Akt/survivin pathway, which suppresses the SR-Ca^{2+}-XO-ROS axis, reduces ROS generation, preserves calcium homeostasis, and decreases the susceptibility to arrhythmias.[37] In aged rat models, Liraglutide participates in oxidative stress-induced cardiac injury via the IRS1-eNOS-PKG pathway and significantly improves QRS duration. This mechanism reduces the risk of electrophysiological abnormalities at the source of energy metabolism by maintaining mitochondrial dynamic balance and oxidative phosphorylation efficiency.[38]

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Secondly, GLP-1RAs exert indirect antiarrhythmic effects through systemic metabolic regulation. D'Marco et al showed that GLP-1RAs reduce systemic insulin resistance and visceral adiposity by suppressing central appetite and enhancing peripheral insulin sensitivity, thereby decreasing ectopic lipid deposition in the myocardium. Liraglutide delays gastric emptying, enhances satiety, and results in an average weight loss of 1.5–2.0 kg.[67] Obese patients treated with a weekly 1.5 mg dose of Dulaglutide achieved an average weight loss of 1.44Kg.[68] GLP-1RAs favorably modulate the lipid profile by reducing levels of triglycerides, total cholesterol, and LDL-cholesterol, with minimal effects on HDL-cholesterol. This metabolic improvement, along with a consequent reduction in blood pressure, collectively alleviates cardiac workload and mitigates overall cardiovascular risk. Obesity is often accompanied by chronic inflammation. By reducing weight and improving metabolism, the inflammatory response can also be reduced, thereby reducing the risk of arrhythmia. Clinical evidence supports its efficacy in reducing the risk of atrial fibrillation in both diabetic and non-diabetic populations[38,67,69] (Table 1).

Overall, GLP-1RAs significantly lower the risk of arrhythmias by directly optimizing myocardial energy metabolism involving glucose and fatty acids, as well as through indirect preventive mechanisms, particularly demonstrating notable efficacy in preventing atrial fibrillation. Its cardiovascular protective effects are independent of traditional metabolic parameters, offering novel therapeutic targets for the prevention and treatment of arrhythmias. Future research will focus on uncovering deeper insights into the drug's metabolic pathways and potential new targets.

Inhibit the Inflammatory Response

Accumulating evidence indicates that inflammation plays a central role in the pathogenesis of arrhythmias, primarily through inducing electrophysiological and structural remodeling of cardiomyocytes.[70–75] Chronic inflammatory states may result in impaired tissue repair and subsequent fibrosis. Myocardial fibrosis constitutes a key component of structural remodeling and serves as a critical substrate for the maintenance of sustained arrhythmias.[76,77] Although cardiac inflammation is most commonly associated with conditions such as myocardial infarction, heart failure, and myocarditis, systemic inflammatory disorders also confer a significant risk of arrhythmias. Clinical observations demonstrate that patients with rheumatoid arthritis or systemic lupus erythematosus present with significantly elevated plasma concentrations of characteristic inflammatory biomarkers, including C-reactive protein (CRP), interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor-alpha. These patients concurrently show substantial leukocyte infiltration in atrial tissues, a pathological combination that may collectively heighten arrhythmia susceptibility.[78,79]

Emerging evidence suggests that GLP-1RAs effectively attenuate the production of major inflammatory mediators, including TNF-α, IL-6, and IL-1β, as shown in Figure 1, primarily through inhibition of NF-κB activation.[80,81] In rat models of experimentally induced myocardial infarction via left anterior descending coronary artery ligation, Exendin-4 significantly reduced cardiac fibrosis, electrophysiological disturbances, and structural remodeling, potentially via modulation of the Wnt1/β-catenin signaling pathway.[48] Moreover, Exendin-4 ameliorated post-infarction cardiac remodeling, possibility through SIRT1-dependent suppression of the PARP1/NF-κB axis. Specifically, Exendin-4 improved cardiac architecture and left ventricular function while decreasing TNF-α and IL-6 mRNA and protein expression, as well as NF-κB p65 activation. Furthermore, Exendin-4 inhibited the interaction of PARP1 with both TGF-β1 and NF-κB p65.[49] Beyond Exendin-4, Liraglutide exhibited anti-inflammatory effects in a polymicrobial sepsis model (cecal ligation and puncture), where it attenuated inflammation via the AMPKα1 and cAMP/PKA signaling pathways.[39] Furthermore, Liraglutide suppresses angiotensin II–induced proliferation, migration, and extracellular matrix deposition in cardiac fibroblasts through modulation of the miR-21/PTEN/PI3K pathway, possibly representing an additional mechanism by which GLP-1RAs counteract inflammation and improve cardiac remodeling.[40] In diabetic mice, Semaglutide could alleviate cardiac inflammation by inhibiting the RKIP-dependent TBK1/NF-κB pathway.[51] It is worth noting that, as a clear risk factor for the development of arrhythmia, atherosclerosis itself is driven by inflammation. Liraglutide can inhibit the secretion of TNF-α and IL-1β, thereby possibly reducing the risk of atherosclerosis and related arrhythmias.[41] The clinical research conducted by Marchen's team provides support for this transformation potential. In a study on T2DM patients with dyslipidemia, 180-day GLP-1RA treatment significantly reduced key biochemical markers for the initiation of atherosclerosis, including oxidized low-density lipoprotein (OxLDL), TNF-α, and IL-1β. Additionally, another clinical evidence suggests that there may be a synergistic anti-inflammatory effect between GLP-1 and vitamin

D/calcitriol, which is mediated by regulating p65, IL-6, IL-8.[55] These findings collectively indicate that GLP-1RAs can significantly reduce the concentration of pro-inflammatory cytokines, highlighting their dual potential as a therapeutic strategy in reducing atherosclerotic burden and the risk of arrhythmia[82] (Table 1).

Promote Autophagy

Autophagy functions as a critical cellular quality control mechanism by degrading damaged proteins, organelles, and macromolecules through lysosomal pathways, thereby preserving cellular homeostasis.[83,84] This process is fundamentally involved in the regulation of multiple physiological systems, particularly the cardiovascular system, where its dysregulation has been strongly associated with the development of arrhythmias.[85–88] For example, cardiomyocyte-specific deletion of autophagy-related gene 7 (ATG7) results in impaired autophagic activity, leading to myocardial fibrosis, contractile dysfunction, and heightened susceptibility to arrhythmias.[89] Conversely, excessive activation of autophagy-such as that induced by sunitinib-can disrupt calcium homeostasis by degrading essential proteins such as myosin light chain kinase 3 (MYLK3), thereby further promoting arrhythmogenesis.[90] Collectively, these findings highlight autophagy as a promising therapeutic target for the prevention and treatment of cardiac arrhythmias.

Notably, GLP-1RAs exert pleiotropic protective effects on the cardiovascular system through activation of the autophagy pathway.[26,42,43] Experimental studies have shown that Liraglutide activates autophagy in cardiomyocytes via the AMPK-mTOR signaling pathway, resulting in reduced infarct size and attenuated ischemia-reperfusion injury in diabetic animal models.[42] Similarly, in the Zucker diabetic rat model, it is also shown that Liraglutide can improve myocardial damage by promoting autophagy.[43] Zheng et al further revealed that Liraglutide improves cardiac fibrosis and dysfunction by suppressing the mTOR/p70S6K signaling pathway and enhancing autophagic activity.[44] Yu et al further demonstrated that both Exendin-4 and Liraglutide can alleviate high glucose-induced cardiomyocyte injury by restoring mTOR/ULK1-dependent autophagy,[91] suggesting that they may exert potential antiarrhythmic effects. Given that autophagy contributes to electrophysiological stability through the removal of dysfunctional mitochondria, reduction of oxidative stress, and prevention of calcium overload[86,92,93] (Table 1), the autophagy-enhancing properties of GLP-1RAs could indirectly contribute to their potential antiarrhythmic effects, as outlined in Figure 1. However, direct evidence linking GLP-1RA-induced autophagy to arrhythmia suppression is still limited, these mechanistic insights suggest a promising pathway that warrants further investigation.

Maintain Ion Homeostasis in Cardiomyocytes

Cardiac contractions, triggered by action potential (AP), are mediated through the physiological mechanism of excitation-contraction coupling.[94] The generation of AP involves the coordinated opening and closing of various transmembrane proteins, including ion channels and transporters such as pumps and exchangers. Cardiac arrhythmias can arise from abnormal impulse formation, such as early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs), or from abnormal conduction of electrical activity in the heart.[95] In cardiomyocytes, potassium (K^+), sodium (Na^+), and calcium (Ca^{2+}) ions play pivotal roles in regulating the AP cycle. The following summarizes the molecular mechanisms by which GLP-1RAs regulate cardiac ion homeostasis and influence electrical remodeling, as shown in Figure 1.

K^+ Channels

K^+ channels constitute the most diverse class of ion channels in cardiac tissue and are critically involved in all phases of the cardiomyocyte AP. These channels primarily regulate the amplitude and duration of the action potential, while also modulating myocardial excitability and autorhythmicity.[96,97] Cardiomyocyte K^+ channel dysfunction is closely associated with various types of arrhythmias, particularly with arrhythmias associated with atrial and ventricular remodeling.[98–101] The K^+ channel has become an important therapeutic target for the development of antiarrhythmic drugs.[102]

Experimental studies have demonstrated that Liraglutide exerts cardioprotective effects by modulating K_{ATP} channel-mediated signaling pathways, thereby alleviating cardiac hypertrophy and apoptosis and reducing susceptibility to arrhythmias.[45] In rat models of metabolic syndrome, Liraglutide administration significantly corrected QT interval prolongation by shortening the AP duration and restoring impaired potassium currents.[46] Moreover, in diabetic rat

hearts, Liraglutide was shown to normalize both the expression levels and spatial distribution of Cx43 and transient outward potassium (I_{to}) channels, thereby mitigating pathological electrical remodeling.[47] Studies demonstrate that Exenatide exerts antiarrhythmic effects through dual inhibition of atrial-specific hKv1.5 potassium channels and hNav1.5 sodium channels, prolonging action potential duration and reducing atrial fibrillation susceptibility. Notably, this mechanism operates independently of GLP-1R activation, providing experimental evidence for the direct antiarrhythmic properties of GLP-1RAs.[103] Collectively, these findings indicate that GLP-1RAs confer myocardial protection and ameliorate electrical remodeling through the regulation of K^+ ion homeostasis in cardiomyocytes, ultimately reducing the risk of arrhythmias.

Na^+ and Ca^{2+} Homeostasis

The precise regulation of Na^+ and Ca^{2+} ion homeostasis represents a fundamental determinant of cardiac electrophysiological stability.[104] As established in previous studies,[105] the coordinated activity of key ion channels and transporters-including ryanodine receptor 2 (RYR2), sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA), Na^+/Ca^{2+} exchanger (NCX), and L-type calcium channels ($I_{Ca,L}$)-governs the delicate balance of intracellular ion concentrations essential for normal cardiac rhythm. Enhanced inward currents through $I_{Ca,L}$, late sodium current ($I_{Na,L}$), or NCX current (I_{NCX}) are closely associated with EADs, which can lead to excessive prolongation of the AP. Furthermore, elevated intracellular calcium levels activate the NCX exchanger, generating an inward current that promotes the occurrence of DADs. When either EADs or DADs reach the threshold for cellular excitation, triggered activity may occur, potentially initiating reentrant circuits, an important mechanism underlying arrhythmia generation. Several comprehensive reviews provide further details and references regarding ion homeostasis-related arrhythmias.[106–109]

Encouragingly, research in this field has remained a consistent focus. Accumulating evidence suggests that GLP-1RAs exert cardioprotective effects and improve cardiac electrical remodeling by modulating intracellular Na^+ and Ca^{2+} homeostasis, thereby reducing the risk of arrhythmias. Durak et al reported that Liraglutide restored normal electrical function and Ca^{2+} homeostasis in ventricular cardiomyocytes of metabolic syndrome (MetS) rats via normalization of I_{NCX}.[46] Chen et al found that Exendin-4 improves Ca^{2+} handling and attenuates cardiac remodeling by activating the eNOS/cGMP/PKG pathway and inhibiting the Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) pathway.[50] Similarly, Chan et al demonstrated that GLP-1RAs may reduce the incidence of pulmonary vein arrhythmias by modulating PKA, CaMKII, and NCX activity, as well as maintaining intracellular Ca^{2+} homeostasis, such as by decreasing L-type Ca^{2+} current, NCX current, and late Na^+ current[14] (Table 1). This cumulative evidence provides a strong scientific basis for considering GLP-1RAs as promising candidates for arrhythmia therapy.

Regulates the Autonomic Nervous System

The autonomic nervous system, comprising the sympathetic and parasympathetic divisions, plays a pivotal role in modulating cardiac electrophysiology and arrhythmogenesis.[110] Dysfunction of the autonomic nervous system is associated with a spectrum of arrhythmias and related conditions, including atrial fibrillation, ventricular tachycardia, long QT syndrome, catecholamine-sensitive polymorphic ventricular tachycardia, Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy, ventricular fibrillation, and sudden cardiac death.[111–115] Autonomic nervous system regulation therapy has become the basis for the treatment of arrhythmia.[110,116,117] For example, β-blockers, which treat arrhythmia by inhibiting the activity of sympathetic nerves, have been the cornerstone of the prevention and treatment of cardiovascular diseases such as arrhythmia.[110] Studies have shown that GLP-1RAs can stimulate parasympathetic neurons through acetylcholine and nitric oxide to counteract the activation of sympathetic nerves, reduce cardiac ventricular excitability, and reduce the occurrence of arrhythmia.[16] Exendin-4 can reduce renal sympathetic nerve activity, promote urine excretion and inhibit sodium reabsorption by renal tubules, reduce cardiac volume load, and reduce the risk factors for arrhythmia.[51] GLP-1RAs can also regulate the sympathetic nervous system, regulate lipid and brown fatty acid metabolism, improve myocardial metabolism, and thus reduce the occurrence of atrial fibrillation[13] (Table 1). However, some studies have reported that GLP-1RAs can increase heart rate by regulating autonomic nervous system and activating atrial GLP-1R, causing increased myocardial oxygen consumption and increasing the risk of arrhythmia.[118] However, current evidence suggests that moderate GLP-1RAs do not significantly increase heart rate in

patients to induce arrhythmia, and GLP-1RAs-induced heart rate increase does not increase the risk of cardiovascular events in diabetic patients and patients with cardiovascular disease.[119] On the contrary, in some heart disease conditions, an appropriate increase in heart rate may be beneficial.[120] Of course, the mechanism by which GLP-1RAs resist arrhythmia by regulating the autonomic nervous system may need further study.

The Existing Studies on GLP-1RAs Antiarrhythmic are Insufficient

The antiarrhythmic effect of GLP-1RAs is relatively clear, but there are many shortcomings in the existing studies. A large number of literature have proved that intestinal microbiota imbalance and its metabolites are closely related to arrhythmia, which can cause myocardial fibrosis, lead to cardiac remodeling, and promote the occurrence of arrhythmia.[121,122] As a novel drug for the treatment of metabolic diseases (T2DM and obesity), GLP-1RAs have been shown to exert anti-inflammatory, immunosuppressive, cardiovascular and kidney protection by improving intestinal microbiota imbalance and regulating its metabolites.[123–125] However, it has not been reported in the literature that GLP-1RAs can play a role in the prevention and treatment of arrhythmia by regulating intestinal microbiota imbalance and its metabolites. The effects of GLP-1RAs on cardiac electrophysiology by modulating the gut microbiota can be further investigated by optical mapping and whole-cell patch clamp techniques. The relationship between autophagy dysregulation and arrhythmogenesis follows a biphasic pattern, wherein both impaired and excessive autophagic activity may contribute to cardiac electrical instability.[126] Current research indicates that GLP-1RAs can promoting autophagy, thereby exhibiting antiarrhythmic properties.[43,86] However, whether these agents induce excessive autophagy activation, with subsequent arrhythmic consequences, remains a critical but understudied aspect of their treatment regimens. Anniek et al showed that GLP-1RAs could directly act on the Sinoatrial node (SAN) cells of female pigs, causing the increase of heart rate and the shortening conduction time from atrium to ventricle, and shortening the action potential duration of SAN cells, which seemed to provide a way to treat chronic arrhythmia,[127] and further studies could be conducted to confirm its feasibility. Emerging evidence indicates that GLP-1R is expressed across multiple cardiovascular cell types, including mononuclear macrophages, vascular smooth muscle cells, and endothelial cells.[8,9] Given the established role of mononuclear macrophages in arrhythmogenesis through mechanisms such as inflammatory cytokine release, fibrosis promotion, and electrical remodeling,[128,129] it is plausible that GLP-1RAs may modulate arrhythmia susceptibility via macrophage-mediated pathways. However, the current understanding of this potential interaction remains limited, with few studies directly investigating the correlation between GLP-1RA-mediated macrophage regulation and cardiac electrophysiological outcomes. At present, the antiarrhythmic effects of various GLP-1RAs are relatively clear, but whether all GLP-1RAs have antiarrhythmic effects remains to be discussed. Liraglutide is currently the most widely studied drug in GLP-1RAs,[12] and there are relatively few studies on other types of GLP-1RAs. Subsequent studies on other types of GLP-1RAs can be increased to discover more antiarrhythmic mechanisms of GLP-1RAs. At present, the antiarrhythmic studies of GLP-1RAs mainly focus on the animal level and the cellular level, and the clinical experimental studies are relatively few. In the future, more clinical studies may be needed to more fully clarify the efficacy and safety of GLP-1RAs antiarrhythmic.

The Side Effects and Drug Resistance of GLP-1RAs

While the preceding discussion has detailed the promising antiarrhythmic potential of GLP-1RAs, a comprehensive evaluation necessitates a balanced consideration of their common side effects and the clinically pertinent issue of drug resistance. The therapeutic application of GLP-1RAs is invariably accompanied by a spectrum of adverse effects, predominantly of a gastrointestinal nature.[11,130] Other rare but serious potential risks include diabetic retinopathy,[130,131] pancreatitis, and pancreatic cancer,[132,133] warranting vigilance during treatment. In addition, a notable side effect is a modest, dose-dependent increase in heart rate.[118] As discussed in Regulates the Autonomic Nervous System, this is believed to be mediated through direct action on the sinoatrial node and modulation of the autonomic nervous system.[127] Importantly, current evidence suggests that this increase does not elevate the risk of major adverse cardiovascular events and may even be beneficial in certain heart failure contexts.[119,120]

True pharmacodynamic tolerance to GLP-1RAs, is not widely reported in long-term clinical studies.[5,11] Instead, the perceived diminution of effect, particularly for weight loss, often represents a plateau as the body reaches a new metabolic steady state, rather than a loss of drug efficacy.[11,68,134] Strategies to mitigate this include dose escalation, as per clinical guidelines, and combination therapy with other agents like SGLT2 inhibitors, which has shown synergistic benefits.[132,135]

Conclusion

The emerging role of GLP-1RAs in arrhythmia management signifies a paradigm shift in the understanding of cardiac electrophysiology, where metabolic regulation intersects with electrical stability. In contrast to conventional antiarrhythmic agents that primarily target specific ion channels, GLP-1RAs exert a broad spectrum of cardioprotective effects, encompassing cellular survival, metabolic optimization, inflammatory modulation, autophagic regulation, ion homeostasis, and neural balance (Table 1). This multifaceted mechanism uniquely positions them to address the complex pathophysiological processes underlying arrhythmogenesis, particularly in patients with metabolic impairments. Although preclinical evidence is robust, translating these findings into clinical practice necessitates rigorous investigation into the relative importance of these mechanisms, agent-specific electrophysiological profiles, and their integration with established therapeutic strategies. Definitive validation will require not only demonstrating a reduction in arrhythmia burden but also elucidating the fundamental biological pathways involved, which may lead to novel insights into the interplay between cardiac metabolism and electrophysiology. As this field advances, future research should incorporate systems biology methodologies, advanced cardiac electrophysiology tools, and innovative clinical trial designs to fully harness the therapeutic potential of GLP-1RAs while ensuring their safe and effective incorporation into arrhythmia management protocols.

Abbreviations

GLP-1RAs, Glucagon-Like Peptide-1 Receptor Agonists; GLP-1, Glucagon-like peptide-1; GLP-1R, Glucagon-like peptide-1 receptor; GPCR, G-protein-coupled receptor; SGLT2, Sodium-Glucose Cotransporter 2; T2DM, type 2 diabetes Mellitus; I/R, ischemia/reperfusion; PKG, Protein kinase G; PKCε, Protein kinase C epsilon; ERK1/2, Extracellular regulated protein kinases 1/2; SIRT1, silent information regulator 1; AMPK, Adenosine 5′-monophosphate (AMP)-activated protein kinase; Cx43, Connexin 43; DCM, diabetic cardiomyopathy; PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B; NLRP3, nod-like receptor family pyrin domain containing 3; MDA, malondialdehyde; ROS, reactive oxygen species; GSSG, glutathione; SOD, superoxide dismutase; GSH, glutathione; ATP, adenosine triphosphate; BCL-2, B-cell lymphoma-2; BAX, BCL2-Associated X Protein; CCK-8, Cell Counting Kit-8; GLUT4, glucose transporter 4; Creb5, cyclic adenosine monophosphate Responsive Element Binding Protein 5; NR4a1, Nuclear Receptor Subfamily 4 Group A Member 1; FFA, free fatty acid; SREBP-1c, sterol regulatory element binding protein-1c; LXRα, Liver X Receptor α; ABCA1, ATP-binding cassette transporter A1; LDL-C, Low-Density Lipoprotein Cholesterol; HDL-C, High-Density Lipoprotein Cholesterol; GIP, Gastric inhibitory polypeptide; IRS1, Insulin Receptor Substrate 1; eNOS, endothelial nitric oxide synthase; CRP, C-reactive protein; TNF-α, tumor necrosis factor-α; IL-1, interleukin-1; IL-6, interleukin-6; IL-8, interleukin-8; NF-κB, Nuclear factor kappa-B; PARP1, poly(ADP-ribose) polymerase-1; AMPKα1, AMP-activated protein kinase alpha 1 catalytic subunit; cAMP, cyclic adenosine monophosphate; PKA, Protein Kinase A; miR-21, microRNA-21; PTEN, Phosphatase and tensin homolog; RKIP, Raf kinase inhibitor protein; TBK1, TANK-binding kinase 1; OxLDL, oxidized low-density lipoprotein; ATG7, autophagy-related gene 7; MYLK3, myosin light chain kinase 3; mTOR, Mammalian Target of Rapamycin; p70S6K, p70 Ribosomal Protein S6 Kinase; ULK1, Unc-51-like kinase 1; AP, action potential; EADs, early afterdepolarizations; DADs, delayed afterdepolarizations; K^+, potassium ions; Na^+, sodium ions; Ca^{2+},calcium ions; K_{ATP}, ATP-sensitive potassium channel; Ito, Transient outward potassium current; hKv1.5, potassium voltage-gated channel subfamily A member 5; hNav1.5; sodium voltage-gated channel alpha subunit 5; SERCA2a, Sarcoplasmic/Endoplasmic Reticulum Calcium ATPase 2a; I_{NCX}, Na^+/Ca^{2+} exchanger currents; NCX, Na^+/Ca^{2+} exchanger; $I_{Na\text{-}Late}$, Late Sodium Current; $I_{Ca\text{-}L}$, L-type calcium current; RyR2, Ryanodine receptor2; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; MetS, metabolic syndrome; cGMP, Cyclic Guanosine Monophosphate; SAN, Sinoatrial node; i.h., subcutaneous injections; CV, Conduction Velocity; AF, Atrial fibrillation; i.p., Intraperitoneal injection; CMECs, Microvascular endothelial cells; APD, Action potential duration; AngII, Angiotensin II; ECM, Extracellular Matrix; HFD, high-fat diet; p-mTOR, Phosphorylated mammalian target of rapamycin; p62, Sequestosome 1; p-AMPK, Phosphorylated AMP-activated protein kinase; SD, Sprague-Dawley; LC3-II, Microtubule-associated protein 1A/1B-light chain 3-phosphatidylethanolamine conjugate; LC3-I, Microtubule-associated protein 1A/1B-light chain 3; QTc, Corrected QT interval; i.v., intravenous injection; LAD, Left Anterior Descending artery; SIRT3, silent information regulator 3;

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MnSOD, Manganese Superoxide Dismutase; MI, myocardial infarction; HR, heart rate; HF, heart failure; FA, fatty acid; RR, R wave to R wave interval; PV, pulmonary vein.

Data Sharing Statement

The current study was based on the results of relevant published studies.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflict of interest to declare.

References

1. Sivakumar R, Senghor KAA, Vinodhini VM, Kumar JS. Metformin: an old drug with new tricks-promising role in vascular aging and cardioprotection. *Drugs Aging*. 2025;42(8):709–731. doi:10.1007/s40266-025-01215-3
2. Fujiki S. Antiarrhythmic potential of SGLT2 inhibitors: mechanistic insights and clinical evidence. *J Cardiol*. 2025. doi:10.1016/j.jjcc.2025.09.018
3. Chaiyakunapruk N, Tan X, Liang Y, Guevarra M, Xie L, Cheng AYY. Real-world effectiveness of adding newer generation GLP-1RA to SGLT2i in type 2 diabetes. *Cardiovasc Diabetol*. 2025;24(1):177. doi:10.1186/s12933-025-02737-1
4. Gajjar A, Raju AK, Gajjar A, et al. SGLT2 inhibitors and GLP-1 receptor agonists in cardiovascular-kidney-metabolic syndrome. *Biomedicines*. 2025;13(8):1924. doi:10.3390/biomedicines13081924
5. Mullur N, Morissette A, Morrow NM, Mulvihill EE. GLP-1 receptor agonist-based therapies and cardiovascular risk: a review of mechanisms. *J Endocrinol*. 2024;263(1):e240046. doi:10.1530/JOE-24-0046
6. Campbell JE, Drucker DJ. Pharmacology, physiology, and mechanisms of incretin hormone action. *Cell Metab*. 2013;17(6):819–837. doi:10.1016/j.cmet.2013.04.008
7. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. *Gastroenterology*. 2007;132(6):2131–2157. doi:10.1053/j.gastro.2007.03.054
8. Ussher JR, Drucker DJ. Glucagon-like peptide 1 receptor agonists: cardiovascular benefits and mechanisms of action. *Nat Rev Cardiol*. 2023;20(7):463–474. doi:10.1038/s41569-023-00849-3
9. Ma X, Liu Z, Ilyas I, et al. GLP-1 receptor agonists (GLP-1RAs): cardiovascular actions and therapeutic potential. *Int J Biol Sci*. 2021;17(8):2050–2068. doi:10.7150/ijbs.59965
10. Ruff CT, Baron M, Im K, O'Donoghue ML, Fiedorek FT, Sabatine MS. Subcutaneous infusion of exenatide and cardiovascular outcomes in type 2 diabetes: a non-inferiority randomized controlled trial. *Nat Med*. 2022;28(1):89–95. doi:10.1038/s41591-021-01584-3
11. Drucker DJ. The benefits of GLP-1 drugs beyond obesity. *Science*. 2024;385(6706):258–260. doi:10.1126/science.adn4128
12. Chowdhary A, Thirunavukarasu S, Joseph T, et al. Liraglutide improves myocardial perfusion and energetics and exercise tolerance in patients with type 2 diabetes. *J Am Coll Cardiol*. 2024;84(6):540–557. doi:10.1016/j.jacc.2024.04.064
13. Zhong J, Chen H, Liu Q, Zhou S, Liu Z, Xiao Y. GLP-1 receptor agonists and myocardial metabolism in atrial fibrillation. *J Pharm Anal*. 2024;14(5):100917. doi:10.1016/j.jpha.2023.12.007
14. Chan CS, Lin FJ, Chen YC, et al. Glucagon-like peptide-1 receptor activation reduces pulmonary vein arrhythmogenesis and regulates calcium homeostasis. *Int J Mol Sci*. 2023;24(17):13100. doi:10.3390/ijms241713100
15. Nakamura H, Niwano S, Niwano H, et al. Liraglutide suppresses atrial electrophysiological changes. *Heart Vessels*. 2019;34(8):1389–1393. doi:10.1007/s00380-018-01327-4
16. Ang R, Mastitskaya S, Hosford PS, et al. Modulation of cardiac ventricular excitability by GLP-1 (Glucagon-Like Peptide-1). *Circ Arrhythm Electrophysiol*. 2018;11(10):e006740. doi:10.1161/CIRCEP.118.006740
17. Bohne LJ, Jansen HJ, Dorey TW, et al. Glucagon-like peptide-1 protects against atrial fibrillation and atrial remodeling in type 2 diabetic mice. *JACC Basic Transl Sci*. 2023;8(8):922–936. doi:10.1016/j.jacbts.2023.01.005
18. Rizzo M, Nikolic D, Patti AM, et al. GLP-1 receptor agonists and reduction of cardiometabolic risk: potential underlying mechanisms. *Biochim Biophys Acta Mol Basis Dis*. 2018;1864(9 Pt B):2814–2821. doi:10.1016/j.bbadis.2018.05.012
19. Schubert M, Hansen S, Leefmann J, Guan K. Repurposing antidiabetic drugs for cardiovascular disease. *Front Physiol*. 2020;11:568632. doi:10.3389/fphys.2020.568632

20. Liu D, Li Y, Zhao Q. Effects of inflammatory cell death caused by catheter ablation on atrial fibrillation. *J Inflamm Res*. 2023;16:3491–3508. doi:10.2147/JIR.S422002
21. James TN, St Martin E, Willis PW, Lohr TO. Apoptosis as a possible cause of gradual development of complete heart block and fatal arrhythmias associated with absence of the AV node, sinus node, and internodal pathways. *Circulation*. 1996;93(7):1424–1438. doi:10.1161/01.cir.93.7.1424
22. Fu Y, Jiang T, Sun H, et al. Necroptosis is required for atrial fibrillation and involved in aerobic exercise-conferred cardioprotection. *J Cell Mol Med*. 2021;25(17):8363–8375. doi:10.1111/jcmm.16796
23. Song ZH, Gong Q, Guo JW. Pyroptosis: mechanisms and links with fibrosis. *Cells-Basel*. 2021;10(12):3509. doi:10.3390/cells10123509
24. Zhang XQ, Qu HY, Yang T, Kong XN, Zhou H. Regulation and functions of NLRP3 inflammasome in cardiac fibrosis: current knowledge and clinical significance. *Biomed Pharmacother*. 2021;143:112219. doi:10.1016/j.biopha.2021.112219
25. Rose RA, Sellan M, Simpson JA, et al. Iron overload decreases CaV1.3-dependent L-type Ca2+ currents leading to bradycardia, altered electrical conduction, and atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2011;4(5):733–742. doi:10.1161/CIRCEP.110.960401
26. Boshchenko AA, Maslov LN, Mukhomedzyanov AV, et al. Peptides are cardioprotective drugs of the future: the receptor and signaling mechanisms of the cardioprotective effect of glucagon-like peptide-1 receptor agonists. *Int J Mol Sci*. 2024;25(9):4900. doi:10.3390/ijms25094900
27. Shen J, Fu H, Ding Y, et al. The role of iron overload and ferroptosis in arrhythmia pathogenesis. *Int J Cardiol Heart Vasc*. 2024;52:101414. doi:10.1016/j.ijcha.2024.101414
28. Konstantinidis K, Whelan RS, Kitsis RN. Mechanisms of cell death in heart disease. *Arterioscl Throm Vas*. 2012;32(7):1552–1562. doi:10.1161/Atvbaha.111.224915
29. Zhu Q, Luo Y, Wen Y, Wang D, Li J, Fan Z. Semaglutide inhibits ischemia/reperfusion-induced cardiomyocyte apoptosis through activating PKG/PKCepsilon/ERK1/2 pathway. *Biochem Biophys Res Commun*. 2023;647:1–8. doi:10.1016/j.bbrc.2023.01.049
30. Yan M, Lin K, Huang D, Li J, Qu X, Chen K. Semaglutide attenuates pathological electrophysiological remodeling in diabetic cardiomyopathy via restoring Cx43 expression. *Endocrine*. 2024;84(3):969–979. doi:10.1007/s12020-024-03823-2
31. Zhou G, Wu H, Yang J, et al. Liraglutide attenuates myocardial ischemia/reperfusion injury through the inhibition of necroptosis by activating GLP-1R/PI3K/Akt pathway. *Cardiovasc Toxicol*. 2023;23(3–4):161–175. doi:10.1007/s12012-023-09789-3
32. Naryzhnaya NV, Maslov LN, Popov SV, et al. Pyroptosis is a drug target for prevention of adverse cardiac remodeling: the crosstalk between pyroptosis, apoptosis, and autophagy. *J Biomed Res*. 2022;36(6):375–389. doi:10.7555/JBR.36.20220123
33. Trang NN, Chung CC, Lee TW, et al. Empagliflozin and liraglutide differentially modulate cardiac metabolism in diabetic cardiomyopathy in rats. *Int J Mol Sci*. 2021;22(3):1177. doi:10.3390/ijms22031177
34. Ryabov VV, Maslov LN, Vyshlov EV, et al. Ferroptosis, a regulated form of cell death, as a target for the development of novel drugs preventing ischemia/reperfusion of cardiac injury, cardiomyopathy and stress-induced cardiac injury. *Int J Mol Sci*. 2024;25(2):897. doi:10.3390/ijms25020897
35. Eid RA, Bin-Meferij MM, El-Kott AF, et al. Exendin-4 protects against myocardial ischemia-reperfusion injury by upregulation of SIRT1 and SIRT3 and activation of AMPK. *J Cardiovasc Transl Res*. 2021;14(4):619–635. doi:10.1007/s12265-020-09984-5
36. Chang G, Zhang D, Yu H, et al. Cardioprotective effects of exenatide against oxidative stress-induced injury. *Int J Mol Med*. 2013;32(5):1011–1020. doi:10.3892/ijmm.2013.1475
37. Zhang Y, Zhou H, Wu W, et al. Liraglutide protects cardiac microvascular endothelial cells against hypoxia/reoxygenation injury through the suppression of the SR-Ca(2+)-XO-ROS axis via activation of the GLP-1R/PI3K/Akt/survivin pathways. *Free Radic Biol Med*. 2016;95:278–292. doi:10.1016/j.freeradbiomed.2016.03.035
38. Durak A, Turan B, et al. Liraglutide provides cardioprotection through the recovery of mitochondrial dysfunction and oxidative stress in aging hearts. *J Physiol Biochem*. 2023;79(2):297–311. doi:10.1007/s13105-022-00939-9
39. Helmstadter J, Keppeler K, Aust F, et al. GLP-1 Analog Liraglutide Improves Vascular Function in Polymicrobial Sepsis by Reduction of Oxidative Stress and Inflammation. *Antioxidants*. 2021;10(8):1175. doi:10.3390/antiox10081175
40. Wang J, Guo R, Ma X, et al. Liraglutide inhibits AngII-induced cardiac fibroblast proliferation and ECM deposition through regulating miR-21/PTEN/PI3K pathway. *Cell Tissue Bank*. 2023;24(1):125–137. doi:10.1007/s10561-022-10021-9
41. Bruen R, Curley S, Kajani S, et al. Liraglutide attenuates preestablished atherosclerosis in apolipoprotein E-deficient mice via regulation of 550 immune cell phenotypes and proinflammatory mediators. *J Pharmacol Exp Ther*. 2019;370(3):447–458. doi:10.1124/jpet.119.258343
42. Fang B, Liu F, Yu X, et al. Liraglutide alleviates myocardial ischemia-reperfusion injury in diabetic mice. *Mol Cell Endocrinol*. 2023;572:111954. doi:10.1016/j.mce.2023.111954
43. Zhang Y, Ling Y, Yang L, et al. Liraglutide relieves myocardial damage by promoting autophagy via AMPK-mTOR signaling pathway in 565 Zucker diabetic fatty rat. *Mol Cell Endocrinol*. 2017;448:98–107. doi:10.1016/j.mce.2017.03.029
44. Zheng RH, Zhang WW, Ji YN, et al. Exogenous supplement of glucagon like peptide-1 protects the heart against aortic banding induced myocardial fibrosis and dysfunction through inhibiting mTOR/p70S6K signaling and promoting autophagy. *Eur J Pharmacol*. 2020;883:173318. doi:10.1016/j.ejphar.2020.173318
45. Bai XJ, Hao JT, Zheng RH, et al. Glucagon-like peptide-1 analog liraglutide attenuates pressure-overload induced cardiac hypertrophy and apoptosis through activating ATP sensitive potassium channels. *Cardiovasc Drugs Ther*. 2021;35(1):87–101. doi:10.1007/s10557-020-07088-5
46. Durak A, Akkus E, Canpolat AG, Tuncay, E, Corapcioglu, D, Turan, B, et al. Glucagon-like peptide-1 receptor agonist treatment of high carbohydrate intake-induced metabolic syndrome provides pleiotropic effects on cardiac dysfunction through alleviations in electrical and intracellular Ca(2 590 +) abnormalities and mitochondrial dysfunction. *Clin Exp Pharmacol Physiol*. 2022;49(1):46–59. doi:10.1111/1440-1681.13590
47. Ramadan NM, Malek HA, Rahman KA, El-Kholy E, Shaalan, D, Elkashef, W. Liraglutide effect on ventricular transient outward K + channel and Connexin-43 protein expression. *Exp Clin Endocrinol Diabetes*. 2021;129((12):899–907. doi:10.1055/a-1162-8196
48. Eid RA, Khalil MA, Alkhateeb MA. Exendin-4 attenuates remodeling in the remote myocardium of rats after an acute myocardial infarction by activating beta-Arrestin-2, Protein Phosphatase 2A, and Glycogen Synthase Kinase-3 and inhibiting beta-Catenin. *Cardiovasc Drugs Ther*. 2021;35(6):1095–1110. doi:10.1007/s10557-020-07006-9

49. Eid RA, Alharbi SA, El-Kott AF, et al. Exendin-4 ameliorates cardiac remodeling in experimentally induced myocardial infarction in rats by inhibiting PARP1/NF-kappaB axis in A SIRT1-dependent mechanism. *Cardiovasc Toxicol*. 2020;20(4):401–418. doi:10.1007/s12012-020-49009567-5
50. Chen J, Wang, D, Wang, F. Exendin-4 inhibits structural remodeling and improves Ca(2+) homeostasis in rats with heart failure via the 605 GLP-1 receptor through the eNOS/cGMP/PKG pathway. *Peptides*. 2017;90:69–77. doi:10.1016/j.peptides.2017.02.008
51. Liu X, Patel KP, Zheng H. Role of renal sympathetic nerves in GLP-1 (Glucagon-Like Peptide-1) receptor agonist exendin-4-mediated diuresis and natriuresis in diet-induced obese rats *J Am Heart Assoc*. 2021;10(21):e022542. doi:10.1161/JAHA.121.022542
52. Ma YL, Kong CY, Guo Z, et al. Semaglutide ameliorates cardiac remodeling in male mice by optimizing energy substrate utilization through the Creb5/NR4a1 axis. *Nat Commun*. 2024;15(1):4757. doi:10.1038/s41467-024-48970-2
53. Lin K, Wang A, Zhai C, et al. Semaglutide protects against diabetes-associated cardiac inflammation via Sirt3-dependent RKIP pathway. *Br J Pharmacol*. 2025;182(7):1561–1581. doi:10.1111/bph.17327
54. Xie S, Zhang M, Shi W, et al. Long-term activation of glucagon-like peptide-1 receptor by dulaglutide prevents diabetic heart failure and metabolic remodeling in type 2 diabetes. *J Am Heart Assoc*. 2022;11(19):e026728. doi:10.1161/JAHA.122.026728
55. Wisneski JA, Stanley WC, Neese RA, Gertz EW. Effects of acute hyperglycemia on myocardial glycolytic activity in humans. *J Clin Invest*. 1990;85(5):1648–1656. doi:10.1172/JCI114616
56. Al Batran R, Almutairi M, Ussher JR. Glucagon-like peptide-1 receptor mediated control of cardiac energy metabolism. *Peptides*. 2018;100:94–100. doi:10.1016/j.peptides.2017.12.005
57. Luna-Marco C, Iannantuoni F, Hermo-Argibay A, et al. Cardiovascular benefits of SGLT2 inhibitors and GLP-1 receptor agonists through effects on mitochondrial function and oxidative stress. *Free Radic Biol Med*. 2024;213:19–35. doi:10.1016/j.freeradbiomed.2024.01.015
58. Xue L, Liu W, Sun YX, et al. Protective effects on hypoxia reoxygenation cardiomyocytes by GLP-1R agonists via PI3K/AKT signaling pathway. *Int J Gerontol*. 2020;14(3):168–173. doi:10.6890/Ijge.202008_14(3).0004
59. Ma Z, Jin K, Yue M, Chen X, Chen J. Research progress on the GIP/GLP-1 receptor coagonist tirzepatide, a rising star in type 2 diabetes. *J Diabetes Res*. 2023;2023:5891532. doi:10.1155/2023/5891532
60. Sun F, Wu S, Wang J, et al. Effect of glucagon-like peptide-1 receptor agonists on lipid profiles among type 2 diabetes: a systematic review and network meta-analysis. *Clin Ther*. 2015;37(1):225–241e8. doi:10.1016/j.clinthera.2014.11.008
61. Bu T, Sun Z, Pan Y, Deng X, Yuan G. Glucagon-like peptide-1: new regulator in lipid metabolism. *Diabetes Metab J*. 2024;48(3):354–372. doi:10.4093/dmj.2023.0277
62. Bagherzadeh-Rahmani B, Marzetti E, Karami E, et al. Tirzepatide and exercise training in obesity. *Clin Hemorheol Microcirc*. 2024;87(4):465–480. doi:10.3233/CH-242134
63. Yu D, Shen S, Zhang J, Wang Q. Effect of the dual glucose-dependent insulinotropic peptide/gulcagon-like peptide 1 receptor agonist tirzepatide on lipid profile and waist circumference: a systematic review and meta-analysis. *Clin Ther*. 2023;45(8):787–796. doi:10.1016/j.clinthera.2023.06.008
64. Yin Y, Zhang M, Cao Q. Efficacy of GLP-1 receptor agonist-based therapies on cardiovascular events and cardiometabolic parameters in obese individuals without diabetes: a meta-analysis of randomized controlled trials. *J Diabetes*. 2025;17(4):e70082. doi:10.1111/1753-0407.70082
65. Qi R, Jingjing Z, Hongchang G, et al. Agonizing GABA(B)R suppresses GLP-1RA's chronotropic effect and reduces post-myocardial infarction arrhythmogenesis. *Front Pharmacol*. 2025;16:1616181. doi:10.3389/fphar.2025.1616181
66. Karakasis P, Vlachos K, Antoniadis AP, et al. Effect of GLP-1 receptor agonists and co-agonists on atrial fibrillation risk in overweight or obesity: systematic review and meta-analysis of randomized controlled trials. *Metabolism*. 2026;175:156463. doi:10.1016/j.metabol.2025.156463
67. D'Marco L, Morillo V, Gorriz, JL. SGLT2i and GLP-1RA in cardiometabolic and renal diseases: from glycemic control to adipose tissue inflammation and senescence. *J Diabetes Res*. 2021;2021:9032378. doi:10.1155/2021/9032378
68. Li Y, Gong X, Gaman MA, Hernandez-Wolters, B, Velu, P, Li, Y, et al. The effect of subcutaneous dulaglutide on weight loss in patients with Type 2 diabetes mellitus: systematic review and meta-analysis of randomized controlled trials. *Eur J Clin Invest*. 2024;54(4):e14125. doi:10.1111/515eci.14125
69. Caruso I, Cignarelli A, Giorgino F. Heterogeneity and similarities in GLP-1 receptor agonist cardiovascular outcomes trials. *Trends Endocrinol Metab*. 2019;30(9):578–589. doi:10.1016/j.tem.2019.07.004
70. Grune J, Yamazoe M, Nahrendorf M. Electroimmunology and cardiac arrhythmia. *Nat Rev Cardiol*. 2021;18(8):547–564. doi:10.1038/s41569-021-00520-9
71. Issac TT, Dokainish H, Lakkis NM. Role of inflammation in initiation and perpetuation of atrial fibrillation: a systematic review of the published data. *J Am Coll Cardiol*. 2007;50(21):2021–2028. doi:10.1016/j.jacc.2007.06.054
72. Schnabel RB, Larson MG, Yamamoto JF, et al. Relation of multiple inflammatory biomarkers to incident atrial fibrillation. *Am J Cardiol*. 2009;104(1):92–96. doi:10.1016/j.amjcard.2009.02.053
73. Friedrichs K, Klinke A, Baldus S. Inflammatory pathways underlying atrial fibrillation. *Trends Mol Med*. 2011;17(10):556–563. doi:10.1016/j.molmed.2011.05.007
74. Lewek J, Kaczmarek K, Cygankiewicz I, Wranicz JK, Ptaszynski P. Inflammation and arrhythmias: potential mechanisms and clinical implications. *Expert Rev Cardiovasc Ther*. 2014;12(9):1077–1085. doi:10.1586/14779072.2014.942286
75. Hu YF, Chen YJ, Lin YJ, Chen SA. Inflammation and the pathogenesis of atrial fibrillation. *Nat Rev Cardiol*. 2015;12(4):230–243. doi:10.1038/nrcardio.2015.2
76. Nguyen TP, Qu Z, Weiss JN. Cardiac fibrosis and arrhythmogenesis: the road to repair is paved with perils. *J Mol Cell Cardiol*. 2014;70:83–91. doi:10.1016/j.yjmcc.2013.10.018
77. Morita N, Mandel WJ, Kobayashi Y, Karagueuzian HS. Cardiac fibrosis as a determinant of ventricular tachyarrhythmias. *J Arrhythm*. 2014;30(6):389–394. doi:10.1016/j.joa.2013.12.008
78. Seferovic PM, Ristic AD, Maksimovic R, et al. Cardiac arrhythmias and conduction disturbances in autoimmune rheumatic diseases. *Rheumatology*. 2006;45(Suppl 4):iv39–42. doi:10.1093/rheumatology/kel315
79. Makaryus JN, Catanzaro JN, Goldberg S, Makaryus, AN, et al. Rapid progression of atrioventricular nodal blockade in a patient with systemic lupus 480 erythematosus. *Am J Emerg Med*. 2008;26(8):967e5–7. doi:10.1016/j.ajem.2008.02.010

80. Lee YS, Park MS, Choung JS, et al. Glucagon-like peptide-1 inhibits adipose tissue macrophage infiltration and inflammation in an obese mouse model of diabetes. *Diabetologia*. 2012;55(9):2456–2468. doi:10.1007/s00125-012-2592-3
81. Tang ST, Zhang Q, HQ HQ, et al. Effects of glucagon-like peptide-1 on advanced glycation endproduct-induced aortic endothelial dysfunction in streptozotocin-induced diabetic rats: possible roles of Rho kinase- and AMP kinase-mediated nuclear factor κB signaling pathways. *Endocrine*. 2016;53(1):107–116. doi:10.1007/s12020-015-0852-y
82. Hachuła M, Kosowski M, Ryl S, Basiak M, Okopień B. Impact of glucagon-like peptide 1 receptor agonists on biochemical markers of the initiation of atherosclerotic process. *Int J Mol Sci*. 2024;25(3):1854. doi:10.3390/ijms25031854
83. Parzych KR, Klionsky DJ. An overview of autophagy: morphology, mechanism, and regulation. *Antioxid Redox Signal*. 2014;20(3):460–473. doi:10.1089/ars.2013.5371
84. Pohl C, Dikic I. Cellular quality control by the ubiquitin-proteasome system and autophagy. *Science*. 2019;366(6467):818–822. doi:10.1126/science.aax3769
85. Russell RC, Guan KL. The multifaceted role of autophagy in cancer. *EMBO J*. 2022;41(13):e110031. doi:10.15252/embj.2021110031
86. Bravo-San Pedro JM, Kroemer G, Galluzzi L. Autophagy and mitophagy in cardiovascular disease. *Circ Res*. 2017;120(11):1812–1824. doi:10.1161/CIRCRESAHA.117.311082
87. Puleston DJ, Simon AK. Autophagy in the immune system. *Immunology*. 2014;141(1):1–8. doi:10.1111/imm.12165
88. Huang ST, Hsu WF, Huang HS, et al. Improved survival in hepatocellular carcinoma patients with cardiac arrhythmia by amiodarone treatment through autophagy. *Mol Cell Endocrinol*. 2019;20(16):3978. doi:10.3390/ijms20163978
89. Meyer G, Czompa A, Reboul C, et al. The cellular autophagy markers Beclin-1 and LC3B-II are increased during reperfusion in fibrillated 470 mouse hearts. *Curr Pharm Des*. 2013;19(39):6912–6918. doi:10.2174/13816128193913127122510
90. Pan Z, Zhu L, Wang X, et al. Excessive autophagic degradation of MYLK3 causes sunitinib-induced cardiotoxicity. *Autophagy*. 2025;21(12):2730–2749. doi:10.1080/15548627.2025.2524290
91. Yu W, Zha W, Ren J. Exendin-4 and liraglutide attenuate glucose toxicity-induced cardiac injury through mTOR/ULK1-dependent autophagy. *Oxid Med Cell Longev*. 2018;2018:5396806. doi:10.1155/2018/5396806
92. He CW, Shi K, Liang T, et al. Energy stress induced cardiac autophagy detection via a chronic and dynamic cardiomyocytes-based biosensing platform. *Biosens Bioelectron*. 2025;267:116821. doi:10.1016/j.bios.2024.116821
93. Wiersma M, Meijering RAM, Qi XY, et al. Endoplasmic reticulum stress is associated with autophagy and cardiomyocyte remodeling in experimental and human atrial fibrillation. *J Am Heart Assoc*. 2017;6(10):e006458. doi:10.1161/JAHA.117.006458
94. Bers DM. Cardiac excitation-contraction coupling. *Nature*. 2002;415(6868):198–205. doi:10.1038/415198a
95. Waldo AL, Wit AL. Mechanisms of cardiac arrhythmias. *Lancet*. 1993;341(8854):1189–1193. doi:10.1016/0140-6736(93)91012-b
96. Deal KK, England SK, Tamkun MM. Molecular physiology of cardiac potassium channels. *Physiol Rev*. 1996;76(1):49–67. doi:10.1152/physrev.1996.76.1.49
97. Barry DM, Nerbonne JM. Myocardial potassium channels: electrophysiological and molecular diversity. *Annu Rev Physiol*. 1996;58:363–394. doi:10.1146/annurev.ph.58.030196.002051
98. Yue L, Feng J, Gaspo R, Li GR, Wang Z, Nattel S. Ionic remodeling underlying action potential changes in a canine model of atrial fibrillation. *Circ Res*. 1997;81(4):512–525. doi:10.1161/01.res.81.4.512
99. Volders PG, Sipido KR, Vos MA, Kulcsár A, Verduyn SC, Wellens HJ. Cellular basis of biventricular hypertrophy and arrhythmogenesis in dogs with chronic complete atrioventricular block and acquired torsade de pointes. *Circulation*. 1998;98(11):1136–1147. doi:10.1161/01.cir.98.11.1136
100. Volders PG, Sipido KR, Vos MA, et al. Downregulation of delayed rectifier K(+) currents in dogs with chronic complete atrioventricular block and acquired torsades de pointes. *Circulation*. 19999;100(24):2455–2461. doi:10.1161/01.cir.100.24.2455
101. Tsuji Y, Opthof T, Yasui K. Ionic mechanisms of acquired QT prolongation and torsades de pointes in rabbits with chronic complete 475 atrioventricular block. *Circulation*. 2002;106(15):2012–2018. doi:10.1161/01.cir.0000031160.86313.24
102. Lei M, Wu L, Terrar DA, Huang CL. Response by Lei et al to Letter Regarding Article, "Modernized classification of cardiac antiarrhythmic drugs". *Circulation*. 2019;139(13):1652–1653. doi:10.1161/circulationaha.118.039292
103. Zhou Q, Hao G, Xie W, et al. Exenatide reduces atrial fibrillation susceptibility by inhibiting hKv1.5 and hNav1.5 channels. *J Biol Chem*. 2024;300(5):107294. doi:10.1016/j.jbc.2024.107294
104. Yang D, Wan X, Schwieterman N, et al. MicroRNA-1 deficiency is a primary etiological factor disrupting cardiac contractility and electrophysiological homeostasis. *Circ Arrhythm Electrophysiol*. 2024;17(1):e012150. doi:10.1161/CIRCEP.123.012150
105. Bers DM, Despa S, Bossuyt J. Regulation of Ca2+ and Na+ in normal and failing cardiac myocytes. *Ann N Y Acad Sci*. 2006;1080:165–177. doi:10.1196/annals.1380.015
106. Remme CA. Cardiac sodium channelopathy associated with mutations: electrophysiological, molecular and genetic aspects. *J Physiol*. 2013;591(17):4099–4116. doi:10.1113/jphysiol.2013.256461
107. Makielski JC. Late sodium current: a mechanism for angina, heart failure, and arrhythmia. *Trends Cardiovasc Med*. 2016;26(2):115–122. doi:10.1016/j.tcm.2015.05.006
108. Yu SD, Li G, Huang CLH, Lei M, Wu, L. Late sodium current associated cardiac electrophysiological and mechanical dysfunctionLate sodium current associated cardiac electrophysiological and mechanical dysfunction. *Pfiug Arch Eur J Phy*. 2018;470(3):461–469. doi:10.1007/s00424-017-2079-7
109. Keefe JA, Moore Ho, Ho KS, Wehrens, XHT, et al. Role of Ca in healthy and pathologic cardiac function: from normal excitation-contraction coupling to mutations that cause inherited arrhythmia. *Arch Toxicol*. 2023;97(1):73–92. doi:10.1007/s00204-022-03385-0
110. Grandi E, Ripplinger CM. Antiarrhythmic mechanisms of beta blocker therapy. *Pharmacol Res*. 2019;146:104274. doi:10.1016/j.phrs.2019.104274
111. Shen MJ, Zipes DP. Role of the autonomic nervous system in modulating cardiac arrhythmias. *Circ Res*. 2014;114(6):1004–1021. doi:10.1161/CIRCRESAHA.113.302549
112. Li Y, Liu Z, O'Shea C, et al. Dual calcium-voltage optical mapping of regional voltage and calcium signals in intact murine RyR2-R2474S hearts. *J Mol Cell Cardiol Plus*. 2024;10:100121. doi:10.1016/j.jmccpl.2024.100121

113. DeMaria N, Selmi A, Kashtan S, et al. Autonomic and cardiac repolarization lability in long QT syndrome patients. *Auton Neurosci*. 2020;229:102723. doi:10.1016/j.autneu.2020.102723
114. Wichter T, Matheja P, Eckardt L, et al. Cardiac autonomic dysfunction in Brugada syndrome. *Circulation*. 2002;105(6):702–706. doi:10.1161/hc0602.103677
115. Manolis AA, Manolis TA, Apostolopoulos EJ, Apostolaki NE, Melita, H, Manolis, AS. The role of the autonomic nervous system in cardiac 485 arrhythmias: the neuro-cardiac axis, more foe than friend?. *Trends Cardiovasc Med*. 2021;31(5): 290–302. doi:10.1016/j.tcm.2020.04.011
116. Jing Y, Yang R, Chen W, Ye Q. Anti-arrhythmic effects of sodium-glucose co-transporter 2 inhibitors. *Front Pharmacol*. 2022;13:898718. doi:10.3389/fphar.2022.898718
117. Lei M, Wu L, Terrar DA, Huang CL. Modernized classification of cardiac antiarrhythmic drugs. *Circulation*. 2018;138(17):1879–1896. doi:10.1161/CIRCULATIONAHA.118.035455
118. Kumarathurai P, Anholm C, Larsen BS, et al. Effects of liraglutide on heart rate and heart rate variability: a randomized, double-blind, placebo-controlled crossover study. *Diabetes Care*. 2017;40(1):117–124. doi:10.2337/dc16-1580
119. Baggio LL, Ussher JR, McLean BA, et al. The autonomic nervous system and cardiac GLP-1 receptors control heart rate in mice. *Mol Metab*. 2017;6(11):1339–1349. doi:10.1016/j.molmet.2017.08.010
120. Esfandiari S, Fuchs F, Wainstein RV, et al. Heart rate-dependent left ventricular diastolic function in patients with and without heart failure. *J Card Fail*. 2015;21(1):68–75. doi:10.1016/j.cardfail.2014.10.013
121. Gawalko M, Agbaedeng TA, Saljic A, et al. Gut microbiota, dysbiosis and atrial fibrillation. Arrhythmogenic mechanisms and potential clinical implications. *Cardiovasc Res*. 2022;118(11):2415–2427. doi:10.1093/cvr/cvab292
122. Fan HX, Liu XC, Ren ZY, et al. Gut microbiota and cardiac arrhythmia. *Front Cell Infect Microbiol*. 2023;13:1147687. doi:10.3389/fcimb.2023.1147687
123. Wong CK, Yusta B, Koehler JA, et al. Divergent roles for the gut intraepithelial lymphocyte GLP-1R in control of metabolism, microbiota, and T cell-induced inflammation. *Cell Metab*. 2022;34(10):1514–1531.e7. doi:10.1016/j.cmet.2022.08.003
124. Liu TS, Liang WZ, Xu FH, et al. Effects of beinaglutide on visceral fat area and gut microbiota in obesity. *Eur J Med Res*. 2025;30(1):448. doi:10.1186/s40001-025-02585-5
125. Zeng Y, Wu YF, Zhang Q, Xiao XH. Crosstalk between glucagon-like peptide 1 and gut microbiota in metabolic diseases. *mBio*. 2024;15(1): e02032–23. doi:10.1128/mbio.02032-23
126. Duan HY, Barajas-Martinez H, Antzelevitch C, Hu D. The potential anti-arrhythmic effect of SGLT2 inhibitors. *Cardiovasc Diabetol*. 2024;23 (1):252. doi:10.1186/s12933-024-02312-0
127. Lubberding AF, Veedfald S, Achter JS, et al. Glucagon-like peptide-1 increases heart rate by a direct action on the sinus node. *Cardiovasc Res*. 2024;120(12):1427–1441. doi:10.1093/cvr/cvae120
128. Xia RB, Tomsits P, Loy S, et al. Cardiac macrophages and their effects on arrhythmogenesis. *Front Physiol*. 2022;13:900094. doi:10.3389/fphys.2022.900094
129. Zhang DZ, Hu WF, Tu HY, et al. Macrophage depletion in stellate ganglia alleviates cardiac sympathetic overactivation and ventricular arrhythmogenesis by attenuating neuroinflammation in heart failure. *Basic Res Cardiol*. 2021;116(1):28. doi:10.1007/s00395-021-00871-x
130. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *New Engl J Med*. 2016;375 (19):1834–1844. doi:10.1056/NEJMoa1607141
131. Vilsboll T, Bain SC, Leiter LA, et al. Semaglutide, reduction in glycated haemoglobin and the risk of diabetic retinopathy. *Diabetes Obes Metab*. 2018;20(4):889–897. doi:10.1111/dom.13172
132. Gerstein HC, Sattar N, Rosenstock J, et al. Cardiovascular and renal outcomes with Efpeglenatide in type 2 diabetes. *New Engl J Med*. 2021;385 (10):896–907. doi:10.1056/NEJMoa2108269
133. Wang HN, Liu Y, Tian Q, et al. Incretin-based therapies and risk of pancreatic cancer in patients with type 2 diabetes: a meta-analysis of randomized controlled trials. *Diabetes Obes Metab*. 2018;20(4):910–920. doi:10.1111/dom.13177
134. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. *New Engl J Med*. 2021;384 (11):989–1002. doi:10.1056/NEJMoa2032183
135. Ludvík B, Giorgino F, Jódar E, et al. Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, Phase 3 trial. *Lancet*. 2021;398 (10300):583–598. doi:10.1016/S0140-6736(21)01443-4