Reviews in Cardiovascular Medicine

Rev. Cardiovasc. Med. **2026**; 27(11): 54498
https://doi.org/10.31083/RCM54498

Review

Obesity-Related Atrial Fibrillation: Insights Into Pathogenesis and Treatment

Wen-rui Wang[1,†], Hai-wei Geng[1,†], Tian-peng Wei[1,†], Xiao-lu Zhang[1], Huan-huan Liu[1], Ying Liu[1], Ling-ling Qian[1,*], Ru-xing Wang[1]

[1]Department of Cardiology, The Affiliated Wuxi People's Hospital of Nanjing Medical University, 214023 Wuxi, Jiangsu, China
*Correspondence: qianlingling@njmu.edu.cn (Ling-ling Qian)
[†]These authors contributed equally.

Academic Editor: Vladimir M. Pokrovskii
Submitted: 3 June 2026 Revised: 10 July 2026 Accepted: 27 July 2026 Published: 9 November 2026

Abstract

Obesity is an established independent risk factor for the initiation and progression of atrial fibrillation (AF). This review synthesizes current evidence on the epidemiological association between obesity and AF. It also discusses the multifaceted pathophysiological mechanisms that link them, including structural remodeling, electrical remodeling, and autonomic dysfunction. We summarize current preventive and therapeutic strategies for AF in the context of obesity. These encompass lifestyle intervention with sustained weight loss, pharmacological approaches that prioritize agents with dual cardiometabolic benefits, integration of catheter ablation with weight management, and the selection of anticoagulants. Emerging investigational targets in preclinical stages are also briefly discussed to highlight future directions. We provide a comprehensive mechanistic and practical perspective to inform clinical management of obesity-related AF, advocating for a personalized, multi-targeted therapeutic paradigm that addresses the root causes of this arrhythmia.

Keywords: atrial fibrillation; obesity; epicardial adipose tissue; fibrosis; electrical remodeling; precision medicine

1. Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice. Its prevalence is increasing globally, posing a significant threat to human health [1] and becoming a heavy public health burden [2]. In China, a large national cross-sectional study reported a prevalence of 1.6% among adults, with a higher incidence in older age groups [3]. Obesity is considered to be an independent risk factor for AF, contributing to the onset and progression of this condition [4]. However, the precise pathophysiology linking obesity to AF involves complex and interrelated mechanisms, and the presence of obesity complicates the efficacy and selection of AF therapies. This review synthesizes the current evidence supporting these multifaceted mechanisms and summarizes the evolving landscape of preventive and therapeutic strategies specifically for obesity-related AF. Our aim is to bridge insights from pathogenesis to clinical practice, thus providing a comprehensive perspective for managing this common clinical association.

2. Search Strategy and Selection Criteria

We conducted a comprehensive literature search in the PubMed database for articles published between January 2000 and June 2026. The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords related to obesity and AF, including their clinical subtypes and related conditions, using Boolean operators. We also manually screened the reference lists of retrieved articles and relevant reviews to identify additional studies not captured by the initial database search.

Studies were included if they met the following criteria: (1) study design: original research articles, randomized controlled trials, prospective or retrospective cohort studies, cross-sectional epidemiological surveys, Mendelian randomization studies, systematic reviews, meta-analyses, high-quality narrative reviews, and clinical practice guidelines; (2) language: articles published in English; (3) relevance: studies directly addressing the epidemiology, pathophysiological mechanisms, or clinical management of obesity-related AF; and (4) study population: human subjects or established animal/*in vitro* models specifically employed for the investigation of obesity-related AF mechanisms or therapeutic targets. We excluded case reports, conference abstracts, editorials, commentaries, studies not directly pertinent to the core topic, and duplicate publications.

Given the narrative nature of this review, we prioritized evidence from large-scale cohort studies and randomized controlled trials for clinical recommendations. Mechanistic evidence from preclinical studies was interpreted with appropriate caution given its inherent limitations. Both authors independently screened the titles and abstracts of all retrieved records, and discrepancies were resolved through discussion. This systematic approach was intended to ensure comprehensive and unbiased coverage of the available literature.

Copyright: © 2026 The Author(s). Published by IMR Press.
This is an open access article under the CC BY 4.0 license.

Publisher's Note: IMR Press stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

3. Obesity Promotes Atrial Fibrillation

According to the World Health Organization, overweight is defined as a body mass index (BMI) ≥25 kg/m^2. Obesity is further classified into class I (30.0–34.9 kg/m^2), class II (35.0–39.9 kg/m^2), and class III (≥40.0 kg/m^2) [5]. China employs national BMI cut-off points, defining obesity as BMI ≥28 kg/m^2 and overweight as BMI ≥24 kg/m^2. These values are lower than the WHO standards (≥30 kg/m^2 and ≥25 kg/m^2, respectively) and are based on evidence of higher health risks at lower BMI levels among Asian populations [6]. Regardless of which standard is applied, a higher BMI has been conclusively linked to an increased risk of AF. A large Chinese cohort study recruited 44,135 participants with an average follow-up of 9.68 years. The study found that for each unit increase in BMI and waist circumference over time, the risk of AF increased by 6% and 2%, respectively [7]. In a cohort of 18,290 participants, Berkovitch et al. [8] reported that weight loss was independently associated with a reduced risk of AF. For every 5 kg of weight loss, the risk of developing AF showed a significant decrease of 12%. Additionally, for every 1 kg/m^2 decrease in BMI, the risk of a first AF event was significantly reduced by 7%. Current research suggests that BMI is positively correlated with AF risk. Importantly, long-term obesity or abdominal fat accumulation can promote the occurrence of AF [7]. Studies on Asian [9] and European [10] populations found that central obesity (abdominal fat) had a significant impact on the risk of AF. When BMI increased, the risk of AF varied across different ethnic groups. For example, at higher BMIs, Black individuals showed the smallest increase in AF risk, while Chinese-Americans experienced the greatest increase [11]. However, the underlying causes of these significant differences between populations remain unknown.

The enlargement of epicardial adipose tissue (EAT), located between the visceral layer of the pericardium and the myocardium, is closely associated with the occurrence of AF [12]. Quantitative data indicate that for each one standard deviation increase in EAT volume, the risk of new-onset AF increases by 25%. More importantly, EAT volume demonstrated even stronger associations with the risk of AF following cardiac surgery, increasing the risk of in-hospital AF by 2.67-fold, and the risk of long-term postoperative AF by 2.14-fold [12]. A nationwide cohort study suggested that weight variability was an independent risk factor for AF [13]. This defined high weight variability as the highest quintile of fluctuation (approximately 4.6 kg in mean absolute successive variability), which was associated with a 16% increased risk of new-onset AF [13].

In addition, the impact of obesity on the cardiovascular system varies between sexes [14]. Specifically, men with obesity have a significantly higher risk of developing AF compared with their female counterparts [14]. This disparity may be linked to sex-specific factors, including differences in body fat distribution, sex hormone profiles, inflammatory responses, and function of the autonomic nervous system [14].

Furthermore, the obesity paradox cannot be ignored [15]. While obesity increases the risk of developing AF, patients with both obesity and AF tend to have lower mortality rates after diagnosis compared to AF patients with normal weight [15]. A study of 1804 patients with AF demonstrated that obesity (BMI ≥30 kg/m^2) was associated with lower risks of stroke/systemic embolism, bleeding, heart failure admission, and all-cause mortality [16]. As BMI increased, the risk of these adverse events showed a decreasing trend. Possible explanations for this observation include: (1) patients with obesity may receive more aggressive treatment and closer follow-up; (2) patients with obesity are more likely to visit the emergency department for AF, leading to timely management; (3) in the Middle East region, a higher BMI may indicate better nutritional status and greater access to medical resources; and (4), patients with obesity may engage in more cardiorespiratory fitness exercise [16]. These intriguing possibilities warrant further investigation (Table 1, Ref. [7,8,9,10,11,12,13,14,16]).

4. Mechanisms Linking the Development of Atrial Fibrillation With Obesity

The precise mechanisms through which obesity promotes AF remain incompletely understood, but are believed to involve a combination of structural remodeling and electrical remodeling. Epidemiological studies have consistently demonstrated a strong association between obesity and increased risk of AF, highlighting the need to elucidate the underlying pathways.

4.1 Structural Remodeling

4.1.1 Fibrosis

Obesity-associated AF is closely linked to atrial fibrosis. In individuals with obesity, increased EAT volume and elevated inflammatory mediators such as myeloperoxidase upregulate the expression of collagen type I alpha 1 chain (*COL1A1*), fibronectin 1 (*FN*), transforming growth factor-β (TGF-β), and matrix metalloproteinases, promoting AF and creating a pathological basis for AF [17]. Importantly, this obesity-induced remodeling was partly reversible. Weight reduction in an obese sheep model decreased atrial TGF-β1 expression, reduced fibrosis and adipocyte infiltration, reversed structural remodeling, and lowered the incidence and duration of AF [18]. Obesity enhanced oxidative stress, downregulated Nuclear factor erythroid 2-related factor 2 (NRF2), and activated TGF-β1, rendering cardiomyocytes vulnerable to reactive oxygen species (ROS) and establishing a cycle that exacerbates fibrosis [19].

4.1.2 Inflammation

Obesity is associated with adipose tissue inflammation, characterized by macrophage accumulation and in-

Table 1. Summary of epidemiological studies on the association between obesity and atrial fibrillation.

Study design	Study population (sample size)	Key findings	Reference
Prospective Cohort	Chinese adults (44,135)	Long-term increases in BMI and waist circumference independently associated with elevated AF risk (HR 1.06 per BMI unit; HR 1.02 per WC unit)	[7]
Cohort Study	Israeli adults (18,290)	Weight loss significantly reduced AF risk (12% per 5 kg; 7% per 1 kg/m^2 BMI reduction)	[8]
Mendelian Randomization	Asian population (GWAS)	Central obesity (WHR) was a potential causal AF risk factor (OR 1.24)	[9]
Prospective cohort study	Swedish adults (4021)	Obesity (BMI ≥30) increased AF risk regardless of metabolic syndrome; BMI, waist circumference and sagittal abdominal diameter similarly predicted AF risk.	[10]
Prospective Cohort	Multi-ethnic U.S. (6814)	Obesity-AF association varied by race (HR 1.71 in Chinese Americans vs. 1.09 in Black individuals per SD increase in BMI)	[11]
Observational Study	Multi-national cohort	EAT volume strongly predicted AF (new-onset OR 1.25 per SD; postoperative HRs 2.67–2.14)	[12]
Nationwide Cohort	Korean patients with T2DM (89,494)	High weight variability was an independent risk factor for AF (HR 1.16), especially in non-obese individuals	[13]
Cohort Study	Korean & UK (>900,000)	Obesity-related AF risk was higher in males than females, with incidence ratios of 2.00 (UK) and 1.40 (Korea)	[14]
Prospective Observational Cohort	Middle Eastern AF patients (Gulf SAFE) (1804)	Obesity (BMI ≥30) was associated with lower risks of stroke/SE (aOR 0.40), bleeding (aOR 0.44), HF admission (aOR 0.61), and composite outcome (aOR 0.65). However, all-cause mortality was not significantly reduced (aOR 0.69, 95% CI 0.47–1.03; $p = 0.066$), so the "obesity paradox" should be interpreted cautiously.	[16]

This table summarizes key epidemiological studies investigating the association between obesity (measured by BMI, weight variability, fat distribution, or weight loss) and the risk of AF or its prognosis. Evidence spans diverse populations and includes associations, risk estimates (e.g., HR, OR, aOR), and notable phenomena such as the "obesity paradox" and variations according to race/ethnicity or sex. Abbreviations: AF, atrial fibrillation; aOR, adjusted odds ratio; SD, standard deviation; BMI, body mass index; EAT, epicardial adipose tissue; GWAS, genome-wide association study; HR, hazard ratio; OR, odds ratio; SE, systemic embolism; T2DM, type 2 diabetes mellitus; WC, waist circumference; WHR, waist-to-hip ratio.

creased expression of pro-inflammatory mediators [20]. In patients undergoing cardiac surgery, increased interleukin-1β (IL-1β) secretion from epicardial adipose tissue (EAT) has been associated with postoperative atrial fibrillation [21]. In vitro, IL-1β and IL-18 promote human atrial fibroblast proliferation, collagen production, and transforming growth factor-β1 (TGF-β1) expression, suggesting a potential contribution to atrial fibrotic remodeling [21]. Higher EAT-derived IL-6 levels have also been associated with postoperative atrial fibrillation [22]. The NLR family pyrin domain containing 3 (NLRP3) inflammasome is activated by pro-inflammatory stimuli and processes IL-1β and IL-18 into their mature forms, thereby amplifying inflammation and the propensity for AF [23,24,25]. Inhibition of NLRP3 via MCC950 or through genetic means suppressed AF in experimental models [23]. Additionally, the upregulation of hypoxia-inducible factor-1α in adipose tissue under obesity conditions promoted chronic inflammation and macrophage recruitment, further driving atrial fibrosis [26].

4.1.3 Oxidative Stress

Oxidative stress and ROS are critical in obesity-induced atrial remodeling. Increased lipolysis elevates the level of intracellular fatty acids, which activates the Toll-like receptor 4 pathway and nicotinamide adenine dinucleotide phosphate, reduced form (NADPH) oxidase 2, a major source of ROS [27]. Gut microbiota dysbiosis from a high-fat diet exacerbates this process by promoting endotoxin translocation, toll-like receptor 4 (TLR4) activation, and pro-inflammatory cytokine release, while reducing antioxidant enzyme activity, increasing ROS accumulation and the incidence of AF [28].

4.1.4 Endocrine-Metabolic Dysregulation

Insulin resistance is a hallmark of obesity and contributes to structural remodeling. It activates phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) and mitogen-activated protein kinase (MAPK) pathways, disrupts calcium handling, and upregulates proteins such as calcium/calmodulin-dependent protein kinase II delta (CaMKIIδ) and sodium/calcium exchanger 1 (NCX1), lead-

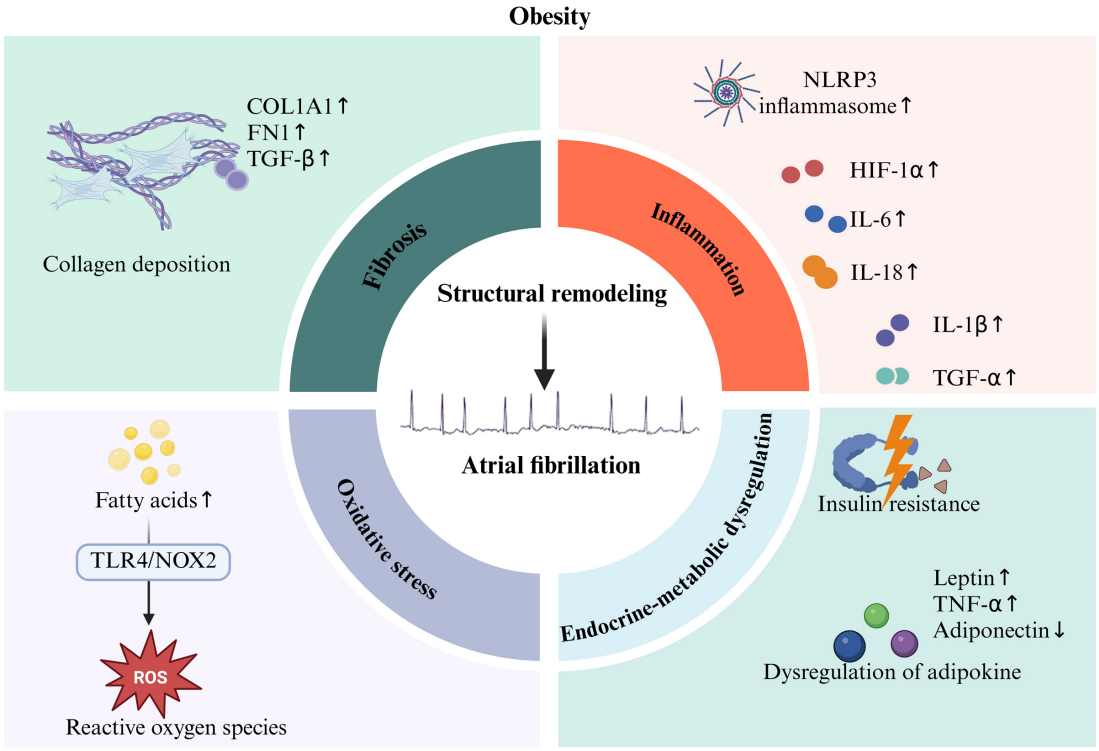


Fig. 1. Mechanisms of atrial structural remodeling in obesity-related atrial fibrillation. The main mechanisms include: fibrosis (increased expression of COL1A1, FN1, and TGF-β leads to collagen deposition); inflammation (increased NLRP3 inflammasome, HIF-1α, IL-6, IL-18, IL-1β, and TGF-α); oxidative stress (excess fatty acids activate abundant ROS via the TLR4/NOX axis); and endocrine-metabolic dysfunction (insulin resistance and adipokine dysregulation increase leptin secretion, decrease adiponectin, and increase TNF-α). The small upward and downward arrows indicate increases and decreases, respectively, in the indicated expression levels, abundance, or activity. AF, atrial fibrillation; COL1A1, collagen type I alpha 1 chain; FN1, fibronectin 1; HIF-1α, hypoxia-inducible factor 1-alpha; IL-1β, interleukin-1 beta; IL-6, interleukin-6; IL-18, interleukin-18; NLRP3, NLR family pyrin domain containing 3; NOX2, NADPH oxidase 2; ROS, reactive oxygen species; TGF-α, transforming growth factor-alpha; TGF-β, transforming growth factor-beta; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-alpha. Created in BioRender.

ing to calcium overload, interstitial fibrosis, atrial dilation, and slower conduction [29,30]. Insulin resistance is also associated with elevated inflammatory markers and oxidative stress [30].

Adiponectin levels are decreased in obesity [31], whereas pro-fibrotic leptin [32] and pro-inflammatory/pro-fibrotic tumor necrosis factor-alpha (TNF-α) levels are elevated [33]. Thus, obesity drives structural remodeling through fibrosis, inflammation, oxidative stress, and endocrine-metabolic dysregulation (Fig. 1).

4.2 Electrical Remodeling

4.2.1 Sodium Channel Dysfunction

Obesity directly affects atrial electrophysiology through alterations in ion channels. In obese mice, activation of serum and glucocorticoid-regulated kinase 1 (*SGK1*) alters the biophysical properties and trafficking of the voltage-gated sodium channel Nav1.5 (encoded by *SCN5A*), disrupting the rapid inward sodium current (INa) that initiates cardiac depolarization [34]. This dysregulation enhances the late sodium current, delays repolarization, increases cellular excitability, and creates a substrate for AF.

4.2.2 Alterations in Potassium Channels

Obesity increases atrial Kv1.5 (KCNA5) expression in high-fat diet-induced obese mice, accompanied by enhanced ultrarapid delayed rectifier potassium current (IKur) and shortened atrial action potential duration, which predisposes the atria to arrhythmia [35]. These changes shorten action potential duration, reduce conduction velocity, and lower the maximum rate of depolarization, thereby promoting AF [36]. In addition, adipocyte-incubated atrial myocytes exhibit a significant reduction in the inward rectifier potassium current (IK1), leading to depolarization of the resting membrane potential, slowed conduction, increased heterogeneity, and ultimately facilitating re-entrant arrhythmias [37].

4.2.3 Calcium Handling Dysfunction

Under conditions of obesity, activation of the stimulator of interferon genes (*STING*) pathway downregulates L-type calcium channel Cav1.2 expression and reduces L-type calcium current (ICa,L) density, thereby impairing Ca^{2+} transient triggering and amplitude. Concurrently, STING signaling upregulates the inositol 1,4,5-trisphosphate receptor type 1 (IP3R1)–voltage-dependent anion channel 1 (VDAC1) calcium transfer complex and enhances mitochondria-endoplasmic reticulum (ER) coupling, leading to mitochondrial calcium overload and establishing a pro-arrhythmic vicious cycle [38].

4.2.4 Hyperpolarization-Activated Cyclic Nucleotide–Gated (*HCN*) Channel Dysfunction

The HCN1 and HCN4 channels, which generate the sinoatrial pacemaker current (If), are downregulated in the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (*Pgc-1α*)-deficient model of obesity-related metabolic stress. This impairs cardiac automaticity and creates an unstable electrophysiological background conducive to AF [39].

4.2.5 Na^+/K^+-ATPase Dysfunction

In the same model of obesity-induced metabolic stress, key subunits of the ATP-dependent Na^+/K^+-ATPase (*Atp1a1*, *Atp1a2*, *Atp1b1*) are downregulated. The resulting disturbance in the ionic gradient disrupts membrane stability, forming a pro-arrhythmic substrate that links metabolic stress to AF in obesity [39].

4.2.6 Connexin Dysfunction

Connexin 43 (Cx43) is a major protein component of gap junctions and is responsible for electrical signal transmission between cardiomyocytes [18]. The expression of Cx43 was significantly reduced in an obese sheep model, leading to slowed conduction velocity and increased conduction heterogeneity, contributing to the electrophysiological substrate for AF. A 30% weight loss was shown to reverse the downregulation of Cx43, improve conduction velocity and heterogeneity, and reduce both the inducibility and duration of AF [18].

Furthermore, in an obese rat model, the atrial gap junction protein Cx40 was downregulated and exhibited disrupted spatial distribution under obese conditions [38]. This impairment severely compromises intercellular electrical coupling and forms a pro-arrhythmic substrate characterized by slowed conduction and increased heterogeneity, thereby elevating susceptibility to AF [38].

Obesity induces multifaceted atrial electrical remodeling mainly through the dysfunction of sodium (Nav1.5), potassium (Kv1.5, Kir2.1), calcium (Cav1.2), HCN, and Na^+/K^+-ATPase channels, as well as impaired gap junction coupling (Cx40, Cx43). This creates a pro-arrhythmic substrate characterized by shortened action potential, slowed conduction, and increased heterogeneity, thereby promoting the occurrence of AF (Fig. 2).

4.3 Autonomic Dysfunction

In patients with obesity, inflammatory factors and free fatty acids from EAT activate sympathetic neurons and increase the release of neuropeptide Y. Neuropeptide Y, via its Y1 receptor, increases Na^+/Ca^{2+} exchanger and calcium/calmodulin-dependent protein kinase II (CaMKII) activity, causing abnormal calcium handling and delayed afterdepolarizations in cardiomyocytes, thereby increasing the risk of AF [40]. Elevated ROS oxidizes and activates CaMKII, leading to ryanodine receptor 2 activation and aberrant Ca^{2+} release from the sarcoplasmic reticulum. This establishes the pro-arrhythmic substrate for cellular triggered activity, directly initiating and sustaining AF [41,42]. Obesity also disrupts the autonomic balance. Elevated leptin levels in obesity further stimulate sympathetic activation [43].

4.4 Preclinical Models: Mechanistic Insights and Translational Gaps

Mice fed a high-fat diet (HFD) have revealed the NLRP3 inflammasome–NADPH oxidase 2 (NOX2)–ROS axis [23,27], the SGK1–Nav1.5 pathway [34], and multi-ion-channel remodeling [40]. The obese sheep model has revealed the reversibility of atrial structural remodeling and Cx40/Cx43 gap-junction remodeling following weight loss [18]. *In vitro* EAT secretome/co-culture systems have elegantly dissected the paracrine effects of IL-1β, TNF-α, and leptin [40,44]. The aldehyde dehydrogenase 2 (ALDH2) knock-in mouse model with HFD has further revealed the modulatory role of genetic background. Despite elevated ROS levels, AF susceptibility is not increased due to compensatory upregulation of the nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) antioxidant pathway [45]. The human-derived, 3D bioprinted fat–myocardium model has validated, in a human cellular context, that hypertrophic adipocytes directly impair cardiomyocyte beating, calcium handling, and Cx43 expression through metabolic inflexibility, insulin resistance, and ER stress [46].

However, each of these models carries inherent limitations. In rodent models, obesity is induced too rapidly (over weeks to months), thus failing to recapitulate the decades-long progressive course of human obesity. Moreover, the electrophysiological parameters of rats—such as heart rate and action potential duration—differ substantially from those of humans, and their EAT is scarce. This makes it difficult to model the key pathological feature of EAT thickening observed in human obesity. Large animal models, while offering better clinical relevance, are costly and time consuming. Although capable of dissecting cellular interactions at high resolution, *in vitro* and 3D bioprinted systems cannot replicate the intact neuro-hormonal-hemodynamic

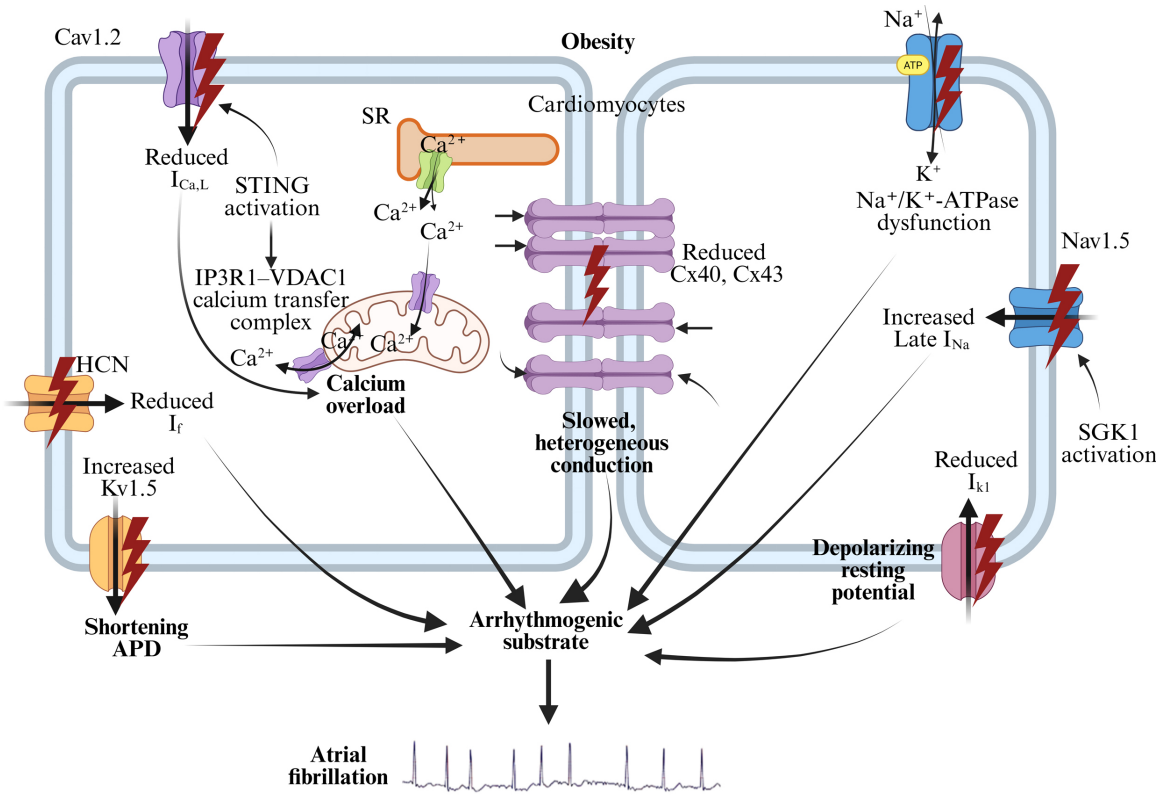


Fig. 2. Mechanisms of atrial electrical remodeling in obesity-related atrial fibrillation. This figure delineates the integrated electrical remodeling mechanisms underlying obesity-related AF. Key alterations include: sodium channel dysfunction (increased late sodium current via Nav1.5), potassium channel remodeling (increased Kv1.5 shortening APD; decreased Kir2.1 depolarizing resting potential), calcium handling impairment (STING pathway downregulates Cav1.2 and promotes calcium overload), impaired gap junction coupling (downregulated Cx40 and Cx43), and dysfunction of HCN channels and Na^+/K^+-ATPase. These defects collectively establish an arrhythmogenic substrate characterized by shortened action potential duration, slowed conduction and increased conduction heterogeneity, and increased excitability. AF, atrial fibrillation; APD, action potential duration; Cx, connexin; HCN, hyperpolarization-activated cyclic nucleotide–gated channel; STING, stimulator of interferon genes; $I_{Ca,L}$, L-type calcium current; I_f, "funny" current; I_{K1}, inward rectifier potassium current; Kv1.5, voltage-gated potassium channel subfamily A member 5; Nav1.5, voltage-gated sodium channel type V subunit alpha; Kir2.1, inward rectifier potassium channel 2; Cav1.2, voltage-dependent L-type calcium channel subunit alpha-1C; SGK1, serum and glucocorticoid-regulated kinase 1; IP3R1, inositol 1,4,5-trisphosphate receptor type 1; SR, sarcoplasmic reticulum; VDAC1, voltage-dependent anion channel protein 1. Created in BioRender.

milieu present *in vivo*. More importantly, several translational gaps exist across all of these models: the vast majority require exogenous stimulation to induce AF, thus studying "inducible" rather than "spontaneous" AF. Hence, this may reflect susceptibility rather than the true maintenance mechanisms of the arrhythmia. Furthermore, most models focus on obesity as a single factor, whereas human obesity-related AF frequently coexists with hypertension, diabetes, and sleep apnea. Single-factor models may therefore overestimate or underestimate the contribution of specific mechanisms.

Recognizing these limitations identifies priority directions for future research. For example, multi-factor "two-hit" models that combine obesity with hypertension, diabetes, or sympathetic activation should be developed. Human induced pluripotent stem cell (hiPSC)-derived atrial cardiomyocytes should be utilized to study electrical remodeling in a human genetic background. Finally, preclinical targets (such as the NOX2, SGK1, and NAD^+ axes) should be prioritized for validation in well-designed human observational studies or post-hoc analyses of large randomized controlled trials.

5. Multidimensional Management of Obesity-Related AF

5.1 Lifestyle Interventions

Patients with AF who undergo supervised and personalized weight loss, including dietary control and improvements in physical activity, can achieve meaningful metabolic benefits. The PRAGUE-25 trial demonstrated that lifestyle intervention combined with anti-arrhythmic

drug therapy resulted in a mean weight loss of 6.4 kg, with significant improvements in glycemic control, cardiorespiratory fitness, and quality of life [47].

5.2 Pharmacological Treatment

5.2.1 Metformin

Metformin is effective in diabetic patients and protects against cardiovascular diseases, especially AF, through the regulation of fat metabolism and inflammation [48]. Metformin reduced AF vulnerability in a canine pacing model by improving atrial electrophysiology [48]. It reversed effective refractory period shortening, reduced electrical dispersion, and decreased AF inducibility and duration. These benefits were mediated by remodeling of the EAT. Metformin downregulates pro-inflammatory cytokines (IL-6, TNF-α, TGF-β1), enhances adiponectin signaling via upregulation of peroxisome proliferator-activated receptor gamma (PPARγ), a key regulator of adiponectin expression, and suppresses ROS/NF-κB activation. The improved calcium handling in cardiomyocytes stabilizes electrical activity by restoring the function of sarcoplasmic/endoplasmic reticulum (ER) Ca^{2+} ATPase 2a (SERCA2a), a Ca^{2+} pump that is critical for calcium reuptake into the sarcoplasmic reticulum [48].

5.2.2 Glucagon-Like Peptide-1 Receptor Agonists

Glucagon-like peptide-1 (GLP-1) receptor agonists are commonly used in diabetes and obesity and have shown potential in treating obesity-related AF. A primary mechanism by which GLP-1 receptor agonists reduce AF risk is through substantial weight loss, thereby alleviating obesity-related cardiac strain and metabolic dysregulation [49]. Exenatide enhances muscle glucose utilization, reduces fatty acid accumulation, activates the adenosine monophosphate-activated protein kinase (AMPK) signaling pathway, alleviates insulin resistance, and decreases intracellular fat deposition in muscle cells. In diet-induced obese mice, these effects were accompanied by reduced body weight, whereas in ob/ob mice exenatide ameliorated intramyocellular lipid deposition without weight loss [49]. Semaglutide reduces the progression of left atrial remodeling and right ventricular dilation, significantly improving cardiac diastolic function. It also effectively reduced body weight and improved metabolic parameters (such as blood glucose levels and insulin sensitivity), which may indirectly enhance cardiac function [50].

5.2.3 Inhibitors of Sodium-glucose cotransporter 2

Inhibitors of sodium-glucose cotransporter 2 (SGLT2) are commonly used in the treatment of diabetes. Recent studies have found they can also be used in the treatment of patients affected by obesity and AF [51]. These inhibitors reduce renal glucose reabsorption, promoting the excretion of glucose in the urine and thus effectively lowering blood glucose levels. SGLT2 inhibitors improve cardiac load by reducing body weight, which helps to decrease atrial dilation and electrophysiological abnormalities [51]. In patients treated with SGLT2 inhibitors, the risk of new-onset AF in patients with a weight loss of ≥5% was significantly lower than in patients with a weight loss of <5% (1.8% vs 4.0%, respectively) [51]. The evidence for direct electrophysiological effects of SGLT2 inhibitors on the atria is currently less well established compared to their strong indirect benefits. Additionally, SGLT2 inhibitors can alleviate cardiac stress and load by promoting diuresis, lowering blood pressure, and improving vascular function, thereby reducing atrial dilation and electrophysiological disturbances [51]. Therefore, SGLT2 inhibitors are beneficial not only for the treatment of diabetes, but also for managing AF in patients with obesity, highlighting their considerable clinical importance.

5.2.4 Emerging Investigational Targets and Future Directions

In addition to established pharmacotherapies, several novel metabolic targets have shown promise in preclinical models of obesity-related AF. However, it is important to emphasize that the following interventions are still at the experimental stage, and their clinical translation requires rigorous validation in future human trials.

Regulation of the nicotinamide adenine dinucleotide (NAD^+)/nicotinamide phosphoribosyltransferase (Nampt) pathway: Nampt is a rate-limiting enzyme that catalyzes NAD^+ salvage pathway and influences cellular energy metabolism and antioxidant capacity by regulating NAD^+ levels [52]. In an obese mouse model of AF, *Nampt* gene knockout led to a significant reduction in NAD^+ levels in cardiac tissue, along with a marked decrease in sirtuin 1 (SIRT1) expression [52]. Concurrently, ROS accumulation in cardiac tissue led to abnormal calcium dynamics in cardiomyocytes, characterized by an imbalance in calcium release and reuptake. Significant changes occurred in the expression of calcium pumps (SERCA) and channels, including ryanodine receptors, while the incidence and duration of AF increased significantly. Supplementation with the NAD^+ precursor nicotinamide riboside (NR) restored cardiac NAD^+ levels, reducing AF duration by approximately 36% (~110 seconds to ~70 seconds) without significantly altering AF incidence [52]. This suggests the NAD/Nampt axis may serve as a novel therapeutic target for AF.

Mitochondrial function activators: Ezetimibe is a cholesterol-lowering drug, while disulfiram is used to treat alcohol dependence. A recent study found these drugs may have useful anti-arrhythmic properties for AF treatment [53]. In mouse models, the application of ezetimibe and disulfiram enhanced calcium ion uptake into mitochondria via the sarcoplasmic reticulum, improving mitochondrial function. This restored cellular energy metabolism and electrophysiological stability, and significantly reduced the frequency and duration of AF [53]. However, the cytotoxic-

ity of these agents at high doses remains a concern, and their safety requires further evaluation. Therefore, while ezetimibe and disulfiram have been identified as effective AF inhibitors in preliminary work, more evidence is needed.

The novel exercise factor β-aminoisobutyric acid (BAIBA): In obese mouse models, BAIBA significantly attenuated atrial structural changes such as myocardial fibrosis and hypertrophy through the dual mechanisms of AMPK signaling pathway activation and improvement in insulin sensitivity. This effectively prevented or delayed the onset of AF [54]. However, BAIBA has not been validated in human models, and its long-term effects remain unclear, requiring further investigation.

Long non-coding RNA (lncRNA) H19: This lncRNA is crucial for metabolic regulation, and its expression is significantly upregulated in the obese state. It regulates the Pink1/Parkin signaling pathway, promoting the autophagy of damaged mitochondria, preventing cellular damage, and reducing oxidative stress and inflammation, thus effectively lowering the risk of arrhythmias such as AF [55]. While lncRNA H19 may play a protective role in the heart, this research remains at the animal experimental stage, and the underlying mechanisms have yet to be fully elucidated.

5.2.5 Pharmacological Efficacy in Obesity

Obesity affects the absorption, excretion, pharmacokinetics, and pharmacodynamics of various anticoagulants. Increased body fat due to obesity may affect warfarin's volume of distribution, necessitating dosage increases to ensure its effectiveness.

A meta-analysis of 89,494 patients with obesity and AF found that novel direct oral anticoagulants (DOACs) such as dabigatran, rivaroxaban, apixaban, and edoxaban were associated with lower risks of stroke and major bleeding [56], while also showing improved adherence [15] compared with warfarin. In subgroup analyses, rivaroxaban and especially apixaban demonstrated better efficacy and safety compared to warfarin. Dabigatran was superior to warfarin only in terms of safety outcomes and required consideration of renal function [57]. Therefore, apixaban appears to have a relative advantage for anticoagulation therapy in patients with obesity and AF.

Beyond the comparative efficacy between DOACs and warfarin, the specific question of whether standard dosing applies to patients with morbid obesity (BMI ≥40 kg/m^2 or weight ≥120 kg) warrants careful consideration. A comprehensive review by Zhao et al. [58] systematically synthesized available pharmacokinetic/pharmacodynamic and clinical data on DOACs in this population, providing drug-specific guidance on whether standard dosing is appropriate. For apixaban and rivaroxaban, standard dosing is effective and safe for both venous thromboembolism (VTE) and AF patients with morbid obesity, as body weight has only a modest or minor influence on drug exposure [58]. For edoxaban, standard dosing may be considered in AF patients, given that trough concentrations and anti-Xa activity appear to be similar across BMI groups. However, data are still lacking for VTE treatment, and its use should be avoided for this indication [58]. Although the use of dabigatran is effective for stroke prevention in AF patients with morbid obesity, pharmacokinetic data show an inverse relationship between body weight and trough concentrations [58]. Furthermore, clinical studies have reported an increased risk of gastrointestinal bleeding, and therefore it should be used with caution. These findings are consistent with the 2023 ACC/AHA/ACCP/HRS atrial fibrillation guideline, which supports the use of DOACs over warfarin in patients with AF and class III obesity (BMI ≥40 kg/m^2) [59].

Obesity exacerbates the difficulty of controlling heart rate, and beta-blockers are commonly used to slow the heart rate in AF patients [60]. A study on diltiazem showed that patients with obesity required higher therapeutic doses to achieve optimal control of heart rate [61]. Thus, obesity increases the difficulty of heart rate control in AF patients.

5.3 Catheter Ablation

Catheter ablation is an effective rhythm-control strategy for AF [47], with primary endpoint analysis showing the 1-year AF-free survival rate was significantly higher in the catheter ablation group than in the combination therapy group (73.0% vs 34.6%). In patients with obesity and AF, catheter ablation carries a significantly higher risk of failure, primarily due to the presence of epicardial fat accumulation, inflammation, and atrial fibrosis, creating a substrate that is conducive to the initiation of AF, but suboptimal for ablation [62]. These patients are also at high risk of developing stiff left atrial syndrome, which occurs in approximately 10% of the general ablation population. The procedure itself can lead to scar formation replacing up to 30–35% of the left atrial wall, and may cause short-term worsening of heart failure in 15–30% of patients [62]. Therefore, proactive weight loss is a cornerstone strategy for improving atrial substrate, enhancing ablation efficacy, and reducing procedural risks [62]. In clinical practice, the recommendation is to integrate catheter ablation with structured lifestyle intervention and individualized treatment strategies, thereby achieving the dual goals of arrhythmia control and systemic improvement of metabolic risk (Table 2, Ref. [47,48,50,51,52,53,54]).

These observations have prompted large-scale studies to systematically evaluate the safety and efficacy of catheter ablation across the full spectrum of obesity categories. A meta-analysis by Wong et al. [63], encompassing 51 studies and 626,603 individuals, found a dose-response relationship between BMI and post-ablation AF recurrence, with a 13% greater risk for every 5-unit increase in BMI. Tabaja et al. [64] further evaluated 5841 patients and reported that major procedural complications were low (1.5%) across all BMI groups. However, class III obesity (BMI ≥40 kg/m^2)

Table 2. Management of obesity-related atrial fibrillation.

Clinical evidence level	Intervention	Rationale	Notes	Reference
Established	Lifestyle (weight loss)	PRAGUE-25: 6.4 kg weight loss with significant metabolic benefits, although inferior to ablation for rhythm control at 1 year.	Cornerstone cardiometabolic therapy; essential adjunct to ablation.	[47]
Established	Catheter ablation	Eliminates pulmonary vein triggers. PRAGUE-25 study: superior to drug/lifestyle therapy in patients with obesity (AF-free survival: 73.0% vs 34.6%).	Effective rhythm control. Success depends on concomitant weight management.	[47]
Preclinical	Metformin	Activates AMPK, reduces epicardial adipose tissue inflammation. Preclinical studies confirm reduced AF susceptibility.	Pleiotropic agent. Should be prioritized for patients with insulin resistance/diabetes.	[48]
Established	GLP-1 RAs (e.g., Semaglutide)	Potent weight loss, direct cardioprotection. Significant weight reduction and improved cardiac outcomes.	Transformative therapy. Targets the root cause (obesity). Monitor heart rate.	[50]
Established	SGLT2is (e.g., Empagliflozin)	Weight loss, hemodynamic improvement. ≥5% weight loss → lower risk of new-onset AF.	Established cardiovascular benefits. AF protection is linked to weight loss.	[51]
Preclinical	NAD^+ precursors (e.g., NR)	Improves energy/redox balance. Preclinical studies show shortened AF duration.	Metabolic target. Preclinical stage.	[52]
Preclinical	Mitochondrial modulators (e.g., Ezetimibe)	Enhances mitochondrial Ca^{2+} uptake. Preclinical studies show anti-arrhythmic effects.	Drug repurposing. Awaiting clinical validation.	[53]
Preclinical	β-aminoisobutyric acid	Activates AMPK, anti-fibrotic. Prevents AF in preclinical studies.	Exercise mimetic. Promising, but not yet in clinical trials.	[54]

This table outlines a stratified, multi-target management strategy for obesity-related AF. Lifestyle intervention for weight loss is the indispensable foundation of all therapy. Catheter ablation is an effective rhythm-control procedure, and its success in patients with obesity is enhanced by concurrent weight management. Pharmacotherapy should prioritize agents offering dual benefits of weight loss and cardiometabolic improvement (e.g., GLP-1 RAs, SGLT2is). Investigational strategies represent novel therapeutic targets, which are still primarily in the preclinical stage. Abbreviations: AF, atrial fibrillation; AMPK, AMP-activated protein kinase; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; NR, nicotinamide riboside; SGLT2is, sodium-glucose cotransporter 2 inhibitors.

was independently associated with a 30% increased risk of AF recurrence at 3 years (HR 1.30, 95% CI 1.06–1.60), with the recurrence rate reaching 48% in morbidly obese patients compared with approximately 35% in normal weight and class I obesity groups [64]. The safety of AF ablation across all obesity categories was further confirmed by Bar-Moshe et al. [65], who reported low and comparable periprocedural complication rates between groups. Notably, Ciconte et al. [66] demonstrated that metabolic therapy as an adjunct can improve ablation outcomes—in patients with obesity and paroxysmal AF, semaglutide therapy was associated with significantly higher 18-month freedom from recurrence (80.2% vs 65.2%, HR 0.52, 95% CI 0.34–0.78) and substantial weight reduction (–11.8 kg vs –1.9 kg). Collectively, these findings reinforce that catheter ablation is safe in patients with obesity, with complication rates comparable to those in non-obese individuals. Nevertheless, its efficacy is attenuated by higher BMI and can be enhanced by concomitant weight management and metabolic therapy.

6. Conclusions

Obesity significantly increases the risk of AF through multiple mechanisms, including structural remodeling, electrical remodeling, and autonomic dysfunction. Lifestyle modification and sustained weight management are core components of AF management and substantial weight loss forms an indispensable foundation of therapy. Pharmacological strategies must be adapted to the individual, and caution is advised with sodium channel blockers. Antiarrhythmic agents that are less affected by obesity, and medications with dual cardiometabolic benefits (e.g., SGLT2 inhibitors, GLP-1 receptor agonists) should be prioritized where appropriate. Catheter ablation should be integrated with sustained weight management, and DOACs

are preferred for stroke prevention. Obesity necessitates a shift in AF care, focusing on personalized treatment plans that address its root causes rather than a one-size-fits-all approach to improve therapeutic efficacy and safety.

Thus, a personalized, multi-targeted approach that addresses obesity is essential for improving outcomes. Future research should further clarify the hierarchy of pathogenic mechanisms and validate integrated management strategies within this population.

Author Contributions

WRW, HWG, and TPW wrote the manuscript. XLZ, HHL, and YL provided help and advice. WRW, HWG, TPW, XLZ, HHL, and YL all made substantial contributions to the conception or design of the work and the acquisition, analysis, interpretation of data. LLQ and RXW designed the title and research direction and critically revised the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Dai H, Zhang Q, Much AA, Maor E, Segev A, Beinart R, et al. Global, regional, and national prevalence, incidence, mortality, and risk factors for atrial fibrillation, 1990-2017: results from the Global Burden of Disease Study 2017. European Heart Journal. Quality of Care & Clinical Outcomes. 2021; 7: 574–582. https://doi.org/10.1093/ehjqcco/qcaa061

[2] Kornej J, Börschel CS, Benjamin EJ, Schnabel RB. Epidemiology of Atrial Fibrillation in the 21st Century: Novel Methods and New Insights. Circulation Research. 2020; 127: 4–20. https://doi.org/10.1161/CIRCRESAHA.120.316340

[3] Shi S, Tang Y, Zhao Q, Yan H, Yu B, Zheng Q, et al. Prevalence and risk of atrial fibrillation in China: A national cross-sectional epidemiological study. The Lancet Regional Health. Western Pacific. 2022; 23: 100439. https://doi.org/10.1016/j.lanwpc.2022.100439

[4] Joglar JA, Chung MK, Armbruster AL, Benjamin EJ, Chyou JY, Cronin EM, et al. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2024; 149: e1–e156. https://doi.org/10.1161/CIR.0000000000001193

[5] World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organization Technical Report Series. 2000; 894: 1–253.

[6] Wang L, Zhou B, Zhao Z, Yang L, Zhang M, Jiang Y, et al. Body-mass index and obesity in urban and rural China: findings from consecutive nationally representative surveys during 2004-18. Lancet (London, England). 2021; 398: 53–63. https://doi.org/10.1016/S0140-6736(21)00798-4

[7] Zhao M, Song L, Zhao Q, Chen Y, Li B, Xie Z, et al. Elevated levels of body mass index and waist circumference, but not high variability, are associated with an increased risk of atrial fibrillation. BMC Medicine. 2022; 20: 215. https://doi.org/10.1186/s12916-022-02413-1

[8] Berkovitch A, Kivity S, Klempfner R, Segev S, Milwidsky A, Erez A, et al. Body mass index and the risk of new-onset atrial fibrillation in middle-aged adults. American Heart Journal. 2016; 173: 41–48. https://doi.org/10.1016/j.ahj.2015.11.016

[9] Deng Y, Li L, Li Q, Guo J, Cai B, Zhou F, et al. Central obesity as a potential causal risk factor for atrial fibrillation: evidence from Mendelian randomization study. Europace : European Pacing, Arrhythmias, and Cardiac Electrophysiology : Journal of the Working Groups on Cardiac Pacing, Arrhythmias, and Cardiac Cellular Electrophysiology of the European Society of Cardiology. 2024; 26: euae061. https://doi.org/10.1093/europace/euae061

[10] Nyström PK, Carlsson AC, Leander K, de Faire U, Hellenius ML, Gigante B. Obesity, metabolic syndrome and risk of atrial fibrillation: a Swedish, prospective cohort study. PLoS One. 2015; 10: e0127111. https://doi.org/10.1371/journal.pone.0127111

[11] Singleton MJ, German CA, Carnethon M, Soliman EZ, Bertoni AG, Yeboah J. Race, Body Mass Index, and the Risk of Atrial Fibrillation: The Multi-Ethnic Study of Atherosclerosis. Journal of the American Heart Association. 2021; 10: e018592. https://doi.org/10.1161/JAHA.120.018592

[12] West HW, Siddique M, Williams MC, Volpe L, Desai R, Lyasheva M, et al. Deep-Learning for Epicardial Adipose Tissue Assessment With Computed Tomography: Implications for Cardiovascular Risk Prediction. JACC. Cardiovascular Imaging. 2023; 16: 800–816. https://doi.org/10.1016/j.jcmg.2022.11.018

[13] Lee HJ, Choi EK, Han KD, Kim DH, Lee E, Lee SR, et al. High variability in bodyweight is associated with an increased risk of atrial fibrillation in patients with type 2 diabetes mellitus: a nationwide cohort study. Cardiovascular Diabetology. 2020; 19: 78. https://doi.org/10.1186/s12933-020-01059-8

[14] Choi SH, Yang PS, Kim D, Sung JH, Jang E, Yu HT, et al. Association of obesity with incident atrial fibrillation in Korea and the United Kingdom. Scientific Reports. 2023; 13: 5197. https://doi.org/10.1038/s41598-023-32229-9

[15] Lima Filho AIN, do Rego Barros MC, de Barros Guimarães AA, Celestino Sobral Filho D. Obesity Paradox in Atrial Fibrillation and its Relation with the New Oral Anticoagulants. Current Cardiology Reviews. 2022; 18: 8–10. https://doi.org/10.2174/1573403X18666220324111343

[16] Li YG, Xie PX, Alsheikh-Ali AA, AlMahmeed W, Sulaiman K, Asaad N, et al. The "obesity paradox" in patients with atrial fibrillation: Insights from the Gulf SAFE registry. Frontiers in Cardiovascular Medicine. 2022; 9: 1032633. https://doi.org/10.3389/fcvm.2022.1032633

[17] Meulendijks ER, Al-Shama RFM, Kawasaki M, Fabrizi B, Neefs J, Wesselink R, et al. Atrial epicardial adipose tissue abundantly secretes myeloperoxidase and activates atrial fibroblasts in patients with atrial fibrillation. Journal of Translational Medicine. 2023; 21: 366. https://doi.org/10.1186/s12967-023-04231-2

[18] Mahajan R, Lau DH, Brooks AG, Shipp NJ, Wood JPM, Manavis J, et al. Atrial Fibrillation and Obesity: Reverse Remodeling of Atrial Substrate With Weight Reduction. JACC. Clinical Electrophysiology. 2021; 7: 630–641. https://doi.org/10.1016/j.jacep.2020.11.015

[19] Gutiérrez-Cuevas J, Galicia-Moreno M, Monroy-Ramírez HC, Sandoval-Rodriguez A, García-Bañuelos J, Santos A, et al. The Role of NRF2 in Obesity-Associated Cardiovascular Risk Factors. Antioxidants (Basel, Switzerland). 2022; 11: 235. https://doi.org/10.3390/antiox11020235

[20] Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. The Journal of Clinical Investigation. 2003; 112: 1796–1808. https://doi.org/10.1172/JCI19246

[21] Cabaro S, Conte M, Moschetta D, Petraglia L, Valerio V, Romano S, et al. Epicardial Adipose Tissue-Derived IL-1β Triggers Postoperative Atrial Fibrillation. Frontiers in Cell and Developmental Biology. 2022; 10: 893729. https://doi.org/10.3389/fcell.2022.893729

[22] Petraglia L, Conte M, Comentale G, Cabaro S, Campana P, Russo C, et al. Epicardial Adipose Tissue and Postoperative Atrial Fibrillation. Frontiers in Cardiovascular Medicine. 2022; 9: 810334. https://doi.org/10.3389/fcvm.2022.810334

[23] Yao C, Veleva T, Scott L, Jr, Cao S, Li L, Chen G, et al. Enhanced Cardiomyocyte NLRP3 Inflammasome Signaling Promotes Atrial Fibrillation. Circulation. 2018; 138: 2227–2242. https://doi.org/10.1161/CIRCULATIONAHA.118.035202

[24] Xiao L, Magupalli VG, Wu H. Cryo-EM structures of the active NLRP3 inflammasome disc. Nature. 2023; 613: 595–600. https://doi.org/10.1038/s41586-022-05570-8

[25] Christgen S, Place DE, Kanneganti TD. Toward targeting inflammasomes: insights into their regulation and activation. Cell Research. 2020; 30: 315–327. https://doi.org/10.1038/s41422-020-0295-8

[26] Balan AI, Halațiu VB, Scridon A. Oxidative Stress, Inflammation, and Mitochondrial Dysfunction: A Link between Obesity and Atrial Fibrillation. Antioxidants (Basel, Switzerland). 2024; 13: 117. https://doi.org/10.3390/antiox13010117

[27] Sridhar A, DeSantiago J, Chen H, Pavel MA, Ly O, Owais A, et al. Modulation of NOX2 causes obesity-mediated atrial fibrillation. The Journal of Clinical Investigation. 2024; 134: e175447. https://doi.org/10.1172/JCI175447

[28] Kong B, Fu H, Xiao Z, Zhou Y, Shuai W, Huang H. Gut Microbiota Dysbiosis Induced by a High-Fat Diet Increases Susceptibility to Atrial Fibrillation. The Canadian Journal of Cardiology. 2022; 38: 1962–1975. https://doi.org/10.1016/j.cjca.2022.08.231

[29] Zhang Y, Fu Y, Jiang T, Liu B, Sun H, Zhang Y, et al. Enhancing Fatty Acids Oxidation *via* L-Carnitine Attenuates Obesity-Related Atrial Fibrillation and Structural Remodeling by Activating AMPK Signaling and Alleviating Cardiac Lipotoxicity. Frontiers in Pharmacology. 2021; 12: 771940. https://doi.org/10.3389/fphar.2021.771940

[30] Chan YH, Chang GJ, Lai YJ, Chen WJ, Chang SH, Hung LM, et al. Atrial fibrillation and its arrhythmogenesis associated with insulin resistance. Cardiovascular Diabetology. 2019; 18: 125. https://doi.org/10.1186/s12933-019-0928-8

[31] Considine RV, Premkumar A, Reynolds JC, Sebring NG, Ricks M, Sumner AE. Adiponectin and leptin in African Americans. Obesity (Silver Spring, Md.). 2008; 16: 428–434. https://doi.org/10.1038/oby.2007.80

[32] Ahiante BO, Smith W, Lammertyn L, Schutte AE. Leptin and the vasculature in young adults: The African-PREDICT study. European Journal of Clinical Investigation. 2019; 49: e13039. https://doi.org/10.1111/eci.13039

[33] Fukui A, Ikebe-Ebata Y, Kondo H, Saito S, Aoki K, Fukunaga N, et al. Hyperleptinemia Exacerbates High-Fat Diet-Mediated Atrial Fibrosis and Fibrillation. Journal of Cardiovascular Electrophysiology. 2017; 28: 702–710. https://doi.org/10.1111/jce.13200

[34] Bapat A, Li G, Xiao L, Yeri A, Hulsmans M, Grune J, et al. Genetic inhibition of serum glucocorticoid kinase 1 prevents obesity-related atrial fibrillation. JCI Insight. 2022; 7: e160885. https://doi.org/10.1172/jci.insight.160885

[35] Chen Y, Li B, Liu J, Liu J, Liu C, Zhu Y, et al. Association of the chemerin-CMKLR1 with atrial potassium current dysregulation and atrial fibrillation in obese mice. Channels (Austin, Tex.). 2026; 20: 2611704. https://doi.org/10.1080/19336950.2025.2611704

[36] McCauley MD, Hong L, Sridhar A, Menon A, Perike S, Zhang M, et al. Ion Channel and Structural Remodeling in Obesity-Mediated Atrial Fibrillation. Circulation. Arrhythmia and Electrophysiology. 2020; 13: e008296. https://doi.org/10.1161/CIRCEP.120.008296

[37] Lin YK, Chen YC, Chen JH, Chen SA, Chen YJ. Adipocytes modulate the electrophysiology of atrial myocytes: implications in obesity-induced atrial fibrillation. Basic Research in Cardiology. 2012; 107: 293. https://doi.org/10.1007/s00395-012-0293-1

[38] Cao Z, Fu Y, Ke Y, Li Y, Guo K, Long X, et al. Mitochondrial damage mediates STING activation driving obesity-mediated atrial fibrillation. Europace : European Pacing, Arrhythmias, and Cardiac Electrophysiology : Journal of the Working Groups on Cardiac Pacing, Arrhythmias, and Cardiac Cellular Electrophysiology of the European Society of Cardiology. 2025; 27: euaf081. https://doi.org/10.1093/europace/euaf081

[39] Chadda KR, Edling CE, Valli H, Ahmad S, Huang CLH, Jeevaratnam K. Gene and Protein Expression Profile of Selected Molecular Targets Mediating Electrophysiological Function in *Pgc-1α* Deficient Murine Atria. International Journal of Molecular Sciences. 2018; 19: 3450. https://doi.org/10.3390/ijms19113450

[40] Fan Y, Huang S, Li S, Wu B, Zhao Q, Huang L, et al. The adipose-neural axis is involved in epicardial adipose tissue-related cardiac arrhythmias. Cell Reports. Medicine. 2024; 5: 101559. https://doi.org/10.1016/j.xcrm.2024.101559

[41] Yoo S, Aistrup G, Shiferaw Y, Ng J, Mohler PJ, Hund TJ, et al. Oxidative stress creates a unique, CaMKII-mediated substrate for atrial fibrillation in heart failure. JCI Insight. 2018; 3: e120728. https://doi.org/10.1172/jci.insight.120728

[42] Dobrev D, Wehrens XHT. Calcium-mediated cellular triggered activity in atrial fibrillation. The Journal of Physiology. 2017; 595: 4001–4008. https://doi.org/10.1113/JP273048

[43] Sha R, Baines O, Hayes A, Tompkins K, Kalla M, Holmes AP, et al. Impact of Obesity on Atrial Fibrillation Pathogenesis and Treatment Options. Journal of the American Heart Association. 2024; 13: e032277. https://doi.org/10.1161/JAHA.123.032277

[44] Parisi V, Petraglia L, Cabaro S, D'Esposito V, Bruzzese D, Ferraro G, et al. Imbalance Between Interleukin-1β and Interleukin-1 Receptor Antagonist in Epicardial Adipose Tissue Is Associated With Non ST-Segment Elevation Acute Coronary Syndrome. Frontiers in Physiology. 2020; 11: 42. https://doi.org/10.3389/fphys.2020.00042

[45] Hsu LA, Yeh YH, Chang CJ, Chen WJ, Tsai HY, Chang GJ. Aldehyde Dehydrogenase 2 (ALDH2) Deficiency, Obesity, and Atrial Fibrillation Susceptibility: Unraveling the Connection. International Journal of Molecular Sciences. 2024; 25: 2186. https://doi.org/10.3390/ijms25042186

[46] Celebi LE, Zorlutuna P. 3D Bioprinted Fat-Myocardium Model Unravels the Role of Adipocyte Hypertrophy in Atrial Dysfunction. Advanced Science (Weinheim, Baden-Wurttemberg, Germany). 2026; 13: e16114. https://doi.org/10.1002/advs

.202516114

[47] Osmancik P, Roubicek T, Havranek S, Chovancik J, Bulkova V, Herman D, et al. Catheter Ablation vs Lifestyle Modification With Antiarrhythmic Drugs to Treat Atrial Fibrillation: PRAGUE-25 Trial. Journal of the American College of Cardiology. 2025; 86: 18–28. https://doi.org/10.1016/j.jacc.2025.04.042

[48] Li B, Po SS, Zhang B, Bai F, Li J, Qin F, et al. Metformin regulates adiponectin signalling in epicardial adipose tissue and reduces atrial fibrillation vulnerability. Journal of Cellular and Molecular Medicine. 2020; 24: 7751–7766. https://doi.org/10.1111/jcmm.15407

[49] Xu F, Cao H, Chen Z, Gu H, Guo W, Lin B, et al. Short-term GLP-1 receptor agonist exenatide ameliorates intramyocellular lipid deposition without weight loss in ob/ob mice. International Journal of Obesity (2005). 2020; 44: 937–947. https://doi.org/10.1038/s41366-019-0513-y

[50] Solomon SD, Ostrominski JW, Wang X, Shah SJ, Borlaug BA, Butler J, et al. Effect of Semaglutide on Cardiac Structure and Function in Patients With Obesity-Related Heart Failure. Journal of the American College of Cardiology. 2024; 84: 1587–1602. https://doi.org/10.1016/j.jacc.2024.08.021

[51] Chan YH, Chen SW, Chao TF, Kao YW, Huang CY, Chu PH. The impact of weight loss related to risk of new-onset atrial fibrillation in patients with type 2 diabetes mellitus treated with sodium-glucose cotransporter 2 inhibitor. Cardiovascular Diabetology. 2021; 20: 93. https://doi.org/10.1186/s12933-021-01285-8

[52] Feng D, Xu D, Murakoshi N, Tajiri K, Qin R, Yonebayashi S, et al. Nicotinamide Phosphoribosyltransferase (Nampt)/Nicotinamide Adenine Dinucleotide (NAD) Axis Suppresses Atrial Fibrillation by Modulating the Calcium Handling Pathway. International Journal of Molecular Sciences. 2020; 21: 4655. https://doi.org/10.3390/ijms21134655

[53] Sander P, Feng M, Schweitzer MK, Wilting F, Gutenthaler SM, Arduino DM, et al. Approved drugs ezetimibe and disulfiram enhance mitochondrial Ca^{2+} uptake and suppress cardiac arrhythmogenesis. British Journal of Pharmacology. 2021; 178: 4518–4532. https://doi.org/10.1111/bph.15630

[54] Qin X, Liu P, Jin L, Zhu K, Yang Y, Hou Z, et al. Exerkine β-aminoisobutyric acid protects against atrial structural remodeling and atrial fibrillation in obesity via activating AMPK signaling and improving insulin sensitivity. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie. 2024; 171: 116137. https://doi.org/10.1016/j.biopha.2024.116137

[55] Wang SH, Zhu XL, Wang F, Chen SX, Chen ZT, Qiu Q, et al. LncRNA H19 governs mitophagy and restores mitochondrial respiration in the heart through Pink1/Parkin signaling during obesity. Cell Death & Disease. 2021; 12: 557. https://doi.org/10.1038/s41419-021-03821-6

[56] Zhou Y, Ma J, Zhu W. Efficacy and Safety of Direct Oral Anticoagulants Versus Warfarin in Patients with Atrial Fibrillation Across BMI Categories: A Systematic Review and Meta-Analysis. American Journal of Cardiovascular Drugs : Drugs, Devices, and other Interventions. 2020; 20: 51–60. https://doi.org/10.1007/s40256-019-00362-4

[57] Mhanna M, Beran A, Al-Abdouh A, Sajdeya O, Abdulsattar W, Srour O, et al. Direct Oral Anticoagulants Versus Warfarin in Morbidly Obese Patients With Nonvalvular Atrial Fibrillation: A Systematic Review and Meta-analysis. American Journal of Therapeutics. 2021; 28: e531–e539. https://doi.org/10.1097/MJT.0000000000001403

[58] Zhao Y, Guo M, Li D, Xu W, Pan C, He C, et al. Pharmacokinetics and Dosing Regimens of Direct Oral Anticoagulants in Morbidly Obese Patients: An Updated Literature Review. Clinical and Applied Thrombosis/hemostasis : Official Journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis. 2023; 29: 10760296231153638. https://doi.org/10.1177/10760296231153638

[59] Writing Committee Members, Joglar JA, Chung MK, Armbruster AL, Benjamin EJ, Chyou JY, et al. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Journal of the American College of Cardiology. 2024; 83: 109–279. https://doi.org/10.1016/j.jacc.2023.08.017

[60] Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. European Heart Journal. 2021; 42: 373–498. https://doi.org/10.1093/eurheartj/ehaa612

[61] Ward SM, Radke J, Calhoun C, Caporossi J, Hall GA, Matuskowitz AJ, et al. Weight-based versus non-weight-based diltiazem dosing in the setting of atrial fibrillation with rapid ventricular response. The American Journal of Emergency Medicine. 2020; 38: 2271–2276. https://doi.org/10.1016/j.ajem.2019.09.020

[62] Packer M. Effect of catheter ablation on pre-existing abnormalities of left atrial systolic, diastolic, and neurohormonal functions in patients with chronic heart failure and atrial fibrillation. European Heart Journal. 2019; 40: 1873–1879. https://doi.org/10.1093/eurheartj/ehz284

[63] Wong CX, Sullivan T, Sun MT, Mahajan R, Pathak RK, Middeldorp M, et al. Obesity and the Risk of Incident, Post-Operative, and Post-Ablation Atrial Fibrillation: A Meta-Analysis of 626,603 Individuals in 51 Studies. JACC. Clinical Electrophysiology. 2015; 1: 139–152. https://doi.org/10.1016/j.jacep.2015.04.004

[64] Tabaja C, Younis A, Santageli P, Farwati M, Braghieri L, Nakagawa H, et al. Impact of obesity on catheter ablation of atrial fibrillation: Patient characteristics, procedural complications, outcomes, and quality of life. Journal of Cardiovascular Electrophysiology. 2023; 34: 1648–1657. https://doi.org/10.1111/jce.15987

[65] Bar-Moshe A, Tsaban G, Dan I, Marai I, Michowitz Y, Glikson M, et al. Does obesity affect atrial fibrillation ablation outcomes? Insights from a national atrial fibrillation catheter ablation registry: One-year follow-up. Heart Rhythm O2. 2025; 7: 27–36. https://doi.org/10.1016/j.hroo.2025.10.008

[66] Ciconte G, Salerno R, Fuga A, Vuturo A, Boccellino A, Negro G, et al. Semaglutide as adjunctive therapy to catheter ablation in obesity-related paroxysmal atrial fibrillation. Europace : European Pacing, Arrhythmias, and Cardiac Electrophysiology : Journal of the Working Groups on Cardiac Pacing, Arrhythmias, and Cardiac Cellular Electrophysiology of the European Society of Cardiology. 2026; 28: euag018. https://doi.org/10.1093/europace/euag018