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REVIEW

Obesity and Atrial Fibrillation: From Mechanisms to Treatment

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By 2050, it is projected that 3.8 billion people worldwide will be overweight or obese. Alongside this growing burden of obesity is a parallel rise in the incidence and prevalence of atrial fibrillation (AF). Obesity promotes the onset of AF through several pathways, including left atrial remodelling, accumulation of epicardial adipose tissue, alterations in cardiac loading, increased inflammation, and renin-angiotensin-aldosterone system activation. In parallel, obesity frequently coexists with and can contribute to comorbidities, including hypertension, type 2 diabetes, and obstructive sleep apnoea. The past decade has seen the introduction of comorbidity and risk factor treatment as the central pillar in the care of patients with AF based on studies showing that weight loss reduces the recurrence of symptomatic AF. As we move deeper into the era of pharmacological treatment for obesity, new opportunities will appear to refine the care of patients living with AF. This review summarises the existing evidence supporting obesity as a major risk factor for AF and discusses the therapeutic options to treat obesity and prevent the growing burden of AF in the community.

Keywords Adiposity • Arrythmia • Risk factor • Prevention

Introduction

Long before obesity became a global health crisis, Hippocrates observed that "corpulence is not only a disease itself but the harbinger of others." Over two millennia later, this ancient insight has been supported through decades of observation and research highlighting the profound and sustained effects of obesity on health. Obesity is strongly associated with increased risk of diabetes, hypertension, stroke, coronary disease, and sudden cardiac death [1]. Despite these well-documented adverse health outcomes, obesity rates continue to rise worldwide. Worldwide, >45% or >2.1 billion adults are overweight or obese [2], a value projected to exceed 3.8 billion by 2050.

The upward trend in obesity prevalence parallels that seen with atrial fibrillation (AF), in which incident AF has almost doubled since 1990. Recent estimates suggest over 59 million people are now affected by AF worldwide [3]. In Australia, AF cases are projected to double between 2014 and 2034, increasing prevalence to 6.4% [4]. The growing prevalence of obesity is probably a significant contributor to the growth of AF in the community (Figure 1). Each 5-unit rise in body mass index (BMI) confers a 29% increased risk of developing AF [5]. Moreover, individuals with at least one cardiometabolic risk factor, including obesity, have a one in three lifetime risk of developing AF [6]. Obesity is second only to hypertension in contributing to the population attributable risk for developing AF, even when stratified by age or genetic risk tertile

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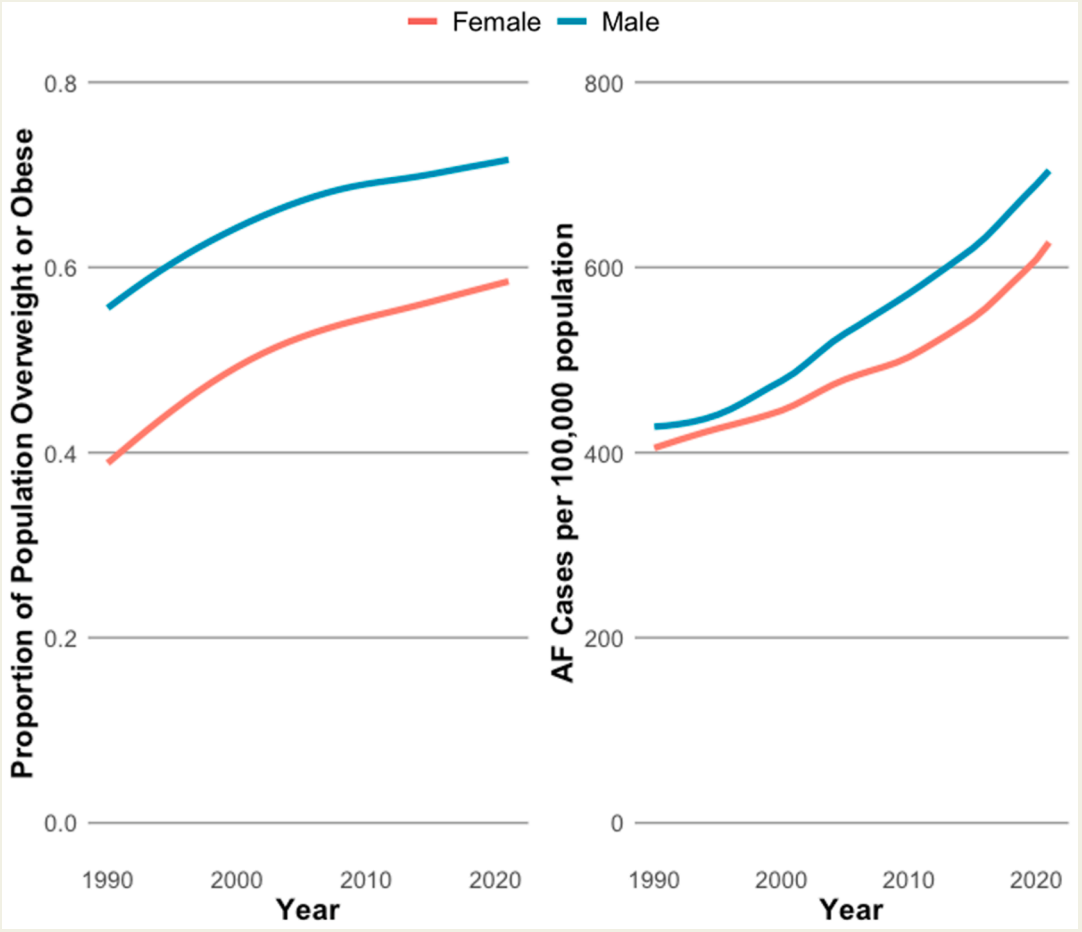

Figure 1 Trends in overweight and obesity (body mass index >25 kg/m^2) and AF in Australia from 1990 to 2021. Data are adapted from the NCD Risk Factor Collaboration (https://ncdrisc.org/index.html) and the Global Burden of Disease study (https://ghdx.healthdata.org/).
Abbreviation: AF, atrial fibrillation.

[7]. Beyond the initiation of AF, obesity contributes to its persistence [8], clinical severity [9,10], and progression [11]. The effect of obesity is probably driven through several mechanisms, including inflammation [12], neurohormonal alterations [13], and electrical and structural remodelling of the atria that contributes to the development of an arrhythmogenic substrate [14].

As a modifiable risk factor for AF, obesity provides a target for lifestyle, surgical, and pharmacological intervention. Over the past decade, weight loss, alongside aggressive risk factor reduction, has emerged as a frontline treatment in the care of patients living with AF as an effective strategy to restore and maintain sinus rhythm. The relevance of obesity management in the AF clinic has garnered greater attention in the era of new therapies, including glucagon-like peptide-1 (GLP-1) receptor agonists, that may play a substantial role in primary and secondary AF prevention.

This review explores the complex interplay between obesity and AF, focusing on the underlying mechanisms linking the two conditions: the development of comorbidities such as heart failure with preserved ejection fraction (HFpEF) and the effect of weight loss therapies, including the emergence of GLP-1 receptor agonists.

Mechanisms Linking Obesity to Atrial Fibrillation

The relationship between obesity and AF are well-established for men and women, with large cohort data showing that each unit increase in BMI is associated with a 5% and 4% increase in risk of AF, respectively [15]. There are several known pathways by which obesity mediates the development and progression of AF, including inflammation, neurohormonal activation, alterations in cardiac structure and function, and the effects of cardiac fat depots (Figure 2).

Left Atrial Haemodynamics and Enlargement

An increase in atrial size provides greater opportunity for re-entry mechanisms, leading to the initiation of AF.

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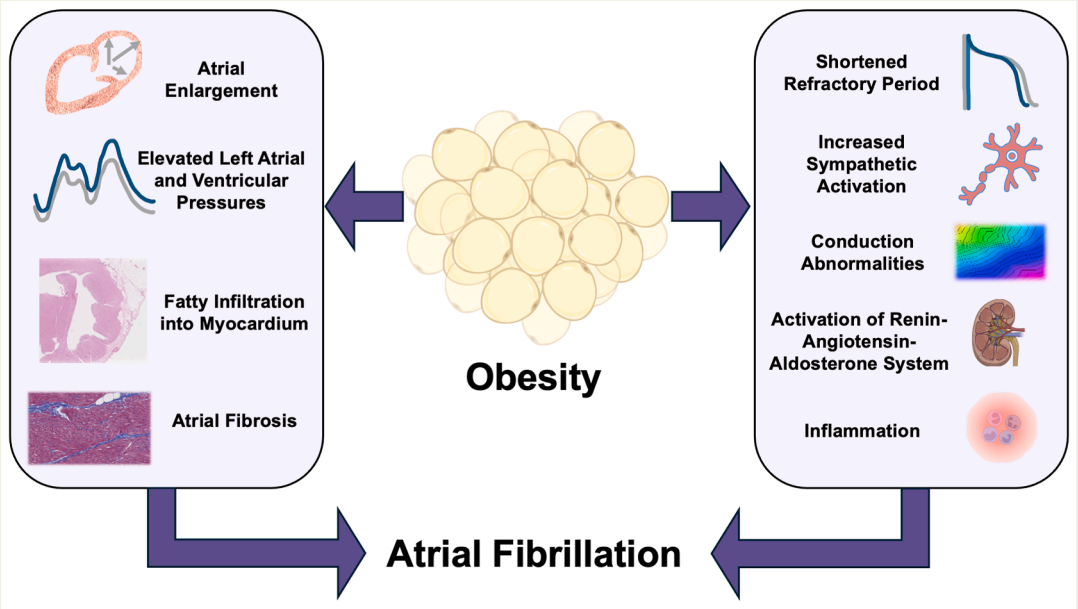

Figure 2 Summary of mechanisms promoting atrial fibrillation as a consequence of obesity. *Created with BioRender.com.*

Imaging studies [16,17] consistently show a strong association between left atrial (LA) enlargement and the incidence of AF. With the onset of obesity, an increase in plasma volume and cardiac output contributes to a volume load that increases LA pressure, stretch, and enlargement [18]. In addition, increased wall stress in the left ventricle leads to concentric remodelling [19] that creates an afterload on the LA. Longitudinal data support that BMI and hypertension are key modifiable determinants of LA size [20].

Epicardial Fat

Pericardial adipose tissue and epicardial adipose tissue (EAT), located in close proximity to the myocardium, exert effects through the circulation and via paracrine signalling. Numerous studies have documented the detrimental effect of EAT on the risk of AF. Individuals with AF have higher EAT volume than healthy individuals [21,22], and EAT is associated with prevalent and incident AF, even when adjusted for other risk factors, including BMI [22]. Greater EAT volumes are associated with lower rates of sinus rhythm maintenance after pulmonary vein isolation [21].

The arrhythmogenic effects of EAT are thought to be mediated by several mechanisms. In obesity, epicardial fat accumulates, leading to reactive inflammation and the synthesis of proinflammatory adipokines that also lead to activation of profibrotic pathways [23]. The absence of a distinct boundary at the epicardial-myocardial surface results in exposure of the underlying atrial myocardium to the proinflammatory and profibrotic effects of EAT. The profibrotic effects of EAT were elegantly demonstrated in an organo-culture model of rat atria, showing that exposure to the human EAT secretome from patients undergoing cardiac surgery induced global fibrosis mediated by specific adipo-fibrokines (activin A) [24]. The influence of the EAT secretome is not only because of this profibrotic effect. In atrial myocytes conditioned with cardiac adipose tissue, there is evidence of conduction slowing and an increase in activation time, providing direct evidence for a paracrine influence of EAT on atrial electrophysiology [25]. Furthermore, epicardial fat secretes extracellular vesicles harbouring increased proinflammatory and profibrotic cytokines that contribute to the pathogenesis of AF [26].

In a large animal model of weight gain, Mahajan et al. [27] showed an increase in LA haemodynamic loading coupled with periatrial epicardial fat accumulation and infiltration into the atrial myocardium. These changes were accompanied by evidence of atrial fibrosis on histology, local inflammation, and electrophysiological changes, including shortened atrial refractory periods and conduction disturbances. Interestingly, after a period of 15% and 30% weight loss, there was partial but not full regression of EAT volume and myocardial infiltration. Based on existing evidence, EAT probably plays a considerable role in the promotion of AF with obesity through several pathways related to factors secreted directly from EAT and the anatomical effects of EAT infiltration into the atrial myocardium.

Inflammation

Adipose tissue functions as an active endocrine organ, releasing proinflammatory cytokines that are increased in patients with obesity. Large cohort data show a positive association between systemic markers of inflammation, such as C-reactive protein, and the incidence and prevalence of AF [28]. Moreover, observational studies show an association between inflammatory biomarker levels and disease

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burden, where higher levels are observed among patients with persistent compared with paroxysmal AF [29].

Excess adipose tissue is associated with increased systemic concentrations of proinflammatory biomarkers including tumour necrosis factor-α [30,31], and interleukin-6 [32]. In obesity, macrophages accumulate within adipose tissue amplifying proinflammatory cytokine production [33] and contributing to insulin resistance [34]. Higher levels of proinflammatory cytokines contribute to a state of chronic low-grade inflammation, which is consistently observed in individuals with obesity [35]. Occurring in the absence of illness or injury, this inflammation is not a protective response but rather a systemic and persistent condition with adverse effects, including electrical and structural atrial remodelling that predispose towards AF [36].

There is evidence that inflammation may contribute to AF pathogenesis through inflammasome signalling in atrial cardiomyocytes [37]. The inflammasome protein complex promotes inflammatory signalling in response to specific stimuli. In a study of atrial tissues sampled from rodents, sheep, and humans, obesity was associated with greater activation of the NLRP3 inflammasome [38]. In support of a direct arrhythmogenic effect of NLRP3, the selective inhibition of NLRP3 in mice with obesity prevents obesity-induced AF [38], raising the potential for novel pharmaceutical agents to target this pathway.

Neurohormonal Effects

Obesity enhances sympathetic nervous system activity and promotes activation of the renin-angiotensin-aldosterone system (RAAS), both of which are key drivers of hypertension and atrial remodelling. Obesity is associated with increased serum levels of angiotensinogen [39] and aldosterone [40], contributing to an increase of vascular resistance, atrial stretch, and structural remodelling via modulation of blood pressure. The mechanisms promoting RAAS activation, particularly, in the context of visceral obesity, are largely because of sympathetic nervous system activation and renal compression [41] as well as dysfunctional adipose tissue that provides a direct local source of RAAS activation [42]. The consequences of RAAS activation are mediated not only through its hypertensive effects but also through direct profibrotic signalling pathways initiated by angiotensin II [43].

The sympathetic overactivation that accompanies obesity leads to chronic increases in heart rate and peripheral vascular resistance, driving hypertension [44]. Individuals with visceral obesity demonstrate greater sympathetic activation than those with peripheral obesity [45], further exacerbating these effects. In the atria, sympathetic activation can induce delayed afterdepolarisations that trigger the initiation of AF, particularly, in the setting of structural heart disease [46]. In parallel, adipokine dysregulation further contributes to these pathological changes. Excess adipose tissue increases leptin secretion, which, when chronically increased, augments sympathetic activity [47]. Conversely, obesity supresses adiponectin levels [48], with low adiponectin associated with sympathetic activation, endothelial dysfunction, impaired nitric oxide production, increased tumour necrosis factor-α expression, and vascular smooth muscle proliferation [49], all mechanisms that promote hypertension and the development of AF.

The EAT that accumulates with obesity may also promote AF through neuromodulation of local cardiac autonomic innervation. Nagashima et al. [50] demonstrated that regions of high dominant frequency, critical for sustaining AF, are located adjacent to EAT deposits, further reinforcing the role of EAT in directly creating the substrate for AF.

Electroanatomical Remodelling

The final common pathway of the mechanisms linking obesity to the risk of AF is probably electroanatomical remodelling in the atria, creating the substrate for AF. In pre-clinical models, the effect of obesity in the LA is evident through slower, fragmented, and more disorganised atrial conduction, resulting in increased inducibility of AF [14,51]. These findings are supported in studies of obese humans in which slowed, fragmented conduction has been observed [52], along with shorter effective refractory periods [18], creating a substrate for AF initiation and maintenance. Regions of low voltage, indicative of fibrosis and loss of viable atrial myocardium, have been demonstrated in patients with obesity, particularly, in regions proximal to deposits of EAT [52].

Development of Comorbidities Associated with Obesity and AF

In patients with AF, the risk of stroke, major cardiac events, and cardiovascular mortality is double that of individuals without AF [53]. Although preventing thromboembolic stroke remains a key priority in AF management, the highest risk is for the development of heart failure. Recent data show that heart failure is the most frequent complication after AF diagnosis, with a lifetime risk of 41.2%, compared with 21.4% for the risk of stroke [54]. Patients with AF also live with a higher burden of comorbidities and risk factors that are accentuated in the presence of obesity, contributing to maintenance and progression of AF, as well as its consequences [55].

Heart Failure With Preserved Ejection Fraction

Heart failure remains a major clinical challenge, marked by poor outcomes, with a 1-year mortality rate of 33% and a 5-year mortality approaching 50% [56]. Obesity is associated with an increased risk of heart failure [57], and this association is stronger in HFpEF than heart failure with reduced ejection fraction. This relationship is particularly pronounced in females in whom obesity appears to predispose women to a higher risk of developing future HFpEF [58].

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Several studies have proposed an obesity-related phenotype of HFpEF [59], characterised by cardiomegaly, increased pericardial restraint, and ventricular interdependence contributing to a rise in LA pressure. Beyond general measures of adiposity, EAT has emerged a contributor to the haemodynamic and functional impairments observed in HFpEF. In an obese cohort, individuals with higher EAT demonstrated increased pericardial restraint, probably contributing to the high resting and exercise left ventricular filling pressures and reduced exercise capacity that are hallmarks of HFpEF [60].

Atrial fibrillation and HFpEF share common risk factors, including age, hypertension, obesity, and diabetes, and can be indistinguishable in some patients because of overlapping symptoms and pathophysiology [61]. In a cohort of consecutive patients undergoing catheter ablation for symptomatic AF, 73% of patients had increased LA pressures (>15 mmHg) at rest or after a 500 mL fluid challenge, indicating high burden of subclinical HFpEF [62]. In this study, patients with evidence of HFpEF had a greater BMI than those without HFpEF. These findings have been reinforced elsewhere using right-sided cardiac catheterisation to diagnose the haemodynamic features of HFpEF [63]. Beyond the shared risk factors such as hypertension and type II diabetes (T2DM) that promote AF and HFpEF, it is probable that pericardial and epicardial adiposity may be a central mechanism promoting electrophysiological effects through its infiltration into the atrial myocardium, coupled with external mechanical constraint contributing to the increase in left-sided filling pressures.

Stroke Risk

General and central adiposity are associated with increased risk of ischaemic stroke [64]. In large cohort studies, central adiposity measures (i.e., waist circumference) carry a stronger association with stroke risk than general adiposity measures (i.e., BMI) [65]. In patients with AF, measures of adiposity are not featured in the CHA_2DS-VA scoring system to determine thromboembolic stroke risk and subsequent need for anticoagulation. However, obesity is probable to mediate influence through hypertension, T2DM, and the presence of vascular disease, all of which are independently promoted by obesity. Additionally, obesity is well-recognised to promote the atrial remodelling that underlies the atrial cardiomyopathy, leading to embolic stroke independent of the atrial rhythm [66].

Hypertension

Obesity is a key risk factor for the development of hypertension, which, in turn, contributes to the pathogenesis of AF. The strength of this relationship is highlighted by Framingham data showing that obesity accounts for 65% of hypertension cases in women and 78% in men [67]. Hypertension is the most prevalent modifiable risk factor in AF, with large registry data reporting a prevalence as high as 83% [68]. In large animal models, hypertension accelerates structural and electrical changes in the atria, independent of obesity [69]. As reviewed previously, obesity contributes to RAAS activation and sympathetic drive that leads to the onset of hypertension.

Type 2 Diabetes Mellitus

Obesity is a primary driver in the development of T2DM, with approximately 90% of T2DM cases attributable to excess weight [70]. T2DM contributes to the development of AF through several mechanisms of atrial remodelling, including structural [71], electrical [72], and electromechanical [73], and autonomic changes [74]. Obesity, particularly, with excess central adiposity, directly induces B-cell dysfunction and insulin resistance that leads towards T2DM diagnosis, which subsequently complicates the management of AF by reducing the outcomes of rhythm control interventions [75] and raising thromboembolic stroke risk [76].

Obstructive Sleep Apnoea

Obesity is a well-established risk factor for obstructive sleep apnoea (OSA) [77]. Although central adiposity has been shown to have a stronger correlation with OSA in some studies [78], other studies have identified an effect of fat distributed around the upper airway [79]. Beyond its association with obesity, OSA is an independent risk factor for AF [80]. In individuals aged <65 years, OSA has been shown to strongly predict the development of AF within 5 years of diagnosis, with a two-fold increased risk of developing AF compared with healthy controls [81]. Several studies have demonstrated a dose-dependent relationship between OSA severity and AF risk, with increasing severity associated with progressively higher incidence of AF [81]. The association is thought to be mediated by several interrelated mechanisms driven by intermittent hypoxia, including increased oxidative stress, increased sympathetic activation, and consequent atrial structural and electrical remodelling [80]. Together, obesity and OSA are potent overlapping drivers in the development and persistence of AF.

Effect of Weight Loss on Atrial Fibrillation

Lifestyle Intervention

Given the significant role of obesity in AF pathogenesis and its association with the development of other significant comorbidities, targeting weight loss provides an opportunity to improve disease outcomes. Initially, observational studies showed that reversal of obesity was associated with lower AF risk compared with sustained or increasing obesity [82]. This finding was subsequently reinforced by a randomised trial of 150 individuals with AF and a BMI >27kg/m^2. Allocation to weight loss, alongside a structured risk factor reduction program, significantly reduced AF frequency, duration, and severity. These results were

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objectively validated by 7-day ambulatory rhythm monitoring, which showed significantly lower number and duration of AF episodes in the intervention group [10].

To assess the durability and dose-dependent effects of weight loss, the LEGACY study grouped patients by the magnitude of weight loss over a 5-year follow-up. Over this period, there was a graded improvement in AF freedom with greater weight loss. Patients who achieved >10% weight loss were six times more probable to maintain sinus rhythm than those who did not achieve weight loss [83] (Table 1). It is well-recognised that AF is a progressive condition that typically advances from short, infrequent episodes to longer, continuous episodes over time. The REVERSE-AF study explored whether weight loss could halt the natural progression of AF. In this analysis, patients who achieved >10% weight loss experienced greater reversal from longer persistent episodes to shorter episodes, indicative or regression in the underlying atrial disease [84].

Catheter ablation has emerged as a first-line therapy for the treatment of symptomatic AF. Given the association between obesity and post-ablation arrhythmia recurrence, the ARREST-AF cohort study compared structured risk factor management, with a focus on weight loss, to standard medical care in patients undergoing catheter ablation. Over a 3-year follow-up, patients in the intervention arm achieved ∼13% weight loss through lifestyle change, which was associated with a substantial reduction in AF recurrence, alongside improvements in AF symptom severity [85]. Similar findings were seen in a cohort of patients with morbid obesity undergoing risk factor management after AF ablation, where weight loss >5% was associated with lower AF recurrence compared with patients with <5% weight loss or weight gain [92]. Recent preliminary outcomes from the ARREST-AF randomised controlled study reinforce the benefits of weight loss and risk factor reduction to improve ablation outcomes. Over a 1-year follow-up, the weight loss arm achieved ∼9% weight loss, leading to a 47% reduction in recurrent arrhythmia over the 12-months after ablation [93].

The benefit of weight loss may be dependent on the extent of weight loss achieved and the degree of AF progression before weight loss initiation. In the SORT-AF study, a randomised controlled trial of patients with obesity undergoing AF ablation, structured weight reduction led to a modest weight loss <4% and no significant difference in AF burden between the weight loss and control group by 12-months post-ablation [86]. These findings may be explained by the lower weight loss achieved, resulting in participants maintaining a state of obesity. An earlier observational study also highlighted a potential "point of no return" in which patients with long-standing persistent AF did not experience any difference in rates of recurrence despite >10% weight loss [87]. Although requiring further investigation, it may be that the atrial disease progresses to an extent beyond which it is no longer reversible through weight loss and other risk factor reduction.

Lifestyle intervention is one component of AF treatment and is not probable to systematically negate the need for appropriate rhythm management. In the recent PRAGUE-25 trial [88], lifestyle intervention plus antiarrhythmic therapy was compared with catheter ablation. As might be expected given the already established benefits of catheter ablation compared with antiarrhythmic therapy, the recurrence of AF over 1-year was lower in those who underwent catheter ablation. However, this finding should be interpreted in the context of several caveats. First, the degree of weight loss achieved was ∼6%, which was short of the target weight loss of 10%. Second, additional risk factors, such as alcohol intake, were relatively well-controlled at baseline, whereas others, such as OSA, were not routinely reviewed. Finally, despite more frequent AF recurrence in the lifestyle intervention plus drug therapy group, there were no between group difference in AF burden or AF symptoms.

Bariatric Surgery

Weight loss through bariatric surgery results in substantial weight loss, accompanied by a reduction of incident and recurrent AF. In a cohort of patients with a mean BMI >40kg/m^2, bariatric surgery resulted in 1-year weight loss of 25% and 20-year weight loss of 18%. Over the 20-year follow-up, there was a 29% lower rate of incident AF in the bariatric surgery group than control [89]. In patients with established AF and morbid obesity (BMI ≥40 kg/m^2), the reduction in AF burden from appears to be proportional to the extent of weight loss achieved through different bariatric procedures [90]. Patients undergoing gastric bypass achieved the highest mean weight loss (25%) and AF reversal rate (71%), followed by sleeve gastrectomy with 19% weight loss and 56% reversal rate. Gastric banding resulted in the lowest weight loss (16%) and a 50% AF reversal rate [90]. This trend suggests that greater weight loss is associated with higher AF reversal rates.

GLP-1 Receptor Agonists

Glucagon-like peptide-1 (GLP-1) receptor agonists have emerged as an effective therapeutic option for the management of overweight and obesity. Originally approved for glycaemic control in patients with T2DM, these incretin-based therapies enhance glucose-dependent insulin secretion, suppress glucagon release, and slow gastric emptying [94]. These effects collectively promote satiety, reduce appetite, and facilitate weight loss by reducing energy intake.

A series of multicentre trials have evaluated the efficacy and safety of semaglutide for weight management in adults with overweight or obesity. These trials have consistently demonstrated dose-dependent, substantial weight loss with semaglutide, with reductions in body weight of up to 14.9% over 68 weeks [95]. In patients with obesity and HFpEF, semaglutide led to improved symptoms and physical function, as well as reduced systemic inflammation [96]. In patients with obesity and preexisting cardiovascular

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Table 1 Summary of studies assessing the effect of weight loss on AF outcomes.

Study (author, year)	Population	Design	Weight loss	AF outcomes	Follow-up	Notes/limitations
Lifestyle Intervention						
Abed et al. 2013 [10]	150 overweight/obese patients with AF	RCT	Intervention: 14.6 kg Control: 3.6 kg	• ↓ AF symptom burden and severity ($p<0.001$) • ↓ number of AF episodes ($p=0.01$) and duration ($p=0.002$)	12 mo	• Atrial Fibrillation Severity Scale • 7-day Holter • single centre
Pathak et al. 2015 (LEGACY) [83] Middeldorp et al. 2018 (REVERSE-AF) [84]	355 patients with AF and BMI≥27 kg/m^2	Observational	Weight loss <3%: +2 kg (gain) Weight loss: 3%–9%: 6 kg Weight loss >10%: 16 kg	• Weight loss>10% resulted in 6-fold increased probability of arrhythmia-free survival ($p<0.001$) • >5% weight fluctuation of 2-fold ↑ risk arrhythmia recurrence ($p=0.02$) • >10% weight loss with risk factor management associated with greater reversal from persistent to paroxysmal AF	5 yrs	• 7-day Holter
Pathak et al. 2014 (ARREST-AF) [85]	149 patients post AF ablation with BMI≥ 27kg/m^2	Cohort	Intervention: 13.2 kg Control: 0.8 kg	• ↑ single and multi-procedure arrhythmia-free survival ($p<0.001$) • ↓ AF frequency, duration, symptom and symptom severity ($p<0.001$)	3.5 yrs	• Atrial Fibrillation Severity Scale • 7-day Holter • single centre • multiple risk factors targeted
Gessler et al. 2021 (SORT-AF) [86]	133 patients with symptomatic AF and BMI 30kg/m^2 - 40kg/m^2	RCT	Intervention: 5 kg Control: 1 kg	• No significant difference in post-ablation burden between groups ($p=0.815$)	12 mo	• Implantable loop recorder • 33% non-compliant to weight reduction
Mohanty et al. 2018 [87]	90 patients with long-standing persistent AF	Prospective cohort	Weight loss: 24.9 kg (median) Control: 0.9 kg (median)	• Weight loss improved QoL ($p>0.02$) but had no impact on symptom severity ($p=0.84$) and long-term ablation outcome ($p=0.68$)	12 mo	• Later disease stage; limited potential for remodelling
Osmancik et al. 2025 (PRAGUE-AF) [88]	212 patients with symptomatic AF and BMI 30kg/m^2 - 40kg/m^2	RCT	LFM + AADs: 6.2 kg Catheter ablation: 0.3 kg	• AF freedom significantly greater in catheter ablation group	12 mo	• Different rhythm control strategies in each group

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Table 1. (continued).

Study (author, year)	Population	Design	Weight loss	AF outcomes	Follow-up	Notes/limitations
Bariatric Intervention						
Jamaly et al. 2016 [89]	4047 obese patients	Prospective matched cohort	Surgery: 21.8 kg Control: <1 kg	• Bariatric surgery resulted in 29% ↓ AF risk compared to matched controls (HR 0.71; 95% CI: 0.60–0.83; p<0.001)	19 yrs	• AF not a pre-specified endpoint
Donnellan et al. 2020 [90]	220 morbidly obese BMI≥ 40kg/m^2: bariatric surgery (n =220) vs no surgery (n =200)	Matched cohort	Gastric bypass: 25% Gastric sleeve: 19% Gastric banding: 16%	• Percentage weight loss was significantly associated with AF reversal (p=0.0002)	>7 yrs	• Heterogenous cardiac monitoring methods
GLP-1 Receptor Agonists						
Satti. et al. 2024 [91]	AF ablation cohort; GLP-1 RA-treated vs untreated (n = 1,625 each)	Retrospective cohort (PSM)	Not reported	• No difference in composite AF recurrence (HR 1.04; 95% CI 0.92–1.19; p = .51) • No difference in stroke, hospitalization, or mortality	12 mo	• No weight data • GLP-1 receptor agonists use only reported pre-ablation

Weight loss values are reported as mean or median as per original studies.

Abbreviations: AF, atrial fibrillation; RCT, randomised controlled trial; PSM, propensity score–matched; QoL, quality of life; LFM+AADs, lifestyle modification and antiarrhythmic drugs; HR, hazard ratio; CI, confidence interval; OR, odds ratio; GLP-1 RA, glucagon-like peptide-1 receptor agonist.

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disease, the SELECT trial showed a reduction in the composite end point of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke [97].

Similar results have also been reported in other GLP-1 receptor agonists, including dual agonist tirzepatide. In the SUMMIT trial of patients with obesity with HFpEF, tirzepatide lowered the composite end point of cardiovascular death or worsening heart failure and improved functional status compared with placebo. Recently, a head-to-head comparison of semaglutide (1.7–2.4 mg) and tirzepatide (10–15 mg) among participants with obesity found greater weight loss and fewer side effects with tirzepatide use [98], highlighting favourable weight loss efficacy.

Given the well-established associations between obesity, T2DM, and AF, GLP-1 receptor agonists may offer therapeutic potential in AF prevention and treatment. Although randomised controlled trials are lacking, data from a pooled analysis of clinical trials provide evidence that GLP-1 receptor agonists may reduce incident AF. However, the reporting of AF in this analysis is obtained from reporting of adverse events within clinical trial databases and requires further investigation in which AF episodes are carefully adjudicated. To date, only preliminary reports have assessed whether GLP-1 receptor agonists are associated with reduced risk of AF recurrence after catheter ablation [99–101]. In a large, propensity-matched analysis of over 3,000 patients undergoing AF ablation, preprocedural GLP-1 receptor agonist use was not associated with a reduction in AF recurrence or related adverse outcomes, such as stroke, hospital admission, or mortality [91]. Randomised trials are required to determine the rhythm control benefits of GLP-1 receptor agonists.

One potential drawback of GLP-1 receptor agonist use is the longer-term sustainability of weight loss. The STEP 4 trial compared continued semaglutide use vs placebo after an initial period (20 weeks) of weight loss with semaglutide [102]. Cessation of semaglutide led to a 6.9% weight gain compared with ongoing weight loss that was observed with semaglutide continuation. In patients with obesity with AF, weight fluctuation significantly dampens the benefits of weight loss [83]. Therefore, the proposed benefits of GLP-1 receptor agonists may require careful consideration of the long-term maintenance of treatment and weight loss.

Mechanisms Promoting Benefits of Weight Loss in Patients With AF

Several mechanisms have been proposed to explain the benefits of weight loss seen in previous studies. With weight loss in patients with obesity with AF, there is evidence reverse remodelling of the atria, including reductions in LA size, as well as improvement in diastolic function [83]. Ovine models of 30% weight reduction resulted in positive electroanatomical remodelling, reversal of atrial fibrosis, and lowering of epicardial fat volume [27]. This reduction in epicardial fat has also been shown in recent studies in response to GLP-1 receptor agonist therapy [103].

Weight loss has been linked to lower levels of inflammatory markers after lifestyle [104], pharmacological [96], and bariatric [90] interventions. Weight reduction has also been associated with a reduction in RAAS [105] and sympathetic activity [106], as well as improvements in central cardiac haemodynamics, including reductions in pulmonary capillary wedge pressure and mean pulmonary artery pressure [107]. Weight loss results in improvements in the commonly associated comorbid conditions as well. In individuals with sleep apnoea, weight loss with tirzepatide reduces the apnoea-hypopnoea index, hypoxic burden, and hypertension [108], which may contribute to the onset and recurrence of AF [80]. In the setting of hypertension, a 1 kg loss of body weight was associated with an approximate 1 mmHg drop in blood pressure [109]. It is probable that these positive adaptations with weight loss converge to reduce the atrial substrate and subsequent recurrence of AF.

Guidelines Promoting Weight Loss in Patients With AF

The benefits of weight loss in managing AF are clearly identified, with the American College of Cardiology, American Heart Association, American College of Clinical Pharmacy, and Heart Rhythm Society guidelines [110] acknowledging the assessment of risk factors using the $HEAD_2TOES$ schema for the primary and secondary prevention of AF [55]. In all major clinical guidelines for the treatment of AF, weight reduction with a target of 10% weight loss is a class 1 recommendation model [111], including for patients undergoing catheter ablation [112].

Future Directions and Research Opportunities

Despite substantial progress in the treatment of obesity, there are notable research priorities to be addressed to improve outcomes among patients living with AF [113]. Although GLP-1 receptor agonists have shown promising results for cardioprotective effects, randomised trials are required to establish their efficacy in the reduction of incident and recurrent AF, as well as the longer-term consequences of AF, such as stroke and heart failure. The timing of intervention is also a key detail, given the evidence that long-term progression of AF may reduce the efficacy of weight loss and risk factor reduction. Whether early weight loss with risk factor reduction is an effective alternative to early rhythm control, with catheter ablation, is of particular interest. The structure of AF care, potentially including other modalities of lifestyle intervention such as exercise intervention, as well as novel modes of delivery using digital health, will require further investigation, particularly, in settings where alternatives to pharmacotherapy may be preferred. Finally, culturally sensitive, tailored interventions for groups including Indigenous Australians are required to address the disproportionate effect of obesity and AF in this portion of the population.

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Conclusions

The global rise in obesity and its associated comorbidities remain a major public health concern. As a modifiable risk factor, obesity must be a central focus in health care strategies. In atrial fibrillation, where therapies are often not curative, weight management offers a valuable opportunity to target several mechanisms implicated in the pathogenesis and persistence of AF. Furthermore, weight loss potentially modifies the risk of downstream events after AF diagnosis such as stroke, heart failure, and cardiovascular mortality. However, broad population-wide strategies to promote weight loss based on lifestyle intervention are challenging to incorporate into daily practice. The emergence of GLP1-receptor agonists strengthens the options available for the clinician to achieve clinically significant weight loss and promote beneficial AF outcomes. Given the widespread benefits of lifestyle intervention beyond weight loss alone, GLP-1 receptor agonists may be just one of the methods necessary for risk factor modification to alleviate the growing burden of AF in the community.

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Declaration of Competing Interests

P.S. reports serving on the medical advisory board for Abbott, Medtronic, Boston-Scientific, CathRx, and Pacemate. The University of Adelaide has received on behalf of P.S. research funds from Boston-Scientific, Medtronic, Abbott, and Becton Dickenson. The remaining authors have no conflicts of interest to declare.

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