

## THE PRESENT AND FUTURE

### STATE-OF-THE-ART REVIEW

# Obesity and Atrial Fibrillation Prevalence, Pathogenesis, and Prognosis



## Effects of Weight Loss and Exercise

Carl J. Lavie, MD,<sup>a</sup> Ambarish Pandey, MD,<sup>b</sup> Dennis H. Lau, MBBS, PhD,<sup>c</sup> Martin A. Alpert, MD,<sup>d</sup> Prashanthan Sanders, MBBS, PhD<sup>c</sup>

### ABSTRACT

Both obesity and atrial fibrillation (AF) are increasing in epidemic proportions, and both increase the prevalence of cardiovascular disease events. Obesity has adverse effects on cardiovascular hemodynamics and cardiac structure and function, and increases the prevalence of AF, partly related to electroanatomic remodeling in obese patients. However, numerous studies, including in AF, have demonstrated an obesity paradox, where overweight and obese patients with these disorders have a better prognosis than do leaner patients with the same degree of severity of cardiovascular disease/AF. In this paper, the authors discuss special issues regarding AF in obesity, as well as the evidence that despite the presence of an obesity paradox, there are benefits of weight loss, physical activity/exercise training, and increases in cardiorespiratory fitness on the prognosis of obese patients with AF. (J Am Coll Cardiol 2017;70:2022-35) © 2017 by the American College of Cardiology Foundation.

Obesity has been increasing in epidemic proportions in the United States and in most of the Westernized world. The prevalence of obesity (based on body mass index [BMI]  $\geq 30$  kg/m<sup>2</sup>) in U.S. adults from 2013 to 2014 is 38%, and with Class III obesity (BMI  $\geq 40$  kg/m<sup>2</sup>) approaches 8% (1). Considering the adverse effects that obesity has on cardiovascular hemodynamics and cardiovascular structure and function, not surprisingly, almost all cardiovascular diseases (CVDs) increase in frequency in the setting of obesity, including hypertension, coronary heart disease

(CHD), heart failure (HF), and atrial fibrillation (AF) (2,3). However, in most CVDs, an obesity paradox has been demonstrated, where overweight (BMI 25.0 to 29.9 kg/m<sup>2</sup>) and those with mild obesity (BMI 30.0 to 34.9 kg/m<sup>2</sup>) have a better prognosis than do underweight persons (BMI  $\leq 18.5$  kg/m<sup>2</sup>) and those with “normal” weight (BMI 18.5 to 24.9 kg/m<sup>2</sup>) (2,3).

Although AF is already considered the most common sustained arrhythmia in adults, its prevalence is expected to increase by nearly 3-fold during the next 3 decades, with experts now categorizing this epidemiologic trend as an AF epidemic (4).



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From the <sup>a</sup>Department of Cardiovascular Diseases, John Ochsner Heart and Vascular Institute, Ochsner Clinical School-The University of Queensland School of Medicine, New Orleans, Louisiana; <sup>b</sup>Division of Cardiology, University of Texas Southwestern Medical Center, Dallas, Texas; <sup>c</sup>Centre for Heart Rhythm Disorders, South Australian Health and Medical Research Institution, University of Adelaide and Royal Adelaide Hospital, Adelaide, Australia; and the <sup>d</sup>Division of Cardiovascular Medicine, University of Missouri School of Medicine, Columbia, Missouri. Dr. Sanders is supported by a Practitioner Fellowship from the National Health and Medical Research Council of Australia. Dr. Lavie is author of the book *The Obesity Paradox*; and has served as a promotional speaker and consultant for Bristol-Myers Squibb, Pfizer, and Boehringer Ingelheim. Dr. Lau has received lecture and/or consulting fees from St. Jude Medical, Boehringer Ingelheim, Bayer, and Pfizer. Dr. Sanders has been on advisory boards of Biosense Webster, Medtronic, St. Jude Medical, Boston Scientific, and CathRx; has received lecture and/or consulting fees from Biosense Webster, Medtronic, St. Jude Medical, and Boston Scientific; and has received research funding from Medtronic, St. Jude Medical, Boston Scientific, Biotronik, and Sorin. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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The estimated prevalence in the United States is approximately 5.2 million, and is expected to increase to 12.1 million by the year 2030 (4,5). Although numerous factors contribute to this epidemic of AF, the obesity epidemic, which leads to left atrial (LA) remodeling by various mechanisms (4,6,7), is associated with a marked increase in the risk of developing AF. As with other CVDs, however, there is evidence that although obesity increases the risk for the development of AF, overweight and obese patients with AF seem to have a better prognosis, including CVD and all-cause survival, compared to lean AF patients, indicating an apparent obesity paradox (2,7,8).

Although we and others have reviewed the association and impact of obesity on AF (9-11), we believe that this current state-of-the-art review of AF and obesity most comprehensively reviews the adverse effects of obesity on cardiovascular hemodynamics, cardiac structure and function, the electrophysiological effects of obesity, and other mechanisms that may increase the prevalence of AF. We review data on the impact of obesity on prognosis in AF, special management issues in the obese patient with AF, and implications for weight loss and increases in physical activity, exercise training, and improvements in cardiorespiratory fitness (CRF) on prognosis of AF.

## OBESITY AND AF: EPIDEMIOLOGICAL CONSIDERATIONS

Early epidemiological studies have uncovered a host of established cardiovascular conditions that are independently associated with the development of AF. More recently, obesity has emerged as an independent risk factor for AF (12-15). For example, long-term prospective data from the Framingham Heart Study with almost 14 years of follow-up has identified obesity as an important modifiable risk factor for AF (12). Importantly, the association between obesity and AF has been shown to be independent of obstructive sleep apnea, a common comorbid condition in obese individuals (13). Furthermore, data from the Women's Health Study have elegantly demonstrated the dynamic nature of the risk for AF with weight changes (14). Specifically, short-term weight gain to BMI >25 kg/m<sup>2</sup> was found to be associated with substantial risk of developing AF, and obese individuals who lost weight to BMI <30 kg/m<sup>2</sup> over 5 years were found to have reduced AF risk similar to those who maintained BMI <30 kg/m<sup>2</sup> over the same period of time (14). Obesity represents the second highest population-attributable risk for AF behind hypertension and will likely escalate the global burden of AF in the

coming decades given its burgeoning epidemic worldwide (16). A recent large study reports the association between genetically predicted obesity and AF incidence, making the case that primordial prevention may be needed in the AF epidemic (17).

The ARIC (Atherosclerosis Risk In Communities) study estimates that almost 1 in 5 cases of AF can be attributable to overweight or obesity (16), and another report from the ARIC study showed that trajectories of various CVD risk factors many years before the diagnosis of AF impacted the subsequent development of AF (18). A recent meta-analysis of 51 studies involving more than 600,000 individuals has evaluated the impact of obesity on AF in different clinical scenarios (19). Specifically, every 5-unit increment in BMI was found to confer an additional 19% to 29% risk of incident AF, a 10% risk of post-operative AF, and a 13% risk of post-ablation AF (19). Not surprisingly, longitudinal cohort data from the Women's Health Study and Olmsted

County both demonstrated that the obese state contributes to disease progression, whereby increasing BMI was associated with incremental risk of developing a persistent or permanent form of AF (20,21).

## IMPACT OF OBESITY ON CARDIAC PERFORMANCE AND MORPHOLOGY

### EFFECTS OF OBESITY ON CARDIAC PERFORMANCE AND MORPHOLOGY: GENERAL CONSIDERATIONS.

Obesity is associated with a variety of hemodynamic alterations that predispose to changes in cardiac morphology, which may result in ventricular dysfunction (22-24). The effects of obesity on hemodynamics and cardiac structure and function are summarized in Table 1 and Figure 1. These alterations are most pronounced in severely obese patients, but may occur to a lesser extent in those with mild-to-moderate obesity. Excessive adipose accumulation, in association with increased lean body mass, produces an increase in total and central blood volume. In most obese individuals, these alterations promote an increase in cardiac output, a response that is facilitated by a decrease in systemic vascular resistance (SVR). Because there is little change in heart rate, the rise of cardiac output is attributable predominantly to an increase in left ventricular (LV) stroke volume. Augmentation of cardiac output predisposes to LV enlargement and eccentric LV hypertrophy (LVH). Recent studies suggest that central obesity is not always associated with elevated

## ABBREVIATIONS AND ACRONYMS

<b>AF</b>	= atrial fibrillation
<b>BMI</b>	= body mass index
<b>CHD</b>	= coronary heart disease
<b>CRET</b>	= cardiac rehabilitation and exercise training
<b>CRF</b>	= cardiorespiratory fitness
<b>CVD</b>	= cardiovascular disease
<b>EAT</b>	= epicardial adipose tissue
<b>HF</b>	= heart failure
<b>LA</b>	= left atrial
<b>LAE</b>	= left atrial enlargement
<b>LV</b>	= left ventricle/ventricular
<b>LVH</b>	= left ventricular hypertrophy
<b>MET</b>	= metabolic equivalent of task
<b>PV</b>	= pulmonary vein
<b>RV</b>	= right ventricle/ventricular
<b>SVR</b>	= systemic vascular resistance

**TABLE 1** Impact of Obesity on Hemodynamics and Cardiac Structure and Function

A. Hemodynamics
1. Increased blood volume
2. Increased stroke volume
3. Increased arterial pressure
4. Increased LV wall stress
5. Pulmonary artery hypertension
B. Cardiac structure
1. LV concentric remodeling
2. LV hypertrophy (eccentric and concentric)
3. Left atrial enlargement
4. RV hypertrophy
C. Cardiac function
1. LV diastolic dysfunction
2. LV systolic dysfunction
3. RV failure
D. Inflammation
1. Increased C-reactive protein
2. Overexpression of tumor necrosis factor
E. Neurohumoral
1. Insulin resistance and hyperinsulinemia
2. Leptin insensitivity and hyperleptinemia
3. Reduced adiponectin
4. Sympathetic nervous system activation
5. Activation of renin-angiotensin-aldosterone system
6. Overexpression of peroxisome proliferator-activator receptor
F. Cellular
1. Hypertrophy
2. Apoptosis
3. Fibrosis

LV = left ventricular; RV = right ventricular.

cardiac output or reduced SVR. LV remodeling in such patients is more likely to be concentric rather than eccentric. Evidence is accumulating that concentric LV remodeling and hypertrophy occur as often or more often than eccentric LVH in obese patients with abnormal LV geometry. Comorbidities such as systemic and neurohormonal and metabolic alterations associated with obesity (activation of the renin-angiotensin-aldosterone system and sympathetic nervous systems, hyperinsulinemia due to insulin resistance, hyperleptinemia due to the leptin resistance, and possibly lipotoxicity) may contribute to the development of LVH. If LV wall stress increases adequately, LV diastolic dysfunction may ensue. If LV wall stress fails to keep pace with LVH, LV systolic dysfunction may accompany LV diastolic dysfunction (22-24). LVH and associated adverse LV loading conditions many produce LV failure leading to increased left LA pressure and volume, increased pulmonary venous pressure, and an increase in pulmonary capillary pressure (22-26). Pulmonary arterial hypertension occurs commonly in severe obesity (22-26). It is due predominantly to left-sided HF, but may be facilitated by hypoxia due to sleep apnea and obesity hypoventilation, both of which occur commonly in severe obesity (22-24). Pulmonary hypertension, in association with elevated cardiac output, may result

in right ventricular (RV) enlargement and hypertrophy, right atrial enlargement, and RV failure (22-24); HF due entirely or predominantly to severe obesity is referred to as obesity cardiomyopathy (24).

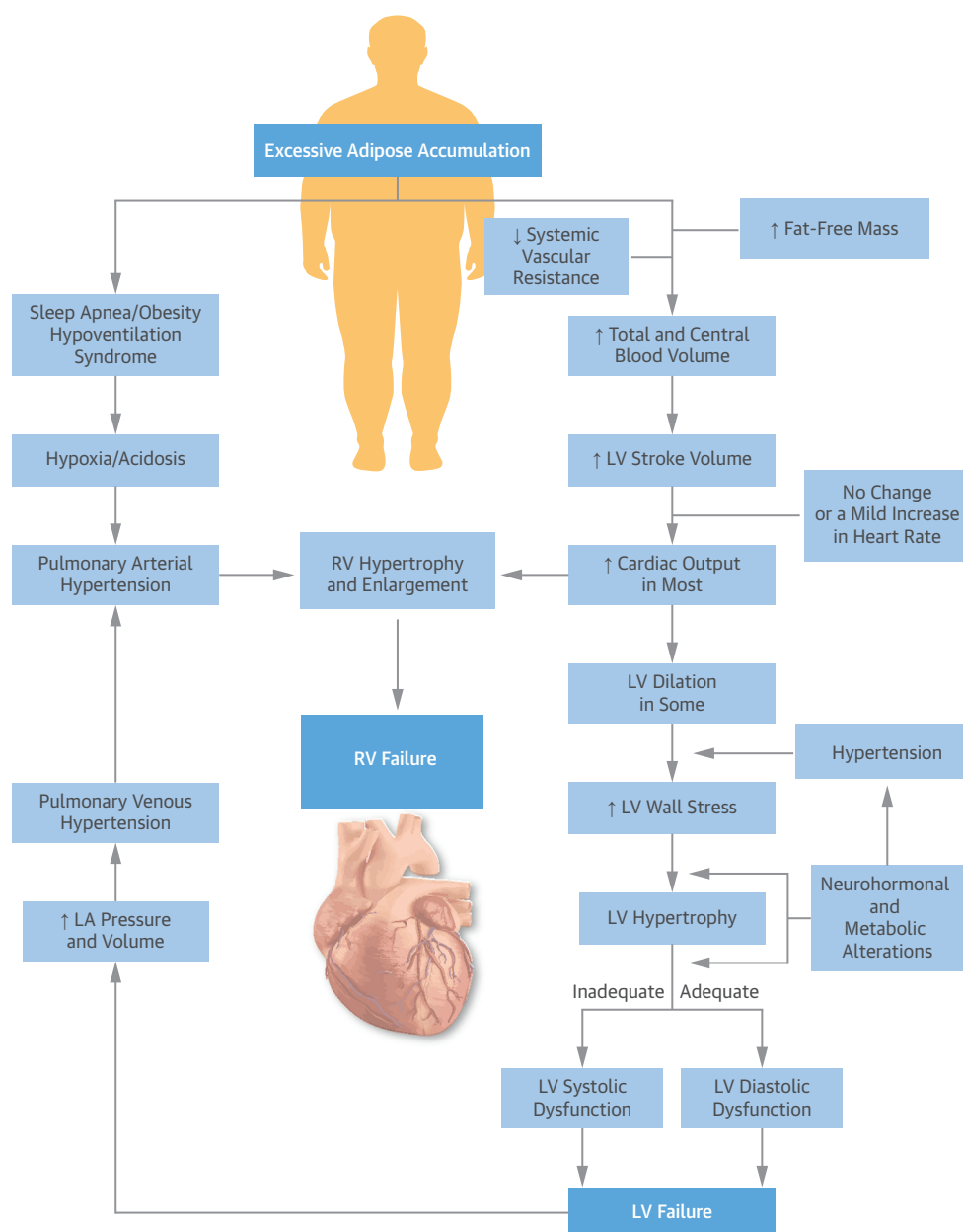
**RELATION OF LA REMODELING AND ALTERED LA FUNCTION TO AF IN OBESITY.** Postmortem studies of severely obese patients found LA enlargement (LAE) to be present in nearly all subjects (22-24). However, these studies did not exclude comorbidities, such as hypertension and CHD, which could potentially contribute to LA dilation, pressure overload, and hypertrophy. The reported prevalence of LAE in overweight and obese subjects is variable, depending on severity and duration of obesity, the presence or absence of comorbidities, such as hypertension and a variety of metabolic, neurohormonal, and growth-promoting factors, the effects of adipocytokines and chemokines, and the presence of inflammation (9,27-29). This is discussed in greater detail in the section on pericardial fat and epicardial adipose tissue (EAT). LA remodeling is an important determinant of AF in obese patients (9,27-33).

Some individual studies have reported a significant difference in LA size between obese and nonobese groups (9,27-33). Multiple studies have identified LA size as an independent predictor of AF (9,20,27-35). In a 10-year longitudinal study, obesity and hypertension were identified as independent predictors of LAE (35). Somewhat surprisingly, obesity was found to be a more potent predictor of LAE than hypertension, even after adjusting for age and sex (35). In a 21-year cohort study of 3,248 patients with paroxysmal AF, BMI and LA volume incrementally predicted risk of developing permanent AF (20).

The variability in the reported relation between obesity and LA size, and the relation of LA size to AF may in part relate to the methods used to assess LA size. Most studies have measured LA dimension using 2-dimensional echocardiography in the parasternal long-axis view with the cursor aligned along the anteroposterior axis. This method may underestimate LA size. More recent studies have measured LA volume indexed to body surface area. This too may be problematic, particularly for severely obese patients in whom increased fat mass may exceed augmentation of non-osseous lean body mass. Some have advocated indexing LA volume to height, but this method has not been extensively used in obese patients.

The mechanisms by which overweight and obesity contribute to the risk, progression, and severity of AF are multifactorial (9,22-33,36-39). Key elements include the high cardiac output state and the

**FIGURE 1** Obesity and CVD



Proposed pathophysiology of obesity cardiomyopathy. This diagram shows the central hemodynamic alterations that result from excessive adipose accumulation in severely obese patients and their subsequent effects on cardiac morphology and ventricular function. Left ventricular (LV) hypertrophy in severe obesity may be eccentric or concentric. Factors influencing LV remodeling and geometry include severity and duration of obesity, duration and severity of adverse LV loading conditions (particularly hypertension), and, possibly, neurohormonal and metabolic abnormalities such as increased sympathetic nervous system tone, activation of the renin-angiotensin-aldosterone system, insulin resistance with hyperinsulinemia, leptin resistance with hyperleptinemia, adiponectin deficiency, lipotoxicity, and lipoapoptosis. These alterations may contribute to the development of LV failure. LV failure, facilitated by pulmonary arterial hypertension from sleep apnea/obesity hypoventilation, may subsequently lead to right ventricular (RV) failure. Adapted from Alpert et al. (22). CVD = cardiovascular disease; LA = left atrial.

presence of LVH (eccentric or concentric) in association with LV diastolic dysfunction (9,22-28,32). The hypercirculatory state serves as both a direct contributor to LAE and as a major cause of LVH, LV diastolic dysfunction, and elevated LA pressure (9,22-28,32). Hypertension occurs in nearly one-half of obese patients and more than 60% of severely obese patients (22-24). Hypertension is a well-established cause of LAE, increased LA pressure, and LA hypertrophy. This is due primarily to the development of LVH and LV diastolic dysfunction, but also to comorbidities, such as diabetes mellitus, CHD, and obstructive sleep apnea. All of these comorbidities are commonly associated with obesity and may contribute to LA remodeling and LV diastolic dysfunction by various mechanisms (22-27,33). Recently, abnormal LA strain has been described during diastole in obese subjects (22-24). Increased LA stretch and insufficient LA emptying have also been reported in obese patients (27). Various neurohormonal, and metabolic factors, growth factors, adipocytokines, and inflammatory markers were described in a study of 30 obese sheep (29). Abed et al. (29) reported increases in LA volume ( $p = 0.01$ ), transforming growth factor  $\beta 1$  ( $p = 0.02$ ), platelet-derived growth factor ( $p = 0.02$ ), LA fibrosis ( $p = 0.02$ ), LA inflammatory infiltrates ( $p = 0.01$ ), and lipidosis ( $p = 0.02$ ) in LA myocardium (33). It has been proposed that many of these factors contribute to LA remodeling and dysfunction in humans, and as such may serve as both triggers and substrates for AF. EAT is thought to be a source of many of these factors. This is discussed in more detail in the following section. The changes in LA morphology may provide a substrate for electrophysiological remodeling of the LA, which may predispose to and perpetuate AF, affecting its severity and the response to catheter ablation.

#### RELATION OF EAT AND PERICARDIAL FAT TO AF.

In recent years, there has been increasing interest in the role of cardiac fat in the development of AF, particularly EAT and pericardial fat (36-40). EAT is located between the visceral pericardium and the epicardial layer of myocardium (36,37). Pericardial adipose tissue or pericardial fat is located beyond the parietal pericardium (36,37). Both forms of cardiac fat are derived from brown fat, but are embryologically distinct (36,37). EAT is highly biologically active. It secretes metabolic factors (free fatty acids and uncoupling protein-1), angiogenic factors (angiotensin, endostatin, vascular endothelial growth factor-1, thrombospondin-2, angiopoietin), growth and remodeling factors (activin A, follistatin, transforming growth factors 1-3, matrix metalloproteinases

1-13), adipocytokines (adiponectin, leptin, resistin, visfatin, omentin), inflammatory cytokines and chemokines and various interleukins (including IL1 $\beta$  and IL6), plasminogen activator inhibitor-1, tumor necrosis factor alpha, monocyte chemotactic protein 1, chemokine ligands, adrenomedullin, and phospholipase A2 (36,37). Pericardial fat is also biologically active and is a depot of visceral adipose tissue (27,36,37). As such, it provides endocrine, paracrine, and autocrine functions that are similar to those of visceral adipose tissue elsewhere in the body (27,36,37). Cardiac adipose is most pronounced over the RV, but can also be found to a lesser extent over the surface of the LV, in the atrioventricular grooves, and along the posterior surface of the LA (22-24,36). Pericardial fat and EAT have been shown to wrap around the pulmonary veins (PVs) as they enter the LA (36,37). EAT contains a dense network of autonomic ganglia (consisting predominantly of parasympathetic nerve fibers) (27,28,36,37).

Multiple controlled studies employing cardiac imaging techniques (primarily computed tomography) have demonstrated an association of pericardial fat and AF (36-38). Most of these studies did not distinguish between pericardial fat and EAT. It is thought however, that fat deposits directly in contact with LA myocardium (EAT) are more likely to contribute to the development of AF (36-38). Nearly all of these studies showed that greater volumes or thicknesses of pericardial fat were associated with a higher prevalence of paroxysmal and persistent AF (36-39). In one study, each SD increase in pericardial fat volume was associated with a 28% increase in the prevalence of AF (38). In another study, a 10% increase in pericardial fat volume increased the odds of AF by 13% (37). Several studies have reported an association between pericardial fat volume and severity of AF (trends toward persistent AF and more symptoms) (27,36-39). Multiple studies have identified excessive pericardial fat as a predictor of a higher recurrence rate of AF after catheter ablation (27,36-39). In one study, respective pericardial thicknesses of 6.0 and 6.9 mm identified patients who were at higher risk of recurrence of paroxysmal and nonparoxysmal AF after catheter ablation (37). Indeed, a recent meta-analysis has suggested that the associations of AF with pericardial fat were stronger than those with abdominal or overall adiposity (40). Pericardial fat volumes correlated with complex fragmented LA electrograms in patients with AF (37). Excessive interatrial adiposity may also predispose to AF (41).

Obesity, particularly central obesity, is associated with increased pericardial fat volumes (22-24).

In severely obese patients, pericardial fat deposits may be voluminous and more diffuse than in non-obese subjects (22-24). The mechanisms by which increased pericardial fat and EAT contribute to the development of AF are uncertain. It has been postulated that augmented sympathetic or parasympathetic tone related to dense innervation of fat depots in contiguity with the LA and PVs may play a role. The pathogenic effects of epicardial fat include induction of atrial fibrosis via paracrine action of adipocytokines, contiguous fatty infiltration to the atrial myocardium and fibrotic remodeling of the adipose tissue in the atrial subepicardium through immune or inflammatory responses (42-44). It has also been hypothesized that inflammatory cytokines and chemokines may facilitate fibrosis of LA myocardium, predisposing to the development of micro-re-entry circuits. Growth and remodeling factors may cause LA hypertrophy and dilation, thus contributing to the substrate for AF. It also appears that some of the paracrine effects of EAT may contribute to the development of LA remodeling and fibrosis, thereby creating an arrhythmogenic substrate that facilitates the development AF.

In summary, the paracrine effects of excessive cardiac fat (particularly EAT) in obese patients, in association with modulation of the autonomic nervous system may serve as triggers for the development of AF and contribute to its severity.

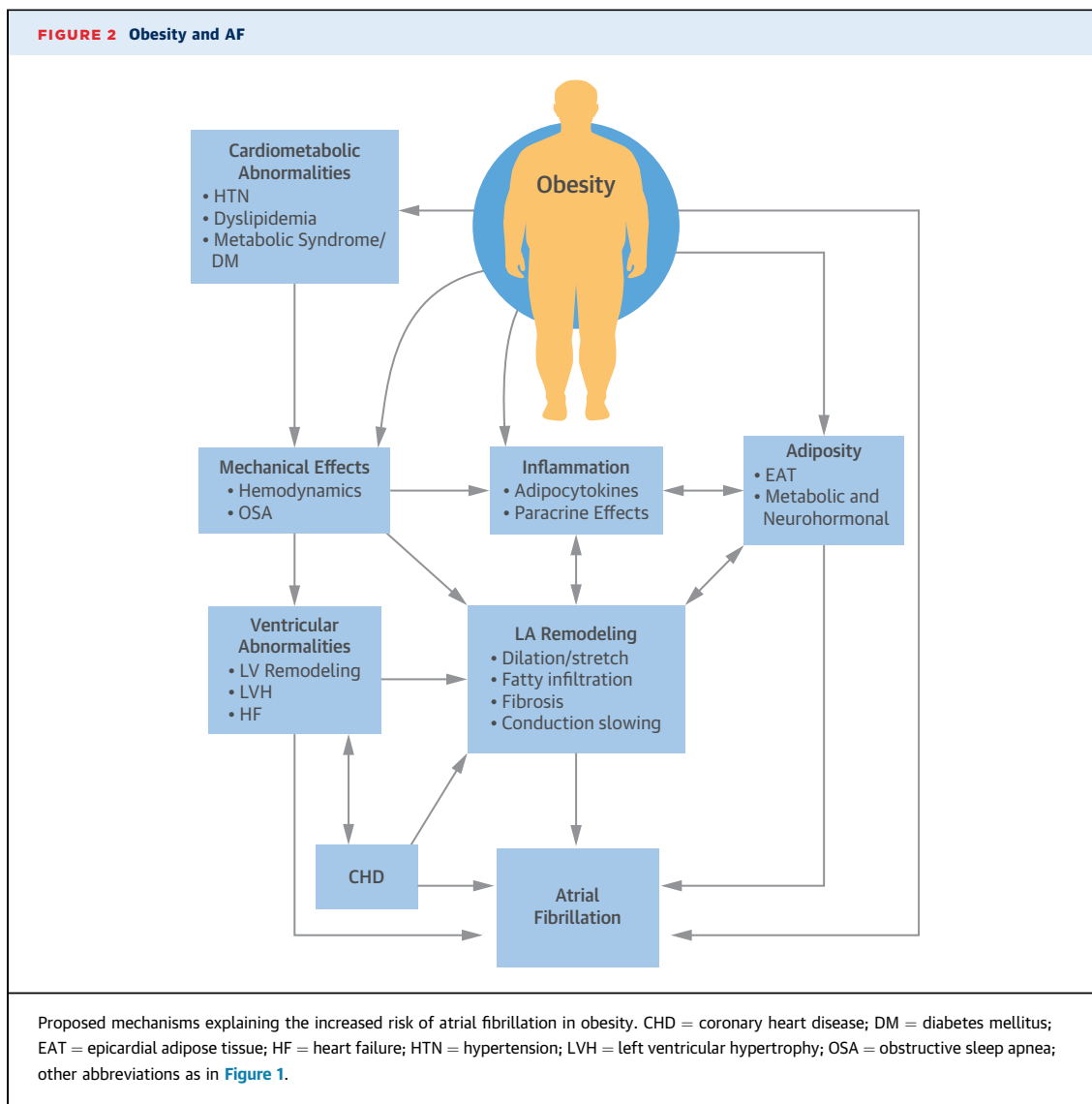
**ELECTROANATOMIC ATRIAL REMODELING DUE TO OBESITY.** Consequent to obesity, the LA remodels in such a way as to produce a milieu conducive to AF. In an ovine model of obesity due to high-caloric diet, weight gain over 8 months resulted in progressive atrial electrical and structural remodeling (29). These included LAE, conduction slowing, increased conduction heterogeneity, increased interstitial fibrosis, inflammation, and myocardial lipidosis to result in increased spontaneous and induced AF despite unchanged atrial refractoriness (29,45). Furthermore, endocardial mapping in sheep following sustained obesity over 72 weeks showed significant atrial electrogram fractionation and reduced posterior LA voltage, whereas histological examination revealed infiltration of the contiguous atrial myocardium by epicardial fat, a unique phenomenon not seen in other predisposing conditions for AF (42). In obese individuals with AF, conduction slowing in the PV ostia and shortened effective refractory period in the PVs and atria are key electrophysiological changes in conjunction with LA enlargement, elevated LA pressure, and impaired LA stretching and contraction (32,42).

**TABLE 2 Causes of AF in Obesity**

1. Increased Prevalence of HF
2. Increased CHD
3. Increased HTN
4. Increased LV geometric abnormalities
  - a) Concentric remodeling
  - b) Concentric and eccentric LV hypertrophy
5. Altered hemodynamics (e.g., increased blood volume)
6. Left atrial abnormalities
  - a) Remodeling
  - b) Enlargement
  - c) Fibrosis
7. Increased epicardial and pericardial fat
8. Neurohumoral
9. Inflammation
10. Cardiometabolic abnormalities
11. Autonomic dysfunction
12. Obstructive sleep apnea
13. Low cardiorespiratory fitness

AF = atrial fibrillation; CHD = coronary heart disease; HF = heart failure; HTN = hypertension; LV = left ventricular.

**AF MECHANISMS IN OBESITY.** The pathophysiological mechanisms linking obesity and AF are highly complex and remain incompletely understood, but include dysregulation in different domains, such as hemodynamics, neurohumoral, inflammatory, metabolic, adipokines, and autonomic (10,11), as well as the impact of obesity to increase HF and CHD (Table 2, Figure 2). It is likely that a combination of these contribute to the initiation and maintenance of AF in the obese atria by the 2 main prevailing AF mechanisms of focal ectopic activity or re-entry (46). In brief, the hemodynamic changes encompass elevation in LA and systolic blood pressure, and LV diastolic dysfunction to result in atrial stretch and “triggers” for AF (47). Increased adipose tissue can result in a hypoxic state due to inadequate capillarization, which is proinflammatory with cytokine release that may alter adipokine levels, ion channel function, calcium homeostasis, and increase atrial fibrosis as well as PV arrhythmogenesis to result in AF (11,48). Activation of key signaling pathways, including the renin-angiotensin-aldosterone system, TGF- $\beta$ , connective tissue growth factor and endothelin-1 can result in increased interstitial collagen deposition, which may disrupt atrial conduction leading to a substrate that favors re-entry and AF perpetuation (29). Autonomic dysregulation as a result of obesity can trigger AF in an obese individual with concomitant obstructive sleep apnea (49). Very recent studies, however, suggest that lean body mass, as opposed to specific parameters of adiposity, are the predominant anthropometric risk factor for AF (50,51).



**PROGNOSIS OF AF RELATED TO BODY COMPOSITION-OBESITY PARADOX.** There has been increasing interest in evaluating the impact of obesity on long-term clinical outcomes among individuals with established AF. Several studies have implicated obesity in progression of AF and recurrence after ablation or cardioversion. Recent studies have demonstrated a strong graded association between higher overall adiposity, as measured by BMI, and risk of persistent and post-ablation AF ([40,52](#)). Similar associations have also been reported for measures of site-specific adiposity, such as epicardial fat and visceral adiposity, and risk of AF progression and recurrence ([51](#)).

In contrast to the higher risk of AF recurrence and progression with increasing adiposity, recent cohort studies have demonstrated the phenomenon of an “obesity paradox” for risk of mortality among patients with prevalent AF, such that overweight and obesity (vs. normal BMI) was associated with a significantly lower risk of all-cause mortality on long-term follow-up ([53-55](#)). In a study from the ORBIT-AF registry (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation), a contemporary cohort of patients with prevalent AF, Pandey et al. ([55](#)) demonstrated a 35% lower risk of all-cause mortality among Class I obese patients with AF as compared with those with normal BMI. Similar

**TABLE 3 Potential Reasons for the Obesity Paradox in AF**

1. Nonpurposeful weight loss
2. Greater metabolic reserves
3. Less cachexia
4. Protective cytokines
5. Earlier presentation*
6. Attenuated response to renin-angiotensin-aldosterone system
7. Higher blood pressure leading to more cardiac medications
8. Different cause of CVD and AF
9. Increase muscle mass and muscular strength
10. Implications related to cardiorespiratory fitness
11. Confounders and collider bias

\*Caused by lower atrial natriuretic peptide levels, restrictive lung disease, venous insufficiency, and so on.

AF = atrial fibrillation; CVD = cardiovascular disease.

findings have also been reported from secondary analyses of randomized controlled trial populations, such as the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) study and the AFFIRM (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) study (53,54). This finding of an obesity paradox for all-cause mortality in AF patients was recently confirmed in a large meta-analysis of 8 such cohort studies (56).

The mechanisms underlying the phenomenon of an obesity paradox are not well understood (Table 3), and it remains unclear whether this is a true biological phenomenon or related to residual confounding factors. First, normal BMI patients are significantly older than those with higher BMI in most observational cohorts, and the confounding effects of age may not be completely accounted for by statistical adjustment. This is particularly relevant because age is one of the major predictors of all-cause mortality among patients with AF (37). Previous studies have also observed significant differences in AF management strategies across BMI categories, with greater use of rhythm control interventions, beta-blockers, and anticoagulants among overweight and obese, as compared with normal weight patients (54,57,58). Furthermore, “normal BMI” may not be essentially physiological and could be related to underlying medical conditions or proinflammatory states. Thus, normal BMI patients may have lower metabolic reserve to counterbalance the increased catabolic stress of AF. Finally, similar to HF, it is plausible that an obesity paradox in AF is largely related to differences in CRF (59). It is noteworthy that the obesity paradox is not consistently observed for nonfatal clinical outcomes, such as stroke and HF incidence among AF patients (54-56,58). Although

future studies are needed to determine the clinical relevance of this phenomenon, the current evidence from weight-loss intervention studies, as discussed in the following text, argue that the obesity paradox should not be used as a rationale against aggressive lifestyle risk factor modification, including weight loss for management of AF patients. Additionally, some have argued that the obesity paradox, as well as other paradoxes, should be met with skepticism, suggesting that this apparent paradox is simply the result of collider stratification, a source of selection bias (60-63).

#### MANAGEMENT ISSUES SPECIFIC TO OBESE PATIENTS WITH AF

Limited data exist on the management issues specific to obese patients with AF. It is well known that obesity can impact the pharmacokinetics and pharmacodynamics of various drugs. For example, it has been shown that clearance of amiodarone was significantly reduced in those with BMI >25 kg/m<sup>2</sup>, and obese subjects had reduced response to warfarin anticoagulation to require higher dosage and longer time to reach therapeutic range (64,65). Furthermore, the obese state is known to impact exposure to direct oral anticoagulants, such as apixaban and rivaroxaban, whereas clinical outcome data in the usage of these novel agents remain lacking in obese individuals (66). Higher shock energy was needed for increased first-shock success when transthoracic direct current cardioversion was studied in overweight and obese individuals (67). Data from the AFFIRM study suggested that success of rhythm control strategies using antiarrhythmic drugs and cardioversions did not differ according to BMI category (68). However, in the same study, obese patients undergoing rate control strategy were more likely to have higher and uncontrolled resting heart rate as compared with their leaner counterparts (68). Obese patients undergoing catheter ablation for AF had higher radiation exposure and longer procedural time than their normal weight counterparts, although there were no differences in major complication rates (69,70). However, the complication rate for catheter ablation of AF was found to be significantly higher in the morbidly obese (BMI >40 kg/m<sup>2</sup>) group to the tune of 5% increase per 1-U increase in BMI (71). Further dedicated research is therefore needed to improve outcomes in obese patients with AF, particularly given the clear signal of higher AF recurrence despite invasive catheter ablation procedures (19).

Little information exists concerning the effects of interventions to reduce pericardial fat volume (37,72-75). The most compelling studies have

involved cardiac surgery patients (37,74,75). A meta-analysis of 6 studies of patients undergoing coronary artery bypass surgery suggested that posterior pericardiectomy significantly reduced the incidence of post-operative AF (74). More recently, a study assessing injections of botulinum toxin into the epicardial fat pad reduced the recurrence rate of AF after cardiac surgery (75).

**IMPLICATIONS REGARDING WEIGHT LOSS IN AF AND PROGNOSIS.** Substantial weight loss in normotensive persons with expanded total and central blood volume is capable of reducing total and central blood volume, LV stroke volume, and cardiac output (22-24). Weight loss in such individuals increases SVR in most, but this depends on the blood pressure response, but regardless produces regression in LVH. The effects on LV end-diastolic pressure and LA pressure are more variable, with reduction in some patients and no significant change in others (22-24). Impaired noninvasive LV diastolic filling parameters generally improve with weight loss (22-24). LV systolic function usually does not change with weight loss or slightly decreases (22-24). However, LV systolic function may improve in patients with a reduced LV ejection function (22-24). Symptoms and signs of HF generally improve in those with obesity cardiomyopathy (24). The effect of weight loss on pulmonary artery pressure, pulmonary vascular resistance, and right heart pressures is variable, depending on the contributions of left-sided HF and the hemodynamic response to sleep apnea and obesity hypoventilation (22-24). In many patients, pulmonary hemodynamics and right heart pressures improve as HF and sleep-disordered breathing improves (22-24). These weight loss-related alterations have been associated with reductions in the frequency, symptom burden, and severity of AF (72,73).

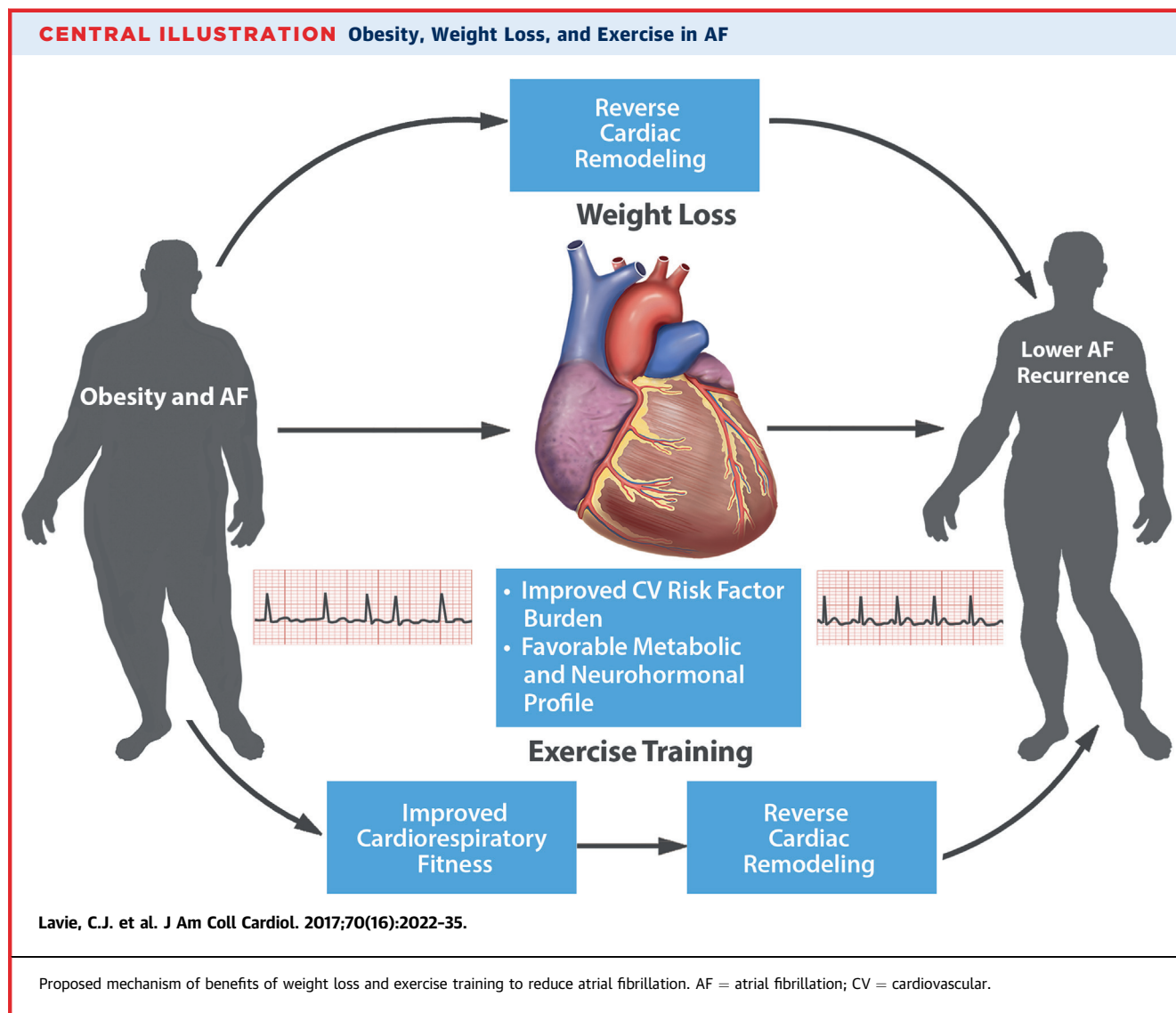
Findings from large prospective cohort studies, such as the Women's Health Study and the ARIC study, have shown that weight gain is associated with increased risk of AF (14,76). Similarly, several lifestyle intervention studies have demonstrated that lifestyle risk factor modification with intentional weight loss has a favorable impact on the epidemiology of AF. In a cohort study of Swedish Obese Subjects, Jamaly et al. (77) demonstrated that weight loss through bariatric surgery is associated with lower incidence of AF among individuals with severe obesity (77). This is in contrast to the findings from the Look AHEAD (Look AHEAD: Action for Health in Diabetes) study, where modest weight loss from intensive lifestyle interventions was not associated with lower risk of AF in subjects with diabetes (78). Taken together,

these findings suggest that substantial amount of weight loss may be needed to significantly lower the AF incidence in at-risk patients.

Among patients with established AF, lifestyle interventions with sustained weight loss have been associated with reduction in the AF burden and symptom severity in a dose-dependent fashion. In a randomized controlled trial with 248 prevalent AF patients, Abed et al. (72) demonstrated that weight reduction through participation in a structured weight management program was associated with significant reduction in AF symptom burden and lower risk of AF recurrence. Similarly, in the observational LEGACY (Long-Term Effect of Goal Directed Weight Management on Atrial Fibrillation Cohort: A 5 Year Follow-Up Study) cohort, Pathak et al. (73) demonstrated that AF patients with significant intentional weight loss over a 5-year follow-up (>10%) had 6-fold higher likelihood of arrhythmia-free survival, as compared with those with modest-to no-weight change (<3%). Similar findings were also observed in a Mediterranean cohort of AF patients, where individuals with higher and increasing BMI over long-term follow-up had higher risk of AF recurrences (79).

Structured physician-directed risk factor and weight management programs have also been shown to improve long-term success of AF ablation with better symptom control and recurrence-free survival (80). The mechanism underlying the favorable impact of weight loss on AF related outcomes are related to both indirect effects on CVD risk factors and direct effects on cardiac structure and function (73,80,81). Weight loss has been associated with favorable cardiac structural remodeling, with decreases in LA volumes, LV wall thickness, and improvements in LV diastolic function (73,80,81). Furthermore, recent studies have also demonstrated that intentional weight loss is associated with significant reduction in EAT, a well-established mediator of AF through proinflammatory and fibrotic paracrine effects (52,81,82). Taken together, these studies provide strong evidence in favor of management strategies aimed at weight loss and associated cardiac substrate modification among symptomatic AF patients. Future studies are needed to determine if weight loss strategies can lower long-term risk of adverse clinical outcomes, such as mortality, stroke, and HF hospitalization.

**IMPLICATIONS REGARDING PHYSICAL ACTIVITY, EXERCISE, CRF, AND AF.** Physical inactivity and low CRF have been traditionally associated with higher risk of CVD, such as CHD and HF (83-87).



The relationship between PA levels and risk of AF is more complex. Multiple longitudinal and case control studies have reported that a higher risk of AF is particularly present among athletes who participate in endurance sports (88-91). Among healthy, but nonathletic, individuals, the association between physical activity and risk of AF is less well established. Some studies have reported a higher risk of AF with increased PA levels over a lifetime, whereas others have reported an inverse or J-shaped association between physical activity levels and risk of AF (76,90,92-97). In a recent meta-analysis of 19 cohort studies, Kwok et al. (98) observed no association between physical activity and risk of AF, although a

more recent review suggests a modest benefit of physical activity at approximately 1,000 to 1,500 metabolic equivalents of task (MET) minutes per week (99). Taken together, findings from these studies suggest that higher levels of PA within the optimal range may be beneficial and not associated with increased risk of AF.

Recent studies have also explored the association between CRF levels, an accurate and objective measure of exercise capacity, and risk of AF in the general population. These studies have demonstrated a consistent dose-dependent inverse association between CRF and risk of AF (100-102). Thus, low CRF could represent an important modifiable risk factor

for AF that could be targeted with exercise interventions. However, in a recent study from the Look AHEAD trial, Alonso et al. (78) did not observe a significant association between improvement in CRF with intensive lifestyle interventions and risk of AF among individuals with diabetes. This could be related to the only relatively modest changes in CRF levels among Look AHEAD study participants with lifestyle intervention (<1 MET by the end of the study) and relatively small number of incident AF events in this large study.

Among patients with existing AF, however, higher CRF levels have been associated with greater arrhythmia-free survival. In the CARDIOFIT (Impact of Cardiorespiratory Fitness on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation) study, Pathak et al. (103) demonstrated that 1-MET higher CRF at baseline was associated with 13% lower risk of AF recurrence. Furthermore, improvement in CRF on long-term follow-up was also associated with significantly lower AF symptom burden and AF recurrence. Similarly, in a recent randomized controlled trial, Malmö et al. (104) showed that aerobic interval exercise training was associated with significantly lower burden of AF among patients in short-term follow-up. They also observed a trend towards improvement in clinical outcomes, such as need for cardioversion and hospitalization among exercise participants.

Several factors may underlie the observed beneficial effects of exercise and higher CRF in lowering AF burden, including improvement in cardiometabolic risk factor profile, lower sympathetic drive, and favorable changes in cardiac structure and function (103,105). This is consistent with the previously reported favorable pleiotropic effects of exercise among healthy individuals, as well as those with HF (106-108).

Cardiac rehabilitation and exercise training (CRET) programs have been shown to improve exercise capacity, symptom burden, and lower hospitalization rates in patients with other CVD conditions, such as CHD and HF (108,109). The American College of Cardiology/American Heart Association guidelines have strong recommendations for CRET as a key component of management of these CVDs (110,111). However, the role of exercise for management of AF is not well defined in the current guidelines. Findings from the studies discussed above provide strong evidence in favor of incorporating exercise as an adjunct strategy for AF management (Central Illustration). Future large randomized controlled trials are needed

to determine if the beneficial effects of exercise in AF patients in the short-term may translate into favorable CVD outcomes in the long-term follow-up.

#### LIMITATIONS AND FUTURE RESEARCH.

- Current data on the obesity paradox and mortality outcomes are statistically adjusted from non-matched cohorts with very different baseline characteristics, including age, CVD risk profile, and medications usage.
- There is a clear lack of dedicated research in obese individuals, with limited data available to guide safe use of various antiarrhythmic and anti-coagulation therapies.
- More work is needed to evaluate the impact of epicardial adiposity on AF pathogenesis to guide potential specific therapeutics.
- It is unknown whether intentional weight loss and exercise in obese individuals with AF may confer mortality benefits in addition to improved AF outcomes and quality of life.

#### CONCLUSIONS

Obesity and AF have been increasing in epidemic proportions in the United States and in most of the Westernized world. These disorders are strongly interrelated, and the risk of AF is markedly increased in the setting of obesity and weight gain. However, as with other established CVDs, a strong obesity paradox in AF has been reported in many individual trials and large meta-analyses, showing that overweight and obese with AF appear to have a better prognosis than do their leaner counterparts with AF. Nevertheless, recent evidence indicates that weight-loss programs, as well as programs increasing physical activity, exercise, and levels of CRF, reduce recurrences of AF in patients with a history of AF, and higher levels of CRF appear to be associated with the primary prevention of AF. Future studies are needed to assess the impacts of CRET and other weight-loss programs, as well as physical activity/exercise, on the prevention of other major CVD events, including CHD and HF, as well as CVD- and all-cause mortality, among patients with AF.

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**ADDRESS FOR CORRESPONDENCE:** Dr. Carl J. Lavie, Cardiac Rehabilitation, Exercise Laboratories, John Ochsner Heart and Vascular Institute, Ochsner Clinical School - The University of Queensland School of Medicine, 1514 Jefferson Highway, New Orleans, Louisiana 70121-2483. E-mail: [clavie@ochsner.org](mailto:clavie@ochsner.org).

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**KEY WORDS** cardiac arrhythmia, cardiovascular diseases, fat, fitness, heart rhythm