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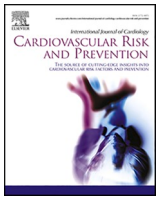

Review Article

# Obesity and cardiovascular disease: Risk assessment, physical activity, and management of complications

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ABSTRACT

The patient with obesity is at risk of developing cardiovascular disease and risk factors. Obesity negatively impacts prognosis and increases cardiovascular morbidity and mortality. Therefore, a comprehensive risk assessment is needed to define the cardiovascular risk of the patient and, thus, a tailored management and treatment. Chronic and successful management of these patients involves the evaluation of the various therapeutic strategies available (comprehensive lifestyle intervention, weight-loss medications, and bariatric surgery) and the diagnosis and treatment of cardiovascular complications (coronary artery disease, heart failure, and atrial fibrillation). Cardiac rehabilitation in patients with obesity is showing beneficial effect and a positive impact on weight loss, cardiovascular risk factors, mental health, functional capacity, and adherence to lifestyle interventions and pharmacological treatment. Long-term weight loss and maintenance represent a key objective during the management of the patient with obesity to reduce the risk of future adverse events. Multidisciplinary management and interventions are necessary to prevent and reduce overall cardiovascular risk and mortality. The aim of our review is to propose a comprehensive, critical and updated overview regarding risk assessment, physical activity, and the management of cardiovascular complications in patient with obesity.

## 1. Introduction

Obesity is deemed to be the pandemic of our times, surging to unprecedented levels of prevalence, with estimates indicating a two-fold increase compared to the mid-20th century [1]. This phenomenon is particularly pronounced in Western countries and the younger population, outlining a substantial challenge for public health [2]. Globally, it is estimated that 39%–49 % of the population is either overweight or obese [2]. According to the World Health Organization (WHO), obesity is defined as an abnormal accumulation of adipose tissue, with diagnosis based on the Body Mass Index (BMI) [2]. A BMI of 25 signifies overweight, while 30 characterizes obesity type 1, however, this BMI-centric definition may prove limiting as it does not discriminate between fatty mass and muscle mass [2,3]. Consequently, recent insights indicate the existence of various obesity phenotypes, advocating for the integration to BMI of tools such as abdominal circumference assessment and visceral fat evaluation [2,3]. The complexity of obesity emerges from genetic, organic, socio-economic, and psycho-social factors, contributing to its characterization as a multifactorial condition [2,4]. This intricate context becomes even more critical when considering the interplay between obesity, dysmetabolism, and cardiovascular risk factors/complications [1]. The scientific community is increasingly focusing on enhancing outcomes and the quality of life for patients dealing with both obesity and cardiovascular comorbidities [2,5]. Recent developments, exemplified by the SELECT [6] and STEP-HFpEF [7] trials in 2023, underscore the utilization of Glucagon-like peptide 1 (GLP-1)

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receptor agonist antidiabetic drugs within the specific context of obesity. This because obesity propels the development of numerous cardiovascular risk factors, thereby facilitating the onset of cardio-metabolic imbalance [2,3]. The link between obesity and cardiovascular risk factors, for instance, it is acknowledged as a robust independent risk factor for arterial hypertension. Indeed, weight loss is recommended as first-line treatment in hypertension management, as emphasized by current guidelines [8]. Furthermore, obesity is correlated with heart failure, particularly with preserved ejection fraction [2,9]. Obesity can exert an impact on both diastolic and systolic function, with the incidence of heart failure escalating in relation to BMI [2,10]. Noteworthy inflammatory burden, fibroadipose infiltration, and the activation of various systems are believed to contribute to the myocardial remodeling underlying the development of heart failure with preserved ejection fraction (HFpEF) and atrial fibrillation [11]. In addition is getting clear and clearer the role of epicardial fat, acting as a producer of inflammatory mediators in an autocrine/paracrine manner, influencing coronary microcirculation and myocardial cells, thereby promoting the mechanisms that lead to HFpEF [11]. Another crucial aspect involves the interplay between dyslipidemia and obesity, given that high rates of dyslipidemia are prevalent in obesity, as evidenced by studies reporting rates of 42.9 % in obese children and adolescents [12]. Moreover, obese patients exhibit significantly elevated levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides compared to non-obese individuals [2]. Given this profound connection, obesity can aptly be recognized as a cardio-metabolic disease. Therefore, the aim of this review is to provide a comprehensive and current overview of cardiovascular assessment, physical activity, and the management of cardiovascular complications, such as coronary artery disease, heart failure, and atrial fibrillation, in patients with obesity.

## 2. Risk assessment in patient with obesity

A holistic approach to risk assessment in obese patients involves a thorough examination of cardiovascular risk factors, consideration of risk modifiers, psychological assessment, evaluation of inflammatory burden, cardiovascular imaging, and assessment of visceral fat (Fig. 1) [8]. To effectively mitigate this risk, a comprehensive risk assessment is pivotal, encompassing various dimensions of the patient's health [8]. Integrating these components into clinical practice facilitates a more nuanced understanding of the cardiovascular risk profile in obese individuals, paving the way for personalized and effective risk management strategies, as well as the multidisciplinary treatment and management of cardiovascular complications (Fig. 2).

### 2.1. Control of cardiovascular risk factors

Central to any risk assessment in obese patients is the meticulous control of cardiovascular risk factors. Elevated blood pressure, dyslipidemia, and impaired glucose metabolism are common companions of obesity [2,3]. The assessment must include a thorough examination of these factors, employing a combination of lifestyle modifications and pharmacological interventions [2,3]. Lifestyle interventions encompass dietary changes, regular physical activity, and smoking cessation, aiming to address the modifiable risk factors directly linked to obesity [3]. However, it should be borne in mind that a basal cardiovascular assessment, involving electrocardiogram (ECG), echocardiogram and blood analysis (e.g. lipid profile) should be undertaken even in absence of cardiological red flags or symptoms in obese patients [2,8]. Blood pressure values should be also taken into account, possibly through a home-monitoring approach [2,3]. Poor evidence regards stress-ECG, given also the limited functional capacity affecting many obese patients [2].

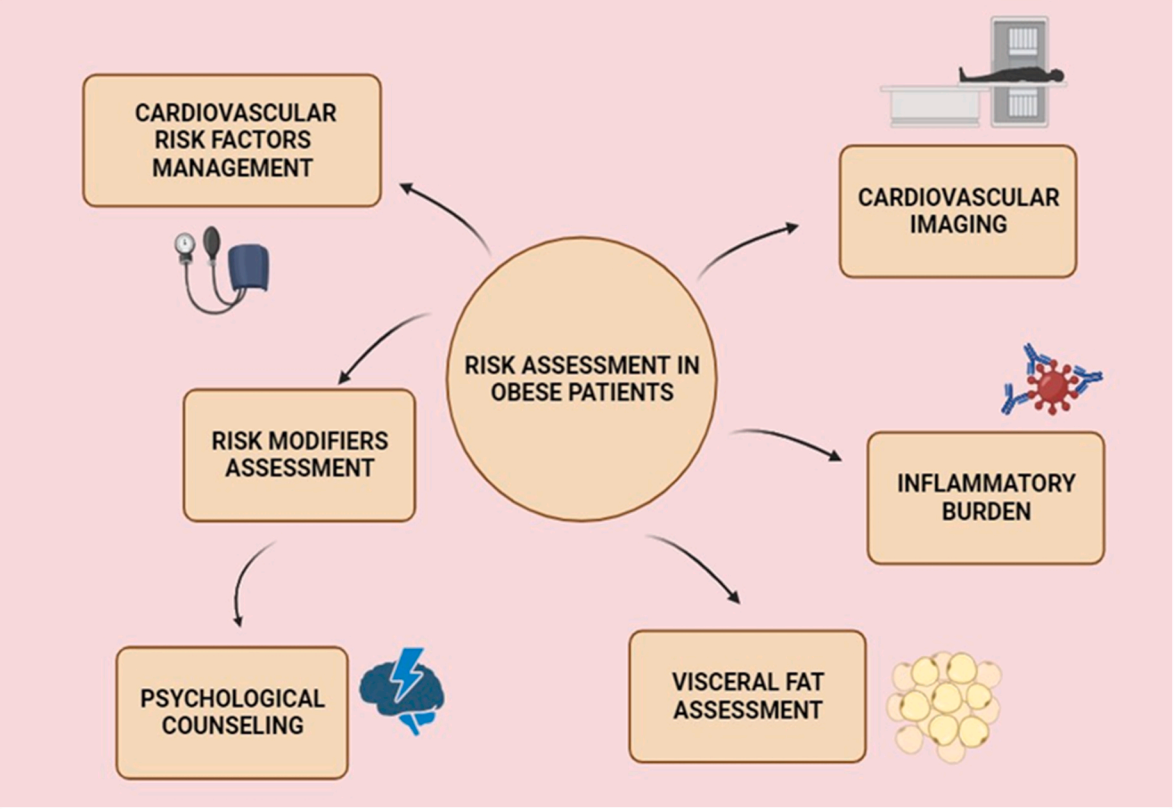


**Fig. 1.** Domains to be considered in risk assessment for the obese patient.

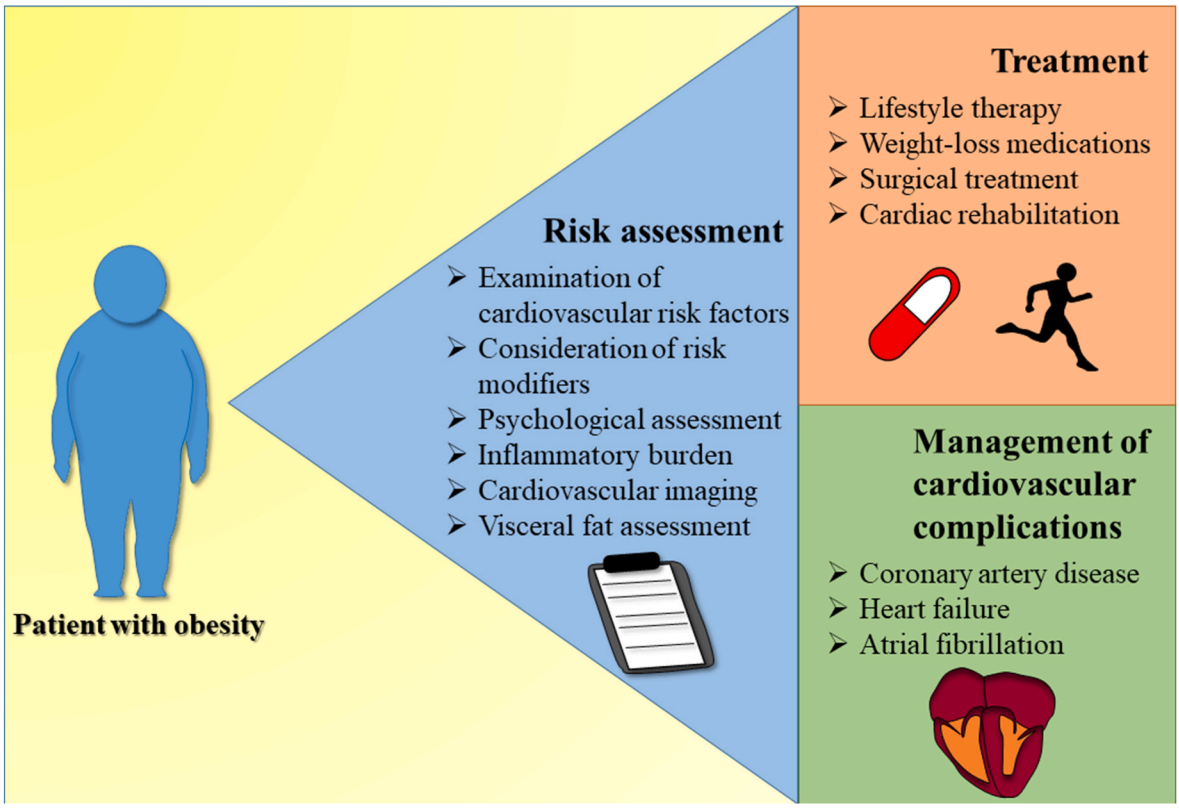


**Fig. 2.** Pathway and comprehensive management of the patient with obesity: risk assessment, treatment and cardiovascular complications.

### 2.2. *Risk modifiers*

Risk modifiers are an important domain to be assessed when exploring a patients' cardiovascular risk, as clarified by 2021 European Society of Cardiology (ESC) guidelines on cardiovascular disease prevention [8]. Risk modifiers are more frequent in the obese population than in the non-obese population [2,3]. Factors such as genetic predisposition, socio-economic status, and ethnicity can modify the cardiovascular risk associated with obesity [8]. Furthermore, it is essential to take into consideration comorbidities such as endocrinological and nephrological ones, chronic inflammatory diseases and also the possible presence of obstructive sleep apnea [3]. Tailoring risk assessment to account for these modifiers ensures a personalized approach to patient care, acknowledging the diverse nature of cardiovascular risk among obese individuals [2,3].

### 2.3. *Psychological assessment*

The intricate interplay between mental health and cardiovascular risk cannot be overstated [8]. Obesity often coexists with psychological factors such as stress, depression, and anxiety, which can significantly impact cardiovascular health [13]. A comprehensive risk assessment should, therefore, integrate a psychological evaluation, recognizing and addressing mental health aspects that may contribute to the overall cardiovascular risk profile [13].

### 2.4. *Evaluation of inflammatory burden*

Obesity is characterized by a chronic low-grade inflammatory state, and assessing the inflammatory burden becomes pivotal in understanding cardiovascular risk. Elevated levels of inflammatory markers, such as C-reactive protein, may serve as indicators of heightened cardiovascular risk in obese patients [4]. A thorough evaluation of inflammatory status provides valuable insights for risk stratification and aids in tailoring interventions to address the inflammatory component of cardiovascular risk. Anti-inflammatory therapies, such as colchicine, can now be administered in secondary prevention when traditional risk factors are poorly tamed despite optimal medical therapy: this paradigm may hold particular importance in obese patients, given the great inflammatory burden in this setting [2,3].

### 2.5. *Cardiovascular imaging*

Advancements in imaging technologies have revolutionized the assessment of cardiovascular risk, with particular regard to obesity [2]. Non-invasive imaging modalities as computed tomography (CT) angiography and magnetic resonance imaging (MRI) provide detailed insights into the structural and functional aspects of the cardiovascular system in obese patients, especially for the fact that their acoustic windows are quite often suboptimal [2]. These imaging techniques aid in the early detection of atherosclerotic plaques, cardiac remodeling, and other cardiovascular abnormalities, allowing for a more precise risk assessment and targeted intervention in obese patients [2,3]. Last but not least, as highlighted previously, great importance is given nowadays to the evaluation of epicardial and pericardial adipose tissue [2].

### 2.6. *Assessment of visceral fat*

Visceral fat is a key player in the pathophysiology of obesity-related cardiovascular complications [3]. Its close association with insulin resistance and dyslipidemia makes it a crucial parameter for cardiovascular risk assessment [2]. Goossens [14] highlighted the significance of body fat distribution and adipose tissue function in metabolic health, noting that metabolically healthy obese individuals exhibit improved adipose tissue function. Other authors have emphasized the existence of normal-weight individuals with metabolic disorders, emphasizing the necessity for a deeper understanding of these obesity phenotypes [15]. For instance, some specific serum biomarkers such as glutamine and

lactate are being tested, distinguishing between normal-weight and obese individuals and among different obesity types [16]. Utilizing imaging techniques, such as dual-energy X-ray absorptiometry (DEXA) or abdominal CT scans, may allow an accurate quantification of visceral fat, enabling a more comprehensive evaluation of the patient's cardiovascular risk [17]. The assessment of visceral fat is not yet routine in clinical practice; however, it is undoubted that, due to the analyzed physiopathological pathways, it can be of great assistance in the approach to cardiovascular risk in this setting.

## 3. Obesity, physical activity, and cardiac rehabilitation

Physical activity is a key intervention in patients with obesity to reduce cardiovascular risk and promote long-term weight loss (Fig. 3) [5]. A systematic review and meta-analysis of randomized controlled trials (RCTs) demonstrated that lifestyle interventions prevented cumulative weight gain among non-obese adults and physical activity is considered a cornerstone of public health programs in prevention perspective [18,19]. European Guidelines suggest to perform at least 150 min per week of moderate-intensity endurance exercise training combined with three sessions of resistance exercise per week in individuals with obesity [20]. In addition to weight reducing, the beneficial effect of this intervention has a wide-ranging action by improving glucose tolerance, insulin sensitivity, lipid level, and general well-being and reducing blood pressure, chronic inflammation, intra-abdominal fat mass, depression, and anxiety [8].

Cardiac rehabilitation in patients with obesity is showing interesting and emerging data on the beneficial effect both before (defined as "prehabilitation") [21] and after acute events, heart failure or invasive interventions [5]. The aim of rehabilitation program is to improve weight loss, adherence to a healthy diet, cardiovascular risk factors, psychological well-being, and functional capacity. Several programs have been suggested [22–25] but further studies are needed to standardize exercise training and better characterize the prognostic role. Resistance training should be performed with exercises involving the main muscle groups, from 1 to 3 sets of 8–12 repetitions at a load equal to 60–80 % (10–15 repetitions at 40–50 % for elderly subjects) of the single repetition maximum for at least 2 days per week. Cardiac rehabilitation program improves baseline metabolic equivalents, cardiorespiratory fitness, and exercise tolerance in this setting [5].

## 4. Obesity, gender, and cardiovascular disease

The contribution of gender medicine, that is the branch of medicine that studies how biological (defined by sex) and socioeconomic and cultural (defined by gender) differences influence people's health, in the field of obesity is undoubtedly crucial. Even starting from the mere epidemiological observation of the distribution of the obesity pandemic in time and space, we could identify possible areas of intervention to implement primary and secondary prevention strategies. It is well known that obesity tends to mostly interest poor populations and lower socio-economic adults living in high-income countries with a low cultural level [26], affecting nowadays more women than men [27]. Indeed, obesity is a common disease in women who experience biological and lifestyle changes at midlife and menopause period [28]. It is estimated that midlife women gain weight at an average of approximately 1.5 pounds per year [29]. The change in the hormonal profile which occurs progressively from the age of 40 onwards determines a redistribution of body fat from the subcutaneous to the visceral areas, with a consequent increase in pro-inflammatory and atherogenic adipose tissue, and therefore in cardiovascular risk [28,30]. However, it should be remembered that obesity was found to be the most important modifiable risk factor for hypertension and pre-hypertension even in reproductive age [31]. Also in women, obesity increases the risk of metabolic disorders (diabetes mellitus, dyslipidemia, polycystic ovary syndrome, and fatty liver disease), cardiovascular diseases (arterial hypertension, coronary artery disease, heart failure, and stroke) and cancers (endometrium, ovary, and breast) [28]. The Framingham Heart Study revealed that the excess risk of cardiovascular disease attributed to obesity was 64 % in women and 46 % in men [32].

In approaching obesity, it is crucial hot to measure the excess of weight and the distribution of adiposity, to better profile the real cardiovascular burden (Table 1). However, a very large study, who recruited more than 500000 patients, showed that higher waist circumference and waist-to-hip ratio, that are measures of central adiposity, are associated to a greater risk of myocardial infarction in women [33]. Even more, the waist-to-hip ratio seems to relate stronger with myocardial infarction than BMI in both sexes, especially in women [33]. In conclusion, obesity is a prevalent syndrome in women, leading to chronic and life-threatening diseases. Considering this, the Women's Preventive Services Initiative, a United States coalition of more than 21 health professional organizations and patient representatives, developed some recommendations with the aim to reduce the burden of obesity and its complications [34]. Among those, there is counseling for midlife women aged 40–60 years with normal BMI, with the aim to investigate diet and exercise habits, but also chronic stress, trauma and socioeconomic conditions, and then to tailor specific interventions [34]. Outpatient prevention clinics and cardiac rehabilitation may be optimal settings to implement these strategies, intercepting obese women or with normal weight but at high cardiovascular risk. Further research is needed to identify optimal and more sustainable behavioral and pharmacological interventions. Promising data derived from studies on liraglutide and semaglutide, in which the gender gap is inverted in favor of women, that are more represented in the main trials of these drugs [35,36].

## 5. Management of cardiovascular complications

### 5.1. Coronary artery disease

Obese patients with coronary artery disease represent a common and

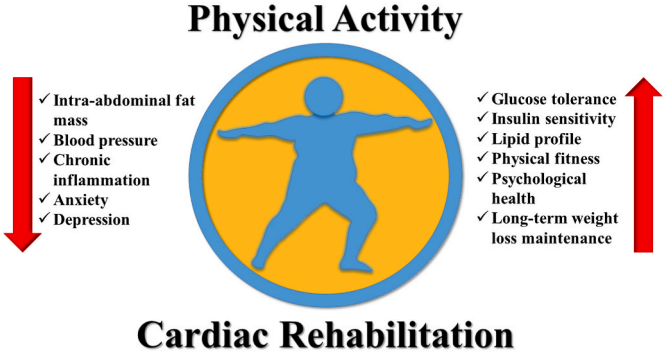


**Fig. 3.** Beneficial effects of physical activity and cardiac rehabilitation in patient with obesity.

**Table 1**
Optimal cut-off values for anthropometric measures of obesity in screening for cardiometabolic disorders in adults, according to sex.

| Parameter | Male | Female |
|---|---|---|
| WHR | 0.96 | 0.85 |
| WHtR | 0.57 | 0.54 |
| WC | 100 | 87 |
| BMI | 28.1 | 27.5 |

BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.
**Modified from**: Macek et al. [37]. Optimal cut-off values for anthropometric measures of obesity in screening for cardiometabolic disorders in adults. Sci Rep. 2020 Jul 9; 10(1):11253, https://doi.org/10.1038/s41598-020-68265-y.

challenge profile to manage. Obesity is associated with elevated risk of incident coronary artery disease [2,38], involving not only epicardial vessels but also the coronary microvasculature [39,40]. Cardiovascular outcome in individual post-percutaneous coronary intervention is characterized by a lower mortality rates in overweight individuals at 6 months but, at 5- and 10-year intervals, severe obesity and high-risk coronary anatomy were associated with higher mortality [41,42]. This paradox might be due in part to earlier cardiovascular disease diagnosis and treatment in overweight or obese individuals, and it may be more relevant to focus on low body fat percentage and low BMI as predictors of adverse cardiovascular disease outcomes [2]. On the other side, the relationship between obesity and mortality (in-hospital and long-term) after coronary artery bypass grafting remains inconclusive [2]. Patients with obesity face a higher risk of post-operative deep sternal wound infections, attributable to factors such as poorly vascularized adipose tissue and a higher incidence of dysglycemia [43,44]. Obesity can lead to increased platelet activation, potentially reducing the effectiveness of antiplatelet drugs, linked to factors like endothelial dysfunction, chronic inflammation, and bioactive substances produced by adipose tissue [44]. This phenomenon has been observed with aspirin, clopidogrel, and prasugrel, with prasugrel showing potential advantages in platelet reactivity [45]. In patients with obesity and coronary artery disease, a comprehensive risk assessment and multidisciplinary management are required to treat this major comorbidity. Behavior modifications, healthy diet, and increased physical activity are strongly recommended. Weight management and intentional loss are critical to significantly reduce the risk of future adverse clinical events in these type of patients [46]. Adopting lifestyle changes with weight loss has shown promise in addressing metabolic syndrome and related issues such as inflammation and endothelial dysfunction [2]. Medical weight loss interventions are suggested to supplement lifestyle modifications and maintenance of weight loss over time, however clinical trials have not consistently showed the reduction of coronary artery disease rates [47]. Bariatric surgery has consistently reduced major cardiovascular events, particularly coronary artery disease, compared to non-surgical weight management, likely due to substantial weight loss and its impact on long-term obesity [48].

### 5.2. Heart failure

Obesity predisposes to heart failure due to the development of subclinical cardiac damage over time. This consists of atrioventricular remodeling, increased filling and pulmonary pressures, and left ventricular systolic and diastolic dysfunction [3]. Indeed, the latest Guidelines [9] indicate obesity as a risk factor for heart failure and suggest a prompt counseling to prevent and delay its onset. Pathophysiological processes affecting the myocardium and vascular system are associated with the development of HFpEF [9,49]. Obese patients with HFpEF are characterized by greater right ventricular dilatation and dysfunction, left ventricular remodeling, epicardial fat thickness and volume, and lower exercise capacity [2]. Weight loss is a key intervention in these patients due to its multiple beneficial effects [50]. A recent systematic review and meta-analysis [51] documented that weight loss improves long-term rehospitalization (>3 months), quality of life, cardiac function, and exercise capacity, and bariatric surgery reduces mortality in overweight and obese heart failure patients. The optimal way of weight loss should be selected based on the patient's condition to acquire the best prognosis. Furthermore, a healthy diet and physical activity are also suggested as a corrective action for the heart failure or as a preventive strategy to avoid its development [10]. Indeed, in obese patients with HFpEF, caloric restriction and aerobic exercise training significantly improve exercise capacity by increasing peak VO2 [52]. Exercise interventions in patients with heart failure lead to a reduction in adipose tissue, increased blood flow to the respiratory and skeletal muscles, and improved pulmonary function, functional capacity, left ventricular ejection fraction and mitochondrial function. Exercise training, especially aerobic and concurrent interventions, in overweight middle-aged and elderly patients is effective to promote anti-inflammatory responses [53]. Regarding pharmacological treatment, beta-blockers can lead to tiredness and reduced exercise tolerance and are associated with weight gain in individuals with overweight or obesity [50]. Sodium glucose cotransporter-2 inhibitors (SGLT2i) are recommended to reduce the risk of heart failure hospitalization and cardiovascular death, and also reduce body weight and blood pressure and improve physical function and quality of life [10,54]. Long-term adherence is required to achieve therapeutic goals and improve healthy weight control, quality of life, exercise capacity, and prognosis. Motivated patients continue with a structured and specific follow-up and home exercises with the benefit of mobile device-based healthcare delivery or telehealth to evaluate and support patients over long time periods [10].

### 5.3. Atrial fibrillation

Obesity is among risk factors for atrial fibrillation development and progression [55]. Indeed, weight gain is related to the risk of incident atrial fibrillation and for every 5-unit increase in BMI this risk is 29 % greater [56]. The management of atrial fibrillation in obese patients involves several important aspects to consider regarding cardiometabolic risk factors and lifestyle changes, anticoagulants, and rhythm control [57]. Compelling evidence supports the benefits of weight loss in individuals with atrial fibrillation, emphasizing the impactful role of adiposity [58]. Intensive weight loss and comprehensive management of cardiometabolic risk factors lead to more significant reduction in atrial fibrillation duration, symptom severity, and intensity [59]. Weight loss ≥10 % and long-term sustained loss are associated with reduced atrial fibrillation burden and maintenance of arrhythmia-free survival [58]. Lifestyle changes are protective for atrial fibrillation and reduce its recurrence [60,61]. Physical activity has a central role in addition to weight loss. Indeed, improved cardiorespiratory fitness (≥2 metabolic equivalents) reduces atrial fibrillation recurrence and enhances the beneficial effect of weight loss [62]. Bariatric surgery reduces the risk of new-onset atrial fibrillation [63] and is associated with a significant reversal of the type [64]. In terms of thromboembolism risk management, obese patients may require higher doses of vitamin K oral anticoagulants (VKAs) and extended treatment initiation periods to achieve therapeutic INR levels [65]. Instead, regarding non-vitamin K oral anticoagulants (NOACs), measurement of serum levels may be necessary in certain situations such as severely obese patients with a BMI exceeding 35 or a weight exceeding 120 kg [66]. However, this approach is discouraged for the majority of patients due to insufficient outcome data [67].

For rhythm control in these patients, success following electrical cardioversion may be decreased due to the expansion of epicardial adipose tissue, promoting atrial fibrillation recurrence [68]. Routine use of adhesive patches at 200 J is inadequate in obesity, and more effective strategies include the use of paddles, Manual Pressure Augmentation, and escalating to 360 J [69]. Obese patients with a management of weight loss and risk factors result in an enhanced arrhythmia-free survival after atrial fibrillation ablation [60,70].

## 6. Conclusions

Obesity is linked to the development of cardiovascular disease and risk factors and increases the risk of mortality. Patients with obesity are a common profile in clinical practice and appropriate chronic management is necessary to improve their quality of life and prognosis. A holistic risk assessment is the first step to evaluate the category and level of risk in patients with obesity. This stratification is key to defining tailored management and multidisciplinary treatment for each patient. Cardiac rehabilitation in these patients is an intervention with multiple benefits, in addition to improving functional capacity. Finally, a comprehensive

clinical evaluation also includes the detection of cardiovascular complications, such as heart failure, coronary artery disease, and atrial fibrillation, to ensure appropriate management and treatment.

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## CRediT authorship contribution statement

**Francesco Perone:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing. **Luigi Spadafora:** Conceptualization, Writing – original draft, Writing – review & editing. **Alessandra Pratesi:** Conceptualization, Writing – original draft, Writing – review & editing. **Giulia Nicolaio:** Conceptualization, Writing – original draft, Writing – review & editing. **Barbara Pala:** Writing – original draft, Writing – review & editing, Conceptualization. **Giulia Franco:** Conceptualization, Writing – original draft, Writing – review & editing. **Matteo Ruzzolini:** Conceptualization, Supervision, Writing – review & editing. **Marco Ambrosetti:** Conceptualization, Supervision, Writing – review & editing.

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