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REVIEW

Targeting Overweight and Obesity Phenotypes for Secondary Prevention of Cardiovascular Disease: A Call to Action for the Middle East and Beyond

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Received: 19 August 2025 | **Revised:** 14 May 2026 | **Accepted:** 20 July 2026

Keywords: cardiovascular disease | glucagon-like peptide-1 receptor agonist | Middle East | obesity | secondary prevention | semaglutide | weight loss

ABSTRACT

Although there are conflicting clinical data on the efficacy of weight reduction in reducing secondary events in patients with comorbid overweight and obesity (OAO) and cardiovascular disease (CVD), there is excellent epidemiological and biological evidence of a cause–effect relationship between OAO, CVD, and other systemic complications. There is also new interventional evidence that pharmacotherapies improve cardiovascular, hepatic, and renal outcomes in individuals with OAO and pre-existing CVD. New trial data confirm that not all weight loss strategies are equal in terms of reducing cardiovascular risk. Using Global Burden of Disease data and a pooled analysis of registry data on ~30,000 patients with CVD, we estimate that about 34 million patients across the Middle East could benefit from secondary prevention of CVD by targeting OAO phenotypes. Implementing secondary prevention in practice will require updating clinical guidelines on both obesity management and CVD secondary prevention, as well as policy changes that allow for reimbursement. Crucially, it will also require a philosophical shift that there exist distinct OAO phenotypes for which treatment success is not solely dictated by weight loss. The cumulative burden of future cardiovascular risk is set to increase, mandating comprehensive strategies to implement secondary prevention in at-risk groups, including children.

1 | Introduction

By any health, societal, or economic measure, overweight and obesity (OAO) constitutes a major global crisis. The World Health Organization estimated that, in 2022, 2.5 billion adults aged 18 and over were living with OAO (prevalence 43%) worldwide [1, 2]. Of these, 890 million were living with obesity (BMI ≥ 30 kg/m^2), corresponding to 16% of individuals, a figure

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that has nearly doubled over the last 30 years [1, 2]. The OAO crisis is similarly mirrored and has undergone an even worse upward trajectory in children and adolescents, quadrupling since 1990 to over 390 million 5- to 19-year-olds living with OAO (BMI > 1 standard deviation above the median) in 2022 [1, 2]. Eastern Mediterranean countries, especially in the Arabian Gulf, have reported the largest increases in OAO [3]. In 2016, the United Arab Emirates (UAE) was ranked 26th worldwide in terms of obesity prevalence [3], with Global Health Observatory data indicating that the prevalence of OAO in adults in the UAE was higher than the global average at 71.3% (32.1% living with obesity, BMI ≥ 30 kg/m^2) [1]. The economic impacts from OAO in the UAE are already 2.8% of gross domestic product (GDP), and if current trends in OAO prevalence, economics, and demographics continue, this is projected to rise to 11% of GDP in the UAE by 2060 [4].

OAO is a chronic and complex disease with multifaceted psychosocial impacts on quality of life and through stigmatization, discrimination, and bullying, especially in children. It is also a well-established risk factor for many chronic diseases including diabetes mellitus, chronic kidney disease, cancer, musculoskeletal disorders, and cardiovascular disease (CVD) [5]. The 2021 Global Burden of Diseases Collaborators' analysis reported that elevated BMI contributed to 3.7 million (95% confidence interval [CI], 1.97–5.49 million) deaths in 2021 [6], with CVD, principally ischemic heart disease (IHD) and stroke, responsible for 1.95 million (95% CI, 1.12–2.91 million) deaths in individuals with OAO [5].

Prevalence rates of CVD (IHD, stroke, lower extremity peripheral artery disease, atrial fibrillation (AF), hypertensive heart disease, cardiomyopathy, acute myocarditis, and endocarditis and rheumatic heart disease) in the Middle East and North Africa (MENA) region are the highest in the world at 9978.7 per 100,000, respectively [7]. Age-standardized death rates from CVD in the MENA region (at 361.4 per 100,000) are also among the highest in the world (compared with 145.4 per 100,000 in North America) [7]. Although the UAE enjoys relatively low age-standardized death rates (Figure 1B) in the region (257.4 per 100,000 vs., e.g., 10,472 per 100,000 in Egypt, 483.1 per 100,000 in Oman, and 364.6 per 100,000 in Saudi Arabia [7]), the UAE is estimated to have the highest age-standardized CVD prevalence in the region (11,056.7 per 100,000, Figure 1C [7]). There is still work to be done in protecting this large CVD population from unnecessary morbidity and mortality due to attributable risk factors, of which OAO is a leading candidate [8]. Although recent Global Burden of Disease data show that the high BMI-CVD risk-outcome association (i.e., the burden of CVD directly attributable to the risk factor of high BMI) is relatively weak (ranked 85th in terms of risk-outcome associations, compared with, for instance, the high systolic blood pressure-IHD association, ranked 10th), this does not take into account other indirect associations between OAO and CVD-related outcomes, such as high BMI and type 2 diabetes (ranked 18th [8]).

Nevertheless, OAO is the fifth leading modifiable risk factor contributing to CVD burden after high systolic blood pressure, dietary risks, high low-density lipoprotein LDL cholesterol, and air pollution [9], and the sixth leading risk factor contributing to disability-adjusted life years (DALYs) overall [6]. However, the interaction between OAO and other well-established risk factors for CVD (hyperlipidemia, hypertension, and diabetes) has often meant that OAO has been viewed—especially by clinicians—as a minor risk factor or perhaps an amplifier of other cardiovascular risk factors [10]. The fact that no country, including the UAE, has witnessed a decline in the proportion of the population with OAO over the last 30 years [11] reflects how challenging it is to modify the physical inactivity, diet quality, and excess energy intake that contribute to OAO. Given that there is considerable evidence of a cause–effect relationship between OAO and CVD [10, 12] and new clinical evidence supporting that treating OAO reduces the risk of further CVD events in patients with pre-existing CVD (see below), there is a need to raise awareness of the scale and nature of the burden of comorbid OAO and CVD, current strategies available for secondary prevention (i.e., preventing recurrent events in patients with established disease), and the barriers that must be overcome to address this major public health concern, especially in countries like the UAE with an especially high burden of OAO and CVD.

2 | Evidence Identification

This narrative, nonsystematic review synthesized current evidence on the burden, mechanisms, treatment, and policy implications of comorbid OAO and CVD, in particular in the Middle East. Relevant literature was identified through searches of the MEDLINE (via PubMed) and Embase databases from January 2000 to August 2025, supplemented by hand-searching of reference lists of key articles, recent international guidelines (American Gastroenterological Association, American Association of Clinical Endocrinologists, European Society of Cardiology, World Obesity Federation, UAE Department of Health), and conference proceedings of the American Heart Association, American College of Cardiology, European Association for the Study of Obesity, and European Society of Cardiology meetings from 2022 to 2025. Search terms combined the following concepts using Boolean operators: ("obesity" OR "overweight" OR "BMI" OR "adiposity") AND ("cardiovascular disease" OR "coronary" OR "myocardial infarction" OR "stroke" OR "heart failure" OR "atrial fibrillation" OR "secondary prevention") AND, where regional evidence was sought, ("Middle East" OR "Gulf" OR "MENA" OR "United Arab Emirates" OR specific country names). Pharmacotherapy-specific searches additionally combined obesity and CVD terms with "GLP-1 receptor agonist," "semaglutide," "liraglutide," "tirzepatide," "SGLT-2 inhibitor," and named cardiovascular outcome trials (e.g., SELECT, SOUL, FLOW, STEP-HFpEF, SUMMIT, SMART, and ESSENCE).

We restricted included sources to those published in English. Priority was given to (i) randomized controlled trials (RCTs) and their meta-analyses for evidence on intervention efficacy; (ii) large prospective registries and Global Burden of Disease estimates for prevalence and burden data, with preference given to Middle Eastern data sources where available; (iii) recent (post-2015) narrative and systematic reviews for mechanistic and pathophysiological content; and (iv) current national and international clinical practice guidelines and policy documents for the implementation sections. Older landmark studies were retained where they remain definitive (e.g., Look AHEAD,

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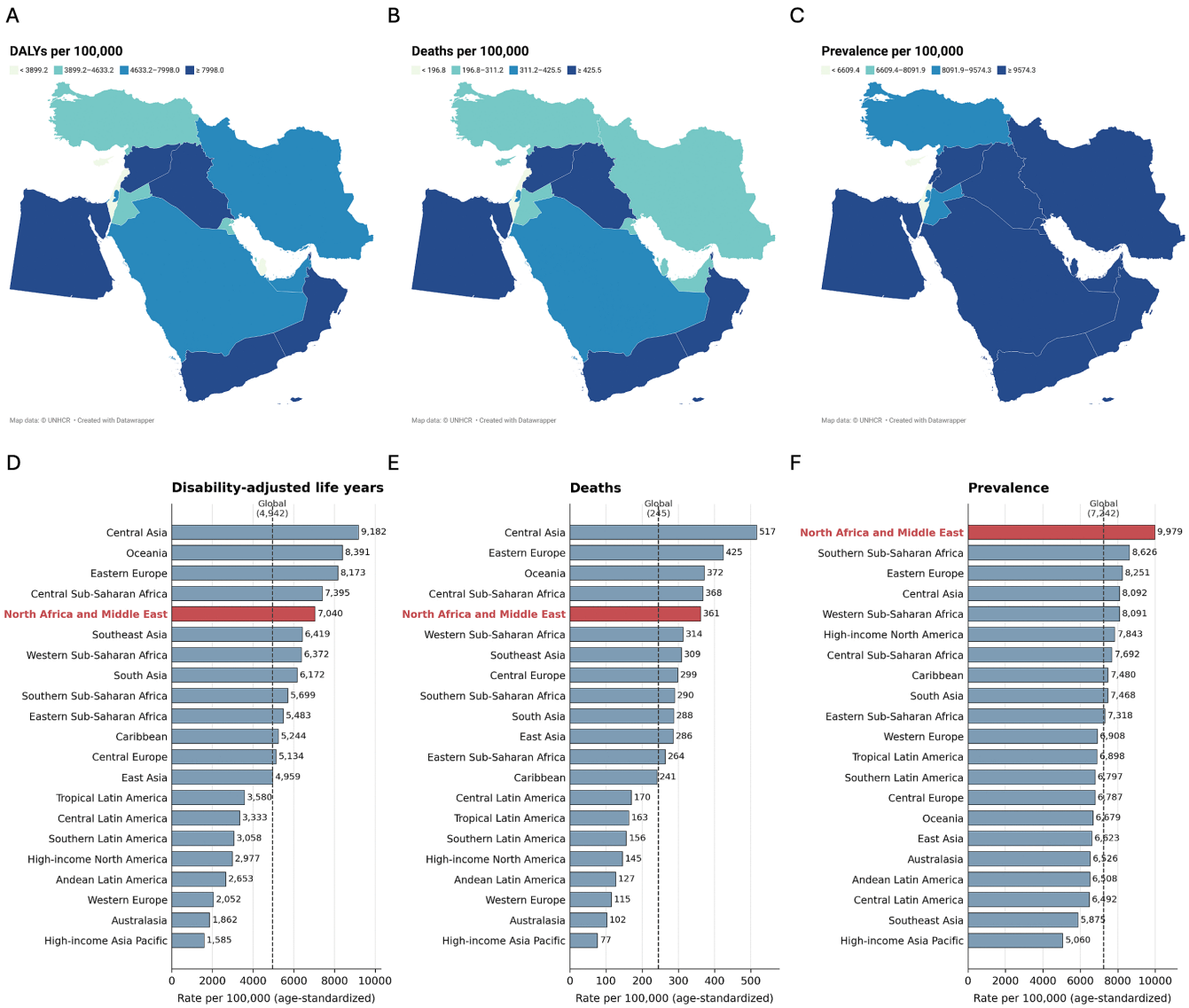

FIGURE 1 | Age-standardized burden of cardiovascular disease in the Middle East compared with global GBD super-regions, 2021. Panels A–C show country-level age-standardized rates per 100,000 population for (A) disability-adjusted life years (range 1525.6–10,670.1), (B) deaths (range 82.4–539.9), and (C) prevalence (range 5127–11,056.7) of cardiovascular disease (heart disease, stroke, lower extremity peripheral artery disease, atrial fibrillation, hypertensive heart disease, cardiomyopathy, acute myocarditis, endocarditis, and rheumatic heart disease) across countries of the Middle East. Panels D–F rank all 21 GBD super-regions by the same three age-standardized metrics; the North Africa and Middle East super-region is highlighted in red and the global average is shown as a dashed reference line. Data are from the Global Burden of Disease 2021 study [7].

SCOUT, and CRESCENDO). The cited works were finally selected based on consensus among the authors, relevance to the review's scope, and strength of the underlying evidence.

3 | Can Treating Obesity Treat CVD?

3.1 | The Evidence Against

Some clinicians regard treating obesity—rather than associated conditions like dyslipidemia, hypertension, and diabetes—as an ineffective means to reduce the risk of CVD. There is also evidence to support this. Clinically, RCT data on the efficacy of lifestyle and pharmacological interventions for OAO have not always supported secondary prevention of CVD through weight loss. For example, a meta-analysis of 54 RCTs ($n = 30,206$ patients) evaluating mainly low fat, weight-reducing trials reported that while weight loss interventions were associated with a decrease in premature all-cause mortality ($n = 34$ trials, 685 events; risk ratio [RR], 0.82; 95% CI, 0.71–0.95), they had no effect on cardiovascular mortality nor new cardiovascular events [13]. Likewise, intensive lifestyle intervention, such as that administered in the Look Action for Health in Diabetes (Look AHEAD) trial to individuals with OAO and type 2 diabetes [14], failed to reduce CVD incidence in the overall population. The Sibutramine Cardiovascular Outcomes Trial (SCOUT) of 9804 patients with OAO reported an increased risk of nonfatal MI and nonfatal stroke in patients with pre-existing CVD receiving daily sibutramine, a serotonin–norepinephrine reuptake inhibitor [15], prompting its withdrawal from the market. Similarly, rimonabant was withdrawn from the market after the Comprehensive Rimonabant

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Evaluation Study of Cardiovascular Endpoints and Outcomes (CRESCENDO) CVOT trial reported an increased risk of serious neuropsychiatric sequelae without a reduction in major cardiovascular events (MACE) in patients taking rimonabant [16]. While lorcaserin, a selective serotonin 2C receptor agonist and appetite suppressant, significantly reduced weight in OAO patients with atherosclerotic cardiovascular disease or multiple cardiovascular risk factors, it had no effect on MACE compared with placebo [17].

A second source of historical skepticism is the so-called "obesity paradox," the observation in cohort studies of patients with established atherosclerotic disease (and especially heart failure) that higher BMI is associated with better survival than normal weight [18–20]. Although initially interpreted as evidence that excess weight is protective once cardiovascular disease is established, the paradox is now thought to reflect limitations of observational data rather than a true biological effect. First, BMI is a poor surrogate for visceral and ectopic adiposity (the metabolically active compartment most relevant to cardiovascular risk) and cannot distinguish excess fat mass from preserved skeletal muscle mass; individuals with similar BMI can have markedly different cardiometabolic phenotypes [10]. Second, in advanced heart failure, chronic kidney disease, malignancy, and other catabolic states, low BMI often reflects disease-driven cachexia rather than independently protective leanness, generating reverse causality. Third, smoking, which lowers BMI while increasing cardiovascular risk, and unmeasured comorbidities introduce residual confounding that has been shown to attenuate or reverse apparent BMI-outcome associations. Fourth, conditioning on prevalent disease introduces collider bias that can distort the BMI-outcome relationship within already-diseased cohorts even in the absence of a true paradoxical effect [18]. Importantly, recent RCTs of intentional pharmacological weight loss (see below) bypass these limitations through randomization and intentional intervention, consistently demonstrating that targeted weight loss reduces cardiovascular events and improves heart failure symptoms. The obesity paradox observed in earlier cross-sectional and cohort studies is therefore best thought of as reflecting measurement and design limitations rather than a genuinely cardioprotective effect of excess adiposity, and that adiposity is a reversible contributor to morbidity in established CVD.

3.2 | The Evidence for

Not all weight loss interventions, however, have reported neutral or negative impacts on CVD outcomes. A post hoc analysis of Look AHEAD reported that the degree of weight loss was important when considering CVD outcomes, with those patients with OAO and type 2 diabetes achieving a ≥ 10% weight loss experiencing significant reductions in the incidence of CVD [21]. In a long-term lifestyle intervention study of diet and exercise in individuals with a BMI > 25, the Da Qing Diabetes Prevention Outcome Study found that the intervention was associated with a delay in diabetes onset, a reduction in CVD events and deaths, and increased life expectancy compared with controls after 30 years [22]. Finally, metabolic and bariatric surgery (MBS), now a recommended treatment option for those with severe obesity (BMI ≥ 35 kg/m^2), has been shown to reduce the risk of cardiovascular events in well-designed prospective, controlled observational studies [23], retrospective cohort studies [24], and a meta-analysis [25]. As weight loss is the primary objective of MBS, cardiovascular outcomes are often framed in the context of % total body weight (TBW) loss. Although it is unclear what metric should be used to define a "good" or "poor" response to surgery, high target thresholds of > 20%–30% TBW loss have permeated the literature as a "successful result" [26]. However, in our experience and supported by meta-analysis and other longitudinal studies [27, 28], 20%–30% TBW loss is a high threshold, and smaller losses can also be effective in reducing cardiovascular risk. Furthermore, newer drugs like glucagon-like peptide-1 receptor agonists (GLP-1-RAs, such as liraglutide and semaglutide) that achieve relatively smaller degrees of weight loss but nevertheless significantly reduce cardiovascular risk (see below) suggest that the biological mechanisms associated with obesity and CVD can be targeted independently of weight loss [29]. The clear message from these data is that not all weight loss strategies are equal in terms of reducing cardiovascular risk.

4 | The Burden of Comorbid Cardiovascular Disease and OAO in the UAE and Middle East

Given that effectively treating OAO with weight-reduction measures appears to reduce the risk of death and morbidity from CVD, it would be useful to quantify the target population for secondary prevention, that is, the prevalence of individuals with comorbid OAO and CVD. As noted above, at the global scale, the estimated burden of OAO is 2.5 billion adults, and GBD data indicate that the global prevalence of CVD is 422 million [6, 7]. Therefore, while there are plenty of estimated data on the prevalence of obesity and CVD and their individual and combined contributions to morbidity and mortality [8], there are relatively little direct, real-world data on the prevalence of obesity in the established CVD population who would benefit from targeted secondary prevention measures.

Clinical registries are observational databases that systematically collect real-world data on clinical conditions and populations for specified scientific, clinical, or policy purposes [30]. Although they do not overcome the inherent biases present in observational data collection and analysis, data are captured in a standardized, granular, and consistent manner, enhancing data quality to develop evidence for best clinical practice. Many national and international CVD registries have been established over the last few decades [31], including in the UAE and wider Middle East, and some of these have collected and reported data on OAO to allow estimation of the prevalence of OAO within the population of patients with CVD and the overall number of patients who might be candidates for secondary prevention through weight loss measures. Deriving prevalence data from local populations (country or region specific) is likely to be more accurate than generalizing from global data, as there are large differences in OAO and CVD prevalence in different countries [5, 6, 8].

Registries from the Middle East reporting BMI prevalence in relevant populations of patients with CVD are shown in

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TABLE 1 | Prevalence of OAO in CVD registries from the Middle East, including the UAE.

Registry	Author, year, reference	Countries	*N*	Cardiovascular disease	BMI category (kg/m²)	Prevalence (%)
Gulf COAST	Zubaid et al., 2014, [32]	Bahrain, Kuwait, Oman, UAE	3188	Acute coronary syndrome[a]	25 to < 30	39.4
					≥ 30	36.2
DYSIS II	Al Mahmeed et al., 2019, [33]	UAE	216	Stable coronary heart disease	≥ 30	46.8
			200	Acute coronary syndrome[b]	≥ 30	23.5
Gulf RACE	El-Menyar et al., 2011, [34]	Bahrain, Kuwait, Qatar, Oman, UAE, Yemen	6704	Acute coronary syndrome[c]	≥ 30	27.0
REACH	Alsheikh-Ali et al., 2011, [35]	Middle East: Israel ($n = 374$), Lebanon ($n = 120$), Saudi Arabia ($n = 196$), UAE ($n = 150$)	840	45 or older with established coronary artery disease, cerebrovascular disease or peripheral arterial disease, or with at least three atherosclerotic risk factors	25 to < 30	46.1
					≥ 30	29.9
KHF RACE[d]	Unpublished	Kuwait	8913	Acute coronary syndrome[a]	25 to < 30	49.8
					≥ 30	28.9

[a]ACS diagnosed according to American College of Cardiology (ACC) clinical data standards [36].
[b]ST-segment elevation myocardial infarction (STEMI)/left bundle branch block myocardial infarction (LBBB MI), non-ST-STEMI (NSTEMI), or unstable angina (UA).
[c]ST–elevation myocardial infarction (STEMI) and non-ST elevation ACS (NSTEACS).
[d]Kuwait Heart Foundation Registry of Acute Coronary Events.

Table 1. Other CVD registries in which BMI is reported as a population average are shown in Table S1. Reflecting the overall population prevalence of OAO in these countries, nearly half of patients with established CVD were overweight (average 45.1%, $n = 3$ studies) and nearly a third were living with obesity (average 32.1%, $n = 6$ studies). Although there are fewer ischemic stroke registries (SITS-MENA [37] nor the Saudi Stroke Data Bank [38] reported BMI data), one multicenter prospective stroke registry [39] containing 780 patients from Kuwait, Oman, Qatar, and the UAE reported a 36.6% prevalence of obesity (BMI ≥ 30 kg/m²).

As only a limited number of registries have reported OAO prevalence data, we extracted BMI data from a pooled analysis of seven major prospective ACS registries in the Arabian Gulf region from 2005 to 2017 (see Table S2 for details of the included registries and [40]) representing 31,510 patients; 29,248 entries had BMI data available for analysis; patients with available BMI data ($n = 29{,}248$; 92.7%) were broadly comparable to those without ($n = 2262$; 7.3%) for most baseline characteristics, the main source of imbalance being the source registry rather than clinical features (Table S3), supporting the representativeness of the cohort. Of these patients, 43.6% (95% CI, 43.0%–44.1%) had a BMI 25–29.9 kg/m² (overweight) and 29.4% (95% CI, 28.8%–29.8%) had a BMI ≥ 30 kg/m² (obese) (Figure 2). These data are similar to population estimates of OAO prevalence in the UAE

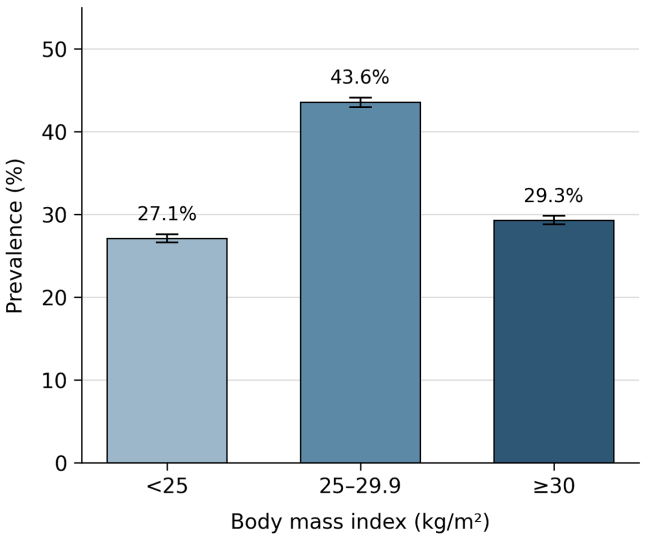

FIGURE 2 | Prevalence of body mass index (BMI) categories in 29,248 patients with available BMI data from a pooled analysis of 31,510 patients with ACS enrolled across seven prospective Arabian Gulf registries between 2005 and 2017 (Gulf RACE, Gulf RACE-2, Gulf RACE-3Ps, GULF One, Gulf Coast, SPACE, STARS-1; see Table S2 for registry details). Bars show prevalence; error bars show 95% Wilson confidence intervals.

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TABLE 2 | Estimated burden of comorbid overweight and obesity (OAO) and cardiovascular disease (CVD) in the Middle East. Estimated prevalence of CVD is from the Global Burden of Disease 2021 study [6]. The OAO proportion applied (72.9%) is the pooled estimate from our meta-analysis of 29,248 patients with available BMI data from seven prospective Arabian Gulf acute coronary syndrome registries (Table S2). The range reflects the 95% Wilson CI of this pooled OAO proportion (72.4%–73.4%).

Country	Estimated prevalence of CVD	OAO proportion applied	Estimated prevalence of comorbid CVD and OAO	Range (95% CI)
Afghanistan	1,640,000	72.9%	1,195,068	1,186,704–1,203,432
Algeria	3,800,000	72.9%	2,769,060	2,749,680–2,788,440
Bahrain	129,000	72.9%	94,002	93,344–94,660
Egypt	7,630,000	72.9%	5,559,981	5,521,068–5,598,894
Iran (Islamic Republic of)	8,310,000	72.9%	6,055,497	6,013,116–6,097,878
Iraq	2,910,000	72.9%	2,120,517	2,105,676–2,135,358
Jordan	764,000	72.9%	556,727	552,830–560,623
Kuwait	325,000	72.9%	236,828	235,170–238,485
Lebanon	564,000	72.9%	410,987	408,110–413,863
Libya	630,000	72.9%	459,081	455,868–462,294
Morocco	3,480,000	72.9%	2,535,876	2,518,128–2,553,624
Palestine	267,000	72.9%	194,563	193,201–195,925
Oman	270,000	72.9%	196,749	195,372–198,126
Qatar	163,000	72.9%	118,778	117,947–119,609
Saudi Arabia	2,200,000	72.9%	1,603,140	1,591,920–1,614,360
Syrian Arab Republic	1,390,000	72.9%	1,012,893	1,005,804–1,019,982
Sudan	2,320,000	72.9%	1,690,584	1,678,752–1,702,416
Tunisia	1,250,000	72.9%	910,875	904,500–917,250
Türkiye	8,120,000	72.9%	5,917,044	5,875,632–5,958,456
United Arab Emirates	729,000	72.9%	531,222	527,504–534,940
Yemen	1,640,000	72.9%	1,195,068	1,186,704–1,203,432
Total	48,531,000	72.9%	35,364,540	35,117,032–35,612,048

Note: Estimated prevalence of comorbid CVD and OAO is calculated as follows: (estimated CVD prevalence)×(OAO proportion). The 95% CI range is calculated by applying the Wilson 95% CI bounds of the pooled OAO proportion (lower 72.36%, upper 73.38%) to the country-level CVD prevalence estimate. As a sensitivity analysis, applying the lowest and highest OAO prevalences observed across the seven contributing registries (67.3% in Gulf RACE to 80.2% in STARS-1) yields a wider plausibility range that captures between-registry heterogeneity in case mix; for the regional total, this corresponds to ~32.7 to 39.0 million comorbid cases.
Abbreviations: CI, confidence interval; CVD, cardiovascular disease; OAO, overweight and obesity.

of 39.2% living with a BMI of 25–29.9 kg/m^2 (overweight) and 32.1% living with obesity [3].

Overall, therefore, and acknowledging the limitations of the above approach (the registries do not contain the full spectrum of CVD, and data from the wider Middle East may not fully reflect the local situation in the UAE), the data suggest that the proportion of CVD patients with OAO is roughly similar to that in the wider population (about 70%). Given an estimated prevalence of 729,000 CVD cases in the UAE in 2021 [6], we estimate that about half a million (1 in 20) individuals in the UAE and ~35 million individuals in the Middle East have comorbid CVD and OAO that might benefit from secondary prevention of adverse CVD outcomes through weight loss or other strategies (Table 2).

5 | Toward Secondary Prevention in Patients With Comorbid CVD and Obesity

5.1 | Establishing a Mechanistic Rationale

Despite these mixed clinical data, there is a good mechanistic rationale for obesity participating in the development of CVD (for excellent reviews, see [10, 41]). There are, of course, indirect effects by association with other CVD risk factors including

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insulin resistance, type 2 diabetes, hypertension, and dyslipidemia [10, 41]. However, obesity also has direct effects on the cardiovascular system. First, the cardiovascular system must adapt to accommodate excess body weight: (i) sodium retention increases intravascular volume and hence circulating blood volume; (ii) there is sympathetic activation to increase cardiac output and meet the metabolic demands of excess adipose tissue; and (iii) low-grade inflammation, hyperinsulinemia, and sympathetic activation increase systemic vascular resistance which, together with increased cardiac output, increase blood pressure and contribute to hypertension [41]. The increased cardiac work adversely effects left ventricular and atrial remodeling and consequently function, increasing the risk of heart failure and AF [41, 42]. Second, at the molecular and tissue levels, adipose tissue can and should be considered an active endocrine organ that secretes adipokines: bioactive hormones, cytokines, and chemokines that impact glucose and lipid metabolism, immunity, vascular homeostasis and angiogenesis [43]. The maladapted expansion of the adipose compartment leads to proinflammatory phenotypic changes in adipocytes and tissue-resident macrophages together with proinflammatory adipokine release (e.g., of leptin, tumor necrosis factor α [TNF-α], interleukin 6 [IL-6], IL-18, and IL-1β [44]), together with a reduction in anti-atherogenic adiponectin [45], which together promote atherosclerosis through inflammation, oxidative stress, reduced nitric oxide availability, and dyslipidemia [10]. Furthermore, epicardial and perivascular adipose tissue are in direct contact with the underlying vascular tissue, so proatherogenic factors such as free fatty acids, cytokines, and adipokines released from dysfunctional adipocytes may directly influence vascular smooth muscle cell tone, contractility, inflammation, and endothelial cell function and promote the development of atherosclerosis and CVD directly [46–48]. The net result of these systemic and local paracrine molecular changes is endothelial dysfunction, atherogenesis, and a prothrombotic state that promote CVD.

Given the disconnect between epidemiological, clinical, and biological data, it is perhaps unsurprising that there has been a lack of enthusiasm for treating obesity as a cause of CVD. Nevertheless, OAO represents a common and distinct clinical phenotype within the CVD population that could benefit from targeted and personalized therapy approaches. The controversial clinical data do not mean that people living with OAO should be ignored; like any patient with established CVD, this population remains at very high risk of future CVD events [49]. Instead, patients living with comorbid OAO-CVD need to be regarded as a distinct clinical phenotype requiring a personalized cardioprotective approach, the benefit of which might not necessarily be reflected in weight loss.

5.2 | Pharmacotherapy for Obesity and CVD

In this regard, there may be some progress in the choice of cardioprotective agent. GLP-1-RAs (e.g., semaglutide and liraglutide) and sodium/glucose cotransporter 2 inhibitors (SGLT-2i; e.g., dapagliflozin and empagliflozin), are glucose-lowering medications that result in weight loss and reduce MACE in patients with type 2 diabetes at high cardiovascular risk (by 11% for SGLT-2i [50] and by 14% for GLP-1RAs [51] in meta-analyses of RCTs). These agents are also showing impressive efficacy for patients with other obesity-related complications (see Table 3). For instance, results from the Semaglutide cardiOvascular oUtcomes triaL (SOUL) trial (mean BMI 31.1 kg/m^2) [53, 58], in which oral semaglutide was compared with placebo as an adjunct to standard of care for the prevention of MACE (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) in patients with type 2 diabetes and established CVD and/or chronic kidney disease (CKD), reported a 14% reduction in risk of major adverse cardiovascular events in adults with type 2 diabetes [53, 59]. In another study of patients with type 2 diabetes and CKD, the FLOW trial reported that semaglutide 1.0 mg once weekly reduced urine albumin-to-creatinine ratio (UACR) by 32% [54].

The critical question, however, is whether pharmacotherapy is also effective in the population of patients with comorbid OAO and CVD but *without* type 2 diabetes. The Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) trial reported that weekly injections of the long-acting GLP-1 analog semaglutide reduced death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke by 20% in patients with preexisting CVD and a BMI > 27 without diabetes compared with placebo (in 6.5% of patients in the semaglutide group and in 8.0% of patients in the placebo group; HR, 0.80; 95% CI, 0.72–0.90; $p < 0.001$) [52]. This was associated with a 9.39% decrease in body weight in the treatment arm and a 0.88% decrease in the placebo arm [52]. Further analysis of SELECT data at 4 years suggests that this magnitude of treatment effect on CVD outcomes was independent of the start weight and the degree of weight loss, consistent with the hypothesis that it is possible to target the biological mechanisms associated with obesity and CVD independently of weight loss [29]. In the case of GLP-1-RAs, animal studies suggest that this might be due to mitigating inflammation, improving endothelial function, stabilizing atherosclerotic plaques, and decreasing platelet aggregation [60].

5.3 | Beyond Atherosclerotic Disease: Other Obesity Phenotypes in Patients With CVD Amenable to Pharmacotherapy

Although by far the largest population of patients living with comorbid OAO and CVD have myocardial infarction, previous stroke, or symptomatic peripheral arterial disease, there are other important cardiovascular phenotypes that might benefit from treatment of obesity, including patients with obesity and heart failure (mainly with preserved ejection fraction [HFpEF] [61], but also heart failure with reduced ejection fraction [HFrEF]) and patients with nonvalvular atrial fibrillation (NVAF). HFpEF accounts for over half of all cases of heart failure, and these patients often have comorbid obesity and worse clinical outcomes in terms of symptoms, functional capacity, and quality of life than counterparts without obesity [61]. Similarly, data from Gulf documentation of ambulatory sick patients with HF (Gulf DYSPNEA) registry (covering Bahrain, Kuwait, Oman, Qatar, and the UAE) show that OAO is extremely common in patients with HFrEF, with 35% of patients with overweight and 28% with obesity ($n = 2808$) [62]. Similarly, obesity is prevalent in patients with NVAF, with analysis of the Gulf Survey of Atrial

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TABLE 3 | Published RCTs examining pharmacotherapies in patients with obesity and CVD phenotypes.

Trial name, year	Drug	Population characteristics	Number of participants	Primary outcome (CVD phenotype)	Follow-up	Outcome and effect size	Adverse events	Reference
SELECT, 2023	Semaglutide, 2.5 mg, once-weekly s.c.	> 45 years, BMI ≥ 27.0, no history of diabetes	17,604: 8803 semaglutide, 8801 placebo	Cardiovascular, MACE	Mean 39.8 ± 9.4 months	6.5% in the semaglutide group and 8.0% in the placebo group (HR, 0.80; 95% CI, 0.72–0.90; $p < 0.001$)	16.6% in the semaglutide group, 8.2% in the placebo group	[52]
SOUL, 2025	Semaglutide, 3 mg escalated to 7 mg and then 14 mg, orally	> 50 years, T2D (HbA1c 6.5%–10%), known atherosclerotic cardiovascular disease, chronic kidney disease, or both	9650: 4825 semaglutide, 4825 placebo	Cardiovascular, MACE	Median 49.5 months	12.0% in the oral semaglutide group and 13.8% in the placebo group (HR, 0.86; 95% CI, 0.77–0.96; $p = 0.006$)	47.9% in the oral semaglutide group and 50.3% in the placebo group	[53]
FLOW, 2024	Semaglutide, 1.0 mg, once-weekly s.c.	≥ 18 years, T2D (HbA1c < 10%), high-risk chronic kidney disease and receiving RAS inhibitors	3533: 1767 semaglutide, 1766 placebo	Renal, MKDE	Median 3.4 years	331 vs. 410 first events; 24% risk reduction (HR, 0.76; 95% CI, 0.66–0.88; $p = 0.0003$)	49.6% in the semaglutide group, 53.8% in the placebo group	[54]
STEP-HFpEF, 2023	Semaglutide, 2.5 mg, once-weekly s.c.	≥ 18 years, HFpEF, BMI ≥ 30.0	529: 263 semaglutide, 266 placebo	Heart failure, change from baseline in the KCCQ-CSS and change in body weight	Limited to 1 year	Mean change in KCCQ-CSS 16.6 with semaglutide and 8.7 points with placebo (estimated difference, 7.8 points; 95% CI, 4.8–10.9; $p < 0.001$); mean percentage change in body weight −13.3% with semaglutide and −2.6% with placebo (estimated difference, −10.7 percentage points; 95% CI, −11.9 to −9.4; $p < 0.001$)	SAEs in 13.3% in the semaglutide group and 26.7% in the placebo group	[55]

(Continues)

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TABLE 3 | (Continued)

Trial name, year	Drug	Population characteristics	Number of participants	Primary outcome (CVD phenotype)	Follow-up	Outcome and effect size	Adverse events	Reference
SUMMIT, 2025	Tirzepatide, 2.5 mg, once-weekly s.c.	≥ 18 years, HFpEF, BMI ≥ 30.0	731: 364 semaglutide, 367 placebo	Heart failure, change from baseline in the KCCQ-CSS and adjudicated death from cardiovascular causes or a worsening heart-failure event	Median 104 weeks	Adjudicated death from cardiovascular causes or a worsening heart-failure event occurred in 9.9% in the tirzepatide group and in 15.3% in the placebo group (HR, 0.62; 95% CI, 0.41–0.95; $p = 0.026$); mean (±SD) change in the KCCQ-CSS was 19.5 ± 1.2 in the tirzepatide group and 12.7 ± 1.3 in the placebo group (between-group difference, 6.9; 95% CI, 3.3–10.6; $p < 0.001$)	6.3% in the tirzepatide group and 1.4% in the placebo group	[56]
SMART, 2024	Semaglutide, 2.5 mg, once-weekly s.c.	≥ 18 years without diabetes, CKD defined as eGFR ≥ 25 mL min^{-1} 1.73 m^{-2} and UACR ≥ 30 mg g^{-1} and ≤ 3500 mg g^{-1} and with a BMI of ≥ 27 kg m^{-2}	101: 51 semaglutide, 50 placebo	Renal: % change from baseline in UACR at week 24	24 weeks	Treatment for 24 weeks with semaglutide compared with placebo reduced UACR by −52.1% (95% CI, −65.5 to −33.4; $p < 0.0001$)	74.5% in the semaglutide group, 64.0% in the placebo group	[57]

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire clinical summary score; MACE, major adverse cardiovascular events (composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke); MKDE, major kidney disease events (composite of the onset of kidney failure (dialysis, transplantation, or an eGFR of < 15 mL per minute per 1.73 m^2), at least a 50% reduction in the eGFR from baseline, or death from kidney-related or cardiovascular causes); RAS, renin-angiotensin system; SAE, serious adverse event; s.c., subcutaneously; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio.

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Fibrillation Events (Gulf SAFE) registry (covering Bahrain, Kuwait, Qatar, Oman, the UAE, and Yemen) [63] showing that 37.0% of patients with NVAF had overweight and 33.1% had obesity ($n = 1721$). Therefore, there exists a population of patients with other, often serious cardiovascular disorders and comorbid obesity who may benefit from weight-reduction strategies.

The benefits of weight reduction in these populations are now supported by very recent high-quality trial evidence (Table 3). Similar to patients with atherosclerotic disease, the STEP-HFpEF trial recently reported that semaglutide resulted in a mean % TBW loss of 13.3% and reduced symptom severity and physical limitations and increased exercise capacity significantly more than placebo in patients with obesity and HFpEF [55]. Furthermore, AF is common in patients with obesity-related HFpEF. A secondary analysis of pooled data from the STEP-HFpEF and STEP-HFrEF DM trials showed that semaglutide significantly improved HF-related symptoms, physical limitations, and exercise function in patients with and without AF and, furthermore, these improvements were more marked in patients with AF at baseline [64]. Further supporting the benefits of GLP-1 RAs for heart failure, a recent prespecified analysis of the SELECT trial reported that weekly semaglutide improved MACE, composite heart failure, cardiovascular deaths, and all-cause deaths in patients with atherosclerotic CVD and OAO and heart failure (and no diabetes), regardless of the type of heart failure (HFpEF or HFrEF) [65]. This effect seems to persist in individuals with type 2 diabetes mellitus, overweight/obesity, and HFpEF already taking SGLT2i therapy, who experienced a lower risk of heart failure exacerbations, all-cause emergency department visits/hospitalizations, new-onset atrial arrhythmias, new-onset acute kidney injury, and pulmonary hypertension when also administered a GLP-1 RA in a real-world study [66]. This latter finding that the addition of GLP-1 RAs to SGLT2is further improves outcomes now needs further prospective validation.

Further supporting a direct effect of weight loss pharmacotherapy on obesity-related outcomes independent of diabetes, results from the SeMaglutide and Albuminuria Reduction Trial (SMART), in which adults with CKD (estimated glomerular filtration rate [eGFR] $\geq 25\,mL\,min^{-1}\,1.73\,m^{-2}$ and urine albumin-to-creatinine ratio [UACR] ≥ 30 and $< 3500\,mg\,g^{-1}$, and body mass index $\geq 27\,kg\,m^{-2}$) without diabetes were randomized to semaglutide 2.4 mg per week or placebo [57]. Semaglutide resulted in a clinically meaningful reduction in albuminuria (UACR reduction of 52.1%; 95% CI, 33.4–65.6; $p < 0.0001$) in patients with OAO and nondiabetic CKD. Interestingly, while the reduction in body weight positively correlated with the reduction in UACR and urinary albumin concentration, the effect of semaglutide on UACR seemed to occur prior to the maximal effect on body weight, suggesting at least some of the observed benefit may be due to direct structural effects of semaglutide on kidney tissues [57].

Finally, with respect to treatment of other important obesity-related complications, early results from the first part of the Effect of Semaglutide in Subjects with Non-cirrhotic Non-alcoholic Steatohepatitis (ESSENCE) trial (mean BMI 34.6 kg/m^2) [67] showed that once-weekly semaglutide 2.4 mg resulted in a significant improvement in liver fibrosis with no worsening of steatohepatitis and resolution of steatohepatitis with no worsening of liver fibrosis in patients with metabolic dysfunction-associated steatohepatitis (MASH) [68].

6 | Implications for Management and Standard-of-Care of Patients Living With OAO and CVD

There are therefore distinct populations of patients living with comorbid OAO, CVD, and other obesity-related complications who might benefit from personalized secondary preventative management. There are several international and national guidelines on the medical management of obesity [69–72], including from the UAE [73]. Interestingly, even as far back as 2018, UAE clinical practice recommendations for the management of OAO recommended, as part of multidisciplinary team management and after a comprehensive lifestyle modification, modification of the standard obesity management plan (consideration of orlistat or liraglutide pharmacotherapy in patients with a BMI $> 30\,kg/m^2$ with no comorbidities or BMI $\geq 27\,kg/m^2$ with comorbidities in addition to lifestyle intervention) to consideration of liraglutide as first-line treatment in patients with CVD based on the positive CVD outcomes in patients with type 2 diabetes [73]. While more recent 2022 American Gastroenterological Association guidelines on pharmacological interventions for adults with obesity do not specifically consider patients with CVD separately, they recommend pharmacotherapy with semaglutide 2.4 mg, liraglutide 3.0 mg, phentermine–topiramate ER, and naltrexone–bupropion ER (based on moderate certainty evidence), and phentermine and diethylpropion (based on low certainty evidence) in addition to a lifestyle intervention in adults with a BMI $\geq 27\,kg/m^2$ with weight-related complications who have had an inadequate response to lifestyle intervention [71]; note, however, that phentermine is sympathomimetic and bupropion increases blood pressure and should not be used in people with CVD, supporting a need for specific guidance for the population of patients with comorbid CVD. Another 2022 clinical practice guideline for adults with obesity from Ireland makes a similar recommendation for pharmacotherapy in adults with a BMI $\geq 27\,kg/m^2$ with weight-related complications, again in conjunction with medical nutrition therapy, physical activity, and/or psychological interventions [69]. Therefore, while current guidance on OAO management recommends pharmacotherapy, usually with GLP-1-RAs as first-line therapy, that would capture the at-risk CVD population, this is in the context of comprehensive lifestyle interventions rather than as pharmacotherapy alone. Similar to how SGLT-2is and GLP-1 RAs have become standard secondary prevention for patients with pre-existing CVD and type 2 diabetes [74], there is now a need to revisit recommendations on secondary prevention of CVD in patients with comorbid OAO and CVD, including in special subgroups such as patients with heart failure, AF, or MASH. Doing so requires recognition from policymakers, payers, and medics that comorbid OAO-CVD is a phenotype as distinct as OAO-diabetes. One logical point of intervention would be to integrate pharmacotherapy into cardiac rehabilitation programs, that is, that population at known high baseline risk associated with adverse outcomes. In this setting, intentional weight loss has already been shown to be associated with

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reduced all-cause mortality, cardiovascular mortality, and MACE [75]. Cardiac rehabilitation has already evolved from an exercise-only intervention to improve cardiorespiratory fitness to an individualized multirisk intervention to modify coronary risk factors [76], so, given the burden of evidence of benefit of SGLT-2is and GLP-1 RAs in CVD risk reduction, it seems an opportune time to integrate pharmacotherapy into these programs to further optimize their management.

7 | Barriers to Targeting OAO for Secondary Prevention

There is therefore growing evidence that OAO should be considered a therapeutic target for secondary prevention in the population with CVD, and there are now therapies that have been shown to be effective in this specific subgroup. The administration of any medication or intervention must be based not only on knowledge and adherence to best practice but also willingness to prescribe (i.e., physician-based barriers) and the needs of the patient, including, their preferences, costs, and access to the therapy (i.e., patient-based barriers). Even for basic, inexpensive, and effective cardioprotective secondary prevention drugs such as antiplatelets or β-blockers, use in the target population is low: only 62.0% for antiplatelet drugs, 40.0% for β-blockers, 49.8% for ACE inhibitors, and 66.5% for statins in high-income countries, including the UAE [77]. Administering a new cardioprotective drug in the OAO population also has specific challenges and barriers.

7.1 | Addressing Weight Bias and Recognizing OAO as a Chronic Disease

Although obesity has appeared in the International Classification of Diseases since 1949, the European Commission only classified obesity as a chronic disease in 2021 [78]. This challenge of treating OAO is often perceived as so great that many clinicians simply "give up" on OAO, choosing instead to focus on immediate medical issues or those problems that can be remedied through simple pharmacological interventions. Weight bias—negative attitudes, beliefs, judgments, stereotypes, and discriminatory acts aimed at individuals simply because of their weight—is also a serious problem in healthcare settings that reduces the quality of care delivery [79]. To address this, weight bias interventions can have a positive effect on attitudes and beliefs [80], and addressing weight bias might mean introducing training on weight bias, stigma, and discrimination.

There is also the widespread and deeply rooted misconception—including in healthcare professionals (HCPs)—that obesity is not a disease at all, rather a lifestyle choice, failure of willpower or lack of will, or act of laziness. Consistent with this, HCPs ($n = 200$, 69% obesity specialists) from the UAE participating in the ACTION-IO study, a cross-sectional study of the perceptions, attitudes, and behaviors of people with OAO and HCPs, reported that they did not discuss weight loss with their patients with OAO due to a perception that their patients were not interested in losing weight (69%) or were not motivated to lose weight (66%), despite only 10% and 30% of people with OAO citing a lack of interest or motivation as reasons for not discussing weight with their HCP, respectively [81]. In the same study [81], over one-fourth of HCP respondents still failed to recognize obesity as a chronic disease and the same number did not agree that obesity had a large impact on health, compared with only 9% regarding stroke as having little or no impact on health, despite it often being comorbid with OAO. This latter finding underscores the misconception by some health professionals noted above that OAO and CVD are not causally related [10].

In January 2025, the Lancet Diabetes & Endocrinology Commission published a new definition and diagnostic criteria of clinical obesity [82], defining clinical obesity as "a chronic, systemic illness characterized by alterations in the function of tissues, organs, the entire individual, or a combination thereof, due to excess adiposity." To meet diagnostic criteria for clinical obesity, individuals must: (i) have excess body fat as confirmed by at least one other anthropometric criterion to BMI such as waist circumference or a direct fat measurement; and (ii) have signs or symptoms of ongoing dysfunction of 17 organ systems and/or age-adjusted limitations of mobility or other basic activities of daily living. In operationalizing the diagnosis of clinical obesity in this way, the Commission's approach explicitly relates obesity to CVD, as hypertension, DVT/PE, AF, and HFrEF/HFpEF are all regarded as diagnostic criteria for clinical obesity. However, of concern, these 18 diagnostic criteria do not include atherosclerotic disease or stroke, raising concern that applying such criteria could potentially exclude a large proportion of individuals with an OAO-CVD phenotype who might benefit from secondary prevention. Indeed, a recent study applying the Lancet criteria to a large population of adults from the UAE found that only a third of individuals with class III obesity also had diagnostic criteria of clinical obesity, in effect downgrading the obesity epidemic [83]. Therefore, the adoption of new definitions or criteria for OAO must consider the potential wider impact on how this might affect eligibility for preventative therapy and future disease risk.

Clearly, there is some need to increase awareness of the cause–effect relationship between obesity and CVD to support clinical decision-making. As noted above, HCPs need to regard OAO as a distinct, chronic disease characterized by dysfunctional adipose tissue and adipokine secretion, just as diabetes is a disease characterized by dysfunctional insulin secretion or resistance and glucose abnormalities. In that regard, the World Obesity Federation's Strategic Centre for Obesity Professional Education (SCOPE) provides internationally recognized online and in-person training for healthcare professionals to equip them with the knowledge and skills to support people living with obesity. Completing SCOPE certification could form part of mandatory training for HCPs and be a requirement for successful annual appraisals and medical revalidation to help tackle this awareness gap and improve standards.

7.2 | Access to Services and a Lack of Adherence to Guidelines

Despite the extremely high prevalence of OAO, and clear clinical guidelines on its management, only a fraction of individuals with OAO receive the necessary assistance and treatment. In a nationally representative cross-sectional survey in the United

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Kingdom, less than half of individuals with OAO had received advice about their weight, despite having seen an HCP in the preceding year [84]. In another analysis of a large primary care database in the UK ($n = 91{,}413$ patients with OAO), 90% of patients with OAO had no documented record of a weight management intervention [85]. Even when patients do access specialist weight management services, only a third attend [86] and anywhere between 10% and 80% fail to complete treatment [87]. Although primary data on barriers to access in the UAE are lacking, health insurance does not cover GLP-1 RAs or a risk-centered approach to obesity, and access depends on reimbursement in insurance-based systems. Given the burden of the disease in the country and region, this is an issue that needs addressing urgently.

Although there are little direct data from cardiology practice, it is likely that cardiologists, who are usually responsible for secondary prevention, similarly do not "do enough" to treat obesity in their practice. Supporting this, in one analysis of 10,507 CHD patients participating in the EUROASPIRE IV and V trials, a substantial proportion had not been informed by their HCP that they were OAO, and a third of patients with obesity reported not having received dietary advice or recommendations to participate in regular physical activity after discharge [88]. By definition, a failure to address OAO in the CVD population reflects a deviation from best practice and guidelines. In addition to weight bias, clinicians also report that a lack of time and confidence in their obesity management skills are barriers to discussing weight [68]. Clearly, any expansion of secondary prevention measures must include specific measures to address barriers to specific conversations about OAO, which might include physician education to improve adherence to guidelines [89] and inclusion of a weight loss component in cardiovascular prevention and rehabilitation programs. Given that GLP-1 RAs like semaglutide have special demands including frequent dose titration and a need for patient education for subcutaneous administration, other opportunities for enhancing quality of care and reducing demands on physicians might include embedding pharmacist-led weight management into cardiology clinics [90].

7.3 | Push-Back Against GLP-1 Agonists

It is well recognized that the translation of high-quality trial data and clinical guidelines into mainstream practice is slow for any intervention. Despite growing high-quality evidence of cardiovascular benefit of SGLT-2is and GLP-1 RAs, overall usage remains low, with only 1 in 20 eligible patients receiving SGLT-2is and GLP-1 RAs in one large US outpatient registry [91]. This lag between establishing efficacy and safety and real-world clinical implementation occurs due to a variety of physician, patient, system, and economic/policy factors, all of which have been evidenced for SGLT-2is and GLP-1 RAs.

Therapeutic inertia—a failure to initiate or increase therapy when treatment goals are unmet—is a well-recognized barrier to improving patient care that is exacerbated by poor guideline implementation and slow integration into clinical practice (knowledge diffusion delay), made even worse by resistance to changing established habits [92]. Barriers reported by cardiologists to prescribing SGLT-2is and GLP-1 RAs include a lack of knowledge and concerns about prescribing medications out with their main field of expertise (i.e., to patients with diabetes), especially given the novelty of their approval and need to manage side-effects appropriately [93]. Although secondary prevention of CVD with GLP-1 RAs as cardioprotective agents should fall within a cardiologist's expertise, they may still feel that this falls under the auspices of endocrinology or primary care and so fail to prescribe to their patients [93]. Furthermore, the need to initiate and up-titrate other recommended agents, such as β-blockers and renin–angiotensin–aldosterone system (RAAS) inhibitors in patients with heart failure, could outcompete prescription of other, newer agents [94].

Strategies to address therapeutic inertia could include educating physicians about clinical practice guideline changes (such as easy-to-read, modular delivery), improving guideline dissemination, team-based care, and continuing quality improvement initiatives [92].

From the patient perspective, uptake mandates that patients consistently prioritize the desired outcomes over the potential adverse effects (commonly gastrointestinal side effects such as nausea, vomiting, anorexia, diarrhea, dyspepsia, and constipation for GLP-1 RAs), reluctance to subcutaneous administration, polypharmacy [95], potentially high cost, and the burden of monitoring and dose titration. Again, strategies to mitigate these challenges include education and placing the patient at the center of care. Within the context of the UAE and Middle East, multidisciplinary programs must be culturally acceptable and might benefit from peer support, as these factors might positively influence weight management strategies [96] and cultural behaviors, such as timing of medication alterations during Ramadan, might impact adherence [97]. With respect to this latter issue, it is reassuring to note that recent meta-analyses suggest that use of DPP-4 inhibitors, GLP-1 agonists, and SGLT-2 inhibitors reduce HbA1c, weight, and blood pressure in patients with T2DM [98, 99], but further studies are needed to establish safety with respect to the critical endpoint of hypoglycemia and in our population of interest, that is, individuals with OAO and CVD.

7.4 | Regulatory, Policy, and Reimbursement Issues

Accessibility of pharmacotherapies remains a problem in many jurisdictions, including the UAE. Most anti-obesity medications, including liraglutide and semaglutide, are approved for use in patients with BMI $\geq 30\,kg/m^2$ or $\geq 27\,kg/m^2$ in the presence of obesity-related complications in many MENA countries and the Asia-Pacific region [100]. In the most recent (February 2025) UAE standards for the nonsurgical management of obesity [101], these criteria are even more stringent, with starting criteria for GLP-1 receptor agonists of a BMI of at least $30.0\,kg/m^2$ *and* one or more weight-related comorbidities (or BMI $> 40\,kg/m^2$), and there is no mention of CVD. Furthermore, these drugs are only reimbursed for the treatment of patients with OAO and diabetes and not obesity. This is despite payers reimbursing for MBS. There appears to be resistance to recognizing the cardiovascular phenotype

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as equivalent to diabetes, and, given the recent data from SELECT and STEP-HFpEF, a policy change in this regard seems timely.

Nevertheless, the Department of Health (DoH) in Abu Dhabi has taken the lead in developing official guidelines for nonsurgical obesity management, which notably include reimbursement for pharmacological therapies in cardiovascular patients with a BMI starting at 30. This marks a significant advancement in access to cardiovascular care in the UAE and represents a very innovative approach to addressing obesity as a CV/metabolic disease among high-risk patients in the region. As far as the authors are aware, this is the first regulatory and funding guidance linking risk, prevention, and management of evidence-based OAO and greatly expands access appropriately to specific high-risk individuals with obesity.

8 | Future Directions and Unmet Needs

There are decades of epidemiological evidence that obesity is a risk factor not only for ACS and stroke but also for HF, metabolic, renal, and hepatic complications and their end-organ morbidities. However, direct evidence for this association has hitherto been lacking. The preceding discussion highlights that we now have primary, experimental, interventional evidence—driven and supported by recent high-quality trials like STEP-HFpEF [55], SELECT [65], SMART [57], and ESSENCE [67] - that obesity is pathogenic for HF, CKD, and MASH and can be reversed. Furthermore, these trials are providing new insights into the underlying pathobiology of the diseases, with the exact contributions of obesity and the cellular effects of the specific agents still to be determined.

This evidence and understanding have become especially important as there is a massive and growing burden of obesity in the child and adolescent population. Like in other countries, OAO is a major public health concern in the United Arab Emirates (UAE) [102], and approximately one-third of children and adolescents in the UAE have OAO [103]. These children are therefore exposed to the cumulative cardiovascular risks of obesity, and it is well established that childhood obesity is a risk factor for future metabolic disorders, cardiovascular disease, cancer, and, ultimately, premature death [104, 105]. There is now evidence that these specific cardiovascular risks accumulate from a very early age. When considered according to the atherogenic index of plasma (AIP), a relatively novel index calculated using triglyceride levels and high-density lipoprotein cholesterol constructed as a biomarker of plasma atherosclerosis [106], Ali et al. found that 14% and 6% of children and adolescents with OAO were at intermediate and high risk of cardiovascular disease compared with only 4.7% and 1.2% in the normal weight group ($n = 10,241$ participants with complete lipid profiles) [107]. Children and adolescents with OAO have a high prevalence of dyslipidemia and prediabetes (24%) and the potential for detrimental cumulative metabolic and cardiovascular disease risk [108]. Given the data in adults that weight loss pharmacotherapy is cardioprotective, the question now arises which children might most benefit from these agents to prevent long-term harmful sequelae. Doing so will require careful weighing of the risks and benefits of all of these agents (semaglutide is the only one currently approved for use in children) on developing bodies and the implications of potentially lifelong therapy in a large proportion of the population.

9 | Conclusions

About half a million patients with comorbid CVD and OAO in the UAE and over 34 million across the Middle East could benefit from secondary prevention of CVD with therapies that result in weight loss. Conflicting clinical data and negative attitudes toward OAO have reduced enthusiasm for actively treating OAO to reduce the burden of associated CVD. However, new clinical evidence that semaglutide reduces death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke in individuals with OAO and pre-existing CVD paves the way for the pharmacological secondary prevention of cardiovascular disease. Furthermore, there is growing direct evidence from interventional studies that obesity is pathogenic for other complications of obesity including HF, CKD, and MASH and can be reversed with pharmacotherapy. Achieving change in practice will require further clinical studies and longer term follow-up to embed high-quality evidence into clinical practice guidelines on both obesity management and secondary prevention of CVD. Crucially, it will also require a change in mindset in clinicians and patients that OAO represents a distinct and targetable clinical phenotype in CVD, heart failure, and other special subgroups of patients that can be managed chronically like diabetes or cancer. Any change in defining obesity, such as that proposed by the Lancet Commission, must be implemented with a complete understanding of how this might affect eligibility for therapy. Furthermore, treatment "success" cannot be solely measured by the outcome of weight loss but rather a reduction in associated morbidity. In that regard, future studies need to explore biomarkers of adipose dysfunction to develop accurate quantitative measures of cardioprotective efficacy that do not rely on weight measures alone. Other challenges to introducing new secondary prevention measures in the OAO population include overcoming therapeutic inertia and counteracting weight bias, most likely through the promotion of existing health initiatives like SCOPE or new, focused programs. Given the worrisome rise in children and adolescents with OAO, the cumulative burden of future cardiovascular risk is set to increase, mandating comprehensive strategies to implement secondary prevention in this at-risk group while maintaining health equity.

Acknowledgments

The authors would like to thank Novo Nordisk Pharma Gulf FZE-UAE for their educational grant to support this work and to Dr. Omniyat Al Hajeri for her leadership in the field of cardiometabolic prevention in the region as well as her recommendations in the design and content of this paper, specifically to the UAE.

Funding

Novo Nordisk Pharma Gulf FZE-UAE, who provided an unrestricted educational grant to support this work, had no role in the study design,

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data collection, data analysis, data interpretation, or writing of the report. All authors had final responsibility for the decision to submit for publication.

Conflicts of Interest

Dr. Al Ozairi has an unpaid leadership role at the World Obesity Federation. The other authors have no conflicts of interest to declare.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Grouped BMI values in CVD registries from the Middle East, including the UAE. **Table S2:** The seven registries used to derive BMI prevalence data. **Table S3:** Baseline characteristics of patients with available versus missing BMI in the pooled analysis of seven Arabian Gulf acute coronary syndrome registries ($n = 31{,}510$).

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