MEDBULLETIN
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HARLEY STREET
HEART & VASCULAR CENTRE
A MEMBER OF HMI MEDICAL

INTRODUCTION

Greetings from the Harley Street Heart and Vascular Centre!

To keep our primary care colleagues up to date with the latest advances in the management of patients with cardiovascular diseases, we have prepared three interesting articles written by our Harley Street Specialists. The theme of the current newsletter is on metabolic diseases and obesity.

Dr. Rohit Khurana has prepared a succinct summary of the cardiovascular benefits of GLP-1 agonists, including their benefits in treating obesity, and how we can best select which patients are likely to benefit from this newer class of medication. Dr Michael MacDonald elaborates further in his article on the different types of GLP-1 agonists and compares their relative effectiveness in reducing the HbA1c and weight. His article also introduces some of the novel GLP-1 agonists that are still being studied in clinical trials which may have potential clinical use in the future. Dr. Peter Ting's article on how stress and sleep have an impact obesity, highlights the important link between these conditions.

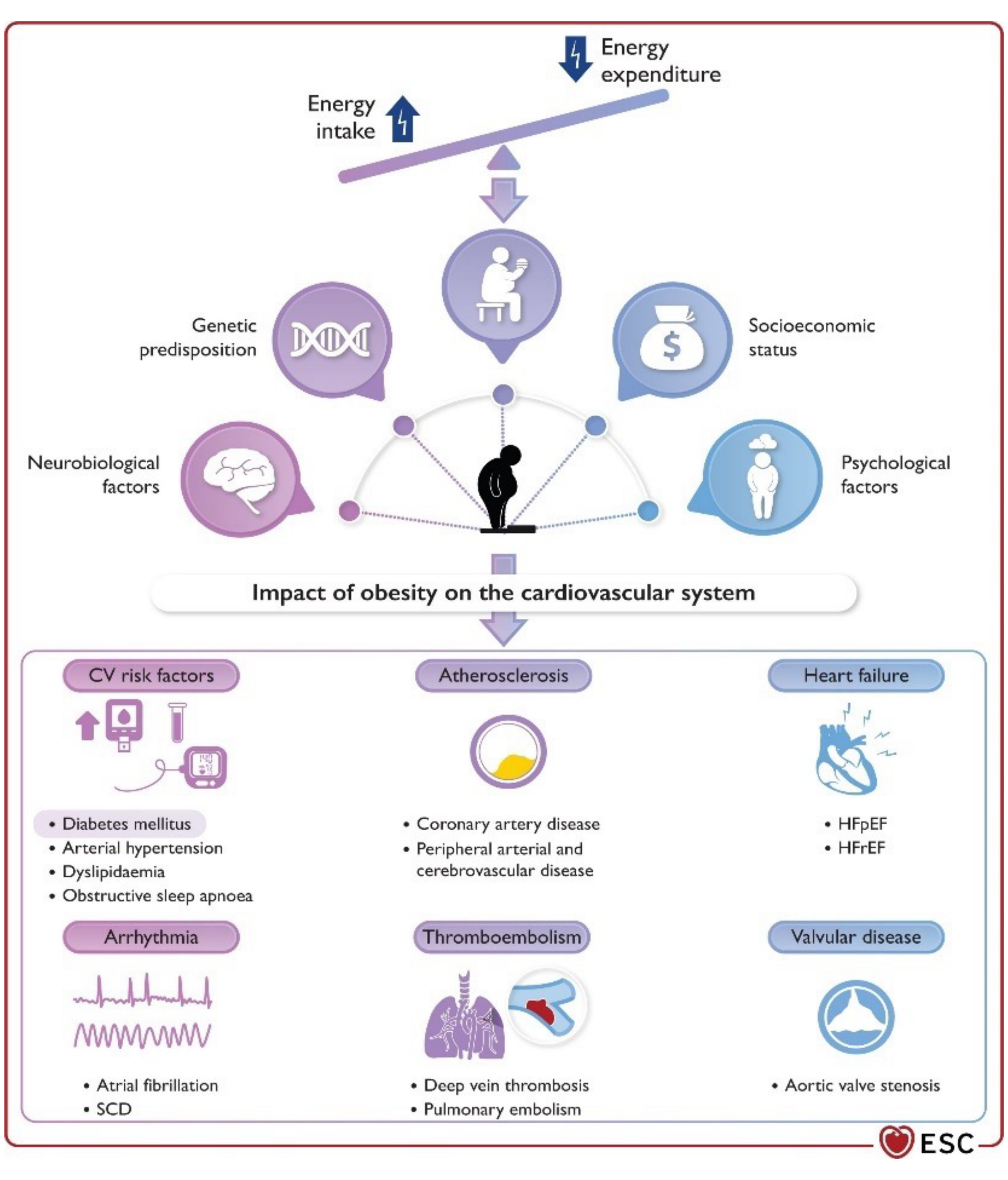
The newsletter ends with an interesting case vignette prepared by Dr. Reginald Liew aimed to test your clinical skills. The answer to the quiz will be posted on our website. (https://www.harleystreet.sg/medbulletin/).

We hope these articles will be useful to your daily practice and help challenge and improve your management of patients with cardiovascular disease. Please feel free to contact us (at enquiries@harleystreet.sg) if you would like to provide any feedback or request a specific topic in future editions.

From The Harley Street Heart and Vascular Centre

OBESITY, CARDIOVASCULAR RISK AND SELECTING THE APPROPRIATE PATIENT FOR GLP1 AGONIST TREATMENT

Obesity in Singapore is a serious and escalating problem, mirroring global trends driven by changes in lifestyle, diet, and urbanization with broad implications for individual health, healthcare systems, and the economy. The National Population Health Survey (NPHS) 2022 showed that **11.6% of adults aged 18 to 74 years were obese in 2022**, an increase from 10.5% in 2019/2020. Obesity significantly increases the risk of chronic diseases including type 2 diabetes, cardiovascular disease (CVD), stroke, certain cancers, and musculoskeletal disorders. Notably, 2/3 of obesity-related excess mortality is attributable to CVDd. The cardiovascular consequences of obesity are summarized (Reference 1):



Historically, there has been a reluctance around using pharmacotherapy for the management of obesity, at least by cardiologists, compared to other modifiable risk factors for CVD. There are currently six drugs approved both by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) for long-term weight management in patients with obesity: orlistat, naltrexone extended release (ER)/bupropion (ER), liraglutide, semaglutide, tirzepatide, and setmelanotide for treatment of rare obesity-related monogenetic deficiencies. They predominantly decrease energy intake by means of reducing appetite, increasing satiety, and slowing gastric emptying.

The SELECT (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity) trial was a randomized, double-blind, placebo-controlled study involving 17,604 adults aged ≥45 years with a body mass index (BMI) ≥27 kg/m^2 and established cardiovascular disease, but no history of diabetes. Of the enrolled patients, 82.1% had known coronary disease at baseline (prior myocardial infarction in 76.3%), and 24.3% had chronic heart failure [HF with preserved ejection fraction (HFpEF) in 12.9%]. Participants were randomized to receive either weekly **subcutaneous injections of semaglutide 2.4 mg (GLP1 receptor agonist, GLP1Ra)** or placebo. The median follow-up period was approximately 39.8 months. The trial's primary endpoint was the occurrence of major adverse cardiovascular events (MACE), a composite of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke.

Key Findings

1.Significant Reduction in Cardiovascular Events
Semaglutide reduced the risk of MACE by 20% compared to placebo (HR: 0.80; 95% CI: 0.72–0.90; p<0.001). This was the first time a weight loss drug showed a statistically significant and clinically meaningful cardiovascular benefit in a population without diabetes.

2. Weight Loss Achieved and Sustained
Participants on Semaglutide lost an average of 9.4% of body weight compared to 0.9% in the placebo group. Weight loss was sustained throughout the trial, reinforcing the drug's long-term efficacy in managing obesity.

3. **Improved Risk Factor Profiles**
Beyond weight loss, Semaglutide recipients also experienced improvements in cardiovascular risk factors, including reductions in blood pressure, waist circumference, and inflammatory markers such as CRP. This supports a broader therapeutic role for GLP-1 receptor agonists in cardiometabolic disease prevention.

4. Safety Profile
Gastrointestinal side effects (nausea, vomiting, diarrhea) were more common in the treatment group but generally mild to moderate and transient. Importantly, there was no increase in serious adverse events or new safety signals.

The trial's results are reflected in the European Society of Cardiology (ESC) clinical guidelines to include GLP-1 receptor agonists like semaglutide in the management of overweight or obese individuals with cardiovascular disease, regardless of diabetic status (Class IIa, Level of Evidence B). This has wide-reaching implications for public health strategies and healthcare resource allocation.

This is an exciting landscape for obesity and CVD risk reduction. SELECT marks a turning point, offering compelling evidence that obesity medications can deliver more than aesthetic or metabolic benefits—they can reduce morbidity and mortality. This challenges traditional reluctance around long-term pharmacotherapy for obesity. Another promising drug is Tirzepatide, which has a dual mode of action based on the stimulation of the endogenous glucose-dependent insulinotropic polypeptide (GIP) and GLP1Ra. The SURMOUNT-MMO trial is currently underway evaluating the effect of tirzepatide on CV outcomes in adults with obesity without T2 diabetes. Several dual or triple agonist combinations, mostly based on the GLP-1RA mode of action, are currently in development.

Reference
Obesity and cardiovascular disease: an ESC clinical consensus statement
European Heart Journal, Volume 45, Issue 38, 7 October 2024, Pages 4063–4098

By **Dr Rohit Khurana**
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GLP-1 AGONISTS: KEY DIFFERENCES AND WHAT'S ON THE HORIZON

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have revolutionized the management of type 2 diabetes mellitus (T2DM) and obesity. Beyond glycaemic control, these agents offer benefits in weight reduction and cardiovascular outcomes, making them increasingly relevant in primary care. This article compares four widely used GLP-1 RAs—semaglutide, liraglutide, tirzepatide, and dulaglutide—and highlights emerging therapies that may soon expand our therapeutic arsenal.

At the moment Semaglutide is the only GLP-1 to have CV outcome benefits in a non-diabetic population with obesity.

Agent	Brand Name	Dosing	Mechanism	HbA1c Reduction	Weight Loss	Key Considerations
Semaglutide	zempic/ Wegovy/Rybelsus	Weekly injection/ daily tablet	GLP-1 RA	~1.5–1.8%	10–15%	Also available orally (Rybelsus); high efficacy; GI side effects common
Liraglutide	Victoza / Saxenda	Daily injection	GLP-1 RA	~1.0–1.5%	5–8%	First with CV benefit; higher GI side effects ; daily dosing may affect adherence
Tirzepatide	Mounjaro	Weekly injection	Dual GLP-1/ GIP RA	~2.0%	15–22%	Superior glycaemic and weight outcomes; pending CV data; GI side effects common
Dulaglutide	Trulicity	Weekly injection	GLP-1 RA	~1.0–1.5%	3–5%	Once-weekly dosing; lower GI side effects; moderate efficacy

Emerging GLP-1 Therapies on the Horizon
Several novel agents are in advanced clinical trials:

- **Orforglipron:** An oral, non-peptide GLP-1 RA that unlike Rybelsus (oral semaglutide) does not have restrictions on how it is to be taken. Results of its Phase 3 trial in type 2 diabetes have just been announced (April 2025) – ACHIEVE-1. It demonstrated a mean weight loss of 7.9% over 40 weeks and HbA1c reductions of 1.3–1.6%.
- **CagriSema:** A combination of semaglutide and cagrilintide (an amylin analogue). Recent data in obese type 2 diabetics showed a weight loss of 15.7% over 68 weeks.
- **Retatrutide:** A triple agonist targeting GLP-1, GIP, and glucagon receptors. Phase 2 data in obese patients revealed up to 24% weight loss, suggesting potential as a highly effective obesity treatment.

Implications for General Practice
As GLP-1 therapies evolve, GPs play a crucial role in patient selection, initiation, and monitoring:

- **Patient Selection:** Consider GLP-1 RAs for patients with T2DM who have obesity, established cardiovascular disease, or require weight management.
- **Monitoring:** Regularly assess glycaemic control, weight, gastrointestinal tolerance, and adherence. Monitor for potential side effects, including nausea and vomiting.

Conclusion
GLP-1 receptor agonists have significantly advanced the management of T2DM and obesity. Understanding the nuances among current agents and staying abreast of emerging therapies will enable GPs to optimize treatment strategies, tailoring interventions to individual patient needs and improving long-term health outcomes.

By **Dr Michael MacDonald**
Senior Consultant Cardiologist
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SLEEP AND ITS IMPACT ON OBESITY AND HEALTH

Why is sleep important?
Sleep is an underrated activity that is crucial for our good mental and physical health. During sleep the body repairs and rejuvenates itself. Consequently, the lack of sleep or sleep deprivation is associated with many health problems, including higher risk of hypertension, diabetes, heart disease and stroke. Research has shown that getting less than 7 hours of sleep a night is linked to weight gain and obesity [1]. Despite all this, Singaporeans are not getting enough sleep. In a survey of 43 cities, Singapore was ranked the third most sleep-deprived city. Only 25% of adults get the recommended 7-9 hours of sleep a night [2]. Correlating with this lack of sleep, Singapore's obesity rate is rising. Approximately 30% of Singaporeans are overweight and 11% are obese [3].

Obesity itself can also lead to sleep issues such as Obstructive sleep apnoea
While lack of sleep leads to weight gain and obesity, this often becomes a vicious cycle as being overweight can also lead to worsening sleep problems, leading to more weight gain. Research suggests that obesity may change metabolism and/or sleep-wake cycles in such a way that causes sleep quality to deteriorate. Overweight patients are more likely to have disorders such as obstructive sleep apnoea, gastroesophageal reflux disease, depression, anxiety, insomnia, asthma which themselves may affect the quality of sleep. One example is obstructive sleep apnoea (OSA) which is more common than we think. A local study showed that almost 1 in 3 individuals may have OSA, and 1 in 10 may be severe [4]. Who then should we screen for sleep issues or OSA? It is recommended we screen patients who are overweight or obese, snore and/or experience daytime sleepiness, have chronic conditions like hypertension, coronary disease, heart failure, strokes, and cardiac arrhythmias such as atrial fibrillation [5].

Screening for Obstructive sleep apnoea
A quick easy way in clinic to assess for OSA is using a STOPBANG questionnaire.

STOP	BANG
Snore loudly during sleep +1 **T**ired often, fatigued or sleepy during the day +1 **O**bserved to stop breathing during sleep by others +1 **P**ressure, high blood pressure with or without treatment +1	**B**MI over 35kg/m2 +1 **A**ge over 50 years old +1 **N**eck circumference > 40cm (16 inches) +1 **G**ender Male +1

Score 5-8 = High risk of OSA
Score 3-4 = Intermediate risk of OSA
Score 0-2 = Low risk of OSA

Diagnosing Obstructive Sleep Apnoea or other sleep disorders
If OSA or other sleep disorders are suspected, they may be diagnosed with a sleep study. There are different sleep studies to choose from - Polysomnography (PSG) is a comprehensive overnight sleep study conducted in a sleep lab/hospital, monitoring various aspects of sleep. This can diagnose OSA, narcolepsy, insomnia, restless leg syndrome and other sleep disorders. Home sleep studies are simplified studies conducted at home, often focusing on specific parameters like breathing and oxygen levels. These primarily diagnose OSA and other related breathing disorders.
Managing sleep problems and OSA
So how do we address sleep issues in our patients? Advising proper sleep hygiene is first line, to improve sleep duration and quality. These include:

- A regular sleep schedule.
- Avoiding heavy eating, nicotine, caffeine, and alcohol before bed.
- Ensuring a conducive sleep environment.
- Limiting daytime naps to <30min.
- Regular physical activity in one's daily routine.
- Stress relieving techniques such as deep breathing, mediation, hobbies and socialising.
- Avoid excessive stimulation by mobile phones, TV, tablets and computer screens for at least 30 min before bed.

If OSA is diagnosed, treatments aim to keep the airway open during sleep, reducing or eliminating breathing pauses. Common treatments include are:

- Continuous Positive Airway Pressure (CPAP) machines deliver a constant stream of pressurized air through a mask worn over the nose or mouth, keeping the airway open. This is considered the gold standard for OSA treatment.
- Lifestyle Modifications: Weight loss, positional therapy (i.e. sleeping on the side), avoiding alcohol and sedatives which may relax the throat and worse OSA. Regular exercise, healthy diet and smoking cessation may also benefit.
- Oral Appliances: These custom-made mouthpieces, designed and fitted by a dentist or orthodontist, help to move the lower jar forward to keep the airway open.
- Surgery: Tonsillectomy and adenoidectomy (removal of enlarged tonsils and adenoids), radiofrequency ablation of the soft palate, and uvulopalatopharyngoplasty (UPPP) can be considered. Success rate is variable and OSA may recur after surgery.
- Other Treatment Options: Hypoglossal nerve stimulation (HNS) where a device is implanted to stimulate the hypoglossal nerve, which controls the tongue muscles, helping to keep the airway open. Upper airway stimulation (UAS): Like HNS but uses a different device to stimulate the muscles in the upper airway.

If you think just because patients are eating right and exercising regularly, they will have a healthy body and healthy weight, think again. Adequate and good quality sleep is just as important for weight maintenance and overall health. Always include sleep assessment as part of your evaluation of patients who are overweight or obese or suffer from chronic diseases or metabolic disturbances. Remember to ask about sleep, advise good sleep hygiene and screen for obstructive sleep apnoea or other sleep disorders when suspected.

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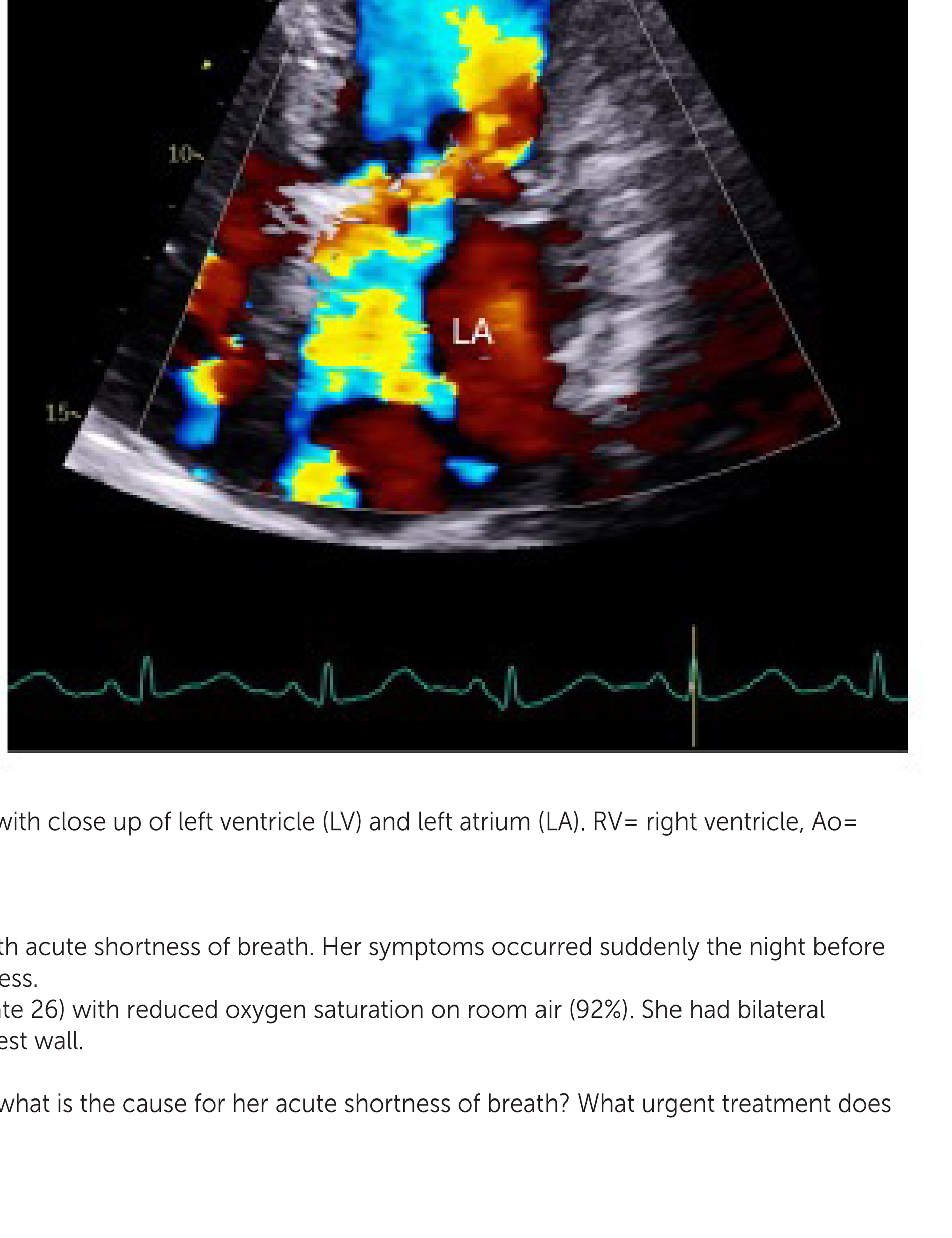
QUIZ



Echocardiogram- parasternal long axis view (left image); four chamber view (right image) with close up of left ventricle (LV) and left atrium (LA). RV= right ventricle, Ao= aorta.

Case Vignette:
A 56-year-old woman with no cardiac history presented to the emergency department with acute shortness of breath. Her symptoms occurred suddenly the night before her presentation and gradually worsened. She was unable to lie flat due to her breathlessness.
On examination, she was tachycardic (heart rate 100 regular) and dyspnoeic (respiratory rate 26) with reduced oxygen saturation on room air (92%). She had bilateral crepitations in her lung fields and a loud pan systolic murmur was heard in her anterior chest wall.

The above are bedside echo images taken at presentation. What do the images show and what is the cause for her acute shortness of breath? What urgent treatment does she need?

Answer is available here: