European Heart Journal (2024) **00**, 1–3
https://doi.org/10.1093/eurheartj/ehae091

EDITORIAL
Epidemiology, prevention, and health care policies

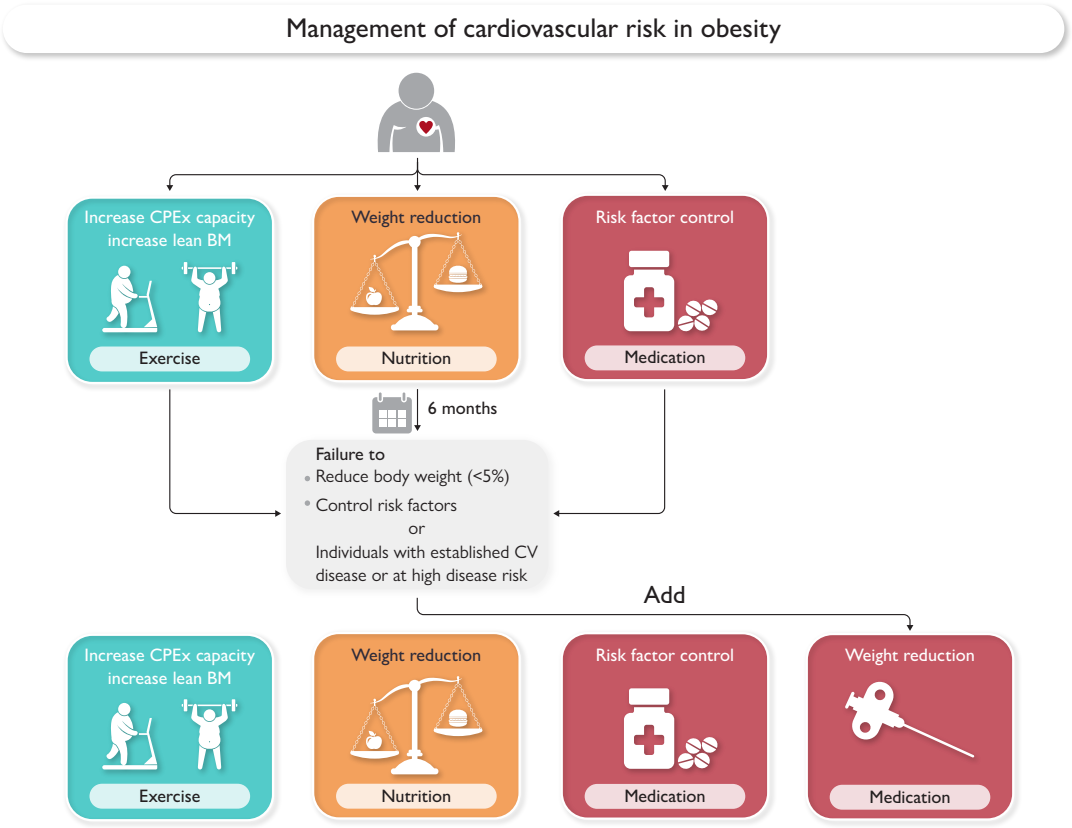
A new dawn of managing cardiovascular risk in obesity: the importance of combining lifestyle intervention and medication

Martin Halle [1]* **and Michael Papadakis** [2]

[1]Department of Preventive Sports Medicine and Sports Cardiology, TUM School of Medicine and Health, University Hospital 'Klinikum rechts der Isar', Technical University of Munich, Georg-Brauchle-Ring 56, D-80992 Munich, Germany; and [2]Cardiovascular Clinical Academic Group, St. George's University Hospitals NHS Foundation Trust, St. George's, University of London, Cranmer Terrace, London, SW17 0RE, UK

This editorial refers to 'Aerobic, resistance, or combined exercise training and cardiovascular risk profile in overweight or obese adults: the CardioRACE trial', by D. Lee *et al.*, https://doi.org/10.1093/eurheartj/ehad827.

Graphical Abstract



The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

* Corresponding author. Tel: +49 89 289 24431, Email: Martin.Halle@mri.tum.de

Obesity has finally entered the clinical scope of the cardiology community, as being an independent pathophysiological mediator and accelerator of a broad spectrum of cardiovascular diseases. This is demonstrated by the next European Society of Cardiology congress in London in 2024, which will focus on the topic of obesity within all section topics of the congress, ranging from preventive cardiology to heart failure, arrhythmias, imaging, coronary heart disease, acute cardiovascular care, and nursing. One of the main drivers for this general change in mindset is the recent results of clinical trials of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) for patients with obesity, diabetes, and heart failure with mildly reduced and preserved ejection fraction, which have shown improvements in cardio-metabolic risk profile,[1] accompanied by a reduction in cardiovascular outcomes.[2]

Lifestyle intervention by nutritional counselling and exercise training have so far been the primary approach to treat obesity and an integral part of any pharmacological or surgical obesity therapy.[3] In clinical practice, lifestyle intervention is often accompanied by the addition of medication to improve co-existing cardiovascular risk factors such as dyslipidaemia, arterial hypertension, and (pre-) diabetes, as in a significant proportion of patients, the impact of lifestyle is often small or not sustained over a longer period of time. Exercise training is seen as a key component of lifestyle intervention as endurance training will increase energy expenditure acutely and resistance training chronically by increasing muscle mass, the latter being important for long-term weight reduction. However, the effects of combining both types of exercise, rather than just a single type, on cardiovascular risk factors are less clear.

In the current issue of the *European Heart Journal*,[4] the kinesiologist Duck-chul Lee and colleagues from Iowa University in the USA have addressed the role of different types of exercise interventions in predominantly non-diabetic overweight and obese individuals with relatively low cardiovascular risk. Both sexes were equally represented in the trial, which also including a broad age range. The novelty of this randomized controlled trial is the comparison of the same exercise time of 60 min thrice weekly by either (i) aerobic endurance exercise, (ii) resistance exercise, (iii) combined training, or (iv) no intervention over 12 months. Importantly, the investigators achieved a high adherence to the intervention, with an average attendance rate for supervised exercise sessions of 82%, thereby overcoming the problem of low adherence, a common problem in lifestyle intervention trials.[5–7] Therefore the results demonstrate the maximal effects that can be achieved by different exercise modes over a year. Exercise interventions which included endurance exercise significantly improved a four-factor combination score of risk factors comprising LDL cholesterol, glucose levels, systolic blood pressure, and body fat content. However, the overall improvement of each individual risk factor was small and non-significant after 12 months, with the exception of a reduction in percentage body fat in all exercise groups.[4] Similarly, maximal cardiopulmonary exercise capacity (VO_2peak) also improved most in the groups including endurance exercise training, while muscular power assessed by chest and leg press improved in the resistance exercise groups only. Overall, these findings are not unexpected, and a more detailed assessment of pathophysiology, e.g. endothelial function, left ventricular diastolic function, liver fat content, peripheral muscle metabolism, or a detailed metabolic profile, could have been added in order to better understand the physiological effects of different training modes, thereby improving individual exercise prescription.

In general, lifestyle intervention may reduce body weight by up to ~5%. In comparison, GLP-1 RAs and glucose-dependent insulinotropic polypeptide/GLP-1 RAs can attain weight loss of ~20%, and bariatric surgery of ~25%–30%, both improving clinical cardiovascular outcome.[2,8] A reduction in clinical event rates has, however, so far not been shown by previous exercise or lifestyle intervention trials. The largest trial in obese patients with type 2 diabetes, the LOOK Ahead trial, did not demonstrate a reduction in clinical events over 10 years.[5] Other trials such as the Generation 100 trial which employed moderate continuous endurance training or high intensity interval training in an elderly population without obesity,[9] trials in chronic heart failure,[6,7,10] and trials in chronic kidney disease[11] could not show a reduction in cardiovascular events.

Therefore, current management strategies for obesity should now be reconsidered. Although the role of a comprehensive obesity treatment scheme combining behavioural interventions, nutrition and physical activity, and psycho-social support is undisputed,[8] introducing GLP-1 RAs into the scheme seems necessary and has already been accepted by physicians and the public alike (*Graphical Abstract*). However, despite the positive effects of GLP-1 RAs, the main challenges remain to introduce lifestyle interventions when introducing medication as well as to sustain these effects once medication is discontinued. Therefore, introducing viable and effective lifestyle interventions, e.g. exercise during the initiation of a GLP-1 RA, is essential.

The evaluation of different exercise programmes in overweight and obese individuals by Duck-chul Lee and colleagues is of particular interest,[4] GLP-1 RAs may reduce both fat and muscle mass, unless exercise is increased. Because muscle mass and activity are important determinants of basal metabolic rate, a reduction in muscle mass during weight reduction increases the likelihood of rebound weight gain after discontinuation of medication, and a yo–yo effect thereafter.

This underscores the importance of introducing an exercise programme in overweight and obese subjects that encompasses endurance and resistance training as outlined in the current study.[4] Moreover, beneficial effects of exercise beyond its role on cardiovascular risk factors have to be considered.[12] Based on the results of the current trial, a combined exercise training programme of 60 min thrice weekly should be considered in those patients in whom a GLP-1 RA is initiated (*Graphical Abstract*). Compliance with exercise intervention is best assessed by adherence to supervised sessions or objectively measured by monitoring devices, e.g. wearables, beyond the supervised phases or objectively tested improvement of cardio-pulmonary exercise capacity. Introducing such a scheme into the long-term care of obesity will be beneficial for the patient and may be a useful prerequisite for continuation of long-term GLP-1 RA therapy as well as reimbursement strategies by health systems.

The management of obesity has been a domain of diabetology and nutrition medicine. Now it has reached cardiology and will remain there. The introduction of the optimal exercise[4,13] and lifestyle programme[3] in addition to medication for overweight and obese subjects with or without diabetes will be a key challenge for the multidisciplinary obesity and metabolic team. Therefore, a clear educational strategy on obesity and obesity-associated diabetes management[14] for the general cardiologist is essential, which is already on the preventive cardiology curriculum of the European Association of Preventive Cardiology.[15] Effective management of obesity provides an important addition to the armamentarium of preventive cardiology that should benefit many hundreds of millions of patients worldwide.

Declarations

Disclosure of Interest

All authors declare no disclosure of interest for this contribution.

References

1. Blüher M, Aras M, Aronne LJ, Batterham RL, Giorgino F, Ji L, *et al.* New insights into the treatment of obesity. *Diabetes Obes Metab* 2023;**25**:2058–72. https://doi.org/10.1111/dom.15077
2. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, *et al.* Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med* 2023;**389**:2221–32. https://doi.org/10.1056/NEJMoa2307563
3. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, *et al.* 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021;**42**:3227–337. https://doi.org/10.1093/eurheartj/ehab484
4. Lee D, Brellenthin AG, Lanningham-Foster LM, Kohut ML, Li Y. Aerobic, resistance, or combined exercise training and cardiovascular risk profile in overweight or obese adults: the CardioRACE trial. *Eur Heart J* 2024;**45**:ehad827. https://doi.org/10.1093/eurheartj/ehad827
5. Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M, *et al.* Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013;**369**:145–54. https://doi.org/10.1056/NEJMoa1212914
6. Mueller S, Winzer EB, Duvinage A, Gevaert AB, Edelmann F, Haller B, *et al.* Effect of high-intensity interval training, moderate continuous training, or guideline-based physical activity advice on peak oxygen consumption in patients with heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA* 2021;**325**:542–51. https://doi.org/10.1001/jama.2020.26812
7. Molloy CD, Long L, Mordi IR, Bridges C, Sagar VA, Davies EJ, *et al.* Exercise-based cardiac rehabilitation for adults with heart failure—2023 Cochrane systematic review and meta-analysis. *Eur J Heart Fail* 2023;**25**:2263–73. https://doi.org/10.1002/ejhf.3046
8. Elmaleh-Sachs A, Schwartz JL, Bramante CT, Nicklas JM, Gudzune KA, Jay M. Obesity management in adults: a review. *JAMA* 2023;**330**:2000–15. https://doi.org/10.1001/jama.2023.19897
9. Letnes JM, Berglund I, Johnson KE, Dalen H, Nes BM, Lydersen S, *et al.* Effect of 5 years of exercise training on the cardiovascular risk profile of older adults: the Generation 100 randomized trial. *Eur Heart J* 2022;**43**:2065–75. https://doi.org/10.1093/eurheartj/ehab721
10. Ellingsen O, Halle M, Conraads V, Stoylen A, Dalen H, Delagardelle C, *et al.* High-intensity interval training in patients with heart failure with reduced ejection fraction. *Circulation* 2017;**135**:839–49. https://doi.org/10.1161/CIRCULATIONAHA.116.022924
11. Anding-Rost K, von Korn P, Ihorst G, Josef A, Kaufmann M, Huber M, *et al.* Exercise during hemodialysis in patients with chronic kidney failure. *N Engl J Med Evid* 2023;**2**:EVIDoa2300057. https://doi.org/10.1056/EVIDoa2300057
12. Tucker WJ, Fegers-Wustrow I, Halle M, Haykowsky MJ, Chung EH, Kovacic JC. Exercise for primary and secondary prevention of cardiovascular disease: jACC focus seminar 1/4. *J Am Coll Cardiol* 2022;**80**:1091–106. https://doi.org/10.1016/j.jacc.2022.07.004
13. Kemps H, Krankel N, Dorr M, Moholdt T, Wilhelm M, Paneni F, *et al.* Exercise training for patients with type 2 diabetes and cardiovascular disease: what to pursue and how to do it. A position paper of the European Association of Preventive Cardiology (EAPC). *Eur J Prev Cardiol* 2019;**26**:709–27. https://doi.org/10.1177/2047487318820420
14. Marx N, Federici M, Schütt K, Müller-Wieland D, Ajjan RA, Antunes MJ, *et al.* 2023 ESC guidelines for the management of cardiovascular disease in patients with diabetes. *Eur Heart J* 2023;**44**:4043–140. https://doi.org/10.1093/eurheartj/ehad192
15. Wilhelm M, Abreu A, Adami PE, Ambrosetti M, Antonopoulou M, Biffi A, *et al.* EAPC core curriculum for preventive cardiology. *Eur J Prev Cardiol* 2022;**29**:251–74. https://doi.org/10.1093/eurjpc/zwab017