outcome (recovery), the win ratio approach might have worked well by ranking death and new or worsening organ dysfunction, but it might have not worked so well by adding very soft outcomes (eg, need for oxygen during hospitalisation) to the equation, and might have diluted any potential treatment effect. Regardless of the p value (p=0·14 for the hierarchical testing), we wonder whether it might be clinically relevant, in absolute terms, to observe a difference of 547 (87·5%) of 625 patients in the dapagliflozin group versus 532 (85·1%) of 625 patients in the placebo group for clinical improvement at day 30. Effectively, the win ratio approach added little statistical gain in this case.

DARE-19 trial suggests some lessons. First, dapagliflozin can be safely used in patients with cardiometabolic risk factors who were hospitalised with COVID-19 pneumonia, regardless of their diabetes status. Second, although findings of dapagliflozin failed to show efficacy in the acute setting, SGLT2 inhibitors have a promising future not only in patients with diabetes but also in patients with chronic cardiovascular disease, chronic kidney disease, and perhaps even in asymptomatic people.[1,7,8] Third, a trial done in the middle of a pandemic in such a short time is not an easy task and the authors should take credit for adding evidence when it was most needed. Regardless of the significance of the primary hypothesis, the authors adequately tested whether dapagliflozin was effective and safe in hospitalised patients with cardiometabolic risk factors and COVID-19. Finally, the win ratio is still a new method that needs to be optimised in future trials, especially when it comes to selecting its individual components.

We declare no competing interests.

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1 McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019; **381:** 1995–2008.
2 Rossello X, Yellon DM. A new era in the management of type 2 diabetes: is cardioprotection at long last a reality? *Int J Cardiol* 2017; **228:** 198–200.
3 Kosiborod M, Esterline R, Furtado RHM, et al. Dapagliflozin in patients with cardiometabolic risk factors hospitalised with COVID-19 (DARE-19): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Diabetes Endocrinol* 2021; published online July 21. https://doi.org/10.1016/S2213-8587(21)00180-7.
4 Rodríguez-Leor O, Cid-Álvarez B, Pérez de Prado A, et al. Impact of COVID-19 on ST-segment elevation myocardial infarction care. The Spanish experience. *Rev Esp Cardiol* 2020; **73:** 994–1002.
5 Rossello X, González-Del-Hoyo M. Survival analyses in cardiovascular research, part I: the essentials. *Rev Esp Cardiol (Engl Ed)* 2021; published online June 29. https://doi.org/10.1016/j.rec.2021.06.003.
6 Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. *Eur Heart J* 2012; **33:** 176–82.
7 Heerspink HJL, Stefánsson B V, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020; **383:** 1436–46.
8 Rossello X, Raposeiras-Roubin S, Oliva B, et al. Glycated hemoglobin and subclinical atherosclerosis in people without diabetes. *J Am Coll Cardiol* 2021; **77:** 2777–91.

Targeting visceral adiposity with pharmacotherapy

Visceral adipose tissue (VAT), which is often accompanied by other ectopic fat deposits, is associated with increased cardiometabolic risks including insulin resistance, atherogenic dyslipidaemia, hypertension, inflammation, and coronary heart disease.[1] In *The Lancet Diabetes and Endocrinology*, Ian J Neeland and colleagues[2] report a randomised, controlled trial in which 185 participants aged 35 years and older, with BMI of at least 30 kg/m^2 or BMI of at least 27 kg/m^2 with metabolic syndrome, but without diabetes, were assigned to treatment with daily subcutaneous injections of liraglutide 3·0 mg or placebo for 40 weeks in addition to counselling to increase physical activity and following a hypocaloric diet. The primary endpoint was percentage reduction in VAT measured with MRI. Analysis of the primary endpoint included 128 participants who completed the study (55 in the placebo group, 73 in the liraglutide group) and had evaluable pretreatment and post-treatment MRI scans. Mean (SD) change in VAT for the liraglutide group was −12·49% (9·3) and for the placebo group was −1·63% (12·3), over a median follow-up of approximately 36 weeks. In absolute numbers, both liraglutide and placebo groups had a baseline VAT of 4·5 L, and the average changes over time for the respective groups were −0·53 L and −0·10 L. Liraglutide treatment was associated with 5·4% placebo-subtracted


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weight loss (–6·59% *vs* –1·19%). Hepatic fat decreased slightly more in the liraglutide group. As expected, liraglutide treatment led to greater reduction in fasting glucose whereas relative changes in other biomarkers were marginal or non-existent.

In the current trial, liraglutide treatment yielded an average 6·6% weight loss with associated reductions of 9·59% in total body adipose tissue and 12·49% in VAT. The relatively large VAT reduction led the authors to suggest that liraglutide might have a weight-loss independent effect on adipose tissue distribution. However, VAT is rapidly mobilised during periods of negative energy balance. Lifestyle interventions leading to 7% weight loss also report relatively large reductions in VAT,[3] and thus liraglutide's effects on this highly lipolytic compartment might not be related to its pharmacological mechanisms of action. The hypothesis proposed by the authors can be tested in future studies using previously reported analytical methods designed to establish whether an agent or activity selectively targets the VAT compartment.[4,5]

Separate from the question of the selective effects of liraglutide on mobilisation of VAT, so far there is no evidence that moderate weight loss or VAT reduction achieved with lifestyle and pharmaceutical interventions is associated with reduction in major adverse cardiovascular events among patients with obesity without diabetes. GLP-1 receptor agonists, including liraglutide, have been shown to reduce major adverse cardiovascular events among patients with overweight or obesity and comorbid type 2 diabetes, chronic kidney disease, and other complications, but not among patients with obesity without diabetes.[6] The ongoing SELECT study (NCT03574597) of semaglutide, expected to be completed at the end of 2023, will answer whether anti-obesity pharmacotherapy can reduce major adverse cardiovascular events in patients with obesity and a history of cardiovascular disease, but without type 2 diabetes.

The strengths of the current study are the randomised, controlled design, racially and ethnically diverse sample, and MRI-based quantification of VAT and other adipose tissue compartments. The study has several limitations. Men, especially those middle-aged and older, have greater accumulation of VAT compared with women of the same age. Yet, men comprised only 8% of the study sample. At baseline, the study participants had normal or almost normal average values of blood pressure, fasting glucose, triglycerides, HDL cholesterol, and N-terminal pro-brain natriuretic peptide, and only 4% had prediabetes. Risk reduction is best demonstrable when patients with significant comorbidities and those at high risk are studied. The overall attrition rate of 31%, although not extremely high, was imbalanced with paired MRI assessment of VAT available for only 59% of the participants in the placebo group.

Despite the above-mentioned limitations, the study by Neeland and colleagues is a step in the right direction. Endpoints such as changes in VAT and liver fat have far more clinical relevance and pathophysiological implications than changes in bodyweight or BMI, typical primary endpoints in randomised, controlled trials of anti-obesity drugs. Advances in imaging methods[7] now make it feasible to move beyond these classical primary endpoints towards inclusion of adipose tissue compartments and ectopic lipids as key outcome variables in future trials of new weight loss medicines.

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1 Piché ME, Tchernof A, Després JP. Obesity phenotypes, diabetes, and cardiovascular diseases. *Circ Res* 2020; **126:** 1477–500.
2 Neeland IJ, Marso SP, Ayers CR, et al. Effects of liraglutide on visceral and ectopic fat in overweight and obese adults at high cardiovascular risk: a randomised, double-blind, placebo-controlled, clinical trial. *Lancet Diabetes Endocrinol* 2021; published online Aug 3. https://doi.org/10.1016/S2213-8587(21)00179-0.
3 Neeland IJ, Ross R, Després JP, et al. Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: a position statement. *Lancet Diabetes Endocrinol* 2019; **7:** 715–25.
4 Smith SR, Zachwieja JJ. Visceral adipose tissue: a critical review of intervention strategies. *Int J Obes* 1999; **23:** 329–35.
5 Hallgreen CE, Hall KD. Allometric relationship between changes of visceral fat and total fat mass. *Int J Obes* 2008; **32:** 845–52.
6 Kalyani RR. Glucose-lowering drugs to reduce cardiovascular risk in type 2 diabetes. *N Engl J Med* 2021; **384:** 1248–60.
7 Forsgren MF, West J. Rapid body composition measurements reveal detailed metabolic changes in large scale population studies. *MAGNETOM Flash* 2017; **69:** 65–69.