B.S.,[3] Megan Freer, B.S.,[3] Taylor Lehmann, B.S.,[3] Won-Mean Lee, M.S.,[3] Emily Ormbrek, B.S.,[3] Marc J. Prindle, Ph.D.,[3] Melud Nabavi, B.S.,[3] Amal Chaturvedi, Ph.D.,[3] Chuck Seberino, B.S.,[3] Daniel N. Baker, Ph.D.,[3] Cara Williams, B.A.,[3] Diana Toledo, Ph.D.,[2] Edyta Malolepsza, Ph.D.,[2] Mark Fleharty, Ph.D.,[2] Andrea Oza, M.S.,[2] Sophie Low, B.S.,[2] Alan H. Beggs, Ph.D.,[1] Casie A. Genetti, M.S., C.G.C.,[1] Gwendolyn Strickland, M.S., M.P.H.,[1] Katherine N. Anderson, M.S., C.G.C.,[1] Wendy K. Chung, M.D., Ph.D.,[1] Heidi L. Rehm, Ph.D.,[2] Sean Hofherr, Ph.D.,[2] Mark Kokoris, B.S.,[3] and Niall Lennon, Ph.D.[2]

[1] Boston Children's Hospital, Boston; [2] Broad Clinical Labs, Burlington, MA; [3] Roche Sequencing Solutions, Seattle.

Niall Lennon can be contacted at nlennon@broadinstitute.org.

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Cagrilintide–Semaglutide in Adults with Overweight or Obesity

TO THE EDITOR: In the REDEFINE 1 trial, Garvey and colleagues (Aug. 14 issue)[1] report the efficacy of combination therapy with cagrilintide and semaglutide (known as CagriSema) in patients with overweight or obesity who did not have diabetes. The authors acknowledge the predominance of female participants as a limitation. However, this sex distribution aligns with previous trials involving patients with obesity who did not have diabetes, such as those from the STEP Program,[2] in which women are frequently overrepresented. Conversely, trials involving patients with type 2 diabetes, including the REDEFINE 2 trial by Davies et al. (Aug. 14 issue),[3] more commonly have enrolled men.

This divergence probably reflects sex-based differences in metabolic progression. Men tend to receive a diagnosis of type 2 diabetes at lower body-mass index (BMI) thresholds than women because of higher visceral adiposity and insulin resistance.[4] Consequently, in trials involving participants with obesity but without diabetes, many men may already have met the criteria for diabetes and have therefore been excluded.

This observation suggests that semaglutide tends to reach a predominantly female population when it is used to treat obesity but a predominantly male population when it is used to treat diabetes — an indication-dependent shift with implications for generalizability. We advocate that future trials consider these sex-based patterns through targeted recruitment and stratified analyses to better reflect disease burden and therapeutic response across sexes.

Federica Fogacci, M.D.,[1] and Arrigo F.G. Cicero, M.D., Ph.D.[1]

[1] Alma Mater Studiorum University of Bologna, Bologna, Italy.

Arrigo F.G. Cicero can be contacted at arrigo.cicero@unibo.it.
No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Garvey et al. and Davies et al. report the results of well-powered major trials — REDEFINE 1 and REDEFINE 2 — that reinforce the movement toward hormonal analogues in the treatment of obesity in patients with and without type 2 diabetes. As in many precedent studies, the established allometric relationship between height and weight is presented as BMI, but not the allometry of waist circumference and height and weight as approximated by a body-shape index[1,2] — a strong predictor of mortality across BMI levels, as established in studies worldwide.[3,4] To more comprehensively assess the health effects of pharmaceutical interventions, the change in the body-shape index could easily be evaluated in studies such as these trials in which waist circumference has been measured.

Jesse C. Krakauer, M.D.,[1] and Nir Y. Krakauer, Ph.D.[2]

[1]Corewell Health William Beaumont University Hospital, Royal Oak, MI; [2]City College of New York, New York.

Nir Y. Krakauer can be contacted at nkrakauer@ccny.cuny.edu.
No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: In the REDEFINE 2 trial, Davies et al. report that in adults with obesity and type 2 diabetes, once-weekly cagrilintide–semaglutide resulted in an estimated mean change in body weight from baseline to week 68 of –13.7%; the percentage of patients who had a glycated hemoglobin level of 6.5% or less was 73.5%. These results are encouraging but create a clinical dilemma as compared with tirzepatide, which resulted in a weight reduction of 14.7% and a reduction in the glycated hemoglobin level of 2.4% in 76% of the patients in the SURMOUNT-2 trial.[1]

Cross-trial comparisons reveal broadly similar efficacy, with differences in weight reduction and glycemic regulation. Gastrointestinal adverse events were more frequent with cagrilintide–semaglutide (72.5%) than with tirzepatide (approximately 50%), although the frequency of discontinuation was similar (8.4% vs. 7.1%).[2]

Such findings must be interpreted cautiously, given the differences in populations. The REDEFINE 2 trial included more Asian participants (28.7%) than the SURMOUNT-2 trial (13.4%).

The amylin component in cagrilintide–semaglutide may enhance satiety, which would benefit patients with hyperphagia, whereas the dual action of GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (glucagon-like peptide-1) in tirzepatide benefits patients with insulin resistance.[3] Head-to-head randomized, controlled trials comparing cagrilintide–semaglutide with tirzepatide seem to be necessary in order to determine superiority; indirect comparisons cannot replace direct evidence.

Vivek Lnu, M.B., B.S.,[1] and Fatima Noor, M.B., B.S.[1]

[1]Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan.

Vivek Lnu can be contacted at viveksuther2019@gmail.com.
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TO THE EDITOR: Davies et al. report substantial weight loss and glycemic reduction with once-weekly cagrilintide–semaglutide in adults with type 2 diabetes. We highlight two considerations to refine interpretation.

First, without monotherapy comparators, the incremental efficacy of the fixed combination over semaglutide alone (at a dose of 2.4 mg) remains uncertain. In the STEP 2 trial,[1] patients had a weight loss of 9.6% with semaglutide alone. In the cagrilintide–semaglutide group, 61.9% of the patients were receiving the 2.4-mg dose at the end of the treatment period. Among the patients who received oral glucose-lowering medication in the cagrilintide–semaglutide group, 5.8% had an increase in medication intensity and 35.3% had a decrease; in the placebo group, the percentages were 34.2% and 7.8%, respectively. Thus, analyses that were adjusted for changes in the use of glucose-lowering medications would clarify the added effects of these drugs.

Second, safety and glycemic outcomes are influenced by protocol flexibility. Two severe hypoglycemic events occurred only in participants receiving sulfonylureas, and four deaths were reported in the cagrilintide–semaglutide group as compared with none in the placebo group.

Hao Chi, M.D.,[1] Hua Yang, M.B.A.,[1] and Youping Deng, Ph.D.[1]

[1]John A. Burns School of Medicine, University of Hawaii at Manoa, Honolulu.

Youping Deng can be contacted at dengy@hawaii.edu.

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W. TIMOTHY GARVEY AND COLLEAGUES REPLY: We agree with Fogacci and Cicero that greater proportions of women than men have been enrolled in obesity trials, whereas trials involving patients with diabetes have had a more balanced sex representation. We also agree with their contention that sex-based metabolic differences may explain greater weight loss in women. Although more data are required to understand these differences, both men and women with overweight or obesity, with or without diabetes, have lost substantial weight and had a reduction in cardiometabolic risk factors with cagrilintide–semaglutide, as well as with other agents.

In response to Krakauer and Krakauer, BMI is not a marker of fat distribution, despite being the globally accepted indicator of obesity recognized by regulatory agencies. For that reason, we measured waist circumference (a marker of central adiposity reflecting the risk of cardiometabolic disease) and waist-to-height ratio in REDEFINE 1 and 2, as recommended by the Lancet Commission on Obesity and others.[1,2] We recognize the value of a body-shape index and await data that may show its superiority to other measures (e.g., waist-to-height ratio) for assessing disease risk.

W. Timothy Garvey, M.D.,[1] Cynthia Karenina Osorto Contreras, M.D.,[2] and Melanie J. Davies, M.D.[3]

[1]University of Alabama at Birmingham, Birmingham; [2]Novo Nordisk, Søborg, Denmark; [3]University of Leicester, Leicester, United Kingdom.

W. Timothy Garvey can be contacted at garveyt@uab.edu.

W. Timothy Garvey reports having served on advisory boards for Allurion, Corcept, MetSera, AbbVie, and the Milken Foundation and having served as site principal investigator for multicentered clinical trials sponsored by his university and funded by Novo Nordisk, Epitomee, Neurovalens, Zealand, Carmot/Roche, and TERNS Pharmaceuticals. An updated disclosure form is available with the full text of the article at NEJM.org. No further potential conflict of interest relevant to this letter was reported.

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MELANIE J. DAVIES AND COLLEAGUES REPLY: Lnu and Noor comment that cagrilintide–semaglutide and tirzepatide are highly efficacious medicines for obesity and highlight certain differences between the two clinical trials. We also note that the REDEFINE 2 trial had a shorter

dose-escalation period and overall duration and greater representation of Asian participants than the SURMOUNT-2 trial. These differences call attention to the caution required with cross-trial comparisons and underline the need for head-to-head trials to address the authors' conjectures. Accordingly, cagrilintide–semaglutide is currently being directly compared with tirzepatide in patients with obesity and type 2 diabetes in two trials (ClinicalTrials.gov numbers, NCT06131437 and NCT06534411).

In response to Chi et al., we maintain that a weight reduction of 13.7% with cagrilintide–semaglutide in REDEFINE 2 is substantially higher than the reduction of 9.6% observed with semaglutide monotherapy in the STEP 2 trial. We also would note that greater weight reduction was reported with cagrilintide–semaglutide than with semaglutide monotherapy in REDEFINE 1 and in a phase 2 study.[1] The two severe hypoglycemic events in REDEFINE 2 occurred during the maintenance phase in participants receiving concomitant sulfonylureas. The overall incidence of hypoglycemia was low, considering that nearly 75% of the participants met a glycated hemoglobin target of 6.5% or less. We agree that careful consideration should be given to the use of concomitant medications in the clinical setting.

Melanie J. Davies, M.D.,[1] Christa Broholm, Ph.D.,[2] and W. Timothy Garvey, M.D.[3]

[1]University of Leicester, Leicester, United Kingdom; [2]Novo Nordisk, Søborg, Denmark; [3]University of Alabama at Birmingham, Birmingham.

Melanie J. Davies can be contacted at melanie.davies@uhl-tr.nhs.uk.

W. Timothy Garvey reports having served on advisory boards for Allurion, Corcept, MetSera, AbbVie, and the Milken Foundation and having served as site principal investigator for multicentered clinical trials sponsored by his university and funded by Novo Nordisk, Epitomee, Neurovalens, Zealand, Carmot/Roche, and TERNS Pharmaceuticals. An updated disclosure form is available with the full text of the article at NEJM.org. No further potential conflict of interest relevant to this letter was reported.

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Neoadjuvant Nivolumab plus Chemotherapy in Lung Cancer

TO THE EDITOR: The landmark findings of the CheckMate 816 trial, conducted by Forde et al. (Aug. 21/28 issue),[1] showed a significant survival benefit with neoadjuvant nivolumab plus chemotherapy in patients with resectable non–small-cell lung cancer. In an exploratory analysis involving patients with a pathological complete response, the 5-year overall survival in the nivolumab-plus-chemotherapy group was 95.3%, with only three deaths (7.0% of the patients) reported, none due specifically to lung cancer.

These practice-changing results naturally prompt a critical question: whether adjuvant therapy remains appropriate for patients who have a pathological complete response after such effective neoadjuvant therapy. We note that the trial protocol, which is available with the full text of their article at NEJM.org, permitted optional adjuvant chemotherapy, radiotherapy, or both. Could the authors provide additional data on the proportion of patients with a pathological complete response who subsequently received adjuvant therapy, as well as a comparative analysis of long-term survival between those who received adjuvant treatment and those who did not? Although we recognize the very low number of events among patients with a pathological complete response, any available data from exploratory analyses would be helpful for generating hypotheses and guiding risk-adapted strategies, potentially influencing future clinical guidelines.

Xuesong Li, M.D.,[1] and Xiangdong Mu, M.D.[1]

[1]Beijing Tsinghua Changgung Hospital, Beijing.

Xiangdong Mu can be contacted at muxiangdong@medmail.com.cn.