Title

Tirzepatide for Heart Failure and Obesity (Correspondence)

Journal

New England Journal of Medicine, 392(16)

ISSN

0028-4793 1533-4406

Authors

Marine, Joseph
Mandrola, John
Prasad, Vinay

Publication Date

2025-04-24

DOI

10.1056/NEJMc2502743

Peer reviewed

Table 1. (Continued.)

Measure	2021 (95% CI)	2022 (95% CI)	Change from 2021 to 2022 (95% CI)†‡
			percentage points
Social risk indicator of ≥2 — % of facilities	2.4 (–0.2 to 5.1)	0.2 (–0.2 to 0.6)	–2.2 (–4.9 to 0.4)
Difference between facilities with indicators of 0 and 1 — percentage points†	0.7 (–0.4 to 1.8)	0.1 (–1.2 to 1.5)	–0.8 (–2.3 to 0.7)
Difference between facilities with indicators of 0 and ≥2 — percentage points†	1.9 (–0.8 to 4.7)	–0.9 (–1.6 to –0.2)	–3.0 (–5.8 to –0.2)

* Composite social risk indicators represent the number of measures of social risk among patients at each facility; a facility receives 1 point for being in the highest quintile of social risk for each of four categories of patient characteristics (Black race, Hispanic ethnic group, being uninsured or covered by Medicaid, and living in the most socially disadvantaged neighborhoods). All analyses reported in this table were conducted on this level. The widths of the confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing. ETC denotes End-Stage Renal Disease Treatment Choices.

† Linear regression models were used to generate estimates and confidence intervals, with regional fixed effects and standard errors clustered by hospital referral region. Within-year estimates compare each cohort of facilities with the cohort with a social risk indicator of 0; across-year estimates compare 2022 with 2021.

‡ The changes in performance differences across cohorts from 2021 to 2022 were calculated with the use of a linear regression model in which year and cohort variables interact, with regional fixed effects and standard errors clustered by hospital referral region.

§ Achievement of transplantation is defined as a patient's receiving a living-donor kidney transplant or being placed on a transplant waiting list in a given year.

¶ Improvement in transplantation is defined as the mean percent improvement in the percentage of patients receiving a living-donor kidney transplant or being placed on a waiting list for a deceased-donor transplant in a given year as compared with the percentage in the specific benchmark period for that year (Supplementary Appendix).

Kalli G. Koukounas, M.P.H.,[1] Meehir N. Dixit, B.A.,[1] Rebecca Thorsness, Ph.D.,[2] Rachel E. Patzer, Ph.D., M.P.H.,[3] Adam S. Wilk, Ph.D.,[3] Kelsey M. Drewry, Ph.D.,[3] Rajnish Mehrotra, M.D.,[4] Maricruz Rivera-Hernandez, Ph.D.,[1] David J. Meyers, Ph.D., M.P.H.,[1] Daeho Kim, Ph.D.,[1] Ankur D. Shah, M.D.,[5] Christopher H. Schmid, Ph.D.,[1] and Amal N. Trivedi, M.D., M.P.H.[1]

[1] Brown University School of Public Health, Providence, RI; [2] VA Boston Healthcare System, Boston; [3] Indiana University School of Medicine, Indianapolis; [4] University of Washington School of Medicine, Seattle; [5] Warren Alpert Medical School of Brown University, Providence, RI.

Dr. Trivedi can be contacted at amal_trivedi@brown.edu.

The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the U.S. government.

Supported by grants from the National Institute on Minority Health and Health Disparities (R01 MD017080) and the National Institute of Diabetes and Digestive and Kidney Diseases (R01DK113298 and K01DK128384) of the National Institutes of Health and from the Agency for Healthcare Research and Quality (R01HS28285).

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

1. End-stage renal disease treatment choices (ETC) model: performance payment adjustment (PPA) report user guide (measurement years 3–4). Baltimore: Centers for Medicare and Medicaid Services, June 2023 (https://www.cms.gov/priorities/innovation/media/document/etc-4i-ppa-report-user-guide-my3-4).
2. Koukounas KG, Thorsness R, Patzer RE, et al. Social risk and dialysis facility performance in the first year of the ESRD treatment choices model. JAMA 2024;331:124-31.
3. Thorsness R, Wang V, Patzer RE, et al. Association of social risk factors with home dialysis and kidney transplant rates in dialysis facilities. JAMA 2021;326:2323-5.
4. Shen JI, Chen L, Vangala S, et al. Socioeconomic factors and racial and ethnic differences in the initiation of home dialysis. Kidney Med 2020;2:105-15.
5. Mehrotra R, Soohoo M, Rivara MB, et al. Racial and ethnic disparities in use of and outcomes with home dialysis in the United States. J Am Soc Nephrol 2016;27:2123-34.

DOI: 10.1056/NEJMc2413208

Tirzepatide for Heart Failure and Obesity

TO THE EDITOR: Packer et al. (Jan. 30 issue)[1] report the highly anticipated results of the SUMMIT trial, which compared tirzepatide with placebo in patients with heart failure with preserved ejection fraction and assessed clinical end points over a 1-year period. The trial showed a lower risk of the composite primary end point (death from cardiovascular causes or a worsening heart-failure event) with tirzepatide than with placebo, a result driven mainly by a lower risk of heart-failure events in the tirzepatide group.

According to Table 1 of the article, 69 of 364

patients (19.0%) in the tirzepatide group and 57 of 367 patients (15.5%) in the placebo group were receiving sodium–glucose cotransporter 2 (SGLT2) inhibitors, a class of drugs that has been shown to reduce the risk of hospitalization for heart failure among patients with heart failure with preserved ejection fraction.[2] Could the authors provide a subgroup analysis involving patients treated with tirzepatide and SGLT2 inhibitors as compared with those treated with SGLT2 inhibitors alone? Although any results would only be hypothesis-generating, it would be an important exploratory comparison, given the greater adoption of both drugs for similar clinical end points in patients with heart failure.

Jeffrey Wagner, M.D., M.C.R.[1]

[1] University of Colorado School of Medicine, Aurora.

Dr. Wagner can be contacted at jeffrey.wagner@cuanschutz.edu.

No potential conflict of interest relevant to this letter was reported.

1. Packer M, Zile MR, Kramer CM, et al. Tirzepatide for heart failure with preserved ejection fraction and obesity. N Engl J Med 2025;392:427-37.
2. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med 2021;385:1451-61.

DOI: 10.1056/NEJMc2502743

TO THE EDITOR: The SUMMIT trial quantified adiposity at baseline according to patients' body weight, body-mass index (BMI), and waist-to-height ratio. The percent change in body weight at 52 weeks was a secondary end point, but the change in the waist-to-height ratio was not reported. The waist-to-height ratio has been promoted as a surrogate of abdominal girth and as a simple but useful predictor of coronary risk.[1] However, in a recent study, the waist-to-height ratio was not predictive of 48-month mortality among patients with preserved ejection fraction at baseline, yet was paradoxically predictive of mortality among patients with a reduced ejection fraction (lower mortality with an elevated waist-to-height ratio).[2] The BMI–obesity paradox in some populations may also hold when the waist-to-height ratio is the obesity indicator, given the correlation of 0.7 between this ratio and BMI.[2,3] In contrast, an allometrically adjusted waist circumference calculated with a body-shape index has minimal correlation with BMI and is directly associated with mortality.[4] Analysis with the use of a body-shape index to assess the relative loss of waist girth accompanying weight loss with tirzepatide may facilitate understanding of the long-term health outcomes in this trial.

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.

Dr. N. Krakauer can be contacted at nkrakauer@ccny.cuny.edu.

No potential conflict of interest relevant to this letter was reported.

1. Hsieh SD, Yoshinaga H. Abdominal fat distribution and coronary heart disease risk factors in men-waist/height ratio as a simple and useful predictor. Int J Obes Relat Metab Disord 1995;19:585-9.
2. Wang P, Zhao Y, Wang D, et al. Relationship between waist-to-height ratio and heart failure outcome: a single-centre prospective cohort study. ESC Heart Fail 2025;12:290-303.
3. Elagizi A, Kachur S, Lavie CJ, et al. An overview and update on obesity and the obesity paradox in cardiovascular diseases. Prog Cardiovasc Dis 2018;61:142-50.
4. Krakauer NY, Krakauer JC. A new body shape index predicts mortality hazard independently of body mass index. PLoS One 2012;7(7):e39504.

DOI: 10.1056/NEJMc2502743

TO THE EDITOR: We have a concern regarding the composite primary end point in the SUMMIT trial. The reported deaths were numerically higher in the tirzepatide group than in the placebo group (19 vs. 15), so the primary end-point results were driven entirely by the component of worsening heart-failure events. Our question centers on whether this end point captures a net benefit, as opposed to an end point of all-cause hospitalization. For instance, we note that the incidence of adverse events of diarrhea, nausea, constipation, vomiting, urinary tract infection, dizziness, atrial fibrillation, hypotension, and upper abdominal pain was 2 to 3 times as high in the tirzepatide group (356 total events) as in the placebo group (147 total events). If even a modest percentage of these events resulted in hospitalization or led to urgent visits for therapy, then the apparent effect of a lower risk of heart-failure events could be negated. Can the authors provide an analysis of all-cause hospitalization?

Joseph E. Marine, M.D.,[1] John Mandrola, M.D.,[2] and Vinay Prasad, M.D., M.P.H.[3]

[1] Johns Hopkins University School of Medicine, Baltimore; [2] Baptist Health Louisville, Louisville, KY; [3] University of California, San Francisco, San Francisco.

Dr. Marine can be contacted at jmarine2@jhmi.edu.

No potential conflict of interest relevant to this letter was reported.

DOI: 10.1056/NEJMc2502743

TO THE EDITOR: With regard to this trial assessing the effect of tirzepatide therapy on improving quality of life in patients with obesity-related heart failure with preserved ejection fraction, I was particularly impressed by the decision to include patients without elevated natriuretic peptide levels. However, the lack of echocardiographic data leaves important questions unanswered regarding the effect of tirzepatide on cardiac structure and function. Heart failure with preserved ejection fraction is characterized by diastolic dysfunction and myocardial remodeling. Reporting echocardiographic metrics such as the ratio of E-wave velocity to e′ velocity (E/e′ ratio), left atrial volume, and mitral inflow velocities would help to further elucidate the effect of tirzepatide on diastolic pressures and relaxation, if any. In addition, reductions in left ventricular mass or epicardial fat volume — key contributors to the pathophysiological features of heart failure with preserved ejection fraction — could be assessed by means of magnetic resonance imaging or computed tomography of the heart. Global longitudinal strain could provide insight into subclinical systolic dysfunction, an increasingly recognized feature in heart failure with preserved ejection fraction.

Understanding whether tirzepatide directly alters these variables, or whether its benefits are mediated predominantly by weight loss and inflammation reduction, is critical for our understanding of where to focus future research. The inclusion of imaging end points in future trials may strengthen mechanistic insights and refine patient selection.

M. Kasim Ali, M.B., B.S.[1]

[1]Greenslopes Private Hospital, Brisbane, QLD, Australia.

Dr. Ali can be contacted at kasimali@doctors.org.uk.

No potential conflict of interest relevant to this letter was reported.

DOI: 10.1056/NEJMc2502743

THE AUTHORS REPLY: In response to Wagner: the use of SGLT2 inhibitors at baseline did not influence any of the effects of tirzepatide in the SUMMIT trial. With regard to the primary end point, tirzepatide therapy led to a lower risk of a composite of death from cardiovascular causes or worsening heart failure than placebo among both patients taking SGLT2 inhibitors (hazard ratio vs. placebo, 0.63; 95% confidence interval [CI], 0.23 to 1.74) and those not taking SGLT2 inhibitors (hazard ratio vs. placebo, 0.63; 95% CI, 0.40 to 1.01).

In response to Krakauer and Krakauer: we agree that central adiposity has substantial advantages over BMI with regard to the evaluation of excess fat mass, especially visceral fat. Typically, central adiposity is assessed by the waist-to-height ratio, thus making it independent of body weight. We have found that the waist-to-height ratio is abnormally elevated in 96% of patients with heart failure with preserved ejection fraction; the waist-to-height ratio is superior to BMI for the prediction of adverse heart-failure outcomes, and it is free from the obesity paradox.[1] In our trial, tirzepatide therapy reduced the waist-to-height ratio (placebo-corrected difference at 52 weeks, −0.07; 95% CI, −0.08 to −0.06).

In response to Marine et al.: the expected increase in adverse events with tirzepatide did not result in an increase in all-cause hospitalizations related to an adverse event other than heart failure; there were 157 such events, and the hazard ratio as compared with placebo was 1.18 (95% CI, 0.86 to 1.61). This result contrasts with our finding that tirzepatide therapy led to a lower risk of hospitalization for heart failure than placebo (hazard ratio, 0.44; 95% CI, 0.22 to 0.87). Owing to the burden of coexisting conditions, patients with heart failure with preserved ejection fraction have many hospitalizations due to noncardiovascular causes, but because these hospitalizations will not be influenced by a treatment directed to heart failure, they have not been included in the analysis of net benefit in any trial involving persons with heart failure with preserved ejection fraction. In the DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure) trial, which recorded more than 40 times the number of hospitalizations as were observed in the SUMMIT trial, a small decrease in the incidence of all-cause hospitalization in the dapagliflozin group was driven entirely by a reduction in hospitalizations for heart failure.[2]

In response to Ali: in a substudy of the SUMMIT trial that reported the results of cardiac magnetic resonance imaging, left ventricular mass and paracardiac fat were reduced significantly in patients in the tirzepatide group as compared with those in the placebo group.[3] These findings may underscore some of the benefits of tirzepatide therapy with respect to outcomes in patients with heart failure.

Milton Packer, M.D.,[1] Christopher M. Kramer, M.D.,[2] and Barry A. Borlaug, M.D.[3]

[1] Baylor University Medical Center, Dallas; [2] University of Virginia Health System, Charlottesville; [3] Mayo Clinic, Rochester, MN.

Dr. Packer can be contacted at milton.packer@baylorhealth.edu.

Since publication of the article, the authors report no further potential conflict of interest.

1. Peikert A, Vaduganathan M, Claggett BL, et al. Near-universal prevalence of central adiposity in heart failure with preserved ejection fraction: the PARAGON-HF trial. Eur Heart J 2025 January 28 (Epub ahead of print).
2. Vaduganathan M, Claggett BL, Jhund P, et al. Dapagliflozin and all-cause hospitalizations in patients with heart failure with preserved ejection fraction. J Am Coll Cardiol 2023;81:1004-6.
3. Kramer CM, Borlaug BA, Zile MR, et al. Tirzepatide reduces LV mass and paracardiac adipose tissue in obesity-related heart failure: SUMMIT CMR substudy. J Am Coll Cardiol 2025;85:699-706.

DOI: 10.1056/NEJMc2502743

Oral Anticoagulation during TAVI

TO THE EDITOR: In the POPular PAUSE TAVI (Periprocedural Continuation versus Interruption of Oral Anticoagulant Drugs during Transcatheter Aortic Valve Implantation) trial, van Ginkel et al. (Jan. 30 issue)[1] found that among patients undergoing transcatheter aortic-valve implantation (TAVI) who were being treated with oral anticoagulation, the continuation of periprocedural oral anticoagulation was not noninferior to the interruption of oral anticoagulation with respect to a composite of death from cardiovascular causes, stroke from any cause, myocardial infarction, major vascular complications, or major bleeding within 30 days after TAVI. We have two key concerns related to the management of perioperative oral anticoagulants.

First, most patients receive direct oral anticoagulants, which have rapid onset and offset.[2] Second, time-based interruption of direct oral anticoagulants is generally safe, with the therapy usually restarted 6 to 8 hours after the intervention if hemostasis is achieved. In cases in which the bleeding risk outweighs the thromboembolic risk, full-dose anticoagulation may be delayed by 48 to 72 hours after a procedure or surgery.[3] Bridging is not recommended for patients with low-to-moderate thromboembolic risk.[3] In this trial, the incidence of major bleeding was similar in the continuation group and the interruption group (11.1% and 8.9%, respectively), but minor bleeding was more common in the continuation group than in the interruption group (21.6% vs. 12.9%). Minor bleeding is a common concern, affecting approximately one third of patients with atrial fibrillation treated with oral anticoagulants.[4] Minor bleeding predicts a higher rate of discontinuation of oral anticoagulant therapy (hazard ratio for discontinuation vs. no bleeding, 1.9),[5] and discontinuation is associated with increased risks of composite and individual end points of death, stroke, and myocardial infarction.[5]

Bartosz Hudzik, M.D., Ph.D.,[1] Przemysław Skulik, M.D.,[2] and Mariusz Gąsior, M.D., Ph.D.[1]

[1] Medical University of Silesia, Zabrze, Poland; [2] Silesian Center for Heart Disease, Zabrze, Poland.

Dr. Hudzik can be contacted at bartekh@mp.pl.

No potential conflict of interest relevant to this letter was reported.

1. van Ginkel DJ, Bor WL, Aarts HM, et al. Continuation versus interruption of oral anticoagulation during TAVI. N Engl J Med 2025;392:438-49.
2. Ingrasciotta Y, Crisafulli S, Pizzimenti V, et al. Pharmacokinetics of new oral anticoagulants: implications for use in routine care. Expert Opin Drug Metab Toxicol 2018;14:1057-69.
3. Halvorsen S, Mehilli J, Cassese S, et al. 2022 ESC guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery. Eur Heart J 2022;43:3826-924.
4. Ueda I, Kohsaka S, Ikemura N, et al. Patient concern regarding bleeding side effects from oral anticoagulation therapy for atrial fibrillation: an analysis from the multicentre KiCS-AF registry. Eur J Cardiovasc Nurs 2024;23:358-66.
5. Cools F, Johnson D, Camm AJ, et al. Risks associated with discontinuation of oral anticoagulation in newly diagnosed patients with atrial fibrillation: results from the GARFIELD-AF Registry. J Thromb Haemost 2021;19:2322-34.

DOI: 10.1056/NEJMc2502740

THE AUTHORS REPLY: Hudzik et al. elaborate on concerns associated with perioperative oral anticoagulation management. We agree that the majority of patients undergoing TAVI with a concomitant indication for long-term oral anticoagulation are currently treated with direct oral anticoagulants (81.9% in our trial population). In a prespecified substudy, we measured multiple variables of hemostasis, which confirmed the rapid onset and offset of direct oral anticoagulants. In patients who had oral anticoagulation interrupted, the endogenous thrombin potential was restored to almost-normal levels at the start of the TAVI procedure.