Research Open

Endocrinology, Diabetes and Metabolism Journal

Volume 8 Issue 1

Review Article

Glucagon-like Peptide 1 Receptor Agonists, Heart Failure, and Critical Appraisal: How the STEP-HFpEF Trial Unmasks the Need for Improved Reporting of Blinding

Jeffrey R. Wagner*, MD. MCR

The Division of Hospital Medicine at the University of Colorado Hospital Anschutz Medical Campus, USA

Corresponding author: Jeffrey Wagner, MD MCR, Clinical Instructor Division of Hospital Medicine, The University of Colorado Anschutz Medical Campus-12401 E.17th Ave 4th Floor Aurora CO 80045, USA, Office: (720) 848-4289

Received: March 20, 2024; **Accepted:** March 25, 2024; **Published:** April 04, 2024

The history of medical science demonstrates the effects of randomness where chance unmasks nature's secrets. Penicillin's accidental discovery of a contaminated Petri dish led to a new paradigm in the landscape of illness where the primary cause of human mortality was no longer infectious diseases but rather chronic, non-communicable disease, namely cardiovascular disease (CVD) [1]. Diabetes mellitus is an independent risk factor associated with a 2-to-4-fold increase in CVD-related mortality, and thus researchers have sought to identify new efficacious treatments [2,3]. One potential modality was identified in the 1980s as a mediator of glucagon-like effects: increased insulin secretion in a glucose-dependent manner while simultaneously blocking gastric acid secretion and motility [4]. It was named glucagon-like peptide 1 (GLP1) and synthetic forms of receptor agonists (GLP1RA) were later studied in clinical trials for the treatment of diabetes mellitus type 2. Despite numerous FDA approvals for this class of drugs due to their impact on blood glucose control, the promise around GLP1RAs seems somewhat analogous to penicillin: a chance finding of improved CVD outcomes and weight loss for patients with obesity who were treated, first with diabetes but then even those without a diabetes diagnosis [5,6]. Beyond the excitement surrounding these drugs and their impact on patient outcomes for CVD, there also exists significant market pressure from the financial sector with a projected $1 trillion in revenue globally over the next 30 years related to GLP1Ras [7]. In such a climate, the voice of clinicians can help ensure new treatments are adopted through the lens of the quintuple aim of healthcare [8]. This is to ensure implementation occurs with the greatest fidelity equitably and could optimally function within the infrastructure of a healthcare system with limited resources. However, barriers in the standard reporting of data related more broadly to blinded randomized controlled trials (RCTs) impede clinicians' ability to complete the appraisal process. The 2023 RCT titled STEP-HFpEF (Effect of Semaglutide 2.4 mg Once Weekly on Function and Symptoms in Subjects with Obesity-related Heart Failure with Preserved Ejection Fraction) demonstrated the possible benefit of GLP1RA in heart failure. The trial was funded by the manufacturer of the study drug, and included adults with a left ventricular ejection fraction greater than 45%, and a body mass index greater than 30 kg/m^2. It assessed a primary two-part endpoint of both numeric change in subjective scoring of the Kansas City Cardiomyopathy Questionnaire (KCCQ) score plus a percentage change in body weight over a 12-month time frame. The KCCQ is a validated questionnaire that assesses subjective data related to a patient's symptoms with scores ranging from 0 to 100. Results showed those treated with semaglutide had an average decrease in KCCQ of 7.8 (16.7 with semaglutide versus 8.7) and a 10% decrease in body weight loss (13.3% versus 2.6%). The authors concluded the use of GLP1RA improved heart failure symptoms in the heart failure population though it had limitations given a small proportion of enrollees were of non-white ethnicity which such that it could limit the external validity of the results. However, STEP-HFpEF offers a key lesson related to the application of critical appraisal that clinicians and researchers alike can glean when first evaluating the internal validity of a trial. Clinicians must assess for the preservation of blinding in RCTs where this is performed. Unmasking, where the blinding process fails to be implemented appropriately for either patients or care staff, could compromise a study's results via the entry of ascertainment bias [9,10]. In response to a letter to the editor for the STEP-HFpEF trial, the authors said, "38% of the responding placebo recipients believed they had received semaglutide" [11]. Worded another way, it is inferred that 62% of respondents guessed correctly in the placebo group. Unfortunately, no data was provided for the semaglutide arm. With such a large proportion of patients identifying their assigned arm, it may be reasonable to question whether the behaviors and expectations of participants were compromised. Did a similar percentage of participants in the treatment arm guess correctly given their achieved weight loss, and thus had a higher subjective rating in the KCCQ questionnaire? A conservative goal should be for less than 20% of participants to identify their assignment where the blinding process is preserved correctly. Given that possibly more than three times that threshold guessed correctly, even despite differences in secondary endpoints of the trial, clinicians would be wise to think critically about adding this study as evidence to expand the use GLP1RAs for the indication of heart failure.

Though blinding is essential to the internal validity of a trial, STEP-HFpEF reveals a shortcoming of the status quo regarding information dissemination within the research community for blinded RCTs. The manuscript and supplement do not report data or blinding indices related to the evaluation of the blinding process despite the investigators having at least assessed for this in the placebo group based on their response. For greater transparency, publishers of blinded RCTs would benefit from making the assessment and reporting of blinding in both intervention and control arms a standard practice. In fairness to the authors, since it is not standard to have such data provided as part of the peer-review process, it is reasonable to have foregone this step at present. However, my question is, "*should we though?*". Adding such reporting is imperative given the potential of ascertainment bias to inaccurately inflate efficacy outcomes, Objective demonstration of a trial's internal validity will more readily ensure high-value practices are appropriately adopted [12]. Going forward, let us be thoughtful and transparent in the assessment of efficacy for new practices, ensuring the innovations of today achieve their desired outcome tomorrow in improving human health based on sound evidence versus adopting low-value practices based on noise. When nature reveals its secrets at random, the onus is on us to determine how best to apply that new knowledge.

References

1. Maeda H (2018) The Rise of the Current Mortality Pattern of the United States, 1890-1930. *Am J Epidemiol* 187(4): 639-46. [crossref]
2. Raghavan S, Vassy JL, Ho Y-L, et al. (2019) Diabetes Mellitus-Related All-Cause and Cardiovascular Mortality in a National Cohort of Adults. *J Am Heart Assoc* 8(4): e011295. [crossref]
3. Skyler JS, Bergenstal R, Bonow RO, et al. (2009) Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. *Diabetes Care* 32(1): 187-92. [crossref]
4. Holst JJ (2007) The physiology of glucagon-like peptide 1. *Physiol Rev* 87(4): 1409-39.
5. Leite AR, Angélico-Gonçalves A, Vasques-Nóvoa F, et al. (2022) Effect of glucagon-like peptide-1 receptor agonists on cardiovascular events in overweight or obese adults without diabetes: A meta-analysis of placebo-controlled randomized trials. *Diabetes Obes Metab* 24(8): 1676-80.
6. Iqbal J, Wu H-X, Hu N, et al. (2022) Effect of glucagon-like peptide-1 receptor agonists on body weight in adults with obesity without diabetes mellitus-a systematic review and meta-analysis of randomized control trials. *Obes Rev* 23(6): e13435. [crossref]
7. The battle over the trillion-dollar weight-loss bonanza (2024) *The Economist* .
8. Nundy S, Cooper LA, Mate KS (2022) The Quintuple Aim for Health Care Improvement: A New Imperative to Advance Health Equity. *JAMA* [crossref]
9. Schulz KF, Grimes DA (2002) Blinding in randomised trials: hiding who got what. *Lancet* 359(9307): 696-700. [crossref]
10. H B, L N, Ce D (2004) Assessment of blinding in clinical trials. *Controlled clinical trials* 25(2) [crossref]
11. Semaglutide and Heart Failure with Preserved Ejection Fraction and Obesity (2023) *New England Journal of Medicine* 389(25): 2397-9.
12. Wang Y, Parpia S, Couban R, et al. (2024) Compelling evidence from meta-epidemiological studies demonstrates overestimation of effects in randomized trials that fail to optimize randomization and blind patients and outcome assessors. *J Clin Epidemiol* 165: 111211. [crossref]

Citation:

Wagner JR (2024) Glucagon-like Peptide 1 Receptor Agonists, Heart Failure, and Critical Appraisal: How the STEP-HFpEF Trial Unmasks the Need for Improved Reporting of Blinding. *Endocrinol Diabetes Metab J* Volume 8(1): 1-2.