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## Tirzepatide versus Semaglutide Once Weekly in Type 2 Diabetes

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## TO THE EDITOR:

Frías et al. report on the favorable effects of tirzepatide on glucose homeostasis. The authors also found that tirzepatide had relatively rapid and strong antihypertensive effects (as evidenced by a decrease from baseline in systolic blood pressure of 6.5 mm Hg in the group that received the 15-mg dose). A subgroup analysis involving the patients in the trial who had hypertension could be valuable. It would also be important to know whether the use of beta-blockers, angiotensin-converting–enzyme (ACE) inhibitors, or angiotensin-receptor blockers (ARBs) was similar in the trial groups and whether patients who were receiving these drugs at enrollment were allowed to continue taking them during the trial.

The antihypertensive effect of tirzepatide should not depend on the regulation of the insulin level; indeed, since insulin has been shown to stimulate both nitric oxide production and endothelin-1 secretion, <sup>1</sup> its net hemodynamic effect on blood pressure is minimal. <sup>2</sup> Moreover, insulin therapy can lead to microcirculatory disorders. <sup>3</sup> Given the complex relationship linking GLP-1, endothelial dysfunction, and diabetes, <sup>4,5</sup> it would be informative if the authors could provide data on endothelial function, inflammation, and oxidative stress.

## References

- 1. Cardillo C, Nambi SS, Kilcoyne CM, et al. Insulin stimulates both endothelin and nitric oxide activity in the human forearm. Circulation 1999;100:820–5. [PubMed: 10458717]
- Muniyappa R, Montagnani M, Koh KK, Quon MJ. Cardiovascular actions of insulin. Endocr Rev 2007;28:463–91. [PubMed: 17525361]
- 3. Arcaro G, Cretti A, Balzano S, et al. Insulin causes endothelial dysfunction in humans: sites and mechanisms. Circulation 2002;105:576–82. [PubMed: 11827922]
- 4. Ceriello A, Novials A, Ortega E, et al. Glucagon-like peptide 1 reduces endothelial dysfunction, inflammation, and oxidative stress induced by both hyperglycemia and hypoglycemia in type 1 diabetes. Diabetes Care 2013;36:2346–50. [PubMed: 23564922]
- Matarese A, Gambardella J, Lombardi A, et al. miR-7 regulates GLP-1-mediated insulin release by targeting β-arrestin 1. Cells 2020;9:1621.