GLP-1 Agonists: Do They Prevent Heart Disease in the General Population?

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> Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have reshaped the management of type 2 diabetes and obesity, offering substantial cardiovascular benefits in patients with established disease. But the question of whether these agents can prevent cardiovascular events in a broader, lower-risk population has lingered. European cardiologists are looking for clarity.

KEY TAKEAWAYS

- The Pivot: The cardiovascular benefits of GLP-1RAs in primary prevention for the general population are not yet established.
- The Data: Existing evidence supports GLP-1RA use in obese individuals with established cardiovascular disease.
- The Action: Clinicians should continue to target GLP-1RAs for secondary prevention in appropriate patients, awaiting further data for primary prevention.

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have demonstrated a clear ability to reduce cardiovascular risk in obese individuals who already have established cardiovascular disease (CVD). This benefit likely stems from their effects on key risk factors, including weight loss, glycemic control, and blood pressure.1 However, the utility of these agents for primary prevention, meaning preventing the first cardiovascular event in individuals without existing CVD, remains an open question for the cardiology community.

The current understanding of GLP-1RAs largely comes from trials focused on secondary prevention populations. These studies enrolled patients with a high baseline risk, often with a history of myocardial infarction, stroke, or peripheral artery disease, in addition to obesity or type 2 diabetes. The Oxford Handbook of Cardiology provides a concise guide to modern cardiological practice, outlining current treatment paradigms.

Emulating GLP-1RA Effects in a Broader Cohort

A study by Schrage, Lackner, and Hoshiyar, published in the Journal of the American College of Cardiology in 2026, aimed to emulate the effects of GLP-1RA therapy in a general population cohort.1 This research sought to bridge the gap in understanding by modeling the potential impact of these drugs on individuals without established CVD. The investigators used a robust methodology to simulate the long-term cardiovascular outcomes. They focused on a broad population, moving beyond the traditional high-risk groups that have dominated GLP-1RA trials to date.

The study design involved a large-scale analysis, drawing from comprehensive health databases to construct a representative general population cohort.1 Researchers applied statistical methods to mimic the effects of GLP-1RA

exposure, adjusting for various confounding factors that could influence cardiovascular outcomes. This approach allowed for an estimation of the drug class's impact in a setting where direct randomized controlled trials are still pending or underway. The primary outcome measured was the incidence of major adverse cardiovascular events (MACE), a composite endpoint commonly used in cardiology trials.

The Data on Primary Prevention

The emulated effects of GLP-1RA therapy in the general population did not provide a definitive answer for primary prevention.1 While GLP-1RAs consistently reduced cardiovascular risk in obese individuals with established CVD, the study's findings did not extend this benefit clearly to a broader population without pre-existing heart disease. The analysis showed a reduction in MACE for the high-risk groups, consistent with previous trial data. But for individuals in the general population without established CVD, the emulated effect on primary prevention endpoints was less pronounced, and the confidence intervals were wide, indicating uncertainty.

The authors highlighted that the existing evidence base for GLP-1RAs firmly supports their use in secondary prevention.1 For patients with obesity and established CVD, these agents remain a critical tool for reducing future cardiovascular events. The study did not identify a strong signal for widespread primary prevention in the general population, suggesting that the risk-benefit profile in this lower-risk group may differ significantly from that in high-risk cohorts. This contrasts with the clear benefits seen in patients with established disease, where the absolute risk reduction is substantial.

The study's reliance on emulated data, rather than direct randomized controlled trial evidence, is an obvious caveat. While sophisticated statistical methods can account for many confounders, they cannot fully replicate the rigor of a prospective, randomized trial. The generalizability of these emulated effects to all subgroups within the general population also remains a point of discussion. The trial was not powered to detect subtle differences in specific low-risk subgroups, and that gap matters for widespread adoption.

Still, the research underscores the need for dedicated primary prevention trials with GLP-1RAs. Such trials would need to enroll a large number of individuals without established CVD and follow them for an extended period to capture sufficient events. Until then, the role of GLP-1RAs in preventing the first cardiovascular event in the general population remains an unanswered question, awaiting more definitive evidence from ongoing or future randomized controlled trials.

CLINICAL IMPLICATIONS

The current data on GLP-1RAs reinforces their established role in secondary cardiovascular prevention for obese patients with existing heart disease. Clinicians should continue to prioritize these agents for individuals who meet the criteria for established CVD, where the evidence of benefit is robust and clear. This is not a class of drugs for everyone, yet.

But the lack of a clear primary prevention signal in the general population means we must temper expectations for broader use. Prescribing GLP-1RAs for individuals without established CVD, solely for primary prevention, lacks strong evidence at this time. The cost-effectiveness and potential side effects in a lower-risk population would need careful consideration.

The industry will undoubtedly push for expanded indications, but the data must support it. Until dedicated primary prevention trials deliver definitive results, the focus for GLP-1RAs should remain on those patients

> who stand to gain the most, those with established cardiovascular disease. We need to see the numbers before we broaden the scope.

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REFERENCES

1. 1. Schrage B, Lackner MK, Hoshiyar A. Emulated Effects of Glucagon-Like Peptide 1 Receptor Agonist Therapy in the General Population. J Am Coll Cardiol 2026;87(1):1-10.

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