GLP-1s: Is eligibility missing half your high-risk patients?

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> GLP-1 receptor agonists are approved for weight loss at a BMI of 30 or above, or 27 and above with a weight-related condition. Below that, at a BMI of 25-26.9, someone is classed as overweight but currently has no route to the drugs, regardless of their actual cardiovascular risk. New data presented at the EASD Annual Meeting in Milan tests whether that cutoff is drawn in the right place.

KEY TAKEAWAYS

- The Pivot: Roughly half of people just below the current GLP-1 weight-loss threshold (BMI 25-26.9) carry cardiovascular risk markers putting them at the same coronary heart disease risk as people who already qualify.
- The Data: Elevated remnant cholesterol plus hsCRP carried HRs of 1.41-1.47 in this group, statistically indistinguishable from the 1.35-1.41 HR seen in people who meet the current indication.
- The Action: The authors call for clinical trials of GLP-1 RAs specifically in this biomarker-defined, currently-ineligible group, this is a case for testing the idea, not evidence the drugs already work here.

Dr Karen Hvid at Copenhagen University Hospital and colleagues combined two prospective cohorts, the Copenhagen General Population Study and the UK Biobank, covering 313,145 people with overweight (BMI ≥25) free of coronary heart disease or diabetes at baseline, followed for more than ten years. GLP-1 RA indication was defined per current criteria: BMI ≥30, or BMI ≥27 with a weight-related comorbidity. Everyone else, including the entire BMI 25-26.9 band, was classified as not indicated.

The same heart risk, without the eligibility

Roughly half of people in the BMI 25.0-26.9 band, currently outside the indication entirely, had elevated remnant cholesterol (≥0.8 mmol/L), elevated hsCRP (≥2 mg/L, a marker of low-grade inflammation), or both. Among the 313,145 participants, 23,134 developed coronary heart disease over follow-up.

People without a GLP-1 indication but with both elevated remnant cholesterol and hsCRP had adjusted hazard ratios for coronary heart disease of 1.41 (95% CI 1.22-1.64) in the Copenhagen cohort and 1.47 (95% CI 1.36-1.60) in UK Biobank, compared with non-indicated people with healthy levels of both markers. For comparison, people who did qualify for GLP-1 RAs under the current indication had hazard ratios of 1.41 (95% CI 1.31-1.51) in Copenhagen and 1.35 (95% CI 1.30-1.41) in UK Biobank. The risk in the two groups was, in practical terms, the same.

What the authors are, and are not, claiming

Elevated remnant cholesterol alone carried hazard ratios of 1.22 and 1.21 in the two cohorts; elevated hsCRP alone carried 1.39 and 1.28. GLP-1 RAs are already known to lower both biomarkers and reduce cardiovascular events in people who qualify for them, which is the basis for the authors' proposal, not a claim that this population has already been shown to benefit from the drugs. "Our study makes the case for extending the indication to this group. Clinical trials are now needed," said Dr Hvid.

The authors disclose several industry relationships: Dr Hvid reports consultancy for MSD; co-author Børge Nordestgaard reports consultancies or talks for AstraZeneca, Sanofi, Ionis, Amgen, Novartis, Novo Nordisk, Esperion, Lilly, Arrowhead, Marea, MSD and Sobi; a co-author reports a travel grant from Abbott. Some of the study's academic funders are themselves funded by the Novo Nordisk Foundation, Novo Nordisk being a GLP-1 RA manufacturer.

The implications of these findings are substantial for current clinical practice and future guidelines. If the proposed expansion of GLP-1 RA eligibility were adopted, it would significantly broaden the patient population considered for these agents, moving beyond the traditional BMI thresholds to incorporate a more nuanced cardiovascular risk assessment. This shift could lead to earlier intervention in individuals who, despite not meeting current BMI criteria, exhibit a similar cardiovascular risk profile to those who do. Such a strategy aligns with a growing emphasis on personalized medicine, where treatment decisions are guided by an individual's specific risk factors rather than solely by broad demographic or anthropometric measures.

However, the study's observational nature necessitates caution. While the association between elevated remnant cholesterol and hsCRP with increased CHD risk in the non-indicated group is compelling, it does not establish causality or demonstrate that GLP-1 RAs would definitively mitigate this risk in this specific cohort. The authors' call for clinical trials is therefore critical. Such trials would need to be adequately powered, randomized, placebo-controlled, and sufficiently long-term to assess the impact of GLP-1 RAs on hard cardiovascular endpoints (e.g., MACE) in individuals with BMI 25.0-26.9 and elevated biomarkers. Furthermore, these trials would need to consider the cost-effectiveness of expanding GLP-1 RA use to a broader population, given the relatively high cost of these medications.

Another important consideration is the generalizability of these findings. While both the Copenhagen General Population Study and the UK Biobank are large, well-characterized cohorts, they primarily represent populations of European descent. Further research would be needed to determine if these risk associations and potential benefits of GLP-1 RAs extend to diverse ethnic and racial groups, who may have different metabolic profiles and cardiovascular risk factors. Additionally, the study focused on individuals free of coronary heart disease or diabetes at baseline, meaning the findings may not directly apply to patients with pre-existing conditions or those with more complex comorbidities.

Ultimately, this research provides a strong rationale for re-evaluating the current GLP-1 RA eligibility criteria. By highlighting a substantial group of high-risk individuals currently overlooked by existing guidelines, Dr. Hvid and

colleagues have opened a crucial dialogue about optimizing cardiovascular prevention strategies. Clinicians should remain aware of these emerging data, recognizing that a patient's cardiovascular risk extends beyond their BMI, and that biomarkers like remnant cholesterol and hsCRP may serve as valuable indicators for identifying those who could benefit from earlier, more aggressive interventions, pending the results of confirmatory clinical trials.

CLINICAL IMPLICATIONS

This is a biomarker-matching argument, not a treatment trial: it shows a currently-excluded population has comparable baseline cardiovascular risk to an included one, not that GLP-1 RAs would reduce that risk in the excluded group specifically. The authors are explicit that dedicated clinical trials are the necessary next step, not a formality.

The disclosed industry relationships, including consultancy income from multiple GLP-1 RA and cardiovascular drug manufacturers, and academic funders tied to Novo Nordisk's foundation, don't invalidate the epidemiology, but they're relevant context for a study whose conclusion is "this population should be considered for a drug class several of the authors have financial ties to."

As an observational analysis, residual confounding between the biomarker-defined risk groups cannot be excluded, and extending a drug indication on the basis of comparable risk profiles, without an actual outcomes trial in the new population, would be a real departure from how indications are normally expanded.

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REFERENCES

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