UKE Paper of the Month April 2026

Emulated Effects of Glucagon-Like Peptide 1 Receptor Agonist Therapy in the General Population

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ABSTRACT:

Background: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) reduce cardiovascular risk in obese individuals with established cardiovascular disease (CVD), potentially through modulating key risk factors. However, their benefit in primary prevention remains unclear.

Objectives: This study aims to emulate GLP-1RA use for primary prevention by applying risk factor changes observed in the SELECT (Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes) trial to obese individuals at risk of but without established CVD.

Methods: In 610,789 CVD-free individuals from European and North American Global Cardiovascular Risk Consortium cohorts, a model to estimate 10-year incidence of CVD and death from any cause was fitted using prespecified risk factors: body mass index (BMI), glycosylated hemoglobin, systolic blood pressure, high-sensitivity C-reactive protein, and non-high-density-lipoprotein cholesterol. This model was applied to 200,012 individuals from 2 contemporary health examination surveys to emulate GLP-1RA therapy by using sex-stratified, placebo-adjusted changes in the 5 risk factors observed with GLP-1RA therapy in SELECT. Primary analyses included individuals with a BMI ≥27 kg/m2 and a SCORE2 (Systematic Coronary Risk Evaluation 2)-derived baseline risk ≥7.5%. Secondary analyses examined nonobese and lower SCORE2 groups and accounted for reduced compliance.

Results: In the surveys, 21,720 individuals had a BMI ≥27 kg/m2 and a SCORE2-derived baseline risk ≥7.5%. Observed 10-year CVD incidence was 13.82% (95% CI: 11.94%-15.71%). Emulated GLP-1RA therapy lowered projected CVD incidence to 10.83% (95% CI: 9.27%-12.39%), an absolute reduction of 2.99% (95% CI: 2.67%-3.31%) and a relative reduction of 22%. Absolute reductions were larger in men than in women (3.14% [95% CI: 2.82%-3.47%] vs 2.7% [95% CI: 2.23%-3.16%]), with similar potential relative reductions across sexes (21% vs 23%). Modeled risk reductions were attenuated in nonobese and lower SCORE2 groups and diminished further with lower compliance assumptions.

Conclusions: In appropriately selected individuals at high CVD risk, GLP-1RA therapy may complement existing primary prevention strategies, supporting the rationale for future randomized studies.

STATEMENT:

This is the first and largest emulation trial of a targeted pharmacological intervention for the primary prevention of cardiovascular disease in the general population. This opens a whole new chapter of applying pharmaco-driven prevention to high-risk individuals.

BACKGROUND:

This work was performed in the Department of Cardiology at the University Heart Center Hamburg by PD Dr. Benedikt Schrage under leadership from Prof. Dr. Christina Magnussen with crucial input from Prof. Dr. Stefan Blankenberg, Francisco M. Ojeda and Aisouda Hoshiyar.