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ORIGINAL RESEARCH

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/m^2 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/m^2 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. (JACC. 2026;87:2948–2959)

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Cardiovascular disease (CVD) remains the leading cause of death worldwide, making effective prevention an urgent global priority. Primary prevention focuses on targeting 5 modifiable risk factors: hypertension, dyslipidemia, obesity, diabetes, and smoking. Despite public health efforts, these risk factors remain highly prevalent and poorly controlled in the general population.[1,2] Given their association with considerable morbidity and mortality, identifying ways to improve primary prevention is therefore crucial.

In recent years, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as a promising pharmacological strategy for CVD prevention.[3] The SELECT (Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes) trial demonstrated a 20% reduction of major adverse cardiovascular events with semaglutide in individuals with a body mass index (BMI) ≥27 kg/m^2 and established CVD.[4] The cardioprotective effect of GLP-1RA therapy is likely mediated in part through favorable effects on modifiable risk factors, including body weight, glycemic status, blood pressure, lipids, and systemic inflammation. Improvement in risk factors with GLP-1RA suggests that these agents might also have a role in the primary prevention of CVD, although no direct evidence currently supports this approach. Because the large required sample size, associated costs, and lack of exploratory data make a randomized primary prevention trial difficult to conduct, this emulation study provides a pragmatic way to estimate the modeled population-level impact of GLP-1RA therapy. In doing so, it offers complementary insight to existing secondary prevention data and may help to guide the design and prioritization of future trials. By assuming changes in 5 key risk factors based on observations made in the SELECT trial, this study aims to emulate GLP-1RA therapy in SELECT-like individuals from the European and North American cohorts of the Global Cardiovascular Risk Consortium, estimating its potential impact as a primary prevention therapy.

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CVD = cardiovascular disease

GLP-1RA = glucagon-like peptide-1 receptor agonist

HbA_{1c} = glycosylated hemoglobin

HDL = high-density lipoprotein

hsCRP = high-sensitivity C-reactive protein

SCORE2 = Systematic Coronary Risk Evaluation 2

METHODS

EMULATION APPROACH. Emulation of GLP-1RA therapy in a primary prevention setting was conducted as follows (**Figure 1**). First, individual-level data from a large consortium of prospective, population-based studies (Supplemental Table 1) was used to build a statistical model estimating the probability of incident CVD and mortality from 5 prespecified CVD risk factors that were modified by GLP-1RAs in the SELECT trial: body weight (ie, BMI), glycemic status (ie, glycosylated hemoglobin [HbA_{1c}]), hypertension (ie, systolic blood pressure), hyperlipidemia (ie, non-high-density-lipoprotein [HDL] cholesterol), and inflammatory burden (ie, high-sensitivity C-reactive protein [hsCRP]). Non-HDL cholesterol was used instead of low-density-lipoprotein cholesterol because it more comprehensively captures atherogenic lipoproteins and was more widely available, thereby increasing sample size. Variable definitions are given in Supplemental Table 2. Then, the model was used to estimate the probability of incident CVD and mortality under 2 scenarios: a baseline scenario (without GLP-1RA therapy) and a treatment scenario (with emulated GLP-1RA-induced risk factor changes). Because the studies used to develop the statistical

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RESEARCH IN CONTEXT

Current evidence on GLP-1RA for CVD prevention

GLP-1RAs have been shown to reduce major adverse cardiovascular events in high-risk individuals with established CVD and coexisting risk factors such as diabetes and obesity. This positions GLP-1RA as an important pillar of secondary CVD prevention by slowing the progression of established disease. It also raises the question of whether GLP-1RA might have a role in primary CVD prevention by preventing CVD from manifesting in the first place. Unfortunately, randomized trials in primary prevention are complex and challenging, as event rates are relatively low and accrue slowly over long periods, and no study has yet adequately addressed this question.

Why an emulation study?

Emulation studies approximate a randomized controlled trial within an existing, retrospectively analyzed data set. Although they do not provide definitive evidence, they offer a useful approach to address hypotheses that are logistically difficult to test in conventional trials. In the present study, we applied the GLP-1RA–mediated, placebo-adjusted changes in 5 key risk factors observed in the SELECT trial to more than 610,000 CVD-free individuals from European and North American general population cohorts. This approach allowed us to emulate GLP-1RA use in a primary prevention setting rapidly and at a fraction of the cost and time required for a randomized controlled trial.

Implications of this study

This emulation study suggests that GLP-1RA therapy is associated with modeled reductions in cardiovascular risk in a primary prevention setting, particularly when applied to obese individuals at higher baseline CVD risk. Although lifestyle interventions remain the foundation of population-level prevention, pharmacological strategies such as GLP-1RAs may represent a viable adjunct in selected high-risk subgroups. The study provides a pragmatic framework to inform the design of a randomized trial, including sample size calculations across different risk strata.

model may not fully reflect contemporary risk factor distributions, which may have changed over time, the model was then applied to individuals from 2 contemporary health examination surveys. Finally, the difference in event probabilities between the baseline and treatment scenarios was calculated to estimate the potential impact of GLP-1RA therapy.

STUDY POPULATION. For derivation of the risk prediction model, data from individuals without prevalent CVD from European and North American cohorts of the Global Cardiovascular Risk Consortium were pooled and harmonized after obtaining ethical and Institutional Review Board approval. Prevalent CVD was defined as a history of myocardial infarction and ischemic or hemorrhagic stroke plus unstable angina or coronary revascularization depending on availability. Inclusion was further restricted to cohorts with available data on the preselected CVD risk factors. For therapy emulation, data from 2 contemporary health examination surveys (the U.S.-based National Health and Nutrition Examination Survey and the German National Cohort), which provided independent, population-based risk factor distributions, were used.

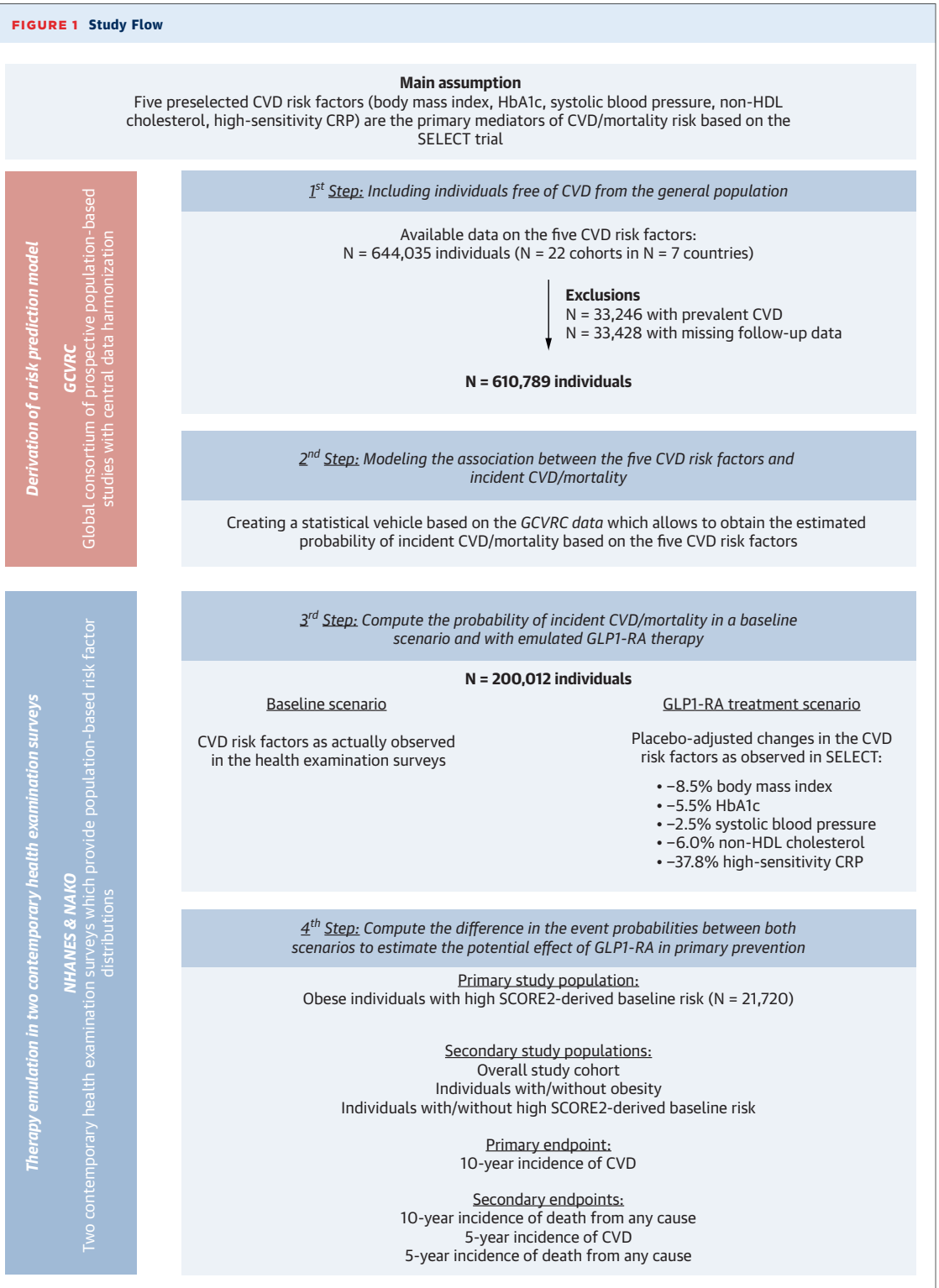
RISK FACTOR AND OUTCOME DEFINITION. BMI, HbA_{1c}, systolic blood pressure, non-HDL cholesterol, hsCRP, smoking status, and prevalent CVD were collected at baseline according to the protocols of the respective studies. Data were harmonized with the use of the variable definitions of the MONICA (Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases) and/or MORGAM (MOnica Risk, Genetics, Archiving and Monograph) projects.[5] Incident CVD was defined as first fatal or nonfatal myocardial infarction or ischemic or hemorrhagic stroke plus unstable angina or coronary revascularization depending on availability or death from a cardiovascular or unknown cause. Endpoint definitions are shown in Supplemental Table 3.

STATISTICAL ANALYSES. For the primary analysis, individuals with obesity (eg, BMI ≥27 kg/m^2) and at high risk of CVD (eg, SCORE2 [Systematic Coronary Risk Evaluation 2]-derived baseline CVD risk ≥7.5%) but without established CVD were subselected, representing a SELECT-like cohort in a primary prevention setting. To evaluate the association between GLP-1RA therapy and the 10-year incidence of CVD and death from any cause in these individuals, it was assumed that GLP-1RA therapy in this setting would produce changes in the preselected key risk factors comparable with those observed in the SELECT trial. To account for the placebo effect, the delta risk factor changes between the GLP-1RA arm and the placebo arm from the SELECT trial were assumed (ie, an 8.5% reduction in BMI, a 5.5% reduction in HbA_{1c}, a 2.5% reduction in systolic blood pressure, a 6.0% reduction in non-HDL cholesterol, and a 37.8% reduction in hsCRP), and all risk factor changes were applied jointly.

In the individual participant data from the Global Cardiovascular Risk Consortium, sex-specific proportional hazards Weibull models, with age as the time scale, were computed for each study, and the parameters were pooled across studies using a 2-stage random-effects multivariate individual participant data meta-analysis.[6] The continuous covariates, BMI, HbA_{1c}, systolic blood pressure, non-HDL cholesterol, and log-transformed hsCRP, were modeled using restricted cubic splines with 4 knots. Smoking status was included as a covariate in the models. Cause-specific Weibull models were used in the case of CVD, treating death before experiencing CVD as a competing event.

The purpose of the estimated models was to apply them to each individual in the 2 health examination surveys to obtain estimated 10-year probabilities of event as a baseline scenario and to emulate GLP-1RA therapy by repeating this computation after modifying each preselected risk factor in the data set assuming the placebo-adjusted risk factor changes observed in the SELECT trial as a treatment scenario.

FIGURE 1 Study Flow



CRP = C-reactive protein; CVD = cardiovascular disease; GCVRC = Global Cardiovascular Risk Consortium; GLP-1RA = glucagon-like peptide 1 receptor agonist; HbA_{1c} = glycosylated hemoglobin; HDL = high-density lipoprotein; NAKO = German National Cohort; NHANES = National Health and Nutrition Examination Survey; SELECT = Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes; SCORE2 = Systematic Coronary Risk Evaluation 2.

The difference between the 10-year probabilities in both scenarios was taken as the estimated effect of GLP-1RAs in a primary prevention setting, and the absolute and relative reductions with GLP-1RAs were calculated accordingly. The emulation of GLP-1RA therapy was performed separately in both health examination surveys individually, followed by a univariate meta-analysis to account for between-survey heterogeneity. A random-effects model was conducted to pool the risk estimates across both health examination surveys.

CIs were obtained through bootstrapping using 1,000 iterations, followed by pooling using the mixmeta package.[7] Computations were performed separately for each sex and both sexes together and, additionally, for obese individuals with a BMI ≥27 kg/m^2 (irrespective of SCORE2), those with a SCORE2-derived CVD risk ≥7.5% (irrespective of BMI) as well as for the overall study cohort (irrespective of both SCORE2 and BMI), and for the outcomes 5-year incidence of CVD or death from any cause, respectively. To account for a potentially lower compliance with GLP-1RA therapy in a real-world population, 3 additional scenarios were modeled in which the risk factor change was only applied to a random sample of 90%, 70%, and 50% of the individuals.

Sample sizes were estimated for a fixed-sample randomized controlled trial with 2 parallel groups and 1:1 randomization using the method of Lakatos.[8] Calculations for the log-rank test were based on the absolute risk estimates with and without GLP-1RA therapy derived from the 2 emulated scenarios, assuming a power of 90%, a 2-sided type I error level of 5%, and a trial duration of 5 years, with no dropout. Statistical analyses were performed with the use of R statistical software, version 4.3.3, and multiple imputation with chained equations was used to handle missing data on the key risk factors.[9] A prespecified analysis plan, a more detailed version of the statistical analysis as well as cohort descriptions are provided in the Supplemental Methods section of the Appendix.

RESULTS

BASELINE CHARACTERISTICS. Overall, 610,789 individuals from 22 cohorts across Europe and North America without CVD at baseline served as the model derivation cohort. The median age was 58.1 years, and 54% were women. Median BMI was 26.7 kg/m^2, HbA_{1c} 5.4%, systolic blood pressure 136 mm Hg, non-HDL cholesterol 4.2 mmol/L, and hsCRP 1.3 mg/L (**Table 1**). Then, 200,012 individuals from 2 contemporary health examination surveys without CVD at baseline served as the emulation cohort. The median age was 45.0 years, and 52.6% were women. Median BMI was 28.4 kg/m^2, HbA_{1c} 5.4%, systolic blood pressure 120 mm Hg, non-HDL cholesterol 3.4 mmol/L, and hsCRP 1.8 mg/L (**Table 2**). In the emulation cohort, 80,663 individuals had a BMI ≥27 kg/m^2, 36,109 individuals had a SCORE2-derived baseline risk ≥7.5%, and 21,720 individuals met both criteria (BMI ≥27 kg/m^2 and a SCORE2-derived baseline risk ≥7.5%), constituting the primary study cohort.

EMULATION OF GLP-1RA THERAPY. The 10-year CVD incidence in individuals with BMI ≥27 kg/m^2 and a SCORE2-derived baseline risk ≥7.5% was estimated at 13.82% (95% CI: 11.94%-15.71%): 12.01% (95% CI: 9.25%-14.76%) in women and 14.86% (95% CI: 12.8%-16.91%) in men. Applying the assumed aggregate risk factor modifications of GLP-1RA therapy was associated with a reduction in CVD risk to 10.83% (95% CI: 9.27%-12.39%), being 9.3% (95% CI: 7.01%-11.58%) in women and 11.71% (95% CI: 9.99%-13.43%) in men; corresponding to an absolute reduction of 2.99% (95% CI: 2.67%-3.31%), which was 2.7% (95% CI: 2.23%-3.16%) in women and 3.14% (95% CI: 2.82%-3.47%) in men; and a relative reduction of 22% (95% CI: 21%-22%), 23% (95% CI: 22%-24%) in women and 21% (95% CI: 21%-22%) in men (**Table 3**).

The 10-year incidence of death from any cause in obese individuals with high CVD risk was estimated at 13.96% (95% CI: 6.38%-21.54%) in the overall study cohort, at 13.02% (95% CI: 6.36-19.68) in women and at 14.63% (95% CI: 6.07%-23.19%) in men. Applying the assumed aggregate risk factor modifications of GLP-1RA was associated with a reduction in mortality incidence to 11.63% overall (10.72% in women, 12.3% in men), corresponding to an absolute reduction of 2.32% (95% CI: 1.19%-3.45%) overall: 2.3% (95% CI: 1.19%-3.41%) in women and 2.32% (95% CI: 1.18%-3.47%) in men (**Table 3**).

The assumed 10-year incidence of CVD and death from any cause with vs without emulated GLP-1RA therapy in different risk groups (eg, obesity and high CVD risk, high CVD risk alone, obesity alone, overall study cohort) is provided in **Figure 2** and Supplemental Tables 4 and 8. Although the modeled absolute reduction was larger in men across all risk strata, relative effects were comparable across sexes.

For the scenarios assuming lower GLP-1RA therapy compliance of 90%, 70%, and 50%, the estimated CVD and mortality incidences, along with the associated reductions, are provided in **Figure 3** and Supplemental Tables 5 to 7 and 9 to 11. Overall, lower therapy compliance was associated with a gradual

TABLE 1 Baseline Characteristics of 610,789 Individuals From the Global Cardiovascular Risk Consortium

	All (N = 610,789)	Missing Data (%)	Women (n = 338,267)	Men (n = 272,522)
No. of cohorts	22		20	22
Survey year range	1989-2021	3	1989-2021	1989-2021
Age, y	57.6 (49.8-63.6)	0	57.4 (49.7-63.4)	58.0 (49.9-64.0)
Body mass index, kg/m^2	26.6 (24.0-29.7)	0.7	26.0 (23.4-29.6)	27.1 (24.9-29.8)
Body mass index ≥27 kg/m^2	281,208 (46.4)	0.7	141,524 (42.1)	139,684 (51.7)
Non-high-density-lipoprotein cholesterol, mmol/L	4.2 (3.5-4.9)	16.3	4.2 (3.5-4.9)	4.2 (3.5-5.0)
Systolic blood pressure, mm Hg	135.5 (123.5-149.0)	0.4	132.5 (120.0-146.5)	138.5 (128.0-151.0)
Diastolic blood pressure, mm Hg	81.5 (75.0-89.0)	0.4	80.0 (73.0-87.0)	83.5 (77.0- 90.5)
High-sensitivity C-reactive protein, mg/L	1.3 (0.7-2.8)	9.8	1.4 (0.6-3.0)	1.3 (0.7-2.5)
Glycosylated hemoglobin, %	5.4 (5.1-5.6)	15.1	5.4 (5.1-5.6)	5.4 (5.1-5.6)
Diabetes	30,355 (5.0)	1.3	13,337 (4.0)	17,018 (6.3)
Current smoking	79,087 (13.1)	1.4	39,117 (11.7)	39,970 (14.9)
Antihypertensive medication	117,500 (19.7)	2.4	59,686 (18.0)	57,814 (21.8)
Lipid-lowering medication	73,963 (13.4)	9.5	32,521 (10.6)	41,442 (16.9)
SCORE2, %	4.4 (2.5-7.0)	0	3.3 (1.8-5.3)	6.1 (3.8-8.7)
SCORE2 <2.5%	154,774 (25.3)		126,739 (37.5)	28,035 (10.3)
SCORE2 2.5% to <7.5%	325,396 (53.3)		177,914 (52.6)	147,482 (54.1)
SCORE2 ≥7.5%	130,619 (21.4)		33,614 (9.9)	97,005 (35.6)

Values are n (%) or median (IQR).
SCORE2 = Systematic Coronary Risk Evaluation 2.

TABLE 2 Baseline Characteristics of 200,012 Individuals From the Health Examination Surveys

	All (N = 200,012)	Missing Data (%)	Women (n = 103,003)	Men (n = 97,009)
No. of cohorts	2		2	2
Survey year range	2014-2019	0	2014-2019	2014-2019
Age, y	45.0 (31.0-59.0)	0	46.0 (32.0-61.0)	43.0 (30.0-58.0)
Body mass index, kg/m^2	28.4 (24.3-33.4)	0.5	28.2 (23.7-33.8)	28.7 (25.0-33.0)
Body mass index ≥27 kg/m^2	118,417 (59.2)	0.5	58,711 (57.0)	59,757 (61.6)
Non-high-density-lipoprotein cholesterol, mmol/L	3.4 (2.7-4.1)	4.6	3.4 (2.7-4.0)	3.5 (2.8-4.2)
Systolic blood pressure, mm Hg	120.0 (111.0-132.0)	0.4	117.0 (117.0-131.0)	122.0 (113.0-132.0)
Diastolic blood pressure, mm Hg	73.0 (65.0-79.0)	0.4	71.0 (64.0-77.0)	74.0 (67.0-82.0)
High-sensitivity C-reactive protein, mg/L	1.8 (0.8-4.1)	39.2	2.1 (0.9-5.1)	1.6 (0.8-3.3)
Glycosylated hemoglobin, %	5.4 (5.2-5.8)	4.6	5.5 (5.2-5.7)	5.4 (5.2-5.8)
Diabetes	17,001 (8.5)	0.3	8,343 (8.1)	8,730 (9.0)
Current smoking	37,002 (18.5)	4.0	15.4	22.0
Antihypertensive medication	20.0	0.1	20.2	19.8
Lipid-lowering medication	33.0	1.3	36.4	30.0
SCORE2, %	2.1 (0.6-5.8)	0	1.6 (0.4-4.8)	2.8 (1.0-6.8)
SCORE2 <2.5%	53.9		61.1	46.9
SCORE2 2.5% to <7.5%	27.2		22.2	32.6
SCORE2 ≥7.5%	18.9		16.7	21.4

Values are n (%) or median (IQR). Sampling weights were used to weight the estimates.
Abbreviation as in Table 1.

TABLE 3 10-Year Incidence of Cardiovascular Disease or Death From Any Cause With vs Without Emulated GLP-1RA Therapy in Obese Individuals With a High SCORE2-derived Baseline Risk

	10-Year Incidence			
	Without GLP-1RA Therapy	With GLP-1RA Therapy	Absolute Risk Reduction	Relative Risk Reduction
Cardiovascular disease				
Overall, %	13.82 (11.94-15.71)	10.83 (9.27-12.39)	2.99 (2.67-3.31)	22 (21-22)
Women, %	12.01 (9.25-14.76)	9.3 (7.01-11.58)	2.7 (2.23-3.16)	23 (22-24)
Men, %	14.86 (12.8-16.91)	11.71 (9.99-13.43)	3.14 (2.82-3.47)	21 (21-22)
Death from any cause				
Overall, %	13.96 (6.38-21.54)	11.63 (5.18-18.09)	2.32 (1.19-3.45)	17 (16-18)
Women, %	13.02 (6.36-19.68)	10.72 (5.17-16.27)	2.3 (1.19-3.41)	18 (18-18)
Men, %	14.63 (6.07-23.19)	12.3 (4.88-19.71)	2.32 (1.18-3.47)	16 (15-18)

Values in parentheses are 95% CIs. Obesity was defined as a body mass index ≥27 kg/m^2, and a high SCORE2-derived baseline risk defined as a SCORE2 ≥7.5%. Event probabilities were calculated based on 21,720 individuals (5,339 women and 16,381 men) with obesity and a high SCORE2-derived baseline risk drawn from 2 contemporary health examination surveys. Numbers were estimated using multiply imputed data.

GLP-1RA = glucagon-like peptide 1 receptor agonist; other abbreviations as in Table 1.

attenuation of both absolute and relative reductions with emulated GLP-1RA therapy. Similarly, restricting the endpoint follow-up to 5 years was associated with a smaller modeled reduction for emulated GLP-1RA therapy (Supplemental Table 12).

SAMPLE SIZE CALCULATION. For a randomized controlled trial with 2 parallel groups testing the hypothesis that GLP-1RA therapy reduces cardiovascular risk in individuals with obesity and a high SCORE2-derived baseline risk but without established CVD, 7,244 individuals (ie, 3,622 per treatment group) would be required. This number increases to 9,095, 15,515, or 29,528 individuals if a lower therapy compliance of 90%, 70%, or 50% was assumed (Table 4).

DISCUSSION

Emulating GLP-1RA therapy in a primary prevention setting yielded the following modeled assumptions. First, GLP-1RA therapy may lower incident CVD and mortality in obese individuals at high risk of but without established CVD. Second, although the absolute reduction appeared to be higher in men, the relative reduction was similar across sexes. Third, both absolute and relative reductions were attenuated in individuals with lower baseline CVD risk, as indicated by absence of obesity or lower SCORE2. Fourth, accounting for lower compliance in a real-world setting and a shorter treatment duration, the modeled reductions were attenuated but the association with lower CVD risk persisted (**Central Illustration**).

Smoking cessation, promotion of physical activity, and healthy nutrition remain the cornerstones of primary CVD prevention at the population level.[10] Drug-based strategies are typically reserved for high-risk individuals with established disease, and broader pharmacological prevention has not been widely implemented. Barriers include public and scientific scepticism as well as generally low compliance with long-term pharmacological treatment among individuals without manifest disease.[11-15] Moreover, primary prevention trials require large sample sizes and extended follow-up, leading to selective enrollment criteria (eg, inclusion of participants with higher baseline risk), which constrain generalizability.

GLP-1RAs present a novel opportunity in this context.[16,17] Largely because of their weight-reducing effects, these agents are increasingly used even among low-risk individuals. Leveraging harmonized data from 22 prospective, population-based cohorts within the Global Cardiovascular Risk Consortium, we applied the placebo-adjusted changes in 5 key risk factors as observed in the SELECT trial: BMI (-8.5%),

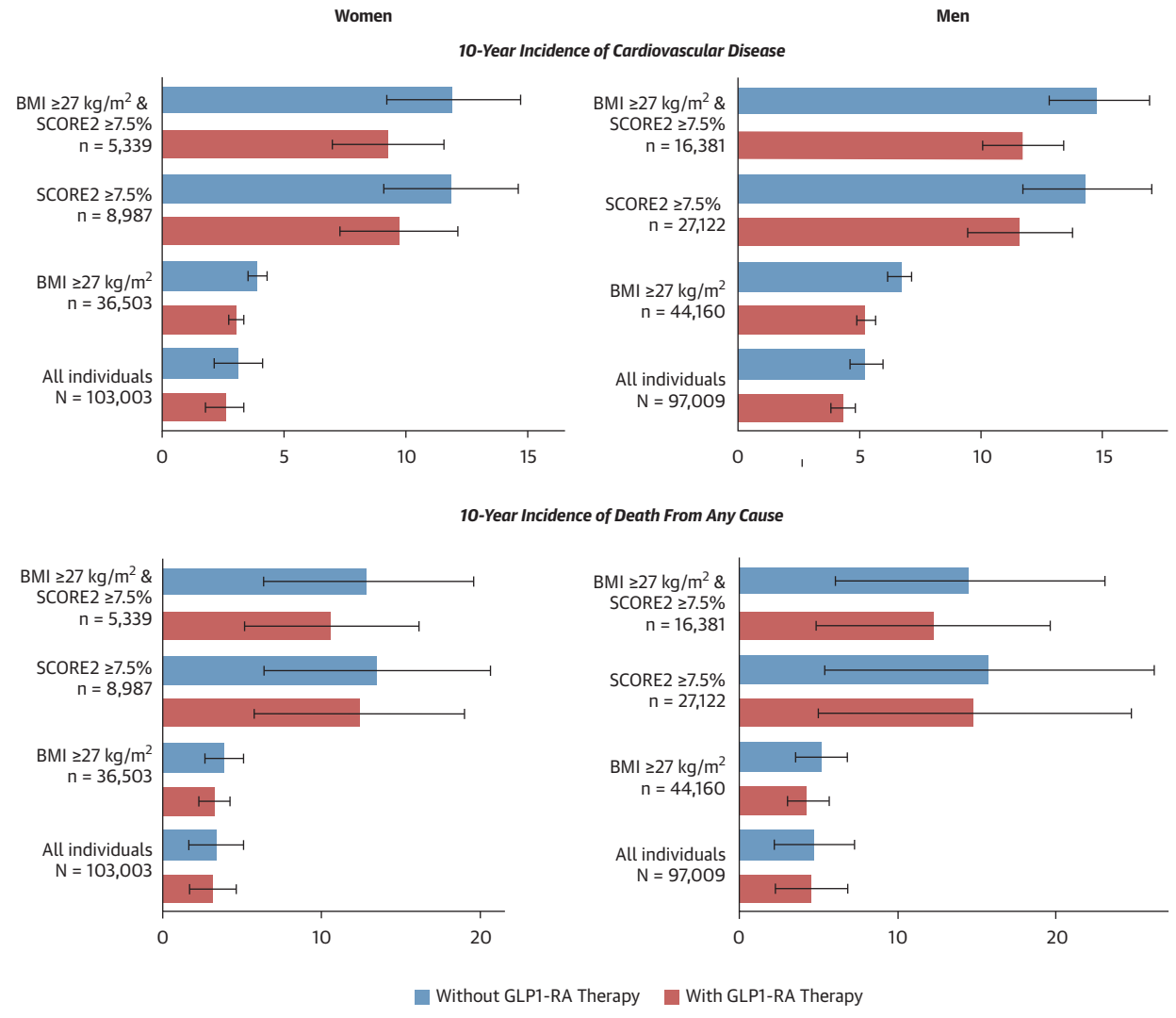
TABLE 4 Power Calculation for a Randomized Controlled Trial Comparing the Effect of GLP-1RA vs Placebo on the Incidence of Cardiovascular Disease at the Population Level in Obese Individuals With a High SCORE2-Derived Baseline Risk and Assuming Different Compliance Scenarios

Therapy Compliance	Sample Size	Expected Number of Events (Placebo Group)	Expected Number of Events (GLP-1RA Group)
100%	7,244	342.4	264.3
90%	9,095	429.8	341.8
70%	15,515	733.3	616.9
50%	29,528	1,395.6	1,233.3

Obesity was defined as a body mass index ≥27 kg/m^2 and a high SCORE2-derived baseline risk was defined as a SCORE2 ≥7.5%. Sample size assumes a 1:1 randomization, power of 90%, 2-sided alpha of 0.05, and enrollment time of 3 years.

Abbreviations as in Tables 1 and 3.

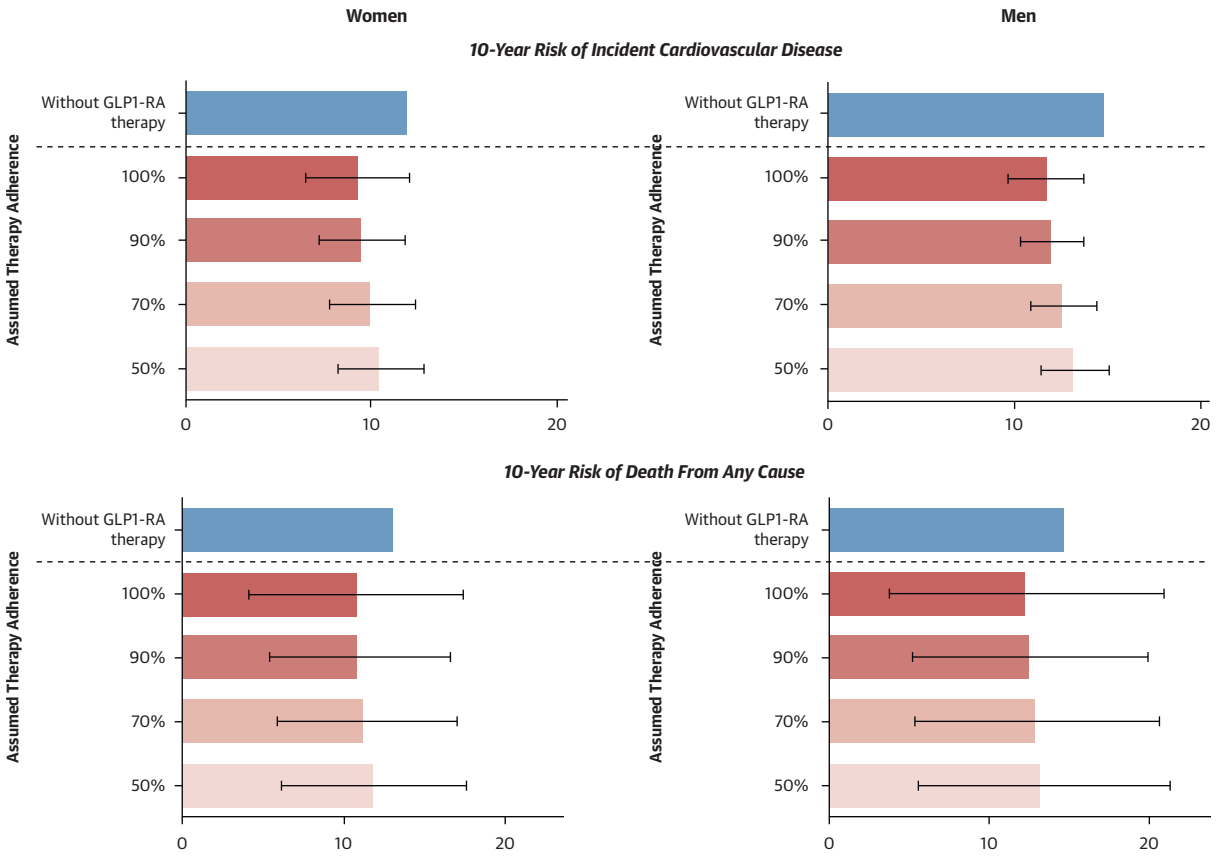
FIGURE 2 **Outcomes Across Different Risk Strata**



Ten-year risk of incident cardiovascular disease and death from any cause in women and men without vs with emulated GLP-1RA therapy across different risk strata, stratified by BMI or SCORE2-derived baseline risk. Event probabilities were calculated based on 2 contemporary health examination surveys with 200,012 individuals, with sample sizes for the individual strata, estimated using multiple imputed data, as shown. BMI = body mass index; other abbreviations as in **Figure 1**.

HbA_{1c} (-5.5%), systolic blood pressure (-2.5%), non-HDL cholesterol (-6.0%), and hsCRP (-37.8%). This study offers initial insights into the potential of GLP-1RA application at the population level, similar to other emulation studies that have transferred the effect of known therapies from 1 indication to another.[18] By targeting multiple key CVD risk factors through a single, widely accepted pharmacological approach, GLP-1RA therapy may provide a viable option for sustained risk reduction, particularly in settings where long-term compliance with lifestyle interventions is difficult to achieve.[19] Translation into clinical practice would require a randomized controlled trial, for which these population-based findings offer a strong rationale, data-driven selection criteria, and testable hypotheses. However, the use of preventive medication in a clinical trial setting also requires careful scientific and ethical considerations of the target population. Although the association between GLP-1RA therapy and a lower relative risk was consistent across the tested strata, the higher absolute risk reduction in obese individuals

FIGURE 3 Outcomes in Different Compliance Scenarios



Ten-year risk of incident cardiovascular disease and death from any cause among 5,339 women and 16,381 men with a body mass index ≥7.5% and a SCORE2-derived baseline risk of ≥7.5% without vs with emulated GLP-1RA therapy assuming different therapy compliance scenarios. Event probabilities were calculated based on 2 contemporary health examination surveys. Numbers were computed after multiple imputation. Abbreviations as in Figure 1.

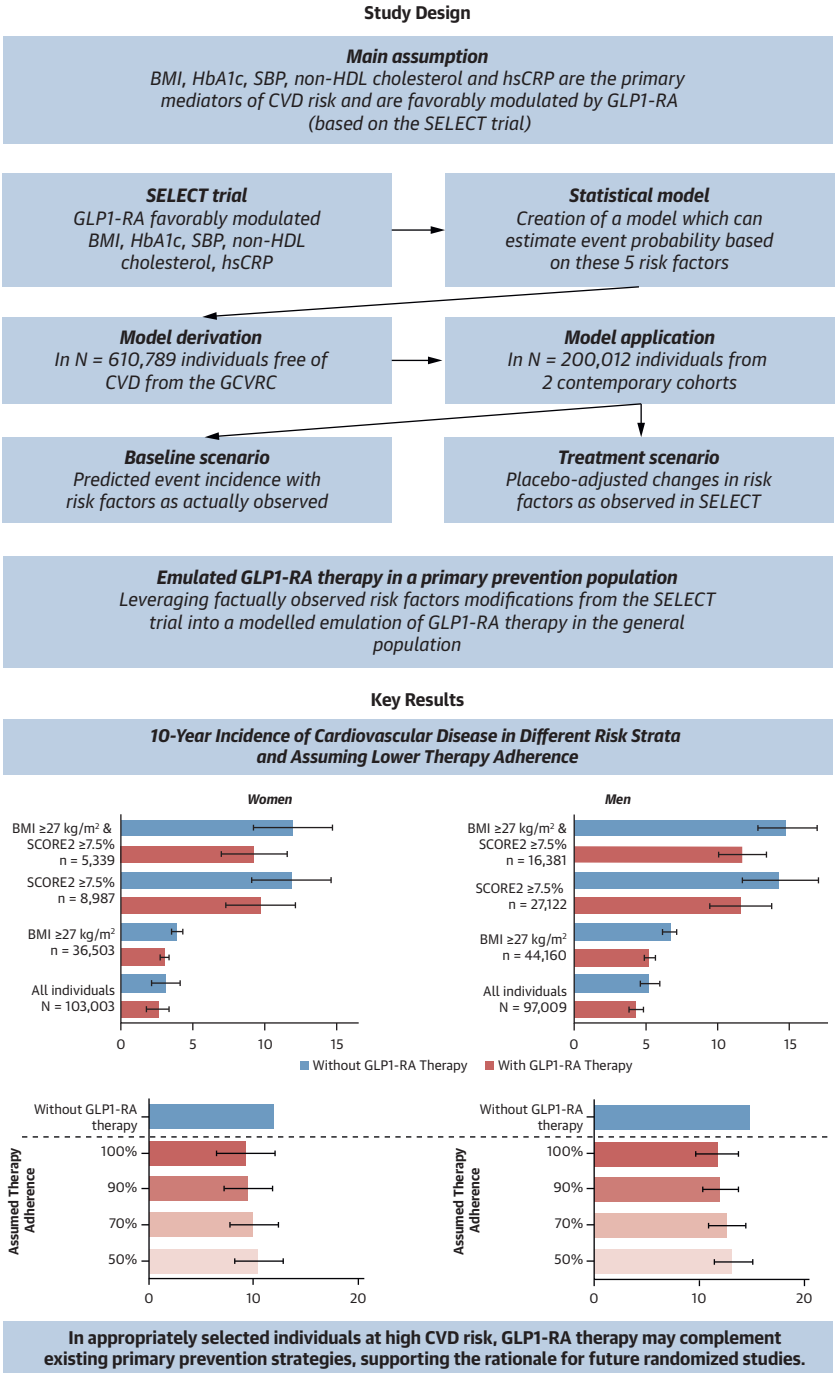
with a higher baseline CVD risk likely demands a primary focus on these high-risk individuals.

STUDY LIMITATIONS. Cohorts within the Global Cardiovascular Risk Consortium vary in representativeness, data completeness, follow-up duration, and endpoint definitions. Although we included the key CVD risk factors, residual confounding from unmeasured variables, such as dietary patterns or socioeconomic status, cannot be excluded and may influence the true treatment effect. The study assumes that GLP-1RA-induced risk factor changes in primary prevention mirror those observed in secondary prevention, which may not be the case. Smaller effects in a primary prevention population could translate into proportionally smaller risk reductions. Also, the assumption that short-term risk factor changes induced by drug therapy confer the same benefit as never having had those risk factors is probably not true.

The cardiovascular benefits of GLP-1RAs appear to be pleiotropic and may extend beyond the 5 key CVD risk factors modeled in our analysis, for example, through endothelial, myocardial, or renal effects. These potential pathways were not incorporated in the analysis and could, if included, alter results.

The main assumptions for this study were derived from the SELECT trial, which tested the GLP1-RA semaglutide; therefore, the results may not be generalizable to other GLP-1RAs. Several factors influence therapy compliance in real-world settings, including coexisting diseases, treatment side effects, and changes in health behaviors or functional status. Although we conducted sensitivity analyses assuming a less than optimal GLP-1RA compliance, this might still underestimate this effect. Indeed, adverse drug events might even lead to an increased morbidity and mortality risk in very low risk subpopulations.

CENTRAL ILLUSTRATION Emulated Effects of GLP1-RA in the General Population



Schrage B, et al. JACC. 2026;87(21):2948-2959.

BMI = body mass index; CRP: C = reactive protein; CVD = cardiovascular disease; GLP1-RA = glucagon-like peptide 1 receptor agonist; GCVRC = Global Cardiovascular Risk Consortium; SBP = systolic blood pressure; SELECT = Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes.

The observation periods for the endpoints in this study (5 and 10 years) exceed the lag-to-benefit observed with GLP-1RAs in the SELECT trial (<1 year). We therefore did not model biological latency in our emulation, which may lead to an overestimation of GLP-1RA–mediated risk reduction in the primary prevention setting. Most importantly, the assumption that changes in the 5 selected risk factors fully mediate the benefit of GLP-1RAs is unproven, and even modifying these factors alone does not necessarily translate into proportionally greater risk reduction. A recent meta-regression analysis among adults with type 2 diabetes mellitus in placebo-controlled GLP-1RA outcome trials suggested that only HbA_{1c}, but not BMI, was proportionally associated with CVD risk reduction.[20] Ultimately, although this emulation study uses extensively harmonized data, well-known risk factors, and multiple secondary and sensitivity analyses to combine real-world data from population-based cohorts with risk modeling derived from a randomized controlled secondary prevention trial, it may not replace such a randomized controlled trial in a primary prevention setting but only foster its design and conduction.

CONCLUSIONS

This emulation study suggests that GLP-1RAs are associated with lower CVD risk in a primary prevention setting. Notably, this benefit appears to be concentrated among appropriately selected individuals at high baseline cardiovascular risk, underscoring the importance of careful patient stratification in real-world clinical practice. These findings support the potential role of GLP-1RA therapy not only as a glucose-lowering intervention, but also as a preventive strategy for cardiovascular risk modification in the community and should therefore be validated in carefully designed randomized controlled trials.

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KEY WORDS GLP-1 RA, population health, primary prevention, risk factor modulation

APPENDIX For a complete list of study collaborators, an expanded methods section, and supplemental tables, please see the online version of this paper.