Effect of PCSK9 Inhibitors on Coronary Artery Disease Progression


Study Overview

Objective. To determine if evolocumab, a PCSK9 inhibitor, affects the progression of coronary artery disease in patients treated with statins.

Design. Multicenter, international, double-blind, placebo-controlled, randomized clinical trial.

Setting and participants. 197 community and academic hospitals worldwide enrolled 978 participants who underwent serial intravascular ultrasounds (IVUS) to measure their burden of coronary atherosclerosis. A total of 2628 patients were screened. Patients were considered for inclusion if they were 18 years of age or older and had at least 1 coronary artery stenosis of at least 20% on a clinically indicated catheterization. Additionally, the target vessel had to meet IVUS imaging quality and visibility standards. Participants were required to have been on stable statin therapy for at least 4 weeks with an LDL level of ≥ 80 mg/dL or between 60–80 mg/dL with either 1 major or 3 minor cardiovascular risk factors. Major risk factors were noncoronary atherosclerotic disease, myocardial infarction (MI) or hospitalization for unstable angina within the past 2 years, or type 2 diabetes. Minor risk factors included current tobacco use, hypertension, low HDL-C levels, family history of early coronary disease, hsCRP level of 2 mg/L or greater, and age older than 50 years for men and 55 years for women. Patients with uncontrolled hypertension, uncontrolled diabetes, heart failure, renal insufficiency, or liver disease were excluded.

Intervention. Patients were randomized to either treatment with monthly subcutaneous injections of 420 mg evolocumab or placebo injections for 76 weeks. Participants attended 7 follow-up visits during the study period and then underwent repeat IVUS imaging at the 78th week. Research staff, who were blinded to both treatment status and imaging sequence, collected and assessed target vessel measurements, including the vessel lumen and external elastic membrane dimensions. IVUS imaging has been used in numerous clinical studies and has been shown to be accurate and reliable [1].

Main outcome measures. The primary outcome was the target artery change in percent atheroma volume (PAV) from baseline to week 78. PAV was calculated from IVUS measurements. Nominal change in PAV was then determined by calculating the difference of the PAV at baseline and at week 78.

The secondary measure was the normalized total atheroma volume (TAV). TAV addresses variability in the length of vessel segments and the number of images
collected during IVUS catheter pullback. The nominal change in TAV was then determined by the difference at baseline and at week 78.

Additional secondary efficacy endpoints included number of patients with regression of plaque and change in lipid parameters. Safety outcomes were investigated through evaluation of the incidence of adjudicated clinical events, including all-cause mortality, cardiovascular death, MI, unstable angina requiring hospitalization, coronary revascularization, stroke, transient ischemic attack, and heart failure requiring hospitalization. Post-hoc analysis compared baseline LDL-C level and change in PAV and regression of PAV. The association between LDL lowering and plaque progression was also assessed post hoc.

IVUS measurements were evaluated as least squares means. Comparison of treatment groups was conducted using analysis of covariance on rank transformed data that accounted for baseline value and geographic location. Investigators used a step-down statistical procedure to evaluate primary and secondary endpoints. The statistical model accounted for confounders such as baseline LDL-C, baseline PAV, intensity of statin therapy, geographic region, age, and sex.

Main results. 484 participants were randomized to the evolocumab group and 484 to the placebo group, and 423 participants in both groups completed both baseline and follow-up IVUS imaging. Treatment and control groups contained participants matched for age, gender, ethnicity, cardiovascular risk factors, and baseline medication use, including lipid-lowering agents, ACE inhibitors, ARBs, beta-blockers, and antiplatelet therapies. Both groups consisted of a majority of white (93.4% in placebo and 94.2% in treatment) males (72.3% in placebo and 72.1% in treatment). Approximately 20% of participants had hypertension (83.7% in placebo and 82.2% in treatment), about 35% had prior MIs (35.3% in placebo and 34.9% in treatment), and roughly a fifth of participants had diabetes (21.5% in placebo and 20.2% in treatment). At baseline 98.6% of participants were treated with statins, with 58.9% on high-intensity therapy and 39.4% on moderate-intensity. Mean LDL-C level at baseline was 92.5 (SD, 27.2) mg/dL.

After 76 weeks of treatment, mean LDL-C level in the placebo group was 93.0 mg/dL and 36.6 mg/dL in the treatment group, which corresponds to a 0.2 mg/dL increase in the placebo group and a 56.3 mg/dL reduction in the treatment group. The change in LDL-C level was statistically significant (P < 0.001).

Placebo group participants had no significant change in PAV (0.05%, P = 0.78), but the evolocumab group experienced a 0.95% decrease from baseline (P < 0.001). Similarly, the placebo group had no change in TAV from baseline (–0.9 mm², P = 0.45), but the treatment group had a 5.8 mm² reduction in TAV from baseline (P < 0.001). The treatment group had a greater proportion of patients who experienced PAV regression (64.3% vs. 47.3%, P < 0.001) and TAV regression (61.5% vs. 48.9%, P < 0.001).

Subgroup analysis did not demonstrate a significant association between change in PAV and specific study participant characteristics (eg, age, gender, ethnicity).

Post-hoc analysis using local regression (LOESS) curve revealed a linear relationship between achieved LDL-C level and change in PAV for LDL-C levels from 110 mg/dL to 20 mg/dL.

The treatment group did not exhibit a significant increase in adverse drug events, which included injection site reactions, myalgias, neurocognitive events, and incidence of diabetes. There was no significant difference in adverse cardiovascular outcomes between groups; however, there were numerically fewer nonfatal MIs and coronary revascularizations in the treatment group.

Conclusion. The use of evolocumab in statin-treated patients resulted in greater reduction of PAV than use of statins alone.

Commentary

Evolocumab is a monoclonal antibody that inhibits proprotein convertase subtilisin-kexin type 9 (PCSK9), which is involved in LDL-C receptor recycling. By reducing removal of LDL-C receptors, evolocumab amplifies LDL-C clearance and has been shown to reduce LDL-C levels by approximately 61% from baseline with 12 weeks of treatment [2]. Studies have shown that the lipid-lowering potential of evolocumab is superior to statins alone and to combination therapy with statins and ezetimibe [2]. Furthermore, PCSK9 inhibitors have been effective at LDL-lowering in patients who failed or could not tolerate standard of care therapy with statins and ezetimibe [3,4]. PCSK9 inhibitors hold great promise for reducing morbidity and mortality of cardiovascular disease; however, LDL-lowering is not equivalent to improved clinical outcomes.
The GLAGOV study moves toward demonstration of the clinical benefit of evolocumab. The study shows that combined therapy with statins and evolocumab, versus statins alone, not only achieves better stability of atherosclerotic plaque dimensions but actually results in regression of plaque size. In the study, plaque burden is extrapolated from vessel measurements obtained through IVUS, and nominal changes in PAV and TAV serve as markers for atherosclerosis, but these surrogates cannot be equated to a reduction in cardiovascular events. The GLAGOV trial does explore clinical outcomes such as MI, stroke, unstable angina, coronary revascularization, and death; however, the study is not powered to evaluate the statistical significance of these events. We await sufficiently powered phase 3 clinical trials to determine the clinical benefits of PCSK9 inhibitors on cardiovascular disease.

The GLAGOV trial has several strengths, including its design as an international, double-blind, placebo-controlled, randomized clinical trial. The intervention is simple and the outcomes are clearly defined. The statistical assessment yields significant results. Nonetheless, there are multiple limitations to the study. The lead author has received research support from Amgen, the maker of evolocumab. Amgen also participated in study design and maintenance of trial databases; however, data analysis was conducted by an independent statistician. Additionally, the majority of study participants were white males with very few minority patients despite inclusion of study sites around the globe. The homogeneity of the study cohort makes the data difficult to generalize to a larger population. Similarly, patients who lacked a clinical indication for coronary catheterization and those with uncontrolled diabetes, hypertension, and heart failure were excluded, which further limits application of this study to many patients with atherosclerosis. Another limitation is study attrition; only 87% of participants completed the 78-week IVUS and were included in the data analysis, and results may have differed if those lost to follow-up had completed the trial. Furthermore, study duration was limited to 76 weeks and the magnitude and durability of study outcomes after this time point remain unknown.

**Applications for Clinical Practice**

Reduction in PAV and TAV are surrogate endpoints and are not indicative of a clinical benefit. Nonetheless, the GLAGOV study demonstrates that evolocumab, when used in conjunction with statins, can promote regression of atherosclerosis greater than treatment with statins alone. More studies are needed to evaluate a clinical benefit of adding evolocumab to the regularly used arsenal of lipid-lowering therapies for the treatment of atherosclerosis. Furthermore, cost-effectiveness of evolocumab has not been shown. In 2015 the yearly wholesale price of evolocumab was $14,350. A cost-effectiveness analysis based on this price estimates that treatment of atherosclerotic coronary vascular disease with evolocumab has a cost of $414,000 per quality-adjusted life year [5]. Evolocumab is well tolerated, but additional studies for cardiovascular and mortality outcomes are needed before it can be considered part of the standard of treatment for coronary artery disease.

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**References**

Are There Racial/Ethnic Differences in Weight-Related Care Encounters Reported by Patients?


Study Overview

Objective. To compare patients’ health care experiences related to their weight across racial and ethnic groups.


Setting and participants. Between March and July 2015, 5400 individuals were randomly sampled from the Patient Outcomes to Advance Learning (PORTAL) obesity cohort, which includes over 5 million adults. The PORTAL network is a clinical data research network funded by the Patient Centered Outcomes Research Institute to promote collaboration across several large health systems with electronic medical records (EMRs), including all the Kaiser Permanente regions, Group Health Cooperative, Health Partners, and Denver Health. The selected 5400 cohort members were equally distributed across 3 geographically diverse Kaiser Permanente regions (Southwest, Northern and Southern California, Hawaii, Colorado, and Northwest) and Denver sites. Selected individuals were non-pregnant English or Spanish speakers with a body mass index (BMI) ≥ 25 kg/m² (per their EMR) who were members of a participating health plan and had at least 1 outpatient visit in the last 12 months. Patients with BMI ≥ 40 kg/m² were oversampled. Individuals were mailed a written 10-minute survey (offered in English or Spanish based on a patient's written language preference noted in their EMR), consisting of 36 multiple-choice and fill-in-the-blank items. Telephone contact for verbal administration was attempted if a mailed response was not received within 4 weeks.

Main measures and analysis. The primary independent variable was a respondent’s racial/ethnic group, categorized as (1) non-Hispanic white (White), (2) non-Hispanic black (Black), (3) Hispanic, (4) Asian, or (5) Native Hawaiian/Other Pacific Islanders/American Indian/Native Alaskan (NA/PI).

Dependent variables focused on patients’ perceptions of the health care experience (based on services received at their usual place of care from their primary care providers) related to being overweight or obese using items based on the Rudd Center’s Patient Survey of Weight-Sensitive Healthcare Practices. Respondents described (1) whether and how often they avoid coming to their provider because they do not want to be weighed or have a discussion about their weight; (2) how often does their provider ask their permission before discussing their weight; (3) how often has their provider been supportive of their weight concerns and efforts to be healthy; (4) whether they think that their provider understands the physical and emotional challenges faced by individuals who are overweight or obese; (5) how often has their provider brought up their weight during a clinic visit; (6) whether their provider has ever given or discussed resources on healthy eating and weight loss; and (7) what types of weight loss resources were discussed with their provider and which types did they want more information about (ie, dietary changes, physical activity, classes, medications, meal replacements, and bariatric surgery). Covariate variables derived from EMR data included sex, age category, diabetes, hypertension, Charlson Index score (overall measures of morbidity), Medicaid enrollment, language preferences, site, and BMI. Survey-derived covariate variables included emotional well-being, perceived weight status, and educational attainment.

Descriptive statistics were generated and compared across racial/ethnic groups using Kruskal-Wallis and chi-square testing, as appropriate. To evaluate the association between a patient’s race/ethnicity and their perceived weight management experience, multinomial logistic regression adjusted for covariates was used to estimate odds ratios (OR).

Main results. From the original sample (n = 5400), 1569 individuals (29%) did not respond, 925 (17%) refused, and 114 (2%) were ineligible, leaving an eligible sample
pool of 5286 individuals. The overall response rate was 53% (2197 written; 614 phone, n = 2811). Those with missing data were excluded (6 with missing race/ethnicity; 80 missing other covariates), leaving a final group of 2725 respondents for analysis. Mean age was 52.7 years (SD 15), almost 62% of participants were female, 51.7% identified as White, 21.1% identified as Black, 14.6% identified as Hispanic, 6.7% identified as NA/PI. About a quarter (24.4%) had diabetes, less than half (43.5%) had hypertension, and most (86.2%) perceived themselves to be overweight. There were significant differences in measured baseline covariates by racial/ethnic groups including mean BMI, diabetes, and being a Medicaid beneficiary.

In response to the 7 key areas assessed regarding patients’ perceptions of the health care experience related to being overweight or obese:

• Black respondents were less likely than Whites to report that they frequently avoided care from their provider because they did not want to be weighed or discuss their weight (OR 0.49 [95% confidence interval, 0.26–0.90]), with a trend toward all groups being less likely to report frequent avoidance compared to Whites.

• While just over half of respondents (59.3%) indicated that their providers never asked for their permission before discussing their weight, Asians and NA/PI were more likely to report that their providers either frequently (Asians: OR 2.7 [1.3–5.6]; NA/PI: OR 2.3 [1.1–5.0]) or sometimes (Asians: OR 2.3 [1.2–4.3]; NA/PI: OR 2.1 [1.1–4.1]) asked their permission before discussing their weight compared to Whites.

• Over half (61.9%) indicated that their providers were sometimes or frequently supportive of their weight concerns, with no significant differences among racial/ethnic groups.

• Just over half (52.0%) indicated they felt their providers understood the physical and emotional challenges faced by people who are overweight/obese, with Blacks more likely to feel this way (OR 1.8 [1.2–2.8]) compared to Whites.

• Black patients were more likely than Whites (OR 2.0 [1.4–2.8]) to report that their providers discussed their weight with them at a clinic visit.

• While over half (59.7%) indicated that their providers had given or discussed resources with them on healthy eating and weight loss, Black and Asian respondents were more likely than Whites to recall these discussions (Black: OR 1.6 [1.2–2.1]; Asians: OR 1.8 [1.1–2.9]).

• Most weight loss resources or recommendations received were related to lifestyle changes, with very few resources given related to weight loss medications, meal replacement products, or bariatric surgery—few differences across racial/ethnic groups were identified. However, respondents from racial/ethnic minority groups were more likely than Whites to say that they wanted more information about lifestyle changes, classes, and meal replacements. Other than Blacks, all other racial/ethnic groups were also more likely than Whites to indicate that they wanted more information about bariatric surgery.

Conclusions. Most patients across racial/ethnic groups are having positive experiences with weight-related care. However, race/ethnicity correlates with patients’ perception of weight-related care and discussions in clinic encounters.

Commentary
The obesity epidemic in the United States is well-established [1], and recent data from 2014 show that over 37% of adults in the US are obese (defined as having a body mass index greater than 30 kg/m²) [2]. However, while obesity prevalence rates have increased over the past several decades across all genders, ethnicities, income levels, and education levels, important racial/ethnic disparities exist [2,3]. Primary care physicians (PCPs) are ideally situated to promote weight loss via effective obesity counseling since multiple clinic visits over time have the potential to enable rapport building and behavioral change management [4]. In fact, the US Preventive Services Task Force (USPTF) recommends that all patients be screened for obesity and offered intensive lifestyle counseling, as modest weight loss can have significant health benefits [5]. However, some studies have found racial/ethnic differences and disparities in weight-related diagnoses, counseling, and treatment by providers, but also patient perceptions of care and preferred interventions [6–10]. Other studies have described racial/ethnic differences in weight-related concerns and behaviors, body satisfaction, and body image [11–13]. Thus, research is needed to examine these differences.
This cross-sectional study contributes to the limited literature examining the potential for heterogeneity of care according to patient characteristics like race and ethnicity. Key strengths of the design include a large and both geographically and racially/ethnically diverse sample of patients (increased generalizability), the use of mailed brief surveys (reduces non-response rate and reporting bias) and telephone follow-up for verbal administration (reduces non-response rate, though it increases interviewer bias), oversampling of respondents with BMI ≥ 40 kg/m², and the controlling of key covariates including sex, age, Medicaid enrollment, site, and BMI.

However, there are several important limitations, many of which are acknowledged by the authors. While respondents were overall representative of the targeted sample population, the final respondent population was comprised of mostly older females who received managed care, which may have contributed to selection bias and impacted generalizability of findings. Further, Whites were overrepresented, Hispanics were underrepresented, and the small combined sample of NA/PI may have masked important distinctions between these subpopulations. Importantly, this study only provided the survey in English and Spanish and did not include other language translations (eg, Chinese, Japanese, Tagalog), which likely contributed to underrepresented perspectives of immigrants and ESL patients who may struggle with receiving/discussing weight management counseling and resources. The use of a surveys collected subjective and self-reported data on patient encounters as opposed to objective observations. Lastly, the study did not adjust for individual provider factors or assess the potential impact of provider-level differences on care, such as provider-patient concordance on race, ethnicity, language, and/or weight. The incorporation of qualitative interviewers or focus groups with a subsample of each racial/ethnic may have also provided relevant context to understand differences in weight-related care experiences.

Applications for Clinical Practice
As the authors suggest, this study highlights several opportunities to continue improving weight-related care and weight management counseling. PCPs should engage all overweight/obese patients in weight management discussions, and in particular, high-risk minority patients who may desire these conversations and more weight loss advice and resources. However, these discussions require sensitivity and can benefit from the simple practice of asking permission of the patient to talk about their weight in order to reduce care avoidance and improve perceptions of care. Providers should also be mindful of patient priorities and assess patient preferences for all the different weight loss strategies, including lifestyle changes, meal replacements, medications, and surgery.

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References