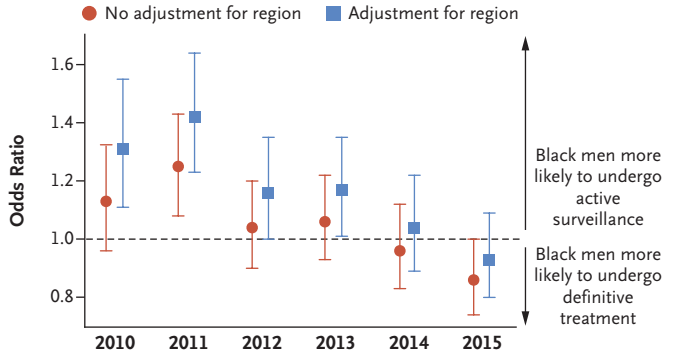

Figure 1. Odds of Undergoing Active Surveillance for Low-Risk Prostate Cancer among Black Men, as Compared with Men of Other Races.

Shown are the adjusted odds of undergoing active surveillance or definitive treatment (radiation therapy or radical prostatectomy) for low-risk prostate cancer (defined as a prostate-specific antigen level of <10 ng per milliliter, a clinical stage of T1 to T2a, and a Gleason score of 6) among black men, as compared with men of other races, with or without adjustment for geographic region during the period from 2010 through 2015. I bars indicate 95% confidence intervals.

effect on the selection of active surveillance as compared with definitive treatment. Given the presence of such confounding factors, further study is needed to ascertain the true effect of geography and race on the choice of management for low-risk prostate cancer in the United States.

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Volanesorsen, Familial Chylomicronemia Syndrome, and Thrombocytopenia

TO THE EDITOR: In the APPROACH trial (Aug. 8 issue),[1] volanesorsen — an antisense oligonucleotide targeting *APOC3* messenger RNA — reduced circulating triglycerides in patients with familial chylomicronemia syndrome, but thrombocytopenia developed in 76% of treated patients. This unexpected adverse event raises a key question regarding inhibition of apolipoprotein C-III synthesis as a therapeutic strategy: is thrombocytopenia an on-target effect of reduced apolipoprotein C-III activity or an off-target effect of volanesorsen?

We therefore asked whether heterozygous carriers of an inactivating mutation in *APOC3* are at increased risk for thrombocytopenia. Among 42,503 participants in the UK Biobank, 235 (0.6%) were found to carry any of four previously described inactivating mutations in *APOC3*.[2] As expected, carriers had significantly lower levels of triglycerides than noncarriers (median, 71 mg per deciliter and 129 mg per deciliter, respectively; P<0.001), as well as a lower risk of hypertriglyceridemia (odds ratio, 0.05; 95% CI, 0.03 to 0.11; P<0.001) (Fig. 1A and 1B). We found no significant difference between carriers and noncarriers in platelet count (median, 239,000 and 238,000 per microliter, respectively; P=0.21) or in the prevalence of thrombocytopenia (1.3% and 1.8%, respectively; P=0.63) (Fig. 1C and 1D). These results suggest that the effect of volanesorsen is medication- or class-specific rather than an inherent property of apolipoprotein C-III inhibition.

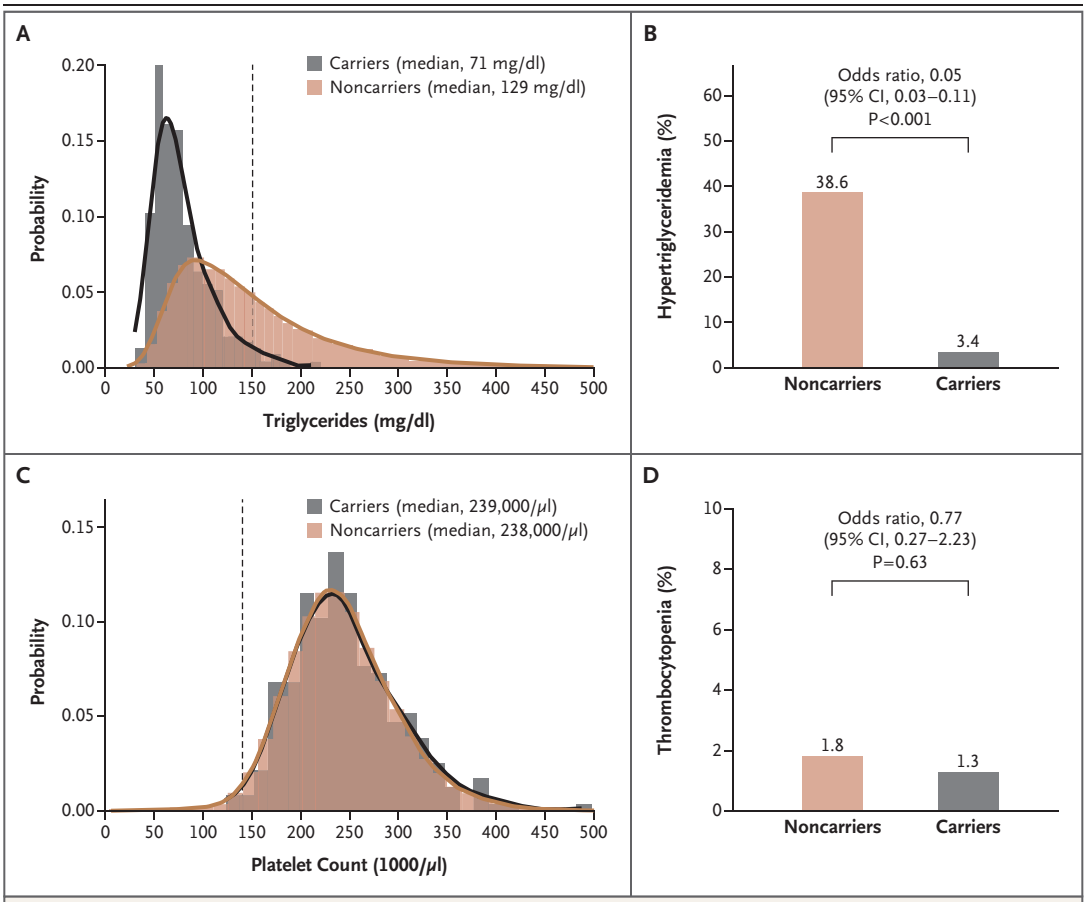

Figure 1. Inactivating Mutations in *APOC3* and the Risk of Hypertriglyceridemia or Thrombocytopenia.

Gene sequencing of specimens from 42,503 participants in the UK Biobank identified an inactivating mutation in *APOC3* in 235 (0.6%). Panel A shows the distribution of triglyceride levels in carriers and noncarriers. The vertical dashed line indicates a triglyceride level of 150 mg per deciliter, the cutoff value for hypertriglyceridemia. Panel B shows the percentage of participants with hypertriglyceridemia. In a logistic-regression model with adjustment for age, sex, fasting duration at time of blood collection, and genetic ancestry, carriers had a significantly lower risk of hypertriglyceridemia than noncarriers. Panel C shows the distribution of platelet counts in carriers and noncarriers. In a linear regression model with adjustment for age, sex, fasting duration at time of blood collection, and genetic ancestry, there was no significant difference in platelet counts between carriers and noncarriers. The vertical dashed line indicates 140,000 per microliter, the cutoff value for thrombocytopenia. Panel D shows the percentage of participants with thrombocytopenia. In a logistic-regression model with adjustment for age, sex, fasting duration at time of blood collection, and genetic ancestry, there was no evidence of a higher risk of thrombocytopenia among carriers than among noncarriers. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129.

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THE AUTHORS REPLY: We previously conducted a thorough database assessment and found no antisense oligonucleotide class–specific effect on platelets.[1] Patients with familial chylomicronemia syndrome, who often have triglyceride levels greater than 2000 mg per deciliter, have an increased incidence of both thrombocytopenia and thrombocytosis.[2] As noted by Khetarpal and colleagues, in the APPROACH trial, thrombocytopenia developed in 24% of participants with familial chylomicronemia syndrome who received placebo and in 76% of those who received volanesorsen, suggesting that there was a volanesorsen–disease interaction in the trial participants, an effect we have not seen to this degree in other populations who have received the same dose (unpublished data). Thrombocytopenia is dose-dependent, and core management of familial chylomicronemia syndrome in patients who receive volanesorsen includes monitoring for this effect and early intervention to mitigate and maintain patients on treatment. We are currently investigating a galactosamine-conjugated *APOC3* oligonucleotide that, in a phase 1–2a study conducted over the course of 3 months, achieved similar levels of triglyceride reduction at lower doses, with no reported changes in platelet counts.[3]

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Since publication of their article, the authors report no further potential conflict of interest.

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Gender Parity in Clinical PrEP Trials

TO THE EDITOR: The Perspective article by Goldstein and Walensky (in this issue of the *Journal*; originally published online on Oct. 30)[1] addresses the approval by the Food and Drug Administration (FDA) of a new human immunodeficiency virus (HIV)–prevention indication for emtricitabine and tenofovir alafenamide (F/TAF) that unfortunately excludes cisgender (nontransgender) women because of a lack of clinical data. Approval was based on a single noninferiority trial, DISCOVER, that compared F/TAF with emtricitabine and tenofovir disoproxil fumarate (F/TDF), primarily in men who have sex with men. When DISCOVER was designed, the FDA encouraged the sponsor to conduct a second trial involving women.[2] DISCOVER excluded women because of a lack of consensus among stakeholders regarding a scientifically rigorous design to assess efficacy in women in the era of F/TDF, not because of a lack of forethought or disregard for diversity. A noninferiority trial such as DISCOVER that used F/TDF as a control in women was not considered to be scientifically appropriate because previous trials had not shown a consistently positive treatment effect of F/TDF in women[3]; constancy of a control's treatment effect is necessary to justify the noninferiority margin and to ensure an interpretable study result.[4] Other designs, such as superiority to placebo or to F/TDF, were considered to be unethical or unlikely to succeed, respectively. In fact, although F/TAF was found to be noninferior to F/TDF in DISCOVER, it was not superior.

Going forward, the sponsor will conduct a trial involving women in high-incidence settings with a primary efficacy comparison between women receiving F/TAF and two external control groups (without F/TDF).[5] Although the trial will