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Volanesorsen, Familial Chylomicronemia Syndrome, and Thrombocytopenia

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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.

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Drs. Khetarpal and Wang contributed equally to this letter.

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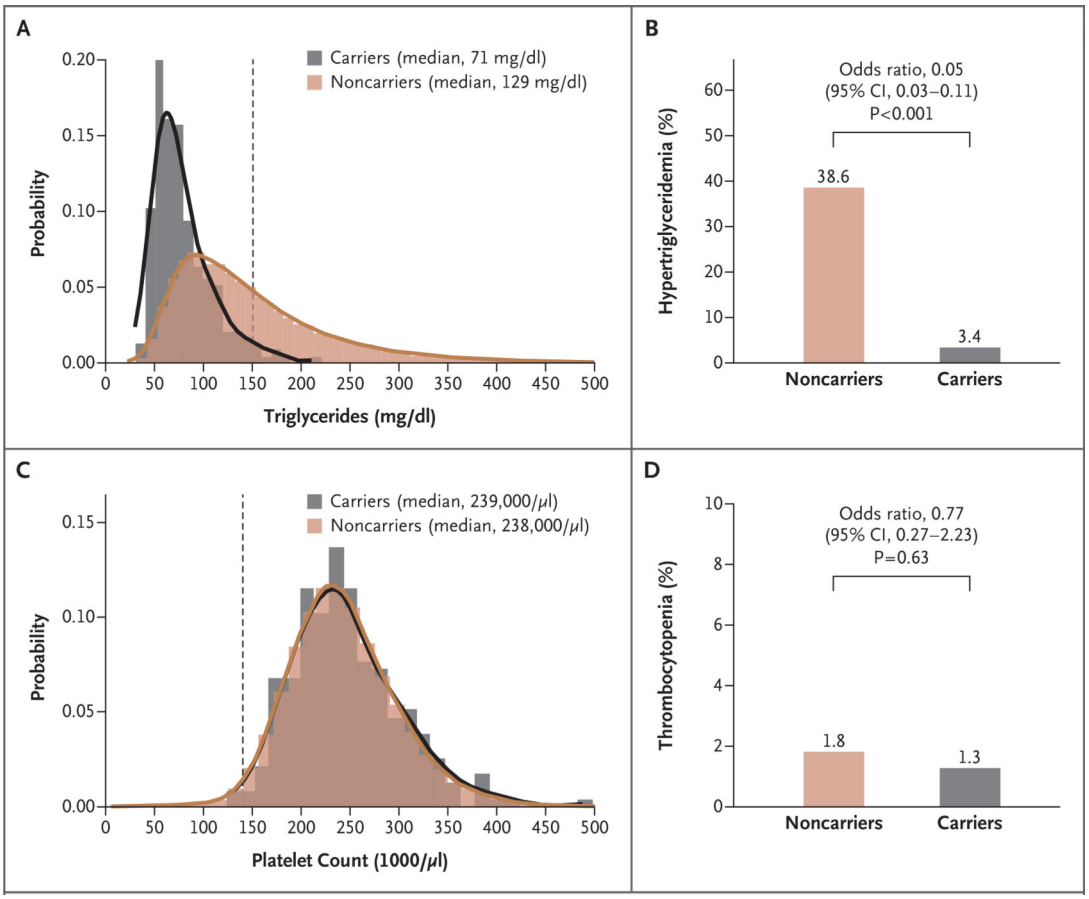

Figure 1. Inactivating Mutations in *APOC3* and the Risk of Hypertriglyceridemia or Thrombocytopenia.

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.