Hepatic Fat Changes after an Antisense Oligonucleotide Therapy Targeting ANGPTL3
A TRANSLATE-TIMI 70 Analysis
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BACKGROUND
Vupanorsen is a GalNAc-conjugated antisense oligonucleotide targeting angiopoietin-like 3 (ANGPTL3) protein that reduced triglycerides (TG) up to 57% but increased hepatic fat fraction (HFF), as assessed by hepatic MRI PDFF. The increase in HFF in different subtypes of patients and the relationship to liver function tests (LFT) remains undefined.

METHODS
227 patients with HFF measurements from the TRANSLATE-TIMI 70 trial completed 24-week follow-up and were included in this analysis. Patients were randomized to placebo or 1 of 7 vupanorsen regimens. We evaluated (1) change in HFF by arm, (2) subgroups at risk for HFF progression, and (3) the correlation between change in LFTs and HFF from baseline to 24 weeks.

RESULTS
• Median HFF at baseline was 8.5%. Median TG level was 216 mg/dL. 114 patients (50.2%) had diabetes.
• Vupanorsen led to progression in HFF ranging from 5% to 76% from baseline in a dose-dependent fashion (p<0.001) (Figure 1).
• Although there was no statistically significant heterogeneity, patients with higher baseline TG, HFF, and those with diabetes had numerically greater increases in HFF with vupanorsen (Figure 2).
• Increases in LFTs were significantly correlated with increased HFF (Spearman’s ρ = 0.45 for AST, 0.48 for ALT, both p < 0.001) (Figure 3).

CONCLUSION
Vupanorsen caused increases in HFF that were associated with dose of drug and increased LFTs. HFF may be important to evaluate for future therapies targeting triglyceride-rich lipoproteins, especially those that work intracellularly.

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