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Statin Effect Heterogeneity on Plaque Volume & Composition in the REPRIEVE Mechanistic Substudy

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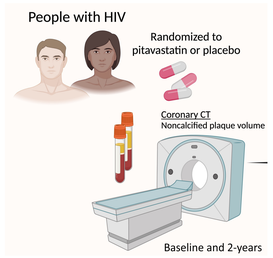
BACKGROUND

- REPRIEVE and its Mechanistic Substudy established that pitavastatin prevents major adverse cardiovascular events and reduces noncalcified coronary plaque (NCP) (density <350 HU) on coronary CT angiography (CTA) among people with HIV who have low-to-moderate traditional atherosclerotic cardiovascular disease (ASCVD) risk.
- We assess the heterogeneity of pitavastatin effects on NCP (density <350 HU) volume and on plaque composition, categorized by density (<130 HU fibrofatty, 130–349 HU fibrous, ≥350 HU calcified) among participants with preexisting coronary plaque on CTA.



METHODS

- 273 REPRIEVE Substudy participants with preexisting coronary plaque on coronary CTA were randomized to pitavastatin calcium 4 mg/day (N=133) or placebo (N=140).
- Log-linear models, incorporating interactions between risk factors and treatment groups, were used to evaluate effect modification on relative changes from baseline over 24 months by various risk factors, including demographic and behavioral characteristics, ASCVD risk score, cardiovascular/metabolic factors, and HIV-related health history.
- Heterogeneities of treatment effects were identified via interaction tests with P<0.10.
- All effects described are geometric mean ratio (GMR) between the pitavastatin and placebo groups, adjusting for risk factors and baseline plaque volumes.

Figure 1. Inclusion in Mechanistic Population with pre-existing plaque at entry

804 randomized
402 Pitavastatin; 402 Placebo

683 completed treatment
341 Pitavastatin; 342 Placebo

563 had CT and biomarker data
281 Pitavastatin; 282 Placebo

273 had pre-existing plaque at entry
133 Pitavastatin; 140 Placebo

The effect of pitavastatin appears greatest in reducing fibrofatty plaque volume, thought to be the most biologically active component.

Pitavastatin effects on non-calcified plaque vary by demographic and cardiovascular risk factors but not by HIV risk factors.

RESULTS

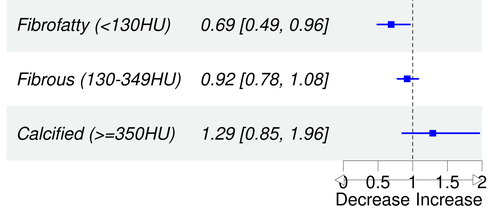
- Participants were median age 52 years, 90% male, 61% white, 29% Black or African American. (**Table 1**)
- The relative reduction from baseline in NCP with pitavastatin was 13% greater than with placebo (GMR 0.87, 95%CI [0.75,1.01]), which is mostly attributed to its effect on fibrous plaque, with some contribution from fibro-fatty plaque. (**Figure 2**)
- Pitavastatin showed a greater volume-reducing effect on fibro-fatty plaque (0.69 [0.49, 0.96]), with a marginal effect on fibrous plaque (0.92 [0.78, 1.08]) and a trend towards increased volume of calcified plaque (1.29 [0.85, 1.96]). (**Figure 2**)
- Some heterogeneity in pitavastatin effects on NCP volume was observed. (**Figure 3**)
  - The volume-reducing effect of pitavastatin on NCP was greater among females (0.67 [0.41, 1.10]), Hispanic or Latinos (0.57 [0.42, 0.77]), those with systolic blood pressure >140 mmHg (0.43 [0.26,0.69]), and those using non-statin lipid-lowering therapy (0.51 [0.31, 0.85]).
  - HIV-related and other factors did not relate to plaque composition changes.

Table 1. Participant Characteristics

Demographics	Total (N=273)
Age	52 (47, 56) years
Male sex, n (%)	245 (90%)
White race, n (%)	167 (61%)
Black race, n (%)	79 (29%)
10-year ASCVD risk	5.2 (3.2, 7.7) %
Baseline NCP (<350 HU) volume	53.5 (20.5, 121.1) mm^3
Baseline fibrofatty (<130 HU) volume	14.2 (2.1, 47.4) mm^3
Baseline fibrous (130–349 HU) volume	33.7 (12.0, 65.9) mm^3
Baseline calcified (≥350 HU) volume	9.2 (1.4, 25.0) mm^3

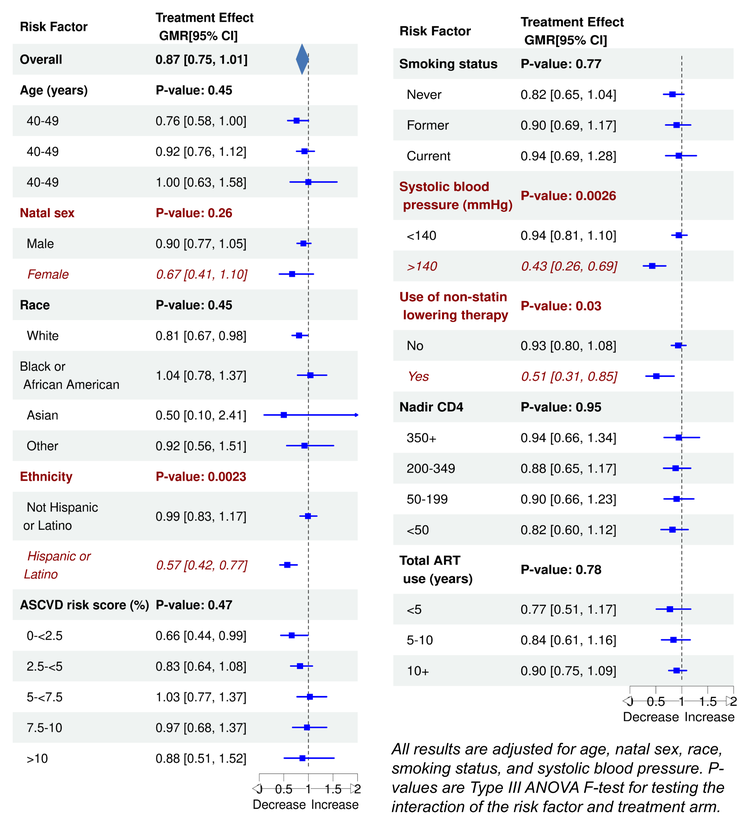
Statistics for continuous variables present Median (Q1,Q3)

Figure 2. Statin Effects on Plaque Composition



To test whether the effect of statin differs depending on the density of the plaque, a multivariate statistical approach (Pillai's trace test) was used. The p-value of Pillai's test is 0.10, which provides evidence that statin effect varies depending on density.

Figure 3. Statin Effect on NCP and Effect Modification.



All results are adjusted for age, natal sex, race, smoking status, and systolic blood pressure. P-values are Type III ANOVA F-test for testing the interaction of the risk factor and treatment arm.

Other risk factors evaluated and not presented, include baseline plaque volumes, biomarkers (MCP-1, IL-6, Lp-PLA2, oxLDL), ASCVD risks (substance use, hypertension at entry, LDL-C, family history of premature CVD, use of testosterone, total cholesterol, HDL-C, triglycerides), cardiovascular and metabolic characteristics (BMI, ever been on statin, use of ACE inhibitors or ARBs, use of antiplatelet therapy), HIV-related health (duration of HIV, abacavir exposure, protease inhibitor exposure, thymidine exposure, TDF exposure, CD4 count, HIV-1 RNA, entry ART regimen class, entry NRTI, entry INSTI).

CONCLUSIONS

- The effect of pitavastatin appears greatest in reducing volume of fibrofatty plaque, which is thought to be the most biologically active component, and may increase plaque density.
- These exploratory results suggest pitavastatin effects on NCP vary by demographic and cardiovascular risk factors; modification of statin effects by HIV risk factors was not apparent. The study was not powered to detect effect heterogeneity. These observations warrant further investigation.

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