Pitavastatin Effects on Lipids in Relation to MACE: a REPRIEVE Secondary Analysis

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BACKGROUND

The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) demonstrated a 36% reduction in major adverse cardiovascular events (MACE) with pitavastatin among people with HIV (PWH). Little is known about the relationship between lipid-lowering and MACE in PWH.

We evaluated pitavastatin effects on lipids, relationship of lipid levels to MACE, and examined mediation of pitavastatin effects on MACE through lipid-lowering.

METHODS

- REPRIEVE was a prospective, double-blind, placebo-controlled (1:1) trial evaluating pitavastatin (4mg/day) for primary prevention of MACE among PWH.
- PWH on stable ART with CD4 count >100 cells/mm^3, at low-moderate ASCVD risk by combination of PCE score and LDL-C were followed for a median of 5.6 years.
- Centrally-tested fasting lipids were evaluated at baseline and annually thereafter.
  - LDL-C derived using Friedewald formula (at TG≤400 mg/dL) or direct LDL-C (at 400<TG<500 mg/dL).
- Pitavastatin effect on LDL-C (outcome) was estimated using linear mixed effects models and GEE.
- Relationship between lipid levels (time-updated covariate) and time to first MACE (outcome) was assessed using Cox regression models.
- Mediation of pitavastatin effect on MACE via LDL-C-lowering was examined using Vansteelandt method.

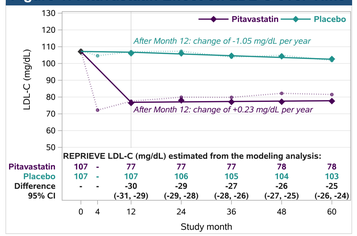
RESULTS

Participant Characteristics	Pitavastatin (N=3888)	Placebo (N=3881)
Age (years)	50	50
Female sex	31%	31%
Black or African American	40%	42%
10-yr ASCVD risk by PCE (%)	4.5	4.5
HIV-1 RNA <400 copies/mL	88%	87%
CD4 (cells/mm^3)	620	622
Screening TC (mg/dL)	186	184
Screening HDL-C (mg/dL)	48	48
Screening TG (mg/dL)	115	114
Screening LDL-C (mg/dL)	109	108

Median for continuous measures, percentage of participants for categorical measures.
HDL-C, LDL-C and TC denote HDL, LDL and total cholesterols; TG triglycerides.

LDL-C reductions with pitavastatin strongly relate to MACE in PWH with minimally elevated LDL-C

Figure 1: Pitavastatin Effect on LDL-C over Time



Dotted lines show Mechanistic substudy means including a month 4 lipid assessment

Figure 2: Pitavastatin Effect on LDL-C Levels at Month 12 Relative to Baseline

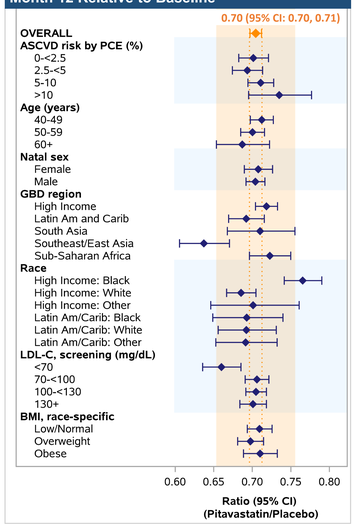
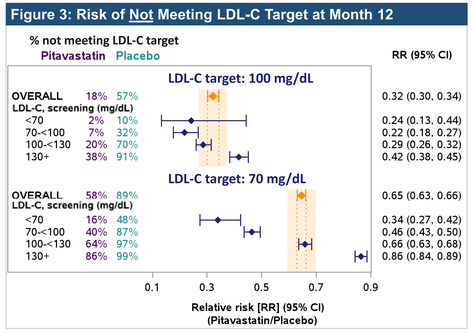
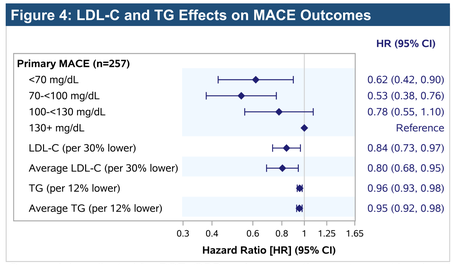


Figure 3: Risk of Not Meeting LDL-C Target at Month 12



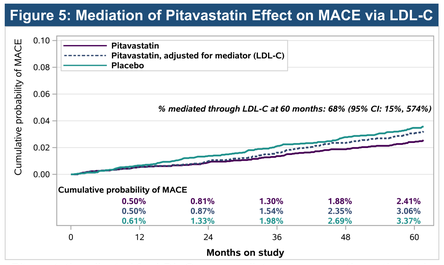
- Pitavastatin effects were primarily observed on LDL-C [Fig. 1].
  - At month 12, LDL-C was 30 mg/dL lower with pitavastatin
    - Corresponds to a 30% reduction [Fig. 2]
    - Relatively stable levels thereafter in both treatment groups
  - Consistent effects on non-HDL-C and TC (not shown)
  - Modest reduction in TG (pitavastatin vs. placebo)
    - Median change from baseline to month 12: -11 vs. 1 mg/dL
  - No effect on HDL-C (1 vs. 0 mg/dL)
- Relative LDL-C-lowering from baseline with pitavastatin was generally consistent across the prespecified baseline subgroups, including by baseline LDL-C [Fig. 2].
  - Slightly larger reduction in Southeast/East Asia (36%) and slightly smaller among Black PWH in High Income countries (23%)
  - No differences by CD4, HIV-1 RNA or ART duration (not shown)
- Pitavastatin lowered the risk of having elevated LDL-C above the clinical care targets [Fig. 3].
  - Risk of LDL-C ≥100 mg/dL was 68% lower with pitavastatin:
    - 82% met target with pitavastatin vs. 43% with placebo
  - Risk of LDL-C ≥70 mg/dL was 35% lower with pitavastatin:
    - 42% met target with pitavastatin vs. 11% with placebo
  - Those with higher baseline LDL-C were less likely to meet the targets, reflective of the observed 30% reduction with pitavastatin.
    - Among those with baseline LDL-C ≥130 mg/dL:
      - 62% vs. 9% met target LDL-C below 100 mg/dL
      - 14% vs. 1% met target LDL-C below 70 mg/dL
- Time-updated average LDL-C was associated with risk of MACE [Fig. 4].
  - 20% lower MACE risk per 30%-lower LDL-C
- Time-updated average TG was associated with risk of MACE [Fig. 4].
  - 5% lower MACE risk per 12%-lower TG
  - Robust to adjustment for LDL-C
- In an exploratory mediation analysis, 68% of the total pitavastatin effect on MACE was estimated to have been mediated through LDL-C, although with low precision [Fig. 5].

Figure 4: LDL-C and TG Effects on MACE Outcomes



Cox models, adjusted for PCE, GBD region, race; the most recent level and the average of levels prior to MACE were used as time-updated covariates

Figure 5: Mediation of Pitavastatin Effect on MACE via LDL-C



Pitavastatin adjusted for LDL-C as a mediator represents the estimated effect of pitavastatin on MACE under the counterfactual condition of no pitavastatin effect on LDL-C

CONCLUSIONS

- Among the cohort of PWH with minimally elevated LDL-C, LDL-C levels strongly related to MACE.
  - This underscores the importance of LDL-C-lowering as a goal in primary CVD prevention in PWH.
- Pitavastatin (4 mg/day) demonstrated a robust 30% reduction in LDL-C.
  - Higher-intensity statin therapy or additional agents may be needed to achieve LDL-C targets for primary CVD prevention among PWH with LDL-C levels ≥130 mg/dL.
- Pitavastatin effects on LDL-C strongly related to MACE but may not fully account for all the MACE reduction, leaving the possibility of contributions from other pathways.
  - In the PWH population with residual MACE risk related to inflammation and immune activation, these mechanisms may warrant further study.
- Interpretation of findings is subject to the REPRIEVE eligibility criteria which required lower LDL-C at higher ASCVD risk, and LDL-C <70 mg/dL among diabetics.

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