Characterization of Heterogeneous Statin Benefit in REPRIEVE to Inform Prevention

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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)** among PWH randomized (1:1) to pitavastatin versus placebo.
  - N=7,769 people with HIV (PWH) aged 40+ with low-to-moderate 10-year CVD risk (median 4%) per the **Pooled Cohort Equations** (**PCE**).
- US guidelines (HHS) now recommend statins for PWH 40+ with CVD risk ≥5% and risk counselling for CVD risk <5%, citing more modest benefit.
  - To inform counselling among PWH with risk <5%, we used causal machine learning to investigate heterogeneous statin benefit.

Research Questions

Among PWH with cardiovascular disease (CVD) risk <5% in REPRIEVE,

1. Are there participant subgroups predicted to benefit from statins?
2. How do key CVD or HIV risk factors inform these subgroups?

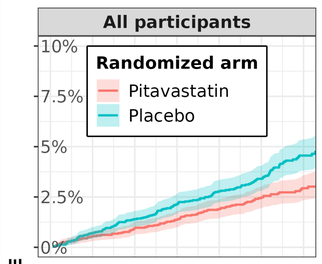
METHODS

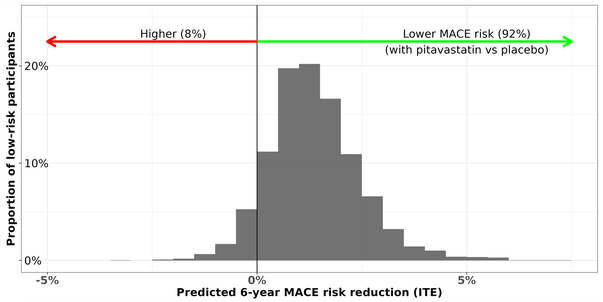
- **Causal survival trees** organize participants into buckets defined by risk factor values and selected to maximize differences in treatment effects.
- Within a bucket, participants share the same predicted **individual treatment effect (ITE)**: an unobservable, counterfactual quantity. Here,
  - **ITE**: Absolute 6-year reduction in MACE risk experienced by a PWH if hypothetically randomized to statin *and* randomized to placebo.
  - ITEs are predicted by the estimated treatment effect within a bucket.
- A **causal survival forest (CSF)** averages an individual's set of predictions across many trees to improve prediction quality (*i.e.*, lower variance).
  - Due to lower event rates among risk <5%, we fit a CSF with 50,000 honest decision trees based on *all* participants with complete data.
  - Sensitivity analysis explored a CSF among those with risk <5% only.
  - The median follow-up time in REPRIEVE was approximately 5.6 years. A time horizon of 6 years was chosen to balance events + censoring.
- Among PWH with risk <5%, risk factor contributions were evaluated by:
  - **Best Linear Projection**: Coefficients represent average contribution of risk factor to predicted ITE, after adjusting for all other risk factors.
  - **Variable Importance**: Frequency at which risk factor is used to define buckets. Higher importance → more buckets defined by risk factor.

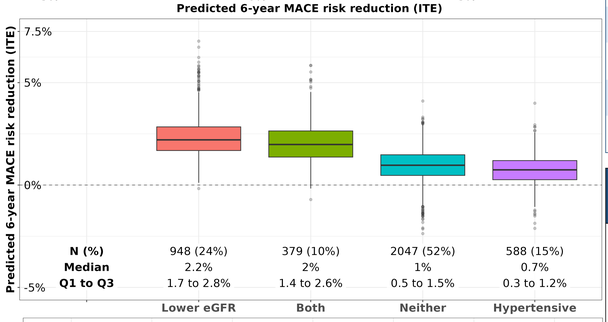
Baseline Risk Factors

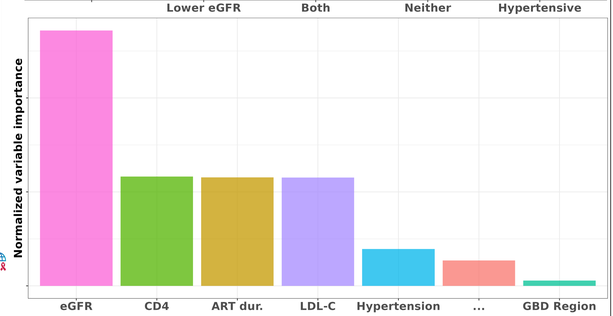
Age, sex, global burden of disease (GBD) region (combined with white/other race in high income); Hypertension, BMI, LDL-C, fasting glucose, eGFR, smoking status; CD4 cell count, lifetime ART duration.

92% of REPRIEVE participants with lower cardiovascular risk (PCE <5%) were predicted to experience a reduction in 6-year MACE risk if randomized to pitavastatin vs placebo. Decreasing eGFR predicted increasing statin benefit, suggesting an otherwise low-risk group for targeted prevention.









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RESULTS

- 7,342 (95%) REPRIEVE participants with complete data were considered.
- Among the 3,962 participants with CVD risk <5%,
  - 66 known events and 1,712 non-events, split equally between arms.
  - Average treatment effect: 0.2% absolute risk reduction (with statin).
  - Majority (92%) predicted to reduce their 6-year MACE risk with pitavastatin versus placebo (ITE>0), median ITE 1.3% (IQR: 0.7 to 2%).
- After adjustment for all other risk factors, lower eGFR and hypertension were only statistically significant predictors of ITE (p<0.05). On average,
  - Lower eGFR (<90 units) increased ITEs by 2.5% (95% CI: 0.2%, 4.9%).
  - Pre-existing hypertension decreased ITEs by 3.3% (CI: -5.8%, -0.7%).
- eGFR was the most important variable by a large margin, suggesting it frequently maximized treatment effect heterogeneity.
- Sensitivity analysis (CSF fit among risk <5%) yielded very similar results.

Baseline characteristics	CVD risk <5% (N=3962)	CVD risk ≥5% (N=3380)
10y CVD risk (PCE), Mean (SD)	2.4% (1.4%)	7.9% (2.6%)
Age ≥ 50 years	1274 (32%)	2564 (76%)
Female	1802 (45%)	503 (15%)
Pre-existing hypertension	**967 (24%)**	**1632 (48%)**
Lower eGFR (<90 mL/min/1.73m²)	**1327 (33%)**	**1651 (49%)**
GBD: High Income (White)	1043 (26%)	1016 (30%)
GBD: High Income (Other)	789 (20%)	1070 (32%)
GBD: Lat Am and Caribbean	780 (20%)	628 (19%)
GBD: Sub-Saharan Africa	683 (17%)	457 (14%)
GBD: Asia	667 (17%)	209 (6%)

CONCLUSIONS

- Statin therapy was predicted to reduce MACE risk vs placebo for most REPRIEVE participants, regardless of CVD risk (aligns with EU guidelines).
- Those with lower eGFR were consistently predicted to experience greater reduction in MACE risk with pitavastatin than their peers.
  - Kidney disease and CVD closely linked, but not in PCE risk equations!
  - Suggests otherwise low-risk subgroup for targeted CVD prevention.
- Those with pre-existing hypertension were predicted to experience less risk reduction than their peers, though most still predicted to benefit.
  - REPRIEVE's primary analysis identified similar interaction.
- Future work: individual risk-benefit considering statin-induced diabetes.