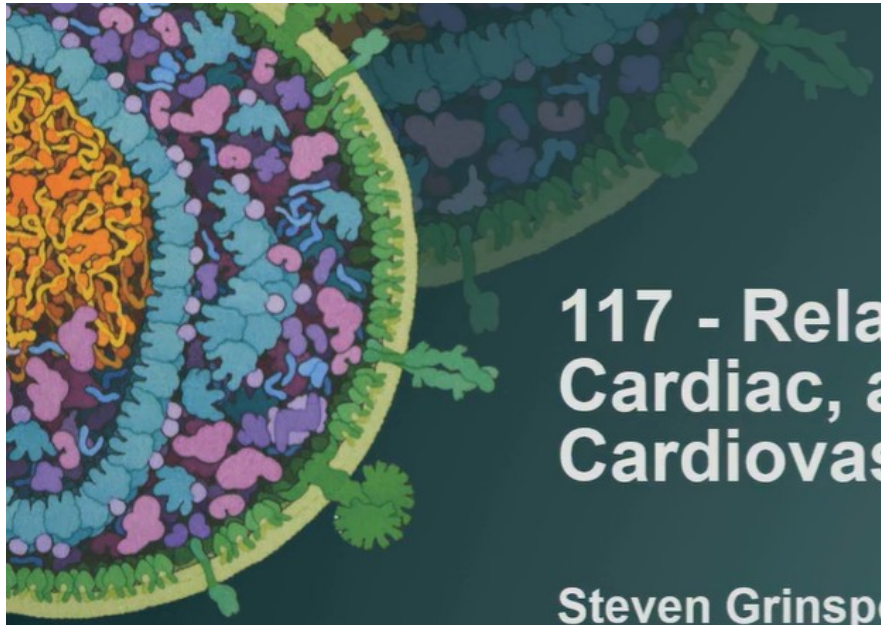

Oral Abstract Session-03

Monday, February 23, 2026

117 - Relationship of Inflammatory, Cardiac, and Lipid Biomarkers to Cardiovascular Events in REPRIEVE

Steven Grinspoon

Massachusetts General Hospital, Boston, MA, USA

Financial Relationships:

Dr Grinspoon reported Self: Grants/grants pending with Gilead Sciences, Inc, Kowa Pharmaceuticals America, Inc, and ViiV Healthcare.

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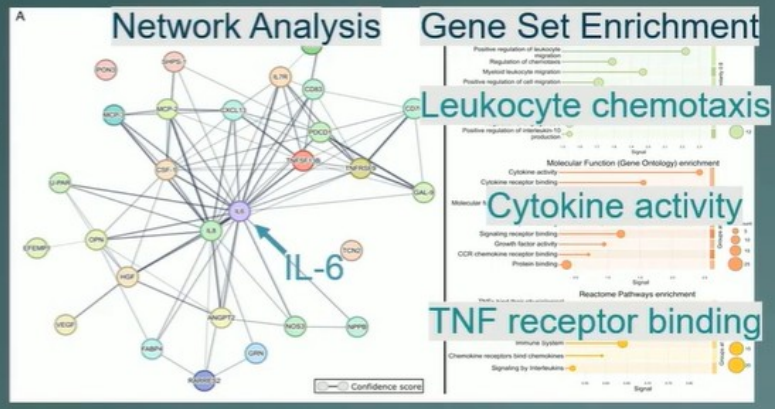
Background and Objectives

- In the global REPRIEVE primary cardiovascular prevention trial, targeting low-moderate traditional risk asymptomatic PWH, a statin strategy reduced MACE 36% over 5.6 yrs f/u

- REPRIEVE mechanistic substudy analyses show strong associations of inflammatory networks with MACE and subclinical cardiovascular dysfunction with high-risk coronary plaque



- We leveraged data from the main REPRIEVE trial of over 7000 participants to provide new insights into associated risk factors for MACE and prediction modeling for primary CVD prevention in PWH

MACE = major adverse cardiovascular events

Kolossvary, JCI 2025
DeFilippi, JACC Advances 2024

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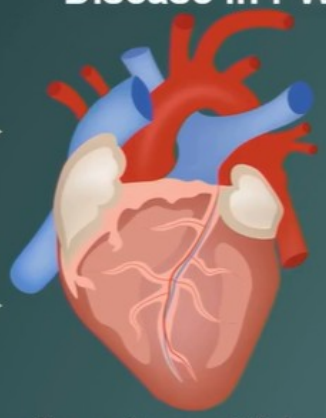
Methods

Atherosclerotic Cardiovascular Disease in PWH



- ✓ ApoB100
- ✓ oxLDL
- ✓ Lp(a)
- → Poster #655 LDL

Dyslipidemia
LDLR, APOB, PCSK9, APOE, etc.

- ✓ hsCRP
- ✓ IL-6

Chronic Inflammation
IL-1β, IL-6, TNF-α, IL-10, etc.

Endothelial Dysfunction
PLA2G7, NOS3, MEF2A, ITGB3, etc.

- ✓ Lp-PLA2

Subclinical Cardiac Dysfunction/ Damage
FABP3, NT-proBNP, cTnT, GDF15, etc.

- ✓ hs-cTnT
- ✓ proBNP

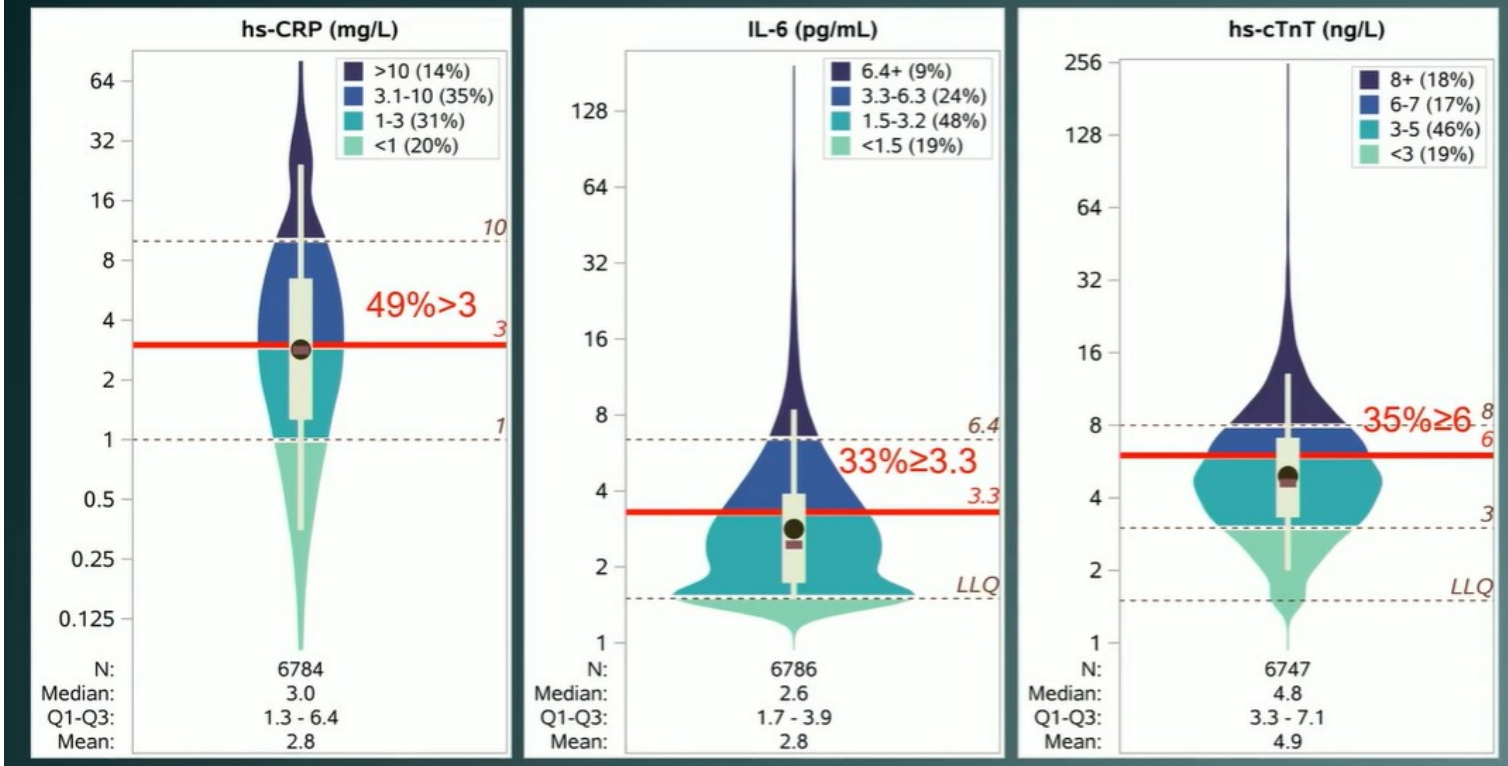
We measured baseline levels of clinically relevant biomarkers and assessed:

- Association with incident MACE in residual risk analyses
  - ⟶ Cox models adjusted for randomization and CVD risk by PCE equation
- Added predictive value of biomarkers for MACE
  - ⟶ C-statistic and AUC at 5-yrs (AUC5)
- Modification of pitavastatin effect by biomarker level
  - ⟶ interaction with randomized treatment

Participant Characteristics

		All (N=7005)	Without MACE (N=6819)	With MACE		
				Pooled Groups (N=186)	Pitavastatin (N=74)	Placebo (N=112)
Natal sex	Male	68%	68%	73%	72%	74%
Age (years)	Median (Q1, Q3)	50 (45, 55)	50 (45, 55)	53 (49, 56)	53 (49, 56)	53 (49, 57)
GBD Super Region	High Income	55%	55%	78%	78%	79%
	Latin Am. and Carib	16%	16%	10%	14%	7%
	S.East/East Asia	8%	8%	5%	4%	5%
	South Asia	4%	4%	4%	1%	6%
	Sub-Saharan Africa	16%	17%	3%	3%	3%
Race	Black or AA	44%	44%	46%	45%	46%
	White	35%	35%	38%	42%	36%
	Asian	13%	13%	9%	5%	12%
PCE risk score (%)	Median (Q1, Q3)	4.5 (2.1, 7.0)	4.4 (2.1, 7.0)	6.4 (4.4, 9.3)	6.3 (3.9, 9.3)	6.7 (4.8, 9.2)
CD4 count (cells/mm³)	Median (Q1, Q3)	455, 834	629 (455, 835)	616 (448, 799)	620 (429, 784)	612 (465, 826)
HIV-1 RNA (copies/mL)	<LLQ	87%	87%	83%	82%	84%
	LLQ -< 400	11%	10%	14%	15%	13%
	400+	2%	2%	3%	3%	3%

Increased Inflammation and Subclinical Cardiac Dysfunction in Asymptomatic Low-Moderate Risk ART-treated PWH



The estimated probability density function, and mean (circle), median (dash), Q1-Q3 (box) and P5-P95 (whiskers).

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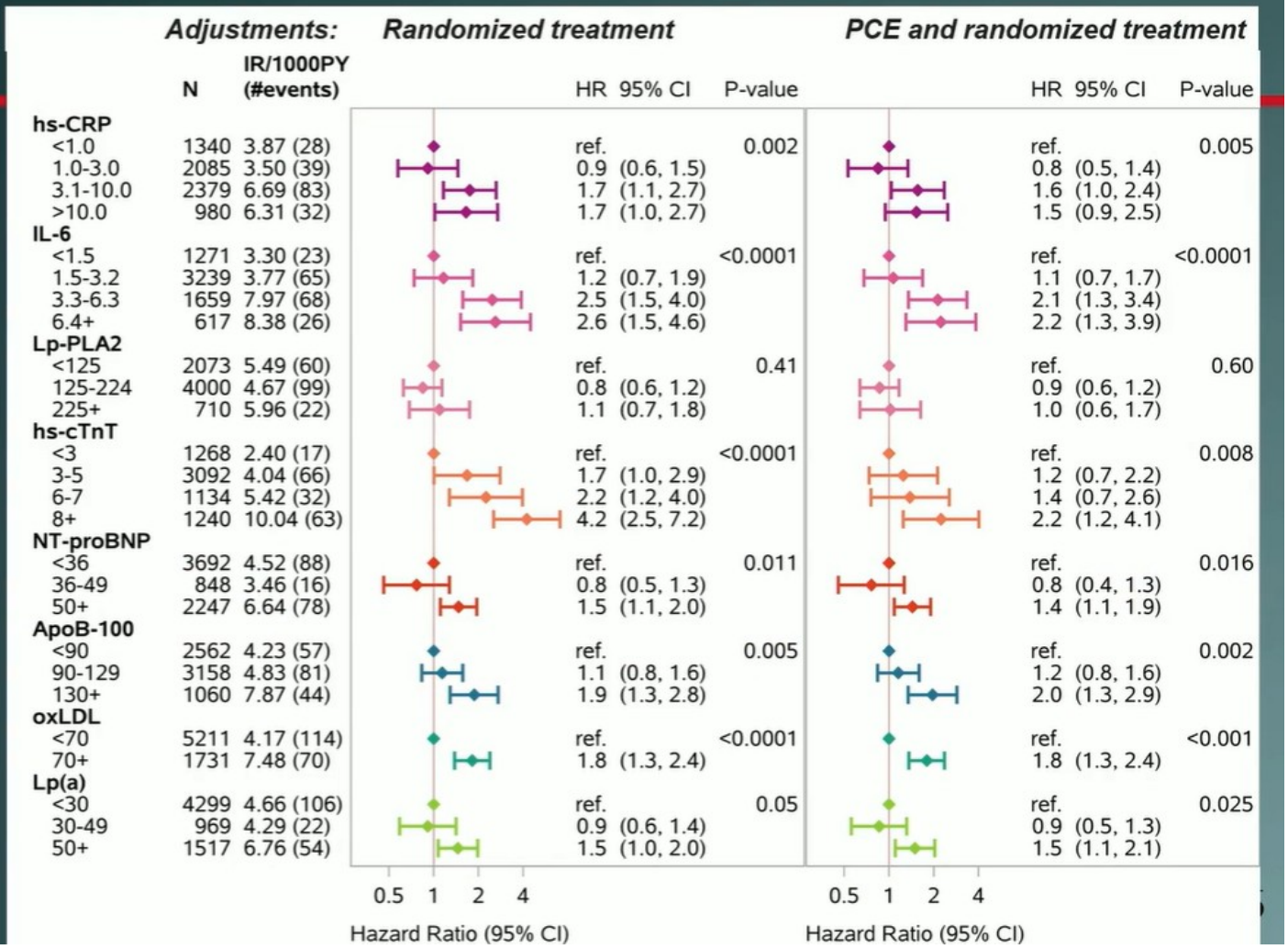
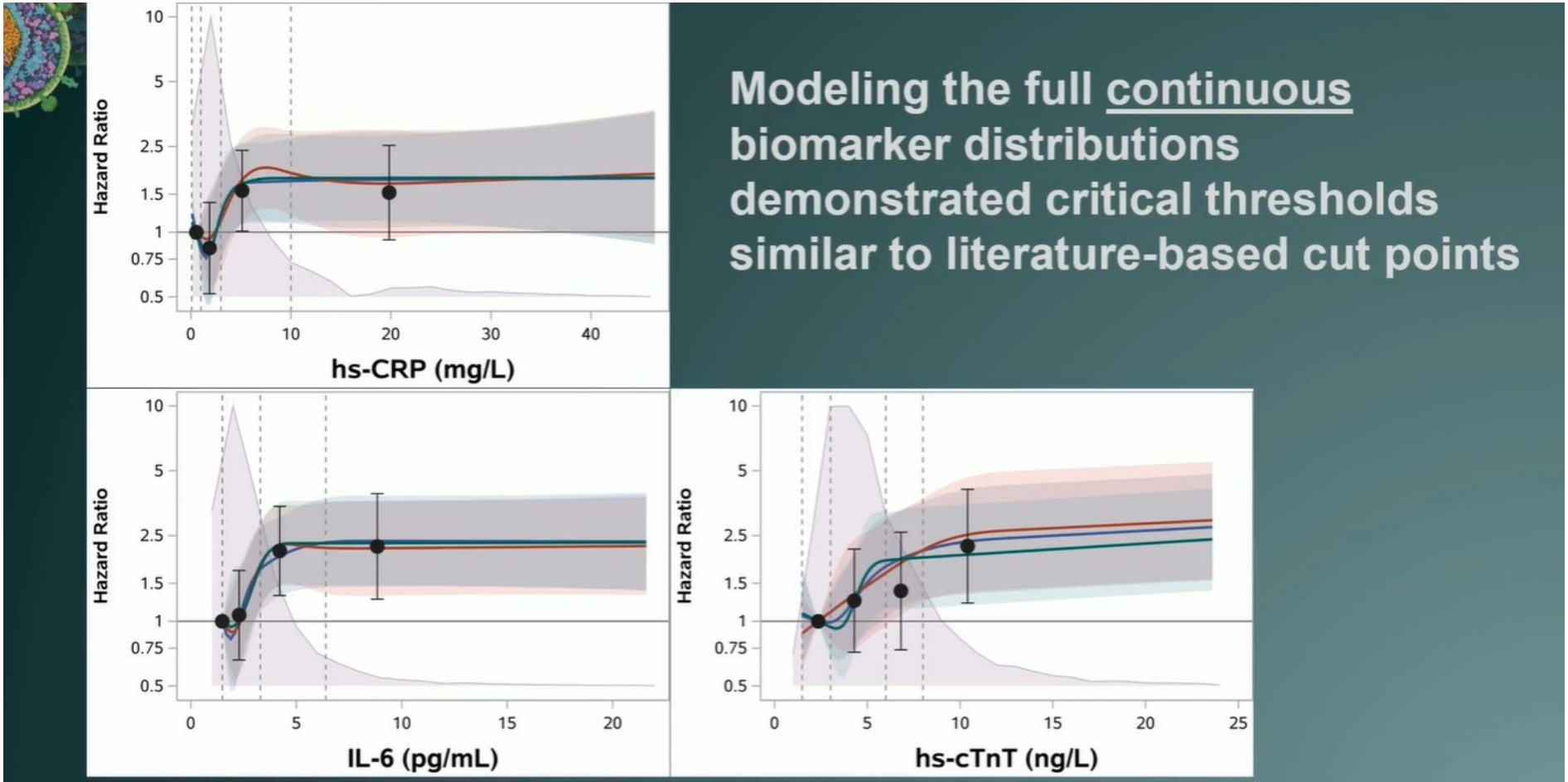
Estimated Baseline Biomarker Effects on MACE Hazard Using Clinically Relevant Thresholds





Modeling the full continuous biomarker distributions demonstrated critical thresholds similar to literature-based cut points

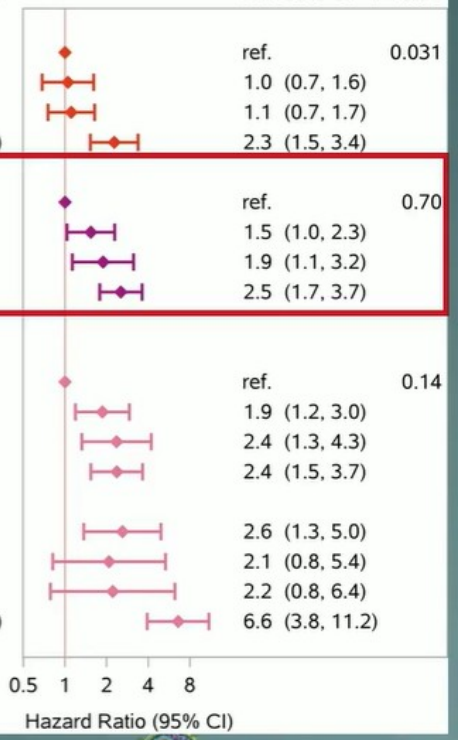
Splines (95% CI) estimated based on 3 scenarios for placements of knots, plotted over a smoothed histogram of the biomarker distribution.
HR (95% CI) from modeling using the clinical cut-offs (previous slide) are shown at the median value for the respective category.
All models adjust for randomized treatment and PCE.

Estimated Effects of Baseline Cardiac and Inflammatory Biomarker Interactions on MACE Hazard (Ad Hoc Analysis)

- Elevations in <u>each inflammatory biomarker alone</u> was associated with a higher hazard of MACE
  - Even higher hazard with elevations in both

Adjusted for PCE and randomized treatment

Interaction between ...	N	IR/1000PY (#events)	HR	95% CI	P-value
... cardiac markers (NT-proBNP x hs-cTnT)	**6665**				
Both normal	2931	3.55 (56)	ref.		0.031
Only NT-proBNP elevated	1396	3.72 (28)	1.0	(0.7, 1.6)	
Only hs-cTnT elevated	1525	5.63 (45)	1.1	(0.7, 1.7)	
Both elevated	813	11.80 (48)	2.3	(1.5, 3.4)	
... inflammatory markers (hs-CRP x IL-6)	**6665**				
Both normal	2776	3.00 (45)	ref.		0.70
Only hs-CRP elevated	1658	4.84 (43)	1.5	(1.0, 2.3)	
Only IL-6 elevated	594	6.39 (20)	1.9	(1.1, 3.2)	
Both elevated	1637	8.26 (69)	2.5	(1.7, 3.7)	
... cardiac and inflammatory markers	**6665**				
Normal or isolated cardiac marker elevation + ...					
Both inflammatory markers normal	2483	2.37 (32)	ref.		0.14
Only hs-CRP elevated	1504	4.69 (38)	1.9	(1.2, 3.0)	
Only IL-6 elevated	481	6.23 (16)	2.4	(1.3, 4.3)	
Both inflammatory markers elevated	1384	6.02 (43)	2.4	(1.5, 3.7)	
Both cardiac markers elevated + ...					
Both inflammatory markers normal	293	8.60 (13)	2.6	(1.3, 5.0)	
Only hs-CRP elevated	154	6.39 (5)	2.1	(0.8, 5.4)	
Only IL-6 elevated	113	7.16 (4)	2.2	(0.8, 6.4)	
Both inflammatory markers elevated	253	21.37 (26)	6.6	(3.8, 11.2)	



Estimated Effects of Baseline Cardiac and Inflammatory Biomarker Interactions on MACE Hazard (Ad Hoc Analysis)

- Elevations in each inflammatory biomarker alone was associated with a higher hazard of MACE
  - Even higher hazard with elevations in both
- Markedly higher MACE hazard among those with elevations in all cardiac and inflammatory markers
  - Although small numbers

Adjusted for PCE and randomized treatment

Interaction between ...	N	IR/1000PY (#events)	HR	95% CI	P-value
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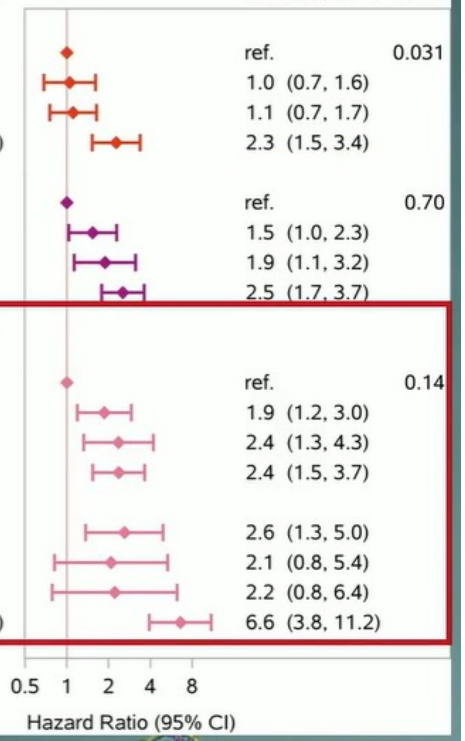
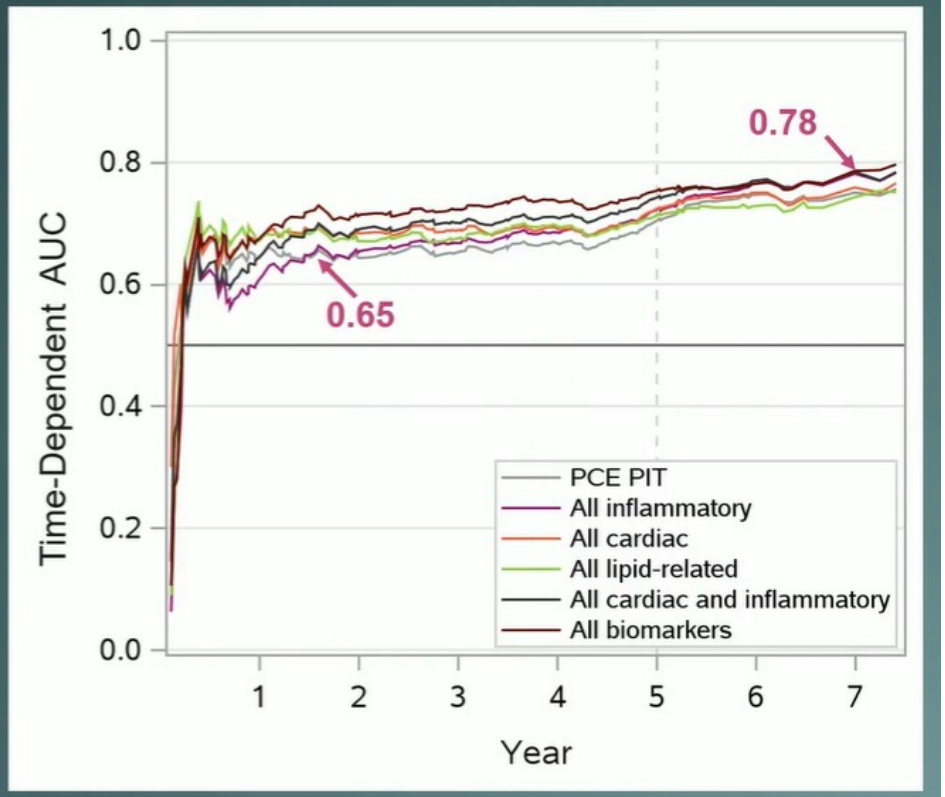
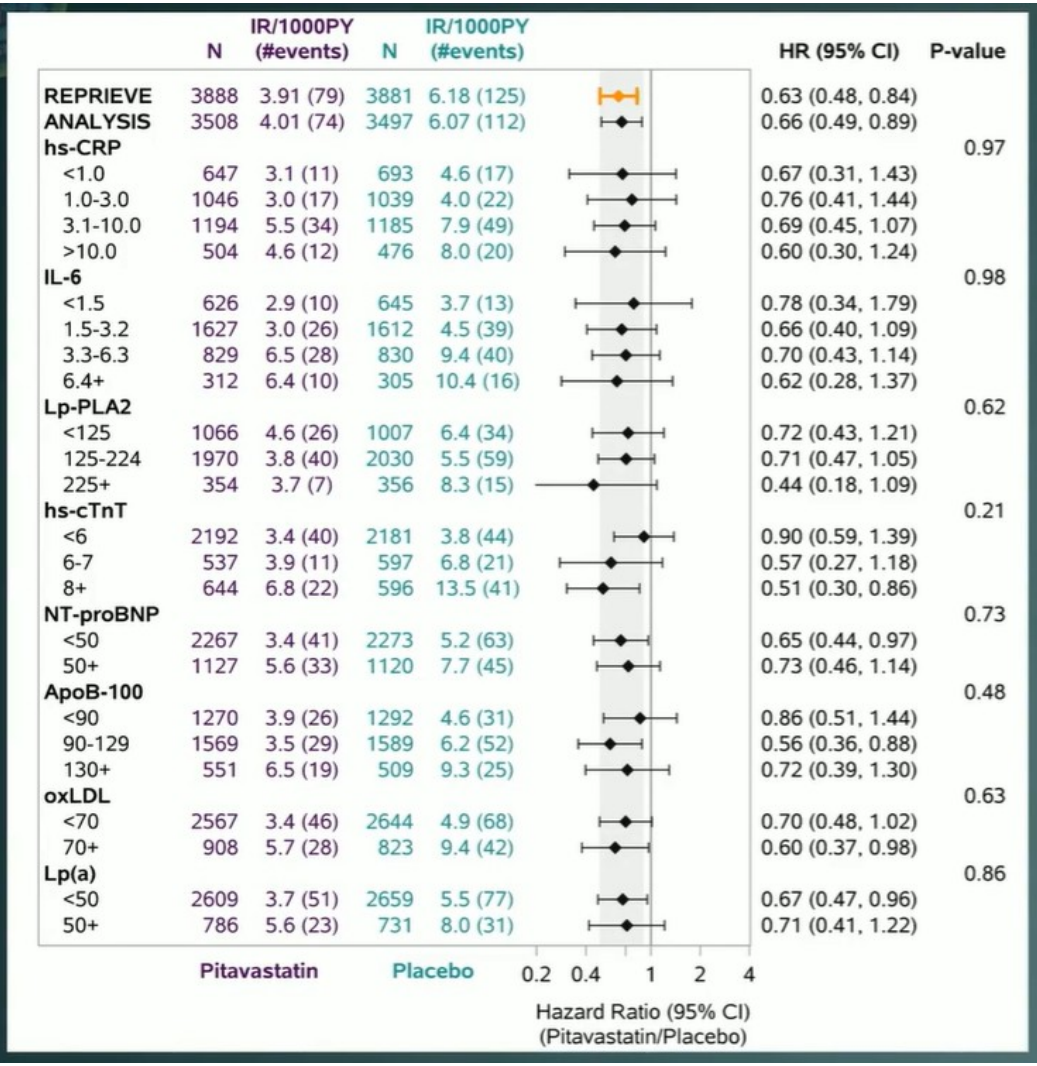


Increasing C-Statistic and AUC5 over PCE with Addition of Inflammatory and Cardiac Parameters

Model	C-statistic (95% CI)	AUC at Year 5 (95% CI)
PCE PIT	0.68 (0.64, 0.72)	0.70 (0.67, 0.74)
hs-CRP	0.70 (0.65, 0.75)	0.72 (0.69, 0.76)
IL-6	0.70 (0.66, 0.75)	0.71 (0.67, 0.75)
All inflammatory	0.71 (0.66, 0.76)	0.72 (0.68, 0.76)
hs-cTnT	0.69 (0.65, 0.74)	0.71 (0.67, 0.75)
NT-proBNP	0.70 (0.65, 0.75)	0.72 (0.68, 0.76)
All cardiac	0.70 (0.65, 0.75)	0.72 (0.68, 0.76)
ApoB-100	0.70 (0.65, 0.74)	0.71 (0.67, 0.75)
oxLDL	0.70 (0.66, 0.74)	0.71 (0.67, 0.75)
Lp(a)	0.69 (0.64, 0.73)	0.70 (0.67, 0.74)
All lipid-related	0.70 (0.65, 0.75)	0.71 (0.67, 0.75)
All cardiac and inflammatory	0.72 (0.66, 0.78)	0.74 (0.70, 0.78)
All biomarkers	0.75 (0.71, 0.80)	0.75 (0.72, 0.79)





No modification of Pitavastatin Effect on MACE by Baseline Biomarkers

Treatment effect was estimated using Cox model, stratified by natal sex and CD4 count; treatment effect modification was assessed via interaction. For reference, the overall treatment effect in REPRIEVE and in analysis population are shown on top.

Strengths, Limitations and Follow-up Analyses

Strengths:

- Large global RCT assessing clinically relevant biomarkers in relationship to adjudicated MACE

Limitations:

- Single baseline measurement assessed in relationship to events
- Other markers may be useful
- Limited power to determine effect modification of statin therapy

Ongoing Follow-up Analyses:

- Treatment effects on clinically relevant pathways in main trial
  - ✓ CRP Decrease
  - ✓ ApoB Decrease
  - ✓ LpPLA2 Decrease
  - ✓ OxLDL Decrease
  - IL-1B Pending
  - ANGPTL3 Pending
- Case cohort analysis of Olink Explore 5400 leveraging all events
- Investigation of sex and GBD effects

Conclusions and Future Directions

- Asymptomatic PWH with low-moderate traditional cardiovascular risk, well-treated on ART are characterized by inflammation and subclinical cardiac dysfunction
- Inflammatory pathways, particularly IL-6, representing innate immune activation, and subclinical myocardial dysfunction related strongly to MACE in residual risk analyses
- Clinically relevant biomarkers in these pathways used in combination may improve risk prediction for CVD in PWH
- Further research is needed to better understand:
  - Mechanisms by which specific inflammatory and cardiac pathways contribute to MACE
  -Utility of biomarkers from these pathways for HIV specific CVD risk prediction algorithms
  -Role of adjunctive therapies for residual immune activation in combination with statins

Thank you and plain language summary

- REPRIEVE participants
- Site teams and investigators
- Funders
  - NIH
  - Gilead
  - Viiv
  - Kowa

Plain language summary:
Markers of inflammation and subclinical cardiovascular injury are associated with future cardiac events in ART-treated PWH, at low to moderate cardiovascular risk, controlling for statin treatment.