178 - Plaque, Inflammation, Subclinical Myocardial Injury and MACE in the REPRIEVE Mechanistic Substudy

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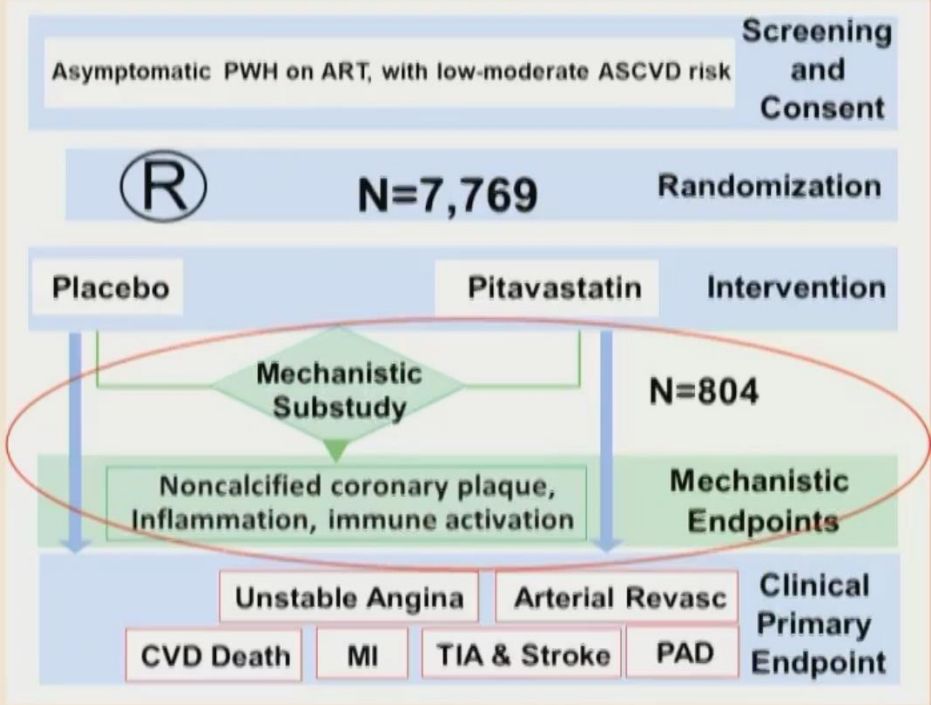
Disclosure: Dr Grinspoon has Self: Grants/grants pending with Gilead Sciences, Inc., Kowa Pharmaceuticals America, Inc, and ViiV Healthcare.

Background

- In REPRIEVE, pitavastatin reduced MACE (-36%) in low-moderate risk, ART-treated PWH, without known ASCVD
- Among 804 US substudy participants, pitavastatin reduced noncalcified coronary plaque (NCP) progression (-33%) and tended to reduce hsCRP (-17% vs placebo)
- We leveraged the REPRIEVE Mechanistic Substudy to determine:

1. Residual risk pathways associated with MACE
2. Utility of prediction algorithms for MACE
3. Treatment effect modification for statin therapy



Hoffmann U, Lu MT, et al. *Am Heart J* 2019.

National Heart, Lung, and Blood Institute

National Institute of Allergy and Infectious Diseases

Grinspoon et al. NEJM 2023, 2024; Lu et al. JAMA Cardiology 2024

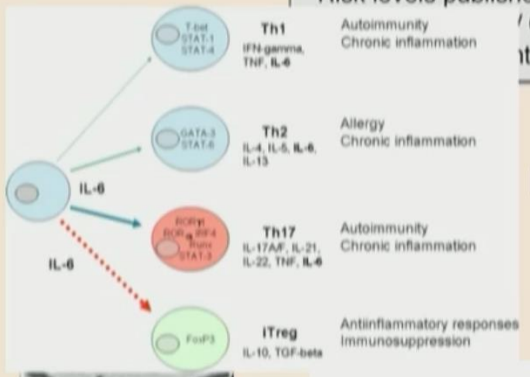
Methods: Relating Entry Risk Factors to MACE

- In the substudy, MACE incidence assessed over 6.2 yrs
- Factors assessed at entry:
  - Biomarkers (hsCRP, IL-6, hs-cTNT, oxLDL, Lp-PLA2)
  - Plaque indices (primary: NCP)
- Effects adjusted for ASCVD risk score and presence of NCP and stratified by treatment group
- Exploratory analyses evaluated the predictive ability of combinations of risk factors for MACE
- Modeling used Fine and Gray subdistribution hazards

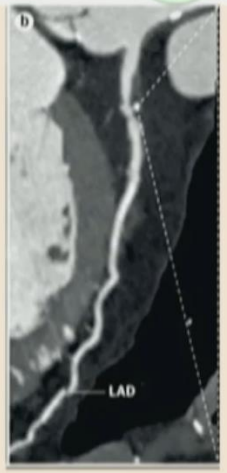
Inflammation

hs-CRP Value	Cardiovascular Disease Risk Level*
< 1 mg/L	**low** risk
1-3 mg/L	**average** risk
> 3 mg/L	**high** risk

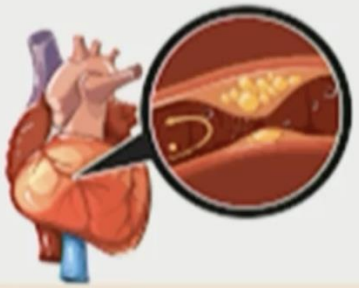
* Risk levels published in 2003. American / Centers for Disease tion Scientific Statement



Innate Immune Activation



Vulnerable plaque



Subclinical Myocardial Injury

Maurovich-Horvat P. Nat Rev Card 2014

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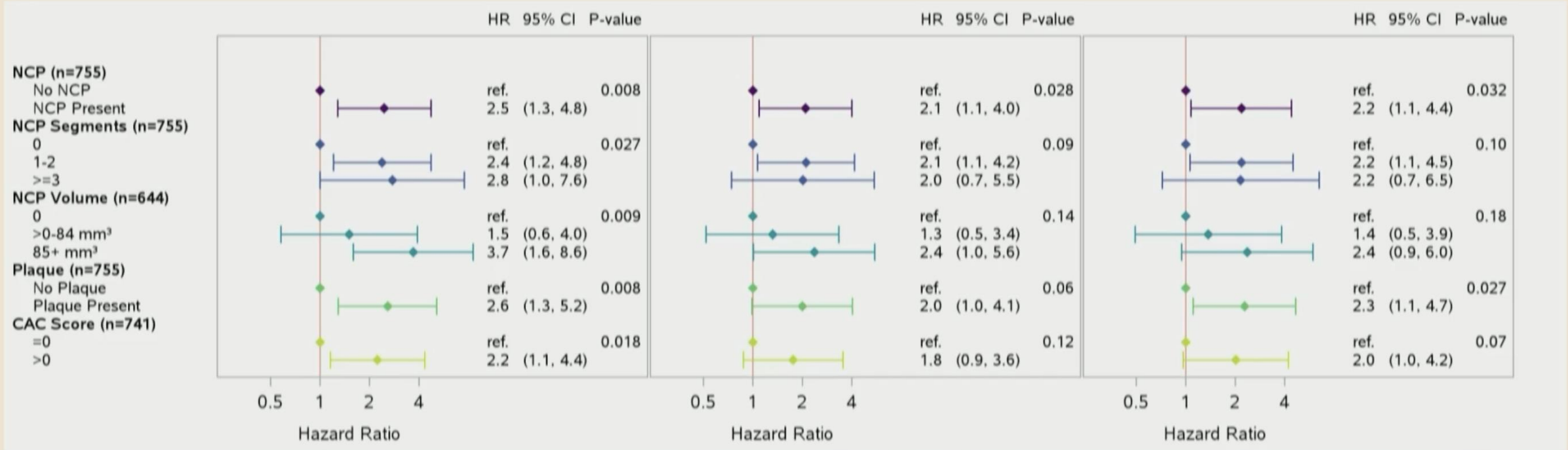
Baseline Characteristics

			With MACE* (N=38)	Without MACE* (N=766)
Demographics	Male		31 (82%)	634 (83%)
	Female		7 (18%)	132 (17%)
	White		17 (45%)	408 (53%)
	Non-White		21 (55%)	358 (47%)
	Age (yrs)		54 (50, 57)	50 (46, 55)
	ASCVD risk %		6.5 (3.6, 9.9)	4.5 (2.6, 6.8)
	LDL mg/dL		93 (87, 113)	106 (89, 127)
Biomarkers	hsCRP (mg/L)	< 1.0 1.0 - 3.0 3.1 - 10.0 > 10	7 (19%) 11 (30%) 14 (38%) 5 (14%)	222 (30%) 308 (41%) 160 (21%) 61 (8%)
	IL-6 (pg/mL)		2.3 (1.4, 2.9)	1.6 (1.0, 2.7)
	hs-cTNT (ng/L)	< 6 6 - 7.52 7.53 - 9.63 > 9.64	5 (16%) 3 (9%) 10 (31%) 14 (44%)	291 (41%) 142 (20%) 143 (20%) 142 (20%)
Plaque	Any Plaque		26 (70%)	342 (48%)
	Any NCP Plaque		23 (62%)	279 (39%)

Higher in those with MACE:

- Age
- ASCVD Risk Score
- hsCRP
- IL-6
- hsTNT
- Total and noncalcified plaque

Estimated Baseline Plaque Effect on Hazard of MACE



Unadjusted

ASCVD Risk Score Adjusted

Risk Score Component Adjusted

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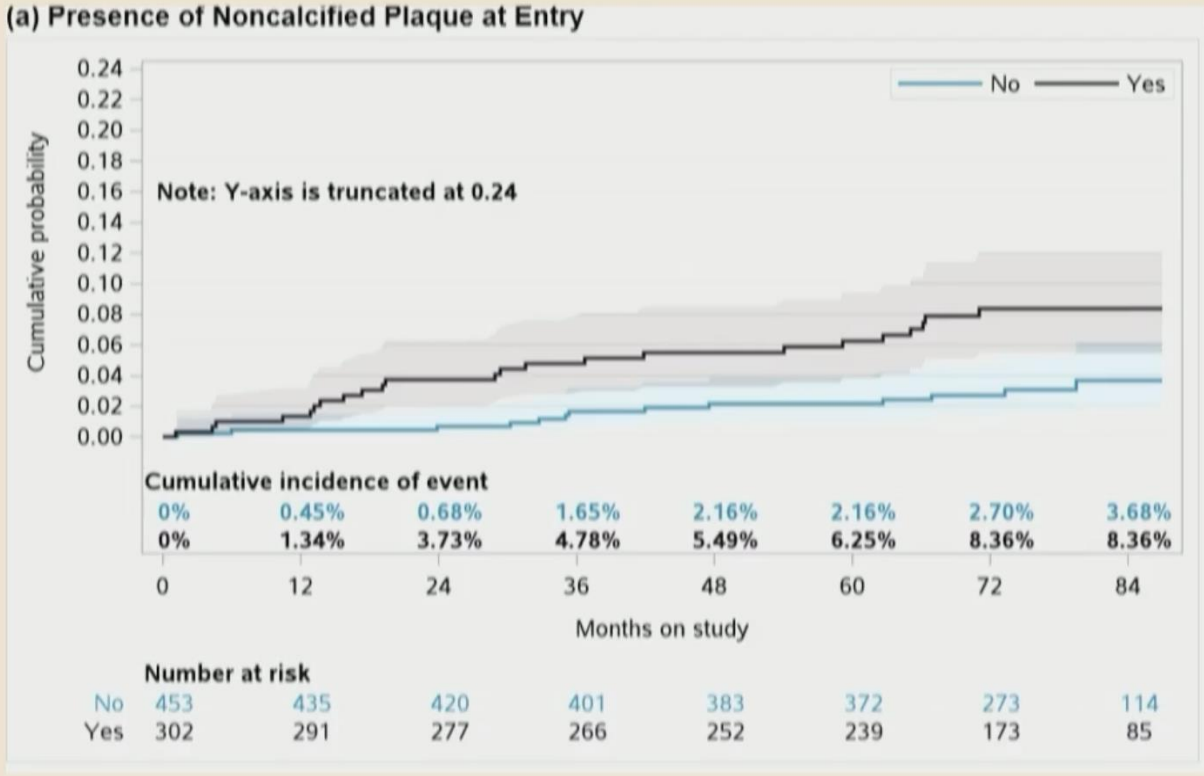
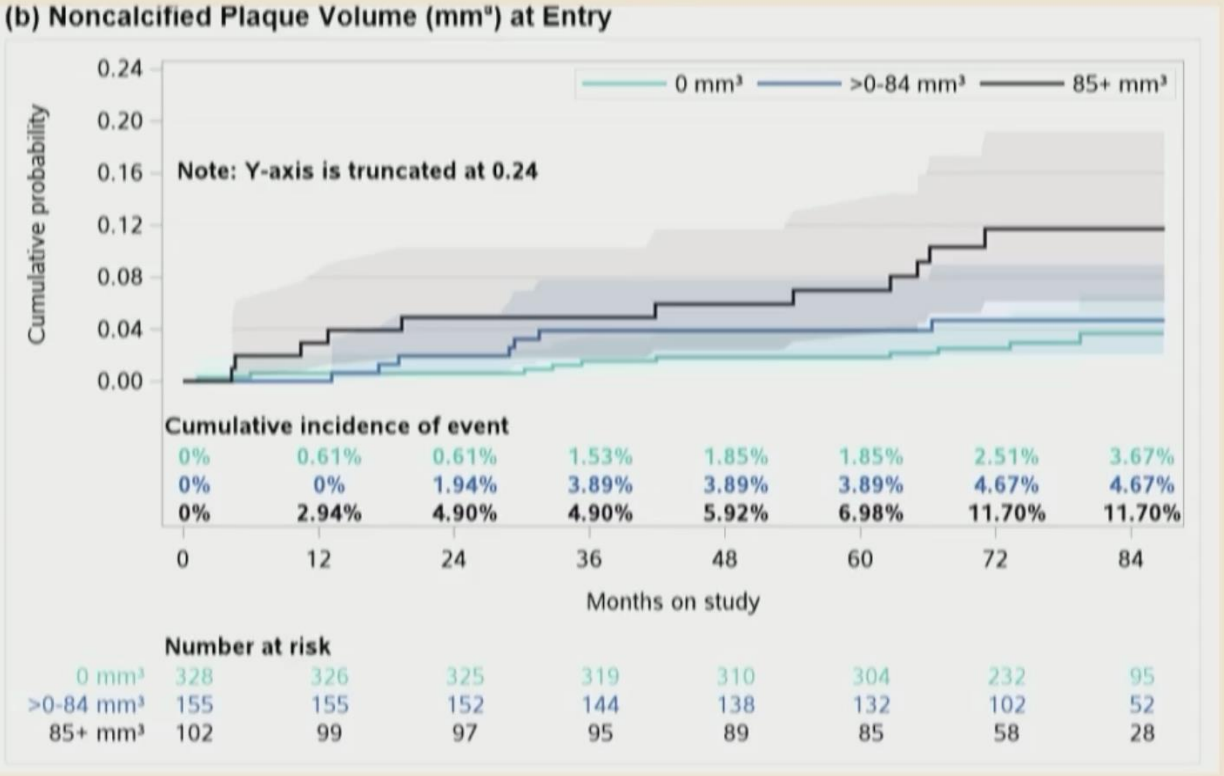
Cumulative Incidence of MACE Over Time, By Baseline Noncalcified Plaque





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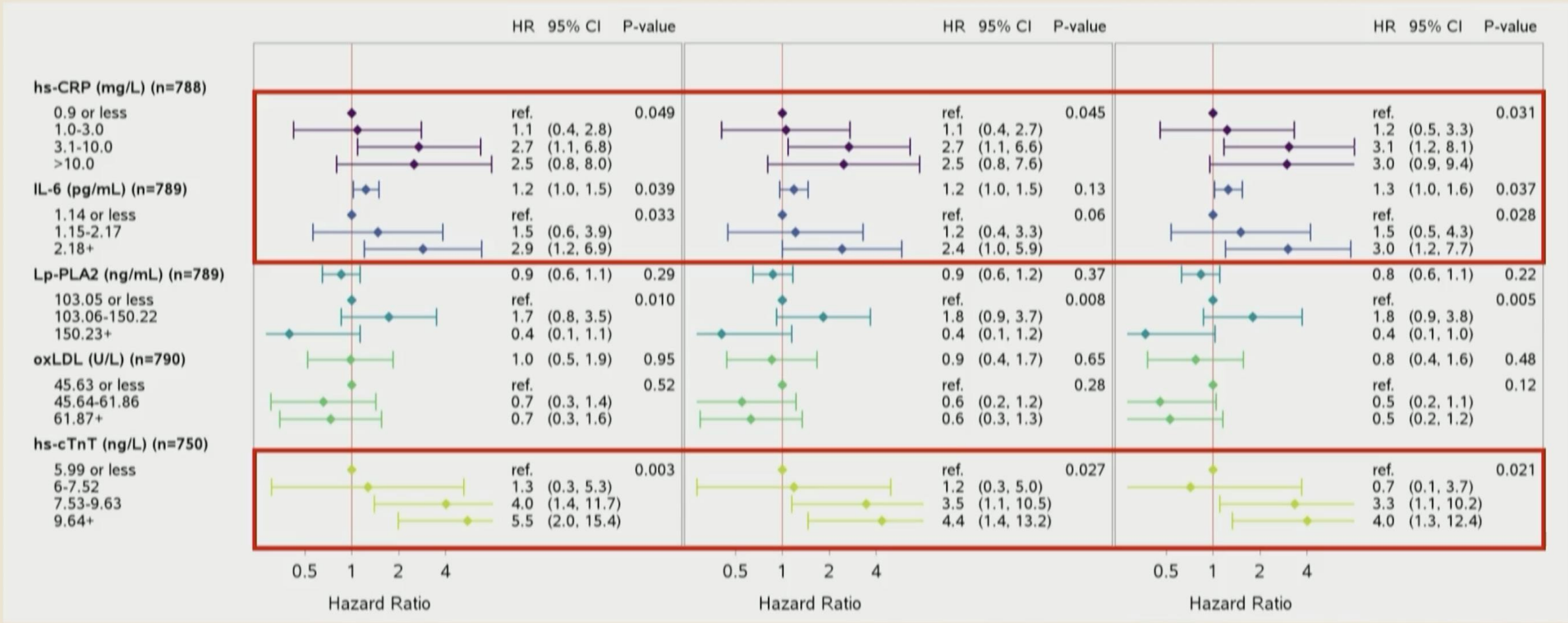
Estimated Baseline Biomarker Effect on Hazard of MACE



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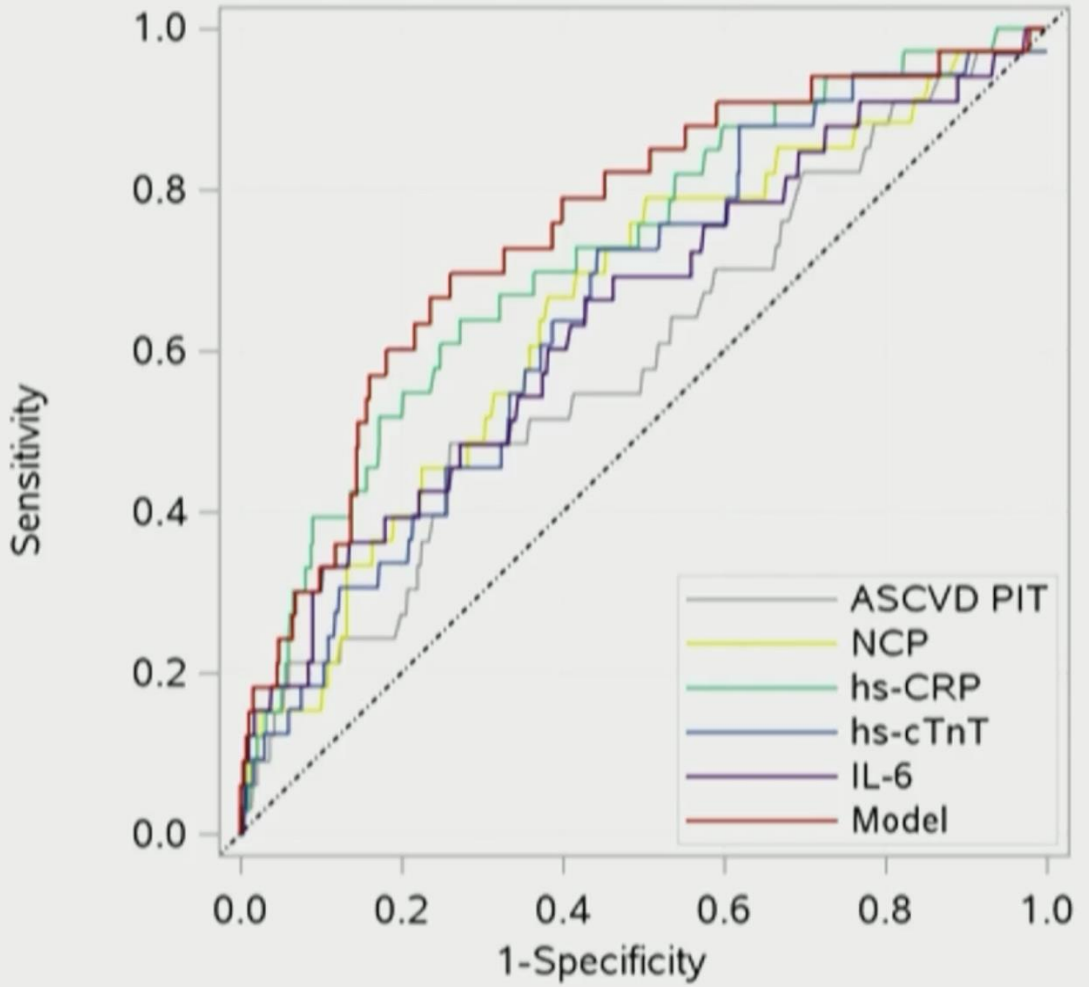
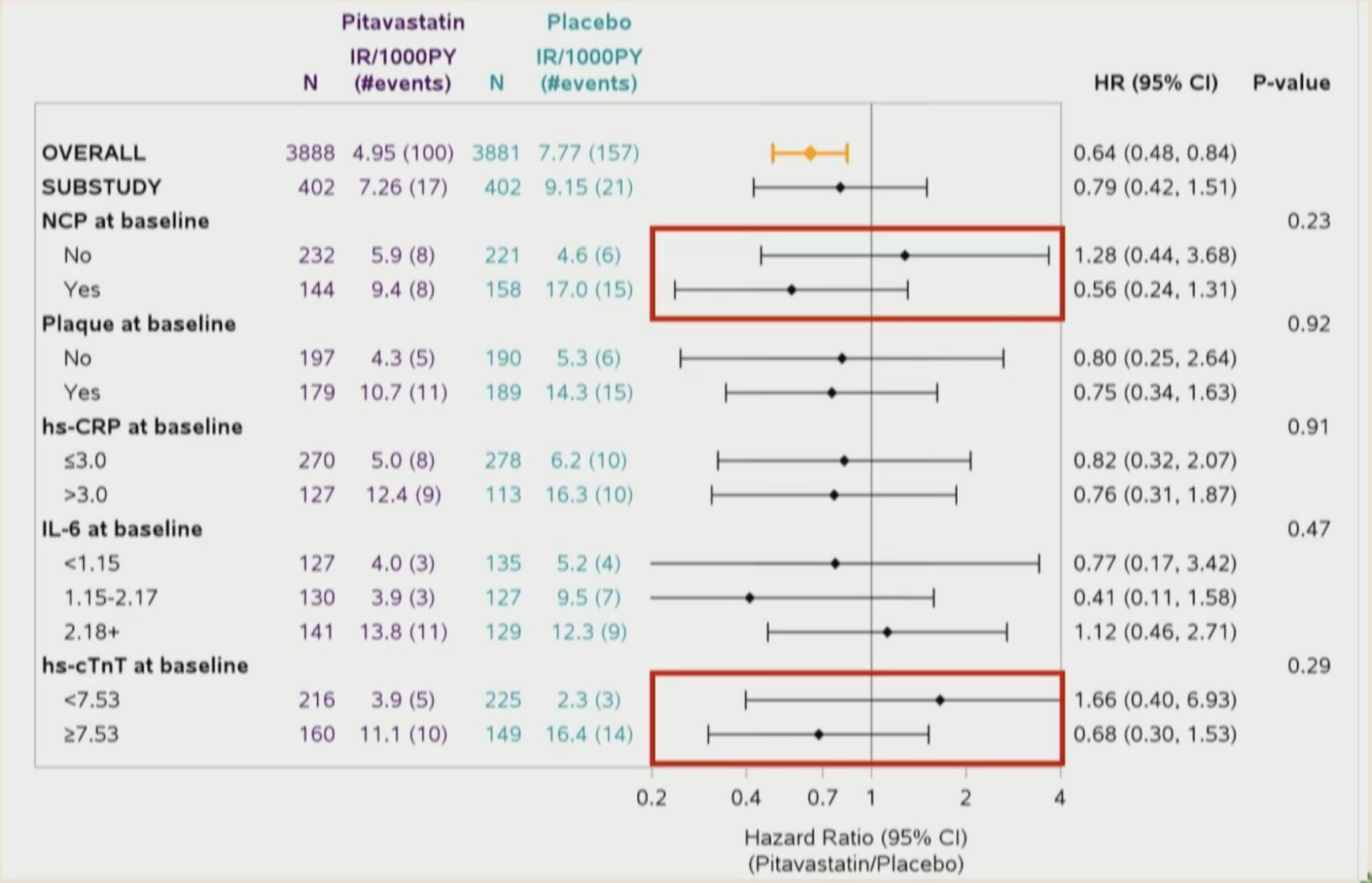
Exploratory Risk Prediction Modeling

Model	Integrated AUC	Uno's C-statistic (SE)
(a) ASCVD PIT	0.585	0.559 (0.057)
IL-6	0.659	0.642 (0.064)
NCP	0.627	0.563 (0.058)
hs-CRP	0.695	0.674 (0.058)
hs-cTnT	0.633	0.676 (0.065)
(b) NCP	0.627	0.563 (0.058)
NCP IL-6	0.670	0.638 (0.057)
NCP hs-CRP	0.700	0.672 (0.058)
NCP hs-cTnT	0.651	0.675 (0.059)
(c) NCP hs-CRP	0.700	0.672 (0.058)
NCP hs-CRP IL-6	0.707	0.678 (0.061)
NCP hs-CRP hs-cTnT	0.720	0.727 (0.055)
NCP hs-cTnT IL-6	0.691	0.705 (0.065)
(d) hs-CRP IL-6	0.699	0.675 (0.063)
hs-CRP hs-cTnT	0.714	0.727 (0.055)
hs-CRP hs-cTnT IL-6	0.722	0.729 (0.058)
hs-cTnT IL-6	0.682	0.706 (0.067)
Full model	0.725	0.729 (0.058)



Modification of Pitavastatin Treatment Effect



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Limitations, Conclusions and Future Directions

- Substudy results may not be generalizable to sicker or more global population
- Plaque, inflammatory and subclinical cardiomyocyte injury markers are related to MACE among ART-treated PWH with low-to-moderate CVD risk
- Statin effects on plaque and specific inflammatory markers may contribute to reduction in MACE beyond LDL
- Future studies among the larger REPRIEVE cohort will:
  - Assess if biomarker/plaque combinations can improve prediction of MACE and benefit from statins
  - Identify mechanistic pathways explaining statin effect and additional pathways to augment statin effects on MACE in PWH

Thank you!

- **Co-Authors:** Lu MT, McCallum S, Ribaudo HJ, Zanni MV, deFilippi C, Taron J, Karady J, Foldyna B, Chu SM, Fichtenbaum CJ, Malvestutto CD, Aberg JA, Mayrhofer T, Douglas PS, Grinspoon SK, and the REPRIEVE Investigators
- **REPRIEVE participants**
- **Site teams and investigators**
- **Funders**