The REPRIEVE trial
What we need to Know

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Disclosures

Type of affiliation / financial interest	**Name of commercial company**
Receipt of grants/research supports:	To my unit from Janssen, Merck, Viiv and Gilead
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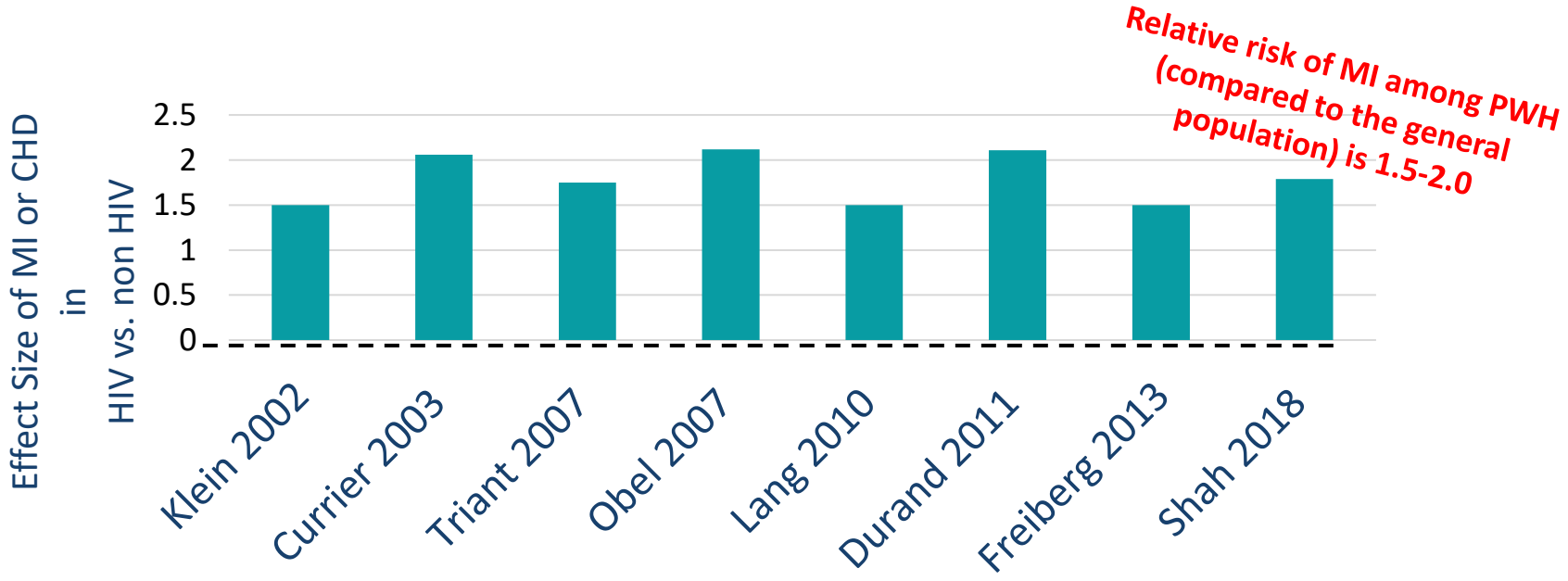
Stock shareholder:	None
Spouse/partner:	None

Why do a trial of Statins in the HIV Population?

Because….
Cardiovascular Disease Risk is Elevated in HIV

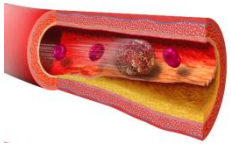
- With newer and more potent ART, death due to AIDS-related complications among PWH has decreased
- However, the risk of **cardiovascular disease** is increased in PWH, and this is now a leading cause of morbidity and mortality among this population
- Importantly, this increased risk of CVD is **beyond that predicted by traditional risk factors** (age, gender, smoking history, etc.)



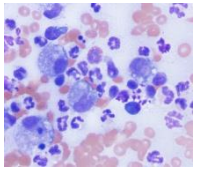
And ….Statins have Effects beyond Lowering LDL

- Statins primary effect is to inhibit HMG-CoA reductase to lower LDL cholesterol
- Statins have many other beneficial effects to reduce vascular disease

Anti-inflammatory



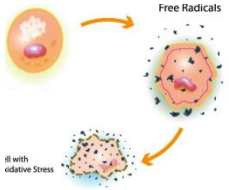
Anti-thrombotic



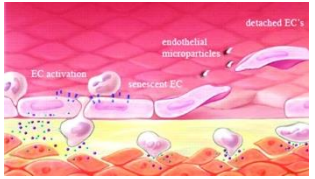
Immunomodulation

STATINS

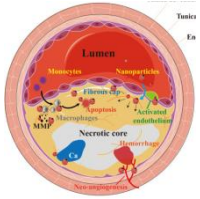
Reduced Oxidative Stress



Improved Endothelial Function/Vascular Tone



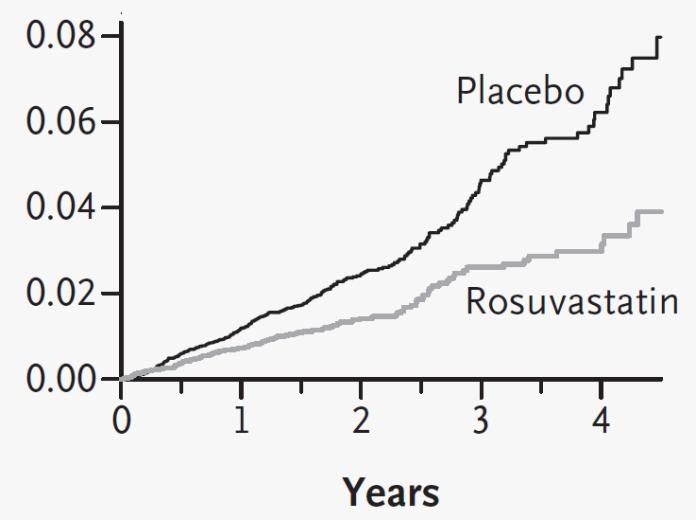
Plaque Stabilization



Arch Toxicol 2023 97:1529

Statins Reduce Vascular Events in Non-HIV Patients with Low LDL and Increased CRP

Events/100p-y:
Placebo: 1.36
Rosuva: 0.77
HR 0.56

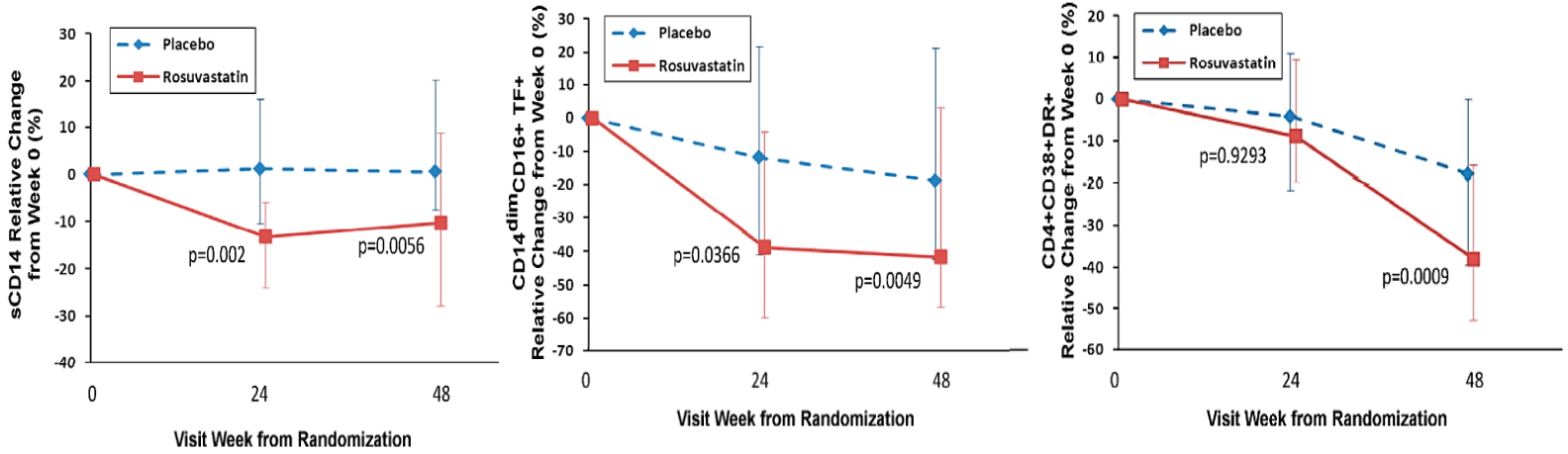


- LDL was reduced 47 mg/dL, and should have resulted in a HR of 0.73 based on LDL lowering alone, according to CTTC meta-analysis.
- Instead, JUPITER showed a HR of 0.56, greater than expected based on LDL lowering alone

Ridker N Engl J Med 2008; CTTC Lancet 2010

Statins Address Both Traditional and Immune Risk Factors in HIV

- LDL Lowering: Statins lower LDL by similar amounts in patients with and without HIV (-26.2% vs -26.9%)
- Reduced Immune Activation: Decrease monocyte activation with decreased circulating levels of sCD14 and the macrophage-derived phospholipase Lp-PLA2



Silverberg Ann Int Med 2009, McComsey CROI 2013, Funderburg JAIDS ePUB

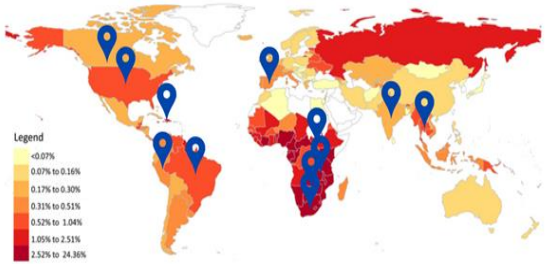
REPRIEVE-METHODS

Inclusion Criteria

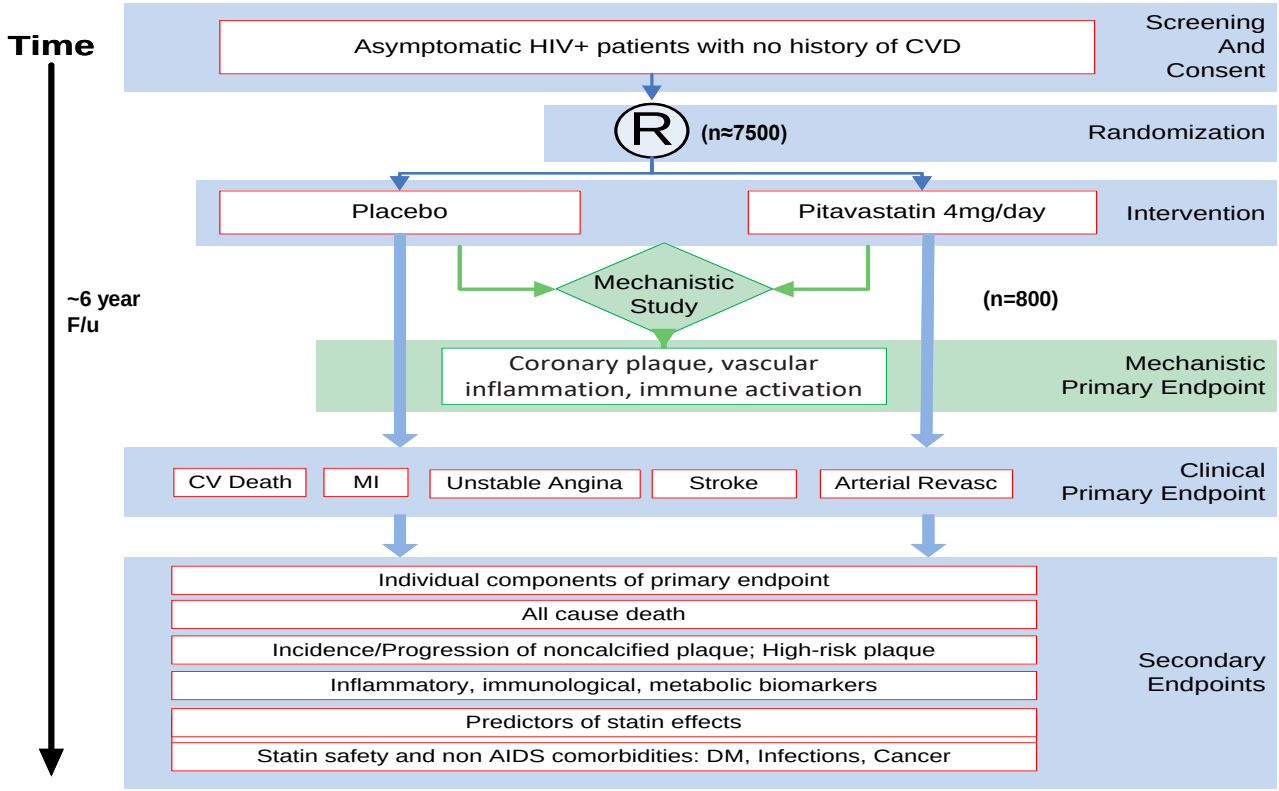
- Documented HIV
- Receiving stable ART
- CD4+ > 100 cells/mm^3
- Age ≥ 40 years, ≤ 75 years
- No known atherosclerotic cardiovascular disease (ASCVD)
- 10-yr ASCVD risk score
  - <7.5%, LDL < 190 mg/dL
  - ≥7.5% and ≤ 10%, LDL < 160 mg/dL
  - >10% and ≤15%, LDL < 130 mg/dL

Exclusion Criteria

- Current use of statins, gemfibrozil, or PCSK9 inhibitors
- Known decompensated cirrhosis



OBJECTIVES



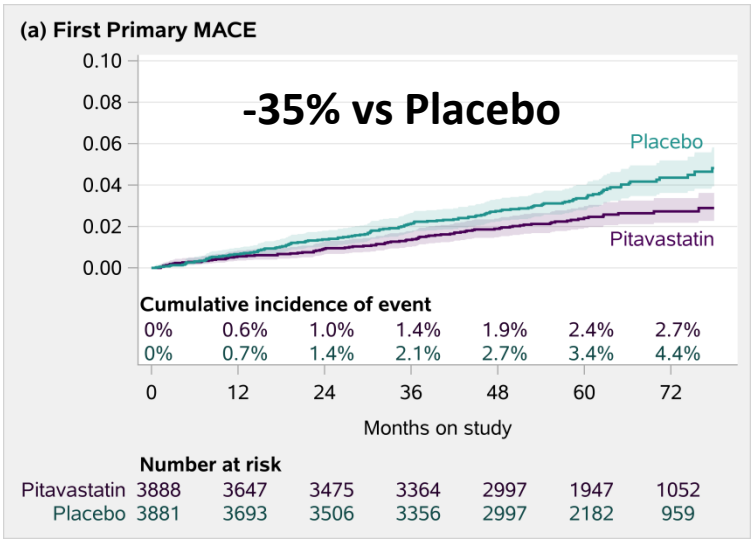
Moderate intensity LDL lowering.
Anti Inflammatory effects.
No DDIs with ARVs.
Neutral or improved effect on glucose metabolism.

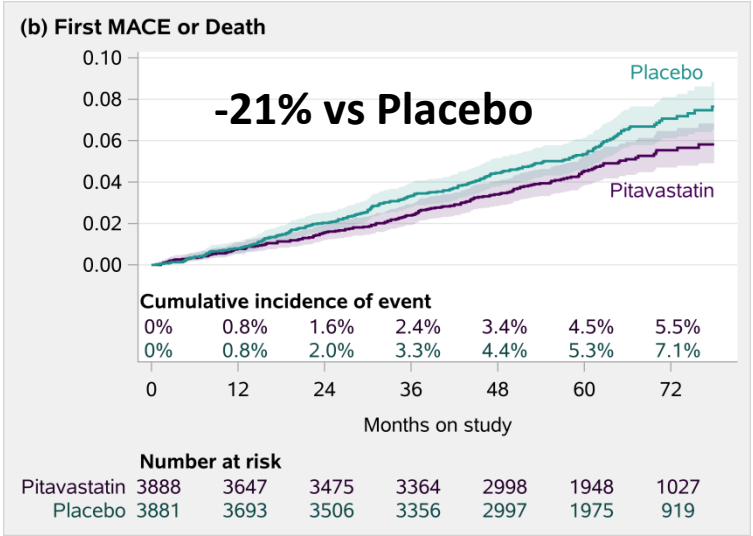
Trial Closure because of a Benefit

- After a median follow-up of approximately 5 years
- ***The DSMB convened at 75% of information and closed the trial for efficacy***, concluding there were no unanticipated safety concerns and that the benefits outweighed the risk of statin therapy in this group

DSMB = data and safety monitoring board

RESULTS - I





Incidence MACE:

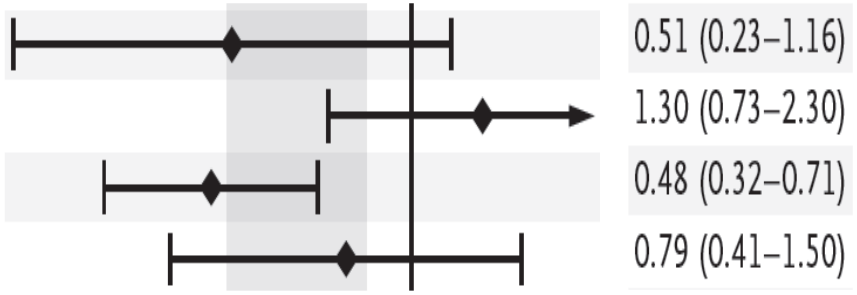
Pitavastatin: 4.81 per 1000 person-years

Placebo: 7.32 per 1000 person-years

Grinspoon S et al. NEJM 2023

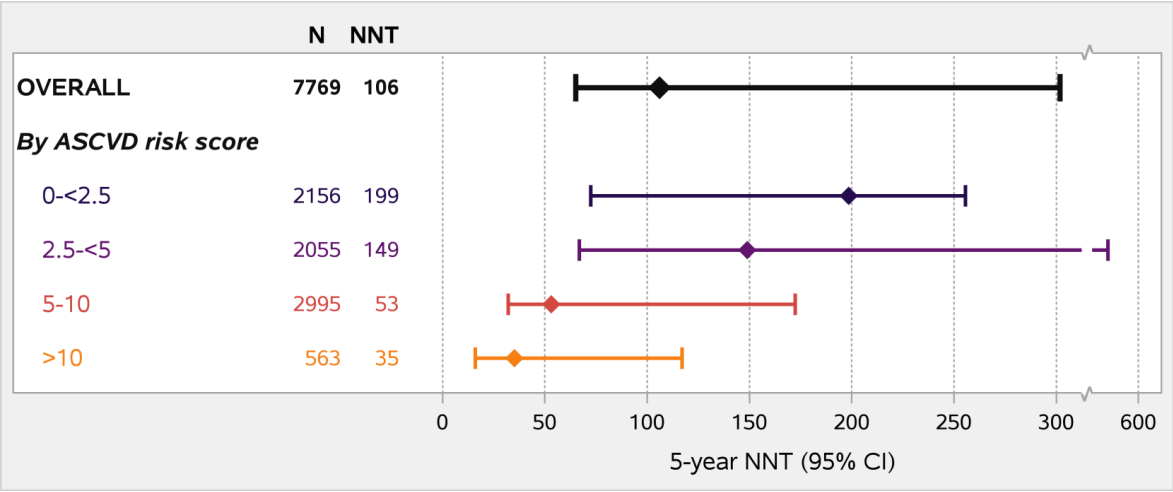
RESULTS - II

ASCVD risk scor	Pitavastatin	Placebo	Pitavastatin	Placebo	Hazard Ratio (95% CI)
	no. of participants		*no./1000 person-yr (no. of events)*		
0 to <2.5%	1096	1060	1.6 (9)	3.1 (17)	0.51 (0.23–1.16)
2.5 to <5%	1030	1025	5.3 (27)	4.1 (21)	1.30 (0.73–2.30)
5 to 10%	1474	1521	5.5 (36)	11.5 (78)	0.48 (0.32–0.71)
>10%	288	275	13.9 (17)	17.5 (20)	0.79 (0.41–1.50)



Grinspoon S et al. NEJM 2023

5-Yr Number Needed To Treat (NNT) overall to Prevent One MACE Event =106



Increasing CVD with increasing ASCVD risk score

Decreasing NNT with increasing ASCVD risk score

https://thennt.com/

Primary prevention CVD

JUPITER statin trial,
5-year NNT value is 57.

Anti BP RX
10-year NNT is 100

Aspirin
10-year NNT is 333.

RESULTS - III

Adverse events	Pitavastatin (N = 3888)		Placebo (N = 3881)		Incidence Rate Ratio (95% CI)*
	No. with Event	Incidence Rate (95% CI) *no./100 person-yr*	No. with Event	Incidence Rate (95% CI) *no./100 person-yr*	
Nonfatal serious adverse event	695	4.16 (3.86–4.48)	694	4.13 (3.84–4.45)	1.01 (0.91–1.12)
Diabetes mellitus†	206	1.13 (0.99–1.30)	155	0.84 (0.72–0.99)	1.35 (1.09–1.66)
Myalgia, muscle weakness, or myopathy of grade ≥3 or treatment-limiting‡	91	0.49 (0.40–0.61)	53	0.28 (0.22–0.37)	1.74 (1.24–2.45)
Rhabdomyolysis of grade ≥3 or treatment-limiting	3	0.02 (0.01–0.05)	4	0.02 (0.01–0.06)	0.75 (0.17–3.37)§
Alanine aminotransferase elevation of grade ≥3	11	0.06 (0.03–0.11)	8	0.04 (0.02–0.08)	1.38 (0.56–3.43)§
Any adverse event¶	1304	8.88 (8.41–9.38)	1256	8.37 (7.92–8.84)	1.06 (0.98–1.15)

Grinspoon S et al. NEJM 2023

REPRIEVE
What we need to Know?

Who Benefits Most from REPRIEVE?

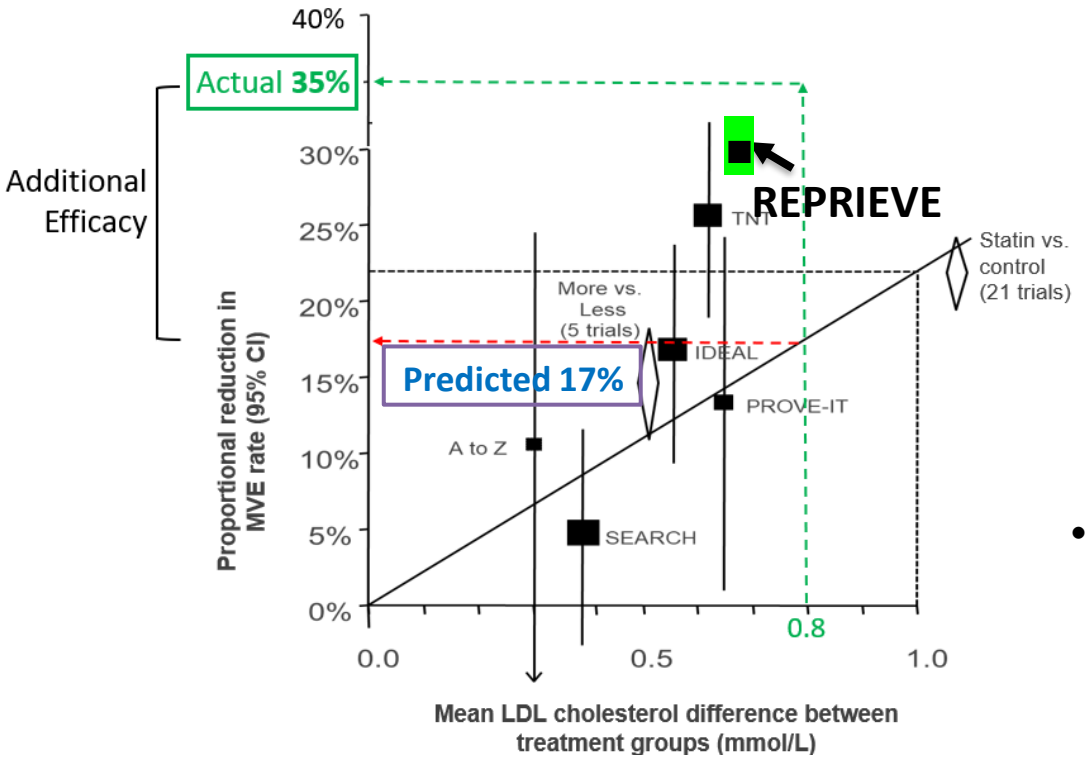
- Significant for those with a CVD risk score > 5% (HR 0.48; 0.32-0.71).

- The benefit of pitavastatin in reducing major CV events was **not statistically significant** for those with
  - very low CVD risk scoring 0 to 2.5%: HR 0.51 (0.23-1.16)
  - those with low CVD risk from 2.5 to 5% (HR 1.30; 0.73-2.30).

  - those with HTN (0.91; 0.63-1.31) WHY?
  - current smokers. (0.75; 0.49-1.14).

    These are two subpopulations we should probably should insist more on putting them on a statin.

Why was the Effect Larger than Anticipated Based on Lowering of LDL?



- **LDL lowering matters but statin effect is beyond what is expected for LDL lowering alone**

Note: 35% is point estimate, CI % is 17 – 52%

Lancet 2010; 376: 1670-81

What is the mechanism of this risk reduction?

The magnitude was greater than would have been expected solely based on the lipid-lowering effect.

Did the anti-inflammatory property of the statin also play a major role?

Or is it is possible that what we saw in REPRIEVE reflects intervention earlier in the atherosclerotic process?

But If statins do have anti-inflammatory effects in people with HIV this may have a positive impact on the risk or progression of other age-related co-morbidities.

Clinical Infectious Diseases
MAJOR ARTICLE

Sex Differences in Subclinical Atherosclerosis and Systemic Immune Activation/Inflammation Among People With Human Immunodeficiency Virus in the United States

Markella V. Zanni,[1,a] Borek Foldyna,[2,a] Sara McCallum,[1] Tricia H. Burdo,[3] Sara E. Looby,[1,4] Kathleen V. Fitch,[1] Evelynne S. Fulda,[1] Patrick Autissier,[5] Gerald S. Bloomfield,[6] Carlos D. Malvestutto,[7] Carl J. Fichtenbaum,[8] Edgar T. Overton,[9] Judith A. Aberg,[10] Kristine M. Erlandson,[11] Thomas B. Campbell,[11] Grant B. Ellsworth,[12] Anandi N. Sheth,[13] Babafemi Taiwo,[14] Judith S. Currier,[15] Udo Hoffmann,[2] Michael T. Lu,[2] Pamela S. Douglas,[16] Heather J. Ribaudo,[17] and Steven K. Grinspoon[1]

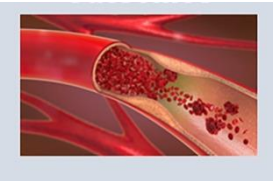
among US REPRIEVE participants

(controlling for 10-y ASCVD risk score + BMI)

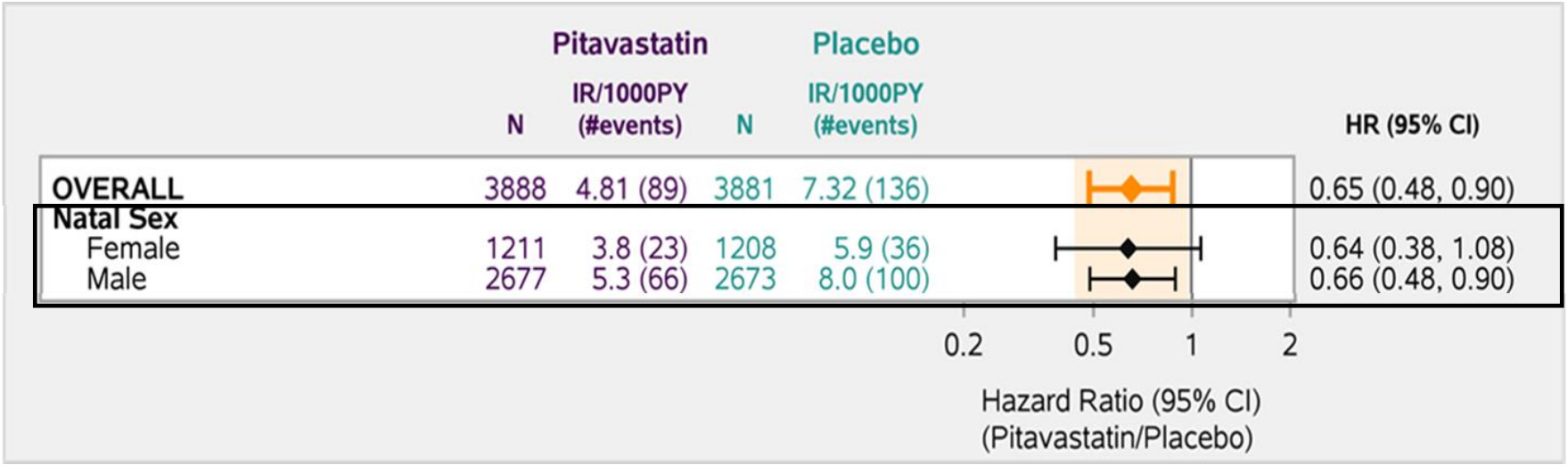
women vs. men:

↑ Immune activation/ inflammatory markers

↓ Coronary artery plaque prevalence



Women vs. Men?
Effect Size of Statin Rx to Reduce MACE Consistent



Key questions: Are there sex-differences in the mechanisms of statin-induced efficacy – i.e. might reduction in MACE be driven to a greater extent by immune modulation among women (vs. men) living with HIV?

Other factors: N° pre and post menopausal and prior BP in pregnancy

Are our risk scores correct?
Underestimating CVD Risk in PLWHIV

Performance of CVD Risk Prediction Models among People with HIV

Risk Prediction Model	# Cases	O:E ratio
D:A:D 2010	804	1.20
D:AD 2016	1629	1.31
Framingham 10yr	1751	0.95
Framingham 5yr	1088	1.51
Pooled Cohort Equations 10yr	1720	1.13
Pooled Cohort Equations 5yr	174	2.31

- **Most scores moderate discrimination (AUC 0.7 to 0.8)**
- **Most underpredict CVD risk (O:E >1)**
- **FRS and PCE 10-year better calibrated**

Soares et al. JAMA Card 2022;1

REPRIEVE

Low-moderate CVD risk based on:
The American Heart Association and American College of Cardiology 2013 Pooled Cohort Equation risk calculator with specific thresholds for LDL-C

Median 10-year risk 4.5%

Median baseline LDL-C of 2.8 mmol/L

However REPRIEVE data is for a 5 year Risk

What is the best Risk Calculator to use?

How will we interpret absolute vs. relative risk in clinical practice?

Those at lowest cardiovascular risk have a higher NNT (200) to benefit one patient.

Even if pitavastatin lowers the risk by 35% in this group, does the low absolute risk make it worthwhile to add another drug?

But..Patients are ageing so the conversation re starting statins can be started before the risk reaches 5%

Side Effects

Serious adverse events similar in each group: IRR 1.02 (0.92-1.14)

Muscle-related symptoms
Were higher in the pitavastatin group but mostly mild and only 1% withdrew with symptomatology

Diabetes
Is the higher incidence of diabetes with statin therapy (1% increase) more than enough to counter any of these favorable results?

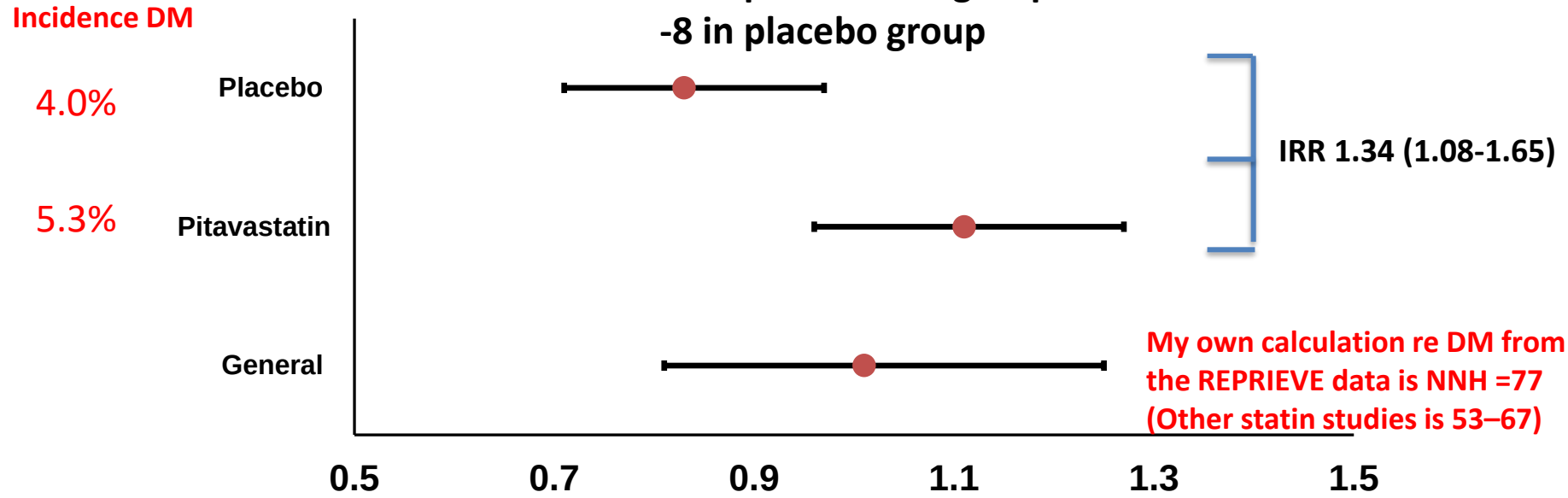
Comments in the Press "some African doctors are unsure whether pitavastatin will provide meaningful benefits when taking into account the added risk for diabetes-,for every case of myocardial infarction prevented by pitavastatin in REPRIEVE, there were 5 additional cases of diabetes"

In regions with high prevalence and propensity to Diabetes need to be concerned?

Diabetics in REPRIEVE gained a benefit.

Diabetes Rates in REPRIEVE vs. General Population
Aged 45-64 per US Centers for Disease Control

12 MACE events in participants with diabetes:
-4 in pitavastatin group
-8 in placebo group



Centers for Disease Control and Prevention. Incidence of Newly Diagnosed Diabetes. https://www.cdc.gov/diabetes/data/statistics-report/newly-diagnosed-diabetes.html#print

IRR: incidence rate ratio

Statins and T2DM risk

Overall treating 255 people (95% CI 150-852) for 4 years results in one extra case of diabetes.

Factors Predicting new onset T2DM with statins

Baseline fasting glucose level

Body mass index,

Hypertension

Fasting triglycerides

J Am Coll Cardiol. 2013 Jan; 61(2): 148-52

More Questions

- How much mortality was due to non CV disease?
- CCF commoner than MIs in some areas of the world ?
- Do Different levels of risk eg smoking rates in some areas of world affect the results?
- In Hypertensives and smokers (where no additional benefit was seen) were the MACE events different ?

Would another statin have comparable results?

- The data from REPRIEVE are specific to pitavastatin, chosen because:
  - ✓ little interaction with ART
  - ✓ potent lipid lowering and anti-inflammatory effects
- Pitavastatin is available in many countries,
- Generic pitavastatin available after Nov. 2023
- But if it is not available, **will other statins be effective?**

Other issues

- What do we do when new lipid drugs are available – take every 6/12 e.g.mRNAs Misiliran
- What might be the effect of Weight loss drugs on CV risk?
- Could an anti-inflammation drug be more useful?

Who should initiate and monitor statin use? Who should pay?

- ID specialists?
- General internists?
- Family Doctors?
- In Europe no overall increase in Statin use in HIV in spite of ageing population
- Will REPRIEVE change this ?

What will the future look like?

What will Guidelines Say?

Will there be a Public Health approach similar to ARV provision with TLD?

Will high Income countries have an Individualised therapy approach?

Implications for Care

- Statin therapy, with lifestyle counselling, should be considered for People Living with HIV, even those with low to moderate predicted traditional risk, to reduce major cardiovascular events and death
- For PWH, the decision to take a statin should be individualized
  - Shared decision making between individual and clinician
  - All relevant factors including statin risks and benefits should be considered, including but not limited to the results of REPRIEVE. This may include drug interactions, metabolic factors, and patient preferences
  - All conversations about risk should emphasize a heart healthy lifestyle, ideal diet, counselling on smoking, blood pressure, dyslipidemia, other CVD risks

Conclusions

Despite HIV being considered a risk equivalent, no prior trial has assessed a primary prevention strategy for this group, who would not typically be recommended for statin therapy

Among PWH 40-75, on ART, with low to moderate risk and normal range LDL, treatment with pitavastatin is effective and prevents MACE

Considerations should be given to expanding treatment guidelines in this regard

Finally

- Remember REPRIEVE was a big randomised study!
- It was stopped early because of significant differences
- Many questions still to be answered-so beware of over optimistic and over pessimistic predictions
- If it needs world wide implementation then we can do it…..!

Thanks

- Esteban Martinez and NEAT ID investigators

- Steve Grinspoon and the REPRIEVE team