Cardiometabolic Prevention for Persons with HIV: Implications of REPRIEVE Trial

Carl J. Fichtenbaum, MD

University of Cincinnati College of Medicine

August 31, 2023

National Heart, Lung, and Blood Institute

National Institute of Allergy and Infectious Diseases

Disclosures

- I receive research grants for studies that go to my institution from Gilead Sciences, Merck, Moderna and ViiV Healthcare/GSK
- I have been a scientific advisor for ViiV Healthcare and Theratechnologies within the past 12 months
- I receive funding from NIH (NIAID, NHLBI) for the conduct of studies.

The REPRIEVE trial: Developing a cardiovascular disease prevention strategy for people with HIV

These slides are to be used for educational purposes only

For the complete manuscript go to https://www.nejm.org/doi/pdf/10.1056/NEJMoa2304146

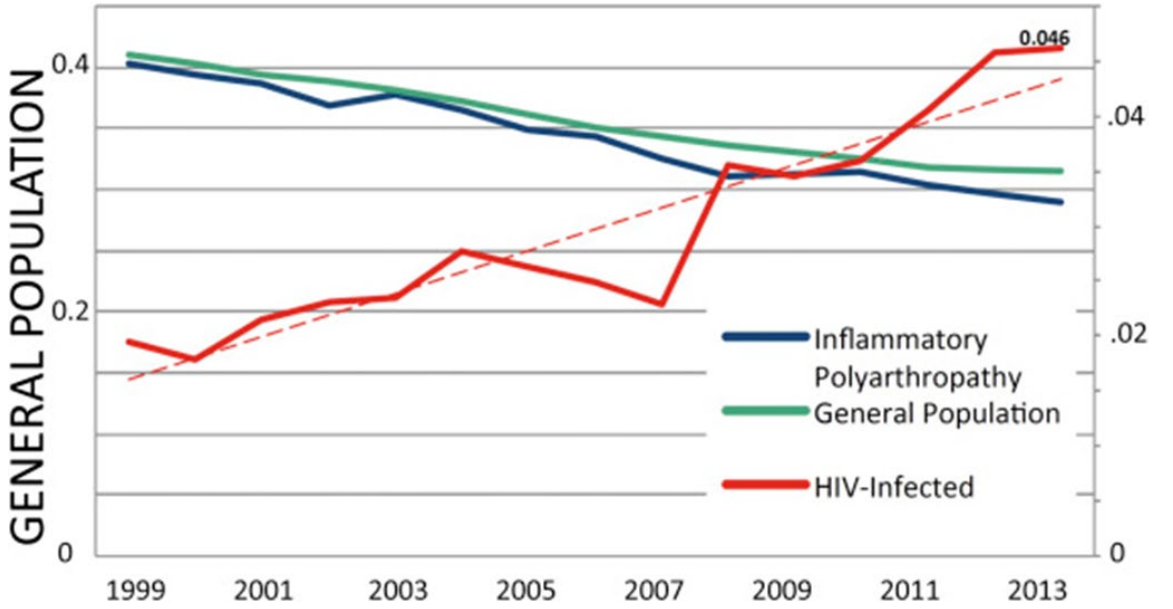
National Heart, Lung, and Blood Institute

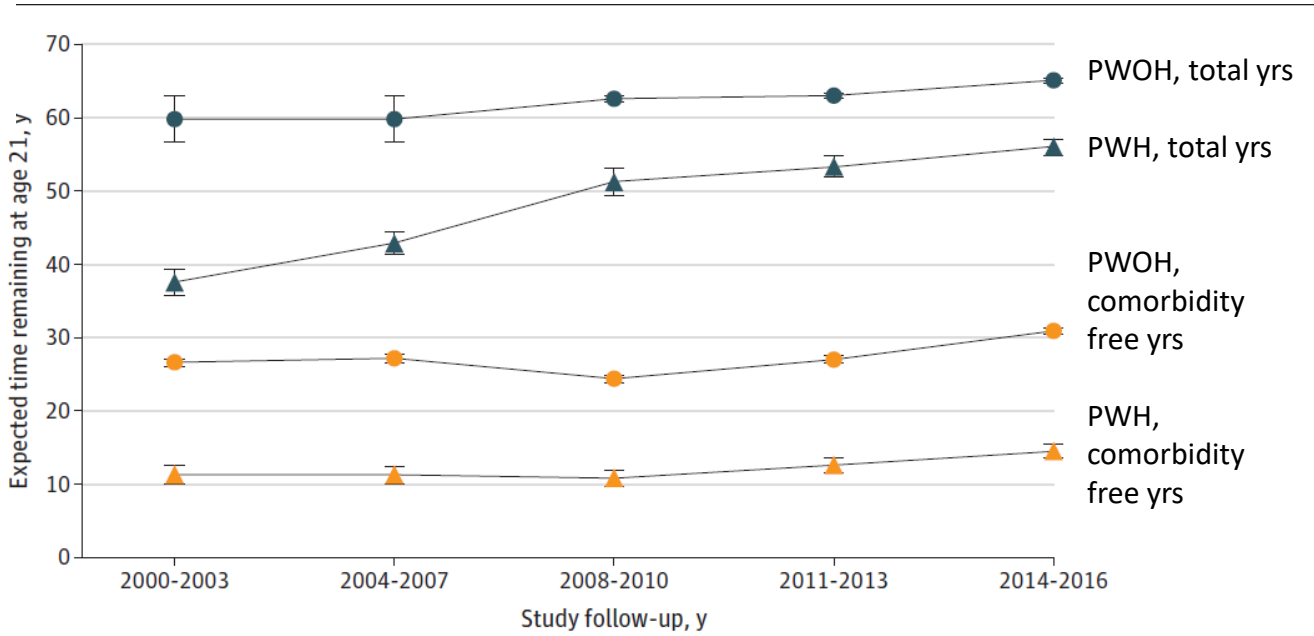
National Institute of Allergy and Infectious Diseases

AIDS CLINICAL TRIALS GROUP

Key REPRIEVE Results and the Utility of Statins Among PWH: What Have We Learned?

Cardiovascular Disease is Increasing in PWH, Contributing to a Persistent Comorbidity Gap





Marcus et al., JAMA Network Open 2020; Feinstein et al., Am J Card 201

Rationale

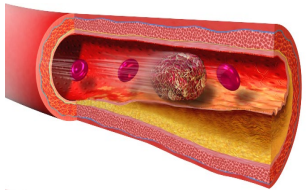
- PWH demonstrate increased cardiovascular disease (CVD) (50-100%) and excess plaque controlling for traditional risk, even at a young age
- ART reduces comorbidities (SMART) but residual immune activation persists, even with good viral suppression - ART alone is not sufficient to prevent CVD
- Statins lower LDL cholesterol, a main driver of CVD in PWH, but also residual immune activation and inflammation, including among PWH
- Pitavastatin is a moderate intensity statin, unaffected by ART, with good LDL and anti-inflammatory properties
- We hypothesized pitavastatin would prevent MACE through these effects in PWH, at low to moderate risk, for whom statins not typically prescribed under current guidelines

MACE = major adverse cardiovascular events

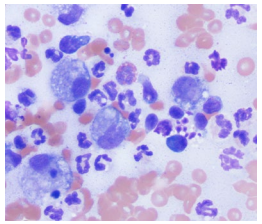
Beyond LDL: Pleiotropic Effects of Statins

- 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



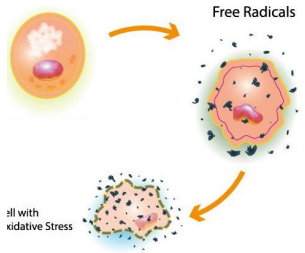
Anti-thrombotic



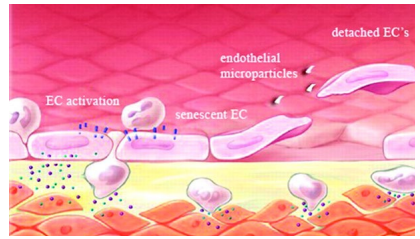
Immunomodulation

STATINS

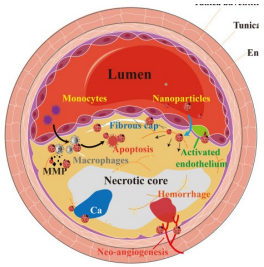
Reduced Oxidative Stress



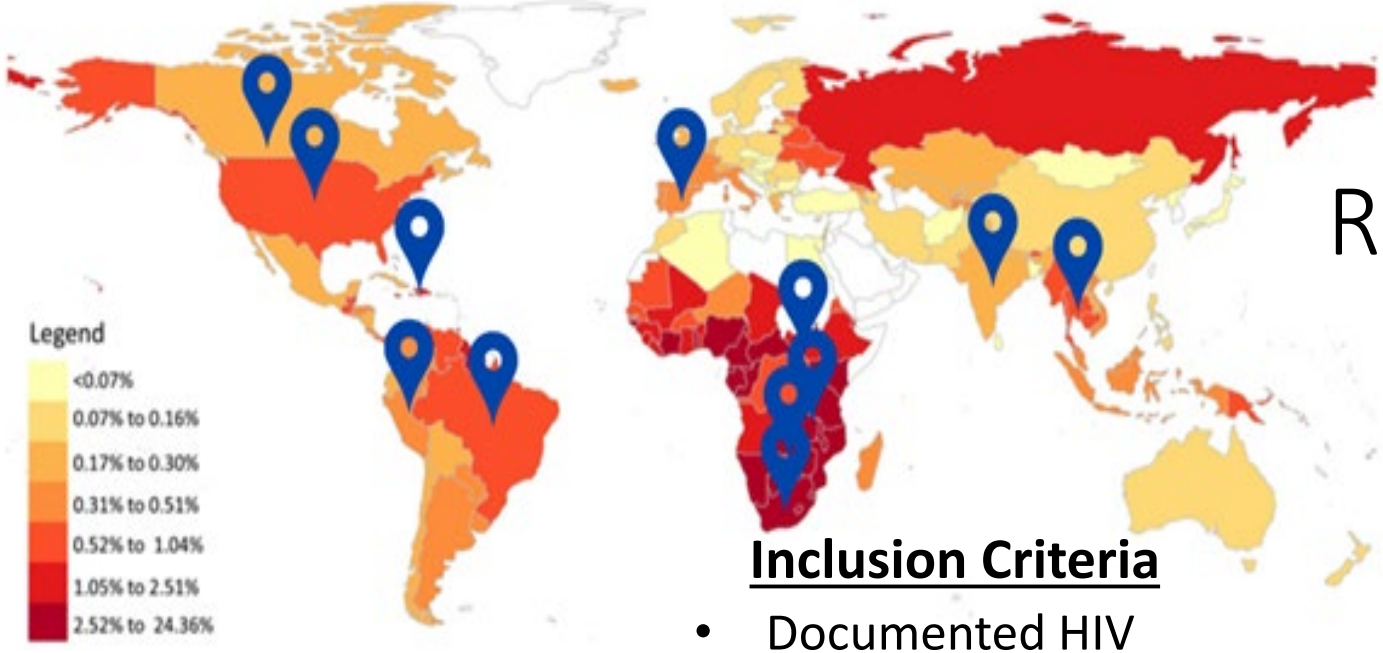
Improved Endothelial Function/Vascular Tone



Plaque Stabilization



Arch Toxicol 2023 97:1529



REPRIEVE Study Population

Inclusion Criteria

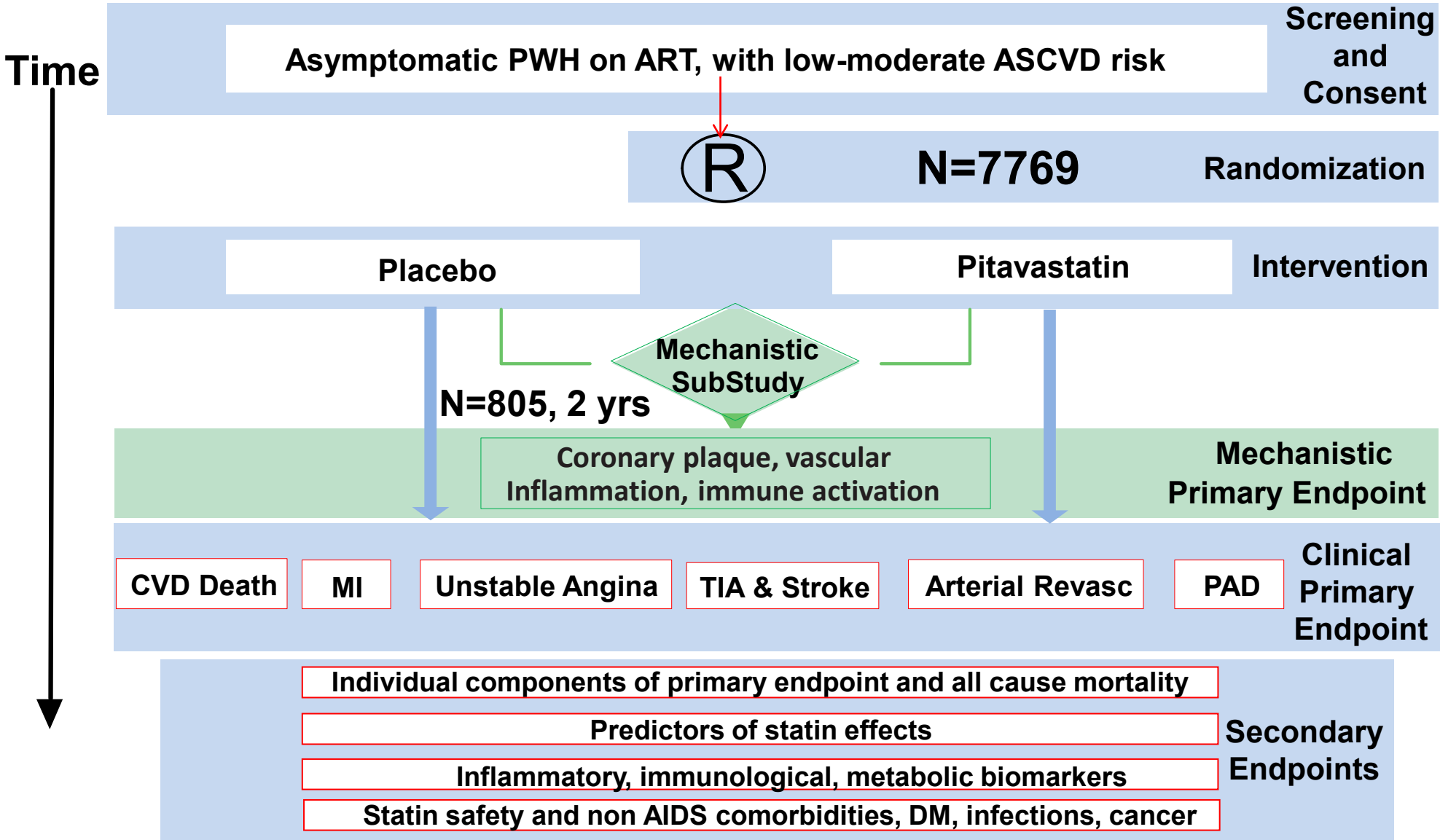
- Documented HIV
- Receiving stable ART
- CD4+ > 100 cells/mm3
- Age ≥ 40 years, ≤ 75 years
- No known atherosclerotic cardiovascular disease (ASCVD)
- 10-yr ASCVD risk score
  - <7.5% LDL < 190 mg/dL
  - ≥7.5% and ≤ 10% LDL, < 160 mg/dL
  - >10% and ≤15%, LDL < 130 mg/dL
- Certain laboratory parameters

Exclusion Criteria

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

Note: For LDL, to convert from mg/dL to SI (in mmol/L) multiply by 0.02586

REPRIEVE Trial Schema



Global Enrollment

	High Income (N=118)	Latin America and Caribbean (N=15)	S. East/East Asia (N=2)	South Asia (N=2)	Sub-Saharan Africa (N=8)	Total (N=145)
Overall Statistics						
Total number screened	5,539	1,953	824	634	1,915	10,865
Total number enrolled	4,095	1,423	590	504	1,157	7,769
Percent of total enrollment	53%	18%	7.6%	6.5%	15%	100%

Baseline Characteristics		Total (N=7769)	Pitavastatin (N=3888)	Placebo (N=3881)
Age (years)	Median (Q1 – Q3)	50 (45-55)	50 (45-55)	50 (45-55)
Natal sex	Male	5350 (69%)	2677 (69%)	2673 (69%)
	Female	2419 (31%)	1211 (31%)	1208 (31%)
Gender identity	Cisgender	7367 (95%)	3687 (95%)	3680 (95%)
	Transgender spectrum	127 (2%)	63 (2%)	64 (2%)
	Not reported	275 (4%)	138 (4%)	137 (4%)
Race	White	2704 (35%)	1634 (35%)	1340 (35%)
	Black/African American	3208 (41%)	1569 (40%)	1639 (42%)
	Asian	1138 (15%)	571 (15%)	567 (15%)
CD4 count (cells/mm3)	Median (Q1 – Q3)	621 (448-827)	620 (449-832)	622 (445-824)
Nadir CD4 count (cells/mm3)	< 50 50-199 ≥ 200	1409 (18%) 2392 (31%) 3706 (48%)	688 (18%) 1202 (31%) 1859 (49%)	721 (19%) 1190 (31%) 1847 (47%)
HIV RNA (Copies/mL)	< LLQ LLQ - < 400 400+ Missing	5250 (88%) 617 (10%) 130 (2%) 1772	2641 (88%) 305 (10%) 63 (2%) 879	2609 (87%) 312 (10%) 67 (2%) 893
ASCVD risk score, (%)	Median (Q1 – Q3)	4.5 (2.1-7.0)	4.5 (2.1-7.0)	4.5 (2.2-7.0)
LDL-C (mg/dL)	Median (Q1 – Q3)	108 (87-128)	109 (87-128)	108 (87-127)

Baseline ART Regimen and Duration

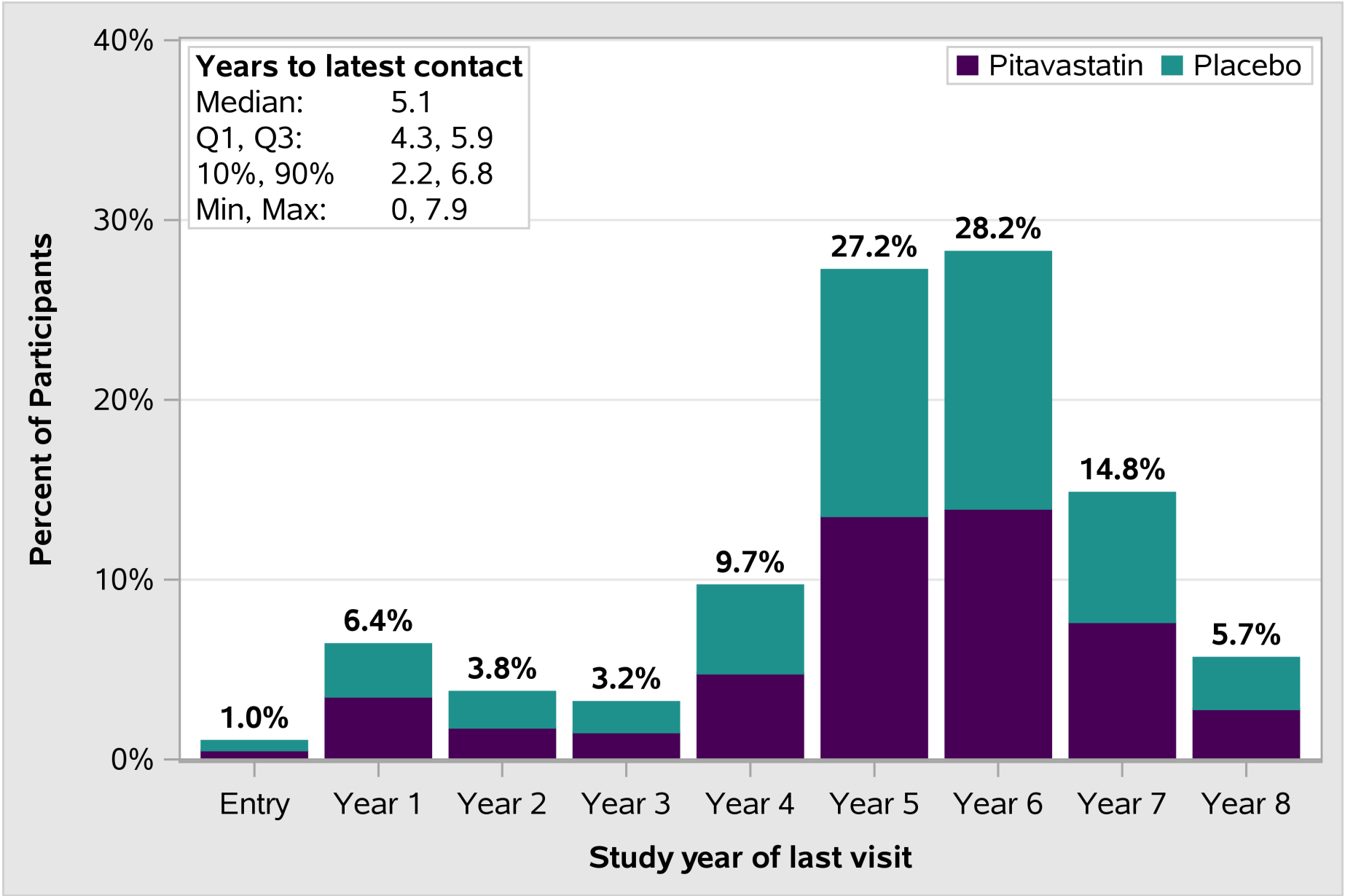
		Pitavastatin (N=3888)	Placebo (N=3881)	Total (N=7769)	High Income (N=4095)	Latin America and Caribbean (N=1423)	S. East/East Asia (N=590)	South Asia (N=504)	Sub-Saharan Africa (N=1157)
Total ART use (years)	<5	847 (22%)	857 (22%)	1704 (22%)	675 (16%)	490 (34%)	55 (9%)	143 (28%)	341 (29%)
	5-10	1190 (31%)	1118 (29%)	2308 (30%)	1115 (27%)	462 (32%)	123 (21%)	205 (41%)	403 (35%)
	10+	1851 (48%)	1904 (49%)	3755 (48%)	2303 (56%)	471 (33%)	412 (70%)	156 (31%)	413 (36%)
Entry ART regimen class	NRTI + NNRTI	1843 (47%)	1826 (47%)	3669 (47%)	996 (24%)	815 (57%)	466 (79%)	410 (81%)	982 (85%)
	NRTI + INSTI	998 (26%)	993 (26%)	1991 (26%)	1875 (46%)	85 (6%)	3 (1%)	3 (1%)	25 (2%)
	NRTI + PI	728 (19%)	708 (18%)	1436 (18%)	674 (16%)	442 (31%)	105 (18%)	82 (16%)	133 (11%)
	NRTI-sparing	95 (2%)	108 (3%)	203 (3%)	164 (4%)	18 (1%)	9 (2%)	9 (2%)	3 (0%)
	Other NRTI-containing	224 (6%)	246 (6%)	470 (6%)	386 (9%)	63 (4%)	7 (1%)	0 (0%)	14 (1%)
Entry ART regimen duration (years)	<1	1128 (29%)	1133 (29%)	2261 (29%)	1441 (35%)	414 (29%)	251 (43%)	64 (13%)	91 (8%)
	1-3	1134 (29%)	1150 (30%)	2284 (29%)	1277 (31%)	415 (29%)	165 (28%)	128 (25%)	299 (26%)
	3-5	611 (16%)	628 (16%)	1239 (16%)	472 (12%)	231 (16%)	61 (10%)	103 (20%)	372 (32%)
	5+	1015 (26%)	970 (25%)	1985 (26%)	905 (22%)	363 (26%)	113 (19%)	209 (41%)	395 (34%)

Recent Events and Trial Closure

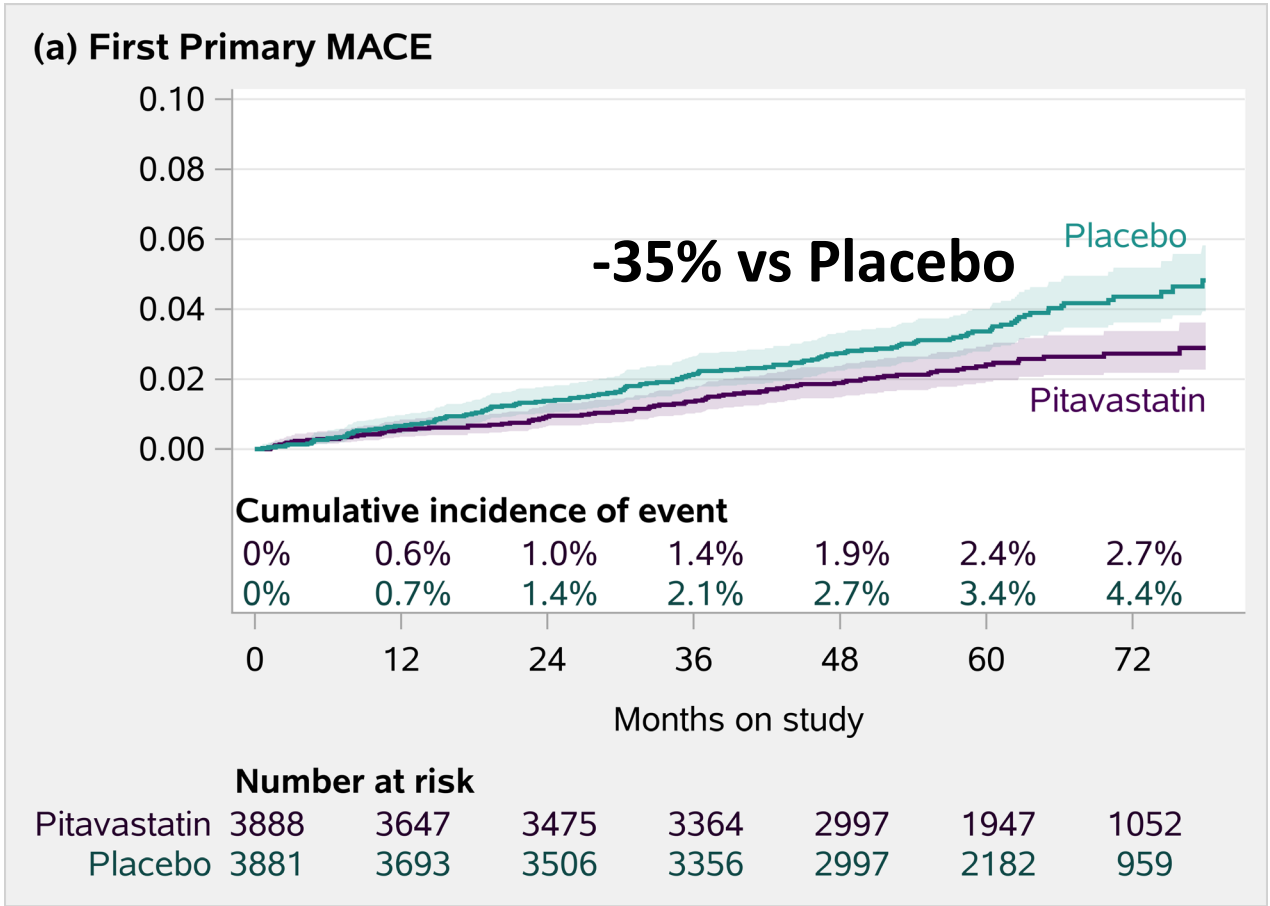
- REPRIEVE is an events driven trial with 85% power to detect a HR of 0.70 with 288 planned events
- ***The DSMB convened at 75% of information for a pre-specified data review and closed the trial for efficacy***, concluding there were no unanticipated safety concerns and that the benefits outweighed the risk of statin therapy in this group

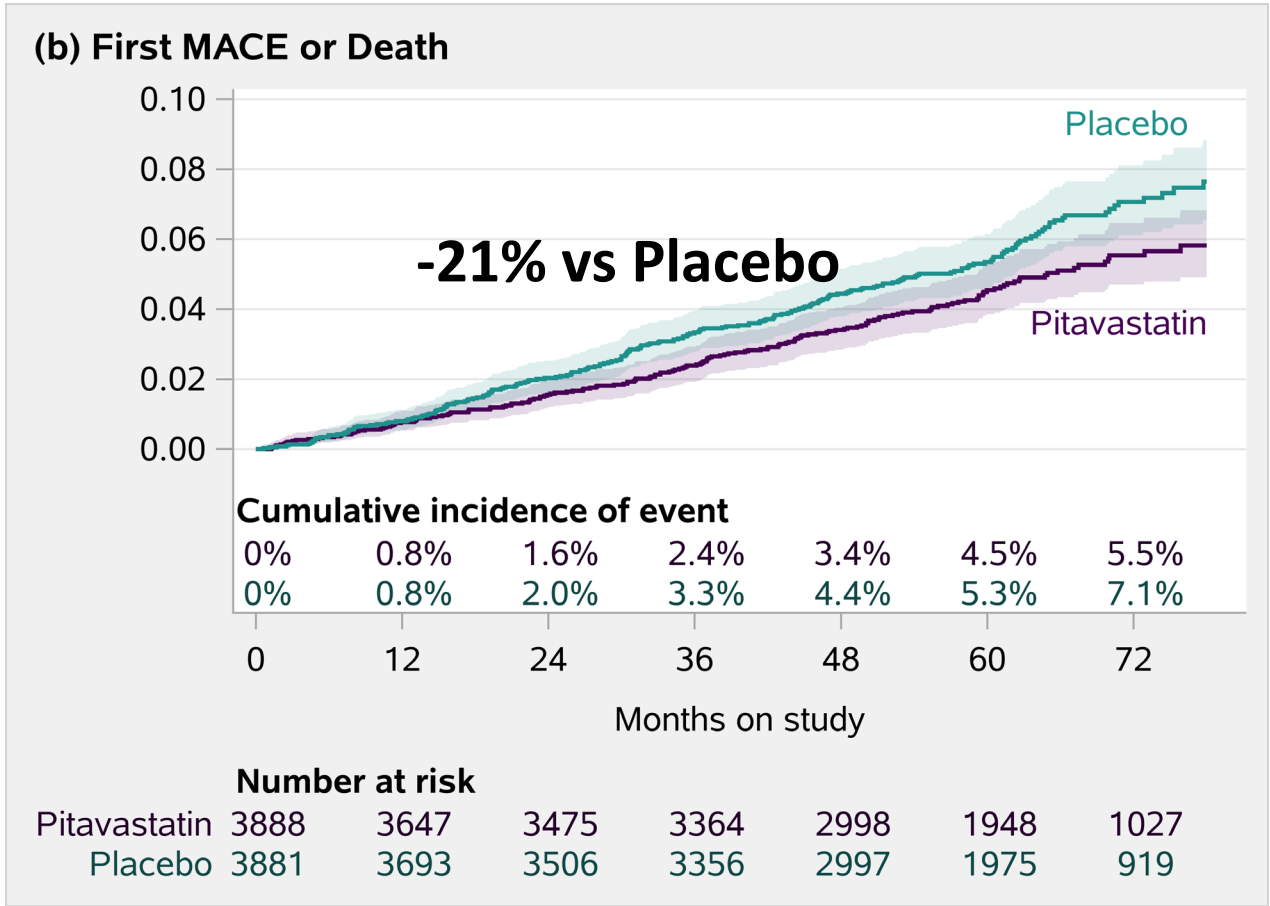
DSMB = data and safety monitoring board

Duration of Follow-Up at Time of DSMB



Primary and Key Secondary Endpoints



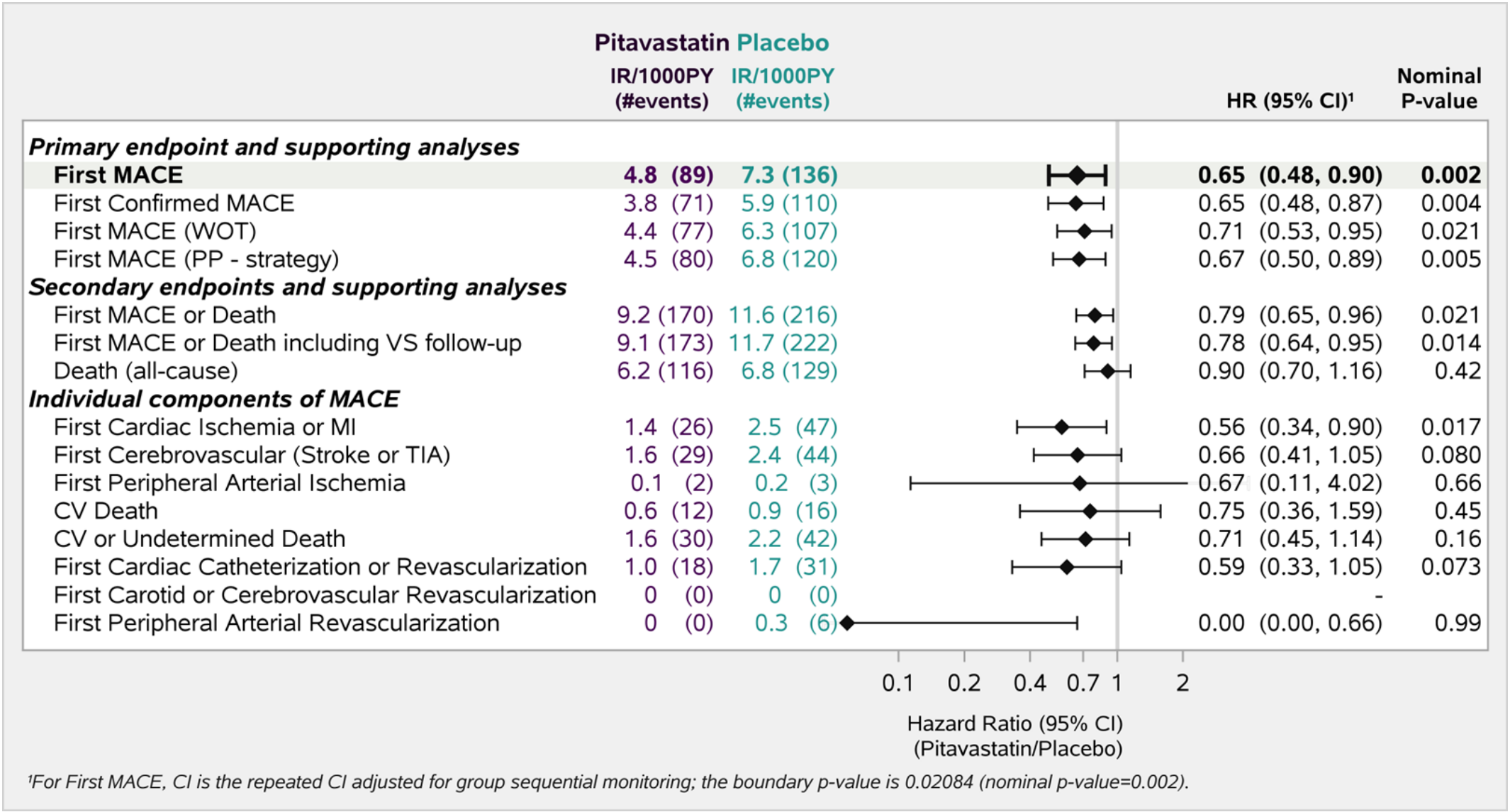


Grinspoon et al. NEJM 2023

Additional Findings

- Greater than 80% in both groups remained in follow up
- Adherence was *very good to excellent* in the great majority of participants
- Adverse event-related discontinuation was low in each group (2% vs 1% pitavastatin vs placebo)
- Clinical initiation of a non-study statin occurred in 5.7% pitavastatin and 9.6% of placebo-treated participants, below threshold of concern
- All events adjudicated vis a vis relationship to COVID; only one MACE event was definitely related to COVID.

Primary Endpoints and MACE Components

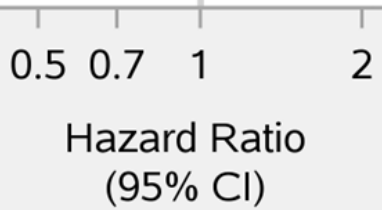


[1]*For First MACE, CI is the repeated CI adjusted for group sequential monitoring; the boundary p-value is 0.02084 (nominal p-value=0.002).*

Grinspoon et al. NEJM 2023

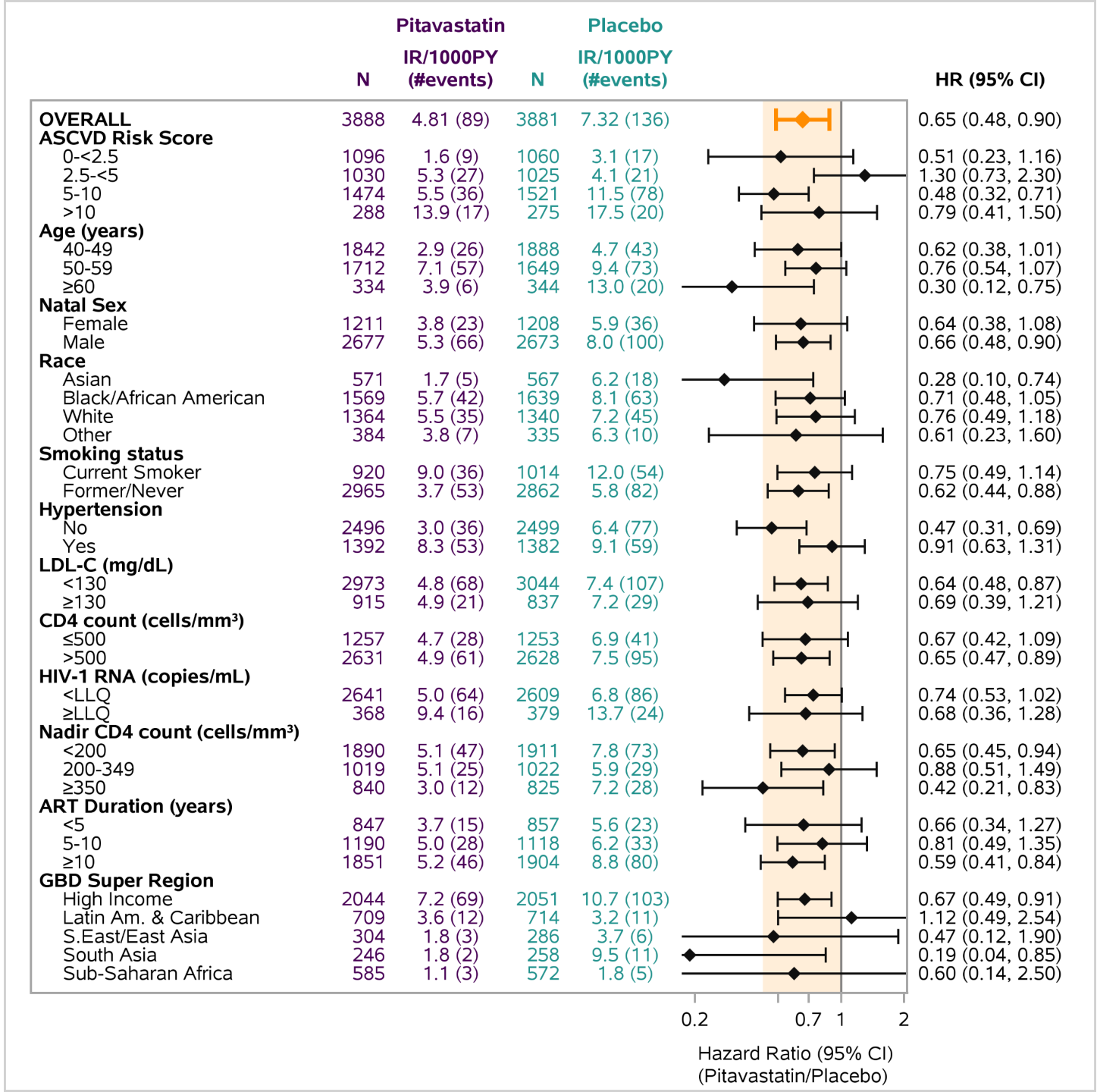
Robust Effect Controlling for ASCVD Score and Other Factors

	Pitavastatin N	Pitavastatin IR/1000PY (#events)	Placebo N	Placebo IR/1000PY (#events)	HR (95% CI)	Nominal P-value
First MACE						
Stratified Cox proportional hazards model (A)	**3888**	**4.8 (89)**	**3881**	**7.3 (136)**	**0.65 (0.48, 0.90)**	**0.002**
> Adjusted for ASCVD risk score (B)	3888	4.8 (89)	3881	7.3 (136)	0.66 (0.48, 0.90)	0.002
> Adjusted for multiple factors (C)	3885	4.8 (89)	3874	7.3 (136)	0.66 (0.48, 0.91)	0.003
First MACE or Death						
Stratified Cox proportional hazards model (A)	3888	9.2 (170)	3881	11.6 (216)	0.79 (0.65, 0.96)	-
> Adjusted for ASCVD risk score (B)	3888	9.2 (170)	3881	11.6 (216)	0.79 (0.64, 0.96)	-
> Adjusted for multiple factors (C)	3885	9.2 (170)	3874	11.7 (216)	0.80 (0.65, 0.98)	-



Adjusted for: age, race, smoking, hypertension, LDL-C, nadir CD4, total ART duration and GBD region as covariates.

Grinspoon et al. NEJM 2023



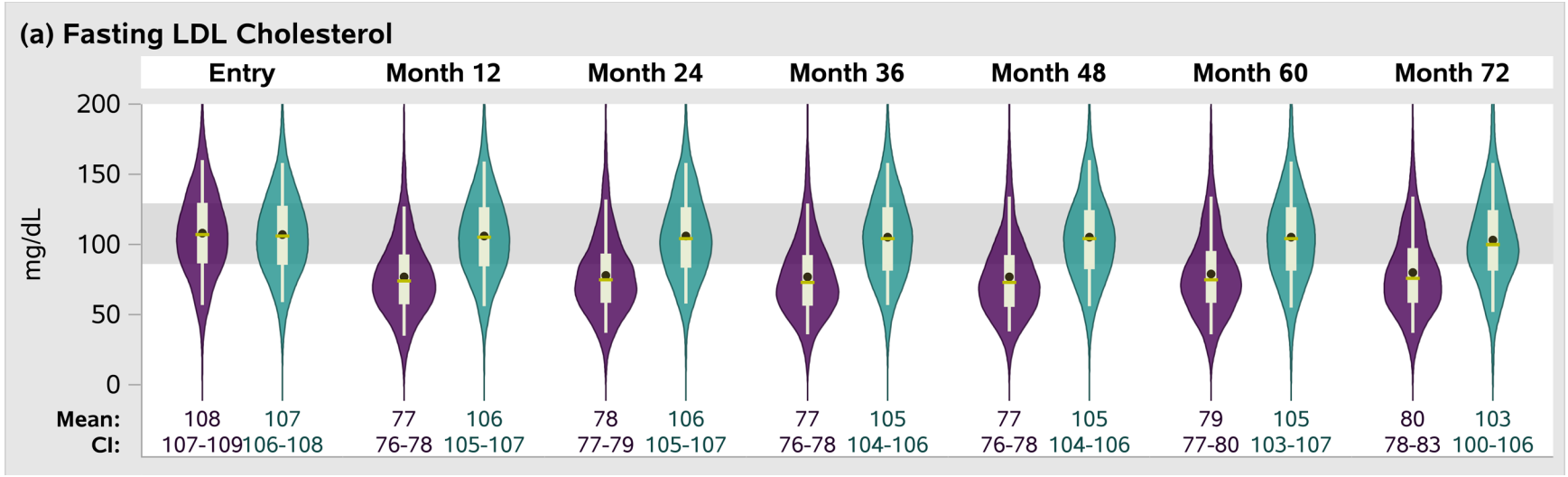
Effects on Key Subgroups

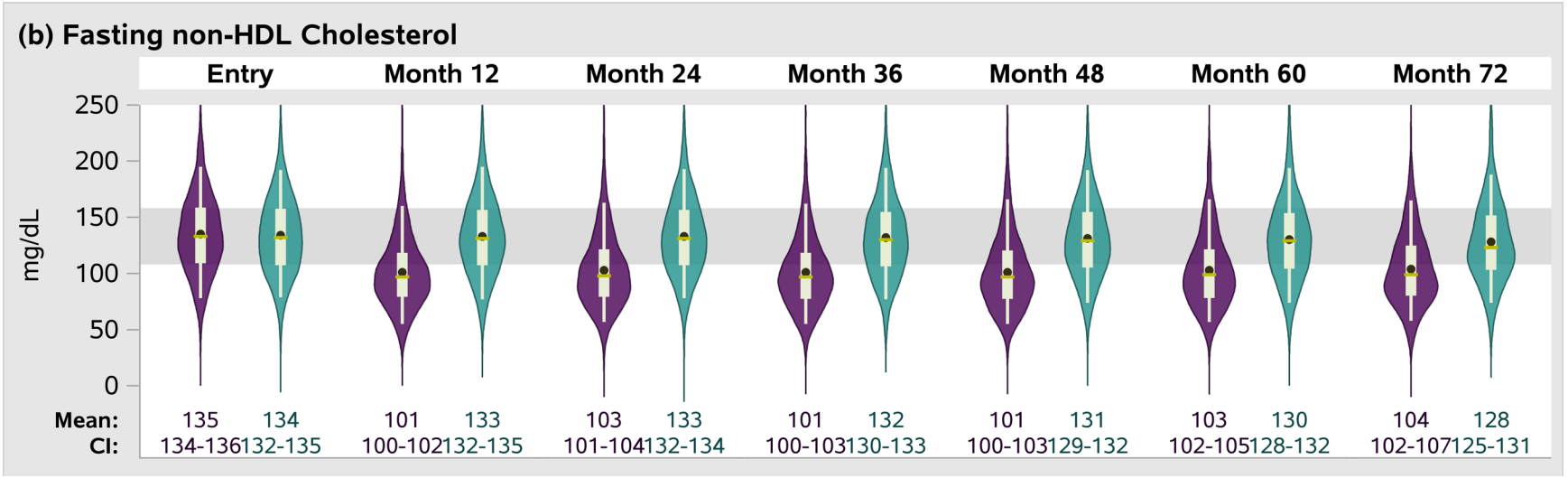
- Very consistent affect across major subgroups
- No treatment modification based on LDL, age, sex
- Generally consistent effects across race and GBD regions
- No treatment modification based on CD4, nadir CD4, HIV RNA, ART Duration

GBD = global burden of disease

Grinspoon et al. NEJM 2023

Effects on LDL and NON-HDL Cholesterol



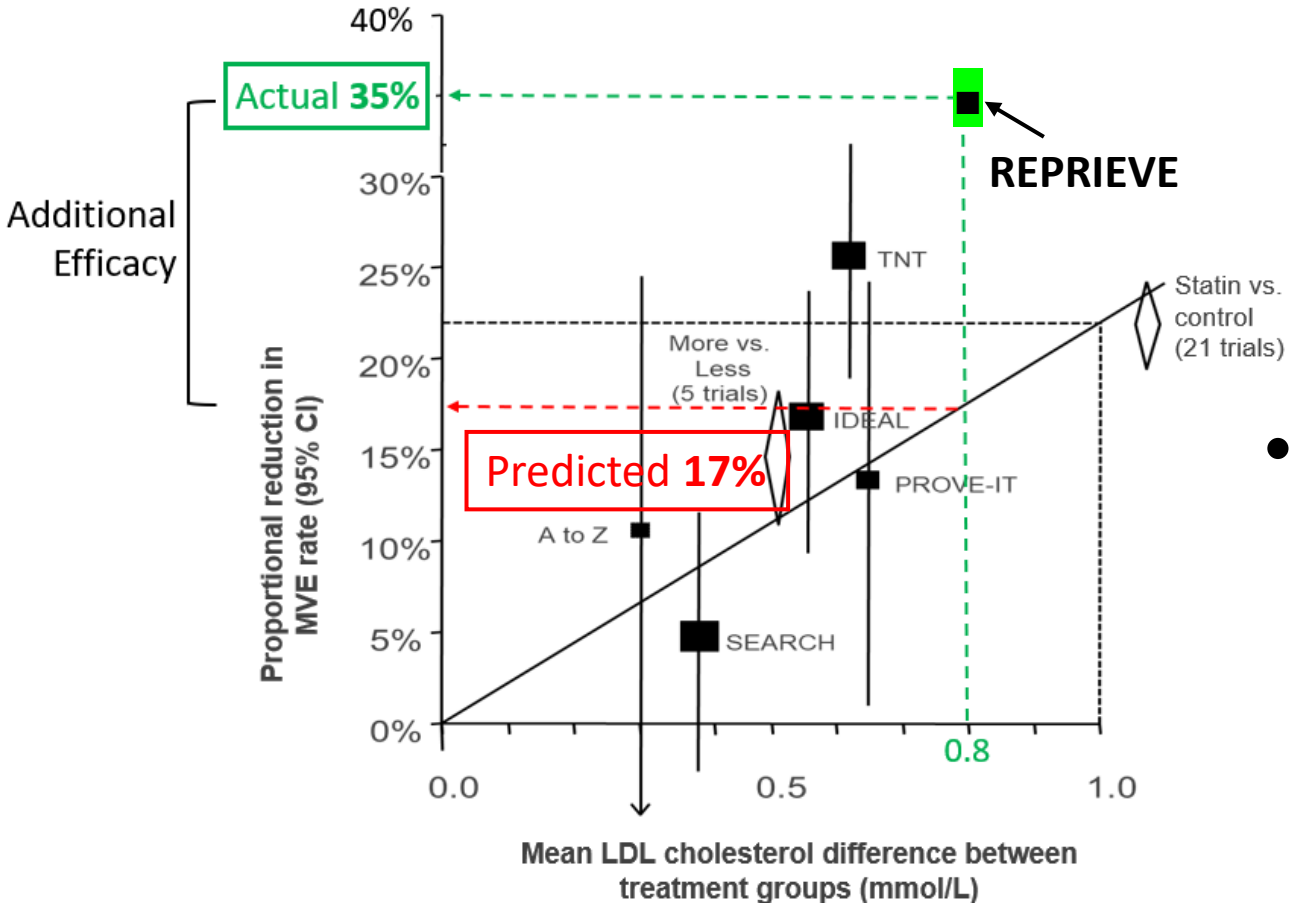


Pitavastatin Placebo

- 30% reduction in LDL in pitavastatin group, no change in placebo
- Durable effect over time

Grinspoon et al. NEJM 2023

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

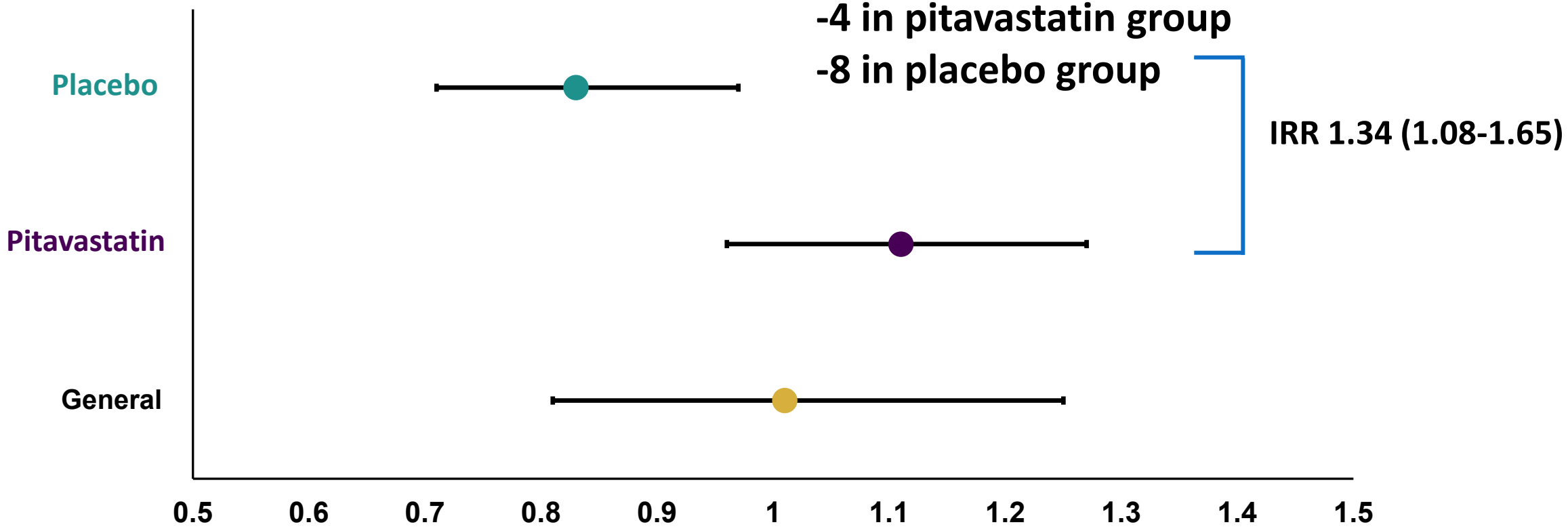
Safety

- DSMB concluded no unanticipated safety concerns
- Serious adverse events similar in each group: IRR 1.02 (0.92-1.14)
- Muscle-related symptoms were higher in the pitavastatin group but were mostly mild and only 1% withdrew for muscle-related symptomatology
- Diabetes rates increased in the pitavastatin group, but this increase was consistent with that seen in prior statin studies, was not significantly above rates demonstrated for the general population, and very few withdrew due to diabetes
- No effect on Grade 3 ALT or rhabdomyolysis was seen

IRR: incidence rate ratio

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

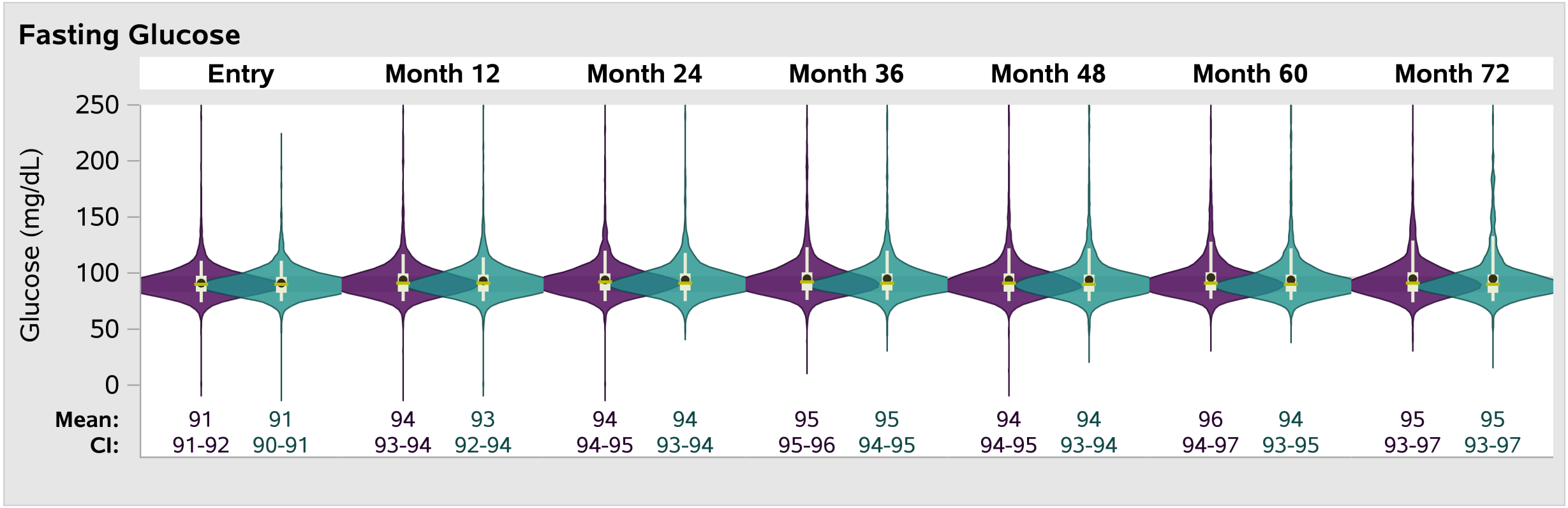
12 MACE events in participants with diabetes:
-4 in pitavastatin group
-8 in placebo group



IRR: incidence rate ratio

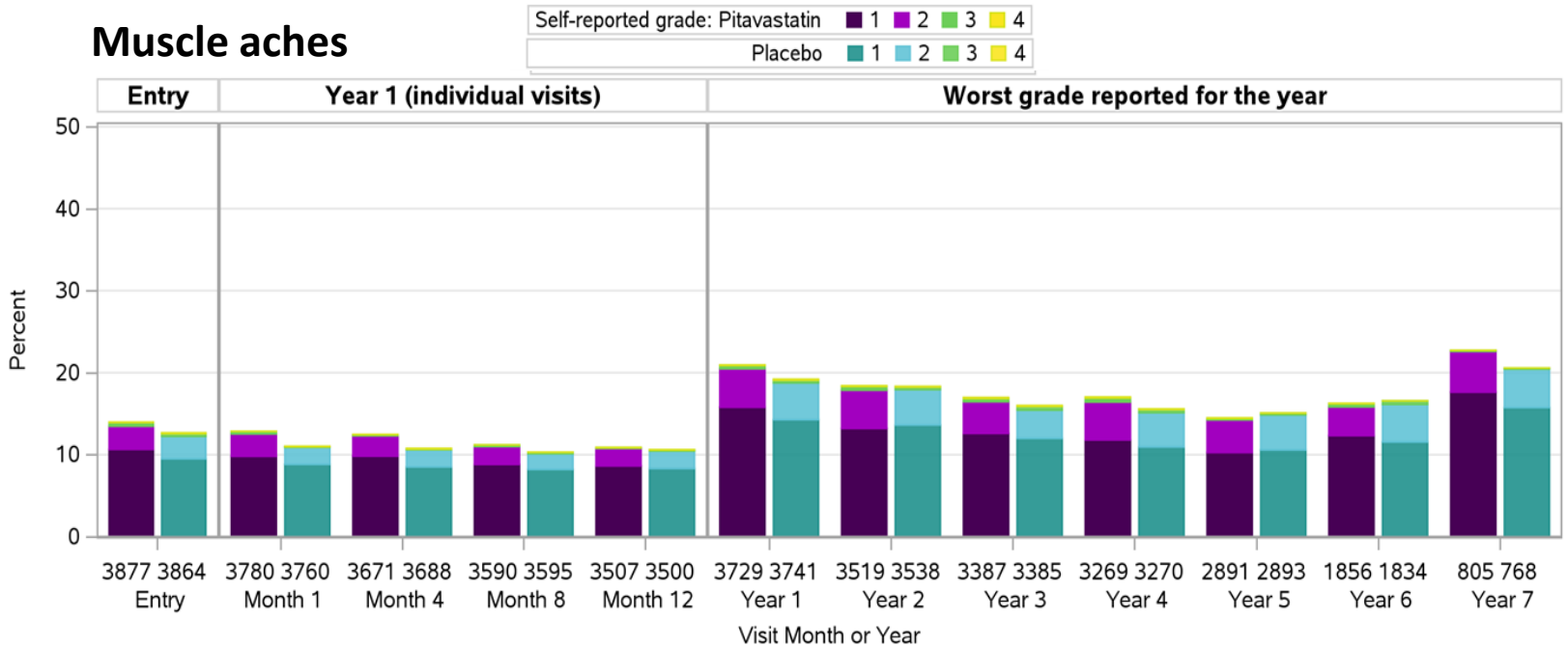
Centers for Disease Control and Prevention. Incidence of Newly Diagnosed Diabetes. https://www.cdc.gov/diabetes/data/statistics-report/newly-diagnosed-diabetes.html#print

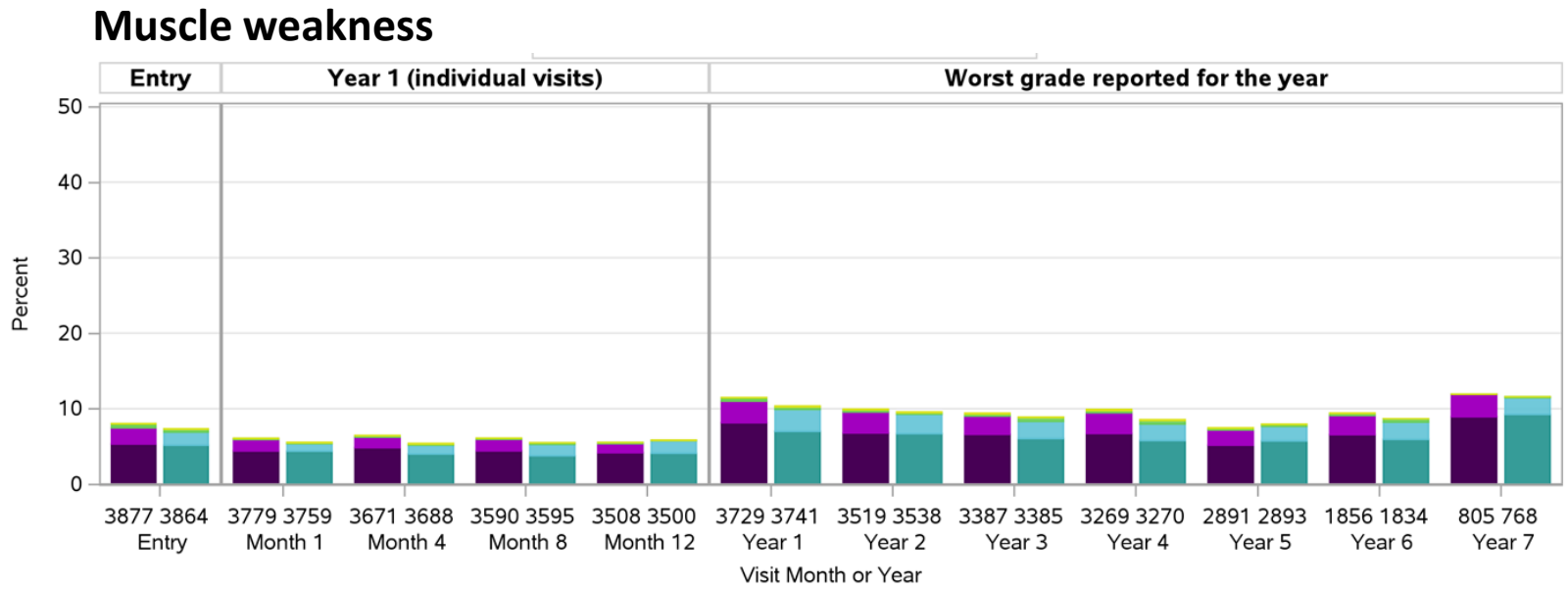
Effects on Glucose



Grinspoon et al. NEJM 2023

Effects on Muscle Aches and Myalgias

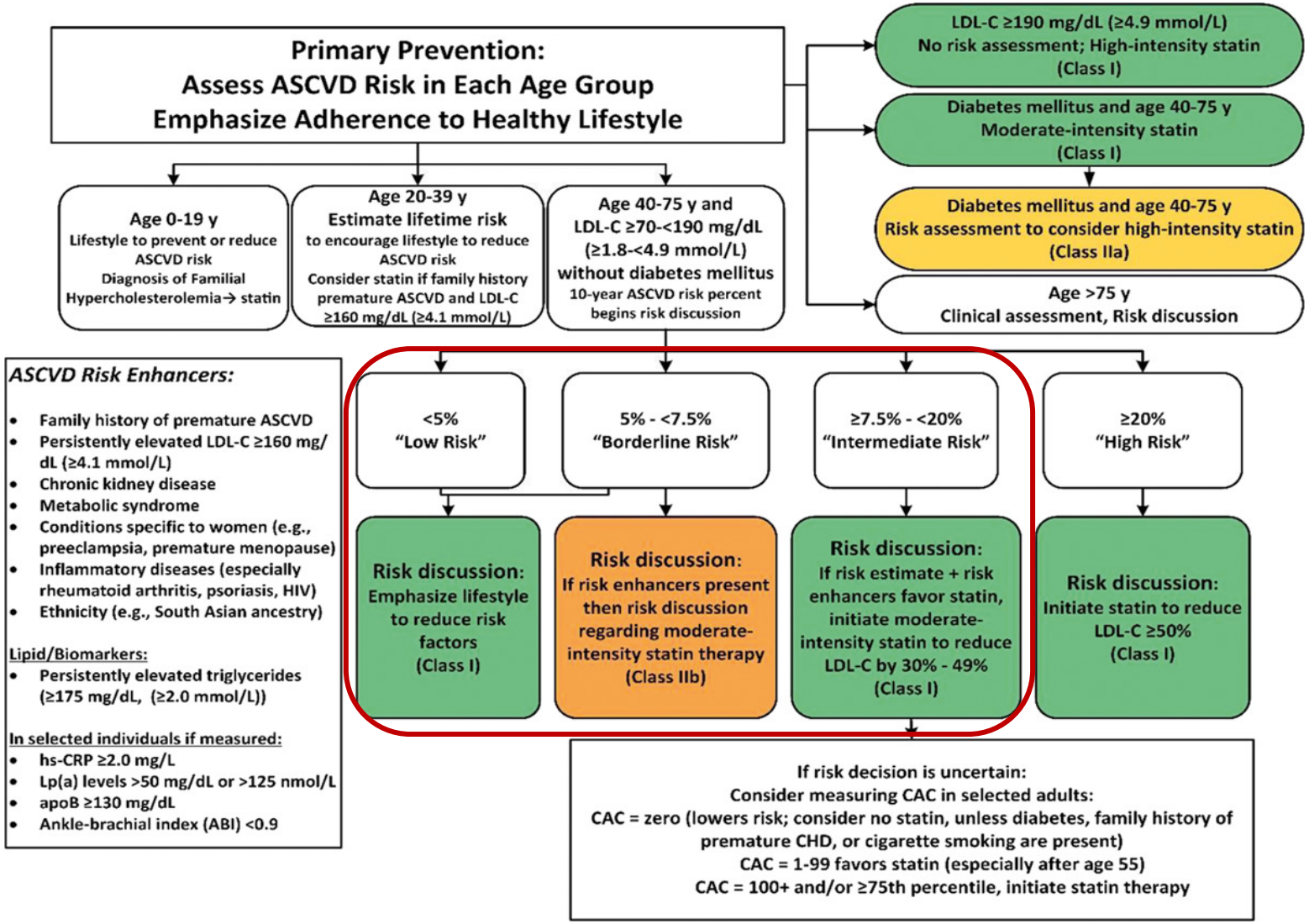




Grinspoon et al. NEJM 2023

How Might the Findings of REPRIEVE Impact the Recommendations for Statin Therapy (2019 ACC/AHA Guidelines)?

- HIV was recently considered a risk enhancer, but its use in primary prevention had not been studied
- Previously unknown if PWH with low to moderate risk should be put on a statin and whether statin therapy would be successful in this context?
- √ REPRIEVE has taught us that yes this is the case, statin therapy will prevent MACE in low to moderate risk PWH



Spectrum of Statin Intensity

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL on average by ≥50%	Daily dose lowers LDL on average by approximately 30-49%	Daily dose lowers LDL on average by <30%
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 2-4 mg	Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg

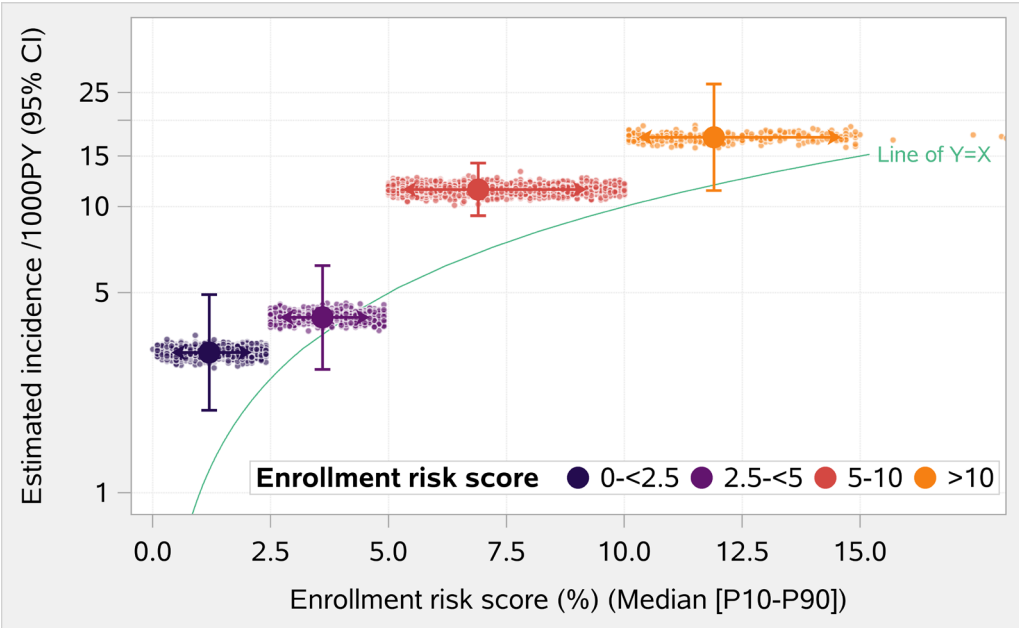
Statin Interactions with ART in PWH

- Protease inhibitors downregulate CYP3A4 activity and can increase concentrations of CYP3A4 metabolized drugs, e.g. statins
- Cobicistat inhibits CYP3A and can increase levels of statins
- Exceptions are pitavastatin and pravastatin which are not metabolized through CYP3A4
- Atorvastatin and rosuvastatin may be used in those on a PI but should be initiated at low doses and titrated carefully
- Efavirenz can induce statin metabolism, resulting in lower statin levels
- Recommended statins in HIV: pravastatin, atorvastatin, rosuvastatin, pitavastatin

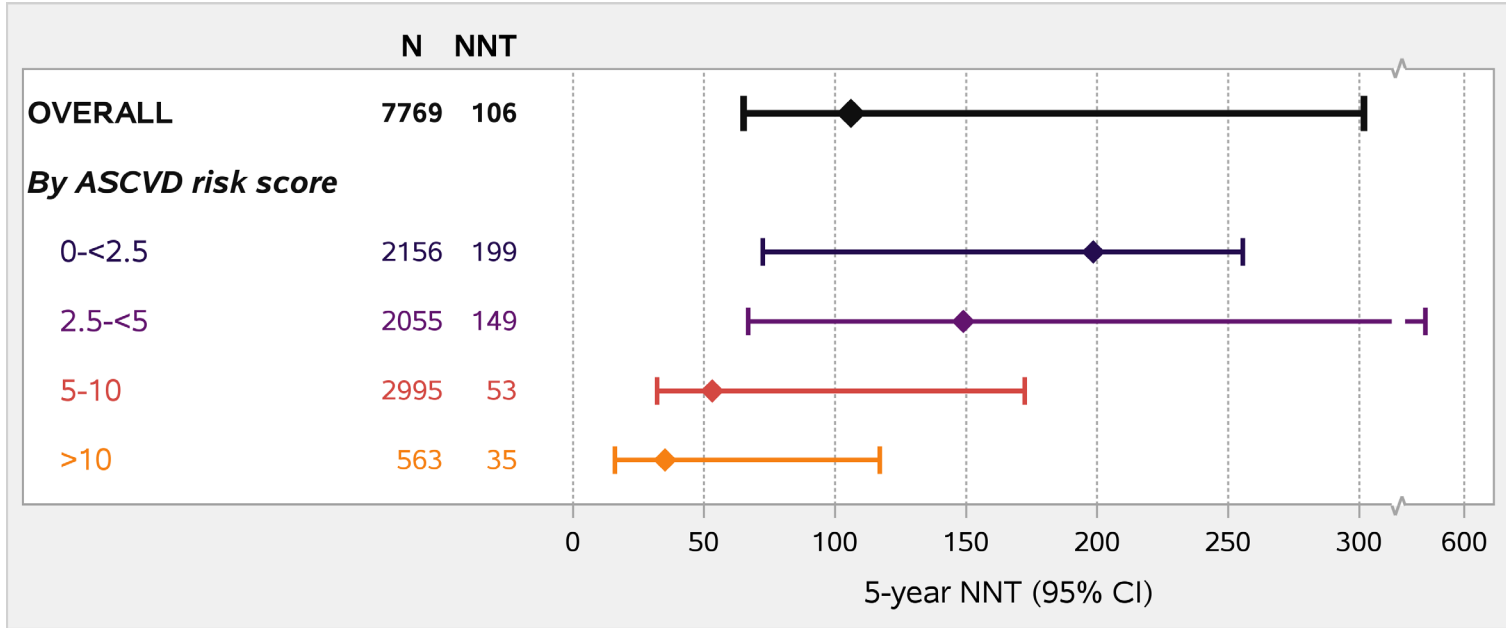
Univ of Liverpool interaction checker: http://www.hiv-druginteractions.org/

Slide Courtesy of Dr. Janet Lo

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



Increasing CVD with increasing ASCVD risk score



Decreasing NNT with increasing ASCVD risk score

NNT = number needed to treat

Grinspoon et al. NEJM 2023

Will Pitavastatin be Available After REPRIEVE?

- 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, but if it is not available, other statins that do not interact with ART may be effective
- Generic pitavastatin calcium will be more broadly available after Nov. 2023

Implications for Care of PWH

- Statin therapy, with lifestyle counselling, should be considered for PWH, 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

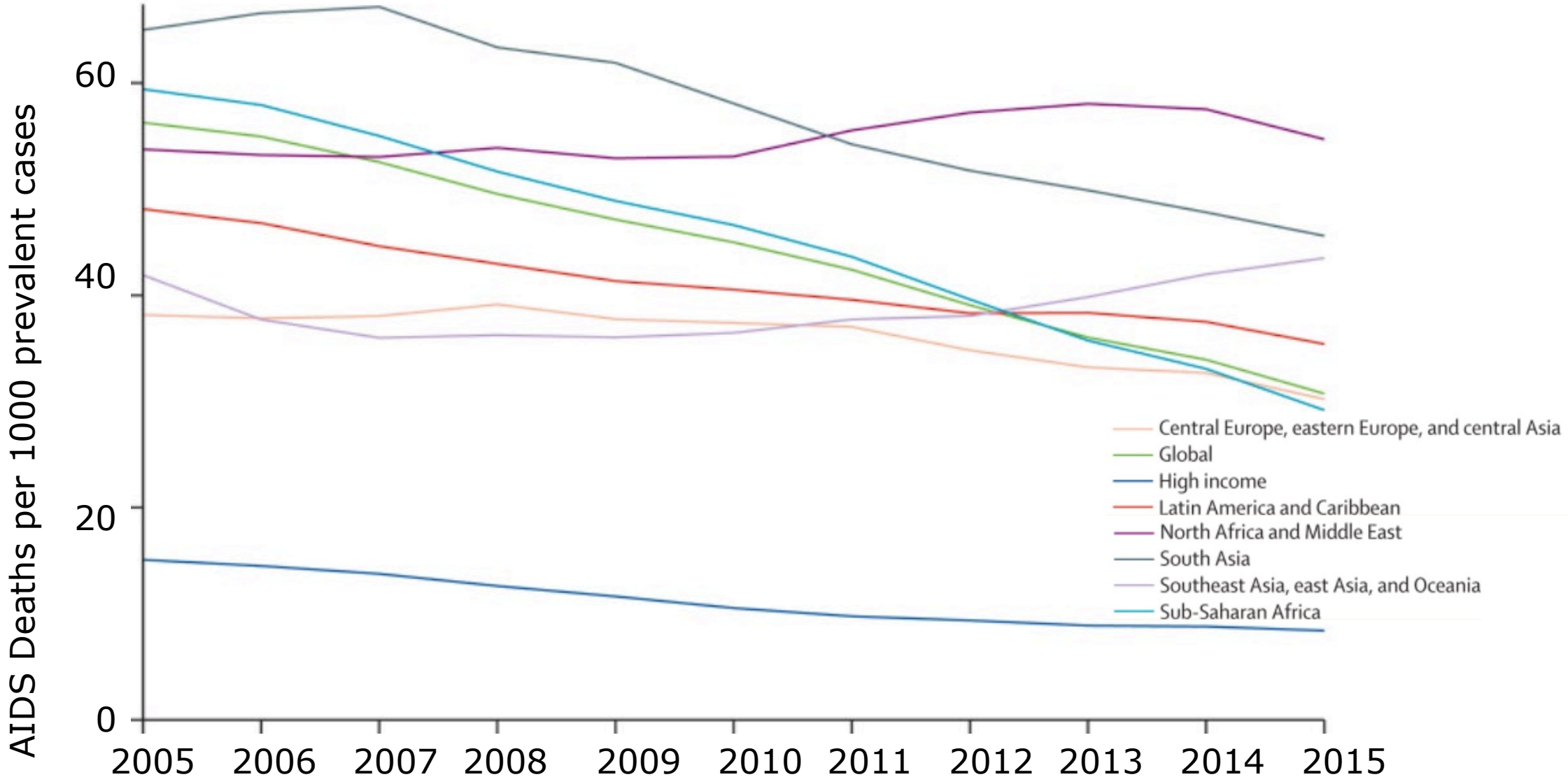
Despite HIV being considered a risk equivalent, no prior trial has assessed a primary prevention strategy for this group, who would not typically be recommended for statin therapy

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

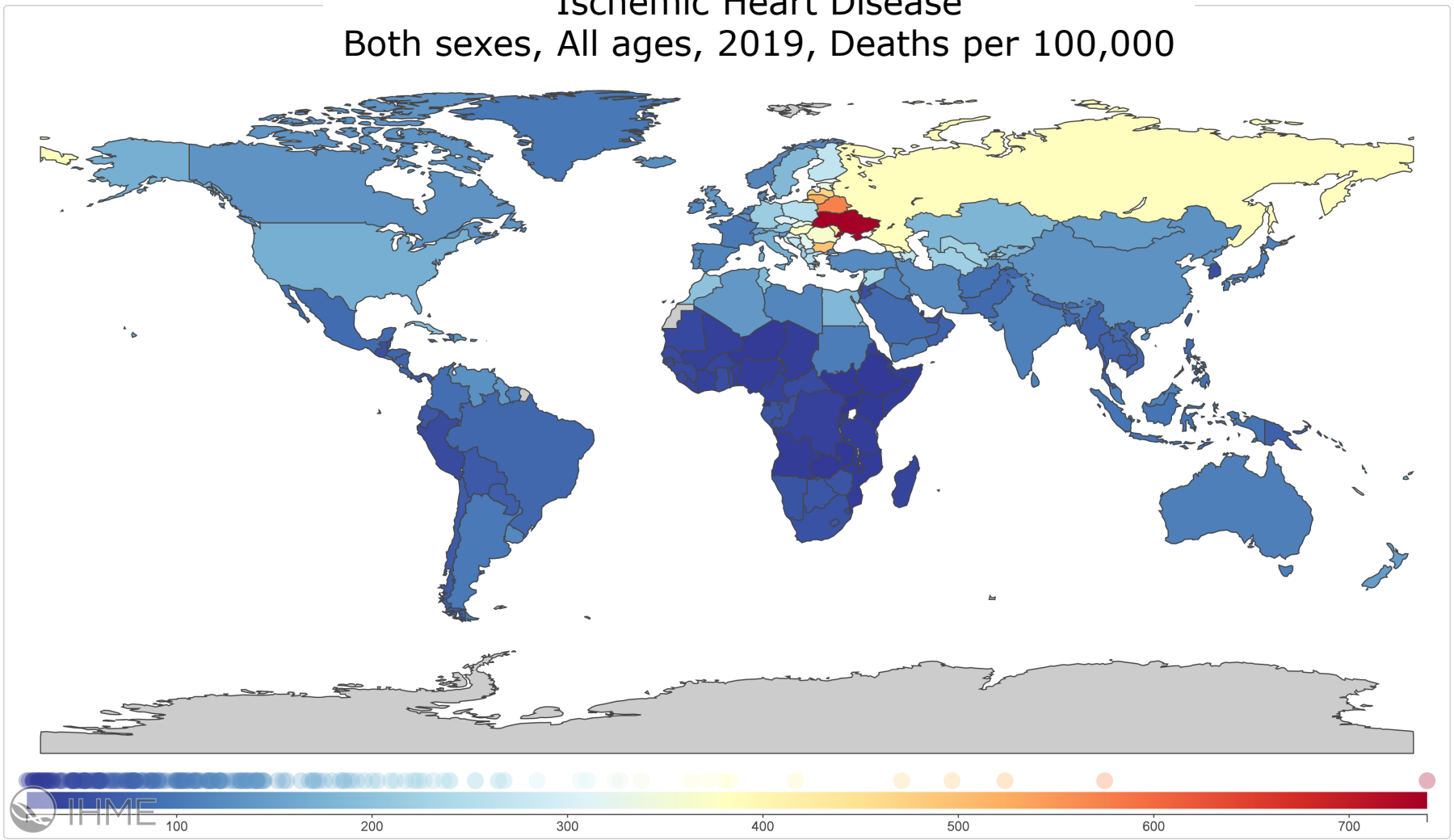
Cardiovascular disease among people with HIV in high- and low-income countries: Can one strategy fit all?

Global Decrease in Deaths Due to HIV/AIDS



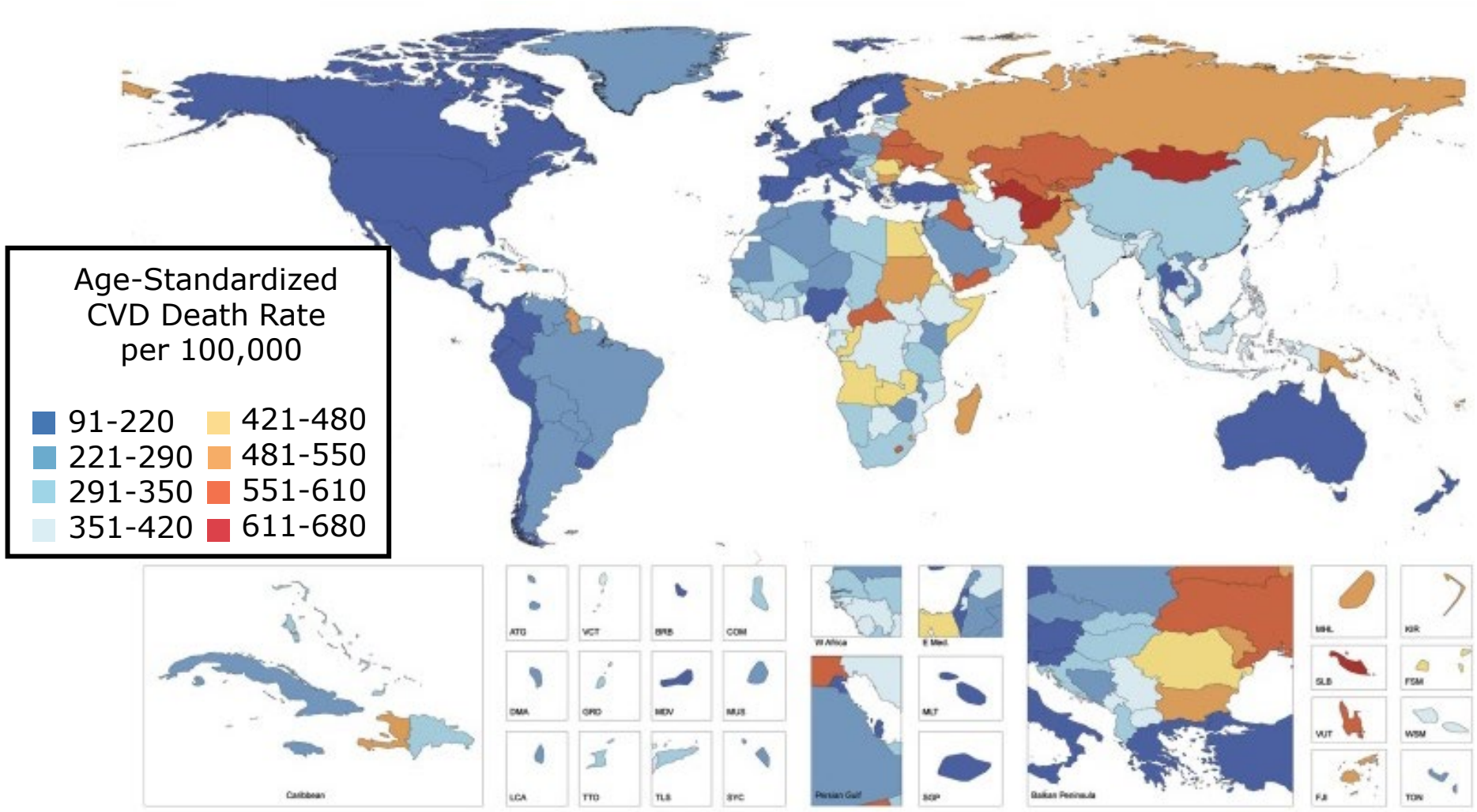
GBD Collaborators. Lancet HIV 2016;3

Ischemic Heart Disease Deaths Overall More Common in HICs



HIC: High income countries

But in LMICs CVD Mortality Rate Higher



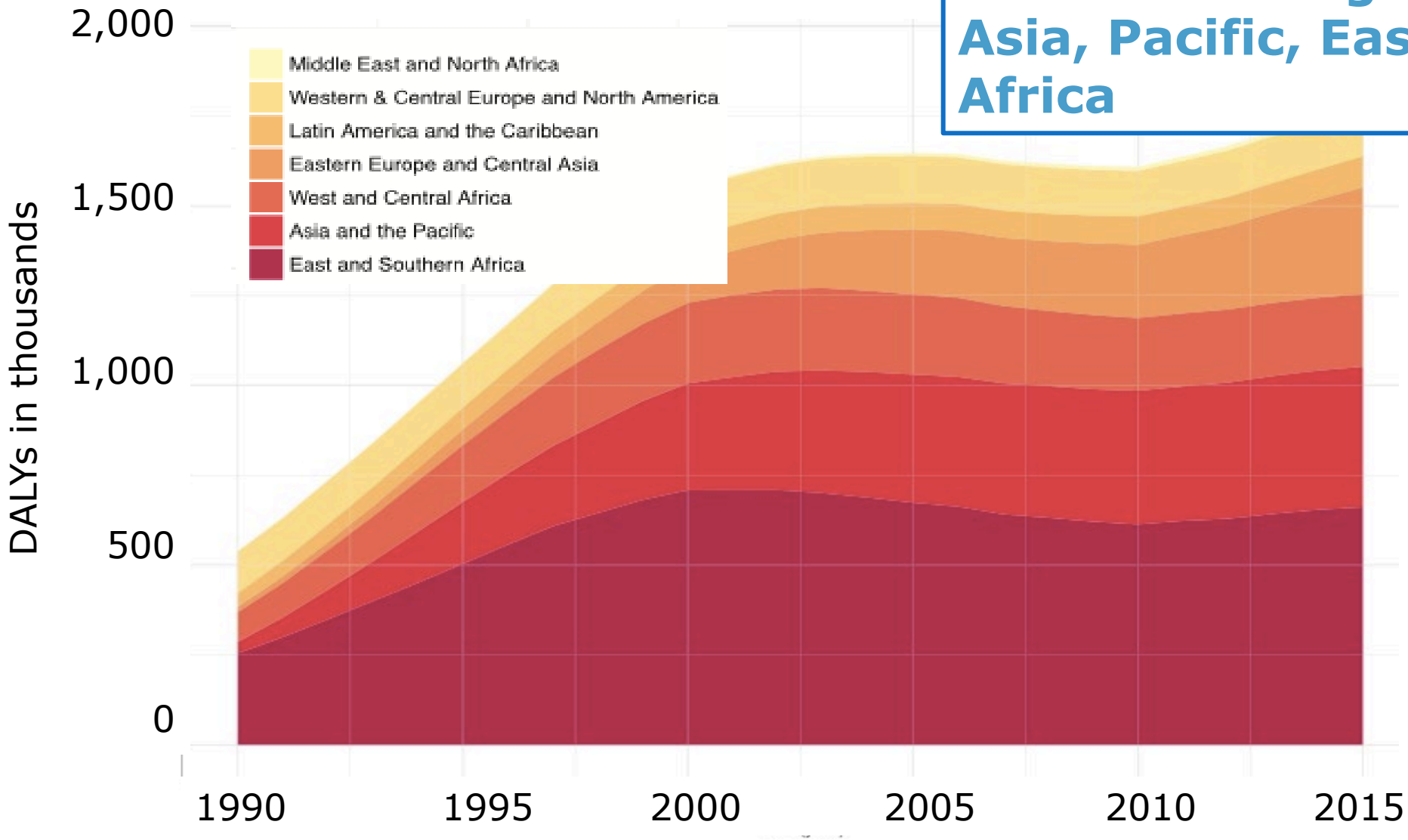
LMICs: Low and middle income countries

Roth et al. JACC 2017;70

Global Burden of CVD in HIV – DALYs

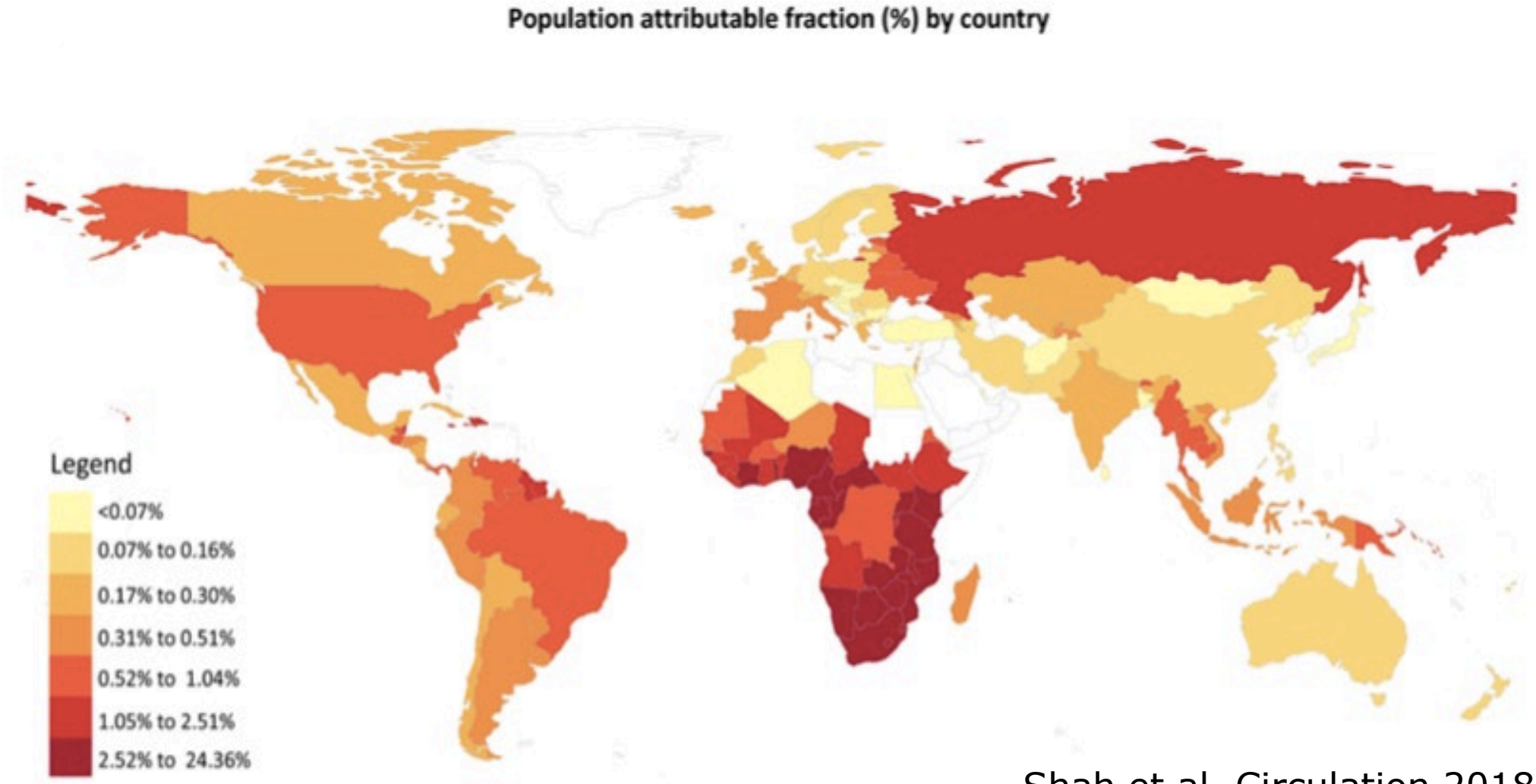
1. CVD DALYs increasing

2. CVD DALYs greatest in Asia, Pacific, East/S Africa



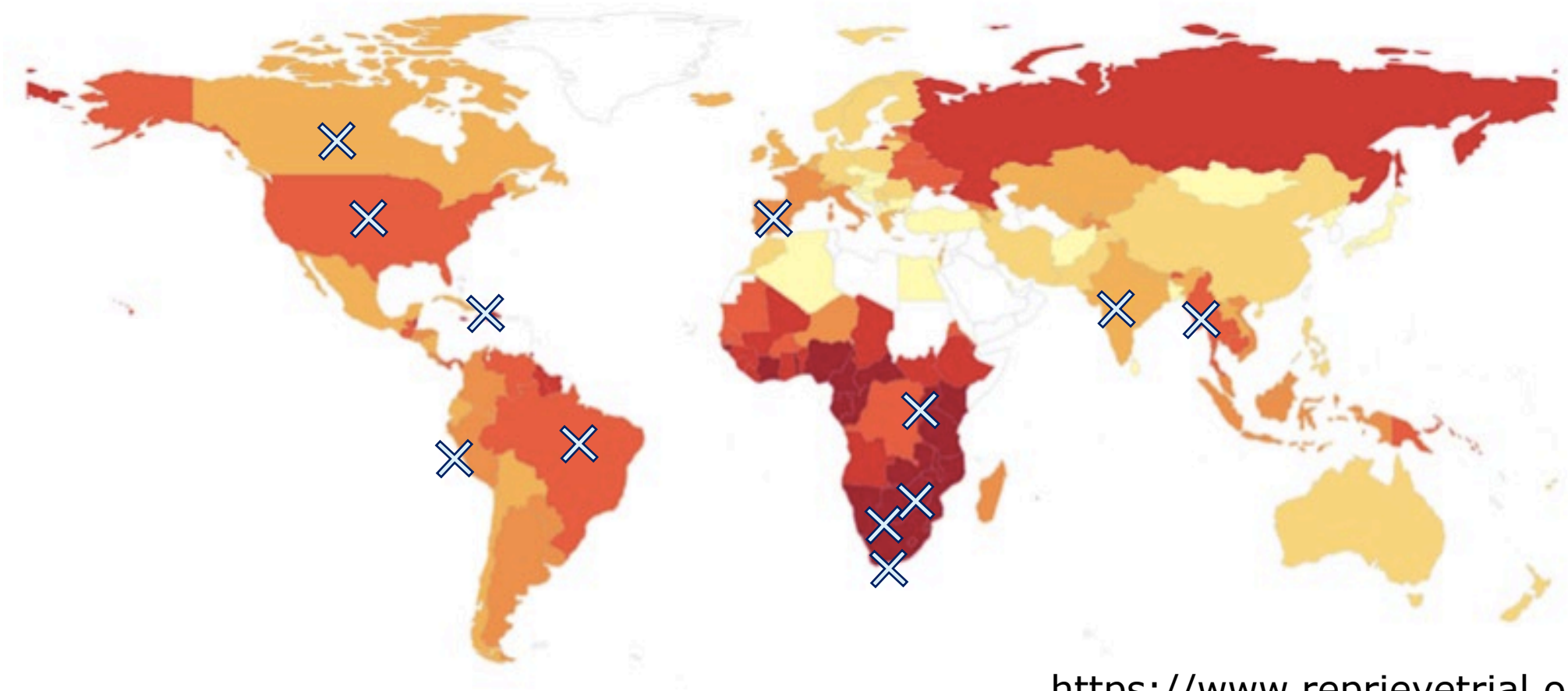
Shah et al. Circulation 2018;138

Fraction of CVD Attributable to HIV



Shah et al. Circulation 2018;138

REPRIEVE: First Globally Representative Trial of CV Primary Prevention in People with HIV



https://www.reprievetrial.org

Given these regional differences, can one CV prevention strategy fit all?

It depends.

Baseline CV Risk Factors in REPRIEVE by Region

		Total (N=7769)	HIC (N=4095)	LAC (N=1423)	SE/E. Asia (N=590)	S. Asia (N=504)	SSA (N=1157)
Smoking	Current	1934 (25%)	1289 (32%)	292 (21%)	69 (12%)	69 (14%)	215 (19%)
Diabetes		37 (<1%)	25 (1%)	5 (<1%)	1 (<1%)	5 (1%)	1 (<1%)
BMI	Median (Q1, Q3)	25.8 (22.8, 29.4)	26.8 (23.9, 30.6)	25.8 (23.3, 28.7)	22.7 (20.5, 25.0)	22.9 (20.2, 25.9)	24.7 (21.2, 29.6)
HTN		2774 (36%)	1538 (38%)	522 (37%)	141 (24%)	165 (33%)	408 (35%)
Family history		1416 (19%)	968 (25%)	296 (22%)	55 (9%)	22 (4%)	75 (7%)
Total chol (mg/dL)	Median (Q1, Q3)	185 (162, 209)	184 (162, 208)	191 (167, 215)	201 (177, 223)	181 (159, 206)	174 (154, 198)
HDL-C (mg/dL)	Median (Q1, Q3)	48 (39, 59)	49 (40, 59)	44 (36, 55)	48 (40, 57)	41 (35, 51)	55 (44, 66)
LDL-C (mg/dL)	Median (Q1, Q3)	108 (87, 128)	107 (87, 126)	114 (93, 134)	122 (103, 141)	107 (87, 126)	97 (78, 118)
Trig (mg/dL)	Median (Q1, Q3)	114 (81, 169)	112 (80, 165)	138 (94, 200)	122 (87, 179)	137 (96, 205)	89 (67, 128)

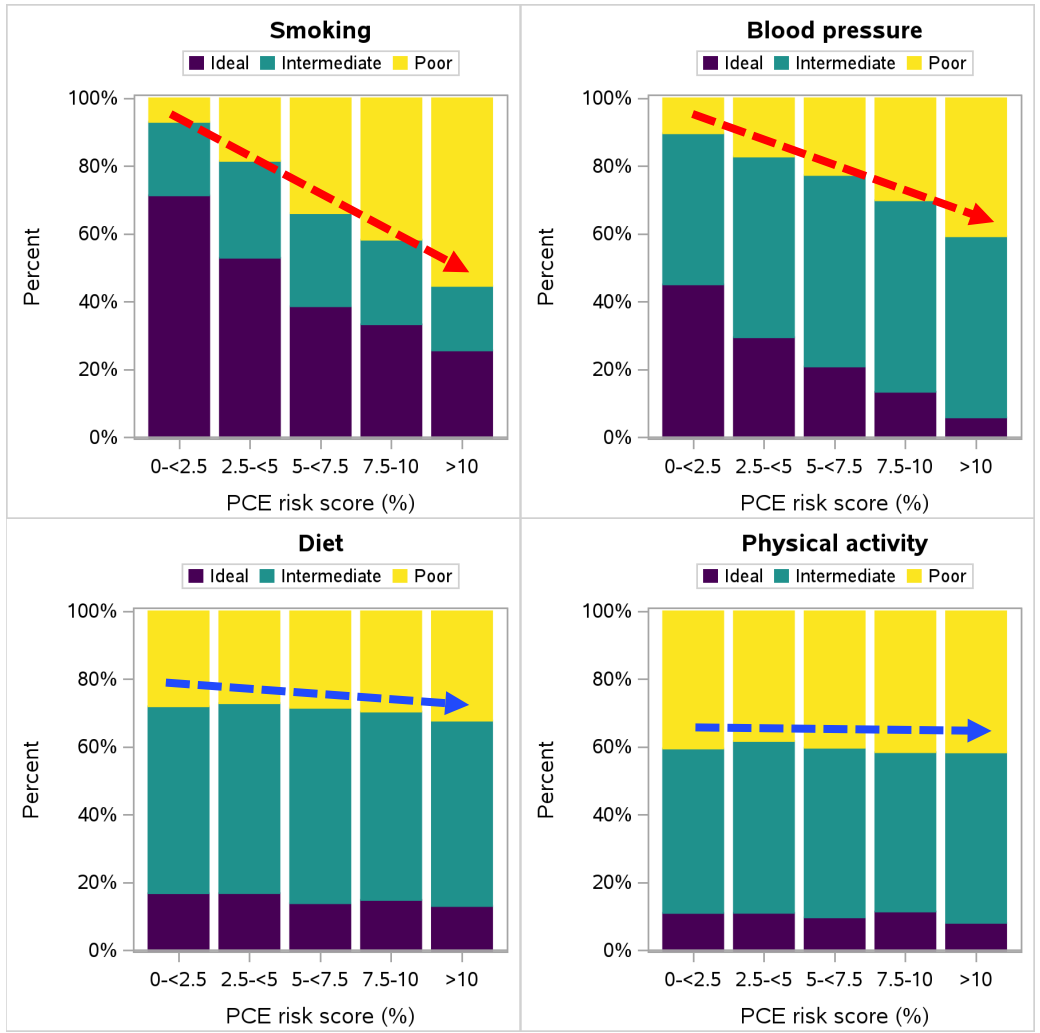
Need to also address regional burden of non-lipid traditional CV risk factors

BMI, body mass index; HTN, hypertension; chol, cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein; Trig, triglycerides; Pitava, pitavastatin; LAC, Latin American and Caribbean; SSA, sub-Saharan Africa

Life's Simple 7s of Cardiovascular Health in REPRIEVE

- AHA Approach to Enhancing Healthy Practices
- Prevalence of healthy factors as a function of CV risk score
- Expected: Higher risk → Worse health practice
- Observed: Healthy diet, adequate physical activity remarkably poor at every CV risk level

Assess and support healthy habits to prevent CV disease

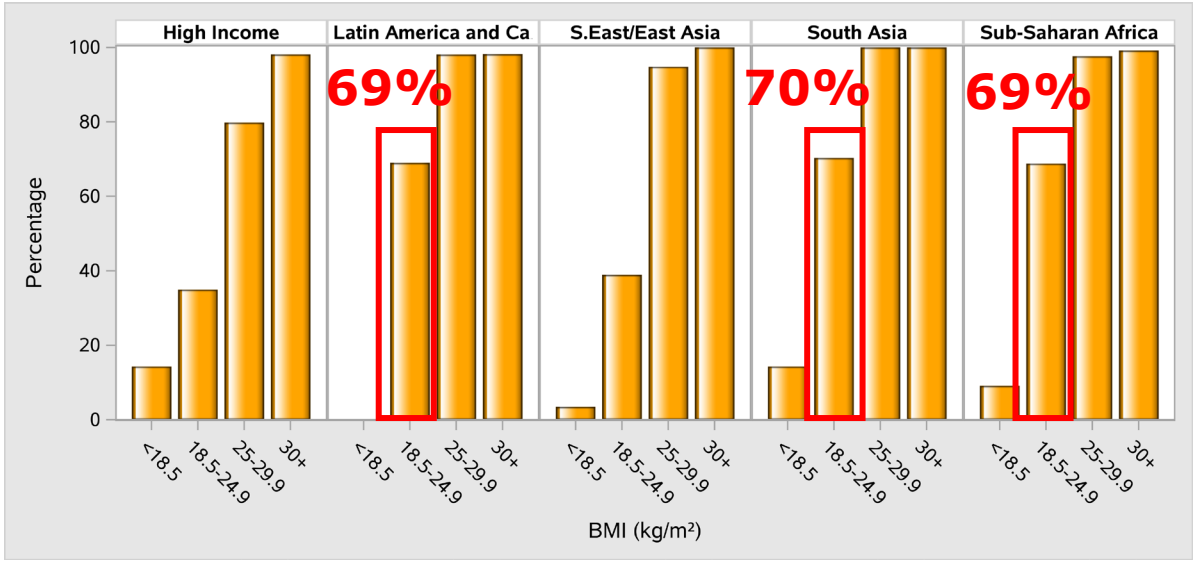


AHA, American Heart Association, Life's Simple 7/Essential 8

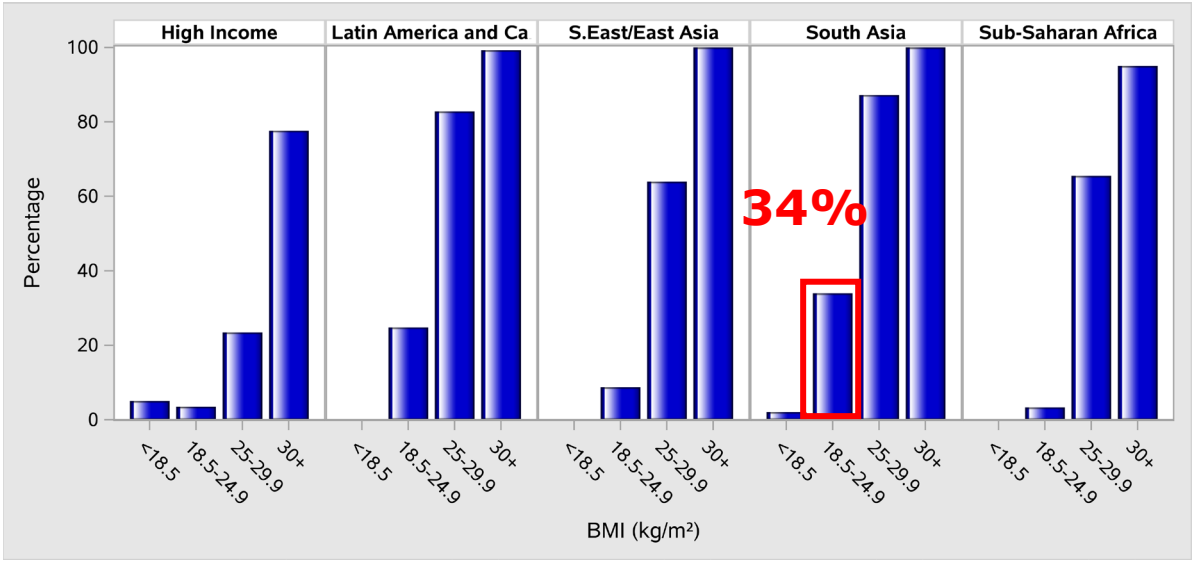
Douglas et al. Clin Inf Dis 2021;73

Baseline High Waist Circumference by BMI, Sex, Region in REPRIEVE

Female



Male



- Higher WC despite normal BMI in LAC, S Asia, SSA, (+ S Asia males)
- Largest MACE effect size seen in S Asia, SE/E Asia

Regional variation in metabolic dysregulation, visceral adiposity despite 'normal' BMI driving CV risk

* Women: ≥88 cm in US, ≥80 cm for all other regions. Men: ≥102 cm in US, ≥90 cm in LAC and Asia, ≥94cm for all other regions.

Performance of CVD Risk Prediction Models among People with HIV

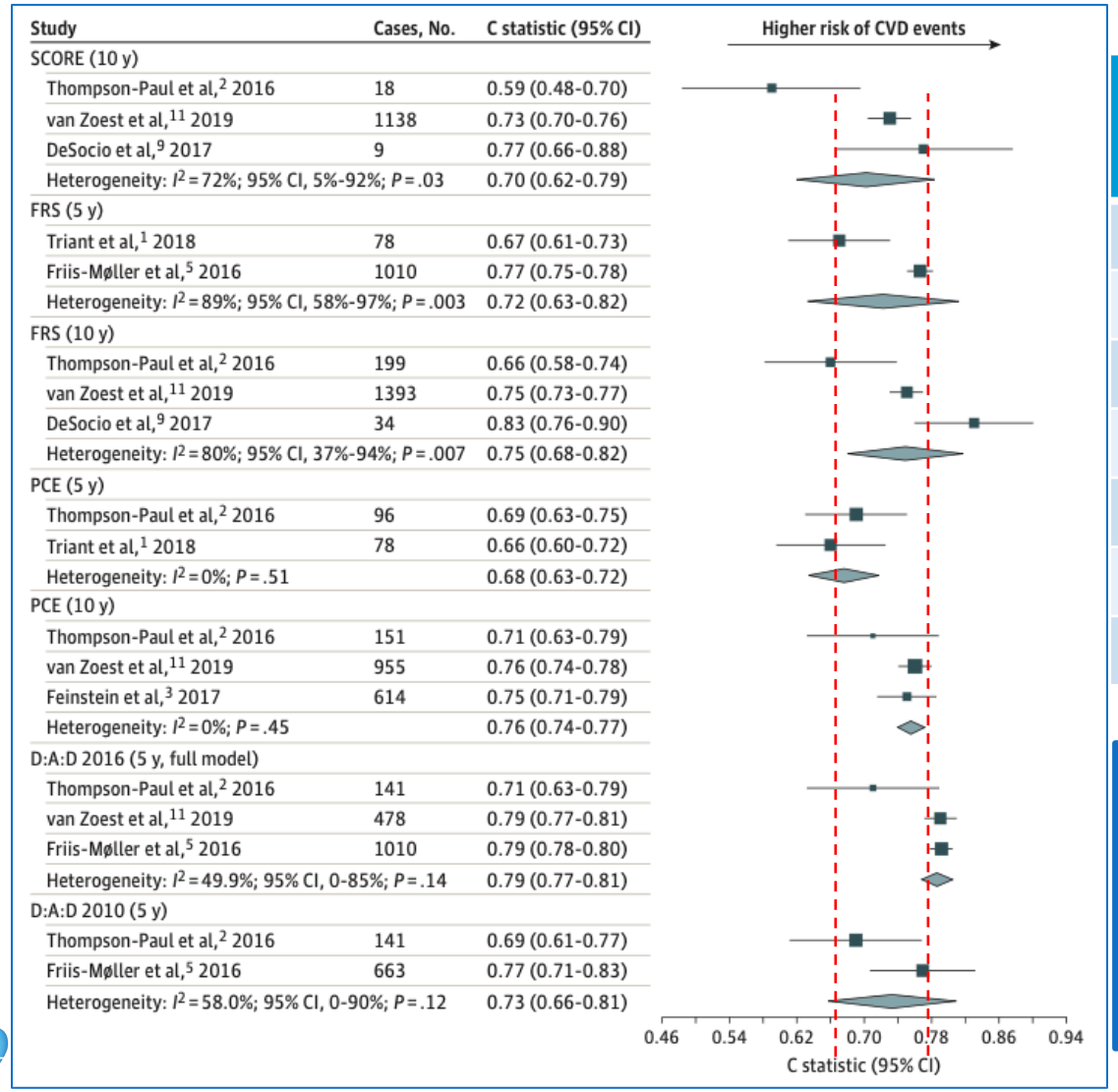
- Systematic review and meta-analysis of
  - retrospective or prospective cohorts with MI, CVD, CAD outcomes,
  - patients with a diagnosis of HIV (with or without HIV-negative controls),
  - studies on adults older than 18 years, and
  - available data on a minimum of 1 cardiac risk score

Table 1. Baseline Characteristics of Included Studies

Characteristic	Source								
	Thompson-Paul et al,[2] 2016	van Zoest et al,[11] 2019	Triant et al,[1] 2018	Feinstein et al,[3] 2017	De Socio et al,[9] 2017	Herrera et al,[10] 2016	Raggi et al,[4] 2016	Salinas et al,[12] 2016	Friis-Møller et al,[5,16,17] 2016
Study name	HIV Outpatient Study (HOPS)	ATHENA National Observational HIV Cohort	Partners HIV Cohort	CNICS Cohort	NR	NR	NR	Veterans Aging Cohort Study (VACS)	D:A:D
Study date(s)	2002-2014	2000-2016	2006-2008	1995-2015	2004-2014	2003-2013	2003-2013	1996-2012	2000
Study design	Retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort	Prospective cohort	Prospective cohort	Retrospective cohort	Retrospective cohort	Prospective cohort
Study location	Multicenter US	The Netherlands	Boston, Massachusetts	Multicenter US	Perugia, Italy	Barcelona, Spain	Modena, Italy	US Veterans Affairs	Denmark, UK, Switzerland, the Netherlands, France, Belgium, Italy, Australia, Argentina, US
Data/population source	Adults with HIV aged 18 y + without prior CVD history	Adults with HIV aged 18 y + without prior CVD history	Adult male patients with HIV aged 34-74 y without prior CVD history	Adults with HIV	Outpatient HIV clinic in Perugia	Adult male and female patients with HIV	HIV metabolic clinic	US veterans	Adult male and female patients with HIV

Soares et al. JAMA Card 2022;1

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
SCORE	1165	1.37

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

Soares et al. JAMA Card 2022;1

Summary

- CVD DALYs attributable to HIV increasing globally
- CVD DALYs greatest in LMICs (Asia, Pacific, East/S Africa)
- In addition to statins for primary prevention of CVD
  - consider regional burden of non-lipid traditional CV risk factors
  - tobacco use, physical function, adiposity, nutrition, others
- Predicting cardiovascular disease risk accurately is the first step to initiate appropriate primary prevention for those at elevated risk
- Risk discussion between individuals and clinicians

Unique Aspects of Cardiovascular Disease among Women with HIV: Lessons from REPRIEVE

Insights from a Key REPRIEVE Baseline Analysis

(prior to unblinding of REPRIEVE)

Clinical Infectious Diseases

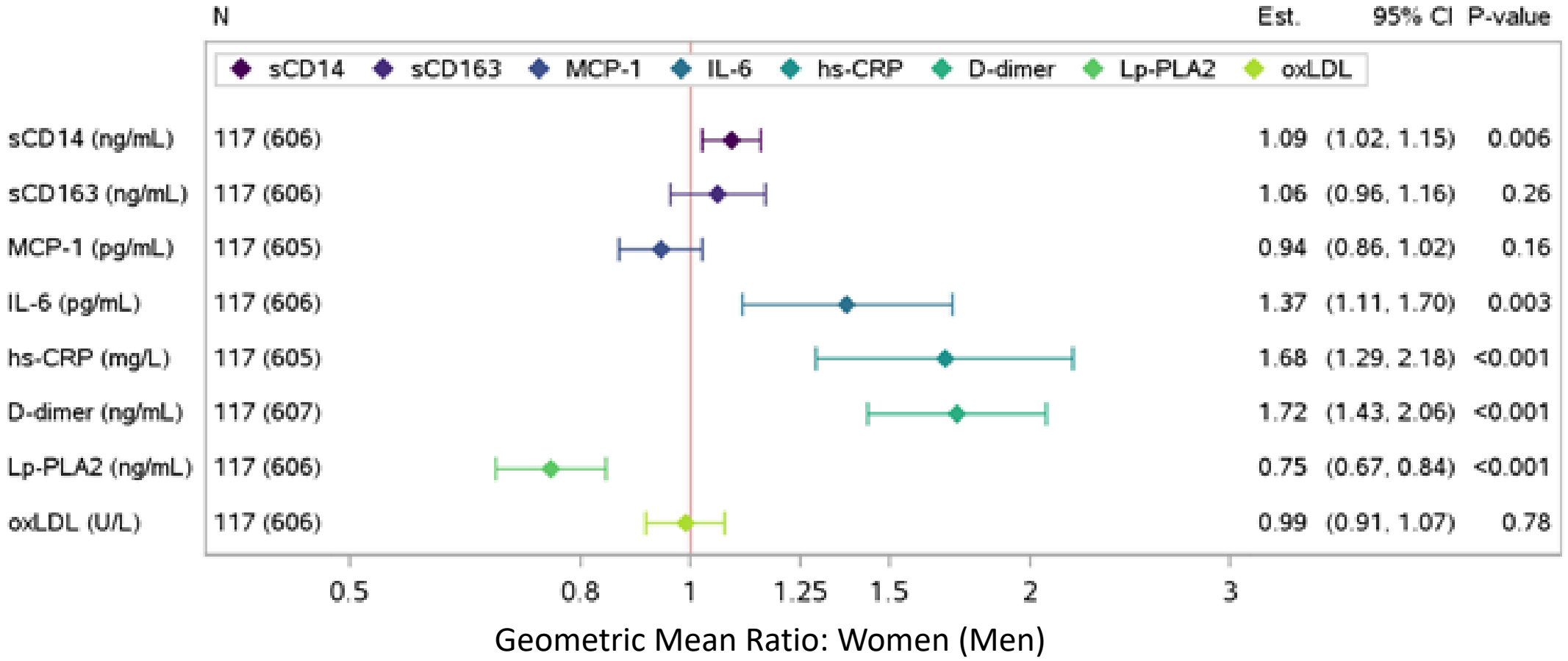
MAJOR ARTICLE

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]

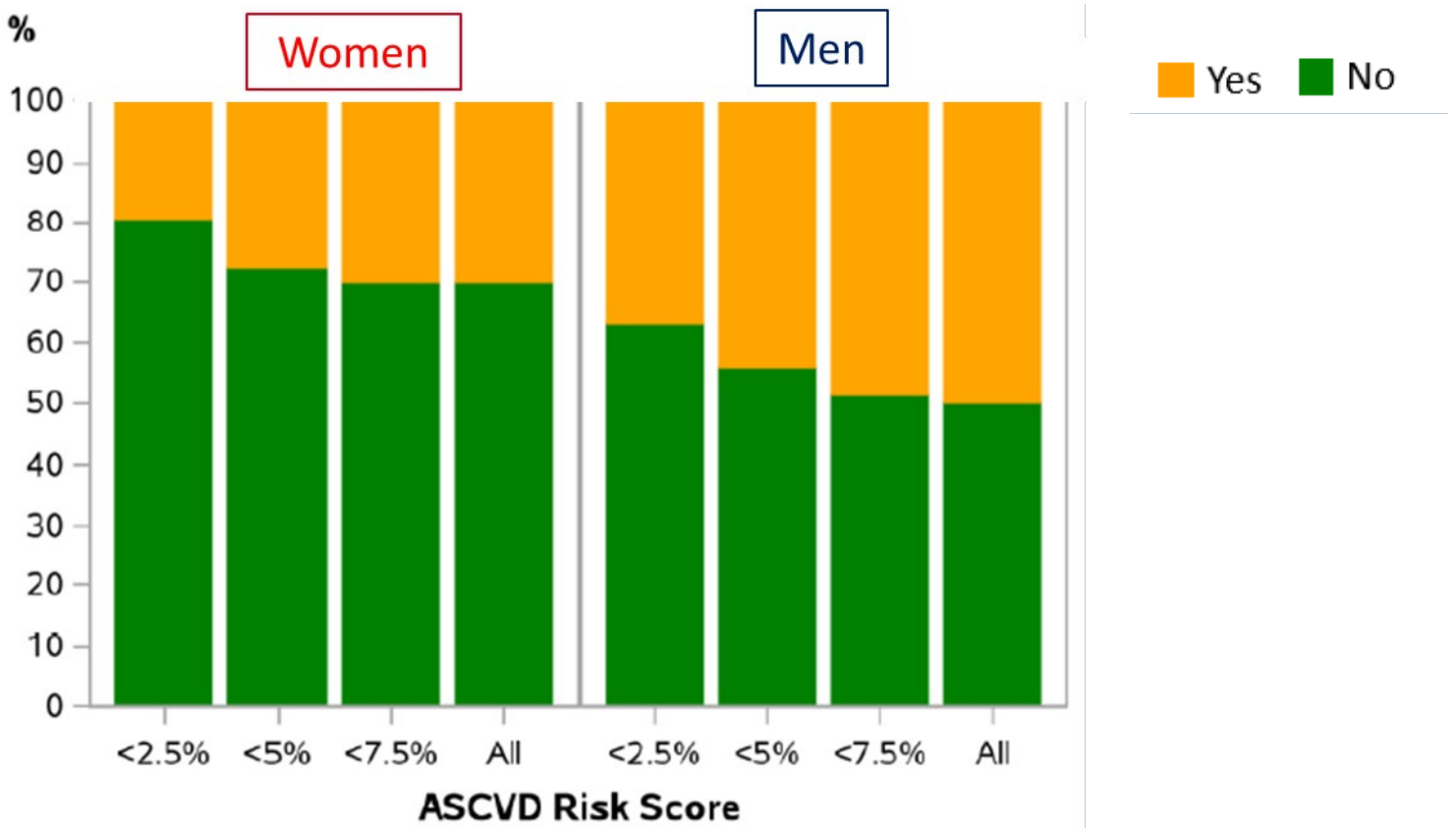
analyzed data from 755 US REPRIEVE participants enrolled in Mechanistic Substudy

Sex-Differences in Immune Activation/Inflammatory Markers



- Women living with HIV (vs. men living with HIV) showed higher levels of IL-6, hsCRP, and D-Dimer and lower levels of LpPLA-2 (*P<0.001 for* all, controlling for 10y ASCVD risk score + BMI)

Sex Differences in Coronary Artery Plaque Prevalence by 10-year ASCVD Risk Score



- Prevalence of coronary artery plaque was lower among women living with HIV vs. men living with HIV overall and controlling for 10y ASCVD risk score + BMI (RR=0.67; 95%CI: 0.50–0.92)

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]

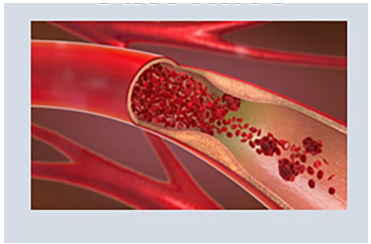
among US REPRIEVE participants

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

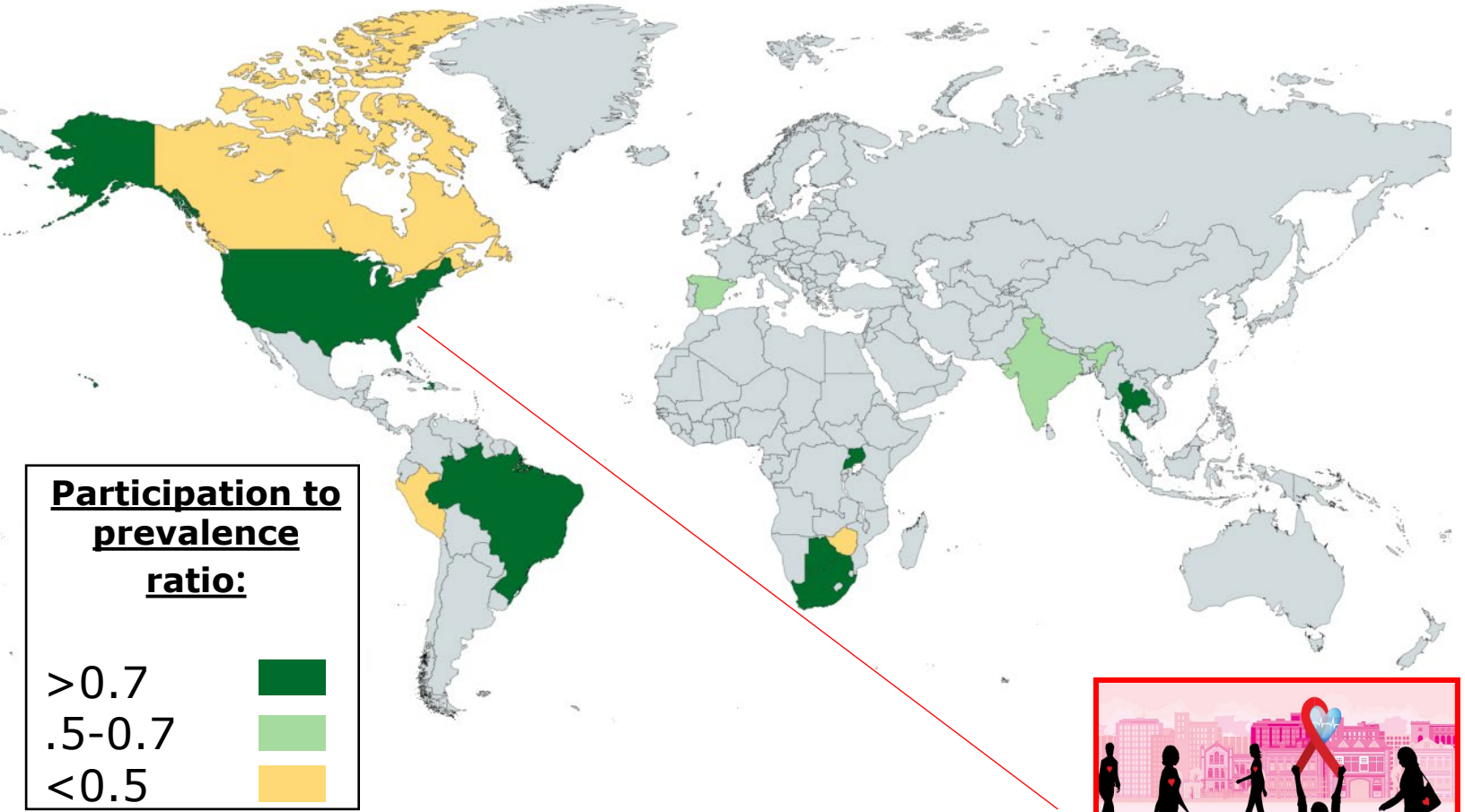
women vs. men:

↑ **Immune activation/ inflammatory markers**

↓ **Coronary artery plaque prevalence**



Women's Enrollment in REPRIEVE Main Study



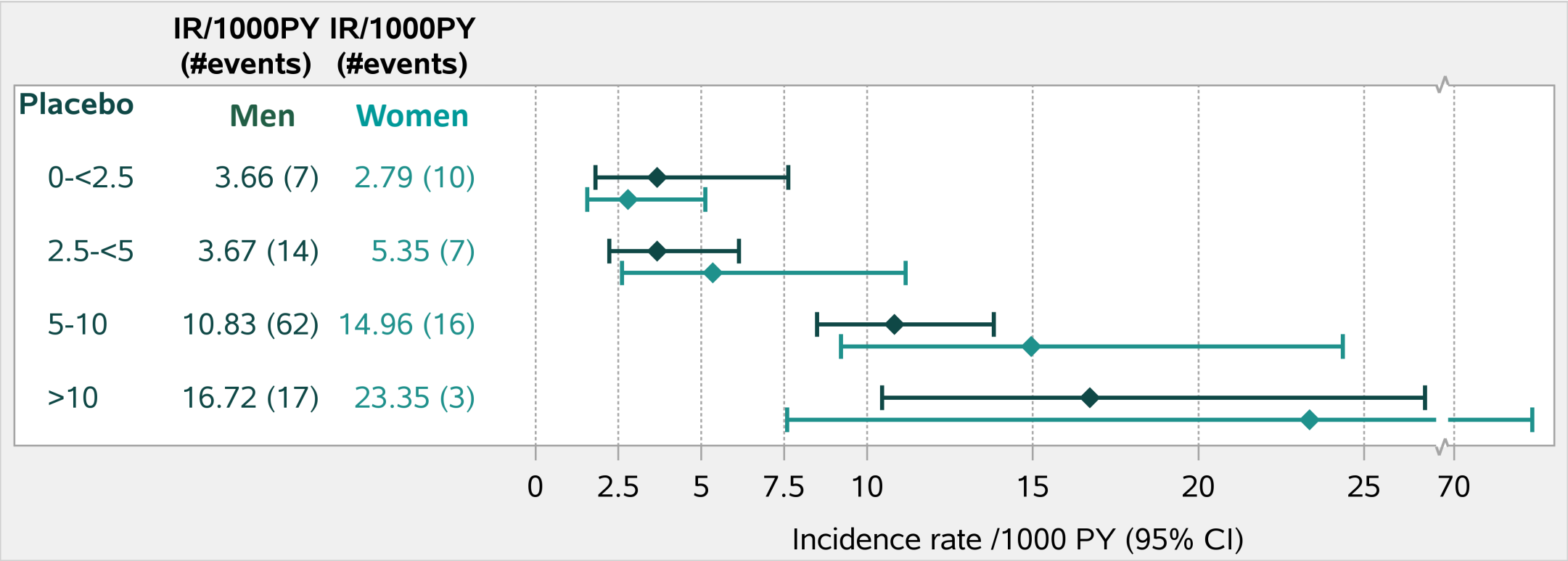
	% Women enrolled in REPRIEVE, by country	% Women among population living with HIV, by country
US	23	23[a]
Canada	10	29[b]
Spain	9	18[c]
Brazil	29	34[d]
Peru	8	24[c]
Haiti	42	57[c]
Thailand	56	42[c]
India	26	39[e]
South Africa	66	64[c]
Botswana	63	61[c]
Uganda	51	60[c]
Zimbabwe	24	58[c]

a. UNAIDS Data 2021. Geneva: Joint United Nations Programme on HIV/AIDS, 2021
b. Haddad et al. HIV in Canada Surveillance Report, 2018. Can Commun Dis Rep 2019
c. UNAIDS Data 2022. Geneva: Joint United Nations Programme on HIV/AIDS, 2022
d. AIDSInfo: Global Data on HIV Epidemiology and Responses, UNAIDS 2022
e. HIV/AIDS in India. Worldbank.org, 2021.

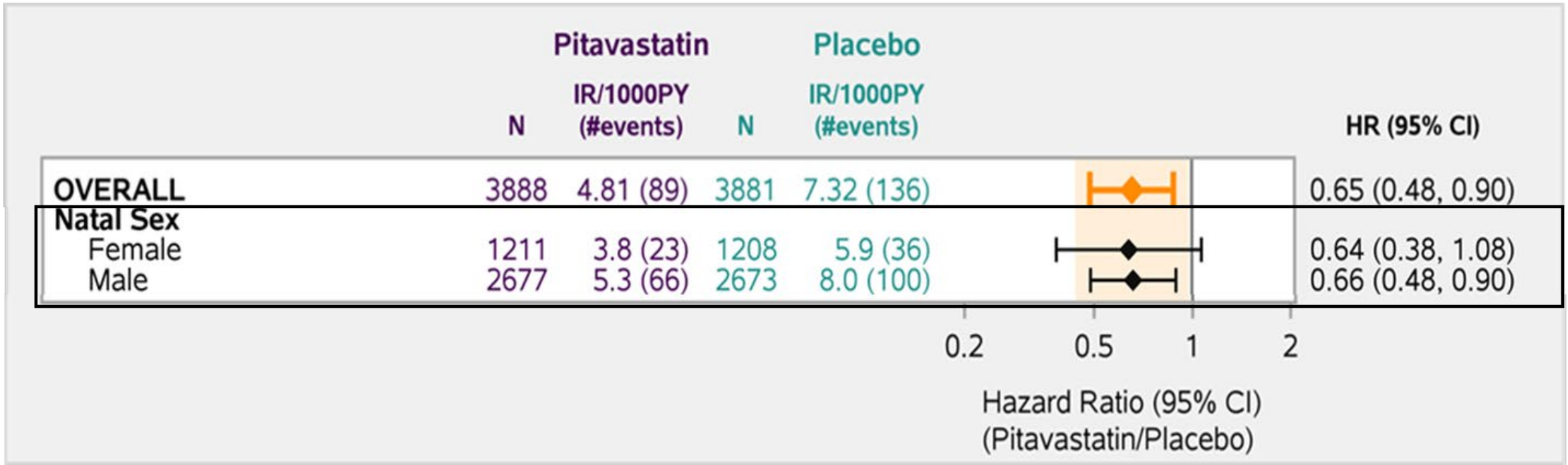
REPRIEVE Population
Baseline Characteristics by Sex

		Total	Men (N=5350)	Women (N= 2419)
Age (years)	Median (Q1-Q3)	50 (45, 55)	**50 (46, 55)**	**49 (44, 55)**
Race	Black/African-American, N (%)	41%	**34%**	**58%**
	White, N (%)	35%	**44%**	**15%**
	Asian, N (%)	15%	**13%**	**19%**
Current Cigarette Smoking	(%)	25%	**28%**	**18%**
Hypertension	(%)	36%	**34%**	**39%**
LDL-C (mg/dL)	Median (Q1-Q3)	108 (87, 128)	**107 (86, 126)**	**111 (90. 131)**
10-y ASCVD Risk Score (%)	Median (Q1-Q3)	4.5 (2.1, 7.0)	**5.4 (3.3, 7.8)**	**1.9 (0.8, 4.3)**
BMI (kg/m2)	Median (Q1-Q3)	25.8 (22.8, 29.4)	**25.3 (22.6, 28.3)**	**27.2 (23.4, 32.1)**
Viral Load < LLQ	(%)	88%	**87%**	**88%**
CD4 count (cells/mm3)	Median (Q1-Q3)	621 (448, 827)	**598 (426, 795)**	**679 (496, 898)**

MACE Rates in 10-year ASCVD Risk Score Subgroups by Sex



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



Thank you!

- Participants
- Site teams
- Our funders, including NIH as well as Kowa, Gilead and ViiV
- DAIDS and ACTG for trial monitoring and collaboration
- The entire REPRIEVE team