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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Grinspoon SK, Zanni MV, Trian VA, et al. Performance of the pooled cohort equations and D:A:D risk scores among individuals with HIV in a global cardiovascular disease prevention trial: a cohort study leveraging data from REPRIEVE. *Lancet HIV* 2025; published online Jan 17. https://doi.org/10.1016/S2352-3018(24)00276-5.

Supplementary Appendix to Grinspoon SK*, Zanni MV*, et al.

Supplement to: Grinspoon SK*, Zanni MV*, et al. Performance of the pooled cohort equations and D:A:D risk scores among individuals with HIV in a global cardiovascular disease prevention trial: a cohort study leveraging data from REPRIEVE. Lancet HIV. DOI: https://doi.org/10.1016/S2352-3018(24)00351-5. *contributed equally

This appendix has been provided by the authors to give readers additional information about the work.

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Supplemental Methods

Recalibration of the PCE in High Income Settings

After observing poor performance of the PCE risk score among PWH in HIC, particularly among women, we attempted PCE recalibration. Recalibration used the observed 5 year cumulative incidence and average PCE risk score score within sex and race subgroups to estimate the average underestimation of the PCE individual risk score and then applied that average underestimation to re-estimate the 5-year PCE risk score for each participant. Alternative recalibrations also considered the cumulative incidence lower 95% confidence bound, and the mid-point between the lower bound and point estimate and by estimating the average PCE risk score via the average of the score components.

The following provides the mathematical justification underlying our approach. Throughout, the term PCE subgroup refers to the four race/sex subgroups for which the PCE were originally derived (i.e., Black/AA men, Black/AA women, non-Black/AA men, non-Black/AA women).

The PCE is calculated as:

$$Predicted\ ASCVD\ risk = 1 - S_0(t)^{e^{(Individual\ score - Mean\ score)}}$$

where,

- $S_o(t)$ is the survival to time t (in this case 5 years) in the base PCE subgroup;
- *Individual score* (IS) is the participant score based on their inputs into their subgroup cohort equation;
- *Mean score* (MS) is the mean score obtained across all individuals in the base PCE cohort subgroup.

Considering that among people with HIV the individual score is underestimated say by an amount of D, i.e.,

$$Predicted\ ASCVD\ risk = 1 - S_0(t)^{e^{(IS + D - MS)}},$$

this expression can be simplified in terms of predicted survival and rearranged in terms of D, i.e.,

$$S_P(t) = S_0(t)^{e^{(IS + D - MS)}} \text{ or } D = \ln\left(\frac{\ln(S_P(t))}{\ln(S_o(t))}\right) - IS + MS$$

Note: While this approach to recalibration was expressed in terms of D as a fixed amount correction to the individual score, it could equivalently be seen as an adjustment baseline survival, i.e., replacing $S_o(t)$ *with* $exp\ (exp(\widehat{D})\ ln(S_o(t)))$.

To recalibrate the original PCE within HICs, PCE subgroup specific values for D were estimated by substituting the observed 5-year survival for $S_p(t)$ and average of the individual scores for IS. i.e.,

$$\widehat{D} = \ln\left(\frac{\ln(S_R(5))}{\ln(S_o(5))}\right) - \overline{IS_R} + MS$$

These PCE subgroup specific estimates for D (the amount of underestimation of the individual score) were then used to re-estimate predicted risk for all individuals from HICs. Summaries of the ratio recalibrated to original 5-year PCE risk are shown in Supplemental Table 1 (row A), grouped by original 5-year PCE risk score.

As an alternative to using the average of the individual scores within each PCE subgroup for the recalibration, an average individual score was also obtained using average covariate values directly in the PCE (Supplemental Table 1, row D).

Further, acknowledging that the observed 5-year survival is estimated with error, alternate estimates for D were obtained by substituting $S_P(t)$ with the lower confidence limit of the observed 5-year survival (Supplemental Table 1, Rows B and E), and a mid-range adjustment factor (Supplemental Table 1, Rows C and F) that was the average underestimation based on the two survival estimates.

Since the PCE seemed to perform quite well among males in general, each recalibration approach was assessed across all participants and also with recalibration limited to females.

Altogether these provided 12 distinct recalibrations.

As a practical approach to recalibration, our results present an approximate recalibration based on multiplication of the original PCE by a recalibration factor derived from the ratio recalibrated to original 5-year PCE risk within our cohort.

Supplemental Table 1: PCE and D:A:D ASCVD Risk Score Inputs and Outcomes

	Risk Score		Risk Score Outcome		Trial Outcome
	PCE	**D:A:D REDUCED**	**Hard MACE**	**D:A:D MACE**	**REPRIEVE Primary MACE**
Inputs[1]					
Age	X	X			
Sex	X	X			
Smoking	X	X			
Diabetes	X	X			
Race	X	-			
Lipids	X	X			
Hypertension therapy	X	-			
Blood pressure	SBP	SBP			
Family history of premature CVD[2]	-	X			
CD4 count	-	X			
Clinical Outcome[3]					
Coronary insufficiency or revascularization	-	X	-	X	X
Angina pectoris	-	-	-	-	X
Unstable angina	-	-	-	-	X
Myocardial infarction	X	X	X	X	X
CHD death	X	X	X	X	X
Stroke	X	X	X	X	X
Stroke death	X	X	X	X	X
Cardiac failure	-	-	-	-	-
Transient ischemic attack	-	-	-	-	X
Peripheral artery disease or revascularization	-	-	-	-	X
Carotid or cerebrovascular revascularization	-	-	-	-	X
Death, all cause	-	-	-	-	-

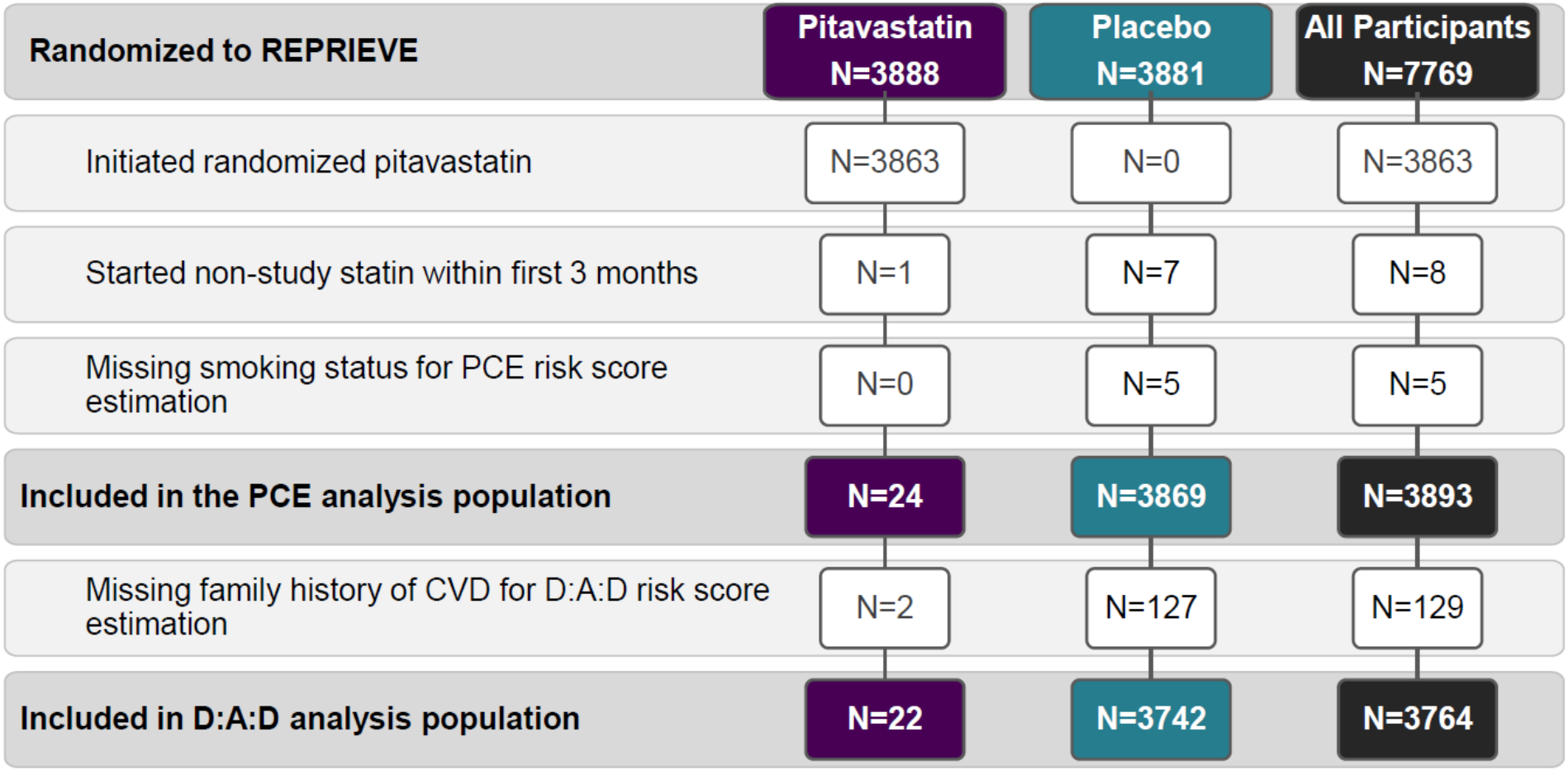
[1]Components used as input to calculate each of the risk scores are shown with 'X'; for blood pressure, inputs are specified as SBP (systolic blood pressure), DBP (diastolic blood pressure). [2]Family history of premature CVD collected in REPRIEVE was defined as immediate relative (parent, sibling) who developed heart disease prior to the age of 55 for men or 65 for women whereas in the D:A:D, family history of premature CVD is defined as first degree relative who experienced myocardial infarction before the age of 50. [3]Endpoints used in the corresponding risk score development are shown with 'X'; the REPRIEVE primary MACE outcome measure is shown for reference. Throughout the table, '-' means not included.

Supplemental Table 2: Recalibration of 5-year PCE Risk Score among PWH within HIC

								Ratio of Recalibrated to Original 5-year PCE Risk (Grouped by Original 5-year PCE Risk)[4]							
	Mean Score		5-year Survival					0%-<1.25%		1.25%-<2.5%		2.5%-<3.75%		>=3.75%	
	PCE	Observed[1]	PCE baseline	Observed[2]	D*[3]		N	Mean	(Min - Max)	Mean	(Min - Max)	Mean	(Min - Max)	Mean	(Min - Max)
Black/AA Women	86.61	86.06	98.194%	95.856%	1.39	(A)	303	3.99	(3.95 - 4.02)	3.91	(3.87 - 3.95)	3.84	(3.81 - 3.87)	3.71	(3.49 - 3.80)
				97.810%	0.74	(B)	303	2.10	(2.09 - 2.10)	2.08	(2.08 - 2.09)	2.07	(2.06 - 2.08)	2.04	(2.00 - 2.06)
				96.833%	**1.07**	**(C)**	**303**	**2.89**	**(2.88 - 2.91)**	**2.86**	**(2.84 - 2.88)**	**2.83**	**(2.81 - 2.84)**	**2.77**	**(2.66 - 2.81)**
		85.91	98.194%	95.856%	1.55	(D)	303	4.64	(4.59 - 4.69)	4.54	(4.48 - 4.58)	4.44	(4.39 - 4.48)	4.26	(3.94 - 4.38)
				97.810%	0.90	(E)	303	2.44	(2.43 - 2.45)	2.42	(2.41 - 2.43)	2.40	(2.39 - 2.41)	2.36	(2.29 - 2.39)
				96.833%	1.22	(F)	303	3.37	(3.34 - 3.39)	3.32	(3.29 - 3.34)	3.27	(3.25 - 3.29)	3.18	(3.03 - 3.24)
	19.54	-	95.726%	-	-	(G)	303	4.89	(1.89 - 24.48)	2.20	(1.27 - 3.75)	1.89	(1.19 - 2.68)	1.49	(0.90 - 1.99)
Black/AA Men	19.54	19.08	95.726%	95.668%	0.47	(A)	571	1.59	(1.59 - 1.60)	1.59	(1.59 - 1.59)	1.58	(1.58 - 1.59)	1.58	(1.54 - 1.58)
				97.239%	0.01	(B)	571	1.01	(1.01 - 1.01)	1.01	(1.01 - 1.01)	1.01	(1.01 - 1.01)	1.01	(1.01 - 1.01)
				96.453%	**0.24**	**(C)**	**571**	**1.27**	**(1.27 - 1.27)**	**1.27**	**(1.27 - 1.27)**	**1.27**	**(1.27 - 1.27)**	**1.26**	**(1.25 - 1.27)**
		19.07	95.726%	95.668%	0.48	(D)	571	1.62	(1.62 - 1.62)	1.61	(1.61 - 1.62)	1.61	(1.60 - 1.61)	1.60	(1.56 - 1.60)
				97.239%	0.03	(E)	571	1.03	(1.03 - 1.03)	1.03	(1.03 - 1.03)	1.03	(1.03 - 1.03)	1.03	(1.02 - 1.03)
				96.453%	0.25	(F)	571	1.29	(1.29 - 1.29)	1.29	(1.29 - 1.29)	1.28	(1.28 - 1.29)	1.28	(1.27 - 1.28)
		-	95.726%	-	-	(G)	571	1.00	(1.00 - 1.00)	1.00	(1.00 - 1.00)	1.00	(1.00 - 1.00)	1.00	(1.00 - 1.00)
Non-Black/AA Women	-29.18	-29.69	98.898%	96.960%	1.53	(A)	143	4.58	(4.53 - 4.62)	4.49	(4.43 - 4.52)	4.39	(4.35 - 4.41)	-	(- - -)
				99.005%	0.40	(B)	143	1.50	(1.49 - 1.50)	1.49	(1.49 - 1.49)	1.49	(1.49 - 1.49)	-	(- - -)
				97.982%	**0.97**	**(C)**	**143**	**2.62**	**(2.61 - 2.63)**	**2.60**	**(2.58 - 2.61)**	**2.57**	**(2.56 - 2.58)**	**-**	**(- - -)**
		-30.18	98.898%	96.960%	2.03	(D)	143	7.46	(7.29 - 7.58)	7.18	(7.03 - 7.29)	6.91	(6.80 - 6.97)	-	(- - -)
				99.005%	0.90	(E)	143	2.45	(2.44 - 2.46)	2.43	(2.42 - 2.44)	2.41	(2.40 - 2.41)	-	(- - -)
				97.982%	1.46	(F)	143	4.28	(4.23 - 4.32)	4.20	(4.15 - 4.23)	4.12	(4.09 - 4.14)	-	(- - -)
	61.18	-	96.254%	-	-	(G)	143	2.88	(1.64 - 3.71)	2.52	(1.34 - 3.20)	2.51	(2.20 - 3.05)	-	(- - -)
Non-Black/AA Men	61.18	60.49	96.254%	97.972%	0.07	(A)	1041	1.07	(1.07 - 1.07)	1.07	(1.07 - 1.07)	1.07	(1.07 - 1.07)	1.07	(1.06 - 1.07)
				98.757%	-0.43	(B)	1041	0.65	(0.65 - 0.65)	0.65	(0.65 - 0.65)	0.66	(0.65 - 0.66)	0.66	(0.66 - 0.66)
				98.365%	**-0.18**	**(C)**	**1041**	**0.83**	**(0.83 - 0.84)**	**0.84**	**(0.84 - 0.84)**	**0.84**	**(0.84 - 0.84)**	**0.84**	**(0.84 - 0.84)**
		60.43	96.254%	97.972%	0.12	(D)	1041	1.13	(1.13 - 1.13)	1.13	(1.13 - 1.13)	1.13	(1.13 - 1.13)	1.13	(1.12 - 1.13)
				98.757%	-0.37	(E)	1041	0.69	(0.69 - 0.69)	0.69	(0.69 - 0.69)	0.70	(0.69 - 0.70)	0.70	(0.70 - 0.70)
				98.365%	-0.12	(F)	1041	0.89	(0.89 - 0.89)	0.89	(0.89 - 0.89)	0.89	(0.89 - 0.89)	0.89	(0.89 - 0.89)
		-	96.254%	-	-	(G)	1041	1.00	(1.00 - 1.00)	1.00	(1.00 - 1.00)	1.00	(1.00 - 1.00)	1.00	(1.00 - 1.00)

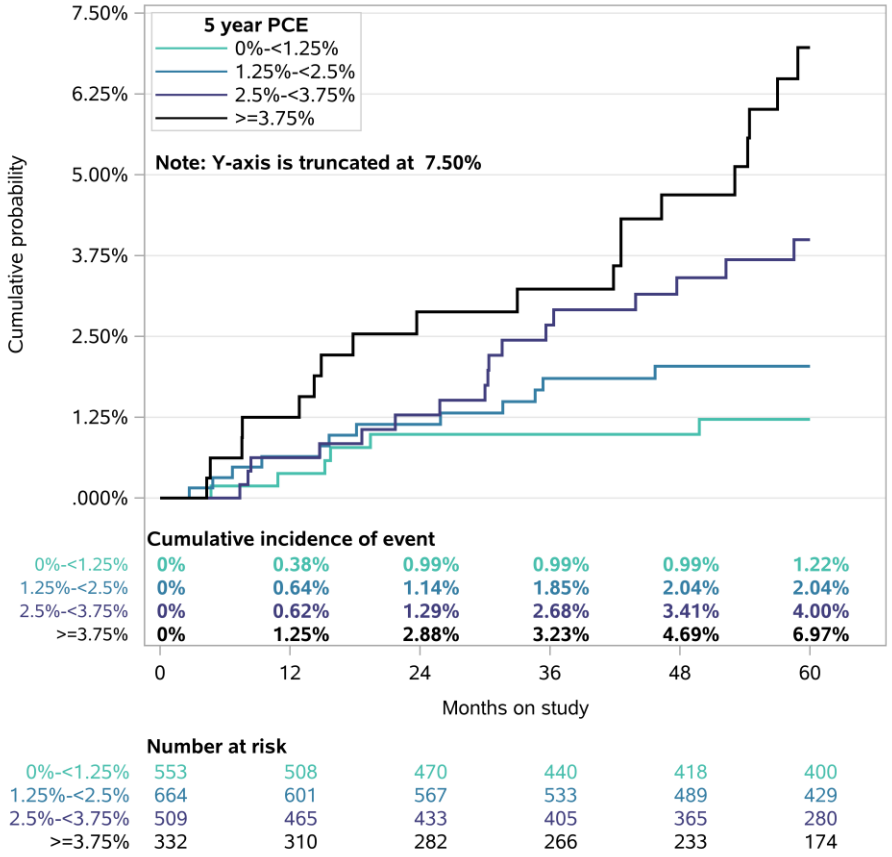
[1]Restricted to REPRIEVE participants enrolled in high-income countries (HIC). For recalibrations (A)-(C), the average PCE individual score is estimated by the mean individual score within PCE subgroup; in (D)-(F) it is estimated using the average value of each component as PCE inputs; for recalibration (G), the PCE risk score for men is used for women. [2]The estimated average survival for each subgroup used in the recalibration attempts ranged from 1 minus the 5-year cumulative incidence [(A) and (D)] to 1 - minus the lower bound of the 95% confidence interval on the 5-year cumulative incidence [(B) and (E)]; recalibrations (C) and (F) use the mid-point of the two estimates. [3]D gives the estimated underestimation of the PCE individual score for each recalibration attempt.[4]The ratio of the recalibrated PCE risk prediction to original prediction is shown stratified by the original; table shows the mean, minimum, and maximum ratio within each strata of risk. Black/AA=Black/African American*

Supplemental Figure 1: Consort Diagram



Supplemental Figure 2: Cumulative Incidence of Hard MACE Over 5-years Stratified by 5-Year PCE, by GBD Region

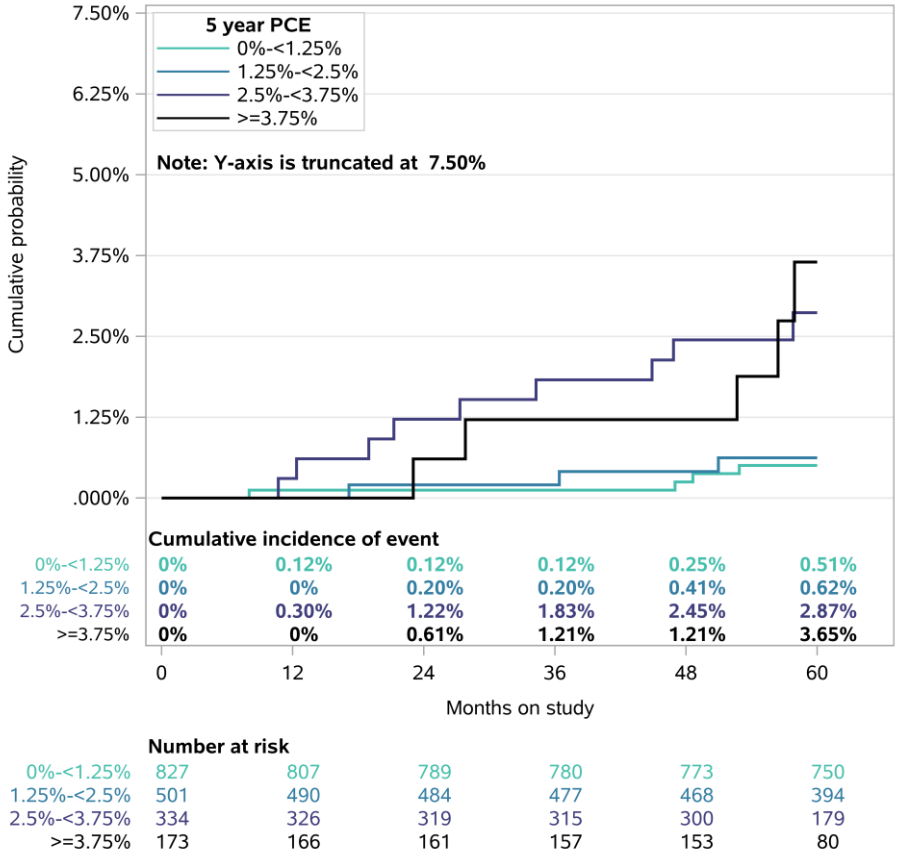
(a) First Hard MACE by 5 Year PCE within HIC



Cumulative incidence of event						
0%-<1.25%	0%	0.38%	0.99%	0.99%	0.99%	1.22%
1.25%-<2.5%	0%	0.64%	1.14%	1.85%	2.04%	2.04%
2.5%-<3.75%	0%	0.62%	1.29%	2.68%	3.41%	4.00%
>=3.75%	0%	1.25%	2.88%	3.23%	4.69%	6.97%

Number at risk						
0%-<1.25%	553	508	470	440	418	400
1.25%-<2.5%	664	601	567	533	489	429
2.5%-<3.75%	509	465	433	405	365	280
>=3.75%	332	310	282	266	233	174

(b) First Hard MACE by 5 Year PCE within LMIC



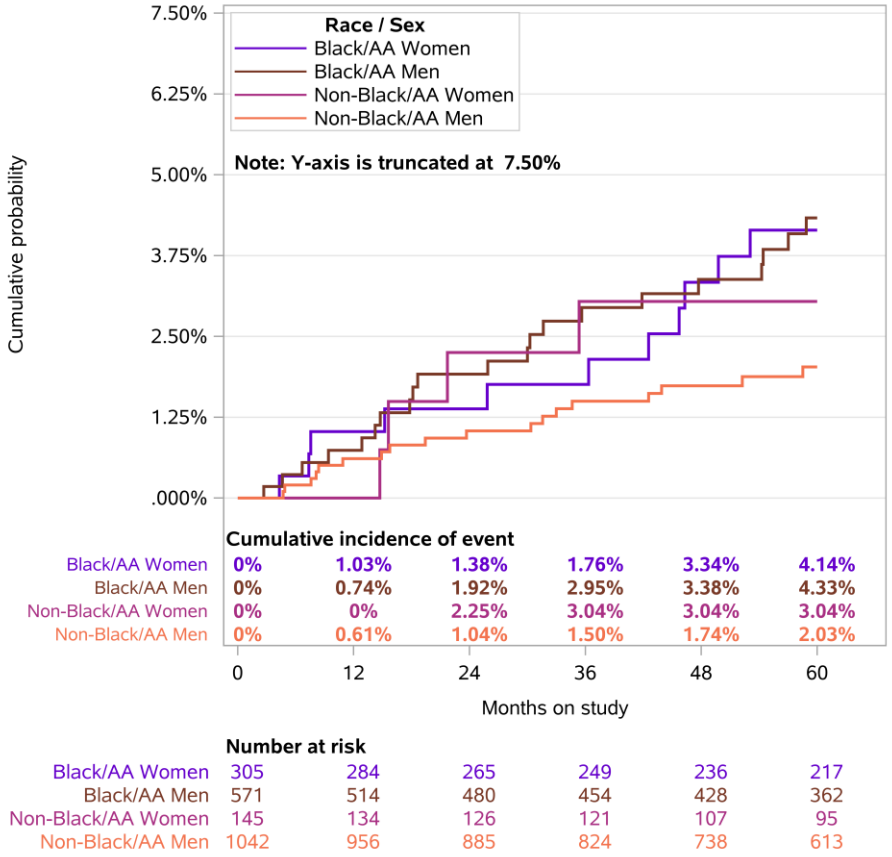
Cumulative incidence of event						
0%-<1.25%	0%	0.12%	0.12%	0.12%	0.25%	0.51%
1.25%-<2.5%	0%	0%	0.20%	0.20%	0.41%	0.62%
2.5%-<3.75%	0%	0.30%	1.22%	1.83%	2.45%	2.87%
>=3.75%	0%	0%	0.61%	1.21%	1.21%	3.65%

Number at risk						
0%-<1.25%	827	807	789	780	773	750
1.25%-<2.5%	501	490	484	477	468	394
2.5%-<3.75%	334	326	319	315	300	179
>=3.75%	173	166	161	157	153	80

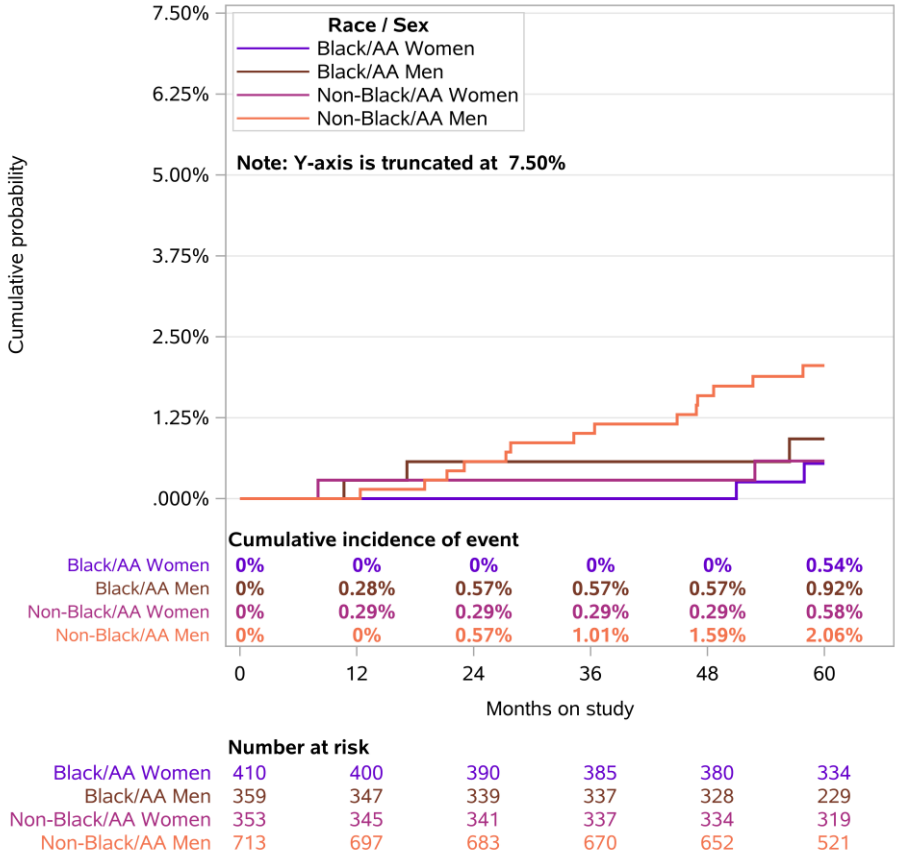
Cumulative incidence was calculated using the Aalen estimator for probability of subdistribution of failure of interest.
Participant follow-up was calculated as the number of days from randomization date to the date of event, last contact, or 5 years after randomization, whichever was earlier; participants with no contact after entry were included with 1 day imputed as censoring time. Months on study is defined in terms of calendar months (30.44 days). HIC=high-income countries; LMIC=low- and middle-income countries.

Supplemental Figure 3: Cumulative Incidence of Hard MACE Over 5-years Stratified by Race and Sex, by GBD Region

(a) First Hard MACE by Race/Sex within HIC

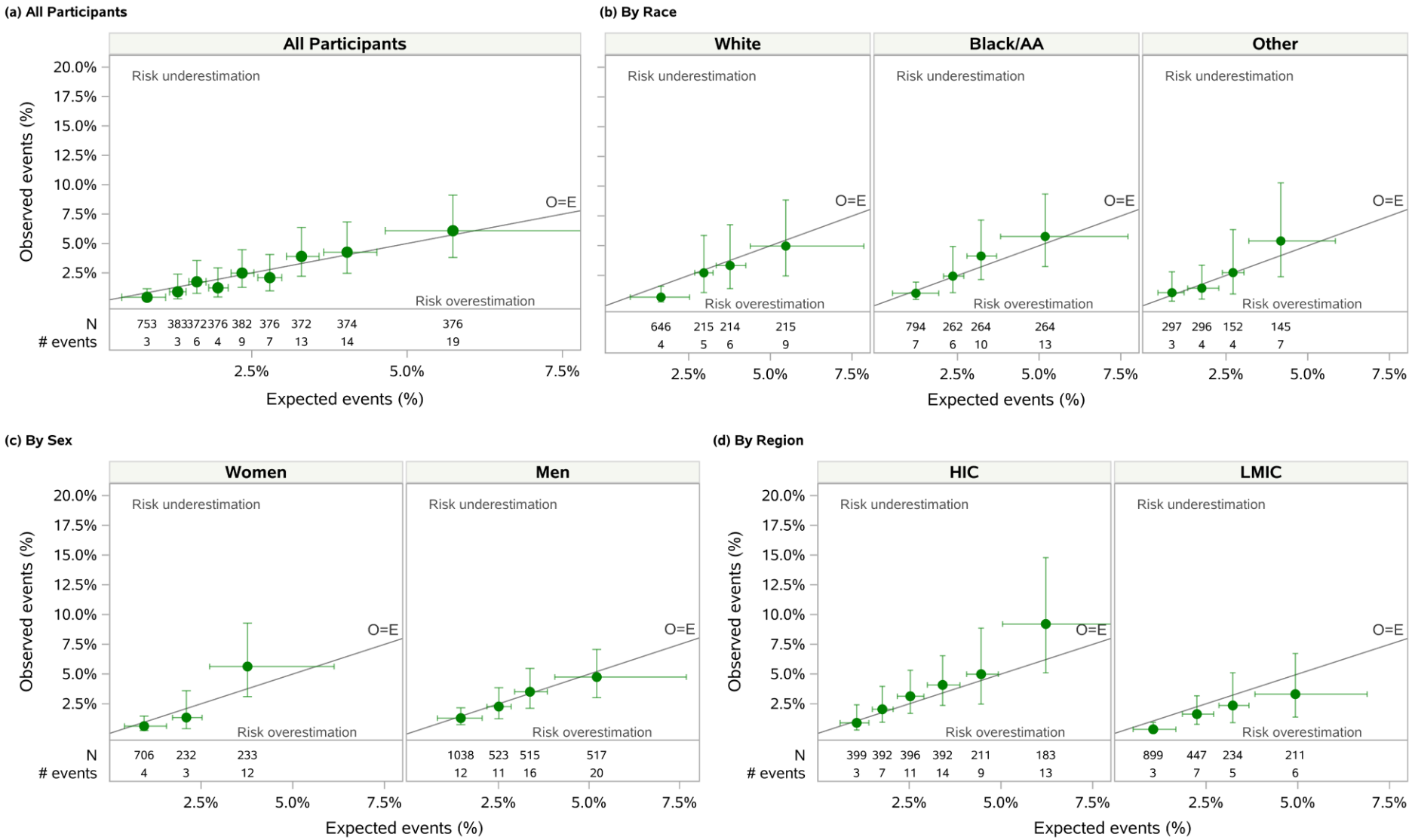


(b) First Hard MACE by Race/Sex within LMIC



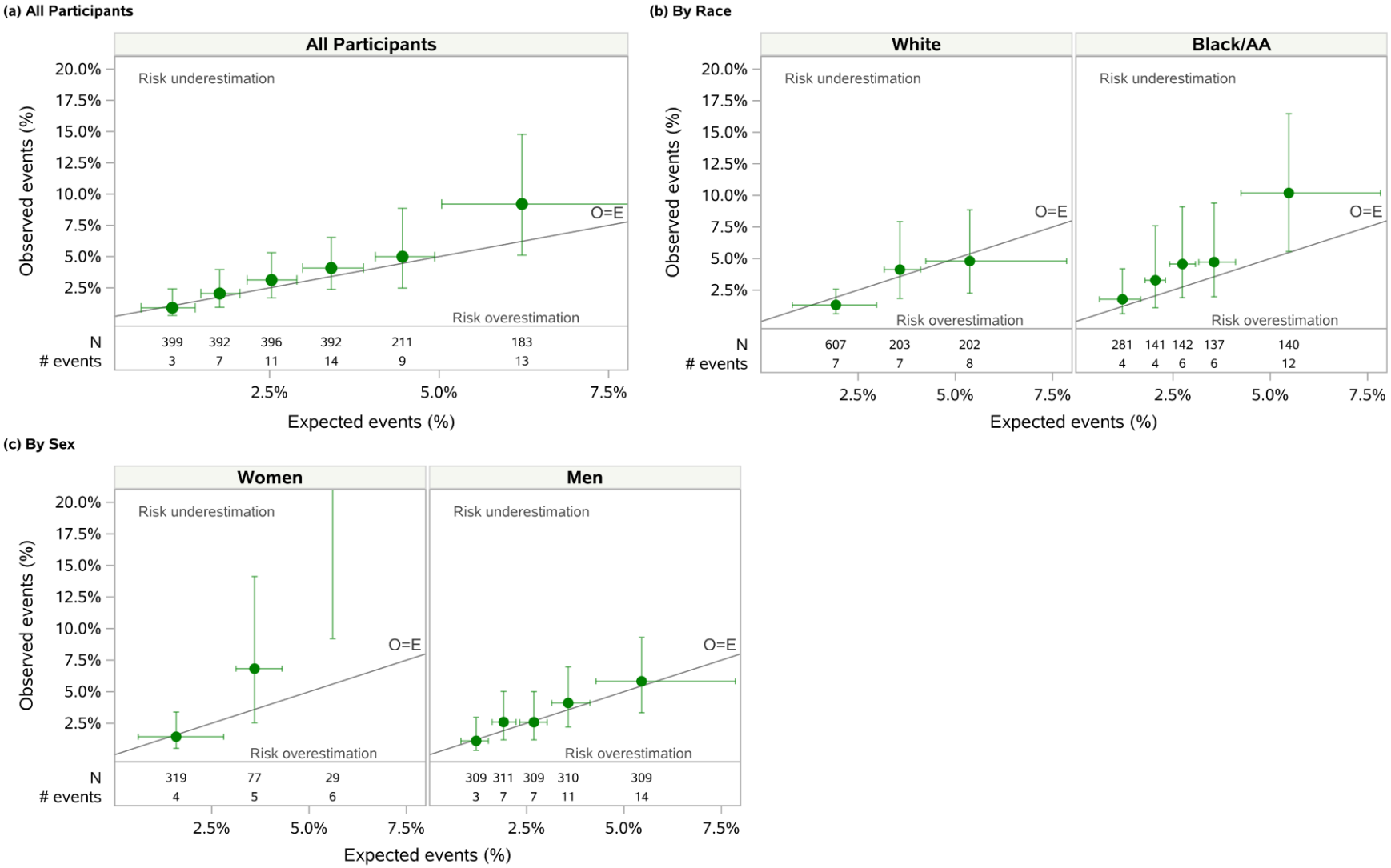
Cumulative incidence was calculated using the Aalen estimator for probability of subdistribution of failure of interest.
Participant follow-up was calculated as the number of days from randomization date to the date of event, last contact, or 5 years after randomization, whichever was earlier; participants with no contact after entry were included with 1 day imputed as censoring time. Months on study is defined in terms of calendar months (30.44 days).
Black/AA=Black/African American. HIC=high-income countries; LMIC=low- and middle-income countries.

Supplemental Figure 4: Calibration Plots for 5-year D:A:D for First Primary MACE (excluding TIA, PAD, and deaths of undetermined cause)



Observed versus expected event rates across ordered groups (ntiles) of predicted CVD risk. Deciles were used for the overall analysis; quintiles for the subgroup analyses. Groups were combined when they contained <2 events. As the numbers of events allowed, the group at the highest end of the risk score distribution was split to avoid an excessive range in the scores. Within each ordered group, the observed rate reflects the estimated 5-year cumulative incidence; the expected rate mean predicted risk score within the group. Error bars show the 95% confidence interval for the observed rates and 5th and 95th percentiles of the predicted risk within the ordered group.
Black/AA=Black/African American; HIC=high-income countries; LMIC=low- and middle-income countries; O=Observed; E=Expected.

Supplemental Figure 5: Calibration Plots for 5-year D:A:D for First Primary MACE (excluding TIA, PAD, and deaths of undetermined cause) among PWH within HIC



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Black/AA=Black/African American; HIC=high-income countries; LMIC=low- and middle-income countries; O=Observed; E=Expected.