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

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Summary

Background Risk estimation is an essential component of cardiovascular disease prevention among people with HIV. We aimed to characterise how well atherosclerotic cardiovascular disease (ASCVD) risk scores used in clinical guidelines perform among people with HIV globally.

Methods In this prospective cohort study leveraging REPRIEVE data, we included participants aged 40–75 years, with low-to-moderate traditional cardiovascular risk, not taking statin therapy. REPRIEVE participants were enrolled from sites in 12 countries across Global Burden of Disease Study (GBD) regions. We assessed the performance of the pooled cohort equations (PCE) risk score for ASCVD and the data-collection on adverse effects of anti-HIV drugs (D:A:D) risk score. We calculated C statistics, observed-to-expected (OE) event ratios, and Greenwood–Nam–D'Agostino goodness-of-fit (GND) statistics, overall and in subgroups by race, sex, and GBD regions (clustering low-income and middle-income countries and high-income countries). We did a recalibration for PCE risk score among people with HIV in high-income countries. REPRIEVE was registered with ClinicalTrials.gov, NCT02344290.

Findings We included 3893 participants, recruited between March 26, 2015, and July 31, 2019. The median age was 50 years (IQR 45–55), with 2684 (69%) male and 1209 (31%) female participants. 1643 (42%) were Black or African American, 1346 (35%) participants were White, 566 (15%) were Asian, and 338 (9%) were recorded as other race. Overall, discrimination of the PCE risk score was moderate (C statistic 0·72 [95% CI 0·68–0·76]) and calibration was good (OE event ratio 1·11; GND p=0·87). However, calibration suggested overprediction of risk in low-income and middle-income countries and corresponding underprediction in high-income countries. When restricted to high-income countries, we found underprediction (OE event ratio >1·0) among women (2·39) and Black or African American participants (1·64). Findings were similar for the D:A:D risk score (C statistic 0·71 [0·65–0·77]; OE event ratio 0·89; p=0·68). Improved calibration of the PCE risk score in high-income countries was achieved by multiplying the original score by 2·8 in Black or African American women, 2·6 in women who were not Black or African American, and 1·25 in Black or African American men.

Interpretation Among the global cohort of people with HIV in REPRIEVE, the PCE risk score underpredicted cardiovascular events in women and Black or African American men in high-income countries and overpredicted cardiovascular events in low-income and middle-income countries. Underprediction in subgroups should be considered when using the PCE risk score to guide statin prescribing for cardiovascular prevention among people with HIV in high-income countries. Additional research is needed to develop risk scores accurate in predicting ASCVD among people with HIV in low-income and middle-income countries.

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Introduction

People with HIV have an approximately two-times increased risk for atherosclerotic cardiovascular disease (ASCVD), including myocardial infarction and stroke, compared with individuals without HIV.[1] Drivers of HIV-associated ASCVD risk include traditional risk factors, as well as HIV-specific risk factors, such as immune dysfunction, heightened systemic and arterial inflammation, and off-target effects of antiretroviral therapeutics.[2–4] Previous studies assessing, among people with HIV, the performance of traditional ASCVD risk scores (such as the pooled cohort equations [PCE][5]) and HIV-specific ASCVD risk scores (such as the data-collection on adverse effects of anti-HIV drugs [D:A:D]

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Research in context

Evidence before this study

We searched PubMed without language restrictions for literature published on or before July 12, 2024, using the terms "HIV and cardiovascular disease risk scores". People with HIV have higher burden of cardiovascular disease than the general population and estimating this risk is an essential component of cardiovascular prevention. Previous studies assessing, among people with HIV, the performance of traditional atherosclerotic cardiovascular disease (ASCVD) risk scores (such as the pooled cohort equations [PCE] score) and HIV-specific ASCVD risk scores (such as the data-collection on adverse effects of anti-HIV drugs [D:A:D] score) have yielded conflicting results. Cross-study discrepancies are likely to reflect differences in the populations to which these ASCVD risk scores were applied, as well as disparate strategies for characterising ASCVD events in these populations. A systematic review and meta-analysis examined the performance of ASCVD risk scores among 75 304 people with HIV engaged in one of nine observational cohorts. Among these cohorts, four followed up people with HIV in the USA, four in Europe, and one in nine high-income countries and one Latin American upper-middle-income country. To date, no study has systematically assessed the performance of ASCVD risk scores in a global population of people with HIV, including individuals residing in low-income and middle-income countries.

Added value of this study

Leveraging the global REPRIEVE trial, we assessed the performance of the PCE ASCVD risk score, used in US clinical guidelines, and the D:A:D risk score, which incorporates HIV-specific data elements, among participants not taking statin therapy. Three key findings emerged. First, among our analysis cohort (n=3893), overall discrimination of the PCE risk score was moderate (C statistic 0·72 [95% CI 0·68–0·76]) and calibration was good (observed-to-expected [OE] events ratio 1·11; Greenwood–Nam–D'Agostino goodness-of-fit p=0·87). However, calibration suggested overprediction of risk in low-income and middle-income countries and corresponding underprediction of risk in high-income countries. Second, in analyses restricted to people with HIV in high-income countries, we found underprediction by the PCE risk score (OE event ratio >1·0) among women (2·39) and Black or African American participants (1·64). Findings were similar for D:A:D risk score performance. Finally, improved calibration of the PCE risk score among people with HIV in high-income countries was achieved by multiplying the original score by 2·8 in Black or African American women, 2·6 in women who were not Black or African American, and 1·25 in Black or African American men.

Implications of all the available evidence

Our findings on geographical region-based discrepancies in the performance of ASCVD risk scores underscore an important research priority to develop strategies for accurately predicting ASCVD risk among people with HIV globally. From a clinical standpoint, PCE-based underestimation of ASCVD risk among women and among Black or African American men with HIV in high-income countries might be expected to hinder cardiovascular disease preventive care on several levels. Our identification of recalibration factors for the PCE score in key subgroups is highly relevant to optimising cardiovascular disease preventive care for women and for Black or African American men in high-income countries. Additional research is needed to understand whether the apparent overestimation of ASCVD risk among REPRIEVE participants in low-income and middle-income countries is applicable to broader groups of people with HIV living in these countries, including those with a greater burden of traditional risk factors. Research is also needed to develop novel population-specific ASCVD risk assessment algorithms factoring in region-specific contributors to major adverse cardiovascular events among people with HIV.

model[6]) have yielded conflicting results.[7,8] Cross-study discrepancies probably reflect differences in the populations to which these ASCVD risk scores were applied, as well as disparate strategies for characterising ASCVD events in these populations. To date, no study has systematically assessed the performance of ASCVD risk scores in a global population of people with HIV, including individuals residing in low-income and middle-income countries.

To address key knowledge gaps in the HIV–cardiovascular disease field, we analysed the performance of widely used ASCVD risk scores among a prespecified subset of participants in the Randomized Trial To Prevent Vascular Events In HIV (REPRIEVE). Through REPRIEVE, 7769 people with HIV with low-to-moderate traditional ASCVD risk were enrolled between March 26, 2015, and July 31, 2019, and randomly assigned to receive pitavastatin 4 mg daily or placebo.[9,10] REPRIEVE participants, all of whom were on stable antiretroviral therapy (ART), were from five continents and 12 countries, including low-income, middle-income, and high-income countries. Over a median follow-up of approximately 5 years, major adverse cardiovascular events (MACE) were confirmed through independent adjudication.[9] In April, 2023, the Data and Safety Monitoring Board (DSMB) stopped the trial early because of the finding that pitavastatin therapy (*vs* placebo) reduced MACE by 35%.[10] REPRIEVE results catalysed the February 2024 release of revised US guidelines on statin prescribing for people with HIV aged at least 40 years.[11] These guidelines, developed by the US Department of Health and Human Services, in conjunction with the American College of Cardiology, the American Heart Association, and the HIV Medicine

Association, strongly recommended statin therapy for people with HIV with a PCE risk score at or above 5%. For people with HIV with scores below 5%, statin therapy was favoured, with lower grade of evidence, given the lower anticipated absolute risk reduction.[11] The present analysis of ASCVD risk score performance is limited to REPRIEVE participants who did not take statin therapy as study treatment. We focus primarily on the PCE risk score which, in US general and HIV-specific guidelines, informs statin prescribing recommendations.[5,11] For comparison, we also show data on the performance of the reduced-model D:A:D risk score, which integrates HIV-specific data such as current CD4 T-cell count.[6]

Despite the fact that US guidelines now broadly recommend statin therapy for ASCVD risk reduction among adults with HIV,[11] the performance of risk prediction scores among people with HIV globally remains important. In general, risk score performance is characterised based on discrimination—ie, the ability to differentiate people who go on to develop an event from those who do not—and calibration—ie, the extent to which the risk prediction score accurately reflects observed risk.[7] On an individual level, personalised risk prediction helps provider–patient dyads participate in shared decision making about risk-reduction strategies such as lifelong statin therapy, for which the strength of guideline-based recommendations is based on risk score thresholds. On a public health level, characterisation of risk in a population informs the development, funding, operationalisation, and cost-effectiveness assessment of policies geared towards large-scale disease prevention.

Methods

Study design and participants

Our analysis represents an observational analysis of data from a subset of participants enrolled in REPRIEVE and prospectively monitored for development of MACE (prospective cohort study). The analysis sample included participants randomly assigned to placebo and participants randomly assigned to pitavastatin who never started treatment. REPRIEVE enrolled a global primary cardiovascular disease prevention cohort of ART-treated people with HIV, aged 40–75 years, with low-to-moderate traditional cardiovascular risk (as characterised by PCE risk score and circulating levels of LDL cholesterol). The trial was stopped on March 30, 2023, and additional data were accrued up to completion of the final study visit on Aug 21, 2023. REPRIEVE participants were enrolled from sites in 12 countries across Global Burden of Disease Study (GBD) regions, as previously described.[9] World Bank classifications of countries featuring REPRIEVE sites are USA (except Puerto Rico), Canada, and Spain as high-income countries; and Brazil, Haiti, Peru, Puerto Rico, Thailand, India, Botswana, South Africa,

	Total (n=3893)	High-income countries (n=2058)	Low-income and middle-income countries (n=1835)
Demographic and behavioural characteristics			
Age, years			
Mean	50 (6)	51 (6)	49 (7)
Median	50 (45–55)	51 (46–55)	49 (44–54)
40–49	1890 (49%)	891 (43%)	999 (54%)
50–59	1661 (43%)	981 (48%)	680 (37%)
≥60	342 (9%)	186 (9%)	156 (9%)
Natal sex			
Male	2684 (69%)	1612 (78%)	1072 (58%)
Female	1209 (31%)	446 (22%)	763 (42%)
Race			
White	1346 (35%)	1059 (51%)	287 (16%)
Black	1643 (42%)	874 (42%)	769 (42%)
Asian	566 (15%)	23 (1%)	543 (30%)
Other*	338 (9%)	102 (5%)	236 (13%)
Smoking status			
Current	1019 (26%)	682 (33%)	337 (18%)
Former	920 (24%)	579 (28%)	341 (19%)
Never	1954 (50%)	797 (39%)	1157 (63%)
Substance use†			
Current	78 (2%)	64 (3%)	14 (1%)
Former	1141 (29%)	1030 (50%)	111 (6%)
Never	2673 (69%)	963 (47%)	1710 (93%)
Cardiovascular risk factors			
Atherosclerotic cardiovascular disease risk score	4·5% (2·2–7·1)	5·3% (2·9–7·5)	3·6% (1·4–6·3)
0 to <5·0	2088 (54%)	953 (46%)	1135 (62%)
5·0 to <7·5	969 (25%)	580 (28%)	389 (21%)
≥7·5	836 (21%)	525 (26%)	311 (17%)
BMI, kg/m²	25·8 (22·7–29·2)	26·7 (24·0–30·5)	24·5 (21·7–27·9)
<25·0	1715 (44%)	713 (35%)	1002 (55%)
25·0–29·9	1339 (34%)	776 (38%)	563 (31%)
≥30·0	835 (21%)	565 (28%)	270 (15%)
Systolic blood pressure, mm Hg	122 (114–132)	123 (115–133)	120 (111–131)
Use of antihypertensive medication	782 (20%)	458 (22%)	324 (18%)
Pre-existing diabetes	14 (<1%)	11 (1%)	3 (<1%)
Family history of premature cardiovascular disease	691 (18%)	465 (24%)	226 (13%)
Lipids‡			
Total cholesterol, mg/dL	182 (160–208)	183 (160–208)	182 (159–208)
HDL cholesterol, mg/dL	47 (39–58)	48 (40–59)	47 (39–58)
LDL cholesterol, mg/dL	106 (86–127)	106 (87–127)	106 (86–127)
Triglycerides, mg/dL	113 (79–167)	108 (77–156)	120 (81–181)
Cardiovascular-related medication use			
History of statin use	243 (6%)	155 (8%)	88 (5%)
Antidiabetic medication	15 (<1%)	8 (<1%)	7 (<1%)
Antihypertensive medication	782 (20%)	458 (22%)	324 (18%)
ACE inhibitors or ARBs	474 (12%)	285 (14%)	189 (10%)
Antiplatelet therapy (including aspirin)§	145 (4%)	128 (6%)	17 (1%)
Non-statin lipid-lowering therapy	78 (2%)	71 (3%)	7 (<1%)

(Table 1 continues on next page)

	Total (n=3893)	High-income countries (n=2058)	Low-income and middle-income countries (n=1835)
(Continued from previous page)			
HIV-related health			
Total antiretroviral therapy use, years			
<5	860 (22%)	340 (17%)	520 (28%)
5–10	1124 (29%)	549 (27%)	575 (31%)
≥10	1907 (49%)	1167 (57%)	740 (40%)
Abacavir exposure	818 (21%)	711 (35%)	107 (6%)
Protease inhibitor exposure	1843 (47%)	1242 (60%)	601 (33%)
CD4 count, cells/μL	621 (446–823)	614 (444–828)	629 (450–813)
<350	542 (14%)	299 (15%)	243 (13%)
350–499	713 (18%)	384 (19%)	329 (18%)
≥500	2638 (68%)	1375 (67%)	1263 (69%)
HIV-1 RNA, copies per mL			
<LLQ	2611 (87%)	1695 (86%)	916 (91%)
LLQ to <400	312 (10%)	241 (12%)	71 (7%)
≥400	67 (2%)	43 (2%)	24 (2%)

Data are n (%), median (IQR), or mean (SD). All statistics are calculated out of participants with data collected. Missing data: substance use (n=1), BMI (n=4), LDL cholesterol (n=218), triglycerides (n=204), family history of premature cardiovascular disease (n=127), total antiretroviral therapy use (n=2), and HIV-1 RNA (n=903). ACE=angiotensin-converting enzyme. ARB=angiotensin receptor blocker. LLQ=lower limit of quantification. *Other race includes participants self-identifying as native or indigenous to the enrolment region, more than one race (with no single race noted as predominant), or of unknown race. †Substance use includes use of cocaine, methamphetamine, and intravenous drugs. ‡Lipids values are those from central testing of fasting specimens; when unavailable, total and HDL cholesterol values are from screening. LDL was calculated unless triglycerides were greater than 400 mg/dL, in which case direct LDL was used. §Aspirin use in antiplatelet therapy is limited to chronic aspirin use defined as more than 60 days.

Table 1: **Baseline characteristics**

Uganda, and Zimbabwe as low-income and middle-income countries. Full details on trial design (including enrolment inclusion and exclusion criteria)[9] and on primary trial findings[10,12] have been previously reported. The study was approved by the Massachusetts General Brigham (MGB) Human Research Committee, and participating clinical research sites secured necessary regulatory approvals, including those of their local institutional review board or ethics committee. Our work follows the STROBE reporting guideline.[13] The REPRIEVE protocol is available online. Study participants provided written informed consent for taking part in REPRIEVE.

For the **REPRIEVE protocol** see https://www.reprievetrial.org/collaborate-with-us/

Procedures

Data elements assessed among REPRIEVE participants as per previously described procedures[9,10,14] were used for risk score calculation. The PCE risk score integrates data on age, sex at birth (sex), race (categorised by the risk calculator as African American or White[5]), diabetes, cigarette smoking, total cholesterol, HDL cholesterol, systolic blood pressure, and hypertension therapy. The reduced-model D:A:D risk score does not include race or hypertension therapy but includes data on family history of premature cardiovascular disease and current CD4 cell count. All these variables were assessed at REPRIEVE entry (appendix p 4). Data on race were collected as per the Advancing Clinical Therapeutics Globally (ACTG) trials network guidance. Self-identification of Black or predominantly Black race was counted as African American in the PCE ASCVD risk score calculation (*vs* the alternative calculator-provided option of White). In describing findings in subgroups of REPRIEVE participants by race, we thus grouped the terms Black and African American. We used fasting total cholesterol and HDL cholesterol data collected at study entry and tested at a central laboratory. If these values were unavailable, we used values provided at the screening visit regardless of their documented fasting status. If any of these values were below or above the defined bounds of the risk score, the values at the lower or upper bounds, respectively, were used.

See **Online** for appendix

Outcomes

In characterisation of the performance of ASCVD risk scores (PCE and D:A:D), clinical outcomes were aligned with the respective risk score. The PCE risk score was designed to predict risk of myocardial infarction, stroke, and cardiovascular death (hard MACE), whereas the reduced-model D:A:D risk score predicts hard MACE plus coronary revascularisation (D:A:D MACE; appendix p 4). All such outcomes were prospectively captured and independently adjudicated in a manner blinded to participants' randomisation.

Statistical analysis

We estimated the observed event incidence of each outcome at 5 years using the Aalen estimator for probability of sub-distribution (cumulative incidence) of each respective outcome, treating non-cardiovascular deaths as a competing risk. We estimated 5-year predicted risk for each participant according to the published risk scores.[5,6] In the case of the PCE risk score, this involved adjustment for the 5-year time horizon.[15] No such adjustment was required for the D:A:D risk score, which is designed to predict risk of events over 5 years. Participants lost to follow-up without a previous event within the 5-year study period relevant to this analysis were considered non-informatively censored at the time of their last contact. We assessed risk score performance across all included participants and by sex, race (White, Black or African American, and other), and enrolment region (high-income country *vs* low-income and middle-income country).

We assessed model discrimination using Uno's C statistic, with a value between 0·70 and 0·80 considered moderate to good and 0·80 or more as excellent. We assessed model calibration using the mean observed-to-expected (OE) event ratio, calibration plots, and the Greenwood–Nam–D'Agostino goodness-of-fit (GND) test (a small p value indicates poor calibration). Specifically, the cohort was divided into ordered groups of predicted cardiovascular disease risk: deciles for the overall analysis and quintiles for the subgroup analyses. Groups were

combined when they contained fewer than two 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. Given the small number of events in subgroups, the GND analysis was underpowered to detect poor calibration. These analyses are considered exploratory and used the more liberal p value of 0·10 as being suggestive of poor calibration. After observing poor performance of the PCE risk score among people with HIV in high-income countries, we attempted PCE recalibration (appendix p 3). Recalibration used the observed 5-year cumulative incidence and average PCE risk score within sex and race subgroups to quantify 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. Since the largest risk underestimation occurred in women, we also assessed applying the male risk equation for female participants. Recalibration efforts were centred on the PCE and not the D:A:D risk score, given that the PCE risk score is essential to clinical guideline-based recommendations for statin prescribing.[11] All analyses were done using SAS (version 9.4 for Linux Operating System).

Role of the funding source

The US National Institutes of Health (NIH) supported the study and had a role in study design. All other funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

We included 3893 participants (3869 [99·4%] randomly assigned to placebo and 24 [0·6%] randomly assigned to pitavastatin who never started treatment; appendix p 6). Characteristics were similar to those among the full REPRIEVE study population (table 1). Participants who initiated a non-study statin within the first 3 months of their enrolment were excluded (eight [0·1%] of 7769). Five (0·1%) participants were missing data on cigarette smoking status and were consequently excluded from all analyses. An additional 129 (1·7%) participants were excluded from D:A:D risk score analyses because of missing records of family history of cardiovascular disease (appendix p 6). The median age was 50 years (IQR 45–55), 1209 (31%) participants were women, 2684 (69%) were men, 1643 (42%) were Black or African American, 566 (15%) were Asian, and 1835 (47%) were from low-income and middle-income countries. The median 10-year ASCVD risk score at enrolment was 4·5% (2·2–7·1). Notably, a larger percentage of women were enrolled in low-income and middle-income countries (763 [42%]) compared with high-income countries (446 [22%]) and overall median 10-year ASCVD risk scores were lower (3·6% [1·4–6·3]) within low-income and middle-income countries compared with in high-income countries (5·3% [2·9–7·5]).

Median follow-up was 5·6 years (10th to 90th percentile 2·3–7·2). Cumulative incidence curves for first hard MACE over 5 years stratified by the 5-year PCE score and by race and sex subgroups suggested the respective risk score categories reasonably differentiate observed

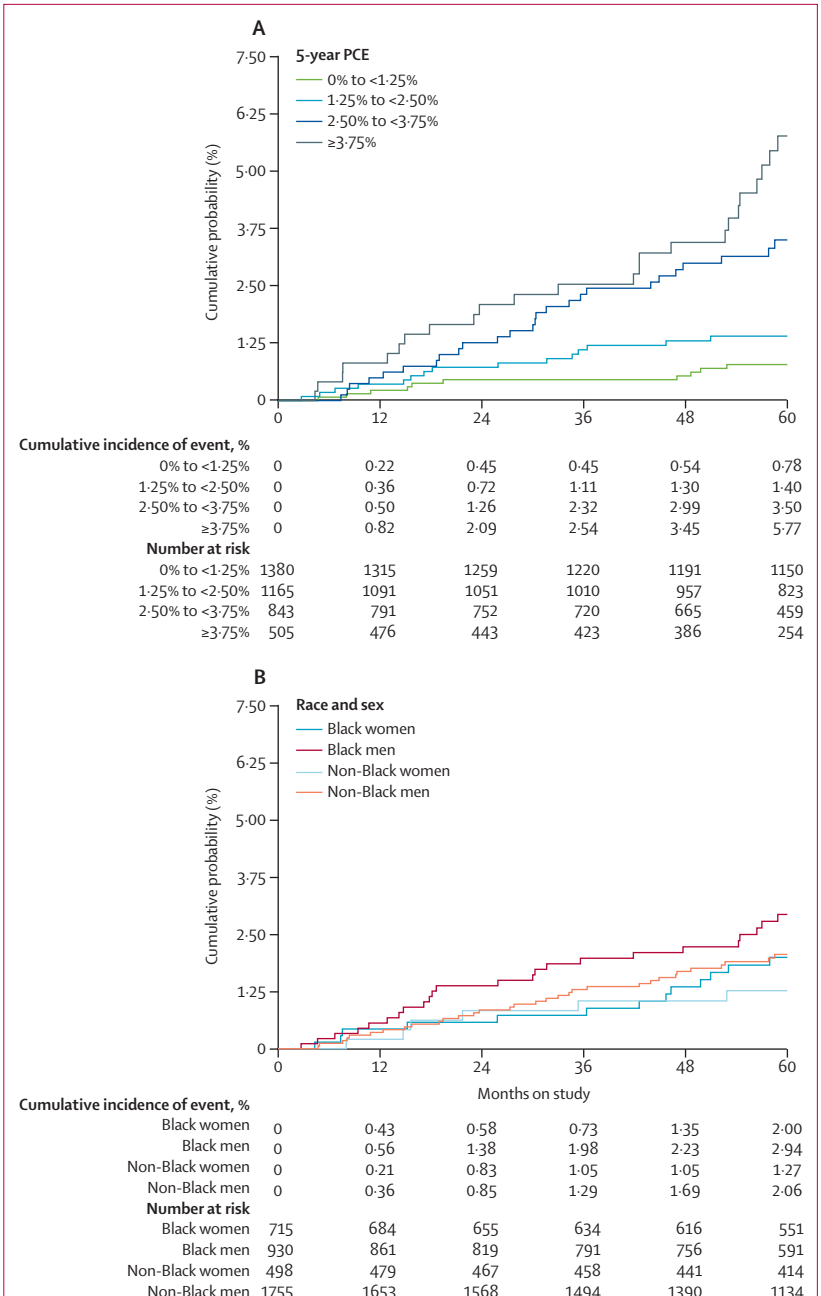

Figure 1: **Cumulative incidence of hard MACE over 5 years stratified by 5-year PCE and PCE subgroups (by race and sex)**

Cumulative incidence was calculated using the Aalen estimator for probability of sub-distribution of failure of interest. Participant follow-up was calculated as the number of days from randomisation date to the date of event, last contact, or 5 years after randomisation, whichever was earlier; participants with no contact after entry were included with 1 day imputed as censoring time. Months on study were defined in terms of calendar months (30·44 days). The y-axis is truncated at 7·50%. PCE=pooled cohort equations. MACE=major adverse cardiovascular events.

	N (events*)	Discrimination, C statistic (95% CI)	Calibration				
			Observed†	Expected‡	Observed-to-expected event ratio§	GND statistic	
						χ^2 (df)	p value
PCE							
All participants	3893 (75)	0·72 (0·68–0·76)	85·8	80·4	1·11	3·9 (8)	0·87
By race							
White	1346 (21)	0·72 (0·62–0·81)	24·8	29·6	0·89	2·7 (3)	0·45
Black or African American	1643 (37)	0·74 (0·68–0·80)	42·3	37·9	1·12	4·6 (4)	0·33
Other	904 (17)	0·70 (0·59–0·81)	18·3	12·9	1·62	2·2 (2)	0·34
By sex							
Female	1209 (19)	0·80 (0·69–0·90)	20·5	14·2	1·46	2·3 (2)	0·32
Male	2684 (56)	0·68 (0·62–0·75)	65·0	66·2	1·09	2·0 (4)	0·74
By region							
HICs	2058 (54)	0·70 (0·63–0·76)	63·7	48·2	1·43	6·8 (5)	0·24
LMICs	1835 (21)	0·73 (0·63–0·83)	23·3	32·2	0·73	6·8 (2)	0·033
HICs only							
By race¶							
White	1059 (19)	0·69 (0·59–0·79)	22·7	24·1	0·96	3·5 (2)	0·17
Black or African American	874 (32)	0·71 (0·61–0·80)	37·1	22·1	1·64	5·7 (2)	0·057
By sex¶							
Women	446 (15)	0·81 (0·70–0·91)	16·7	6·4	2·39	6·3 (2)	0·044
Men	1612 (39)	0·67 (0·60–0·74)	46·5	41·7	1·24	2·5 (4)	0·65
D:A:D (reduced)							
All participants	3764 (78)	0·71 (0·65–0·77)	88·6	92·9	0·89	5·7 (8)	0·68
By race							
White	1290 (24)	0·73 (0·63–0·82)	28·0	36·9	0·78	8·8 (3)	0·033
Black or African American	1584 (36)	0·74 (0·67–0·80)	40·4	38·1	1·06	1·0 (3)	0·80
Other	890 (18)	0·67 (0·54–0·80)	19·3	17·9	1·09	0·7 (3)	0·87
By sex							
Female	1171 (19)	0·79 (0·67–0·91)	20·6	20·3	0·93	3·5 (2)	0·18
Male	2593 (59)	0·66 (0·60–0·73)	67·9	72·5	0·94	0·5 (3)	0·91
By region							
HICs	1973 (57)	0·68 (0·62–0·73)	67·4	55·3	1·17	2·6 (5)	0·76
LMICs	1791 (21)	0·71 (0·60–0·83)	23·0	37·5	0·62	15·4 (3)	0·0015
HICs only							
By race¶							
White	1012 (22)	0·70 (0·61–0·79)	26·1	29·8	0·91	1·7 (2)	0·42
Black or African American	841 (32)	0·69 (0·60–0·78)	36·8	22·7	1·59	5·2 (4)	0·27
By sex¶							
Women	425 (15)	0·81 (0·73–0·89)	16·6	9·5	2·32	5·5 (2)	0·065
Men	1548 (42)	0·64 (0·56–0·71)	50·2	45·9	1·09	0·8 (4)	0·94

Data are n (%), unless otherwise indicated. For the calibration analysis, the cohort was divided into ordered groups (ntiles) of predicted cardiovascular disease risk groups. 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. Sample sizes and observed numbers of events within each order group are shown in the corresponding calibration plot. D:A:D=data-collection on adverse effects of anti-HIV drugs. GND=Greenwood–Nam–D'Agostino goodness-of-fit. HIC=high-income country. LMIC=low-income and middle-income country. MACE=major adverse cardiovascular events. PCE=pooled cohort equations. *Number of events observed during study follow-up. †Number of events that would have been observed if all participants were followed up for 5 years based on the estimated 5-year cumulative incidence. ‡Expected number of events based on the respective risk predictions algorithm. §Mean observed-to-expected ratio over all ntiles. ¶Within high-income countries.

Table 2: **Predictive performance of PCE risk prediction algorithm for first hard MACE and D:A:D risk prediction algorithm for first primary MACE (excluding transient ischaemic attack, peripheral artery disease, and deaths of undetermined cause) over 5 years**

cumulative incidence over a 5-year period (figure 1). Overall, Black or African American men had the highest cumulative incidence of MACE over 5 years. Non-Black or African American women had the lowest cumulative incidence; rates for Black or African American women and non-Black or African American men were

intermediate. Further stratification by enrolment region highlighted higher-than-expected rate of events for 5-year PCE risk score among people with HIV in high-income countries and lower-than-expected rate in low-income and middle-income countries (appendix p 7). Notably, MACE incidence was similar for non-Black or African American men within high-income countries compared with low-income and middle-income countries but was markedly lower for all other sex and race subgroups within low-income and middle-income countries compared with high-income countries (appendix p 8).

With respect to PCE risk score performance, the ability of the PCE score to discriminate between those who did and did not have events was moderate overall (C statistic 0·72 [95% CI 0·68–0·76]) and across most subgroups (table 2). In the full cohort, the best discrimination was observed among women (0·80 [0·69–0·90]) and Black or African American participants (0·74 [0·68–0·80]). Discrimination was lower among Black or African American participants when restricted to participants in high-income countries (0·71 [0·61–0·80]), although all CIs overlap. Calibration statistics (measuring how well the observed rates reflect those expected on the basis of the predicted risk of the cohort) across all participants suggested good performance of the PCE risk score overall (OE event ratio 1·11; GND p=0·87; figure 2A, table 2), and in groups stratified by race and by sex (0·89–1·62; p>0·30; figure 2B, C, table 2). However, stratification by enrolment region revealed poor score performance (overprediction of risk) among people with HIV in low-income and middle-income countries (0·73; p=0·033) and a corresponding suggestion of underprediction of risk among people with HIV in high-income countries (1·43; p=0·24; figure 2D). In analyses restricted to people with HIV in high-income countries, the PCE risk score was well calibrated among White participants (0·96; p=0·17) and men (1·24; p=0·65), but underestimated risk among Black or African American participants (1·64; p=0·057) and among women (2·39; p=0·044), despite good discrimination (figure 3). Subgroup analyses within low-income and middle-income countries were not possible because of the small number of events, which limited the ability to estimate 5-year cumulative incidence within quintiles of the risk score distribution.

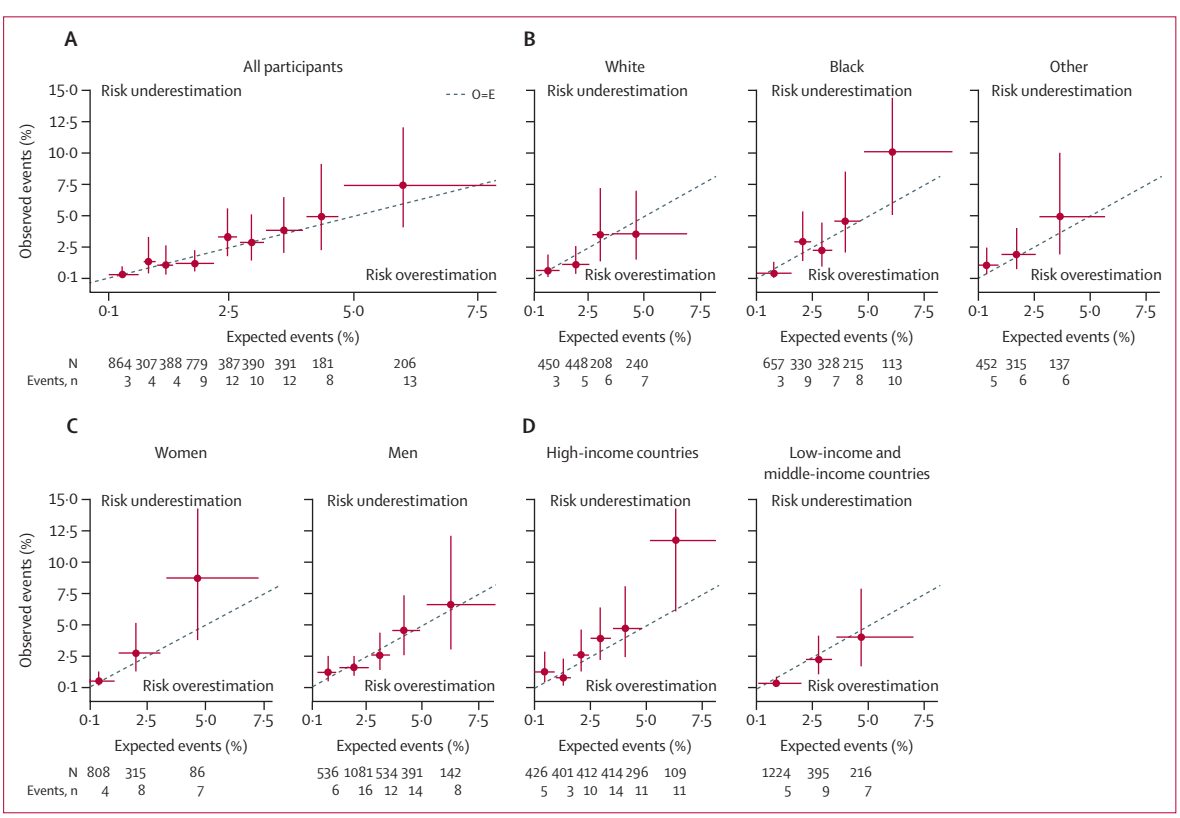

Figure 2: **Calibration plots for 5-year PCE for first hard MACE**

Observed versus expected event rates across ordered groups (ntiles) of predicted cardiovascular risk. Deciles were used for the overall analysis and quintiles for the subgroup analyses. Groups were combined when they contained fewer than two 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 is the mean predicted risk score within the group. Error bars show the 95% CI for the observed rate and 5th and 95th percentiles of the predicted risk within the ordered group. E=expected. MACE=major adverse cardiovascular events. O=observed. PCE=pooled cohort equations.

With respect to D:A:D risk score performance, in the full cohort, discrimination was moderate overall (C statistic 0·71 [95% CI 0·65–0·77]) and calibration was good (OE event ratio 0·89; p=0·68; table 2; appendix p 9). While the discriminative properties of the risk score were maintained in groups stratified by race and sex (C statistic 0·66–0·79), the score overestimated events among White participants (OE ratio 0·78; p=0·033); the score appeared well calibrated among other subgroups (appendix p 9). However, as with the PCE score, the D:A:D risk score tended to overpredict events among people with HIV in low-income and middle-income countries (OE ratio 0·62; p=0·0015; table 2; appendix p 9). Repeating the subgroup analyses within high-income countries again suggested underprediction of events among women (OE ratio 2·32; p=0·065; table 2; appendix p 10).

We attempted recalibration for the PCE risk score. Across the various recalibration approaches assessed, improved performance of the PCE risk score in high-income countries was achieved by inflating the original score by an approximate recalibration factor of 2·8 in Black or African American women and 2·6 in women who were not Black or African American (table 3; appendix p 5). We found marginal improvement in score performance when a recalibration factor of 1·25 was also applied among Black or African American men (table 3). These approaches performed more favourably than applying the male PCE to women (table 3). Recalibration of the PCE risk score in low-income and middle-income countries was not possible because of low event numbers.

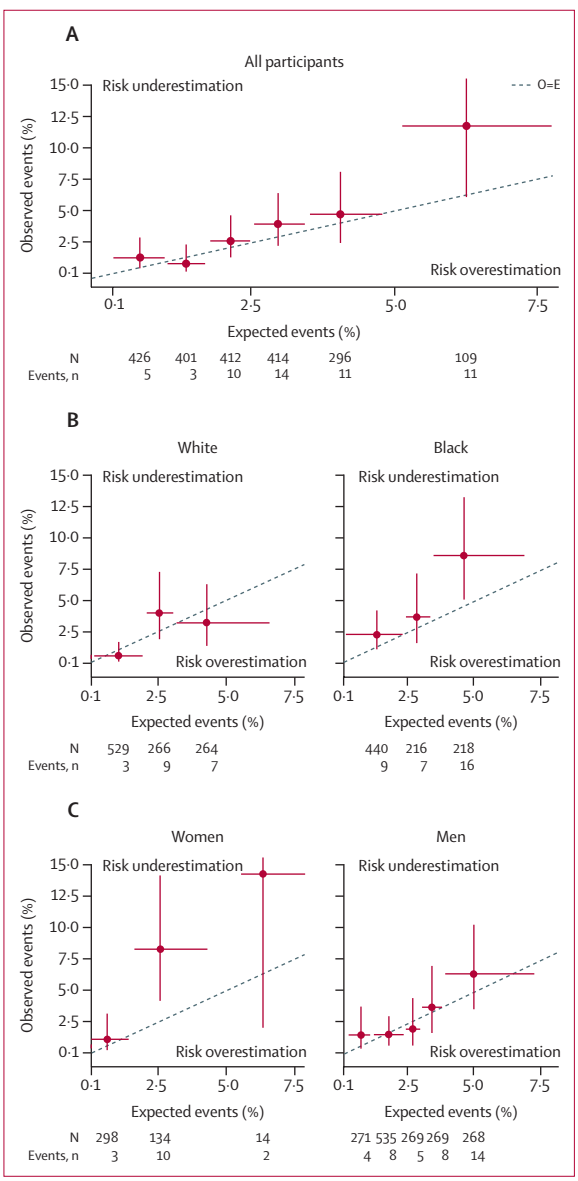

Figure 3: **Calibration plots for 5-year PCE for first hard MACE, within high-income countries**

Observed versus expected event rates across ordered groups (ntiles) of predicted cardiovascular risk. Deciles were used for the overall analysis; quintiles for the subgroup analyses. Groups were combined when they contained fewer than two 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 is the mean predicted risk score within the group. Error bars show the 95% CI for the observed rate and 5th and 95th percentiles of the predicted risk within the ordered group. E=expected. MACE=major adverse cardiovascular events. O=observed. PCE=pooled cohort equations.

Discussion

Among a global cohort of ART-treated people with HIV with low-to-moderate traditional ASCVD risk enrolled in REPRIEVE and not started on statin therapy, the PCE ASCVD risk score, adapted to 5 years of follow-up, showed moderate discrimination and good calibration overall. However, the PCE risk score overpredicted hard MACE among participants in low-income and middle-income countries and underpredicted events among subgroups of participants in high-income countries, particularly women and Black or African American men. These findings have important implications for matching the intensity of preventive care to risk among people with HIV.

Assessment of the PCE risk score among REPRIEVE participants stratified by GBD region revealed poor score performance (overprediction of risk) among people with HIV in low-income and middle-income countries. We found underprediction of risk among people with HIV in high-income countries, similar to previous observations from the US HOPS database[16] and the US Partners/MGB database.[17] Of note, the PCE risk score was not developed in low-income and middle-income countries and, in the absence of validation for population-specific usage, is not applied to guide clinical decision making among individuals in low-income and middle-income countries. Indeed, the source population for PCE score development was comprised of adults from four US cohorts.[5] Among people with HIV in low-income and middle-income countries, there might be a different degree to which traditional ASCVD risk factors contribute to hard MACE. Further, there might be region-specific contributors to

MACE that are not accounted for in the PCE risk score—eg, types of ART used, co-infections, and household pollution or fine particulate matter exposure. Additionally, the healthy volunteer effect might be particularly salient to PCE-based overestimation of risk among REPRIEVE participants in low-income and middle-income countries: an important driver of ASCVD risk in these countries is undiagnosed, untreated, or uncontrolled hypertension,[18] which, among REPRIEVE participants, was less prevalent than low-income and middle-income country-wide estimates suggest. Additional research is needed to understand whether the apparent overestimation of ASCVD risk among REPRIEVE participants in low-income and middle-income countries is applicable to broader groups of people with HIV living in these countries, including those with greater burden of traditional risk factors. Research is also needed to develop novel population-specific ASCVD risk-assessment algorithms factoring in region-specific contributors to MACE among people with HIV.

PCE risk score performance was also poor among female REPRIEVE participants from high-income countries, with significant underprediction of hard MACE. This finding is consistent with an early observation by Triant and colleagues[19] showing higher HIV-attributable risk of myocardial infarction among women versus men and builds on work by Feinstein and colleagues[20] showing that the PCE score underpredicts incident myocardial infarction among US women with HIV.[20] Specifically, we also now show that among people with HIV in high-income countries, improved calibration is achieved by inflating the original PCE by an approximate recalibration factor of 2·8 in Black or African American women and 2·6 in women who are not Black or African American. Helping to explain our sex-based finding on underprediction in women from high-income countries, we showed in a separate analysis that among REPRIEVE participants, female sex was not protective against MACE when controlling for other ASCVD risk factors.[21] By contrast, with the PCE score, female sex lowers the calculated score markedly as compared with male sex when all other data are constant.[5] PCE-based underestimation of ASCVD risk among women with HIV in high-income countries is crucially important for three reasons. First, among people with HIV aged 40–75 years with low-to-intermediate traditional risk, the revised US statin-prescribing guidelines position "at least moderate intensity statin therapy" as a class A-I recommendation for those with a PCE risk score of 5% to less than 20% and as a class C-I recommendation for those with a score below 5%.[11] PCE-based underestimation of risk might thus lead clinicians to follow weak statin recommendations (class C) in women with HIV potentially warranting strong recommendations (class A). Second, underestimation of ASCVD risk among women with HIV in high-income countries probably fosters less aggressive diagnosis and treatment of other (non-lipid) modifiable ASCVD risk factors and lifestyle modifications. Clinical disease-prevention algorithms are indeed built around the concept of a priori risk influencing action, and previous studies of people with HIV in high-income countries have found sex-based disparities in medical treatment of ASCVD risk factors or ASCVD.[22] Third,

	N (events*)	Discrimination, C statistic (95% CI)	Calibration				
			Observed†	Expected‡	Observed-to-expected event ratio§	GND statistic	
						χ^2 (df)	p value
Recalibration factors applied to women only¶							
All participants	2058 (54)	0·71 (0·65–0·77)	63·1	59·5	1·10	1·6 (3)	0·66
By race							
White	1059 (19)	0·72 (0·63–0·82)	22·7	25·9	0·89	1·7 (2)	0·43
Black	874 (32)	0·69 (0·60–0·79)	36·8	31·2	1·15	1·8 (2)	0·41
By sex							
Women	446 (15)	0·81 (0·70–0·91)	16·6	17·8	0·89	1·3 (1)	0·26
Men	1612 (39)	0·67 (0·60–0·74)	46·5	41·7	1·24	2·5 (4)	0·65
Recalibration factors applied to Black participants only¶							
All participants	2058 (54)	0·70 (0·63–0·76)	63·1	61·5	1·11	2·7 (3)	0·43
By race							
White	1059 (19)	0·69 (0·59–0·79)	22·7	24·1	0·96	3·5 (2)	0·17
Black	874 (32)	0·70 (0·60–0·80)	36·7	35·5	1·00	1·5 (2)	0·48
By sex							
Women	446 (15)	0·77 (0·65–0·88)	16·9	15·5	1·19	1·0 (1)	0·32
Men	1612 (39)	0·68 (0·61–0·75)	46·3	46·0	1·20	7·0 (4)	0·13
Recalibration factors applied to women and Black men¶							
All participants	2058 (54)	0·72 (0·66–0·78)	63·0	63·7	1·04	1·9 (3)	0·60
By race							
White	1059 (19)	0·72 (0·63–0·82)	22·7	25·9	0·89	1·7 (2)	0·43
Black	874 (32)	0·70 (0·60–0·80)	36·7	35·5	1·00	1·5 (2)	0·48
By sex							
Women	446 (15)	0·81 (0·70–0·91)	16·6	17·8	0·89	1·3 (1)	0·26
Men	1612 (39)	0·68 (0·61–0·75)	46·3	46·0	1·20	7·0 (4)	0·13
PCE for men applied to women							
All participants	2058 (54)	0·72 (0·66–0·78)	63·1	56·1	1·11	2·9 (3)	0·41
By race							
White	1059 (19)	0·73 (0·63–0·82)	22·7	25·9	0·86	1·1 (2)	0·58
Black	874 (32)	0·71 (0·62–0·81)	36·6	27·8	1·25	3·4 (2)	0·18
By sex							
Women	446 (15)	0·85 (0·77–0·93)	16·4	14·4	1·18	6·7 (1)	0·0097
Men	1612 (39)	0·67 (0·60–0·74)	46·5	41·7	1·24	2·5 (4)	0·65

Data are n (%), unless otherwise indicated. For calibration the cohort was divided into ordered groups (ntiles) of predicted cardiovascular disease risk groups. Deciles were used for the overall analysis and quintiles for the subgroup analyses. Groups were combined when they contained fewer than two 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. GND=Greenwood–Nam–D'Agostino goodness-of-fit. MACE=major adverse cardiovascular events. PCE=pooled cohort equations. *Number of events observed during study follow-up. †Number of events that would have been observed if all participants were followed up for 5 years based on the estimated 5-year cumulative incidence. ‡Expected number of events based on the respective risk prediction algorithm. §Mean observed-to-expected event ratio over all ntiles. ¶A recalibration factor of 2·8 was applied for Black women, 2·6 for women of other races, and 1·25 for Black men.

Table 3: **Predictive performance of recalibrated PCE for first hard MACE over 5 years**

underestimation of ASCVD risk among women with HIV might contribute to less thorough diagnostic work-up of potential ASCVD symptoms, which, among women, tend to be atypical.[23] Compounding this problem, standard diagnostic work-ups of myocardial infarction symptoms often centre on epicardial artery pathology, whereas immune-based risk among women with HIV might be mediated through other pathways, such as coronary microvascular dysfunction.[24–26] Taken together, accurately appreciating ASCVD risk among women with HIV represents a key prerequisite to properly modifying risk (through statin and non-statin strategies) and to assessing and treating potential manifestations of disease.

The PCE score underpredicted hard MACE among Black or African American REPRIEVE participants from high-income countries. As mentioned, underappreciation of risk might foster weaker statin recommendations, less aggressive diagnosis and treatment of modifiable ASCVD risk factors, and inadequate diagnostic work-up of ASCVD symptoms. Our finding reinforces previous observations by Feinstein and colleagues[20] showing that the PCE score underpredicts incident myocardial infarction among Black or African American people with HIV in the USA. Importantly, there is a burgeoning movement in the USA and beyond to eliminate race from clinical algorithms across disciplines.[27] In this context, the American Heart Association has introduced the PREVENT score, which omits race-based and ethnicity-based data elements in calculating risk for ASCVD, heart failure, or both.[28] The working group developing and validating PREVENT highlights that consideration of race as an incontrovertible biological risk factor for ASCVD (as opposed to a social construct) exacerbates disparities in the provision of health care.[28] In lieu of race-based data elements, the novel scoring system incorporates data elements standing in for modifiable indices of social deprivation.[28] Of note, the PREVENT score had not been developed at the time of REPRIEVE enrolment.

Among our analysed cohort of REPRIEVE participants, the PCE and D:A:D risk scores showed similar discrimination (moderate) and calibration (good), despite key differences in the way these scoring systems integrate data elements. Whereas the PCE risk score exclusively incorporates data on traditional ASCVD risk factors,[5] the reduced-model D:A:D risk score also incorporates data on current CD4 cell count.[6] Of relevance to the performance of the D:A:D risk score in REPRIEVE (for which inclusion criteria included stable ART), the median CD4 cell count of analysed participants was high at 621 cells per µL, and the median CD4 cell count among people with HIV in the D:A:D study was significantly lower.[6] Further, in a separate multivariable adjusted analysis of factors contributing to incident MACE among the full REPRIEVE population, CD4 cell count was not associated with MACE.[21] Instead, detectable viral load was the most salient HIV-specific risk factor for incident MACE,[21] in line with findings from observational studies linking viral load to incident myocardial infarction among people with HIV.[29,30] Of note, observational studies have revealed relationships between levels of systemic immune activation or inflammation markers (eg, interleukin 6 or C-reactive protein) and incident myocardial infarction among people with HIV;[31] however such data elements are not presently integrated into ASCVD risk equations (PCE or D:A:D), nor are such data yet available study-wide for REPRIEVE participants. Future efforts to develop novel ASCVD risk prediction algorithms for people with HIV might usefully include assessment of whether score performance improves through integration of viral load or markers of immune activation or inflammation.

One limitation of our analysis entails potential lack of generalisability of findings to all people with HIV, particularly those who are not engaged in health care, lack access to ART, or harbour high-level traditional ASCVD risk. However, the performance of ASCVD risk scores among those individuals engaged in care, on ART, and with low-to-moderate traditional ASCVD risk (such as those studied in REPRIEVE) might be especially salient to shifting paradigms in evidence-based statin prescribing and uptake. Another potential limitation of our work is that the low number of events observed among REPRIEVE participants in low-income and middle-income countries precluded analysis of risk score performance by subregion and by other within-region subgroupings (eg, subgroupings by sex). Ongoing observational follow-up of the global REPRIEVE trial population would facilitate subgroup analyses among participants in low-income and middle-income countries, based on accrual of events over time. Additionally, we did not analyse the performance of SCORE-2,[32] which is widely used in Europe, because of the absence of accepted procedures in converting from a 10-year to a 5-year ASCVD risk score. Key strengths of our analysis include the global nature of our study population and cardiovascular trial-level rigour in prospective adjudication of incident MACE. A systematic review and meta-analysis by Soares and colleagues[8] examined the performance of ASCVD risk scores among 75 304 people with HIV engaged in one of nine observational cohorts. Strikingly, among the nine observational cohorts, four followed up people with HIV in the USA, four followed up people with HIV in Europe, and one (D:A:D) followed up people with HIV from nine high-income countries and one Latin American upper-middle-income country,[8] which do not include data from low-income and middle-income countries. This work underscores the manner in which our present analysis addresses key knowledge gaps.

Leveraging REPRIEVE to study the performance of established cardiovascular disease risk scores among a global cohort of ART-treated people with HIV with low-to-moderate traditional ASCVD risk, we found these

scores performed well overall but overestimated risk among people with HIV in low-income and middle-income countries and underestimated risk among people with HIV in high-income countries, particularly women and Black or African American men. Our findings spotlight clinical and research imperatives relevant to preserving cardiovascular health among people with HIV globally. Clinically, shifting our perceptions of risk among key subgroups of people with HIV in high-income countries (women and Black or African American men), we must actively seek opportunities to mitigate ASCVD risk and to appropriately assess and treat potential ASCVD symptoms. Our findings on recalibration factors for improved performance of the PCE among women and Black or African American participants in REPRIEVE living in high-income countries will require external validation among US people with HIV before direct implementation in clinical practice. From a research standpoint, we must pursue strategies for accurately predicting ASCVD risk among people with HIV, giving particular attention to the development of risk scores applicable to people with HIV in low-income and middle-income countries. Such efforts would help harmonise presently discrepant approaches to assessing[33] and reducing ASCVD risk among people with HIV globally.

Contributors

SKG, MVZ, HJR, and PSD conceptualised the study. HJR, AK, and TU contributed to data curation, formal analysis, and visualisation. HJR, AK, TU, and VAT contributed to the methodology. SKG, MVZ, JSC, MTL, HJR, and PSD contributed to funding acquisition. SKG, MVZ, VAT, AK, TU, MRD, SMC, KVF, JSC, GSB, JLC, MdlP, LEF, EG, JAA, CDM, CJF, MTL, HJR, and PSD carried out the investigation. SMC, KVF, and MRD contributed to project administration. SKG, MVZ, HJR, and PSD wrote the original draft. All authors contributed to manuscript review and editing. HJR, AK, and TU had full access to and verified all the data in the study. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

SKG reports grant support through his institution from the NIH, Kowa Pharmaceuticals America, Gilead Sciences, and ViiV Healthcare for the conduct of the study; personal fees from Theratechnologies and ViiV; and service on the Scientific Advisory Board of Marathon Asset Management, all outside the submitted work. MVZ reports grant support through her institution from the NIH/National Institute of Allergy and Infectious Diseases (NIAID) and Gilead Sciences, relevant to the conduct of the study, as well as grants from the NIH/NIAID and the NIH/National Heart, Lung, and Blood Institute (NHLBI); support for attending the Conference on Retroviruses and Opportunistic Infections and the International Workshop for HIV and Women from the conference organising committee when she served as an abstract reviewer and/or speaker; and participation in the DSMB for NIH-funded studies, outside the submitted work. VAT reports grants from the NIH/National Institute of Aging (NIA) and NIH/NHLBI, outside of the submitted work. AK reports grants from NIH/NIAID, NIH/NHLBI, NIH/National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and NIH/NIA, outside of the submitted work. TU reports grants from NIH/NHLBI and Kowa Pharmaceuticals during the conduct of the study, as well as grants from NIH/NIAID and NIH/NIA, outside the submitted work. JSC reports consulting fees from Merck and Company and Resvirlogix, outside the submitted work. JLC reports honoraria for presentations for Gilead, MSD, and ViiV, and honoraria from Gilead Sciences for Advisory Board membership, all outside the submitted work. EG reports institutional research support for clinical trials from Gilead Sciences and ViiV Healthcare. JAA reports grants from Massachusetts General Hospital during the conduct of the study; institutional research support for clinical trials from Emergent Biosolutions, Gilead Sciences, Glaxo Smith Kline, Janssen, Merck, Pfizer, Regeneron, and ViiV Healthcare; personal fees for advisory boards from Glaxo Smith Kline/ViiV, Invivyd, Merck and Regeneron; and participation on the DSMB for Kintor Pharmaceuticals, all outside the submitted work. CDM reports institutional research support by Lilly and honoraria from ViiV Healthcare, Gilead Sciences, and Pfizer for Advisory Board membership, all outside the submitted work. CJF reports research grant support through his institution from Gilead Sciences, ViiV Healthcare, GSK, and Merck, all outside the submitted work. MTL reports grant support through his institution from the NIH/NHLBI and Kowa Pharmaceuticals America for the conduct of the study. He also reports research support to his institution from the American Heart Association, AstraZeneca, Ionis, Johnson & Johnson Innovation, MedImmune, the National Academy of Medicine, the NIH/NHLBI, and the Risk Management Foundation of the Harvard Medical Institutions Incorporated, outside of the submitted work. HJR reports grants from Kowa Pharmaceuticals during the conduct of the study, as well as grants from NIH/NIAID, NIH/NHLBI, NIH/NIDDK, and NIH/NIA, outside of the submitted work. All other authors declare no competing interests.

Data sharing

Data are available from the REPRIEVE Trial Team (mghreprievetrial@mgb.org) upon reasonable request. In this case, shared data may include individual participant data that underlie the results reported in this Article, after de-identification (text, tables, figures, and appendices). To gain access, data requestors will need to sign a data access agreement. Study protocols are available on ClinicalTrials.gov. Data will be available following publication, pending approval by the parent study data sharing committee and the ACTG. The Greenwood–Nam–D'Agostino calibration test for survival data used an SAS macro developed by the Division of Preventive Medicine at Brigham and Women's Hospital, Boston, MA, USA, available at http://ncook.bwh.harvard.edu/sas-macros.html.

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