Predictive Performance of Cardiovascular Disease Risk Prediction Algorithms in People Living with HIV

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Abstract

Background. People living with HIV (PLWH) experience a higher cardiovascular disease (CVD) risk. Yet, traditional algorithms are often used to estimate CVD risk. We evaluated the performance of four commonly used algorithms.

Setting. The Netherlands.

Methods. We used data from 16,070 PLWH aged ≥18 years, who were in care between 2000-2016, had no pre-existing CVD, had initiated first combination antiretroviral therapy >1 year ago, and had available data on CD4 count, smoking status, cholesterol and blood pressure. Predictive performance of four algorithms (Data Collection on Adverse Effects of Anti-HIV Drugs Study [D:A:D]; Systematic COronary Risk Evaluation adjusted for national data [SCORE-NL]; Framingham CVD Risk Score [FRS]; American College of Cardiology and American Heart Association Pooled Cohort Equations [PCE]) was evaluated using a Kaplan-Meier approach. Model discrimination was assessed using Harrell's C-statistic. Calibration was assessed using observed-versus-expected-ratios, calibration plots, and Greenwood-Nam-D'Agostino goodness-of-fit-tests.

Results. All algorithms showed acceptable discrimination (Harrell's C-statistic 0.73-0.79). On a population level, D:A:D, SCORE-NL, and PCE slightly underestimated, whereas FRS slightly overestimated CVD risk (observed-versus-expected-ratios 1.35, 1.38, 1.14, 0.92, respectively). D:A:D, FRS, and PCE best fitted our data, but still yielded a statistically significant lack of fit (Greenwood-Nam-D'Agostino χ^2 ranged from 24.57 to 34.22, $P<0.05$). Underestimation of CVD risk was particularly observed in low predicted CVD risk groups.

Conclusions. All algorithms perform reasonably well in PLWH, with SCORE-NL performing poorest. Prediction algorithms are useful for clinical practice, but clinicians should be aware of their limitations (i.e., lack of fit and slight underestimation of CVD risk in low risk groups).

Key Words: HIV; cardiovascular disease; risk prediction algorithms

Introduction

A higher burden of cardiovascular disease (CVD) has been observed among people living with HIV (PLWH) when compared to HIV-negative controls [1–4], likely due to a complex interplay between traditional CVD risk factors and HIV-related factors such as persistent inflammation and immune activation, certain antiretrovirals, and damage to the immune system. As the age of the HIV-positive population increases, so does the CVD burden [5]. CVD prevention strategies might be able to mitigate this burden [6].

CVD risk management guidelines recommend initiation of primary prevention based on a person's estimated risk [7–12]. Accurate CVD risk assessment is key in identifying those individuals who will benefit most from primary prevention. The Systematic COronary Risk Evaluation (SCORE), Framingham CVD Risk Score (FRS), and American College of Cardiology and American Heart Association Pooled Cohort Equations (PCE) are amongst the most commonly used CVD risk prediction algorithms. These general population-derived algorithms do not take into account any HIV-related CVD risk factors. In an attempt to more accurately predict CVD risk in PLWH, the Data Collection on Adverse Effects of Anti-HIV Drugs (D:A:D) Study algorithm was developed. Unlike SCORE, FRS and PCE, the D:A:D algorithm includes HIV-related variables such as CD4 count and exposure to certain antiretrovirals.

Theoretically, one would expect the D:A:D algorithm to predict CVD risk more accurately in PLWH. To date, many studies have focused on the agreement between predicted risks provided by different algorithms, which varied from poor to excellent [13–16], and does not reflect their predictive ability. In contrast, studies which have actually investigated the predictive performance of different algorithms have shown conflicting results [15,17–23]. However, these studies were limited by the use of cross-sectional measurements of subclinical CVD endpoints (for which the algorithms were not designed) [24–28], relatively small sample sizes resulting in a limited number of observed CVD events [17,21,23,25,27–29], a limited selection of algorithms for comparison [17–21,23,25,29], and/or by not providing external validation [19,20].

Since comprehensive assessment of CVD risk prediction algorithms is lacking in PLWH, the primary aim of the current study was to compare the performance of D:A:D, SCORE-NL (SCORE adjusted for national data), FRS, and PCE in the national observational "AIDS Therapy Evaluation in the Netherlands" (ATHENA) cohort. Our secondary aim was to investigate whether we could improve the performance of SCORE-NL (used in the national guidelines) by assigning PLWH an additional CVD risk.

Method

Study population

The ATHENA cohort is a national observational HIV cohort that includes data from PLWH in care in one of 26 designated HIV treatment centers in the Netherlands. The dataset, which is systematically collected from patient charts and electronically entered by trained staff, includes information on socio-demographic characteristics, established CVD risk factors, co-morbidities, antiretroviral therapy, prescribed co-medication, AIDS events, and laboratory measurements.

For the current analysis we included data from ATHENA participants with ≥2 outpatient clinic visits between 1 January 2000 and 31 December 2016 who met the following inclusion criteria: HIV-1-positive, aged ≥18 years, no pre-existing CVD, initiated first combination antiretroviral therapy (cART) regimen >1 year ago, with available data on smoking status, total/HDL cholesterol, blood pressure, and CD4 count. Baseline was defined as the first outpatient visit after meeting the abovementioned inclusion criteria. CVD was the primary outcome and follow-up was censored at the earliest of: 10 years after baseline, 31 December 2016 or last outpatient visit prior to 31 December 2016, death, or loss-to-follow-up.

CVD risk prediction algorithms (see Table, Supplemental Digital Content 1)

We compared four commonly used algorithms: D:A:D, SCORE-NL, FRS, and PCE. Since European HIV treatment guidelines [7] recommend the use of D:A:D, FRS or any algorithm recommended by national guidelines (i.e. SCORE-NL in the Netherlands), we investigated their predictive performance. PCE was included for comparison with existing studies.

D:A:D predicts the five-year risk of incident CVD and has been developed using pooled datasets of 11 HIV cohorts across 212 clinics in Europe (including part of the ATHENA cohort), Argentina, Australia, and the United States (US) [20]. For appropriate comparison with other algorithms we also calculated ten-year

risk, using the same algorithm, but including the Cox ten-year instead of the five-year survival estimate at the mean values of the predictors included in the D:A:D algorithm (provided by the authors [20]).

SCORE was originally developed to estimate ten-year risk of fatal CVD in Europe using a pooled dataset of general population cohorts from 12 European countries [30]. In the current analysis we used SCORE-NL, which uses age-specific conversion factors to translate ten-year CVD mortality risk into ten-year CVD mortality and morbidity risk. Dutch guidelines recommend using SCORE-NL to estimate an individual's CVD risk [10]. We also evaluated a self-adapted version of SCORE-NL by assigning PLWH an additional CVD risk by artificially increasing a person's age (as is being done in patients with diabetes or rheumatoid arthritis). We investigated an arbitrarily chosen age increase of five or ten years in PLWH (referred to as SCORE-NL+5Y and SCORE-NL+10Y, respectively).

FRS estimates the ten-year probability of a first CVD event based on data collected in the US-based Framingham Heart Study and the Framingham Offspring study [31].

More recently, the ethnicity- and sex-specific PCE was developed to estimate the ten-year risk for a first atherosclerotic CVD event using a pooled dataset of general population cohorts from the US [8,9,11,12].

Definitions

Each algorithm studied comprises different CVD risk factors and endpoints. Four algorithm-specific CVD endpoints were defined covering the events listed in Table Supplemental Digital Content 1. Myocardial infarctions, strokes, invasive cardiovascular procedures, and deaths reported in patient charts were centrally validated according to previously reported D:A:D procedures [32,33]. Other events (i.e., angina, coronary insufficiency, heart failure, peripheral artery disease, and transient ischemic attack) were not validated.

Blood pressure, total cholesterol, HDL cholesterol, and CD4 count were measured as part of standard care, and measurements prior to baseline were used to estimate CVD risk. For most participants

smoking status was not updated over time. Therefore, we assumed that smoking status remained constant over time. Diabetes was defined as (1) use of antidiabetic medication, or (2) a reported diagnosis of diabetes mellitus in a patient's clinical record combined with either fasting plasma glucose ≥7.0 mmol/L (126 mg/dL), non-fasting plasma glucose ≥11.1 mmol/L (200 mg/dL) or HbA1c ≥48 mmol/mol (6.5%). Family history of CVD was collected at entry into ATHENA and was defined as having a first degree relative who experienced myocardial infarction or stroke before the age of 50 years. Ethnicity was based on an individual's region of origin and subsequently categorized into four groups: (1) white/Caucasian (the Netherlands, North America, Australia, Central Europe, Eastern Europe), (2) black (sub-Saharan Africa, Caribbean), (3) Hispanic (Latin America), and (4) other (North-Africa, Asia-Pasific, South-East Asia).

Statistical analysis

Statistical analyses were performed using Stata (version 12; StataCorp, College Station, Texas, USA), except for the Greenwood-Nam-D'Agostino (GND) goodness of fit test, which was performed with R version 3.5.1 as described by Demler et al [34].

The distribution of demographic characteristics, CVD risk factors and HIV-specific characteristics was described using absolute numbers (and percentages) and medians (and interquartile range) for categorical and continuous variables, respectively. At baseline, we calculated and categorized an individual's CVD risk for each algorithm as recommended for clinical practice [8–12,20,31]. Data were incomplete for some predictors, and assumptions used to substitute missing data are described in Table Supplemental Digital Content 2.

The Kaplan-Meier method was used to obtain estimates of observed CVD events accounting for variable follow-up time. Model discrimination (the ability to differentiate people who developed CVD from those who did not) was evaluated using Harrell's C-statistics. Harrell's C-statistic values between 0.50-0.59

were considered poor, 0.60-0.69 moderate, 0.70-0.79 acceptable, and 0.80-1.00 very good to excellent. Model calibration (the extent to which the algorithm accurately reflects observed CVD risk) was assessed using the mean observed-versus-expected-ratio (O:E-ratio), calibration plots and the GND goodness-of-fit-test [34]. For the calibration plot and GND test we divided the cohort into deciles of predicted CVD risk for each algorithm. Groups were collapsed when they contained <5 events to ensure calculation of a stable GND χ^2 statistic.

Sensitivity analyses

A number of sensitivity analyses were performed to assess the robustness of the results:

A. Restricting the analysis to those aged 40 years or over;
B. Using cumulative incidence function to estimate the number of observed events, considering non-CVD deaths as competing events;
C. Excluding data from PLWH who contributed to the D:A:D study (n=8,826);
D. Substituting the D:A:D algorithm by a recalibrated algorithm in which data from ATHENA participants were excluded (provided by the authors [20]).

Results

Characteristics of the study population

Data from 16,070 PLWH were included in the main analysis, representing 63% of the total population in care in the Netherlands and registered within ATHENA between January 2000 and December 2016. Common reasons for exclusion were insufficient follow-up or missing data (Figure 1).

Participants had a median age of 43 years (interquartile range, 36-50), 82.4% were male, 94.5% used cART, and 88.6% had HIV-RNA <200 copies/mL (Table 1). Depending on the algorithm used, between 2.4 and 11.4% of individuals were predicted to have a CVD risk ≥20% (Table, Supplemental Digital Content 3).

The algorithms used different endpoints and hence follow-up and number of events varied between algorithms (Figure 1, Table Supplemental Digital Content 1). During 88,929, 88,623, 87,310, and 89,271 person-years of follow-up (PYFU) a CVD incidence of 6.5, 6.9, 8.6 and 5.8/1,000 PYFU was observed, for D:A:D, SCORE-NL, FRS and PCE, respectively.

Performance of CVD risk prediction algorithms (Table 2, Figure 2)

All algorithms yielded acceptable discrimination (Harrell's C-statistics ranged from 0.73 to 0.79).

On a population level, D:A:D, SCORE-NL, and PCE slightly underestimated CVD risk (O:E-ratios 1.35, 1.38, and 1.14, respectively), whereas FRS somewhat overestimated CVD risk (O:E-ratio 0.92). The slight overestimation of CVD risk by FRS was mainly observed in those with ≥20% predicted risk (O:E-ratios, 1.06, 0.94, and 0.78 in those with a predicted risk of <10%, 10-20%, and ≥20%, respectively). D:A:D, SCORE-NL, and PCE underestimated CVD risk in the low and intermediate risk groups (O:E-ratios: D:A:D, 1.34 [<10%] and 1.37 [10-20%]; SCORE-NL, 2.20 [<10%] and 1.20 [10-20%]; PCE, 1.55 [<7.5%]). While risk prediction in those with high predicted risk was rather accurate for D:A:D and PCE; SCORE-NL clearly overestimated CVD risk (O:E-ratios, 0.99 [≥20%], 1.09 [≥7.5%], and 0.65 [≥20%], respectively). D:A:D,

FRS, and PCE best fitted our data, as reflected in the calibration plots and GND test statistics (GND χ^2, 30.00 [D:A:D], 34.22 [FRS], 24.57 [PCE], 119.22 [SCORE-NL]). Yet, all algorithms yielded a statistically significant lack of fit (GND P<0.05).

The mean O:E-ratio of SCORE-NL changed from 1.38 to 0.86 by assigning PLWH an additional CVD risk equivalent of a five-year increase in age. Though risk prediction was more accurate in those with a predicted CVD risk <10% (O:E-ratio changed from 2.20 to 1.41), CVD risk prediction deteriorated in those with CVD risk ≥20% (O:E-ratio changed from 0.65 to 0.54). A ten-year increase in age led to an overestimation of CVD risk over the whole range. Overall, model fit worsened by increasing CVD risk (GND χ^2 = 119.22 [SCORE-NL]; 169.01 [SCORE-NL+5Y]; 621.81 [SCORE-NL+10Y]).

Sensitivity analyses

Only minor modifications in the results were observed in the sensitivity analysis that applied age limits to the study population (i.e., including individuals aged 40 years or over) (Table 3). Discrimination was slightly worse, but still acceptable for D:A:D, FRS, and PCE (Harrell's C-statistics ranged from 0.70 to 0.75). The over- or underestimation of CVD risk on a population level was in the same direction as in the primary analysis (O:E ratio 1.31 [D:A:D], 1.19 [SCORE-NL], 0.89 [FRS], 1.08 [PCE]). As per the primary analysis, D:A:D, FRS, and PCE best fitted our data (GND χ^2, 24.79 [D:A:D], 44.65 [FRS], 18.25 [PCE], 91.47 [SCORE-NL]) and all algorithms yielded a statistically significant lack of fit (GND P<0.05). While risk prediction on a population level was slightly more precise when assigning PLWH an additional CVD risk equivalent of a five-year increase in age in the main analysis (i.e., the O:E ratio was closer to one in the latter scenario), this was no longer the case in this sensitivity analysis.

Sensitivity analyses (Table, Supplemental Digital Content 4) using cumulative incidence functions to obtain the estimated number of observed events and using a recalibrated D:A:D algorithm (excluding

ATHENA participant data) did not substantially modify the results. However, excluding data from PLWH who contributed to the D:A:D study yielded a good model fit for D:A:D, FRS, and PCE (GND P>0.05).

Discussion

Within this largely well-treated HIV-positive population in the Netherlands all assessed CVD risk prediction algorithms reasonably distinguished individuals who developed CVD from those who did not. Though all algorithms yielded a statistically significant lack of fit, D:A:D, PCE, and FRS best predicted CVD risk, with calibration being considerably poorer for SCORE-NL. Assigning PLWH an additional CVD risk equivalent to a five-year increase in age (SCORE-NL+5Y) improved CVD risk prediction by SCORE-NL in the low to intermediate CVD risk group (<20%) and led to a more pronounced overestimation in those with high CVD risk; the overall model fit did not improve. D:A:D, PCE, and FRS would be suitable for use in clinical practice, with the caveat of slightly under-predicting CVD risk in the low CVD risk group.

Our results partly agree with recently published studies on CVD risk prediction [15,18,20,23]. Most studies demonstrated acceptable discrimination for D:A:D [15,20] and PCE [15,18], and moderate to acceptable discrimination for FRS [15,20,23]. SCORE was only evaluated in two studies which revealed poor to acceptable discrimination [15,21]. However, these studies evaluated different versions of SCORE and had insufficient statistical power to reliably validate the algorithm. While discrimination is acceptable for most algorithms, accurately estimating a person's CVD risk in an external population is known to be a bigger challenge. On a population level, D:A:D and PCE slightly underestimated CVD risk in our study, consistent with results from the D:A:D study, the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS), the HIV Outpatient Study (HOPS), and the Partners HIV Cohort [15,18,20,23]. Within D:A:D and CNICS the slight underestimation was reflected in a good model fit, which was not the case for HOPS and the Partners HIV Cohort. In our study there was a statistically significant lack of fit, which might in part be driven by our large sample size, as a sensitivity analysis in a smaller subpopulation (those who did not participate in the D:A:D study) yielded a good model fit for D:A:D, PCE and FRS, while the mean calibration and slope/intercept of the calibration plot did not necessarily improve for all algorithms. FRS overestimated CVD risk on a population level in our study, but not in US-based studies

[15,23]. This difference might in part be attributable to intercontinental population differences, as previous studies in the general population also showed that algorithms developed in the US tend to overestimate CVD risk in European populations [35,36]. Over- or underestimation by D:A:D, FRS, and PCE can potentially be corrected by recalibrating the risk to the absolute risk of the target population, which is an additional advantage of these algorithms compared with SCORE.

SCORE-NL, used by Dutch CVD risk management guidelines, assigns an additional CVD risk to individuals diagnosed with diabetes or rheumatoid arthritis by artificially increasing their age by fifteen years [10]. In an attempt to improve the predictive performance of SCORE-NL in PLWH, we used a similar and easy-to-implement strategy by increasing a person's age by five or ten years, respectively, resulting in a marginal improvement in discriminative abilities. On a population level, calibration slightly improved (though moving towards overestimation of CVD risk) when increasing the risk by five, but not ten, years in the primary analysis, while no improvement was observed in the analysis limited to individuals aged 40 years or over. The improvement was mainly driven by those with a low to intermediate CVD risk (<20%). Within the high CVD risk group, a more pronounced overestimation of CVD risk was observed, which was also reflected in a higher GND χ^2. This underlines that HIV-related CVD risk is not a straight-forward fixed risk but likely a complex interaction of a person's inflammation and immune activation level, established CVD risk factors, as well as use of certain antiretrovirals, and potentially other, as yet unknown, HIV-related risk factors.

The pathogenesis of CVD in the context of HIV is complex, and involves both traditional and HIV-related risk factors. The role of traditional risk factors is vital, also in PLWH, and should not be underestimated [6,37]. Yet, management of traditional risk factors is currently suboptimal in PLWH, with studies describing low rates of awareness, treatment, and control [38–40]. Given the higher burden of CVD in HIV-positive populations, efforts should be made to improve CVD risk management particularly in this high-risk population.

While the contribution of traditional CVD risk factors cannot be disputed, an excess CVD risk remains in PLWH, in which HIV-related risk factors are likely involved. Since none of the investigated algorithms predicted CVD risk perfectly in PLWH, the algorithms could potentially benefit from including additional predictors, in a way that they fully represent the multifactorial pathogenesis of CVD. Two of the most important missing risk factors are inflammation and immune activation, processes that are thought to be key in the pathogenesis of CVD [41,42]. In the general population, there is a signal of improved risk prediction by an algorithm including high sensitivity C-Reactive Protein (hsCRP) in addition to traditional risk factors [43]. Associations between CVD and markers of inflammation, coagulation and immune activation markers have been observed in PLWH [44,45]. For example, the SMART study showed that hsCRP, interleukin-6 and D-dimer were independently associated with an increased CVD risk [45]. However, it remains to be elucidated whether these markers improve CVD risk prediction algorithms and extend preventive treatment options in the context of HIV. Data collected as part of the ongoing REPRIEVE trial [46] might provide an opportunity to address this. Another potentially relevant HIV-related factor is antiretroviral toxicity, which is currently already addressed in the D:A:D algorithm. However, this is an area of ongoing investigation, given the reported inconsistencies in the association between antiretroviral drugs and CVD, and the ongoing drug development over the years. Finally, given the heterogeneity within the HIV-positive population, for example regarding the moment of cART initiation, it remains to be elucidated how the investigated risk prediction algorithms perform in different subpopulations. Given the global recommendation to initiate cART in all PLWH, regardless of CD4 count, we believe that PLWH who initiate cART soon after HIV diagnosis and/or HIV infection would be of particular interest for future studies.Strengths of our study include the large dataset, and comprehensive evaluation of four commonly used algorithms, including several sensitivity analyses. Our results should however also be interpreted in the context of several limitations. First, data were incomplete and not time-updated for some parameters, resulting from ATHENA data collection being

practice-driven. Since data on smoking, systolic blood pressure, and cholesterol measurements were included by all algorithms, their effect is less likely to differentially impact predictive performance. However, family history of CVD is only included by D:A:D and our assumptions regarding missing data and changes in this factor over time may have contributed to the underestimation by D:A:D. Second, TIA, angina, heart failure, peripheral artery disease and coronary insufficiency diagnoses were not validated in ATHENA. These diagnoses might be less reliable, potentially affecting the performance of FRS and SCORE-NL. Third, ATHENA and D:A:D study populations partially overlap, but sensitivity analyses centered around this overlap did not reveal different results. Fourth, the D:A:D algorithm was originally developed to estimate five-year CVD risk. Ten-year CVD risk estimates might therefore be less reliable. Fifth, we excluded over 30% of ATHENA participants, mainly because of missing data and insufficient follow-up. Excluded participants had lower CVD rates than included individuals (data not shown). Since PLWH with low CVD risk were already well-represented in the included population, we believe it is unlikely that the excluded sample influenced our results. Sixth, ATHENA participants were mainly men and of white ethnicity. Due to the small number of female and non-white participants we were not able to perform any sex- or ethnicity-stratified analyses. Our results might therefore not be generalizable to HIV-positive populations with different demographic compositions. In addition, we specifically investigated the Dutch adaptation of the SCORE algorithm, and we might therefore not be able to translate our results to countries where other adaptations of SCORE are being used. Lastly, the number of PLWH with high predicted CVD risk was limited in our study and repeating this analysis in a high-risk cohort could provide further guidance regarding the best use of these algorithms in clinical practice.

Conclusion and future perspectives

All CVD risk prediction algorithms performed reasonably well, with SCORE-NL performing the poorest. For predicting CVD risk in PLWH in clinical practice we would recommend D:A:D, FRS, or PCE. In PLWH

with a low predicted CVD risk, clinicians should be aware of risk being somewhat underestimated and act accordingly. Future studies should investigate the effect of immune activation and inflammatory markers, newer antiretrovirals, and cART initiation soon after HIV diagnosis on CVD risk and prediction algorithms in PLWH.

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FIGURES

FIGURE 1: Flow chart of selection of individuals and reasons for exclusion

[Insert Figure 1]

Abbreviations: cART, combination antiretroviral therapy; CVD, cardiovascular disease; D:A:D, Data collection on Adverse Effects of Anti-HIV Drugs Study risk prediction algorithm; FRS, Framingham CVD Risk Score; HDL, HDL cholesterol; PCE, American College of Cardiology and American Heart Association Pooled Cohort Equations; PYFU, person-years of follow-up; SBP, systolic blood pressure; SCORE-NL, Systematic COronary Risk Evaluation equation adjusted for national data; SCORE-NL+5Y, SCORE-NL assigning PLWH an additional CVD risk equivalent to an age increase of five years; TC, total cholesterol.

FIGURE 2: Calibration plots of the D:A:D, SCORE-NL, SCORE-NL+5Y, FRS, and PCE using Kaplan-Meier Function to estimate observed CVD prevalence

[Insert Figure 2]

The calibration plot of SCORE-NL+10Y (SCORE-NL assigning PLWH an additional CVD risk equivalent to an age increase of ten years) was not shown to maintain the scale of the x-axis equal to the calibration plots of other algorithms. SCORE-NL+10Y overestimated CVD risk in almost all deciles.

Abbreviations: CVD, cardiovascular disease; D:A:D, Data collection on Adverse Effects of Anti-HIV Drugs Study risk prediction algorithm; FRS, Framingham CVD Risk Score; PCE, American College of Cardiology and American Heart Association Pooled Cohort Equations; SCORE-NL, Systematic COronary Risk Evaluation equation adjusted for national data; SCORE-NL+5Y, SCORE-NL assigning PLWH an additional CVD risk equivalent to an age increase of five years.

TABLES

TABLE 1: Characteristics of included ATHENA participants at baseline

	ATHENA participants included in this analysis (n=16,070)[1]
FOLLOW-UP FOR EACH ALGORITHM IN YEARS	
D:A:D	5.4 (2.5, 8.9)
SCORE-NL	5.3 (2.5, 8.9)
FRS	5.2 (2.4, 8.8)
PCE	5.4 (2.5, 9.0)
DEMOGRAPHIC CHARACTERISTICS	
Age in years	43 (36, 50)
Male sex	13,243 (82.4%)
Ethnicity, based on an individual's region of origin[2]	
White/Caucasian	11,129 (69.4%)
Black (sub-Saharan African / Caribbean)	1,970 (12.3%)/1,043 (6.5%)
Hispanic	1,100 (6.9%)
Other	795 (5.0%)
CVD RISK FACTORS	
Family history of CVD	434 (10.3%)
Smoking status	
never	6,561 (40.8%)
former	2,819 (17.5%)
current	6,690 (41.6%)
Systolic blood pressure in mmHg	124 (115, 136)
Diastolic blood pressure in mmHg	80 (70, 85)
Total cholesterol in mmol/L	4.80 (4.10, 5.60)
HDL cholesterol in mmol/L	1.15 (0.93, 1.40)
Diabetes	457 (2.8%)
CVD MEDICATION USE	
Use of antihypertensive drugs	1,499 (9.3%)
Use of lipid lowering drugs	971 (6.0%)
Use of antidiabetic drugs	432 (2.7%)
Use of vitamin K antagonists	166 (1.0%)
Use of platelet inhibitors	368 (2.3%)
HIV-RELATED RISK FACTORS	
Years since HIV diagnosis	3.8 (1.7, 8.1)
Current use of cART	15,180 (94.5%)
Current CD4 cell count in cells/µL	510 (350, 690)
Nadir CD4 cell count in cells/µL	220 (100, 330)
Prior clinical AIDS diagnosis[3]	3,548 (22.1%)
HIV-RNA <200 copies/mL	14,216 (88.6%)
Year of first ART exposure	
Prior to 1996	981 (6.1%)

Between 1996 and 2000	2,453 (15.3%)
In 2000 or thereafter	12,636 (78.6%)
Current abacavir use	1,976 (12.3%)
Cumulative NRTI use in years	1.4 (1.1, 4.3)
Cumulative PI use in years	0.3 (0.0, 1.5)
Cumulative NNRTI use in years	1.1 (0.0, 1.5)

Abbreviations: ART, antiretroviral therapy; cART, combination antiretroviral therapy; CVD, cardiovascular disease; D:A:D, Data collection on Adverse Effects of Anti-HIV Drugs Study risk prediction algorithm; FRS, Framingham CVD Risk Score; IQR, interquartile range; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PCE, American College of Cardiology and the American Heart Association Pooled Cohort Equations; PI, protease inhibitor; SCORE-NL, Systematic COronary Risk Evaluation equation adjusted for national data.

[1] Data are reported as number (%) or median (interquartile range).

[2] Ethnicity was based on an individual's region of origin and subsequently categorized into four groups: (1) white/Caucasian (the Netherlands, North America, Australia, Central Europe, Eastern Europe), (2) black (sub-Saharan Africa, Caribbean), (3) Hispanic (Latin America), and (4) other (North-Africa, Asia-Pasific, South-East Asia).

[3] AIDS was defined as the presence of any Centers for Disease Control (CDC) category C condition.

TABLE 2: Predictive performance of CVD risk prediction algorithms in the entire population

	DISCRIMINATION		CALIBRATION					
	Harrell's C-statistic (95%-CI)	**Observed events No (%)**	**Expected events No (%)**	**O:E-ratio**	**Slope**	**Intercept**	**GND chi^2**	**GND P**
D:A:D								
5-year risk	0.79 (0.77-0.81)	478 (2.98%)	391 (2.44%)	1.22	1.38	-0.005	27.01	0.0007
10-year risk	0.77 (0.76-0.79)	1,062 (6.62%)	787 (4.91%)	1.35	1.24	0.002	30.00	0.0004
SCORE-NL	0.73 (0.71-0.76)	1,138 (7.12%)	824 (5.16%)	1.38	0.71	0.035	119.22	<0.0001
SCORE-NL+5Y	0.74 (0.71-0.76)	1,138 (7.12%)	1,316 (8.23%)	0.86	0.50	0.030	169.01	<0.0001
SCORE-NL+10Y	0.74 (0.72-0.76)	1,138 (7.12%)	2,014 (12.60%)	0.57	0.37	0.024	621.81	<0.0001
FRS	0.75 (0.73-0.77)	1,393 (8.78%)	1,506 (9.49%)	0.92	0.75	0.015	34.22	<0.0001
PCE	0.76 (0.74-0.78)	955 (5.94%)	838 (5.22%)	1.14	0.86	0.013	24.57	0.0035

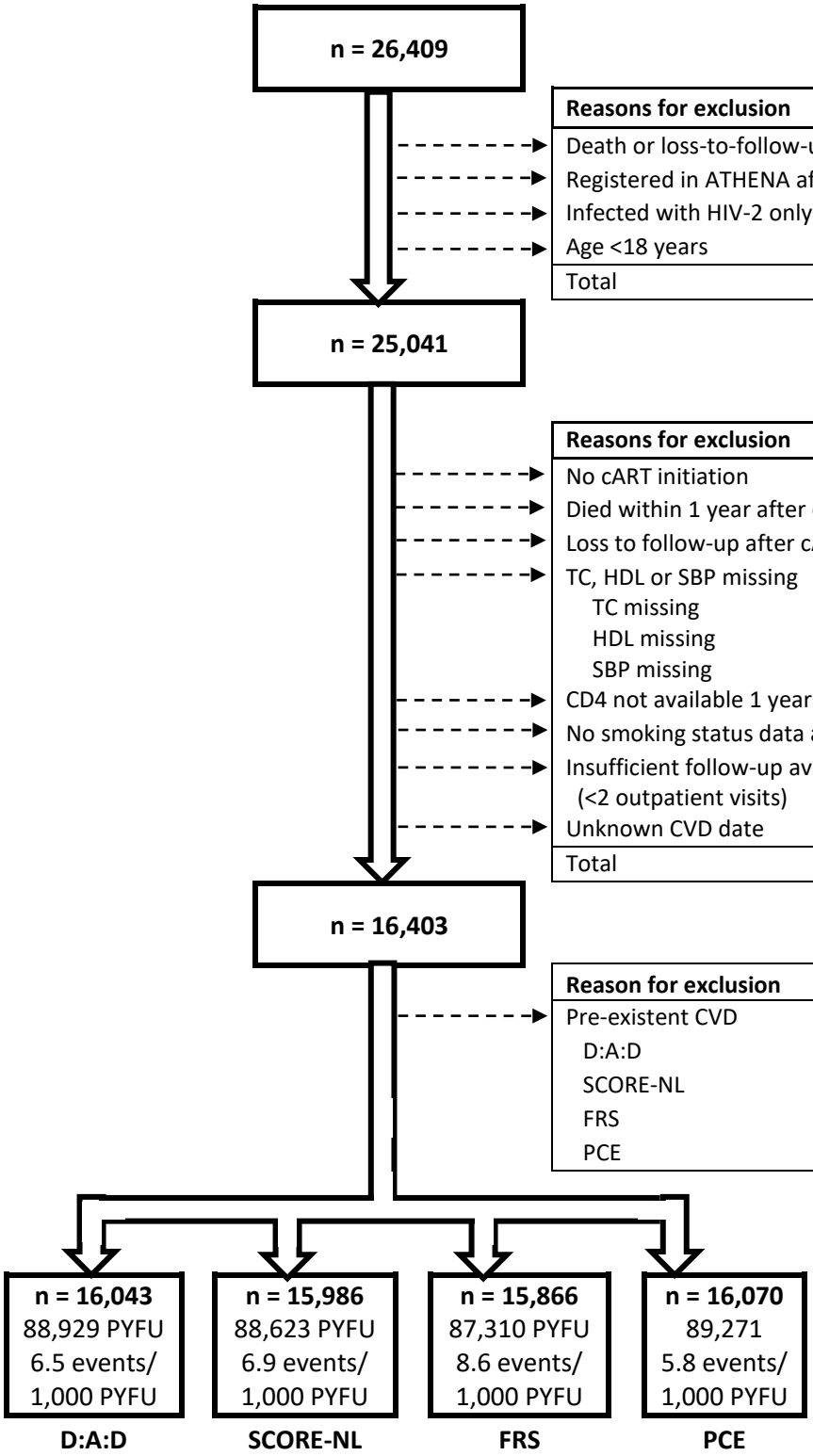
Abbreviations: CVD, cardiovascular disease; D:A:D, Data collection on Adverse Effects of Anti-HIV Drugs Study risk prediction algorithm; FRS, Framingham CVD Risk Score; GND, Greenwood-Nam-D'Agostino goodness of fit test; O:E-ratio, ratio between observed versus expected events; PCE, American College of Cardiology and the American Heart Association Pooled Cohort Equations; SCORE-NL, Systematic COronary Risk Evaluation equation adjusted for national data; SCORE-NL+5Y, SCORE-NL assigning PLWH an additional CVD risk equivalent to an age increase of five years; SCORE-NL+10Y, SCORE-NL assigning PLWH an additional CVD risk equivalent to an age increase of ten years.

TABLE 3: Predictive performance of CVD risk prediction algorithms when restricting the analysis to PLWH aged 40 or over (n=9,736)

	DISCRIMINATION			CALIBRATION				
	Harrell's C-statistic (95%-CI)	**Observed events No (%)**	**Expected events No (%)**	**O:E-ratio**	**Slope**	**Intercept**	**GND chi^2**	**GND P**
D:A:D								
5-year risk	0.75 (0.72-0.77)	417 (4.29%)	341 (3.52%)	1.22	1.38	-0.006	26.31	0.0009
10-year risk	0.74 (0.71-0.76)	894 (9.21%)	685 (7.06%)	1.31	1.18	0.005	24.79	0.0032
SCORE-NL	0.69 (0.67-0.72)	932 (9.64%)	783 (8.10%)	1.19	0.58	0.050	91.47	<0.0001
SCORE-NL+5Y	0.69 (0.67-0.72)	932 (9.64%)	1,148 (12.67%)	0.76	0.42	0.044	199.57	<0.0001
SCORE-NL+10Y	0.69 (0.67-0.72)	932 (9.64%)	1,833 (18.97%)	0.51	0.32	0.036	672.56	<0.0001
FRS	0.70 (0.68-0.73)	1,158 (12.12%)	1,298 (13.59%)	0.89	0.67	0.030	44.65	<0.0001
PCE	0.72 (0.70-0.75)	791 (8.12%)	733 (7.53%)	1.08	0.79	0.022	18.25	0.0324

[1] Deciles 1-2 were collapsed due to the low number of observed events in these deciles (<5).

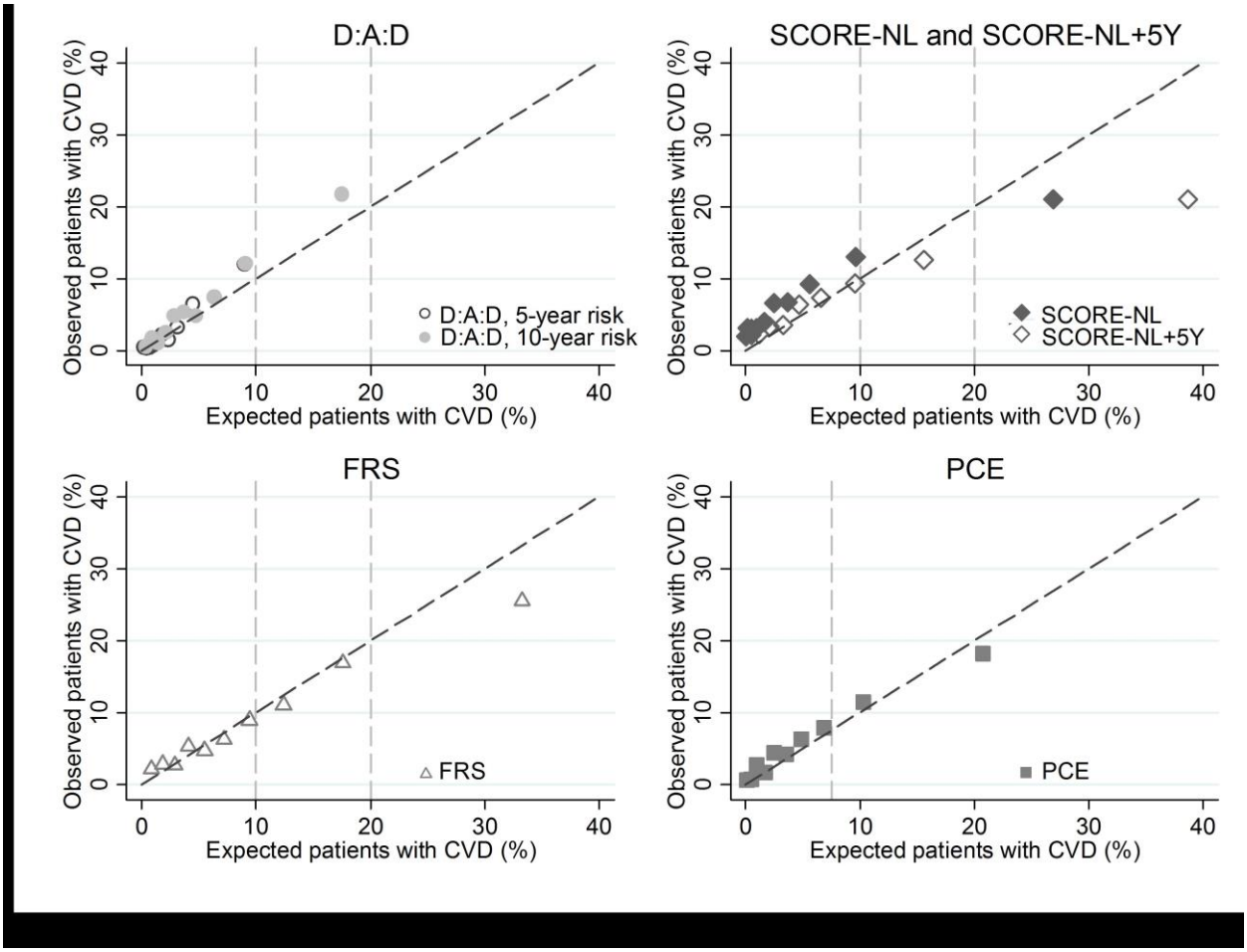
Abbreviations: CVD, cardiovascular disease; D:A:D, Data collection on Adverse Effects of Anti-HIV Drugs Study risk prediction algorithm; FRS, Framingham CVD Risk Score; GND, Greenwood-Nam-D'Agostino goodness of fit test; O:E-ratio, ratio between observed versus expected events; PCE, American College of Cardiology and the American Heart Association Pooled Cohort Equations; SCORE-NL, Systematic COronary Risk Evaluation equation adjusted for national data; SCORE-NL+5Y, SCORE-NL assigning PLWH an additional CVD risk equivalent to an age increase of five years; SCORE-NL+10Y, SCORE-NL assigning PLWH an additional CVD risk equivalent to an age increase of ten years.



Reasons for exclusion	N
Death or loss-to-follow-up prior to 1 January 2000	647
Registered in ATHENA after 31 December 2016	396
Infected with HIV-2 only	98
Age <18 years	227
Total	1,368

Reasons for exclusion	N
No cART initiation	1,385
Died within 1 year after cART initiation	340
Loss to follow-up after cART initiation	416
TC, HDL or SBP missing	3,031
TC missing	653
HDL missing	2,565
SBP missing	857
CD4 not available 1 year prior/after baseline	186
No smoking status data available	1,463
Insufficient follow-up available (<2 outpatient visits)	1,789
Unknown CVD date	28
Total	8,638

Reason for exclusion	N
Pre-existent CVD	
D:A:D	360
SCORE-NL	417
FRS	537
PCE	333


D:A:D
Observed patients with CVD (%)
Expected patients with CVD (%)
D:A:D, 5-year risk
D:A:D, 10-year risk
SCORE-NL and SCORE-NL+5Y
SCORE-NL
SCORE-NL+5Y
FRS
FRS
PCE
PCE
0
10
20
30
40