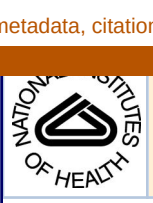

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Baseline cardiovascular risk in the INSIGHT Strategic Timing of AntiRetroviral Treatment trial

Elsayed Z. Soliman[1], **Shweta Sharma**[2], **Keikawus Arasteh**[3], **David Wohl**[4], **Amit Achhra**[5], **Giuseppe Tambussi**[6], **Jemma O'Connor**[7], **James H. Stein**[8], **Daniel A. Duprez**[9], **James D. Neaton**[2], and **Andrew Phillips**[7] **for the INSIGHT START study group**

[1]Epidemiological Cardiology Research Center (EPICARE), Department of Epidemiology and Prevention, and Department of Internal Medicine-Cardiology, Wake Forest School of Medicine, Winston Salem, NC, USA

[2]Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis, MN, USA

[3]EPIMED/Vivantes Auguste-Viktoria-Klinikum, Berlin, Germany

[4]Department of Medicine, School of Medicine, University of North Carolina-Chapel Hill, Chapel Hill, NC, USA

[5]The Kirby Institute, University of New South Wales, Sydney, Australia

[6]Ospedale San Raffaele, Milan, Italy

[7]Research Department of Infection & Population Health, UCL Medical School, London, UK

[8]Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

[9]Department of Medicine, Cardiovascular Division, University of Minnesota, Minneapolis, MN, USA

Abstract

Introduction—The Strategic Timing of AntiRetroviral Treatment (START) trial has recruited antiretroviral-naïve individuals with high CD4 cell counts from all world regions. We describe the distribution of cardiovascular (CVD) risk factors, overall and by geographic region, at study baseline.

Methods—The distribution of CVD risk factors was assessed and compared by geographic region among START participants who had baseline electrocardiogram (n=4019; 11% North

Corresponding Author: Elsayed Z. Soliman MD, MSc, MS, Epidemiological Cardiology Research Center (EPICARE), Wake Forest School of Medicine, Medical Center Blvd. Winston Salem, NC 27157, Tel: (336) 716-8632., Fax: (336) 716-0834, esoliman@wakehealth.edu.

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Conflict of interest: None

America; 36% Europe/Australia/Israel; 26% South America; 4% Asia; 23% Africa; median age 36 years; 26% females).

Results—About 58.3% (n=2344) of the participants had at least one CVD risk factor and 18.9% (n=761) had two or more. The most common CVD risk factors were current smoking (32%), hypertension (19.3%) and obesity (16.5%). There were significant differences in the prevalence of CVD risk factors among geographic regions. The prevalence of at least one risk factor across regions was as follows: 70.0% North America, 65.1% Europe/Australia/Israel, 49.4% South America, 37.0% Asia, and 55.8% Africa (p-value<0.001). Significant regional differences were also observed when risk factors were used as part of the Framingham and D:A:D risk scores or used to define favourable risk profile.

Conclusions—CVD risk factors are common among START participants, and their distribution varies by geographic region. Better understanding of how and why CVD risk factors develop in people with HIV and their geographical distributions could shed light on appropriate strategies for CVD prevention and may inform the interpretation of the results of START as CVD is expected to be a major fraction of the primary endpoints observed.

Keywords

Cardiovascular risk; HIV; START trial

INTRODUCTION

The survival of individuals with HIV infection who have access to highly active antiretroviral therapy has dramatically increased. This increase in survival has been associated with emergence of cardiovascular disease (CVD) as a significant contributor to mortality. About 8–22% of deaths occuring in HIV-positive individuals have been attributed to CVD, and the number of individuals at significant risk appears to be increasing as the HIV-positive population ages (1–4).

Several studies, largely from the United States and Europe, have already shown that there is an increased risk of CVD in HIV-positive populations compared to HIV-negative populations (5–10). This increased risk has been attributed to different distributions of traditional CVD risk factors in HIV or the presence of additional risk factors related to HIV infection such as the impact of the HIV virus itself on the myocardium and arteries, inflammation, immune activation, or the metabolic abnormalities associated with antiretroviral therapy (ART) (11, 12). Nevertheless, the distribution of CVD risk factors in asymptomatic HIV-positive individuals with high CD4 cell counts, and how this varies by geographic region, has not been studied. A better understanding of the regional differences in the distribution of CVD risk factors could shed light on the appropriate cost-effective strategies that should be pursued for CVD prevention in this high-risk population group.

In this report, we describe the baseline distribution of CVD risk factors, overall and by geographic region, in HIV-positive individuals enrolled in the international Strategic Timing of AntiRetroviral Treatment (START) trial. Understanding the distribution of CVD risk

factors may ultimately inform the interpretation of the results of START as CVD is expected to be a major fraction of the primary endpoints observed.

METHODS

The design and rationale of the START trial have been described in detail elsewhere (13). Briefly, START is an ongoing multicentre international trial designed to assess the risks and benefits of early initiation of ART. A total of 4685 ART-naïve HIV-positive individuals with CD4 cell counts >500 cells/μL from 215 clinical sites in 35 countries were randomised in a 1:1 ratio to start ART immediately (early ART) or defer treatment until CD4 cell count is <350 cells/μL (deferred ART). It is estimated that a minimum follow up of three years will result in the targeted number of primary events (13).

For the purpose of this report, we included only START participants who underwent 12-lead electrocardiogram (ECG). Due to budgetary limitations, ECGs were not obtained in certain countries (Czech Republic [n=13], India [n=91], Malaysia [n=18], Mexico [n=48], and Nigeria [n=49]; total = 219 participants) and select sites in some countries (Argentina [n=49], Australia [n=33], Belgium [n=18], France [n=8], Italy [n=3], Portugal [n=23], South Africa [n=17], Sweden [n=1], Switzerland [n=1], Thailand [n=92], United Kingdom [n=52], United States [n=46]; total = 343 participants). Participants with expected but missing (n=56) or poor-quality ECG (n=48) were excluded from the analysis. After all exclusions (n=666), 4019 participants remained and were included in the analysis (Figure 1). In additional analyses (provided as online supplemental tables), we utilised all randomised HIV-positive START participants (n=4685) to present the distribution of CVD risk factors and other data that are not dependent on the availability of ECG.

Before study entry the following data were collected: demographics, data on diagnosis and mode of HIV infection, medical history including concomitant medications, self-reported cigarette smoking status, CD4 cell count and HIV RNA, fasting glucose and lipids, a brief clinical evaluation including blood pressure measurements, and a 12-lead resting ECG.

Electrocardiograms were recorded by identical ECG machines (GE MAC 1200 model, GE, Milwaukee, Wisconsin, United States) in all of the study clinical sites using strictly standardised procedures. The digital ECG tracings stored in the electrocardiographs were transmitted regularly over analogue phone lines to the START ECG Reading Center (The Epidemiological Cardiology Research Center [EPICARE], Wake Forest School of Medicine, Winston Salem, North Carolina, United States) for analysis. ECGs were evaluated by readers blinded to treatment strategy. After being visually checked for quality, the study ECGs were automatically processed using the 2001 version of the GE Marquette 12-SL program (GE, Milwaukee, Wisconsin, United States). ECG abnormalities were classified using the standard Minnesota ECG Classification (14). These abnormalities included ECG evidence of myocardial infarction (MI) and myocardial ischaemia (major ST/T abnormalities) (15).

Body mass index (BMI) values of 18.5–24.9 kg/m^2 were considered as normal weight, <18.5 kg/m^2 as underweight, 25.0–29.9 kg/m^2 as overweight, and ≥30 kg/m^2 as obese.

Diabetes was defined by self-report or documentation of a prior diagnosis, use of medications, or fasting glucose ≥126 mg/dL. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of blood-pressure-lowering medications. Dyslipidemia was defined as LDL cholesterol ≥160 mg/dL or use of cholesterol-lowering medications. Prior CVD was defined as self-reported history or documentation of a prior MI, coronary revascularisation or stroke as well as baseline ECG evidence of MI or myocardial ischaemia. Favourable CVD risk profile was defined on the basis of a number of modifiable risk factors as follows: total cholesterol <200 mg/dL, systolic blood pressure ≤120 mmHg, diastolic blood pressure ≤80 mmHg, no current smoking, no diabetes and no prior CVD (16).

The following risk prediction equations were also calculated: 1) The Framingham 10-year estimated CVD risk score, which is based on age, gender, total cholesterol, HDL cholesterol, systolic blood pressure, use of blood-pressure-lowering medications, current smoking, and diabetes (17); 2) the Framingham 10-year estimated coronary heart disease (CHD) risk score, which is based on age, gender, the Joint National Committee (JNC-V) blood pressure categories, the National Cholesterol Education Program (NCEP) total cholesterol and HDL categories, current smoking, and diabetes (18); and 3) the Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) 10-year estimated CVD and CHD risk scores, which are based on age, gender, current smoking, ex-smoking status, total and HDL cholesterol, systolic blood pressure, diabetes, family history of CVD and prior use of specific ART (19). START participants were ART-naive at enrolment and data on family history of CVD were not collected in START. Therefore, the specific ART drugs were set to zero and no prior family history of CVD was assumed in the calculation of the D:A:D risk prediction equations.

Statistical Methods

Continuous variables are presented as medians with the interquartile ranges (IQR) and categorical variables as percentages. Unadjusted regional comparisons of demographics and HIV characteristics were performed using Kruskal Wallis tests or chi-square tests. Individual CVD risk factors, favourable CVD risk profile, and the Framingham and D:A:D CHD and CVD risk scores were tabulated and compared across regions with age- and gender-adjusted models using quantile regression (medians) and logistic regression (binary outcomes).

As sensitivity analysis, we repeated all the analyses after including all START participants regardless of the availability of ECG data (data presented as online supplemental tables).

All reported p-values are 2-sided, and a p-value <0.05 was considered statistically significant. SAS software version 9.3 (SAS Institute Inc., Cary, North Carolina, United States, 2002–2010) was used.

RESULTS

A total of 4019 START participants (median age 36 years; 25.9% females, 32.4% black, 13.3% Latino/Hispanics, 4.5% Asians, 45.9% whites and 3.9% others) with available ECG data were included in this analysis. There were significant differences in the participants'

characteristics across geographic regions (Table 1). Compared to participants from other regions, especially North America, participants from Asia were more likely to be younger in age and with lower median values of BMI, systolic blood pressure, diastolic blood pressure and CD4 cell count, but with higher median values of total cholesterol, LDL cholesterol and HDL cholesterol (Table 1). Not surprisingly, race/ethnicity was highly correlated with region; blacks were the majority (93.5%) in Africa, Asians were the majority (97.4%) in Asia, and whites were the majority (86.1%) in Europe/Australia/Israel.

More than half (58.3%) of the START participants included in this analysis had at least one risk factor (current smoking, obesity, diabetes, prior CVD, hypertension or dyslipidemia), and 18.9% had two or more risk factors (Table 2). The most common risk factors were current smoking (32.0%), hypertension (19.3%) and obesity (16.5%). Significant differences in the prevalence of CVD risk factors among regions were observed. The highest prevalence of CVD risk factors was observed in North America (70.0% had at least one CVD risk factor) followed by Europe/Australia/Israel (65.1% had at least one CVD risk factor). On the other hand, the lowest prevalence of CVD risk factors was observed in Asia (37.0% had at least one CVD risk factor).

Prevalent CVD was detected in 182 (4.5%) of the participants (37 with MI [ECG evidence and/or past history], 10 with history of coronary revascularisation, 6 with history of stroke, and 146 with ECG evidence of myocardial ischaemia). The highest prevalence of CVD was observed in Africa (6.1%) followed by Europe/Australia/Israel and North America (both 4.6%), Asia (3.9%) and South America (3.1%) (age and sex adjusted p=0.427) (Table 2).

About 24.6% (n=988) of the participants had favourable CVD risk profile, with women being more likely to have a favourable risk profile compared to men (Table 3). Significant regional differences in the favourable risk profile, overall and by gender, were observed ($p<0.001$)

Table 4 shows the 10-year estimated CVD and CHD risks using Framingham and D:A:D risk equations. Overall, the median values of CVD and CHD 10-year estimated risk using Framingham equations were 2.9% and 3.0%, respectively. This compares to only 1.8% and 1.4% estimated 10-year risk using D:A:D risk equations. The proportions of START participants with >10% estimated 10-year risk of CVD and CHD were 13.7% and 9.4% using Framingham and 4.4% and 2.9% using D:A:D. The estimated 10-year CVD and CHD risks varied by region with higher estimates in North America and Europe/Australia/Israel compared to Africa and Asia ($p<0.001$).

Similar trends in the regional differences in the distribution of CVD risk factors, favourable risk profile, and risk prediction scores were also observed when all analyses were repeated using all START participants (n=4685) regardless of the availability of ECG data (Tables S1–S4). As expected, however, the prevalence of risk factors became slightly lower and the favourable risk profile became slightly higher (especially in Asia) when ECG abnormalities (MI and ischaemia) were not considered in this sensitivity analysis.

DISCUSSION

We described the baseline distribution of CVD risk factors, overall and by geographic region, in the START trial. The key findings are: 1) CVD risk factors are common in HIV-positive individuals; at least one in every two participants had one or more CVD risk factors; 2) there are significant regional differences in the distribution of CVD risk factors and in risk prediction scores; and 3) the distribution of favourable CVD risk profile varies by sex and region.

The observed prevalence of CVD risk factors in START accords with the previous studies that examined the epidemiology of CVD in HIV-positive patients (20–23). We have shown, however, that these risk factors vary significantly by geographic region. Better understanding of how and why CVD risk factors develop in HIV and their geographical distributions could shed light on the appropriate strategies for CVD prevention.

In START, it is expected that CVD will account for a large fraction of non-AIDS endpoints, and our results of regional differences in CVD risk factors indicate that the incidence of CVD endpoints (MI, stroke and coronary revascularisation) might vary considerably by geographic region. Another factor that may impact the CVD endpoints expected to occur in START is the regional differences in the favourable risk profile. Previous studies have shown that favourable risk profile is associated with significantly lower risk of CVD events (16, 24). As we showed, about 24.6% of START participants have a favourable risk profile; this varied significantly by region ranging from 15.0% in Europe/Australia/Israel to 32.8% in South America. Interestingly, although the South America region had the highest prevalence of favourable risk profile (which aims to identify low-risk group based on prevalence of favourable levels of modifiable risk factors), this region is not the one with lowest average 10-year estimated risk based on risk prediction equations (which aim to identify high-risk group). There were also differences by gender in favourable risk profile, with a particularly low proportion of women having a favourable risk profile in North America (13.2%, compared with 32.6% overall), while in men the proportion (20.3%) was similar to the overall average (21.8%).

Regional differences in CVD risk factors could be due to differences in lifestyle and health behaviours across regions. Although the fold increase in risk associated with each CVD risk factor should be similar in all HIV-positive populations regardless of region, regional differences in the prevalence of risk factors would yield differences in the population-attributable risk associated with these CVD risk factors. This may require different prevention strategies and/or risk assessment tools that take into account the most highly prevalent risk factors in each region.

CVD risk assessment equations play an important role in CVD prevention by identifying high-risk groups that would benefit from careful evaluation and management of their risk factors. The estimated 10-year CVD and CHD risks by Framingham risk scores (developed in the general population) were consistently higher than the estimated risk by D:A:D score (developed in HIV-positive individuals) as has been previously noted (19). These findings suggest that although risk assessment models developed in the general population may still

work in an HIV-positive population, they may not be optimal for risk stratification in HIV-positive individuals. Reasons for differences in the risk estimates by the Framingham and D:A:D scores could be related to the inherent differences in the source populations of and the methodology applied in the Framingham and D:A:D studies. Also, the START trial did not collect data on family history of CVD, and all participants were ART-naïve at the time of enrolment. Both family history of CVD and ART use are components of the D:A:D scores, which may explain the lower estimated 10-year CVD and CHD risk by D:A:D risk score. When the START trial accumulates CVD events in the upcoming years of follow-up, it will be possible to compare calibration of the D:A:D, Framingham and other risk assessment scores. Notably, none of the risk prediction equations includes inflammatory markers. Results from the SMART, ESPRIT and SILCAAT trials have shown that HIV-positive individuals have higher levels of inflammatory markers even on suppressive treatment (25, 26) and that these markers are associated with CVD (27) and CVD severity (28). With this in mind, future data from the START trial may provide useful information on the risk of CVD in the absence of traditional risk factor elevations but in the presence of elevated inflammatory markers.

The findings we provided in this report should be read in the context of certain limitations. The main analysis was limited to START participants who underwent ECG recording so that we can have an objective tool to assess CVD status (MI and ischaemia). This might have limited the generalisability of our findings to all of START participants as sites in some countries did not collect ECGs. Nevertheless, the majority of START participants already underwent ECG (about 88%), and the results were in the same direction when all START participants were included in the analyses. Another limitation is that we could not examine the association between CVD risk factors and prevalent CVD because of the small number of CVD cases that were mainly driven by ECG abnormalities (MI and myocardial ischaemia).

In summary, this report provides the first comprehensive summary of CVD risk factors, overall and by geographic region, for HIV-positive participants who are ART-naïve and have CD4 cell counts >500 cells/μL. These data may inform the interpretation of the results of START and could guide future studies addressing CVD prevention in HIV-positive individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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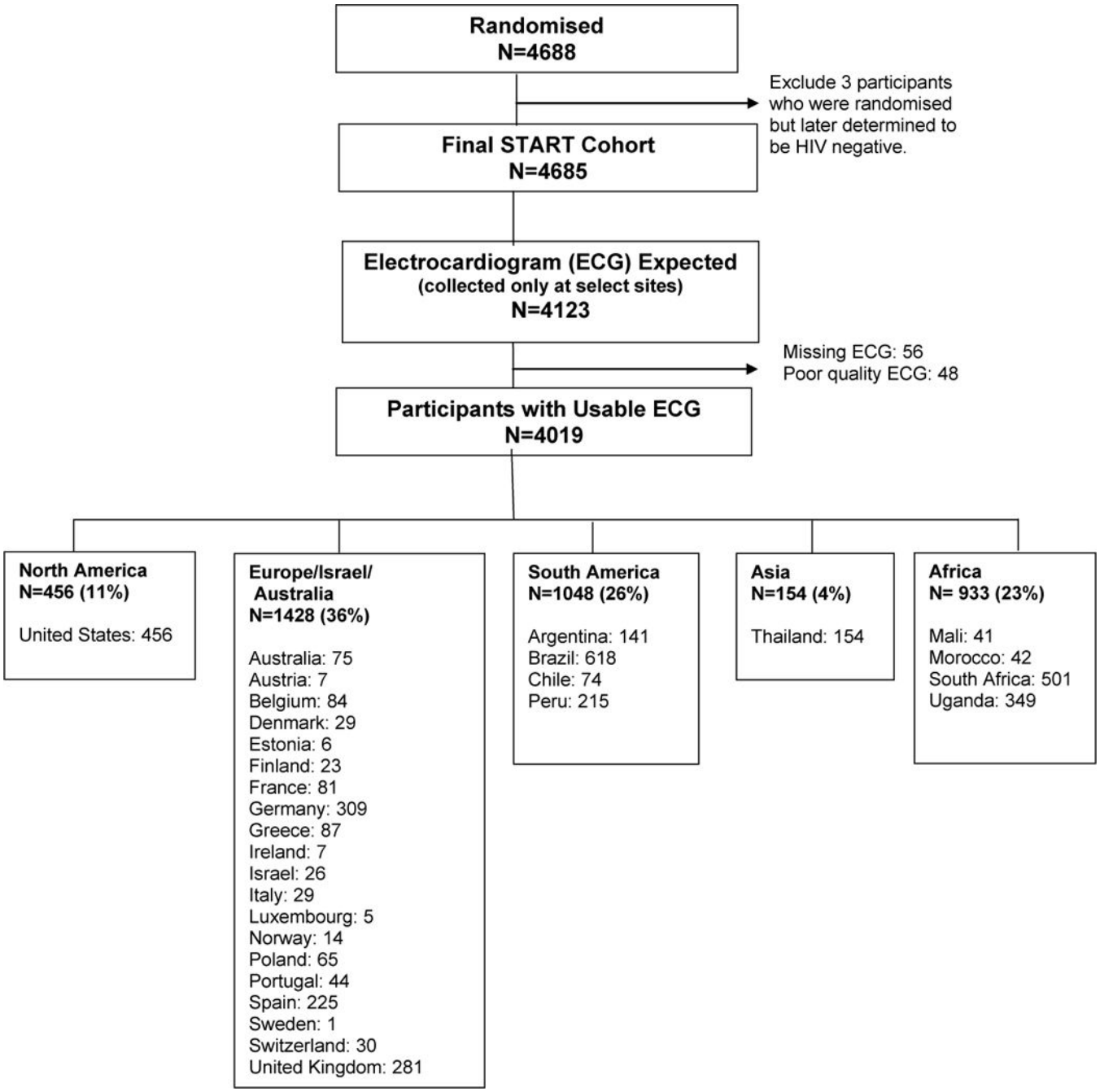

Figure 1.
Flow chart of inclusion and exclusion criteria

Table 1

Participant characteristics, START baseline (2009–2013)[a]

Factor, N (%) or Median [IQR]	Overall *N=4019*	North America *N=456*	Europe/Australia/Israel *N=1428*	South America *N=1048*	Asia *N=154*	Africa *N=933*	Region p-value[b]
Age (years)	36 [29, 44]	37 [29, 47]	38 [30, 45]	32 [26, 40]	30 [24, 37]	38 [31, 45]	<0.001
Female	1041 (25.9)	91 (20.0)	117 (8.2)	149 (14.2)	30 (19.5)	654 (70.1)	<0.001
Race							<0.001
Black	1303 (32.4)	213 (46.7)	85 (6.0)	133 (12.7)	0 (0.0)	872 (93.5)	
Latino/Hispanic	534 (13.3)	74 (16.2)	63 (4.4)	397 (37.9)	0 (0.0)	0 (0.0)	
Asian	182 (4.5)	9 (2.0)	23 (1.6)	0 (0.0)	150 (97.4)	0 (0.0)	
White	1845 (45.9)	156 (34.2)	1229 (86.1)	415 (39.6)	2 (1.3)	43 (4.6)	
Other	155 (3.9)	4 (0.9)	28 (2.0)	103 (9.8)	2 (1.3)	18 (1.9)	
Body mass index (kg/m^2)	24.5 [22.1, 27.9]	26.7 [23.6, 31.0]	23.9 [22.0, 26.6]	24.6 [22.5, 27.3]	21.1 [19.8, 23.6]	25.7 [22.1, 30.9]	<0.001
Systolic blood pressure (mmHg)	120 [111, 130]	123 [114, 133]	123 [113, 132]	120 [110, 129]	118 [111, 126]	119 [110, 131]	<0.001
Diastolic blood pressure (mmHg)	77 [70, 83]	78 [71, 84]	77 [70, 83]	75 [67, 81]	74 [68, 80]	78 [70, 85]	<0.001
Glucose (mg/dL)	85 [79, 92]	87 [79, 94]	86 [79, 93]	86 [80, 92]	83 [79, 89]	83 [77, 90]	<0.001
Total cholesterol (mg/dL)	166 [143, 193]	166 [143, 186]	174 [151, 201]	163 [140, 189]	186 [162, 217]	158 [135, 185]	<0.001
LDL cholesterol (mg/dL)	101 [82, 124]	101 [81, 118]	108 [87, 128]	99 [81, 121]	120 [95, 147]	97 [77, 120]	<0.001
HDL cholesterol (mg/dL)	42 [35, 50]	42 [35, 51]	42 [35, 52]	38 [32, 44]	45 [37, 55]	42 [35, 54]	<0.001
Triglycerides (mg/dL)	96 [71, 141]	98 [72, 142]	100 [71, 147]	105 [75, 154]	98 [74, 129]	80 [55, 115]	<0.001
Time since HIV diagnosis (years)	1.0 [0.4, 3.0]	1.4 [0.4, 4.2]	1.1 [0.5, 3.0]	0.5 [0.2, 1.5]	0.6 [0.2, 2.2]	1.5 [0.5, 4.5]	<0.001
CD4 (cells/μL)	651 [583, 764]	665 [591, 770]	644 [581, 737]	642 [580, 760]	604 [561, 677]	684 [598, 808]	<0.001
HIV RNA ($\log_{10}$ copies/mL)	4.1 [3.5, 4.6]	3.9 [3.3, 4.5]	4.3 [3.7, 4.7]	4.1 [3.5, 4.6]	4.4 [3.9, 4.9]	3.8 [3.0, 4.5]	<0.001

[a] Excluding participants without 12-lead electrocardiogram (ECG) data.

[b] Unadjusted p-value comparing regions.

Table 2

Prevalence of cardiovascular risk factors – START baseline (2009–2013)

Risk Factor, N(%)	Overall *N=4019*	North America *N=456*	Europe/Australia/Israel *N=1428*	South America *N=1048*	Asia *N=154*	Africa *N=933*	Region p-value[a]
Smoking status							<0.001
Current	1287 (32.0)	165 (36.2)	665 (46.6)	296 (28.2)	26 (16.9)	135 (14.5)	
Former	531 (13.2)	64 (14.0)	198 (13.9)	172 (16.4)	30 (19.5)	67 (7.2)	
Never	2201 (54.8)	227 (49.8)	565 (39.6)	580 (55.3)	98 (63.6)	731 (78.3)	
Body mass index (BMI) (kg/m^2)							<0.001
Underweight (< 18.5)	107 (2.7)	10 (2.2)	26 (1.8)	19 (1.8)	17 (11.0)	35 (3.8)	
Normal (18.5 – 24.9)	2092 (52.1)	166 (36.4)	861 (60.3)	559 (53.3)	112 (72.7)	394 (42.2)	
Overweight (25.0 – 29.9)	1156 (28.8)	142 (31.1)	411 (28.8)	349 (33.3)	20 (13.0)	234 (25.1)	
Obese (> 30)	664 (16.5)	138 (30.3)	130 (9.1)	121 (11.5)	5 (3.2)	270 (28.9)	
Diabetes mellitus	133 (3.3)	30 (6.6)	36 (2.5)	18 (1.7)	2 (1.3)	47 (5.0)	0.001
Prior CVD (past history or ECG)	182 (4.5)	21 (4.6)	66 (4.6)	32 (3.1)	6 (3.9)	57 (6.1)	0.43
Myocardial infarction (ECG or past history)	37 (0.9)	9 (2.0)	20 (1.4)	4 (0.4)	0 (0.0)	4 (0.4)	
Stroke (past history)	6 (0.1)	2 (0.4)	2 (0.1)	2 (0.2)	0 (0.0)	0 (0.0)	
Coronary revascularisation (past history)	10 (0.2)	4 (0.9)	5 (0.4)	0 (0.0)	1 (0.6)	0 (0.0)	
Myocardial ischaemia (ECG)[b]	146 (3.6)	12 (2.6)	47 (3.3)	27 (2.6)	5 (3.2)	55 (5.9)	
Hypertension	776 (19.3)	134 (29.4)	276 (19.3)	155 (14.8)	13 (8.4)	198 (21.2)	<0.001
Dyslipidemia	333 (8.3)	77 (16.9)	127 (8.9)	66 (6.3)	20 (13.0)	43 (4.6)	<0.001
Number of risk factors[c]							
None	1675 (41.7)	137 (30.0)	499 (34.9)	530 (50.6)	97 (63.0)	412 (44.2)	<0.001
At least one	2344 (58.3)	319 (70.0)	929 (65.1)	518 (49.4)	57 (37.0)	521 (55.8)	<0.001
Only one	1583 (39.4)	163 (35.7)	645 (45.2)	383 (36.5)	47 (30.5)	345 (37.0)	<0.001
Two or more	761 (18.9)	156 (34.2)	284 (19.9)	135 (12.9)	10 (6.5)	176 (18.9)	<0.001

[a] p-value adjusted for age and gender

[b] Defined as major ST depression or T wave inversion by Minnesota ECG classification on the 12-lead ECG

[c] Composite of current smoker, BMI > 30 kg/m^2, diabetes, prior CVD, hypertension or dyslipidemia

CVD=cardiovascular disease

Table 3

Distribution of favourable cardiovascular risk profile[a] – START baseline (2009–2013)

N(%)	Overall *N=4019*	North America *N=456*	Europe/Australia/Israel *N=1428*	South America *N=1048*	Asia *N=154*	Africa *N=933*	Region p-value[b]
All participants	988 (24.6)	86 (18.9)	214 (15.0)	344 (32.8)	35 (22.7)	309 (33.1)	<0.001
Men[c]	649 (21.8)	74 (20.3)	191 (14.6)	287 (31.9)	26 (21.0)	71 (25.4)	<0.001
Women[c]	339 (32.6)	12 (13.2)	23 (19.7)	57 (38.3)	9 (30.0)	238 (36.4)	<0.001

[a] Favourable cardiovascular risk profile defined as total cholesterol < 200 mg/dL, systolic blood pressure ≤ 120 mmHg, diastolic blood pressure ≤ 80 mmHg, no current smoking, no diabetes and no prior CVD (past history or baseline ECG)

[b] p-value adjusted for age

[c] Percent within subgroup

Table 4

Estimated 10-year cardiovascular risk – START baseline (2009–2013)

Risk Score, Median[IQR] or N(%)	Overall *N=4019*	North America *N=456*	Europe/Australia/Israel *N=1428*	South America *N=1048*	Asia *N=154*	Africa *N=933*	Region p-value[a]
Framingham CVD risk score[b]	2.9 [1.3, 6.2]	3.5 [1.4, 8.4]	4.0 [1.9, 8.4]	2.2 [1.0, 5.1]	1.6 [0.8, 3.2]	2.1 [1.0, 4.4]	<0.001
Risk < 10%	3430 (86.3)	355 (78.9)	1120 (80.3)	939 (89.7)	144 (93.5)	872 (93.7)	
Risk 10 – <20%	389 (9.8)	59 (13.1)	197 (14.1)	82 (7.8)	6 (3.9)	45 (4.8)	
Risk ≥ 20%	157 (3.9)	36 (8.0)	77 (5.5)	26 (2.5)	4 (2.6)	14 (1.5)	
Framingham CHD risk score [c]	3.0 [1.5, 5.9]	3.3 [1.8, 6.3]	4.1 [2.2, 7.3]	2.8 [1.4, 5.1]	2.1 [1.0, 3.8]	2.0 [0.7, 4.4]	<0.001
Risk < 10%	3601 (90.6)	397 (88.2)	1217 (87.3)	964 (92.1)	146 (94.8)	877 (94.2)	
Risk 10 – <20%	306 (7.7)	38 (8.4)	146 (10.5)	75 (7.2)	6 (3.9)	41 (4.4)	
Risk ≥ 20%	69 (1.7)	15 (3.3)	31 (2.2)	8 (0.8)	2 (1.3)	13 (1.4)	
D:A:D CVD risk score[d]	1.8 [0.9, 3.5]	2.1 [1.1, 4.1]	2.5 [1.3, 4.8]	1.5 [0.8, 2.9]	1.1 [0.7, 2.1]	1.2 [0.7, 2.4]	<0.001
Risk < 10%	3801 (95.6)	413 (91.8)	1299 (93.2)	1022 (97.6)	151 (98.1)	916 (98.4)	
Risk 10 – <20%	143 (3.6)	31 (6.9)	76 (5.5)	21 (2.0)	2 (1.3)	13 (1.4)	
Risk ≥ 20%	32 (0.8)	6 (1.3)	19 (1.4)	4 (0.4)	1 (0.6)	2 (0.2)	
D:A:D CHD risk score[d]	1.4 [0.7, 2.9]	1.6 [0.9, 3.2]	2.0 [1.1, 4.0]	1.2 [0.6, 2.4]	0.9 [0.5, 1.8]	0.9 [0.5, 1.8]	<0.001
Risk < 10%	3861 (97.1)	422 (93.8)	1334 (95.7)	1030 (98.4)	151 (98.1)	924 (99.2)	
Risk 10 – <20%	94 (2.4)	25 (5.6)	47 (3.4)	13 (1.2)	2 (1.3)	7 (0.8)	
Risk ≥ 20%	21 (0.5)	3 (0.7)	13 (0.9)	4 (0.4)	1 (0.6)	0 (0.0)	

[a] P-value adjusted for age and sex.

[b] Score based on age, gender, total and HDL cholesterol, systolic blood pressure, use of blood pressure lowering medications, current smoking, and diabetes

[c] Score based on Joint National Committee (JNC-V) blood pressure groups, National Cholesterol Education Program (NCEP) total and HDL cholesterol categories, age, gender, current smoking, diabetes

[d] Score based on age, gender, current smoker, ex-smoker, total and HDL cholesterol, systolic blood pressure, and diabetes. No data available on family CVD and no prior ART use in START, and therefore ART use was set to zero and no prior history was assumed in the calculation of the D:A:D risk prediction equations.

CVD=cardiovascular disease; CHD=coronary heart disease.