



Framingham Risk Score and Early Markers of Atherosclerosis in a Cohort of Adults Infected with HIV

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Abstract:

Background: Cardiovascular (CV) complications in HIV infection appear to be prevalent and therefore concerning. The Framingham risk score (FRS) is used to predict CV events in the general population. However, its application in individuals infected with HIV is not clear. We examined the association of Framingham risk scores with surrogate markers of atherosclerosis in a carefully characterized cohort of adults infected with HIV.

Methods: We calculated Framingham risk scores, and measured carotid intima-media thickness (c-IMT) and coronary artery calcium (CAC) scores in 334 Nutrition for Healthy Living (NFHL) participants. We assessed CV risk factors, HIV viral load, CD4 count, HAART use, c-IMT and CAC scores for each Framingham risk subgroup (low vs intermediate/high risk) using χ^2 test for binary and student t-test for continuous variables. We performed multivariate logistic regression of surrogate markers by Framingham risk group.

Results: Subjects with intermediate/high FRS were older ($p < .001$), male ($p < .001$), with higher serum CRP levels ($p = .03$) and a longer duration of HIV infection ($p = .03$). Patients with intermediate/high FRS were more likely to have internal c-IMT ≥ 1.0 mm (21.1% vs 9.2%, $p = .003$) and common c-IMT ≥ 0.8 mm (16.2% vs 2.2%, $p < .001$). Patients with intermediate/high FRS were also more likely to have detectable CAC (70.6% vs 41.6%, $p < .001$). In the multivariate analysis, intermediate/high FRS were significantly associated with internal c-IMT ≥ 1.0 mm (OR: 2.22, 1.12-4.43) and common c-IMT ≥ 0.8 mm (OR: 0.70, 2.33-21.42). Intermediate/high FRS were also significantly associated with detectable CAC (OR: 3.44, 2.11-5.63).

Conclusions: Our study shows that elevated Framingham risk scores are associated with abnormal early and late surrogate markers of atherosclerosis in adults infected with HIV, and may predict the risk of CV complications in this population. Our findings support the use of the Framingham predictive instrument for CV risk stratification in individuals infected with HIV.

Introduction:

Given the increasing prevalence of cardiovascular disease (CVD) in adults infected with HIV, assessment of cardiovascular risk should be performed on a regular basis.

In the general population, the Framingham risk score (FRS) has been validated as a tool to estimate cardiovascular risk¹.

However, the accuracy of the FRS in the HIV-infected population remains unclear.

If the FRS is associated with the presence of atherosclerosis in the HIV population, then it may serve as a valuable screening tool for cardiovascular risk stratification.

Surrogate markers of CVD include coronary artery calcium (CAC) scores and, ultrasonographic measurements of common and internal carotid intima-media thickness (c-IMT).

In this study, we analyzed the association of the Framingham risk equation with c-IMT and CAC scores in a cohort of adults infected with HIV.

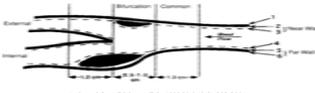
Methods:

Cross-sectional analysis.
334 participants from the NFHL study, a longitudinal cohort that examines nutritional and metabolic issues in HIV-infected patients at 6 month intervals.

For the c-IMT measurements, multiple images were obtained of the right and left CCA, and ICA by high-resolution B ultrasound: 1 longitudinal lateral view of the distal 10 mm of right and left CCA of neck, and far wall; 3 longitudinal views in different imaging planes (anterior, lateral and posterior) of right and left ICA of neck, and far wall².

The mean of the maximum of near, and far-wall c-IMT measurements was used for the final analysis.

Quality control analysis of 32 subjects resulted in intra-class correlation coefficients of 0.911 for CCA and 0.883 for ICA.



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CAC score was obtained by CT³.

FRS were calculated based on the algorithm presented by Wilson et al.¹

Demographic and clinical data were obtained within 12 months of the carotid ultrasound and CT.

Statistical analyses were performed with SAS for windows, version 9.0 (SAS Institute, Cary, NC).

Non-normally distributed variables were log transformed and non-parametric measures were applied where necessary.

We assessed CVD risk factors, HIV viral load, CD4 count, HAART use, c-IMT and CAC scores for each Framingham risk subgroup (low risk < 6% vs. intermediate/high risk $\geq 6\%$) using χ^2 test for binary and student t-test for continuous variables.

We performed multivariate logistic regression of surrogate markers by Framingham risk group adjusted for race, BMI, hs-CRP, CD4+cell count, HIV RNA level, duration of HIV infection and duration of HAART.

P values of < 0.05 were considered statistically significant.

Results:

Table 1. Demographic and clinical characteristics by 10-year CVD risk

Variable	Low (<6%)	Intermediate/High ($\geq 6\%$)	P
N	180	154	
Age, years	41.3 \pm 6.4	47.8 \pm 6.7	<.001
Men	109 (60.6)	139 (90.3)	<.001
Women	71 (39.4)	15 (9.7)	
Ethnicity:			
African American	61 (33.9)	54 (35.1)	.52
Latino/Hispanic	17 (9.2)	6 (3.2)	
White	92 (51.1)	84 (54.6)	
Other	10 (5.6)	8 (5.2)	
Family history of CHD (N=320)	20 (11.6)	14 (9.5)	.53
Family history of stroke (N=319)	14 (8.2)	13 (8.8)	.85
Smoker	82 (45.6)	83 (53.9)	.13
Non-smoker	98 (54.4)	71 (46.1)	
IV drug use:			
Currently using	5 (2.8)	4 (2.6)	.92
Never used	113 (62.8)	98 (63.6)	.87
Body mass index, kg/m ²	26.8 \pm 5.8	26.8 \pm 4.7	.99
Waist circumference, cm	91.0 \pm 13.1	94 \pm 11.5	.03
Systolic blood pressure, mmHg	113.2 \pm 14.1	124.2 \pm 17.4	<.001
Diastolic blood pressure, mmHg	72.8 \pm 8.8	78.9 \pm 11.3	<.001
Ever had hypertension	28 (15.6)	43 (27.9)	.006
Glucose, mg/dL	82.7 \pm 19.1	86.3 \pm 23.5	.14
QUICKI	0.347 \pm 0.036	0.338 \pm 0.037	.02
Cholesterol level, mg/dL:			
Total	173.2 \pm 41.6	203.5 \pm 52.6	<.001
LDL	101.1 \pm 33.2	121.0 \pm 40.7	<.001
HDL	45.2 \pm 18.7	37.5 \pm 16.8	<.001
Triglycerides, mg/dL	134.5 \pm 88.2	235.6 \pm 213.3	<.001
ApoA1 level, mg/dL	134.0 \pm 30.9	122.0 \pm 28.0	<.001
ApoB level, mg/dL	76.6 \pm 17.3	94.3 \pm 20.1	<.001
ApoE level, mg/dL	4.3 \pm 1.6	5.4 \pm 3.0	<.001
Homocysteine	8.7 \pm 3.8	9.2 \pm 3.9	.31
hs-CRP reactive protein, mg/L	2.4 \pm 2.9	3.6 \pm 6.5	.03
Total fat intake, g	101.5 \pm 48.3	104.7 \pm 45.7	.54

Table 2. HIV and treatment characteristics by 10-year CVD risk

Variable	Low (<6%)	Intermediate/High ($\geq 6\%$)	P
N	180	154	
Duration of HIV infection, years	9.2 \pm 4.8	10.4 \pm 4.7	.02
CD4+cell count, cells/mm ³	454.8 \pm 270.2	453.9 \pm 329.5	.98
HIV RNA level, log copies/ml ³	3.05 \pm 1.02	3.12 \pm 1.08	.50
On HAART	132 (73.3)	114 (74.0)	.89
Never been on HAART	43 (23.9)	35 (22.7)	.06
Duration of HAART, months	28.9 \pm 25.0	34.6 \pm 25.8	.05
On PI	80 (44.4)	71 (46.1)	.76
On NNRTI	57 (31.6)	52 (33.8)	.68

Note: Data are no. (%) or mean \pm SD. P-values reflect log-transformed data for non-normally distributed variables. CHD, coronary heart disease; Apo, apolipoprotein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; QUICKI, quantitative insulin sensitivity check index; hs-CRP, high sensitivity C-reactive protein; HAART, highly active anti-retroviral therapy; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor.

Results:

Table 3. Surrogate markers by 10-year CHD risk

Surrogate marker	Low (<6%) (N=180)	Intermediate/High ($\geq 6\%$) (N=154)	P
c-IMT measurement			
Common	0.54 (0.48-0.60)	0.61 (0.54-0.70)	<.001
Internal	0.55 (0.49-0.64)	0.65 (0.58-0.95)	<.001
c-IMT measurement cutoff*			
Common	4 (2.2)	25 (16.2)	<.001
Internal	16 (9.2)	31 (21.1)	.003
	(N=173)	(N=146)	
Coronary artery calcium score			
0	101 (58.4)	43 (29.5)	<.001
>0	72 (41.6)	103 (70.6)	

Note: Data are no. (%) of patients or median (inter-quartile range). c-IMT, carotid intima-media thickness. P-values reflect log-transformed data for non-normally distributed variables.

* The cutoff for common c-IMT was 0.8 mm, and the cutoff for internal c-IMT was 1.0 mm.

Table 4. Variables Correlating with Surrogate Markers by Univariate Logistic Regression Analysis

Marker, predictor variable	Univariate model estimate, Mean value \pm SE	P
Internal c-IMT		
Framingham Risk Score (Low vs Intermediate/High Risk)	0.970 \pm 0.331	.003
Hs-CRP	0.380 \pm 0.144	.008
Duration of HAART	0.012 \pm 0.006	.05
Common c-IMT		
Framingham Risk Score (Low vs Intermediate/High Risk)	2.143 \pm 0.551	<.001
Hs-CRP	0.404 \pm 0.175	.02
CAC Score		
Framingham Risk Score (Low vs Intermediate/High Risk)	1.212 \pm 0.238	<.001
Body mass index	0.065 \pm 0.024	.007
Hs-CRP	0.333 \pm 0.104	.001

Note: All non-normally distributed variables were log-transformed. c-IMT, carotid intima-media thickness; CAC, coronary artery calcium; CHD, coronary heart disease; hs-CRP, high sensitivity C-reactive protein.

Table 5. ORs (95% CIs) of Abnormal Surrogate Markers Comparing Patients with Low vs Intermediate/High 10-year CHD Risk

Surrogate Marker	Adjusted OR (95% CI) ^a	C-Statistic	P
Common c-IMT measurement: ≥ 0.8 mm vs. < 0.8 mm	7.067 (2.332-21.421)	0.773	.001
Internal c-IMT measurement: ≥ 1.0 mm vs. < 1.0 mm	2.222 (1.166-4.426)	0.670	.023
CAC Score 0 vs. > 0	3.444 (2.105-5.635)	0.710	<.001

Note: All surrogate markers were log-transformed. c-IMT, carotid intima-media thickness; CAC, coronary artery calcium.

^a Multivariate analysis for internal and common c-IMT was adjusted for race, hs-CRP, CD4+cell count, HIV RNA level and duration of HAART. Multivariate analysis for CAC was adjusted for race, hs-CRP, CD4+cell count, HIV RNA level and BMI.

Summary of Results:

Of the participants, 74.3% were men, the mean age was 44.3 \pm 7.3 years, 52.7% were Caucasian and 49.5% were smokers.

The mean FRS for the total population was 7.0% \pm 5.2%.

Individuals with Intermediate/High FRS were older, more likely to be male and have a history of hypertension.

Patients with Intermediate/High FRS had higher waist circumference, blood pressure (systolic and diastolic), serum cholesterol levels (total, LDL), serum triglyceride levels, serum apolipoprotein levels (A1, B, E) and serum hs-CRP levels.

Of the participants, 73.7% were on HAART, with 45.2% on a PI-based regimen and 32.6% on an NNRTI-based regimen.

Individuals with Intermediate/High FRS had a longer duration of HIV infection and HAART, but did not show a significant difference in CD4+ count or HIV viral load, and were not more likely to be on a PI or NNRTI-based regimen.

The median of common c-IMT for the total population was 0.58 (0.51-0.66) and the median of internal c-IMT was 0.60 (0.51-0.76).

A higher proportion of patients with Intermediate/High FRS had common c-IMT ≥ 0.8 mm ($p < .001$) and internal c-IMT ≥ 1.0 mm ($p < .001$).

Of the total population, 54% had detectable CAC scores.

Patients with Intermediate/High FRS were more likely to have detectable CAC scores ($p < .001$).

In the univariate analysis, FRS and hs-CRP were associated with c-IMT (common and internal) and CAC score.

In the multivariate analysis, Intermediate/High FRS independently predicted higher common and internal c-IMT, and detectable CAC scores.

Conclusions:

The accelerated onset of CVD is a concerning complication of long-term HIV infection.

Traditional cardiovascular risk factors are prevalent in our cohort of patients infected with HIV.

Elevated Framingham risk scores are associated with abnormal early and late surrogate markers of atherosclerosis.

Framingham risk scores may predict the risk of cardiovascular complications in this population.

Our findings support the use of the Framingham predictive instrument for cardiovascular risk stratification in individuals infected with HIV.

References:

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