

LMAP
2023

LIVERPOOL MASTERCLASS IN
ANTIVIRAL PHARMACOLOGY



An update in Cardiovascular Prevention

Dr Thomas Heseltine

- HIV and Cardiovascular Disease
- Individualised Risk Prediction using imaging surrogates
- What's new in the world of Prevention?
- Risk Reduction Strategies

HIV and CVD

- HIV = double the risk of CVD event
- Traditional risk score perform poorly
- 16.4 events / 1000 person years¹

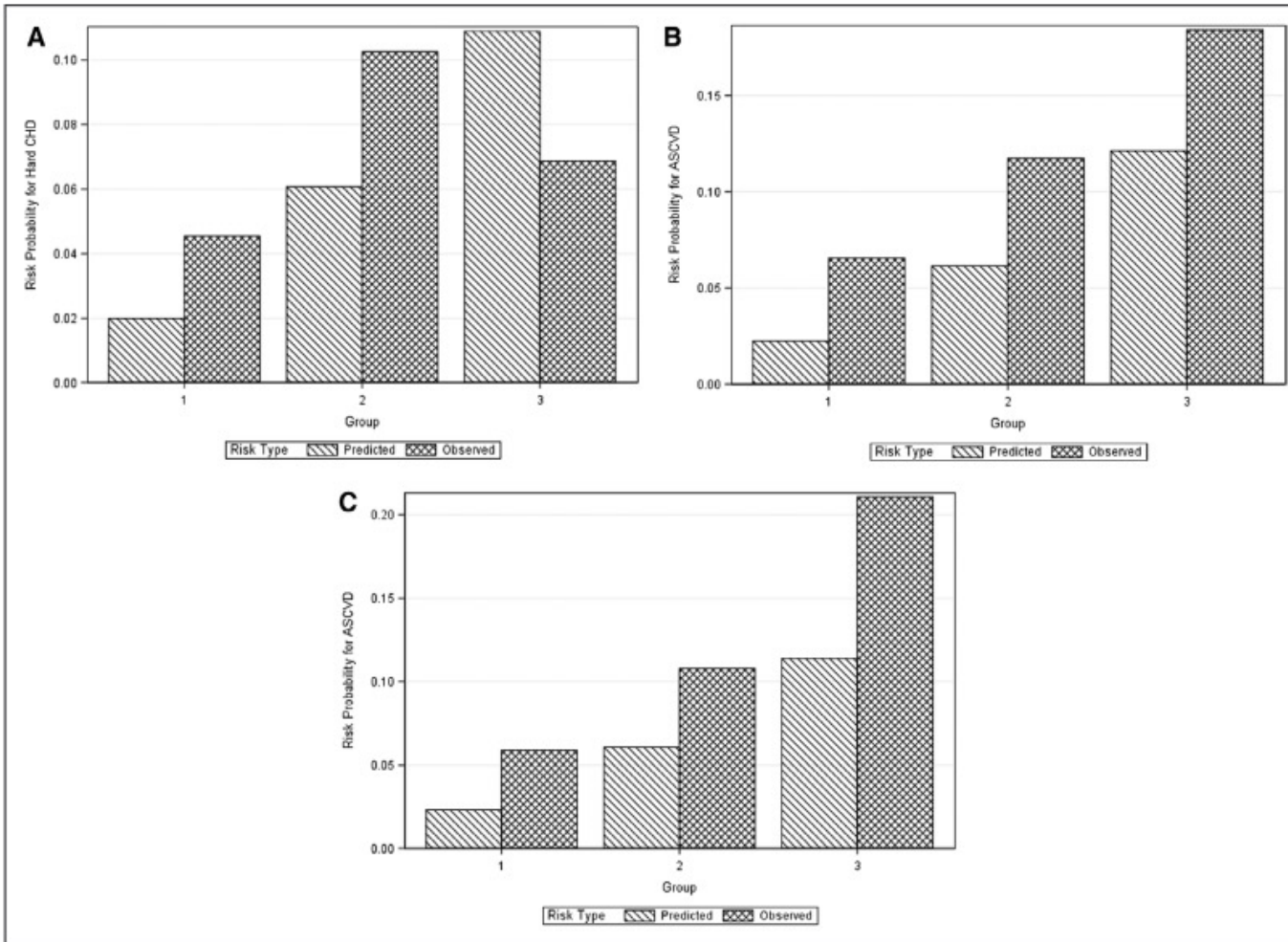
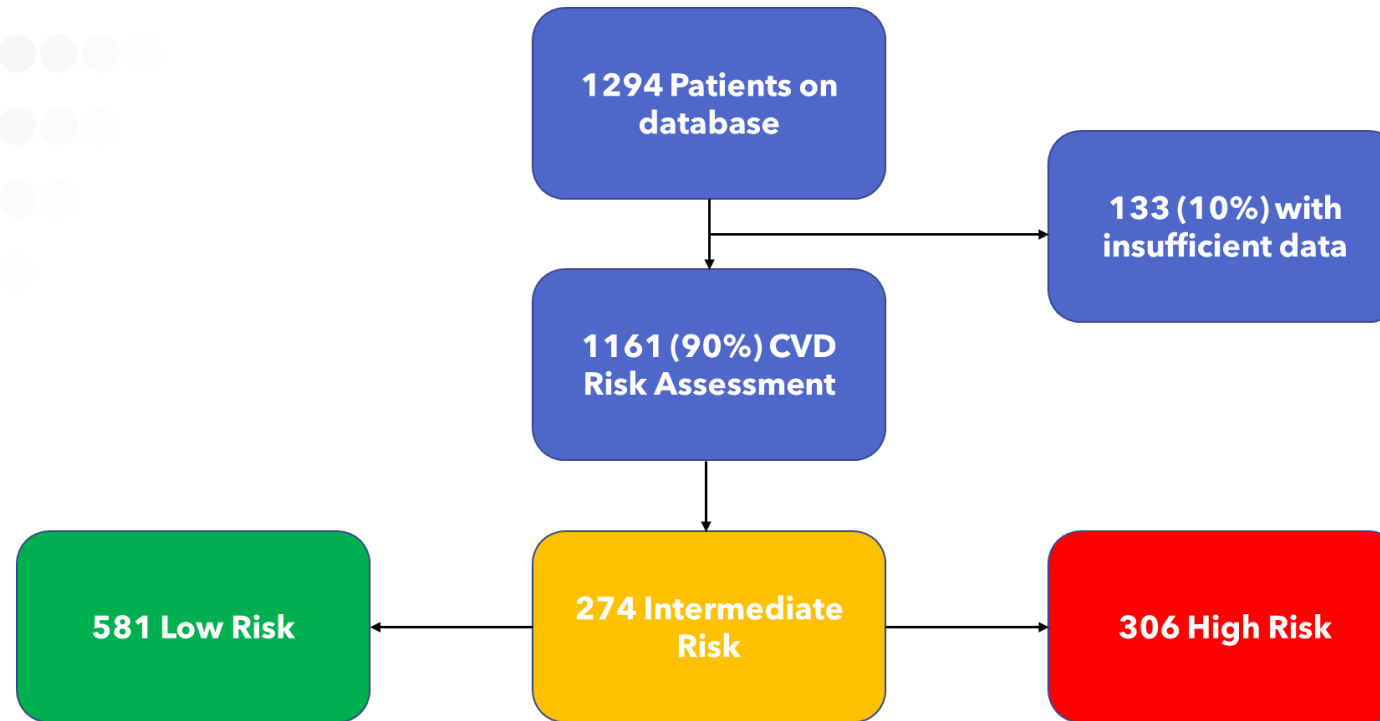


Figure 2. Observed and predicted 5-year risk by predicted risk group (Group 1:<5%, Group 2: 5%–7.5%, Group 3: >7.5%). **A,** FHS CHD. **B,** ACC/AHA. **C,** FHS ASCVD. ACC/AHA indicates American College of Cardiology/American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; and FHS, Framingham Heart Study.

¹Cardiovascular Risk Prediction Functions Underestimate Risk in HIV Infection. *Circulation*. 2018;137:2203–2214.

Merseyside HIV Database

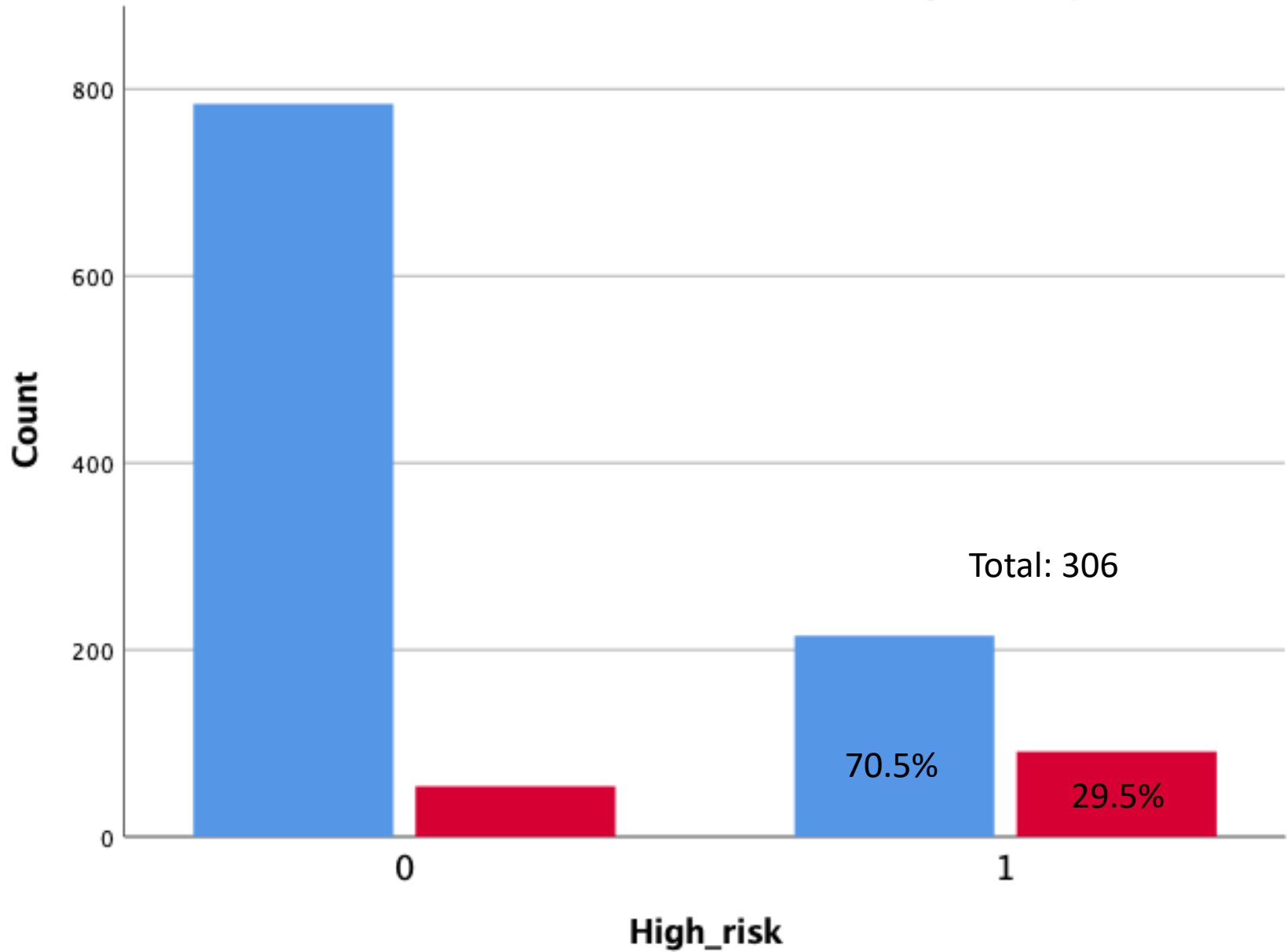


- Demographics, clinical characteristics, medications, FRS, Imaging

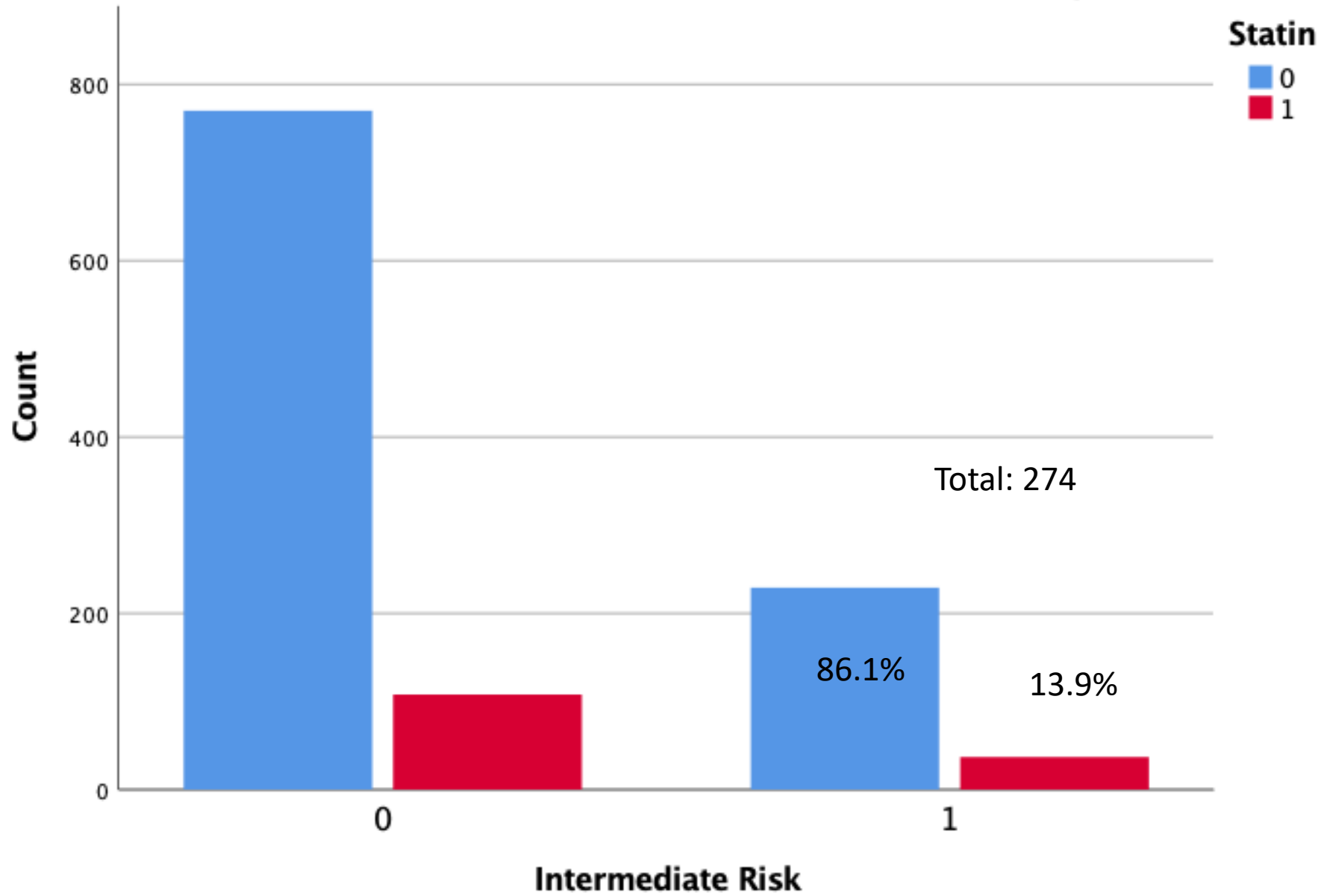
Clustered Bar Count of High_risk by Statin

Statin

- 0
- 1

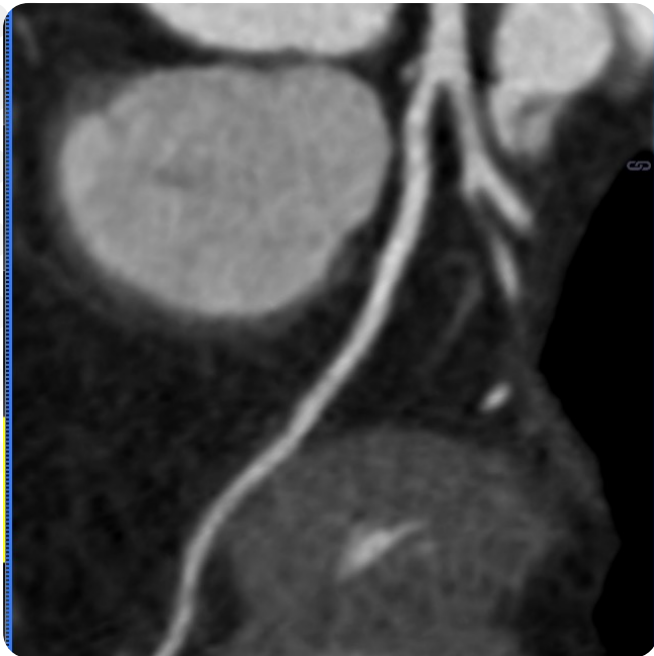


Clustered Bar Count of Intermediate Risk by Statin

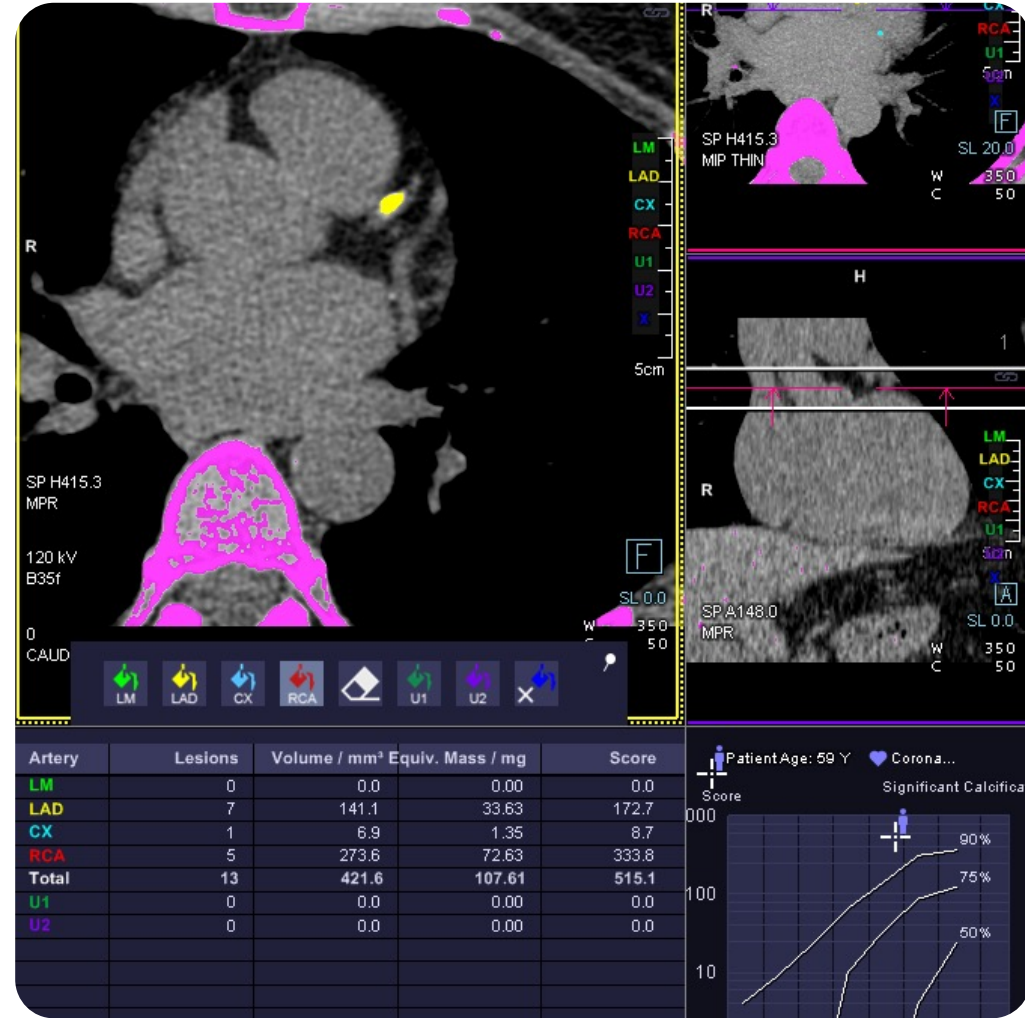


Surrogates for Risk

- Cardiovascular CT
- Calcium Score, CT coronary angiogram

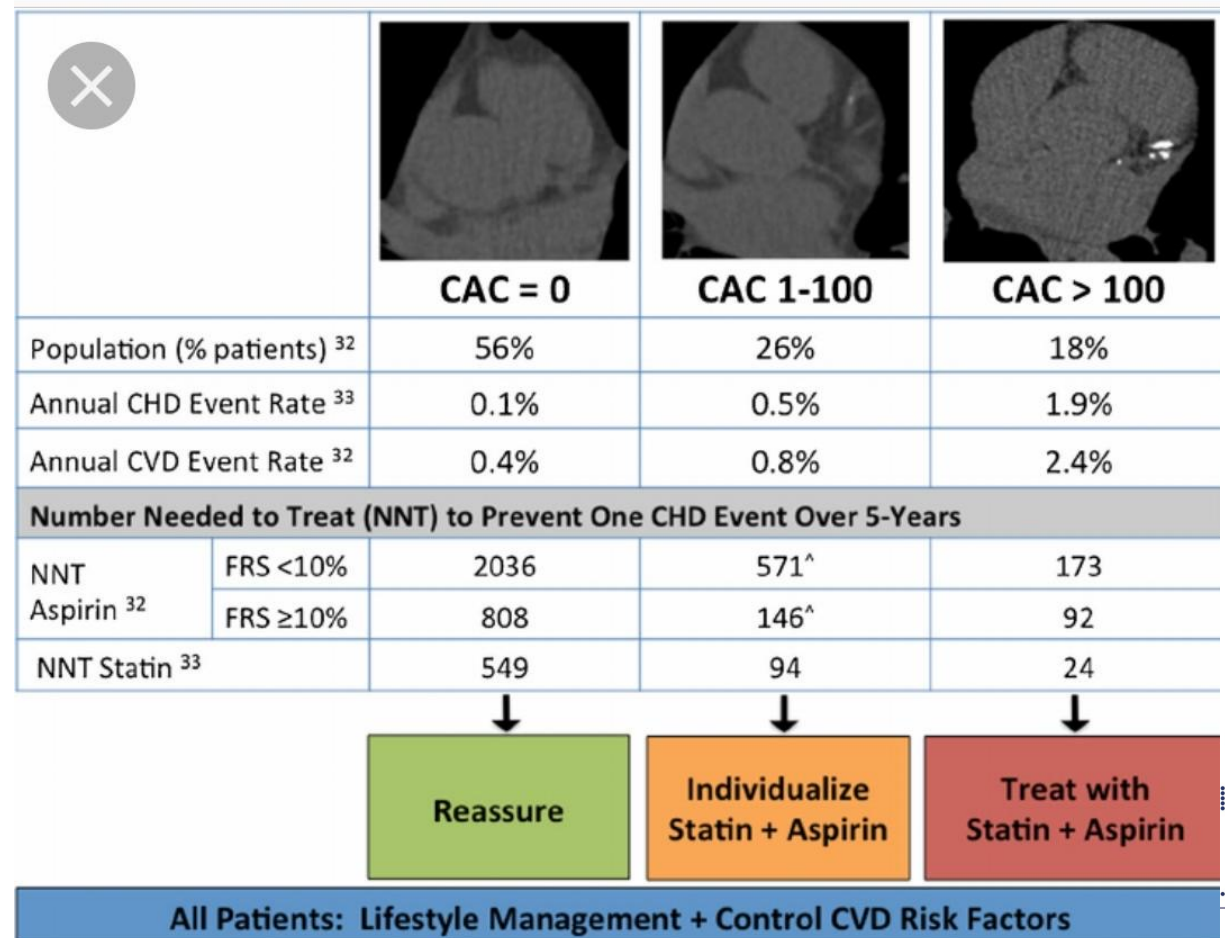


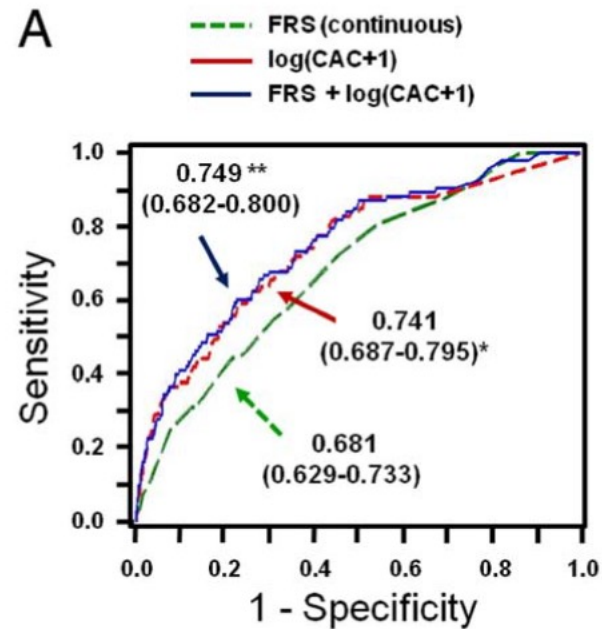
Calcium Score



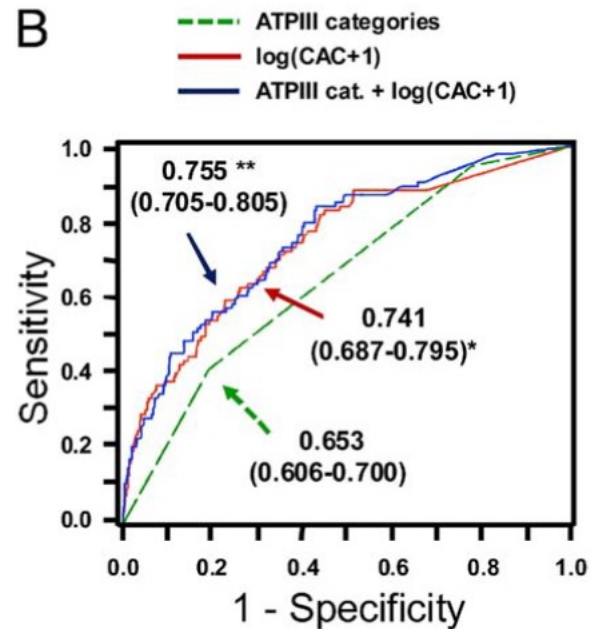
Cardiovascular Event Prediction and Risk Reclassification by Coronary, Aortic, and Valvular Calcification in the Framingham Heart Study

Udo Hoffmann, MD, MPH; Joseph M. Massaro, PhD; Ralph B. D'Agostino, Sr, PhD; Sekar Kathiresan, MD; Caroline S. Fox, MD, MPH; Christopher J. O'Donnell, MD, MPH





** $p=0.003$ versus FRS
 * $p=0.046$ versus FRS



** $p=0.0001$ versus ATPIII categories
 * $p=0.003$ versus ATPIII categories

Coronary Risk Stratification, Discrimination, and Reclassification Improvement Based on Quantification of Subclinical Coronary Atherosclerosis. JACC. 2010;56:1397-406

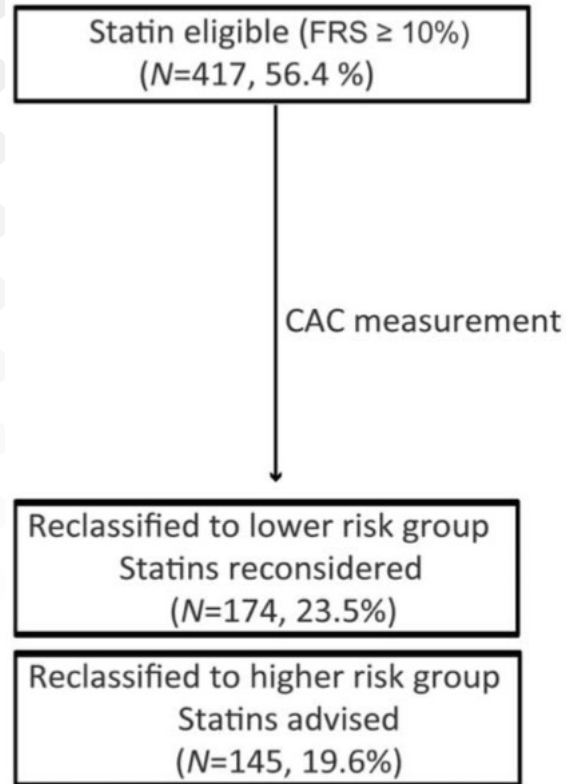


TABLE 2. Agreement and Correlation Between CVD Risk Scores and CAC Scores

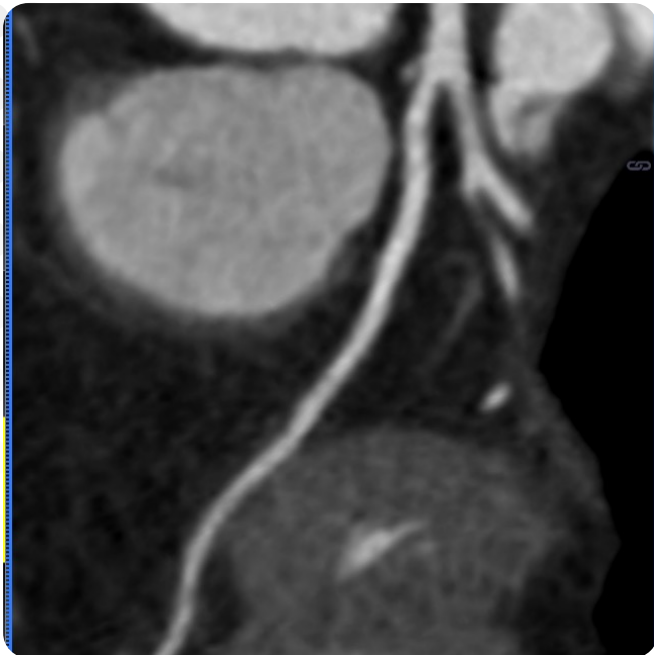
	κ	95% CI	P	Agreement		κ	95% CI	P	Agreement
FRS vs QRISK2	0.48	0.44–0.52	<0.01	Moderate	CAC vs FRS	0.07	0.02–0.12	>0.05	Poor
FRS vs DAD	0.43	0.39–0.47	<0.01	Moderate	CAC vs QRISK2	0.05	0.0–0.11	>0.05	Poor
QRISK2 vs DAD	0.37	0.33–0.42	<0.01	Fair	CAC vs DAD	0.06	0.01–0.13	>0.05	Poor

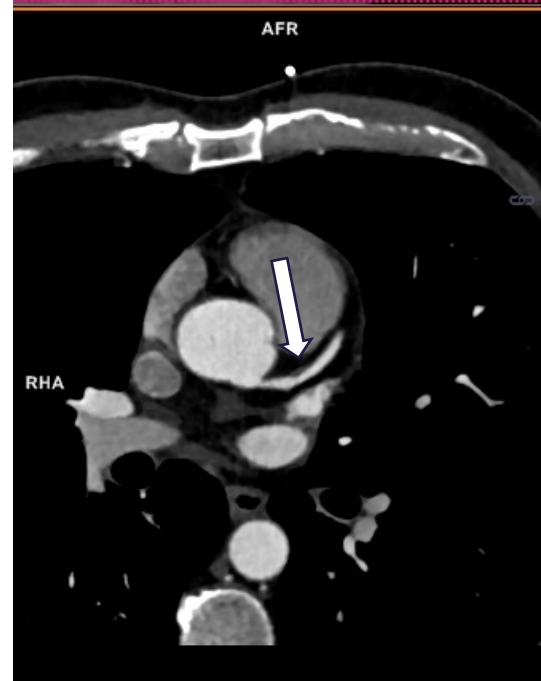
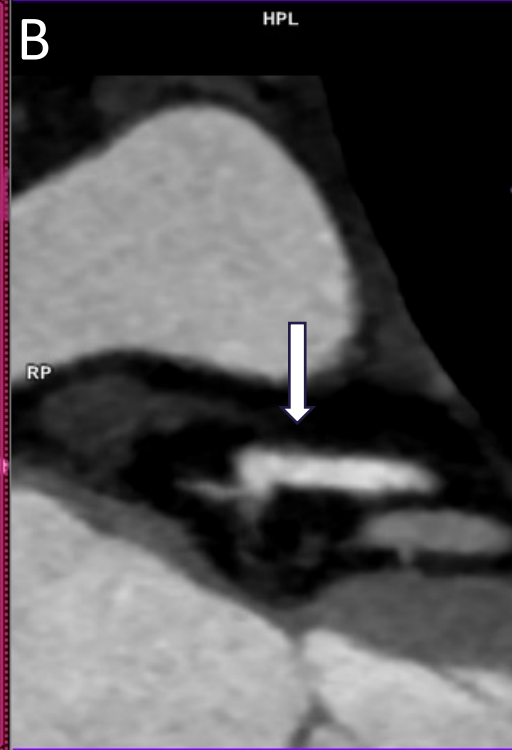
	R	P	Correlation		R	P	Correlation
FRS vs QRISK2	0.75	<0.001	Strong	CAC vs FRS	0.20	>0.05	Weak
FRS vs DAD	0.73	<0.001	Strong	CAC vs QRISK2	0.30	>0.05	Weak
QRISK2 vs DAD	0.68	<0.001	Strong	CAC vs DAD	0.21	>0.05	Weak



CTCA

1. Atherosclerotic plaque burden
2. Plaque morphology
3. Stenosis grading





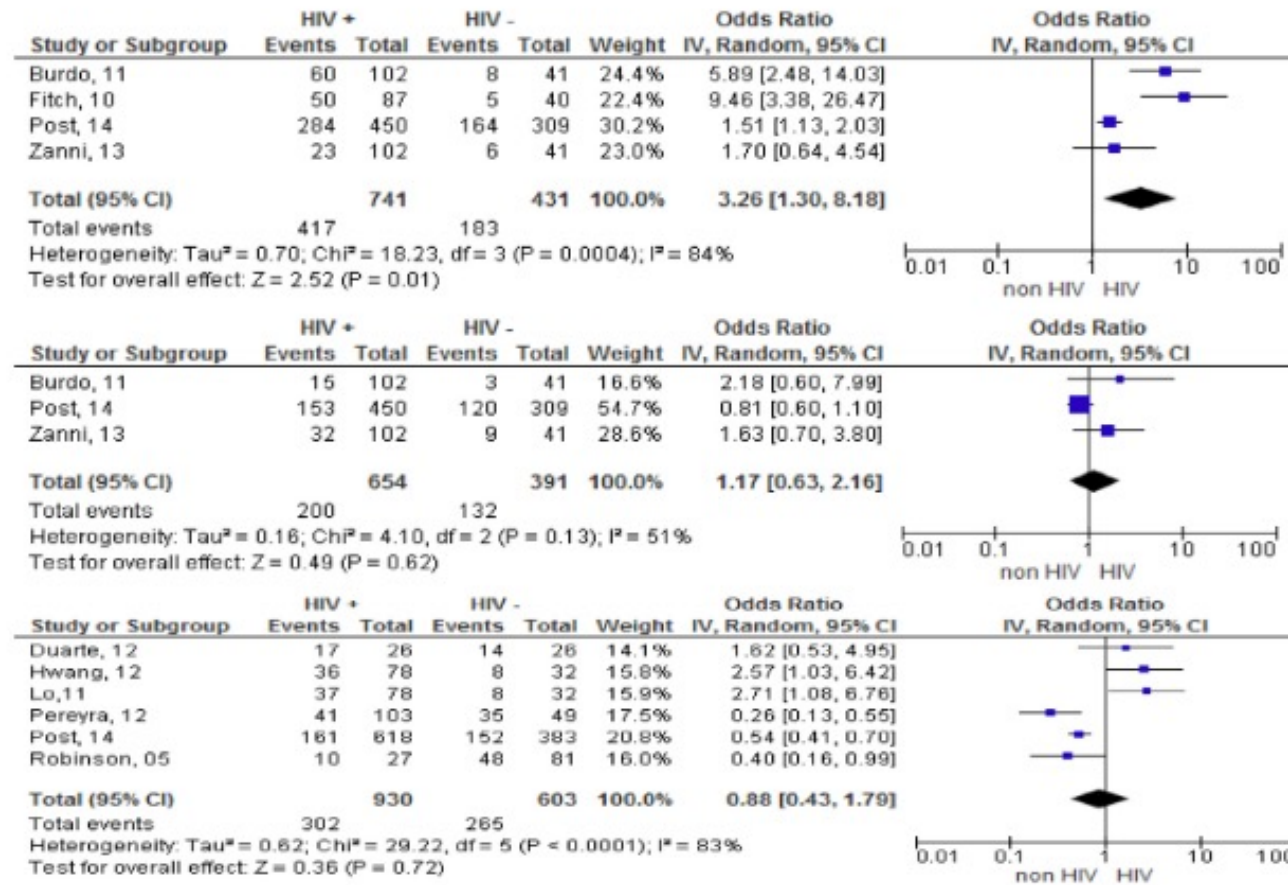
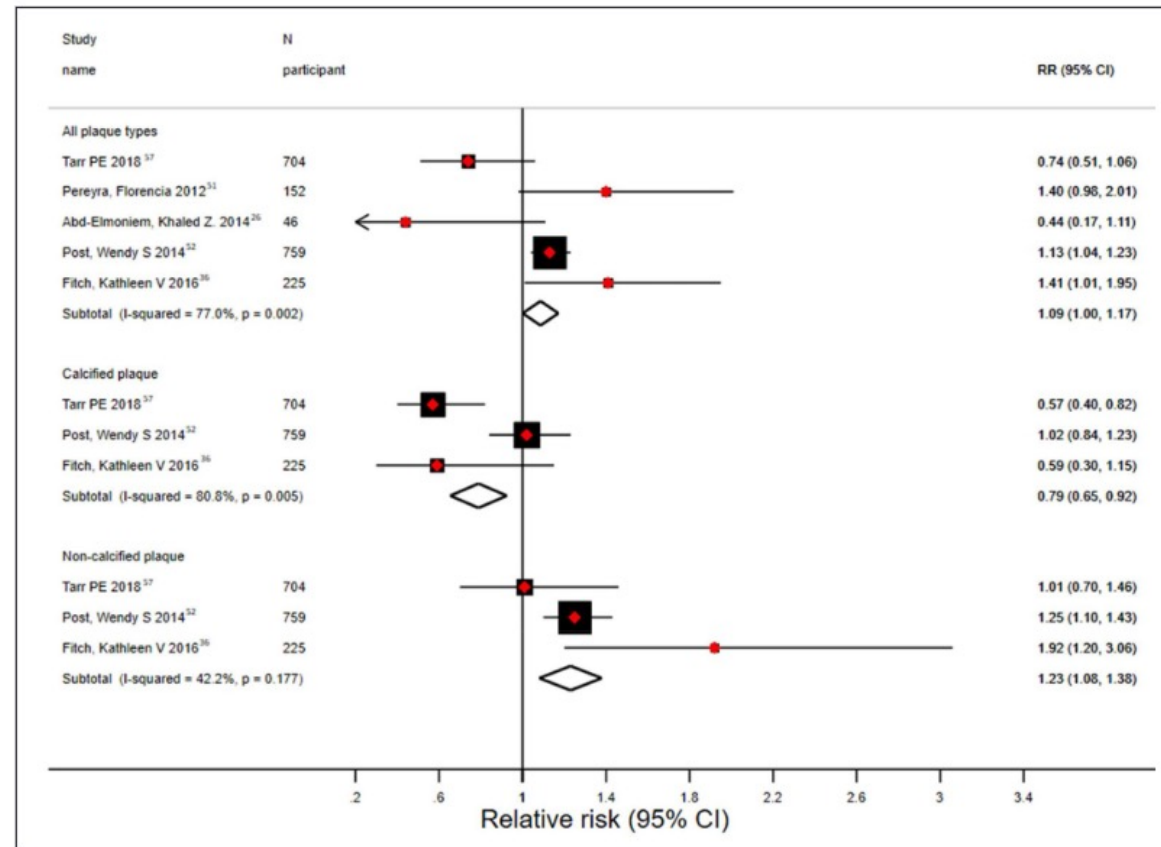


Fig. 4. Risk of non calcified, of calcified and of CAC more than 0 (from above to below).



- Poor disease control¹
- Use of PI²
- Abacavir
- Visceral adipose tissue

¹Suboptimal HIV suppression is associated with progression of coronary artery stenosis: The Multicenter AIDS Cohort Study (MACS) longitudinal coronary CT angiography study. *Atherosclerosis* 2022;353:33-40

²Cardiovascular disease and use of contemporary protease inhibitors: the D:A:D international prospective multicohort study, *Lancet HIV*.2018;5:291-300

- Fatty Liver
- Epicardial Adipose Tissue (EAT)
- Skeletal muscle
- Ectopic Fat

Panel B

Inflammatory response



Atherogenic lipid profile

Lipotoxicity

Hepatic gluconeogenesis

Coronary inflammation



Insulin Resistance

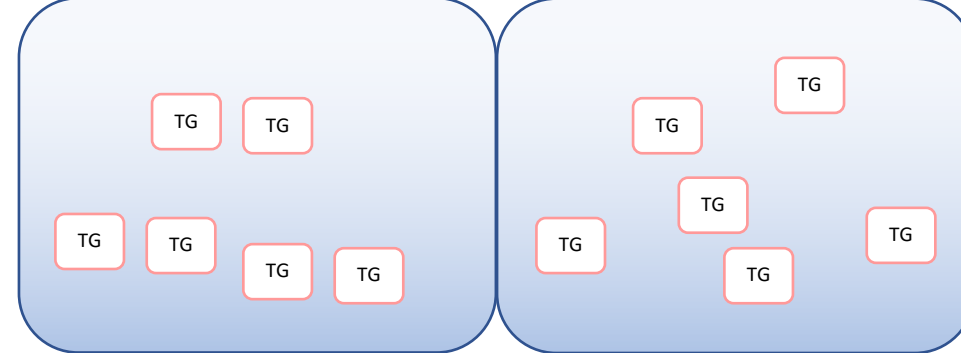
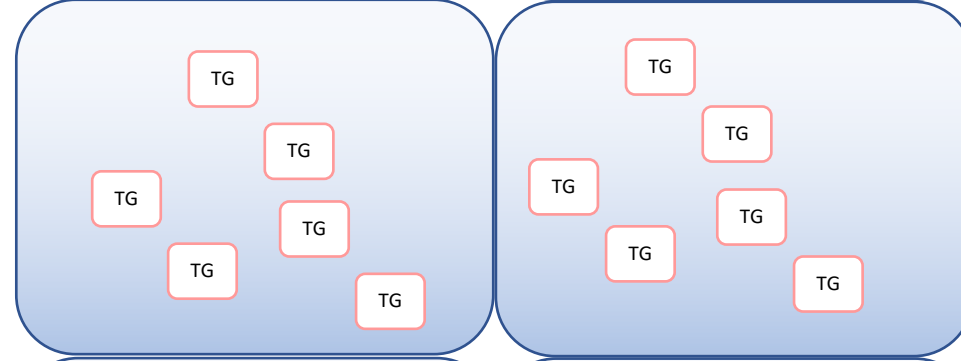
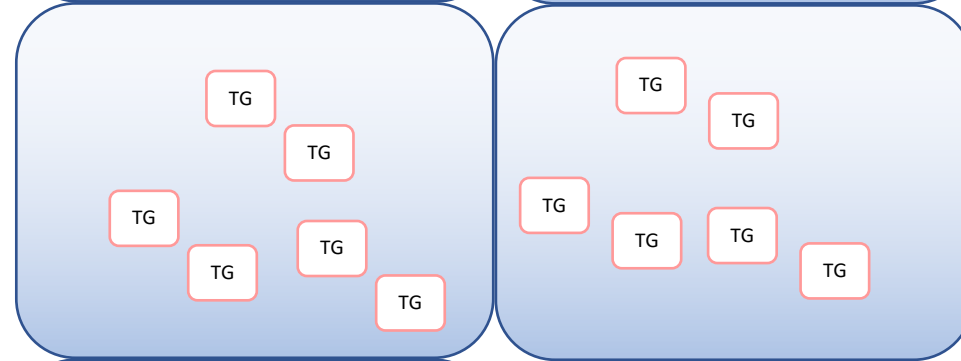
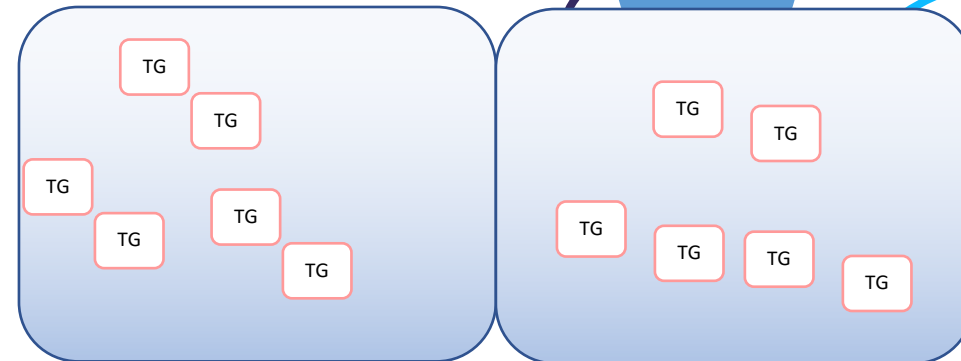
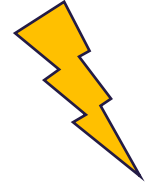
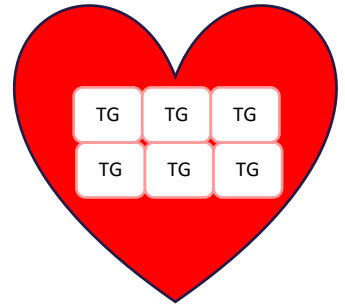
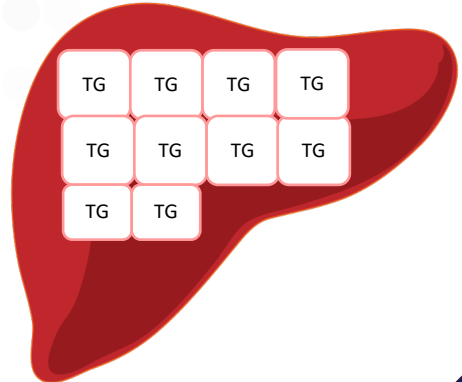


TABLE 2. Multivariate Analysis in HIV-Positive Patients for the Association of Coronary Calcification

	Odds Ratio (95% CI)	P
Age	1.15 (1.10 to 1.20)	<0.005*
Male sex	3.77 (1.37 to 11.69)	0.014*
Current smoker	2.14 (0.93 to 5.06)	0.077
HTN	0.58(0.19 to 1.67)	0.317
DMII	0.75 (0.14 to 3.45)	0.718
Dyslipidemia	2.89 (0.84 to 10.73)	0.097
HS	3.13 (1.51 to 6.63)	0.005*
Obesity	1.58 (0.70 to 3.56)	0.269

*Denotes significant association.

DMII, type II diabetes; HTN, hypertension; HS, hepatosteatosi.

TABLE 3. Multivariate Analysis in HIV-Negative Patients for the Association of Coronary Calcification

	Odds Ratio (95% CI)	P
Age	1.11 (1.09 to 1.13)	<0.005*
Male sex	2.97 (2.19 to 4.05)	<0.005*
Current smoker	1.96 (1.37 to 2.81)	<0.005*
HTN	1.39 (1.02 to 1.90)	0.04
DMII	1.14 (0.72 to 1.82)	0.58
Dyslipidemia	1.66 (1.24 to 2.22)	<0.005
HS	1.08 (0.81 to 1.44)	0.60
Obesity	0.95 (0.54 to 1.65)	0.87

*Denotes significant association.

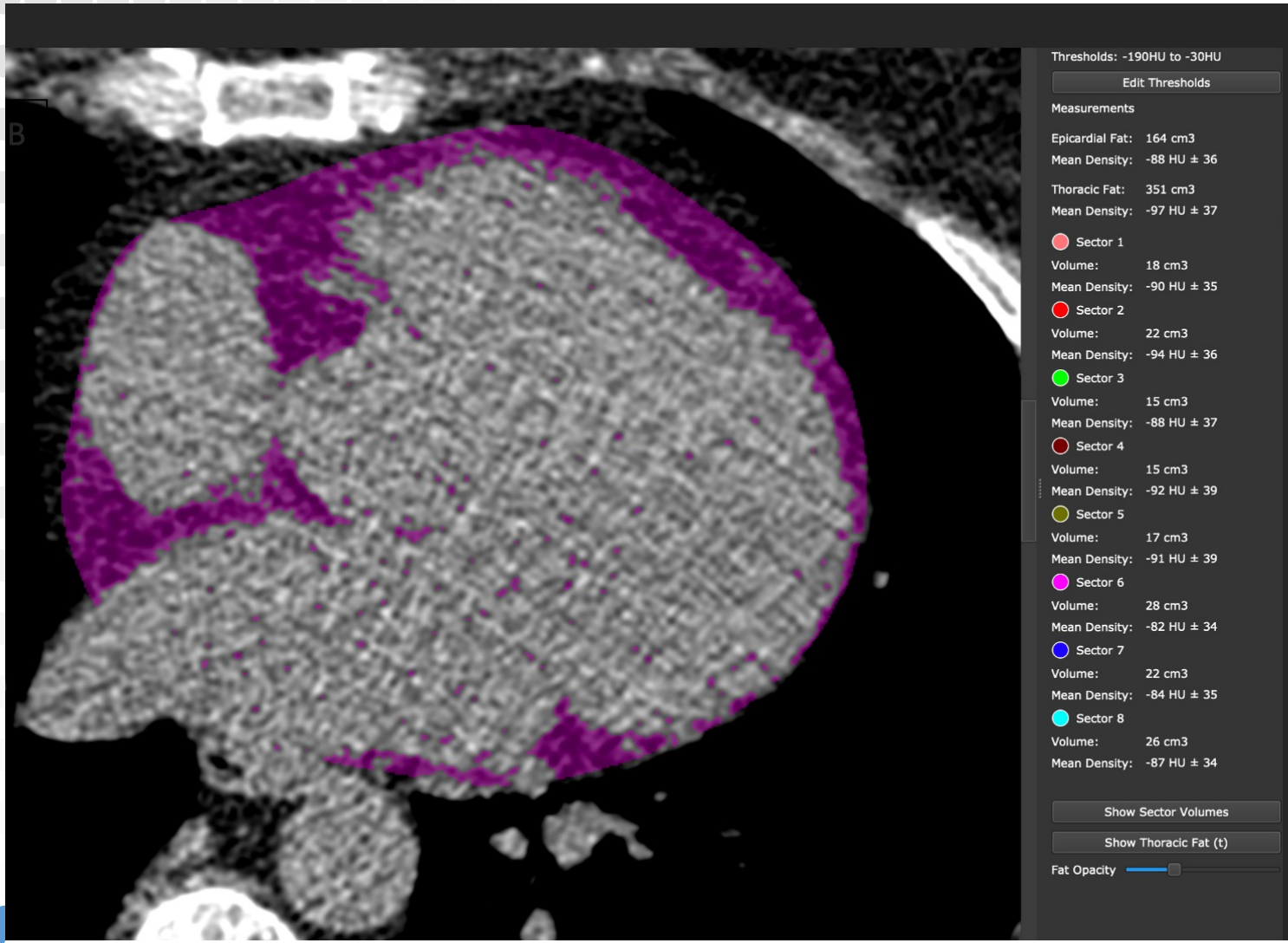
DMII, type II diabetes; HTN, hypertension; HS, hepatosteatosi.

TABLE 2. Factors Associated With NAFLD in Individuals With HIV

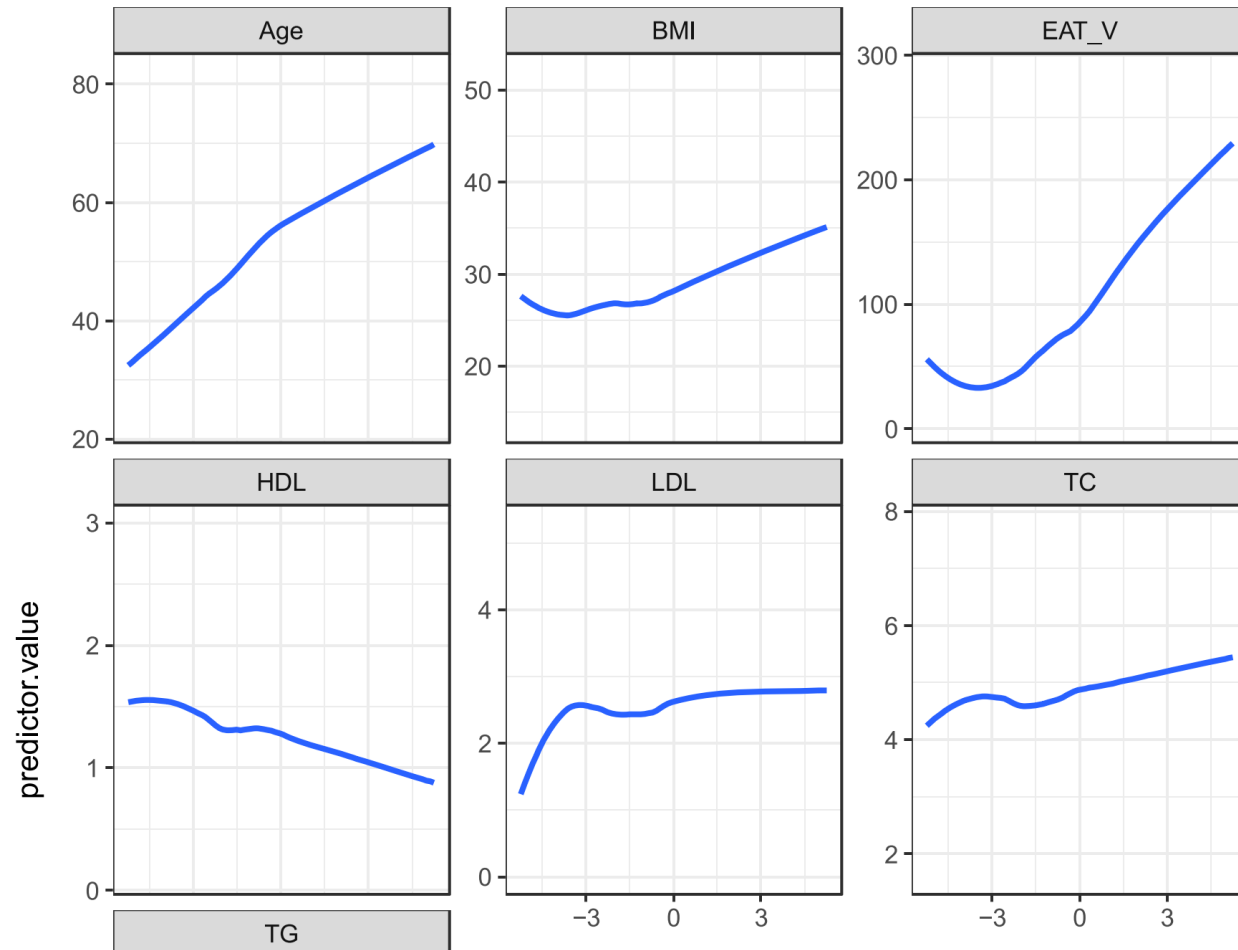
Variable	OR (95% CI)
BMI	1.10 (1.04 to 1.17)
HTN	1.36 (0.71 to 2.60)
OSA	1.89 (0.59 to 6.02)
Smoking	0.74 (0.30 to 1.78)
Dyslipidemia	1.67 (0.89 to 3.14)
T2DM	1.13 (0.51 to 2.52)
CD4 ⁺ count <200	4.67 (1.82 to 12.02)
Diagnosis of HIV in last 10 yrs	1.00 (0.96 to 1.03)
CVD*	3.08 (1.37 to 6.94)

*Composite CVD includes: CAD, CHF, PVD, stroke, TIA, MI, and coronary revascularization.

CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; HTN, hypertension; MI, myocardial infarction; OR, odds ratio; PVD, peripheral vascular disease; T2DM, type 2 diabetes mellitus; TIA, transient ischemic attack.



(b) Association of continuous covariates with logit odds of coronary calcification in the HIV-positive group.



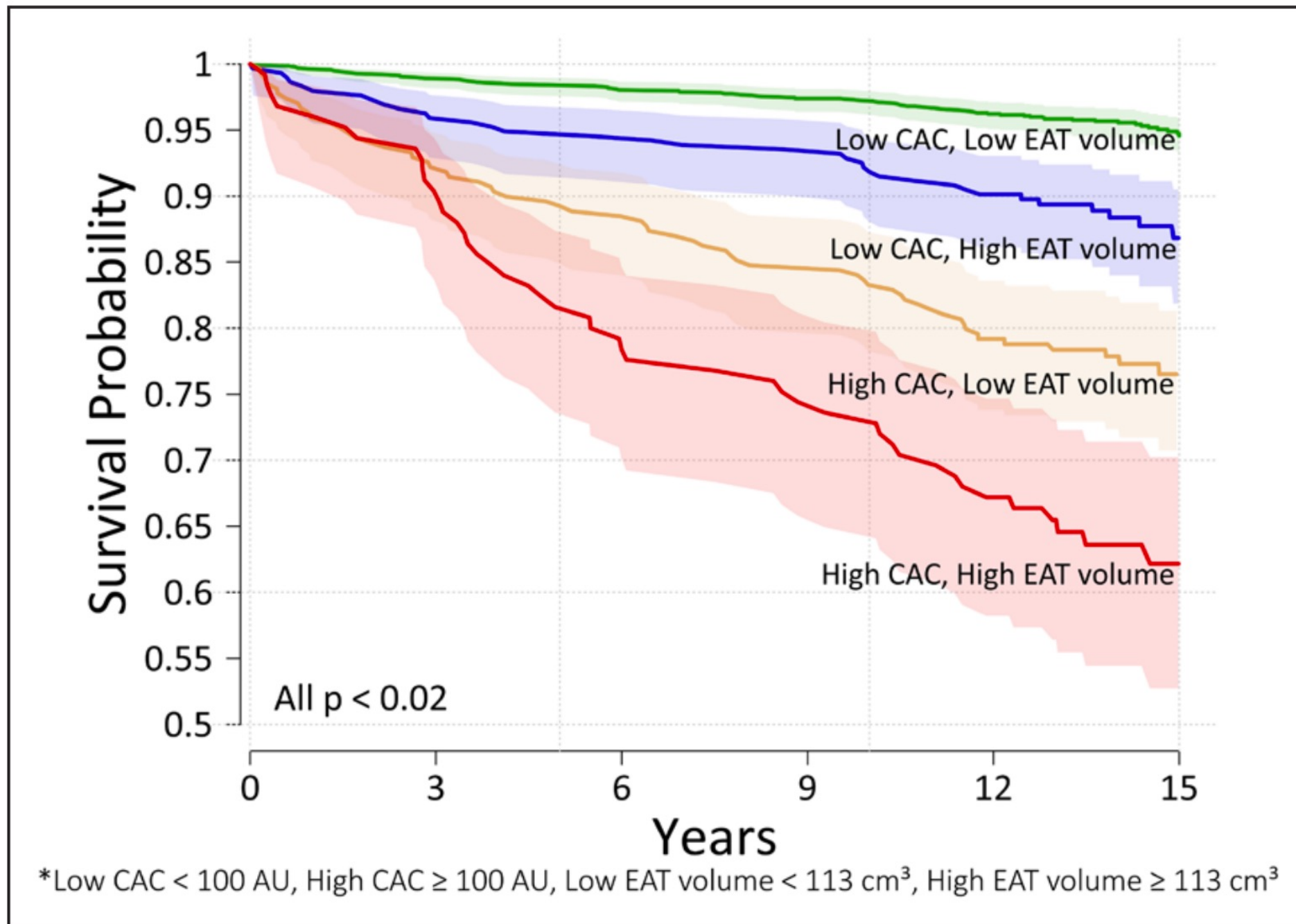
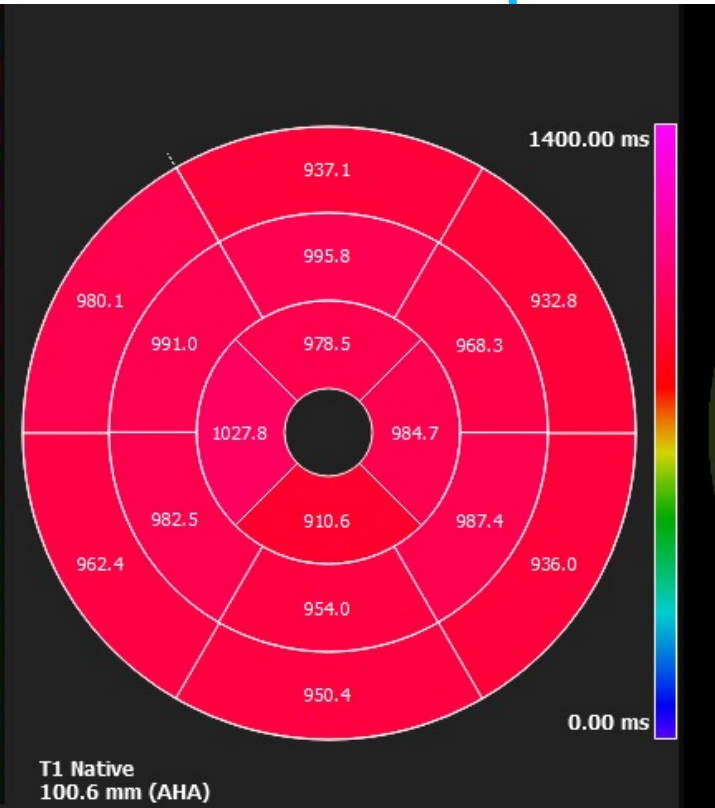
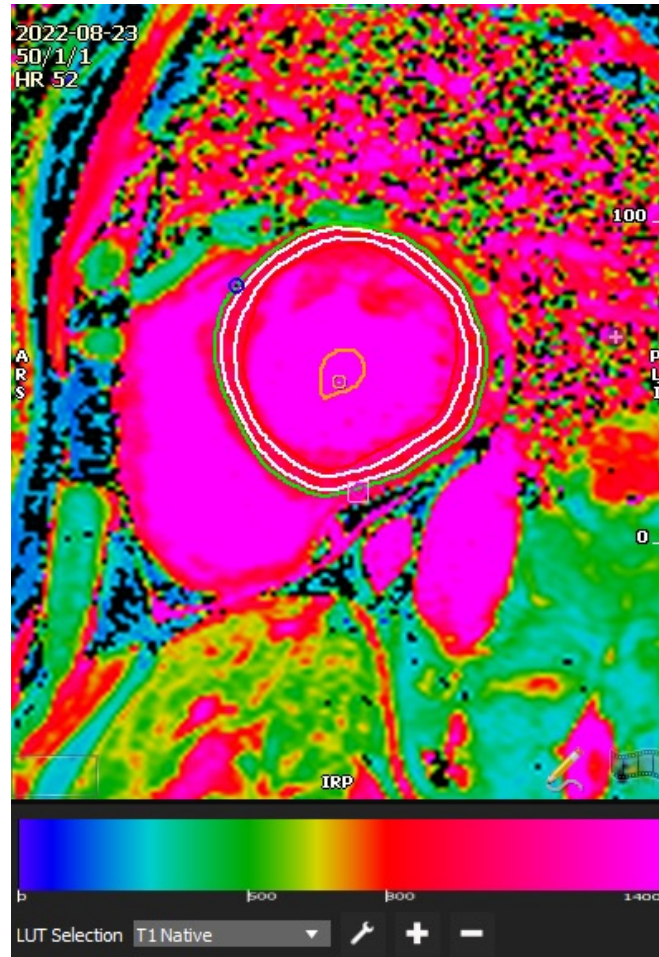


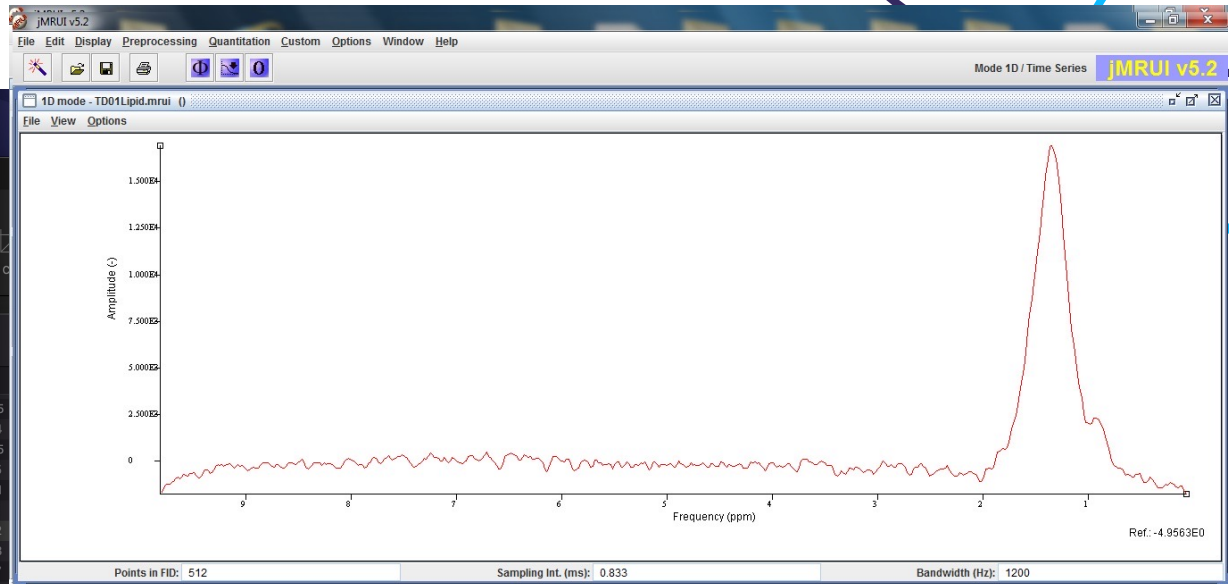
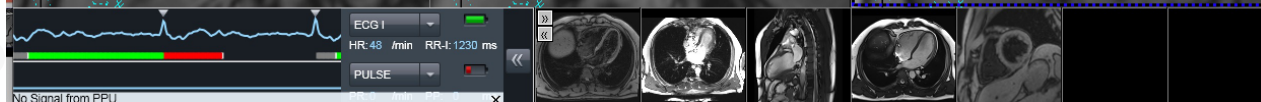
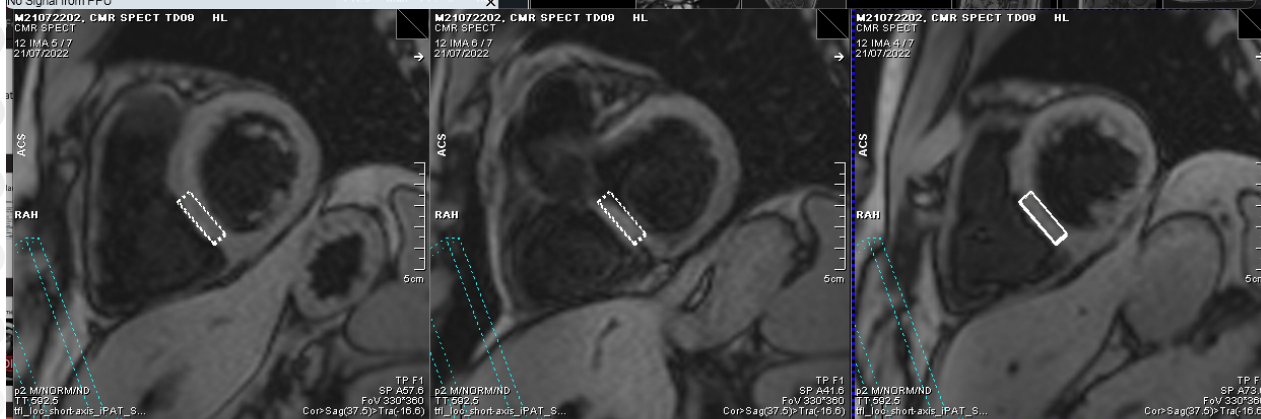
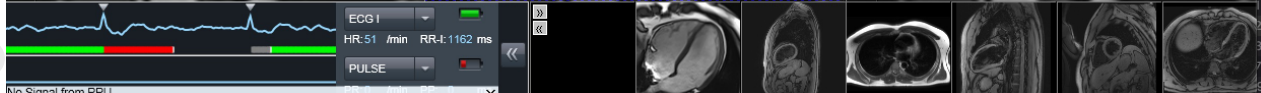
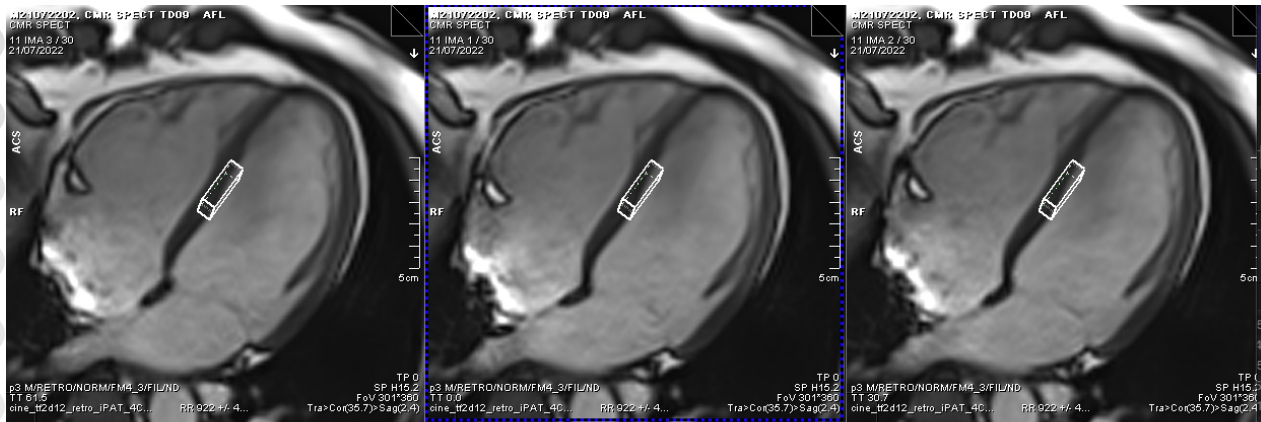
Table 4. Multivariable linear regression analysis on log-transformed epicardial adipose tissue volume in HIV-positive participants (N = 339).

HIV-related parameters	Univariate analysis			Multivariate analysis		
	Coefficient	95% CI	P value	Coefficient	95% CI	P value
Male (vs. female)	0.08	-0.01 to 0.16	0.059	0.10	0.01-0.19	0.033
Age (per 1 year increase)	0.02	0.01-0.03	<0.001	0.02	0.01-0.02	<0.001
HOMA-IR (≥ 2 vs. < 2)	0.18	0.10-0.27	<0.001	0.10	0.02-0.19	0.011
Abnormal waist circumference ^a (yes vs. no)	0.27	0.19-0.35	<0.001	0.12	0.04-0.19	0.002
Abnormal triglyceride at least 150 mg/dl	0.22	0.14-0.30	<0.001	0.05	-0.04 to 0.13	0.294
Smoking status (ever smoke vs. never smoke)	0.07	-0.02 to 0.15	0.112	0.24	0.16-0.32	<0.001
Hypertension (yes vs. no)	0.16	0.08-0.24	<0.001	0.01	-0.07 to 0.09	0.775
Diabetes mellitus (yes vs. no)	0.12	0.02-0.23	0.023	-0.08	-0.18 to 0.02	0.135
Current statin use (yes vs. no)	0.14	0.05-0.22	0.002			
Nadir CD4 ⁺ cell count (<100 vs. ≥ 100 cells/ μ l)	0.05	-0.04 to 0.14	0.277			
Current CD4 ⁺ cell count (<500 vs. ≥ 500 cells/ μ l)	0.00	-0.09 to 0.09	0.996			
Current CD4 ⁺ /CD8 ⁺ ratio (≥ 1 vs. < 1)	0.01	-0.02 to 0.05	0.512			
Duration of HIV (>15 vs. < 15 years)	0.16	0.06-0.25	0.002	0.10	0.01-0.19	0.028
Duration of ART (>15 vs. < 15 years)	0.10	0.01-0.18	0.021			
Current ART regimen			0.380			
NNRTI	Ref					
PI	0.06	-0.03 to 0.15	0.220			
Other	0.06	-0.06 to 0.19	0.336			
Lipodystrophy (yes vs. no)	0.12	0.03-0.20	0.006	0.05	-0.03 to 0.12	0.253
Stavudine exposure (yes vs. no)	0.08	-0.01 to 0.16	0.166			
Abacavir exposure (yes vs. no)	0.10	-0.05 to 0.25	0.187			

- EAT volume / density as HIV-specific risk factor
- VAT as therapeutic target
- PVAT in risk prediction?

Multiparametric MRI





1H CMR TESTING (44 y., 44 y)
Christine Denby Cardiac Spectroscopy
vibe_q-dixon_tra_bh

512 x 512
WL: 127 WW: 255

Liver Evaluation

	voxels	mean fit error
ROI Segmentation Volume	38	1.3%
	43500	3.9%

ROI Segmentation

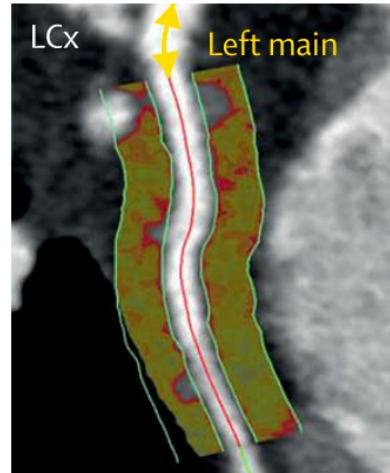
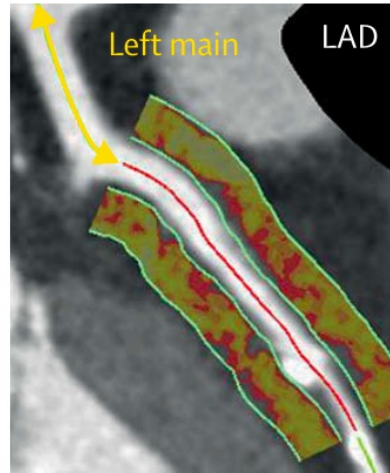
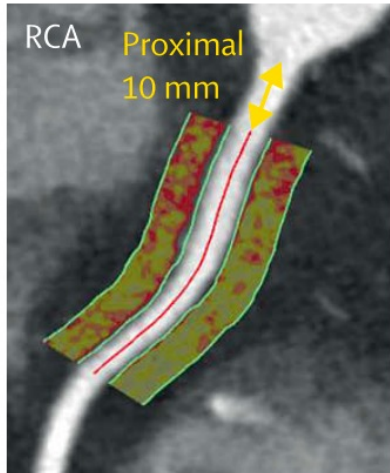
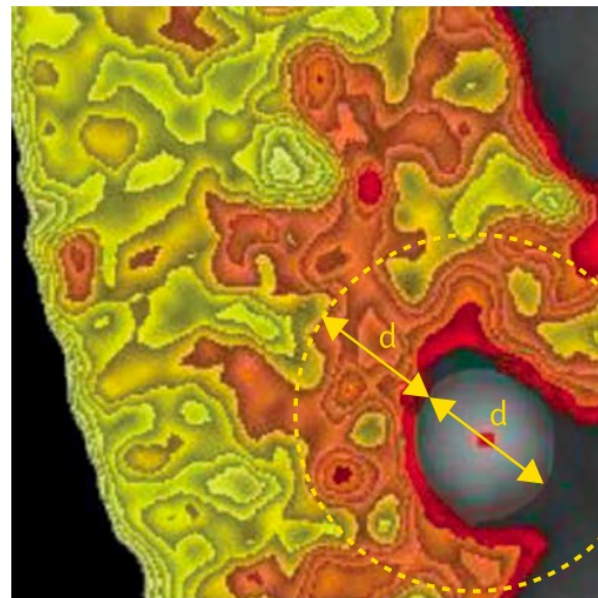
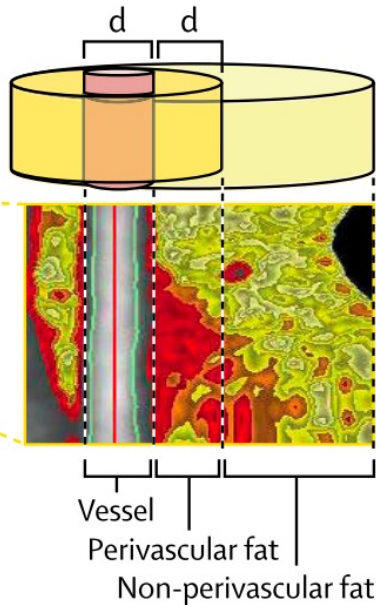
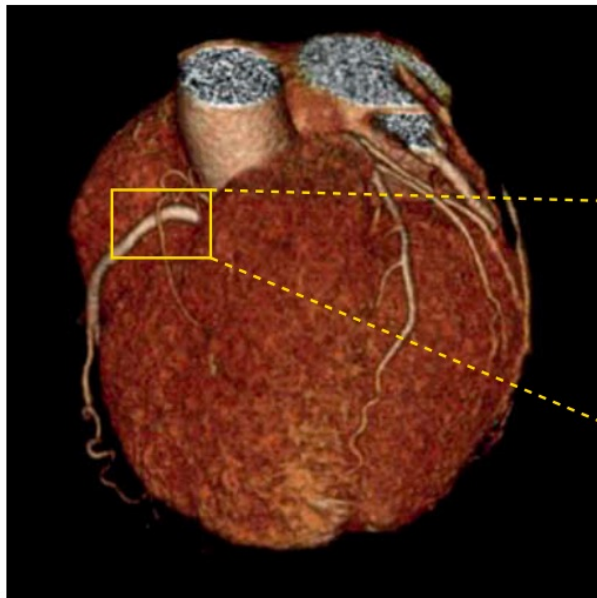
	mean	std
ROI Segmentation Volume	3.0%	0.8%
	5.3%	11.9%

ROI Segmentation

	mean	std
ROI Segmentation Volume	74.7s^-1	3.5s^-1
	86.2s^-1	53.9s^-1

384%
39 : 1 / 2
Uncompressed
Position: HFS

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A-190 HU  -30 HU**B**

Non-invasive detection of coronary inflammation using computed tomography and prediction of residual cardiovascular risk (the CRISP CT study): a post-hoc analysis of prospective outcome data
 Oikonomou et al. Lancet 2018

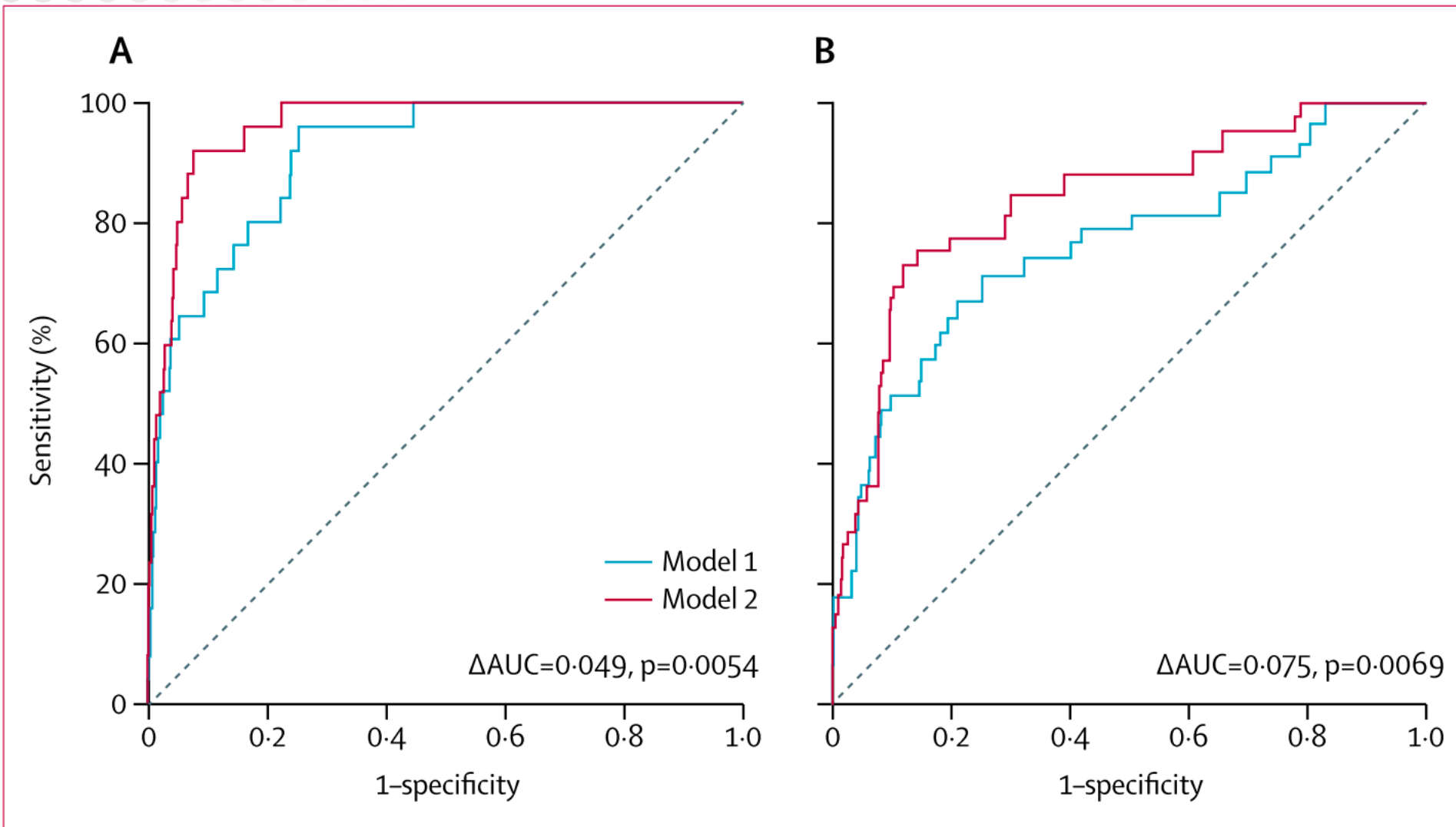


Figure 3: Incremental prognostic value of the perivascular FAI beyond current coronary CTA-based risk stratification

Non-invasive detection of coronary inflammation using computed tomography and prediction of residual cardiovascular risk (the CRISP CT study): a post-hoc analysis of prospective outcome data
Oikonomou et al. Lancet 2018



Novel therapeutics

- SGLT2-I
- GLP-1 agonists
- Tirzepatide
- Inclisiran
- mRNA based drugs

CVS Risk Scores

- Framingham
- QRISK
- DAD, etc



This is usually as far as it goes
in HIV clinics

Cardiac CT

- Coronary Calcium Score
- CT Angiography
- Epicardial Adipose Tissue
- Hepatosteatorosis assessment
- Perivascular adipose tissue



Thank you and
Questions

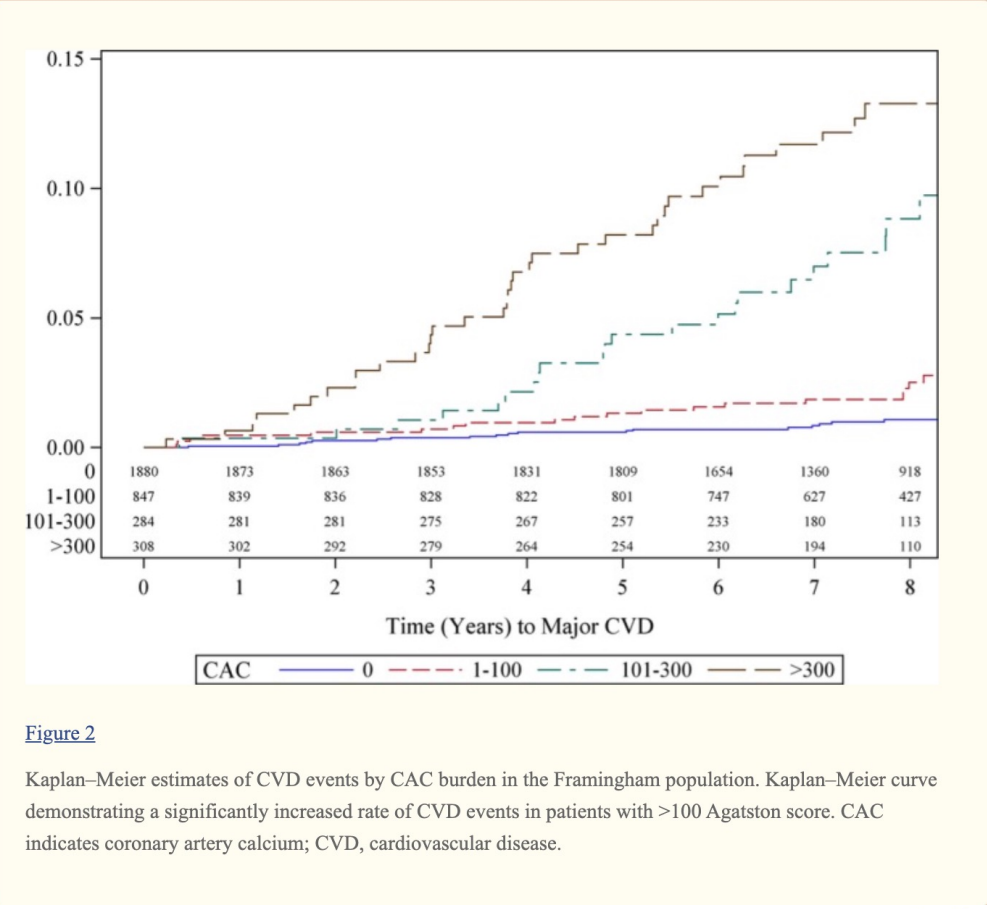


Figure 2

Kaplan–Meier estimates of CVD events by CAC burden in the Framingham population. Kaplan–Meier curve demonstrating a significantly increased rate of CVD events in patients with >100 Agatston score. CAC indicates coronary artery calcium; CVD, cardiovascular disease.

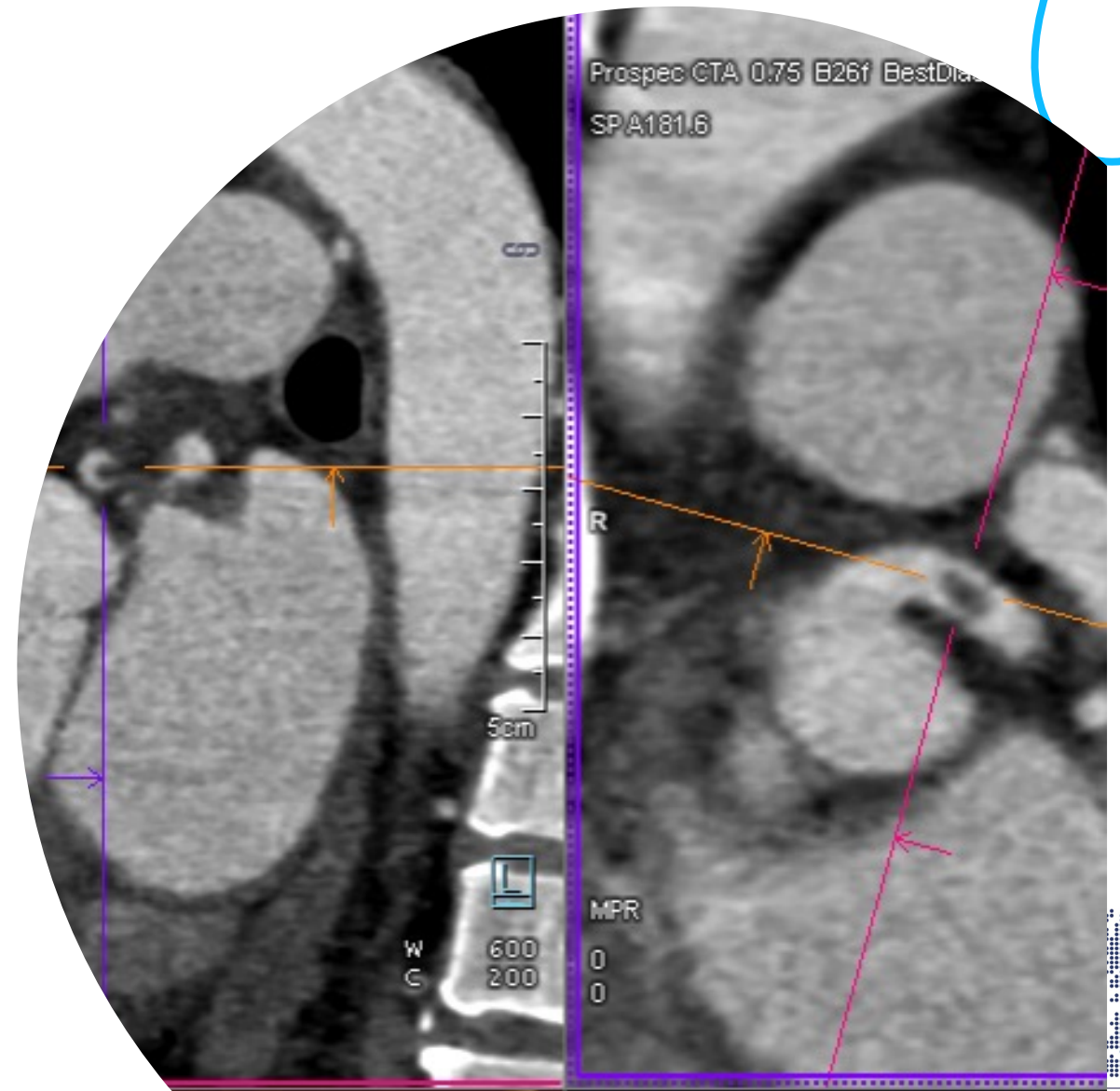
Hoffman et al. Cardiovascular Event Predication. J Am Heart Assoc. 2016;22,5(2)



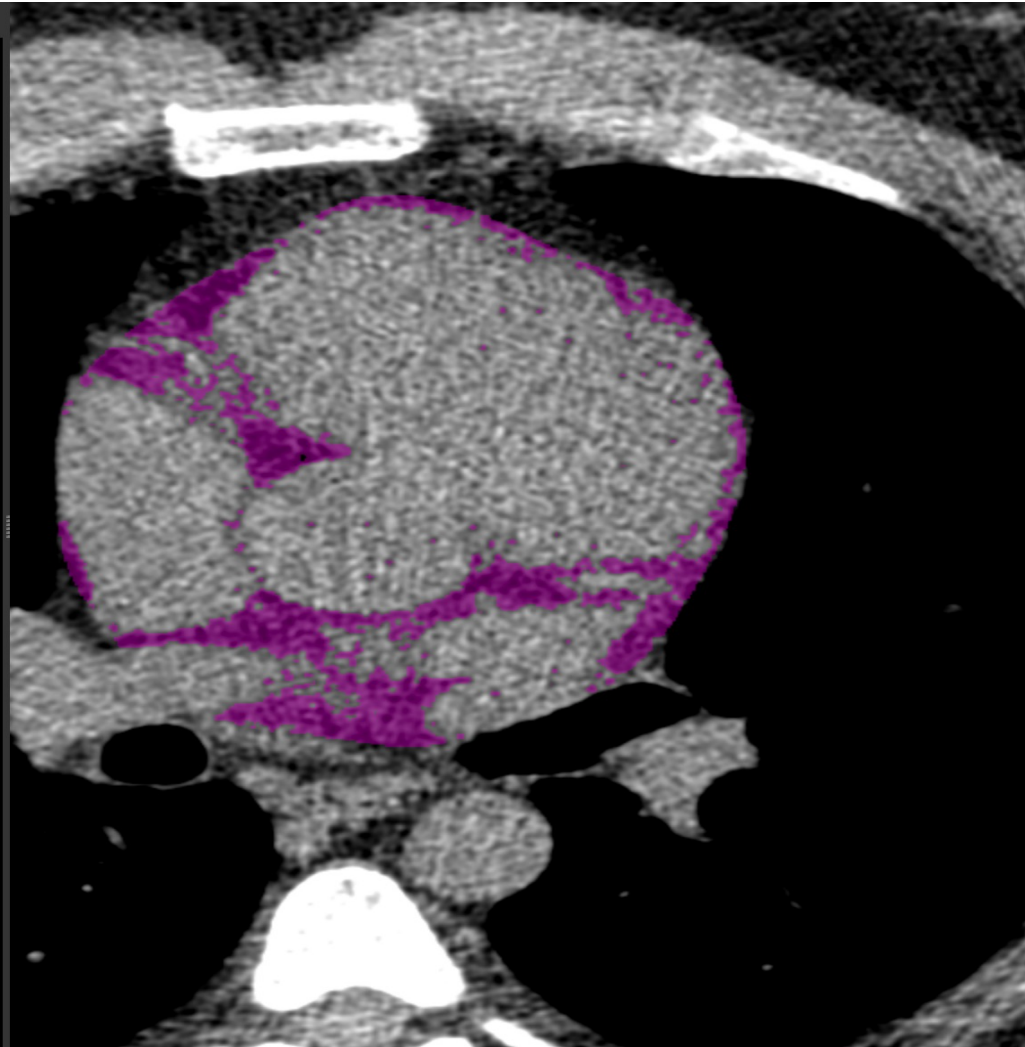
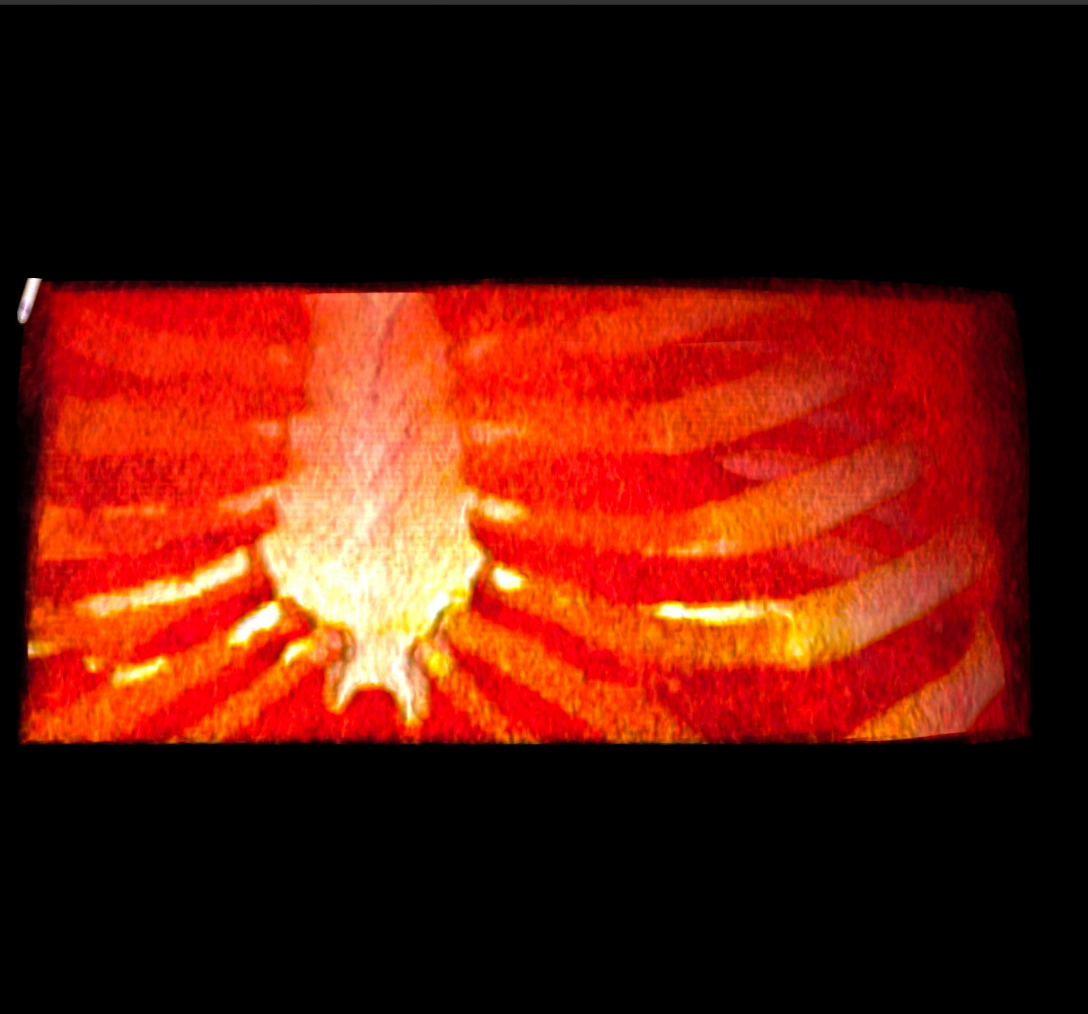
- Incremental value above traditional risk prediction tool
- Net reclassification of 66% of intermediate risk patients
- Combination scores: MESA and ASTROCHARM
- Recommendation 2a AHA

CT Angiography

- Non-calcified plaque more common in HIV
- Thought to be higher risk



Display: Epicardial Mask Sectors Update Reset Camera Axial Plane Color: —



Operator Name: heseltine Add

- 1 - Epicardial Editor
- 2 - Thoracic Editor
- 3 - Quantification

Thresholds: -190HU to -30HU Edit Thresholds

Measurements

Epicardial Fat:	125 cm ³
Mean Density:	-79 HU ± 34
Thoracic Fat:	346 cm ³
Mean Density:	-96 HU ± 37

- Sector 1
- Volume: 15 cm³
- Mean Density: -79 HU ± 34
- Sector 2
- Volume: 17 cm³
- Mean Density: -82 HU ± 35
- Sector 3
- Volume: 15 cm³
- Mean Density: -86 HU ± 36
- Sector 4
- Volume: 19 cm³
- Mean Density: -77 HU ± 34
- Sector 5
- Volume: 19 cm³
- Mean Density: -74 HU ± 31
- Sector 6
- Volume: 11 cm³
- Mean Density: -71 HU ± 30
- Sector 7
- Volume: 17 cm³
- Mean Density: -79 HU ± 35
- Sector 8
- Volume: 12 cm³
- Mean Density: -80 HU ± 36

4 - 2D Tool

Non-HIV

	OR	95% CI	P value
Age	1.11	1.09-1.13	<0.005
Male Sex	3.15	2.30-4.31	<0.005
Hypertension	1.45	1.05-1.98	0.02
Dyslipidaemia	1.56	1.16-2.10	<0.005
Type II diabetes	1.17	0.73-1.88	0.51
Current smoker	2.00	1.39-2.90	<0.005
Ex-smoker	1.42	0.91-2.23	0.13
Family history	0.69	0.51-0.93	0.02
Obesity	1.03	0.59-1.81	0.92
HS	1.10	0.82-1.46	0.54

HIV

Variable	OR (95% CI)	P Value
Age	1.10 (1.04-1.162)	0.001
Male Sex	2.77 (0.986-7.766)	0.53
TG/HDL	1.09 (0.913-1.292)	0.295
eGFR	0.99 (0.965-1.013)	0.377
FRS	1.04 (0.963-1.131)	0.295
Hepatosteatosi	3.46 (1.755-6.823)	<0.005

Options for Treatment?



LIFESTYLE
MODIFICATION



PHARMACOTHERAPY



CORONARY ARTERY
CALCIUM SCORE

- Unmet need to apply appropriate CVD risk stratification in HIV positive patients
- Cardiac CT to understand mechanistic processes that drive heightened CVD risk in HIV
- Opportunities for collaborative work