

HIV and CARDIOVASCULAR DISEASE



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5th October 2019 Istanbul



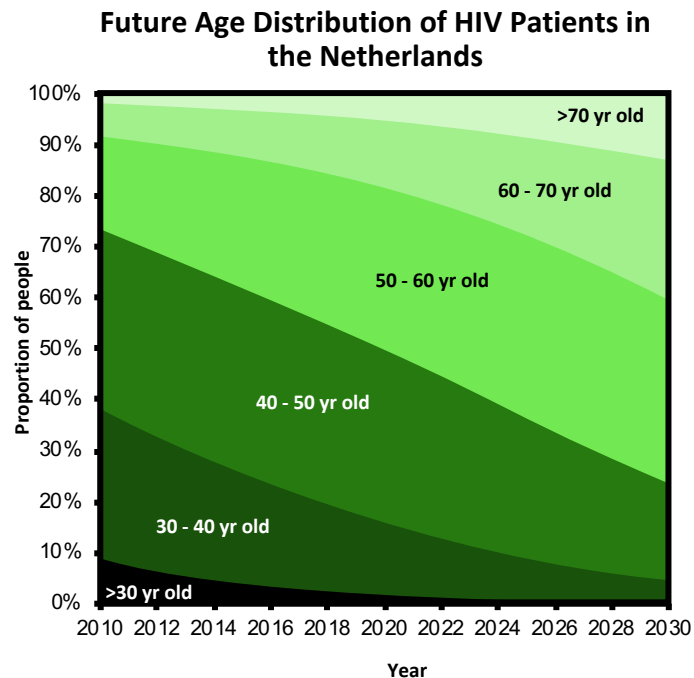
TALK OUTLINE

- BURDEN OF CVD IN HIV
- PATHOPHYSIOLOGY OF CVD
- CVD RISK
- SCREENING APPROACHES & INTERVENTION
 - 1. Risk Assessment
 - 2. Guidelines
 - 3. What do I do?

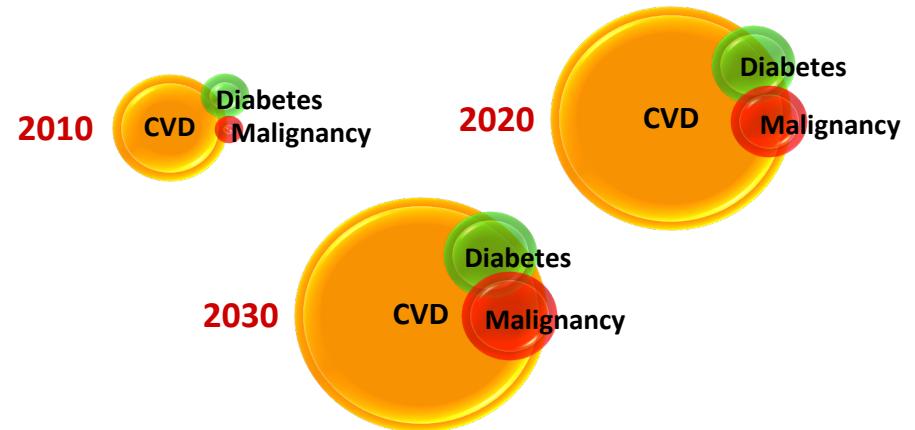
BURDEN OF CVD IN HIV

Increased Burden of Non-Communicable Diseases (NCDs) and Polypharmacy

An individual-based model of an ageing HIV-population following patients on treatment as they age, develop NCDs and start co-administered medications

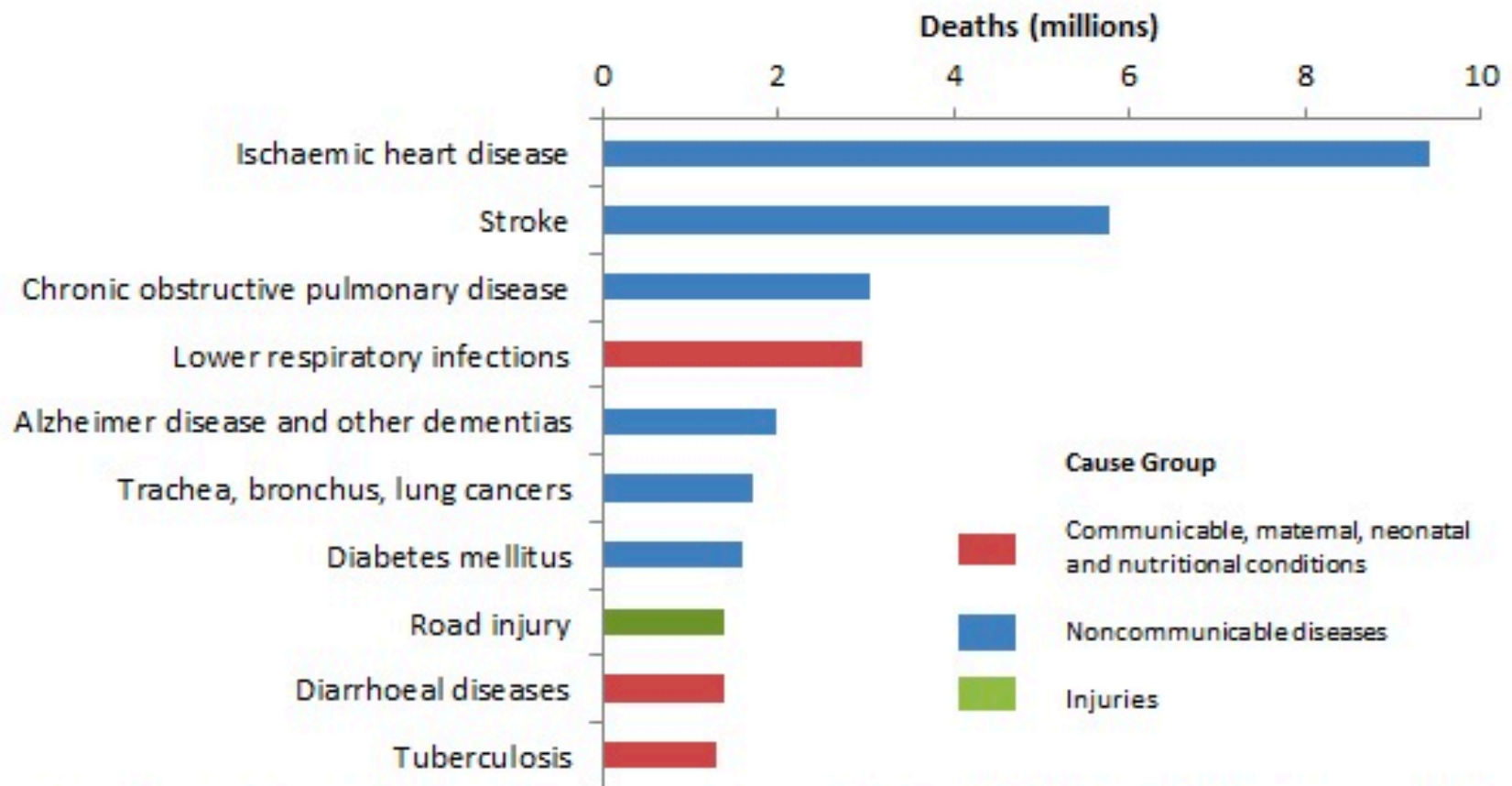


Changes in Relative Number of Patients with Specific NCDs



- In the ATHENA cohort, proportion of patients on ART aged ≥ 50 years old will increase from 28% to 73% between 2010 and 2030
- Burden of NCDs mostly driven by larger increases in cardiovascular disease compared with increases in other comorbidities
- Polypharmacy is being driven by increase in cardiovascular medications

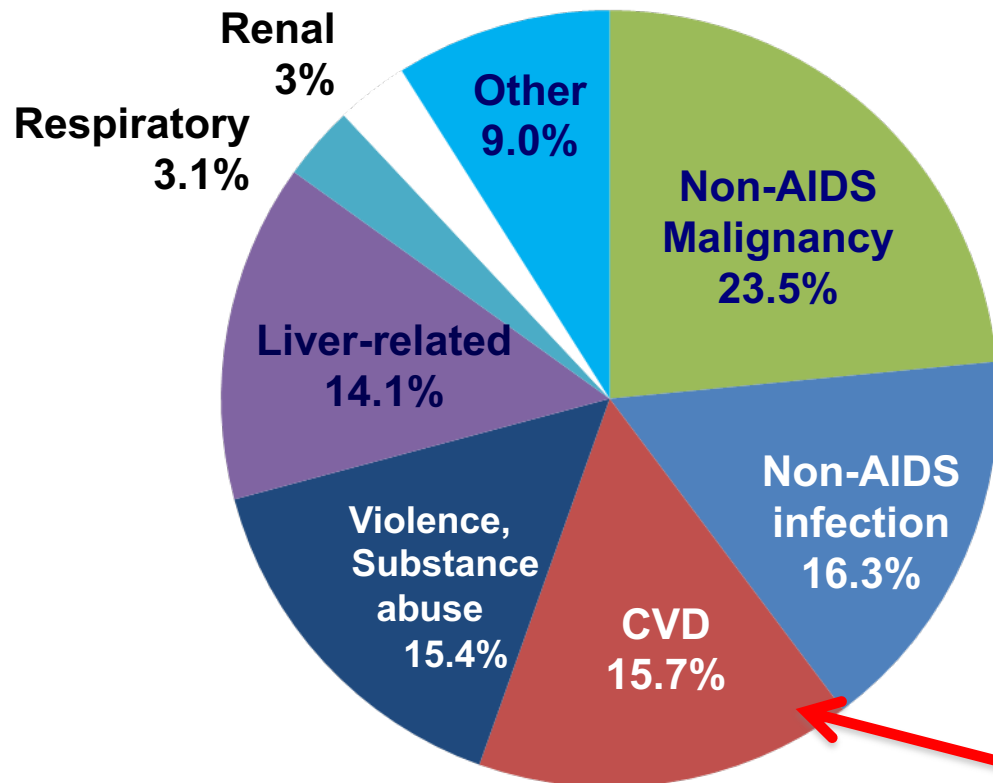
Top 10 global causes of deaths, 2016



Source: Global Health Estimates 2016: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2016. Geneva, World Health Organization; 2018.

HIV-related CVD – Significant Mortality

- 1,876 deaths among 39,727 patients
- Non-AIDS related deaths accounted for 50.5%
- *~16% were due to CVD*



**13 HIV Cohorts
1996-2006 Europe
& N America**

Management of cardiovascular conditions in a cohort of patients with HIV: experience from a joint HIV/cardiology clinic

Authors: Sudheer Koganti,^A Sabine Kinloch-de Loes,^B Samantha Hutchinson,^C Margaret Johnson^D and Roby D Rakhit^E

Diagnoses n=316

- CAD

Hypertension

Arrhythmia
- Cardiomyopathy

Others

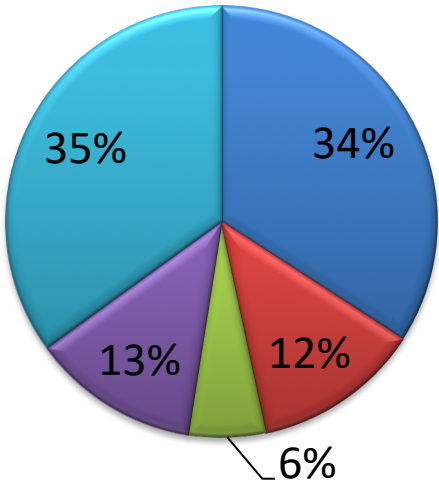
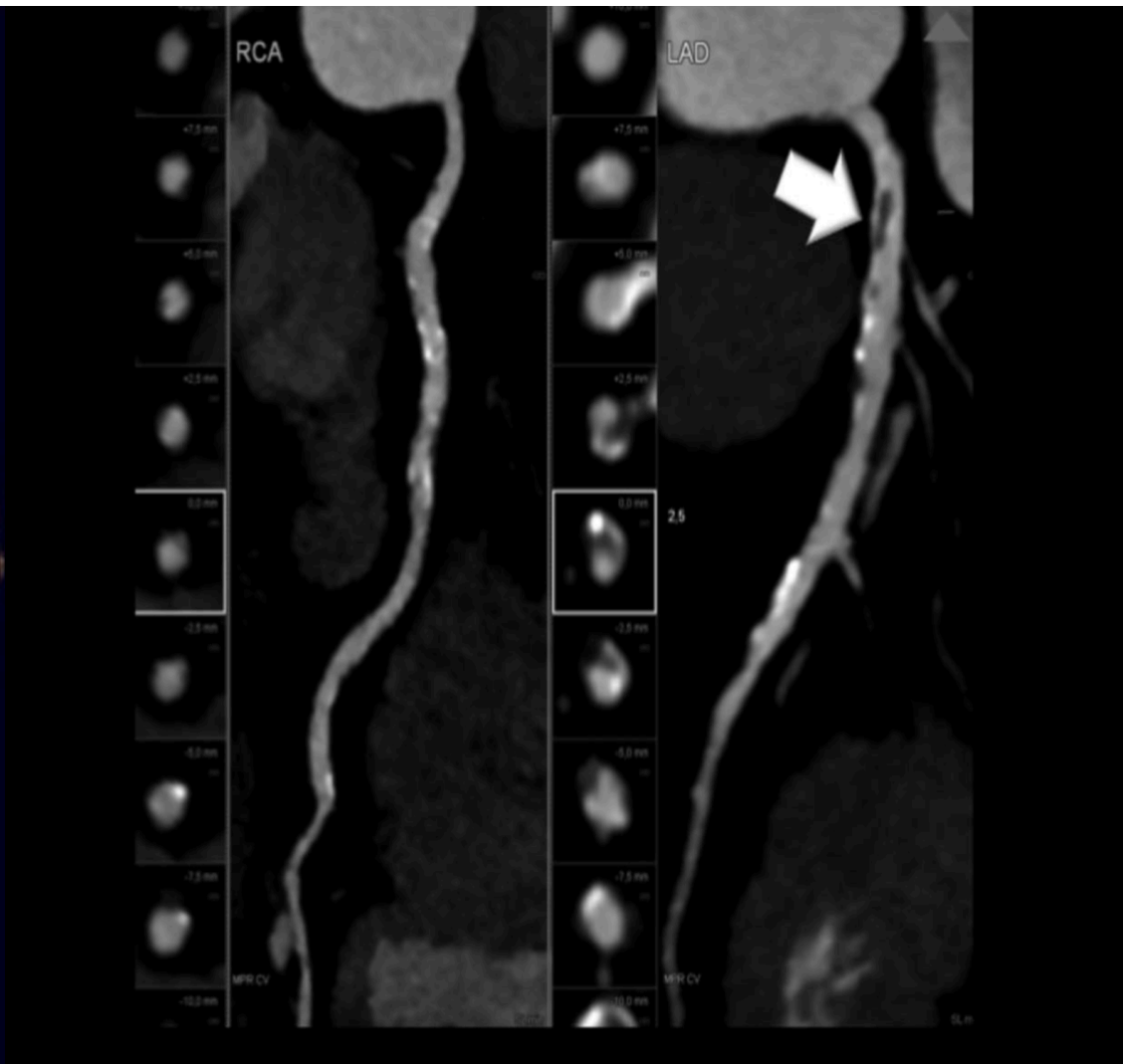


Table 4. Other diagnoses.	
Diagnosis	n
Non cardiac chest pain	14
Palpitations	14 (normal 24-hour Holter in all cases)
Ventricular septal defect	2
PE	2
Stoke/TIA	2
Cardiac amyloid	1
Pericardial cyst	1 (required surgical removal)
Spontaneously resolved pericardial effusion	1
Aortic stenosis requiring AVR	1
Abnormal ECG	1
Infective endocarditis	1 (required mitral valve replacement)
Syncope	1

AVR = aortic valve replacement; ECG = electrocardiogram; PE = pulmonary embolism; TIA = transient ischaemic attack.



Coronary Artery Calcium in HAART-treated HIV patients

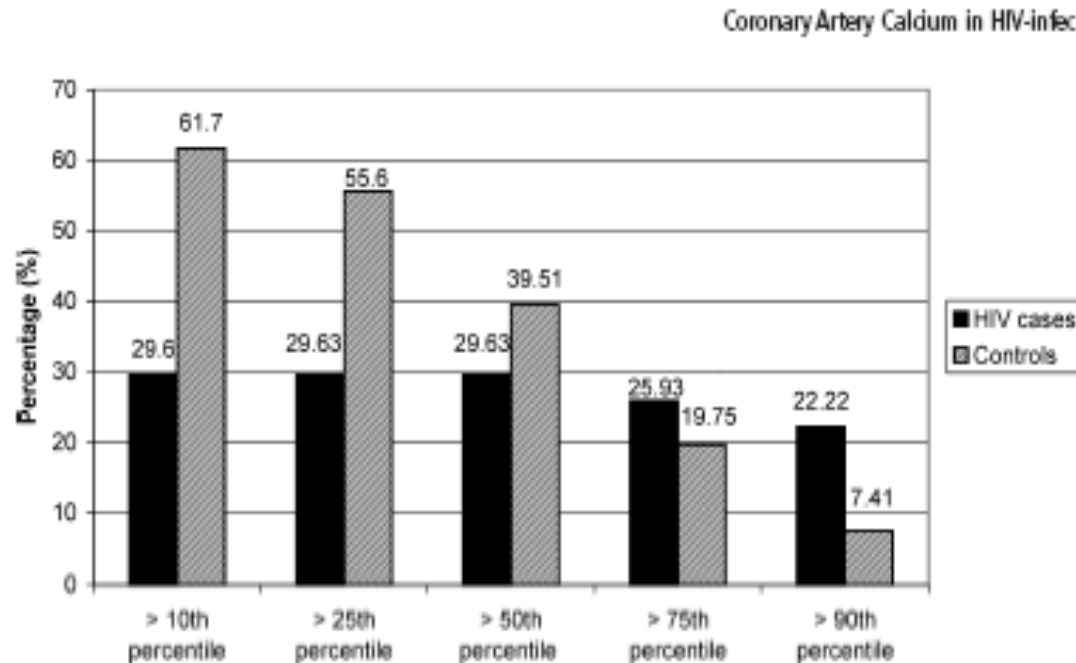
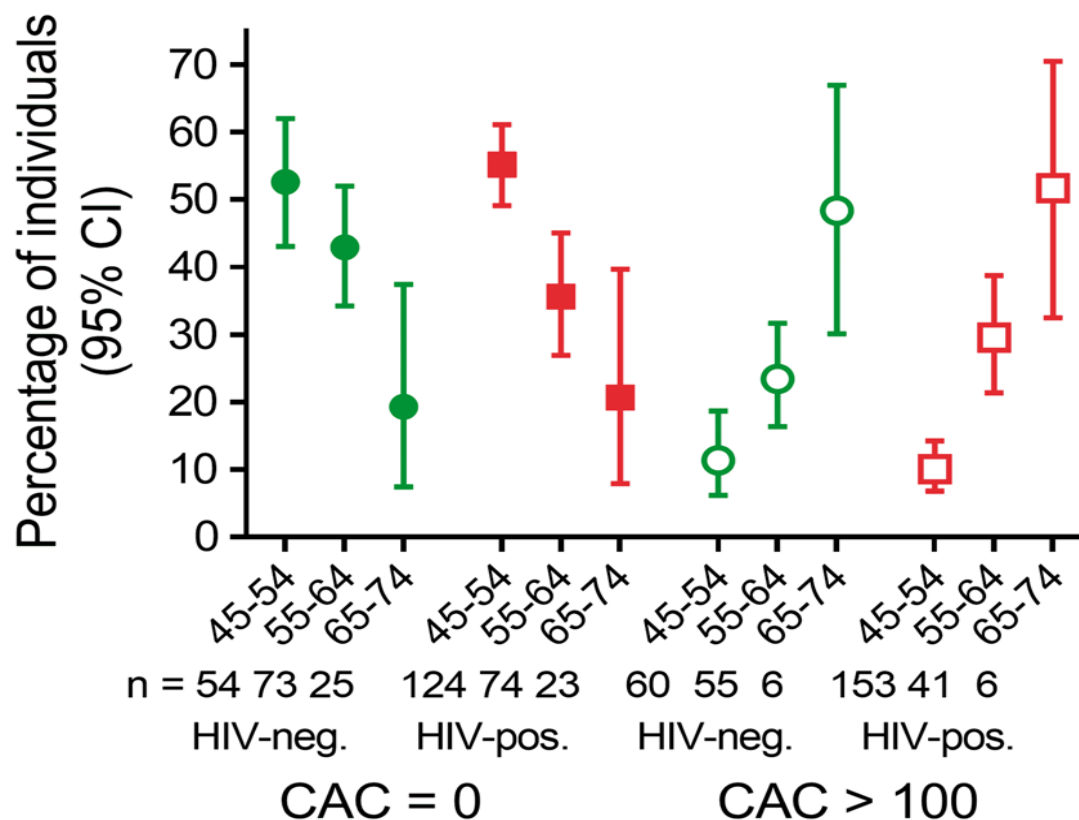


FIGURE 1. Percentage of HIV cases ($n = 27$) and controls ($n = 81$) scoring above the mean specified percentile of the control database ($n = 25,250$) of coronary artery calcium scores. The frequency of controls scoring above the 10th ($\chi^2(1) = 8.39$, $P = .004$) and 25th ($\chi^2(1) = 5.45$, $P = .02$) percentiles is significantly greater than the frequency of HIV cases, and the frequency of HIV cases scoring above the 90th percentile is significantly greater than the frequency of controls ($\chi^2(1) = 4.5$, $P = .034$). There are no significant differences between groups above the 50th or 75th percentiles.

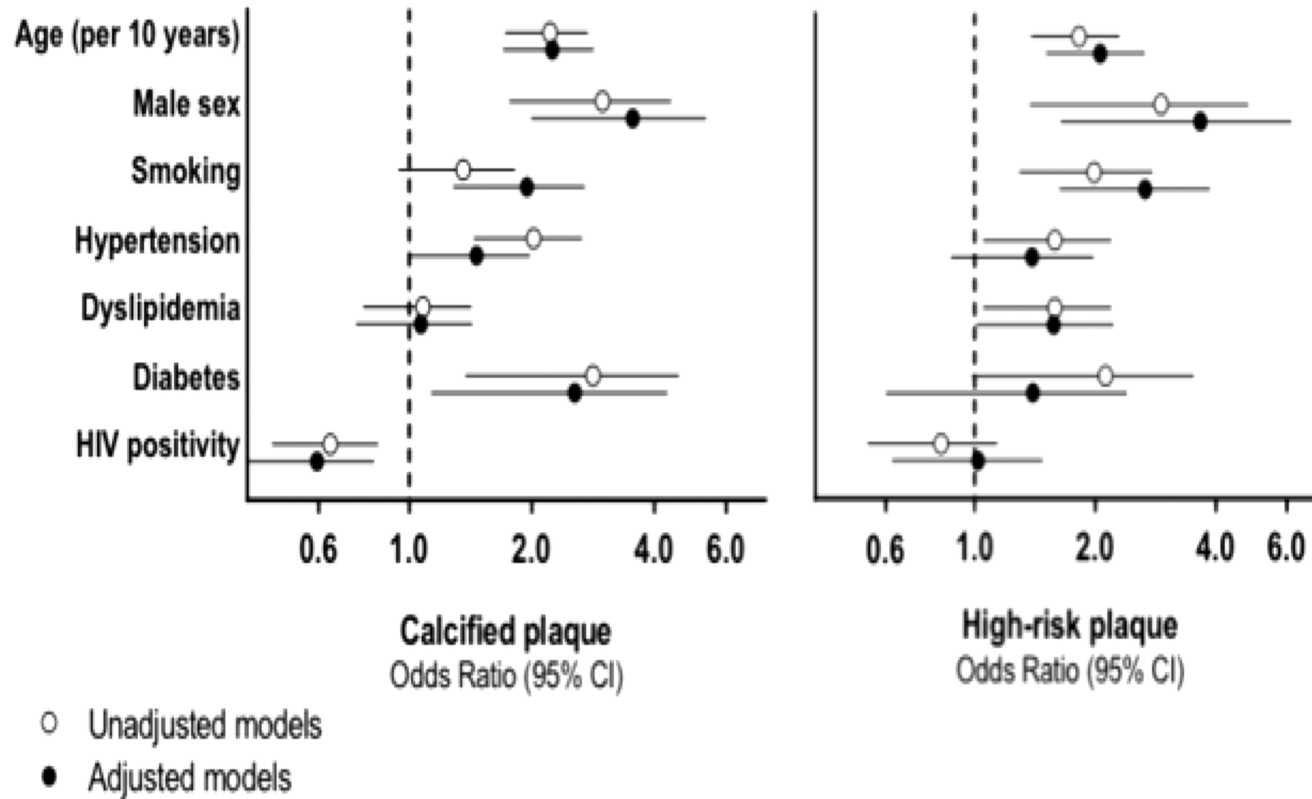
Subclinical coronary artery disease in Swiss HIV-positive and HIV-negative persons

Philip E. Tarr^{1*}, Bruno Ledergerber², Alexandra Calmy³, Thanh Doco-Lecompte³, Alex Marzel², Rainer Weber², Philipp A. Kaufmann⁴, René Nkoulou^{5†}, Ronny R. Buechel^{4†}, and Helen Kovari^{2†}; and the Swiss HIV Cohort Study

Figure 1 Prevalence of coronary artery calcification by age in HIV-positive and HIV-negative study participants. ...



Subclinical atherosclerosis associated with traditional cardiovascular risk factors but NOT HIV



Coronary atherosclerosis characteristics in HIV-infected patients on long-term antiretroviral therapy: insights from coronary computed tomography–angiography

AIDS 2019, **33**:1853–1862

Table 2. Computed tomography–angiography results.

	HIV+ (<i>n</i> = 67)	HIV– (<i>n</i> = 67)	<i>P</i> value
CAD prevalence (any plaque), <i>n</i> (%)	56 (83.6)	46 (68.7)	0.043
SSS, mean ± SD	1.16 ± 1.6	0.95 ± 2.1	0.038
CAD RADS			
0	11	22	<0.001
1	11	7	
2	10	21	
3	23	4	
4	12	13	
Total greater than 50%, <i>n</i> (%)	35 (52.2)	17 (25.4)	0.001
CAD RADS, mean ± SD	2.21 ± 1.4	1.69 ± 1.5	0.031
SIS, mean ± SD	3.93 ± 3.0	3.06 ± 3.1	0.067
G-score mean ± SD	10.04 ± 8.5	5.76 ± 5.9	0.003
Calcium score mean ± SD	149.4 ± 287.1	133.2 ± 329.3	0.015
HRP, <i>n</i> (%)	23 (34.3)	8 (12.1)	0.002
HRP, <i>n</i>	36	10	<0.001
Noncalcifying plaque component, <i>n</i> (%)	44 (65.7)	34 (51.5)	0.097
Ectatic coronary segments, <i>n</i> (%)	10 (14.5)	0 (0)	0.003

CAD RADS, coronary artery disease reporting and data system; CCS, coronary calcium score; HRP, high-risk plaque; SIS, segment involvement score; SSS, stenosis severity score.

Our unpublished data

Comparison of HIV cohort and GRACE UK–Belgian Study in people with ACS

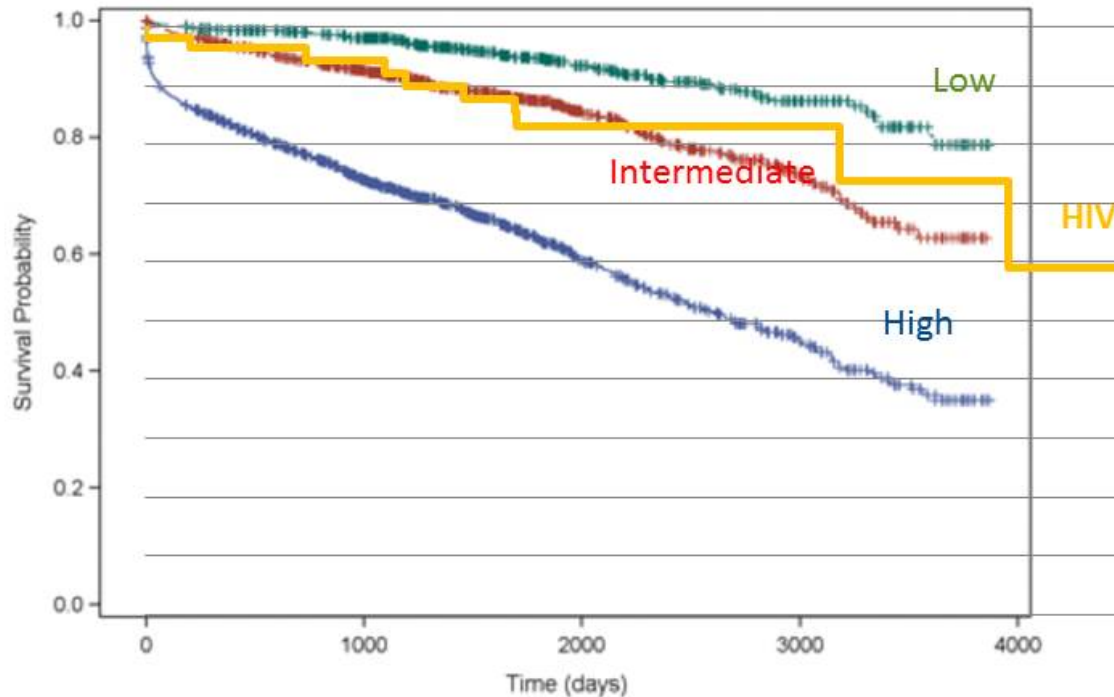


Figure 1. Survival according to GRACE score. Green = low risk, Red = intermediate risk, Blue = high risk (categories as in ESC Guidelines <108, 109-140, >140). Orange = HIV Cohort.

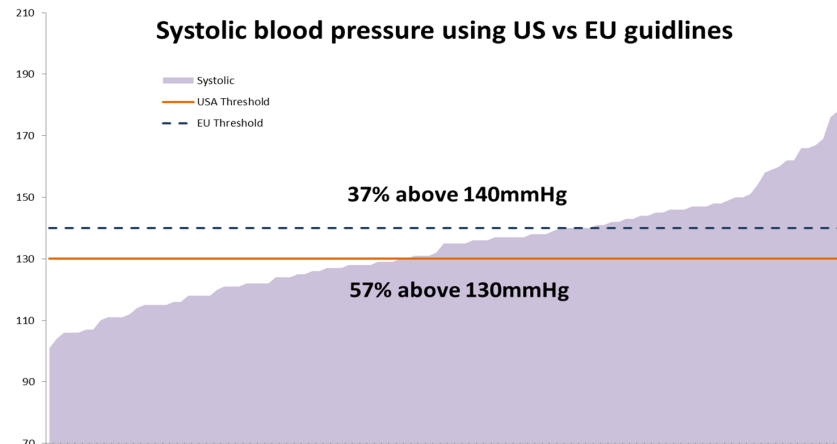
UK Data from British Heart Foundation

Hypertension
UK

High Blood Pressure

- Nearly 30% of adults in the UK have **high blood pressure** and up to half are not receiving treatment.
- People with high blood pressure are up to **three times** more likely to develop heart disease or have a stroke.

Nearly
30%
of adults have
high blood pressure
in the UK



BLOOD PRESSURE CATEGORY	SYSTOLIC mm Hg (upper number)		DIASTOLIC mm Hg (lower number)
NORMAL	LESS THAN 120	and	LESS THAN 80
ELEVATED	120 – 129	and	LESS THAN 80
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 1	130 – 139	or	80 – 89
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 2	140 OR HIGHER	or	90 OR HIGHER
<u>HYPERTENSIVE CRISIS</u> (consult your doctor immediately)	HIGHER THAN 180	and/or	HIGHER THAN 120

1. ACC (2017) New ACC/AHA High Blood Pressure Guidelines Lower Definition of Hypertension. Strategy Retrieved from <https://www.acc.org/latest-in-cardiology/articles/2017/11/08/11/47/mon-5am-bp-guideline-aha-2017-on-december-2018>.

Audit Results

Demographics

1 week in March

111 patients attended outpatient appointments

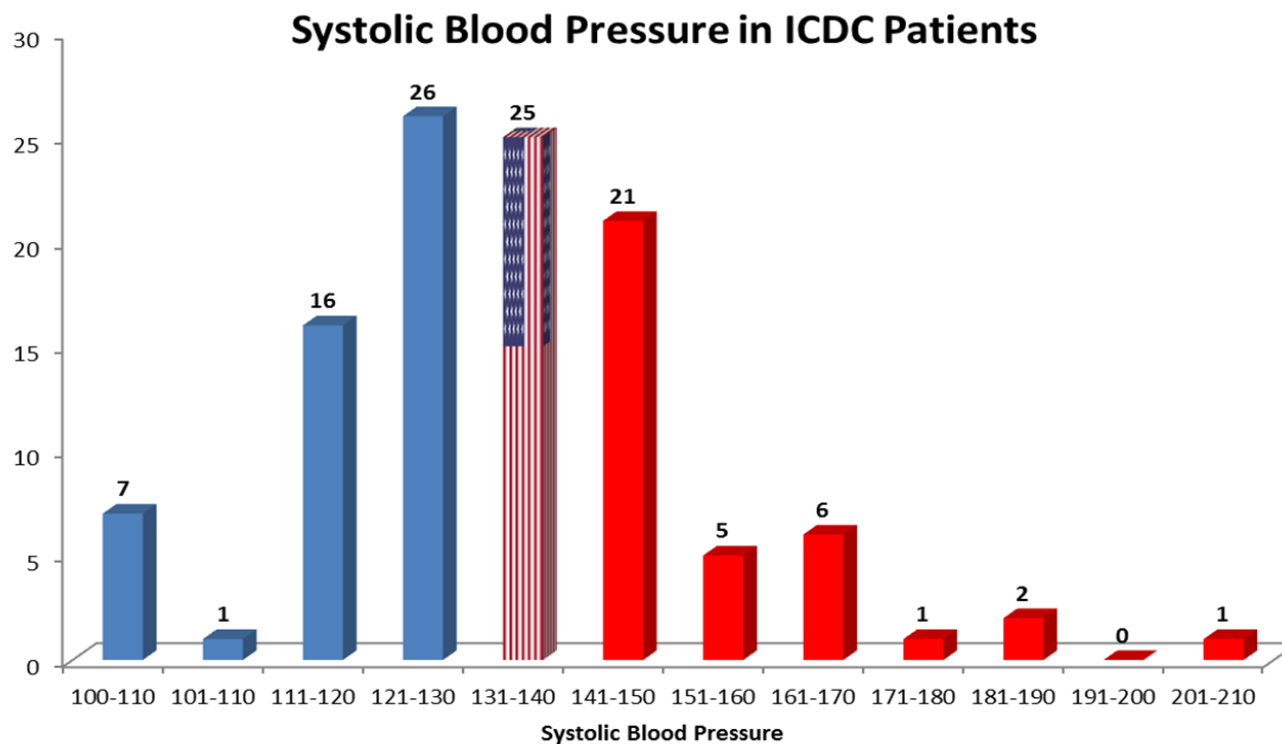
Males n81 (73%) Females n30 (27%)

Average age 49.6 years old

Average Blood Pressure (BP) 134.6/82.2 mmHg

Extra patients that would have hypertension using American

Hypertension
Audit

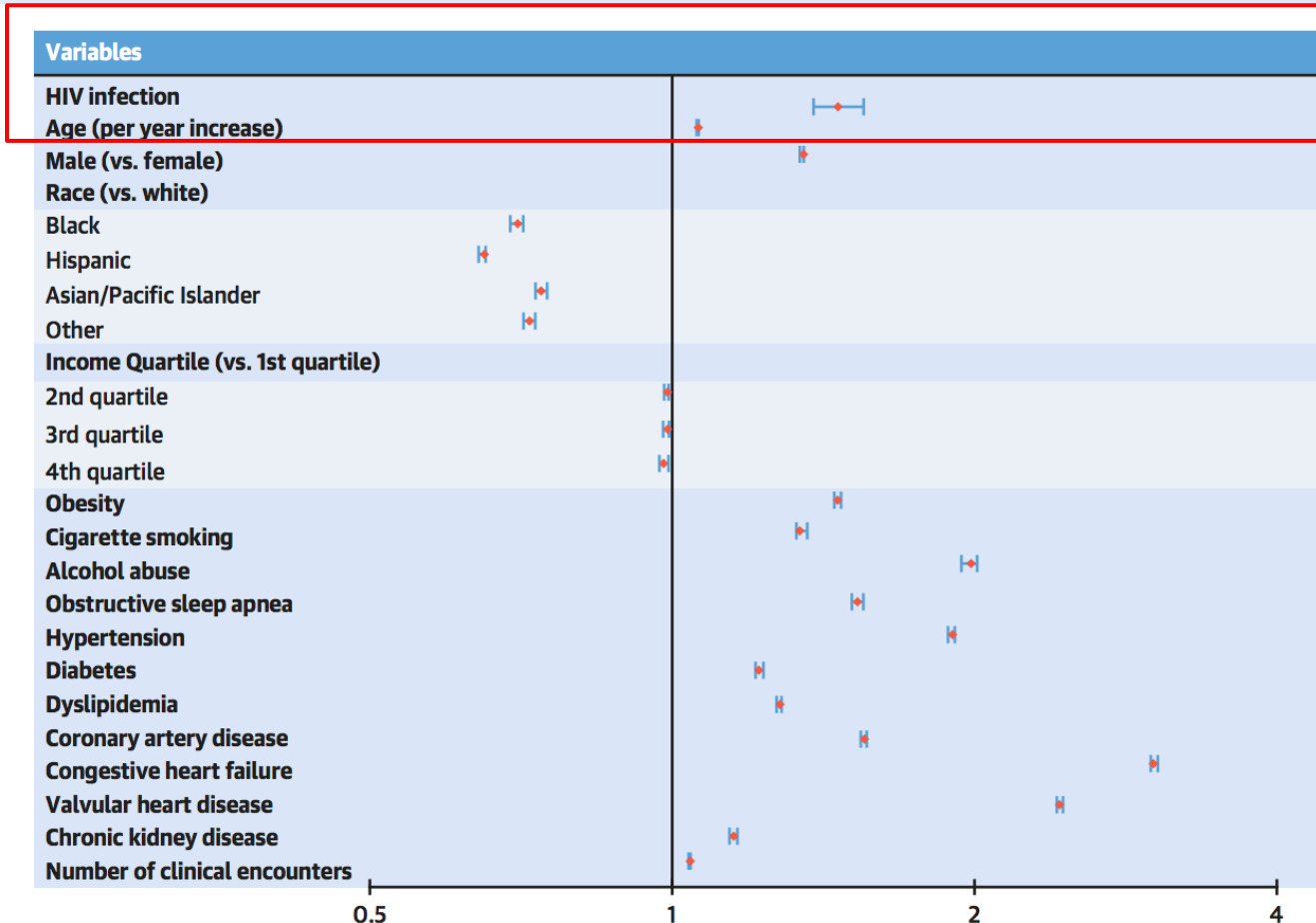


ICDC, Ian Charles Day Centre

HIV and Incident AF

Sardana M et al | JACC 2019; 74:1512

FIGURE 1 Forest Plot Depicting Predictors of Incident AF From the Multivariable-Adjusted Cox Proportional Hazards Model



UCUP California
State Database

PLWH = 18242

AF incidence
18.2 vs 8.9 per
100- person
years fu

Hazard ratios (red diamonds) and 95% confidence intervals (blue Y-error bars) are depicted for each variable included in the Cox proportional hazards model. Of note, human immunodeficiency virus (HIV) infection was a time-updated covariate in the model. AF = atrial fibrillation.



The Risk for Sudden Cardiac Death Among Patients Living With Heart Failure and Human Immunodeficiency Virus

Raza M. Alvi, MD,^{a,b} Anne M. Neilan, MD, MPH,^c Noor Tariq, MD,^d Malek O. Hassan, MD,^a Magid Awadalla, MD,^a Lili Zhang, MD, ScM,^a Maryam Afshar, MD,^b Adam Rokicki, BS,^a Connor P. Mulligan, BA,^a Virginia A. Triant, MD, MPH,^e Markella V. Zanni, MD,^f Tomas G. Neilan, MD, MPH^a

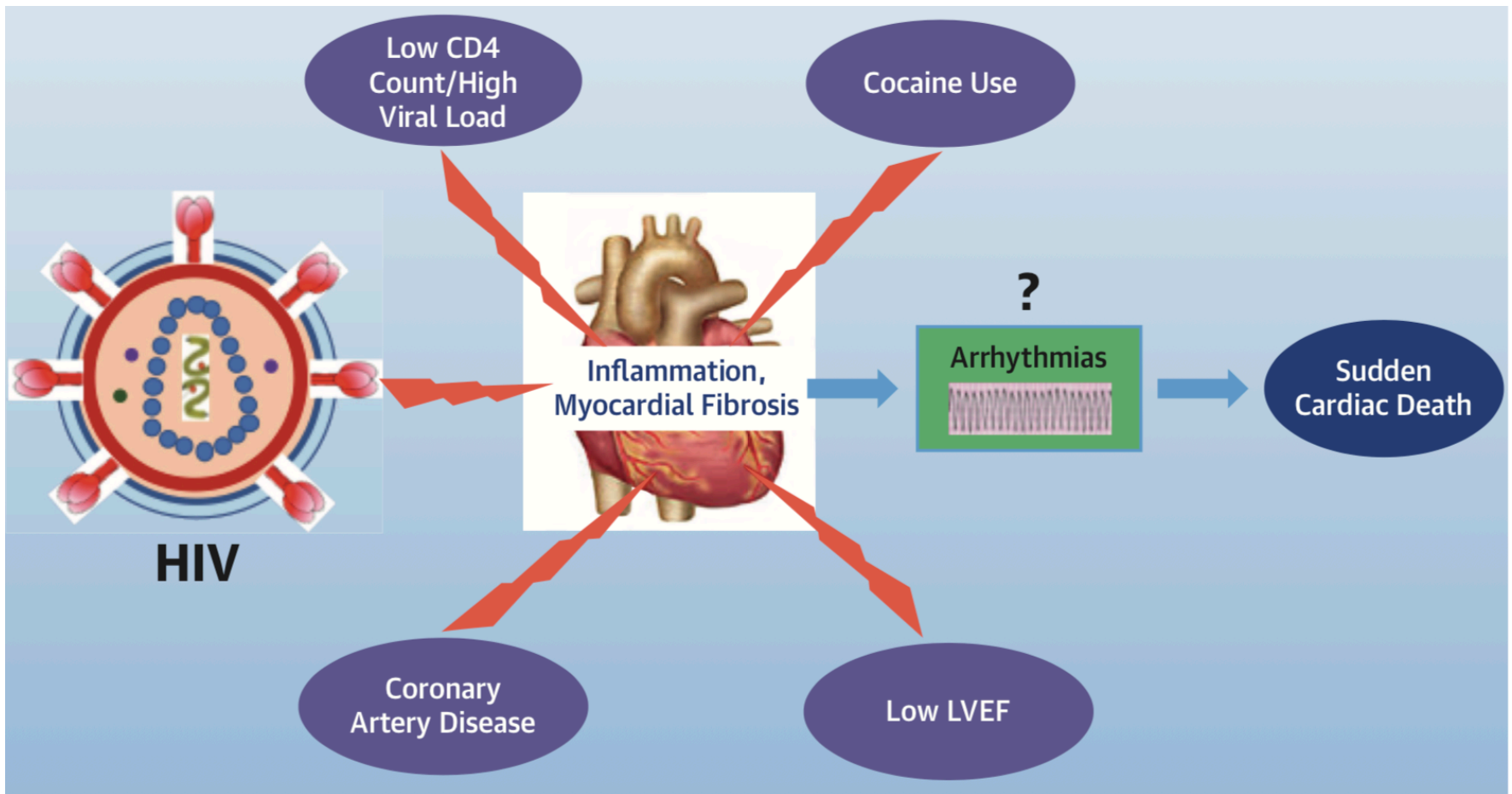
TABLE 2 Analysis of Association and Predictors of Sudden Cardiac Death Among Persons Living With Human Immunodeficiency Virus With Heart Failure

	Univariate Analysis				Multivariate Analysis*			
	Hazard Ratio	95% CI		p Value	Hazard Ratio	95% CI		p Value
		Lower	Upper			Lower	Upper	
Gender	1.223	0.821	1.843	0.28				
Age	1.027	0.965	1.086	0.22				
BMI	0.937	0.856	1.018	0.14				
Diabetes	1.453	0.827	2.639	0.27				
Hypertension	1.077	0.652	1.745	0.83				
Hyperlipidemia	1.242	0.854	1.866	0.16				
Smoking	1.162	0.825	1.724	0.37				
History of CAD	1.231	1.127	1.311	<0.001†	1.772	1.264	2.368	<0.001
Cocaine	1.372	1.185	1.516	<0.001†	1.571	1.223	2.113	0.002
LVEF	0.956	0.929	0.983	0.009†	0.803	0.727	0.985	0.017
PASP	1.035	0.986	1.164	0.09				
SBP	1.122	0.632	1.868	0.53				
DBP	1.138	0.588	1.726	0.50				
HR	1.151	0.863	1.611	0.47				
QRS duration	1.654	1.136	2.842	<0.001†	1.433	1.175	2.151	0.005
QTc interval duration	1.132	1.008	1.648	0.009†				
SA	1.020	0.814	1.253	0.97				
Viral load	1.211	1.123	1.492	<0.001†				
CD4 count	0.983	0.969	0.991	<0.001†	0.907	0.861	0.997	0.004
ART duration	1.011	0.933	1.245	0.83				
Beta-blocker	0.754	0.622	0.944	<0.001†	0.535	0.341	0.773	0.002
ACE inhibitor/ARB	0.966	0.842	1.224	0.73				
Spironolactone	1.114	0.883	1.463	0.81				
Furosemide	1.231	0.655	2.453	0.56				

*Cox proportional hazard regression for multivariate analysis for primary outcome (sudden cardiac death) among persons living with human immunodeficiency virus infection with heart failure, adjusting for

N=344 PLWH AND HF

- 3 Fold increase in SCD in HIV
- 10% risk of SCD per year



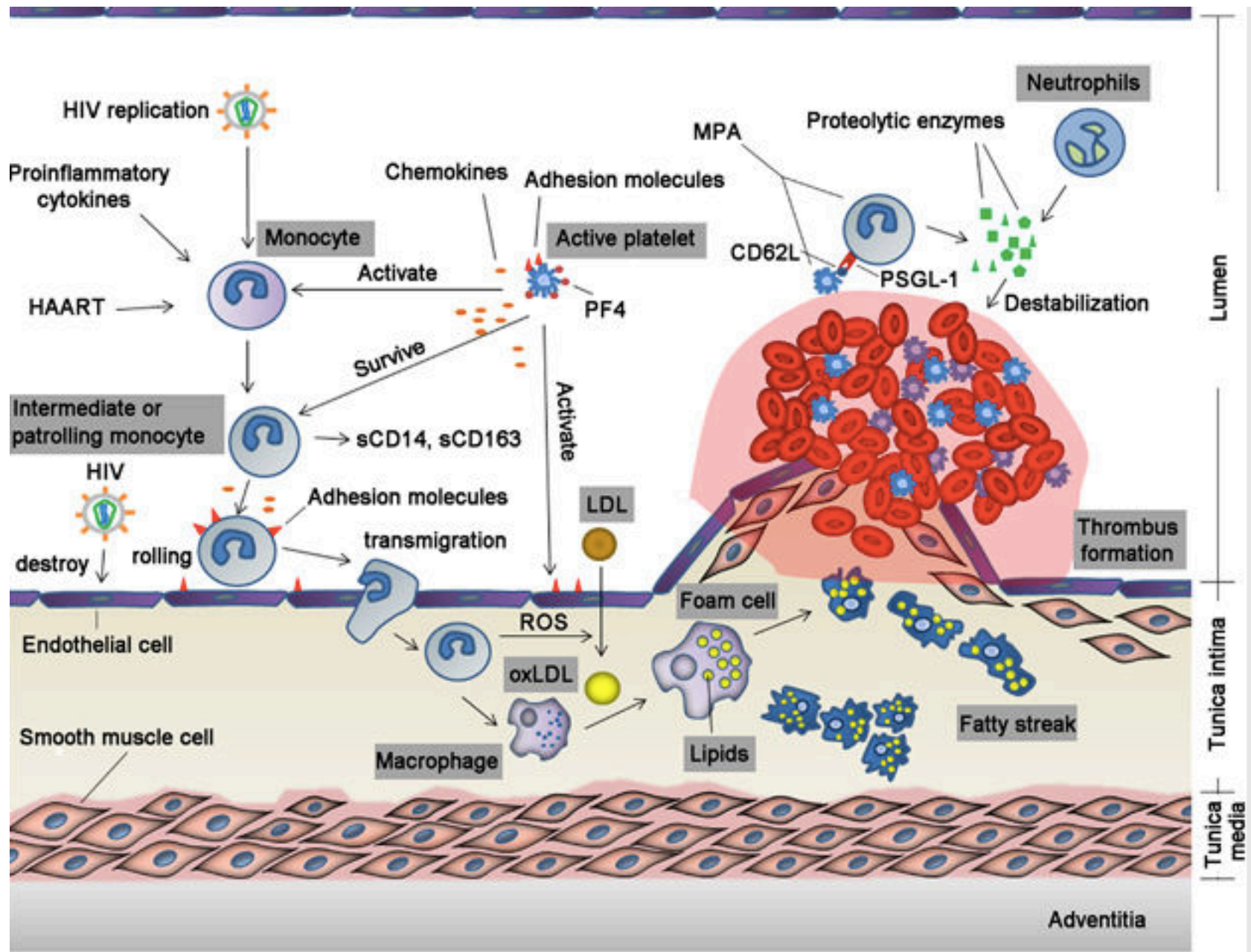
PATHOPHYSIOLOGY OF CVD IN HIV

HIV and Coronary Disease

- HIV infection is atherogenic
 - T cell proliferation/activation
 - Inflammatory markers
 - HIV coronary “arteriopathy”
- Protease inhibitors
 - 1998 first report of severe CAD in HAART patients
 - HAART-associated metabolic syndrome (Fat redistribution, dyslipidaemia, insulin resistance)

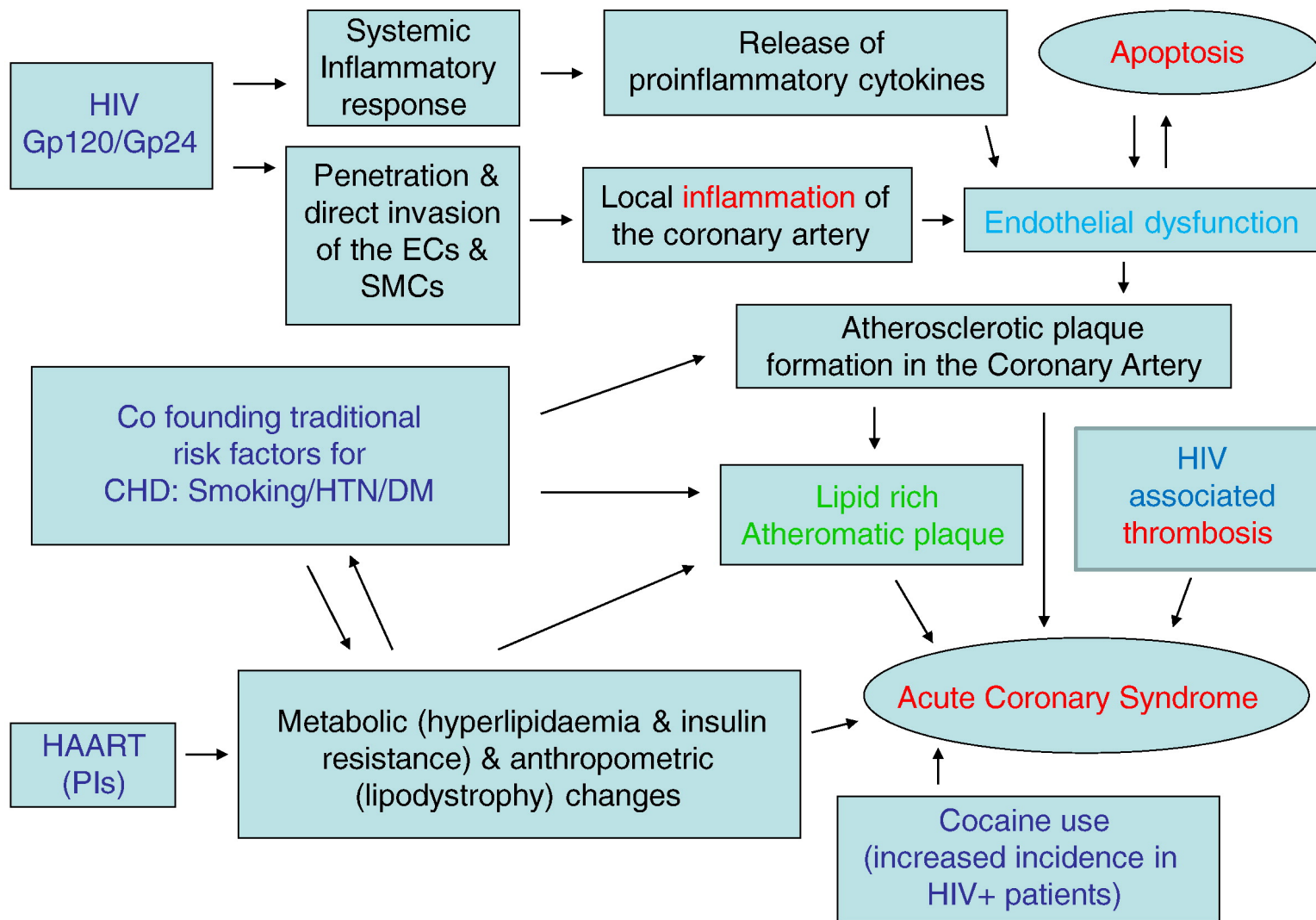
Combination ART and the metabolic syndrome

- Hyperlipidaemia
 - Affects 50% of patients using PI`s
 - 28% average increase in cholesterol
 - 96% average increase in triglycerides
- Hyperglycaemia
- Hypertension
- Lipodystrophy (lipoatrophy or lipohypertrophy)



Role of monocyte activation

- Monocyte activation occurs in HIV due to different mechanisms:
 - Replicating virus
 - Microbial translocation
 - Cytokine activation
 - Platelet activation
- SCD14 & SCD 163 are specific markers of monocyte activation in HIV



CVD RISK

Early Studies signaling risk of MI in HIV

Study	Event	N	Comment
VA ¹	1,207 CHD	36,766	No increase risk of MI with HAART or PI
DAD ²	126 MI	23,490	Greater risk with CART
Kaiser ³	65 MI	4408	Greater risk of MI HIV+ vs HIV- No greater risk on PIs
Medi-Cal ⁴	N/A	20,742	Greater risk of CHD with ART in 18 to 33 year olds, but not older individuals
French ⁵	49 MI	34,976	Greater risk of MI on PI vs HIV-
Johns Hopkins ⁶	43 CHD	2671	Greater risk of CHD HIV+ vs HIV-
German ⁷	29 MI	4993	Greater risk of MI prior to HAART
HOPS ⁸	21 MI	5672	Greater risk of MI PI vs no PI

***Retrospective and prospective studies; others retrospective.**

¹Bozzette SA, et al. N Engl J Med. 2003;348:702-710.

²Friis-Moller N, et al. N Engl J Med. 2003;349:1993-2003.

³Klein D, et al. JAIDS. 2002;30:471-477.

⁴Currier JS, et al. JAIDS. 2003;33:506-512.

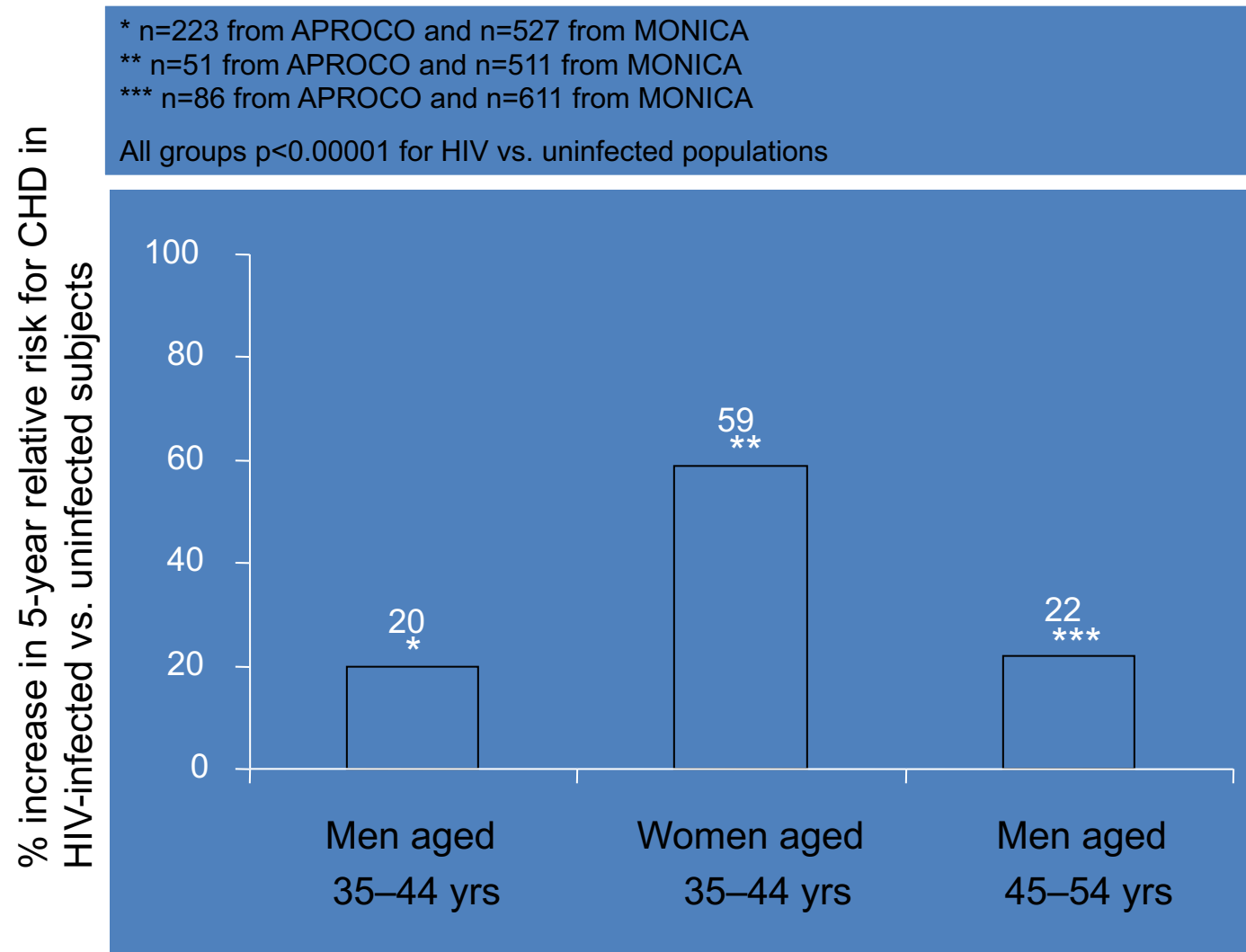
⁵Mary-Krause M, et al. AIDS. 2003;21:2479-2486.

⁶Moore RD, et al. 10th CROI. Boston. 2003. Abstract 132.

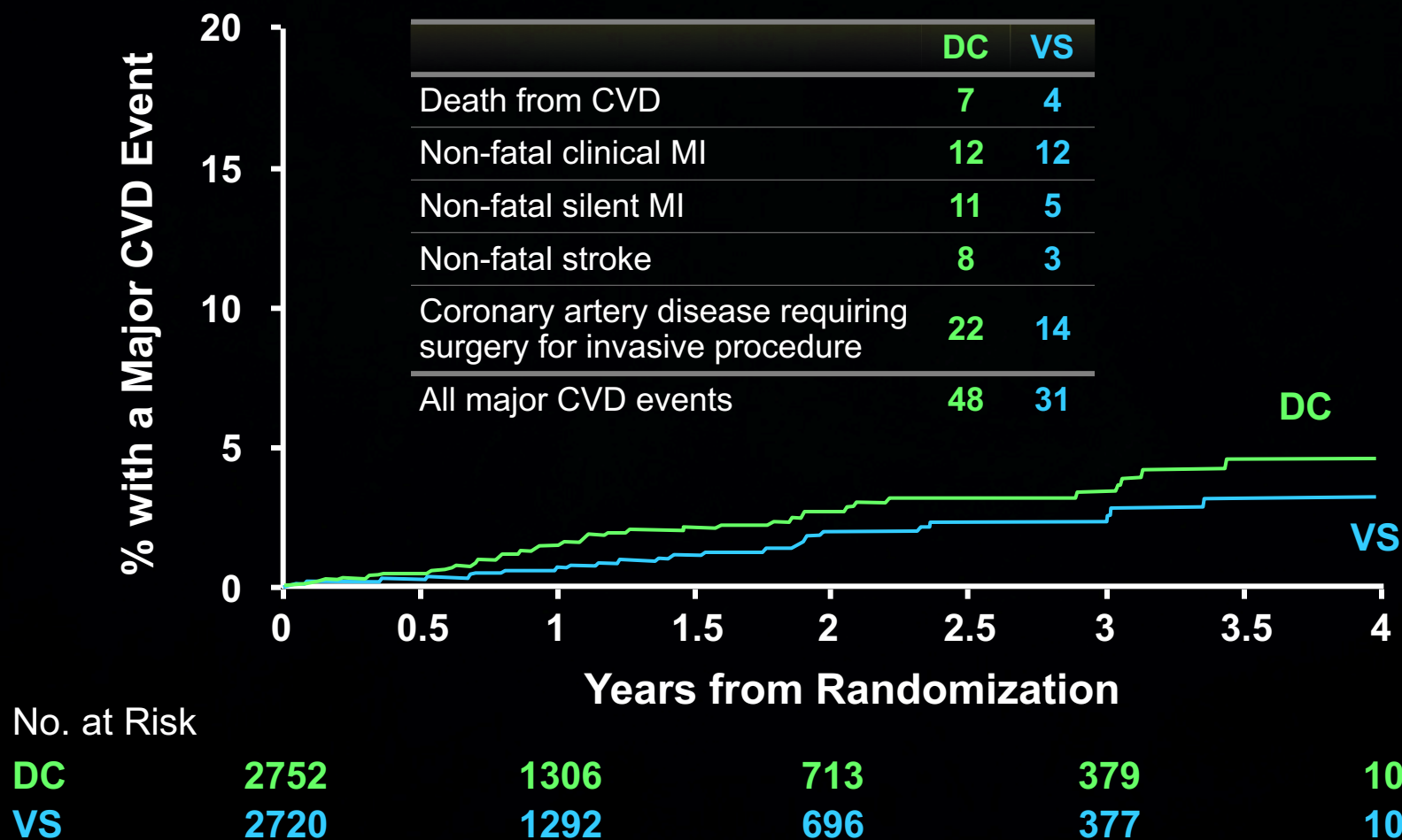
⁷Rickerts V, et al. Eur J Med Res. 2000;5:329-333.

⁸Homberg SD, et al. Lancet. 2002;360:1747-1748.

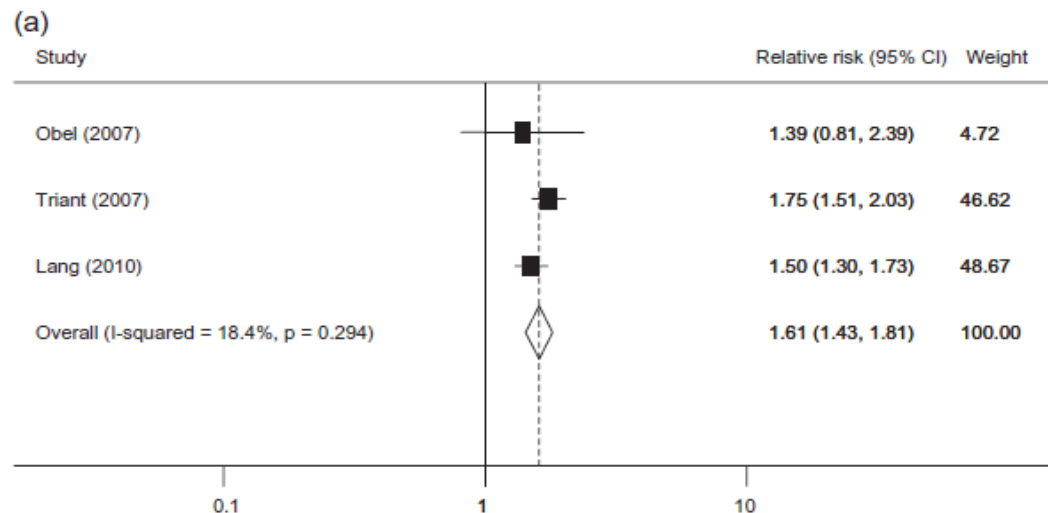
Increased risk of CHD in HIV infected subjects vs. the general population



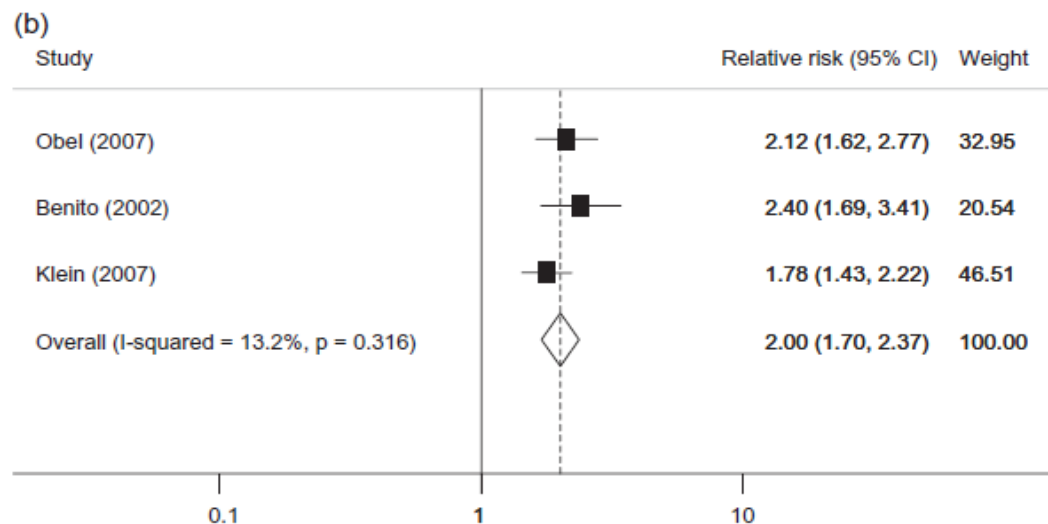
Risk of CVD with ART Interruptions



Risk of CVD in HIV vs. Non-HIV Patients



HIV – no ART
RR 1.61 (1.43-1.81)
p<0.001



HIV – on ART
RR 2.0 (1.7-2.37)
P<0.001

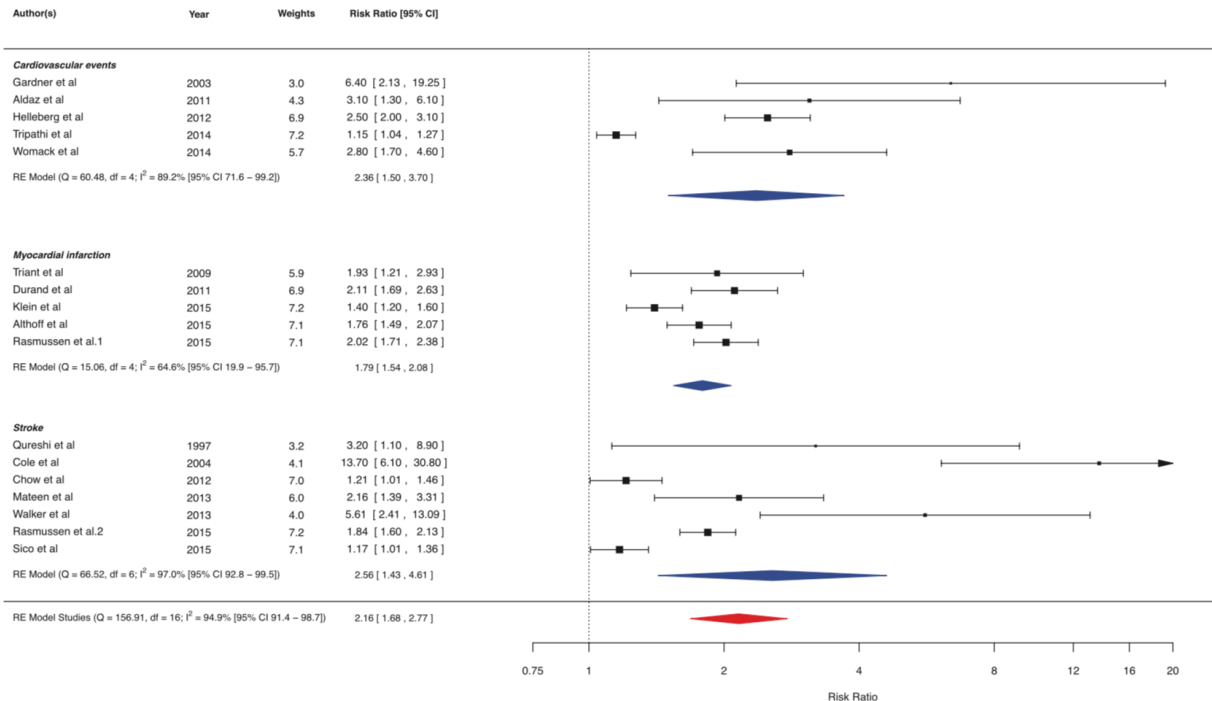
Circulation

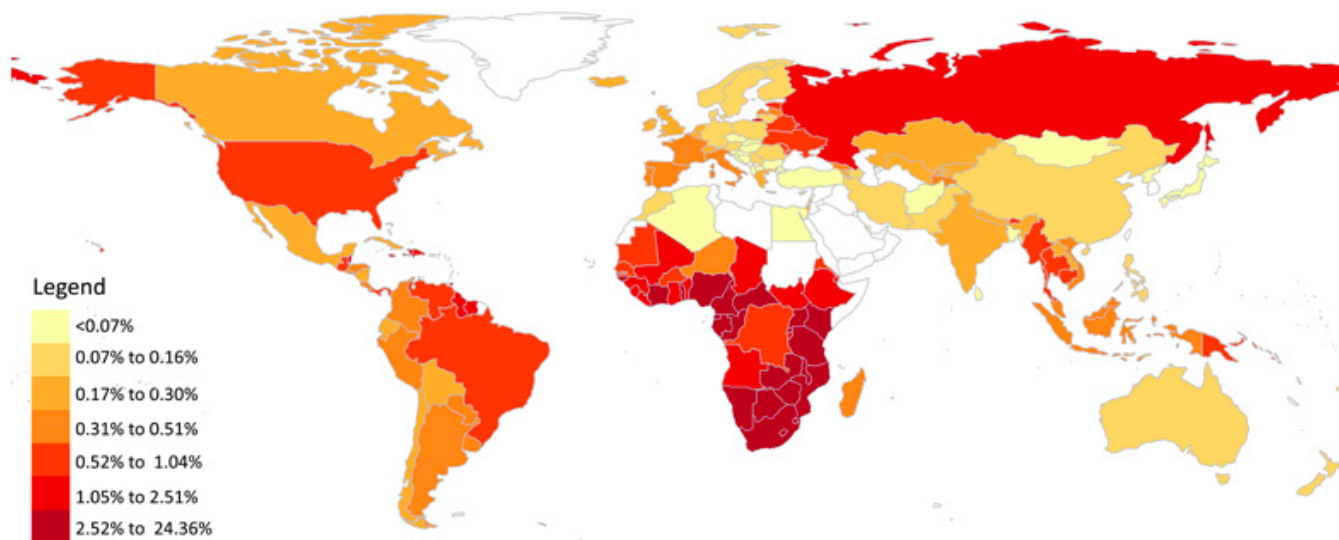
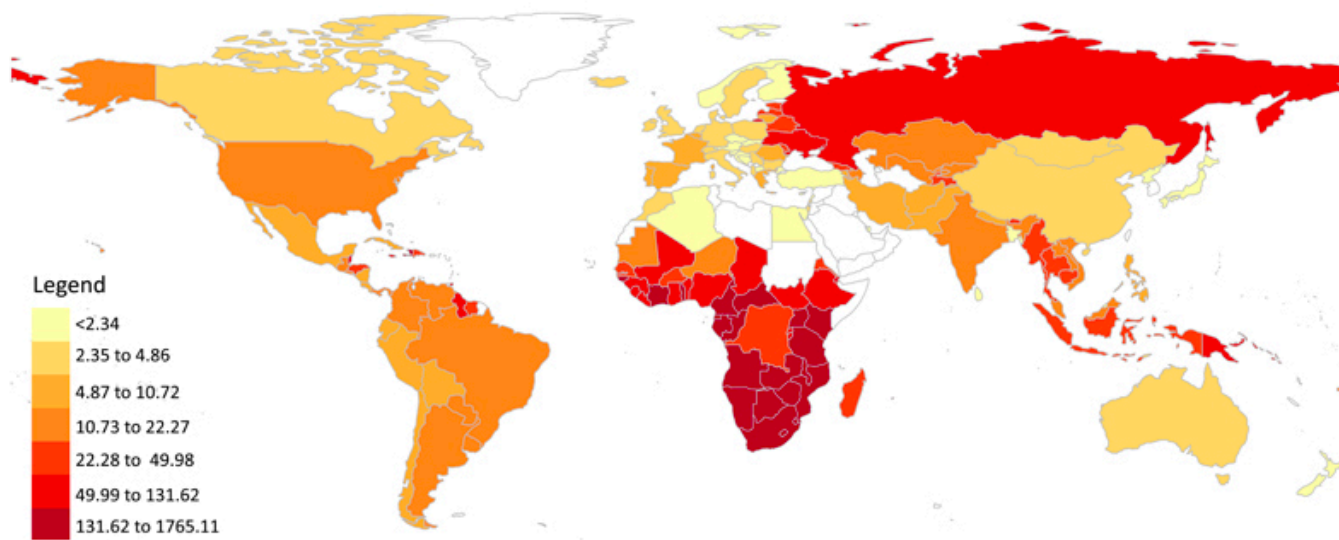
Vol. 138, No. 11 Originally published 10 Sep 2018

Global Burden of Atherosclerotic Cardiovascular Disease in People Living With HIV

Systematic Review and Meta-Analysis

- 793635 PLWH
- Random-effects metaanalysis
- 80 studies
- Over 26 years global population attributable fraction of CVD attributable to HIV increased from 0.36% to 0.92%
- DALYs increased from 0.74 to 2.6 million
- RR 2.16
- sub-Saharan Africa and Asia++



A**Population attributable fraction (%) by country****B****Disability adjusted life years per 100,000 persons by country**

Cardiovascular risk: our patients

Royal Free Hospital Q-Risk 2 Audit:

Average Q risk

HIV+ Women 3.5 % Vs National 1.5 %
(aged 46yrs in our area) **RR = 2.33**

HIV+ Men 12.46 % Vs National 7.9 %
(aged 54yrs in our area) **RR = 1.58**

No Association of Abacavir Use With Myocardial Infarction: Findings of an FDA Meta-Analysis

Xiao Ding, PhD,* Eugenio Andraca-Carrera, PhD,* Charles Cooper, MD,† Peter Miele, MD,‡ Cynthia Kornegay, PhD,§ Mat Soukup, PhD,* and Kendall A. Marcus, MD‡

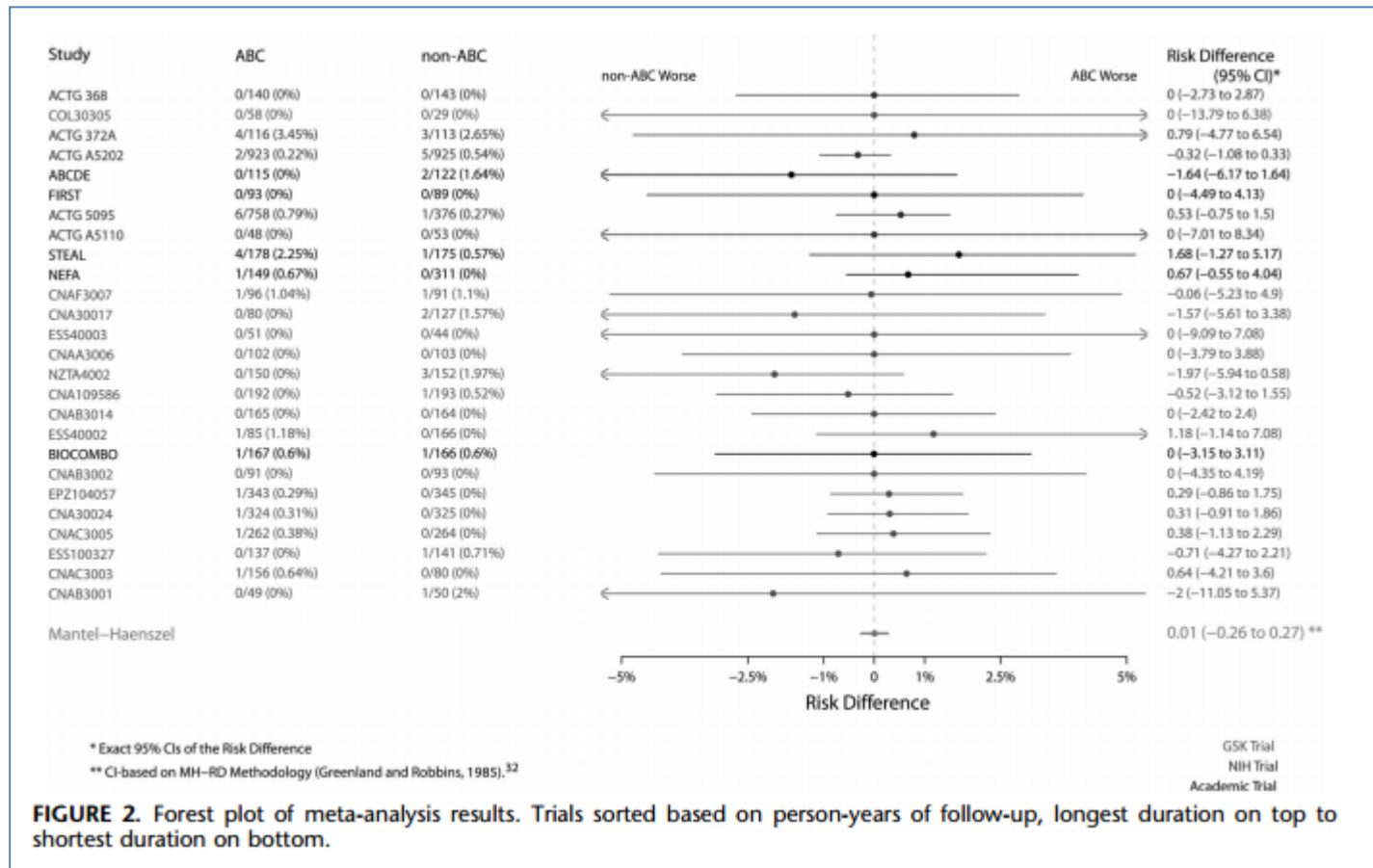
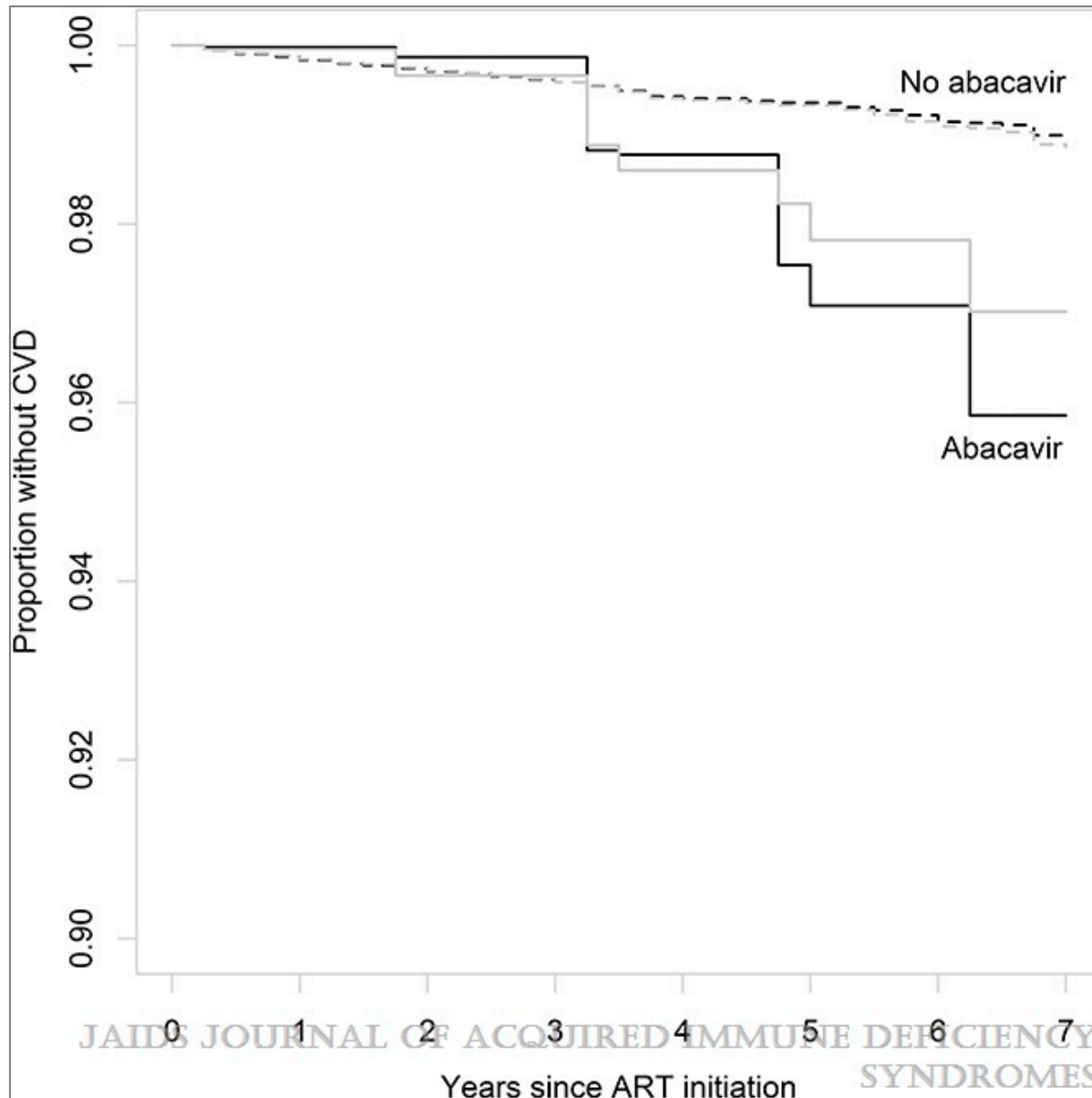


FIGURE 1



Use of Abacavir and Risk of Cardiovascular Disease Among HIV-Infected Individuals

Marcus, Julia L.; Neugebauer, Romain S.; Leyden, Wendy A.; Chao, Chun R.; Xu, Lanfang; Quesenberry, Charles P. Jr; Klein, Daniel B.; Towner, William J.; Horberg, Michael A.; Silverberg, Michael J.
JAIDS Journal of Acquired Immune Deficiency Syndromes 71(4):413-419, April 1st, 2016.

Risk of CVD among HIV-infected individuals initiating ART regimens with and without abacavir, Kaiser Permanente California, 1998–2011. Survival curves show the cumulative proportion without CVD after ART initiation.

SCREENING APPROACHES

1. RISK ASSESSMENT

- Global risk scores (such as the Framingham, Q-risk, JBS-3) use multiple traditional cardiovascular risk factors for risk assessment in all asymptomatic adults without a clinical history of CHD
- The problem is that all risk scores are weighted heavily upon age such that risk assessment in the younger HIV population tends to underestimate risk

Framingham*	Q-risk	JBS
Age Sex Total cholesterol HDL cholesterol Smoking, Systolic blood pressure	Age Sex Ethnicity Post Code Smoking Diabetes CKD Family history Atrial Fibrillation Blood pressure Cholesterol/HDL ratio Rheumatoid Arthritis BMI	As Q-risk Uses Townsend quintile Gives Heart Age

How to risk assess in HIV?

- Framingham X 1.5_1
- Q RISK 2 X 1.6_2
- D:A:D score₃

1 Veterans administration cohort

2 Q Risk UK

2 D:A:D study group

D:A:D model

- Based on observations in **32,663** HIV-positive persons from 20 European countries and Australia
- Participants were free of CVD at study entry and who provided full information on cardiovascular risk factors.
- The rate of a composite CVD end point, comprising myocardial infarction (MI), stroke, coronary artery revascularization, carotid endarterectomy, or any CVD death, was assessed over **186,364.5** person-years.
- Full and reduced D:A:D models were developed to calculate estimated 5-year risks of CVD.

D:A:D model

- **Currently Cigarette Smoker?:** Yes/No
- **Previous Cigarette Smoker?:** Yes/No
- **Diabetic ?:** Yes/No
- **Family CVD history?:** Yes/No
- **Currently using Indinavir? (Y/N):** Yes/No (no of years)
- **Currently using Lopinavir?:** Yes/No (no of years)
- **Currently using abacavir?: (Y/N):** Yes/No
- **Systolic blood pressure:**
- **Total cholesterol: HDL:**

About you

Age (25-84):

Sex: ☒ Male ☐ Female

Ethnicity:

UK postcode: leave blank if unknown

Postcode:

Clinical information

Smoking status:

Diabetes status:

Angina or heart attack in a 1st degree relative < 60? ☐

Chronic kidney disease (stage 4 or 5)? ☐

Atrial fibrillation? ☐

On blood pressure treatment? ☐

Rheumatoid arthritis? ☐

Leave blank if unknown

Cholesterol/HDL ratio:

Systolic blood pressure (mmHg):

Body mass index

Height (cm):

Weight (kg):

Calculate risk

Q RISK 2 2017

% 10 year risk of MI & CVA

About you

Age (25-84):

64

Sex:

☒ Male ☐ Female

Ethnicity:

White or not stated

UK postcode: leave blank if unknown

Postcode:

Clinical information

Smoking status:

non-smoker

Diabetes status:

none

Angina or heart attack in a 1st degree relative < 60? ☐

Chronic kidney disease (stage 3, 4 or 5)? ☐

Atrial fibrillation? ☐

On blood pressure treatment? ☐

Do you have migraines? ☐

Rheumatoid arthritis? ☐

Systemic lupus erythematosus (SLE)? ☐

Severe mental illness? ☐

On atypical antipsychotic medication? ☐

Are you on regular steroid tablets? ☐

A diagnosis of or treatment for erectile dysfunction? ☐

Leave blank if unknown

Cholesterol/HDL ratio:

Systolic blood pressure (mmHg):

Standard deviation of at least two most recent systolic blood pressure readings (mmHg):

Body mass index

Q RISK 3 2018

Welcome to the QRISK[®]3-2017 risk calculator

Welcome to the QRISK[®]3-2017 Web Calculator. You can use this calculator to work out your risk of developing a heart attack or stroke over the next 10 years by answering some simple questions.

The QRISK[®]3 algorithm has been developed by doctors and academics working in the UK National Health Service and is based on routinely collected data from many thousands of GPs across the country who have freely contributed data to the QResearch database for medical research.

QRISK[®]3 has been developed for the UK population, and is intended for use in the UK. All medical decisions need to be taken by a patient in consultation with their doctor. The authors and the sponsors accept no responsibility for clinical use or misuse of this score.

The science underpinning QRISK[®]3 has been published in the BMJ -- see the publications tab for details.

What is the difference between QRISK[®]3 and QRISK[®]2?

QRISK[®]3 includes more factors than QRISK[®]2 to help enable doctors to identify those at most risk of heart disease and stroke.

These are

- Chronic kidney disease, which now includes stage 3 CKD
- Migraine
- Corticosteroids
- Systemic lupus erythematosus (SLE)
- atypical antipsychotics
- severe mental illness
- erectile dysfunction
- a measure of systolic blood pressure variability

How do the scoring systems compare?

	Framingham 10 year risk N=195/1153	QRISK2 10 year risk N=195	DAD 5 year risk N=195
Number of patients with a risk of $\geq 20.0\%$	25 (12.8%)	41 (21.0%)	4 (2.1%)
Number of patients with a risk of 10.0%- 19.9%	170 (87.2%)	83 (42.6%)	19 (9.7%)
Number of patients with a risk of 5.0% - 9.9%	0	50 (25.6%)	66 (33.8%)
Number of patients with a risk of $< 5.0\%$	0	21 (10.8%)	106 (54.4%)

Cardiovascular assessment

- Estimate overall cardiac risk⁽¹⁻³⁾
 - Fasting assessments prior to ART initiation or switching, 3 to 6 months later, and annually during stable ART¹
 - Total, HDL, and LDL cholesterol, triglycerides, and glucose^{2,3}
 - HbA1c or oral glucose tolerance test in those at risk of type 2 diabetes or with severe lipodystrophy³
- Assess ALL other modifiable cardiac risk factors
 - Blood pressure
 - Smoking
 - Exercise/BMI
 - Recreational drugs

1. Schambelan M et al. *JAIDS* 2002;31:257–275

2. Dube MP et al. *CID* 2003;37:613–627

3. Grinspoon S and Carr A. *N Engl J Med* 2005;352:48–62

2. GUIDELINES

BHIVA 2016



BHIVA guidelines on the routine investigation and monitoring of HIV-1-positive adults

Recommendations

- We recommend that patients with established CVD and those at increased risk of CVD (10 year CVD risk >10%) are screened annually for hypertension, diabetes, dyslipidaemia and chronic kidney disease, and that BMI, smoking status and antiretroviral therapy are reviewed annually (GPP).
- We recommend against the evaluation of inflammatory or coagulation biomarkers and imaging studies as part of routine clinical care (GPP).

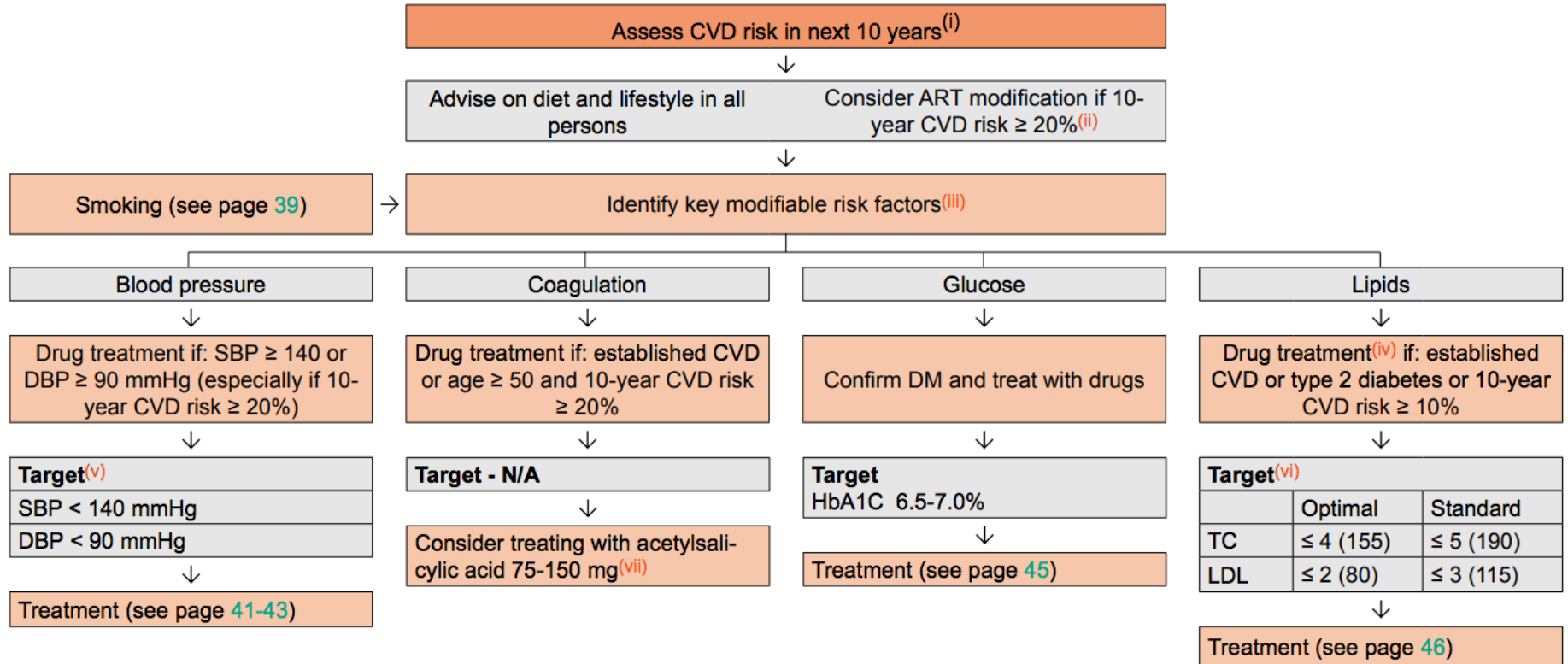
Evidence

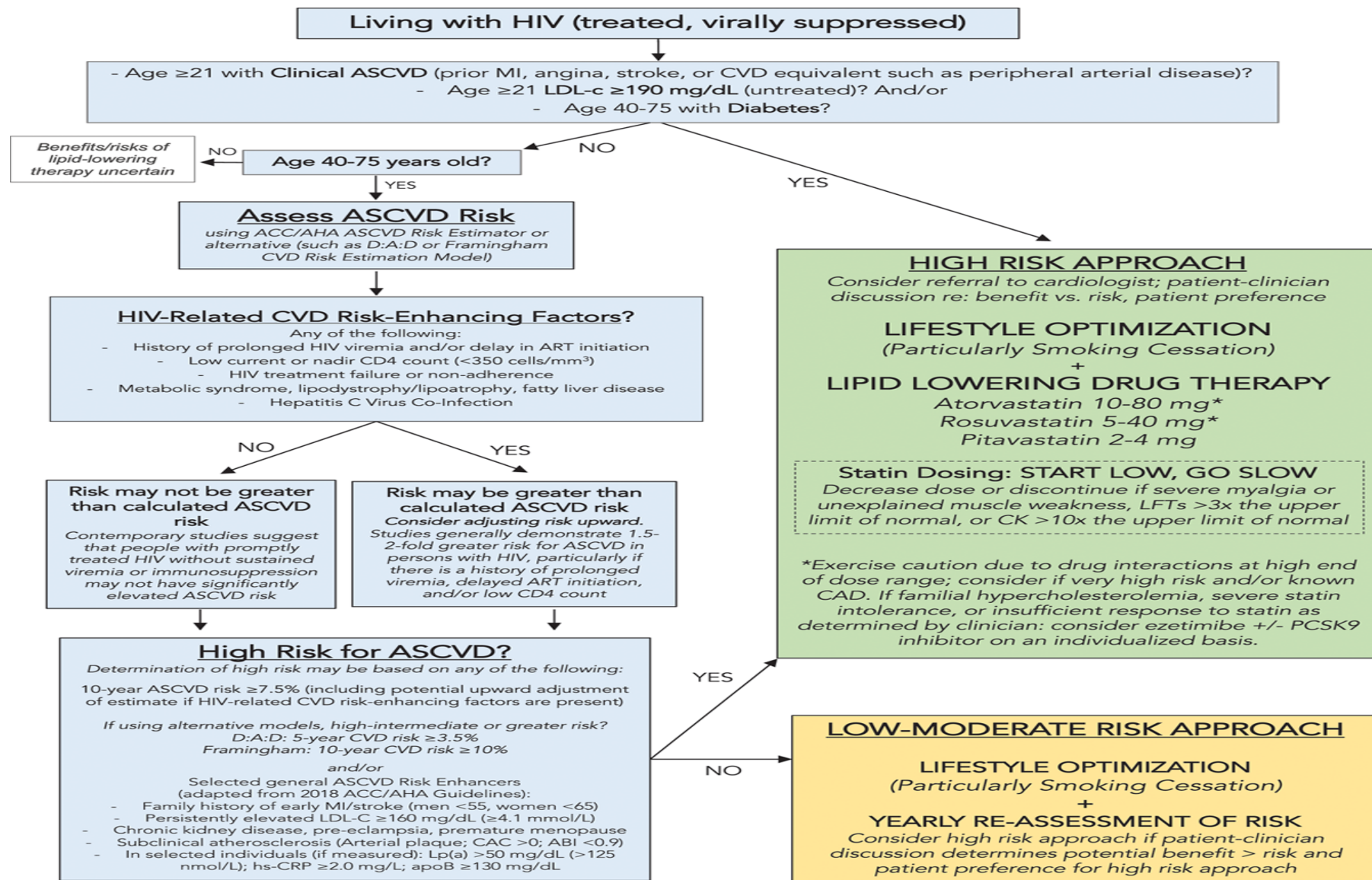
HIV-positive patients are at increased risk of myocardial infarction (MI) and other manifestations of cardiovascular disease [1,2], although the CVD incidence may be decreasing due to better control of modifiable risk factors such as hypertension and dyslipidaemia [3]. Hypertension, dyslipidaemia, diabetes and smoking are major, modifiable risk factors [4]. In addition, some studies have identified an association between MI or cardiovascular disease (CVD) events and exposure to abacavir, didanosine and/or lopinavir [5-7], and these drugs may be best avoided in patients at high CVD risk [8]. Poor HIV control may further contribute to the heightened risk of cardiovascular complications in this population [9].

NICE guidelines recommend that patients with established CVD receive advice on restricting dietary salt, saturated fat, cholesterol and alcohol intake, weight reduction, physical activity and smoking cessation, and receive high-dose (80 mg) atorvastatin [10]. Although firm evidence in HIV populations is lacking, we endorse this recommendation for HIV-positive patients.

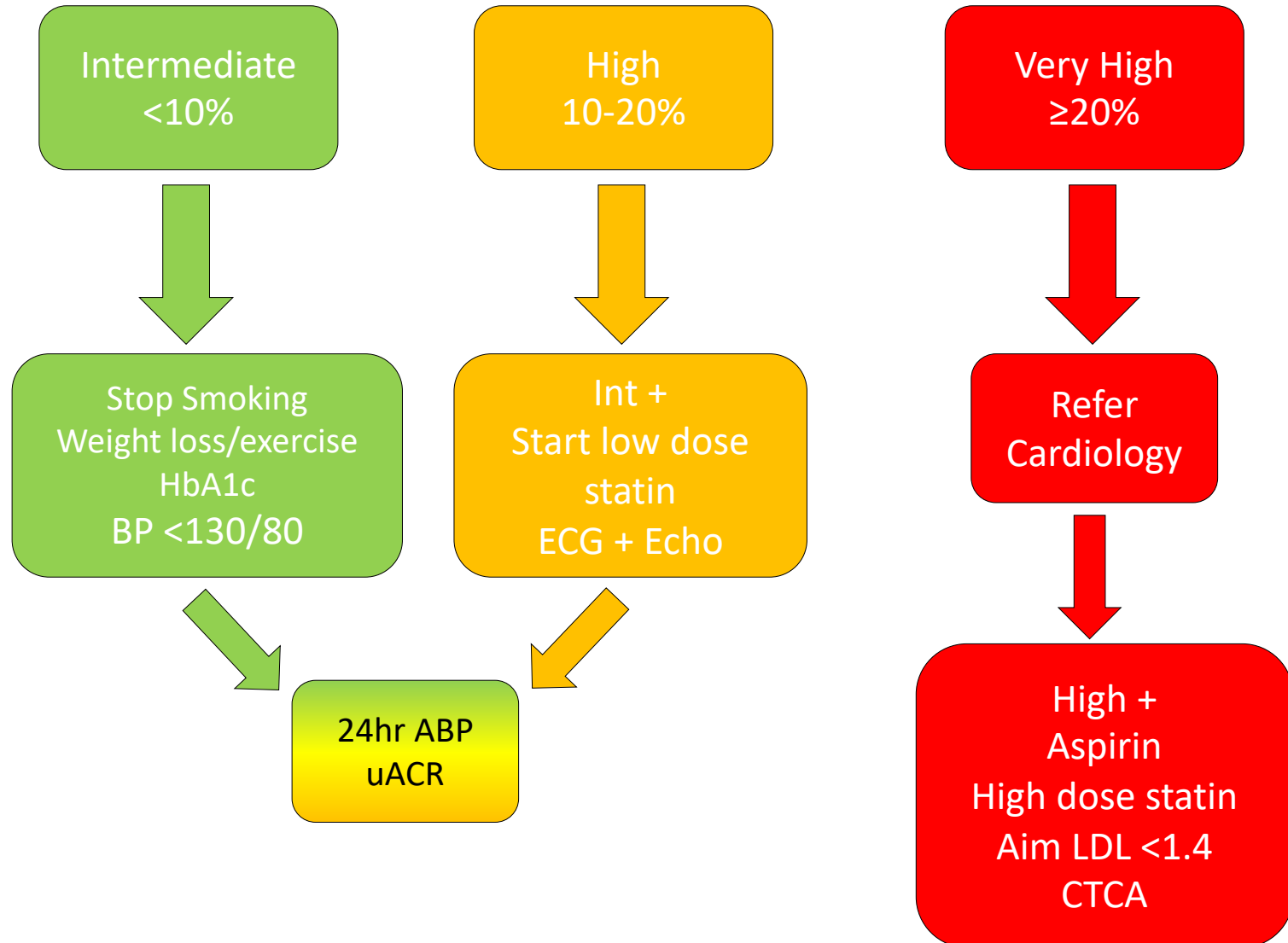
Prevention of CVD

Principles: The intensity of efforts to prevent CVD depends on the underlying risk of CVD, which can be estimated⁽ⁱ⁾. The preventive efforts are diverse in nature and require involvement of a relevant specialist, in particular if the risk of CVD is high and always in persons with a history of CVD.

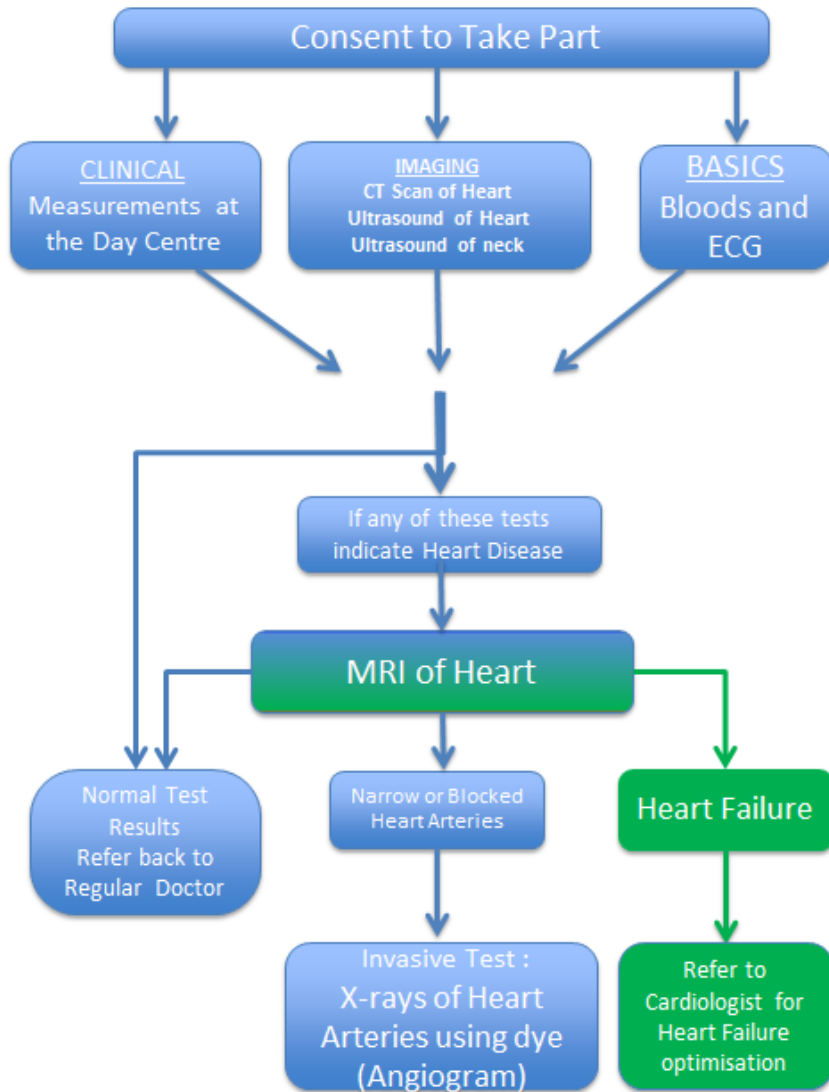




Royal Free PLWH Modified Q-Risk Pathway



H-ART to HEART



35 – 55 yrs. old
African/Caribbean Women
Or Caucasian Men (MSM)
No known Cardiac Risk Factors
No Symptoms of Chest Pain or SOB
Non-smokers
Not on statin therapy

Contact: g.manmathan@nhs.net
Or Ext 37002

Email: rf.hart2heart@nhs.net

Conclusions

- Patients with HIV are at risk of premature coronary disease due to an interplay between conventional risk factors, the effects of ART and immune reactivation
- CVD burden will increase as this population ages
- Cardiomyopathy, HT and arrhythmia are also common problems seen
- Risk stratification and early detection is important for patients on ART. Current risk assessment tools are limited
- Interventions should be aimed at increasing awareness, lifestyle modification and aggressive treatment of HT, Dyslipidaemia and glucose intolerance
- A dedicated Multi-disciplinary HIV – Cardiac clinic is a proposed model of care

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