HIV ve KVS

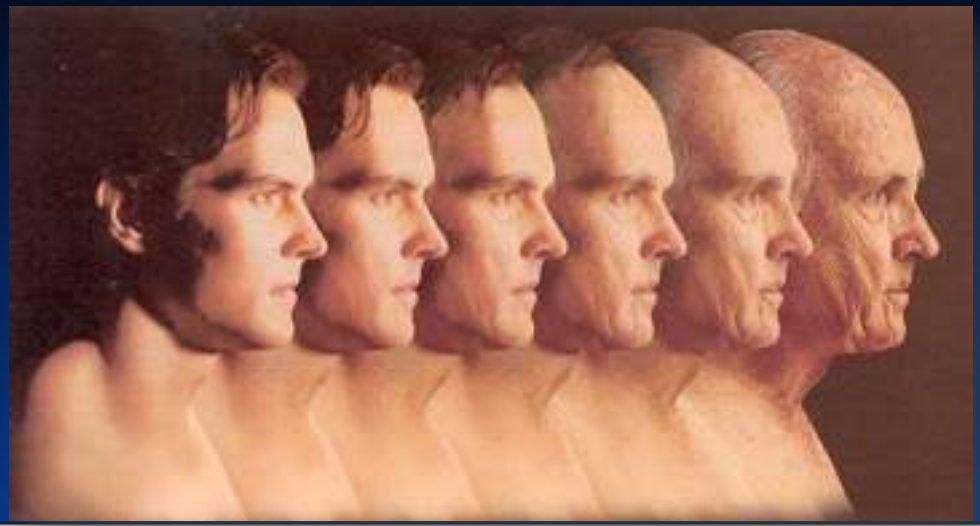
Dr. Serap Gençer

Acıbadem MAA Üniversitesi Maslak Hastanesi, İstanbul

Ulusal HIV Kongresi, Antalya

20.11.2021

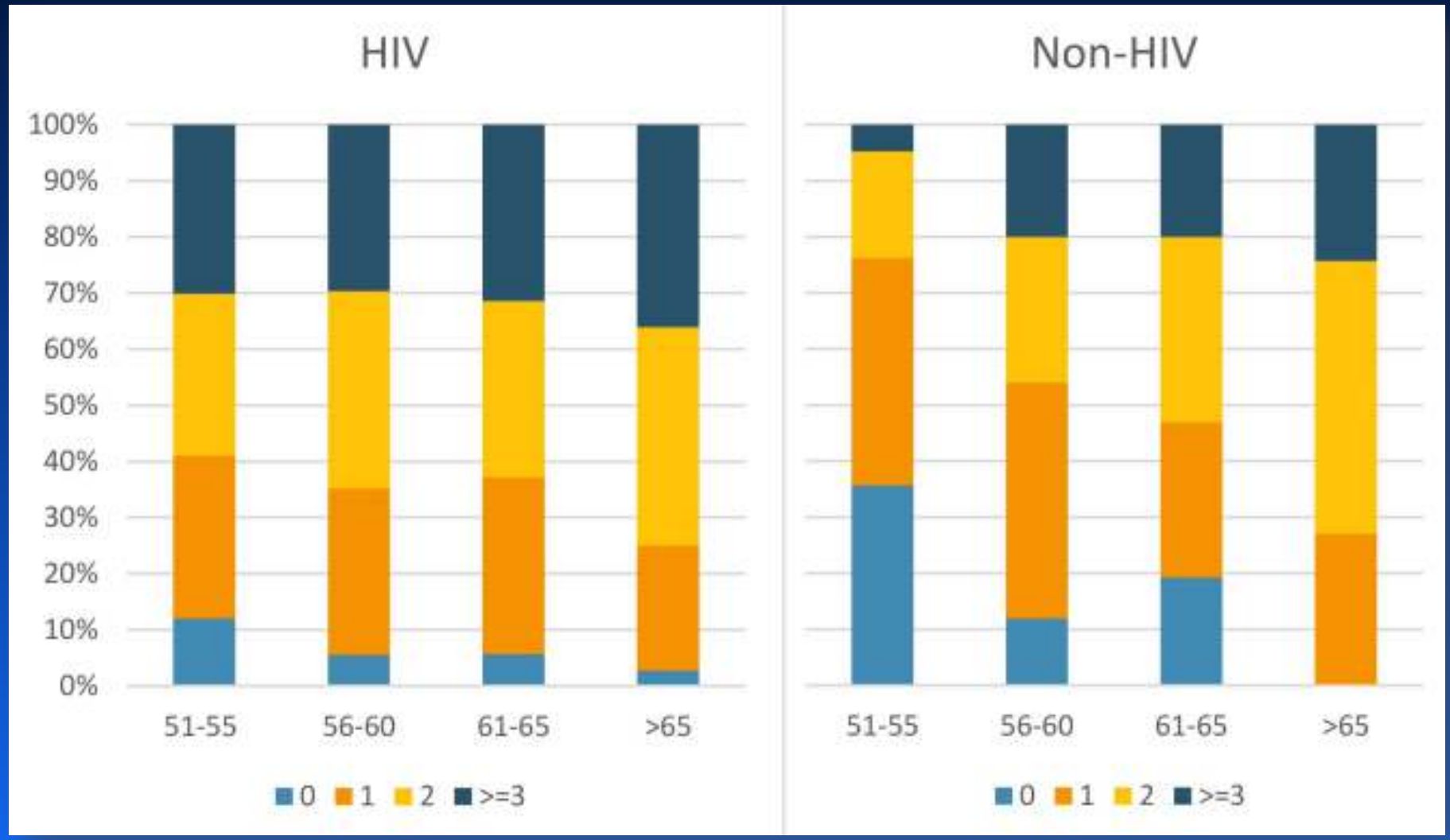
- Epidemiyoloji
- Risk faktörleri
- Göstergeler
- Değerlendirme
- Tedavi ve yönetim



Yaşam süresi

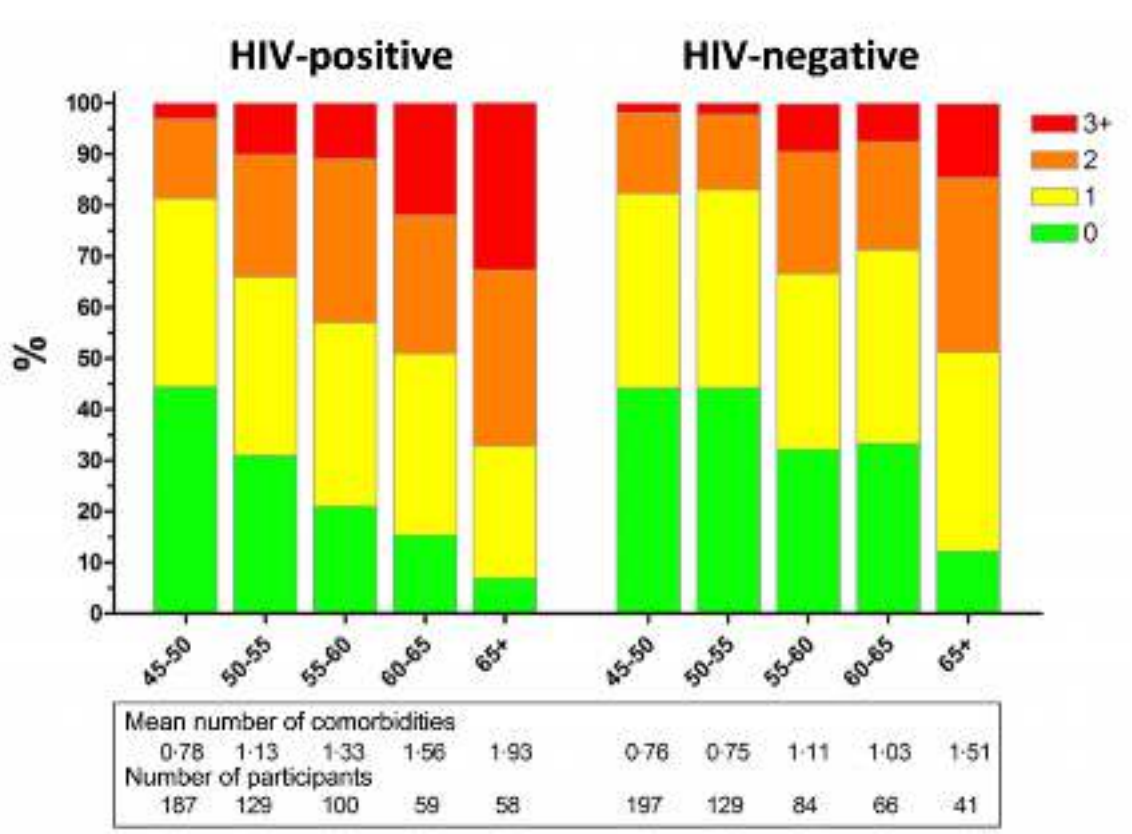
Komorbiditeler

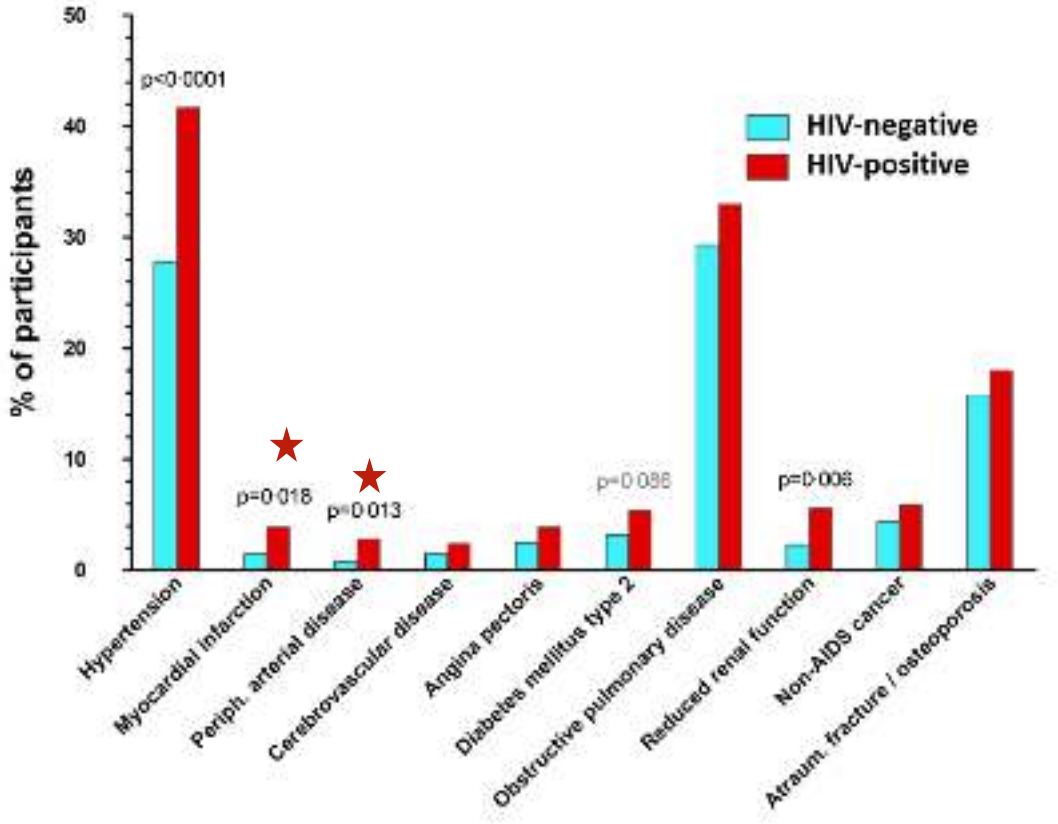
Comorbidity is more common and occurs earlier in persons living with HIV than in HIV-uninfected matched controls, aged 50 years and older: A cross-sectional study



Maciel RA, et al. International Journal of Infectious Diseases 2018; 70: 30–35

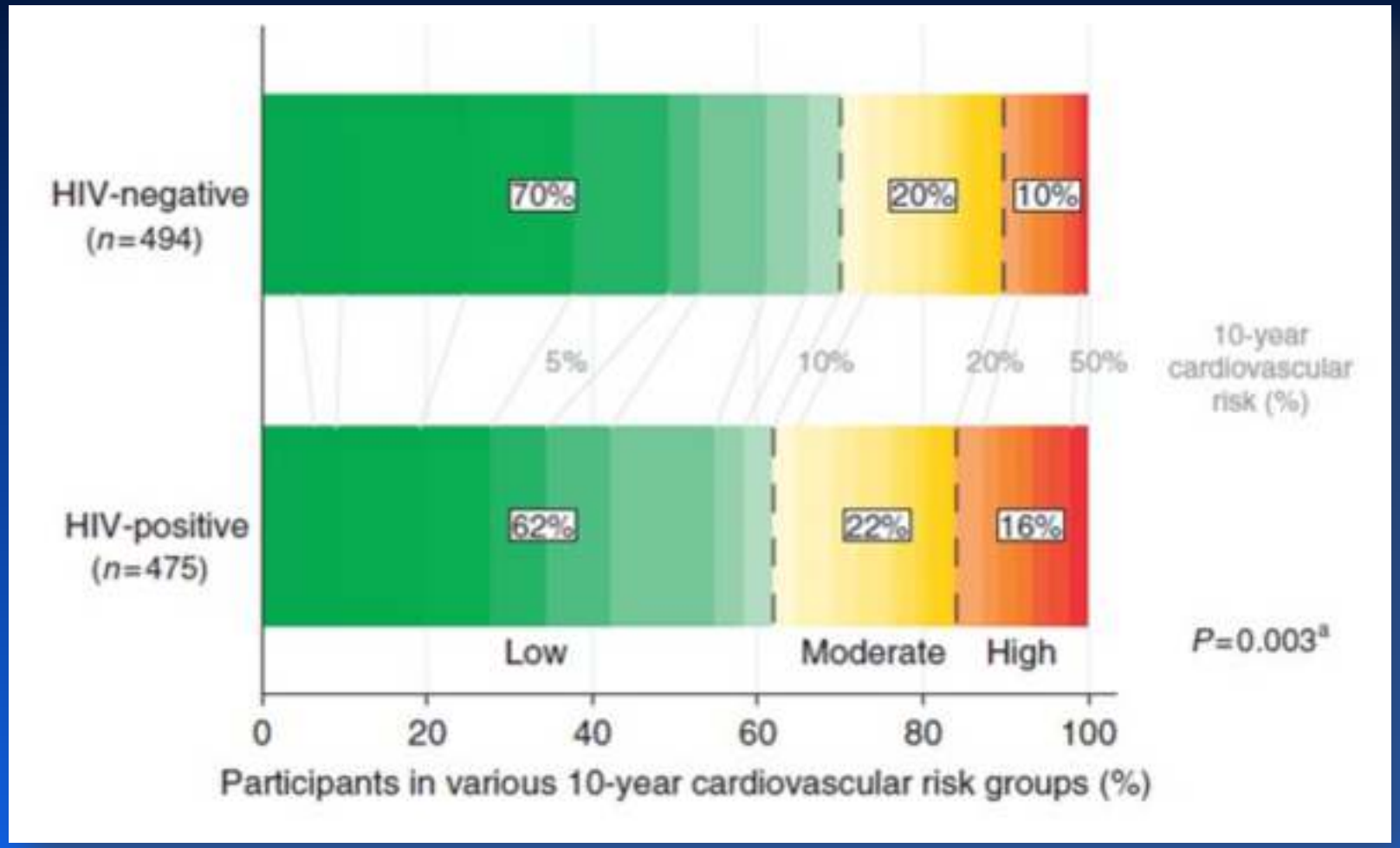
Cross-sectional Comparison of the Prevalence of Age-Associated Comorbidities and Their Risk Factors Between HIV-Infected and Uninfected Individuals: The AGEhIV Cohort Study





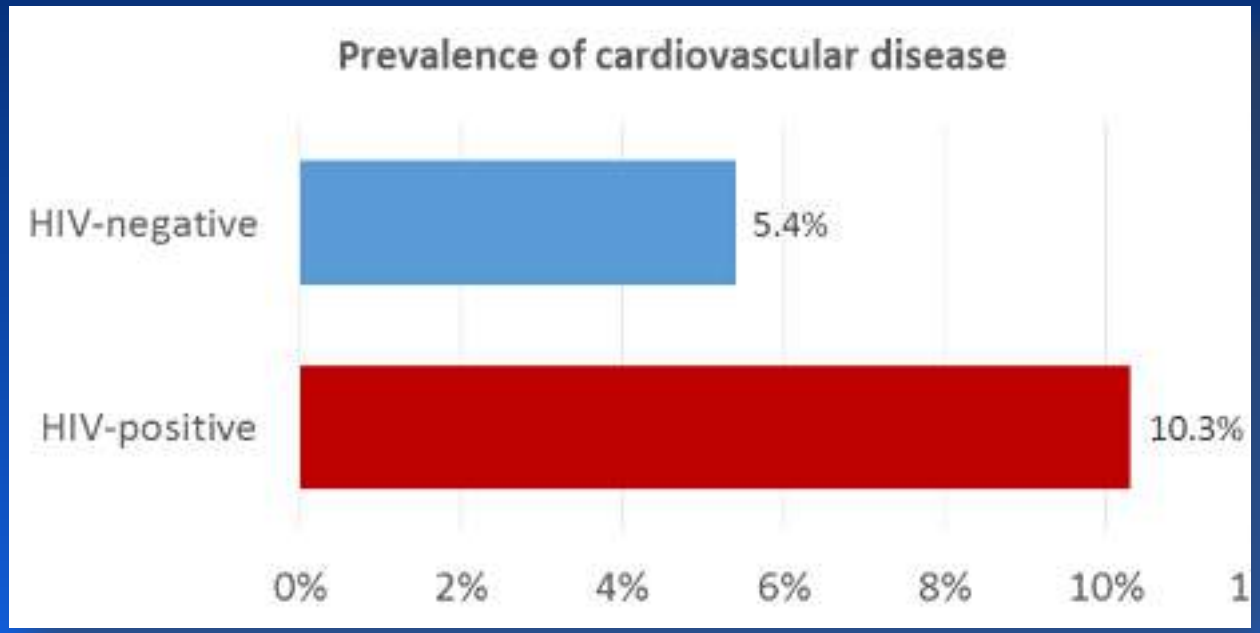
SG-2021/11

Clinical Infectious Diseases® 2014;59(12):1787–97


HIV-negative
(n=494)
70%
20%
10%
5%
10%
20%
50%
10-year cardiovascular risk (%)
HIV-positive
(n=475)
62%
22%
16%
Low
Moderate
High
P=0.003a
0
20
40
60
80
100
Participants in various 10-year cardiovascular risk groups (%)

KVH Prevalansı

- Yaklaşık %20
- Enfekte bireylerde >2 kat yüksek



Circulation 2018;138:1100-1112

Global Burden of Atherosclerotic Cardiovascular Disease in People Living With HIV: Systematic Review and Meta-Analysis

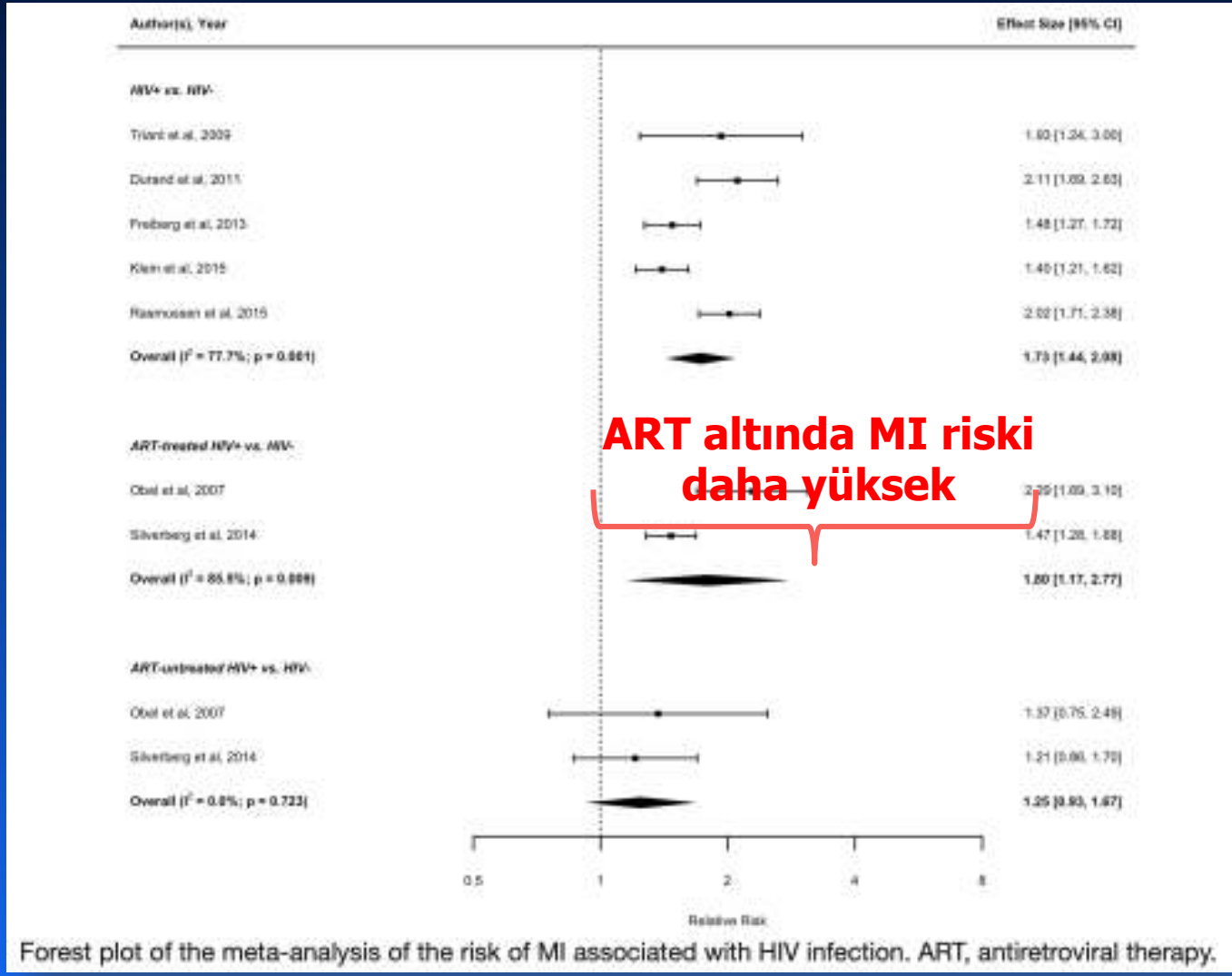
- KVH insidansı
- RR: 2.16
  - MI için 1.79
  - Stroke için 2.56

Shah ASV, Stelzle D, Lee KK, et al. Circulation 2018; 138:1100-1112.

- KKH (AMI, diğer iskemik kalp hast., koroner AS) insidansı
  - Erkekler için RR: 6.76, 95% CI 3.36–13.58
  - Kadınlar için RR: 2.47, 95% CI 1.23– 4.95
  - 45 yaş üzerinde daha belirgin artış
- MI riski 2 kat yüksek
- Ani kalp ölümü 4 kat yüksek
- Kadınlarda metabolik sendrom daha fazla

Freiberg MS, Chang CC, Kuller LH, et al. JAMA Intern Med 2013; 173:614.
Currier JS, Taylor A, Boyd F, et al. J Acquir Immune Defic Syndr 2003; 33:506.

Risk of myocardial infarction among people living with HIV: an updated systematic review and meta-analysis



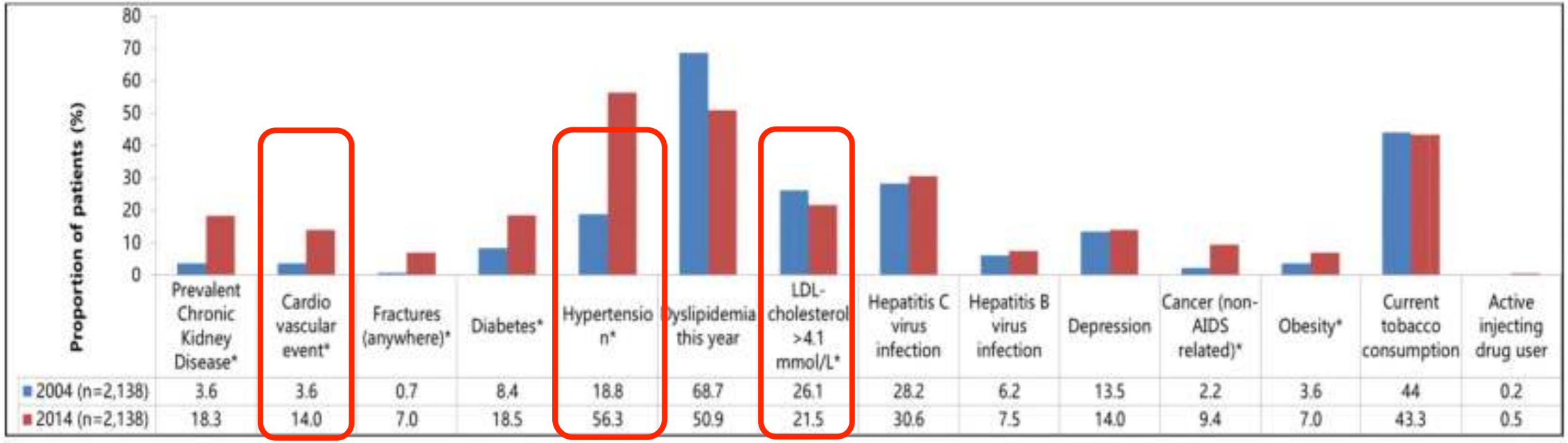
Forest plot of the meta-analysis of the risk of MI associated with HIV infection. ART, antiretroviral therapy.

Eyawo O, et al. BMJ Open 2019;9:e025874.

- **Global HIV ilişkili MI ve stroke yükü son 2 dekatta 3 kat arttı.**

Circulation 2018;138:1100-1112

Evolution of comorbidities in people living with HIV between 2004 and 2014: cross- sectional analyses from ANRS CO3 Aquitaine cohort

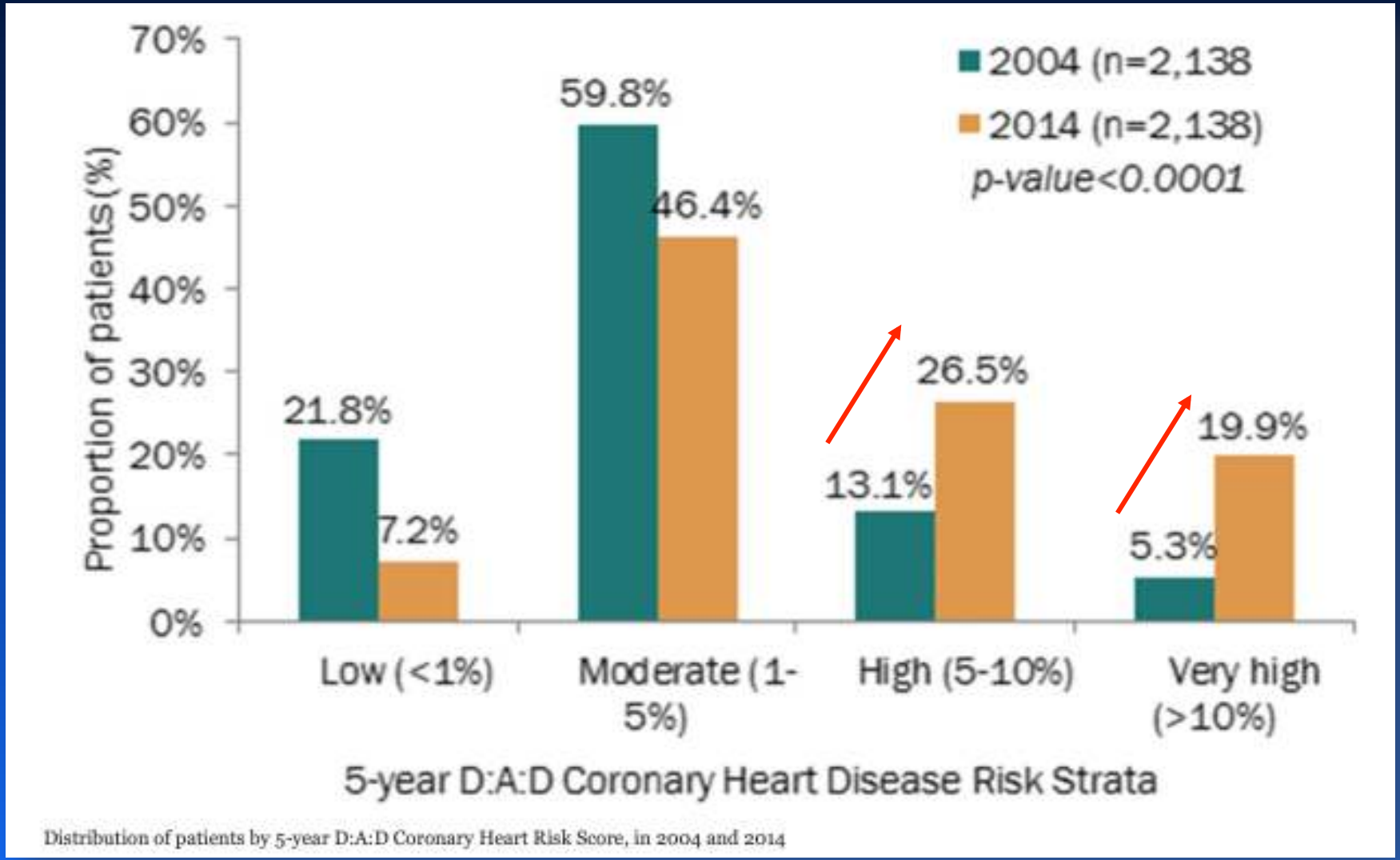


	Prevalent Chronic Kidney Disease*	Cardio vascular event*	Fractures (anywhere)*	Diabetes*	Hypertension*	Dyslipidemia this year	LDL-cholesterol >4.1 mmol/L*	Hepatitis C virus infection	Hepatitis B virus infection	Depression	Cancer (non-AIDS related)*	Obesity*	Current tobacco consumption	Active injecting drug user
2004 (n=2,138)	3.6	3.6	0.7	8.4	18.8	68.7	26.1	28.2	6.2	13.5	2.2	3.6	44	0.2
2014 (n=2,138)	18.3	14.0	7.0	18.5	56.3	50.9	21.5	30.6	7.5	14.0	9.4	7.0	43.3	0.5

*p<0.01 for comparison between 2004 and 2014

Chronic Comorbidities in 2004 and 2014, ANRS CO3 Aquitaine Cohort

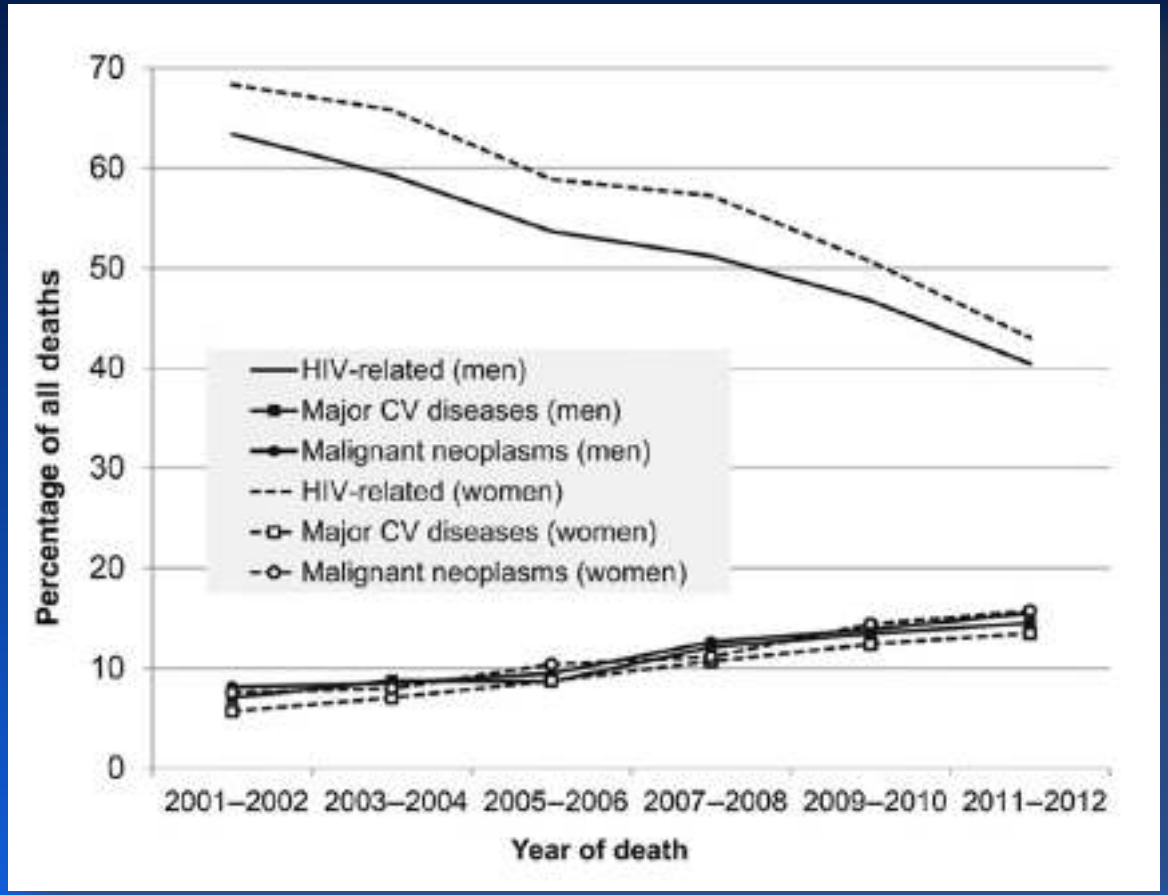
Bonnet et al. BMC Infectious Diseases 2020; 20:850



Distribution of patients by 5-year D:A:D Coronary Heart Risk Score, in 2004 and 2014

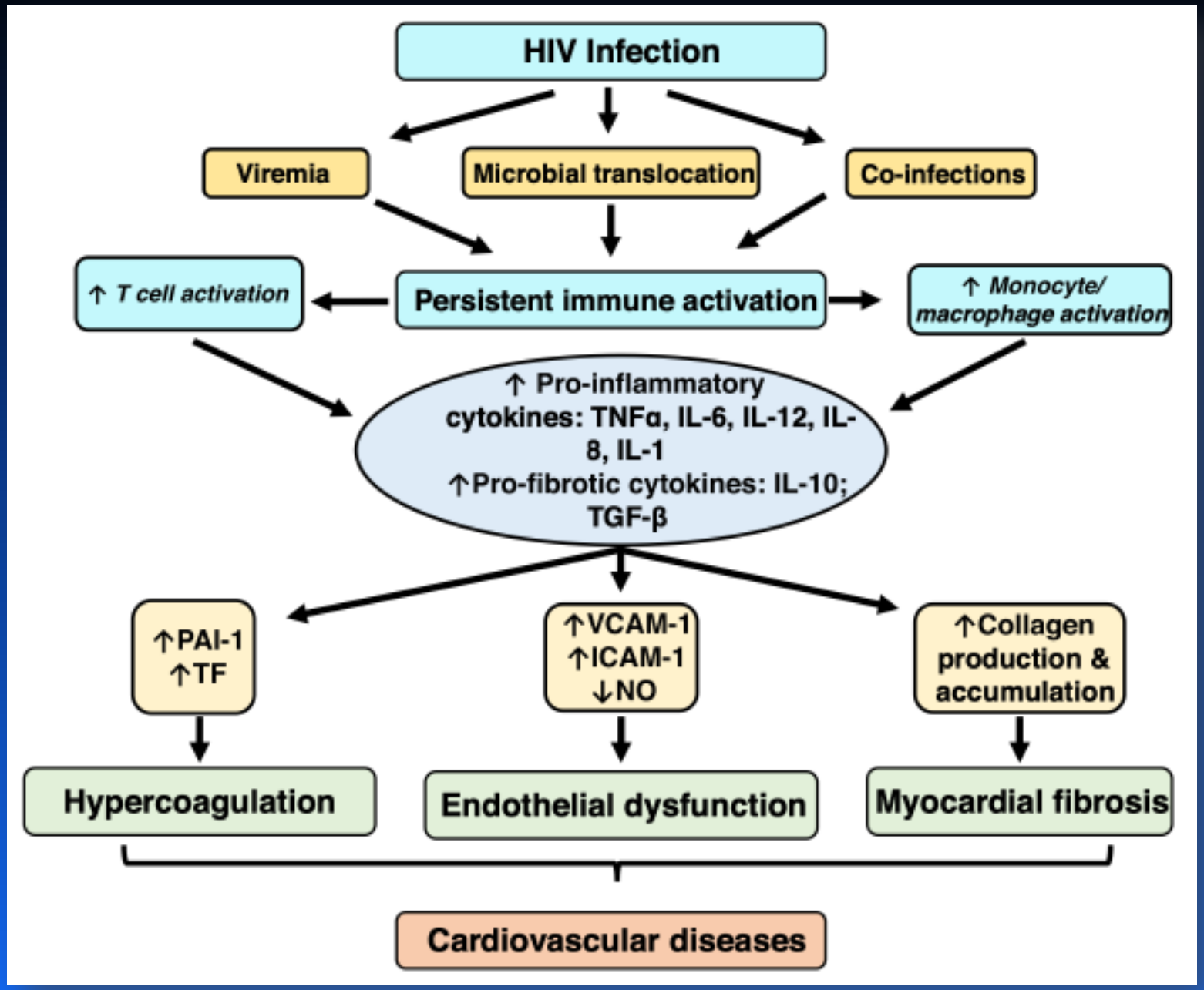
Bonnet et al. BMC Infectious Diseases (2020) 20:850

Trends in Cardiovascular Disease Mortality Among Persons With HIV in New York City, 2001–2012



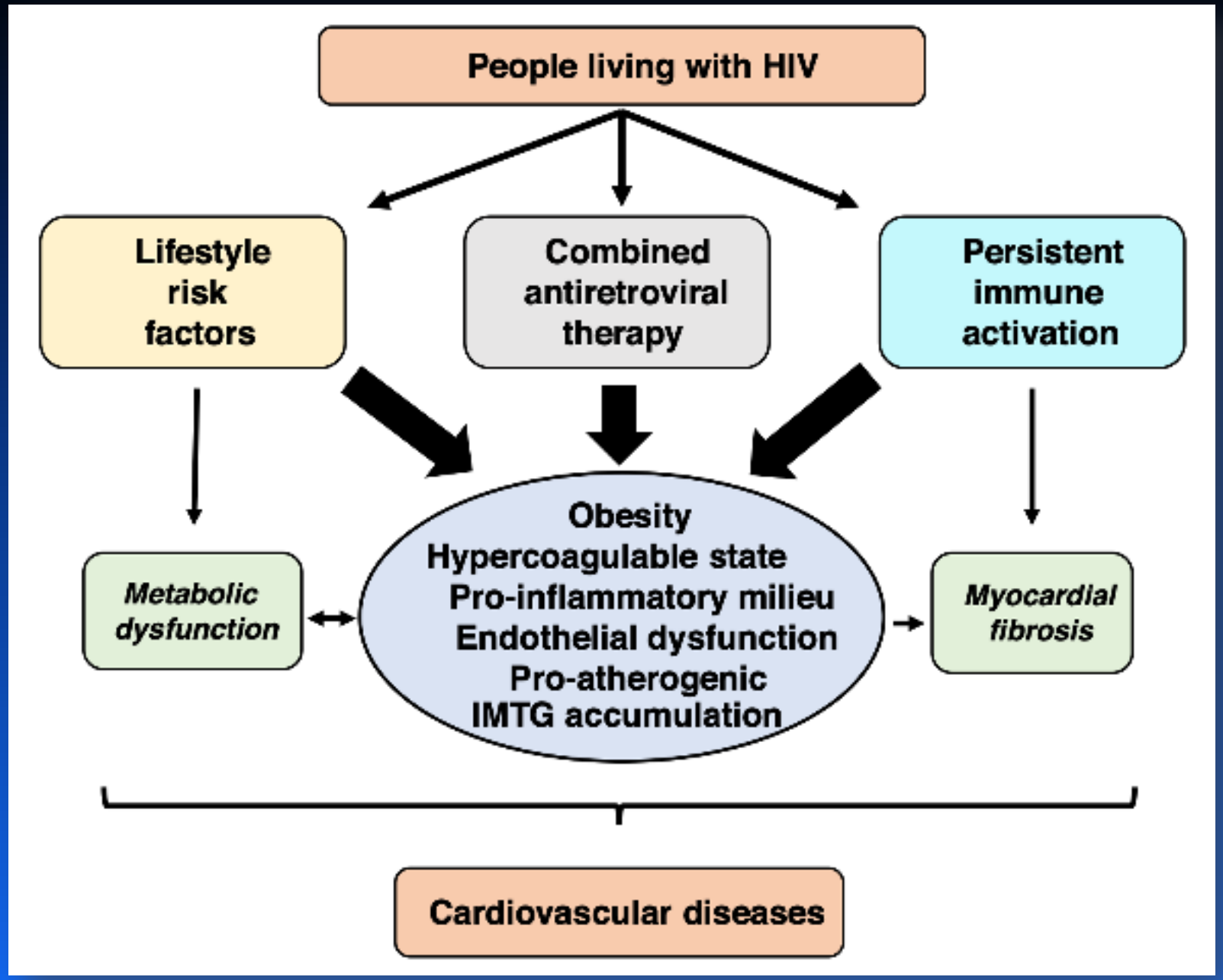
SG-2021/11

Clinical Infectious Diseases 2016;63(8):1122–9



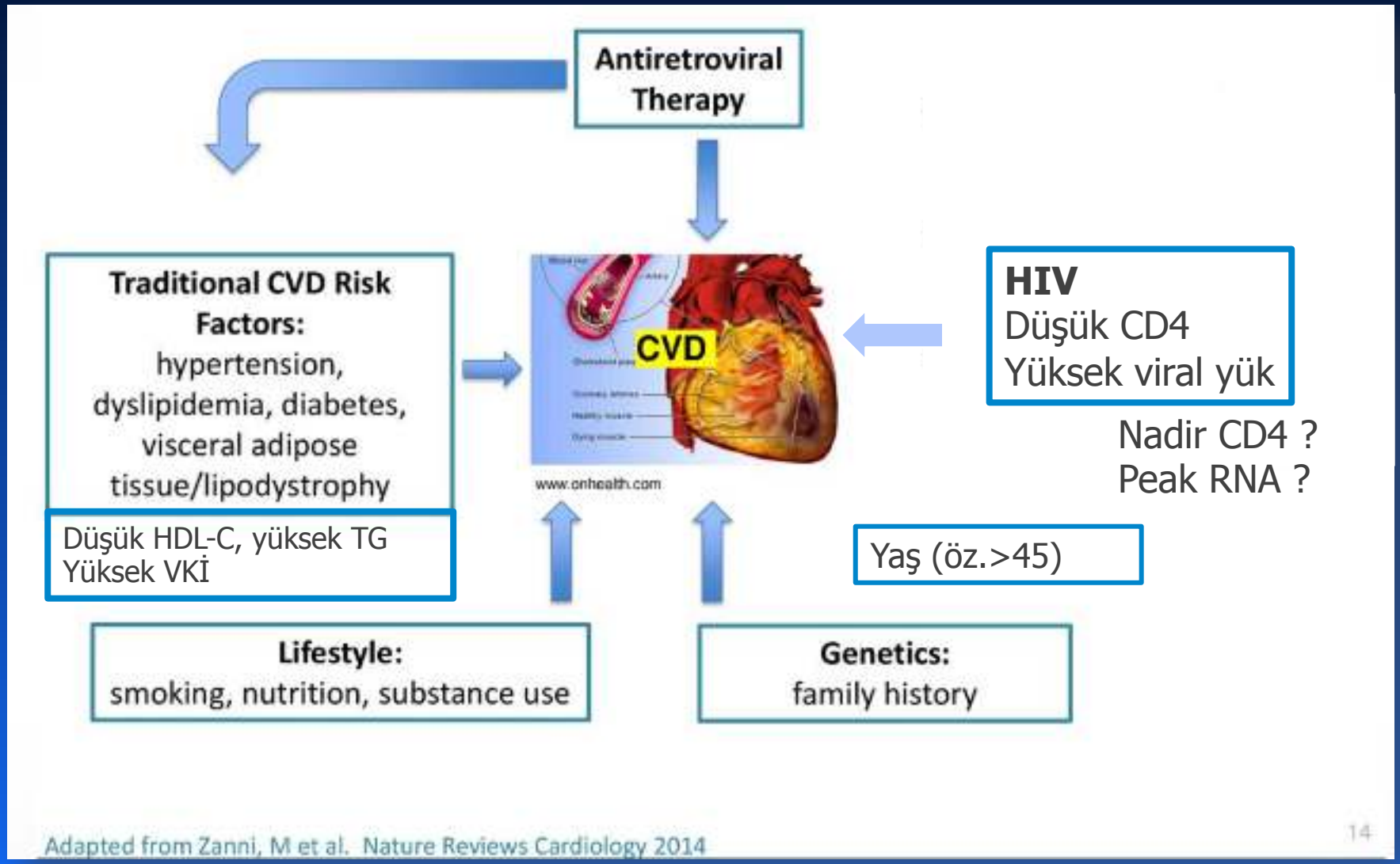
SG-2021/11

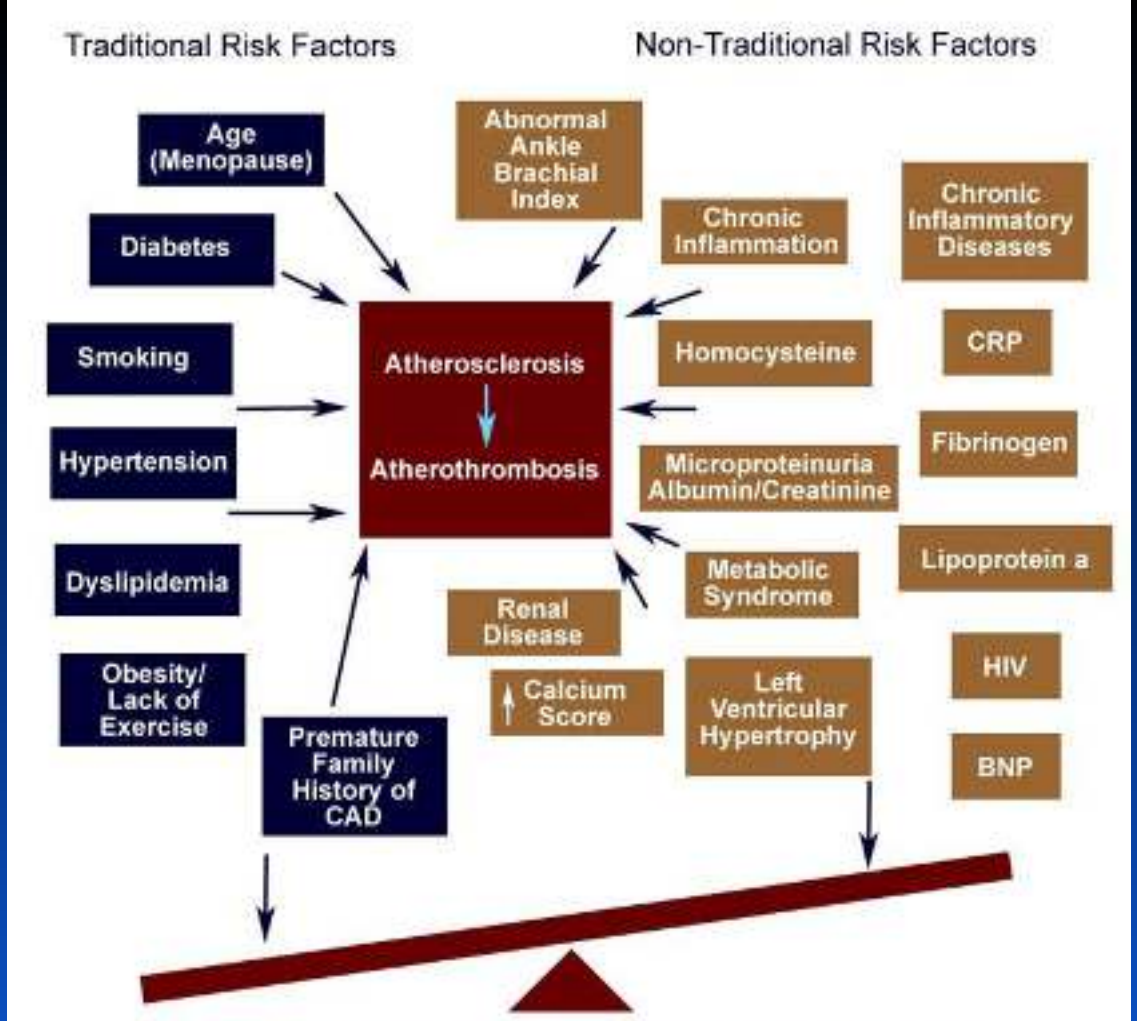
Am J Physiol Heart Circ Physiol 2020:318: H731–H746



Am J Physiol Heart Circ Physiol 2020:318: H731–H746

Risk faktörleri





Major Risk Factors for Coronary Artery Disease

-Age (men ≥ 45 years; women ≥ 55 years)
-Family history of premature coronary artery disease (CAD in male first-degree relative < 65 years)
-Hypertension (BP > 140/90 mmHg or on antihypertensive medications)
-Cigarette Smoking
-Diabetes
-Hypercholesterolemia
-Low HDL cholesterol (< 40 mg/dl)
-Hypertriglyceridemia (> 200 mg/dl)
-Obesity

ART ve KVS

- ART ile birlikte
  - ilaç toksisitesi,
  - düşük HDL-C, yüksek TG
  - vücut yağ dağılımda bozukluk,
  - metabolik sorunlar (dislipidemi, DM, ve KVH) artıyor
- ART kesilmesi ile de KVH riski artıyor
  - Kardioprotektif etki ortadan kalkıyor, tekrar proinflamatuvar sitokinler artıyor, HDL-C azalıyor.

- **Proteaz inhibitörleri**
  - **Dislipidemi, hiperkolesterolemi, hipertrigliseridemi**
  - **Lopinavir-r, indinavir →KVH riski yüksek**
  - **Atazanavir-r, darunavir-r → risk düşük**
  - **Atazanavir →kolesterol ve TG düşürücü etki**
- **NNRTIs**
  - **Tot.kolesterol ve LDL-C artışı**
  - **Rilpivirine < efavirenz**
- **NRTIs**
  - **Abacavir ve didanozin → MI riski yüksek ?**
    - D.A.D. cohort verisi (RR:1.98).
      - ✓ Metabolik send. ve renal hast. → yanıltıcı sonuçlar
    - SMART verisi. MI riski 4X yüksek
  - **TAF → tot.kol, LDL ve HDL-C'de hafif artış → klinik önemi ?**

Table 4 | **Effect of antiretroviral therapies on blood lipid levels**[190]

Class	Drug	Effect on blood lipids	Refs
Protease inhibitors	Atazanavir	Increases HDL-C and decreases LDL-C levels	191
	Darunavir	Increases HDL-C levels	191
	Fosamprenavir	Hypertriglyceridaemia	192
	Ritonavir[a]	Increases HDL-C levels	191
	Saquinavir	Neutral	192
	Tipranavir	Dyslipidaemia	192
NRTIs	Abacavir	Increases total cholesterol, LDL-C and HDL-C levels	193
	Lamivudine	Increases total cholesterol, LDL-C and HDL-C levels	193
	Tenofovir fumarate disoproxil	Lowers LDL levels	194
	Zidovudine	Hypertriglyceridaemia	194
NNRTIs	Efavirenz	Increases total cholesterol, LDL-C, HDL-C and triglyceride levels	193
	Nevirapine	Neutral or decreases lipid levels	195
	Rilpivirine	Neutral	193
Integrase inhibitors	Dolutegravir	Neutral	133
	Raltegravir	Increases HDL levels	191

HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; NNRTI, non-nucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor. [a]Although ritonavir is a protease inhibitor, this drug is generally used as a pharmacokinetic enhancer.

Hsue, P.Y., Waters, D.D. *Nat Rev Cardiol* **16,** 745–759 (2019)

Table 2 | Effect of antiretroviral therapy on the risk of cardiovascular disease

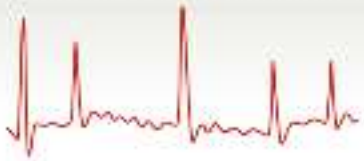
Study (year)	Study population	ART	Number of patients	Follow-up	Cardiovascular end points	Findings	Refs
Bozzette et al. (2003)	Patients with HIV infection who received care at a VA centre	Combination therapy with PIs, nucleoside analogues and NNRTIs	36,766	8.5 years	CVD and cerebrovascular disease	Use of ART was associated with a reduction in the risk of CVD	
D:A:D study group (2003)	Patients with HIV infection	Combination regimen including a PI or an NNRTI	23,468	2.2 years	MI	Use of ART was associated with a 26% relative increase in rate of MI per year of exposure	
SMART (2006)	Patients with well-controlled HIV infection; cohort from 33 countries	Continuous ART versus episodic use of ART	5,472	16 months	Opportunistic disease or death from any cause; major cardiovascular, renal or hepatic disease	Continuous ART reduced the risk of CVD compared with episodic use of ART	
D:A:D study group (2007)	Patients with HIV infection	PIs or NNRTIs	23,437	5.2 years	MI	Exposure to PIs was associated with a higher rate of MI per year of exposure	
D:A:D study group (2008)	Patients with HIV infection	NRTIs	33,347	7.2 years	MI	Use of abacavir or didanosine in the previous 6 months was associated with increased risk of MI	
Stein et al. (2015)	Patients with HIV infection without known CVD or diabetes mellitus who were initiating their first ART	NRTI, PI or integrase inhibitor	328	6.4 years	Changes in carotid artery IMT	Atazanavir had a protective effect, with slower carotid IMT progression in the setting of high plasma bilirubin levels compared with other ART regimens	
START (2015)	Patients with HIV infection; cohort from 35 countries	Immediate initiation of ART versus deferred initiation of ART	4,299	6.4 years	MI, stroke, coronary revascularization or CVD-related death	Early initiation of ART did not significantly reduce the incidence of the cardiovascular end point	
Marconi et al. (2018)	Individuals with or without HIV infection and without known CVD	NRTI, PI or NNRTI	96,381	8.8 years	CVD including acute MI, heart failure and stroke	Decreased risk of CVD in the setting of high plasma bilirubin levels irrespective of HIV infection status	
Elion et al. (2018)	Patients with HIV infection	NRTI	8,265	12 years	Type 1 and type 2 MI	Use of abacavir in the past 6 months was associated with increased risk of MI	
D:A:D study group (2018)	Patients with HIV	PIs	49,709	>15 years	CVD	Use of ritonavir-boosted darunavir but not ritonavir-boosted atazanavir was associated with increased risk of CVD	

ART, antiretroviral therapy; CVD, cardiovascular disease; IMT, intima–media thickness; MI, myocardial infarction; NNRTI, non-nucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; VA, Veterans Affairs.

Hsue, P.Y., Waters, D.D. *Nat Rev Cardiol* **16,** 745–759 (2019)

KV Hastalıklar

	Pre-ART	First-generation ART regimens	Contemporary ART regimens	Future: Optimized ART regimens	Future: Curative therapies
HIV treatment	No HIV-specific therapy	• PI • NRTI • NNRTI	• PI • NRTI • NNRTI • CCR5 antagonist • Integrase inhibitor	• Early ART initiation • Two-drug regimens • Injectable medications • New therapeutic targets	• Stem-cell-based therapies • Strategies to eliminate latency • Genome editing • Broadly neutralizing antibodies
Inflammatory and immunological status	• AIDS • Inflammation	• Immunodeficiency • Chronic inflammation	• Immunodeficiency • Chronic inflammation	Chronic inflammation	Eradication of HIV infection
Cardiovascular complications	• Pericardial effusion • Dilated cardiomyopathy	• Atherosclerosis • Myocardial infarction • Dilated cardiomyopathy • Stroke • Peripheral artery disease	• Heart failure • Atrial fibrillation • Sudden cardiac death • Coronary heart disease	• Increased risk of cardiovascular diseases	



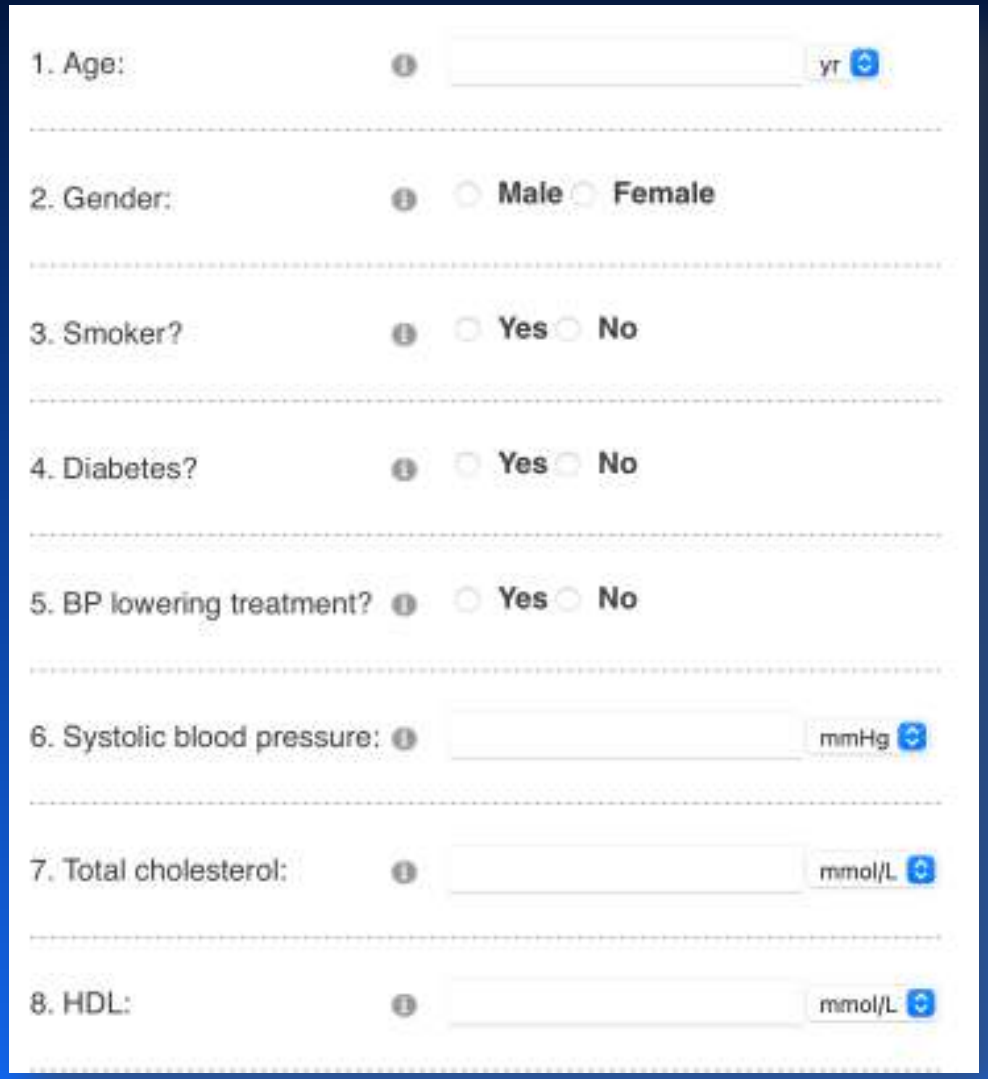
Hsue, P.Y., Waters, D.D. *Nat Rev Cardiol* **16,** 745–759 (2019)

İlk değerlendirmede…

Risk faktörlerinin araştırılması:

- **Sigara alışkanlığı**
- **Diyet**
- **Egzersiz**
- **Ailede KAH, HT, DM**
- **FM.de KB, bel çevresi, VKİ**
- **Lab: Açlık lipid seviyeleri, AKŞ, HbA1c**

Framingham hesaplaması



https://www.chip.dk/Resources/Clinical-risk-scores

Risk hesaplaması

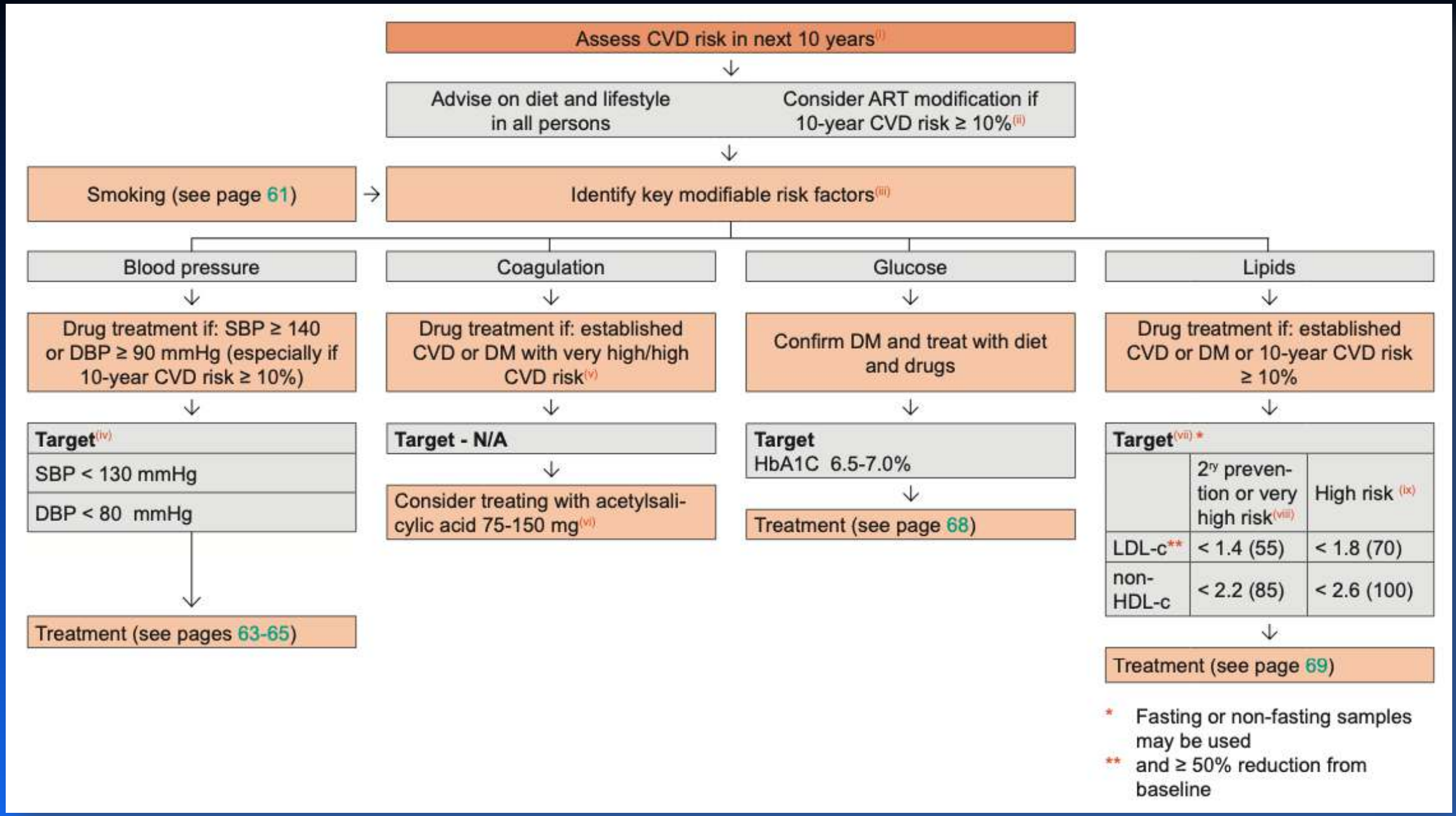
Risk Score	Population	Target Cardiovascular Events	Variables Included
FRS- CHD (Framingham)	30 – 74 years	Angina, MI, CHD death, coronary insufficiency	Age, Total Cholesterol, HDL-C, BP, Diabetes status, Smoking, Gender
ATP3-FRS-CHD (ATP3)	>20 years	MI, CHD death	Age, Total Cholesterol, HDL-C, BP, Smoking, Gender, Antihypertension Medication use
DAD (DAD)	HIV, European	MI	Age, Total Cholesterol, HDL-C, BP, Diabetes status, Smoking, Gender, Abacavir use, Duration of indinavir use, Duration of lopinavir use
2013 ACC/AHA ASCVD Pooled Cohort Equations (ASCVD)	40 – 79 years	MI, CHD death, stroke	Age, Total Cholesterol, HDL-C, BP, Diabetes status, Smoking, Gender, White or African American Ethnicity, Antihypertension Medication use

İlave faktörler

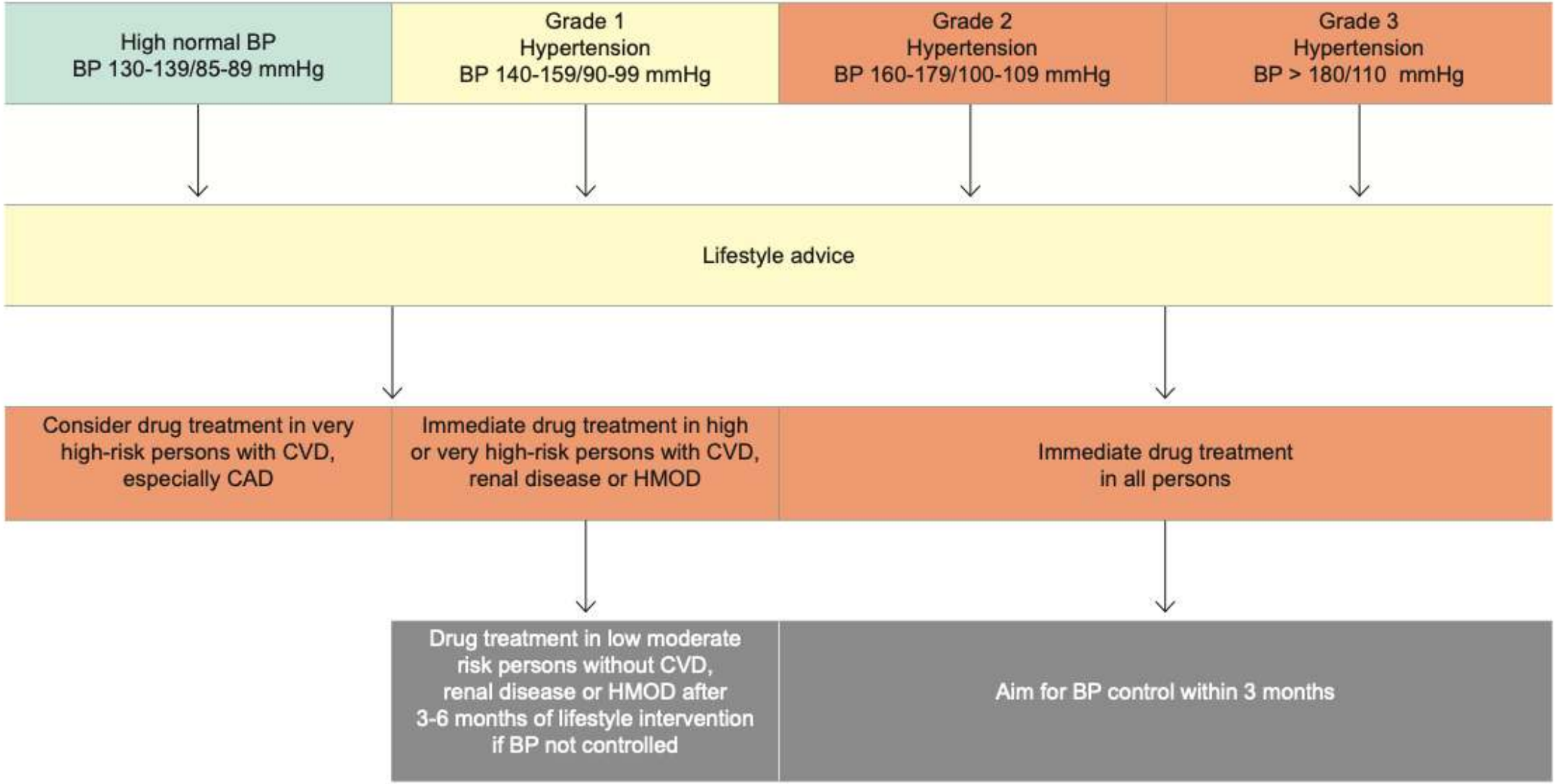
- HCV koenfeksiyonu
- Metabolik sendrom
- Lipodistrofi veya yağlı KC
- HIV tedavi başarısızlığı veya uyumsuzluğu
- Düşük CD4 sayısı (<350 /mm3)
- Uzamış HIV viremisi ve geç ART başlanmış olması

Riski azaltmak

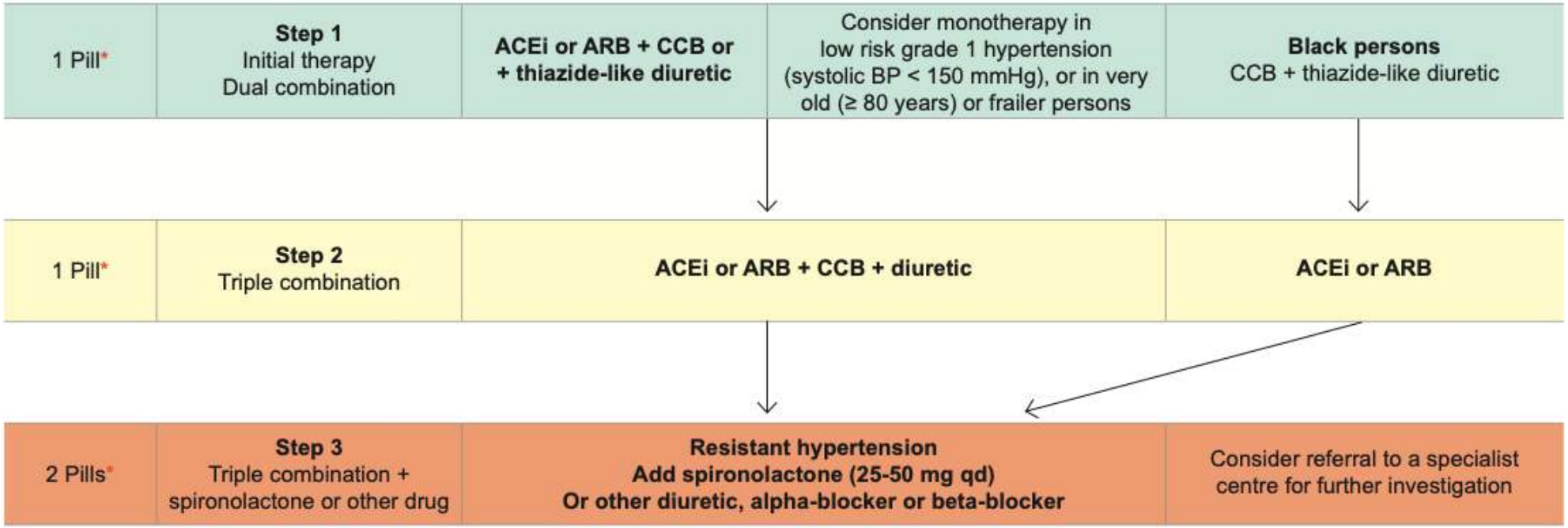
- Yaşam stilinin değişmesi (sigara, alkol, diyet, fiziksel aktivite,…)
- Gereğinde statin tedavisi
- KB kontrolü
- DM tedavisi


Assess CVD risk in next 10 years(i)
Advise on diet and lifestyle in all persons
Consider ART modification if 10-year CVD risk ≥ 10%(ii)
Smoking (see page 61)
Identify key modifiable risk factors(iii)
Blood pressure
Drug treatment if: SBP ≥ 140 or DBP ≥ 90 mmHg (especially if 10-year CVD risk ≥ 10%)
Target(iv)
SBP < 130 mmHg
DBP < 80 mmHg
Treatment (see pages 63-65)
Coagulation
Drug treatment if: established CVD or DM with very high/high CVD risk(v)
Target - N/A
Consider treating with acetylsalicylic acid 75-150 mg(vi)
Glucose
Confirm DM and treat with diet and drugs
Target
HbA1C 6.5-7.0%
Treatment (see page 68)
Lipids
Drug treatment if: established CVD or DM or 10-year CVD risk ≥ 10%
Target(vii) *
2ry prevention or very high risk(viii)
High risk (ix)
LDL-c**
< 1.4 (55)
< 1.8 (70)
non-HDL-c
< 2.2 (85)
< 2.6 (100)
Treatment (see page 69)
* Fasting or non-fasting samples may be used
** and ≥ 50% reduction from baseline

Hypertension: Diagnosis, Grading and Management



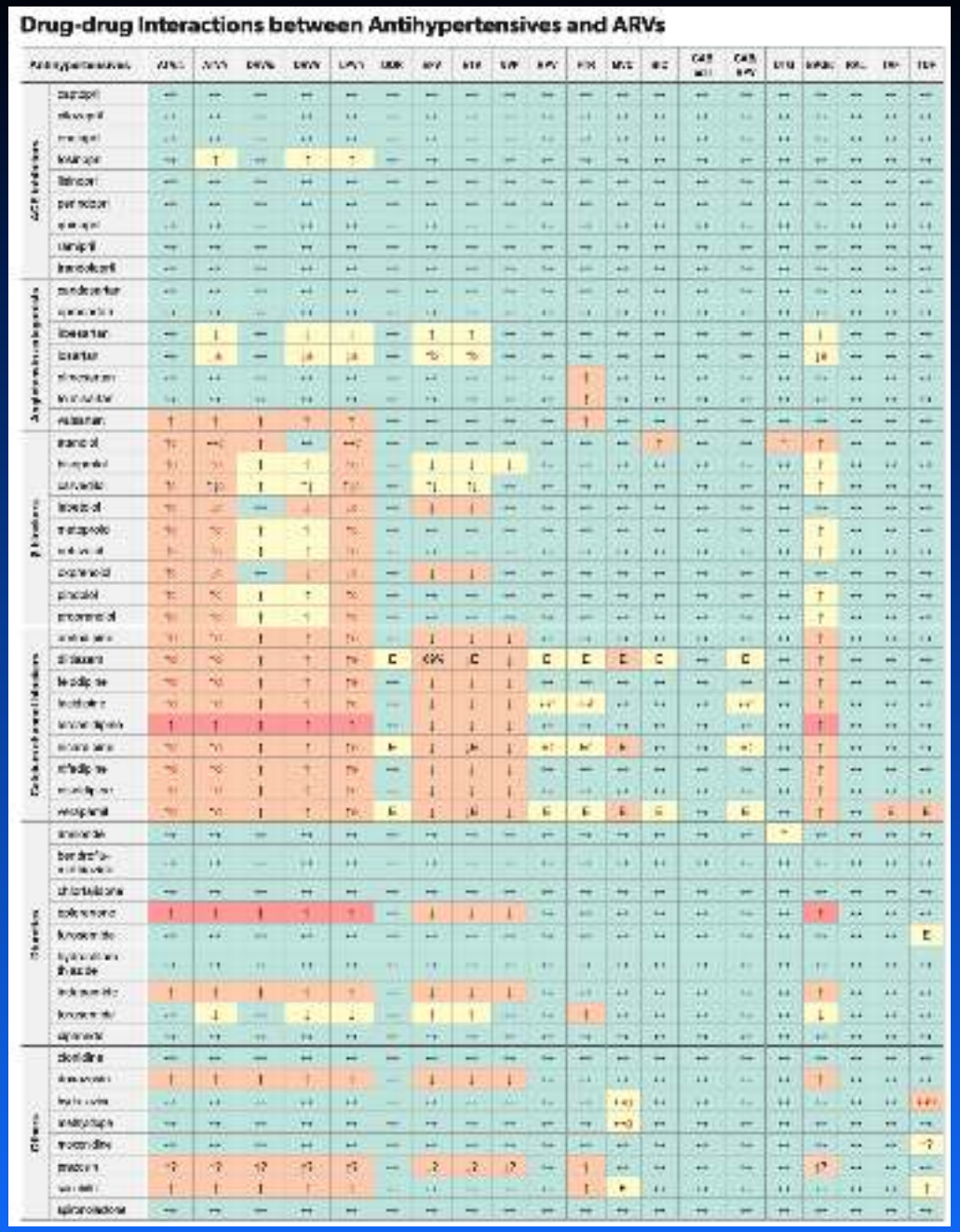
Hypertension: Drug Sequencing Management

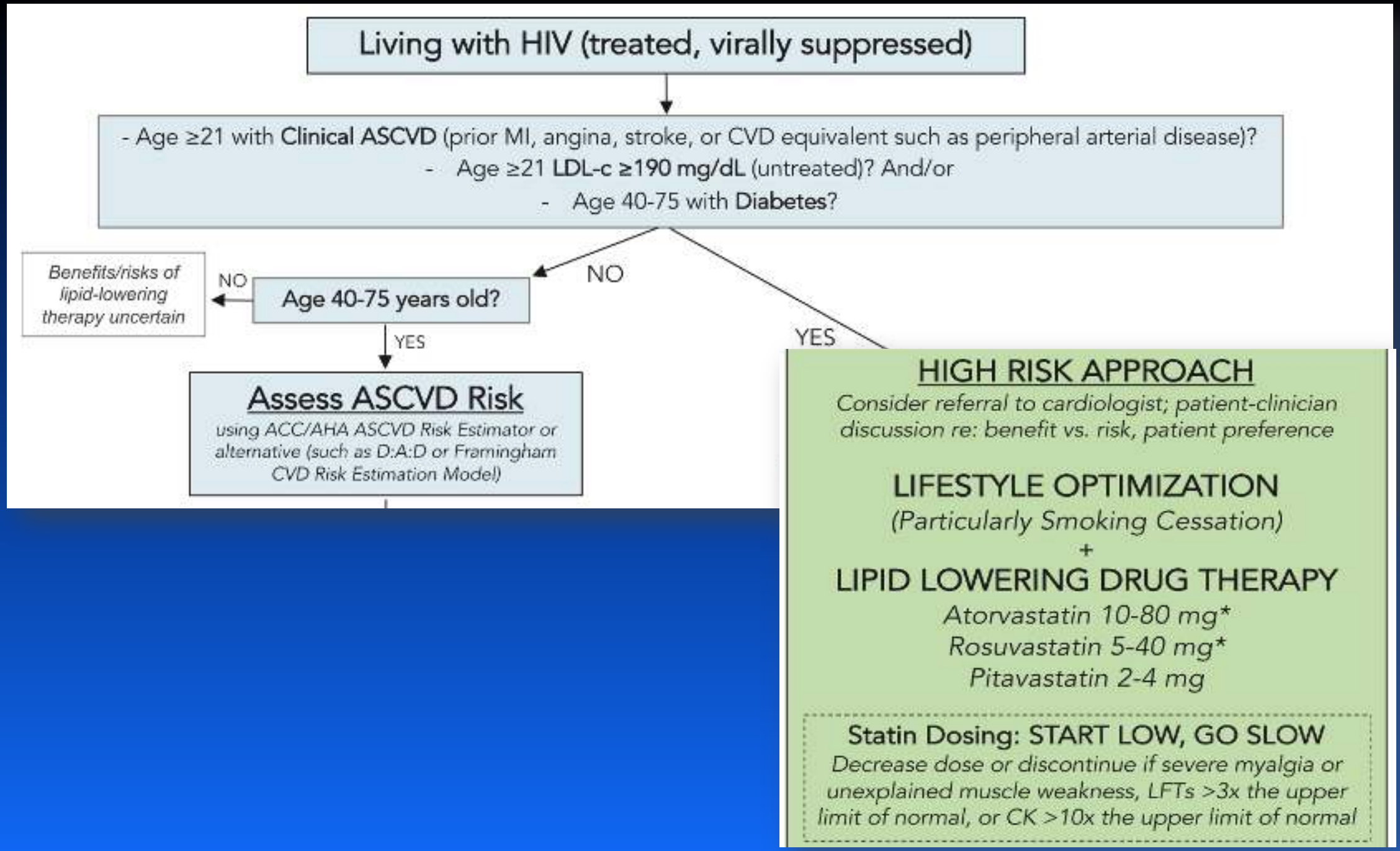


Beta-blockers
Consider beta-blockers at any treatment step, when there is a specific indication for their use, e.g. heart failure, angina, post-MI, atrial fibrillation, or younger women with, or planning, pregnancy

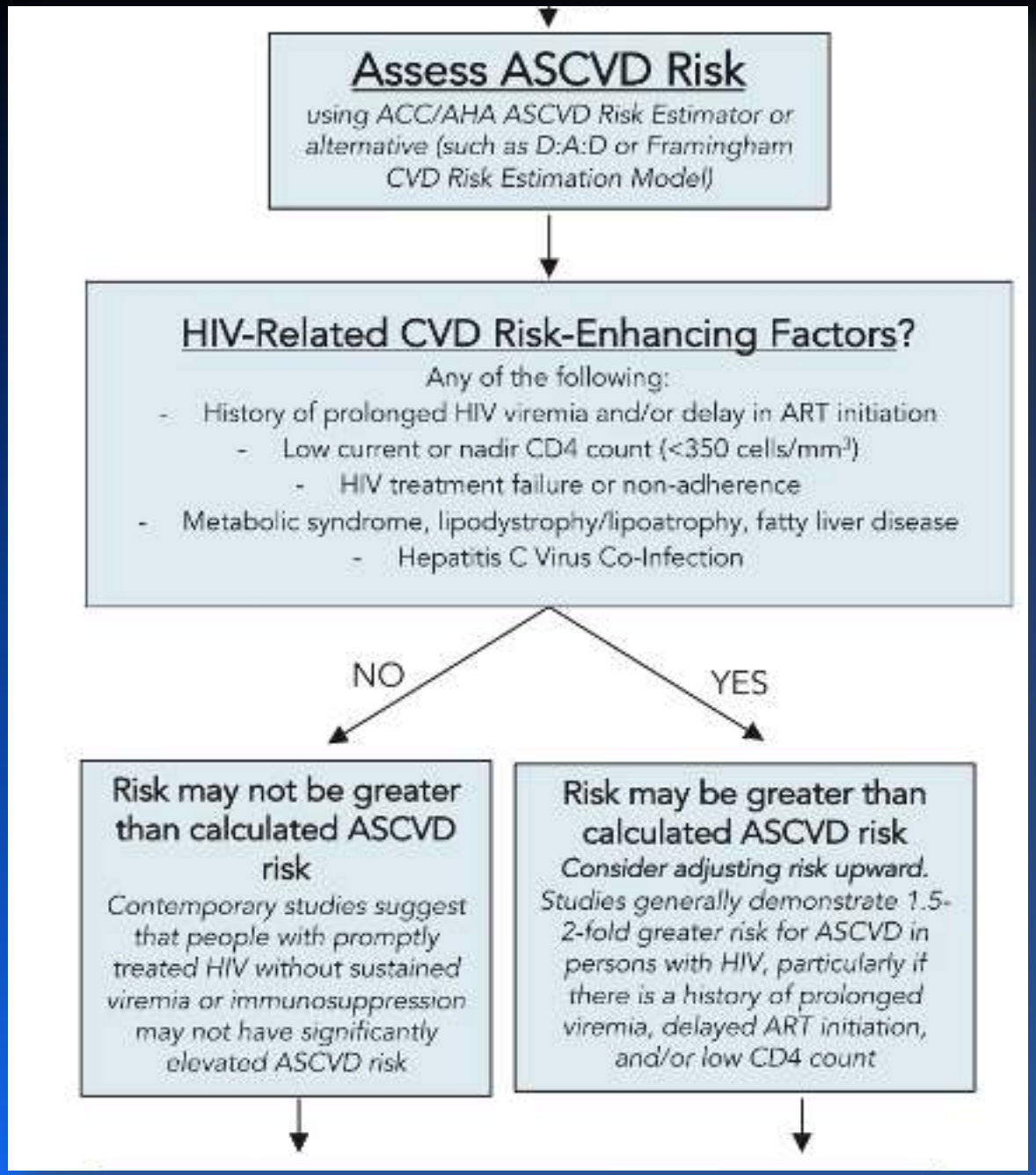
The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hyper- tension (ESH) European Heart Journal (2018) 39, 3021–3104

Drug-drug Interactions between Antihypertensives and ARVs

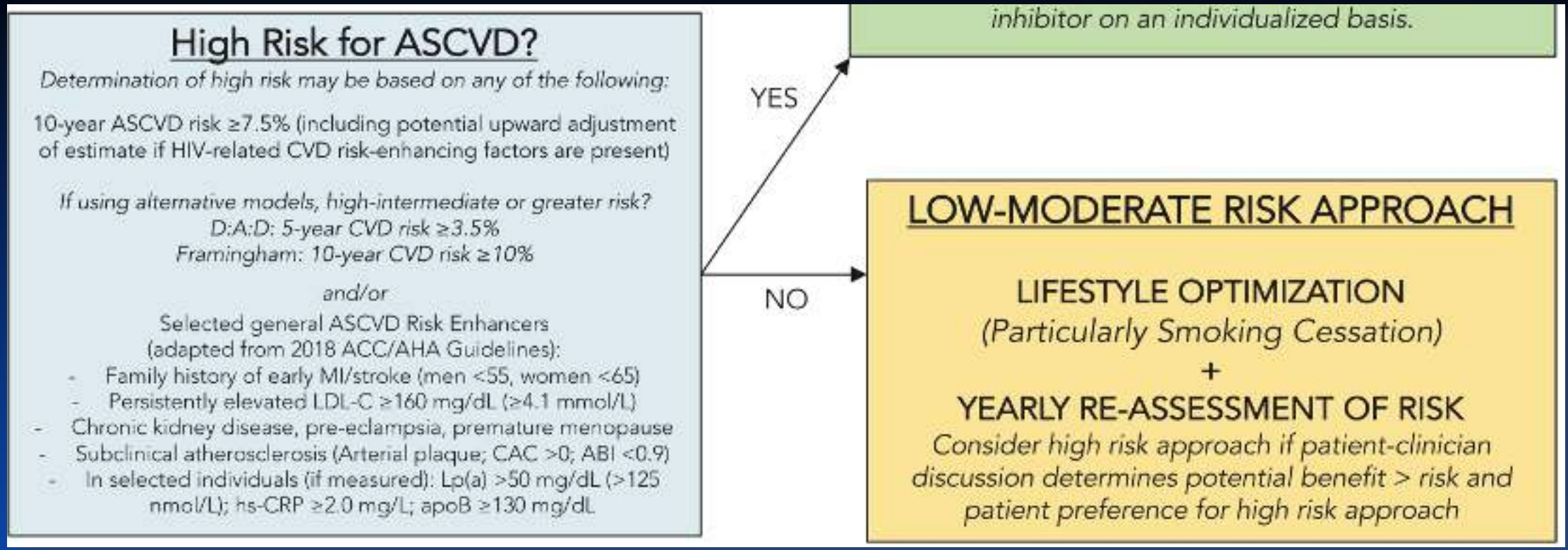




AHA. Circulation. 2019;140:e98–e124.



AHA. Circulation. 2019;140:e98–e124.



AHA. Circulation. 2019;140:e98–e124.

HIGH RISK APPROACH

Consider referral to cardiologist; patient-clinician discussion re: benefit vs. risk, patient preference

LIFESTYLE OPTIMIZATION

(Particularly Smoking Cessation)

+

LIPID LOWERING DRUG THERAPY

*Atorvastatin 10-80 mg**

*Rosuvastatin 5-40 mg**

Pitavastatin 2-4 mg

Statin Dosing: START LOW, GO SLOW

Decrease dose or discontinue if severe myalgia or unexplained muscle weakness, LFTs >3x the upper limit of normal, or CK >10x the upper limit of normal

**Exercise caution due to drug interactions at high end of dose range; consider if very high risk and/or known CAD. If familial hypercholesterolemia, severe statin intolerance, or insufficient response to statin as determined by clinician: consider ezetimibe +/- PCSK9 inhibitor on an individualized basis.*

AHA. Circulation. 2019;140:e98–e124.

Lipid düşürücü tedavi

- KVH, Tip-2 DM, Yüksek KVH riski varsa →statinler kullanılmalı !!!
  - Statin tedavisi KVH riskini %20-30 azaltır.
  - İlaç etkileşimlerine dikkat!!!
- Ciddi TG yüksekliği (>500 mg/dL) varsa
  - Gemfibrozil (600 mg tid)
  - Fenofibrate (54- 160 mg/gün)

Drugs used to lower LDL-c

Drug class	Drug	Dose	Adverse effects	Advice on use of lipid lowering therapy together with ART	
				use with PI/r	use with NNRTIs
Statin[i,viii]	Atorvastatin[ii]	10-80 mg qd	Gastrointestinal symptoms, headache, insomnia, rhabdomyolysis (rare) and toxic hepatitis	Start with low dose[v] (max daily dose: 10 mg (ATV/r); 20 mg (LPV/r); 40 mg (DRV/r)	Consider higher dose[vi]
	Fluvastatin[iii]	20-80 mg qd		Consider higher dose[vi]	Consider higher dose[vi]
	Pravastatin[iii]	20-80 mg qd		Consider higher dose[vi,vii]	Consider higher dose[vi]
	Rosuvastatin[ii]	5-40 mg qd		Start with low dose[v] (max daily dose: 10 mg (ATV/r, LPV/r) 20 mg (DRV/r)	Start with low dose[v]
	Simvastatin[ii]	10-40 mg qd		Contraindicated	
	Pitavastatin[viii]	1-4 mg qd		No interaction expected	
Intestinal cholesterol absorption inhibitor↓[i,ix]	Ezetimibe[iv]	10 mg qd	Gastrointestinal symptoms	No interaction expected	
PCSK9-inhibitors[x]	Evolocumab	140 mg 2 weekly or 420 mg monthly	Nil	No interaction expected	
	Alirocumab	75 mg or 150 mg 2 weekly			

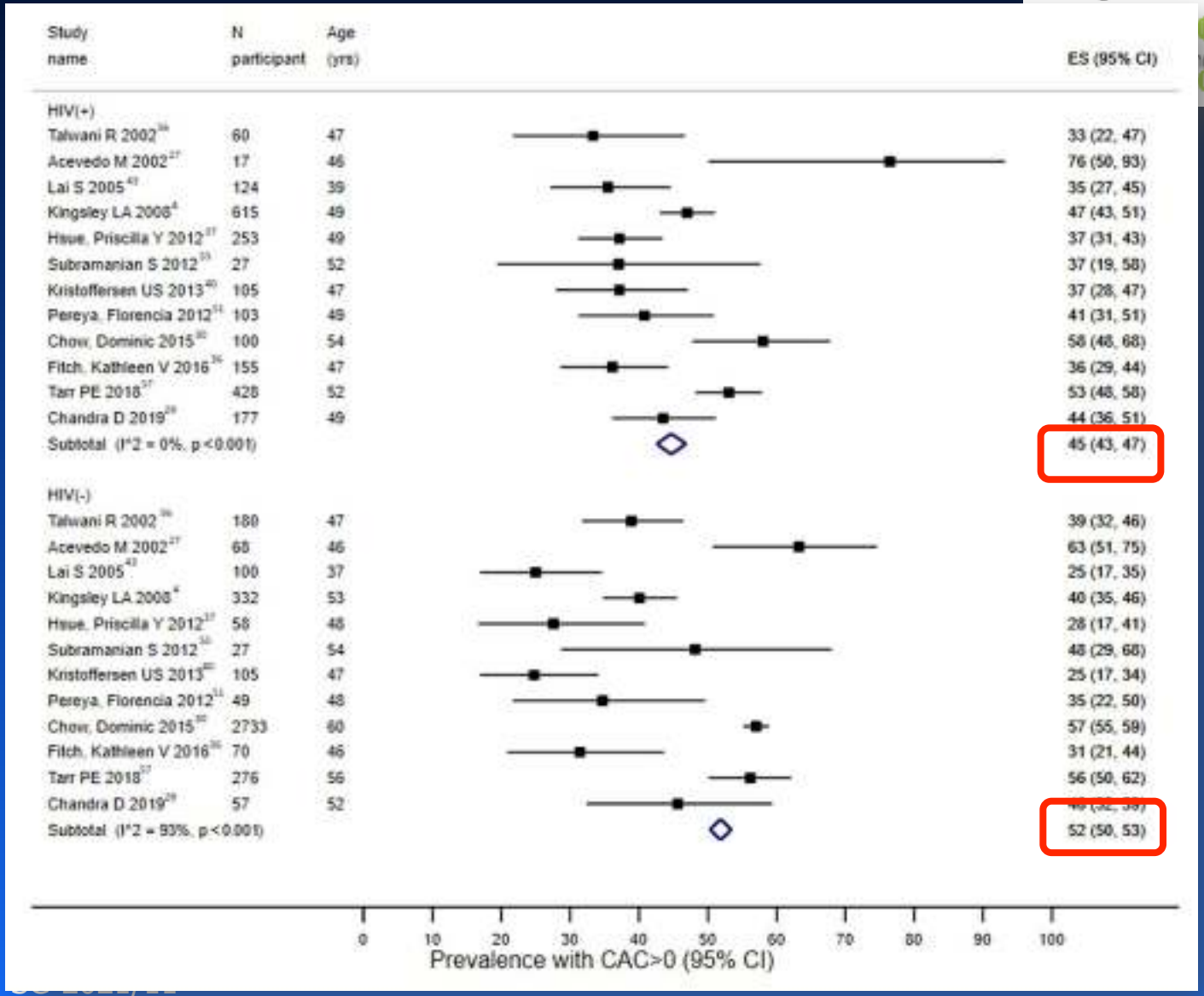
- Düşük dozda statin başlanıp toksisiteden kaçarak LDL-kol düşüşünü arttırmaya çalışılır.
- CPK ve KCFT izlenir

ART seçimi

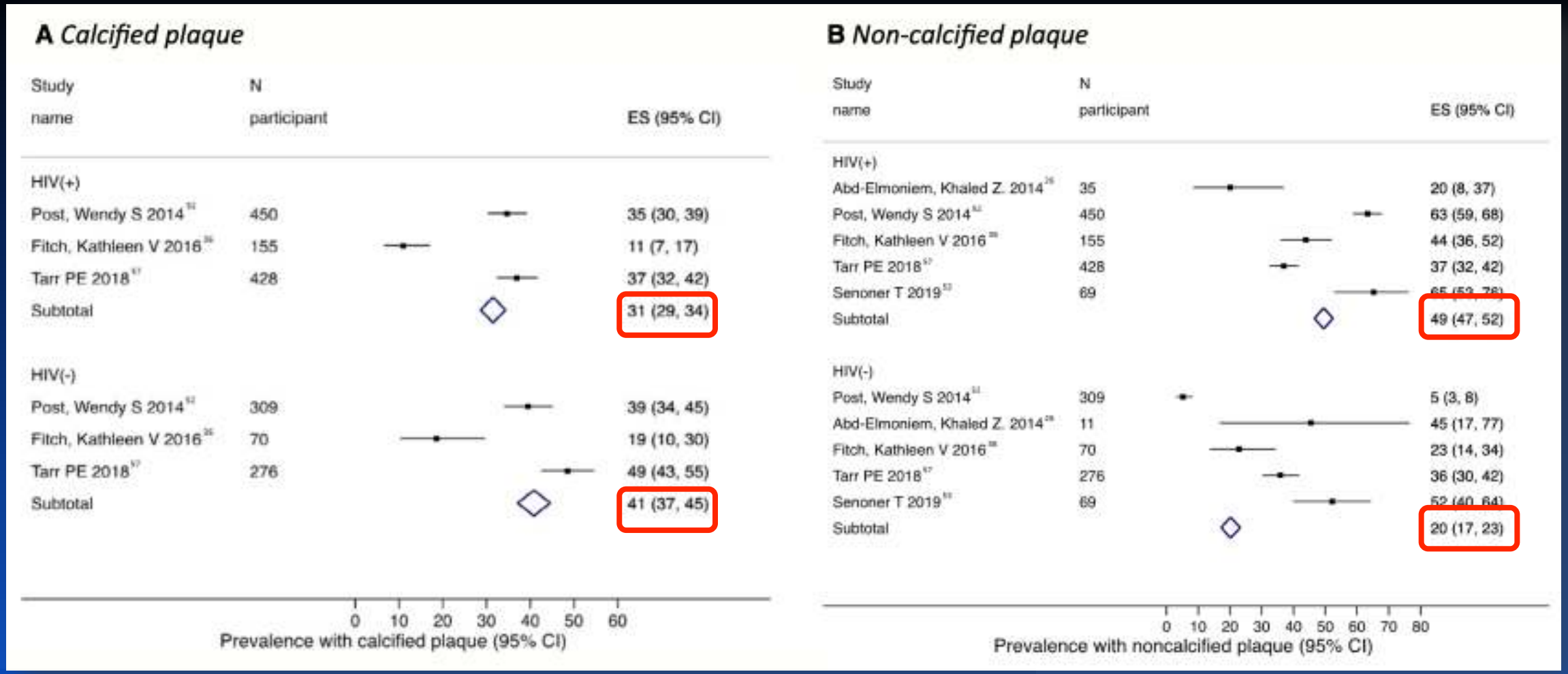
- Naif hastada ilk seçenekler uygun
- Deneyimli, ART altında ve lipid profili bozuk hastada rejimi değiştirmenin kısıtlı faydası olabilir…??
- Dislipidemik, viral supresyon sağlanmış hastada lopinavir/r veya diğer PIs > INSTIs
- PIs >NNRTI (rilpivirin, darunavir)

Coronary Artery Calcification and Plaque Characteristics in People Living With HIV: A Systematic Review and Meta-Analysis

, MD; Amjad Samara, MD; Matthew F. Yuyun , MD, PhD; Justin B. Echouffo-Tcheugui , MD, mad Masri , MD, MS; Ahmad Samara, MD; Alan R. Morrison , MD, PhD; Nina Lin , MD; , MD, MPH; Sebhat Erqou , MD, PhD



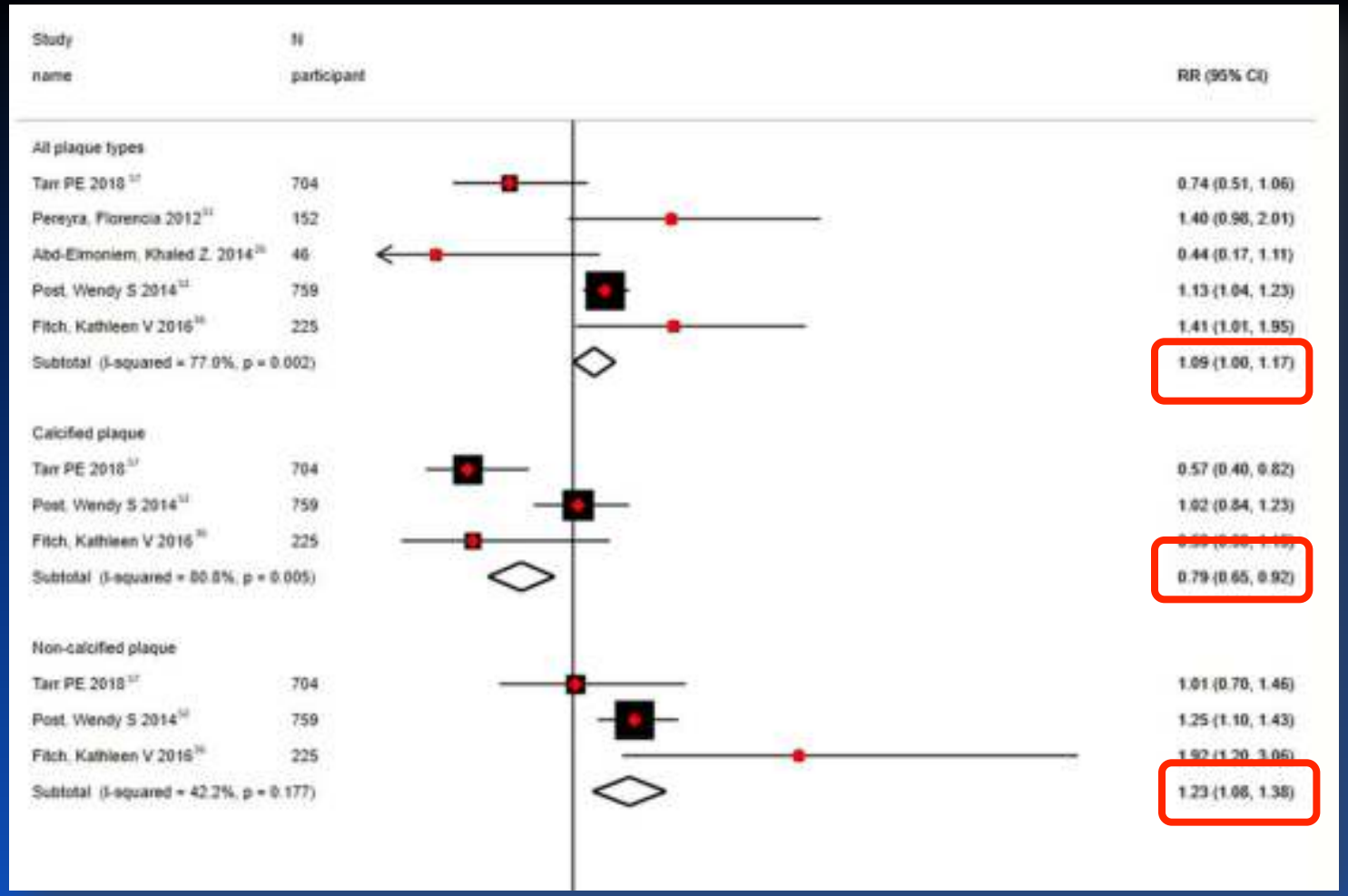
Cullen S, et al. J Am Heart Assoc. 2021;10:e019291.



Kalsifiye plak prevalansı 31% vs 41%

Nonkalsifiye plak prevalansı 49% vs 20%

J Am Heart Assoc. 2021;10:e019291



Plak varlığı için OR: 1.09 (95% CI, 1.00–1.17).

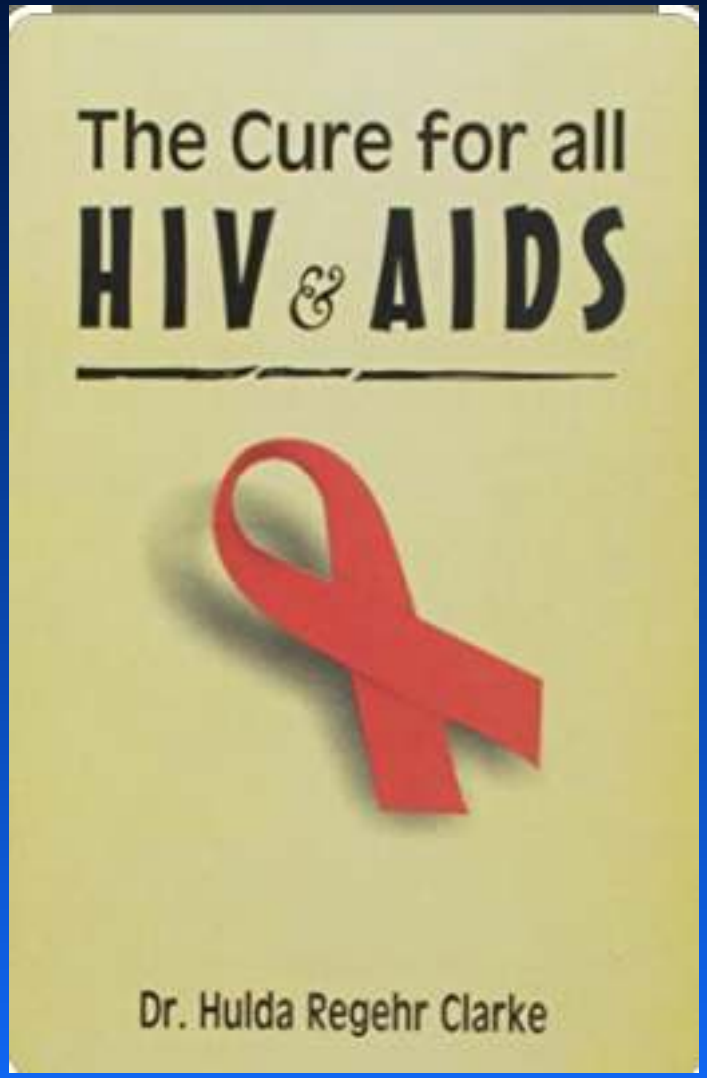
Kalsifiye plak varlığı için OR: 0.79 (95% CI, 0.65–0.92);

Non-kalsifiye plak için OR: 1.23 (95% CI, 1.08–1.38) (subklinik AS !!!)

J Am Heart Assoc. 2021;10:e019291

Sonuç olarak

- Kronik inflamasyon devam ettiği sürece KVH riski devam edecektir
- Erken ART, yaşam tarzında iyileştirme, düzenli kontolde kalmak ve risk değerlendirmesi ile riski azaltmak mümkün olacaktır.


The Cure for all
HIV & AIDS
Dr. Hulda Regehr Clarke