

Taller práctico de escalas de riesgo cardiovascular y/o cómo medir aterosclerosis subclínica en personas con VIH

GRUPO DE ESTUDIO DEL SIDA-SEIMC

Esteban Martinez

 @Esteban09090



UNIVERSITAT DE BARCELONA



estebanm@clinic.cat

CLÍNIC
BARCELONA
Hospital Universitari

Disclosures

- Research Grant / Principal investigator:

Gilead Sciences, MSD and ViiV Healthcare

- Consultant:

Gilead Sciences, Janssen, MSD and ViiV Healthcare

- Lectures:

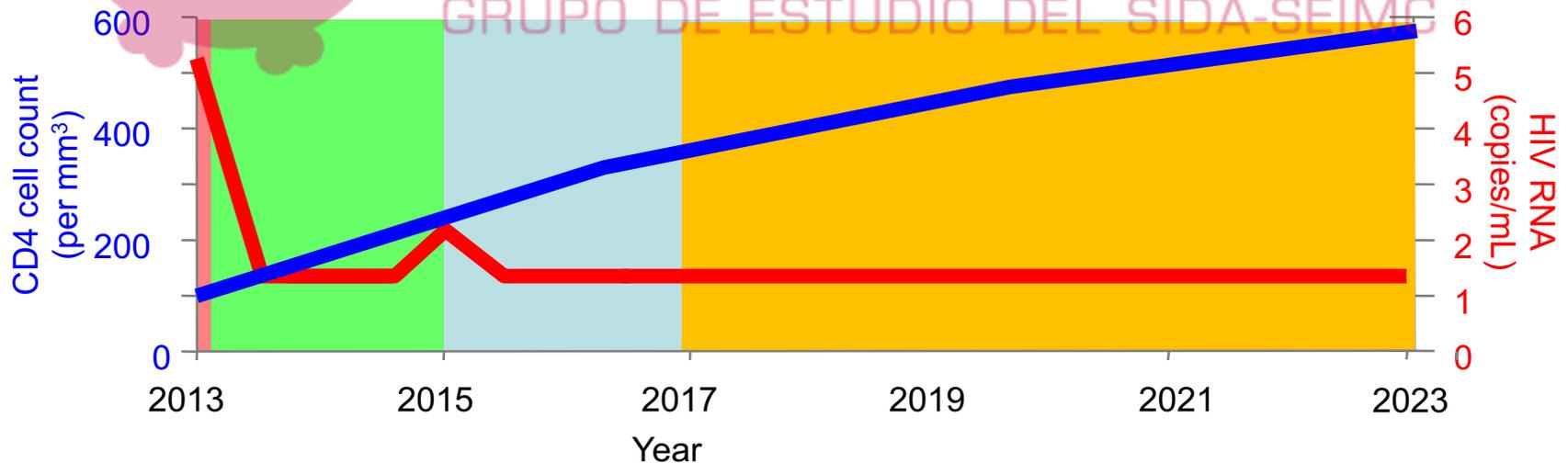
Gilead Sciences, Janssen, MSD and ViiV Healthcare



Patient's HIV and cART history

- Male, born 1973
- HIV+ 11/2013, sexual transmission
- Antiretroviral history:

| Period | Regimen | Reason for discontinuation |
|------------|--------------------------|--------------------------------|
| 2013-2013: | ABC/3TC + Efavirenz | sleep disturbances |
| 2013-2015: | ABC/3TC + Nevirapine | low-level viral rebound |
| 2015-2017: | ABC/3TC + Lopinavir/rit | simplification for convenience |
| 2017-: | ABC/3TC + Darunavir/cobi | |



Patient's characteristics

Smoker 10 cigarettes per day

No illicit drugs

Blood pressure 140/80 mmHg

No hypertension, no diabetes

BMI 25 kg/m²

Total cholesterol 240 mg/dL

HDL cholesterol 40 mg/dL

LDL cholesterol 180 mg/dL

MDRD GFR 70 mL/min/1.73m²

No proteinuria

•The patient feels great.

•He accepts and tolerates his antiretroviral regimen.

•He is not taking any chronic medication other than antiretroviral therapy

•Smoker since a teenager, but has substantially reduced number of cigarettes per day

Prevention and management of co-morbidities in PWH



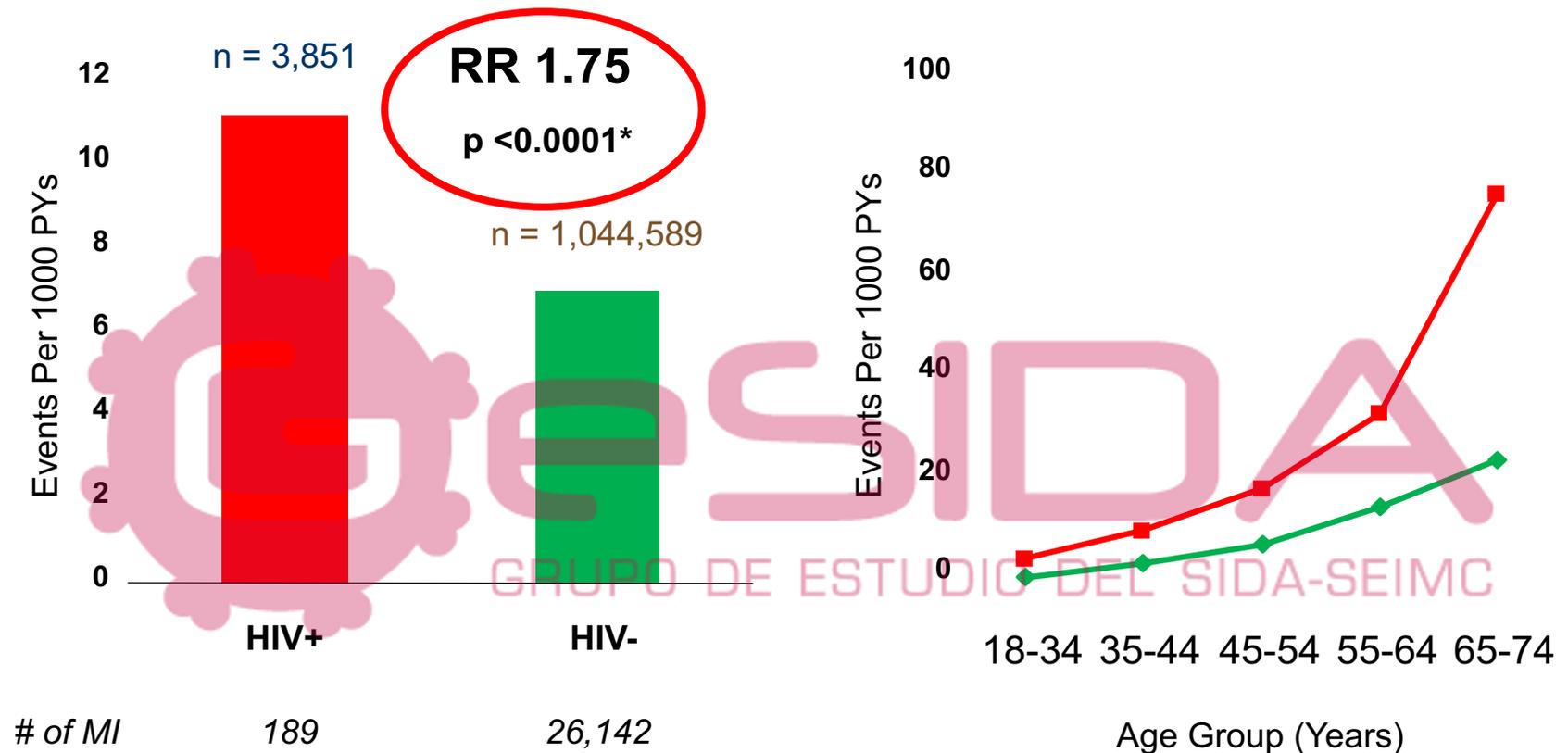
EACS guidelines: Screening for co-morbidities

Assessment of HIV-positive persons at initial & subsequent visits

| CO-MORBIDITIES | | | | | CO-MORBIDITIES | | | | |
|-------------------------------|--|-----------------------|---------------------|--------------|----------------------------------|--|---------------------|---|--------------|
| Assessment | At HIV diagnosis | Prior to starting ART | Follow-up frequency | Assessment | At HIV diagnosis | Prior to starting ART | Follow-up frequency | | |
| Haematology | FBC | + | + | 3-12 months | Renal Disease | Risk assessment ^(vi) | + | + | Annual |
| | Haemoglobinopathies | + | | | | eGFR (CKD-EPI) ^(vii) | + | + | 3-12 months |
| | G6PD | + | | | | Urine dipstick analysis ^(viii) | + | + | Annual |
| Body Composition | Body-mass index | + | + | Annual | Bone Disease | Bone profile: calcium, PO ₄ , ALP | + | + | 6-12 months |
| Cardiovascular Disease | Risk assessment (Framingham score ⁽ⁱⁱⁱ⁾) | + | + | 2 years | | Risk assessment ^(x) (FRAX ^{®(xi)} in persons > 40 years) | + | + | 2 years |
| | ECG | + | +/- | As indicated | | Vitamin D | 25(OH) vitamin D | + | |
| Hypertension | Blood pressure | + | + | Annual | Neurocognitive Impairment | Screening questionnaire | + | + | As indicated |
| Lipids | TC, HDL-c, LDL-c, TG ^(iv) | + | + | Annual | Depression | Questionnaire | + | + | As indicated |
| Glucose | Serum glucose | + | + | Annual | Cancer | Mammography | | | 1-3 years |
| Pulmonary Disease | CXR | +/- | | As indicated | | Cervical PAP | | | 1-3 years |
| | Spirometry | | | As indicated | | Rectal exam and anoscopy (MSM) | | | 1-3 years |
| Liver Disease | Risk assessment ^(v) | + | + | Annual | | Ultrasound and alpha-foe-toprotein | | | 6 months |
| | ALT/AST, ALP, Bilirubin | + | + | 3-12 months | | | | | |
| | Staging of liver fibrosis | | | 12 months | | | | | |
| | Hepatic ultrasound | | | 6 months | | | | | |

In addition to data collection regarding: medical history, HIV disease and co-infections

2-fold higher risk of myocardial infarction in HIV+ patients vs. general population



* Adjusted for age, gender, race, hypertension, diabetes and dyslipidaemia.

Proportion of patients with hypertension, diabetes and dyslipidemia significantly higher in HIV+ vs HIV- cohort

Differences in the screening of comorbidities in HIV-infected persons

| | Kidney | Bone | CV | Cancer | Cognitive |
|--------------------------------|-------------------------|---------------------|-------------------------------|-------------------------------|--------------------------|
| Screening | Blood & Urine chemistry | DEXA +/- FRAX score | Framingham (or similar) score | No (cytology cervical cancer) | No (psychometric tests?) |
| Prediction of clinical problem | Accurate | Less accurate | More innaccurate | More innaccurate or lacking | Lacking |

Cardiovascular screening

Smoker 10 cigarettes per day

Alcohol 2-3 wine glasses per day

No illicit drugs

Blood pressure 140/80 mmHg

No hypertension, no diabetes

BMI 25 kg/m²

Total cholesterol 240 mg/dL

HDL cholesterol 40 mg/dL

MDRD GFR 70 mL/min/1.73m²

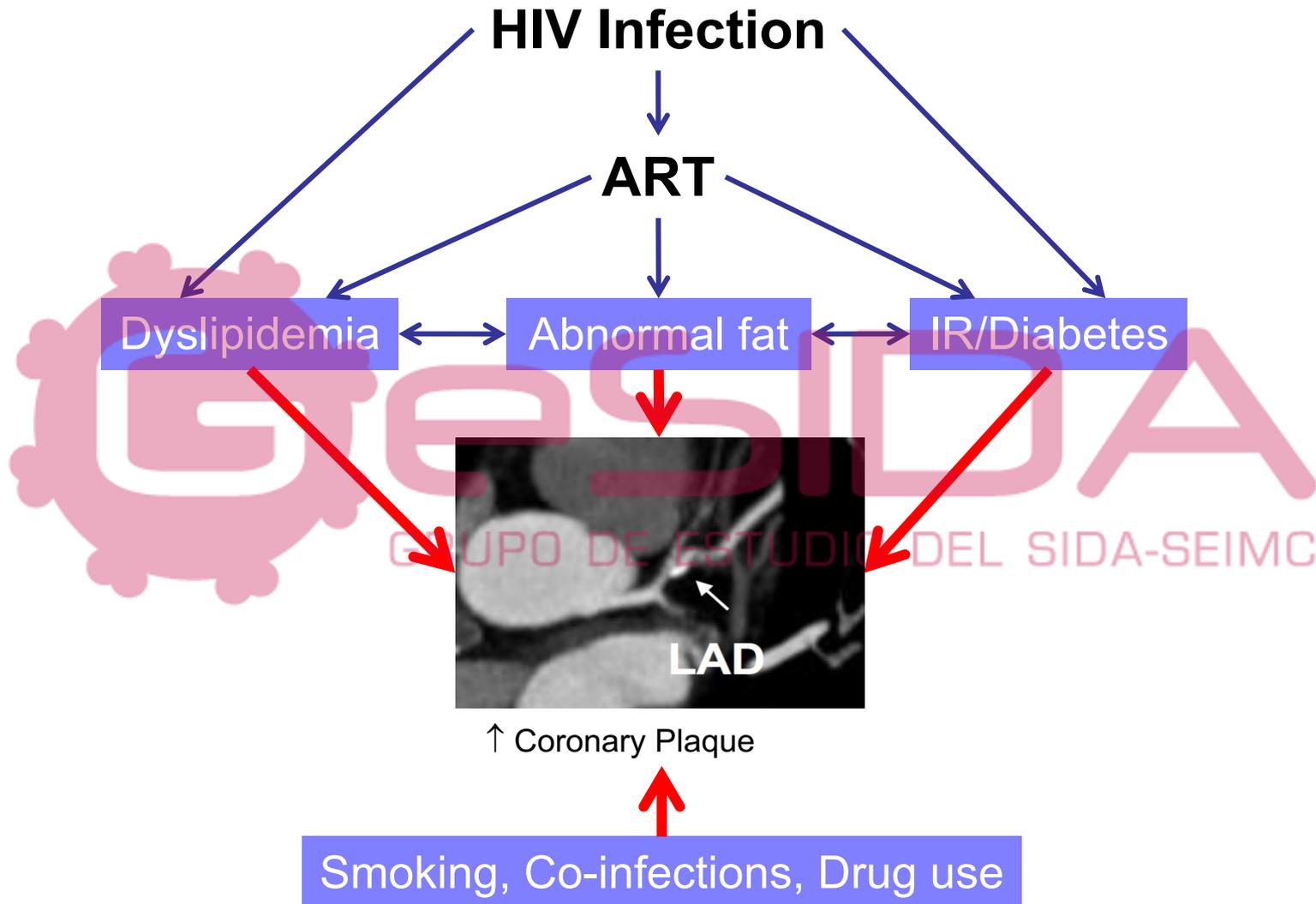
No proteinuria

ECG: Normal

| FRAMINGHAM score | Patient case |
|-----------------------------------|--------------|
| Age, years | 50 |
| Gender, male/female | Male |
| Smoker, yes/no | Yes |
| Systolic blood pressure, mmHg | 140 |
| Total cholesterol, mg/dL (mmol/L) | 240 (6.2) |
| HDL cholesterol, mg/dL (mmol/L) | 40 (1.0) |
| CHD Risk Score at 10 years (%) | 20% |

Modifiable risk factors

Traditional factors explain a lot of CVD in HIV pts, ...but not all



New paradigm for atherosclerosis in HIV pts

but not ready for prevention scores yet!

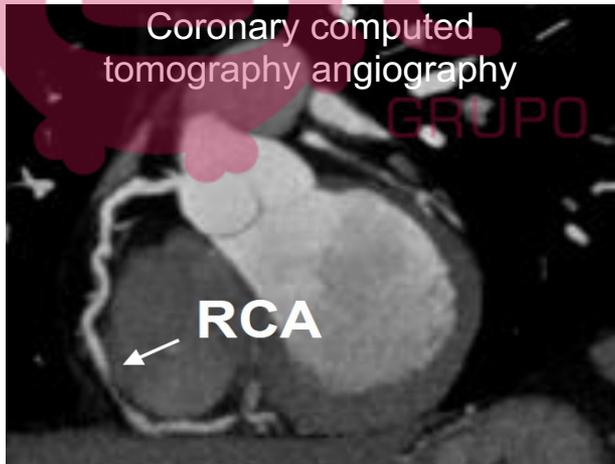
Residual Viral
Replication

Microbial
Translocation

Immune
Deficiency

T-cell Activation

Monocyte Activation



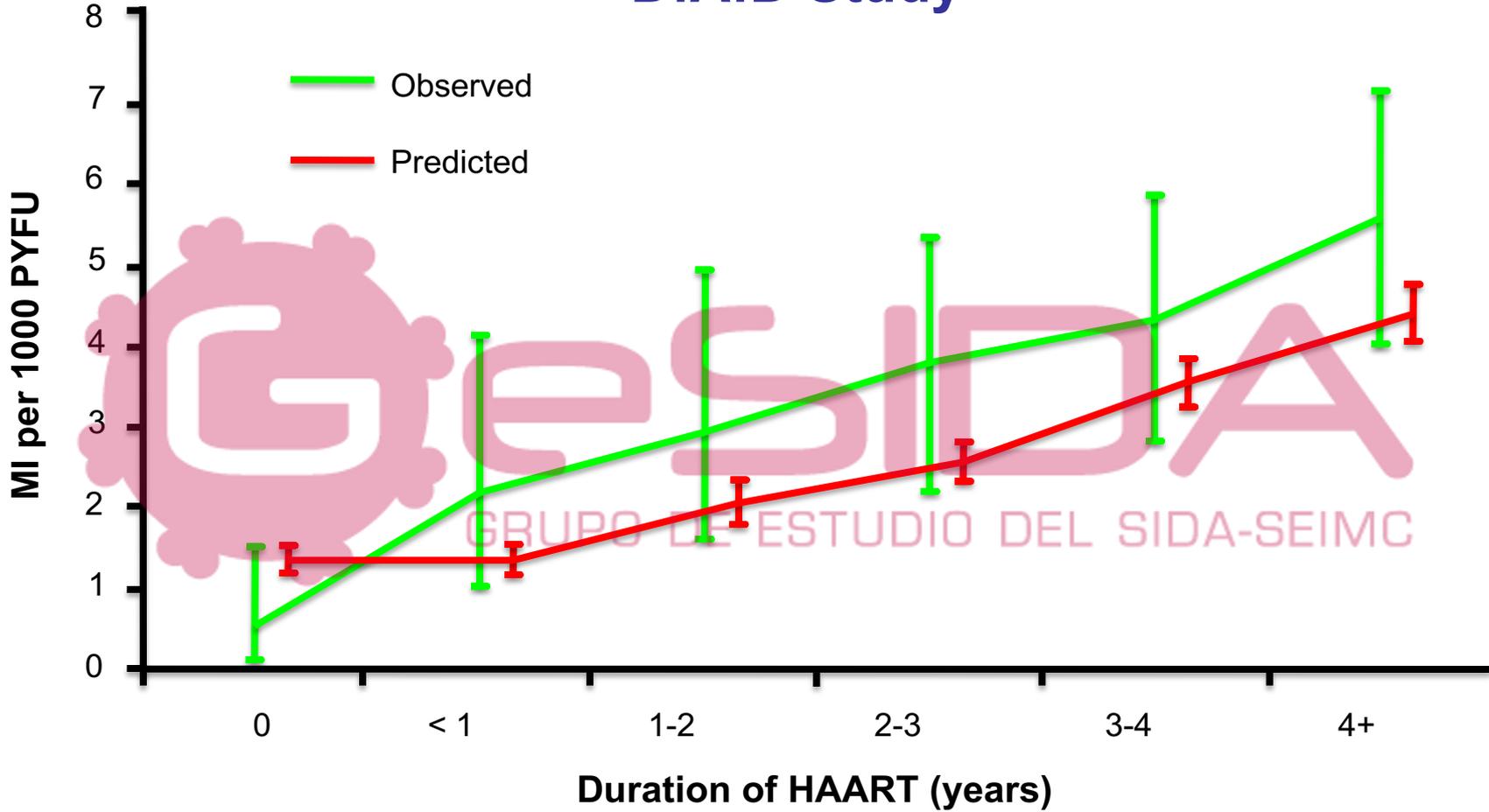
↑ High-Risk Plaque



↑ Inflammation

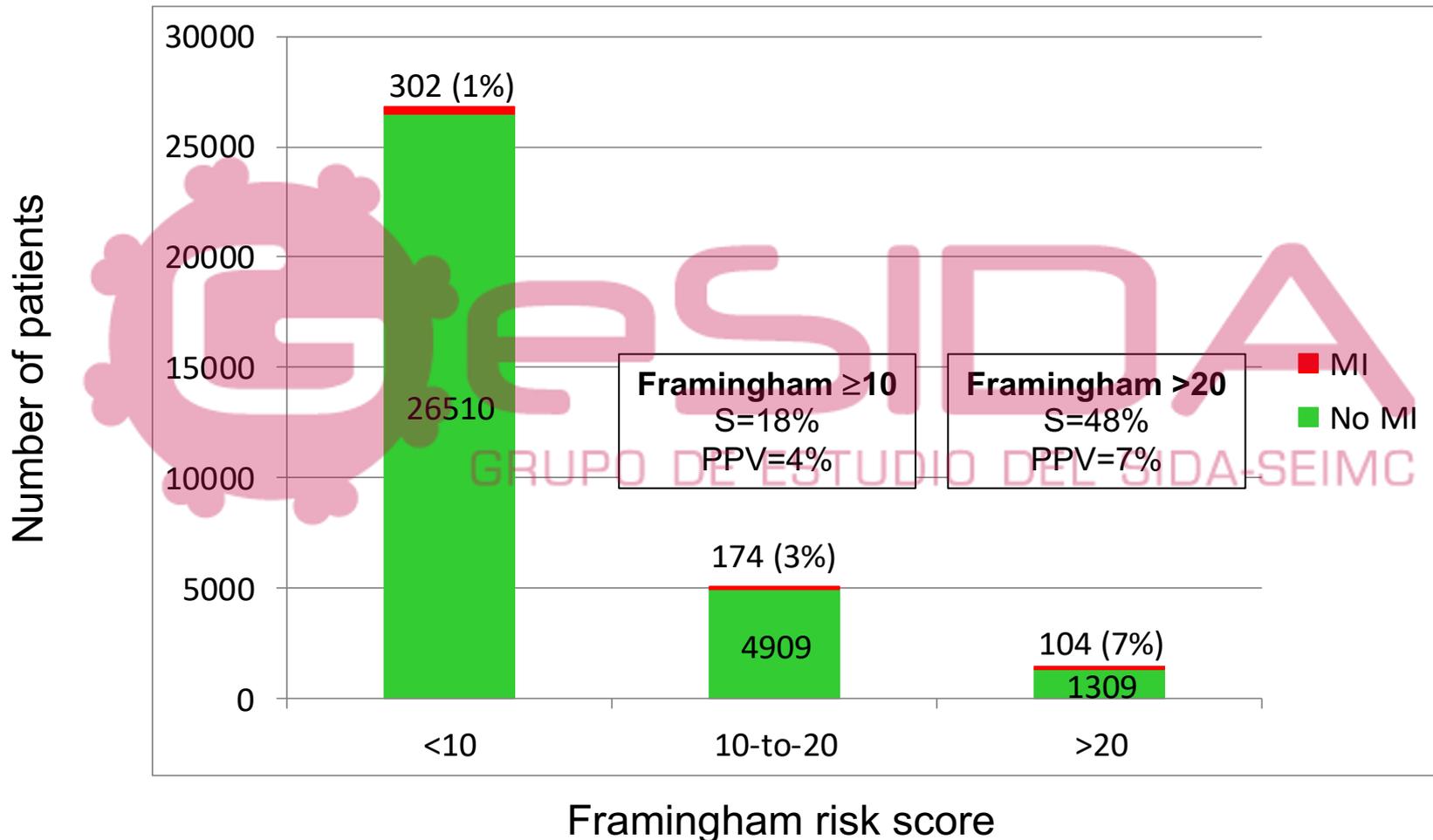
Risk of myocardial infarction in HIV-infected patients can be estimated with the Framingham score

D:A:D Study



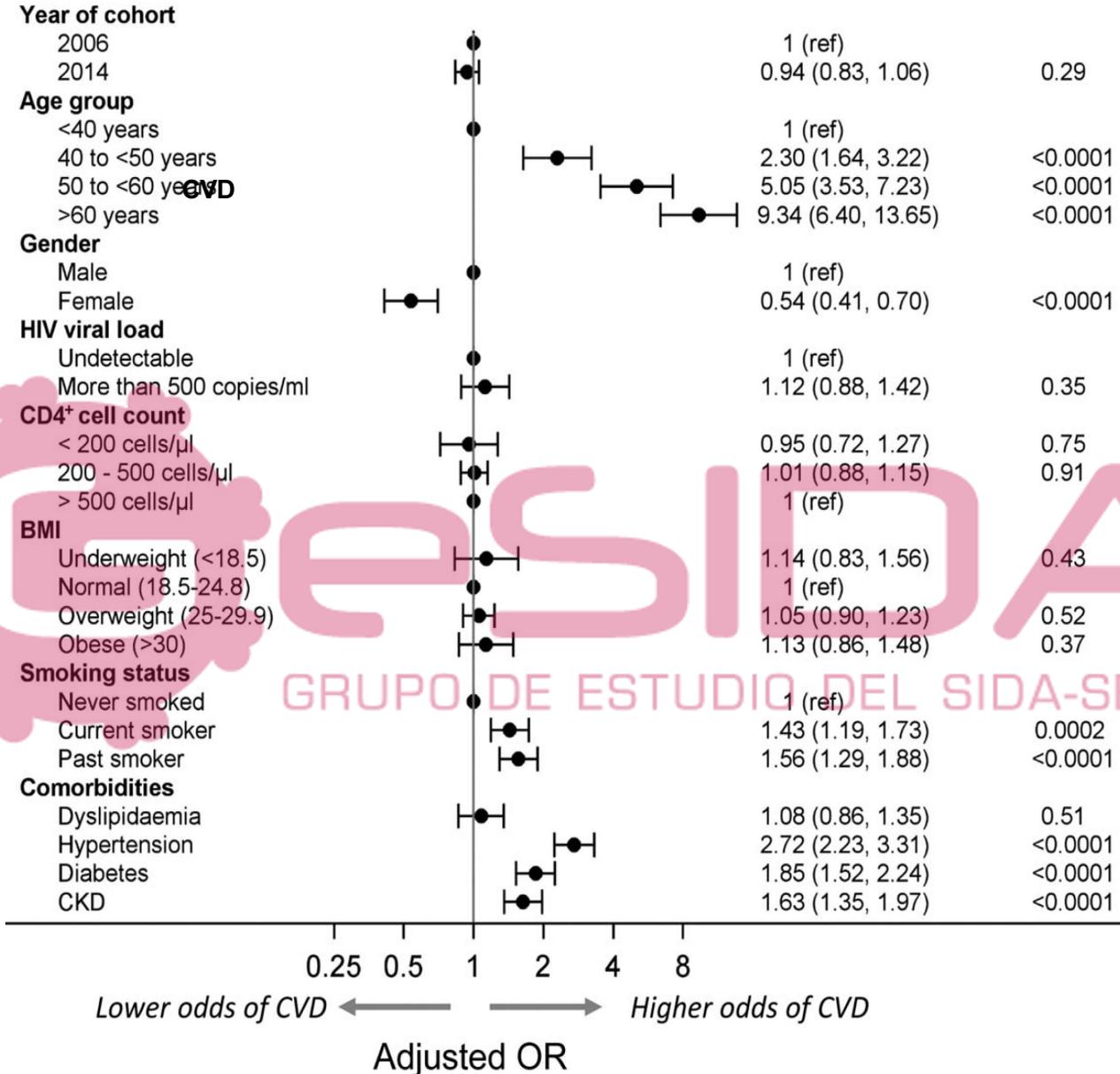
Framingham score: gender, smoking, age, systolic BP, total and HDL cholesterol

Framingham score has a low sensitivity, but a high negative predictive value



Age is the most important risk factor

EuroSIDA



Men have worse CV risk than women

| | | |
|--------------------------|-----------|-----------|
| Age: | 50 | 50 |
| Gender: | male | male |
| Total Cholesterol: | 200 mg/dL | 240 mg/dL |
| HDL Cholesterol: | 40 mg/dL | 40 mg/dL |
| Smoker: | Yes | Yes |
| Systolic Blood Pressure: | 120 mm/Hg | 120 mm/Hg |
| On medication for HBP: | No | No |
| Risk Score* | 12% | 17% |

Man, ≥ 50 y, smoker = risk $>10\%$

| | | |
|--------------------------|-----------|-----------|
| Age: | 64 | 64 |
| Gender: | male | male |
| Total Cholesterol: | 200 mg/dL | 240 mg/dL |
| HDL Cholesterol: | 40 mg/dL | 40 mg/dL |
| Smoker: | No | No |
| Systolic Blood Pressure: | 120 mm/Hg | 120 mm/Hg |
| On medication for HBP: | No | No |
| Risk Score* | 12% | 14% |

If non-smoking you need to be almost 15y older to have the same CV risk

| | | |
|--------------------------|-----------|-----------|
| Age: | 50 | 99 |
| Gender: | female | female |
| Total Cholesterol: | 200 mg/dL | 200 mg/dL |
| HDL Cholesterol: | 40 mg/dL | 40 mg/dL |
| Smoker: | Yes | Yes |
| Systolic Blood Pressure: | 120 mm/Hg | 120 mm/Hg |
| On medication for HBP: | No | No |
| Risk Score* | 3% | 8% |

Woman, any age, even smoker = risk $<10\%$

However, Framingham does not include HIV-specific factors

- Immune status
- Increased inflammatory markers
- Insulin resistance
- Time on HAART

Calculation of 10-year CHD Risk

Calculation of 10-year CHD in men risk using the Framingham risk equation

Step 1: age

| Years | Points |
|-------|--------|
| 20-34 | -9 |
| 35-39 | -4 |
| 40-44 | 0 |
| 45-49 | 3 |
| 50-54 | 6 |
| 55-59 | 8 |
| 60-64 | 10 |
| 65-69 | 11 |
| 70-74 | 12 |
| 75-79 | 13 |

Step 2: total-cholesterol

| TC mmol/l (mg/dL) | Points at age 20-39 | Points at age 40-49 | Points at age 50-59 | Points at age 60-69 | Points at age 70-79 |
|-------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| <4.1 (160) | 0 | 0 | 0 | 0 | 0 |
| 4.1-5.1 (160-199) | 4 | 3 | 2 | 1 | 0 |
| 5.2-6.2 (200-239) | 7 | 5 | 3 | 1 | 0 |
| 6.2-7.2 (240-279) | 9 | 6 | 4 | 2 | 1 |
| ≥ 7.2 (280) | 11 | 8 | 5 | 3 | 1 |

Step 3: HDL-cholesterol

| HDL-C mmol/l (mg/dL) | Points |
|----------------------|--------|
| ≥ 1.55 (60) | -1 |
| 1.29-1.53 (50-59) | 0 |
| 1.03-1.27 (40-49) | 1 |
| < 1.03 (40) | 2 |

Step 4: systolic blood pressure

| Systolic BP (mmHg) | Points if untreated | Points if treated |
|--------------------|---------------------|-------------------|
| < 120 | 0 | 0 |
| 120-129 | 0 | 1 |
| 130-139 | 1 | 2 |
| 140-159 | 1 | 2 |
| ≥ 160 | 2 | 3 |

Step 5: smoking status

| | Points at age 20-39 | Points at age 40-49 | Points at age 50-59 | Points at age 60-69 | Points at age 70-79 |
|-----------|---------------------|---------------------|---------------------|---------------------|---------------------|
| Nonsmoker | 0 | 0 | 0 | 0 | 0 |
| Smoker | 8 | 5 | 3 | 1 | 1 |

CV score developed from D:A:D study

DAD 5 Year Estimated Risk calculator

The risk during the next **5 years** of CHD is: **11.8%**

Number of years on:

indinavir: 0

lopinavir: 4

Currently on:

indinavir?: No Yes

lopinavir?: No Yes

abacavir?: No Yes

Gender: Female Male

Current age in years: 50

Current cigarette smoker?: No Yes

Previous cigarette smoker?: No Yes

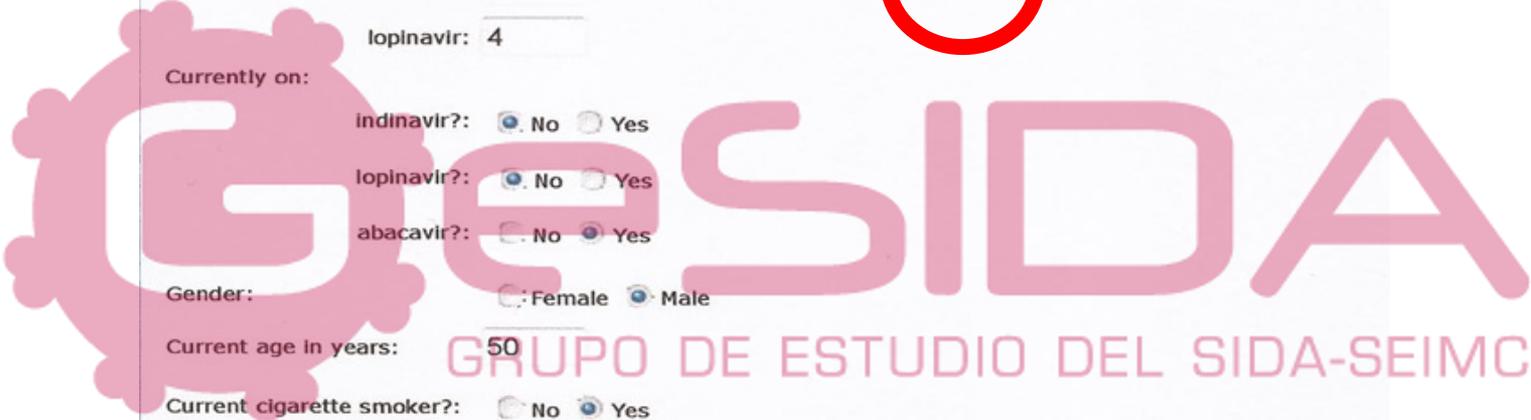
Diabetic?: No Yes

Family CVD history?: No Yes

Systolic blood pressure: 140 unit: mm/Hg cm/Hg kPa

Total cholesterol: 240 unit: mmol/L g/L g/dL mg/dL

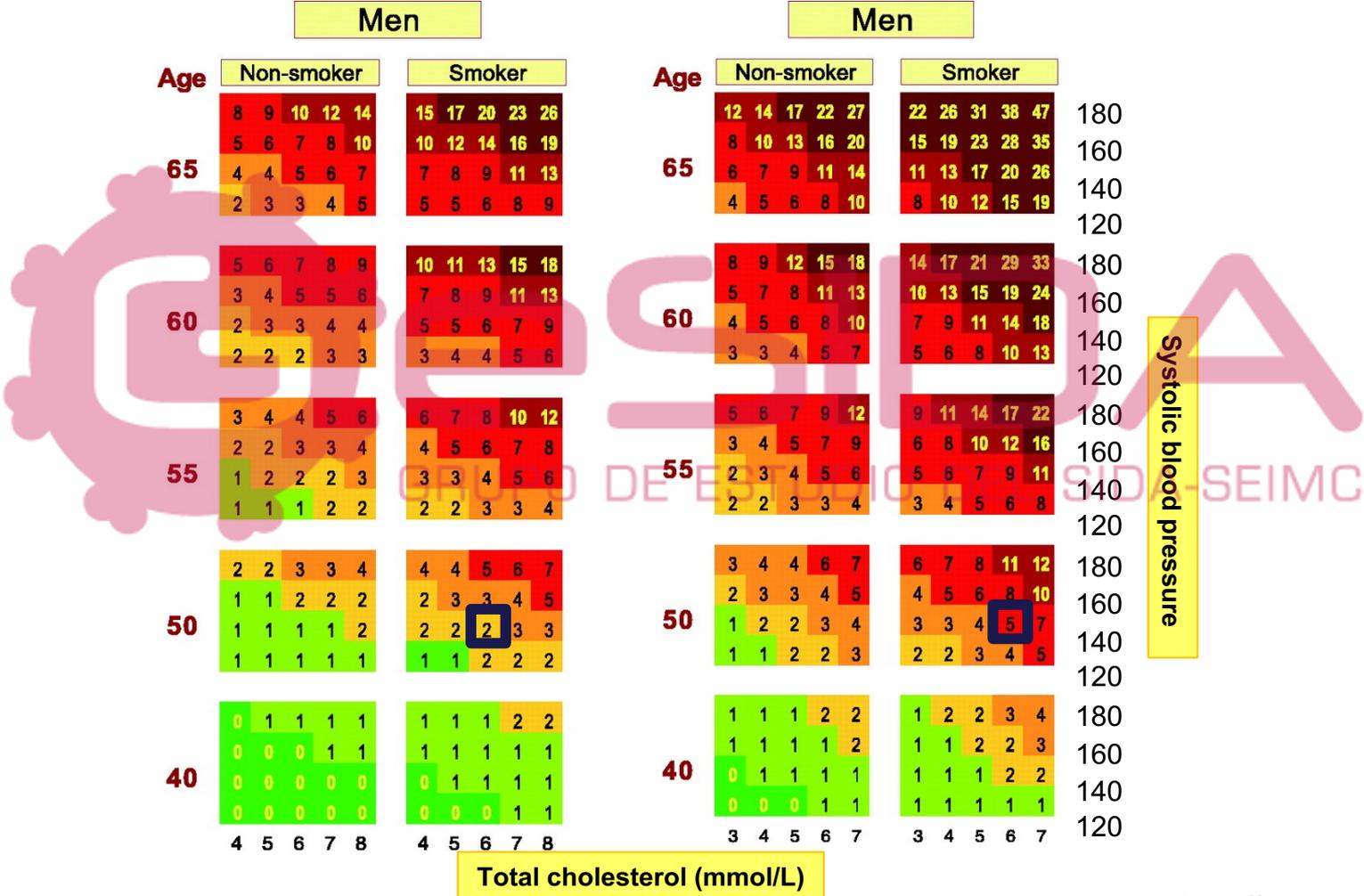
HDL: 40 unit: mmol/L g/L g/dL mg/dL



SCORE estimates risk of CV death (used in Europe)

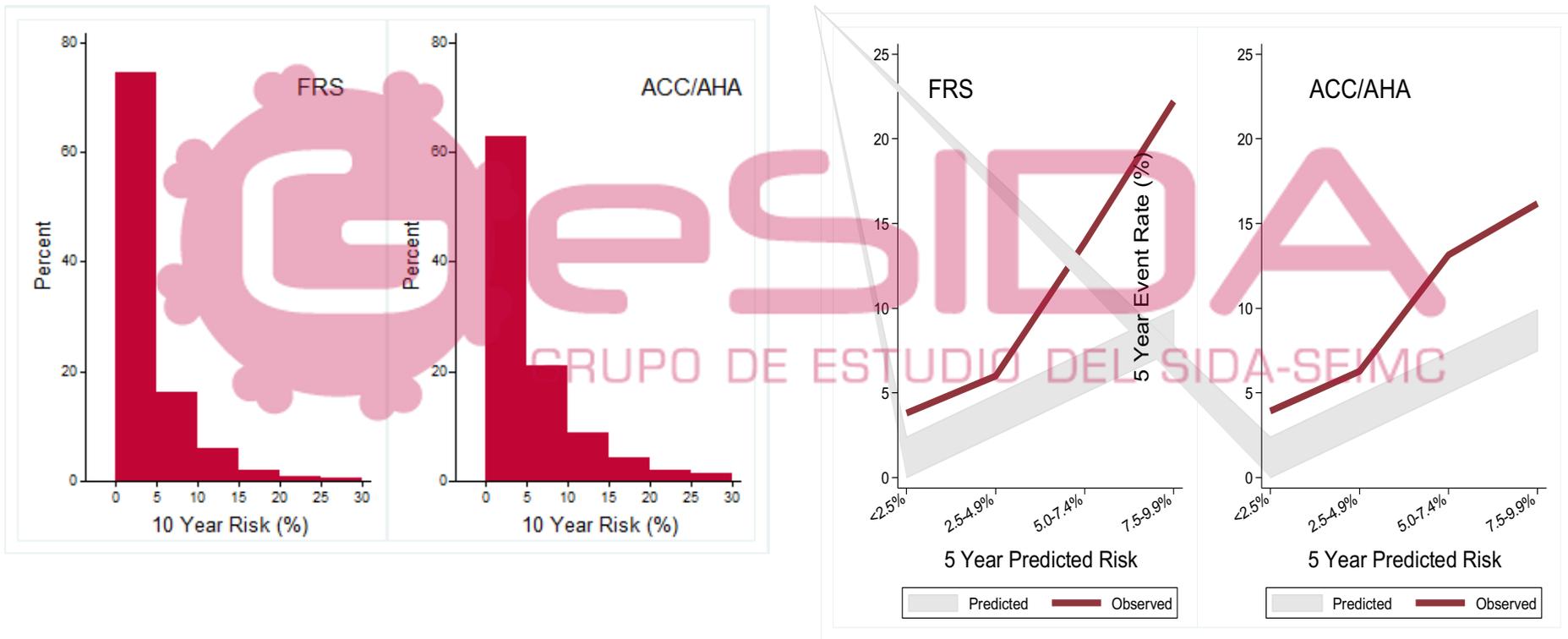
Low-risk countries

High-risk countries



2013 ACC/AHA score may estimate CV events better than Framingham score

Partners HealthCare System HIV longitudinal cohort (n=2270), comprised of patients seen at Brigham & Women's Hospital or Massachusetts General Hospital in Boston, MA



ASCVD estimator based on 2013 ACC/AHA guidelines (used in US)

| | |
|-----------------------|--|
| ASCVD Risk Estimator* | |
| 10-Year ASCVD Risk | 14.2% calculated risk |
| | 2.1% risk with optimal risk factors** |

Gender: Male Female

Age:

Race: White African American Other

HDL - Cholesterol (mg/dL):

Total Cholesterol (mg/dL):

Systolic Blood Pressure:

Diabetes: Yes No

Treatment for Hypertension: Yes No

Smoker: Yes No

Optimal CV risk score for HIV-infected patients

| | Framingham | | ATP3 | | DAD | | ASCVD | |
|--------|------------|-----------|-------|-----------|-------|-----------|-------|-----------|
| | HC | CI | HC | CI | HC | CI | HC | CI |
| Type 1 | 0.73* | 0.69,0.77 | 0.74* | 0.70,0.78 | 0.73* | 0.68,0.78 | 0.77 | 0.73,0.81 |
| Type 2 | 0.63* | 0.57,0.69 | 0.63* | 0.56,0.69 | 0.62* | 0.55,0.68 | 0.72 | 0.67,0.78 |
| All MI | 0.68* | 0.65,0.72 | 0.69* | 0.65,0.72 | 0.68* | 0.64,0.71 | 0.74 | 0.71,0.77 |

* Harrell's C significantly different from ASCVD HC

Plaque rupture with thrombus



Vasospasm



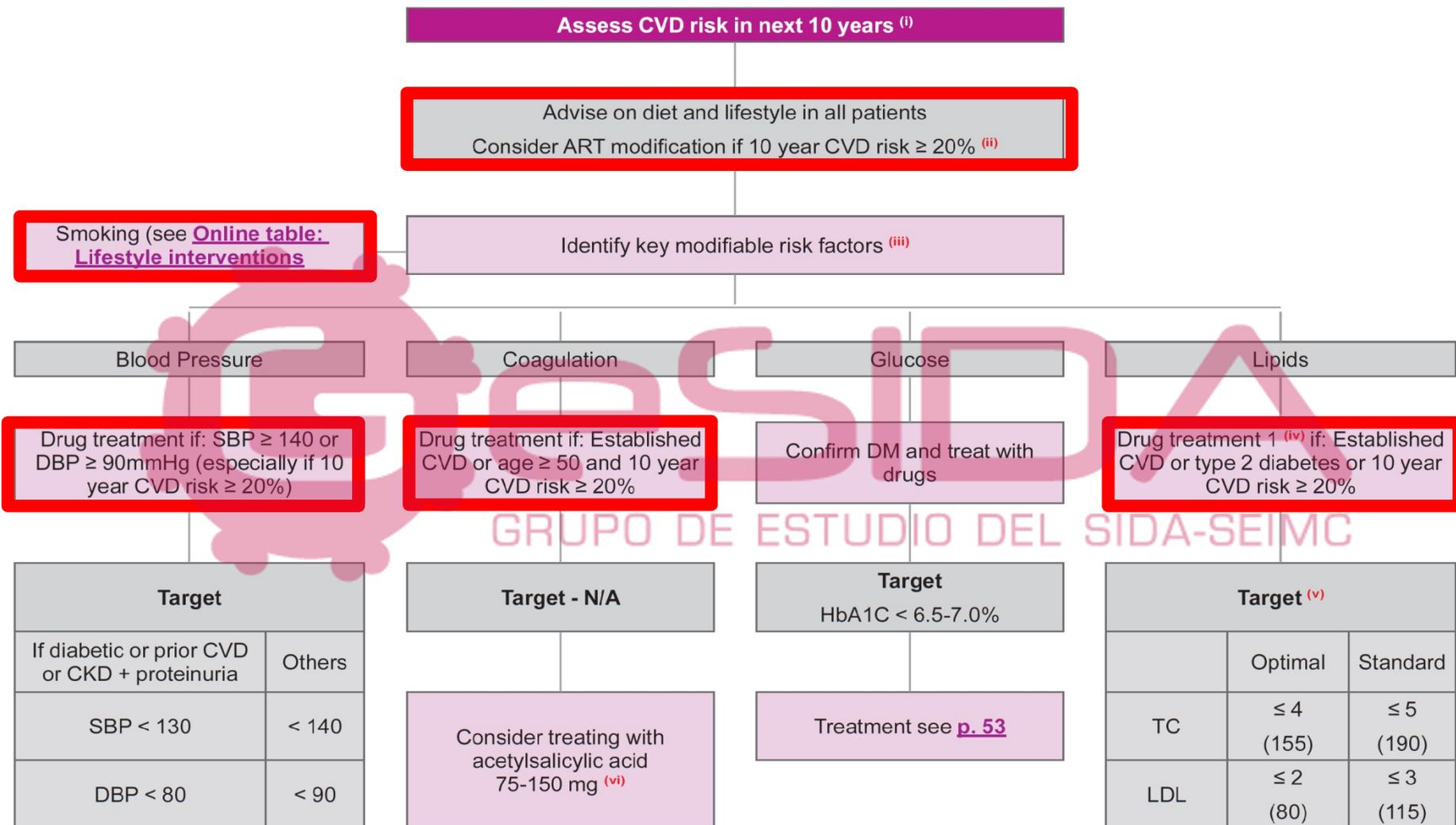
The addition of specific antiretroviral medications in the DAD score did not improve discrimination or calibration compared with ASCVD

ASCVD performed better than the other risk scores, doing better than both older more outdated scores and an HIV score with antiretroviral medications

Risk of subclinical CV disease is higher than predicted

| | |
|--|---------------|
| Nr of patients | 108 |
| Age, years (IQR) | 46 (40-52) |
| Current smoking (%) | 50 |
| Total cholesterol (mg/dL) | 175 |
| LDL cholesterol (mg/dL) | 98 |
| HDL cholesterol (mg/dL) | 49 |
| 10-year Framingham score, % (IQR) | 3 (1-5) |
| 10-year ASCVD score, % (IQR) | 3.3 (1.6-6.6) |
| CD4 cells/mm ³ | 528 |
| Viral load (copies/mL) | <50 |
| Patients with any coronary plaque (%) | 45 |
| Patients with high-risk plaques (%) | 36 |
| Statins recommended 2004 ATP III (%) | 8 |
| Statins recommended 2013 ACC/AHA (%) | 21 |

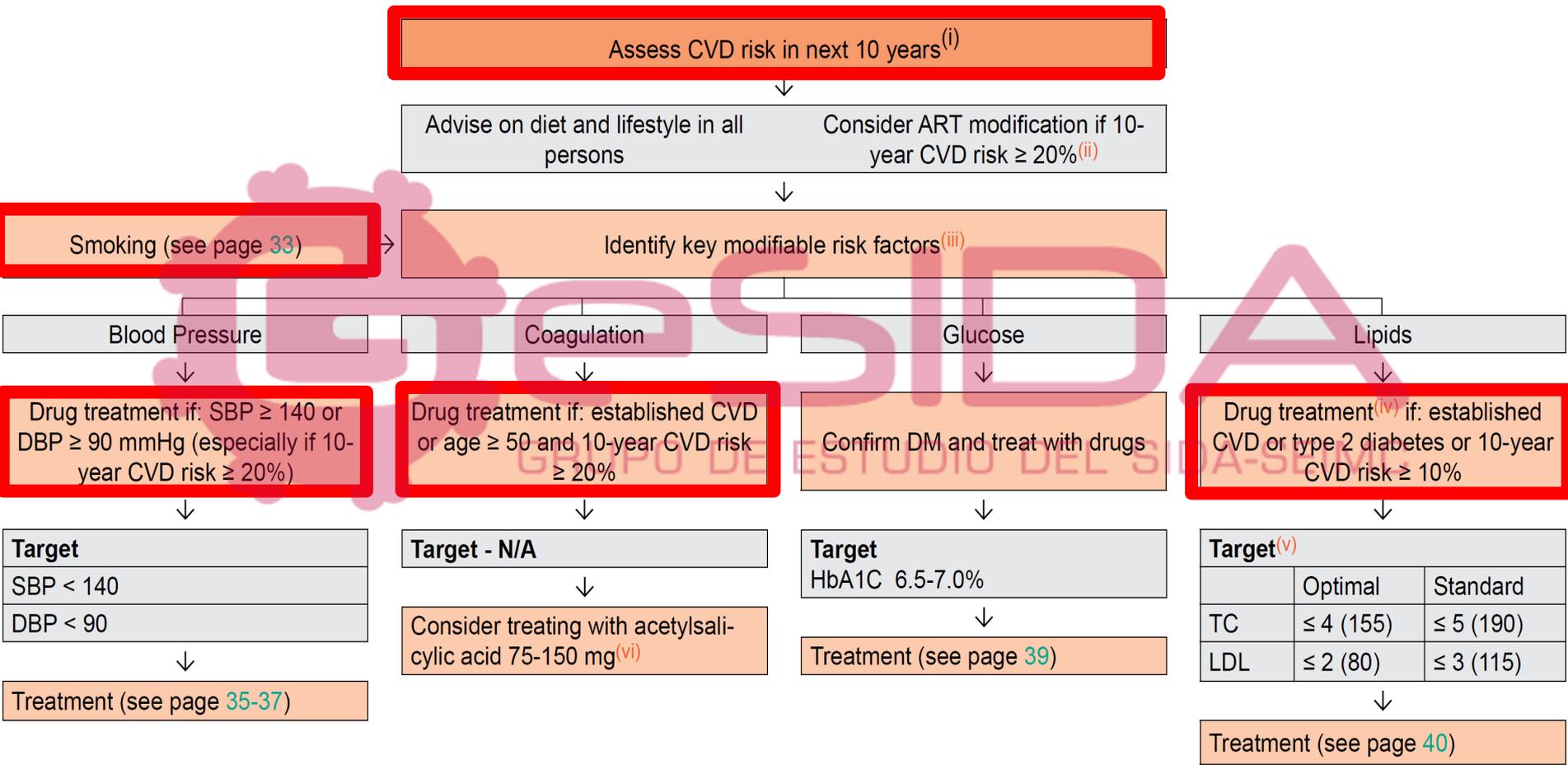
Principles: The intensity of efforts to prevent CVD depends on the underlying risk of CVD, which can be estimated ⁽ⁱ⁾. The preventive efforts are diverse in nature and require involvement of a relevant specialist, in particular if the risk of CVD is high and always in patients with a history of CVD.



Prevention of CVD

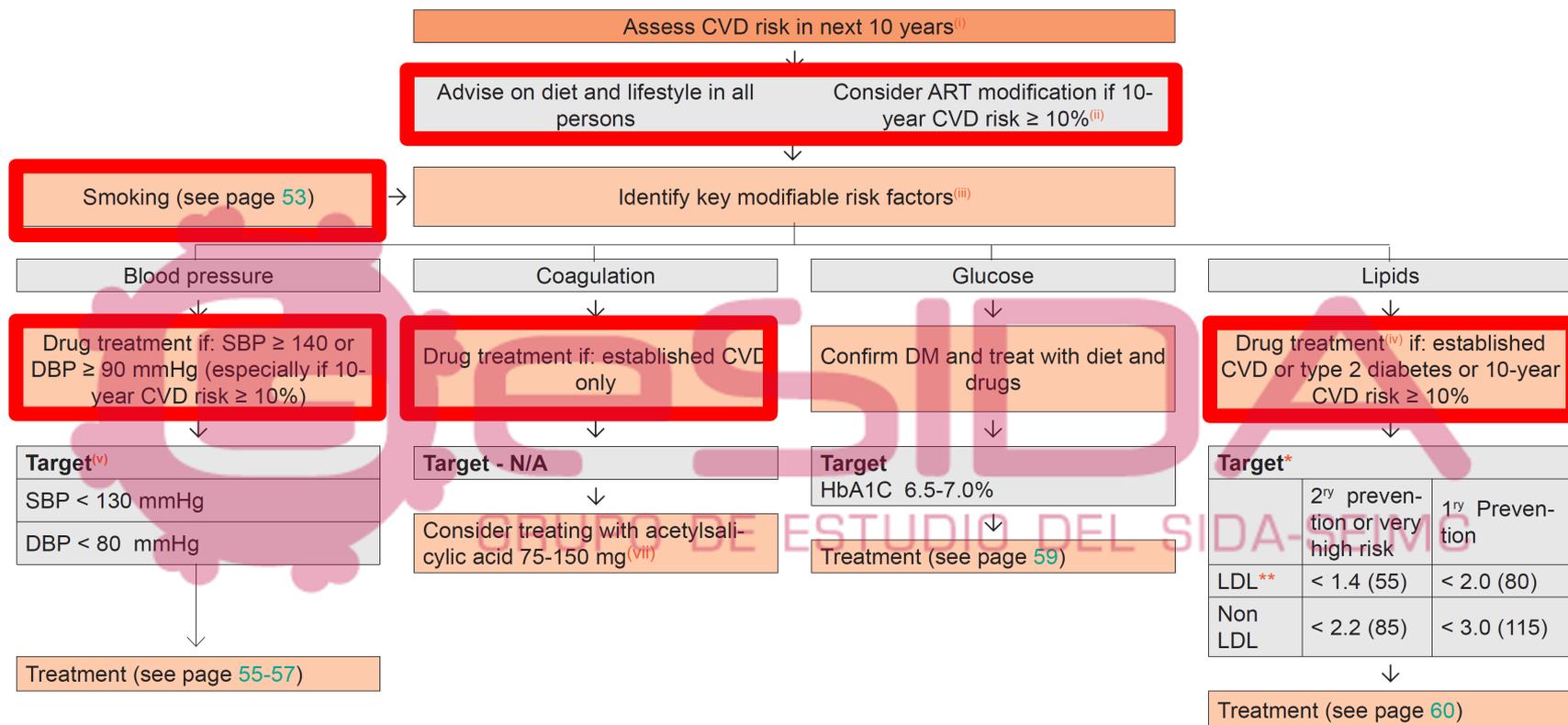
EACS from 2015 on

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.



Prevention of Cardiovascular Disease (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



Intervention strategies as a function of total CV risk and LDL-C level

| Total CV risk (SCORE) % | LDL-C levels | | | | |
|---------------------------|---------------------------------------|--|--|--|--|
| | < 70 mg/dL < 1.8 mmol/L | 70 to < 100 mg/dL 1.8 to < 2.5 mmol/L | 100 to < 155 mg/dL 2.5 to < 4.0 mmol/L | 155 to < 190 mg/dL 4.0 to < 4.9 mmol/L | > 190 mg/dL > 4.9 mmol/L |
| < 1 | No lipid intervention | No lipid intervention | Lifestyle intervention | Lifestyle intervention | Lifestyle intervention, consider drug if uncontrolled |
| Class/Level | I/C | I/C | I/C | I/C | Ila/A |
| ≥ 1 to < 5 | Lifestyle intervention | Lifestyle intervention | Lifestyle intervention, consider drug if uncontrolled | Lifestyle intervention, consider drug if uncontrolled | Lifestyle intervention, consider drug if uncontrolled |
| Class/Level | I/C | I/C | Ila/A | Ila/A | I/A |
| > 5 to < 10, or high risk | Lifestyle intervention consider drug* | Lifestyle intervention consider drug* | Lifestyle intervention and immediate drug intervention | Lifestyle intervention and immediate drug intervention | Lifestyle intervention and immediate drug intervention |
| Class/Level | Ila/A | Ila/A | Ila/A | I/A | I/A |
| ≥ 10 or very high risk | Lifestyle intervention consider drug* | Lifestyle intervention and immediate drug intervention |
| Class/Level | Ila/A | Ila/A | I/A | I/A | I/A |

European Heart Journal 2011;32 (14):1769–1818
Atherosclerosis 2011 Jul;217(1):3-46

ASCVD estimator (based on 2013 ACC/AHA guidelines)

| | |
|-----------------------|---|
| ASCVD Risk Estimator* | |
| 10-Year ASCVD Risk | 14.2% <small>calculated risk</small> |
| | 2.1% <small>risk with optimal risk factors**</small> |

Adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL with no diabetes and estimated 10-year ASCVD risk $\geq 7.5\%$ should be treated with moderate to high-intensity statin therapy

Gender

Male

Female

Age

50

Race

White

African American

Other

HDL - Cholesterol (mg/dL)

40

Total Cholesterol (mg/dL)

240

Systolic Blood Pressure

140

Diabetes

Yes

No

Treatment for Hypertension

Yes

No

Smoker

Yes

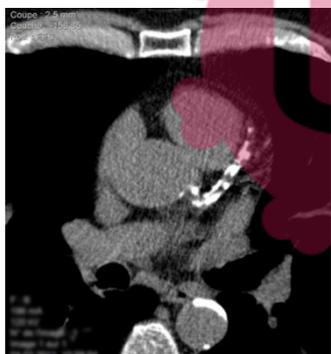
No

Increased prevalence of subclinical coronary atherosclerosis detected by coronary computed tomography angiography in HIV-infected men

Janet Lo^a, Suhny Abbara^b, Leon Shturman^c, Anand Soni^c, Jeffrey Wei^a, Jose A. Rocha-Filho^c, Khurram Nasir^{c,d} and Steven K. Grinspoon^a

AIDS 2008, **22**:257–267

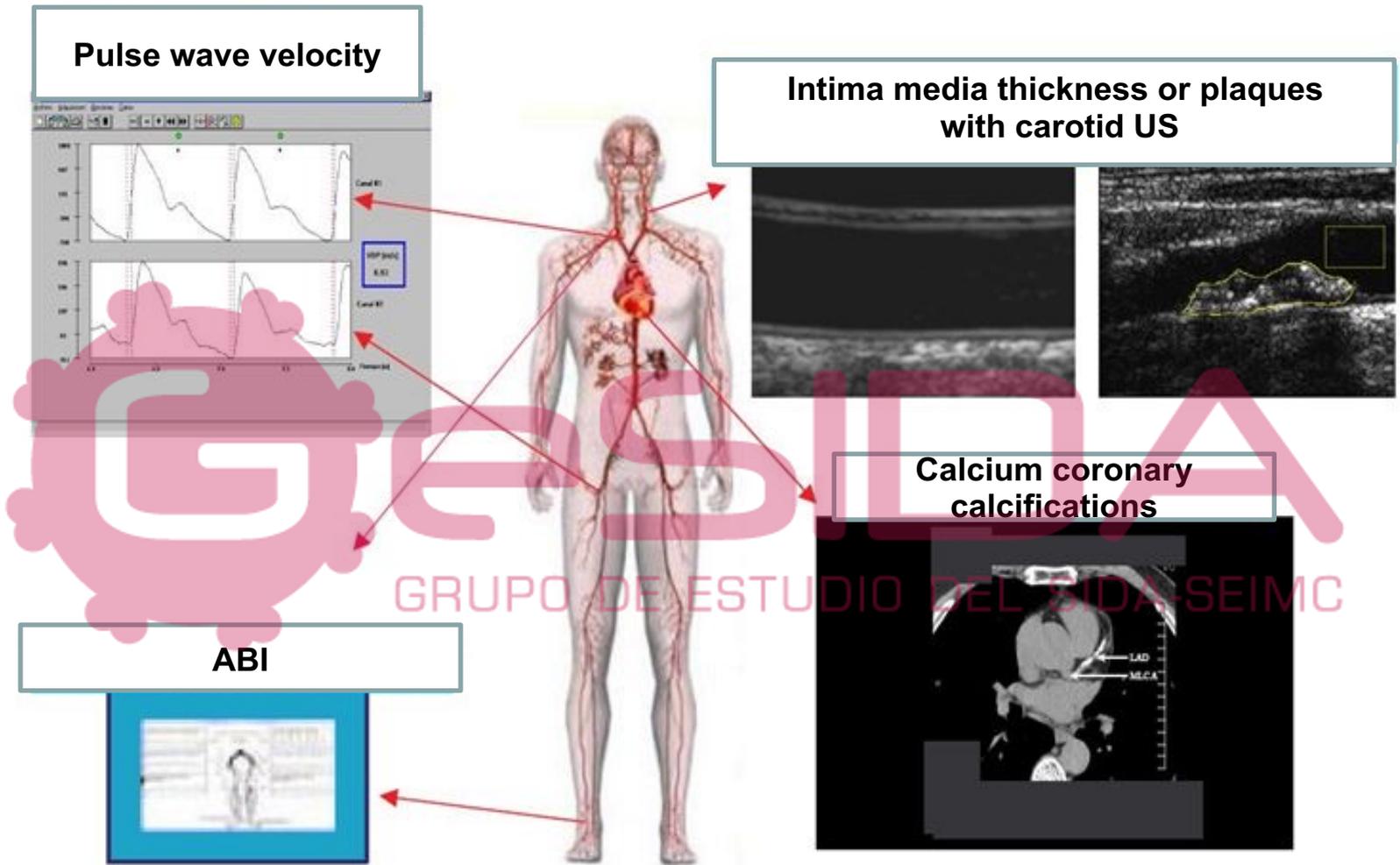
Tabac, FRS,
ATCD Fx CAD
similaire

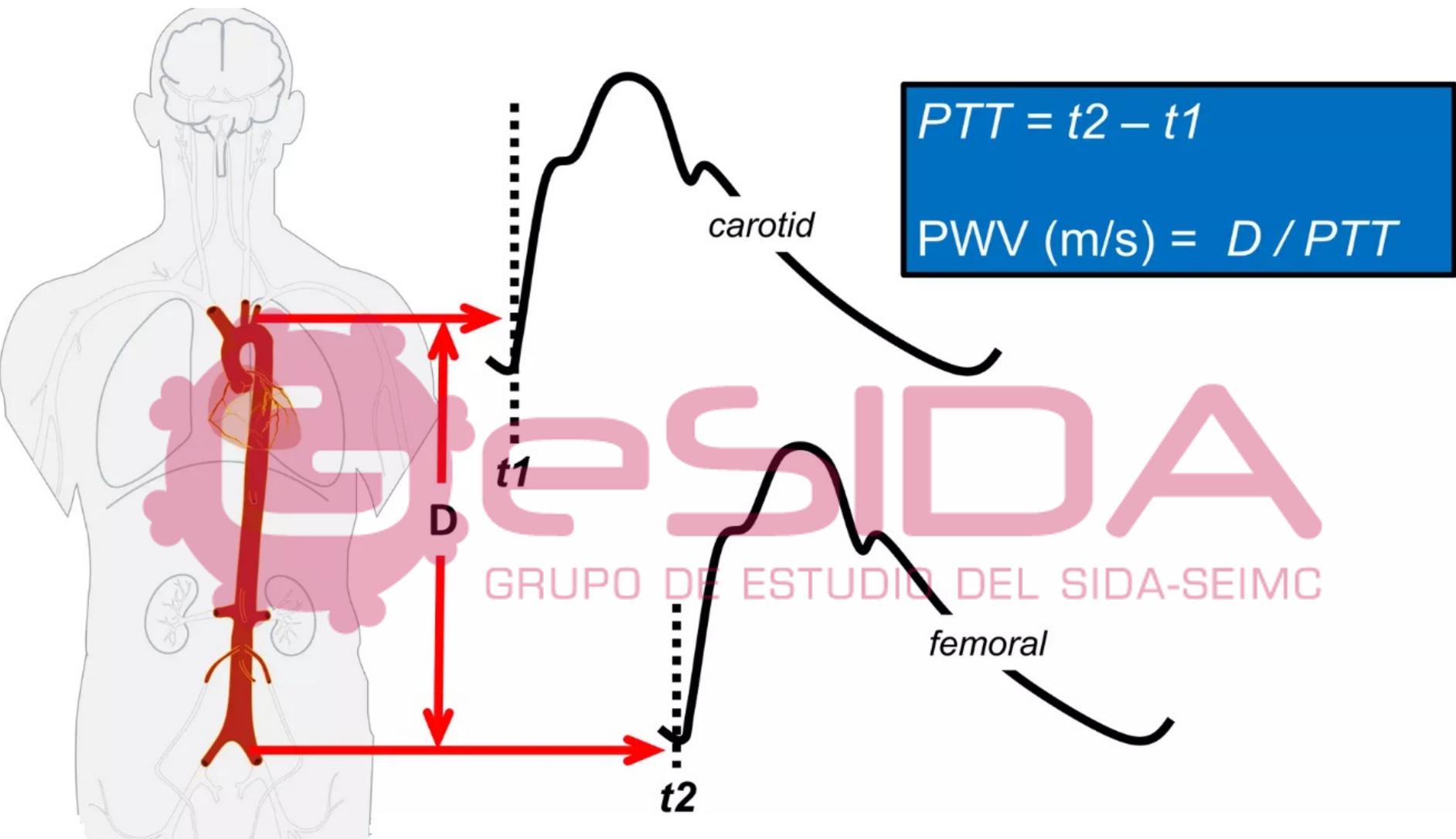


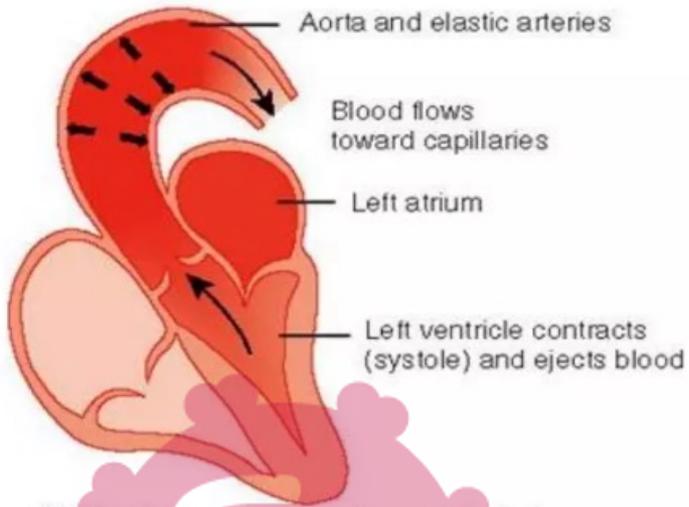
| | VIH-, n=32 | VIH+, n= 78 | p |
|---|------------------------|-------------------------|------|
| Presence of coronary plaque (%) | 34.4 | 59.0 | 0.02 |
| Agatston calcium score, median (IQR); mean ± SD | 0 (0–4.5); 21.6 ± 64.1 | 0 (0–20.7); 37.4 ± 93.3 | 0.08 |
| Agatston calcium score >0 (%) | 25.0 | 46.2 | 0.04 |
| Segments with plaque, n, median (IQR); mean ± SD | 0 (0–1); 1.2 ± 2.2 | 1 (0–3); 2.2 ± 2.7 | 0.03 |
| Plaque volume, µl, median (IQR); mean ± SD | 0 (0–81); 85 ± 193 | 56 (0–208); 173 ± 250 | 0.02 |
| Participants found to have coronary stenosis >70% (%) | 0 | 6.5% | 0.06 |

P value by Wilcoxon rank-sum test. IQR, interquartile range.

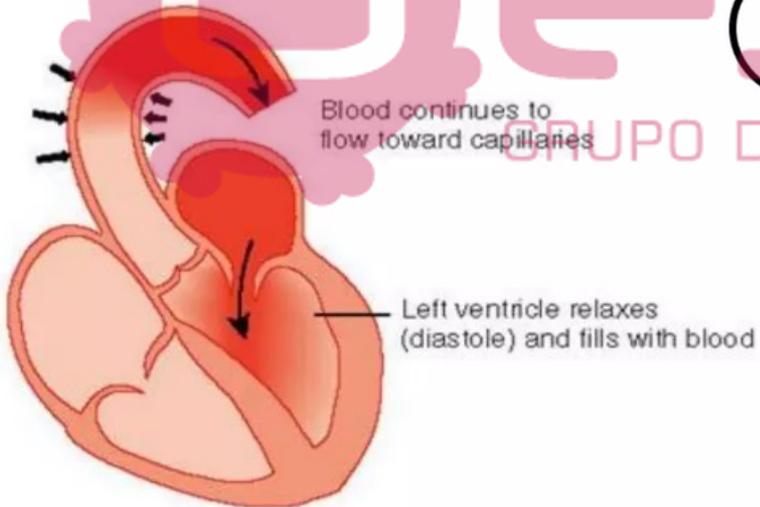
How to assess subclinical atherosclerosis?



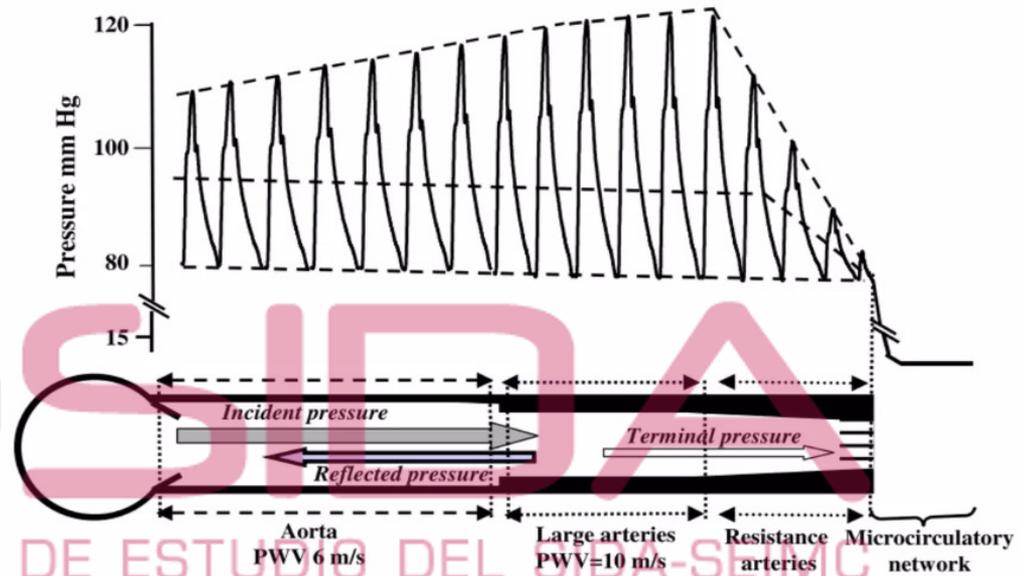




(a) Elastic aorta and arteries stretch during ventricular contraction

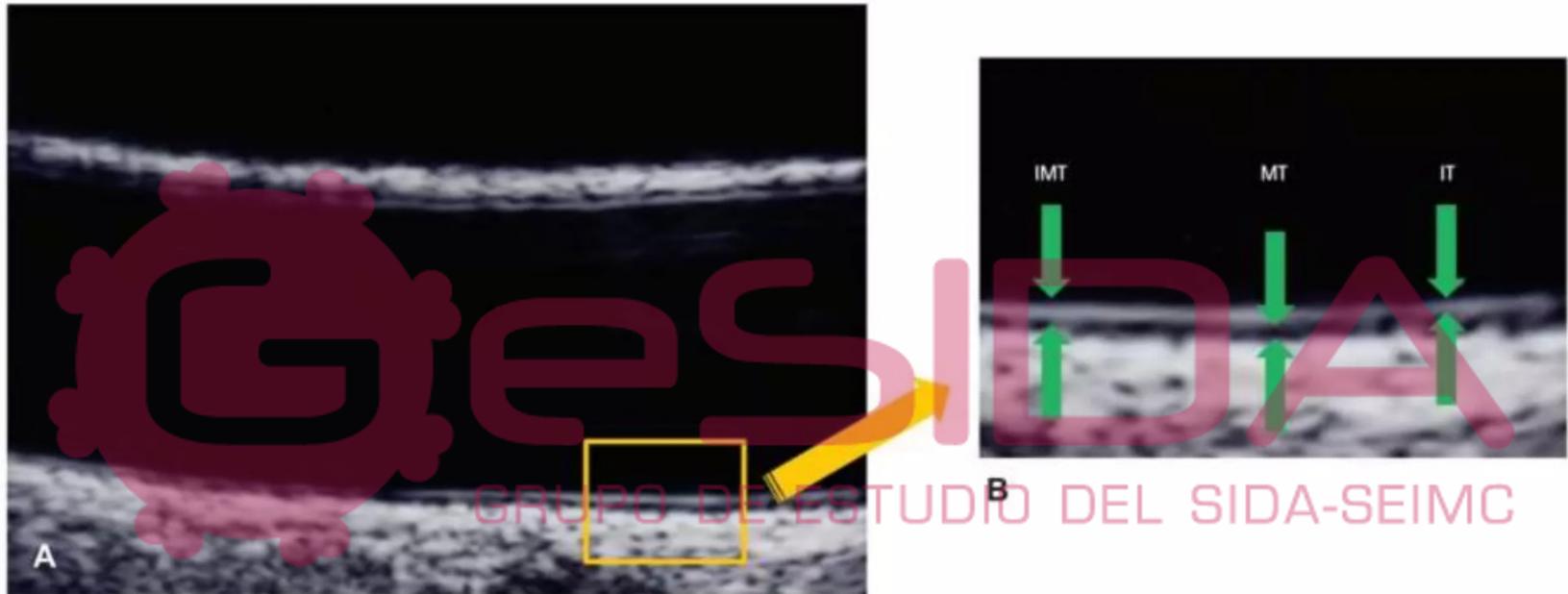


(b) Elastic aorta and arteries recoil during ventricular relaxation



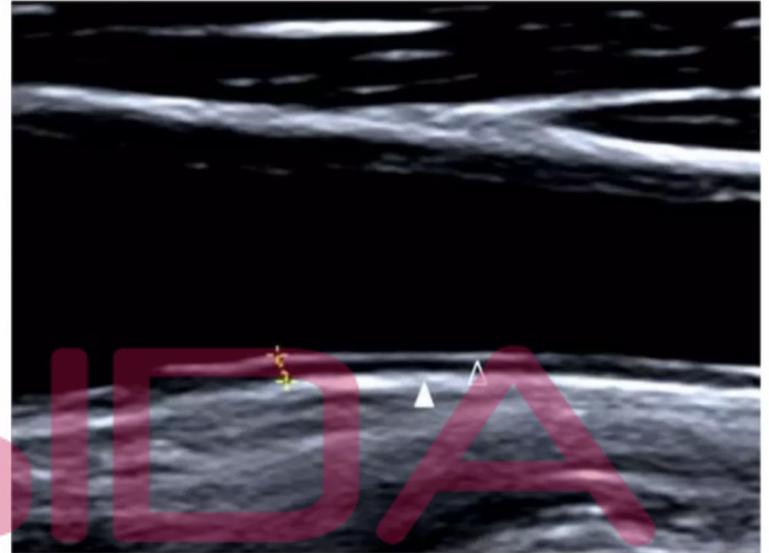
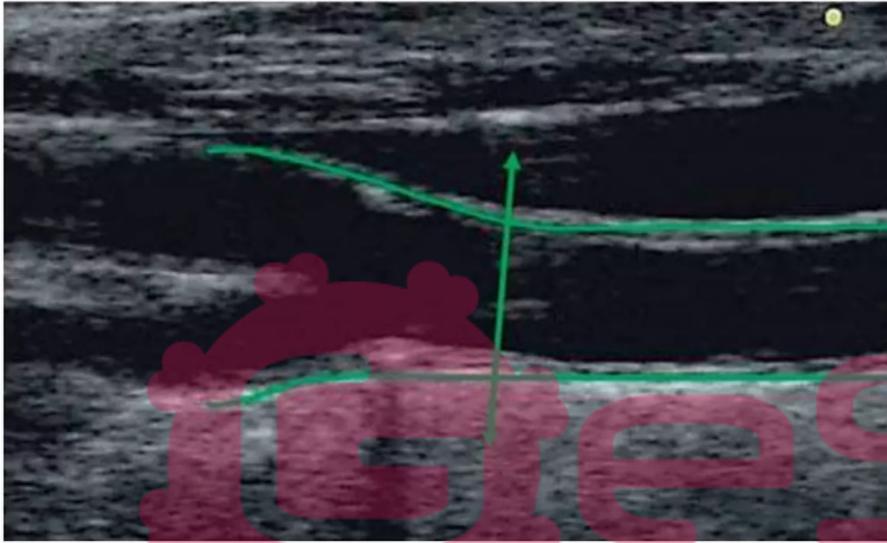
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Carotid intima-media thickness (CIMT)



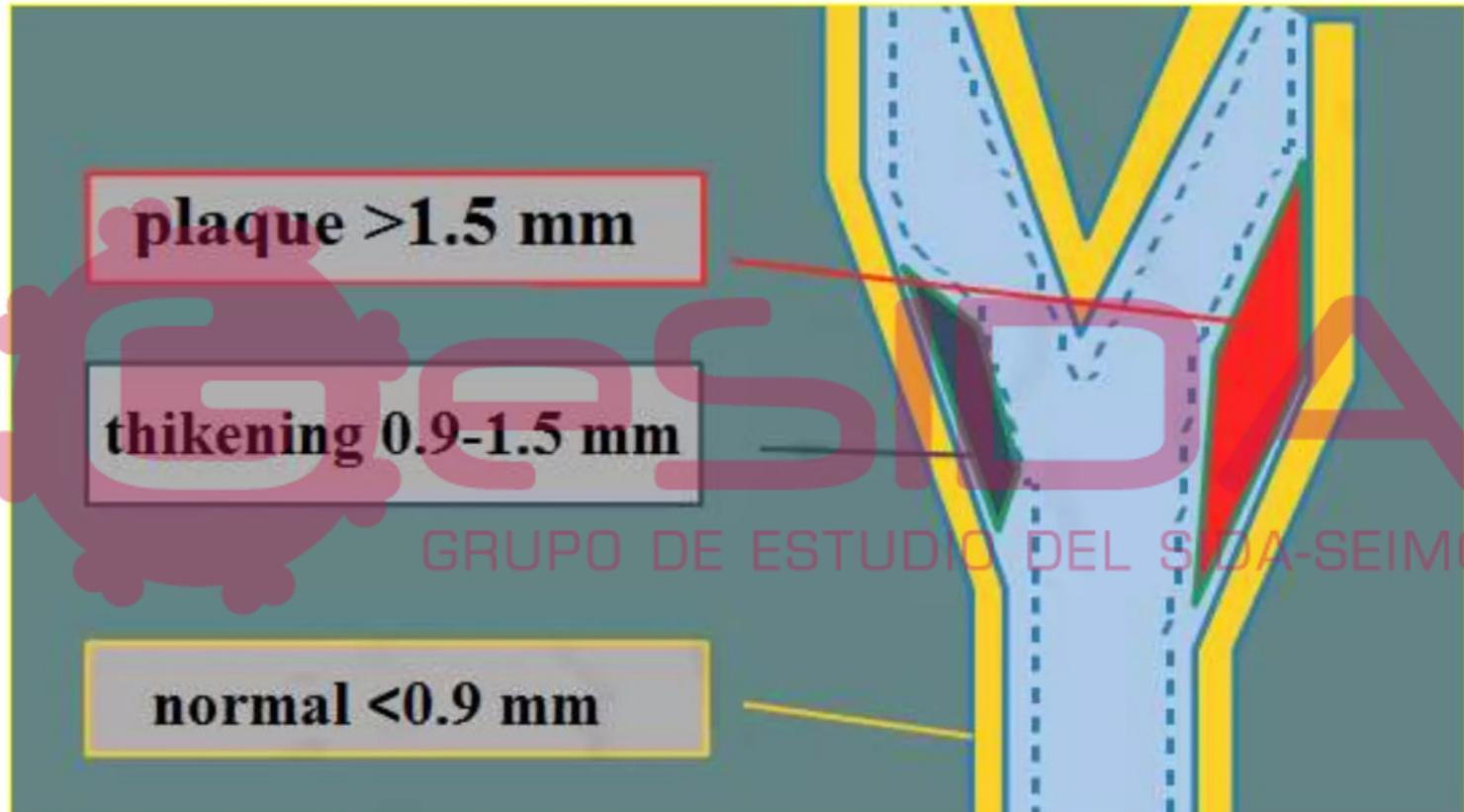
Good correlation of CIMT between histology & ultrasound

Double-line pattern



Double arrow line corresponds to end of CCA
where near & far walls start diverging

CIMT & plaque



ARIC study

CIMT & carotid plaque included in FRS

13,145 participants without CVD

7% improvement in all subjects

17% improvement in intermediate risk subjects

ARIC Coronary Heart Disease Risk Calculator that includes Carotid Ultrasound Information

This risk assessment tool uses information from the ARIC Study. It is designed for adults, 45-65 years old, who do not have heart disease to predict a person's chance of having a heart attack in the next 10 years. To find your risk score, enter your information in the calculator below then click the 'Calculate Risk' button.

Gender Female Male

Are you a cigarette smoker? Yes No

Age

Total Cholesterol mg/dL

HDL (Good Cholesterol) mg/dL

Systolic Blood Pressure mm Hg

Carotid Artery Wall Thickness mm
* See Note below

Carotid Plaque? Yes No

Are you currently taking any medication to treat high blood pressure? Yes No

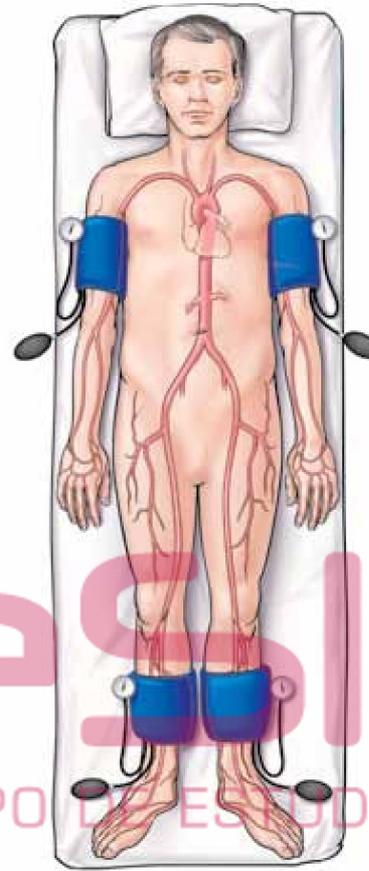
Do you have Diabetes? Yes No

* Note: Carotid artery wall thickness used in the development of this risk score was the mean of the mean measurements of the distal common carotid, internal carotid and carotid artery bifurcation, of both right and left carotid arteries. For measurements that were not available in the above listed segments, imputed values were used.

FRS: Framingham risk score

<http://www.csc.unc.edu/aricnews/CIMTCHD/RiskCalc2.html>

How to calculate the ankle-brachial index



Right arm:

Systolic pressure **120** mm Hg

Left arm:

Systolic pressure **100** mm Hg

Right ankle: Systolic pressure

Posterior tibial (PT) **68** mm Hg

Dorsalis pedis (DP) **64** mm Hg

Left ankle: Systolic pressure

Posterior tibial (PT) **136** mm Hg

Dorsalis pedis (DP) **132** mm Hg

Right ABI equals ratio of:

Higher of the right ankle pressure (PT or DP)
Higher arm pressure (right or left arm)

$$\frac{68 \text{ mm Hg}}{120 \text{ mm Hg}} = 0.57^*$$

Left ABI equals ratio of:

Higher of the left ankle pressure (PT or DP)
Higher arm pressure (right or left arm)

$$\frac{136 \text{ mm Hg}}{120 \text{ mm Hg}} = 1.13^*$$

*The lower of these numbers is the patient's overall ankle-brachial index. Overall ankle-brachial index = **0.57**

Can we measure plaque?

- Plaque consists of fatty substances, LDL cholesterol, and fibrin. The plaque is initially soft, and gets hard with deposition of calcium phosphate which starts nearly six months later.
- This calcium deposition can be detected by electron beam CT scan (EBCT) or a multidetector CT scan (MDCT) as spotty or speckled pattern.



An interesting property of the calcium score is its **high negative predictive value**.

| Diagnostic procedure | Typical effective dose (mSv) | Number of chest X-rays leading to comparable exposure |
|-------------------------------------|------------------------------|---|
| Chest (p.a) | 0.02 | 1 |
| Extremities and joints | 0.01 | 0.5 |
| Skull | 0.07 | 3.5 |
| Thoracic vertebra | 0.7 | 35 |
| Lumbar vertebra | 1.3 | 65 |
| Hip | 0.3 | 15 |
| Pelvis | 0.7 | 35 |
| Abdomen | 1.0 | 50 |
| Mammography (bilateral in 2 planes) | 0.5 | 25 |
| Intravenous urography | 2.5 | 125 |
| Head CT | 2.3 | 115 |
| Chest CT | 8 | 400 |
| Abdomen or pelvis CT | 10 | 500 |
| Renal function scintigraphy | 0.8 | 40 |
| Thyroid scintigraphy | 0.9 | 45 |
| Lung perfusion scintigraphy | 1.1 | 55 |
| Skeletal scintigraphy | 4.4 | 220 |
| Brain scintigraphy | 5.1 | 255 |
| Myocardial perfusion scintigraphy | 6.8 | 340 |
| Positron emission tomography | 7.2 | 360 |
| Myocardial scintigraphy | 17 | 865 |

Interpretation of the coronary calcium scoring

| Score | Presence of Plaque | Heart disease | Risk of Heart attack |
|---------|--|---------------|----------------------|
| 0 | No identifiable plaque. You have less than 5% chance of having heart disease. | <5% chance | Very low |
| 1-10 | Minimal identifiable plaque. You have less than 10% chance of having heart disease. | <10% chance | Low |
| 11-100 | Mild plaque is present. You have mild heart disease. | Mild | Moderate |
| 101-400 | Moderate amount of plaque is present. You have heart disease and plaque may be blocking an artery. | Moderate | Moderate to high |
| >400 | Large amount of plaque is present. You have more than a 90% chance that plaque is blocking one of your arteries. | Severe | High |

Framingham Score 10 yr. event risk recalculated according to Coronary Calcium Score range

| Framingham 10 yr risk | CAC = 0 | CAC 1-80 | CAC 81-400 | CAC 401-600 | CAC > 600 |
|-----------------------|---------|----------|------------|-------------|-----------|
| 1% | 0.3% | 0.6% | 2% | 4% | 7% |
| 2% | 0.6% | 1.1% | 4% | 7% | 13% |
| 3% | 0.9% | 1.7% | 6% | 10% | 18% |
| 4% | 1.2% | 2.2% | 7% | 13% | 23% |
| 5% | 1.5% | 2.8% | 9% | 16% | 27% |
| 6% | 1.7% | 3.2% | 11% | 19% | 31% |
| 7% | 1.9% | 3.8% | 13% | 22% | 35% |
| 10% | 2.4% | 5.4% | 16% | 25% | 36% |
| 15% | 3.2% | 8.3% | 23% | 33% | 45% |
| 20% | 3.8% | 9.8% | 28% | 38% | 48% |

Low-risk = Green, Intermediate-risk = Yellow and High-risk = Red

2004, Johns Hopkins University

Alternatively, the FRS can be recalculated by adding the following points for coronary calcium score ranges

| CAC Score Range | Adjustment to Framingham Point Score | |
|-----------------|--------------------------------------|-------|
| | Men | Women |
| 0 | -5 | -5 |
| 1 to 80 | -3 | -3 |
| 81 to 400 | +2 | +4 |
| 401 to 600 | +5 | +9 |
| >600 | +8 | +12 |

Consider potential for drug-drug interactions between ARVs and other drugs

High

ATV/rit

DRV/rit

ATV/cobi

DRV/cobi

EVG/cobi

Moderate

NVP

EFV

ETV

Low/No

NRTIs (all)

RPV

MVC

RAL

DTG



GESIDA
GRUPO DE ESTUDIO DEL SIDA-SEIMC

Risk of interactions between statins and PI/r or NNRTI

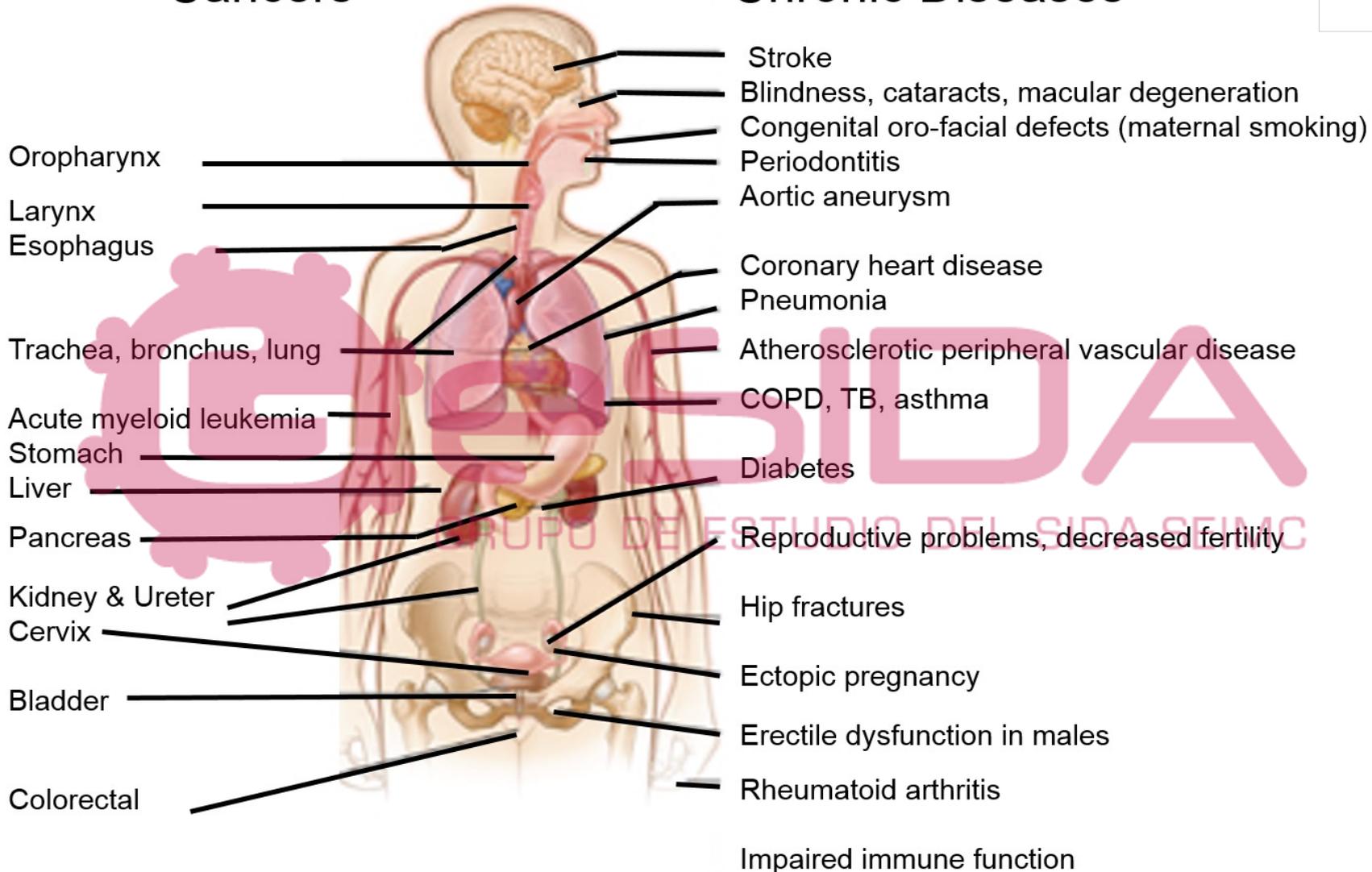
Drugs used to lower LDL-c

| DRUG CLASS | DRUG | DOSE | SIDE EFFECTS | ADVISE ON USE OF STATIN TOGETHER WITH ART | |
|-------------------------|-------------------|-------------|--|---|---------------------------|
| | | | | use with PI/r | use with NNRTI |
| Statin (i) | Atorvastatin (ii) | 10-80 mg qd | Gastrointestinal symptoms, headache, insomnia, rhabdomyolysis (rare) and toxic hepatitis | Start with low dose (v) (max: 40 mg) | 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: 20 mg) | Start with low dose (v) |
| | Simvastatin (iii) | 10-40 mg qd | | Contraindicated | Consider higher dose (vi) |
| Cholesterol uptake↓ (i) | Ezetimibe (iv) | 10 mg qd | Gastrointestinal symptoms | No known drug-drug interactions with ART | |

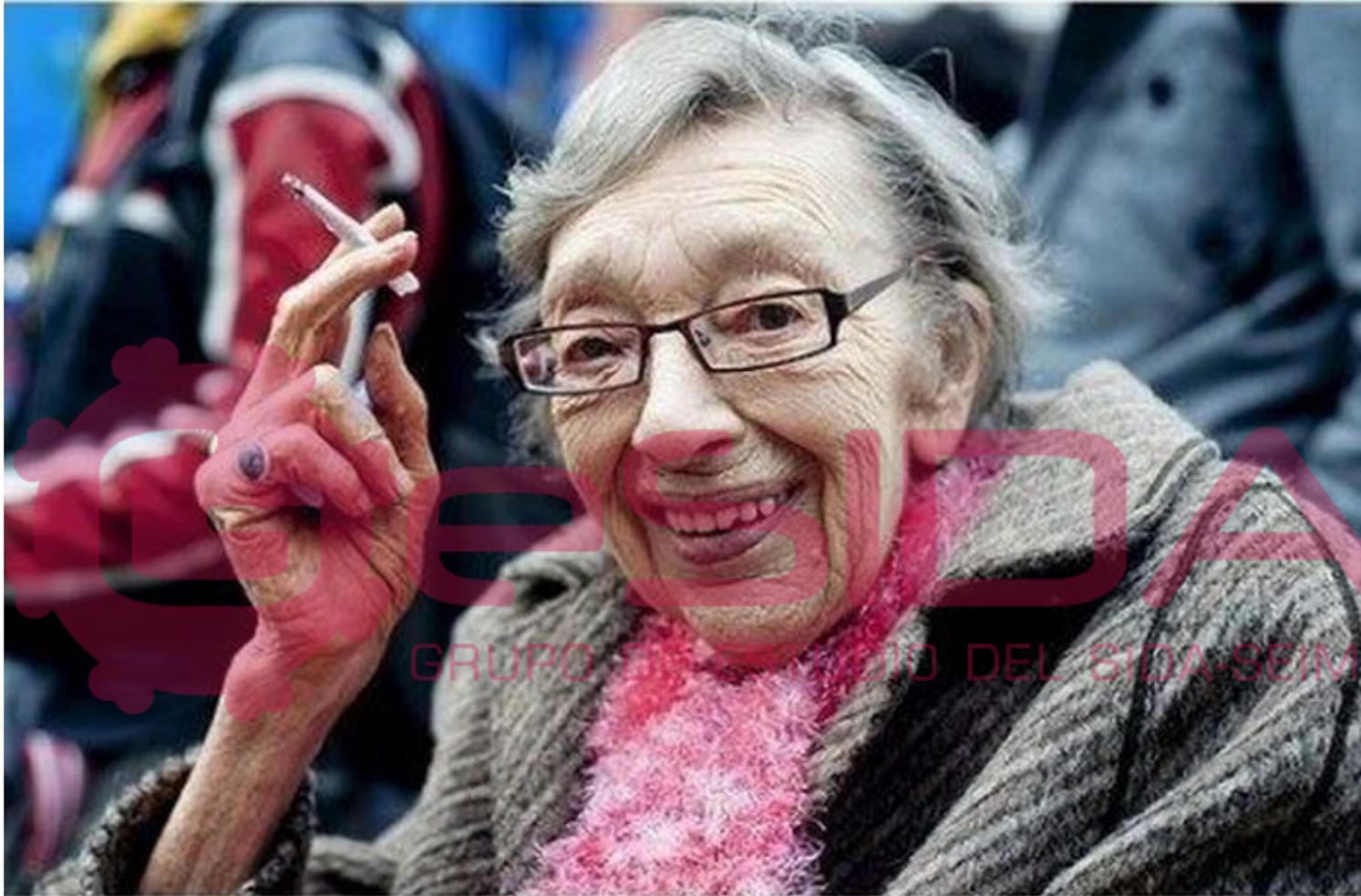
Health effects of tobacco smoking go beyond cardiovascular disease

Cancers

Chronic Diseases

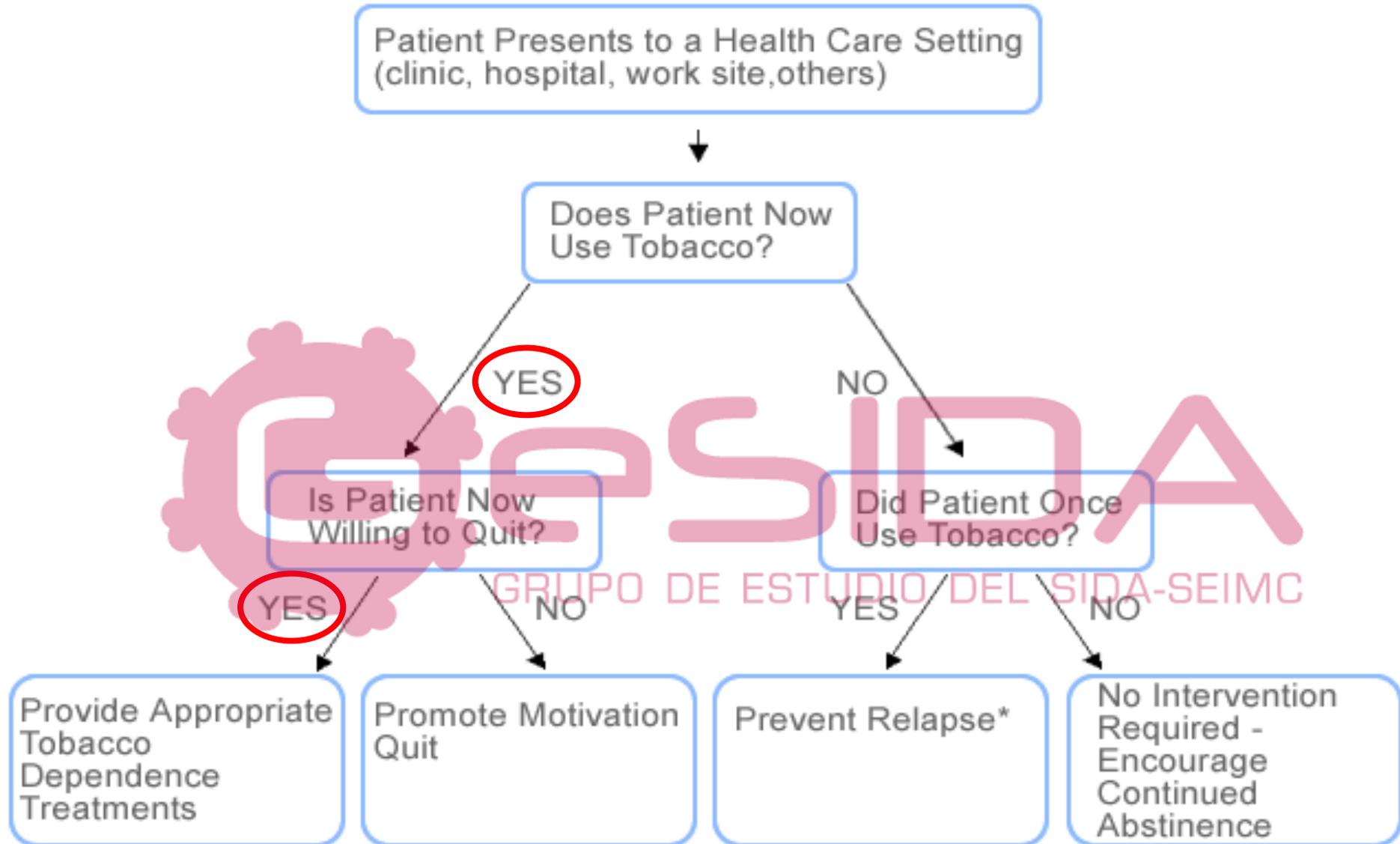


Who said cigarette kills ?



I'm 48 and still feeling good.

Major steps to intervention on smoking cessation



Anti-smoking campaign messages may be explicit enough to make smokers aware of quitting

Effects of smoking on appearance

Non-smoker
Aged 35

Smoker
Aged 35

Smokers face is the result of puckering on a cigarette and squinting in reaction to smoke, which creates deep wrinkles around the mouth and eyes

Healthy hair, skin and nails of a non-smoker

Dull, yellow-grey complexion

Skin damage from low levels of Vitamin A

Chemicals break down hair cells, leading to hair damage

A breakdown of collagen supply to skin results in less firmness and elasticity

Damage to skin fibres:

- Wrinkles
- Sagging of the eyelids
- Bags under eyes
- Premature aging of skin on our body

Smoking accelerates the aging process by 10-20 years

Advertisement

STOP SMOKING START REPAIRING

In 1 week
your sense of taste and smell improves

In 3 months
your lung function begins to improve

In 8 hours
excess carbon monoxide is out of your blood

In 1 year
a pack-a-day smoker will save over \$4,000

In 5 years
your risk of a stroke has dramatically decreased

In 12 weeks
your lungs regain the ability to clean themselves

In 12 months
your risk of heart disease has halved

In 5 days
most nicotine is out of your body

EVERY CIGARETTE YOU DON'T SMOKE IS DOING YOU GOOD

Quitline.13 7848
australia.gov.au/quitnow

Authorised by the Australian Government, Capital Hill, Canberra
Printed by PMP Limited, 31-37 Heathcote Road, Moorebank, NSW, 2170

Australian Government

Smoking cessation studies in HIV patients

| Authors, year | Design | Interventions | n | Follow-up | Outcome: smoking cessation |
|--|--------|---|----------------------|-----------------|--|
| Wewers <i>et al.</i> 2000 [72] | NR | NRT + counselling + skills training | n = 8 | 8 months (bcv) | 50% |
| | | Self-help (standard care) | n = 7 (total n = 15) | | 0% |
| Cummins <i>et al.</i> 2005 [73] | NR | NRT + motivational counselling + diary | n = 27 | 5 months (sr) | 6/27 (22%) |
| Elzi <i>et al.</i> 2006 [74] | NR | Counselling + NRT | n = 34 | 12 months (sr) | 13/24 (38%) |
| | | Control group: no intervention at all | n = 383 | | 27/383 (7%) |
| Pedrol-Clotet <i>et al.</i> 2006 [75] | NR | BUP | n = 21 | 12 months (sr) | 8/21 (38%) |
| Vidrine <i>et al.</i> 2006 [60] | NR | Usual care (counselling + self-help material + NRT) | n = 77 (total) | 3 months (bcv) | 10.3% |
| | | Cell phone intervention + usual care | | | 36.8% |
| Fuster <i>et al.</i> 2009 [39] | NR | Counselling + BUP, VAR and/or NRT | n = 33 | 12 months (bcv) | 8/33 (25%) |
| Tornero and Mafé 2009 [76] | NR | VAR | n = 22 | 6 months (bcv) | 5/21 (24%) |
| Ingersoll <i>et al.</i> 2009 [10] | R | NRT + self-help | n = 18 | 3 months (bcv) | 9/40 (22%) |
| | | NRT + MOT | n = 22 | | Overall, ns group difference |
| Lloyd-Richardson <i>et al.</i> 2009 [40] | R | NRT + MOT | n = 232 | 6 months (bcv) | 21/232 (9%) |
| | | NRT + standard care | n = 212 | | 21/212 (10%) |
| Cui <i>et al.</i> 2012 [77] | NR | VAR | n = 36 | 3 months (bcv) | 15/36 (42%) |
| Vidrine <i>et al.</i> 2012 [61] | R | Cell phone counselling | n = 236 | 3 months (bcv) | 21/236 (8.9%) |
| | | Standard care | n = 238 | | 7/238 (2.9%) |
| Moadel <i>et al.</i> 2012 [56] | R | Group treatment | n = 73 | 3 months (bcv) | 14/73 (19.2%) |
| | | Standard care | n = 72 | | 7/72 (9.7%) |
| Humfleet <i>et al.</i> 2013 [43] | R | Counselling + NRT | n = 53 | 12 months (bcv) | 25.6% |
| | | Computer-based intervention + NRT | n = 43 | | 20.4% |
| | | Self-help + NRT | n = 73 | | 19.7% |
| Matthews <i>et al.</i> 2013 [57] | NR | Tailored group counselling + NRT | n = 21 | 3 months (bcv) | 10% (when at least three sessions completed) |

Adapted from Niaura *et al.* [66].

bcv, biochemical verification; BUP, bupropion; sr, self-report; MOT, motivational intervention; NR, nonrandomized; NRT, nicotine replacement therapy; R, randomized; VAR, varenicline.

ABC and MI risk persists in D:A:D despite change in ABC use

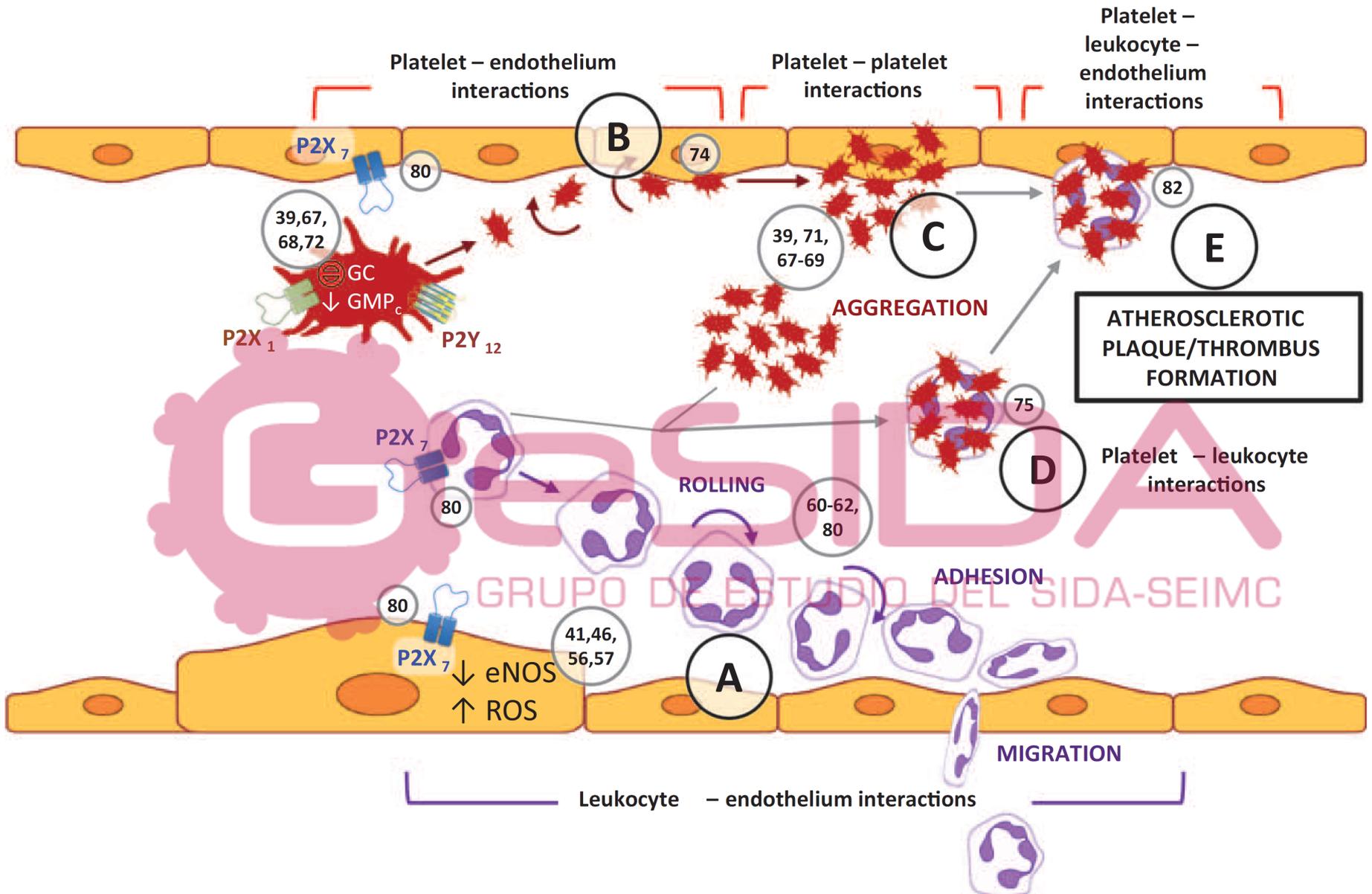
- Analysis of MI risk with ABC pre and post 3/08 in D:A:D cohort
- There were trends to less ABC use in high risk individuals post 3/08
- RR with ABC 1.98 (1.72-2.29), Pre 3/08 1.97, Post 3/08 1.97



ABC exposure and risk of CV events



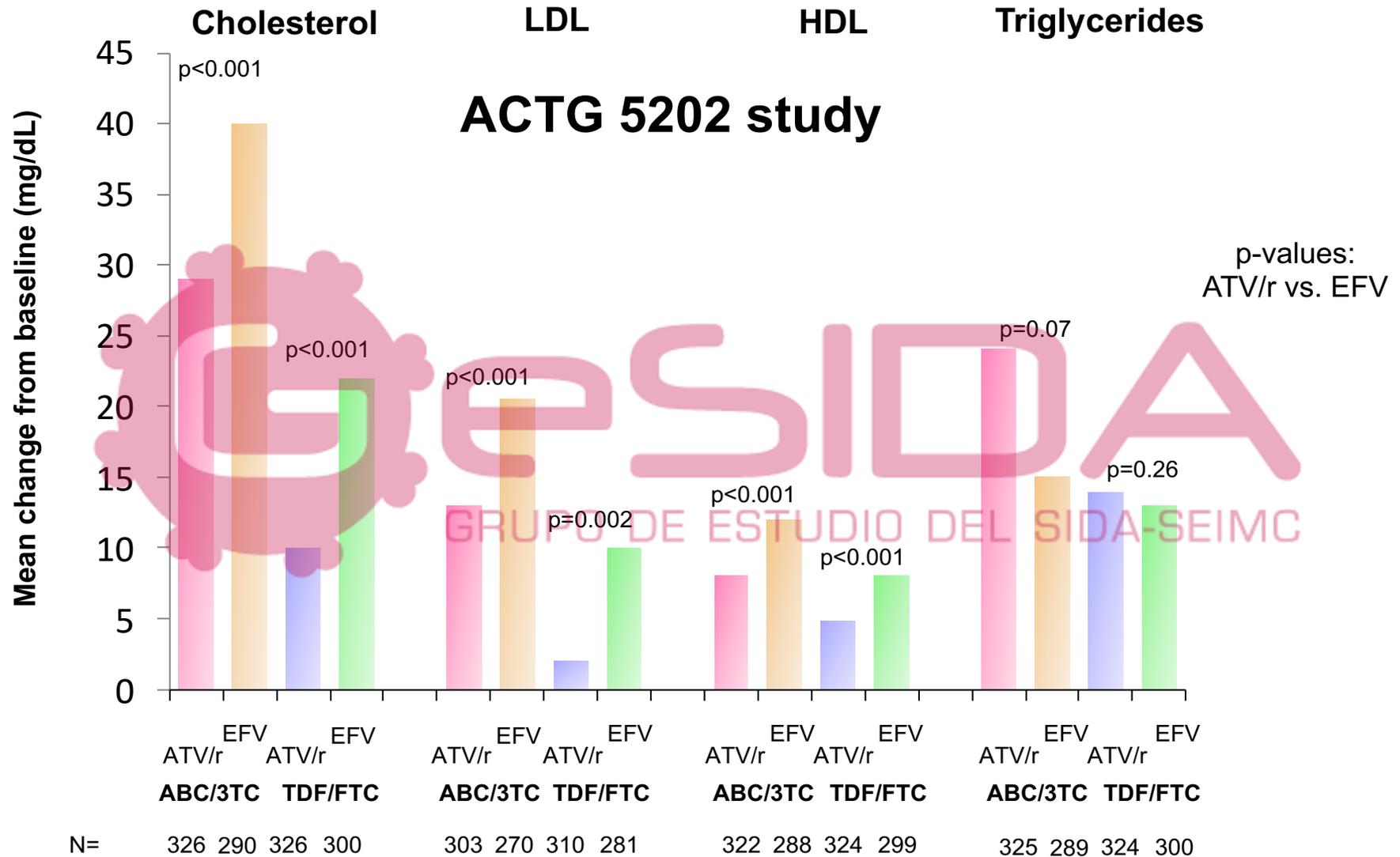
Abacavir and myocardial infarction: Pathogenesis



Approximately one third of the PI-related excess risk for MI in D:A:D is due to DM, HT, or lipids

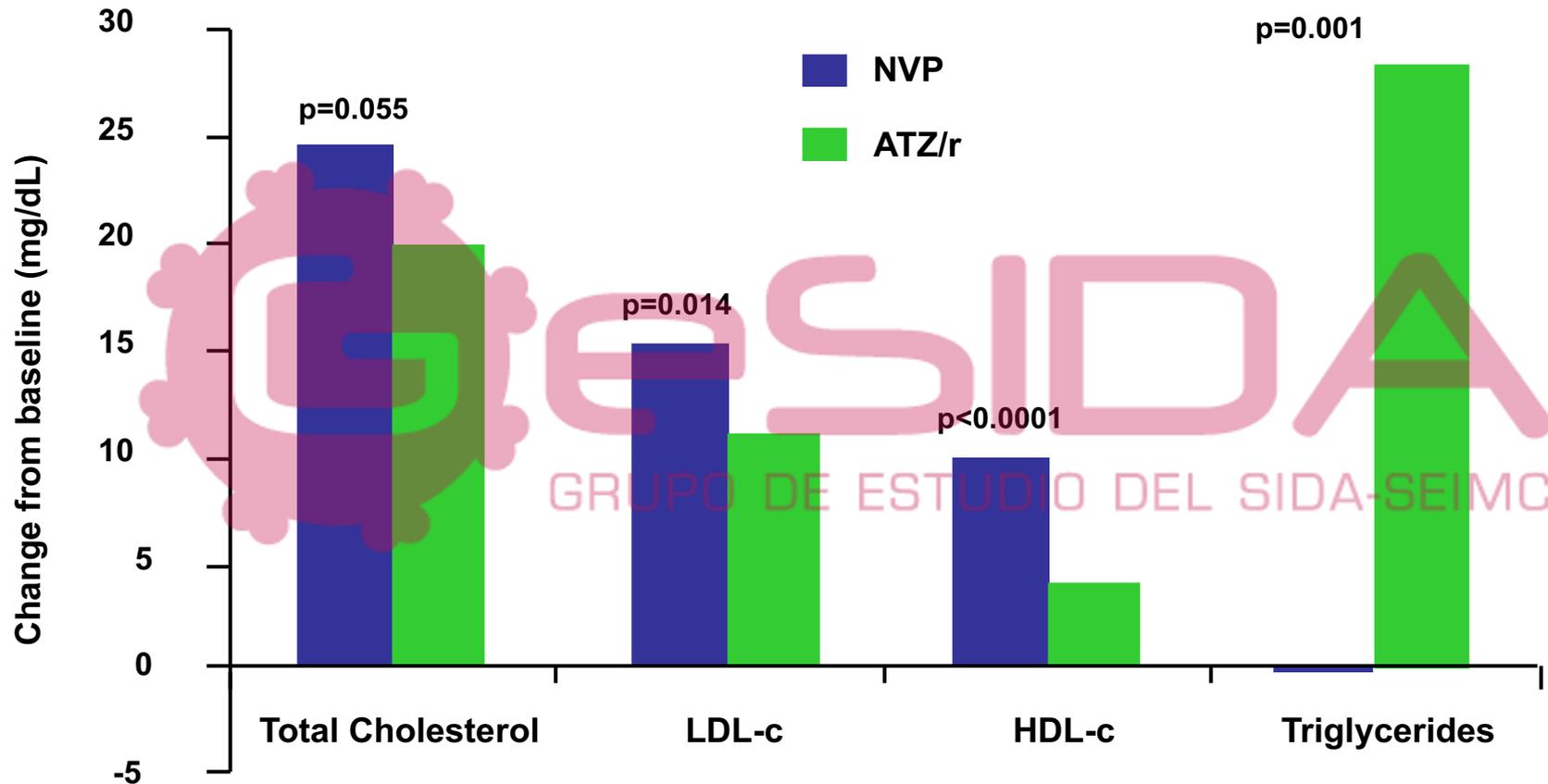
| | Adjusted Model 1 | | Adjusted Model 2 | |
|--|---------------------------|------------------|---------------------------|------------------|
| | Relative Rate (95% CI) | P Value | Relative Rate (95% CI) | P Value |
| Exposure to PIs (per year) | 1.16 (1.10-1.23) | <0.001 | 1.10 (1.04-1.18) | 0.002 |
| Age (per 5 yr) | 1.39 (1.31-1.46) | <0.001 | 1.32 (1.23-1.41) | <0.001 |
| Male sex | 1.91 (1.28-2.86) | 0.002 | 2.13 (1.29-3.52) | 0.003 |
| BMI >30 kg/m ² | 1.70 (1.08-2.69) | 0.02 | 1.34 (0.77-2.34) | 0.31 |
| Family history of CHD | 1.56 (1.10-2.23) | 0.01 | 1.40 (0.96-2.05) | 0.08 |
| Smoking status | | | | |
| Current | 2.83 (2.04-3.93) | <0.001 | 2.92 (2.04-4.18) | <0.001 |
| Former | 1.65 (1.12-2.42) | 0.01 | 1.63 (1.07-2.48) | 0.02 |
| Previous cardiovascular event | 4.30 (3.06-6.03) | <0.001 | 4.64 (3.22-6.69) | <0.001 |
| Diabetes mellitus | - | - | 1.86 (1.31-2.65) | <0.001 |
| Hypertension | - | - | 1.30 (0.99-1.72) | 0.06 |
| Total cholesterol (per mmol/L increase) | - | - | 1.26 (1.19-1.35) | <0.001 |
| HDL cholesterol (per mmol/L increase) | - | - | 0.72 (0.52-0.99) | 0.05 |

The distinctive lipid effect of ATV/r is an increase in triglycerides, but not cholesterol



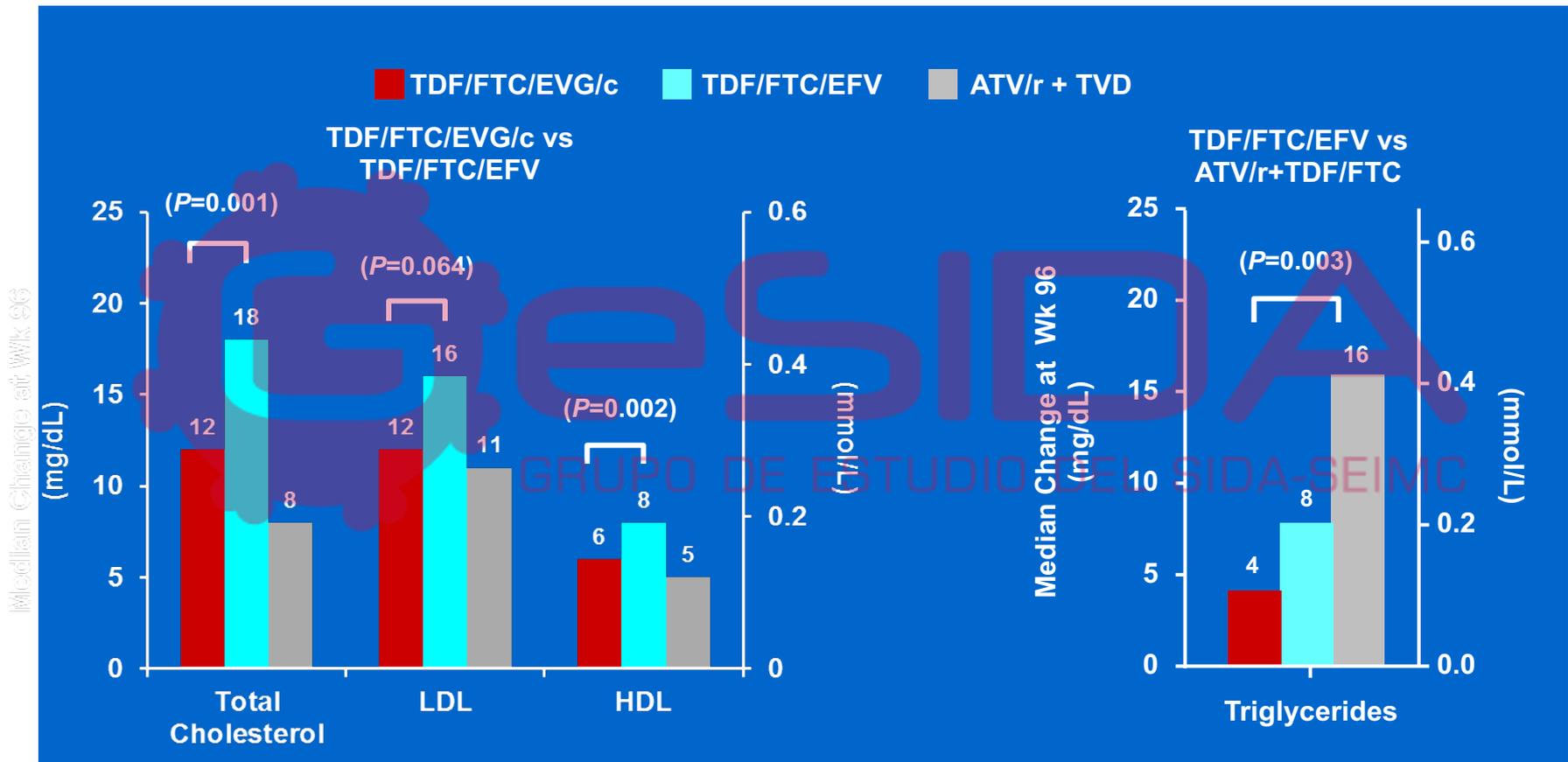
The distinctive lipid effect of ATV/r is an increase in triglycerides, but not cholesterol

ARTEN study

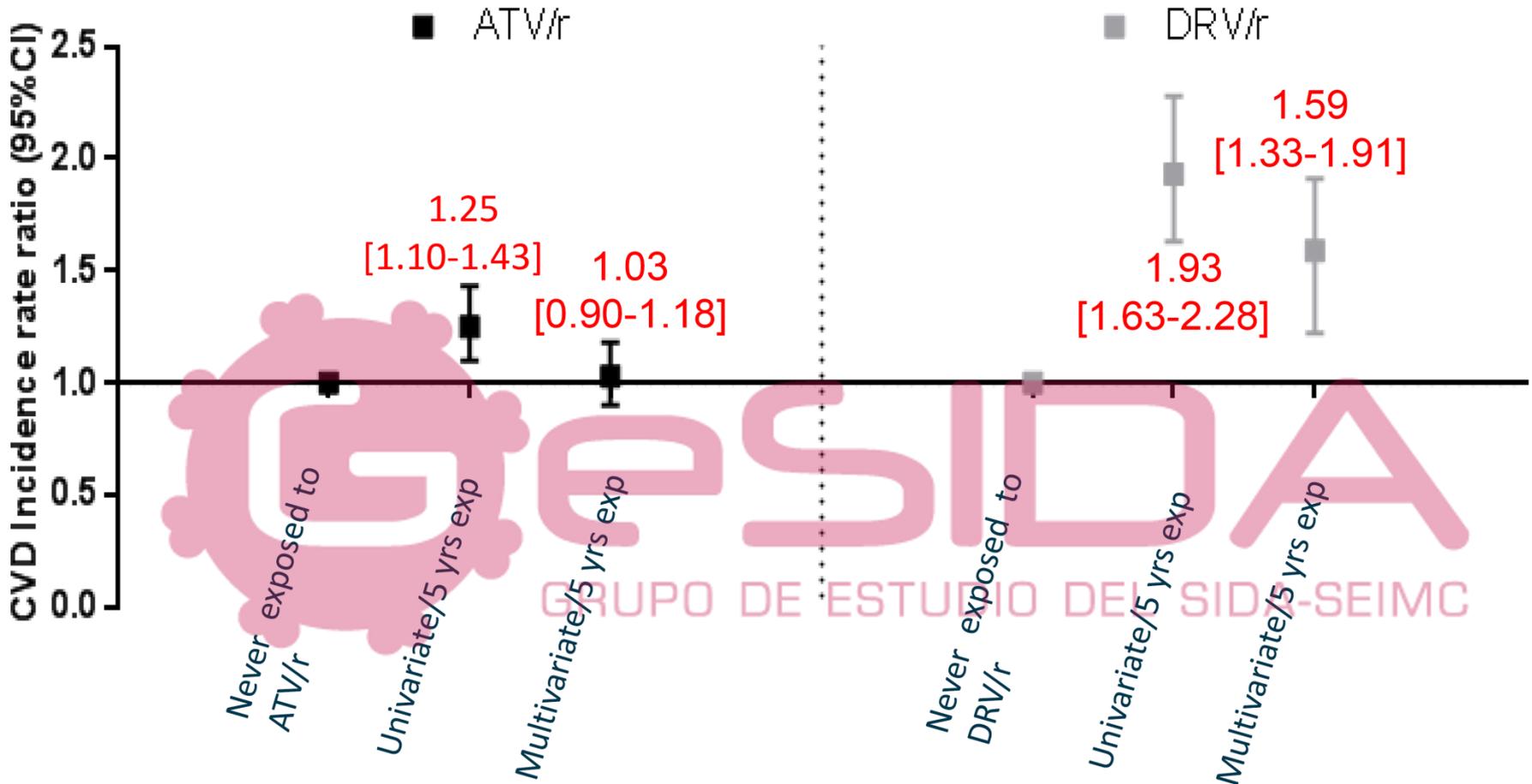


The distinctive lipid effect of ATV/r is an increase in triglycerides, but not cholesterol

Studies 102 and 103



Association between CVD and cumulative ATV/r or DRV/r use



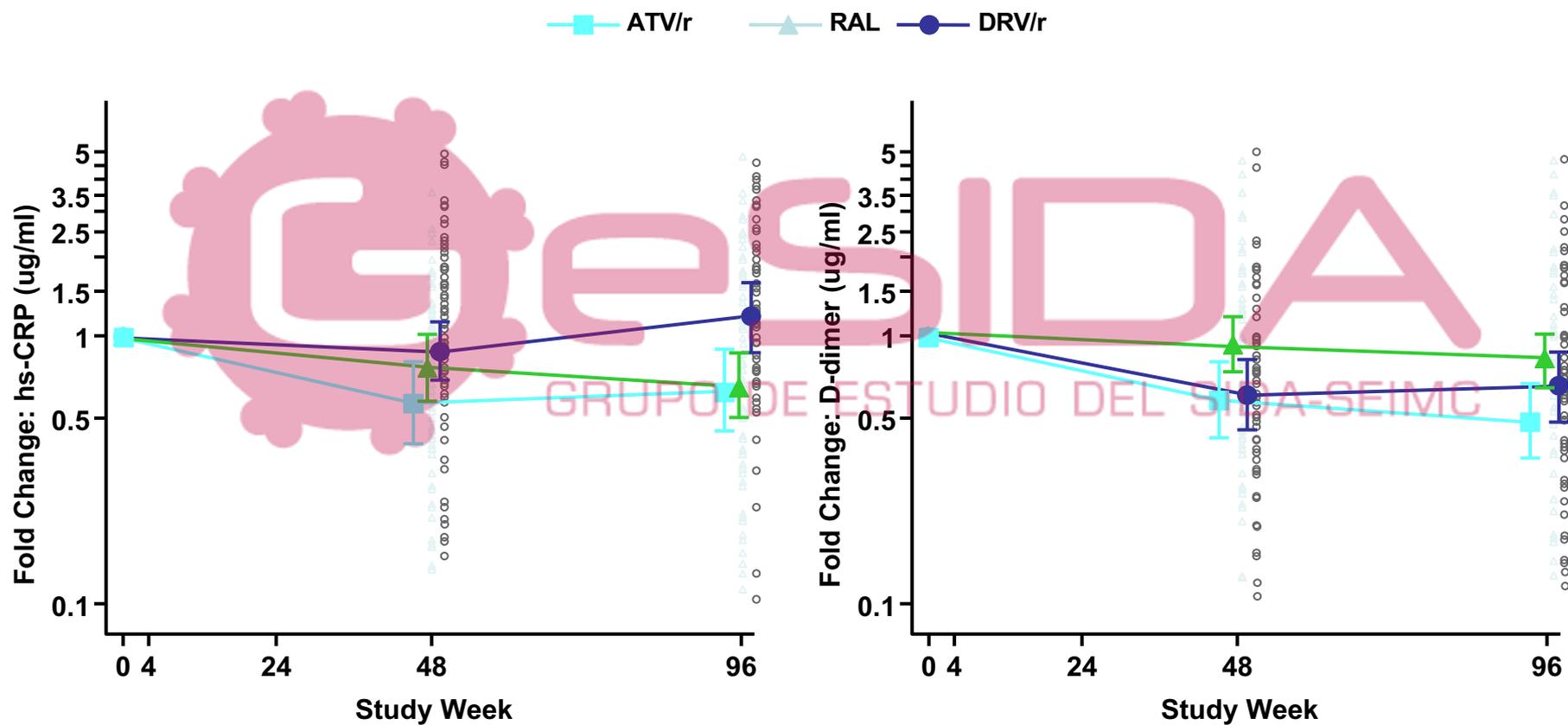
Multivariate models were adjusted for gender, age, race, HIV risk of acquisition, enrollment cohort, baseline date, prior CVD, CD4 nadir, CD4, BMI, diabetes, dyslipidemia, eGFR (all fixed at baseline), cumulative exposure to DRV/r, ATV/r, LPV/r and IDV, recent exposure ABC, prior AIDS, viral load, hepatitis B & C, family history of CVD, hypertension, smoking (all time updated)

Less inflammation and hypercoagulability with ATV/r

ACTG 5257

Hs-CRP Declined with ATV/r and RAL

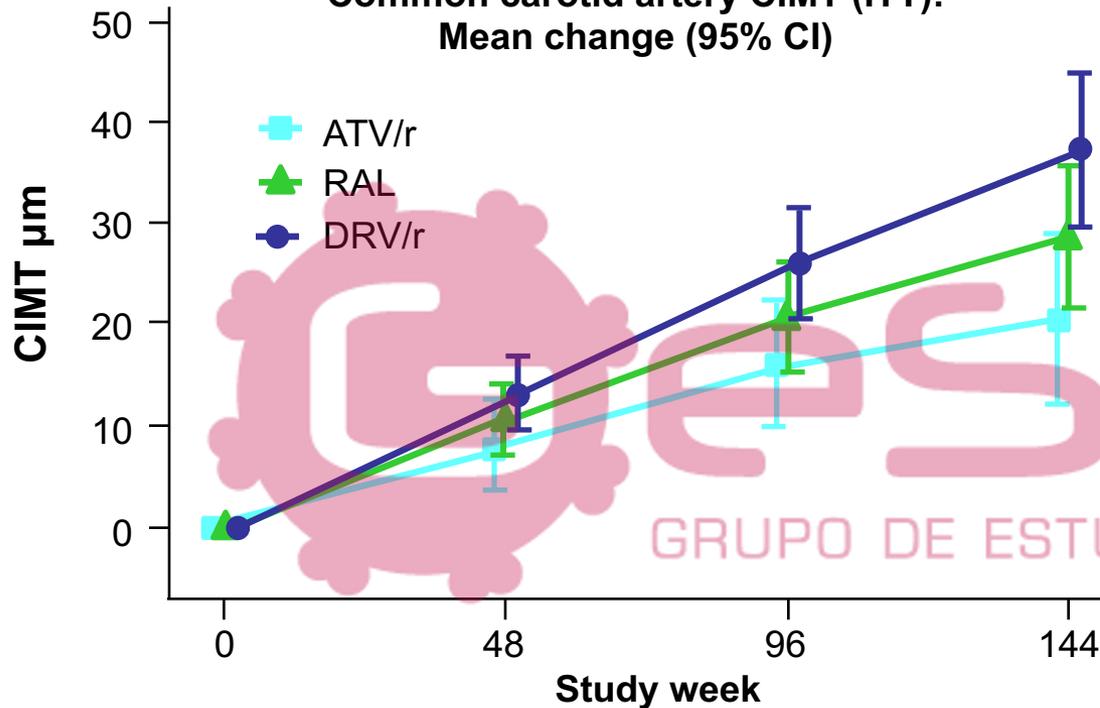
D-dimer Declined with ATV/r and DRV/r



Slower progression of cIMT with ATV/r vs. DRV/r

ACTG 5260s

Common carotid artery CIMT (ITT):
Mean change (95% CI)



- ATV/r progressed more slowly than DRV/r (ATV/r (8.2 µm/year 95% CI [5.6–10.8]) vs DRV/r (12.9 µm/year [10.3–15.5])); $p=0.013$)

- Intermediate progression for RAL (10.7 µm/year [9.2–12.2] ($p=0.15$ vs ATV/r; $p=0.31$ vs DRV/r))

*CIMT is used as a measure of atherosclerotic cardiovascular disease
CIMT: Carotid intima-media thickness

Switching studies showing evidence for improvement in plasma lipids

- **PI switch:**

PI \Rightarrow ABC (CNA30017)

PI \Rightarrow NVP, EFV, o ABC (NEFA)

PI / Plr \Rightarrow ATV (SWAN)

LPV/r \Rightarrow ATVr (ATAZIP)

LPV/r or FPV//r \Rightarrow ATVr or DRV/r (LARD)

ATV/r \Rightarrow ATV (ARIES)

LPV/r \Rightarrow RAL (SWITCHMRK)

PI/r \Rightarrow RAL (SPIRAL)

PI/r-based \Rightarrow RPV/TDF/FTC (SPIRIT)

PI/r-based \Rightarrow c/EVG/TDF/FTC (STRATEGY-PI)

- **EFV switch:**

EFV \Rightarrow NVP (SIROCCO)

EFV \Rightarrow ETV (SWITCH-EE)

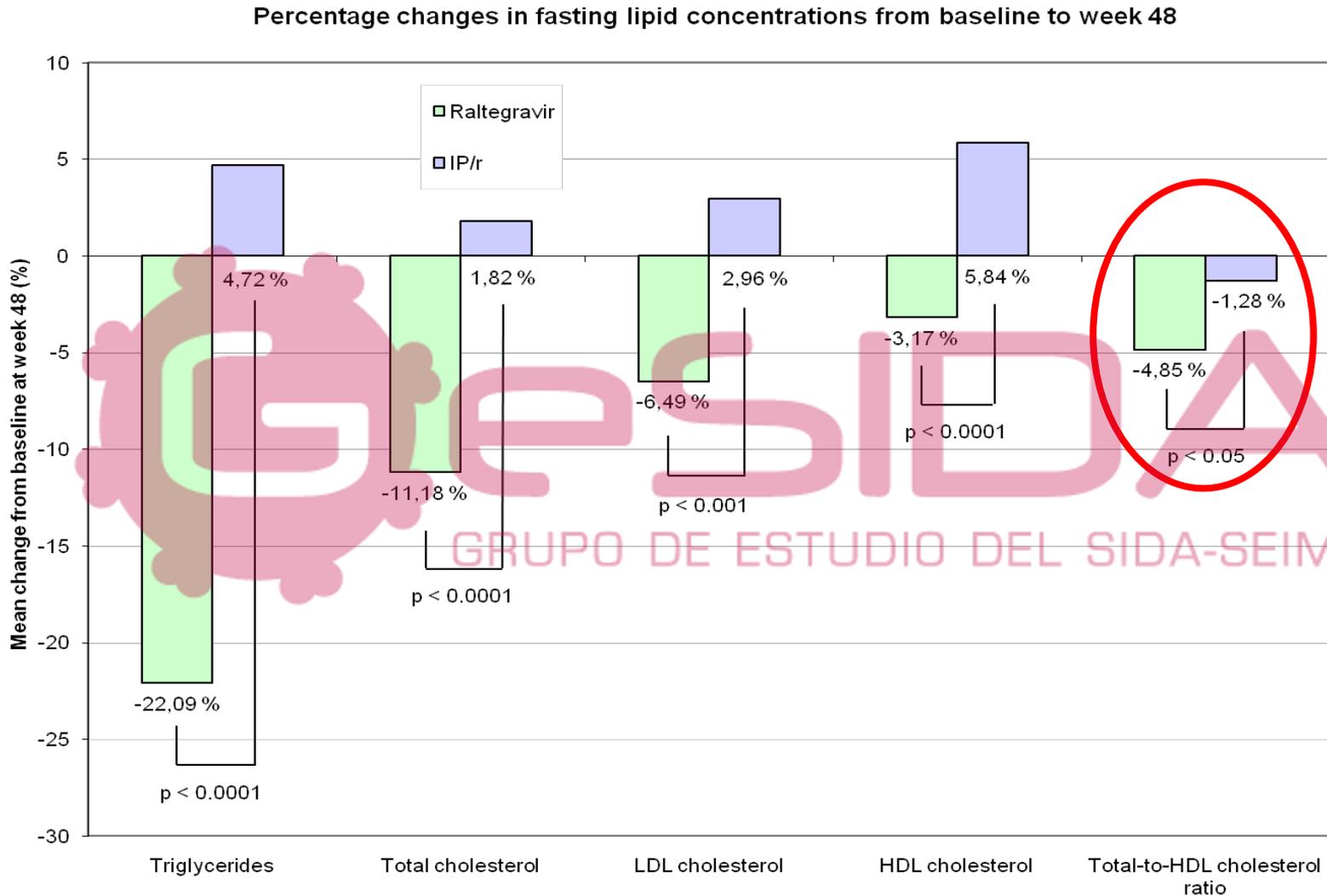
- **AZT or ABC switch:**

AZT/3TC \Rightarrow TDF/FTC (SWEET)

ABC/3TC \Rightarrow TDF/FTC (ROCKET)

**Most studies did not require hyperlipidemia among inclusion criteria
Lipids decrease limited and may not translate into CV risk decrease**

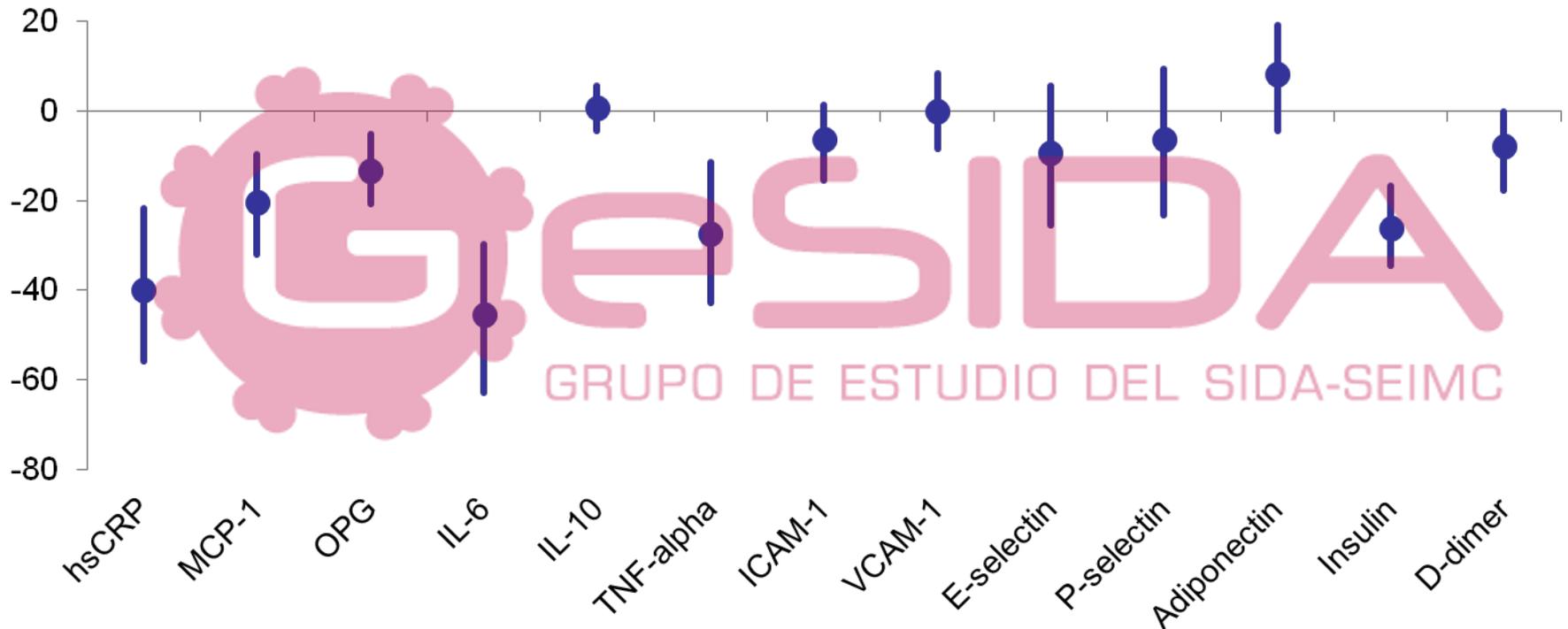
RAL arm in SPIRAL led to ↓total-to-HDL cholesterol ratio



Switching from PI/r to RAL decreased CV biomarkers

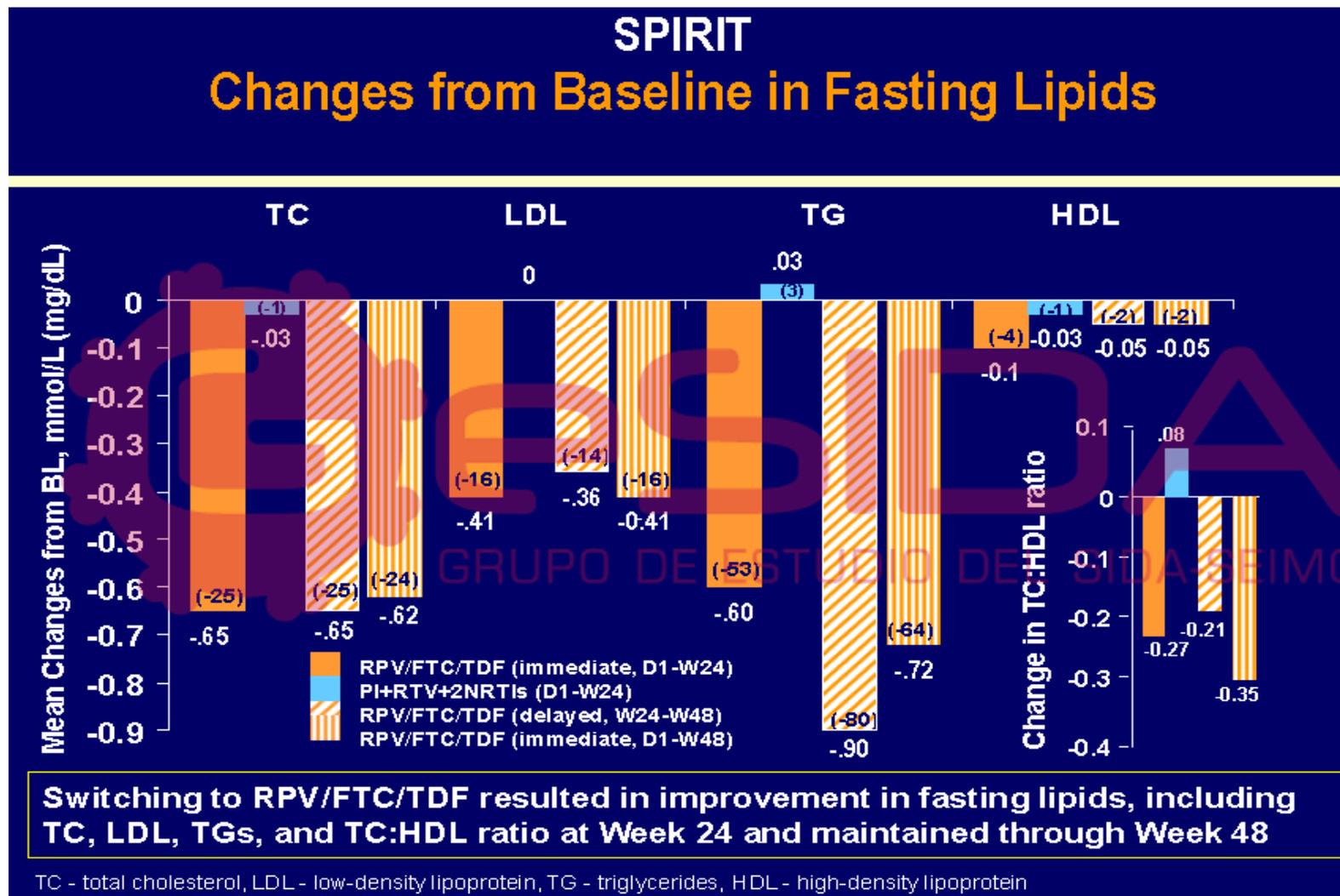
SPIRAL Biomarkers Sub-study

Median difference of percent change RAL minus PI/r (95% CI)



- **Generally modest or no significant correlation between changes in biomarkers and changes in lipids**

Switch to RPV/TDF/FTC in SPIRIT led to ↓total-to-HDL cholesterol ratio



Switch to EVG/cobi/TDF/FTC in STRATEGI-PI did not lead to lower lipids

Change From Baseline in Fasting Lipids at Week 48

STRATEGY-PI: Darunavir Subgroup

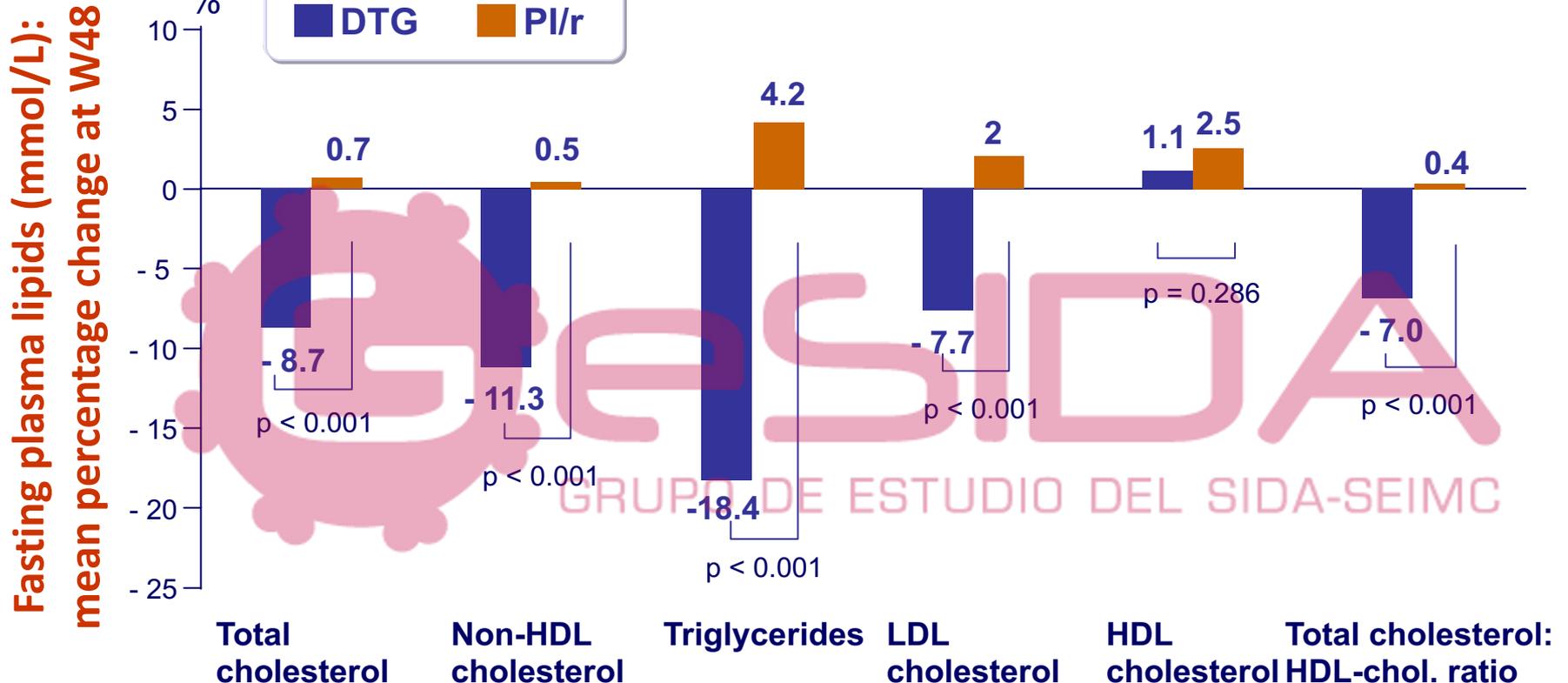
| | Total-c | LDL-c | Triglycerides | HDL-c |
|---|----------------|----------------|---------------|-------------|
| Baseline: median, Q1, Q3 (mg/dL) | | | | |
| E/C/F/TDF (n=107) | 182 (160, 206) | 115 (96, 139) | 111 (89, 157) | 48 (42, 56) |
| Darunavir (n=58) | 193 (169, 219) | 128 (105, 152) | 112 (79, 180) | 51 (43, 57) |
| Change at Week 48: median, Q1, Q3 (mg/dL) | | | | |
| E/C/F/TDF (n=105) | 0 (-13, 16) | 0 (-13, 15) | -11 (-35, 16) | 3 (-2, 9) |
| Darunavir (n=53) | 0 (-20, 13) | 0 (-14, 13) | -5 (-31, 26) | 0 (-5, 5) |
| P value † | 0.43 | 0.56 | 0.32 | 0.03 |

†Comparison between treatment group using the Wilcoxon Rank Sum test.

Changes from baseline in total cholesterol/HDL ratios were not statistically significant.

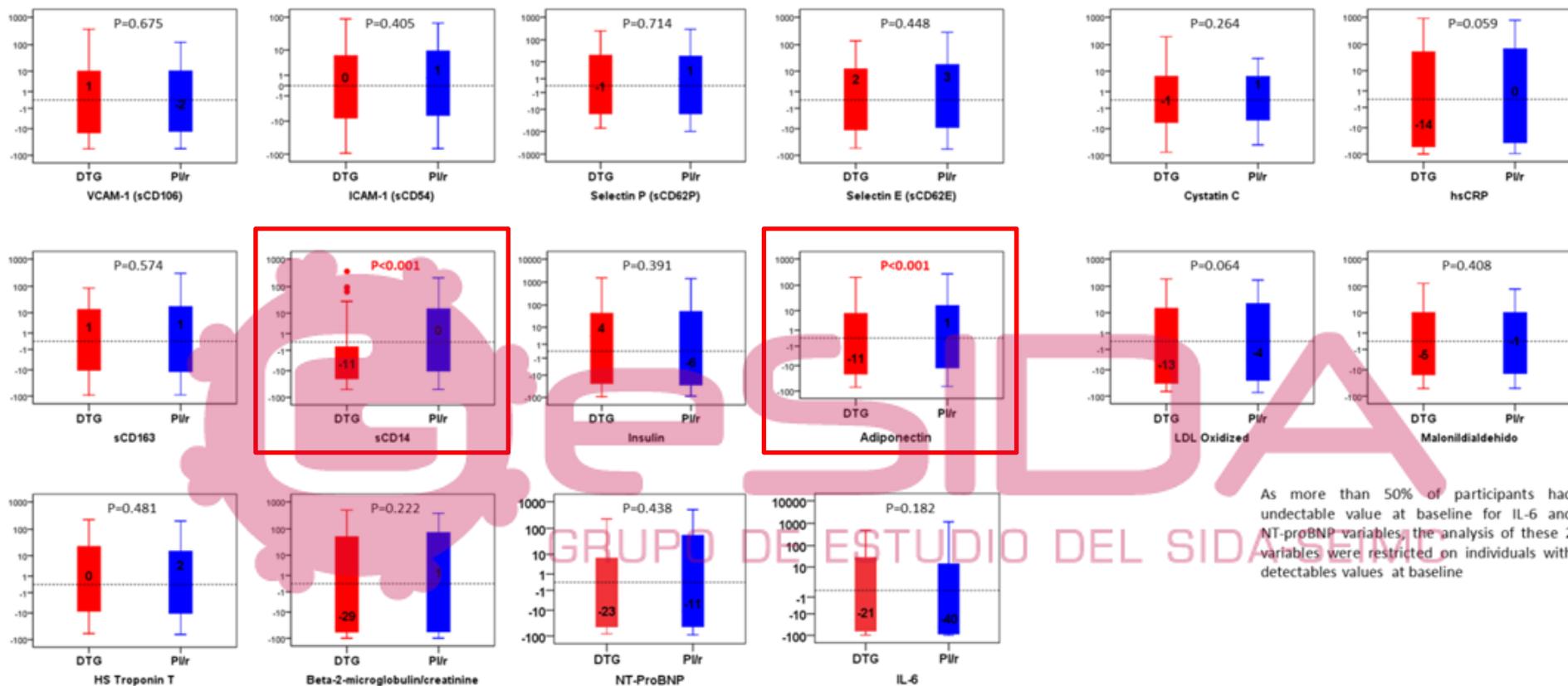
Switch to DTG in NEAT022 led to ↓total-to-HDL cholesterol ratio

Switch to DTG vs continuation of PI/r in patients with high CV risk



- No changes in the utilization of lipid lowering agents (around 30% in each arm, both at baseline and W48)

Switch to DTG in NEAT022 decreased sCD14 but also adiponectin



As more than 50% of participants had undetectable value at baseline for IL-6 and NT-proBNP variables, the analysis of these 2 variables were restricted on individuals with detectable values at baseline

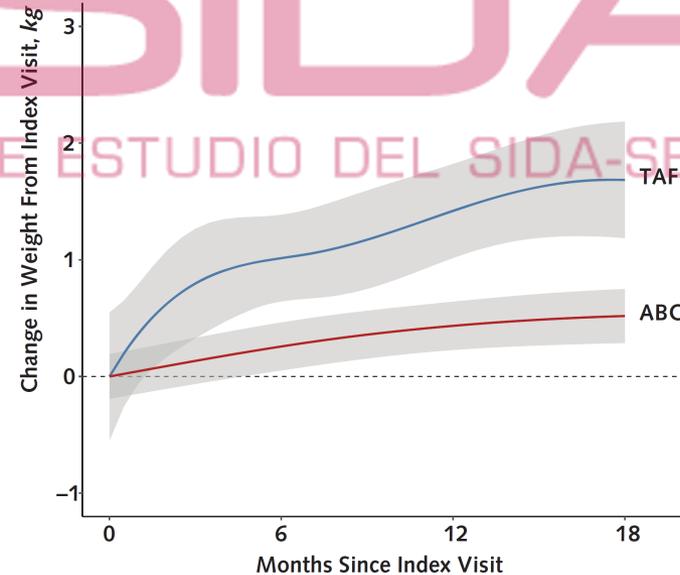
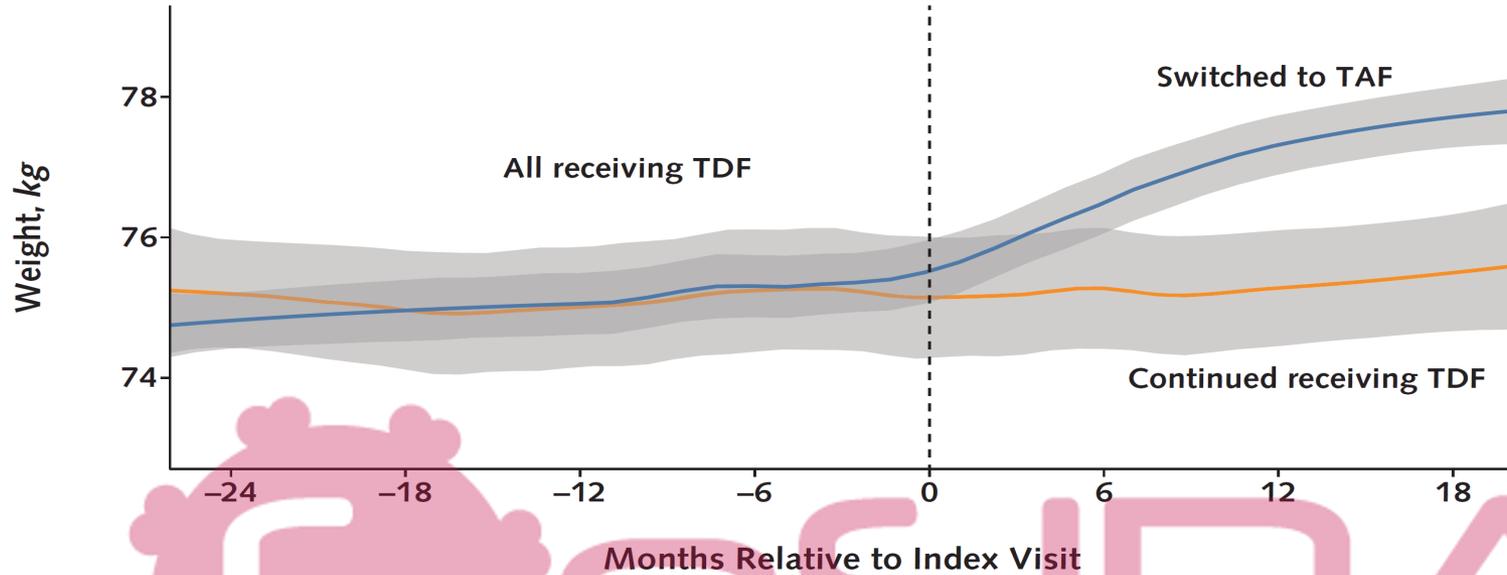
The significance threshold is set at 0.01 to allow for the multiplicity of tests

*P-values are calculated using GEE models

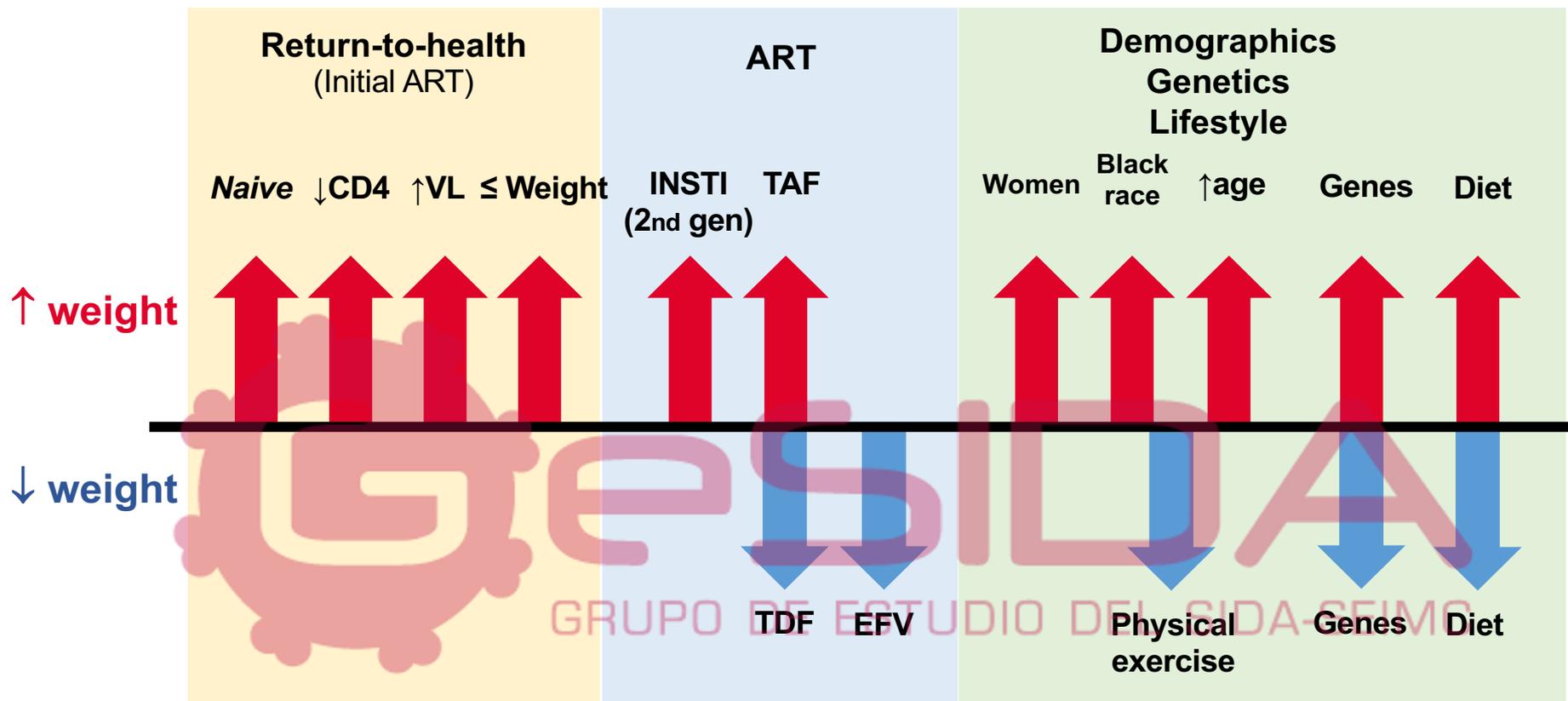


neatid | The European treatment network for HIV, hepatitis and global infectious diseases

Switch to TAF increases weight, while maintaining TDF preserves weight gain

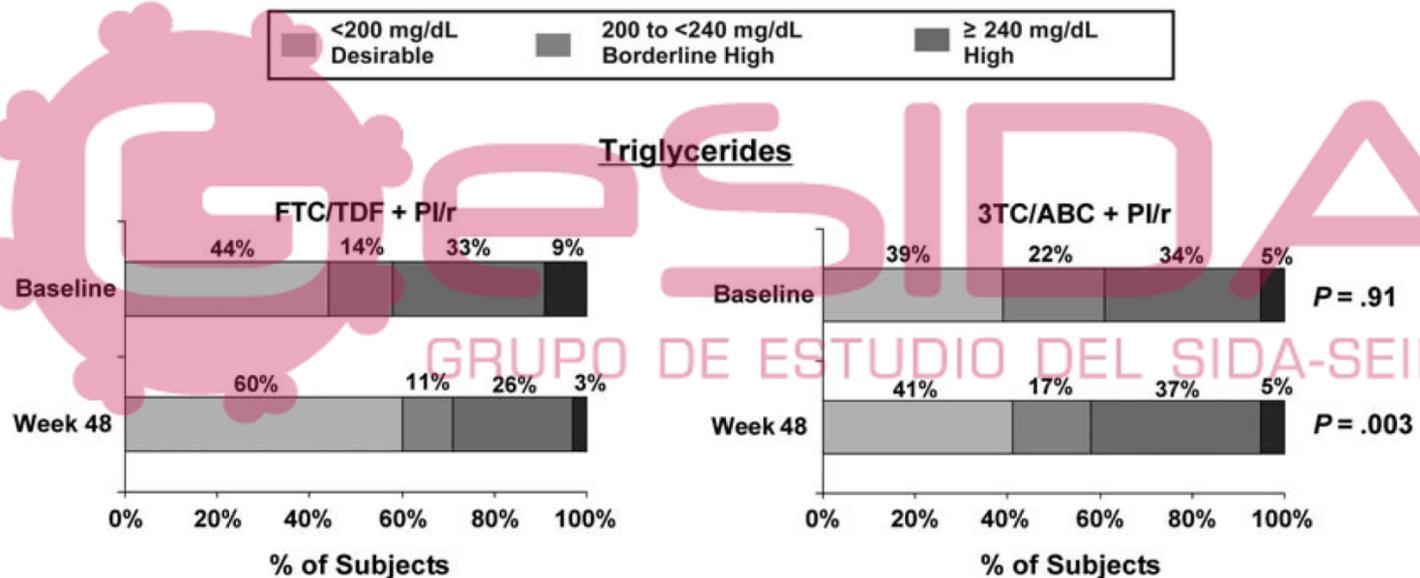
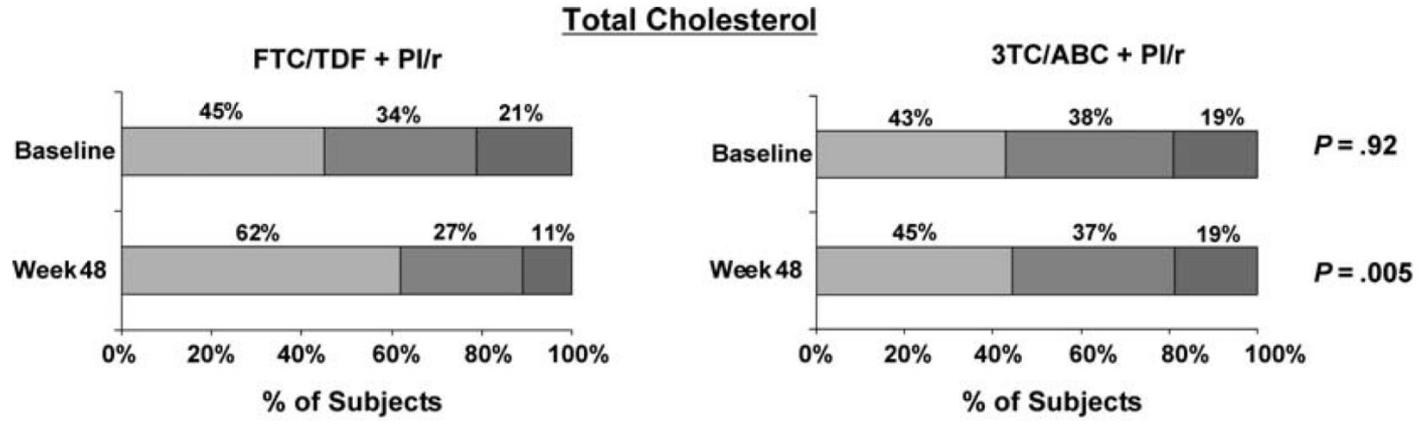


Factors associated with weight change in PLWH



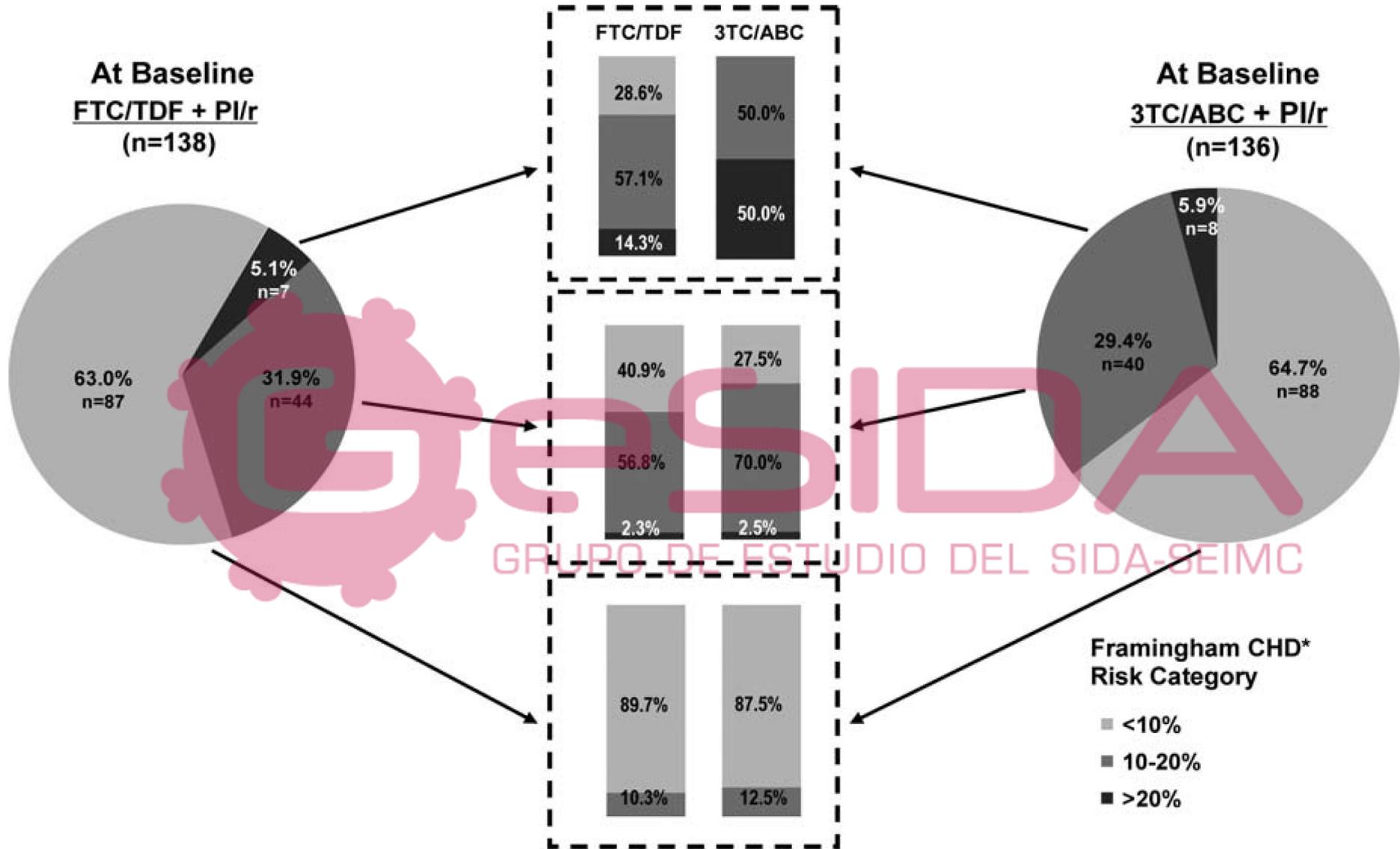
Adapted from: Bourgi. CROI 2019 # 670; Bakal DR, et al. JAC 2018;73:2177-2185; Menard A, et al. AIDS 2017;31:1499-1500; Kerchberger AM, et al. CROI 2019 #672; Norwood J et al. JAIDS 2017;5:527-31; Pallela F, et al. CROI 2019. Seattle, WA # 674; Gomez M, et al. Infection 2019;47:95-102; Schafer JJ, et al. Open Forum Infect Dis 2019 Oct 4;6(10); Burns JE, et al. AIDS 2019; McComsey GA, et al. CROI 2019 #671; Taramasso L, et al. Open Forum Infect Dis 2017;4:ofx239; Mounzer K, et al. IDWeek 2019 #978; Caniglia E, et al. IAS 2019 # MOPEB241; Hsu et al. EACS 2019 # PE2/32; Mallon P. AIDS 2020, OAB0604; Orkin C, et al. EACS 2019 #PS3/2; Sax P, et al. Clin Infect Dis 2020;71(6):1380-9; Cahn P. Lancet 2019;393:143-55; Venter W, et al. NEJM 2019;381:803-815

Switching from ABC to TDF decreased plasma lipids



No difference in LDL, HDL, TC:HDL ratio

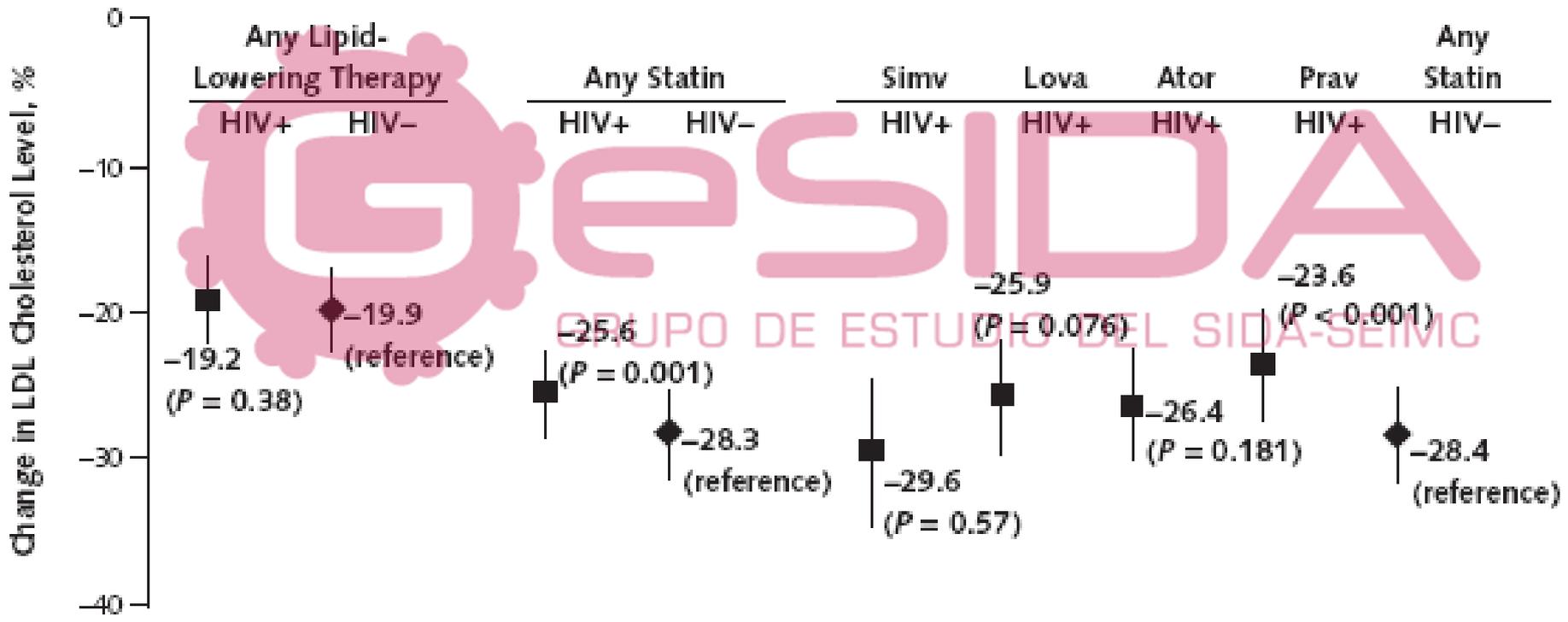
Switching from ABC to TDF decreased plasma lipids



How well do statins work to lower LDL-cholesterol in HIV+ patients?

Actually Quite Good!

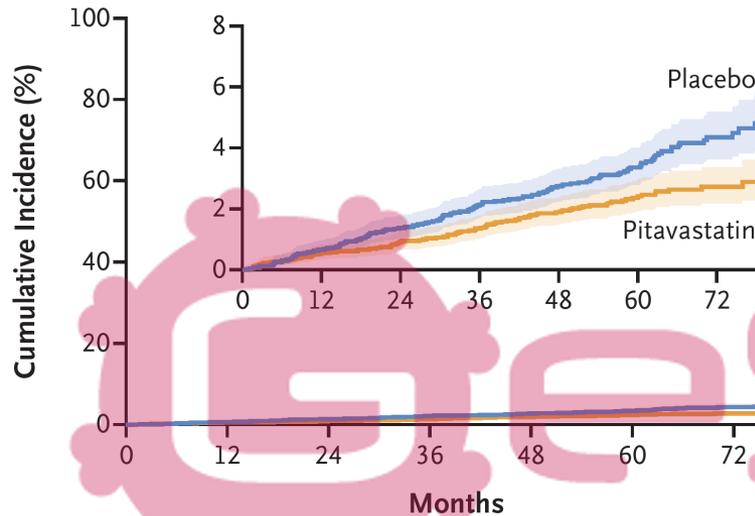
■ HIV-infected
◆ HIV-uninfected



Pitavastatin decreased major adverse CV events in PWH with a low estimated CV risk

B First MACE

HR: 0.65 (95%CI 0.48-0.90)



Cumulative Incidence of Event (%)

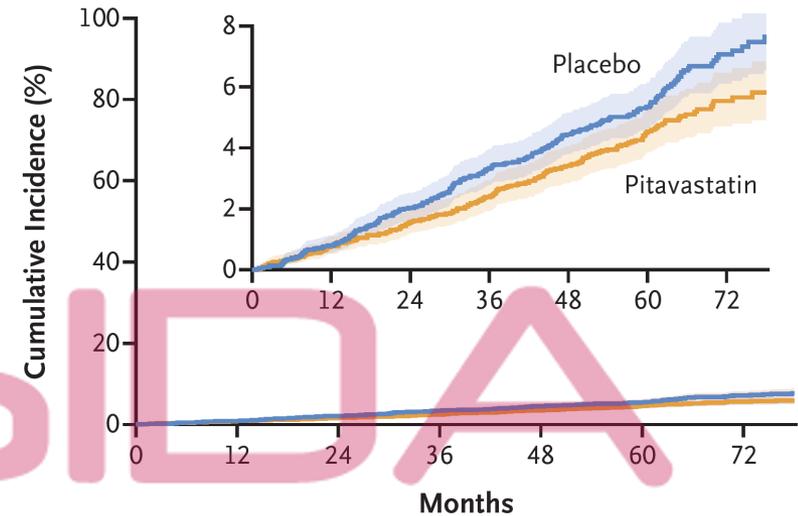
| | | | | | | | |
|--------------|------|------|------|------|------|------|------|
| Placebo | 0.00 | 0.66 | 1.38 | 2.14 | 2.74 | 3.36 | 4.36 |
| Pitavastatin | 0.00 | 0.56 | 0.95 | 1.35 | 1.89 | 2.41 | 2.73 |

No. at Risk

| | | | | | | | |
|--------------|------|------|------|------|------|------|------|
| Placebo | 3881 | 3693 | 3506 | 3356 | 2997 | 2182 | 959 |
| Pitavastatin | 3888 | 3647 | 3475 | 3364 | 2997 | 1947 | 1052 |

C First MACE or Death

HR: 0.79 (95%CI 0.65-0.96)



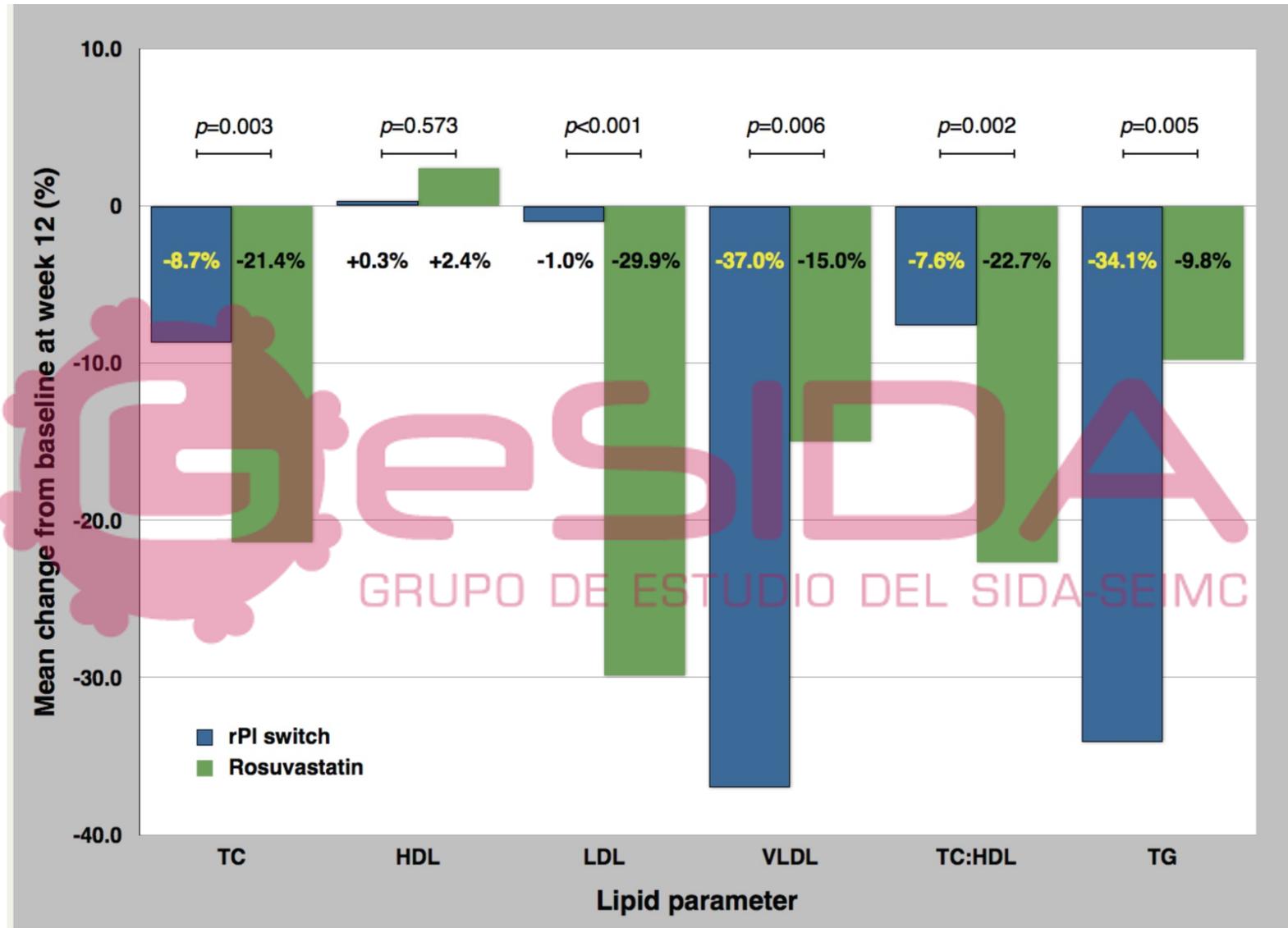
Cumulative Incidence of Event (%)

| | | | | | | | |
|--------------|------|------|------|------|------|------|------|
| Placebo | 0.00 | 0.80 | 2.03 | 3.34 | 4.44 | 5.35 | 7.06 |
| Pitavastatin | 0.00 | 0.77 | 1.58 | 2.39 | 3.40 | 4.54 | 5.54 |

No. at Risk

| | | | | | | | |
|--------------|------|------|------|------|------|------|------|
| Placebo | 3881 | 3693 | 3506 | 3356 | 2997 | 1975 | 919 |
| Pitavastatin | 3888 | 3647 | 3475 | 3364 | 2998 | 1948 | 1027 |

Larger decrease in cholesterol fractions with statin as compared with PI/r switch



Decisions made

Smoker 10 cigarettes per day

No illicit drugs

Blood pressure 140/80 mmHg

No hypertension, no diabetes

BMI 25 kg/m²

Total cholesterol 240 mg/dL

HDL cholesterol 40 mg/dL

LDL cholesterol 180 mg/dL

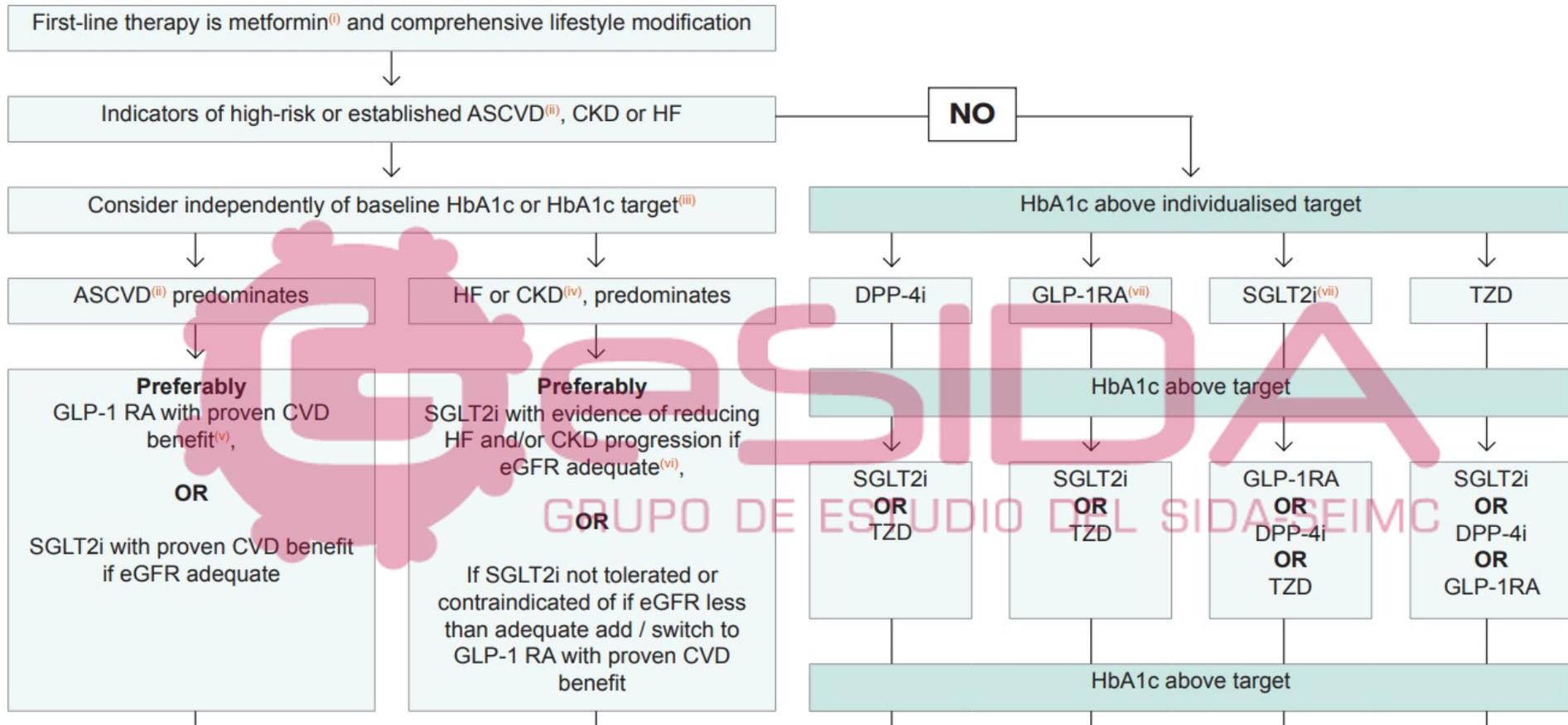
MDRD GFR 70 mL/min/1.73m²

No proteinuria

- Smoking cessation considered
- Healthy lifestyle (food, exercise)
- Boosted darunavir discontinued
- ABC/3TC discontinued
- Integrase inhibitor (monitor weight) considered
- TDF (monitor kidney) or TAF (monitor weight) considered
- Atorvastatin 20 mg initiated

If the patient has diabetes, how to treat?

Type 2 Diabetes: Management



Profiles of antidiabetic medications

| | MET | glutidas GLP-1 RA | glifozinas SGLT-2i | gliptinas DPP-4i | acarbosa AGi | TZD (moderate dose) | SU GLN | COLSVL | BCR-QR | INSULIN | PRAML |
|-------------------------|--|--|--|---|-----------------|--|--------------------------------------|--------------------|-----------------|-----------------------|----------|
| HYPO | Neutral | Neutral | Neutral | Neutral | Neutral | Neutral | Moderate/ Severe Mild | Neutral | Neutral | Moderate to Severe | Neutral |
| WEIGHT | Slight Loss | Loss | Loss | Neutral | Neutral | Gain | Gain | Neutral | Neutral | Gain | Loss |
| RENAL / GU | Contra- indicated if eGFR < 30 mL/min/ 1.73 m ² | Exenatide Not Indicated CrCl < 30 | Not Indicated for eGFR < 45 mL/ min/1.73 m ² Genital Mycotic Infections | Dose Adjustment Necessary (Except Linagliptin) Effective in Reducing Albuminuria | Neutral | Neutral | More Hypo Risk | Neutral | Neutral | More Hypo Risk | Neutral |
| GI Sx | Moderate | Moderate | Neutral | Neutral | Moderate | Neutral | Neutral | Mild | Moderate | Neutral | Moderate |
| CHF CARDIAC ASCVD | Neutral | See #1 | See #2 | See #3 | Neutral | Moderate May Reduce Stroke Risk | Neutral Possible ASCVD Risk | Neutral Benefit | Neutral Safe | CHF Risk Neutral | Neutral |
| BONE | Neutral | Neutral | Mild Fracture Risk | Neutral | Neutral | Moderate Fracture Risk | Neutral | Neutral | Neutral | Neutral | Neutral |
| KETOACIDOSIS | Neutral | Neutral | DKA Can Occur in Various Stress Settings | Neutral | Neutral | Neutral | Neutral | Neutral | Neutral | Neutral | Neutral |

■ Few adverse events or possible benefits
 ■ Likelihood of adverse effects
 ■ Use with caution

1. Liraglutide—FDA approved for prevention of MACE events.
2. Empagliflozin—FDA approved to reduce CV mortality. Canagliflozin shown to reduce MACE events.
3. Possible increased hospitalizations for heart failure with alogliptin and saxagliptin.