# Inflammation: a new target in cardiology?

*Implications of the CANTOS trial*

**WCN**

*24 nov 2017*

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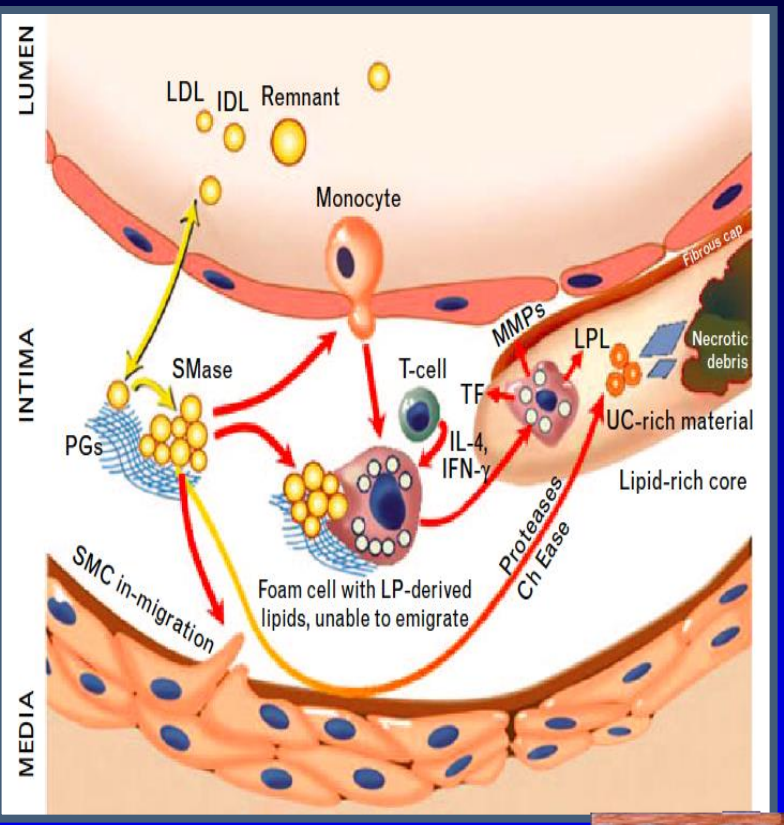
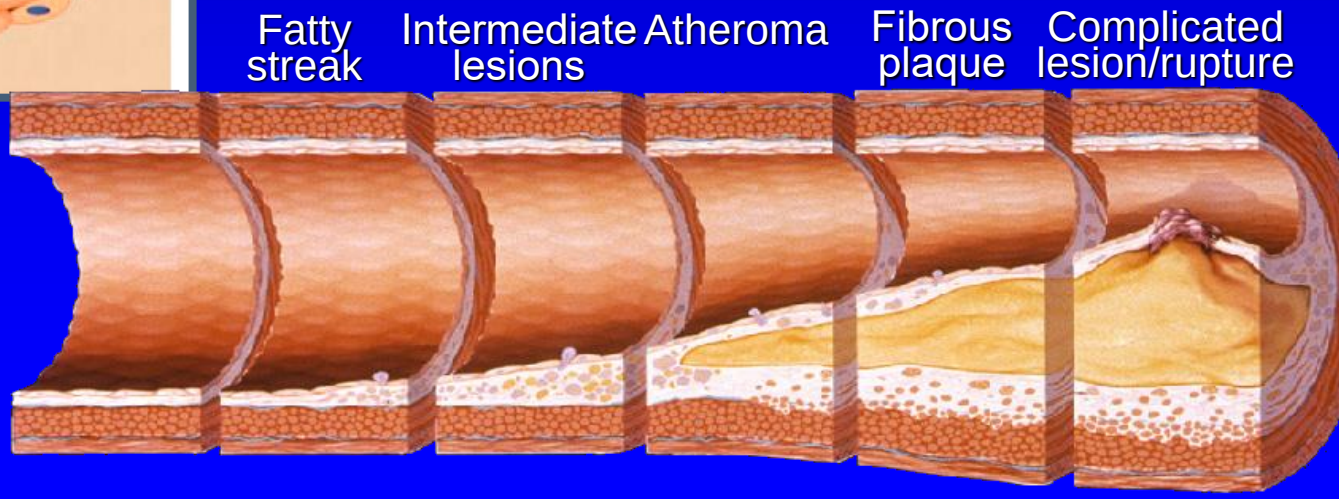
Vasculaire geneeskunde
AMC

# Cardiovascular disease caused by atherogenesis

## *LDLc accumulation in lipid-rich core*

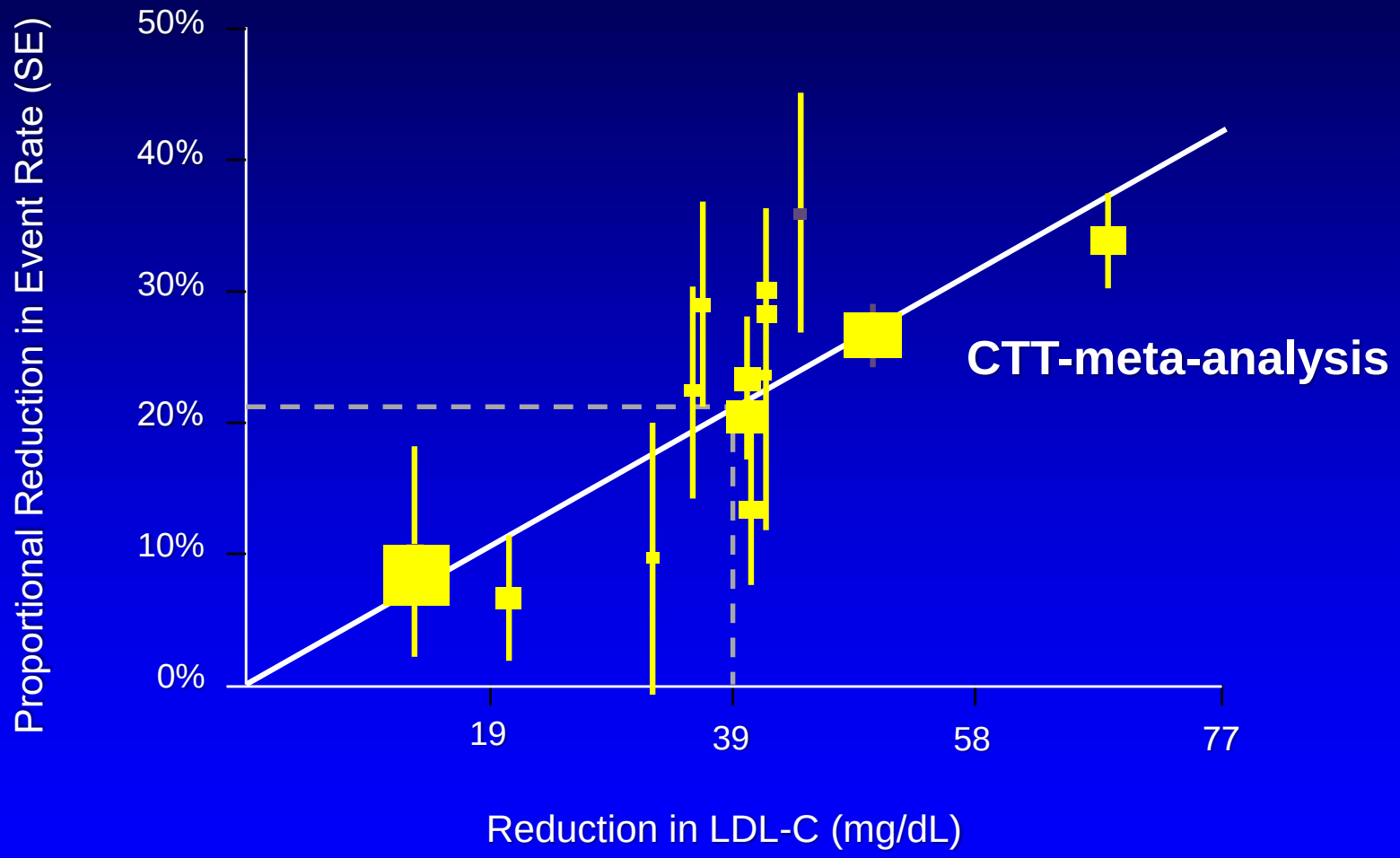



Boren J. Curr Opin Lipidol 2016
Koenig W, ATvB 2007

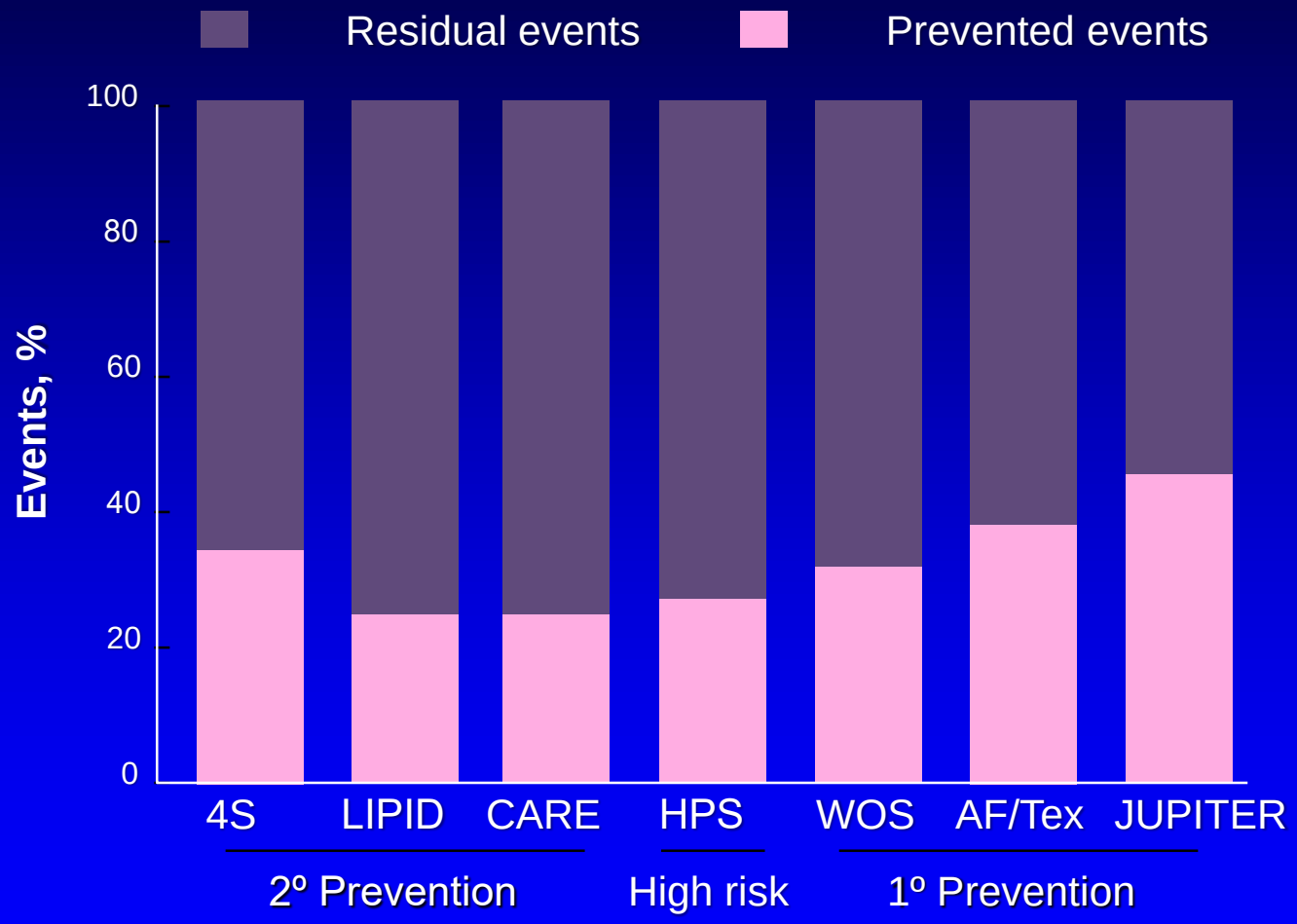
# Lowering of LDL-C reduces CV event rates

***The lower, the better***



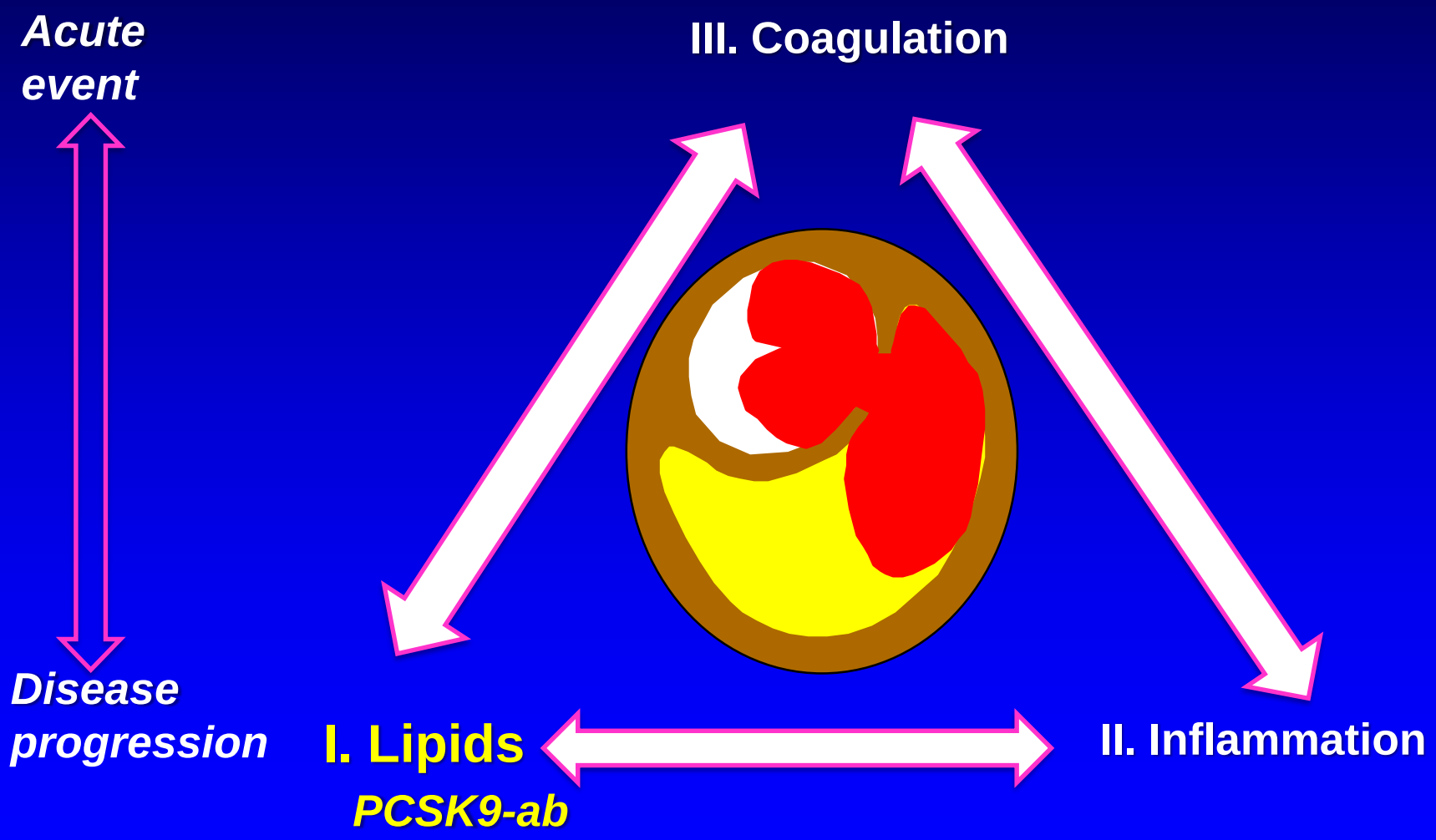

CTTC. Lancet 2005;366:1267–1278. CTTC. Lancet 2010;376:1670–1681.
Cannon et al. N Engl J Med 2015;372:2387 – 2397.

# However, majority of events *NOT* prevented by LDL-c lowering alone

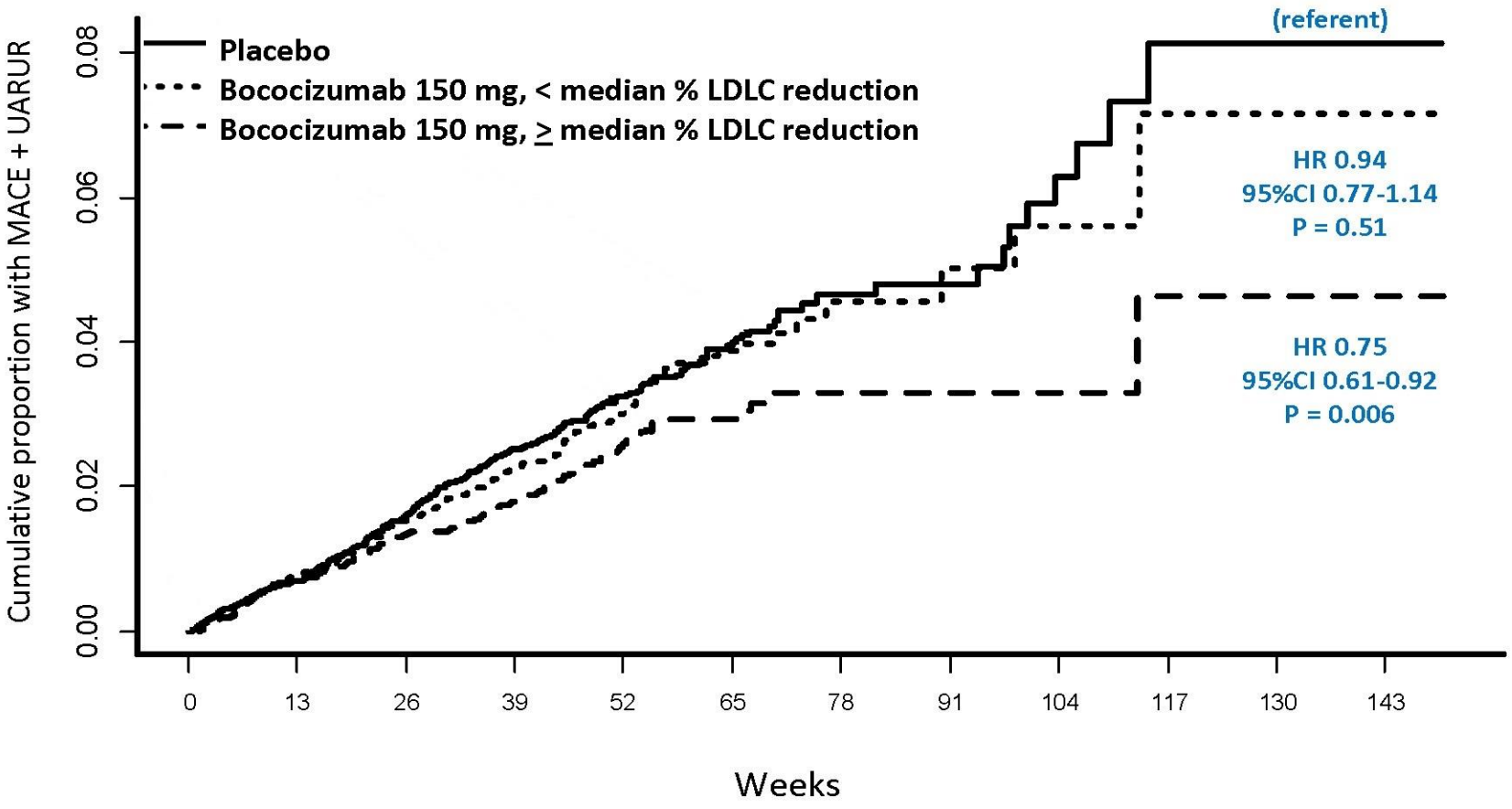



Circulation 1999;99:736–743. Lancet 1995;345:1274–1275. N Engl J Med 1998;339:1349–1357.
J Am Coll Cardiol 1999;33:125–130. N Engl J Med 1995;333:1301–1307.
JAMA 1998;279:1615–1622. Lancet 2010;376:333–339.

# Lowering residual cardiovascular risk
## *on top of statin therapy*



# 1 The SPIRE 1 and SPIRE 2 Cardiovascular Outcomes Trials: Combined Trials Primary Endpoint*, Stratified By Magnitude of LDLC Reduction (%)




*Nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death

Ridker ACC 2017

# 2. Identification of high-risk patients
## *based on High-Risk MI Features*

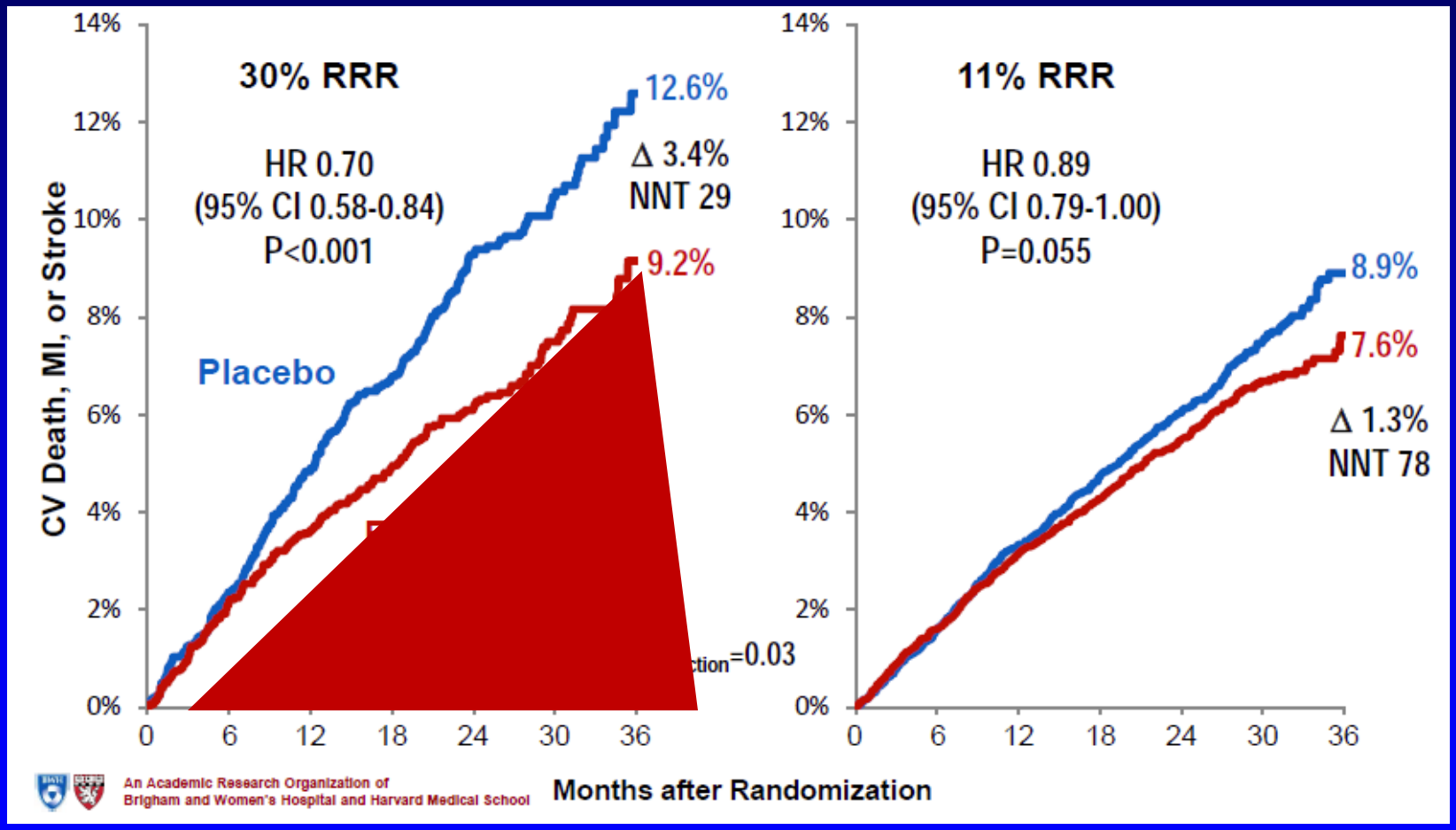
| | N | Cumulative incidence of CV death, MI, or stroke (secondary endpoint) *Placebo* | RRR | ARR |
|---|---|---|---|---|
| **Overall patients with prior MI** | N= 22,351 | -- | 18% | -- |
| **Time from Qualifying MI** | **< 2 y ago** N=8,402 | 10.8% | 24% | 2.9% |
| | **≥ 2 y ago** N=13,918 | 9.3% | 13% | 1.0% |
| **Number of Prior MIs** | **≥ 2** N=5,285 | 15.0% | 21% | 2.6% |
| | **1** N=17,047 | 8.2% | 16% | 1.7% |
| **Residual Multivessel CAD** | **MVD** N=5,618 | 12.6% | 30% | 3.4% |
| | **No MVD** N=16,715 | 8.9% | 11% | 1.3% |



**Sabatine M, AHA 2017.**

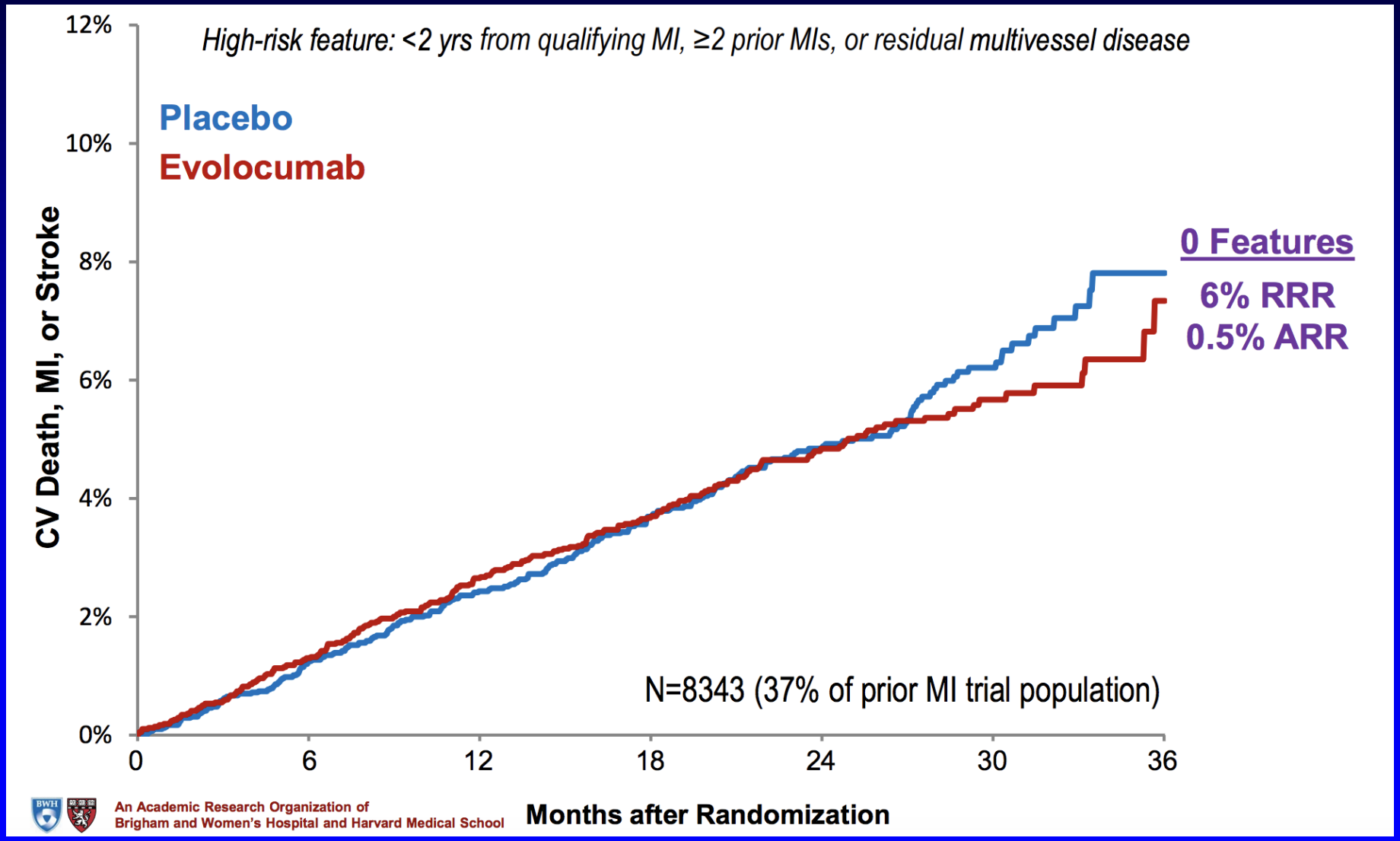
# Benefit of Evolocumab in high risk patients

## *Based on multivessel disease*




Sabatine M, AHA 2017.

# Benefit of Evolocumab
## *in absence of high-risk features*




Sabatine M, AHA 2017

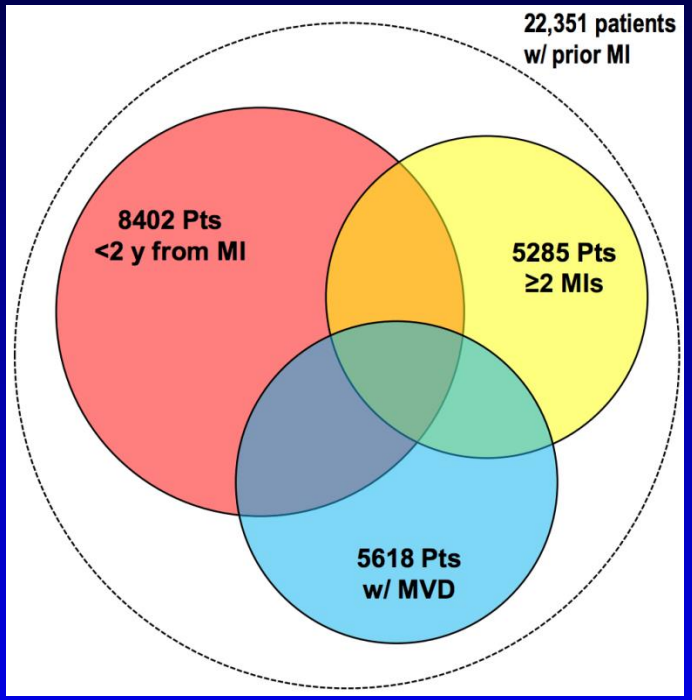
# FOURIER: Evolocumab Reduced MI, Stroke, but Not Mortality…

| | Number of events | | HR [CI] | P-value |
|---|---|---|---|---|
| | Evolocumab | Placebo | | |
| **MI** | **468** | **639** | **0.73** [0.65-0.82] | **<0.001** |
| **Stroke** | **207** | **262** | **0.79** [0.66-0.95] | **0.01** |
| **Coronary revasc** | **759** | **965** | **0.78** [0.71-0.86] | **<0.001** |
| **All-cause death** | **444** | **426** | **1.04** [0.91-1.19] | 0.54 |
| **CV death** | **251** | **240** | **1.05** [0.88-1.25] | 0.62 |

Sabatine M, N Engl J Med 2017

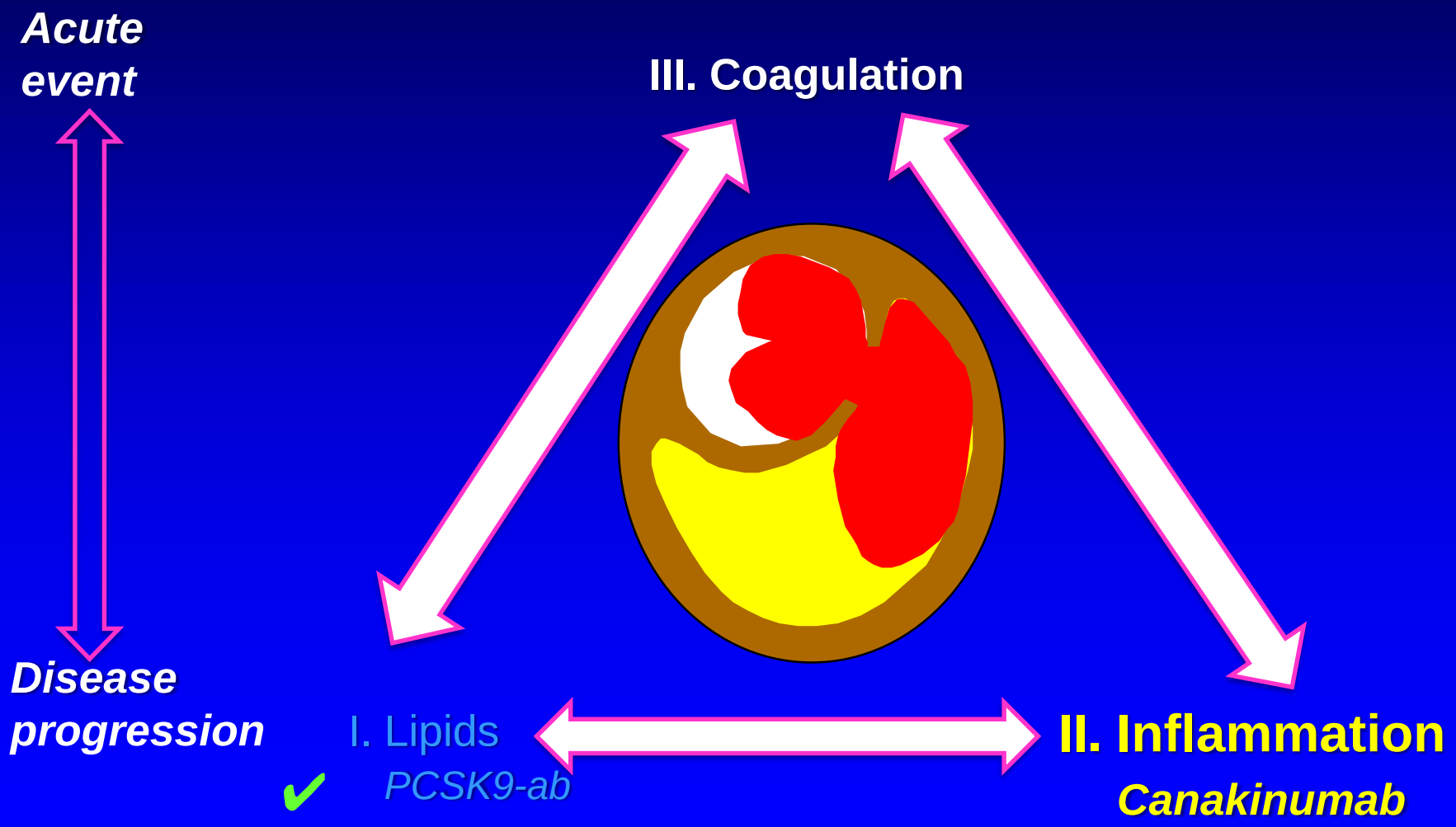
# Summary benefit of additional LDL-c lowering by PCSK9-ab to reduce residual CV-risk

- **Clinical features offer an approach to tailor PCSK9-ab therapy**
  - Recent MI (< 2 yrs)
  - **Recurrent events**
  - **Multivessel disease**
  - **PAD**
  - **Absolute baseline LDLc level**

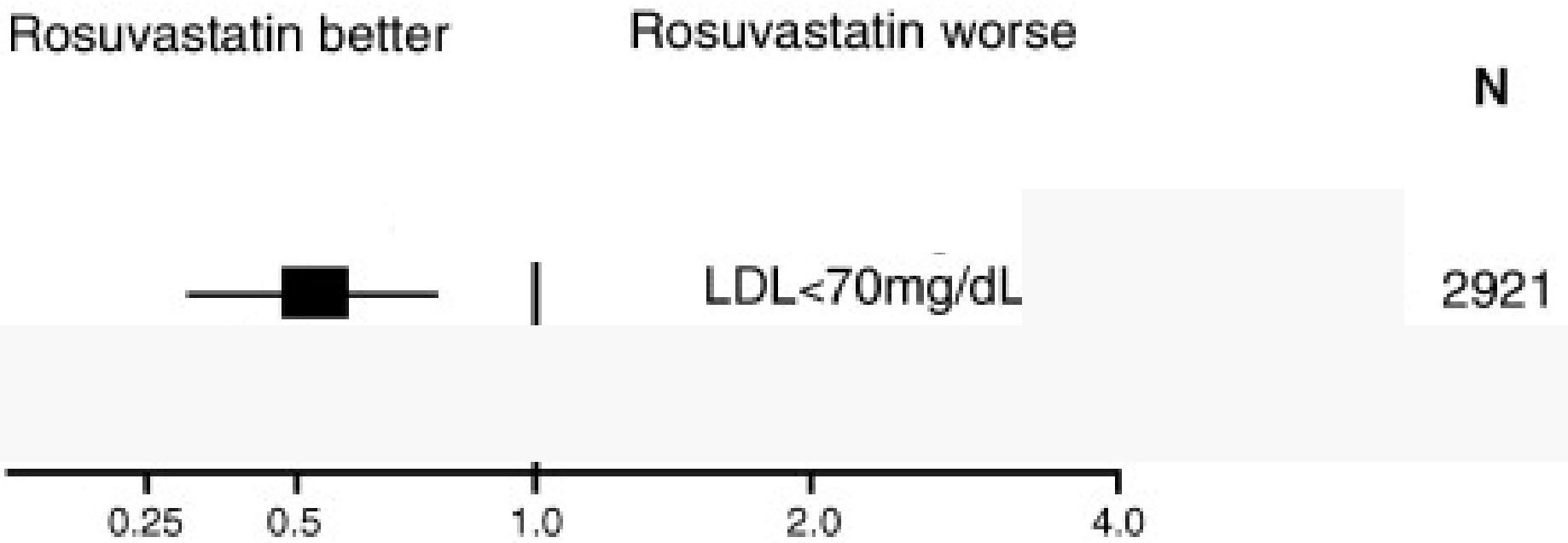



- Despite LDL-c lowering to virtually undetectable levels
  - Substantial residual CV-risk is not prevented
  - Most likely, a multifactorial disease requires a multifactorial therapy

# Lowering residual cardiovascular risk *on top of statin therapy*

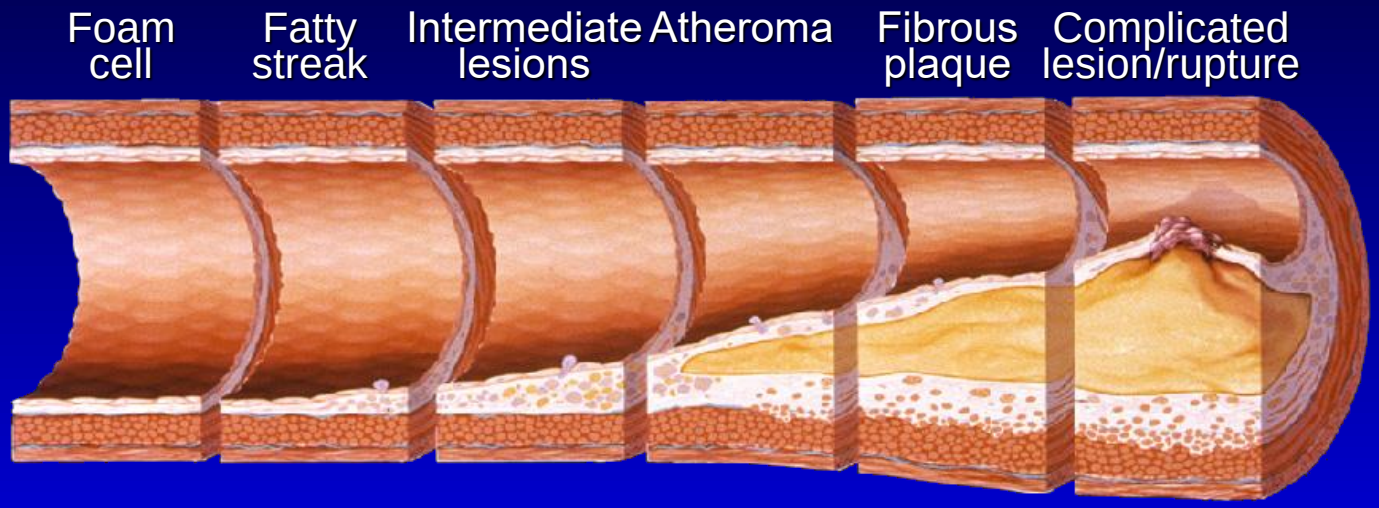


# LDL & CRP lowering
## *in JUPITER*




Ridker et al. 2008 *N Engl J Med*; **359**: 2195-207.
Libby et al. 2009 *JACC*; **54**: 2129-2138

# Inflammation, Plaque Instability and Rupture:
## *from Foam Cell Formation to Ischaemic Events*

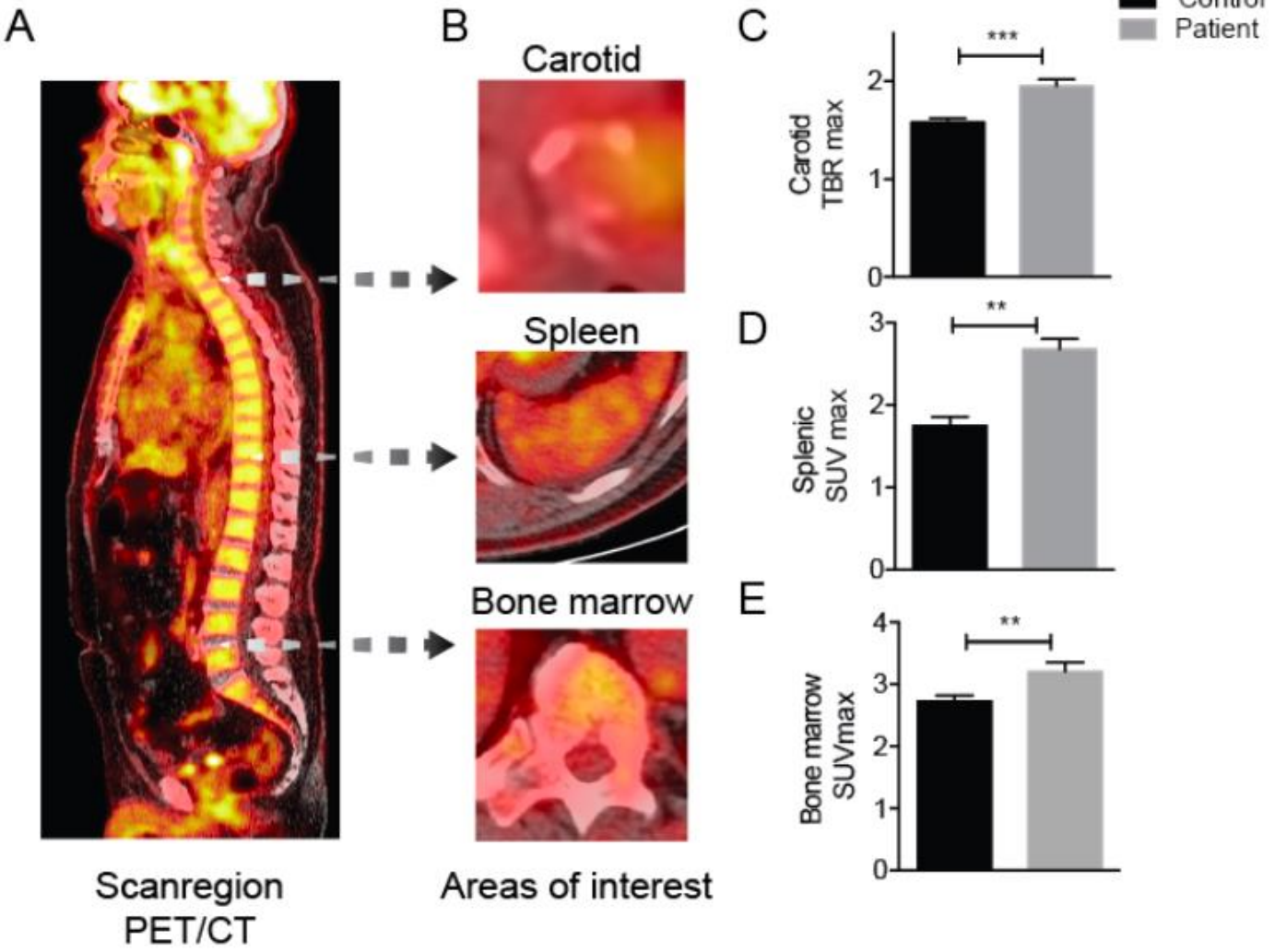



| 1° & messenger inflamm chemokines | | Cellular adhesion molecules | Plaque destabilisation | | Plaque rupture |
|---|---|---|---|---|---|
| ▪ IL-1 | ▪ IL-6 | ▪ sICAM | ▪ IL-18 | ▪ MPO | ▪ PAPP-A |
| ▪ TNF-α | ▪ IL-18 | ▪ sVCAM | ▪ oxLDL | ▪ MMPs | ▪ sCD40L |
| | ▪ MCP-1 | ▪ Selectins | ▪ $LpPLA_2$ | ▪ MCP-1 | ▪ Neopterin |
| | | ▪ ADMA | ▪ GPx-1 | ▪ PlGF | ▪ $sPLA_2$ |

Koenig W, Arterioscler Thromb Vasc Biol 2007;27:15–26.

# Persistent increased hematopoietic activity

*in CVD patients*

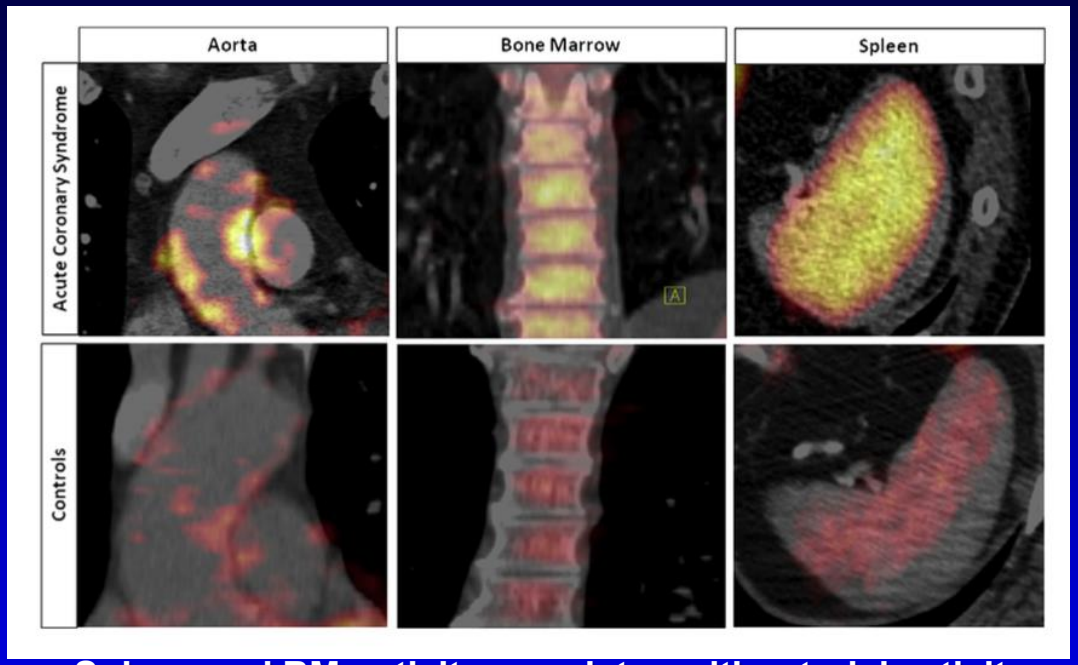



Van der Valk, Stroes, *Eur Heart J 2016*

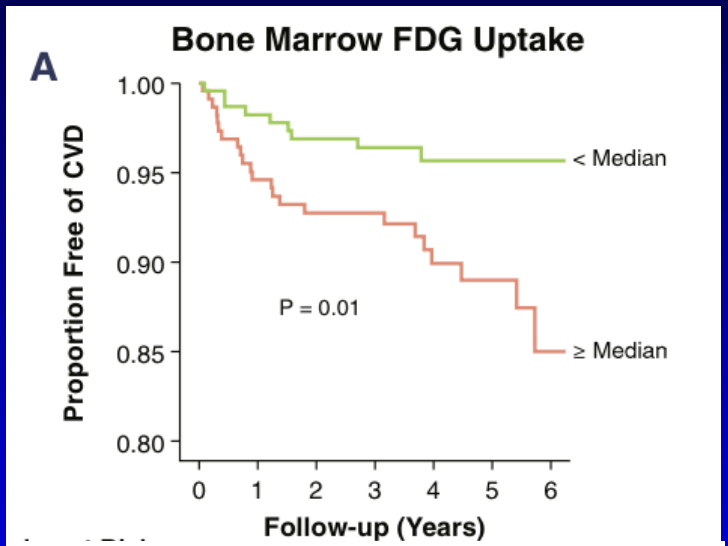
# Hematopoietic activity predicts CV-risk

## *in patients following myocardial infarction*

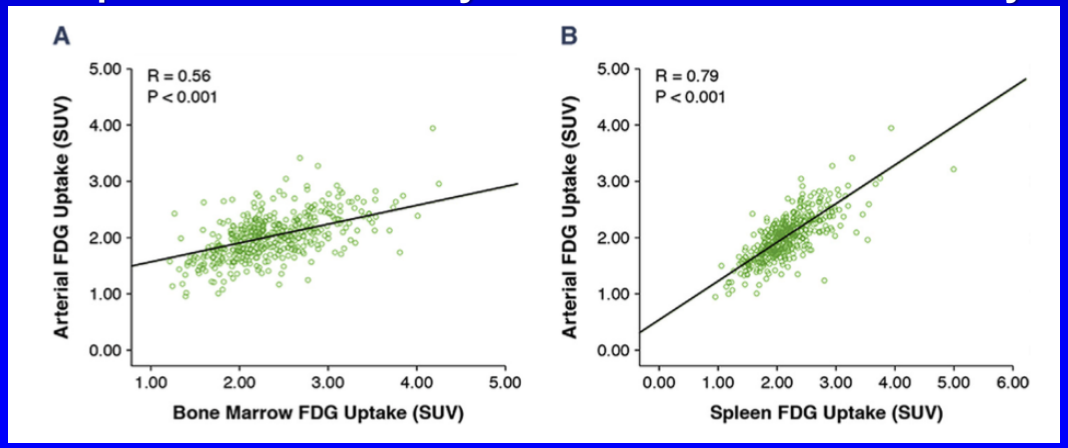
**Spleen and BM activity increased in ACS patients**

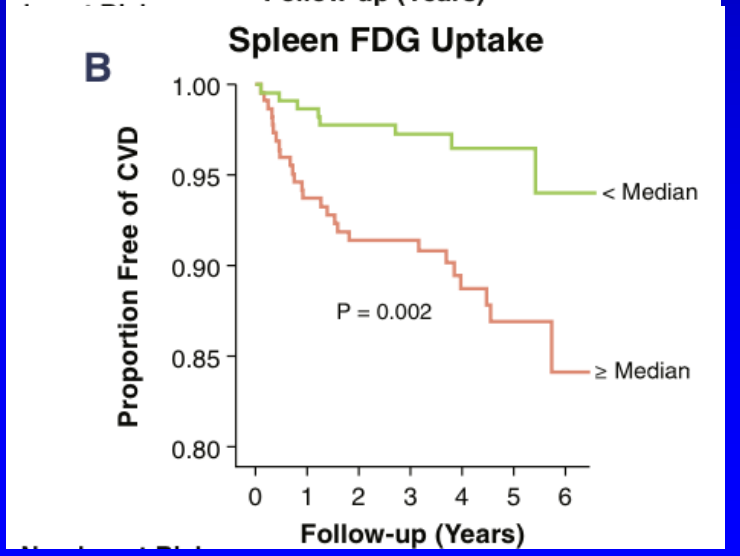



**Spleen and BM activity Correlate with CVD risk**




**Spleen and BM-activity correlates with arterial activity**

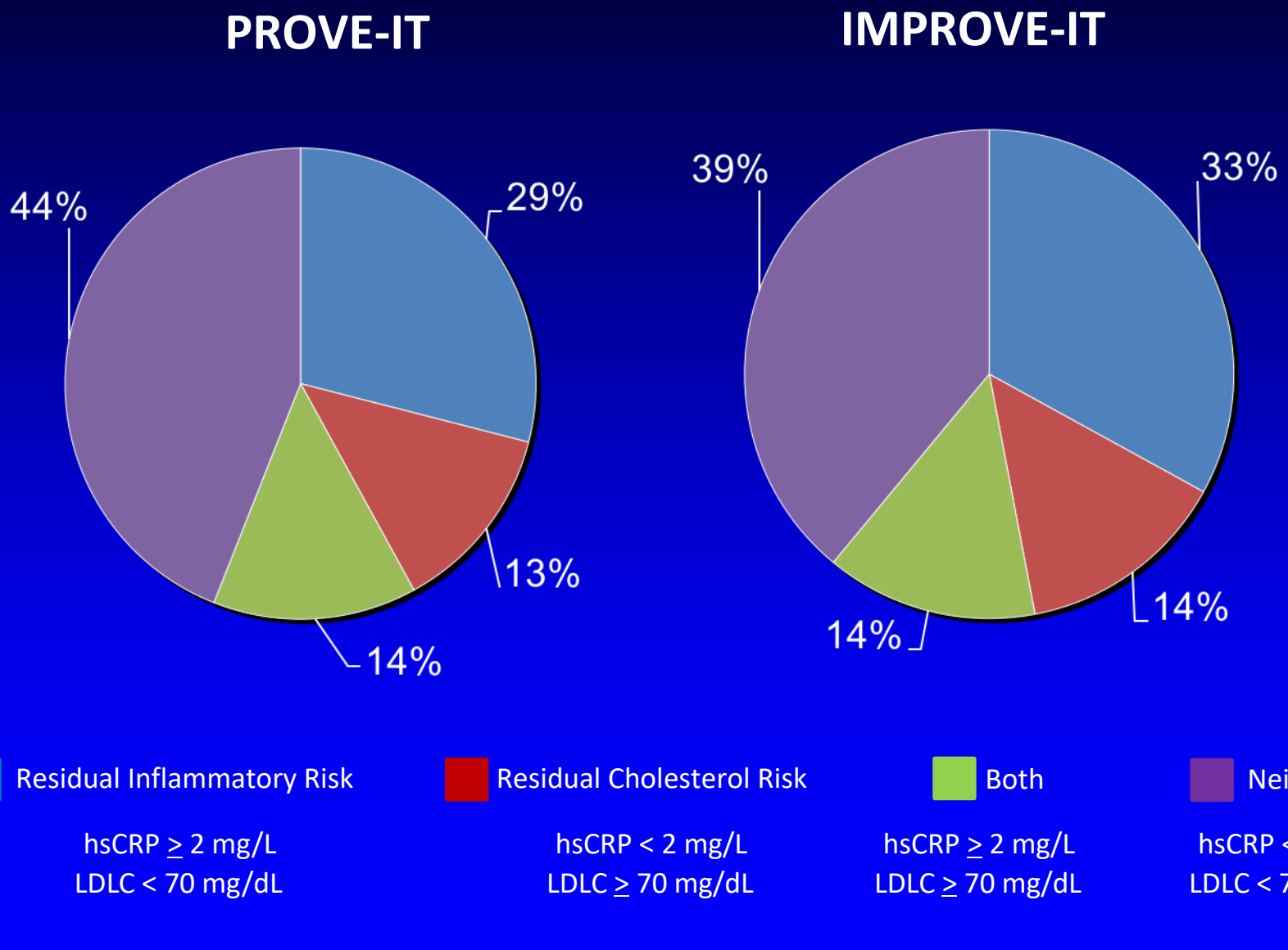



Emami, JACC CV imaging 2015

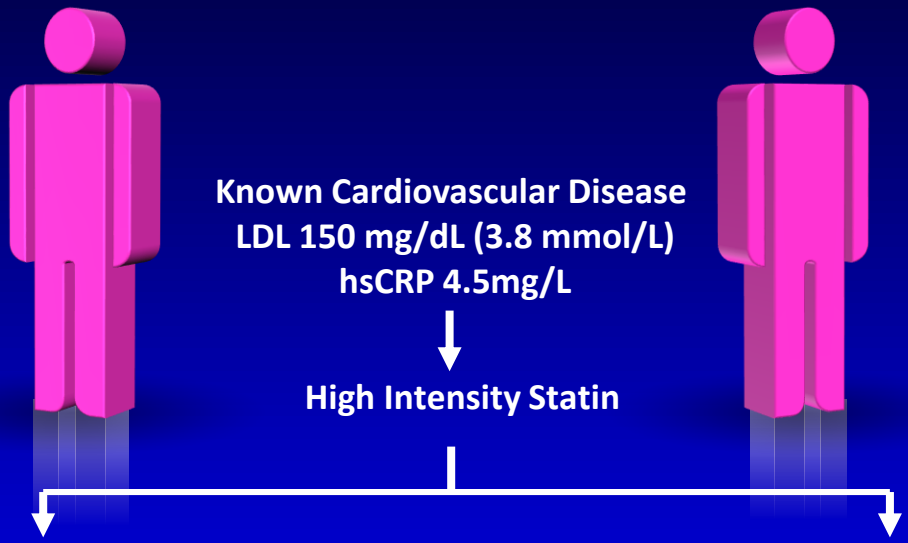
# Residual Inflammatory Risk very common

## *Statins little impact on inflammation*




Ridker PM. Circulation Res 2017;120:617-9.

# Do anti-inflammatory interventions reduce CV-risk?



Known Cardiovascular Disease
LDL 150 mg/dL (3.8 mmol/L)
hsCRP 4.5mg/L

↓

High Intensity Statin

## "Residual Cholesterol Risk"

LDL 110 mg/dL (2.8 mmol/L)
hsCRP 1.8 mg/L

↓

Additional
LDL Reduction

IMPROVE-IT : Ezetimibe 6% RRR
FOURIER/SPIRE: PCSK9 Inhibition q2 weeks 15% RRR

## "Residual Inflammatory Risk"

LDL 70 mg/dL (1.8 mmol/L)
hsCRP 3.8 mg/L

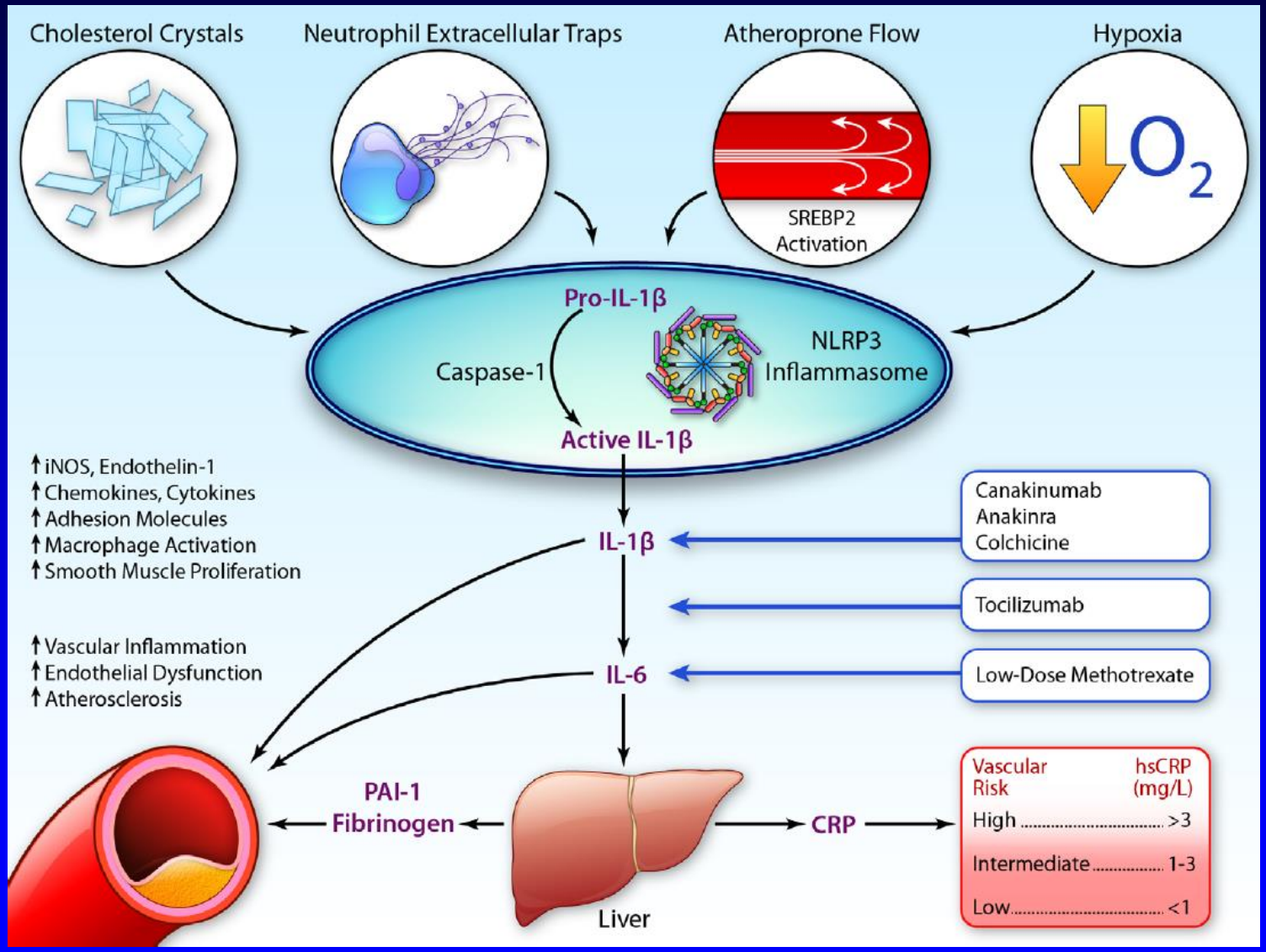
↓

Additional
Inflammation Reduction

**No Prior Proof of Concept**

# IL-1 beta inhibition

## *Identifying Upstream Targets for Atheroprotection*

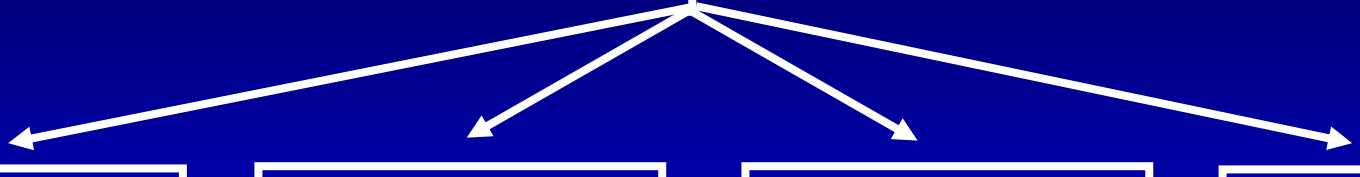



Ridker PM. Circ Res 2016;118:145-156.

# Canakinumab Anti-Inflammatory Thrombosis Outcomes Study

Stable CAD (post MI)
On Statin, ACE/ARB, BB, ASA
Persistent Elevation
of hsCRP (≥ 2 mg/L)

N = 10,061
39 Countries
April 2011 - June 2017
1490 Primary Events



| Randomized Canakinumab 50 mg SC q 3 months | Randomized Canakinumab 150 mg SC q 3 months | Randomized Canakinumab 300 mg SC q 3 months* | Randomized Placebo SC q 3 months |
|---|---|---|---|

Primary CV Endpoint: Nonfatal MI, Nonfatal Stroke, Cardiovascular Death (MACE)

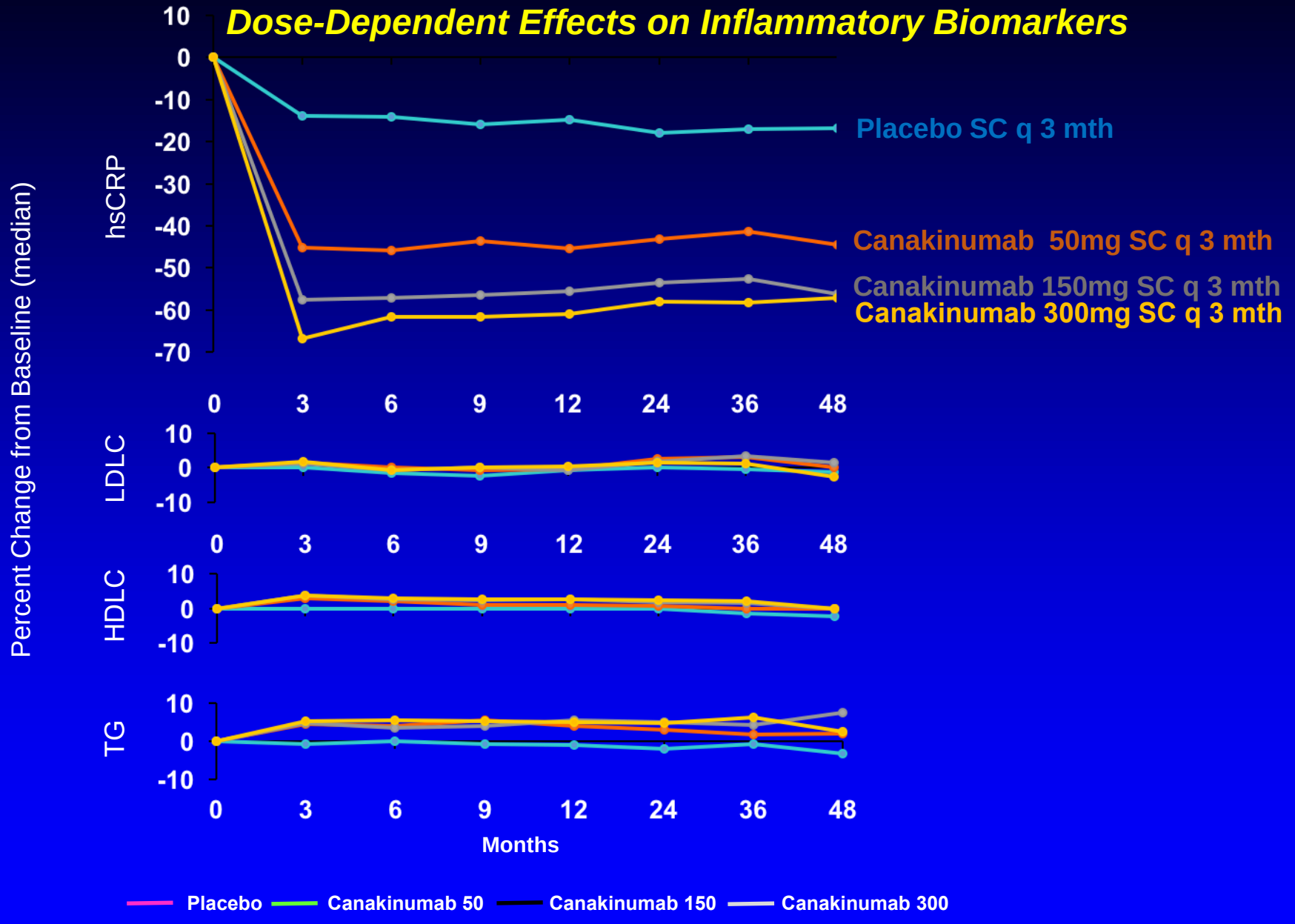
Key Secondary CV Endpoint: MACE + Unstable Angina Requiring Unplanned Revascularization (MACE+)

Critical Non-Cardiovascular Safety Endpoints: Cancer and Cancer Mortality, Infection and Infection Mortality

Ridker PM, et al. N Engl J Med. 2017;377:1119-31

# CANTOS:

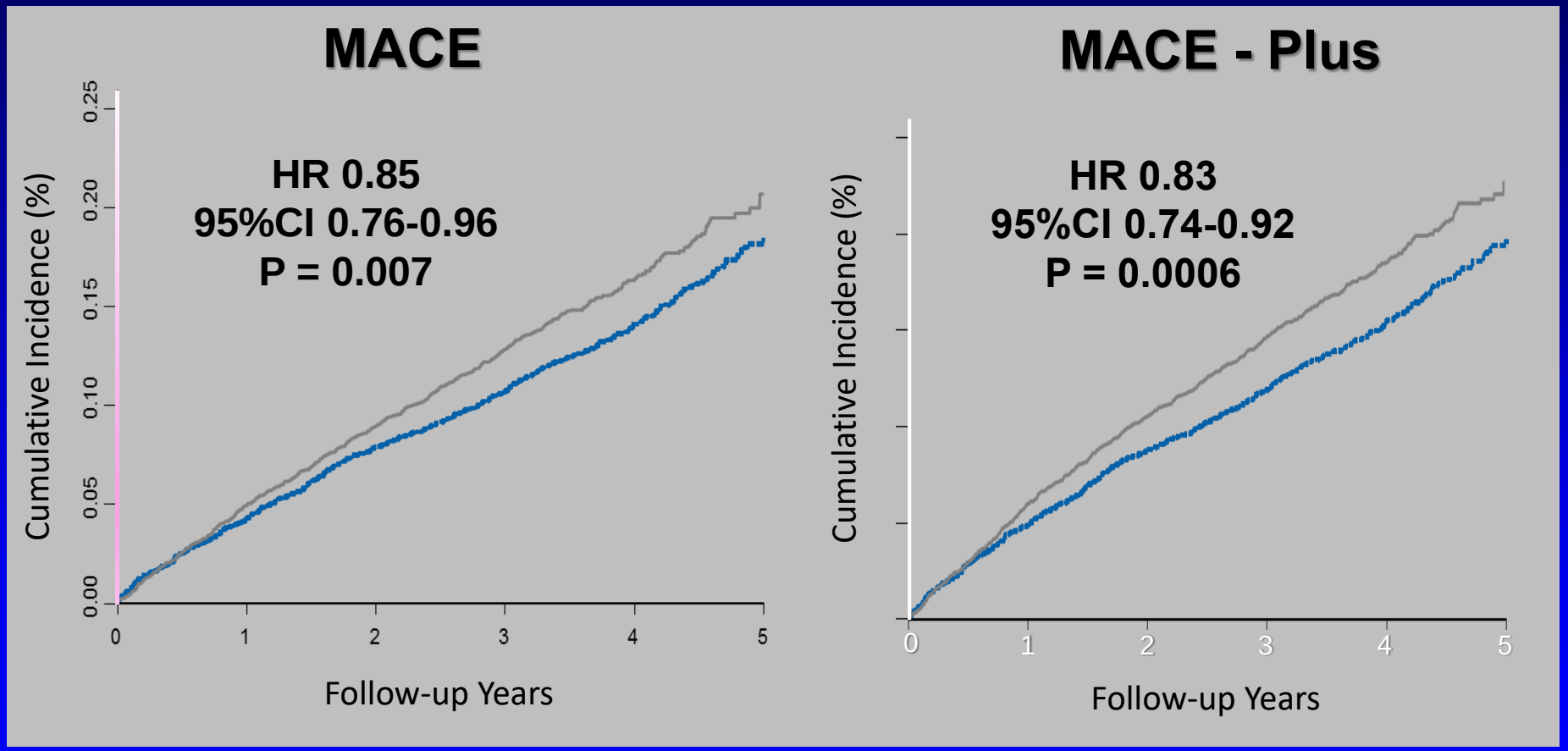
## *Dose-Dependent Effects on Inflammatory Biomarkers*




Ridker PM et al. N Engl J Med. 2017;377:1119-31

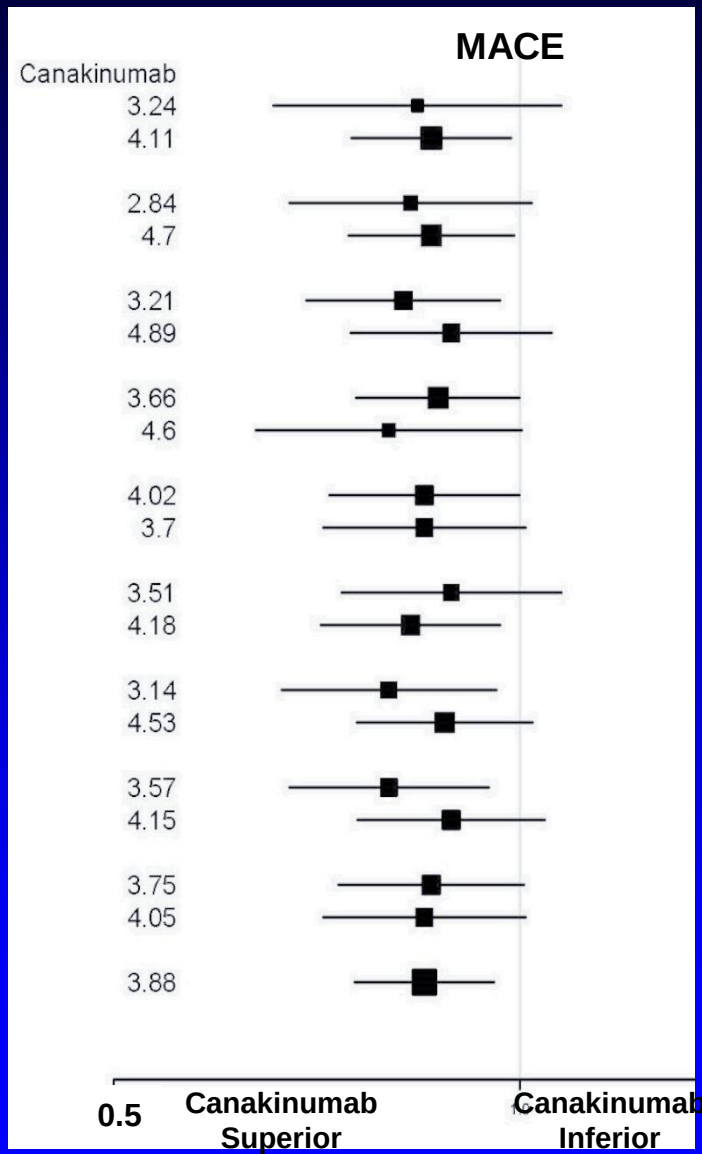
# CANTOS: Primary Cardiovascular Endpoints

Placebo SC q 3 months
Canakinumab 150/300 mg SC q 3 months




Ridker PM et al. N Engl J Med. 2017;377:1119-31

# Consistency of Effect Across All patient Groups Defined By Baseline Clinical Characteristics




Ridker PM et al. N Engl J Med. 2017;377:1119-31

# Benefit of Canakinumab Across CV Endpoints

| | | Canakinumab SC q 3 months | | | |
|---|---|---|---|---|---|
| **Endpoint** | **Placebo (N=3347)** | **50 mg (N=2170)** | **150 mg (N=2284)** | **300 mg (N=2263)** | **P-trend** |
| Primary | 1.00 | 0.93 | 0.85 | 0.86 | 0.020 |
| Secondary | 1.00 | 0.90 | 0.83 | 0.83 | 0.002 |
| Myocardial Infarction | 1.00 | 0.94 | 0.76 | 0.84 | 0.028 |
| Urgent Revascularization | 1.00 | 0.70 | 0.64 | 0.58 | 0.005 |
| Any Coronary Revascularization | 1.00 | 0.72 | 0.68 | 0.70 | <0.001 |
| Stroke | 1.00 | 1.01 | 0.98 | 0.80 | 0.17 |
| Cardiac Arrest | 1.00 | 0.72 | 0.63 | 0.46 | 0.035 |
| CV Death | 1.00 | 0.89 | 0.90 | 0.94 | 0.62 |
| All Cause Mortality | 1.00 | 0.94 | 0.92 | 0.94 | 0.39 |

Ridker PM et al. N Engl J Med. 2017;377:1119-31

# Adverse effects of Canakinumab

## *per 100 person years of exposure*

| | | Canakinumab SC q 3 months | | | |
|---|---|---|---|---|---|
| **Adverse Event** | **Placebo (N=3347)** | **50 mg (N=2170)** | **150 mg (N=2284)** | **300 mg (N=2263)** | **P-trend** |
| Any SAE | 12.0 | 11.4 | 11.7 | 12.3 | 0.43 |
| Leukopenia | 0.24 | 0.30 | 0.37 | 0.52 | 0.002 |
| Any infection | 2.86 | 3.03 | 3.13 | 3.25 | 0.12 |
| Fatal infection | 0.18 | 0.31 | 0.28 | 0.34 | **0.09/0.02*** |
| Injection site reaction | 0.23 | 0.27 | 0.28 | 0.30 | 0.49 |
| Any Malignancy | 1.88 | 1.85 | 1.69 | 1.72 | 0.31 |
| Fatal Malignancy | 0.64 | 0.55 | 0.50 | 0.31 | 0.0007 |
| Arthritis | 3.32 | 2.15 | 2.17 | 2.47 | 0.002 |
| Osteoarthritis | 1.67 | 1.21 | 1.12 | 1.30 | 0.04 |
| Gout | 0.80 | 0.43 | 0.35 | 0.37 | 0.0001 |
| ALT > 3x normal | 1.4 | 1.9 | 1.9 | 2.0 | 0.19 |
| Bilirubin > 2x normal | 0.8 | 1.0 | 0.7 | 0.7 | 0.34 |

* P-value for combined canakinumab doses vs placebo

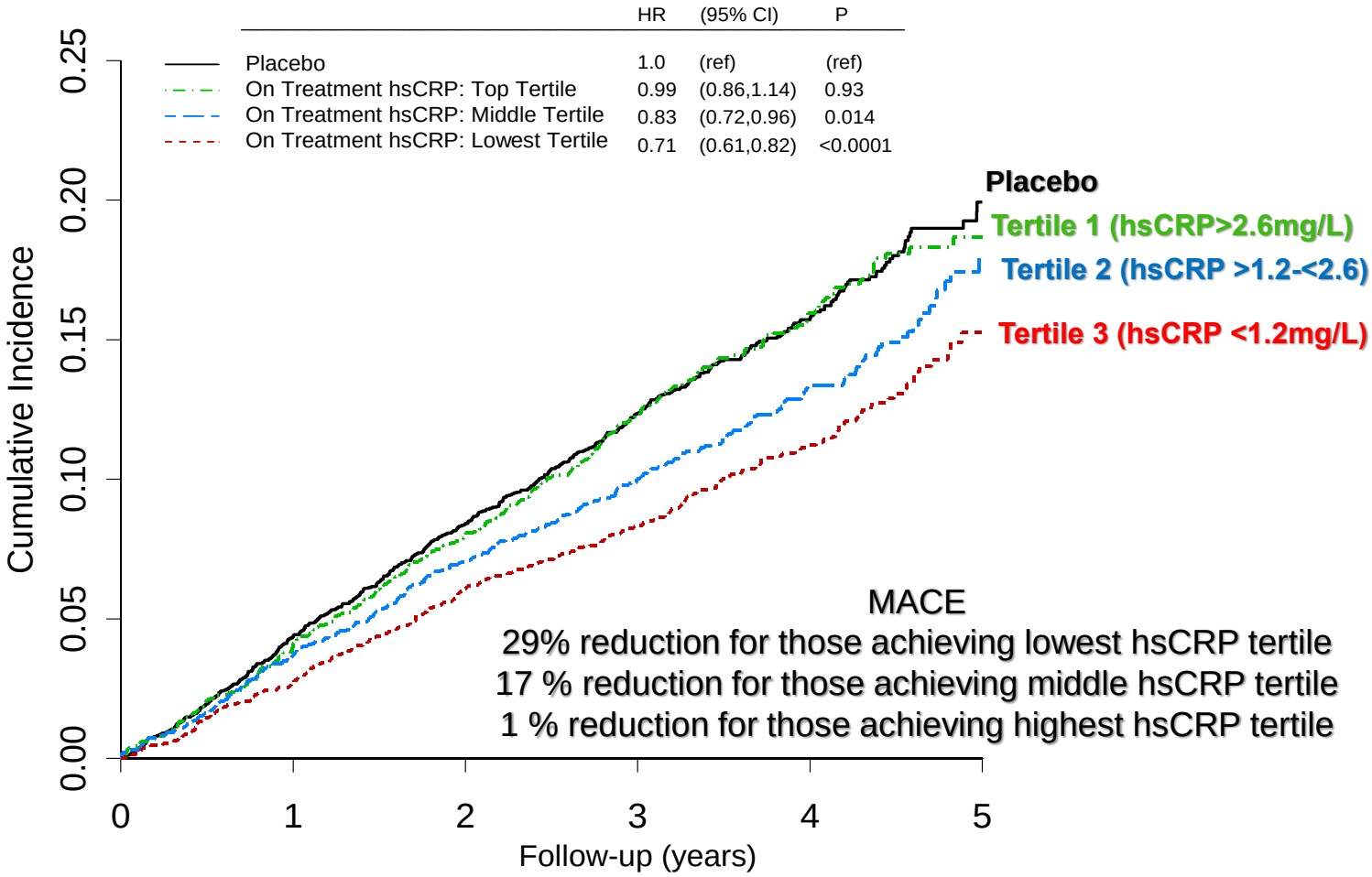
Ridker PM, et al. N Engl J Med. 2017;377:1119-31

# Interleukin-1β Inhibition with Canakinumab

**Can we identify evidence of individual drug response to define patient groups likely to benefit?**

**Does the magnitude of CRP reduction identify individual patients most likely to benefit?**

# CRP Tertiles Measured After the Initial Canakinumab dose




No. at risk:

| | | | | | | |
|---|---|---|---|---|---|---|
| Placebo | 3182 | 3014 | 2853 | 2525 | 1215 | 200 |
| Canakinumab: | | | | | | |
| Top Tertile | 2090 | 1983 | 1866 | 1632 | 789 | 139 |
| Middle Tertile | 2044 | 1947 | 1866 | 1660 | 821 | 146 |
| Lowest Tertile | 2218 | 2147 | 2056 | 1856 | 888 | 153 |

Ridker PM et al. N Engl J Med. 2017;377:1119-31

# Impact on mortality

## *According to On-treatment CRP > or < 2 mg/L After Drug Initiation*

| Clinical Outcome | | Placebo (N = 3182) | Canakinumab On-treatment hsCRP ≥ 2mg/L (N = 2868) | Canakinumab On-treatment hsCRP < 2 mg/L (N = 3484) |
|---|---|---|---|---|
| MACE | HR (adjusted)<br>95% CI<br>P | 1.0<br>Referent<br>Referent | 0.90<br>0.79-1.02<br>0.11 | 0.75<br>0.66-0.85<br><0.0001 |
| MACE - Plus | HR (adjusted)<br>95% CI<br>P | 1.0<br>Referent<br>Referent | 0.91<br>0.81-1.03<br>0.14 | 0.74<br>0.66-0.83<br><0.0001 |
| CV Death | HR (adjusted)<br>95% CI<br>P | 1.0<br>Referent<br>Referent | 0.99<br>0.82-1.21<br>0.95 | 0.69<br>0.56-0.85<br>0.0004 |
| All-Cause Mortality | HR (adjusted)<br>95% CI<br>P | 1.0<br>Referent<br>Referent | 1.05<br>0.90-1.22<br>0.56 | 0.69<br>0.58-0.81<br><0.0001 |

HRs adjusted for age, gender, smoking, HTN, diabetes, BMI, baseline hsCRP, Baseline LDLC

Ridker PM et al. N Engl J Med. 2017;377:1119-31

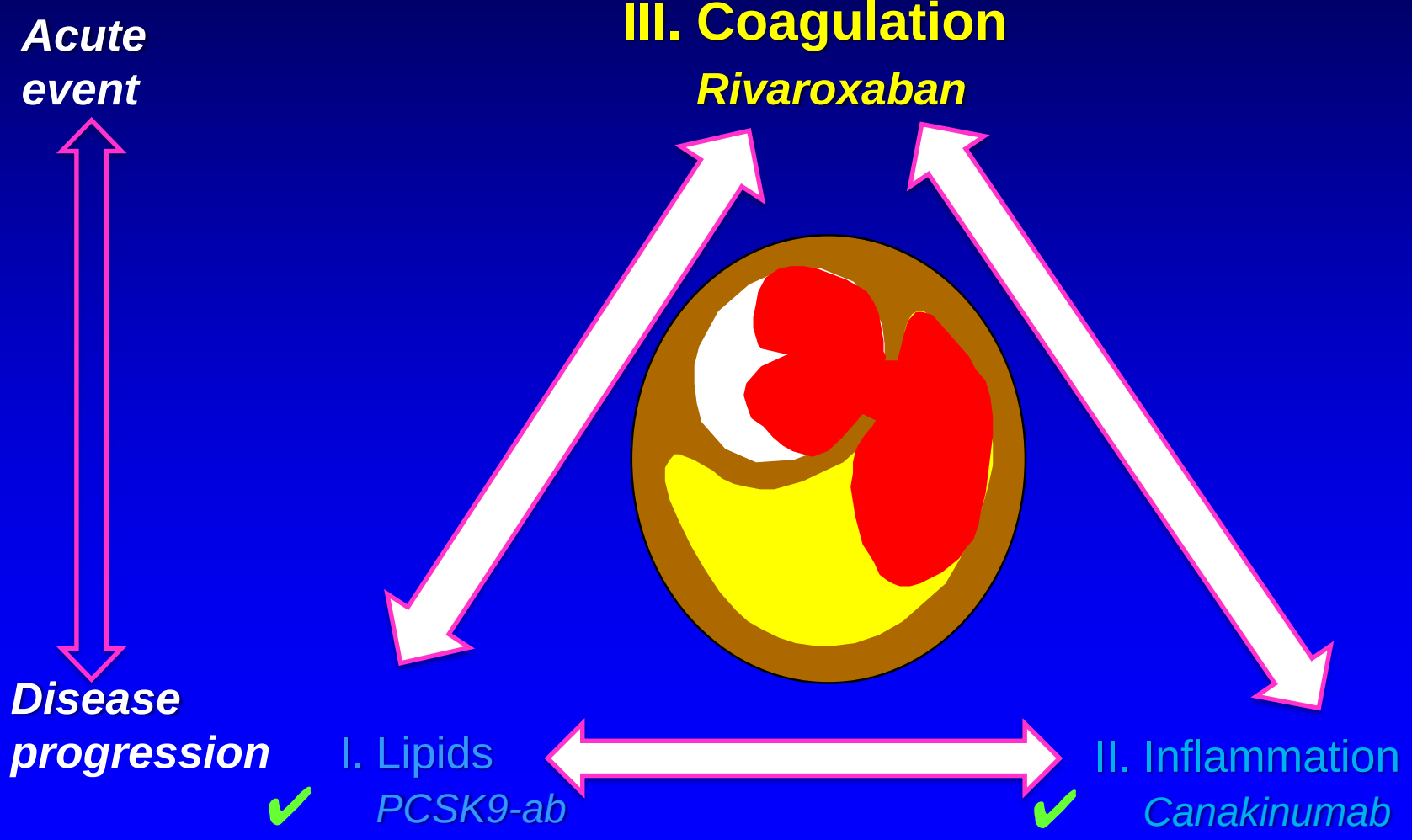
# CANTOS : Adverse Effects

*Incidence Rates of Fatal Infection Not Related to On-Treatment Levels of hsCRP*

| Clinical Outcome | Placebo (N = 3182) | Canakinumab On-treatment hsCRP ≥ 2mg/L (N = 2868) | Canakinumab On-treatment hsCRP < 2 mg/L (N = 3484) |
|---|---|---|---|
| Fatal Infection Incidence rate (per 100 person years) | 0.18 | 0.35 | 0.27 |

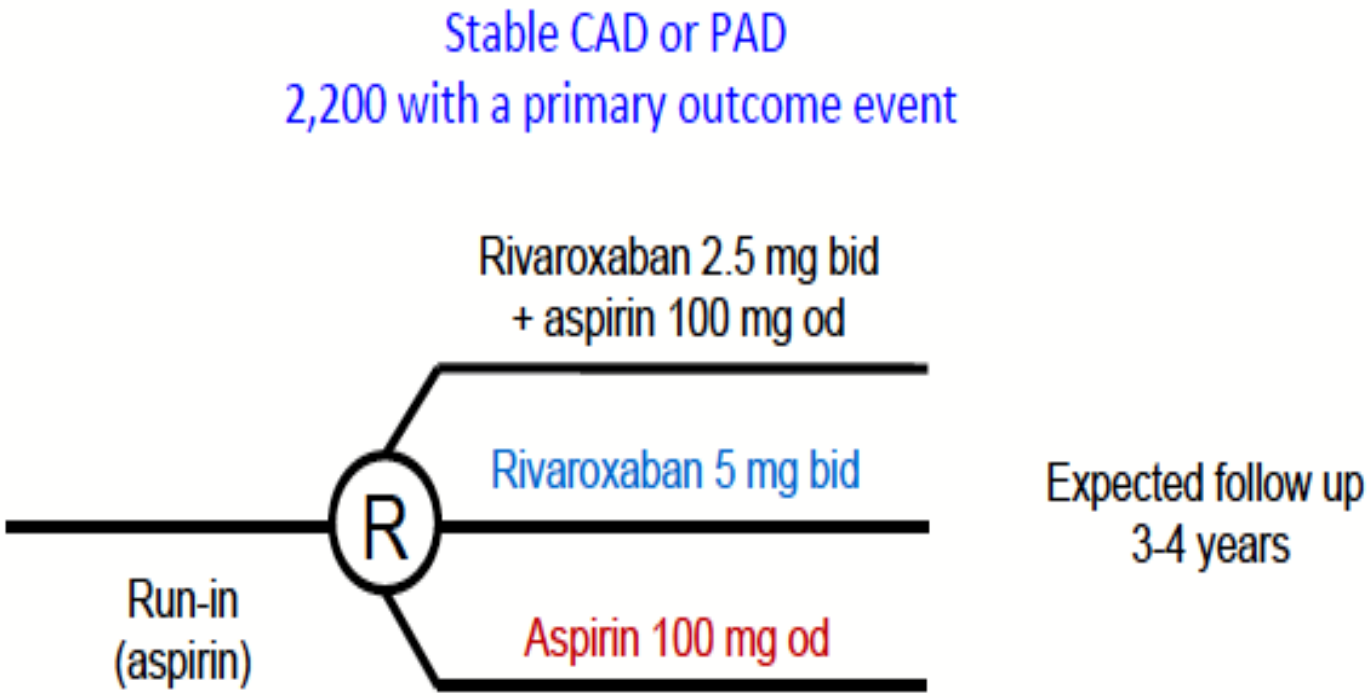
Ridker PM et al. N Engl J Med. 2017;377:1119-31

# Lowering residual cardiovascular risk *on top of statin therapy*



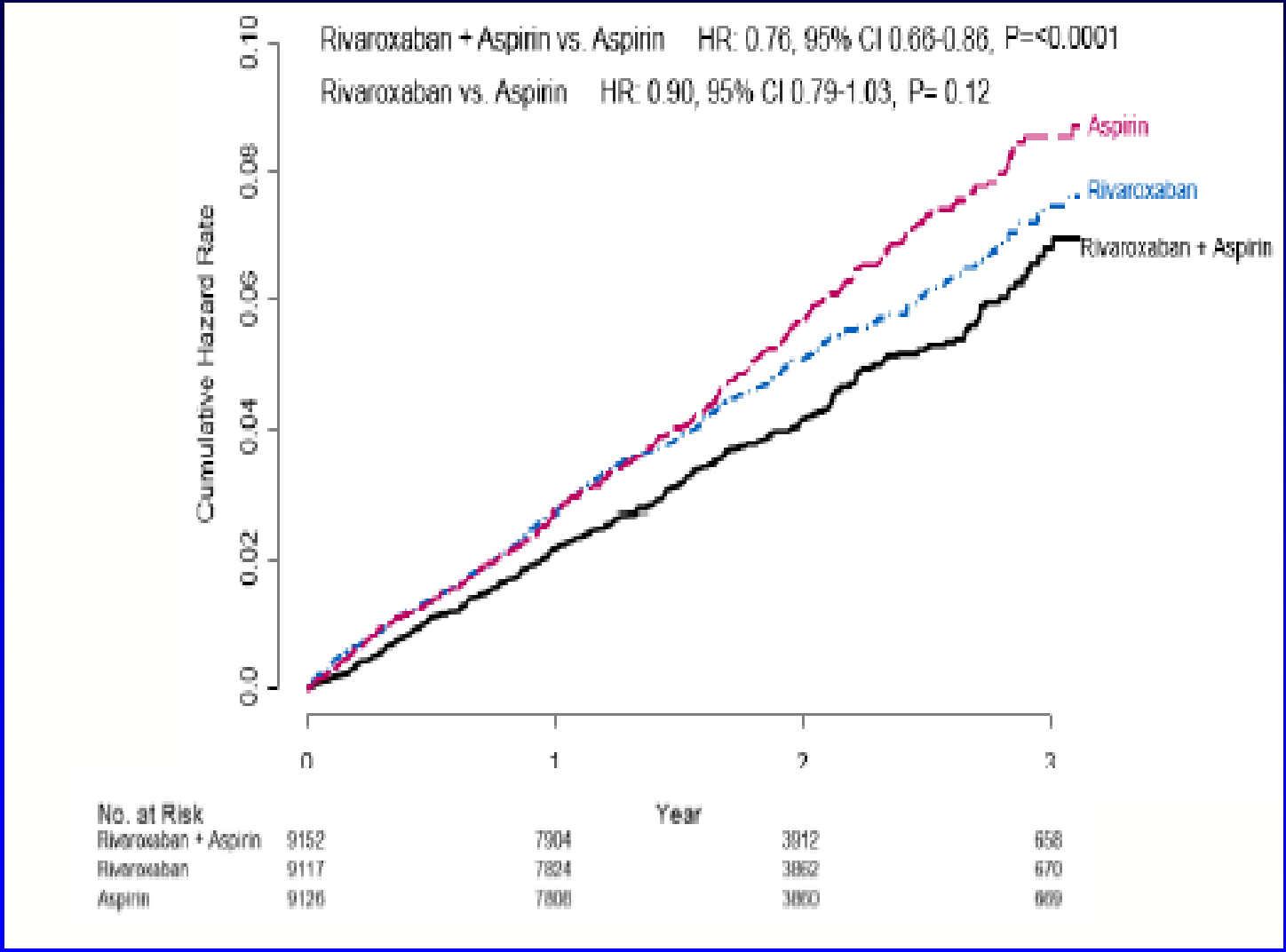
# COMPASS design

## *Low-dose Rivaroxaban on top of aspirin*




Eikelboom, N Engl J Med 2017

# Primary endpoint:
## *CV-death, MI, stroke*



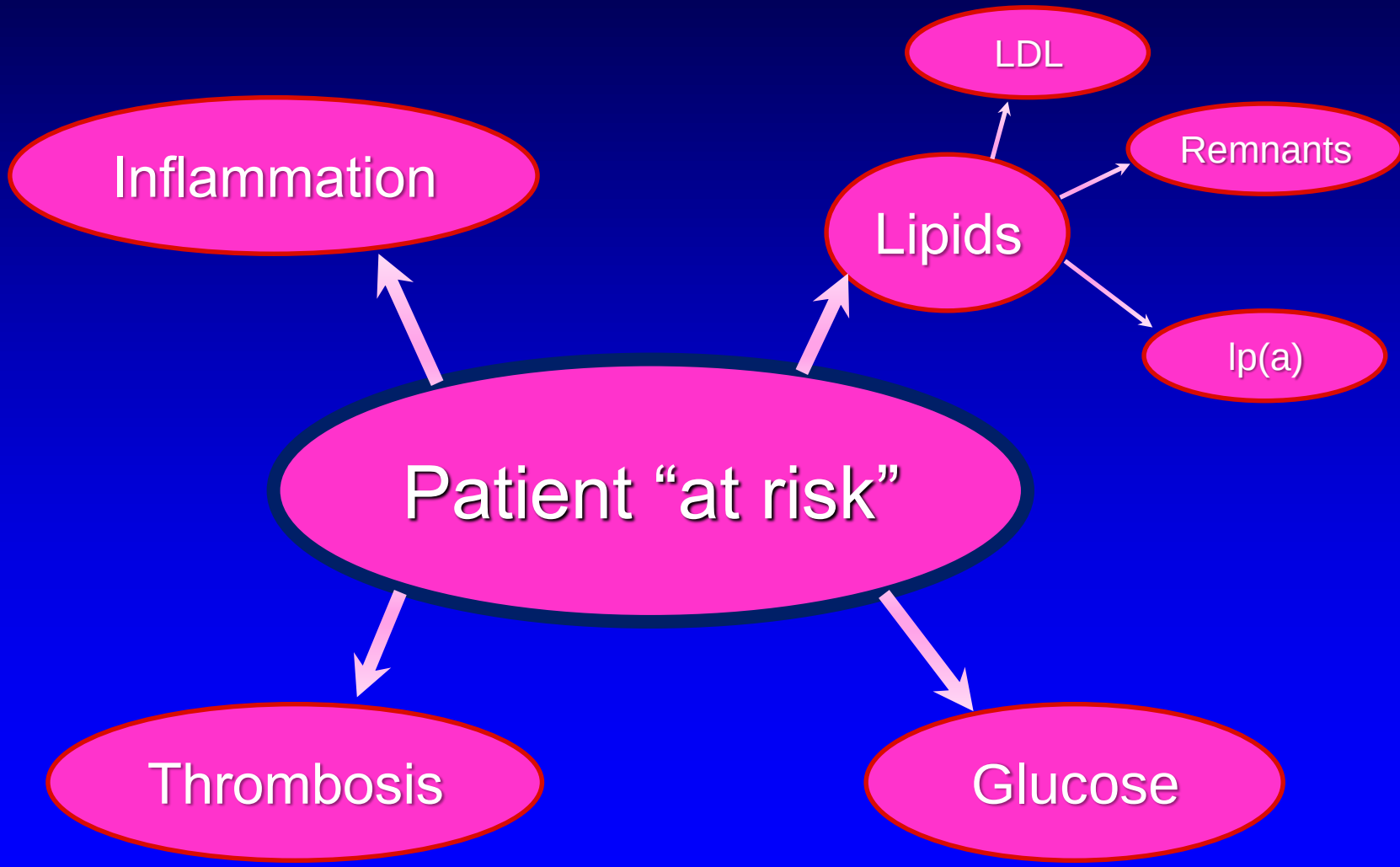

Eikelboom, N Engl J Med 2017

# We can choose in high CV-risk

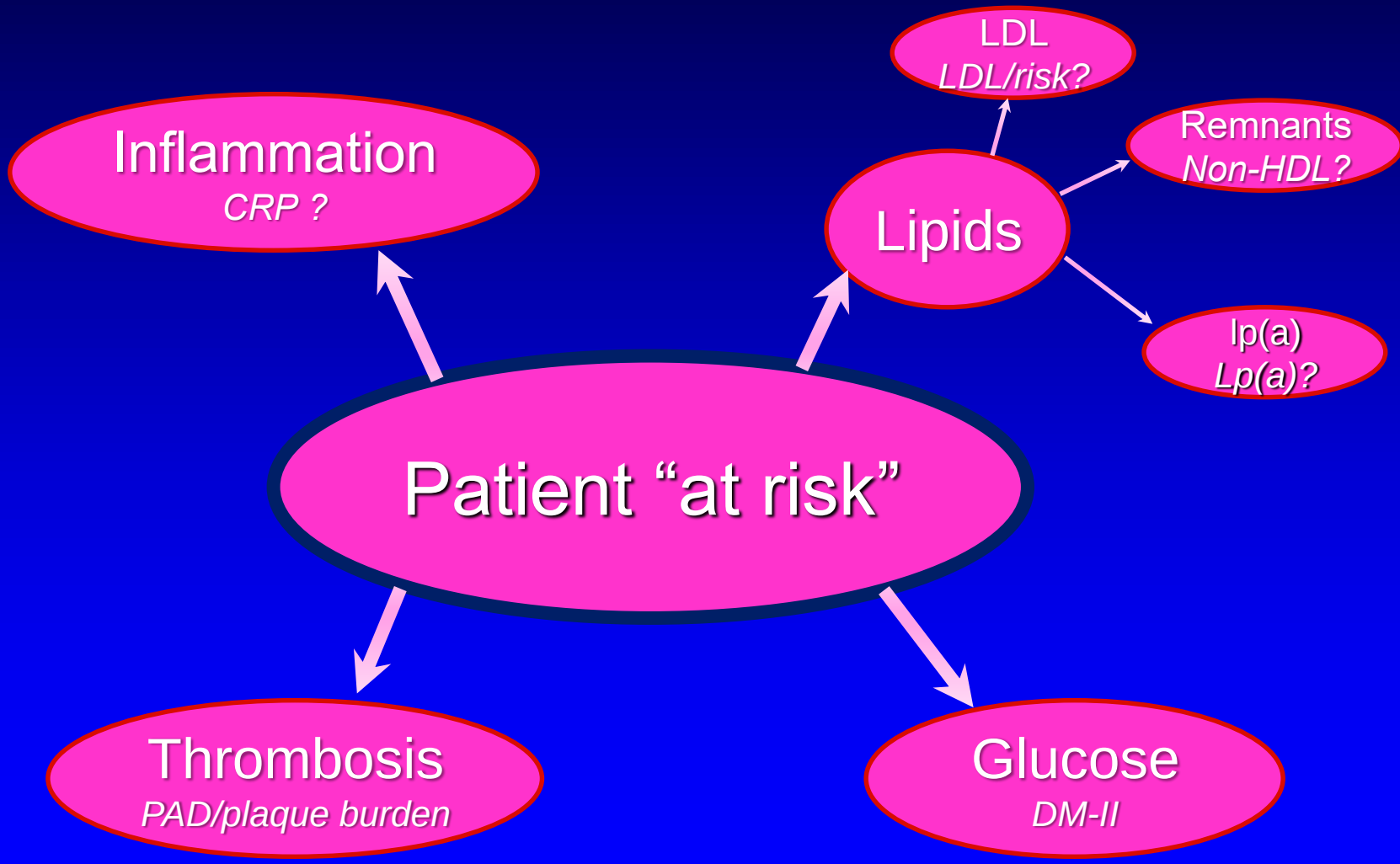
## *depending on 'most active pathway' per patient?*

| Study | target | CVD risk reduction | Special details | Safety |
|---|---|---|---|---|
| ***FOURIER*** *Evolocumab* | Lipids / LDL-C | -15 - -41% *(lower LDL – higher benefit)* | CV-mortality unchanged | No safety signals |
| ***CANTOS*** *Canakinumab* | Inflammation | -15 - -27% *(lower CRP – higher benefit)* | Urgent revasc. -36% | Fatal infections ↑ |
| ***COMPASS*** *Rivaroxaban* | Coagulation | -24% | CV-mortality -22%<br>Stroke -42% | Major bleeds +70%<br>Fatal bleeds unchanged |

# How can we select best treatment for individual patient ?



# Simple ‘benefit’ predictors ?



# Future selection for personalized medicine:

## *Most effective 'drug' for most suitable patient*

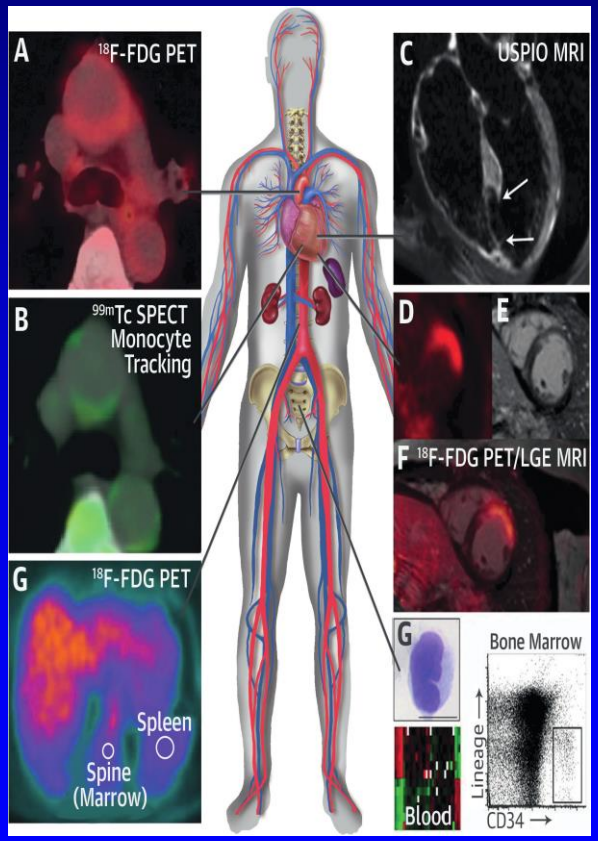
*Routine chemistry*

Detect major 'residual' risk factor:

- Residual LDL-c
- Residual CRP
- Residual remnant cholesterol
- Residual 'coagu-lation' risk

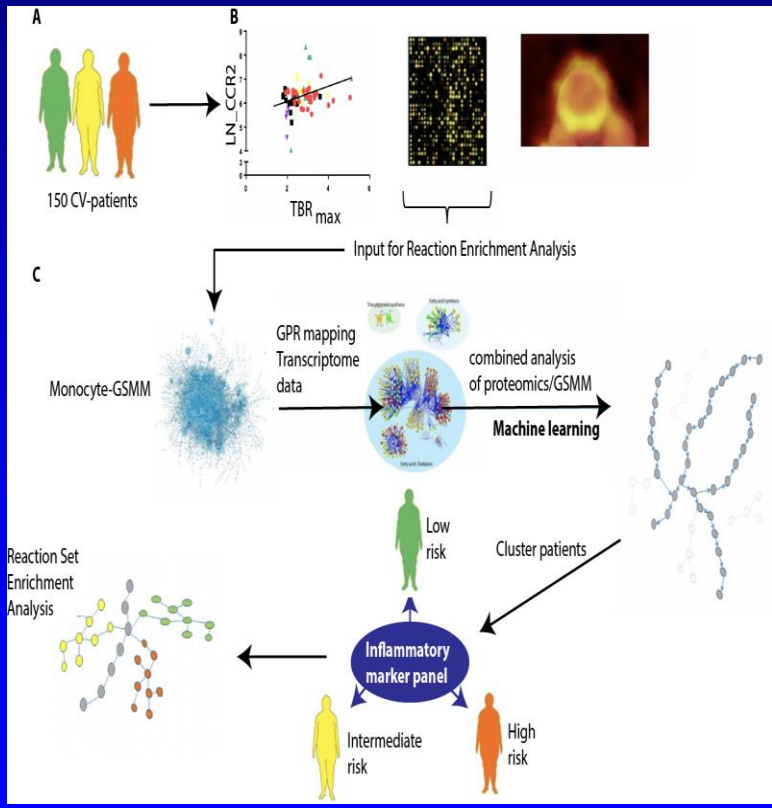
Averna, Stroes
*Atherosclerosis suppl* 2017

*Multimodal imaging*




Nahrendorf, Stroes, et al
*J Am Coll Cardiol* 2015;65(15)1583-91.

*Active pathway analysis using "proteomics"*




Ganz, P. et al.
.*JAMA 2016;***315:**2532-41

# The future: from ‘block-buster therapies’ to ‘tailored’ therapy

From ‘*random*’ group-polypharmacy towards ‘*tailored*’ individual therapy

*New Need for Cardiologist brains!@*

**Further LDLc lowering :**

- *PCSK9-ab*

**Inflammation inhibition :**

- *Canakinumab*

**Anticoagulants :**

- *Rivaroxaban*

**Other :**

- *Lp(a) lowering?*
- *remnant chol lowering?*

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