# Lipoprotein(a)

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# Disclosure potential conflicts of interest

| | |
|---|---|
| **Voor bijeenkomst mogelijk relevante relaties:** | **Bedrijfsnamen** |
| Sponsoring of onderzoeksgeld | • Athera, Resverlogix, Sanofi |
| Honorarium of andere (financiële) vergoeding | • Amgen, Sanofi-Regeneron, Novartis, Akcea, Novo-Nordisk |
| Aandeelhouder | • -- |
| Andere relatie, namelijk … | -- |

# Case

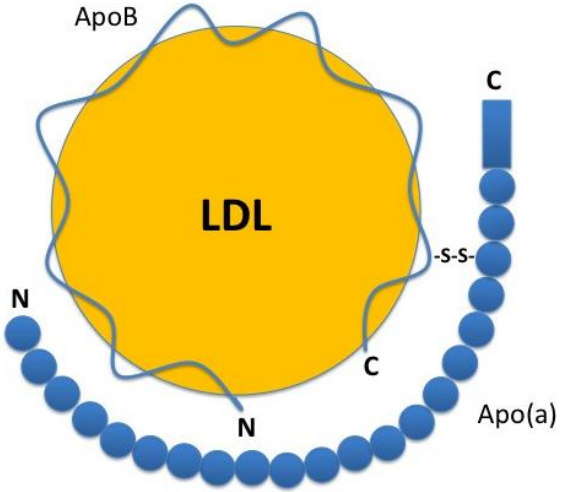
Male, 47 years old

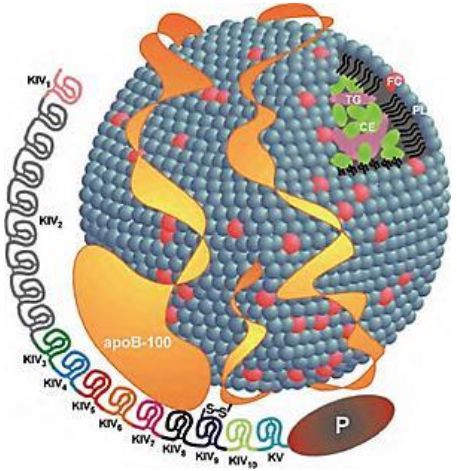
Hypertension: –
DM: –
Smoking: –
Dyslipidemia: –
Fam history: brother MI (55yr)

Lipoprotein(a): 1240 mg/L!!!

(brother also elevated lp(a))

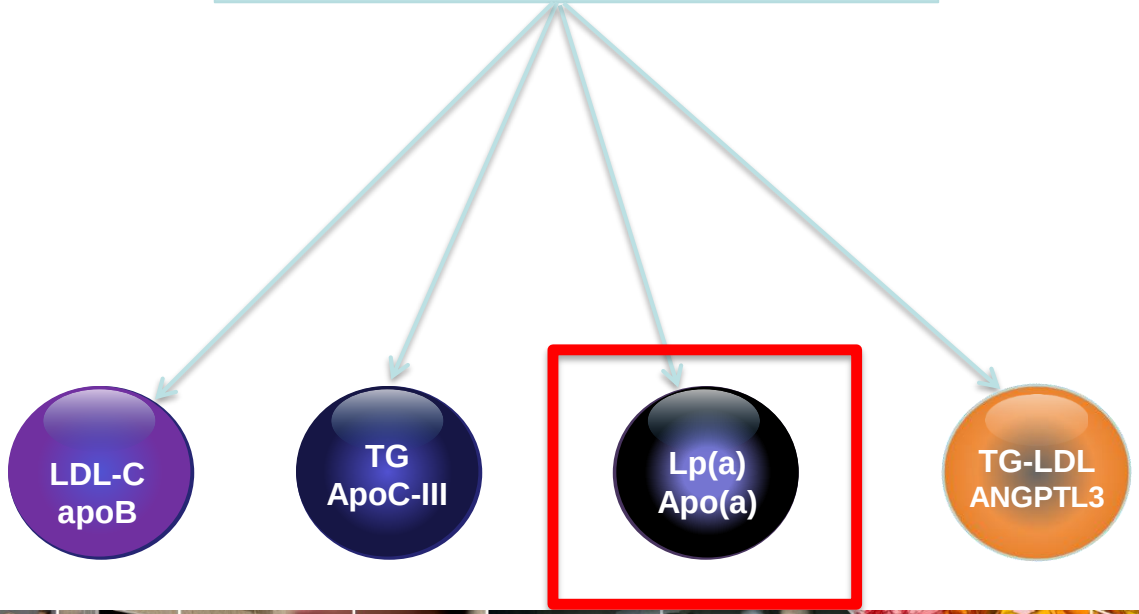
# Lipoprotein(a) = LDL + apo(a) tail + OxPls



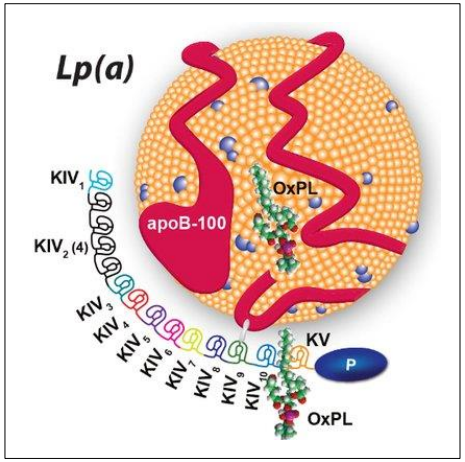




# Lipoprotein Targets in Preventing and Treating Cardiovascular Disease

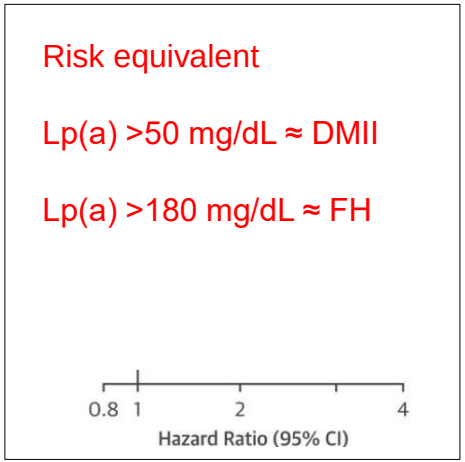
## Genetically Validated Targets



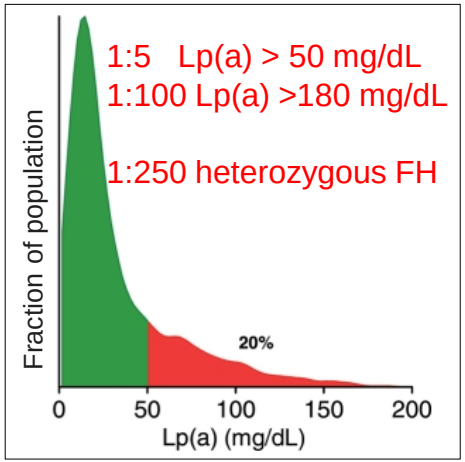

# Lp(a) elevation is highly prevalent, causal risk factor for ASCVD




***Tsimikas, JACC, 2017***




***Kamstrup, JAMA, 2009***

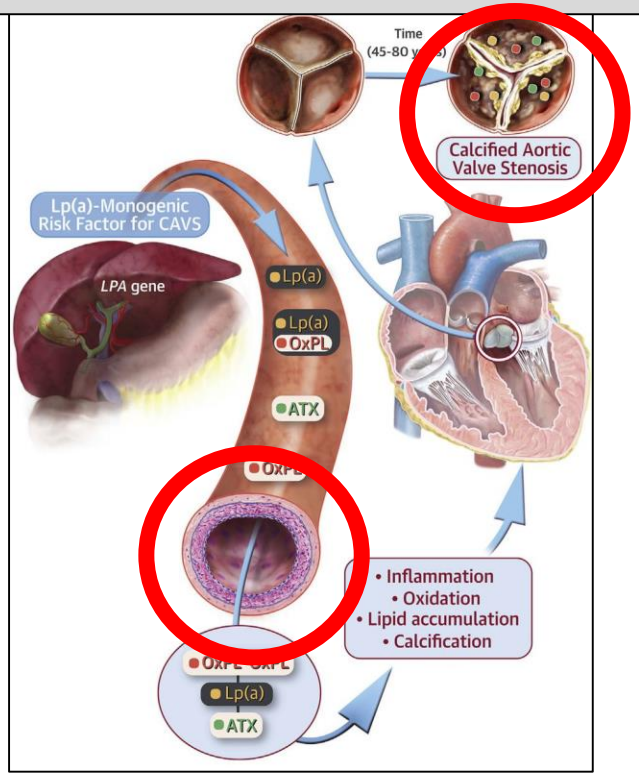



***Nordestgaard, EHJ, 2010***

FH, familial hypercholesterolemia; Lp(a), lipoprotein(a)

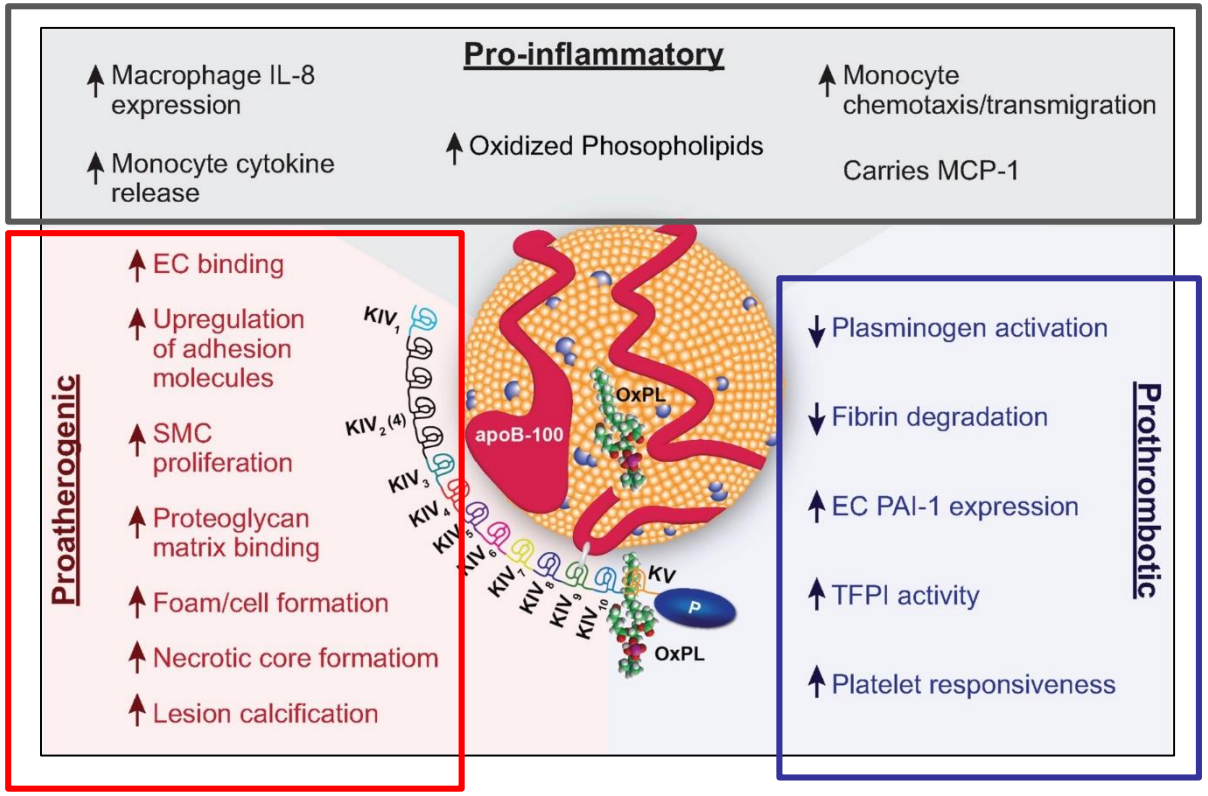
Kamstrup PR, et al. *JAMA*. 2009;301:2331-9; Nordestgaard BG, et al. *Eur Heart J*. 2010 Dec; 31: 2844–2853; Tsimikas S. *J Am Coll Cardiol*. 2017;69:692-711.

# Lp(a) is associated with atherosclerosis ánd calcified aortic valve stenosis



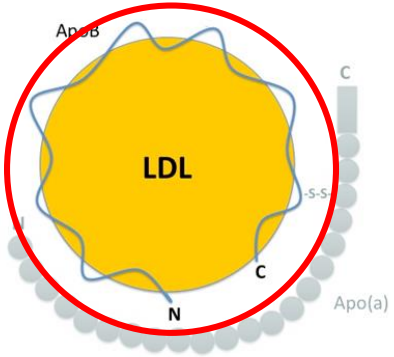

Torzewski, M. et al. J Am Coll Cardiol Basic Trans Science (2017). 2(3):229-41

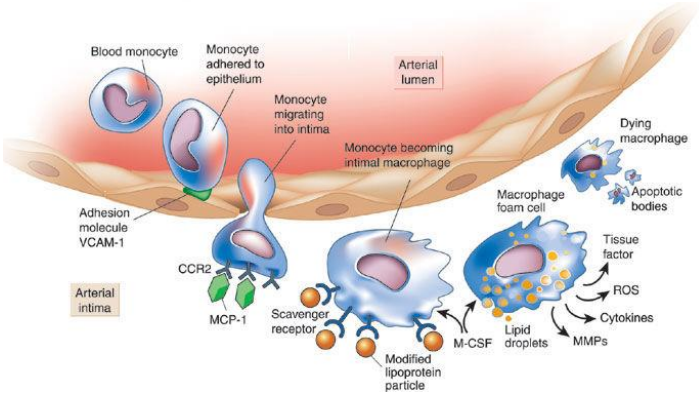
# Pathogenic mechanisms of Lp(a)

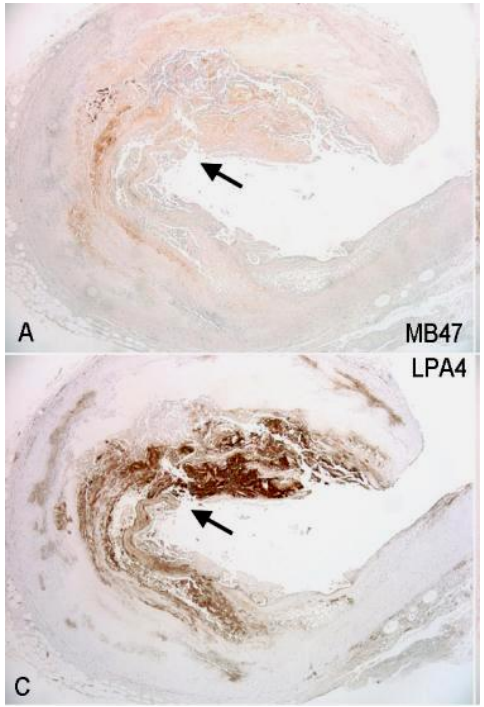



Tsimikas S. JACC (2017). 69(6):692-711

# 1. Lp(a) atherogenic trough it's LDL moiety
## → *accumulation in atherosclerotic plaques*

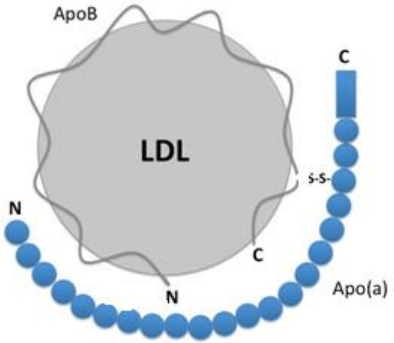


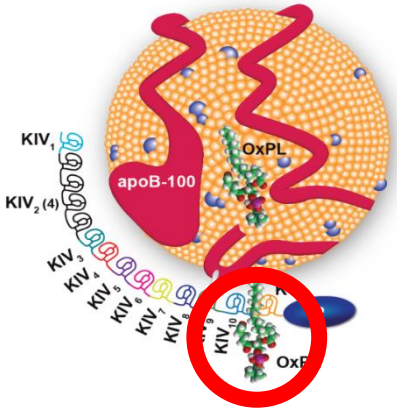



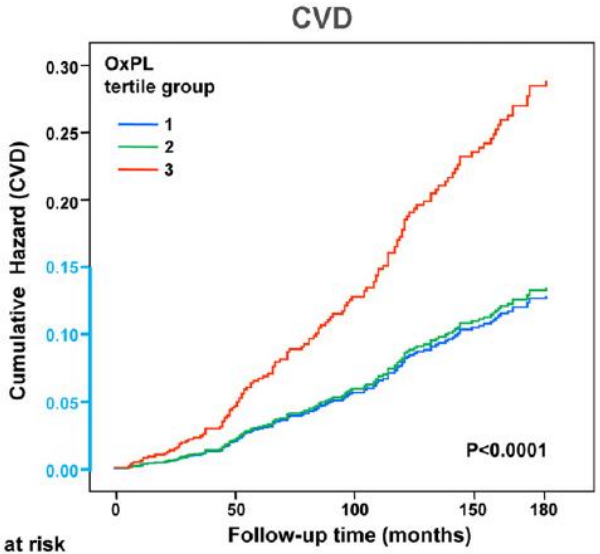




Libby. Nature (2002). 420, 868-874 / Van Dijk et al. JLR (2012). 53, 2773-2790.

# 2. Lp(a) also atherogenic via apo(a) tail / OxPL



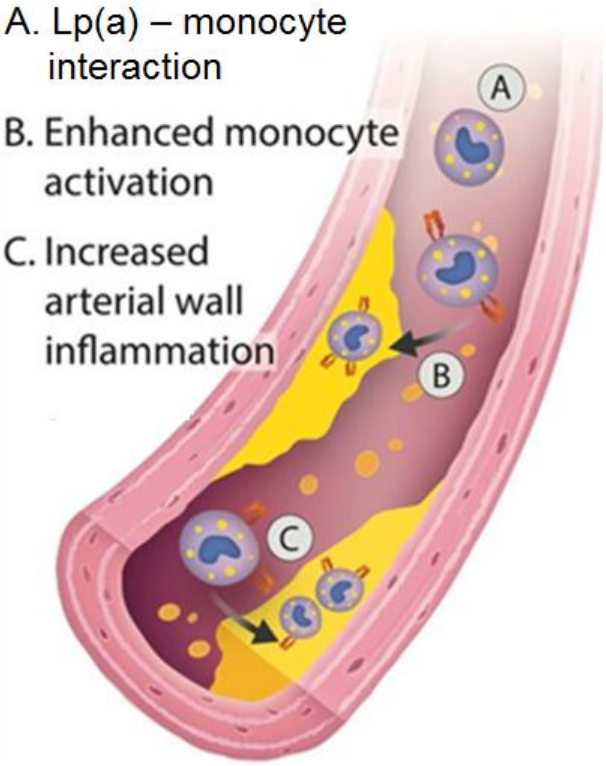




**No. at risk**

| OxPL tertile | | | | | |
|---|---|---|---|---|---|
| Lowest | 255 | 224 | 198 | 175 | 163 |
| Middle | 255 | 228 | 195 | 171 | 158 |
| Highest | 255 | 223 | 194 | 157 | 145 |

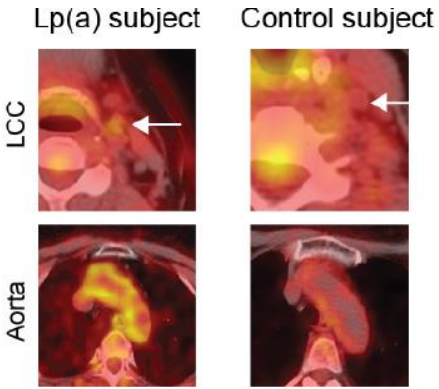
Tsimikas S. JACC (2012).

# OxPls on Lp(a) induce a systemic pro-inflammatory response



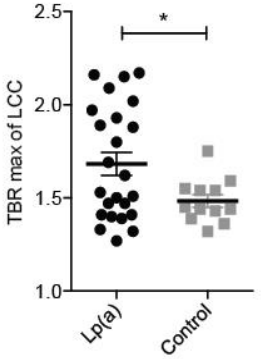

Bernelot Moens et al, Eur hrt J, 2017 & vd Valk et al, Circulation 2016

# Lp(a) patients have increased vessel wall inflammation measured with 18F-FDG PET/CT-scan




18F-FDG PET/CT-scan

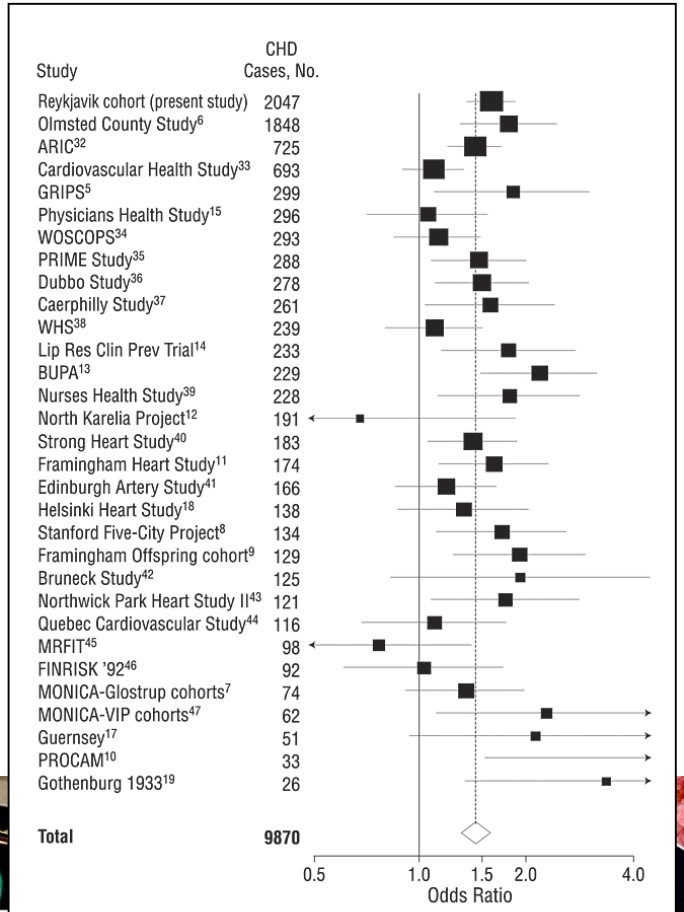
**Yellow** = metabolic activity




| Characteristic | Healthy controls (n=30) | Subjects with elevated lp(a) (n=30) |
|---|---|---|
| Age, y | 53±12 | 52±11 |
| Gender, %male | 45 (9) | 43 (15) |
| BMI | 24±4 | 24±3 |
| **Lp(a), mg/dl** | **7[2-28]** | **108[50-195]** |
| Total cholesterol | 5.21±0.83 | 5.79±1.44 |
| LDL-c | 2.91±0.8 | 2.80±1.16 |
| HDL-c | 1.68±0.42 | 1.60±0.40 |
| Triglycerides | 0.8[0.24-2.18] | 0.82[0.39-2.16] |

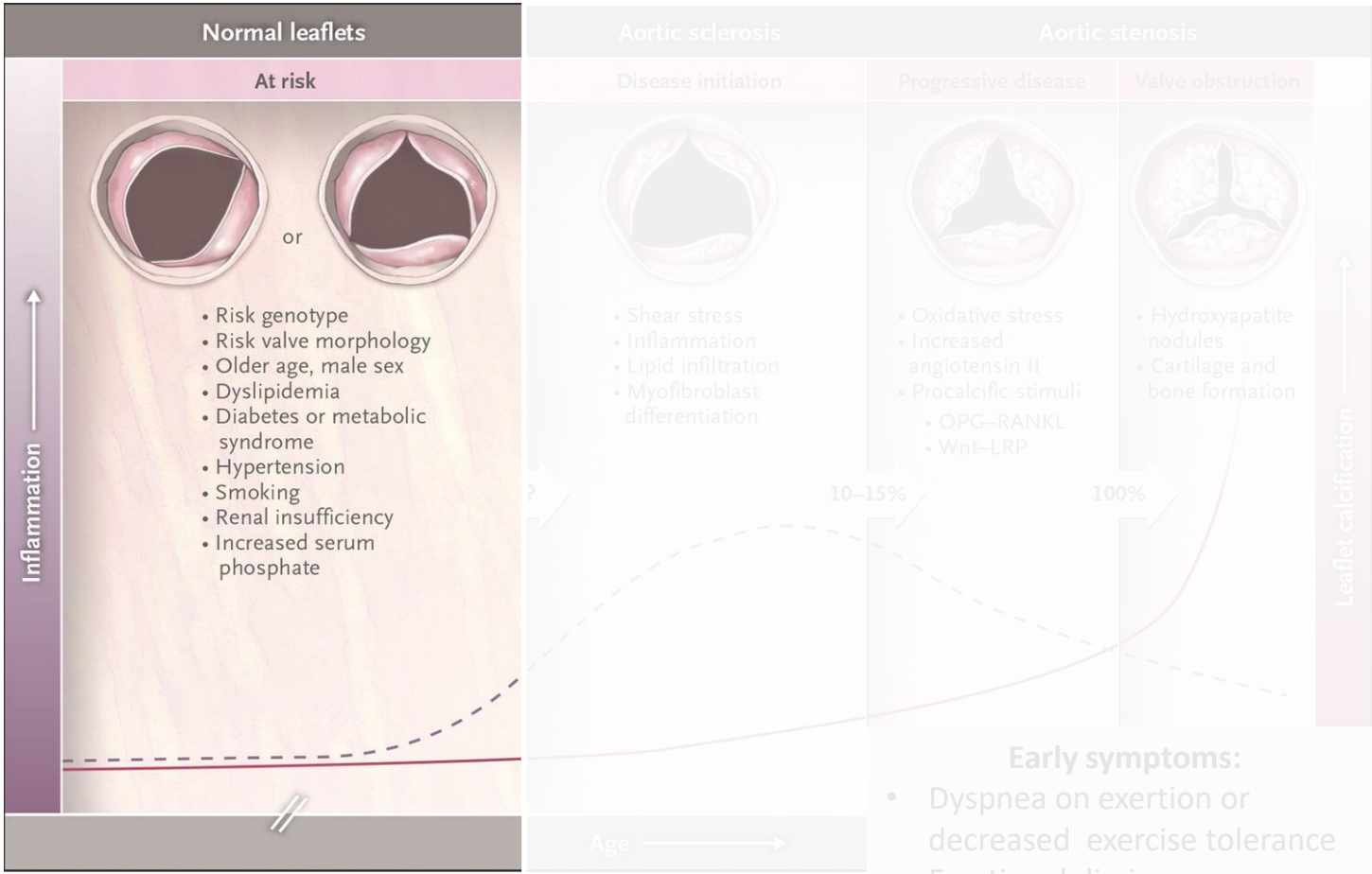
Van Der Valk et al. Circ 2016. 134(8):611-24

# Meta-analysis of Lp(a) and CV-risk in 31 prospective studies




Bennet, Ann Int Med 2012

# Calcific aortic valve disease (CAVD)

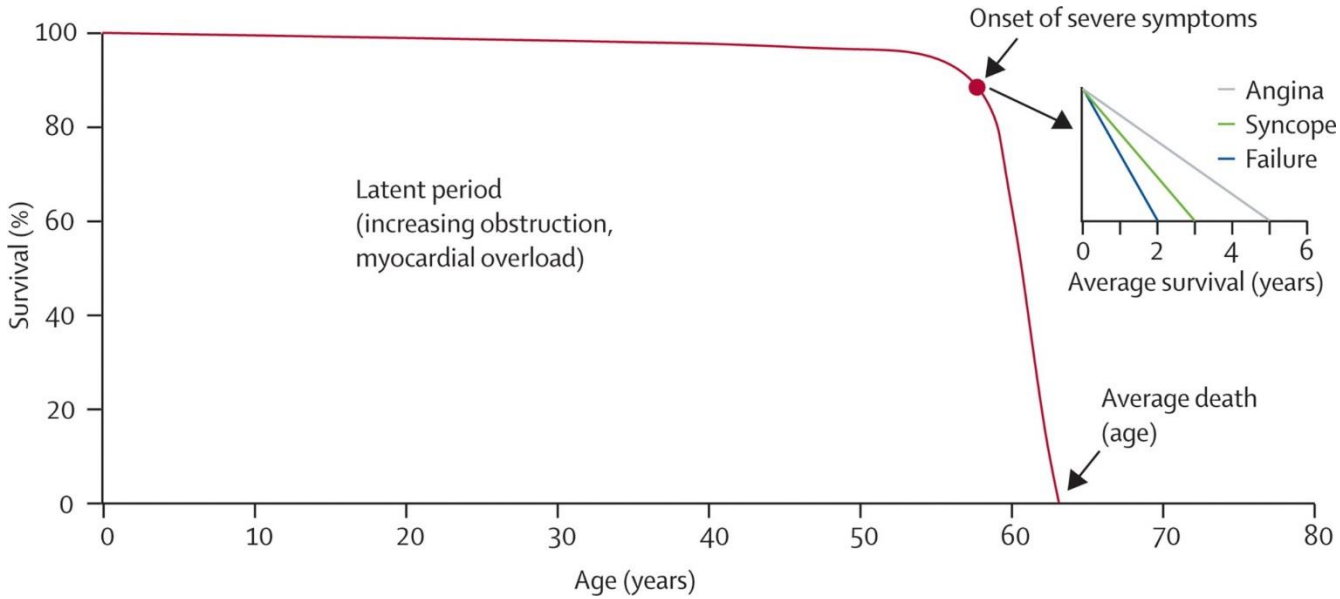



**Early symptoms:**

- Dyspnea on exertion or decreased exercise tolerance
- Exertional dizziness or syncope
- Exertional angina pectoris

Otto CM, Prendergast B. N Engl J Med 2014;371:744-756.

# Symptomatic aortic stenosis has mortality rate of 25% per year!




Carabello – Lancet 2009

Stewart – JACC 1997

**Table 3.** Clinical Factors Associated With Aortic Stenosis or Sclerosis by Stepwise Multiple Logistic Regression

| Variable | p Value | Odds Ratio | 95% Confidence Limits |
|---|---|---|---|
| Age | <0.001 | 2.18* | 2.15, 2.20 |
| Male gender | <0.001 | 2.03 | 1.7, 2.5 |
| Lp(a) | <0.001 | 1.23† | 1.14, 1.32 |
| Height (cm) | 0.001 | 0.84‡ | 0.75, 0.93 |
| History of hypertension | 0.002 | 1.23 | 1.1, 1.4 |
| Present smoking | 0.006 | 1.35 | 1.1, 1.7 |
| LDLc (mg/dl) | 0.008 | 1.12† | 1.03, 1.23 |

*± 75th vs. 25th percentile. †± 10-year increase. ‡± 10-unit increase. LDLc = low density lipoprotein cholesterol; Lp(a) = lipoprotein(a).

What about treatment?

Same risk factors as atherosclerosis…

…however, statin trials did not improve CAVD!

**Table 1** | Summary of studies involving statins to treat CAVD

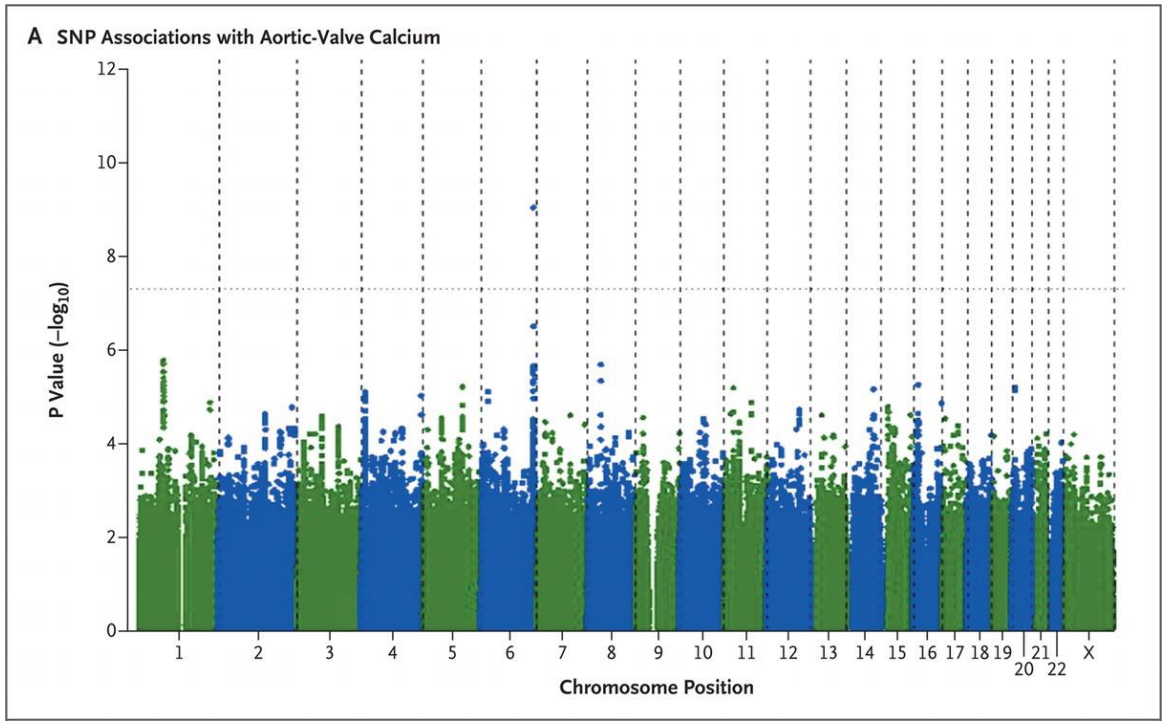
| Study (year) | Participants | Outcomes |
|---|---|---|
| Retrospective study (2001)[73] | 180 participants aged >60 years | Significant decrease in peak systolic pressure gradient (a marker of aortic valve function) in patients taking statins |
| Retrospective study (2001)[75] | 174 patients with mild-to-moderate CAVD (57 statin-treated, 117 not taking statins) | Patients taking statins had a slight improvement in aortic valve remodelling |
| Prospective analysis (2002)[82] | 156 patients (38 statin-treated, 118 not receiving any lipid-lowering treatment) | Patients taking statins had a slight improvement in aortic valve area |
| SALTIRE trial (2005)[83] | Randomized, double-blind trial of 155 patients given atorvastatin or placebo (mean follow-up 25 months) | No significant difference in aortic jet velocity or valve calcification between atorvastatin and placebo |
| RAAVE trial (2007)[74] | Prospective study of 121 patients with moderate-to-severe CAVD (61 patients received rosuvastatin, 60 received no treatment) | Statin treatment seemed to slow haemodynamic progression of CAVD, as indicated by changes in aortic jet velocity |
| SEAS trial (2008)[84] | Randomized, double-blind trial of 1,873 patients with mild-to-moderate asymptomatic aortic stenosis receiving either simvastatin or placebo daily | Statin treatment did not reduce cardiovascular events associated with CAVD |
| SEAS follow-up (2010)[85] | 1,763 patients from the SEAS trial divided into tertiles according to CAVD severity on the basis of peak aortic jet velocity | Statins did not improve CAVD outcomes regardless of initial severity of disease |
| ASTRONOMER trial (2010)[86] | Randomized, double-blind trial of 269 patients given rosuvastatin or placebo | Statin treatment did not reduce deterioration in peak aortic pressure gradient |

Abbreviation: CAVD, calcific aortic valve disease.

The NEW ENGLAND JOURNAL of MEDICINE

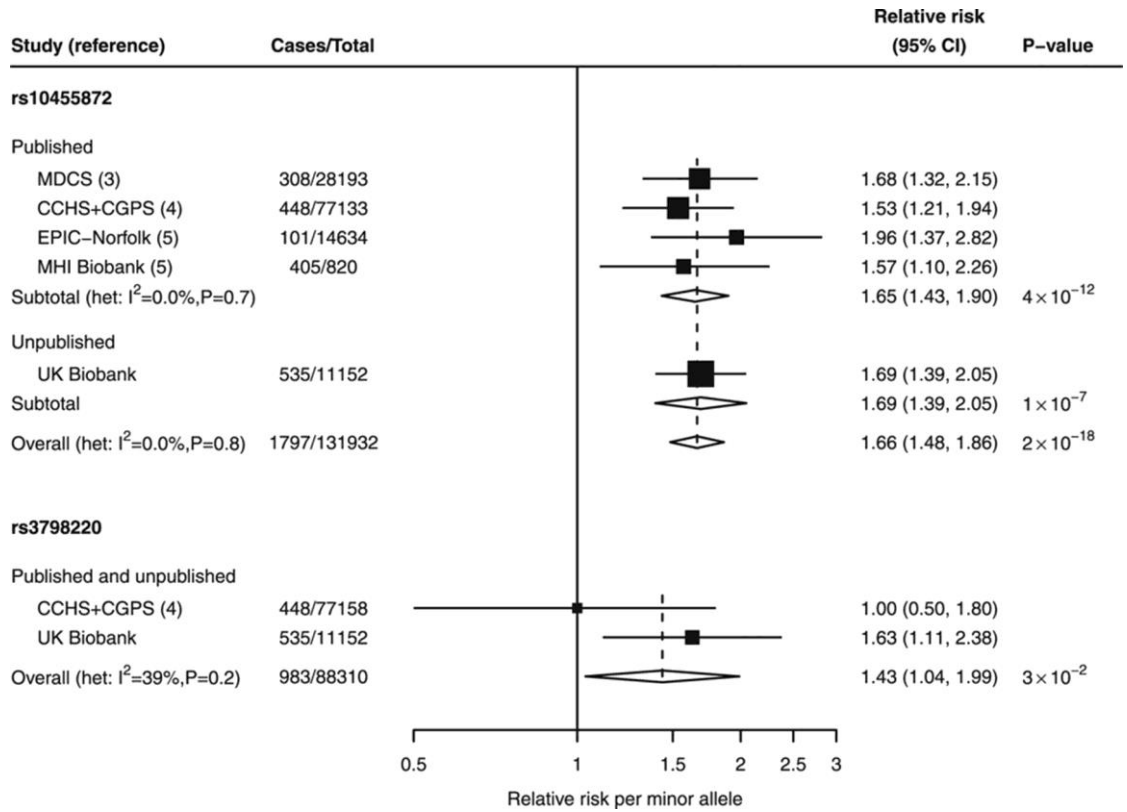
ESTABLISHED IN 1812 FEBRUARY 7, 2013 VOL. 368 NO. 6

# Genetic Associations with Valvular Calcification and Aortic Stenosis



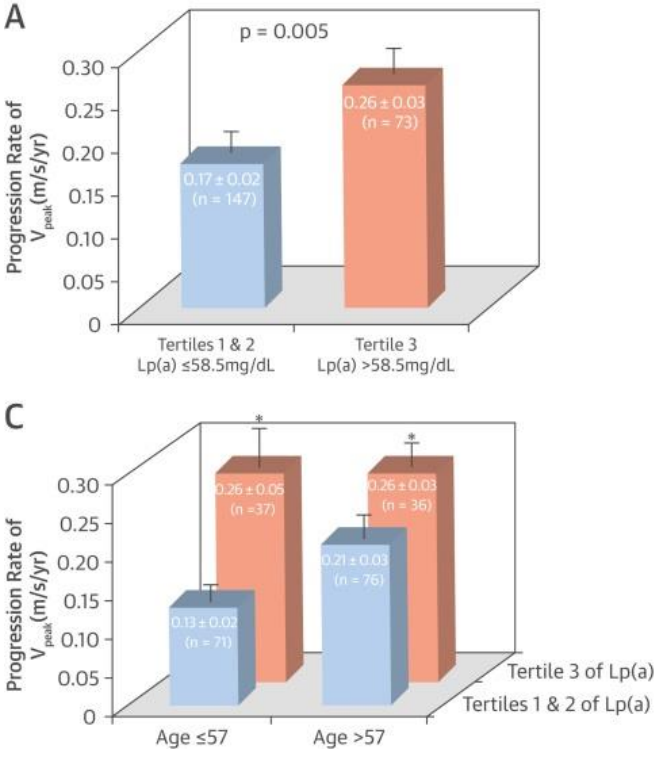

Thanassoulis – NEJM 2013

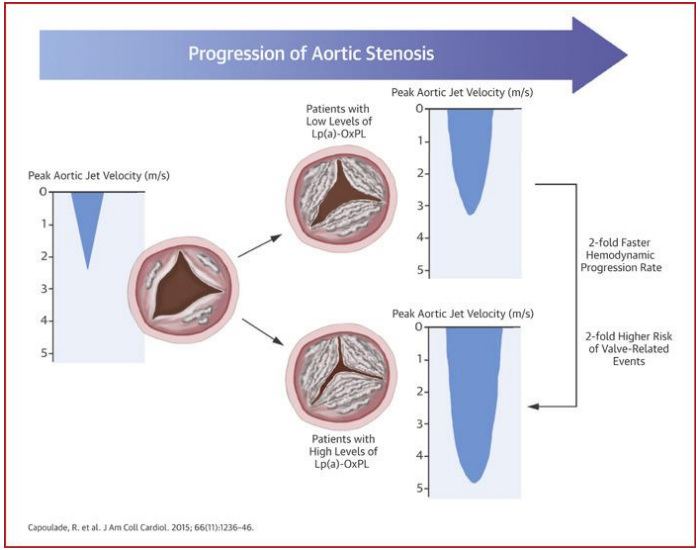
# LPA polymorphisms associated with aortic stenosis

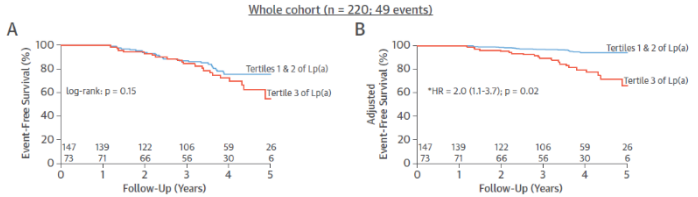



Cairns – Circulation 2017

# Elevated Lp(a) is associated with 2-fold faster progression of mild-moderate aortic stenosis



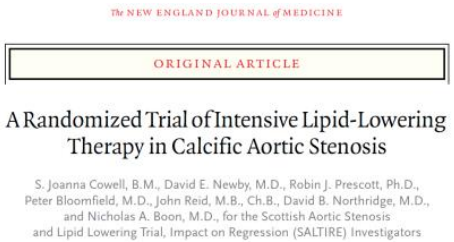




Capoulade – JACC 2015

**Impact of Lp(a) in outpatient clinic AS**
*Combining SALTIRE and RING-of-Fire studies*

- SALTIRE-1 (statin trial)
  - 155 AS patients, Vmax>2.5 m/s
  - Lp(a) measured in 65 subjects
  - Hemodynamics, outcome

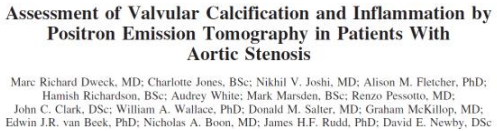
- Ring of Fire (original 18F-NaF study)
  - 81 AS patients (Vmax>2.0)
  - Lp(a) measured in 80 AS patients
  - 18F-NaF PET/CT, CT-calcium score, hemodynamics, outcome


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

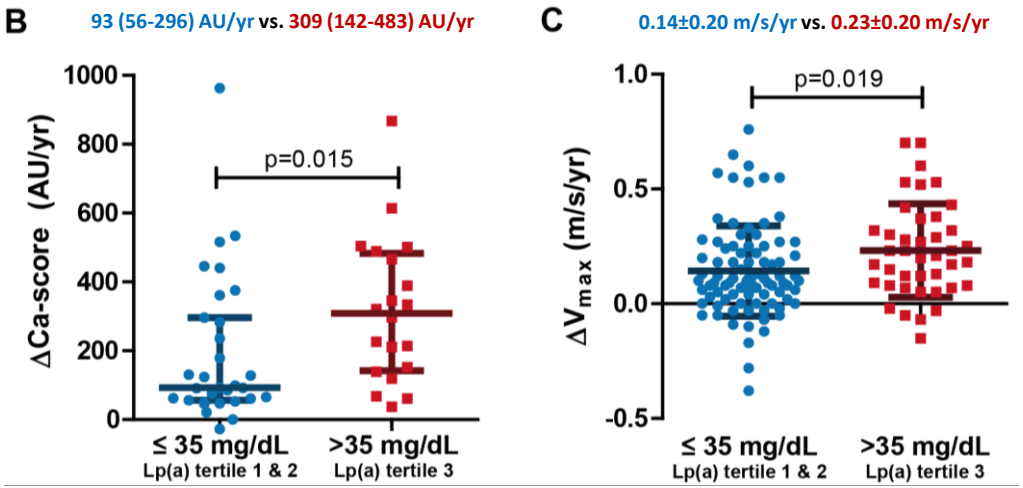
A Randomized Trial of Intensive Lipid-Lowering Therapy in Calcific Aortic Stenosis

S. Joanna Cowell, B.M., David E. Newby, M.D., Robin J. Prescott, Ph.D., Peter Bloomfield, M.D., John Reid, M.B., Ch.B., David B. Northridge, M.D., and Nicholas A. Boon, M.D., for the Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE) Investigators


Assessment of Valvular Calcification and Inflammation by Positron Emission Tomography in Patients With Aortic Stenosis

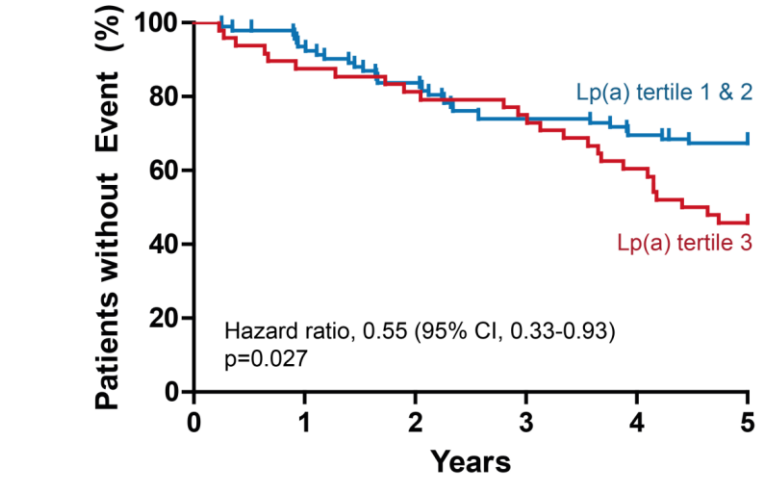
Marc Richard Dweck, MD; Charlotte Jones, BSc; Nikhil V. Joshi, MD; Alison M. Fletcher, PhD; Hamish Richardson, BSc; Audrey White; Mark Marsden, BSc; Renzo Pessotto, MD; John C. Clark, DSc; William A. Wallace, PhD; Donald M. Salter, MD; Graham McKillop, MD; Edwin J.R. van Beek, PhD; Nicholas A. Boon, MD; James H.F. Rudd, PhD; David E. Newby, DSc

# Elevated Lp(a) is associated with increased disease progression during follow-up




Zheng, Stroes, Dweck, JACC revision

# Elevated Lp(a) is associated with increased clinical outcomes




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Tertile 1 & 2 | 93 | 87 | 78 | 70 | 65 | 61 |
| Tertile 3 | 48 | 43 | 40 | 37 | 30 | 22 |

Zheng, Stroes, Dweck, JACC revision

## Summary on Lp(a) in CVD:

- Highly prevalent & relevant:

| | | |
|---|---|---|
| > 50mg/dl: | 1 : 5 patients | CV-risk 1.8 – 2.2 fold increase |
| > 180 mg/dl: | 1:100 patients | CV-risk 2.8 – 4.8 fold increase |

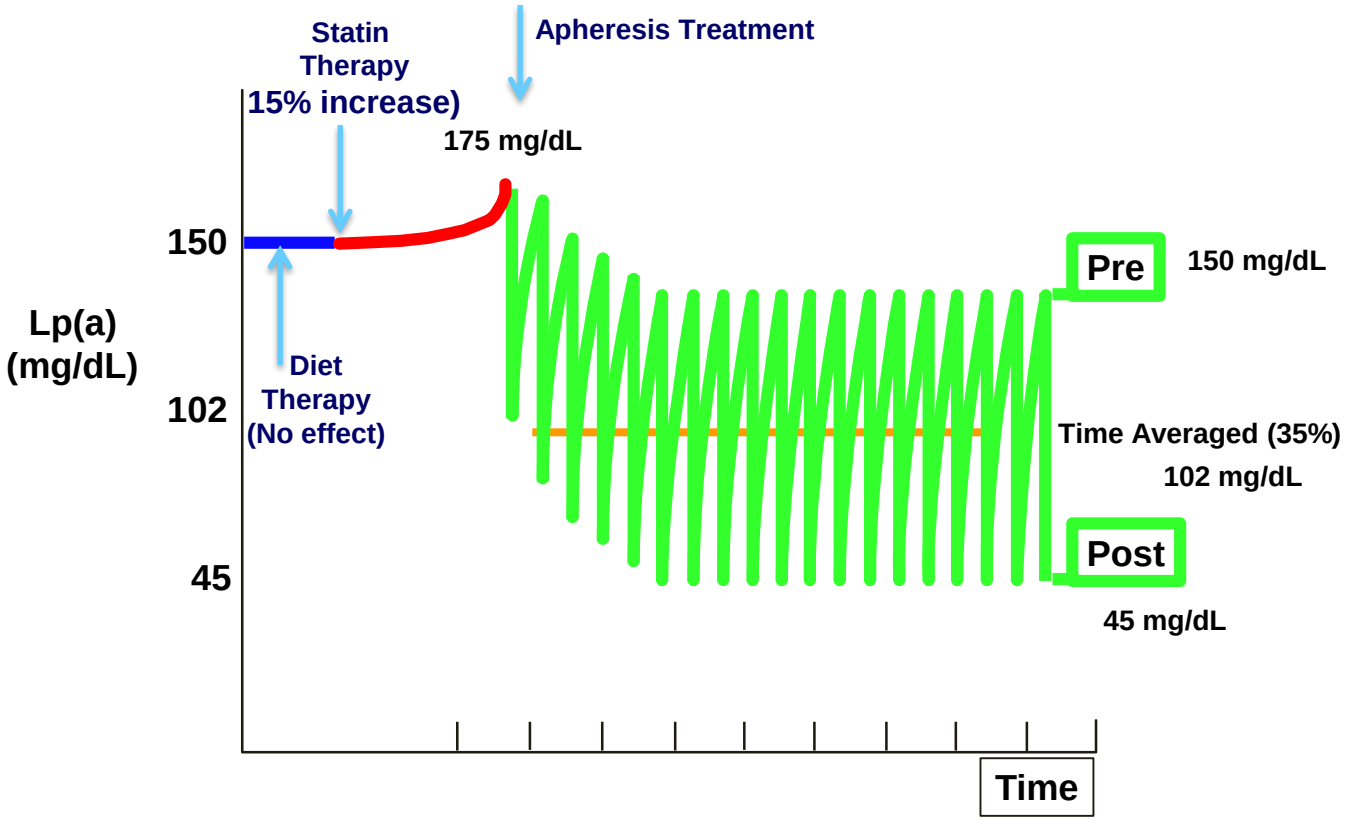
- Heavily underdiagnosed:
  < 1-2 % of all subjects ‘identified’

- No treatment option available
  no registered drug lowers Lp(a)
  efficacy of LDL-C lowering in Lp(a) subjects?

# Therapeutic agents affecting Lp(a) levels

- Increase:
  - Statins
  - Low fat diets
  - Garlic supplements
- ‘small’ decrease:
  - Niacin
  - LDL-apheresis
  - CETP-inhibition
  - apoB-antisense
  - MTP inhibitors
  - Anabolic steroids
  - aspirin

# Effect of diet, statin therapy and apheresis on Lp(a)



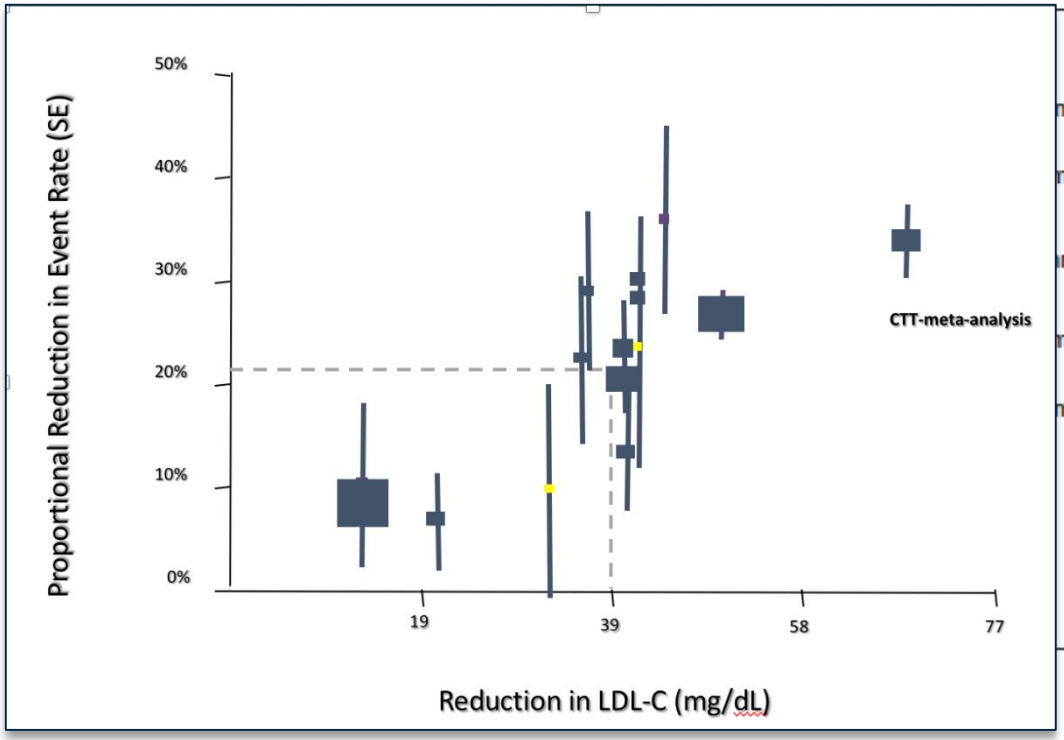
## Mean Annual Rates for MACE, ACVE, MI, PCI, and CABG for 2 Years Before (y-2, y-1) and After (y+1, y+2) Commencing Chronic lipid Apheresis and Percentage Changes (Δ) Between Periods Before and During Apheresis

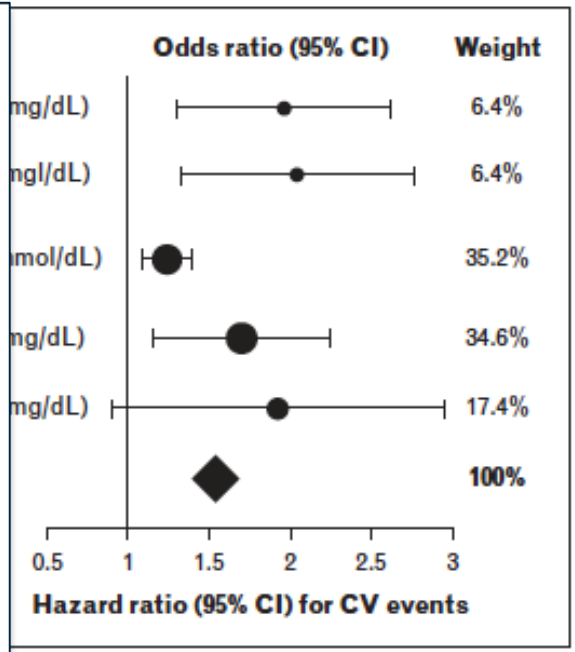
| | (y-2 + y-1) | (y+1 + y+2) | Δ, % | *P* Value |
|---|---|---|---|---|
| MACE | 0.41±0.45 | 0.09±0.22 | −78.0 | <0.0001 |
| ACVE | 0.58±0.53 | 0.14±0.31 | −75.9 | <0.0001 |
| MI | 0.14±0.24 | 0.02±0.10 | −85.7 | <0.0001 |
| PCI | 0.22±0.35 | 0.07±0.19 | −68.2 | <0.0001 |
| CABG | 0.05±0.15 | 0.01±0.05 | −80.0 | 0.001 |

ACVE indicates adverse cardiac or vascular events; CABG, coronary artery bypass graft; LA, lipoprotein apheresis; MACE, major adverse coronary events;
MI, myocardial infarction; and PCI, percutaneous coronary intervention.

Leebman et al. *Circulation 2013;128:2567–2576*

# Contribution of lp(a) to ‘residual risk’ after statin treatment

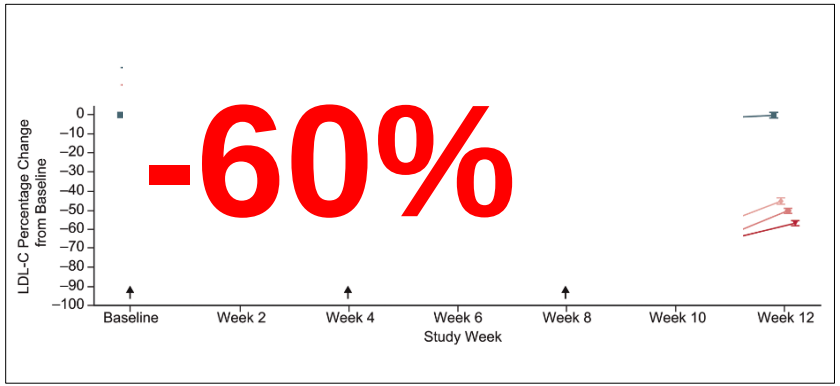


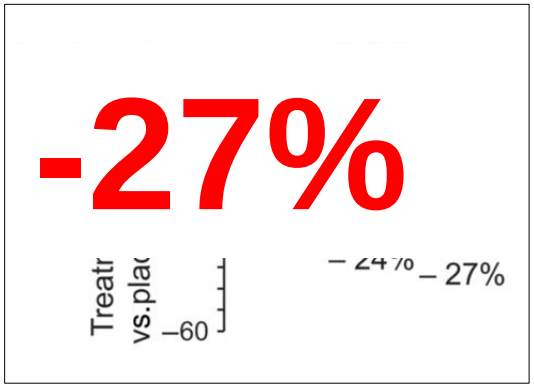

Tsimikas, JCEM 2017

# What if we lower LDL-c and Lp(a)? Anitschkow study

Is potent LDL-C lowering, combined with modest Lp(a) lowering, with the PCSK9 antibody evolocumab able to attenuate arterial wall inflammation in patients with markedly elevated Lp(a)?




***Stein, EHJ, 2014***




***Stein, EHJ, 2014***

PCSK9, proprotein convertase subtilisin/kexin type 9; SC, subcutaneous; Q2W, every 2 weeks; Q4W, every 4 weeks
Stein EA, et al. *Eur Heart J.* 2014;35:2249–2259.

Stiekema, Stroes, et al. Eur Heart J 2019

# Effect of Evolocumab on Lipids

| | Evolocumab (n=65) | Placebo (n=64) |
|---|---|---|
| **Lipid levels – absolute change**[a] | | |
| Total cholesterol, mmol/L | -2.2 (0.8) | 0.0 (0.6) |
| HDL-cholesterol, mmol/L | 0.1 (0.2) | 0.0 (0.2) |
| LDL-cholesterol, mmol/L | -2.2 (0.8) | 0.0 (0.6) |
| LDL-cholesterol corrected for Lp(a), mmol/L | -2.1 (0.8) | 0.0 (0.5) |
| Triglycerides, mmol/L | -0.3 (0.4) | -0.0 (0.5) |
| Lp(a), nmol/L | -28.0 (-56.5, 9.0) | 1.5 (-19.0, 18.0) |
| ApoB, g/L | -0.5 (0.2) | 0.0 (0.1) |
| **Lipid levels – LS mean percent change (95% CI)** | | |
| LDL-cholesterol, % | -59.0 (-62.6, -55.4) | 1.6 (-2.0, 5.3) |
| Treatment difference[b] | **-60.7 (-65.8, -55.5)** | |
| LDL-cholesterol corrected for Lp(a) | -74.53 (-79.69, -69.36) | 1.23 (-4.03, 6.50) |
| Treatment difference[b] | -75.76 (-83.13, -68.39) | |
| Lp(a), % | -12.8 (-16.6, -9.0) | 1.1 (-2.8, 4.9) |
| Treatment difference[b] | **-13.9 (-19.3, -8.5)** | |
| ApoB | -48.3 (-51.3, -45.3) | 3.3 (0.3, 6.3) |
| Treatment difference[b] | -51.6 (-55.9, -47.3) | |
| Total cholesterol | -37.99 (-40.59, -35.38) | 0.83 (-1.82, 3.48) |
| Treatment difference[b] | -38.82 (-42.53, -35.10) | |
| HDL-cholesterol | 9.31 (5.66, 12.95) | 0.00 (-3.72, 3.73) |
| Treatment difference[b] | 9.30 (4.09, 14.52) | |
| Triglycerides | -16.45 (-22.67, -10.22) | -0.06 (-6.43, 6.30) |
| Treatment difference[b] | -16.38 (-25.29, -7.48) | |

**-61%**

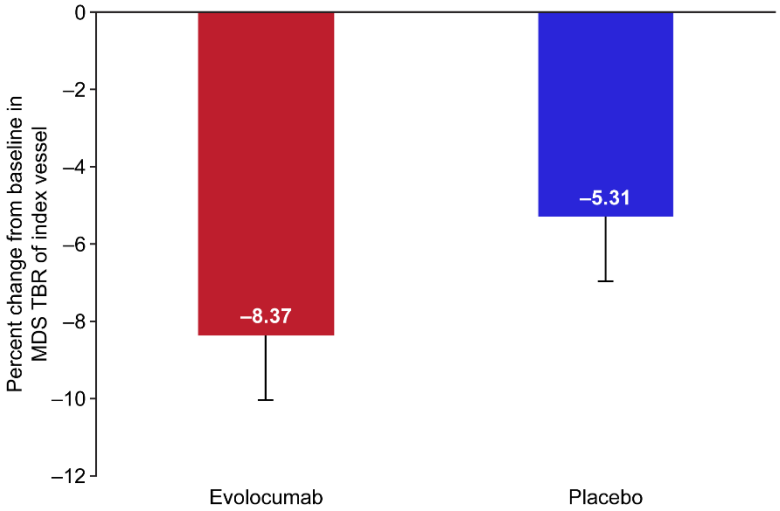
**-14%**

ApoB, apolipoprotein B; HDL, high-density lipoprotein

[a]*Values are mean (SD) with the exception of Lp(a), which is median (IQR).*
[b]*P<0.0001 for evolocumab vs placebo*

Stiekema, Stroes, et al. Eur Heart J 2019

# *Effect of Evolocumab on Arterial Wall Inflammation*




We expected a ~3.3% reduction in arterial wall inflammation for every 10% reduction in LDL-C

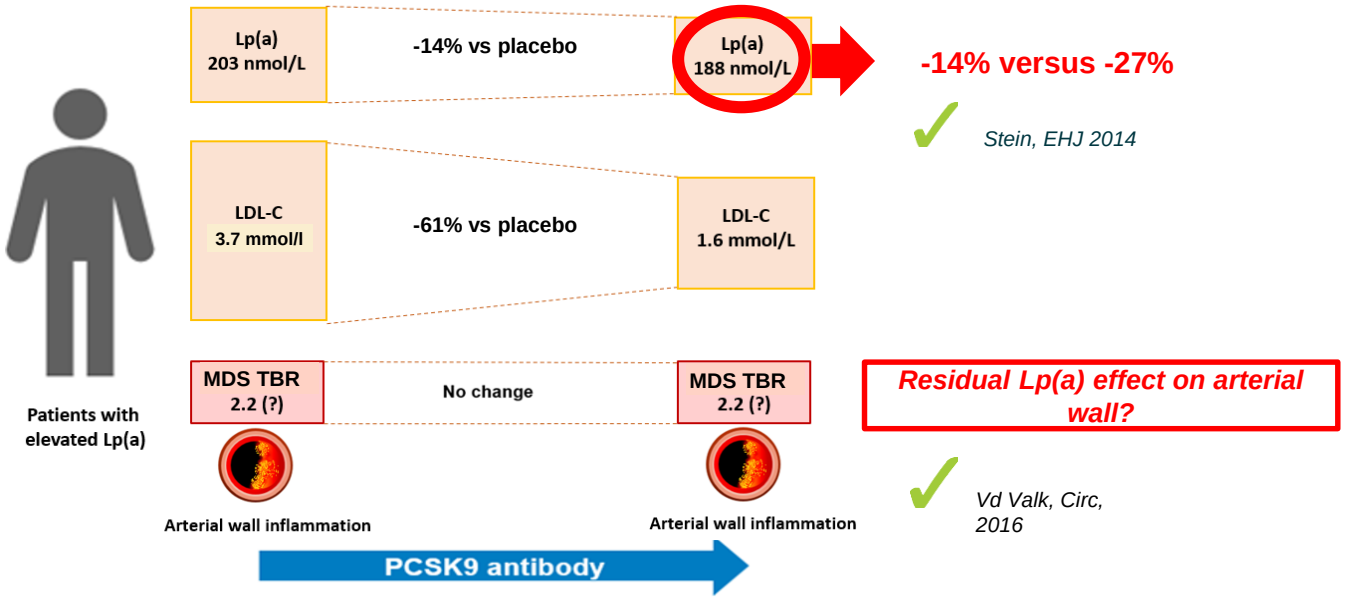
3.3 × 6 = 19.8% MDS TBR reduction expected

Mean of the Maximum MDS TBR of the Index Vessel, %

| | Evolocumab | Placebo |
|---|---|---|
| LS mean percent change from baseline (95% CI) | −8.3 (−11.6, −5.0) | −5.3 (−8.6, −2.0) |
| Treatment difference (evolocumab–placebo) (95% CI) | **−3.0 (−7.4, 1.4)** | |
| *P*-value | **.18** | |

Stiekema, Stroes, et al. Eur Heart J 2019

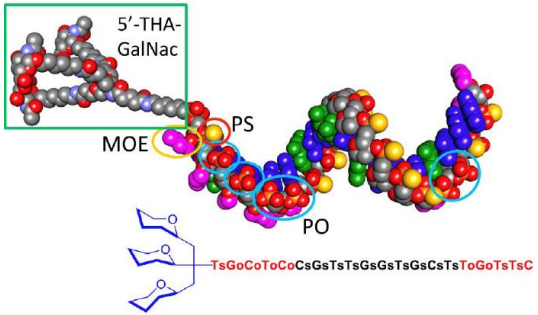
# *Evolocumab has no effect on arterial wall Inflammation in patients with elevated Lp(a)*




Stiekema, Stroes, et al. Eur Heart J 2019

# More potent and specific Lp(a) lowering is needed: AKCEA-APO(a)-$L_{Rx}$ (ISIS 681257)

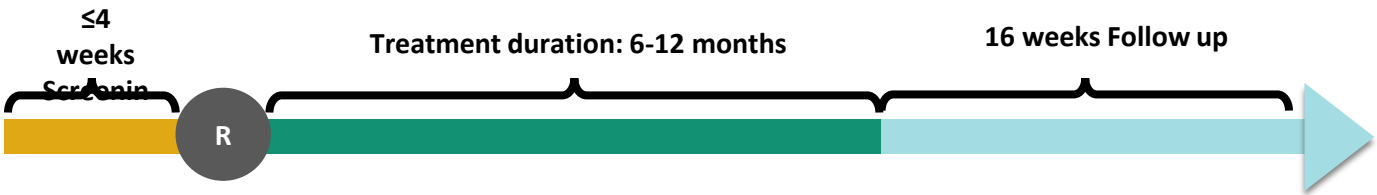
- **AKCEA-APO(a)-$L_{Rx}$ is an antisense oligonucleotide (ASO) that mediates cleavage of apolipoprotein(a) mRNA in hepatocytes through an RNaseH1 mechanism, leading to lower plasma Lp(a) levels**
- **It is a 2' methoxyethyl ASO containing a triantennary N-acetyl-galactosamine (GalNac) ligand binding to the asialoglycoprotein receptor of hepatocytes that leads to enhanced cellular uptake**
- **This approach results in 30-fold higher potency compared with non-GalNac ASOs, thus allowing lower doses/dose intervals for similar therapeutic efficacy***
- **A phase 1 trial with AKCEA-APO(a)-$L_{Rx}$ in healthy volunteers with elevated Lp(a) showed a dose dependent, mean 68–92% reduction in plasma Lp(a)***




ISIS 681257 contains 20 nucleic acids, 13 phosphorothioate (PS) linkages, 6 phosphodiester (PO) linkages and the GalNAc3 complex linked to the 5' end of the ASO with a THA linker.

* Viney, Stroes, Tsimikas, et al Lancet 2016; 388:2239-53.

# Study Design and Endpoints




**Five cohorts*,**
**N per cohort=54, randomized 5:1**
**(45 active, 9 placebo)**

***Cohorts (SC administration):**
20 mg AKCEA-APO(a)-$L_{Rx}$ or placebo Q4W
40 mg AKCEA-APO(a)-$L_{Rx}$ or placebo Q4W
60 mg AKCEA-APO(a)-$L_{Rx}$ or placebo Q4W
20 mg AKCEA-APO(a)-$L_{Rx}$ or placebo Q2W
20 mg AKCEA-APO(a)-$L_{Rx}$ or placebo QW

**The primary endpoint was the mean percent change in Lp(a) from baseline at the primary analysis timepoint of 25–27 weeks depending on dose regimen**

**Secondary endpoints included:**

- **Mean percent change from baseline in LDL-C, apoB, OxPL-apoB, OxPL-apo(a) plasma levels**
- **Number of patients reaching pre-specified thresholds of <50 mg/dL (<125 nmol/L)**

**QW = every week; Q2W = every 2 weeks; Q4W = every 4 weeks; R = randomization; SC = subcutaneous.**

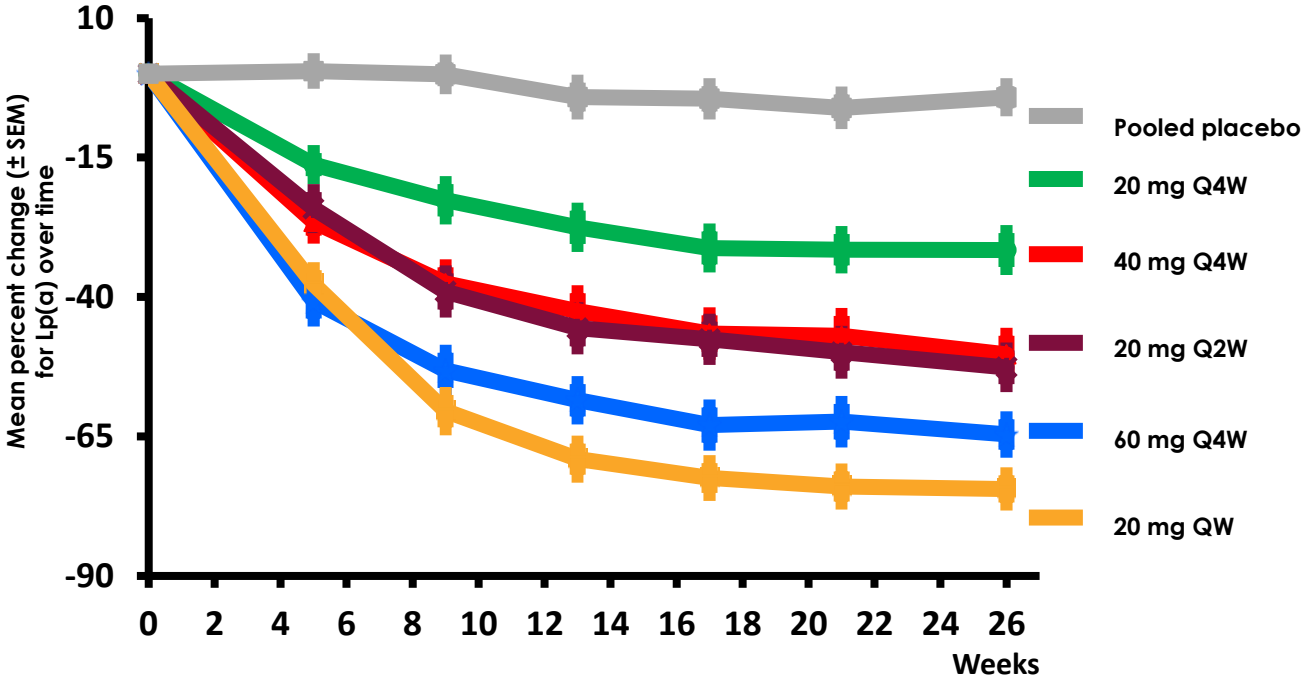
Tsimikas, Stroes et al. AHA 2018

# Baseline laboratory variables

| | AKCEA-APO(a)-$L_{Rx}$ dose/regimen | | | | | | |
|---|---|---|---|---|---|---|---|
| | 20 mg/Q4W N=48 | 40 mg/Q4W N=48 | 20 mg/Q2W N=48 | 60 mg/Q4W N=47 | 20 mg/QW N=48 | Pooled Rx N=239 | Pooled Placebo N=47 |
| Lp(a), nmol/L, Mean/Median | 279.7/247 | 236.6/220 | 250.6/238 | 233.9/205 | 248.2/234 | 249.9/224 | 258.2/232 |
| Lp(a), mg/dL, estimated Mean, median | 111.9/98.6 | 94.7/88.0 | 100.3/95.3 | 93.6/81.8 | 99.3/93.5 | 100.0/89.7 | 103.3/92.6 |
| LDL, mg/dL, mean (SD) | 89.3 (37.1) | 77.4 (39.5) | 74.4 (28.8) | 67.6 (28.3) | 76.1 (28.4) | 77.0 (33.3) | 79.4 (29.2) |
| ApoB, mg/dL, mean (SD) | 80.7 (23.6) | 71.9 (23.4) | 69.3 (19.8) | 68.5 (18.8) | 70.6 (19.2) | 72.2 (21.3) | 73.8 (16.9) |
| Triglycerides, mg/dL, median (IQR) | 97 (44, 230.3) | 97 (35, 283) | 106 (35, 204) | 106 (53, 567) | 89 (35, 266) | 97 (35, 567) | 106 (35, 576) |
| OxPL-apoB, nmol/L, median (IQR) | 24.6 (18.1, 33.1) | 23.1 (16.2, 32.5) | 23.9 (17.9, 29.2) | 20.3 (16.6, 28.5) | 23.7 (17.2, 30.7) | 23.3 (17.4, 30.5) | 21.2 (17.2, 31.5) |
| OxPL-apo(a), nmol/L, median (IQR) | 66.3 (57.8, 75.0) | 65.9 (56.6, 71.9) | 67.3 (60.8, 73.2) | 61.9 (53.4, 72.7) | 67.1 (60, 74.6) | 65.8 (58.6, 73.8) | 69.2 (59.6, 76.5) |
| hsCRP, mg/L, mean (SD) | 2.9 (5.3) | 2.3 (4.5) | 1.6 (2.5) | 2 (2.5) | 2.2 (4.4) | 2.2 (4.0) | 2.4 (4.4) |

Tsimikas, Stroes et al. AHA 2018

# Primary endpoint: Mean percent change (SEM) in Lp(a) from baseline to week 25-27




Tsimikas, Stroes et al. AHA 2018

# Summary of treatment emergent adverse events (TEAE) by treatment group

| | AKCEA-APO(a)-$L_{Rx}$ dose/regimen | | | | | | |
|---|---|---|---|---|---|---|---|
| Event, N (%) | 20 mg/Q4W N=48 | 40 mg/Q4W N=48 | 20 mg/Q2W N=48 | 60 mg/Q4W N=47 | 20 mg/QW N=48 | Pooled Rx N=239 | Pooled placebo N=47 |
| At least one TEAE | 46 (95.8) | 41 (85.4) | 41 (85.4) | 43 (91.5) | 42 (87.5) | 213 (89.1) | 39 (83.0) |
| At least one related serious TEAE | 1 (2.1) | 0 (0.0) | 0 (0.0) | 1 (2.1) | 0 (0.0) | 2 (0.8) | 0 (0.0) |
| At least one TEAE leading to treatment discontinuation | 2 (4.2) | 0 (0.0) | 1 (2.1) | 3 (6.4) | 5 (10.4) | 11 (4.6) | 2 (4.3) |
| Discontinuations due to AE at injection site | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.0) | 1 (1.6) | 0 (0.0) |

TEAE, treatment-emergent adverse event

Tsimikas, Stroes et al. AHA 2018

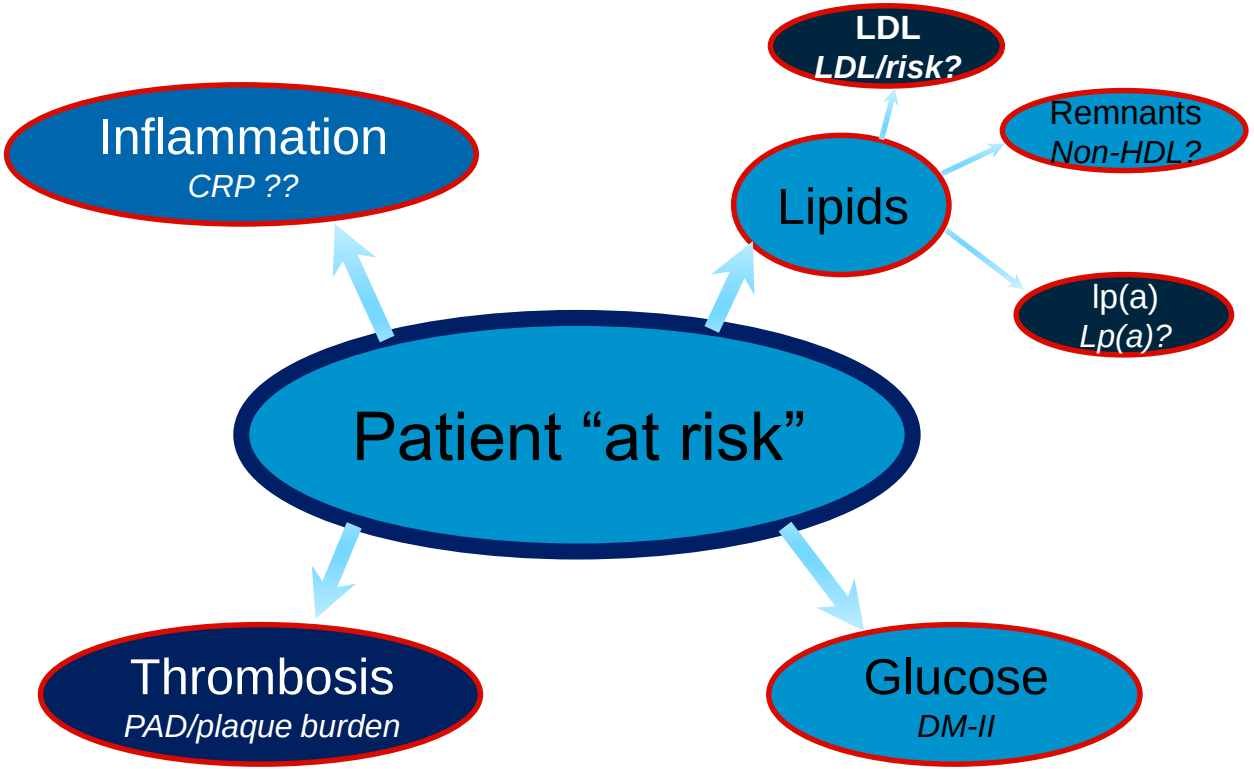
# Conclusions

- AKCEA-APO(a)-$L_{Rx}$ potently reduces Lp(a) levels in a dose-dependent manner
- At the highest dose, 97.7% of patients achieved an Lp(a) level ≤50 mg/dL the level at which Lp(a)-mediated risk has been shown to be minimal
- A favorable safety/tolerability profile was present

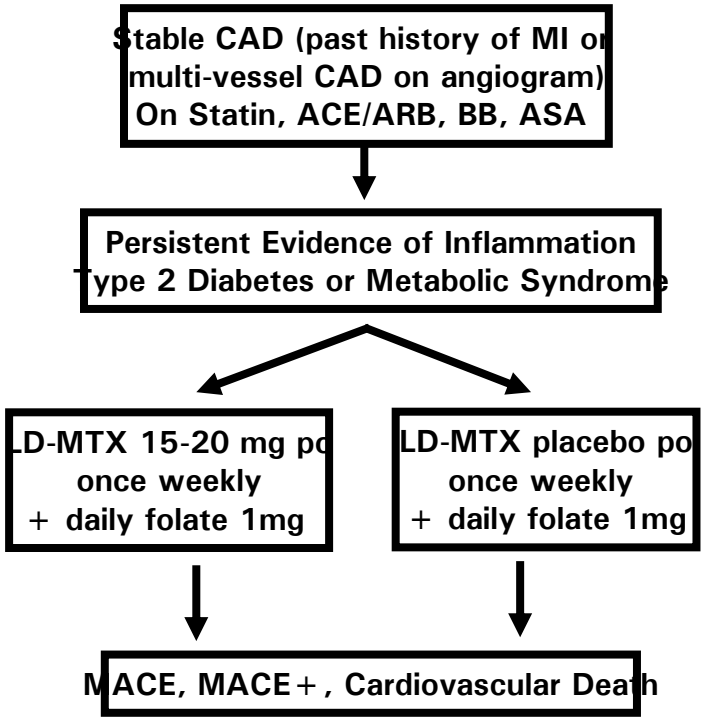
# Future CV-therapeutic regimen: *'most active pathway' per patient*

| Study | target | CVD death MI/stroke | Mortality benefit | Safety |
|---|---|---|---|---|
| ***FOURIER*** *Evolocumab* | Lipids / LDL-C | -15 - -41% *(lower LDL – higher benefit)* | CV-mortality unchanged | Very safe to lower LDL without adverse signals |
| ***CANTOS*** *Canakinumab* | Inflammation | -15 - -27% *(lower CRP – higher benefit)* | CV mortality -31% Responder selection | Fatal infections ↑ |
| ***COMPASS*** *Rivaroxaban* | Coagulation | -24% | CV-mortality -22% Stroke -42% | Major bleeds +70% Fatal bleeds n.s |
| ***PEGASUS*** *Ticagrelor* | Coagulation | -16% | CV death -12% | Major bleeds +83% Fatal bleeds n.s |
| ***EMPAREG*** *SGLT2-inh* | Glucose regulation | -14% | CV-death: -38% Hosp HF: -35% | Urinary tract infections |

# Selection of ‘additional’ therapies based on extensive fenotyping



# Cardiovascular Inflammation Reduction Trial (CIRT)
## Flow Diagram



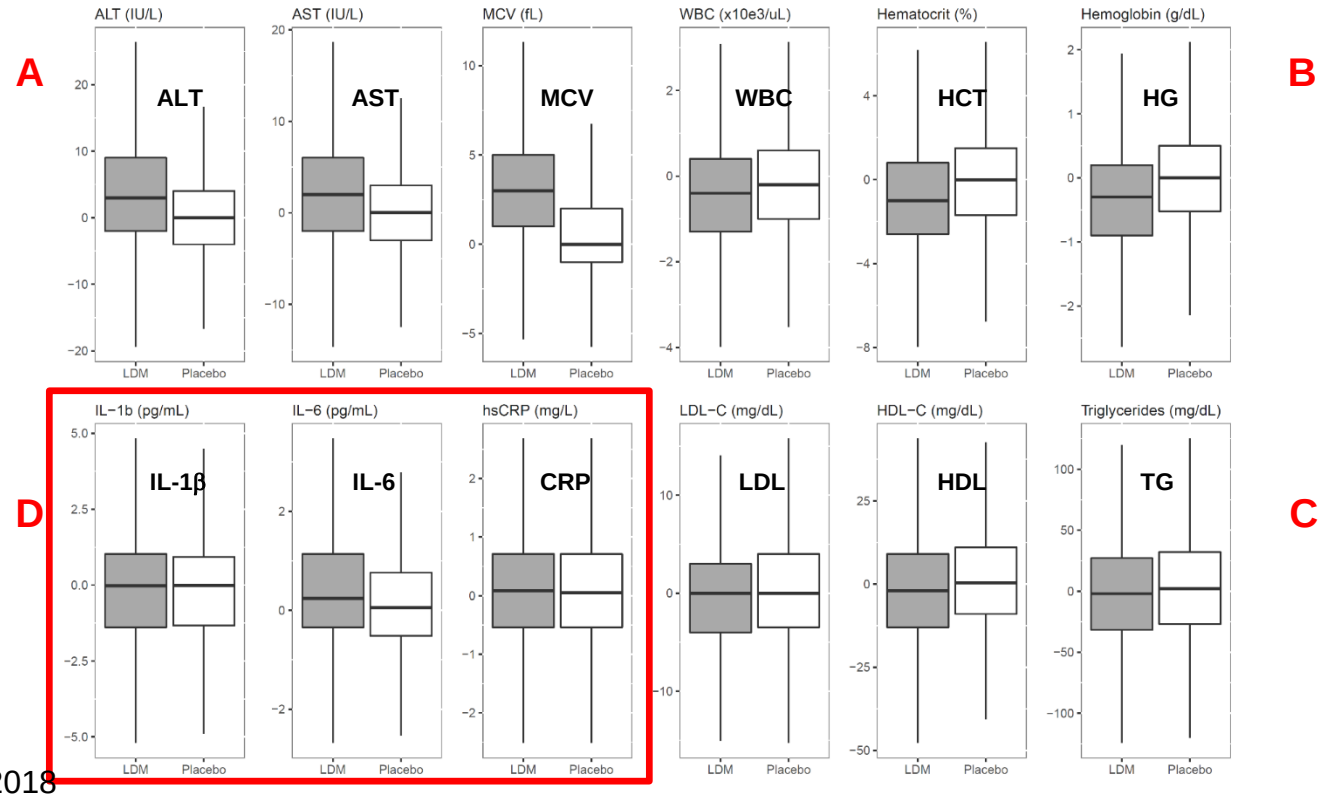

- To evaluate in a randomized, double-blind, placebo-controlled trial whether LD-MTX given at a target dose of 15 to 20 mg po weekly will reduce rates of myocardial infarction, stroke, or cardiovascular death among patients with stable coronary artery disease and either type 2 diabetes or metabolic syndrome.

417 US and Canadian Sites
4786 Patients Randomized
10 Patients Lost to Follow Up

Ridker N Engl J Med 2018

# Cardiovascular Inflammation Reduction Trial (CIRT)

Results Part 1: Low-Dose Methotrexate vs Placebo at 8 Months

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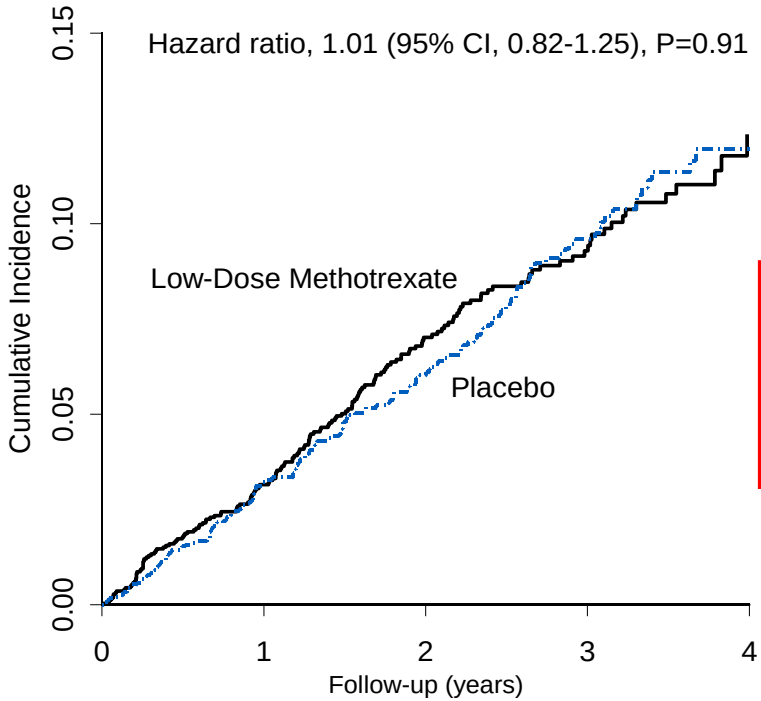
# Cardiovascular Inflammation Reduction Trial (CIRT)

## Primary Result : Major Adverse Cardiovascular Events (MACE)




No. at risk:

| | | | | | |
|---|---|---|---|---|---|
| Low-Dose Methotrexate | 2391 | 1771 | 1193 | 621 | 157 |
| Placebo | 2395 | 1745 | 1194 | 612 | 148 |

**MACE**
**N (Incidence Rate Per 100 person years)**

**170 (3.46) LD-MTX**
**167 (3.43) Placebo**

Ridker N Engl J Med 2018

CANTOS

Canakinumab Anti-inflammatory Thrombosis Outcomes Study

**Interleukin-1β Inhibition**

- ↓ IL-1β
- ↓ IL-6
- ↓ hsCRP
- ↓ 17% reduction in MACE+

---

CIRT | CARDIOVASCULAR INFLAMMATION REDUCTION TRIAL

**Low-Dose Methotrexate**

- ↔ IL-1β
- ↔ IL-6
- ↔ hsCRP
- ↔ No reduction in MACE+

# Take home message

“Lp(a) elevation is Prevalent, Relevant and Underdiagnosed”

Lp(a) measurement in:
- Patients above 50yr (both primary and secondary prevention)
- (Premature) atherosclerosis patients
- ‘Unexplained’ CVD
- Progressive disease

For questions:

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