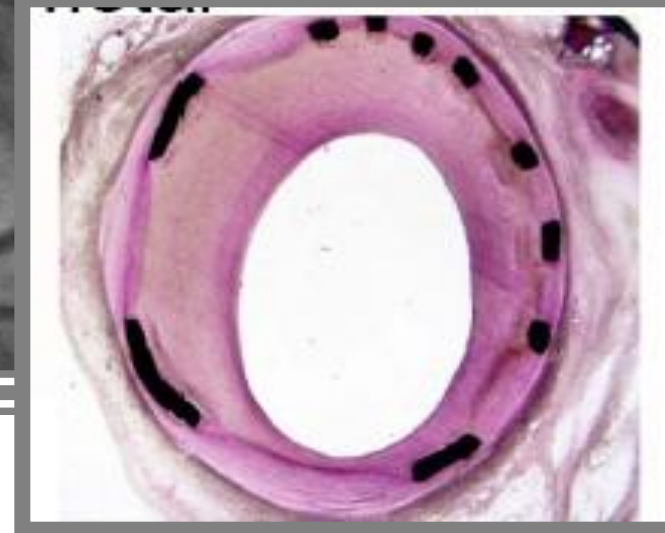
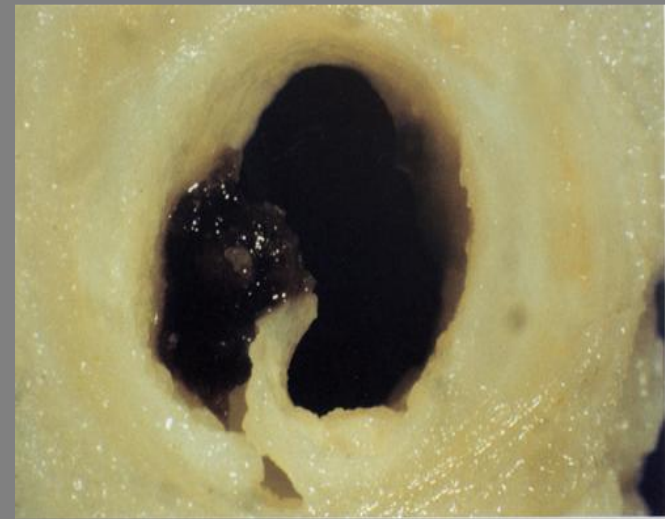
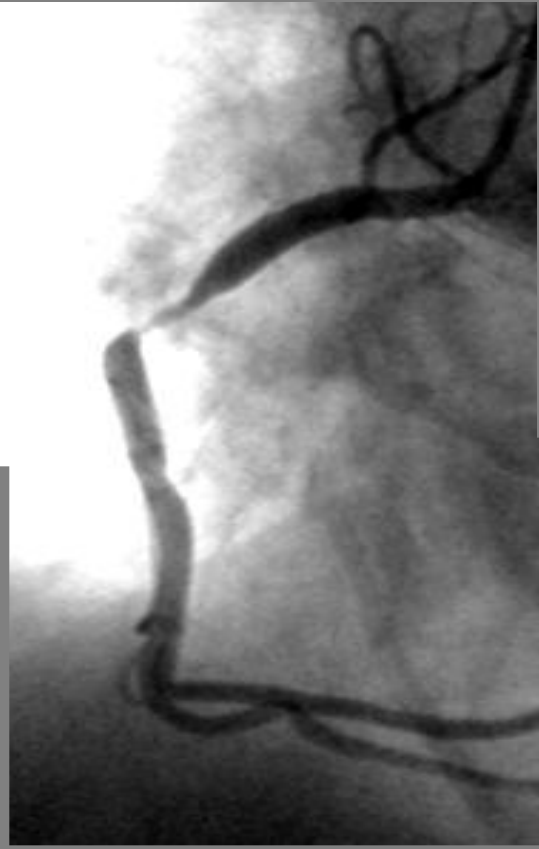
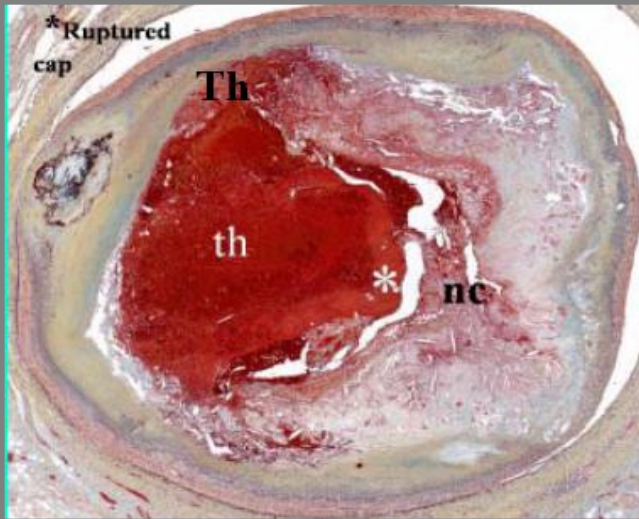


Doença aterosclerótica

Alvos terapêuticos

João Morais

Placa de ateroma o centro das atenções na doença aterosclerótica



Aterosclerose

doença difusa com manifestações focais



Coronária direita



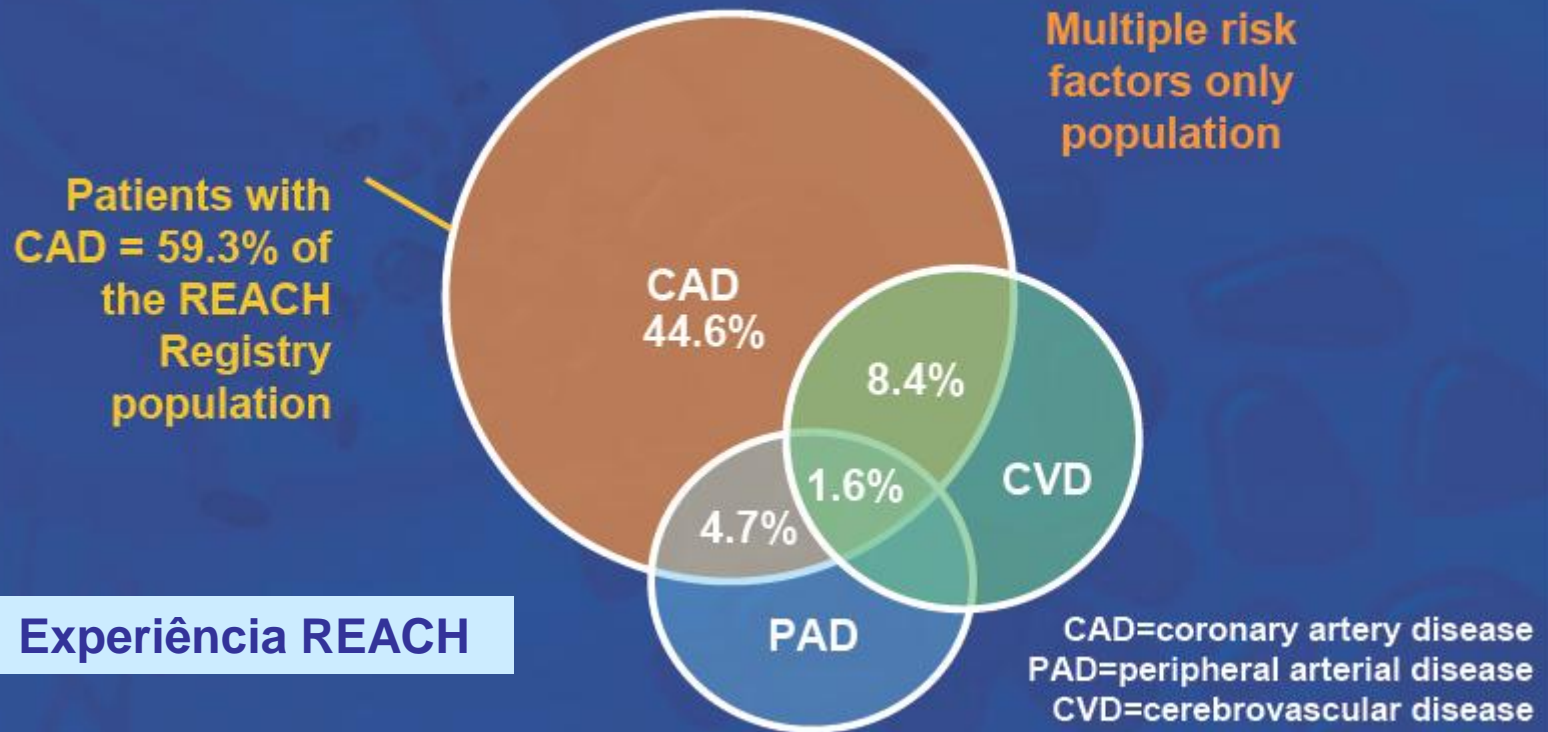
Carótida interna



Iliaca comum

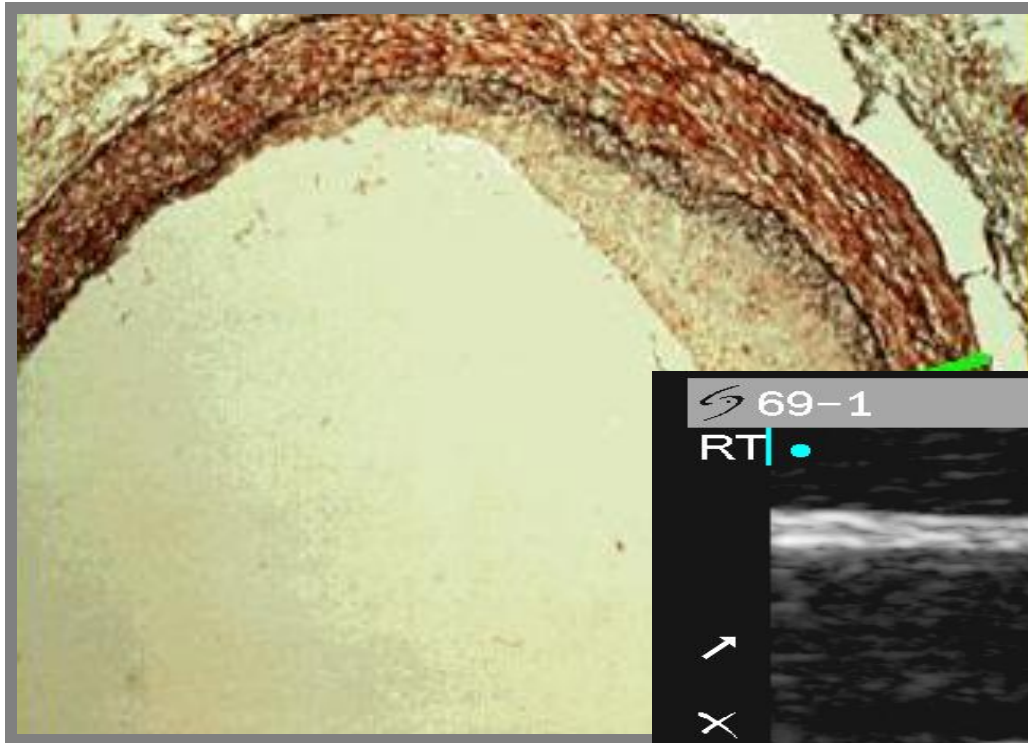
Aterosclerose doença plurivascular

~ 1/4 of the 40,258 patients with CAD also have atherothrombotic disease in other arterial territories
(%s are of total population)

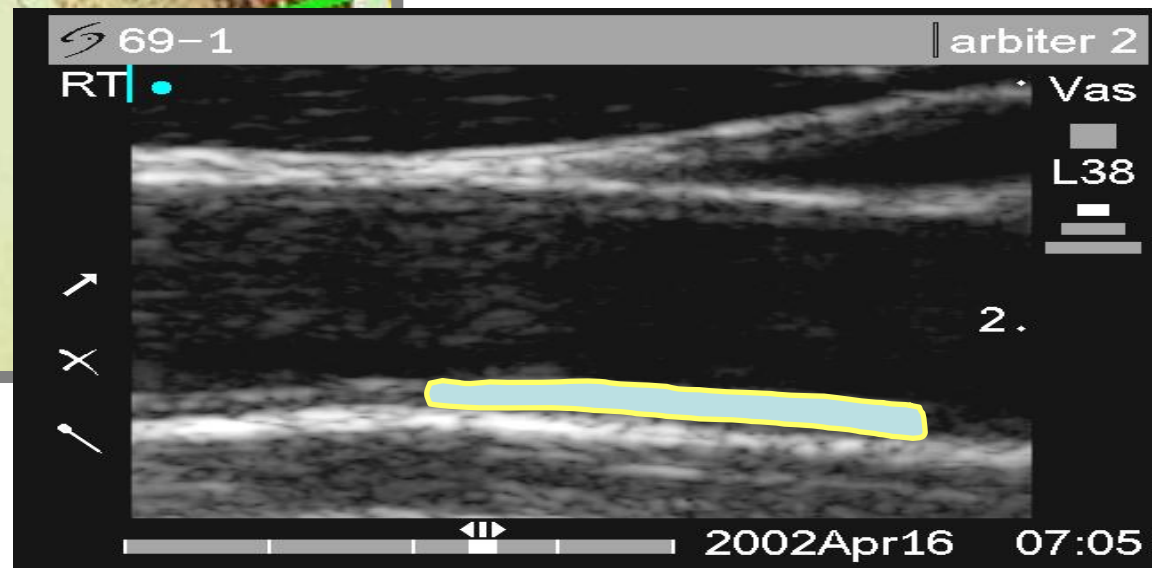


Aterosclerose

doença evolutiva com formas subclínicas



**Complexo
média/intima carotídeo**



Aterosclerose

doença evolutiva com formas subclínicas

**Complexo
média/intima carotídeo**

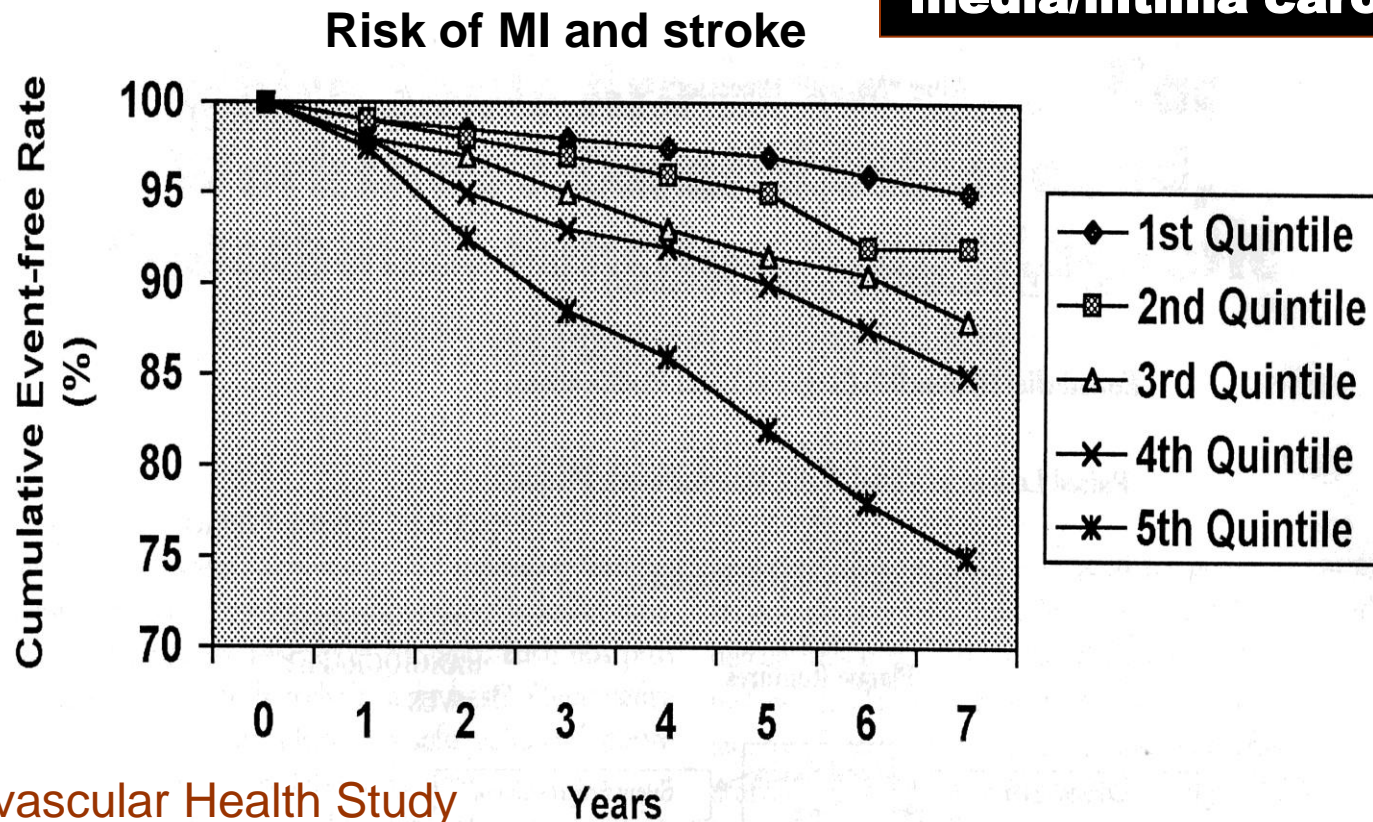
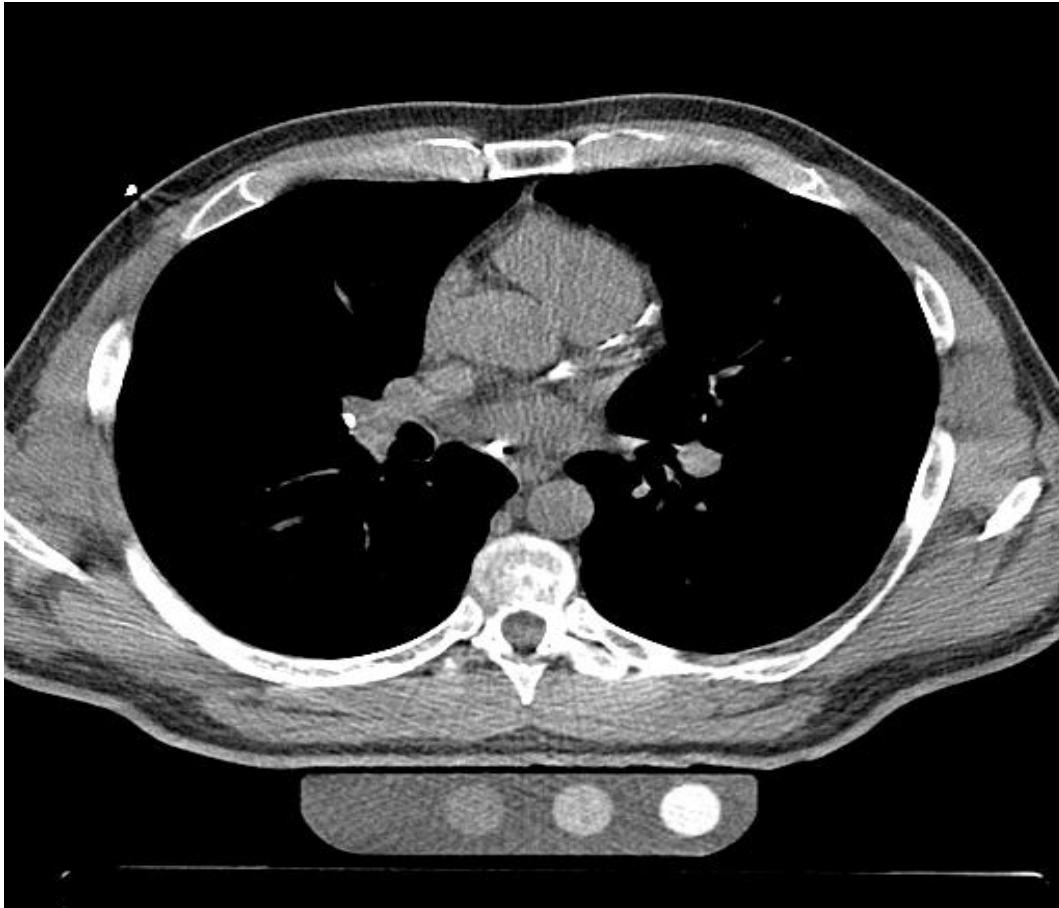


FIGURE 3. Unadjusted cumulative event-free rates for the combined endpoint of myocardial infarction or stroke, according to quintile of combined intima-medial thickness. (Adapted from *N Engl J Med*.⁷)

Aterosclerose

doença evolutiva com formas subclínicas

Carga de cálcio



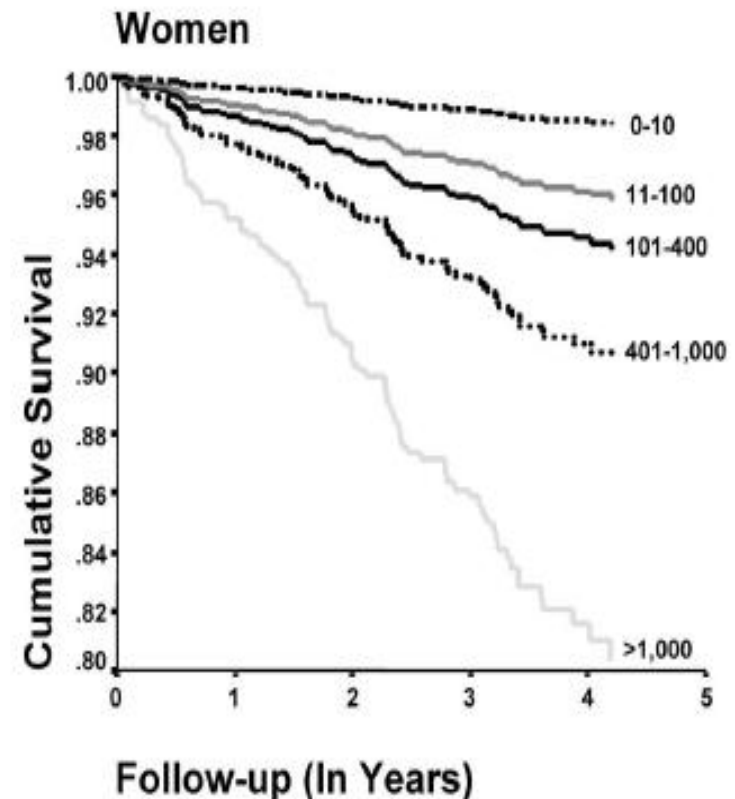
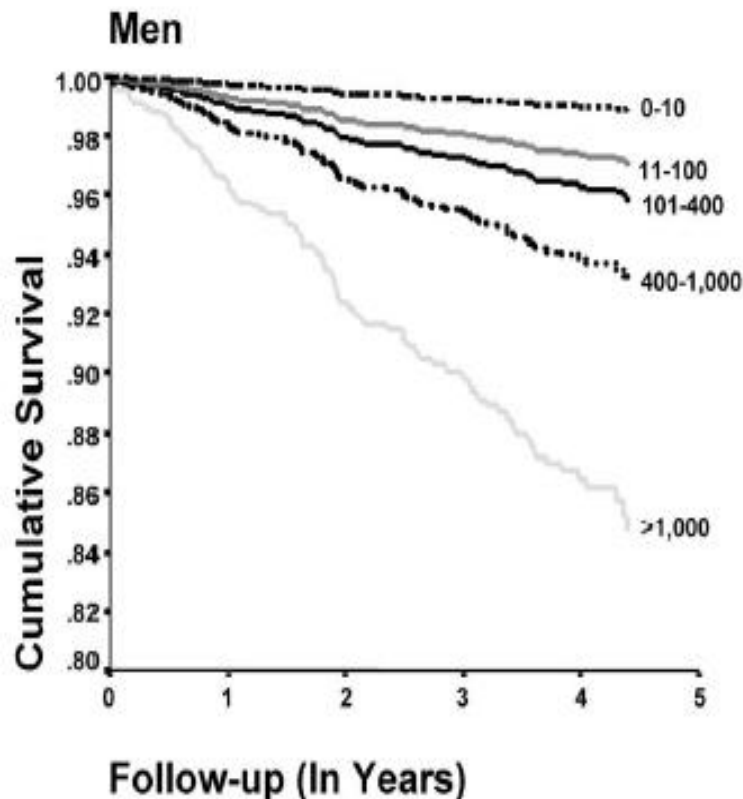
Aterosclerose

doença evolutiva com formas subclínicas

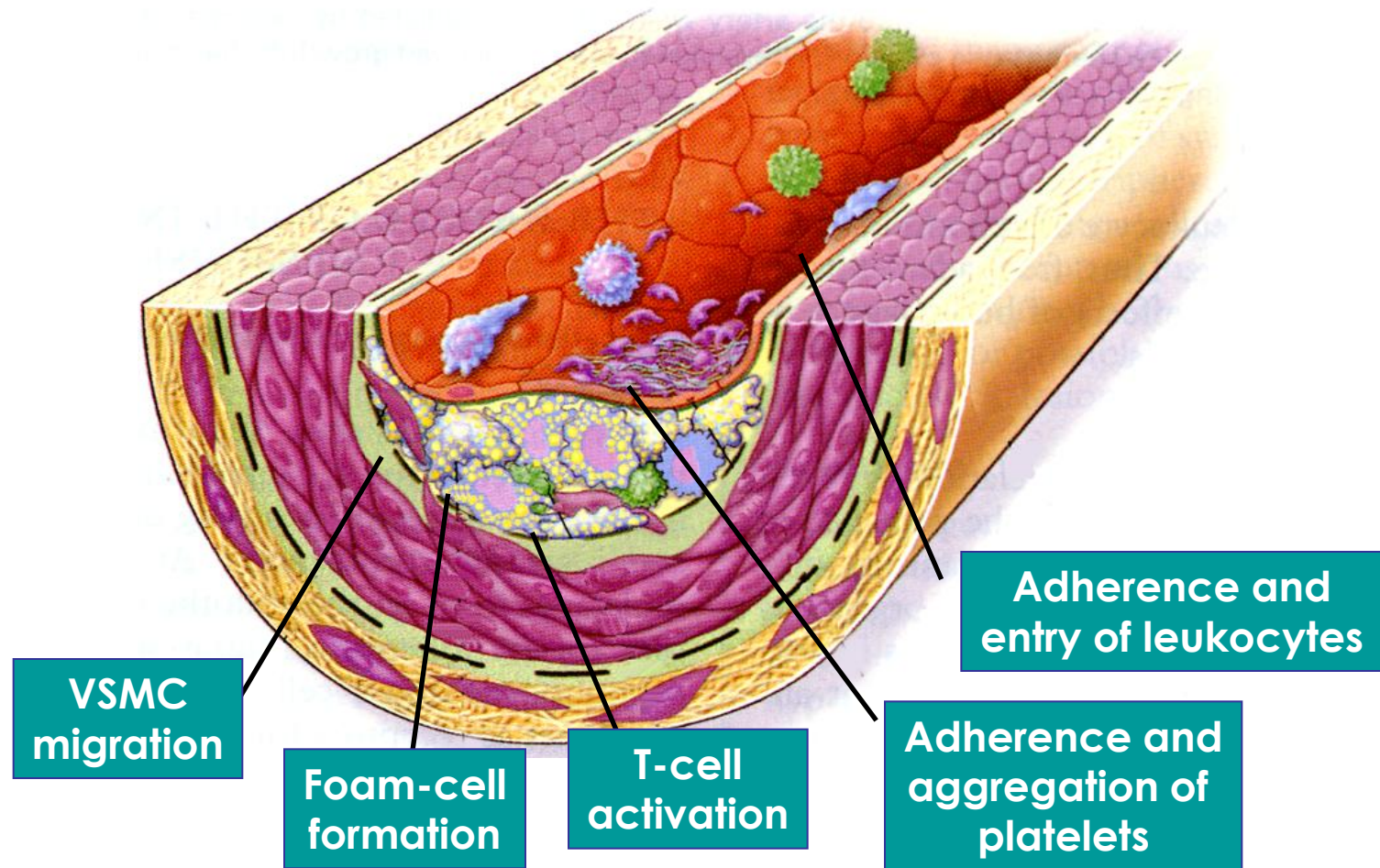
Carga de cálcio

Shaw LJ et al., Radiology 2003; 228: 826-33

Risk of total mortality in 10377
asymptomatic individuals

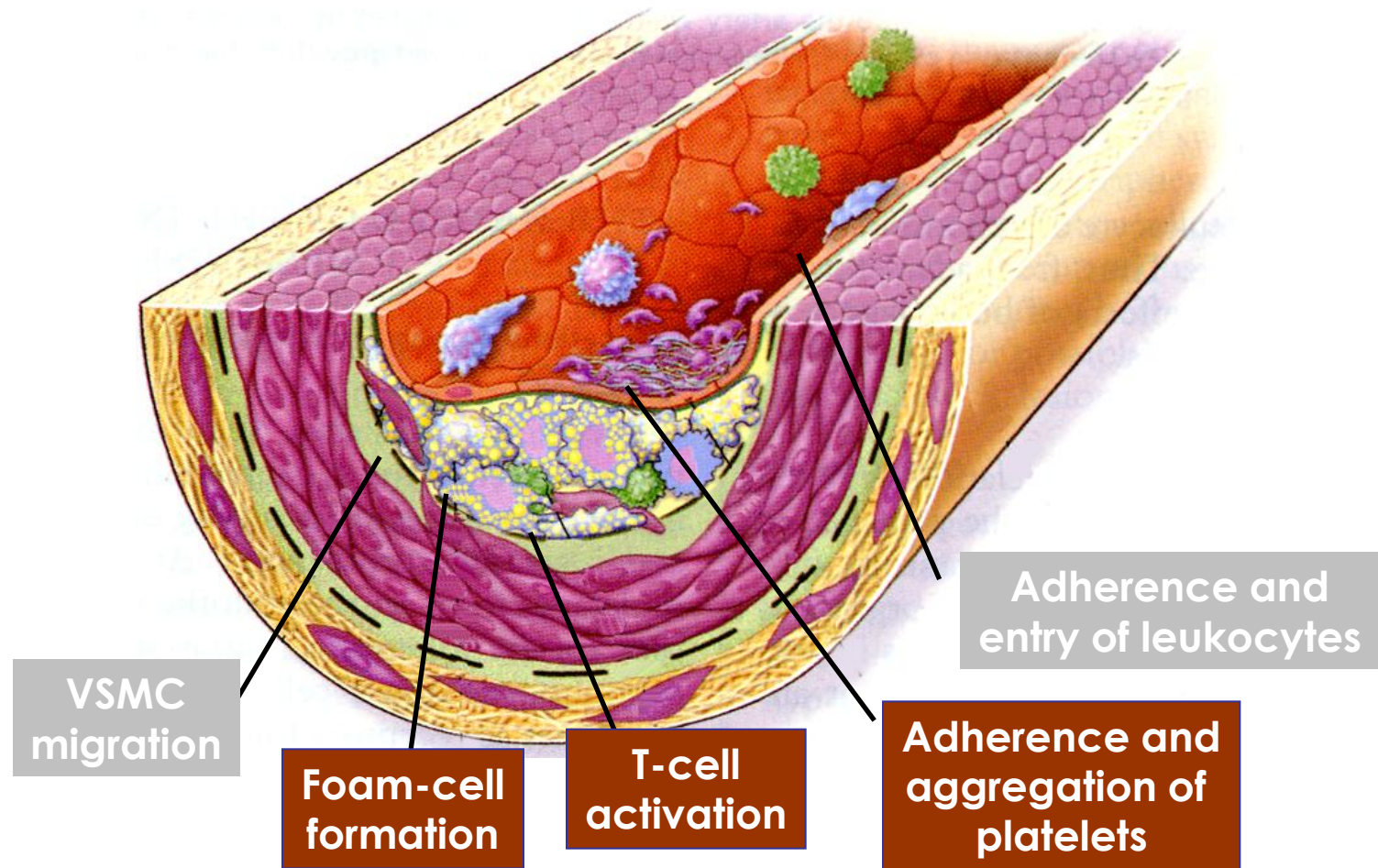


Vários componentes de uma doença complexa



VSMC, vascular smooth muscle cell migration.

Vários componentes de uma doença complexa



Lípidos Inflamação Trombose

Colesterol-LDL o alvo preferencial para a terapêutica

1. Benefícios inequívocos na redução de eventos

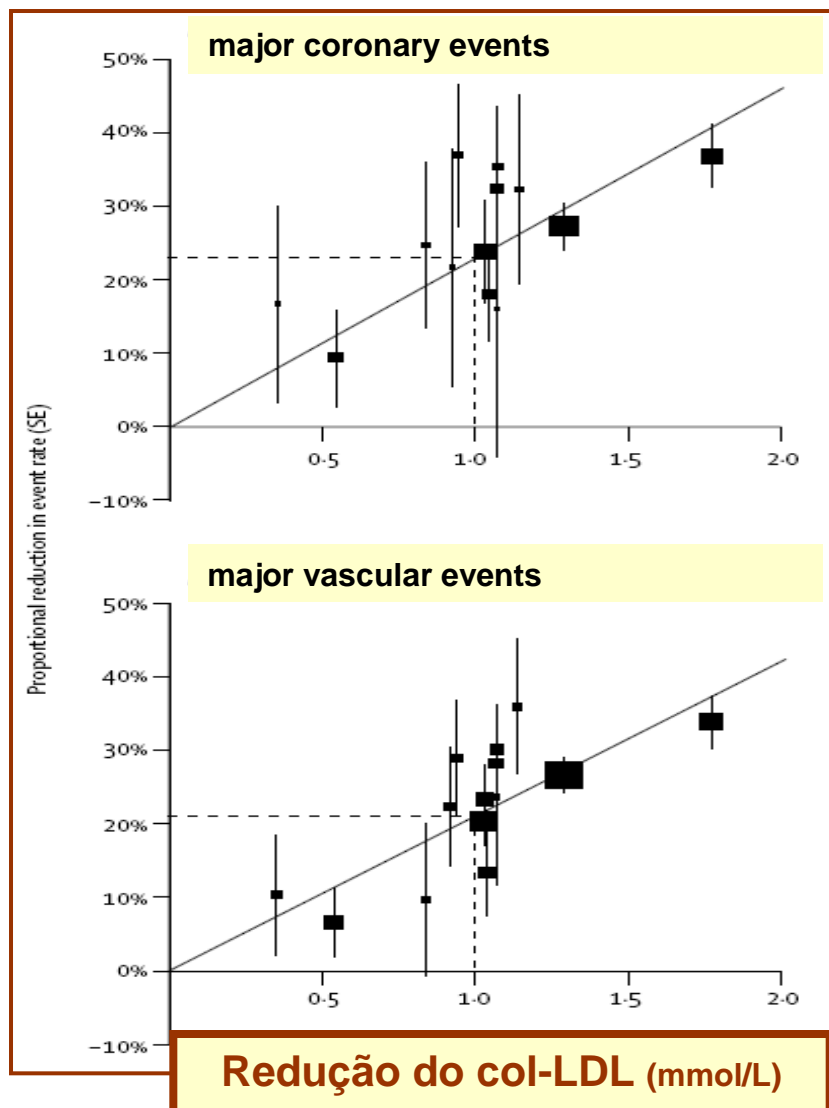
1. Benefícios inequívocos na redução de eventos

↓ 30 mg c-LDL

↓ 30 % eventos

Cholesterol Treatment Trialists' (CTT) Collaborators

Lancet 2005;366:1267



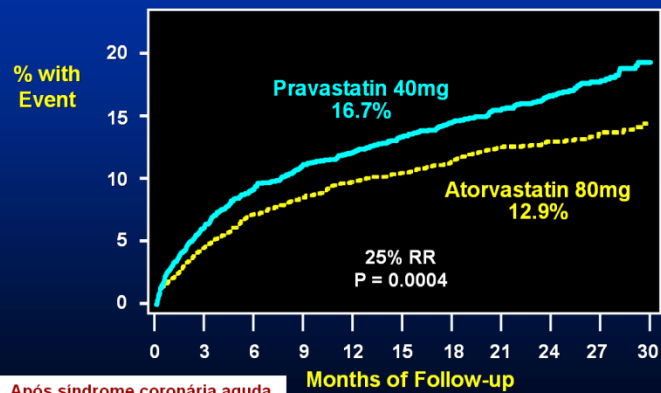
Colesterol-LDL o alvo preferencial para a terapêutica

1. Benefícios inequívocos na redução de eventos
- 2. Consistência nas várias áreas da doença vascular**

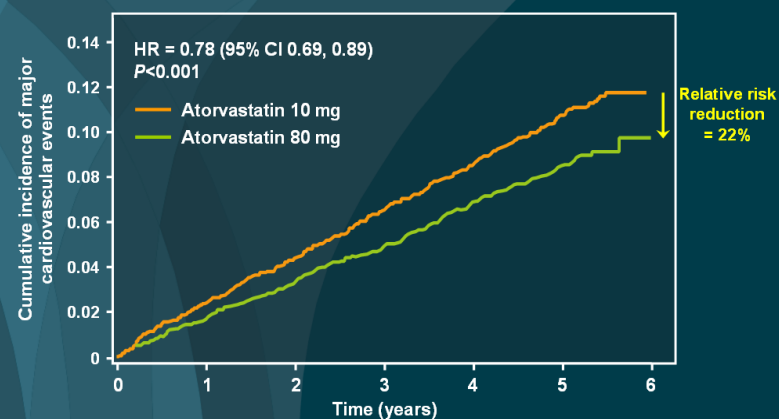
2.



All-Cause Death, Non-Fatal MI, or Urgent Revascularization



Primary Efficacy Outcome Measure: Major Cardiovascular Events*

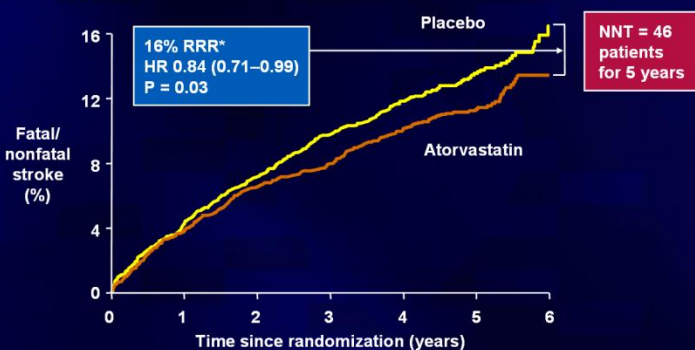


*CHD death, nonfatal non-procedure-related MI, resuscitated cardiac arrest, fatal or nonfatal stroke

LaRosa JC, et al. *N Engl J Med.* 2005;352

SPARCL: High-dose statin treatment reduces fatal/nonfatal stroke

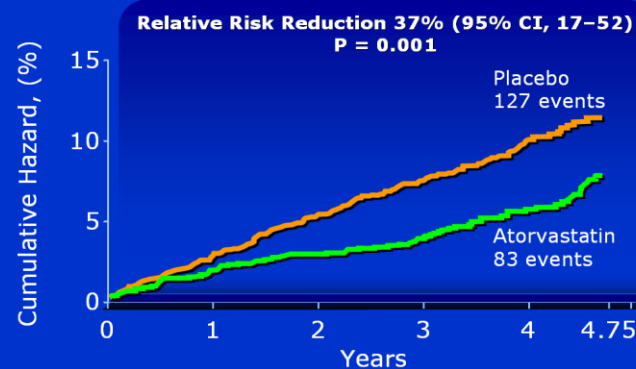
Primary outcome



*Adjusted

SPARCL Investigators. *N Engl J Med.* 2006;355:549-59.

CARDS: Effect of Atorvastatin on the Primary Endpoint: Major CV Events Including Stroke



Placebo	1410	1351	1306	1022	651	305
Atorvastatin	1428	1392	1361	1074	694	328

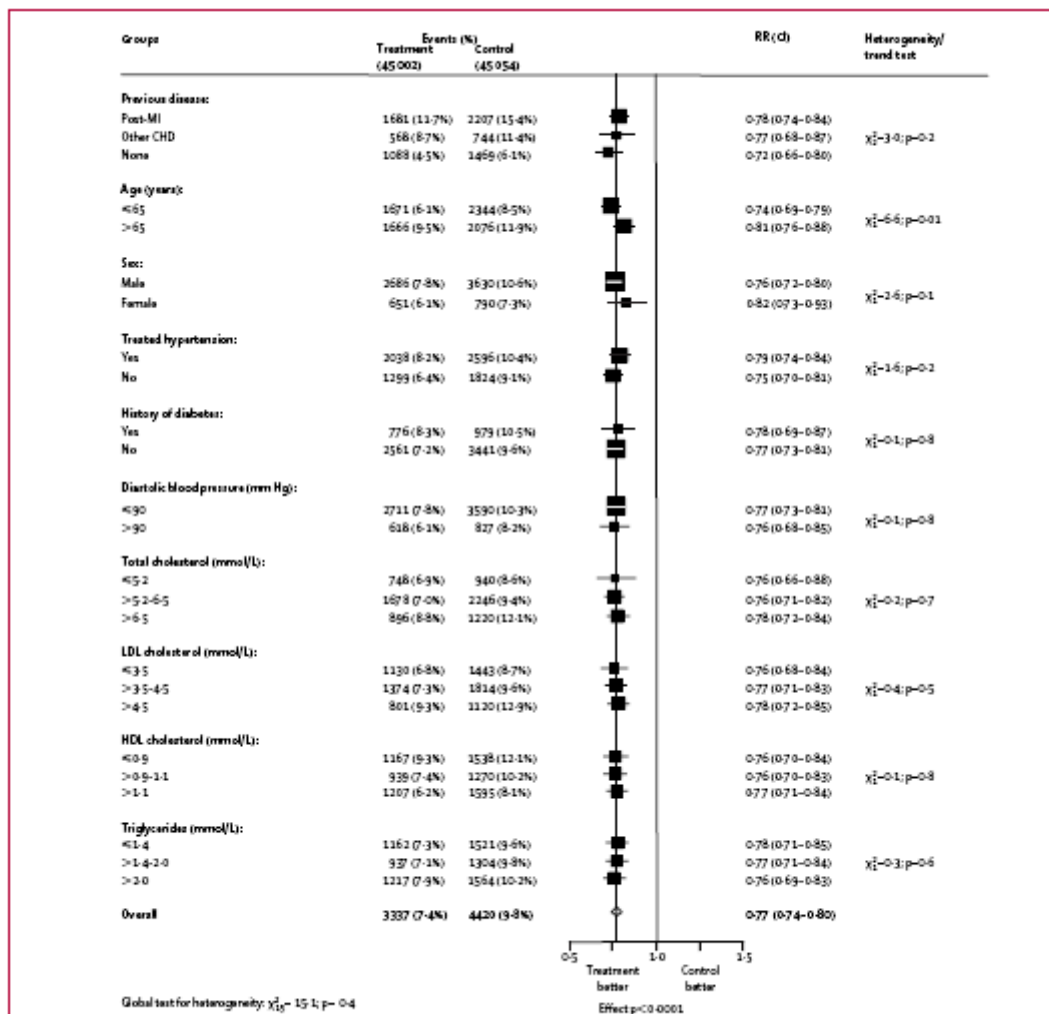
Colhoun HM et al. *Lancet* 2004;364:685-696.
Reprinted with permission from Elsevier.

Slide Source:
Lipids Online Slide Library
www.lipidsonline.org

Colesterol-LDL o alvo preferencial para a terapêutica

1. Benefícios inequívocos na redução de eventos
2. Consistência nas várias áreas da doença vascular
- 3. Consistência nos diferentes subgrupos testados**

3. Consistência nos diferentes subgrupos



Doença prévia

Idade

Gênero

Hipertensão arterial

História de diabetes

TA diastólica

Nível de colesterol total

Nível de colesterol LDL

Nível de colesterol HDL

Nível de triglicerídeos

Cholesterol Treatment Trialist's (CTT) Collaborators

Lancet 2005;366:1267

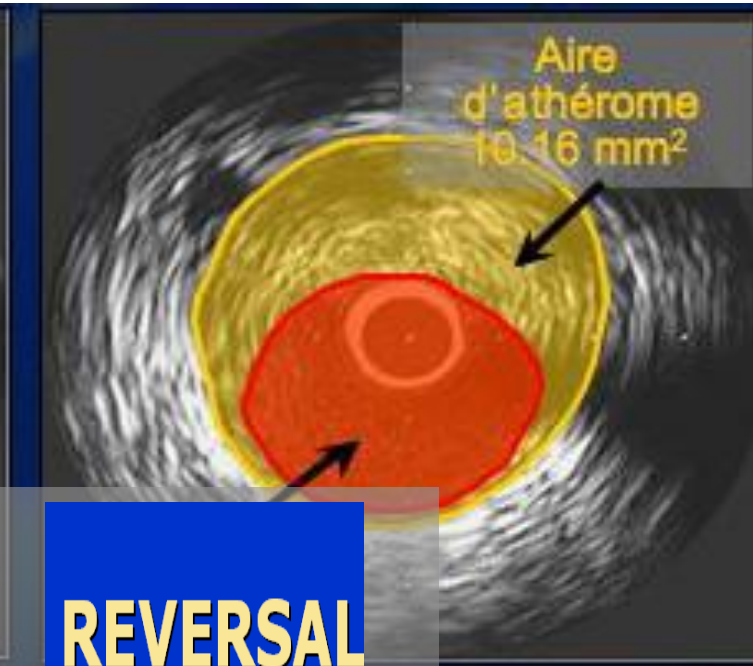
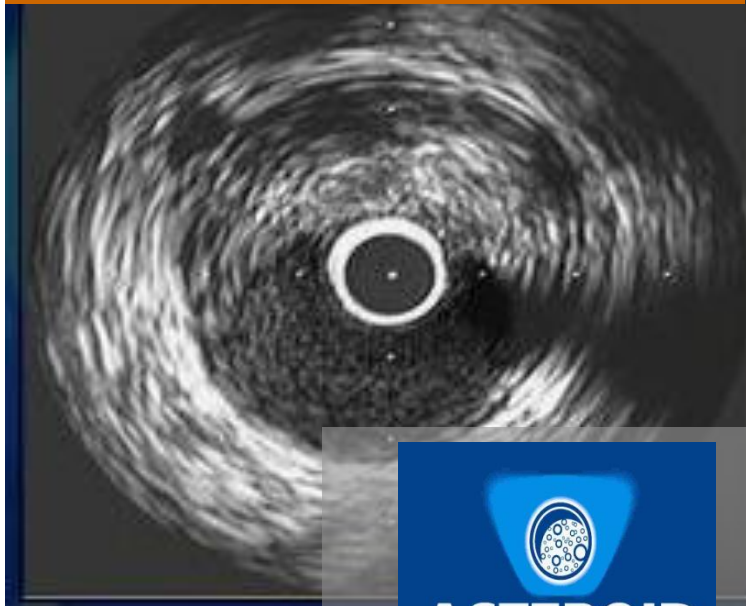
Figure 5: Proportional effects on major coronary events per mmol/L LDL cholesterol reduction subdivided by baseline prognostic factors. Symbols and conventions as in figure 1.

Colesterol-LDL o alvo preferencial para a terapêutica

1. Benefícios inequívocos na redução de eventos
2. Consistência nas várias áreas da doença vascular
3. Consistência nos diferentes subgrupos testados
4. **Eficácia sobre a progressão da placa de ateroma**

4. Eficácia sobre a progressão da placa de ateroma

Ultrasonografia intra-coronária



**Rosuvastatina
promove a
regressão da
placa**

REVERSAL

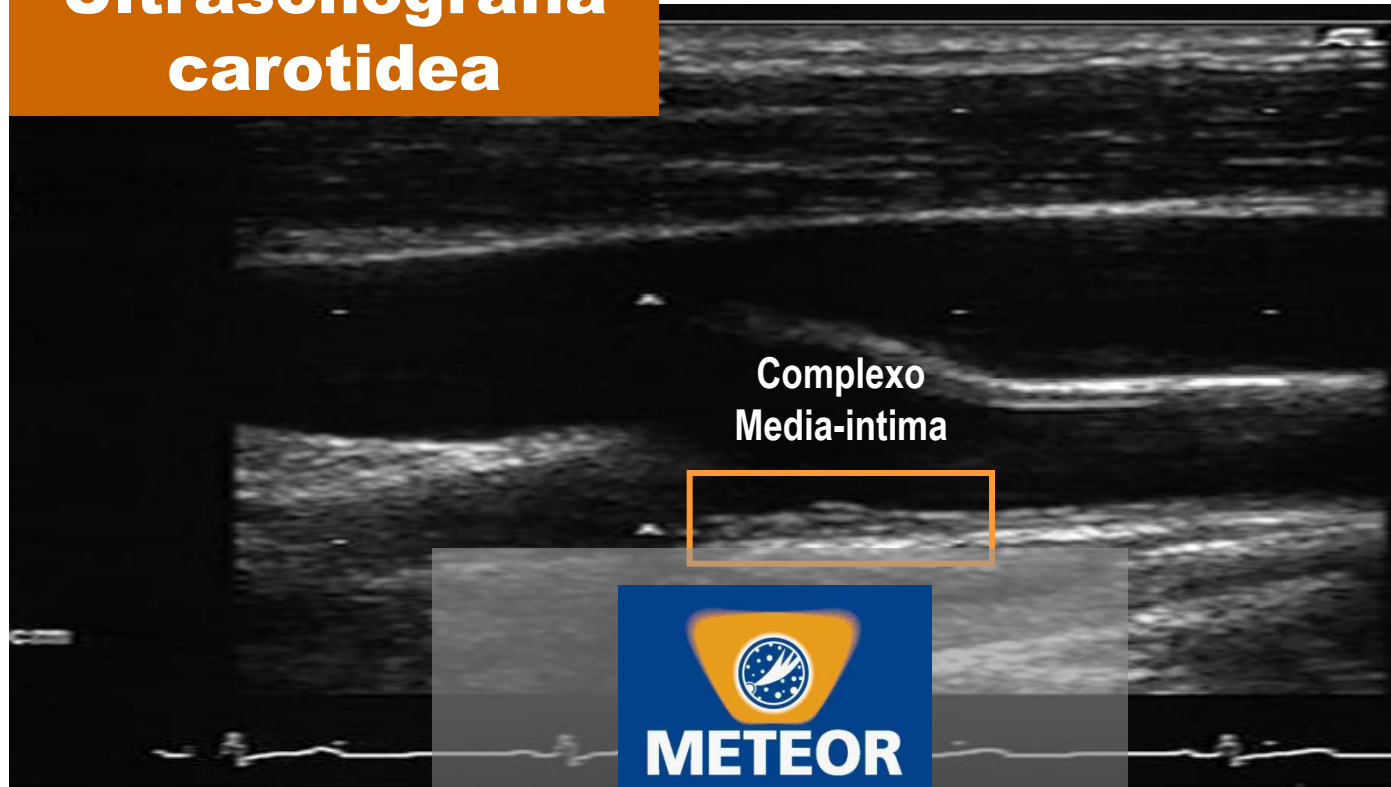
**Atorvastatina
interrompe a
progressão da
placa**

Colesterol-LDL o alvo preferencial para a terapêutica

1. Benefícios inequívocos na redução de eventos
2. Consistência nas várias áreas da doença vascular
3. Consistência nos diferentes subgrupos testados
4. Eficácia sobre a progressão da placa de ateroma
- 5. Eficácia sobre formas subclínicas da d. aterosclerótica**

4. Eficácia sobre formas subclínicas da d. aterosclerótica

Ultrasonografia carotídea

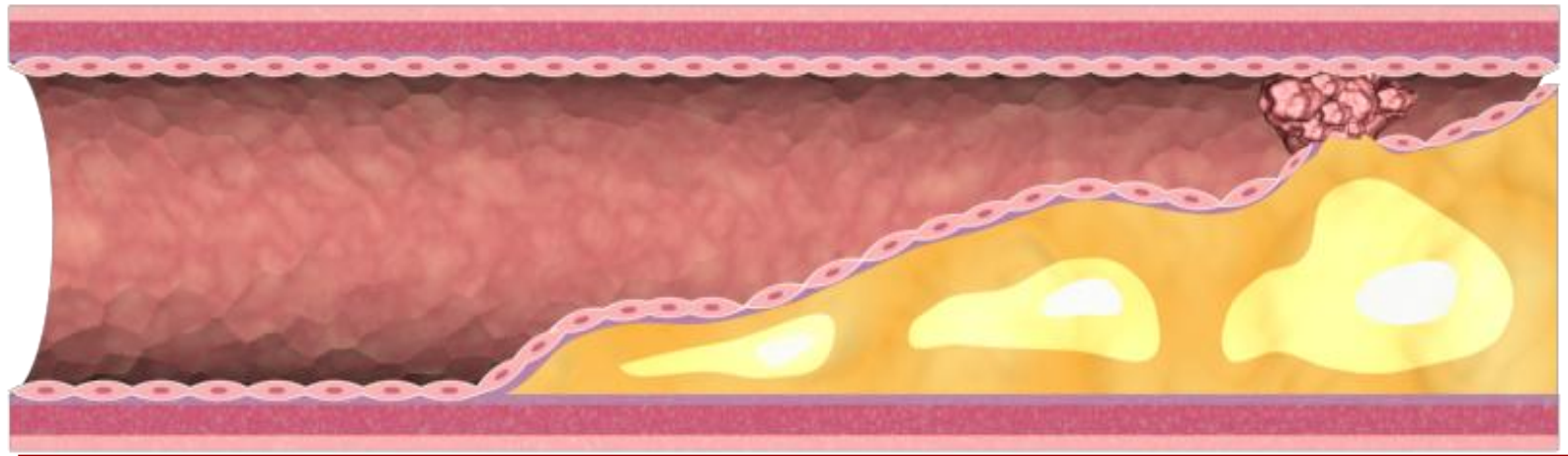


**Rosuvastatina reduz a
progressão da doença
aterosclerótica**

Colesterol-LDL o alvo preferencial para a terapêutica

1. Benefícios inequívocos na redução de eventos
2. Consistência nas várias áreas da doença vascular
3. Consistência nos diferentes subgrupos testados
4. Eficácia sobre a progressão da placa de ateroma
5. Eficácia sobre formas subclínicas da d. aterosclerótica
- 6. Permite objectivos individualizados de acordo com o risco**

6. Permite objetivos individualizados de acordo com o risco

col-LDL
mg/dl

$< 115 \dots \dots < 100$

Prevenção risco primária

Fase subclínica

Alto e Prev.

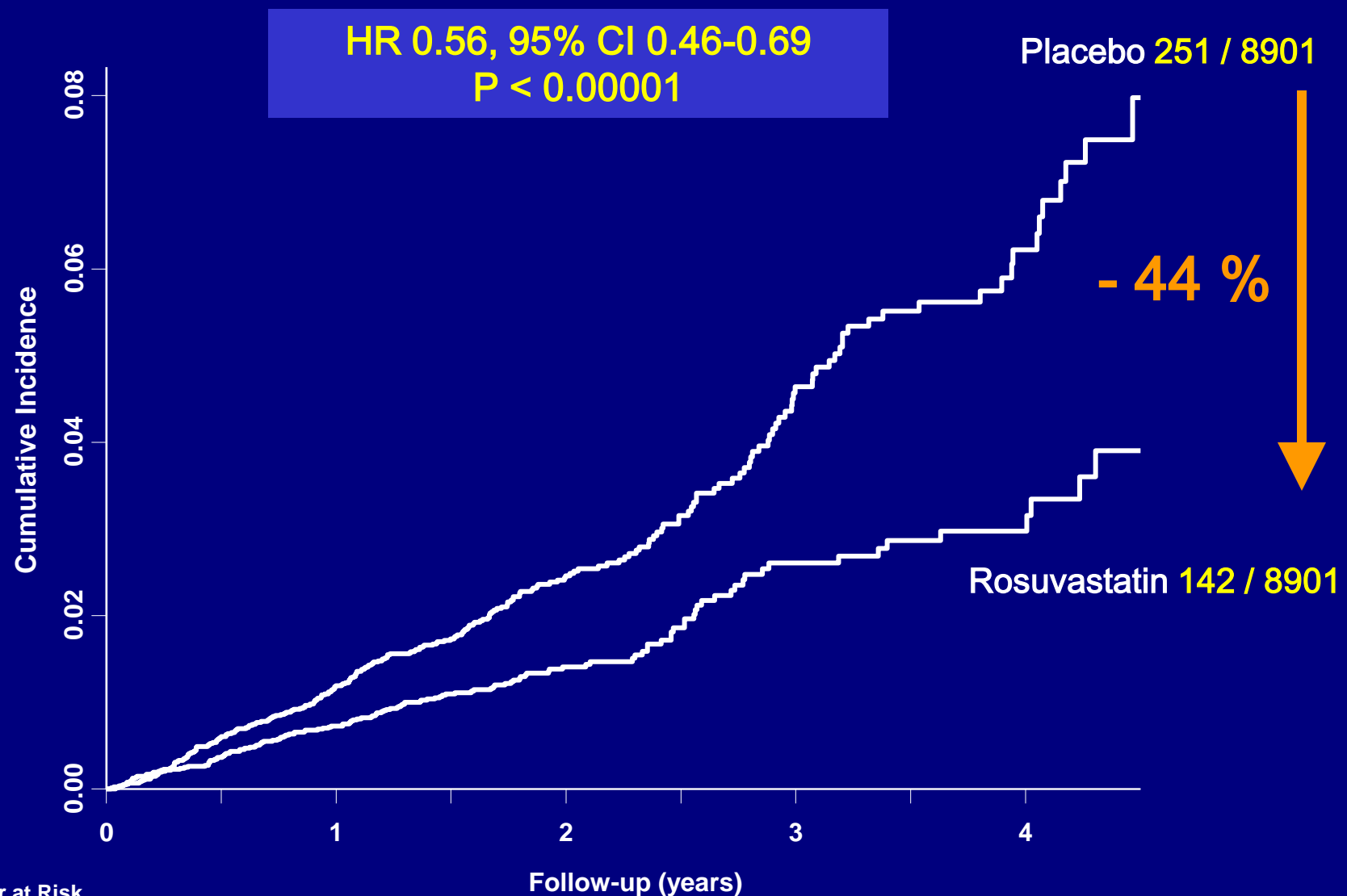
Estratégia de acordo com a fase evolutiva da doença

Colesterol-LDL o alvo preferencial para a terapêutica

1. Benefícios inequívocos na redução de eventos
2. Consistência nas várias áreas da doença vascular
3. Consistência nos diferentes subgrupos testados
4. Eficácia sobre a progressão da placa de ateroma
5. Eficácia sobre formas subclínicas da d. aterosclerótica
6. Permite objectivos individualizados de acordo com o risco
- 7. Eficaz mesmo em prevenção primária**



Primary Trial Endpoint : MI, Stroke, UA/Revascularization, CV Death



Number at Risk

Rosuvastatin	8,901	8,631	8,412	6,540	3,893	1,958	1,353	983	544	157
Placebo	8,901	8,621	8,353	6,508	3,872	1,963	1,333	955	534	174

Colesterol-LDL o alvo preferencial para a terapêutica

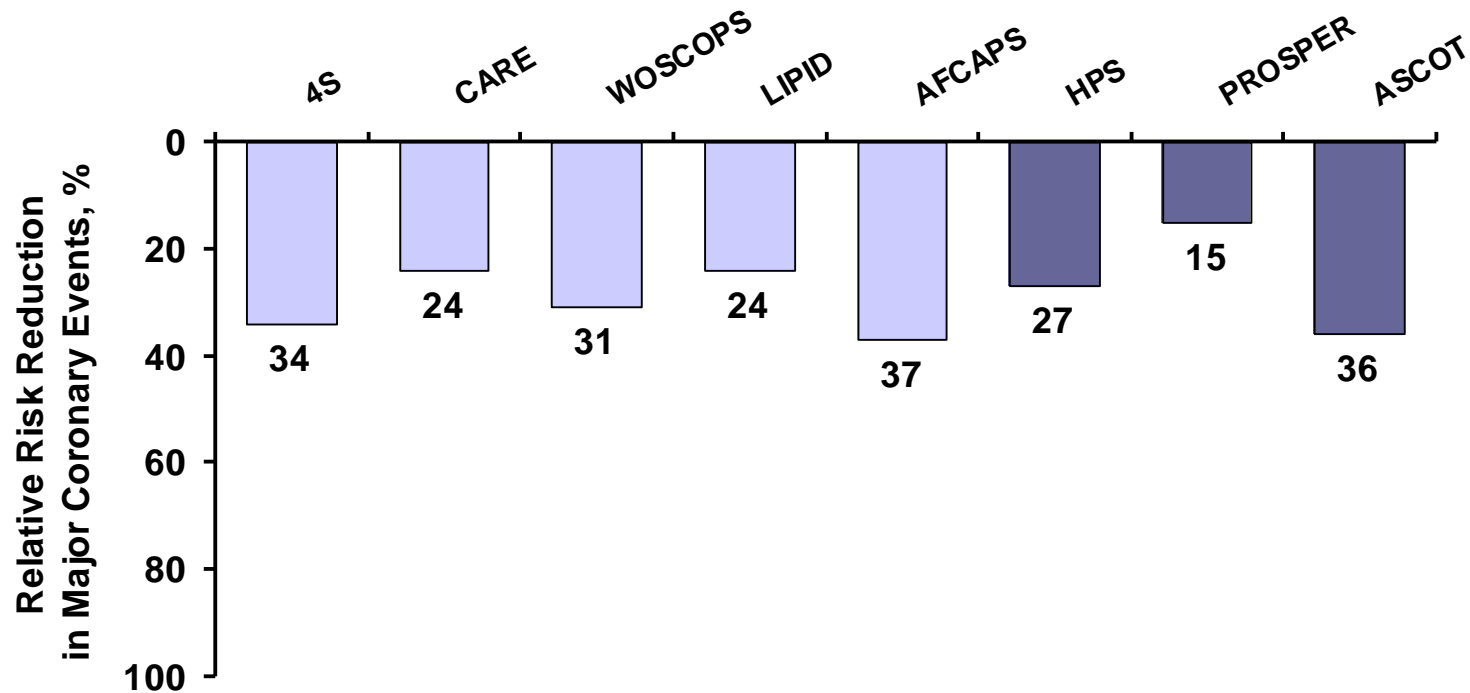
- 1. Benefícios inequívocos na redução de eventos**
- 2. Consistência nas várias áreas da doença vascular**
- 3. Consistência nos diferentes subgrupos testados**
- 4. Eficácia sobre a progressão da placa de ateroma**
- 5. Eficácia sobre formas subclínicas da d. aterosclerótica**
- 6. Permite objectivos individualizados de acordo com o risco**
- 7. Eficaz mesmo em prevenção primária**

Colesterol-LDL o alvo preferencial para a terapêutica

1. Benefícios inequívocos na redução de eventos
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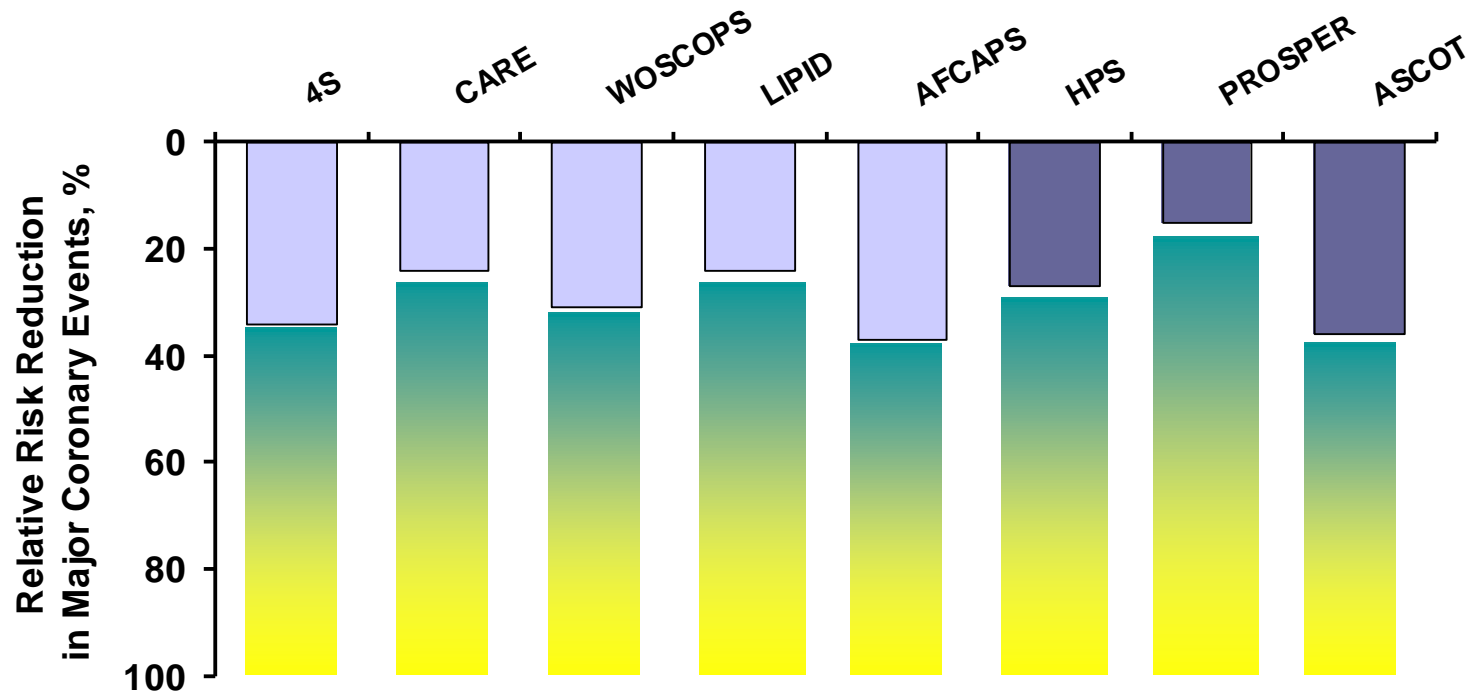
As estatinas são a forma mais eficaz de tratamento da doença aterosclerótica, influenciando o seu curso de forma determinante

Colesterol-LDL o alvo preferencial para a terapêutica



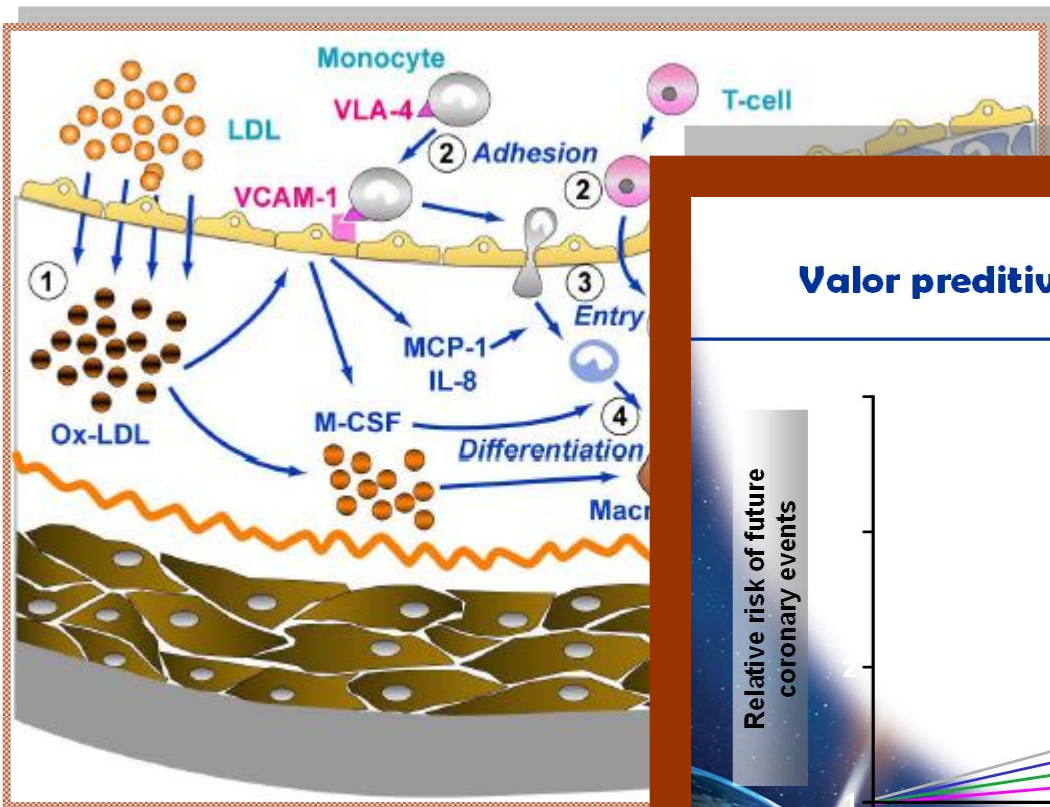
A redução de risco possível

Colesterol-LDL o alvo preferencial para a terapêutica



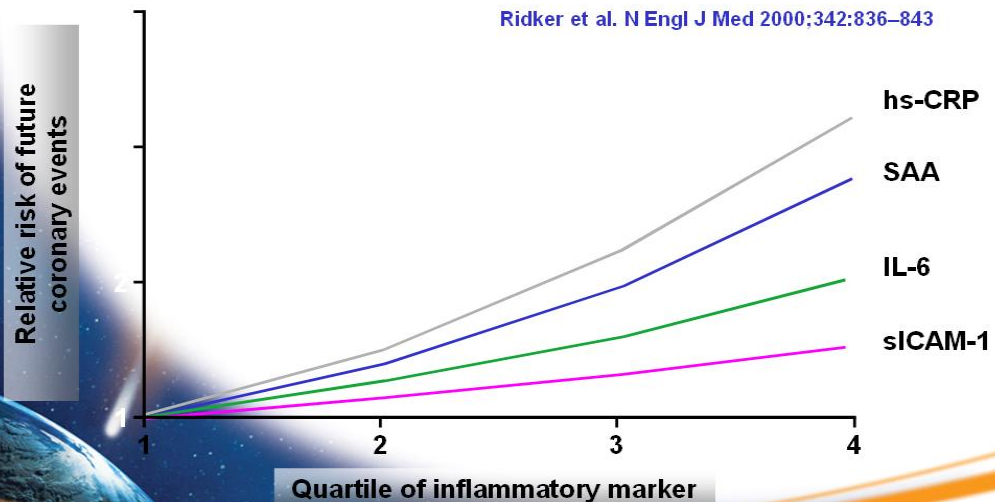
O caminho que ainda falta percorrer

Para além do col-LDL **INFLAMAÇÃO**

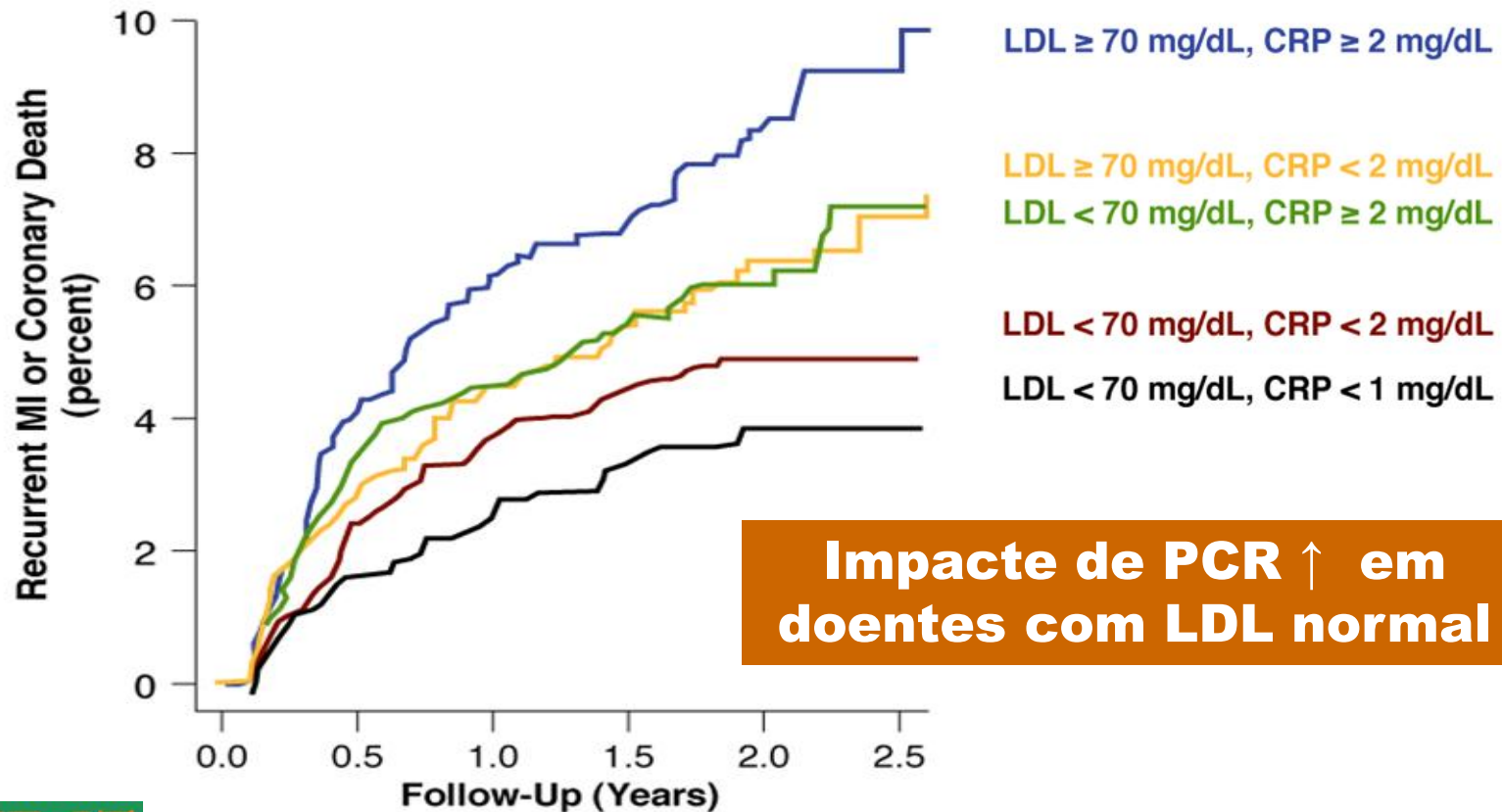


Valor preditivo dos marcadores de inflamação (LDL < 130 mg/dl)

Ridker et al. N Engl J Med 2000;342:836–843



PCR no contexto de SCA (PROVE-IT)



Impacte de PCR \uparrow em doentes com LDL normal

O efeito sinérgico de PCR \uparrow e LDL \uparrow



O que sabemos sobre inflamação

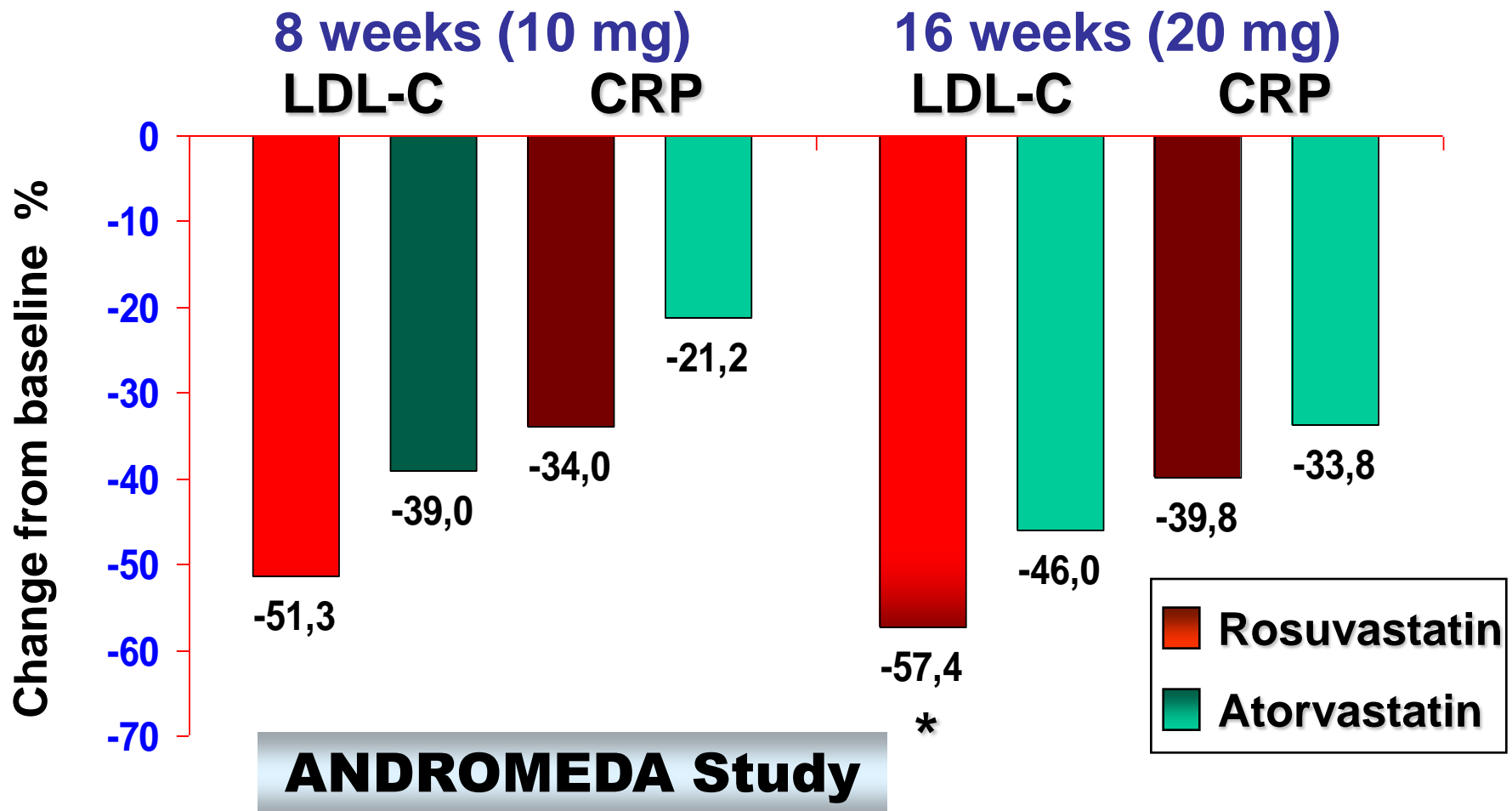
A doença aterosclerótica pode ser considerada como uma doença inflamatória, local e sistémica

A inflamação precede as manifestações clínicas em mais de dez anos

A detecção precoce de inflamação sugere risco vascular aumentado, mas só após exclusão de outras causas

A PCR parece ser um bom candidato para uso clínico

A inflamação como alvo terapêutico a par do c-LDL

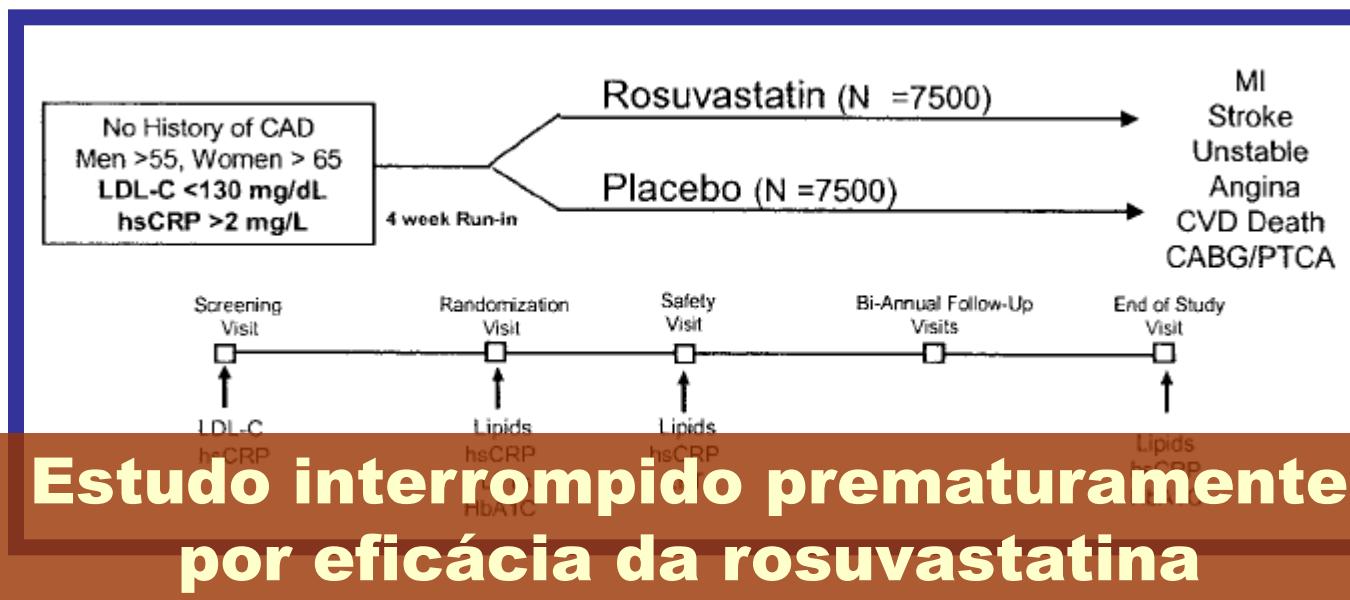


A inflamação como alvo terapêutico para além do c-LDL



Rosuvastatin in the Primary Prevention of Cardiovascular Disease Among Patients With Low Levels of Low-Density Lipoprotein Cholesterol and Elevated High-Sensitivity C-Reactive Protein Rationale and Design of the JUPITER Trial*

Paul M Ridker, MD, MPH; on behalf of the JUPITER Study Group





Baseline Blood Levels (median, interquartile range)

	Rosuvastatin (N = 8901)		Placebo (n = 8901)	
hsCRP, mg/L	4.2	(2.8 - 7.1)	4.3	(2.8 - 7.2)
LDL, mg/dL	108	(94 - 119)	108	(94 - 119)
HDL, mg/dL	49	(40 – 60)	49	(40 – 60)
Triglycerides, mg/L	118	(85 - 169)	118	(86 - 169)
Total Cholesterol, mg/dL	186	(168 - 200)	185	(169 - 199)
Glucose, mg/dL	94	(87 – 102)	94	(88 – 102)
HbA1c, %	5.7	(5.4 – 5.9)	5.7	(5.5 – 5.9)

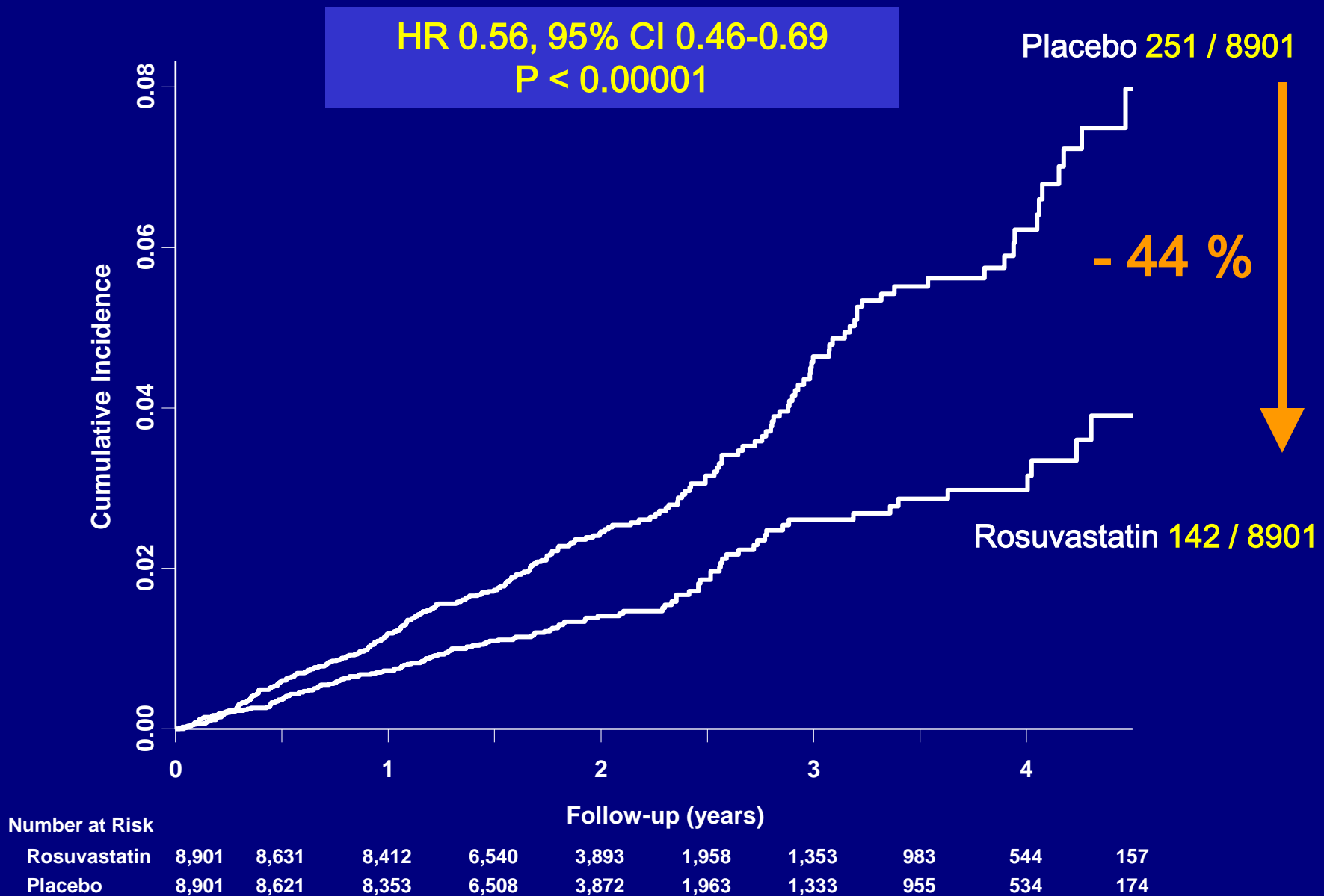
All values are median (interquartile range). [Mean LDL = 104 mg/dL]

JUPITER

Ridker et al NEJM 2008



Primary Trial Endpoint : MI, Stroke, UA/Revascularization, CV Death





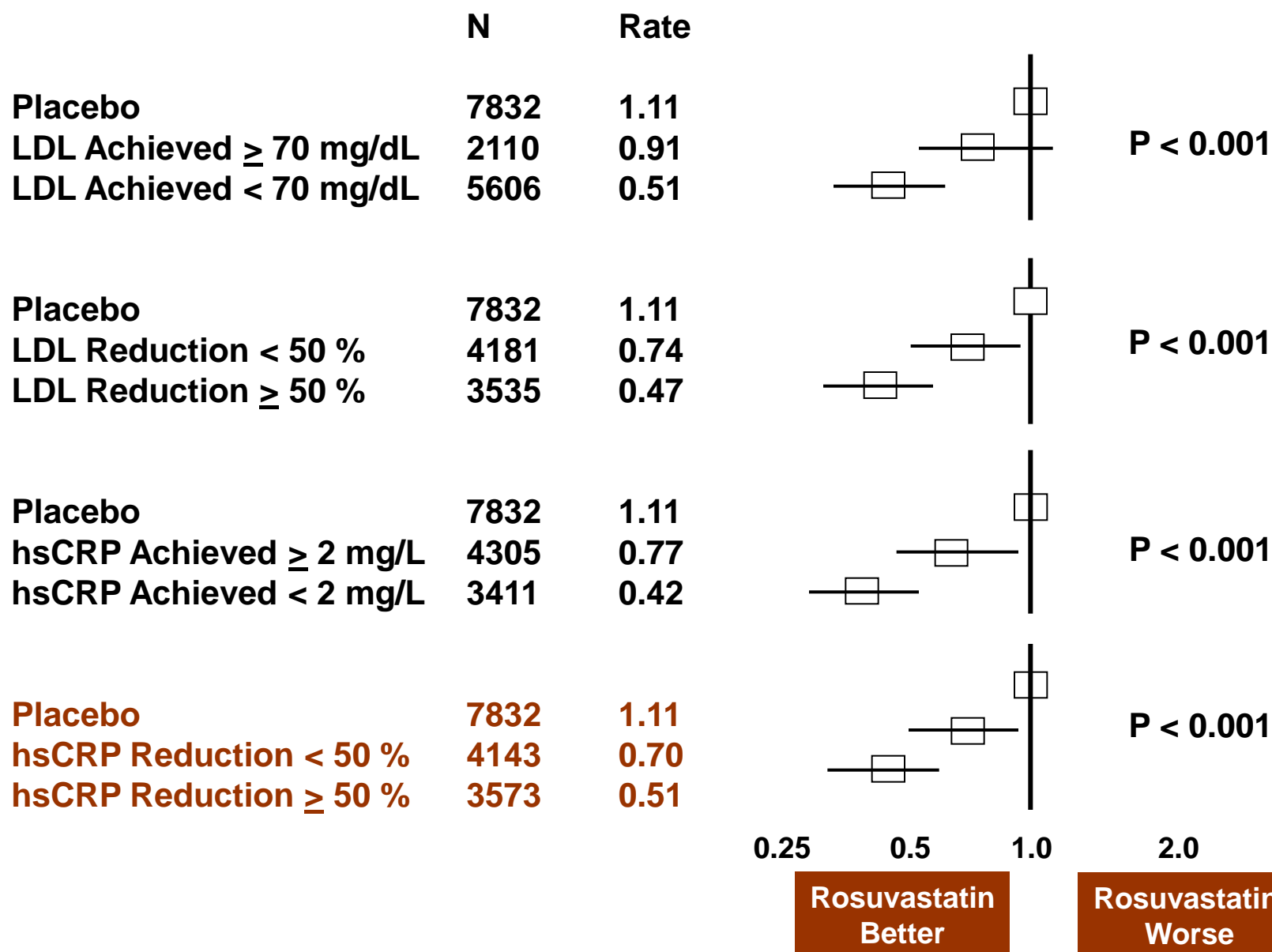
Individual Components of the Primary Endpoint

Endpoint	Rosuvastatin	Placebo	HR	95%CI	P
Primary Endpoint*	142	251	0.56	0.46-0.69	<0.00001
Non-fatal MI	22	62	0.35	0.22-0.58	<0.00001
Any MI	31	68	0.46	0.30-0.70	<0.0002
Non-fatal Stroke	30	58	0.52	0.33-0.80	0.003
Any Stroke	33	64	0.52	0.34-0.79	0.002
Revascularization or Unstable Angina	76	143	0.53	0.40-0.70	<0.00001
MI, Stroke, CV Death	83	157	0.53	0.40-0.69	<0.00001

*Nonfatal MI, nonfatal stroke, revascularization, unstable angina, CV death

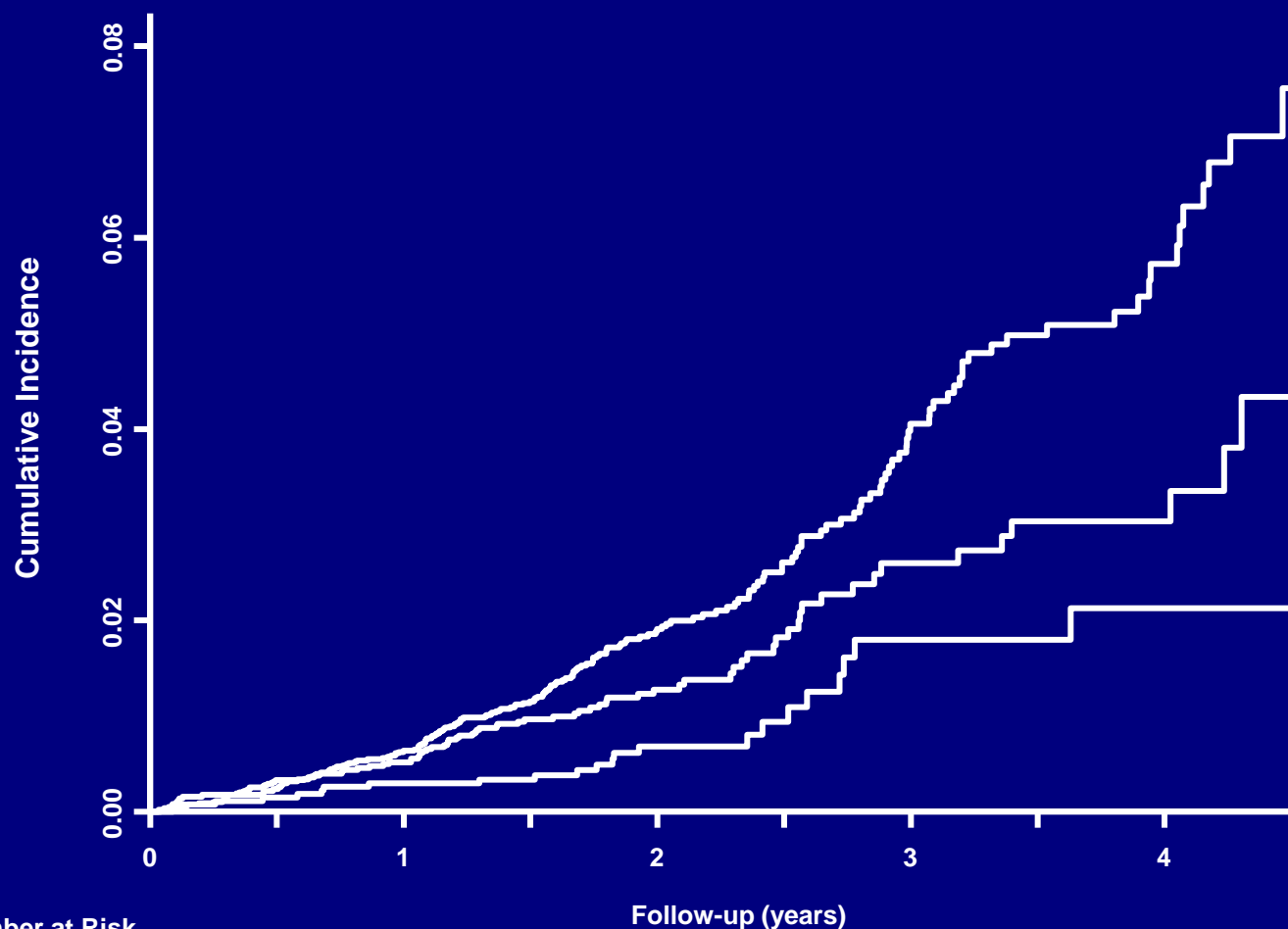
JUPITER

LDL reduction, hsCRP reduction, or both?



JUPITER

Dual Target Analysis: LDLC < 70 mg/dL, hsCRP < 2 mg/L



Placebo
HR 1.0 (referent)

LDL > 70 mg/dL
and / or
hsCRP > 2 mg/L
HR 0.64 (0.49-0.84)

LDL < 70 mg/dL
and
hsCRP < 2 mg/L
HR 0.35 (0.23-0.54)

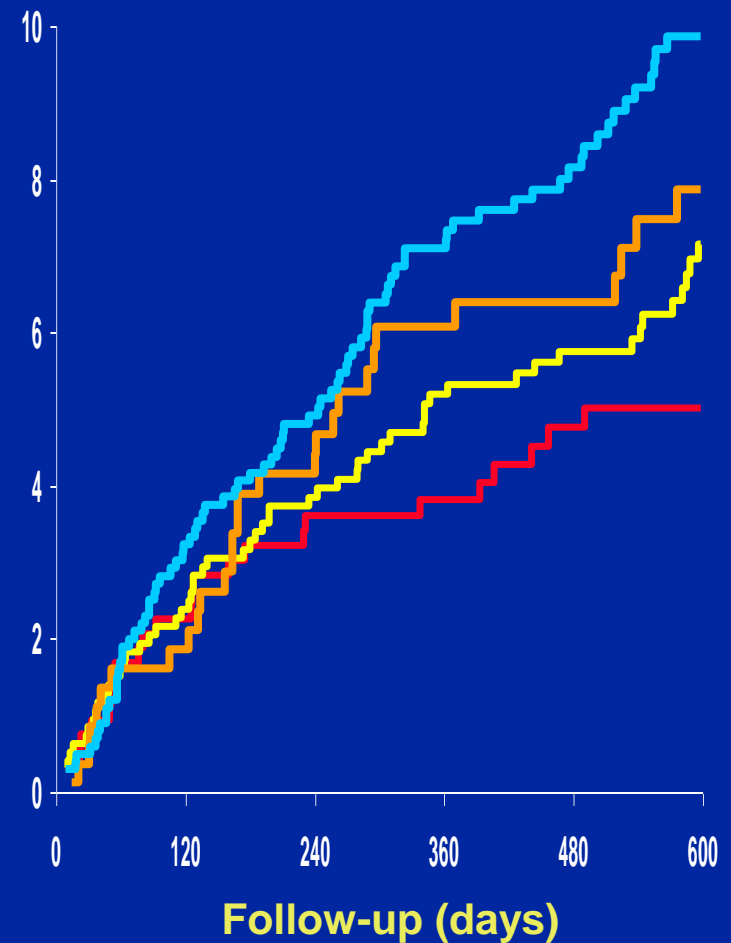
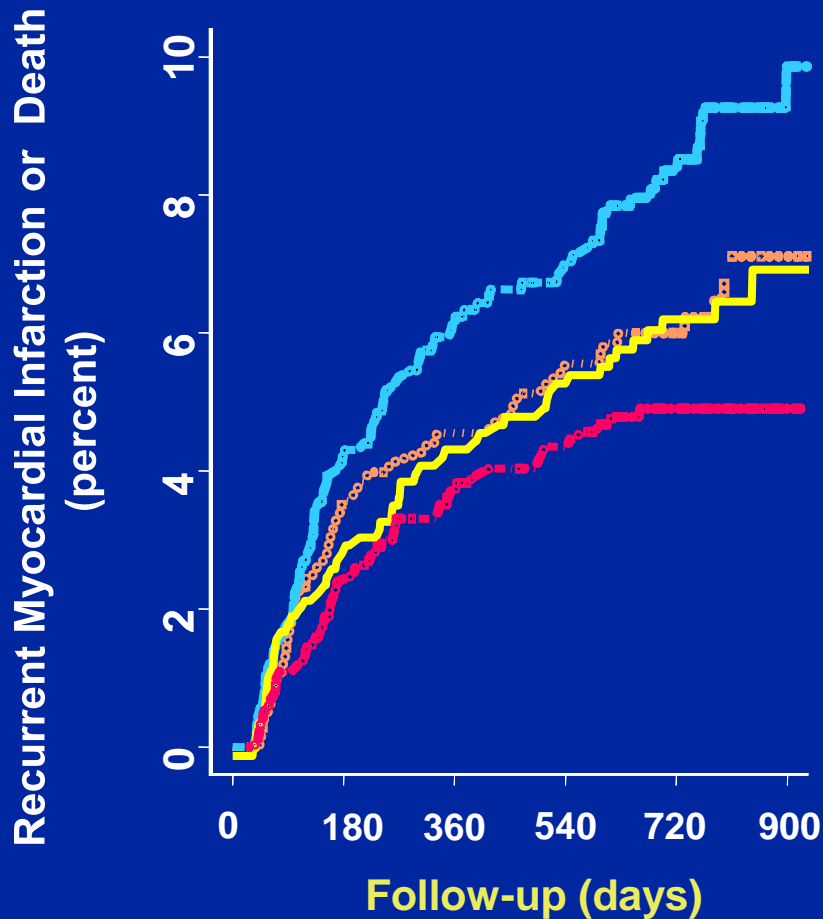
Number at Risk

Rosuvastatin	7,716	7,699	7,678	6,040	3,608	1,812	1,254	913	508	145
Placebo	7,832	7,806	7,777	6,114	3,656	1,863	1,263	905	507	168

P < 0.0001

Clinical Relevance of Achieving LDL-C < 70 mg/dL and hsCRP < 2 mg/L Following Initiation of Statin Therapy

LDL>70, hsCRP>2 LDL<70, hsCRP>2 LDL>70, hsCRP<2 LDL<70, hsCRP<2



JUPITER – algumas implicações

1. A eficácia das estatinas (rosuvastatina) em prevenção primária, após JUPITER, fica

F.D.A.

Aprovou a rosuvastatina como 1º fármaco com eficácia no contexto da doença aterosclerótica, tendo a inflamação como alvo terapêutico

das estatinas, abrindo hipóteses até então não exploradas.

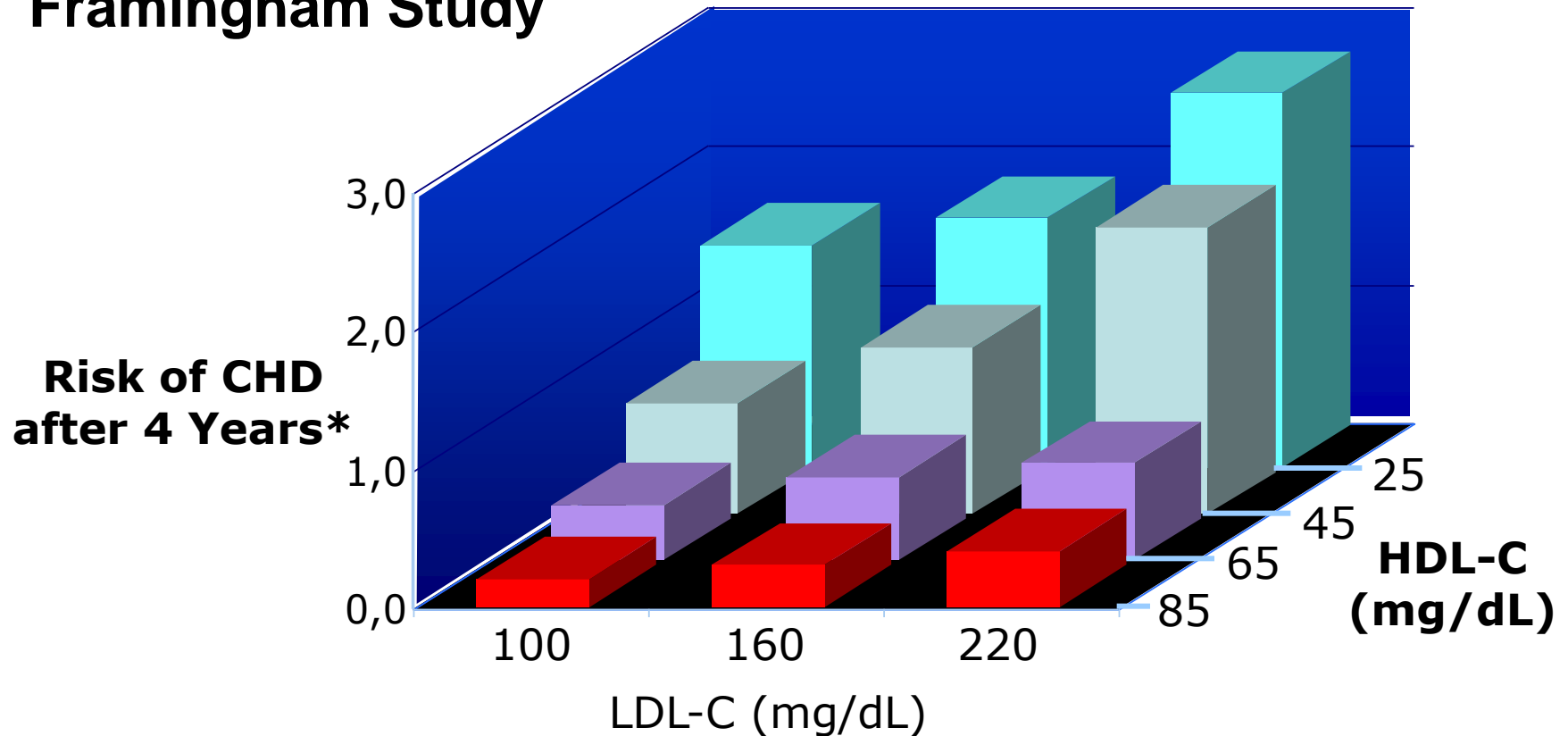
Para além do col-LDL

HDL

um velho problema a
aguardar novas soluções

Low HDL-C Levels Substantially Increase CHD Risk at all LDL-C Levels

Framingham Study

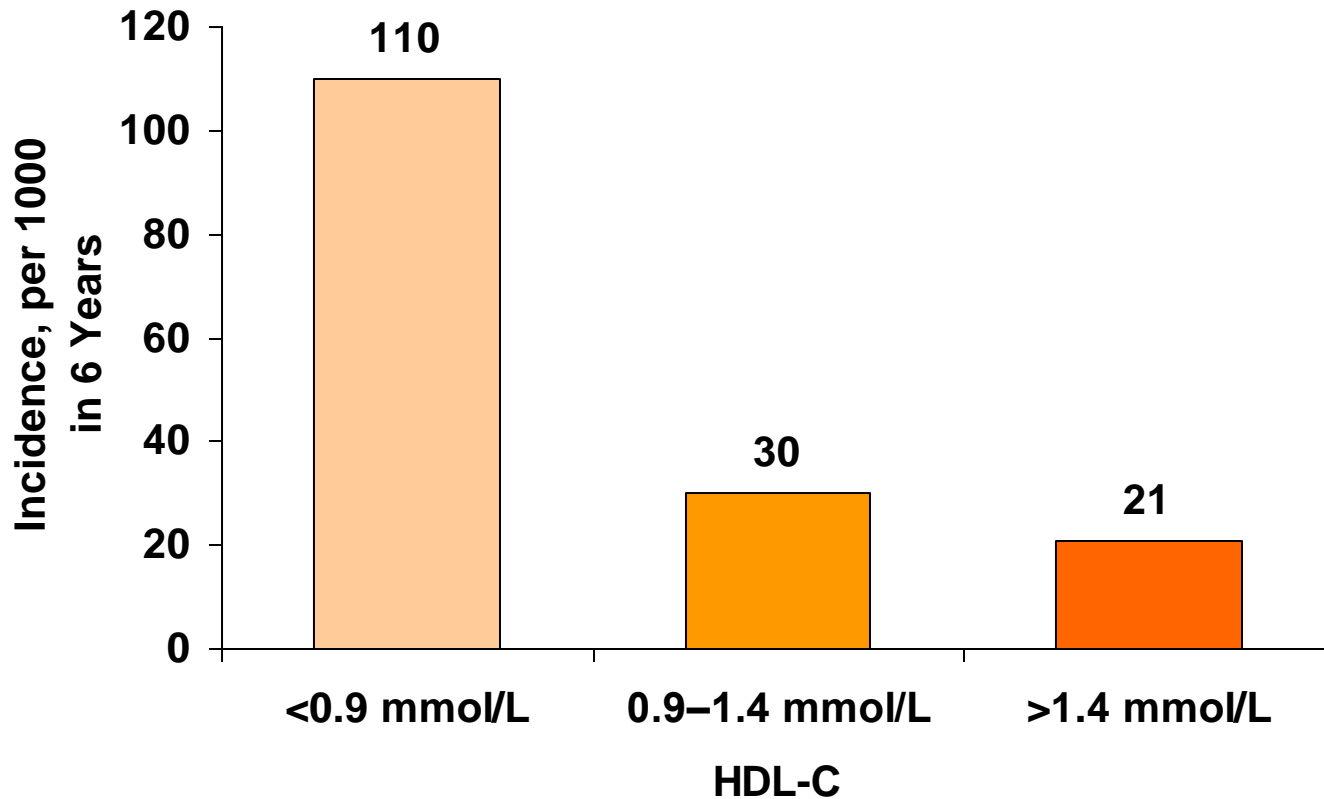


*Risk of coronary heart disease (CHD) over 4 years of follow-up for men ages 50 to 70

Adapted from Castelli WP. *Can J Cardiol* 1988;4 Suppl A:5A-10A.

HDL-C: Inverse Correlation With CHD Risk

Prospective Cardiovascular Münster (PROCAM) Study

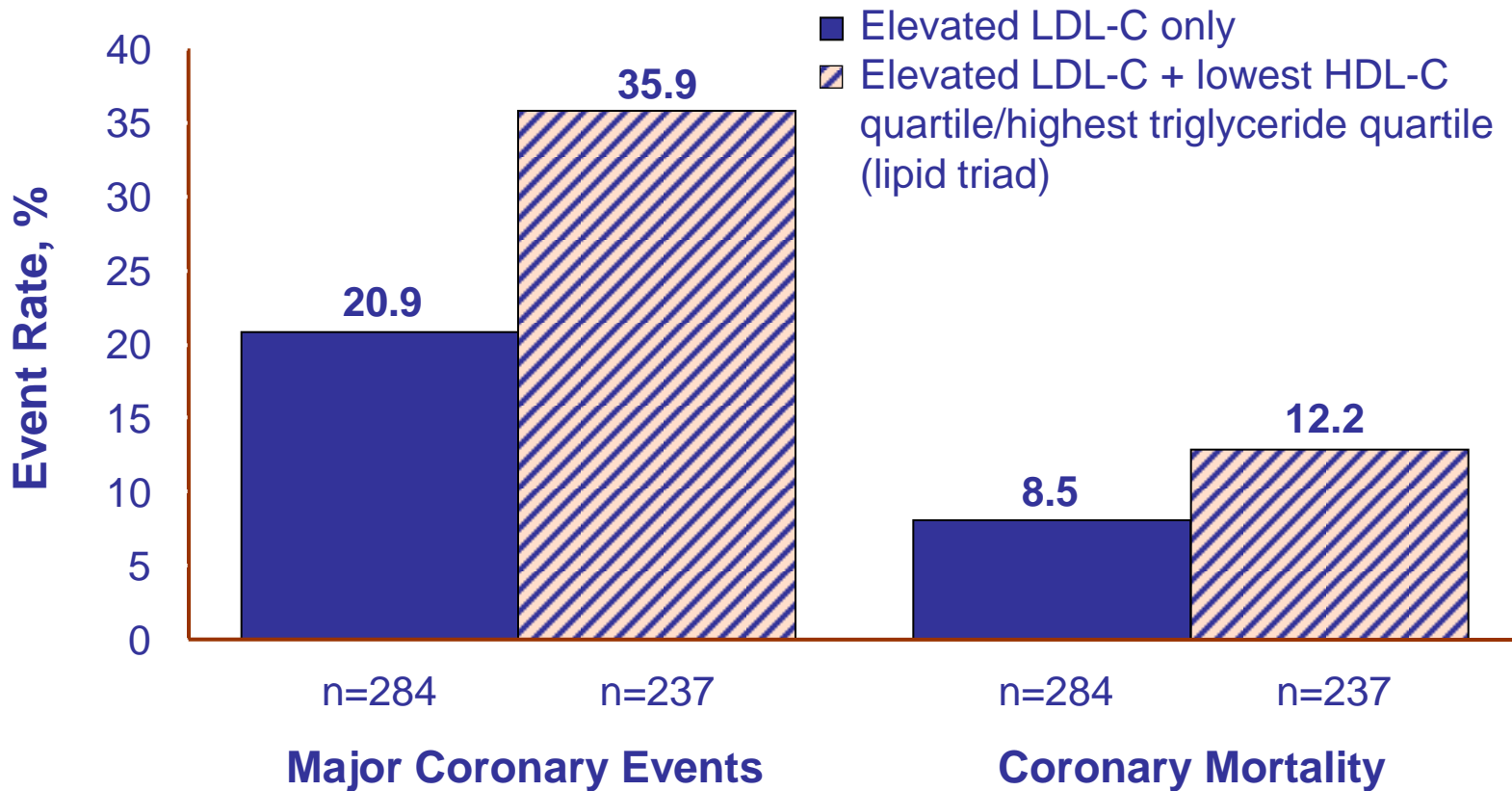


HDL-C=high-density lipoprotein cholesterol; CHD=coronary heart disease

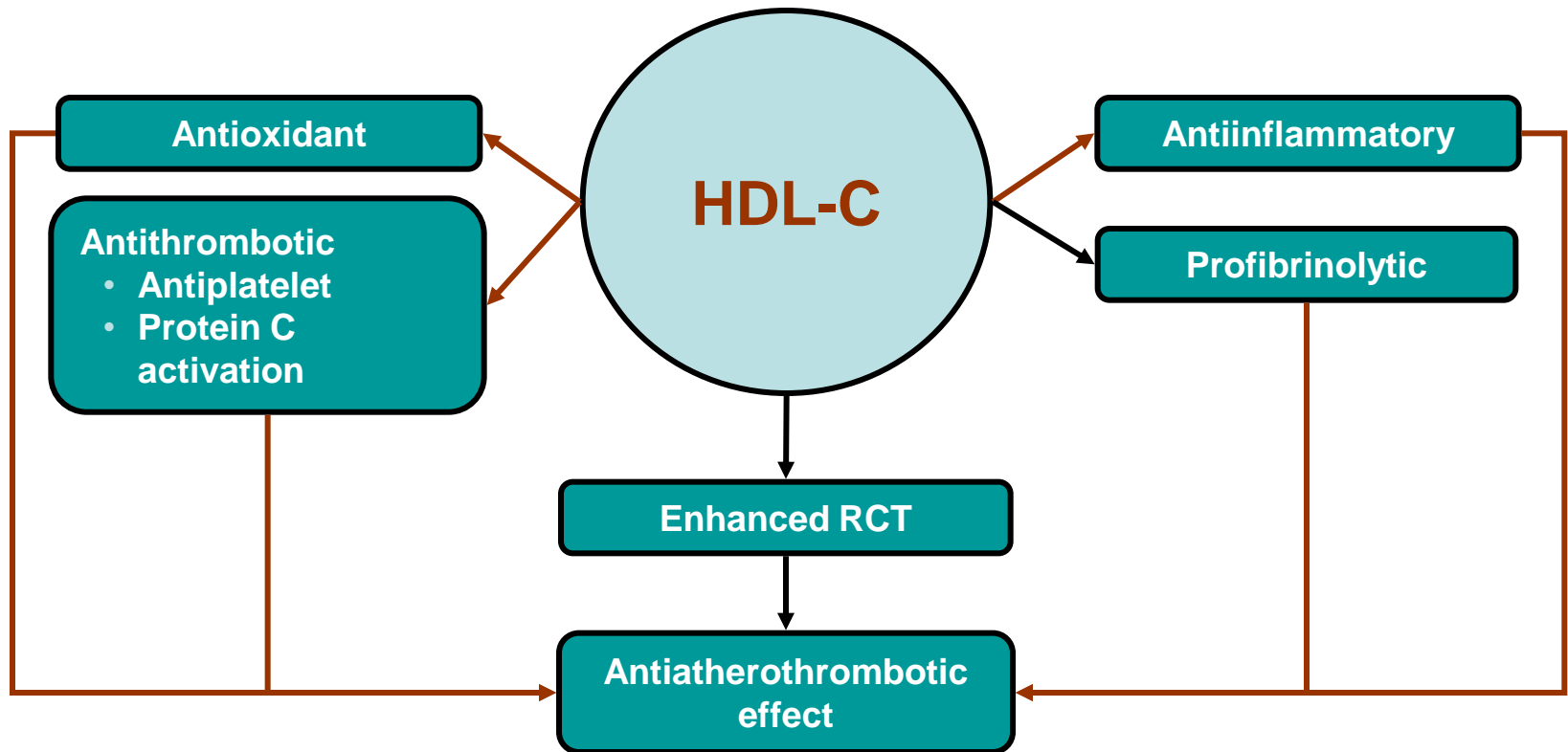
Adapted from Assmann G et al. In: *Lipid Metabolism Disorders and Coronary Heart Disease: Primary Prevention, Diagnosis and Therapy Guidelines for General Practice*. 2nd ed. Munich: MMV Medizin Verlag; 1993:19–67. Permission pending.

“Lipid Triad” Increases Coronary Risk vs Elevated LDL-C Only

Scandinavian Simvastatin Survival Study (4S) Placebo Arm — Subgroup Analysis



Multiple Biological Actions of HDL-C as a Potential Basis for Antiatherosclerotic Activity



HDL como novo alvo terapêutico

Como intervir ?

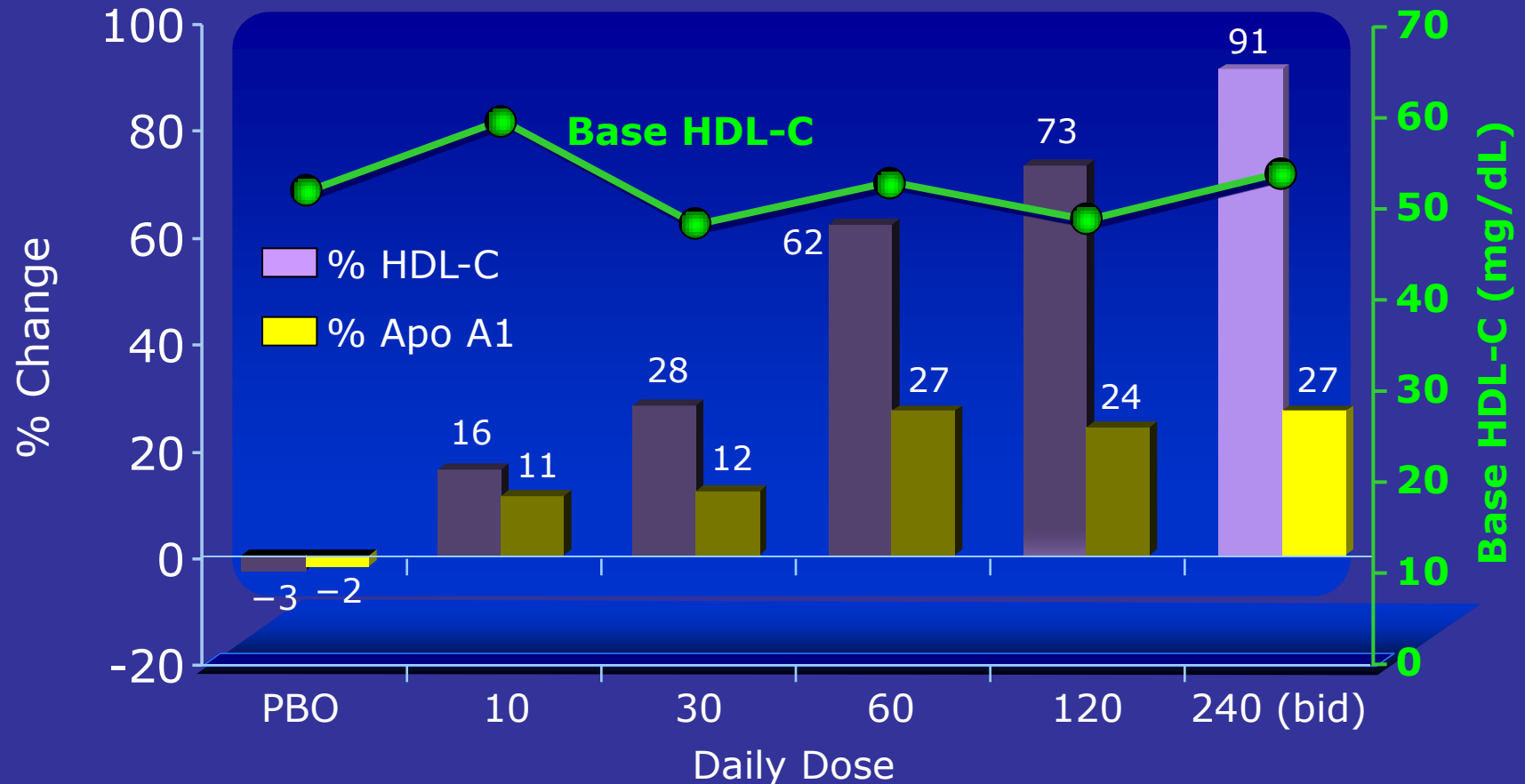
Nonpharmacologic Therapies to Raise HDL-C

Therapeutic Intervention	Increase in HDL-C Levels (%)	Mechanism of Action
Aerobic exercise	5–10	<ul style="list-style-type: none"> • ↑ Pre-β-HDL • ↑ Reverse cholesterol transport • ↑ LPL and atheroprotective subpopulations
Tobacco cessation	5–10	<ul style="list-style-type: none"> • ↑ LCAT and reverse cholesterol transport • ↓ CETP
Weight loss	0.009 mmol/L for each kilogram of weight lost	<ul style="list-style-type: none"> • ↑ LCAT • ↑ Reverse cholesterol transport • ↑ LPL
Alcohol consumption	5–15	<ul style="list-style-type: none"> • ↑ ABCA1 • ↑ apo A-1 and paraoxonase • ↓ CETP
Dietary factors (n-3 PUFA, n-6 PUFA, MUFA)	0–5	<ul style="list-style-type: none"> • Improves LDL-C: HDL-C ratio and ↑ atheroprotective subpopulations

HDL-C=high-density lipoprotein cholesterol; LPL=lipoprotein lipase; LCAT=lecithin-cholesterol acyltransferase; CETP=cholesteryl ester transfer protein; ABCA1=adenosine triphosphate-binding cassette transporter A1; apo A-1=apolipoprotein A-1; PUFA=polyunsaturated fatty acid; MUFA=monounsaturated fatty acid
 Reprinted with permission from Singh IM et al. *JAMA*. 2007;298:786–798.

Torcetrapib: Pharmacodynamic Effect on HDL-C in Phase 1

Phase I Summary of Lipid and Lipoprotein Changes



Changes are following 2 weeks of treatment; n=6 per active dose group; n=9 placebo (PBO)
Created from Clark RW et al. *Arterioscler Thromb Vasc Biol* 2004;
24:490-497.

Torcetrapib (Study A3071007) Consistent HDL-C Raising by Gender and Baseline HDL-C

Mean % Change:

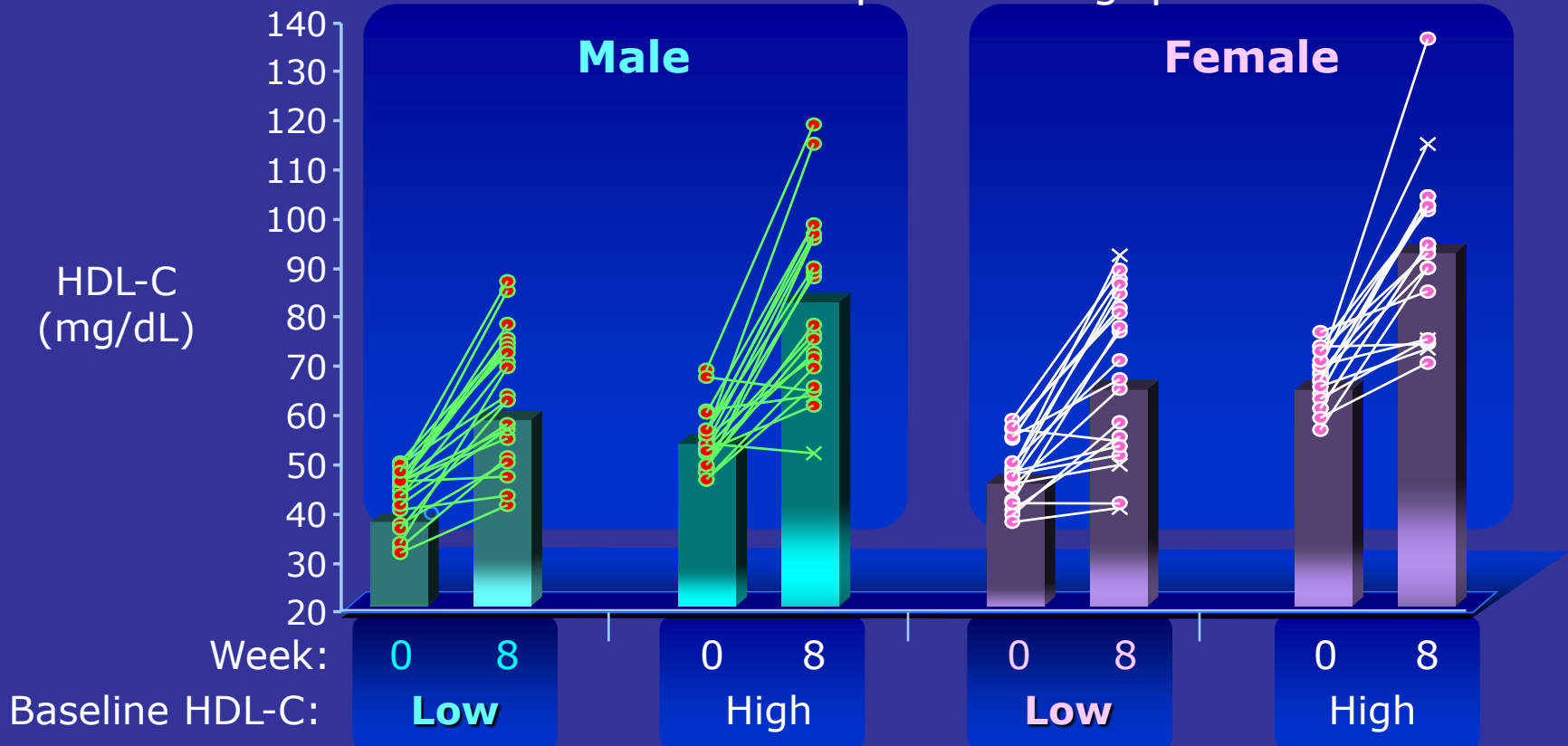
58%

55%

45%

42%

Torcetrapib 120 mg qd



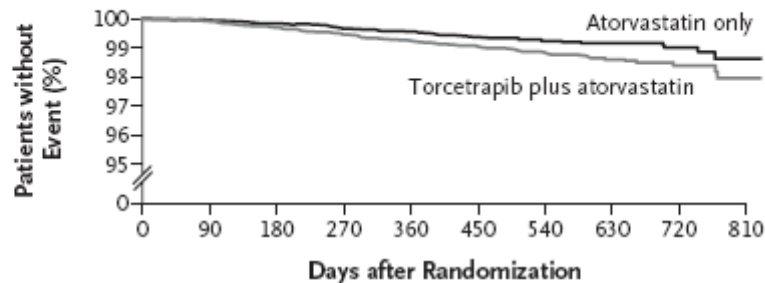
Created from Bamberger MJ et al. *Circulation* 2005;112:II-179.

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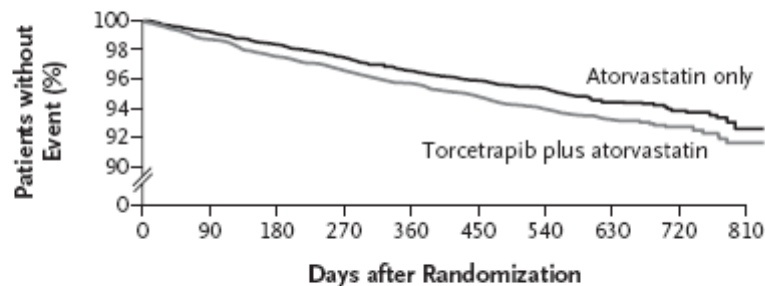
A Death from Any Cause



No. at Risk

Atorvastatin only	7534	7530	7521	7509	7487	5833	4043	2078	956	109
Torcetrapib plus atorvastatin	7533	7526	7511	7494	7464	5827	4049	2069	943	114

B Major Cardiovascular Events

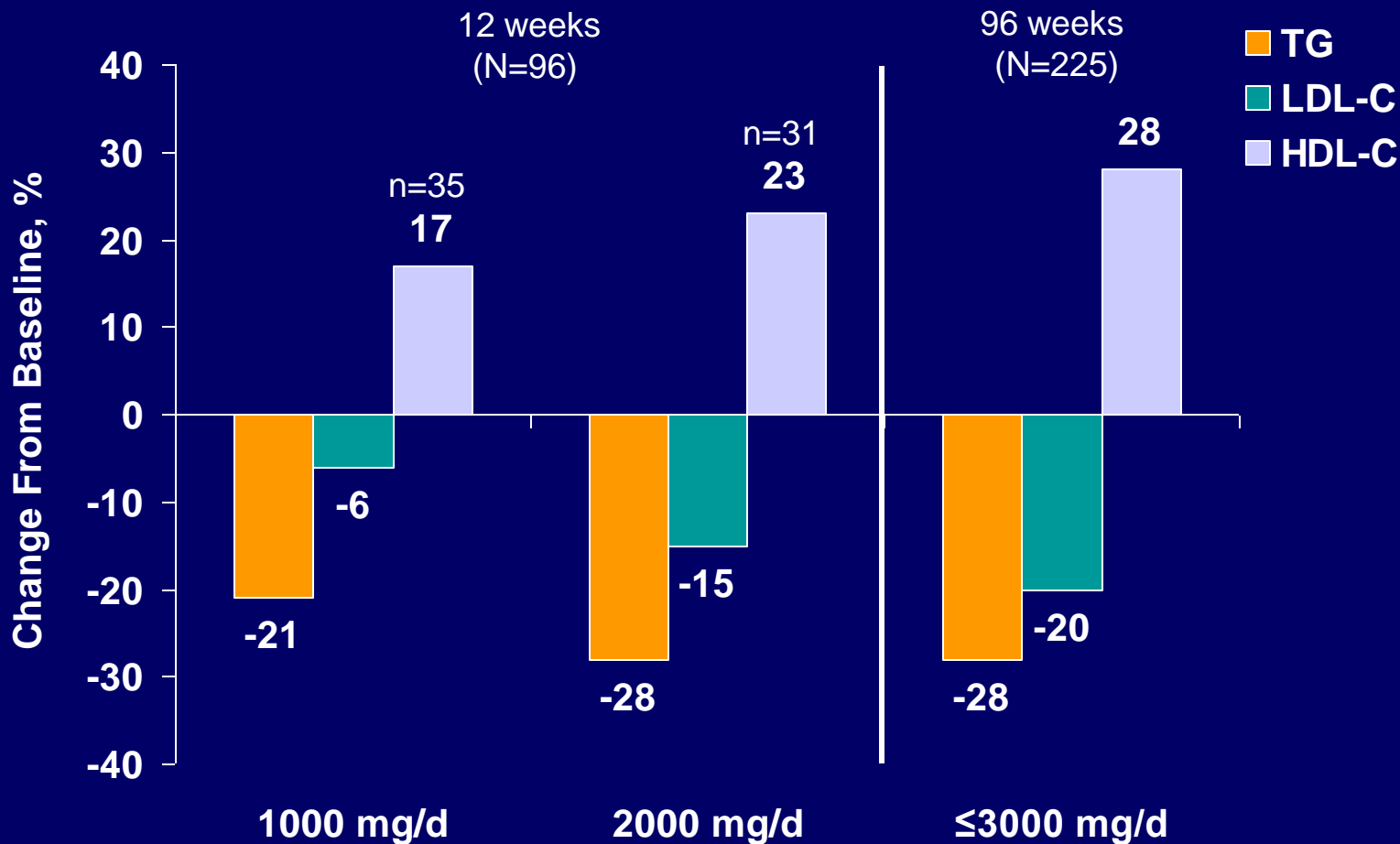


No. at Risk

Atorvastatin only	7534	7479	7406	7340	7255	5627	3872	1965	898	103
Torcetrapib plus atorvastatin	7533	7434	7345	7267	7177	5567	3838	1953	888	107

↑ HDL – 72%
↑ mortalidade – 58%
↑ eventos CV – 25%

ER Niacin for Treatment of Dyslipidemia

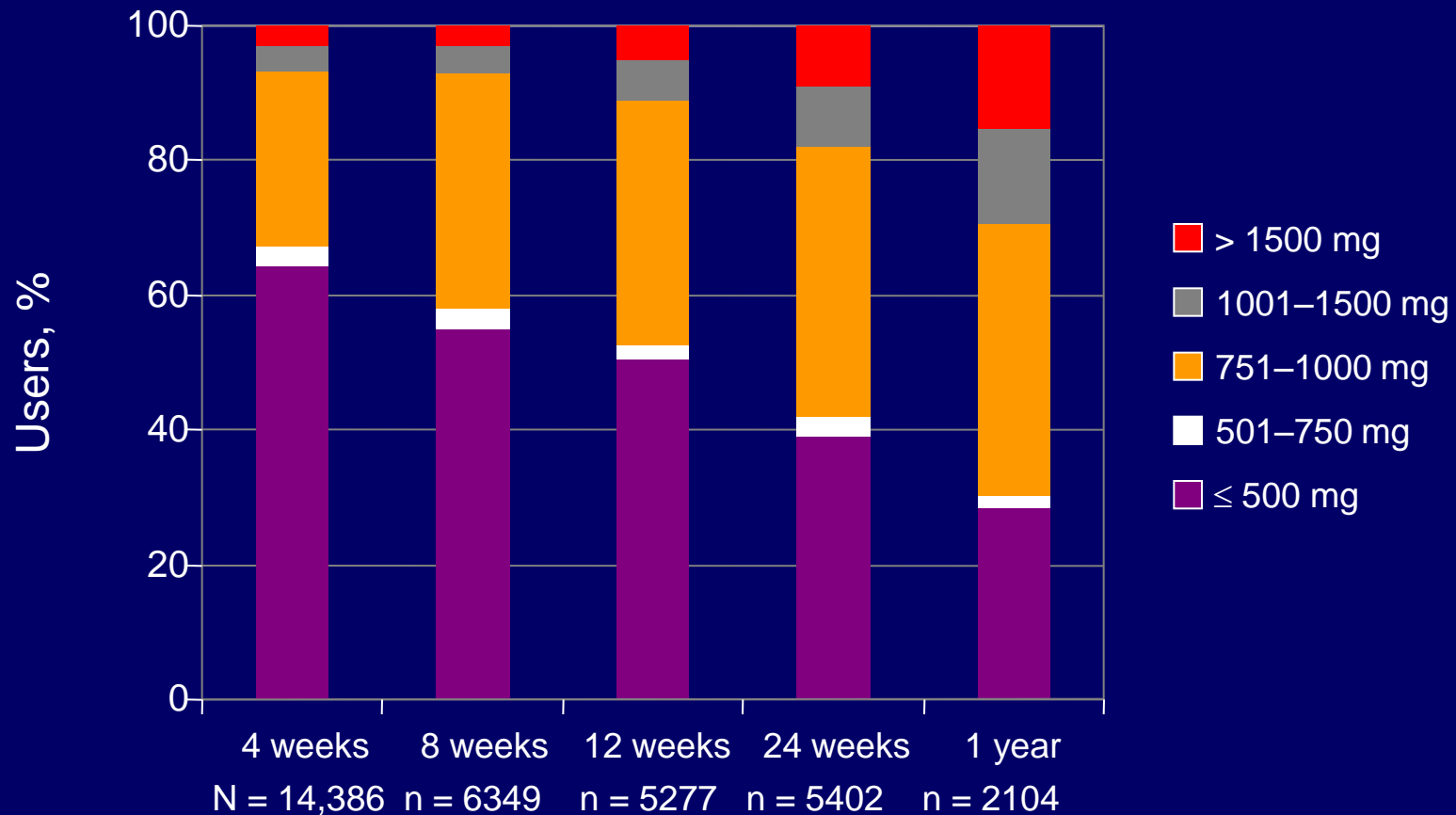


All, significant change from baseline, $P < 0.001$

ER=extended release; TG=triglycerides; LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol

Morgan JM et al. *Am J Cardiol.* 1998;82(12A):29U–34U; Capuzzi DM et al. *Am J Cardiol.* 1998;82(12A):74U–81U.

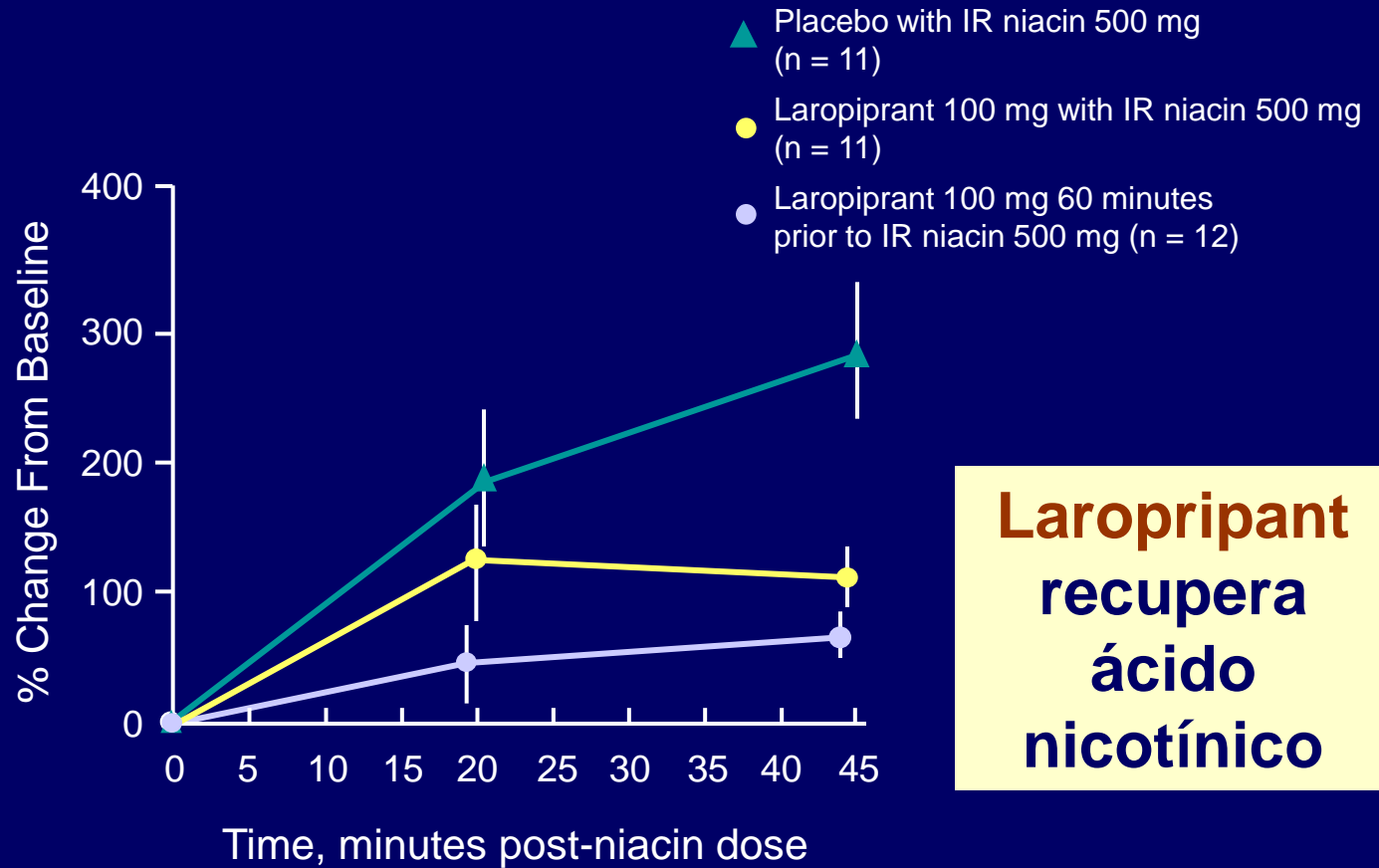
Most Patients on ER Niacin Therapy Do Not Reach a 2-g Dose



Retrospective cohort study using administrative claims data from 2000 to 2003 Ingenix Lab/Rx Database™.
Kamal-Bahl S, Burke T, Watson D et al. Dosage and titration patterns of extended release niacin in clinical practice. Abstract presented at the 7th American Heart Association Scientific Forum on Quality of Care and Outcomes Research in Cardiovascular Disease and Stroke; May 2006; Washington, DC, USA.

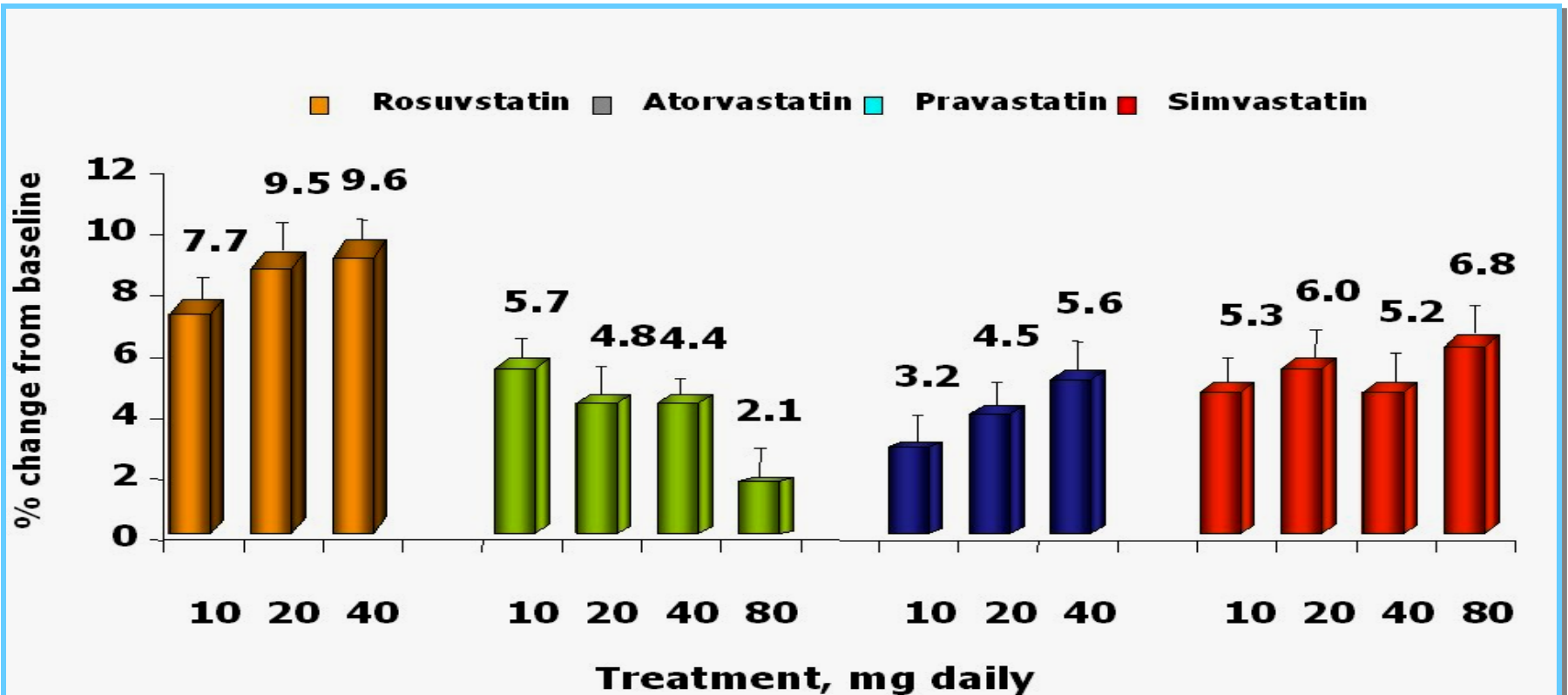
Proof of Concept in Humans: Laropiprant Reduces Niacin-Induced Vasodilation

As seen with laser Doppler perfusion imaging



Adapted from Cheng K et al. *Proc Natl Acad Sci U S A*. 2006;103:6682–6687.

Eficácia relativas das estatinas sobre c-HDL



$P < .002$ Rosuvastatin 10 mg vs Pravastatin 10 mg.

$P < .002$ Rosuvastatin 20 mg vs Atorvastatin 20 mg, 40 mg, 80 mg; Pravastatin 20 mg, 40 mg; Simvastatin 40 mg.

$P < .002$ Rosuvastatin 40 mg vs Atorvastatin 40 mg, 80 mg; Pravastatin 40 mg; Simvastatin 40 mg.
Data presented as least squares means \pm standard errors.

Para uma estratégia global de prevenção

