Enhancing CV outcomes:
Treat CV risk factors, not just cholesterol

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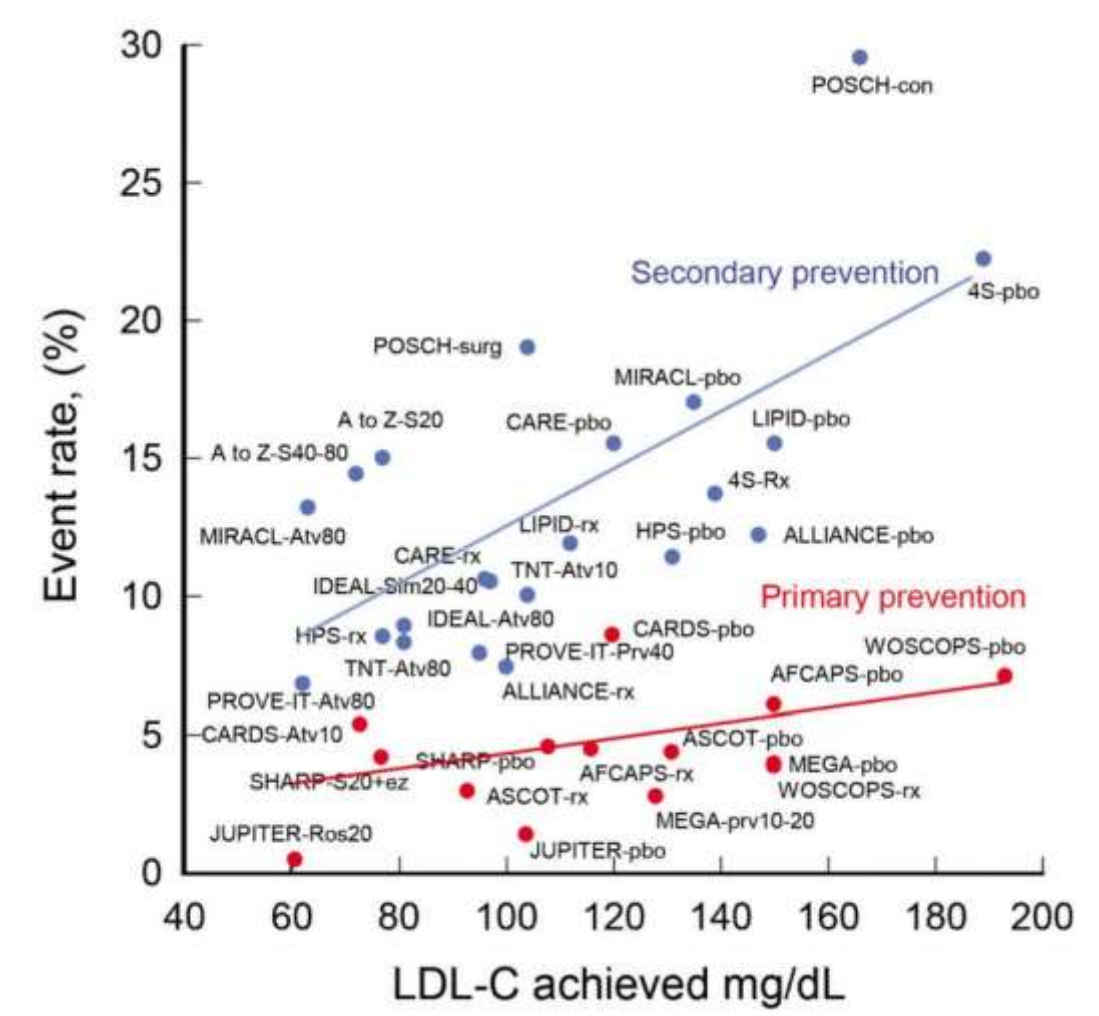
The Lower, The better

Benefits of lowering LDL-cholesterol and CHD risk

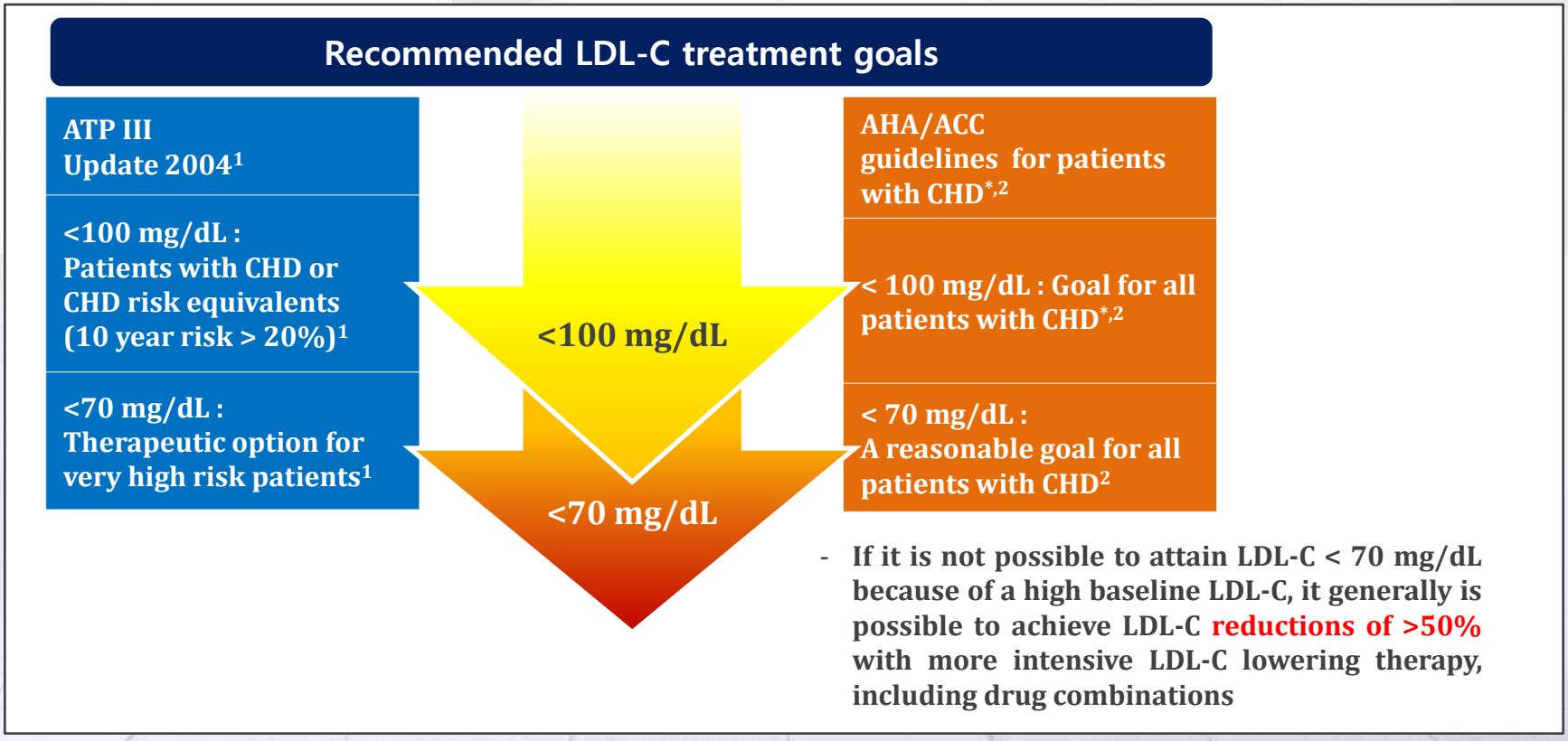
Major lipid trials: LDL-C levels vs rate of coronary event rate



Raymond C et al. Cleve Clin J Med. 2014 Jan;81(1):11-9

Changing Target !

- **LDL was the primary target.**
- **Guideline has been changed to the lower goal.**

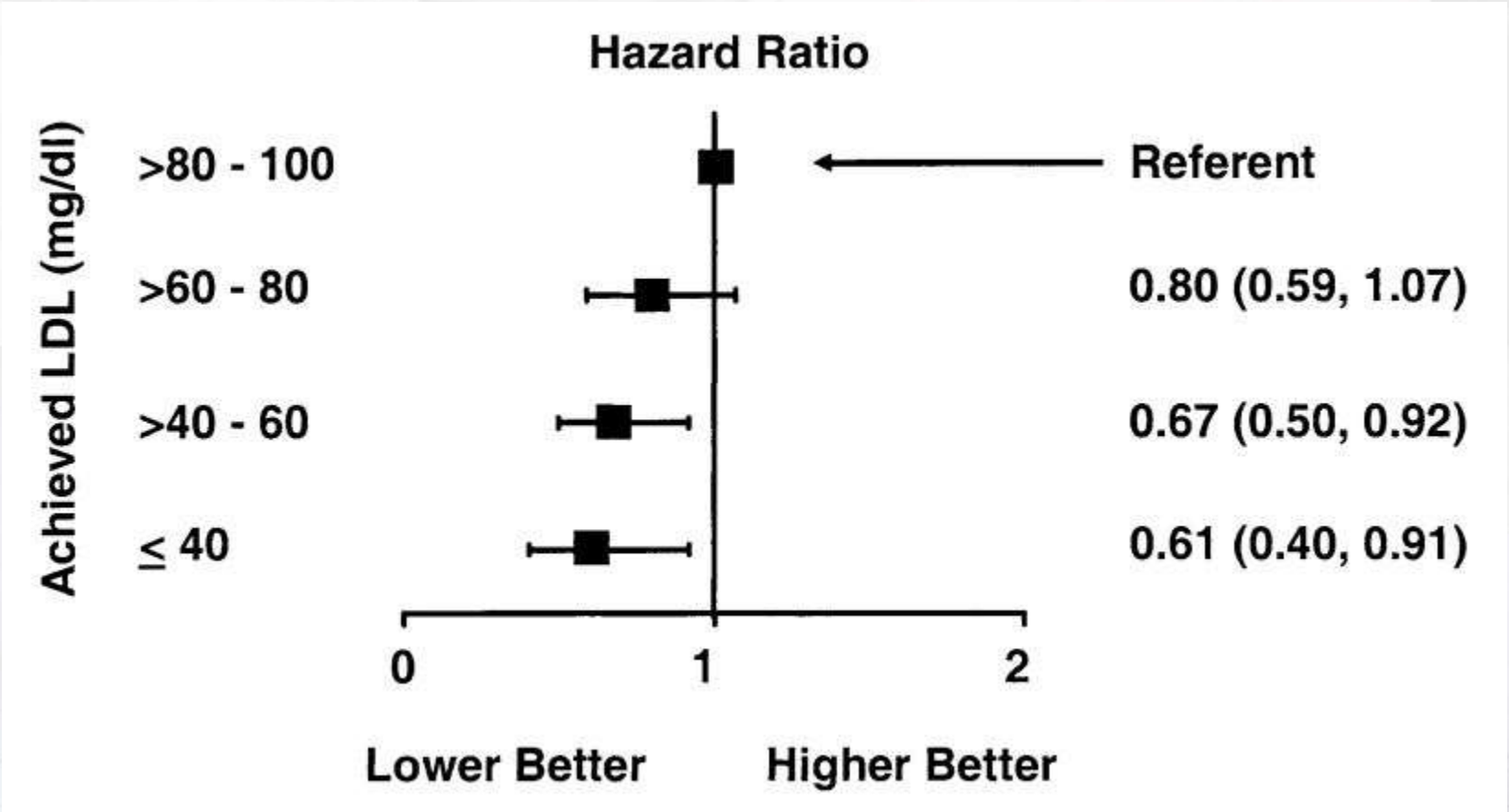


† Factors that place a patient at very high risk: established cardiovascular disease plus: multiple major risk actors (especially diabetes); severe and poorly controlled risk factors (e.g., cigarette smoking); metabolic syndrome (triglycerides ≥200 mg/dL + non–HDL-C ≥130 mg/dL with HDL-C <40 mg/dL); and acute coronary syndromes.[1] *And other forms of atherosclerotic disease.[2]

1. Grundy SM et al. Circulation 2004;110:227–239.
2. Smith SC Jr et al. Circulation 2006; 113:2363–2372.

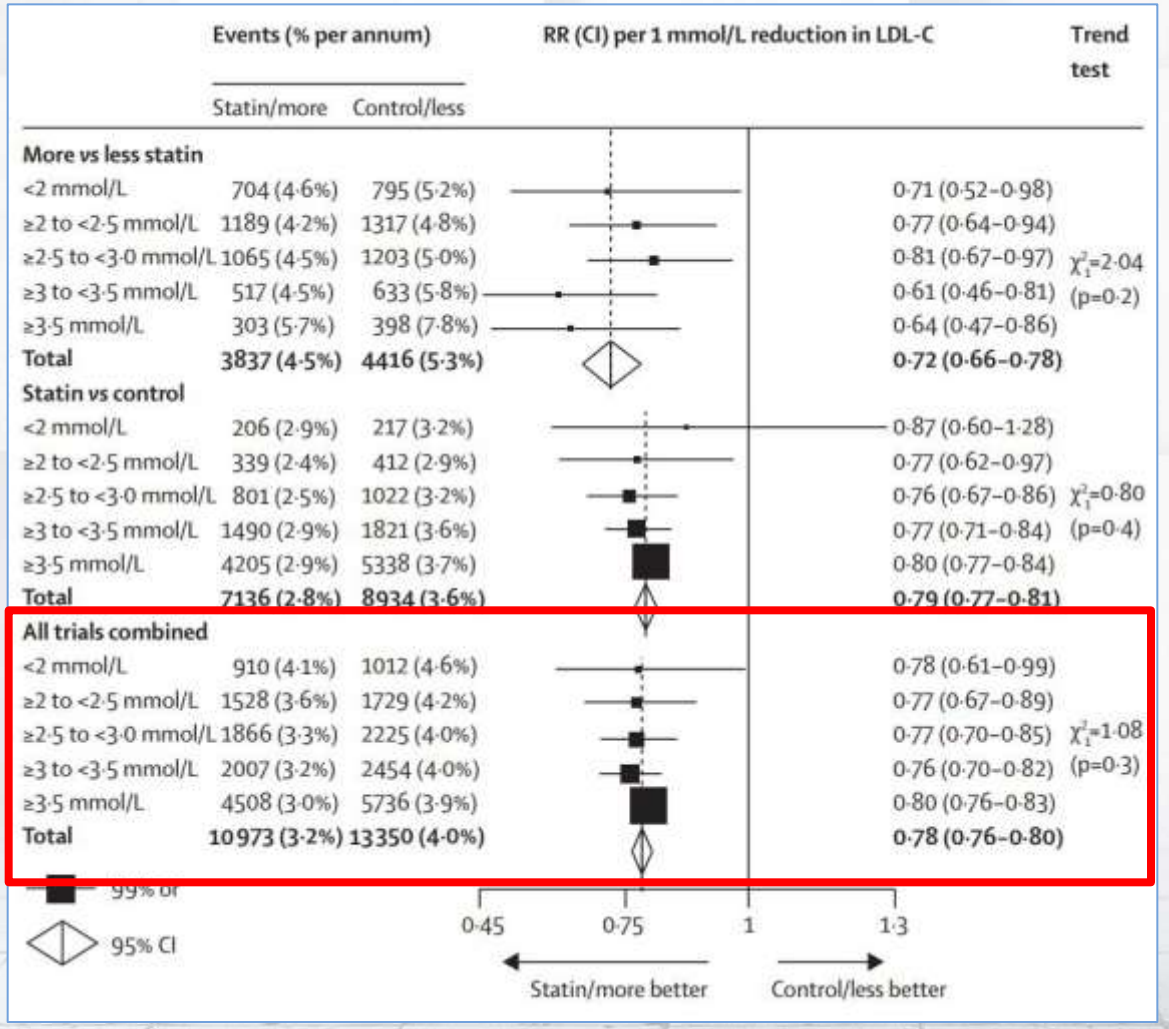
Adapted from Wang CY, et al. Trends Mol Med 2008;14:37–44.

PROVE IT-TIMI 22 in ACS :
The Lower LDL, The Lower Event, even under 100 mg/dL



Wiviott SD et al. J Am Coll Cardiol. 2005;46:1411-6.

Effects of 1.0 mmol/L reduction in LDL-cholesterol



No evidence of a lower limit of LDL-Cholesterol, below which a reduction did not provide benefit.

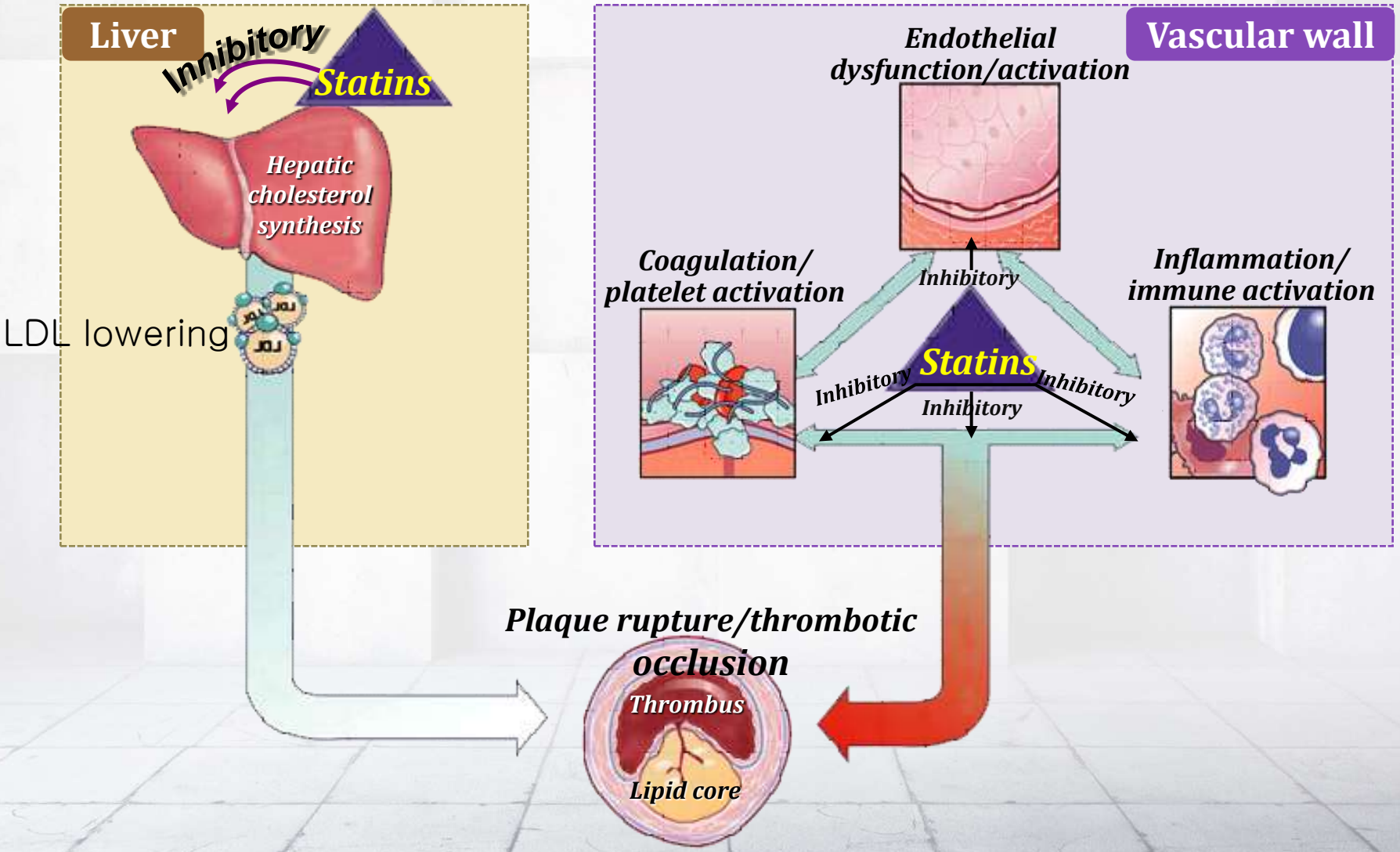
Cholesterol Treatment Trialists' (CTT) Collaboration. Lancet 2010;376:1670-81

Statin - CV outcome studies demonstrating significant benefit

	Primary Prevention				Secondary prevention		
	High-cholesterol with multiple risk factor	ELEVATED CRP and low/ normal LDL-C	Hypertension+ multiple risk factors	Type 2 Diabetes	Stable CHD	Stroke /TIA	ACS
Atorvastatin			ASCOT-LLA	CARDS	GREACE ALLIANCE TNT	SPARCL	MIRACL PROVE-IT
Rosuvastatin		JUPITER	HOPE-3				
Simvastatin				HPS-DM	4S		A TO Z
Pravastatin	WOSCOPS				CARE LIPID		

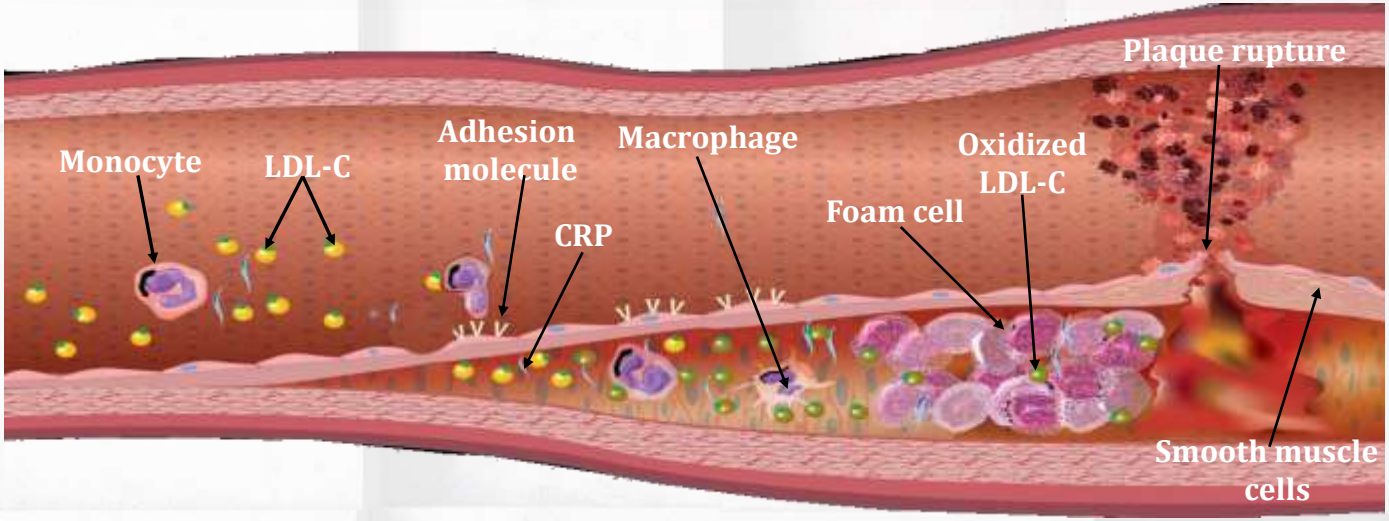

What is possible mechanism proven by trial?

Not just LDL lowering, but also Pleiotropic effects of statin, in Acute Coronary Syndrome



Adapted from Ray KK et al. J Am Coll Cardiol. 2005;46:1425-1433.

Benefits of statins beyond lipid lowering



Endothelial dysfunction → Inflammation → Oxidation → Plaque instability and thrombus

- Improve Endothelial function
- Anti-inflammatory actions
- Antioxidant Action
- Plaque Stabilization
- Antithrombotic effects

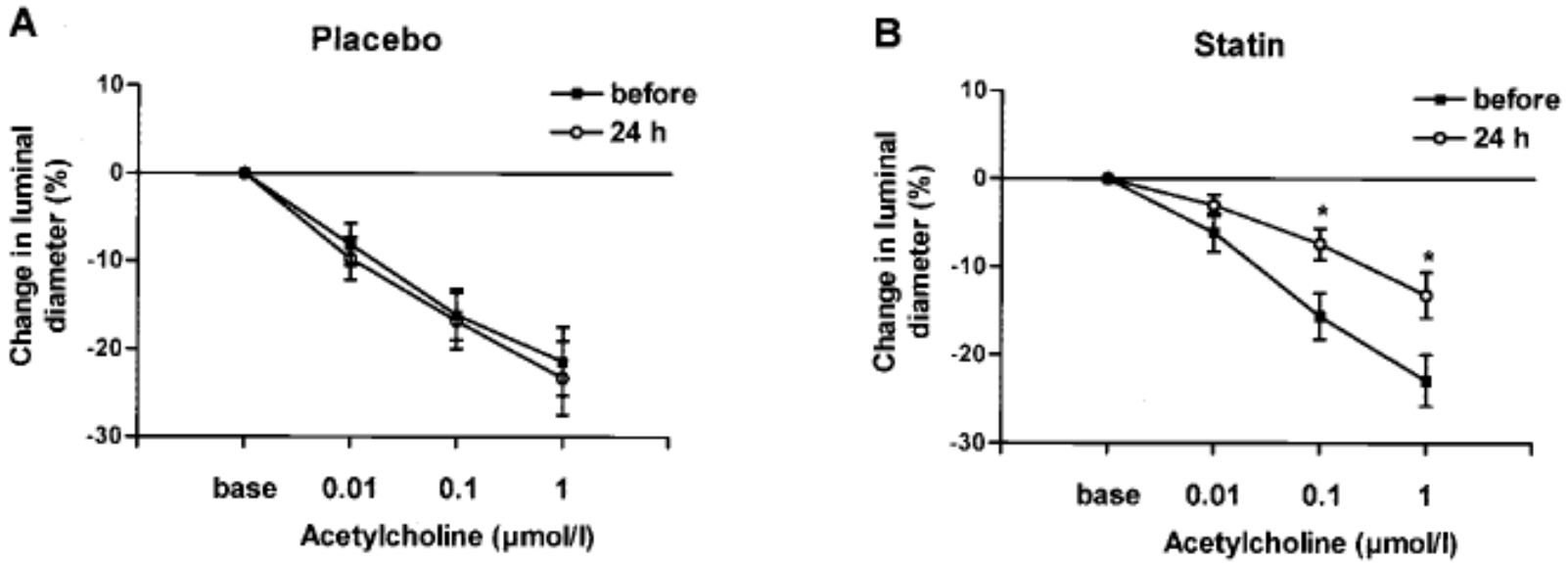
Adapted from Libby P, et al. Circulation. 2001;104:365-372.

Improvement of Endothelial Function

Endothelial function

N=27 pts with stable angina,
randomized to placebo or pravastatin (single dose of 40 mg).

[Changes in coronary luminal diameter in response to increasing doses of acetylcholine]



At 24 hrs, significant attenuation of acetylcholine-mediated vasoconstriction

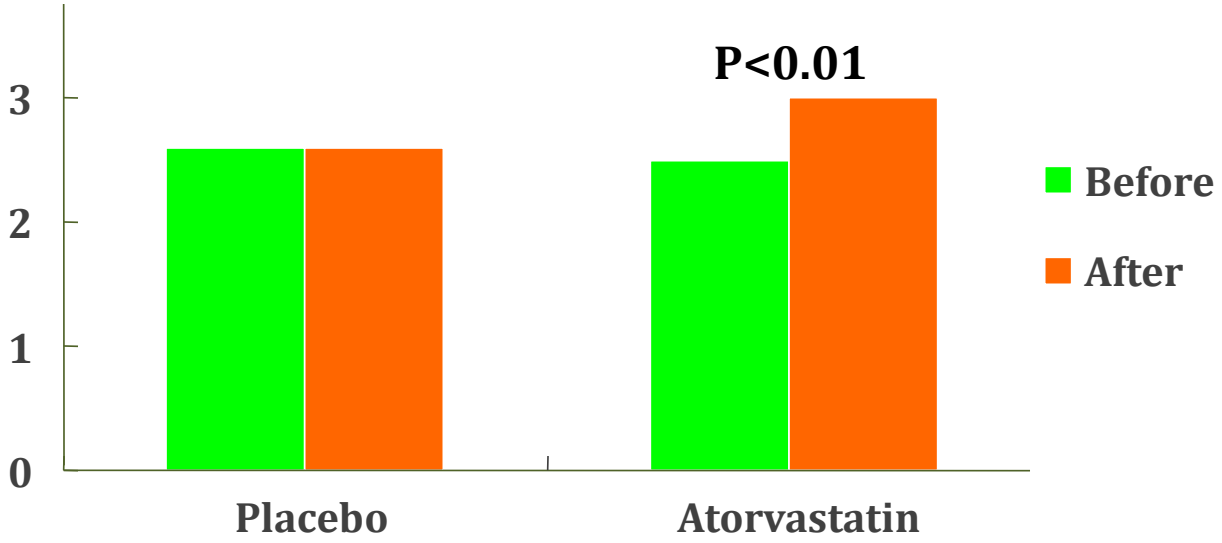
Wassmann S, et al. Circ Res 2003.

Vasodilation of Coronary Microvessels

Endothelial function

N=32 pts without CAD,
randomized to placebo or atorvastatin (single dose of 40 mg).

The time-averaged peak diastolic velocity (APDV) of the left anterior descending artery without stenosis was measured by transthoracic Doppler echocardiography at rest and under hyperemic conditions before and 1 hour after treatment.



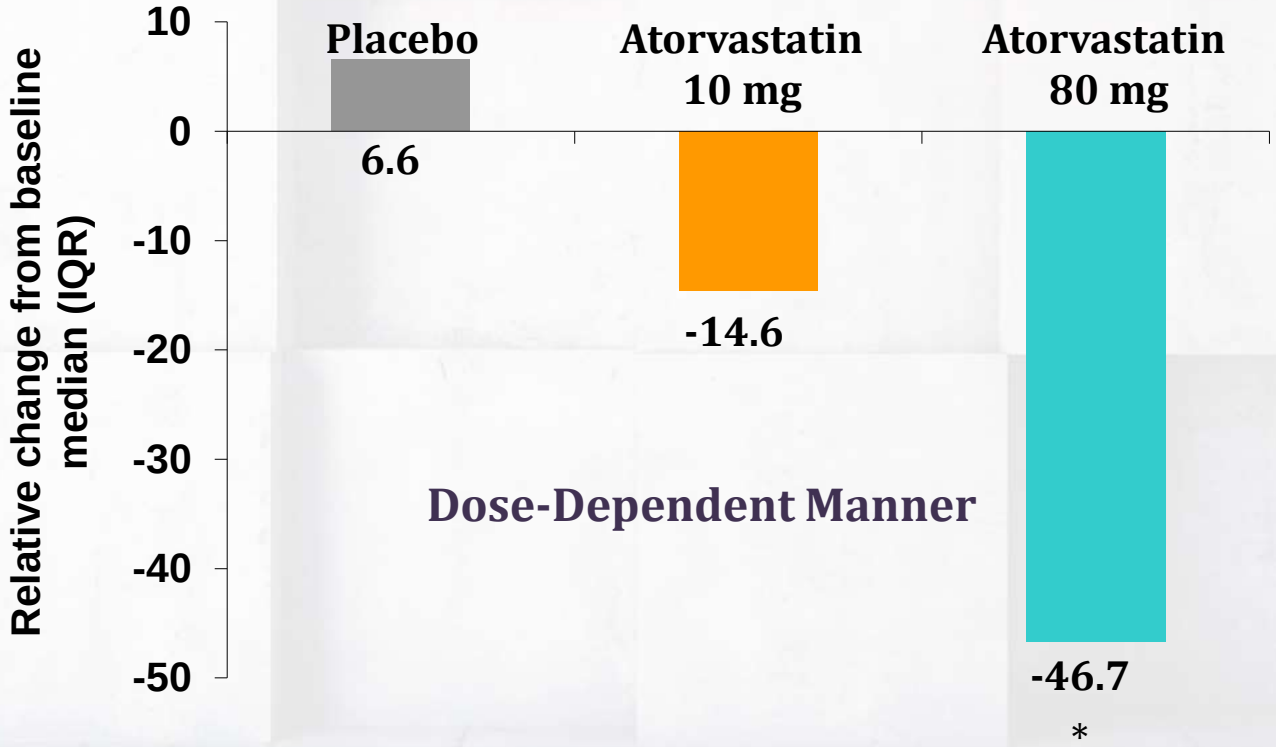
Significantly improvement of
the blood flow velocityof the normal coronary artery

Hinoi T, et al. Am J Cardiol 2005.

CRP Lowering in Type 2 Diabetes

anti inflammatory effect

after 6 weeks of therapy



*P<.001.

DALI=diabetes atorvastatin lipid intervention study.
IQR=interquartile range

van de Ree MA et al. *Atherosclerosis*. 2003;166:129-135.

van de Ree MA, Huisman MV, Princen HMG, et al. Strong decrease of high sensitivity C-reactive protein with high-dose atorvastatin in patients with type 2 diabetes mellitus. Atherosclerosis. 2003;166:129-135.

Simvastatin Versus Atorvastatin on Oxidative Stress in Coronary Heart Disease

Antioxidant Action

[Lipid Concentrations and Markers of Oxidative Stress Before and After Statin Treatment]

	Control Group (n = 122)	Simvastatin Group (n = 80)			Atorvastatin Group (n = 84)		
		Before Treatment	After Treatment	Change %	Before Treatment	After Treatment	Change %
LDL-C, mmol/L	2.59 ± 0.36	3.29 ± 0.76[a]	2.60 ± 0.57[b]	21.58 ± 3.46	3.31 ± 0.64[a]	2.55 ± 0.59[b]	22.97 ± 3.53
SOD, U/mgHb	39.06 ± 14.27	33.28 ± 11.63[a]	37.94 ± 16.11[b]	13.06 ± 2.15	32.23 ± 13.28[a]	38.25 ± 12.61[b]	18.25 ± 3.78[c]
MDA, μmol/L	3.76 ± 0.11	5.23 ± 0.13[a]	4.057 ± 0.14[b]	2.26 ± 0.37	5.42 ± 0.15[a]	3.82 ± 0.12[b]	2.95 ± 0.59[c]
NO, μmol/L	75.49 ± 10.21	59.25 ± 6.87[a]	68.72 ± 10.03[b]	13.18 ± 1.25	58.23 ± 9.28[a]	70.19 ± 10.08[b]	17.04 ± 2.66[c]
GPx, U/gHb	72.14 ± 22.16	87.36 ± 24.51[a]	78.48 ± 25.96[b]	11.81 ± 1.56	89.05 ± 27.94[a]	75.36 ± 25.85[b]	15.46 ± 2.89[c]

Abbreviations: GPx, glutathione peroxidase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDA, malondialdehyde; NO, nitric oxide; SOD, superoxide dismutase; TC, total cholesterol; TG, triglyceride; VLDL-C, very-low-density lipoprotein cholesterol.
Values are expressed as mean ± standard deviation, median (95% confidence interval).
[a] $P < 0.05$ compared with controls.
[b] $P < 0.05$ compared with before treatment.
[c] $P < 0.05$ compared with simvastatin group.

Atorvastatin reduces oxidative stress more effectively than simvastatin.

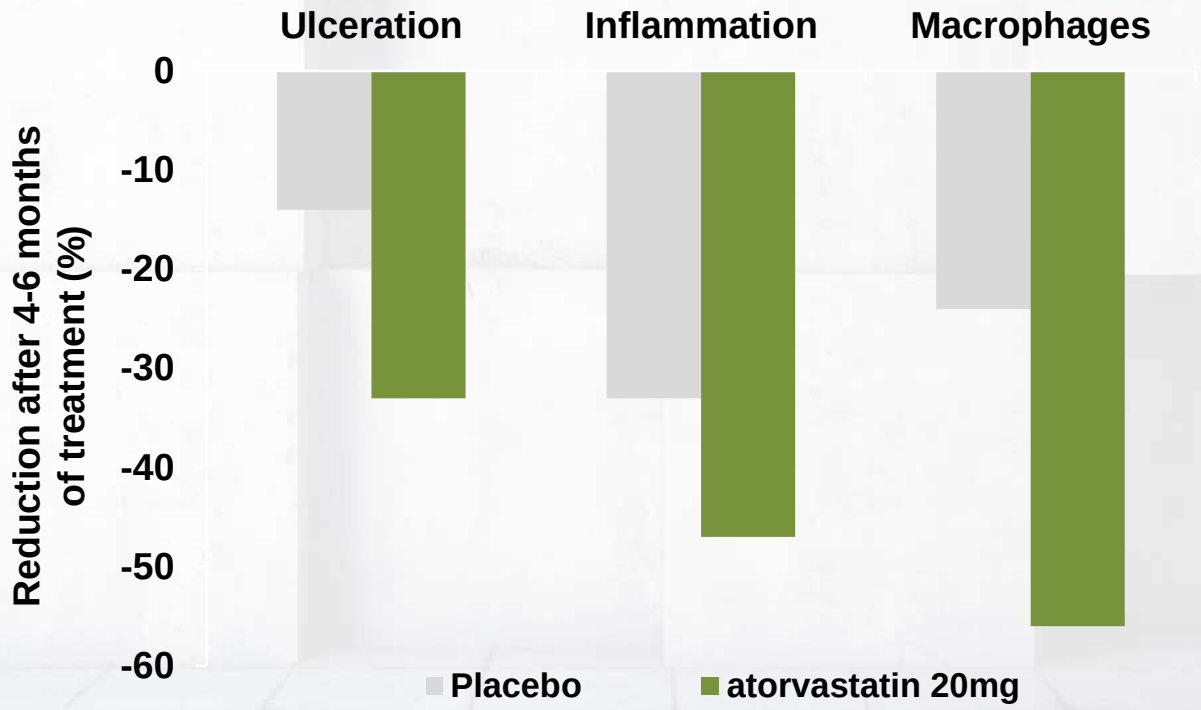
The changes in the markers of oxidative stress did not correlate with the changes in the plasma lipid profile.

J. Li et al: Simvastatin versus atorvastatin for oxidative stress in CHD Clin. Cardiol. 33, 4, 222–227 (2010

ATROCAP: Stabilize Carotid Plaques

Anti thrombotic effects

N=59 pts with bilateral carotid stenosis for two-step carotid endarterectomy (CEA) randomized to placebo or atorvastatin 20 mg.



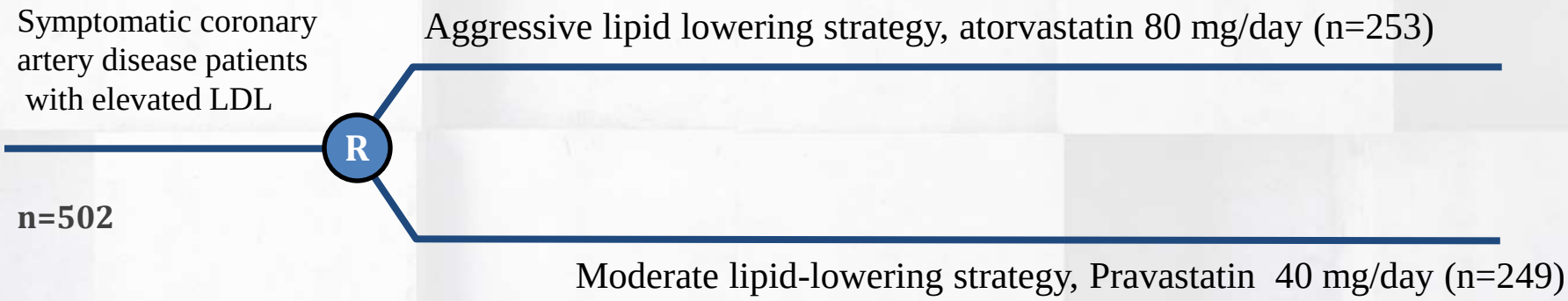
"Plaque stabilization may be an important process by which statins reduce vascular event rates."

Cortellaro M, et al. Thromb Haemost. 2002;88:41-47.

Plaque Stabilized effect

REVERSAL : Reversal of Coronary Atherosclerosis with Aggressive Lipid Lowering

- **Objectives :** Comparison of intensive lipid lowering effect of atorvastatin 80 mg with pravastatin 40 mg, in symptomatic CAD
- **Methods:** Prospective, randomized, double-blind, multicenter



- **Primary end point :**

  Percent change in atheroma volume on IVUS between baseline

- **Secondary end point :**

  Absolute change in atheroma volume; change in the percent obstructive volume

- **Follow-up duration** : 18 months

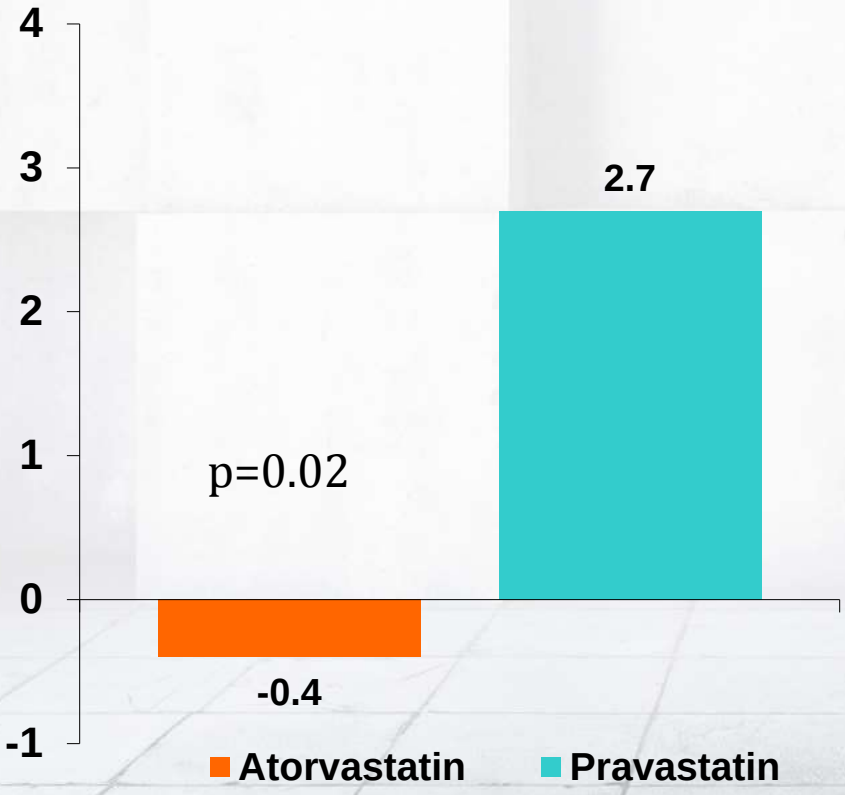
http://www.lipidsonline.org/commentaries/al_abstract.cfm?abs_id=abs048

N Engl J Med. 2005 Jan 6;352(1):29-38.

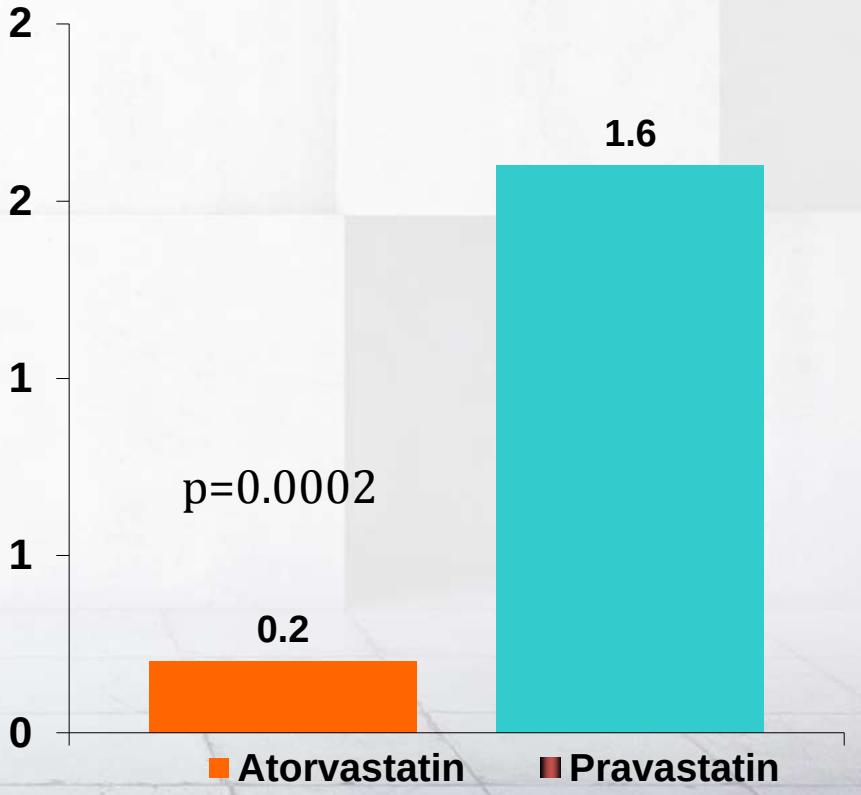
Plaque Stabilized effect

REVERSAL : Reversal of Atherosclerosis with Aggressive Lipid Lowering (18 months)

Change in atheroma volume



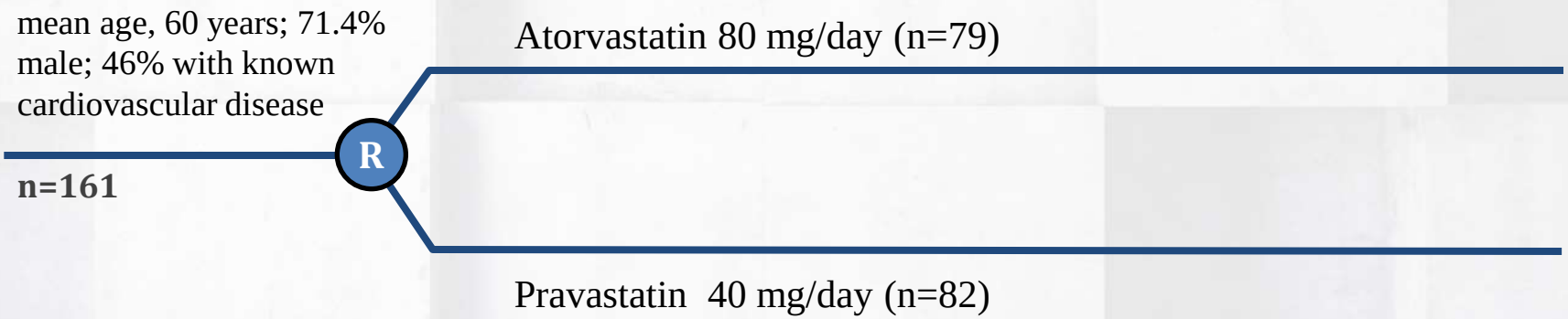
Change in percent obstruction volume



Plaque Stabilized effect

ARBITER: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol on Carotid Intima Medial Thickness

- **Objectives :** Comparison of intensive lipid lowering effect of atorvastatin 80 mg with pravastatin 40 mg
- **Methods:** Prospective, randomized, double-blind, single-center



- **Primary end point :**

LDL reduction, **Carotid intima-media thickness (CIMT)**

- **Follow-up duration** : 12 months

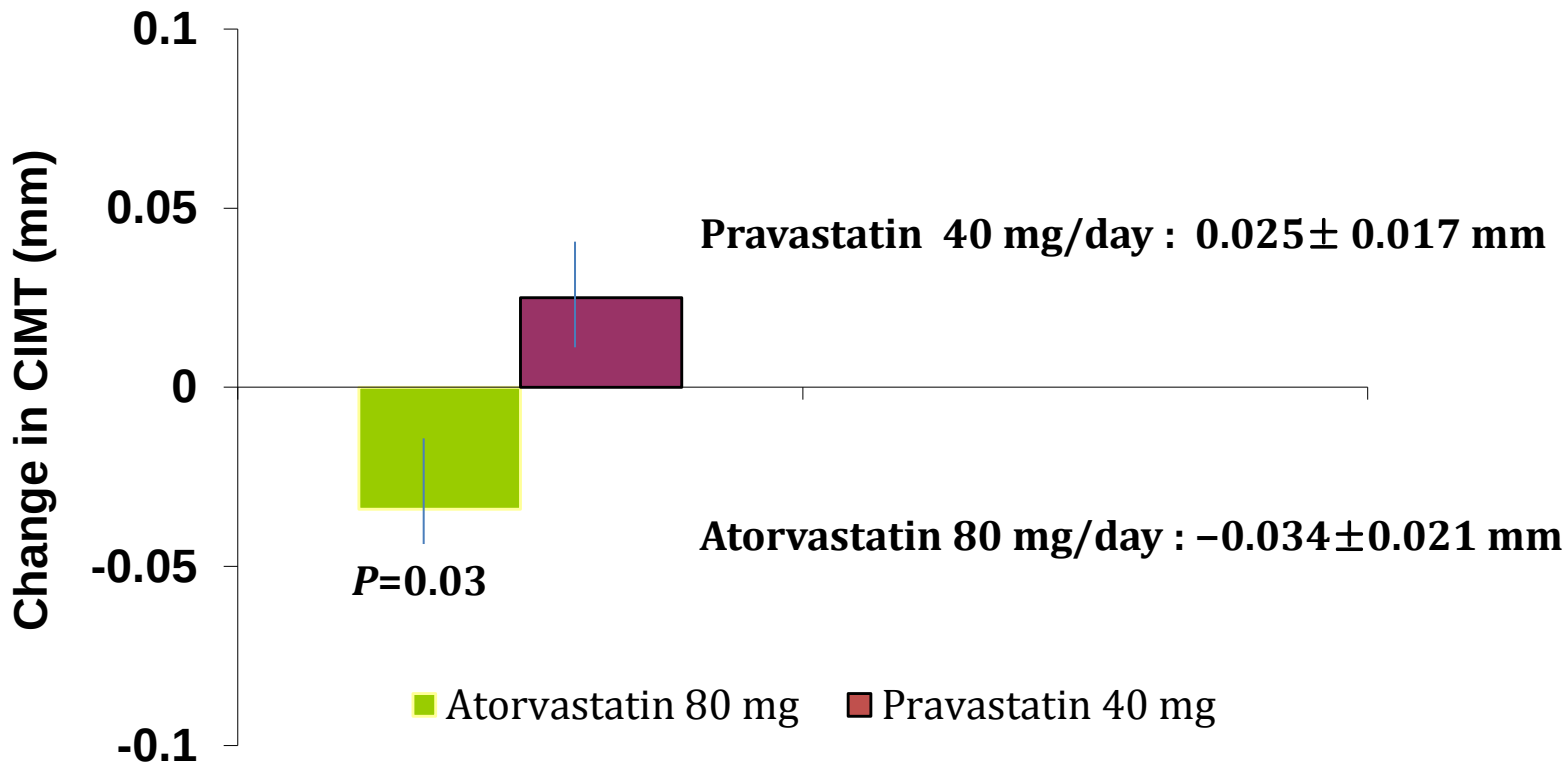
Circulation. 2002; 106: 2055-2060

Reduced Progression of Carotid Plaque

Plaque Stabilized effect

ARBITER study : N=161 pts with CVD
randomized to pravastatin 40 or atorvastatin 80 mg.

[Change in Carotid intima-media thickness (CIMT) at 18 months]

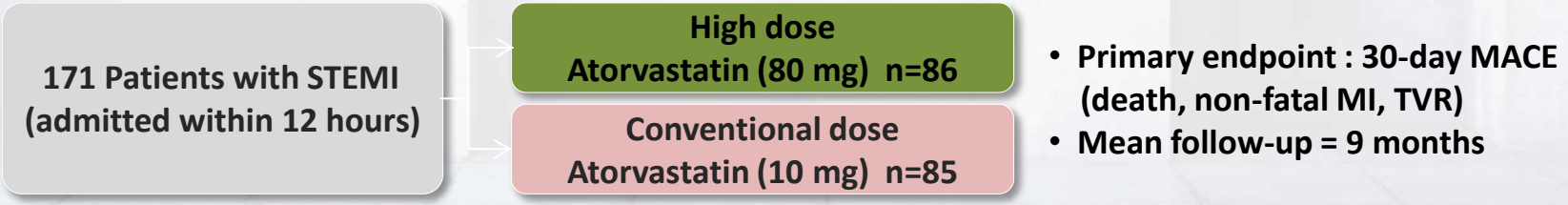


Taylor AJ, et al. Circulation. 2002;106:2055-2060.

The benefit of statin: Secondary prevention

STATIN STEMI

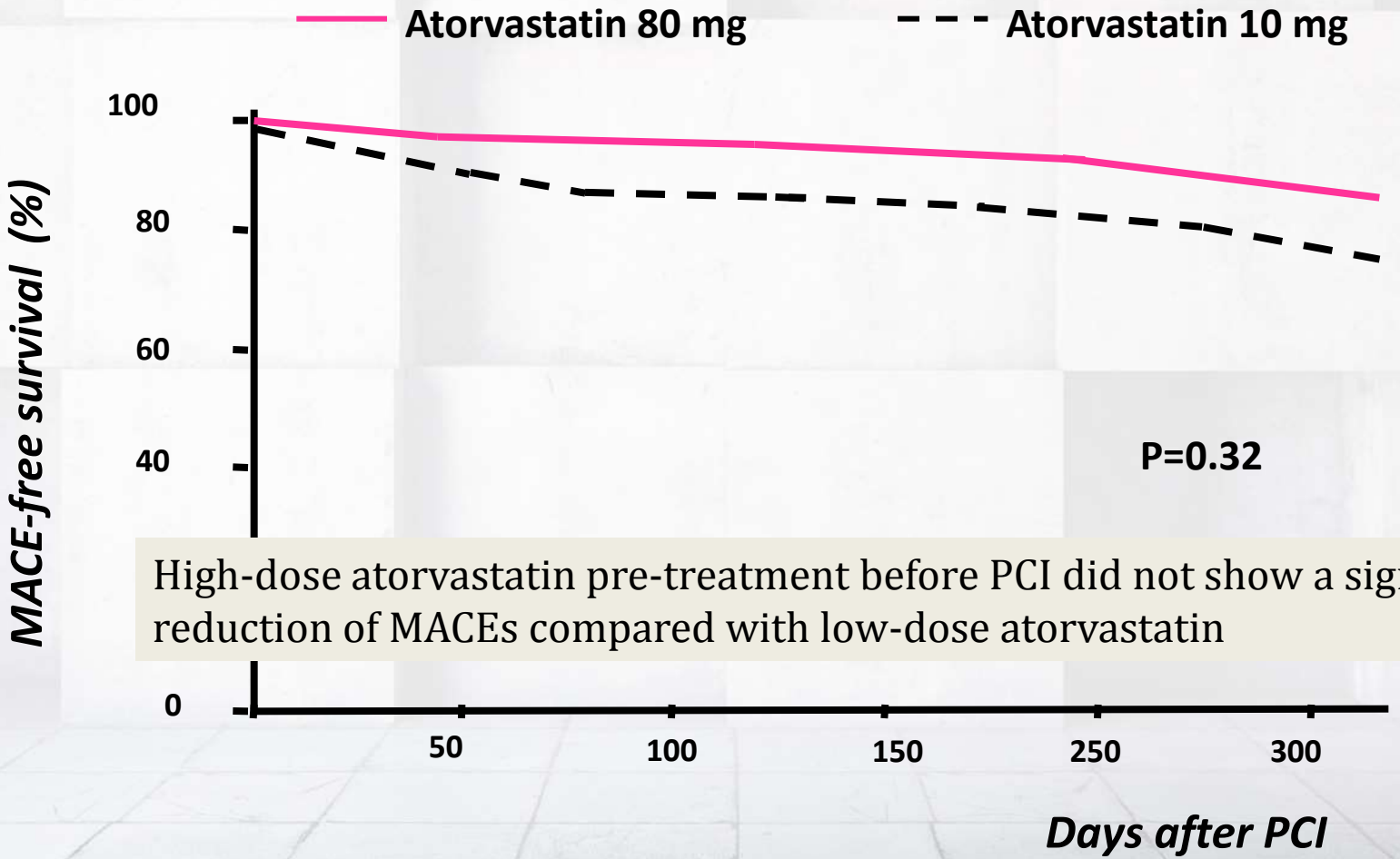
efficacy of high dose atorvaSTATIN loading before primary percutaneous coronary intervention in ST Elevation Myocardial Infarction



- **Primary endpoint : 30-day MACE (death, non-fatal MI, TVR)**
- **Mean follow-up = 9 months**

JACC Cardiovasc Interv. 2010;3:332-339.

STATIN STEMI : Event-Survival Curve



High-dose atorvastatin pre-treatment before PCI did not show a significant reduction of MACEs compared with low-dose atorvastatin

JACC Cardiovasc Interv. 2010;3:332-339.

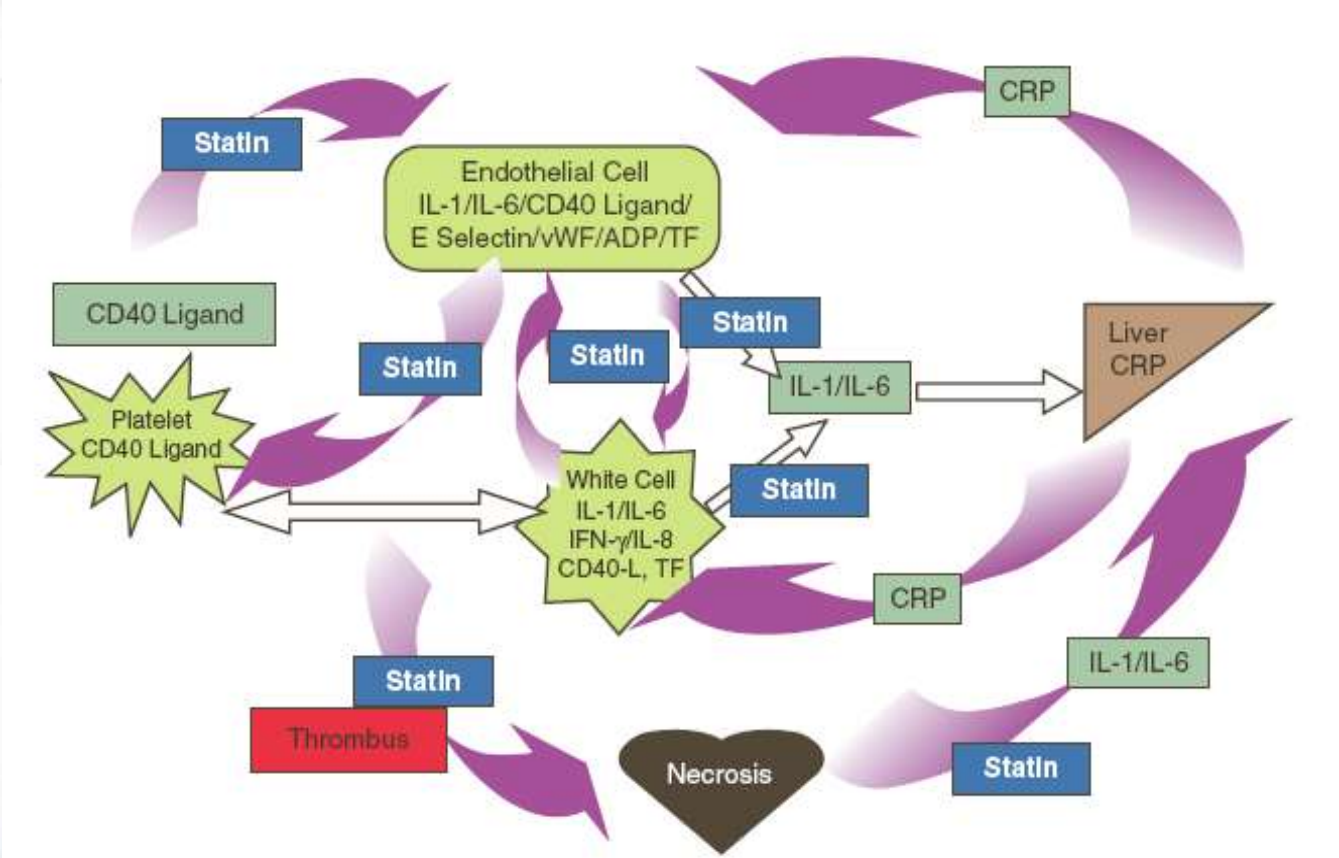
STATN STEMI: Improvement in immediate coronary flow

	Atorvastatin 80 mg (n = 86)	Atorvastatin 10 mg (n = 85)	P-value
Peak CK-MB (ng/dL)	239±162	239±227	0.99
hsCRP (mg/L) at 24 hr after PCI	4.14 ± 7.99	7.45 ± 22.81	0.10
TIMI grade 3 after procedure	83 (96.5 %)	76 (89.4 %)	0.07
TIMI blush grade	2.2±0.8	1.9±0.8	0.01
Corrected TIMI frame count	26.7±12.2	34.1±19.0	0.01
Mean STR at 90 min	61.8±26.2	50.6±25.8	0.01
Complete STR at 90 min	34 (39.5 %)	19 (23.8 %)	0.03

show improved immediate coronary flow after primary PCI.

JACC Cardiovasc Interv. 2010;3:332-339.

Statins In ACS: More than Lipid



Independent of LDL effects, statins rapidly inhibit a number of pathologic processes that have been implicated in the pathogenesis of ACS and the recurrent events following ACS.

ADP = adenosine diphosphate; CD40-L = CD40 ligand; IFN = interferon; IL = interleukin; vWF = von Willebrand factor.

Reproduced from Ray and Cannon. *J Thromb Thrombolysis*. 2004;18:89

Am J Cardiol. 2005;96:54F.

Intensive & early statin treatment prior to PCI for ACS patients

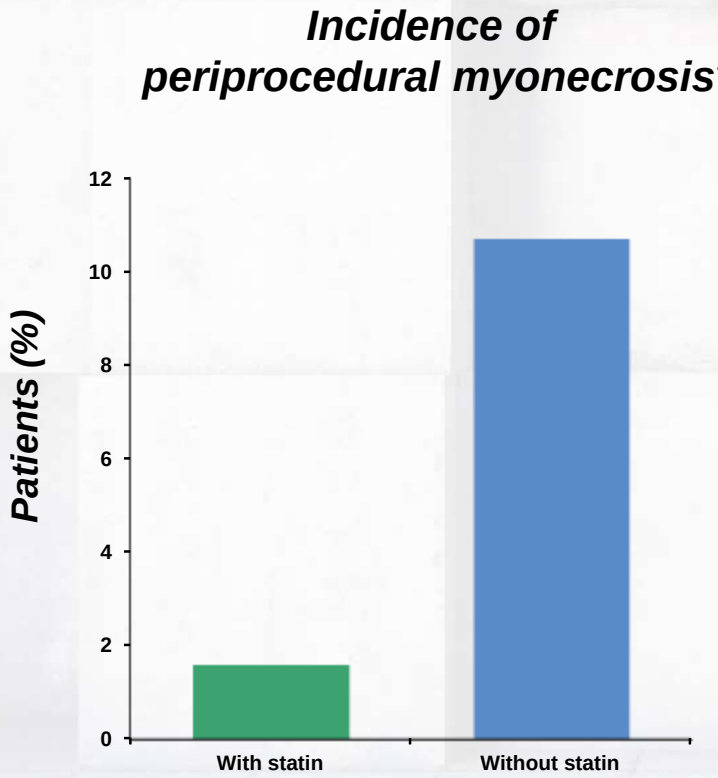
The benefit of statin: Primary & Secondary prevention

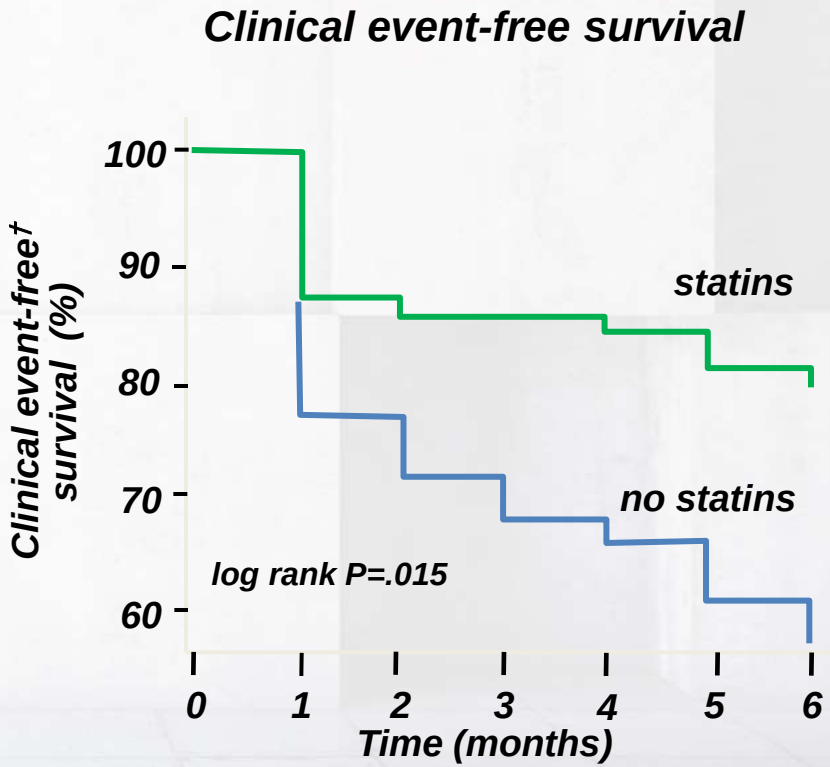
Secondary Prevention

ARMYDA

Atorvastatin for Reduction of MYocardial Damage during Angioplasty

Statins Prior to PCI Improves Clinical Outcomes





Study of 119 patients undergoing nonprimary PCI who received (n=63) or did not receive (n=56) statins prior to procedure.
**Myonecrosis defined as elevations in creatine kinase-myocardial band (CKMB) or CK >3 times the upper limit of normal within 24 hours of PCI in patients without recent MI, or 25% increase from trough value in patients with an MI <72 hours before procedure.*
†Events defined as death, nonfatal MI unrelated to PCI, target vessel revascularization, and UA requiring hospitalization.

Chang SM et al. Catheter Cardiovasc Interv. 2004;62:193-197.

ARMYDA – ACS Trial

Inclusion Criteria:

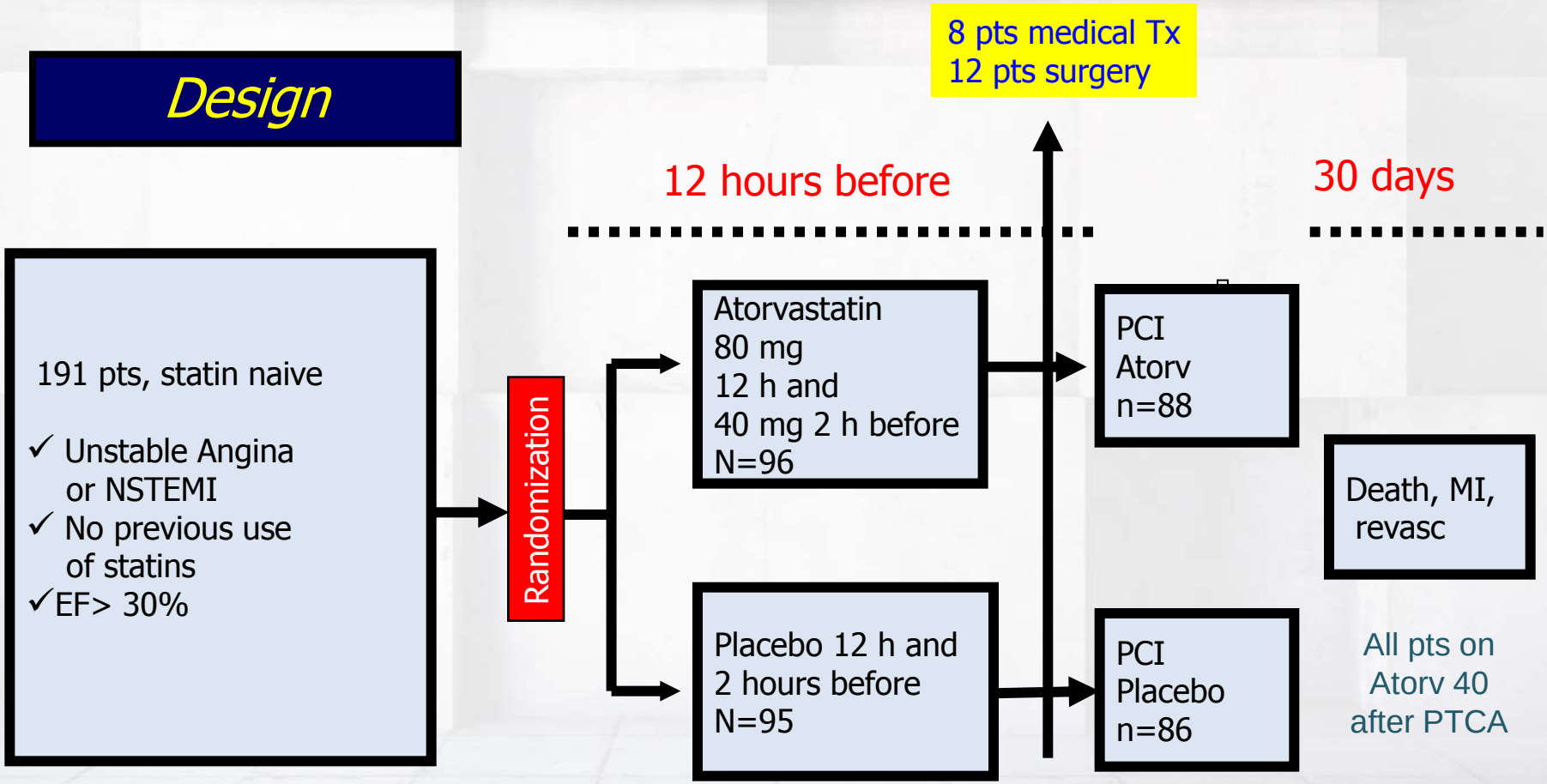
- ✓ Patients with NSTEMI or Unstable Angina
- ✓ treated with early invasive strategy (angio at 12-24 hours)

Exlusion Criteria:

- ✓ Previous or current statin therapy
- ✓ Need for emergency angio (<12 hours from admission)
- ✓ LVEF <30%
- ✓ Controindications to statins, liver or renal failure

Patti G, et al. *J Am Coll Cardiol. 2007;49:1272-1278*

METHODS

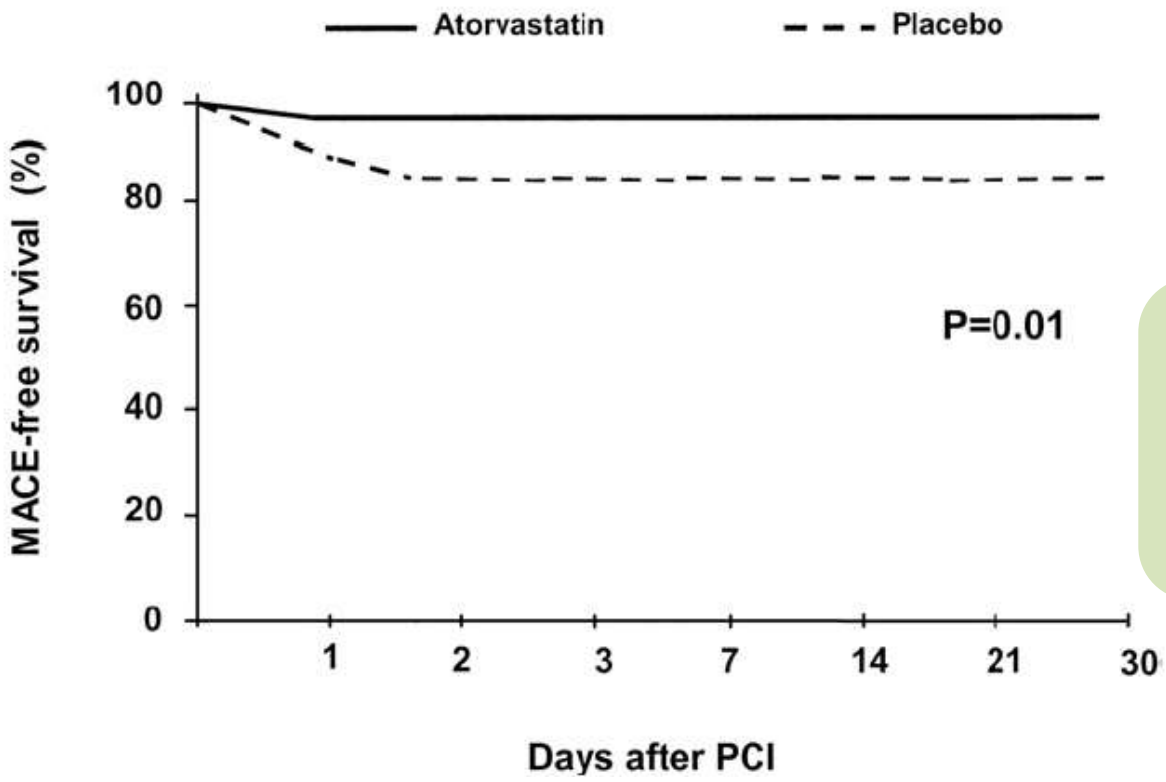


Patti G, et al. *J Am Coll Cardiol. 2007;49:1272-1278*

High dose atorvastatin improved outcome

ARMYDA-ACS trial : N=171 Statin Naïve pts with NSTEMI-ACS randomized to placebo or atorvastatin (LIPITOR 80 mg 12 hrs before angiogram, Further 40 mg 2 hrs before angiogram)

[Survival Curves]



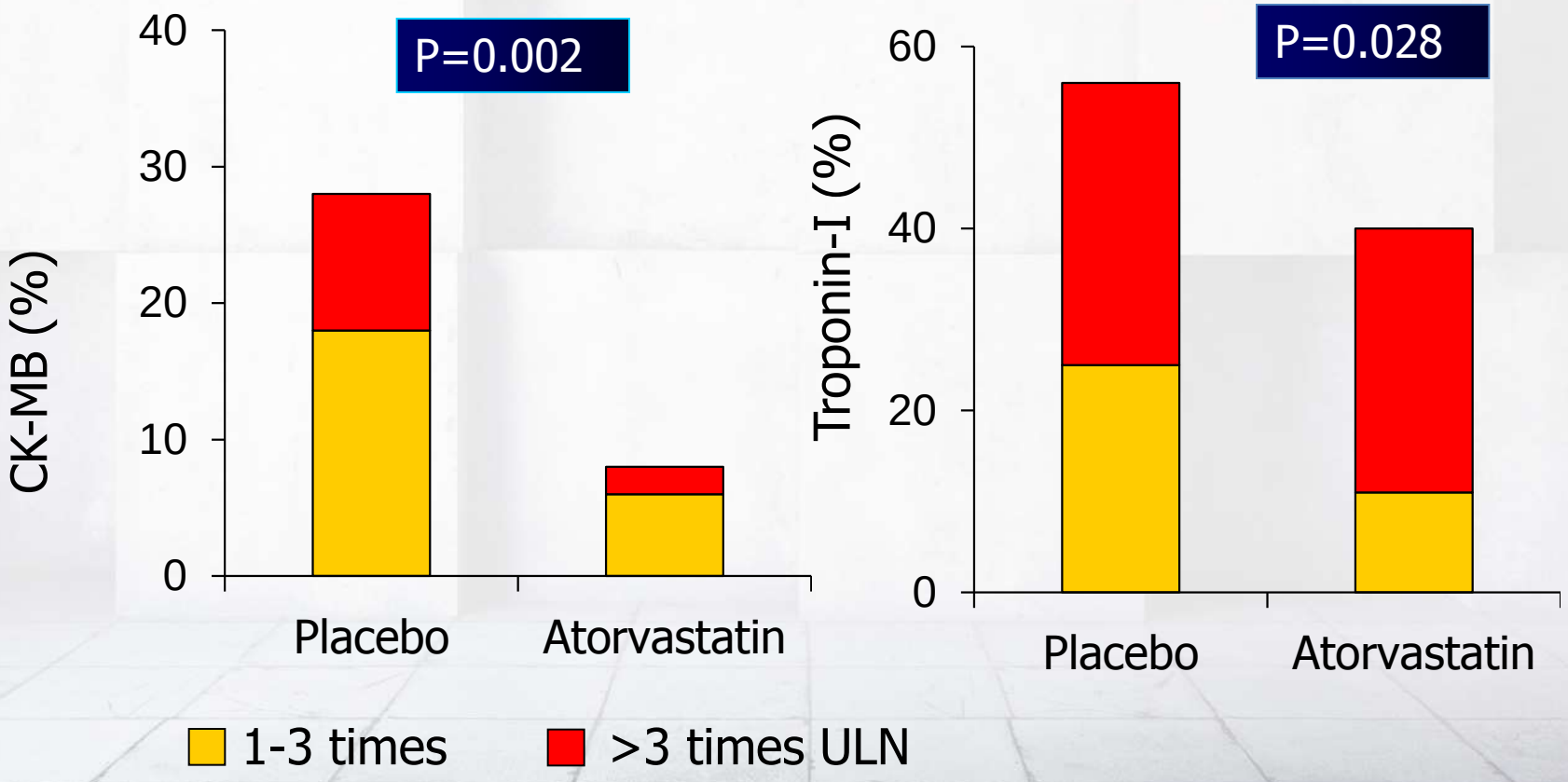
30-day major adverse cardiac events 12% ↓

(95% CI 0.05 -0.50, p=0.004)

Pati G, et al. J Am Coll Cardiol. 2007;49:1272-8.

AMRYDA – ACS: Secondary End Points

CK-MB or Troponin-I Increase

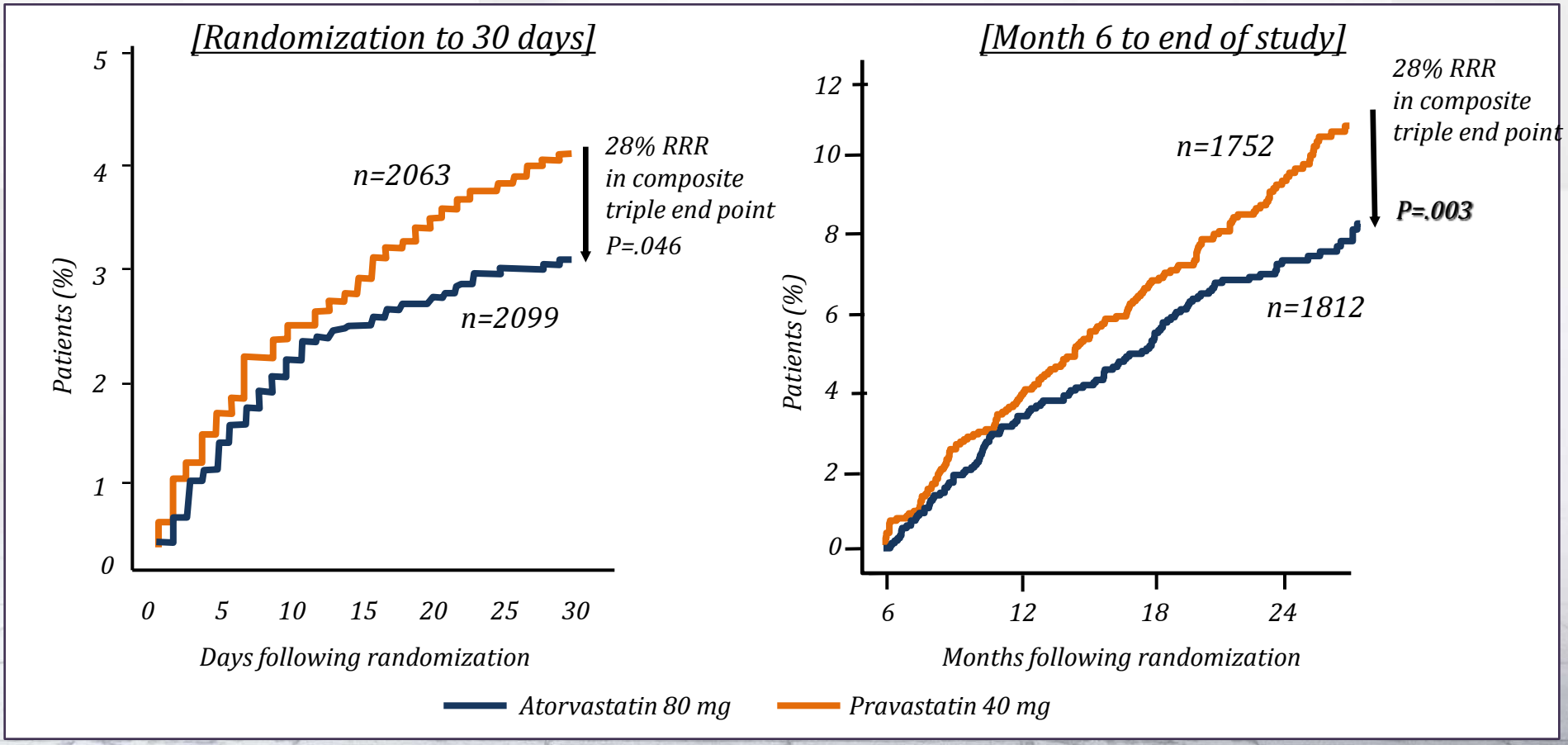


Patti G, et al. *J Am Coll Cardiol. 2007;49:1272-1278*

ARMYDA-RECAPTURE (chronic statin therapy)

Reloading with high dose atorvastatin improved outcome

: N=383 pts with stable angina, NSTEMI ACS-PCI on chronic statin therapy, randomized to placebo or atorvastatin 80 mg (LIPITOR 80 mg 12 hrs before angiogram, further 40 mg 2 hrs before angiogram)



Adapted from Ray KK et al. J Am Coll Cardiol. 2005;46:1405-1410.

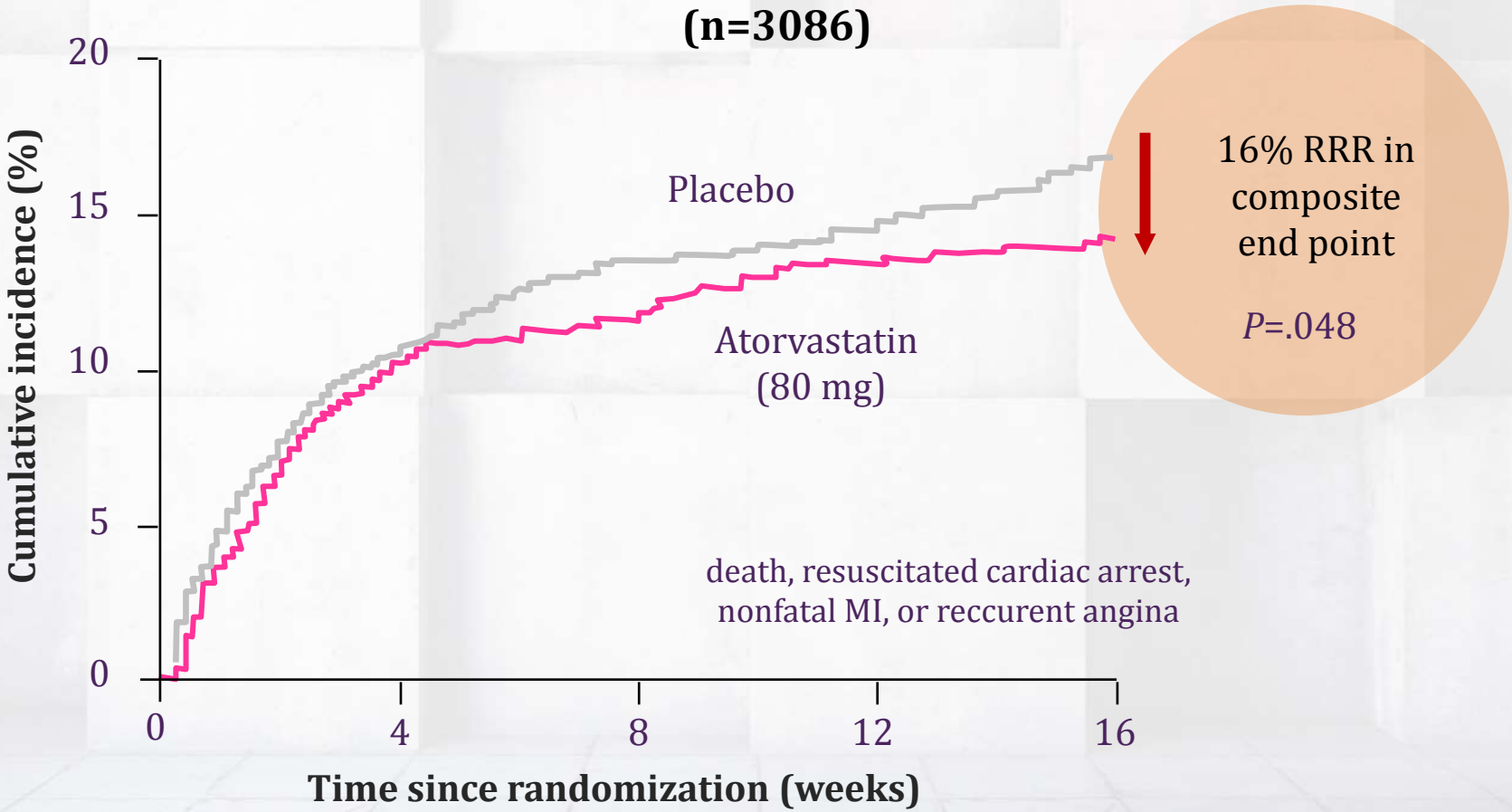
Statins and Myocardial Proctection: Possible Mechanisms

- Independent from cholesterol levels
- Plaque Stabilization (reduced microembolization)
- Improved Endothelial Function and Microcirculation
- Reduced Platelet Aggregation
- Antinflammatory effect (reduced hsCRP)
- Direct Effcect on Myocardial Cells

Patti G, et al. *J Am Coll Cardiol. 2007;49:1272-1278*

Effect of statin
: LDL and Beyond

MIRACL in ACS

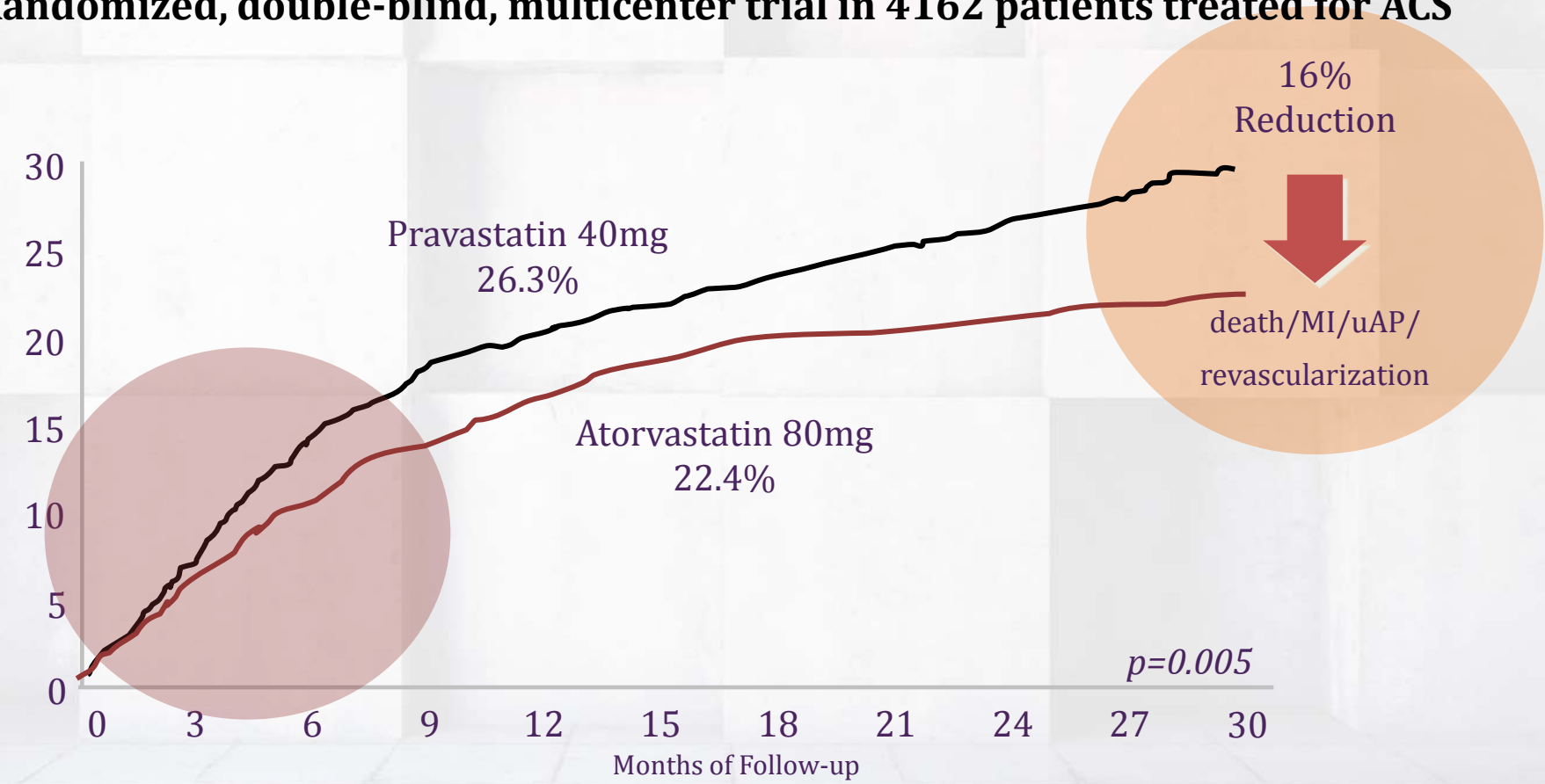


For patients with ACS, lipid-lowering therapy with atorvastatin, 80 mg/d, reduces recurrent ischemic events in the first 16 weeks, mostly recurrent symptomatic ischemia requiring rehospitalization.

Circulation. 2004;110:1406-1412. Schwartz GG et al for the Myocardial Ischemia Reduction With Aggressive Cholesterol Lowering Study Investigators. JAMA. 2001;285:1711-1718.

PROVE-IT

Randomized, double-blind, multicenter trial in 4162 patients treated for ACS



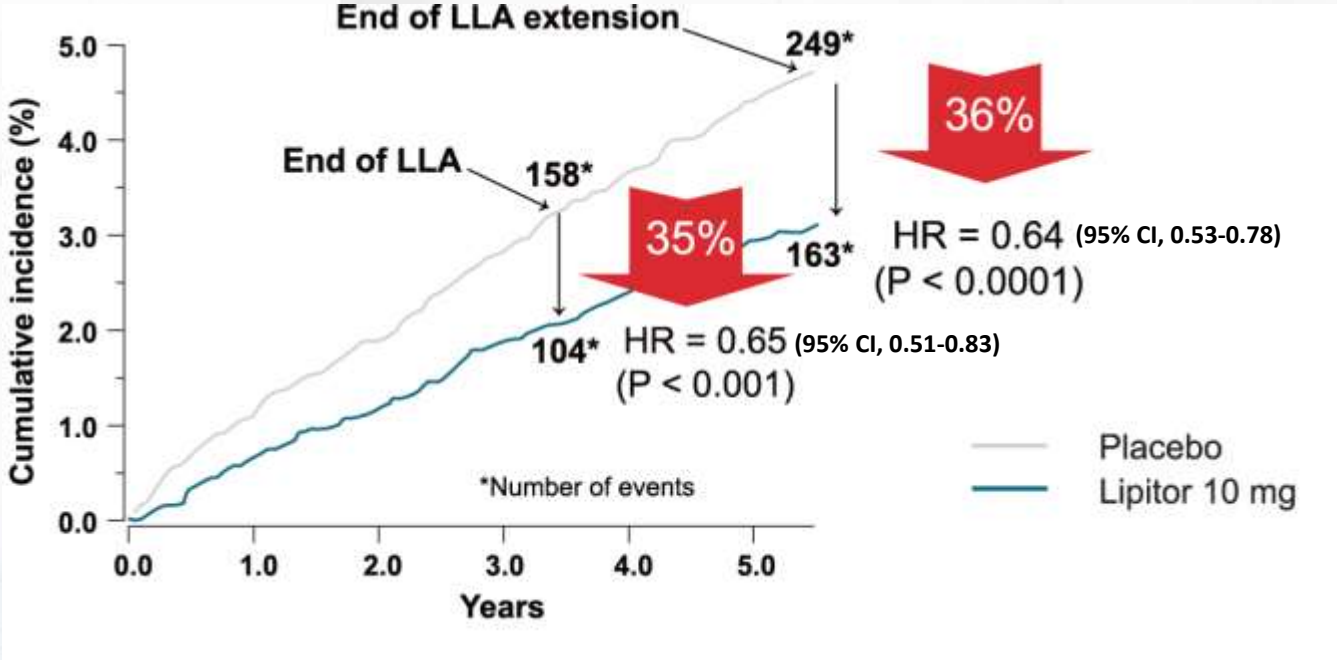
- N=4,162 ACS (early invasive-3/4; multiple medications)
- Among patients who have recently had an ACS, an intensive lipid-lowering statin regimen provides greater protection against death or major cardiovascular events than does a standard regimen.

NEJM 2004;350:1495

ASCOT LLA-extension: Carry over effect

Randomized, double-blind, multicenter trial in 10,305 patients treated for hypertension with no prior CHD

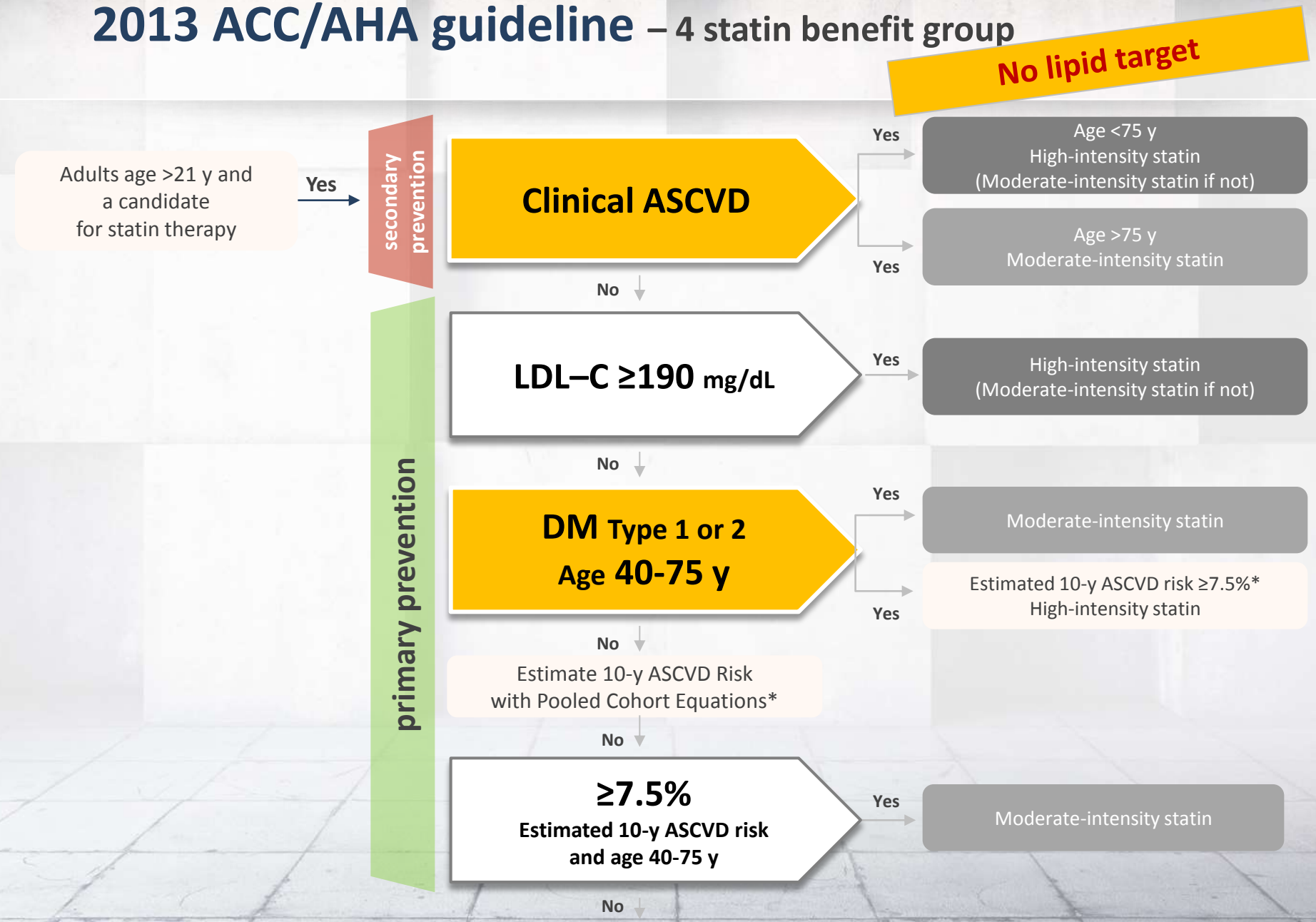
Primary End Point :Non Fatal MI, Fatal CVD



Carry-over benefits from those originally assigned atorvastatin but no longer taking the drug may, account for unchanged relative risk reductions in most cardiovascular endpoints observed 2 years after ASCOT-LLA closed.

Sever PS, et al. European Heart Journal 2008; 29: 499-508

2013 ACC/AHA guideline – 4 statin benefit group



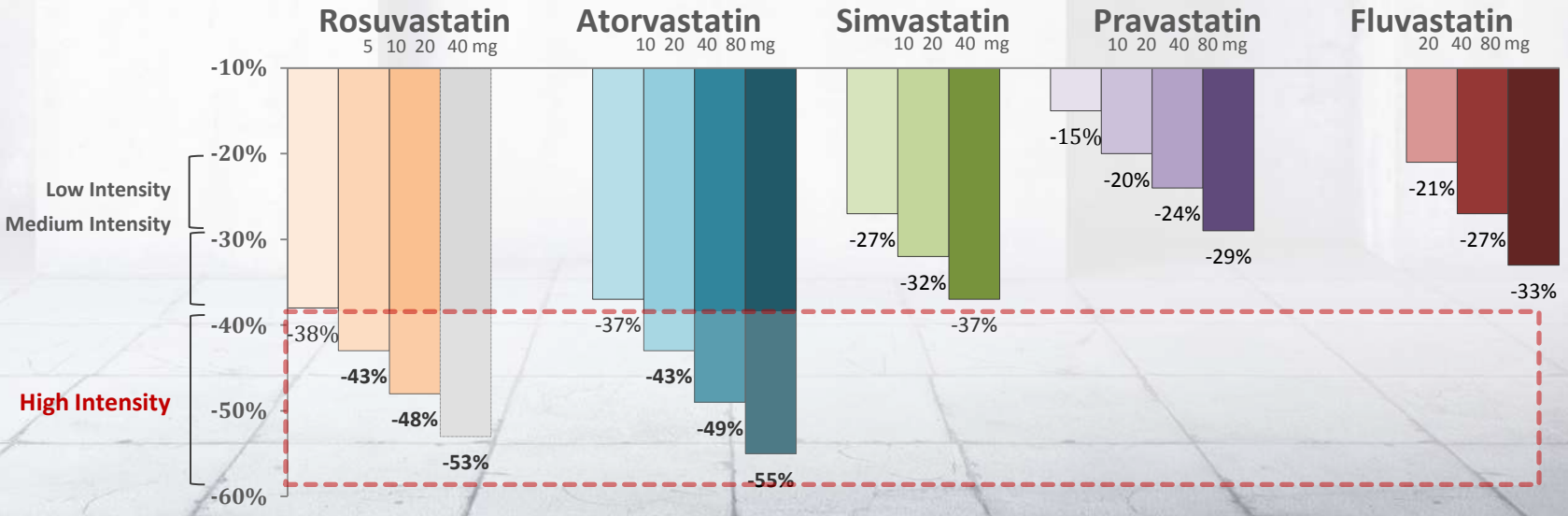
Reference. Stone NJ, et al. published online November 12, 2013 Circulation.

Intensity of Statin Therapy

2013 ACC/AHA guideline[1]

Intensity	High-Intensity	Moderate-Intensity	Low-Intensity
Reduction % in LDL-C	**> 50% reduction of LDL with daily statin**	30-50% reduction of LDL with daily statin	<30% reduction of LDL with daily statin
Statin and dose	**Atorvastatin *(40)*-80 mg** **Rosuvastatin 20 *(40)* mg**	Atorvastatin 10 *(20)* mg Rosuvastatin *(5)* 10 mg Simvastatin 20-40 mg Pravastatin 40 *(80)* mg Lovastatin 40 mg *Fluvastatin XL 80 mg* Fluvastatin 40 mg bid *Pitavastatin 2-4 mg*	*Simvastatin 10 mg* Pravastatin 10-20 mg Lovastatin 20 mg *Fluvastatin 20-40 mg* *Pitavastatin 1 mg*

2014 NICE guideline[2]



Reference. 1. Stone NJ, et al. published online November 12, 2013 Circulation. 2. 2014 NICE LIPID modified guidelines

2014 NICE guideline

No lipid target

Primary prevention for people with type 2 diabetes

1.3.26 Offer atorvastatin 20 mg for the primary prevention of CVD to people with type 2 diabetes who have a 10% or greater 10-year risk of developing CVD. Estimate the level of risk using the QRISK2 assessment tool. **[new 2014]** [This recommendation updates and replaces recommendations 1.10.1.2, 1.10.1.3, and 1.10.1.5 from Type 2 diabetes (NICE clinical guideline 87).]

Secondary prevention

1.3.20 Start statin treatment in people with CVD with atorvastatin 80 mg[6]. Use a lower dose of atorvastatin if any of the following apply:

- potential drug interactions
- high risk of adverse effects
- patient preference. **[new 2014]**

Reference. 2014 NICE guideline. Accessed at http://www.nice.org.uk/guidance/cg181

2016 ADA guideline

The 2016 ADA Standards of Care have been revised to recommend
when to initiate and intensify statin therapy (high versus moderate) based on risk profile

No lipid target

[Recommendations for statin treatment in people with diabetes]

Age	Risk factors	Recommended statin intensity*
<40 years	None	None
	ASCVD risk factor(s)**	Moderate or high
	ASCVD	High
40–75 years	None	Moderate
	ASCVD risk factors	High
	ASCVD	High
	ACS and LDL cholesterol >50 mg/dL (1.3 mmol/L) in patients who cannot tolerate high-dose statins	Moderate plus ezetimibe
>75 years	None	Moderate
	ASCVD risk factors	Moderate or high
	ASCVD	High
	ACS and LDL cholesterol >50 mg/dL (1.3 mmol/L) in patients who cannot tolerate high-dose statins	Moderate plus ezetimibe

*In addition to lifestyle therapy.
**CVD risk factors include LDL cholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, and overweight and obesity.
***Overt CVD includes those with previous cardiovascular events or acute coronary syndromes.

Reference. 2015 ADA clinical practice recommendations. Diabetes Care 2016;39:S63–S66.

2015 한국지질동맥학회 이상지질혈증 치료지침

[Recommendations for statin treatment]

표 2-3. 위험도 분류에 따른 LDL 콜레스테롤 및 non-HDL 콜레스테롤의 목표치

위험도	LDL 콜레스테롤 목표 (mg/dL)	non-HDL 콜레스테롤 목표 (mg/dL)
초고위험군 관상동맥질환 허혈성 뇌졸중 일과성 뇌허혈발작 말초혈관질환	<70	<100
고위험군 경동맥질환* 복부동맥류 당뇨병	<100	<130
중등도 위험군 주요위험인자 2개 이상	<130	<160
저위험군 주요위험인자 1개 이하	<160	<190

*50%가 넘는 경동맥 협착이 확인된 경우

(2) 고콜레스테롤혈증

	내용	권고 수준	근거 수준
1	고위험군, 초고위험군에서는 치료 기준에 따라 LDL 콜레스테롤의 목표 수치에 도달할 수 있도록 스타틴 용량을 적절하게 조절하여 투여한다.	I	A
2	저위험군 또는 중등도 위험군에서는 수주 또는 수개월간 생활교정 요법후에도 목표치 이하로 LDL 콜레스테롤이 감소하지 않으면 스타틴을 사용해야 한다.	IIa	B
3	스타틴 내약성이 없는 경우, 담즙산 결합수지나 니코틴산을 사용할 수 있다.	IIa	B
4	스타틴을 투여해도 LDL 콜레스테롤 목표 수치 미만으로 감소하지 않으면 ezetimibe를 병용할 수 있다.	IIa	B
5	스타틴을 투여해도 LDL 콜레스테롤 목표 수치 미만으로 감소하지 않으면 니코틴산, 담즙산 결합수지를 병용할 수 있다.	IIb	C
6	초고위험군에서 스타틴 단독 또는 병용요법에도 불구하고 목표치에 도달하지 못하는 경우, 기저 LDL 콜레스테롤 수치에 비하여 50% 이상 감소시키는 것이 효과적이다.	I	A
7	급성심근경색의 경우에는 기저 LDL 콜레스테롤 농도와 상관없이 바로 스타틴을 투약한다.	I	A

Conclusions

- The efficacy and early benefits as a result of high dose statin therapy have so far been greater than the beneficial effects of equivalent lipid-lowering therapies.

- Early reduction in clinical events may be related to not only LDL, but also pleiotropic effects.