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Optimizing strategies for CV risk reduction in patients with ASCVD
When and How

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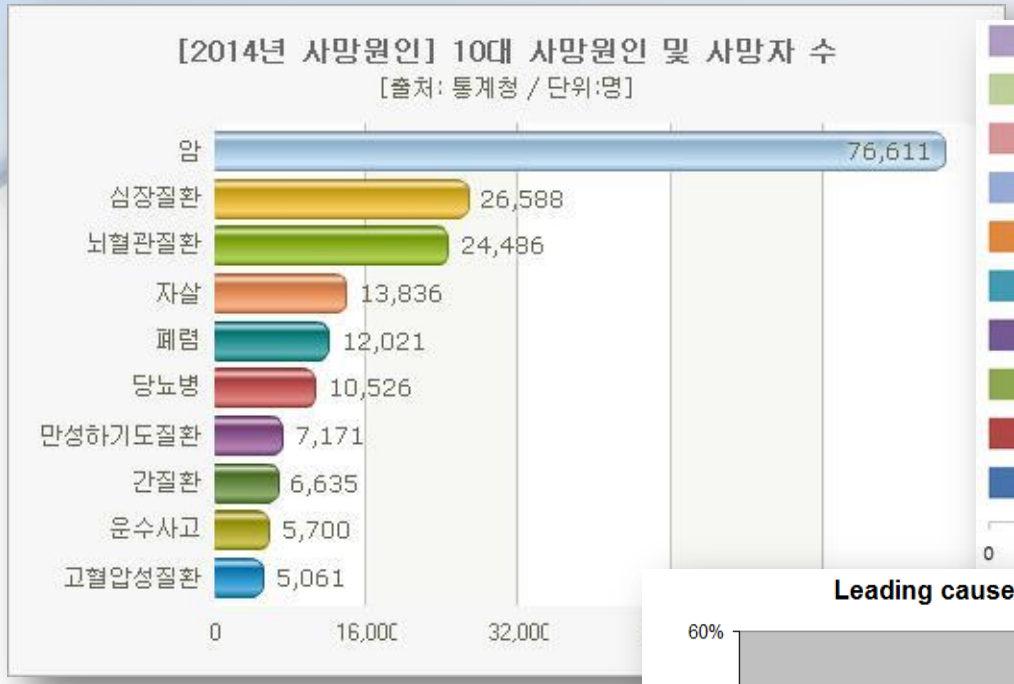
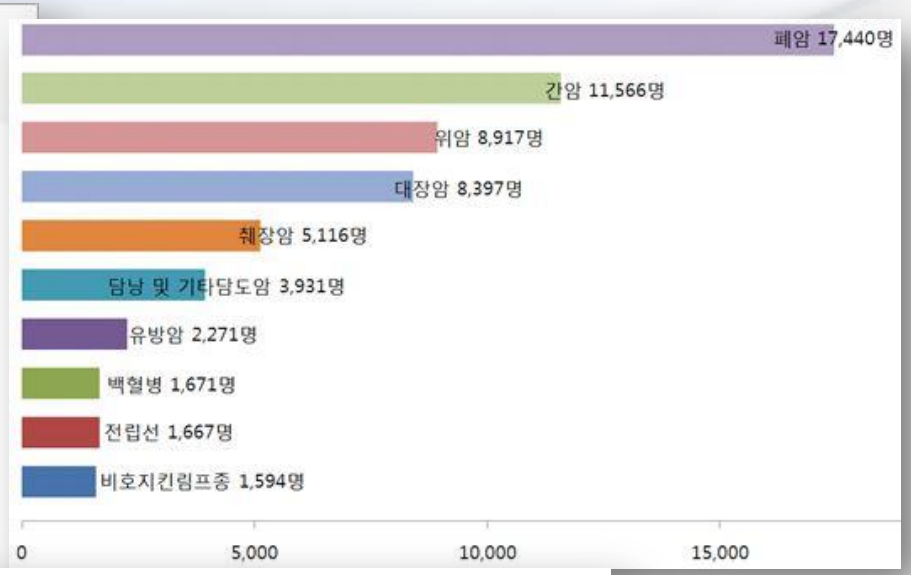
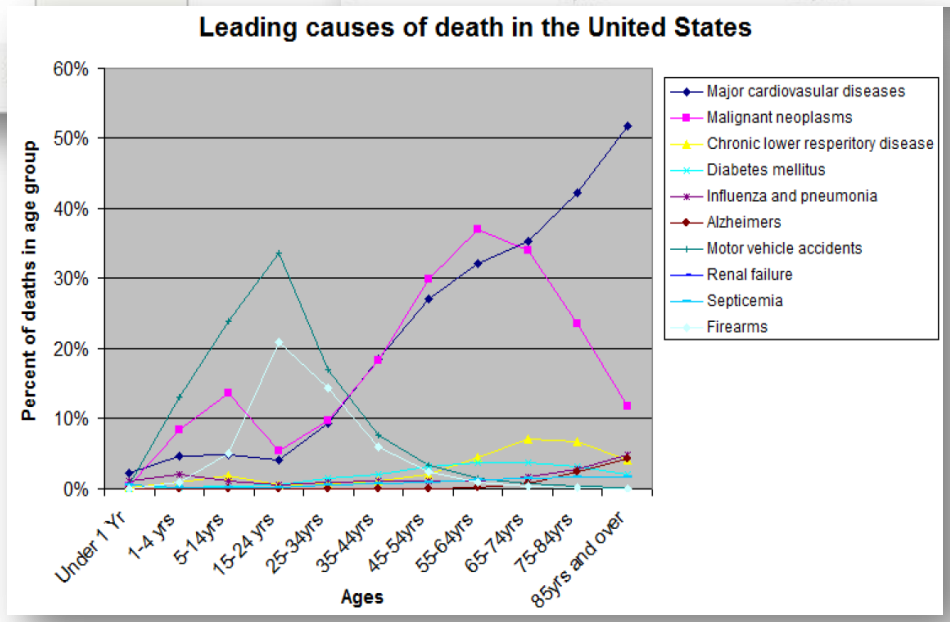
남창욱

2014년 주요 사망원인별 사망률 비교





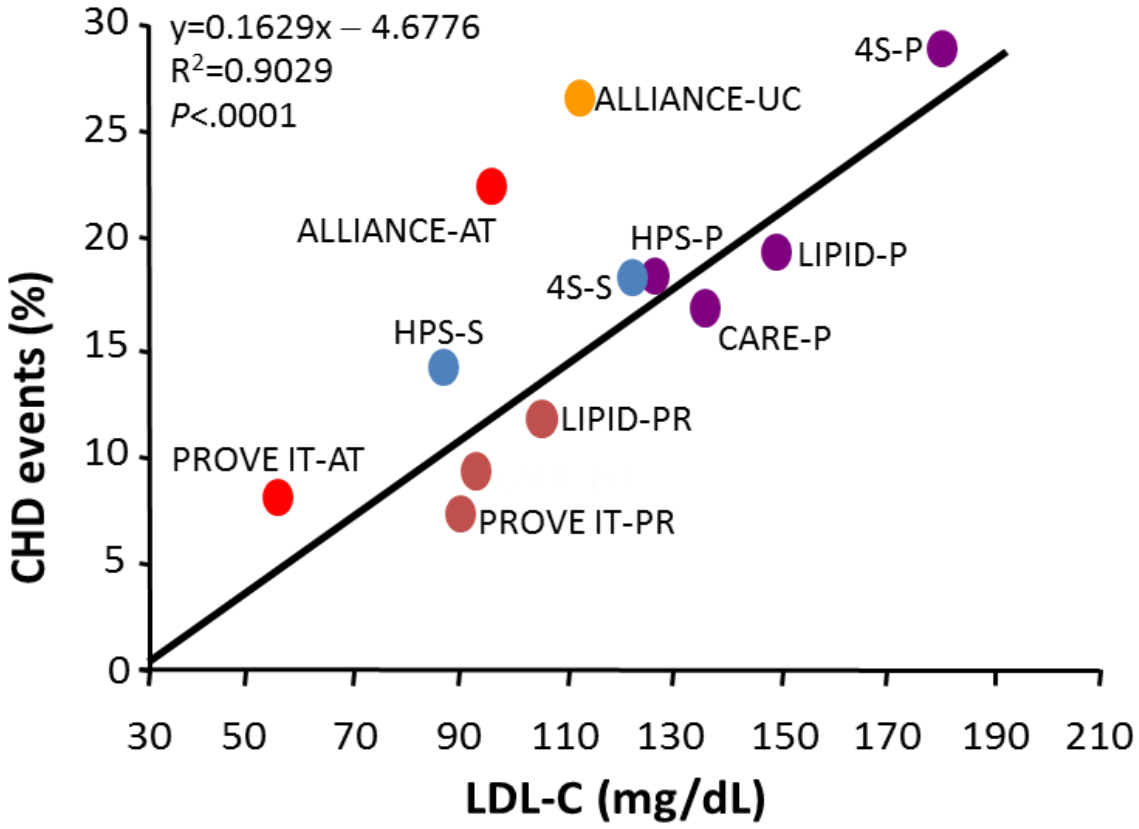


2015.9.14. 통계청 발표자료

Table of Contents

1 Lipid Management for Proven ASCVD & Background

Statin Therapy: Secondary Prevention Trials

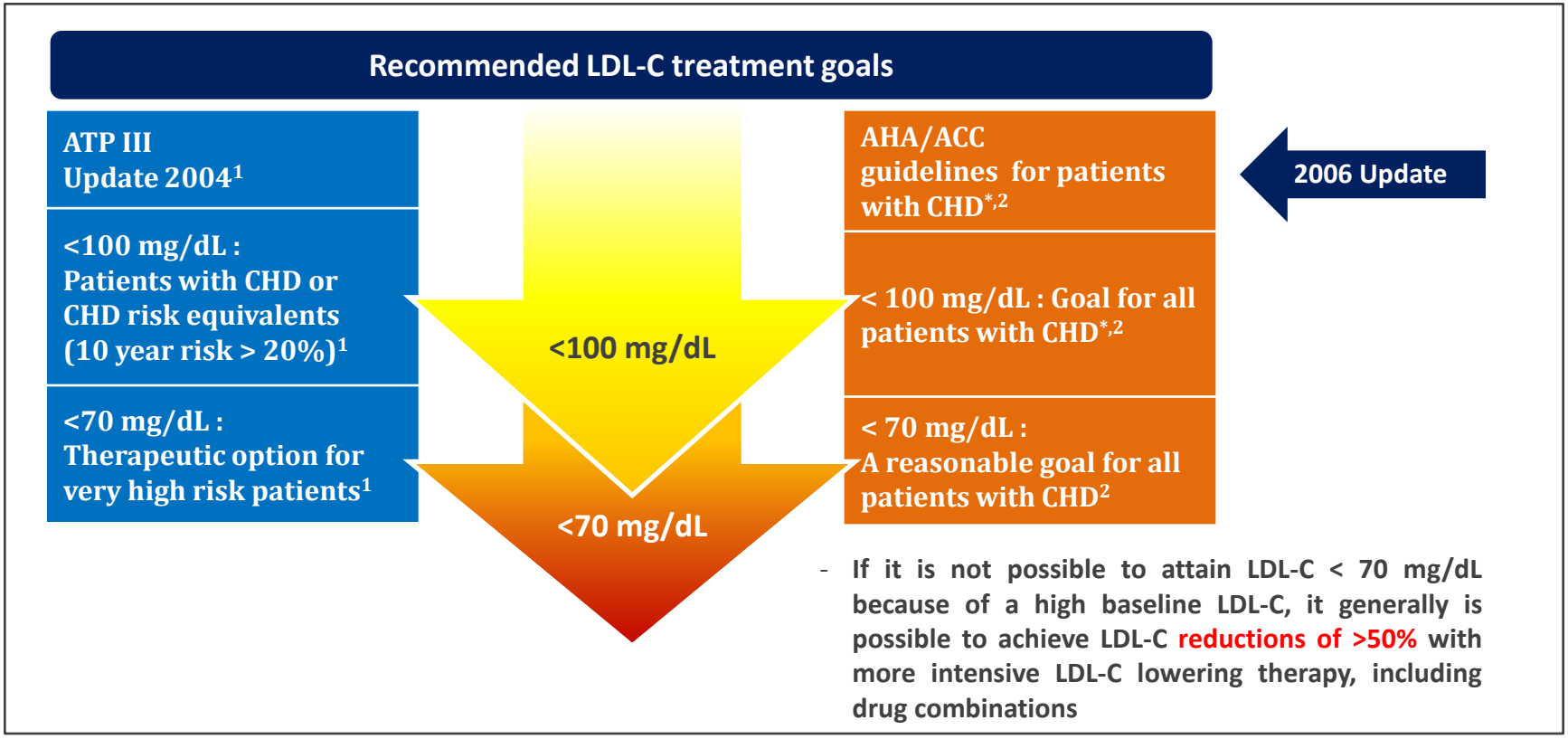


Atorvastatin Pravastatin Simvastatin Usual care Placebo

O'Keefe JH et al. JACC 2004;43:2142-2146
Koren MJ et al. JACC 2004;44:1772-1779.

Treat to goal paradigm

- LDL was the primary target.
- Treat to goal was more aggressive.



† 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.

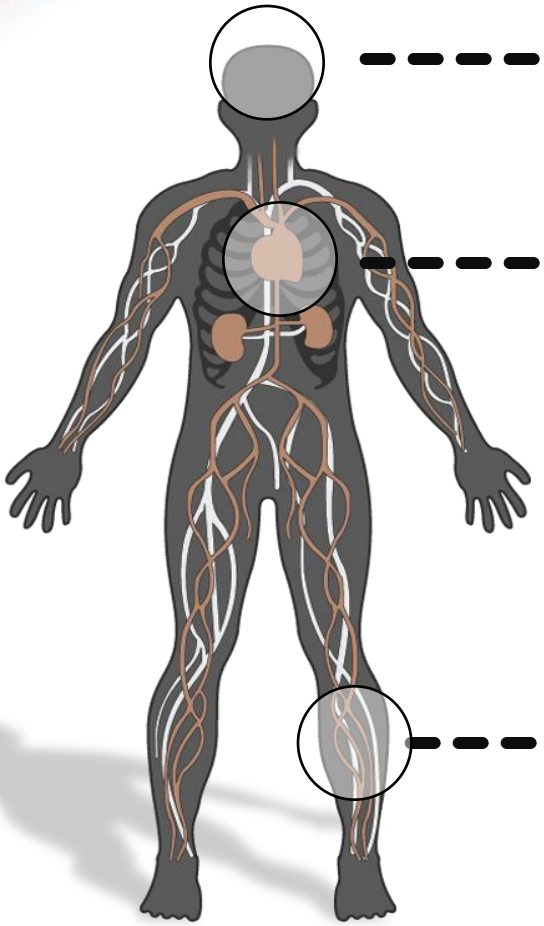
Adapted from Wang CY, et al. Trends Mol Med 2008;14:37–44.

Treat to goal paradigm

	Treatment group
2013 ACC/AHA guideline[1]	Clinical ASCVD
	LDL–C ≥190 mg/dL
	Diabetes without clinical ASCVD
	10-year ASCVD risk ≥7.5% (Pooled Cohort Equations)
2014 NICE guideline[2]	People with CVD
	People without CVD and 10-year CV risk ≥ 10% (QRISK 2 assessment tool)

Stone NJ, et al. 2013 Circulation
NICE Guideline: lipid modification, 2014

Clinical AtheroSclerotic CardioVascular Disease



Stroke or TIA presumed to be of atherosclerotic origin

Stable CHD : history of MI, stable angina, coronary revascularization

Acute CHD : Acute coronary syndrome

Peripheral arterial disease or revascularization

Ref. Stone NJ, et al. Circulation, 2013.

Evidence in 2013 ACC/AHA guideline update

Clinical ASCVD

Yes →

Age ≤ 75 y ➡ High-intensity statin
(if not candidate ➡ Moderate-intensity statin)

Evidence statement 6

In adult with CHD/CVD, fixed high intensity statin treatment (atorvastatin 40-80 mg) that achieved a mean LDL-C 67-79 mg/dL reduced the RR for CHD/CVD events more than fixed lower-dose statin treatment that achieved a mean LDL-C 97-102 mg/dL. In these trials, the mean LDL-C levels achieved differed by 23-30 mg/dL, or 22%-30%, between the 2 groups. Simvastatin 80 mg did not decrease CVD events compared with simvastatin 20-40 mg	**H**	***Secondary Prevention***	**Benefit:** **TNT**(46), IDEAL(47), **PROVE-IT(48)** **Lower LDL-C reduction, no benefit :** A-Z(119), ACCORD(14) **No difference in LDL-C between groups :** (SEARCH (128) not included in CQ1)

Clinical ASCVD: Stable CHD

TNT

10,001 Patients aged 35 to 75 years with stable CHD

- Atorvastatin 10 mg/day
- Atorvastatin 80 mg/day

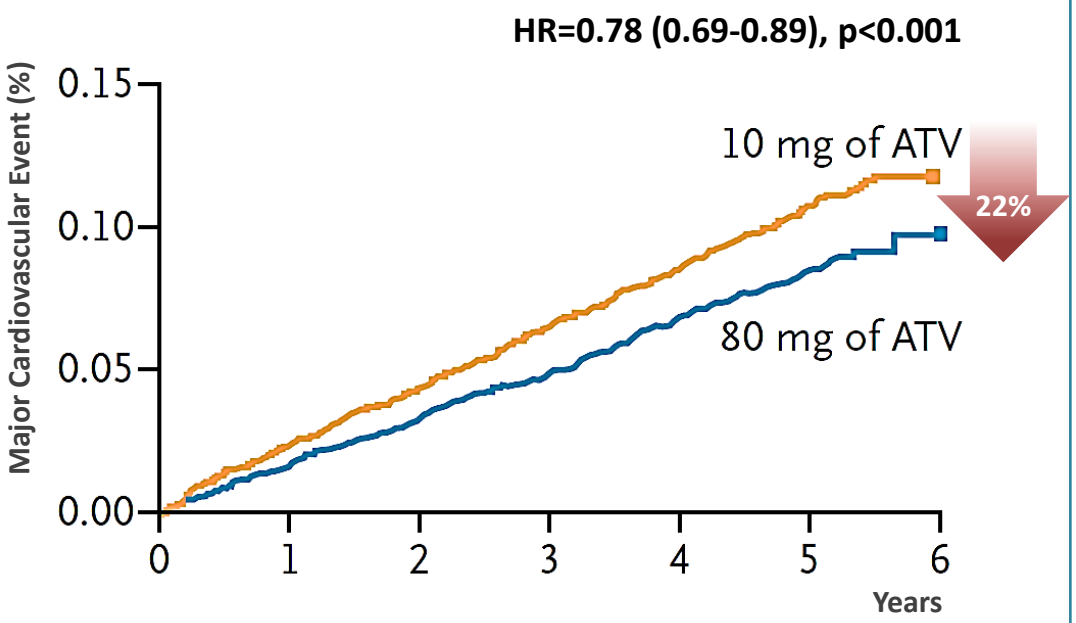
- Primary endpoint : CHD death, nonfatal MI, resuscitated cardiac arrest, or stroke
- Median follow-up = 4.9 years

Change of LDL-cholesterol

	Atorvastatin 80 mg	Atorvastatin 10 mg
N	4,995	5,006
Baseline median, mg/dl	97±18	98±18
End of follow-up mean, mg/dl	77	101
LDL-C difference (mg/dL)(%)	-20(-21%)	3(3%)

21%

Primary endpoint



RLaRosa JC, et al. NEJM 2005;352:1425–35.

Clinical ASCVD: ACS

IDEAL

8,888 CHD Patients aged ≤ 80 years with AMI

- **Simvastatin 20-40 mg/day**
- **Atorvastatin 10-80 mg/day**

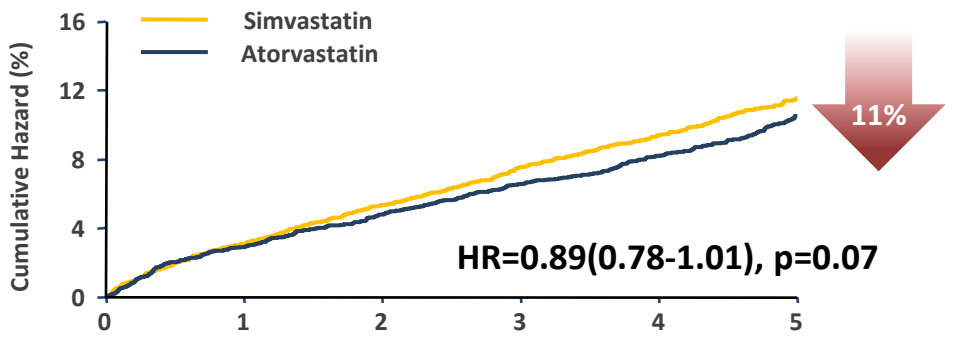
- **Primary endpoint : CHD death, non fatal AMI, resuscitated cardiac arrest**
- **Mean follow-up = 4.8 years**

Change of LDL-cholesterol

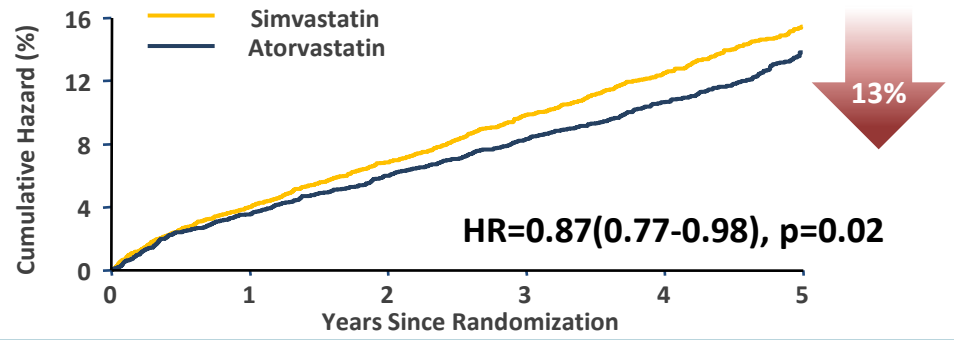
	Atorvastatin 10-80 mg	Simvastatin 20-40 mg
N	4,438	4,425
Baseline median, mg/dl	121.6	121.4
End of follow-up mean, mg/dl	80.0	99.8
LDL-C difference (mg/dL)(%)	42(-34%)	21(-17%)

34%

Primary endpoint



Secondary endpoint : Major CV events



Ref. Pedersen TR, et al. JAMA 2005;294:2437–45.

Clinical ASCVD: ACS

PROVE-IT

4,162 Patients aged ≥ 18 years with ACS

- **Pravastatin 40 mg/day**
- **Atorvastatin 80 mg/day**

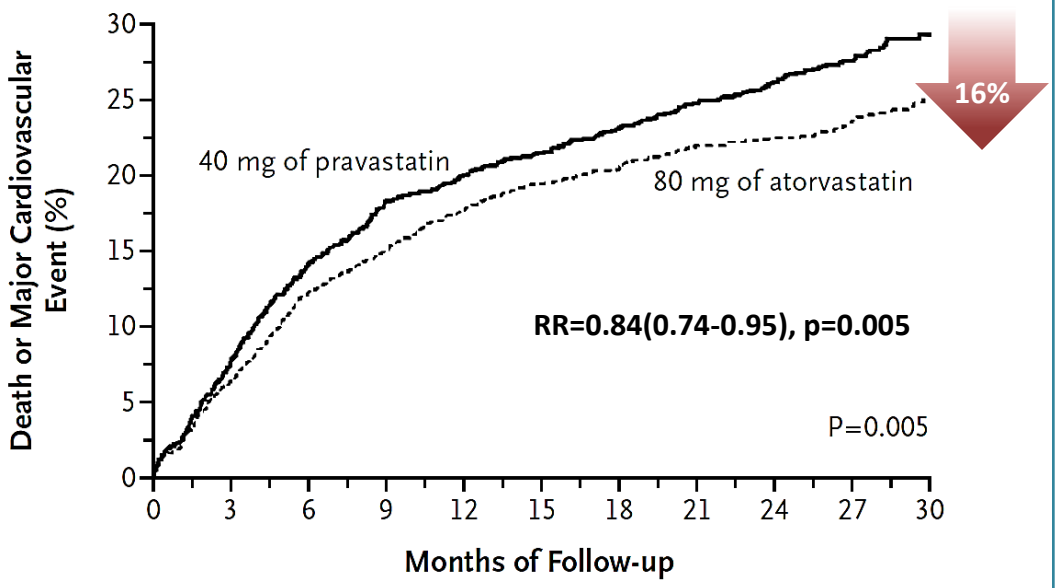
- **Primary endpoint : Death, MI, documented UA requiring rehospitalization, revascularization**
- **Mean follow-up = 24 months**

Change of LDL-cholesterol

	Atorvastatin 80 mg	Pravastatin 40 mg
N	2,099	2,063
Baseline median, mg/dl	106	106
End of follow-up mean, mg/dl	62	95
LDL-C difference (mg/dL)(%)	-44(-42%)	-11(-10%)

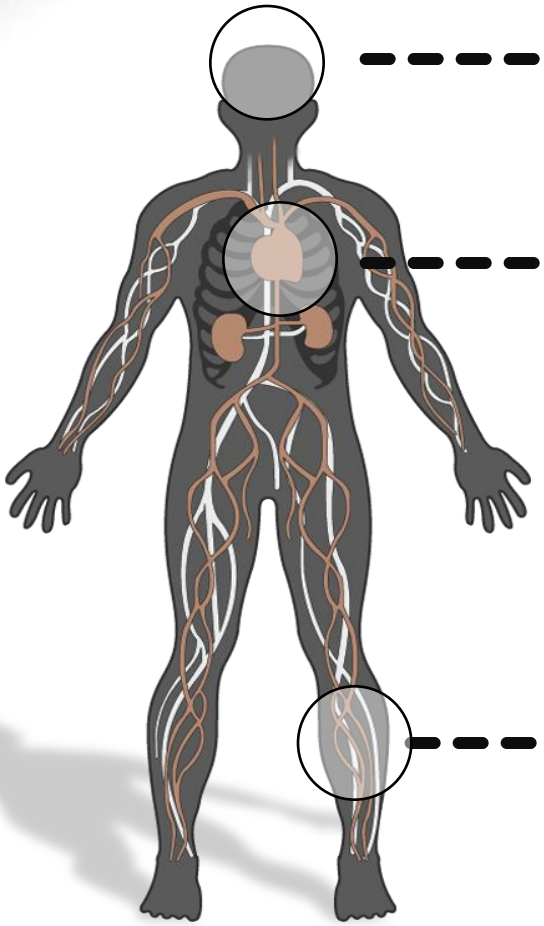
42%

Primary endpoint



Ref. Cannon CP, et al. N Engl J Med 2004;350:1495–504.

Clinical AtheroSclerotic CardioVascular Disease



Stroke or TIA presumed to be of atherosclerotic origin

Stable CHD : history of MI, stable angina, coronary revascularization

Acute CHD : Acute coronary syndrome

Peripheral arterial disease or revascularization

Ref. Stone NJ, et al. Circulation, 2013.

Clinical ASCVD: Stroke

SPARCL

4,731 Patients aged ≥ 18 years with stroke or TIA within 6 months

- Placebo
- Atorvastatin 80 mg/day

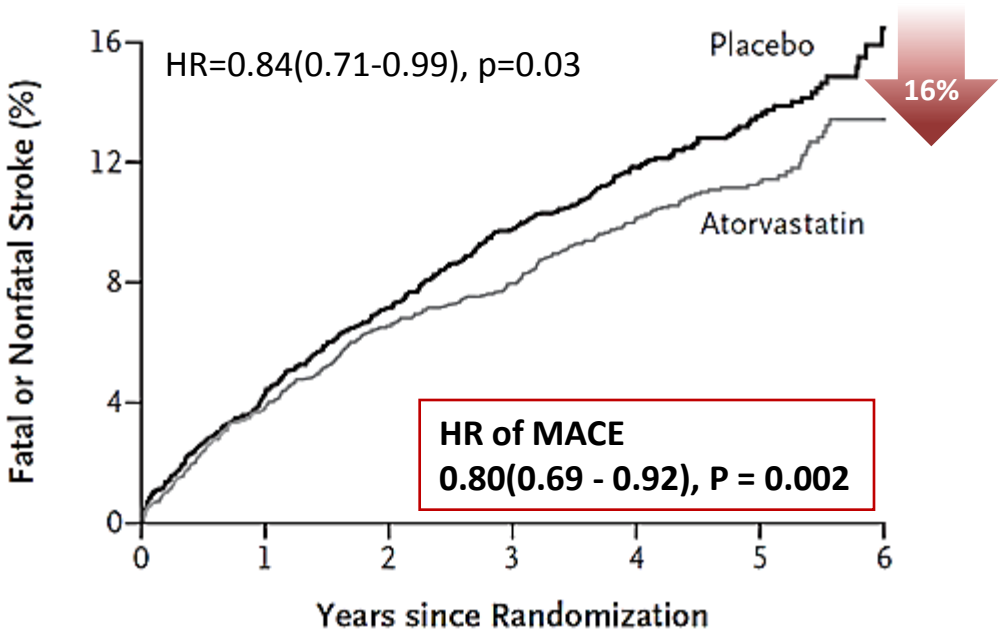
- Primary endpoint
  : nonfatal or fatal stroke
- Median follow-up = 4.9 years

Change of LDL-cholesterol

	Atorvastatin 80 mg	Placebo
N	**2,365**	2,366
Baseline median, mg/dl	**132.7±0.5**	133.7±0.5
End of follow-up mean, mg/dl	**73**	129
LDL-C difference (mg/dL)(%)	**-60(-45%)**	-4(-3%)

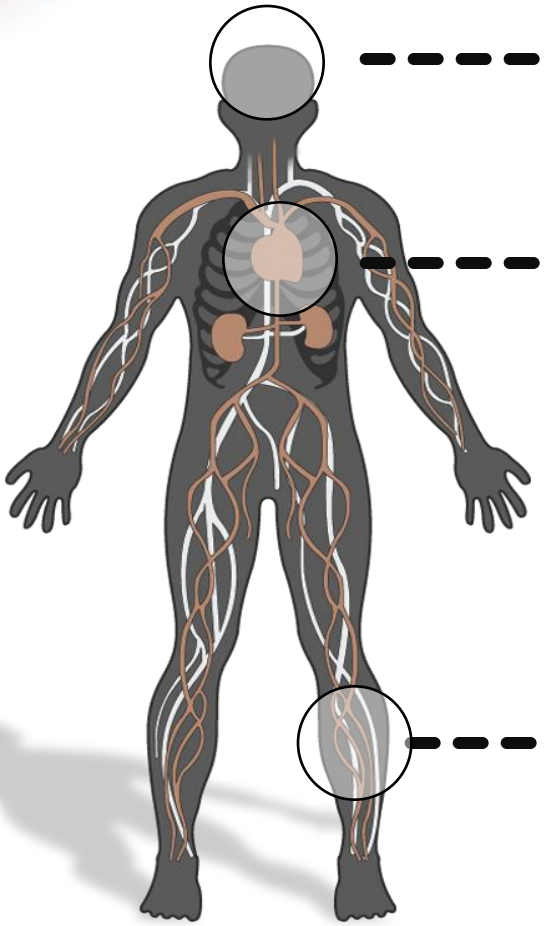
45%

Primary endpoint



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

Clinical AtheroSclerotic CardioVascular Disease



Stroke or TIA presumed to be of atherosclerotic origin

Stable CHD : history of MI, stable angina, coronary revascularization

Acute CHD : Acute coronary syndrome

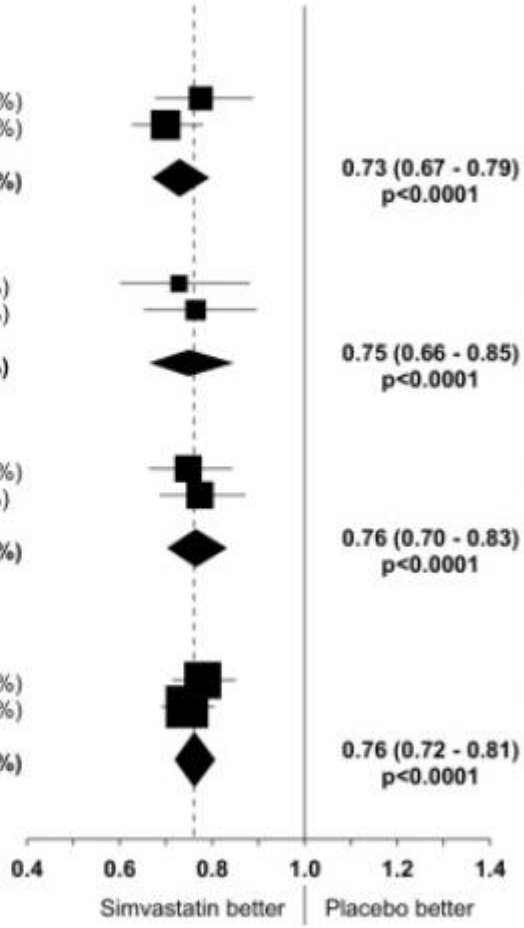
Peripheral arterial disease or revascularization

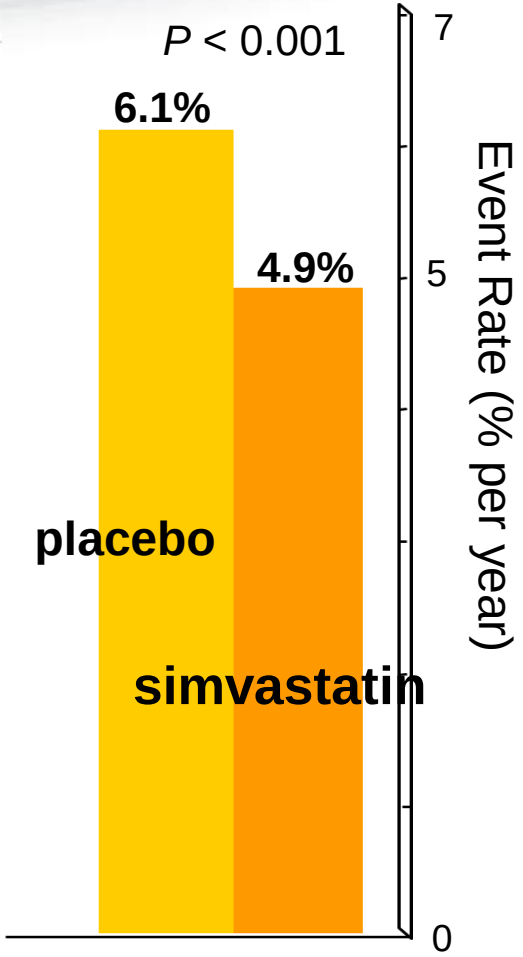
Ref. Stone NJ, et al. Circulation, 2013.

Clinical ASCVD: PAD

HPS

Major vascular event & prior disease group	Simvastatin -allocated (10,269)	Placebo -allocated (10,267)	Event rate ratio (95% CI)	Heterogeneity p-value
Major coronary events				
PAD	369 (10.9%)	465 (13.8%)		p=0.3
No PAD	529 (7.7%)	747 (10.8%)		
Subtotal: coronary	**898 (8.7%)**	**1212 (11.8%)**	**0.73 (0.67 - 0.79) p<0.0001**	
Strokes				
PAD	179 (5.3%)	242 (7.2%)		p=0.7
No PAD	265 (3.8%)	343 (5.0%)		
Subtotal: stroke	**444 (4.3%)**	**585 (5.7%)**	**0.75 (0.66 - 0.85) p<0.0001**	
Revascularisations				
PAD	466 (13.8%)	603 (17.9%)		p=0.7
No PAD	473 (6.9%)	602 (8.7%)		
Subtotal: revascularisation	**939 (9.1%)**	**1205 (11.7%)**	**0.76 (0.70 - 0.83) p<0.0001**	
MAJOR VASCULAR EVENTS				
PAD	895 (26.4%)	1101 (32.7%)		p=0.5
No PAD	1138 (16.5%)	1484 (21.5%)		
ALL PATIENTS	**2033 (19.8%)**	**2585 (25.2%)**	**0.76 (0.72 - 0.81) p<0.0001**	





PAD subgroups
(2701 pts)

HPS *Lancet.* 2002;360:7–22.

Recommendation Dose of Statin

Group 1

Clinical ASCVD

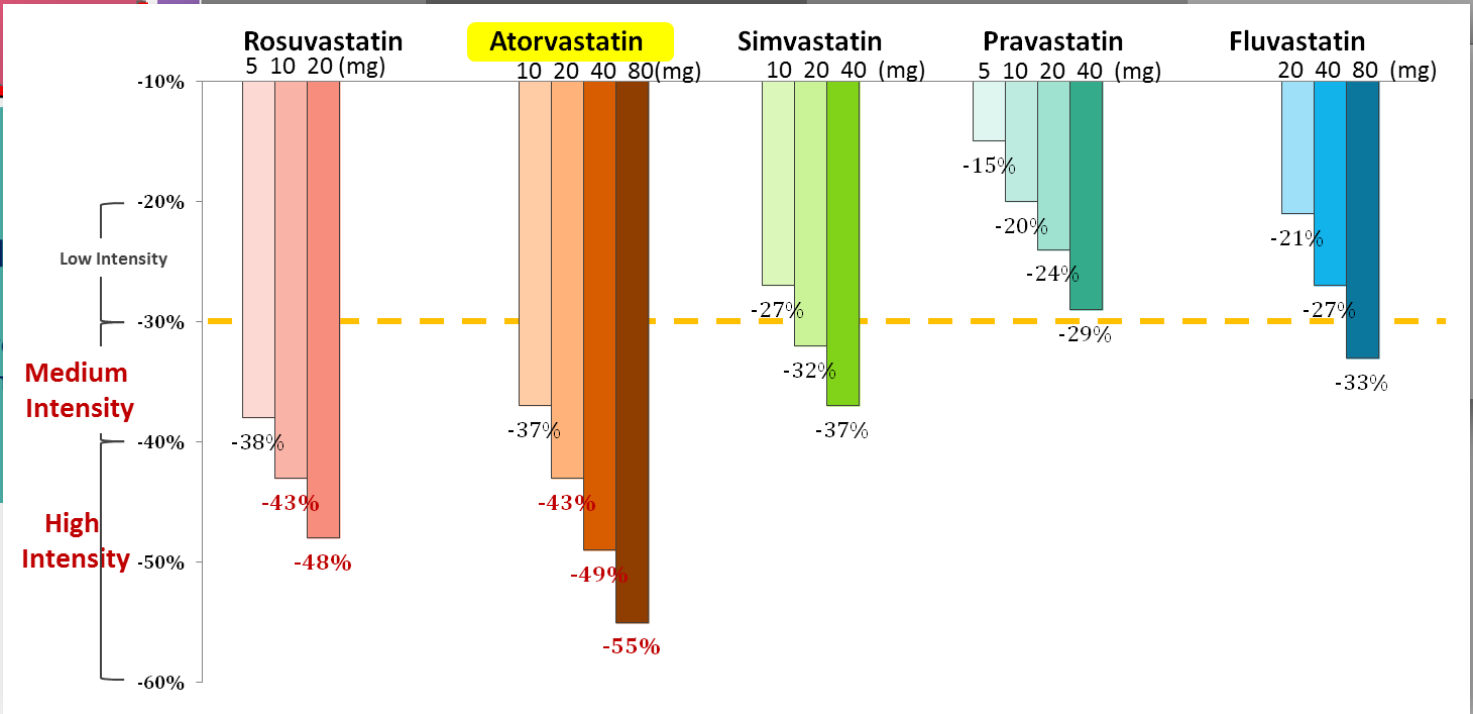
CHD, stroke, and peripheral arterial disease, all of presumed atherosclerotic origin

Group 3

Diabetes mel

+ aged 40–75 y
+ LDL-C 70–189 r

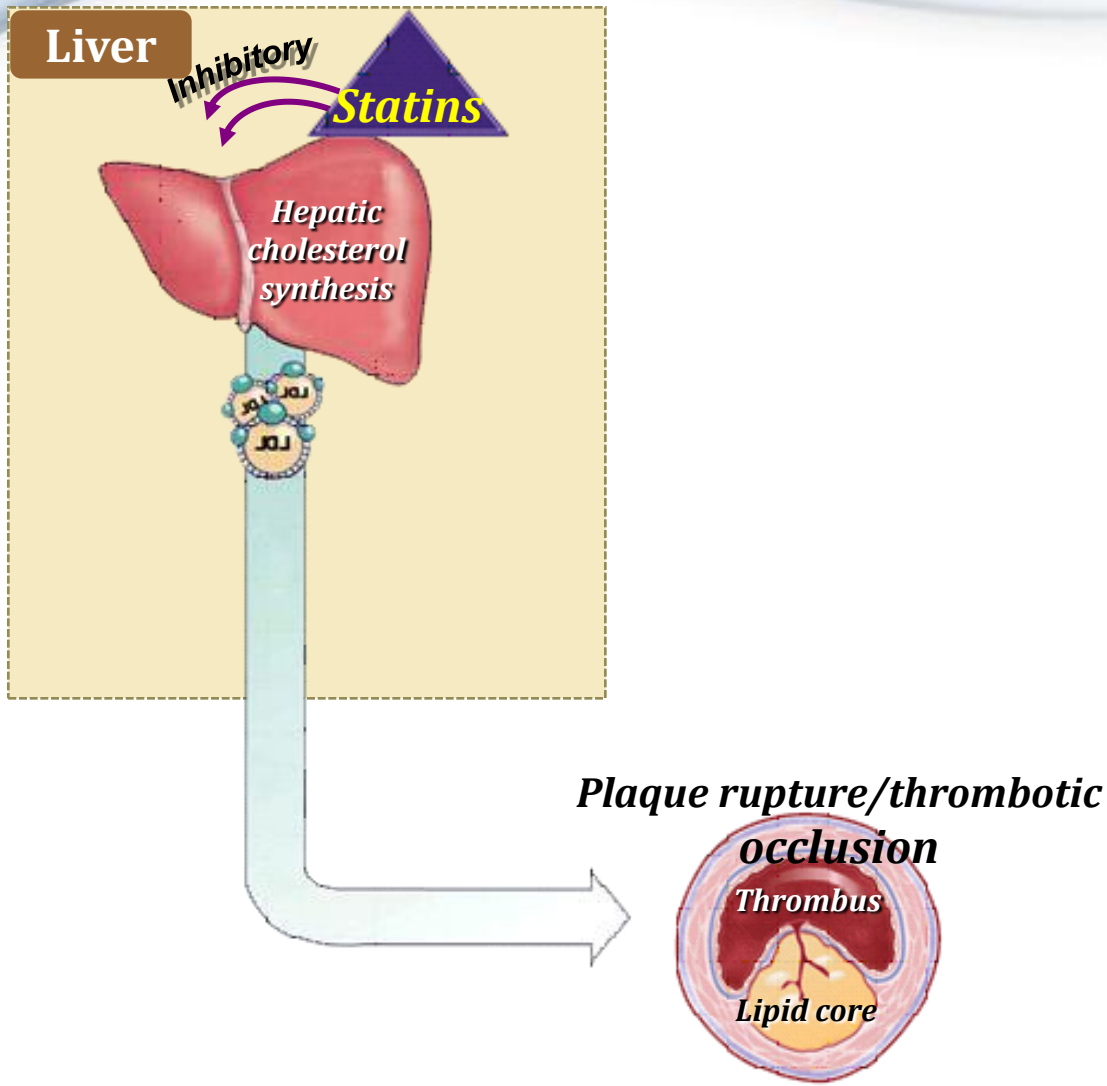
Intensity	High-Intensity	Moderate-Intensity	Low-Intensity
Reduction % in LDL-C	> 50% reduction of LDL with daily statin	30-50% reduction of LDL with daily statin	<30-50% reduction of LDL with daily statin



Stone NJ, et al. 2013 Circulation
NICE Guideline: lipid modification, 2014

2 Beyond Lipid lowering for ASCVD

Statin: Lipid lowering agent !

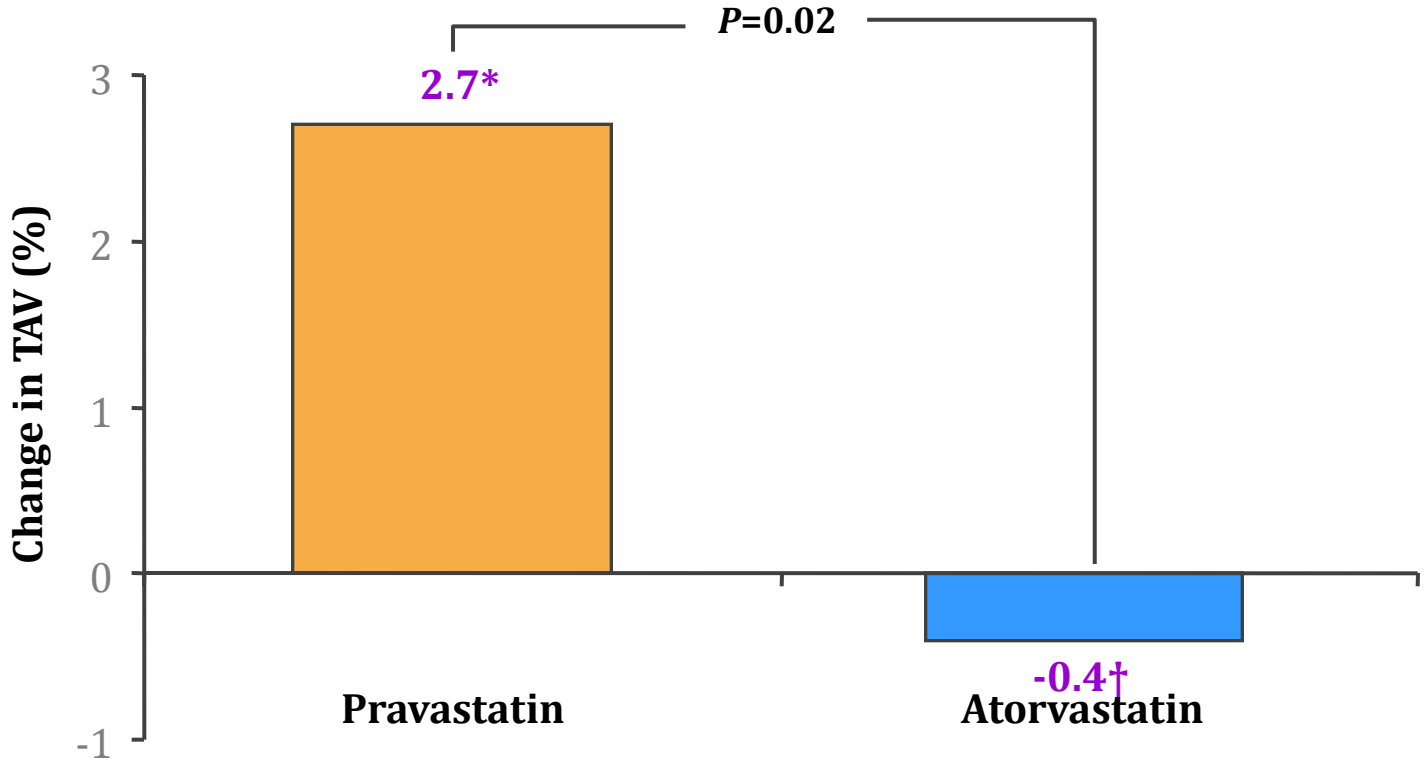


Adapted from Ray KK et al. JACC. 2005;46:1425-1433.

Reduced progression of atherosclerotic plaque

REVERSAL study : N=502 pts with atherosclerosis randomized to pravastatin 40 or atorvastatin 80 mg.

[Change in atheroma volume at 12 months]

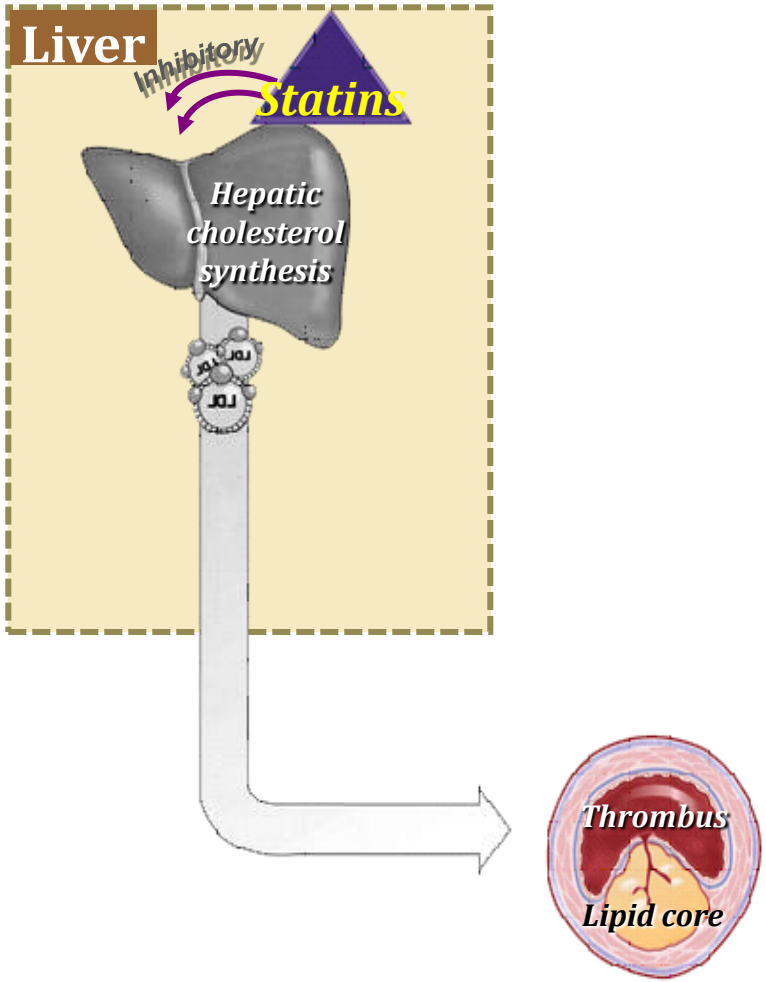


*Progression vs baseline (P=0.001); †No change vs baseline (P=0.98)

Nissen SE, et al. Lancet. JAMA. 2004;291:1071-1080.

Relative timing of effect

Slower/late effect



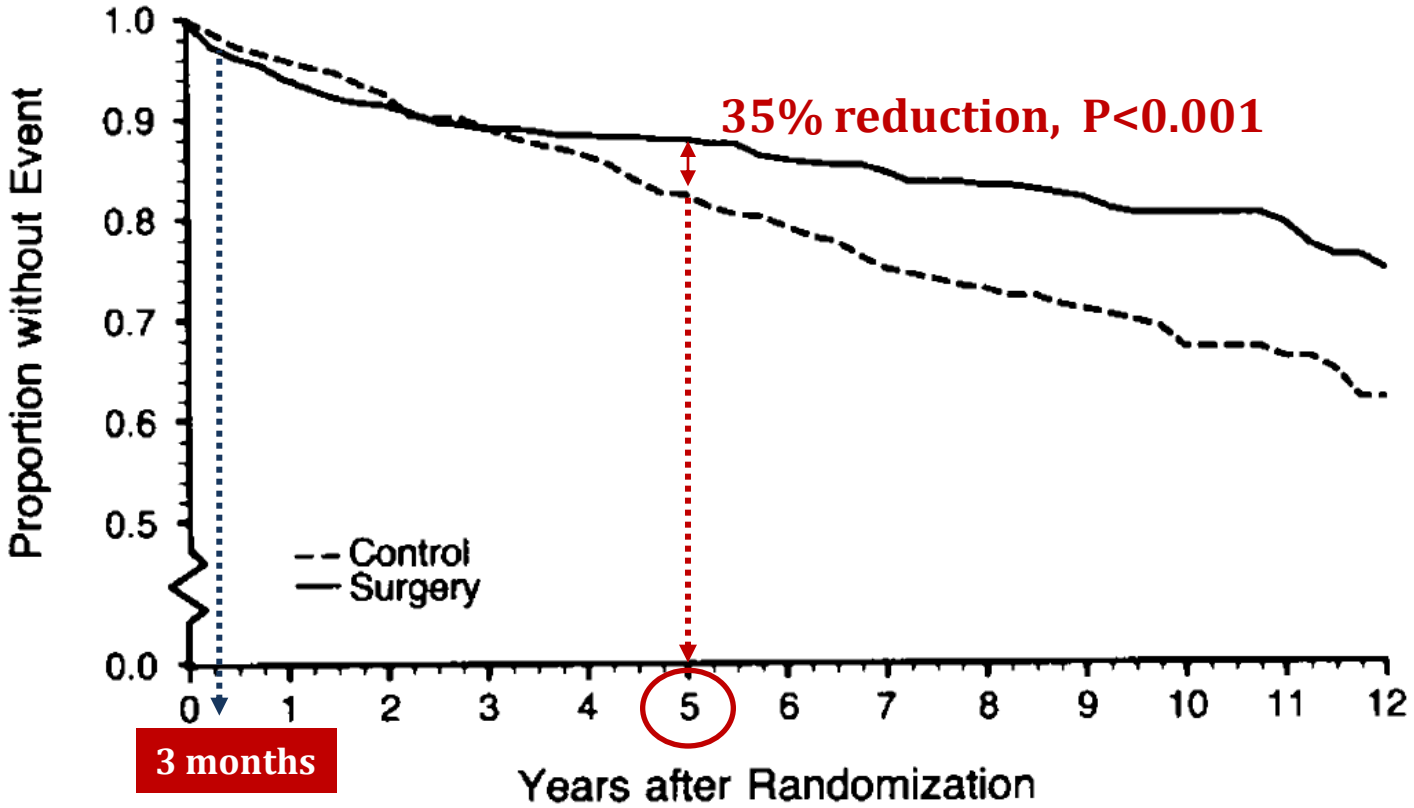
Adapted from Ray KK et al. JACC. 2005;46:1425-1433.

Early reduction in LDL-C, but Delayed Benefit after ileal bypass surgery

POSCH

POSCH trial : N=838 pts with 1st MI
randomized to control group vs ileal bypass surgery group

[combined endpoint as death and confirmed nonfatal MI]



34% LDL-C reduction in surgery group

Buchwald H, et al. N Engl J Med. 1990 Oct 4;323(14):946-55.

Early Reduction, Early Benefit…

MIRACL

3,086 Patients with NSTE-ACS

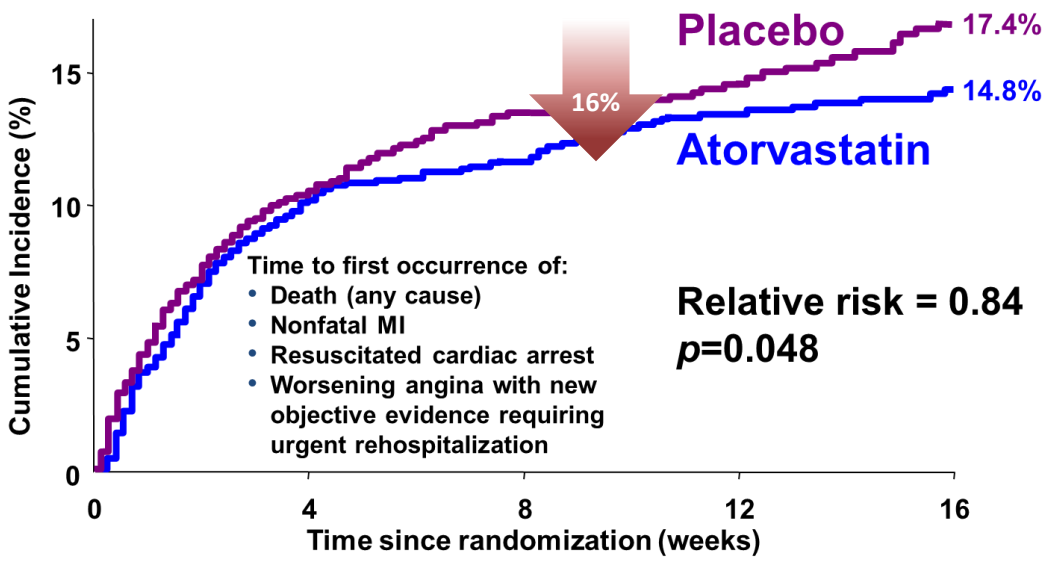
- Placebo + Diet
- Atorvastatin 80 mg/day + Diet

- Primary endpoint : Death, MI, Resuscitated cardiac arrest, Documented UA requiring rehospitalization
- Follow-up = 16 weeks

Change of LDL-cholesterol

	Atorvastatin	Usual Care
N	1538	1548
Baseline median, mg/dl	123	125
End of follow-up mean, mg/dl	72	135
LDL-C difference (mg/dL)(%)	-40%	+12%

Primary endpoint



JAMA. 2001 Apr 4;285(13):1711-8.

Statin benefit in early period, Why?

GRACE

94 hospitals in 14 countries participating in the Global Registry of Acute Coronary Events (GRACE)

Effect of Initiation of In-Hospital Statin Therapy on Statin-Naive Patients

The composite end point : death, in-hospital myocardial infarction, stroke.

Characteristic	Long-Term and In-Hospital Statin Use (n = 3628)	Long-Term Statin Use Only (n = 428)	P Value	No Statin Use (n = 9522)	In-Hospital Statin Use Only (n = 5959)	P Value

Background: Statins administered early in patients with acute coronary syndromes may lead to modest reductions in recurrent ischemic events.

Objective: To examine the association between previous and early in-hospital statin therapy and the presentation and outcomes of an acute coronary syndrome.

Design: Cohort study.

Setting: 94 hospitals in 14 countries participating in the Global Registry of Acute Coronary Events (GRACE).

Patients: 19 537 patients with an acute coronary syndrome who were enrolled from April 1999 to September 2002.

Measurements: Statin use before and after presentation with an acute coronary syndrome and associated rates of myocardial infarction, hospital complications, and hospital mortality. The composite end point included death, in-hospital myocardial infarction, cardial infarction (OR, 0.78 [CI, 0.70 to 0.86]). Patients who continued to take statins in the hospital were less likely to experience complications or die than patients who never received statins (OR, 0.66 [CI, 0.56 to 0.77]). Patients not previously taking statins who began statin therapy in the hospital were less likely to die than patients who never received statin therapy (OR, 0.38 [CI, 0.30 to 0.48]). However, adjustment for the hospital of admission attenuated the association between initiation of statin therapy and the composite end point (OR, 0.84 [CI, 0.65 to 1.10]).

Limitations: This observational study cannot exclude confounding by clinical and hospital factors.

Conclusions: These data support the hypothesis that statin therapy can modulate early pathophysiologic processes in patients with acute coronary syndromes. A randomized trial of statin therapy in acute myocardial infarction is warranted.

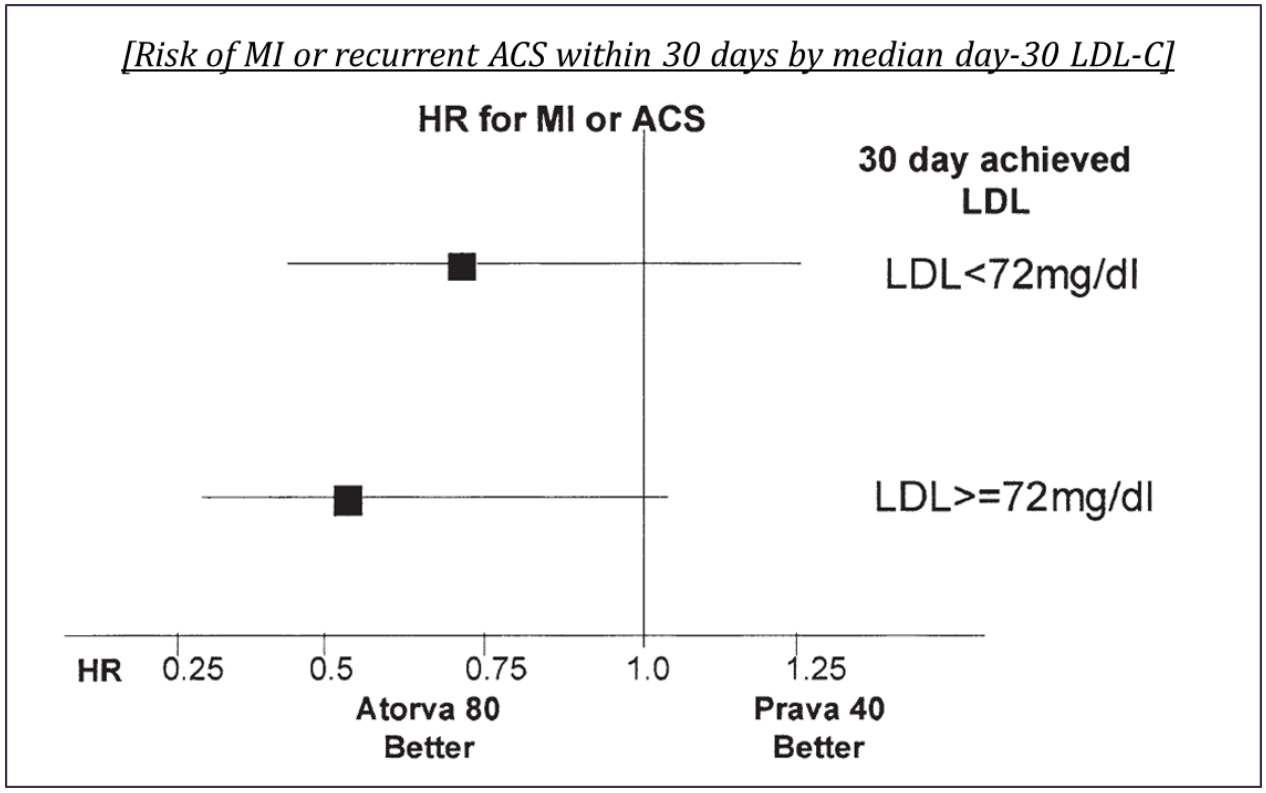
Statin early treatment has benefit on Statin-Naive ACS patients and this ability is **independent of their lipid-lowering capacity**

Spencer FA, et al. Ann. Intern. Med. 2004;140, 857–866

PROVE IT–TIMI-22

4,162 Patients with ACS ≤ 10 days, randomized to pravastatin 40 mg or atorvastatin 80 mg

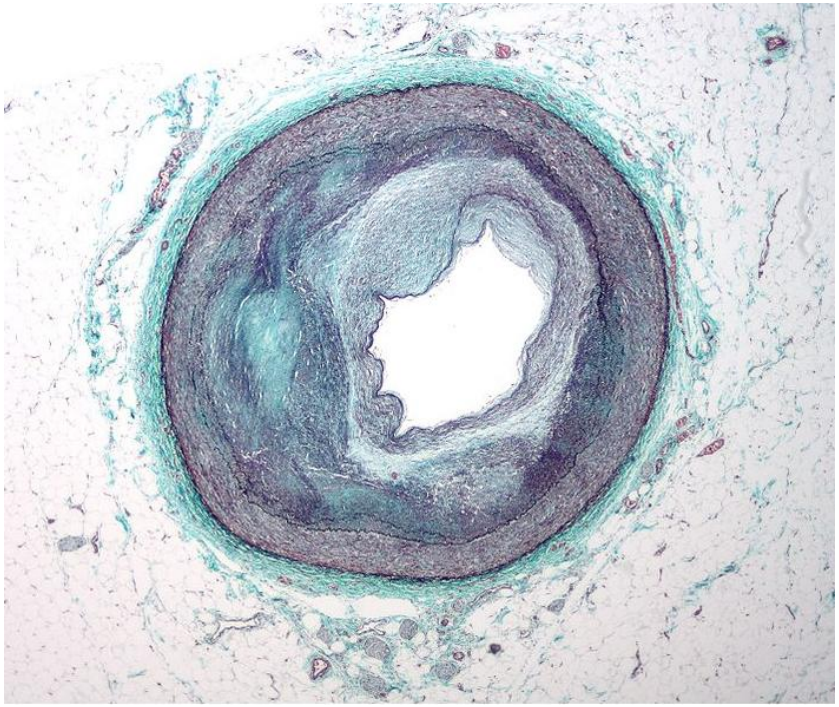
Atorvastatin's CAD benefit regardless of achieved LDL-cholesterol level



Cannon CP, et al. JACC 2006;48:843–53

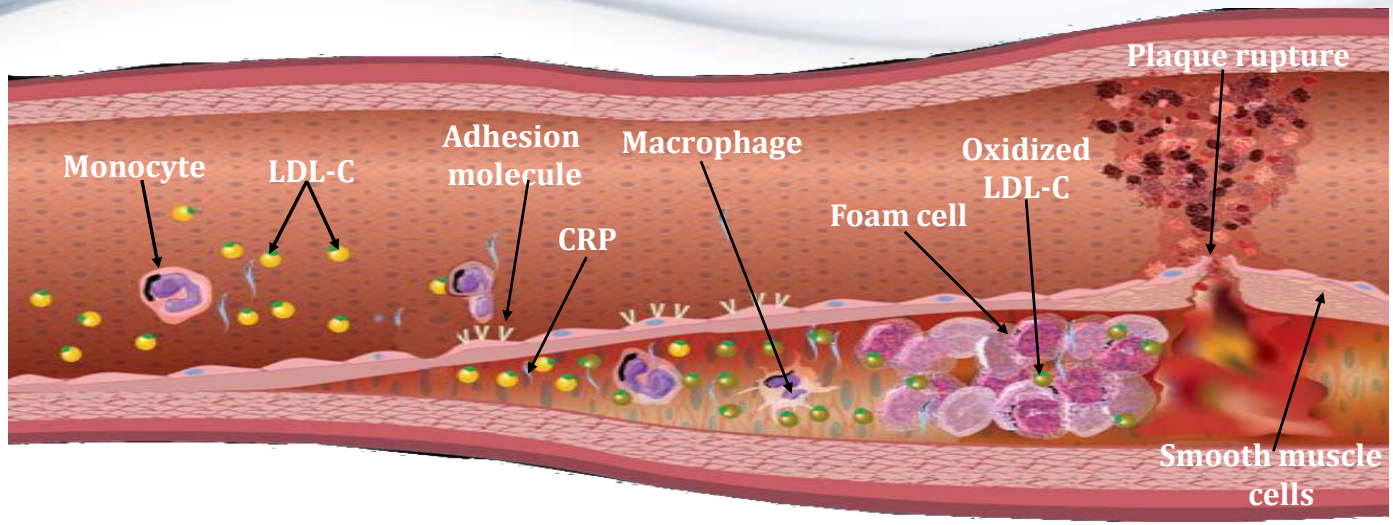
Our concepts & clinical approaches to CAD changed

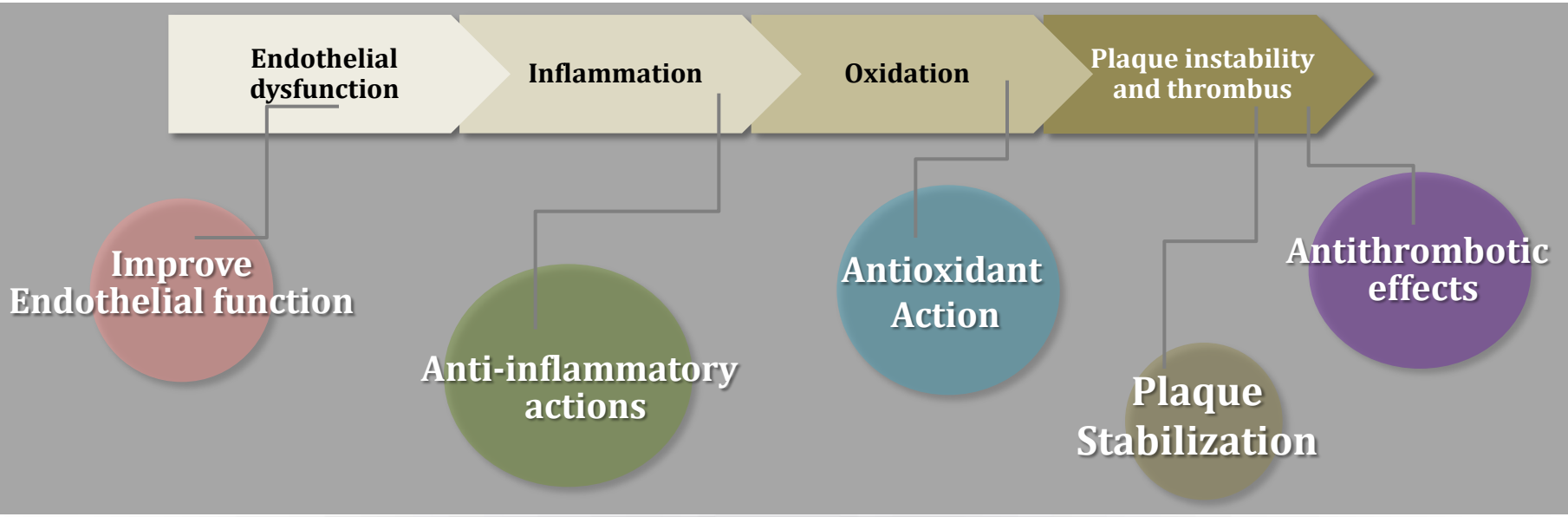
Coronary Artery Disease ?



Cholesterol storage disease → **Inflammatory disorder**

Statin Benefit on CAD



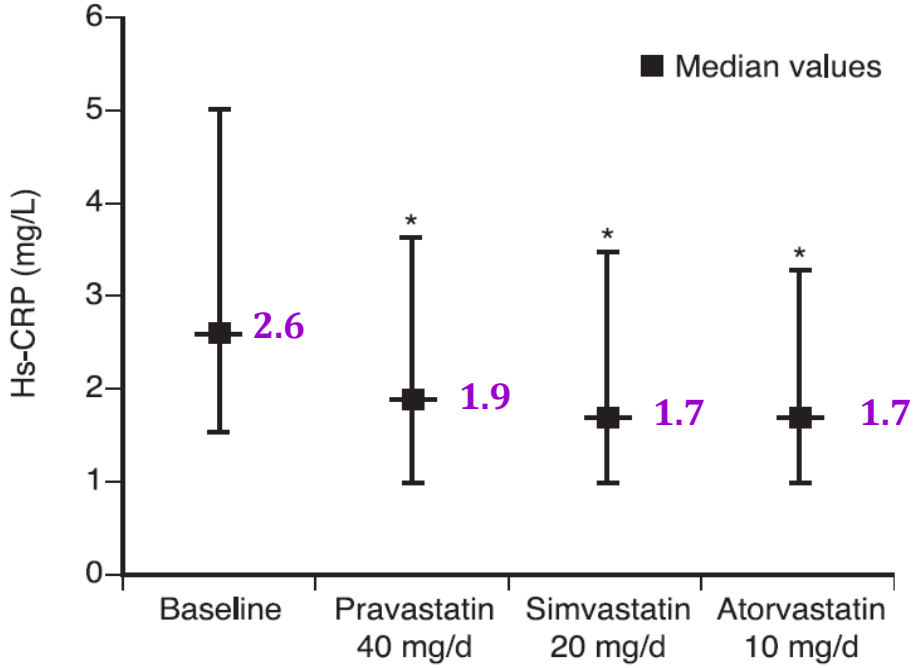


Reductions in plasma hs-CRP levels

anti inflammatory effect

N=22 pts with combined hyperlipidemia
randomized to placebo or one of 3 statin groups for 6weeks.

[Effect of statin therapy on levels of hs-CRP]



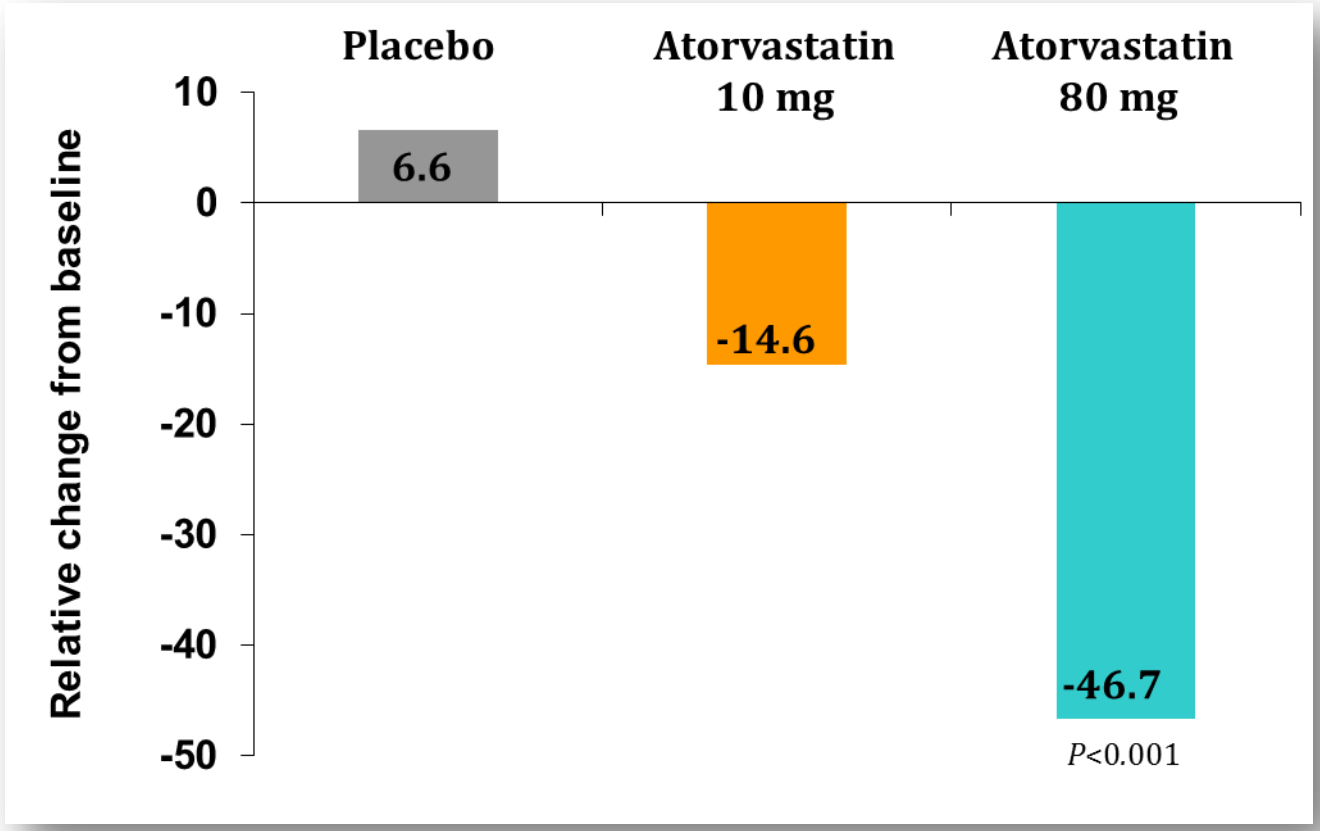
***P=0.025 compared with baseline**

There was no relationship
between reductions in hs-CRP and LDL cholesterol.

Jialal I et al. Circulation. 2001;103:1933–193.

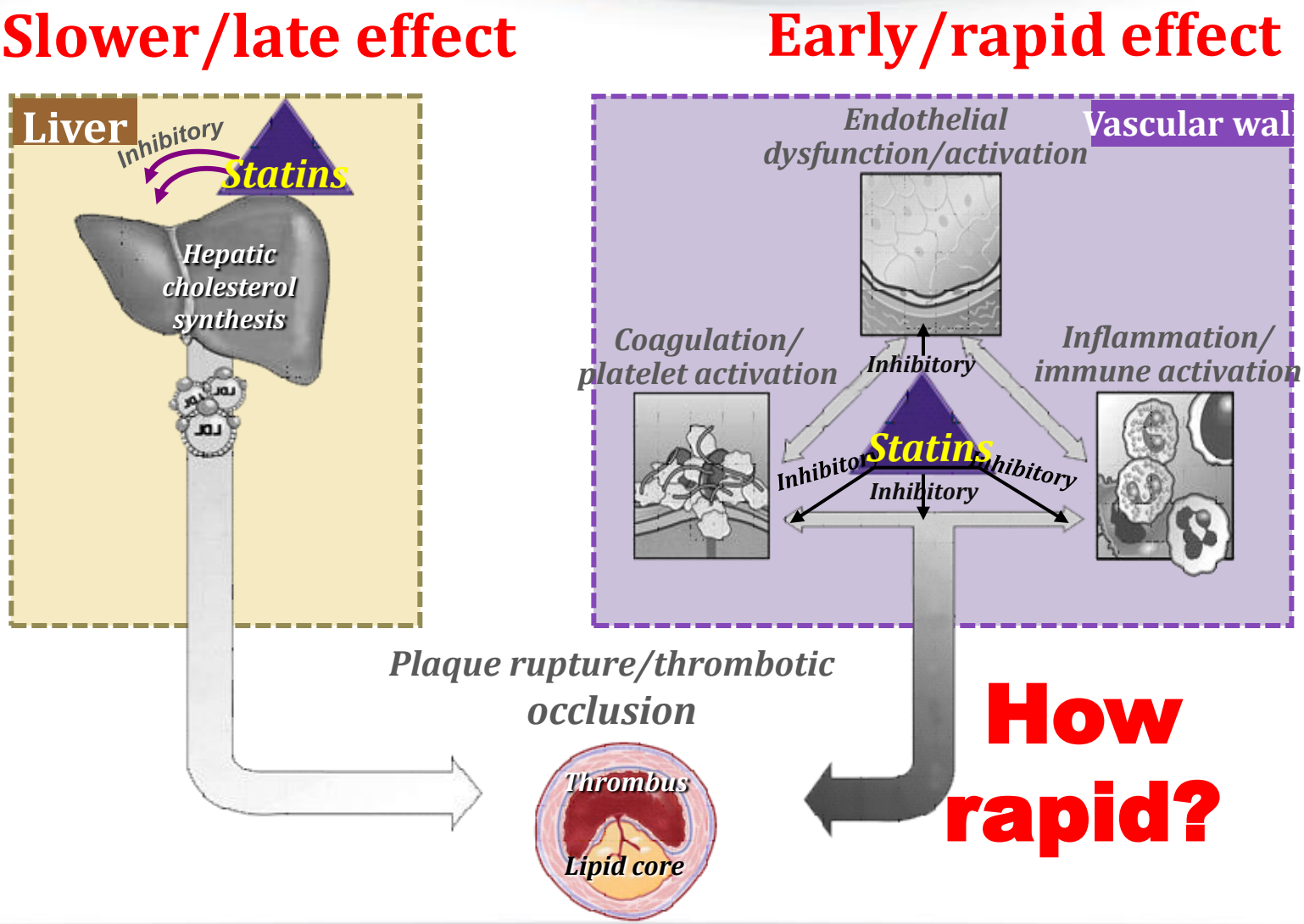
Diabetes Atorvastin Lipid Intervention (DALI)

Atorvastatin significantly lowered CRP levels in Type 2 Diabetic patients in a Dose-Dependent Manner



Atherosclerosis. 2003;166:129-135.

Role of Atorvastatin in ASCVD



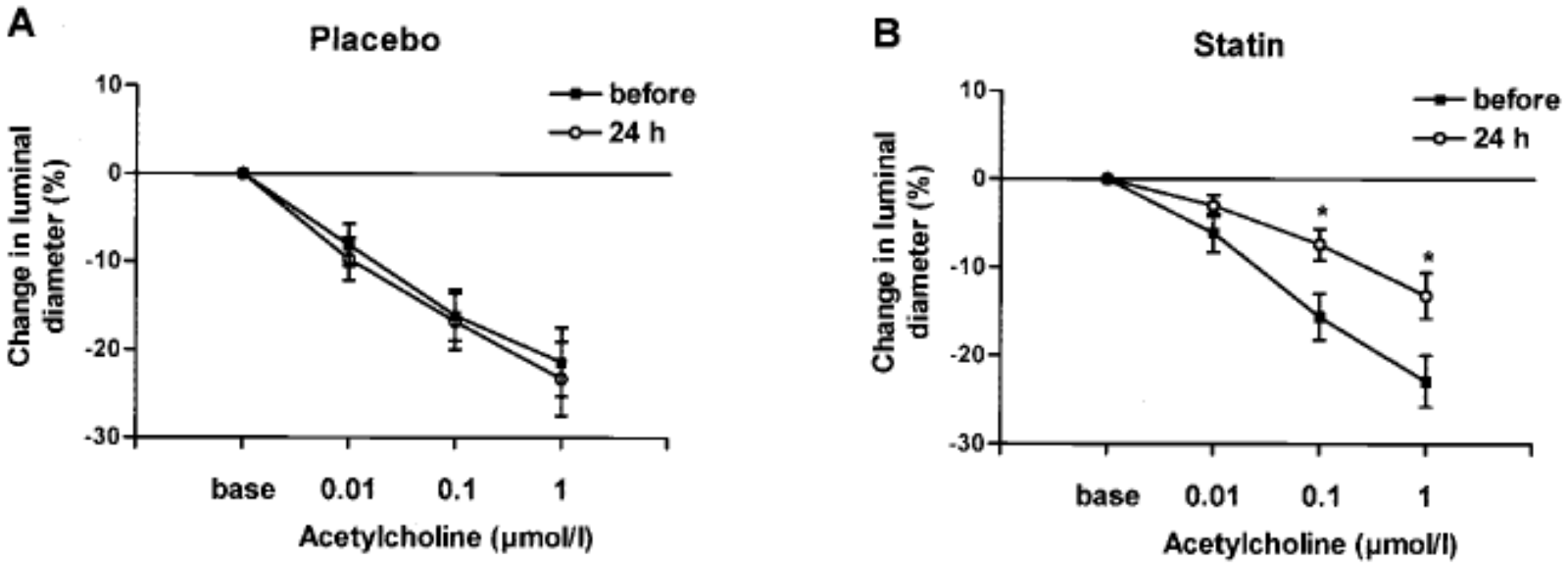
Adapted from Ray KK et al. JACC. 2005;46:1425-1433.

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]



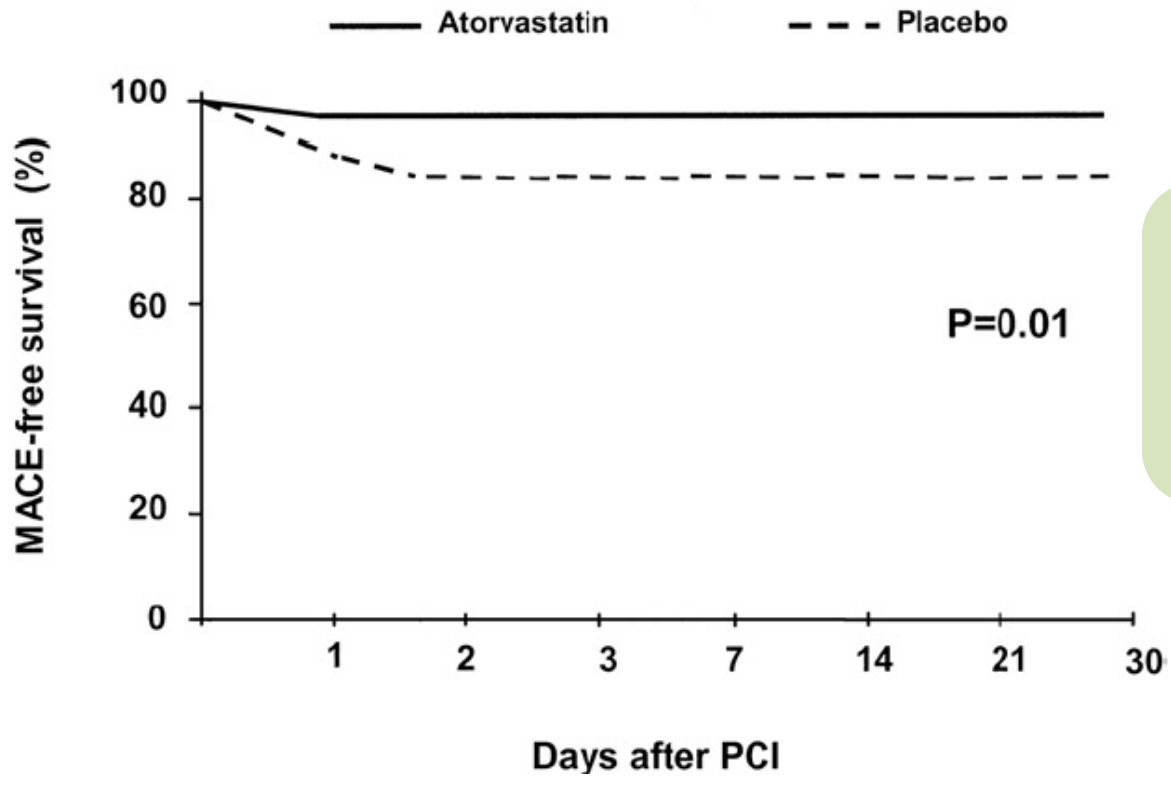
At 24 hrs, significant reduction of acetylcholine-mediated vasoconstriction

Wassmann S, et al. Circ Res 2003.

In ACS pts undergoing PCI, high dose atorvastatin improves outcome

ARMYDA-ACS

N=171 Statin Naïve pts with NSTEMI ACS randomized to placebo or atorvastatin (LIPITOR 80 mg 12 hrs before PCI, Further 40 mg 2 hr before PCI)



30-day major adverse cardiac events 12% ↓

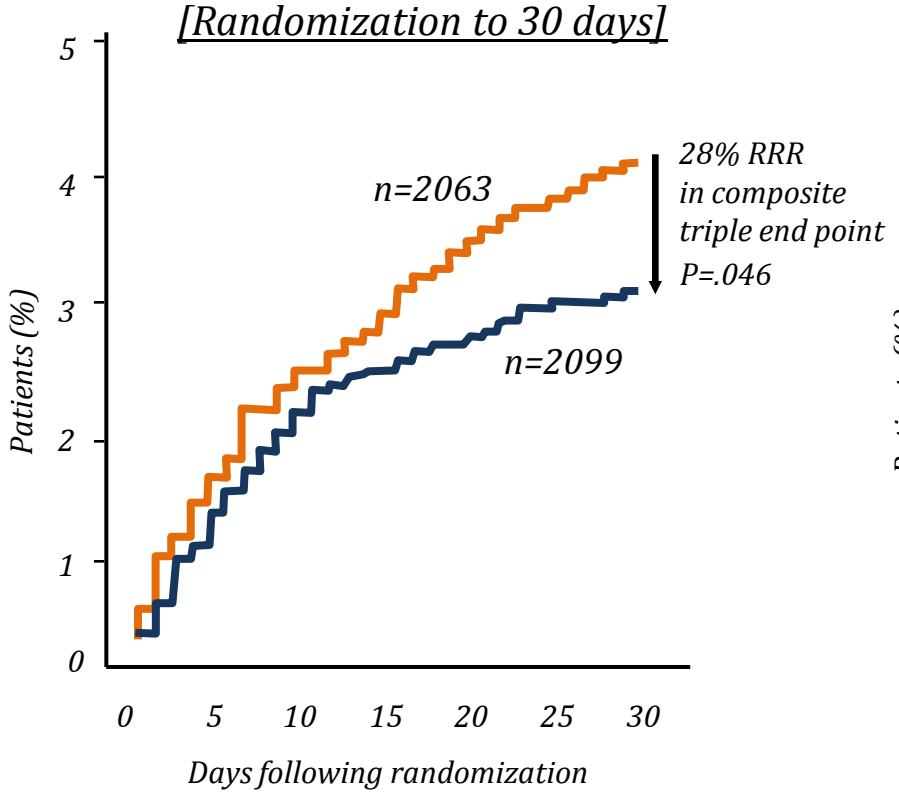
(95% CI 0.05 -0.50, p=0.004)

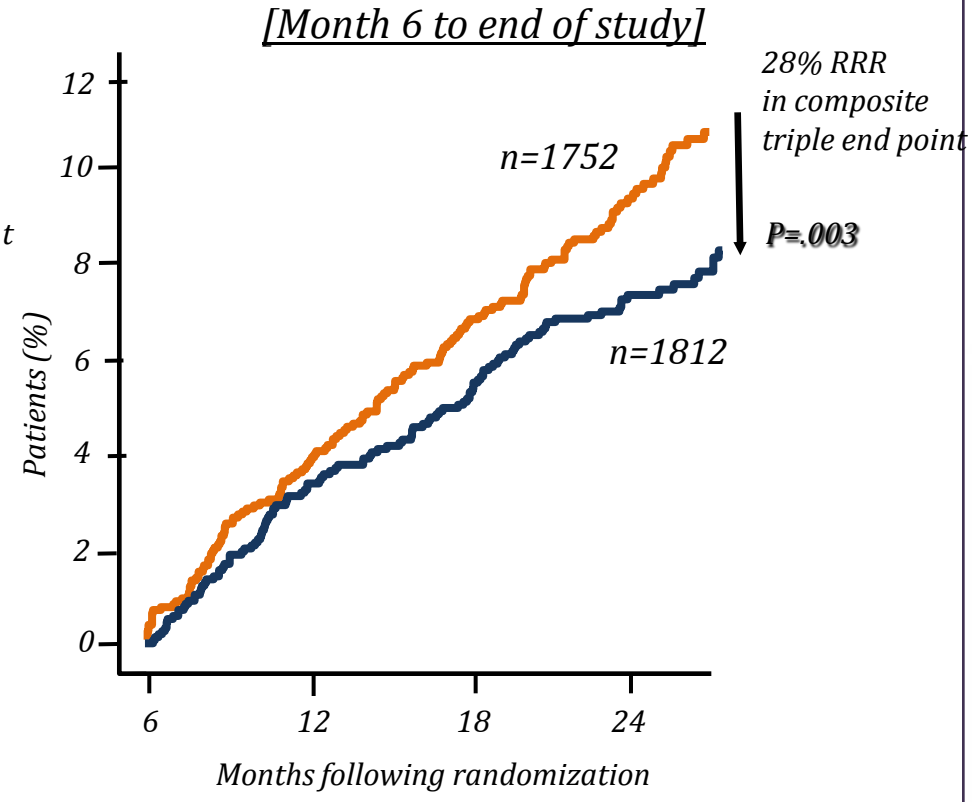
Pati G, et al. J Am Coll Cardiol. 2007;49:1272-8.

In ACS pts undergoing PCI, high dose atorvastatin improves outcome

ARMYDA-RECAPTURE

N=383 pts with stable angina, NSTEMI ACS, chronic statin therapy randomized to placebo or atorvastatin 80 mg (LIPITOR 80 mg 12 hrs before angio, Further 40 mg 2 hr before angio)





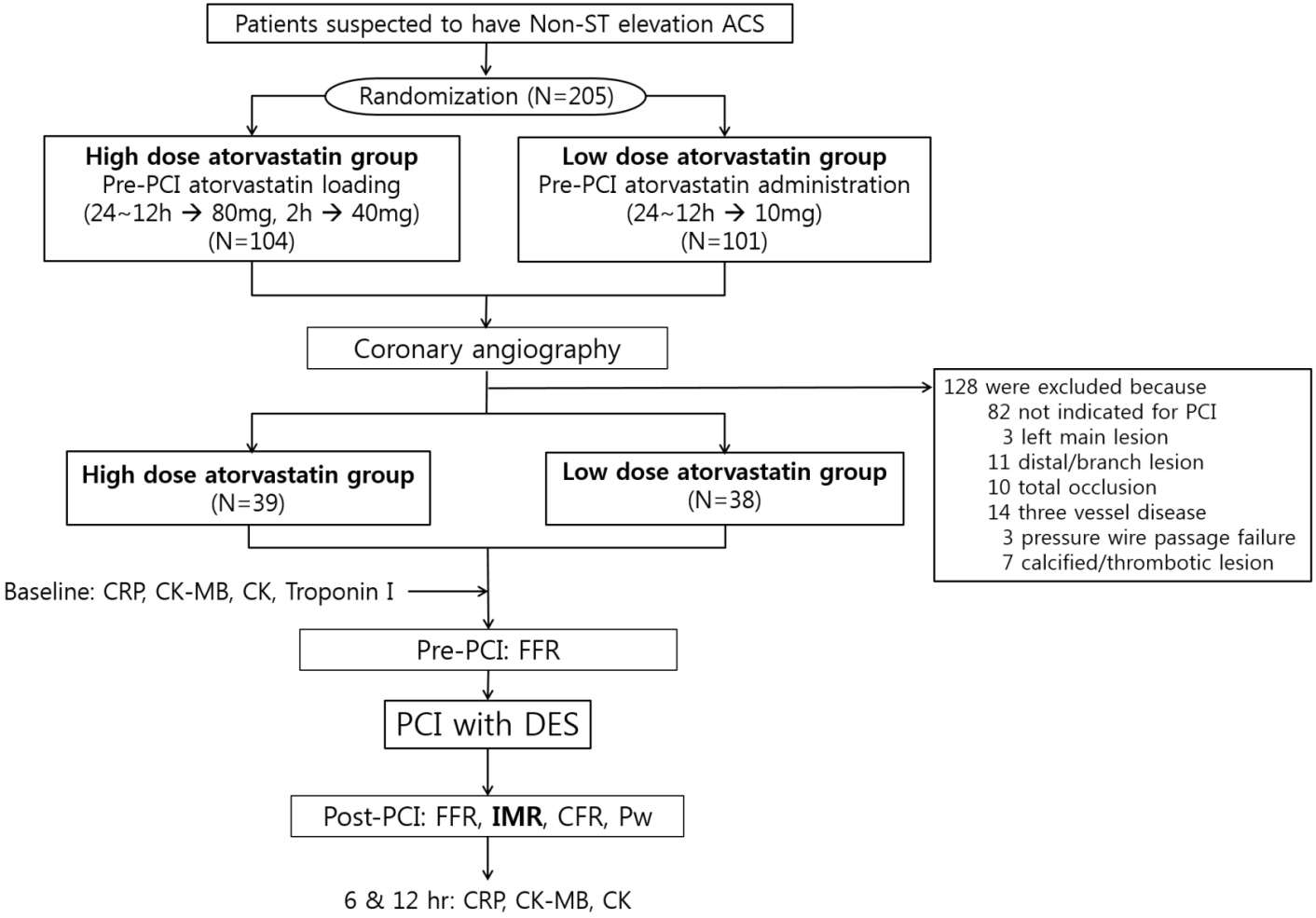
Atorvastatin 80 mg — Pravastatin 40 mg

Sciascio GD, et al. J Am Coll Cardiol. 2009;54:558-65.

In ACS pts undergoing PCI, high dose atorvastatin improves outcome

RESIST-ACS

RESIST-ACS trial

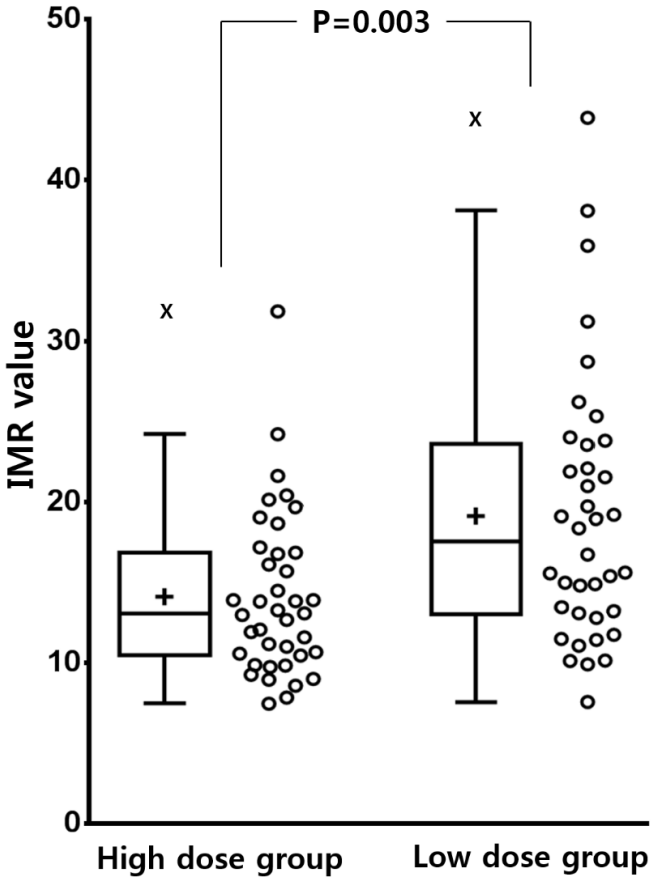


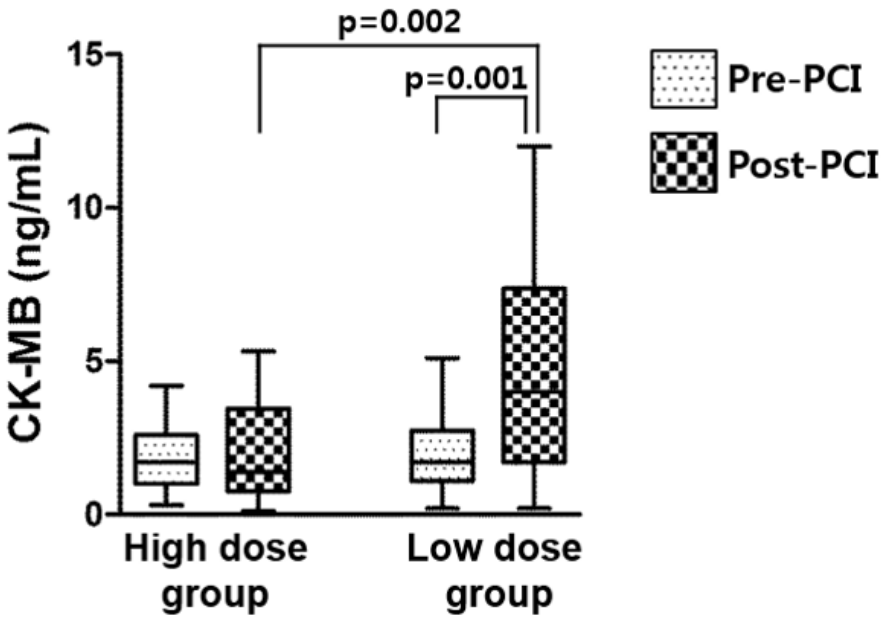
Lee BK, et al. Korean Circulation J 2016

In ACS pts undergoing PCI, high dose atorvastatin improves outcome

RESIST-ACS

RESIST-ACS trial





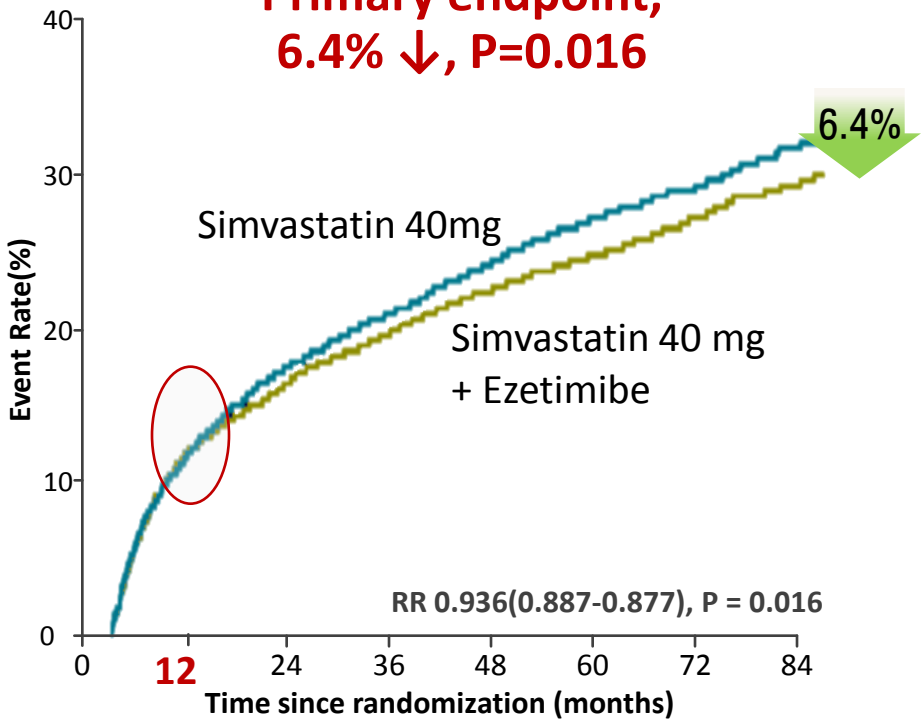
Lee BK, et al. Korean Circulation J 2016

Role of Non-statin Therapy in ACS

IMPROVE IT

18,144 patients stabilized post ACS ≤ 10 days
LDL-C 50-125mg/dL

Primary endpoint,
6.4% ↓, P=0.016

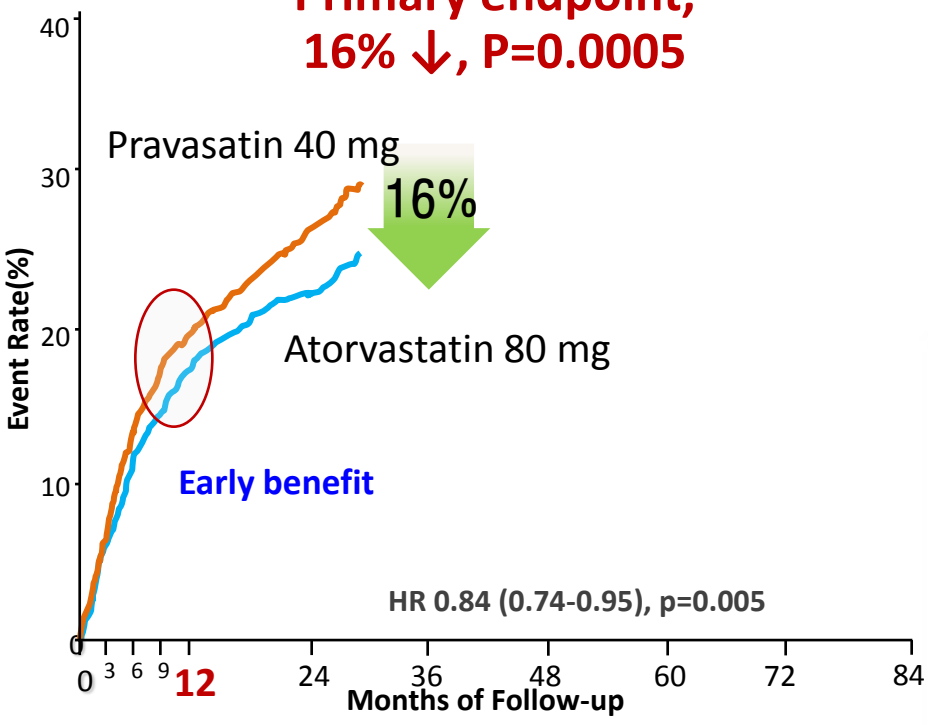


Primary endpoint : CV death, MI, admission for UA, revascularization or stroke

PROVE IT

4,162 Patients stabilized post ACS ≤ 10 days
TC ≤ 240 mg/dL (or 200 mg/dL if prior lipid-lowering Rx)

Primary endpoint,
16% ↓, P=0.0005



Primary endpoint : All cause death, MI, admission for UA, revascularization, or stroke

Current Non-statin Therapy

	2013 ACC/AHA guideline	2013 IAS guideline	2014 NICE guideline	2015 ADA guideline
Secondary prevention	High intensity or Moderate-intensity statin therapy. Non-statin therapy **has been minimized**	Maximal statin therapy if tolerated. **If statin intolerant,** Combination moderate dose of statin with nonstatin.	Atorvastatin 80 mg Nonstatin therapy is **not generally recommended.**	High intensity or Moderate-intensity statin therapy based on risk profile. Nonstatin therapy is **not generally recommended**.
Primary prevention		Statins are first line therapy. **If statin intolerant,** use of nonstatin alone or combination.	Atorvastatin 20 mg Nonstatin therapy is **not generally recommended.**	

Late Benefit, but not only from Lipid: Plaque Stabilization…

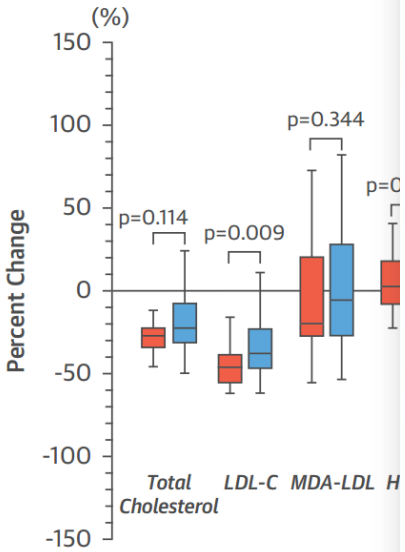
EASY-FIT

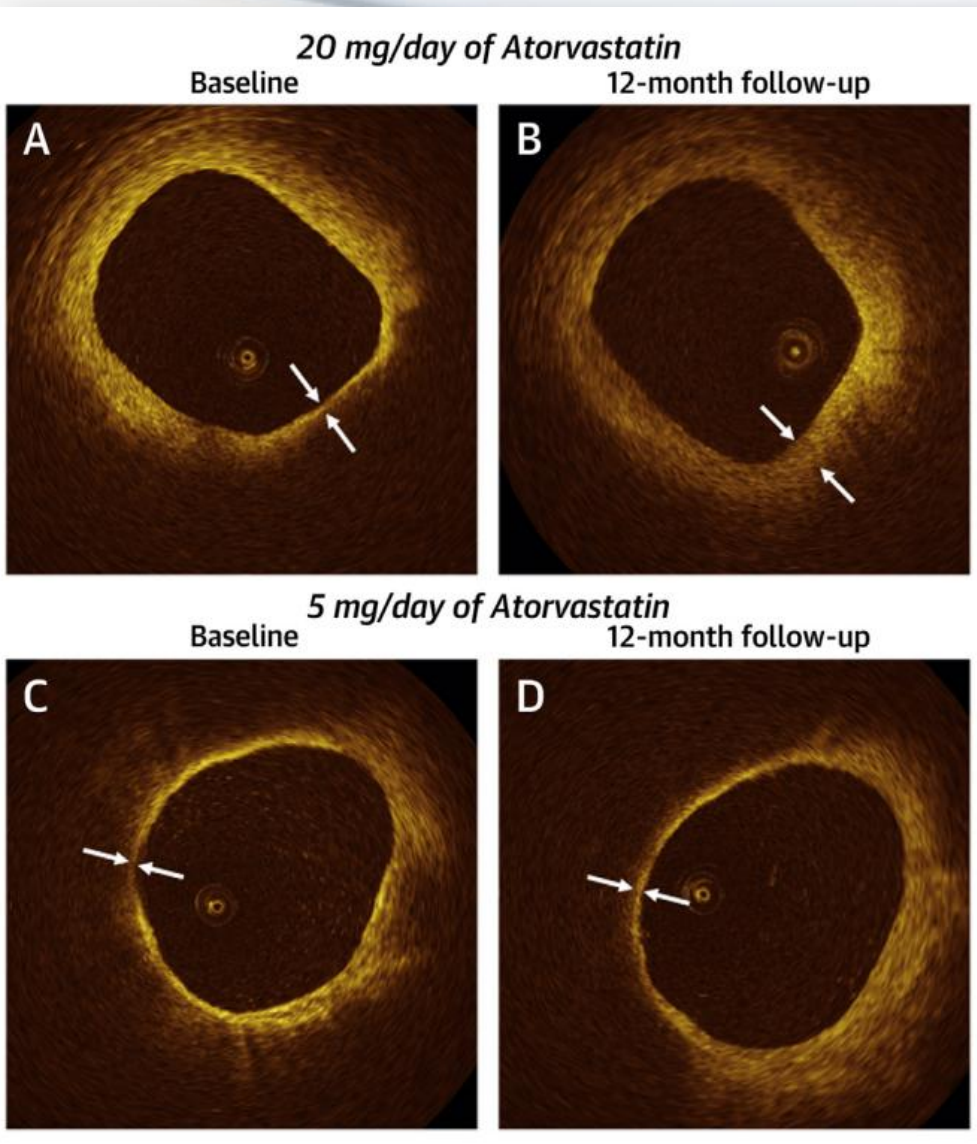
70 Patients with U
Naïve to statin

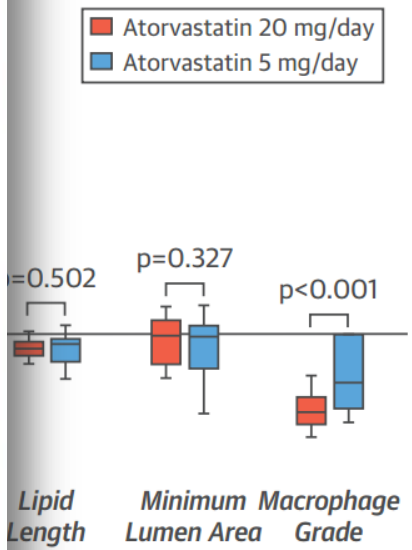
int: Fibrous Cap
oronaryAtherosclerotic
ssed by Optical
nography
months

Char

ndpoint



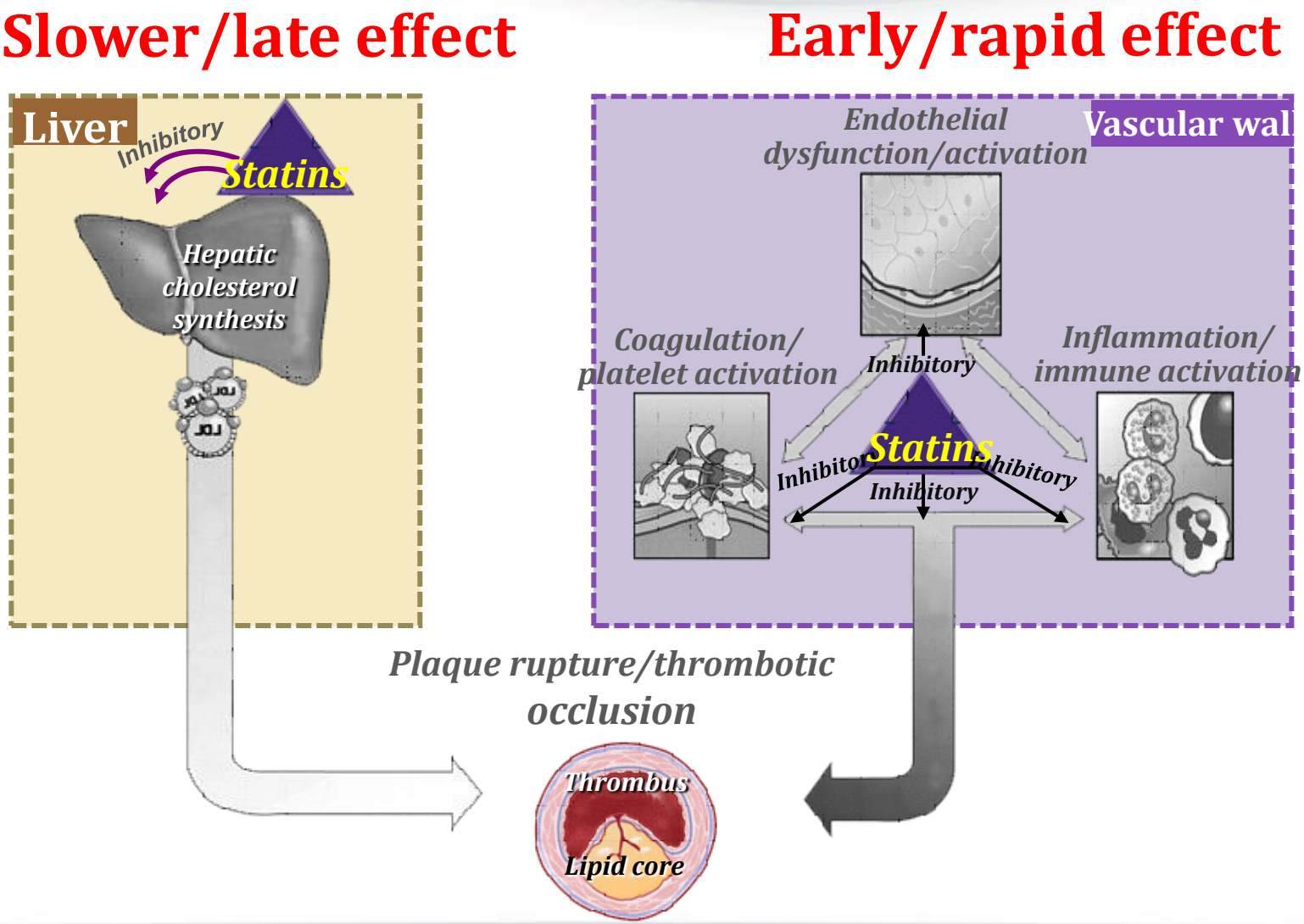




Keimyung University Dongsan Medical Center

J Am Coll Cardiol 2014;64:2207

Summary: Role of Atorvastatin in ASCVD



Adapted from Ray KK et al. JACC. 2005;46:1425-1433.

계명대학교 동산의료원
Keimyung University Dongsan Medical Center

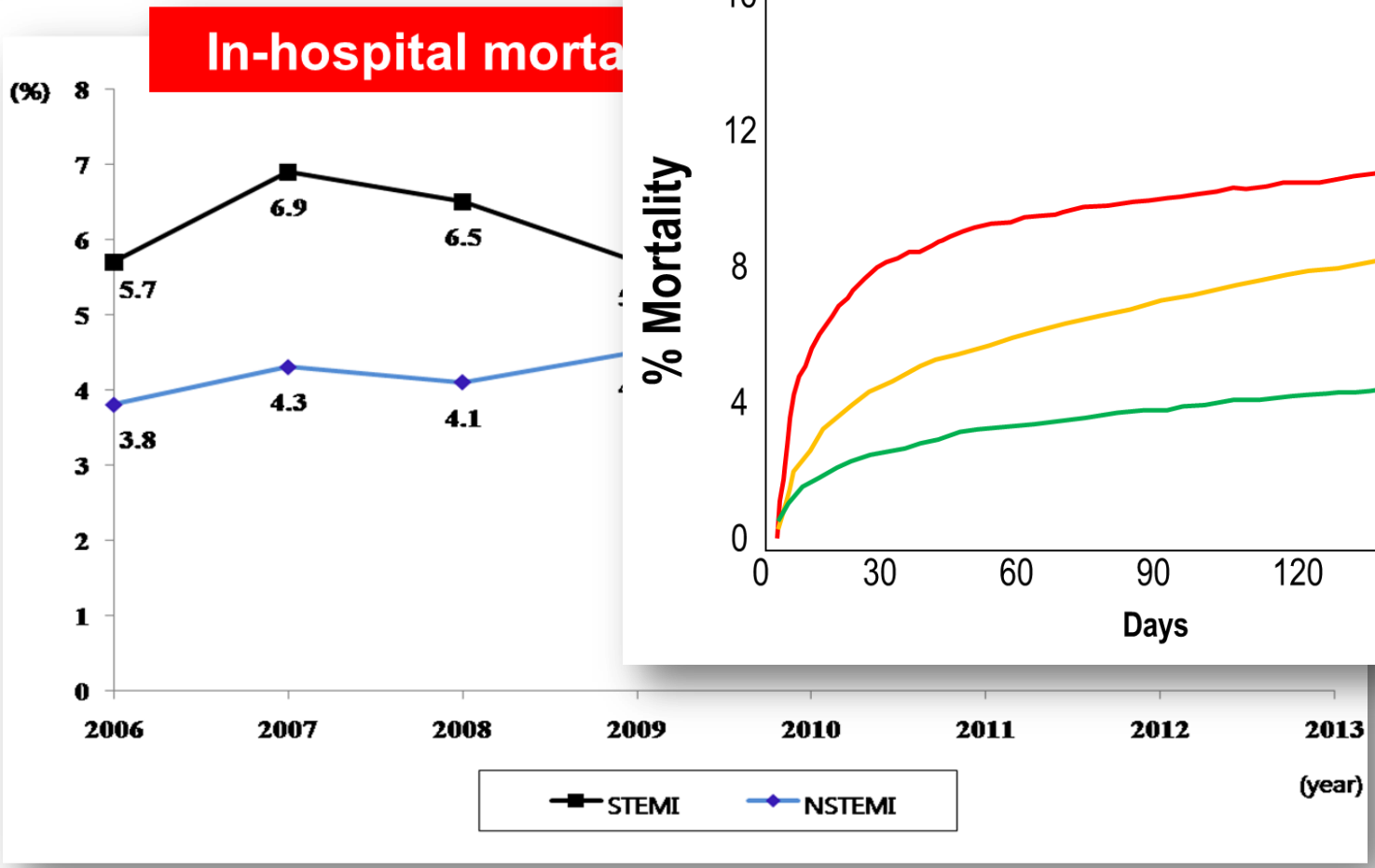
Optimizing strategies for CV risk reduction in patients with ASCVD When and How

계명대학교 동산의료원 심장내과
남창욱

경청에 감사드립니다.

Mortality in Acute Coronary Syndromes

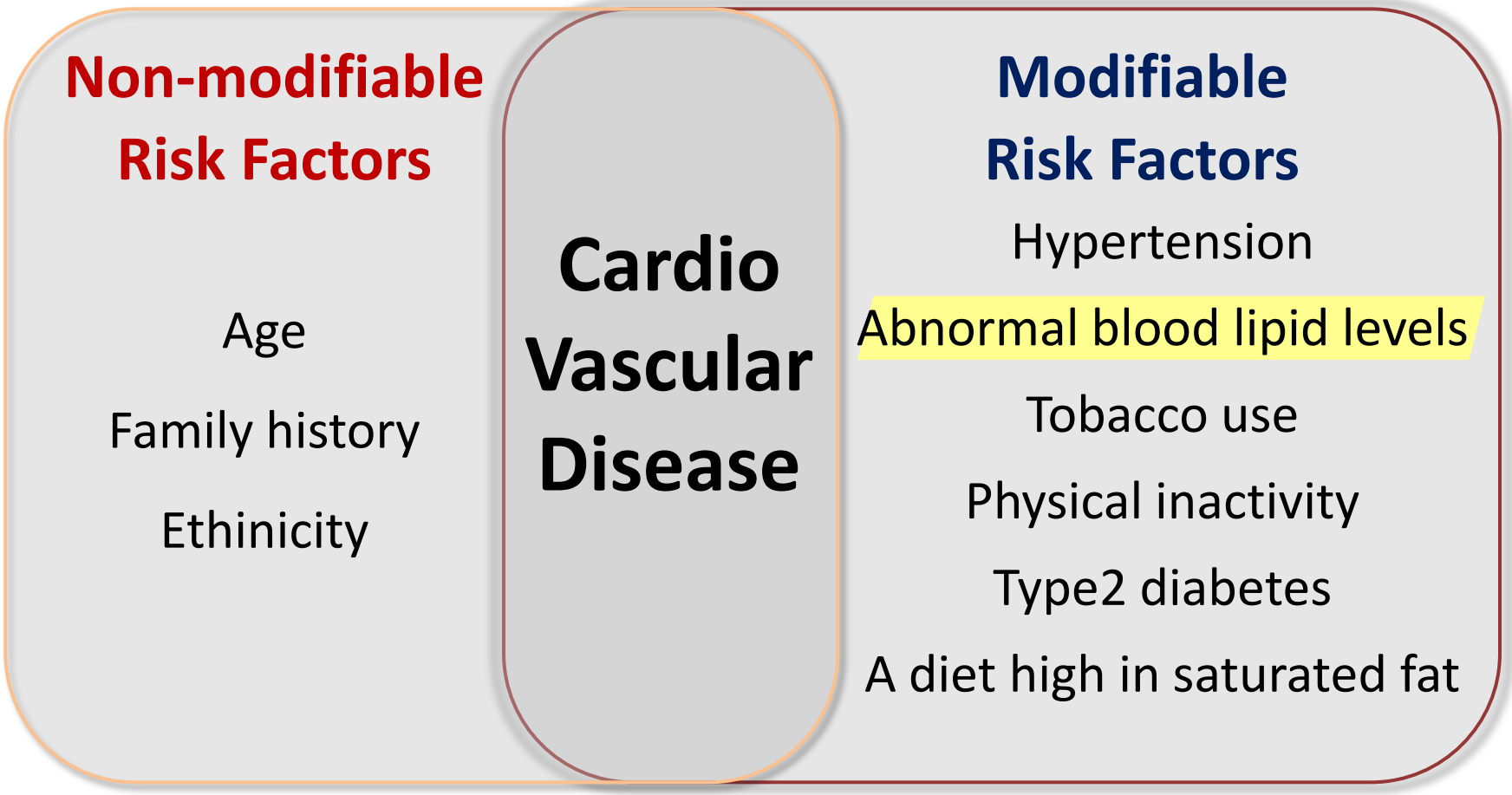
KAMIR n=39,978



GRACE n=43,810

Kook HY et al. Am J Cardiol 2014;114:1817
Fox KAA et al. BMJ. 2006;333:1091

Risk Factors for CardioVascular Disease



Ref. WORLD HEART FEDERATION. Accessed February http://www.world-heart-federation.org/cardiovascular-health/cardiovascular-disease-risk-factors/