Enhancing CV outcomes:

LDL and Beyond

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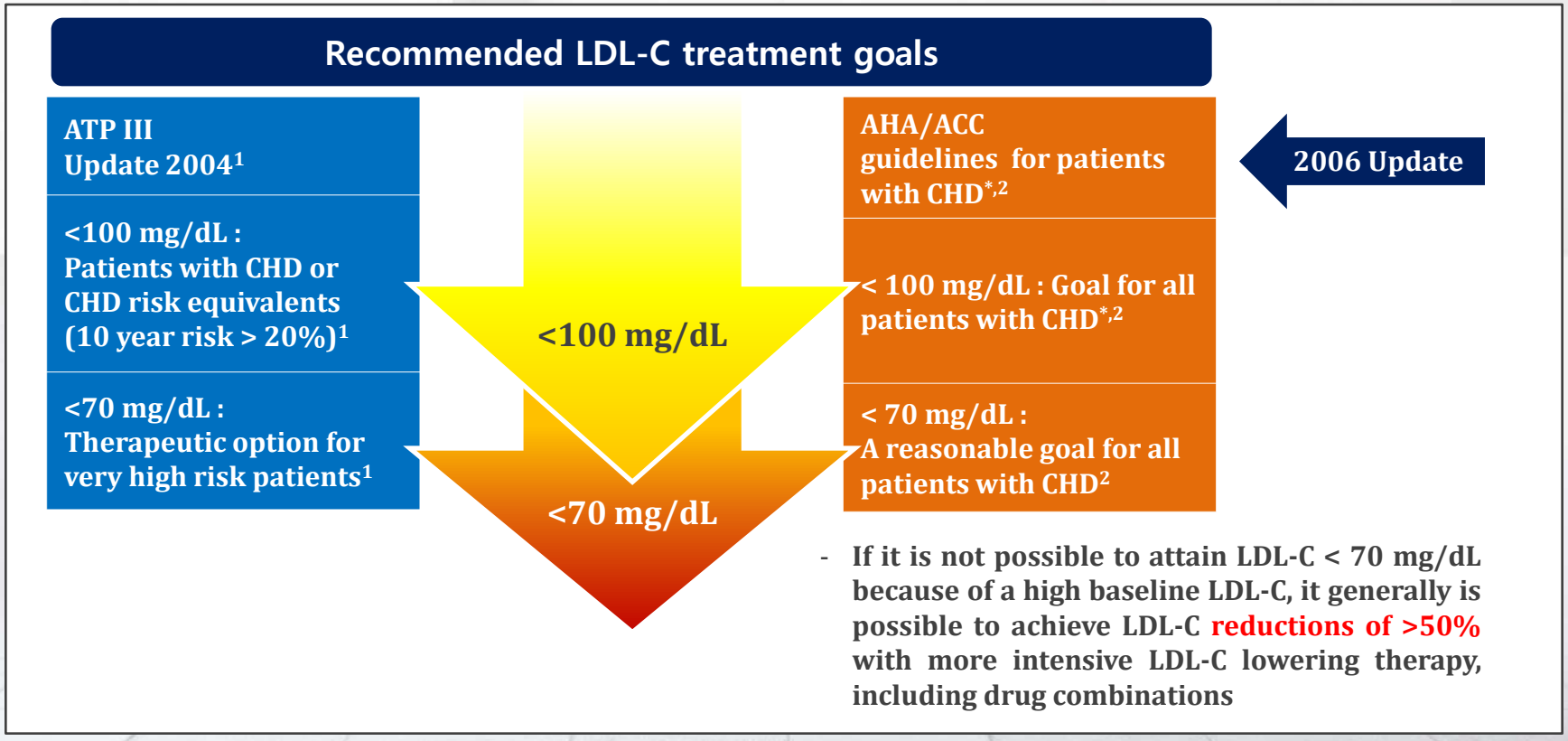
The Lower, The better

Treat to goal paradigm

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

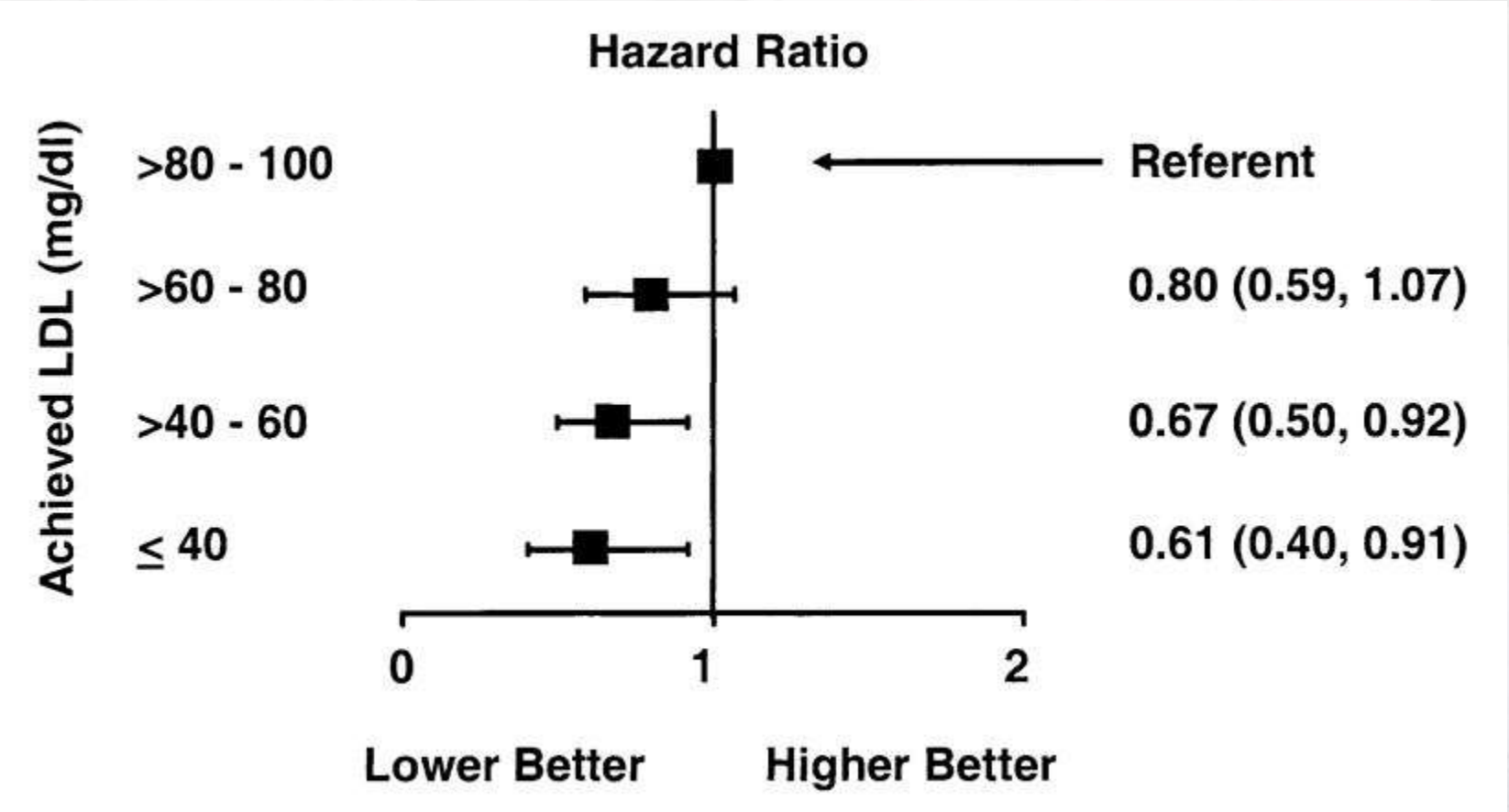


† Factors that place a patient at very high risk: established cardiovascular disease plus: multiple major risk actors (especially diabetes); severe and poorly controlled risk factors (e.g., cigarette smoking); metabolic syndrome (triglycerides ≥200 mg/dL + non–HDL-C ≥130 mg/dL with HDL-C <40 mg/dL);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

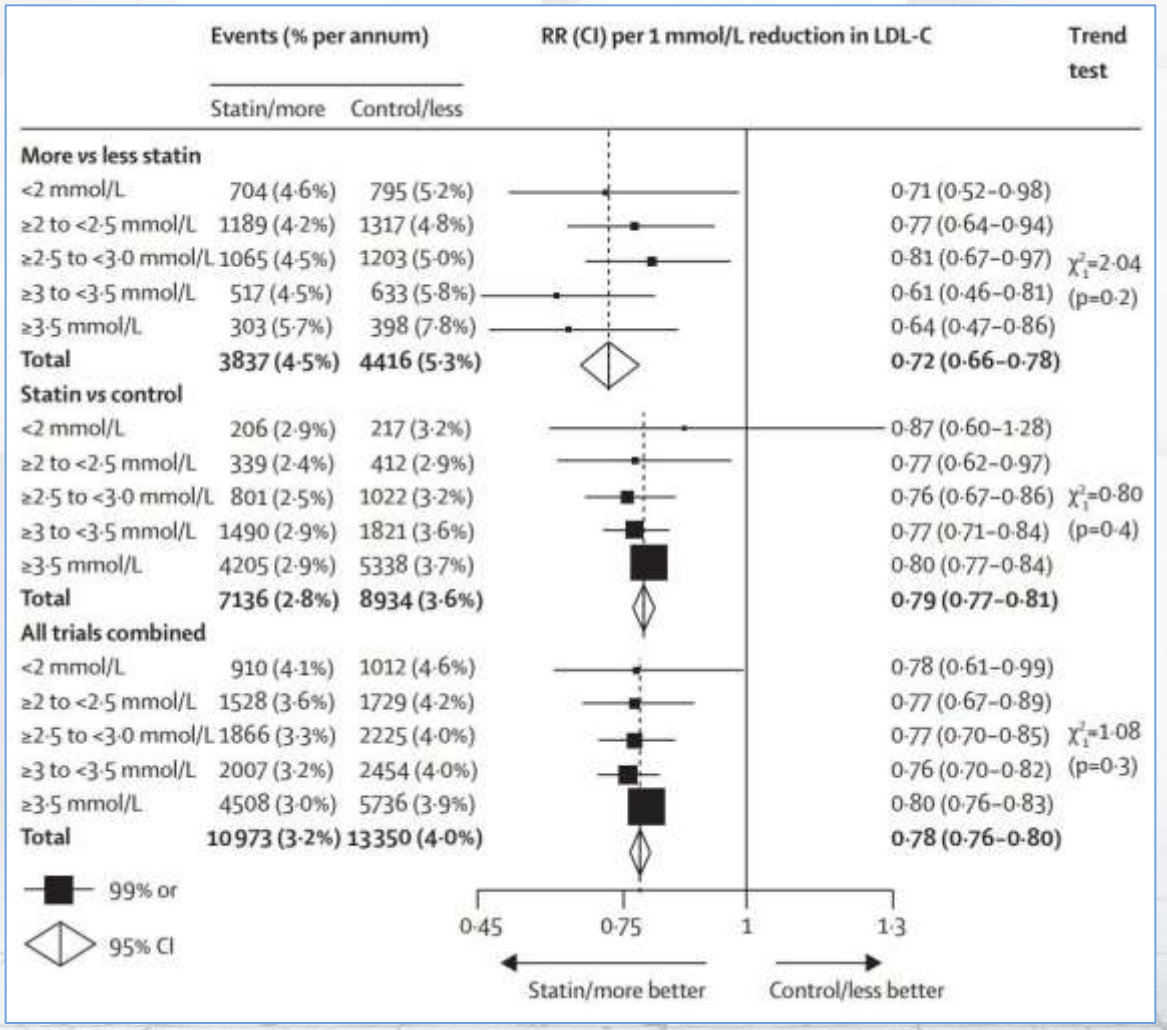
Adapted from Wang CY, et al. Trends Mol Med 2008;14:37–44.

Hazard ratio of the primary end point compared with achieved calculated low-density lipoprotein (LDL) 80 to 100 mg/dl



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

Effects on major vascular events per 1.0 mmol/L reduction in LDL cholesterol, by baseline LDL cholesterol concentration on the less intensive or control regimen

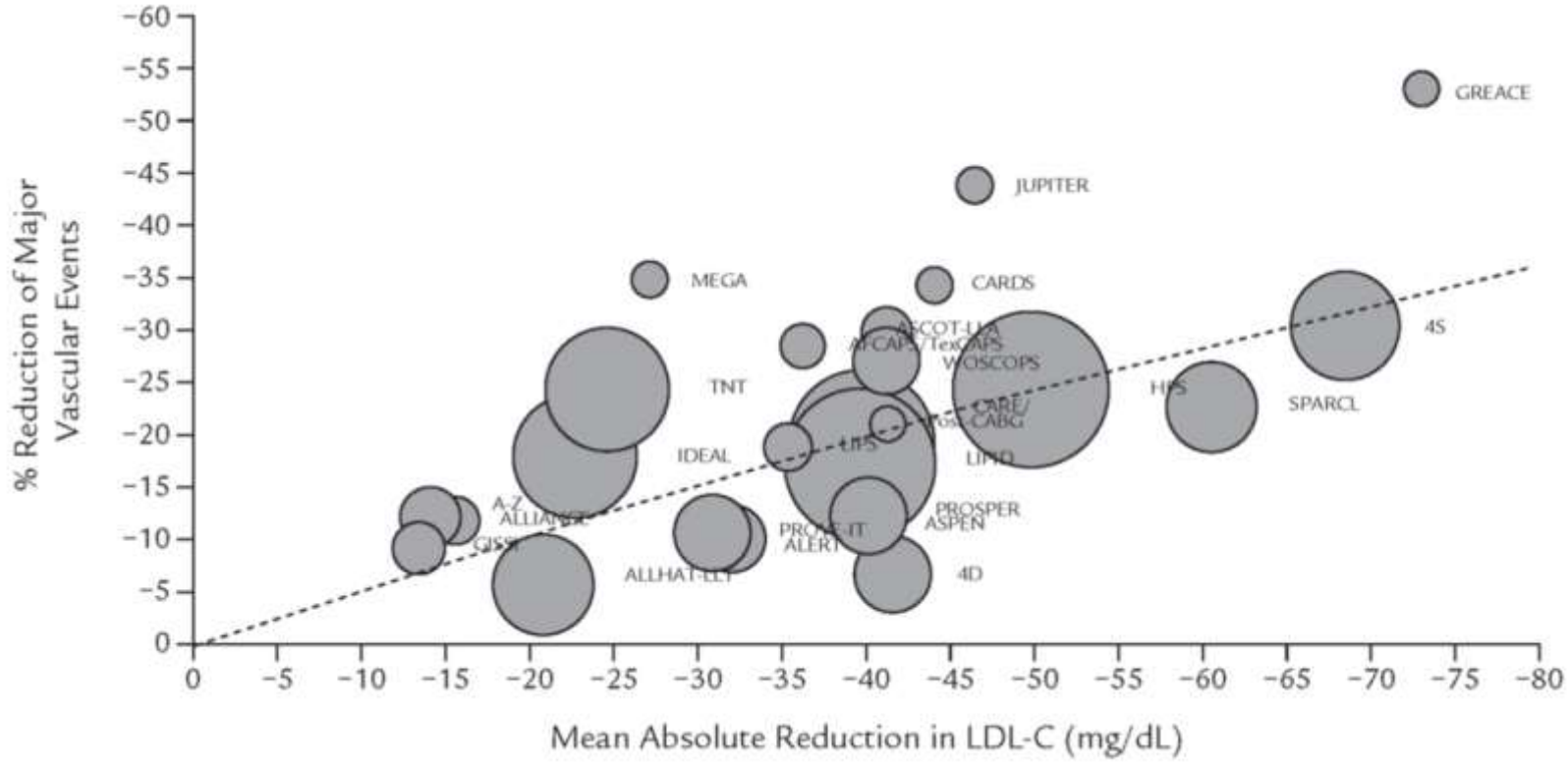


No evidence of a lower limit of LDL-Cholesterol below which a reduction did not provide benefit.

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

LDL-C and vascular events reduction by statin

Meta analysis of 25 RCT, 155,613 subjects

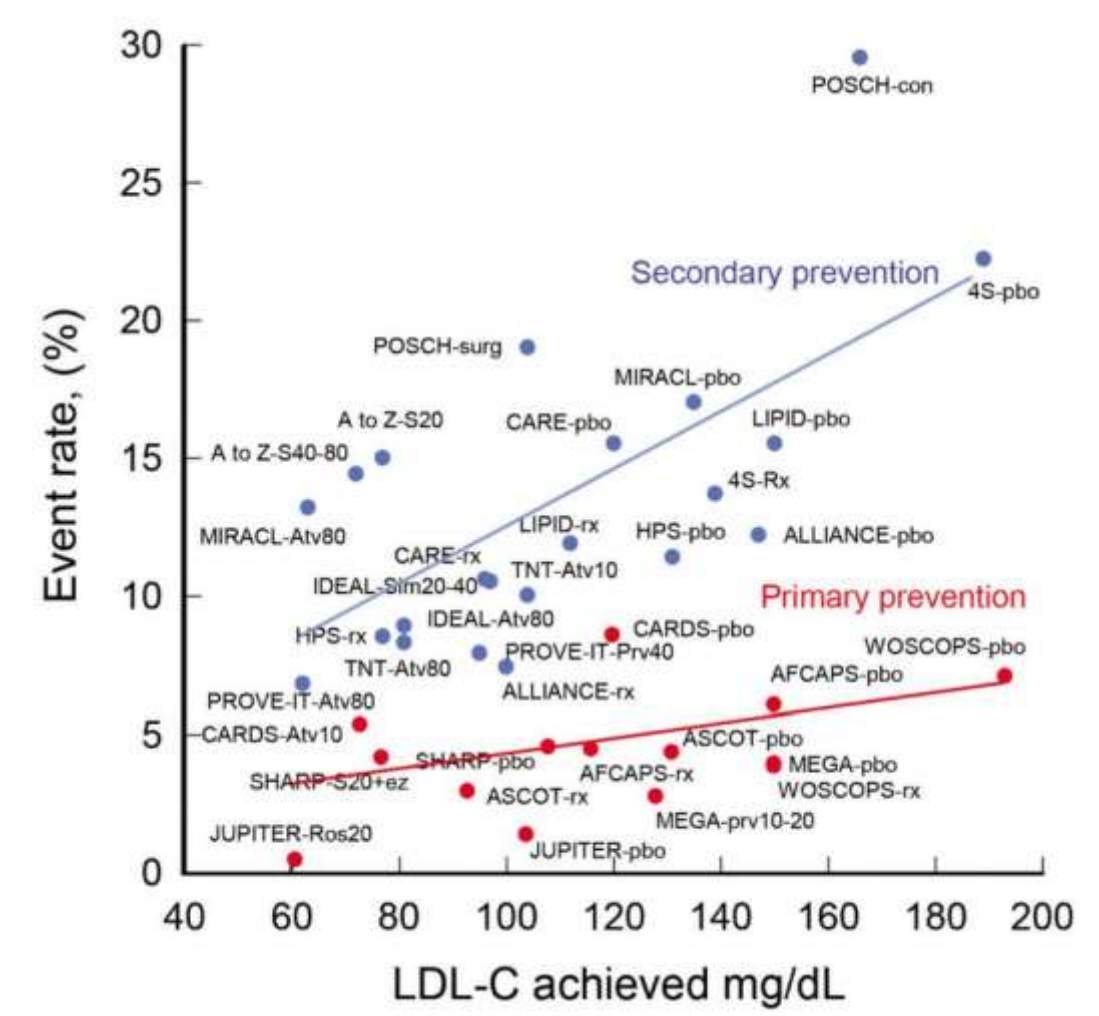


* ***A major coronary event*** **was defined as nonfatal myocardial infarction- or coronary heart disease-related death.**

Delahoy, PJ, et al. Clin Ther. 2009 Feb;31(2):236-44.

Benefits of lowering LDL-cholesterol and CHD risk

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



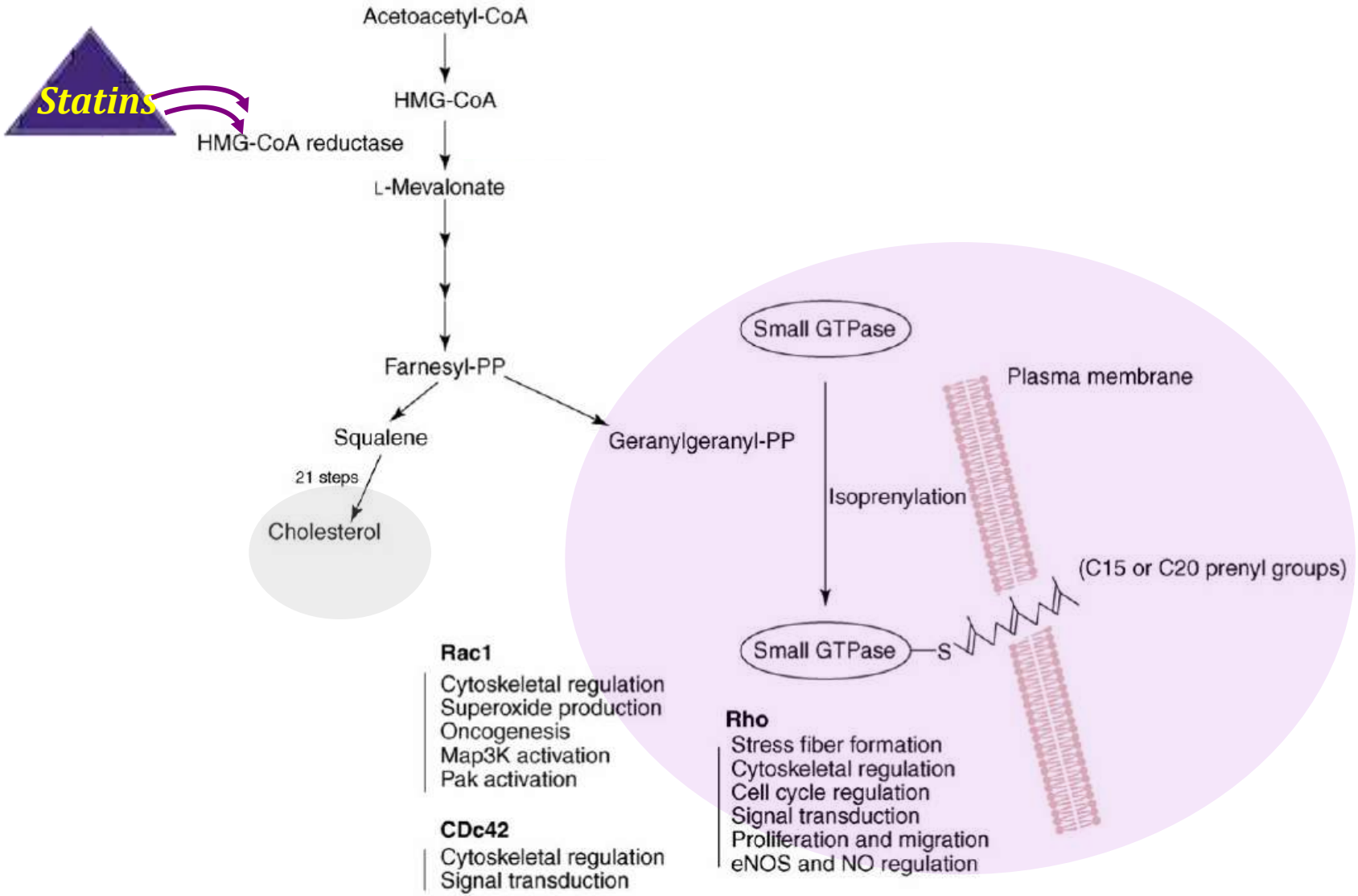
Raymond C et al. Cleve Clin J Med. 2014 Jan;81(1):11-9

CV outcomes studies demonstrating significant primary endpoint

	Primary Prevention				Secondary prevention		
	High-cholesterol with multiple risk factor	ELEVATED CRP and low/normalLDL-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		

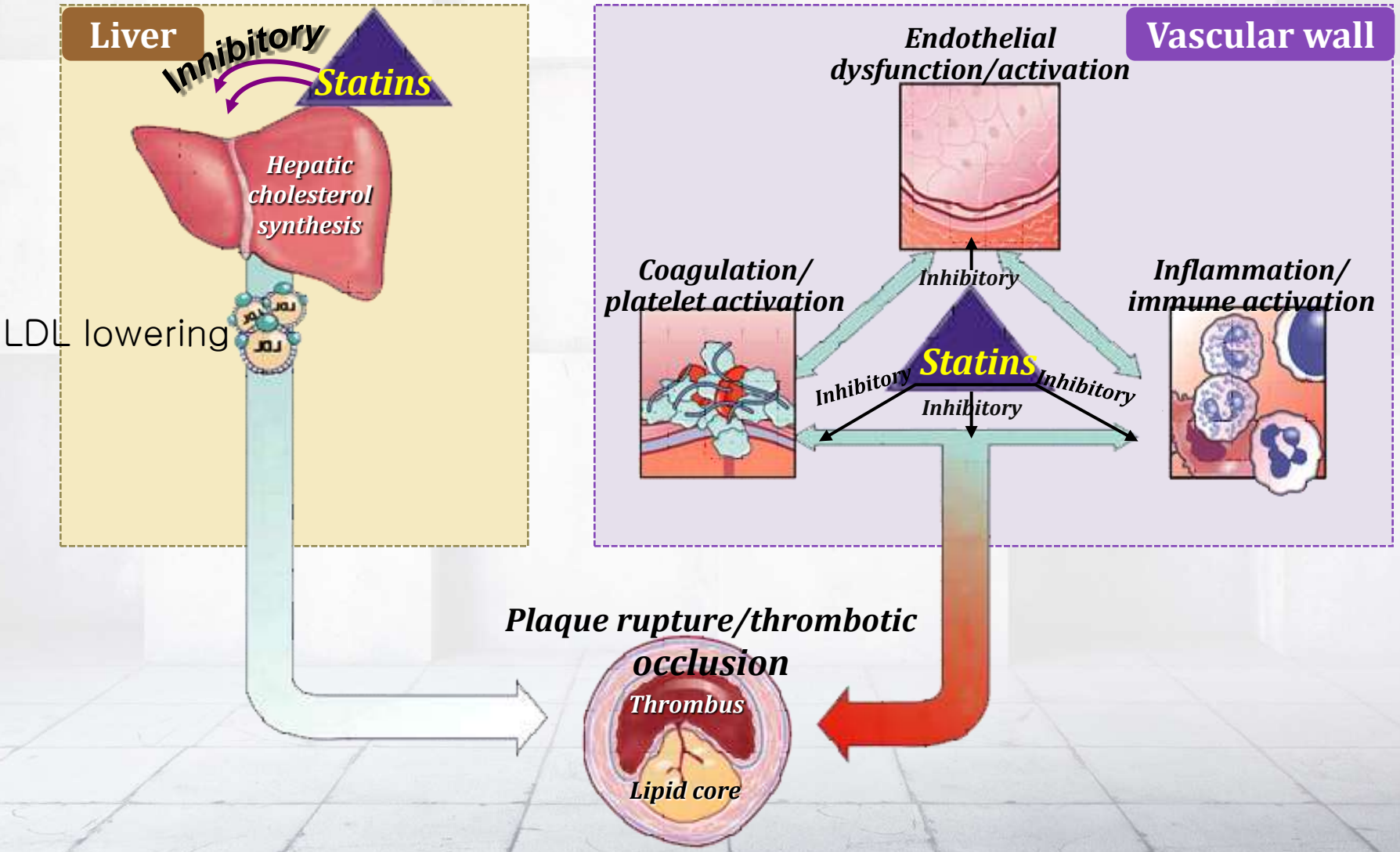
Possible mechanism proven by trial

Statin's mechanism



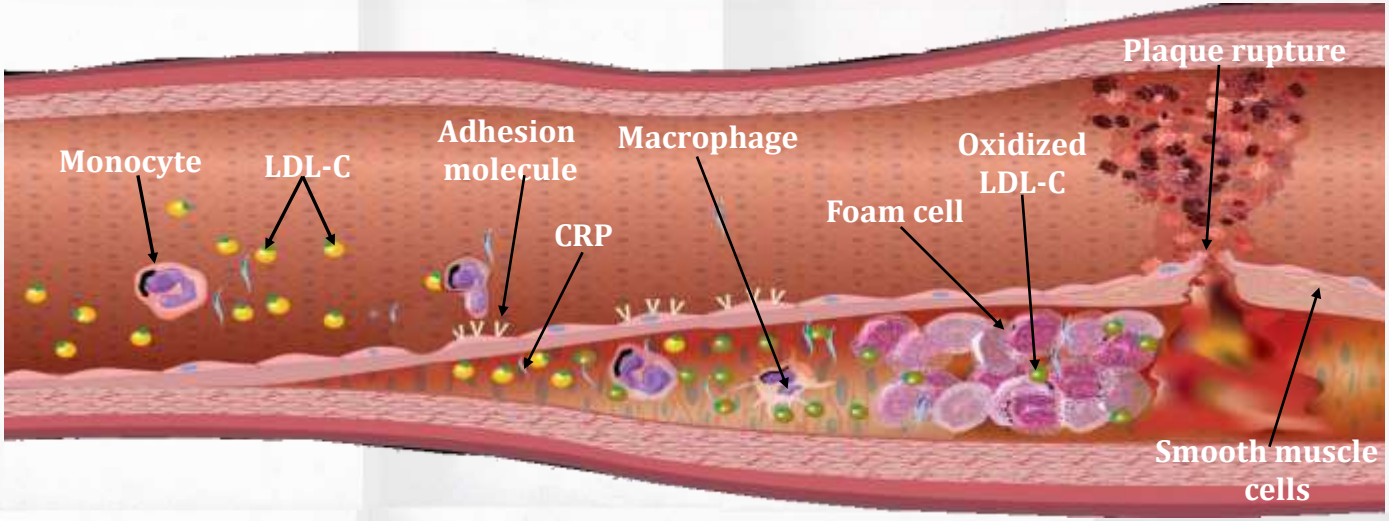
Adapted from Wang CY, et al. Trends Mol Med 2008;14:37–44.

Not just LDL lowering, but also Pleiotropic effects of statin



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.

Endothelial function

High-dose atorvastatin pretreatment could diminishes microvascular impairment in patients undergoing elective PCI

43 patients were randomly assigned to high dose atorvastatin (40 mg/d) for 7 days before PCI (high dose group),

41 patients were assigned to low-dose atorvastatin (20 mg/d) for 7 days before PCI (low-dose group).

All patients received atorvastatin 20 mg/d for 6months after PCI.

Results of PCI.

Variable	High-dose group ($n = 43$)	Low-dose group ($n = 41$)	*P* value
Procedure time, min	75 ± 38	79 ± 42	0.65
Post-dilation, *n*	35	39	0.26
Maximum inflation pressure, atm	21.2 ± 3.1	22.1 ± 1.5	0.09
FFR			
pre-PCI	0.61 ± 0.13	0.55 ± 0.16	0.06
post-PCI	0.93 ± 0.07	0.95 ± 0.04	0.11
IMR post-PCI	16.5 ± 6.1	31.2 ± 16.0	< 0.001
cTnI, ng/mL			
pre-PCI	0.028 ± 0.05	0.022 ± 0.04	0.55
post-PCI	0.11 ± 0.02	0.16 ± 0.09	< 0.001

Data are expressed as mean ± SD or as *n* (%), unless other indicated. cTnI: cardiac troponin I; FFR: fractional flow reserve; IMR: microcirculatory resistance; LAD: left anterior decending coronary artery; LCX: left circumflex coronary artery; RCA: right coronary artery; PCI: percutaneous coronary intervention.

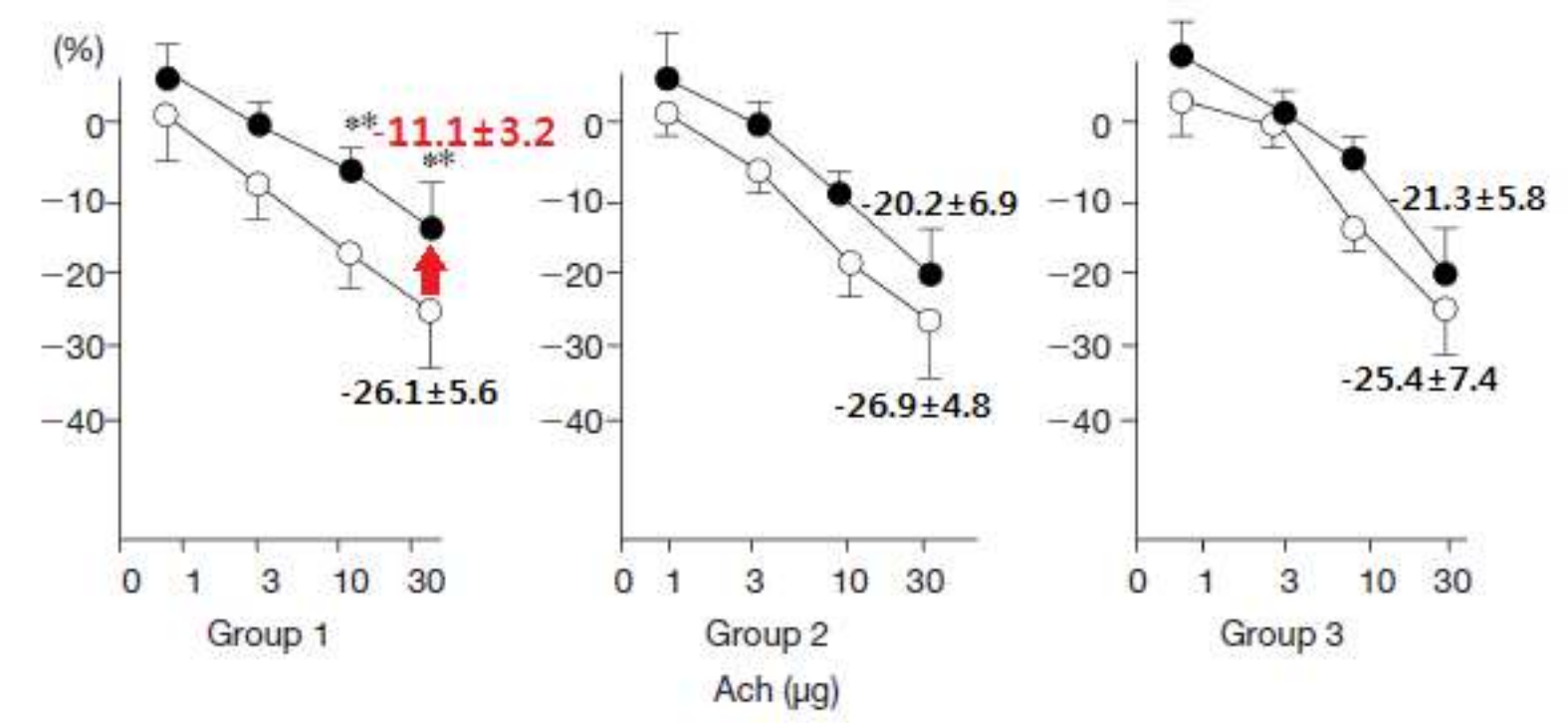
"Routin daily use of high-dose statins pre-teatment is reasonable in patients undergoing elective PCI for stable angina pectoris."

Gui-Xin He et al. J Geriatr Cardiol. 2013;10:355-360.

Atorvastatin improves endothelial function of the coronary artery in patients with MI

Endothelial function

Non-IRA of 48 pts with acute MI who had undergone PTCA were examined. Ach was infused and the diameter was assessed by QCA



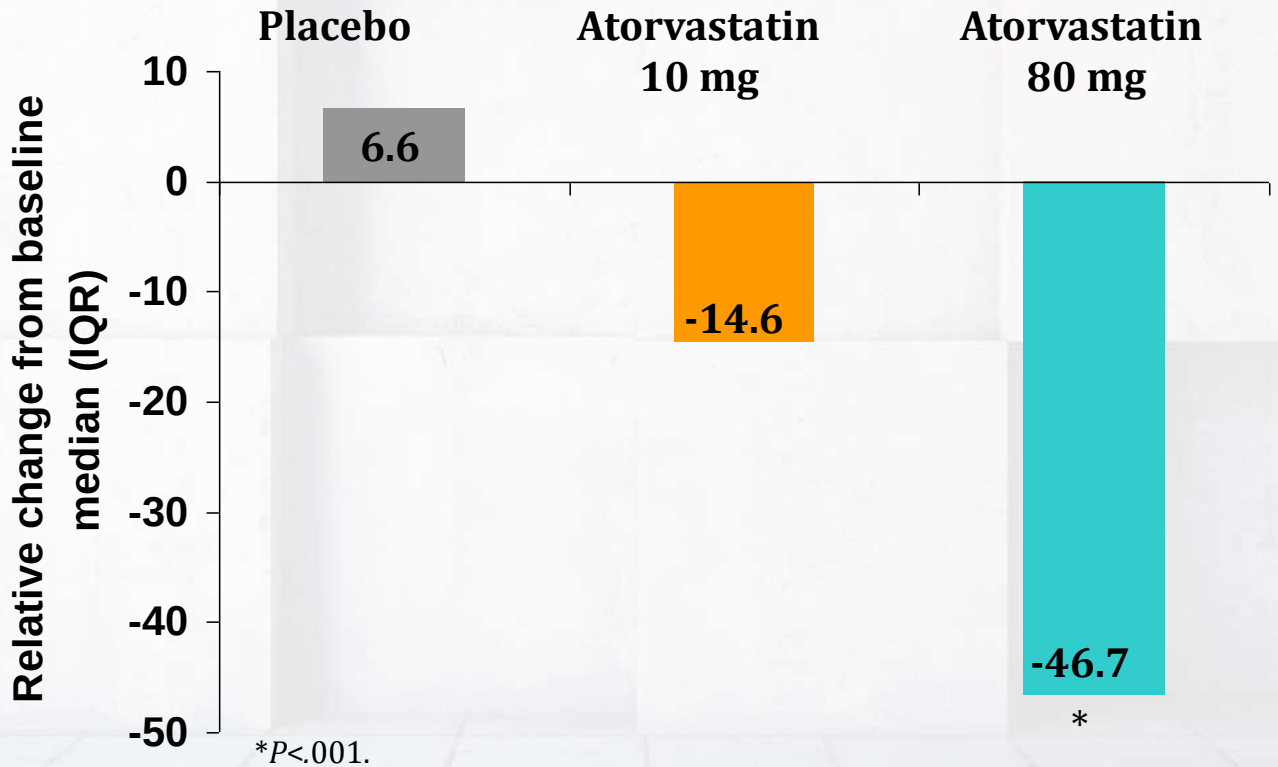
Group 1(n = 17) hyperlipidemia with use of atorvastatin , Group 2,(n = 18) hyperlipidemia without statin use, and Group 3(n = 13) normal cholesterol level controls . Each line (—) represents the change in each subject, and the circles represent the means ± SD.*; p<0.01. ○= Baseline, ●= follow-up.

The mean diameter change after 6 months was significantly improved Group 1 compared with Group 2 and 3

Clin. Cardiol. 29, 357–362 (2006).

DALI: Lipitor Significantly Lowered CRP Levels in Patients With Type 2 Diabetes in a Dose-Dependent Manner

anti inflammatory effect



*P<.001.

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

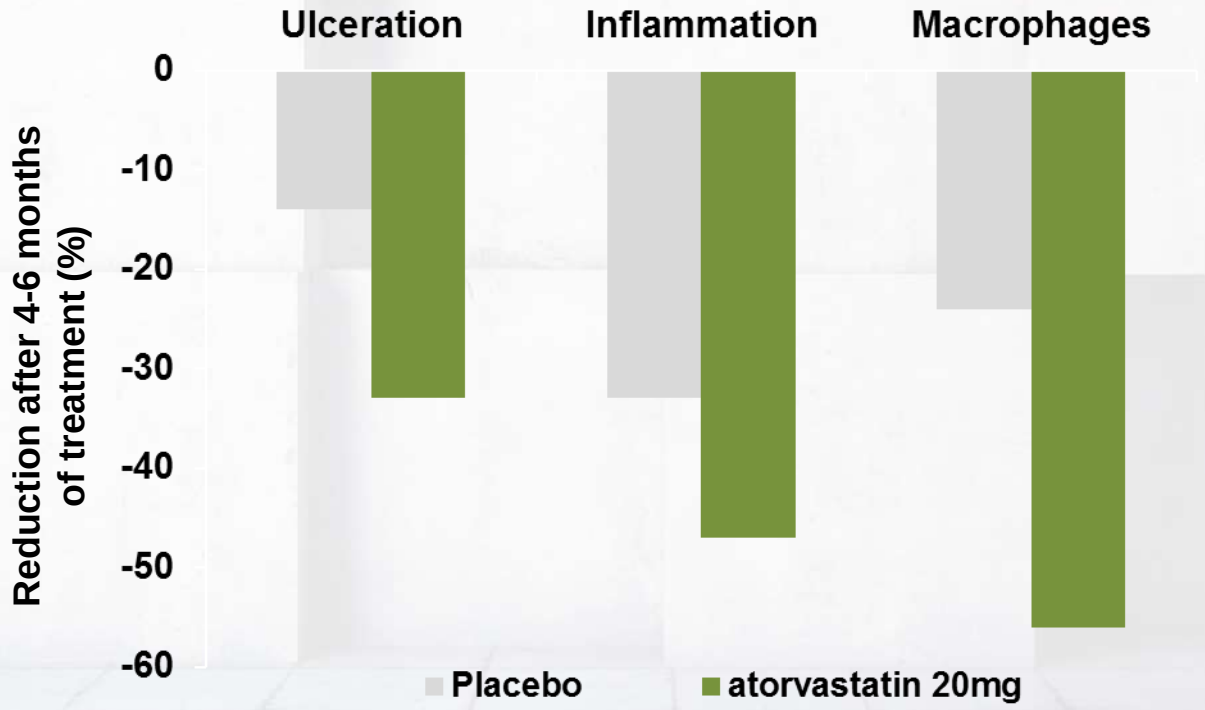
van de Ree MA et al. *Atherosclerosis*. 2003;166:129-135.

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.

ATROCAP Results Suggest That atorvastatin Stabilizes Plaques

Anti thrombotic effects

N=59 pts with bilateral carotid stenosis for 2rd carotid endoarterectomy (CEA) randomized to placebo or atorvastatin 20 mg.



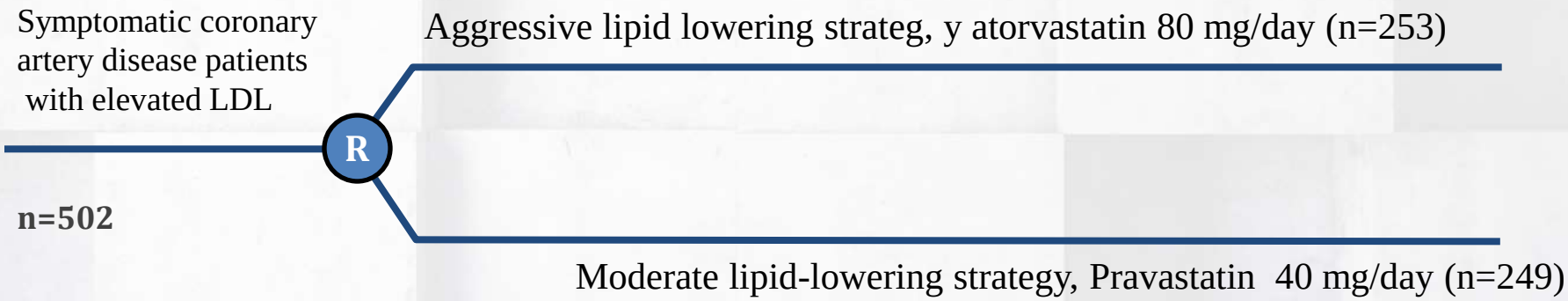
"Plaque stabilization may be an important process by which statins reduce vascular event rates."

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

Plaque Stabilized effect

REVERSAL : Reversal of Atherosclerosis with Aggressive Lipid Lowering

- **Objectives :** Comparison of intensive lipid lowering effect of atorvastatin 80 mg with pravastatin 40 mg
- **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

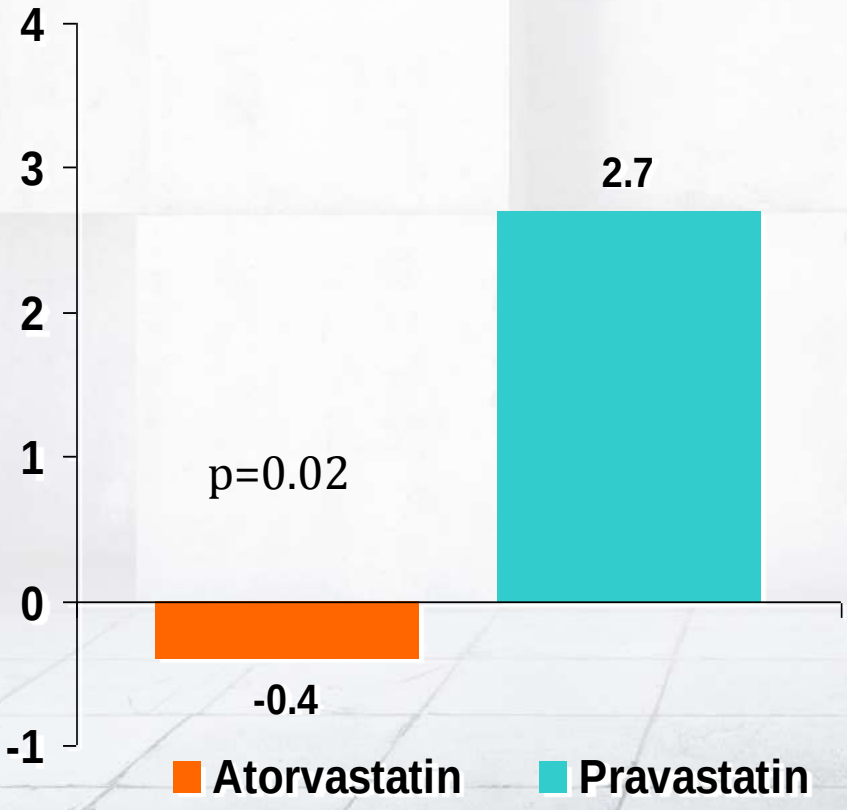
http://www.lipidsonline.org/commentaries/al_abstract.cfm?abs_id=abs048

AHA 2003, Orlando, FL

REVERSAL : Reversal of Atherosclerosis with Aggressive Lipid Lowering

Plaque Stabilized effect

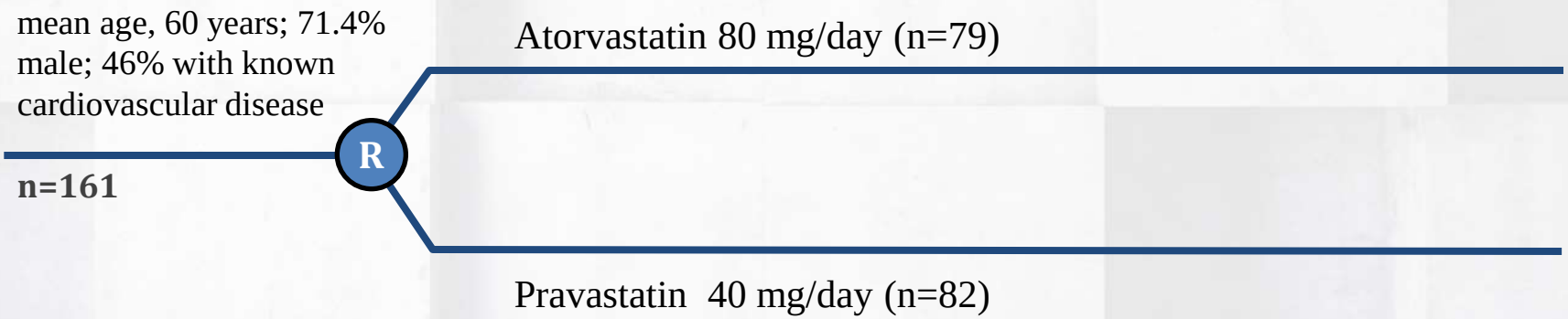
Change in atheroma volume



Change in percent obstruction volume

ARBITER: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol

- **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

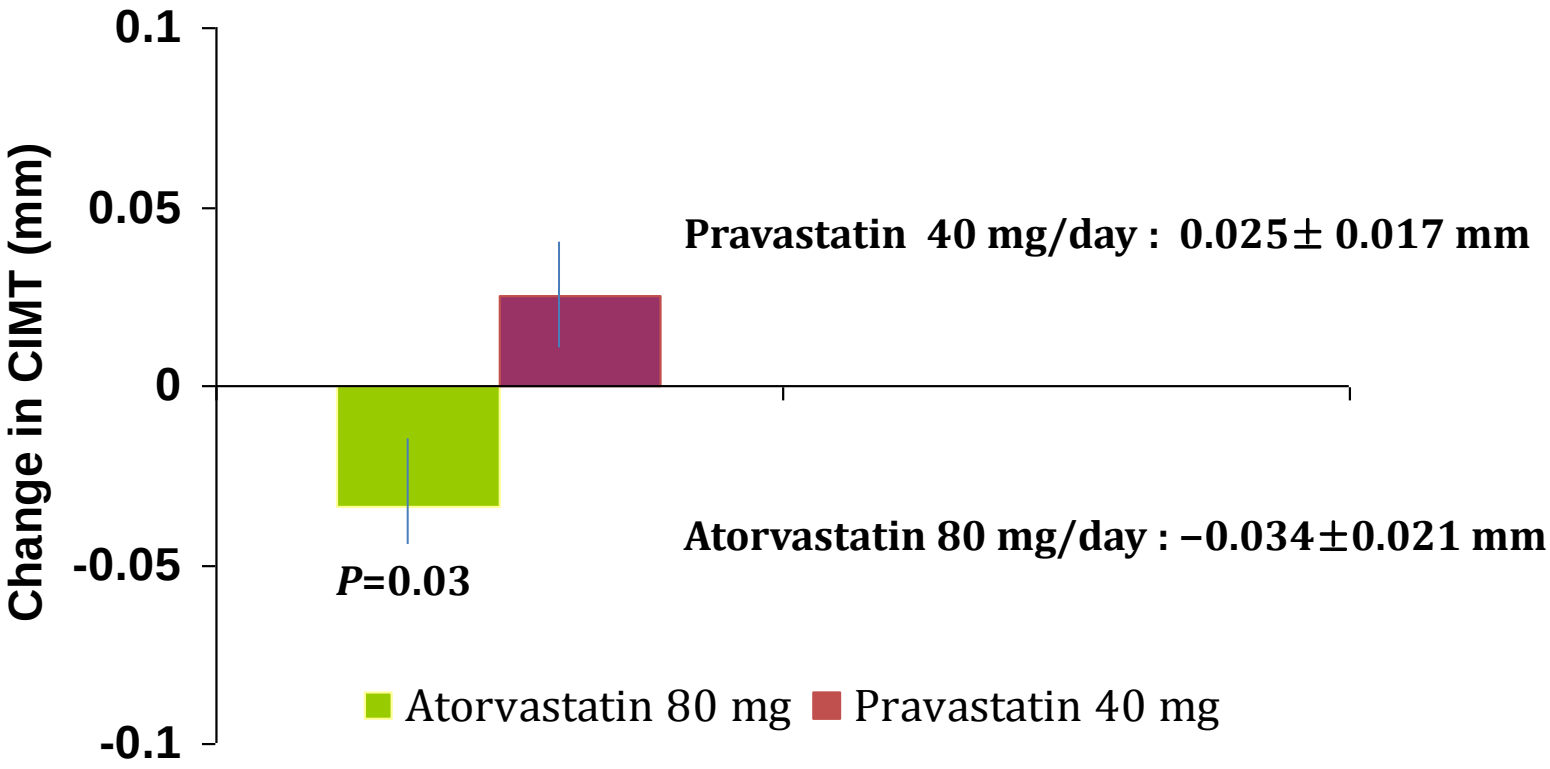
Circulation. 2002; 106: 2055-2060

Reduced progression of atherosclerotic 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]

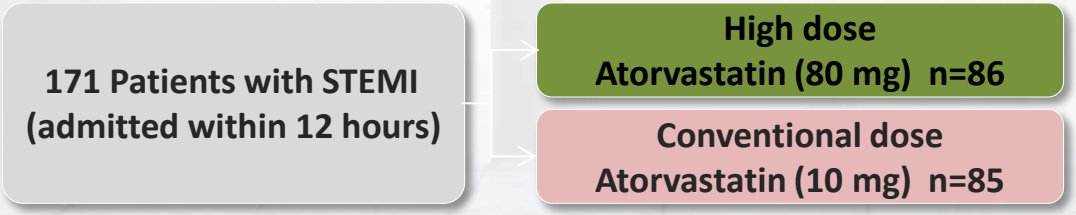


Taylor AJ, et al. Circulation. 2002;106:2055-2060.

The benefit of statin: Primary & Secondary prevention

STATIN STEMI

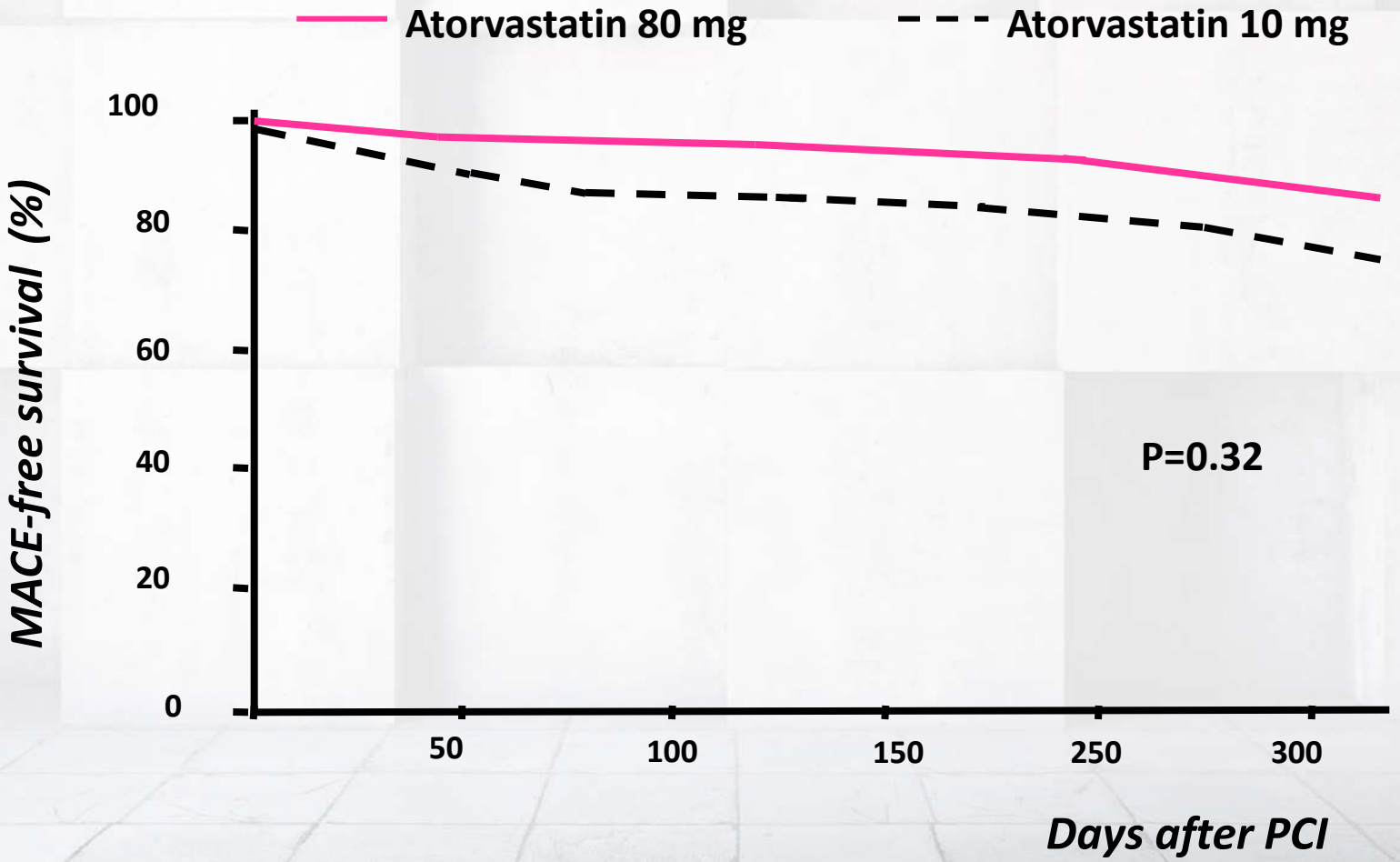
efficacy of high dose atorvaSTATIN loading before primary percutaneous coronary intervention in ST Elevation Myocardial Infarction



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

Kim JS, Choi D, et al. JACC Cardiovasc Interv. 2010;3:332-339.

STATIN STEMI : Survival Curves



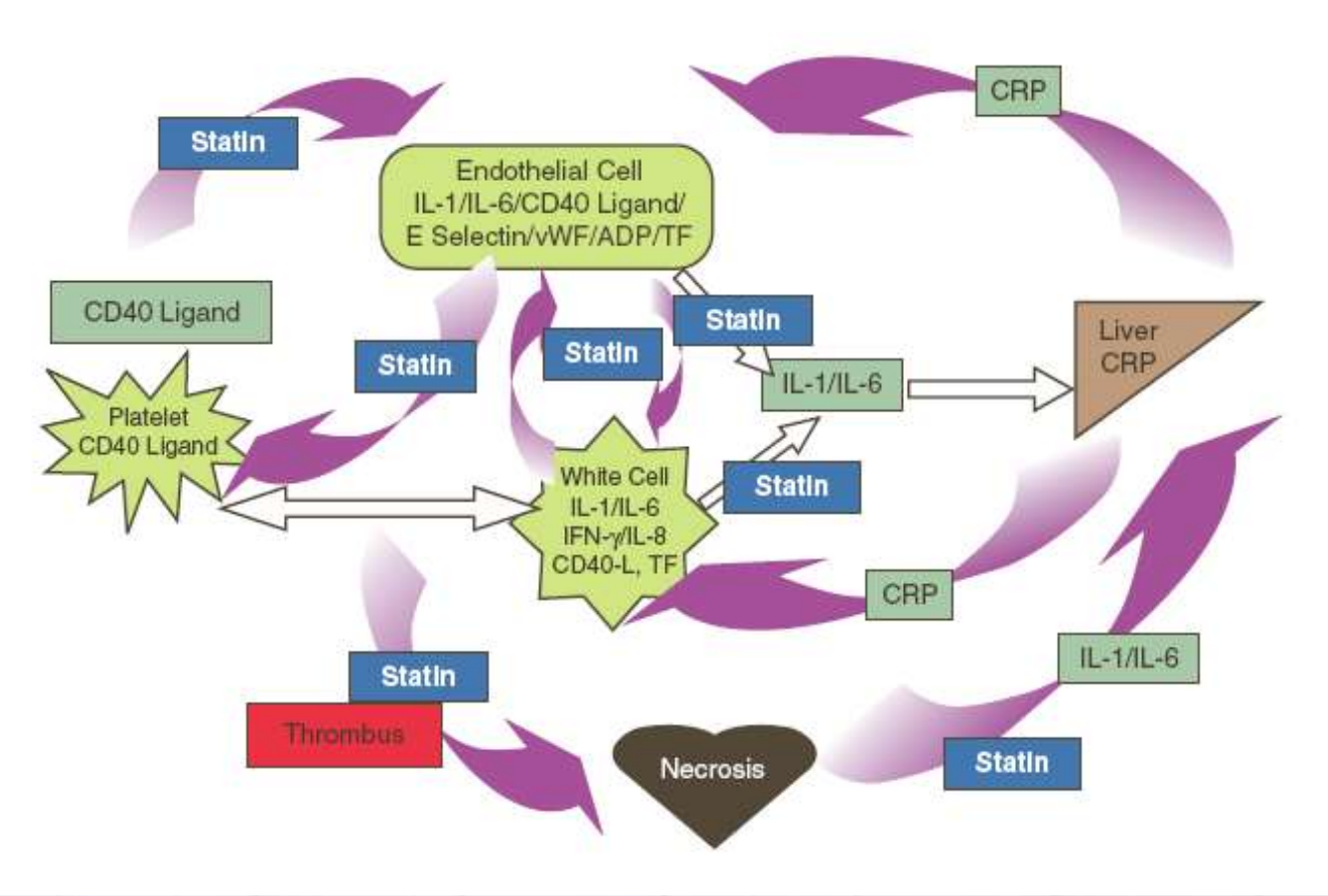
Kim JS, Choi D, et al. JACC Cardiovasc Interv. 2010;3:332-339.

Angiographic and Electrocardiographic Outcomes after Primary PCI

	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

Kim JS, Choi D, et al. JACC Cardiovasc Interv. 2010;3:332-339.

Role Of Statins In ACS: Non-Lipid Effects



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, with permission.

Cannon and Ray. *Am J Cardiol*. 2005;96:54F.

Intensive & early statin treatment prior to PCI for ACS patients

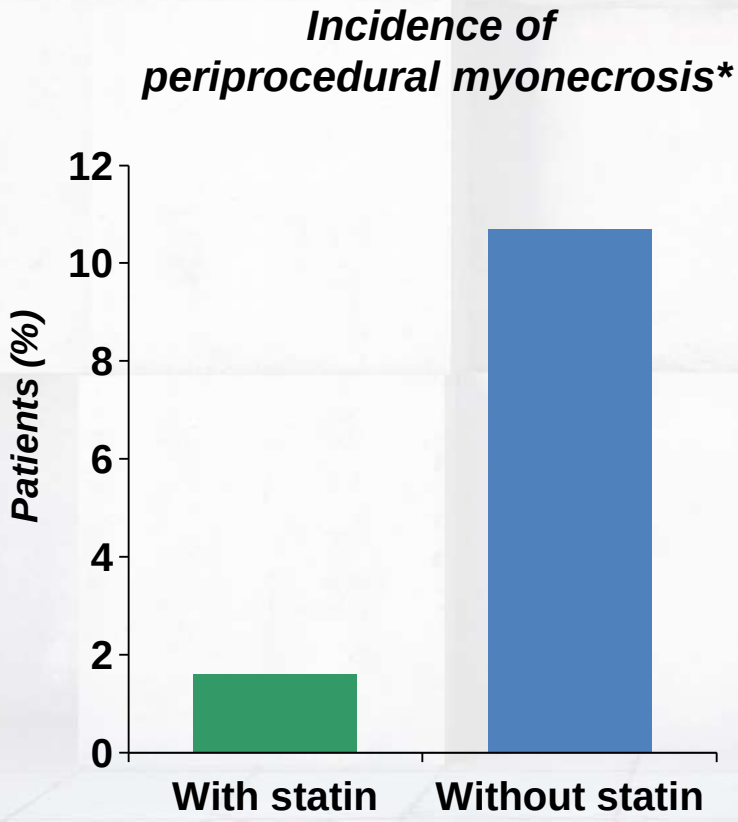
The benefit of statin: Primary & Secondary prevention

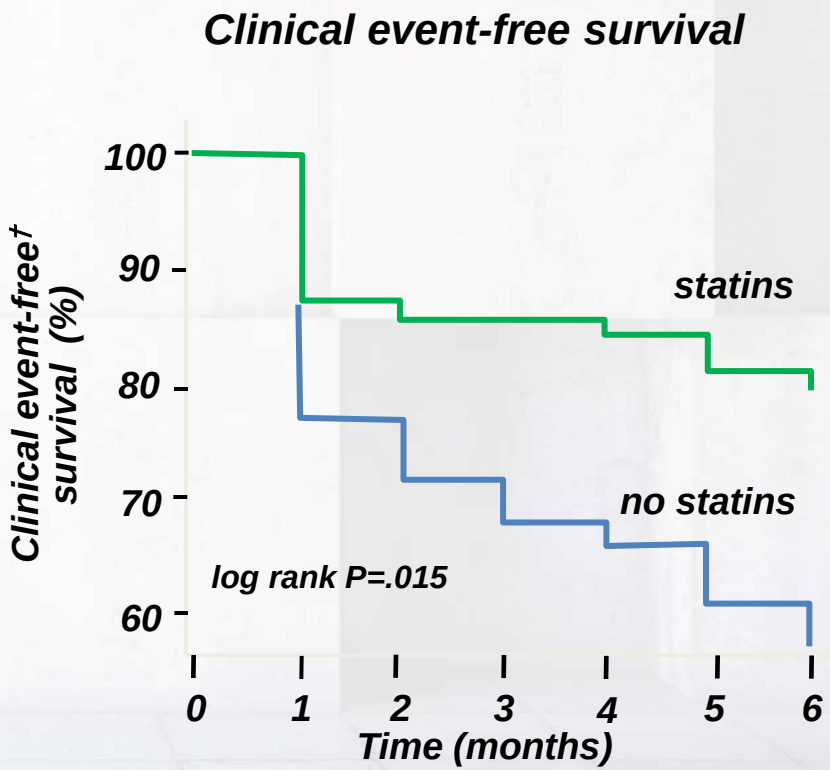
Secondary Prevention

ARMYDA

Atorvastatin for Reduction of MYocardial Damage during Angioplasty

Background: Treatment With 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:

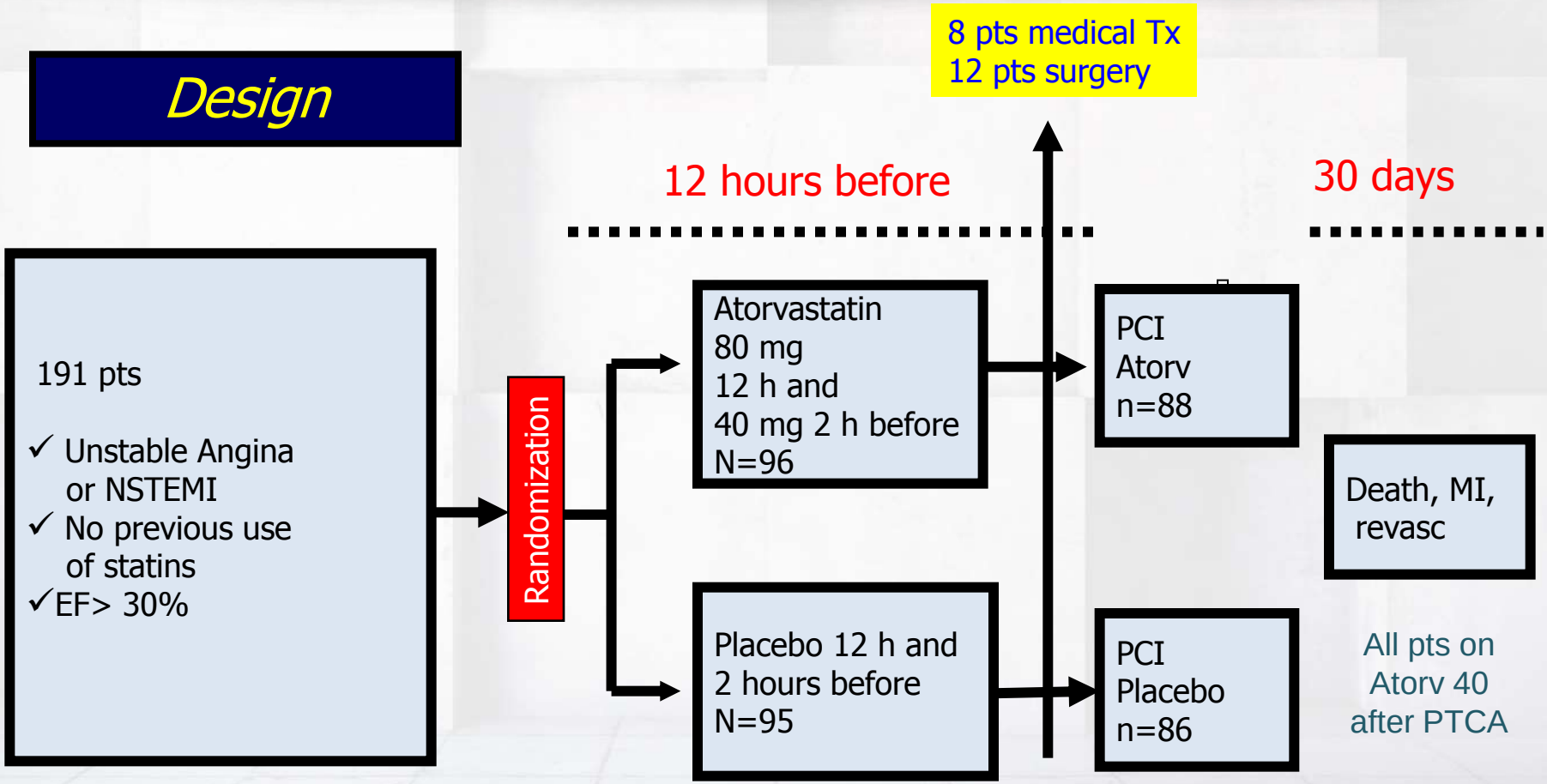
- ✓ Patients with NSTEMI or Unstable Angina
- ✓ treated with early invasive strategy (angio at 12-24 hours)

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

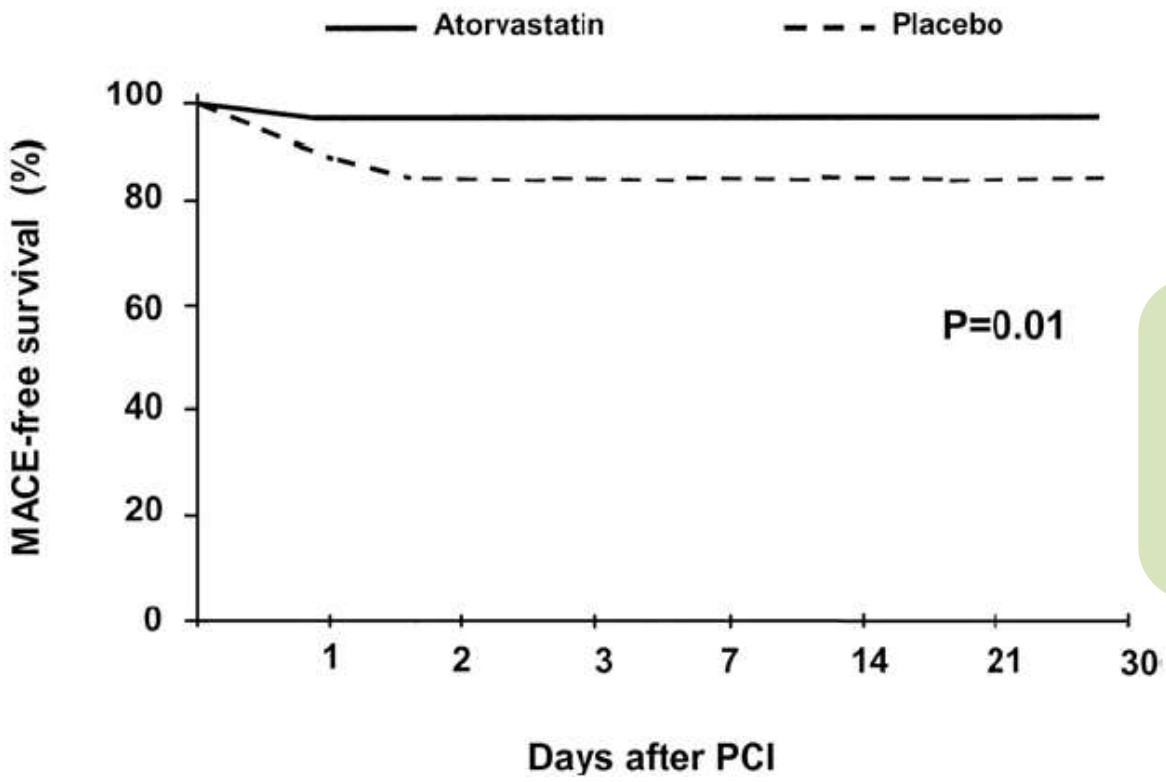


Patti G, et al. J Am Coll Cardiol. 2007;49:1272-1278

In ACS pts undergoing PCI, 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 angio, Further 40 mg 2 hr before angio)

[Survival Curves]



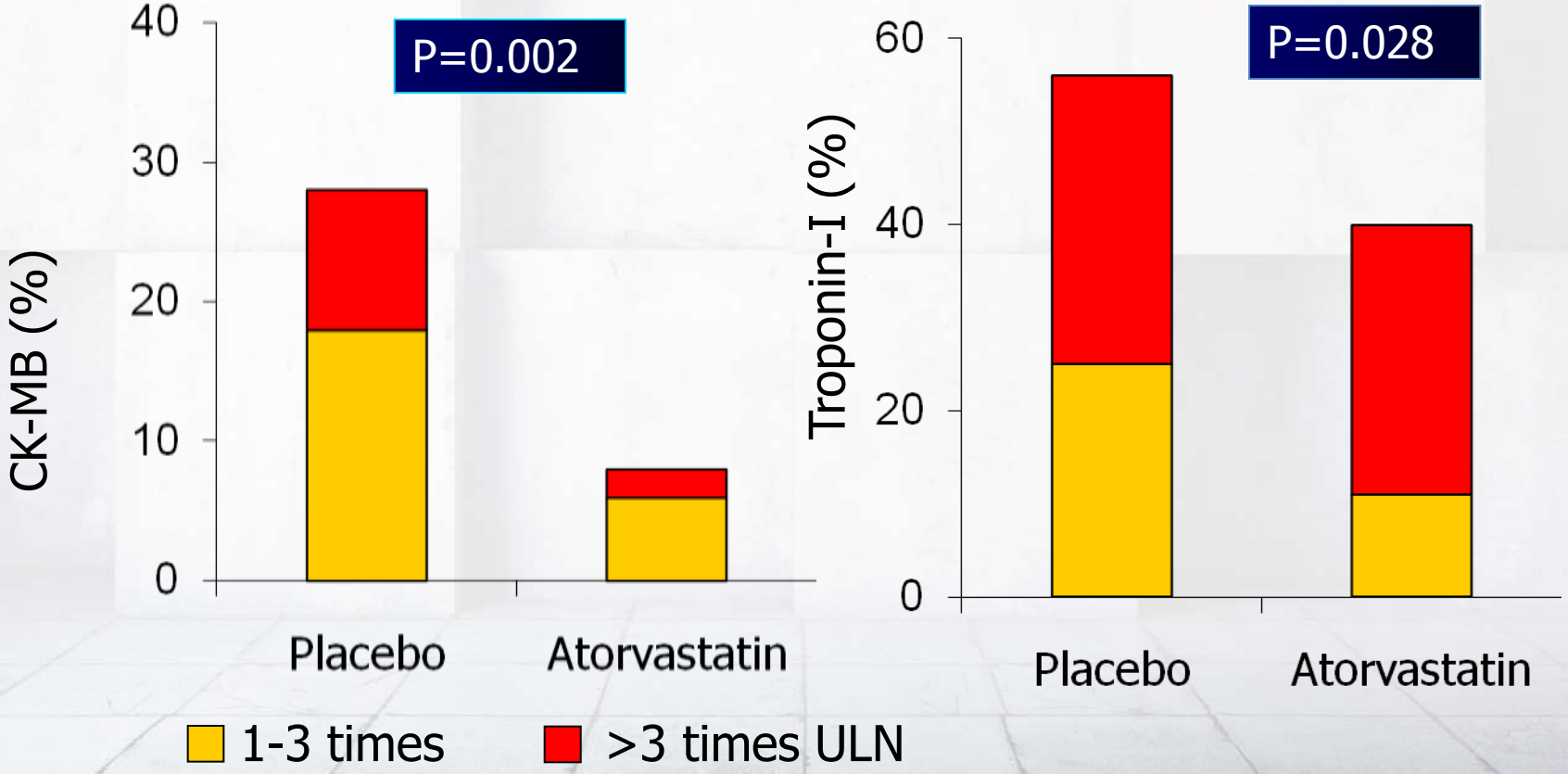
30-day major adverse cardiac events 12% ↓

(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

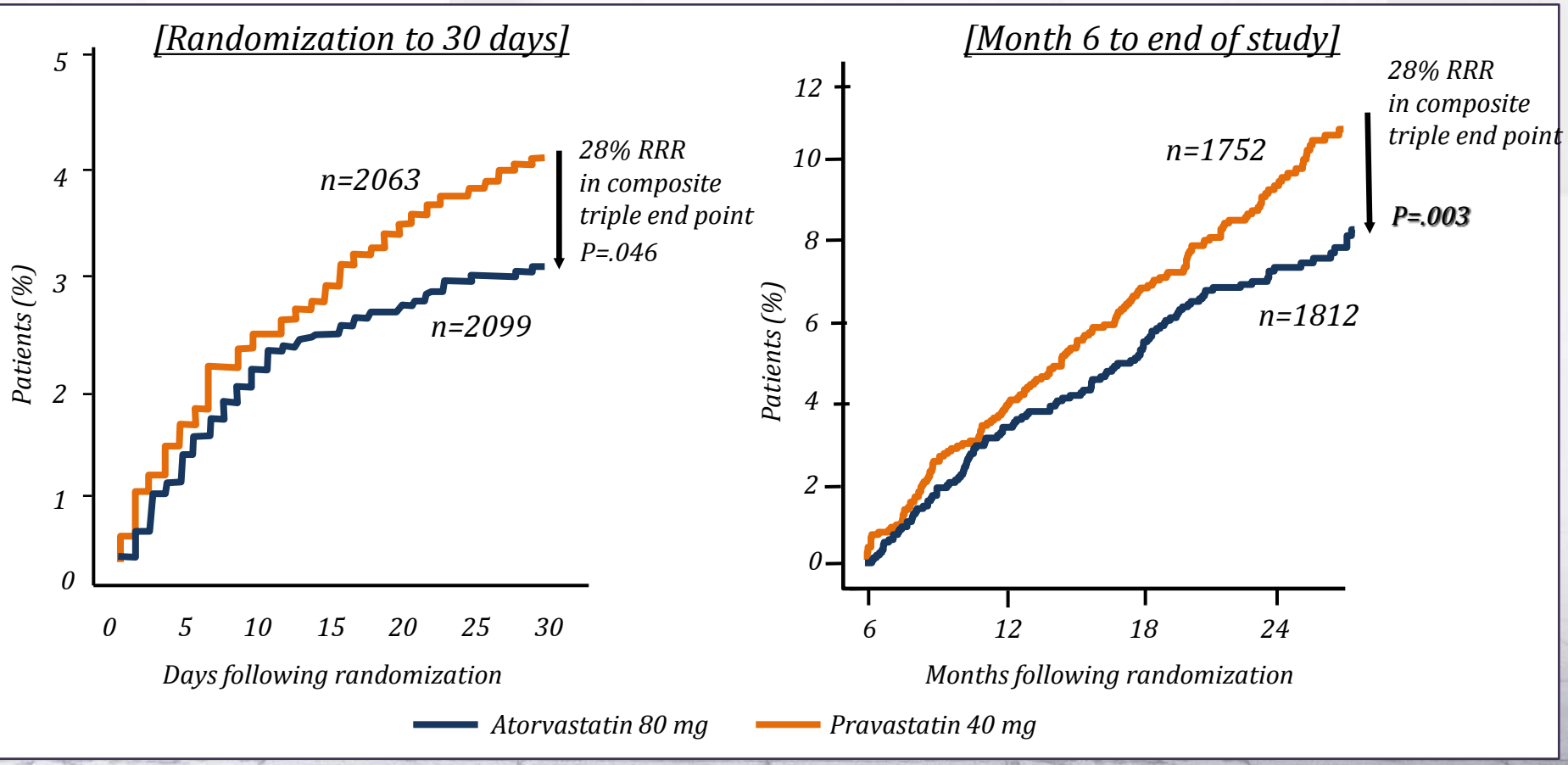
CK-MB or Troponin-I Increase



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

In ACS pts undergoing PCI, high dose atorvastatin improved outcome

ARMYDA-RECAPTURE trial
: 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)



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

Statins and Myocardial Proctection: Possible Mechanisms

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

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

ARMYDA: CONCLUSIONS

❖ Short-term atorvastatin pretreatment prior to PCI reduce peri-procedural myocardial necrosis in patients with Unstable Angina and NSTEMI.

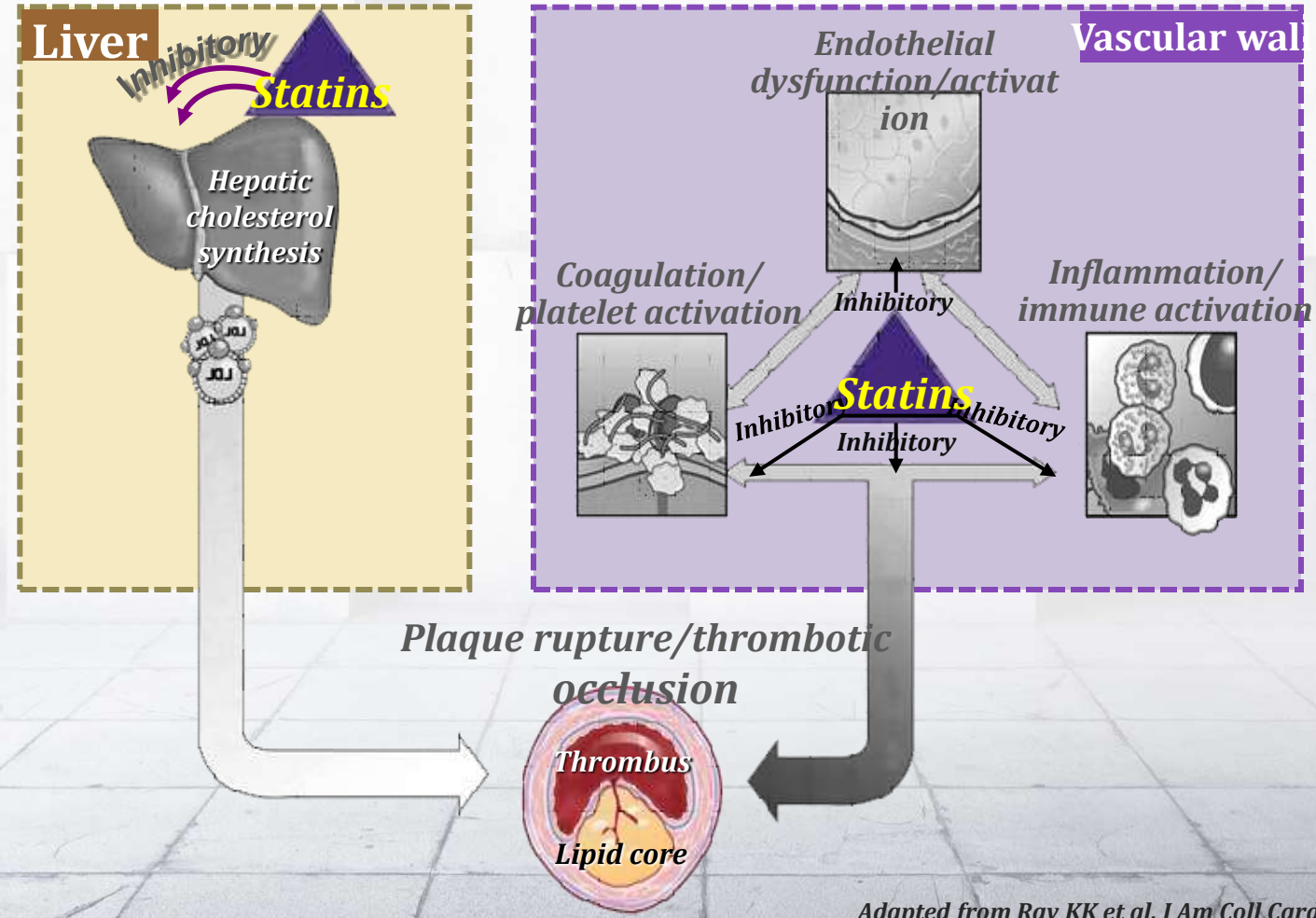
❖ Lipid-independent pleiotropic actions of atorvastatin may explain such effect

❖ These findings may support the indication of "upstream" administration of high dose statins in patients with ACS under early invasive strategy

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

Effect of statin
: LDL and Beyond

Not just LDL lowering, but also Pleiotropic effects of statin



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

Immediate effect

Of the 5 major ACS Trials, only MIRACL and PROVE IT showed a significant benefit and benefits observed as early as 30 days after initiation of statin therapy

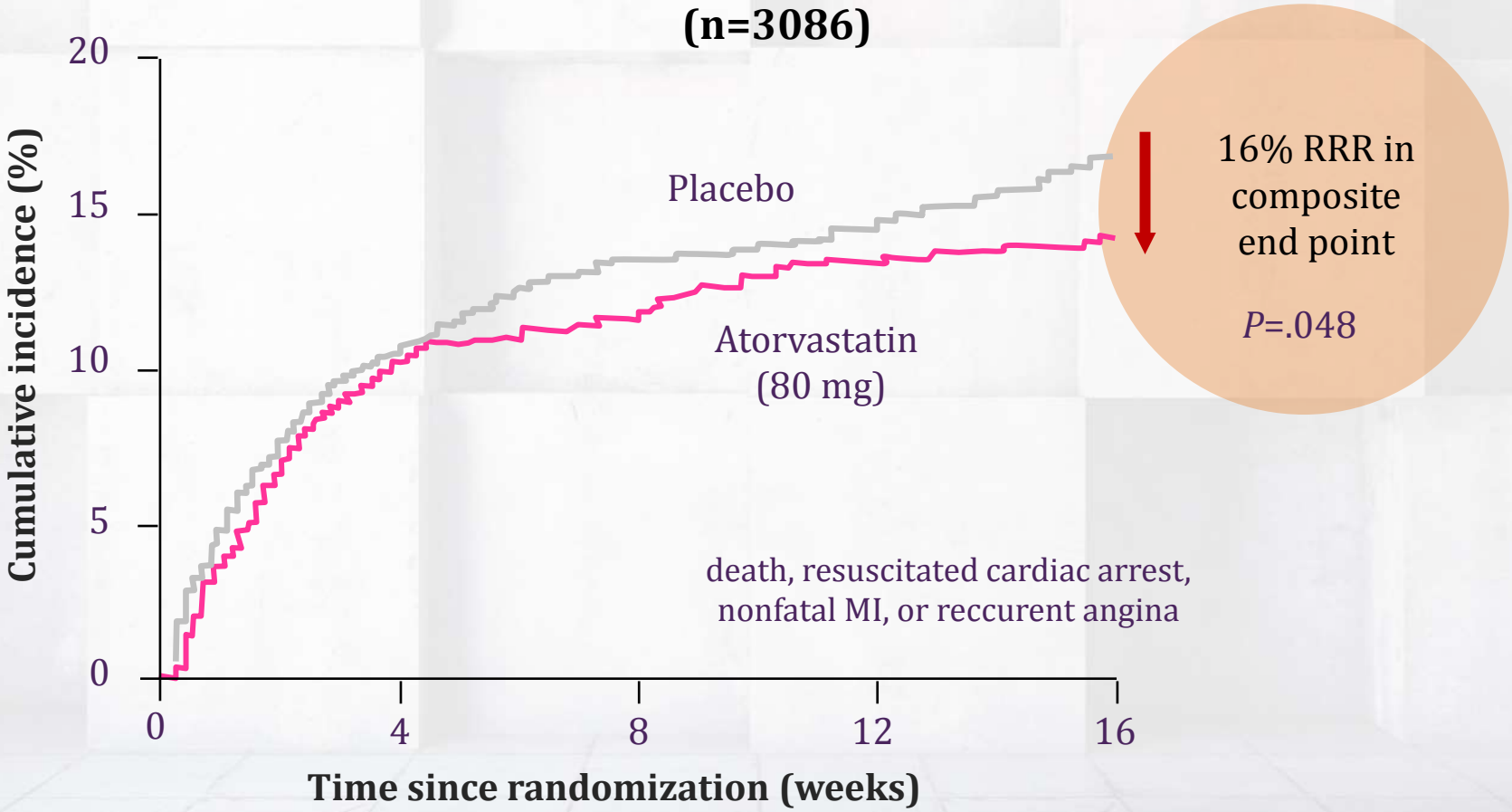
Study	Intervention	Treatment Initiated Within	N	Follow-Up	Risk Reduction (%) In 1° End Point	*P* Value
FLORIDA	Fluva 80 mg vs placebo	8 days	540	1 year	8	NS
PACT	Prava 20/40 mg vs placebo	24 hours	3408	30 days	6.4	NS
A to Z	Simva 40/80 mg vs placebo/simva 20 mg	5 days to 4 months	4497	2 years	11	NS
MIRACL	**Atorva 80 mg vs placebo**	**24–96 hours**	**3086**	**16 weeks**	**16**	**.048**
PROVE IT	**Atorva 80 mg vs prava 40 mg**	**10 days**	**4162**	**4 months 2 years**	**19 16**	**.03 .005**

Atorvastatin is not indicated for secondary prevention of CHD.

Liem AH et al. Eur Heart J. 2002;23:1931-1937; Thompson PL et al. Am Heart J. 2004;148:e2; de Lemos JA et al. JAMA. 2004;292:1307-1316; Schwartz GG et al. JAMA. 2001;285:1711-1718; Cannon CP et al. N Engl J Med. 2004;350:1495-1504; Ray KK et al. Am J Cardiol. 2005;46:1405-1410.

MIRACL in ACS

Atorvastatin 80 mg/d over 16 weeks in ACS patients (n=3086)

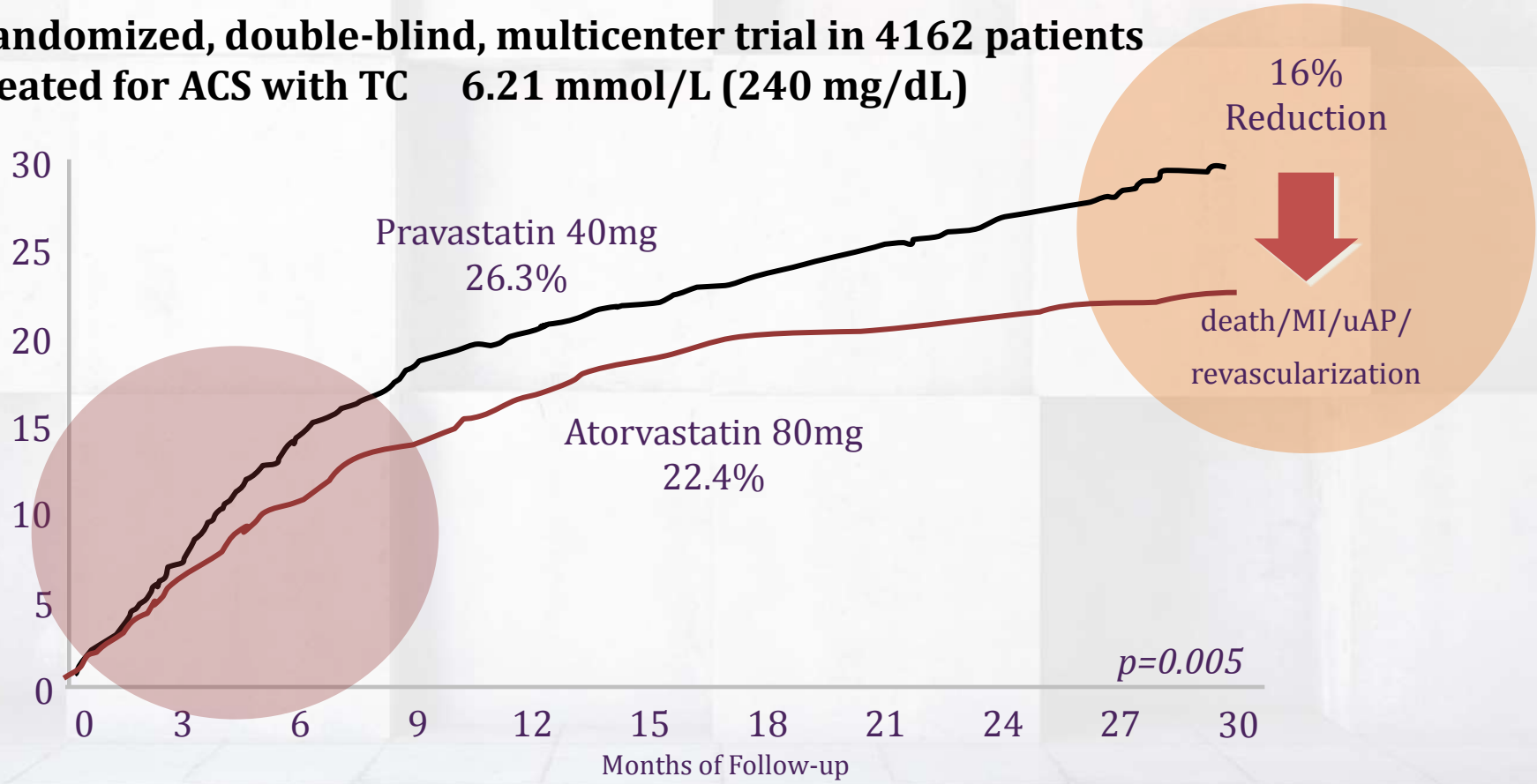


MIRACL investigators hypothesized *"that markers of oxidized LDL provide mechanistic insight into potential clinical benefits of atorvastatin and suggest a novel mechanism of early plaque stabilization."*

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 with TC 6.21 mmol/L (240 mg/dL)



- 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.

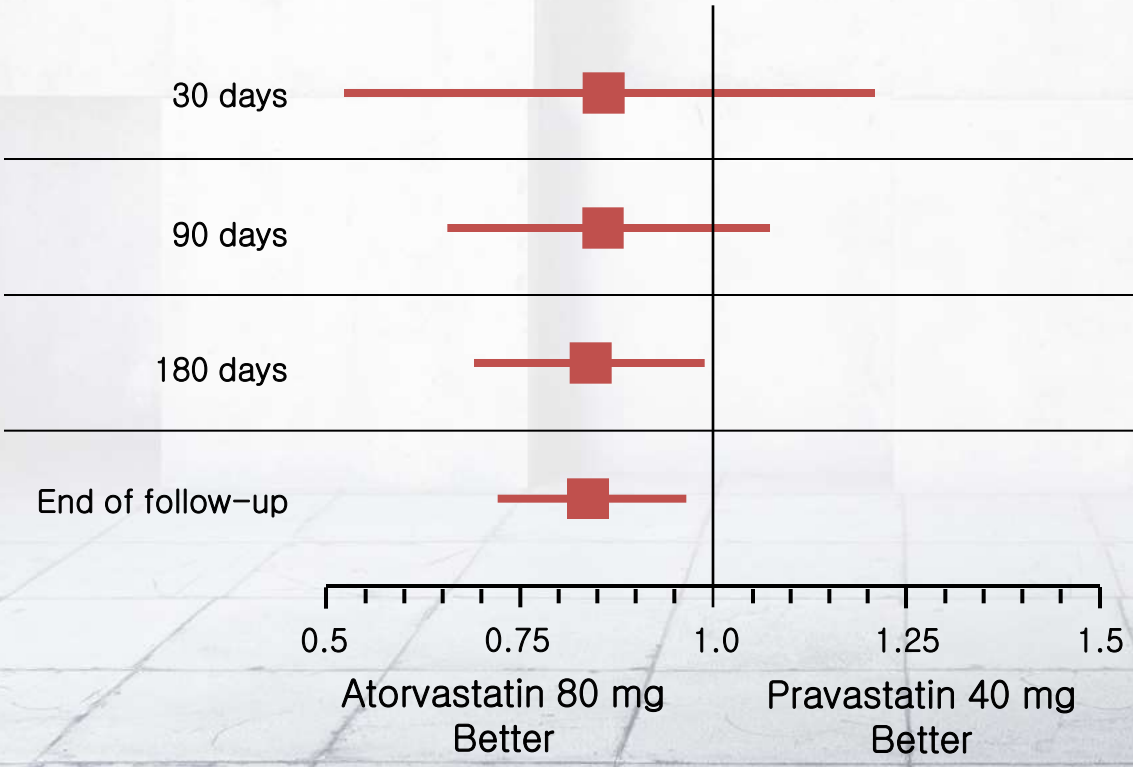
* PROVE-IT was sponsored by Bristol Myers Squibb and Sankyo

NEJM 2004;350:1495

PROVE-IT* : Primary End Point Over Time

The clinical benefits shown within the first 30 days of therapy, and were maintained over follow-up.

Statistical significance between the 2 groups was reached at 180 days.



Event Rates

RR	Atorvastatin 80 mg	Pravastatin 40 mg
17%	1.9%	2.2%
18%	6.3%	7.7%
14%	12.2%	14.1%
16%	22.4%	26.3%

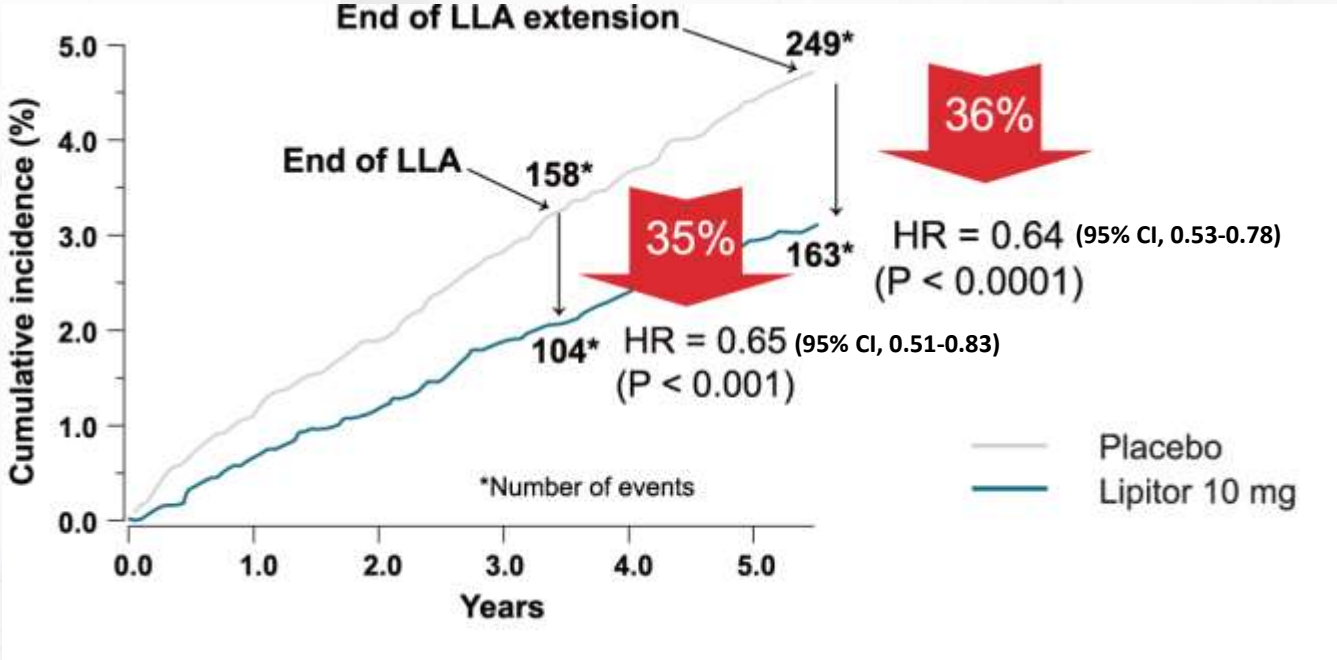
* 2-year event rates

NEJM 2004;350:1495

Carry-Over effect
ASCOT LLA-extension

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

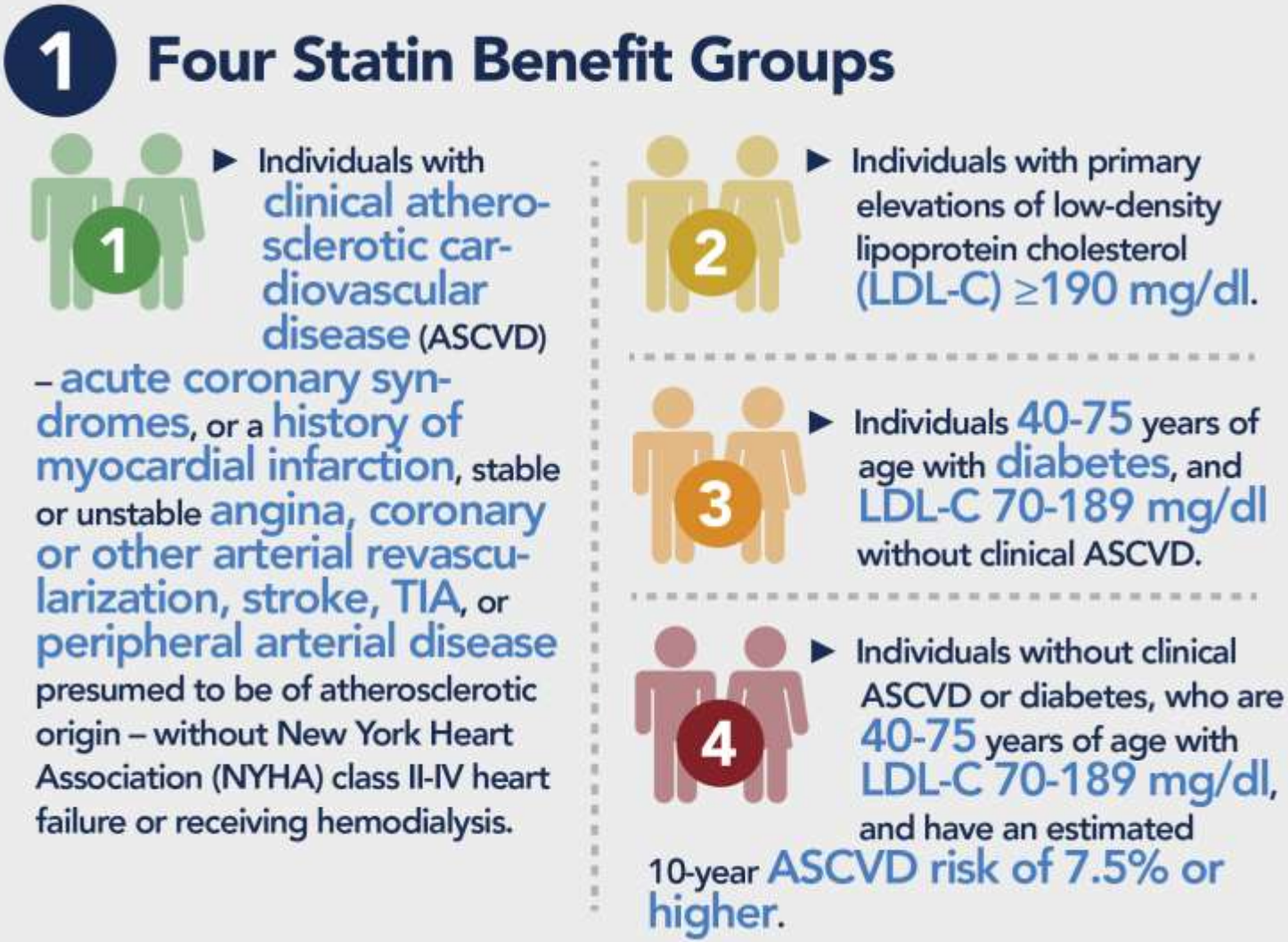
Primary Endo Point :Non Fatal MI, Fatal CVD



Carry Over Effect has shown in following 2 years after the end of LLA trial

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

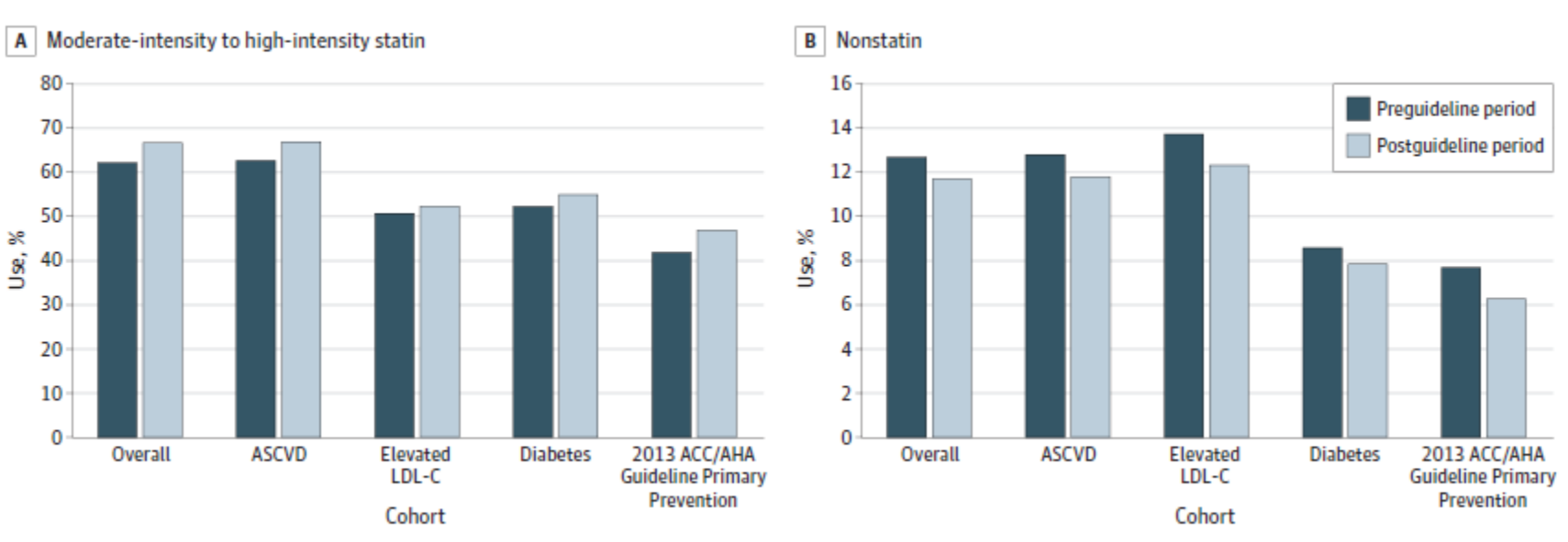
2013 ACC/AHA guideline – 4 statin benefit group



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

A trend toward increasing use of moderate-intensity to high intensity statins overall and in the ASCVD cohort

Overall Use for the Pre-guideline and Post-guideline Periods

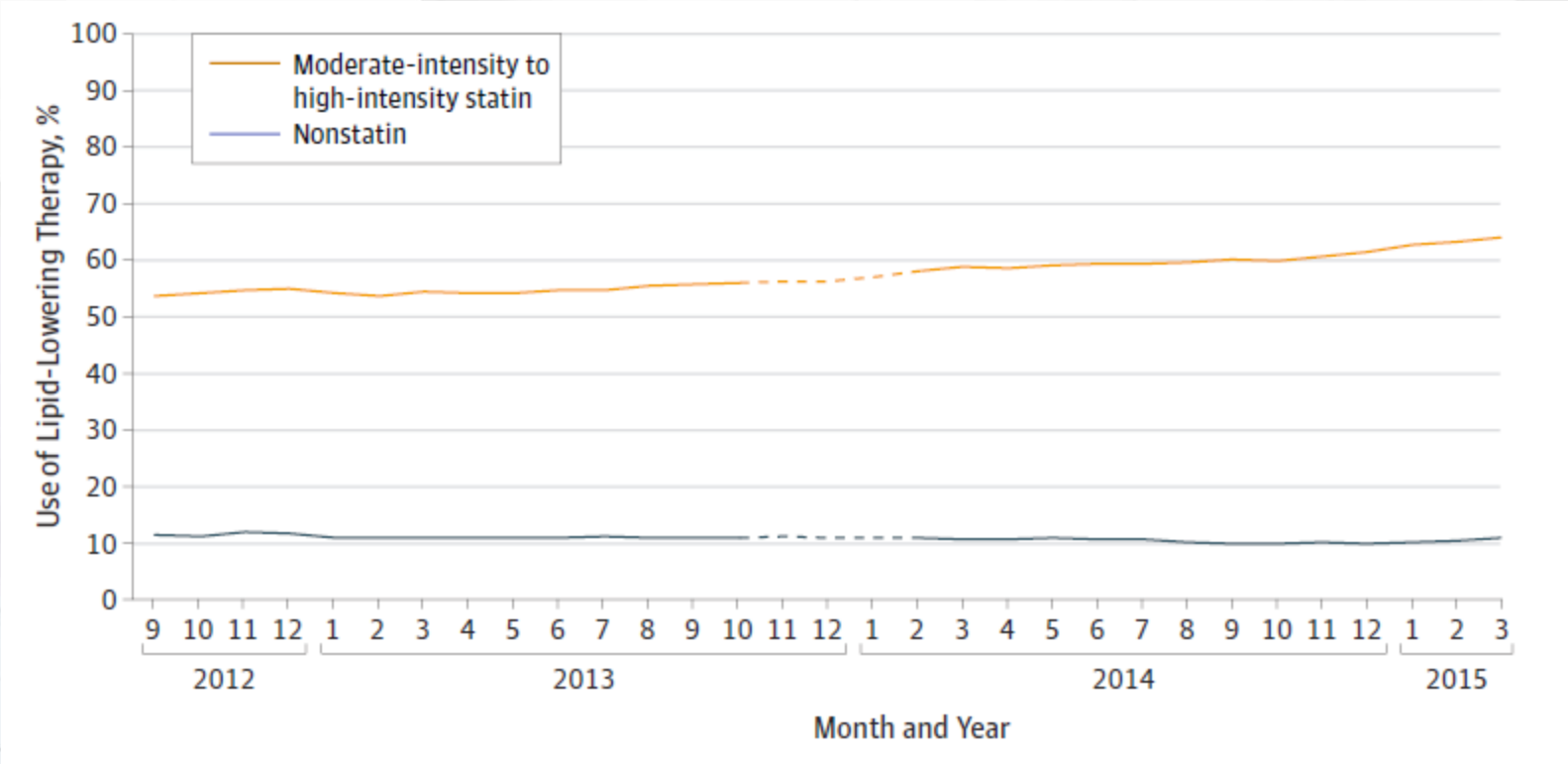


Adoption of the 2013 ACC/AHA Cholesterol Management Guideline in cardiology practices

Ref. Pokharel Y et al. JAMA Cardiol. doi:10.1001/jamacardio.2016.5922 Published online March 1, 2017.

increasing trend in moderate-intensity to high-intensity statin use after publication

Observed Trends in the Use of Moderate-Intensity to High-Intensity Statin and Nonstatin Lipid-Lowering Therapy in the Overall Cohort



Ref. Pokharel Y et al. JAMA Cardiol. doi:10.1001/jamacardio.2016.5922 Published online March 1, 2017.

KSLA Guidelines for Lipid and Atherosclerosis Management ver. 3, 2015

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

Guideline

Risk Factors

흡연

고혈압
- 수축기혈압 140 mmHg 이상 또는 이완기혈압 90 mmHg 이상
- 또는 항고혈압제 복용

저HDL 콜레스테롤(<40 mg/dL)

연령
- 남자 45세 이상
- 여자 55세 이상

관상동맥질환 조기 발병의 가족력
- 부모, 형제자매 중 남자 55세 미만, 여자 65세 미만에서 관상동맥질환이 발병한 경우

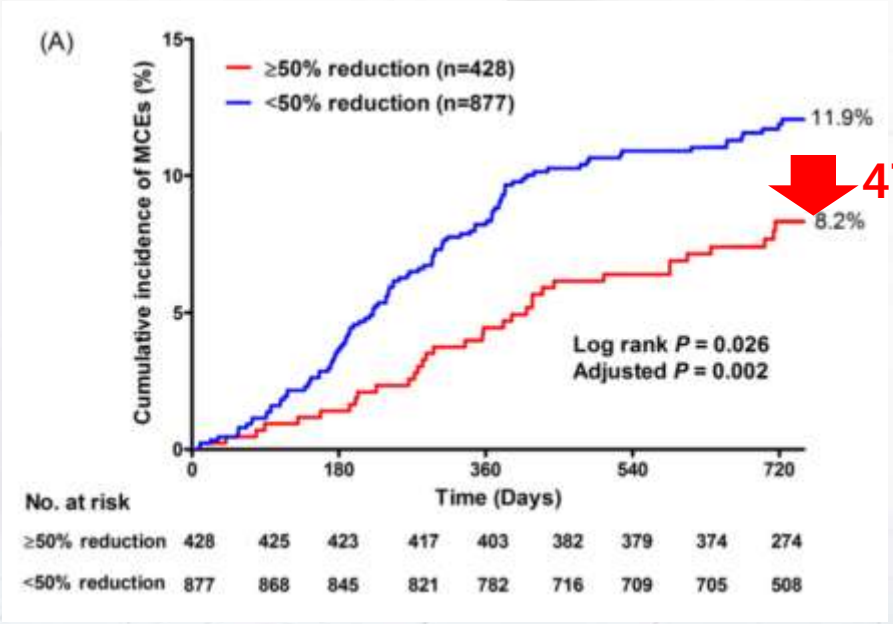
*고HDL 콜레스테롤(60 mg/dL 이상)은 보호인자로 간주하여 총 위험인자 수에서 하나를 감하게 된다.

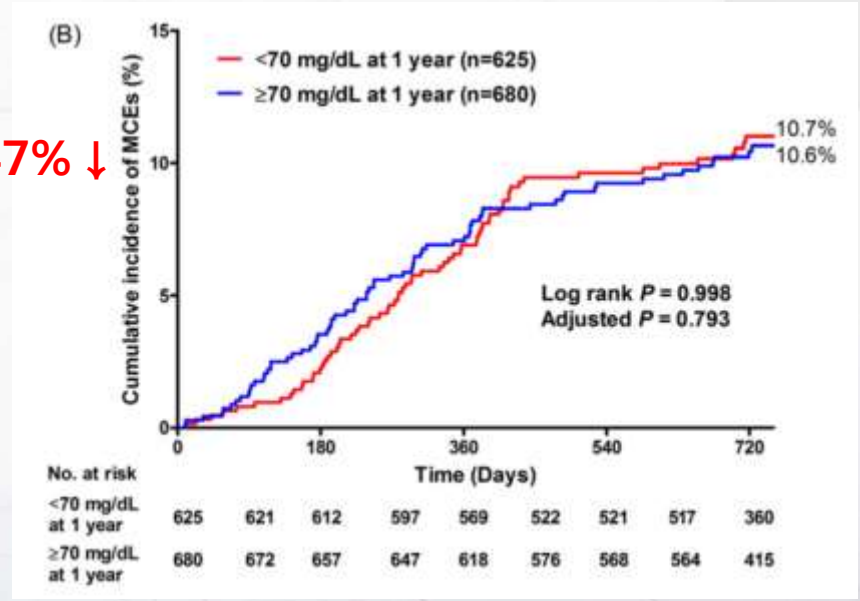
50% Reduction vs. LDL Target 70 mg/dL in AMI pts.

Primary endpoint: 2 year major cardiac event including cardiac death, non-fatal myocardial infraction, percutaneous coronary intervention, and coronary artery by bypass grafting after hospital discharge

KAMIR: n=1305

mean LDL-C: 126mg/dL

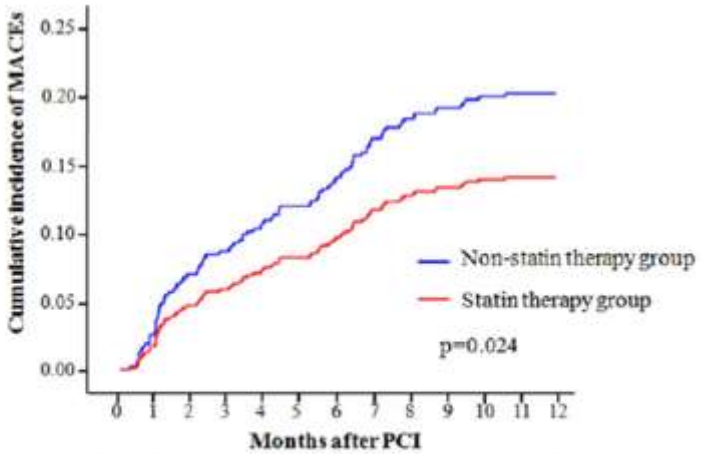




Cho KH et al. International Journal of Cardiology, 2015

Benefit of Early Statin Therapy in Patients With Acute Myocardial Infarction Who Have Extremely Low Low-Density Lipoprotein Cholesterol

Ki Hong Lee, MD,* Myung Ho Jeong, MD, PhD,* Ha Mi Kim, RN,* Youngkeun Ahn, MD, PhD,* Jong Hyun Kim, MD,† Shung Chull Chae, MD, PhD,‡ Young Jo Kim, MD, PhD,§ Seung Ho Hur, MD, PhD,‖ In Whan Seong, MD, PhD,¶ Taek Jong Hong, MD, PhD,# Dong Hoon Choi, MD, PhD,** Myeong Chan Cho, MD, PhD,†† Chong Jin Kim, MD, PhD,‡‡ Ki Bae Seung, MD, PhD,§§ Wook Sung Chung, MD, PhD,§§ Yang Soo Jang, MD, PhD,‖‖ Seung Woon Rha, MD, PhD,¶¶ Jang Ho Bae, MD, PhD,## Jeong Gwan Cho, MD, PhD,* Seung Jung Park, MD, PhD,*** for the KAMIR (Korea Acute Myocardial Infarction Registry) Investigators



Methods We analyzed 1,054 patients with AMI who had baseline LDL-C levels below 70 mg/dl and survived at discharge from the Korean Acute MI Registry between November 2005 and December 2007. They were divided into 2 groups according to the prescribing of statins at discharge (statin group n = 607; nonstatin group n = 447). The primary endpoint was the composite of 1-year major adverse cardiac events, including death, recurrent MI, target vessel revascularization, and coronary artery bypass grafting.

Results Statin therapy significantly reduced the risk of the composite primary endpoint (adjusted hazard ratio [HR]: 0.56; 95% confidence interval [CI]: 0.34 to 0.89; p = 0.015). Statin therapy reduced the risk of cardiac death (HR: 0.47; 95% CI: 0.23 to 0.93; p = 0.031) and coronary revascularization (HR: 0.45, 95% CI: 0.24 to 0.85; p = 0.013). However, there were no differences in the risk of the composite of all-cause death, recurrent MI, and repeated percutaneous coronary intervention rate.

Conclusions Statin therapy in patients with AMI with LDL-C levels below 70 mg/dl was associated with improved clinical outcome. (J Am Coll Cardiol 2011;58:1664–71)

Conclusion

- The level of 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 more to pleiotropic effects (eg, greater reduction in inflammation).