Growing importance of evidence in the management of high CV risk patients

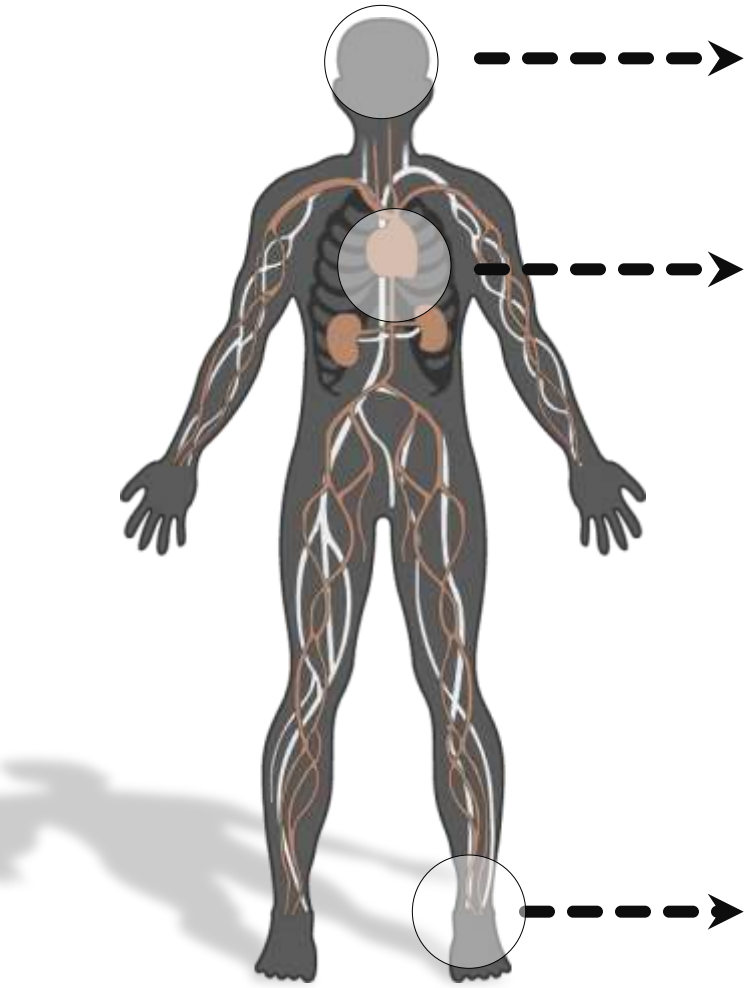
Duk-Woo Park, MD, PhD

Heart Institute, University of Ulsan College of Medicine,

Asan Medical, Seoul, Korea

Secondary Prevention of Cardiovascular Disease

With clinical ASCVD



Stroke or TIA presumed to be of atherosclerotic origin

Stable CHD : history of MI, stable angina,
coronary revascularization
Acute CHD : Acute coronary syndrome (ACS)

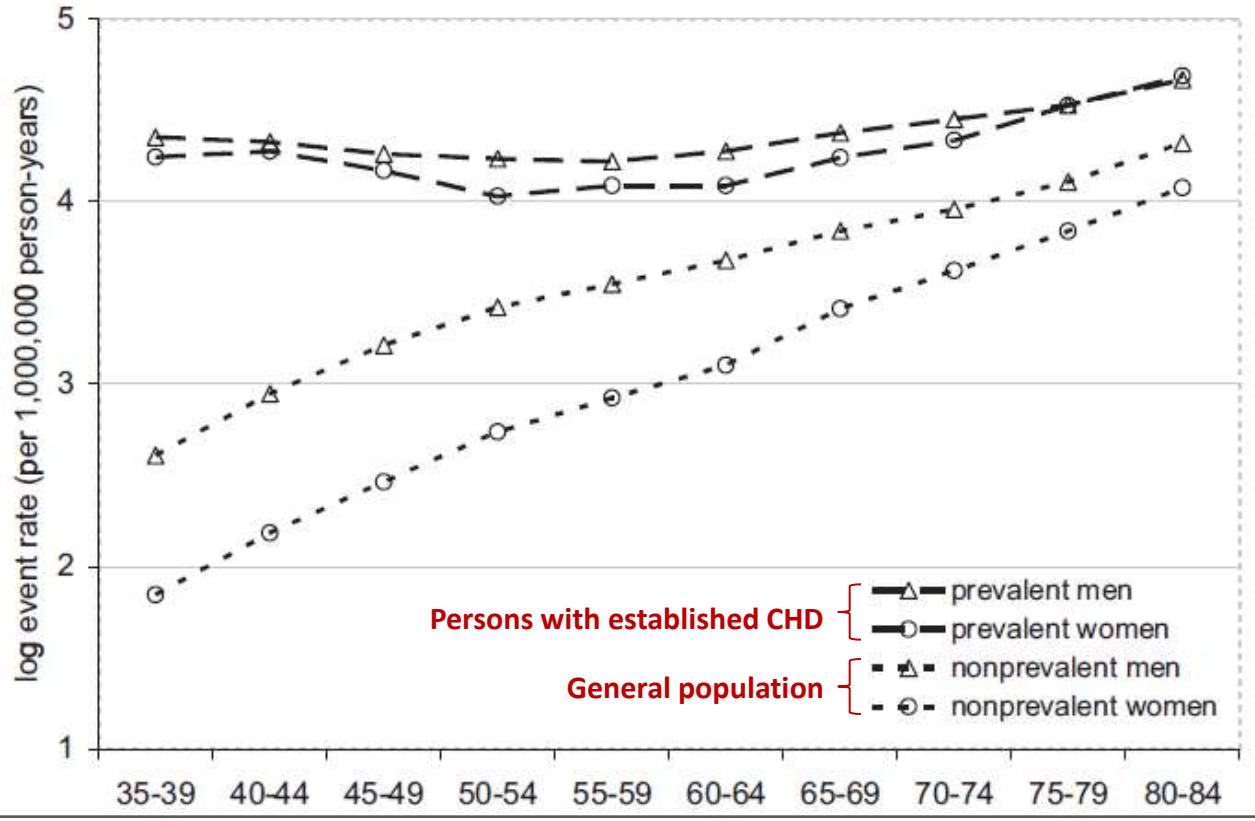
Peripheral arterial disease or revascularization

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

Persons with established CHD are at much higher risk of recurrent events or death than the general population.

A population longitudinal person-based study to examine occurrence of CHD death and nonfatal MI both populations with and without established CHD.

Age-specific rates for major CHD events by disease prevalence and sex for the period 1995 to 2005.



Ref. Briffa TG, et al. Circ Cardiovasc Qual Outcomes. 2011;4:107-113.

More than 40% of major CHD events annually occur in persons with established CHD

The average annual age-standardized prevalence of CHD in the Perth metropolitan region (population 1.6 million) was 28 373 (8.8%) in men and 14 966 (4.0%) in women

Characteristics of Men and Women Ages 35 to 84 Years With and Without Coronary Heart Disease in Perth, Western Australia, Between 1995 and 2005

	Established CHD		CHD Free	
	Men	Women	Men	Women
Average annual population, n	28 373	14 966	313 999	324 409
Average annual prevalence,*† %	8.8	4.0	91.2	96.0
Total nonfatal MI, CHD deaths, n (%)	8335 (43)	4117 (43)	11 121 (57)	5368 (57)
Total CHD deaths, n (%)	4192 (55)	2276 (51)	3470 (45)	2165 (49)
Total nonfatal MI, n (%)	4143 (35)	1841 (36)	7651 (65)	3203 (64)
Average annual crude rates per 100 000 person-years				
Total nonfatal MI+CHD deaths	2686	2513	325	144
CHD deaths	1361	1397	111	63
Nonfatal MI	1325	1116	244	93

*Average prevalence of previous admission for CHD in the past 15 years at June 30 in each calendar year 1995 to 2005.
†Age-standardized.

Ref. Briffa TG, et al. Circ Cardiovasc Qual Outcomes. 2011;4:107-113.

2013 ACC/AHA cholesterol guidelines

Clinical ASCVD

Yes → Age ≤ 75 y
High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)

Yes → Age >75 y
OR if not candidate for **high-intensity statin**
Moderate-intensity statin

* Clinical ASCVD : ACS, or a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or PAD presumed to be of atherosclerotic origin.

High-Intensity Statin Therapy	**Atorvastatin (40†)–80 mg** Rosuvastatin 20 *(40) mg*
Moderate-Intensity Statin Therapy	**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*

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

2014 NICE guideline – Lipid modification

established CVD

Yes → **Start statin treatment in people with CVD with atorvastatin 80 mg**

Yes → **Use a lower dose of atorvastatin if any of the following apply:**
- potential drug interactions
- high risk of adverse effects
- patient preference.

* CVD disease of the heart and blood vessels caused by the process of atherosclerosis.

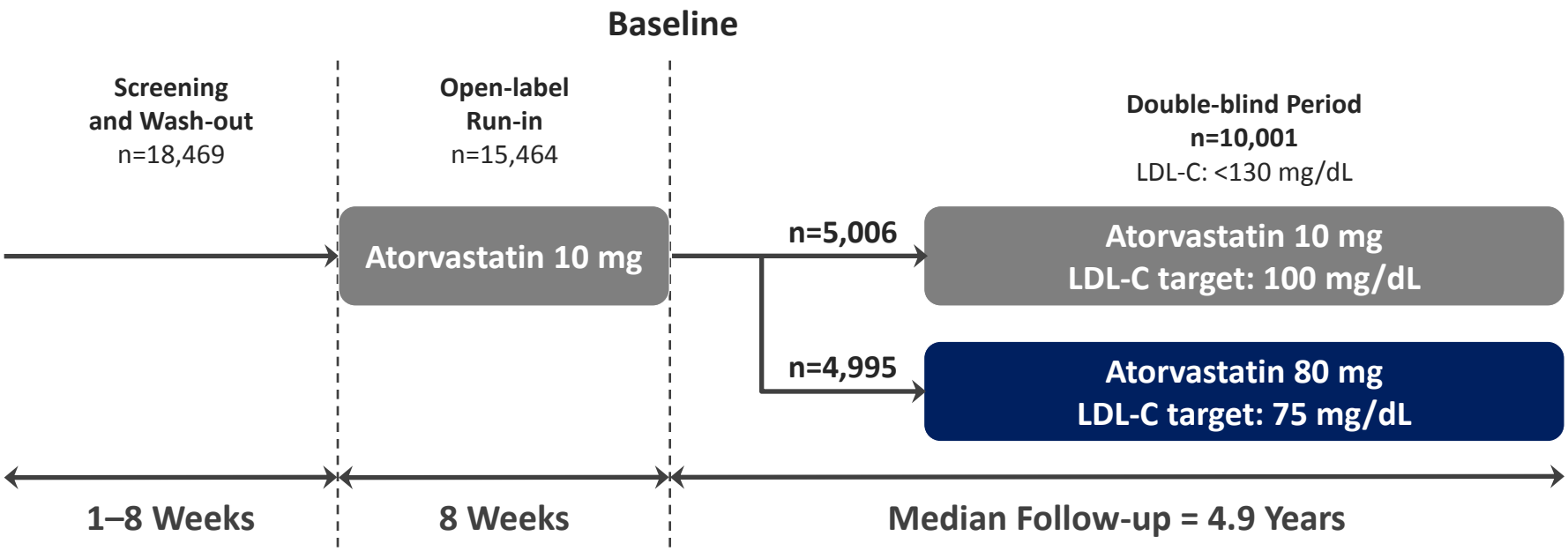
Review question	PICO characteristics		Result
What is the clinical and cost effectiveness of statin therapy for adults with established CVD (secondary prevention)?	- Patient	Adults(18 years and over) with established CVD	Atorvastatin 80 mg
	- Intervention	Atorvastatin / Fluvastatin/ Pravastatin /Rosuvastatin /Simvastatin	
	- Comparison	- Low intensity group(pravastatin 10–40 mg or equivalent) - Medium intensity group(simvastatin 40 mg or equivalent) - High intensity group(atorvastatin 80 mg or equivalent)	
	- Outcome	All-cause mortality, CV mortality, Non-fatal MI , Stroke, Quality of life, Adverse event, LDL-cholesterol reduction	

Ref. NICE clinical guideline 181 Accessed August 8, 2014 at http://www.nice.org.uk/

Effect of Atorvastatin 80 mg in patients with stable CHD

TNT, Treating to the New Target

TNT : Study Design



Patient Population	Primary Efficacy Outcome
35-75 yrs with stable CHD LDL-C: 130-250 mg/dL Triglycerides ≤600 mg/dL	Time to occurrence of a major CV event: • CHD death • Nonfatal, non–procedure-related MI • Resuscitated cardiac arrest • Fatal or nonfatal stroke

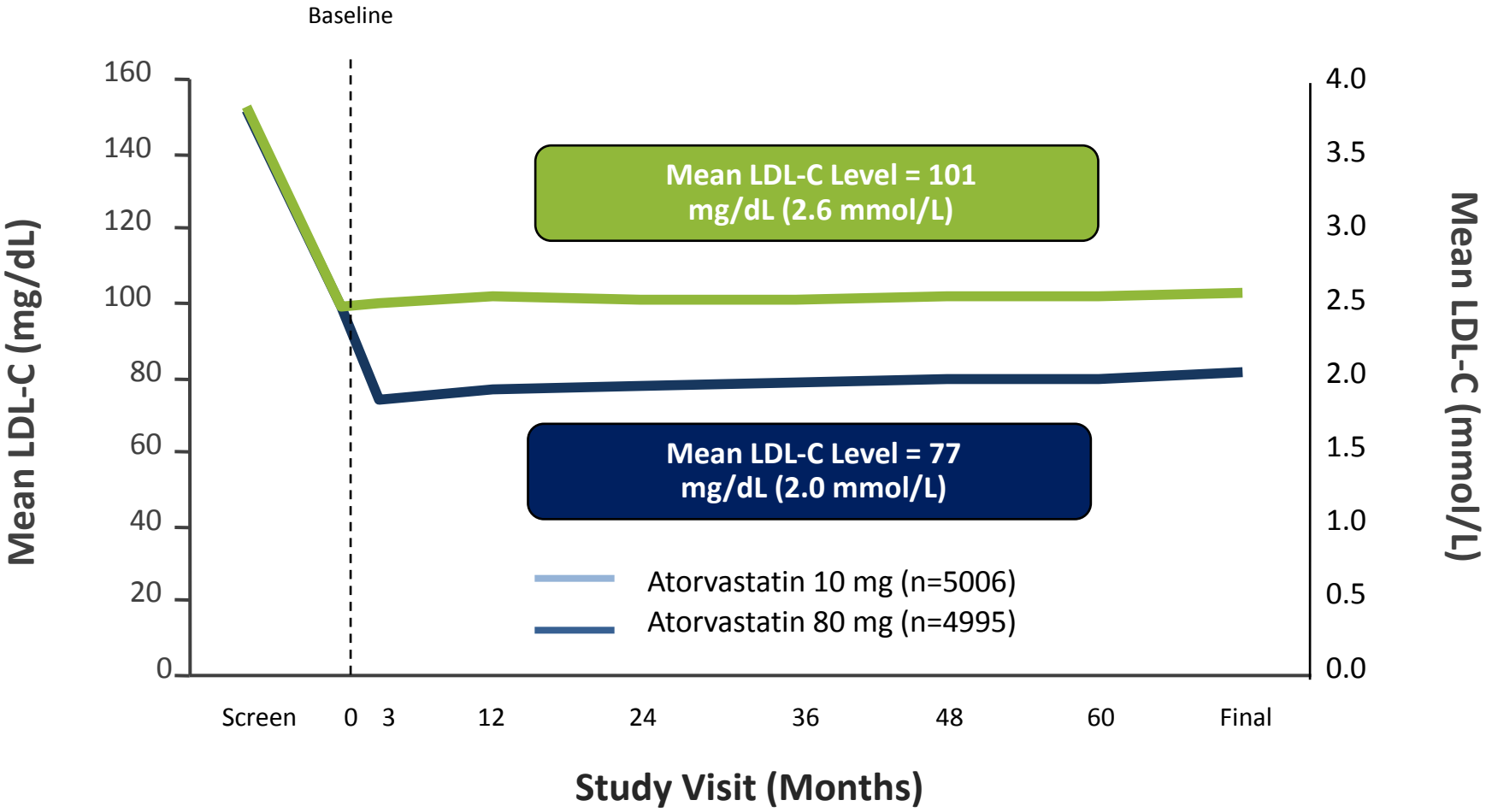
Ref. Adapted from LaRosa JC, et al. N Engl J Med. 2005;352: 1425-1435

TNT : Baseline Patient Characteristics

	Atorvastatin 10 mg (n=5,006)	Atorvastatin 80 mg (n=4,995)
Age (mean ± SD)	61 ± 8.8 yrs	61 ± 8.8 yrs
Men	81%	81%
White	94%	94%
Cardiovascular Risk Factors (%)		
• Current Smoker	13%	13%
• Hypertension	54%	54%
• Diabetes Mellitus	15%	15%
Cardiovascular History (%)		
• **Angina**	**81%**	**82%**
• **Myocardial Infarction**	**58%**	**59%**
• **Coronary Angioplasty**	**54%**	**54%**
• **Coronary Bypass**	**47%**	**47%**
• **Cerebrovascular Accident**	**5%**	**5%**

Ref. Adapted from LaRosa JC, et al. N Engl J Med. 2005;352: 1425-1435

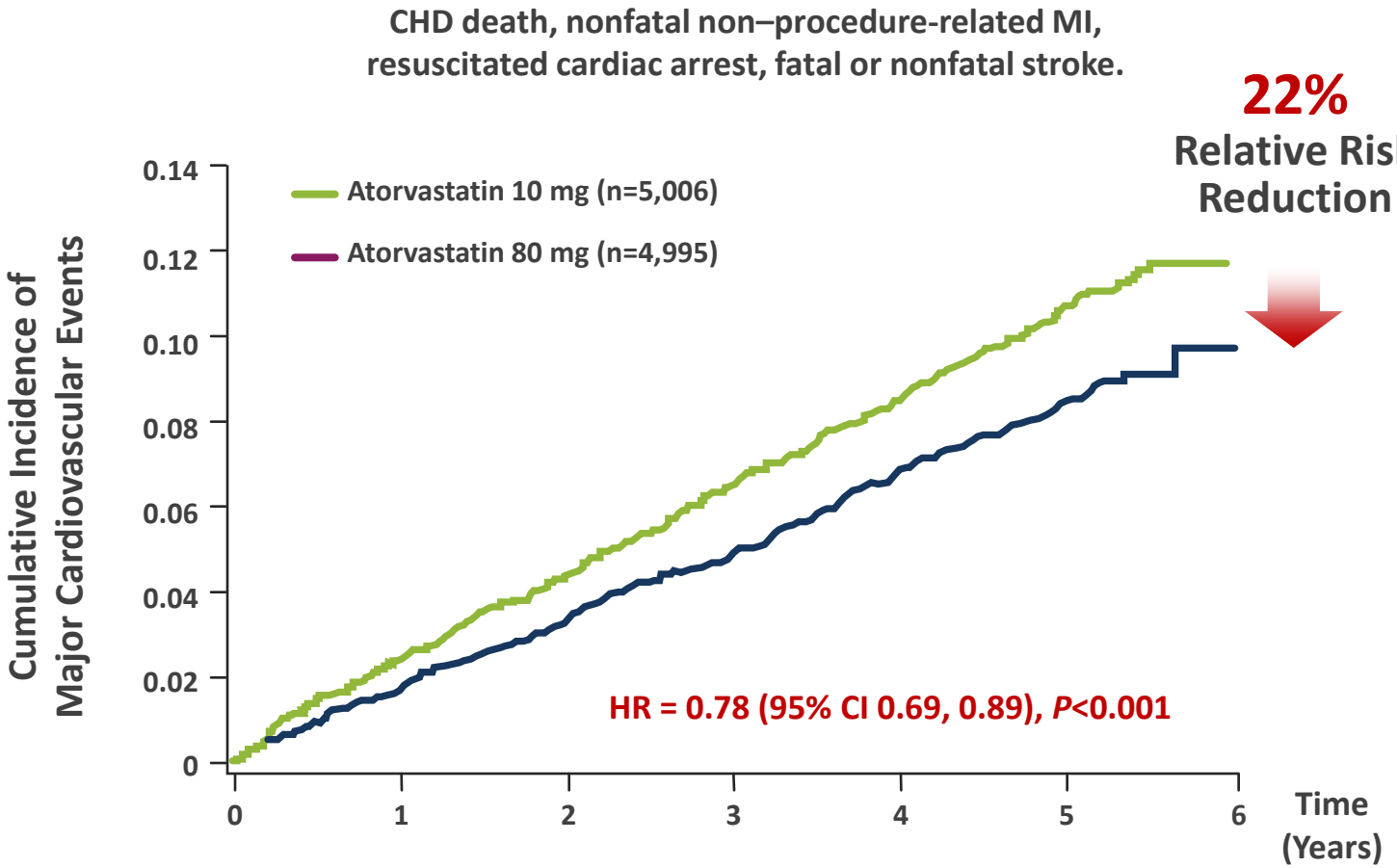
TNT : Changes in Lipid Levels



Ref. Adapted from LaRosa JC, et al. N Engl J Med. 2005;352: 1425-1435

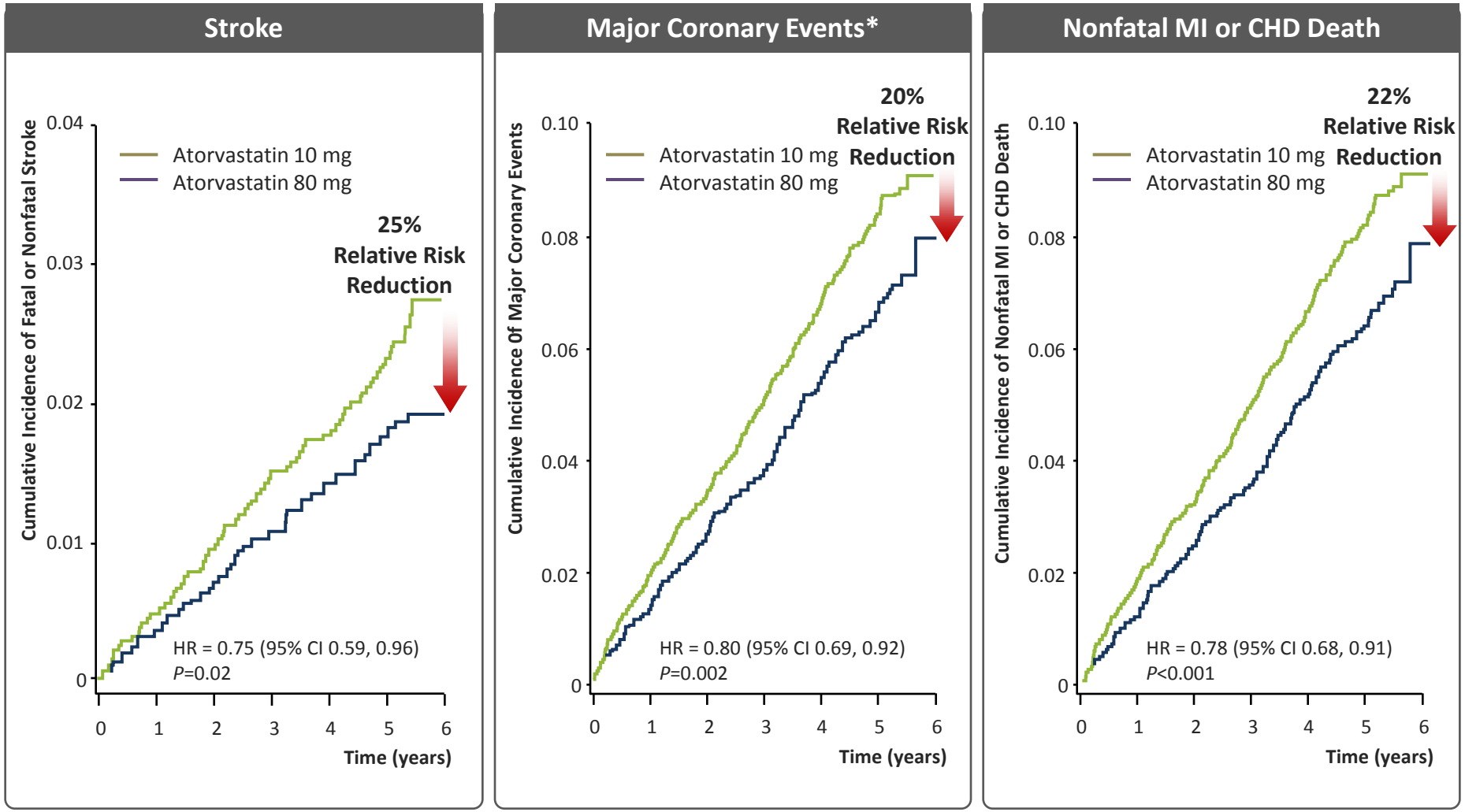
TNT : Primary Efficacy Outcome*

Kaplan–Meier Estimates of the Incidence of the Primary End Point



Ref. Adapted from LaRosa JC, et al. N Engl J Med. 2005;352: 1425-1435

TNT : Secondary Efficacy Outcome



*CHD death, nonfatal non–procedure-related MI, resuscitated cardiac arrest.

Ref. Adapted from LaRosa JC, et al. N Engl J Med. 2005;352: 1425-1435

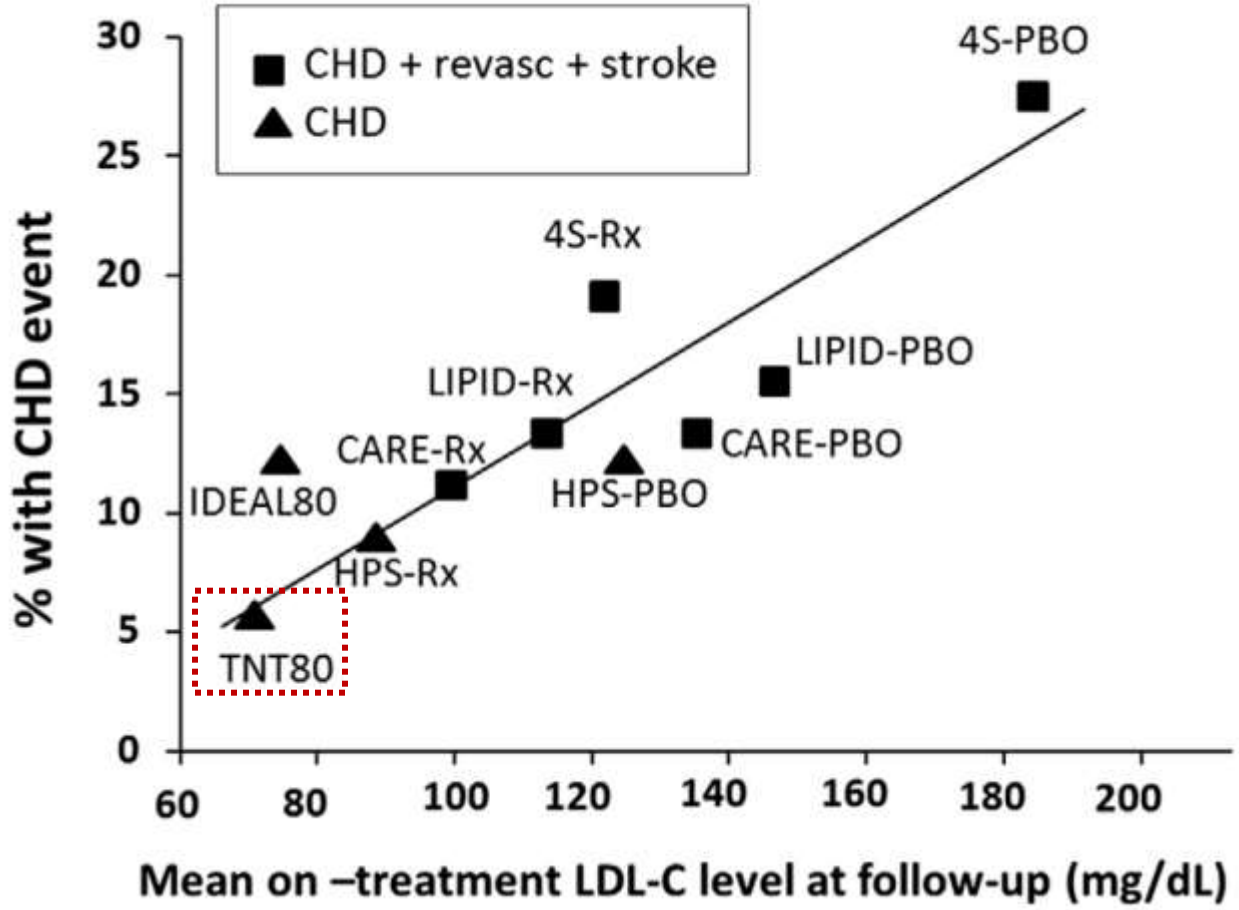
TNT: Safety Profile

	No. of Patients (%)	
	Atorvastatin 10 mg (n=5,006)	Atorvastatin 80 mg (n=4,995)
Treatment discontinuation due to treatment-related AEs	264 (5.3)	359 (7.2)
Myalgia (treatment-related)	234 (4.7)	241 (4.8)
Rhabdomyolysis*	3 (0.06)	2 (0.04)
AST/ALT elevation >3 x ULN†	9 (0.2)	60 (1.2)

*No cases were considered by the investigator with direct responsibility for the patient to be causally related to atorvastatin
†Reported as persistent elevation in ALT, AST, or both on 2 consecutive measures 4-10 days apart

Ref. LaRosa JC, et al. N Engl J Med. 2005;352:1425-1435

The TNT study was the first RCT designed to demonstrate the benefits of lowering LDL-C well below 100 mg/dL in stable CHD patients



*Rx, on-treatment arm of study; PBO, placebo arm. 80, 80 mg atorvastatin.

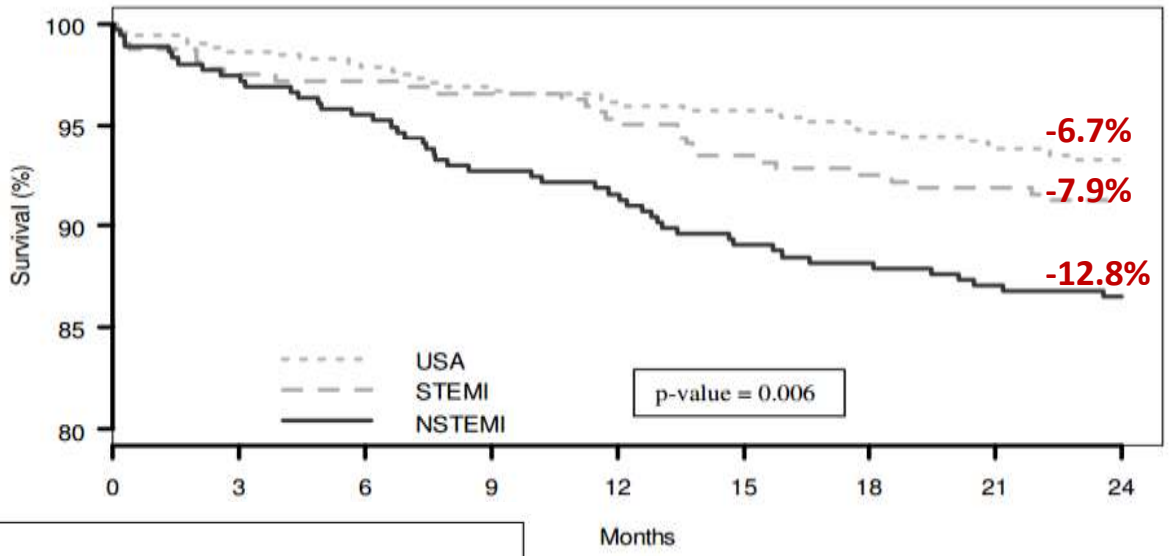
Ref. Adapted from LaRosa JC, et al. N Engl J Med. 2005;352: 1425-1435

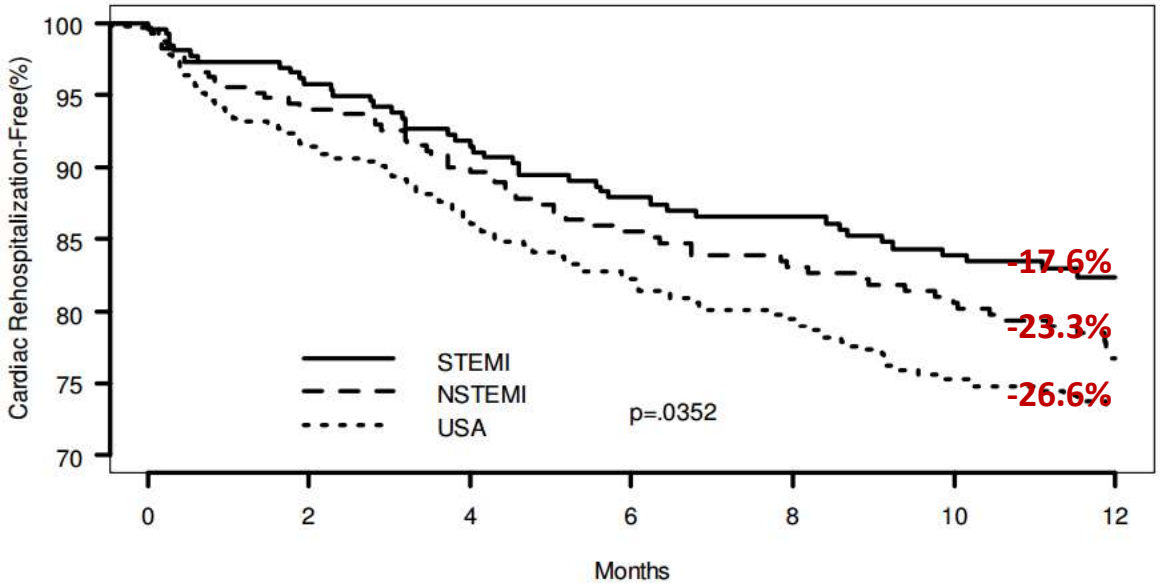
Effect of Atorvastatin 80 mg in patients with acute CHD(ACS)

PROVE-IT, Pravastatin or Atorvastatin Evaluation and Infection Therapy

Risk of Mortality and Rehopitalization in ACS

Kaplan-Meier survival curves of 2-year mortality by ACS presentation



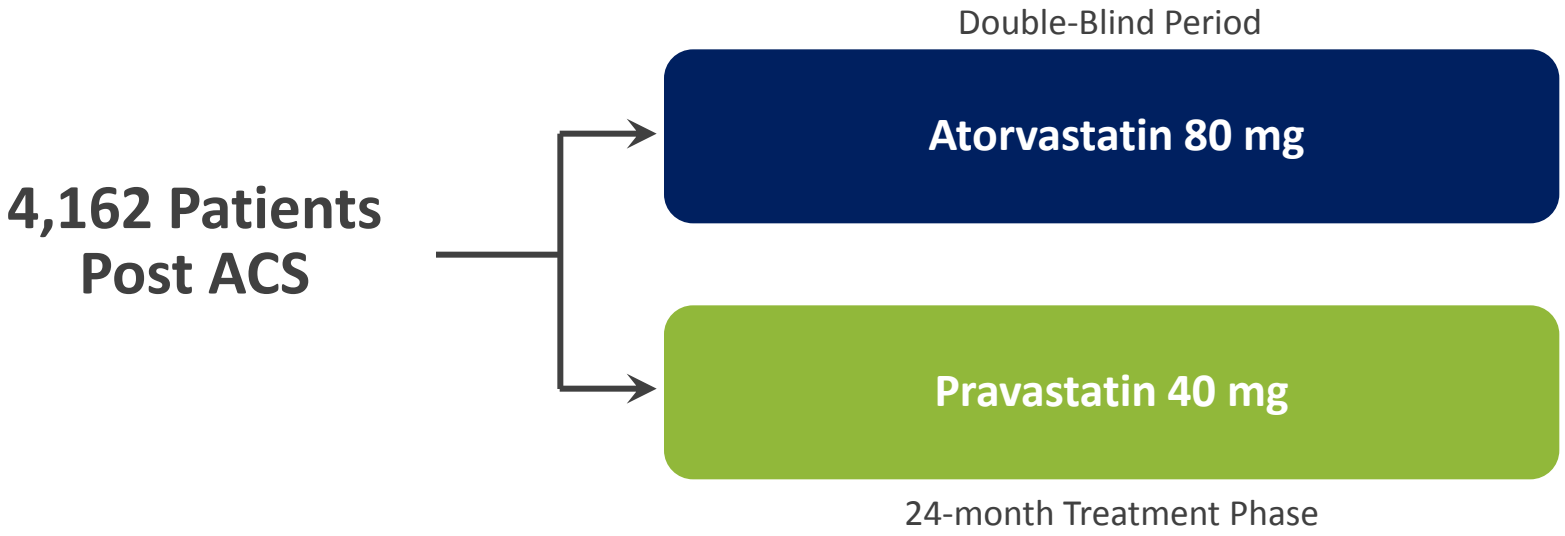


Kaplan-Meier survival curves of 1-year cardiac rehospitalization* by ACS presentation

*Hospitalizations for chest pain, heart failure, MI, cardiac revascularization (PCI, or CABG)

Ref. Adapted from Cannon CP, et al. N Engl J Med. 2004;350:1495-1504.

PROVE IT : Study Design



Patient Population	Primary Endpoint
58 y (mean) TC <6.2 mmol/L **Randomized within 10 days of ACS event (mean: 7 days)**	Time to Occurrence of: Death, Nonfatal MI, Unstable Angina, Stroke, Revascularizatio

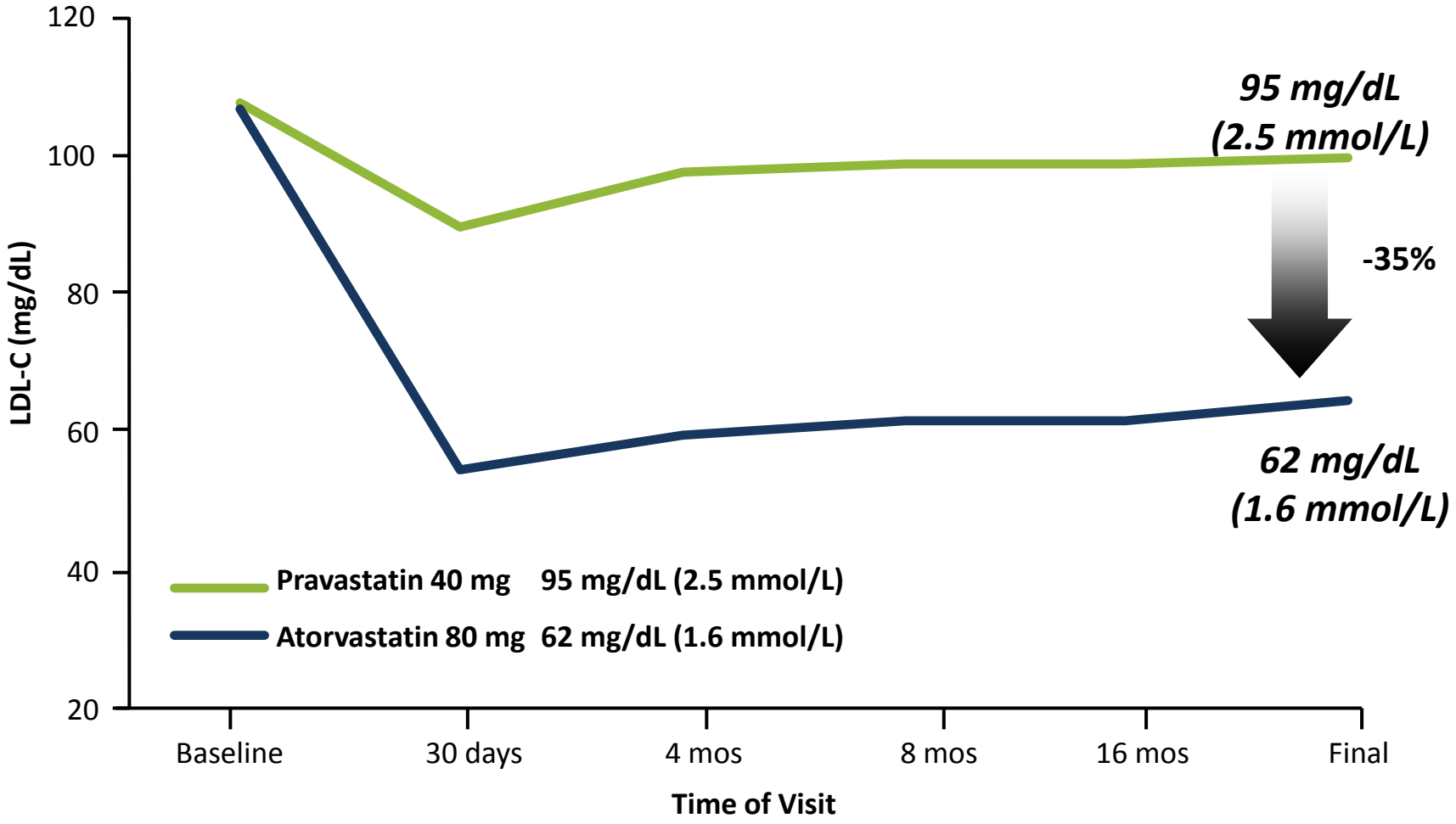
Ref. Adapted from Cannon CP, et al. N Engl J Med. 2004;350:1495-1504.

PROVE IT : Baseline Patient Characteristics

	Atorvastatin 80 mg (n = 2,099)	Pravastatin 40 mg (n = 2,063)
Mean age (y)	58	58
Male/Female (%)	78/22	78/22
History of hypertension (%)	51	49
Current smoker (%)	36	37
History of diabetes (%)	18	18
Prior MI (%)	18	19
STEMI-NSTEMI-UA (%)	**36/36/29**	**33/37/30**
Prior statin use (%)	26	25

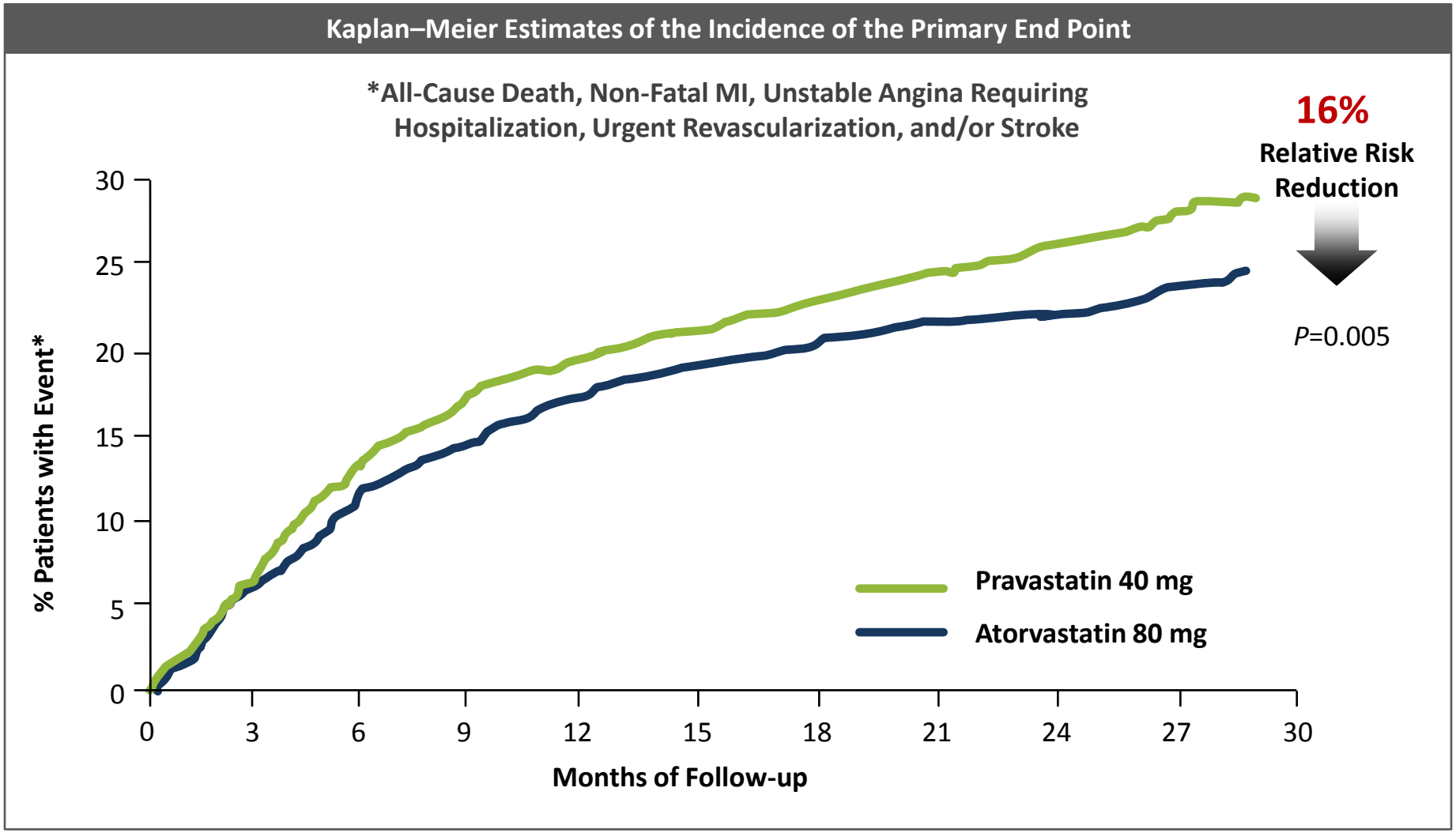
Ref. Adapted from Cannon CP, et al. N Engl J Med. 2004;350:1495-1504.

PROVE IT : Changes in LDL-C



Ref. Adapted from Cannon CP, et al. N Engl J Med. 2004;350:1495-1504.

PROVE IT: Primary End Point*



Ref. Adapted from Cannon CP, et al. N Engl J Med. 2004;350:1495-1504.

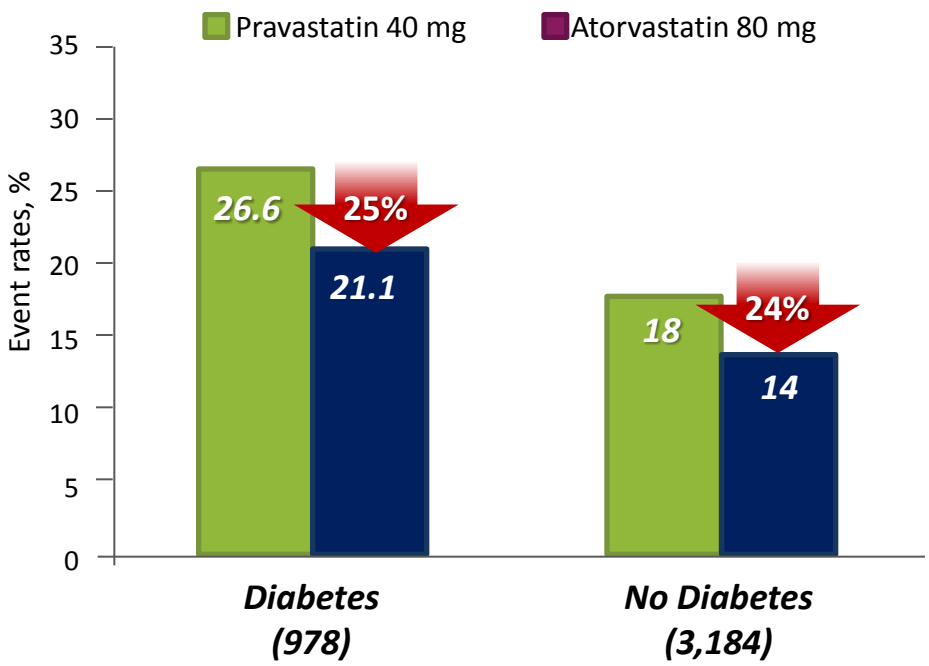
PROVE IT(DM) : Triple endpoint

978 Patients
aged ≥ 18 years
with DM, ACS

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

- Triple endpoint : Death, MI, UA requiring rehospitalization
- Mean follow-up = 24 months

Kaplan–Meier rate of the triple endpoint by 2 years in diabetic vs.non-diabetic patients



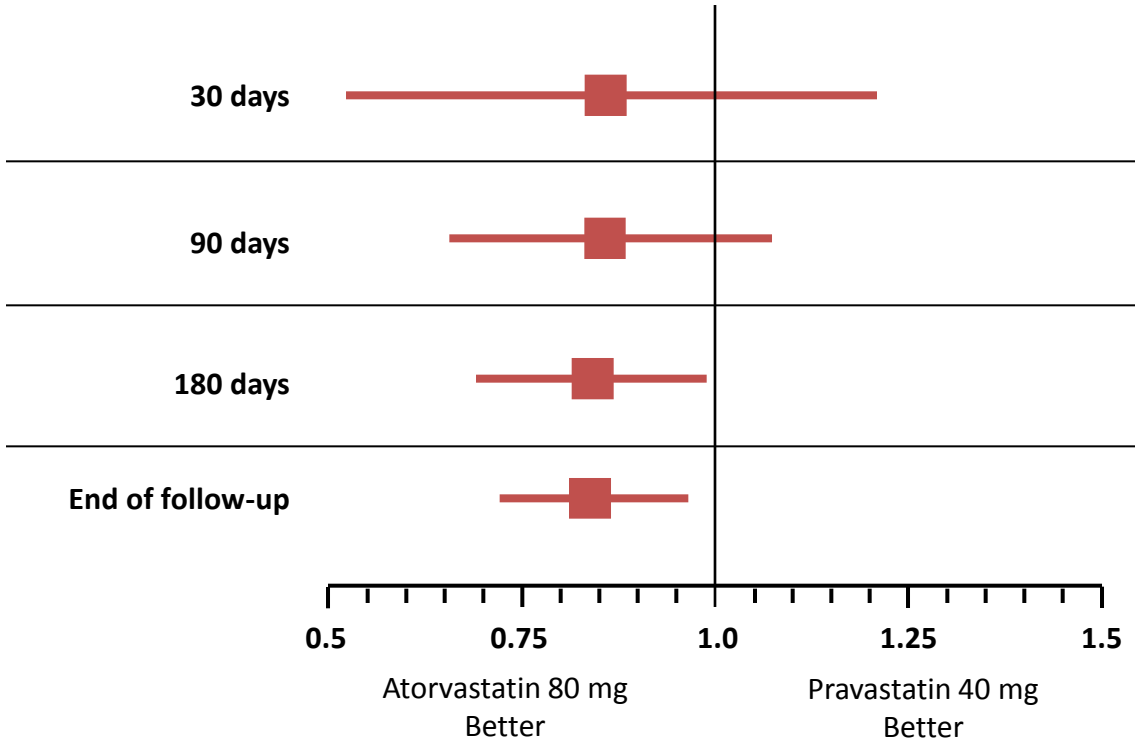
DM HR=0.75(0.58-0.97), p=0.03

no DM HR=0.76(0.64-0.90), p=0.002

Ref. Adapted from Ahmed S, et al. Eur Heart J 2006;27:2323-9.

The benefit of high-dose atorvastatin as compared with standard-dose pravastatin emerged as early as 30 days and was consistent over time

Primary Endpoint Over Time

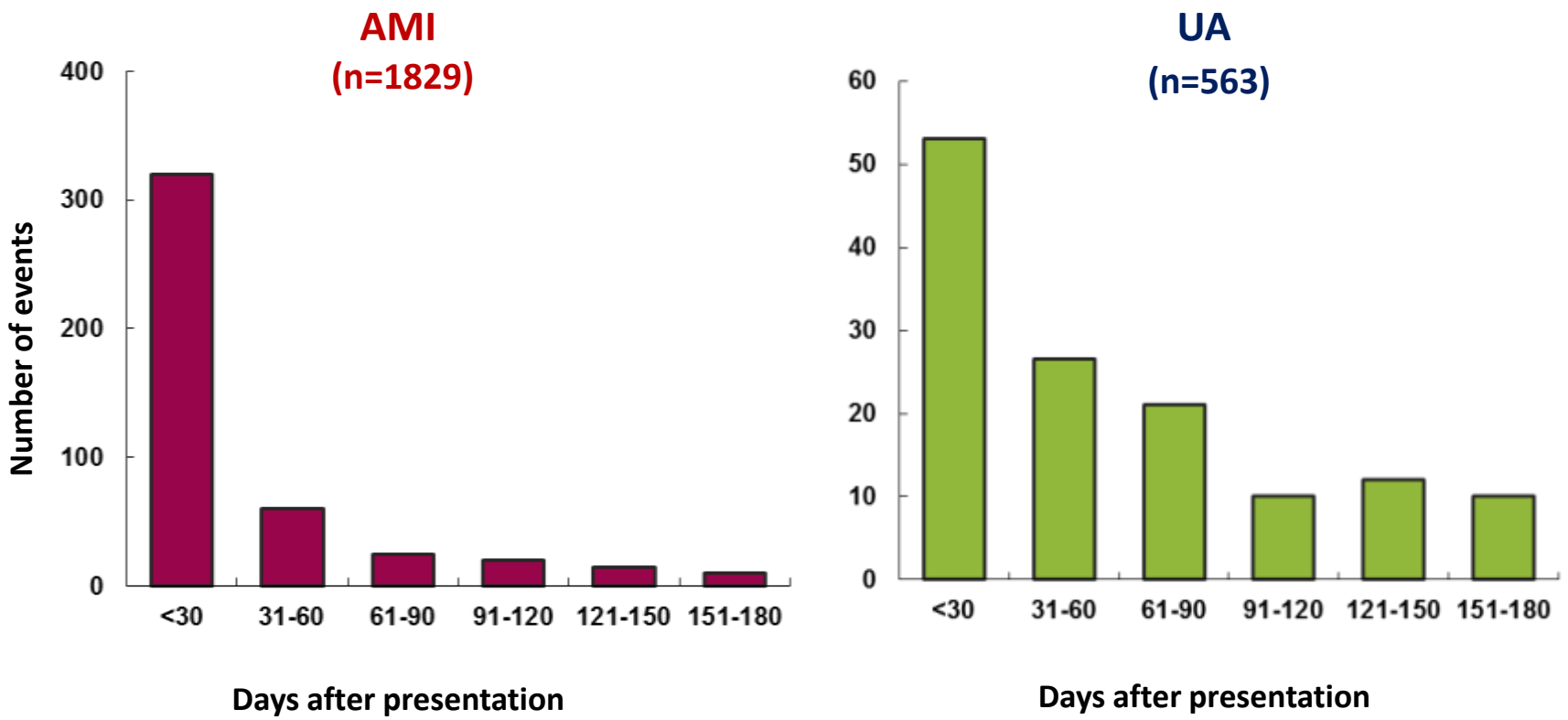


Event Rates		
RR	Atorvastatin 80 mg	Pravastatin 40 mg
17%	1.9%	2.2%
18%	6.3%	7.7%
14%	12.2%	14.1%
16%	22.4%	26.3%

Ref. Adapted from Cannon CP, et al. N Engl J Med. 2004;350:1495-1504.

High risk of recurrence in 30 d after index event

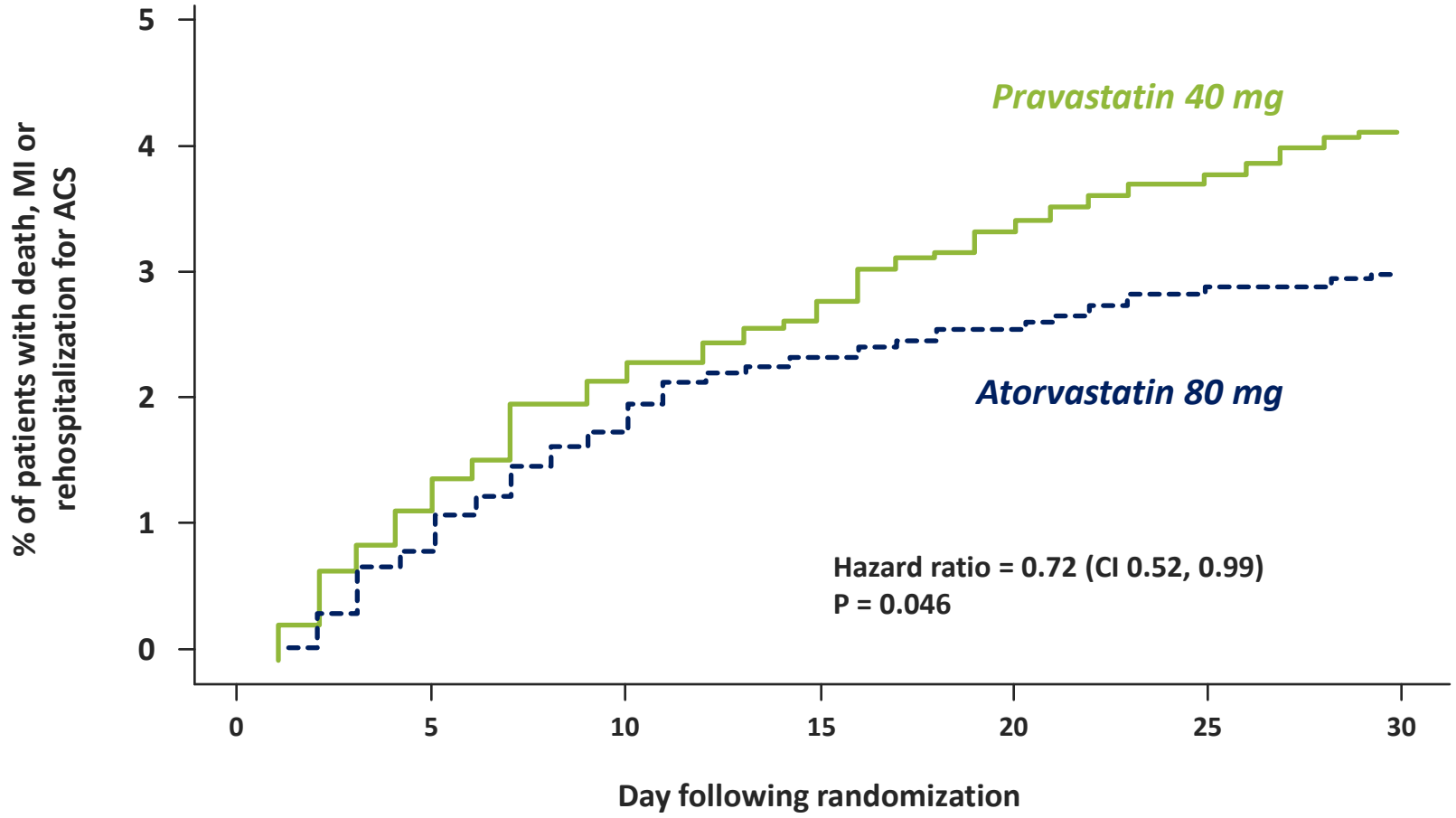
Recurrent events in the first six months after acute coronary syndromes



Ref. Adapted from Heart 2003;89:1268.

Intensive statin therapy early after ACS leads to a reduction in clinical events at 30 days

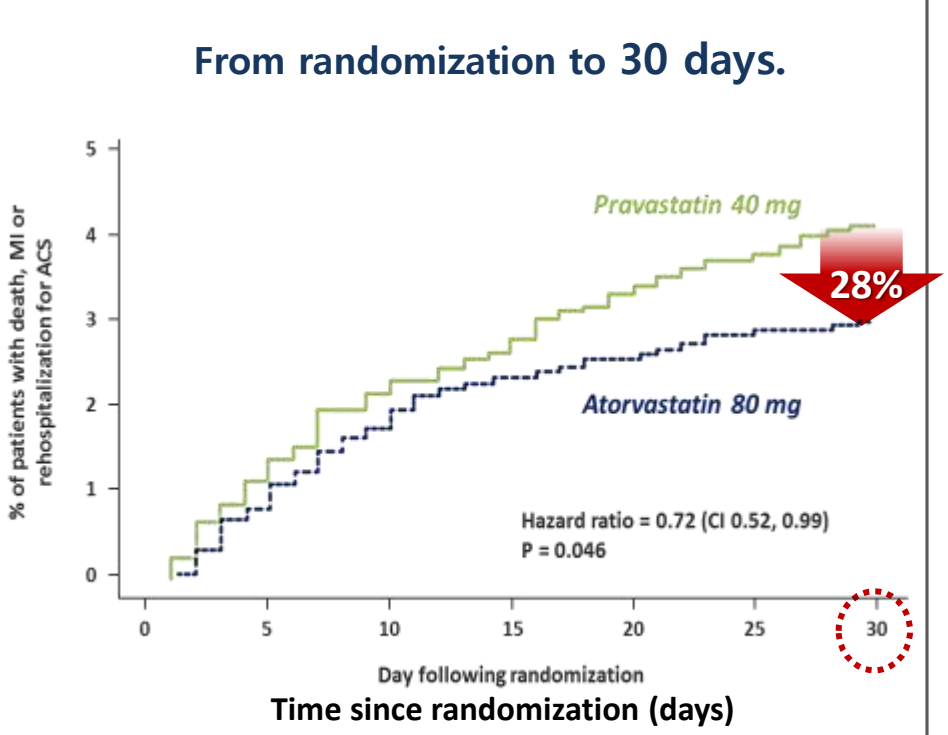
Kaplan-Meier estimates of the composite end point of death, MI, or rehospitalization with recurrent ACS from randomization to 30 days.



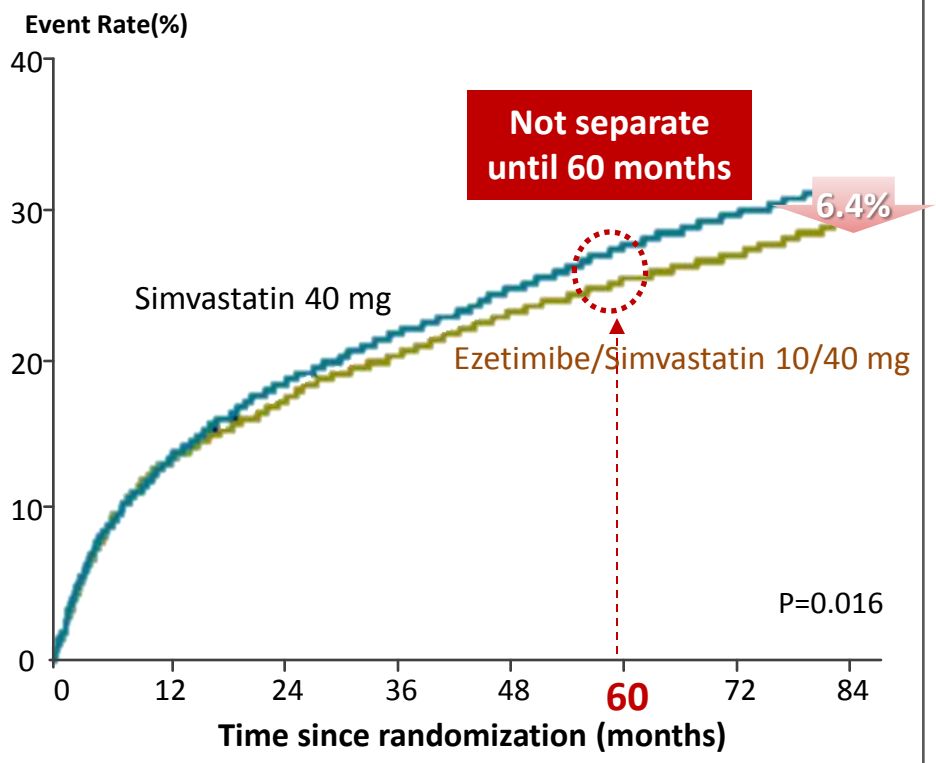
Ref. Adapted from Ray KK, et al. J Am Coll Cardiol 2005;46:1405–10

Intensive Atorvastatin vs Ezetimibe/Simvastatin in patient with ACS

PROVE-IT : death, MI, or rehospitalization



IMPROVE-IT

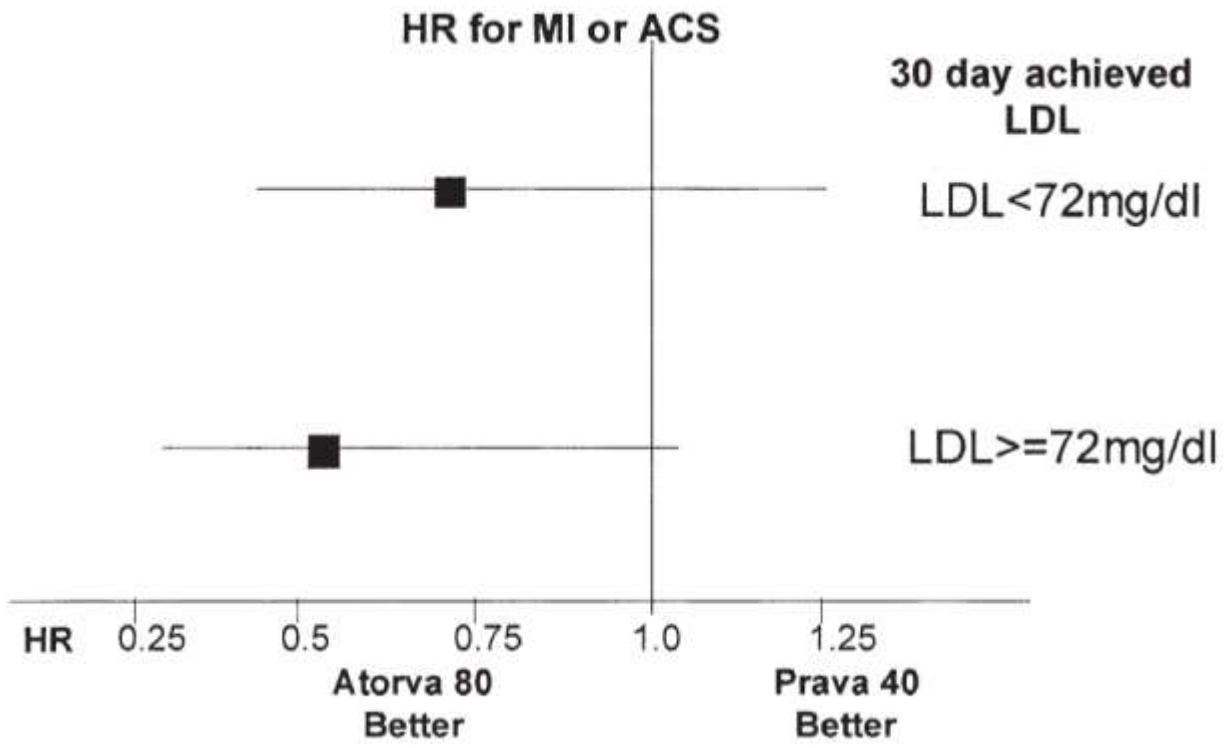


At 30 days vs after 60 month

Ref. Adapted from Ray KK, et al. J Am Coll Cardiol 2005;46:1405–10

Early Benefits of Intensive Statin Therapy at 30 days were present irrespective of LDL-C reduction

Risk of MI or recurrent ACS within 30 days by median day-30 LDL-C



Ref. Adapted from Cannon CP, et al. JACC 2006;48:843–53.

PROVE IT : Safety Profile

	No. of Patients (%)	
	Atorvastatin 80 mg (n=2099)	Pravastatin 40 mg (n=2063)
Treatment discontinuation due to AEs*	13.8%†	10.9%†
Myopathy	NR	NR
Rhabdomyolysis	0	0
Single ALT elevation >3 x ULN	3.3%	1.1%

NR, not reported
ALT, alanine aminotransferase
ULN, upper limit of normal
*elevated liver-enzyme levels, elevated creatinine kinase levels, drug-related side effect, myalgia or arthralgia, or other adverse event
†calculated based on number of patients that started statin treatment (N=2086 for atorvastatin; N=2054 for pravastatin)

Ref. Adapted from Cannon CP, et al. N Engl J Med. 2004;350:1495-1504.

2012 ACCF/AHA Guidelines for the Management of Patients With Unstable Angina/NSTEMI

5.2.7. Lipid Management

Class I

1. **The following lipid recommendations are beneficial:**
   a. **Lipid management should include assessment of a fasting lipid profile for all patients, within 24 h of hospitalization.** *(Level of Evidence: C)*
   b. **Hydroxymethyl glutaryl-coenzyme A reductase inhibitors (statins), in the absence of contraindications, regardless of baseline LDL-C and diet modification, should be given to post-UA/NSTEMI patients, including postrevascularization patients.** *(Level of Evidence: A)*
   c. **For hospitalized patients, lipid-lowering medications should be initiated before discharge.** *(Level of Evidence: A)*
   d. **For UA/NSTEMI patients with elevated LDL-C (greater than or equal to 100 mg per dL), cholesterol-lowering therapy should be initiated or intensified to achieve an LDL-C of less than 100 mg per dL.** *(Level of Evidence: A)* **Further titration to less than 70 mg per dL is reasonable.** *(Class IIa, Level of Evidence: A)*
   e. **Therapeutic options to reduce non–HDL-CII are recommended, including more intense LDL-C–lowering therapy.** *(Level of Evidence: B)*
   f. **Dietary therapy for all patients should include reduced intake of saturated fats (to less than 7% of total calories), cholesterol (to less than 200 mg per d), and trans fat (to less than 1% of energy).** *(Level of Evidence: B)*
   g. **Promoting daily physical activity and weight management are recommended.** *(Level of Evidence: B)*
2. **Treatment of triglycerides and non–HDL-C is useful, including the following:**
   a. **If triglycerides are 200 to 499 mg per dL, non–HDL-CII should be less than 130 mg per dL.** *(Level of Evidence: B)*
   b. **If triglycerides are greater than or equal to 500 mg per dL,¶¶ therapeutic options to prevent pancreatitis are fibrate## or niacin## before LDL-lowering therapy is recommended. It is also recommended that LDL-C be treated to goal after triglyceride-lowering therapy. Achievement of a non–HDL-CII less than 130 mg per dL (ie, 30 mg per dL greater than LDL-C target) if possible is recommended.** *(Level of Evidence: C)*

Ref. Anderson JL, et al. Circulation. published online April 29, 2013.

2013 ACCF/AHA Guideline for the Management of STEMI

8.3. Lipid Management: Recommendations

CLASS I

1. High-intensity statin therapy should be initiated or continued in all patients with STEMI and no contraindications to its use (434–436). (*Level of Evidence: B*)

Ref. O'Gara PT, et al. J Am Coll Cardiol. 2013;61(4):e78-e140.

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), DEAL(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)

Conclusion

- ***Patients with established CHD are at much higher risk of recurrent events or death than the general population.***

- ***Intensive statin therapy with atorvastatin 80 mg/d in patients with stable CHD provides significant clinical benefit compared with atorvastatin 10 mg/d.***

- ***In the PROVE IT trial, Intensive statin therapy with atorvastatin 80 mg/d in patients post-ACS provides demonstrated significant clinical benefits compared to pravastatin 40 mg/d and leads to a reduction in clinical events at 30 days, consistent with greater early pleiotropic effects.***

- ***The TNT and PROVE-IT study is the important evidence of major guidelines on secondary prevention of CHD.***