# Atorvastatin for Secondary Prevention in Patients with Stable IHD

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# Disclosure

▸ Grant support

- Korean Society of Interventional Cardiology
- Ministry of Health & Welfare, Republic of Korea
- Sungkyunkwan University Foundation for Corporate Collaboration
- Abbott Vascular, Boston Scientific, Biotronik, Biometrics, and Medtronic

▸ Consulting Fees/Honoraria

- Abbott Vascular, Astra Zeneca, Biotronik, Biometrics, Daiichi Sankyo, Pfizer, and Sanofi-Aventis

# Atorvastatin 80 mg reduced a mean **LDL–C by 42%,** the **RR for CVD by 16%**

**3,086 Patients aged ≥ 18 years with ACS without NYHA class IIIb-IV HF**
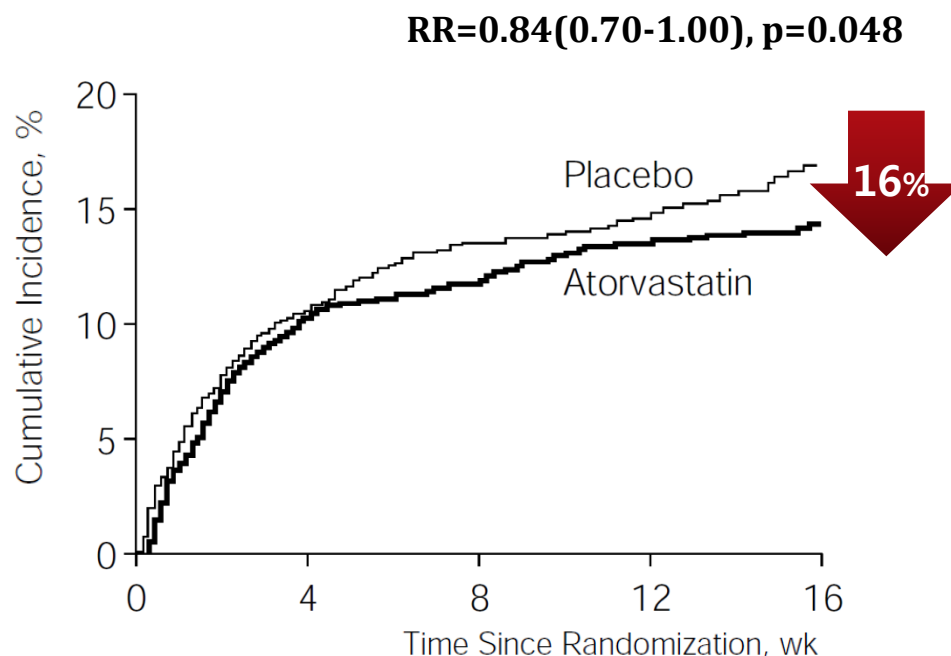
→ Placebo plus usual care

→ Atorvastatin 80 mg/day

- Primary endpoint : CHD death, non fatal AMI, resuscitated cardiac arrest, recurrent symptomatic myocardial ischemia
- Mean follow-up = 16 weeks

## Change of LDL-cholesterol

| | Atorvastatin 80 mg | Placebo |
|---|---|---|
| N | 1,538 | 1,548 |
| Baseline median, mg/dl | 124 | 124 |
| End of follow–up mean, mg/dl | 72 | 135 |
| LDL–C difference (mg/dL)(%) | –50(–42%) | –4(9%) |

42%

## Primary endpoint

**RR=0.84(0.70-1.00), p=0.048**



16%

Placebo

Atorvastatin

Cumulative Incidence, % — Time Since Randomization, wk

*Schwartz GG, et al. JAMA 2001;285:1711–8.*

# Atorvastatin 80 mg reduced a mean LDL–C by 34%, the HR for CVD by 11%

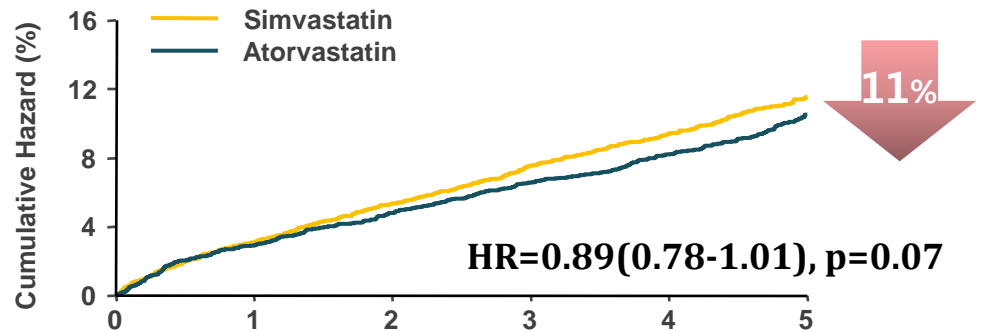**8,888 CHD Patients aged ≤ 80 years with AMI**

→ **Simvastatin 20-40 mg/day**

→ **Atorvastatin 10-80 mg/day**

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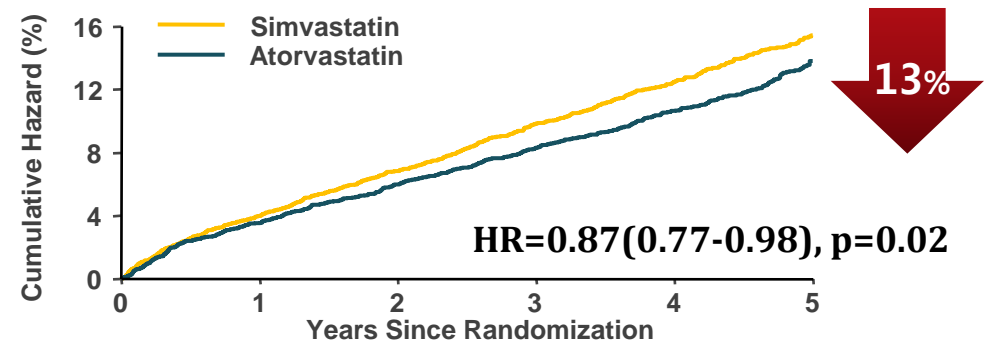- **Mean follow-up = 4.8 years**

## 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



Cumulative Hazard (%) vs Years Since Randomization

Simvastatin, Atorvastatin

**11%**

**HR=0.89(0.78-1.01), p=0.07**

## Secondary endpoint : Major CV events



Cumulative Hazard (%) vs Years Since Randomization

Simvastatin, Atorvastatin

**13%**

**HR=0.87(0.77-0.98), p=0.02**

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

# Atorvastatin 80 mg reduced a mean LDL–C by 42%, the RR for CVD by 16%

**PROVE-IT**

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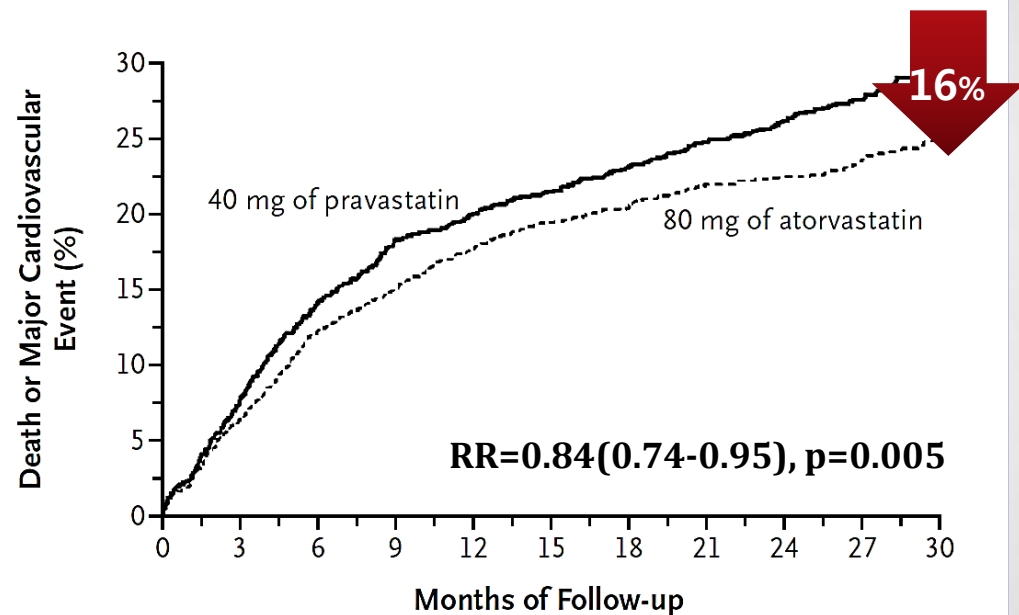**4,162 Patients aged ≥ 18 years with ACS**

→ Pravastatin 40 mg/day

→ Atorvastatin 80 mg/day

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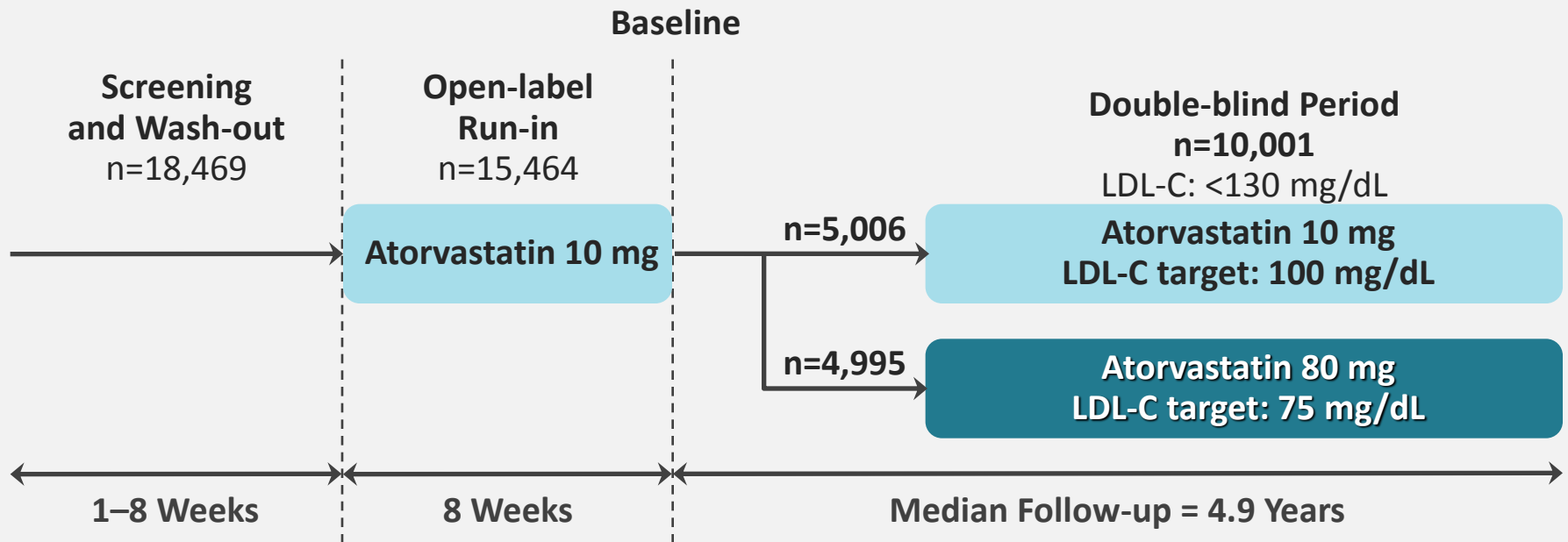- Mean follow-up = 24 months

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## 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



40 mg of pravastatin

80 mg of atorvastatin

RR=0.84(0.74-0.95), p=0.005

Death or Major Cardiovascular Event (%)

Months of Follow-up

**–16%**

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

# Treating to New Targets (TNT) : Decennial Revisit, Value and Considerations for the Next Decade

# TNT: Study Design

**Baseline**

**Screening and Wash-out**
n=18,469

**Open-label Run-in**
n=15,464

**Double-blind Period**
n=10,001
LDL-C: <130 mg/dL

**Atorvastatin 10 mg**

n=5,006 → **Atorvastatin 10 mg**
**LDL-C target: 100 mg/dL**

n=4,995 → **Atorvastatin 80 mg**
**LDL-C target: 75 mg/dL**

**1–8 Weeks**   **8 Weeks**   **Median Follow-up = 4.9 Years**

## Patient Population

- 35-75 yrs with stable CHD
- LDL-C: 130-250 mg/dL
- Triglycerides ≤600 mg/dL

## Primary Efficacy Outcome

- Time to occurrence of a major CV event:
  - CHD death
  - Nonfatal, non–procedure-related MI
  - Resuscitated cardiac arrest
  - Fatal or nonfatal stroke

Ref 1. 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 1. LaRosa JC, et al. N Engl J Med. 2005;352:1425-1435

# TNT: Result

10,001 Patients aged 35 to 75 years with stable CHD
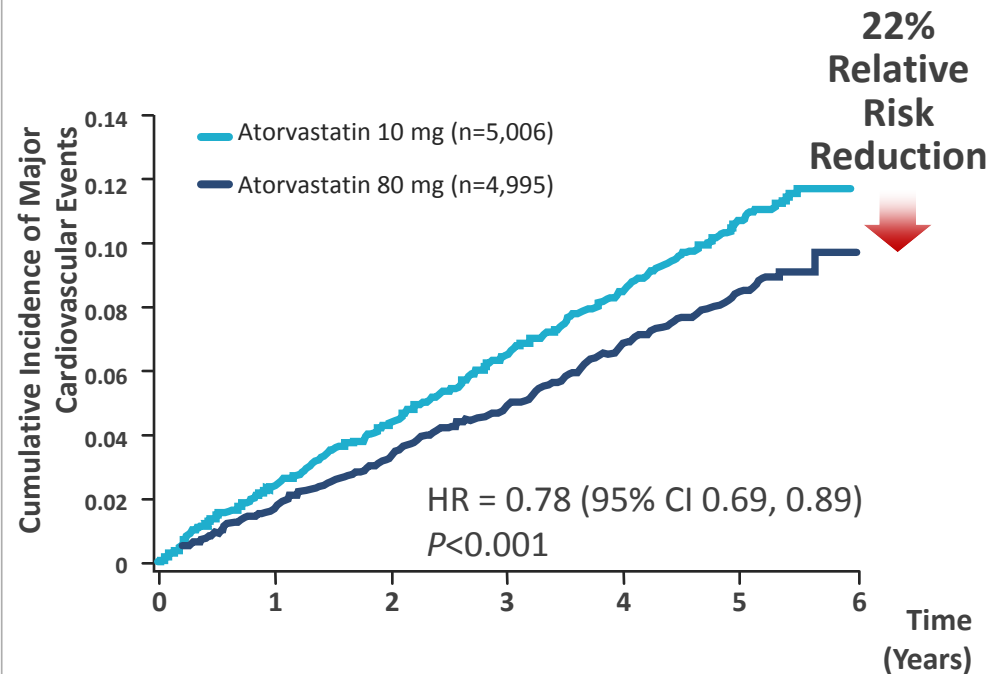
→ Atorvastatin 10 mg/day

→ Atorvastatin 80 mg/day

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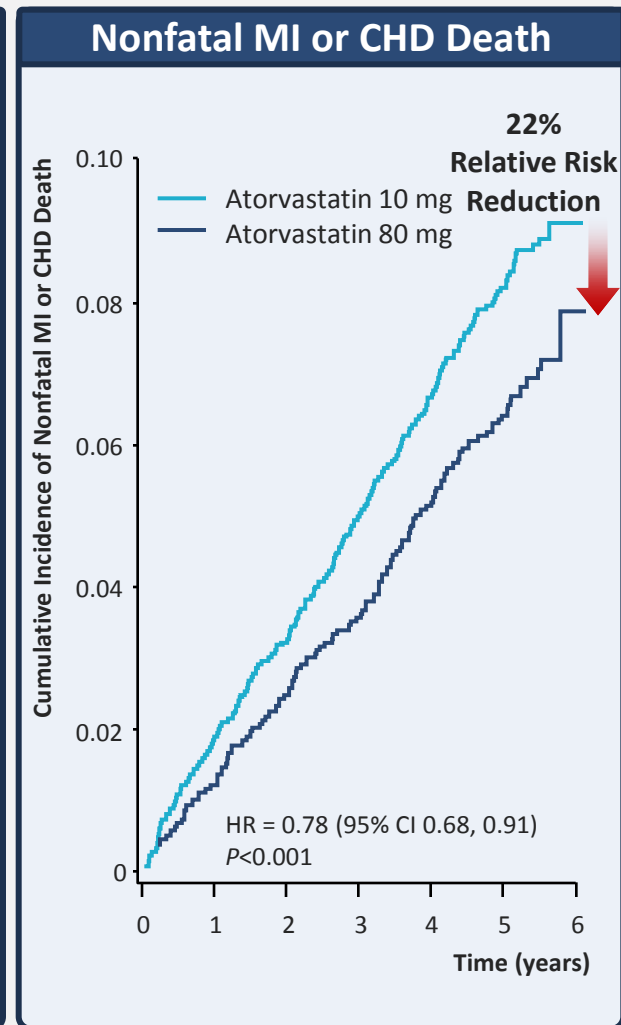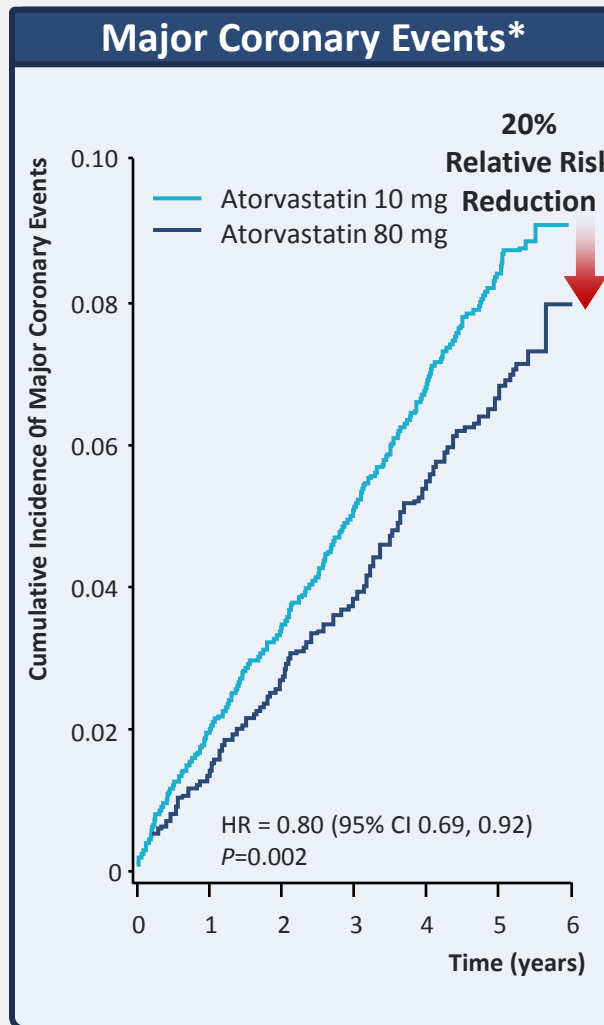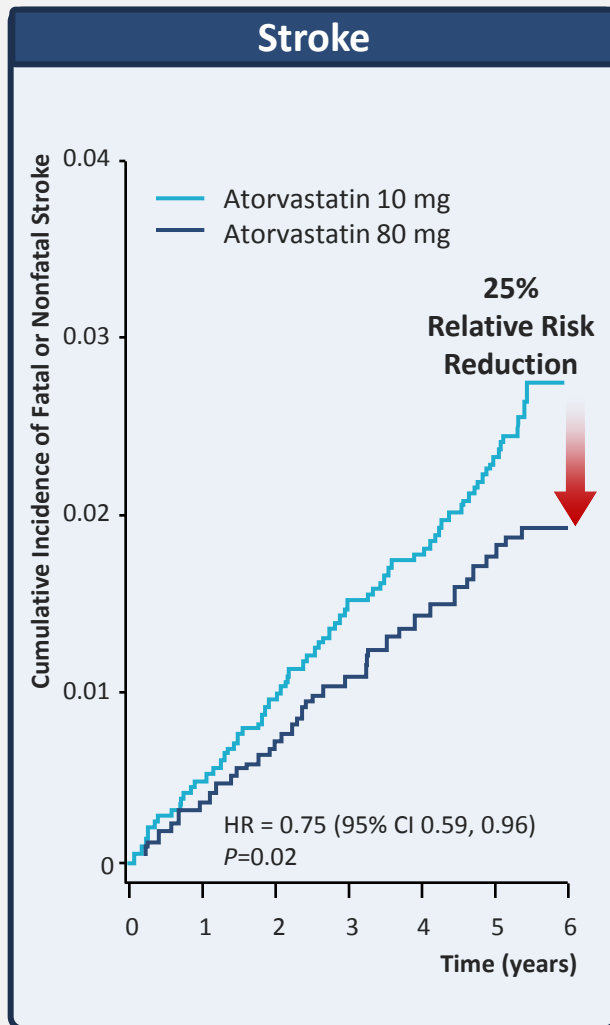- Median follow-up = 4.9 years

## Change of LDL-cholesterol

| | Atorvastatin 80 mg | Atorvastatin 10 mg |
|---|---|---|
| N | 273 | 273 |
| 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(2%) |

21%

## major CV event by baseline diabetes and eGFR status



22% Relative Risk Reduction

- Atorvastatin 10 mg (n=5,006)
- Atorvastatin 80 mg (n=4,995)

HR = 0.78 (95% CI 0.69, 0.89)
$P$<0.001

Cumulative Incidence of Major Cardiovascular Events

Time (Years)

Ref 1. LaRosa JC, et al. N Engl J Med. 2005;352:1425-1435

# TNT: Stroke, Major Coronary Events, Non-Fatal MI/CHD Death



| Stroke | Major Coronary Events* | Nonfatal MI or CHD Death |

Stroke panel:
- Atorvastatin 10 mg
- Atorvastatin 80 mg
- 25% Relative Risk Reduction
- HR = 0.75 (95% CI 0.59, 0.96) P=0.02
- Y-axis: Cumulative Incidence of Fatal or Nonfatal Stroke
- X-axis: Time (years)

Major Coronary Events panel:
- Atorvastatin 10 mg
- Atorvastatin 80 mg
- 20% Relative Risk Reduction
- HR = 0.80 (95% CI 0.69, 0.92) P=0.002
- Y-axis: Cumulative Incidence Of Major Coronary Events
- X-axis: Time (years)

Nonfatal MI or CHD Death panel:
- Atorvastatin 10 mg
- Atorvastatin 80 mg
- 22% Relative Risk Reduction
- HR = 0.78 (95% CI 0.68, 0.91) P<0.001
- Y-axis: Cumulative Incidence of Nonfatal MI or CHD Death
- X-axis: Time (years)

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

Ref 1. LaRosa JC, et al. N Engl J Med. 2005;352:1425-1435

# TNT : Evaluation of individual components of outcome

| Primary Efficacy Measure | HR | P Value |
|---|---|---|
| **Major CV Event** | **0.78** | **<0.001** |
| – CHD death | 0.80 | 0.09 |
| – Nonfatal, non-PR MI | 0.78 | 0.004 |
| – Resuscitated cardiac arrest | 0.96 | 0.89 |
| – Fatal/nonfatal stroke | 0.75 | 0.02 |

| Secondary Efficacy Measures | | |
|---|---|---|
| Any cardiovascular event | 0.81 | <0.001 |
| – Major coronary event* | 0.80 | 0.002 |
| – Any coronary event | 0.79 | <0.001 |
| – Cerebrovascular event | 0.77 | 0.007 |
| – Hospitalization for CHF | 0.74 | 0.01 |
| – Peripheral arterial disease | 0.97 | 0.76 |

0.5   1   1.5

**Atorvastatin 80 mg Better**          **Atorvastatin 10 mg Better**

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

Ref 1. LaRosa JC, et al. N Engl J Med. 2005;352:1425-1435

# TNT: Safety

| | 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) |
| Hemorrhagic stroke | 16 | 17 |
| 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 1. LaRosa JC, et al. N Engl J Med. 2005;352:1425-1435

# LDL-C and Event Rates
# in Secondary Prevention Studies



S = statin treated
P = placebo treated

**LDL-C, mg/dL (mmol/L)**

Ref 1. LaRosa JC, et al. N Engl J Med. 2005;352:1425-1435
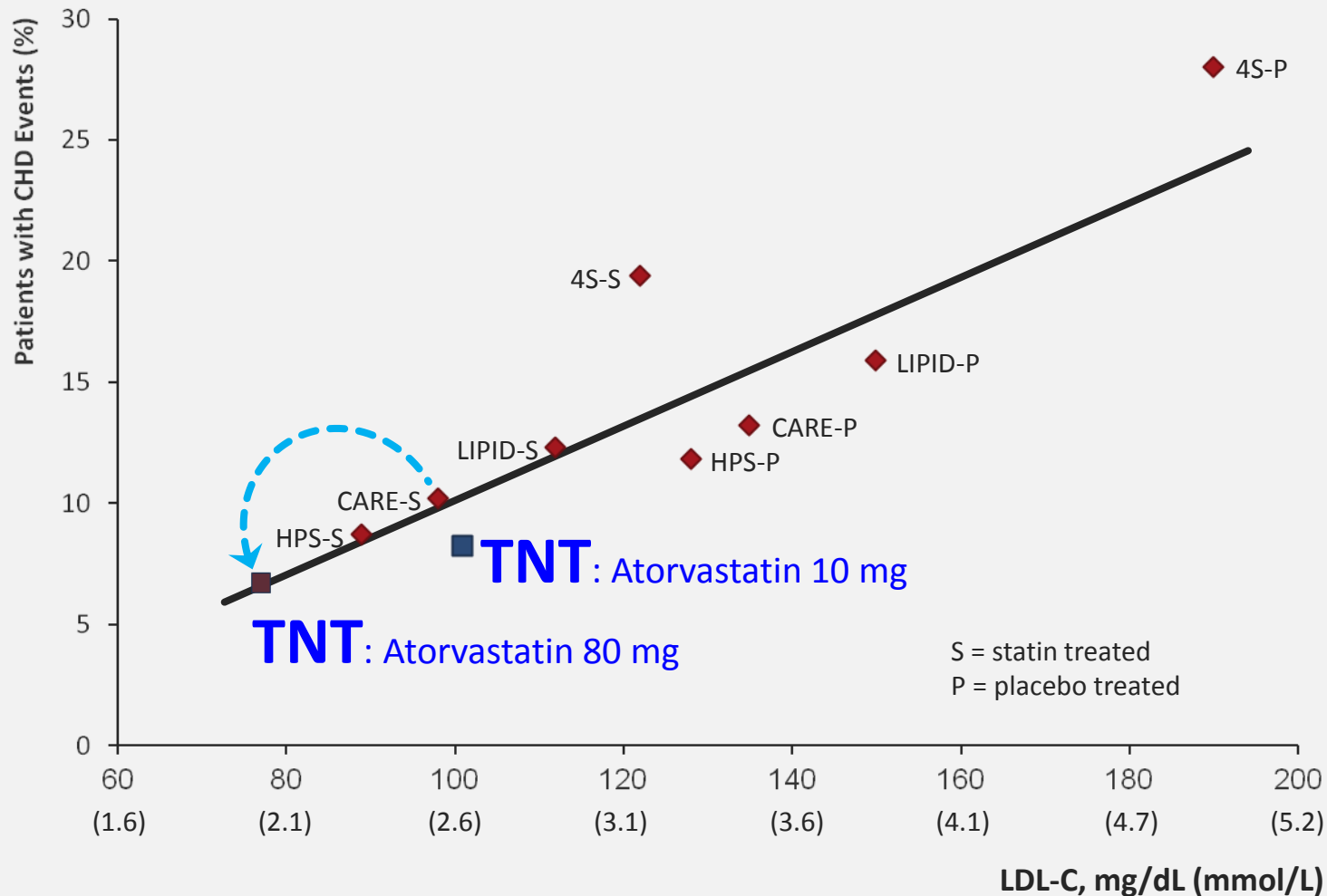
# Evidence in 2013 ACC/AHA guideline update
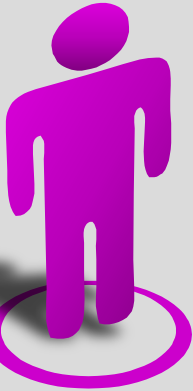
Yes →

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

**Clinical ASCVD**

| 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 treatme**nt 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)<br><br>**Lower LDL-C reduction, no benefit :** A-Z(119), ACCORD(14)<br><br>**No difference in LDL-C between groups :** (SEARCH (128) not included in CQ1) |

# High- Moderate- and Low-Intensity Statin Therapy

| High-Intensity Statin Therapy | Moderate-Intensity Statin Therapy | Low-Intensity Statin Therapy |
|---|---|---|
| Daily dose lowers LDL–C on average, by approximately ≥50% | Daily dose lowers LDL–C on average, by approximately 30% to <50% | Daily dose lowers LDL–C on average, by <30% |
| **Atorvastatin (40†)–80 mg** <br> **Rosuvastatin 20 (40) mg** | **Atorvastatin 10 (20) mg** <br> **Rosuvastatin (5) 10 mg** <br> **Simvastatin 20–40 mg‡** <br> **Pravastatin 40 (80) mg** <br> **Lovastatin 40 mg** <br> *Fluvastatin XL 80 mg* <br> **Fluvastatin 40 mg bid** <br> *Pitavastatin 2–4 mg* | *Simvastatin 10 mg* <br> **Pravastatin 10–20 mg** <br> **Lovastatin 20 mg** <br> *Fluvastatin 20–40 mg* <br> *Pitavastatin 1 mg* |

# NICE guideline: Secondary prevention

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

  - potential drug interactions

  - high risk of adverse effects

  - patient preference. **[new 2014]**

For information about implementing this recommendation, see Implementation: getting started.

1.3.21   Do not delay statin treatment in secondary prevention to manage modifiable
         risk factors. **[2014]**

1.3.22   If a person has acute coronary syndrome, do not delay statin treatment. Take a
         lipid sample on admission and about 3 months after the start of treatment.
         **[2008, amended 2014]**

# ESC/EAS guideline, 2011

| Risk Category | LDL-C Goal (mg/dL) |
|---|---|
| **Very high**<br>**established CVD**, **type 2 diabetes**, type 1 diabetes with target organ damage, moderate to severe CKD or a SCORE level ≥ 10% | **< 70**<br>and/or<br>**≥ 50% reduction**<br>(when target level cannot be reached) |
| **High**<br>markedly elevated single risk factors, SCORE level 5%~10% | <100 |
| **Moderately high**<br>SCORE level 1%~5% | <115 |

*Zeljko Reiner et al. European Heart Journal 2011;32:1769-1818*

# Various Post-hoc-Analysis



*Mets, metabolic syndrome;

# TNT sub-analysis



TNT-
Women
(N=1,902)
2008

TNT-
Cerebrovascular disease
2006

TNT-
DM (N=1,501)
2006

TNT Sub
analysis

TNT-
Hospitalization
for HF
2007

TNT trial
2005

TNT-
CKD (N=3,107)
2008

TNT
Subgroup
analysis

TNT-
Renal function
2007

TNT-
DM&CKD
(N=546)
2008

TNT-
Mets* (N=5,584)
2006

TNT-
after CABG
(N=4,654)
2008

*Mets, metabolic syndrome;
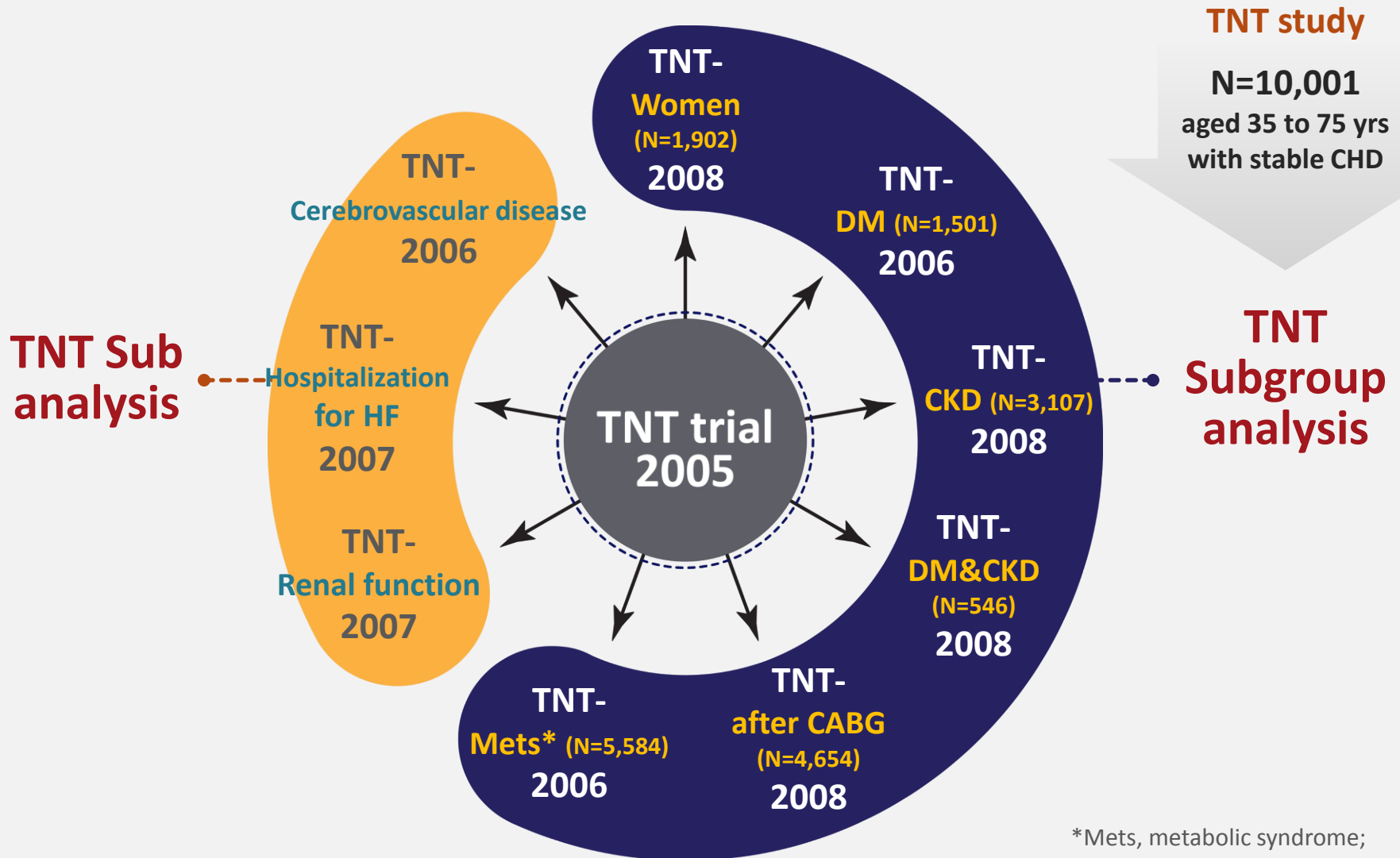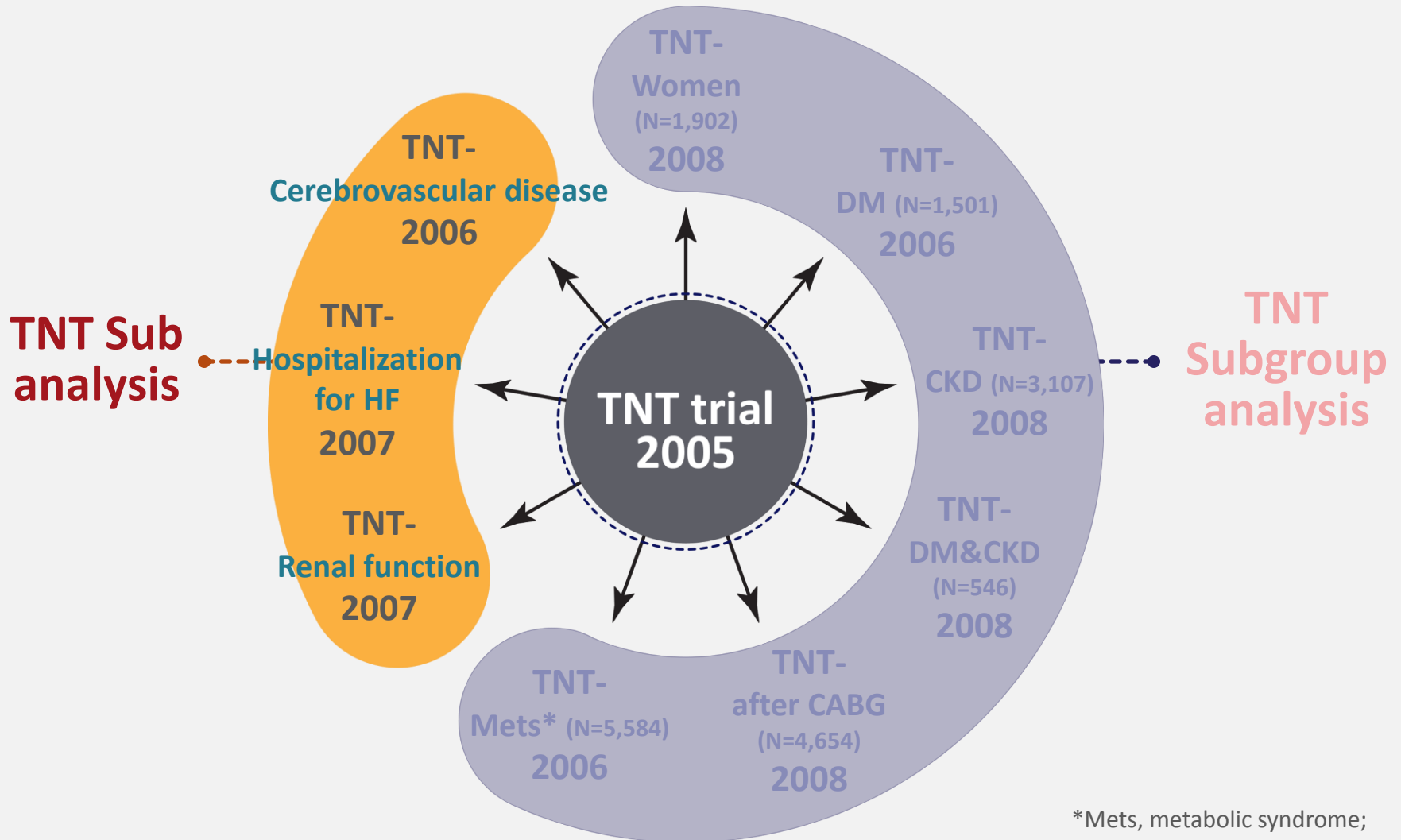
# Intensive Atorvastatin on cerebrovascular events in CHD patients
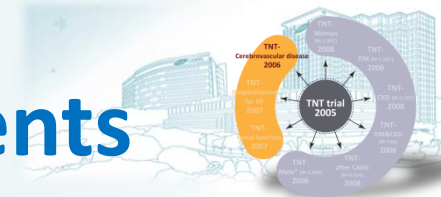
## Kaplan-Meier curves for cerebrovascular events

Hazard ratio = 0.77 (95% CI 0.64, 0.93)
$P = 0.007$

······· Atorvastatin 10 mg
——— Atorvastatin 80 mg

23%

**LDL-C 1 mg/dL ↓, RRR of Cerebrovascular events 0.6% ↓**

Patients with major cardiovascular event (%)

Time (years)
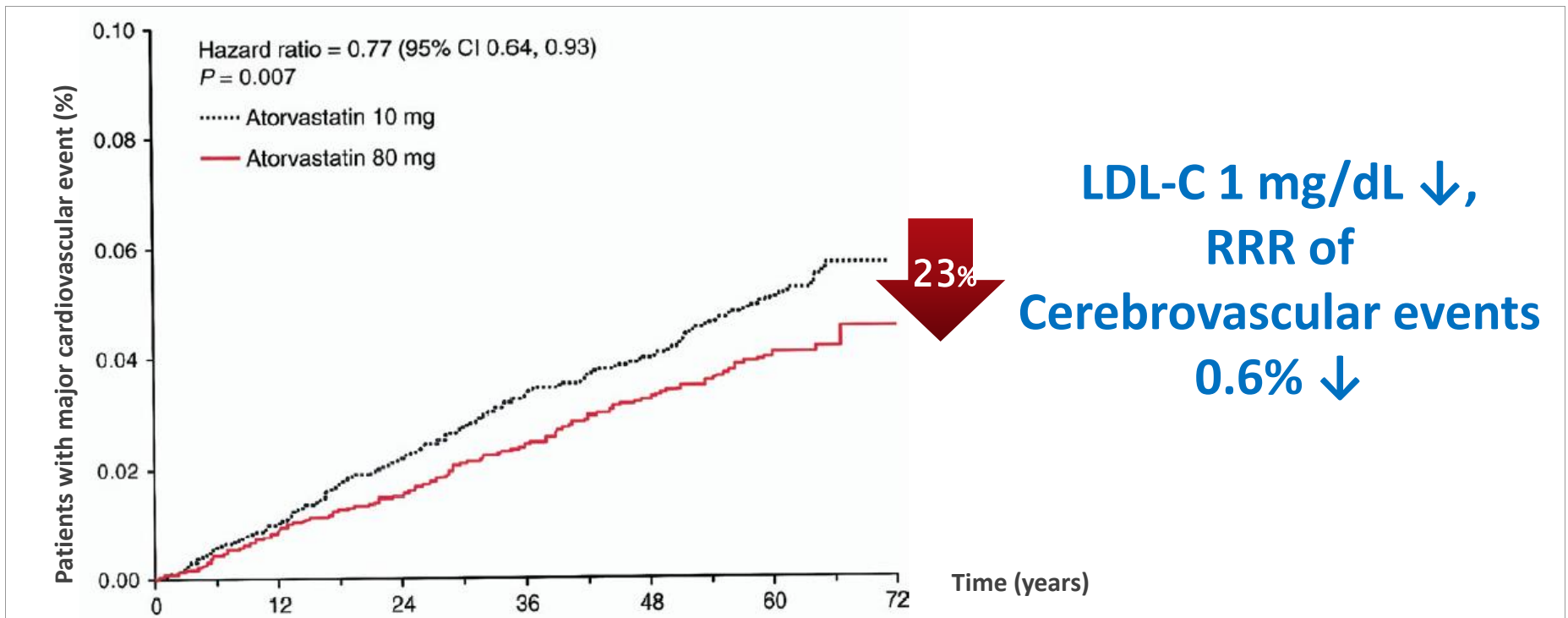
## Types of Stroke in Treatment Groups

|  | Atorvastatin 10 mg/day (n = 5,006) | Atorvastatin 80 mg/day (n = 4,995) | Total Patients (n = 10,001) |
|---|---|---|---|
| Fatal and nonfatal stroke | 155 (3.1%) | 117 (2.3%) | 272 (2.7%) |
| Embolic | 44 (0.9%) | 29 (0.6%) | 73 (0.7%) |
| Ischemic | 90 (1.8%) | 68 (1.4%) | 158 (1.6%) |
| Hemorrhagic | 18 (0.4%) | 16 (0.3%) | 34 (0.3%) |
| Unknown | 15 (0.3%) | 11 (0.2%) | 26 (0.3%) |

**No increase risk of hemorrhagic stroke**

Ref 5. Waters DD, et al. J Am Coll Cardiol 2006;48:1793–9.

# Intensive Atorvastatin on hospitalization for HF in CHD patients

**10,001 Patients
aged 35 to 75 years
with stable CHD
Patient With HF : 781(7.8%)**

**Atorvastatin 10 mg/day**

**Atorvastatin 80 mg/day**

• **Primary endpoint : major CV event***

• **Median follow-up = 4.9 years**

\* A known ejection fraction 30% and advanced HF were exclusion criteria for the study.

## Proportion of patients of TNT hospitalized for HF



Hazard ratio = 0.74 (95% CI 0.59, 0.94)
$P = 0.012$

······· Atorvastatin 10 mg
——— Atorvastatin 80 mg

**26%**

Number at risk:

| | 0 | 12 | 24 | 36 | 48 | 60 | 72 |
|---|---|---|---|---|---|---|---|
| Atv 10 mg | 5006 | 4972 | 4928 | 4877 | 4840 | 4791 | 4746 | 4692 | 4645 | 4566 | 2451 | 514 | 0 |
| Atv 80 mg | 4995 | 4969 | 4937 | 4895 | 4861 | 4825 | 4778 | 4735 | 4687 | 4611 | 2453 | 483 | 0 |
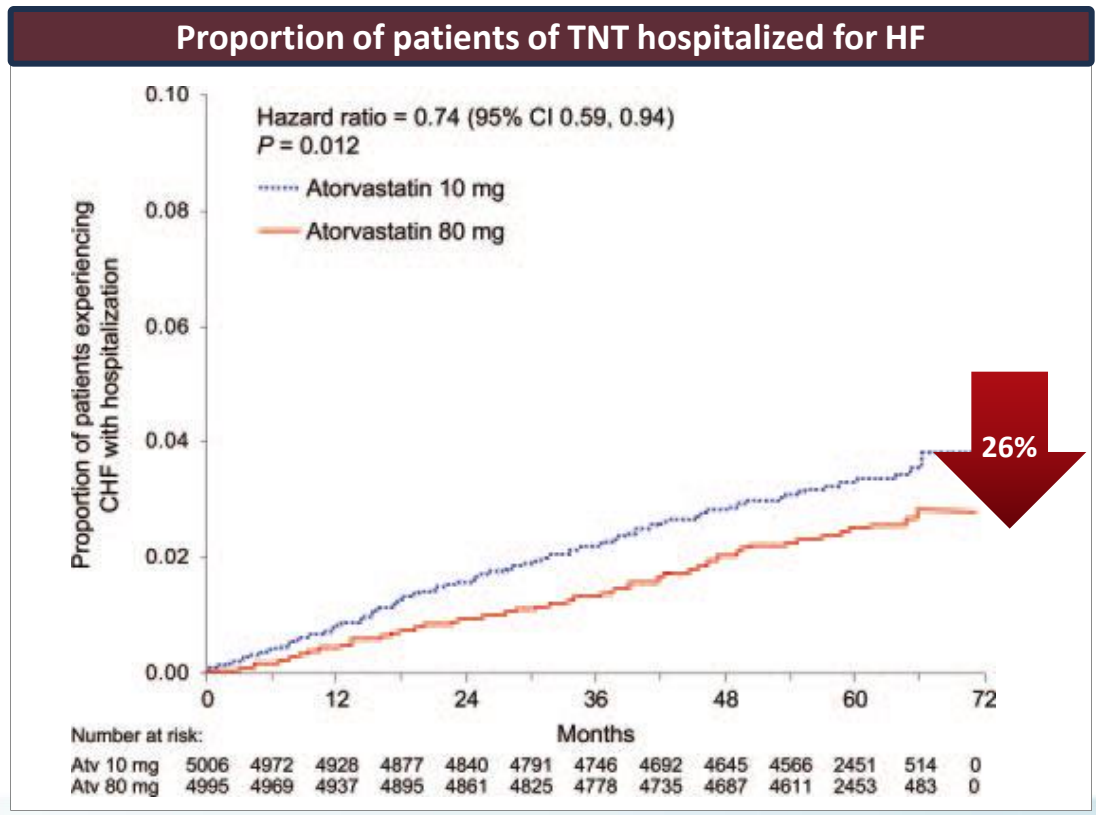
**Most important Predictor
of hospitalization for HF
is History of HF**

**HR (95% CI), Multivariate
5.71 (4.43–7.36), P< 0.0001**

Ref 6. Khush KK, et al. Circulation. 2007;115:576-583.

# Intensive Atorvastatin on hospitalization with HF in CHD patients with HF

**Proportion of patients with and without a history of HF experiencing hospitalization**



**ATV 10 mg + HF**

**41%**

**ATV 80 mg +HF**
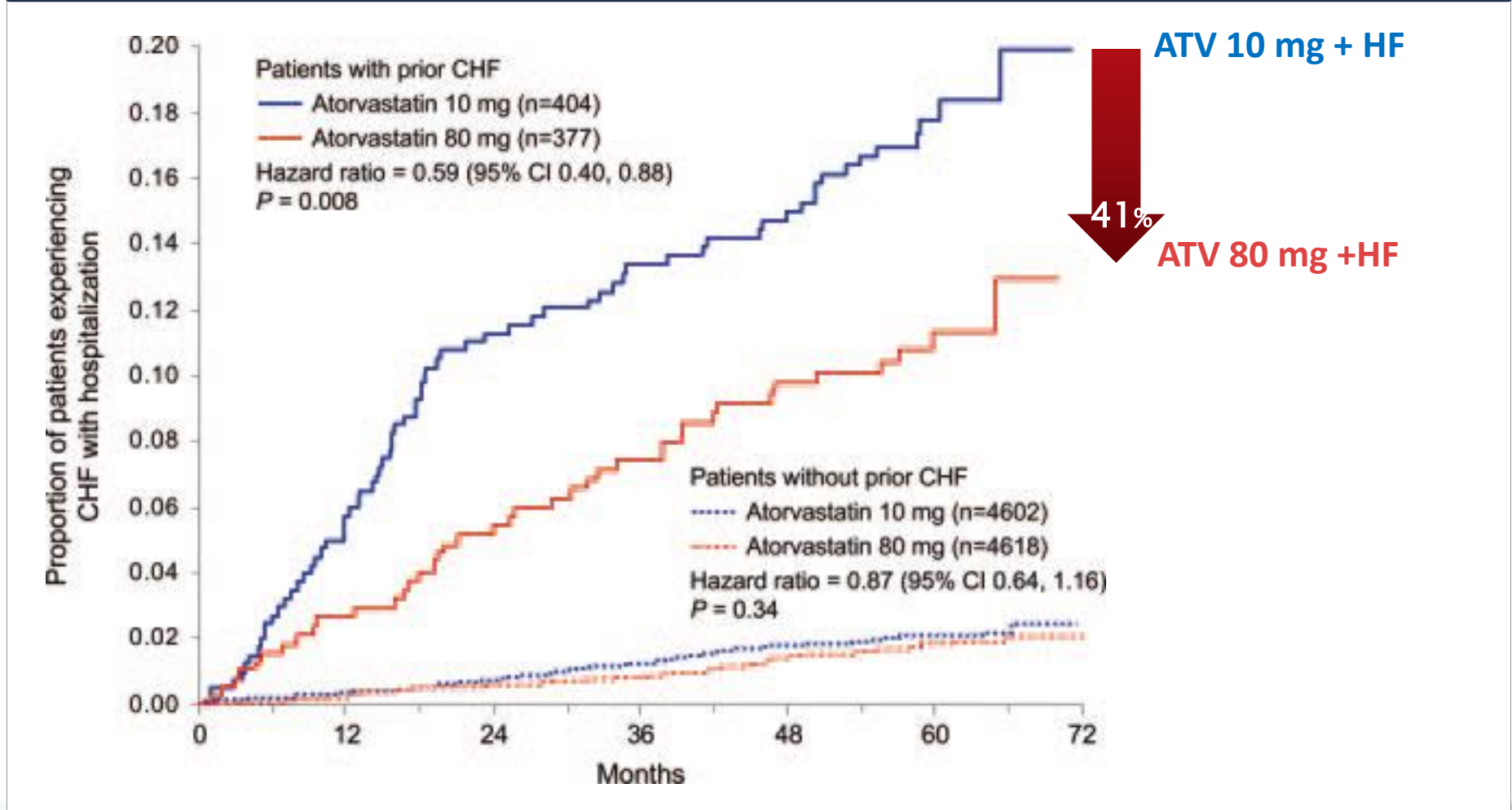
Ref 6. Khush KK, et al. Circulation. 2007;115:576-583.

# Intensive Atorvastatin on Renal Function in CHD patient
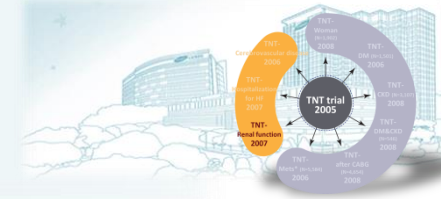
## LS mean change from baseline eGFR



**ATV 80 mg + CKD**

**5.2**

P<0.0001

**3.5**
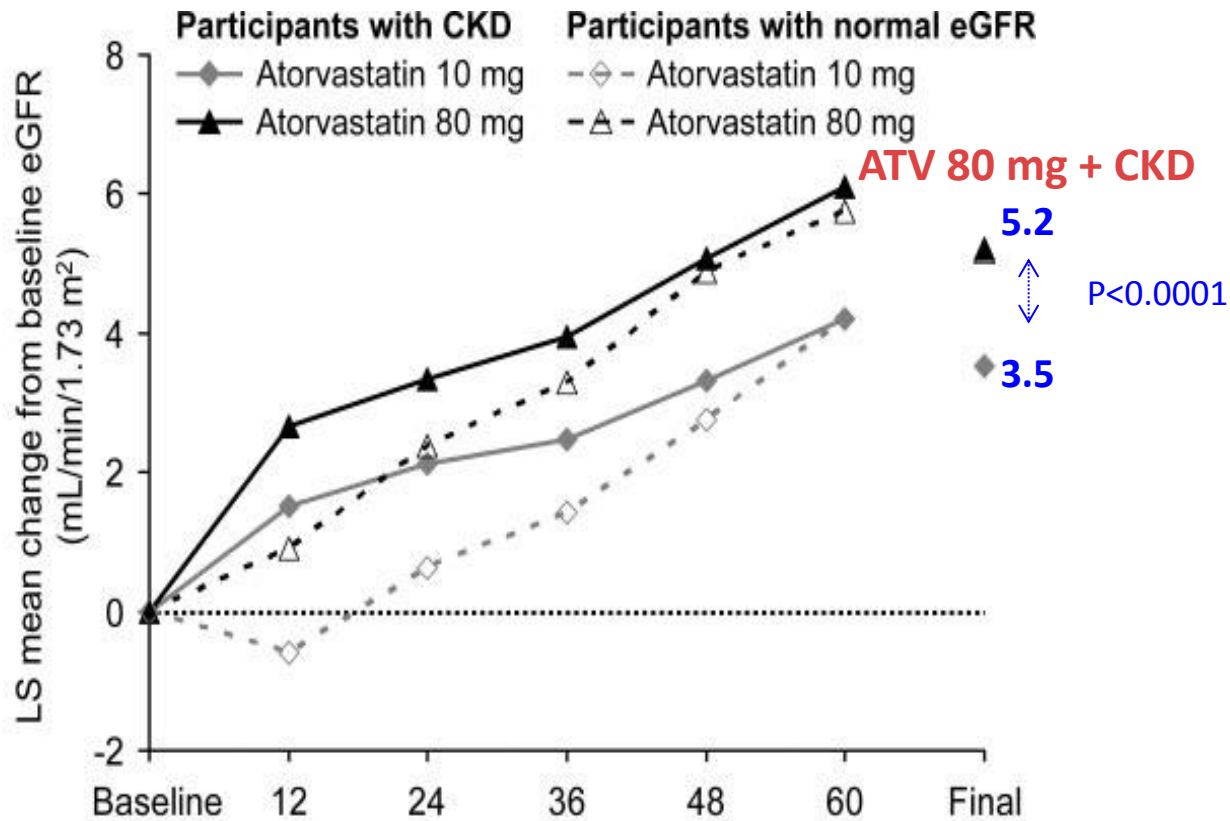
- No occurrences of hematuria or proteinuria were reported as a serious adverse event in either treatment group.

Ref 7. Shepherd J et al. Clin J Am Soc Nephrol 2007:2: 1131–1139

# TNT subgroup-analysis



TNT Sub analysis

TNT-Cerebrovascular disease 2006

TNT-Hospitalization for HF 2007

TNT-Renal function 2007

TNT-Women (N=1,902) 2008

TNT-DM (N=1,501) 2006

TNT trial 2005

TNT-CKD (N=3,107) 2008

TNT-DM&CKD (N=546) 2008

TNT-Mets* (N=5,584) 2006

TNT-after CABG (N=4,654) 2008

TNT study

N=10,001 aged 35 to 75 yrs with stable CHD

TNT Subgroup analysis

*Mets, metabolic syndrome;

# Under-representation of women
# in many major cardiovascular trials

**Of 628 Cardiovascular studies,
only 153(24%) provides sex-specific result.**

(Blauwet LA, et al. Mayo Clin Proc. 2007;82:166-170)

**Reviews and meta-analyses have shown improved outcomes with statins
in both women and men without significant interaction by sex**

**However,
they did not show statistically significant effects in women.**

(Kostis WJ, et al. J Am Coll Cardiol 2012;59:572–82.)

Ref 8. Blauwet LA, et al. Mayo Clin Proc. 2007;82:166-170. 9. Kostis WJ, et al. J Am Coll Cardiol 2012;59:572–82.

# Intensive Atorvastatin
# Women with CHD

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

**Women N=1,902** → **Atorvastatin 10 mg, N=961**
→ **Atorvastatin 80 mg, N=941**

**Men N=8,099** → **Atorvastatin 10 mg, N=4,045**
→ **Atorvastatin 80 mg, N=4,054**

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**Cumulative incidence of a MACE* among Women**

HR = 0.73 (95% CI 0.54, 1.00)
p = 0.049

**27% RRR**

Atorvastatin 10 mg

Atorvastatin 80 mg

0.2
0.1
0  1  2  3  4  5  6
Years

**Cumulative incidence of a MACE* among Men**

HR = 0.79 (95% CI 0.69, 0.91)
p = 0.001

**21% RRR**

Atorvastatin 10 mg

Atorvastatin 80 mg

0.2
0.1
0  1  2  3  4  5  6
Years

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

Ref 10. Wenger NK, et al. Heart 2008;94:434–439.

# Intensive Atorvastatin
# 2013 ACC/AHA guideline update

| Evidence statement 12 | | | |
|---|---|---|---|
| In trials of more intensive statin therapy (atorvastatin 80 mg, simvastatin 80 mg) compared with less intensive statin therapy (atorvastatin 10 mg, pravastatin 40 mg, or simvastatin 20-40 mg), **women with CHD** or acute coronary syndromes **experienced a similar (approximately 25%) magnitude of relative CVD reduction as men (approximately 29%).** Women also experienced a similar magnitude of absolutely risk reduction as men. | H | Secondary Prevention (women included) | CTT 2010(20) - 5 trials<br><br>TNT(46)<br>IDEAL(47)<br>PROVE-IT(48)<br>A-Z(119)<br>SEARCH(128) (not included in CQ1) |

In trials of more intensive statin therapy (atorvastatin 80 mg) compared with less intensive statin therapy (atorvastatin 10 mg) **women with CHD** experienced a similar magnitude of relative CVD reduction as men.

**TNT**

# Intensive Atorvastatin
## CHD patients with DM

| 10,001 Patients aged 35 to 75 years with stable CHD | → | 1,501 Patients aged 35 to 75 years with CHD, DM | → | Atorvastatin 10 mg/day |
| | | | | Atorvastatin 80 mg/day |
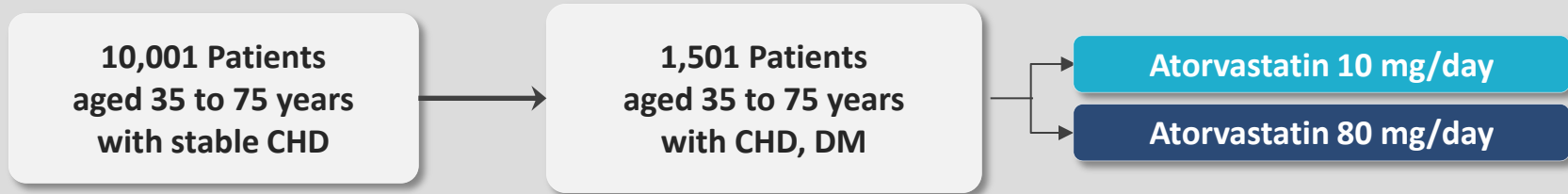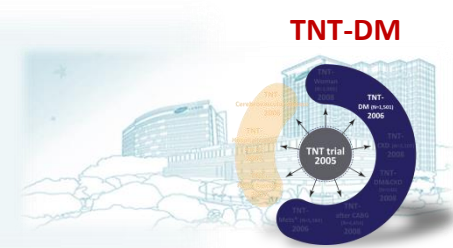
## Change of LDL-cholesterol

|  | Atorvastatin 80 mg | Atorvastatin 10 mg |
|---|---|---|
| N | 748 | 753 |
| Baseline median, mg/dl | 95.6±18.4 | 96.7±17.8 |
| End of follow-up mean, mg/dl | 77.0 | 98.6 |
| LDL-C difference (mg/dL)(%) | −18(19%) | 1.9(3%) |

**19%**

## Primary endpoint : major CV event

**HR=0.75 (0.58-0.97), p=0.026**



HR = 0.75 (95% CI 0.58, 0.97)
$P$ = 0.026

— Atorvastatin 10 mg
........ Atorvastatin 80 mg

Major Cardiovascular Event (%)

Years

**25%**

Ref 11. SHEPHERD J, et al. Diabetes Care. 2006;29:1220 −1226.
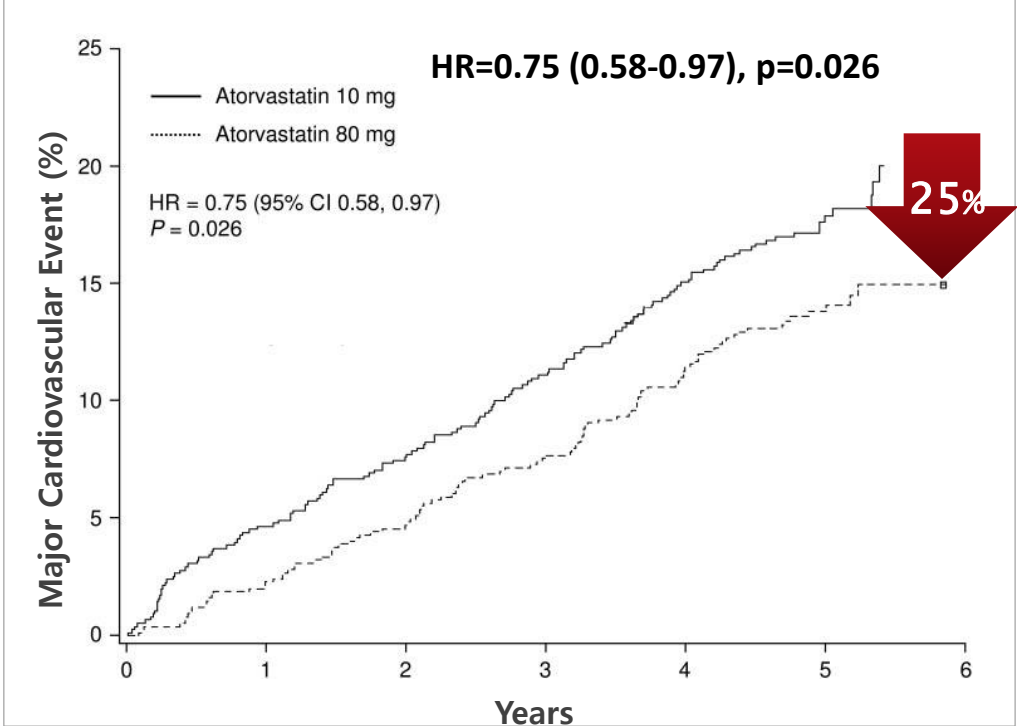
# Intensive Atorvastatin
# ADA guideline update
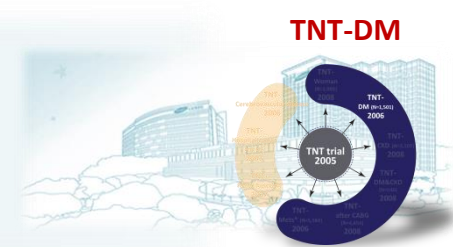
## 2015 ADA guideline - Dyslipidemia/lipid management

*Recommendations*

**For patients of all ages with diabetes and overt CVD, high-intensity statin therapy should be added to lifestyle therapy. A**

(29,30). <u>Subgroup analyses of diabetic patients in larger trials</u> (31–35) and trials in patients with diabetes (36,37) showed significant primary and secondary prevention of CVD events +/− CHD deaths in patients with diabetes. Meta-

# Intensive Atorvastatin
# CHD patients with CKD

| Screening and statin washout | Open-label run-in | Double-blind treatment period ($n = 9656*$) |
|---|---|---|
| | | Baseline |

**10,001 Patients aged 35 to 75 yrs with stable CHD**

**Atorvastatin 10 mg/day ($n = 4829$)**
- 1505 with CKD at baseline (eGFR < 60 mL/min per 1.73 m$^2$)
- 3324 with normal eGFR at baseline[†] (eGFR ≥ 60 mL/min per 1.73 m$^2$)

**Atorvastatin 80 mg/day ($n = 4827$)**
- 1602 with CKD at baseline (eGFR < 60 mL/min per 1.73 m$^2$)
- 3225 with normal eGFR at baseline[†] (eGFR ≥ 60 mL/min per 1.73 m$^2$)

| 1-8 weeks | 8 weeks | Up to 6 years |
|---|---|---|

[†]Included patients with mild (Stage 2) renal impairment.
*Included only patients with complete renal data (baseline and follow-up assessments of eGFR).

Ref 14. Shepherd J, et al. Clin J Am Soc Nephrol. 2007;2:1131-1139.

# Intensive Atorvastatin
# CHD patients with CKD
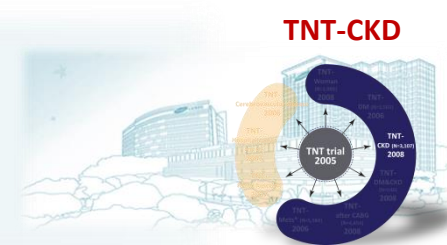
### Time to First Major CV Event by Treatment in Patients With CKD and With Normal eGFR at Baseline



**Patients With CKD at Baseline**
······· Atorvastatin 10 mg
——— Atorvastatin 80 mg

HR=0.68 (95% CI 0.55, 0.84)
$P$=0.0003, ARR=4.1%, NNT=24

**Patients With Normal eGFR at Baseline**
▪▪▪▪▪ Atorvastatin 10 mg
——— Atorvastatin 80 mg

HR=0.85 (95% CI 0.72,1.00)
$P$=0.049, ARR=1.4%, NNT=74

**ATV 10 mg + CKD**

**32%**

**ATV 80 mg + CKD**
**ATV 10 mg - normal eGFR**
**ATV 80 mg - normal eGFR**

Ref 14. Shepherd J, et al. Clin J Am Soc Nephrol. 2007;2:1131-1139.
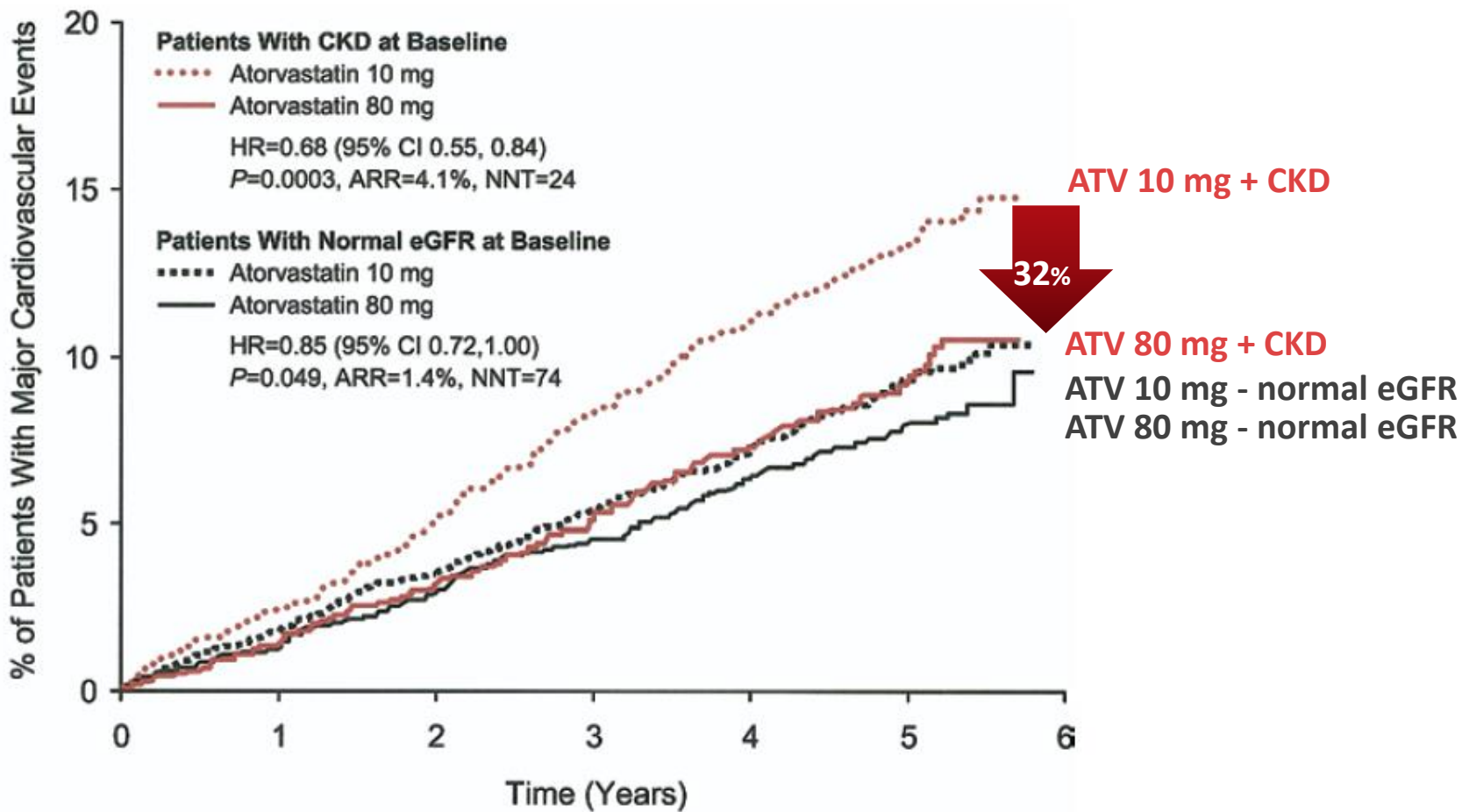
# Evidence in 2013 KDIGO guideline

**KDIGO,** kidney disease improving global outcomes

## Pharmacological cholesterol-lowering treatment
### *Recommendations*

- **In adults aged ≥50 years with CKD and eGFR ≥ 60 ml/min/1.73m2 (GFR categories G1-G2) we recommend treatment with a statin. (1B)**

- **In adults aged 18–49 years with CKD but not treated with chronic dialysis or kidney transplantation, we suggest statin treatment in people with one or more of the following (2A):**
  - **known coronary disease**
  - **diabetes mellitus**
  - **prior ischemic stroke**
  - **estimated 10-year incidence of coronary death or non-fatal MI> 10%**

Subgroup analysis of the TNT trial reported that atorvastatin 80 mg/day reduced major cardiovascular events to a greater extent than atorvastatin 10 mg/day, in 3107 patients with CKD defined by eGFR $<60$ ml/min/1.73 m$^2$ and pre-existing coronary artery disease (HR 0.68; 95% CI 0.55–0.84).[32] Serious adverse events and treatment discontinuation were increased in the high dose statin group for both people with and without CKD; the RRs of these adverse events were numerically higher in people with CKD as compared to those without, but no significance testing was performed. However, TNT participants were pretreated with 10 mg of atorvastatin during the run-in phase, and therefore were preselected for atorvastatin tolerance. In addition, the mean eGFR among TNT participants with CKD was approximately 53 ml/min/1.73 m$^2$, and patients with heavy proteinuria were excluded. Therefore, whether these findings apply to the broader population of people with CKD is uncertain.

# Intensive Atorvastatin in CHD patients with T2DM,CKD

| 10,001 Patients aged 35 to 75 years with stable CHD | → | 1,431 Patients aged 35 to 75 years with DM |
|---|---|---|

**N=546** with DM, CKD → Atorvastatin 10 mg / Atorvastatin 80 mg

**N=885** with DM, no CKD → Atorvastatin 10 mg / Atorvastatin 80 mg
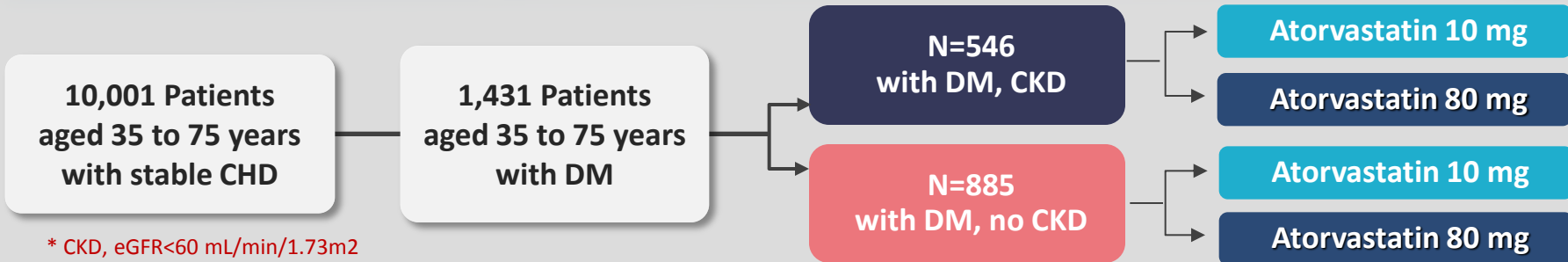
\* CKD, eGFR<60 mL/min/1.73m2

## Change of LDL-cholesterol

|  | Atorvastatin 80 mg | Atorvastatin 10 mg |
|---|---|---|
| N | 273 | 273 |
| Baseline median, mg/dl | 95.5±17.9 | 97.0±17.9 |
| End of follow-up mean, mg/dl | 74.9 | 98.8 |
| LDL-C difference (mg/dL)(%) | −20.6(22%) | 1.8(2%) |

**22%**

## major CV event by baseline diabetes and eGFR status



Patients with major cardiovascular event (%)

Patients with diabetes
— CKD
— Normal eGFR

Patients without diabetes
···· CKD
···· Normal eGFR

Event rates[a]

DM & CKD — 17.4%
DM & no CKD — 13.4%
no DM & CKD — 10.0%
no DM & no CKD — 7.8%

Ref 16. SHEPHERD J, et al. Mayo Clin Proc. 2008;83(8):870-879.
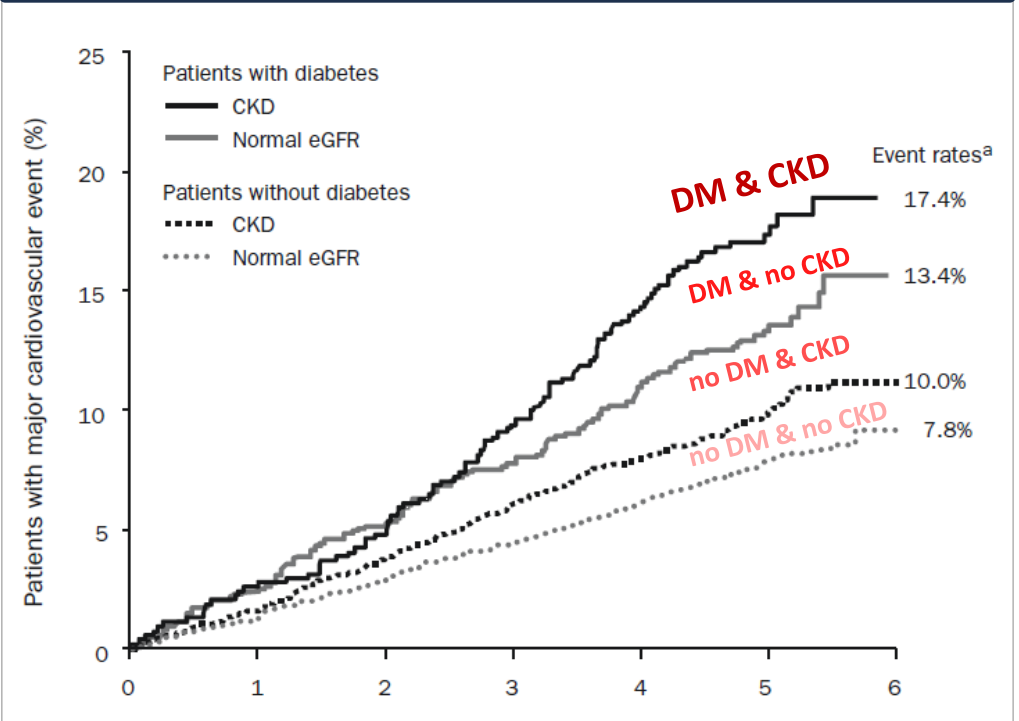
# Intensive Atorvastatin in
# CHD patients with DM,CKD

**Time to first major cardiovascular event in patients with diabetes by treatment and baseline CKD status.**



Patients with diabetes and CKD
— Atorvastatin 10 mg/d
— Atorvastatin 80 mg/d
**HR=0.65 (0.43-0.98), p=0.04**
Patients with diabetes and normal eGFR
······· Atorvastatin 10 mg/d
▪▪▪▪▪▪ Atorvastatin 80 mg/d
HR=0.90 (0.63-1.29), p=0.56

**ATV 10 mg + DM, CKD**

**35%** ATV 10 mg - normal eGFR

**ATV 80 mg + DM, CKD**

ATV 80 mg - normal eGFR

Ref 16. SHEPHERD J, et al. Mayo Clin Proc. 2008;83(8):870-879.
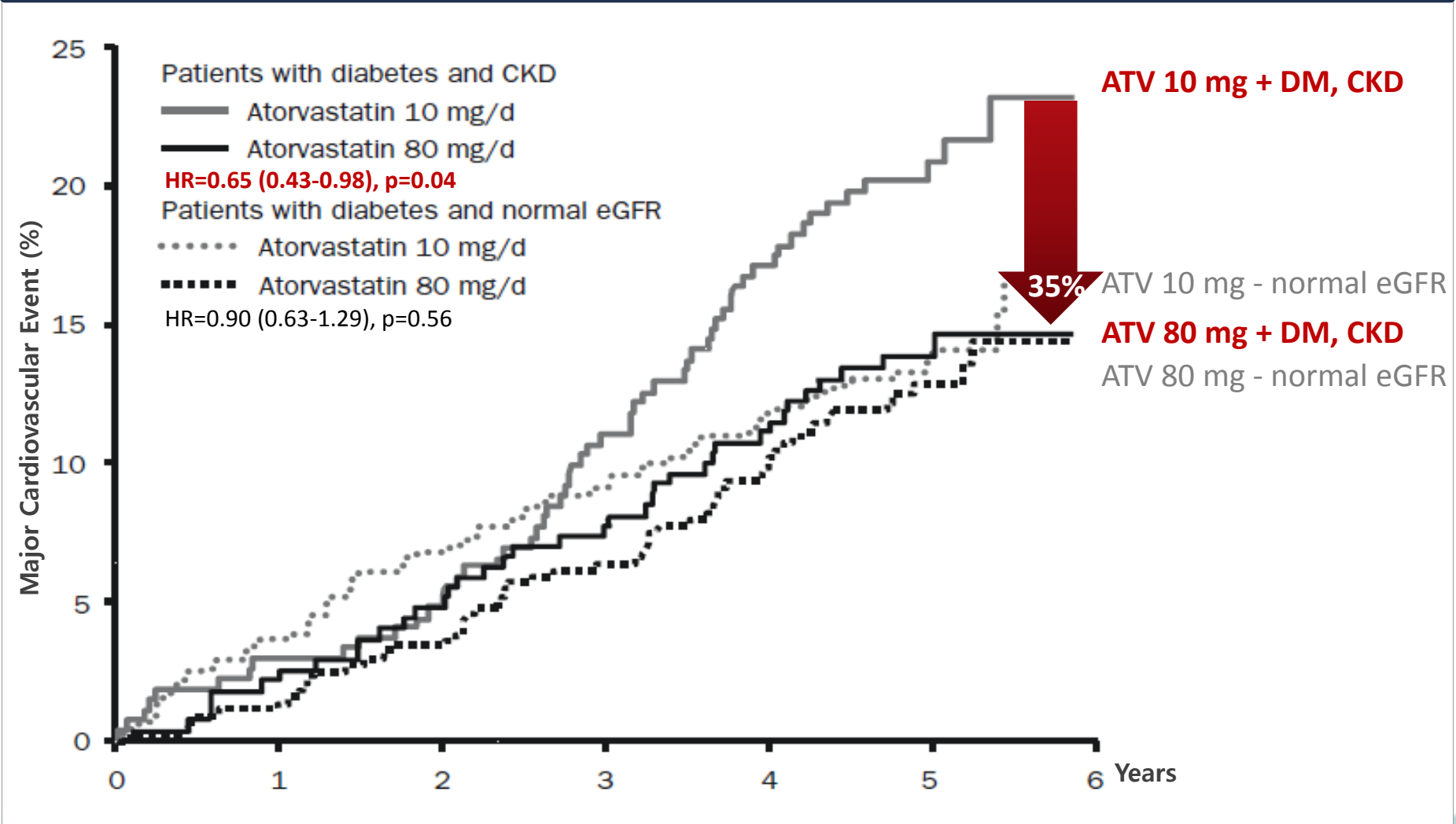
# Evidence in 2012 KDOQI guideline

**KDOQI,** Kidney Disease Outcomes Quality Initiative

## Management of Dyslipidemia in Diabetes and CKD

*Recommendations*

- **We recommend using LDL-C lowering medicines, such as statins** or statin/ezetimibe combination, to reduce risk of major atherosclerotic events **in patients with diabetes and CKD,** including those who have received a kidney transplant. **(1B)**

Higher doses of statins may be beneficial in some patients with diabetes and mild-to-moderate CKD (stages 1-3). The Treating to New Targets trial (TNT)[88] reported a benefit for secondary prevention of major cardiovascular events from treatment with atorvastatin, 80 mg/day compared with atorvastatin, 10 mg/day, in 546 patients with diabetes and CKD and pre-existing coronary artery disease over 5 years of follow-up. The risk of stroke was 4.8% (13/273) for the higher dose, compared with 7.3% (20/271) for the lower dose. There was no reduction in all-cause mortality.

*NKF KDOQI, The National Kidney Foundation Kidney Disease Outcomes Quality Initiative

# Intensive Atorvastatin in
# patients after CABG surgery

| 10,001 Patients aged 35 to 75 years with stable CHD | → | 4,654 Patients aged 35 to 75 years with CHD, previous CABG |

**N=2,338 Atorvastatin 10 mg/day**

**N=2,316 Atorvastatin 80 mg/day**
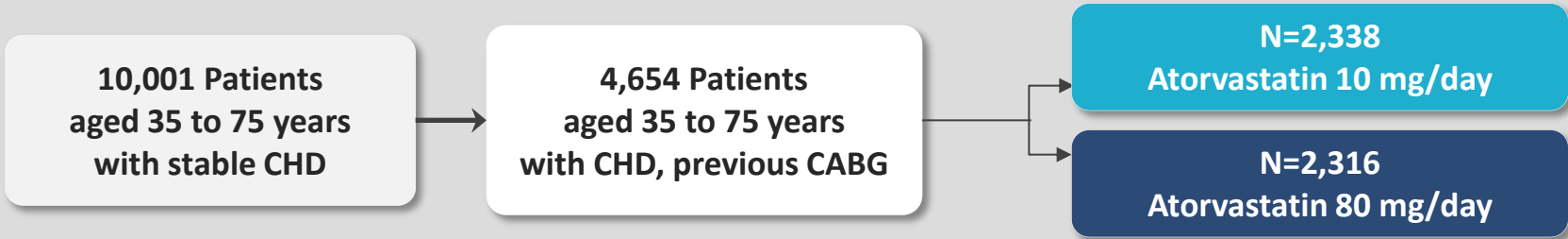
## Change of LDL-cholesterol

|  | Atorvastatin 80 mg | Atorvastatin 10 mg |
|---|---|---|
| N | 2,316 | 2,338 |
| Baseline median, mg/dl | 163 | 163 |
| End of follow–up mean, mg/dl | 79 | 101 |
| LDL–C difference (mg/dL)(%) | –84(–51%) | 62(38%) |

51%

## Primary endpoint

**Primary endpoint : the occurrence of a first MACE**
(cardiac death, nonfatal MI, resuscitated cardiac arrest, or stroke)



HR = 0.73 (95% CI 0.62, 0.87)
P = 0.0004

- - - - Atorvastatin 10 mg
——— Atorvastatin 80 mg

27%

Percent of Post-CABG Patients With Major Cardiovascular Event

Time (Years)

Ref 18. Shah SJ et al. J Am Coll Cardiol 2008;51:1938–43.
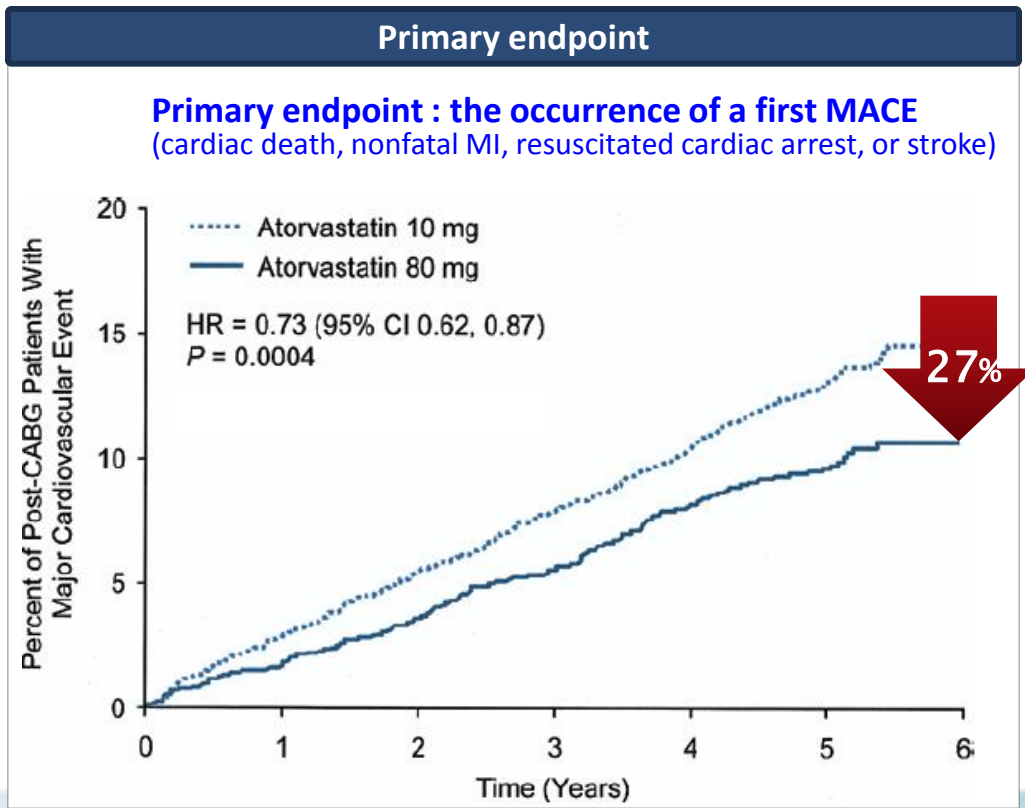
# Evidence in 2011 ACCF/AHA Guideline for CABG surgery
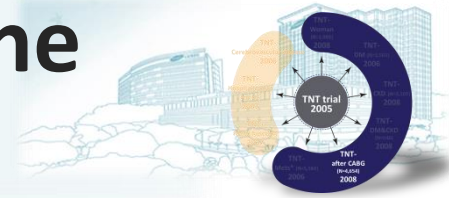
## Management of Hyperlipidemia:

*Recommendations*

*Reference*

- In patients undergoing CABG,
  it is reasonable to treat with statin therapy
  to lower the LDL   cholesterol
  to less than 70 mg/dL  in very high-risk*
  patients.
  **(CLASS IIa, Level of Evidence: C)**

**TNT, IDEAL, PROVE-IT, Meta-analysis**

*Presence of established cardiovascular disease plus 1) multiple major risk factors (especially diabetes), 2) severe and poorly controlled risk factors (especially continued cigarette smoking), 3) multiple risk factors of the metabolic syndrome (especially high triglycerides 200 mg/dL plus non–high–density lipoprotein cholesterol 130 mg/dL with low high–density lipoprotein cholesterol [40 mg/dL]), and 4) acute coronary syndromes

Ref 19. Shah SJ et al. J Am Coll Cardiol 2008;51:1938–43.

# Intensive Atorvastatin in
# CHD patients with Mets

| 10,001 Patients aged 35 to 75 years with stable CHD | → | 5,584 Patients aged 35 to 75 years with Mets | → | N=4,352 with Mets, no DM | → | Atorvastatin 10 mg |
| | | | | | → | Atorvastatin 80 mg |
| | | | → | N=1,231 with Mets, DM | → | Atorvastatin 10 mg |
| | | | | | → | Atorvastatin 80 mg |
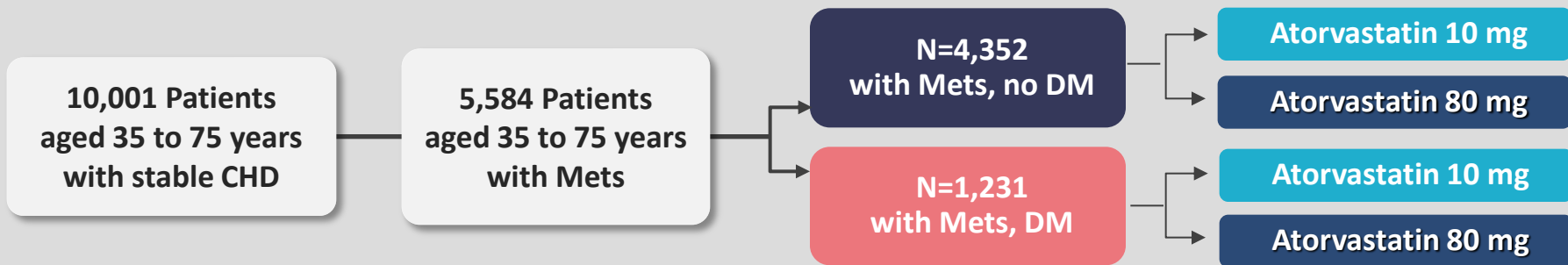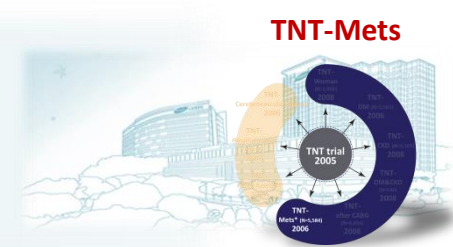
*Mets, Metabolic syndrome. Metabolic syndrome is defined by the 2005 NCEP ATP III criteria.

[Clinical Diagnosis of Metabolic Syndrome by NCEP ATP III 2005]

| Measure (any 3 of 5 constitute diagnosis of metabolic syndrome) | Categorical Cutpoints |
|---|---|
| Elevated waist circumference | 102 cm in men  88 cm in women |
| Elevated triglycerides | 150 mg/dL or On drug treatment for elevated  triglyceride |
| Reduced HDL-C | 40 mg/dL in men 50 mg/dL in women or  On drug treatment for reduced HDL-C |
| Elevated blood pressure | SBP 130 mm Hg or DBP 85 mm Hg or On antihypertensive drug treatment |
| Elevated fasting glucose | 100 mg/dL or On drug treatment for elevated glucose |

Ref 20. Deedwania P, et al. Lancet 2006; 368: 919–28.21. Grundy SM, et al. Circulation. 2005;112:2735-2752.

# Intensive Atorvastatin
# in CHD patients with Mets, no DM
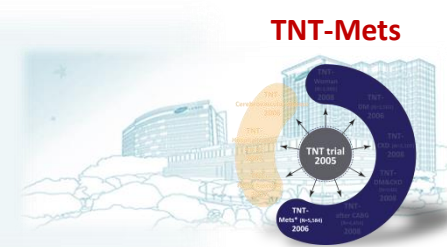
**Kaplan-Meier estimates of the proportion of patients with major cardiovascular events by treatment**



Ref 20. Deedwania P, et al. Lancet 2006; 368: 919–28.
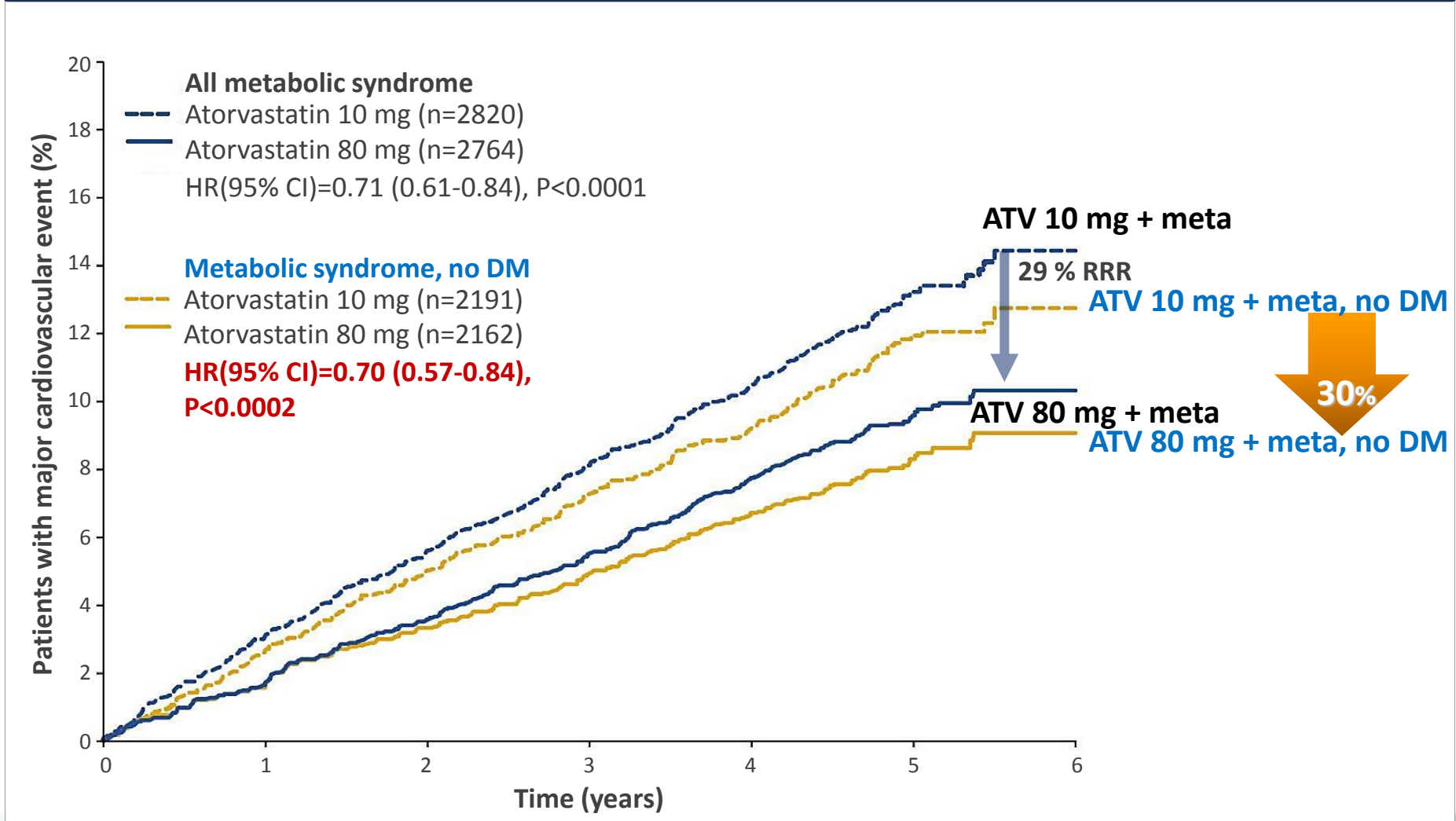
# Evidence in
# 2010 AHA/ASA guideline update
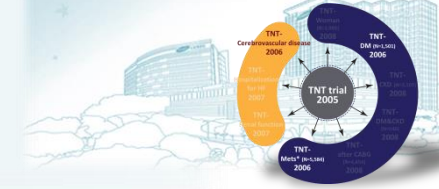
**AHA/ASA,** American Heart Association/American Stroke Association

## Diabetes management for prevention of primary stroke

*Recommendations*

**Treatment of adults with diabetes with a statin, especially those with additional risk factors, is recommended to lower risk of a first stroke** (Class I;Level of Evidence A)

In a post hoc analysis of the Treating to New Targets (TNT) study, the effect of intensive lowering of LDL cholesterol with high-dose (80 mg daily) versus low-dose (10 mg daily) atorvastatin on cardiovascular events was compared for patients with coronary heart disease and diabetes.[186] After a median follow-up of 4.9 years, higher-dose treatment was associated with a 40% reduction in the time to a cerebrovascular event (HR, 0.69; 95% CI, 0.48 to 0.98; $P=0.037$).

## Metabolic syndrome management for prevention of primary stroke

*Recommendations*

**Management of individual components of the metabolic syndrome is recommended, including lifestyle measures (ie, exercise, appropriate weight loss, proper diet) and pharmacotherapy (ie, medications for lowering BP, lowering lipids, glycemic control, and antiplatelet therapy) as reflected in the NCEP ATP III and the JNC 7, and as endorsed or indicated in other sections of this guideline.** (Class I; Level of Evidence A)

metabolic syndrome. The TNT study included 10 001 patients with clinically evident coronary heart disease.[490] Treating to an LDL-cholesterol level substantially lower than 100 mg/dL with a high dose of a high-potency statin reduced both stroke and cerebrovascular events by an additional 20% to 25% compared with a lower dose. Of these subjects, 5584 patients with the metabolic syndrome were randomly assigned to high- or low-dose statin.[491] As expected, the higher dose led to greater reductions in LDL cholesterol (73 versus 99 mg/dL at 3 months). Irrespective of treatment assignment, more patients with the metabolic syndrome (11.3%) had a major cardiovascular event than those without the metabolic syndrome (8.0%; HR, 1.44; 95% CI, 1.26 to 1.64; $P<0.0001$). At a median follow-up of 4.9 years, major cardiovascular events occurred in 13% of patients receiving the low-dose statin compared with 9.5% receiving the higher dose (HR, 0.71; 95% CI, 0.61 to 0.84; $P<0.0001$), and cerebrovascular events were reduced by 26% (HR, 0.74; 95% CI, 0.59 to 0.93; $P=0.011$).

Ref 22. Deedwania P, et al. Lancet 2006; 368: 919–28.

# Conclusion

- **The TNT study is the first randomized trial designed to demonstrate**
  - benefits of lowering LDL-C below 100 mg/dL in stable CHD patients.
  - high intensity statin (Lipitor 80 mg) reduced the RR for CVD events more than fixed lower-dose statin in stable CHD patients.

- **The TNT study is the important evidence of various lipid guidelines.**



**TNT trial**

TNT

TNT-Mets
TNT-DM
TNT-CVD

TNT-CABG

TNT-CKD&DM

**TNT**
TNT-CKD

TNT-DM

TNT-DM

NCEP ATP III

NCEP ATP III
2004 update

NCEP ATP III
2006 update

AHA/ASA
guideline

ACCF/AHA
guideline

KDOQI

KDIGO

**ACC/AHA
guideline**

ADA
guideline

ADA
guideline

2001    2004    2005    2006        2010    2011    2012    2013    2014    2015

# Change in LDL-C levels with increasing dose of each statin
## Results from the whole population VOYAGER individual patient data meta-analysis

Pooled analysis
of 32,258 patients



The VOYAGER Study

CRESTOR
Atorvastatin
Simvastatin

Change in LDL-C from baseline(%)

*p<0.001 rosuvastatin 10 mg vs atorvastatin 10 mg and 20 mg; simvastatin 10 mg, 20 mg and 40 mg
†p<0.001 rosuvastatin 20 mg vs atorvastatin 20 mg and 40 mg; simvastatin 20 mg ,40 mg and 80mg
‡p<0.001 rosuvastatin 40 mg vs atorvastatin 40 mg and 80 mg; simvastatin 40 mg and 80 mg
#p<0.05 atorvastatin 20 mg vs rosuvastatin 5 mg
##p<0.05 atorvastatin 80mg vs rosuvastatin 5mg and 10mg

Nicholls SJ et al. *Am J Cardiol* 2010; 105: 69–76

# Greater reductions in LDL-C and CRP With Atorvastatin compared With Pravastatin

**REVERSAL**

654 patients with obstructive CAD



*P<.001.

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

# ARBITER: Atorvastatin versus Pravastatin on reducing cholesterol ([CIMT](#))

**161 patients with CVD** were randomized to Atorvastatin 80 mg/d or Pravasatin 40 mg/d

# ASAP trial: carotid atherosclerosis progression



Simvastatin 40 mg

Atorvastatin 80 mg

*Lancet* 2001; 357: 577–81

# REVERSAL Study Design



IVUS

IVUS

**Patient Population**

- Patients with CAD
- Age :30-75 years

600 Patients

**Pravastatin 40mg**

**Atorvastatin 80mg**

Brachial Reactivity

18 Months

## Primary Efficacy Parameter

- **Change in Coronary Plaque Volume assessed by IVUS**

# REVERSAL trial: coronary atherosclerosis progression



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

# Case

- M/50
- NSTEMI (2008.06) → PCI on dLCx with Xience 3.0*23
- Mid-LAD diffuse intermediate lesion → medical treatment

- Atorvastatin 40 mg for 1 years

# CAG and PCI

# Non-culprit vessel



Baseline                                    Follow-up
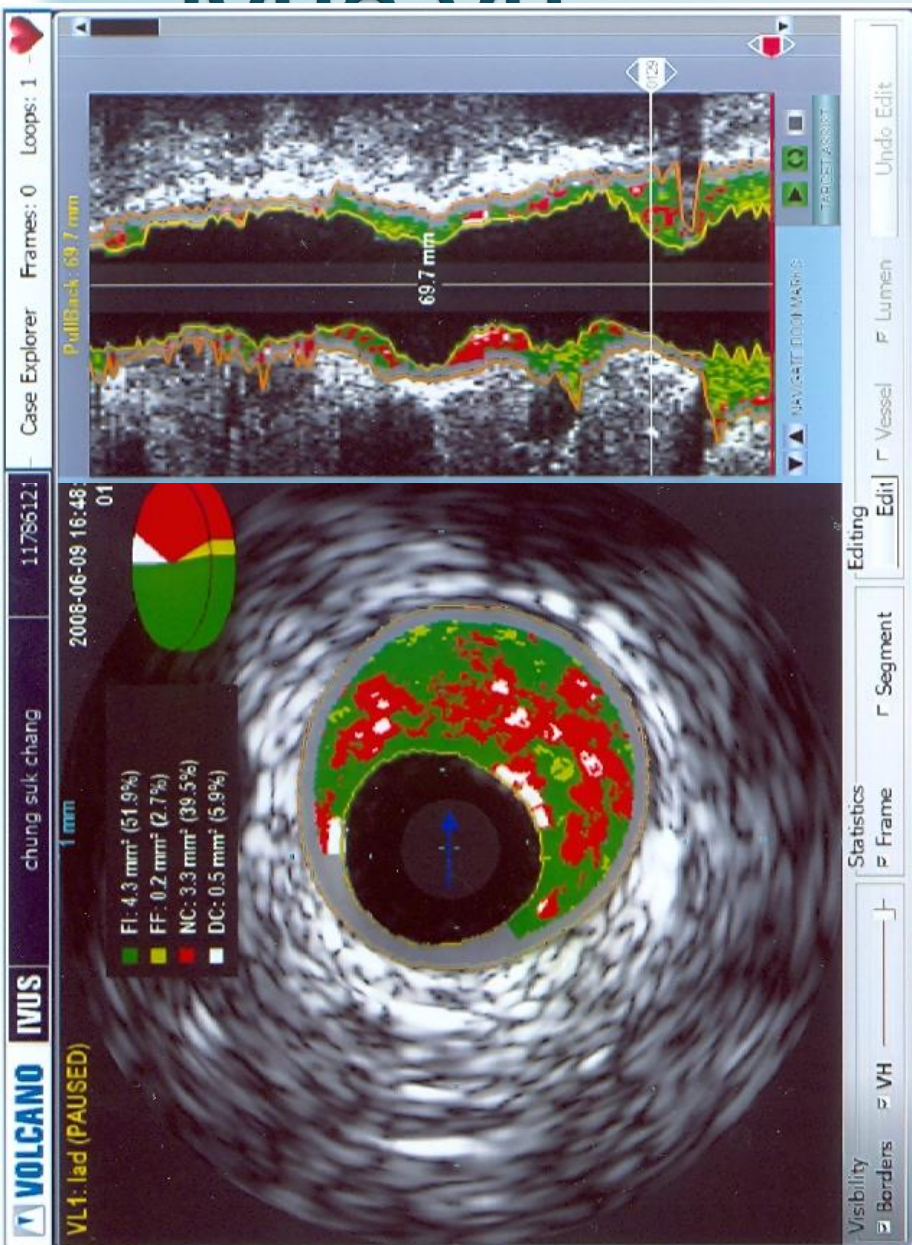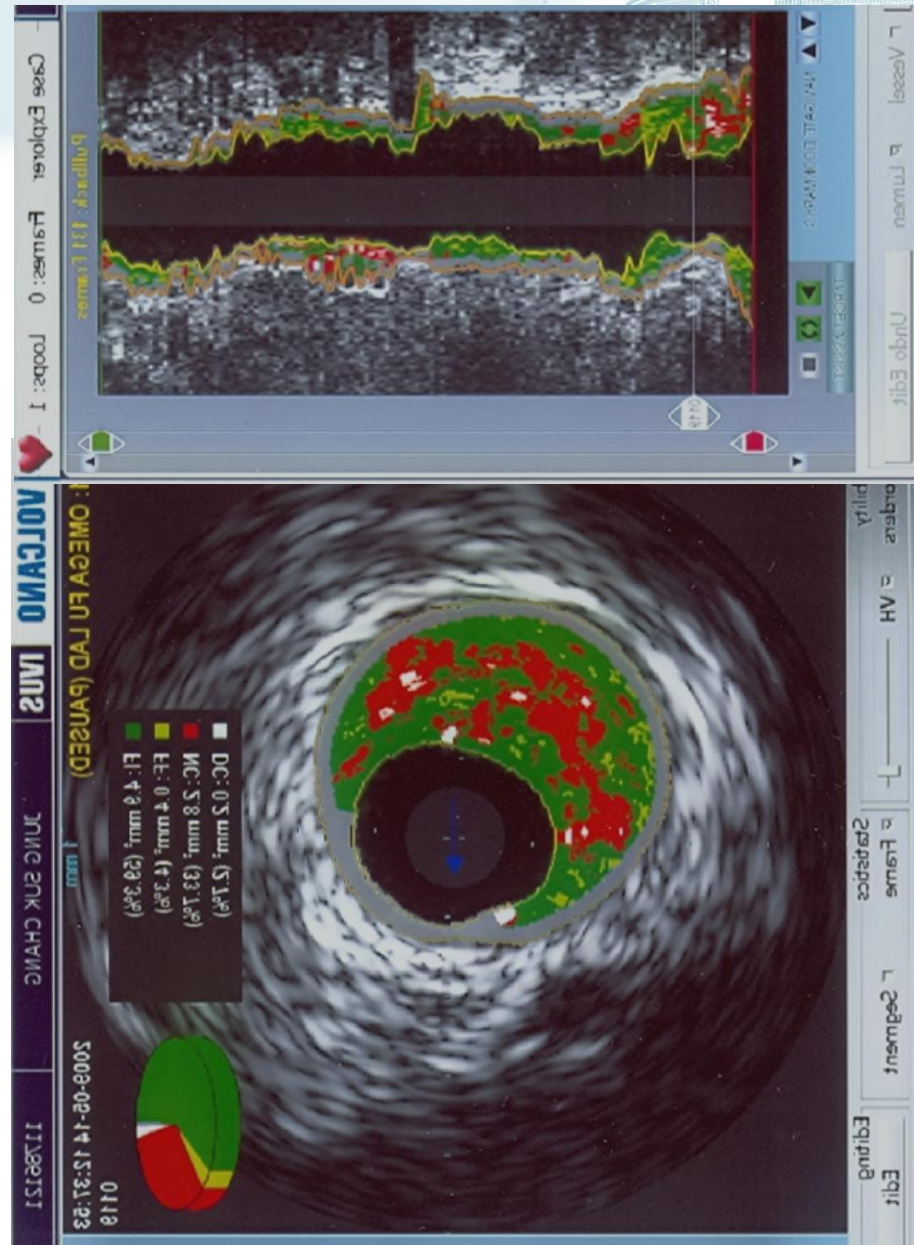
# IVUS-VH



Baseline

Follow-up

# IVUS-VH
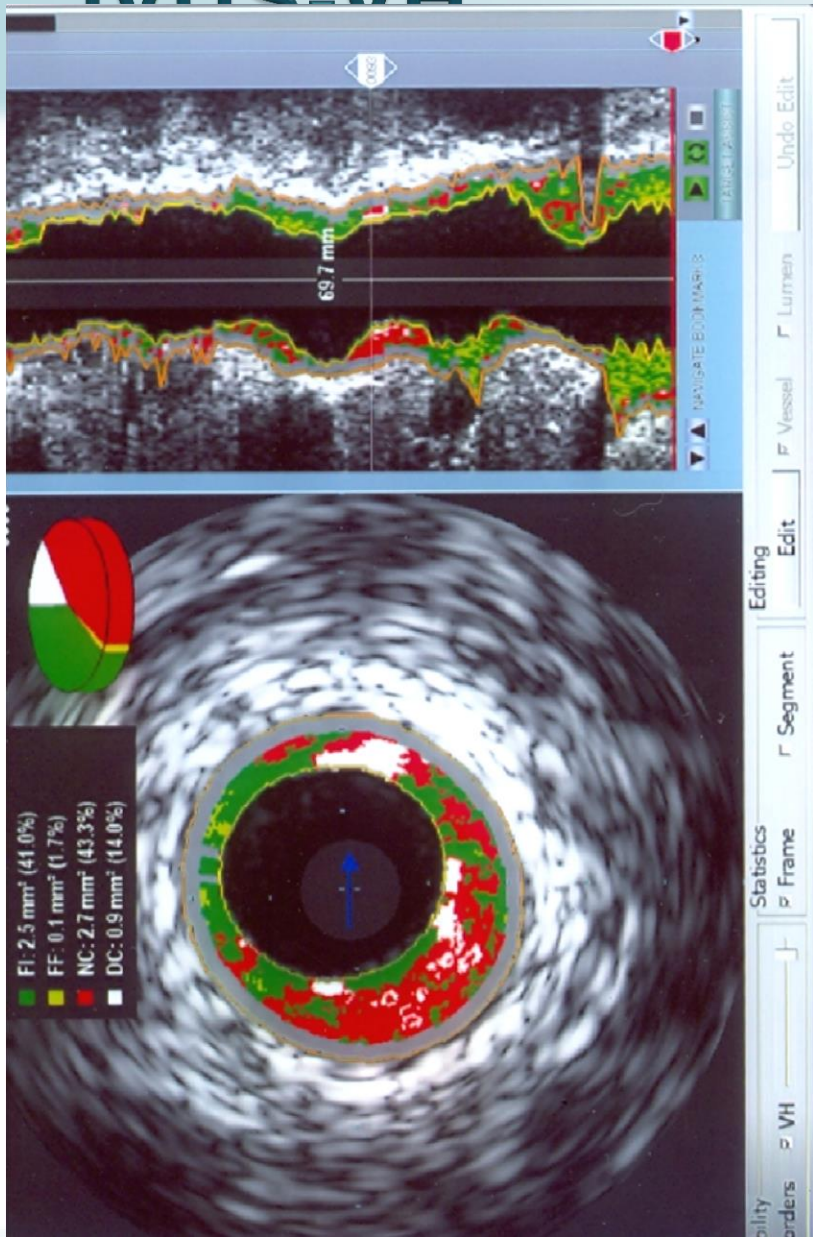


Baseline
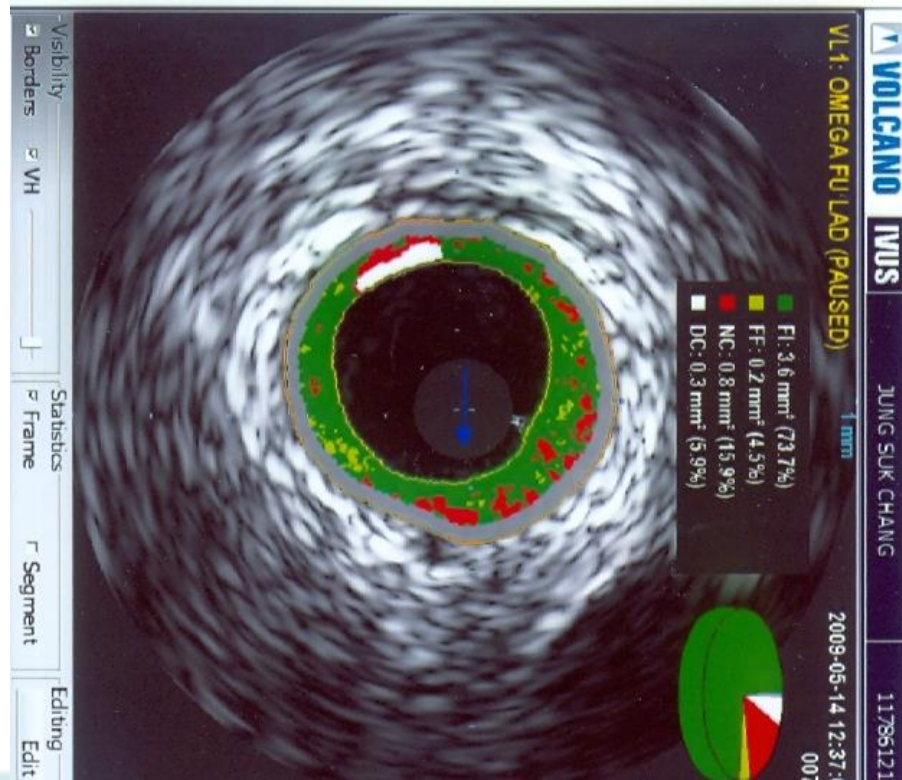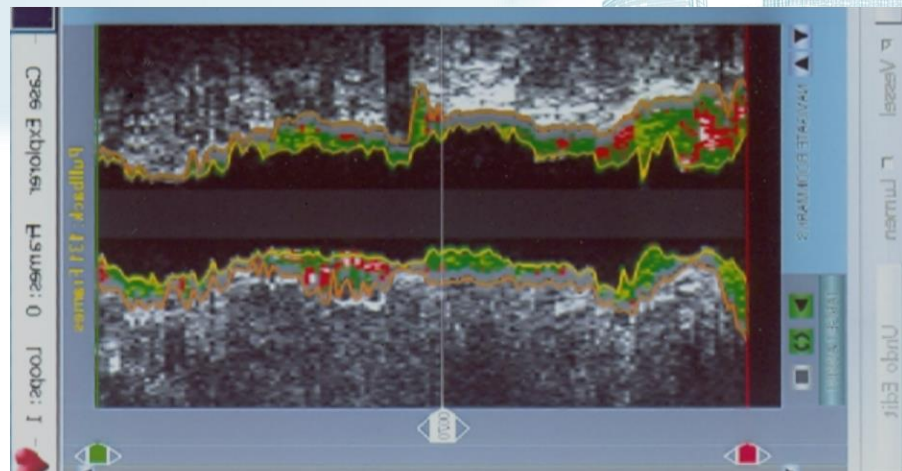
Follow-up

# Similar incidence of adverse events across dose range

_Data from 2006 safety meta-analysis involving 14,236 patients from 49 trials_

| | Number of patients (%) | | |
|---|---|---|---|
| | **Placebo (n=2180)** | **Atortastatin 10 mg (n=7258)** | **Atortastatin 80 mg (n=4798)** |
| Patients with ≥1 AE | | | |
| All | 768 (35.2) | 3870 (53.3) | 2285 (47.6) |
| Treatment-associated | 270 (12.4) | 983 (13.5) | 699 (14.6) |
| Withdrawals due to AEs | | | |
| All | 51 (2.3) | 251 (3.5) | 136 (2.8) |
| Treatment-associated | 27 (1.2) | 171 (2.4) | 84 (1.8) |
| Serious nonfatal AEs | | | |
| All | 122 (5.6) | 453 (6.2) | 385 (8.0) |
| Treatment-associated | 92 (4.2) | 12 (0.2) | 25 (0.5) |

Ref. Newman C et al. Am J Cardiol. 2006;97:61-67.

# Incidence of myalgia with atorvastatin



**■ All-cause  □ Treatment-associated**

| | Atv 10 mg (n=7258) | Atv 80 mg (n=4798) | Pbo (n=2180) |
|---|---|---|---|
| All-cause | 2.9 | 2.7 | 1.2 |
| Treatment-associated | 1.4 | 1.5 | 0.7 |

# Summary

▸ The appropriate type and intensity of statin therapy should be used to reduce ASCVD risk.

▸ Atorvastatin has demonstrated consistent benefit across broad spectrum of patients.

▸ In addition to superior LDL-cholesterol reducing effect, atorvastatin has anti-inflammatory, anti-oxidant, and anti-thrombotic effect and so on.

▸ High does atorvastatin can regress and/or stabilize atherosclerotic plaque and, in turn, improve clinical outcomes.

감사합니다.
Thank you for your attention.

# Summary

**TNT trial**

- main result
- sub analysis
- subgroup analysis

**관련 논문 12개 이상**

**가이드라인 8개**

TNT-DM
TNT-HF
TNT-CKD
TNT-PCI
TNT-Mets
TNT-VLDL
TNT-CABG
TNT-Women
TNT-CKD&DM
TNT-PCSK9 level
TNT-Cerebrovascular
TNT-Renal function
TNT-Hospitalization for HF

2015 ADA
2014 ADA
ACC/AHA
KDIGO
KDOQI
ACCF/AHA
AHA/ASA
NCEP ATP III 2006 update

**2005**

**2015**

**10년**

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

| ATP I 1988 | ATP II 1993 | ATP III 2001 | ATP III Update 2004 |
|---|---|---|---|
| Exclusive focus on LDL-C | Risk assessment guides therapy | Lower LDL-C threshold for therapy initiation in high-risk patients | Lower LDL-C threshold for therapy initiation in very-high-risk patients |

ATP IV
Nov 12
2013

**Abandon LDL-C Targets**
**Goodbye to Old Solution**
**Just Statin It!**

# 1 Four Statin Benefit Groups

**1** ▶ Individuals with **clinical athero-sclerotic cardiovascular disease** (ASCVD) – **acute coronary syndromes**, or a **history of myocardial infarction**, stable or unstable **angina, coronary or other arterial revascularization, stroke, TIA,** or **peripheral arterial disease** presumed to be of atherosclerotic origin – without New York Heart Association (NYHA) class II-IV heart failure or receiving hemodialysis.

**2** ▶ Individuals with primary elevations of low-density lipoprotein cholesterol **(LDL-C) ≥190 mg/dl.**

**3** ▶ Individuals **40-75** years of age with **diabetes,** and **LDL-C 70-189 mg/dl** without clinical ASCVD.

**4** ▶ Individuals without clinical ASCVD or diabetes, who are **40-75** years of age with **LDL-C 70-189 mg/dl,** and have an estimated 10-year **ASCVD risk of 7.5% or higher.**

# Pooled Cohort Equations for ASCVD risk prediction

**2** Individuals in the fourth group can be identified by using the **new Pooled Cohort Equations for ASCVD risk prediction,** developed by the Risk Assessment Work Group.
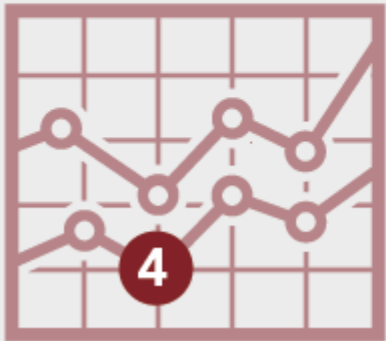
# Lifestyle modification

**3** **Lifestyle modification** (i.e., adhering to a heart healthy diet, regular exercise habits, avoidance of tobacco products, and maintenance of a healthy weight) remains a **critical component** of health promotion and **ASCVD** risk reduction, both prior to and in concert with the use of cholesterol-lowering drug therapies.

# No treat to target



**4** There is **no evidence** to support **continued use of specific LDL-C and/or** non–high-density lipoprotein cholesterol **(non–HDL-C) treatment targets.** It's important to have a physician-patient **discussion** about risk before the statin is prescribed for those who have **>7.5% risk.**

# Evolution of NCEP ATP III to ACC/AHA 2013 Guideline

| | NCEP ATP III | AHA/ACC |
|---|---|---|
| **Year introduced** | **2001 (updated in 2004)** | **2013** |
| **Focus** | • Reducing risk of coronary heart disease (CHD) | • Reducing risk of atherosclerotic CV disease (ASCVD), which includes CHD events as well as stroke/TIA, peripheral arterial disease or revascularization |
| **Risk Assessment** | • Risk categories / major risk factors that modify LDL-C goals<br>• Framingham 10-year Risk Score (CHD death + nonfatal MI) | • Pooled Cohort Equations (Fatal and nonfatal CHD + fatal and nonfatal stroke) |
| **Risk Categories** | • 3 main risk categories : CHD or CHD risk equivalent, 2+ risk factors with 10-yr CHD risk ≤20%, 0-1 risk factor + 10-yr risk <10%<br>• CHD risk equivalent: diabetes, clinical CHD, symptomatic carotid artery disease, peripheral artery disease | • 4 statin benefit groups: Clinical ASCVD, Primary elevations of LDL–C ≥190 mg/dL (≥4.9 mmol/L), Diabetes without clinical ASCVD, No diabetes or CVD with 10-year ASCVD risk ≥7.5% |
| **Treatment Targets** | • LDL-C = primary target<br>• CHD or CHD risk equivalents: <100 mg/dL (<2.6 mmol/L) (option < 70 mg/dL [<1.8 mmol/L] in very high risk patients)<br>• 2+ risk factors with 10-yr CHD risk ≤20%: <130 mg/dL (<3.4 mmol/L) (Option <100 mg/dL [<2.6 mmol/L] if 10-20% risk), 0-1 risk factor + 10-yr risk <10%: <160 mg/dL (<4.1 mmol/L) | • Intensity of statin therapy<br>• High intensity statin therapy (LDL-C reduction ≥50%) recommended for most patients in 4 statin benefit groups:<br>   • Atorvastatin 40 or 80 mg<br>   • Rosuvastatin 20-40 mg |
| **Treatment Recommendations** | • Statin (or bile acid sequestrant or nicotinic acid) to achieve LDL-C goal | • Maximally tolerated statin first-line to reduce risk of ASCVD events |

# Group 2.
# ≥21 Years with LDL–C ≥190 mg/dL

**Age ≥ 21years**
**LDL–C ≥190 mg/dL**

**Yes** →

High-intensity statin
(if not candidate ➡ Moderate-intensity statin)

| Recommendation 2 | NHLBI Grade | NHLBI Evidence statement | ACC/AHA COR | ACC/AHA LOE |
|---|---|---|---|---|
| **Adults ≥21 years of age with primary LDL–C ≥190 mg/dL should be treated with statin therapy (10-year ASCVD risk estimation is not required):**<br>• **Use high-intensity statin therapy** unless **contraindicated.**<br>• For individuals **unable to tolerate** high-intensity statin therapy, **use the maximum tolerated statin intensity.** | **A (Strong)** | 6,19,28, 33-35,37, 38 | **I** | **A** |

# Group 3.

# With DM and LDL–C 70-189 mg/dL

| Recommendation 1 | NHLBI Grade | NHLBI Evidence statement | ACC/AHA COR | ACC/AHA LOE |
|---|---|---|---|---|
| Moderate-intensity statin therapy should be initiated or continued for adults 40 to 75 years of age with DM | A (Strong) | 19, 29-34, 40 | I | A |

**Diabetes Type 1 or 2, Age 40-75 y**

Yes → Moderate-intensity statin

Yes → Estimated 10-y ASCVD risk ≥7.5%* High-intensity statin

# Group 4.

## 40 to 75 years of age with LDL–C 70 to 189 mg/dL, without clinical ASCVD* or diabetes and an estimated 10-year ASCVD risk ≥7.5%

**Yes** →  Moderate- high intensity statin

**≥7.5% estimated 10-y ASCVD risk and age 40-75 y**

| Recommendation 1 | NHLBI Grade | NHLBI Evidence statement | ACC/AHA COR | ACC/AHA LOE |
|---|---|---|---|---|
| Adults 40 to 75 years of age with LDL–C 70 to 189 mg/dL, without clinical ASCVD* or diabetes and an **estimated 10-year ASCVD ‖ risk ≥7.5%** should be treated with moderate- to high-intensity statin therapy | A (Strong) | 28, 34-36, 38, 42-44, 47, 49-56, 76 | I | A |

‖ Estimated 10-year or "hard" ASCVD risk includes first occurrence of nonfatal MI, CHD death, and nonfatal and fatal stroke as used by the Risk Assessment Work Group in developing the Pooled Cohort Equations.

# ATP III risk score vs new Pooled Cohort risk equation

<Risk assessment sample >

| Age | Sex | Race | Total cholesterol | HDL cholesterol | Systolic BP | BP Rx | Diabetes | Smoking |
|-----|-----|------|-------------------|-----------------|-------------|-------|----------|---------|
| 55 | female | white | 220 | 45 | 160 | No | No | Yes |

**CHD risk evaluation**

**ASCVD risk evaluation**

| | |
|---|---|
| **Age:** | 55 |
| **Gender:** | female |
| **Total Cholesterol:** | 220 mg/dL |
| **HDL Cholesterol:** | 45 mg/dL |
| **Smoker:** | Yes |
| **Systolic Blood Pressure:** | 160 mm/Hg |
| **On medication for HBP:** | No |
| **Risk Score*** | 9% |

| | |
|---|---|
| Gender | Male / Female |
| Age | 55 years |
| Race | White or other |
| Total Cholesterol | 220 mg/dL |
| HDL Cholesterol | 45 mg/dL |
| Systolic BP | 160 mmHg |
| Receiving treatment for high blood pressure (if SBP > 120 mmHg) | No / Yes |
| Diabetes | No / Yes |
| Smoker | No / Yes |

10-year risk of atherosclerotic cardiovascular disease: 9.8%

10-year risk in a similar patient with optimal risk factors: 1.4%

**'Low risk'** for hard CHD event

**'Elevated 10-year risk'** for hard ASCVD event

# ATP III risk score vs new Pooled Cohort risk equation

Currently, 1.5%
At 60 years, 9.0%

<Risk assessment sample >

| Age | Sex | Race | Total cholesterol | HDL cholesterol | Systolic BP | BP Rx | Diabetes | Smoking |
|-----|-----|------|-------------------|-----------------|-------------|-------|----------|---------|
| 55 | female | white | 220 | 45 | 160 | No | No | Yes |

## CHD risk evaluation

| | |
|---|---|
| **Age:** | 55 |
| **Gender:** | female |
| **Total Cholesterol:** | 220 mg/dL |
| **HDL Cholesterol:** | 45 mg/dL |
| **Smoker:** | Yes |
| **Systolic Blood Pressure:** | 160 mm/Hg |
| **On medication for HBP:** | No |
| **Risk Score*** | 9% |

'**Low risk**' for hard CHD event

## ASCVD risk evaluation

| Gender | Male | Female | Systolic BP | 160 mmHg |
|--------|------|--------|-------------|----------|
| Age | 55 | years | Receiving treatment for high blood pressure (if SBP > 120 mmHg) | No / Yes |
| Race | White or other | | Diabetes | No / Yes |
| Total Cholesterol | 220 | mg/dL | Smoker | No / Yes |
| HDL Cholesterol | 45 | mg/dL | 10-year risk of atherosclerotic cardiovascular disease: | 9.8% |
| | | | 10-year risk in a similar patient with optimal risk factors: | 1.4% |

'**Elevated 10-year risk**' for hard ASCVD event

# The lower the better?
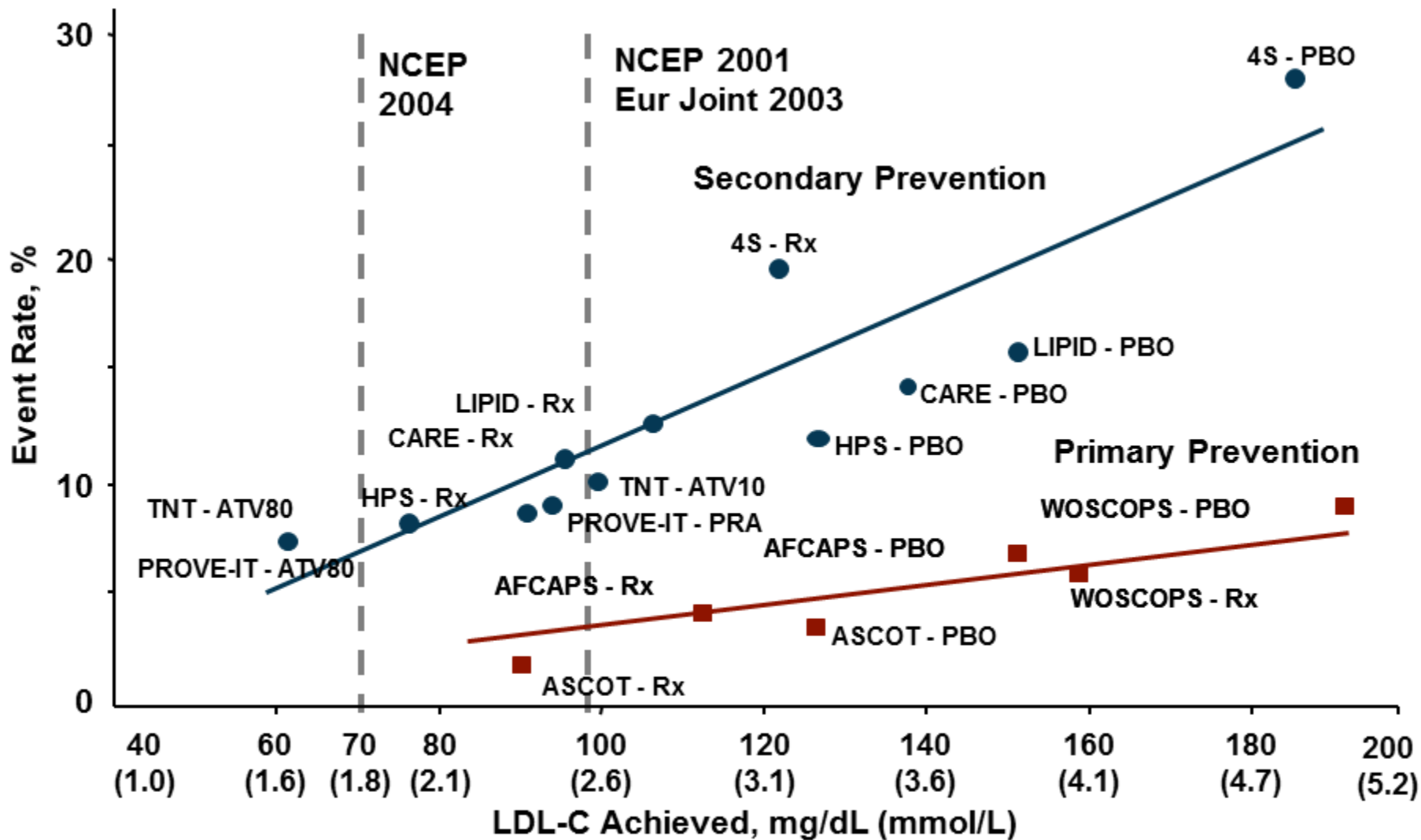
# Role of Biomarkers and Noninvasive Tests

▸ In selected individuals who are not in 1 of the 4 statin benefit groups, and for whom a decision to initiate statin therapy is otherwise unclear, additional factors may be considered to inform treatment decision making.

▸ These factors include
  ◦ Primary LDL–C ≥160 mg/dL or other evidence of genetic hyperlipidemias
  ◦ family history of premature ASCVD with onset <55 years of age in a first degree male relative or <65 years of age in a first degree female relative,
  ◦ hs-CRP >2 mg/L (0.2 mg/dL)
  ◦ CAC score ≥300 Agatston units or ≥75 percentile for age, sex, and ethnicity
  ◦ ABI <0.9

# Monitoring response and adherence
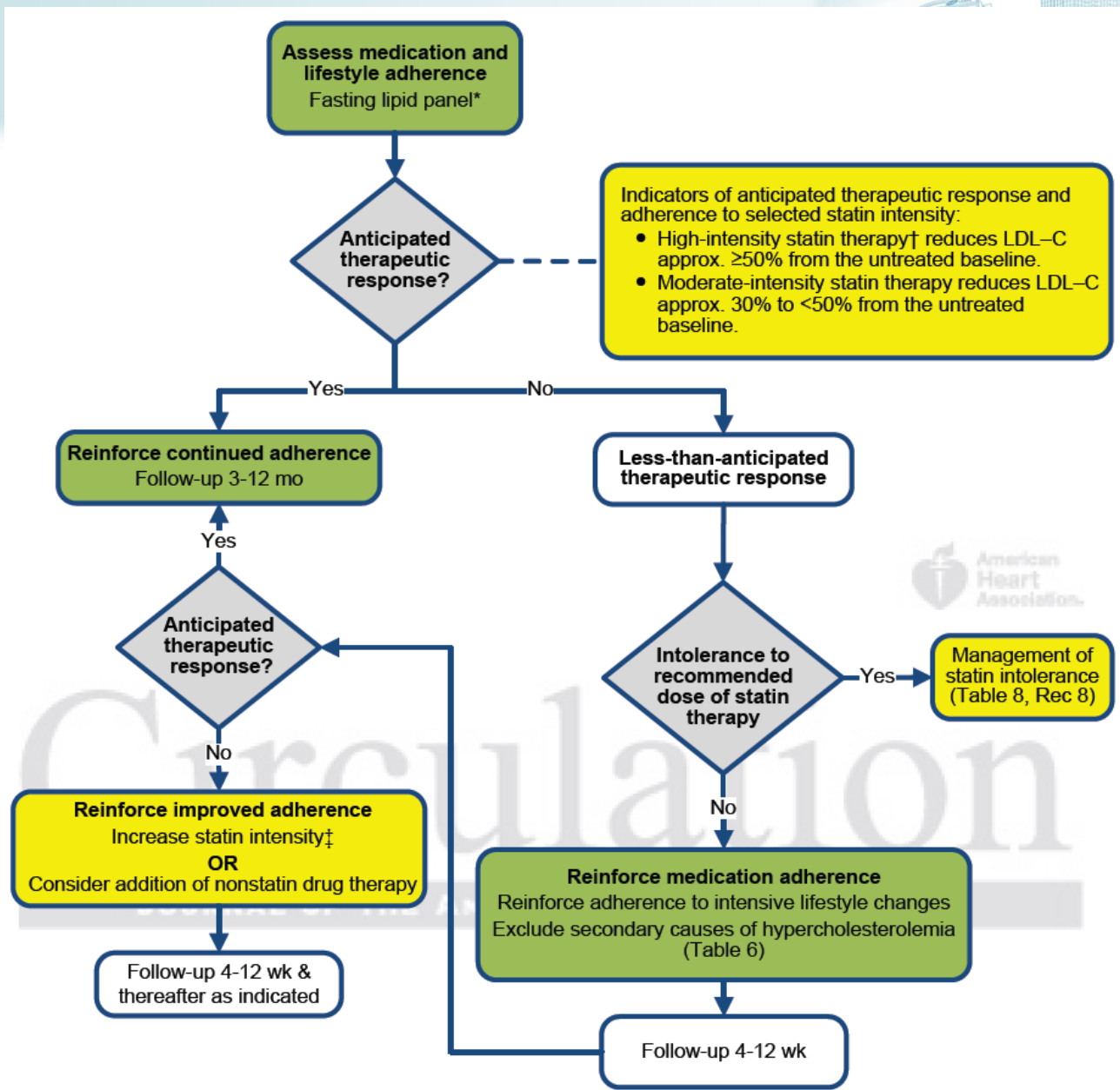
# Heart Failure and Hemodialysis

## Heart Failure(NYHA class II-IV) and Hemodialysis

| Recommendation | NHLBI Grade | NHLBI Evidence Statements | ACC/AHA COR | ACC/AHA LOE |
|---|---|---|---|---|
| 1. The Expert Panel makes no recommendations regarding the initiation or discontinuation of statins in patients with NYHA class II-IV ischemic systolic heart failure or in patients on maintenance hemodialysis | N(No Recommendation) | 71, 72 | — | — |

1. Rosuvastatin in older patients with systolic heart failure. N Engl J Med 2007;357:2248–61.

2. GISSI-HF Investigators. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): A randomised, double-blind, placebo-controlled trial. Lancet 2008;372:1231– 9.

3. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med 2005;353:238–48.

4. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med 2009;360:1395–407.

# Characteristics predisposing individuals to statin adverse effects

▸ Moderate-intensity statin therapy should be used in individuals in whom high-intensity statin therapy would otherwise be recommended when characteristics predisposing them to statin-associated adverse effects are present.

▸ Characteristics predisposing individuals to statin adverse effects include, but are not limited to:
  ◦ Multiple or serious comorbidities, including impaired renal or hepatic function.
  ◦ History of previous statin intolerance or muscle disorders.
  ◦ Unexplained ALT elevations >3 times ULN.
  ◦ Patient characteristics or concomitant use of drugs affecting statin metabolism.
  ◦ >75 years of age.

▸ Additional characteristics that may modify the decision to use higher statin intensities may include, but are not limited to:
  ◦ History of hemorrhagic stroke.
  ◦ Asian ancestry.

# Safety recommendation of statins

| Recommendations | NHLBI | ACC/AHA COR | LOE |
|---|---|---|---|
| 1. Creatine Kinase, routinely not needed | A | III no benefit | A |
| 2. Baseline CK in pts at risk of events | E | IIa | C |
| 3. Baseline ALT before initiating statins | B | I | B |
| 4. Decreasing the statin dose, if 2 consecutive values of LDL-C < 40 mg/dL | C | IIb | C |
| 5. Simvastatin at 80 mg daily harmful | B | III harm | A |
| 6. Evaluate for new onset diabetes during receiving statin therapy | B | I | B |
| 7. If muscle symptoms develop, discontinue, use again | E | IIa | C |
| 8. Confusional state, see secondary causes | E | IIb | C |

\* NHLBI, National Heart, Lung, and Blood Institute; COR, Class of Recommendation; LOE, Level of Evidence;

# Critical Questions for future guidelines could examine:

1. the treatment of hypertriglyceridemia;

2. use of non-HDL-C in treatment decision-making;

3. whether on-treatment markers such as Apo B, Lp(a), or LDL particles are useful for guiding treatment decisions;

4. the best approaches to using noninvasive imaging for refining risk estimates to guide treatment decisions;

5. outcomes of RCTs of new lipid-modifying agents to determine the incremental ASCVD event reduction benefits when added to evidence-based statin therapy.

6. subgroups of individuals with heart failure or undergoing hemodialysis that might benefit from statin therapy;

7. long-term effects of statin-associated new onset diabetes and management;

# Summary

▸ More evidence based medicine from RCT data

▸ Focus on ASCVD risk reduction: 4 statin benefit groups

▸ Use of the New Pooled Cohort Risk Assessment Equations

▸ The appropriate intensity of statin therapy should be used to reduce ASCVD risk.

▸ No recommendations for specific LDL–C or non-HDL–C targets

# Grouping of statins used in the NICE guideline

| | Reduction in low-density lipoprotein cholesterol | | | | |
|---|---|---|---|---|---|
| Dose (mg/day) | 5 | 10 | 20 | 40 | 80 |
| Fluvastatin | – | – | 21%[1] | 27%[1] | 33%[2] |
| Pravastatin | – | 20%[1] | 24%[1] | 29%[1] | – |
| Simvastatin | – | 27%[1] | 32%[2] | 37%[2] | 42%[3,4] |
| Atorvastatin | – | 37%[2] | 43%[3] | 49%[3] | 55%[3] |
| Rosuvastatin | 38%[2] | 43%[3] | 48%[3] | 53%[3] | – |

[1] 20%–30%: low intensity.

[2] 31%–40%: medium intensity.

[3] Above 40%: high intensity.

[4] Advice from the MHRA: there is an increased risk of myopathy associated with high-dose (80 mg) simvastatin. The 80 mg dose should be considered only in patients with severe hypercholesterolaemia and high risk of cardiovascular complications who have not achieved their treatment goals on lower doses, when the benefits are expected to outweigh the potential risks.

# NICE guideline: Primay prevention

1.3.14  Before offering statin treatment for primary prevention, discuss the benefits of lifestyle modification and optimise the management of all other modifiable CVD risk factors if possible. **[new 2014]**

1.3.15  Recognise that people may need support to change their lifestyle. To help them do this, refer them to programmes such as exercise referral schemes. (See Behaviour change: individual approaches [NICE public health guidance 49].) **[new 2014]**

1.3.16  Offer people the opportunity to have their risk of CVD assessed again after they have tried to change their lifestyle. **[new 2014]**

1.3.17  If lifestyle modification is ineffective or inappropriate offer statin treatment after risk assessment. **[new 2014]**

1.3.18  Offer atorvastatin 20 mg for the primary prevention of CVD to people who have a 10% or greater 10-year risk of developing CVD. Estimate the level of risk using the QRISK2 assessment tool. **[new 2014]**

**ClinRisk** ⌗

# Welcome to the QRISK®2-2014 risk calculator: http://qrisk.org

This calculator is only valid if you do not already have a diagnosis.

| Reset | Information | Publications | About | Copyright | Contact Us | Algorithm | Software |

### About you

Age (25-84):  `64`

Sex:  ◉ Male  ○ Female

Ethnicity:  `Other Asian  ▼`

**UK postcode: leave blank if unknown**

Postcode:  `_____`

### Clinical information

Smoking status:  `non-smoker  ▼`

Diabetes status:  `none  ▼`

Angina or heart attack in a 1st degree relative < 60?  ☐

Chronic kidney disease?  ☐

Atrial fibrillation?  ☐

On blood pressure treatment?  ☐

Rheumatoid arthritis?  ☐

**Leave blank if unknown**

Cholesterol/HDL ratio:  `_____`

Systolic blood pressure (mmHg):  `_____`

**Body mass index**

Height (cm):  `_____`

Weight (kg):  `_____`

Calculate risk over `10 ▼` years.  `Calculate risk`

## Welcome to the QRISK®2-2014 cardiovascular disease risk calculator

Welcome to the QRISK®2-2014 Web Calculator. You can use this calculator to work out you simple questions. It is suitable for people who do not already have a diagnosis of heart disea

The QRISK®2 algorithm has been developed by doctors and academics working in the UK thousands of GPs across the country who have freely contributed data for medical research possible.

Whilst QRISK2 has been developed for use in the UK, it is being used internationally. For n average value. Users should note, however, that CVD risk is likely to be under-estimated in medical decisions need to be taken by a patient in consultation with their doctor. The author

The science underpinning the QRISK®2 equations has been published here:

- Predicting cardiovascular risk in England and Wales: prospective derivation and valid

Click here for more information on QRISK®2.

# NICE guideline: Diabetes and CKD

## 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).]

## People with CKD

1.3.27   Offer atorvastatin 20 mg for the primary or secondary prevention of CVD to people with CKD[7].

- Increase thedose if a greater than 40% reduction in non-HDL cholesterol is not achieved (see recommendation 1.3.28) and eGFR is 30 ml/min/1.73 m$^2$ or more.

- Agree the use of higher doses with a renal specialist if eGFR is less than 30 ml/min/ 1.73 m$^2$. **[new 2014]**

# Atorvastatin 80 mg reduced a mean LDL–C by 21%, the HR for CVD by 22%

**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

**HR=0.78 (0.69-0.89), p<0.001**



Major Cardiovascular Event (%) — 0.15, 0.10, 0.05, 0.00

10 mg of ATV

**22%**

80 mg of ATV

Years — 0 1 2 3 4 5 6

*LaRosa JC, et al. N Engl J Med 2005;352:1425–35.*
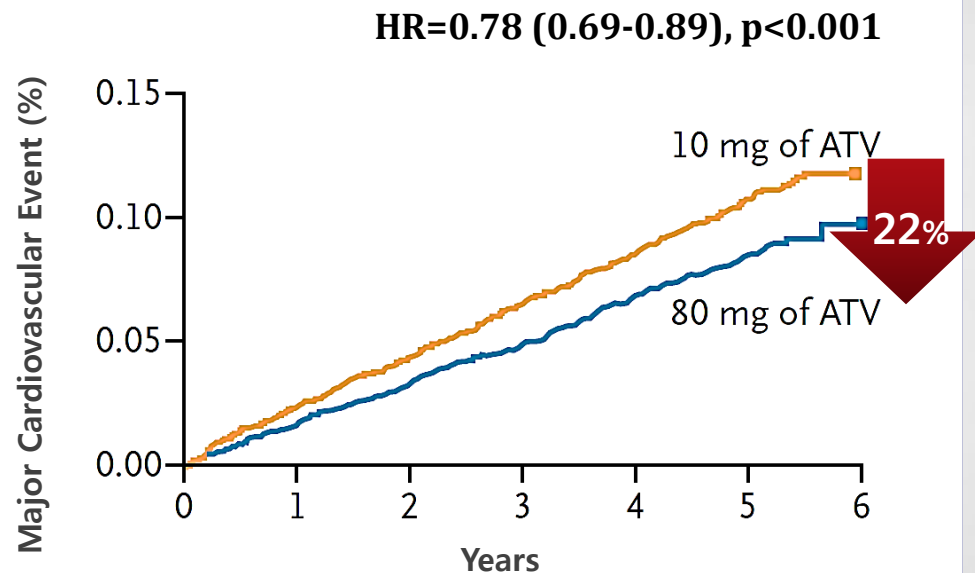
# Atorvastatin 80 mg reduced a mean **LDL–C by 45%,** the **HR for CVD by 16%**

**4,731 Patients aged ≥ 18 years with stroke or TIA within 6 months without CHD**

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 **45%** | 129 |
| LDL–C difference (mg/dL)(%) | –60(–45%) | –4(–3%) |

## Primary endpoint

**HR=0.84(0.71-0.99), p=0.03**

**16%**



Fatal or Nonfatal Stroke (%) vs Years since Randomization — Placebo and Atorvastatin curves

*SPARCL Investigators, et al. N Engl J Med 2006;355:549-59.*
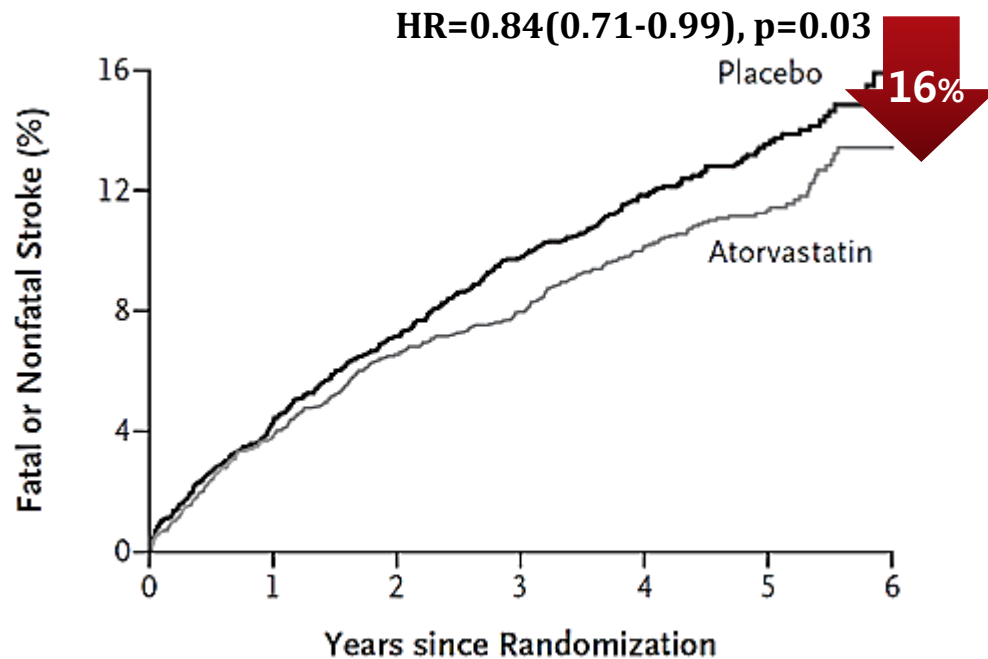
# In adults aged 40 to 75 years with diabetes and >1 risk factor, fixed moderate-dose statin therapy reduced the RR for CVD.

**CARDS**

---

| 2,838 patients aged 40 to 75 years with diabetes and >1 risk factor | → Placebo |
| | → Atorvastatin 10 mg/day |

- **Primary endpoint**
  : Acute CHD event, stroke, coronary revascularization
- **Median follow-up = 3.9 years** (early closure)

---

## Change of LDL-cholesterol

Mean difference -40%(-41 to -39) p<0.0001



Placebo
Atorvastatin

## Primary endpoint

HR=0.63(0.48-0.83)
p=0.001



Placebo
Atorvastatin

Cumulative hazard (%)

**37%**
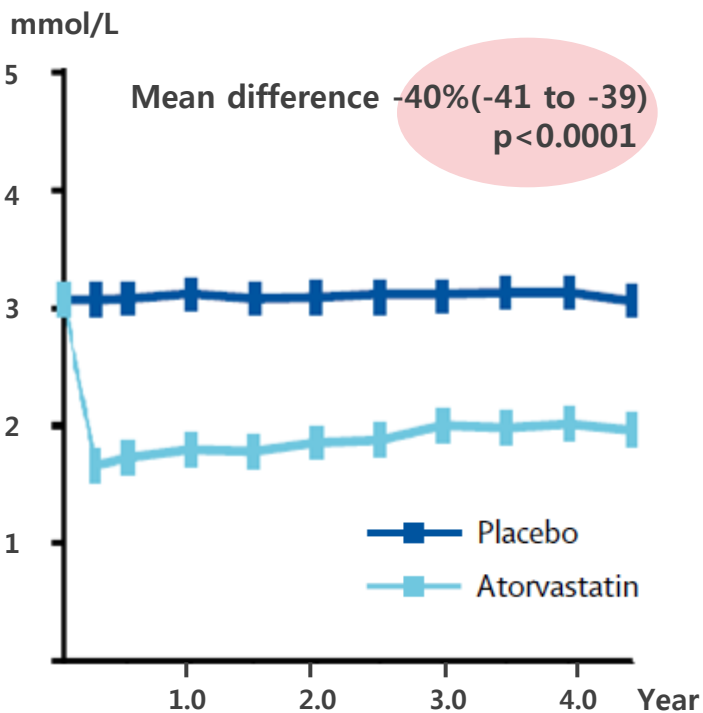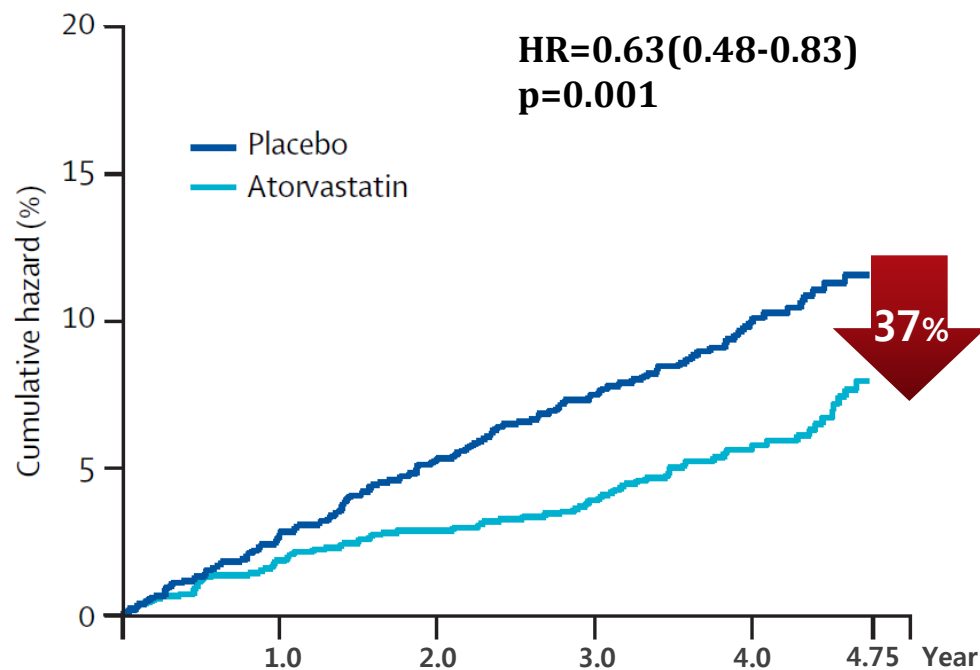
# ASCOT-LLA: primary prevention

## Primary Endpoint

NonFatal MI, Fatal CHD



Placebo
Atorvastatin 10 mg/day

**Relative Risk Reduction**

**36%**

HR = 0.64 (0.50-0.83)
P = 0.0005

"조기종료"

Sever PS, et al., *Lancet* 2003;361:1149-1158.

# Change in LDL-C levels with increasing dose of each statin
## Results from the whole population VOYAGER individual patient data meta-analysis

Pooled analysis
of 32,258 patients

The VOYAGER Study

CRESTOR
Atorvastatin
Simvastatin

| 5 mg | 10 mg | 20 mg |

| 10 mg | 20 mg | 40 mg | 80 mg |

| 10 mg | 20 mg | 40 mg | 80 mg |

0  -5  -10  -15  -20  -25  -30  -35  -40  -45  -50  -55  -60

Change in LDL-C from baseline(%)

*p<0.001 rosuvastatin 10 mg vs atorvastatin 10 mg and 20 mg; simvastatin 10 mg, 20 mg and 40 mg
†p<0.001 rosuvastatin 20 mg vs atorvastatin 20 mg and 40 mg; simvastatin 20 mg ,40 mg and 80mg
‡p<0.001 rosuvastatin 40 mg vs atorvastatin 40 mg and 80 mg; simvastatin 40 mg and 80 mg
#p<0.05 atorvastatin 20 mg vs rosuvastatin 5 mg
##p<0.05 atorvastatin 80mg vs rosuvastatin 5mg and 10mg

Nicholls SJ et al. *Am J Cardiol* 2010; 105: 69–76

# Greater reductions in LDL-C and CRP With Atorvastatin compared With Pravastatin

**REVERSAL**

654 patients with obstructive CAD

**Final Laboratory Results**



*P<.001.

■ Atorvastatin 80 mg  ■ Pravastatin 40 mg

Ref. Nissen SE, et al. JAMA. 2004;291:1071-1080.
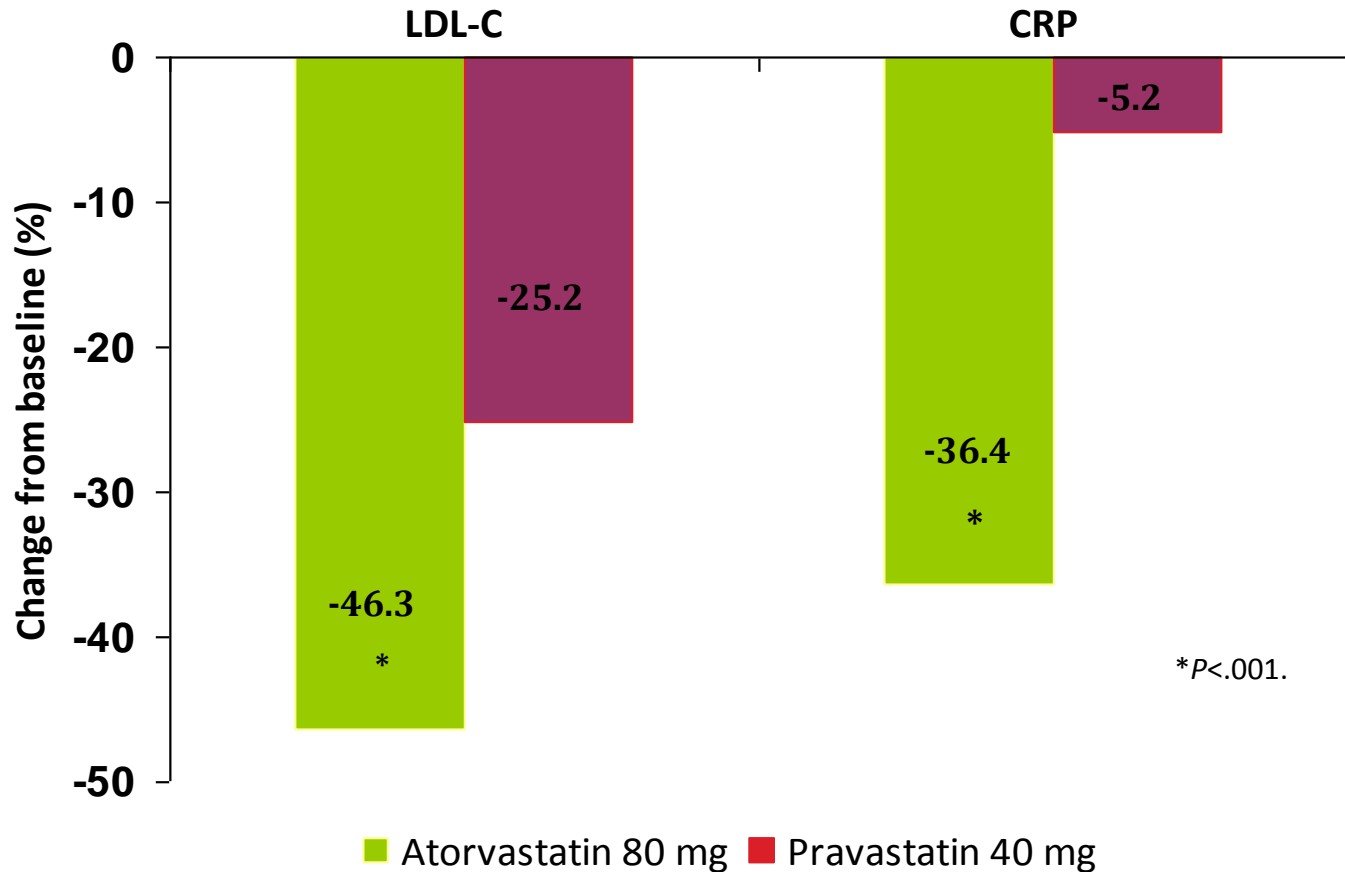
# Anti-inflammatory Activity: Effect on CRP
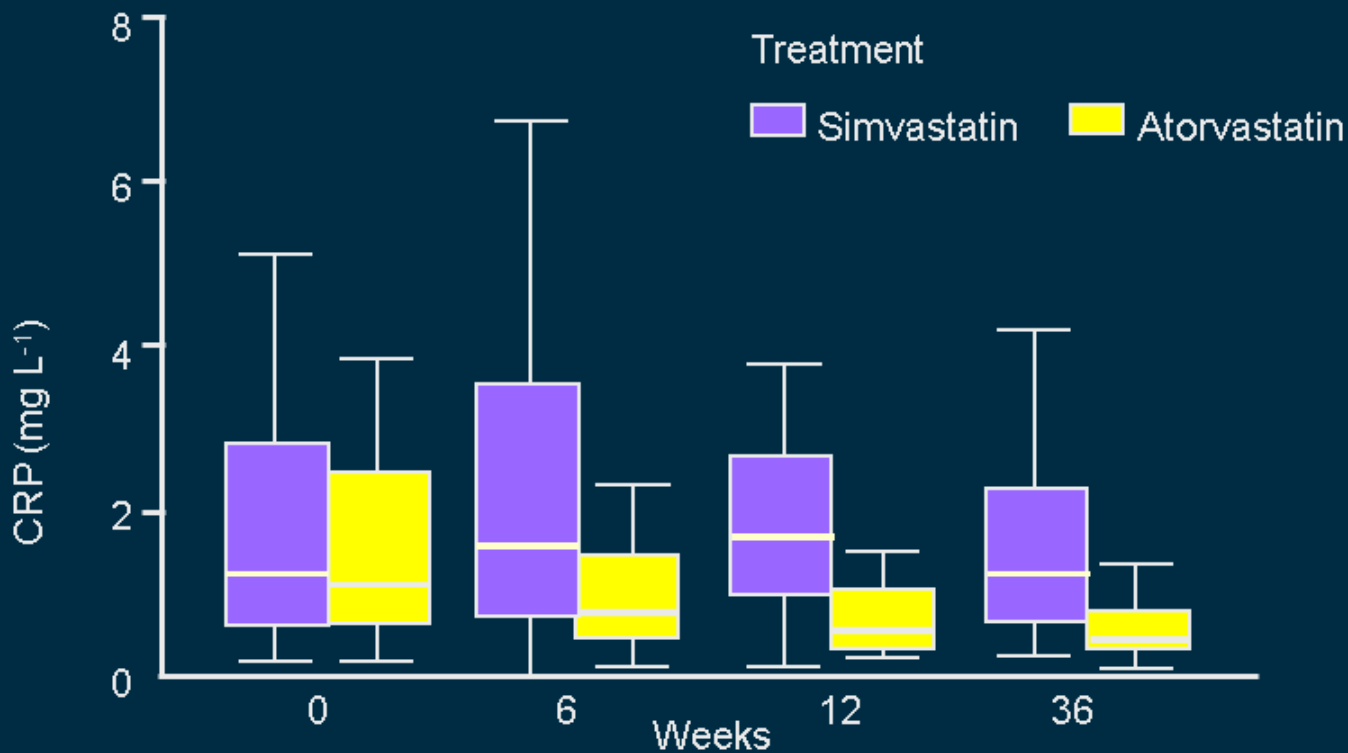
Wiklund O, et al. *J Intern Med*. 2002;251:338–347.

# High dose Atorvastatin significantly lowered CRP levels in patients with type 2 diabetes

186 T2DM patients without manifest coronary artery disease and with dyslipidemia

**Reduction of levels of hs−CRP**

Placebo    Atorvastatin 10 mg    Atorvastatin 80 mg

Relative change from baseline median (IQR)

- Placebo: 6.6
- Atorvastatin 10 mg: -15
- Atorvastatin 80 mg: -47

*P<.001.
IQR=interquartile range

Ref. Van de Ree MA, et al. Atherosclerosis. 2003;166:129-135.
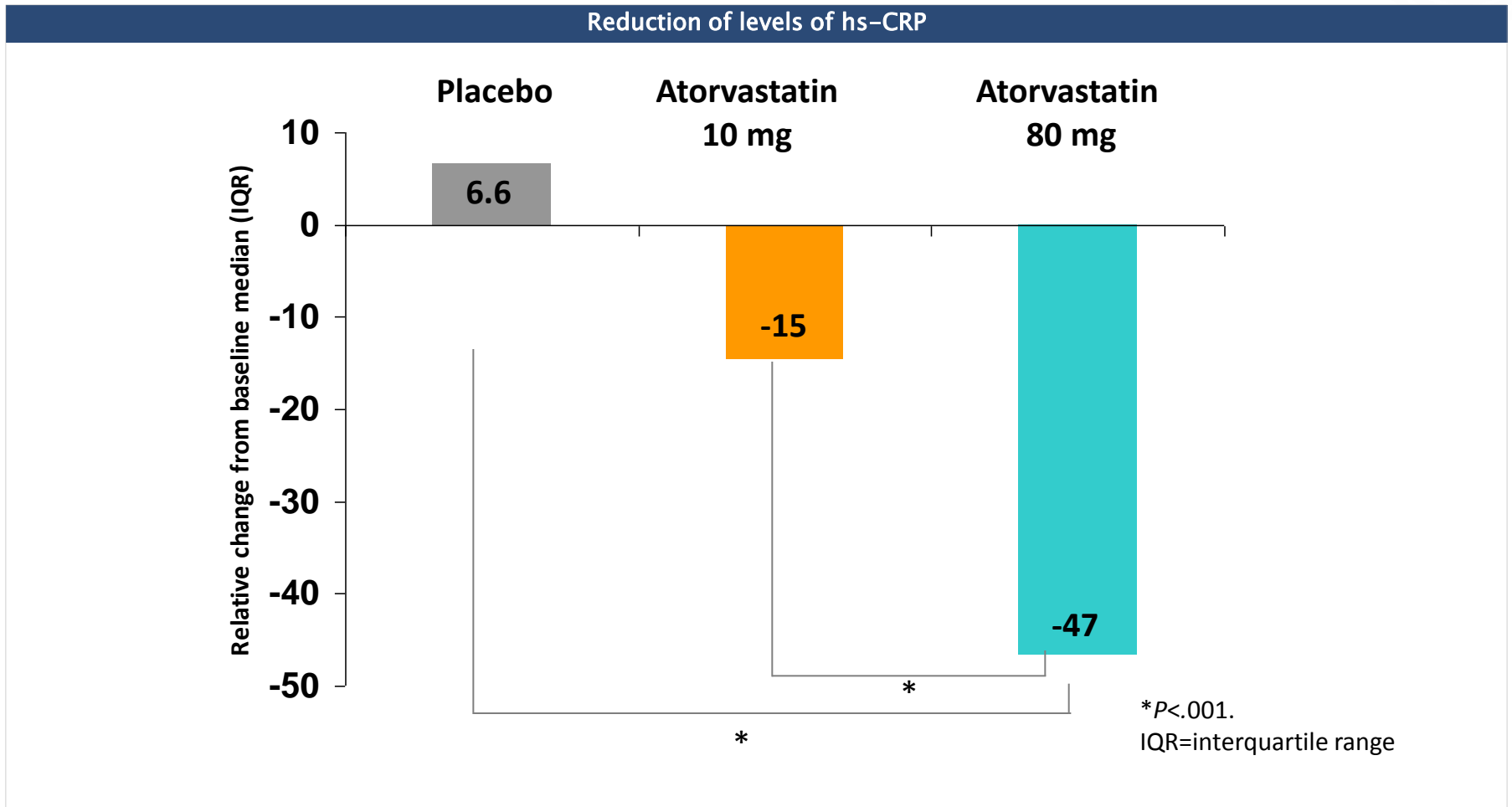
# Comparative Effects of Statins on Oxidative Stress



*P≤ 0.01 vs control
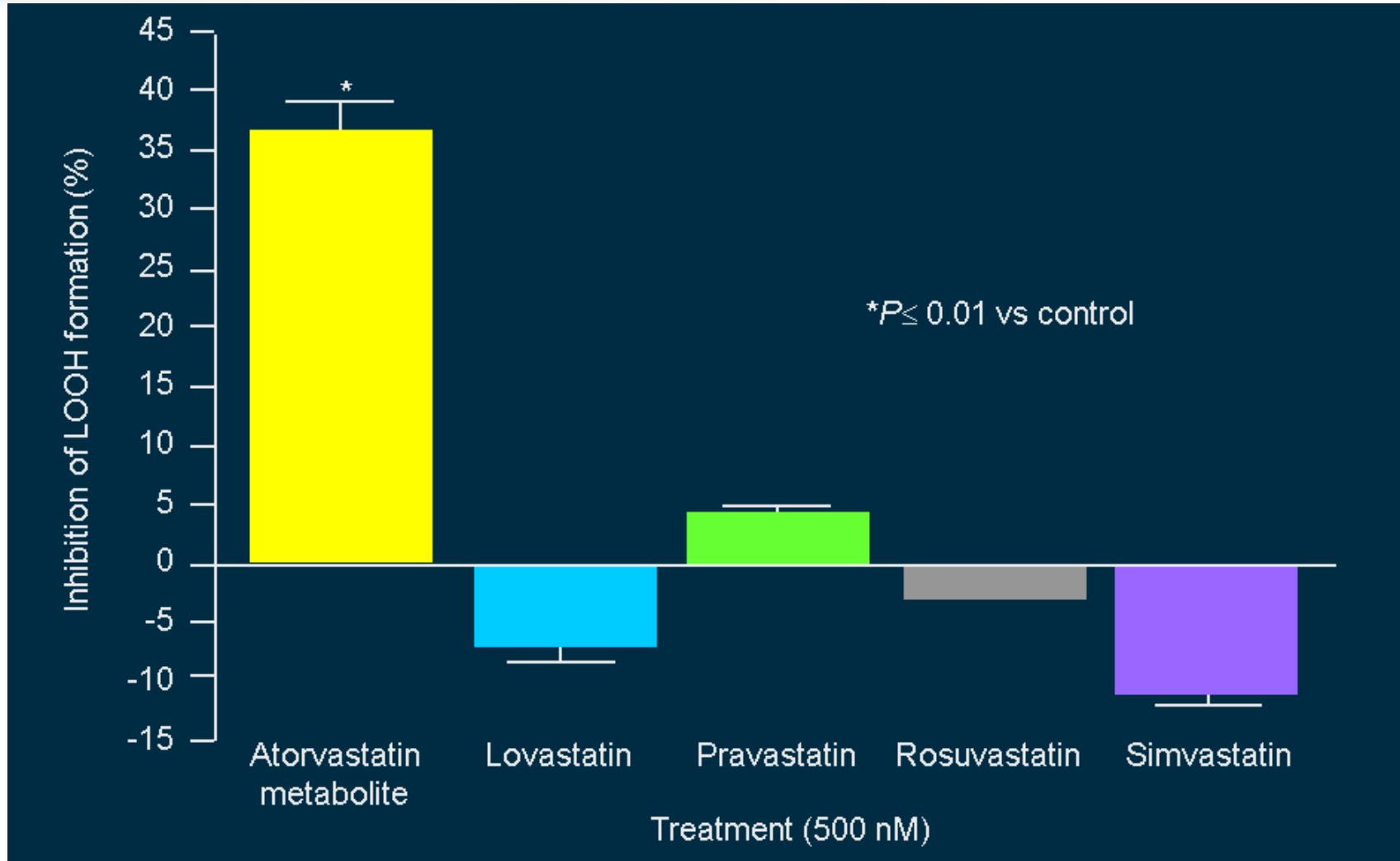
Mason RP. *J Am Coll Cardiol*. 2000;35(Suppl A):317.
Walter MF, et al. ACC. 2004. New Orleans, LA.

# Possible mechanisms of the clinical benefit:

# Vasodilation of coronary microvessels

**N=32 pts without CAD**

**randomized to placebo**

**or**

**atorvastatin (single dose of 40 mg)**

**transthoracic doppler**

**evaluation of LAD (baseline and 1 hr)**

Coronary flow velocity reserve
(hyperemic/basal peak diastolic velocity)



P<0.01

Before
After

Placebo    Atorvastatin

Hinoi T, et al. Am J Cardiol 2005

# Possible mechanisms of the clinical benefit: Antithrombotic effects

**N=30 hypercholesterolemic pts randomized to diet or atorvastatin (10 mg/d) for 3 days**



**PLT CD40L expression (AU)**
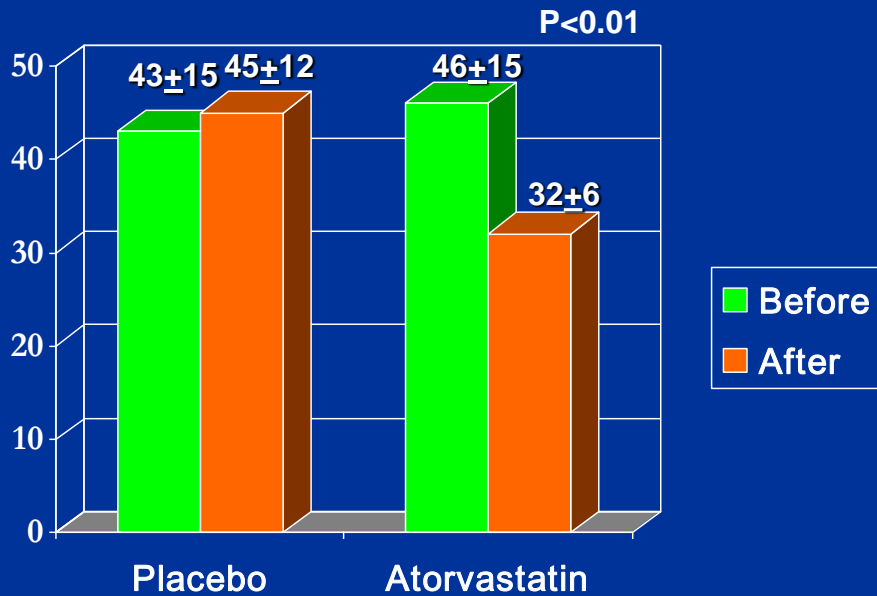
**Prothrombin fragment F1+2 (nM)**
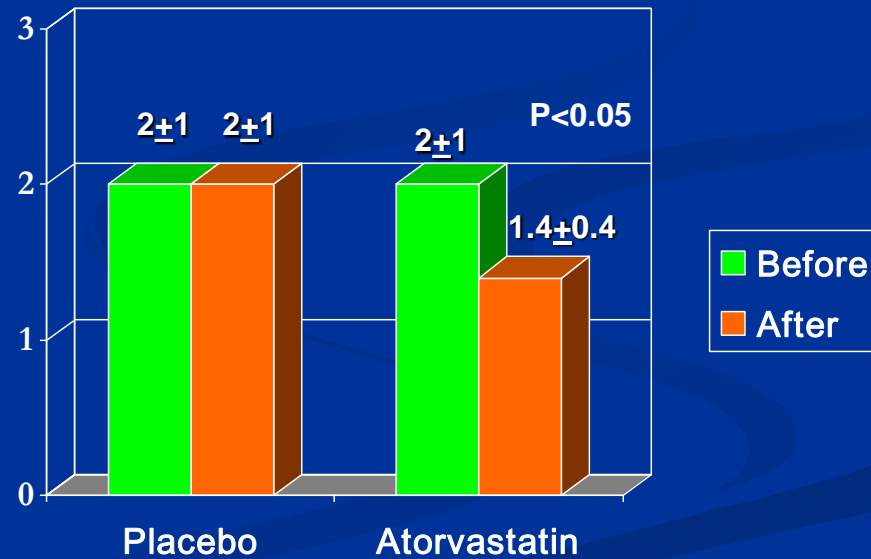
**Possible mechanisms of the clinical benefit:**

**Attenuation of endothelial activation**

**ARMYDA-CAMs RESULTS**

Patti G et al. JACC 2006;48:1560
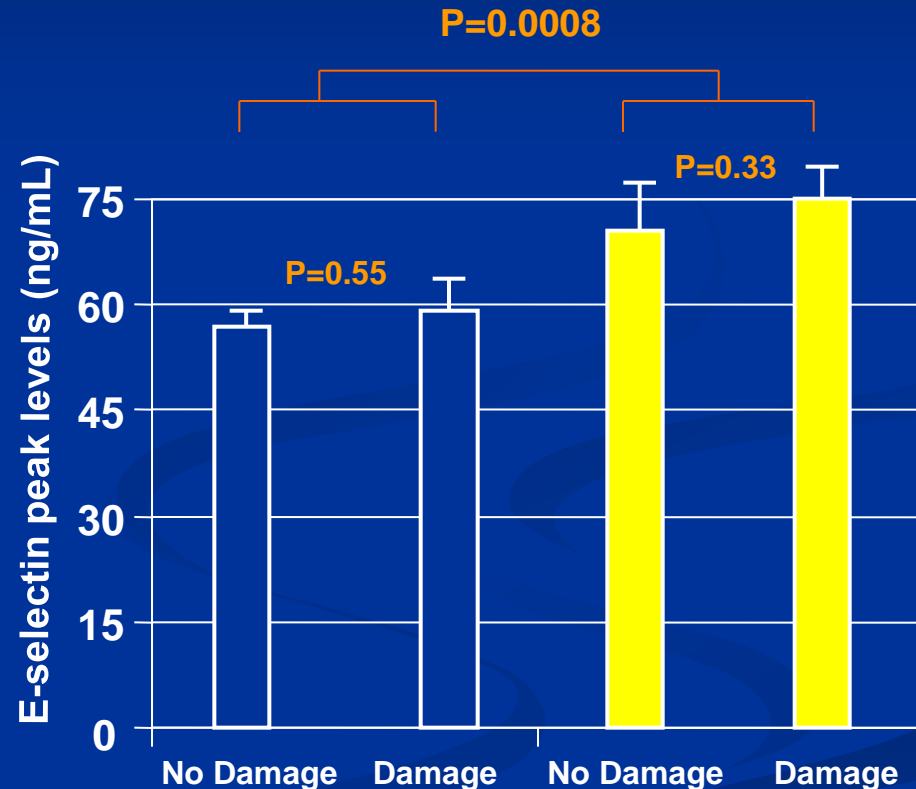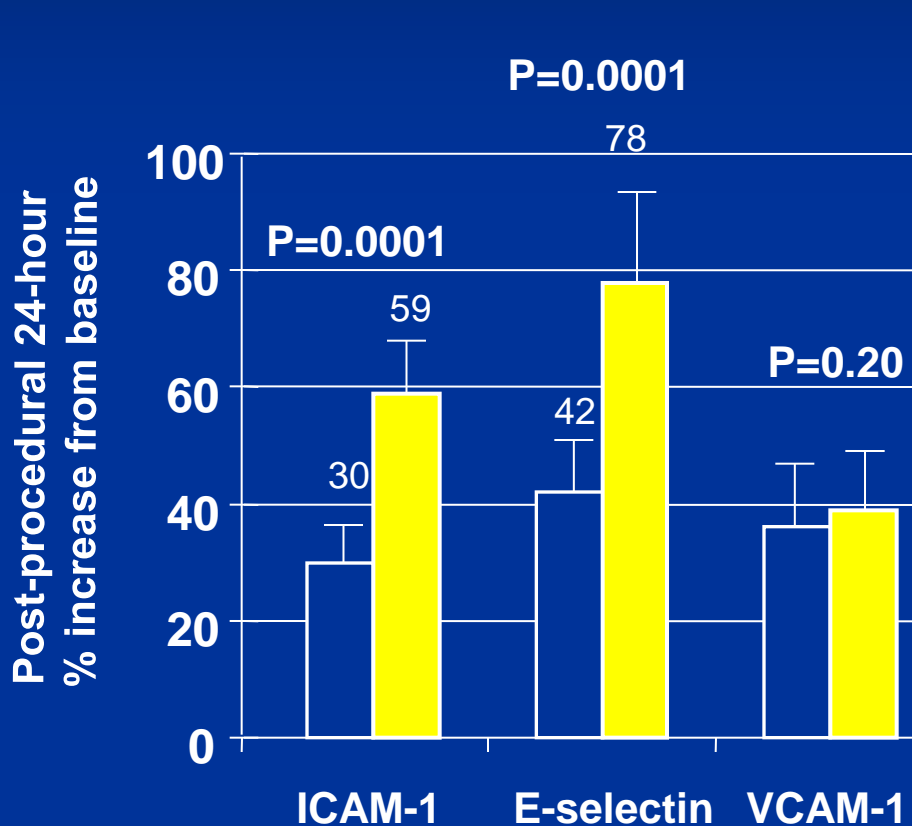
# Expression of HMG-CoA reductase in human coronary atherosclerotic plaques
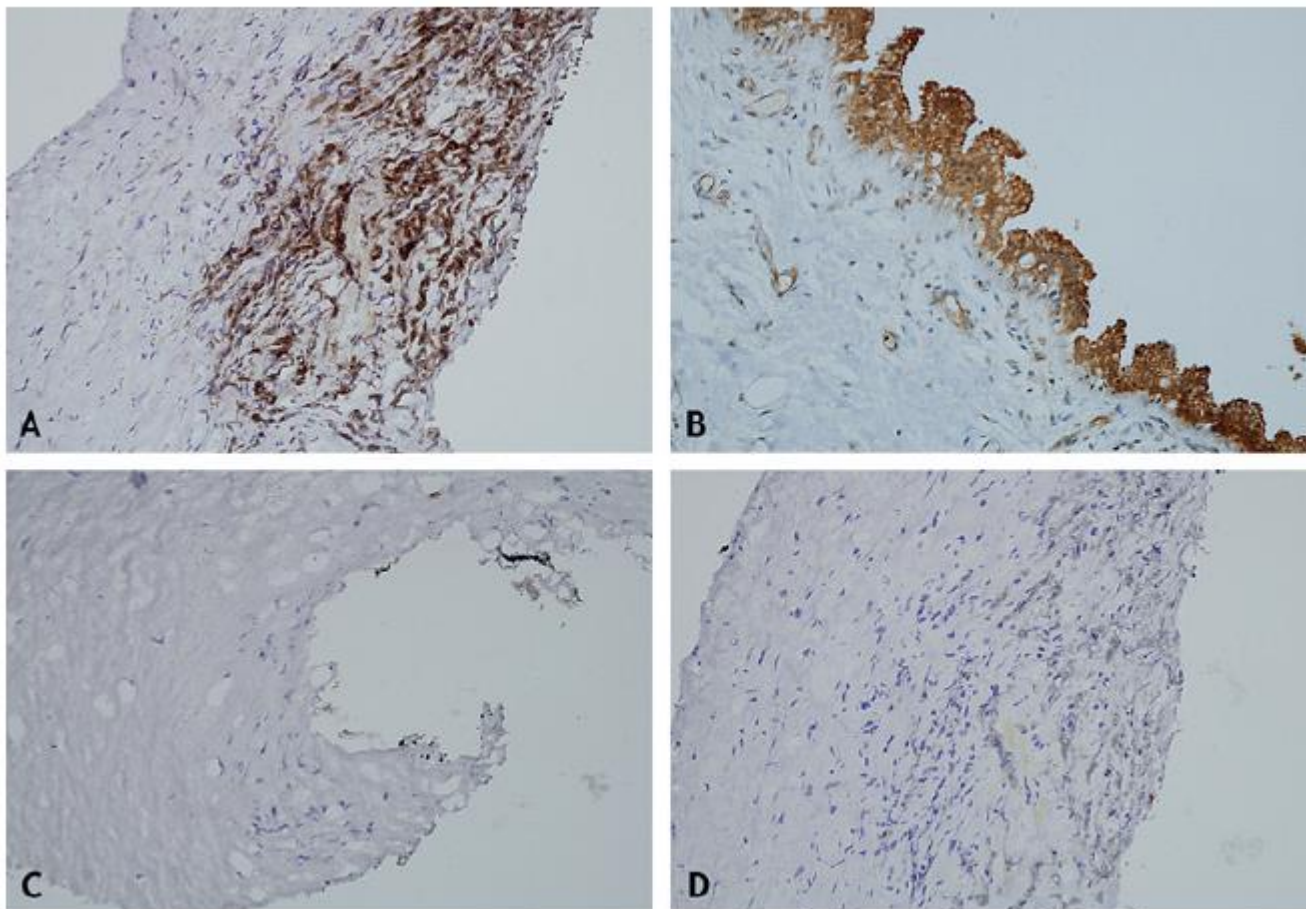


The lipophilic statins seem to penetrate the vessel wall more effectively than the hydrophilic statins, eliciting direct local anti-inflammatory effects.

Lee CW et al. Heart 2011;97:715-720

# ARBITER: Atorvastatin versus Pravastatin on reducing cholesterol (CIMT)

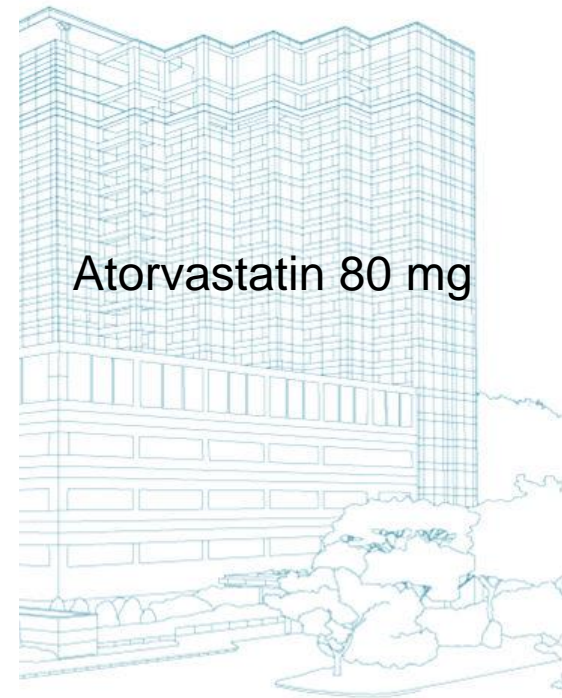**161 patients with CVD** were randomized to Atorvastatin 80 mg/d or Pravasatin 40 mg/d



*P=0.03 for difference between treatment groups.

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

# **ASAP trial:** carotid atherosclerosis progression



Simvastatin 40 mg

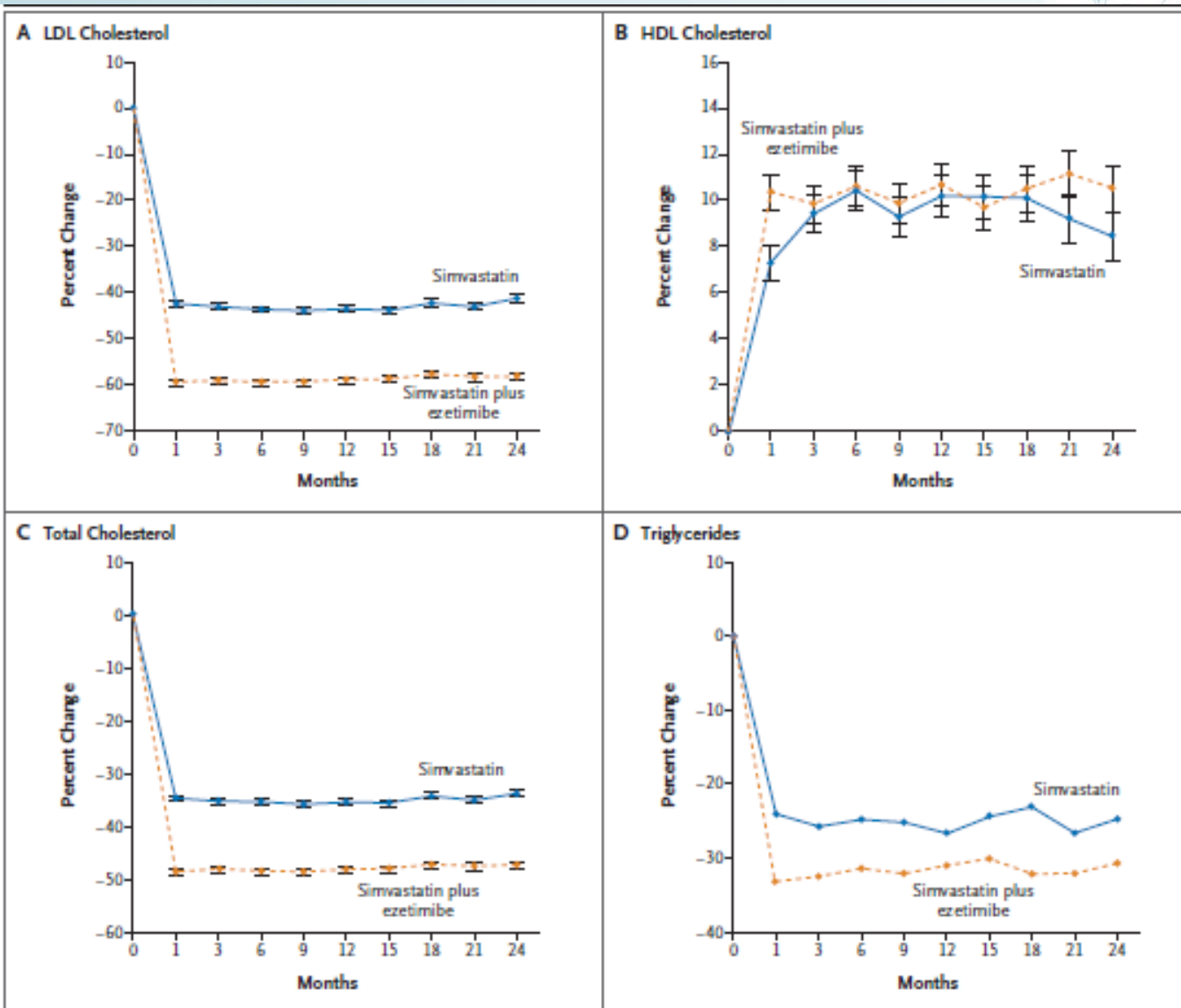Atorvastatin 80 mg

*Lancet* 2001; 357: 577–81
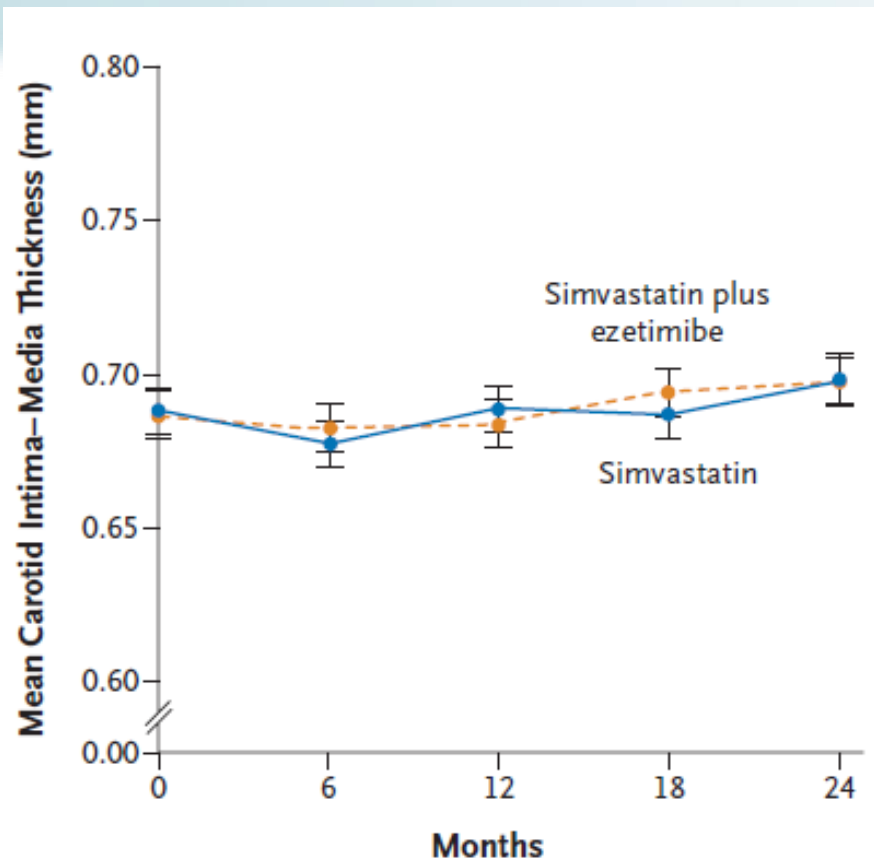
# ENHANCE :Design

Comparison of ezetimibe plus simvastatin versus simvastatin monotherapy on atherosclerosis progression in familial hypercholesterolemia: Design and rationale of the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression

**Randomized, Double-Blinded**

**720 patients**
**Familial Hypercholesterolemia**

**Ezetimibe 10 mg + Simvastatin 80 mg**

**Placebo + Simvastatin 80 mg**

**24 months**

**Primary End Point**

- Change in ultrasound-determined average carotid artery intima-media thickness (IMT) on a per subject basis between baseline and endpoint

# ENHANCE Results

# ENHANCE Results



In patients with familial hypercholesterolemia, combined therapy with ezetimibe and simvastatin did not result in a significant difference in changes in intima–media thickness, as compared with simvastatin alone, despite decreases in levels of LDL cholesterol and C-reactive protein

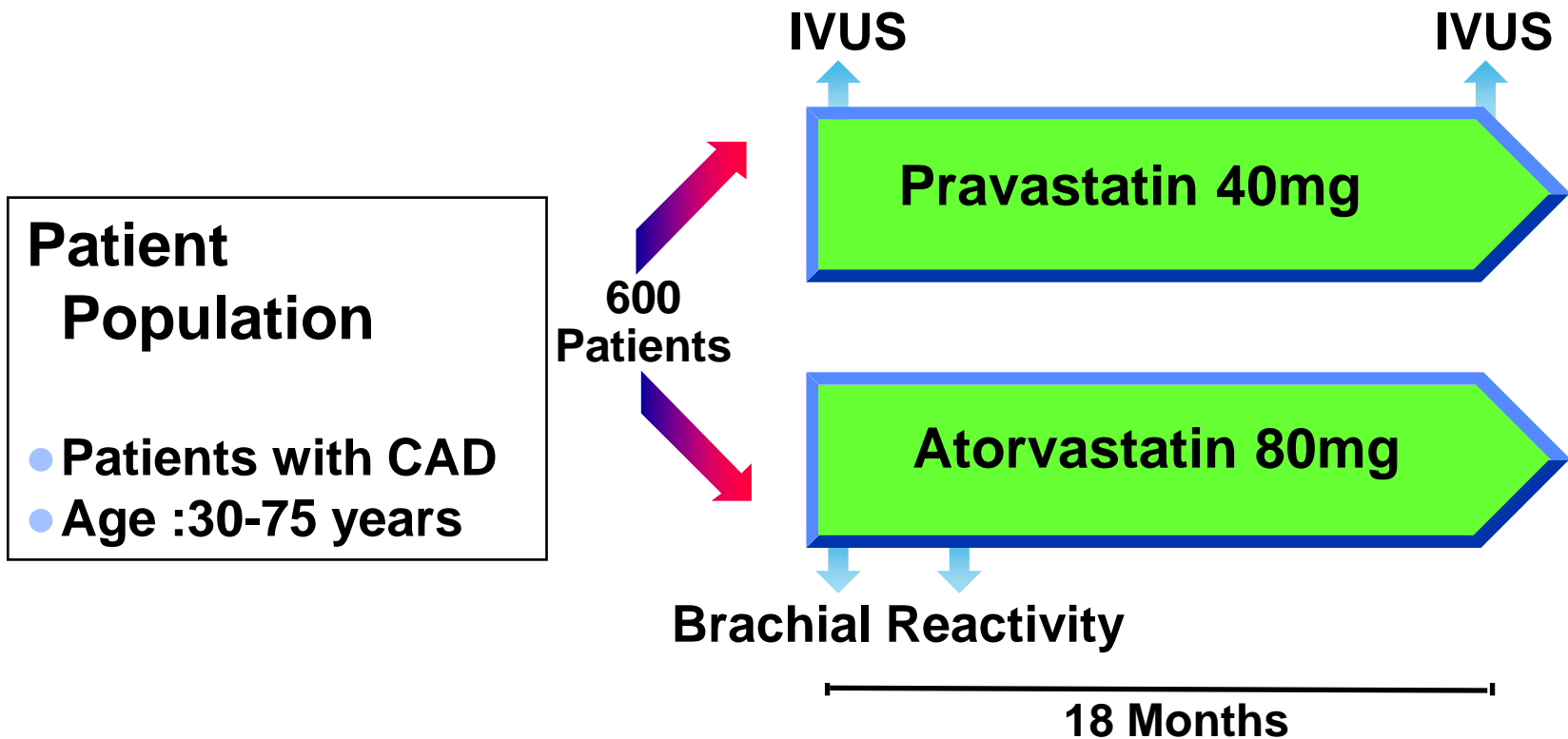# Relationship Between Coronary Atheroma Burden and Cardiovascular Events

**Death, myocardial infarction and coronary revascularization**
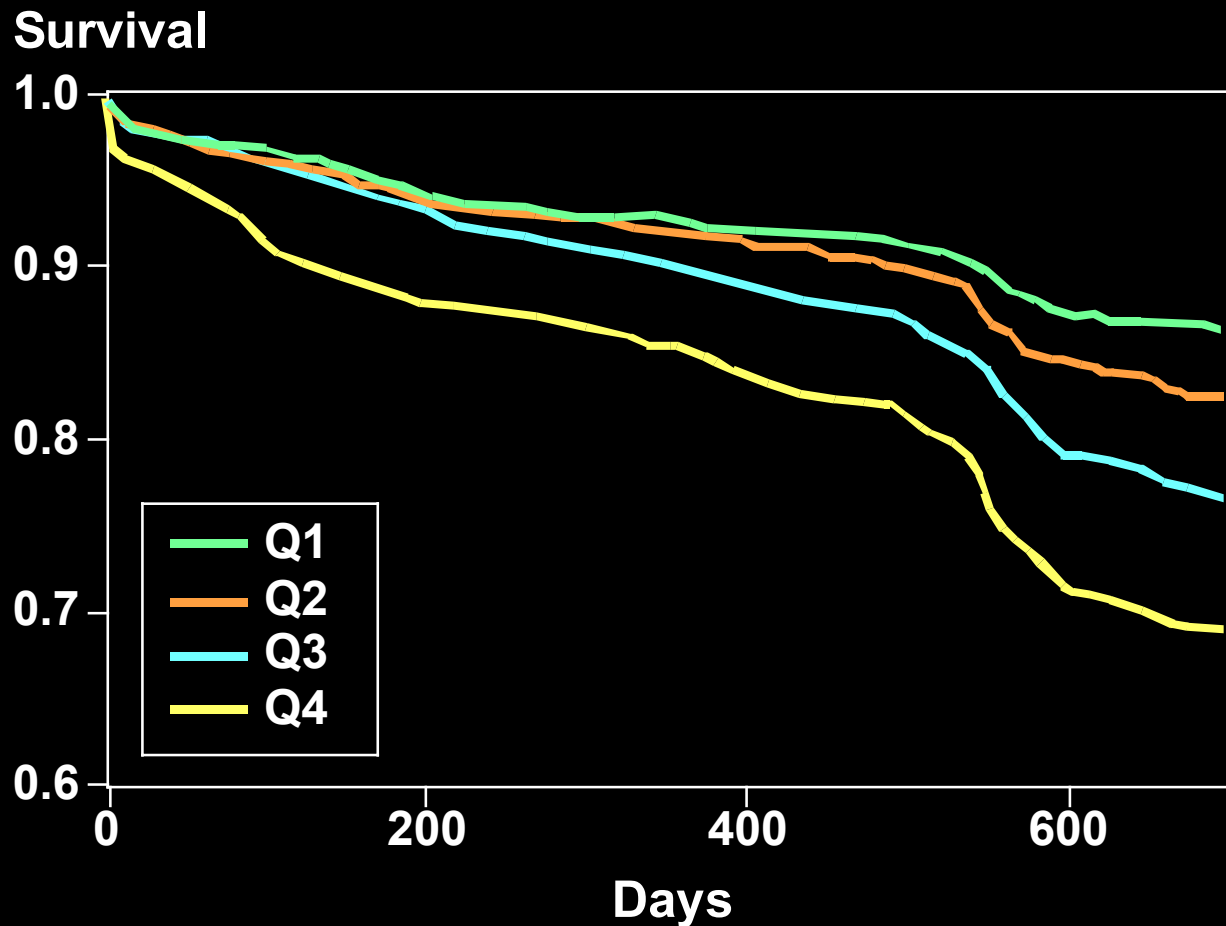
# Changes in atheroma burden according to MACEs

| Clinical Event | Percent Atheroma Volume (%) | | |
| --- | --- | --- | --- |
| | No | Yes | p Value |
| **Entire cohort** | | | |
| Death, myocardial infarction, coronary revascularization | 0.46 ± 0.16 | 0.95 ± 0.19 | <0.001 |
| Death | 0.56 ± 0.17 | −0.60 ± 1.55 | 0.45 |
| Myocardial infarction | 0.56 ± 0.17 | 0.61 ± 0.44 | 0.90 |
| Coronary revascularization | 0.46 ± 0.16 | 0.96 ± 0.19 | <0.001 |
| **Excluding experimental therapies** | | | |
| Death, myocardial infarction, coronary revascularization | 0.44 ± 0.16 | 1.06 ± 0.20 | <0.001 |
| Death | 0.56 ± 0.16 | −1.89 ± 2.14 | 0.25 |
| Myocardial infarction | 0.56 ± 0.16 | 0.76 ± 0.59 | 0.73 |
| Coronary revascularization | 0.44 ± 0.16 | 1.08 ± 0.20 | <0.001 |

# REVERSAL Study Design



**Patient Population**

- **Patients with CAD**
- **Age :30-75 years**

**600 Patients**

IVUS → **Pravastatin 40mg** → IVUS
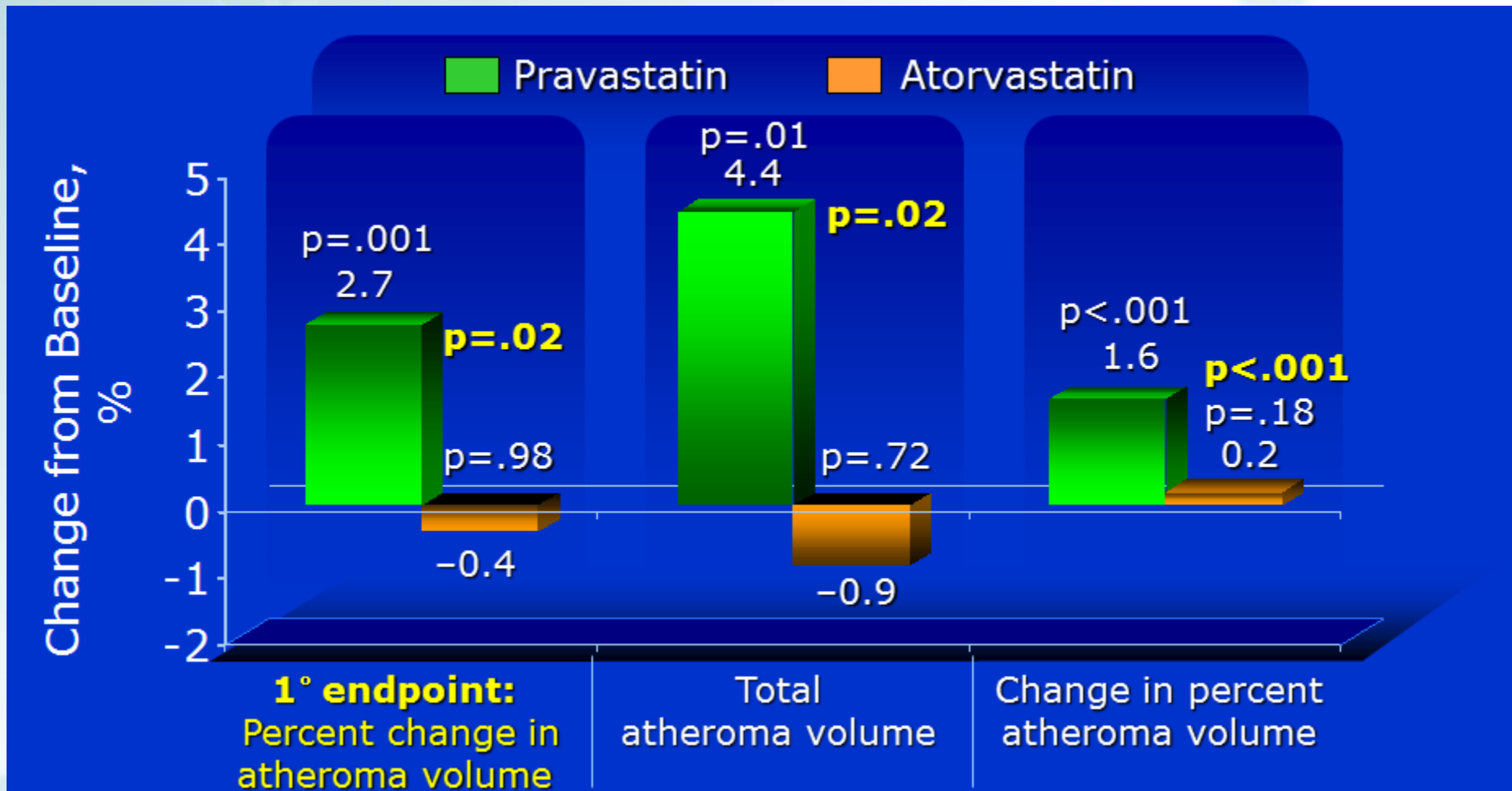
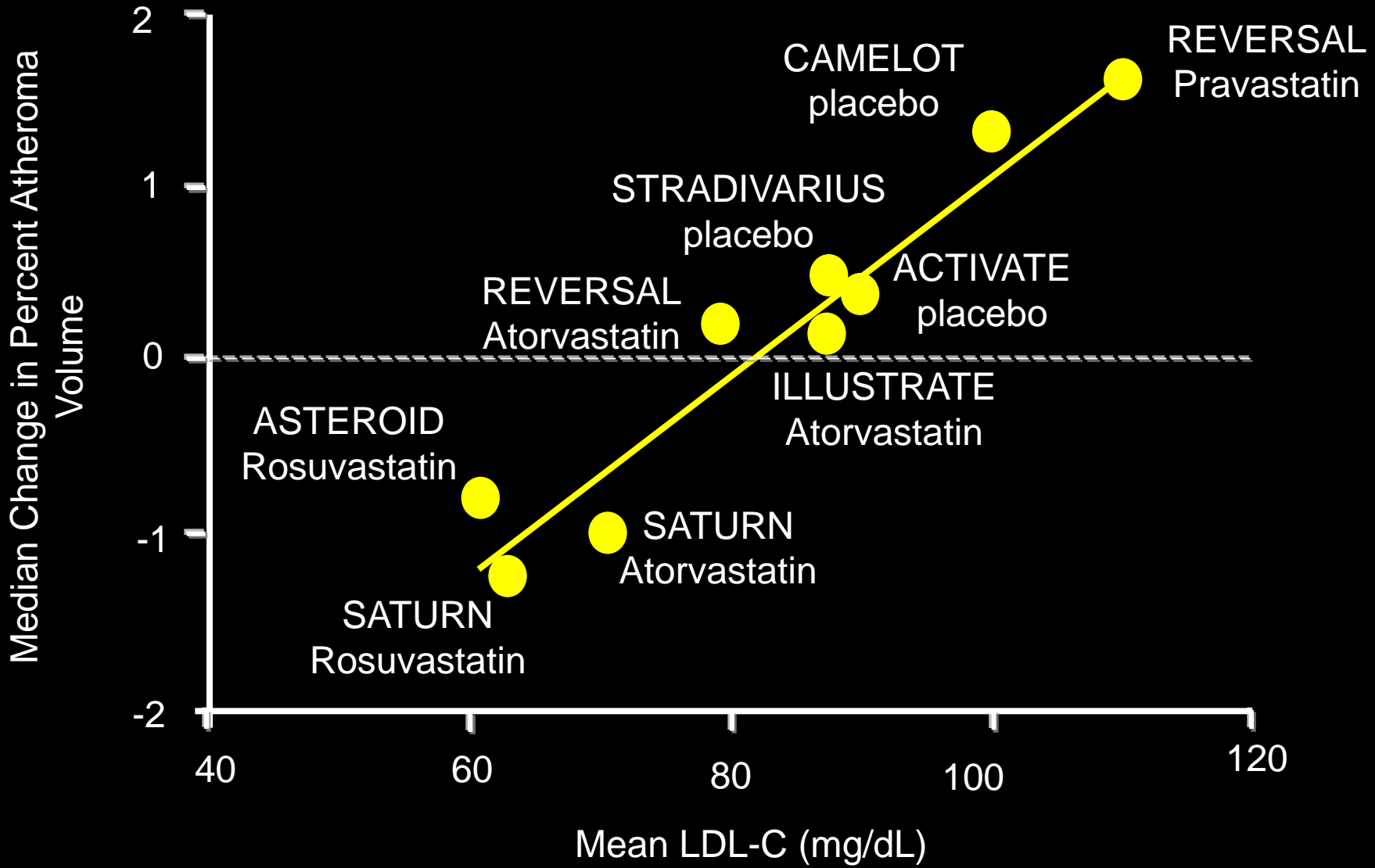→ **Atorvastatin 80mg**

**Brachial Reactivity**

**18 Months**

## Primary Efficacy Parameter

- **Change in Coronary Plaque Volume assessed by IVUS**

# REVERSAL trial: coronary atherosclerosis progression



Nissen SE et al. *JAMA* 2004;291:1071-1080.
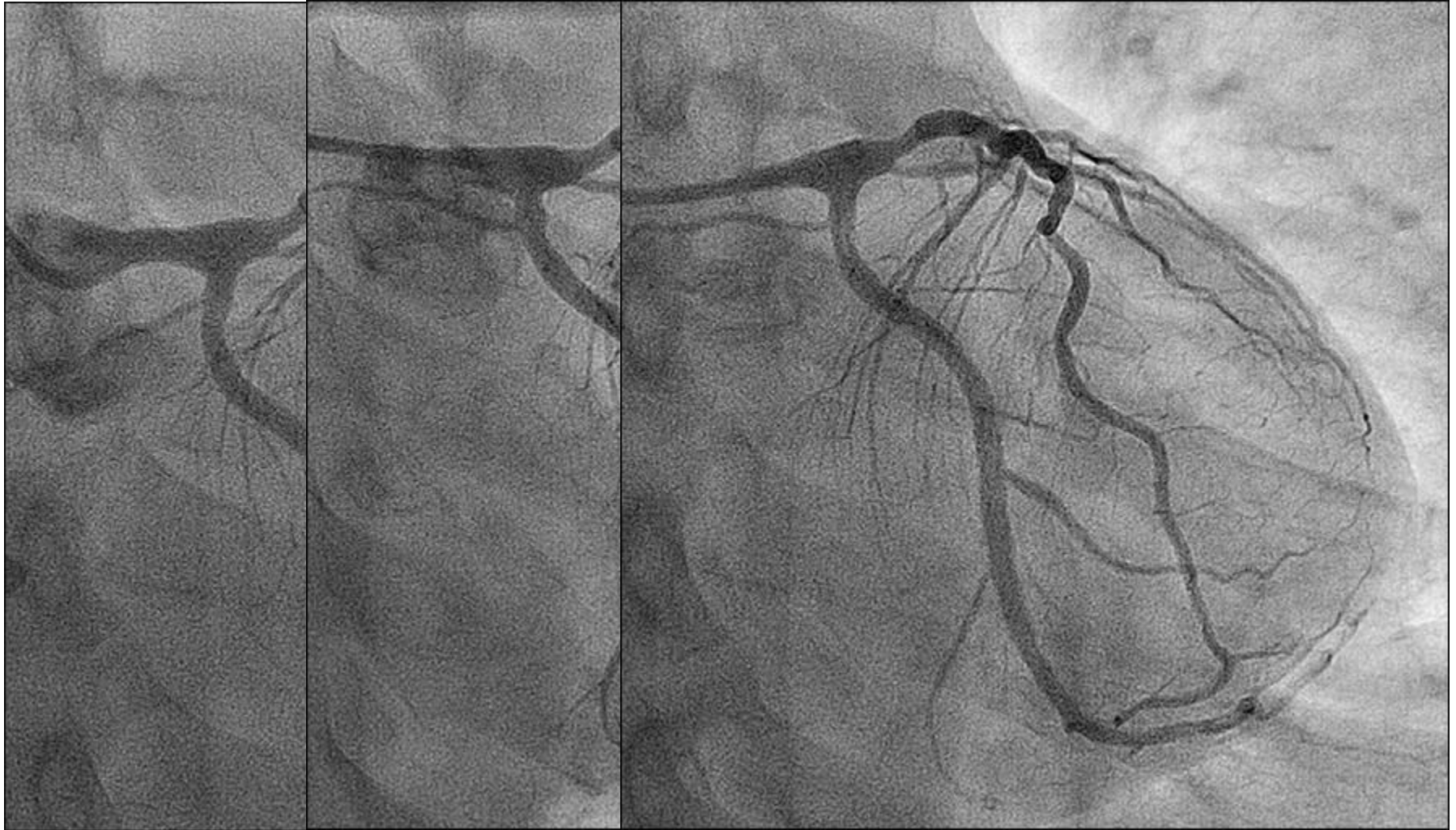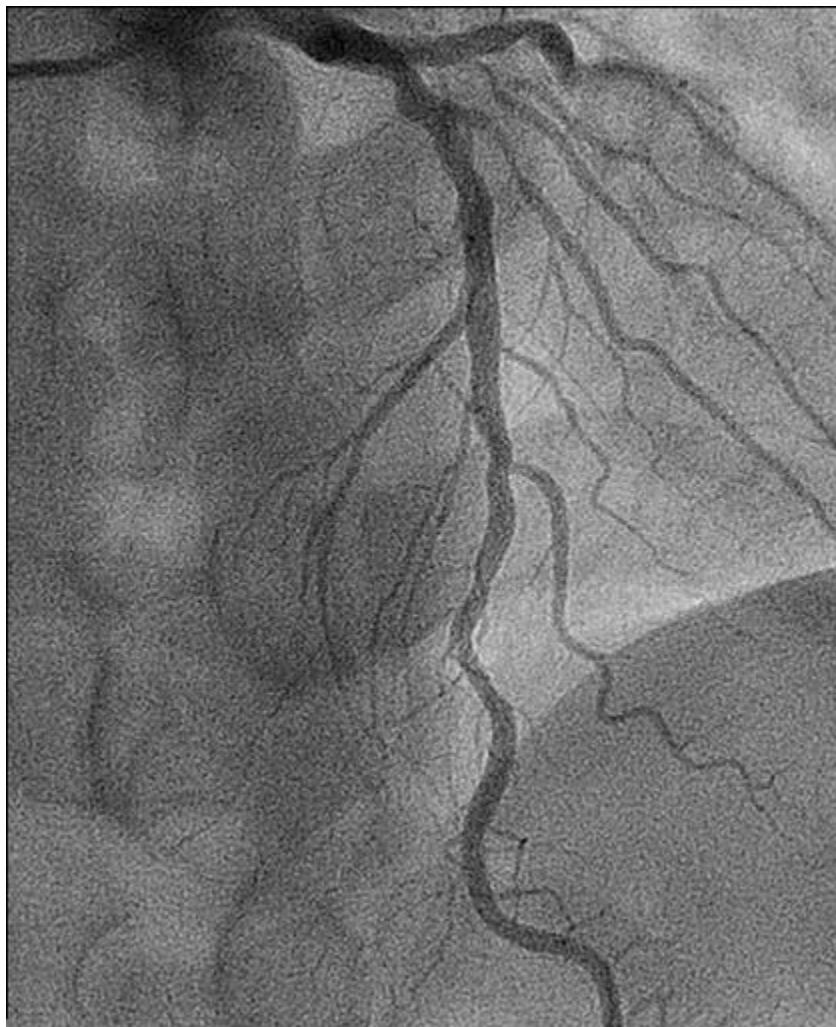
# Achieved LDL-C and Change in Percent Atheroma Volume

# Case

- M/50
- NSTEMI (2008.06) → PCI on dLCx with Xience 3.0*23
- Mid-LAD diffuse intermediate lesion → medical treatment
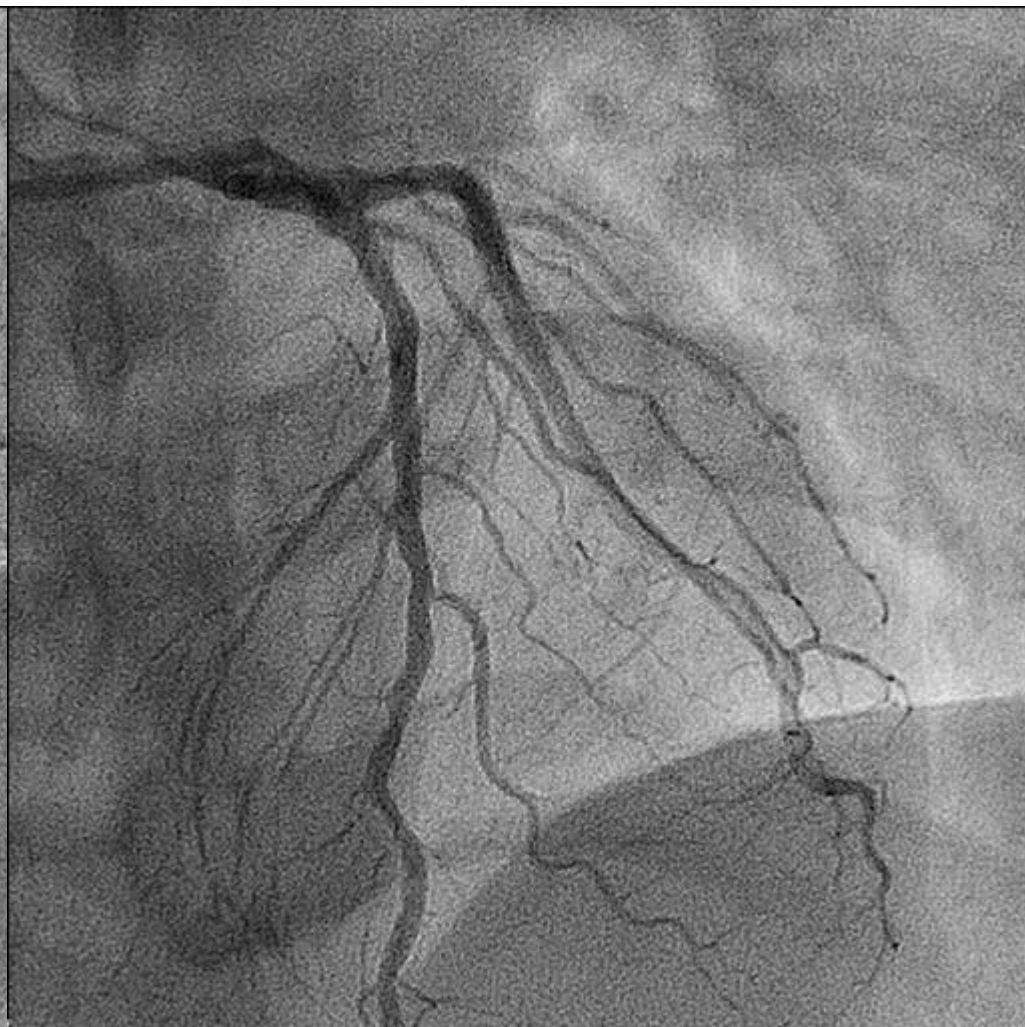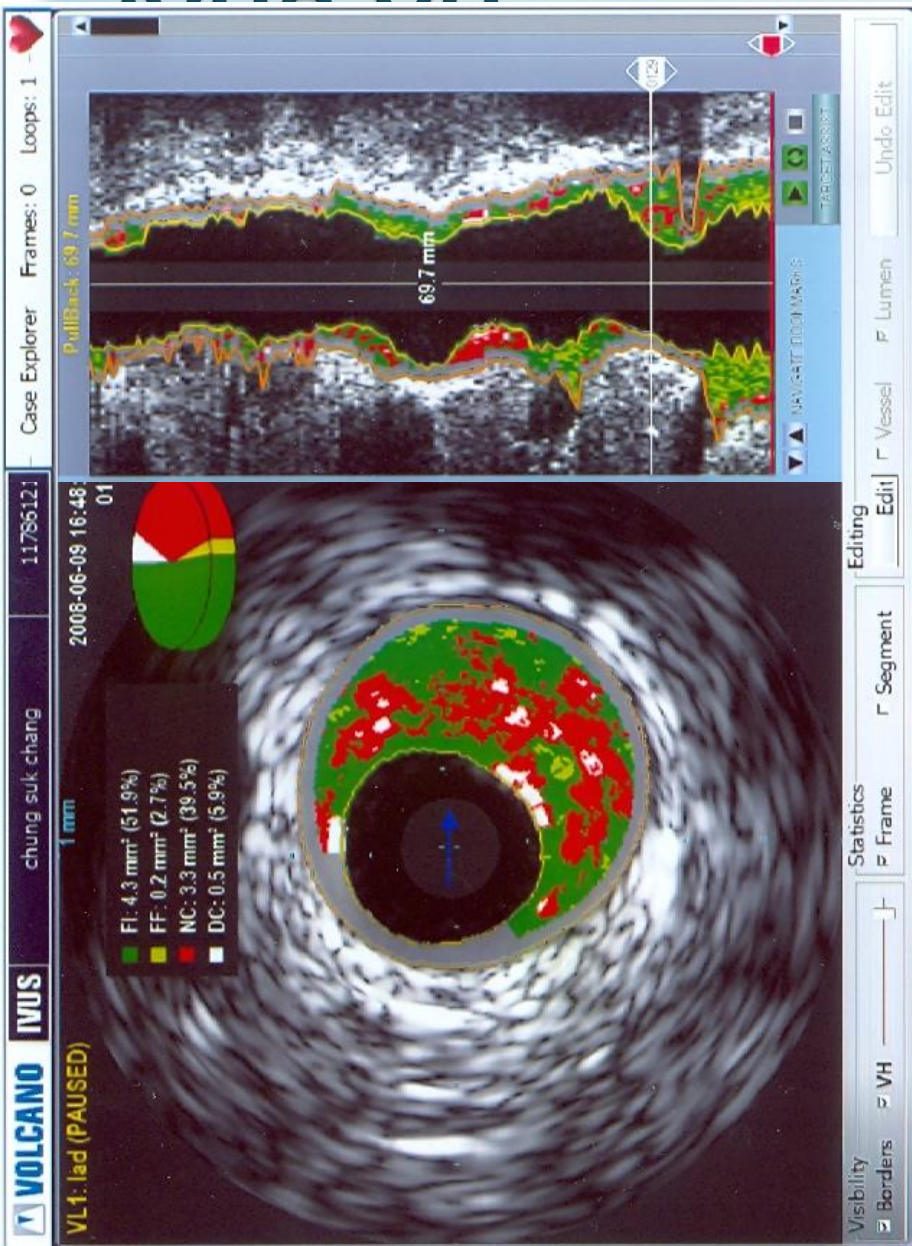
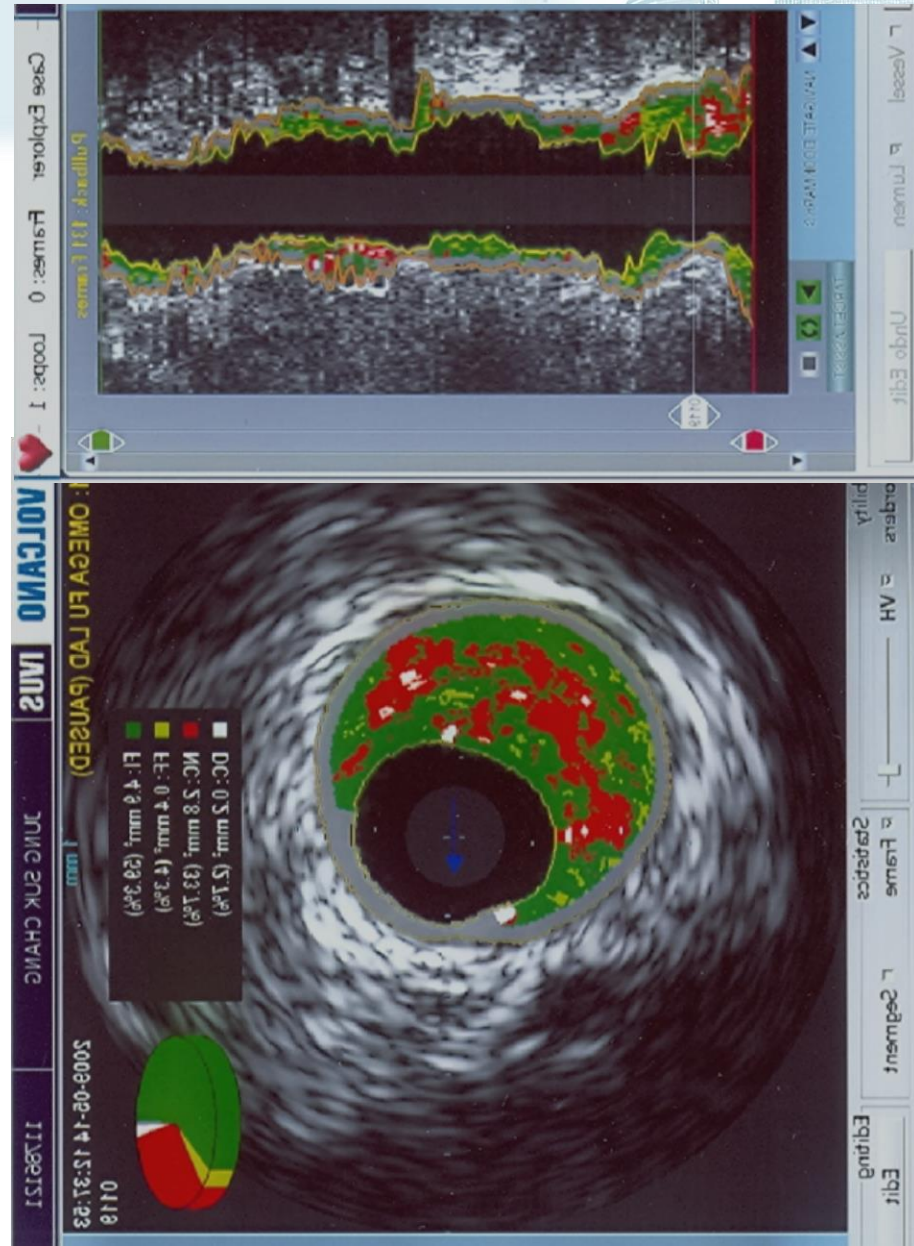- Atorvastatin 40 mg for 1 years

# CAG and PCI

# Non-culprit vessel



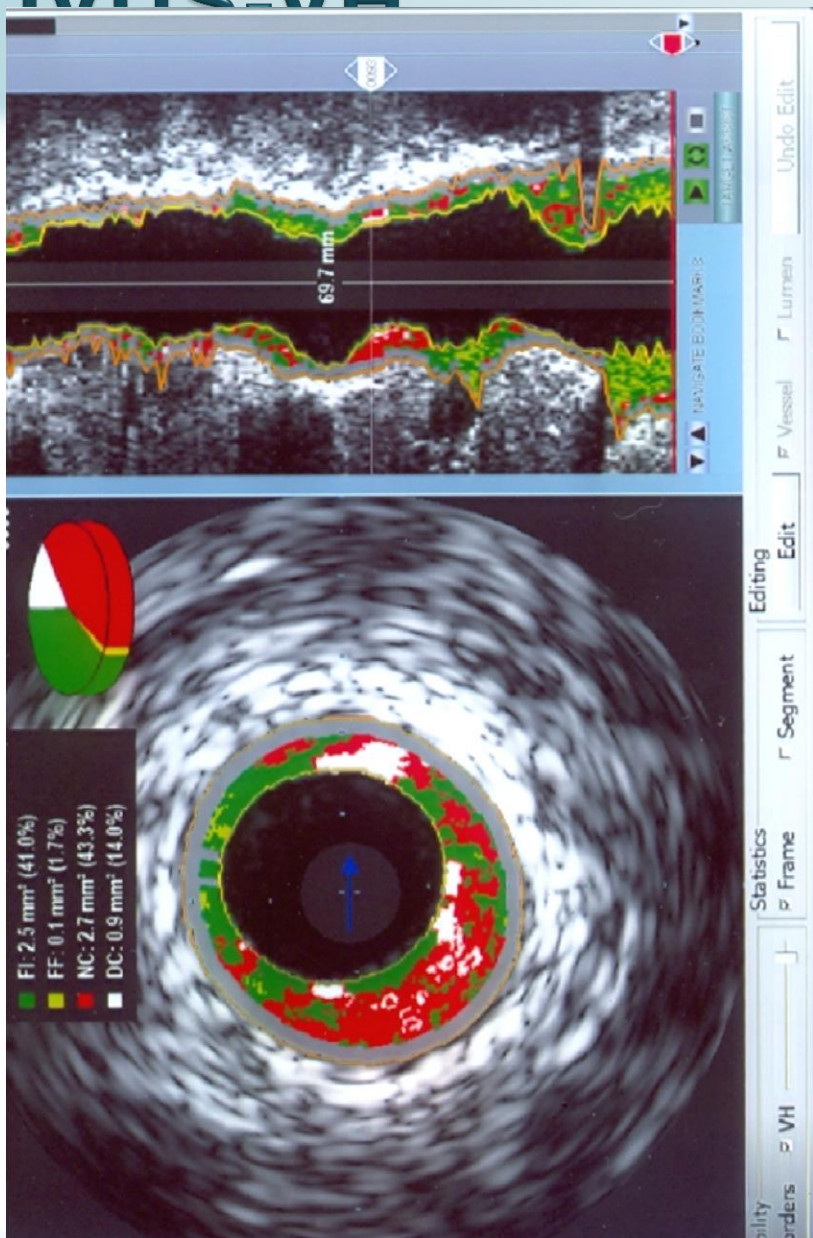Baseline

Follow-up

# IVUS-VH


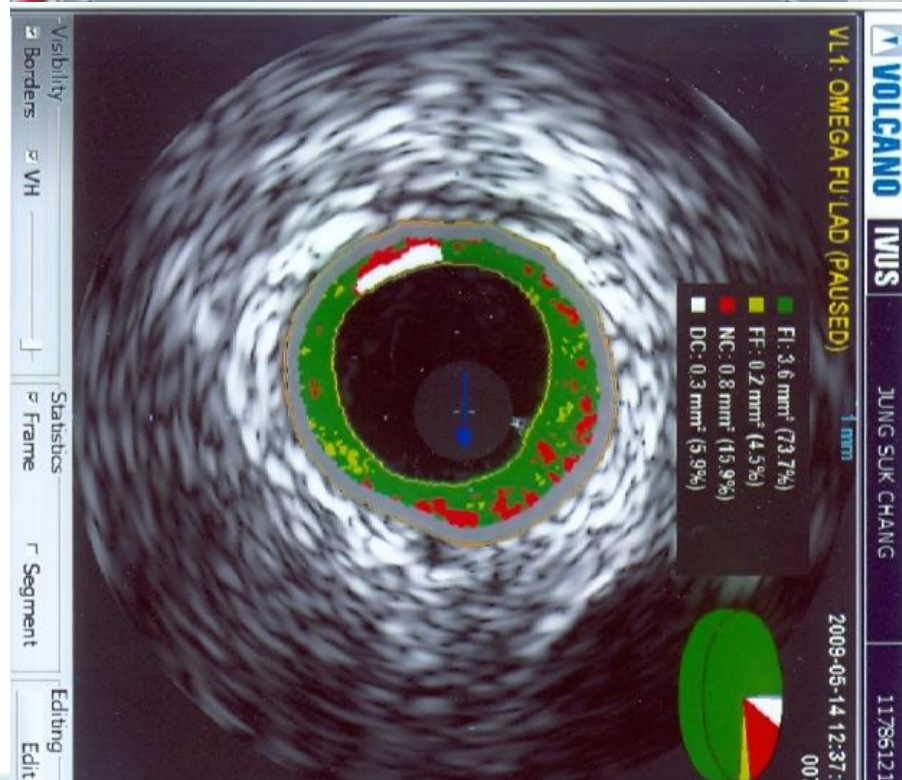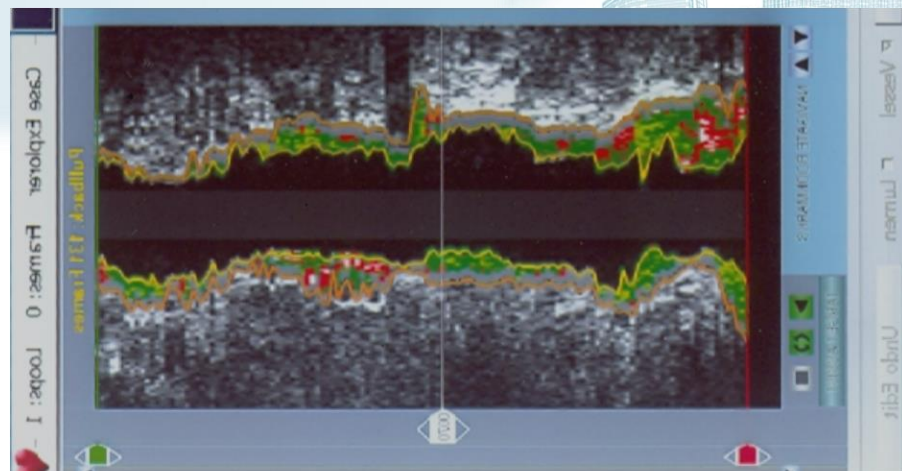
Baseline               Follow-up

# IVUS-VH



Baseline

Follow-up

# Review: Statins & adverse events in placebo-controlled trials

## Statins vs placebo in primary or secondary cardiovascular disease prevention*

| Settings | Outcomes | Number of trials (*n*) | Weighted event rates | | Pooled RRR/RRI (95% CI) | NNT/NNH (CI) |
|---|---|---|---|---|---|---|
| | | | Statins | Placebo | | |
| Primary prevention | Serious adverse events† | 9 (38 257)‡ | 14.8% | 14.9% | RRR 0.9% (−7 to 8) | Not significant |
| | Treatment withdrawal | 10 (27 205)‡ | 12% | 13% | RRR 11% (1 to 21) | NNT 67 (37 to 717) |
| | Diabetes | 2 (20 640) | 2.7% | 2.2% | RRI 25% (5 to 48) | NNH 184 (96 to 918) |
| | All-cause mortality | 10 (43 124) | 3.1% | 3.6% | RRR 14% (5 to 23) | NNT 199 (121 to 556) |
| | MI§ | 8 (37 002) | 2.0% | 3.0% | Not reported | NNT 100 (72 to 143) |
| | Stroke§ | 8 (37 002) | 0.7% | 1.1% | Not reported | NNT 334 (200 to 1000) |
| Secondary prevention | Serious adverse events† | 5 (14 993)‡ | 8.3% | 11% | RRR 26% (−5 to 48) | Not significant |
| | Treatment withdrawal | 9 (22 195)‡ | 12% | 15% | RRR 18% (0 to 33) | Not significant |
| | All-cause mortality | 14 (39 080) | 13% | 14% | RRR 10% (5 to 14) | NNT 70 (50 to 139) |
| | MI§ | 11 (31 193) | 5.8% | 8.0% | Not reported | NNT 44 (36 to 59) |
| | Stroke§ | 7 (27 610) | 3.4% | 4.1% | Not reported | NNT 143 (84 to 334) |

# Similar incidence of adverse events across dose range

*Data from 2006 safety meta-analysis involving 14,236 patients from 49 trials*

| | Number of patients (%) | | |
|---|---|---|---|
| | **Placebo (n=2180)** | **Atortastatin 10 mg (n=7258)** | **Atortastatin 80 mg (n=4798)** |
| Patients with ≥1 AE | | | |
| All | 768 (35.2) | 3870 (53.3) | 2285 (47.6) |
| Treatment-associated | 270 (12.4) | 983 (13.5) | 699 (14.6) |
| Withdrawals due to AEs | | | |
| All | 51 (2.3) | 251 (3.5) | 136 (2.8) |
| Treatment-associated | 27 (1.2) | 171 (2.4) | 84 (1.8) |
| Serious nonfatal AEs | | | |
| All | 122 (5.6) | 453 (6.2) | 385 (8.0) |
| Treatment-associated | 92 (4.2) | 12 (0.2) | 25 (0.5) |

Ref. Newman C et al. Am J Cardiol. 2006;97:61-67.

# Incidence and incidence rate for treatment-associated adverse events by body system

| Body System | Atorvastatin Dose | | | | | | Placebo | |
|---|---|---|---|---|---|---|---|---|
| | 10 mg (n = 7,258) | | | 80 mg (n = 4,798) | | | Placebo (n = 2,180) | |
| | n (%) | Rate* | | n (%) | Rate* | | n (%) | Rate* |
| Digestive | 367 (5.1) | 74.5 | | 298 (6.2) | 63.7 | | 87 (4.0) | 95.9 |
| Body as a whole | 323 (4.5) | 65.6 | | 198 (4.1) | 42.3 | | 95 (4.4) | 104.7 |
| Musculoskeletal | 170 (2.3) | 34.5 | | 129 (2.7) | 27.6 | | 26 (1.2) | 28.7 |
| Nervous | 144 (2.0) | 29.2 | | 72 (1.5) | 15.4 | | 34 (1.6) | 37.5 |
| Skin/appendages | 101 (1.4) | 20.5 | | 39 (0.8) | 8.3 | | 17 (0.8) | 18.7 |
| Metabolic/nutriti | 89 (1.2) | 18.1 | | 100 (2.1) | 21.4 | | 23 (1.6) | 25.4 |
| Special senses | 29 (0.4) | 5.9 | | 11 (0.2) | 2.3 | | 3 (0.1) | 3.3 |
| Urogenital | 27 (0.4) | 5.5 | | 12 (0.3) | 2.6 | | 15 (0.7) | 16.5 |
| Cardiovascular | 46 (0.6) | 9.3 | | 22 (0.5) | 4.7 | | 13 (0.6) | 14.3 |

* Incidence rate per 1,000 patient-years of exposure.

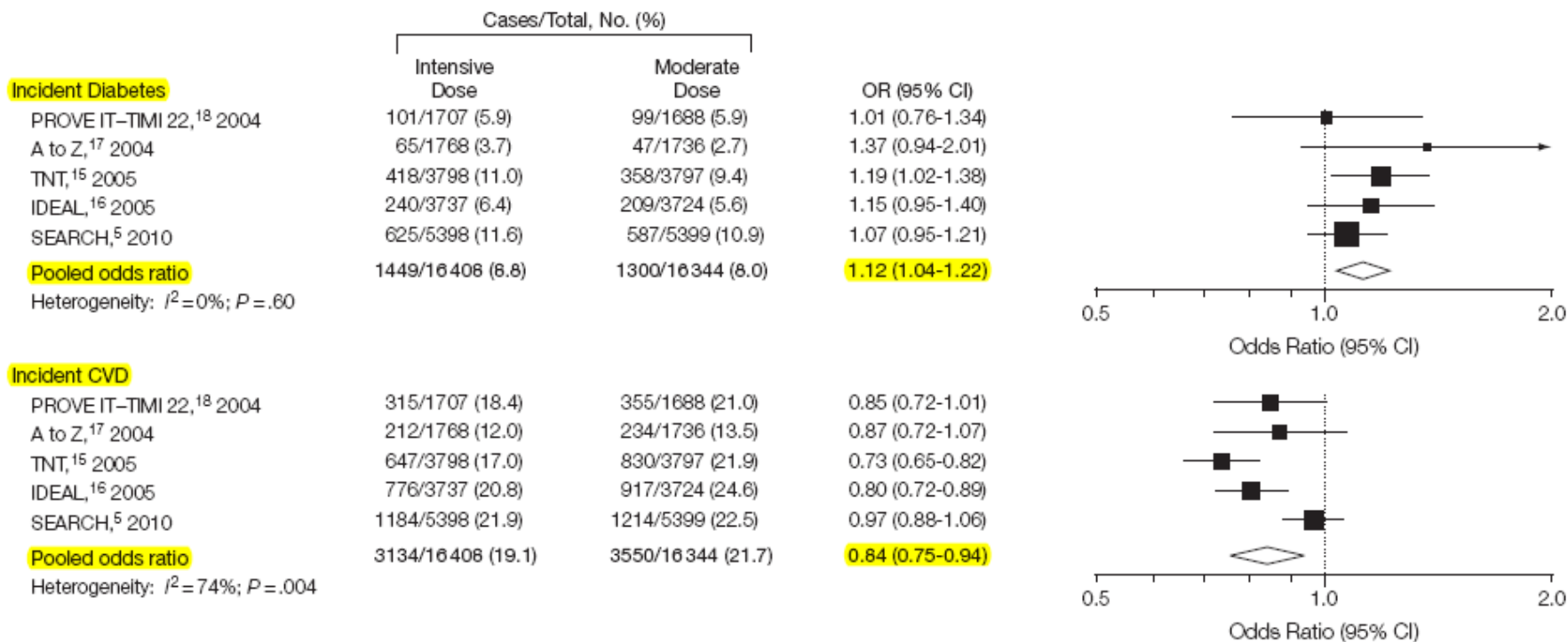# Incidence of myalgia with atorvastatin
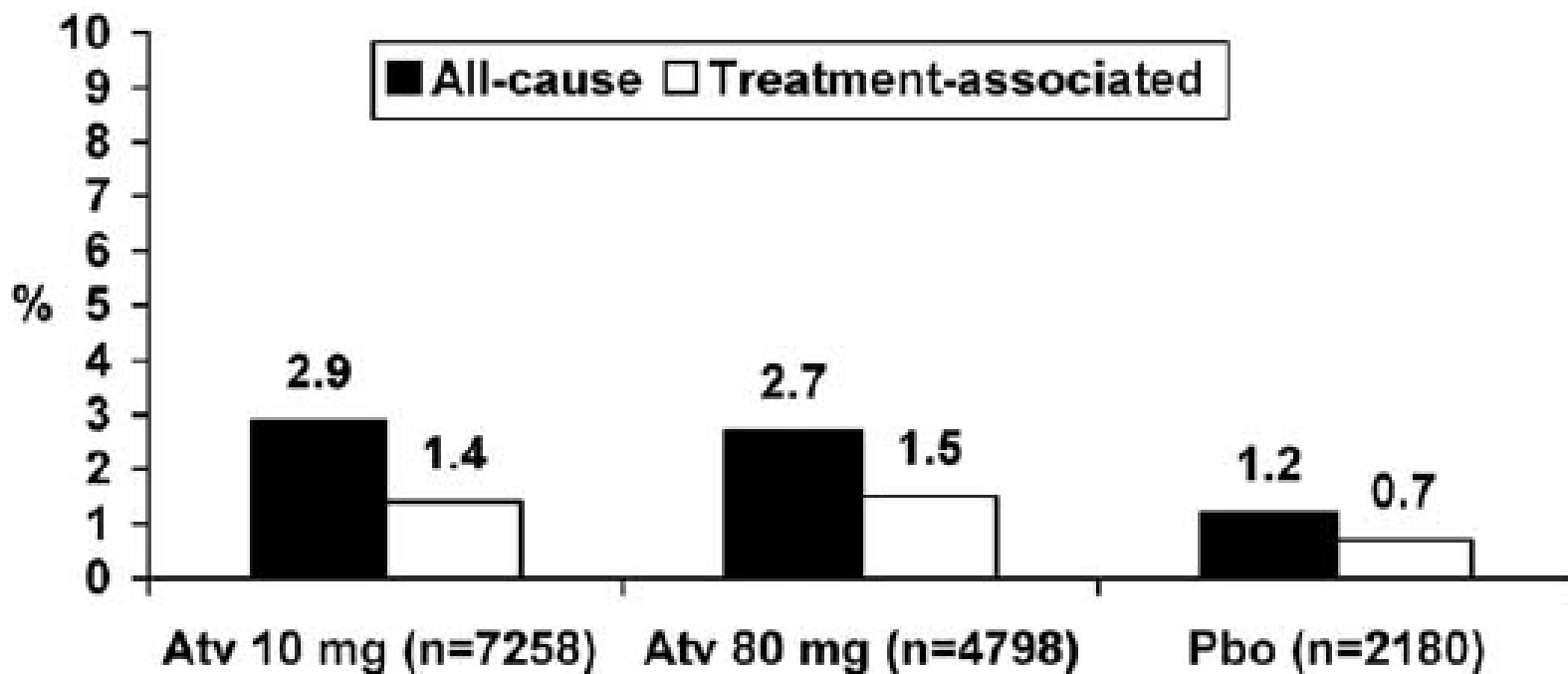
# Risk of Incident Diabetes With Intensive-Dose Compared With Moderate-Dose Statin Therapy
## A Meta-analysis

**Figure 2.** Meta-analysis of New-Onset Diabetes and First Major Cardiovascular Events in 5 Large Trials Comparing Intensive-Dose to Moderate-Dose Statin Therapy
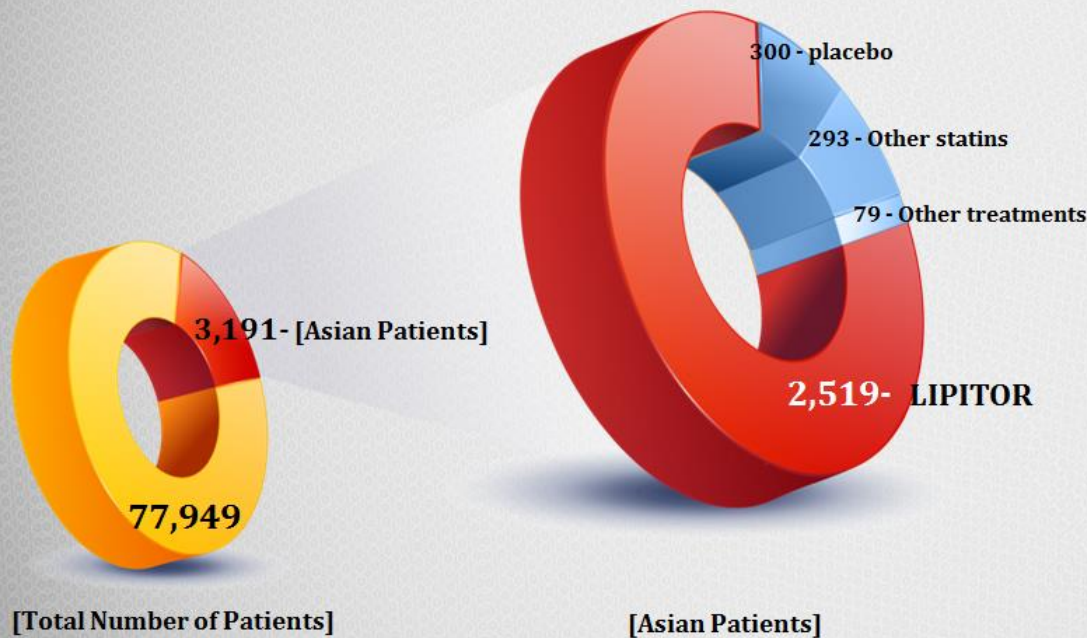
| | Cases/Total, No. (%) | | |
| --- | --- | --- | --- |
| | Intensive Dose | Moderate Dose | OR (95% CI) |
| **Incident Diabetes** | | | |
| PROVE IT–TIMI 22,[18] 2004 | 101/1707 (5.9) | 99/1688 (5.9) | 1.01 (0.76-1.34) |
| A to Z,[17] 2004 | 65/1768 (3.7) | 47/1736 (2.7) | 1.37 (0.94-2.01) |
| TNT,[15] 2005 | 418/3798 (11.0) | 358/3797 (9.4) | 1.19 (1.02-1.38) |
| IDEAL,[16] 2005 | 240/3737 (6.4) | 209/3724 (5.6) | 1.15 (0.95-1.40) |
| SEARCH,[5] 2010 | 625/5398 (11.6) | 587/5399 (10.9) | 1.07 (0.95-1.21) |
| Pooled odds ratio | 1449/16 408 (6.8) | 1300/16 344 (8.0) | 1.12 (1.04-1.22) |
| Heterogeneity: $I^2=0\%$; $P=.60$ | | | |
| **Incident CVD** | | | |
| PROVE IT–TIMI 22,[18] 2004 | 315/1707 (18.4) | 355/1688 (21.0) | 0.85 (0.72-1.01) |
| A to Z,[17] 2004 | 212/1768 (12.0) | 234/1736 (13.5) | 0.87 (0.72-1.07) |
| TNT,[15] 2005 | 647/3798 (17.0) | 830/3797 (21.9) | 0.73 (0.65-0.82) |
| IDEAL,[16] 2005 | 776/3737 (20.8) | 917/3724 (24.6) | 0.80 (0.72-0.89) |
| SEARCH,[5] 2010 | 1184/5398 (21.9) | 1214/5399 (22.5) | 0.97 (0.88-1.06) |
| Pooled odds ratio | 3134/16 408 (19.1) | 3550/16 344 (21.7) | 0.84 (0.75-0.94) |
| Heterogeneity: $I^2=74\%$; $P=.004$ | | | |

Data marker size indicates relative weight of the studies; OR, odds ratio; and CI, confidence interval.

# Safety profile of Lipitor in Asian patients

## Atorvastatin Among Asians Compared to Total patient Population

300 - placebo

293 - Other statins

79 - Other treatments

3,191 - [Asian Patients]

2,519 - LIPITOR

77,949

[Total Number of Patients]

[Asian Patients]

## Important Safety Parameters

◑ **Liver Safety**

**ALT >3xULN**
- Long-term trials: 2.1% vs 2.8% → Similar
- Short-term trials: 2.4% vs 3.0% → Similar

**AST >3xULN**
- Long-term trials: 1.9% vs 2.1% → Similar
- Short-term trials: 2.4% vs 1.8% → Similar

◑ **Musculoskeletal Safety**

**Rhabdomyolysis :** None
**Myalgia :** Lower in Asian patients than in all patients (6.7% vs 8%)

[Median duration]
- Long-term trials: 3.1 to 4.9 years
- Short-term trials: 4 to 72 weeks

- 본 연구는 기 진행된 임상 결과를 토대로 Atorvastatin을 복용한 전체 환자군과 Asian 환자군을 대상으로 안전성에 대한 후향 분석 진행
- Atorvastatin이 임상 약물로 사용된 101개의 결과 중 58개 임상에 포함된 Asian 환자 대상으로 분석 진행
- Asian 환자 정의: Asian, Oriental, South Asian, Indian and Pacific Islanders.

# Korean safety profile

## AT GOAL[13]

- 연구 목적 : 한국인 이상지질혈증 환자를 대상으로 CV risk 및 baseline LDL-C 수치에 따라 리피토의 초회용량 결정, 투여하여 맞춤 치료의 효과 및 안전성 평가
- 연구 디자인 : 다기관, 전향적, 1단계 용량 조절, 공개 연구
- 연구 대상 : 한국인 이상지질혈증 환자, 425명
- 1차 결과 변수 : 치료 8주 후 목표 LDL-C 도달 환자 비율
- 추적 관찰 기간 : 8주

[Comparison of the geographic variations among three similar AT GOAL trials]

| | Korea study | Thai study | US study |
|---|---|---|---|
| Sample size(n) | 425 | 242 | 1,295 |
| Risk category(%) | | | |
| Low | 7 | 22 | 26 |
| Intermediate | 10 | 11 | 20 |
| High | 83 | 67 | 54 |
| LDL-C goal achievement at 4 week(%) | 81.9 | 87.1 | 84.2 |
| LDL-C goal achievement at 8 week(%) | 86 | 89 | 85 |
| LDL-C reduction(%) | 42 | 46 | 42 |
| Treatment-related AEs(%) | 5.6 | 14.9 | 17.4 |
| Serious AE(%) | 0.7 | 0.8 | 1.7 |

## AMADUS[14]

- 연구 목적 : 한국인 제2 당뇨병 환자를 대상으로 LDL-C 치료목표 도달 및 죽종 형성 지질 프로파일 및 염증반응 개선에 대한 맞춤형 리피토 치료의 영향을 확인하기 위함
- 연구 디자인 : 다기관, 전향적, 1단계 용량 조절, 공개 연구
- 연구 대상 : 18세-80세의 제2형 당뇨병을 가진 환자, 440명
- 1차 결과 변수 : 치료 8주 후 목표 LDL-C 도달 환자 비율
- 추적 관찰 기간 : 8주

| | 10 mg (N=194) | 20 mg (N=185) | 40 mg (N=76) | All dose (N=455) |
|---|---|---|---|---|
| All causality, n(%) | 21 (10.82) | 18 (9.73) | 5 (6.58) | 44 (9.67) |
| Adverse events | | | | |
| Dermatitis | 1 (0.52) | 0 | 0 | 1 (0.22) |
| Headache | 1 (0.52) | 0 | 1 (3.32) | 2 (0.44) |
| Fatigue/Malaise | 1 (0.52) | 1 (0.54) | 0 | 2 (0.44) |
| Insomnia | 1 (0.52) | 0 | 0 | 1 (0.22) |
| Anorexia | 1 (0.52) | 0 | 1 (1.32) | 2 (0.44) |
| Respiratory tract disorders | 0 | 2 (1.08) | 0 | 2 (0.44) |
| Chest discomfort | 0 | 0 | 1 (1.32) | 1 (0.22) |
| Gastrointestinal disorders | 6 (3.09) | 6 (3.24) | 0 | 12 (2.64) |
| Musculoskeletal disorders | 1 (0.52) | 1 (0.54) | 1 (1.32) | 3 (0.66) |
| Bladder cancer | 0 | 1 (0.54) | 0 | 1 (0.22) |
| Stomach cancer | 0 | 1 (0.54) | 0 | 1 (0.22) |
| Hyperkalemia | 0 | 2 (1.08) | 0 | 2 (0.44) |
| Hyperglycemia | 0 | 1 (0.54) | 0 | 1 (0.22) |
| Increased LDH | 1 (0.52) | 2 (1.08) | 0 | 3 (0.66) |
| Increased AST or ALT | 3 (1.55) | 0 | 0 | 3 (0.66) |
| Increased CPK | 1 (0.52) | 0 | 0 | 1 (0.22) |
| Others | 4 (2.06) | 1 (0.54) | 1 (1.32) | 6 (1.32) |
| Treatment related adverse events | 4 (2.06) | 4 (2.16) | 1 (1.32) | 9 (1.98) |
| Discontinued due to adverse events | 2 (1.03) | 2 (1.08) | 0 | 4 (0.88) |

Ref 13. Lee CW, et al. Cardiovasc Drugs Ther. 2010;24(2):181-188
Ref 14. Son JW, et al. J Diabetes Investig. 2013;4:466-474.

# Summary

▸ The appropriate type and intensity of statin therapy should be used to reduce ASCVD risk.

▸ Atorvastatin has demonstrated consistent benefit across broad spectrum of patients.

▸ In addition to superior LDL-cholesterol reducing effect, atorvastatin has anti-inflammatory, anti-oxidant, and anti-thrombotic effect and so on.

▸ High does atorvastatin can regress and/or stabilize atherosclerotic plaque and, in turn, improve clinical outcomes.

# • **Reimbursement guideline**

"고지혈증 치료제 급여 기준이 확대"

## 2014년 새로운 보험급여기준

*2014년 1월 1일자 고시 및 시행

고지질혈증 보험급여 기준이 LDL-C 수치 기준으로 개정되었습니다.

| 순수 고-저밀도지단백 콜레스테롤 혈증 투여대상 | | LDL-C 기준수치 |
|---|---|---|
| 위험인자 | 0~1개인 경우 | 160mg/dL 이상 |
| 위험인자 | 2개 이상인 경우 | 130mg/dL 이상 |
| 관상동맥 질환 또는 이에 준하는 위험 (말초동맥 질환, 복부대동맥류, 증상이 동반된 경동맥 질환, 당뇨병) | | 100mg/dL 이상 |
| 급성동맥 증후군 | | 70mg/dL 이상 |

### 위험인자

1. 흡연
2. 고혈압(BP ≥ 140/90 mmHg 또는 항고혈압제제 복용)
3. 낮은 고밀도지단백콜레스테롤(HDL-C ≤ 40mg/dL)
4. 관상동맥질환 조기 발병의 가족력 (부모, 형제자매 중 남자 < 55세, 여자 < 65세에서 관상동맥질환이 발병한 경우)
5. 연령(남자 ≥ 45세, 여자 ≥ 55세)

* HDL-C ≥ 60mg/dL은 보호인자로 간주하여 총 위험요인 수에서 하나를 감한다.

# Safety Recommendation

| | | |
|---|---|---|
| 2a. CK should not be routinely measured in individuals receiving statin therapy. | A (Strong) | 45, 49-51, 54, 55 |
| 2b. Baseline measurement of CK is reasonable for individuals believed to be at increased risk for adverse muscle events based on a personal or family history of statin intolerance or muscle disease, clinical presentation, or concomitant drug therapy that might increase the risk for myopathy. | E (Expert Opinion) | --- |
| 2c. During statin therapy, it is reasonable to measure CK in individuals with muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or generalized fatigue. | E (Expert Opinion) | --- |
| 3a. Baseline measurement of hepatic transaminase levels (ALT) should be performed before initiating statin therapy. | B (Moderate) | 46, 52, 53 |
| 3b. During statin therapy, it is reasonable to measure hepatic function if symptoms suggesting hepatotoxicity arise (e.g., unusual fatigue or weakness, loss of appetite, abdominal pain, dark-colored urine or yellowing of the skin or sclera). | E (Expert Opinion) | --- |

# Safety Recommendation

| | | |
|---|---|---|
| 4. Decreasing the statin dose may be considered when 2 consecutive values of LDL–C levels are <40 mg/dL. | C (Weak) | 45 |
| 5. It may be harmful to initiate simvastatin at 80 mg daily or increase the dose of simvastatin to 80 mg daily. | B (Moderate) | 6, 54 |
| 6. Individuals receiving statin therapy should be evaluated for new-onset diabetes mellitus according to the current diabetes screening guidelines (93). Those who develop diabetes mellitus during statin therapy should be encouraged to adhere to a heart healthy dietary pattern, engage in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce their risk of ASCVD events. | B (Moderate) | 44 |

# Muscle symptoms (I)

▸ To avoid unnecessary discontinuation of statins, obtain a history of prior or current muscle symptoms to establish a baseline before initiating statin therapy.

▸ If unexplained severe muscle symptoms or fatigue develop during statin therapy, promptly discontinue the statin and address the possibility of rhabdomyolysis by evaluating CK, creatinine, and a urinalysis for myoglobinuria.

▸ If mild to moderate muscle symptoms develop during statin therapy:

◦ Discontinue the statin until the symptoms can be evaluated.

◦ Evaluate the patient for other conditions that might increase the risk for muscle symptoms (e.g., hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency, or primary muscle diseases.)

# Muscle symptoms (II)

▸ If muscle symptoms resolve, and if no contraindication exists, give the patient the original or a lower dose of the same statin to establish a causal relationship between the muscle symptoms and statin therapy.

▸ If a causal relationship exists, discontinue the original statin. Once muscle symptoms resolve, use a low dose of a different statin.

◦ Once a low dose of a statin is tolerated, gradually increase the dose as tolerated.

▸ If, after 2 months without statin treatment, muscle symptoms or elevated CK levels do not resolve completely, consider other causes of muscle symptoms listed above.

▸ If persistent muscle symptoms are determined to arise from a condition unrelated to statin therapy, or if the predisposing condition has been treated, resume statin therapy at the original dose.

# Highest doses associated with increased muscle injury(> 10X CK)
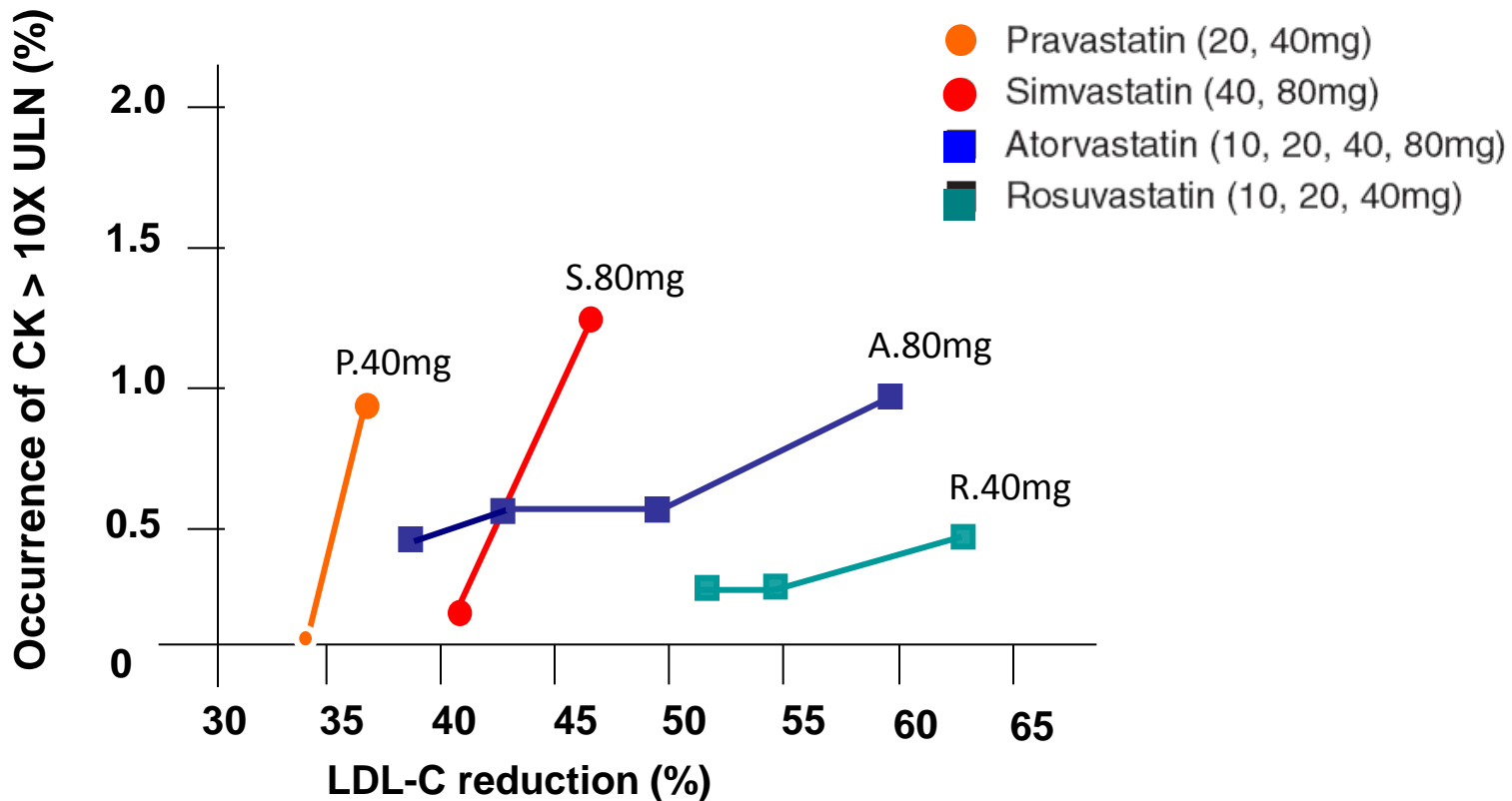
# Very rare fatal myositis

## Number needed to treat for 1 year to:

| Cause | a GI Bleed[1] | Cause a Fatal GI Bleed[1] |
|---|---|---|
| Aspirin | 248 | 2066 |

| Cause | Severe Myositis[2] | Cause Fatal Myositis[2] |
|---|---|---|
| Statins | 100,000 | 1,000,000 |

[1]Derry S, Loke YK. 2000
[2]Thompson PD, et al. 2003

# Effect of Statins on Skeletal Muscle Function

Beth A. Parker, PhD; Jeffrey A. Capizzi, MS; Adam S. Grimaldi, BS; Priscilla M. Clarkson, PhD;
Stephanie M. Cole, PhD; Justin Keadle, BS; Stuart Chipkin, MD; Linda S. Pescatello, PhD;
Kathleen Simpson, MS; C. Michael White, PharmD; Paul D. Thompson, MD

***Background***—Many clinicians believe that statins cause muscle pain, but this has not been observed in clinical trials, and the effect of statins on muscle performance has not been carefully studied.

***Methods and Results***—The Effect of Statins on Skeletal Muscle Function and Performance (STOMP) study assessed symptoms and measured creatine kinase, exercise capacity, and muscle strength before and after atorvastatin 80 mg or placebo was administered for 6 months to 420 healthy, statin-naive subjects. No individual creatine kinase value exceeded 10 times normal, but average creatine kinase increased $20.8\pm141.1$ U/L ($P<0.0001$) with atorvastatin. There were no significant changes in several measures of muscle strength or exercise capacity with atorvastatin, but more atorvastatin than placebo subjects developed myalgia (19 versus 10; $P=0.05$). Myalgic subjects on atorvastatin or placebo had decreased muscle strength in 5 of 14 and 4 of 14 variables, respectively ($P=0.69$).

***Conclusions***—These results indicate that high-dose atorvastatin for 6 months does not decrease average muscle strength or exercise performance in healthy, previously untreated subjects. Nevertheless, this blinded, controlled trial confirms the undocumented impression that statins increase muscle complaints. Atorvastatin also increased average creatine kinase, suggesting that statins produce mild muscle injury even among asymptomatic subjects. This increase in creatine kinase should prompt studies examining the effects of more prolonged, high-dose statin treatment on muscular performance.

***Clinical Trial Registration***—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00609063. (***Circulation.*** 2013;127:96-103.)

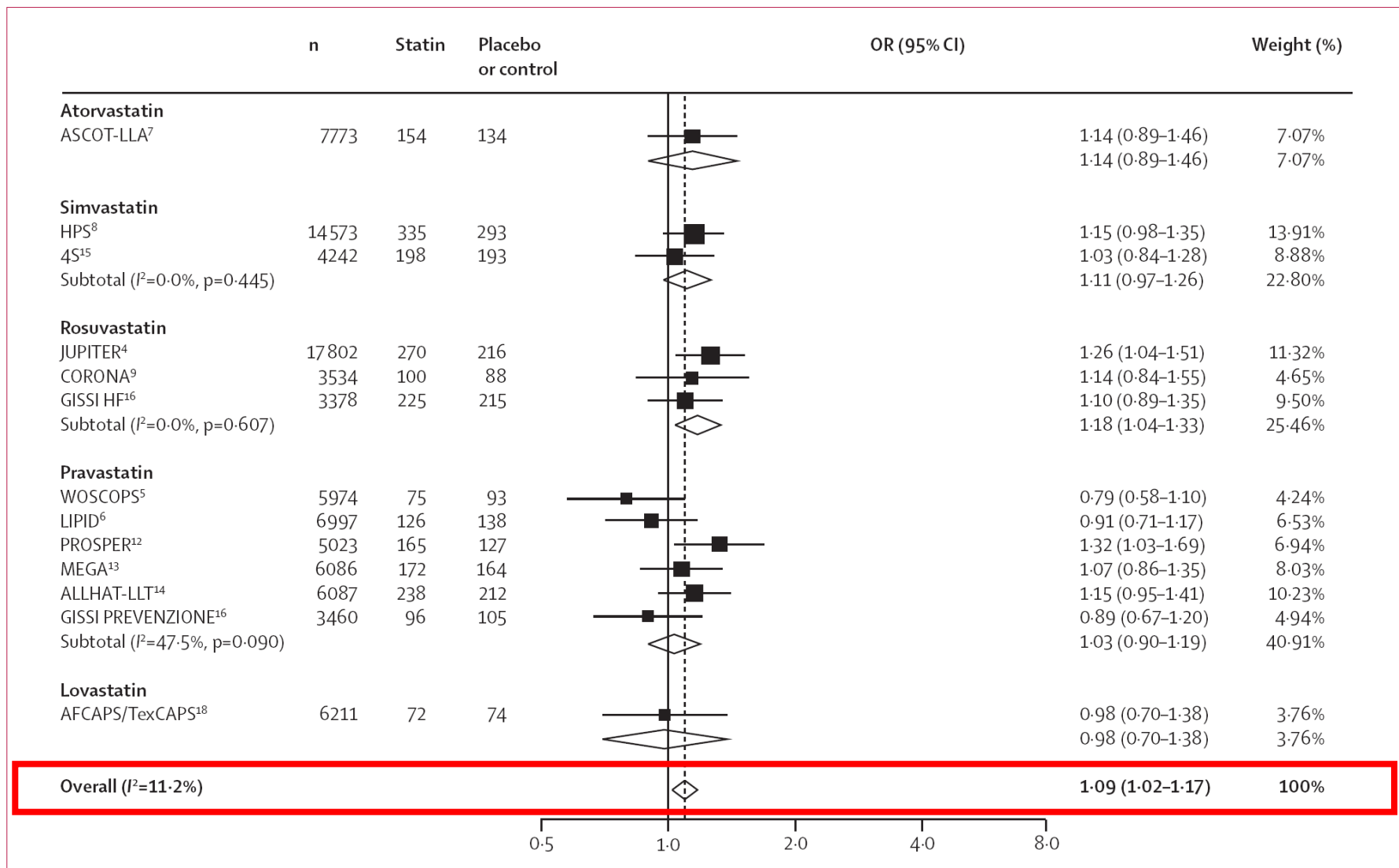# Meta-analysis: Diabetes in 13 statin trials



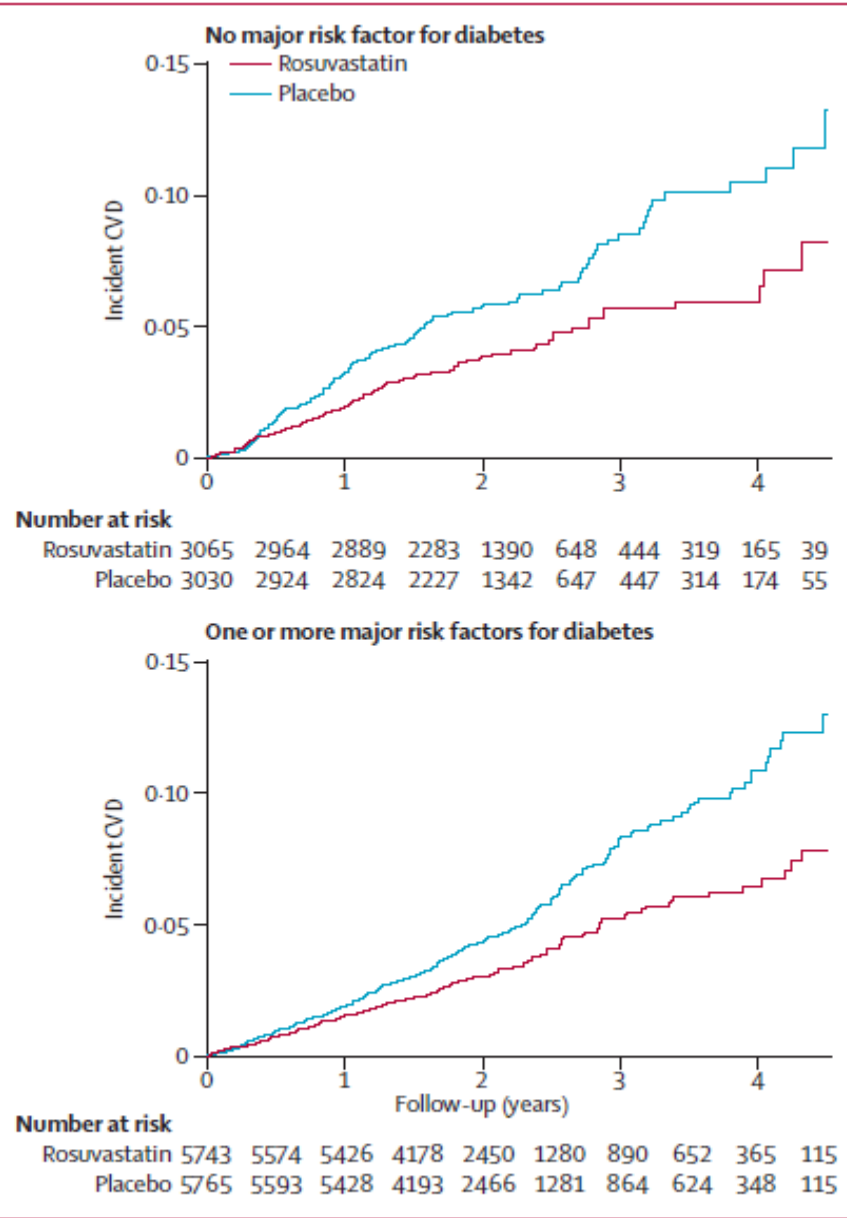**Figure 3:** Association between different statins and development of diabetes

**Figure 2:** Cumulative incidence of cardiovascular events and total mortality in participants with and without major risk factors for diabetes
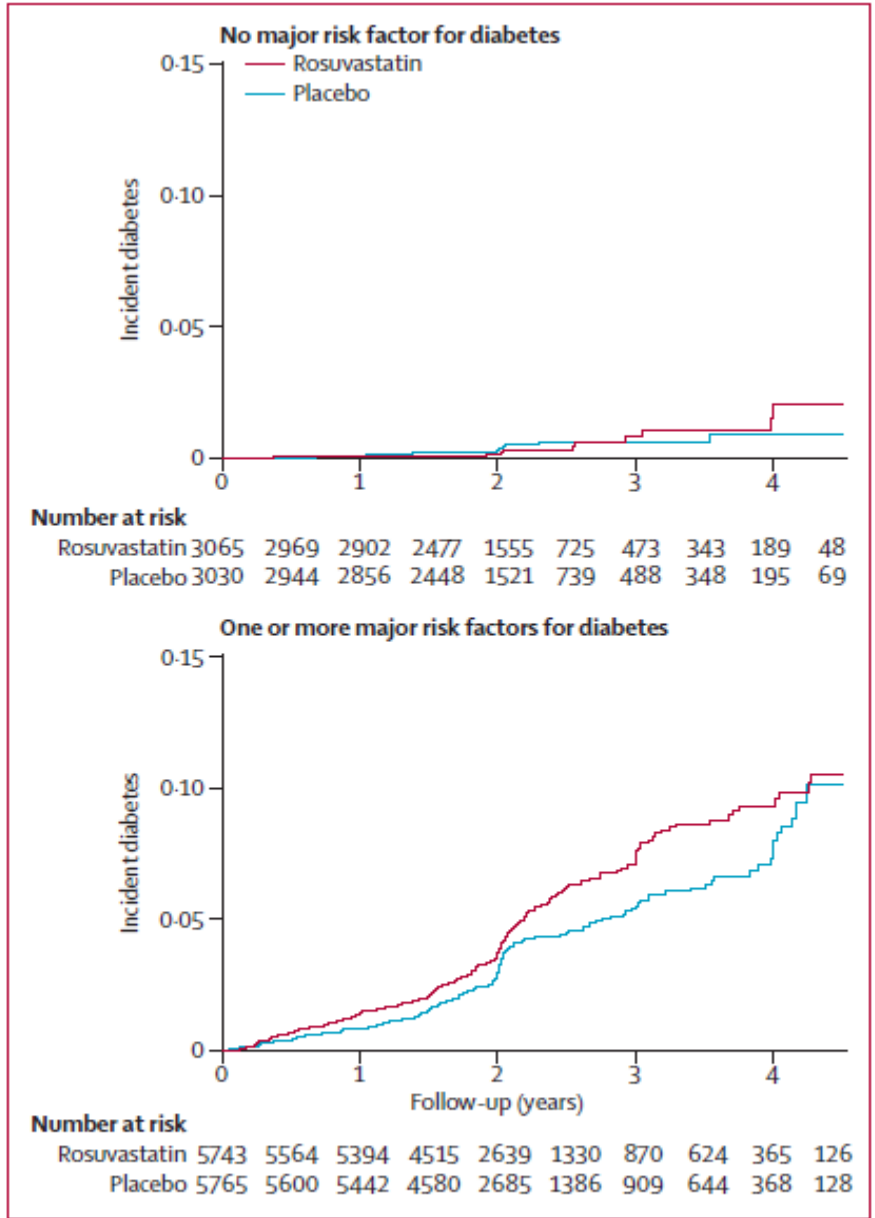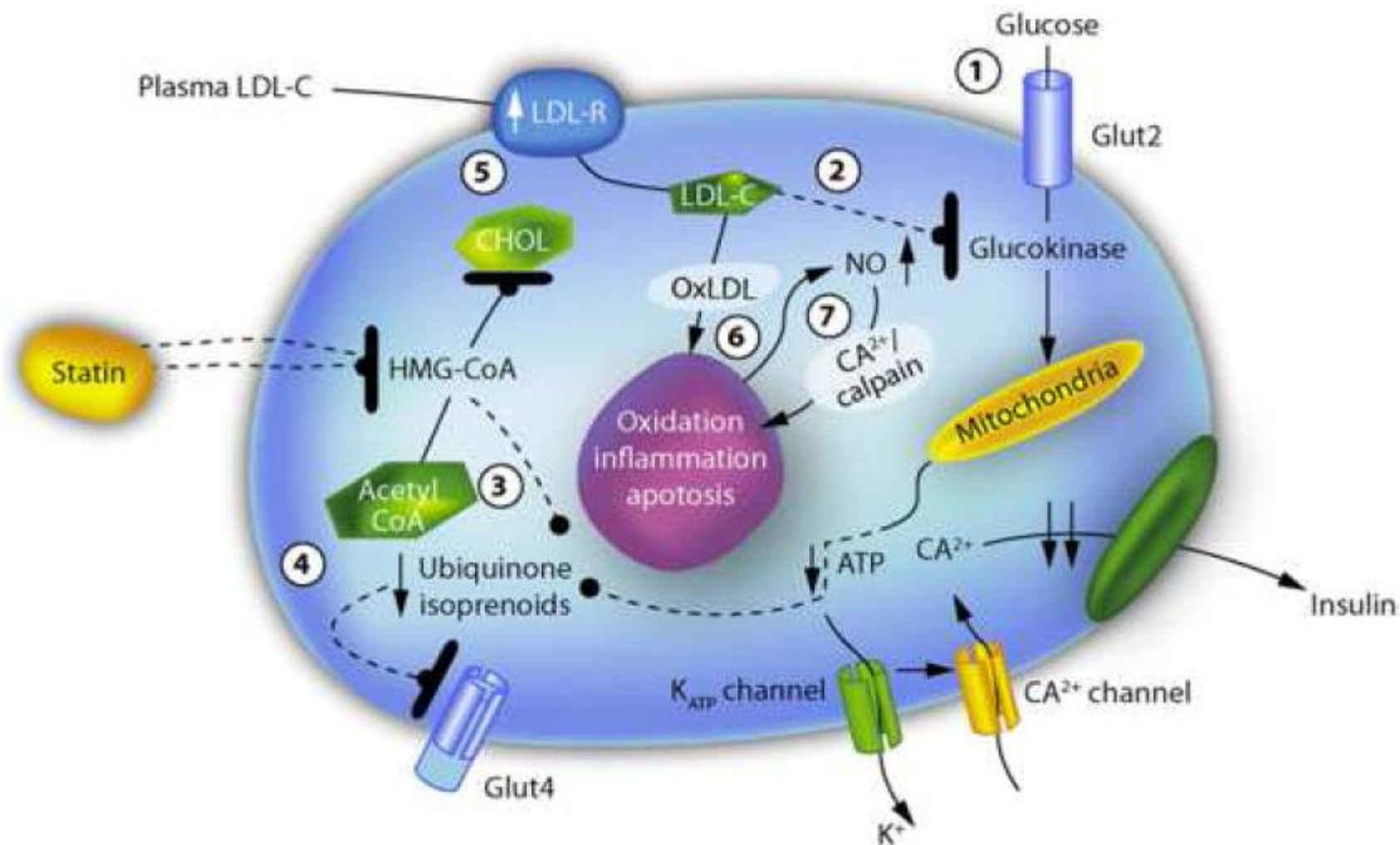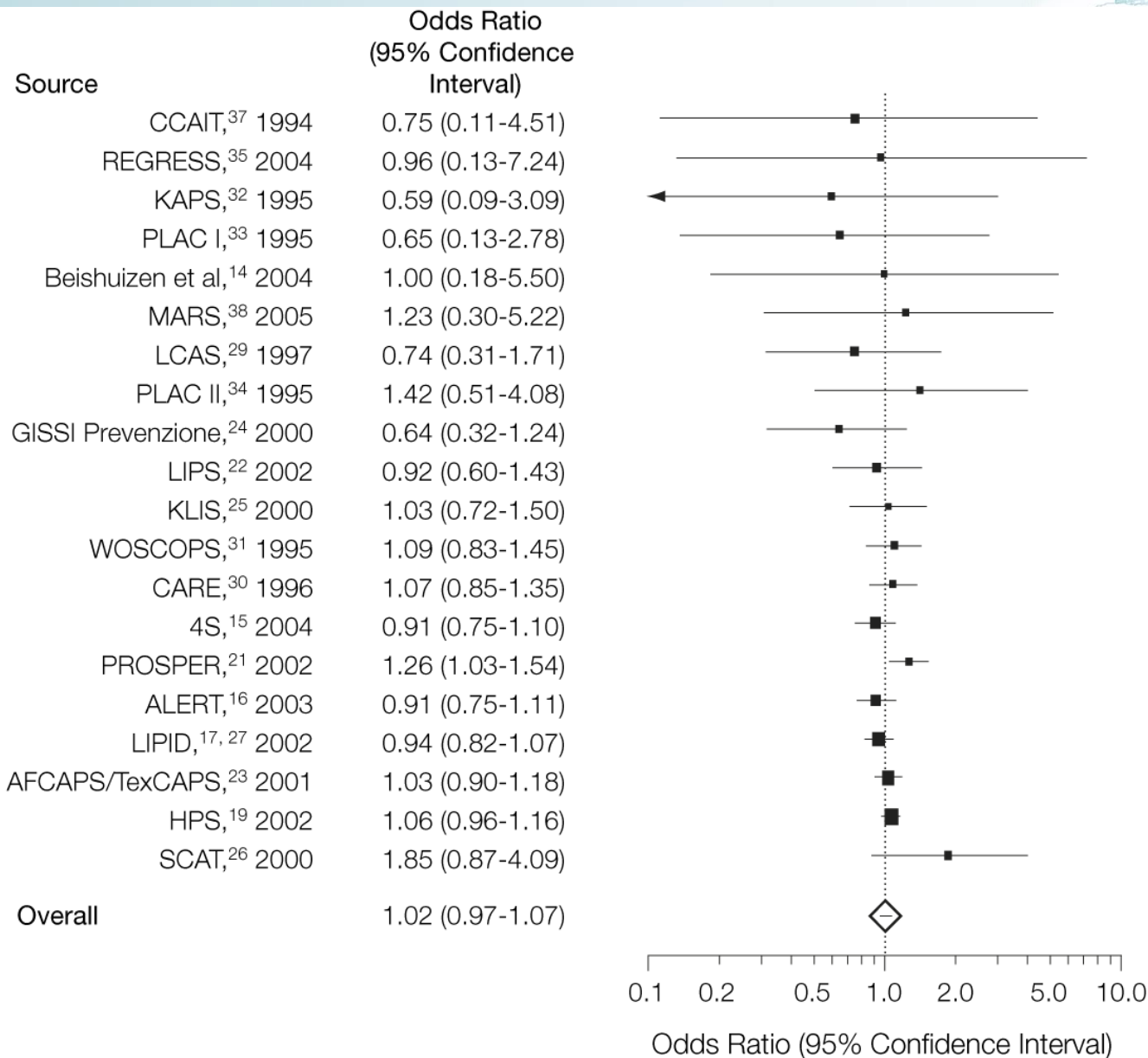CVD=cardiovascular disease.

**Figure 3:** Cumulative incidence of diabetes in participants with and without major risk factors for diabetes

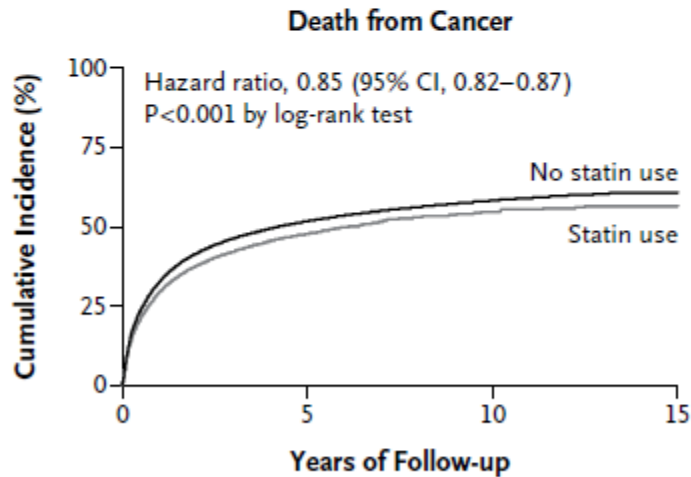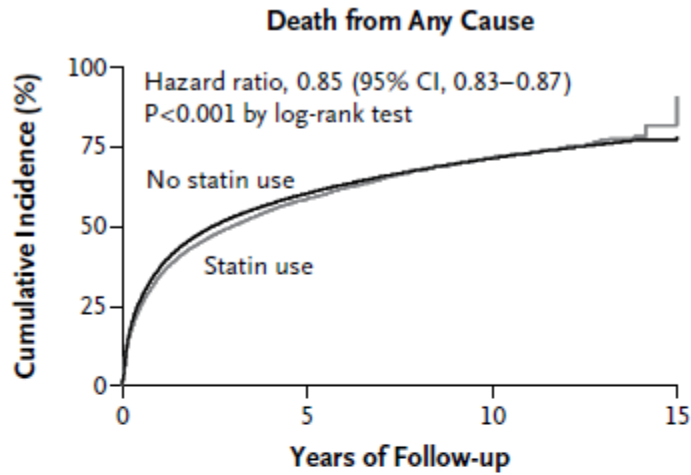# Hypothetical Paradigm for Statin-induced Hyperglycemia

# Statins and cancers



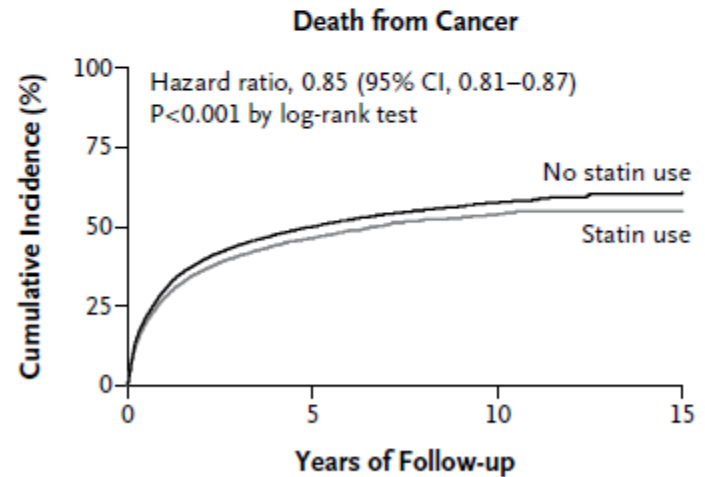| Source | Odds Ratio (95% Confidence Interval) |
|---|---|
| CCAIT,[37] 1994 | 0.75 (0.11-4.51) |
| REGRESS,[35] 2004 | 0.96 (0.13-7.24) |
| KAPS,[32] 1995 | 0.59 (0.09-3.09) |
| PLAC I,[33] 1995 | 0.65 (0.13-2.78) |
| Beishuizen et al,[14] 2004 | 1.00 (0.18-5.50) |
| MARS,[38] 2005 | 1.23 (0.30-5.22) |
| LCAS,[29] 1997 | 0.74 (0.31-1.71) |
| PLAC II,[34] 1995 | 1.42 (0.51-4.08) |
| GISSI Prevenzione,[24] 2000 | 0.64 (0.32-1.24) |
| LIPS,[22] 2002 | 0.92 (0.60-1.43) |
| KLIS,[25] 2000 | 1.03 (0.72-1.50) |
| WOSCOPS,[31] 1995 | 1.09 (0.83-1.45) |
| CARE,[30] 1996 | 1.07 (0.85-1.35) |
| 4S,[15] 2004 | 0.91 (0.75-1.10) |
| PROSPER,[21] 2002 | 1.26 (1.03-1.54) |
| ALERT,[16] 2003 | 0.91 (0.75-1.11) |
| LIPID,[17, 27] 2002 | 0.94 (0.82-1.07) |
| AFCAPS/TexCAPS,[23] 2001 | 1.03 (0.90-1.18) |
| HPS,[19] 2002 | 1.06 (0.96-1.16) |
| SCAT,[26] 2000 | 1.85 (0.87-4.09) |
| Overall | 1.02 (0.97-1.07) |

Odds Ratio (95% Confidence Interval)

# Statins cuts cancer mortality.



A **Nationwide Study**

**Death from Any Cause**

Hazard ratio, 0.85 (95% CI, 0.83–0.87)
P<0.001 by log-rank test

No statin use

Statin use

**Death from Cancer**

Hazard ratio, 0.85 (95% CI, 0.82–0.87)
P<0.001 by log-rank test

No statin use

Statin use

B **Matched Study**

**Death from Any Cause**

Hazard ratio, 0.86 (95% CI, 0.83–0.89)
P=0.01 by log-rank test

Statin use

No statin use

**Death from Cancer**

Hazard ratio, 0.85 (95% CI, 0.81–0.87)
P<0.001 by log-rank test

No statin use

Statin use

| No. of Patients at Risk | | | | |
|---|---|---|---|---|
| Statin use | 18,721 | 3,005 | 365 | 0 |
| No statin use | 227,204 | 82,137 | 27,954 | 378 |

| No. of Patients at Risk | | | | |
|---|---|---|---|---|
| Statin use | 15,247 | 2,779 | 349 | 0 |
| No statin use | 45,741 | 8,060 | 976 | 4 |
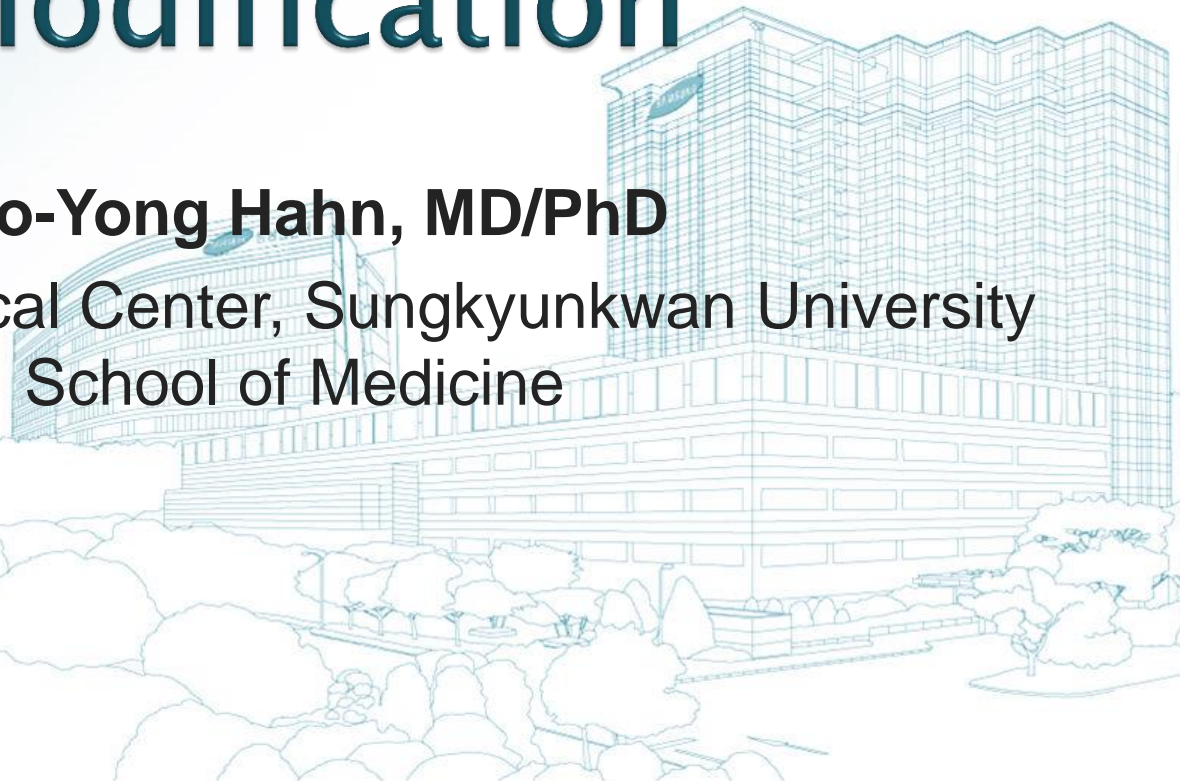
# Residual CV Risk in Statin Trials
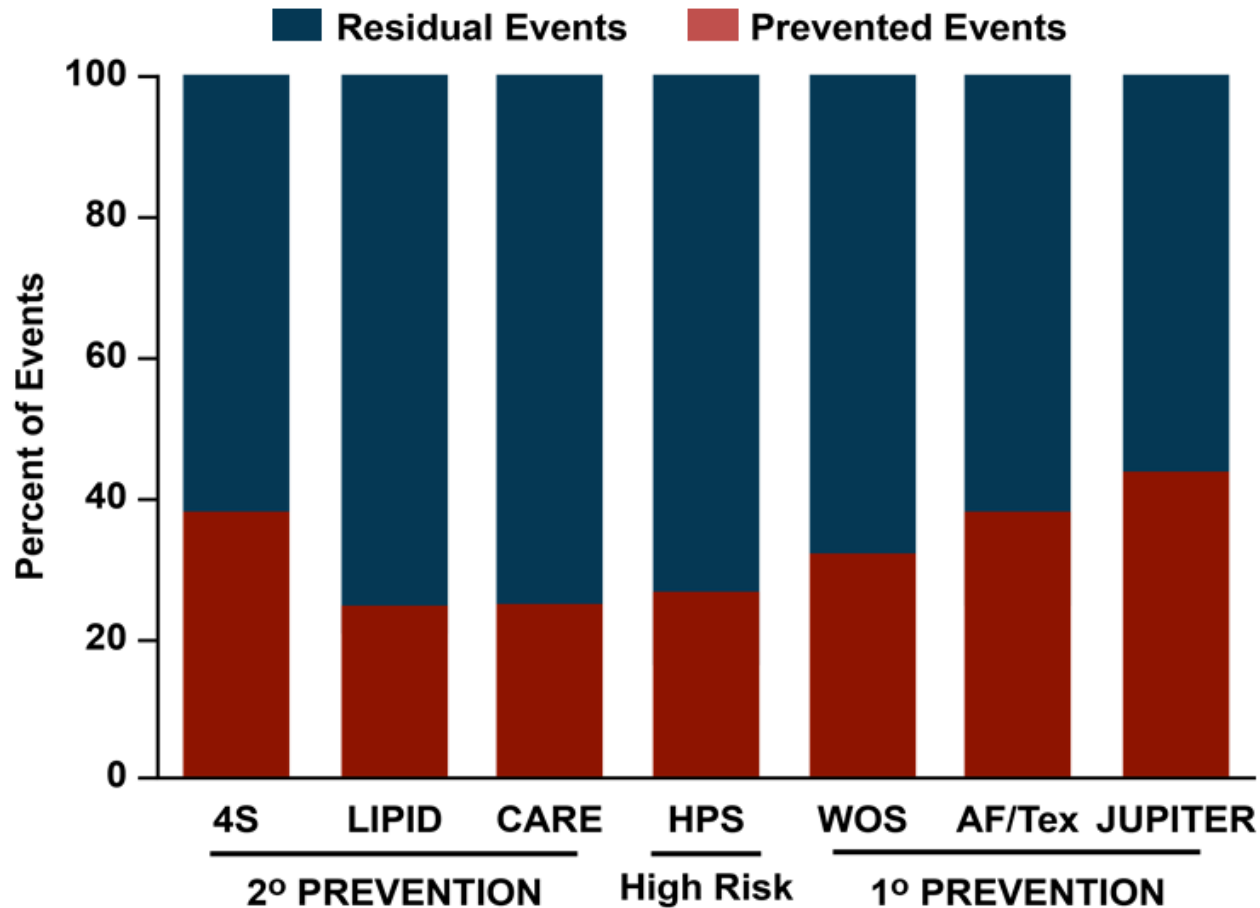


Ballantyne CM, et al. *Circulation.* 1999;99:736-743; Scandinavian Simvastatin Survival Study Group. *Lancet.* 1995;345:1274-1275; The LIPID Study Group. *N Engl J Med.* 1998;339:1349-1357; Pfeffer MA, et al. *J Am Coll Cardiol.* 1999;33:125-130; Shepherd J, et al. *N Engl J Med.* 1995;333:1301-1307; Downs JR, et al. *JAMA.* 1998;279:1615-1622; Ridker PM, et al. Lancet. 2010;376:333-339.

# Residual CV risk in Statin trials

▸ Statin trials show many patients at LDL-C goal have high "residual" CHD risk.

▸ Statins reduce risk by 25 % to 35 % compared with controls, but many patients still have events due to residual risk.

▸ More intensive treatment is needed in addition to statin monotherapy to effectively reduce residual risk.

Am J Cardiol. 2005; 96: 3K-13K. Diab Vasc Dis Res. 2006;3 : S1-S12 .
Lancet. 2005; 366: 1267-1278. JAMA. 1999; 282:2340-2346

# Patients with High Residual Risk

▶ Low HDL-C

▶ High TG and Non-HDL-C

▶ Diabetes Mellitus
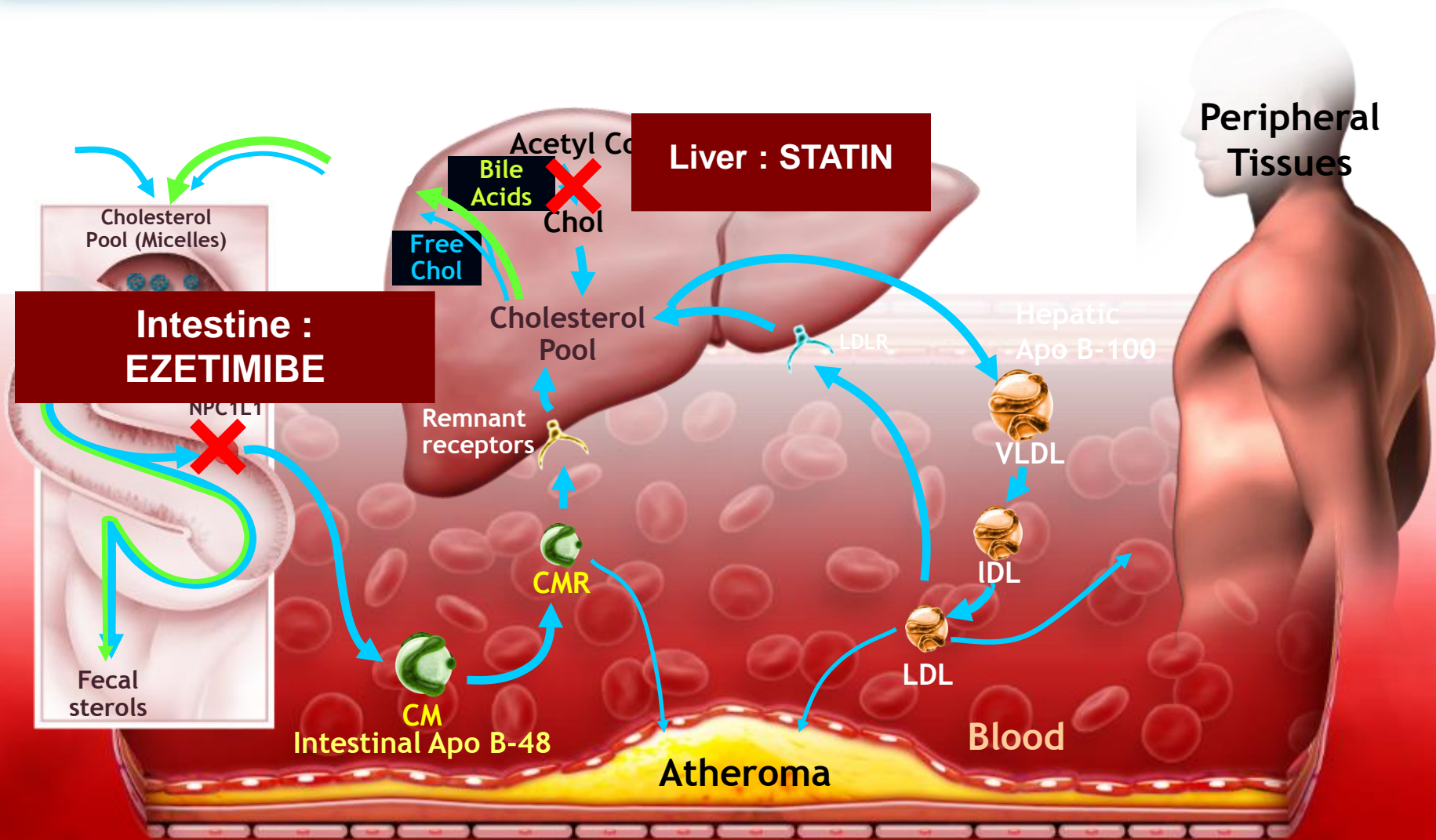
▶ Metabolic Syndrome

▶ Lifestyle

# Adding another therapy to Statin for Further CV risk Reduction

- **Statin + Ezetimibe : ENHANCE, SHARP**
- **Statin + Niacin : AIM-HIGH, HPS2-THRIVE**
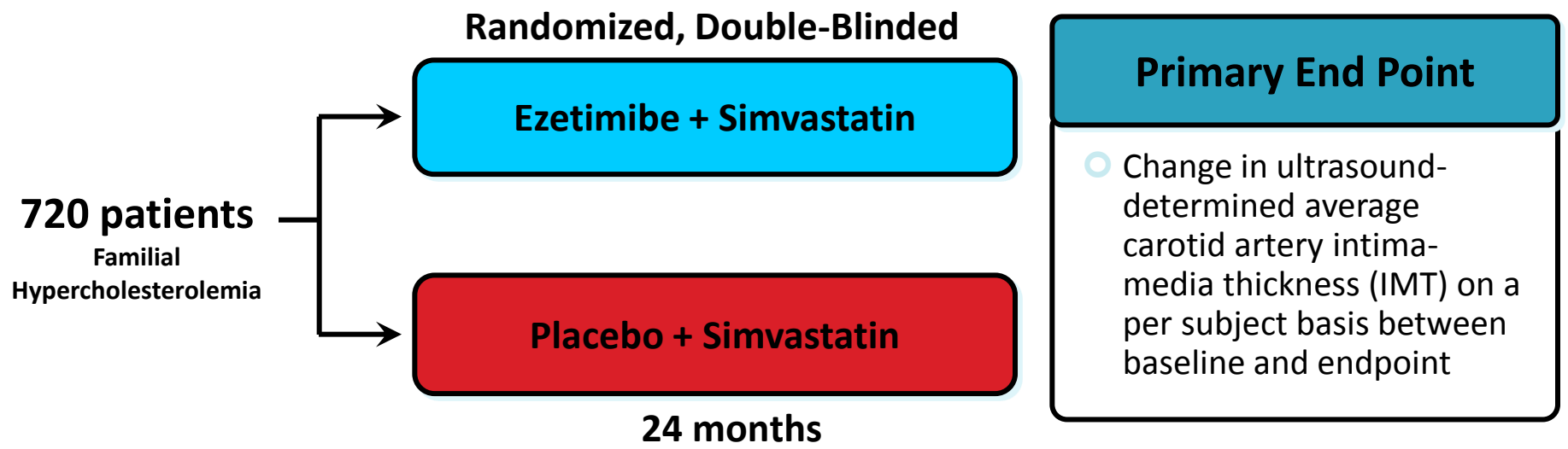- **Statin + Fenofibrate : ACCORD**

# VYTORIN: DUAL INHIBITION in cholesterol

Samsung Medical Center

**Peripheral Tissues**

**Liver : STATIN**

Acetyl Co

Bile Acids

Chol

Free Chol

Cholesterol Pool

Hepatic Apo B-100

LDLR

**Intestine : EZETIMIBE**

Cholesterol Pool (Micelles)

NPC1L1

Remnant receptors

VLDL

IDL

LDL

CMR

Fecal sterols

CM
Intestinal Apo B-48

Atheroma

Blood

Cohen DE, Armstrong EJ. In: *Principles of pharmacology: The pathophysiologic Basis of Drug Therapy.* 2nd ed. Philadelphiak PA:Lippincott, Williams & Wilkins; 2007:417-438; Wang DQH. *Annu Rev Physiol.* 2007;69:221-248
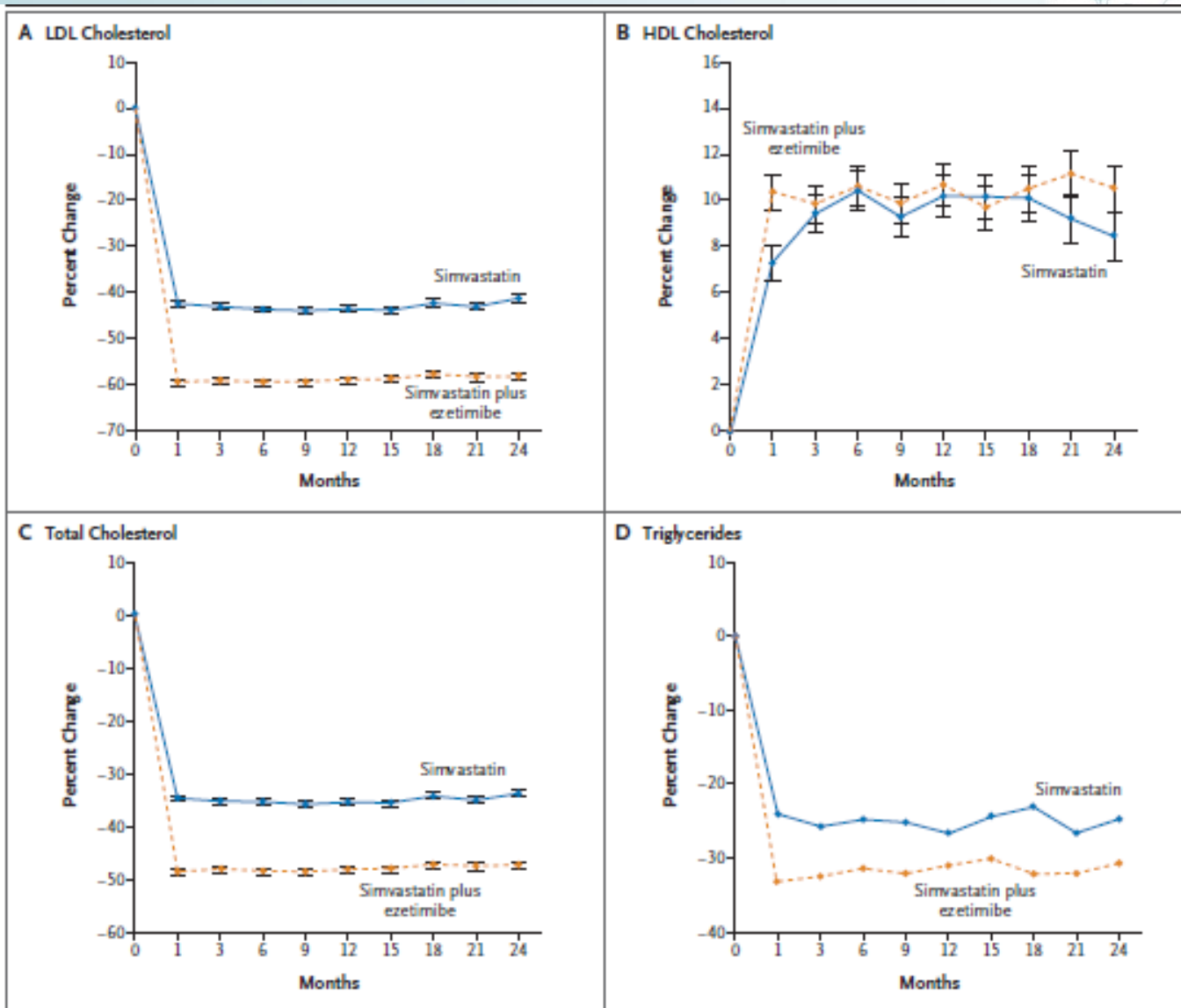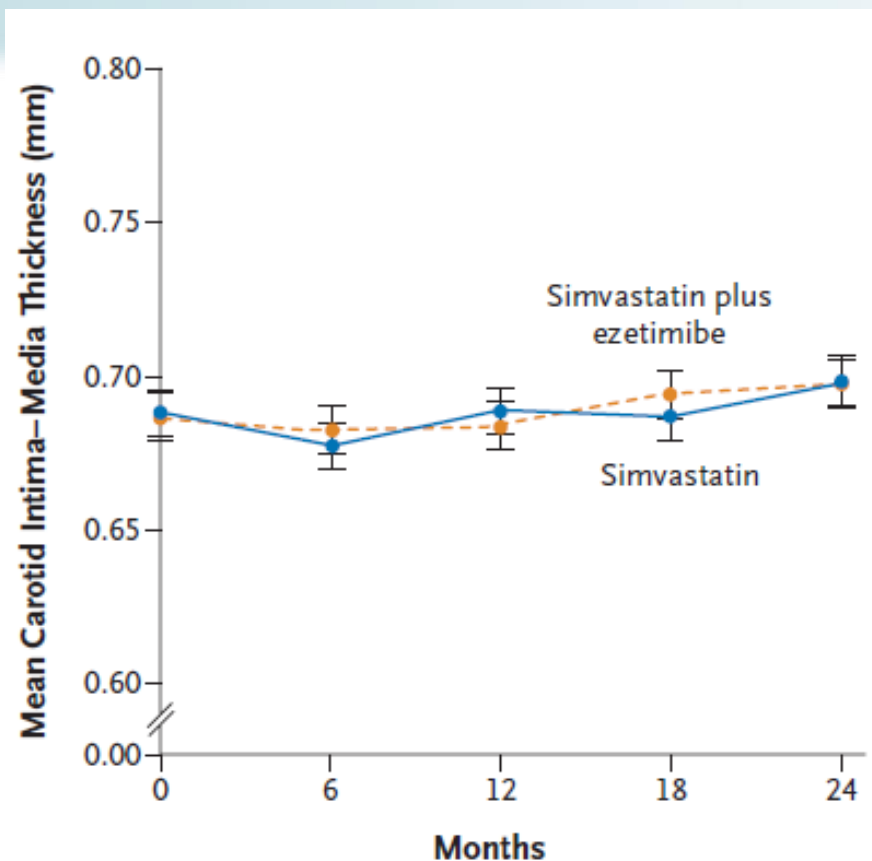
# ENHANCE :Design

Comparison of ezetimibe plus simvastatin versus simvastatin monotherapy on atherosclerosis progression in familial hypercholesterolemia: Design and rationale of the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression

**Randomized, Double-Blinded**

**720 patients**
**Familial Hypercholesterolemia**

→ **Ezetimibe + Simvastatin**

→ **Placebo + Simvastatin**

**24 months**

**Primary End Point**

○ Change in ultrasound-determined average carotid artery intima-media thickness (IMT) on a per subject basis between baseline and endpoint
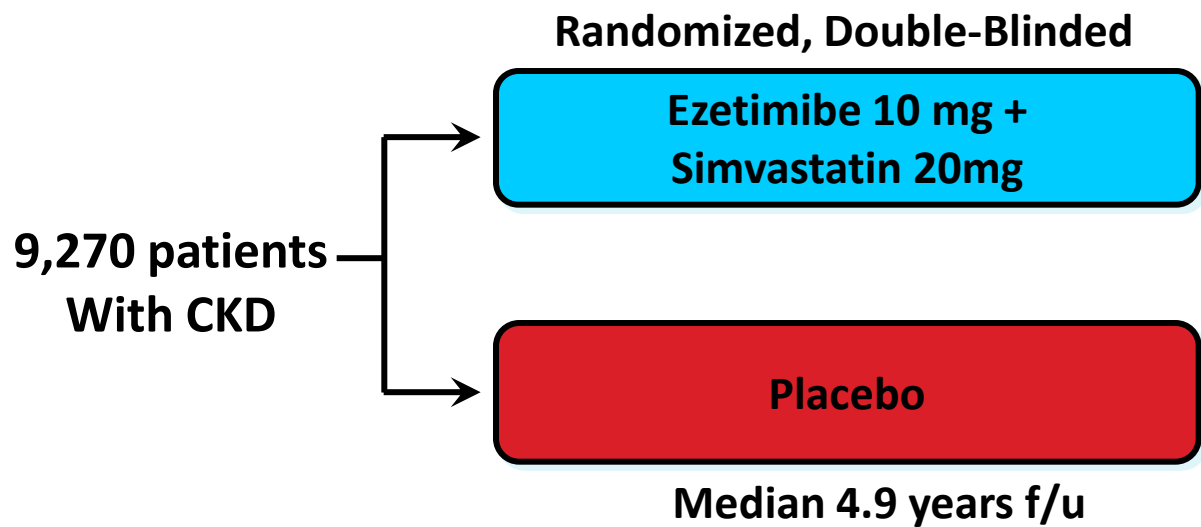
# ENHANCE Results

# ENHANCE Results



In patients with familial hypercholesterolemia, combined therapy with ezetimibe and simvastatin did not result in a significant difference in changes in intima–media thickness, as compared with simvastatin alone, despite decreases in levels of LDL cholesterol and C-reactive protein
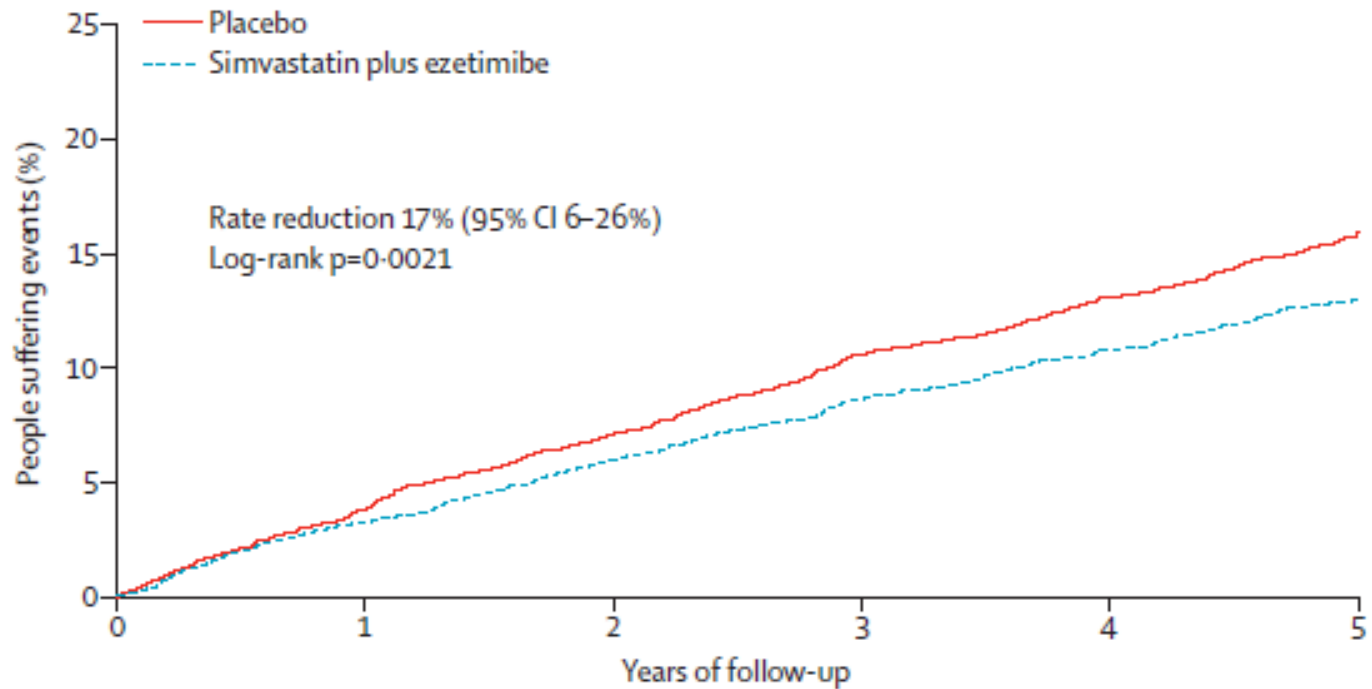
# SHARP Design

The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial

**9,270 patients With CKD**

**Randomized, Double-Blinded**

**Ezetimibe 10 mg + Simvastatin 20mg**

**Placebo**

**Median 4.9 years f/u**

## Primary End Point

○ First major atherosclerotic event (non-fatal myocardial infarction or coronary death, non-haemorrhagic stroke, or any arterial revascularisation procedure.)

Lancet. 2011;377:2181-92

# SHARP Results



Lancet. 2011;377:2181-92

# Position on LDL-C: Moving toward more intensive and safer therapy (IMPROVE-IT)

**High risk patients with Acute Coronary Syndromes**

(Re-)Randomization within 10 days of Hospital Presentation
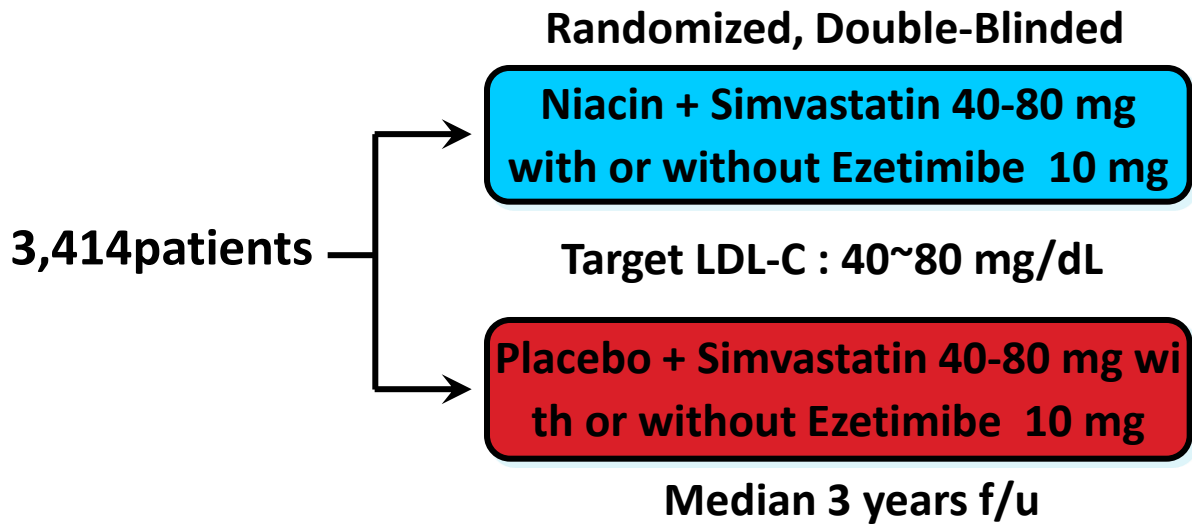
Vytorin 10/40          Simva 40

Enrollment 18-24 months
n = ~18,000
2 $\frac{1}{2}$-year minimum follow-up

**1° Endpoint: Death / MI / Stroke / Hosp admission for ACS / Revasc > 30 days**

Assumptions: projected control event rate 25% over 2.5 yr, 10% treatment effect;
90% power; two-side alpha = 0.05

al Center

# AIM-HIGH

Atherosclerosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/ High Triglyceride and Impact on Global Health Outcomes

**Randomized, Double-Blinded**

**3,414patients**

**Niacin + Simvastatin 40-80 mg with or without Ezetimibe 10 mg**

**Target LDL-C : 40~80 mg/dL**

**Placebo + Simvastatin 40-80 mg with or without Ezetimibe 10 mg**

**Median 3 years f/u**

## Primary End Point

○ The first event of the composite of death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization

## Patient Characteristics

45 years of age or older

Established CVD (stable coronary heart disease, cerebrovascular or carotid disease, or peripheral arterial disease)
HDL-C: < 40 mg/dL  for men, 50 mg/dL for women
TG: 150-400 mg /dL, LDL-C : <180 mg/dL

al Center

# AIM-HIGH:
## Niacin raise HDL-C effectively



NEJM. 2011; 365(24) :2255-67

al Center
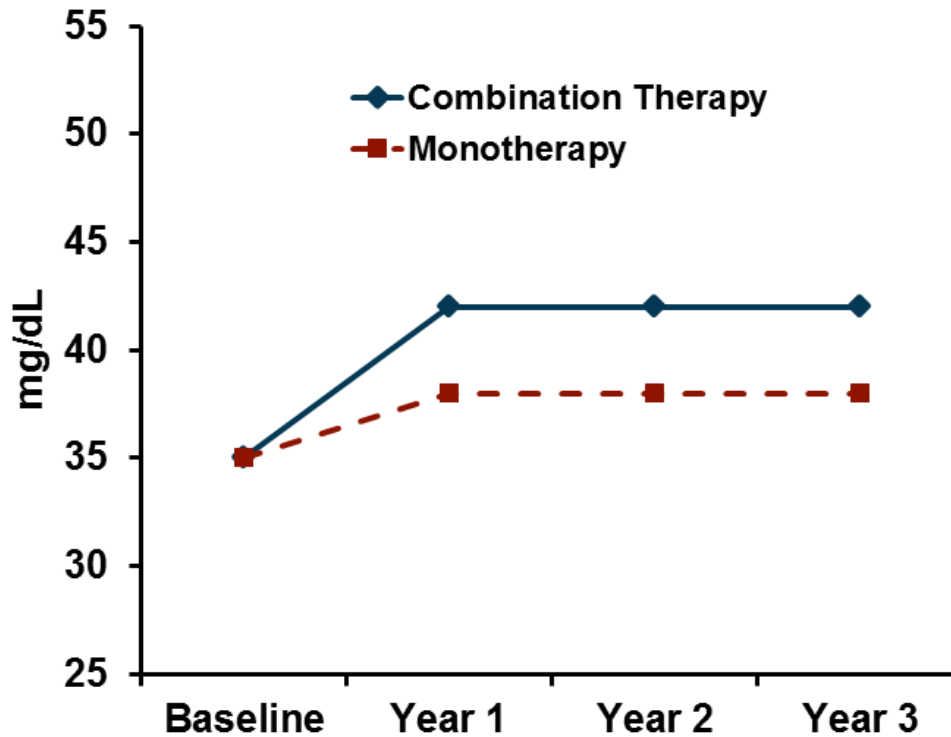
# AIM-HIGH:
## Niacin in Patients with Low HDL-C receiving Intensive Statin



**Stopped prematurely because of futility**

P=0.79 by log-rank test

Placebo plus statin

**No. at Risk**

| | | | | | |
|---|---|---|---|---|---|
| Placebo plus statin | 1696 | 1581 | 1381 | 910 | 436 |
| Niacin plus statin | 1718 | 1606 | 1366 | 903 | 428 |

# HPS2-THRIVE

Heart Protection Study 2– Treatment of HDL to Reduce the Incidence of Vascular Events

**Randomized, Double-Blinded**

**25,673 patients**

**Niacin/Laropiprant + Simvastatin**

**Simvastatin 40 mg with or without Ezetimibe 10 mg**

**Median 3.9 years f/u**

## Primary Composite End Point

○ Coronary deaths, nonfatal heart attack, strokes, and coronary revascularizations

## Patient Characteristics

Age 50-80

History of MI, Cerebrovascular atherosclerotic disease, peripheral artery disease, or diabetes mellitus, with any of the above or with other evidence of symptomatic CHD

# HPS-2 THRIVE vs. AIM HIGH

| Aspect | TREDAPTIVE - HPS2-THRIVE | Niaspan - AIM HIGH |
|---|---|---|
| Study Size | 25,000 | 3300 |
| Primary Endpoint | Composite CHD Death, Non-fatal MI, Stroke, Revascularization | Composite CHD, Death, Non-fatal MI, Non-hemorrhagic Stroke, Hospitalization ACS, Revascularization |
| LDL Management | Pre-randomization titration to target LDL-C <80 mg/dL. No adjustment of statin or ezetimibe post-Randomization<br><br>Allows for LDL-C differences between treatments | Post-randomization titration to achieve LDL ≥40 mg/dL and ≤80 mg/dL<br><br>Minimizes LDL-C differences between treatments |
| Planned Endpoints | 2300 | 850 |
| Power | 95% power to detect 15% risk reduction | 85% power to detect 25% risk reduction |
| Planned/Actual Follow Up | 4 years/to be determined | 3.5 years/2.7 years |

# HPS2-THRIVE

Heart ... scular
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**HPS-2 THRIVE misses primary end point: No benefit of niacin/laropiprant**

Whitehouse Station, NJ (updated) - The Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS-2 THRIVE) study, a secondary-prevention trial testing the addition of extended-release **niacin** to statin therapy, has missed its primary end point and shown no clinical benefit for extended-release niacin [1].

After nearly four years of follow-up, the combination of niacin with the antiflushing agent **laropiprant** did not significantly reduce the risk of the combination of coronary deaths, nonfatal MI, strokes, or coronary revascularizations compared with statin therapy, according to Merck, the sponsor of the HPS-2 THRIVE trial. In a press release announcing the results, Merck said the combination significantly increased the risk of nonfatal but serious side effects.
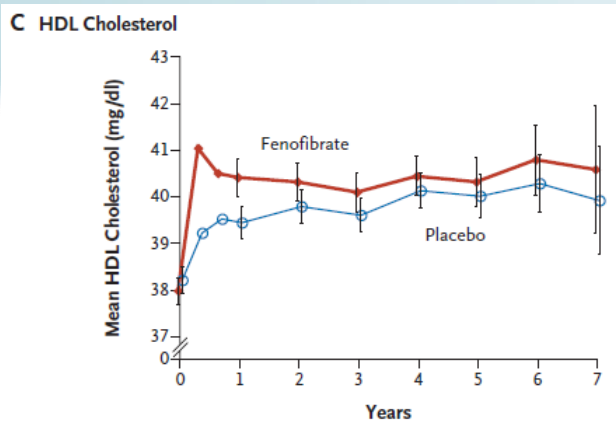
Age 50-80

History of MI, Cerebrovascular atherosclerotic disease, peripheral artery disease, or diabetes mellitus, with any of the above or with other evidence of symptomatic CHD
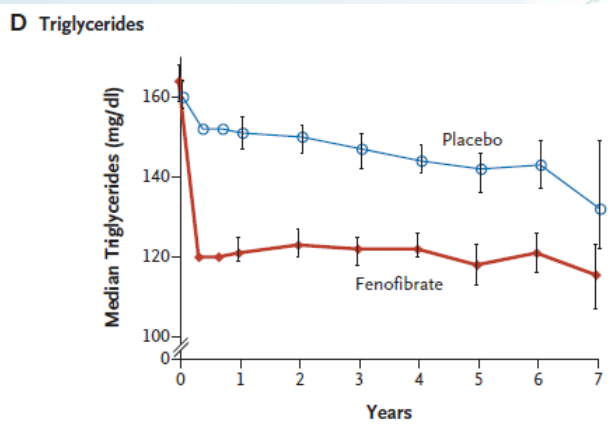
# ACCORD trial



C HDL Cholesterol

D Triglycerides

A Primary Outcome

B Expanded Macrovascular Outcome
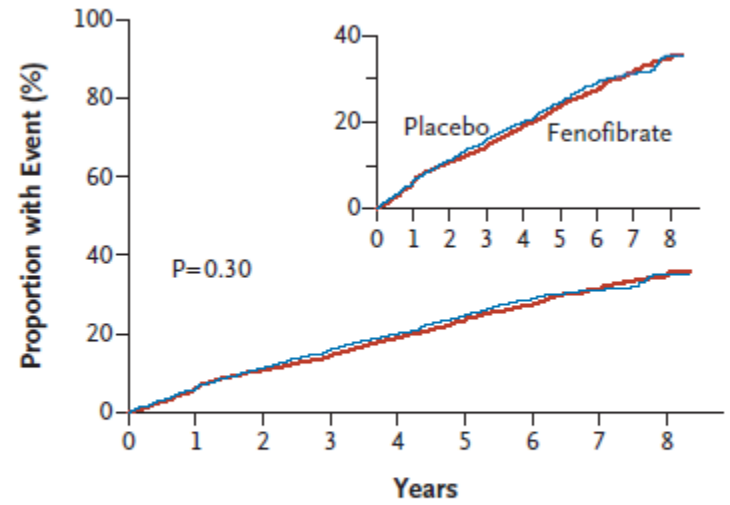
# ACCORD trial

| | | | | p value |
|---|---|---|---|---|
| LDL cholesterol | | | | 0.12 |
| ≤84 mg/dl | 9.38 (938) | 12.23 (891) | | |
| 85–111 mg/dl | 9.85 (934) | 11.17 (922) | | |
| ≥112 mg/dl | 12.43 (877) | 10.57 (927) | | |
| HDL cholesterol | | | | 0.24 |
| ≤34 mg/dl | 12.24 (964) | 15.56 (906) | | |
| 35–40 mg/dl | 10.12 (860) | 9.47 (866) | | |
| ≥41 mg/dl | 9.08 (925) | 8.99 (968) | | |
| Triglycerides | | | | 0.64 |
| ≤128 mg/dl | 9.88 (891) | 11.29 (939) | | |
| 129–203 mg/dl | 10.50 (924) | 9.86 (913) | | |
| ≥204 mg/dl | 11.13 (934) | 12.84 (888) | | |
| Triglyceride–HDL cholesterol combination | | | | 0.06 |
| Triglyceride ≥204 mg/dl and HDL ≤34 mg/dl | 12.37 (485) | 17.32 (456) | | |
| All others | 10.11 (2264) | 10.11 (2284) | | |
| Glycated hemoglobin | | | | 0.20 |
| ≤8.0% | 8.69 (1324) | 10.56 (1335) | | |
| ≥8.1% | 12.20 (1435) | 11.94 (1415) | | |

0    1    2

Fenofibrate Better    Placebo Better
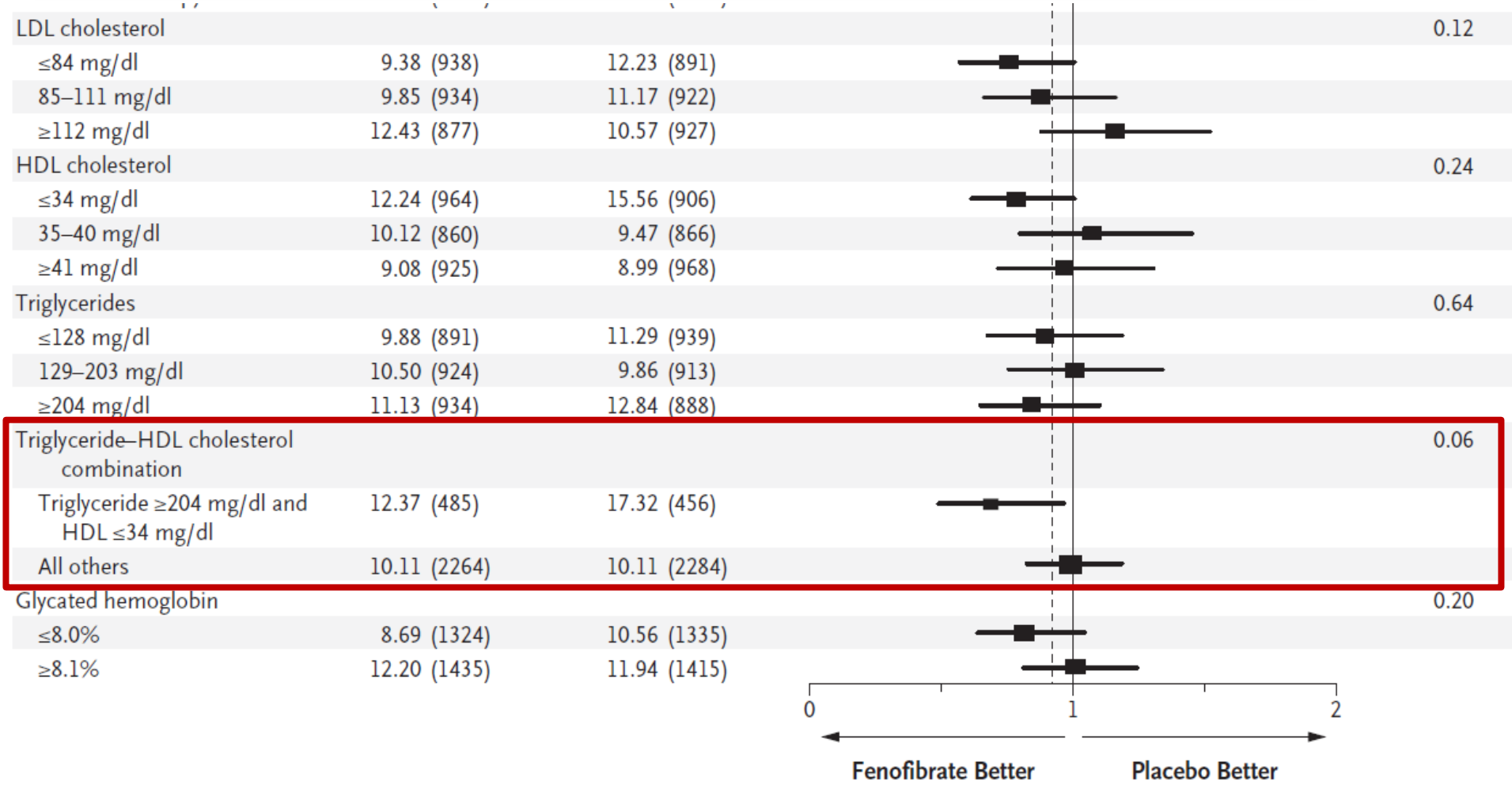
# Emerging Therapies

- **CETP inhibitors**
- **PCSK9 inhibitors**
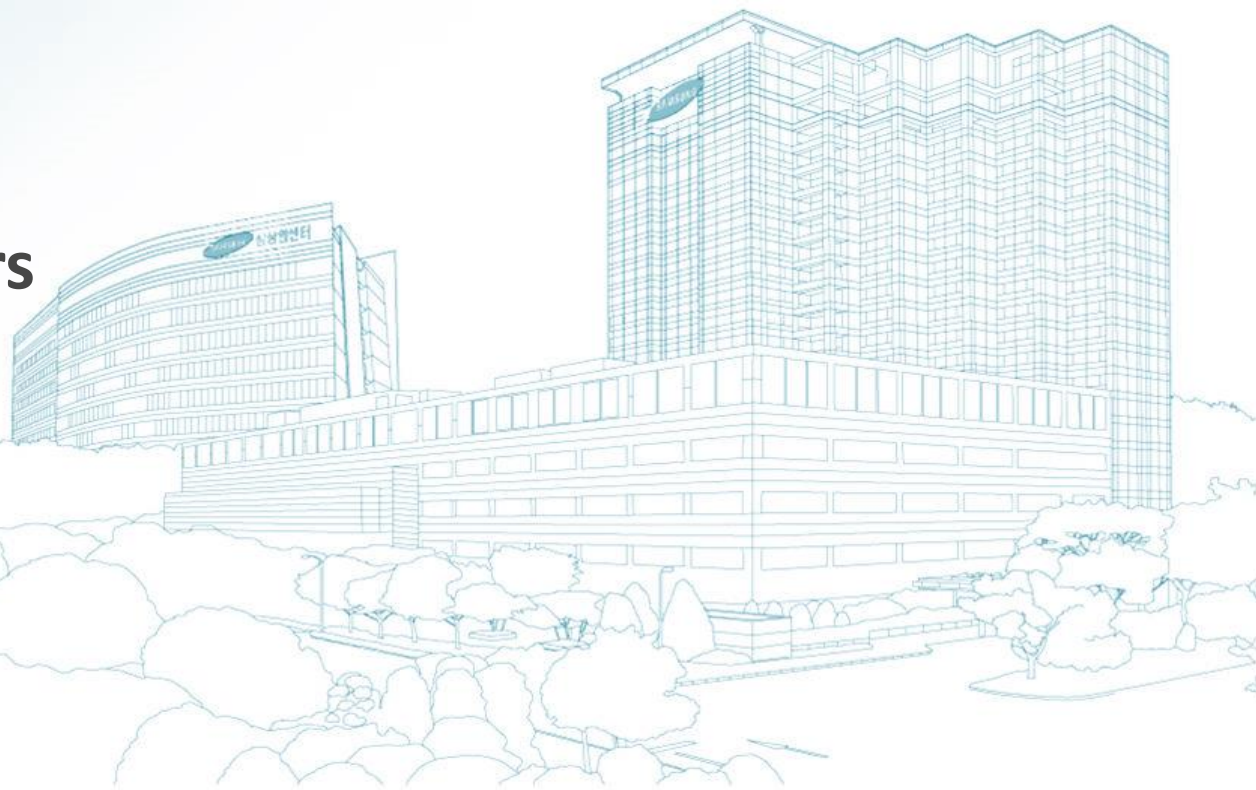
# Role of CETP inhibition



HDL ↑, LDL ↓

VLDL    CETP    HDL₂

CE    TG

Enrichment with cholesteryl esters

Transient enrichment with triglycerides (TG)

Hepatic lipase (HL)

HL

Small, dense LDL

Formation of small, dense LDL

Formation of small HDL₃ and lipid-free ApoA-I

ApoA-I

HDL₃

Facilitated modification of LDL

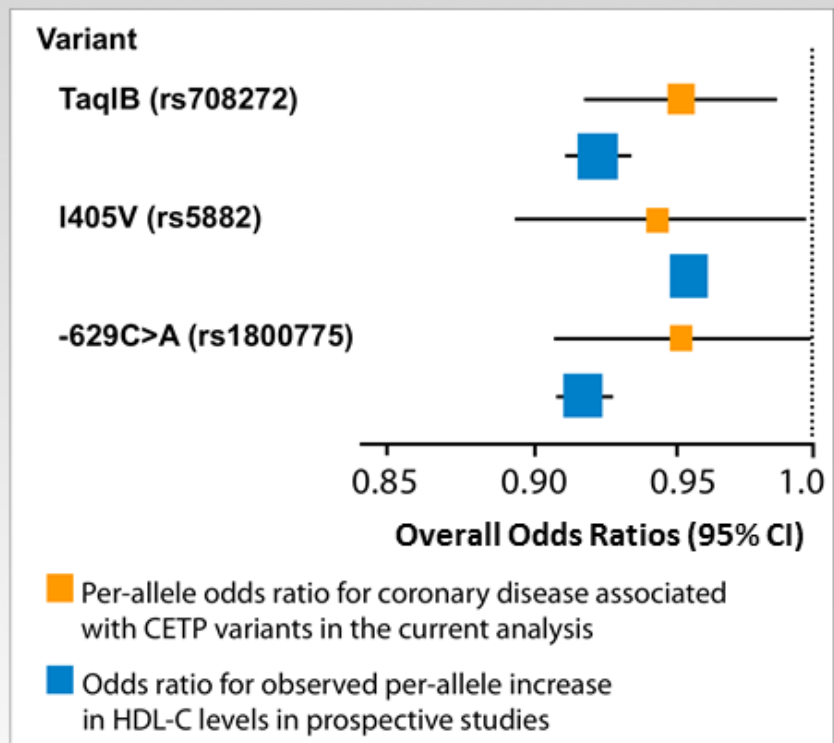Enhanced ApoA-I catabolism (eg, by renal filtration)
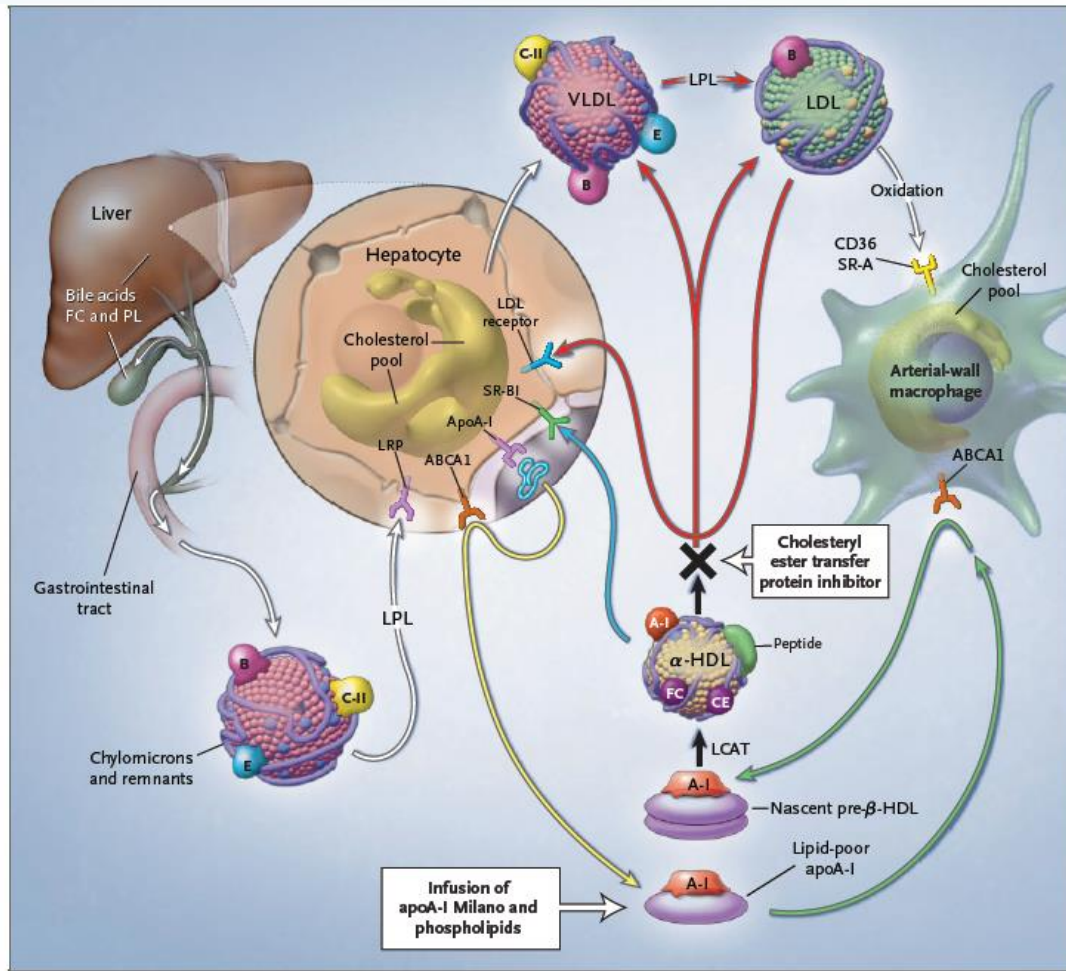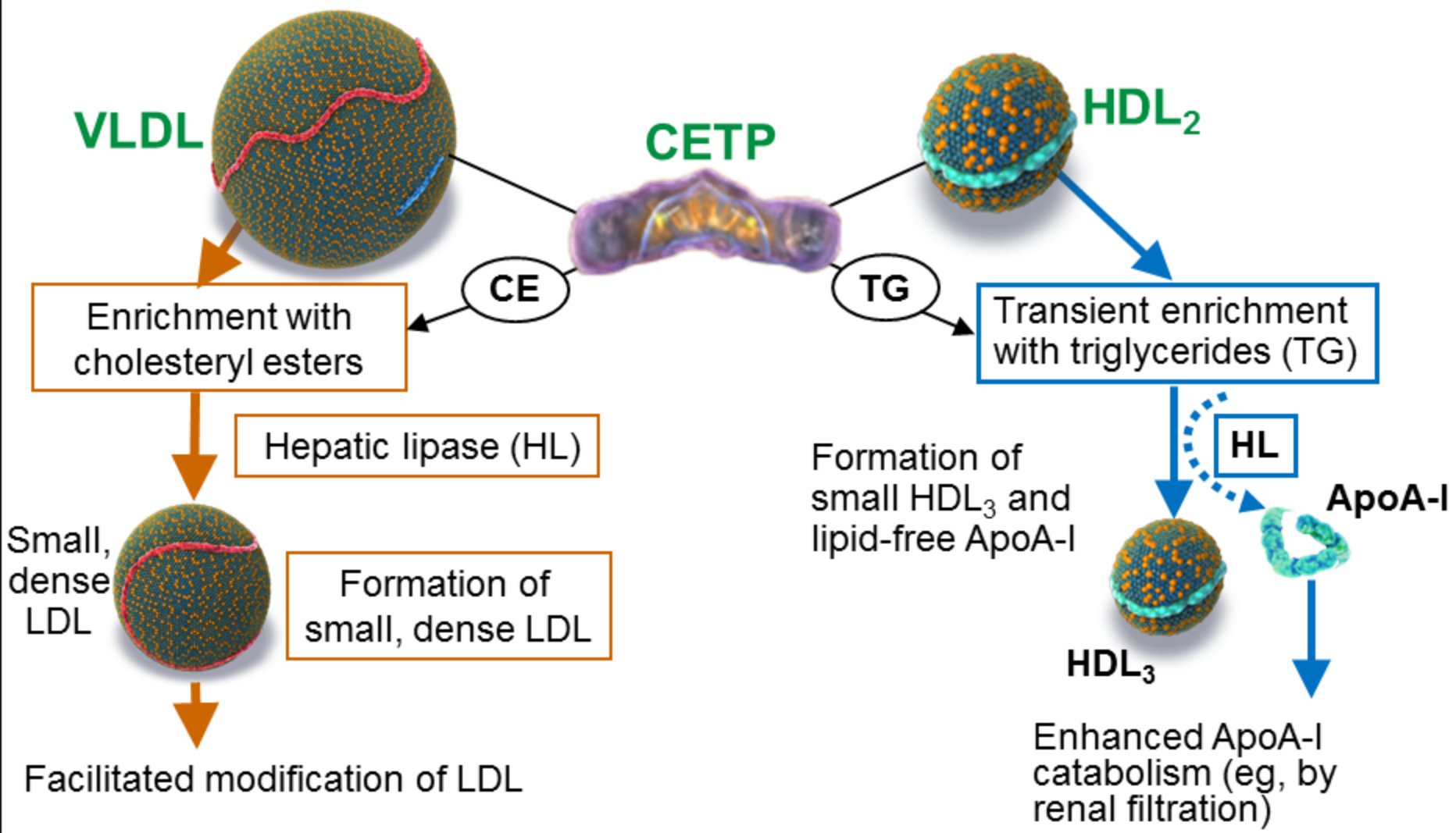
von Eckardstein A. *Eur Heart J.* 2010;31:390-393.

# Role of CETP in the generation of a proatherogenic lipoprotein profile

# CETP Deficiency: Genotype & Risk

| | Mean Difference (mmol/L) | | |
|---|---|---|---|
| | **HDL-C** | **LDL-C** | **TG** |
| *Taq*IB (rs708272) | 0.059 | -0.031 | -0.029 |
| I405V (rs5882) | 0.034 | -0.005 | -0.033 |
| -629C>A (rs1800775) | 0.063 | -0.029 | -0.034 |



Variant

TaqIB (rs708272)

I405V (rs5882)

-629C>A (rs1800775)

0.85   0.90   0.95   1.0

**Overall Odds Ratios (95% CI)**

■ Per-allele odds ratio for coronary disease associated with CETP variants in the current analysis

■ Odds ratio for observed per-allele increase in HDL-C levels in prospective studies

# CETP inhibitor class

| CETP inhibitors | Status | Efficacy | Safety |
|---|---|---|---|
| Torcetrapib (Pfizer) | Terminated | HDL-C: ↑72% <br> LDL-C : ↓25% | Increased CV mortality due to escalation of BP |
| Dalcetrapib (Roche) | PHASE III | HDL-C : ↑32% <br> LDL-C: No change vs. placebo | No increase in BP |
| Anacetrapib (MSD) | PHASE III | HDL-C: ↑138% <br> LDL-C : ↓40% | No increase in BP |
| Evacetrapib (Lilly) | PHASE II | HDL-C: ↑87% <br> LDL-C : ↓13% | Increase in BP when combined with simvastatin |

# Torcetrapib- ILLUMINATE (Phase III)

▸ 15067 patients at high CV risk

▸ Torcetrapib + atorvastatin vs. atorvastatin

▸ Primary outcome : time to the first major CV event (death from coronary heart disease, nonfatal myocardial infarction, stroke, or hospitalization for unstable angina)

▸ At 12 months, in torcetrapib group,
  ◦ 72.1 % ↑ in HDL-C, 24.9 %↓ in LDL -C compared with baseline (p<0.001)
  ◦ SBP , serum aldosterone↑

▸ Terminated prematurely due to increased death and CV events in torcetrapib group

Ref. *N Eng J Med.* 2007; 357: 2109-22
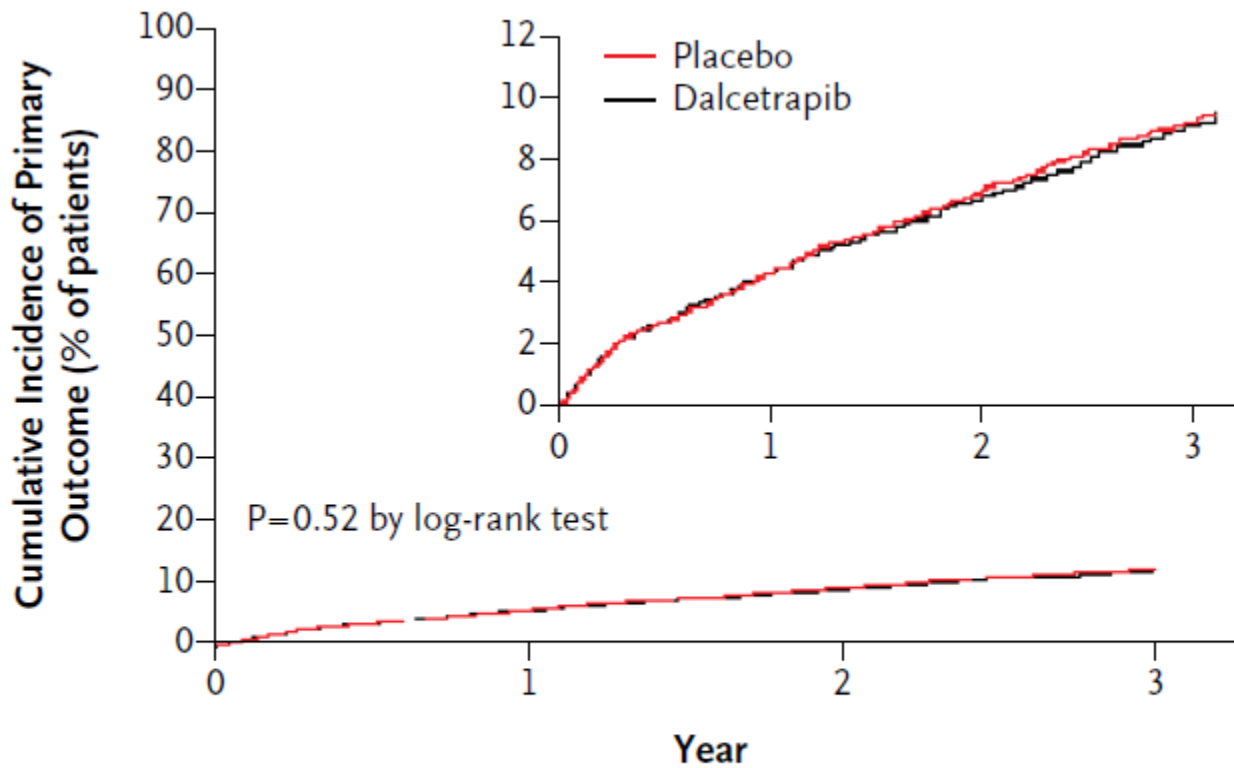
# Dal-OUTCOMES trial
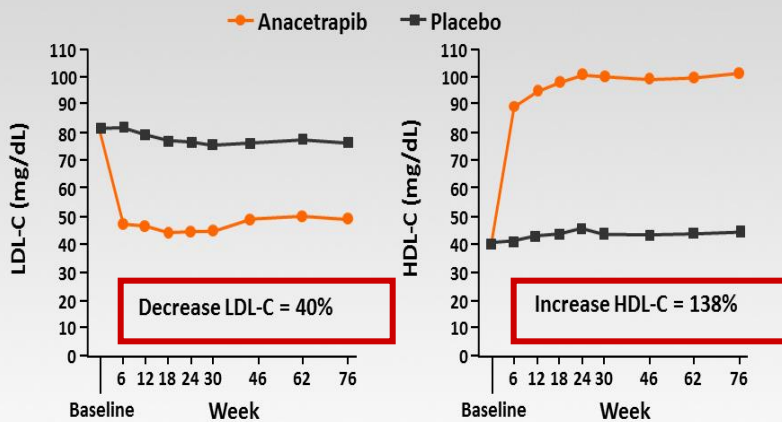
# Potential Reasons Why dal-OUTCOMES Failed to Show Benefit

▸ Moderate HDL elevation in patients optimally treated with statins and other agents has no impact on CHD

▸ CETP inhibition may produce a form of HDL that is dysfunctional e.g. in reverse cholesterol transport

▸ Potential benefit of lipoprotein changes may have been outweighed by effects on BP (+0.6 mm SBP)

▸ Dalcetrapib is a partial CETP inhibitor, may have been insufficiently potent

**One more trial of futility,
calling into question the potential attractiveness of CETP inhibition as an option in CV risk reduction as well as perhaps the overall HDL-hypothesis**

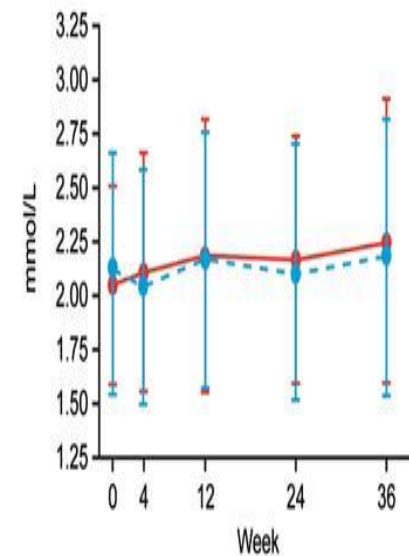# Efficacy :  Anacetrapib more is more potent Vs. Dalcetrapib

# Anacetrapib: On going CV outcome trial



- 30,000 patients with occlusive arterial disease in North America, Europe and Asia

- Background LDL-lowering with atorvastatin

- Randomized to anacetrapib 100 mg vs. placebo

   Scheduled follow-up: 4 years

- Primary outcome: Coronary death, myocardial infarction  or coronary revascularization

# The Role of PCSK9
# in the Regulation of LDL-Receptor Expression

PCSK9: Proprotein convertase subtilisin/kexin type 9

McKenney J. ACC; 2012
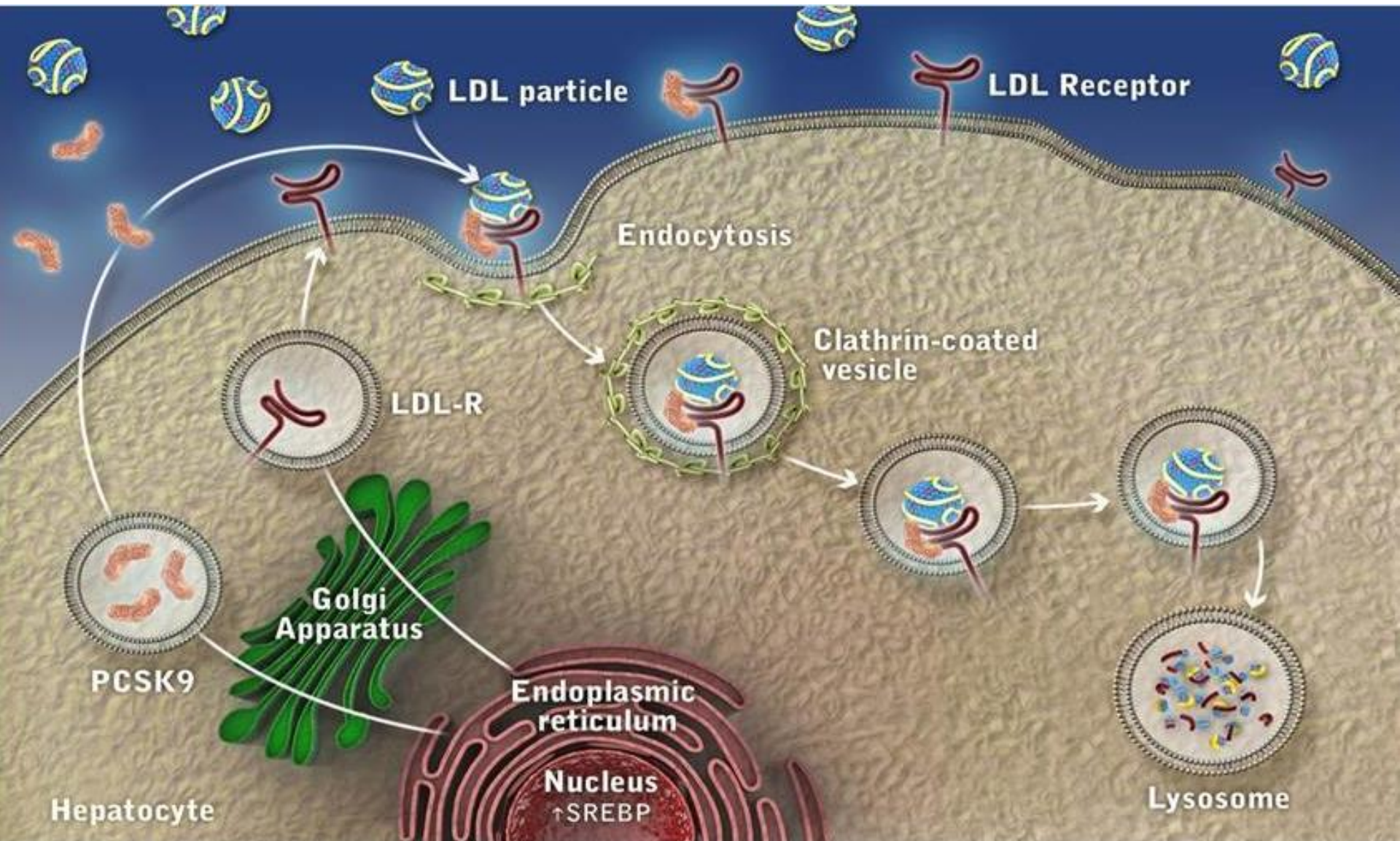
# Proposed mechanism for PCSK9-mediated LDLR downregulation
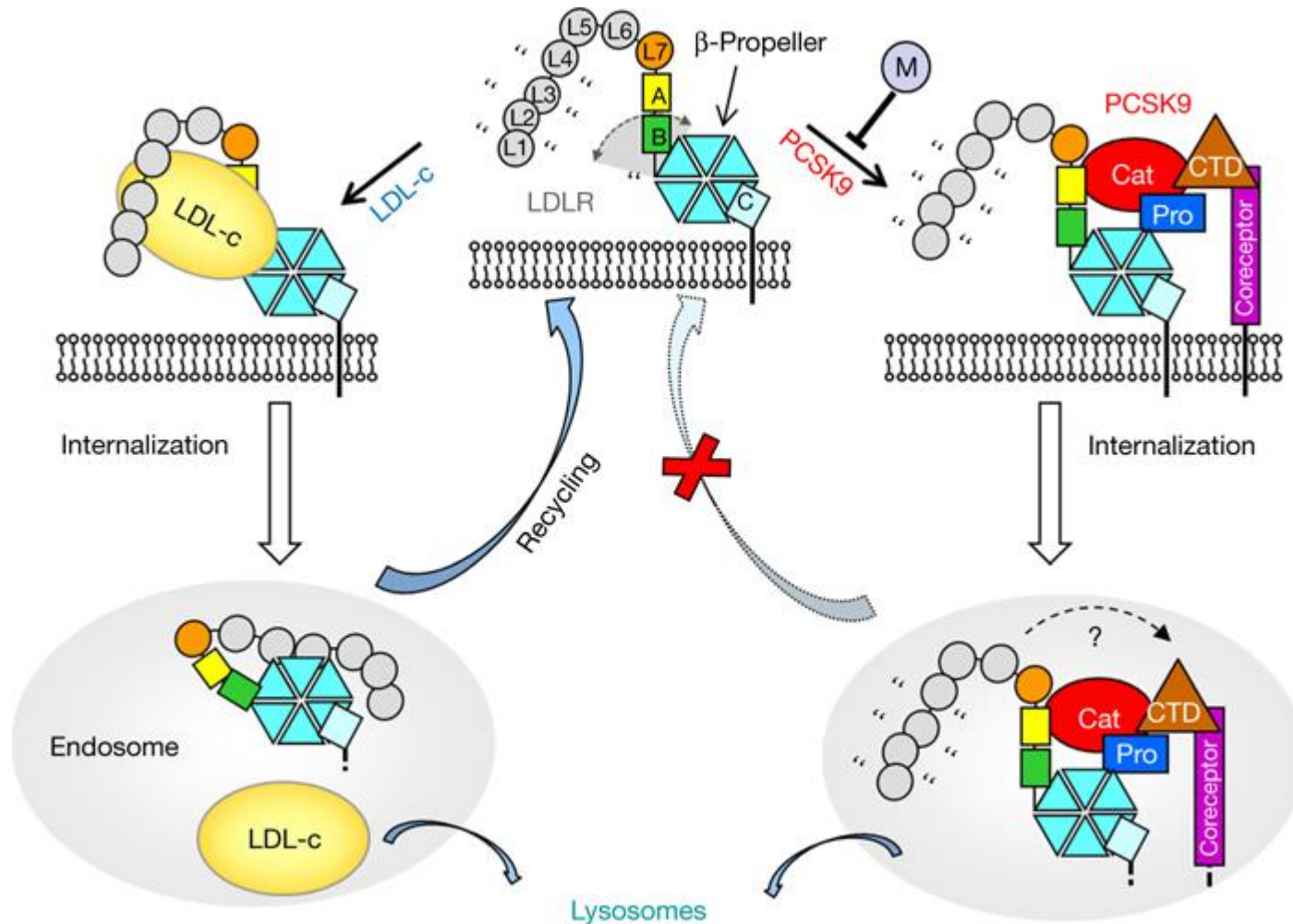
# Population Studies: PCSK9 Loss-of-Function Mutations

- Patients with loss-of-function mutations in PCSK9 or total lack of PCSK9

  - Have naturally low levels of LDL-C and reduced coronary heart disease (→ efficacy)

  - Are not associated with other detectable abnormalities (→ safety)

| | PCSK9 Mutation | LDL-C Reduction | CHD Reduction | Population |
|---|---|---|---|---|
| Benn M | R46L | 12% | 46% | Copenhagen City Heart Study / Copenhagen General Population Study / Copenhagen Ischemic Heart Disease Study |
| Cohen JC | R46L | 14% | 47% | Atherosclerosis Risk Community Study (US) |
| | Y142X or C679X | 28% | 88% | |

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# Effects of anti-PCSK9 mAb on LDL-C level

**Table 2. Baseline and Lowest Values for Low-Density Lipoprotein (LDL) Cholesterol in Single-Dose Studies, According to Route of Administration.***

| Variable | Placebo (N=10) | REGN727 | | | | |
|---|---|---|---|---|---|---|
| | | 0.3-mg/kg Dose (N=6) | 1.0-mg/kg Dose (N=6) | 3.0-mg/kg Dose (N=6) | 6.0-mg/kg Dose (N=6) | 12.0-mg/kg Dose (N=6) |
| **Single-dose, intravenous** | | | | | | |
| LDL cholesterol | | | | | | |
| Baseline (mg/dl) | 137.0±38.9 | 132.0±14.3 | 126.3±16.9 | 151.8±40.7 | 127.2±8.3 | 138.7±28.3 |
| Study day with lowest value | 8 | 11 | 11 | 29 | 22 | 43 |
| Lowest value (mg/dl) | 128.6±30.6 | 88.2±17.4 | 66.7±24.6 | 56.7±24.4 | 55.2± 5.1 | 46.8±15.0 |
| Difference in percent change from baseline vs. placebo (percentage points)† | | −28.1±6.3 | −42.2± 6.3 | −57.4±7.6 | −56.5±5.4 | −65.4±8.4 |
| P value vs. placebo† | | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| | Placebo (N=8) | 50-mg Dose (N=6) | 100-mg Dose (N=6) | 150-mg Dose (N=6) | 250-mg Dose (N=6) | |
| **Single-dose, subcutaneous** | | | | | | |
| LDL cholesterol | | | | | | |
| Baseline (mg/dl) | 133.0±29.8 | 129.8±28.9 | 126.5±29.9 | 142.2±25.7 | 117.2±15.20 | NA |
| Study day with lowest value | 22 | 15 | 11 | 15 | 11 | NA |
| Lowest value (mg/dl) | 115.3±15.6 | 76.5±23.9 | 58.6±9.2 | 62.0±21.9 | 54.5±15.6 | NA |
| Difference in percent change from baseline vs. placebo (percentage points)† | | −32.5±8.5 | −39.9±7.1 | −38.5±8.5 | −45.7±7.2 | NA |
| P value vs. placebo† | | <0.001 | <0.001 | <0.001 | <0.001 | NA |

# Subcutaneous administration



Effects maintained up to 21 days

**No. at Risk**

| | 1 | 2 | 4 | 8 | 11 | 15 | 22 | 29 | 43 | 64 | 106 |
|---------|---|---|---|---|----|----|----|----|----|----|-----|
| Placebo | 8 | 8 | 8 | 8 | 8  | 8  | 8  | 8  | 7  | 7  | 7   |
| 50 mg   | 6 | 6 | 6 | 6 | 6  | 6  | 6  | 6  | 5  | 6  | 5   |
| 100 mg  | 6 | 6 | 6 | 6 | 5  | 6  | 6  | 6  | 5  | 6  | 6   |
| 150 mg  | 6 | 6 | 5 | 5 | 5  | 5  | 5  | 5  | 5  | 4  | 5   |
| 250 mg  | 6 | 6 | 6 | 6 | 6  | 6  | 6  | 6  | 6  | 6  | 6   |

**Table 3. Baseline and Day 57 Values for LDL Cholesterol among Subjects with Familial Hypercholesterolemia (FH) or Non-FH in the Multiple-Dose Study, According to Atorvastatin Use.***

| Variable | Placebo | REGN727 50-mg Dose | 100-mg Dose | 150-mg Dose |
|---|---|---|---|---|
| **Subjects with FH taking atorvastatin** | | | | |
| No. of subjects | 6 | 5 | 5 | 5 |
| LDL cholesterol | | | | |
| At baseline (mg/dl) | 133.2±20.7 | 125.0±12.1 | 135.8±41.1 | 140.2±26.2 |
| On day 57 (mg/dl) | 137.2±12.5 | 80.6±21.9 | 60.0±15.7 | 65.4±21.2 |
| Difference in percent change from baseline vs. placebo (percentage points)† | | −41.4 | −57.6 | −55.7 |
| P value vs. placebo† | | <0.001 | <0.001 | <0.001 |
| **Subjects with non-FH taking atorvastatin** | | | | |
| No. of subjects | 6 | 8 | 8 | 8 |
| LDL cholesterol | | | | |
| At baseline (mg/dl) | 117.7±13.7 | 108.0±14.1 | 112.1±19.9 | 111.9±23.3 |
| On day 57 (mg/dl) | 123.2±13.6 | 75.5±13.7 | 62.1±12.7 | 46.5±19.9 |
| Difference in percent change from baseline vs. placebo (percentage points)† | | −38.2 | −51.5 | −64.7 |
| P value vs. placebo† | | <0.001 | <0.001 | <0.001 |
| **Subjects with non-FH not taking atorvastatin** | | | | |
| No. of subjects | 2 | NA | NA | 8 |
| LDL cholesterol | | | | |
| At baseline (mg/dl) | 151.5±16.3 | NA | NA | 178.6±49.0 |
| On day 57 (mg/dl) | 156.5±23.3 | NA | NA | 81.4±25.7 |
| Difference in percent change from baseline vs. placebo (percentage points)† | | NA | NA | −57.0 |
| P value vs. placebo† | | NA | NA | 0.002 |

Familial or non−familial hypercholesterolemia

Subcutaneously
At 1, 29, 43 days

# Summary

➤ **Combination treatment**

- **Statin + Ezetimibe : awaiting for IMPROVE-IT trial**
- **Statin + Niacin: disappointed**
- **Statin + Fenofibrate: considered in special subgroups**

➤ **Emerging therapies**

- **CETP inhibitors: questionable**
- **PCSK9 inhibitors: promising in pilot studies**

# RCTs of n-3 PUFA and Clinical Cardiovascular Events

| Trials, Year (Ref. #) | Population | Intervention | Duration of Follow-Up, yrs | Events | RR (95% CI) | Achieved Power* |
|---|---|---|---|---|---|---|
| DART, 1989 (222) | 2,033 men with recent (average ~1 month prior) MI | Advice to consume fatty fish 2 servings/week vs. usual care | 2 | IHD events, n = 276<br>IHD deaths, n = 194 | 0.84 (0.66–1.07)<br>0.68 (0.49–0.94) | 0.69<br>0.57 |
| GISSI-Prevenzione Trial, 1999 (169) | 11,324 men with recent (≤3 months prior) MI | 882 mg/day EPA+DHA vs. usual care | 3.5 | Cardiac deaths, n = 520<br>Sudden deaths, n = 286 | 0.78 (0.65–0.92)<br>0.74 (0.58–0.93) | 0.91<br>0.69 |
| DART 2, 2003 (221) | 3,114 men with angina | Advice to consume fatty fish 2 servings/week vs. usual care | 3–9 | Cardiac deaths, n = 319<br>Sudden deaths, n = 120 | 1.26 (1.00–1.58)<br>1.54 (1.06–2.23) | 0.65<br>0.26 |
| JELIS, 2007 (220) | 18,645 men and women with total cholesterol ≥6.5 mmol/l | 1.8 g/day EPA vs. usual care | 5 | Major coronary events, n = 586<br>Coronary deaths, n = 60<br>Sudden deaths, n = 35 | 0.81 (0.69–0.95)<br>0.94 (0.57–1.56)<br>1.06 (0.55–2.07) | 0.93<br>0.17<br>0.13 |
| GISSI-Heart Failure 2008 (223) | 6,975 patients with chronic congestive heart failure | 882 mg/day EPA+DHA vs. placebo | 3.9 | Total mortality, n = 1,969<br>Cardiovascular death, n = 1,477<br>Sudden deaths, n = 632 | 0.91 (0.83–0.99)<br>0.90 (0.81–0.99)<br>0.93 (0.79–1.08) | >0.99<br>>0.99<br>0.94 |
| Alpha-Omega, 2010 (17) | 4,837 patients with a history of past (average ~4.3 yrs prior) MI | 376 mg/day EPA+DHA vs. a combined control group receiving either placebo or ALA 1.9 g/day | 3.3 | Major cardiovascular events, n = 671<br>CHD deaths, n = 138 | 1.01 (0.87–1.17)<br>0.98 (0.68–1.32) | 0.96<br>0.36 |
| Omega, 2010 (219) | 3,851 patients with recent (≤2 weeks prior) MI | 840 mg/day EPA+DHA vs. placebo | 1 | Major cardiovascular events, n = 331<br>Sudden deaths, n = 57 | 1.21 (0.96–1.52)<br>0.95 (0.56–1.60) | 0.72<br>0.17 |
| SU.FOL.OM3, 2010 (224) | 2,501 patients with a history of past (average ~100 days prior) acute coronary or cerebral ischemic event | 600 mg/day EPA+DHA vs. a combined control group receiving either placebo or B vitamins (5-methyltetrahydrofolate, 560 μg; B-6, 3 mg; and B-12, 20 μg) | 4.2 | Major cardiovascular events, n = 157<br>CHD deaths, n = 40 | 1.08 (0.79–1.47)<br>Not reported | 0.4<br>0.14 |