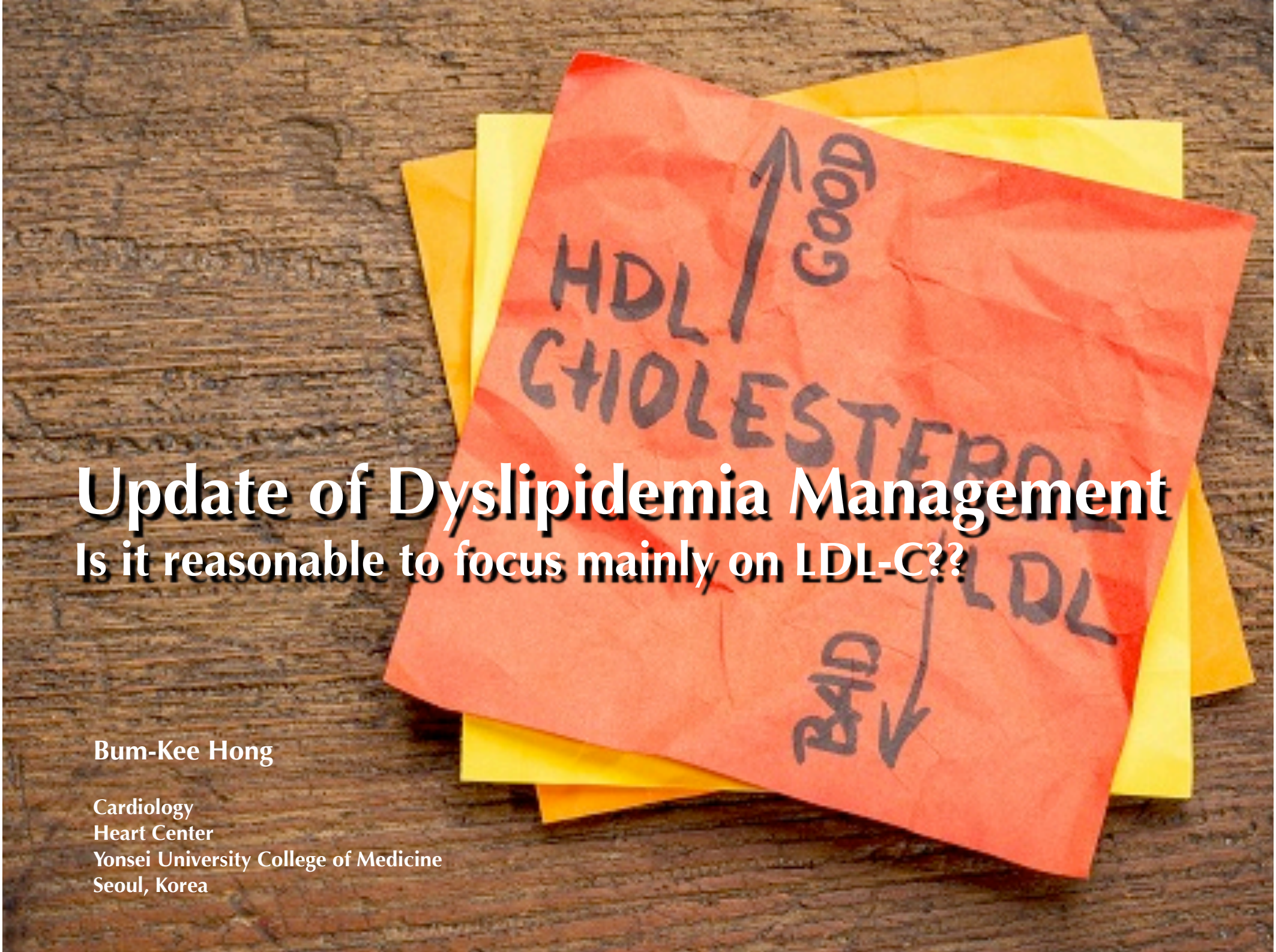
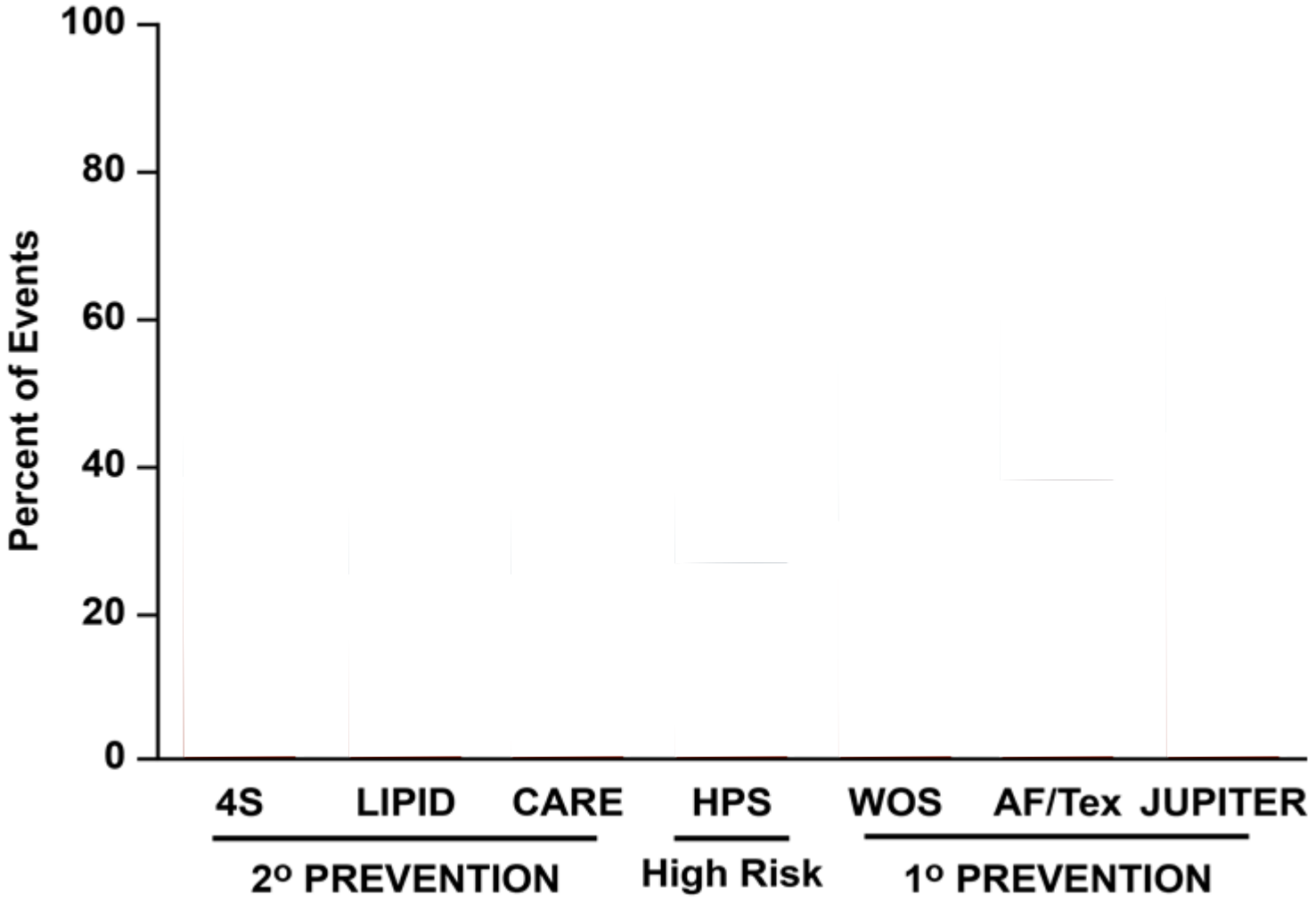



# Update of Dyslipidemia Management

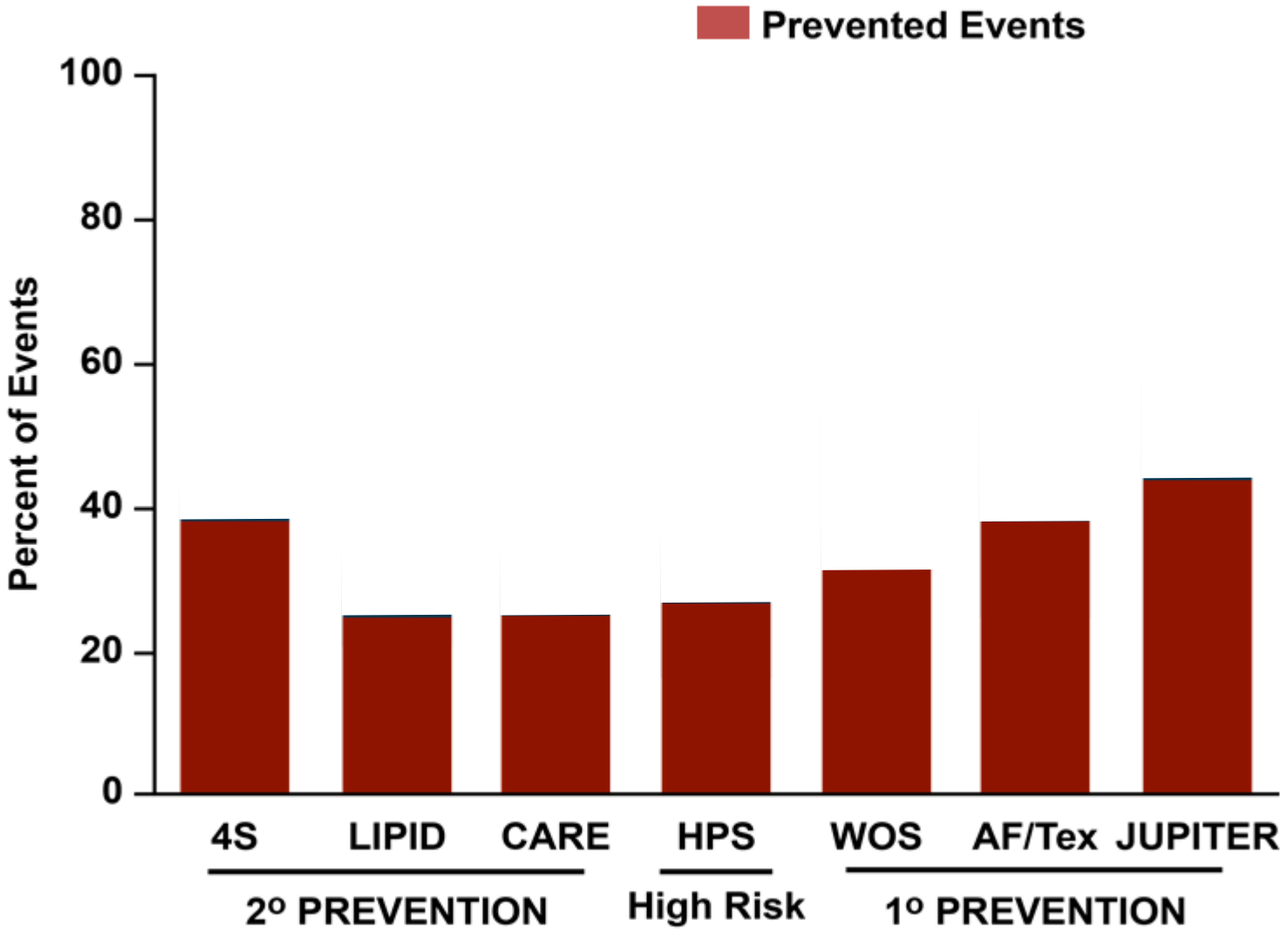
## Is it reasonable to focus mainly on LDL-C??

**Bum-Kee Hong**

Cardiology
Heart Center
Yonsei University College of Medicine
Seoul, Korea




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.

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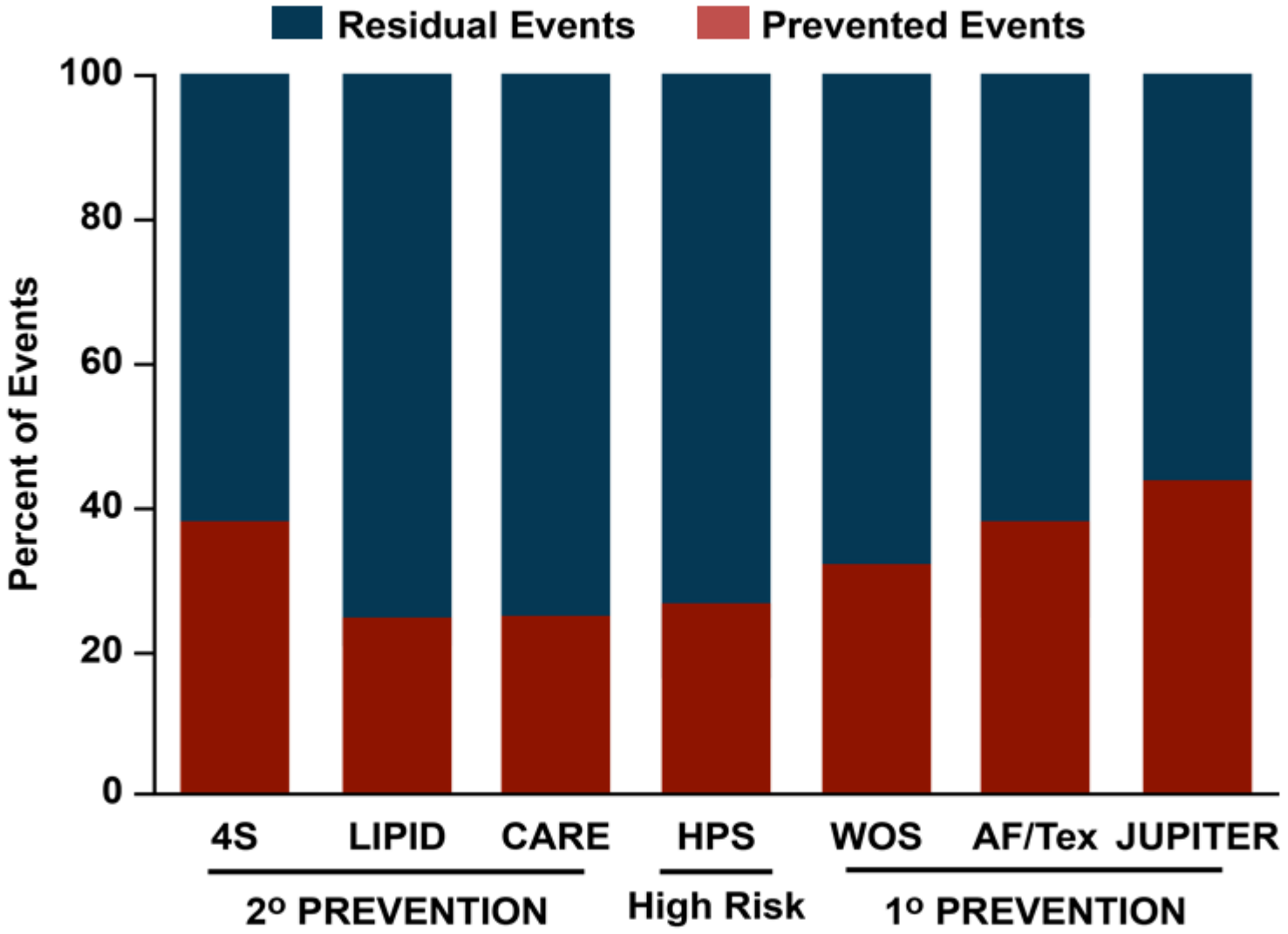


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# Residual CV risk in Statin Trials

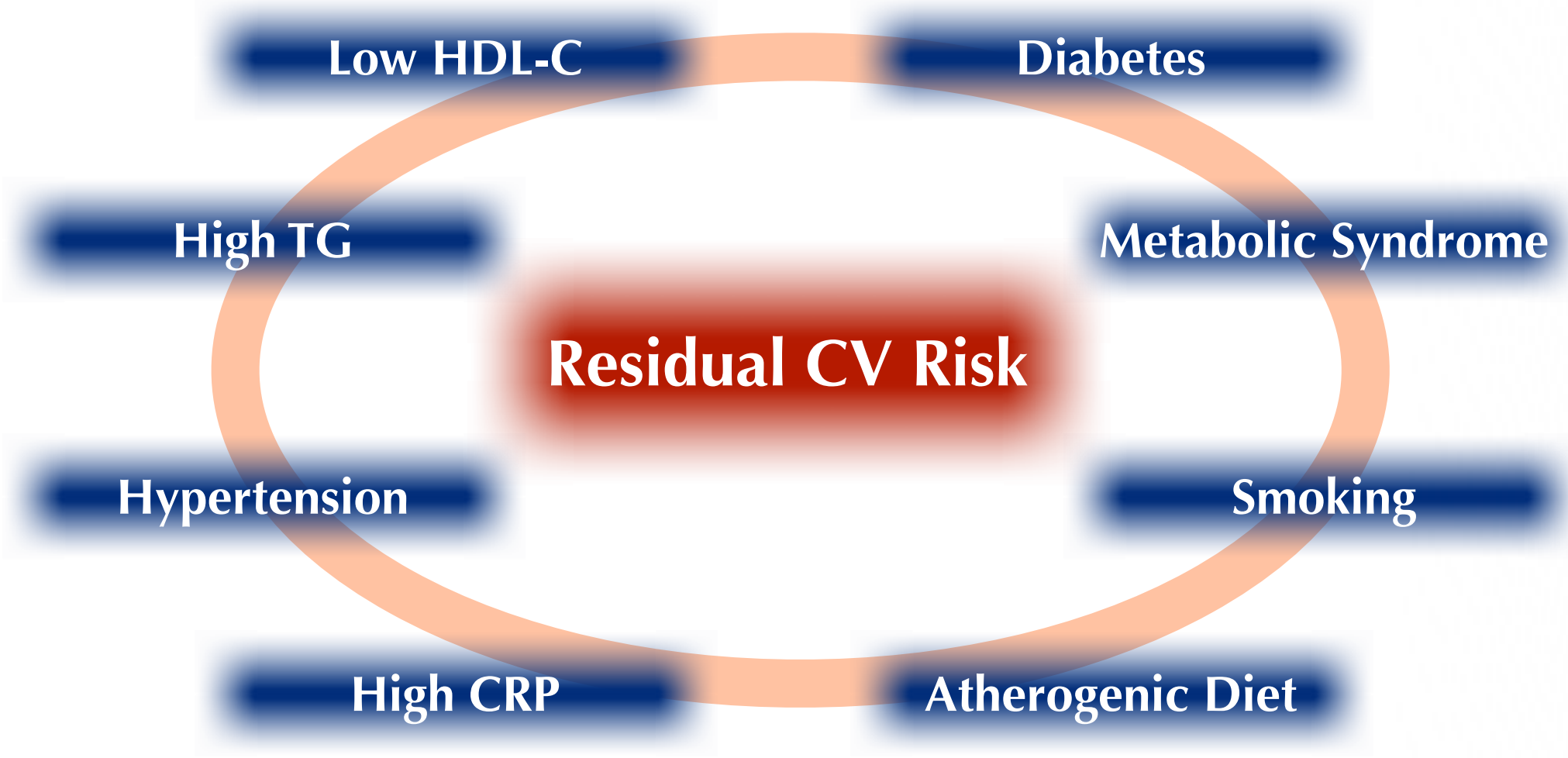
Ballantyne CM, et al. *Circulation*. 1999;99:736-743; Scandinavian Simvastatin Survival Study Group. *Lancet*. 1995;345:1274-1275; The LIPID Study Group. *N Engl J Med*. 1998;339:1349-1357; Pfeffer MA, et al. *J Am Coll Cardiol*. 1999;33:125-130; Shepherd J, et al. *N Engl J Med*. 1995;333:1301-1307;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

# Patients with High Residual Risk

**High LDL-C**

*Current Cardiology Reports. 2007; 9 :499-505*

# Patients with High Residual Risk




*Current Cardiology Reports. 2007; 9 :499-505*

# Non-LDL-Targeted Add-On Therapy to Statin for Further CV risk Reduction

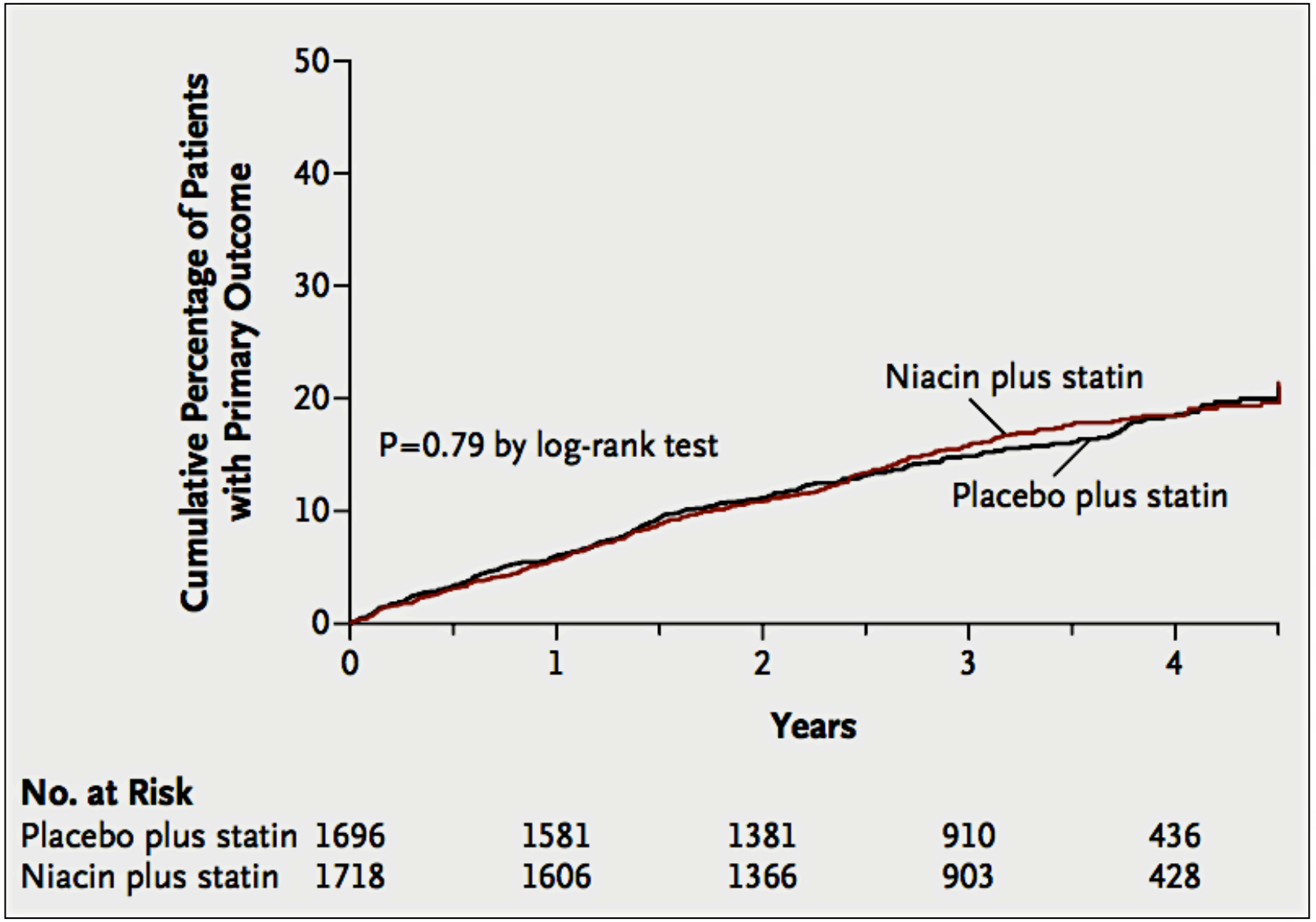
- Statin + Niacin (HDL-C) : AIM-HIGH, HPS2-THRIVE
- Statin + Fenofibrate (TG) : ACCORD Lipid

Placebo+Stain vs. Niacin+Statin

# AIM-HIGH Result

*N Engl J Med 2011;365:2255-67*

AIM-HIGH
Cholesterol Management Program




**No. at Risk**

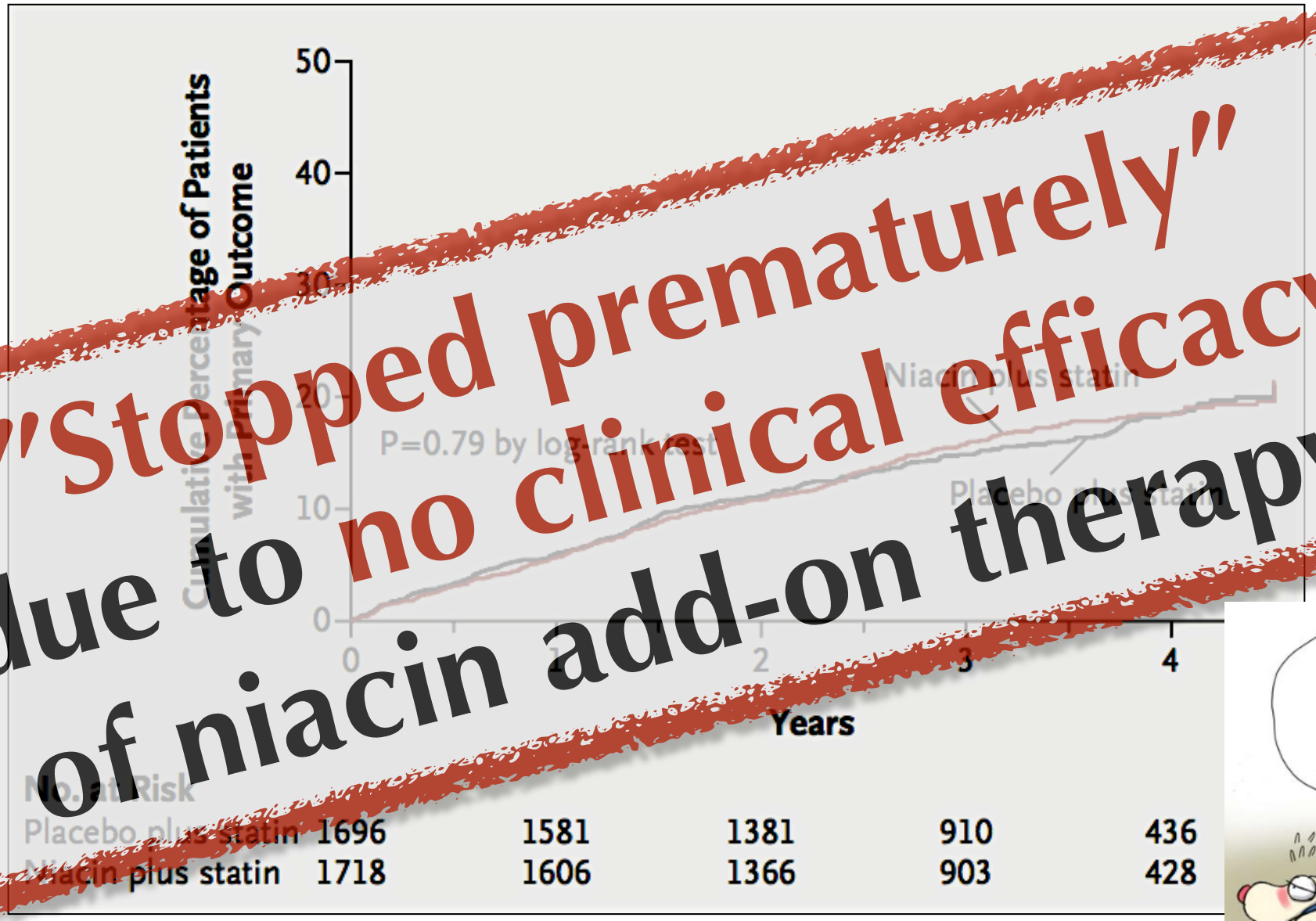
| | | | | | |
|---|---|---|---|---|---|
| Placebo plus statin | 1696 | 1581 | 1381 | 910 | 436 |
| Niacin plus statin | 1718 | 1606 | 1366 | 903 | 428 |

Placebo+Stain vs. Niacin+Statin

# AIM-HIGH Result

*N Engl J Med 2011;365:2255-67*

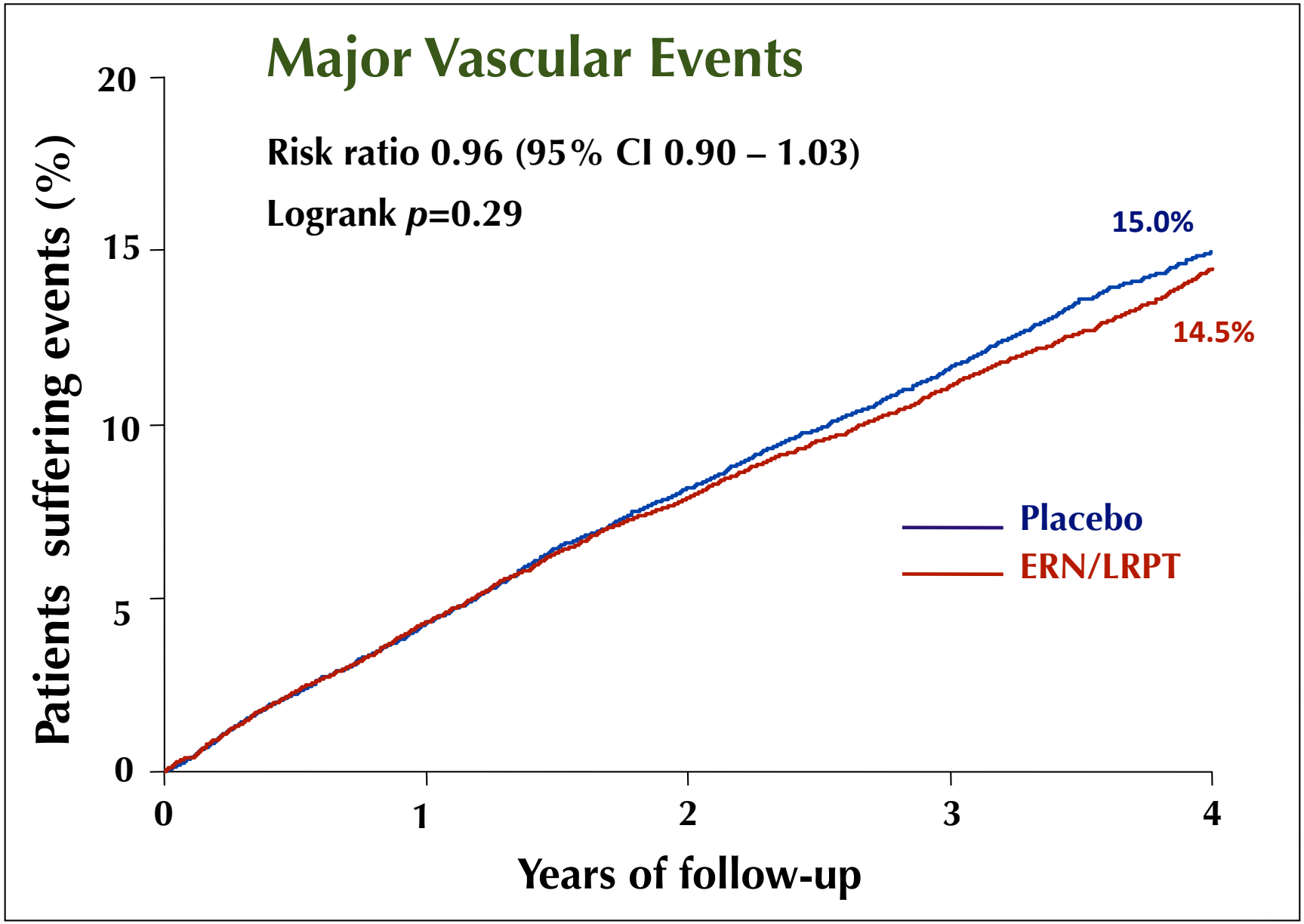
AIM-HIGH
Cholesterol Management Program




"Stopped prematurely" due to no clinical efficacy of niacin add-on therapy

# HPS2-THRIVE Result

*Late Breaking in ACC 2013*



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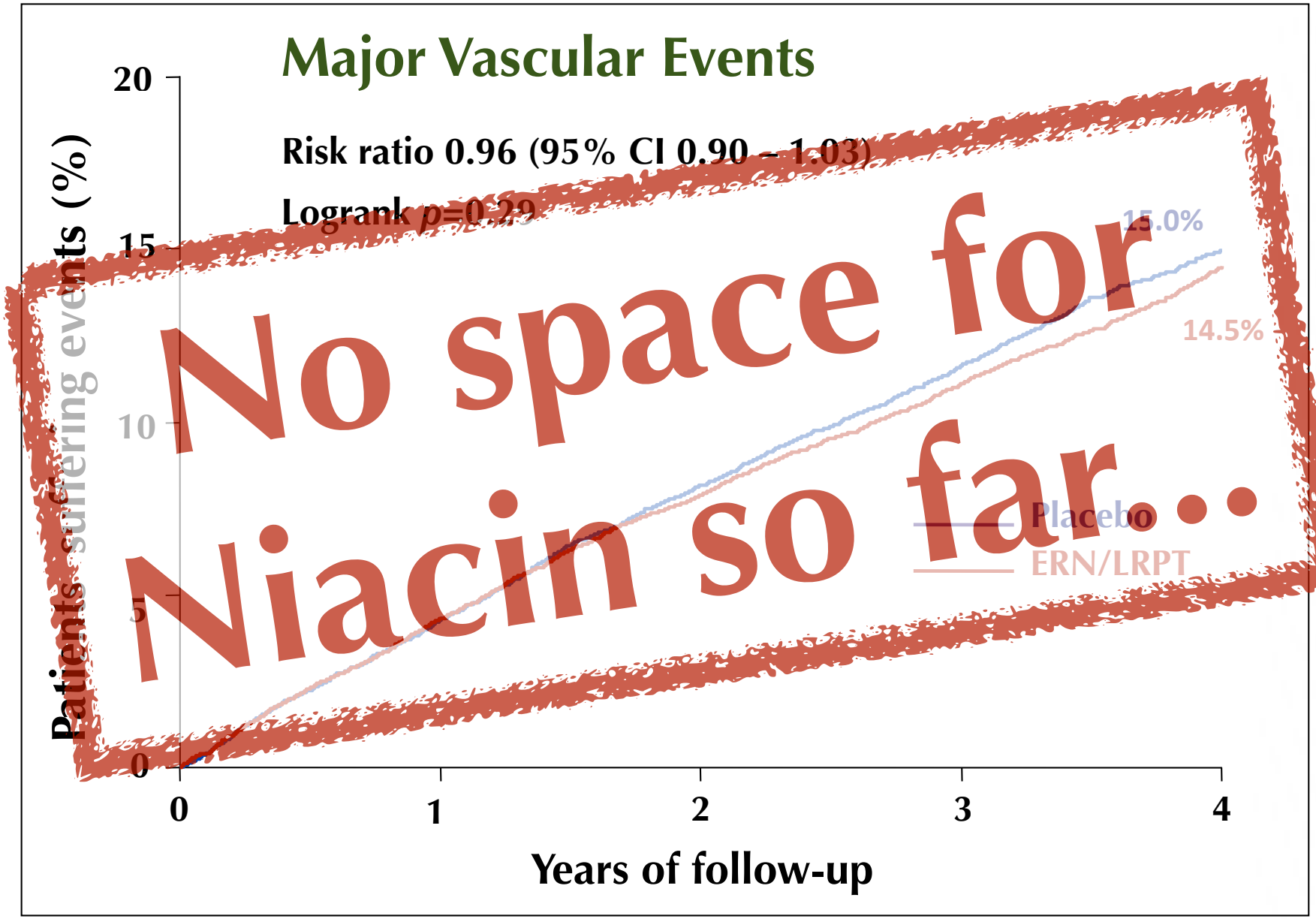
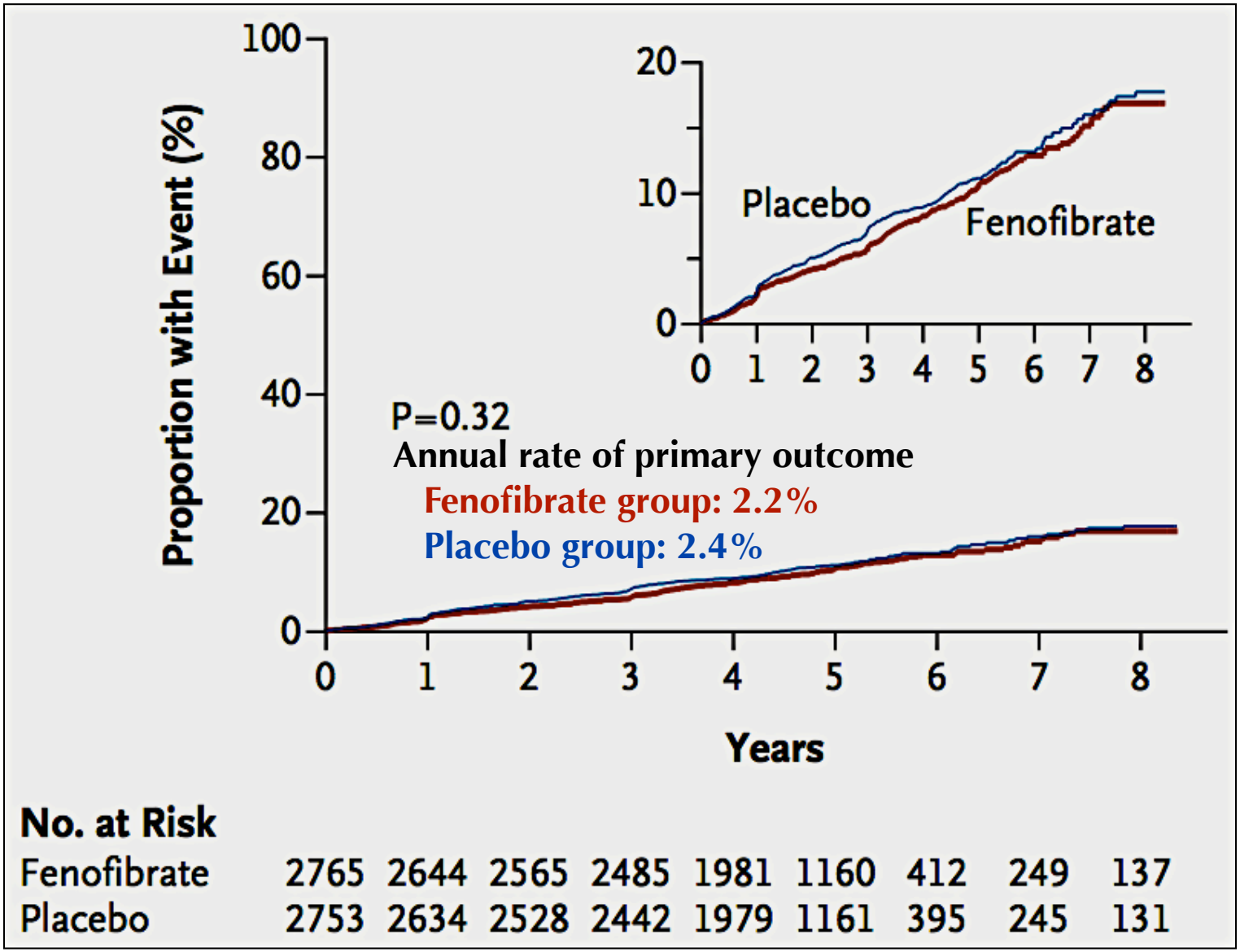


Action to Control Cardiovascular Risk in Diabetes
ACCORD

# ACCORD Lipid Result

N Engl J Med 2011;365:2255-67



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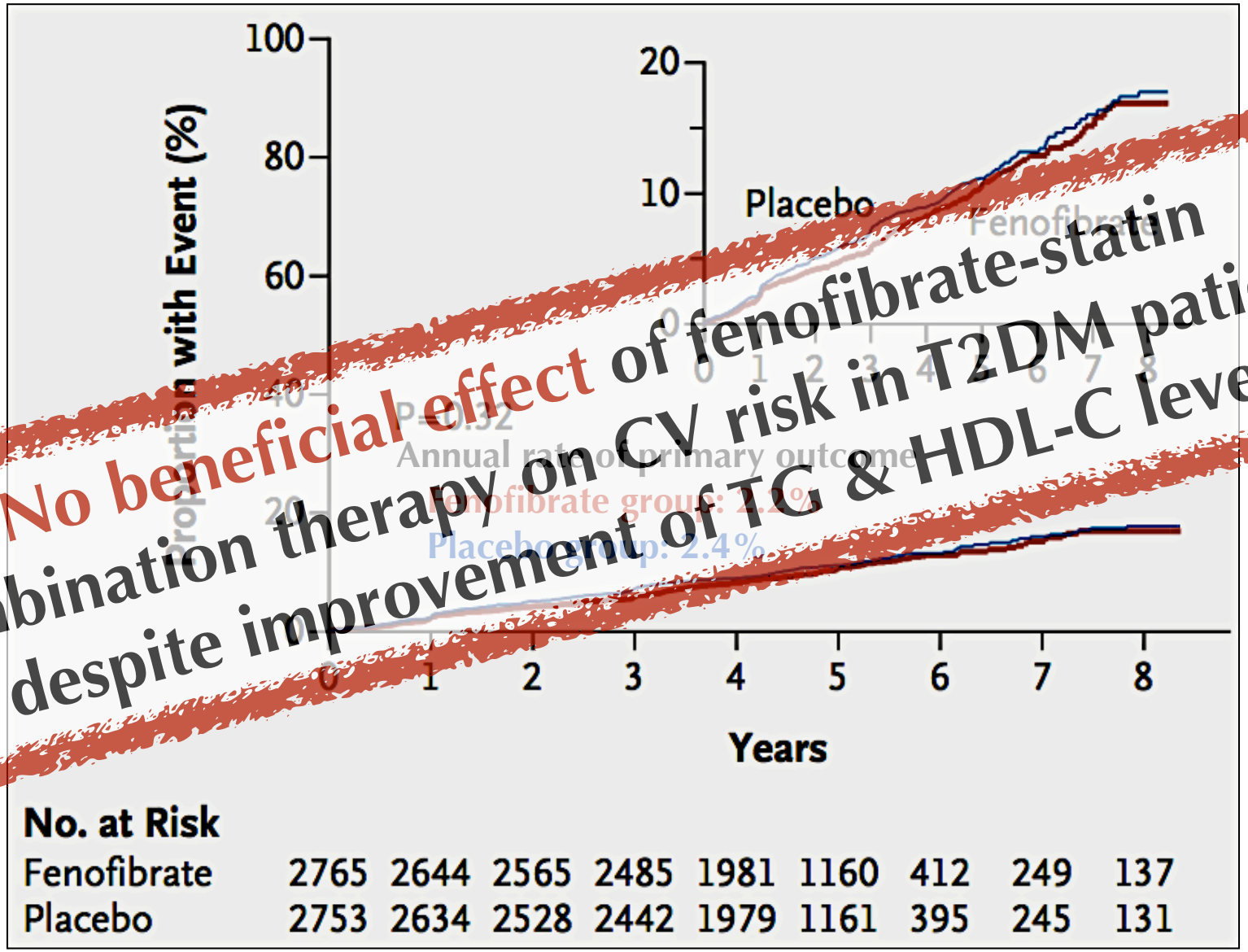
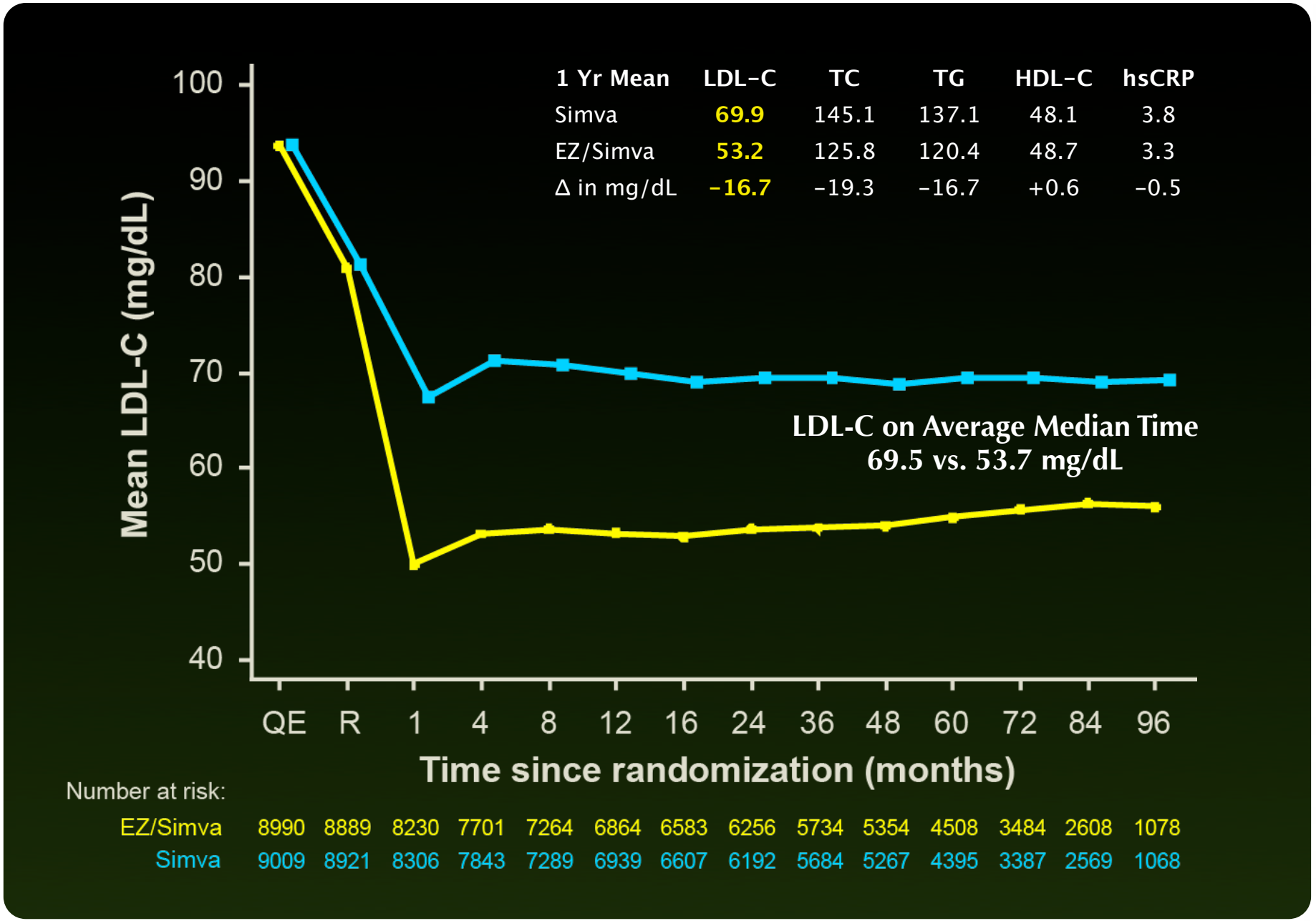



No beneficial effect of fenofibrate-statin combination therapy on CV risk in T2DM patients despite improvement of TG & HDL-C level

# IMPROVE-IT Results

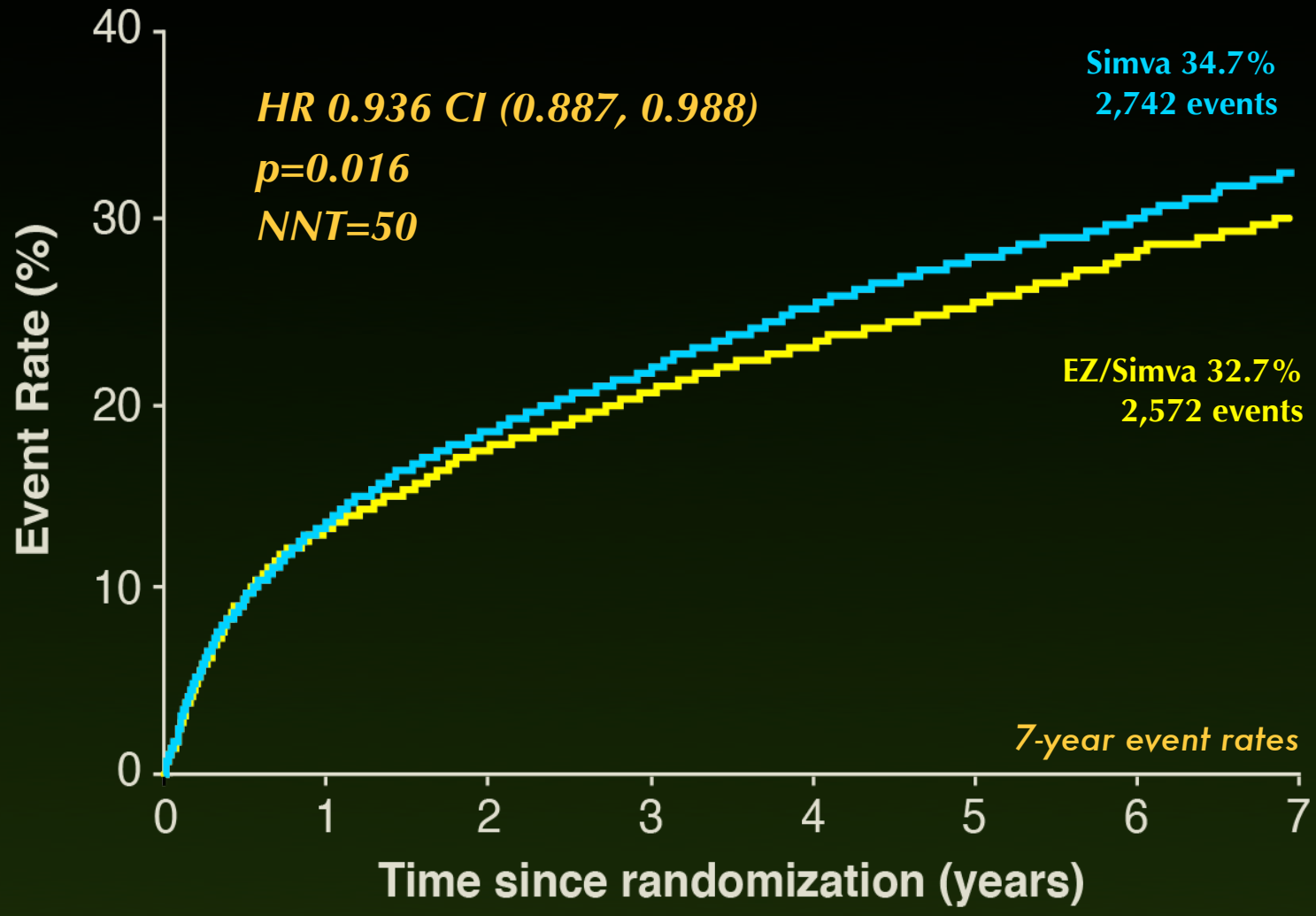
*N Engl J Med 2015; 372:2387-2397*



# IMPROVE-IT Results

*N Engl J Med 2015; 372:2387-2397*

## Primary Endpoint



# IMPROVE-IT Results

IMPROVE-IT

*N Engl J Med 2015; 372:2387-2397*

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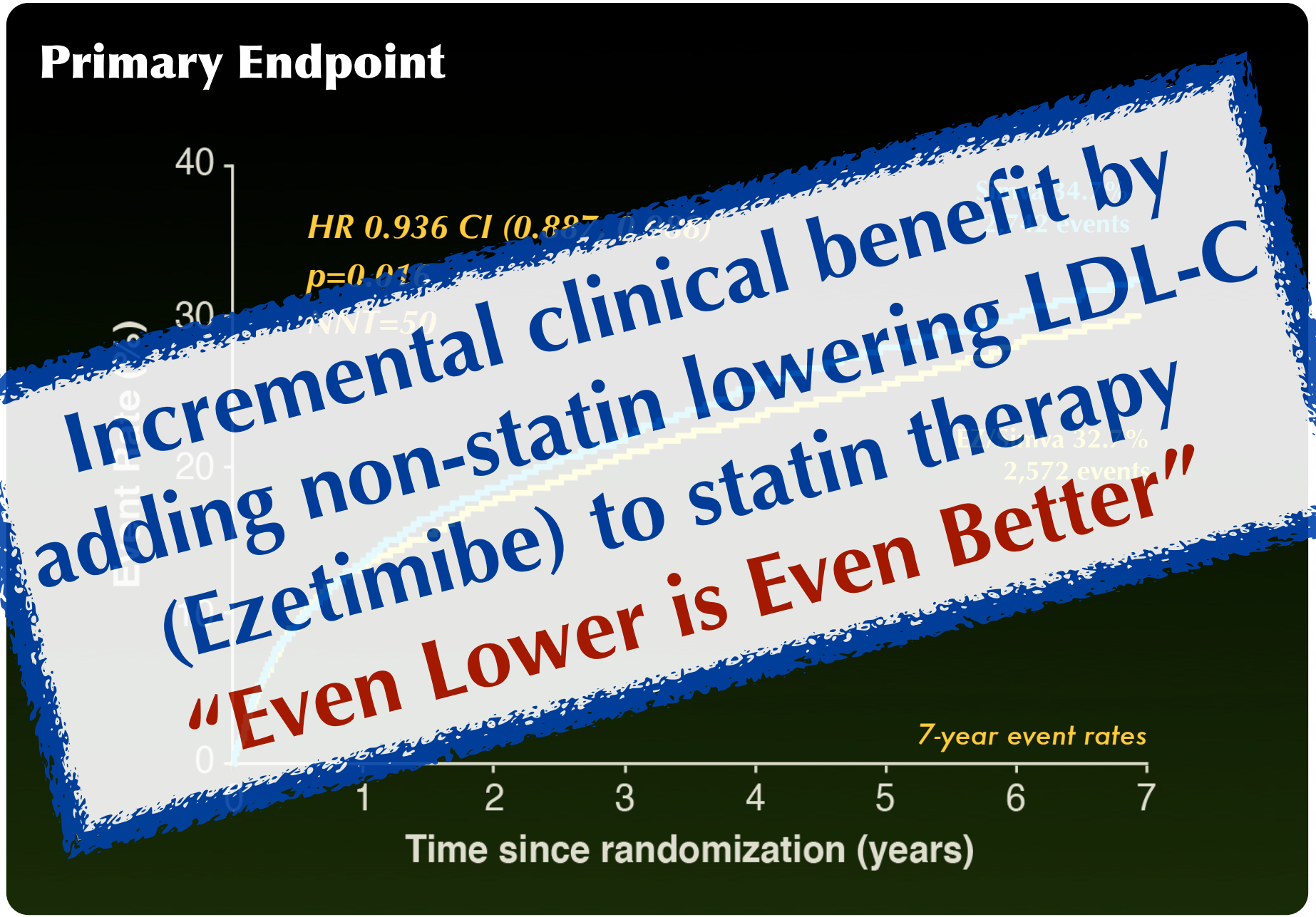



**Incremental clinical benefit by adding non-statin lowering LDL-C (Ezetimibe) to statin therapy**

**"Even Lower is Even Better"**

# Add-On Therapy to Statin
# for Further CV risk Reduction

- Statin + Ezetimibe : IMPROVE-IT
- Statin + Niacin : AIM-HIGH, HPS2-THRIVE
- Statin + Fenofibrate : ACCORD Lipid

# Add-On Therapy to Statin
# for Further CV risk Reduction

## IMPROVE-IT

**Ezetimibe**

# IMPROVE-IT Design

Prespecified Analysis

JAMA Cardiol 2017;2:547-555


**15,281 Patients**

LDL-C at 1 month after randomization regardless of treatment assignment

- LDL-C < 30mg/dL (n=971)
- 30 ≤ LDL-C < 50mg/dL (n=4,780)
- 50 ≤ LDL-C < 70mg/dL (n=5,504)
- LDL-C ≥ 70mg/dL (n=4,026)

Enrolled from Oct 2005 to Jul 2010 (≃ 6 years)

## Primary Efficacy End Point

Composite of

CV death
MI
UA requiring hospitalization
Coronary revascularization after 30 days
Stroke

## Prespecified Safety End Points

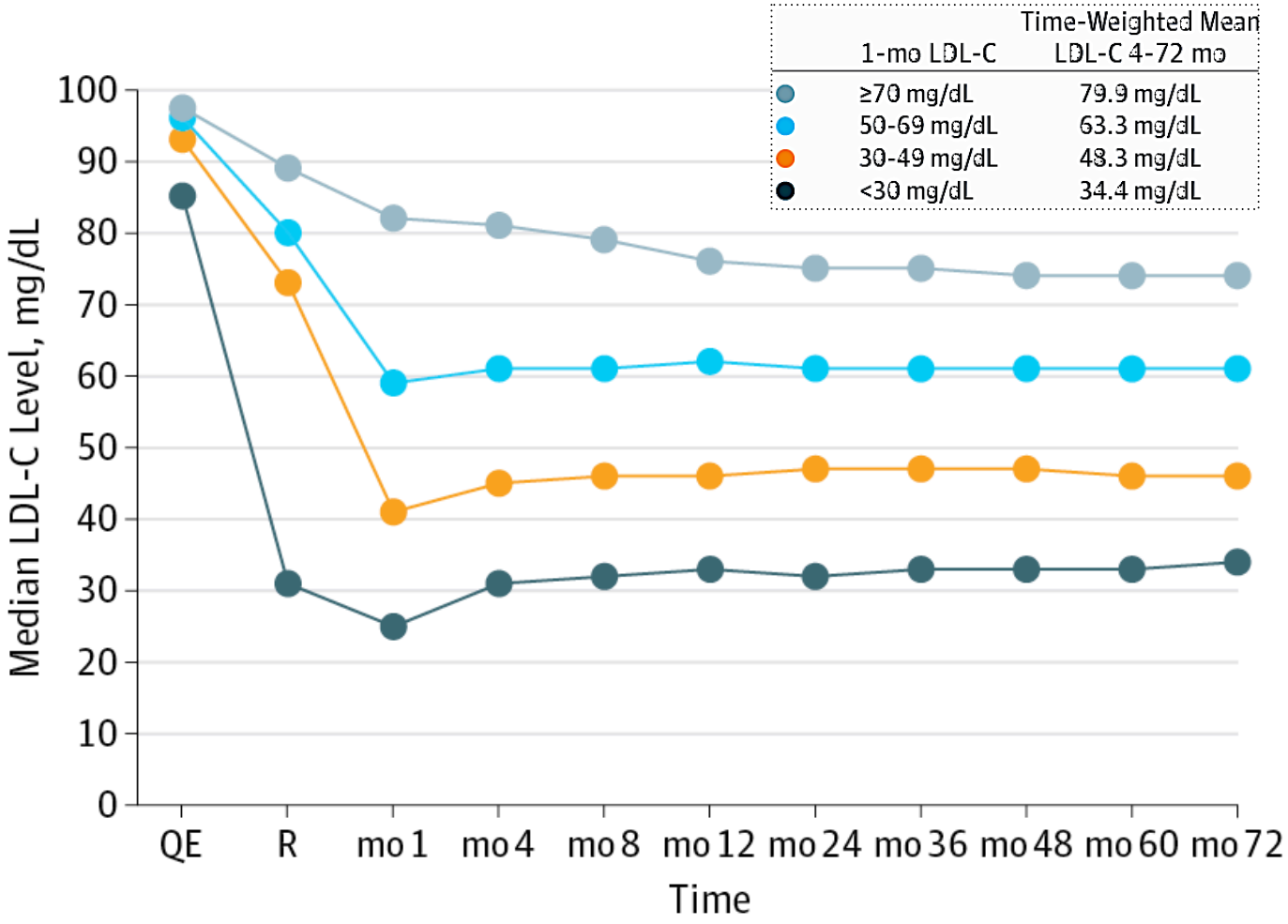
Abnormal elevation of AST/AST and CK
Myopathy
Rhabdomyolysis
Adverse hepatobiliary events
Cancer
Other AE leading to
- Drug discontinuation,
- HF requiring hospitalization
- Non-CV death

# IMPROVE-IT

Prespecified Analysis

## Median LDL-C Level for 6 Years

*JAMA Cardiol 2017;2:547-555*




No. at risk

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ≥70 mg/dL | 3992 | 3951 | 4026 | 3697 | 3427 | 3221 | 2848 | 2568 | 2404 | 2006 | 1547 |
| 50-69 mg/dL | 5472 | 5430 | 5504 | 5229 | 4941 | 4728 | 4273 | 3940 | 3636 | 3062 | 2318 |
| 30-49 mg/dL | 4744 | 4733 | 4780 | 4528 | 4283 | 4073 | 3730 | 3414 | 3167 | 2638 | 2066 |
| <30 mg/dL | 961 | 964 | 971 | 916 | 868 | 832 | 755 | 699 | 661 | 525 | 411 |

# IMPROVE-IT

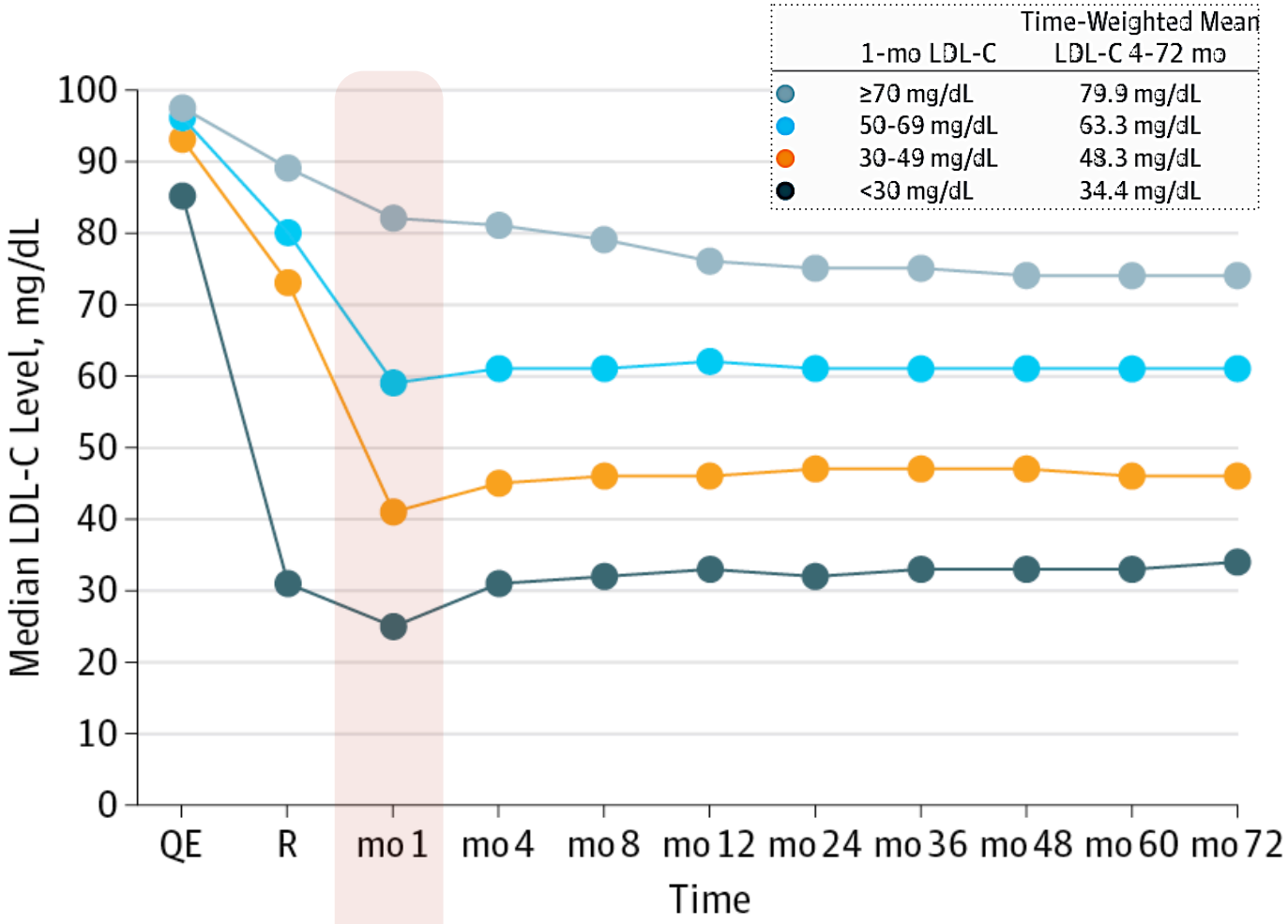
Prespecified Analysis

## Median LDL-C Level for 6 Years

*JAMA Cardiol 2017;2:547-555*

Prespecified Analysis

IMPROVE-IT

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# IMPROVE-IT Efficacy End Points

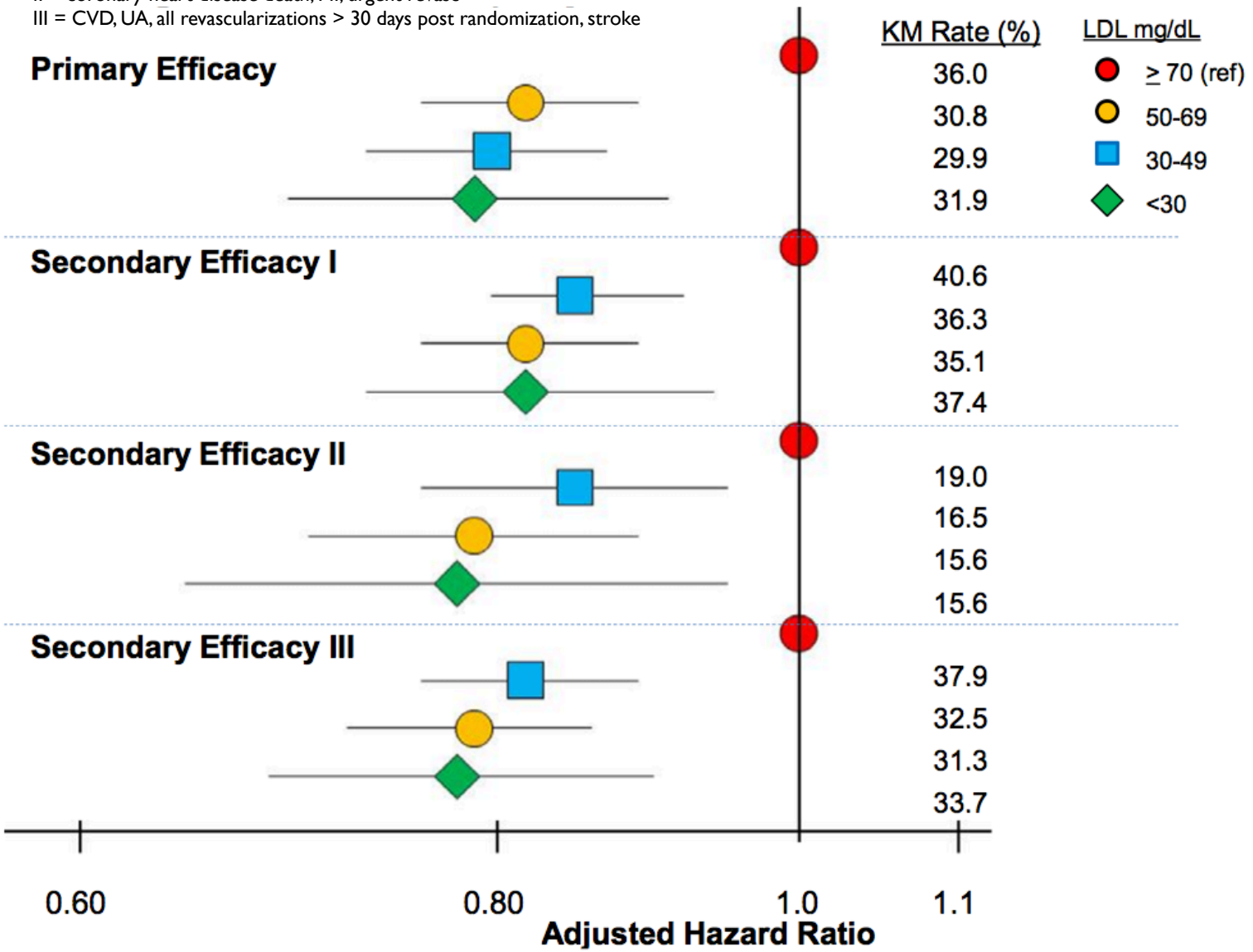
Prespecified Analysis

*JAMA Cardiol 2017;2:547-555*

Prespecified Analysis

IMPROVE-IT

Secondary endpoints were:
I = All death, MI, UA, revasc, stroke
II = coronary heart disease death, MI, urgent revasc
III = CVD, UA, all revascularizations > 30 days post randomization, stroke



# IMPROVE-IT Efficacy End Points

Prespecified Analysis

*JAMA Cardiol 2017;2:547-555*

Prespecified Analysis

IMPROVE-IT

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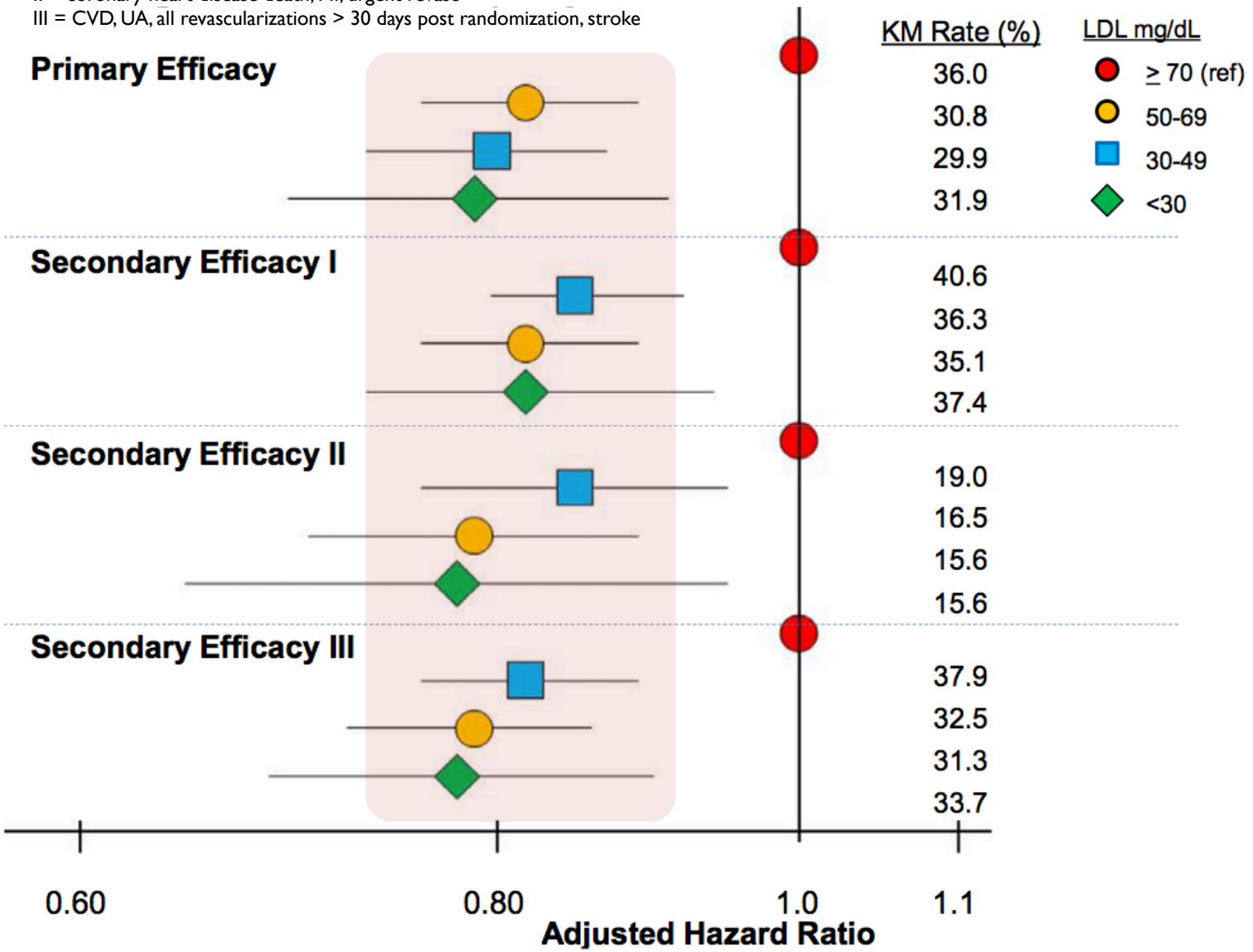

# IMPROVE-IT Efficacy End Points

Prespecified Analysis

*JAMA Cardiol 2017;2:547-555*

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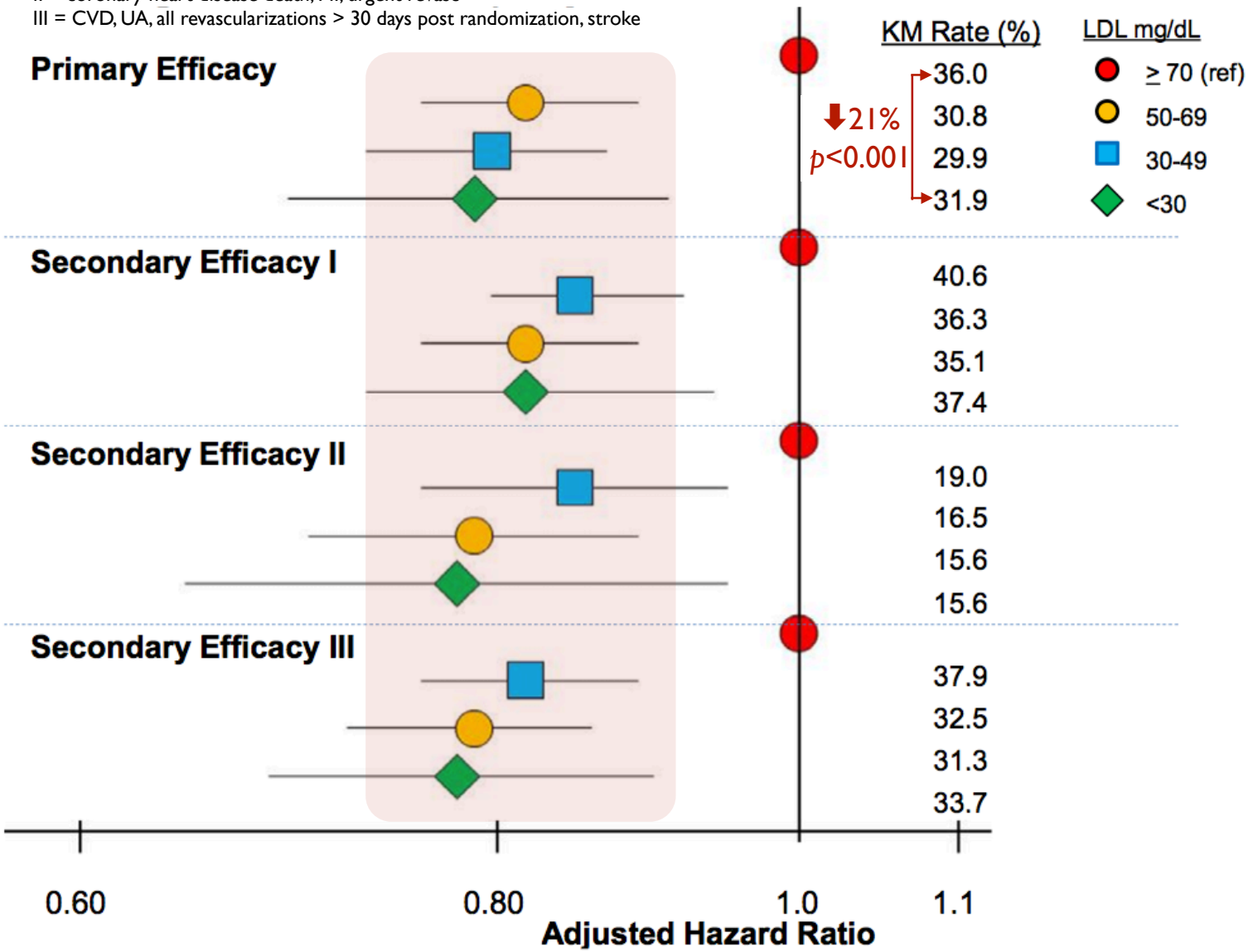

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Prespecified Analysis

*JAMA Cardiol 2017;2:547-555*

Prespecified Analysis IMPROVE-IT

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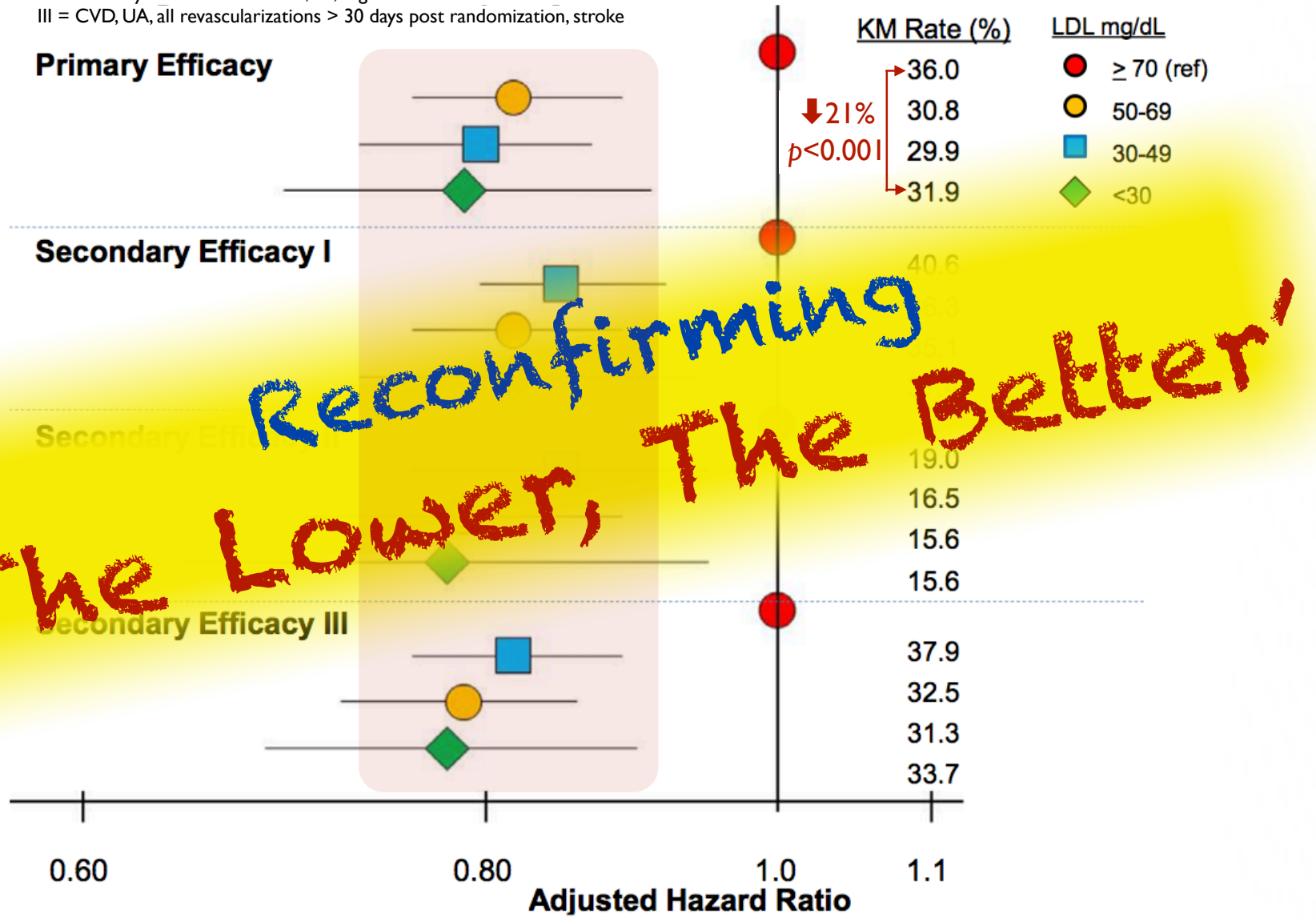


Reconfirming 'The Lower, The Better'

# IMPROVE-IT Prespecified Safety End Points

Prespecified Analysis

*JAMA Cardiol 2017;2:547-555*

Prespecified Analysis IMPROVE-IT

| Prespecified Safety End Points | Achieved LDL-C Level (mg/dL) at 1 mo, No. (%) of Patients | | | | *P* Value for Trend |
|---|---|---|---|---|---|
| | <30 (n = 971) | 30-49 (n = 4780) | 50-69 (n = 5504) | ≥70 (n = 4026) | |
| Adverse event leading to drug discontinuation | 92 (9.5) | 451 (9.4) | 470 (8.5) | 354 (8.8) | .21 |
| Rhabdomyolysis, myopathy, or myalgias with CK elevation >5 times ULN[b] | 4 (0.4) | 30 (0.6) | 26 (0.5) | 25 (0.6) | .81 |
| Rhabdomyolysis or myopathy[b] | 0 | 13 (0.3) | 9 (0.2) | 15 (0.4) | .12 |
| Rhabdomyolysis[b] | 0 | 6 (0.1) | 7 (0.1) | 8 (0.2) | .16 |
| AST or ALT above 3 times ULN | 21 (2.2) | 97 (2.0) | 97 (1.8) | 84 (2.1) | .88 |
| Gall bladder adverse event | 35 (3.6) | 155 (3.2) | 200 (3.6) | 145 (3.6) | .48 |
| Neurocognitive adverse events | 20 (2.1) | 121 (2.5) | 158 (2.9) | 91 (2.3) | .95 |
| Short-term[c] | 12 (1.2) | 61 (1.3) | 91 (1.7) | 48 (1.2) | .98 |
| Longer-term[d] | 8 (0.8) | 60 (1.3) | 67 (1.2) | 43 (1.1) | .89 |
| Hemorrhagic stroke[b] | 3 (0.3) | 41 (0.9) | 23 (0.4) | 25 (0.6) | .50 |
| Hospitalization for heart failure | 45 (4.6) | 200 (4.2) | 189 (3.4) | 148 (3.7) | .06 |
| Noncardiovascular death[b] | 56 (5.8) | 244 (5.1) | 310 (5.6) | 197 (4.9) | .50 |
| Cancer[b] | 87 (9.0) | 413 (8.6) | 477 (8.7) | 300 (7.5) | .04 |

# IMPROVE-IT Prespecified Safety End Points

Prespecified Analysis

*JAMA Cardiol 2017;2:547-555*

Prespecified Analysis IMPROVE-IT

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| Rhabdomyolysis or myopathy[b] | 0 | [illegible] | [illegible] | [illegible] | .12 |
| Rhabdomyolysis[b] | [illegible] | [illegible] | [illegible] | [illegible] | .16 |
| AST or ALT above 3 tim[illegible] | [illegible] | [illegible] | [illegible] | [illegible] | .88 |
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No significant differences in safety end points across the groups

# HOPE-3 Design

Hope-3

*N Eng J Med 2016;374:2009-2043*

| 2×2 Factorial Randomization | | Cholesterol-lowering | |
|---|---|---|---|
| | | Placebo | Rosuvastatin 10mg |
| BP-lowering | Placebo | 3,168 | 3,181 |
| | Candesartan 16mg +HCTZ 12.5mg | 3,176 | 3,180 |

## Endpoints

**First Co-Primary:** Composite of CV death/MI/Stroke

**Second Co-Primary:** Composite of CV death/Resuscitated cardiac arrest/ MI/Stroke/HF/Revascularization

## Inclusion Criteria

**Without known CVD + With an intermediate risk of major CV events (~1% annually)**

**Men ≥55 years, women ≥65 years**

**With at least one of the following CV risk factors:**

- **Elevated waist-to-hip ratio**
- **History of a low level of high-density lipoprotein cholesterol**
- **Current or recent tobacco use, dysglycemia**
- **Family history of premature coronary disease**
- **Mild renal dysfunction**

**Women with at least two of the above risk factors**

# HOPE-3 Design

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*N Eng J Med 2016;374:2009-2043*

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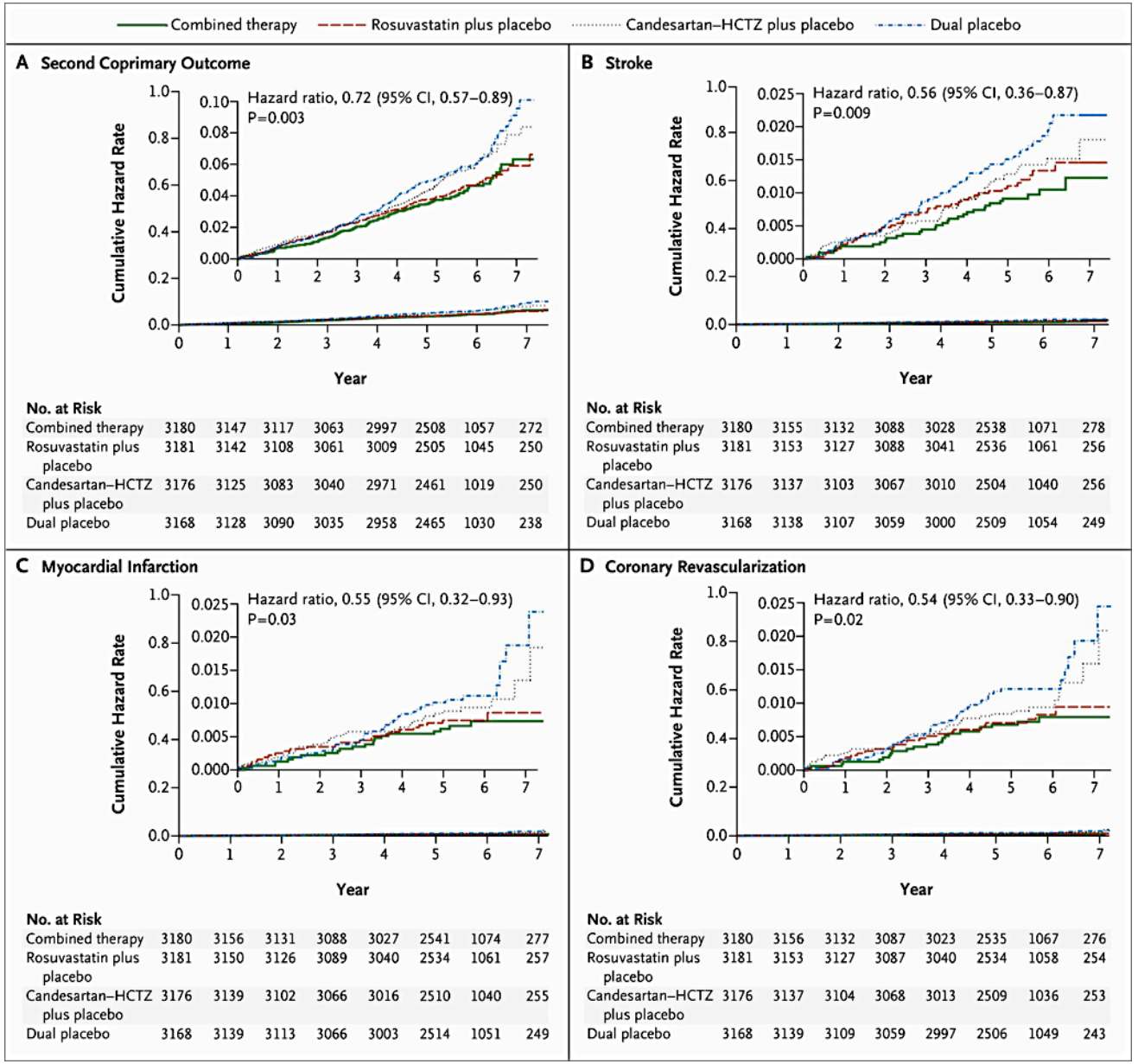
# HOPE-3 BP & Cholesterol-Lowering (2)

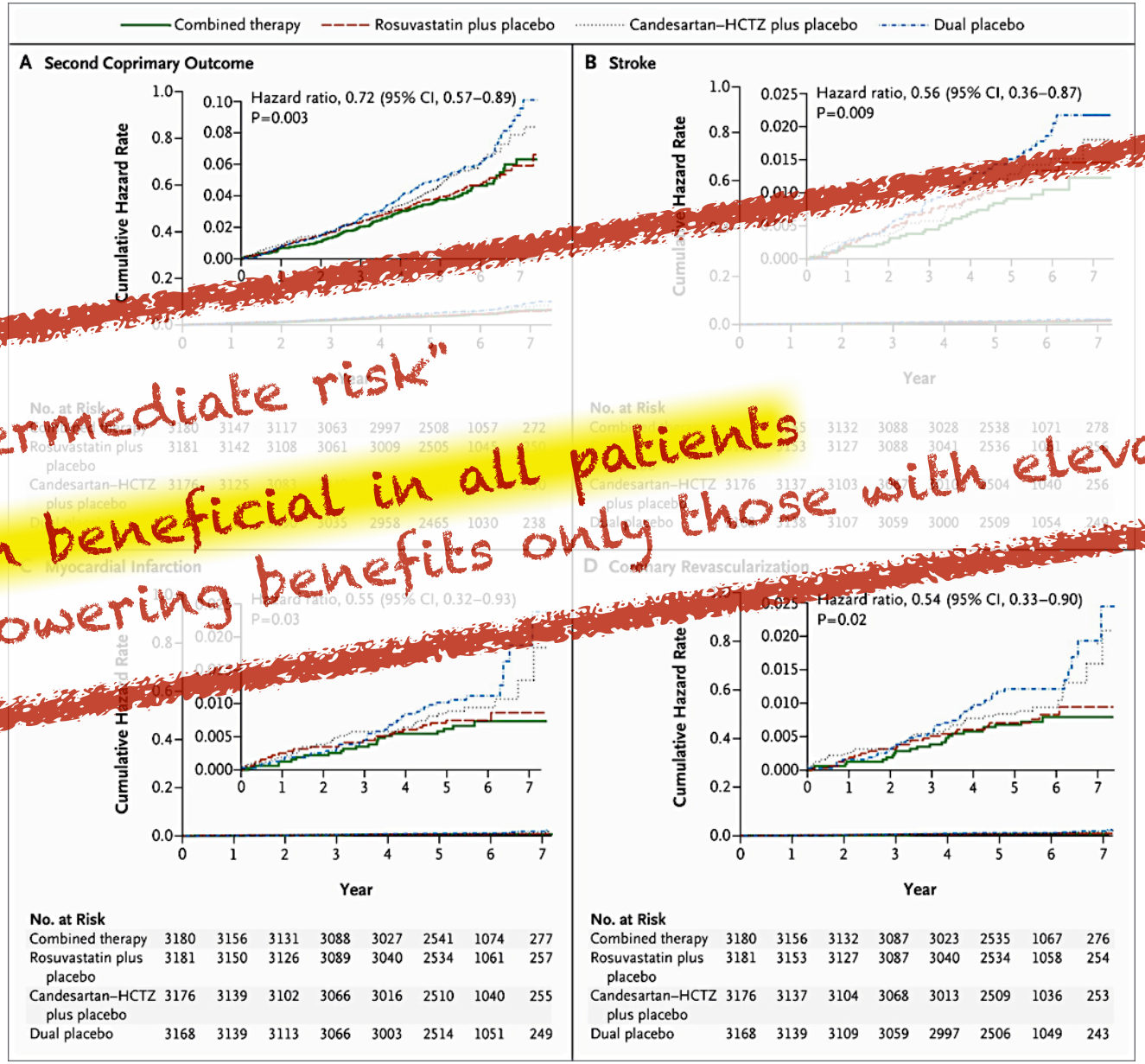
*N Eng J Med 2016;374:2032-2043*



# HOPE-3 BP & Cholesterol-Lowering (2)

Hope-3

*N Eng J Med 2016;374:2032-2043*




"CV intermediate risk"

1. Statin beneficial in all patients
2. BP-lowering benefits only those with elevated BP

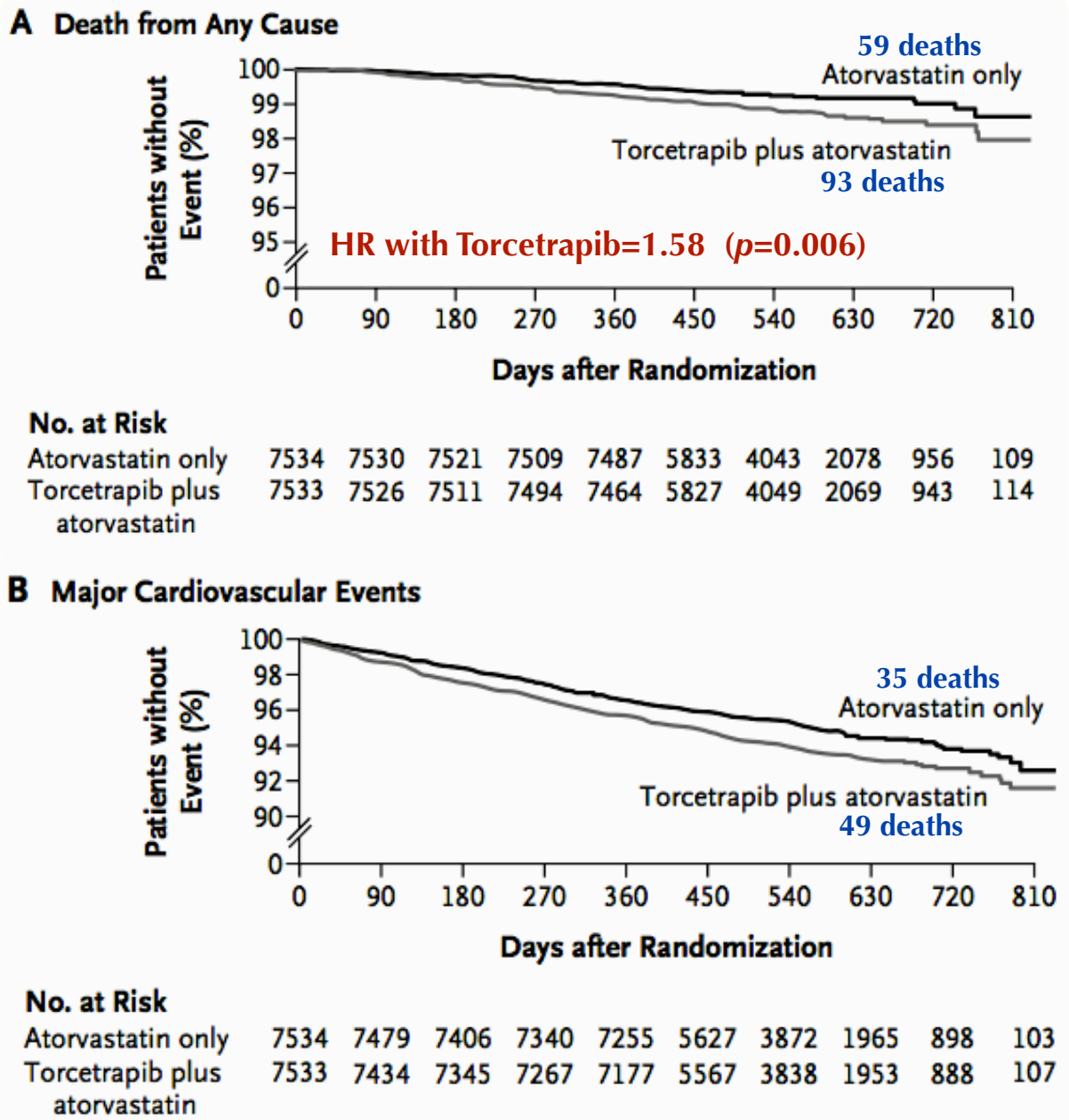
# New Emerging Therapies

## CETP Inhibitors on HDL-C

## PCSK9 Inhibitors on LDL-C

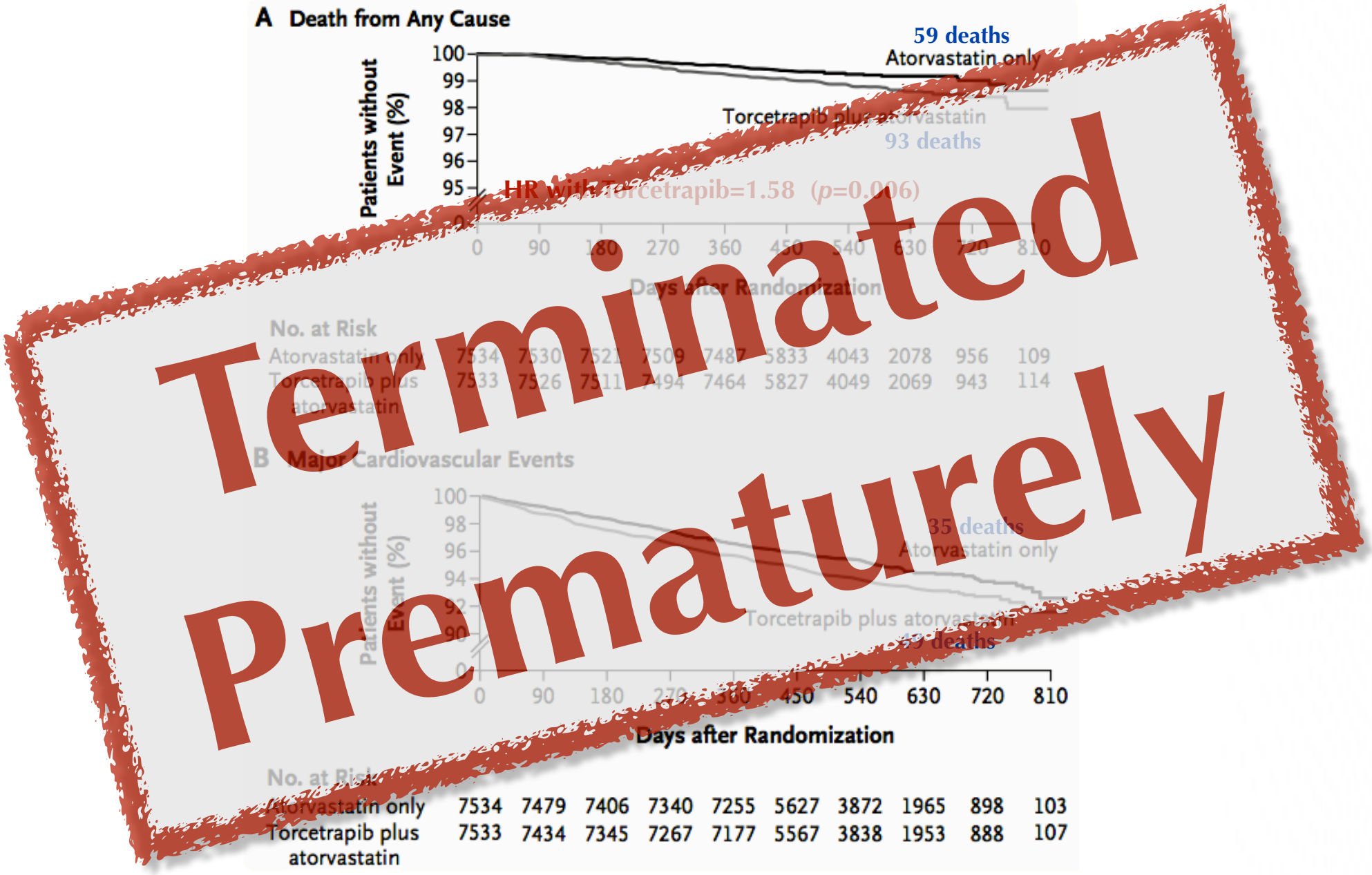
# ILLUMINATE Result

*N Engl J Med 2007;357:2109-22*



# ILLUMINATE Result

*N Engl J Med 2007;357:2109-22*

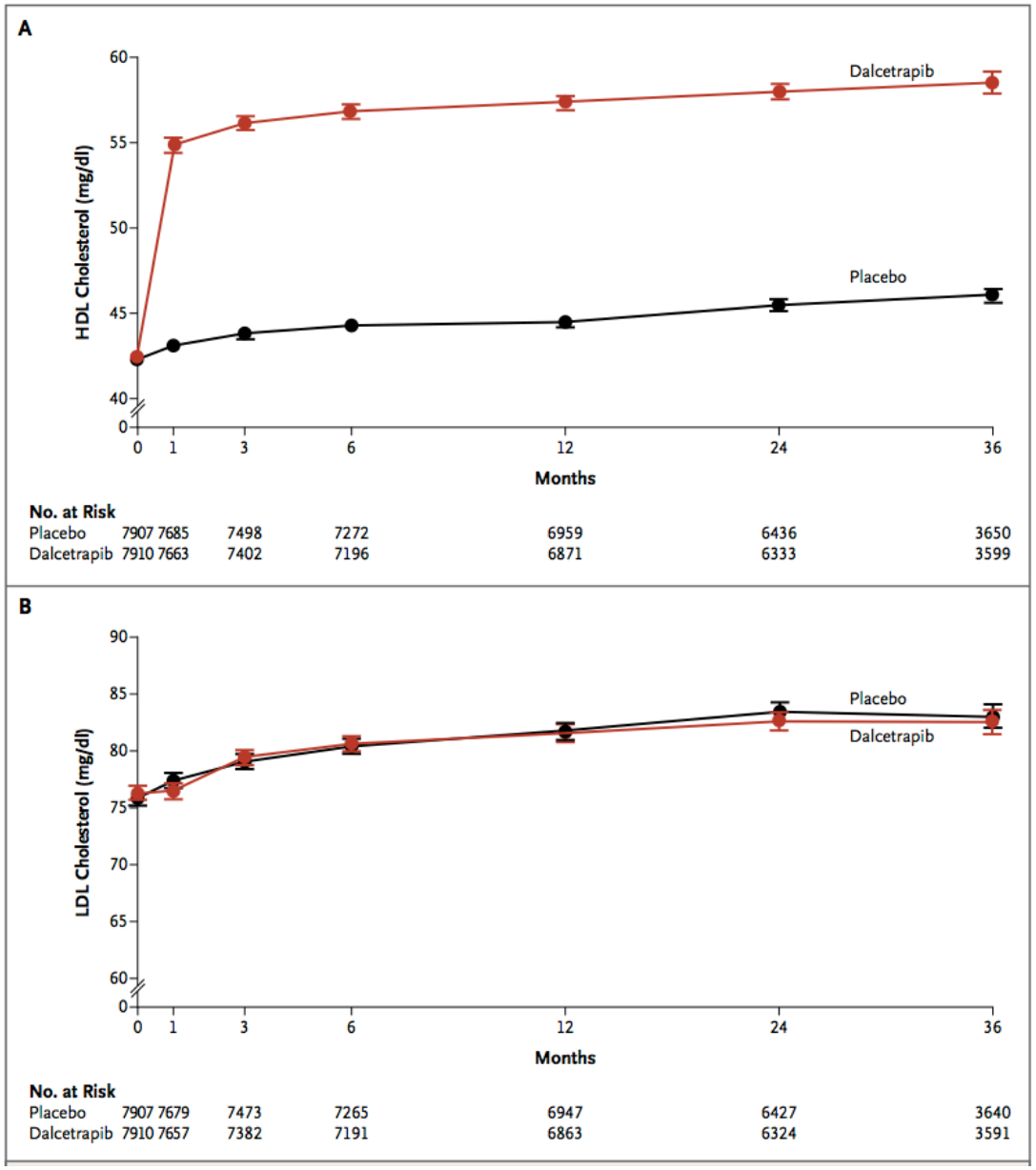



**Terminated Prematurely**

# dal-OUTCOME Result

*N Engl J Med 2012;367:2089-99*

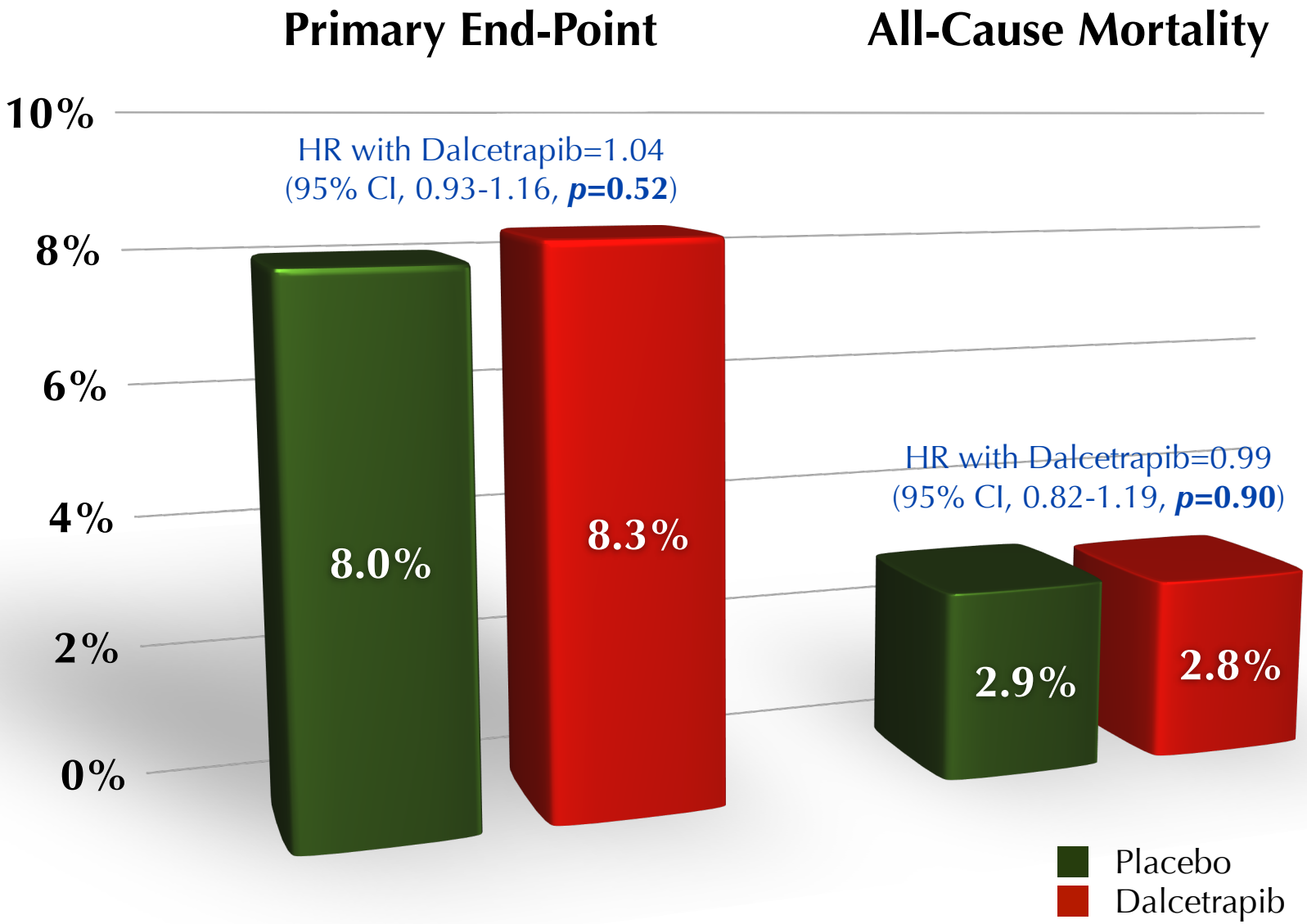
15,600 stable CHD patients with recent ACS



# dal-OUTCOME Result

*N Engl J Med 2012;367:2089-99*

15,600 stable CHD patients with recent ACS

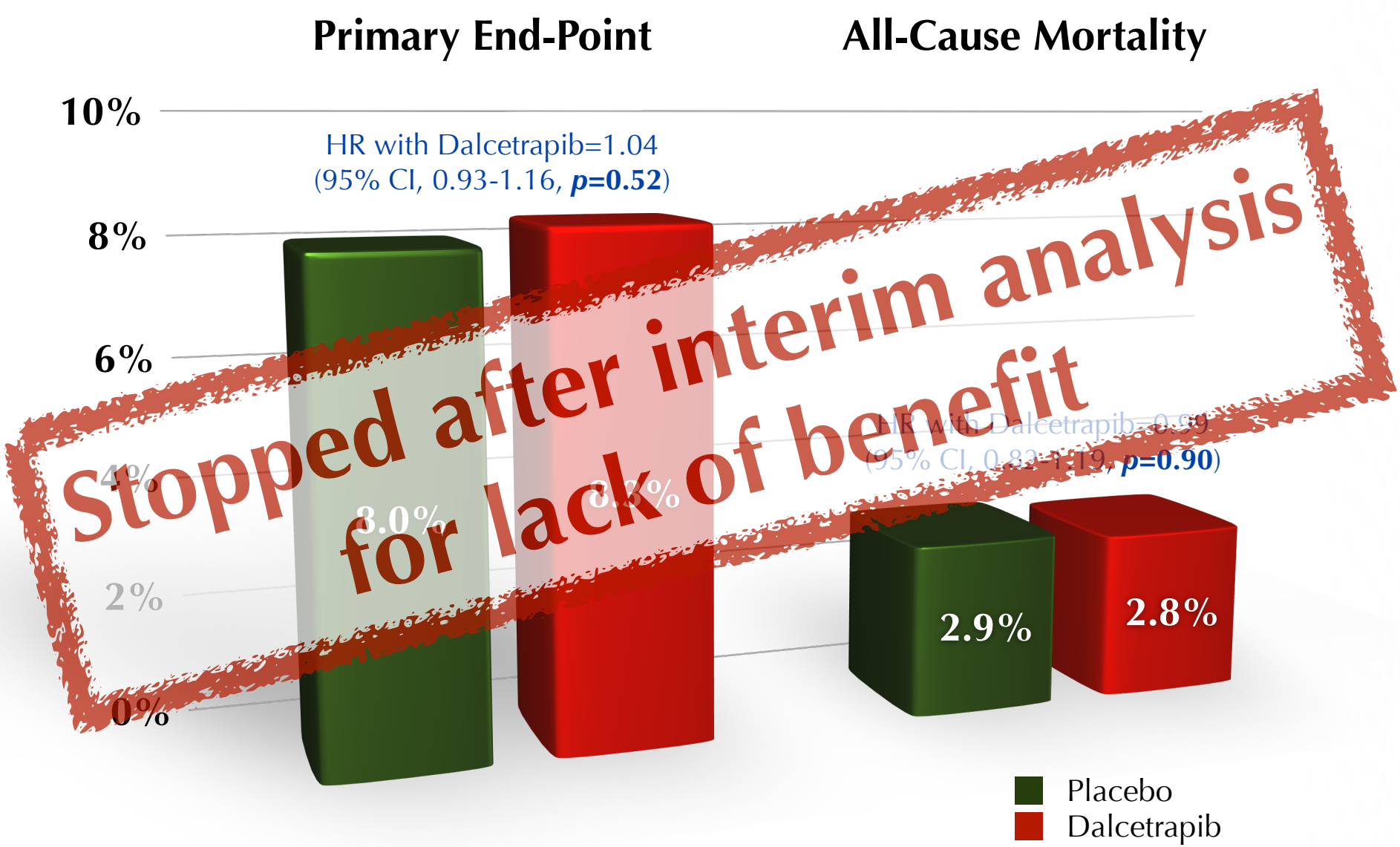


Dalcetrapib

# dal-OUTCOME Result

*N Engl J Med 2012;367:2089-99*

15,600 stable CHD patients with recent ACS




**Stopped after interim analysis for lack of benefit**

| Trial | Benefit |
| --- | --- |
| **AIM-HIGH** | No benefit of Niacin |
| **HPS2-THRIVE** | No benefit of Niacin/Laropiprant |
| **Medelian genetics** | No difference in CV risk with HDL variants |
| **ILLUMINATE** | No benefit (harm) of Torcetrapib |
| **dal-OUTCOMES** | No benefit of Dalcetrapib |

# Bad Years for HDL-C

| Trial | Benefit |
|---|---|
| **AIM-HIGH** | No benefit of Niacin |
| **HPS2-THRIVE** | No benefit of Niacin/Laropiprant |
| **Medelian genetics** | No difference in CV risk with HDL variants |
| **ILLUMINATE** | No benefit (harm) of Torcetrapib |
| **dal-OUTCOMES** | No benefit of Dalcetrapib |

# Next Two CETP Inhibitors
## Outcome Trials

| | Anacetrapib | Evacetrapib |
|---|---|---|
| **Name** | **REVEAL** | **ACCELERATE** |
| **Company** | Merck | Eli Lilly |
| **Dose** | 100 mg/d | 130 mg/d |
| **Sample size** | 30,000 | 12,092 |
| **Inclusion** | Age ≥ 50 years<br>History of MI<br>Stroke or cerebrovascular revascularization<br>PAD repair/revascularization<br>DM with symptomatic CAD | Age ≥ 18 years<br>History of ACS (30-365d)<br>Cerebrovascular<br>PAD<br>DM with documented CAD |
| **Primary end point** | Coronary death, MI, or coronary revascularization | CV death, MI, stroke, coronary revascularization, or hospitalization for UA |
| **Study duration** | Median ≈ 4 years | Median ≈ 2 years |

# Next Two CETP Inhibitors
## Outcome Trials

| | Anacetrapib |
|---|---|
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| **Primary end point** | Coronary death, MI, or coronary revascularization |
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**Terminated due to Insufficient efficacy**

**Oct 2015**

**HDL-C Level**
**Evacetrapib vs. Placebo 104 vs. 46 mg/dL**
**ACC in Chicago, Apr 2016**

# Next Two CETP Inhibitors
## Outcome Trials

| | Anacetrapib |
|---|---|
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**Terminated due to Insufficient efficacy**
Oct 2015

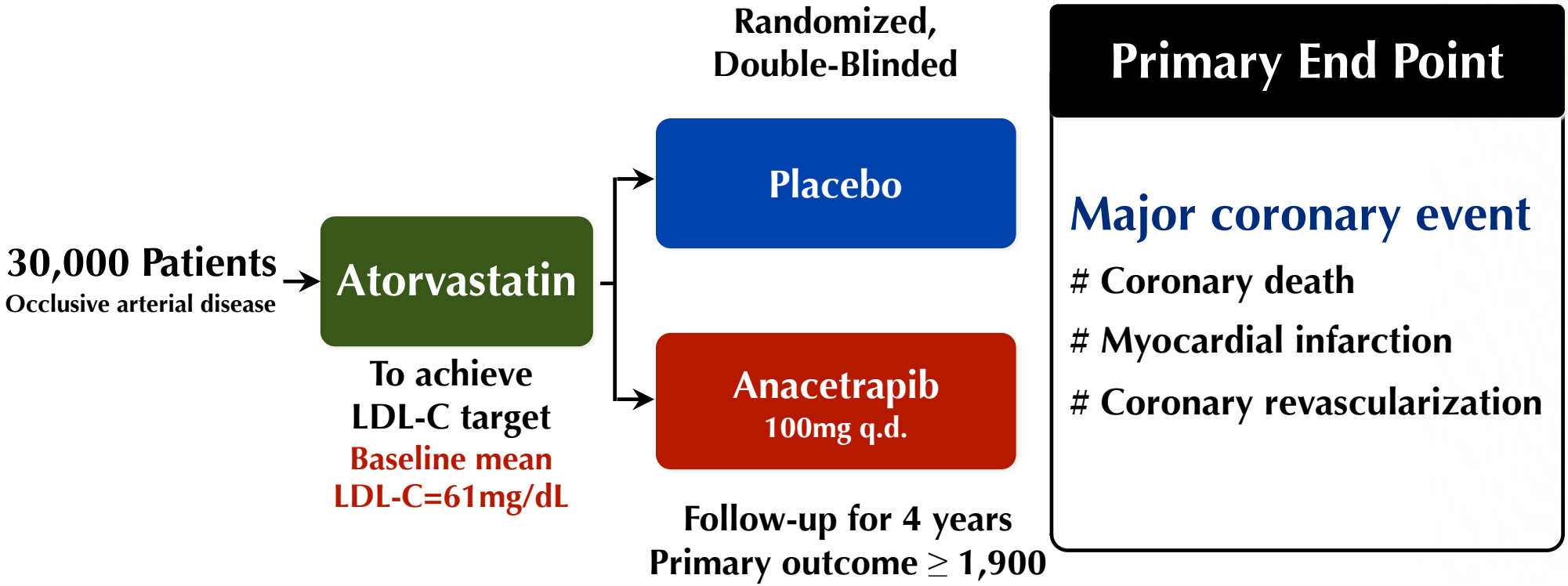
**HDL-C Level**
**Evacetrapib vs. Placebo 104 vs. 46 mg/dL**
ACC in Chicago, Apr 2016

Still...Bad Years...??

# REVEAL Design

*N Engl J Med 2017;377:1217-1227*

hps3·TIMI55
REVEAL
Randomized EValuation of the Effects of Anacetrapib through Lipid-modification




Presented in ESC 2017

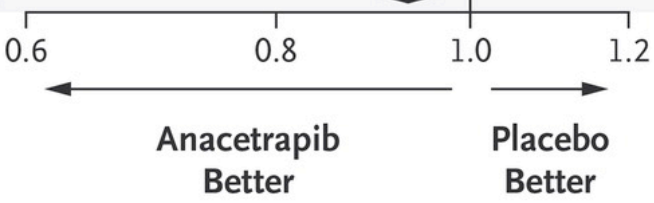
# REVEAL Results

*N Engl J Med 2017;377:1217-1227*

hps3·TIMI55 REVEAL
Randomized EValuation of the Effects of Anacetrapib through Lipid-modification

## Primary & Secondary Outcomes

| Type of Event | Anacetrapib (N=15,225) | Placebo (N=15,224) | Rate Ratio (95% CI) | P Value |
|---|---|---|---|---|
| | *no. of patients with event (%)* | | | |
| Coronary death | 388 (2.5) | 420 (2.8) | 0.92 (0.80–1.06) | 0.25 |
| MI | 669 (4.4) | 769 (5.1) | 0.87 (0.78–0.96) | 0.007 |
| **Coronary death or MI** | **934 (6.1)** | **1048 (6.9)** | **0.89 (0.81–0.97)** | **0.008** |
| Coronary revascularization | 1081 (7.1) | 1201 (7.9) | 0.90 (0.83–0.97) | 0.01 |
| **Major coronary event** | **1640 (10.8)** | **1803 (11.8)** | **0.91 (0.85–0.97)** | **0.004** |
| Presumed ischemic stroke | 485 (3.2) | 489 (3.2) | 0.99 (0.87–1.12) | NA |
| **Major atherosclerotic event** | **1383 (9.1)** | **1483 (9.7)** | **0.93 (0.86–1.00)** | **0.052** |
| **Major vascular event** | **2068 (13.6)** | **2214 (14.5)** | **0.93 (0.88–0.99)** | **0.02** |



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*N Engl J Med 2017;377:1217-1227*

hps3·TIMI55 REVEAL
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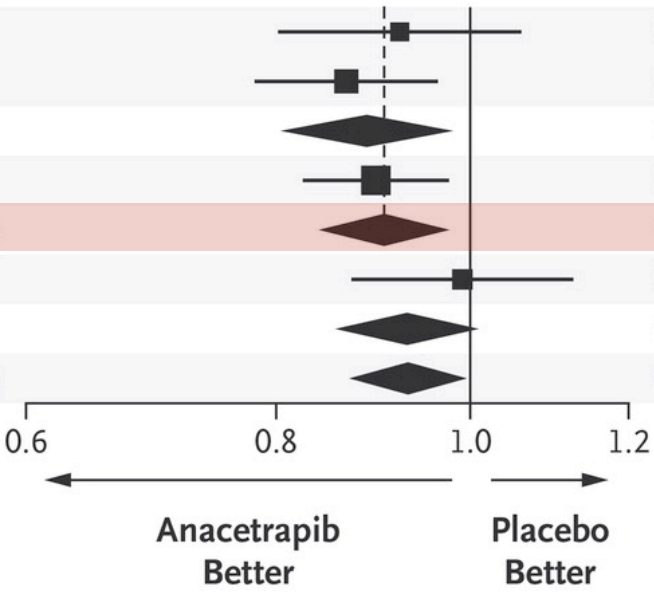


# REVEAL Results

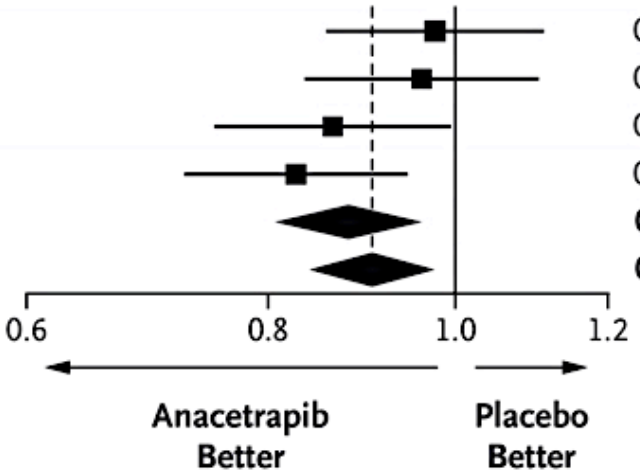
*N Engl J Med 2017;377:1217-1227*

hps3·TIMI55 REVEAL
Randomized EValuation of the Effects of Anacetrapib through Lipid-modification

**B First Major Coronary Event, According to Year of Follow-up**

| Year of First Event | Anacetrapib (N=15,225) | Placebo (N=15,224) | Rate Ratio (95% CI) | P Value |
|---|---|---|---|---|
| | *no. of patients with event (%)* | | | |
| 1 | 465 (3.1) | 476 (3.1) | 0.98 (0.86–1.11) | |
| 2 | 398 (2.7) | 414 (2.8) | 0.96 (0.84–1.10) | |
| 3 | 370 (2.6) | 427 (3.0) | 0.86 (0.75–0.99) | |
| ≥4 | 407 (3.0) | 486 (3.7) | 0.83 (0.73–0.94) | |
| **>1** | **1175 (8.0)** | **1327 (9.1)** | **0.88 (0.81–0.95)** | **0.001** |
| **All** | **1640 (10.8)** | **1803 (11.8)** | **0.91 (0.85–0.97)** | **0.004** |

Test for trend across years, $\chi^2$=4.87 (P=0.03)
Test for heterogeneity between ≤1 yr and >1 yr, $\chi^2$=1.82 (P=0.18)



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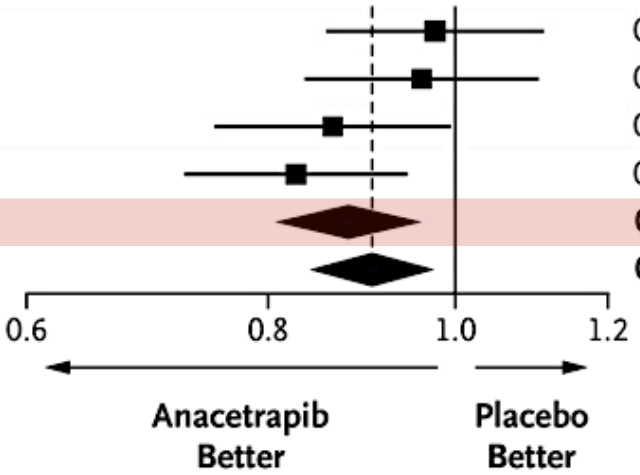

# REVEAL Result

*N Engl J Med 2017;377:1217-1227*

hps3·TIMI55 REVEAL
Randomized EValuation of the Effects of Anacetrapib through Lipid-modification

## Effects of Anacetrapib on Lipid Profiles at Trial Midpoint

| Lipid profiles | Absolute Difference | | % Difference |
|---|---|---|---|
| | mg/dL | SI units | |
| HDL-C | +43 | +1.1 mmol/L | 104 |
| Apo A1 | +42 | +0.4 g/L | 36 |
| LDL-C | -26 | -0.7 mmol/L | -41 |
| Apo B | -12 | -0.1 g/L | -18 |
| NonHDL-C | -17 | -0.4 mmol/L | -18 |

# REVEAL Result

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LDL-C lowering Effect???

# CV Outcome Trials of PCSK9 Inhibitors

| | FOURIER<br>Evolocumab<br>(Amgen) | SPIRE I/II<br>Bocolozumab<br>(Pfizer) | ODYSSEY OUTCOME<br>Alirocumab<br>(Sanofi/Regeneron) |
|---|---|---|---|
| **Timelines** | Jan 2013–Feb 2018 | Oct 2013–Aug 2017 | Oct 2012–Mar 2018 |
| **Inclusion** | Clinically evident CVD (MI, stroke, symptomatic PAD) at high risk for a recurrent event | High risk of CV event receiving background statin | ACS within the last 4 to 52 weeks |
| **Lipid parameters at entry (mg/dL)** | LDL≥70 or<br>Non-HDL≥100 | SPIRE I<br>70≤LDL<100<br>100<Non-HDL<130<br>SPIRW II<br>LDL≥100<br>Non-HDL≥130 | LDL≥70 or<br>Non-HDL≥100 or<br>ApoB≥80 |
| **Statin LMT dose regiment** | Atorvastatin 20 to 80mg (or equivalent regimen) | Not specified | Atorvastatin 40–80mg or Rosuvastatin 20–40mg |
| **Total Number of patients** | 22,500<br>(including 9,000≥65Yr) | SPIRE I: 12,000<br>SPIRE II: 6,200 | 18,000 |
| **Primary Endpoint** | CVD, MI, hospitalization for UA, stroke, or coronary revascularization | CVD, non-fatal MI, non-fatal stroke, or hospitalization for UA needing urgent revascularization | CHD death, MI, stroke, or UA |
| **Dosing regimen** | 140mg q2W or 420mg qM | 150mg q2W | 75mg or 150mg q2W |

# CV Outcome Trials of PCSK9 Inhibitors

| | FOURIER<br>Evolocumab<br>(Amgen) | | ODYSSEY OUTCOME<br>Alirocumab<br>(Sanofi/Regeneron) |
|---|---|---|---|
| **Timelines** | Jan 2013–Feb 2018 | | Oct 2012–Mar 2018 |
| **Inclusion** | Clinically evident CVD (MI, stroke, symptomatic PAD) at high risk for a recurrent event | | ACS within the last 4 to 52 weeks |
| **Lipid parameters at entry (mg/dL)** | LDL≥70 or Non-HDL≥100 | | LDL≥70 or Non-HDL≥100 or ApoB≥80 |
| **Statin LMT dose regiment** | Atorvastatin 20 to 80mg (or equivalent regimen) | | Atorvastatin 40–80mg or Rosuvastatin 20–40mg |
| **Total Number of patients** | 22,500 (including 9,000≥65Yr) | | 18,000 |
| **Primary Endpoint** | CVD, MI, hospitalization for UA, stroke, or coronary revascularization | | CHD death, MI, stroke, or UA |
| **Dosing regimen** | 140mg q2W or 420mg qM | | 75mg or 150mg q2W |

Withdrawal by company 2016

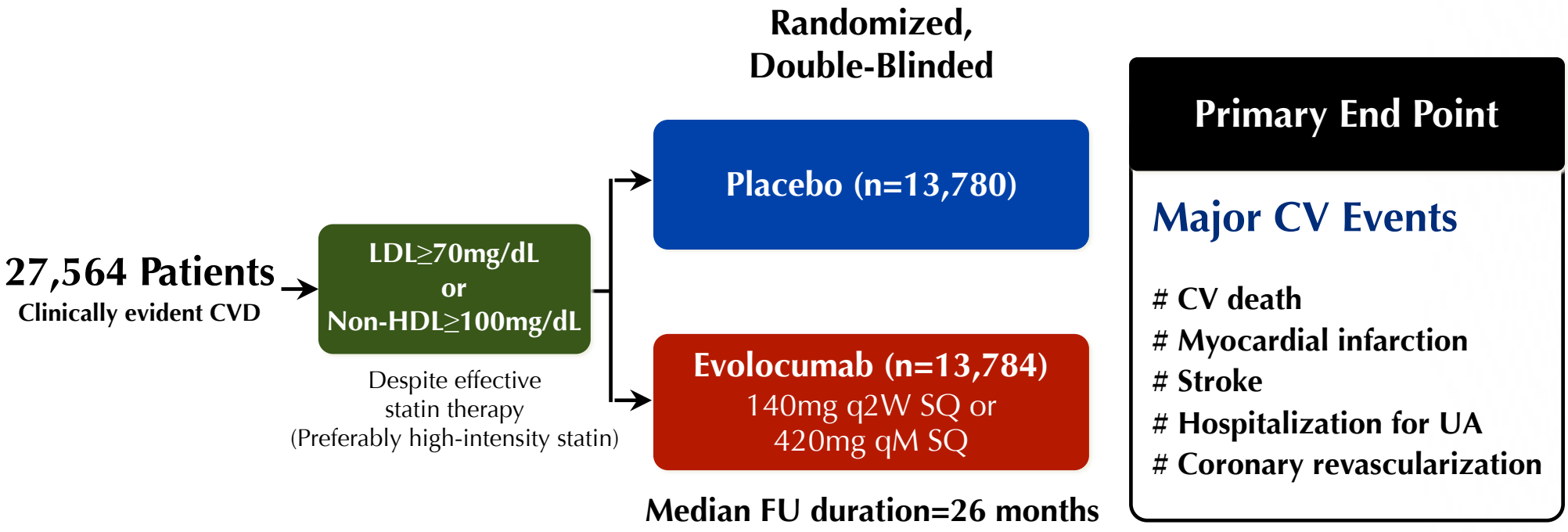
# CV Outcome Trials of PCSK9 Inhibitors

| | FOURIER<br>Evolocumab<br>(Amgen) | ODYSSEY OUTCOME<br>Alirocumab<br>(Sanofi/Regeneron) |
|---|---|---|
| Timelines | Reported in ACC 2017 | Oct 2012–Mar 2018 |
| Inclusion | Clinically evident CVD (MI, stroke, symptomatic PAD) at high risk for a recurrent event | ACS within the last 4 to 52 weeks |
| Lipid parameters at entry (mg/dL) | LDL≥70 or Non-HDL≥100 | LDL≥70 or Non-HDL≥100 or ApoB≥80 |
| Statin LMT dose regiment | Atorvastatin 20 to 80mg (or equivalent regimen) | Atorvastatin 40–80mg or Rosuvastatin 20–40mg |
| Total Number of patients | 22,500 (including 9,000≥65Yr) | 18,000 |
| Primary Endpoint | CVD, MI, hospitalization for UA, stroke, or coronary revascularization | CHD death, MI, stroke, or UA |
| Dosing regimen | 140mg q2W or 420mg qM | 75mg or 150mg q2W |

Withdrawal by company 2016

# FOURIER Design

*New Engl J Med, Mar 2017 (online)*



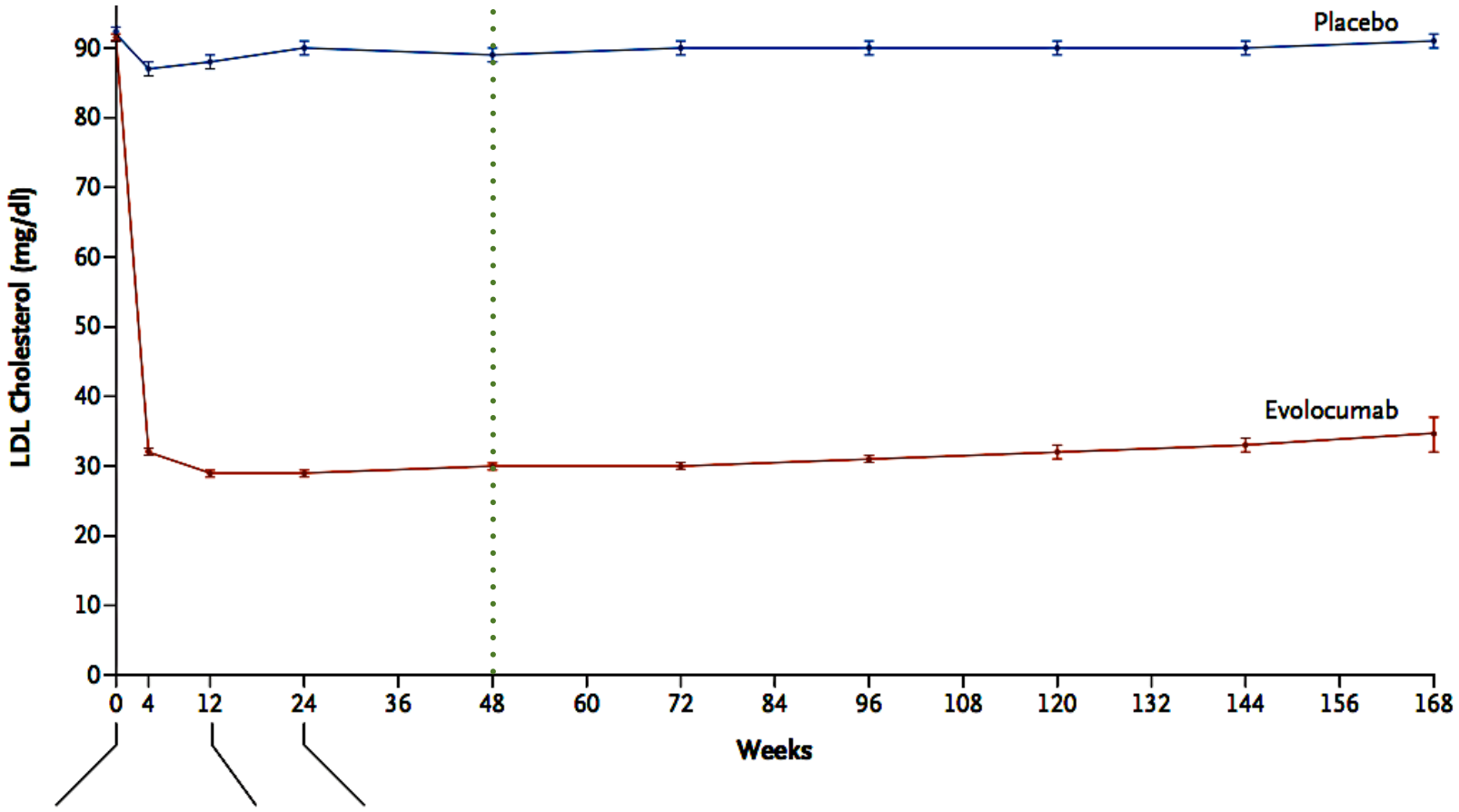

**Inclusion Criteria**

Age: 40-85 years, and Clinically evident atherosclerotic CV disease;
History of MI, ischemic stroke, or symptomatic PAD

# FOURIER Results LDL-C Levels over Time

*New Engl J Med, Mar 2017 (online)*

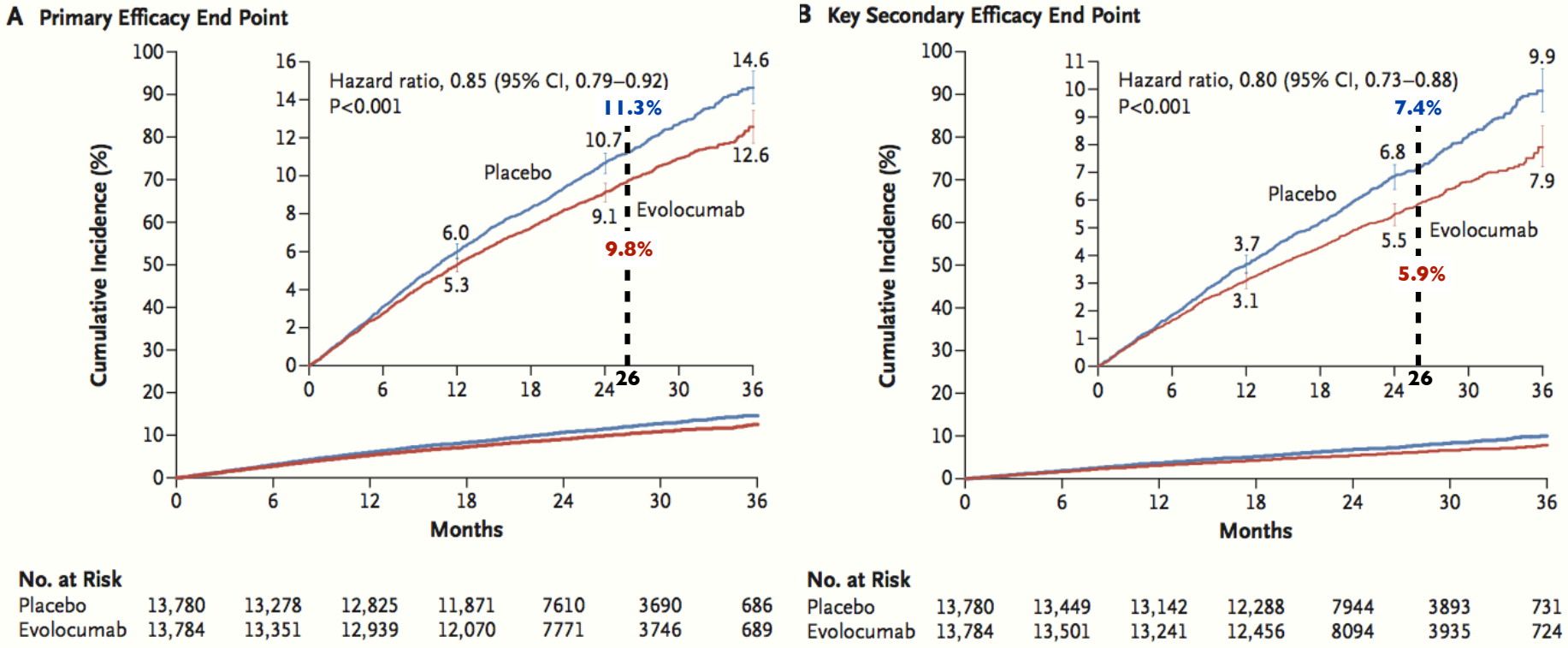
**Median LDL-C at baseline=92mg/dL**




| No. at Risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 13,779 | 13,251 | 13,151 | 12,954 | 12,596 | 12,311 | 10,812 | 6926 | 3352 | 790 |
| Evolocumab | 13,784 | 13,288 | 13,144 | 12,964 | 12,645 | 12,359 | 10,902 | 6958 | 3323 | 768 |
| Absolute difference (mg/dl) | | 54 | 58 | 57 | 56 | 55 | 54 | 52 | 53 | 50 |
| Percentage difference | | 57 | 61 | 61 | 59 | 58 | 57 | 55 | 56 | 54 |
| P value | | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |

# FOURIER Results Efficacy End Point

*New Engl J Med, Mar 2017 (online)*

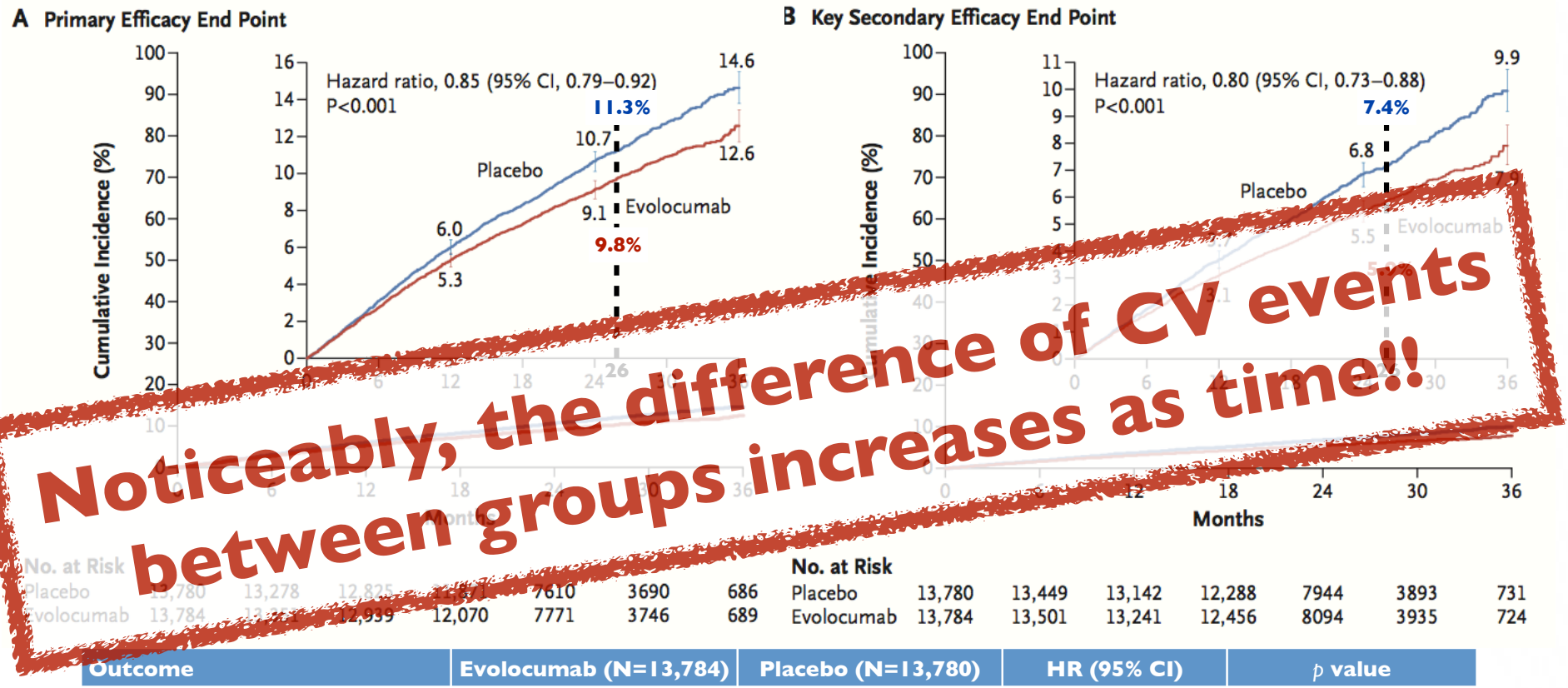



| Outcome | Evolocumab (N=13,784) | Placebo (N=13,780) | HR (95% CI) | *p* value |
|---|---|---|---|---|
| Primary end point | 1,344 (9.8%) | 1,563 (11.3%) | 0.85 (0.79-0.92) | <0.001 |
| Key secondary end point | 816 (5.9%) | 1,013 (7.4%) | 0.80 (0.73-0.88) | <0.001 |
| CV death | 251 (1.8%) | 240 (1.7%) | 1.05 (0.88-1.25) | 0.62 |
| Myocardial infarction | 468 (3.4%) | 639 (4.6%) | 0.73 (0.65-0.82) | <0.001 |
| Hospitalization for unstable angina | 236 (1.7%) | 239 (1.7%) | 0.99 (0.82-1.18) | 0.89 |
| Stroke | 207 (1.5%) | 262 (1.9%) | 0.79 (0.66-0.95) | 0.01 |
| Coronary revascularization | 759 (5.5%) | 965 (7.0%) | 0.78 (0.71-0.86) | <0.001 |
| CTTC composite end point* | 1,271 (9.2%) | 1,512 (11.0%) | 0.83 (0.77-0.90) | <0.001 |

* CTTC (Cholesterol Treatment Trialists Collaboration) composite end point: Coronary heart disease, nonfatal MI, stroke, or coronary revascularization

# FOURIER Results Efficacy End Point

*New Engl J Med, Mar 2017 (online)*




**Noticeably, the difference of CV events between groups increases as time!!**

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# FOURIER Results Safety


*New Engl J Med, Mar 2017 (online)*

## Adverse Events & Laboratory Test Results

| Outcome | Evolocumab (N=13,769) | Placebo (N=13,756) | *p* value |
|---|---|---|---|
| Adverse events — no. of patients (%) | | | |
| Any | 10,664 (77.4) | 10,644 (77.4) | NS |
| Serious | 3410 (24.8) | 3404 (24.7) | NS |
| Thought to be related to the study agent and leading to discontinuation of study regimen | 226 (1.6) | 201 (1.5) | NS |
| Injection-site reaction* | 296 (2.1) | 219 (1.6) | <0.001 |
| Allergic reaction | 420 (3.1) | 393 (2.9) | NS |
| Muscle-related event | 682 (5.0) | 656 (4.8) | NS |
| Rhabdomyolysis | 8 (0.1) | 11 (0.1) | NS |
| Cataract | 228 (1.7) | 242 (1.8) | NS |
| Adjudicated case of new-onset diabetes† | 677 (8.1) | 644 (7.7) | NS |
| Neurocognitive event | 217 (1.6) | 202 (1.5) | NS |
| Laboratory results — no. of patients/total no. (%) | | | NS |
| Aminotransferase level >3 times the upper limit of the normal range | 240/13,543 (1.8) | 242/13,523 (1.8) | NS |
| Creatine kinase level >5 times the upper limit of the normal range | 95/13,543 (0.7) | 99/13,523 (0.7) | NS |

† Evolocumab 8,337 vs. Placebo 8,339 due to exclusion of preexisting diabetic patients

# FOURIER Results Safety

*New Engl J Med, Mar 2017 (online)*

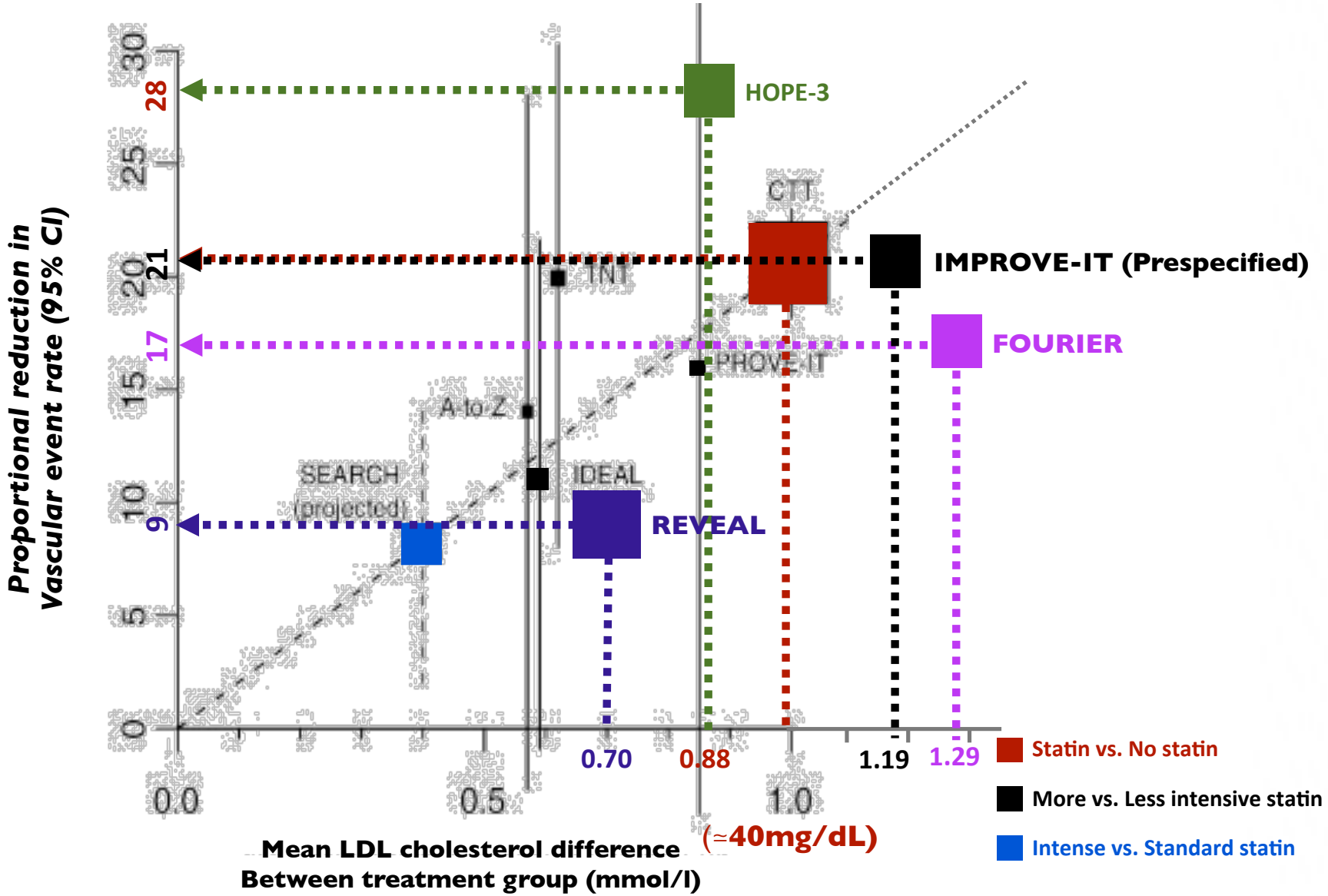
## Adverse Events & Laboratory Test Results

| Outcome | Evolocumab (N=13,769) | Placebo (N=13,756) | *p* value |
|---|---|---|---|
| Adverse events — no. of patients (%) | | | |
| Any | 10,664 (77.4) | 10,644 (77.4) | NS |
| Serious | 3410 (24.8) | 3404 (24.7) | NS |
| Thought to be related to the study agent and leading to discontinuation of study regimen | 226 (1.6) | 201 (1.5) | NS |
| Injection-site reaction* | 296 (2.1) | 219 (1.6) | <0.001 |
| Allergic reaction | 420 (3.1) | 393 (2.9) | NS |
| Muscle-related event | 682 (5.0) | 656 (4.8) | NS |
| Rhabdomyolysis | 8 (0.1) | 11 (0.1) | NS |
| Cataract | 228 (1.7) | 242 (1.8) | NS |
| Adjudicated case of new-onset diabetes† | 677 (8.1) | 644 (7.7) | NS |
| Neurocognitive event | 217 (1.6) | 202 (1.5) | NS |
| Laboratory results — no. of patients/total no. (%) | | | NS |
| Aminotransferase level >3 times the upper limit of the normal range | 240/13,543 (1.8) | 242/13,523 (1.8) | NS |
| Creatine kinase level >5 times the upper limit of the normal range | 95/13,543 (0.7) | 99/13,523 (0.7) | NS |

† Evolocumab 8,337 vs. Placebo 8,339 due to exclusion of preexisting diabetic patients

**No significant adverse events in evolocumab group**

# Relation between Proportional Reduction in Vascular Event Rate & Mean Absolute LDL-C Difference



# Is there a scientific rationale of ‘very’ low LCL-C ?

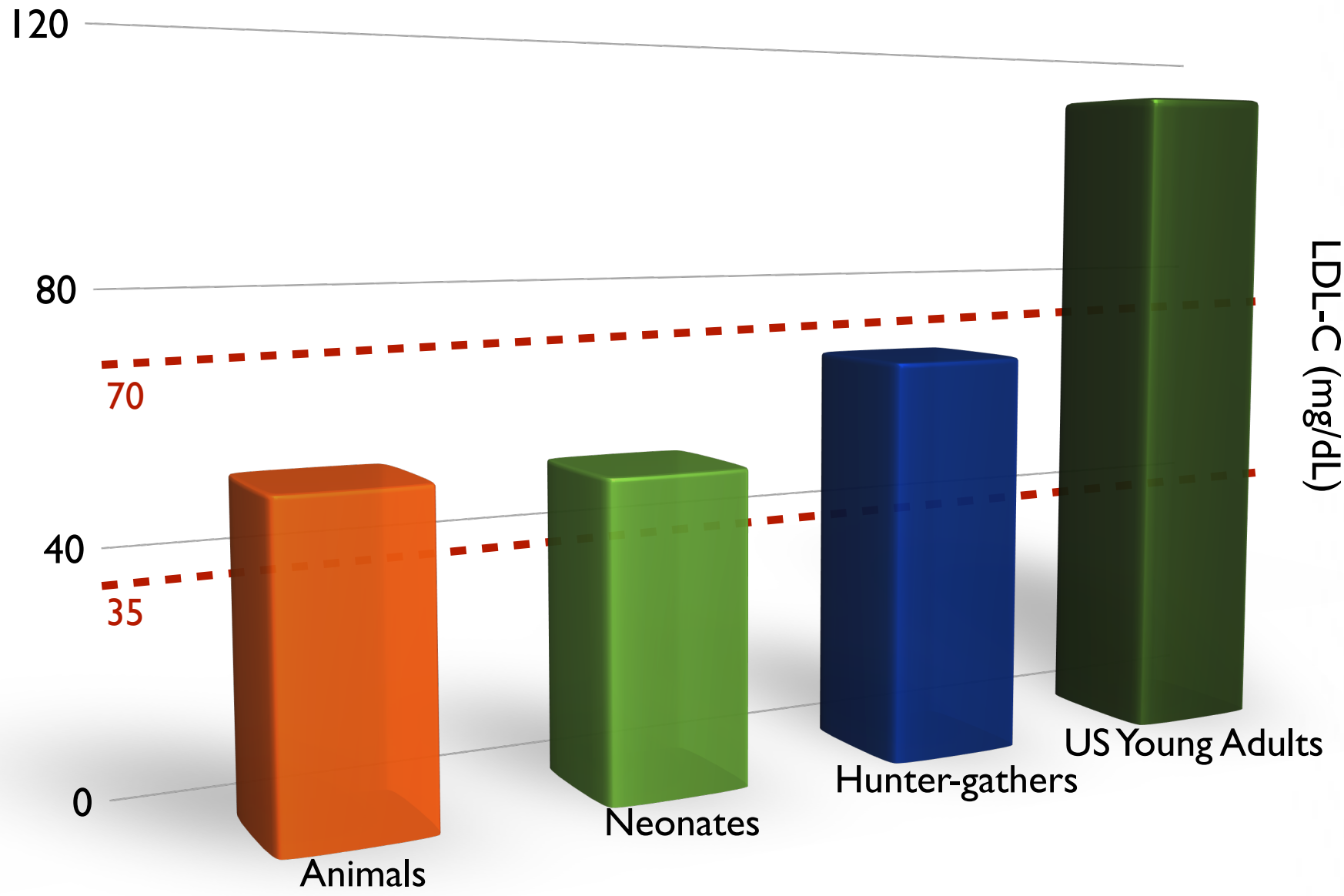
# A Receptor-Mediated Pathway for Cholesterol Homeostasis

MICHAEL S. BROWN AND JOSEPH L. GOLDSTEIN

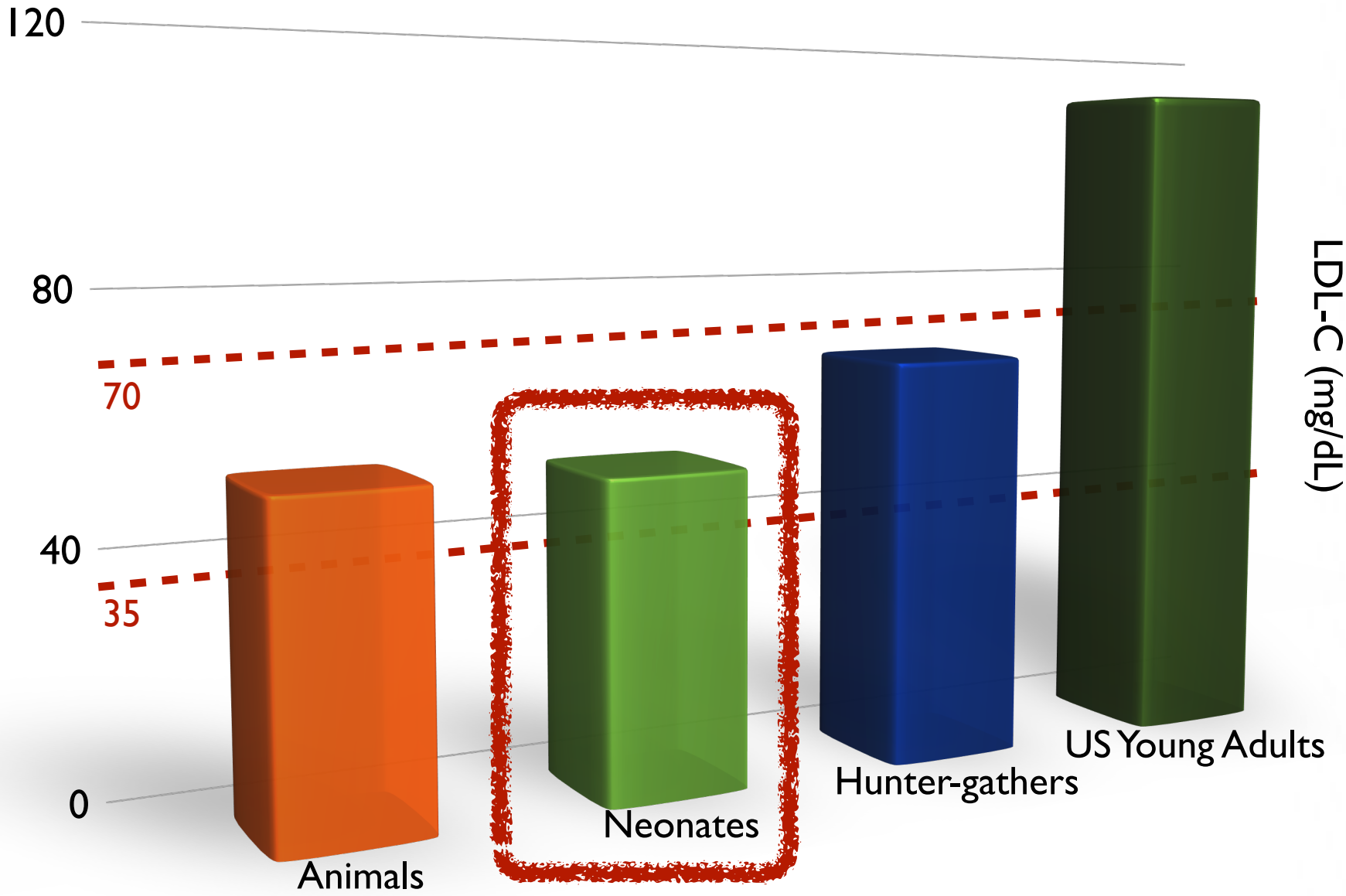
*Science 232:34-47, 1986*

The LDL-receptor studies lend experimental support to the epidemiologists' suggestion that the levels of plasma cholesterol usually seen in Western industrialized societies are inappropriately high (*9*). This support derives from knowledge of the affinity of the LDL receptor for LDL. The receptor binds LDL optimally when the lipoprotein is present at a cholesterol concentration of 2.5 mg/dl (*28*). In view of the 10-to-1 gradient between concentrations of LDL in plasma and interstitial fluid, a level of LDL-cholesterol in plasma of 25 mg/dl would be sufficient to nourish body cells with cholesterol (*118*). This is roughly one-fifth of the level usually seen in Western societies (Fig. 16) (*119*). Several lines of evidence suggest that plasma levels of LDL-cholesterol in the range of 25 to 60 mg/dl (total plasma cholesterol of 110 to 150 mg/dl) might

# Normal LDL-C Levels



# Normal LDL-C Levels

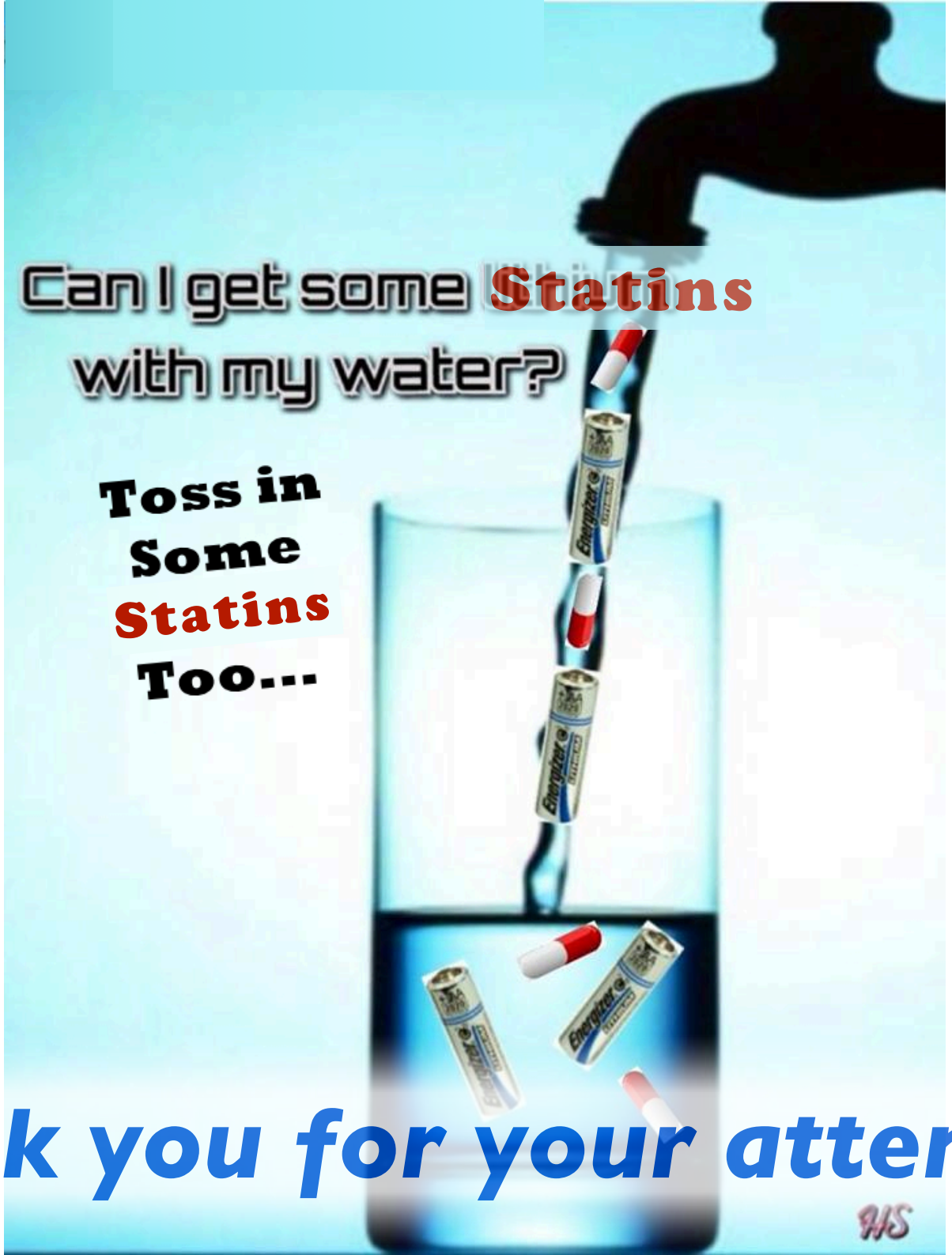


# Summary

- Based on many data suggesting definite benefit of LDL-C reduction, LDL-C has been defined as a primary target in management guidelines.
- Statin use in patients at high risk for CVD has 'consistently' reduced incidence of major clinical events by 25% to 40%.
- However, there are still **high residual CV risks in 2/3 of patients on statins**.
- The combination therapy of **statin with niacin or fibrate for targeting HDL-C or TG** can be an option to reduce residual CV risk, however, almost all of these studies have been **failed to show benefit**.
- Recent study shows **incremental clinical benefits by adding ezetimibe to statin therapy** (IMPROVE-IT and prespecified analysis) suggesting the concept that **'even lower is even better'** for targeting LDL-C.
- Studies for **emerging therapies such as CETP/PCSK9 inhibitors** are **on the process**, where, so far, **anacetrapib and evolocumab** met the primary end points. We have to wait the results of CV outcome trial using alirocumab.

# Conclusion

- **"LCL-C lowering" therapy rather than "Statin" therapy**
  - despite statin-based add-on treatment
- **'The lower, the better' is still alive**
  - although there is still unmet need about residual CV risk
- **No serious problem by very low LCL-C (20mg/dL)**
  - despite no concrete data for longterm safety




# *Thank you for your attentions!*