Need for Additional Emerging Targets?

Ultimate Goal for Lipid Management

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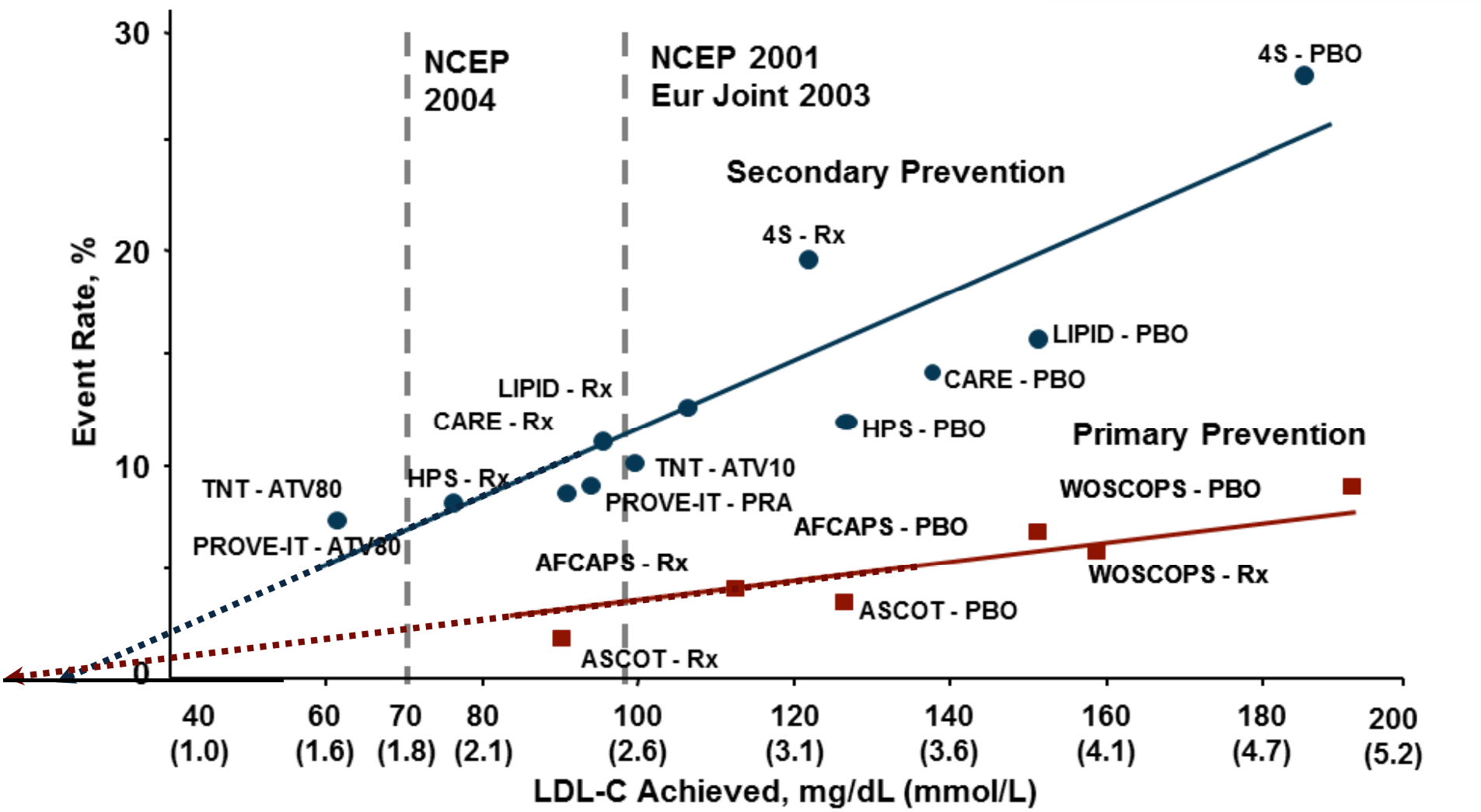
As you know, there are many concrete beneficial evidences of LDL-lowering statin therapy!!!

LDL-C Lowering & Benefit of Statins



Rosensen RS. *Exp Opin Emerg Drugs*. 2004;9:269-279.
LaRosa J, et al. *N Engl J Med*. 2005;352:1425-1435.

CTT (Cholesterol Treatment Trialists' Collaboration)

170,000 patients in various trials (second cycle)

CTT Meta-Analysis

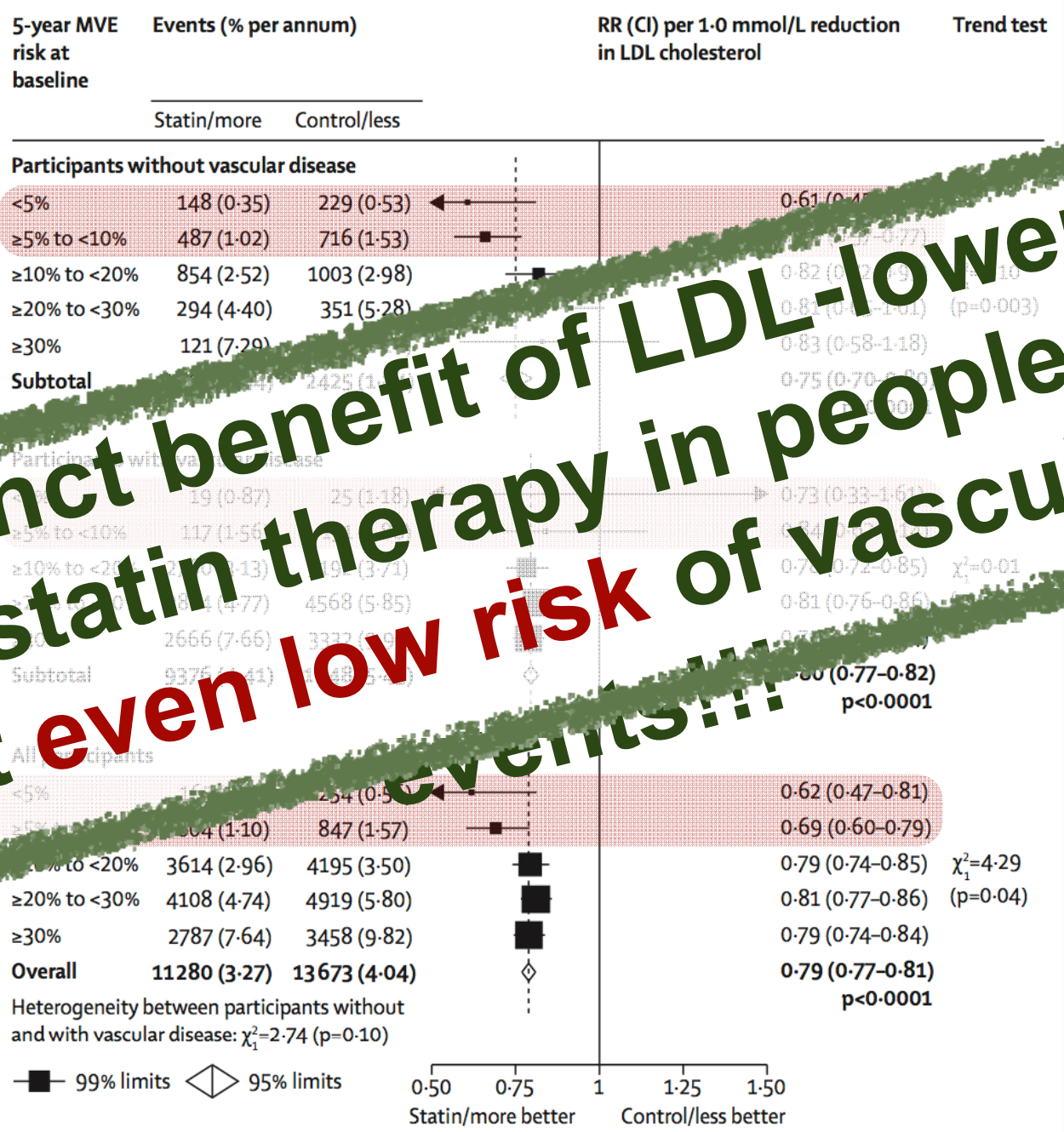
	CTT 2005[1]	CTT 2010[2]	CTT 2012[3]
Number of analyzed trials (Number of patients)	14 (90,056)	26 (169,138)	27 (174,149)
Comparison	Statin vs. Control	More vs. Less intensive statin Statin vs. Control Stain/More vs. Control/Less	Stain/More vs. Control/Less
Classified based on 5-year major vascular event (MVE) risk at baseline	No	No	Yes
Reduction of MVE risk per 1 mmol/L reduction of LDL-C*	21%	More vs. Less intensive statin: 28% Statin vs. Control: 21% Stain/More vs. Control/Less: 22%	Data according to 5-year MVE risk (Next page)

*LDL-C: 1 mmol/L=38.61mg/dL

1. Lancet 2005;366:1267-78
2. Lancet 2010;376:1670-81
3. Lancet 2010;380:581-90

CTT Meta-Analysis from CTT 2012

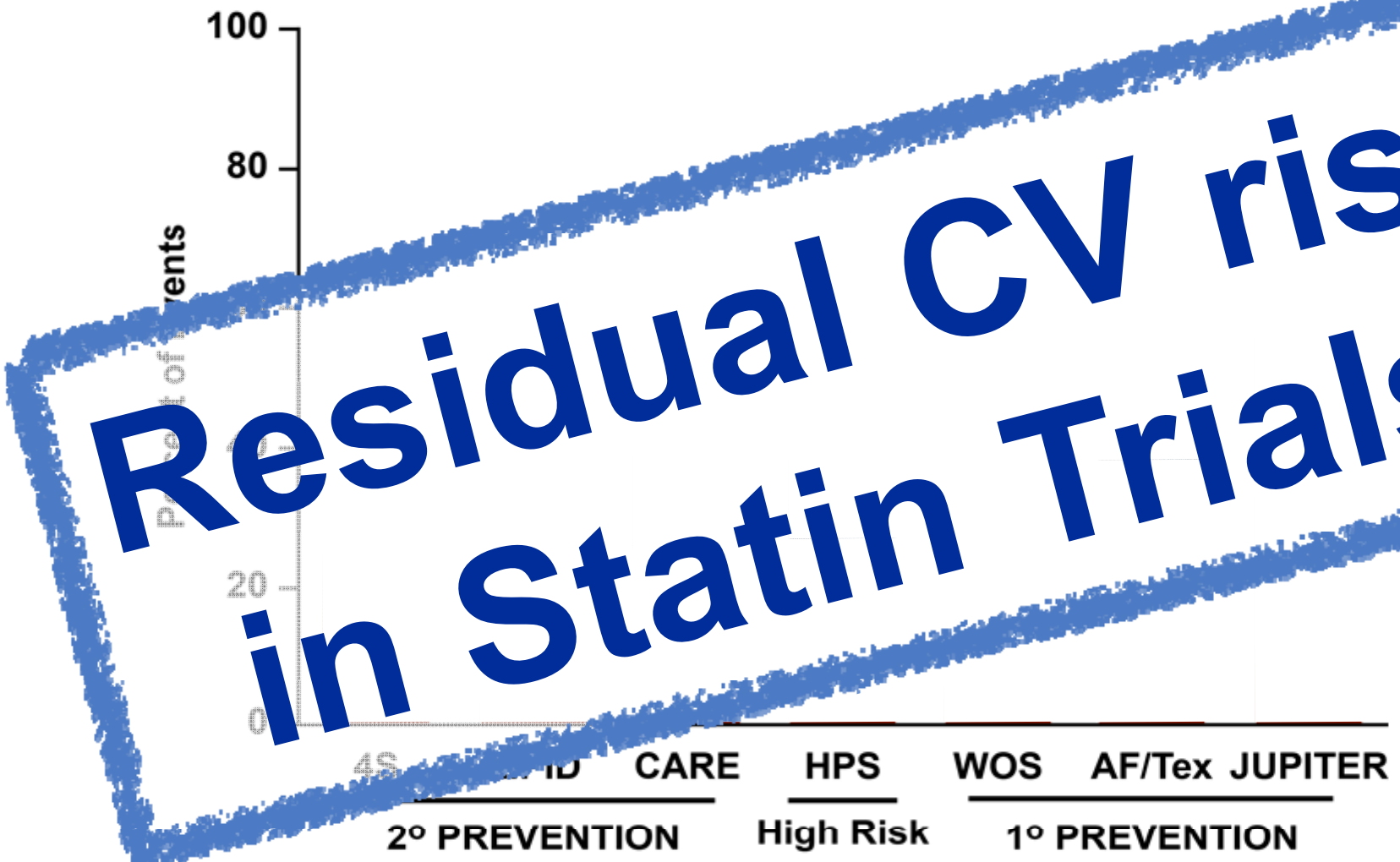
MVE at Difference Risk Levels



Distinct benefit of LDL-lowering statin therapy in people at even low risk of vascular events!!!

However, there is still CV risk despite the use of aggressive statin therapy...

Residual CV risk in Statin Trials



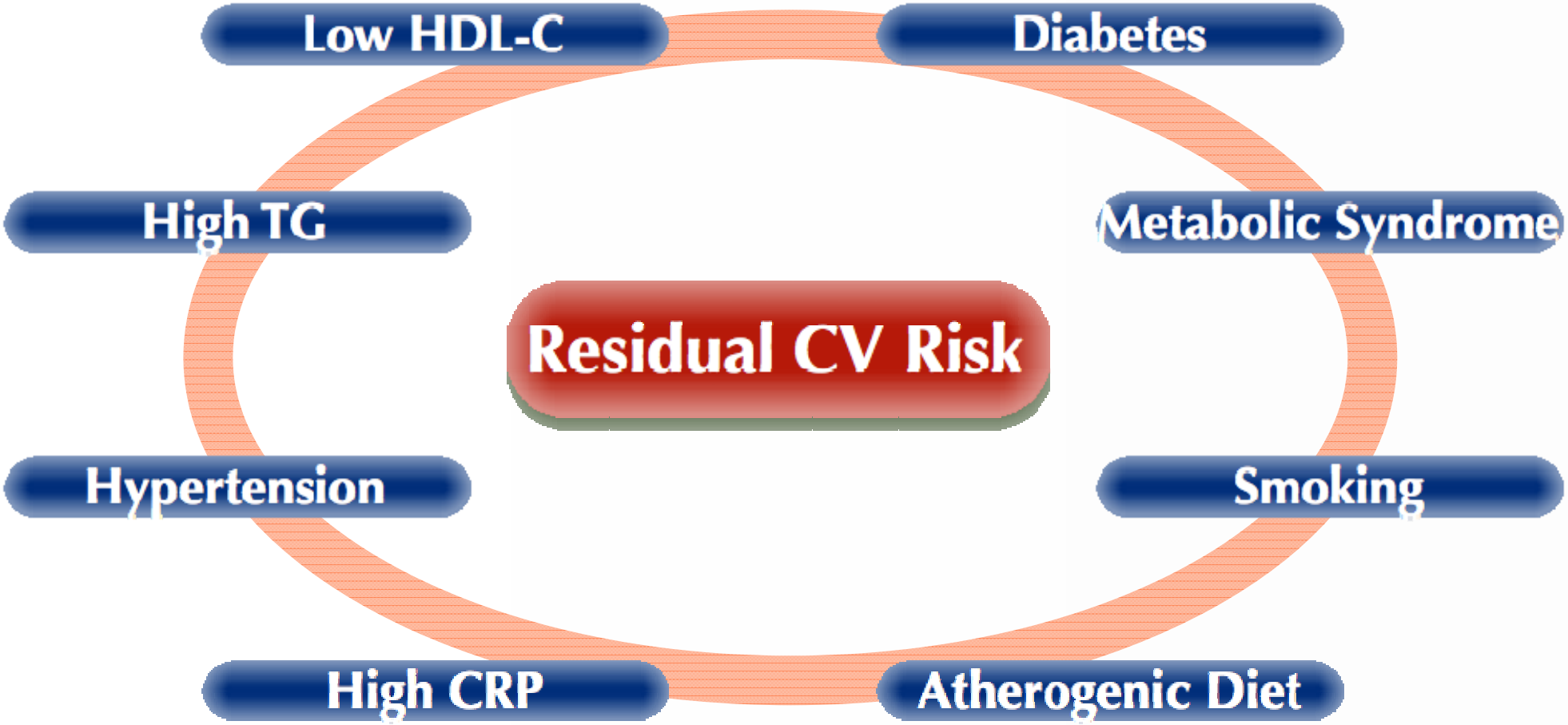
Ballantyne CM, et al. *Circulation*. 1999;99:736-743; Scandinavian Simvastatin Survival Study Group. *Lancet*. 1995;345:1274-1275; The LIPID Study Group. *N Engl J Med*. 1998;339:1349-1357; Pfeffer MA, et al. *J Am Coll Cardiol*. 1999;33:125-130; Shepherd J, et al. *N Engl J Med*. 1995;333:1301-1307;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

What Is Residual Cardiovascular Risk?

- **Statin trials show many patients at LDL-C goal have high "residual" CHD risk[1].**
- **Statins reduce risk by about 30% compared with controls, but many patients still have events due to residual risk[2-4].**
- **More intensive treatment directed to other targets as well as LDL-C is needed in addition to statin monotherapy to reduce residual risk effectively.**

1. Davidson MH. Am J Cardiol. 2005;96:3K-13K
2. Pedersen TR, et al. Diab Vasc Dis Res. 2006;3:S1-S12
3. Baigent C, et al. Lancet. 2005;366:1267-1278
4. LaRosa JC, et al. JAMA. 1999;282:2340-2346.

Patients with High Residual Risk



Current Cardiology Reports. 2007; 9 :499-505

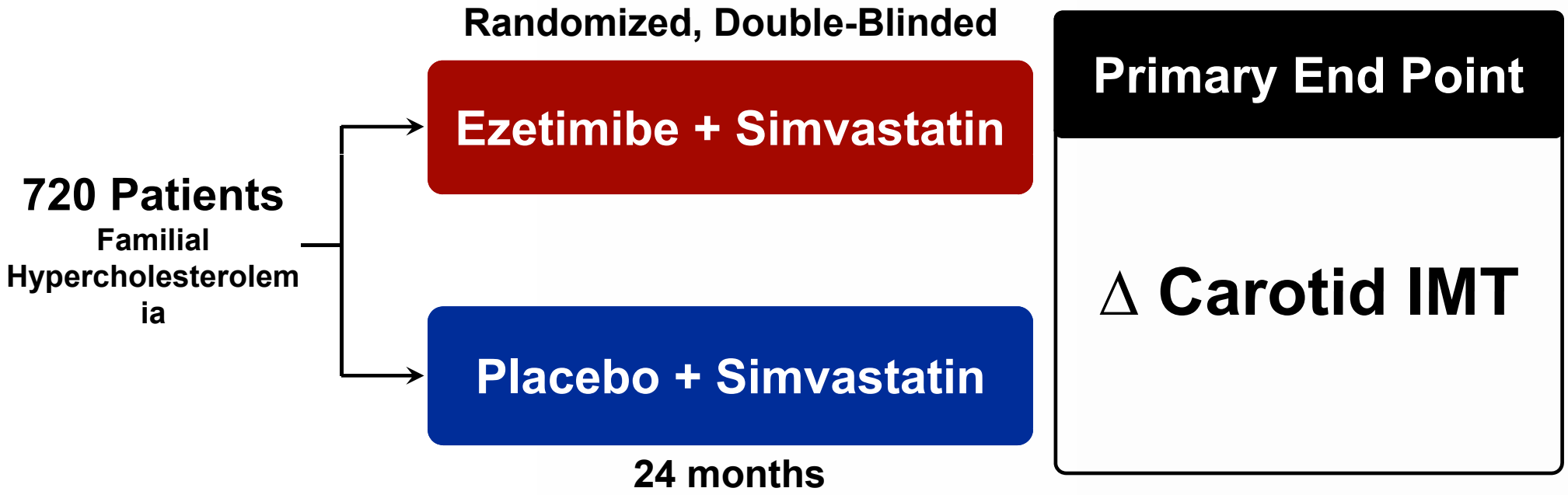
Are you looking for something beyond statin?

Add-On Therapy to Statin for Further CV risk Reduction

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

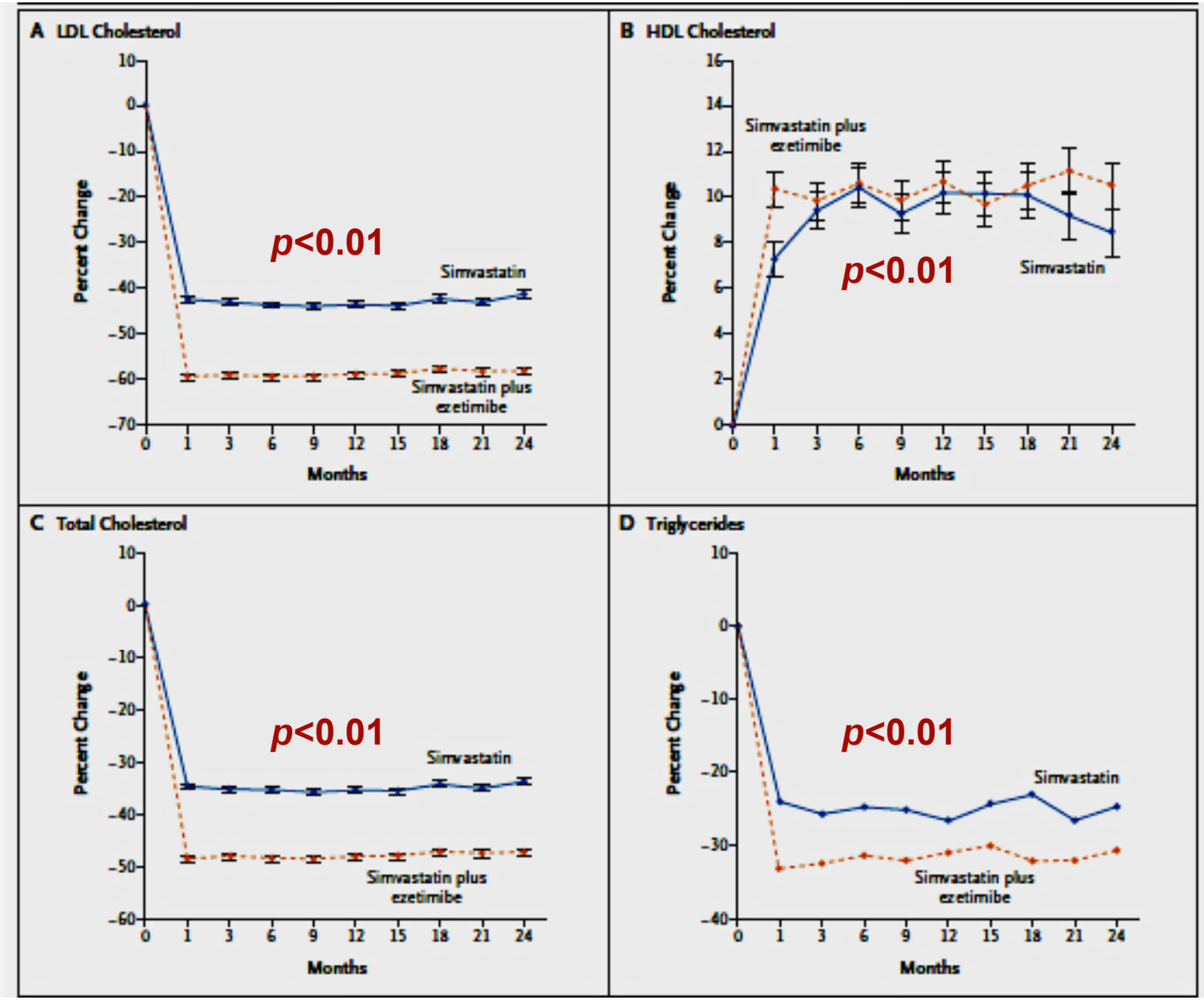
ENHANCE Design

N Engl J Med 2008;358:1431-43



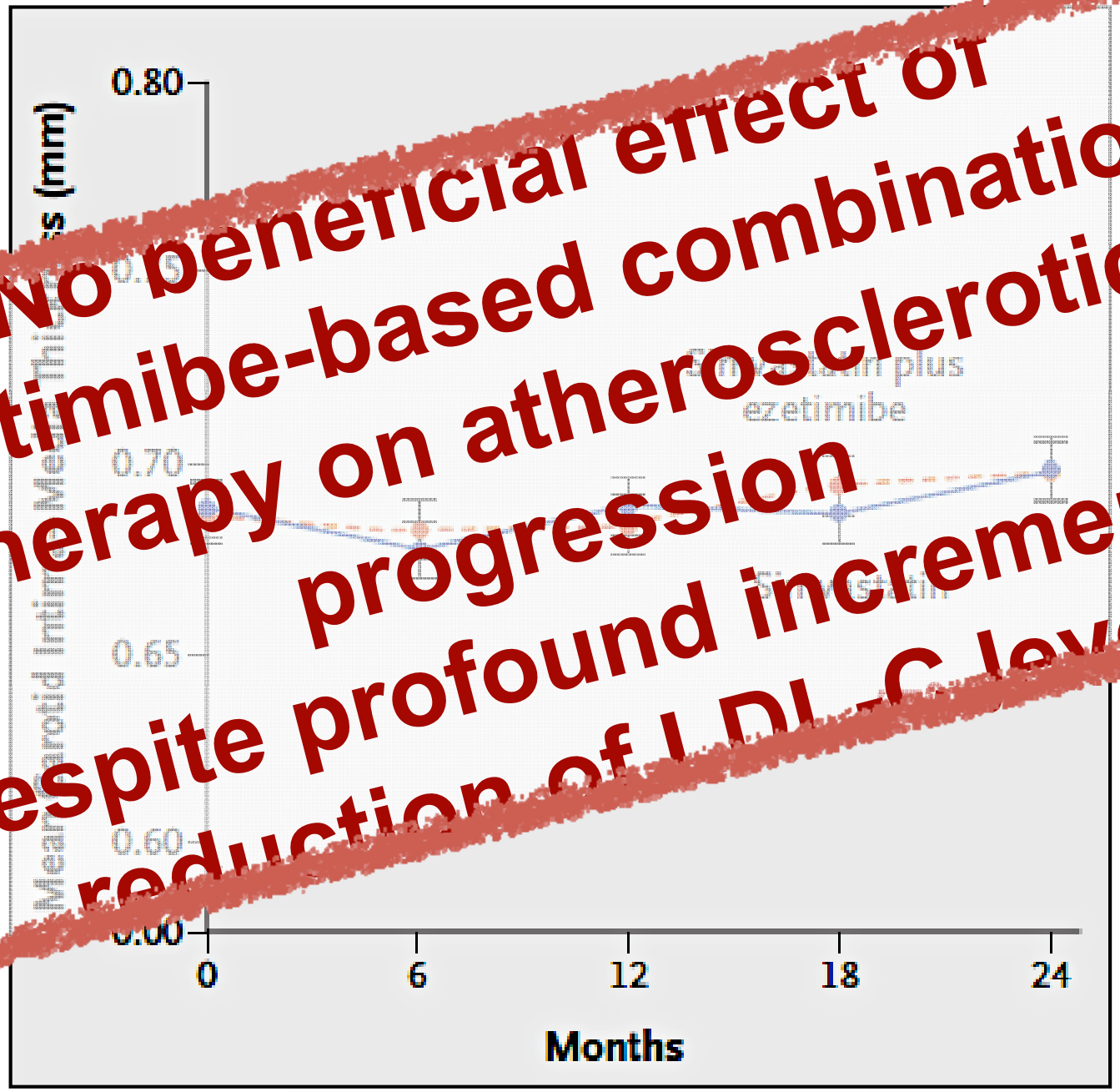
ENHANCE Results

N Engl J Med 2008;358:1431-43



ENHANCE Results

N Engl J Med 2008;358:1431-43

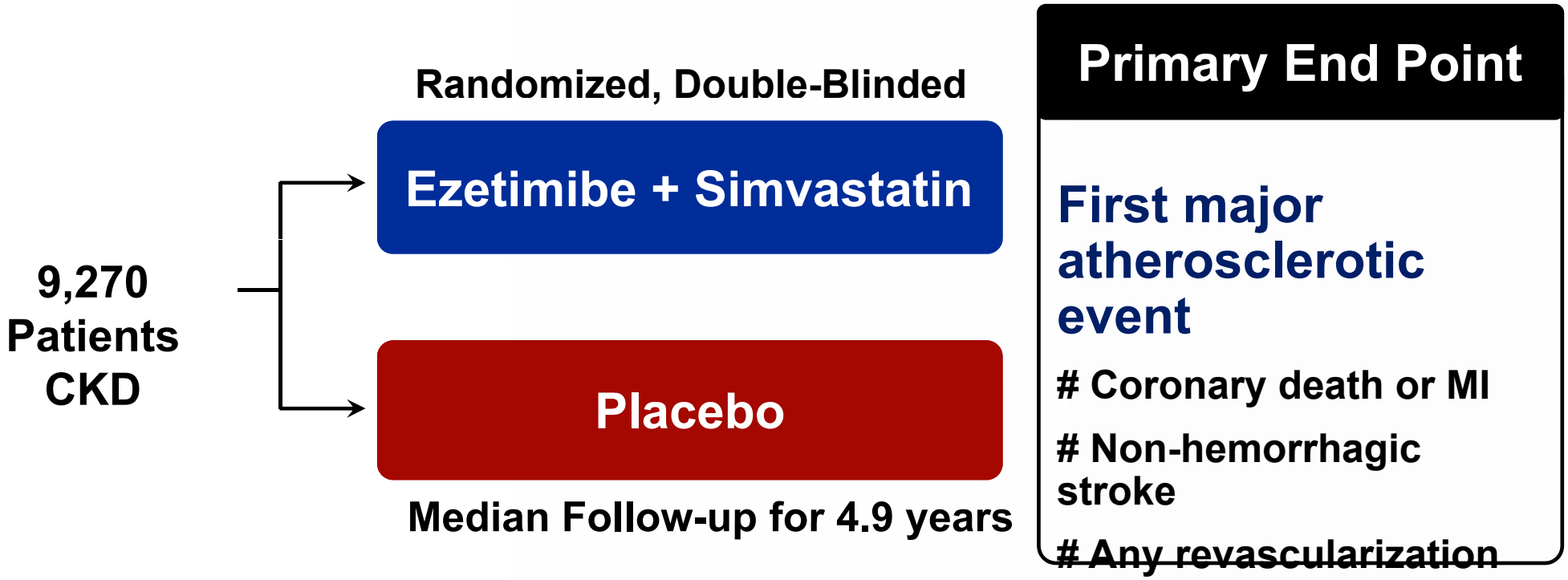


No beneficial effect of ezetimibe-based combination therapy on atherosclerotic progression despite profound incremental reduction of LDL-C level

SHARP Design

Lancet 2012;377:2181-92

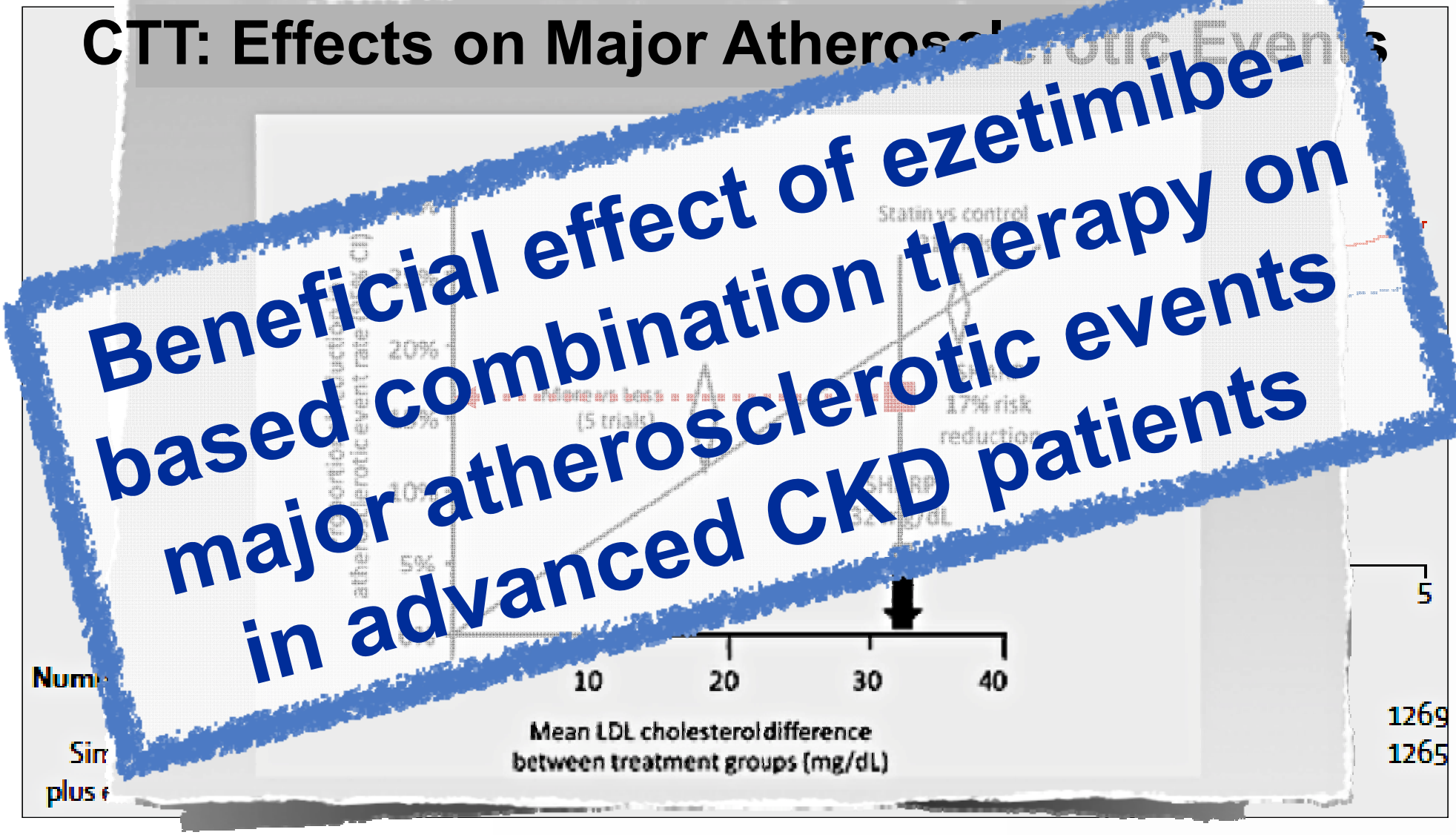
SHARP
STUDY OF HEART AND RENAL PROTECTION



SHARP Result

Lancet 2012;377:2181-92

SHARP
STUDY OF HEART AND RENAL PROTECTION



Beneficial effect of ezetimibe-based combination therapy on major atherosclerotic events in advanced CKD patients

Placebo+Stain vs. Niacin+Statin

AIM-HIGH Design

N Engl J Med 2011;365:2255-67

AIM-HIGH
Cholesterol Management Program

3,414 Patients
Vascular Disease

Randomized, Double-Blinded

Niacin + Simvastatin 40-80 mg

Target LDL-C : 40-80 mg/dL (+Ezetimibe if needed)

Placebo + Simvastatin 40-80 mg

Median Follow-up for 3 years

Primary End Point

First event of composite...

- Death from CHD
- Nonfatal MI
- Ischemic stroke
- Hospitalization for ACS
- Symptom-driven coronary or cerebral revascularization

Patient Characteristics

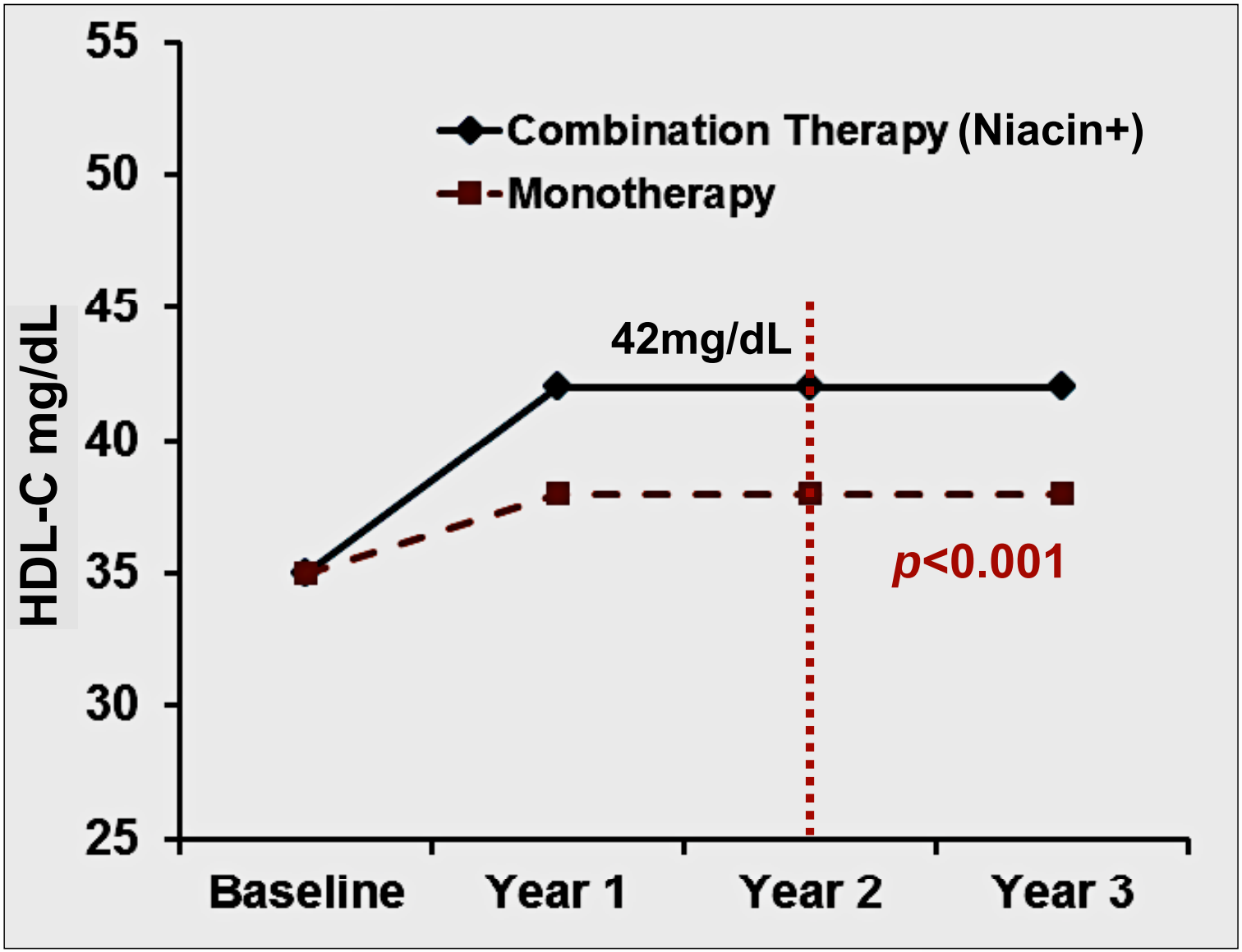
45 years of age or older
Established vascular disease
Low HDL-C: < 40 mg/dL (men) 50 mg/dL (women)
TG: 150-400 mg /dL, LDL-C : <180 mg/dL

Placebo+Stain vs. Niacin+Statin

AIM-HIGH Result

N Engl J Med 2011;365:2255-67

AIM-HIGH
Cholesterol Management Program

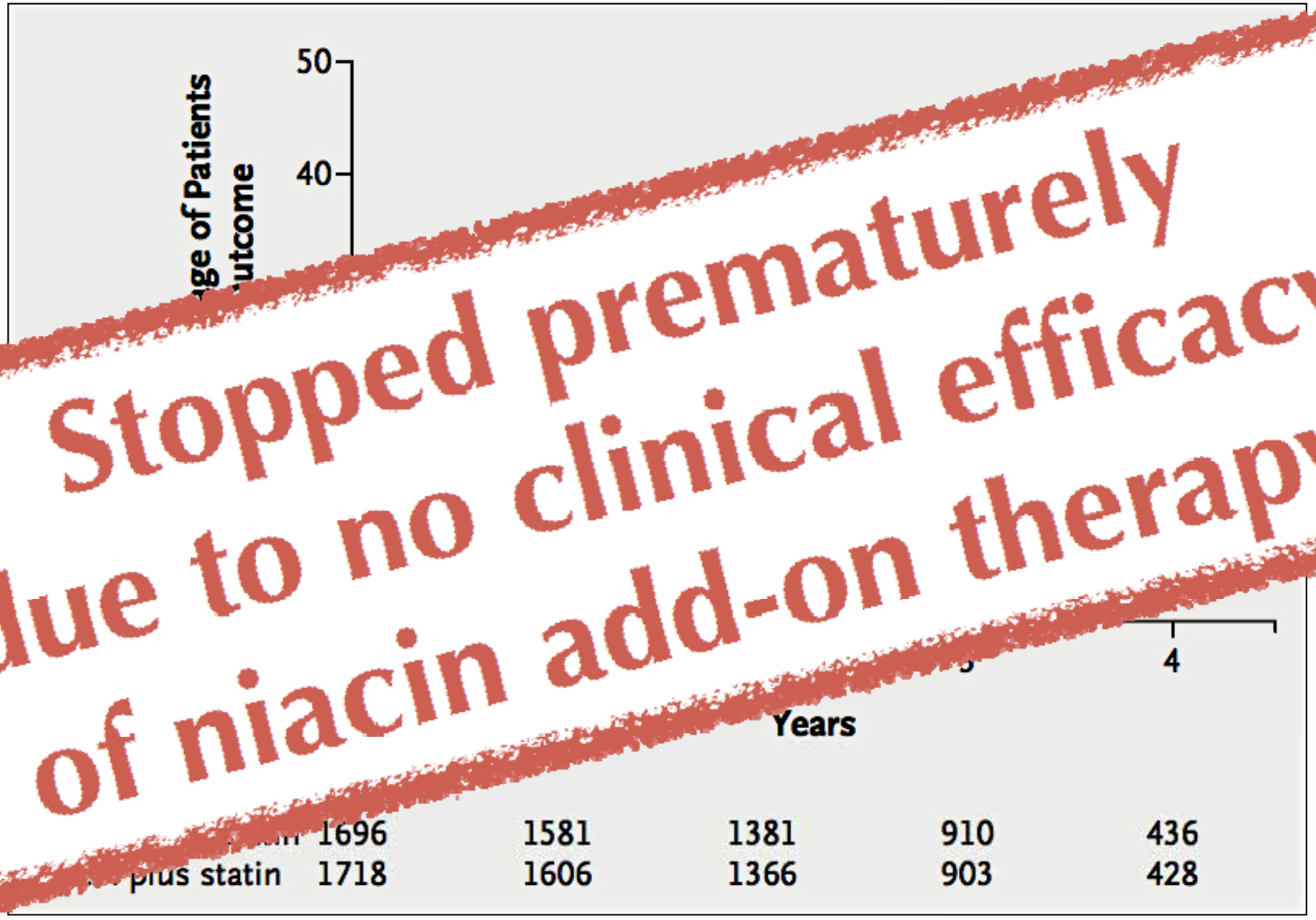


Placebo+Stain vs. Niacin+Statin

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

Action to Control Cardiovascular Risk in Diabetes
ACCORD

ACCORD Lipid Design

N Engl J Med 2010;362:1563-74

Open-labelled for Simvastatin
Randomized, Double-Blinded for Placebo or Fenofibrate

5,518 Patients
Type 2 Diabetes

- **Placebo + Simvastatin**
- **Fenofibrate + Simvastatin**

Median Follow-up for 4.7 years

Primary End Point

First event...

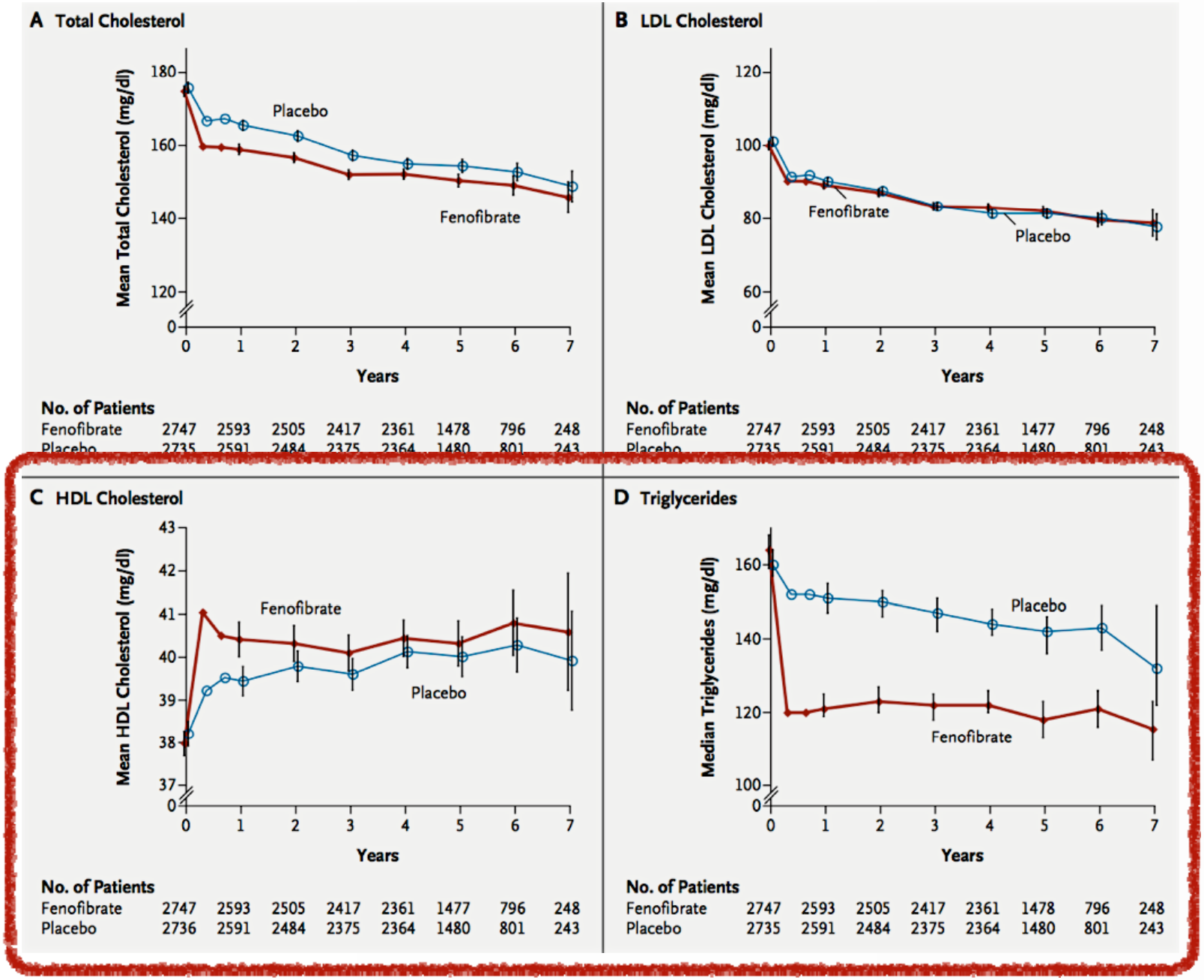
 # Nonfatal MI

 # Non-fatal stroke

 # CV death

Action to Control Cardiovascular Risk in Diabetes
ACCORD

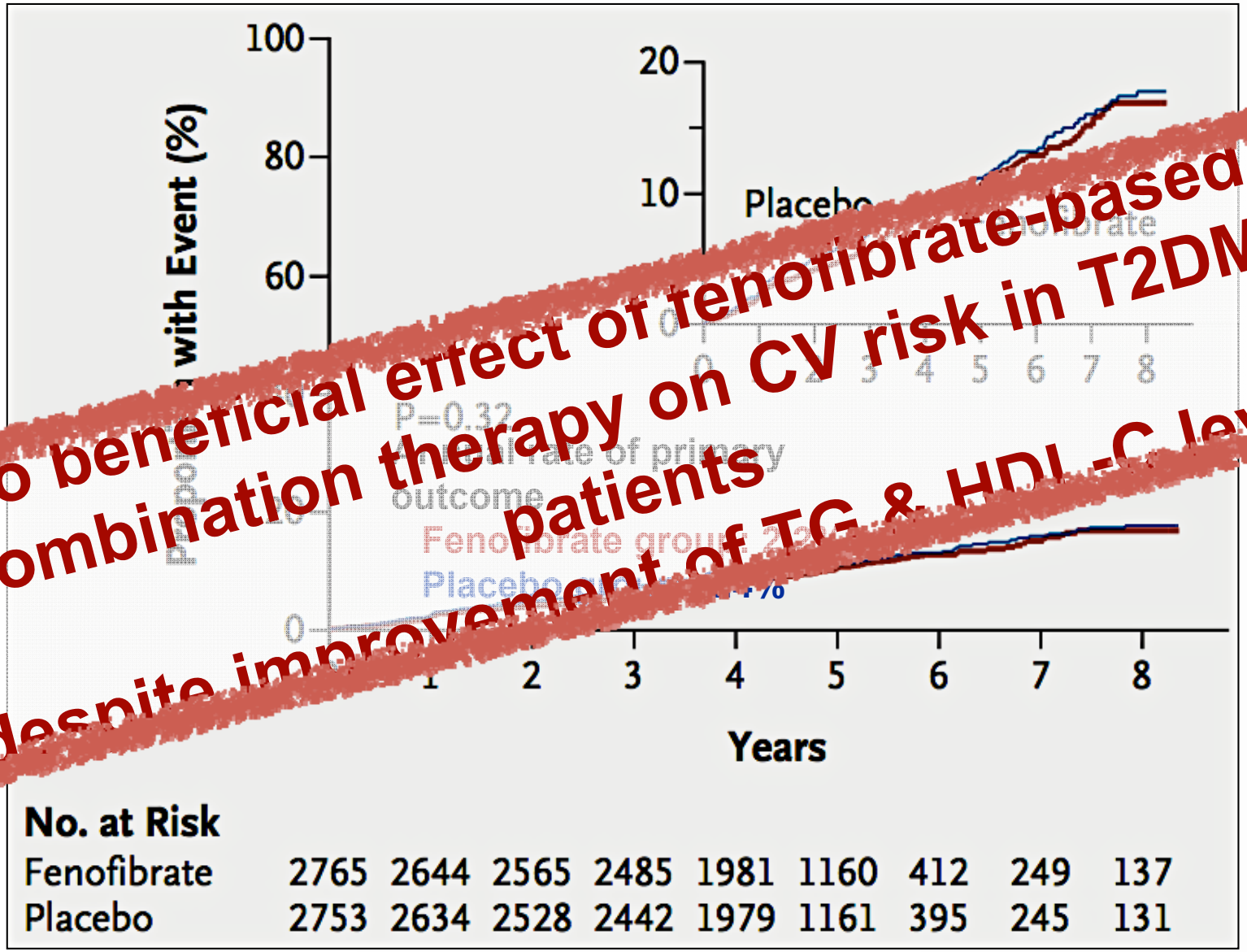
ACCORD Lipid Design



Action to Control Cardiovascular Risk in Diabetes
ACCORD

ACCORD Lipid Result

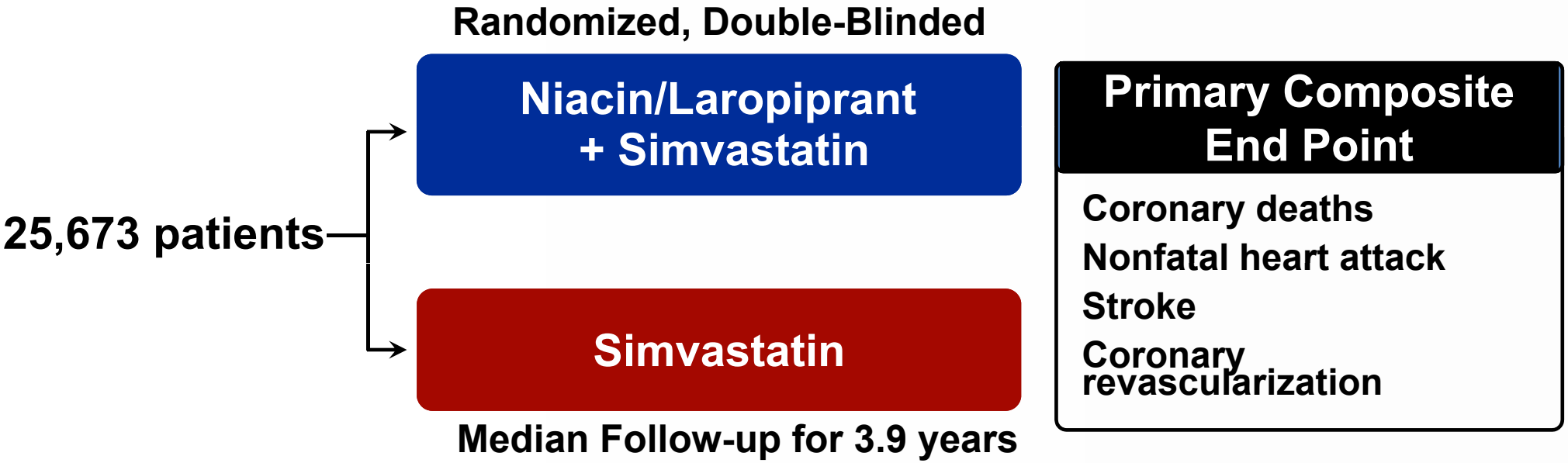
N Engl J Med 2011;365:2255-67



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

HPS2-THRIVE Design

Late Breaking in ACC 2013



Patient Characteristics

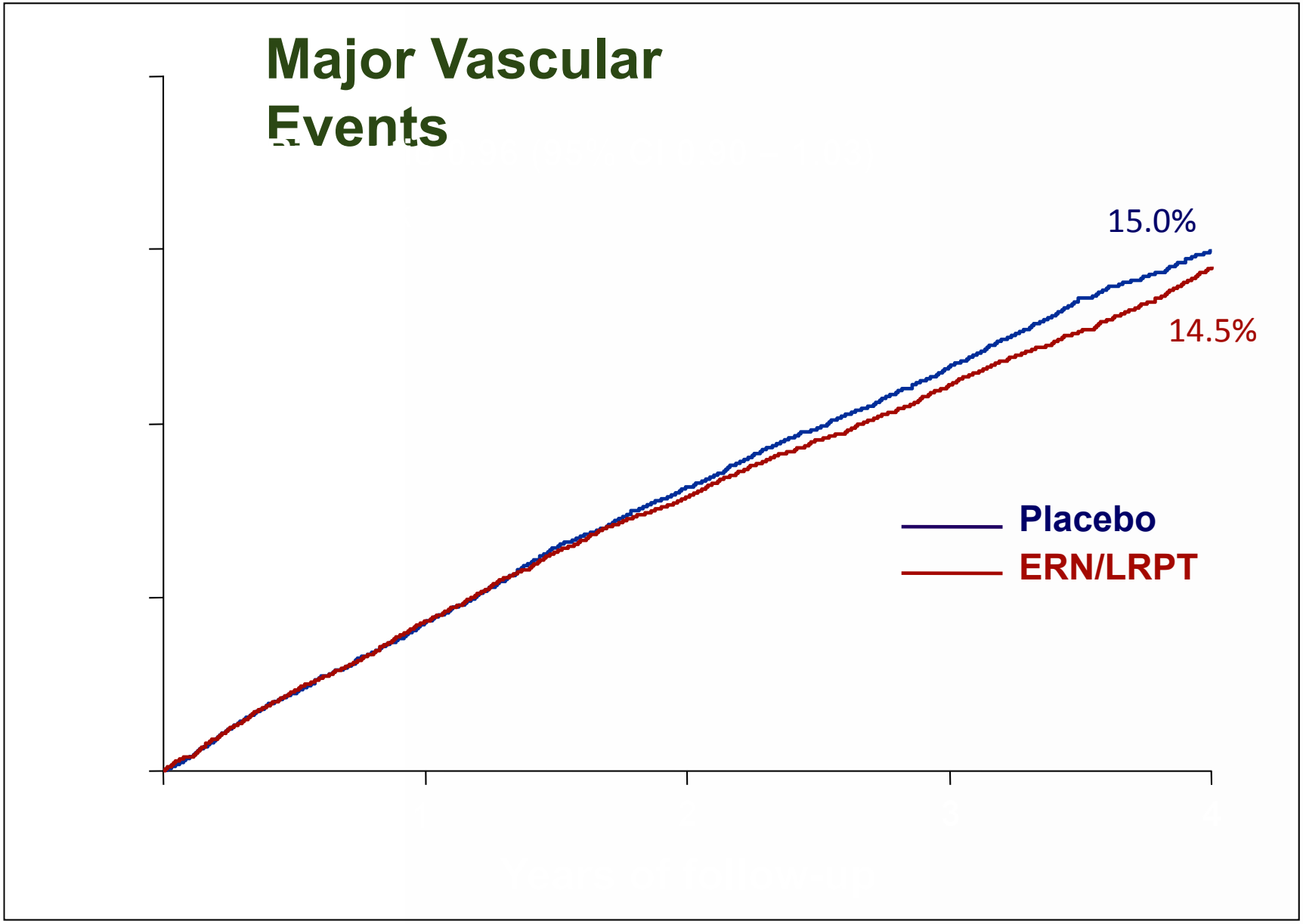
Age 50-80

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

Niacin ER with Laropiprant+Stain vs.

HPS2-THRIVE Result

Late Breaking in ACC 2013



Niacin ER with Laropiprant+Stain vs.

HPS2-THRIVE Result

Late Breaking in ACC 2013

Reasons for stopping study treatment

	ERN/LRPT (n=1[illegible])	Placebo (n=1,835)	Δ
Any m[illegible]	16.4%	7.9%	8.5%
[illegible]kin	5.[illegible]%	1.2%	4.2%
[illegible]astrointe[illegible]stinal	3.9%	1.7%	2.1%
M[illegible]sculoskeletal	1.8%	1.0%	0.8%
D[illegible]betes-related	0.9%	0.4%	[illegible]%
Li[illegible]er	0.4%	[illegible]%	0.1%
Ot[illegible]er	[illegible]%	3.[illegible]%	0.8%
Any non-medical	**8.[illegible]%**	**8.7%**	**0.3%**
Any reason	**25.4%**	**16.6%**	**8.7%**

May signal the end for Niacin...?...!...

Over 4 years, ER niacin/laropiprant caused SAEs in 31 patients/1,000.

All Failed...

Oh, here are “New Emerging Therapies”!!!

Why CETP inhibitors?

- Unmet medical needs about treating and prevention for atherosclerosis
- Existing evidences regarding artheroprotective activity of HDL-C
- Increases in HDL level and reductions in LDL-C level with CETP inhibition

ILLUMINATE

N Engl J Med 2007;357:2109-22

The NEW ENGLAND JOURNAL of MEDICINE

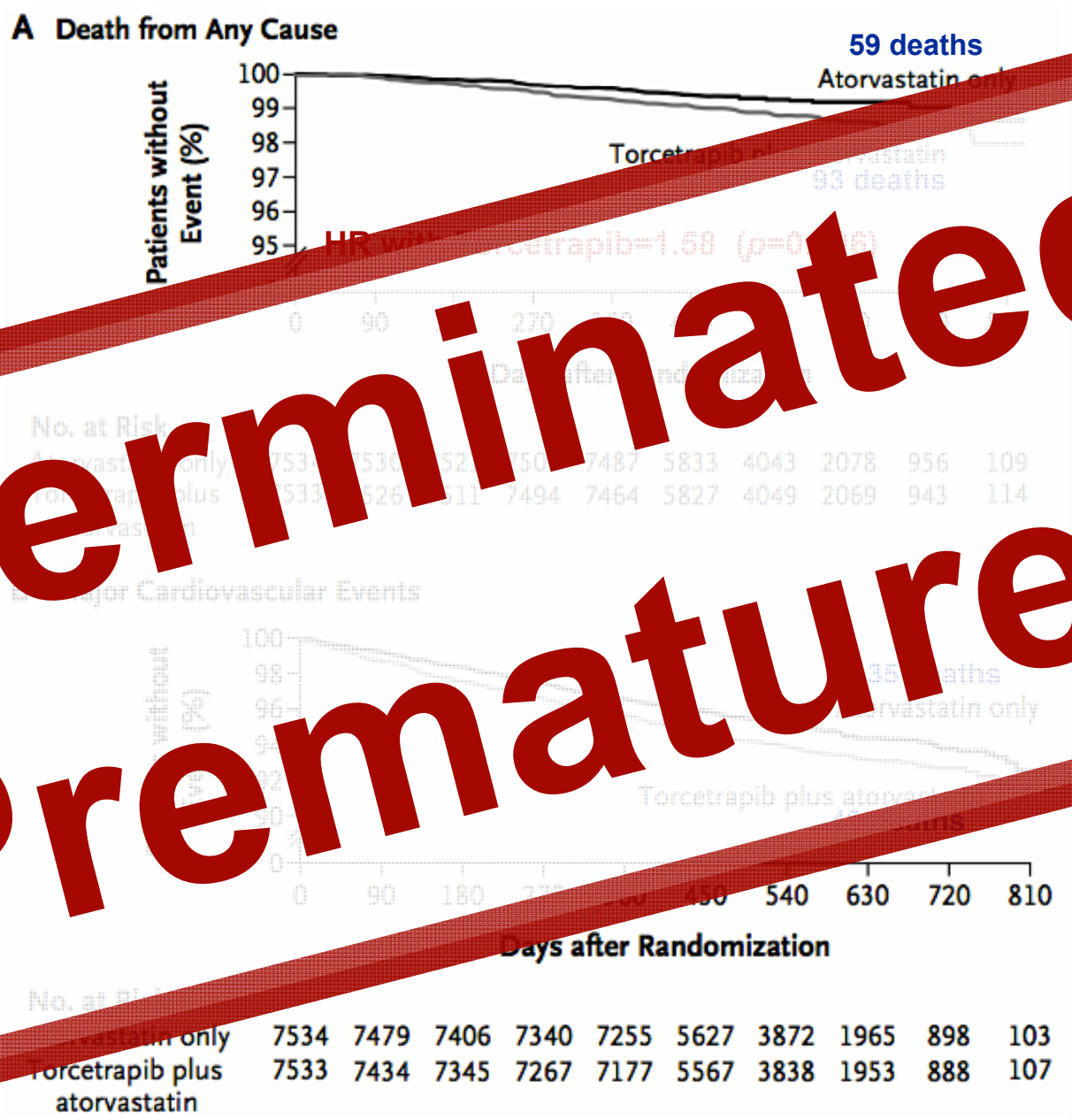
ESTABLISHED IN 1812 NOVEMBER 22, 2007 VOL. 357 NO. 21

Effects of Torcetrapib in Patients at High Risk for Coronary Events

Philip J. Barter, M.D., Ph.D., Mark Caulfield, M.D., M.B., B.S., Mats Eriksson, M.D., Ph.D., Scott M. Grundy, M.D., Ph.D., John J.P. Kastelein, M.D., Ph.D., Michel Komajda, M.D., Jose Lopez-Sendon, M.D., Ph.D., Lori Mosca, M.D., M.P.H., Ph.D., Jean-Claude Tardif, M.D., David D. Waters, M.D., Charles L. Shear, Dr.P.H., James H. Revkin, M.D., Kevin A. Buhr, Ph.D., Marian R. Fisher, Ph.D., Alan R. Tall, M.B., B.S., and Bryan Brewer, M.D., Ph.D., for the ILLUMINATE Investigators*

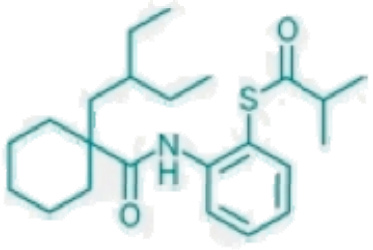
ILLUMINATE Result

N Engl J Med 2007;357:2109-22

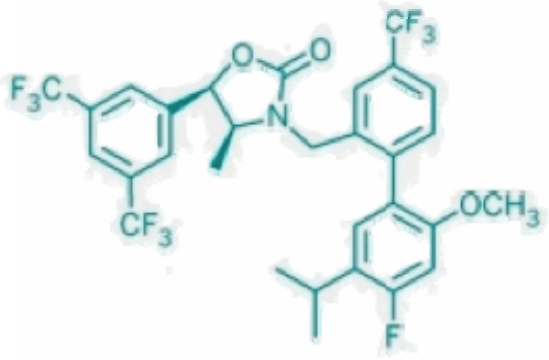


Terminated Prematurely

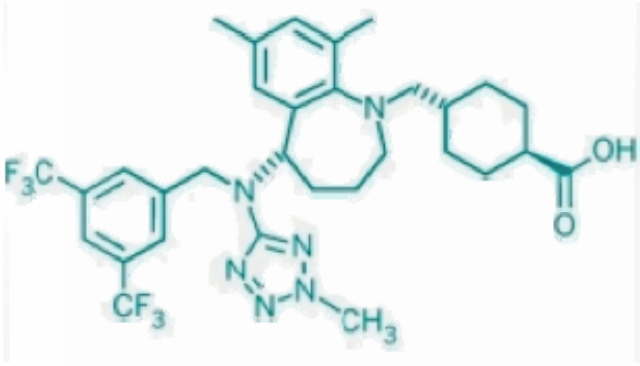
Post-Torcetrapib...



Dalcetrapib



Anacetrapib



Evacetrapib

dal-OUTCOME Result

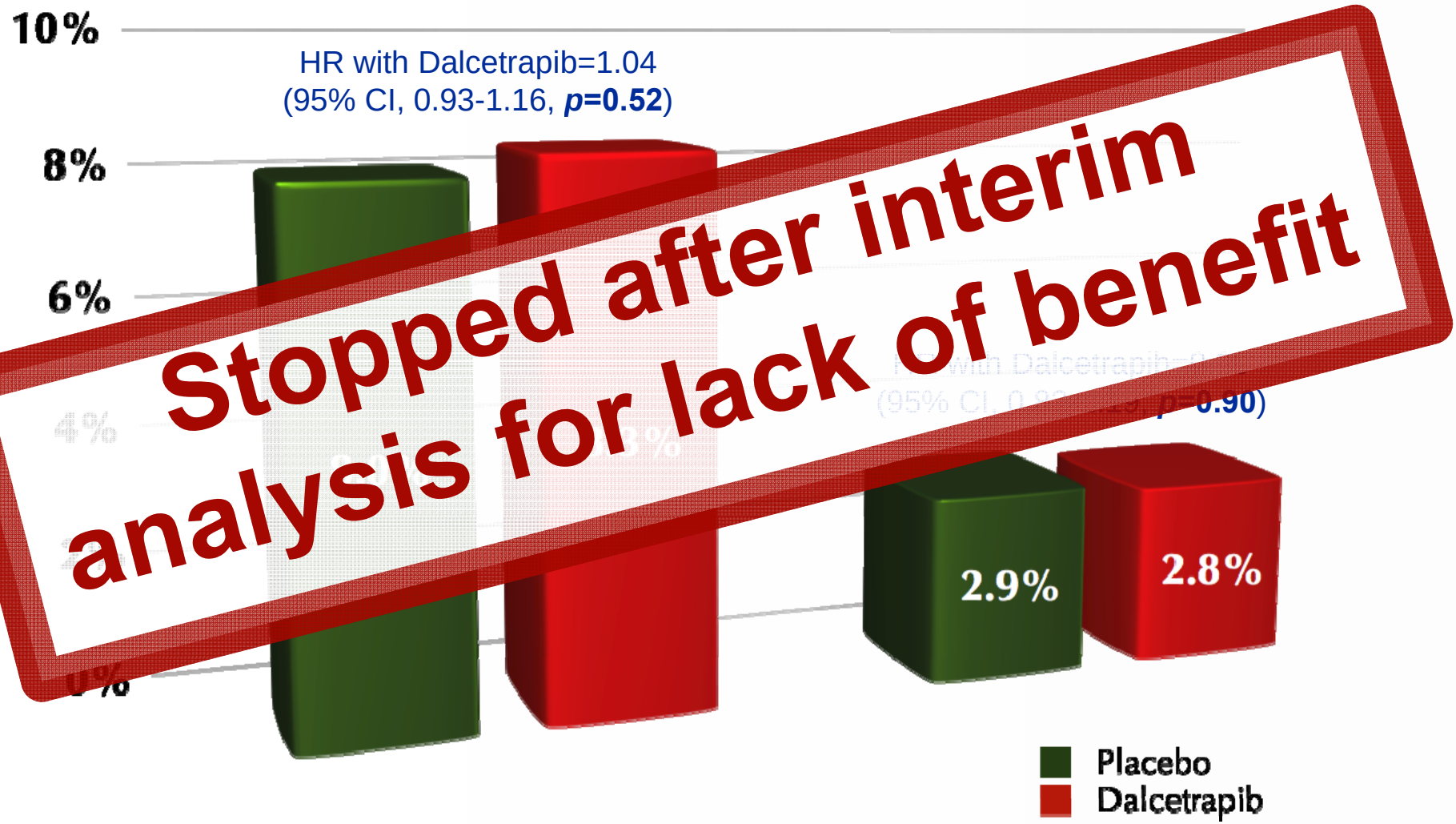
N Engl J Med 2012 DOI: *10.1056/NEJMoa1206797*

15,600 stable CHD patients with recent ACS

Primary End-Point

HR with Dalcetrapib=1.04
(95% CI, 0.93-1.16, ***p*=0.52**)

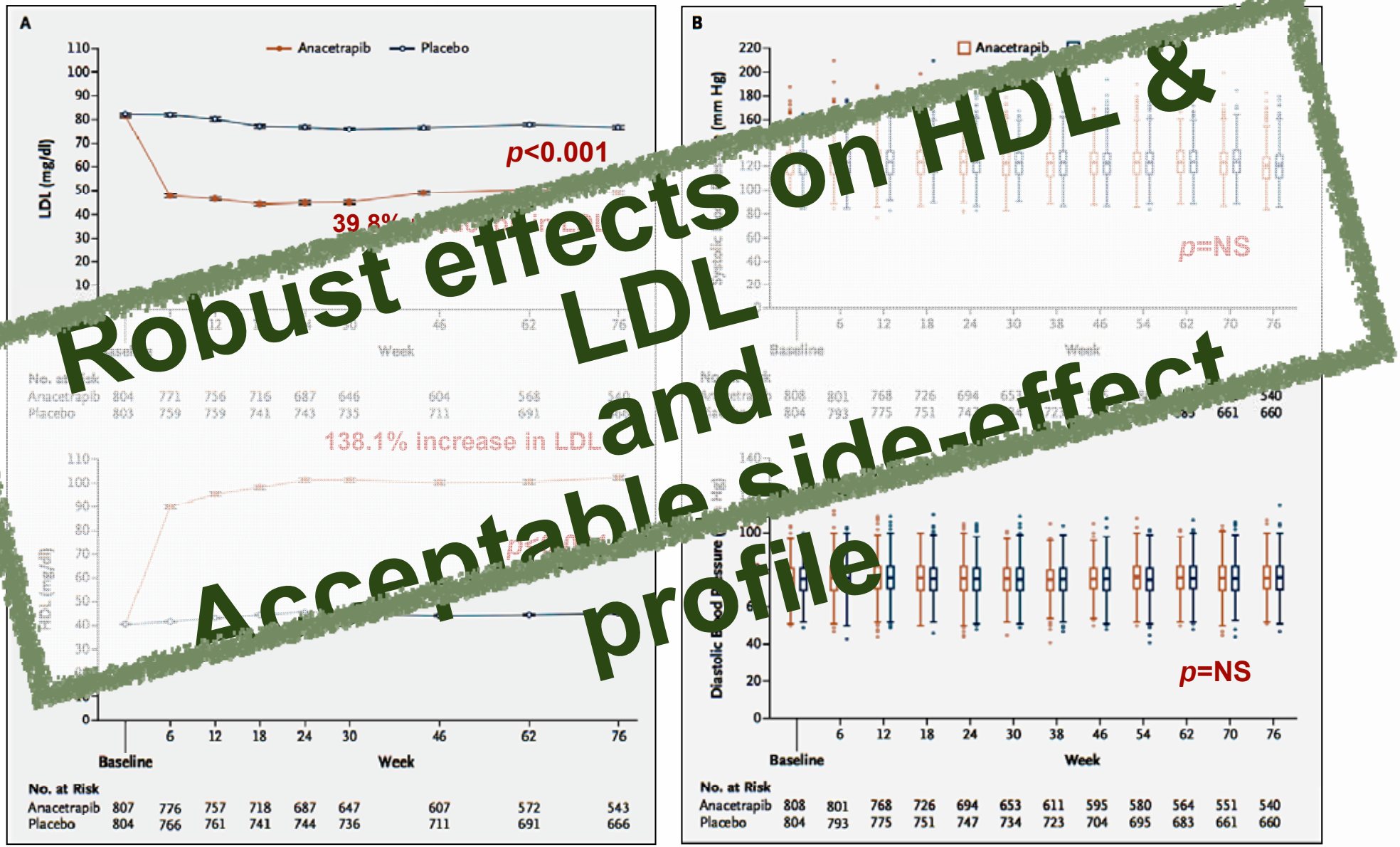
All-Cause Mortality



Stopped after interim analysis for lack of benefit

DEFINE Result

N Engl J Med 2010;363:2406-15

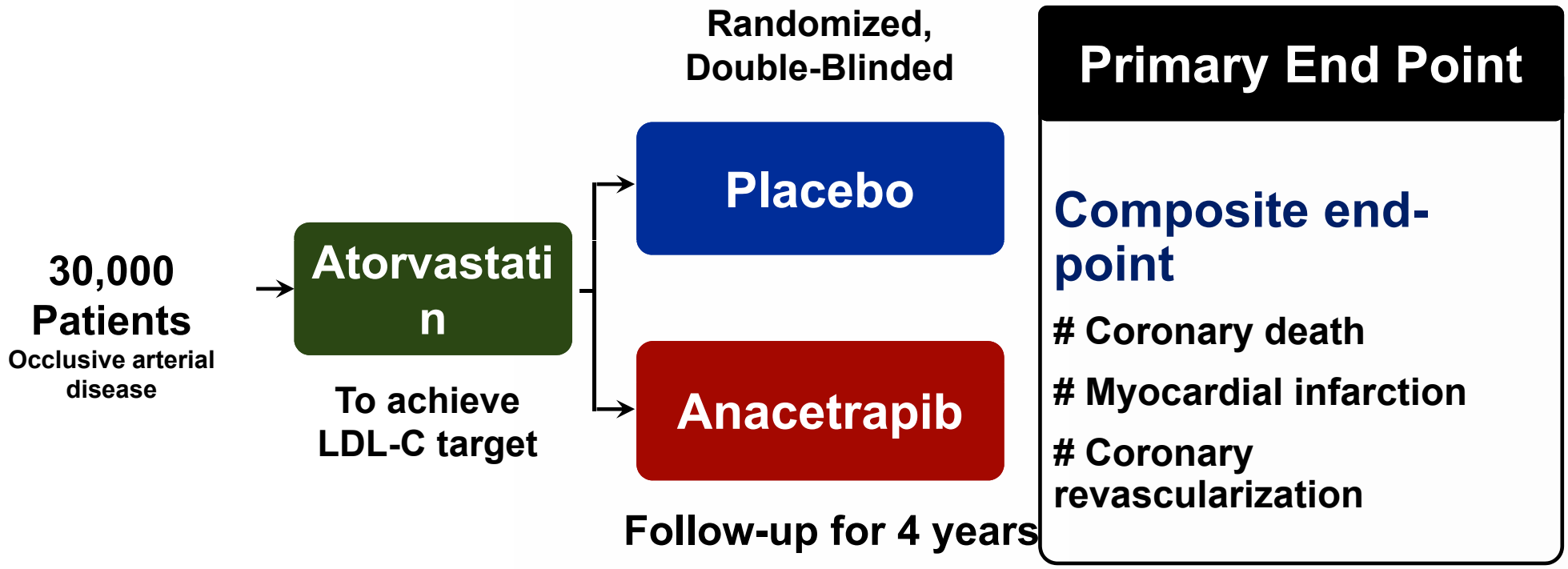


Robust effects on HDL & LDL and Acceptable side-effect profile

REVEAL Design

www.revealtrial.org

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



Planned completion in 2017

JAMA 2011;306:2099-109

Effects of the CETP Inhibitor Evacetrapib Administered as Monotherapy or in Combination With Statins on HDL and LDL Cholesterol

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

A Study of Evacetrapib in High-Risk Vascular Disease (ACCELERATE)

This study is currently recruiting participants.

Verified March 2013 by Eli Lilly and Company

Sponsor:
Eli Lilly and Company

Collaborator:
The Cleveland Clinic

Information provided by (Responsible Party):
Eli Lilly and Company

ClinicalTrials.gov Identifier:
NCT01687998

First received: September 12, 2012
Last updated: March 15, 2013
Last verified: March 2013
History of Changes

duced incidence of coronary heart disease,[8] it has been assumed that finding an appropriate therapy to increase HDL-C levels would yield substantial clinical benefit.

However, development of drugs that increase HDL-C levels has been challenging and fraught with failures, including the premature termination of

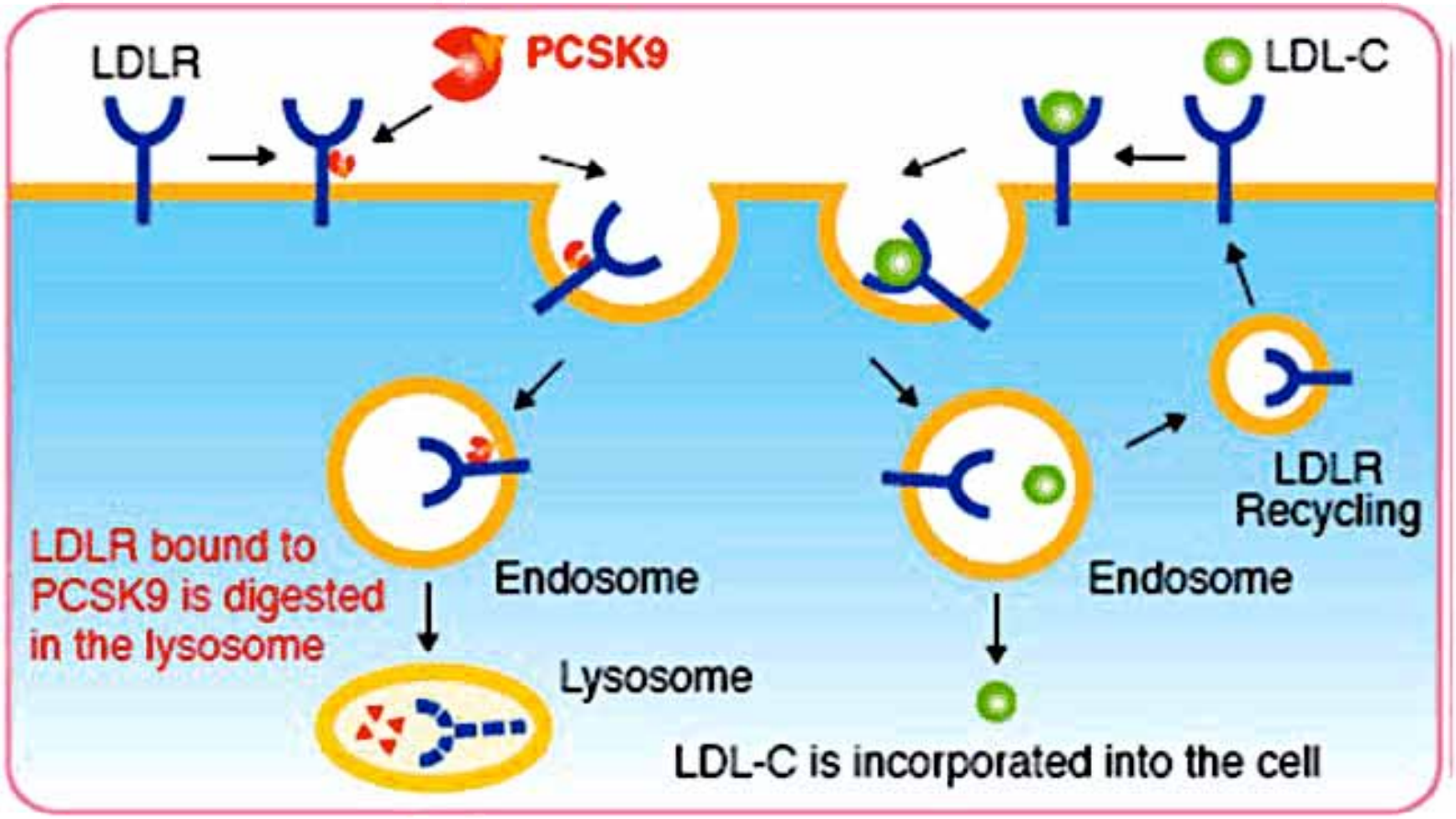
in greater reductions in LDL-C ($P<.001$) but no greater increase in HDL-C ($P=.39$). Although the study was underpowered, no adverse effects were observed.

Conclusions Compared with placebo or statin monotherapy, evacetrapib as monotherapy or in combination with statins increased HDL-C levels and decreased LDL-C levels. The effects on cardiovascular outcomes require further investigation.

Trial Registration clinicaltrials.gov Identifier: NCT01105975

PCSK9

Proprotein convertase subtilisin/kexin type 9



Inhibition of PCSK9 will prevent PCSK9-mediated down regulation of the LDL receptor with improving LDL-C clearance & reducing LDL-C level.

GAUSS Results

JAMA 2012;308:2497-506

Phase 2 study

Statin-intolerant patients (n=160)

Randomized to 5 groups

12-weeks treatment (SQ injection per 4 weeks)

Outcome	AMG-145 280mg	AMG-145 350mg	AMG-145 420mg	AMG-145 280mg + Ezetimibe	Ezetimibe alone
Δ in LDL from baseline (%)	-41	-43	-51	-63	-15
Patients reaching LDL goal of <100mg/dL (%)	47	53	61	90	7
Patients reaching LDL goal of <70mg/dL (%)	9	17	29	62	0

RUTHERFORD Results

Circulation 2012;126:2408-17

Phase 2 study

Heterozygous familial-hypercholesterolemia patients (n=168)

Randomized to 3 groups

12-weeks treatment (SQ injection per 4 weeks)

Outcome	AMG-145 350mg	AMG-145 420mg	Placebo
Δ in LDL from baseline (%)	-43	-55	+1
Patients reaching LDL goal of <100mg/dL (%)	70	89	2
Patients reaching LDL goal of <70mg/dL (%)	44	65	0

RN-316 Results

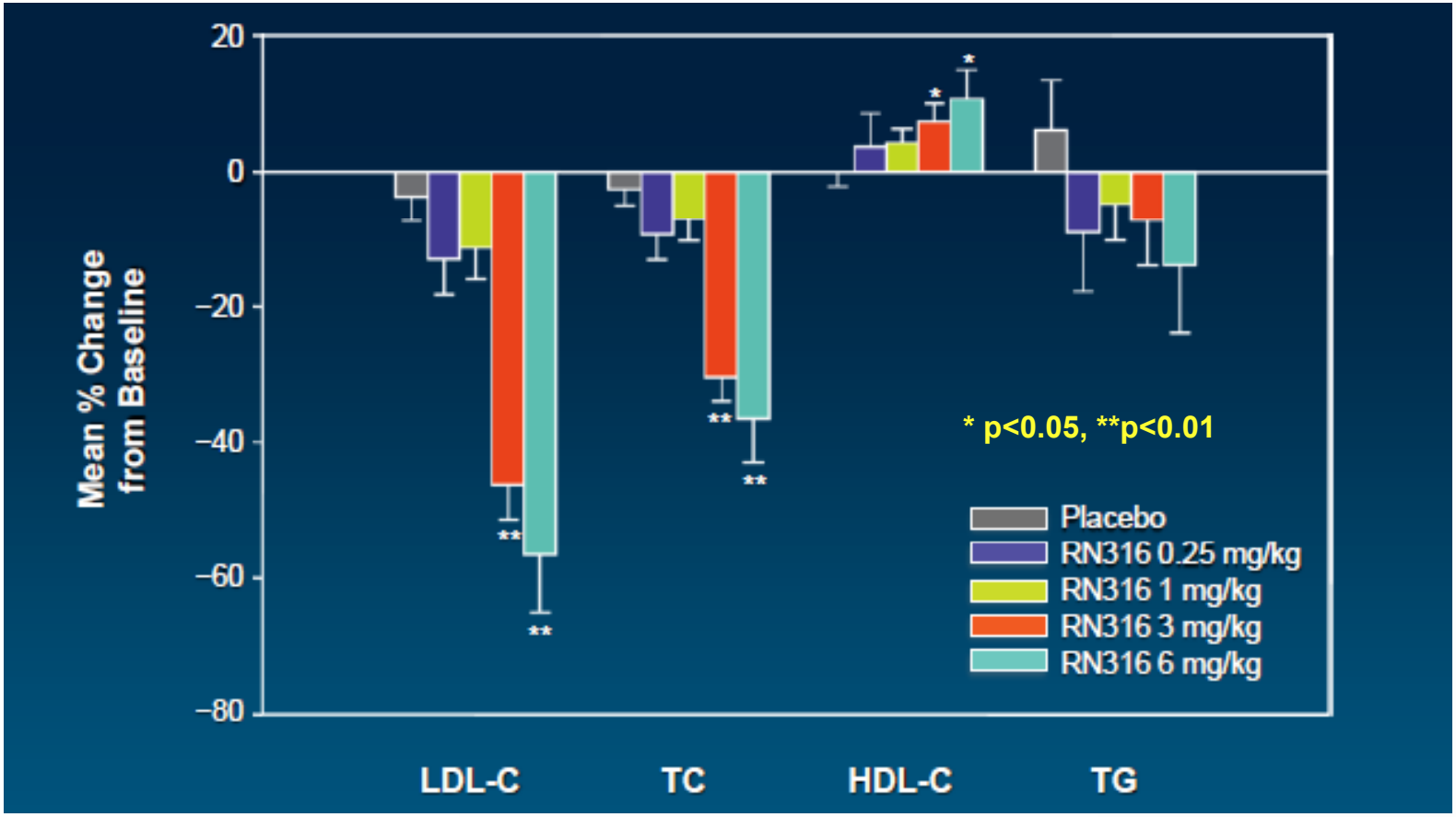
AHA Scientific Session, Los Angeles, 2012

Phase 2 study

Primary hypercholesterolemia patients on high or maximum dose of statins (n=136)

Randomized to 5 groups (Placebo and four-dose RN-316 groups)

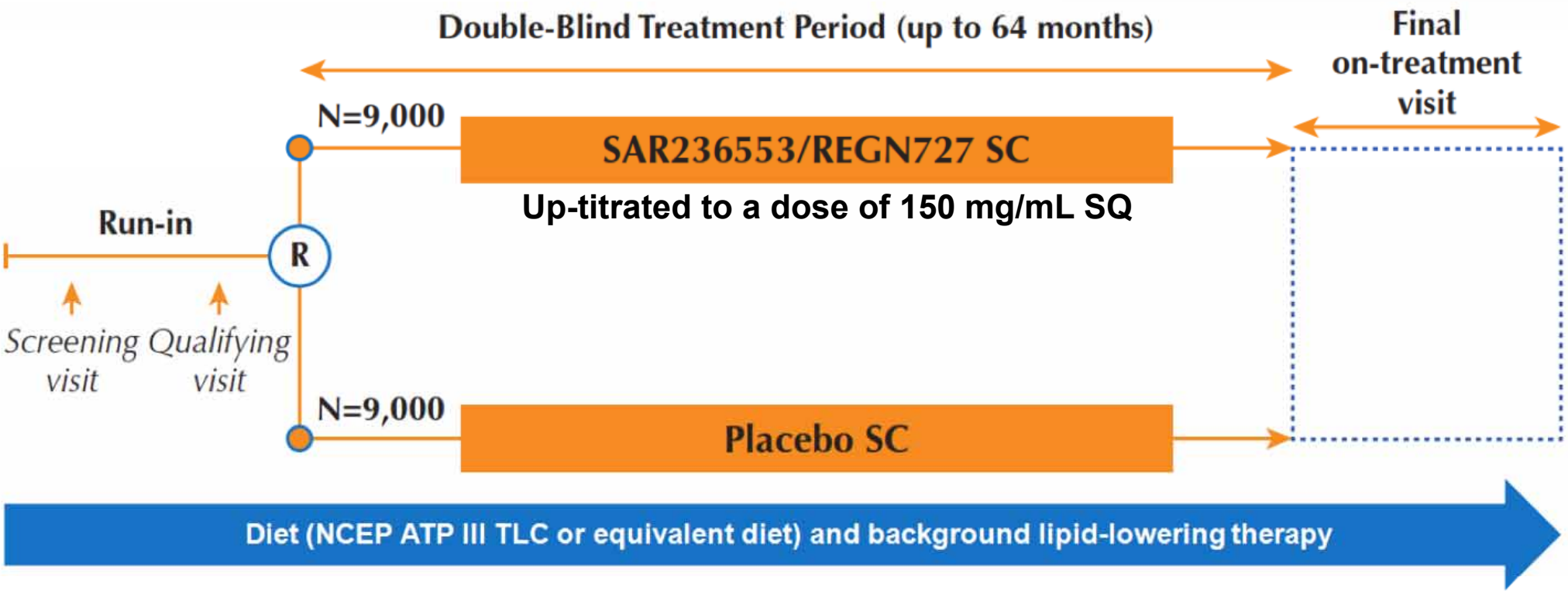
12-weeks treatment (IV injection per 4 weeks)



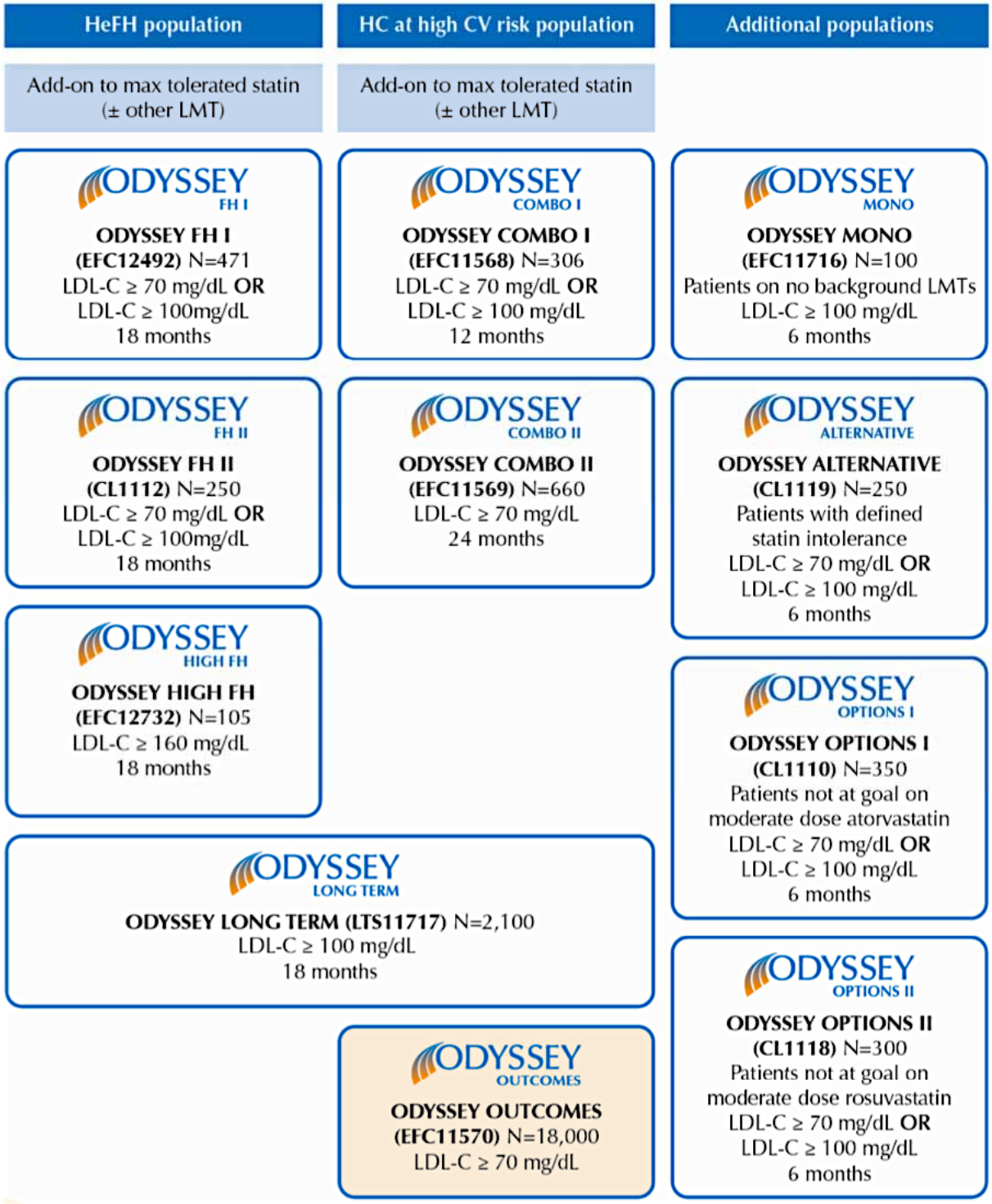
ODYSSEY OUTCOMES Design

www.clinicaltrials.gov/ct2/show/NCT01663402

- Phase 3 study
- Patients with a recent acute coronary event (n=18,000)
- Double-blinded, randomized, placebo controlled, parallel-group (SQ injection per 2 weeks)
- Testing SAR236553/REGN727 in reducing CV events



SAR236553/REGN727



However, we have to wait for concrete beneficial evidences for CV outcome with safety!!!

Summary

- Based on the epidemiological relationship between CVD and LDL-C, and abundant 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 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 ezetimibe, niacin, or fibrate can be an option to reduce residual CV risk, however, almost all of these studies have been failed to show benefit.

- Many studies for emerging therapies are on the process. However, there are definite prerequisites for accepting them such as long-term efficacy & safety profiles, immune effects, and, most importantly, CV outcome efficacy.

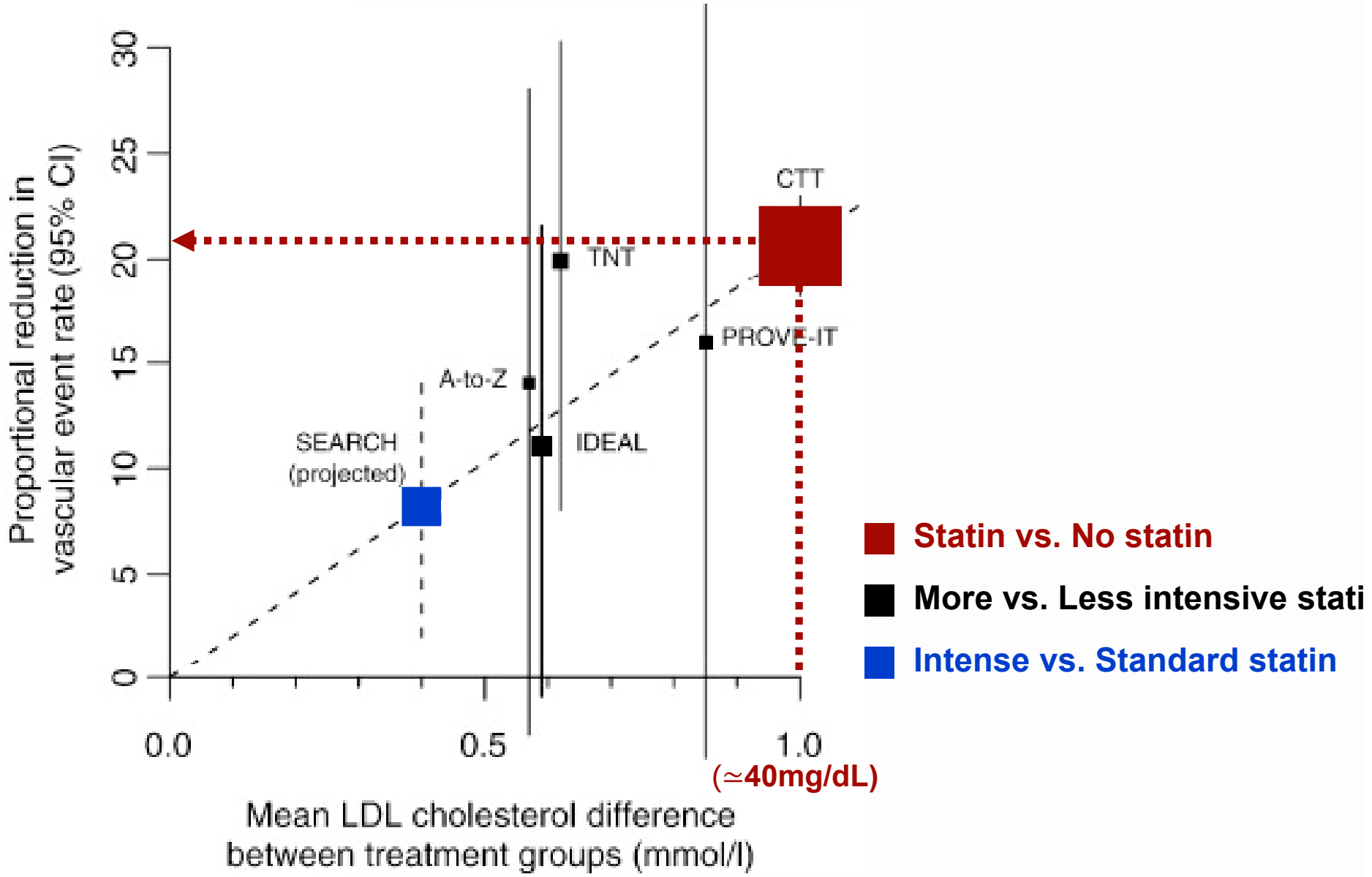
Need for Additional Emerging Targets?


Still it's too early to look for other targets...
BACK to BASICS
...and wait concrete evidences of long-term efficacy and safety in on-going and future trials
...and focus on ultimate goal for lipid management!
Still
STATIN!!!


THANK YOU FOR YOUR ATTENTION !
THE LORD OF THE RINGS
THE RETURN OF THE KING
THE JOURNEY ENDS DECEMBER 17TH
KEYWORD: LORD OF THE RINGS WWW.LORDOFTHERINGS.NET
© MMIII NEW LINE PRODUCTIONS, INC. THE LORD OF THE RINGS, AND THE NAMES OF THE CHARACTERS, EVENTS, ITEMS, AND PLACES THEREIN, ARE TRADEMARKS OF THE SAUL ZAENTZ COMPANY D/B/A TOLKIEN ENTERPRISES UNDER LICENSE TO NEW LINE PRODUCTIONS, INC. ALL RIGHTS RESERVED.

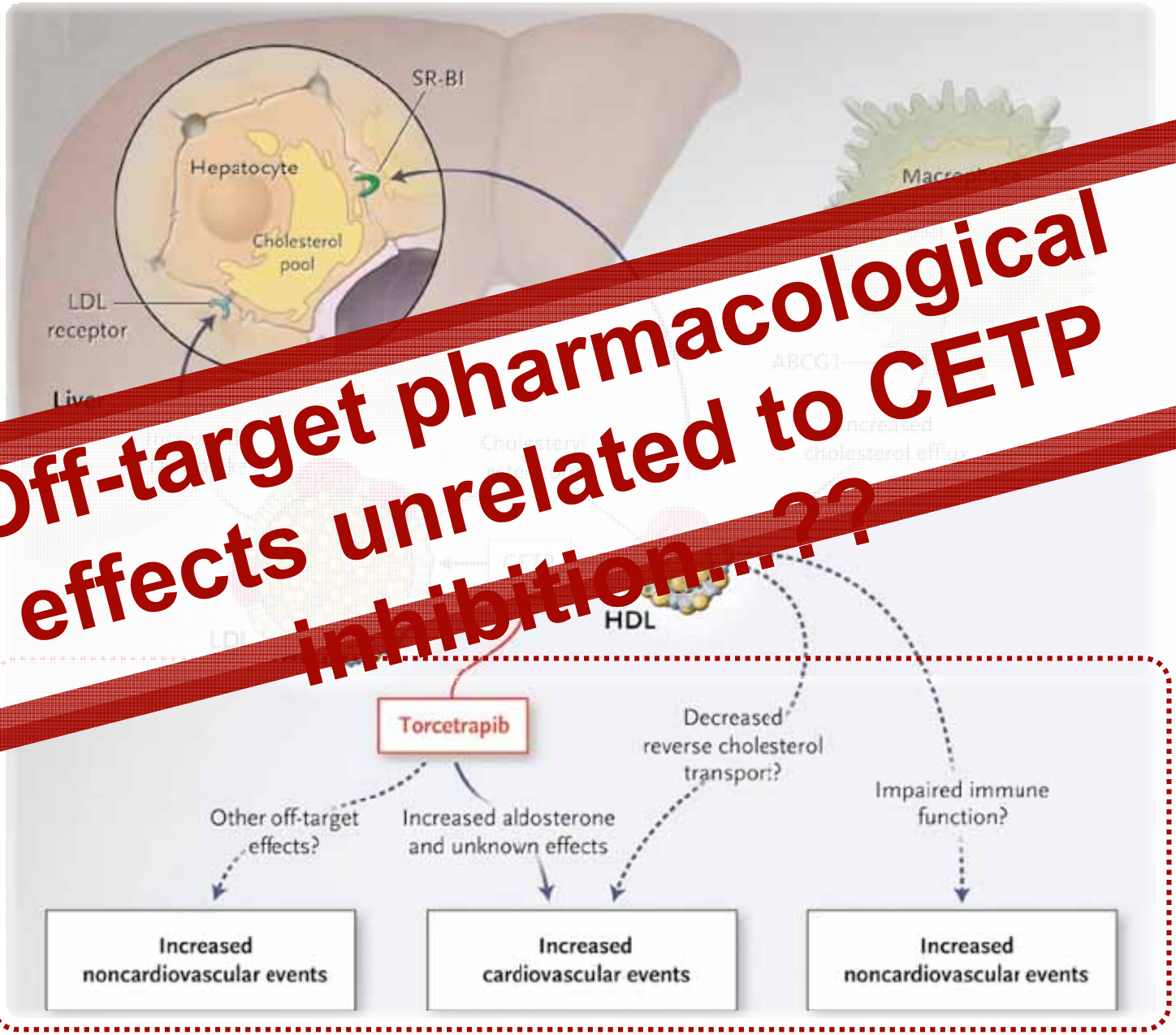
Relation between Proportional Reduction in Vascular Event Rate & Mean Absolute LDL-C Difference

Am Heart J 2007;154:815-23



ILLUMINATE

N Engl J Med 2007;357:2109-22



Off-target pharmacological effects unrelated to CETP inhibition...??