State of the Art 2011: Intensive Lipid Lowering

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TIMI

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HARVARD MEDICAL SCHOOL
TEACHING AFFILIATE

Cardiovascular Disease the Most Common Cause of Death in US and now <u>also Worldwide</u>

- **GOOD: Use of aspirin, statins and other proven therapies + reduction in smoking has ↓ CV mortality 29% in the past decade**
- **BAD: More obesity, diabetes, physical inactivity**
  - **1/3 deaths in the US are due to CVD**
  - **½ of CV deaths are due to coronary heart disease (CHD)**
  - **1.5 million myocardial infarctions in the US in 2009**
- **Every 25 seconds an American will have a coronary event resulting in one death / minute**
- **2010 costs for CVD $503.2 billion (Cancer $228B) in US**
- **16.7 million CV deaths worldwide (2009 est)**

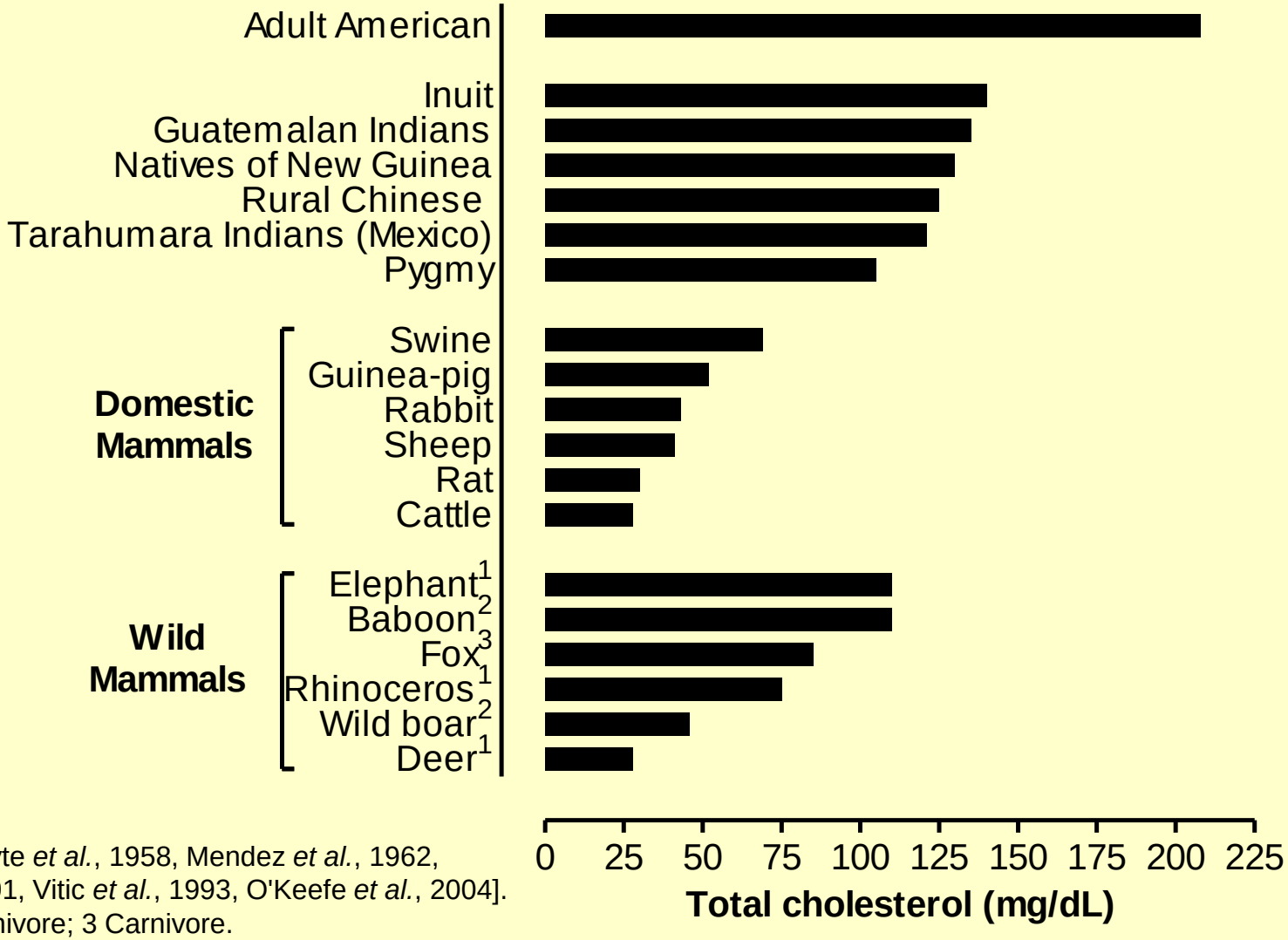
LLoyd-Jones et al. *Circulation.* 2010;121:e1-e170.

Therapeutic Advances in Cardiovascular Disease

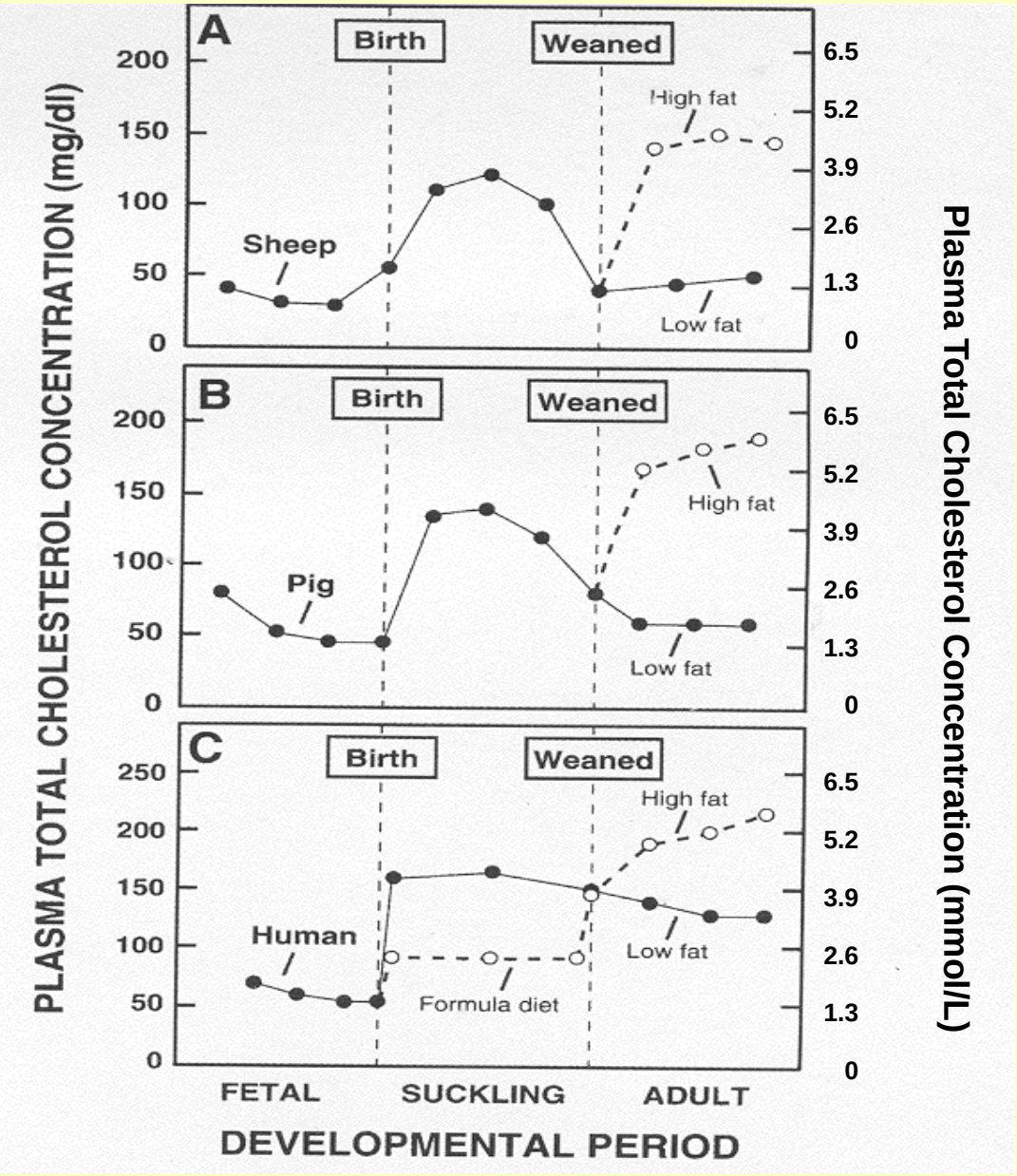
Ther Adv Cardiovasc Dis
(2010) 4(3) 185–191
DOI: 10.1177/1753944710368206

Lipid lowering goals: back to nature?

Willibald Hochholzer and Robert P. Giugliano



Adapted from [Whyte *et al.*, 1958, Mendez *et al.*, 1962, McMurry *et al.*, 1991, Vitic *et al.*, 1993, O'Keefe *et al.*, 2004].
1 Herbivore; 2 Omnivore; 3 Carnivore.



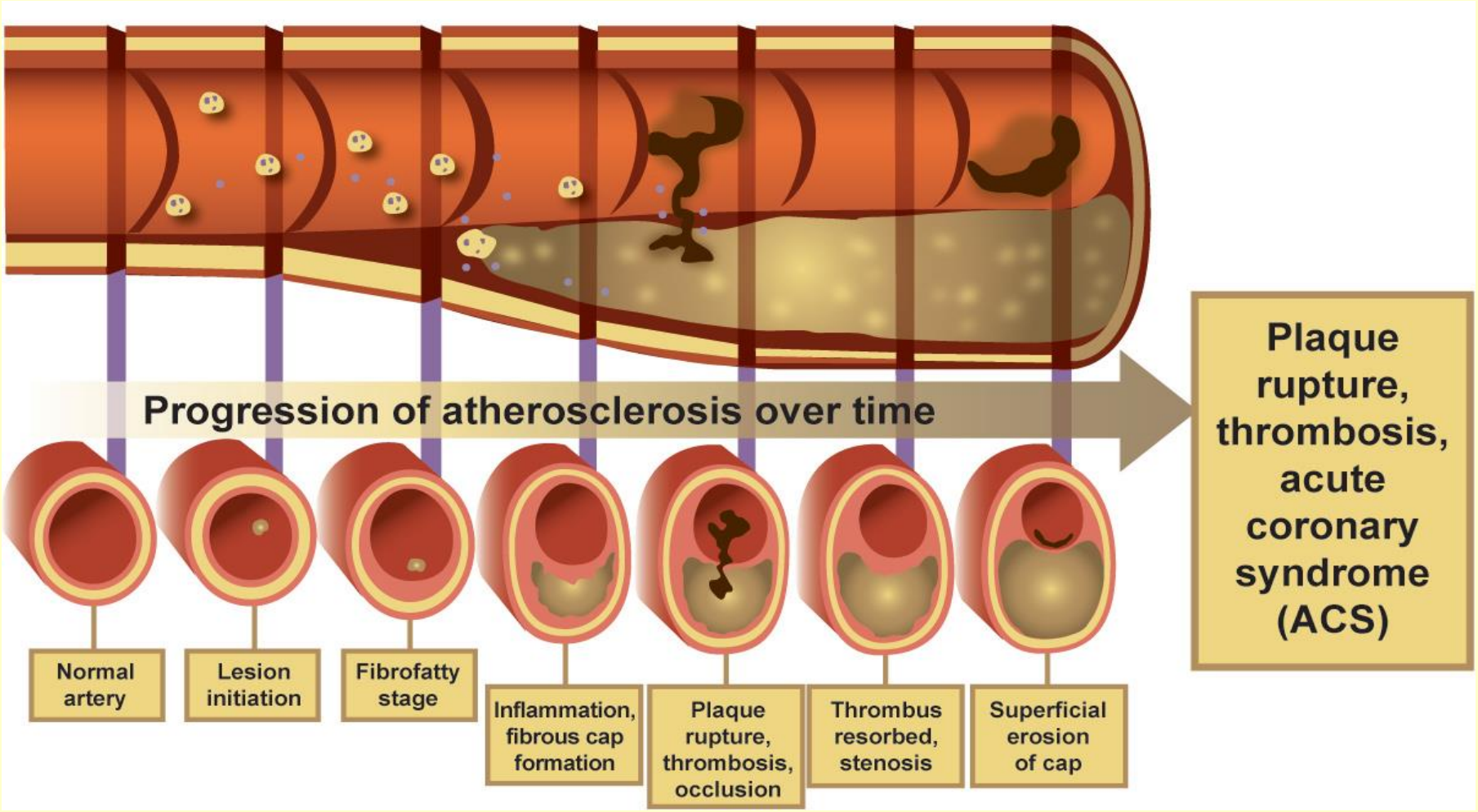
Cholesterol levels: what is normal?

- OLD NEWS: Normal lipid levels are primarily determined by diet
- Just prior to birth, human TC is ~ 60 mg/dL
- On breast milk, TC rises to ~ 170 (LDL 100)
- WHY? → Breast milk provides 18 mg chol/d/kg and infant synthesizes 25 mg/d/kg (ingestion rate ~ 70% of synthesis rate).
- Infants on a low cholesterol synthetic formula (2 mg/d/kg = 8% of synthesis rate) see an LDL-C rise by only 40 mg/dL
- After weaning, animals' TC and LDL-c fall dramatically, but humans' LDL, because of a much higher cholesterol and fat intake don't
- Some cultures have diets with < 100 mg/d chol. Their LDLs are < 75. These cultures have virtually no CAD
- Japanese Zen monks have virtually no animal products in diet and LDL = 70 mg/dL

Dietschy JM J Lipid Res 2004:1375-97

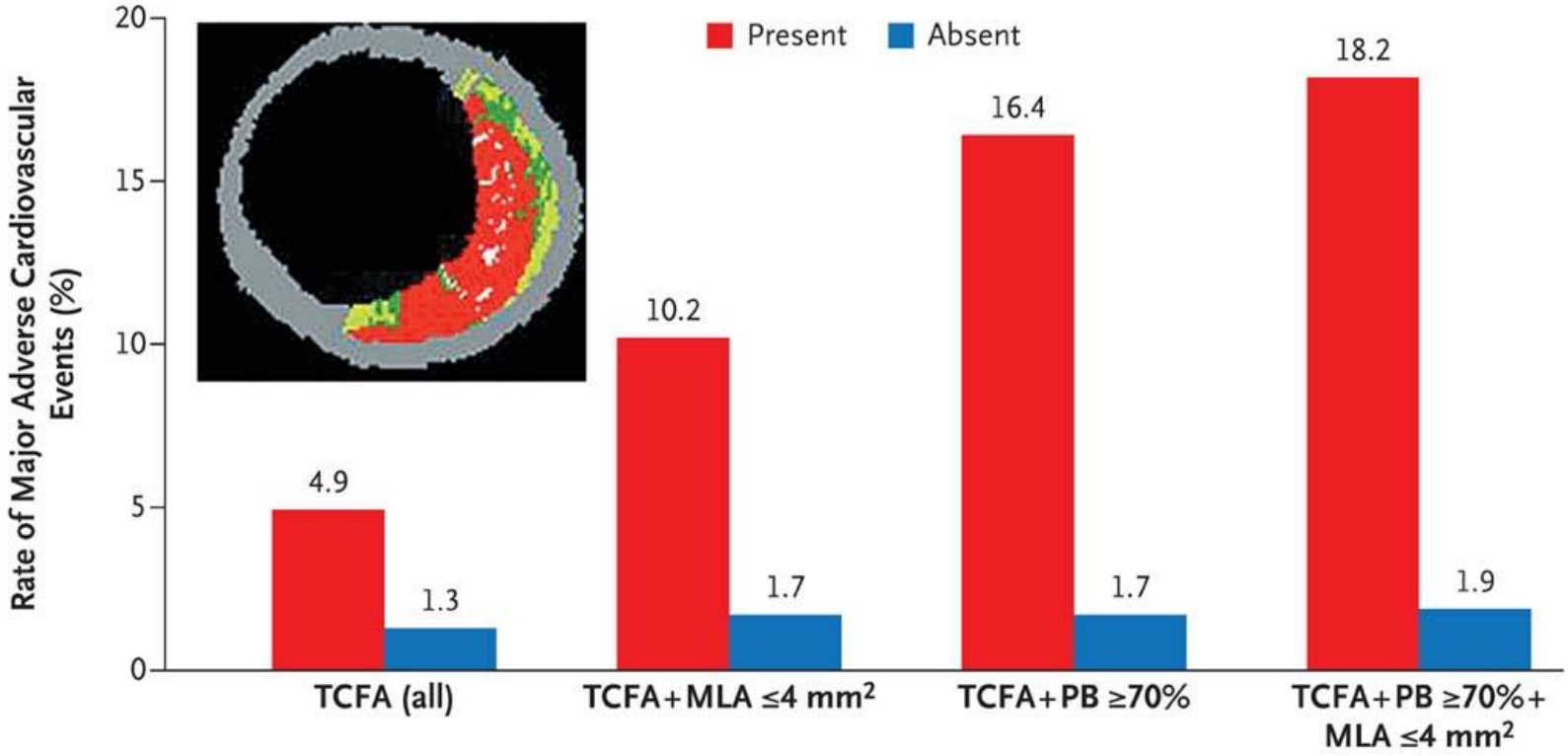
Atherosclerosis, Atherothrombosis, and Plaque Rupture

Major Risk Factors: Cholesterol, smoking, DM, HTN, FHx CAD



Adapted from Libby P. *Circulation.* 2001;104;365-372.

Danger Lurking Below –
High-risk "Non-Culprit" lesion



Lesion hazard ratio (95% CI)	3.90 (2.25–6.76)	6.55 (3.43–12.51)	10.83 (5.55–21.10)	11.05 (4.39–27.82)
P value	<0.001	<0.001	<0.001	<0.001
Prevalence (%)	46.7	15.9	10.1	4.2

Stone GW. NEJM 2011:364:226-35

Diet and Lifestyle Interventions to Lower LDL-C

RECOMMENDED

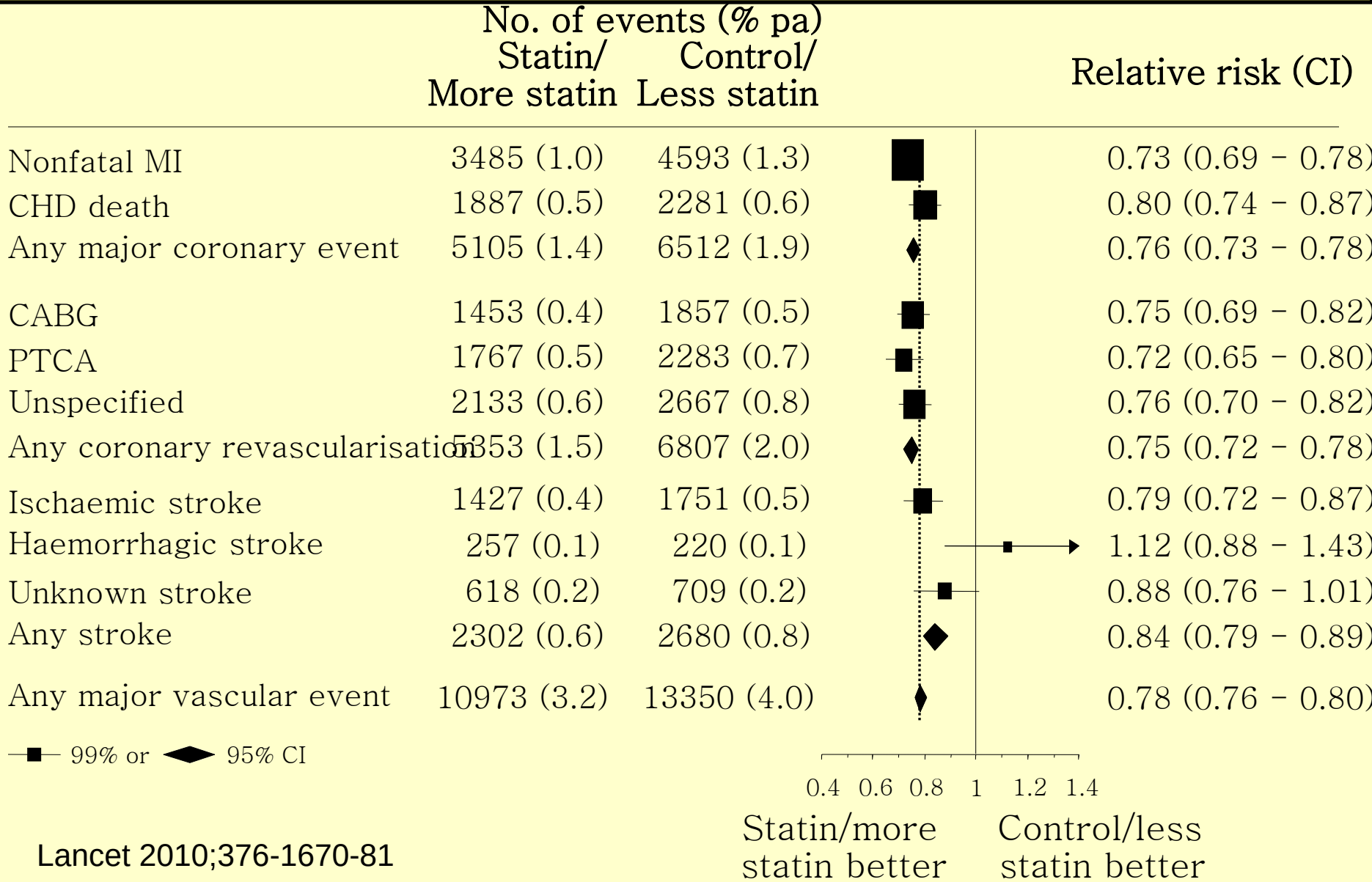
- Dietary Interventions (~10% lowering)
  - Saturated fat <7% of calories
  - <200mg/d of dietary cholesterol
  - Plant stanol esters
- Physical Activity: 30 minutes day/5 days
- Weight Reduction

NOT RECOMMENDED

- Red yeast rice = low-dose lovastatin (additional ~15% lowering)

Key Lessons From Statin Trials (>160,000 pts)

LOWERING LDL REDUCES CV EVENTS

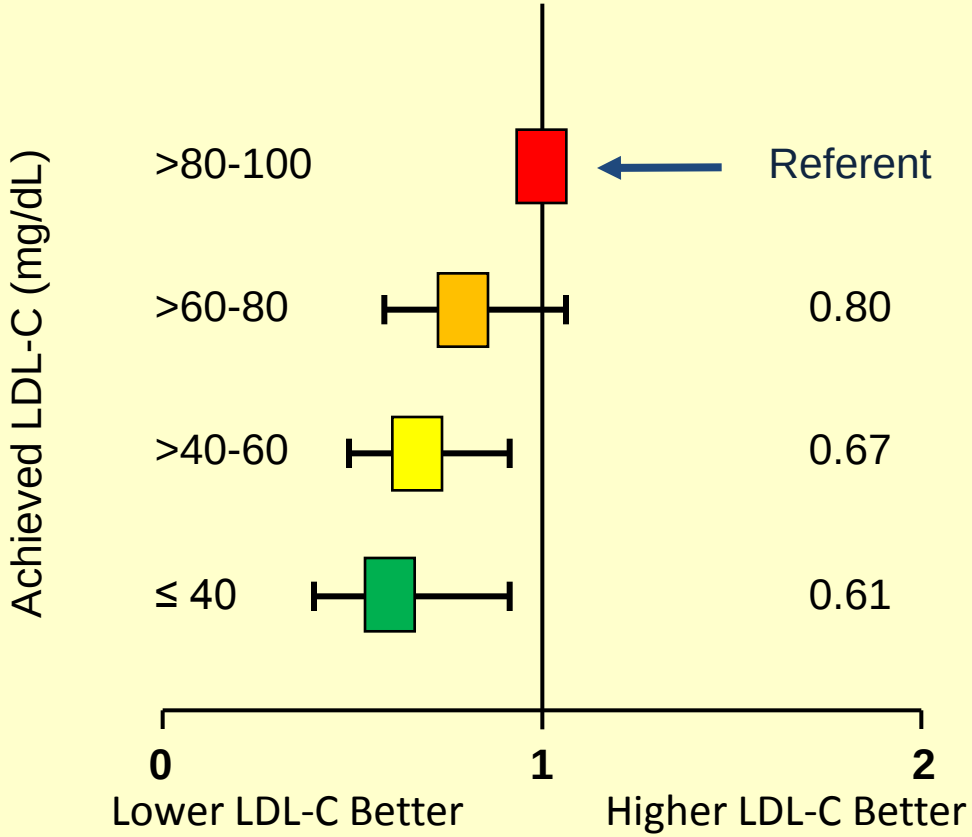


Lancet 2010;376-1670-81

Are Outcomes Better with Lower Achieved LDL-C?

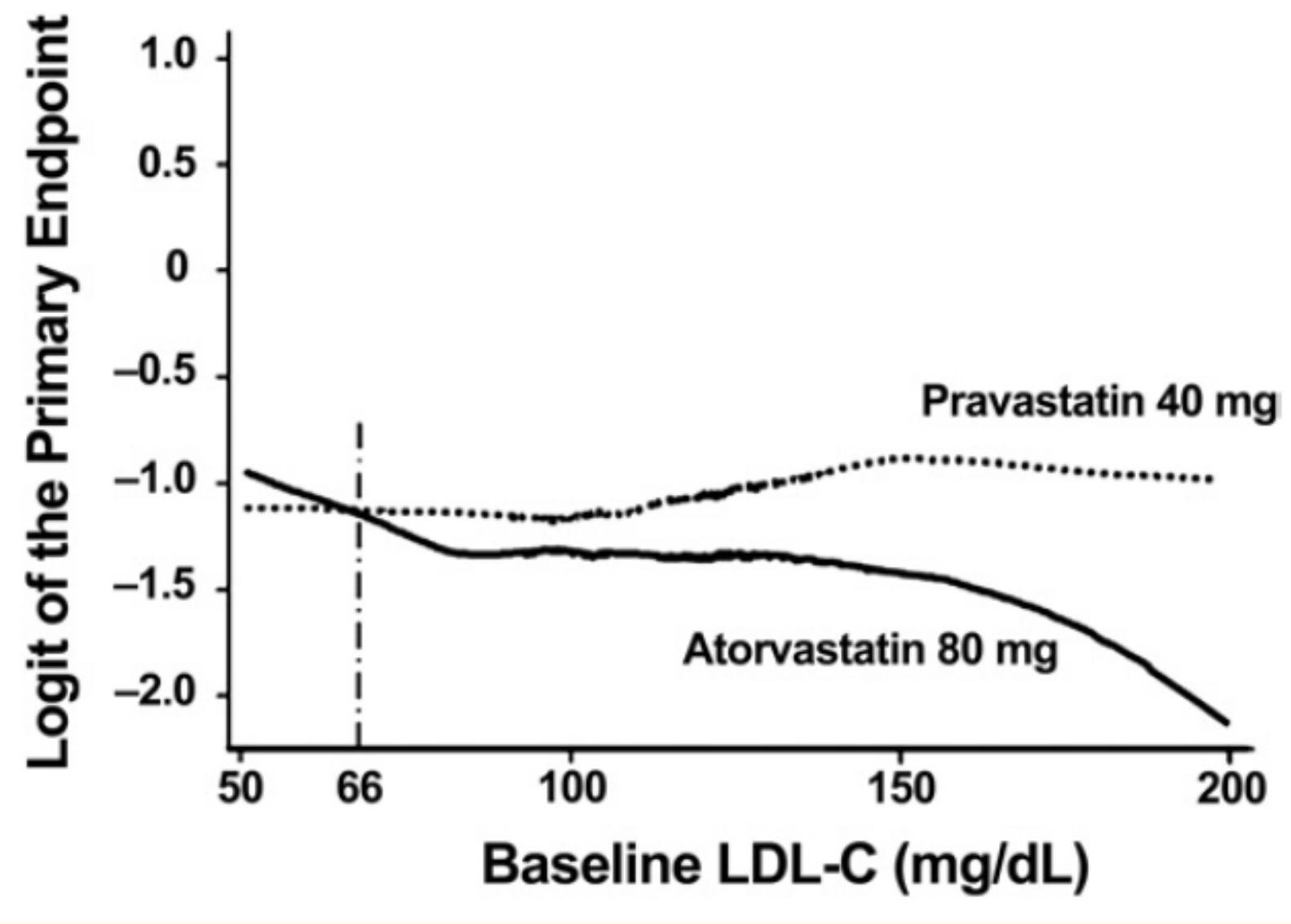
Hazard Ratio for Primary Endpoint (PROVE IT-TIMI 22)

Outcome/events: death, MI, stroke, revascularization and unstable angina requiring hospital admission



Wiviott SD, et al. *J Am Coll Cardiol.* 2005;46:1411-1416.

Benefit of High-Dose Statin in PROVE IT-TIMI 22 According to Baseline LDL-C



Giraldez RR, Giugliano RP et al. *J Am Coll Cardiol.* 2008:914–20

ATP III Update 2004: Pharmacologic Treatment

Risk Category	LDL-C Goal	Initiate TLC	Consider Drug Therapy
Very High risk: ACS, CHD w/DM, mult CRF	<70 mg/dL	≥70 mg/dL	≥ 70 mg/dL
High risk: CHD or CHD risk equivalents (10-year risk >20%)	<100 mg/dL (optional goal: <70 mg/dL)	≥100 mg/dL	≥ 100 mg/dL (<100 mg/dL: consider drug option)
Moderately high risk: 2+ risk factors (10-year risk 10% to 20%)	<130 mg/dL (optional goal < 100 mg/dL)	≥130 mg/dL	≥ 130 mg/dL (100-129 mg/dL: consider drug option)
Moderate risk: 2+ risk factors (risk <10%)	<130 mg/dL	≥130 mg/dL	≥ 160 mg/dL
Lower risk: 0-1 risk factor	<160 mg/dL	≥160 mg/dL	≥190 mg/dL

Adapted from Grundy, S. et al., *Circulation.* 2004;110:227-239.

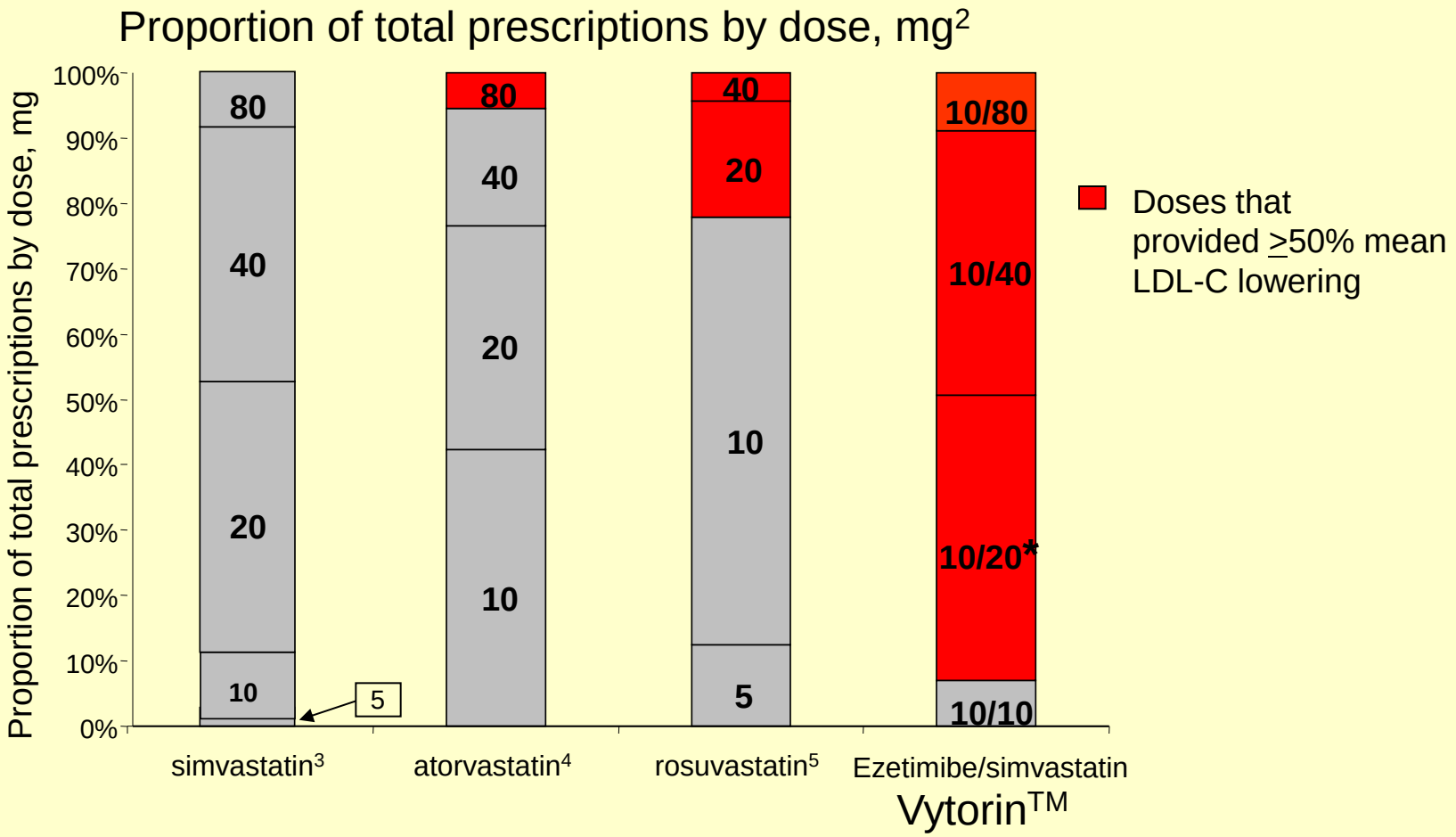
Dyslipidemia is Still Undertreated

AHA “Get With The Guidelines” Registry (2000-2006)

- 231,986 hospitalizations for an acute coronary event. Some *with* history or prior event, some *without* previous history
- 14.2% *without* a prior history of CAD were on lipid lowering medications
- 29% of patients *with* a prior history CAD were on lipid lowering medications

Sachdeva A et al. *Am Heart J.* 2009; 157:111-117.

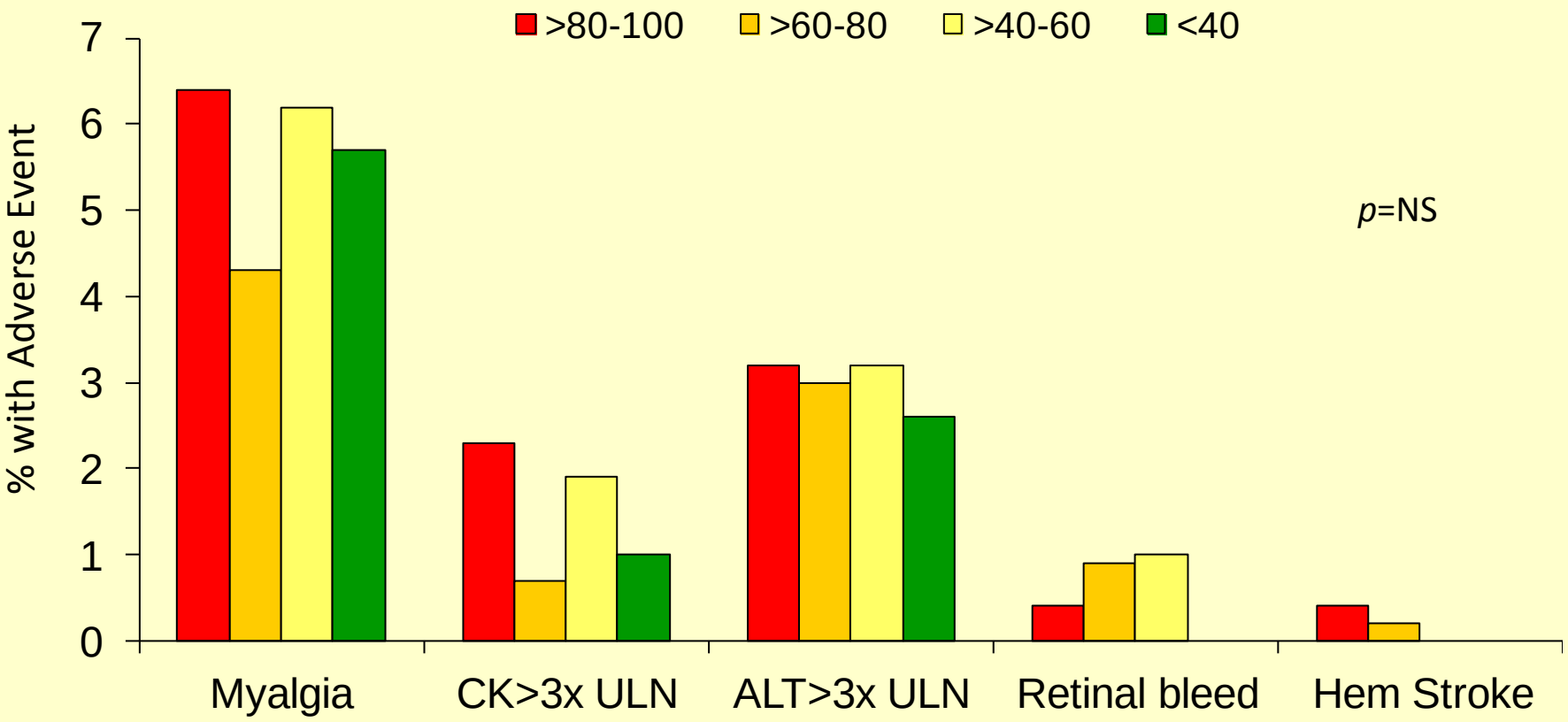
AHA/ACC Update: "… it generally is possible to achieve LDL-C reductions of >50% with either statins or LDL-C–lowering drug combinations"[1]



*Recommended usual starting dose of ezetimibe/simvastatin.

1. Smith SC Jr et al. *Circulation*. 2006;113:236–2372. 2. IMS Xponent TRx 4/06. 3. Bays et al. *Clin Ther*. 2004;26:1758–1773. 4. Ballantyne CM et al. *Am J Cardiol*. 2004;93:1487–1494, 5. Data available on request from Merck & Co., Inc., Professional Services-DAP, WP1-27, PO Box 4, West Point, PA 19486-0004. Please specify information package 20505499(3)-VYT.

Is it Safe to Achieve Low LDL-C Goals? PROVE IT-TIMI 22



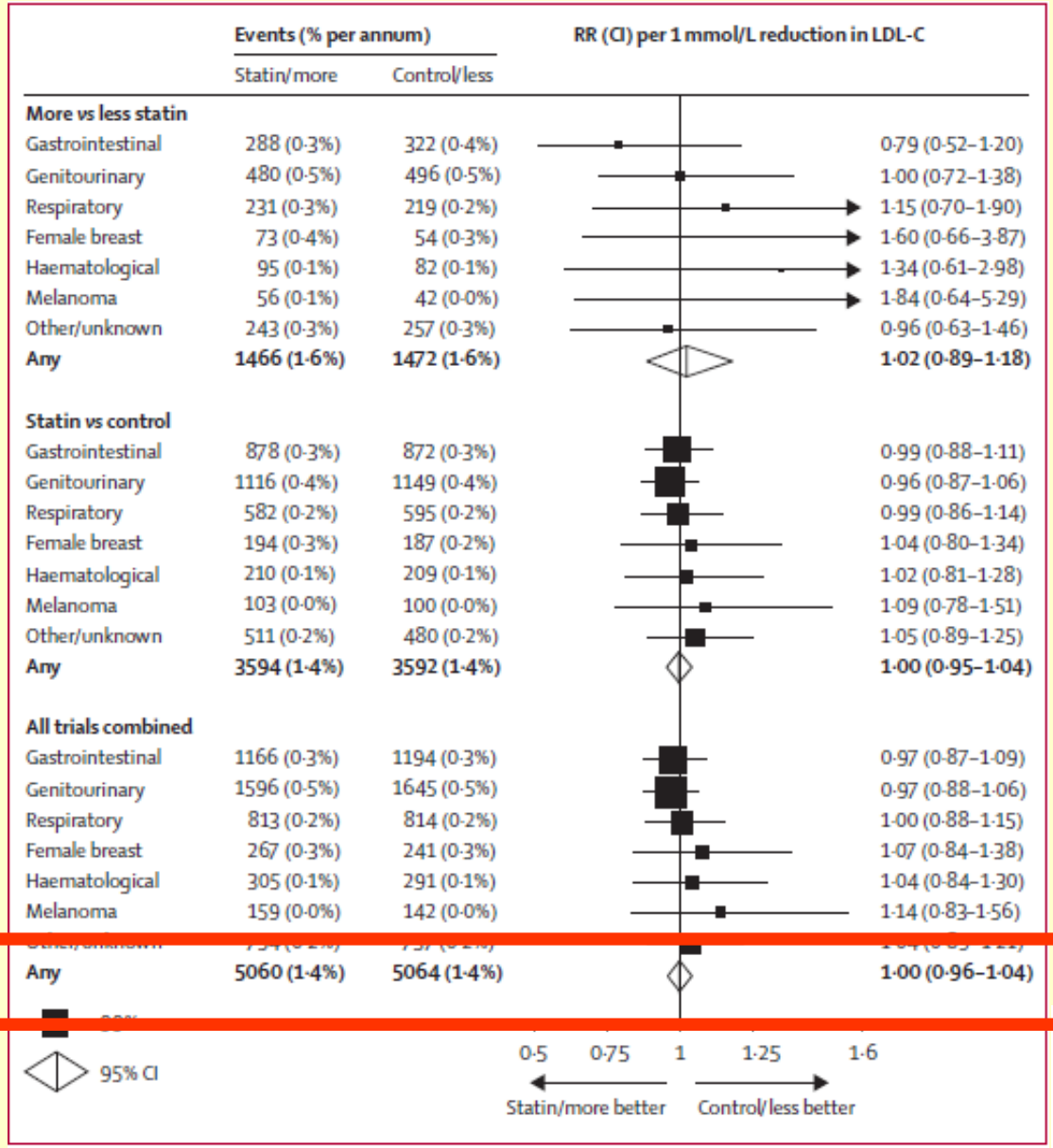
Wiviott SD et al. *J Am Coll Cardiol*. 2005;46:1411-1416.

Safety: Dose and Drug(s), Not the Achieved LDL-C are Critical Issues

- All statins show dose-related increases in liver function test (LFT) abnormalities
- Statins have different risks of myopathy
  - Simvastatin had a dose-related effect in A2Z and SEARCH
  - Atorvastatin did not in TNT
- Use caution with fibrates (esp gembrozil) + statins
- Avoid potent CYP 3A4 inhibitors (e.g., azole antifungals, macrolide antibiotics) with simvastatin, lovastatin
- Use lower dose simva/lovastatin with moderate CYP 3A4 inhibitors (e.g., amiodarone, verapamil, amlodipine)
- Use lower-doses of renally-cleared statins (simva, lova, prava, rosuva) in patients with renal failure

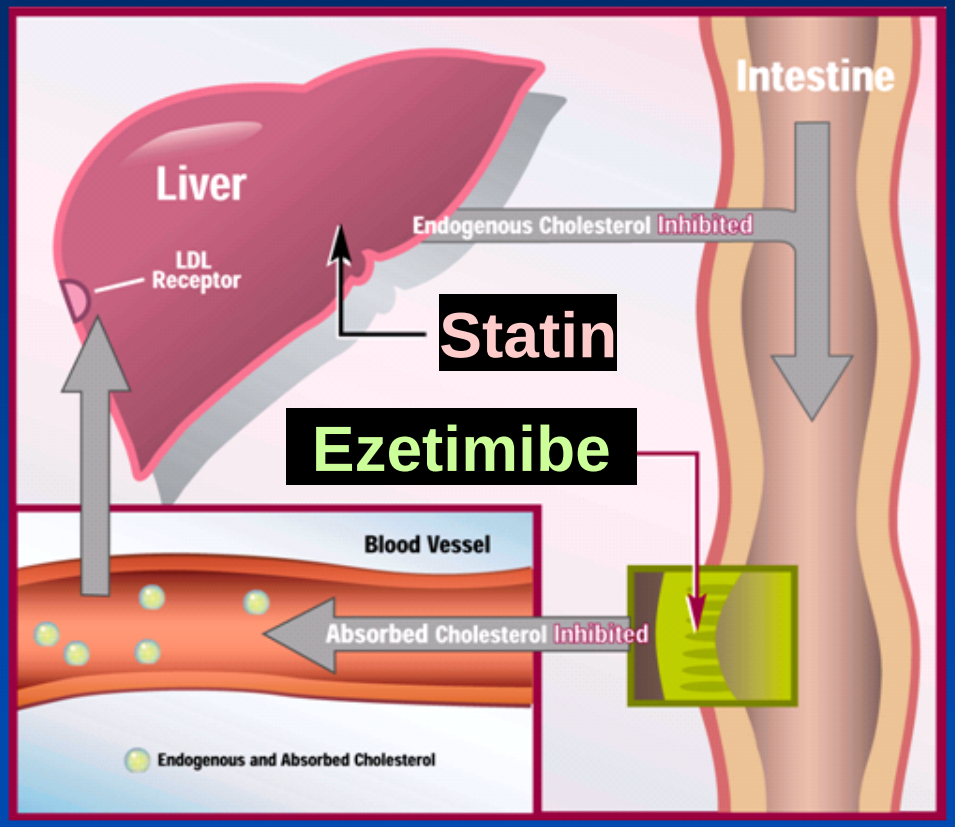
ATP III Final Report National Cholesterol Education Program, National Heart, Lung, and Blood Institute, National Institutes of Health. NIH Publication No. 02-5215 September 2002. deLemos JA et al. *JAMA. 2*004;292:1307-1316. Kashani A. et al. *Circulation*. 2006;114:2788-2797. Larosa T et al. *N Engl J Med* 2005;352. http://www.ctsu.ox.ac.uk/~search/results/search_release_091108.pdf Accessed Jan 21, 2010.

Cancer Incidence per 1 mM/L LDL Reduction in CTT Cycle #2 Metanalysis



CTT Collaborators
Lancet 2010;
376-1670-81

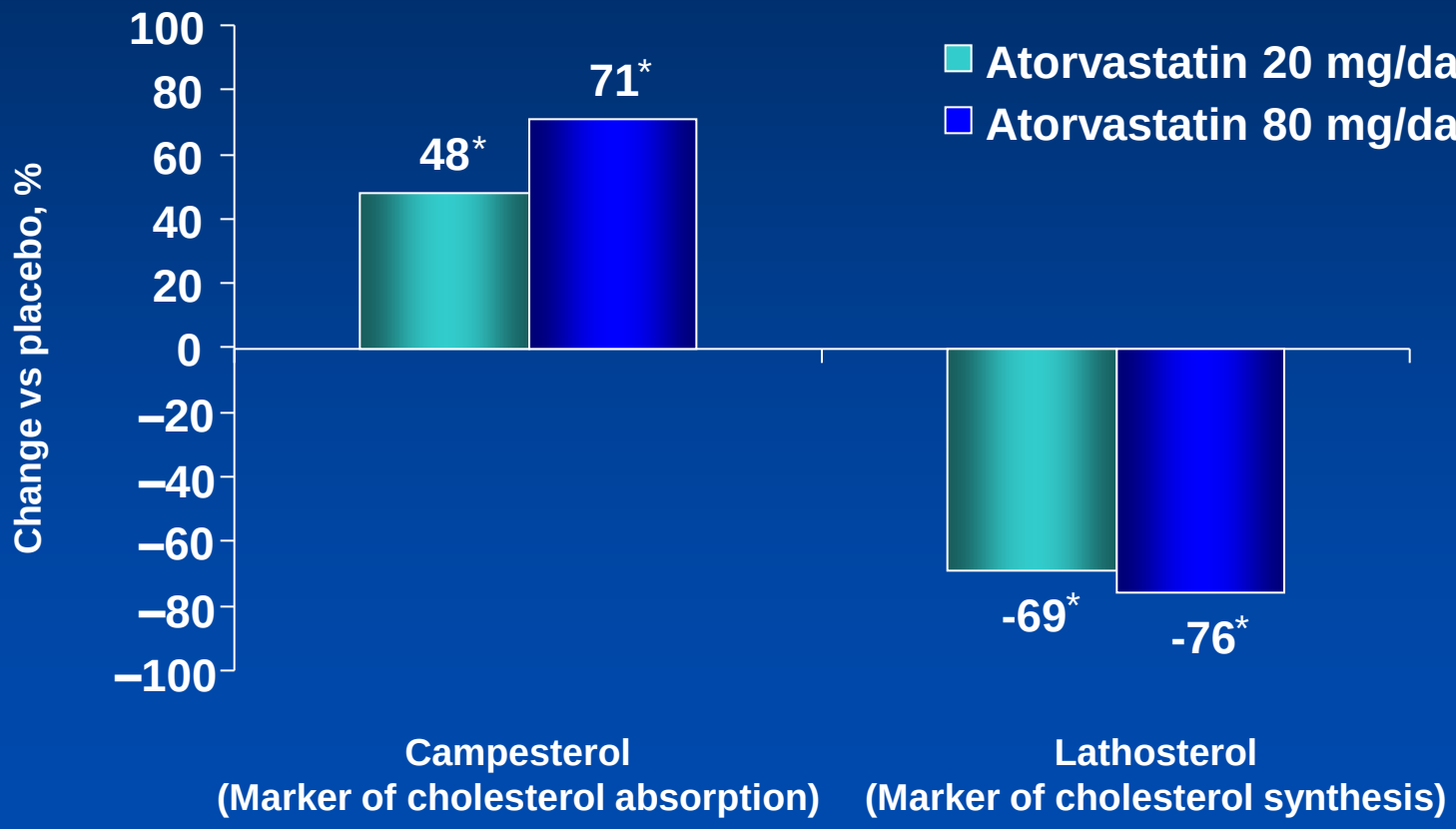
Dual Inhibition Approach: Attacking Cholesterol Production (statin) and Absorption (ezetimibe)



- Inhibit cholesterol *production* with a statin
  - Reduce cholesterol synthesis
  - Increase clearance of LDL-C from the blood via upregulation of LDL receptors
- Inhibit intestinal cholesterol *absorption* with ezetimibe
  - Ezetimibe localizes and appears to act at the brush border of the small intestine
  - 54% less cholesterol was absorbed compared with placebo in a clinical study
  - This action led to a reduction in hepatic cholesterol stores, increasing clearance of cholesterol from the blood

Statins: A Decrease in Markers of Cholesterol Synthesis Was Associated With an Increase in Markers of Cholesterol Absorption

- Crossover study of hypercholesterolemic patients administered atorvastatin for 8 weeks



*P<0.005 vs placebo

Lamon-Fava S et al. *J Lipid Res*. 2007;48:1746–1753.

Study Design

18,057 Patients stabilized post ACS ≤ 10 days
LDL ≤ 125*mg/dL (or ≤ 100mg/dL if prior lipid-lowering Rx)**

Double-blind

ASA + Standard Medical Therapy

Simvastatin 40 mg

Eze/Simva 10/40 mg

Follow-Up Visit Day 30, Every 4 Months

*3.2mM
**2.6mM

Duration: Minimum 2 1/2 year follow-up (5250 events)

Primary Endpoint: CV Death, MI, Hospital Admission for UA, revascularization (> 30 days after randomization), or Stroke

Cannon CP et al, Am Heart J 2008;156:826-32

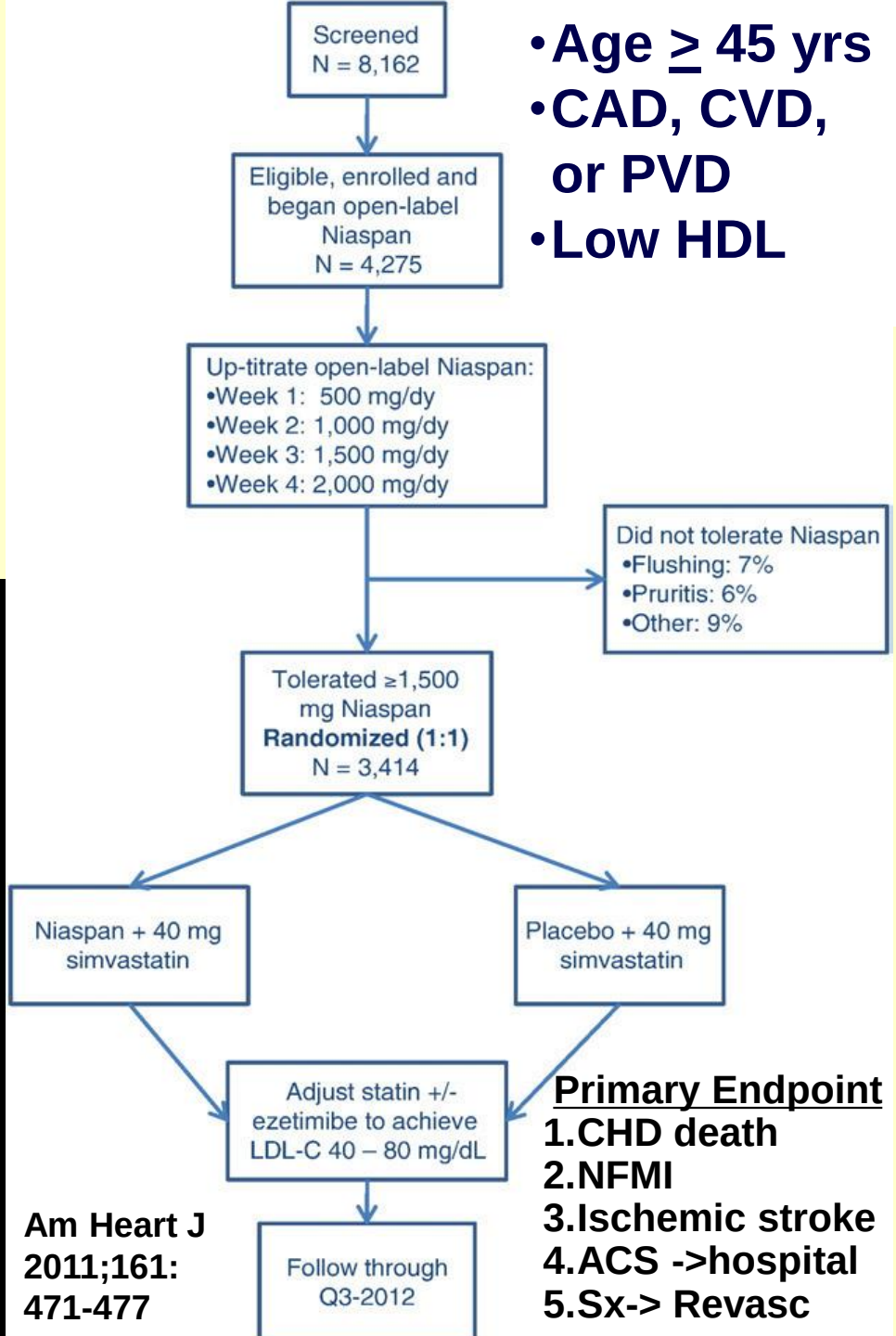
AIM-High:

Niacin in Patients with Established Vascular Disease and Athero-genic Dyslipidemia

SHOCKING NEWS 4/25/11

- DSMB stopped trial early
- "Futility" cited as reason
- 1º EP 5.6% placebo v. 5.8% niacin
- Niacin↑stroke (1.6% v 0.7%)
- Niacin↑HDL 20%, ↓ TG 25%

Bowden W, *NEJM* 2011



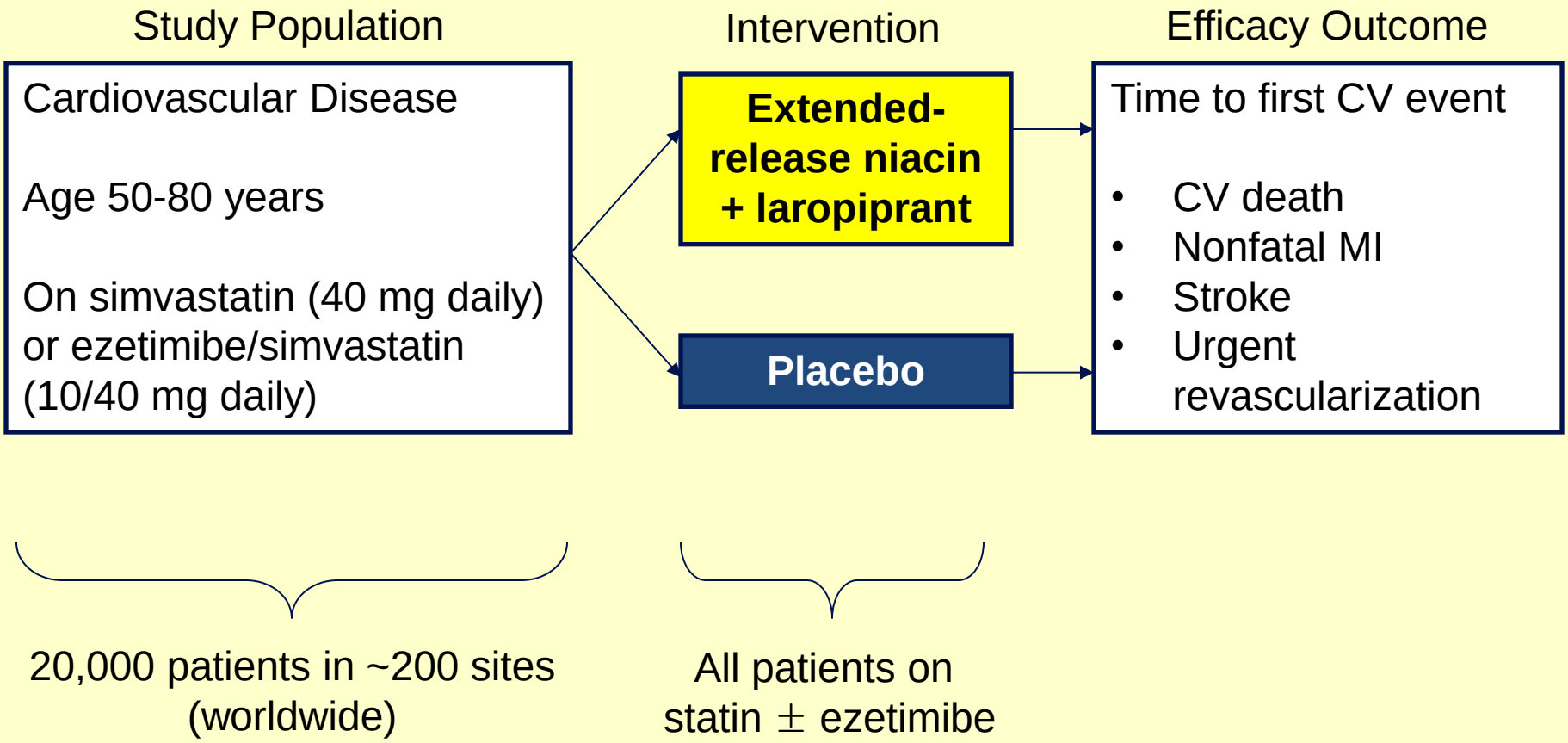
- Age ≥ 45 yrs
- CAD, CVD, or PVD
- Low HDL

Am Heart J 2011;161: 471-477

Primary Endpoint

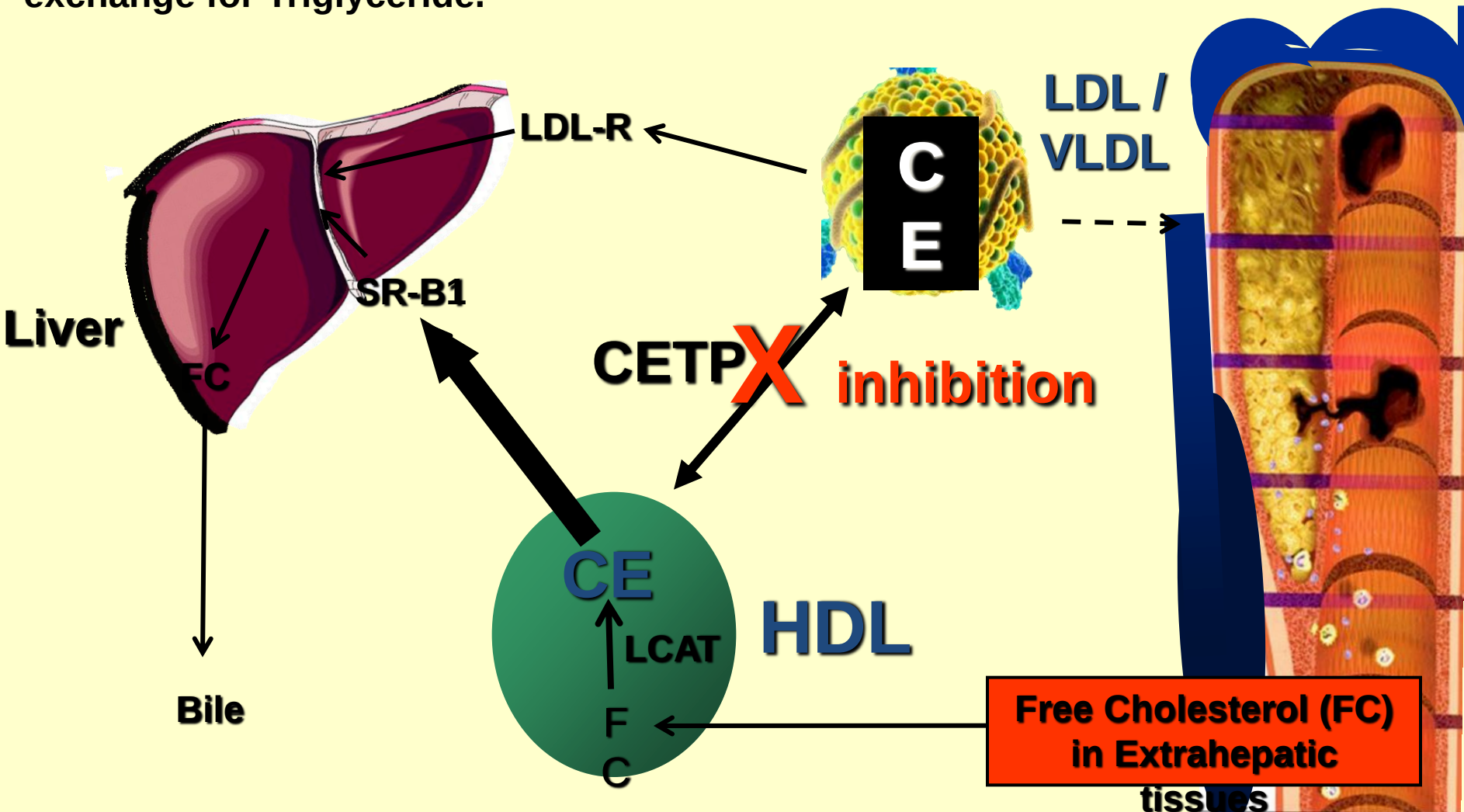
1. CHD death
2. NFMI
3. Ischemic stroke
4. ACS ->hospital
5. Sx-> Revasc

HPS2-THRIVE Trial Design



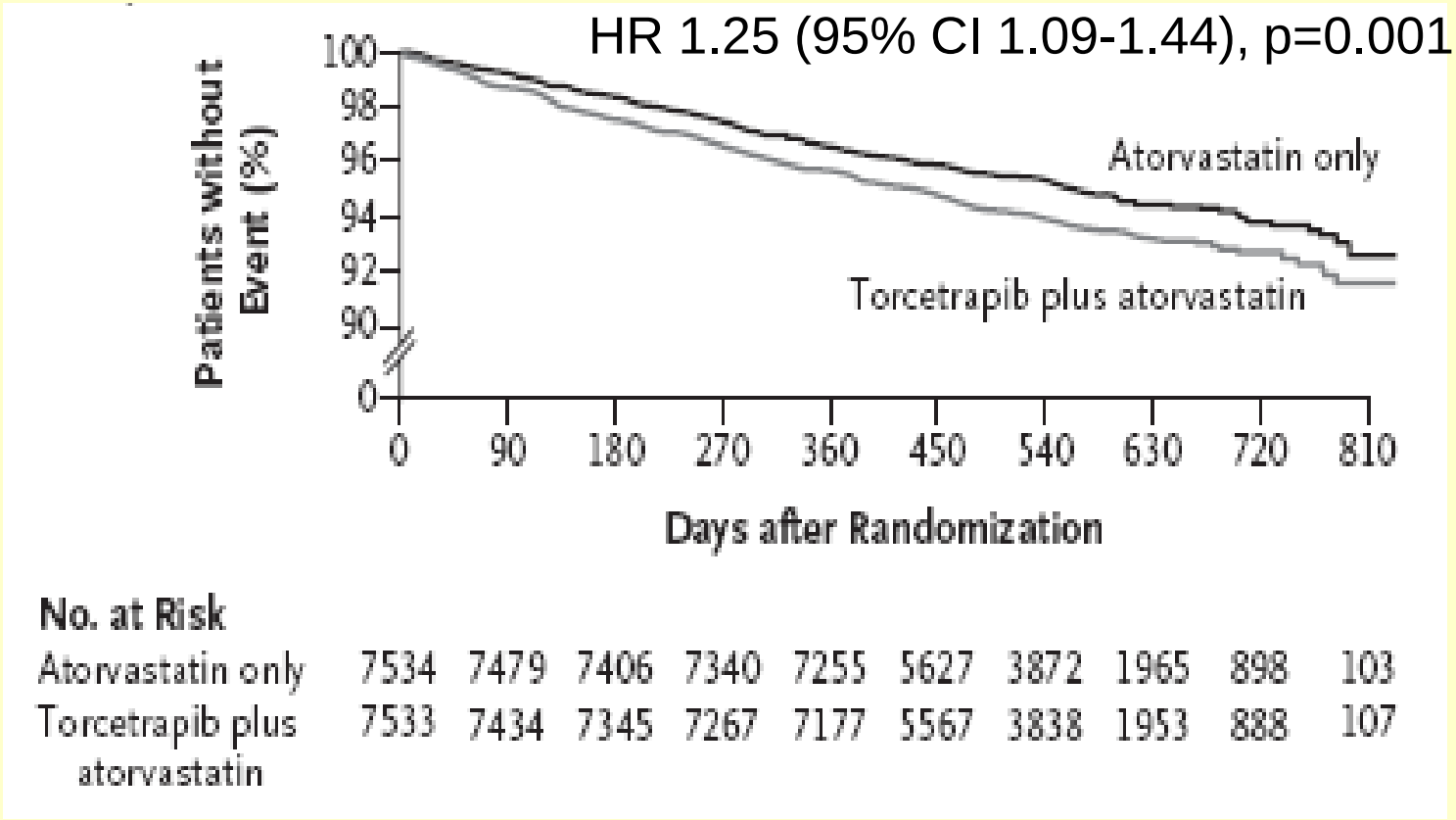
Background: CETP inhibition

Cholesteryl ester transfer protein (CETP) is a plasma protein that catalyzes the transfer of CE from HDL to apoB-containing lipoproteins (VLDL and LDL-C) in exchange for Triglyceride.



ILLUMINATE: Torcetrapib

15,067 high-risk patients on atorvastatin
LDL-cholesterol <2.5 mmol/l (100 mg/dL)
Randomized: torcetrapib 60mg vs placebo
At 12 months: 72%↑ HDL-c, 25%↓ LDL-c



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

CETP Inhibitors

	Torcetrapib	Dalcetrapib	Anacetrapib	
	60 mg daily	600 mg daily	40 mg daily	150 mg daily
Total cholesterol	**4%**	**n/a**	**1%**	**3%**
LDL-cholesterol	**-24%**	**-4%**	**-27%**	**-40%**
Triglycerides	**-9%**	**-3%**	**-11%**	**-11%**
Apolipoprotein B	**-12%**	**n/a**	**-20%**	**-29%**
HDL-cholesterol	**61%**	**25%**	**86%**	**139%**
Apolipoprotein A1	**25%**	**10%**	**32%**	**47%**
	Illuminate NEJM 2007	Dal-OUTCOMES Apr 2013	REVEAL HPS3-TIMI 55 2017	

PCSK9 (Paraprotein convertase subtilisin/kexin type 9)

- Paraprotein converters are proteolytic enzymes that activate precursor proteins into biologically active forms
- PCSK9 plays important role in degrading LDL-receptor (LDL-R)
- Both gain of function and non-sense mutations of PCSK9 exist
- ↓PCSK9 -> ⇑LDL-R -> lower LDL-C levels
- Single IV injection can achieve LDL-C reductions >60% lasting 2-4 weeks*

* Swergold G, AHA 2010 and AHA 2011(REGN727/SAR236553),
* Dias C, AHA 2011 (AMG 145)

Conclusions

- **Cardiovascular disease remains the *leading* cause of *death* in the United States and now worldwide**
- **Traditional risk factors, such as dyslipidemia, explain the majority of the risk for cardiovascular events**
- **Therapeutic Lifestyle Changes form the basis modern treatment strategies**
- **Statin therapy is the best studied approach for the treatment of dyslipidemia**
- **For those who do not tolerate statins or need a very large reduction in LDL-C, other agents will be required**