Ambulatory Care PRN Focus Session—New Developments in Hypertension and Dyslipidemia Management
Activity No. 0217-0000-11-101-L01-P (Application-Based Activity)

Tuesday, October 18
3:30 p.m.–5:30 p.m.
Convention Center: Rooms 315 & 316

Moderator: Candice Garwood, Pharm.D., BCPS
Clinical Assistant Professor, Wayne State University, Detroit, Michigan

Agenda

3:30 p.m.	Updates in Management of Dyslipidemia *Joseph J. Saseen, Pharm.D., FCCP, BCPS* Professor of Clinical Pharmacy and Family Medicine, University of Colorado School of Pharmacy and School of Medicine, Aurora, Colorado
4:30 p.m.	Updates in Hypertension Management *Jonathan D. Ference, Pharm.D., BCPS* Assistant Professor of Pharmacy Practice, Wilkes University School of Pharmacy, Wilkes Barre, Pennsylvania

Faculty Conflict of Interest Disclosures

Jonathan D. Ference: no conflicts to disclose.
Joseph J. Saseen: board member for the Board of Pharmacy Specialties and the National Lipid Association.

Learning Objectives

1. Review clinical trials with clinically relevant endpoints and discuss implications on management strategies.
2. Design evidence-based treatment plans for hyperlipidemia.
3. Discuss recent developments in advanced lipid testing (such as Lp(a), CRP, etc.) and possible implications on practice.
4. Identify clinical trials with cardiovascular endpoints and discuss implications on management strategies.
5. Design evidence-based treatment plans for hypertension.

Self-Assessment Questions

Self-assessment questions are available online at *www.accp.com/am*

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Updates in Management of Dyslipidemia

Joseph Saseen, Pharm.D., BCPS, FCCP, FASHP
Professor
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Skaggs School of Pharmacy and Pharmaceutical Sciences
UNIVERSITY OF COLORADO
ANSCHUTZ MEDICAL CAMPUS

Conflicts of Interest

American College of Clinical Pharmacy

Joseph Saseen is a Board Member of the National Lipid Association

Learning Objectives

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- Review clinical trials with clinically relevant endpoints and discuss implications on management strategies.
- Design evidence-based treatment plans for hyperlipidemia.
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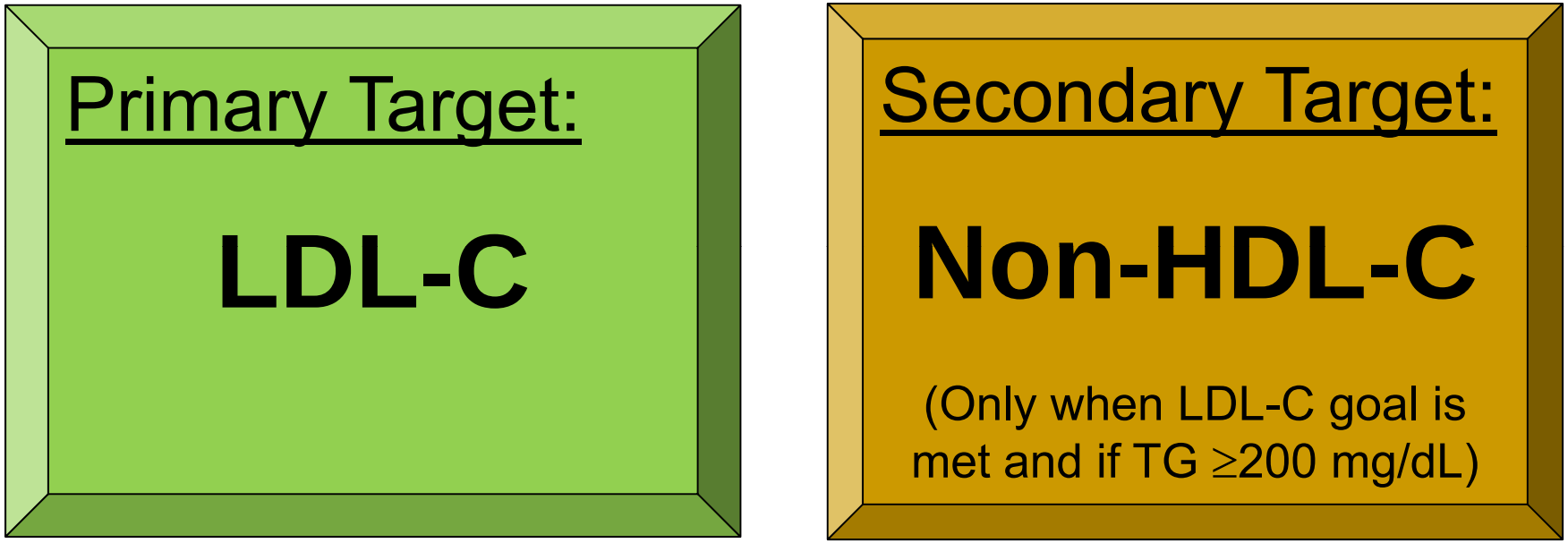
Cardiovascular Risk Reduction Guidelines in Adults: Cholesterol Guideline Update (ATP IV) Hypertension Guideline Update (JNC 8) Obesity Guideline Update (Obesity 2) Integrated Cardiovascular Risk Reduction Guideline

Timeline

- ***Cholesterol Guideline Update (ATP IV)***
  - Expected availability for public review and comment: Fall 2011
  - Expected release date: 2012
- ***Hypertension Guideline Update (JNC 8)***
  - Expected availability for public review and comment: Fall 2011
  - Expected release date: 2012
- ***Obesity Guideline Update (Obesity 2)***
  - Expected availability for public review and comment: Fall 2011
  - Expected release date: 2012

http://www.nhlbi.nih.gov/guidelines/cvd_adult/background.htm#timeline

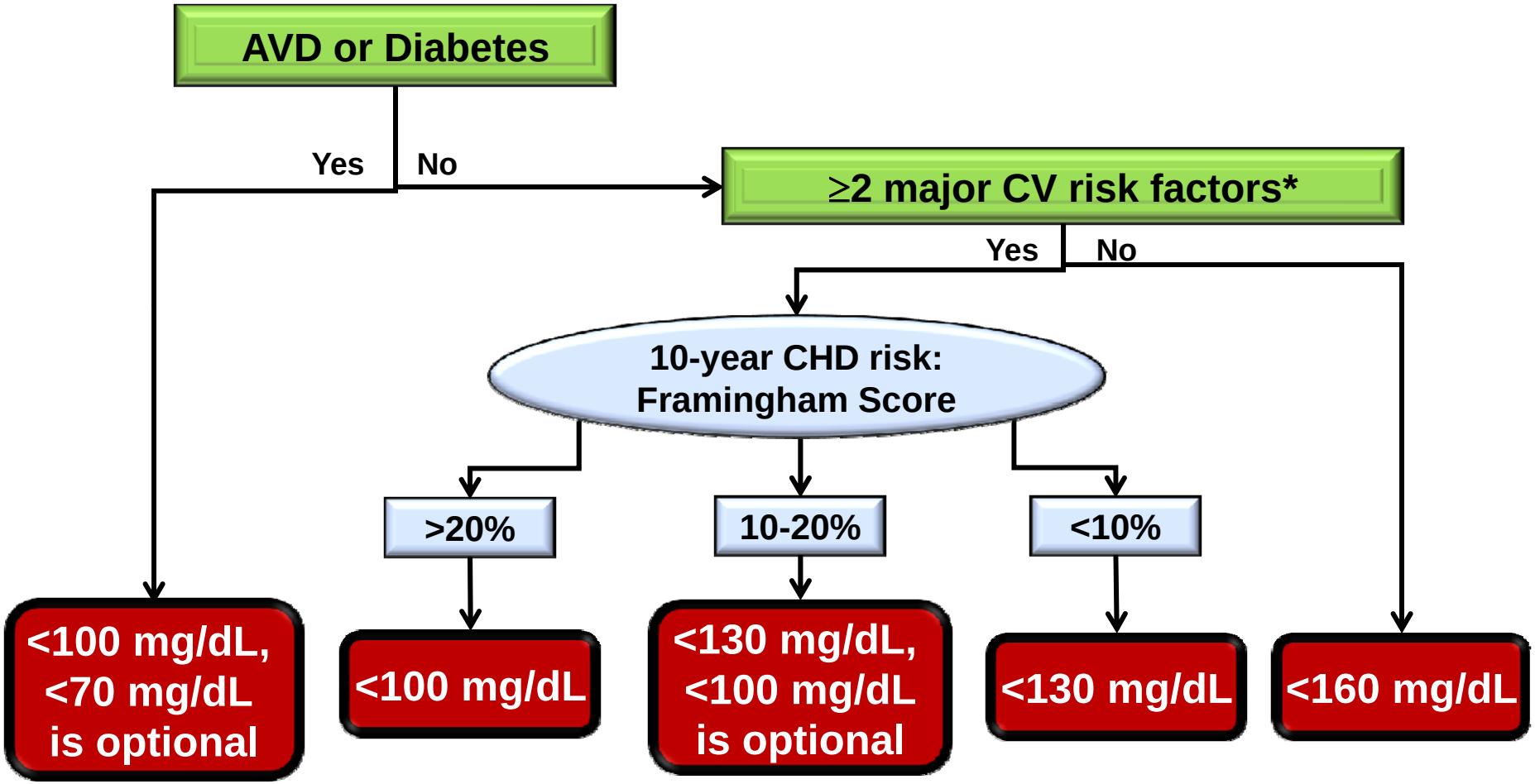
Targets of Treatment in Dyslipidemia



- **EXCEPTION:** Triglyceride lowering is an immediate target of therapy if ≥500 mg/dL
- Raising HDL-C is a tertiary target in certain patients

Grundy SM et al. *Circulation.* 2004; 110:227-39.
Grundy SM et al. *Circulation.* 2005; 112:2735-52.

NCEP ATP III: LDL-C Goals



*Major risk factors include: Age (≥45 years men, ≥55 years women), hypertension, cigarette smoking, family history of premature CHD, HDL-cholesterol <40 mg/dL

Grundy SM et al. *Circulation.* 2004; 110:227-39.

Lipid-Lowering Therapies

	LDL-C	HDL-C	TG
Statins (atorvastatin, fluvastatin, lovastatin, pravastatin, pitavastatin, rosuvastatin, simvastatin)	↓ 18-63%	↑ 5-15%	↓ 7-30%
Bile acid sequestrants (colesevelam, cholestyramine, colestipol)	↓ 15-30%	↑ 3-5%	0 or ↑
Nicotinic acid	↓ 5-25%	↑ 15-35%	↓ 20-50%
Fibric acid derivatives (gemfibrozil, fenofibrate)	↓ 5-20% or ↑	↑ 10-20%	↓ 20-50%
Cholesterol absorption inhibitor (ezetimibe)	↓ 18%	↑ 1%	↓ 7%
Omega-3 fatty acids (Rx strength)	?	↑ 9%	↓ 45%

Executive summary of NCEP ATP III. *JAMA*. 2001; 285:2486-97; Crestor package insert. Astra-Zeneca, 2009; Zetia package insert. Merck/Schering-Plough Pharmaceuticals, 2009; Lovaza package insert. GlaxoSmithKline, 2009; Livalo package insert. Kowa Pharmaceuticals America, 2010.

Landmark Statin-based Trials

Trial	Statin Treatment (mg/day)	LDL-C (mg/dL)		Primary Endpoint/ CV Event Rate (%)	
		Baseline	Statin	Placebo	Statin
4S	Simvastatin 20-40 mg	188	122	28.0	19.4
LIPID	Pravastatin 40 mg	150	112	15.0	12.3
CARE	Pravastatin 40 mg	139	98	13.2	10.2
HPS	Simvastatin 40 mg	132	93	24.4	19.9
PROSPER	Pravastatin 40 mg	147	97	16.2	14.1
WOSCOPS	Pravastatin 40 mg	192	159	7.5	5.3
AFCAPS	Lovastatin 20-40 mg	150	115	5.5	3.5
ASCOT-LLA	Atorvastatin 10 mg	133	90	3.0	1.9
CARDS	Atorvastatin 10 mg	118	77	9.0	5.8
JUPITER	Rosuvastatin 20 mg	108	55	2.8	1.6

Jacobson TA et al. *Arch Intern Med.* 1998; 158:1977-89. Heart Protection Study Collaborative Group. *Lancet.* 2002; 360:7-22. Shepherd J et al. *Lancet.* 2002; 360:1623-30. Sever PS et al. *Lancet.* 2003; 361:1149-58. Colhoun HM et al. *Lancet.* 2004; 364:685-96. Ridker PM et al. *N Engl J Med.* 2008; 359:2195-207.

Clinical Case…

- RP is a 68 year old man who is hospitalized for an acute coronary syndrome. He is discharge on atorvastatin 80 mg daily. His provider 2 weeks later asks you if he can be treated with a lower dose of a statin since his baseline LDL was only 110 mg/dL.

How do you respond?

Would you feel differently if it were simvastatin?

Cholesterol Treatment Trialists' (CTT) Collaboration

- Meta-analysis of large (n>1000), randomized clinical trials that were ≥2 yrs duration
  - More vs. Less intensive statin therapy:
    - 5 trials (n=39,612), median 5 yr follow-up
  - Statin vs. control:
    - 21 trials (n=129,526), median 4.8 yr follow-up
- Average CV event risk reductions per 1.0 mmol/L LDL-C reduction at 1 year after randomization were calculated

Lancet 2010; 376: 1670–81.

CTT Collaboration: More vs. Less Statin Therapy

- Weighted mean further reduction in LDL-C was 0.51 mmol/L (~19 mg/dL)

	Further Event Reduction
Major Vascular Events	15% (P<0.001)
CHD Death or Non-Fatal MI	13% (P<0.001)
Ischemic Stroke	16% (P=0.005)

- CV event reductions were proportionate to LDL-C reductions, even when baseline LDL-C was <2 mmol/L (77 mg/dL)

Lancet 2010; 376: 1670–81.

Simvastatin Label Changes (June 2011)

- Do not start new patients on 80 mg daily
- Contraindicated with:
  - Itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, gemfibrozil, cyclosporine, danazol
- Do not exceed 10 mg daily with:
  - Amiodarone, dilitazem, verapamil
- Do not exceed 20 mg daily with:
  - Amlodipine, ranolazine
- Avoid grapefruit juice (>1 quart daily)

http://www.fda.gov/Drugs/DrugSafety/ucm256581.htm

Statin and Risk of Incident Diabetes

- 2010 meta-analysis of 13 trials (n=91,140)
  - 4278 developed diabetes (2226 with statins vs. 2052 with control) over a mean 4 yrs
    - 9% increased risk (OR 1.09 [1.02–1.17])
    - NNH was 255 patients
- 2011 meta-analysis of 5 trials (n=32,752)
  - 2749 developed diabetes (1449 with intensive-dose statin vs. 1300 with moderate-dose statin) over a mean 1.9 yrs
    - 12% increased risk (OR 1.12 [1.04-1.22])
    - NNH was 498; but, NNT for CV events was 155

Lancet 2010; 375: 735–42.
JAMA. 2011;305(24):2556-2564.

Unwanted Effects of Statins

- Prospective open cohort study in new statin users (n=225,922) and non-users (n=1,778,770)
- Extensive analysis by individual statin and sex
- Results:
  - No risk: Parkinson's disease, RA, VTE, dementia, osteoporotic fracture, several common cancers
  - Lower risk: Esophageal cancer
  - Higher risk: Liver dysfunction, acute renal failure, myopathy, cataracts
- Overall – VERY LOW INCIDENCE RATES

BMJ 2010;340:c2197.

Clinical Scenarios

Goal	Monotherapy	Combination Therapy
LDL-C Lowering	• Statin • Niacin • Bile Acid Sequestrant • Ezetimibe	• Statin + Bile Acid Sequestrant • Statin + Ezetimibe ✓ • Statin + Niacin ✓ • Others
Non-HDL-C Lowering	• Statin (high-dose) • Niacin	• Statin + Fibrate ✓ • Statin + Niacin ✓ • Statin + Omega-3 Fatty Acids • Others
Triglyceride Lowering	• Fibrate • Omega-3 Fatty Acids • Niacin	• Fibrate + Omega-3 Fatty Acids • Fibrate + Niacin • Niacin + Omega-3 Fatty Acids

Clinical Case…

- Several years later, RP is treated with pravastatin 40 mg daily. He will not consider a higher dose or another statin due to cost and perceived risks. His LDL-C is 80 mg/dL, HDL-C is 35 mg/dL, TG are 250 mg/dL, non-HDL is 130 mg/dL. Which of the following would you recommend?

1. Add ezetimibe
2. Add fenofibrate
3. Add niacin
4. Continue current therapy unchanged

Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE)

- Double-blind trial in 720 patients with heterozygous familial hypercholesterolemia randomized to ezetimibe/simvastatin 10/80 mg daily or simvastatin 80 mg daily for 2 yr
  - Significant differences in LDL-C reduction:
    - Baseline LDL-C: 319 and 318 mg/dL
    - LDL- C reductions: 58% and 41% ($p<0.01$)
  - Change in mean carotid IMT after 2 years
    - Ezetimibe/Simvastatin 0.0111 mm
    - Simvastatin 0.0058 mm ($p=0.29$)

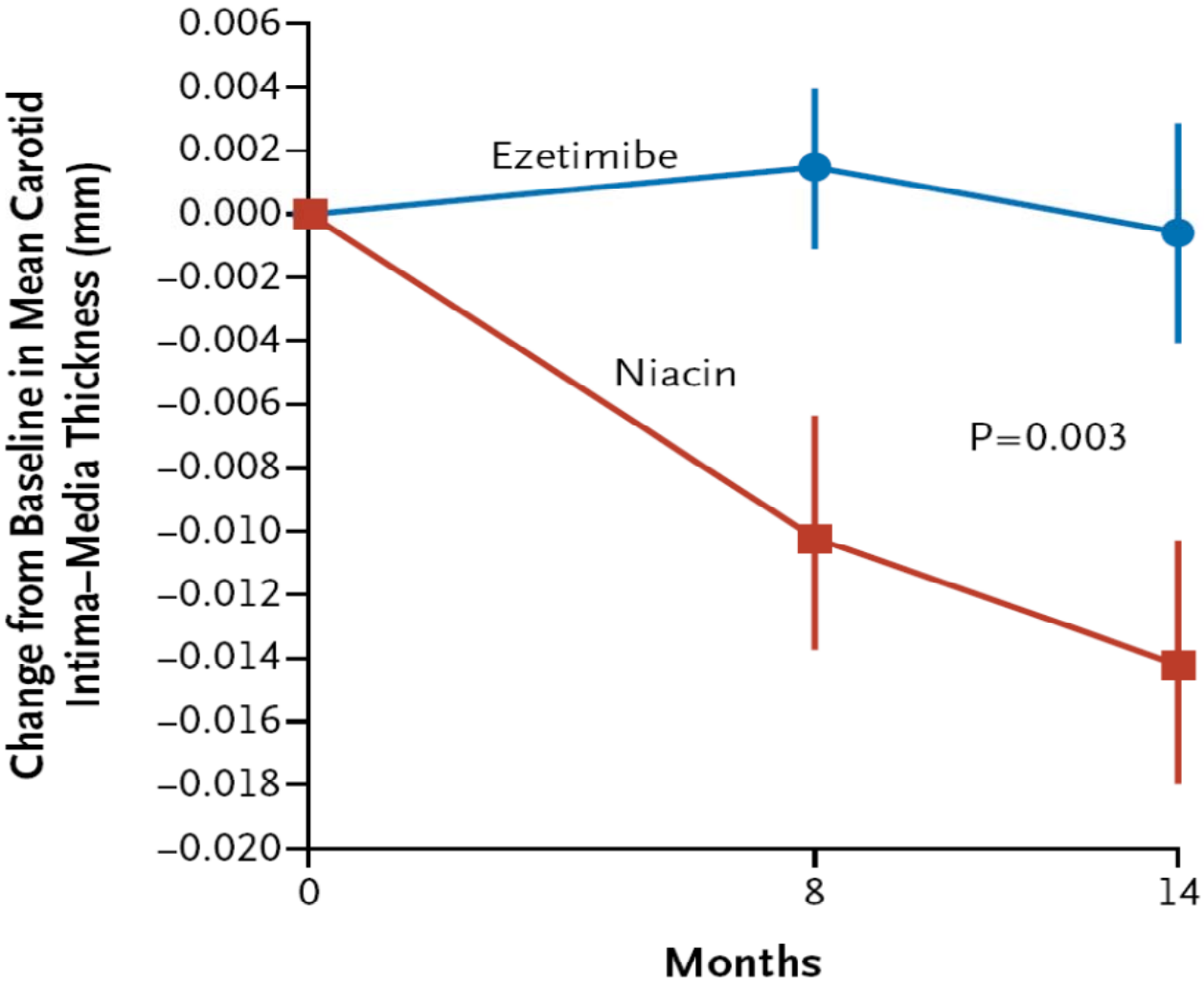
Kastelein JJ et al. *N Engl J Med.* 2008;358:1431-43.

Extended-Release Niacin or Ezetimibe and Carotid Intima–Media Thickness (ARBITER-6)

- Open-label trial in 208 patients with existing CHD or a CHD risk equivalent condition (e.g., diabetes, carotid or peripheral artery disease) who were receiving long-term statin therapy
- Desirable LDL-C < 100 mg/dL and undesirable or low HDL-C < 50 mg/dL for men and < 55 mg/dL for women
- Randomized to addition of:
  - Extended-release niacin up to 2000 mg daily or
  - Ezetimibe 10 mg daily

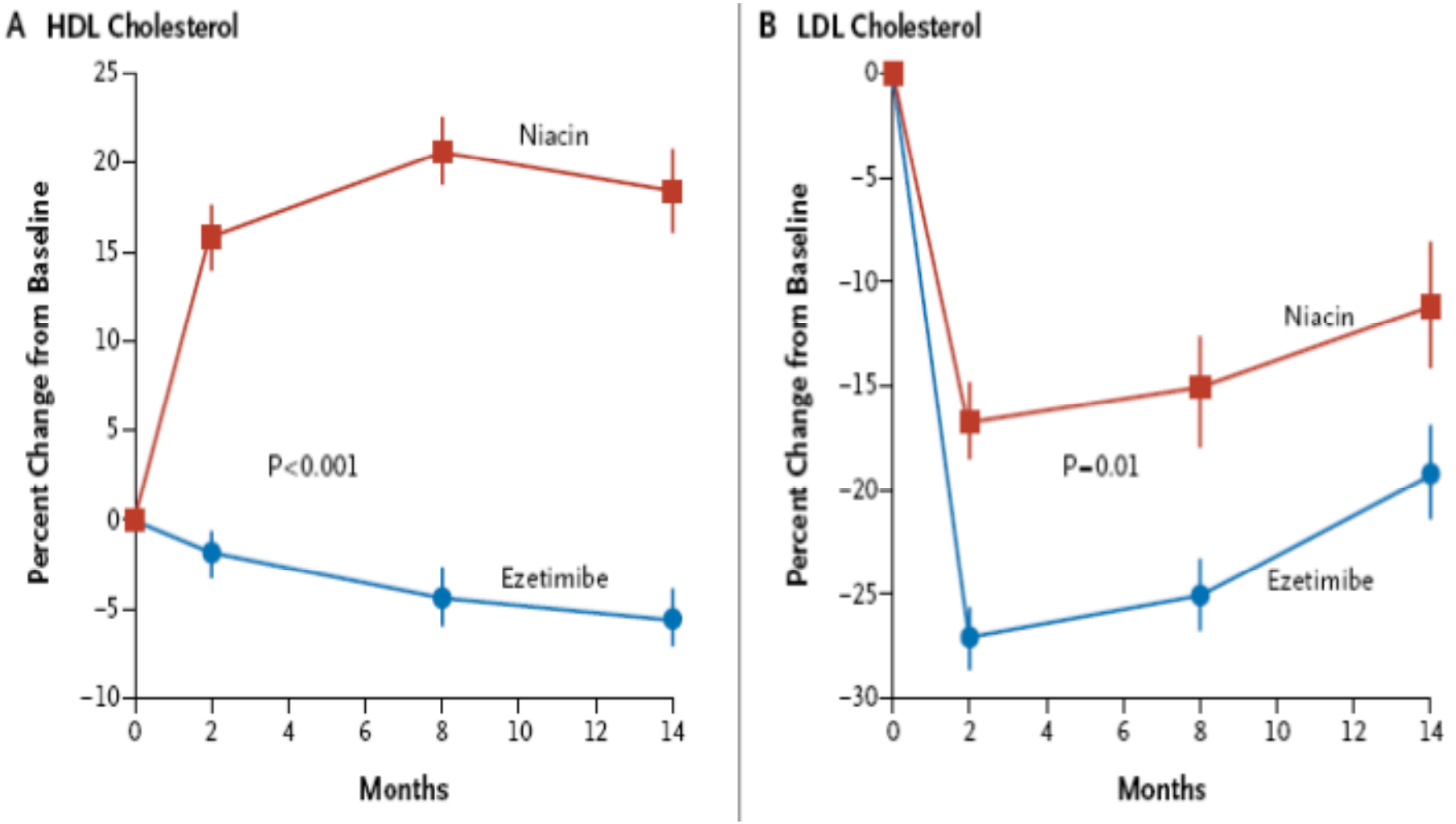
Taylor AJ, et al. *N Engl J Med* 2009;361:2113-22.

ARBITER-6: Primary Endpoint



Taylor AJ, et al. *N Engl J Med* 2009;361:2113-22.

ARBITER-6: Lipid Changes



Taylor AJ, et al. *N Engl J Med* 2009;361:2113-22.

Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH)

- Sponsored by NHLBI
- Double-blind trial in 3114 patients with a history of CVD treated with statin therapy to an LDL-C of 40-80 mg/dL
- Randomized to placebo or extended-release niacin (dosed up to 2000 mg daily)
- Stopped 18 months earlier than planned

http://public.nhlbi.nih.gov/newsroom/home/GetPressRelease.aspx?id=2792

AIM-HIGH… Stopped Early

- NHLBI of the National Institutes of Health stopped the trial earlier than planned:

Lack of efficacy in reducing cardiovascular events prompts decision

- Adding high dose, extended-release niacin to statin treatment in people with CVD, did not reduce the risk of CV events, including heart attacks and stroke.

http://public.nhlbi.nih.gov/newsroom/home/GetPressRelease.aspx?id=2792

American Diabetes Association:
Standards of Medical Care in Diabetes

Dyslipidemia:

- Statin therapy should be added to lifestyle therapy, regardless of baseline lipid levels, for diabetic patients with overt CVD, or without CVD if >40 yrs with ≥ 1 other CVD risk factors
- Triglycerides <150 mg/dL and HDL-C >40 mg/dL in men and >50 mg/dL in women, are desirable. However, LDL-C–targeted statin therapy remains the preferred strategy.
- If targets not reached on maximally tolerated doses of statins, combination therapy using statins and other lipid-lowering agents may be considered but has not been evaluated in outcome studies for either CVD outcomes or safety

Diabetes Care. 2011; 33 (suppl 1):S11-61.

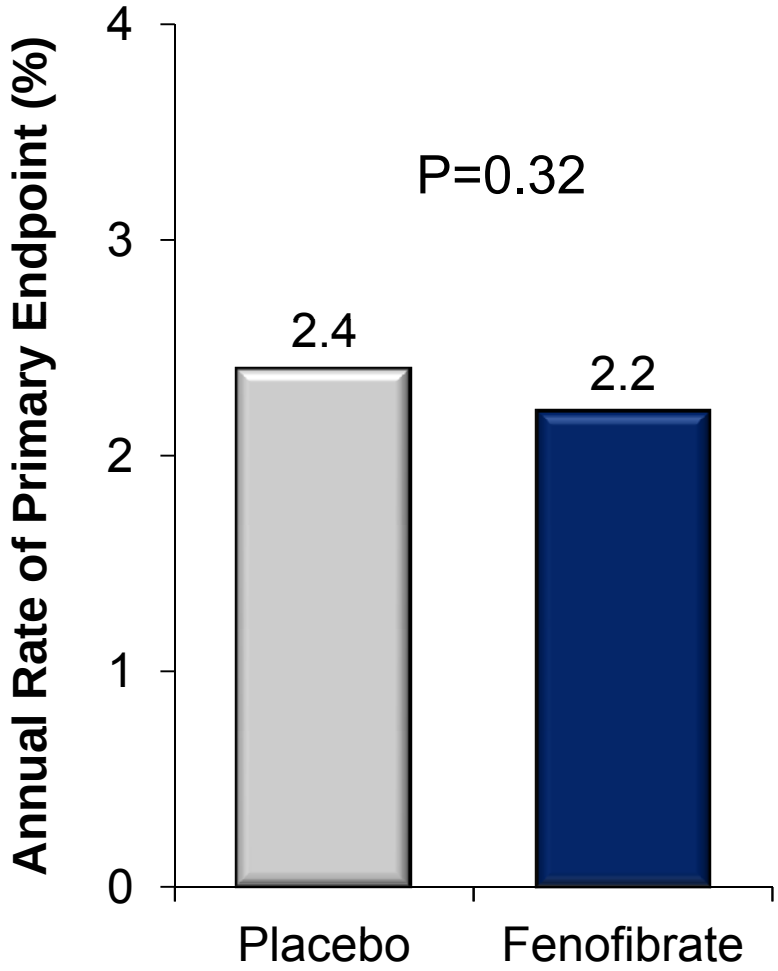
ACCORD Study: Combination Lipid Therapy

- 5518 patients with type 2 diabetes treated with open-label simvastatin randomized to fenofibrate or placebo for 4.7 yr
- Primary outcome: nonfatal MI, nonfatal stroke, or CV death

	Baseline	End of Study	
		Fenofibrate	Placebo
LDL-C (mg/dL)	100.6	81.1	80.0
HDL-C (mg/dL)	38.1	41.2	40.5
Triglycerides (mg/dL)	162	122	144

Ginsberg HN et al. *N Engl J Med.* 2010; 362:1563-74.

ACCORD Study: Results



- Subgroup analyses:
  - Possible benefit for men and possible harm for women
  - Possible benefit in patients with both high baseline triglycerides (≥204) and a low baseline HDL-C (≤34)

    P=0.057 for interaction

Ginsberg HN et al. *N Engl J Med.* 2010; 362:1563-74.

Polling Question…

Which of the following clinical effects related to statin therapy is most likely to occur in patients requiring long-term hemodialysis?

1. Removal of the statin by the hemodialysis
2. Reduction in LDL-C
3. Reduction in CV event risk

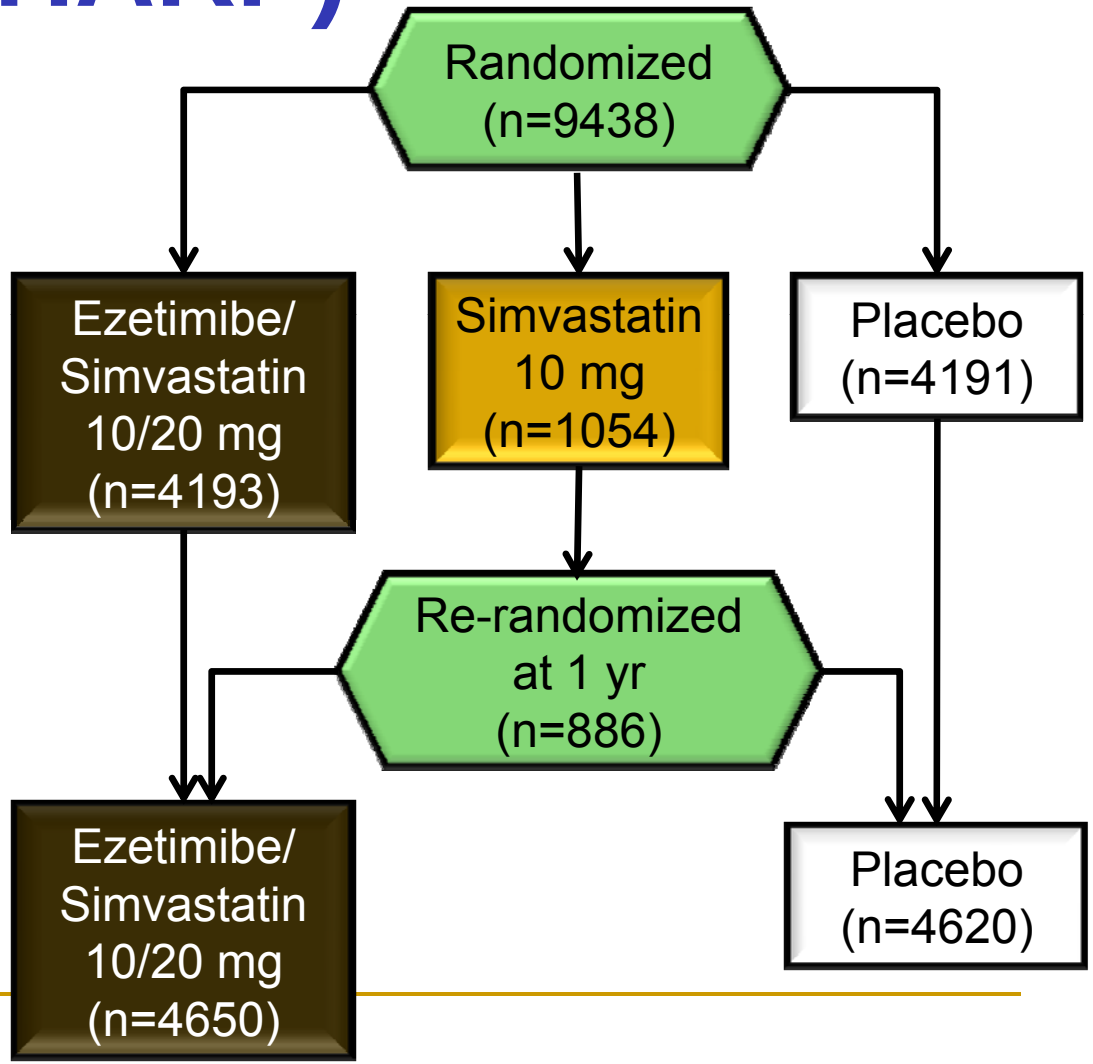
Lipid-Lowering Therapy in Patients with End-Stage Renal Disease (ESRD) Requiring Hemodialysis

Trial	Population	Primary Endpoint	Relative Risk (95% CI)
4D Study: • Atorvastatin 20 mg daily vs placebo for 4 yr	Type 2 diabetes plus long-term hemodialysis (n=1255)	CV death, nonfatal MI, fatal/nonfatal stroke	0.92 (0.77–1.10)
AURORA Study: • Rosuvastatin 10 mg daily vs placebo for 3.8 yr	Long-term hemodialysis (n=2776)	CV death, nonfatal MI, nonfatal stroke	0.96 (0.84–1.11)

Wanner C et al. N Engl J Med. 2005; 353:238-48.
Fellström BC et al. N Engl J Med. 2009; 360:1395-407.

Study of Heart and Renal Protection (SHARP)

- Patients with chronic kidney disease (SCr ≥1.7 mg/dL men, ≥1.5 mg/dL women)
- Age ≥ 40 yrs, without prior MI
- Primary endpoint: major atherosclerotic events
- 4.9 yr median follow-up



Baigent C et al. Lancet 2011 Published online June 9, 2011 DOI:10.1016/S0140-6736(11)60739-3

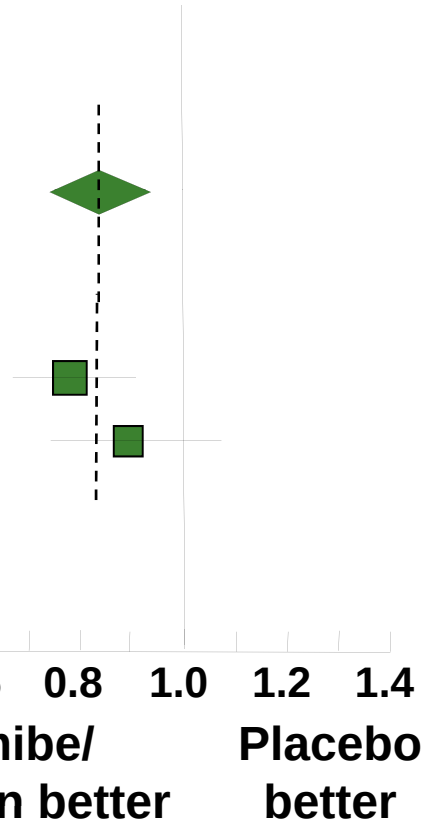
SHARP: Results

- 68% were adherent at the end of study
- LDL-C reductions with ezetimibe/simvastatin:
  - 43 mg/dL at 1 yr, 33 mg/dL at 2.5 yr
- No difference in major adverse events:
  - Muscle pain, hepatic transaminase elevations, hepatitis, gall stones, cancer)
- Myopathy (CK > 10 x ULN)
  - 9 with ezetimibe/simvastatin, 5 with placebo (p=ns)

Baigent C et al. Lancet 2011 Published online June 9, 2011 DOI:10.1016/S0140-6736(11)60739-3

SHARP: Results

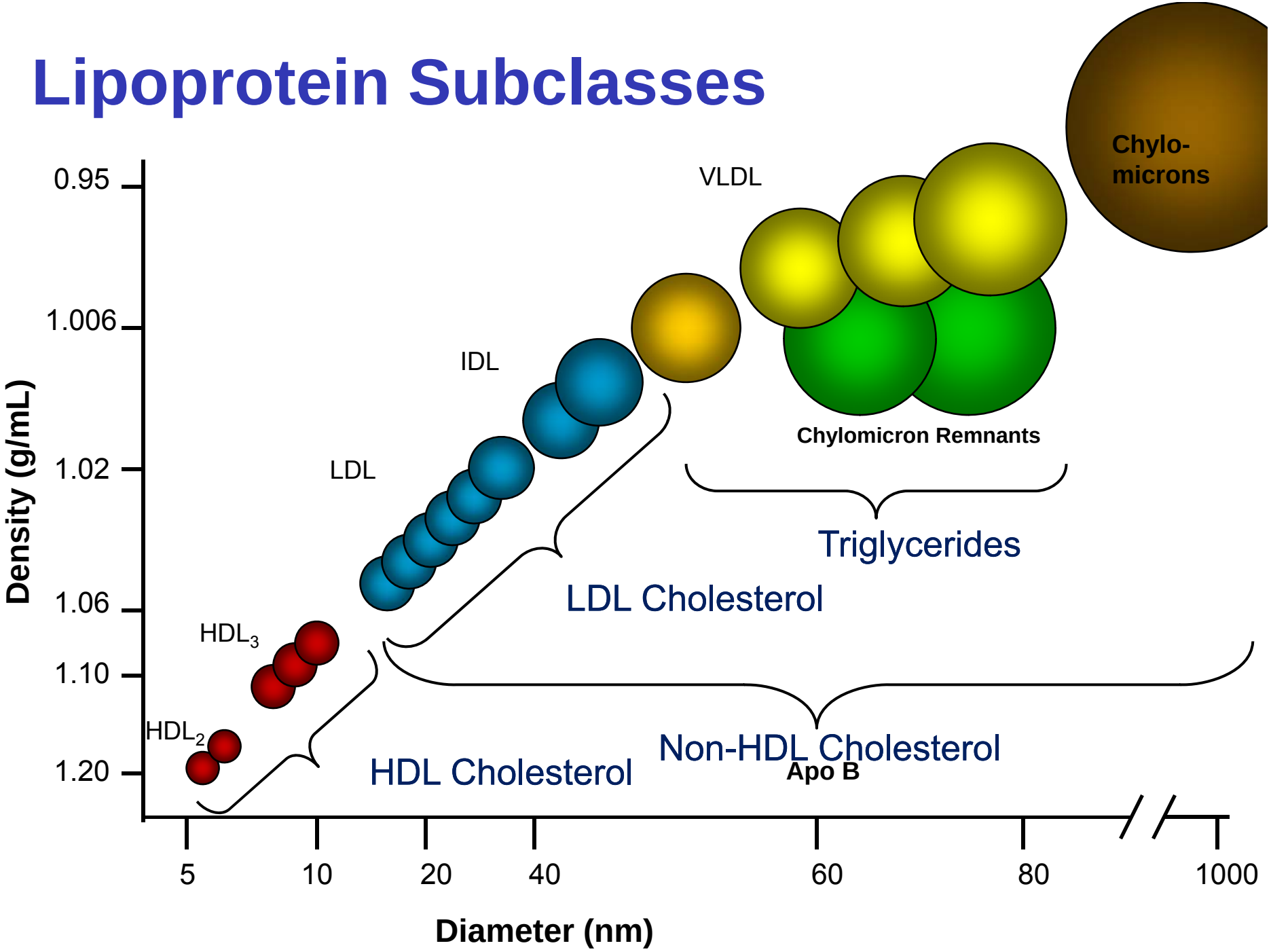
Event	Ezetimibe/ Simvastatin (n=4650)	Placebo (n=4620)
Major atherosclerotic event	526 (11.3%)	619 (13.4%)
Non-dialysis (n=6247)	296 (9.5%)	373 (11.9%)
Dialysis (n=3023)	230 (15.0%)	246 (16.5%)



Note: No significant heterogeneity between non-dialysis and dialysis patients (p=0.25)

Baigent C et al. Lancet 2011 Published online June 9, 2011 DOI:10.1016/S0140-6736(11)60739-3

Lipoprotein Subclasses



ADA and ACC Consensus Statement: Lipoprotein Management in Patients With Cardiometabolic Risk

	Goal Values (mg/dL)		
	LDL-C	**Non-HDL-C**	**Apo B**
Highest Risk: • CVD or • DM with ≥1 major risk factor	<70	<100	<80
High Risk: • No CVD, no DM with ≥2 major risk factors • DM with no major risk factors	<100	<130	<90

Other major risk factors (beyond dyslipidemia) include cigarette smoking, hypertension, and family history of premature coronary artery disease.

Diabetes Care 2008;31:811-822.

Advanced Lipid Testing

- Several commercially available laboratory packages (e.g., NMR Lipoprofile, VAP, Berkley Labs)
- Measure several lipoprotein types and components, including several “biomarkers”
  - Direct LDL, LDL particle size and density, HDL subtypes, IDL, VLDL, Apo A1, Apo B
  - Lp(a), Lipoprotein Phospholipase A2 (Lp-PLA2)
  - hsCRP, homocysteine, fibrinogen,

Polling Question…

Should you consider advanced lipid testing in your high CV risk patient population to further refine their lipid-lowering therapy?

1 Yes

2 No

2010 ACCF/AHA Guideline:
Assessment of CV Risk in Asymptomatic Adults

- Advanced lipid testing:
  - Not recommended
- Lipoprotein Phospholipase A2 (Lp-PLA2)
  - Reasonable in intermediate risk patients
- hsCRP
  - Reasonable in men ≥50 yrs or women ≥60 yrs with LDL<130 mg/dL not on lipid-lowering therapy
  - Reasonable in men <50 yrs or women<60 yrs if intermediate risk (not if low risk)
  - Not recommended in any high risk patients

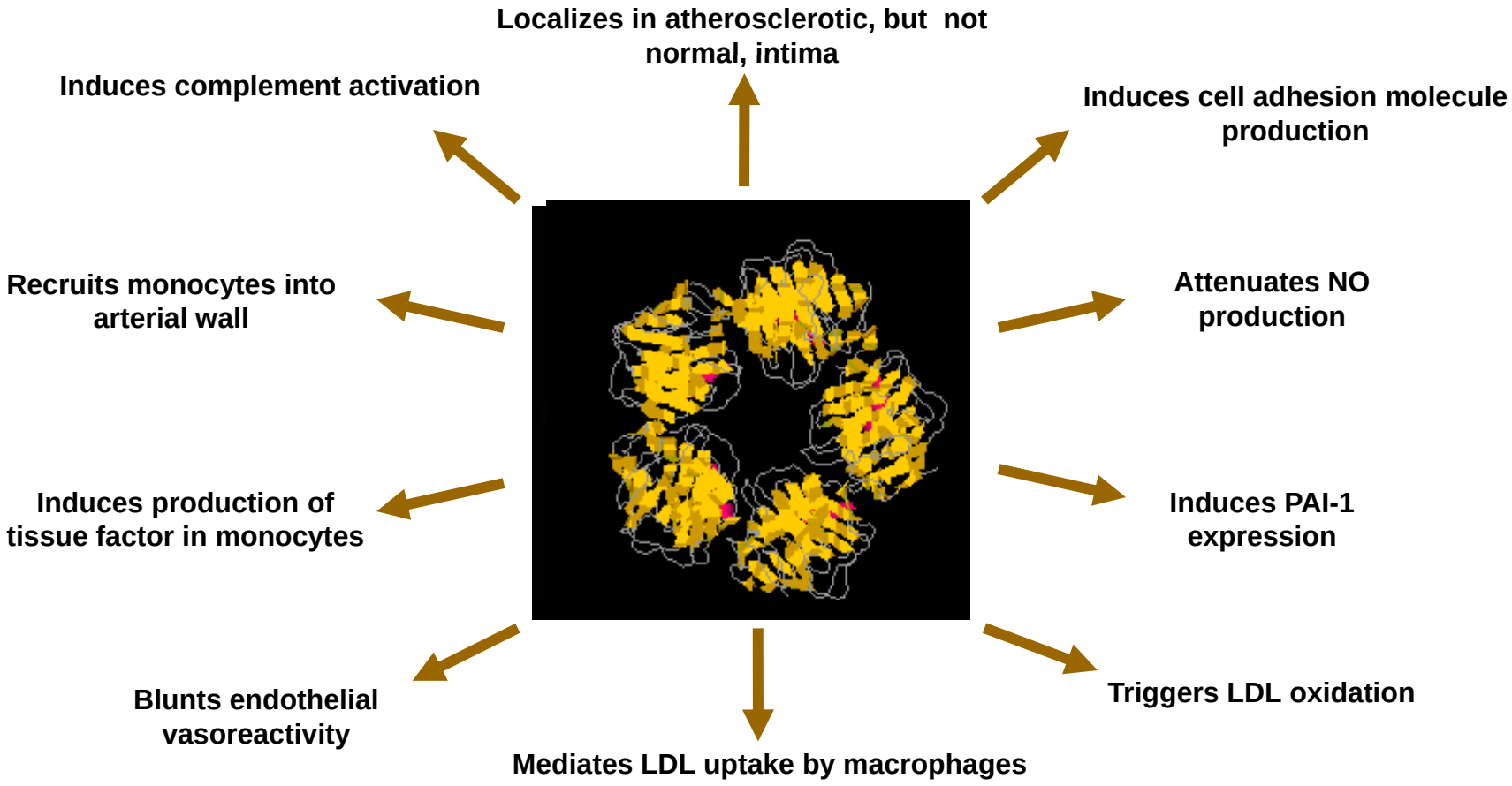
J Am Coll Cardiol 2010;56:2182–99.

Lipoprotein Phospholipase A2 (Lp-PLA2)

- An enzyme bound primarily to atherogenic lipoproteins
- Secreted by inflammatory cells within atherosclerotic plaques
- Expression is significantly increased in advanced atherosclerotic lesions
- Changes in Lp-PLA2 levels have been associated with reduced CV events in subgroup analyses of the PROVE-IT trial

J Am Coll Cardiol 2010;56:2182–99
Circulation. 2006;113:1745-52.

C-Reactive Protein (CRP) and Atherosclerosis



NO = nitric oxide; PAI-1 = plasminogen activator inhibitor-1.

Verma S et al. *Circulation*. 2002; 106:913-9.

hsCRP as a CV Risk Marker

- AHA/CDC Scientific Statement (2003):
  - Endorsement of hsCRP as the analyte of choice to associate inflammation with CV risk
    - Low risk: <1 mg/L
    - Average risk: 1 to 3 mg/L
    - High risk: >3 mg/L
- Emerging Risk Factors Collaboration (2010):
  - Meta-Analysis of 160,309 subjects in 54 long-term prospective studies
    - Elevated CRP continuously associated with the risk of CHD, ischemic stroke, vascular death, and non-vascular death

Pearson TA. *Circulation*. 2003;107:499-511.
Emerging Risk Factors Collaboration. *Lancet* .2010; 375:132–140.

JUPITER Trial

- Primary objective:
  - First major CV event
- Patients randomized to rosuvastatin 20 mg daily or placebo (planned for 3.5 yr)
- Patient profile (n=17,802)
  - Primary prevention
  - Men ≥ 50 yr, women ≥ 60 yr
  - LDL-C <130 mg/dL with hsCRP >2 mg/L

Ridker PM et al. *N Engl J Med.* 2008;359:2195-207.

JUPITER: Median Baseline Values

	Rosuvastatin (n=8901)	Placebo (n=8901)
Age (yr)	66	66
Female (%)	38.5	37.9
White/Black/Hispanic (%)	71.4/12.4/12.6	71.1/12.6/12.8
Body Mass Index (kg/m^2)	28.3	28.4
Blood Pressure (mm Hg)	134/80	134/80
Smoker (%)	15.7	16.0
hsCRP, mg/L	4.2 (2.8-7.1)	4.3 (2.8-7.2)
LDL, mg/dL	108 (94-119)	108 (94-119)
HDL, mg/dL	49 (40-60)	49 (40-60)

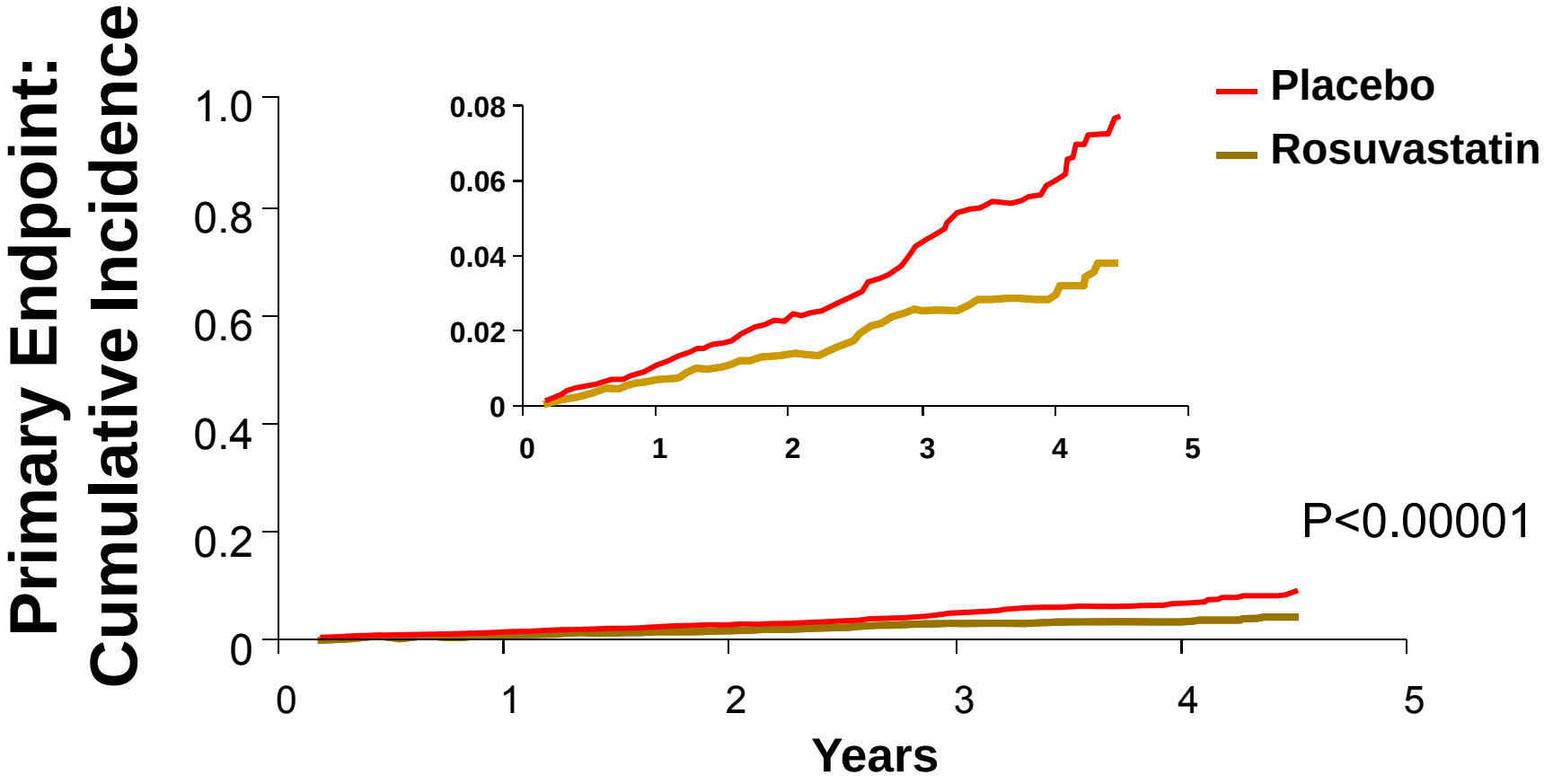
Ridker PM et al. *N Engl J Med.* 2008;359:2195-207.

JUPITER: Results

- Stopped early after a mean of 1.9 years
- Median (interquartile range) LDL-C at 12 mo:
  - Placebo 110 mg/dL (94-125)
  - Rosuvastatin 55 mg/dL (44-72) P<0.001

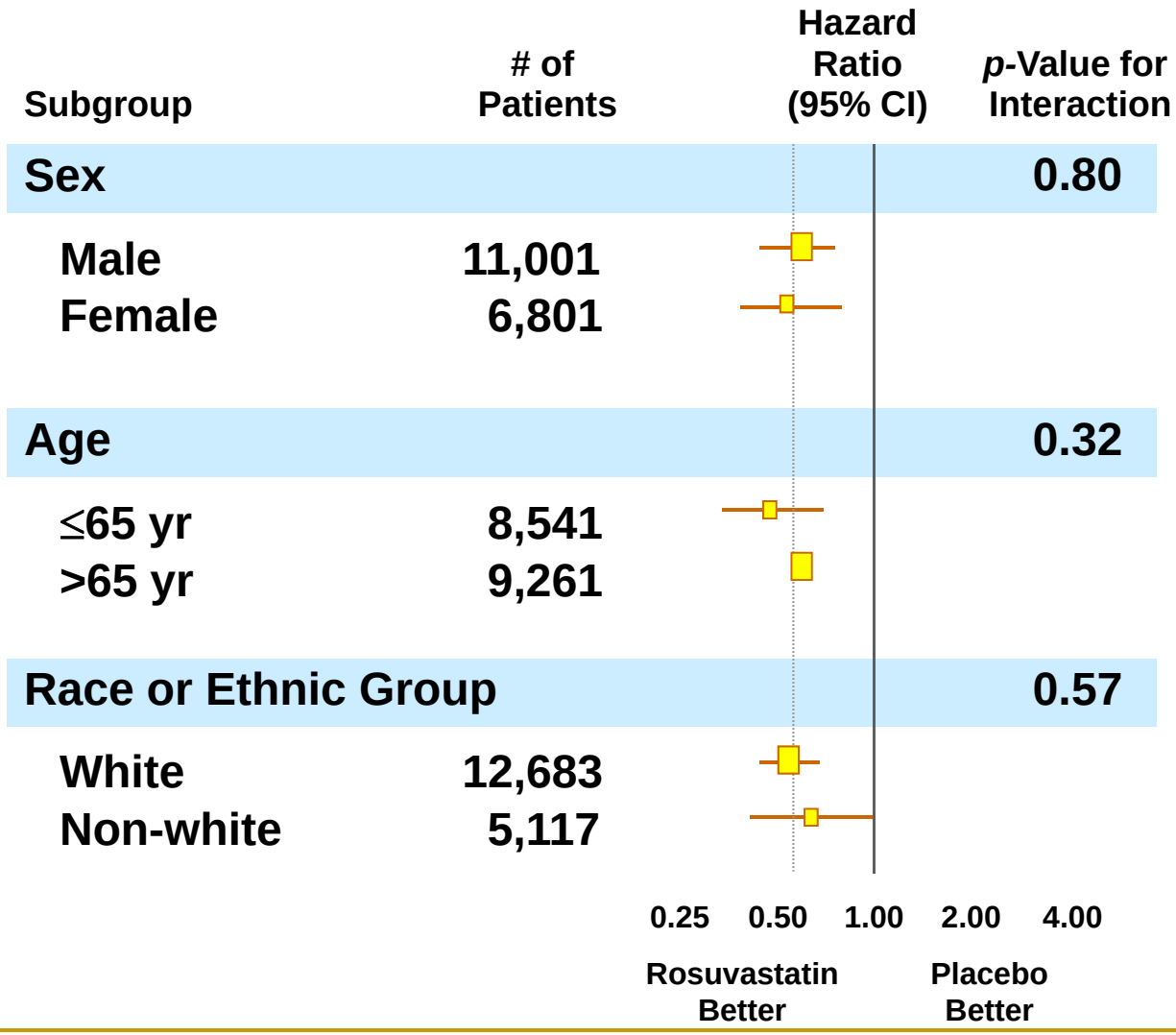
Ridker PM et al. *N Engl J Med.* 2008;359:2195-207.

JUPITER: Results



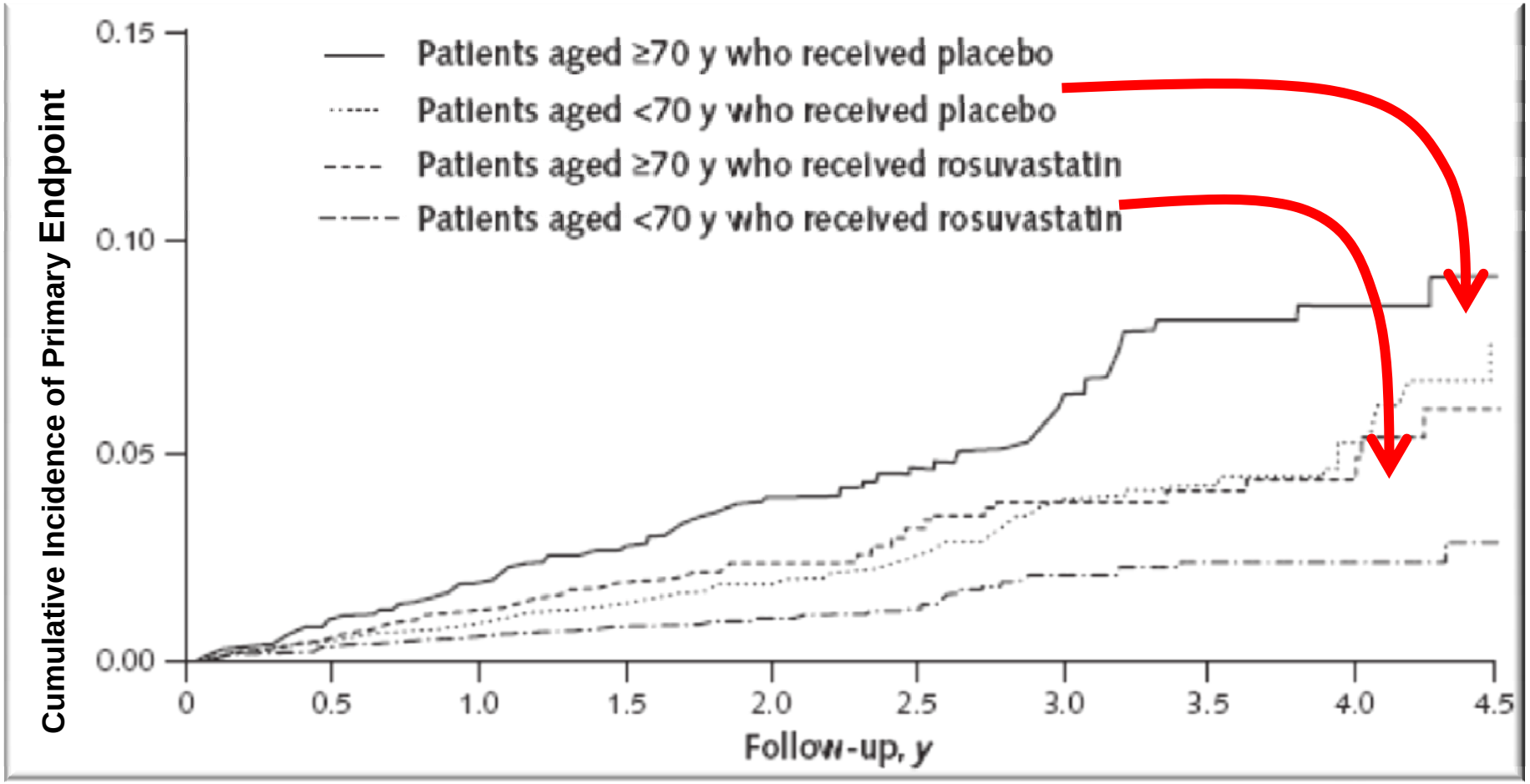
Ridker PM et al. *N Engl J Med.* 2008;359:2195-207.

JUPITER Results: Subgroups



Ridker PM et al. *N Engl J Med.* 2008;359:2195-207.

JUPITER Results in Older Patients:



Glynn RJ, et al. *Ann Intern Med*. 2010;152:488-496.

JUPITER: Subjects attaining LDL values <50 mg/dL

- Of those randomized to rosuvastatin:

	Achieved LDL < 50 mg/dL	Achieved LDL > 50 mg/dL
Patients (n)	4154	4000
Events per 100-patient years*	0.44	0.86

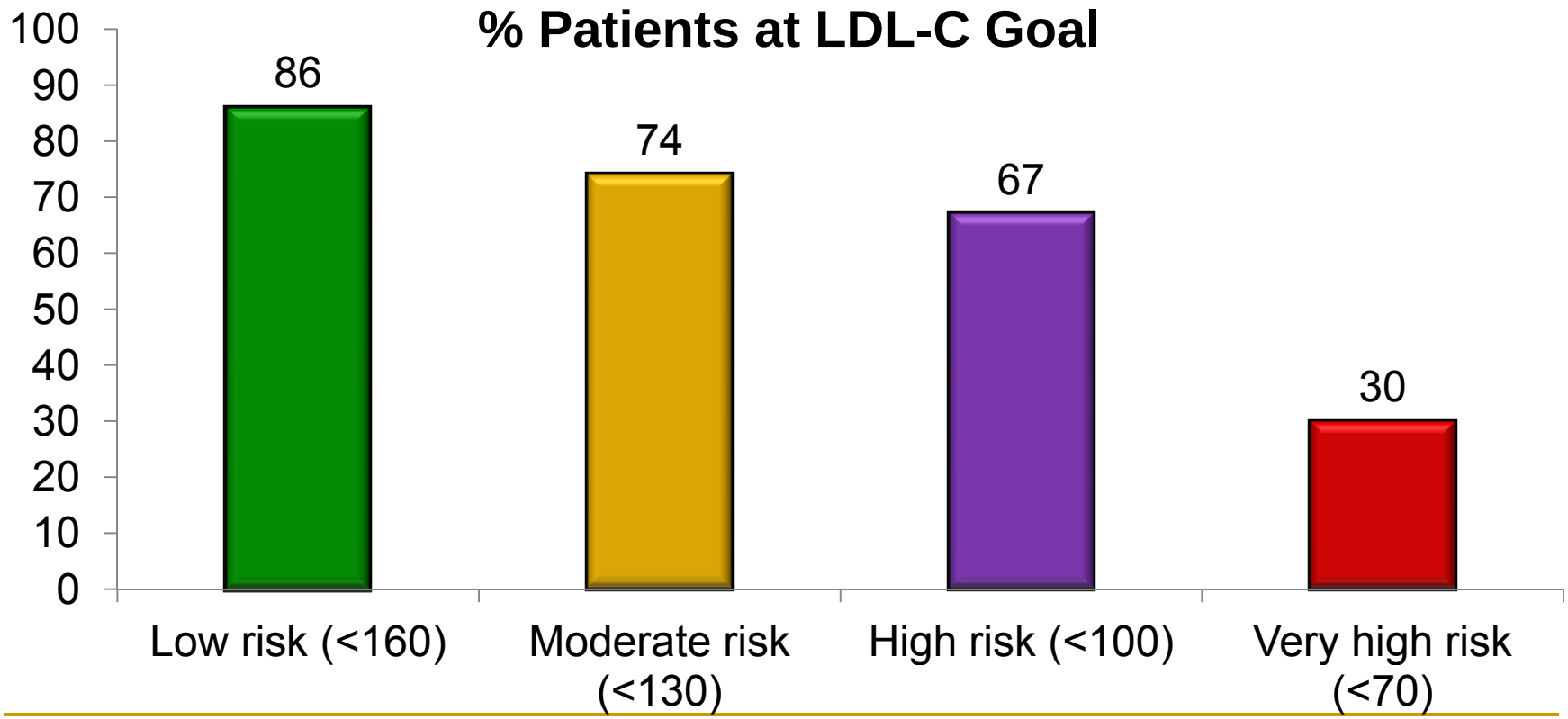
*P<0.001

- Myalgia, muscle weakness, neuropsychiatric conditions, cancer, and diabetes mellitus were not significantly different

J Am Coll Cardiol 2011;57:1666–75.

Lipid Treatment Assessment Project 2 (L-TAP2)

- 9955 patients on stable lipid-lowering therapy



Waters DD, et al. *Circulation.* 2009;120:28-34.

Conclusions

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- Several clinical trials have been published that impact patient care since that are not reflected in the current NCEP guidelines
- Evidence-based treatment plans for hyperlipidemia consist of statin-based therapy
- Advanced lipid testing have little impact in patient care for most patients based on current standards