Practical Lipid Management: Concepts and Controversies

Case Studies

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Case: Mr. Silver

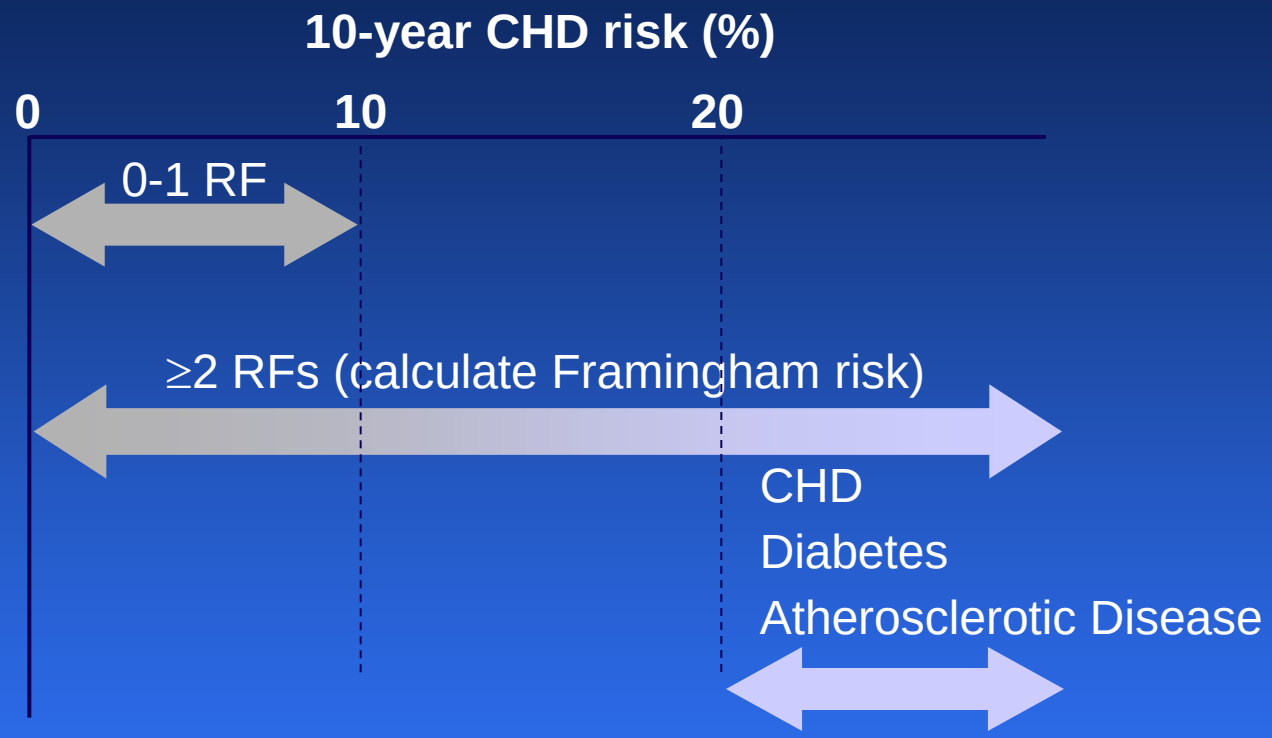
History, Physical Exam & Laboratory Data

- 57-year-old male
- PMH: HTN, treated with diet, exercise
- Smokes 1-1/2 PPD
- FH: Father, 47 years, died of CHD
- Medications
  - None
- Physical examination
  - 5´9˝, 210 lb
  - BMI = 30.2, waist 40.5˝
  - BP: 145/90

Baseline (fasting levels)	
Total C	252
LDL-C	156 (calculated)
HDL-C	38
TG	290
Glucose	107
TSH	1.7

BMI = body mass index; BP = blood pressure;
C = cholesterol; TSH = thyroid-stimulating hormone.

NCEP-ATP III: Risk Assessment – CHD Risk Categories



- For persons *without* known CHD, other forms of atherosclerotic disease, or diabetes:
  - Count the number of risk factors.
  - Use Framingham scoring for persons with ≥2 risk factors* to determine the absolute 10-year CHD risk.

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA*. 2001;285:2486.

Framingham Heart Study Cumulative Point Scale for Estimating 10-Year CHD Risk (Men/Women)

Age

20 – 34 =	-9/-7
35 – 39 =	-4/-3
40 – 44 =	0/0
45 – 49 =	3/3
50 – 54 =	6/ 6
55 – 59 =	8/8
60 – 64 =	10/10
65 – 69 =	11/12
70 – 74 =	12/14
75 – 79 =	13/16

Total Cholesterol

	Age 20–39	Age 40–49	Age 50–59	Age 60–69	Age 70–79
<160	0/0	0/0	0/0	0/0	0/0
160 – 199	4/4	3/3	2/2	1/1	0/1
200 – 239	7/8	5/6	3/4	1/2	0/1
240 – 279	9/11	6/8	4/5	2/3	1/2
≥280	11/13	8/10	5/7	3/4	1/2

HDL-C

≥ 60 = -1/-1
50 – 59 = 0/0
40 – 49 = 1/1
<40 = 2/2

Systolic Blood Pressure

	If Untreated	If Treated
<120	0/0	0/0
120 – 129	0/1	1/3
130 – 139	1/2	2/4
140 – 159	1/3	2/5
≥160	2/4	3/6

Smoker

	Age 20–39	Age 40–49	Age 50–59	Age 60–69	Age 70–79
No	0/0	0/0	0/0	0/0	0/0
Yes	8/9	5/7	3/4	1/2	1/1

Total points:	<0	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	≥17
10-year CHD risk (%) for men:	<1	1	1	1	1	1	2	2	3	4	5	6	8	10	12	16	20	25	≥30

Total points:	<9	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	≥25
10-year CHD risk (%) for women:	<1	1	1	1	1	2	2	3	4	5	6	8	11	14	17	22	27	≥30

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA*. 2001;285:2486–2497

Limitations of Frmingham Risk Score

- Does not take family history into account
- May underestimate lifetime risk in individuals ≤50 years of age with ≥1 NCEP risk factor
- May not accurately calculate risk in certain ethnic groups because original Framingham population was almost entirely of European origin
- May not accurately incorporate risk due to insulin-resistant conditions such as metabolic syndrome
- Does not include emerging risk factors such as CRP, LP(a), apo B and others

ATP III: The Metabolic Syndrome

Diagnosis established with ≥3 of these risk factors.

General Features of the Metabolic Syndrome

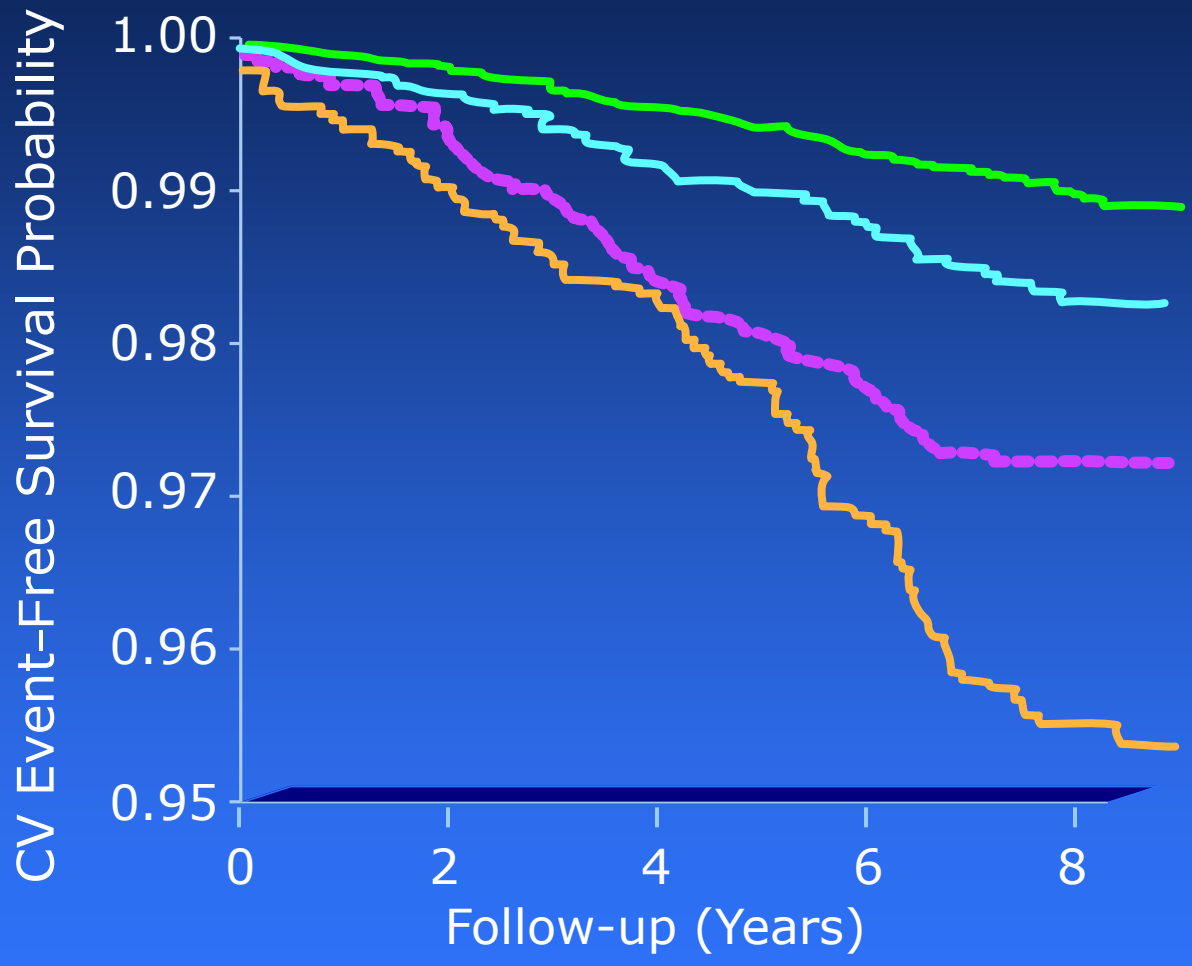
- Abdominal obesity
- Atherogenic dyslipidemia
  - Elevated triglycerides
  - Small LDL particles
  - Low HDL cholesterol
- Raised blood pressure
- Insulin resistance (± glucose intolerance)
- Prothrombotic state
- Proinflammatory state

Risk Factor	Defining Level
Abdominal obesity (Waist circumference)	population specific*
Men	≥102 cm (>40 in)
Women	≥88 cm (>35 in)
TG	≥150 mg/dL
HDL-C	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/≥85 mm Hg
Fasting glucose	≥100 mg/dL

* South Asian: Male ≥90 cm; Female ≥80 cm

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA*. 2001;285:2486-2497.

CV Event–Free Survival according to Metabolic Syndrome Status and CRP Levels: *Women's Health Study*



CRP < 3 mg/L,
No metabolic syndrome

CRP ≥ 3 mg/L,
No metabolic syndrome

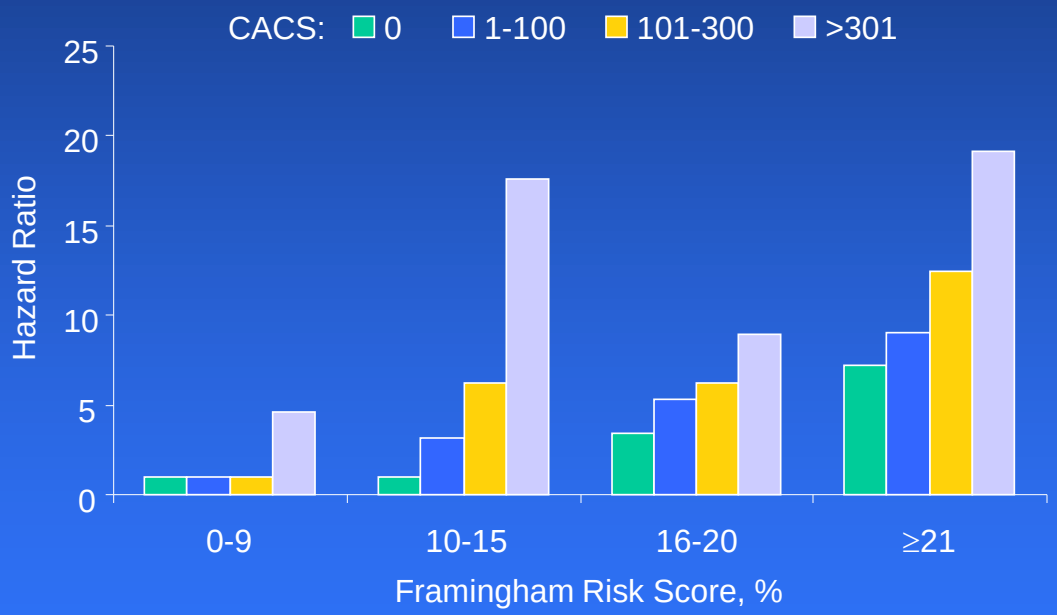
CRP < 3 mg/L,
Metabolic syndrome

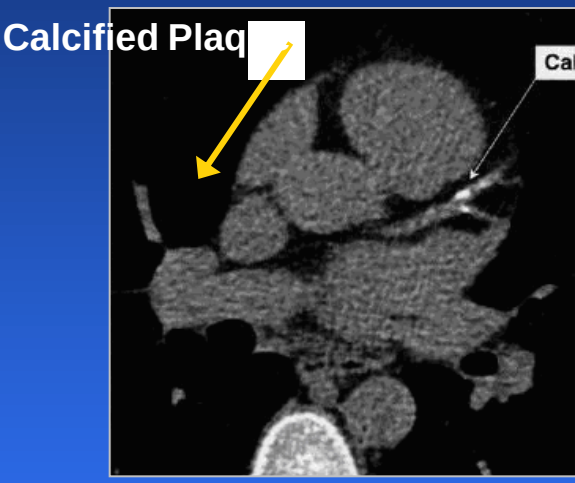
CRP ≥ 3 mg/L,
Metabolic syndrome

Ridker PM et al. *Circulation* 2003;107:391-397.

Noninvasive Screening – Coronary Artery Calcium Score (CACS)

Relationship between CACS and the baseline Framingham risk score in the prediction of coronary death or nonfatal MI*





Multidetector CT calcium scoring image

*Hazard ratio by bivariate Cox regression analysis. Risk categories are the estimated 10-year risk for coronary death or MI based on the Framingham risk score. The CACS is measured by coronary computed tomography (CCT).

Greenland P, et al. *JAMA*. 2004;291:210-215.

ATP III: Additional CHD Risk Factors

- Emerging risk factors: can help reassess risk and guide intensity of risk-reduction therapy
  - Lipoprotein(a)
  - Impaired fasting glucose
  - Subclinical atherosclerosis
  - LDL Particle number
  - Homocysteine
  - Prothrombotic factors
  - Proinflammatory factors
- Life-habit risk factors: targets for intervention; not used to set lower LDL-C goal
  - Obesity
  - Physical inactivity
  - Atherogenic diet

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA*. 2001;285:2486-2497.

Defining the High Risk Patient

- Known CHD: Prior infarction, documented CAD angiographically, positive stress test, typical angina
- Other clinically significant vascular disease such as carotid artery disease, prior stroke, aortic aneurysm, PVD
- Diabetes
- > 20% ten year risk of myocardial infarction (MI) or CHD related mortality: e.g. Framingham risk score (FRS)
- Intermediate risk by clinical criteria (10 to 20% ten year risk) with other risk factors such as strong family history of premature CHD, metabolic syndrome, elevation of other markers of risk or inflammation: e.g. hs-CRP, LP(a), carotid IMT (intimal medial thickness), coronary calcification score, ABI (ankle-brachial index)
- Rheumatoid arthritis, Lupus

Question

What are the LDL and Non-HDL goals for therapy?

1) LDL <70 mg/dL and non-HDL <100 mg/dL
2) LDL <100 mg/dL and non-HDL <130 mg/dL
3) LDL <130 mg/dL and non-HDL <160 mg/dL

NCEP-ATP III and 2004 Modifications

The first priority is to lower LDL-C. The first line drug is statin
Secondary goal is non-HDL-C: LDL-C goal + 30 mg/dL

Risk Category	LDL-C (mg/dL)	Non-HDL-C (mg/dL)
CHD/CHD risk equivalents (10-year risk >20%)	**<100 Optional <70**	**<130 Optional <100**
≥2 risk factors (10-year risk 10%-20%	<130 Optional <100	<160 Optional <130
≥2 risk factors (10-year risk <10%	<130	<160
0–1 risk factor	<160	<190

If LDL-C targets not achieved with maximum tolerated statin therapy treat to achieve at least 30 to 40% reduction in LDL-C

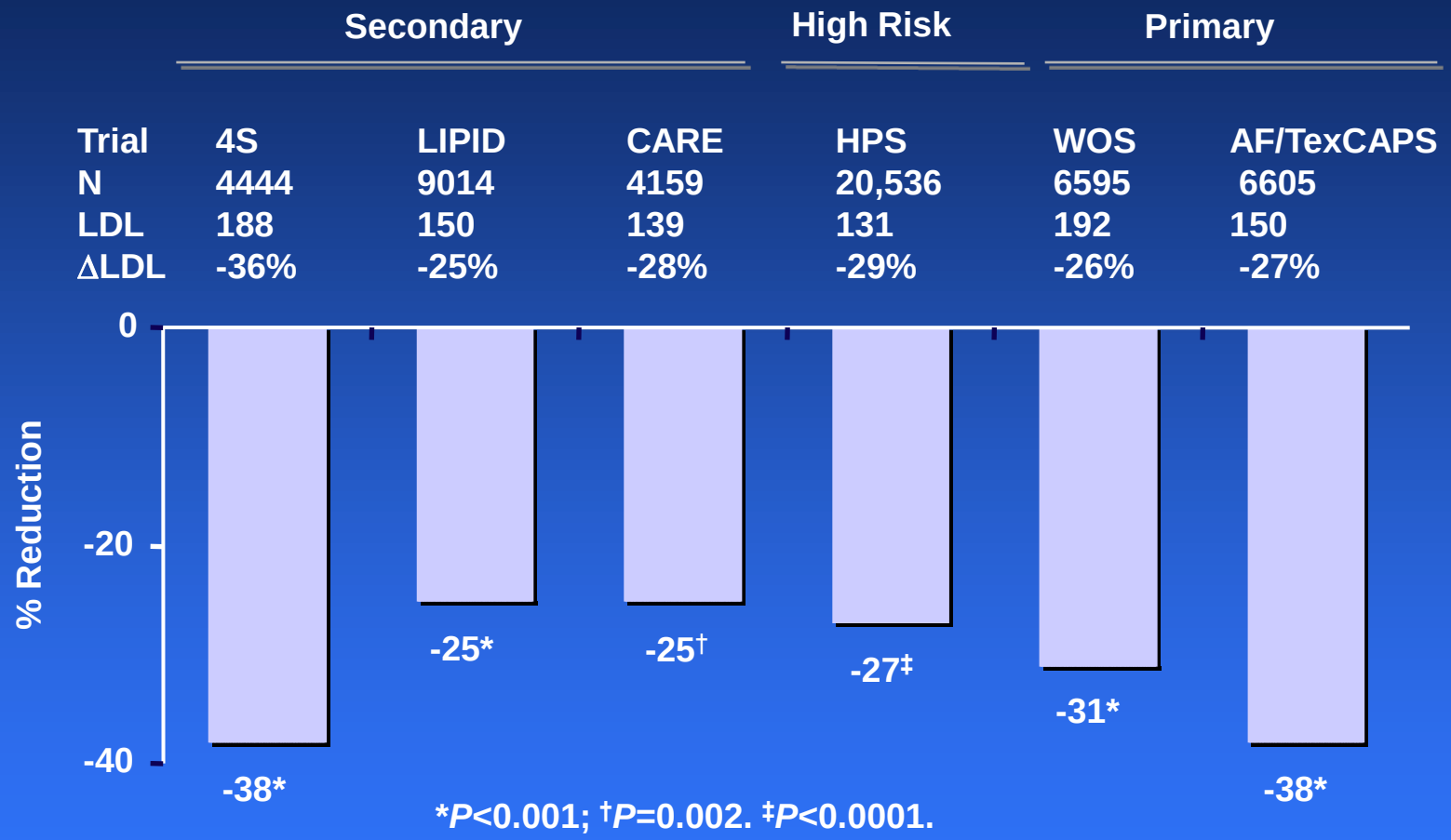
NCEP Report. *Circulation.* 2004;110:227-239.

Question

What should be the initial therapy?

1) Therapeutic life style changes (TLC) trial for 3 months before considering medications
2) Pravastatin 20 mg/day
3) Simvastatin 40 mg/day plus TLC
4) Ezetimibe

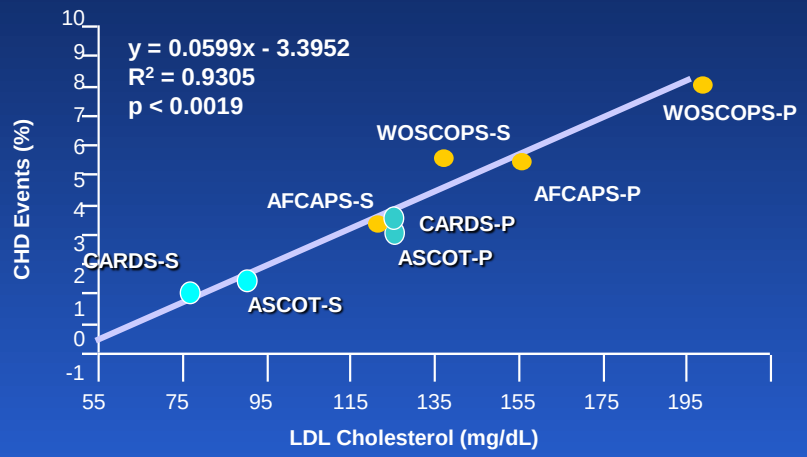
Overview of Statin Trials
Major Coronary Events



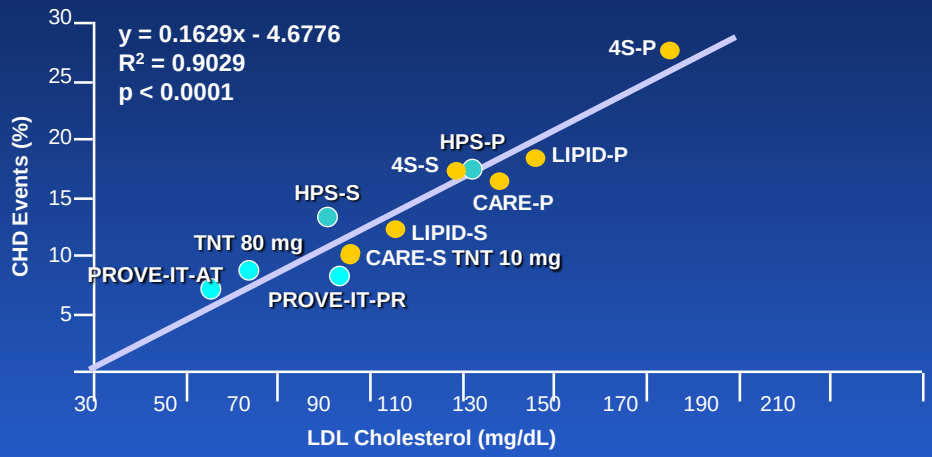
HPS Collaborative Group. *Lancet*. 2002;360:7-22; LaRosa et al. *JAMA*. 1999;282:2340-2346.

Summary of Lipid Lowering Trials

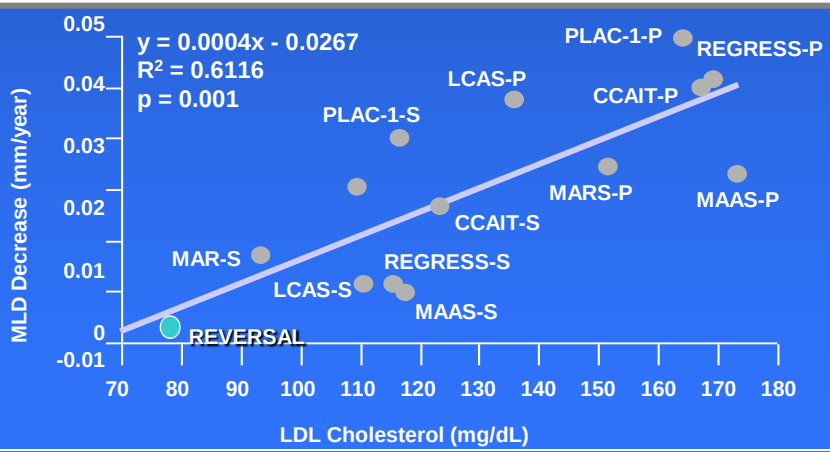
Primary Prevention Trials



Secondary Prevention Trials



Angiographic ("Regression") Trials

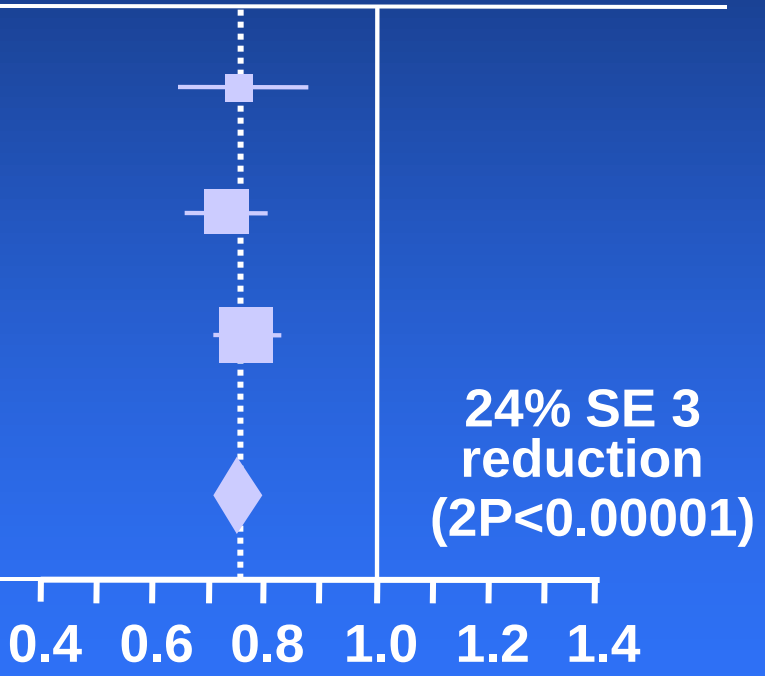


HPS: Statin Benefit is Independent of Baseline LDL

20,536 Patients

Risk ratio and 95% CI

Baseline LDL (mg/dl)	Statin (10,269)	Placebo (10,267)
<100 (n=3,421)	282	358
100–129 (n=7,068)	668	871
≥130 (n=10,047)	1083	1356
All patients	2033 (19.8%)	2585 (25.2%)



Heart Protection Study Collaborative Group. *Lancet* 2002;360:7–22.

Modifications to NCEP-ATP III Based on Recent Clinical Evidence

- LDL-C goal <70 mg/dL is therapeutic option for very high-risk patients
  - Extends to patients at very high risk with baseline LDL-C <100 mg/dL
- Factors that favor the optional goal of <70 mg/dL include CVD plus
  - Multiple major risk factors (especially diabetes)
  - Severe and poorly controlled risk factors (especially smoking)
  - Metabolic syndrome
  - Acute coronary syndromes
- For moderately high risk patients, LDL-C <100 mg/dL is an option
- Treat to achieve at least a 30 to 40% reduction in LDL-C
- Optimize statin therapy to highest tolerated dose to achieve goal before adding additional therapies
- In patients with elevated LDL-C at baseline (≥160 mg/dL)
  - Standard statin doses not sufficient for optimal LDL-C reduction
  - Consider high dose statins and/or combination therapy

Grundy et al. *Circulation.* 2004;110:227.

Reasons for Stopping Statins

- Myalgias, elevated CPK
- LFT abnormalities
- GI intolerance/headache
- Memory loss
- Causes Diabetes
- Bad press/misconceptions/drug resistant patient/cost

- How common are these adverse reactions?
- How would you treat these patients?

Terminology to Describe Muscle Injury

Condition	Definition
Myalgia	muscle ache or weakness *without* creatine kinase (CK) elevation[1]
Myopathy	muscle symptoms *with* increased CK levels >10 x ULN[2]
Rhabdomyolysis	muscle symptoms with marked CK elevation (typically >10 x ULN) and with creatinine elevation (usually with brown urine and urinary myoglobin)[1]

1. Pasternak et al. *Circulation*. 2002;106:1024-1028.
2. Evans et al. *Drug Saf*. 2002;25:649-663.

Case: Question

What is the incidence of rhabdomyolysis with statin use

1) <0.1%
2) 0.1 to 0.5%
3) 0.5 to 1%
4) 1 to 2%

Incidence of Myopathy and Rhabdomyolysis With Statins

- Dose-related myopathy occurs in approximately 0.1% to 0.5% of patients on statin monotherapy[1]
- The incidence of statin-associated rhabdomyolysis across large, randomized, controlled statin trials is <0.1%[2*]
- The reported incidence of fatal rhabdomyolysis with statins is extremely rare:
  - 0.15 death per 1 million prescriptions[3**]
- A review of 5 large-scale controlled clinical trials of statin safety reported the following[2]:
  - Rate of myopathy ranged from 0.1% to 0.6%
  - Rate of rhabdomyolysis ranged from 0.03% to 0.05%
- Myalgias reported in prescribing info: 1.2 to 3.2%

*Based on clinical trials published between 1990 and 2003.
**Based on FDA reports of rhabdomyolysis from January 1, 1990, to March 31, 2002.

1. Omar et al. *Ann Pharmacother*. 2002;36:288-295.
2. Thompson et al. *JAMA*. 2003;289:1681-1690.
3. Staffa et al. *N Engl J Med*. 2002;346:539-540.

Statin Advisory: Risk Factors for Statin-Associated Myopathy

- Myopathy more likely to occur at higher doses
- Attention should be paid to factors that may increase risk for myopathy

Concomitant meds or consumption of:

- Fibrates: gemfibrozil
- Nicotinic acid (rarely)
- Cyclosporine
- Azole antifungals
  - Itraconazole, ketoconazole
- Macrolide antibiotics
  - Erythromycin, clarithromycin
- HIV protease inhibitors
- Nefazodone (antidepressant)
- Verapamil
- Amiodarone
- Large quantities of grapefruit juice (>1 qt/d)
- Alcohol abuse

Other considerations:

- Advanced age (especially >80 yr; women > men)
- Genetics
- Small body frame, frailty
- Multisystem disease (eg, chronic renal insufficiency, especially in DM)
- Multiple medications
- Perioperative periods
- Obstructive liver disease
- Hypothyroid
- Transplant patients

Pasternak RC et al. *J Am Coll Cardiol*. 2002;40:568-573.
Pasternak RC et al. *Circulation*. 2002;106:1024-1028.

CK Elevation

With Symptoms:

- Document severity of symptom
- Evaluate for other causes
- Stop statin if muscle weakness, pain or dark urine
- <3X ULN, then consider lowering the dose, recheck
- >3X ULN then stop statin, recheck CK in 5-7 days, if stable repeat in 4-6 weeks
- >10X ULN, stop statin check for rhabdo

Without Symptoms:

- Recheck CK and document to see if there is weakness on exam. Recheck other medications carefully. Look for secondary causes
- If CK less than 3X ULN, continue statin and recheck in 6 weeks
- CK 3-10X ULN, then either reduce or stop statin
- CK >10X ULN, stop statin and work-up for myositis

Asymptomatic Baseline CK elevation

- CK <3X ULN
  - May start statin, recheck in 2 months
- CK 3-10X ULN
  - Look for cause (hypothyroidism etc)
  - Low dose statin, repeat CK 4-6 weeks
- CK >10X elevated
  - Hold statin
  - Look for cause

Question

The reported dose related range of liver function abnormalities with statin use is

1) <0.1 to 2%
2) 1 to 4%
3) 3 to 6%

Question

Statin	Dose (mg)	Serum Transaminase Elevations (%)
Crestor® (rosuvastatin calcium)	5 10 20 40	0.4 0.0 0.0 0.1
Lipitor ® (atorvastatin calcium)	10 20 40 80	0.2 0.2 0.6 2.3
Pravachol® (pravastatin sodium)	20 40	≤1.2
Vytorin™ (ezetimibe/simvastatin)	All Doses 10/80	1.8 3.6
Zocor® (simvastatin)	20 40 80	~1.0

Statins and ALT/AST Abnormalities

ALT/AST < 3X ULN

- Review meds/ETOH
- Look for other causes
- Repeat labs in 6-12 weeks on same or lower dose

ALT/AST ≥ 3X ULN

- Repeat in 1 to 2 weeks, if persistently high, stop statin
- Recheck in 2 to 4 weeks
- May consider rechallenge with lower dose or different statin

Should you Start Statins in Someone with elevated ALT/AST?

- **Kiyici et al.,**
  - 44 patients with biopsy proven NASH
  - Atorvastatin 10mg for 6 months
  - Decrease in cholesterol, AST, ALT, AP, and GGT

- **Chalasani et al., (moderate AST/ALT elevation)**
  - Effect of statins over 6 months (mild/moderate, severe)
    - High AST/ALT placed on statin (4.7%, 0.6%)
    - High AST/ALT not placed on statin (6.4%, 0.4%)
    - Normal AST/ALT placed on statin (1.9%, 0.2%)

Statin-Associated Transaminase Elevations

- Progression to liver failure due to statins is exceedingly rare
- Reversal of transaminase elevation is frequently noted with a reduction in statin dose
  - Elevations do not often recur with either readministration or selection of another statin
- Statins have not been shown to worsen the outcome in persons with chronic transaminase elevations due to hepatitis B or C
- Treatment of hyperlipidemia may actually improve transaminase elevations in individuals with fatty liver condition

Pasternak et al. ACC/AHA/NHLBI Advisory on the Use and Safety of Statins. *Circulation*. 2002;106:1024-1028.

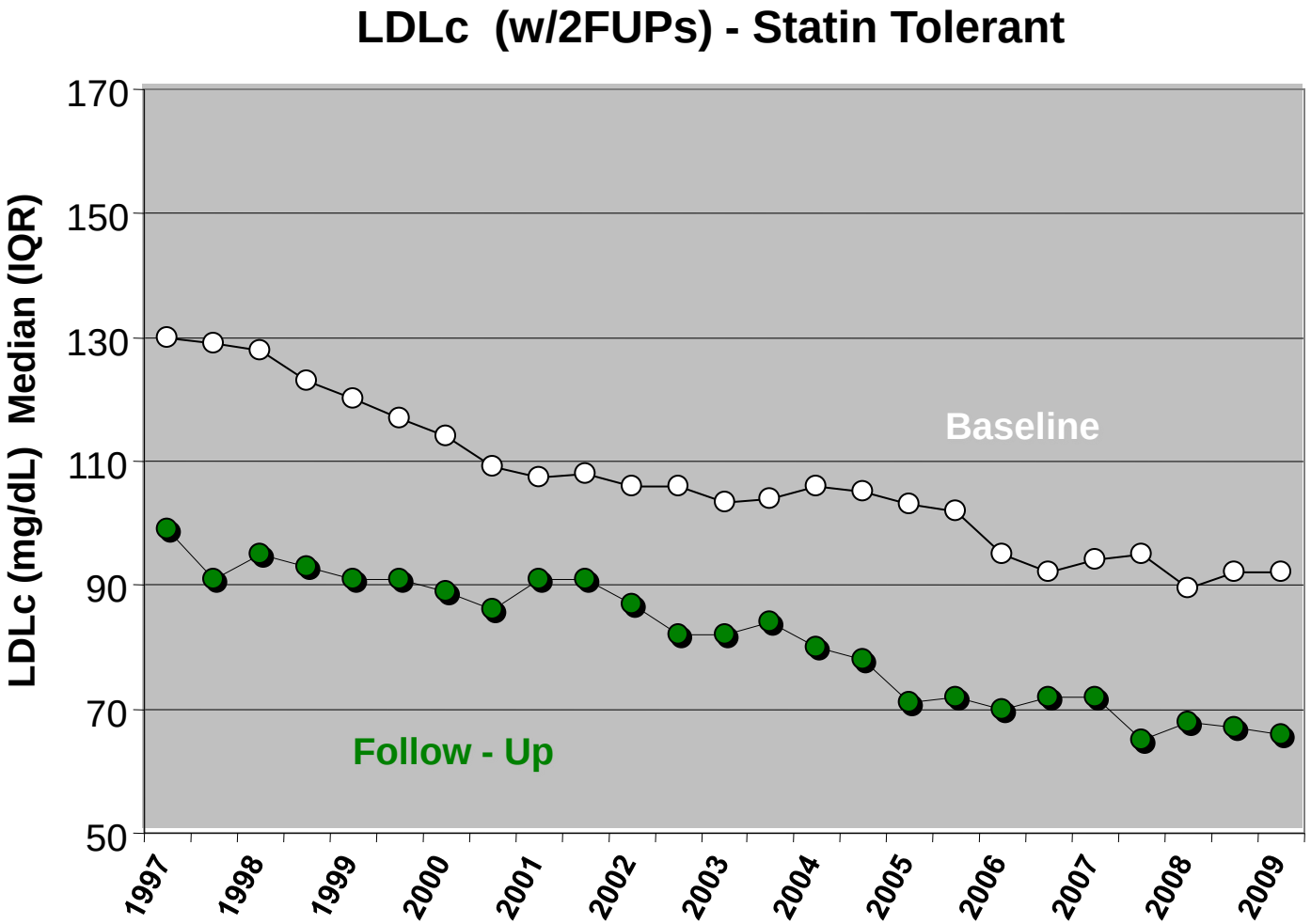
Statin Advisory: Monitoring Parameters, Follow-Up Schedule

Headache, dyspepsia	Evaluate baseline symptoms, 6–8 wk after initiating therapy, then at each follow-up visit
Muscle soreness, tenderness, or pain	Evaluate baseline muscle symptoms and CK levels; muscle symptoms 6–12 wk after initiating therapy and at each follow-up visit; CK measurement when muscle soreness, tenderness, or pain present
ALT, AST	Evaluate baseline ALT/AST, 12 wk after initiating therapy, then annually or as indicated

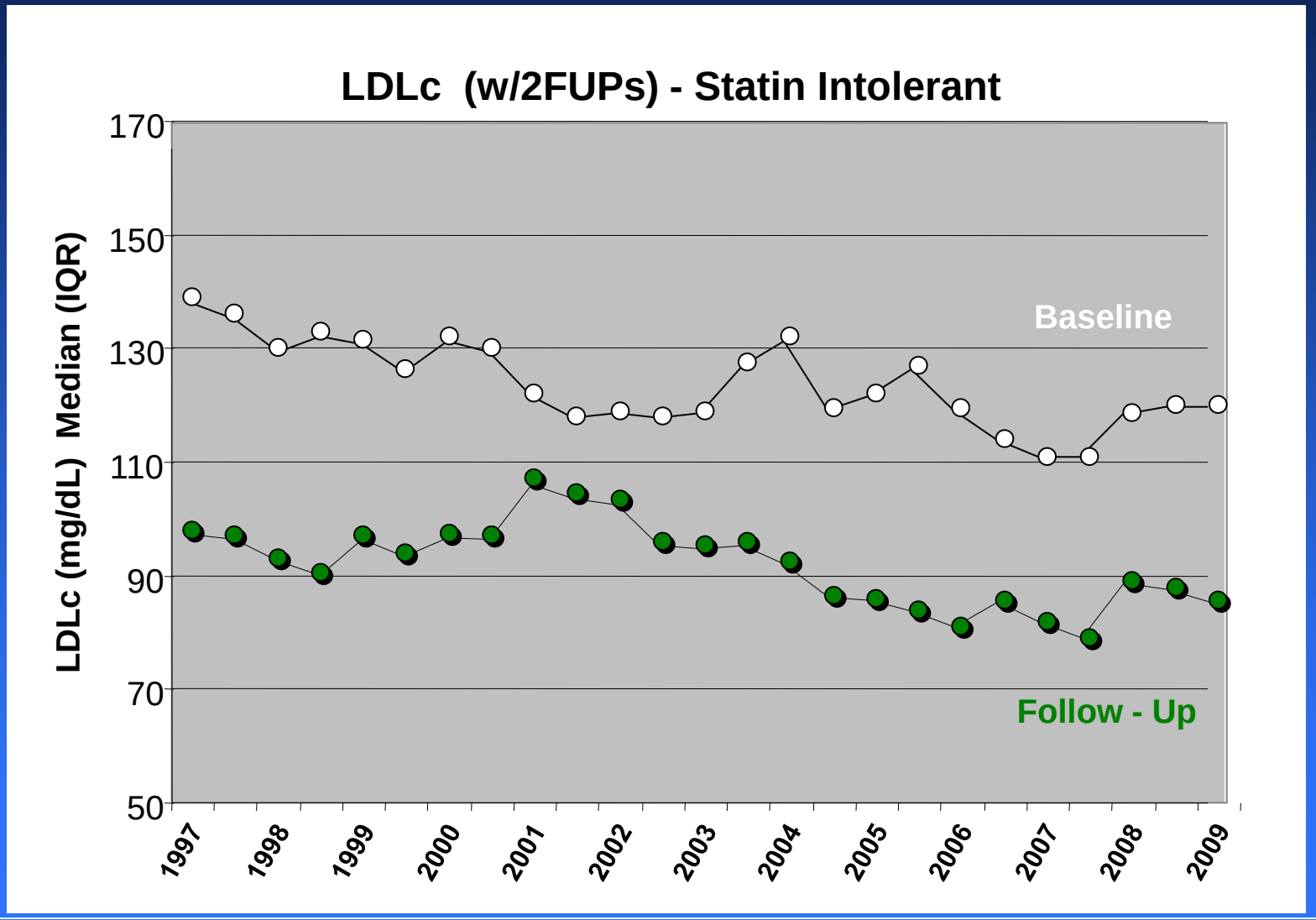
ALT=alanine transferase; AST=aspartate transferase.

Pasternak RC et al. *J Am Coll Cardiol*. 2002;40:568-573.
Pasternak RC et al. *Circulation*. 2002;106:1024-1028.

Prevention – Secondary Population LDL



Prevention - Secondary Population LDL



Statin Intolerance

Comparison of Lipoprotein percent Changes between different strategy groups

a: p<0.05 compared to intermittent dosing; b: p<0.05 compared to daily dosing

Lipoprotein change (%) LS Mean + SE	Statin Discontinued n=442	Intermittent Statin Dosing n=142	Daily statin dosing n=1014
TC	-8.8± 1.5[ab]	-17.2 ± 2.7[b]	-21.2 ± 0.9
LDL-C	-8.3 ± 2.2[ab]	-21.3 ± 4.0[b]	-27.7 ± 1.4
HDL-C	-0.2 ± 1.3[b]	-0.2 ± 2.3[b]	2.9 ± 0.8
TG	-15.1 ± 2.7[b]	-13.7 ± 5.0[b]	-21.1 ± 1.7

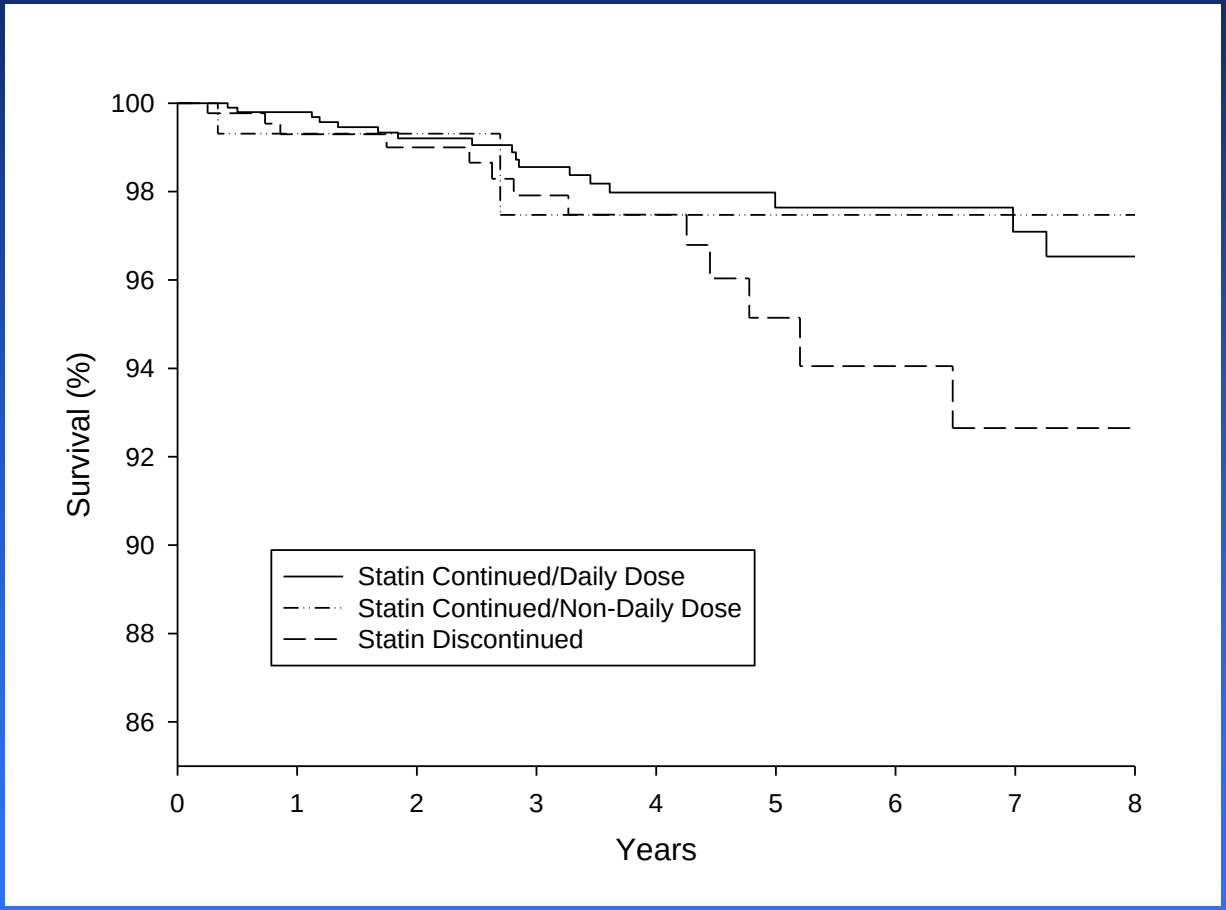
Comparison of Lipoprotein percent Changes between different rosuvastatin 2.5 to 5 mg strategy groups

a: p<0.05 compared to intermittent dosing; b: p<0.05 compared to statin-discontinued group

Lipopro-tein change (%) LS Mean ± SE	Statin disconti-nued n=442	Once per week n=29	Twice per week n=28	Thrice per week n=31	More than trice per week n=9	daily n= 158
TC	-4.5±1.3[a]	-9.2±4.7[a]	-3.1±4.3[a]	-13.8±5.0[b]	-20.3±8.9[b]	-19.7±2.1[b]
LDL-C	1.9±2.7[a]	-12.0±6.8[a]	-10.5±6.1[a]	-16.8 ±7.2[b]	-25.4±12.9[b]	-27.6±3.0[b]
HDL-C	2.8±1.3	-2.1±3.7	4.0±3.4	2.0±3.8	0.1 ±6.9	0.3±1.6
TG	-4.4±2.6[a]	-7.0±8.6	-10.0±7.8	-15.5±8.8	-24.0±16.1	-15.6±3.7

Mampuya w et al. Abstract AHA 2011

Statin Intolerance



Mampuya w et al. Abstract AHA 2011

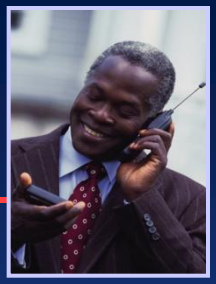
Statin Intolerance

- Search for other causes
- Trial of different statin or stop and rechallenge at lower dose
- Trial of low dose, reduced frequency of potent statin
- Trial of Co Enzyme Q10 for myalgias

- Non-statin drug therapies
  - Niacin with ezetimibe
  - Niacin with Resin

- Emphasis on TLC
  - Nutrition consultation
    - Plant stanols and sterols
    - Soluble fiber: dietary, supplemental
  - Exercise Rx

Case: Mr. Smith
History and Physical Exam

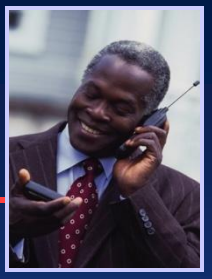


- 49-year-old African-American male recently diagnosed with type 2 diabetes
- Past medical history of hypertension on medications
- Admits to sedentary lifestyle and no time for exercise. When he tries to walk briskly uphill, he develops a cramp in the left calf.
- Denies any other history of previous cardiovascular symptoms or previous cardiovascular testing
- Smokes 1ppd, drinks alcohol occasionally
- No complaint of ED
- Family Hx: Father RCA stent age 54, died age 62 of MI: Mother and aunt have diabetes
- Medications
  - Metformin 500 mg bid
  - Amlodipine 10 mg qd

- 5´10˝, 225 lb
- BMI=32.3; waist 40˝
- BP: 142/90 mm Hg

- Normal S1, S2, no murmurs, rubs or gallops
- Chest clear
- No JVD
- Carotids normal no bruits
- Left femoral bruit
- No edema

Case: Mr. Smith
Laboratory Data



Baseline (fasting levels)	
Total C	232 mg/dL
LDL-C	140 mg/dL (calculated)
HDL-C	36 mg/dL
TG	278 mg/dL
Glucose	156 mg/dL
HbA_{1C}	7.6% (nl: 4–6)
TSH	1.2 mU/L

- **CBC normal**
- **Creatinine: 1.32 Complete metabolic panel otherwise normal**
- **Albumin/creatinine ratio of 56 mcg/mg**
- **Ankle brachial index (ABI) of 0.81 on left (normal >0.90)**
- **EKG: normal sinus rhythm, LVH by voltage criteria**
- **ABI was 0.84 on the left and 1.12 on the right**

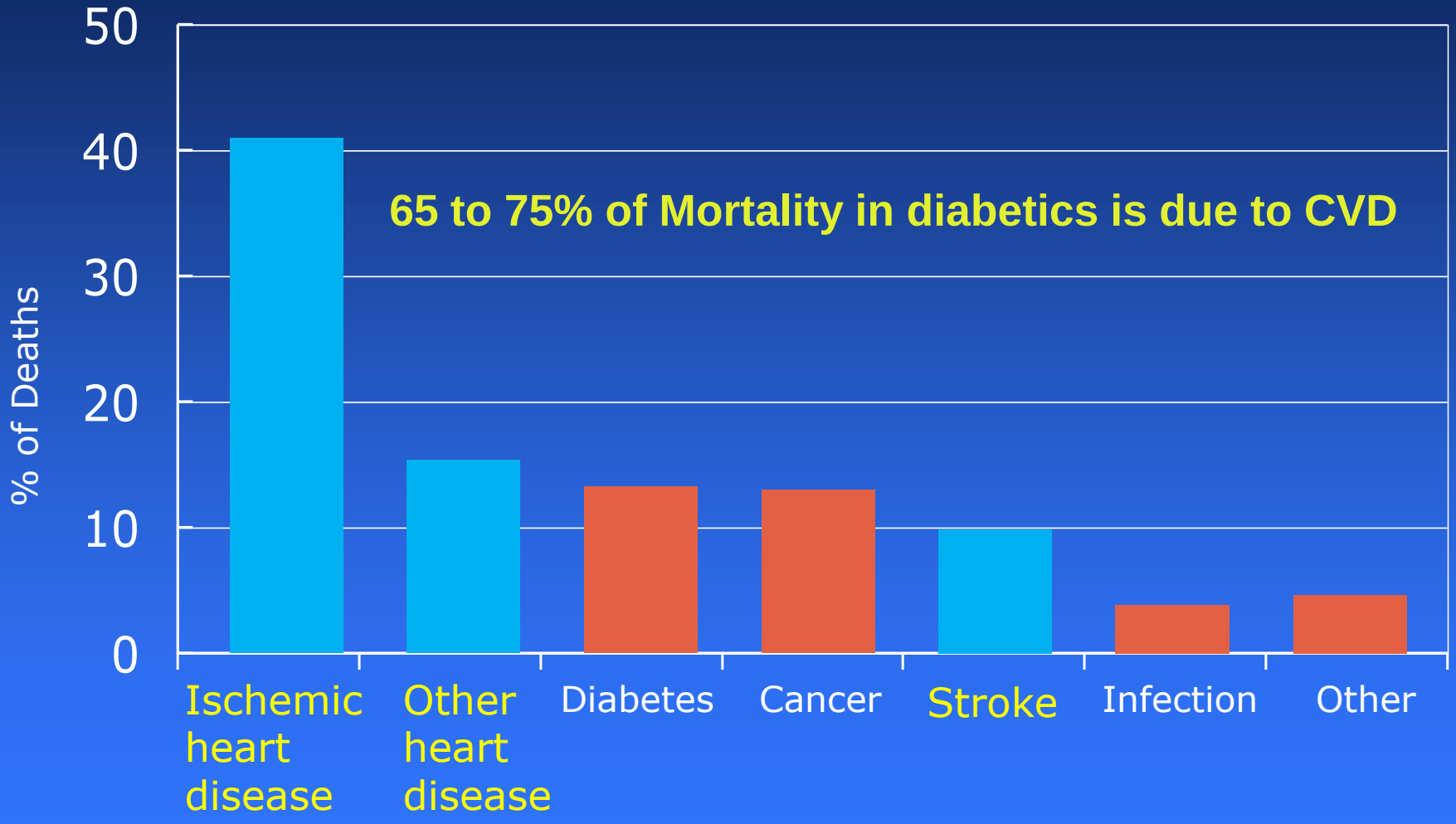
C=cholesterol; TG=triglycerides; HbA_{1c}=hemoglobin A_{1c}; TSH=thyroid-stimulating hormone.

Question

Mr. Smith's CVD Risk (annual CVD event rate) is

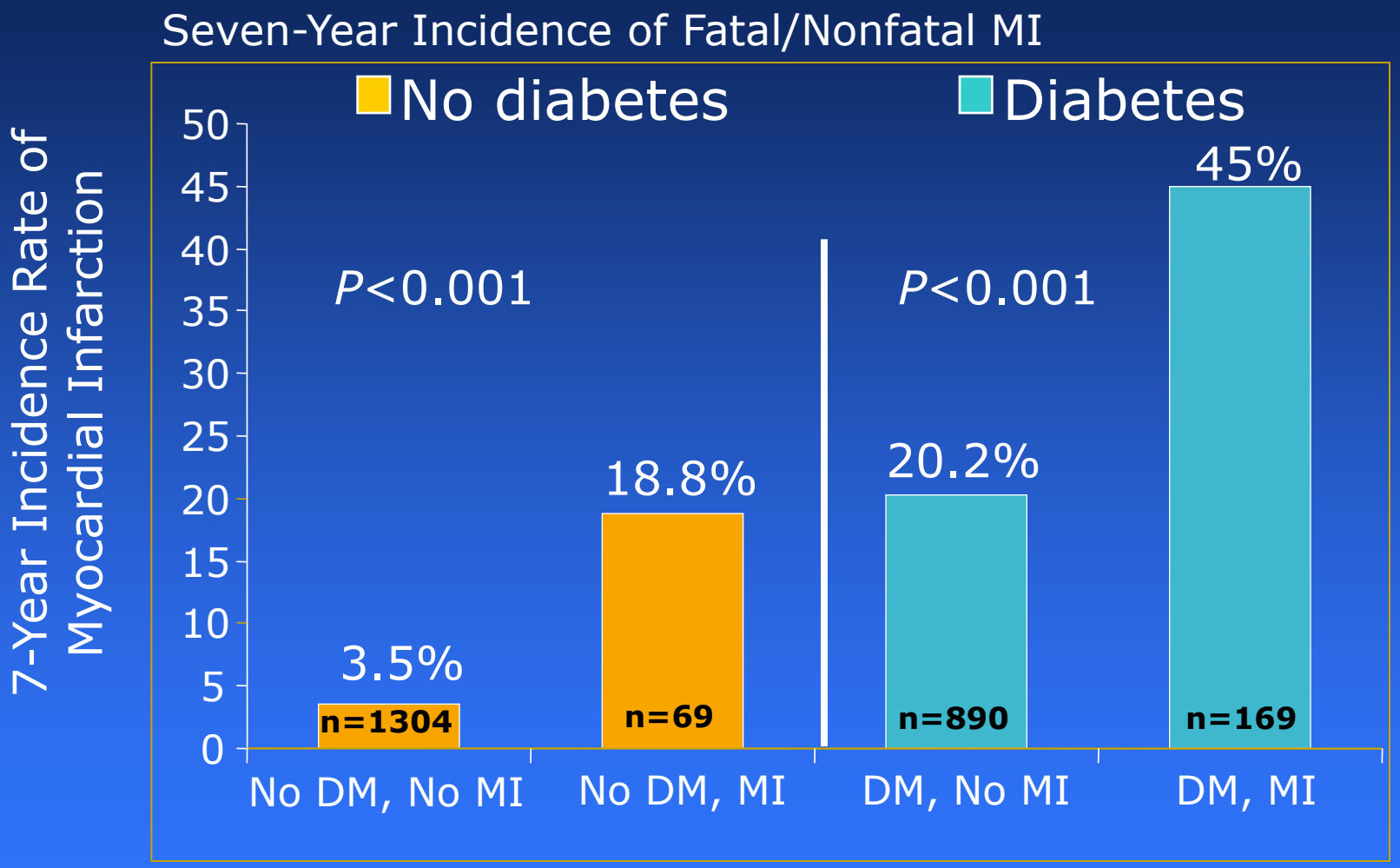
1) Low (< 1%)
2) Intermediate (1 to 1.5%)
3) High intermediate (1.5 to 2%)
4) High (≥ 2%)

Mortality in People with Diabetes
Causes of Death



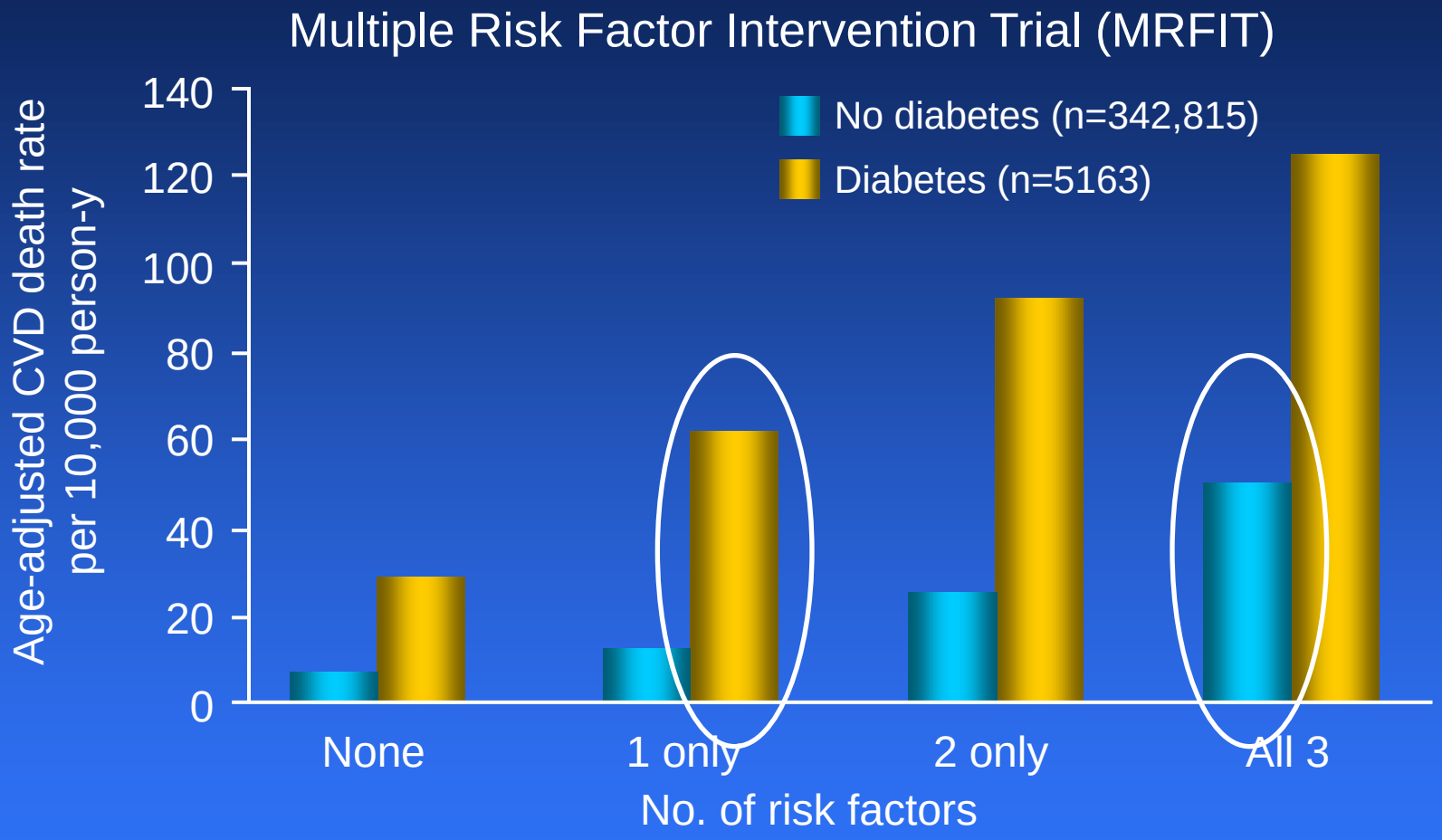
Geiss LS, et al. In: *Diabetes in America*. 2nd ed. 1995.

Type 2 Diabetes and Coronary Heart Disease



Haffner SE et al. *N Engl J Med.* 1998;339:229-234.

Influence of Multiple Risk Factors on CV Mortality in Men With and Without Diabetes



In a diabetic patient without CVD even the presence of a single risk factor confers a very high risk (80% lifetime risk of CVD)

Risk factors: cholesterol >200 mg/dL, smoking, and SBP >120 mm Hg. SBP=systolic blood pressure.

Stamler et al. *Diabetes Care*. 1993;16:434.

Goals in Management of CVD in Diabetics

- **Prevent future adverse cardiovascular events**
  - **Correctly risk stratify patient**
  - **Identify and treat risk factors**

- Improve symptomatic state
  - Enhance quality of life
- Identify extent of ischemia
  - influence revascularization for morbidity and mortality benefits
- Identify subclinical disease
  - Intensify risk factor management
  - Earlier assessment for ischemia

Question

Initial management proven to reduce cardiovascular events should consist of all of the following EXCEPT:

1) Management of lipids
2) Reduction of A1C to <6.0%
3) Aspirin
4) Change amlodipine to an ACE inhibitor
5) Exercise program and weight reduction
6) Discontinue cigarette smoking

Stepwise Selection of Risk Factors* in 2693 White Patients with Type 2 Diabetes: Time to First Event: *UKPDS*

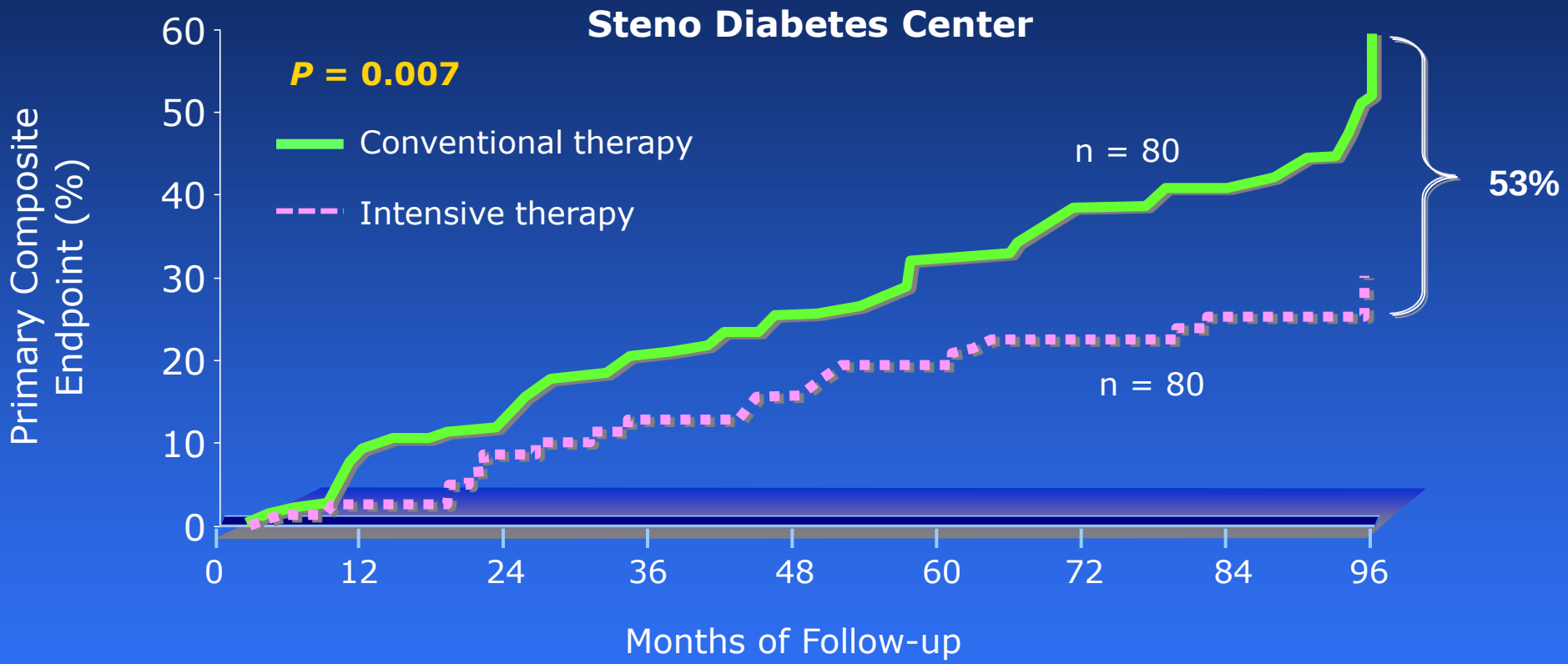
Coronary Artery Disease (n=280)

Position in Model	Variable	
First	**Low-Density Lipoprotein**	**<0.0001**
Second	**High-Density Lipoprotein**	**0.0001**
Third	Hemoglobin A_{1c}	0.0022
Fourth	Systolic Blood Pressure	0.0065
Fifth	Smoking	0.056

*Adjusted for age and sex.

Turner RC et al. *BMJ* 1998;316:823-828.

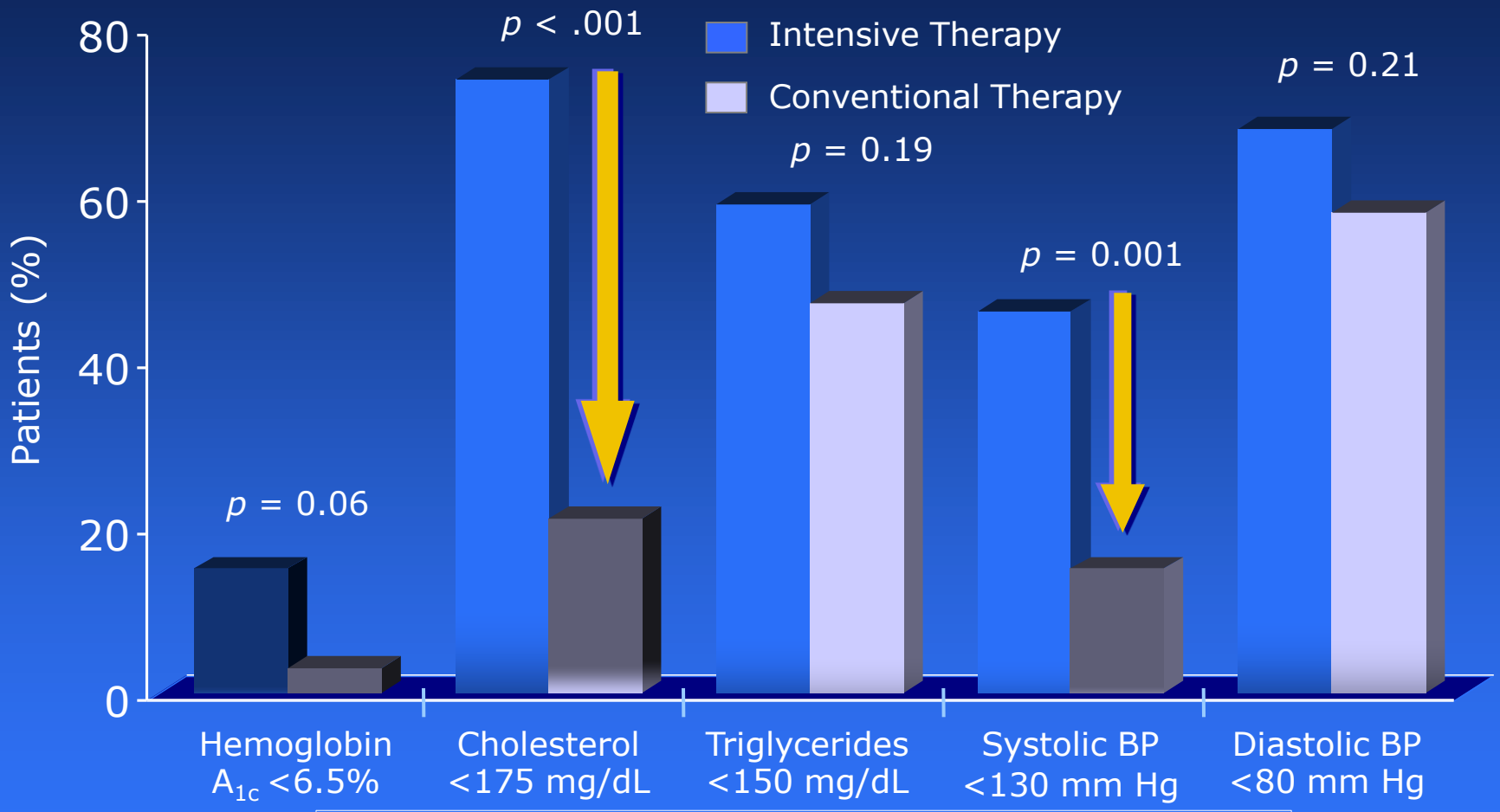
STENO-2: Reduction in Cardiovascular Disease Through a Multifactorial Intervention in Patients Who Have Type 2 Diabetes and Microalbuminuria



Intensive Treatment Goals: hemoglobin A_{1c}, <6.5%; cholesterol, <175 mg/dL; triglycerides, <150 mg/dL; systolic blood pressure, <130 mm Hg; diastolic blood pressure, <80 mm Hg.

Gaede P, et al. *N Engl J Med*. 2003;348:383–393.

STENO-2: Risk-Factor Targets Attained at 7.8 Years With an Intensive Treatment Program

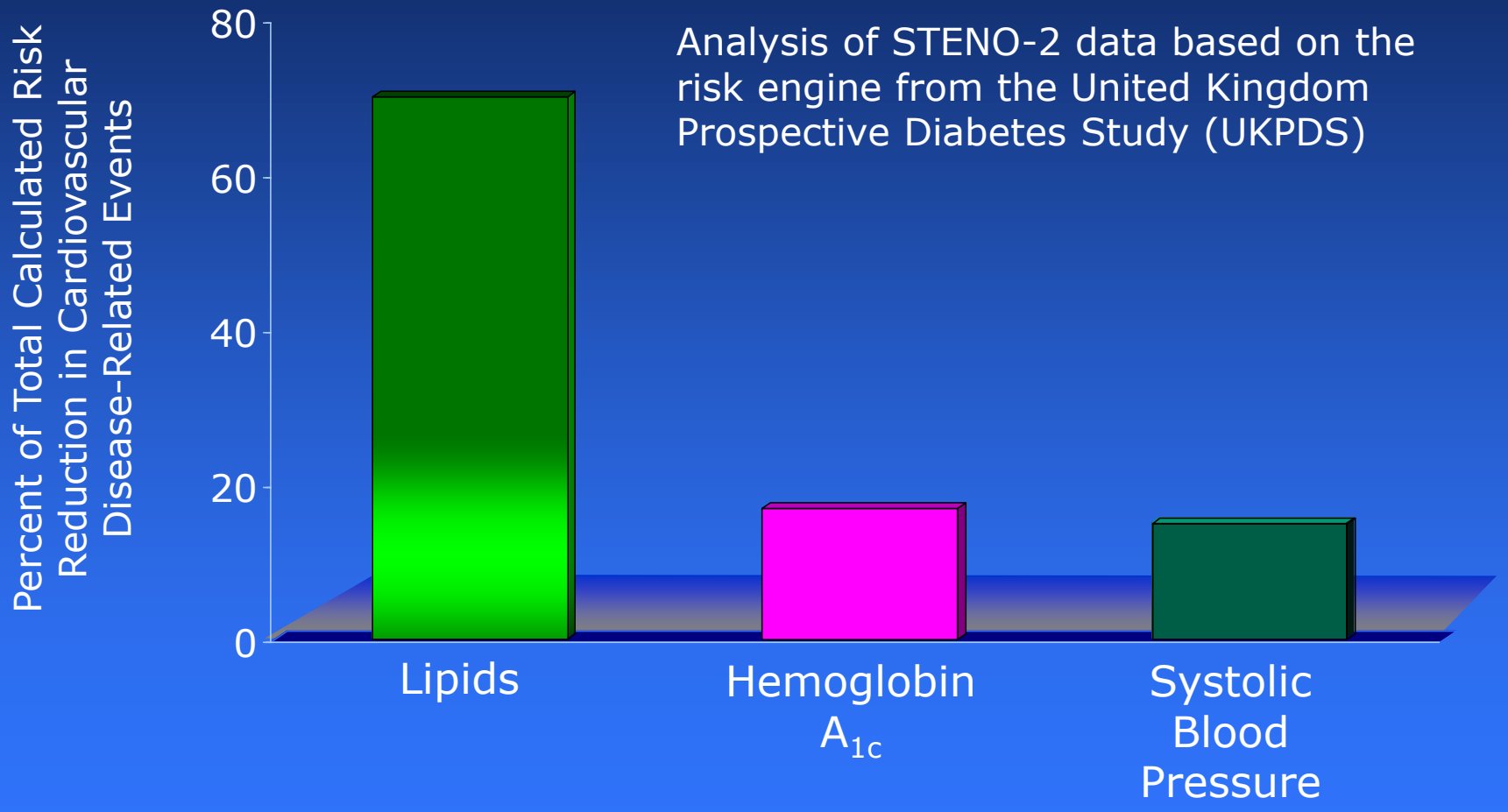


Average in intensive vs conventional group

- HbA1c: 7.9 vs 9.0
- LDL-C: 83 vs 126 mg/dL
- Systolic BP: 131 vs 146 mmHg

Gaede P, et al. *N Engl J Med*. 2003;348:383–393.

STENO-2: Lipid-lowering Therapy Accounted for More Than 70% of Cardiovascular Risk Reduction



Gaede P, Pederson O. *Diabetes.* 2004;53:S39–S47.

Question

What would be his target for therapy

1) LDL <70 mg/dL and non-HDL <100/Apo-B <80 mg/dL
2) LDL <100 mg/dL and non-HDL <130/Apo-B <90 mg/dL
3) LDL <130 mg/dL and non-HDL <160/Apo-B <100 mg/dL

ADA/ACC Consensus Statements for Patients With Diabetes Mellitus or Cardiometabolic Risks

Suggested Treatment Goal in Patients With Cardiometabolic Risk (CMR) and Lipoprotein Abnormalities	Goals		
	LDL-C[1] (mg/dL)	Non-HDL-C[1] (mg/dL)	apo B[1] (mg/dL)
Highest-risk patients: 1) Known CVD or 2) Diabetes plus one or more additional CVD risk factor(s)	<70	<100	<80
High-risk patients: 1) No diabetes or known CVD but 2 or more major CVD risk factors or 2) Diabetes but no other CVD risk factors	<100	<130	<90

Combination therapy of LDL-cholesterol lowering drugs (statins) with fibrates or niacin may be necessary to achieve lipid targets

Diabetes Care. 2008;31 811-822.

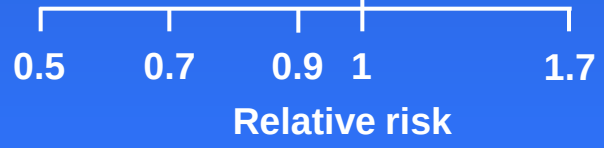
Question

How would you initially treat this patient's lipids?

1) Atorvastatin 40 mg/d
2) Simvastatin 20 mg/d plus Fenofirate 148 mg/d
3) Extended release niacin 2000 mg/d
4) Simvastatin 10 mg/d
5) Ezetimibe 10 mg/d
6) Addition of Pioglitazone
7) Omega 3 Fish oil 4000 mg/d

Benefits of Aggressive LDL-C Lowering in Diabetes

	Primary event rate (%)		Aggressive lipid-lowering better	Aggressive lipid-lowering worse	*P*	Difference in LDL-C (mg/dL)
	Treatment	Control				
ASCOT-LLA						
Diabetes, HTN	9.2	11.9	0.77		0.036	35†
CARDS						
Diabetes, no CVD	5.8	9.0	0.63		0.001	46†
HPS						
All diabetes	9.4	12.6	0.73		<0.0001	39†
Diabetes, no CVD	9.3	13.5	0.67		0.0003	39†
TNT						
Diabetes, CHD	13.8	17.9	0.75		0.026	22*



*Atorvastatin 10 vs 80 mg/day
†Statin vs placebo

HPS Collaborative Group. *Lancet* 2003.
Colhoun HM et al. *Lancet* 2004.

Shepherd J et al. *Diabetes Care* 2006.
Sever PS et al. *Diabetes Care* 2005.

Lipid Management in Diabetes: Meta-analyses

- BMJ 338: 2009
  - 10 Trials: >16,000 with DM compared to >54,000 without DM receiving standard statin therapy for 4.1 years
  - LDL 0f 140, age 63
  - Similar 30% CHD, 19% CVA, 12% mortality in both groups
- Lancet 371: 2008
  - 14 Trials: 6,956 DM with CVD compared to 11,703 without CVD
  - LDL of 132, age 64
  - Similar 22% CHD, 21% CVA, 9% mortality in both groups
- Lancet 376: 2010
  - 5 trials: 39,612 individuals with 5.1 years f/u
  - Further 15% reduction in CV risk for 0.51 mmol/L LDL reduction
  - Similar to proportional reductions of statin vs. control trials
  - Independent of baseline LDL-C

Question

Does statin therapy increase the risk of developing diabetes

1) True
2) False

Statins and Diabetes Risk

- 2012: FDA warns of small increase in blood sugar levles and type 2 diabetes with statins
- However, increase in blood sugar did not diminish the effect of statins on reducing heart disease risk.

- Conflicting results in randomized trials:
  - PROSPER: 32% increase risk of diabetes in elderly
  - JUPITER: 27% increase risk of investigator reported diabetes in rosuvastatin treated patients
  - WOSCOPS: pravastain might reduce frequency of diabetes
  - PROVE-IT: substudy: worse glycemic control with high dose atorvastatin

Sattar et al. Lancet. 2010; 375: 735-42

Statins and Diabetes Risk

- Sattar: meta-analysis of 13 statin trials in 91,140 patients
  - 4278 developed diabetes: 4.89% vs. 4.5% (.39% difference; 174 cases)
    - 9% increased risk of incident diabetes
    - ~1 additional case per 1000 patient-years
  - Highest in older patients but not influenced by statin type, BMI or change in LDL-C

- Preiss: meta-analysis of 5 trials in 32772 patients. High vs moderate dose ev
  - 2749 developed diabetes: 8.8% vs. 8.4% (.4% difference; 149 cases)
    - 12% increased risk of diabetes: 16% reduction in CVD
    - 2 additional cases per 1000 patient years
  - Not influenced by age, BMI, fasting glucose

- Risk is low in both absolute terms and when compared to reduction in CV risk

Sattar et al. Lancet. 2010; 375: 735-42
Preiss et al. JAMA. 2011; 305: 2556-64

Statins and Diabetes Risk: Clinical Implications

- Sattar and Data from Cholesterol Treatment Trialists (CTT) of 71, 370 non-diabetics
  - 5.4 less cardiac events (not including stroke or revascularization) for 255 patients treated for 4 years for each 1 mmol/L reduction in LDL-C
  - One extra case of diabetes treating 255 patients for 4 years.
- Preiss:
  - One additional case of diabetes for every 498 patients over 1 year
  - One fewer CVD event for every 155 patients over 1 year
- Questions:
  - Statin type: Hydrophilic vs. lipophilic
  - Statin dose related or aggressiveness of LDL-C lowering
  - Differential effects in different populations; elderly, metabolic syndrome, asian
  - Diabetes or increased in blood sugar
  - Association vs. causality
- The small increase risk of diabetes is outweighed by the reduction in CV risk in those for whom statin therapy is recommended
- Despite the increased in diabetes, the reduction in CVD risk is maintained across groups.

Sattar et al. Lancet. 2010; 375: 735-42
Preiss et al. JAMA. 2011; 305: 2556-64

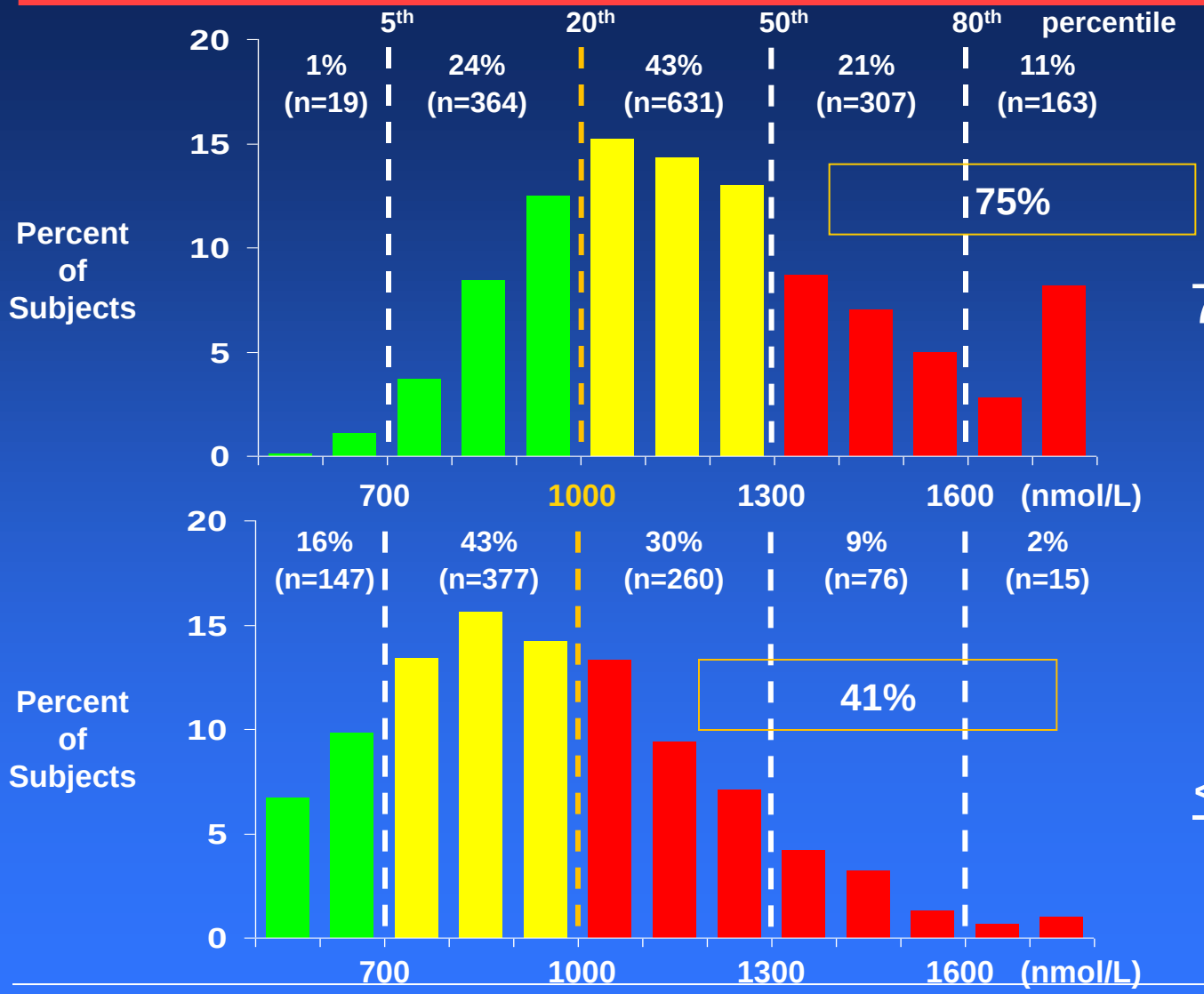
Diabetic Patients Have Particularly High Residual CVD Risk After Statin Treatment

	Event Rate (No Diabetes)		Event Rate (Diabetes)	
	On Statin	On Placebo	On Statin	On Placebo
HPS[1]* (CHD patients)	19.8%	25.7%	33.4%	37.8%
CARE[2]†	19.4%	24.6%	28.7%	36.8%
LIPID[3]‡	11.7%	15.2%	19.2%	22.8%
PROSPER[4]§	13.1%	16.0%	23.1%	18.4%
ASCOT-LLA[5]‡	4.9%	8.7%	9.6%	11.4%
TNT[6]‖	7.8%	9.7%	13.8%	17.9%

*CHD death, nonfatal MI, stroke, revascularizations
†CHD death, nonfatal MI, CABG, PTCA
‡CHD death and nonfatal MI
§CHD death, nonfatal MI, stroke
‖CHD death, nonfatal MI, resuscitated cardiac arrest, stroke
(80 mg versus 10mg atorvastatin)

[1]HPS Collaborative Group. *Lancet*. 2003;361:2005-2016.
[2]Sacks FM, et al. *N Engl J Med.* 1996;335:1001-1009.
[3]LIPID Study Group. *N Engl J Med.* 1998;339:1349-1357.
[4]Shepherd J, et al. *Lancet.* 2002;360:1623-1630.
[5]Sever PS, et al. *Lancet.* 2003;361:1149-1158.
[6]Shepherd J, et al. *Diabetes Care.* 2006;29:1220-1226.

LDL Particle Number Distribution in T2DM Patients with Low LDL-C

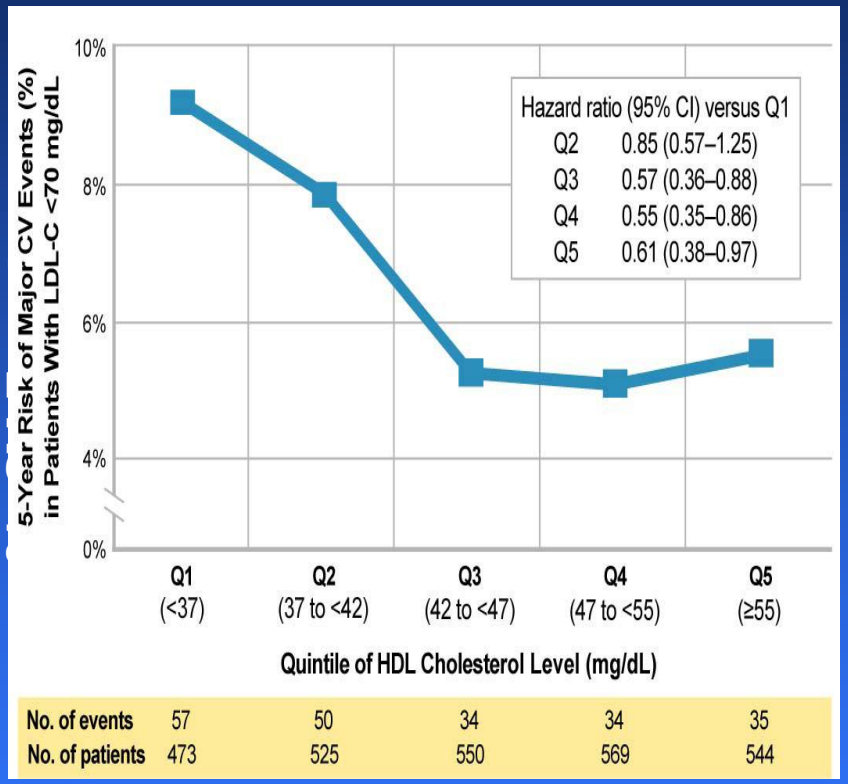


LDL-C
71-99 mg/dL
(n=1,484)

LDL-C
≤70 mg/dL
(n=871)

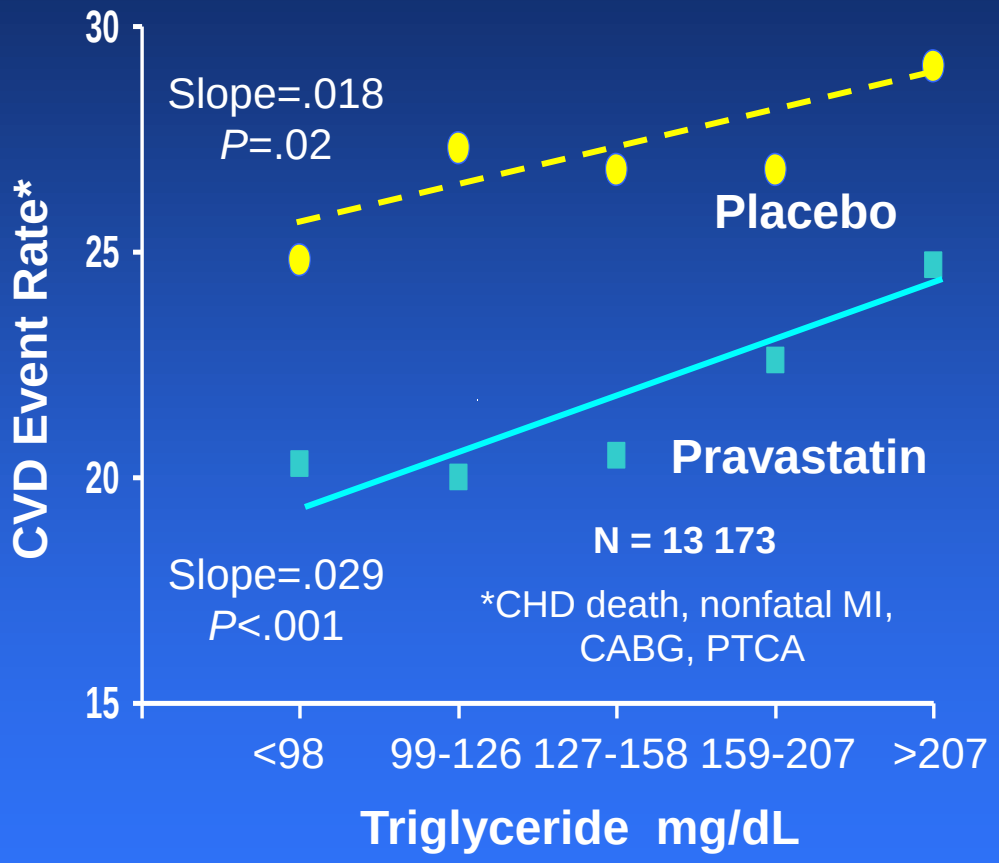
Major Cardiovascular Events on Statins: by HDL-C and Trigycerides

TNT



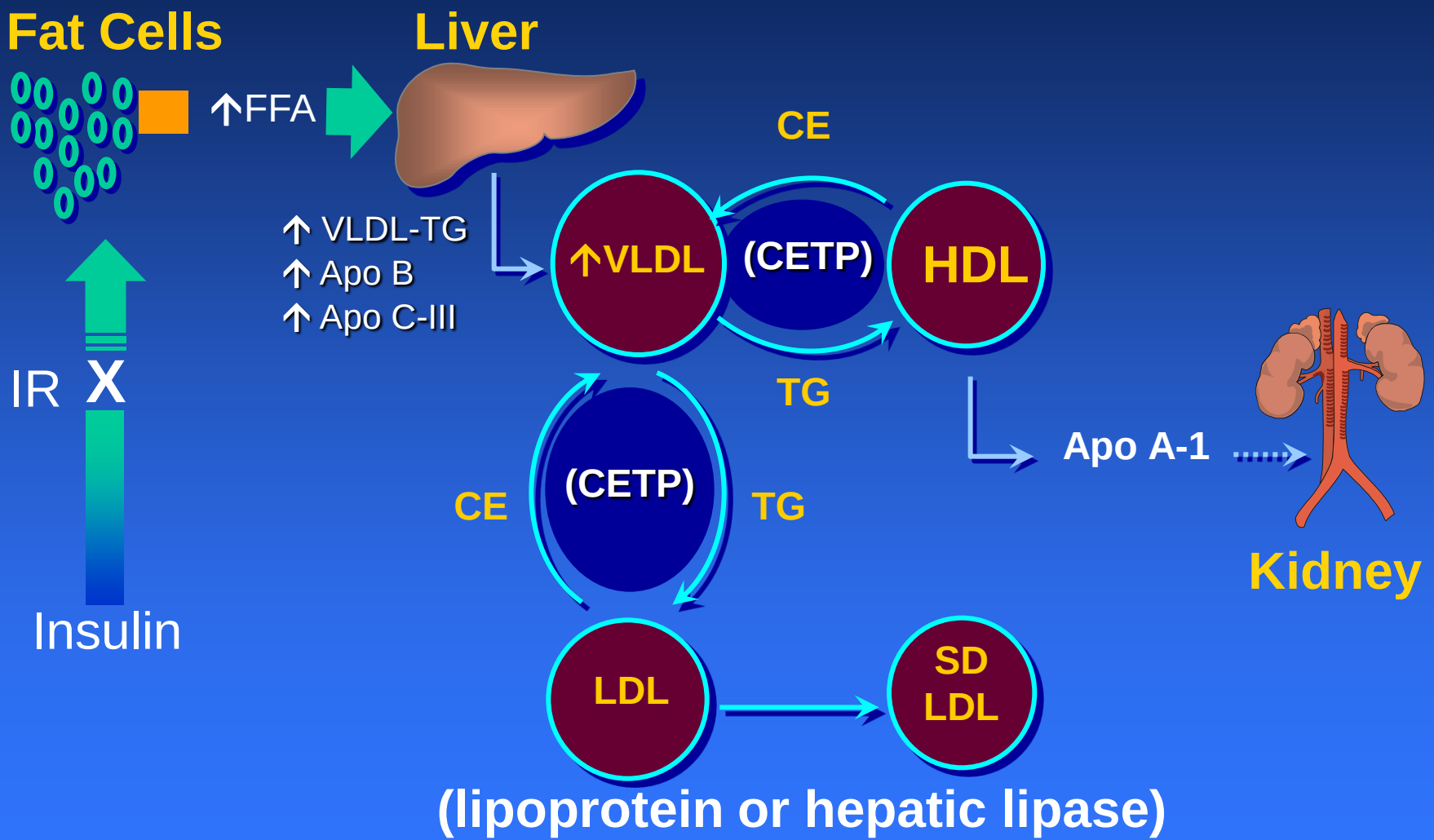
On-treatment HDL-C (mg/dL)

CARE and LIPID

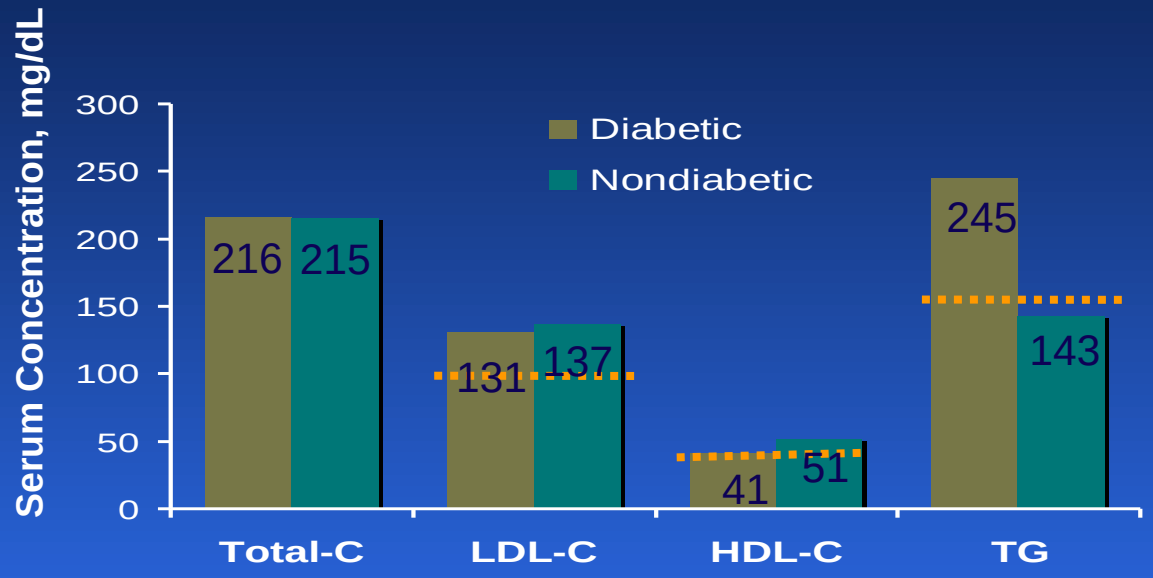


Barter PJ et al. *J Am Coll Cardiol* 2006;47:492-499.
Waters DD et al. *J Am Coll Cardiol* 2006;48:1793.

Mechanisms Relating Insulin Resistance and Dyslipidemia



Lipids in Diabetic and Nondiabetic Subjects

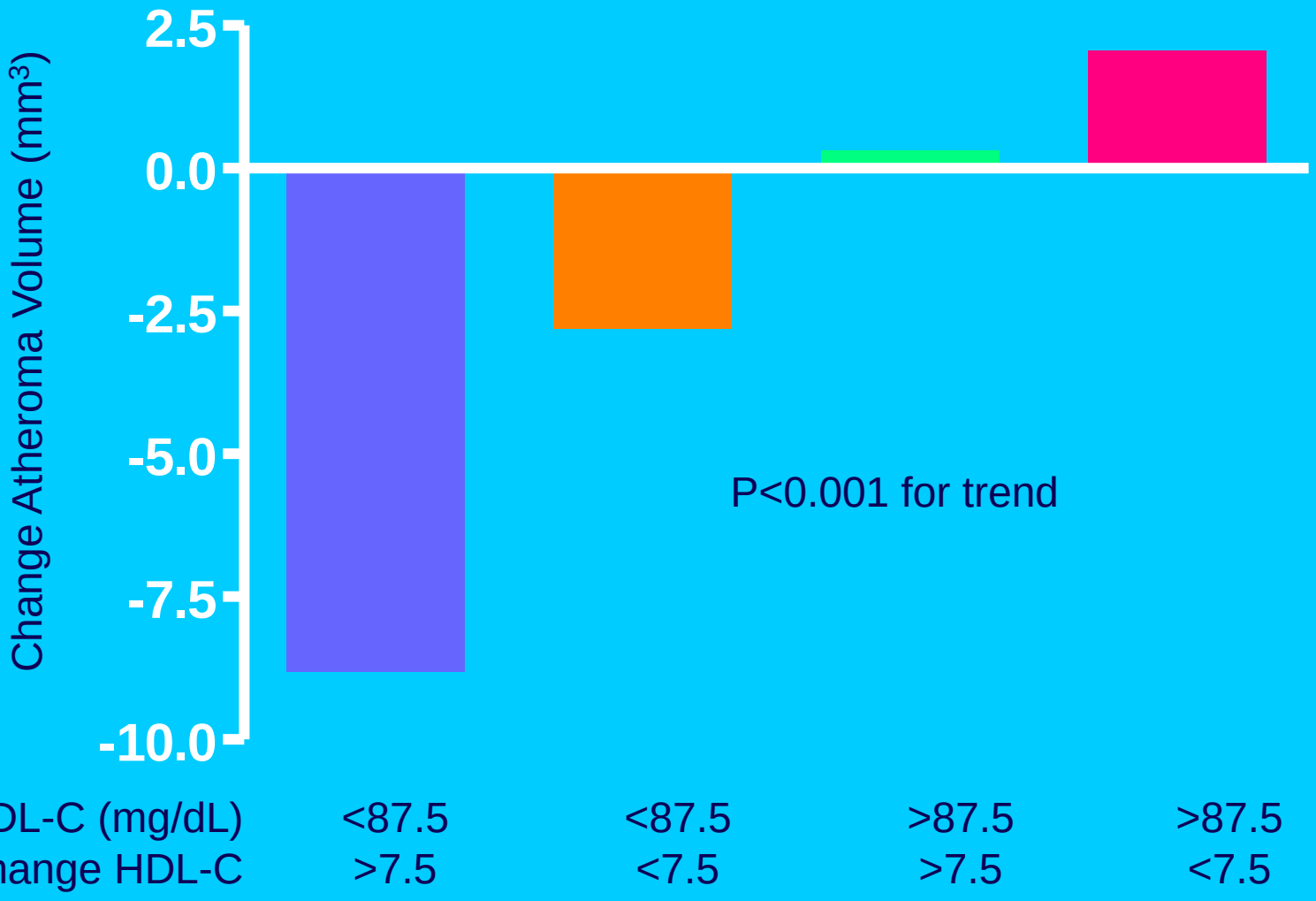


NHANES III
N = 2844

Increased	Decreased
Triglycerides	HDL-C
VLDL	Apo A-1
LDL-P and Small Dense LDL-C	
Apo B	

Resnick HE, et al. *Diabetes Care*. 2000;23:176-180.

IVUS: Benefit of Combination HDL Raising and LDL Lowering with Statins



Nicholls *JAMA.* 2007;297:499-508.

Is Managing LDL-C with Statins Enough?

- Cardiovascular events occur in individuals with treated LDL-C
  - Still occur in treatment groups after LDL lowering with statins
  - Patients with diabetes on statins, have CVD event rates higher than the CVD event rates of those patients without diabetes on placebo.
  - IVUS: LDL <70 mg/dL, 20% with progression associated with DM, increased BP, less increase in HDL, less decrease in Apo-B
    - Progression in DM more strongly related to TG/HDL ratio
- Impact of other atherogenic particles including low or abnormally functioning HDL, VLDL remnants, triglycerides, small dense LDL
  - Independent risk of low HDL, elevated triglycerides
  - Non-HDL-C, Apo B, LDL-C particle number Apo B/Apo A1 ratio better predictor of risk
  - On Rx non-HDL and Apo B better predictor of recurrent events
- Epidemic of obesity, diabetes, metabolic syndrome and associated high risk combined dyslipidemic

Management of Dyslipidemia beyond LDL

- Lifestyle changes and secondary causes
- Pharmacologic therapy
  - **Fibrate**
  - **Niacin**
  - **Ezetimibe**
  - **Resins**
  - Omega-3 fatty acids
  - PPAR-γ or -α agonists
- Secondary causes of Hypertriglceridemia
  - Nephrotic syndrome
  - Diabetes mellitus
  - Hypothyroidism
  - Medications (Estrogens. Tamoxifen, Beta-blocker, Cyclosporin, asparaginase, accutane)

Question

The following statements are true except:

1) Possible concerns with niacin use include risk of gout and worsening glucose control
2) Controlled clinical trials have demonstrated a statistically significant CVD event benefit in all diabetics when niacin/fibrate is added to statins
3) Combination therapy has been shown to favorable effect some surrogate markers for cardiovascular disease outcomes
4) Fibrates should be used with caution with statins due to increased risk of myopathy
5) TZD's favorably benefit the lipid profile

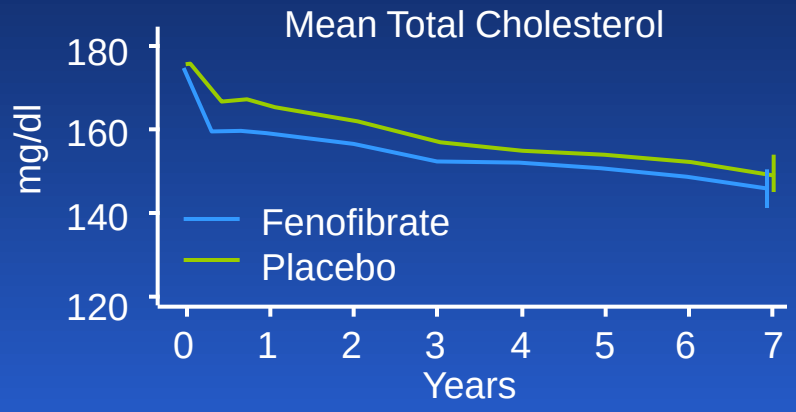
Fibrate Trials

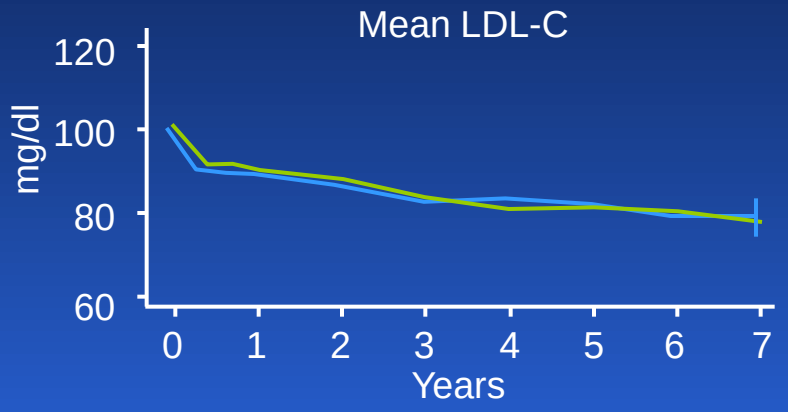
	N	Drug	Duration	ΔLDL	ΔTG	ΔHDL	Results
HHS	4081	Gemfibrozil	5.4 y	-10%	-43%	+>10%	34% ↓ fatal/nonfatal CHD (*P*<0.02)
BIP	3122	Bezafibrate	6.2 y	-6.5%	-21%	+18%	9.4% ↓ nonfatal events *P*=0.26
VA-HIT	2531	Gemfibrozil	5.1 y	0%	-31%	+6%	22% ↓ fatal/ nonfatal CHD *P*=0.006
FIELD	9795	Fenofibrate	5 y	-6%	-22%	+1%	11% ↓ CHD (*P*=.16)

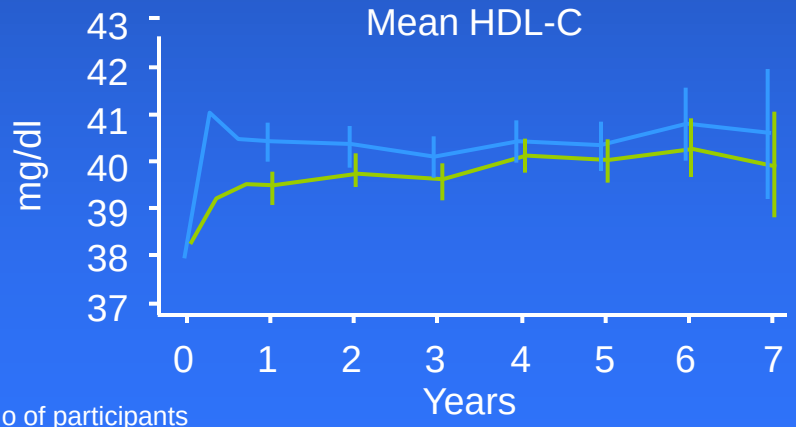
Haffner. *Circulation*. 2000;102:2-4.

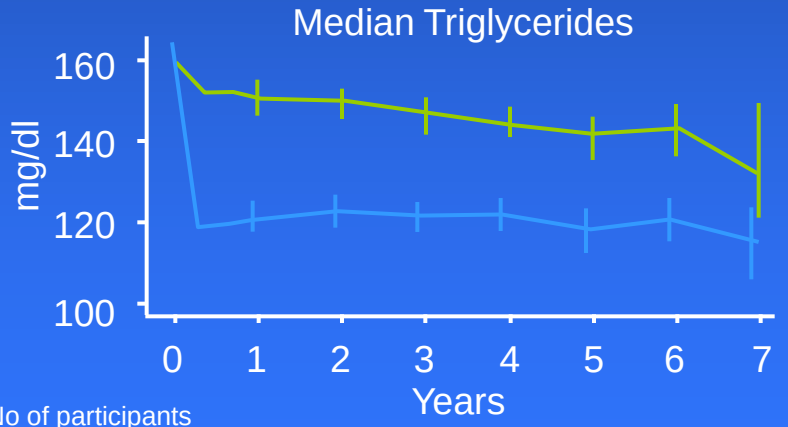
The ACCORD Trial Lipid Study

5518 patients followed for 4.7 years







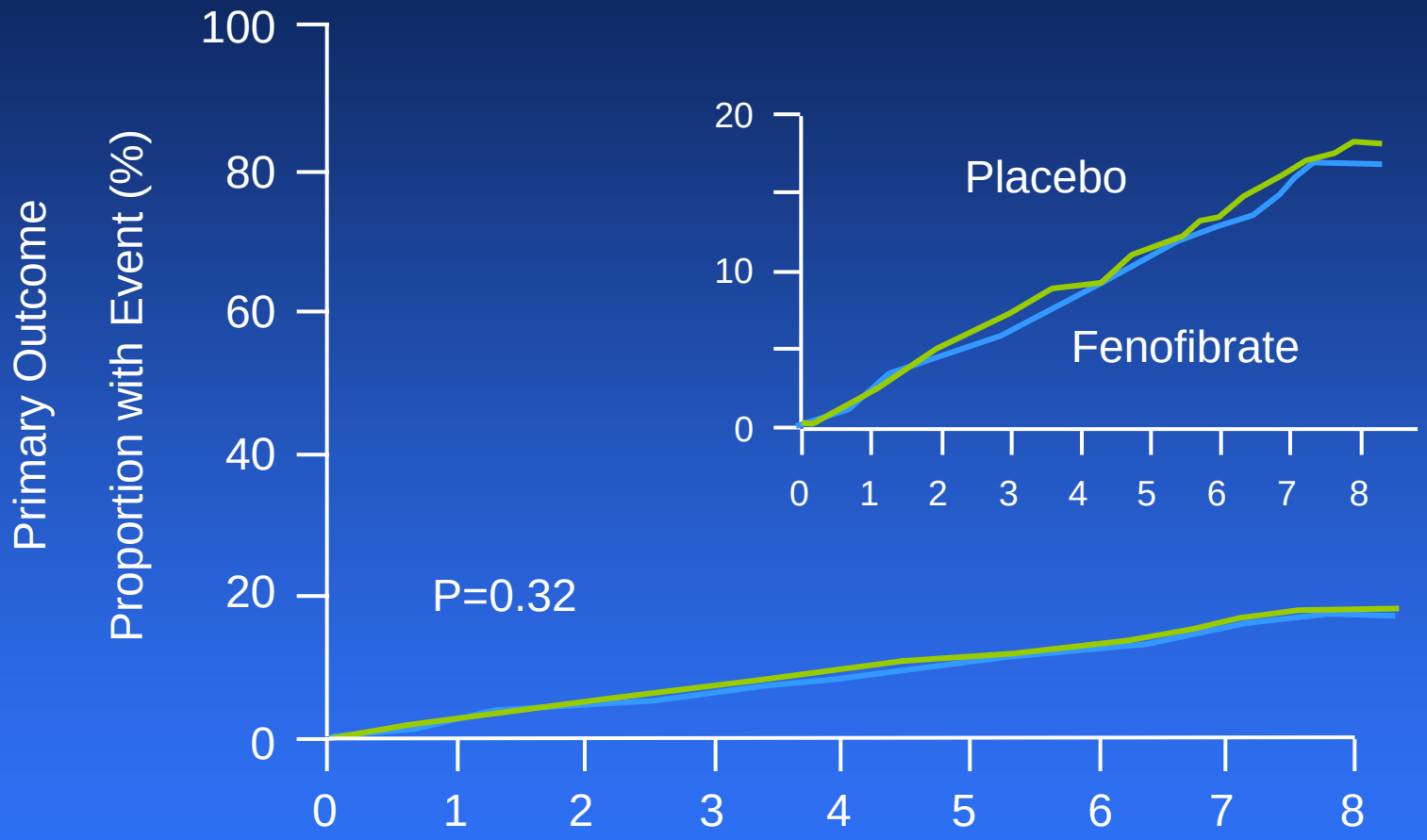


No of participants								
Fenofibrate	2747	2593	2505	2417	2361	1478	796	248
Placebo	2735	2591	2484	2375	2364	1480	801	243

No of participants								
Fenofibrate	2747	2593	2505	2417	2361	1478	796	248
Placebo	2735	2591	2484	2375	2364	1480	801	243

The ACCORD Study Group. *N Engl J Med* 362(17):1563-74, 2010.

The ACCORD Trial
Lipid Study



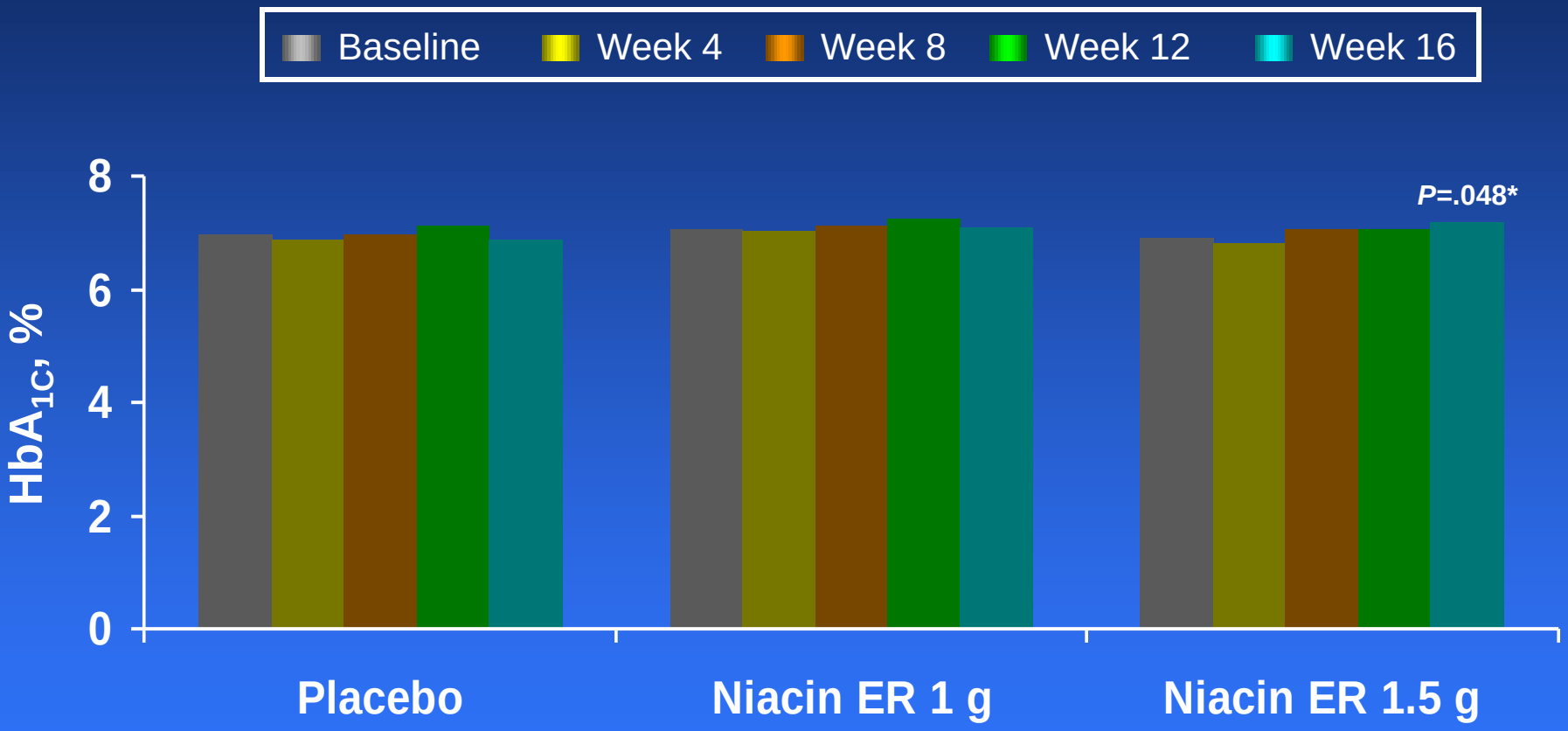
Annual rate of primary outcome was not significantly different:
2.2% in fenofibrate group vs. 2.4 in placebo group
Death: 1.5% vs 1.6%

The ACCORD Study Group. *N Engl J Med* 362(17):1563-74, 2010.

Comparison of ACCORD subgroup results with those from prior fibrate studies

Trial (Drug)	Primary Endpoint: Entire Cohort (P-value)	Lipid Subgroup Criterion	Primary Endpoint: Subgroup
HHS (Gemfibrozil) Circ 1992;85:37-45	-34% (0.02)	TG > 200 mg/dl LDL-C/HDL-C > 5.0	-71% (0.005)
BIP (Bezafibrate) Circ 2000;102:21-7	-7% (0.24)	TG ≥ 200 mg/dl	-40% (0.02)
FIELD (Fenofibrate) DMCare 2009;32:493-8.	-11% (0.16)	TG ≥ 204 mg/dl and HDL-C < 42 mg/dl	-27% (0.005)
ACCORD (Fenofibrate)	**-8% (0.32)**	**TG ≥ 204 mg/dl and HDL-C ≤ 34 mg/dl**	**-31%**

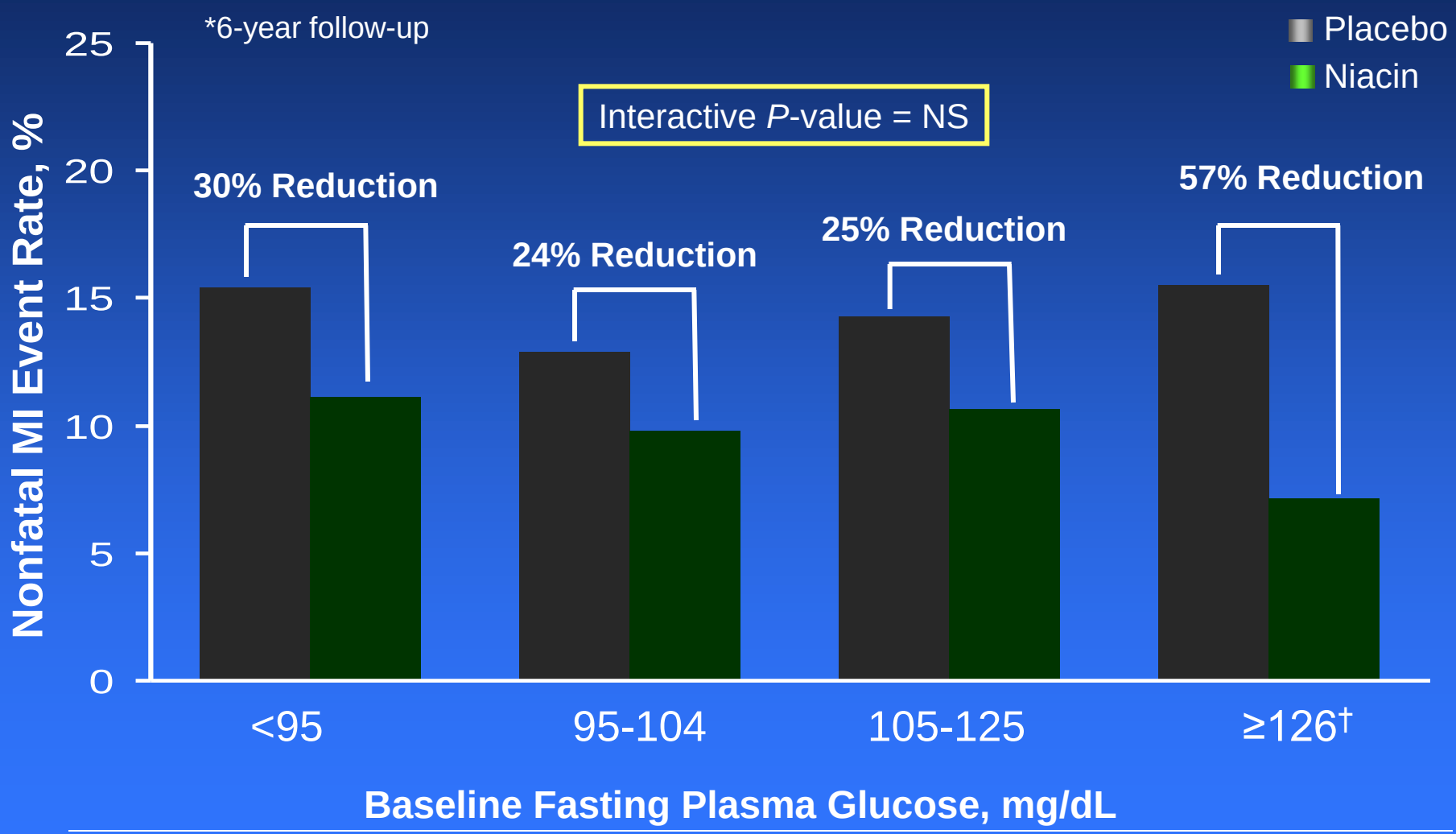
ADVENT: Niacin ER Effects on HbA_{1C} in Patients With Type 2 Diabetes



N =148, 47% were receiving concomitant statin therapy
*Versus placebo at 16 weeks

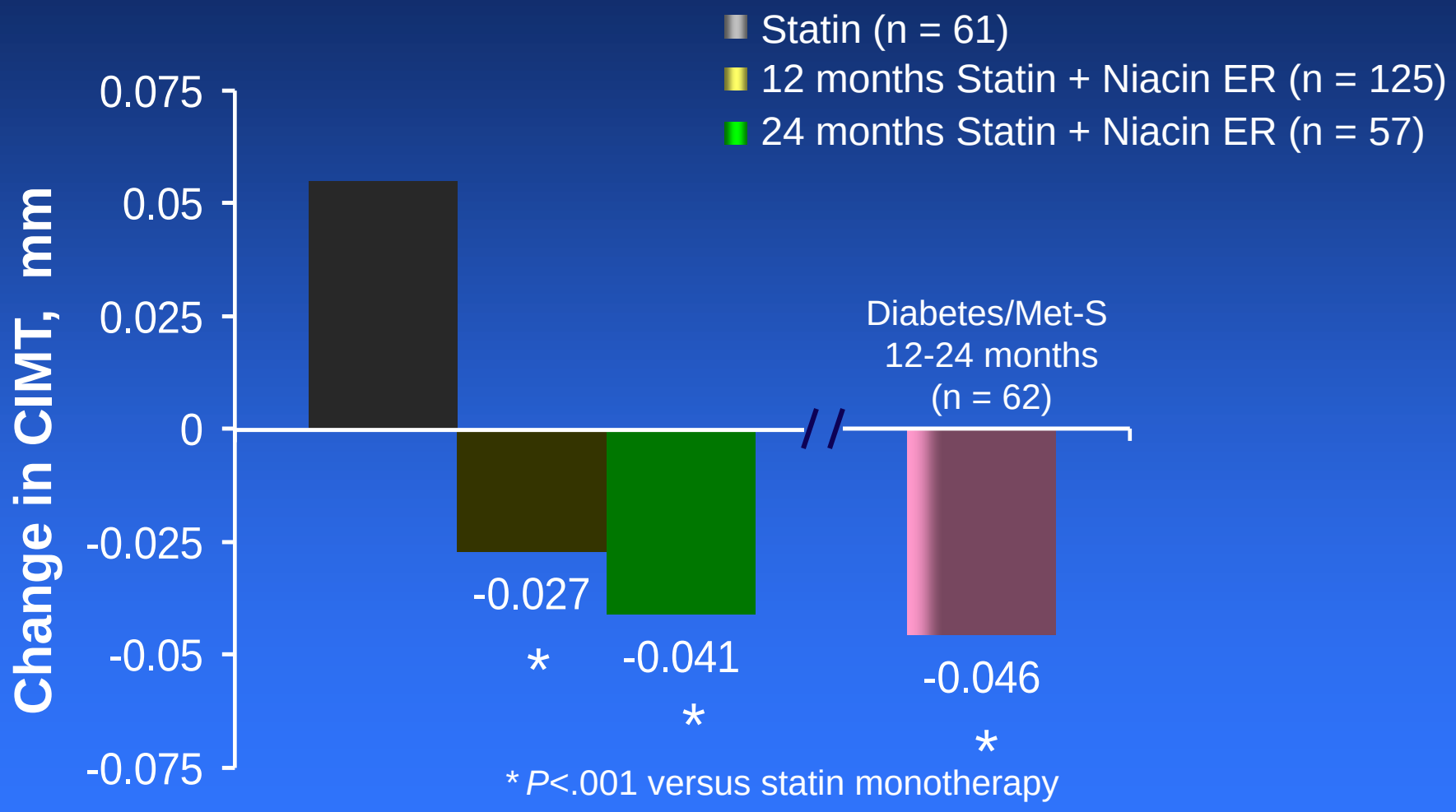
Grundy SM, et al. *Arch Intern Med*. 2002;162:1568-1576.

CDP: Reduction in Recurrence of MI* By Baseline Fasting Plasma Glucose



Canner PL, et al. *Am J Cardiol.* 2005;95:254-257.

ARBITER 3: 24 Months



Taylor AJ, et al. *Curr Med Res Opin.* 2006;22:2243-2250.

Incremental Benefit of Niacin Added to Statin Therapy

- AIM-HIGH was designed to test whether the addition of niacin to statin (± ezetimibe) would provide an additional 25% reduction in CV events in patients with stable, non-acute, established CV deiseae with well controlled LDL-C
- On May 26, 2011 the NHLBI announced that the AIM-HIGH Study was stopped for Futility (lack of efficacy) based on interim results
  - The interim analysis concluded that the trial would not be able to show a significant difference in CV outcome event rates between the two study arms
- The levels of ischemic stroke were low overall, though more were observed in the niacin plus simvastatin arm
- HPS-2 THRIVE is ongoing

ADA Lipid Goals and Recommendations: 2011

- Lifestyle modifications
- Primary LDL-C goal < 100 mg/dL; LDL-C < 70 mg/dL is an option
  - In individuals without overt CVD, the primary goal is an LDL cholesterol <100 mg/dl, <70 mg/dL is option if one or more RF's
  - In individuals with overt CVD, a lower LDL cholesterol goal of 70 mg/dl, using a high dose of a statin, is a reasonable option.
- Statin therapy added to lifestyle changes, regardless of baseline LDL-C, if
  - Overt CVD
  - Without CVD but age > 40 yr + 1 or more other CVD risk factors
- Without overt CVD and age < 40 yr:
  - Consider statin if LDL-C > 100 mg/dL or multiple risk factors, despite lifestyle therapy
- In drug-treated patients, a reduction in LDL-C of ~30–40% from baseline
- TG's < 150 mg/dL, HDL-C > 40 mg/dL (men), > 50 mg/dL (women): desirable
  - Combination therapy to achieve lipid goals may be needed but outcome studies needed

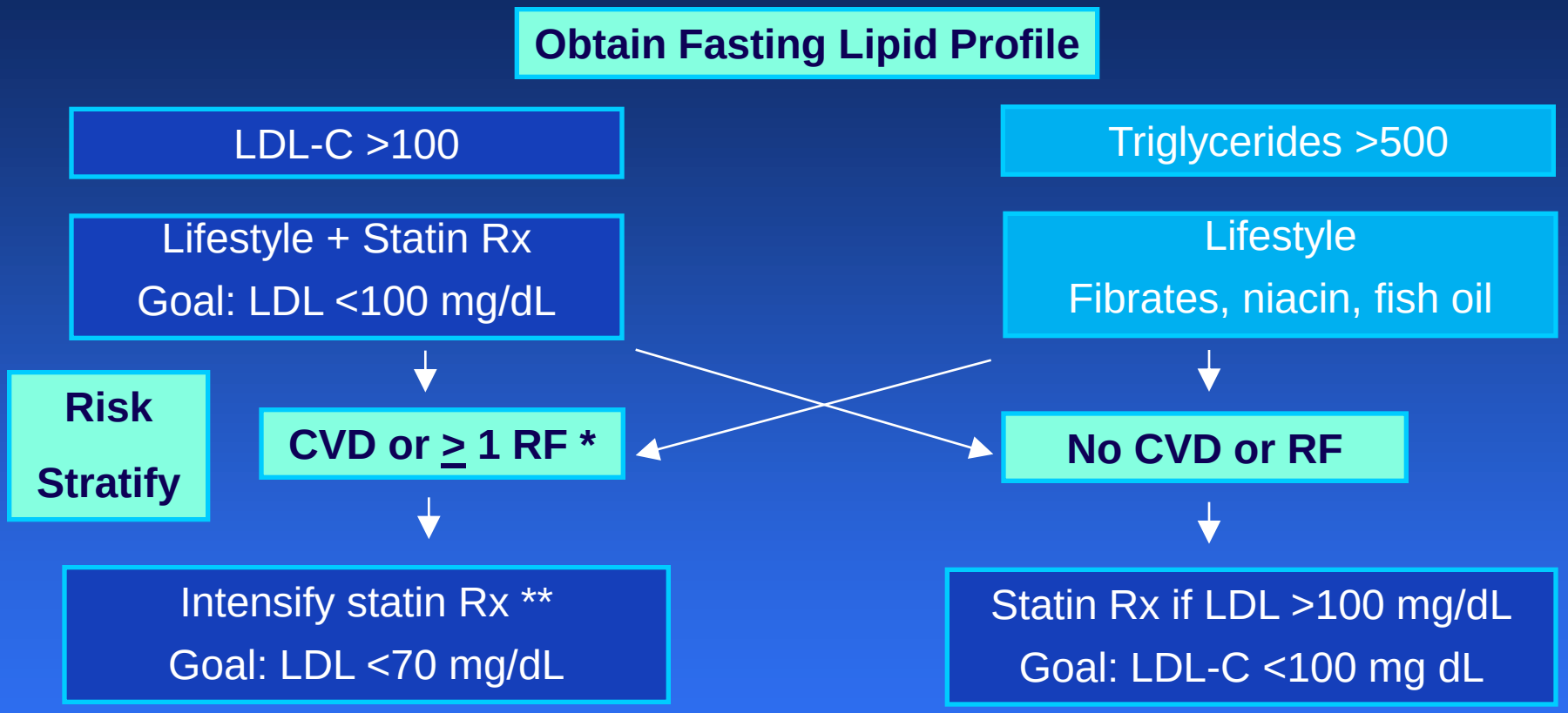
Diabetes Care. 20011;34 (suppl1):S11-S61.

ADA Lipid Goals and Recommendations: 2011

	First Priority	Second Priority
LDL-C Lowering <100 mg/dL <70 mg/dL optional	Therapeutic Lifestyle changes Statins	Additional adjunctive lipid therapies
HDL-C Raising >40 mg/dL-men >50 mg/dL-women	Therapeutic Lifestyle changes Statins	Additional adjunctive lipid therapies
TG Lowering <150 mg/dL	Glycemic control Statins Therapeutic lifestyle changes - Weight loss - Increased physical activity -Smoking cessation	Additional adjunctive lipid therapies

Diabetes Care. 2011;34 (suppl1):S11-S61.

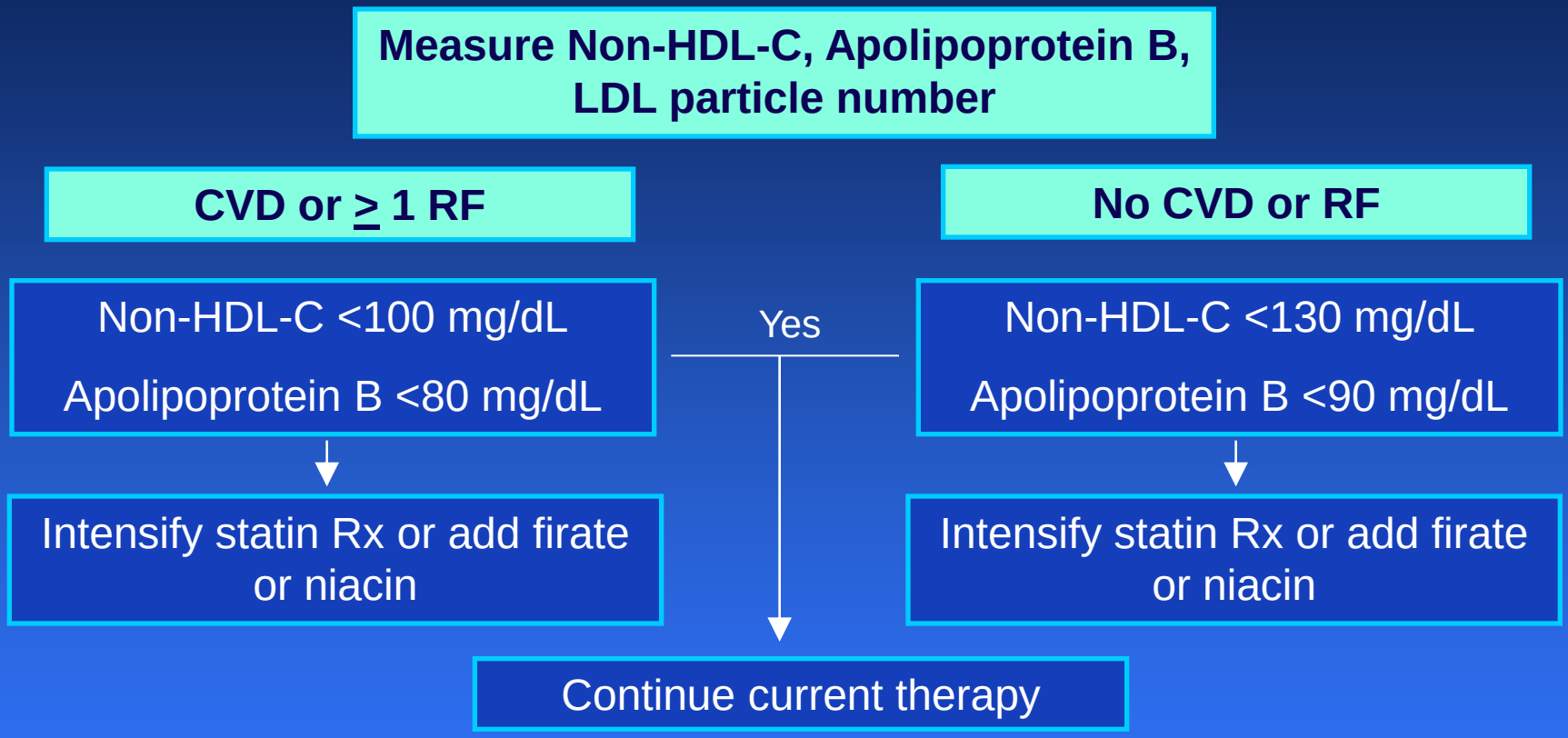
Lipid Management in Patients with Diabetes



* If CVD or 40 yo with ≥1 RF consider statin therapy regardless of baseline LDL

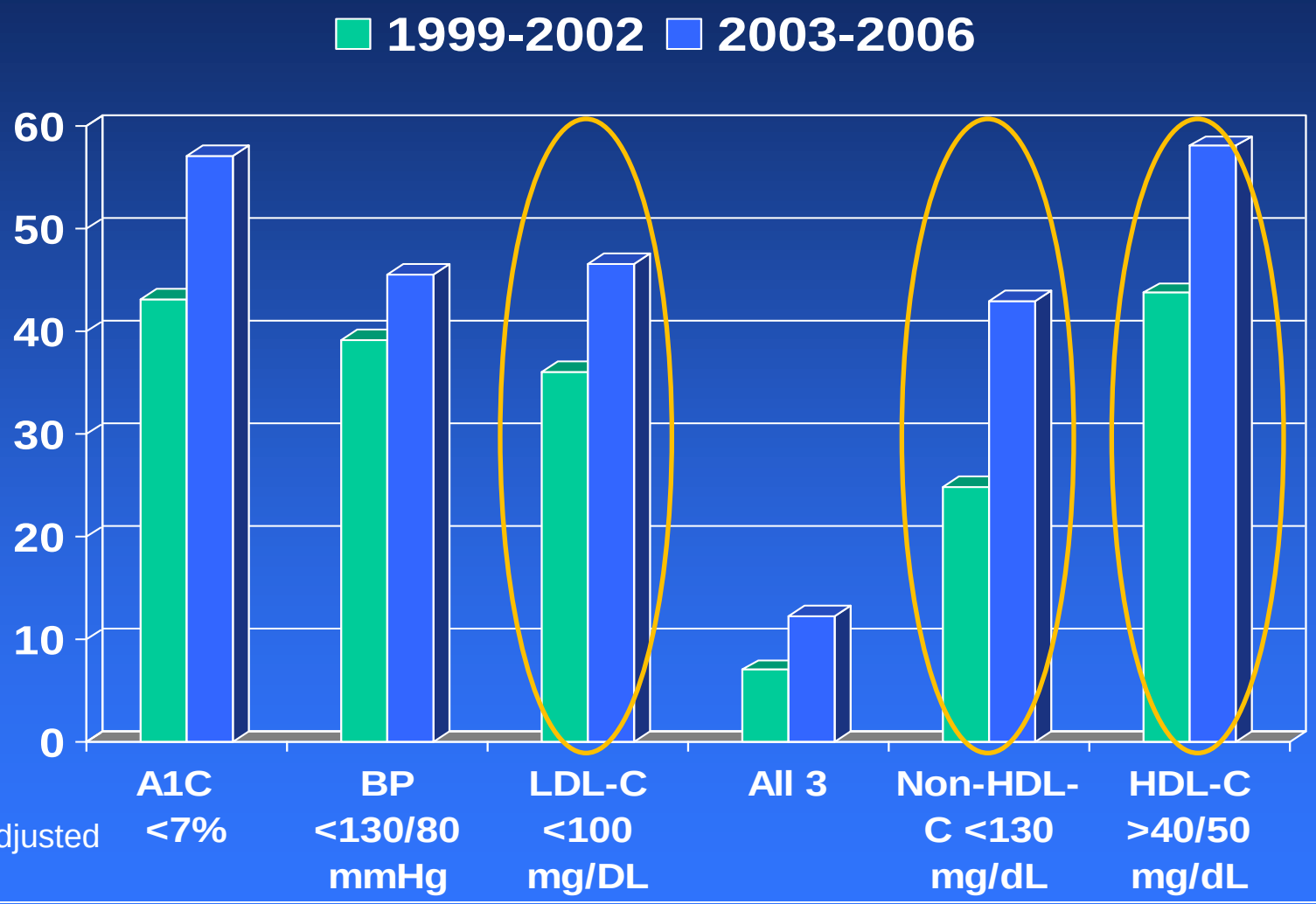
** If not at LDL goal on maximally tolerated statin consider addition of ezetimibe, colesevalem, niacin

Lipid Management in Patients with Diabetes



If LDL at goal: further Non-HDL or Apo B lowering with aggressive lifestyle intervention, glucose management, increase statin, niacin, fibrates, fish oil

NHANES 1999-2006
Proportion of Diabetics Achieving RF Goals



* Age adjusted

Cheung et. *Am J Med* 2009; 122:443-53

Case: Matthew R

History, Physical Exam & Laboratory Data

- 11-year-old white male
- Otherwise healthy
- Admits to sedentary lifestyle
- Pediatrician obtained screening lipid panel due to Family History:
  - Father with HL and history of MI and stent age 47
- Medications
  - none
- Physical examination
  - 59.5″, 104 lb
  - BMI = 20.8 (93th %)
  - BP: 110/70
  - No xanthomas

Baseline* (fasting levels)	
Total C	251
LDL-C	189 (calculated)
HDL-C	41
TG	106
Glucose	89
TSH	1.2
Non-HDL-C	200
LP(a)	75

*Represent results of second lipid panel.

C = cholesterol; TG = triglycerides; HbA_{1c} = hemoglobin A_{1c};
nl = normal; TSH = thyroid-stimulating hormone.

Lipid Management in Children

- What are acceptable lipid levels in children?
- How aggressively to treat ?
- Is lowering chlesterol with drugs safe?
- How early to start?

- Questions:
  - Screening
  - When to initiate medications
  - Defining high risk groups

Lipid Levels for Children and Adolescents

Category	Accetable (mg/dL)	Borderline (mg/dL)	High (mg/dL)
Total Chol	<170	170-199	≥200
LDL=C	<110	110-129	≥130
Non-HDL-C	<123	123-143	≥144
Apolipoprotein B	<90	90-109	≥110
Triglycerides			
0-9 years	<75	75-99	≥100
10-19 years	<90	90-129	≥130
HDL-C	>45	35-45	<35
Apo A-I	>120	110-120	<110

Cholesterol in Youth

- Cholesterol lowest intrauterine and at birth
- Concentrations similar to young adults by 2 years of age
- Decrease 10 to 20% during pubertal development
- Strongest relation to adult levels at 5 to 10 years and 17 to 19 years

- Hyperlipidemia common
  - Child and Adolescent Trial for CV Health: 13.3% 4th graders had TC >200
  - NHANES: 10% of adolescents had TC >200
  - Increase in obesity and metabolic syndrome

- Efficacy and safety of stains similar to that in adults
  - Including prepubertal and between 8 and 10 years
- No effect on sexual or physical maturation
- Impact on atherosclerotic process: FMD and CIMT
- Impact on clinical outcomes lacking: Extrapolation from adult studies
  - No outcome studies to show that treatment in childhood decreases adult CVD

2008 AAP Recommendations

- Population approach to healthful diet to all children >2 years
  - Studies in ages 7 months to adolescents have shown safety of low total fat, saturated fat and cholesterol diets

- Individual approach for those at higher risk for CVD and high LDL
  - Screen earlier between 2 and 10 years
    - FHx of CVD or dyslipidemia (parents or grandparents <55)
    - FHx not known and other RF's (overweight, obese, HTN, smoking, DM)
    - Fasting lipid profile
    - Retest 3 to 5 years if normal range

2008 AAP Giuideline Recommendations

- Earlier start age (for screening and treatment)
- Emphasis on overweight, high TG and low HDL
  - Lifestyle management, weight management
- Change in primary treatment choice: statins rather than resins
- Lower LDL cutpoints dependent on risk

Characteristics	LDL Cut Points
No other RF's *	>190
FHx or other RF's	>160
Diabetes	>130

- For individuals over 8 years of age, pharmacologic therapy considered
  - Fiber up to 20 gm/day/Plant stanols/sterols
- Other high risk patients:Transplantation, HIV, Chronic inflammatory disease (SLE, RA), Renal disease, nephrotic syndrome, Kawasaki Disease, Childhood cancer survivors

* Risk factors defined as obese, overweight, hypertension, cigarette smoking