Statin Intolerance Panel

Harold Bays
Scott Grundy
John Guyton
Terry Jacobson



Charles Peirce (1839-1914)
Founder of Pragmatism

(1) Does statin intolerance exist?

ANSWER: Yes.

STRENGTH OF RECOMMENDATION: A (Strong)

QUALITY OF EVIDENCE: Moderate

Statin Intolerance – 1st definition

In the individual case, statin intolerance is defined as adverse symptoms or objective findings attributed by the patient (or provider) to the statin and in most cases perceived by the patient to interfere unacceptably with activities of daily living, leading to a decision to stop or reduce statin therapy.

Statin Intolerance – 2nd definition

For an aggregate population, statin intolerance is defined as clinical or laboratory adverse experiences linked to statin treatment by validated clinical evidence and presenting with pain, impairment, or risk, which justifies statin cessation or dose reduction..

(2) Are statins generally well tolerated and safe?

ANSWER: Yes.

STRENGTH OF RECOMMENDATION: A (Strong)

QUALITY OF EVIDENCE: High

From clinical trials (27 RCTS, 175,000 patients) and observational data, the benefit from statins in appropriate patient groups is to avoid several hundred to perhaps more than a thousand deaths from ASCVD for every death from statin-associated rhabdomyolysis.

(3) Do large randomized trials provide reliable estimates of statin intolerance?

ANSWER: No.

STRENGTH OF RECOMMENDATION: E (Expert Opinion)

QUALITY OF EVIDENCE: Low

Statin Intolerance in Randomized Trials

- In HPS, no significant difference in muscle symptoms.
- This has been interpreted to mean that muscle adverse effects were “undetectable.”
- The only RCT showing a difference – STOMP 2013.
- In observational data, PRIMO 10.5%, USAGE 29%.
- Problems in RCTs prior to STOMP
  - Avoidance of participation by certain patients.
  - Dropout during run-in phase.
  - Lack of active monitoring.

(4) Is statin intolerance best defined in the context of patient-centered medicine?

ANSWER: Yes.

STRENGTH OF RECOMMENDATION: E (Expert Opinion)

QUALITY OF EVIDENCE: Not Applicable

Patient-centered medicine – 2 parallel agendas

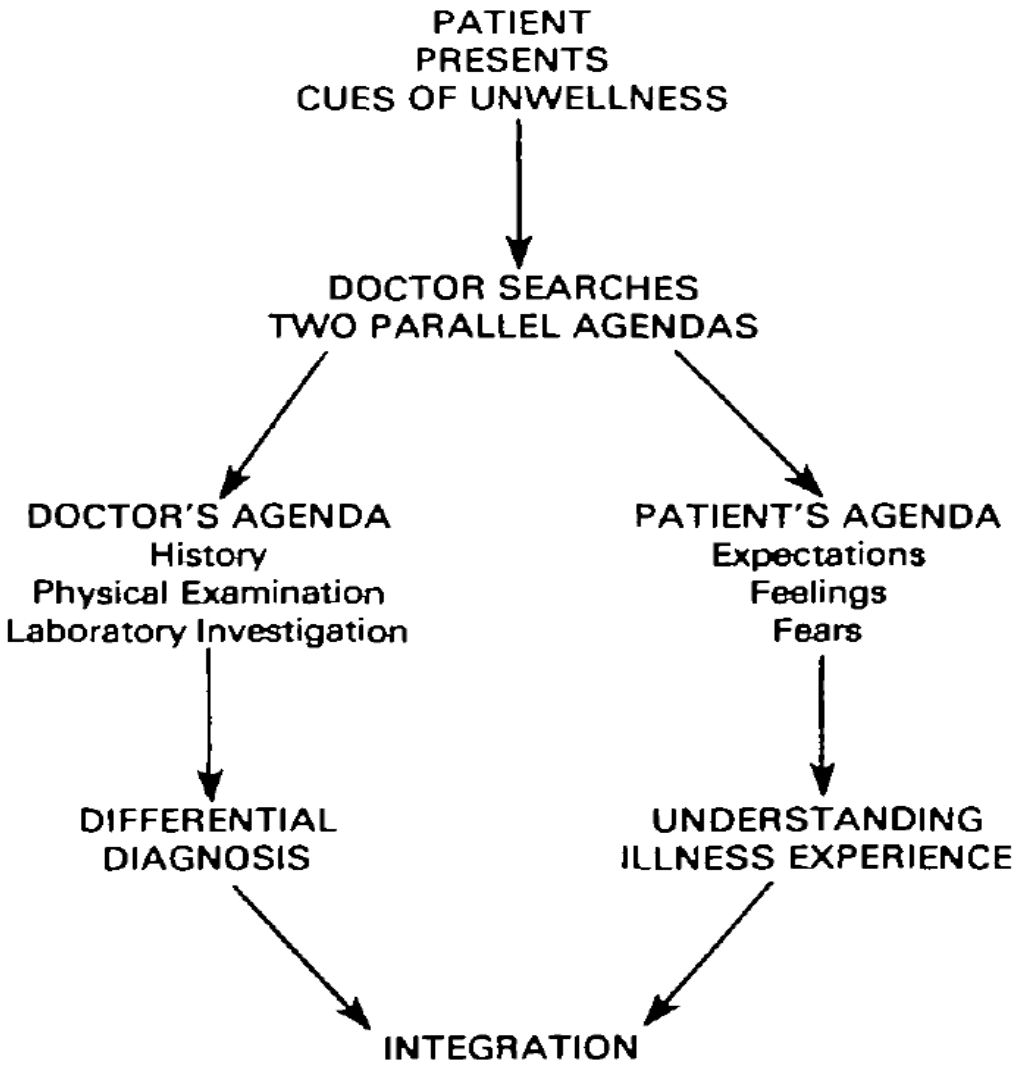


FIGURE 1 *The patient-centred clinical method*

Levenstein et al. Family Practice 1986;3:24-30

(5) Should the clinician sometimes advise patients to continue statin therapy even when some degree of statin intolerance is present?

ANSWER: Yes.

STRENGTH OF RECOMMENDATION: B (Moderate)

QUALITY OF EVIDENCE: Low

Tolerance versus Diagnosis

The decision for or against continuing to take a statin can be simplified by casting it as a question of tolerance (i.e., how bothersome are the symptoms?) rather than a question of diagnosis (i.e., are the symptoms really due to the statin?).

(6) Are recommendations for widespread use of statins to prevent atherosclerotic cardio-vascular disease appropriate, given the emerging evidence with regard to statin intolerance?

ANSWER: Yes.

STRENGTH OF RECOMMENDATION: A (Strong)

QUALITY OF EVIDENCE: High

27 randomized controlled trials

175,000 patients in RCTs

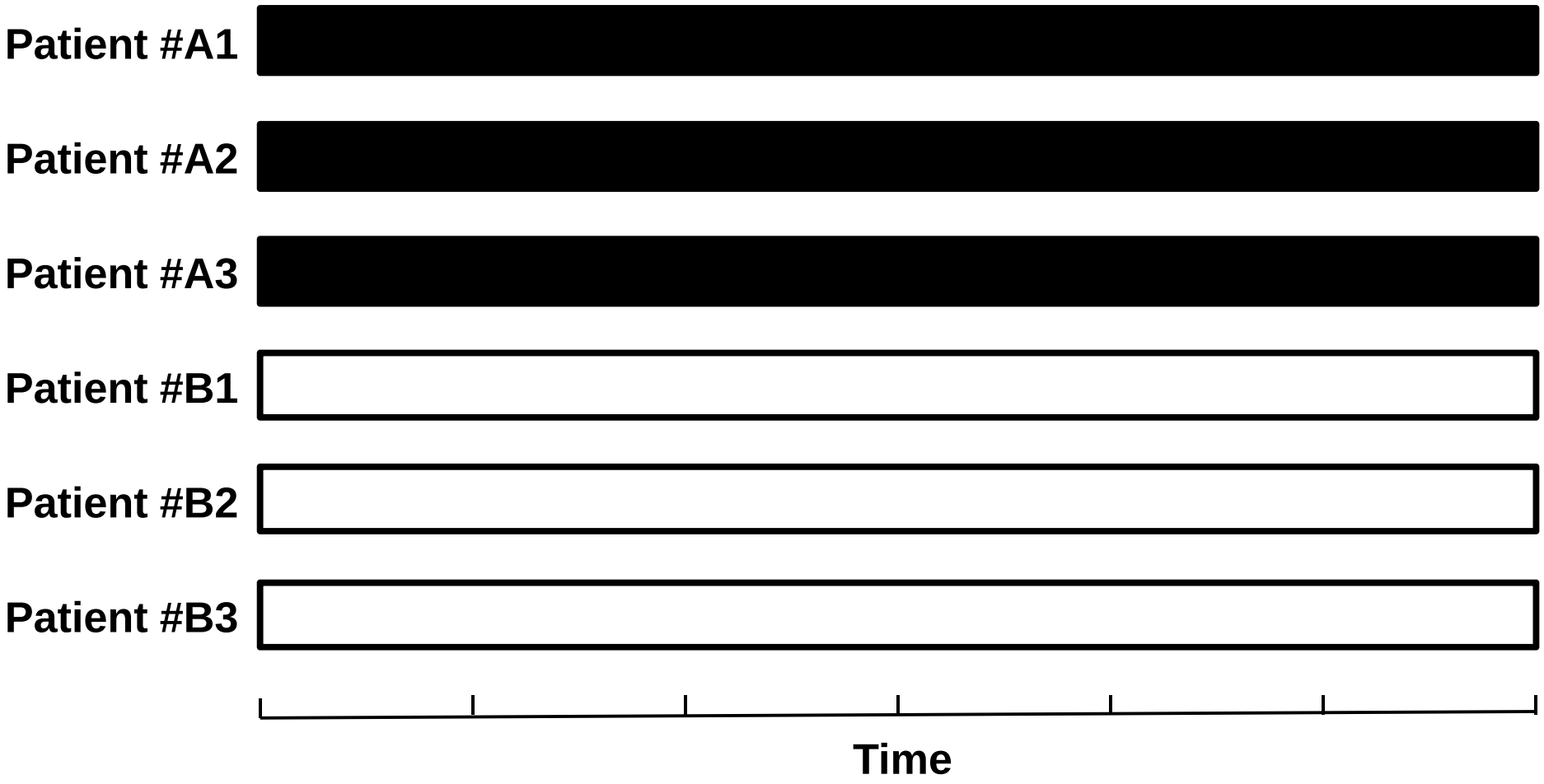
(7) Are there clinical trial designs that may reliably address questions of statin intolerance?

ANSWER: Yes.

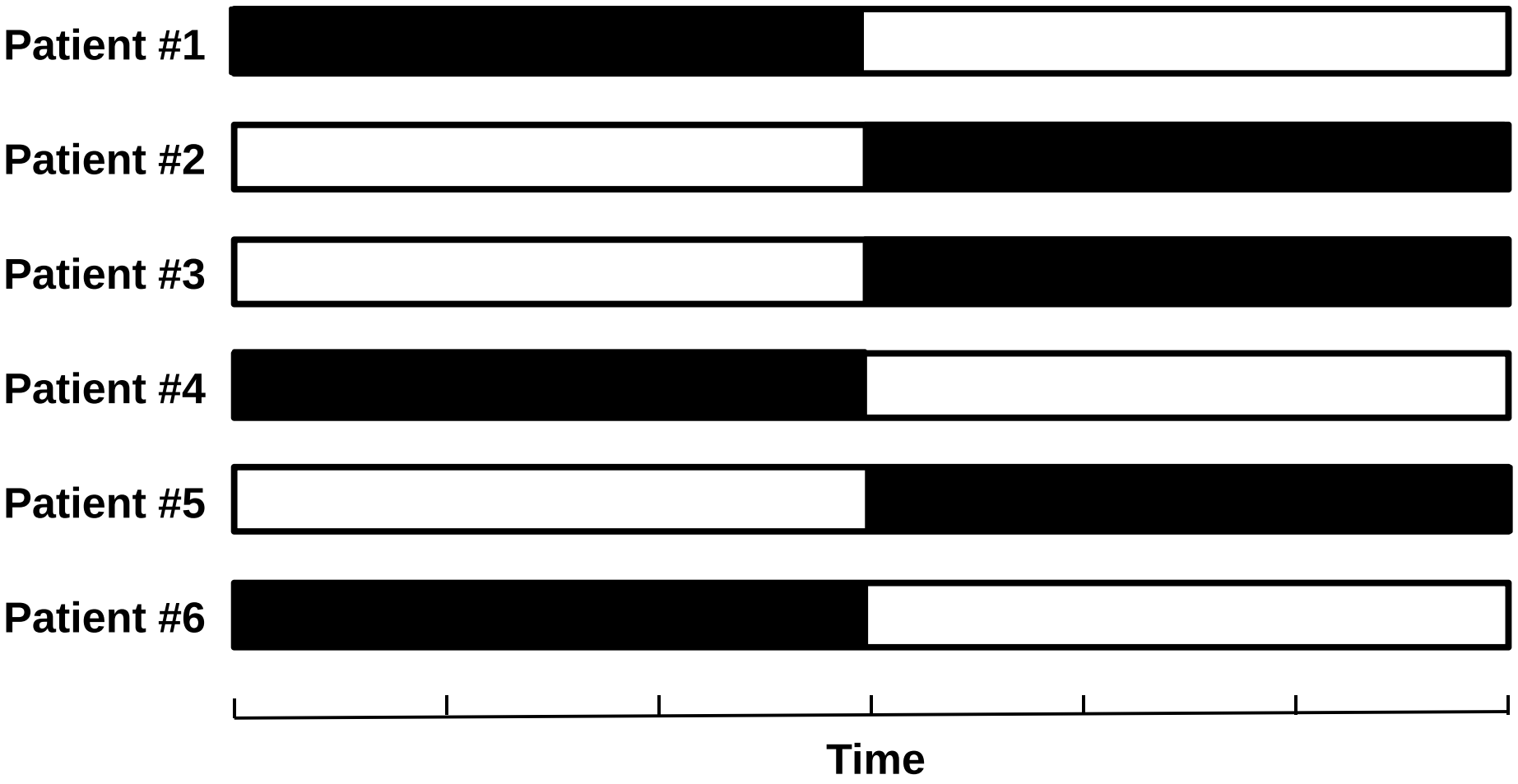
STRENGTH OF RECOMMENDATION: E (Expert Opinion)

QUALITY OF EVIDENCE: Not Applicable

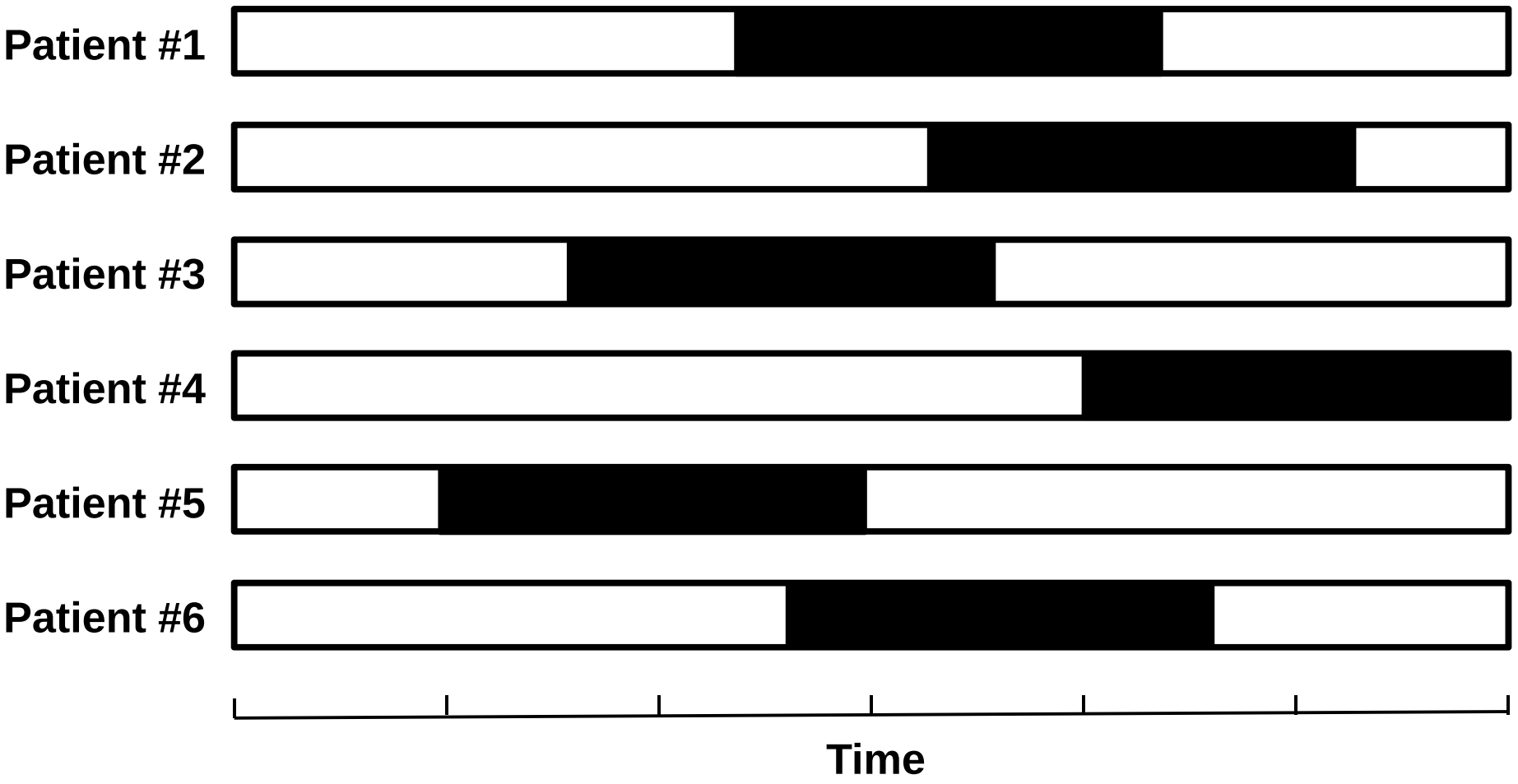
Parallel Group design



Crossover design



Crossover design with variable time-of-onset



Statin Intolerance – 3rd definition

Inability to tolerate at least 2 statins: one at the lowest starting daily dose AND another at any daily dose, due to either objectionable symptoms (real or perceived) or abnormal lab determinations, which are temporally related to statin treatment and reversible upon statin discontinuation, but reproducible by re-challenge with other known determinants being excluded.

Summary and Take-Home Message

Managing statin intolerance requires a pragmatic approach that includes principles of patient-centered medicine as well as new methods for gaining scientific evidence about this commonly encountered clinical problem.

An Assessment by the Statin Cognitive Safety Task Foce: 2014 Update

Vera Bittner, MD, MSPH, FNLA
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Section Head, Preventive Cardiology
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Disclosure of ABIM Service: Vera Bittner, MD

- I am a current member of the Cardiology Board Cardiovascular Disease Exam Committee.
- To protect the integrity of certification, ABIM enforces strict confidentiality and ownership of exam content.
- As a current member of the Cardiology Board Cardiovascular Disease Exam Committee, I agree to keep exam information confidential.
- As is true for any ABIM candidate who has taken an exam for certification, I have signed the Pledge of Honesty in which I have agreed to keep ABIM exam content confidential.
- ***No exam questions will be disclosed in my presentation.***

Outline

- Background
  - Task Force Members
  - Evidence grading
- Definition and assessment of cognition and cognitive dysfunction
- 2014 Questions:
  - Should a baseline cognitive assessment be performed before beginning a statin?
  - Are statins as a class associated with adverse effects on cognition?
  - What should the provider do, if a patient reports cognitive symptoms after beginning a statin?
- Recommendations from the panel
  - Clinicians
  - Patients
  - Future Research

Background

Cognitive Task Force Members

- Carlos H. Rojas-Fernandez BSc (Pharm), PharmD, Univ. of Waterloo, Ontario, Canada
- Larry B. Goldstein, MD, Duke University, Durham, NC
- Allan I. Levey, MD, PhD, Emory University, Atlanta, GA
- Beth A. Taylor, PhD, Hartford Hospital / Univ. of Hartford, Hartford, CT
- Vera Bittner, MD, MSPH, FNLA, Univ. of Alabama at Birmingham, Birmingham, AL

Thanks to Dr. Beatrice Golomb, UCSD, for critical review of the manuscript and many thoughtful suggestions.

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Journal of Clinical Lipidology

Original Contribution

An assessment by the Statin Cognitive Safety Task Force: 2014 update

Carlos H. Rojas-Fernandez, BSc(Pharm), PharmD*, Larry B. Goldstein, MD, Allan I. Levey, MD, PhD, Beth A. Taylor, PhD, Vera Bittner, MD, MSPH, FNLA

Schlegel–UW Research Institute for Ageing; School of Public Health and Health Systems; School of Pharmacy, University of Waterloo, 10 Victoria Street S, Room 7004, Kitchener, Ontario N2G 1C5, Canada (Dr Rojas-Fernandez); Michael G. DeGroote School of Medicine, Department of Family Medicine, McMaster University, University of Waterloo, Hamilton, ON, Canada (Dr Rojas-Fernandez); Duke Stroke Center, Duke University and Durham VAMC, Durham, NC (Dr Goldstein); Department of Neurology, Emory University, Atlanta, GA (Dr Levey); Department of Preventive Cardiology, Hartford Hospital & University of Hartford, Hartford, CT (Dr Taylor); and Division of Cardiovascular Disease, Preventive Cardiology Section, University of Alabama at Birmingham, Birmingham, AL (Dr Bittner)

Evidence Grading: Strength of Recommendation

Evidence grading: Strength of recommendation*

Grade	Strength of recommendation
A	**Strong recommendation** There is high certainty based on the evidence that the net benefit** is substantial
B	**Moderate recommendation** There is moderate certainty based on the evidence that the net benefit is moderate to substantial, or there is high certainty that the net benefit is moderate
C	**Weak recommendation** There is at least moderate certainty based on the evidence that there is a small net benefit
D	**Recommend against** There is at least moderate certainty based on the evidence that it has no net benefit or that the risks/harms outweigh benefits
E	**Expert opinion** There is insufficient evidence or evidence is unclear or conflicting, but this is what the expert panel recommends
N	**No recommendation for or against** There is insufficient evidence or evidence is unclear or conflicting

Rojas-Fernandez et al. J Clin Lipidol 2014;8:S5-S16

Evidence Grading: Quality of Evidence

Evidence grading: Quality of evidence

Type of evidence	Quality rating*
Well-designed, well executed RCTs that adequately represent populations to which the results are applied and directly assess effects on health outcomes Well-conducted meta-analyses of such studies Highly certain about the estimate of effect; further research is unlikely to change our confidence in the estimate of effect	High
RCTs with minor limitations affecting confidence in, or applicability of, the results Well-designed, well-executed nonrandomized controlled studies and well-designed, well-executed observational studies Well-conducted meta-analyses of such studies Moderately certain about the estimate of effect; further research may have an impact on our confidence in the estimate of effect and may change the estimate	Moderate
RCTs with major limitations Non-randomized controlled studies and observational studies with major limitations affecting confidence in, or applicability of, the results Uncontrolled clinical observations without an appropriate comparison group (eg, case series, case reports) Physiological studies in humans Meta-analyses of such studies Low certainty about the estimate of effect; further research is likely to have an impact on our confidence in the estimate of effect and is likely to change the estimate.	Low

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Cognition and Cognitive Dysfunction

Cognition

- Executive function
- Memory
- Language
- Visuospatial ability

Assessment Tools

- MMSE
- MoCA
- Mini-Cog / Clock draw test / Functional Activity Scale

Cognitive Dysfunction

- Minor Cognitive Impairment (MCI)
  - State of cognitive dysfunction between normal cognition and dementia
- Dementia
  - Cognitive dysfunction that involves 2 domains and is sufficiently severe to interfere with daily activities leading to a progressive loss of independence.

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Common Assessment Tools

Mini-Mental Status Exam (MMSE)

- Does not evaluate executive function
- Floor and ceiling effects
- Insensitive to subtle defects
- Very sensitive to educational level
- Proprietary, requires licensing fee
- Takes about 15 min

Montreal Cognitive Assessment (MoCA)

- 7 subscores evaluating visuospatial/executive function, naming and language, memory, attention, abstraction, and orientation
- More sensitive for MCI than MMSE
- Not established to be useful for drug-related MCI
- Takes about 15 min

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Why is it Important to Understand the Relationship Between Statins and MCI?

- Exposure to statins is large – even rare AEs affect a lot of individuals

Example:

- U.S. 2005-2008: 41% of adults 45+ years of age reported using a statin → 126 million people (based on 2010 census).*
- Assume AE incidence of 0.1% → 126,600 people affected.

*CDC. National Center for Health Statistics. Health, United States, 2010: with special feature on death and dying. Available at: http://www.cdc.gov/nchs/data/hus/hus10.pdf. Accessed February 5, 2014.

Why Is It So Difficult to Assess The Literature on Statins and Cognition?

- Cognitive dysfunction is very common: 10-20% in individuals ≥65 years
- Line between MCI and dementia is often blurred
- Many different causes of cognitive dysfunction, some temporary / reversible
- Variable disease progression of dementing illnesses
- Limited F/U in case reports / case series
- Subjective cognitive complaints not evident on testing may predict future cognitive impairment

Rojas-Fernandez et al. J Clin Lipidol 2014;8:S5-S16

1. Should a baseline cognitive assessment be performed before beginning a statin?

- ANSWER: No
- STRENGTH OF RECOMMENDATION: E (expert opinion)
- QUALITY OF EVIDENCE: Low

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2. Are statins as a class associated with adverse effects on cognition?

- ANSWER: No
- STRENGTH OF RECOMMENDATION: A (strong recommendation)
- QUALITY OF EVIDENCE: Low to moderate

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3. What should the provider do if a patient reports cognitive symptoms after beginning a statin?

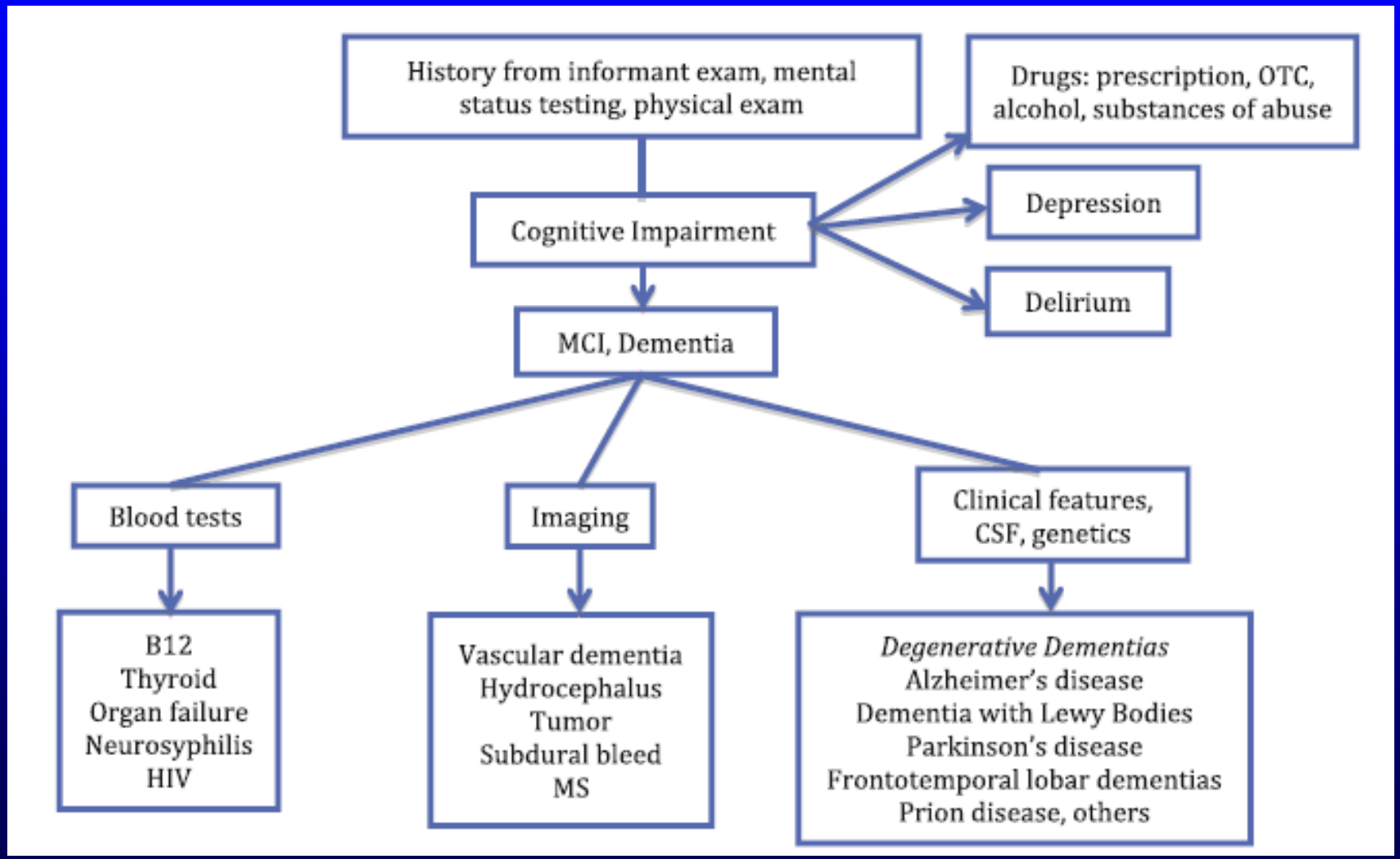
- ANSWER: Cognitive testing should be conducted, other potential contributors should be ruled out, and the risk of stopping the statin should be assessed. Based on the individual patient characteristics, the statin dose could be lowered or the statin could be stopped to assess for reversibility of symptoms. If the statin is stopped, an alternative statin should be considered, preferably a statin that may be less likely to enter the brain (eg, pravastatin, rosuvastatin).

- STRENGTH OF RECOMMENDATION: E (expert opinion)

- QUALITY OF EVIDENCE: Low

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Evaluation of Patient with Cognitive Symptoms



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Some Drugs Commonly Associated with Cognitive Symptoms

Table 2 Examples of drugs commonly associated with adverse effects on cognition

Mechanism	Common examples*
Anticholinergic	Antimuscarinic bladder relaxant drugs: oxybutynin, tolterodine, darifenacin Some tricyclic antidepressants: amitriptyline, imipramine Antimuscarinic drugs for Parkinson's disease: benztropine, trihexylphenidyl Other antidepressants: paroxetine, mirtazapine
First-generation histamine H_1 antagonists	Chlorpheniramine, hydroxyzine, diphenhydramine, dimenhydrinate, promethazine
GABAergic	Any benzodiazepine receptor agonist: diazepam, lorazepam, clonazepam
Opioids	Codeine, morphine, hydromorphone, oxycodone, hydrocodone
Mixed mechanisms	Some antipsychotics: chlorpromazine, olanzapine, quetiapine, thioridazine

GABA, gamma aminobutyric acid.
*Not an exhaustive list.

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Recommendations To Clinicians

- In patients at risk for ASCVD, statins have important health benefits that far outweigh risks of cognitive dysfunction as a side effect.
- Cognitive side effects of statins may occur in rare individuals, the medical evidence supporting a causal effect is weak or nonexistent.
- The true incidence of these side effects cannot be determined with currently available data.
- Patient complaints about cognition should be taken seriously and appropriately evaluated, including undertaking appropriate neuropsychological testing in patients whose symptoms persist despite statin discontinuation.
- If no other causes of cognitive dysfunction are identified, discontinuation of the medication should be considered after a careful review of the benefit:risk ratio.

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Recommendations To Patients

- Cognitive symptoms have been reported by some statin users, but information from such case reports cannot be considered to be reliable, is not conclusive, and has not been proven in a cause-and-effect manner.
- Many other causes of memory complaints exist, including normal aging, the effect of many commonly used medications (e.g. sedative-hypnotics, OTC antihistamines, pain medications), and the effects of many medical conditions (e.g. anxiety, depression, sleep apnea).
- If patients have a concern about their memory or other symptoms, they should first discuss this with their health care provider before considering discontinuing their statin.

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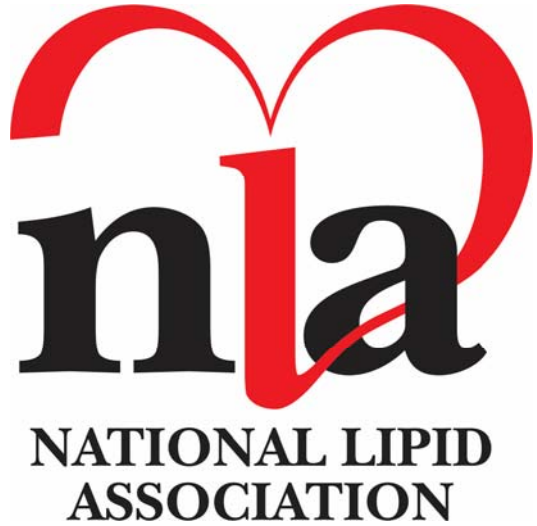
Future Research Directions

- Studies specifically designed to assess the impact of statins on cognition
  - Need to evaluate impact of statin type / dose and effects of co-morbidities and concomitant medications.
  - Need to enroll patients representative of statin users
  - Use instruments sensitive to subtle cognitive deficits
  - Assess clinical significance of any MCI detected
  - Sufficient duration to address statin effects over time
  - Consider dechallenge / rechallenge designs

- Registry of statin users followed over many years and assessed with serial cognitive testing to assess long-term effects of statins.

- All trials involving vascular risk factor modification via pharmacological intervention ideally should include cognitive assessments.
  - The Vascular Cognitive Harmonization Statement includes a 60-min protocol that could be used in studies that require cognition to be assessed in all 4 domains.*
  - Increases cost of trials
  - Increases participant and investigator burden

*Hachinski V et al. National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. Stroke 2006;37:2220–2241
Rojas-Fernandez et al. J Clin Lipidol 2014;8:S5-S16



An Assessment by the Statin Diabetes Safety Task Force: 2014 Update

Kevin C. Maki, PhD, FNLA

Midwest Center for Metabolic & Cardiovascular Research and

DePaul University

Chicago, IL

Background

- In 2012 the US Food and Drug Administration added a statement to the labels of statin medications indicating that increases in glycated hemoglobin (HbA_{1C}) and fasting glucose levels have been reported with statin use.

- The Diabetes Subpanel of the National Lipid Association Expert Panel on Statin Safety reviewed the published evidence relating statin use to the hazard for diabetes mellitus or worsening glycemia, with the aims of summarizing the results and providing practical guidance on how to manage this issue in clinical practice.

Journal of Clinical Lipidology (2014) 8, S17–S29

Journal of Clinical Lipidology

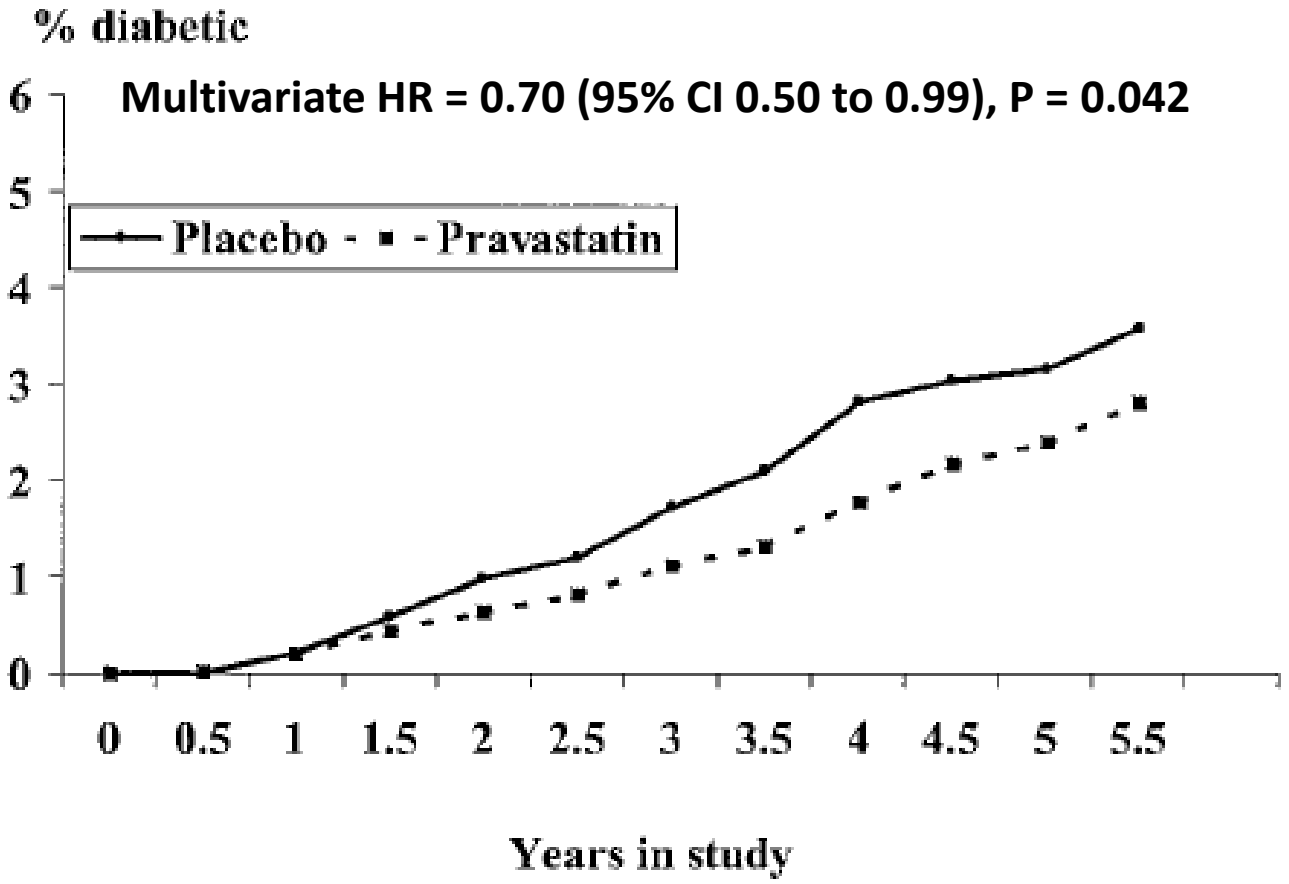
Original Contribution

An assessment by the Statin Diabetes Safety Task Force: 2014 update

Kevin C. Maki, PhD, FNLA*, Paul M Ridker, MD, MPH, W. Virgil Brown, MD, FNLA, Scott M. Grundy, MD, PhD, FNLA, Naveed Sattar, MD, PhD

Maki et al. *J Clin Lipidol.* 2014;8:S17-S29.

WOSCOPS – Statin Treatment Associated with Lower Risk for T2DM



Freeman et al. *Circulation.* 2001;103:357-362.

JUPITER – Increased Risk for T2DM with Rosuvastatin Treatment

Event	Placebo	Rosuvastatin	Δ	P-Value
New T2DM (All)*	216 (2.4%)	270 (3.0%)	+54	0.01
New T2DM (0 DM RF)*	12 (0.2%)	12 (0.2%)	0	0.99
New T2DM (≥1 DM RF)*	204 (1.7%)	258 (2.1%)	+54	0.01
HR (95% CI) 0 DM RF	----	0.99 (0.45-2.21)	----	----
HR (95% CI) ≥1 DM RF	----	1.28 (1.07-1.54)	----	----

*8901 subjects were allocated to each group overall; of the 17,802 participants, 6095 had no major diabetes mellitus (DM) risk factors (RF) and 11,508 ≥1 DM RF; DM RFs included metabolic syndrome, impaired fasting glucose, body mass index ≥30 kg/m^2 and glycated hemoglobin >6%

Ridker et al. *Lancet.* 2012;380:565-572

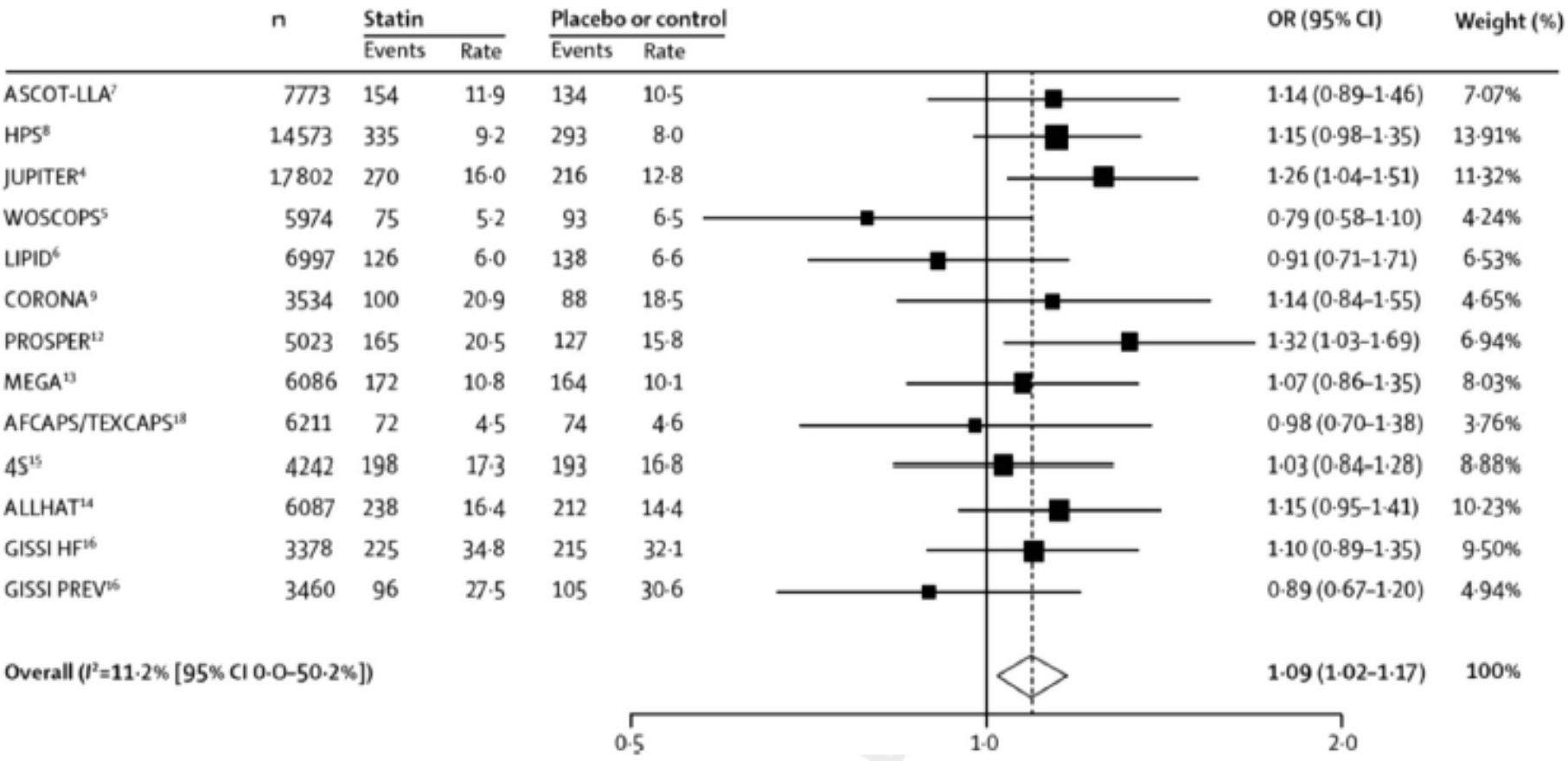
JUPITER – Lower Risk for Primary CVD Endpoint with Rosuvastatin Treatment

Event	Placebo	Rosuvastatin	Δ	P-Value
1º CVD EP (All)*	251 (2.8%)	142 (1.6%)	-109	<0.0001
1º CVD EP (0 DM RF)*	91 (1.5%)	44 (0.7%)	-47	<0.0001
1º CVD EP (≥1 DM RF)*	157 (1.3%)	96 (0.8%)	-61	<0.0001
HR (95% CI) 0 DM RF	----	0.48 (0.33-0.68)	-52%	----
HR (95% CI) ≥1 DM RF	----	0.61 (0.47-0.79)	-39%	----

*8901 subjects were allocated to each group overall; of the 17,802 participants, 6095 had no major diabetes mellitus (DM) risk factors (RF) and 11,508 ≥1 DM RF; DM RFs included metabolic syndrome, impaired fasting glucose, body mass index ≥30 kg/m^2 and glycated hemoglobin >6%

Ridker et al. *NEJM.* 2008;359:2195-2207; Ridker et al. *Lancet.* 2012;380:565-572

Statin Therapy and Incident Diabetes in 13 CVD Endpoint Trials



Sattar et al. *Lancet*. 2010;375:735-742.

Number Needed to Treat – Sattar Meta-Analysis

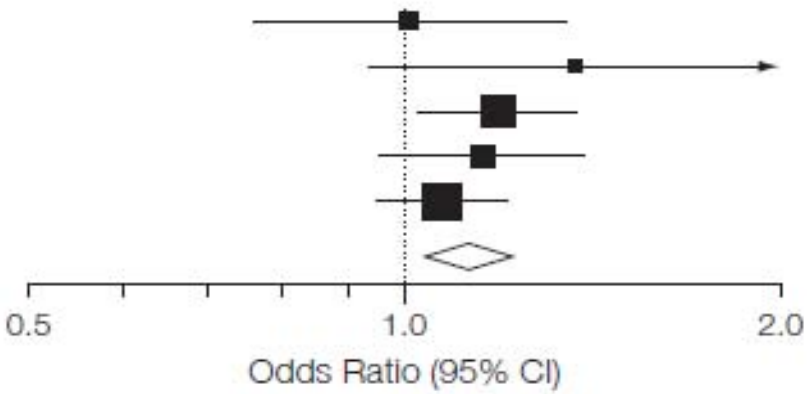
- The number of patients that would need to be treated for 4 years to produce one excess case of T2DM is 255
- Based on the CTT analysis, a 1 mmol/L (38.7 mg/dL) reduction in LDL-C over 4 years would prevent 5.4 CHD events
  - CHD includes myocardial infarction and fatal CHD, but does not include revascularization or stroke
- Thus, 5-10 CVD events and revascularizations might be prevented for each excess case of T2DM associated with use of statin therapy

Sattar et al. *Lancet*. 2010;375:735-742.

Intensive vs. Moderate Statin Therapy: Diabetes and CVD Outcomes

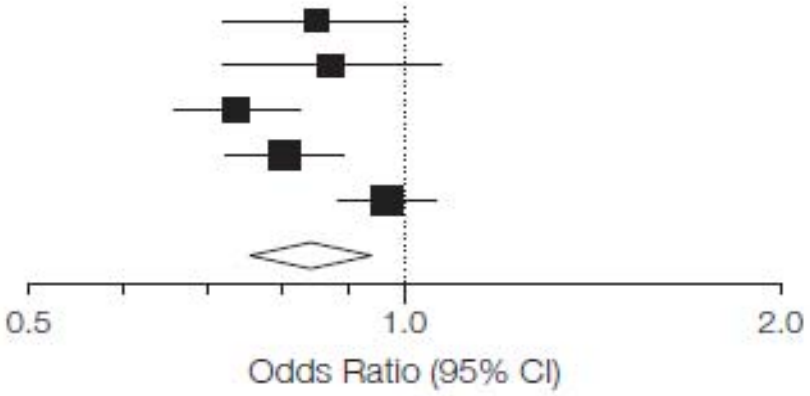
Incident Diabetes

	OR (95% CI)
PROVE IT–TIMI 22,[18] 2004	1.01 (0.76-1.34)
A to Z,[17] 2004	1.37 (0.94-2.01)
TNT,[15] 2005	1.19 (1.02-1.38)
IDEAL,[16] 2005	1.15 (0.95-1.40)
SEARCH,[5] 2010	1.07 (0.95-1.21)
	1.12 (1.04-1.22)



Incident CVD

PROVE IT–TIMI 22,[18] 2004	0.85 (0.72-1.01)
A to Z,[17] 2004	0.87 (0.72-1.07)
TNT,[15] 2005	0.73 (0.65-0.82)
IDEAL,[16] 2005	0.80 (0.72-0.89)
SEARCH,[5] 2010	0.97 (0.88-1.06)
	0.84 (0.75-0.94)



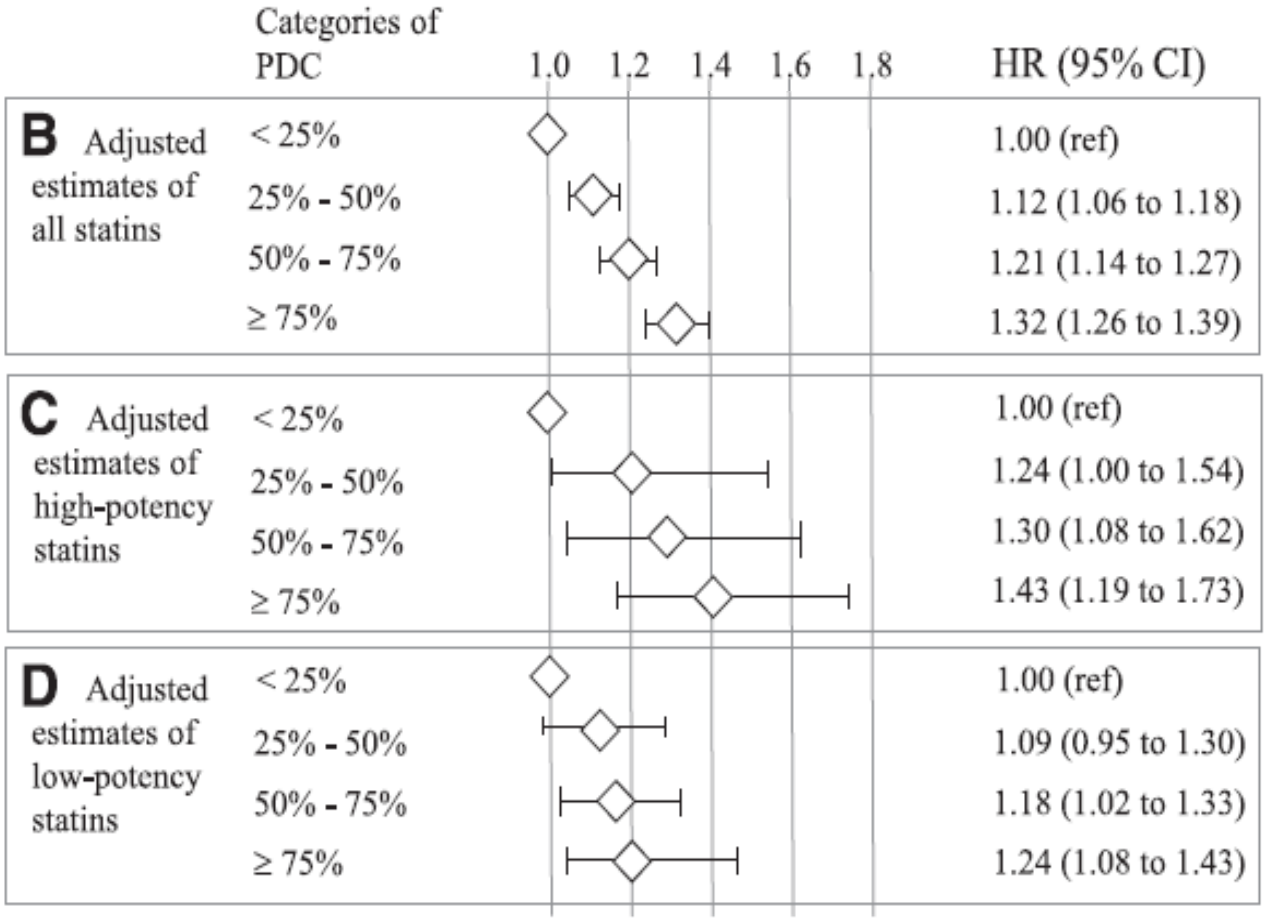
Preiss et al. *JAMA*. 2011;305:2556-2564.

Number Needed to Treat – Preiss Meta-Analysis

- The number of patients that would need to be treated for one year with intensive statin therapy vs. moderate-dose statin therapy to produce an excess case of T2DM is 498
- The number patients that would need to be treated to prevent one CVD event in a year is 155 (cardiovascular death, nonfatal myocardial infarction or stroke, coronary revascularization).
  - Thus, if 498 patients were treated for one year with high-intensity statin therapy rather than moderate intensity statin therapy, this would be expected to produce one excess case of T2DM but to prevent 3.2 CVD events

Preiss et al. *JAMA*. 2011;305:2556-2564.

Effect of Adherence to Statin Therapy on the HRs for Diabetes



Corrao et al. *Diabetes Care*. 2014. DOI: 10.2337/dc13-2215

How robust is the evidence linking statin use to increased risk for diabetes mellitus, and what appears to be the magnitude of risk? How does the increase in diabetes risk compare with the benefit of statin therapy on CVD event risk?

Meta-analyses of statin trials indicate that statin use is associated with a modest, but statistically significant, increase in risk for the development of type 2 diabetes mellitus of approximately 10 to 12%, and that risks are somewhat higher for more intensive statin regimens.

- In both primary and secondary prevention, available data indicate that several fewer major CVD events occur for each excess case of new-onset diabetes associated with statin therapy, or intensification of statin therapy.
- The risk of developing diabetes while on statin therapy ***may*** be limited to those with diabetes risk factors.

What is the impact of statin treatment on glycemic control in patients with diabetes mellitus?

Due to a variety of methodological concerns, the panel members do not feel that sufficient evidence is available from randomized clinical trial data to draw firm conclusions regarding the impact of statin treatment on glycemic control in patients with diabetes mellitus.

- The available data suggest that, if there is an adverse effect of statin treatment on glycemia, it is small (mean increase of ~0.3% HbA_{1C} or less), and has the potential to be attenuated by adjustment of the treatment regimen for glycemic control.

What is known about the mechanisms that mediate the relationship between statin use and risk of new-onset type 2 diabetes mellitus?

No firm conclusions can be drawn at present regarding the potential mechanistic link between statin therapy and increased risk for diabetes mellitus.

- Research is needed to further define the effects of statin therapy on the determinants of glucose homeostasis (insulin sensitivity, pancreatic beta-cell function, hepatic glucose output), particularly in those at high risk for diabetes development.

Should doctors measure glycemic parameters before starting a statin prescription and/or during statin therapy?

The panel endorses application of the current *Standards of Medical Care in Diabetes* recommendations from the American Diabetes Association.

- Ideally, screening should occur prior to initiation of statin therapy in those with at least one major diabetes risk factor, although clinicians should not generally delay the initiation of statin therapy to await results from screening tests in a patient for whom statin therapy is indicated.

Screening and Diagnosis of T2DM

Screening

Testing to detect type 2 diabetes and prediabetes in asymptomatic people should be considered in adults of any age who are overweight or obese (BMI ≥25 kg/m^2) and who have one or more additional risk factors for diabetes.

In those without risk factors, testing should begin at age 45 years.

If tests are normal, repeat testing at 3-year intervals or less is reasonable. However, should repeat within 1 year of staring a statin.

Criteria for diagnosis (asymptomatic patient)

HbA_{1C} ≥6.5%

OR

FPG ≥126 mg/dL
(Fasting = no caloric intake for ≥8 h)

OR

Two-hour PG ≥200 mg/dL during a 75 g OGTT

Diabetes risk factors

-physical inactivity
-first degree relative with T2DM
-HTN or CVD
-PCOS or baby >9 lb
-High TG or low HDL-C
-IFG, IGT or HbA_{1C} 5.7-6.4%
-Condition associated with insulin resistance

Maki et al. *J Clin Lipidol.* 2014;8:S17-S29.

Task Force Conclusions

- Statin use is associated with a modest increase in risk (~10-12%) for new-onset type 2 diabetes mellitus (diabetes), compared with placebo or usual care.
- Intensive statin therapy appears to increase diabetes risk beyond that of moderate-dose statin therapy.
- Excess risk for diabetes with statin use is most clearly evident in those with major risk factors for diabetes.
- The cardiovascular benefits of statin therapy outweigh the potential risk for diabetes development, with several cardiovascular events prevented for each excess case of diabetes.

Task Force Conclusions

- Statin therapy should continue to be recommended where appropriate for the reduction of cardiovascular disease event risk.
- Lifestyle modification should be emphasized to all patients for whom statin therapy is recommended to:
  - Reduce cardiovascular risk and
  - Attenuate the increase in diabetes risk.
- Patients with risk factors for diabetes should be screened, generally with fasting glucose or HbA_{1C}, ideally prior to starting statin therapy, within one year of initiation, and at intervals no longer than 3 years thereafter.



August 22, 2014

Title :Statin Liver Safety Task Force: Update

Harold Bays MD, FTOS, FACC, FACE, FNLA
L-MARC Research Center
Louisville, KY

Introduction / Outline

- Causes of elevated liver enzymes
- Elevated liver enzyme algorithm
- Summary & take home messages

Causes of Elevated Liver Enzymes

Table 3 Illustrative causes of elevated liver enzymes in adolescents and adults*

Celiac disease

Congestive cardiomyopathy

Endocrine diseases

- Adiposity resulting in adiposopathy
- Diabetes mellitus and insulin resistance syndromes
- Hyperthyroidism and hypothyroidism
- Metabolic syndrome

Excessive ethanol intake (with or without alcoholic hepatitis)

- In patients without underlying liver disease, ethanol intake that is more likely to cause increases in liver enzymes include >2 units a day for men and 1 unit per day for women (unit = generally defined as 12 oz of beer, 5 oz of wine, 1.5 oz for 80 proof mixed drinks)

Fatty liver

- Nonalcoholic fatty liver disease
- Nonalcoholic steatohepatitis

Gallbladder disease (eg, cholelithiasis with obstruction)

Genetic diseases

- Alpha 1 antitrypsin deficiency
- Cystic fibrosis
- Hemochromatosis (excessive iron storage)
- Hepatic porphyrias
- Wilson's disease (excessive copper storage)

Infections

Bays H, Cohen DE, Chalasani N, Harrison SA. An assessment by the Statin Liver Safety Task Force: 2014 update. J Clin Lipidol. 2014 May-Jun;8(3 Suppl):S47-57. doi: 10.1016/j.jacl.2014.02.011. PubMed PMID: 24793441.

- Viral infection
  - Adenovirus
  - Cytomegalovirus
  - Coxsackievirus
  - Echovirus
  - Epstein-Barr (eg, mononucleosis)
  - Hepatitis A, B, C, and E
  - Herpes simplex virus
  - Human immunodeficiency virus
  - Rubella
- Bacterial infection, especially with sepsis
  - Chlamydia
  - Rickettsia
  - Spirochetes
  - Tuberculosis and other mycobacteria
- Fungal infection
  - Candidiasis
  - Histoplasmosis
- Parasitic infections (protozoa and helminthes)
  - Schistosomiasis
  - Leptospirosis
  - Toxoplasmosis
  - Visceral larva migrans

Malignancies

- Primary liver cancer
- Metastatic cancer
- Leukemia and lymphoma

Other liver diseases

- Autoimmune hepatitis (eg, idiopathic, inflammatory bowel disease, ulcerative colitis, rheumatoid arthritis, systemic lupus erythematosus)
- HELLP syndrome in pregnancy (*H*emolysis, *EL*evated liver enzymes, *L*ow *P*latelet count)

Bays H, Cohen DE, Chalasani N, Harrison SA. An assessment by the Statin Liver Safety Task Force: 2014 update. J Clin Lipidol. 2014 May-Jun;8(3 Suppl):S47-57. doi: 10.1016/j.jacl.2014.02.011. PubMed PMID: 24793441.

- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Thrombotic occlusion of the hepatic veins (Budd-Chiari syndrome)

Selected medications

- Antibiotics
  - Amoxicillin
  - Amphotericin
  - Azole antifungal agents (eg, fluconazole, ketoconazole)
  - Ciprofloxacin
  - Erythromycin
  - Isoniazid
  - Nitrofurantoin
  - Protease inhibitors
  - Rifampin
  - Sulfonamide antibiotics (eg, sulfamethoxazole)
  - Tetracycline
  - Trimethoprim
- Cardiovascular disease medications
  - Amiodarone
  - Ezetimibe when combined statins
  - Fibrates (gemfibrozil, fenofibrate)
  - Hydralazine
  - Labetalol
  - Methyldopa
  - Niacin (especially over-the-counter slow-release preparations at doses greater than 1500 mg/d)
  - Quinidine
  - Statins

Bays H, Cohen DE, Chalasani N, Harrison SA. An assessment by the Statin Liver Safety Task Force: 2014 update. J Clin Lipidol. 2014 May-Jun;8(3 Suppl):S47-57. doi: 10.1016/j.jacl.2014.02.011. PubMed PMID: 24793441.

- Statins
- Herbal supplements
  - Chaparral
  - Ephedra
  - Gentian
  - Germander
  - Jin Bu Huan
  - Kavakava
  - Ma-huang
  - Scutellaria
  - Senecio/crotalaria (bush teas)
  - Senna
  - Shark cartilage
- Hormones
  - Anabolic steroids (eg, testosterone)
  - Estrogens
  - Excessive thyroid hormone
  - Systemic corticosteroids
  - Tamoxifen
- Illicit drugs
  - Anabolic steroids
  - Cocaine
  - Methylenedioxymethamphetamine (MDMA or ecstasy)
  - Phencyclidine (PCP)
- Neurologic and psychiatric medications
  - Carbamazepine
  - Chlorpromazine
  - Phenobarbital

Bays H, Cohen DE, Chalasani N, Harrison SA. An assessment by the Statin Liver Safety Task Force: 2014 update. J Clin Lipidol. 2014 May-Jun;8(3 Suppl):S47-57. doi: 10.1016/j.jacl.2014.02.011. PubMed PMID: 24793441.

- Phenytoin
- Trazodone
- Valproic acid

- Pain medications
  - Acetaminophen
  - Aspirin
  - Nonsteroidal anti-inflammatory drugs

- Other medications
  - Dantrolene
  - Disulfiram
  - Etretinate
  - Halothane
  - Heparin
  - Orlistat
  - Propylthiouracil
  - Sulfonylureas
  - Vitamin A and derivatives
  - Zafirlukast

Bays H, Cohen DE, Chalasani N, Harrison SA. An assessment by the Statin Liver Safety Task Force: 2014 update. J Clin Lipidol. 2014 May-Jun;8(3 Suppl):S47-57. doi: 10.1016/j.jacl.2014.02.011. PubMed PMID: 24793441.

- Zafirlukast

Toxins

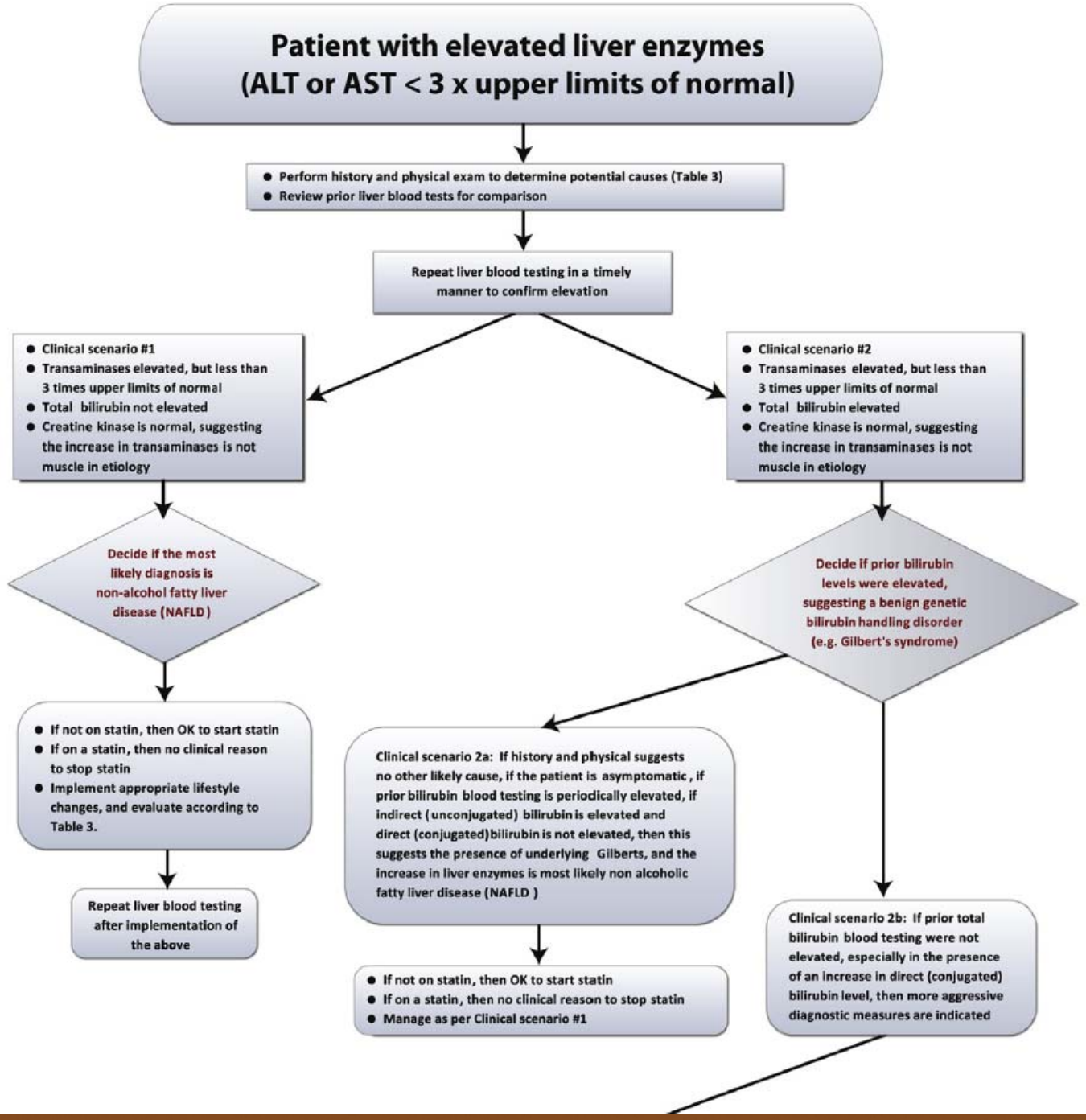
- 2-Nitropropane
- Carbon tetrachloride
- Chloroform
- Dimethylformamide
- Hydrazine
- Hydrocarbons
- Hydrochlorofluorocarbons
- Hypervitaminosis A
- Insecticides
- Mushrooms
- Organophosphates
- Toluene
- Trichloroethylene

"Weight loss" or "workout" or "body building" supplements[†]

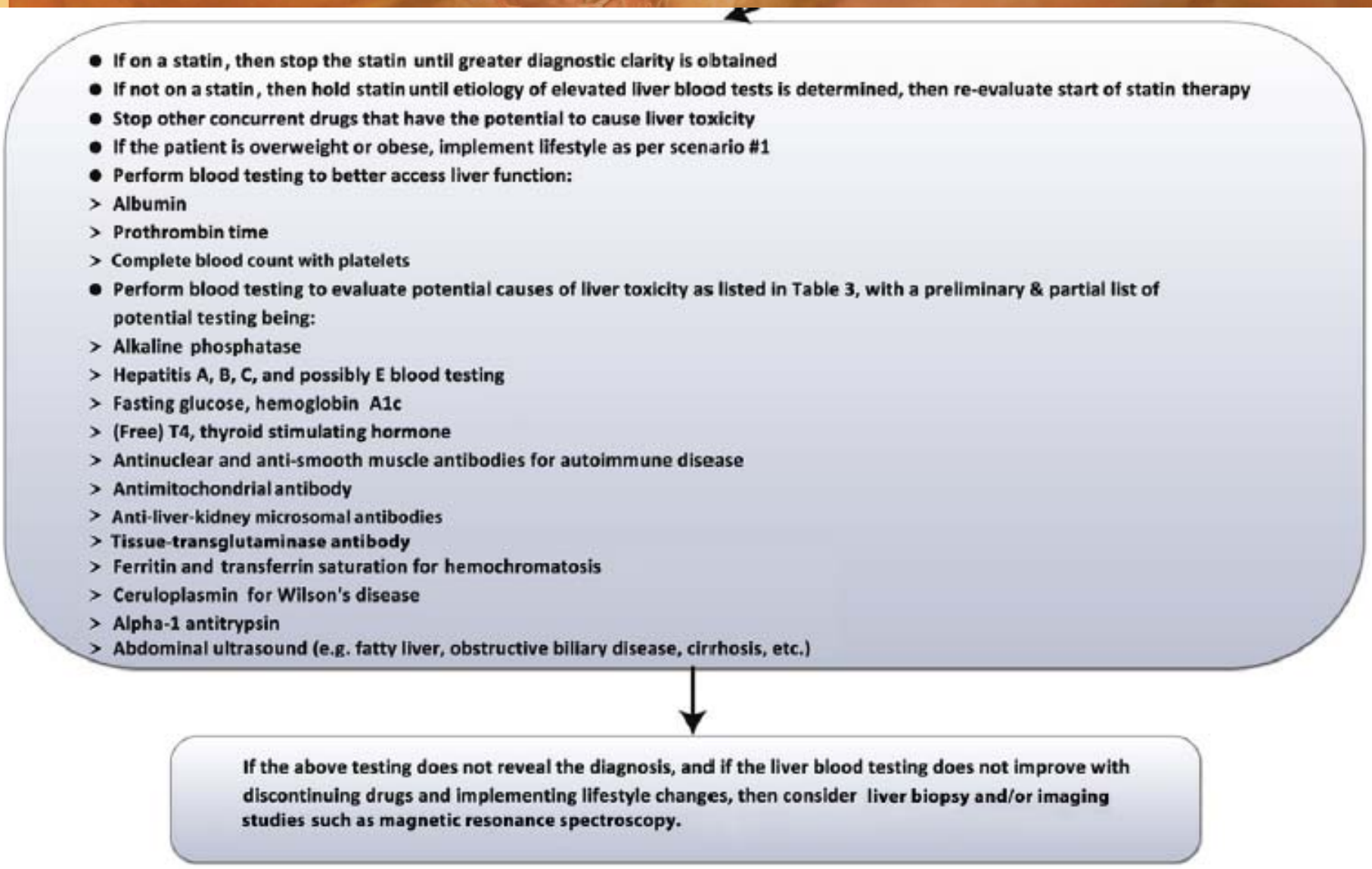
- Liver injury from the supplement itself
- Liver injury from other toxic ingredients
- Liver injury from a bad batch of the supplement

Bays H, Cohen DE, Chalasani N, Harrison SA. An assessment by the Statin Liver Safety Task Force: 2014 update. J Clin Lipidol. 2014 May-Jun;8(3 Suppl):S47-57. doi: 10.1016/j.jacl.2014.02.011. PubMed PMID: 24793441.

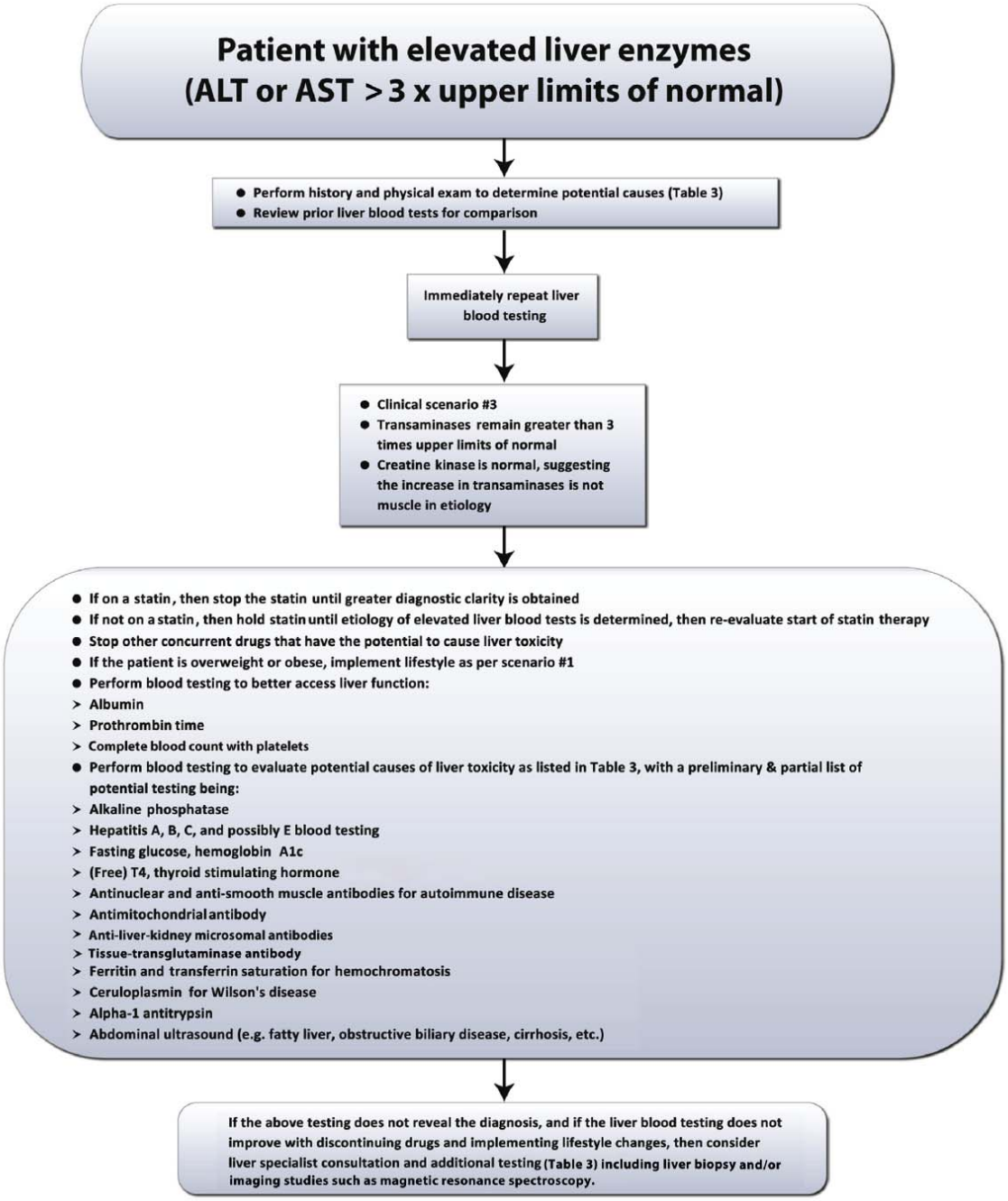
Elevated Liver Enzyme Algorithm



Bays H, Cohen DE, Chalasani N, Harrison SA. An assessment by the Statin Liver Safety Task Force: 2014 update. J Clin Lipidol. 2014 May-Jun;8(3 Suppl):S47-57. doi: 10.1016/j.jacl.2014.02.011. PubMed PMID: 24793441.



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ALT = alanine aminotransferase
AST = aspartate aminotransferase

Figure 2 Comprehensive approach to patients with elevated liver blood testing (transaminases >3 times the upper limits of normal).

Bays H, Cohen DE, Chalasani N, Harrison SA. An assessment by the Statin Liver Safety Task Force: 2014 update. J Clin Lipidol. 2014 May-Jun;8(3 Suppl):S47-57. doi: 10.1016/j.jacl.2014.02.011. PubMed PMID: 24793441.

Summary and take home messages

Table 2 Questions addressed by liver experts in the 2006 and 2014 National Lipid Association Statin Safety Task Force Report[6]

2006 National Lipid Association Statin Safety Task Force Questions	Answer
Are elevations in serum aminotransferase levels associated with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, or statin, therapy?	Yes
Are statin-associated elevations in aminotransferase levels indicative of liver damage or dysfunction?	No
Are statin-associated elevations in aminotransferases a class effect?	Yes
Does statin therapy increase the incidence of liver failure, liver transplants, or death associated with liver failure in the general population?	Yes
Should liver enzymes and liver function tests be monitored in patients receiving long-term statin therapy?	No
Are any of the following conditions a contraindication for statin therapy?	
• Chronic liver disease	No
• Compensated cirrhosis	No
• Decompensated cirrhosis or acute liver failure	Yes
Can statins be used in patients with nonalcoholic fatty liver disease or nonalcoholic steatohepatitis?	Yes
2014 National Lipid Association Statin Safety Task Force Questions	
Have any unexpected safety concerns arisen since the regulatory recommendation that liver enzymes need not be measured after initiating statin therapy?	No
Should baseline liver enzymes be obtained before initiating statin therapy?	Yes
Are statins safe to use in patients with nonalcoholic fatty liver disease?	Yes
Do statins have drug interactions with medications used to treat infections (eg, hepatitis B, C) that require change in statin, change in statin dosing, or change in antiviral regimen dosing?	Yes
Can statins safely be used in liver transplant recipients?	Yes
Can statins safely be used in patients with autoimmune hepatitis?	Yes

Bays H, Cohen DE, Chalasani N, Harrison SA. An assessment by the Statin Liver Safety Task Force: 2014 update. J Clin Lipidol. 2014 May-Jun;8(3 Suppl):S47-57. doi: 10.1016/j.jacl.2014.02.011. PubMed PMID: 24793441.



August 22, 2014

Title :Statin Liver Safety Task Force: Update

Harold Bays MD, FTOS, FACC, FACE, FNLA
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Statin Associated Adverse Skeletal Muscle Events

An Assessment by the Statin Muscle Safety Task Force 2014 Update

Robert S. Rosenson, MD, FNLA
Stephen Baker, MD
Terry Jacobson, MD, FNLA
Stephen Kopecky, MD
Beth Parker, Ph.D

What is the spectrum of statin-associated muscle toxicity?

1. Myalgia
2. Myopathy
3. Myositis
4. Muscle injury with acute renal failure (Clinical “rhabdomyolysis”)

Rosenson RS, Baker SL, Jacobson TA, Kopecky SL, Parker NA. *J Clin Lipidol* 2014;8 (suppl 3):S58-71

What is the definition of statin-associated muscle adverse events?

- Myalgia – unexplained muscle discomfort often described as “flu-like” symptoms with normal CK level
- Myopathy – muscle weakness
- Myositis – muscle inflammation often with muscle enzyme elevations
- Myonecrosis – elevation in muscle enzymes, severity graded by elevation of CK level above pre-treatment baseline levels or ULN.
- Clinical rhabdomyolysis – muscle injury with myoglobinuria and/or acute renal failure

Rosenson RS, Baker SL, Jacobson TA, Kopecky SL, Parker NA. *J Clin Lipidol* 2014;8 (suppl 3):S58-71

What is the Spectrum of Myalgia Symptoms?

- Muscle aches
- Muscle soreness
- Muscle stiffness
- Muscle tenderness
- Muscle cramps with or shortly after exercise. Not nocturnal cramping

Rosenson RS, Baker SL, Jacobson TA, Kopecky SL, Parker NA. *J Clin Lipidol* 2014;8 (suppl 3):S58-71

What clinical scoring index should be used for the accurate diagnosis of statin myalgia in clinical practice?

- Clinical symptoms (new or increased unexplained muscle symptoms)
- Regional distribution/pattern
  - Symmetric pelvic/thigh aches
  - Symmetric calf aches
  - Symmetric upper proximal aches
  - Non-specific asymmetric, intermittent
- Temporal pattern
  - Symptoms onset <4 weeks
  - Symptoms onset 4-12 weeks
  - Symptoms –onset >12 weeks
- Dechallenge
  - Improves upon withdrawal (<2 weeks)
  - Improves upon withdrawal (2-4 weeks)
- Challenge
  - Same symptoms recurs upon re-challenge <4 weeks
  - Same symptoms recur upon re-challenge 4-12 weeks

Rosenson RS, Baker SL, Jacobson TA, Kopecky SL, Parker NA. *J Clin Lipidol* 2014;8 (suppl3):S58-71

What is the definition of myopathy?

- **Muscle weakness (not attributed to pain) and not necessarily associated with elevated CK**

Rosenson RS, Baker SL, Jacobson TA, Kopecky SL, Parker NA. *J Clin Lipidol* 2014;8 (suppl3):S58-71

What are the diagnostic criteria for myopathy?

- Physical examination
  - Proximal weakness in upper and lower extremities ≤4 by MRC definition
- Standardized muscle testing with isokinetic dynamometer, aerobic capacity and respiratory exchange ratio with fasted patient and standardized procedure on metabolic cart (requires off drug/on drug comparison)
- Confirmation by EMG +/- muscle biopsy

Rosenson RS, Baker SL, Jacobson TA, Kopecky SL, Parker NA. *J Clin Lipidol* 2014;8 (suppl3):S58-71

What is the definition of myositis?

- **Pathologic muscle inflammation (biopsy)**

Rosenson RS, Baker SL, Jacobson TA, Kopecky SL, Parker NA. *J Clin Lipidol* 2014;8 (suppl3):S58-71

What is the Definition of Myonecrosis?

- CK elevation indicates severity of muscle damage:
  - Mild hyperCKemia: <10x ULN
  - Moderate hyperCKemia: 10-50x ULN
  - Marked hyperCKemia: >50x ULN

Rosenson RS, Baker SL, Jacobson TA, Kopecky SL, Parker NA. *J Clin Lipidol* 2014;8 (suppl3):S58-71

What tests are available to support or confirm the diagnosis of statin-associated muscle adverse events?

- Muscle adverse event clinic index score
- Muscle enzymes (CK). Serum aldoase and myoglobin not recommended.
- If CK levels > 50 times ULN and/or dark brown, obtain urinary myoglobin
- Pain questionnaires (brief pain inventory [preferred because most widely used], McGill, adaptation of quality of life)
- Strength and aeorobic testing
- Metabolic tests (MRS, O_2 uptake intake)
- Pharmacogentic testing

Rosenson RS, Baker SL, Jacobson TA, Kopecky SL, Parker NA. *J Clin Lipidol* 2014;8 (suppl3):S58-71

What is indication for muscle biopsy?

- EMG myopathic discharges with fibrillations and/or positive sharp waves in affected muscles
- Threshold for biopsy - CK values should be adjusted >3 ULN above sex and racial norms

Rosenson RS, Baker SL, Jacobson TA, Kopecky SL, Parker NA. *J Clin Lipidol* 2014;8 (suppl3):S58-71

What are the rates of myopathy in clinical trials?

- **Twenty-six of 42 trials (62%) reported the number of subjects with muscle complaints including-myalgia, myositis, myopathy, muscle cramps, and muscle weakness**
- **Only one study specifically solicited muscle complaints (Kjekshus et al. 2007: *Rosuvastatin in older patients with systolic heart failure*)**
- **Detailed criteria for evaluating mild to moderate muscle complaints were not presented in the other 41 studies (98%)**

Ganga, Slim and Thompson: A Systematic Review of Statin-Induced Muscle Problems in Clinical Trials; *In Review*

What are the best estimates of rates of myopathy in clinical practice?

Muscle Complaints in Clinical Practice: PRIMO

- Examined the prevalence of mild to moderate muscle side effects among 7924 French patients on moderate to high dose statin therapy
- No control group (unblinded)
- 10.5% muscle complaints
- Median time of onset of 1 month following initiation of statin therapy

Bruckert et al. Cardiovasc Drugs Ther 2005

Muscle Complaints in Clinical Practice: STOMP

- 80 mg atorvastatin for 6 months
  - 9.4% value recently reported
  - 4.6% of the STOMP placebo subjects met the study definition of myalgia
  - True incidence of statin myalgia was 4.8%
  - Healthy, statin-naïve patients
  - No other overt CVD
  - Average time of onset 1 month in true myalgics vs 2 months in placebo myalgics ($p < 0.05$)

Parker et al. 2013

Muscle Complaints in Clinical Practice: NHANES Data

- Cross-sectional analysis NHANES 1999-2002
  - Adults ≥40 years (n=3,580) without arthritis
  - Queried for musculoskeletal pain and medication use in last 30 days
  - 22%of 402 statin users reported musculoskeletal pain
  - 16.7% of non-statin users reported pain
  - Difference of 5.3% (odds ratio 1.50)

Buettner et al. 2008

Why are the rates of myopathy in clinical trials different from clinical experience?

- Failure to query study subjects
  - Only 26/42 clinical trials reported the frequency of muscle complaints
  - Only one study actually queried subjects systematically about muscle complaints
  - "Don't ask, don't tell" phenomenon?
- Failure to define muscle side effects
  - Myalgia, myositis, cramps, weakness, stiffness, soreness, tenderness, aching
  - With or without CK elevations?
  - Baseline CK measurements?

Ganga HV, Slim HB, Thompson PD. Am Heart J 2014;168:6-15.

Difference Between Clinical Trials and Practice

- Placebo effect
  - Side effects mentioned in informed consent
- Effect of run-in phase
  - Typically one month to onset of symptoms
  - HPS: 5 week run-in period
- Different patient/subject populations
  - Clinical trials inclusion/exclusion criteria
- Differences between statin types
  - Fewer muscle complaints with fluvastatin

Ganga HV, Slim HB, Thompson PD. Am Heart J 2014;168:6-15

What are the predictors of statin associated adverse muscle events?

Clinical Predictors of Risk

- Older age, Asian race and gender (F>M)
- Exercise
- Comorbidity *(hypothyroidism, hyeruricemia, alcohol overconsumption)*
- Statin dose
- History of muscle pain with another lipid-lowering therapy
- Family history of muscular symptoms with lipid-lowering agents
- Concomitant medications *(CYP3A4 with simvastatin, inhibitors of CYP3A4 and SLCO1B1 including azole anti-fungals, ritonavir, verapamil and diltiazem; gemfibrozil*

Modified after Feng, Wilke and Baye. Pharmacogenomics 2012;13:579-594

Genetic Determinants of Risk

- Candidate gene studies
  - Phamracokinetic candidate genes
  - Pharmacodynamic candidate genes
- Genome-wide studies
  - Linkage studies in families
  - Genome-wide association studies in unrelated individuals

Modified after Feng et al. Pharmacogneomics 2012:13:579-594

Comments on Statins and Physical Activity

- Assess baseline physical activity
  - Physical activity questionnaire
- Take physical activity into consideration when assessing muscle complaints
  - Physical activity recall
- Acute vs chronic impacts
  - Statin use prior to endurance event
  - Discontinue prior to a bout of exercise?
  - Physically active individuals

Rosenson RS, Baker SL, Jacobson TA, Kopecky SL, Parker NA. *J Clin Lipidol* 2014;8 (suppl 3):S58-71

What is the evidence base for treating patients with statin associated muscle events?

- Ezetimibe
- Bile acid sequestrants
- Niacin
- Red yeast rice
- PCSK9 inhibitors
- CETP inhibitors
- AMP kinase inhibitors

Rosenson RS, Baker SL, Jacobson TA, Kopecky SL, Parker NA. *J Clin Lipidol* 2014;8 (suppl 3):S58-71

Summary

- The major cause of statin intolerance is adverse muscle events
- Imprecise definitions have impaired accurate diagnosis of statin associated adverse events and clinical trials designed to investigate alternative therapies
- The need for a validated clinical myalgia index is a crucial step for accurate diagnosis
- Research into diagnostic studies and procedures will further improve accurate diagnosis of statin associated adverse events, and provide the basis for evaluating other myopathic disorders and justifying alternative cholesterol lowering therapies

Rosenson RS, Baker SL, Jacobson TA, Kopecky SL, Parker NA. *J Clin Lipidol* 2014;8 (suppl 3):S58-71

Statin Safety 2014 NLA Update

Kenneth A. Kellick, PharmD,
Michael Bottorff, PharmD,
Peter P. Toth, MD, PhD

Disclosures: Kenneth Kellick has nothing to disclose

Learning Objectives

The material will allow the practitioner to:

- Better understand the different enzyme systems involved in statin metabolism and intra-patient differences
- Be able to predict potential drug interactions based upon changes in the area under the curve for statin concentrations
- Be able to better interpret package labeling with respect to drug-drug interactions
- Identify common prescription and non-prescription medications that interact with statins
- Identify special populations that may be at risk for statin drug-drug interactions

Special Acknowledgements

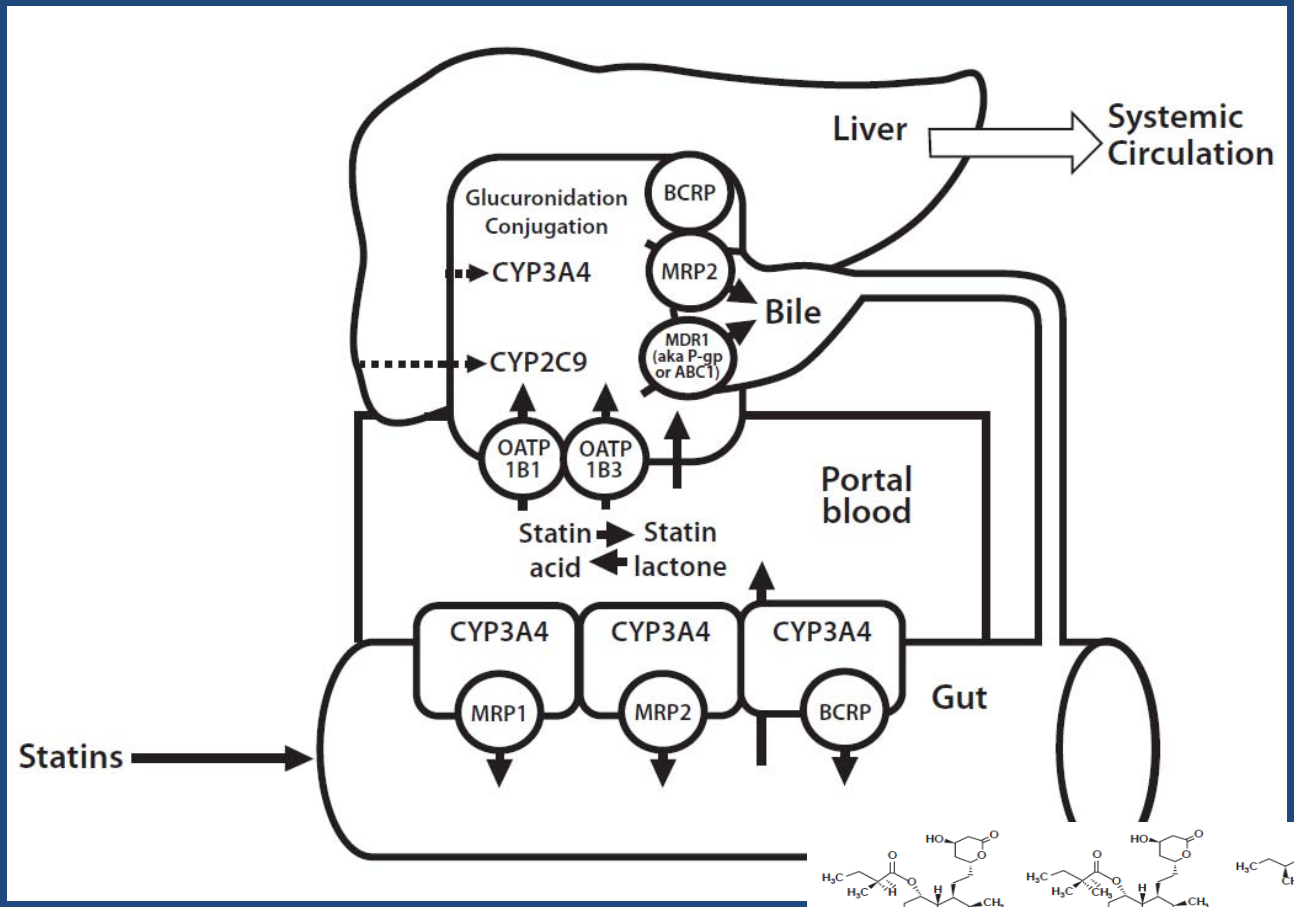
- Terry Jacobsen
- Virgil Brown

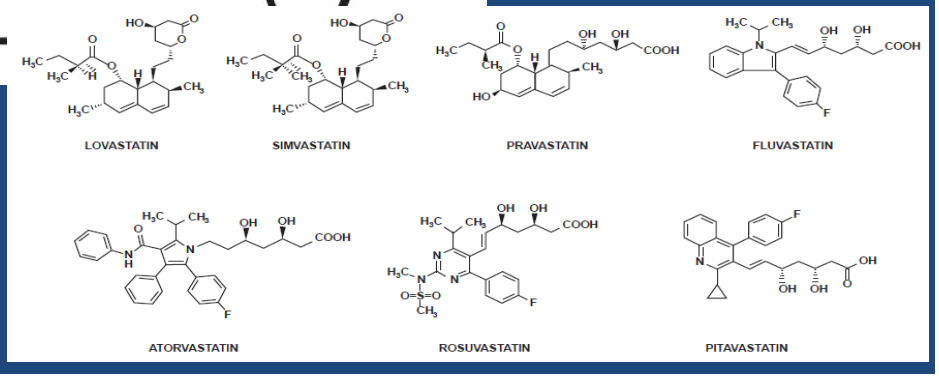
- NLA Staff

Statin pharmaceutics

- Food increases lovastatin absorption, decreases fluvastatin,pravastatin and atorvastatin absorption.
- Food has no effect on rosuvastatin, pitavastatin and simvastatin absorption.
- All statins undergo extensive first pass metabolism, the rate of this first pass hepatic uptake inversely relates to the systemic bioavailability.

Statin Metabolism 101





Lovastatin and simvastatin are given as pro-drugs other statins are administered in the active hydroxyl acid form.

Statin Transporters

Transporter/Alias (Gene)	Organ or Cells	Comment
P-gp/MDR1 (ABCB1)	Intestinal enterocyte Hepatocyte (canalicular) Kidney proximal tubule	Drug absorption, distribution and excretion Source of drug interaction
BCRP (ABCB2)	Intestinal enterocyte Hepatocyte (canalicular) Kidney proximal tubule	Drug absorption, distribution and excretion Genetic polymorphisms Source of drug interaction
OATP1B1/OATP2 (SLCO1B1)	Hepatocyte (sinusoidal)	Drug distribution, excretion Genetic polymorsphisms Source of drug interaction
OATP1A2/ATP-A (SLCO1A2)	Cholangiocyte Distal nephron	Drug distribution, excretion
OATP2B1/ATP-B (SLCO2B1)	Hepatocytes (sinusoidal)	Drug distribution, excretion Source of drug interaction

Sites of metabolism

- Lipophilic lactone pro-drugs such as simvastatin are predominantly CYP metabolized;
- Polar statins such as rosuvastatin and pravastatin are substrates of transporters including the hepatic OATPs, sodium/taurocholate cotransporting peptides (NTCP), and renal OATPs.
- Statins like fluvastatin that are metabolized by CYP access the hepatocyte by active transport.
- In addition, all statins have affinity to the multi-drug-resistance protein (MRP2), P-gp, the bile salt export pump, and the BCRP(Breast Cancer Resistant Protien, aka ATP binding cassette transporter, subfamily G, member 2).

Statins and their transporters

Statin	Transporters and enzymes affecting metabolism
Simvastatin Lovastatin	CYP3A4 (intestinal and hepatic) OAT1B1 p-glycoprotein MDR1 BCRP
Atorvastatin	BCRP (intestinal) CYP3A4 (intestinal and hepatic) OAT1B1 and OAT2B1 p-glycoprotein
Rosuvastatin	BCRP (intestinal) CYP2C9 (minor) OAT1B1 andOAT1B3 NTCP OAT2B1
Pravastatin	BCRP (intestinal) OAT1B1 and OAT1B3 OAT2B1
Fluvastatin	BCRP (intestinal) OATP1B1 OAT1B3 OAT2B1 CYP2C9 CYP3A4
Pitavastatin	BCRP (intestinal) MDR1 OAT1B1 andOAT1B3 OATP2B1 CYP2C9 (minor)

Predicted versus observed fold increases in various statins and enzyme systems

		Predicted fold increase in AUC due to inhibition of composite pathways			CYP3A4 Hepatic	Clinically predicted fold increase in AUC/Observed AUC
Statin	Perpetrator drug	BCRP (intestine)	CYP3A4 (intestine)	OAT1B1		
Simvastatin	Cyclosporine		1.67	4.5(56)	1.0(0.09)	7.5 /8.0
	Telithromycin		1.67	1.2(0.2)	2.0(1.6)	4.0/9.4-12
	Posaconazole		1.67	NI	1.7(0.9)	2.8/8.5
Atorvastatin	Cyclosporine	1.72(174)	1.45	3.2(103)	NA	8.0/8.7
	Lopinavir/ritonavir	NA_low solubility	1.45	1.9(2.3)1.1(0.14)	1.0(0.16)	2.9/5.9
	Clarithromycin	NI	1.45	2.0(2.7)	1.1(0.4)	3.2/4.4
	Itraconazole	NI	1.45	NI	1.0(0.4)	1.45/2.5-3.3
Statin	Perpetrator drug	BCRP (intestine)		OAT1B3	CYP2C9	
Fluvastatin	Cyclosporine	1.72(100)		1.8(19)	NI	3.2/1.9
				NI	1.7(9.9)	1.7/1.84
Statin	Precipitating drug	BCRP (intestine)	Active uptake (OATP1B1:NTCP:OATP1B3) (f_e = 0.38:0.21:0.11 = 0.7)	OAT3	Overall predicted fold increase in AUC	Clinically observed fold increase in AUC
Rosuvastatin	Cyclosporine	2.0(100)	3.2(56)	NI	6.4	7.1
	Gemfibrozil	NI	1.5(OATP1B)(2.0)	1.2(2.1)	1.8	1.9
	Lopinavir/ritonavir	No effect-low solubility	1.5(OATP1B) (1.9 if all inhibited)(2.3)	NA	1.5(1.9)	2.1
	Atazanivr/ritonavir	2.0(25)	1.6(OATP1B)(3.5)	NA	3.2	3.1
		Efflux(intestine)	OATP1B1	OAT3		
Pravastatin	Cyclosporine	2.9	2.0(103)	NI	5.8	3.82
	Clarithromycin	NI	1.6(2.7)	NI	1.6	2.1

*(number), ratio of inlet max, unbound/IC50 or Ki (>0.1 indicates potential for interaction); [number], ratio of [I2]/IC50 or Ki (>10 indicates potential for interaction)

SNPs and Various Groups

- The OATP1B1 (SLBO1B1) and BCRP (ABC2) genes have been studied most extensively.
- Compared to simvastatin and atorvastatin, fluvastatin has no apparent association between with variations in implied OATP1B1 function from studies.
- Differences in the ABC2 gene may explain some ethnic differences. It has been suggested that 1-4% of African Americans, 5-10% Caucasians, and 35-45% of Asian populations carry variations in the ABCG2 (BCRP) gene. These changes suggest differences in the absorption of rosuvastatin, simvastatin-lactone, fluvastatin, and atorvastatin, but not simvastatin acid (active moiety) or pravastatin.

Comparison of peripheral blood plasma concentrations of different statins in individuals with homozygous (OATP1B1) 521CC (dysfunctional) as compared to those with fully functional homozygous (OATP1B1) 521TT (fold area under the curve [AUC] changes are based on group mean AUC 0–∞)

Statin	AUC Change
Simvastatin acid	3.21-fold ↑ (+221%)
Pitavastatin	3.08-fold ↑ (+208%)
Atorvastatin	2.45-fold ↑ (+145%)
Pravastatin	1.91-fold ↑ (+91%)
Rosuvastatin	1.62-fold ↑ (+61%)
Fluvastatin	1.19-fold ↑ (+19%, ns)

Comparison of post dosing plasma concentrations of different statins in homozygous breast cancer resistant protein (BCRP) 421AA individuals as compared with homozygous BCRP 421CC individuals (fold area under the curve [AUC] changes are based on group mean AUC 0–∞)

Drug	AUC Change
Rosuvastatin	2.44-fold ↑ (+144%)
Simvastatin acid	1.22-fold ↑ (+22%)
Simvastatin lactone	2.11-fold ↑ (+111%)
Atorvastatin lactone	1.94-fold ↑ (+94%)
Atorvastatin acid	1.72-fold ↑ (+72%)
Fluvastatin	1.72-fold ↑ (+72%)
Pravastatin	1.13-fold ↓ (ns)

Understanding Package Labeling

Interpreting AUC Changes and relating to Adverse Event Potential

AUC ratio increase	>1.25 - <2.0	>2.0 - <4.9	>5.0
Rank of inhibition of various CYP enzymes	Weak	Moderate	Strong

Abbreviation: AUC = area under the curve, CYP = cytochrome P450

Some Simvastatin Drug Interactions

Coadministered drug and dosing regimen	Simvastatin (mg)	Simvastatin form	Geometric mean ratio (ratio* with/without coadministered drug) No Effect = 1.00 AUC
Contraindicated with simvastatin			
Telithromycin 200 mg QD for 4 days	80 mg	simvastatin acid simvastatin	12 8.9
Nelfinavir 1250 mg BID for 14 days	20 mg QD for 28 days	simvastatin acid	6.2
Posaconazole 100 mg (oral suspension) QD for 13 days	40 mg	simvastatin acid simvastatin	7.3 10.36
Avoid >1 quart of grapefruit juice with simvastatin			
Grapefruit Juice§ (high dose) 200 mL of double-strength TID	60 mg single dose	simvastatin acid simvastatin	7 16
Avoid taking with >10 mg simvastatin, based on clinical and/or post-marketing experience			
Verapamil SR 240 mg QD days 1-7 then 240 mg BID on days 8-10	80 mg on day 10	simvastatin acid simvastatin	2.3 2.5
Diltiazem 120 mg BID for 14 days	20 mg on day 14	simvastatin	4.6

Some Atorvastatin Interactions

Coadministered drug and dosing regimen	Atorvastatin dose (mg)	Atorvastatin change in AUC*
Cyclosporine 5.2 mg/kg/day, stable dose	10 mg QD for 28 days	↑ 8-fold
Tipranavir 500 mg BID/ritonavir 200 mg BID for 7 days	10 mg SD	↑ 9.4-fold
Telaprevir 750 mg every 8 hours for 10 days	20 mg SD	↑ 7.88-fold
Saquinavir 400 mg BID/ ritonavir 400 mg BID for 15 days	40 mg QD for 4 days	↑ 3.9-fold
Clarithromycin 500 mg BID for 9 days	80 mg QD for 8 days	↑ 4.4-fold
Darunavir 300 mg BID/ritonavir 100 mg BID for 9 days	10 mg QD for 4 days	↑ 3.9-fold
Itraconazole 200 mg QD for 4 days	40 mg SD	↑ 3.3-fold
Fosamprenavir 700 mg BID/ritonavir 100 mg BID for 14 days	10 mg QD for 4 days	↑ 2.53-fold
Fosamprenavir 1400 mg BID for 14 days	10 mg QD for 4 days	↑ 2.3-fold
Nelfinavir 1250 mg BID for 14 days	10 mg QD for 28 days	↑ 74%
Grapefruit iuice 240 mL QD	40 mg SD	↑ 37%
Diltiazem 240 mg QD for 28 days	40 mg SD	↑ 51%
Erythromycin 500 mg QID for 7 days	10 mg SD	↑ 51%
Amlodipine 10 mg, single dose	80 mg	↑ 15%

Some Rosuvastatin Interactions

Coadministered drug and dosing regimen	Rosuvastatin dose (mg)*	Rosuvastatin change in AUC
Cyclosporine (stable dose required 75-200 mg BID)	10 mg/day for 10 days	↑ 10-fold
Gemfibrozil 600 mg BID x 7 days	80 mg	↑ 1.9-fold
Lopinavir/ritonavir combination 400 mg/100 mg BID for 10 days	20 mg/day for 7 days	↑ 2-fold
Atazanavir/ritonavir combination 300 mg/100 mg QD for 7 days	10 mg	↑ 3.1-fold
Eltrombopag 75 mg QD for 5 days	10 mg	↑ 3.1-fold
Tipranavir/ritonavir combination 500 mg/200mg BID for 11 days	10 mg	↑ 26%
Dronedarone 400 mg BID	10 mg	↑ 1.4-fold
Itraconazole 200 mg QD for 5 days	10 mg or 80 mg	↑ 39% ↑ 28%
Ezetimibe 10 mg daily for 14 days	10 mg daily for 14 days	↑ 1.2-fold
Fosamprenavir/ritonavir 700 mg/100 mg BID for 7 days	10 mg	↑ 8%
Fenofibrate 67 mg TID for 7 days	10 mg	↑ 7%
Aluminum & magnesium hydroxide combination antacid administered simultaneously; administered 2 hr apart	40 mg 40 mg	↓ 54% ↓ 22%
Erythromycin 500 mg QID for 7 days	80 mg	↓ 20%
Ketoconazole 200 mg BID for 7 days	80 mg	↑ 2%

Interactions across the statin class

Statin/ Interactant`	Simva	Lova	Atorva	Rosuva	Prava	Fluva
Ketoconazole	Avoid	Avoid				
Posaconazole	Avoid	Avoid				
Boceprevir	Avoid	Avoid	No Mention			
Nefazodone	Avoid	Avoid				
Cyclosporine	Avoid	Avoid	Avoid	5 mg/d	20 mg/d	20 mg/d
Gemfibrozil	Avoid	Avoid	Avoid	10 mg/d	Avoid	Caution
Danazole	Avoid	Avoid				
Tiprinavir			Avoid			
Teleprevir			Avoid			
HIV protease inhibitor	Avoid	Avoid	20 mg	10 mg		
Verapamil Diltiazem	10 mg limit					
Clarithromycin			20 mg limit	40 mg limit		
Itraconazole			20 mg limit			
Fosamprenavir +/-ritonavir			20 mg limit			
Nelfanivir			40 mg limit			
Fluconazole						20 mg/d
Amiodarone Amlodipine Ranolazine	20 mg limit					
Grapefruit juice	Avoid large qty	Avoid large qty				
Niacin	Limit to 1 g/d	Limit to 1 g/d	Limit to 1 g/d	Limit to 1 g/d	Limit to 1 g/d	

Some notable drug Interactions

	Level 1 (severe) *Do not use*	Level 2 (major) *Use with caution*	Level 3(moderate) *Less likely to cause severe drug interaction*	Level 4 (mild) *Unlikely to cause drug interaction*
Simvastatin/ Lovastatin	Protease inhibitors Boceprevir Clarithromycin Cobicistat Elvitegravir Emtricitabine Tenofovir Cyclosporine Danazol Delavirdine Erythromycin Gemfibrozil Itraconazole Ketoconazole Nefazodone Posaconazole Red Yeast Rice Telaprevir Telithromycin Voriconazole	Amiodarone Amlodipine Conivaptan Diltiazem Dronedarone Efavirenz Other Fibrates Fluconazole Grapefruit juice Imatinib Lomitapide Ranolazine Ticagrelor Troleandomycin Verapamil	Afatinib Aprepitant Fosaprepitant Bosentan Colchicine Dalfopristin/Quinupristin Daptomycin Digoxin Esomeprazole Fluvoxamine Fosphenytoin Lansoprazole Niacin, Niacinamide Omeprazole Pantoprazole Phenytoin Quinine Repaglinide Rifampin St. John's Wort Warfarin	Barbiturates Carbamazepine Clopidogrel Nevirapine Oxcarbazepine Rifabutin Rifapentine

Some notable Drug Interactions

	Level 1 (severe) *Do not use*	Level 2 (major) *Use with caution*	Level 3(moderate) *Less likely to cause severe drug interaction*	Level 4 (mild) *Unlikely to cause drug interaction*
Atorvastatin	Posaconazole Red yeast rice Telithromycin Voriconazole	Boceprevir Clarithromycin Conivaptan Cyclosporine Darunavir Delavirdine Digoxin.Diltiazem Erythromycin Fluconazole Fosamprenavir Gemfibrozil Grapefruit juice Imatinib,Itraconazole Ketoconazole Lopinavir/Ritonavir Nefazodone,Nelfinavir Other Fibrates Saquinavir,Telaprevir, Tipranavir Troleandomycin Verapamil	Amiodarone Antacids Aprepitant, Fosaprepitant Atazanavir,Bosentan Colchicine,Colestipol Dalfopristin/Quinupristin Danazol,Daptomycin Efavirenz Esomeprazole Fosphenytoin Indinavir Lansoprazole Mifepristone Niacin, Niacinamide Nilotinib,Omeprazole Pantoprazole Phenytoin Quinine Ranolazine Rifampin St. John's Wort Warfarin	Barbiturates Carbamazepine Cimetidine Clopidogrel Miconazole Nevirapine Oral contraceptives Oxcarbazepine Pioglitazone Rifabutin Rifapentine Spironolactone

Some notable Drug Interactions

	Level 1 (severe) *Do not use*	Level 2 (major) *Use with caution*	Level 3(moderate) *Less likely to cause severe drug interaction*	Level 4 (mild) *Unlikely to cause drug interaction*
Rosuvastatin	Red yeast rice	Antacids Atazanavir Clarithromycin Cyclosporine Fosamprenavir Gemfibrozil and other fibrates Lopinavir/Ritonavir Nelfinavir Ritonavir,Saquinavir Telithromycin	Colchicine Daptomycin Darunavir Indinavir Itraconazole Niacin, Niacinamide Warfarin	Erythromycin Oral contraceptives
Pravastatin	Red yeast rice	Bile acid resins Clarithromycin Cyclosporine Darunavir Erythromycin Gemfibrozil and other fibrates Telithromycin	Boceprevir Colchicine Daptomycin Itraconazole Niacin, Niacinamide Orlistat Warfarin	

Some notable Drug Interactions

	Level 1 (severe) *Do not use*	Level 2 (major) *Use with caution*	Level 3(moderate) *Less likely to cause severe drug interaction*	Level 4 (mild) *Unlikely to cause drug interaction*
Pitavastatin	Cyclosporine Red yeast rice	Atazanavir,Darunavir Erythromycin Fosamprenavir Gemfibrozil and other fibrates Lopinavir; Ritonavir Rifampin,Ritonavir Saquinavir, Telithromycin Tipranavir	Colchicine Niacin, Niacinamide Raltegravir	Warfarin
Fluvastatin	Red yeast rice	Cyclosporine Erythromycin Gemfibrozil and other fibrates,Telithromycin	Amiodarone Anti-retroviral prote.inhibi Cholestyramine Cimetidine,Colchicine Daptomycin,Delavirdine Diclofenac,Digoxin,Efavirenz, Ethanol,Fluconazole,Fluoxetine Fluvoxamine,Glyburide,Imatinib Niacin, Niacinamide,Nilotinib, Omeprazole,Phenytoin, Ranitidine,Rifampin, Sulfinpyrazone Sulfonamides,Voriconazole Warfarin	Clopidogrel Irbesartan Rifabutin Rifapentine Zafirlukast

Safety of Statins in CKD

- **Atorvastatin and fluvastatin are minimally excreted by the kidneys**
- **Dosing modifications for other statins (National Kidney Foundation [NKF] recommendations)**
- **Simvastatin and lovastatin: 50% dose reduction if glomerular filtration rate (GFR) <30 mg/mL**
- **Pravastatin: no dose adjustment (package insert – start with 10 mg once daily in renal impairment)**
- **Rosuvastatin: not discussed in NKF guidelines (prescribing information – start at 5 mg and do not exceed 10 mg in severe chronic renal insufficiency [creatinine clearance <30 mL/min] in patients not on dialysis;**
- **Pitavastatin: not discussed in NKF guidelines (package insert – patients with moderate and severe renal impairment [GFR 30-59 mL/min/1.73 m^2 and 15-29 mL/min/1.73 m^2 not receiving hemodialysis, respectively], as well as end-stage renal disease receiving hemodialysis: initial, 1 mg orally daily and maximum 2 mg daily)**

Abbreviations: GFR = glomerular filtration rate, NKF = National Kidney Foundation

Statin Fibrate Combination

Statin	Gemfibrozil	Fenofibrate
Atorvastatin	↑ in C_{max} (expected)	No change
Simvastatin	↑ in C_{max} by 2-fold	No change
Pravastatin	↑ in C_{max} by 2-fold	No change
Rosuvastatin	↑ in C_{max} by 2-fold	No change
Fluvastatin	No change	No change
Lovastatin	↑ in C_{max} by 2.8-fold	No change
Pitavastatin	↑ in C_{max} by 41%	Unknown

Special Populations

- Elderly
  - Metabolic enzymes less efficient
  - Atorvastatin and Rosuvastatin can increase ethinyl estradiol and norgestrel levels (HRT).
- Chinese/Japanese
  - Simvastatin dose limit of 20mg with niacin
  - Rosuvastatin dose limit in other asians-start with 5mg.

Special Populations

- **Human Immunodeficiency Virus (HIV)**
- FDA warnings about protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) used in highly active antiretroviral therapy (HAART) and statins.
- These are usually specific to the drugs metabolized by CYP3A4. Current National Institutes of Health guidelines recommend fluvastatin, pitavastatin, and pravastatin (except for pravastatin with durinavir/ritonavir) over lovastatin and simvastatin.
- Atorvastatin and rosuvastatin may be used with caution. In combination with NNRTIs, some statins may have increased efficacy while others may have decreased efficacy.

Special Populations

- Hepatitis C and non-alcoholic fatty liver disease (NAFLD**):**
- One study suggested that simvastatin administered as monotherapy has the strongest antiviral activity, lovastatin and fluvastatin have a moderate antiviral effect, while pravastatin has no antiviral activity.
- New Hep C drug, boceprivir, classified as a non-structural protein (NS) 3/4A protease inhibitor should not be given with simvastatin or lovastatin.
  - Boceprevir is a potent inhibitor of CYP3A4. An atorvastatin/boceprivir interaction has not been noted.
  - Telaprevir, also an NS3/4A PI, is contraindicated with simvastatin, lovastatin, and atorvastatin.
  - Simeprevir on the other hand inhibits OATP1B1. Rosuvastatin dose should be initiated at 5 mg once daily and not exceed 10mg daily. Atorvastatin should be started at the lowest dose and not exceed 40mg daily. Simvastatin doses should be kept lowest as needed and no data is noted with pitavastatin, lovastatin, fluvastatin, or lovastatin.
  - Sofosubvir does not cause any statin DDIs.

Conclusions

- Statin absorption, distribution, metabolism, and excretion are complex and vary from statin to statin.
- It is important for the clinician to understand how to read package labeling, as new drugs enter the U.S. and understand the potential for these drug drug interactions to be of clinical concern.

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Perspectives on AHA/ACC Guidelines for Risk Assessment

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Director, NUCATS Institute
Eileen M. Foell Professor of Heart Research

Outline

- Why do we estimate absolute risk?
- Review of 2013 AHA/ACC Guideline on Risk Assessment for ASCVD
  - Integration with Cholesterol Treatment Guidelines
  - Possible concerns regarding over-prediction
  - Ancillary testing when risk assessment/decision-making is uncertain
  - Long-term/lifetime risk estimation
- Summary/Take-home

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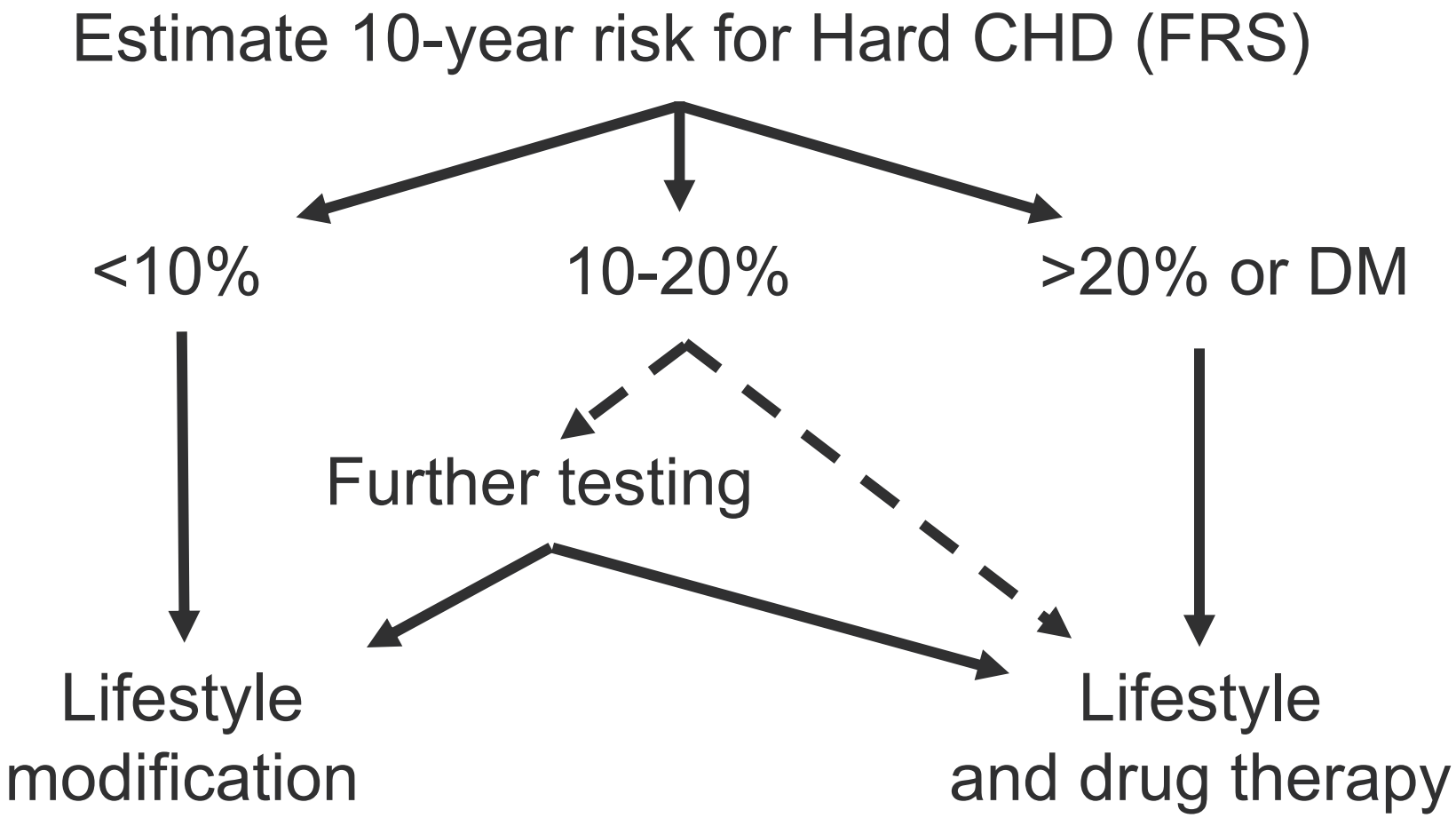
Why Do We Estimate Absolute Risk?

- Cornerstone of "high-risk strategy"
  - Relative risk is poorly understood by clinicians and patients
    - Problem of the referent group
  - Patients and clinicians very poor at intuiting true risk
    - Understand absolute risk for prognosis
  - Improve communication and motivate lifestyle change/adherence to therapy
  - Identify treatment-eligible individuals at sufficiently high risk to merit treatment and expect net clinical benefit
  - Directly compare absolute benefits and harms of therapy

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ATP-III Paradigm for Risk Estimation and Treatment

"Intensity of prevention efforts should match the absolute risk of the patient"



Patients Substantially Overestimate and Underestimate Risk

- 1557 primary care patients asked to estimate risk on a continuous scale of 0% to 100%

- Mean absolute differences between perceived and actual predicted 10-year risk were:
  - 22.9% (95% CI 21.8–24.0%) for MI
  - 24.6% (23.4–25.8%) for stroke

Agree	1.5	2.0
1–20% lower	28.2	21.9
>20% lower	2.0	0.4

Frijling, Patient Educ Couns, 2004

Physicians Overestimate and Underestimate Risk

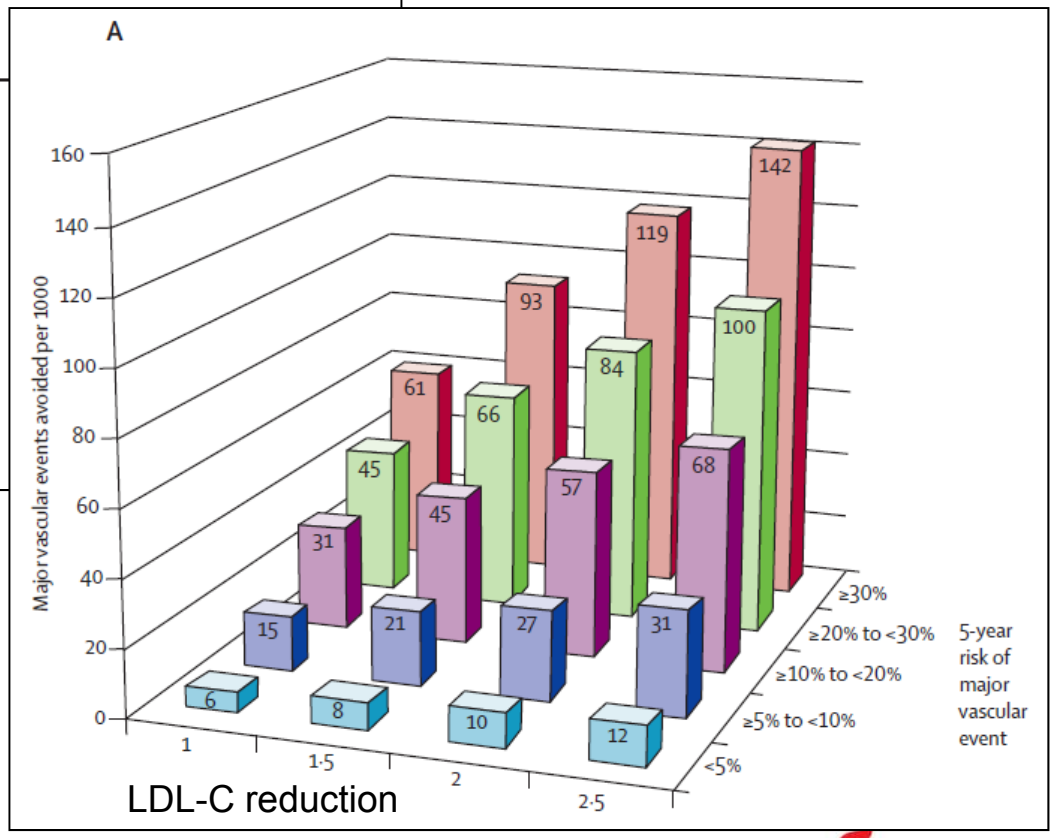
- 79 physicians at all levels at 3 university hospitals
- Surveyed re: 12 primary prevention scenarios
  - Overestimation (MD estimate >1.5x actual risk)
  - Underestimation (MD estimate <0.67x actual risk)
- Only 24% of physicians' risk estimates were accurate
  - Physicians overestimated absolute risk 32% to 92% of the time
  - Physicians made larger errors in patient scenarios involving patients with high total or LDL-c levels

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Pignone, BMC Health Srvcs Res 2003

CTT 2012
RRR Similar; Absolute Risk Rules

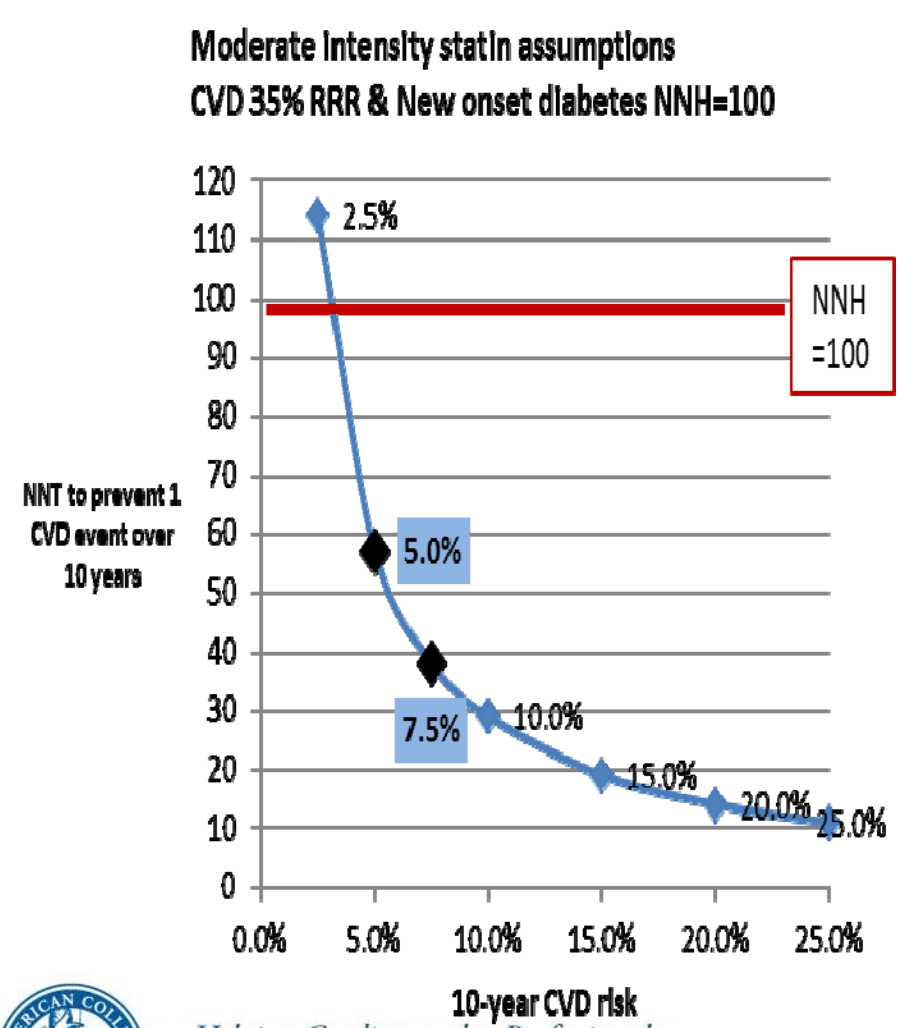
5-year MVE risk at baseline	Events (% per annum)		RR (CI) per 1·0 mmol/L reduction in LDL cholesterol	Trend test
	Statin/more	Control/less		
Participants without vascular disease				
<5%	148 (0·35)	229 (0·53)		
≥5% to <10%	487 (1·02)	716 (1·53)		
≥10% to <20%	854 (2·52)	1003 (2·98)		
≥20% to <30%	294 (4·40)	351 (5·28)		
≥30%	121 (7·29)	126 (8·16)		
Subtotal	1904 (1·44)	2425 (1·84)		

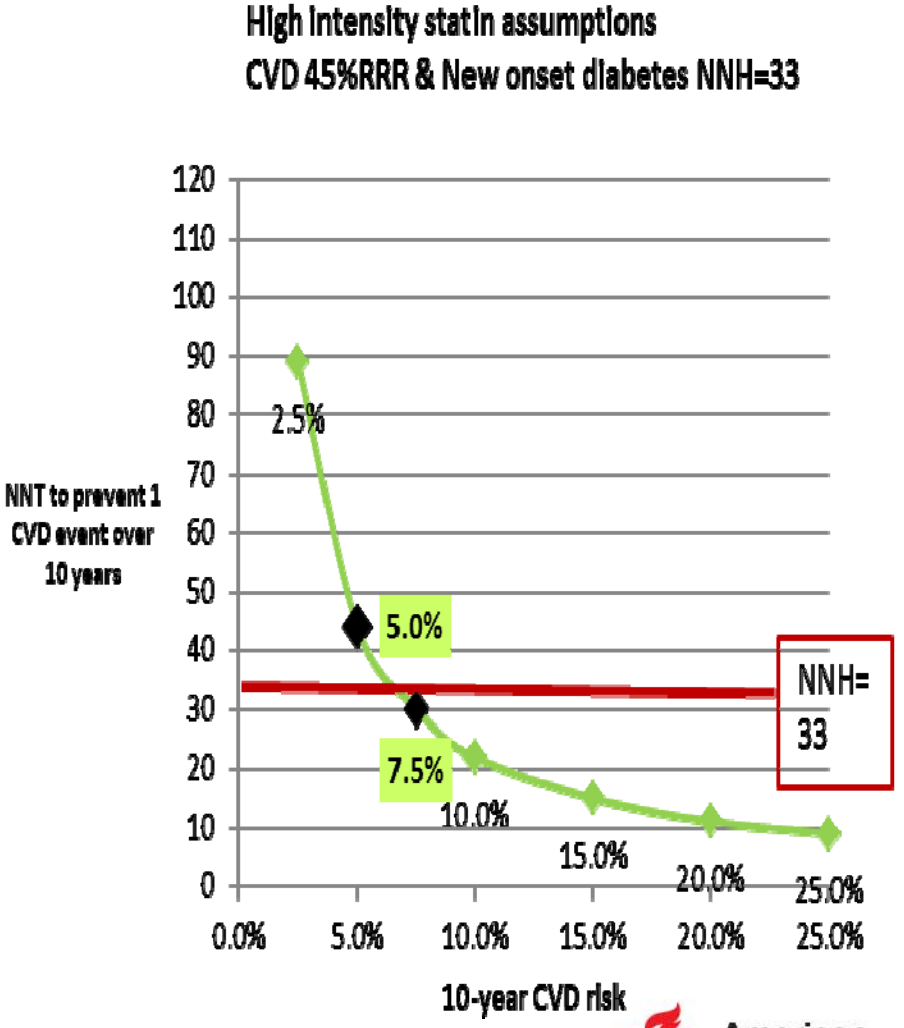


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Understanding Net Clinical Benefit Requires Absolute Risk Estimate





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2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk

Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, American Society for Preventive Cardiology, American Society of Hypertension, Association of Black Cardiologists, National Lipid Association, Preventive Cardiovascular Nurses Association, and WomenHeart: The National Coalition for Women with Heart Disease



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ACC/AHA Risk Assessment Guideline Work Group

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Acknowledgements

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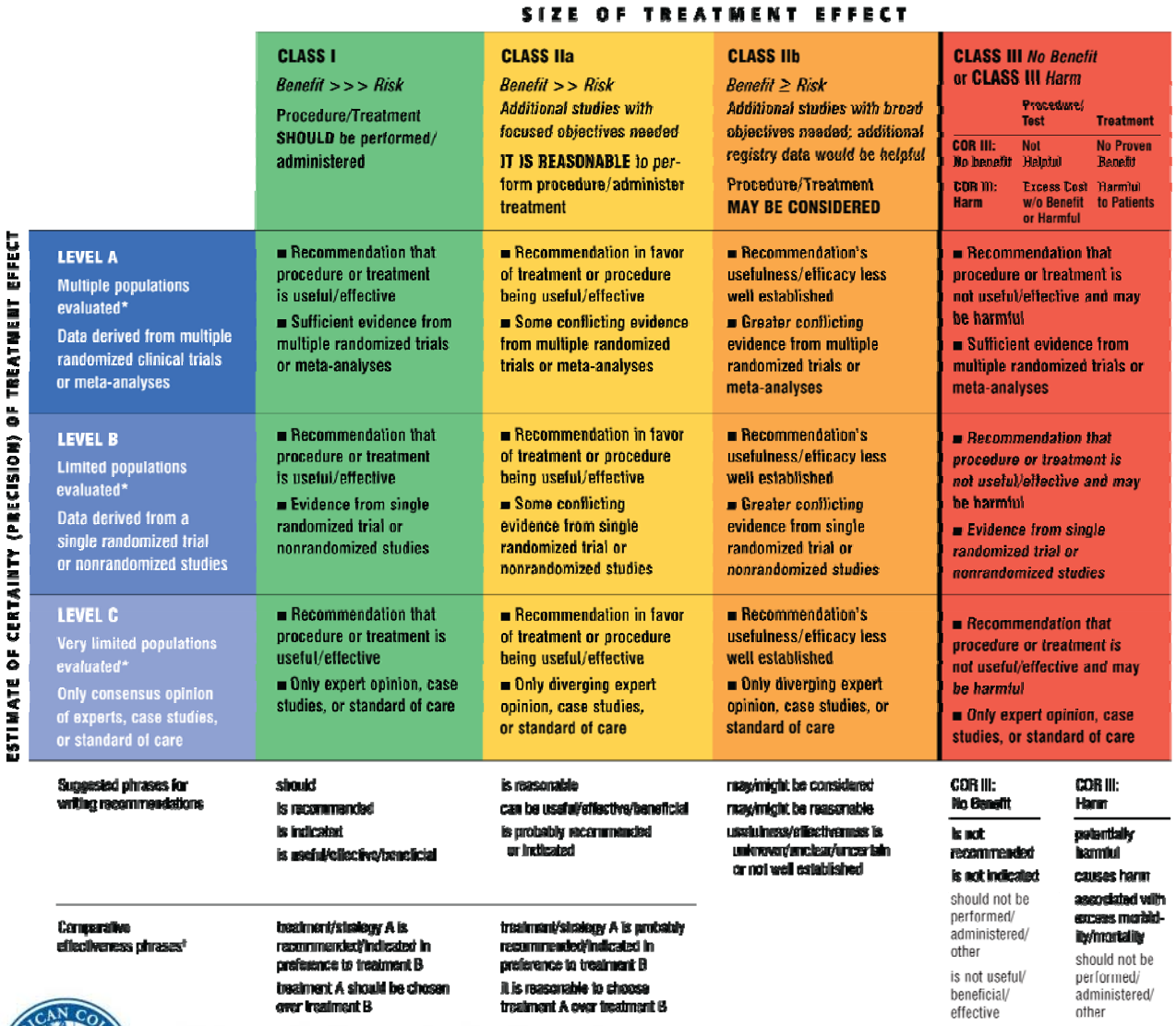
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NHLBI Charge to the Work Group

- Examine the scientific evidence on risk assessment for initial ASCVD events, and develop an approach for risk assessment that could be used in practice and used or adapted by the risk factor panels in their guidelines.

- Specifically, the Work Group was charged with 2 tasks:
  1. To develop or recommend an approach to quantitative risk assessment that could be used to guide care; and
  2. To pose and address a small number of questions judged to be critical to refining and adopting risk assessment in clinical practice, using systematic review methodology.

Classification of Recommendations and Levels of Evidence



SIZE OF TREATMENT EFFECT

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT

	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/ Test: COR III: No benefit — Not Helpful; COR III: Harm — Excess Cost w/o Benefit or Harmful Treatment: No Proven Benefit; Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ *Recommendation that procedure or treatment is not useful/effective and may be harmful* ■ *Evidence from single randomized trial or nonrandomized studies*
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit — is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective COR III: Harm — potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B It is reasonable to choose treatment A over treatment B		

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A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/ efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

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ACC/AHA Cholesterol Treatment Guidelines
4 Statin Benefit Groups

- Clinical ASCVD
- LDL–C ≥190 mg/dL without secondary cause
- Primary prevention/Diabetes: Age 40-75 years, LDL–C 70-189 mg/dL
- Primary prevention/No Diabetes: Age 40-75 years, LDL–C 70-189 mg/dL, ASCVD risk ≥7.5%*

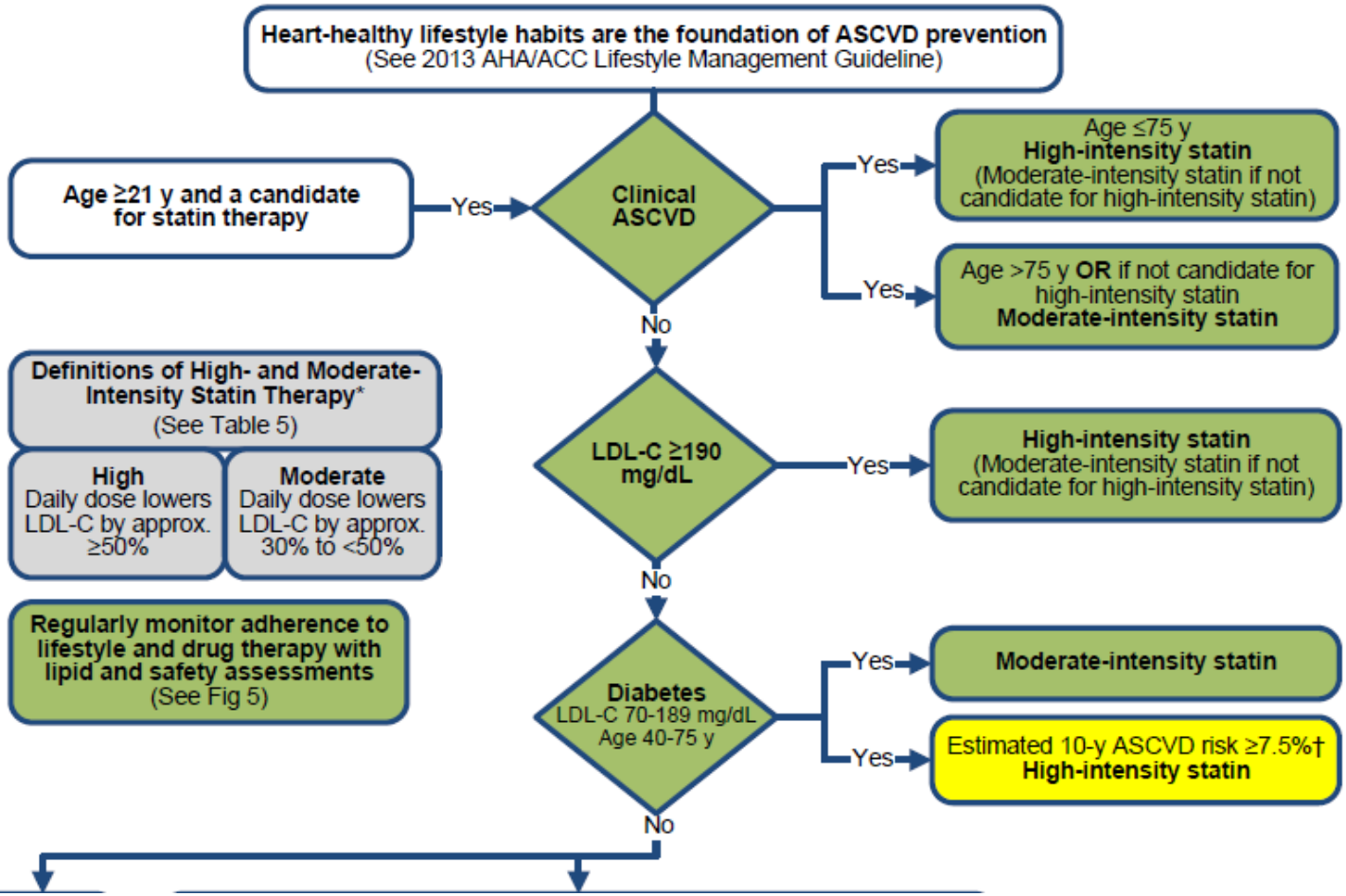
* Requires risk discussion with clinician before statin prescription. Statin therapy or additional testing may be considered if risk decision is uncertain after use of ASCVD risk calculator.

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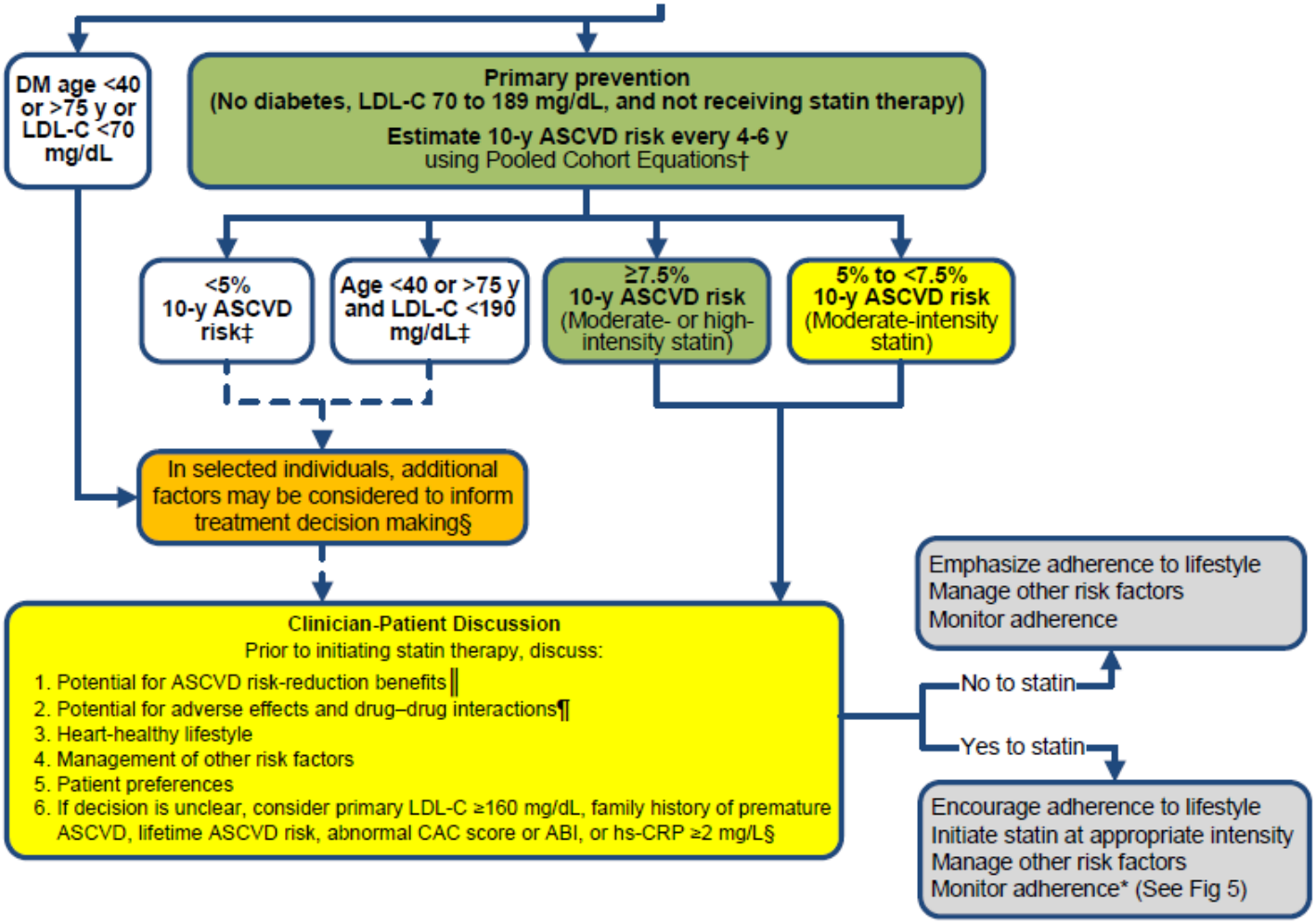
Primary Prevention

Initiating Statin Therapy



Primary Prevention

Initiating Statin Therapy (con't)



ASCVD Risk Calculator
Considerations

- RAWG endorsed the paradigm of 10-year risk estimation
- Existing risk scores vary with regard to:
  - Derivation populations
    - Age, sex, race, birth cohort, country/region of origin
  - Inputs
    - Traditional RFs ± family hx, BMI, SES, region, CRP
  - Outcomes
    - CVD death, Total CHD (incl revasc), Total CHD, Hard CHD, Total CVD (revasc), Hard CVD (incl HF)

ASCVD Risk Calculator
Development

- RAWG judged new risk tool was needed
  - Inclusive of African Americans and with expanded endpoint including stroke
- Sought cohorts representative of the US population as a whole
  - Community- or population-based
  - Whites and African Americans (at a minimum)
  - Recent follow up data of at least 10 years
    - Reflect more contemporary risk factor trends and event rates, ideally without significant downstream uptake of statins/revascularization

ASCVD Risk Calculator
Development

- Pooled Cohort Equations
  - Atherosclerosis Risk in Communities (ARIC)
  - Cardiovascular Heath Study (CHS)
  - Coronary Artery Risk Development in Young Adults (CARDIA)
  - Framingham Original and Offspring
- Hard ASCVD
  - CHD death, non-fatal MI, fatal/non-fatal stroke
- Models tested using traditional RFs + newer markers when possible
- Internal and external validation

ASCVD Risk Calculator

Model Characteristics

	White Women	AA Women	White Men	AA Men
N	11,240	2641	9098	1647
Age Range	40-79	40-79	40-79	40-79
C statistic	0.81	0.82	0.75	0.71
Calibration X^2	6.43	7.25	4.86	6.71

ASCVD Risk Estimator

Search “ASCVD risk estimator”

American Heart Association.

AMERICAN COLLEGE of CARDIOLOGY

2013 Prevention Guidelines Tools

CV RISK CALCULATOR

The American Heart Association and the American College of Cardiology are excited to provide a series of new cardiovascular prevention guidelines for the assessment of cardiovascular risk, lifestyle modifications that reduce risk, management of elevated blood cholesterol, and management of increased body weight in adults. To support the implementation of these guidelines, the new Pooled Cohort Equations CV Risk Calculator and additional Prevention Guideline Tools are available below. Others may be developed and available in the near future.

Available on the App Store

ANDROID APP ON Google play

Download CV Risk Calculator

Launch Web Version

This downloadable spreadsheet is a companion tool to the **2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk**. The spreadsheet enables health care providers and patients to estimate 10-year and lifetime risks for atherosclerotic cardiovascular disease (ASCVD), defined as coronary death or nonfatal myocardial infarction, or fatal or nonfatal stroke, based on the Pooled Cohort Equations and the work of Lloyd-Jones, et al., respectively. The information required to estimate ASCVD risk includes age, sex, race, total cholesterol, HDL cholesterol, systolic blood pressure, blood pressure lowering medication use, diabetes status, and smoking status.

Estimates of 10-year risk for ASCVD are based on data from multiple community-based populations and are applicable to African-American and non-Hispanic white men and women 40 through 79 years of age. For other ethnic groups, we recommend use of the equations for non-Hispanic whites, though these estimates may underestimate the risk for persons from some race/ethnic groups, especially American Indians, some Asian Americans (e.g., of south Asian ancestry), and some Hispanics (e.g., Puerto Ricans), and may overestimate the risk for others, including some Asian Americans (e.g., of east Asian ancestry) and some Hispanics (e.g., Mexican Americans).

Estimates of lifetime risk for ASCVD are provided for adults 20 through 59 years of age and are shown as the lifetime risk for ASCVD for a 50-year old without ASCVD who has the risk factor values entered into the spreadsheet. The estimates of lifetime risk are most directly applicable to non-Hispanic whites. We recommend the use of these values for other race/ethnic groups, though as mentioned above, these estimates may represent under- and overestimates for persons of various ethnic groups. Because the primary use of these lifetime risk estimates is to facilitate the very important discussion regarding risk reduction through lifestyle change, the imprecision introduced is small enough to justify proceeding with lifestyle change counseling informed by these results.

Figure 1. Implementation of Risk Assessment Work Group Recommendations

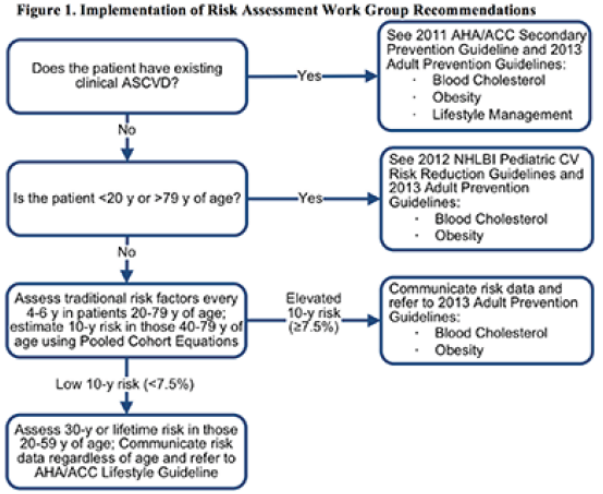


Figure 1. Implementation of Risk Assessment Work Group Recommendations

Clinical Vignettes

ASCVD Risk Calculator

Pooled Cohort Equations

Risk Factor	Units	Value	Acceptable range of values	Optimal values
Sex	M or F		M or F	
Age	years		20-79	
Race	AA or WH		AA or WH	
Total Cholesterol	mg/dL		130-320	170
HDL-Cholesterol	mg/dL		20-100	50
Systolic Blood Pressure	mm Hg		90-200	110
Treatment for High Blood Pressure	Y or N		Y or N	N
Diabetes	Y or N		Y or N	N
Smoker	Y or N		Y or N	N

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ASCVD Risk Calculator

Pooled Cohort Equations

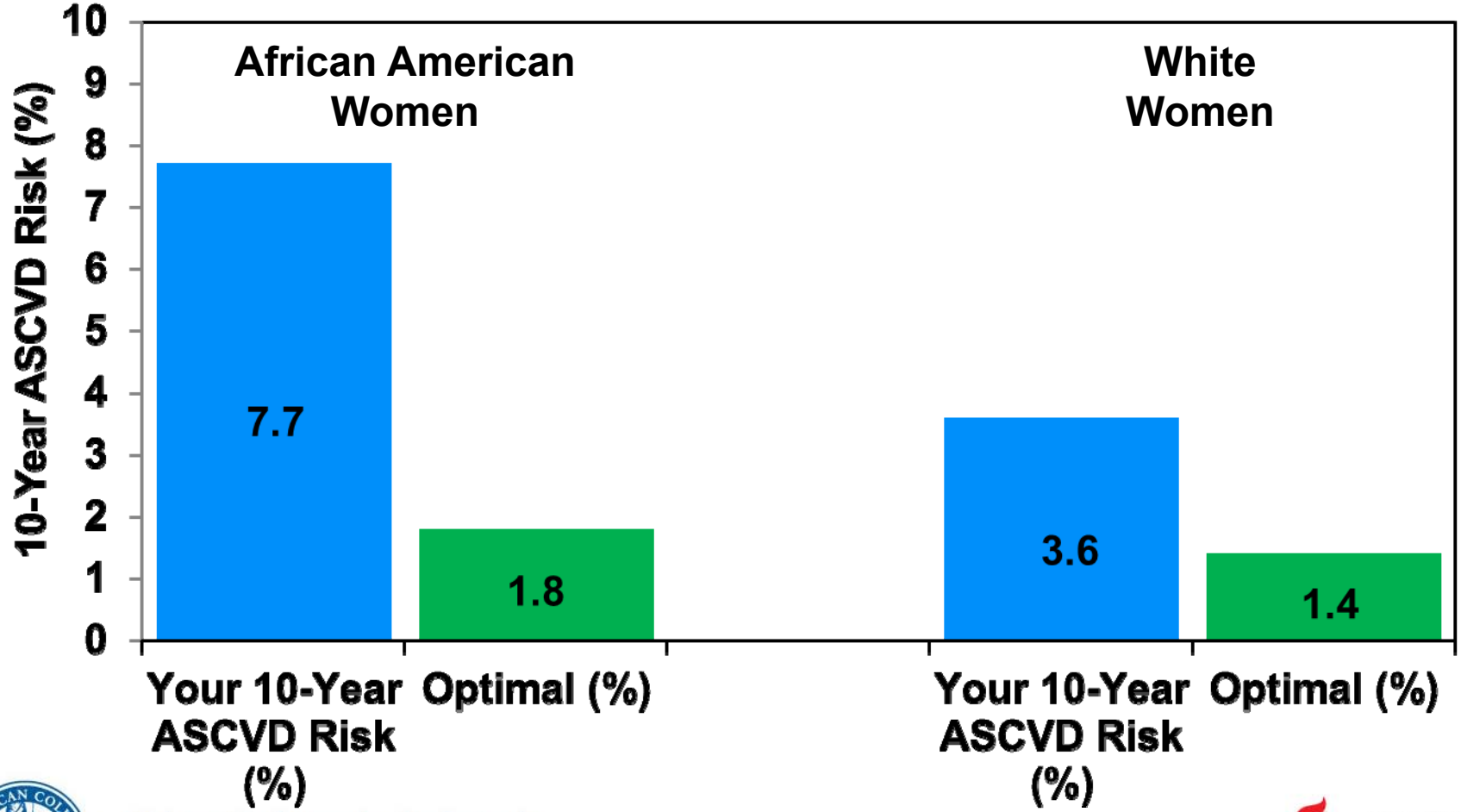
Risk Factor	Units	Value	Acceptable range of values	Optimal values
Sex	M or F	**F**	M or F	
Age	years	**55**	20-79	
Race	AA or WH	**AA**	AA or WH	
Total Cholesterol	mg/dL	**210**	130-320	170
HDL-Cholesterol	mg/dL	**56**	20-100	50
Systolic Blood Pressure	mm Hg	**145**	90-200	110
Treatment for High Blood Pressure	Y or N	**Y**	Y or N	N
Diabetes	Y or N	**N**	Y or N	N
Smoker	Y or N	**N**	Y or N	N

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ASCVD Risk Calculator

55 yo AA and White Women



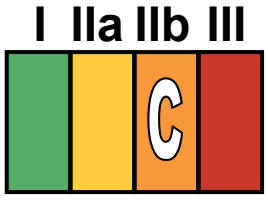
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Recommendations for 10-Year ASCVD Risk Estimation



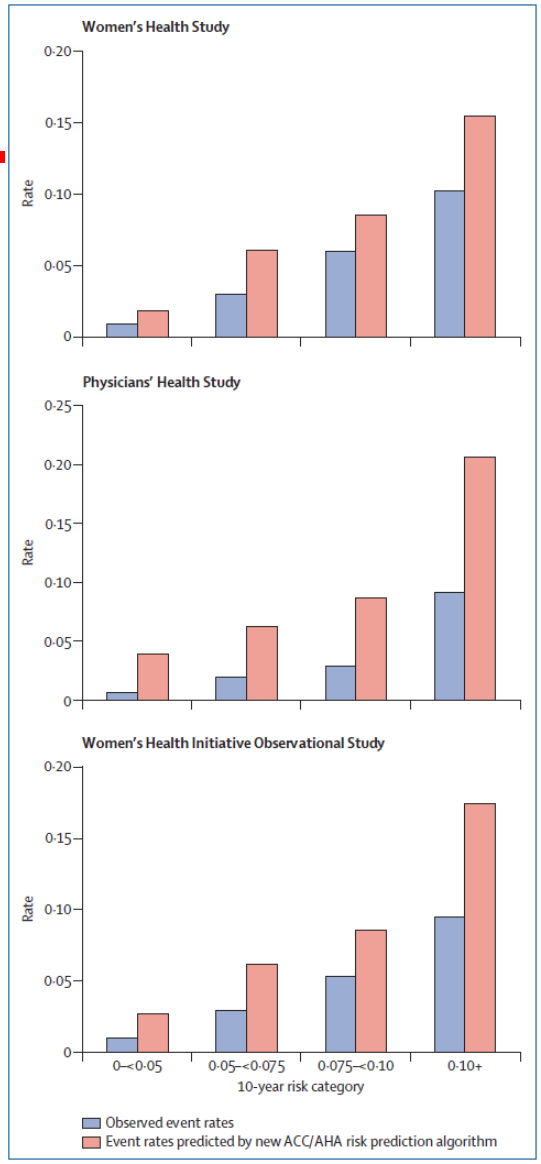
The race- and sex-specific Pooled Cohort Equations to predict 10-year risk for a first hard ASCVD event should be used in non-Hispanic African Americans and non-Hispanic Whites, 40 to 79 years of age.



Use of the sex-specific Pooled Cohort Equations for non-Hispanic Whites may be considered when estimating risk in patients from populations other than African Americans and non-Hispanic Whites.

Over-Prediction?

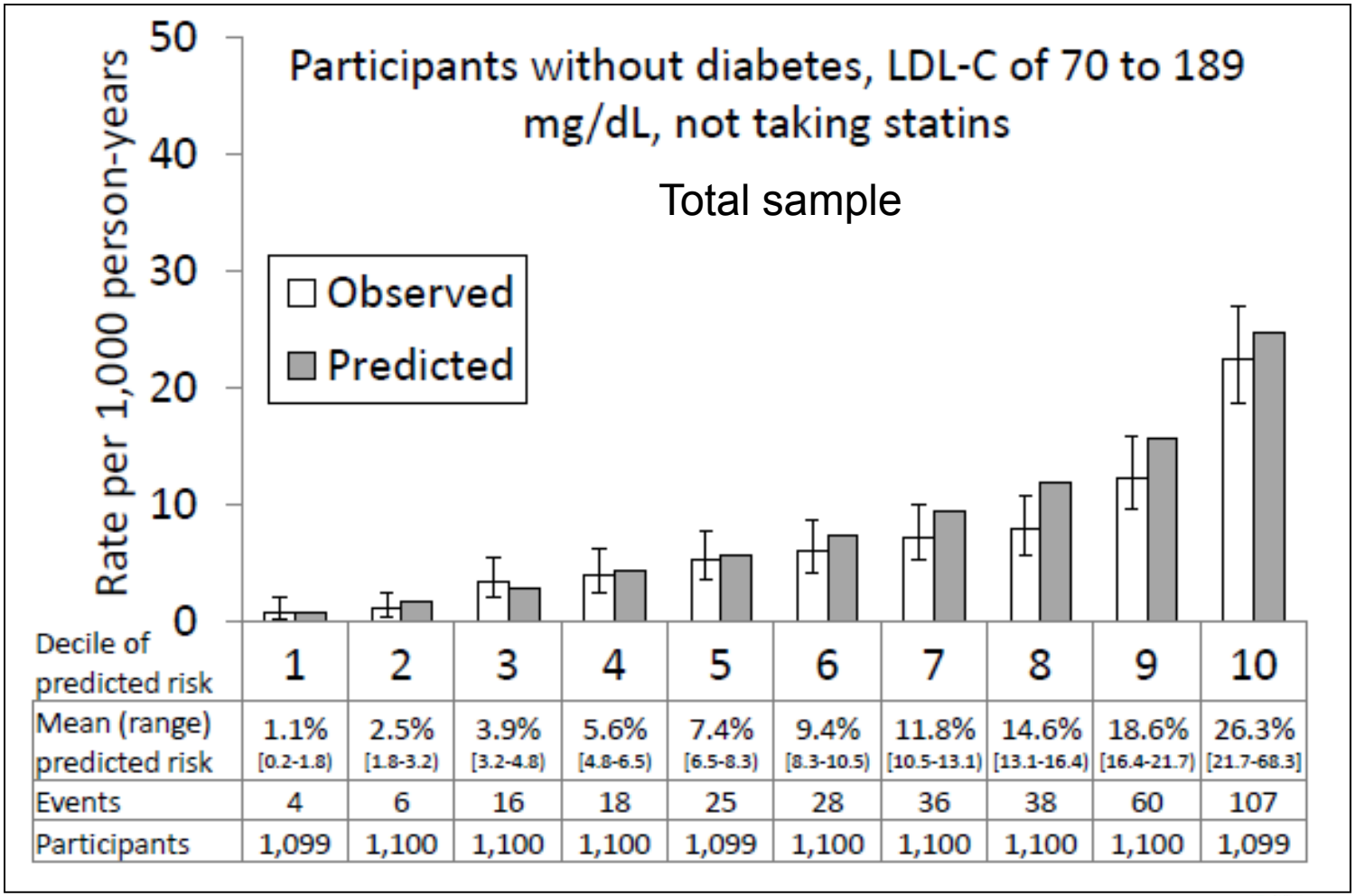
- Ridker & Cook
  - NYT/Lancet
- Not representative of US pop
  - Healthy volunteer RCT ppts
- Self-reported RFs
  - In ranges
- Incomplete event capture
- Downstream therapy



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External Validation: REGARDS*



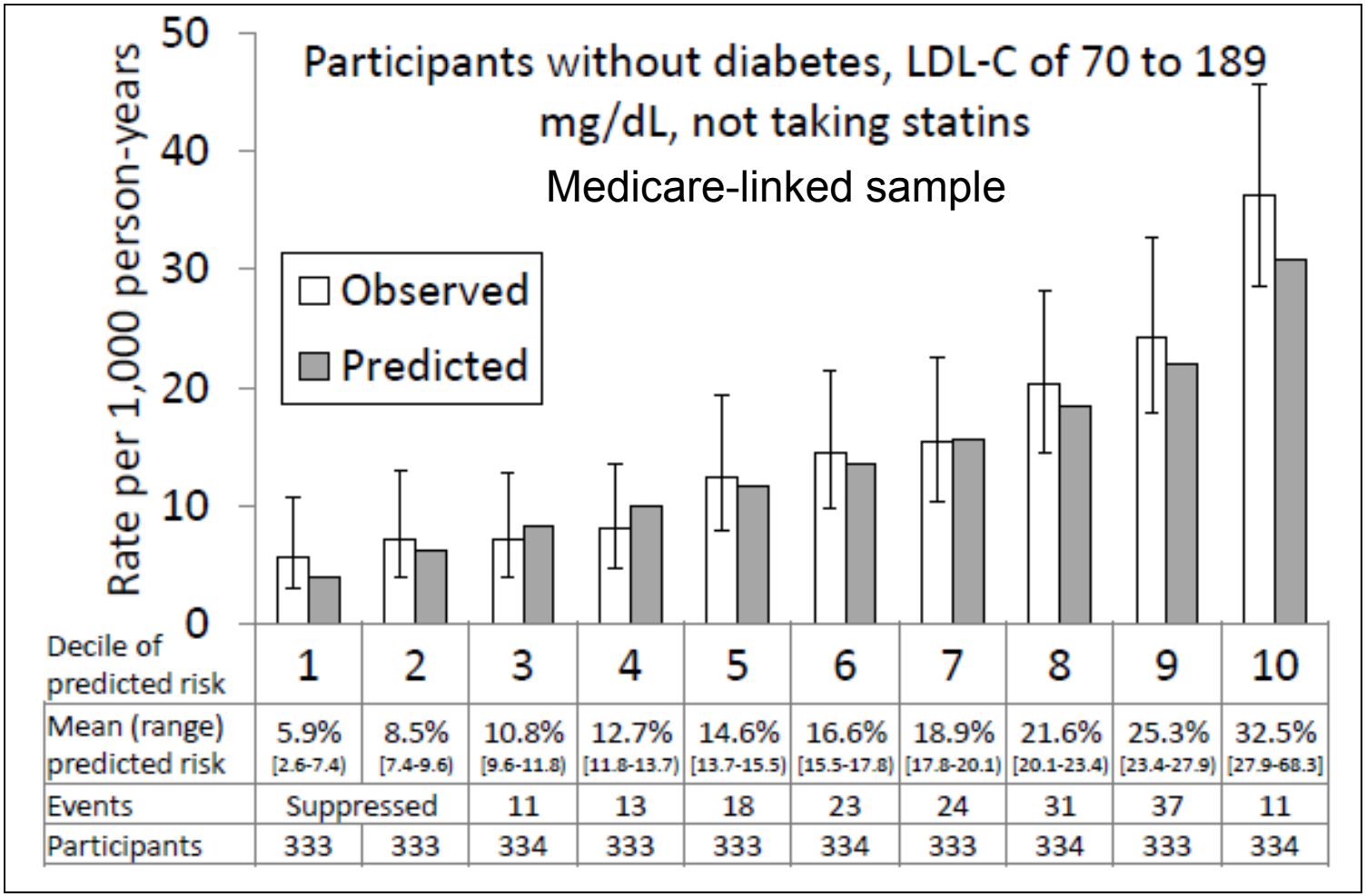
Decile of predicted risk	1	2	3	4	5	6	7	8	9	10
Mean (range) predicted risk	1.1% [0.2-1.8]	2.5% [1.8-3.2]	3.9% [3.2-4.8]	5.6% [4.8-6.5]	7.4% [6.5-8.3]	9.4% [8.3-10.5]	11.8% [10.5-13.1]	14.6% [13.1-16.4]	18.6% [16.4-21.7]	26.3% [21.7-68.3]
Events	4	6	16	18	25	28	36	38	60	107
Participants	1,099	1,100	1,100	1,100	1,099	1,100	1,100	1,100	1,100	1,099

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*5-year follow up
Muntner et al, ACC 2014

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External Validation: REGARDS*



Decile of predicted risk	1	2	3	4	5	6	7	8	9	10
Mean (range) predicted risk	5.9% [2.6-7.4)	8.5% [7.4-9.6)	10.8% [9.6-11.8)	12.7% [11.8-13.7)	14.6% [13.7-15.5)	16.6% [15.5-17.8)	18.9% [17.8-20.1)	21.6% [20.1-23.4)	25.3% [23.4-27.9)	32.5% [27.9-68.3]
Events	Suppressed		11	13	18	23	24	31	37	11
Participants	333	333	334	333	333	334	333	334	333	334

*5-year follow up
Muntner et al, ACC 2014

NHLBI Charge to the Work Group

- Examine the scientific evidence on risk assessment for initial ASCVD events, and develop an approach for risk assessment that could be used in practice and used or adapted by the risk factor panels in their guidelines.

- Specifically, the Work Group was charged with 2 tasks:

  1. To develop or recommend an approach to quantitative risk assessment that could be used to guide care; and

  2. To pose and address a small number of questions judged to be critical to refining and adopting risk assessment in clinical practice, using systematic review methodology.

Systematic Review Process

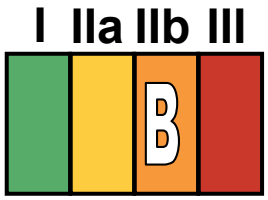
- CQs relevant to clinical practice
- A priori inclusion/exclusion (I/E) criteria
- Independent contractor conducted literature search
- Literature search through April, 2011
- Updated search for CQ#1 through September, 2013

Critical Question #1

- CQ1: “What is the evidence regarding reclassification or contribution to risk assessment when the following are considered in addition to the variables that are in the traditional risk scores?”
  - High-sensitivity C-reactive protein (hs-CRP)
  - Apolipoprotein B (ApoB)*
  - Glomerular filtration rate (eGFR)*
  - Microalbuminuria*
  - Family history
  - Cardiorespiratory fitness*
  - Ankle-brachial index (ABI)
  - Carotid intima-media thickness (CIMT)
  - Coronary artery calcium (CAC) score

* No recommendation

Recommendations for Additional Testing if Uncertainty Remains After 10-Year Risk Assessment



If, after quantitative risk assessment, a risk-based treatment decision is uncertain, assessment of 1 or more of the following — family history, hs-CRP, CAC score, or ABI — may be considered to inform treatment decision making.



No Benefit

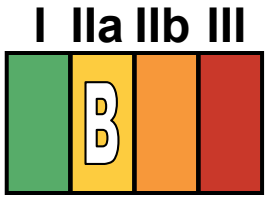
CIMT is not recommended for routine measurement in clinical practice for risk assessment for a first ASCVD event.

Critical Question #2

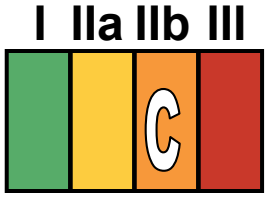
- CQ2: “Are models constructed to assess the long-term (15 years or lifetime) risk for a first CVD event in adults effective in assessing variation in long-term risk among adults at low and/or intermediate short-term risk, whether analyzed separately or combined?”

- Developed to assess the utility of long-term and lifetime risk assessment as an adjunct to short-term (10-year) risk assessment
  - Especially among those at low 10-year risk

Recommendations for Long-Term ASCVD Risk Estimation



It is reasonable to assess traditional ASCVD risk factors every 4 to 6 years in adults 20 to 79 years of age who are free from ASCVD and to estimate 10-year ASCVD risk every 4 to 6 years in adults 40 to 79 years of age without ASCVD.



Assessing 30-year or lifetime ASCVD risk based on traditional risk factors may be considered in adults 20 to 59 years of age without ASCVD and who are not at high short-term risk.

Evidence Gaps and Future Research Needs

- The Work Group strongly recommends continued research to fill gaps in knowledge
  - Short- and long-term ASCVD risk assessment and outcomes in all age/sex/race groups
  - Optimal communication of ASCVD risk
  - Utility of risk assessment for motivating behavioral change and adherence to therapy
  - Utility of differential information conveyed by short- and long-term risk assessment
  - Utility of novel risk markers and disease screening in short- and long-term risk assessment

Summary

- Absolute risk estimation remains important framing principle
  - Short- and long-term
- The Pooled Cohort Equations provide a major step forward in assessing risk for ASCVD (not just CHD)
  - Better representation of risk for women and AA
  - Well calibrated to the broad US population seen in 1^{o} care
  - Well suited for starting a clinician-patient discussion
- Further evidence needed regarding the optimal role for disease screening

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Take Home Message



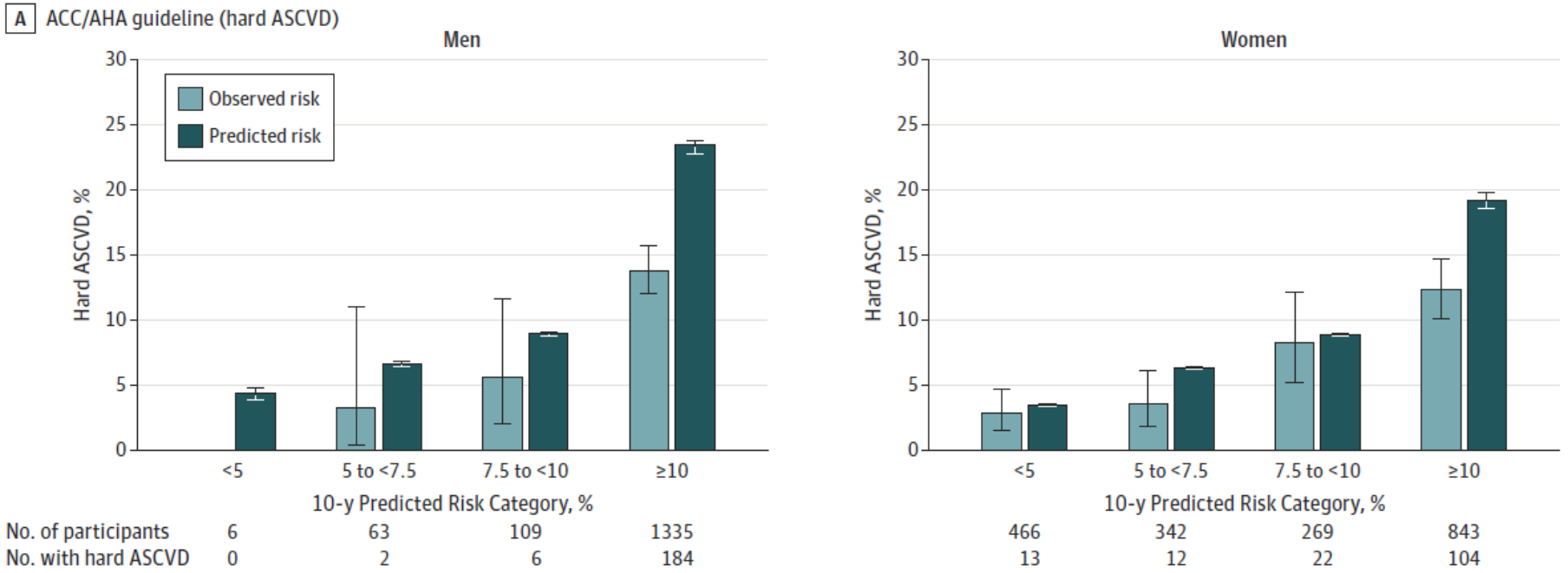
"…the recommendations are designed to inform clinical judgment, not to replace it."

Medicine

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Questions?

Some Irrelevant Data: Rotterdam



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Kavousi, JAMA 2014

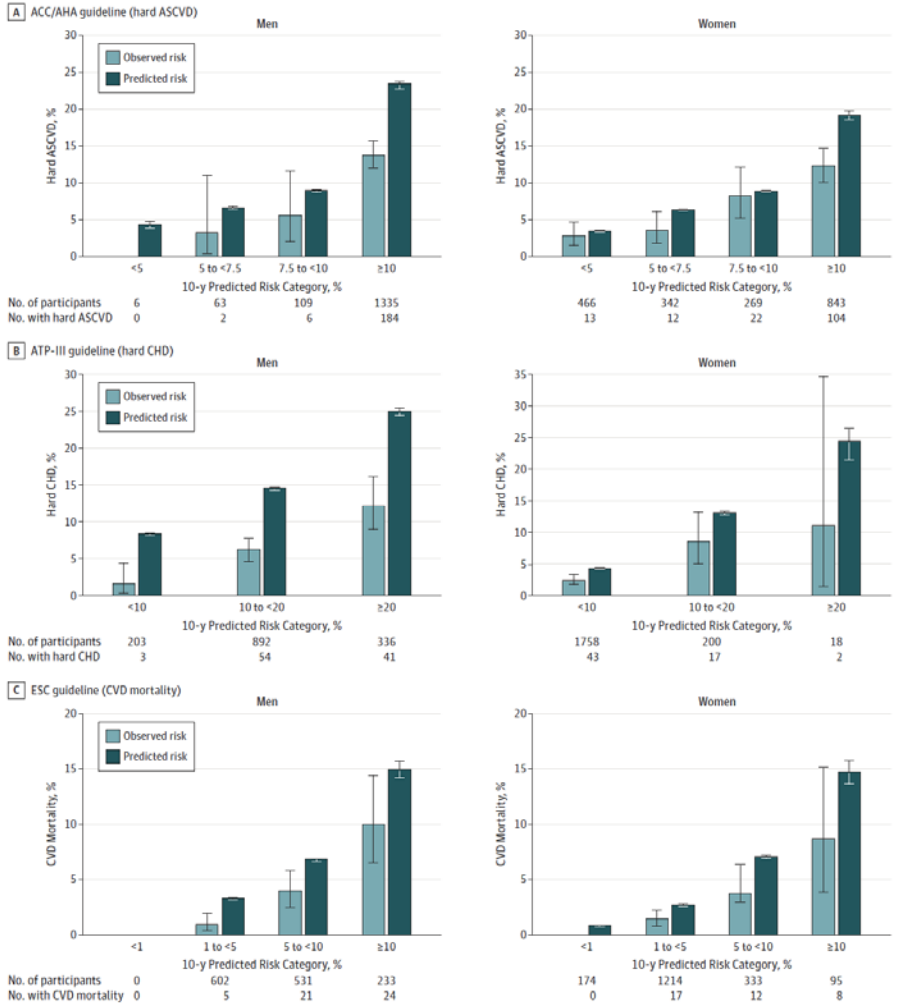
American Heart Association.

Some Irrelevant Data: Rotterdam

ACC/AHA 2013

ATP-III

ESC

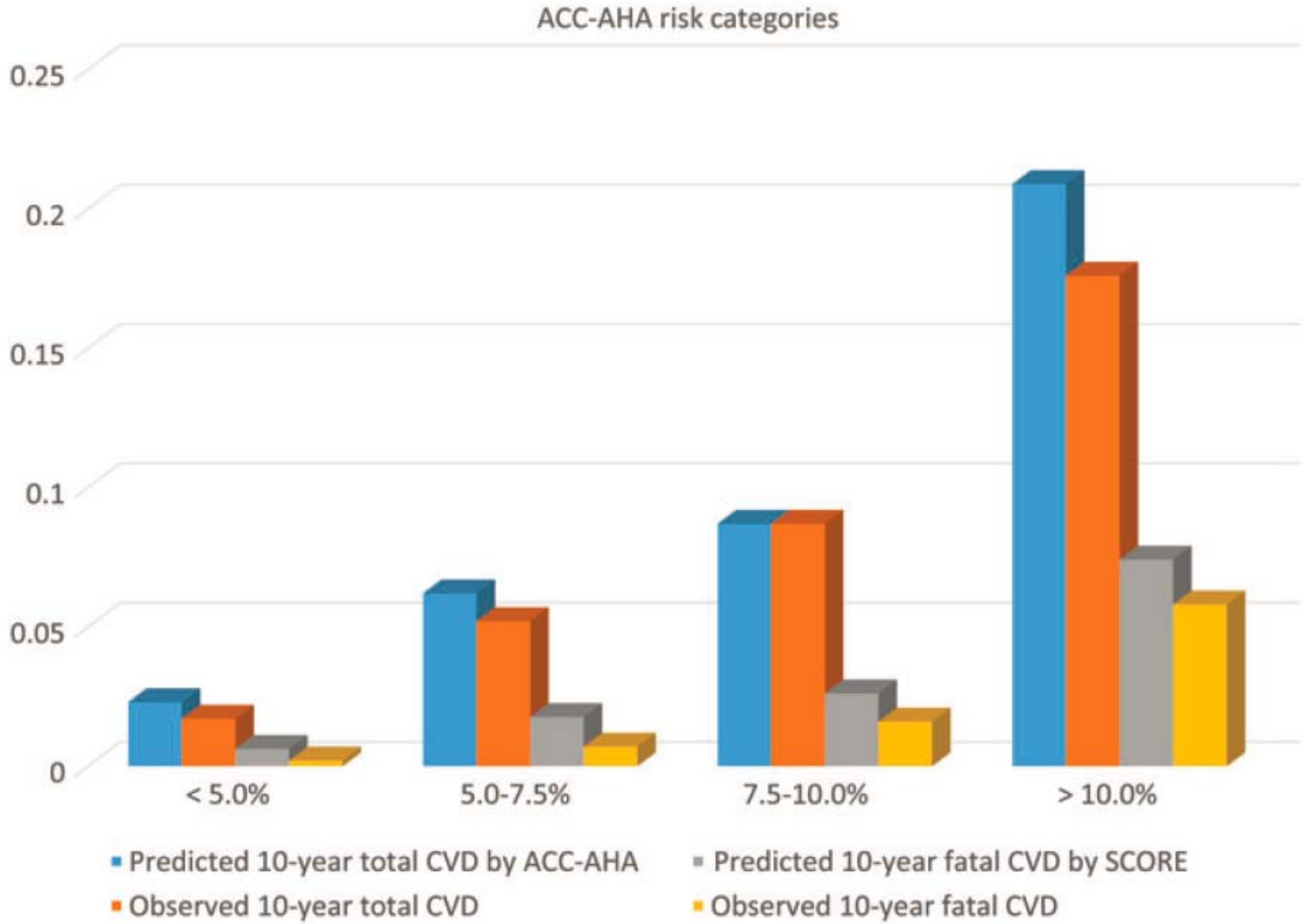


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Kavousi, JAMA 2014

American Heart Association®

Some Equally Irrelevant Data: EPIC-Norfolk



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Ray, EHJ 2014

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Dallas Heart Study

Table. Additional Statin Eligibility and ASCVD Event Rates Among Newly Statin Eligible Individuals

Outcome	Additional Statin Eligibility*	Event Rate Among Newly Statin Eligible	NNT Among Newly Statin Eligible†
Primary analysis			
ASCVD	4.8%	15.8%	14–21
CHD	4.8%	11.7%	19–29
ATPIII statin eligibility determined by optional cholesterol goals			
ASCVD	−2.8%	15.7%	14–21
CHD	−2.8%	12.4%	18–27
Restricting to individuals aged ≥40 years			
ASCVD	9.0%	15.8%	14–21
CHD	9.0%	11.6%	19–29

ASCVD indicates atherosclerotic cardiovascular disease; ATPIII, Third Adult Treatment panel; CHD, coronary heart disease; and NNT, number needed to treat.

*Additional statin eligibility is the net product of those newly statin eligible and those no longer statin eligible under the new guidelines.

†Number needed to treat with moderate to high potency statin to prevent one atherosclerotic cardiovascular event assuming a 30% to 45% relative risk reduction.

Compared with Original ATP-III Recommendations



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Paixio, Circ CQO 2014



American Heart Association®

Dallas Heart Study

Supplemental Table 3: Net Reclassification of Statin Eligibility among Individuals with and without ASCVD Events

Outcome	Additional statin eligibility among events	Additional statin eligibility among non-events	NRI	p-value
Primary analysis				
ASCVD	37.1%	3.9%	0.332	<0.01
CHD	40.4%	4.1%	0.363	<0.01
ATPIII statin eligibility determined by optional cholesterol goals				
ASCVD	16.5%	-3.4%	0.199	<0.01
CHD	19.1%	-3.2%	0.223	<0.01
Restricting to individuals ≥40 years of age				
ASCVD	37.8%	7.6%	0.302	<0.01
CHD	41.3%	8.0%	0.334	<0.01

Compared with Original ATP-III Recommendations



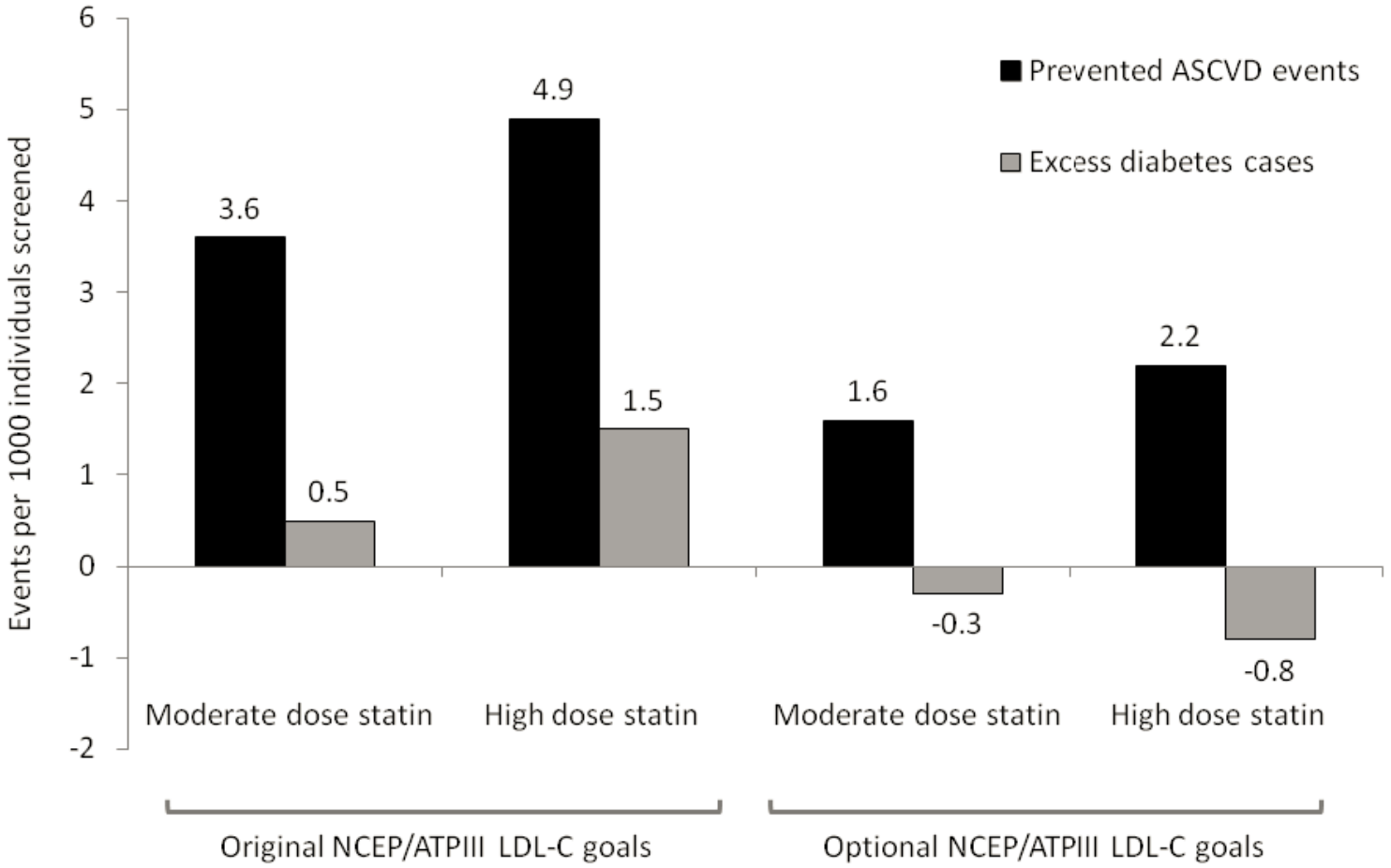
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Dallas Heart Study



ACC/AHA 2013 Strategy Compared with:

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Helping Cardiovascular Professionals
Learn. Advance. Heal.

American Heart Association.

THE 2013 ACC/AHA GUIDELINES ON THE TREATMENT OF BLOOD CHOLESTEROL

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National Lipid Association Indianapolis meeting
August 23, 2014

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

- J Am Coll Cardiol. 2014 Jul 1;63(25 Pt B):2889-934.
- Also see full paper (electronic supplement only) at ACC or AHA websites

ACC/AHA Blood Cholesterol Guideline Panel Members

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NHLBI Charge to the Expert Panel

Evaluate higher quality randomized controlled trial (RCT) evidence for cholesterol-lowering drug therapy to reduce ASCVD risk

- Use Critical Questions (CQs) to create the evidence search from which the guideline is developed
  - Cholesterol Panel: 3 CQs
  - Risk Assessment Work Group: 2 CQs
  - Lifestyle Management Work Group: 3 CQs
- Randomized controlled trials and systematic reviews/meta-analyses of RCTs independently assessed as fair-to-good quality
- Develop recommendations based on RCT evidence
- Less expert opinion than in prior guidelines

Systematic Review Process

The Expert Panel constructed Critical Questions relevant to clinical practice.

The Expert Panel identified (a priori) inclusion/exclusion (I/E) criteria for each Critical Question.

An independent contractor developed a literature search strategy, based on I/E criteria, for published clinical trial reports for each Critical Question.

An independent contractor executed a systematic electronic search of the published literature from relevant bibliographic databases for each Critical Question.

The date for the overall literature search was from January 1, 1995 through December 1, 2009.

However, randomized clinical trials with the ASCVD outcomes of MI, stroke, and cardiovascular death published after that date were eligible for consideration until July 2013.

Process

- Started 2008
- Critical questions
- Evidence review
- Evidence tables
- Evidence statements
- Recommendations
- Writing
- Multiple reviews—NHLBI, other agencies, outside reviewers, etc.—every single comment was answered
- Waiting (NHLBI announces June 2013—not doing guidelines)
- Work with ACC and AHA – remapping the grades
- Presentation and on-line publication—November 2013
- Print—early July 2014

Grades

"A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Even when randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective."

J Am Coll Cardiol. 2014 Jul 1;63(25 Pt B):2889-934.

Synopsis of recommendations

1. Encourage adherence to a healthy lifestyle
2. Statin therapy recommended for adults in groups demonstrated to benefit
3. Statins have an acceptable margin of safety when used in properly selected individuals and appropriately monitored
4. Engage in a clinician–patient discussion before initiating statin therapy--especially for primary prevention in patients with lower ASCVD risk

Stone, NJ et al. Ann Intern Med. 2014;160:339-343.

Synopsis of recommendations

5. Use the newly developed pooled cohort equations for estimating 10-Year ASCVD risk
6. Initiate the appropriate intensity of statin therapy
7. Evidence is inadequate to support treatment to specific LDL-C or non–HDL-C goals
8. Regularly monitor patients for adherence to lifestyle and statin therapy

Stone, NJ et al. Ann Intern Med. 2014;160:339-343.

Emphasis on healthy lifestyle

- Risk estimator provides lifetime risk estimate for patients 20 to 59
- This helps to drive discussions of greater adherence to heart-healthy lifestyle and improved risk factors
- Can be helpful in the decision process in people with lower short term risk but high lifetime risks

4 Statin Benefit Groups

- Clinical atherosclerotic cardiovascular disease
- LDL–C ≥ 190 mg/dL, Age ≥ 21 years
- Primary prevention – Diabetes: Age 40-75 years, LDL–C 70-189 mg/dL
- Primary prevention - No Diabetes[†]: ≥7.5%[‡] 10-year ASCVD risk, Age 40-75 years, LDL–C 70-189 mg/dL

[†]**Requires risk discussion between clinician and patient before statin initiation.**

[‡]Statin therapy may be considered if risk decision is uncertain after use of ASCVD risk calculator.

Statin Benefit Groups

- **Secondary Prevention**: Clinical atherosclerotic cardiovascular disease (ASCVD)
- **Primary prevention: LDL–C ≥190 mg/dL,** Age ≥21 years
- **Primary prevention: Diabetes**: Age 40-75 years, LDL–C 70-189 mg/dL + ASCVD risk ≥7.5%

  In these groups--0ptimal benefit with high intensity statins (lower LDL-C ≥ 50%)

  Diabetes + risk < 7.5% moderate intensity statin

  Age over 75 or can't tolerate high intensity statin– use moderate intensity

---

- **Primary prevention--Risk discussion between clinician and patient before starting medication**

  Age 40 to 75; No Diabetes; LDL-C 70-189

  10-year ASCVD risk ≥ 7.5%

  Consider statin therapy if risk decision is uncertain after use of ASCVD risk estimator

  Moderate or high intensity statin

Clinician – Patient Discussion before Statin Therapy

- Estimate 10-year ASCVD risk
- Review other risk factors and risk factor control
- Review potential for benefit from heart-healthy lifestyle
- Review potential for benefit from statins and potential for adverse effects and drug-drug interactions
- Consider patient preferences

Intensity of Statin Therapy

Table 5. High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)*

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL–C on average, by approximately ≥50%	Daily dose lowers LDL–C on average, by approximately 30% to <50%	Daily dose lowers LDL–C on average, by <30%
Atorvastatin (40†)–80 mg **Rosuvastatin 20** *(40)* **mg**	**Atorvastatin 10** *(20)* **mg** **Rosuvastatin** *(5)* **10 mg** **Simvastatin 20–40 mg‡** **Pravastatin 40** *(80)* **mg** **Lovastatin 40 mg** *Fluvastatin XL 80 mg* **Fluvastatin 40 mg bid** *Pitavastatin 2–4 mg*	*Simvastatin 10 mg* **Pravastatin 10–20 mg** **Lovastatin 20 mg** *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biologic basis for a less-than-average response.
†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL (Pedersen et al).
‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.

Goals versus Intensity of Therapy

- Lack of randomized trial evidence to support titration of drug therapy to specific LDL-C and/or non-HDL-C goals
- Strong evidence that appropriate intensity of statin therapy should be used to reduce ASCVD risk in those most likely to benefit
- Randomized trial data allows quantitative comparison of statin benefits with statin adverse effects
  - Important in discussions regarding benefit/risk of diabetes with statin therapy
  - Number needed to treat compared with number needed to harm

Safety

- Randomized clinical trials and meta-analyses of randomized clinical trials used to identify important safety considerations
- Allow estimation of **net benefit** from statin therapy
  - ASCVD risk reduction versus adverse effects
- Expert guidance on management of statin-associated adverse effects, including muscle symptoms
- Recommendations on non-statin safety issues
- Advise use of additional information including pharmacists, manufacturers prescribing information, and drug information centers for complex cases

Additional factors to consider when evaluating risk

- For those patients where a risk decision is uncertain, these factors may inform clinical decision making in the context of the clinician-patient discussion:
  - LDL-C ≥ 160 mg/dL
  - Family history of premature ASCVD
  - Increased lifetime risk
  - Hs-CRP ≥ 2
  - Coronary calcium score ≥ 300
  - Ankle-brachial index < 0.9

KEY POINT: Guidelines do not supersede clinical judgment. Treatment thresholds and goals without consideration of risk makes less sense than personalizing therapy to the patient's risks and preferences

Monitoring and follow up

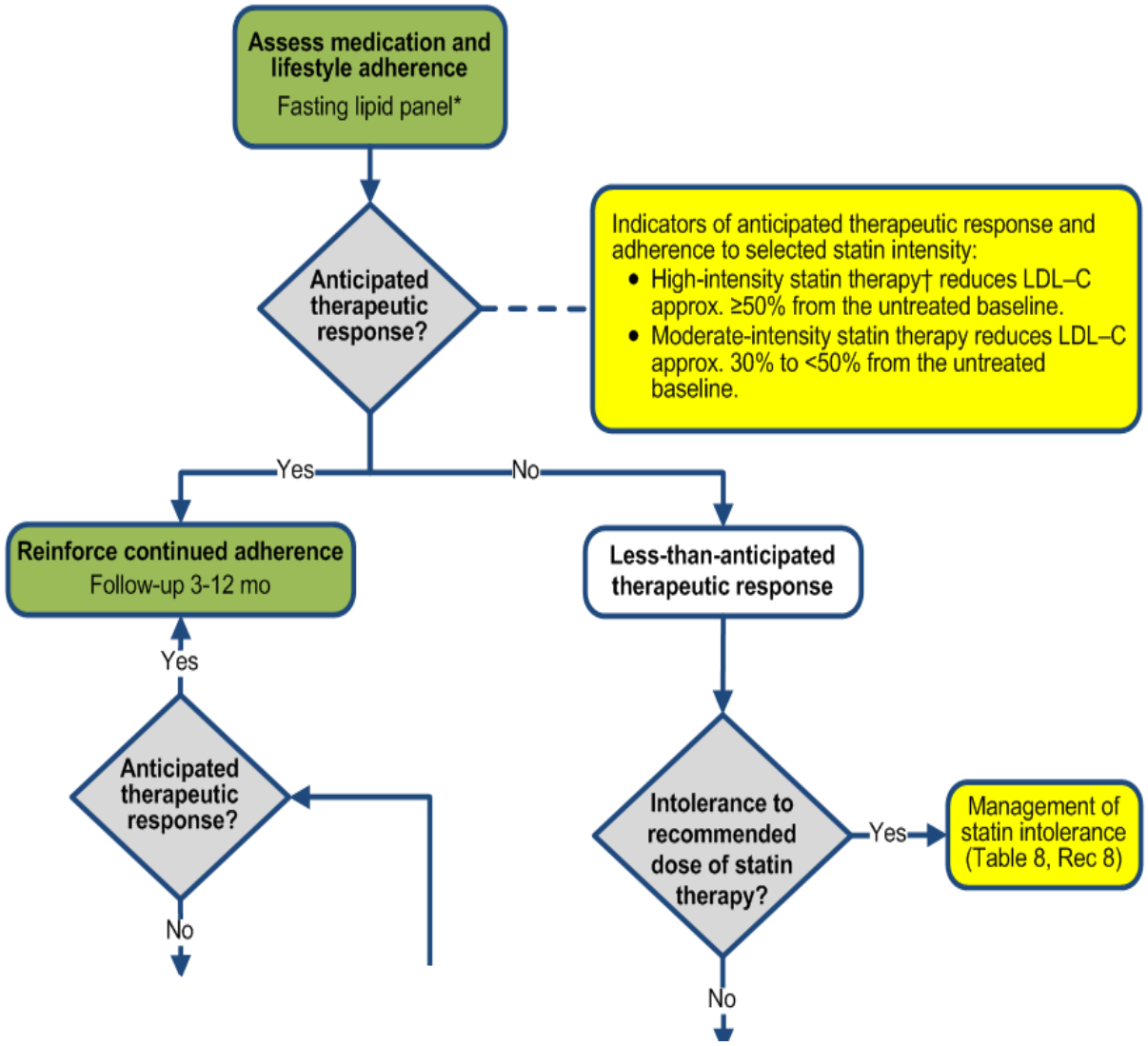
- Adherence to a heart healthy lifestyle
  - Optimal adherence to help improve lipids, affect other risk factors
- Each visit review adherence to statin
  - Maximally tolerated statin intensity and lifestyle to keep LDL-C low
- Measure lipids regularly
  - 3-12 weeks after start, then 4-12 months as appropriate to check adequacy of statin therapy
  - If not taking statin—why?
  - Consider secondary causes
  - If high risk and inadequate response, consider non-statin therapy
  - There are biologic differences in response
- Review safety issues at each visit with history, and labs if appropriate
  - For example: some may need CK, fasting glucose, hemoglobin A1c

Lipid measurements required for follow up

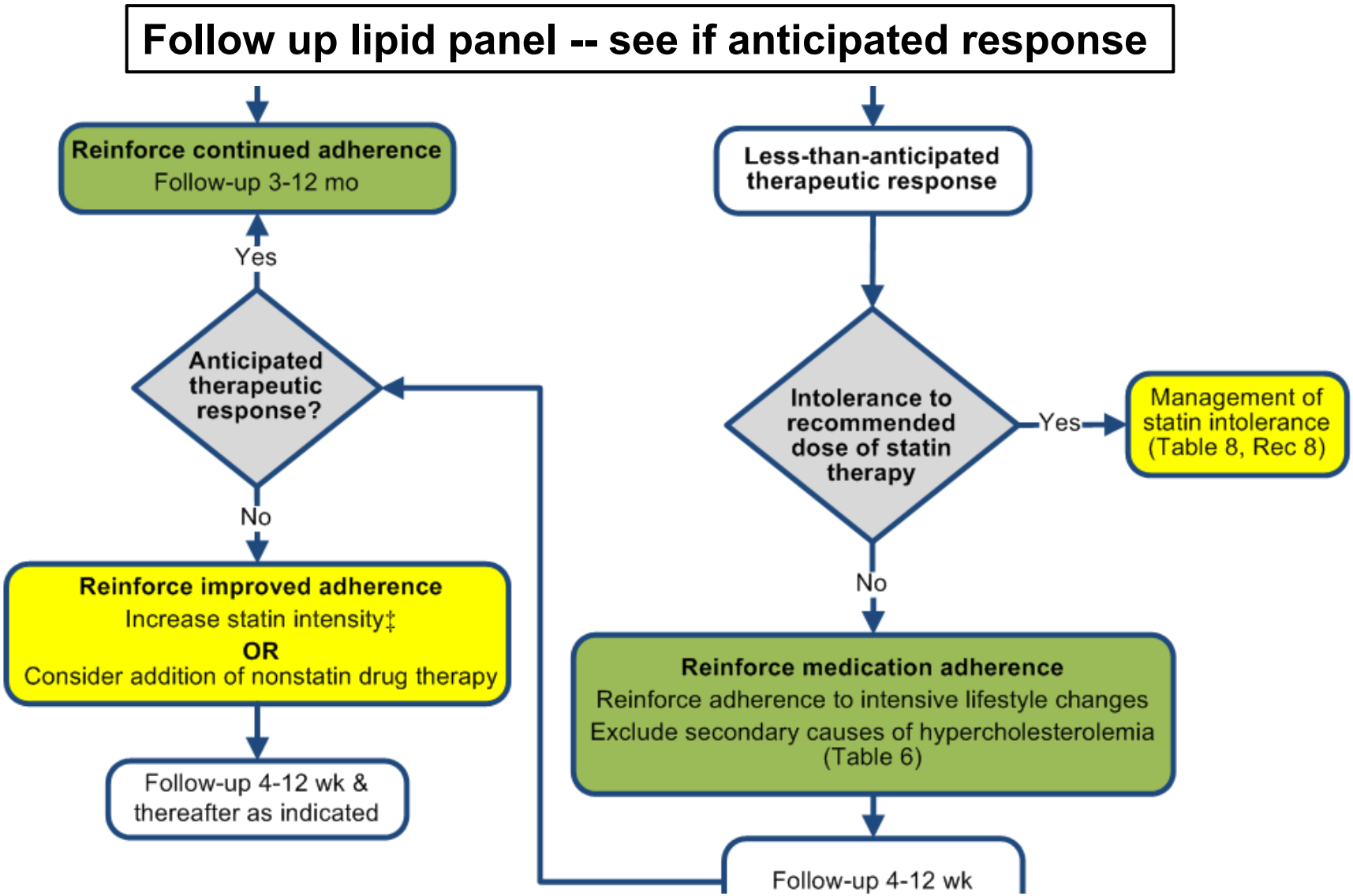
Response needs to be monitored = checking lipid panel

*Fasting lipid panel preferred. In a nonfasting individual, a nonfasting non-HDL–C >220 mg/dL may indicate genetic hypercholesterolemia that requires further evaluation or a secondary etiology. If nonfasting triglycerides are >500 mg/dL, a fasting lipid panel is required.

†In those already on a statin, in whom baseline LDL–C is unknown, an LDL–C <100 mg/dL was observed in most individuals receiving high-intensity statin therapy in RCTs.



Lipids Required for Follow up



Some of the controversies

- Accuracy of ASCVD risk estimator
  - Initial concerns not supported by new data from REGARDS (30,000 people)
  - Over-estimates occur if populations using statins are used
- Faulty assumption that ASCVD risk ≥ 7.5% means automatic statin therapy
  - The clinician-patient discussion comes first
- No LDL-C/non HDL-C goals
  - Panel did not find evidence for or against
  - Lipids followed regularly to assess therapeutic response and adherence
- Confusion regarding role for non-statin treatment
  - Non-statins may be used in high risk patients to further reduce LDL-C levels per clinician judgment (e.g. familial hypercholesterolemia, statin intolerant patients)

Pooled Cohort Equations

- Data from 5 population based NHLBI cohort studies on heart and stroke risk
- Includes African American status as an input
- ATP 3 Framingham Score evaluated 10-year risk of fatal and non-fatal MI—older data, less diverse population, does not include stroke risk
- The Pooled Cohort equations were validated in the REGARDS study of 30,000 black and white Americans from a contemporary population-based sample.

Why not continue to treat to target?

1. Current randomized clinical trial data do not indicate what the target should be
2. Unknown magnitude of additional ASCVD risk reduction with one target compared to another
3. Unknown rate of additional adverse effects from multidrug therapy used to achieve a specific goal
4. Therefore, unknown net benefit from treat-to-target approach

Cholesterol Treatment Trialists meta-analyses suggest greater reductions lead to greater risk reduction, but where that number should be is not clear. Even treating people with lower baseline LDL cholesterol levels shows benefit. Should someone with LDL cholesterol of 65, diabetes, CAD, not be treated with a statin?

Statin-Treated Individuals: Non-statin Therapy Considerations

- Use the maximum tolerated intensity of statin
- Consider addition of a non-statin cholesterol-lowering drug(s)
  - If a less-than-anticipated therapeutic response persists
  - If ASCVD risk-reduction benefits outweigh the potential for adverse effects in higher-risk persons:
    - *Clinical* ASCVD <75 years of age
    - Baseline LDL–C ≥190 mg/dL
    - Diabetes mellitus 40 to 75 years of age
- Non-statin cholesterol-lowering drugs shown to reduce ASCVD events in randomized trials are preferred

Future Updates to the Blood Cholesterol Guideline

- These guidelines represent a change from previous guidelines. They align recommendations more closely to the evidence.
- For primary prevention, they focus on shared decision making
- Guidelines will be improved by future high-quality research

Evidence gaps and future research needs

1. Outcomes of RCTs to evaluate statins for the primary prevention of ASCVD in adults **>** 75 years of age.

2. Outcomes of RCTs to evaluate alternative treatment strategies for ASCVD risk reduction. These RCTs may compare titration to specifi c cholesterol or

apolipoprotein goals versus fi xed-dose statin therapy in high-risk patients.

3. RCTs to determine whether submaximal statin doses, combined with nonstatin therapies, reduce ASCVD risk in statin-intolerant patients.

4. Evaluation of the incidence, pathophysiology, clinical course, and clinical outcomes of new-onset diabetes associated with statin therapy.

5. Outcomes of RCTs of new lipid-modifying agents to determine the incremental ASCVD event-reduction benefits when added to evidence-based statin therapy.

J Am Coll Cardiol. 2014 Jul 1;63(25 Pt B):2889-934.

Complex Lipid Disorders

"For the many questions about complex lipid disorders that are beyond the scope of our systematic evidence review, or for which little or no RCT data are available, it is anticipated that clinicians with lipid expertise can contribute to their management."

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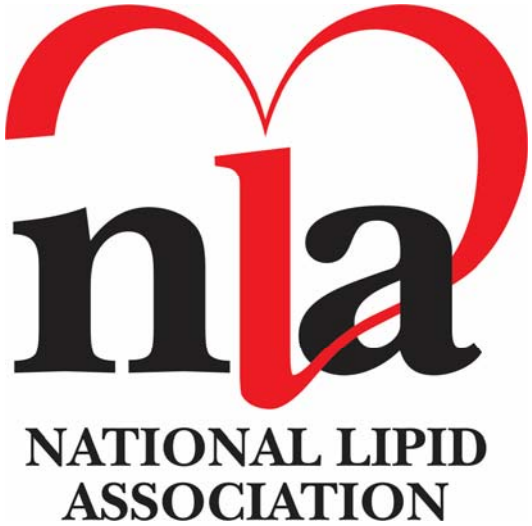
"These guidelines are meant to define practices that meet the needs of patients in most circumstances and are not a replacement for clinical judgment. The ultimate decision about care of a particular patient must be made by the healthcare provider and patient in light of the circumstances presented by that patient. As a result, situations might arise in which deviations from these guidelines may be appropriate. These considerations notwithstanding, in caring for most patients, clinicians can employ the recommendations confidently to reduce the risks of atherosclerotic cardiovascular disease (ASCVD) events."

J Am Coll Cardiol. 2014 Jul 1;63(25 Pt B):2889-934.

Thank you!

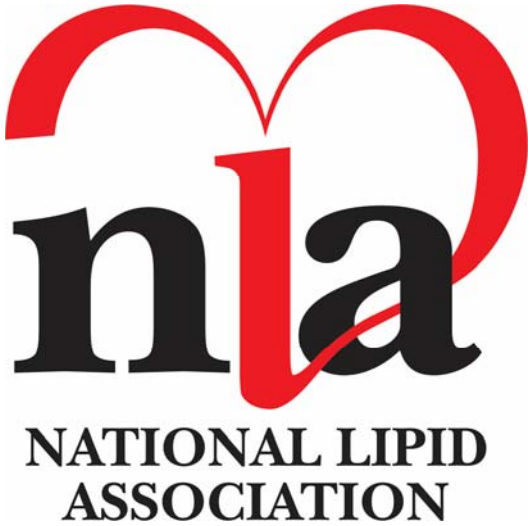
References for further reading

- Stone NJ, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(25 Pt B):2889-934.
- Stone NJ, et al. Treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: synopsis of the 2013 American College of Cardiology/American Heart Association cholesterol guideline. *Ann Intern Med*. 2014;160(5):339-43.
- Cholesterol Treatment Trialists' (CTT) Collaborators The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 2012 ;380(9841):581-90
- Sattar N et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 2010; 375: 735–42



NLA Recommendations for Patient-Centered Management of Dyslipidemia

Part 1



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Conceptual Framework of NLA Recommendations

- The NLA recognizes that dyslipidemia management has made a major contribution to the progressive reduction in ASCVD morbidity and mortality observed in the last decade.
  - This reduction in risk occurred under the guidance provided by previous documents (most notably the National Cholesterol Education Program Adult Treatment Panel III Guidelines).

Conceptual Framework of NLA Recommendations

- The NLA Expert Panel consensus view is that the evidence accumulated since the 2004 update of the National Cholesterol Education Program Adult Treatment Panel III Guidelines warrants a **modest refinement** of previous lipid-related risk management strategies.

Evidence Base

- The panel considered evidence from randomized controlled trials (RCTs), including primary, subgroup and pooled analyses where available, as well as evidence from epidemiological, metabolic, mechanistic and genetic studies.

- The panel acknowledges that the primary results from RCTs represent the strongest evidence from which to draw conclusions about benefits and risks of treatment strategies. However, the available RCT evidence has limitations, is often incomplete, or is of uncertain relevance to patients with characteristics that may differ in important ways from those who participated in the RCTs.

Guiding Principles/Conclusions

- An elevated level of cholesterol carried by circulating Apo B-containing lipoproteins (non-HDL-C and LDL-C, termed atherogenic cholesterol) is a root cause of atherosclerosis, the key underlying process contributing to most clinical ASCVD events.
- Reducing elevated levels of atherogenic cholesterol will lower ASCVD risk in proportion to the extent that atherogenic cholesterol is reduced. This benefit is presumed to result from atherogenic cholesterol lowering through multiple modalities, including lifestyle and drug therapies.

Guiding Principles/Conclusions

- The intensity of risk-reduction therapy should generally be adjusted to the patient's absolute risk for an ASCVD event.
- Atherosclerosis is a process that often begins early in life and progresses for decades before resulting in a clinical ASCVD event. Therefore, both intermediate-term and long-term/lifetime risk should be considered when assessing the potential benefits and hazards of risk-reduction therapies.
- For patients in whom lipid-lowering drug therapy is indicated, statin treatment is the primary modality for reducing ASCVD risk.
- Non-lipid ASCVD risk factors should also be managed appropriately, particularly high blood pressure, cigarette smoking, and diabetes mellitus.

Screening in Adults

- A fasting or non-fasting lipid profile should be measured at least every 5 years, starting at age 20; ideally fasting to allow assessment of LDL-C and triglyceride levels.
  - If non-fasting, focus on non-HDL-C (total-C minus HDL-C) and HDL-C.
- Should be accompanied by an assessment of ASCVD risk factors and risk stratification when indicated.
- If low risk, public health recommendations may be applied for those with atherogenic cholesterol levels in the desirable range (LDL-C <100 mg/dL, non-HDL-C <130 mg/dL)
- Consider rescreening sooner in patients with inappropriate weight gain, new major risk factors, new secondary causes of dyslipidemia, or premature ASCVD in 1° relatives

Classifications of Cholesterol and Triglyceride Levels in mg/dL

Non-HDL-C

<130	Desirable
130-159	Above desirable
160-189	Borderline high
190-219	High
≥220	Very high

HDL-C

<40 (men)	Low
<50 (women)	Low

LDL-C

<100	Desirable
100-129	Above desirable
130-159	Borderline high
160-189	High
≥190	Very high

Triglycerides

<150	Normal
150-199	Borderline high
200-499	High
≥500	Very high

Position on Lipid Goals

- The NLA Expert Panel recommends the use of lipid and lipoprotein goals in clinical decision-making
- These goals are used to enhance provider-patient interaction and maximize adherence to atherogenic lipoprotein-lowering regimens
- While non-HDL-C is the preferred lipoprotein goal because of its superiority in risk prediction to LDL-C, the importance of LDL-C as an atherogenic lipoprotein and risk marker is recognized
- Apolipoprotein B is an optional goal

Identifying Very-High Risk Patients

- Documented CHD
- Thrombotic stroke or TIA
- Atherosclerotic PAD
- Ankle-brachial index <0.9
- Renal atherosclerosis
- Atherosclerotic aortic aneurysm
- Carotid plaque ≥50% stenosis
- DM ± end organ involvement or ≥2 additional major ASCVD risk factors

Begin treatment at

Non-HDL-C ≥100 mg/dL
LDL-C ≥70 mg/dL

Goals

Non-HDL-C <100mg/dL
LDL-C <70 mg/dL
Optional apo B <80 mg/dL

Consider moderate or high-intensity statin therapy, regardless of non-HDL-C or LDL-C

End-Organ Involvement in Type 2 DM

- Urinary albumin/creatinine ratio >30 mg/g
- Chronic kidney disease
- Diabetic retinopathy

Major Risk Factors for ASCVD

1. Age
   - Male ≥45 years
   - Female ≥55 years
2. Family history of early CHD
   - <55 years of age in a male first-degree relative, or
   - <65 years of age in a female first-degree relative
3. Current cigarette smoking
4. High blood pressure (≥140/≥90 mm Hg, or on blood pressure medication)
5. Low HDL-C
   - Male <40 mg/dL
   - Female <50 mg/dL

HDL-C
A Risk Marker but not a Target of Therapy

- The level of HDL-C is an important risk indicator and used in risk factor counting and quantitative risk assessment. Low HDL-C is also a component of the metabolic syndrome.
- HDL-C is not recommended as a target of therapy *per se*, but the level is often raised as a consequence of efforts to reduce atherogenic cholesterol through lifestyle and drug therapies.

Identifying High-Risk Patients

- DM type 1 or 2 with 0-1 additional risk factor and no end-organ involvement
- Chronic kidney disease stage 3B or 4
- LDL-C ≥190 mg/dL
- ≥3 major ASCVD risk factors
- 10-yr. Framingham risk ≥10%; 10 yr. ACC/AHA risk ≥15%; Lloyd-Jones 30-year risk ≥45%
- CACS ≥300 (or 75th%-ile), hs-CRP ≥2 mg/L, Lp(a) ≥50 mg/dL (isoform insensitive assay), urine albumin/creatinine ratio >30 mg/g

Begin treatment at	**Goals**
Non-HDL-C ≥130 mg/dL LDL-C ≥ 100 mg/dL	Non-HDL-C <130 mg/dL LDL-C <100 mg/dL Optional apo B <90 mg/dL

Identifying Moderate-Risk Patients

- 2 major ASCVD risk factors
- No characteristics of very-high or high risk groups
- No evidence of high-risk quantitative risk scoring or key high-risk biomarker abnormalities

Begin treatment at	Goals
Non-HDL-C ≥160 mg/dL LDL-C ≥130 mg/dL	Non-HDL-C <130 mg/dL LDL-C <100 mg/dL Optional apo B <90 mg/dL

Identifying Low-Risk Patients

- 0-1 ASCVD risk factor
- No characteristics of very-high or high-risk groups
- No evidence of high-risk quantitative risk scoring or key high-risk biomarker abnormalities

Begin treatment at	Goals
Non-HDL-C ≥190 mg/dL LDL-C ≥160 mg/dL	Non-HDL-C <130 mg/dL LDL-C <100 mg/dL Optional apo B <90 mg/dL

Criteria to Consider Upward Risk Reclassification in Low- or Moderate-Risk Patients

- History of multi-pack per day cigarette smoking
- Strong family history of premature CHD
- Systolic blood pressure ≥160 mm Hg
- Non-HDL-C ≥190 mg/dL or LDL-C ≥160 mg/dL

The Metabolic Syndrome

- It is a multiplex risk factor of type 2 DM and ASCVD
- It is a marker for high potential to benefit from lifestyle therapy

Lifestyle Therapy

- Dietary therapy in accordance with the AHA recommendations and ≥150 minutes per week of moderate or higher intensity physical activity is recommended
- Weight reduction should be recommended in those who are overweight or obese
- The addition of viscous fiber and/or plant sterol/stanols should be considered in those not responding to dietary change
- Dietitian consultation is recommended, whenever possible

Drug Therapy: Key Considerations

- Provider-patient discussion of risk-benefit ratio and respect for patient preferences are keys to enhancing adherence.
- Moderate or high-intensity statin is the preferred first step except when TG ≥500 mg/dL, when therapy directed at hypertriglyceridemia is the first priority.
- For statin-intolerant patients consider switching statins; alternate-day or lower-dose statins; lower dose statin-non-statin regimens; non-statin monotherapy or combination therapy

Intensity of Statin Therapy*

High Intensity Daily dose ↓ LDL-C ≥50%	Moderate Intensity Daily dose ↓ LDL-C 30 to <50%
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg
Rosuvastatin 20-40 mg	Fluvastatin 40 mg bid
	Fluvastatin XL 80 mg
	Lovastatin 40 mg
	Pitavastatin 2-4 mg
	Pravastatin 40-80 mg
	Rosuvastatin 5-10 mg
	Simvastatin 20-40 mg

*Individual responses to statin therapy should be expected to vary in clinical practice. Moderate or high intensity statin therapy is preferred unless not tolerated.

Drug Therapy: Other Key Points

- For TG ≥1000 mg/dL, consider fibrate, high-dose long chain Ω-3 fatty acids and niacin; for 500-999 mg/dL and no history of pancreatitis, consider statins or any of the above
- For TG 200-499 mg/dL, targets of therapy are non-HDL-C and LDL-C, generally using statins
- If LDL-C falls to <40 mg/dL, therapy may be continued in absence of intolerance

Severe Hypercholesterolemia Phenotype

- Usually due to FH and associated with increased ASCVD risk
- Cascade screening is recommended
- Goals of treatment in absence of a very-high-risk condition are non-HDL-C <130 mg/dL and LDL-C <100 mg/dL, or reduction of atherogenic cholesterol of ≥50% from baseline if goals cannot be achieved
- Consider lower goals in those with multiple or poorly controlled other major ASCVD risk factors

Progressive Atherosclerosis, or Recurrent Events, Despite Evidence-Based Therapy

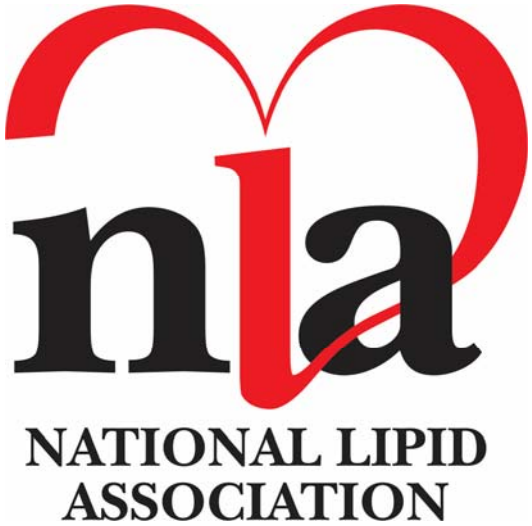
- Consider investigation of potential causes, including Lp(a) elevation or other secondary risk factors
- Non-lipid ASCVD risk factors should be well controlled
- Consider therapy to lower atherogenic cholesterol to well-below goal thresholds, although evidence to support this approach is minimal

NLA Treatment Recommendations: Summary

- Always consider secondary causes before initiating treatment
- Lifestyle therapy begins the treatment paradigm in all risk categories
- Moderate or high intensity statin therapy, as tolerated, is warranted as the first step for those requiring drug therapy
- Lower-dose statin, alternative statin regimens, combination therapy or non-statins should be considered in statin-intolerant patients
- Triglyceride lowering therapy is warranted as the first step in those with serum triglycerides ≥500 mg/dl

Additional Information

- Additional information from the NLA:
  - https://www.lipid.org/practicetools/guidelines/consensus_recommendations
    - Familial Hypercholesterolemia: Screening, Diagnosis and Management of Pediatric and Adult Patients
    - Clinical Utility of Inflammatory Markers and Advanced Lipoprotein Testing: Advice form an Expert Panel of Lipid Specialists
  - https://www.lipid.org/practicetools/guidelines/position_statements



Data Supported Evidence for Differences in the ACC/AHA Guidelines and NLA Recommendations for Dyslipidemia Management

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Midwest Center for Metabolic & Cardiovascular Research and
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Chicago, Illinois

Selected Differences in the ACC/AHA Guidelines and NLA Expert Panel Recommendations

Many similarities, some differences, which include:

1. Evidence considered
2. Inclusion by the NLA panel of atherogenic cholesterol (non-HDL-C and LDL-C) goals
3. Recommended pharmacological therapies
   - Greater support for use of combination drug therapies (to reach goal levels of atherogenic cholesterol) as a therapeutic option in the NLA recommendations, particularly for high and very high risk patients

ACC/AHA - Evidence Considered

- Evaluation was limited to primary analyses from randomized controlled trials (RCTs) with atherosclerotic cardiovascular disease (ASCVD) outcomes and systematic reviews and meta-analyses of RCTs with ASCVD outcomes (published through July 2013).

Stone NJ, et al. J Am Coll Cardiol. 2014;63 (25 Pt B):2889-2934.

NLA - Evidence Considered

- Results from RCTs published through July 2014 to evaluate the effects of lipid-altering interventions on clinical ASCVD events (mainly myocardial infarction, coronary death, and stroke) were examined, as well as subgroup assessments and pooled analyses from multiple trials, where available.
- Epidemiological, genetic, metabolic and mechanistic investigations were also considered.

Jacobson TA, et al. J Clin Lipidol. 2014;in press.

ACC/AHA - Cholesterol Goals

- Recommendation: The Expert Panel made no recommendations for or against specific LDL-C or non-HDL-C targets (goals) for the primary or secondary prevention of ASCVD.
- The ACC/AHA Expert Panel did not find RCT evidence to support titrating cholesterol-lowering drug therapy to achieve LDL-C and non-HDL-C [goal] levels as recommended by the National Cholesterol Education Program Adult Treatment Panel III.
  - The ACC/AHA Expert Panel noted that they did find RCT evidence that use of therapy (e.g., niacin) to additionally lower non-HDL-C after the LDL-C target was achieved did not further reduce ASCVD outcomes.

Stone NJ, et al. J Am Coll Cardiol. 2014;63 (25 Pt B):2889-2934.

NLA - Cholesterol Goals

Expert Panel Consensus Views:

- Treatment goals are useful to ensure that the aggressiveness of therapy to lower atherogenic cholesterol is matched to absolute risk for an event, and also to facilitate effective communication between patients and clinicians to maximize long-term adherence to treatment.

- Treatment goals were recommended
  - Primary prevention: non-HDL-C <130, LDL-C <100 mg/dL
  - Secondary prevention : non-HDL-C <100, LDL-C <70 mg/dL
    - ASCVD or DM plus ≥2 major ASCVD risk factors

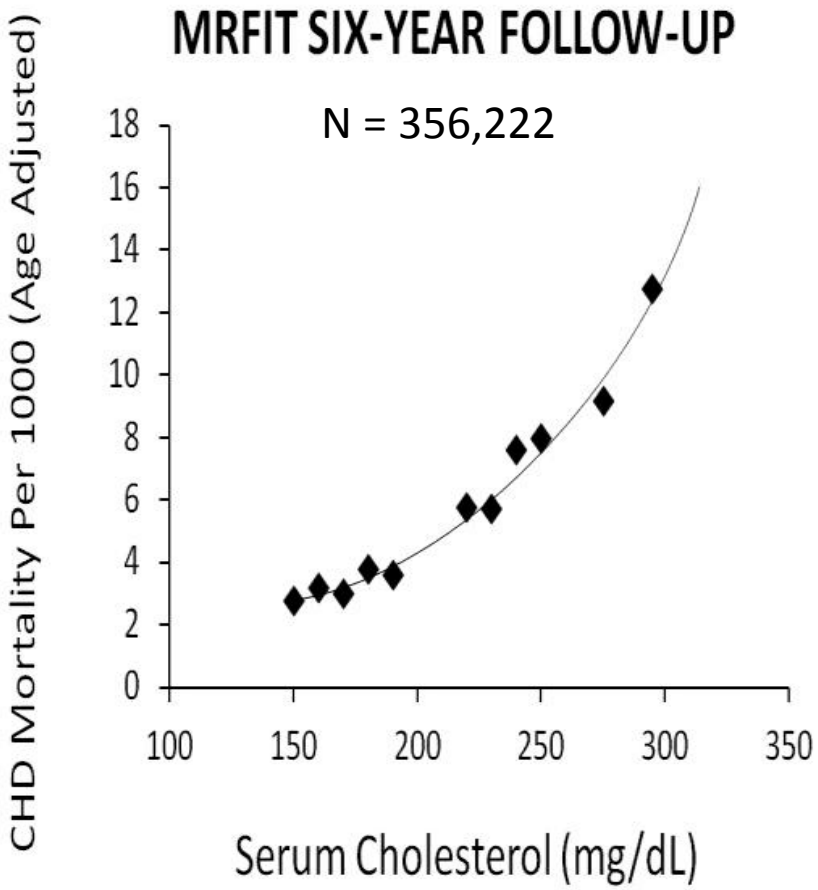
Jacobson TA, et al. J Clin Lipidol. 2014;in press.

NLA Cholesterol Goals - Continued

- Results from RCTs of various methods for lowering atherogenic cholesterol (e.g., pharmacotherapy, diet, ileal bypass surgery) indicate that lower on-treatment levels are consistently associated with lower absolute risk for an ASCVD event.
  - Most RCTs of lipid-lowering drug therapies tested drug treatment against a placebo control, or a more intensive vs. less-intensive statin treatment regimen.
  - The strategy of treating patients to a specific LDL-C or non-HDL-C level has not been tested in any of the large outcomes trials assessing ASCVD morbidity and mortality.
- The evidence from RCTs generally aligns with results from observational studies
  - Consistent with a log-linear relationship between the levels of atherogenic cholesterol and absolute ASCVD event risk
  - Support “lower is better” hypothesis for atherogenic cholesterol

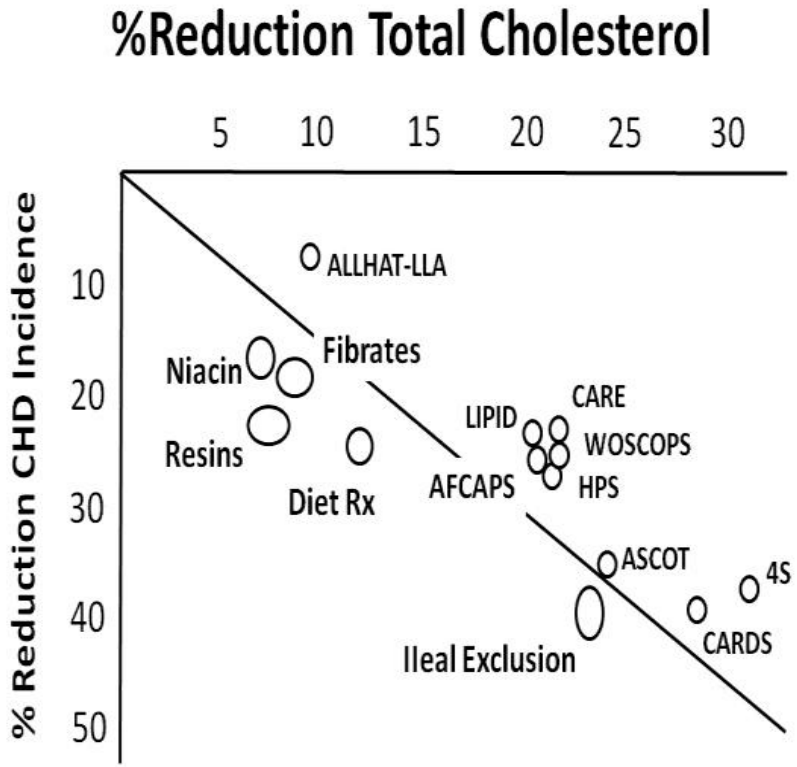
Jacobson TA, et al. J Clin Lipidol. 2014;in press.

Log-Linear Relationship Between Serum Cholesterol and Coronary Heart Disease (CHD) Mortality



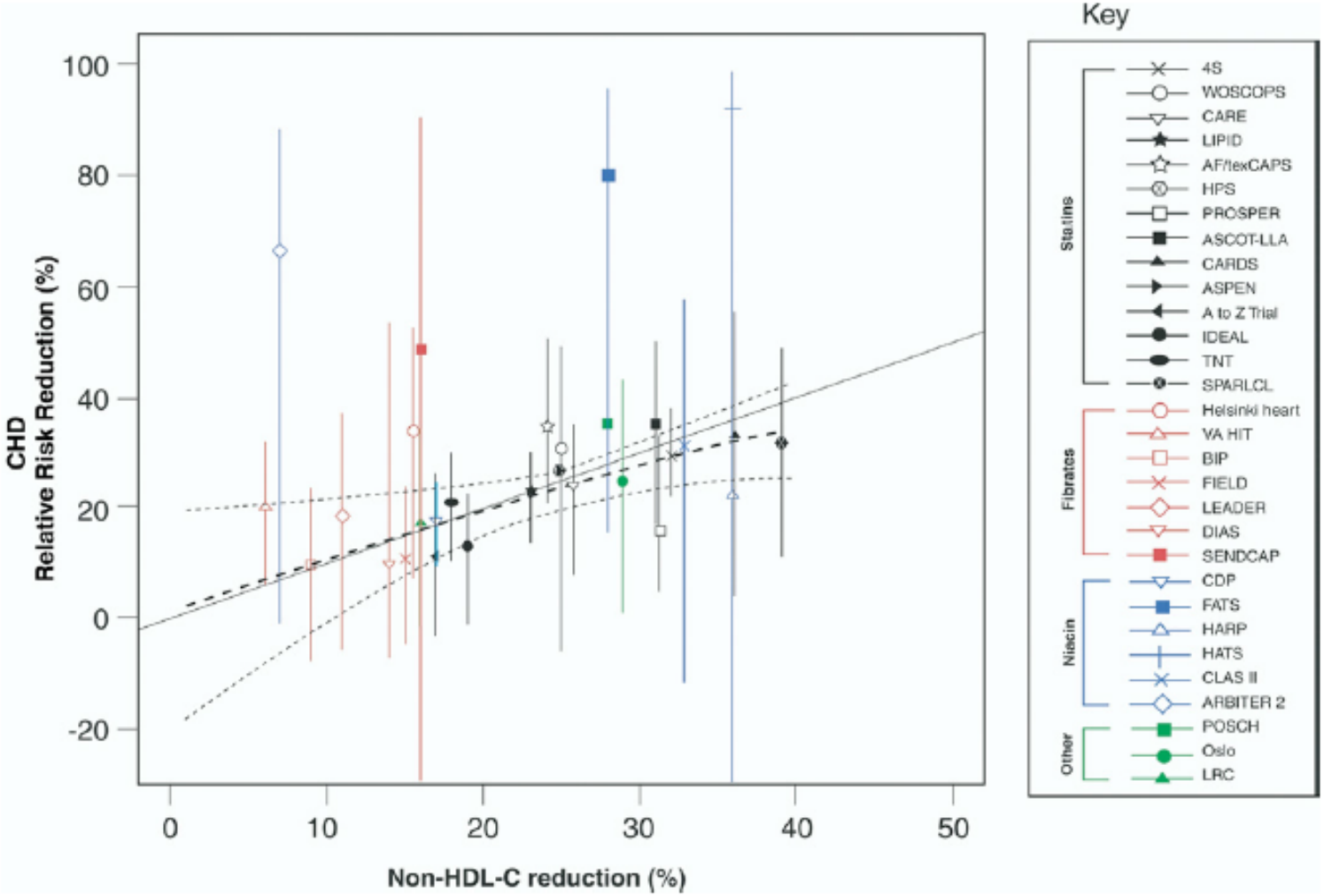
Expert Dyslipidemia Panel of IAS. J Clin Lipidol. 2014;8:29-60.
Stamler J, et al. JAMA. 1986;256:2823-2828.

Relationship Between % Reduction in Total Cholesterol and % Reduction in CHD Incidence



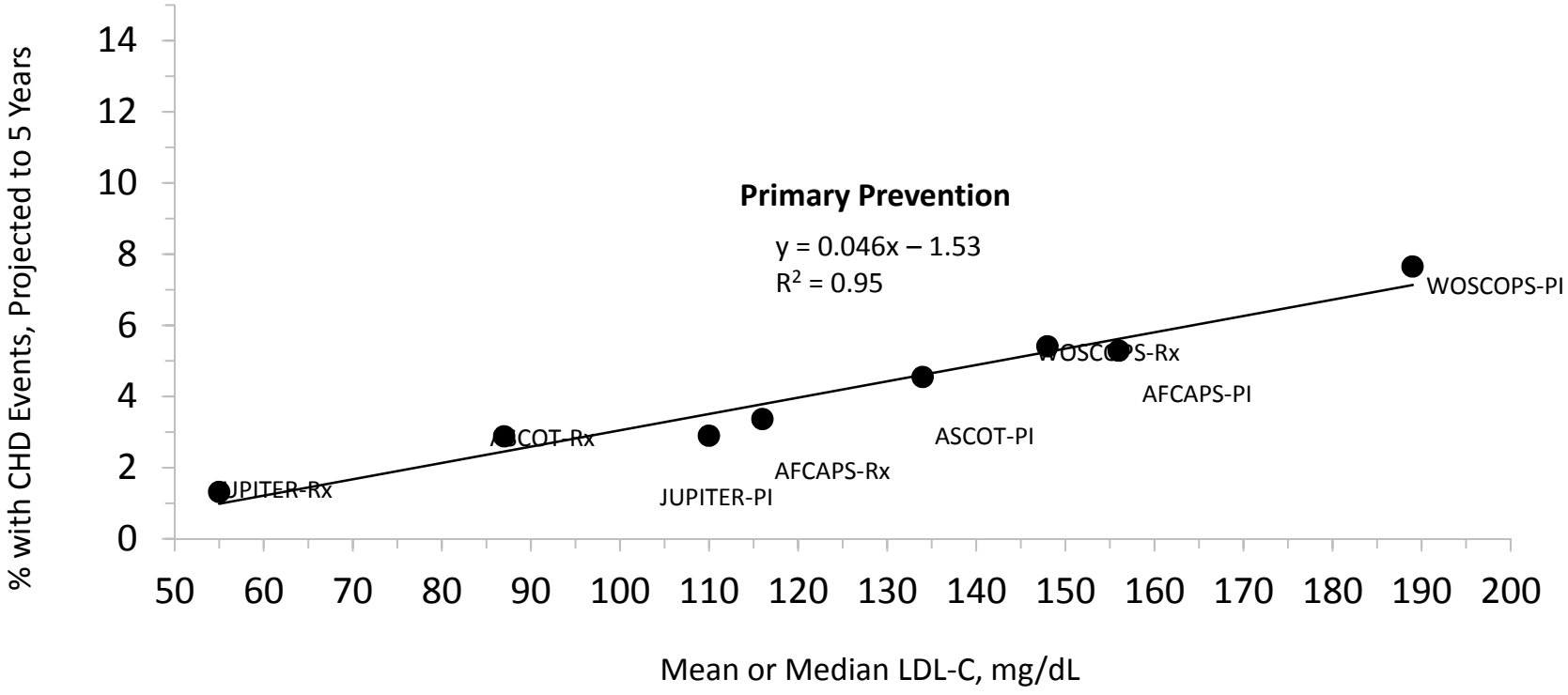
Expert Dyslipidemia Panel of IAS. J Clin Lipidol. 2014;8:29-60.
NCEP Expert Panel. Circulation. 2002;106:3143-3421.
Gordon DJ, In: Rifikind BM, ed. Lowering cholesterol in high-risk individuals and populations. New York: Marcel Dekker, Inc. 1995.
Rossouw JE, et al. N Engl J Med. 1990;323:1112-1119.

Change in Relative Risk of CHD Events According to Non-HDL-C Reduction



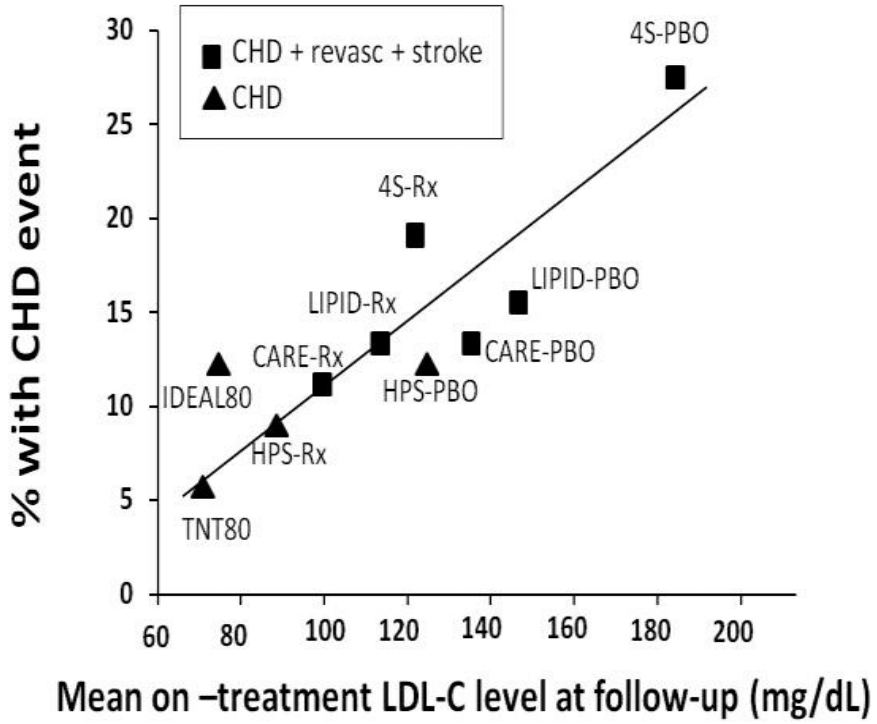
Robinson JG, et al. J Am Coll Cardiol. 2009;53:316-322.

On-Treatment LDL-C and CHD Events



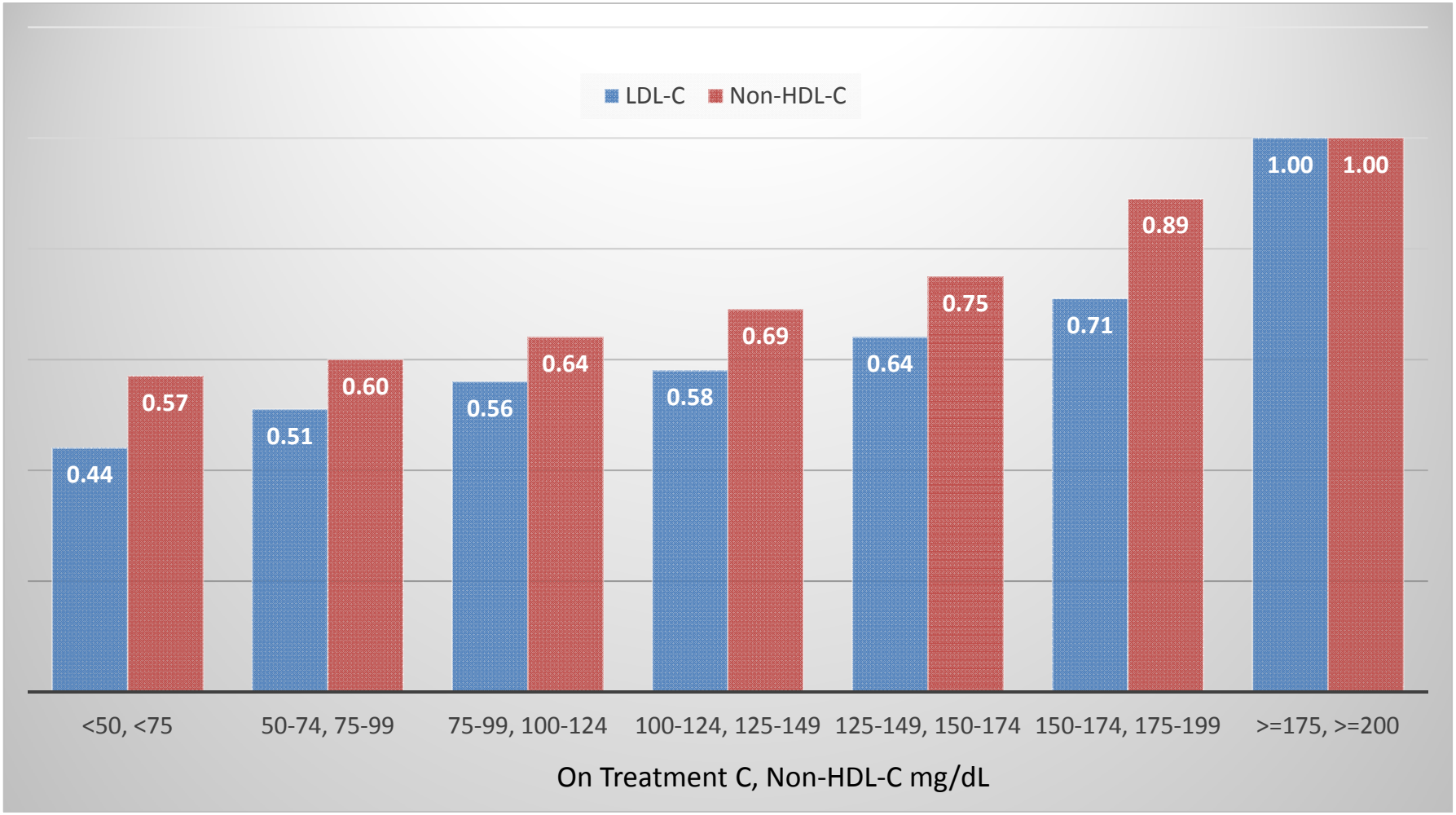
Data abstracted from original publications

Relationship Between LDL-C Levels and CHD Events in Secondary Prevention



Expert Dyslipidemia Panel of IAS. J Clin Lipidol. 2014;8:29-60.

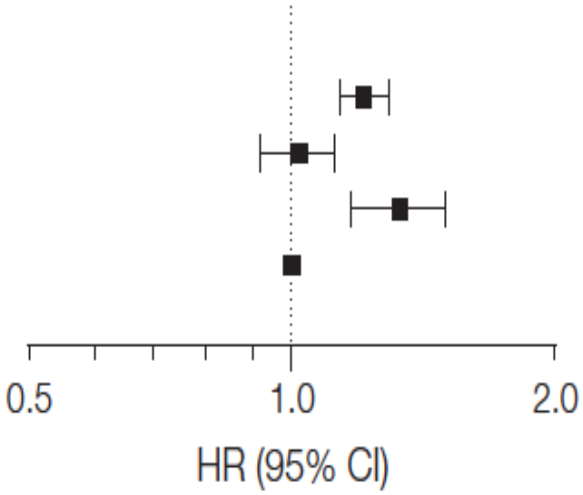
Very Low LDL-C and Non-HDL-C in Statin Trials and Major CVD Event Risk



Boekholdt et al. JACC 2014;64:485-494

Risk of Major Cardiovascular Events by LDL-C and Non-HDL-C Categories

Target Level		No. of Major Cardiovascular Events	Total No. of Participants	HR (95% CI)
LDL-C	Non–HDL-C			
≥100 mg/dL	≥130 mg/dL	1877	10 419	1.21 (1.13-1.29)
≥100 mg/dL	<130 mg/dL	467	2873	1.02 (0.92-1.12)
<100 mg/dL	≥130 mg/dL	283	1435	1.32 (1.17-1.50)
<100 mg/dL	<130 mg/dL	2760	23 426	1.00 [Reference]



Boekholdt SM, et al. JAMA. 2012;307:1302-1309.

ACC/AHA-Statin Therapy

- Recommendation: The appropriate intensity of statin therapy should be used to reduce ASCVD risk in those most likely to benefit:
  a) secondary prevention in individuals with clinical ASCVD,
  b) primary prevention in individuals with primary elevations of LDL-C ≥190 mg/dL,
  c) primary prevention in individuals with diabetes 40 to 75 years of age who have LDL-C 70 to 189 mg/dL, and
  d) primary prevention in individuals without diabetes and with estimated 10-year ASCVD risk ≥7.5%, 40 to 75 years of age who have LDL-C 70 to 189 mg/dL.
- Nonstatin therapies, as compared with statin therapy, do not provide acceptable ASCVD risk-reduction benefits relative to their potential for adverse effects in the routine prevention of ASCVD.

Stone NJ, et al. J Am Coll Cardiol. 2014;63 (25 Pt B):2889-2934.

NLA - Cholesterol-Lowering Drug Therapies

- Expert Panel Consensus View: Unless contraindicated, first-line drug therapy for treatment of elevated atherogenic cholesterol levels is a moderate or high intensity statin. Some patients have contraindications for, or intolerance to, statin therapy. For such patients, non-statin drug therapy may be considered. Non-statin drug classes for lipid management include cholesterol absorption inhibitors, bile acid sequestrants, fibric acids, long-chain omega-3 fatty acid concentrates, and nicotinic acid.
  - Therapy with a statin plus a second (or third) agent may be considered for patients who have not reached their treatment goals for atherogenic cholesterol levels, particularly in patients with high or very high risk.
  - The maximum tolerated statin dosage should generally be used before add-on therapy is considered.
  - Evidence from RCTs does not support the routine use of a second agent when atherogenic cholesterol levels are below goal thresholds while on statin therapy.

Jacobson TA, et al. J Clin Lipidol. 2014;in press.

Rationale for Non-Statin Drug Therapies

- Statins are not unique in their cholesterol-lowering effects, except in potency.
- Results from studies of non-statin approaches to cholesterol lowering suggest that the degree of risk reduction with statin therapy for a given reduction in atherogenic cholesterol is similar to that observed with other cholesterol-lowering interventions.

Jacobson TA, et al. J Clin Lipidol. 2014;in press.
Expert Dyslipidemia Panel of IAS. J Clin Lipidol. 2014;8:29-60.

Rationale for Non-Statin Drug Therapies - Continued

- Much of the available data for the effects of add-on therapy was in studies of administration to patients with relatively low levels of atherogenic cholesterol during statin treatment.
- Limited RCT evidence is available to guide therapy in the patient taking the highest tolerated dosage of a statin whose levels of atherogenic cholesterol remain above goal.
  - Until RCT data are available to better define the potential benefits and risks of add-on therapies in patients whose levels of atherogenic cholesterol remain elevated while taking the highest tolerated dosage of statin, the NLA Expert Panel recommends that consideration be given to use of combination therapy with agents that further lower non-HDL-C and LDL-C to achieve goal levels.

Jacobson TA, et al. J Clin Lipidol. 2014;in press.

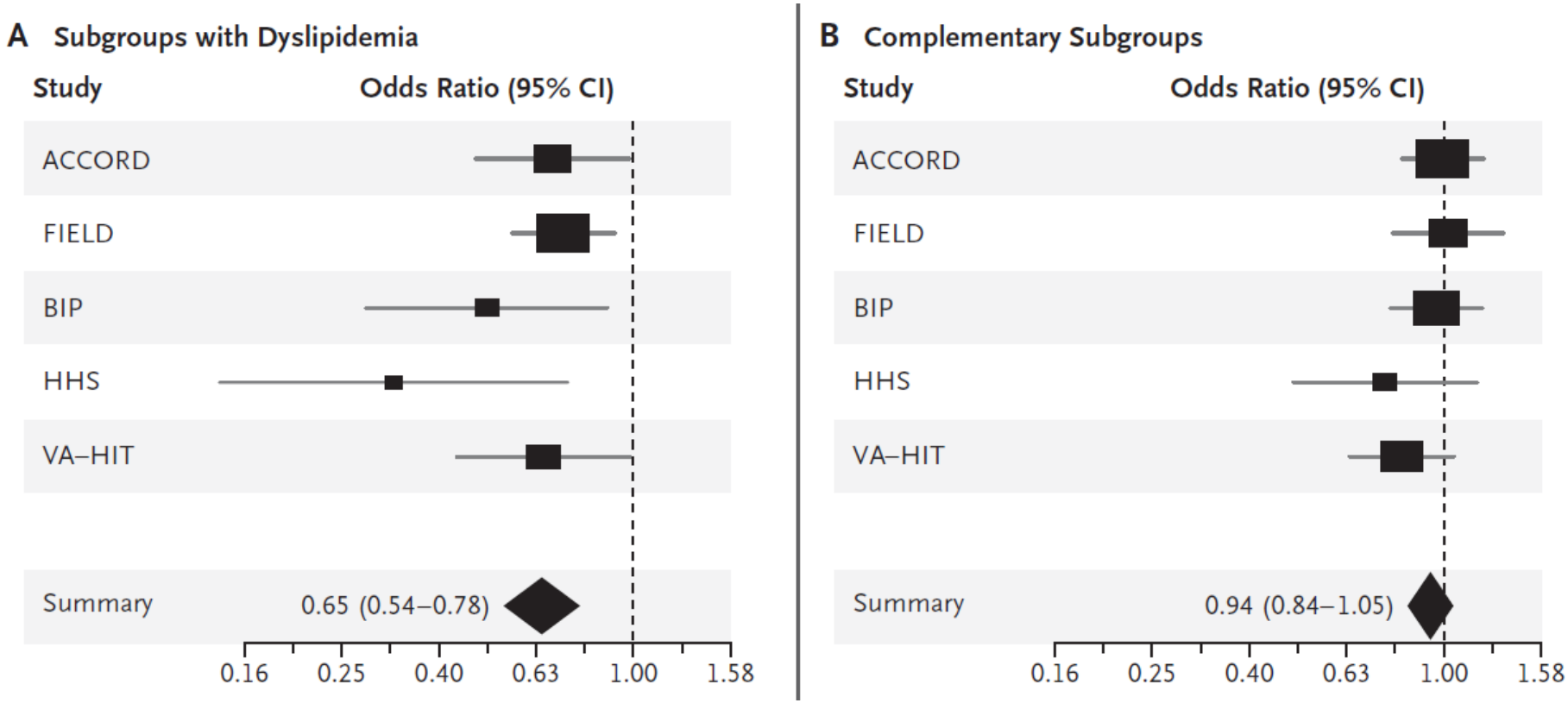
Baseline (On Statin) Mean or Median Atherogenic Cholesterol Levels in Studies of Add-On Therapy

Trial	LDL-C (mg/dL)	Non-HDL-C (mg/dL)
HPS2-THRIVE	64	89
AIM-HIGH	74	111
ACCORD*	101	137

*Median triglyceride concentration 162 mg/dL, top tertile ≥204 mg/dL

The HPS2-THRIVE Collaborative Group. N Engl J Med. 2014;371:203-212.
The AIM-HIGH Investigators. N Engl J Med. 2011;365:2255-2267.
The ACCORD Study Group. N Engl J Med. 2010;362:1563-1574.

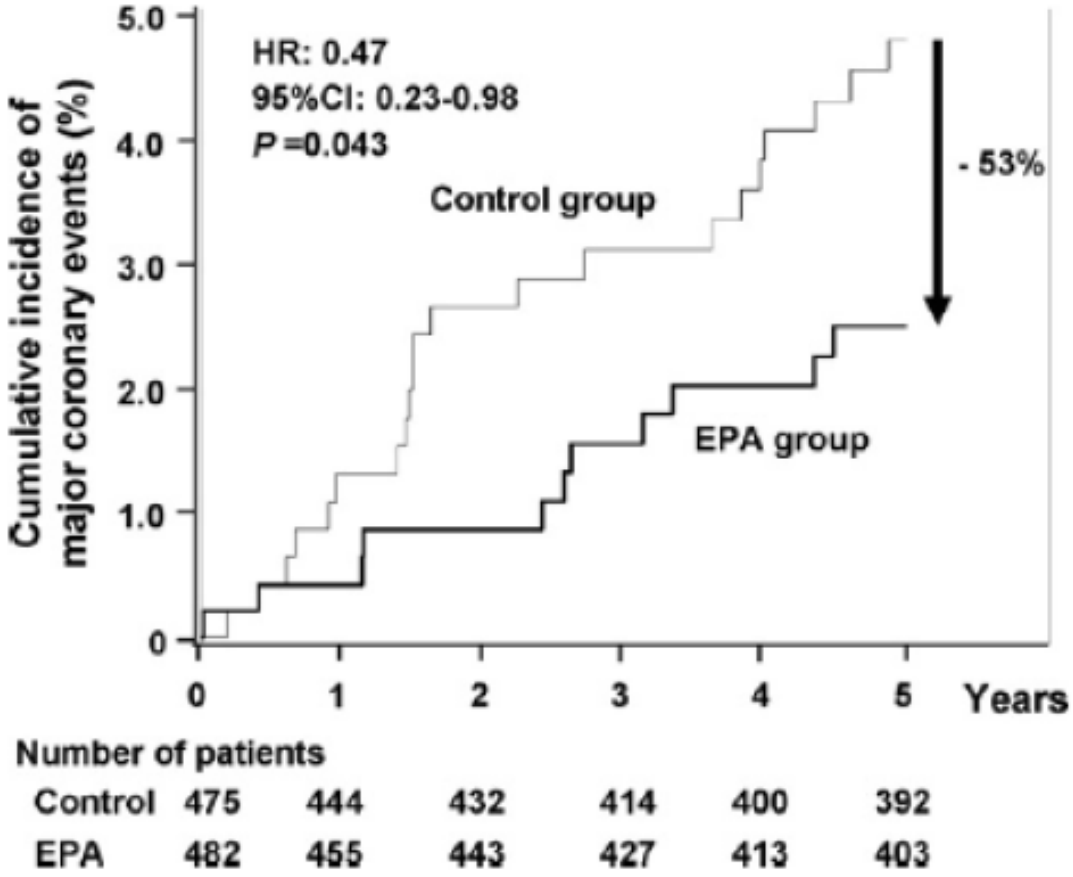
CHD Event Risk in Dyslipidemia Subgroups from Trials of Fibrates



Dyslipidemia subgroups: ACCORD, TG ≥204 mg/dL, HDL-C ≤34 mg/dL; FIELD, TG ≥204 mg/dL, HDL-C <40 mg/dL in men and <50 mg/dL in women; BIP, TG ≥200 mg/dL, HDL-C <35 mg/dL; HHS, TG ≥204 mg/dL, HDL-C <42 mg/dL; VA-HIT, TG >180 mg/dL, HDL-C <40 mg/dL.

Sacks FM, et al. N Engl J Med. 2010;363:692-5.

Japan EPA Lipid Intervention: Subgroup with TG ≥150 mg/dL, HDL-C <40 mg/dL



Saito Y, et al. Atherosclerosis. 2008;200:135-40.

Conclusions

- Commonalities and differences exist between the cholesterol management guidelines recently issued by the ACC/AHA and the recommendations of the NLA Expert Panel.
  - Differences largely reflect a greater willingness of the NLA Expert Panel to consider evidence beyond primary results from RCTs, and to apply expert opinion in areas where RCT evidence is incomplete, such as in the use of combination therapy for patients with elevated levels of atherogenic cholesterol despite maximally tolerated statin therapy.
  - Commonalities include the centrality of lifestyle therapies, use of statins as first-line pharmacotherapy, and a patient-centered approach in which patients and clinicians fully discuss the objectives and potential risks associated with the recommended therapies.

Hypertriglyceridemia awareness survey

National Lipid Association

July 2014

Purpose of the Survey

- Gauge the awareness and attitudes among health care practitioners regarding the risks of high triglycerides and treatment recommendations for hypertriglyceridemia management

- Leverage the learning from the survey to create a multifaceted national education campaign directed towards identified gaps in knowledge

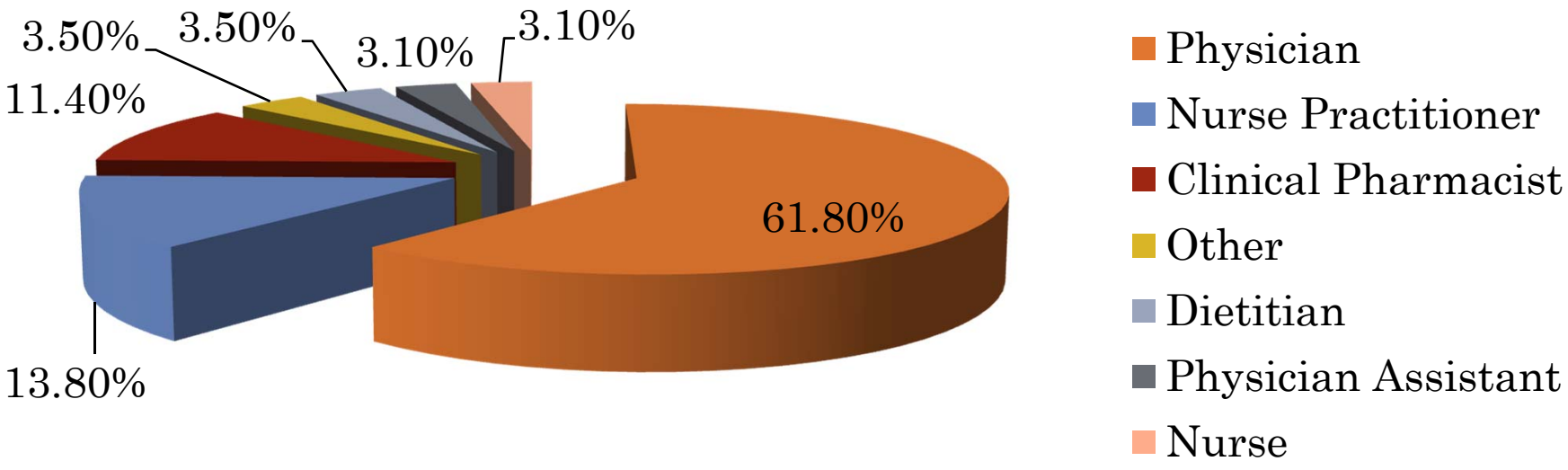
DEMOGRAPHICS OF THE SURVEY

- E-mailed x 4 to all NLA members (approximately 3200 providers)
- NLA staff sent motivational email to all board members in each region to encourage participation
- American College of Osteopathic Family Practitioners emailed the survey to members who utilize their e-newsletter (about 8000 providers)
- *Survey was open from June 6-22, 2014*
- confidential
- estimated completion time was about 10 minutes
- 21 content and 7 demographic questions
- *480 valid responses were obtained*

RESPONDERS

- Physicians, nurse practitioners, nurses and clinical pharmacists
- Majority from primary care and cardiovascular medicine
- 85% were NLA members
- 25% were certified by American Board of Clinical Lipidology
- Adequate geographic cross section

RESPONDENT DEMOGRAPHICS



Question topics

- Prevalence
- Etiology
- Basic pathophysiology
  - Primary
  - Secondary
- Treatment options
  - Lifestyle
  - pharmacotherapy

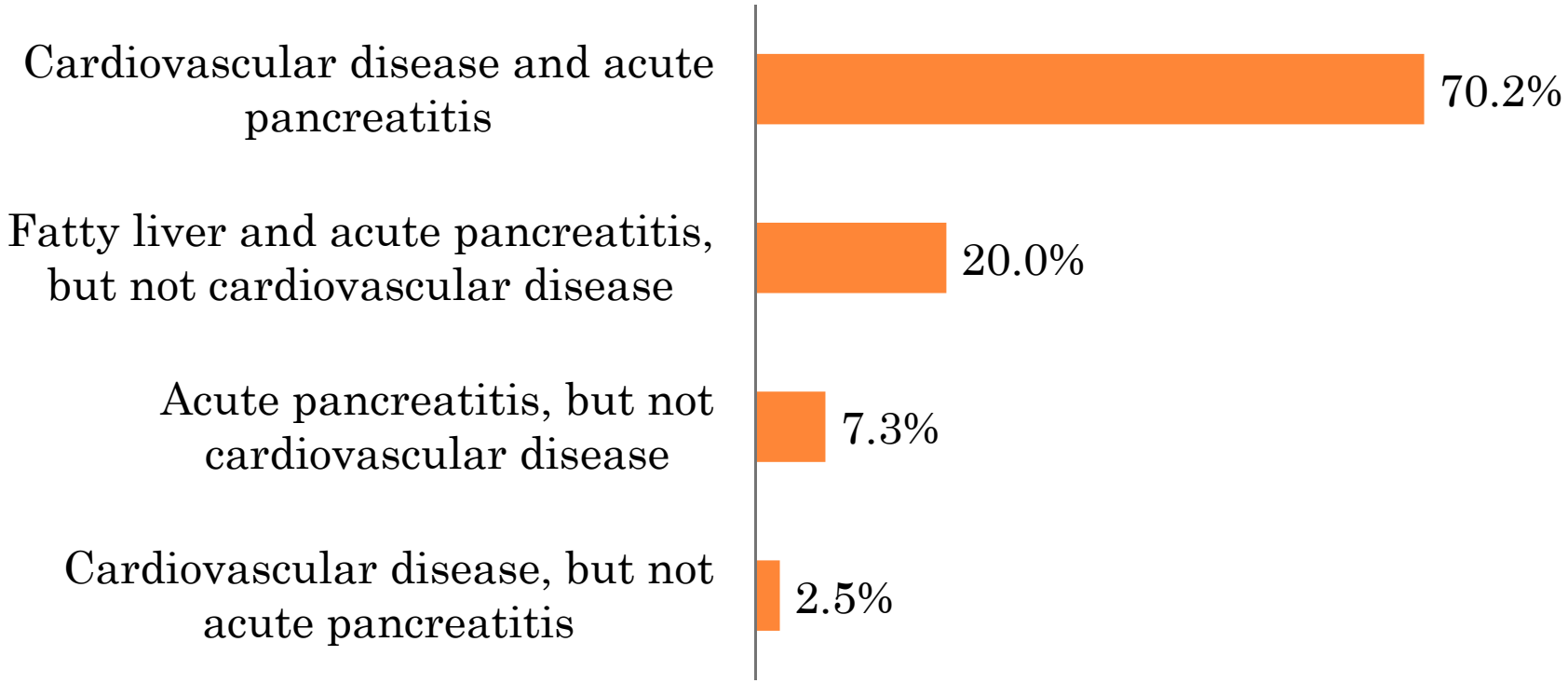
SURVEY REVIEW AND DATA ELEMENTS

ST. JOHN AND PARTNERS
JACKSONVILLE, FLA

Risks in patients with serum triglycerides >500 mg/dL include:

A. Cardiovascular disease and acute pancreatitis
B. Fatty liver and acute pancreatitis but not CV disease
C. Acute pancreatitis but not CV disease
D. CV disease but not acute pancreatitis




Cardiovascular disease and acute pancreatitis
70.2%
Fatty liver and acute pancreatitis, but not cardiovascular disease
20.0%
Acute pancreatitis, but not cardiovascular disease
7.3%
Cardiovascular disease, but not acute pancreatitis
2.5%

I BELIEVE THE MOST USEFUL MARKER OF CV RISK FROM ELEVATED SERUM TRIGLYCERIDES IS:

A. Non HDL-C

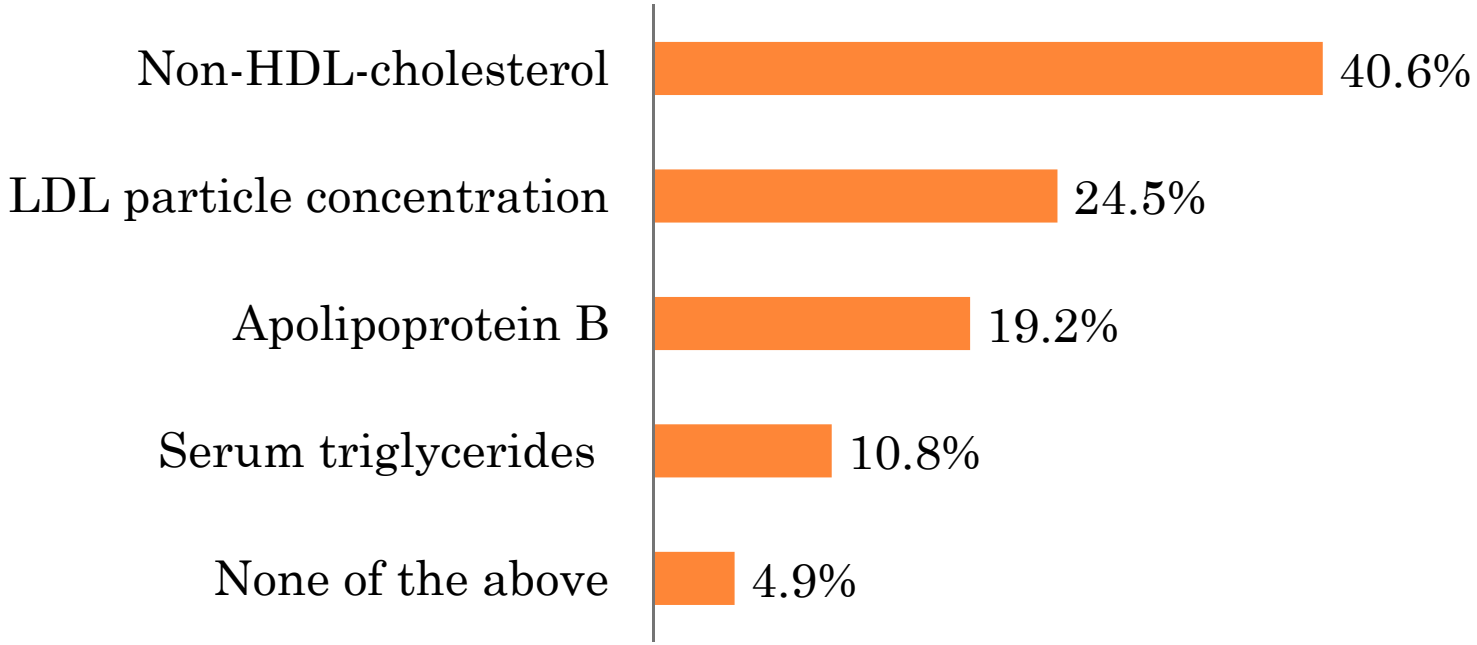
B. LDL-P

C. Apolipoprotein B

D. Serum triglycerides

E. None of the above




Non-HDL-cholesterol
40.6%
LDL particle concentration
24.5%
Apolipoprotein B
19.2%
Serum triglycerides
10.8%
None of the above
4.9%

WHICH OF THE FOLLOWING DO YOU CONSIDER TO BE THE MAIN IMPEDIMENT TO THE WIDESPREAD USE OF NON-HDL-C?

A. Clinicians do not know how to interpret the results

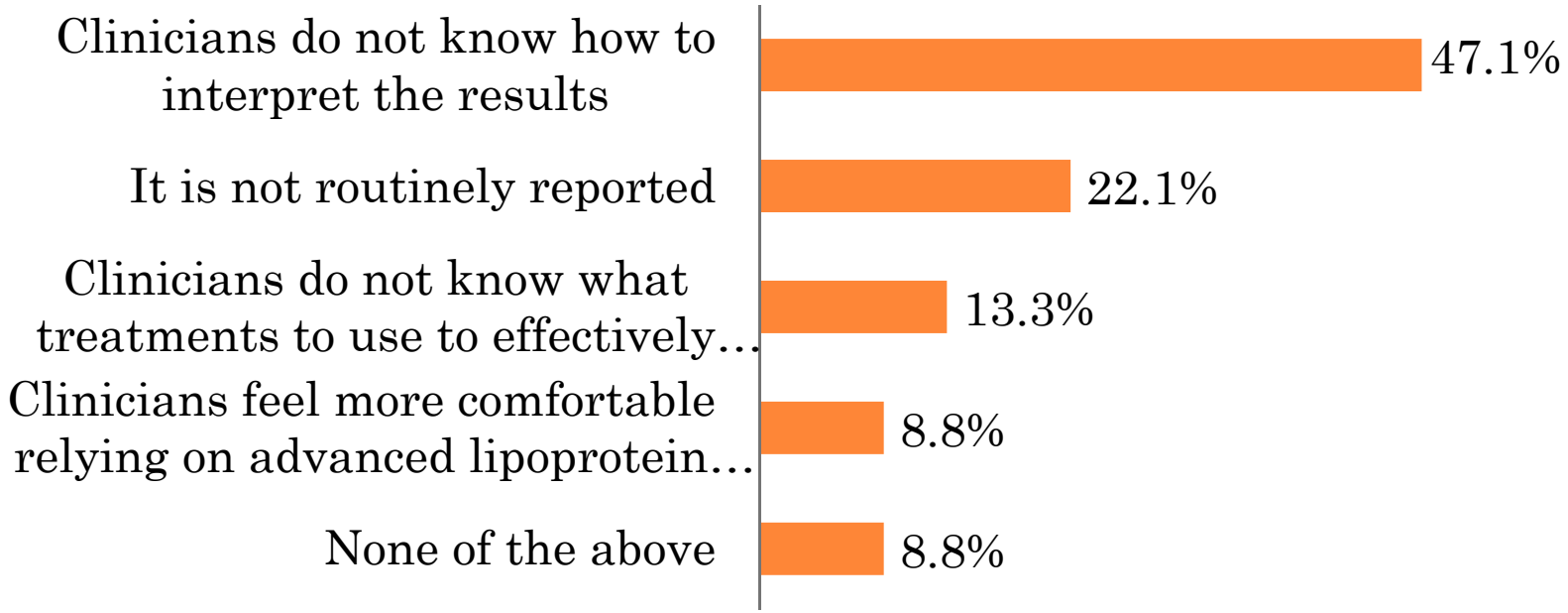
B. It is not routinely reported

C. Clinicians do not know what treatment to use to effectively lower non-HDL-C

D. Clinicians feel more comfortable relying on advanced lipoprotein testing, such as ApoB or LDL-P

E. None of the above




Clinicians do not know how to interpret the results
47.1%
It is not routinely reported
22.1%
Clinicians do not know what treatments to use to effectively…
13.3%
Clinicians feel more comfortable relying on advanced lipoprotein…
8.8%
None of the above
8.8%

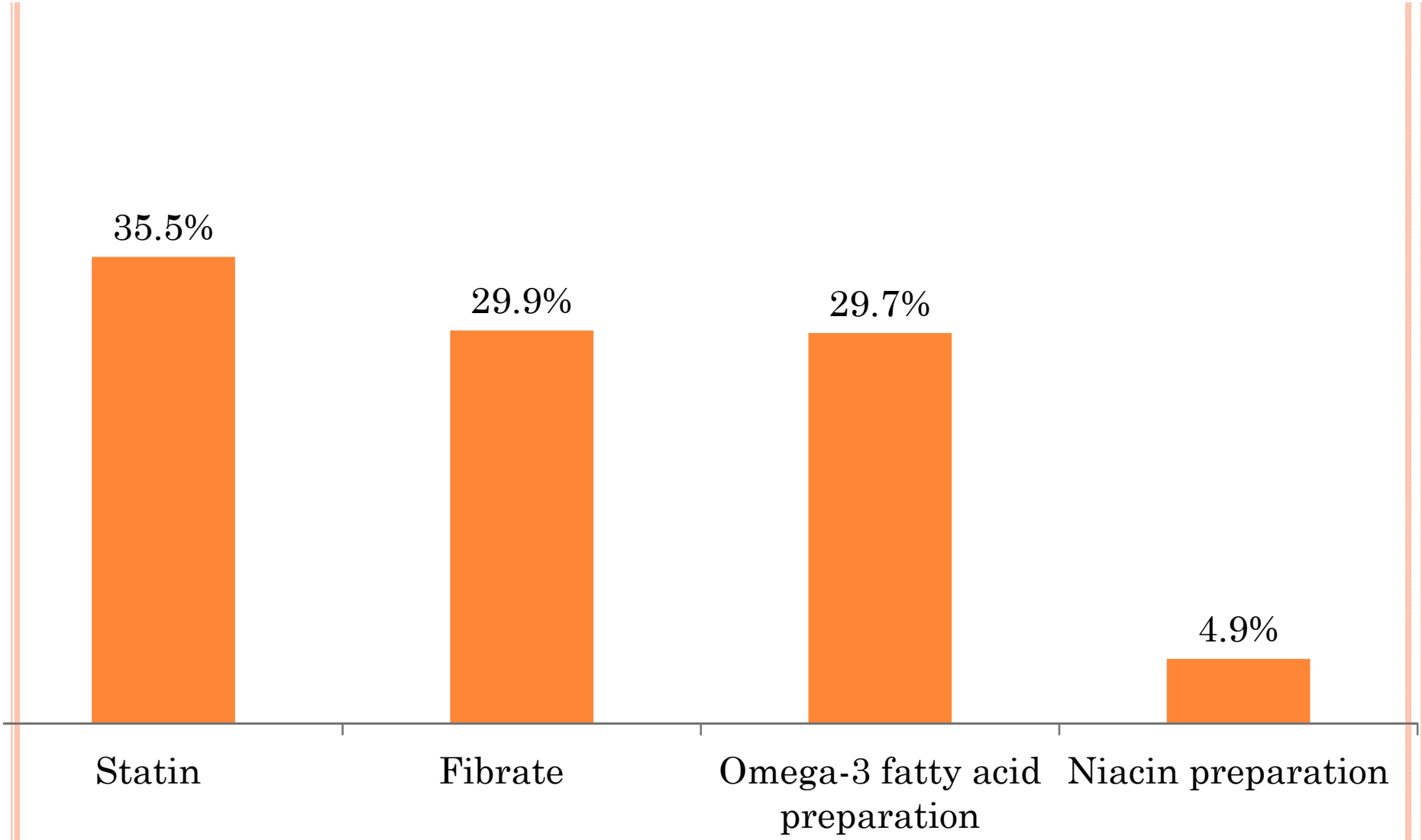
In patients with triglycerides between 200-499 mg/dL, ***after diet and lifestyle*** change, your first choice of lipid lowering medication is?

A. Statin

B. Fibrate

C. Omega III FA

D. Niacin


35.5%
29.9%
29.7%
4.9%
Statin
Fibrate
Omega-3 fatty acid preparation
Niacin preparation

IN PATIENTS WITH TRIGLYCERIDES BETWEEN 200-400 MG/DL FOR WHOM DRUG THERAPY IS WARRANTED, ***YOUR TREATMENT GOAL IS USUALLY BASED ON***:

A. Change in fasting TG

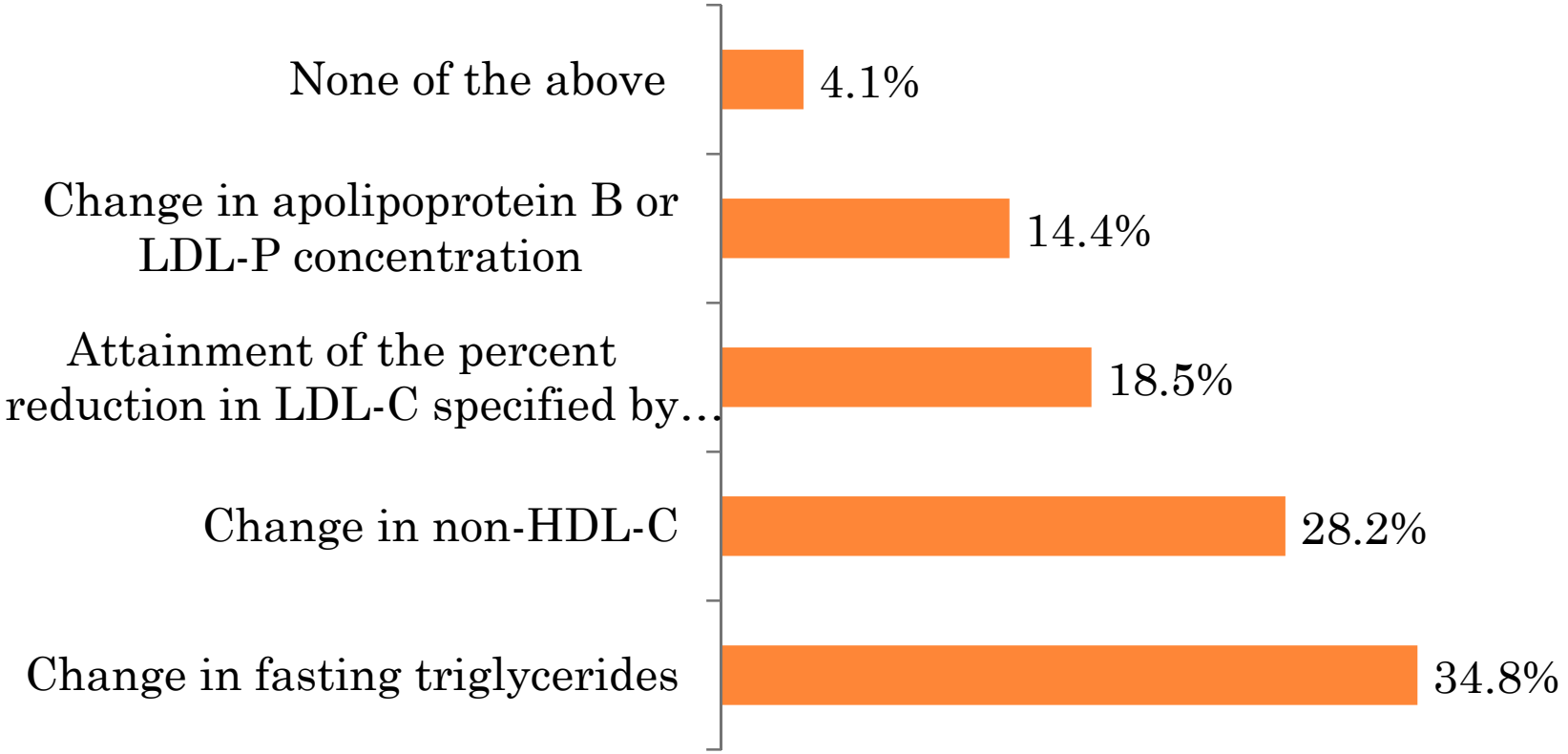
B. Change in non-HDL-C

C. Attainment of the percent reduction in LDL-C specified by the 2013 ACC/AHA guidelines

D. Change in apoB or LDL-P

E. None of the above

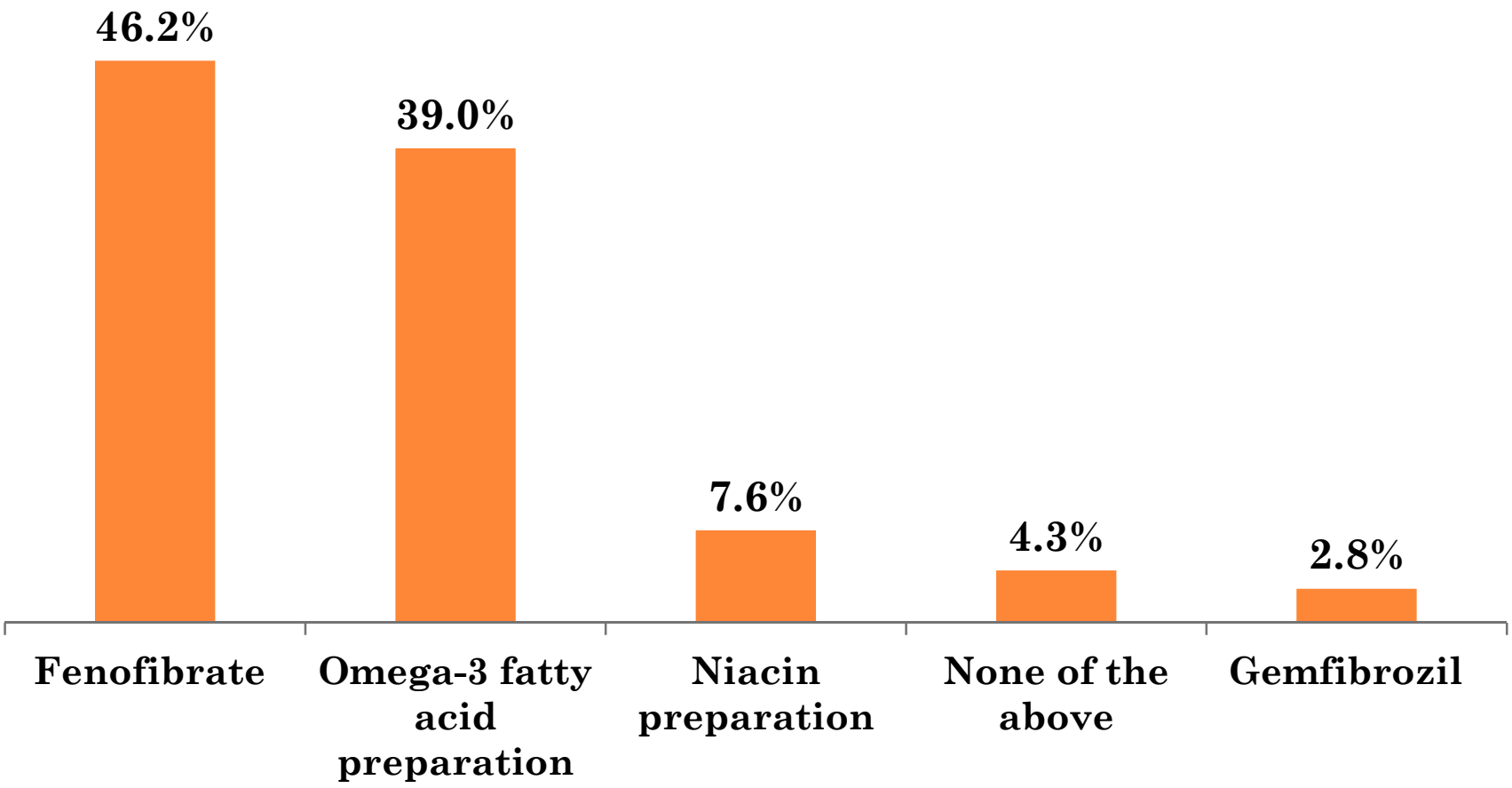



None of the above
4.1%
Change in apolipoprotein B or LDL-P concentration
14.4%
Attainment of the percent reduction in LDL-C specified by…
18.5%
Change in non-HDL-C
28.2%
Change in fasting triglycerides
34.8%

When adding medication to treat triglycerides between 200-499 mg/dL in a patient already on a statin, your most frequent choice of a lipid lowering medication is:

A. Fenofibrate
B. Gemfibrozil
C. Niacin preparation
D. Omega III FA
E. None of the above




46.2%
39.0%
7.6%
4.3%
2.8%
Fenofibrate
Omega-3 fatty acid preparation
Niacin preparation
None of the above
Gemfibrozil

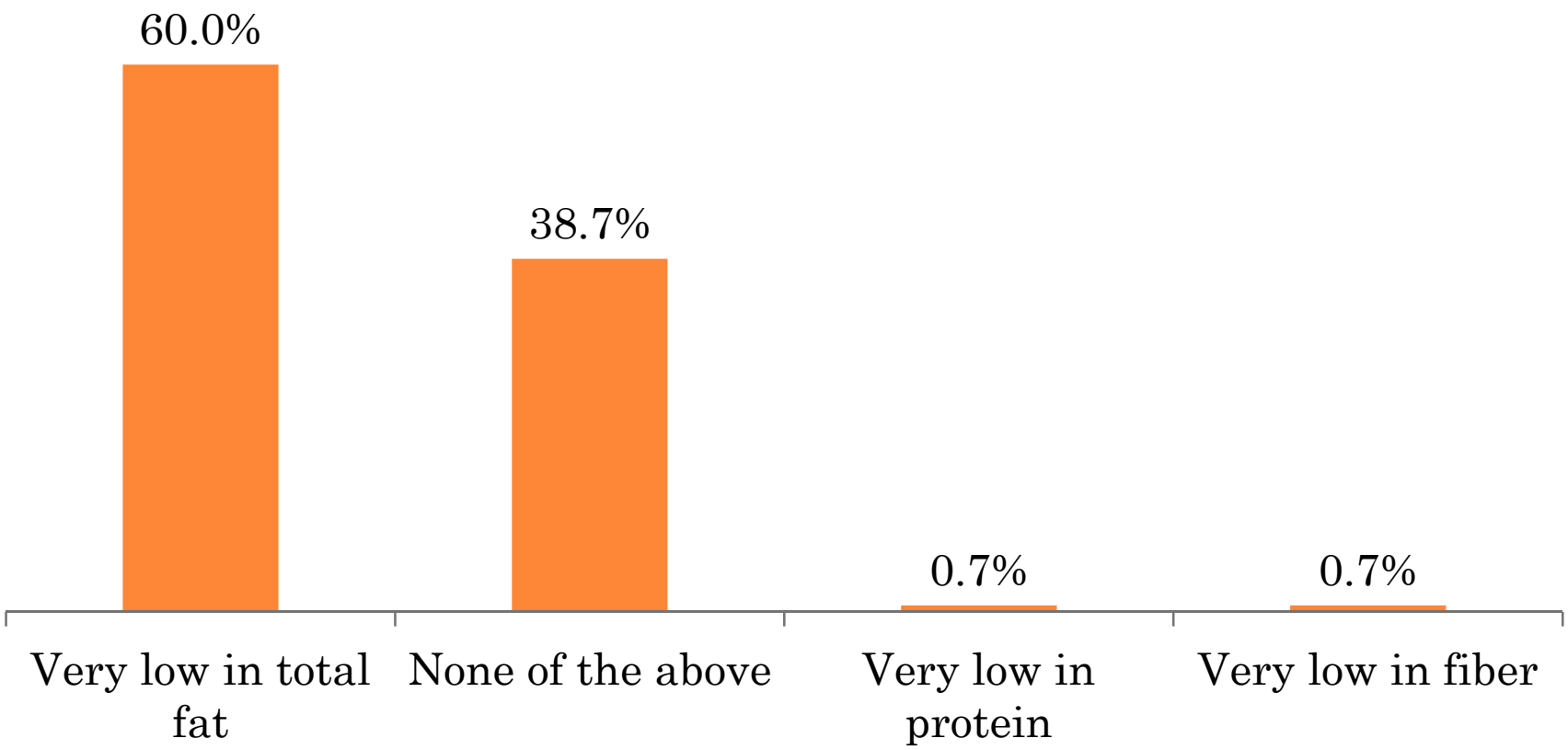
The diet strategy you recommend for most patients with triglycerides >1000 mg/dL is:

A. Very low in protein

B. Very low in total fat

C. Very low in fiber

D. None of the above


60.0%
38.7%
0.7%
0.7%
Very low in total fat
None of the above
Very low in protein
Very low in fiber

EDUCATIONAL OPPORTUNITIES

- 30% respondents were unclear on combined risks of cardiovascular disease ***and*** pancreatitis for patients with TG≥500 mg/dl
- Lack of clarity regarding the most useful marker for CV risk in patients with hypertriglyceridemia
- Omega-3 fatty acid concentrates are not FDA approved for treatment of TG 200-499 mg/dL and yet was frequently the selected medication for such patients
- Non-HDL-C is not uniformly used for risk assessment and setting treatment goals for hypertriglyceridemic patients.
- Dietary recommendations for patients with very high TG are inconsistent.

Next steps

- Provider Educational Goals
  - Promote awareness of HTG risks
  - Clarify best practice for multidisciplinary treatment protocols
- Consumer Educational Goals directed towards the significance of high triglycerides, and lifestyle interventions which are important



Are Triglycerides a Cardiovascular Risk Factor?

Christie M. Ballantyne, MD

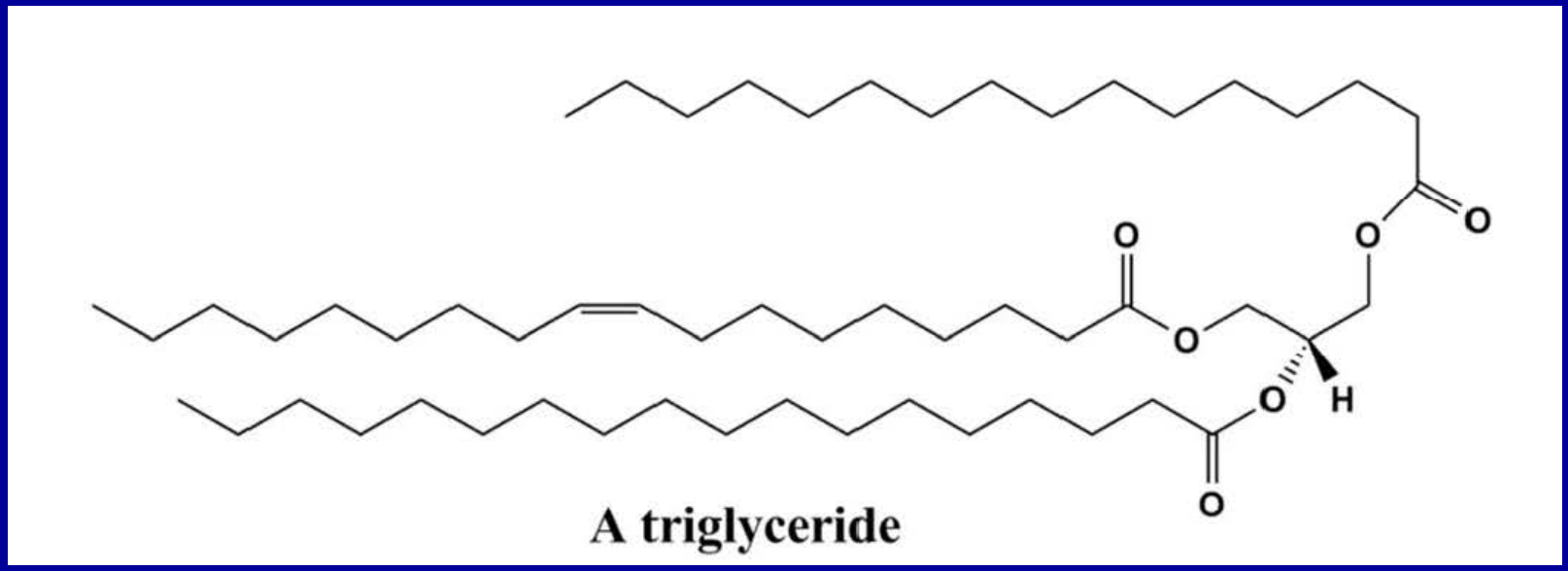
Center for Cardiovascular Disease Prevention
Houston Methodist DeBakey Heart & Vascular Center

Baylor College of Medicine
Houston, Texas

Baylor College of Medicine

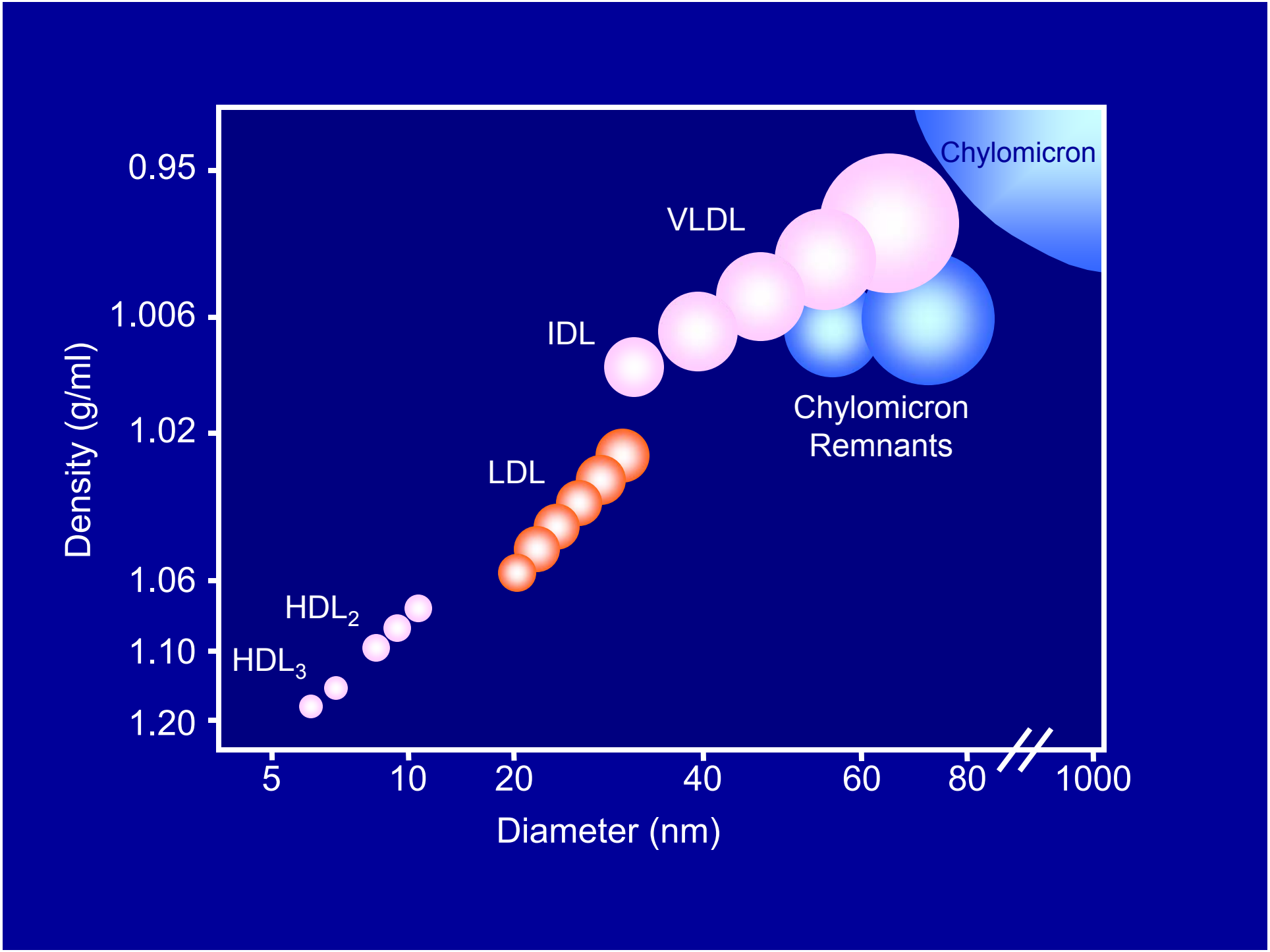
Methodist DeBakey Heart & Vascular Center

Triglyceride



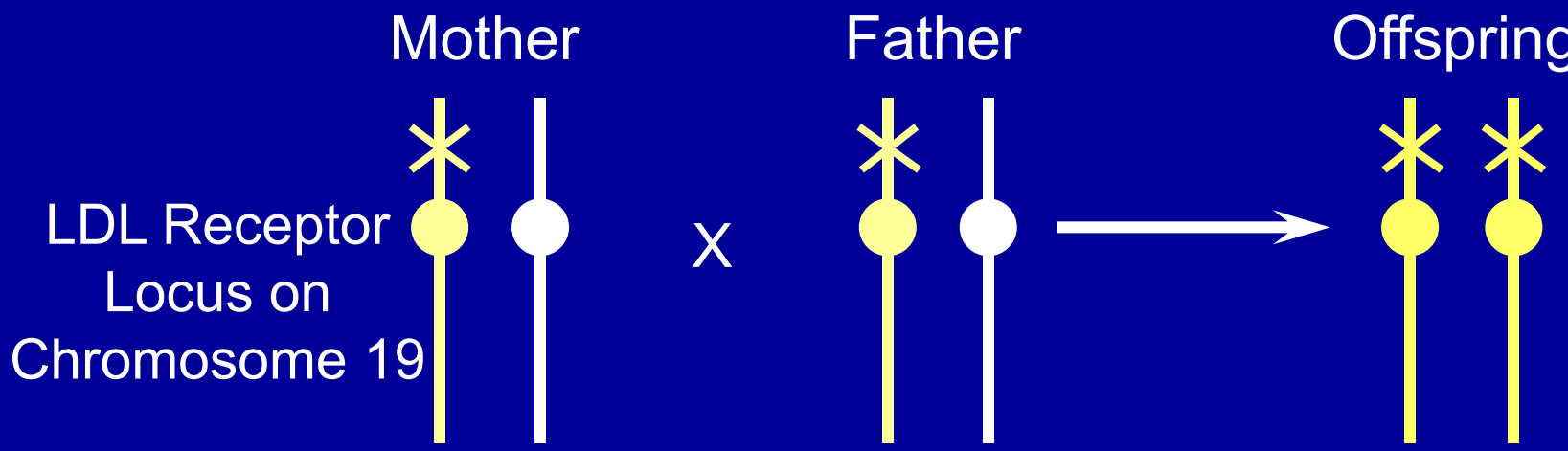
A triglyceride

Is Cholesterol a Cardiovascular Risk Factor?


Chylomicron
VLDL
IDL
LDL
Chylomicron
Remnants
HDL2
HDL3
0.95
1.006
1.02
1.06
1.10
1.20
Density (g/ml)
5
10
20
40
60
80
1000
Diameter (nm)



Familial Hypercholesterolemia (FH)



FH Heterozygotes

1 in 500 in Population
Half-Normal Number of LDL Receptors
2-Fold Increase in Plasma LDL
Heart Attacks Begin at Age 35
5% of All Heart Attacks Under Age 60

FH Homozygote

1 in 1 million in Population
Few or No LDL Receptors
6-Fold Increase in Plasma LDL
Heart Attacks in Childhood



Clinical Findings in Chylomicronemia Syndrome

Recurrent acute pancreatitis

Eruptive xanthomas

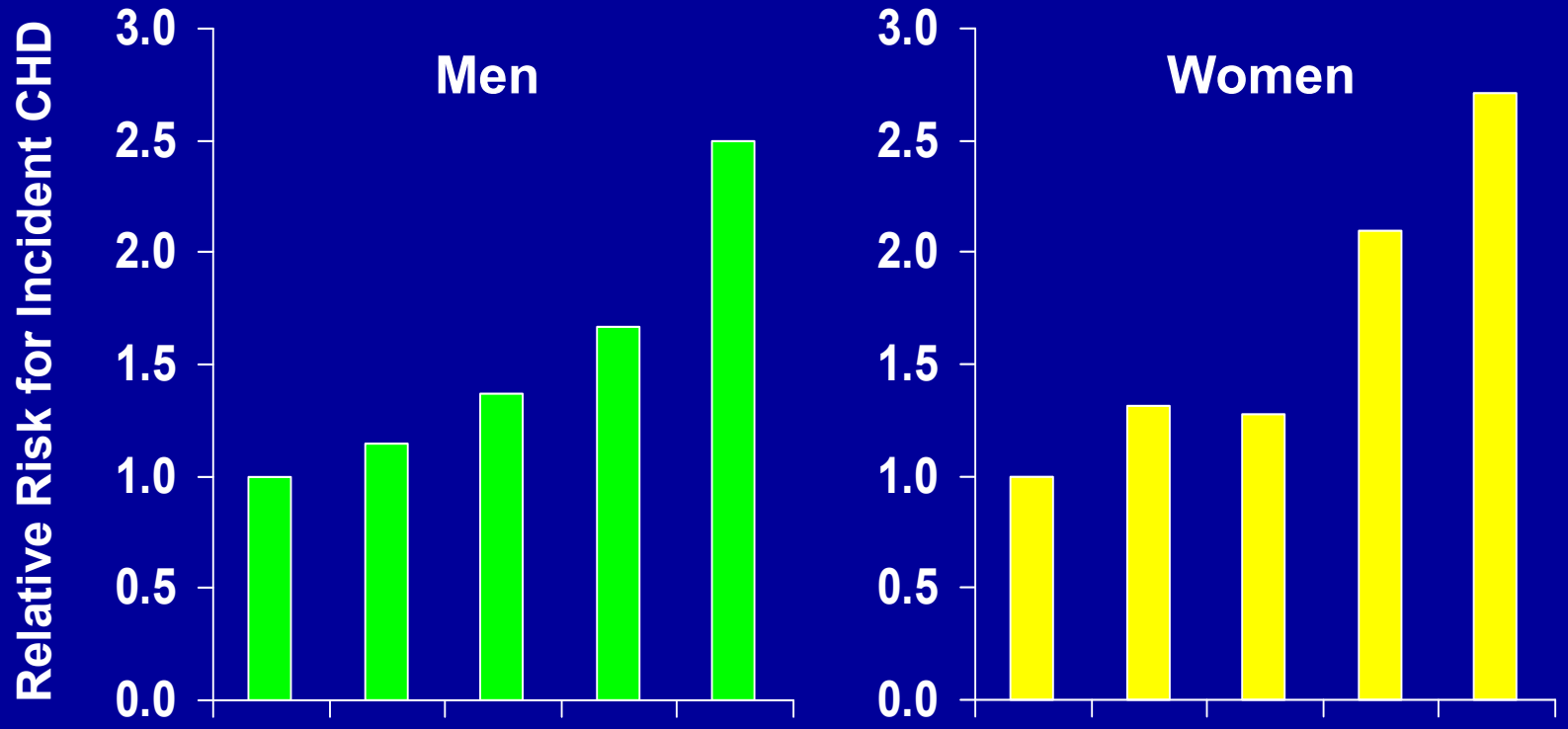
Retinal lipemia

Hepatosplenomegaly

Autosomal recessive inheritance (consanguinity common)

What is the Optimal LDL-C?

ARIC



LDL-C Quintiles	1	2	3	4	5
mmol/L	2.45	3.10	3.55	4.04	4.78
mg/dl	95	120	137	156	185
(median)					

	1	2	3	4	5
	2.27	2.93	3.40	3.94	4.84
	88	113	131	152	187

Adjusted for age and race, 12-year follow-up; N=12,339

Sharrett AR et al. *Circulation* 2001;104:1108-1113.

Predictors of CHD Events in the ARIC Study

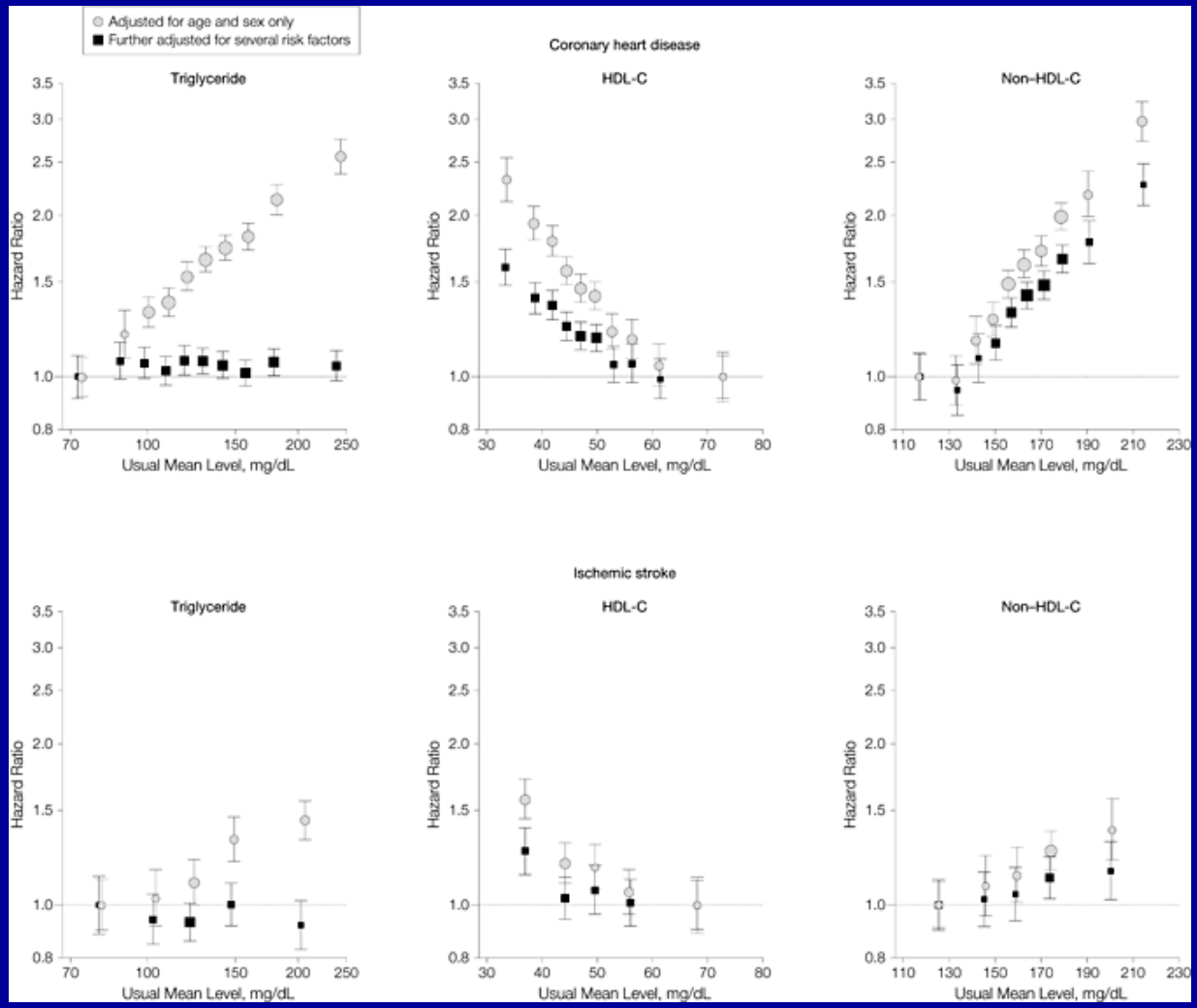
In 10-year follow-up of 12,339 men and women without CHD:

Multivariate predictors

LDL-C	HDL-C
Lp(a)	TG (in women only)

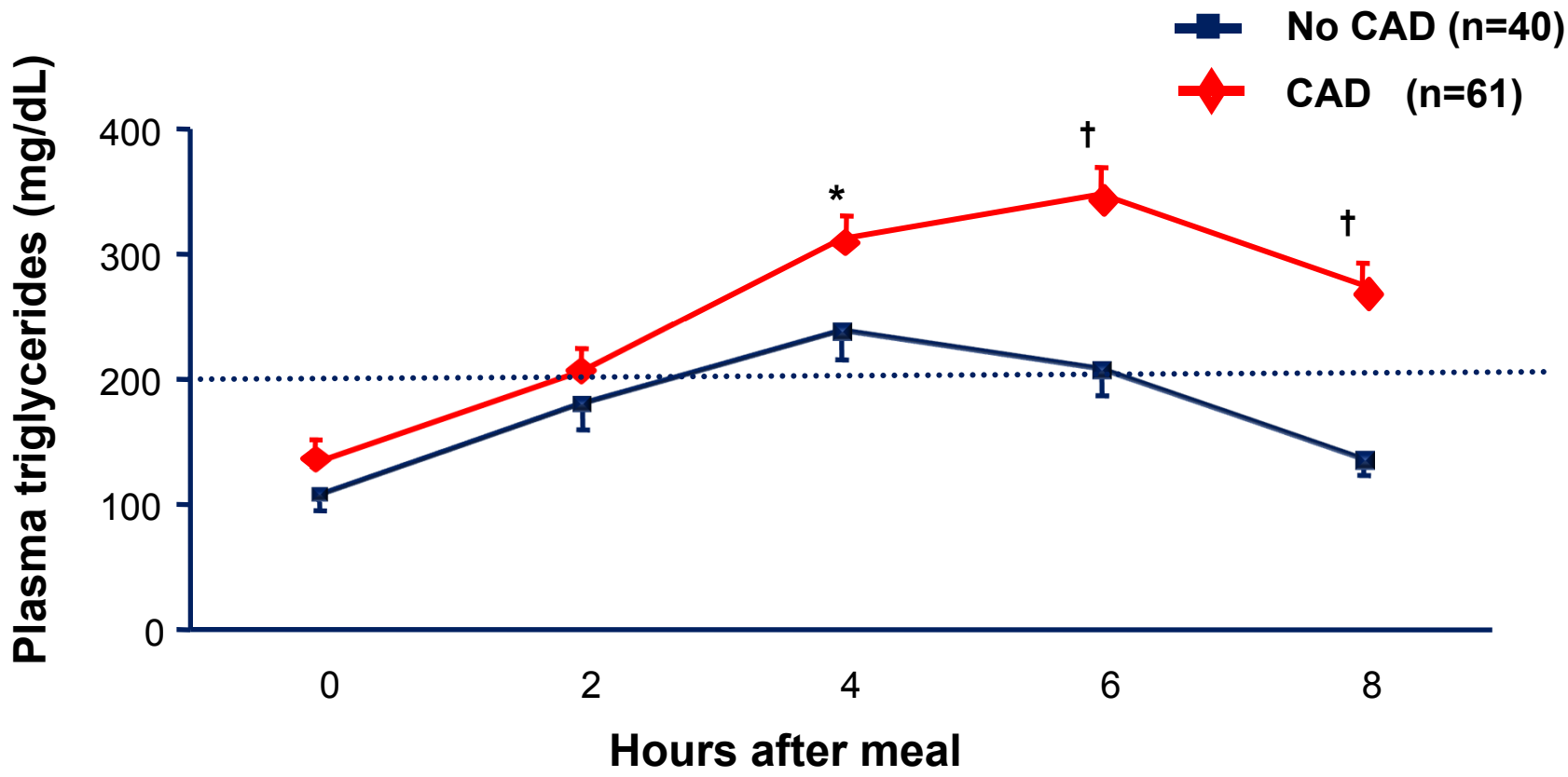
Sharrett AR et al. *Circulation* 2001;104:1108–1113.

Hazard Ratios for CHD or Ischemic Stroke Across Quantiles of Usual Triglyceride, HDL-C, and Non-HDL-C Levels



Emerging Risk Factors Collaboration. JAMA 2009;302:1993–2000.

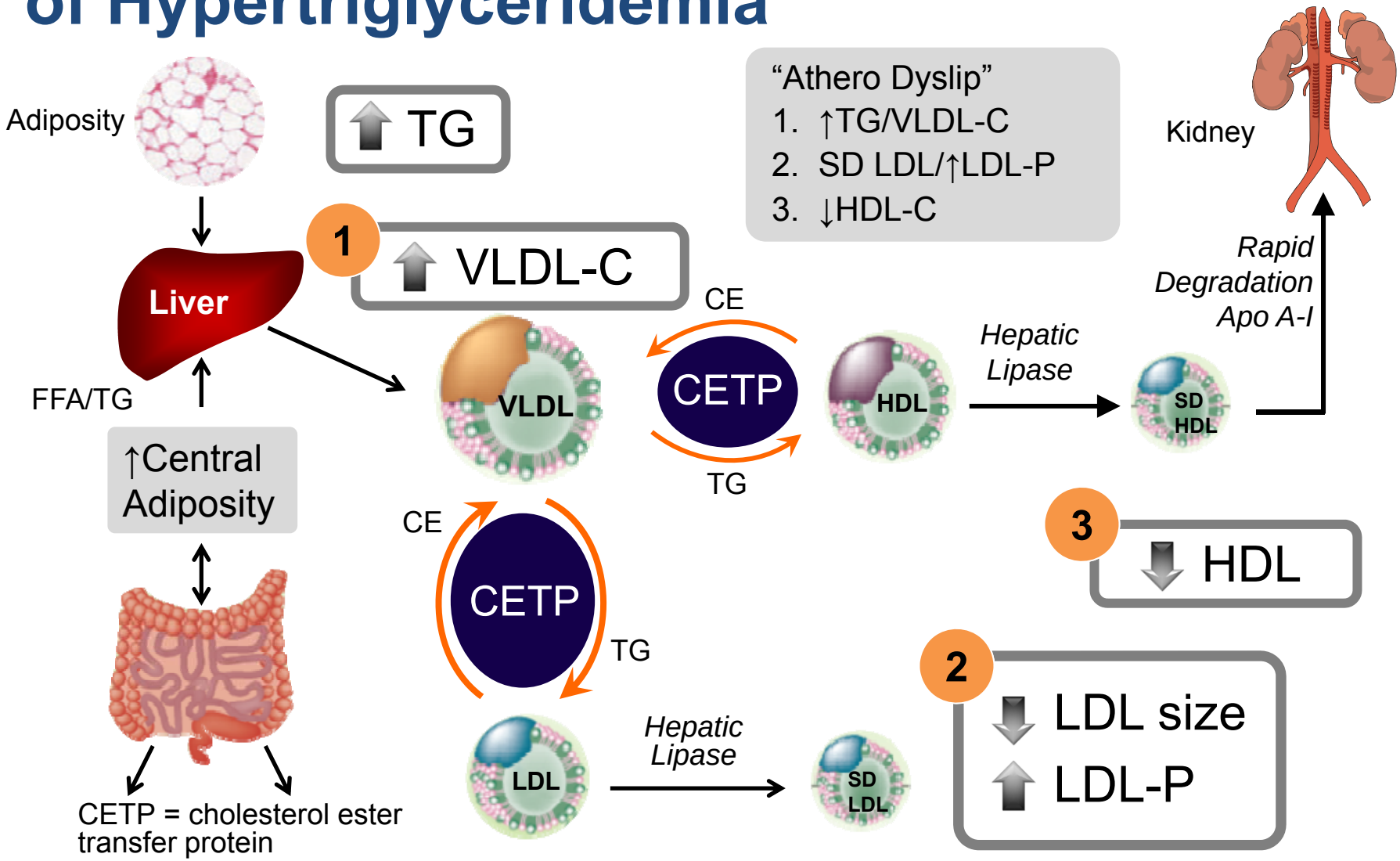
Postprandial Triglyceride Levels in Subjects with and without Coronary Artery Disease (CAD)



*P=0.025; †P≤0.001.

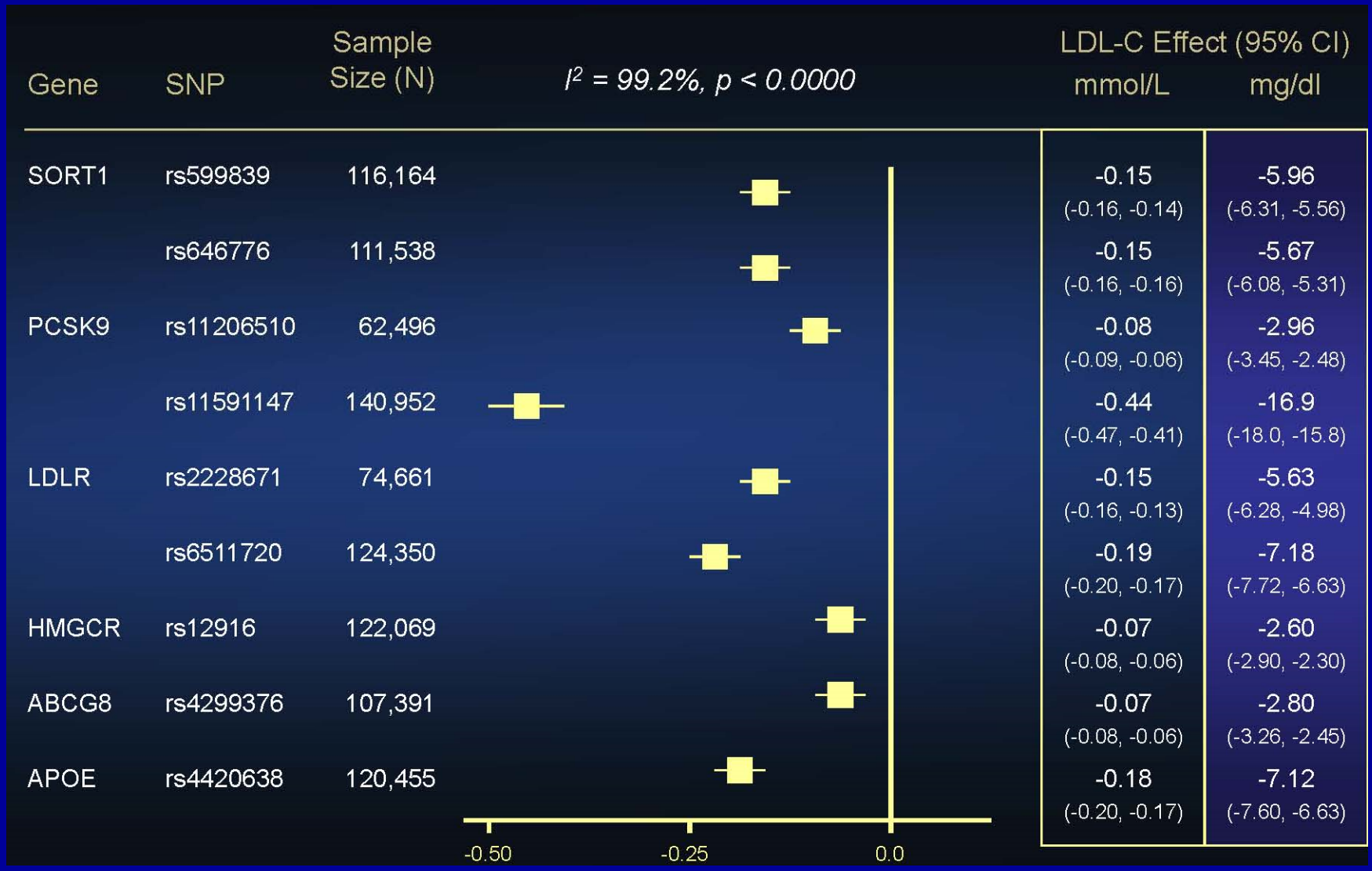
Patsch JR et al. *Arterioscler Thromb*. 1992;12:1336-45.

Three Atherogenic Consequences of Hypertriglyceridemia



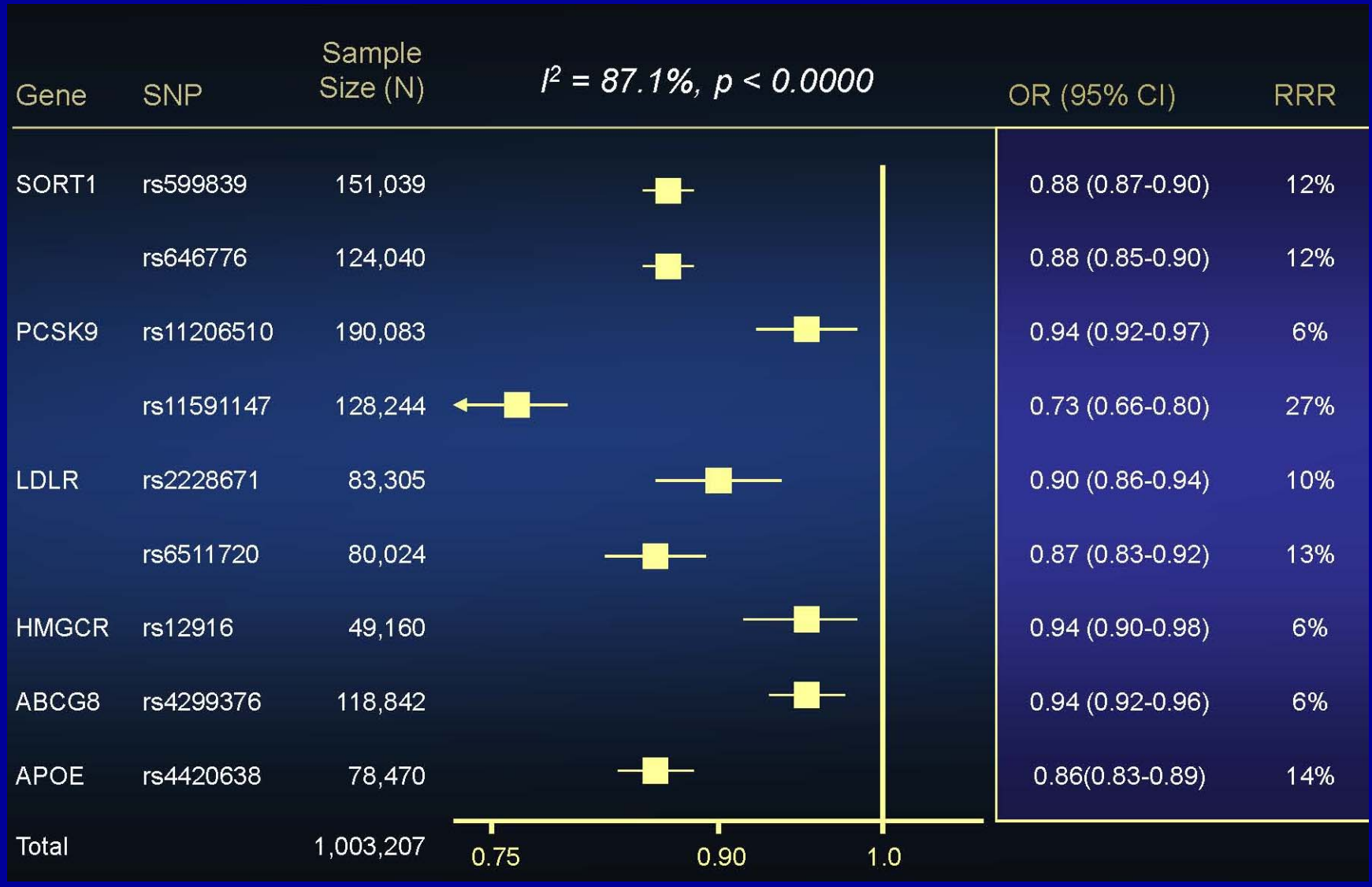
Also, ↑VLDL synthesis is assoc. w/ ↑ plasma Apo B

Associations with LDL-C



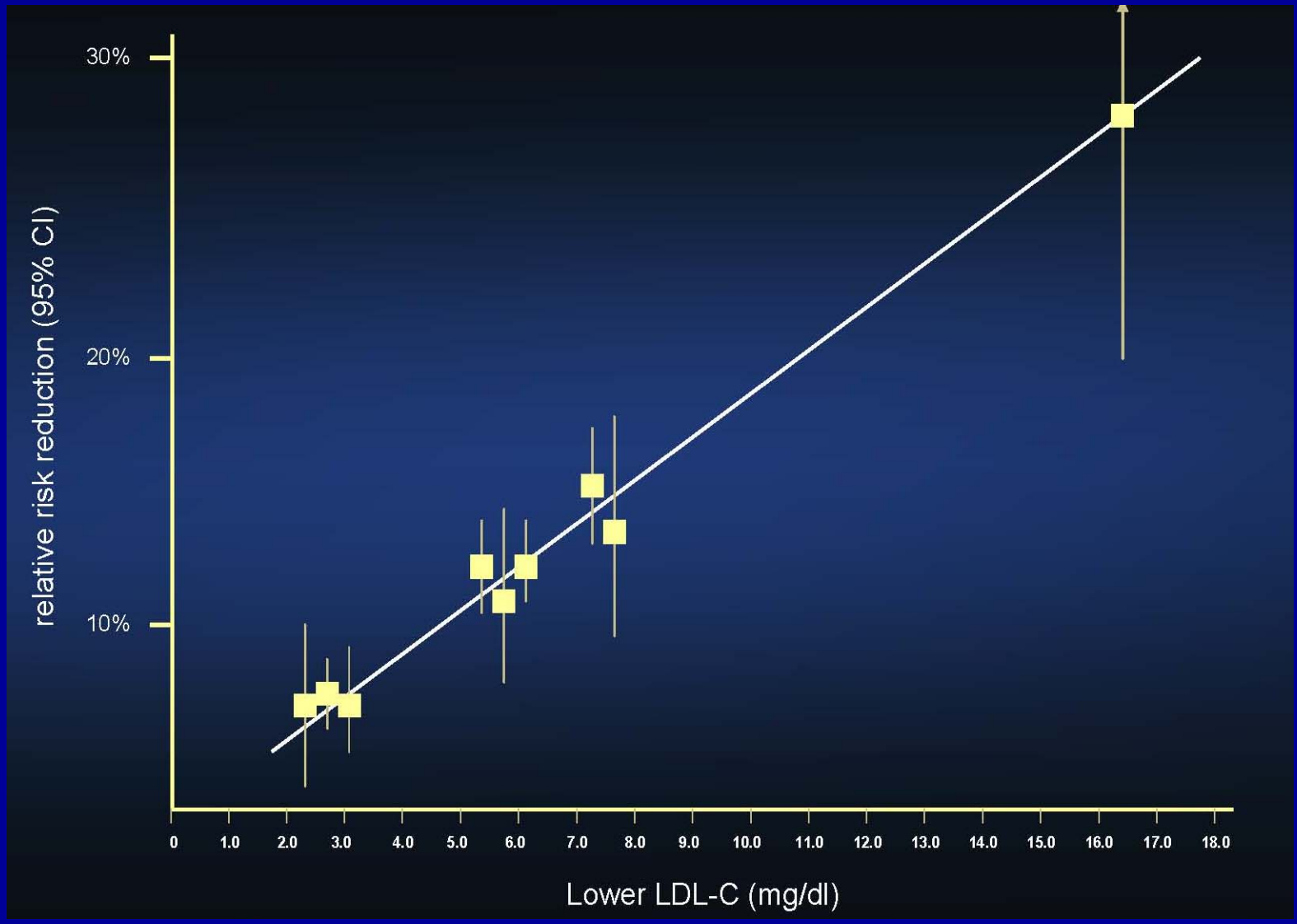
Ference BA et al. J Am Coll Cardiol. 2012;60:2631-9

Associations with CHD



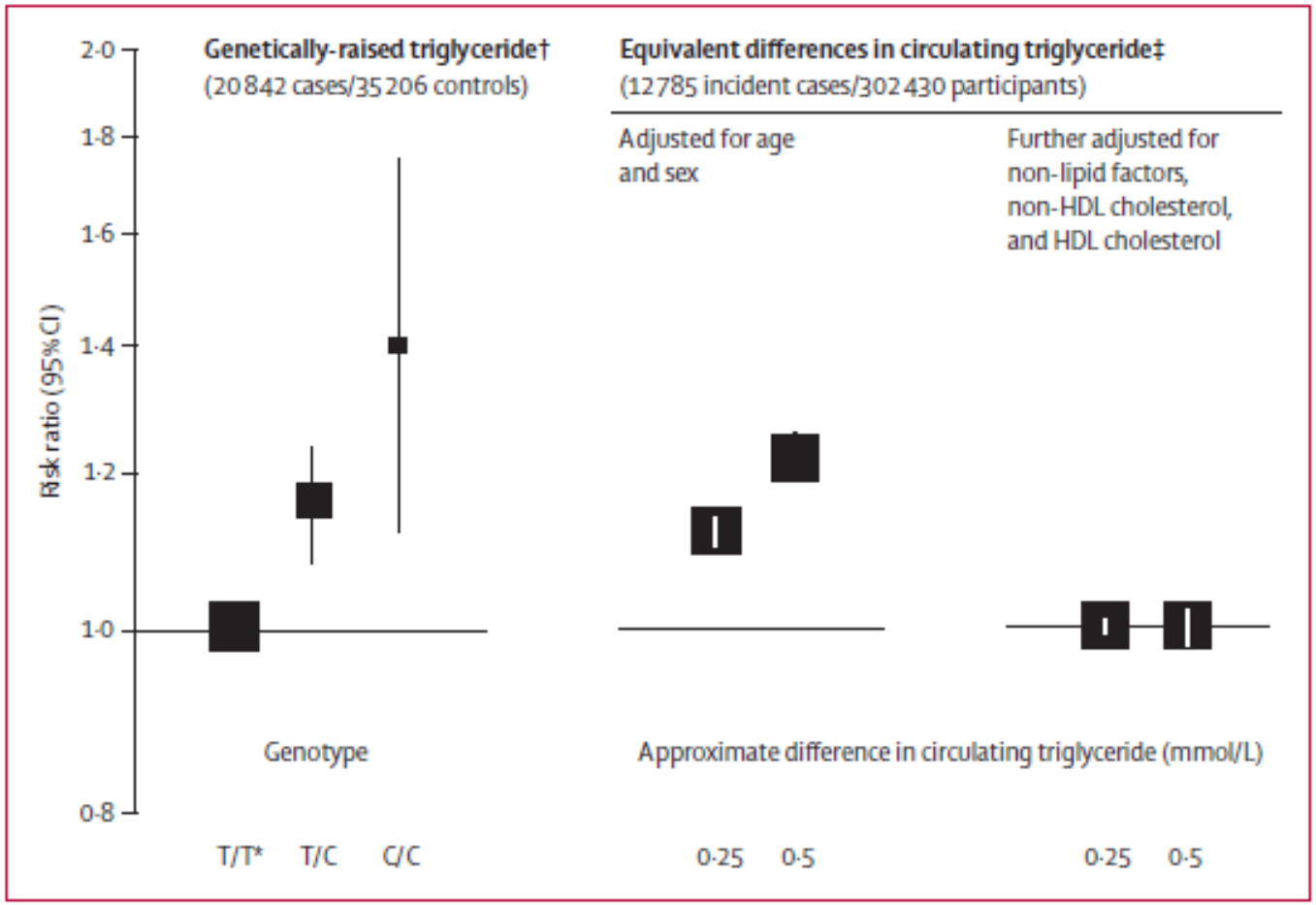
Ference BA et al. J Am Coll Cardiol. 2012;60:2631-9

Linear Effect on CHD (per unit lower LDL-C)



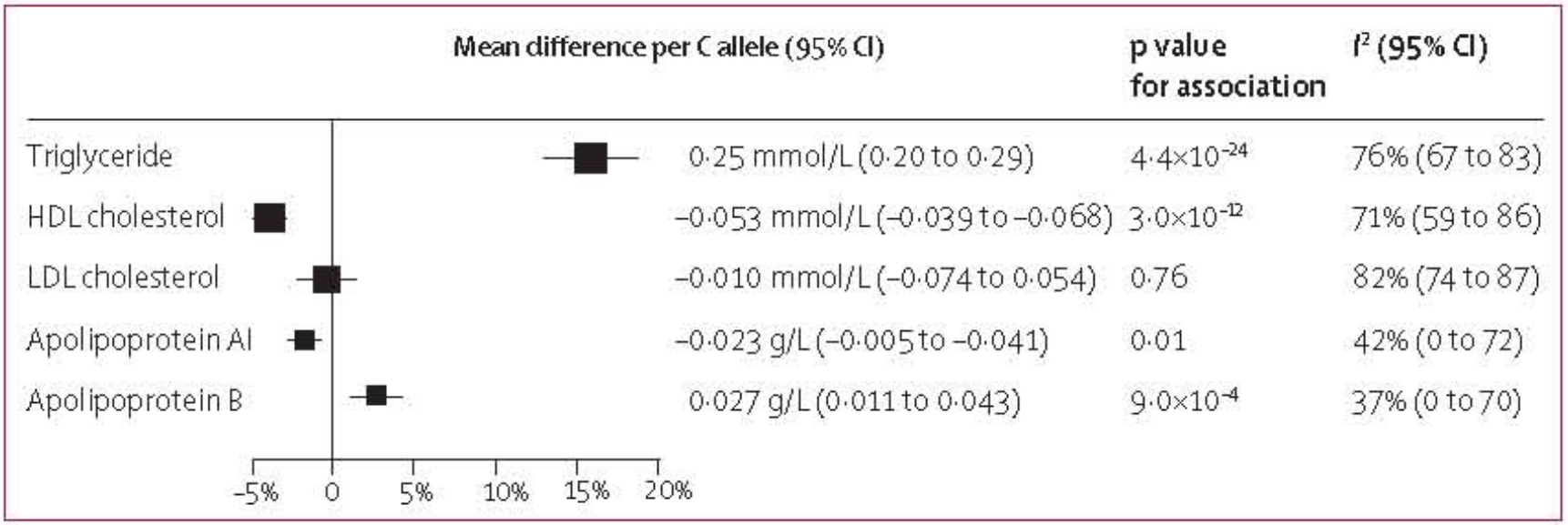
Ference BA et al. J Am Coll Cardiol. 2012;60:2631-9

Association of *APOA5* –1131T>C genotypes and equivalent differences in circulating TG concentration with risk of CHD



Sarwar N et al. *Lancet*. 2010;375(9726):1634-1639.

Association of *APOA5* –1131T>C with circulating lipid concentration per C allele



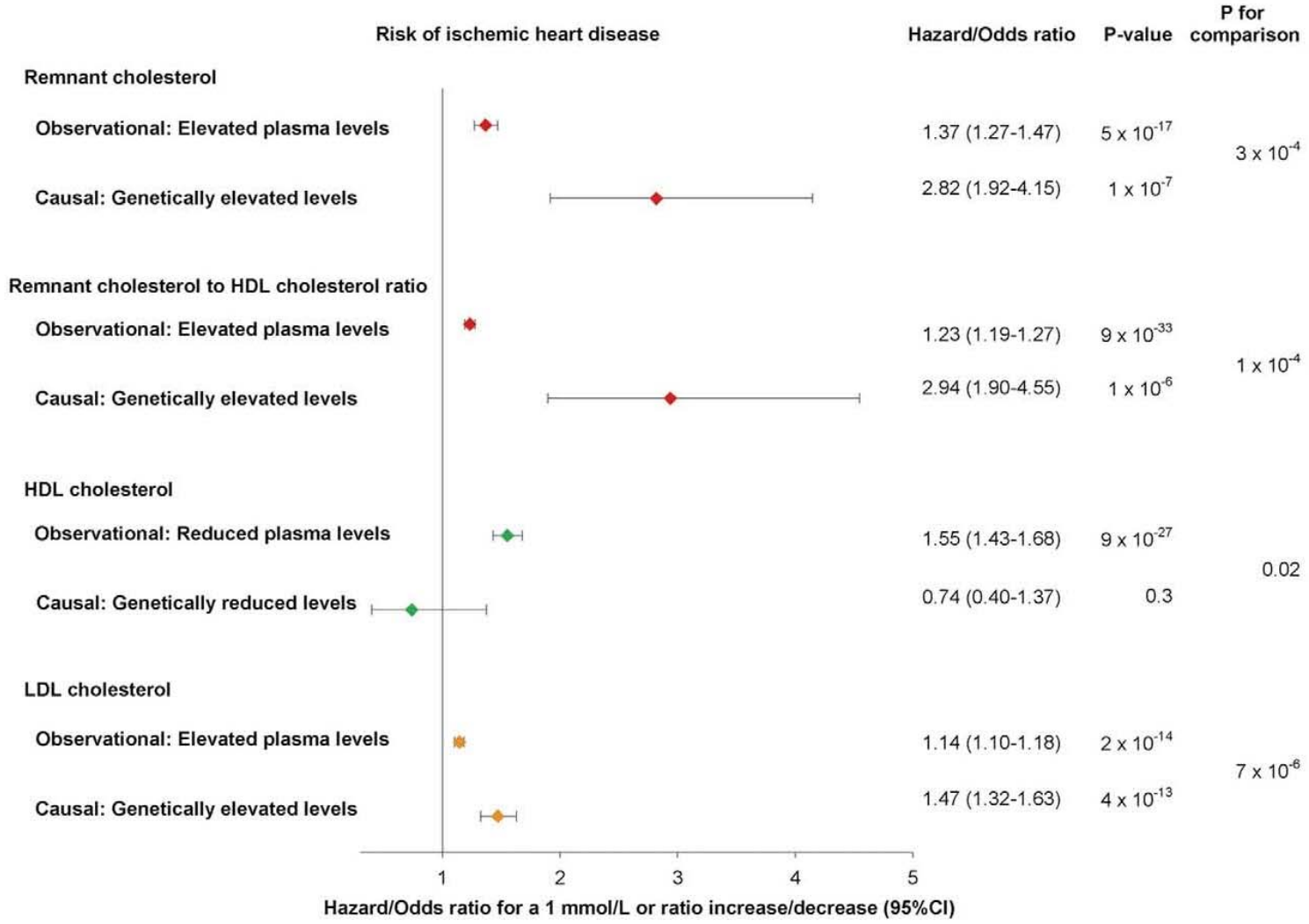
Sarwar N et al. *Lancet*. 2010;375(9726):1634-1639.

TG-mediated pathways and coronary disease: collaborative analysis of 101 studies examining *APOA5* variants—Summary

- Regulatory variant (1131T>C) strongly associated with increased TG levels (16% per allele)
- Also associated with increased CHD risk (18% per allele)
- Association of risk with Apo A5 variant is similar to overall risk observed in TG elevations
- Increased Apo B, LDL and VLDL particle concentration
- Reduced LDL size, HDL-c, A1, HDL size

Sarwar N et al. *Lancet*. 2010;375(9726):1634-1639.

Remnant cholesterol as a causal risk factor for ischemic heart disease



Varbo A et al. *J Am Coll Cardiol*. 2013;61:427–436.

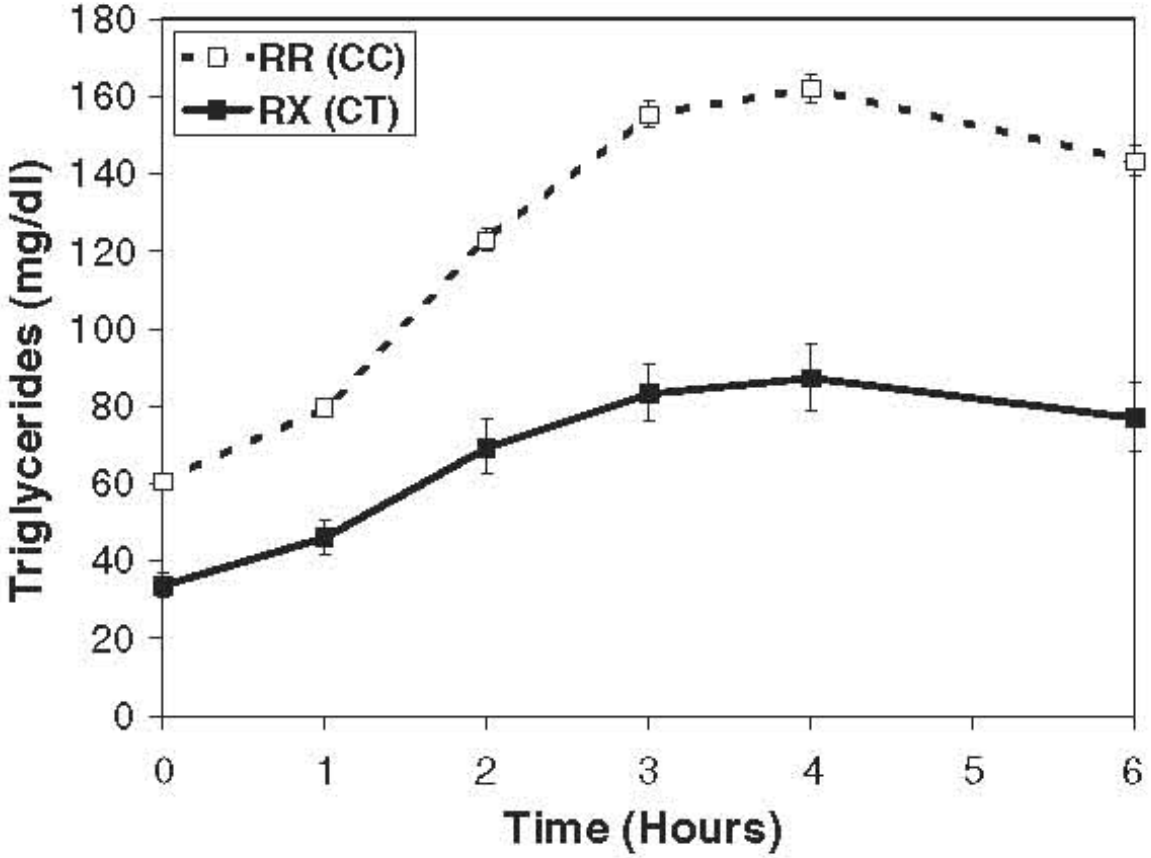
A Null Mutation in Human *APOC3* Confers a Favorable Plasma Lipid Profile and Apparent Cardioprotection

Toni I. Pollin,[1] Coleen M. Damcott,[1] Haiqing Shen,[1] Sandra H. Ott,[1] John Shelton,[1] Richard B. Horenstein,[1] Wendy Post,[2] John C. McLenithan,[1,3] Lawrence F. Bielak,[4] Patricia A. Peyser,[4] Braxton D. Mitchell,[1] Michael Miller,[1] Jeffrey R. O'Connell,[1] Alan R. Shuldiner[1,3]

12 DECEMBER 2008 VOL 322 **SCIENCE**

Pollin TI et al. *Science*. 2008;322:1702-1705.

TG levels before and during high-fat challenge by R19X *APOC3* genotype



Pollin TI et al. *Science*. 2008;322:1702-1705.

Loss of Function Mutation (R19X) in Apo CIII in the Amish

- Reduced Apo CIII levels in heterozygotes by 50%
- Decreased fasting and postprandial TGs
- Decreased non HDL-C, LDL-C, VLDL-C, IDL-C
- Increased HDL-C, HDL-2, HDL-3
- Reduced coronary calcium scores

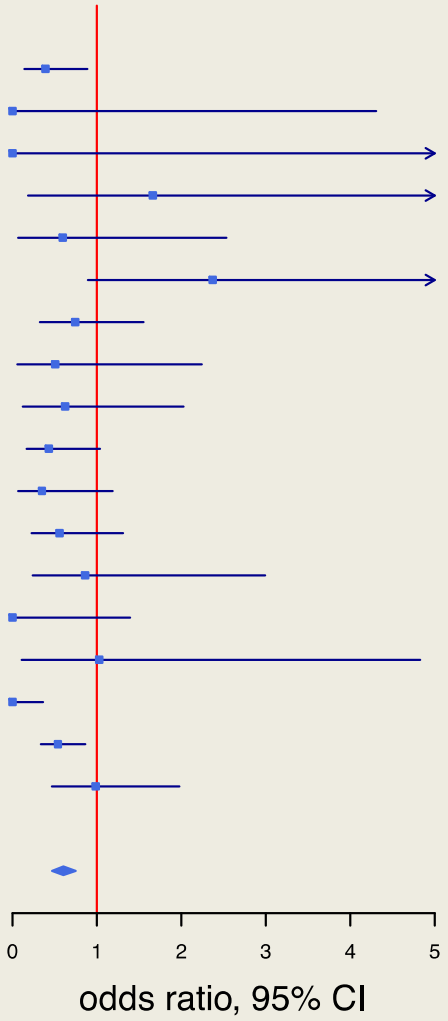
APOC3 LoF carriers with markedly lower triglycerides

Mutation	Type (Carrier Frequency)	Mean TG in carriers (mg/dl)	Mean TG in non-carriers (mg/dl)
R19X	Nonsense (~1:1000)	46	137
IVS2+1 G>A	Splice (~4:1000)	71	
A43T	Missense (~2:1000)	79	
IVS3+1G>T	Splice (~1:1000)	83	

TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute. N Engl J Med 2014;371:22-31.

APOC3 mutation carriers have 40% LOWER risk for CHD

Study	OR	95% CI	P–value
WHI EA	0.39	[0.14, 0.89]	0.019
WHI AA	0	[0, 4.3]	1
FHS EA	0	[0, 13]	1
MDC–CVA EA	1.7	[0.18, 7.1]	0.36
ARIC EA	0.59	[0.066, 2.5]	0.76
ARIC AA	2.4	[0.89, 5.7]	0.053
IPM EA	0.74	[0.32, 1.6]	0.5
IPM HA	0.51	[0.055, 2.2]	0.54
IPM AA	0.62	[0.12, 2]	0.61
ATVB+Verona EA	0.43	[0.17, 1]	0.043
Ottawa EA	0.35	[0.066, 1.2]	0.1
PROCARDIS EA	0.56	[0.23, 1.3]	0.17
HUNT EA	0.86	[0.24, 3]	1
GoDARTS CAD EA	0	[0, 1.4]	0.16
EPIC CAD EA	1	[0.11, 4.8]	1
FIA3 EA	0	[0, 0.36]	0.0015
German CAD EA	0.54	[0.33, 0.86]	0.0068
WTCCC EA	0.98	[0.47, 2]	1
All	**0.6**	**[0.47, 0.75]**	**0.0000041**



TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute. N Engl J Med 2014;371:22-31.

Genetically-altered LDL, TG, & risk for CHD

For every 1SD change (~35mg/dl) in genetically-altered LDL, 50% increase in risk for CHD

Predictor	Effect size	P
$\beta_{LDL\text{-}C}$	0.39	1×10^{-22}
$\beta_{HDL\text{-}C}$	0.04	0.32
β_{TG}	0.40	2×10^{-10}

Genetically-altered LDL, TG, & risk for CHD

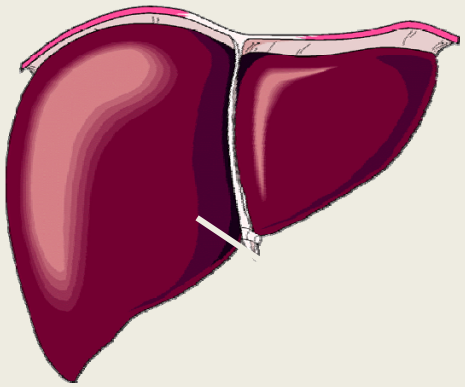
For every 1SD change (~35mg/dl) in genetically-altered LDL, 50% increase in risk for CHD

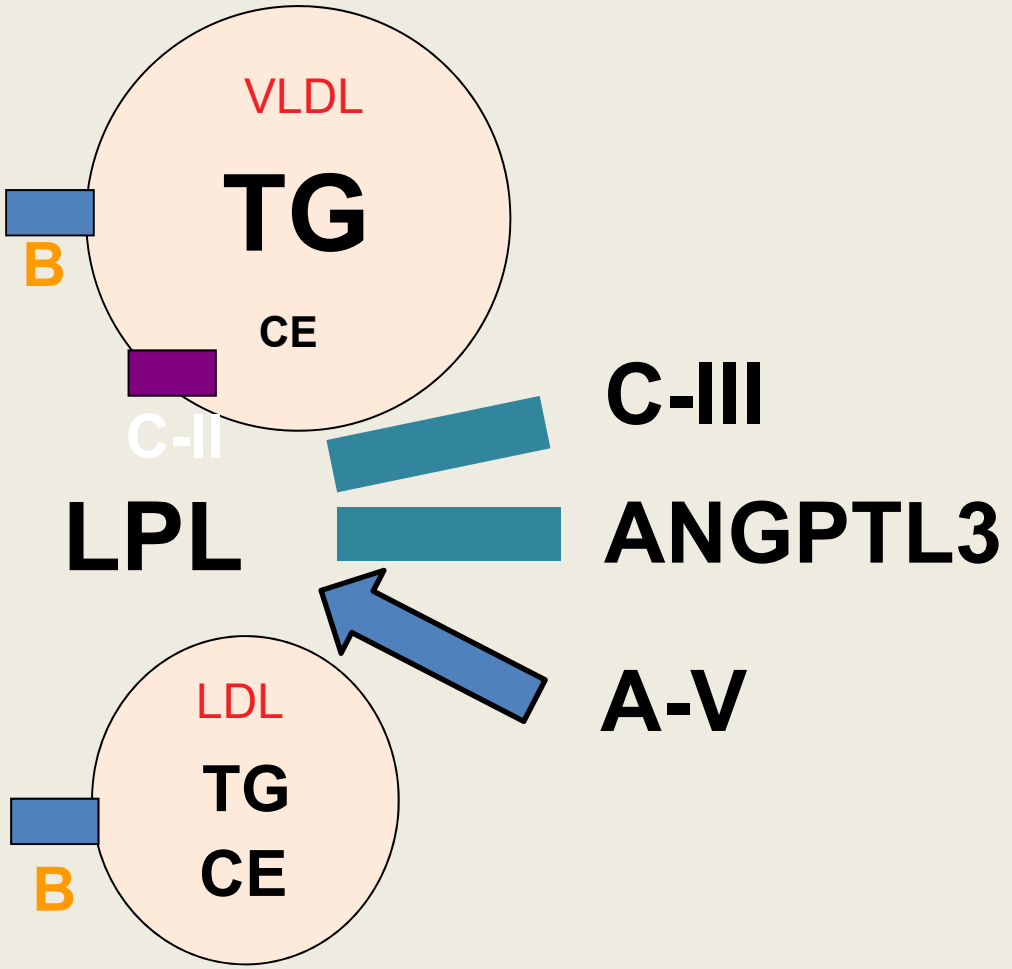
For every 1SD change (~90mg/dl) in genetically-altered TG, 50% increase in risk for CHD

Predictor	Effect size	P
$\beta_{LDL\text{-}C}$	0.39	1×10^{-22}
$\beta_{HDL\text{-}C}$	0.04	0.32
β_{TG}	0.40	2×10^{-10}

Gain of LPL function, gain of APOA5 function, and loss of APOC3 function

reduces risk for MI





THE LANCET

Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study

Benjamin F Voight*, Gina M Peloso*, Marju Orho-Melander, Ruth Frikke-Schmidt, Maja Barbalic, Majken K Jensen, George Hindy, Hilma Hólm, Eric L Ding, Toby Johnson, Heribert Schunkert, Nilesh J Samani, Robert Clarke, Jemma C Hopewell, John F Thompson, Mingyao Li, Gudmar Thorleifsson, Christopher Newton-Cheh, Kiran Musunuru, James P Pirruccello, Danish Saleheen, Li Chen, Alexandre F R Stewart, Arne Schillert, Unnur Thorsteinsdottir, Gudmundur Thorgeirsson, Sonia Anand, James C Engert, Thomas Morgan, John Spertus, Monika Stoll, Klaus Berger, Nicola Martinelli, Domenico Girelli, Pascal P McKeown, Christopher C Patterson, Stephen E Epstein, Joseph Devaney, Mary-Susan Burnett, Vincent Mooser, Samuli Ripatti, Ida Surakka, Markku S Nieminen, Juha Sinisalo, Marja-Liisa Lokki, Markus Perola, Aki Havulinna, Ulf de Faire, Bruna Gigante, Erik Ingelsson, Tanja Zeller, Philipp Wild, Paul I W de Bakker, Olaf H Klungel, Anke-Hilse Maitland-van der Zee, Bas J M Peters, Anthonius de Boer, Diederick E Grobbee, Pieter W Kamphuisen, Vera H M Deneer, Clara C Elbers, N Charlotte Onland-Moret, Marten H Hofker, Cisca Wijmenga, W M Monique Verschuren, Jolanda M A Boer, Yvonne T van der Schouw, Asif Rasheed, Philippe Frossard, Serkalem Demissie, Cristen Willer, Ron Do, Jose M Ordovas, Gonçalo R Abecasis, Michael Boehnke, Karen L Mohlke, Mark J Daly, Candace Guiducci, Noël P Burtt, Aarti Surti, Elena Gonzalez, Shaun Purcell, Stacey Gabriel, Jaume Marrugat, John Peden, Jeanette Erdmann, Patrick Diemert, Christina Willenborg, Inke R König, Marcus Fischer, Christian Hengstenberg, Andreas Ziegler, Ian Buysschaert, Diether Lambrechts, Frans Van de Werf, Keith A Fox, Nour Eddine El Mokhtari, Diana Rubin, Jürgen Schrezenmeir, Stefan Schreiber, Arne Schäfer, John Danesh, Stefan Blankenberg, Robert Roberts, Ruth McPherson, Hugh Watkins, Alistair S Hall, Kim Overvad, Eric Rimm, Eric Boerwinkle, Anne Tybjaerg-Hansen, L Adrienne Cupples, Muredach P Reilly, Olle Melander, Pier M Mannucci, Diego Ardissino, David Siscovick, Roberto Elosua, Kari Stefansson, Christopher J O'Donnell, Veikko Salomaa, Daniel J Rader, Leena Peltonen, Stephen M Schwartz, David Altshuler, Sekar Kathiresan

Lancet. 2012 Aug 11;380(9841):572-80.

Of 15 variants that alter HDL-C, 6 also affect MI risk

Gene(s) of interest within or near associated interval	Major allele, minor allele (minor allele frequency)*	Modelled allele	Effect of modelled allele on plasma HDL cholesterol (mmol/L)*	Effect of modelled allele on plasma triglycerides (mmol/L)*	Effect of modelled allele on plasma LDL cholesterol (mmol/L)*	Sample size (MI cases/ MI-free controls)	For modelled allele, observed change in MI risk (%; 95% CI)	For modelled allele, p value for association with MI
LPL†	G, T (0·10)	T	0·08	−0·24	..	19 139/50 812	−12% (−16 to −7)	4×10^{-7}†
TRIB1†	A, G (0·45)	G	0·02	−0·11	−0·05	19 139/50 812	−7% (−9 to −4)	2×10^{-6}†
APOA1-APOC3-APOA4-APOA5†	A, G (0·07)	A	0·05	−0·27	−0·09	18 310/49 897	−10% (−15 to −5)	8×10^{-5}†
GALNT2†	A, G (0·40)	A	0·02	−0·03	..	19 139/50 812	−3% (−6 to −1)	0·02†
ANGPTL4†	C, T (0·16)	C	0·05	−0·07	..	13 595/16 423	−5% (−10 to −1)	0·03†
CETP†	C, A (0·32)	A	0·10	..	−0·03	16 503/46 576	−4% (−7 to 0)	0·04†
LIPG	A, G (0·015)	G	0·14‡	..	..	17 165/49 077	−6% (−18 to 9)	0·41
MLXIPL	C, T (0·11)	T	0·03	−0·15	..	19 139/50 812	−1% (−4 to 3)	0·61
ABCA1	G, A (0·14)	G	0·03	..	0·05	19 139/50 812	−1% (−5 to 4)	0·76
MMAB, MVK	G, C (0·46)	G	0·03	..	..	19 139/50 812	0% (−3 to 3)	0·85
TTC39B	T, C (0·12)	T	0·03	..	..	15 693/47 098	0% (−5 to 5)	0·97
LCAT	G, A (0·11)	A	0·03	..	..	19 139/50 812	4% (−1 to 8)	0·10
FADS1-FADS2-FADS3	T, C (0·33)	T	0·03	−0·06	..	19 139/50 812	3% (−1 to 6)	0·11
LIPC	C, T (0·22)	T	0·05	0·07	..	17 917/49 514	4% (0 to 7)	0·04
HNF4A	C, T (0·01)	T	0·01	..	..	17 041/20 137	31% (12 to 54)	9×10^{-4}

Lancet. 2012 Aug 11;380(9841):572-80.

Of 15 variants that alter HDL-C, 6 also affect MI risk, and the top 3 are associated with sdLDL-C

Gene(s) of interest within or near associated interval	Major allele, minor allele (minor allele frequency)*	Modelled allele	Effect of modelled allele on plasma HDL cholesterol (mmol/L)*	Effect of modelled allele on plasma triglycerides (mmol/L)*	Effect of modelled allele on plasma LDL cholesterol (mmol/L)*	Sample size (MI cases/ MI-free controls)	For modelled allele, observed change in MI risk (%; 95% CI)	For modelled allele, p value for association with MI
LPL†	G, T (0·10)	T	0·08	−0·24	..	19 139/50 812	−12% (−16 to −7)	4×10⁻⁷†
TRIB1†	A, G (0·45)	G	0·02	−0·11	−0·05	19 139/50 812	−7% (−9 to −4)	2×10⁻⁶†
APOA1-APOC3-APOA4-APOA5†	A, G (0·07)	A	0·05	−0·27	−0·09	18 310/49 897	−10% (−15 to −5)	8×10⁻⁵†
GALNT2†	A, G (0·40)	A	0·02	−0·03	..	19 139/50 812	−3% (−6 to −1)	0·02†
ANGPTL4†	C, T (0·16)	C	0·05	−0·07	..	13 595/16 423	−5% (−10 to −1)	0·03†
CETP†	C, A (0·32)	A	0·10	..	−0·03	16 503/46 576	−4% (−7 to 0)	0·04†
LIPG	A, G (0·015)	G	0·14‡	..	..	17 165/49 077	−6% (−18 to 9)	0·41
MLXIPL	C, T (0·11)	T	0·03	−0·15	..	19 139/50 812	−1% (−4 to 3)	0·61
ABCA1	G, A (0·14)	G	0·03	..	0·05	19 139/50 812	−1% (−5 to 4)	0·76
MMAB, MVK	G, C (0·46)	G	0·03	..	..	19 139/50 812	0% (−3 to 3)	0·85
TTC39B	T, C (0·12)	T	0·03	..	..	15 693/47 098	0% (−5 to 5)	0·97
LCAT	G, A (0·11)	A	0·03	..	..	19 139/50 812	4% (−1 to 8)	0·10
FADS1-FADS2-FADS3	T, C (0·33)	T	0·03	−0·06	..	19 139/50 812	3% (−1 to 6)	0·11
LIPC	C, T (0·22)	T	0·05	0·07	..	17 917/49 514	4% (0 to 7)	0·04
HNF4A	C, T (0·01)	T	0·01	..	..	17 041/20 137	31% (12 to 54)	9×10⁻⁴

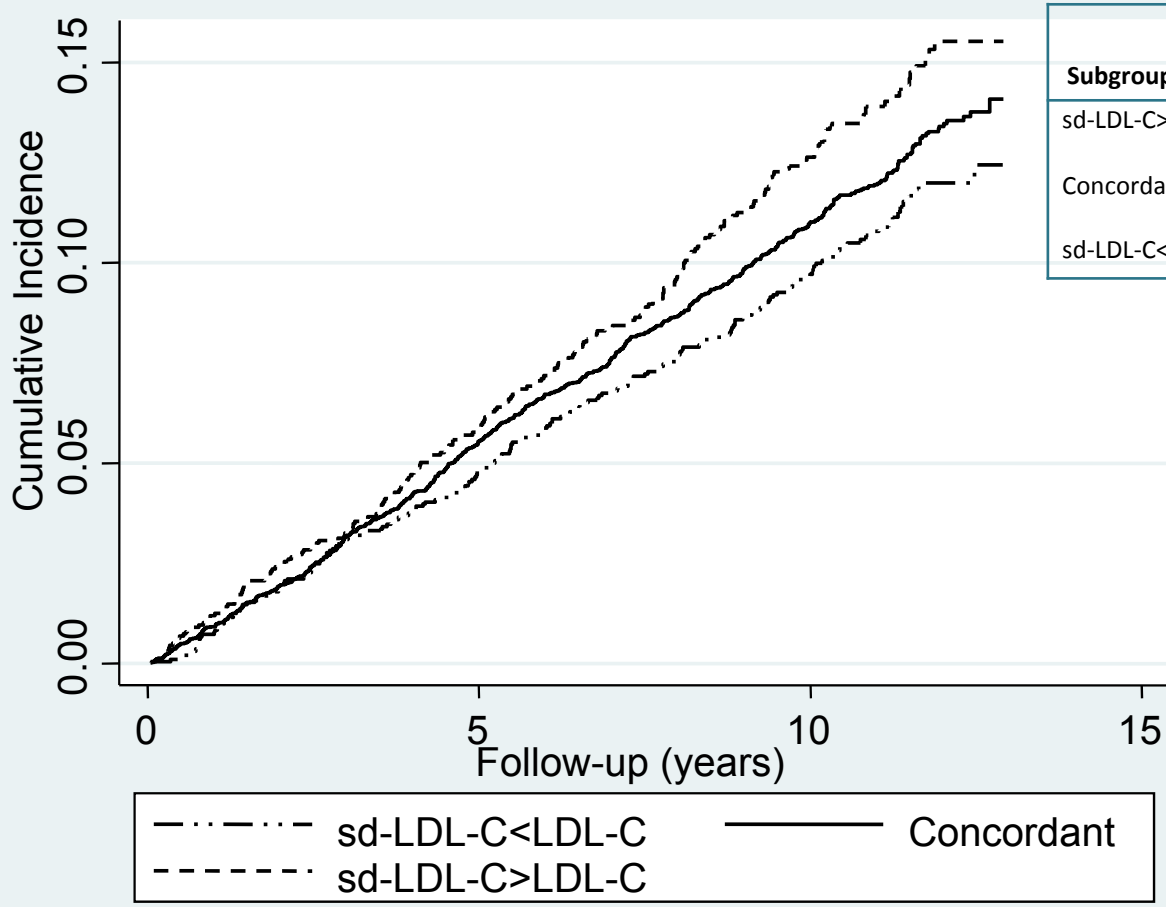
Lancet. 2012 Aug 11;380(9841):572-80.

Baseline characteristics across sd-LDL-C Quartiles

Characteristics	sd-LDL-C Quartiles (mg/dL)				P-trend
	Q1	Q2	Q3	Q4	
Male (%)	40	42	49	45	<0.0001
African American (%)	30	23	19	14	<0.0001
Hypertension (%)	40	46	51	54	<0.0001
Ever smoker (%)	59	62	57	58	0.113
Metabolic Syndrome (%)	23	33	50	73	<0.0001
Diabetes (%)	11	13	17	23	<0.0001
BMI (kg/m^2)	27.8	28.5	29.2	29.8	<0.0001
Triglycerides (mg/dL)	91.7	116.2	154.7	213.5	<0.0001
Total Cholesterol (mg/dL)	172.1	194.6	207.1	229.9	<0.0001
HDL-C (mg/dL)	56.2	52.4	47.9	43.5	<0.0001
LDL-C (mg/dL)	97.6	119.3	129.4	145.6	<0.0001
Log (CRP) (mg/L)	0.75	0.84	0.94	1.05	<0.0001

Values expressed as means or percentages

Discordance Analysis: sd-LDL-C vs LDL-C

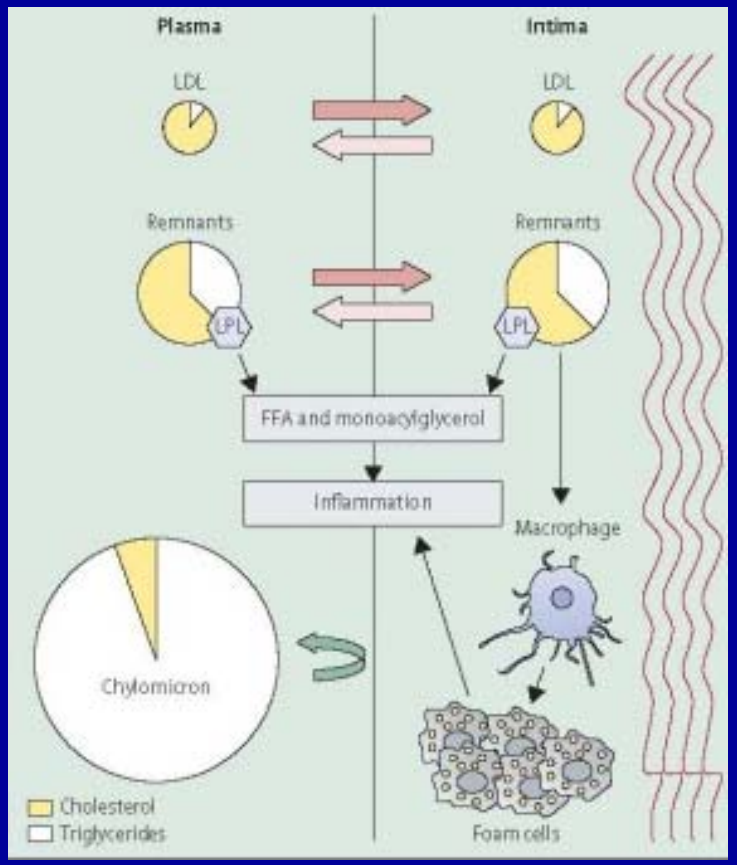


Subgroups	sd-LDL-C (mg/dL)	LDL-C (mg/dL)
sd-LDL-C>LDL-C	56.3	100.1
Concordant	42.6	123.0
sd-LDL-C<LDL-C	31.4	143.4

Cumulative incidence of CV events in subgroups with concordant or discordant LDL-C and sd-LDL-C levels from proportional hazards models adjusted for age, gender, and race.

Hoogeveen RC et al. Arterioscler Thromb Vasc Biol 2014;34:1069-1077.

Suggested role of raised plasma TGs and remnant cholesterol in intimal low-grade inflammation and development of atherosclerosis



Nordestgaard BG et al. Lancet 2014;384:626–635.

CD11c/CD18 Expression Is Upregulated on Blood Monocytes During Hypertriglyceridemia and Enhances Adhesion to Vascular Cell Adhesion Molecule-1

R. Michael Gower, Huaizhu Wu, Greg A. Foster, Sridevi Devaraj, Ishwarlal Jialal, Christie M. Ballantyne, Anne A. Knowlton, Scott I. Simon

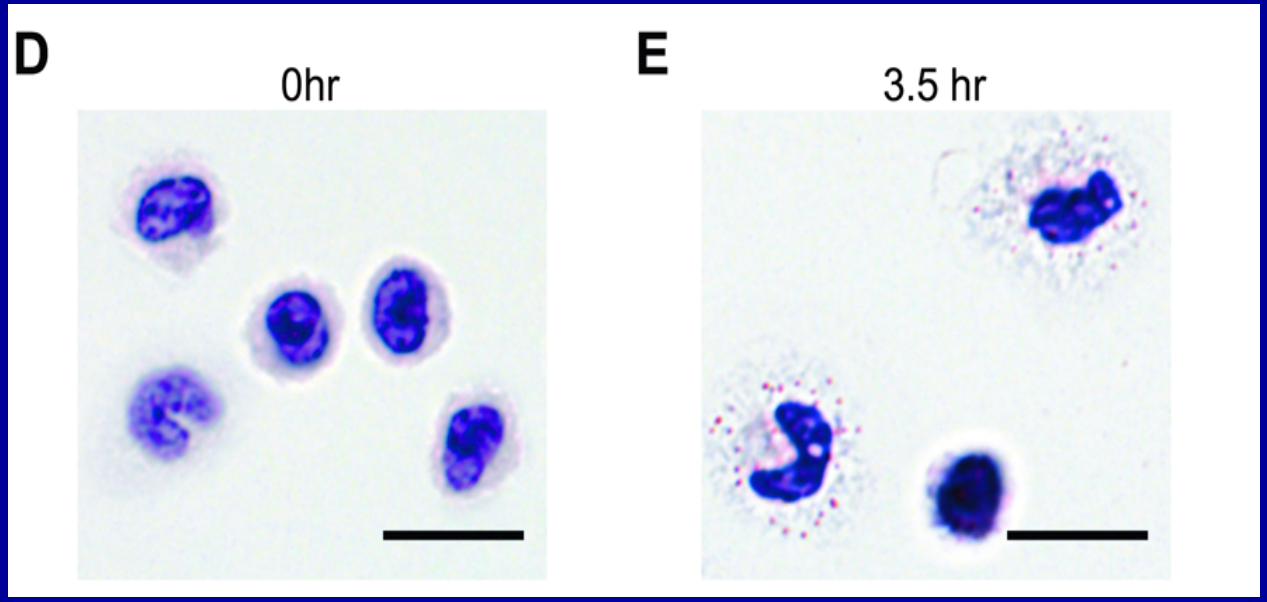
Objective—Atherosclerosis is associated with monocyte adhesion to the arterial wall that involves integrin activation and emigration across inflamed endothelium. Involvement of β_2-integrin CD11c/CD18 in atherogenesis was recently shown in dyslipidemic mice, which motivates our study of its inflammatory function during hypertriglyceridemia in humans.

Methods and Results—Flow cytometry of blood from healthy subjects fed a standardized high-fat meal revealed that at 3.5 hours postprandial, monocyte CD11c surface expression was elevated, and the extent of upregulation correlated with blood triglycerides. Monocytes from postprandial blood exhibited an increased light scatter profile, which correlated with elevated CD11c expression and uptake of lipid particles. Purified monocytes internalized triglyceride-rich lipoproteins isolated from postprandial blood through low-density lipoprotein–receptor–related protein-1, and this also elicited CD11c upregulation. Laboratory-on-a-chip analysis of whole blood showed that monocyte arrest on a vascular cell adhesion molecule-1 (VCAM-1) substrate under shear flow was elevated at 3.5 hours and correlated with blood triglyceride and CD11c expression. At 7 hours postprandial, blood triglycerides decreased and monocyte CD11c expression and arrest on VCAM-1 returned to fasting levels.

Conclusion—During hypertriglyceridemia, monocytes internalize lipids, upregulate CD11c, and increase adhesion to VCAM-1. These data suggest that analysis of monocyte inflammation may provide an additional framework for evaluating individual susceptibility to cardiovascular disease. (***Arterioscler Thromb Vasc Biol*. 2011;31:160-166.**)

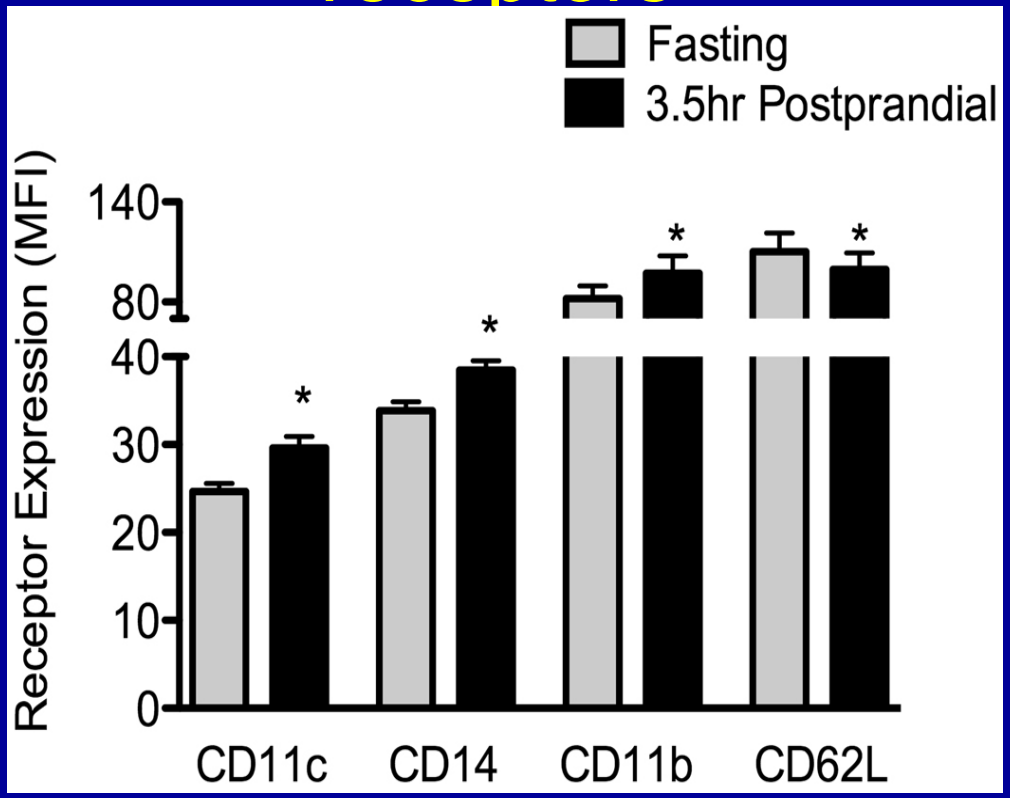
Monocytes exhibit lipid droplets and elevated CD11c postprandial

Representative images of monocytes sorted from fasting and 3.5 hrs postprandial blood stained with Oil Red O (neutral lipid) and hematoxylin (nucleus)



Gower RM et al. *Arterioscler Thromb Vasc Biol* 2011;31:160-166.

Postprandial changes in monocyte surface receptors

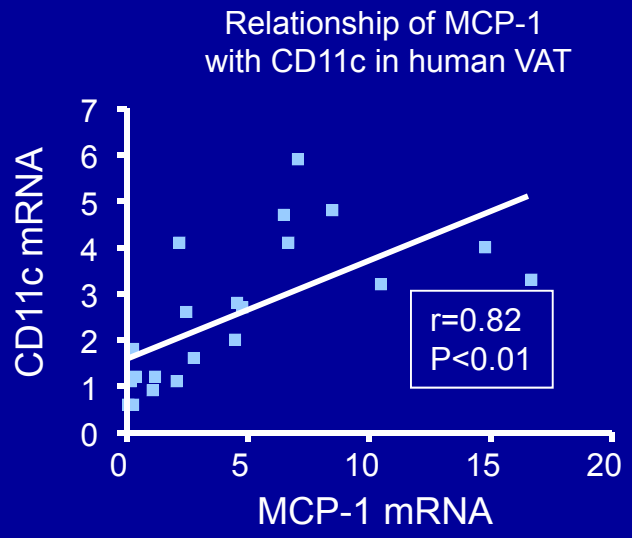


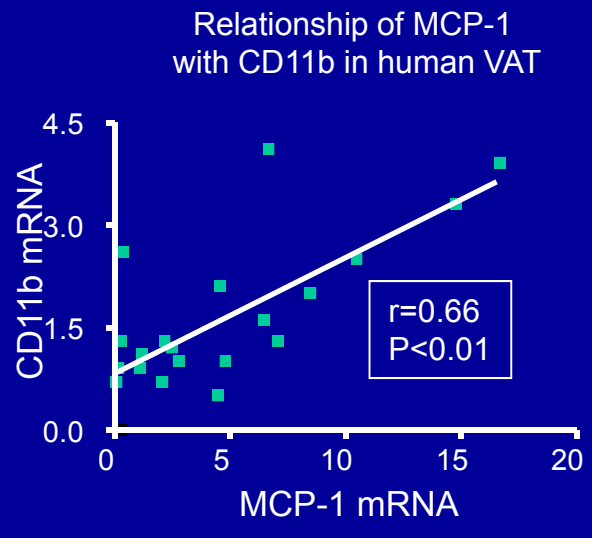
n = 40 subjects

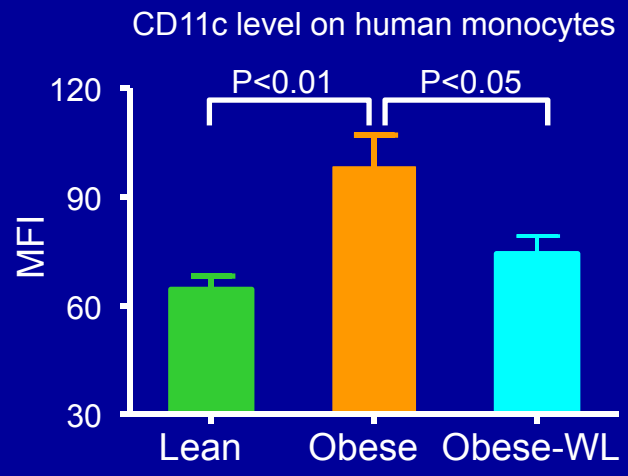
*P<0.001 by Student's paired t-test

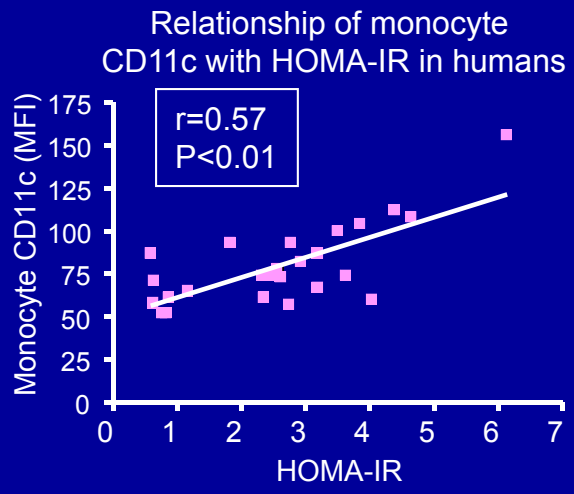
Gower RM et al. *Arterioscler Thromb Vasc Biol* 2011;31:160-166.

CD11c, CD11b, and MCP-1 in Human AT or Bloo



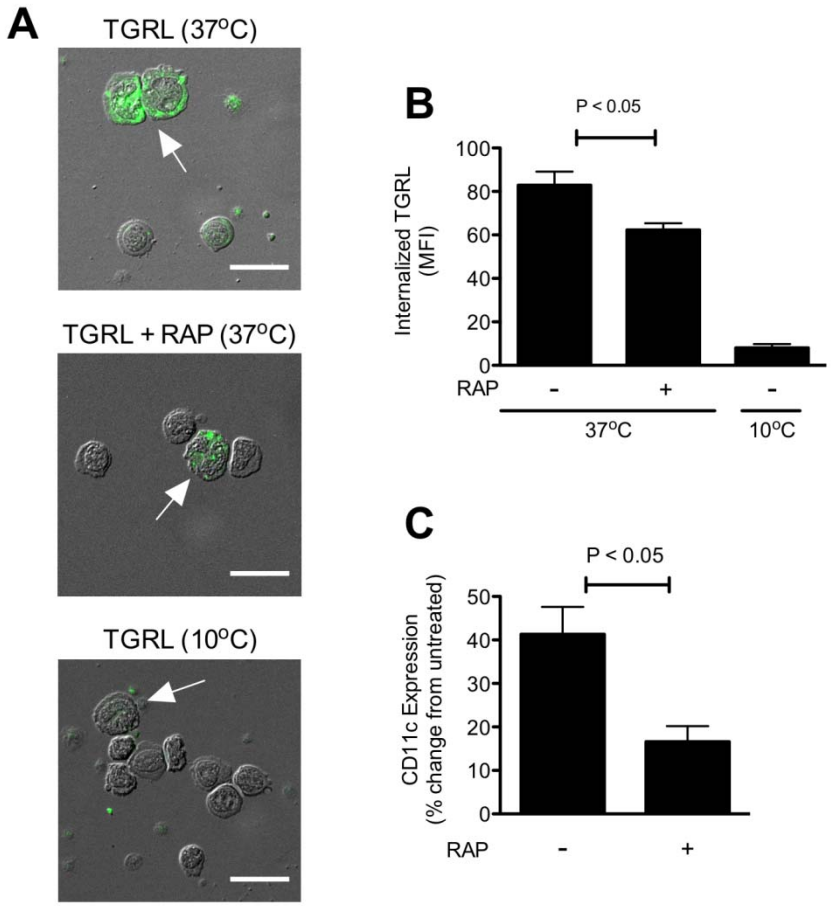






Wu H et al. *Arterioscler Thromb Vasc Biol* 2010;30:186-192.

Internalization of TGRL in vitro increases monocyte surface CD11c.

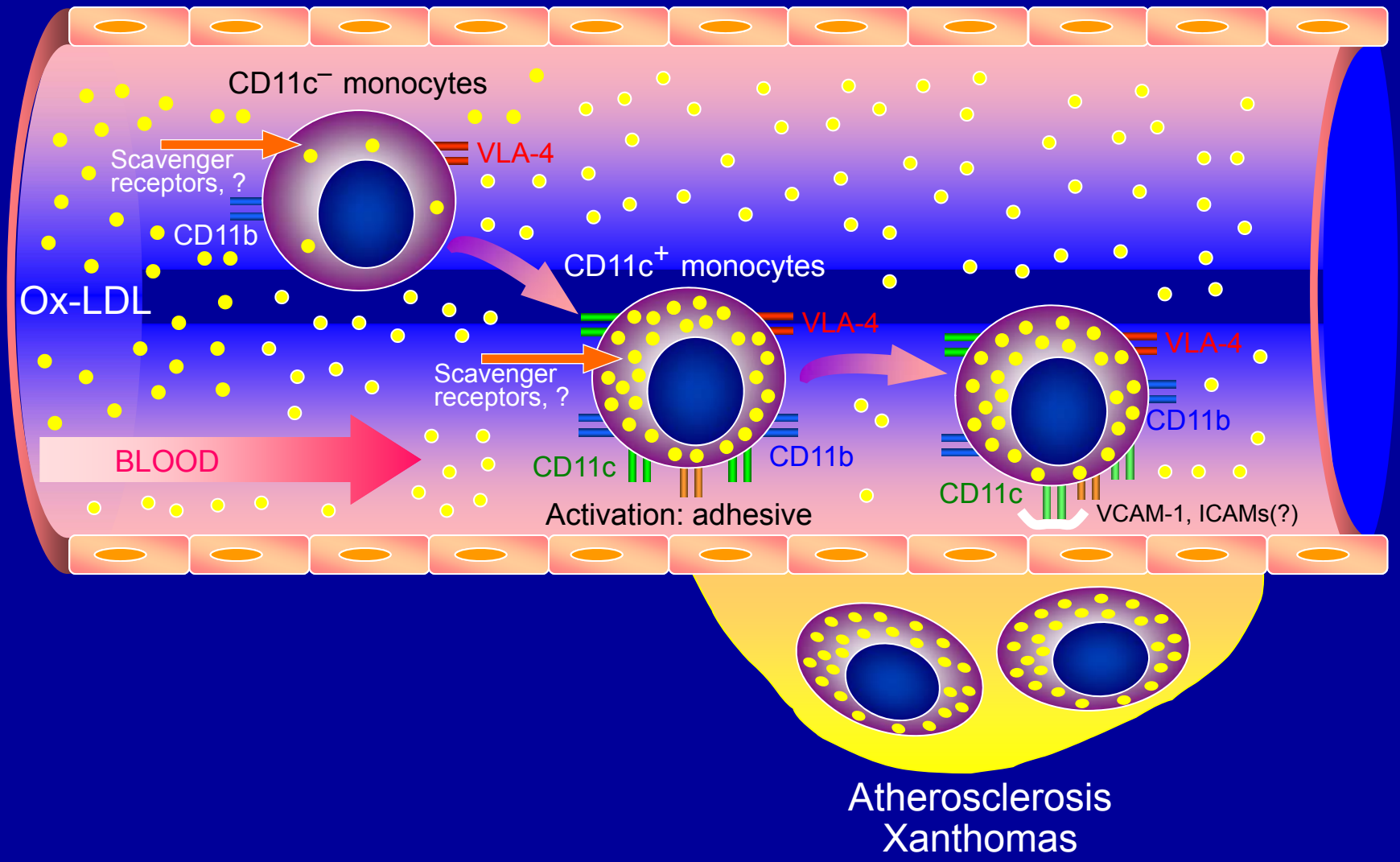


Gower R M et al. Arterioscler Thromb Vasc Biol. 2011;31:160-166

American Heart Association.

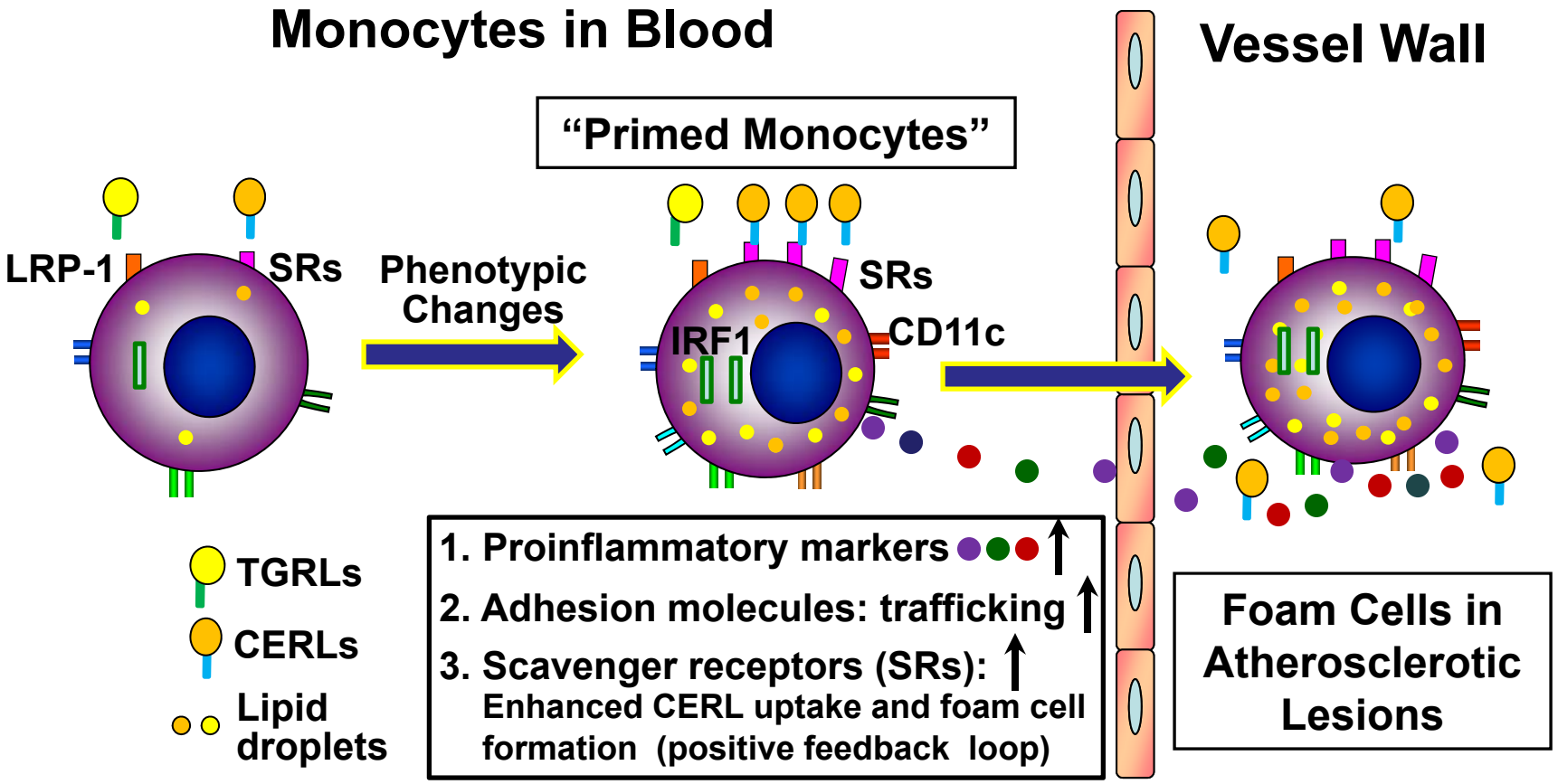
Copyright © American Heart Association, Inc. All rights reserved.

A Model for Involvement of CD11c in Atherogenesis in Hypercholesterolemia

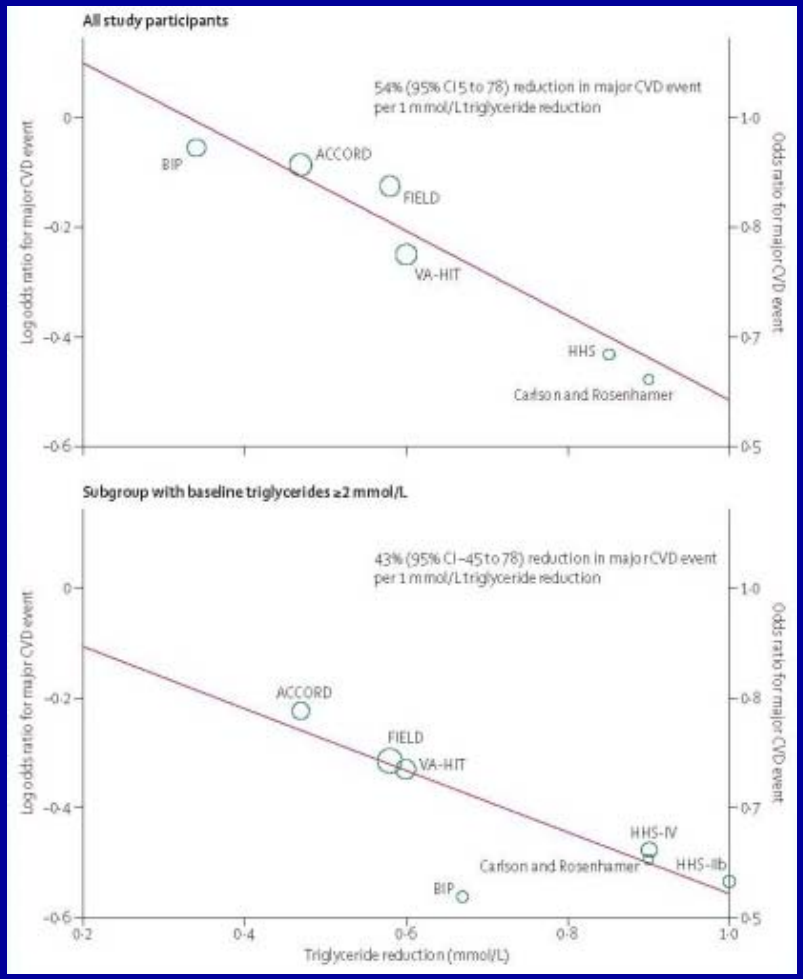


Wu H et al. *Circulation* 2009;119:2708-2717.

Schematic Hypothesis



Association estimated by meta-regression between extent of TG-lowering and reduction in risk of a major CV event in large controlled trials of fibrates



Nordestgaard BG et al. Lancet 2014;384:626–635.

Summary

- Rare and common genetic variants related to LDL-C levels are consistently associated with CHD
- Rare and common variants associated with TGRLs are strongly associated with CHD
- Rare and common variants associated with HDL-C levels are NOT consistently associated with CHD

Summary

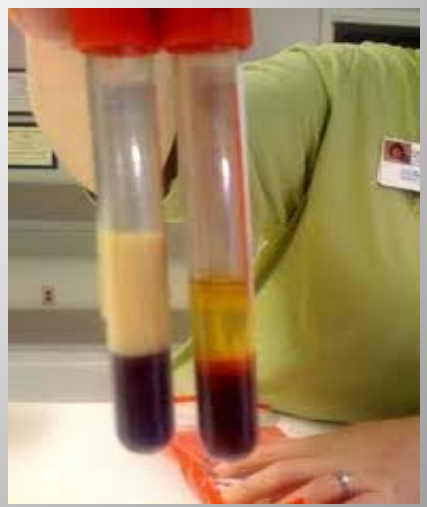
- The genetic data, epidemiological data, clinical trial data and mechanistic studies all suggest that triglyceride rich lipoproteins that carry apo B100 (and in some cases apo B 48) are atherogenic
- Ongoing trials will better define optimal therapy beyond statins

Nutrition in Hypertriglyceridemia
Choosing the “Right” Diet for the “Right” Patient

Wahida Karmally, Dr.PH,RD,CDE,CLS,FNLA
Associate Research Scientist
Director of Nutrition
Irving Institute for Clinical and Translational Research
Columbia University, NY







Objectives

- Describe the evidence-based nutrition and lifestyle recommendations for the treatment of hypertriglyceridemia
- Discuss the strategies for the “right” diet for the “right” patient

OUTLINE

- Definition of normal vs elevated triglycerides

- Mild to moderate triglycerides : a risk factor for CVD as a component of the metabolic syndrome
  Management: lifestyle therapy- weight reduction
  Jacobson TA et al Clin Ther 2007:29;763-777

- Very High levels of TG increase the risk for pancreatitis
  Management : reduction of dietary fat, simple carbohydrates, alcohol

- Omega-3 fatty acids and triglycerides
- Fructose intake and triglycerides
- Alcohol- effect on triglycerides
- Glycemic index?

NCEP ATP III			The Endocrine Society 2010		
Normal	<150 mg/dl	<1.7 mmol/liter	Normal	<150 mg/dl	<1.7 mmol/liter
Borderline-high triglycerides	150–199 mg/dl	1.7–2.3 mmol/liter	Mild hypertriglyceridemia	150–199 mg/dl	1.7–2.3 mmol/liter
High triglycerides	200–499 mg/dl	2.3–5.6 mmol/liter	Moderate hypertriglyceridemia	200–999 mg/dl	2.3–11.2 mmol/liter
Very high triglycerides	≥500 mg/dl	≥5.6 mmol/liter	Severe hypertriglyceridemia	1000–1999 mg/dl	11.2–22.4 mmol/liter
			Very severe hypertriglyceridemia	≥2000 mg/dl	≥22.4 mmol/liter

Berglund L et al
J Clin Endocrinol Metab. 2012 Sep;97(9):2969-89. doi: 10.1210/jc.2011-3213. Review.

Causes of Hypertriglyceridemia

Primary hypertriglyceridemia

FCHL – familial combined hypertriglyceridemia
FHTG- familial hypertriglyceridemia
Familial dysbetalipoproteinemia
FHA – familial hypoalpha-lipoproteinemia
Familial chylomicronemia and related disorders
Primary genetic susceptibility
Metabolic syndrome
Treated type 2 diabetes

Secondary hypertriglyceridemia

Excess alcohol intake
Drug-induced (e.g. thiazides, β-blockers, estrogens, isotretinoin, corticosteroids, bile acid-binding resins, antiretroviral protease inhibitors, immunosuppressants, antipsychotics)
Untreated diabetes mellitus
Endocrine diseases
Renal disease
Liver disease
Pregnancy
Autoimmune disorders

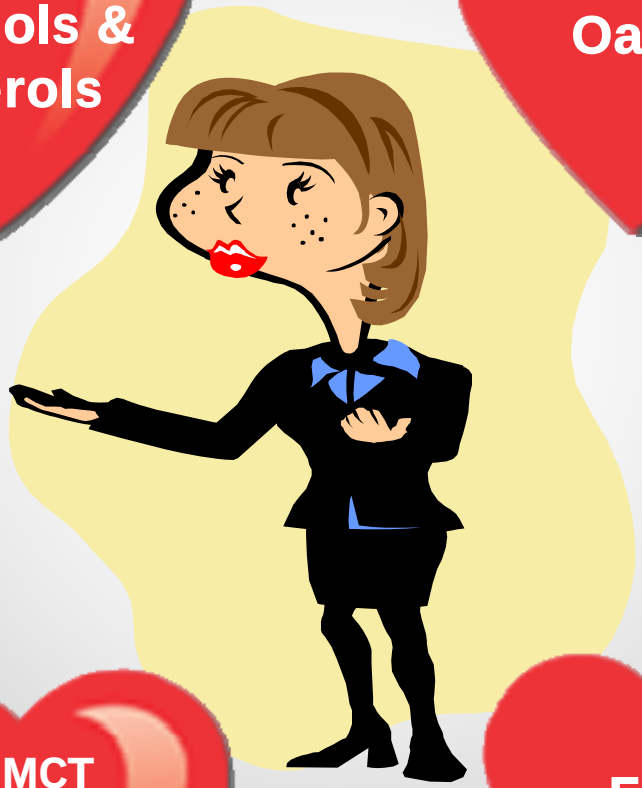
"Evidence-Based Dietetics Practice is the use of systematically reviewed scientific evidence in making food and nutrition practice decisions by integrating best available evidence with professional expertise and client values to improve outcomes."

adaevidencelibrary.com/

The Nutrition Prescription for HTG goes Beyond the Realm of Fat Intake



Individualize the Guidelines



Whole Grains

Plant Stanols & Sterols

Oats

Olive oil, Canola oil, Avocado

Nuts

Fruits & Vegetables

Beans

MCT oil

Fish

Omega 3 FAs

Assessment of Food and Nutrient Intake

Assess the food/nutrition intake and related history of disorders of lipid metabolism (DLM) including, but not limited to the following:

- Food, beverage and nutrient intake including:
  - Energy intake, serving sizes, meal-snack pattern, fat, types of fat and , carbohydrate, fiber, micronutrient intake
  - Bioactive substances (alcohol intake, plant stanols and sterols, soy protein, psyllium, fish oil)
- Food and nutrient administration (patient's experience with food)
  - Previous and current diet history, exclusions and experience, cultural and religious preferences
  - Eating environment, eating out
- Medication and herbal supplement use:
  - Prescription and over-the-counter medications, herbal and complementary product use (coenzyme Q-10, red yeast rice)
- Knowledge, beliefs or attitudes:
  - Motivation, readiness to change, self-efficacy
- Behavior:
  - Diet adherence, disordered eating, meal timing and duration
- Factors affecting access to food:
  - Psychosocial/economic issues (e.g., social support) impacting nutrition therapy
- Physical activity and function:
  - Exercise patterns, functionality for activities of daily living, sleep patterns

Mike U- 50 years

Lab results

Cholesterol: 260mg/dl

TG: 255mg/dl

HDL-C: 37mg/dl

LDL: 172mg/dl

Fasting glucose: 123mg/dl

Waist circumference: 44”

Metabolic Syndrome Markers

Risk Factors	Defining Level
Triglyceride	**≥ 150 mg/dL**
HDL-cholesterol **Men** **Women**	 **< 40 mg/dL** **< 50 mg/dL**
Blood Pressure	**≥ 130/≥ 85 mm Hg**
Fasting Glucose	**≥ 100 mg/dL**
Waist Circumference **Men** **Women**	 **>102 cm (> 40 in)** **> 88 cm (> 35 in)**

IDF Criteria: Abdominal Obesity and Waist Circumference Thresholds

- **AHA/NHLBI criteria: ≥ 102 cm (40 in) in men, ≥ 88 cm (35in) in women**

- Some US adults of non-Asian origin with marginal increases should benefit from lifestyle changes. Lower cut points (≥ 90 cm in men and ≥ 80 cm in women) for Asian Americans

	Men	Women
Japanese	**≥ 85 cm (33.5 in)**	**≥ 90 cm (35.4 in)**
Chinese	**≥ 90 cm (35.4 in)**	**≥ 80 cm (31.5 in)**
South Asian	**≥ 90 cm (35.4 in)**	**≥ 80 cm (31.5 in)**
Europe	**≥ 94 cm (37.0 in)**	**≥80 cm (31.5 in)**

Alberti KGMM et al. Lancet 2005;366:1059-1062.
Grundy SM et al. Circulation 2005;112:2735-2752.

Metabolic Syndrome

Causes

- Acquired causes
  - Overweight and obesity
  - Physical inactivity
  - High carbohydrate diets (>60% of energy intake) in some persons
- Genetic causes

DLM: Metabolic Syndrome

- A calorie-controlled cardioprotective dietary pattern that avoids extremes in carbohydrate and fat intake, limits refined sugar and alcohol, and includes physical activity at a moderate-intensity level for at least 30 minutes on most (preferably all) days of the week, should be used for individuals with metabolic syndrome. Weight loss of 7 to 10% of body weight should be encouraged if indicated. These lifestyle changes improve risk factors of metabolic syndrome.

Fair

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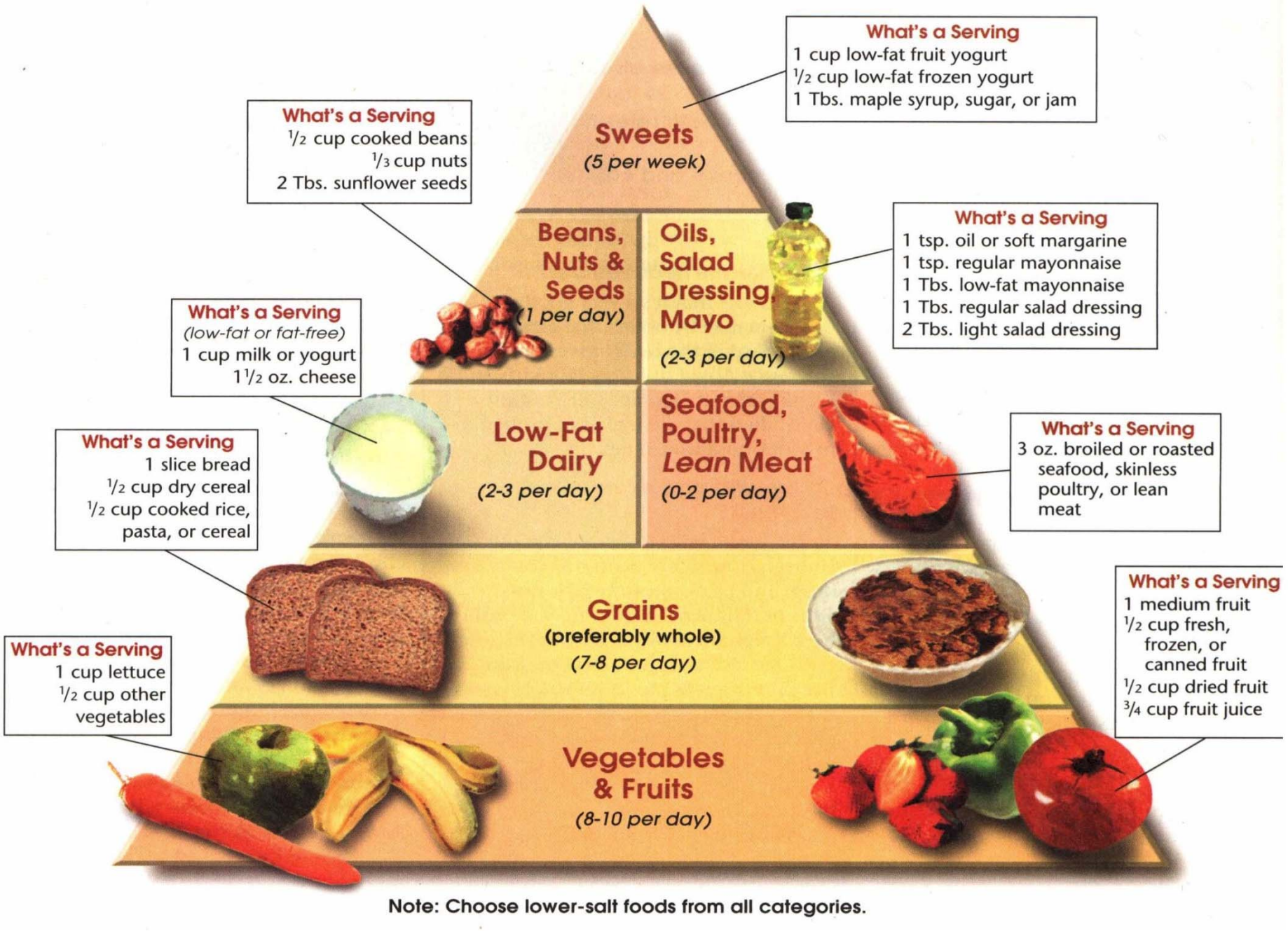
National Cholesterol Education Program Therapeutic Lifestyle Change (TLC) Diet

- Total fat 25-35% (10%-35%)
- <7% saturated fat (AHA/ACC guidelines 5-6% and avoid trans-fat)
  - Up to 10% PUFA; up to 20% MUFA
- <200 mg cholesterol
- 20-30 g fiber
- Adjust total calories for weight goals
- Physical activity: expend at least 200 Kcal/day

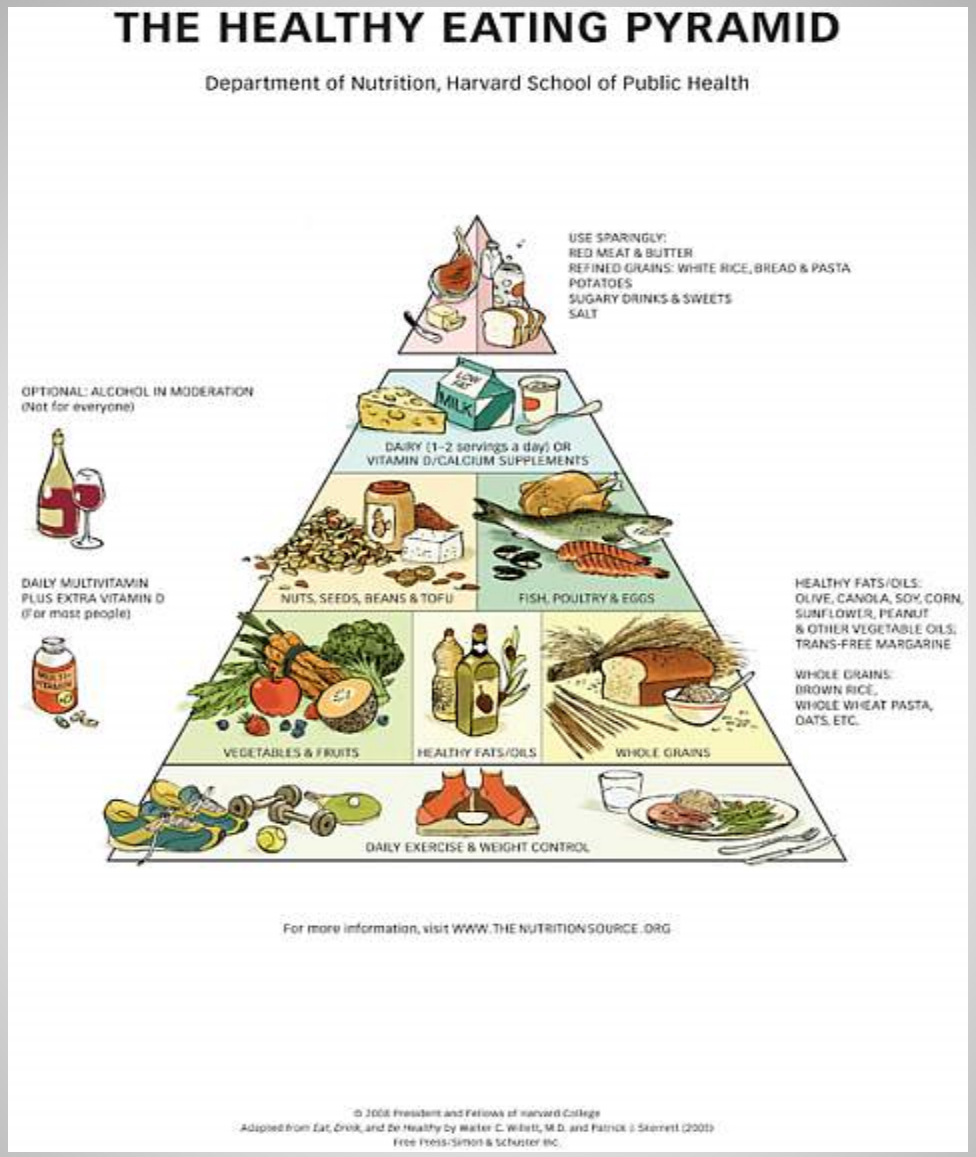
- Options: plant sterols/stanols (2-3g) and soluble fiber (10-25g)

Moderate evidence indicates that increased MUFA intake, rather than high carbohydrate intake, may be beneficial for persons with T2D. High MUFA intake, when replacing a high carbohydrate intake, results in improved biomarkers of glucose tolerance and diabetic control

DASH PYRAMID



Note: Choose lower-salt foods from all categories.



Velázquez-López L et al BMC Pediatr. 2014 Jul 5;14(1):175. doi: 10.1186/1471-2431-14-175.
Trichopoulou A etal BMC Med. 2014 Jul 24;12(1):112. doi: 10.1186/1741-7015-12-112.

Recommendations for Omega-3 Fatty Acids

- American Heart Association Scientific Statements: Fish Consumption, Fish Oil, Omega-3 Fatty Acids and Cardiovascular Disease, 2002

Population	Recommendation
Patients w/o documented CHD	Eat a variety of fish (preferably oily) at least twice a week, include oils and foods rich in ALA
Patients w/ documented CHD	Consume 1 gm of EPA+DHA per day, preferably from fish, supplements could be used in consultation with a physician
Patients needing TG lowering	Two – four gm of EPA+DHA per day provided as capsule under a physician's care

Kris-Etherton et al, Circulation, 2002

What effect does EPA/DHA taken as a fish oil supplement have on triglycerides in hypertriglyceridemic patients who are not taking cholesterol lowering medications?

Conclusion

Subjects with elevated triglycerides (mean values ranged 250-919 mg/dL) taking 2.6-3.6gof commercial EPA/DHA fish oil (approximately 48-60% EPA/ 33-40% DHA) with varied dietary intakes without cholesterol lowering medicines, for 6 weeks to 1 year* had 22-45% reductions in triglyceride values compared to baseline values. Lower doses of fish oil (1.72g; 59% EPA/41% DHA) also resulted in 22-25% reductions in triglycerides vs. baseline values after 6 months to 1 year. *One study was of 1 year duration and was a 6-month open label extension of a 6 month study.

Grade II

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Omega-3 free **fatty acids** for the treatment of severe hypertriglyceridemia: the EpanoVa fOr Lowering Very high triglyceridEs (**EVOLVE**) trial.

Kastelein JJ, Maki KC, Susekov A, Ezhov M, Nordestgaard BG, Machielse BN, Kling D, Davidson MH.

J Clin Lipidol. 2014 Jan-Feb;8(1):94-106.

OM3-FFA achieved the primary end point for TG lowering and secondary end point of non-HDL-C lowering at 2, 3, and 4 g/d in persons with severe hypertriglyceridemia

Sources of Omega-3 Fatty Acids: Seafood

3oz Cooked	Calories	ALA (g)	EPA (g)	DHA (g)
Flounder & Sole	73	0.018	0.143	0.112
Halibut, Atlantic & Pacific	94	0.011	0.065	0.132
Herring, Atlantic	173	0.112	0.773	0.939
Herring, Atlantic , pickled	223	0	0.717	0.464
Herring, Pacific	212	0.062	1.056	0.751
King Mackerel	114	n/a	0.148	0.193
Salmon, Atlantic, farmed	175	0.096	0.586	1.238
Salmon, Pacific, Sockeye	144	0.073	0.228	0.445
Trout, mixedspecies	162	0.169	0.220	0.575
Tuna, white, canned in water, drained	109	0.060	0.198	0.535
Tuna, white, canned in oil, drained	158	0.173	0.056	0.151
Oyster, Eastern, farmed	67	0.054	0.195	0.179
Sardine, Atlantic, canned in oil, drained	177	0.424	0.402	0.433
Sardine, Pacific, canned intomato sauce	157	0.200	0.453	0.735
Scallop, Bay & Sea	94	0.005	0.061	0.085
Tilapia	109	0.038	0.004	0.110

Fish safety

- Mercury concerns
- Limit eating large fish that feed on other fish, making them at greater risk of accumulating mercury
  - Swordfish
  - King mackerel
  - Albacore tuna
  - Shark
  - Tile fish
- It is advisable for pregnant women and young children to avoid eating these fish (USFDA/EPA).

Sources of Omega-3 Fatty Acids: Plants

Food	Calories	ALA (g)	EPA (g)	DHA (g)
Flax seed, 14g (~2 Tbsp)	75	3.194	0	0
Chia seed, 14g (~2 Tbsp)	69	2.527	0	0
Walnuts, 1 oz (14 halves)	185	2.574	0	0
Canola oil, 1 tsp	40	0.411	0	0
Purslane, ½ cup raw*	3	0.011*	0	0
Purslane, ½ cup cooked*	10	0.032*	0	0
Kale, ½ cup cooked	18	0.067	0	0
Spinach, ½ cup cooked	21	0.083	0	0

Sources: U.S. Department of Agriculture, Agricultural Research Service. 2011. USDA National Nutrient Database for Standard Reference, Release 24. Nutrient Data Laboratory Home Page, http://www.ars.usda.gov/ba/bhnrc/ndl

* Nutrition Data System for Research software version 2011, developed by the Nutrition Coordinating Center (NCC), University of Minnesota, Minneapolis, MN.

The DRIs for alpha linolenic acid are:

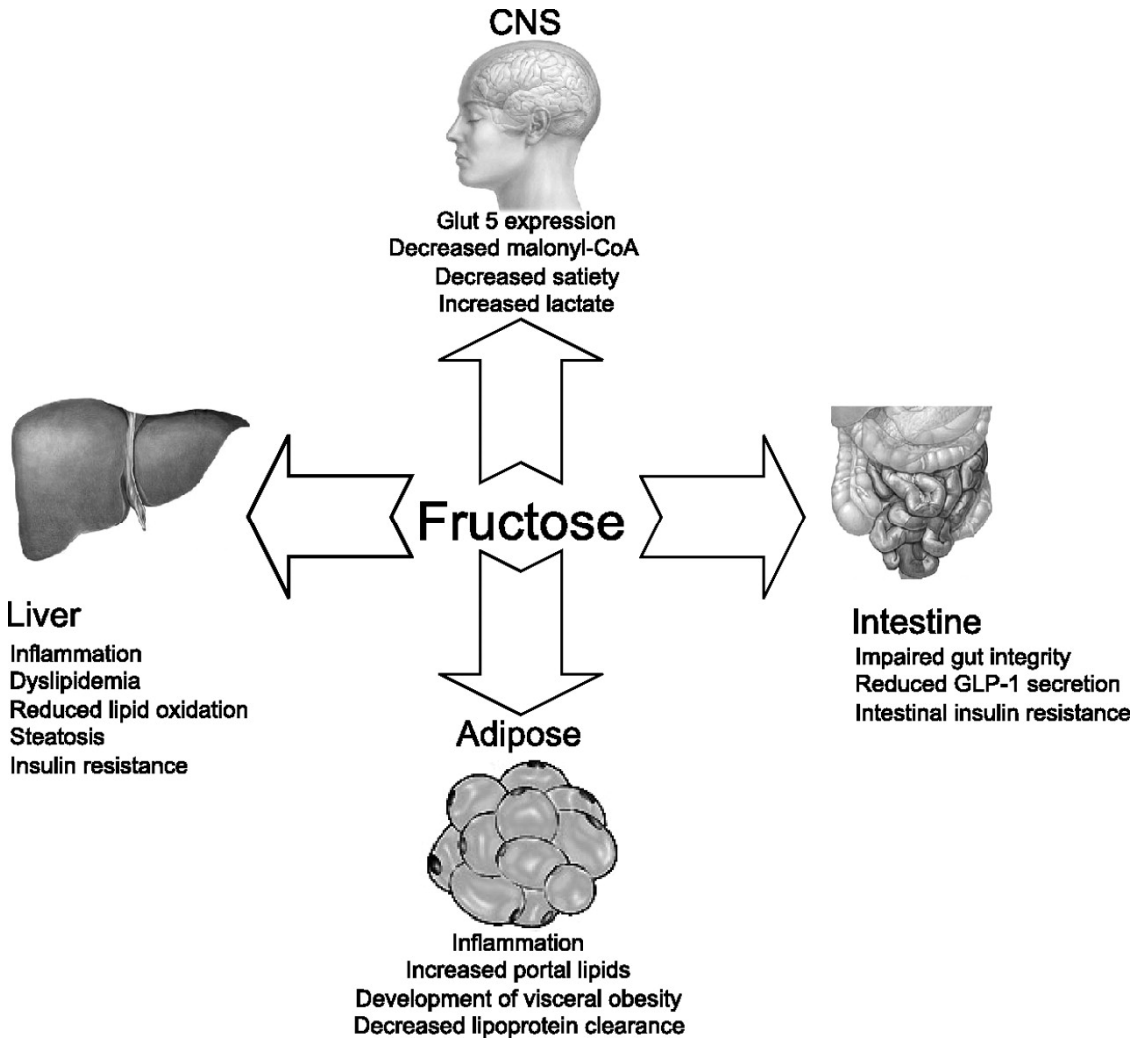
1.1 g for women; 1.6g for men

A standard serving of beer, distilled spirits and wine each contains the same amount of alcohol.



12 oz = 1 1/2 oz = 5 oz

Whole body effects of chronic fructose consumption.



Dekker M J et al. Am J Physiol Endocrinol Metab 2010;299:E685-E694

AMERICAN JOURNAL OF PHYSIOLOGY
Endocrinology and Metabolism

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Fructose Content in Selected Foods and Beverages

Food	Grams of Fructose
Cola with HFCS (12 oz)	22.5
Lemon-lime soda with HFCS (12 oz)	21.7
Ginger ale with HFCS (12 oz)	13.5
Raisins, seedless (1.5-oz box)	13.0
Power bar (chocolate)	10.9
Agave nectar (tbsp)†	8.9
Honey (tbsp)	8.6
Applesauce, sweetened (3.5 oz)	8.0
Fruit (apple, pear)	4–10
Molasses (tbsp)	2.6
Table sugar (tsp)	2.0

Source:US Department of Agriculture;

Miller M et al Circulation. 2011 May 24;123(20):2292-333

What is the evidence from human subject research that consumption of high fructose corn syrup is associated with obesity, metabolic and/or adverse effects in adults?

Conclusion

Four short-term randomized controlled trials (Akhaven 2007, Melanson 2007, Soenen 2008, Stanhope 2008), two longitudinal studies (Monsivais 2007, Streigel-Moore 2006), two cross-sectional studies (Duffey 2008, Mackenzie 2006) and five review articles (Angelopoulos 2009, Bray 2004, Forshee 2007, Melanson 2008, White 2009) examined the effects of high fructose corn syrup (HFCS) compared with other nutritive sweeteners. These studies consistently found little evidence that HFCS differs uniquely from sucrose and other nutritive sweeteners in metabolic effects (circulating glucose, insulin, postprandial triglycerides, leptin and ghrelin), subjective effects (hunger, satiety and energy intake at subsequent meals) and adverse effects such as risk of weight gain. Randomized trials dealing specifically with HFCS were of limited number, short duration and of small sample size; therefore, long-term data are needed.

Grade II

Familial Chylomicronemia Syndrome

Rare Disease affecting 1 in 1,000,000 presents in patients with severe lipemia associated with TG levels greater than 2000mg/dl and recurrent pancreatitis.

They have a functional deficiency of lipoprotein lipase, an autosomal recessive disorder.

Nutrition Prescription for Chylomicronemia Syndrome

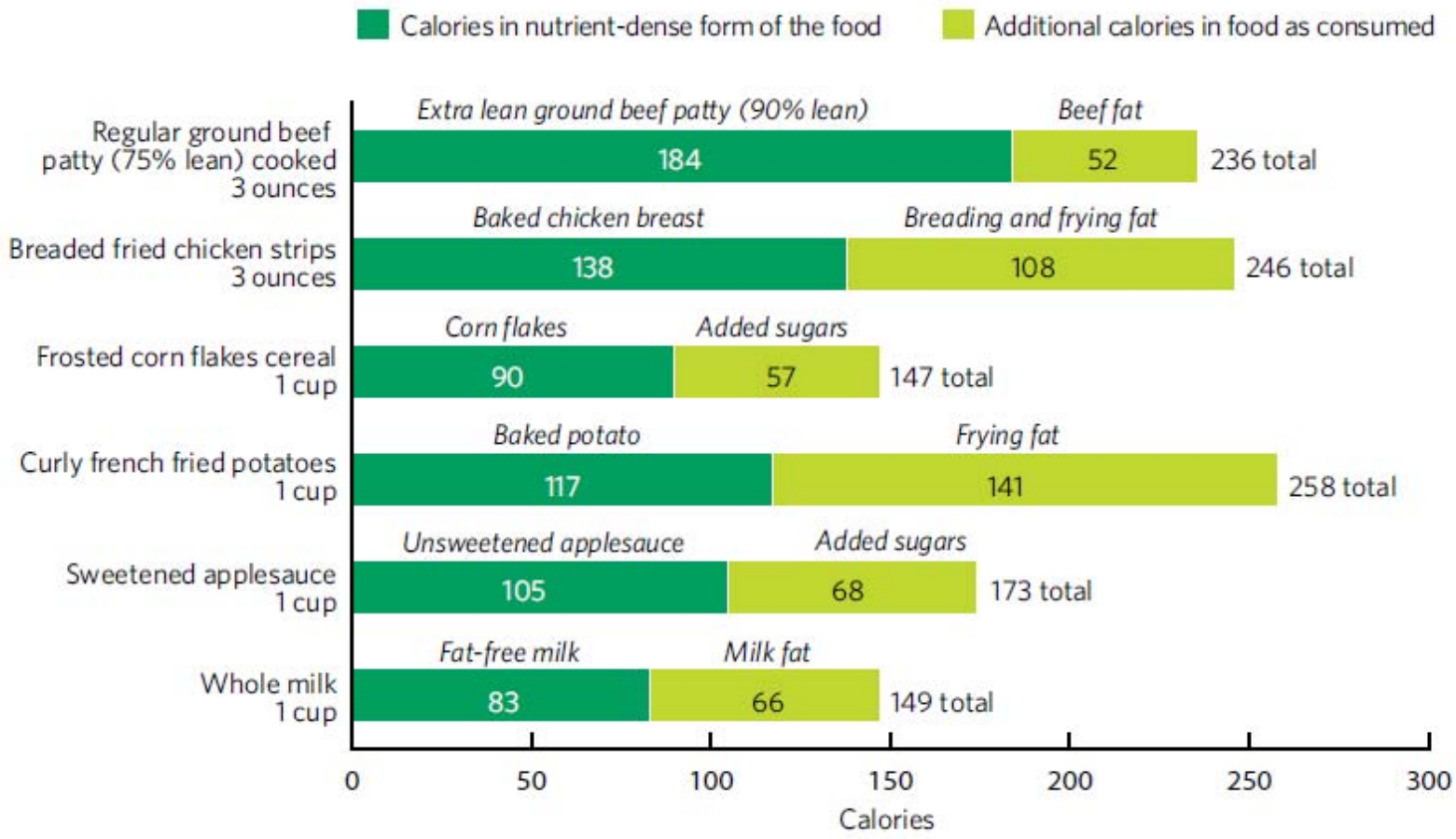
- Very low-fat diet (10-15% of calories from fat)
- Meet requirements for EFAs- omega 6 and omega 3
- Low in simple carbohydrates; limit total carbs
- Weight management and physical activity
- Eliminate alcohol
- Meet nutrient recommendations
- Instructions for delicious meals





Nutrient Dense and Non-Nutrient Dense Forms of Sample Foods

FIGURE 5-2. Examples of the Calories in Food Choices That Are Not in Nutrient Dense Forms and the Calories in Nutrient Dense Forms of These Foods



We Need Fat in the Diet

- Major source of fuel energy
- Aids in the absorption of fat-soluble vitamins
- Essential fatty acids
- Serve other biochemical functions

2000 kcalories Can Include:

- 22-33g of Fat
- 11g/d omega-6
- 1.1-1.6g/d α- linolenic acid

Fat Content in Foods

Food	Total Fat (g)	Saturated Fat (g)
3 oz. cooked leg of lamb, lean	7.8	2.8
3 oz. cooked beef sirloin	4.3	1.5
3 oz. cooked pork chops, loin	8.6	3
3 oz. cooked pork, sirloin cutlet	8.6	3
3 oz. cooked chicken breast, skin removed before cooking	3.8	1
3 oz. cooked chicken, dark meat, skin removed before cooking	8.9	2.8
1 oz. American cheese, processed	8.9	5.6
1 oz. Cheddar cheese, processed	8.9	5.6
1 oz. Swiss cheese, processed	7	4.5
1 oz. Feta cheese	6	4.2
1 oz. Mozzarella cheese, part-skim	5.7	3.1
1 T grated parmesan cheese	1.8	1.1
3 oz. cooked Atlantic salmon	6.9	1.1
3 oz. cooked sole	2	0.5
6 cooked pieces of large shrimp	0.6	0.1

MCT Oil



Medium Chain Triglycerides
HCPCS Code B4155
Price:$399.99 (6 one Qt. bottles)

- For Patients Unable to Digest or Absorb Conventional Fats

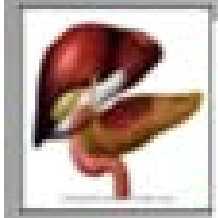
  MCTs are more readily hydrolyzed and absorbed than conventional food fat

- MCTs are absorbed directly into the portal circulation and do not require bile salts for emulsification

Sound Bytes That Are Confusing to a Patient

- Cut fat
- No red meat
- Exercise
- Increase fiber
- Lose weight
- Don’t eat white foods

Consider Both…



The patient's risks and therapeutic needs



The patient's readiness and personal choices



What you think

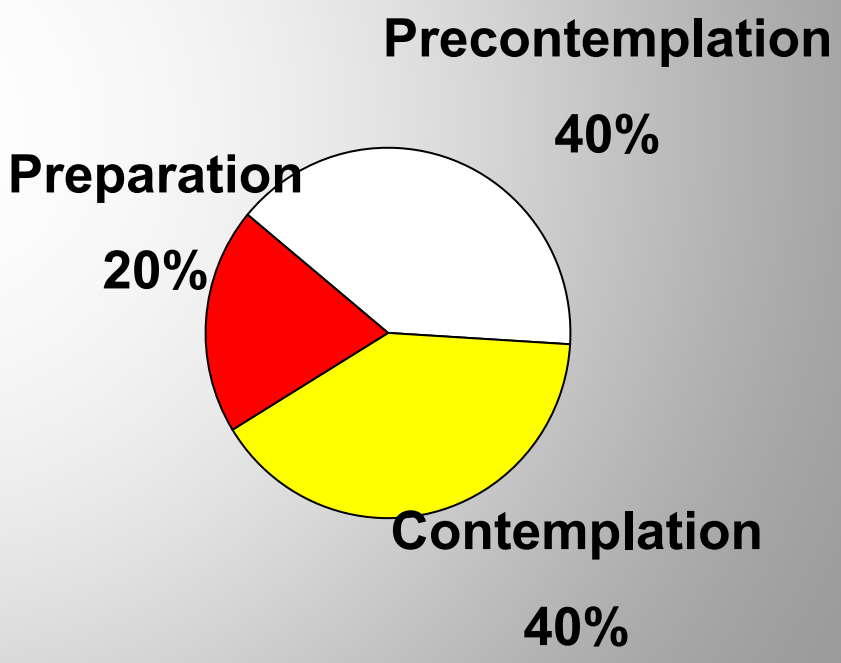


What your patient thinks

Assess Readiness to Change

Stage of Change	Attitude Toward Change
Pre contemplation	"never"
Contemplation	"Someday"
Preparation	"Soon"
Action	"Now"
Maintenance	"Forever"

Stages of Change for Those Needing Behavior Modification



Prochaska et al., *Am J Health Promotion*, 1997;12:38-48



Skim Milk
Serving Size 8 fl oz (240mL)
Servings Per Container 2

Amount Per Serving	
Calories 80	Calories from Fat 0
	% Daily Value*
Total Fat 0g	**0%**
Saturated Fat 0g	**0%**
Cholesterol less than 5mg	**1%**
Sodium 130mg	**5%**
Total Carbohydrate 12g	**4%**
Dietary Fiber 0g	**0%**
Sugars 11g	
Protein 8g	

Vitamin A 8% • Vitamin C 4%
Calcium 30% • Iron 0% • Vitamin D 25%

* Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs.

	Calories:	2,000	2,500
Total Fat	Less than	65g	80g
Sat Fat	Less than	20g	25g
Cholesterol	Less than	300mg	300mg
Sodium	Less than	2,400mg	2,400mg
Total Carbohydrate		300g	375g
Dietary Fiber		25g	30g



Whole Milk
Serving Size 8 fl oz (240mL)
Servings Per Container 2

Amount Per Serving	
Calories 150	Calories from Fat 70
	% Daily Value*
Total Fat 8g	**12%**
Saturated Fat 5g	**25%**
Cholesterol 35mg	**12%**
Sodium 125mg	**5%**
Total Carbohydrate 12g	**4%**
Dietary Fiber 0g	**0%**
Sugars 11g	
Protein 8g	

Reduced fat chocolate milk



Nutrition Facts

Serving Size 35 3/100 g (1.2 oz)
Servings Per Container 8

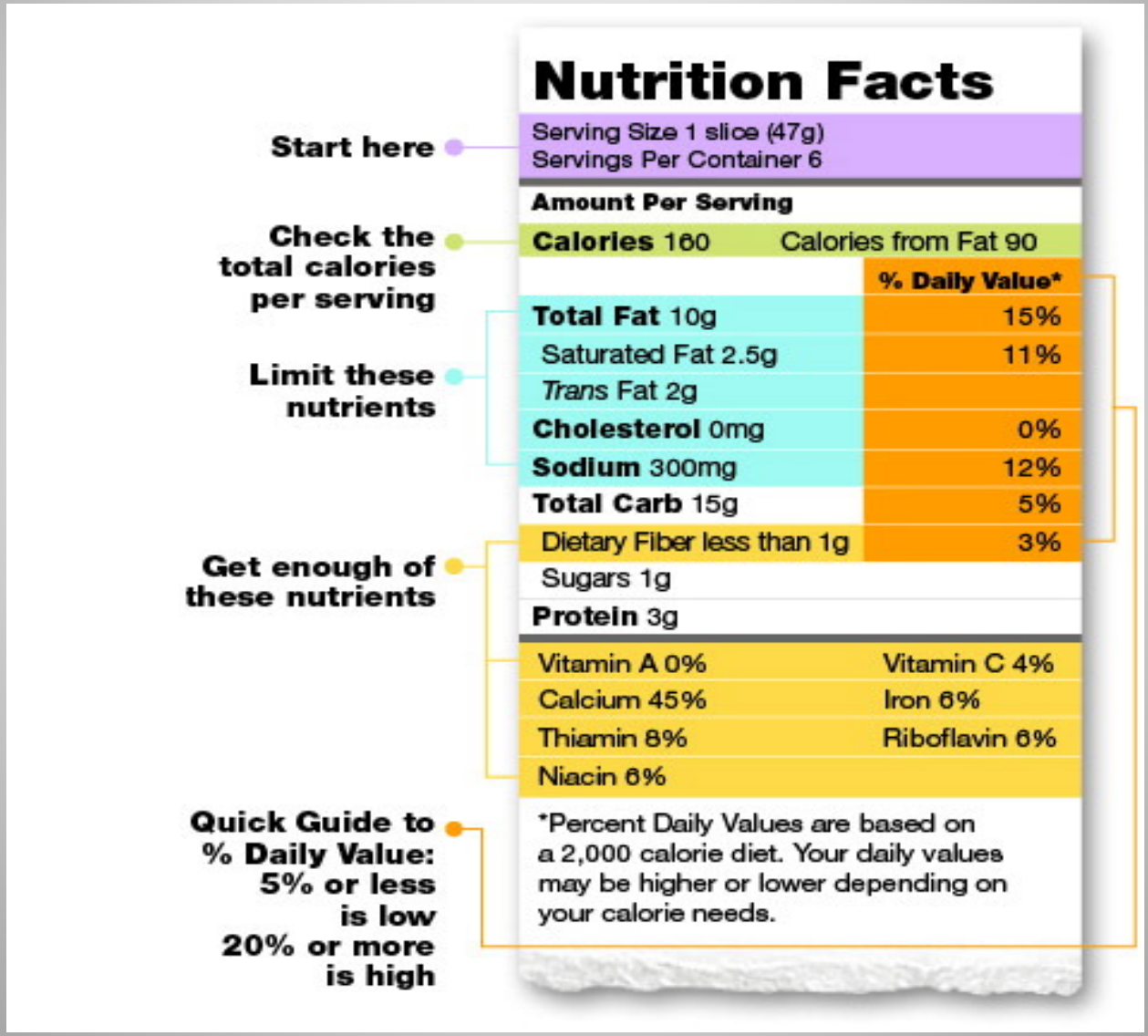
Amount Per Serving	
Calories 130	Calories from Fat 20
	% Daily Value*
Total Fat 2g	**3%**
Saturated Fat 1g	**6%**
Trans Fat 0g	
Cholesterol 0mg	**0%**
Sodium 280mg	**12%**
Potassium 240mg	**7%**
Total Carbohydrate 29g	**10%**
Dietary Fiber 1g	**4%**
Sugars 24g	
Protein 2g	

Vitamin A 0%	• Vitamin C 0%
Calcium 2%	• Iron 4%
Vitamin D 2%	• Vitamin E 0%
Thiamin 0%	• Riboflavin 0%
Niacin 0%	• Vitamin B6 0%
Folate 0%	• Vitamin B12 0%
Copper 0%	

* Percent Daily Values are based on a 2,000 calorie diet.

Calories per gram:
Fat 9 • Carbohydrate 4 • Protein 4

Label Reading



DLM: MNT and Referral to a RD

- Medical Nutrition Therapy (MNT) provided by a registered dietitian (RD) is recommended for patients with an abnormal lipid profile as defined by current National Heart, Lung and Blood Institute (NHLBI) Clinical Practice Guidelines and low-density lipoprotein cholesterol (LDL-C) goals.

- Patients who attend multiple RD visits for MNT lasting an average of 45 minutes (30-60 minutes per session) over six to twelve weeks can reduce daily dietary fat (5% to 8%), saturated fat (2% to 4%) and energy intake (232-710kcal per day). This can result in a reduction in serum total cholesterol (TC) (↓7% to 21%), LDL-C (↓7% to 22%) and **triglycerides (↓11% to 31%).**

- **Strong**

Update3/21/2010

Effects of Diet Interventions on Triglyceride Lowering

Nutrition Practice	TG-Lowering Response, %
Weight loss (5% to 10% of body weight)	20
Implement a Mediterranean-style diet vs a low-fat diet	10-15
Add marine-derived PUFA (EPA/DHA) (per gram)	5–10
Decrease carbohydrates1%	
Energy replacement with MUFA/PUFA	1–2
Eliminate *trans* fats 1%	
Energy replacement with MUFA/PUFA	1

TG indicates triglyceride; PUFA, polyunsaturated fatty acid; EPA, eicoeicosapentaenoic acid; DHA, docosahexaenoic acid; and MUFA, monounsaturated fatty acid

Miller M et al Circulation. 2011 May 24;123(20):2292-333

What to Say About Physical Activity

- Walking 1 mile = 100 kcal
- WHO, ADA, AHA, NIH:
  - 60 min./day for weight loss
  - 60-90 min./day for maintaining weight loss



Effective Lifestyle Counseling

- Participant motivation to change is essential
- Goals must be clear and outcomes must be measurable
- Strategies must be practical
- Interventions must be culturally compatible

Improving Adherence Strategies for Physicians and Health Professionals

- Be clear that the patient knows the rationale for food choices (why)
- Identify a goal and establish a specific plan (what)
- Identify facilitators and barriers to success (how)
- Follow-up at the next visit

Foster and Makris- Managing Obesity: A Clinical Guide, 2004

Approaches to Improving Adherence

Multidisciplinary approaches are critical:

- Physician
- Registered Dietitian
- Nurse
- Physician Assistant
- Pharmacist
- Dentist



Patient-focused process

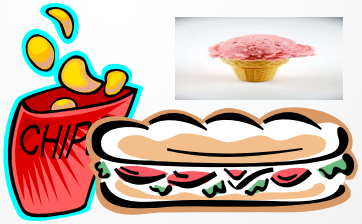
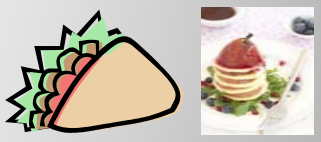
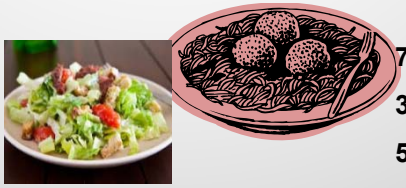
Simplify
Encourage family support
Reward adherence
Involve patients

Count Your Fats:
Self- Monitoring Food Diary

_____ Patient Initials _____ Date of Diary Day (circle): SUN MON TUE WED THUR FRI SAT

A	B	C	D	E	F
Time of Day	* Where Food Prepared	Description of food or beverage (Record one food item per line) Be specific…give details	Indicate Amount Food	Indicate Cooking Method	**Staff notes**

Very Low Fat Menu

	INSTEAD OF	TRY…
Breakfast	 394 kcal, 12g fat, 2g fiber Bagel with cream cheese and coffee	 355 kcal, 3g fat, 9g fiber Oatmeal with blueberries and skim milk
Mid-Morning Snack	 1045 kcal, 7g fat, 0g fiber Sweetened ice tea and a donut	 105 kcal, 0.54g fat, 3g fiber Non fat Yogurt dip with veggies
Lunch	 1025 kcal, 54g fat, 1g fiber Tuna sub with chips and ice cream	 234 kcal, 1.7 g fat, 9g fiber Shrimp wrap with veggies on a whole wheat tortilla, and fruit salad
Dinner	 772 kcal, 35g fat, 5g fiber Pasta with meat sauce, garlic bread and a Caesar salad with croutons	 873kcal, 8g fat, 23g fiber Fish kebobs with vegetables over brown rice, spinach salad with vinaigrette Strawberry smoothie
	3875 kcal / 108 g fat/ 8g fiber	1567kcal 13g fat/ 44g fiber

Summary

Management of Hypertriglyceridemia:

Mild to moderate HTG: Lifestyle therapy focusing on diet macronutrient composition, glycemic index, omega-3 fatty acids, weight reduction, physical activity

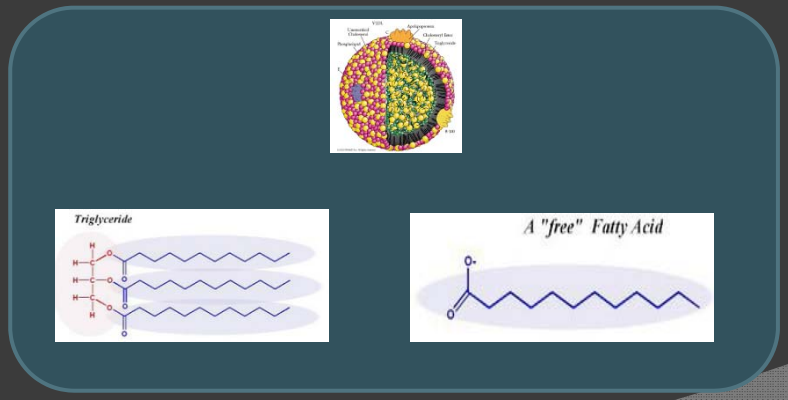
Severe hyperchylomicronemia: dietary fat restriction, MCT oil Weight management, physical activity, reduced simple carbohydrates

Thank you



The Role and Impact of Exercise in Managing Triglycerides and Triglyceride-rich Lipoproteins

Ralph LaForge, MSc
Durham NC
Albuquerque NM



25-minute AGENDA

Overview

Recent trial trends in 2014

Key points in exercise TG metabolism

Principle mechanisms for exercise generated TG reduction

Postprandial TG and remnant lipoprotein response to acute exercise

Provider recommendations

Effects of physical exercise on health-related quality of life and blood lipids in perimenopausal women: a randomized placebo-controlled trial.
Zhang J t.al. Menopause, 2014 Jun 16.
N=157 women (40-55 yrs), kuperman index >15. 12 weeks
↓ **9% TG vs controls**

Tai chi for primary prevention of cardiovascular disease.
Hartley L. et.al. Cochrane Database Syst 2014; Apr 9;4
Review of 13 trials (1520 participants randomised) and three ongoing trials
↓ **32-40 mg/dL TG reduction**

Effect of Exercise Intervention on Changes in Free Fatty Acid Levels and Metabolic Risk Factors in Stroke Patients
Dae-Young Kim et.al. J. Phys. Ther. Sci. 26: 275–279, 2014
N=20 male stroke patients 47-59 yrs; 5X/wk, 12 weeks
↓ **22% TG**

Effects of high-intensity circuit training, low-intensity circuit training and endurance training on blood pressure and lipoproteins in middle-aged overweight men
Paoli et.al. Lipids in Health and Disease 2013, 12:131 Padova Italy
N=58 men, 61 yrs, BMI 29.8 randomly assigned to one of the 3 exercise treatment groups: HICT, LICT and ET. Rx 3X/wk, 50 min per session for 12 weeks.
↓**15% TG**

Effects of Moderate- and Intermittent Low intensity Exercise on Postprandial Lipemia.
Kim Y, Coyle EF et.al. Med Sci Sports Exerc. 2014
N=9 men MOD and LOW reduced incremental TG area under the curve **34 and 20%** respect.

A randomised trial comparing weight loss with aerobic exercise in overweight individuals with coronary artery disease: The CUT-IT trial.
Pedersen LR et.al. Eur J Prev Cardiol. 2014 Jul 31. pii: 2047487314545280
↓ 25% TG after 12 weeks of cycle AIT @ 90% MV02 (P=.03)

Effects of Regular Physical Exercises in the Water on the Metabolic Profile of Women with Abdominal Obesity.
Kasprzak Z, et.al. J Hum Kinet. 2014 Jul 8;41:71-79
32 women aged 41-72 years 3 months Ex
11% reduction in TG

Impact of exercise training without caloric restriction on inflammation, insulin resistance and visceral fat mass in obese adolescents.
Mendelson M et.al. Pediatr Obes. 2014 Aug 4. doi: 10.1111/ijpo.255

Bottom line

So how much TG reduction can we expect from a 12-16 week aerobic exercise program of sufficient energy expenditure:

✓ Exercise programs have been shown to decrease fasting TGs by 4–37% (approximate mean change of 24% depending on baseline fasting TG).

Fletcher, 2005
Helge, 2006
Trejo-Gutierrez, 2007
Kraus, 2009
Magkos, 2010

Variables influencing TG response to exercise and exercise training

Baseline TG

Session energy expenditure

Exercise intensity

Apo C and E genotypes

Fatty acid transporters

VLDL clearance

Muscle TAG stores

Hepatic and lipoprotein lipase

Post-prandial influences

Gender *

* Women use more intra-muscular TAG as energy source during moderate-intensity exercise than men, possibly because they have higher baseline (i.e., resting) intra-muscular TAG content

Key Point 1

The **acute** TG response to a single session of exercise, e.g., 400 kcal 4-mile walk

vs

Chronic TG response to exercise training, e.g., 2000 kcal/wk,

= contrasting TG responses

What is the most immediately available form of TG for oxidative energy production in contracting muscle?

a. Plasma free fatty acids (albumin-bound)

b. Plasma VLDL - TG

c. Intramuscular TG

d. Adipose tissue TG

Key Point 2

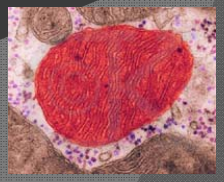
The source of exercise generated fatty acid oxidation in muscle:

- ✓ *Plasma fatty acids*
- ✓ *TG carried/stored in*

  Very low density lipoprotein particles

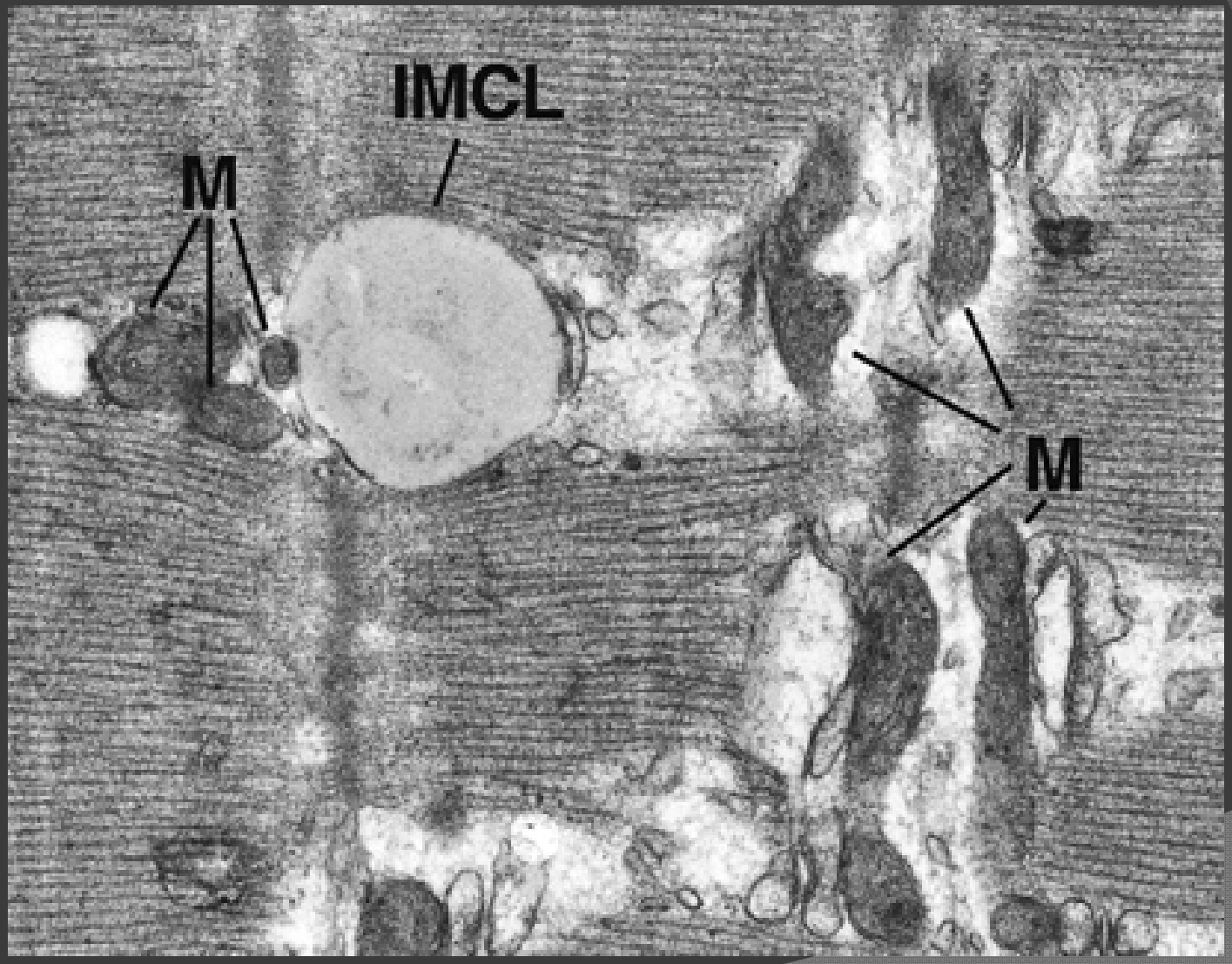
  TG stored in muscle – IMTG

  - then hydrolyzed to free fatty acids for mitochondrial uptake and oxidation



- ✓ *Adipose tissue*

Intramuscular TG Storage



IMCL, intramyocellular lipid

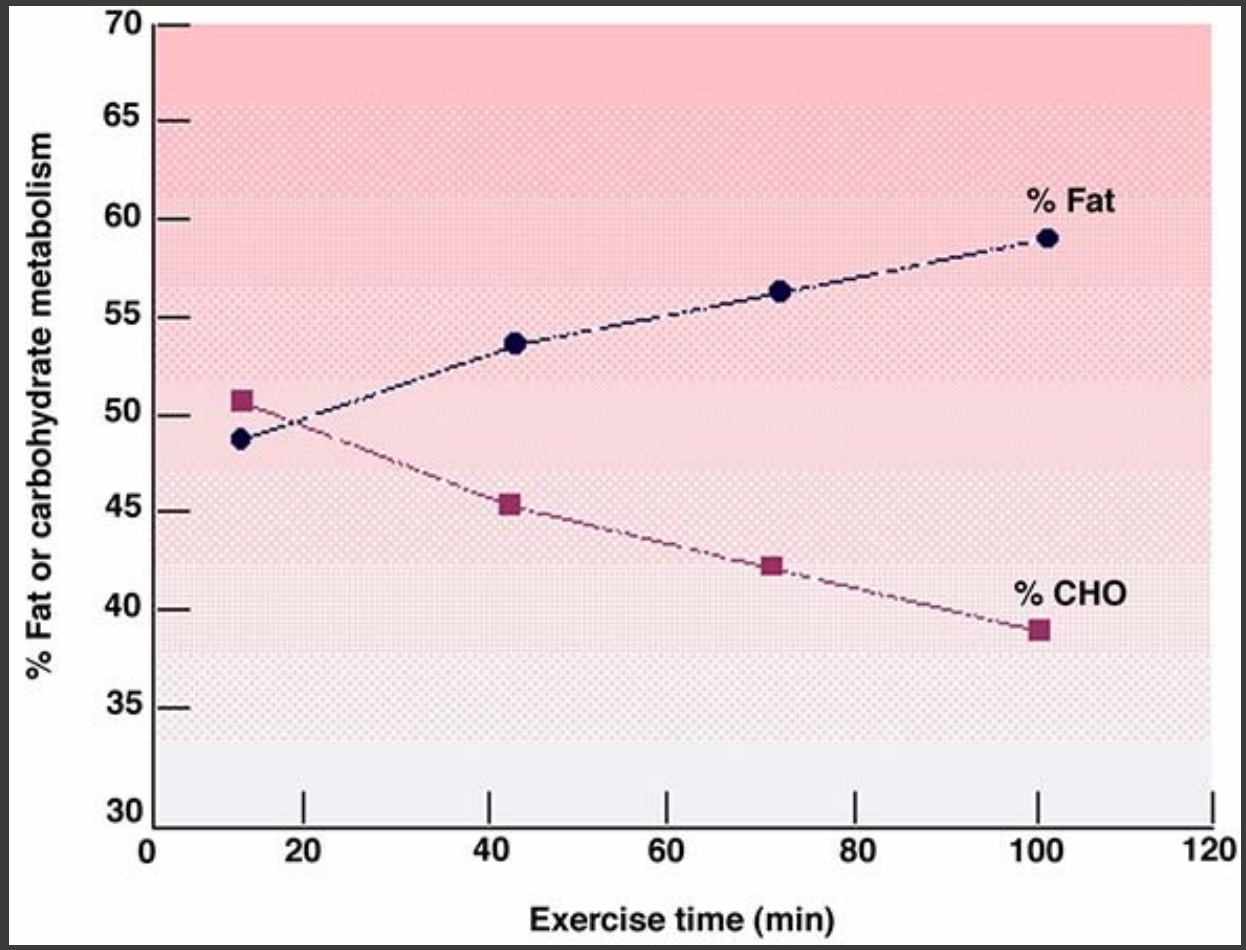
Interaction of Exercise Duration

and Exercise Intensity and Fatty Acid Oxidation

i.e., exercise time and speed

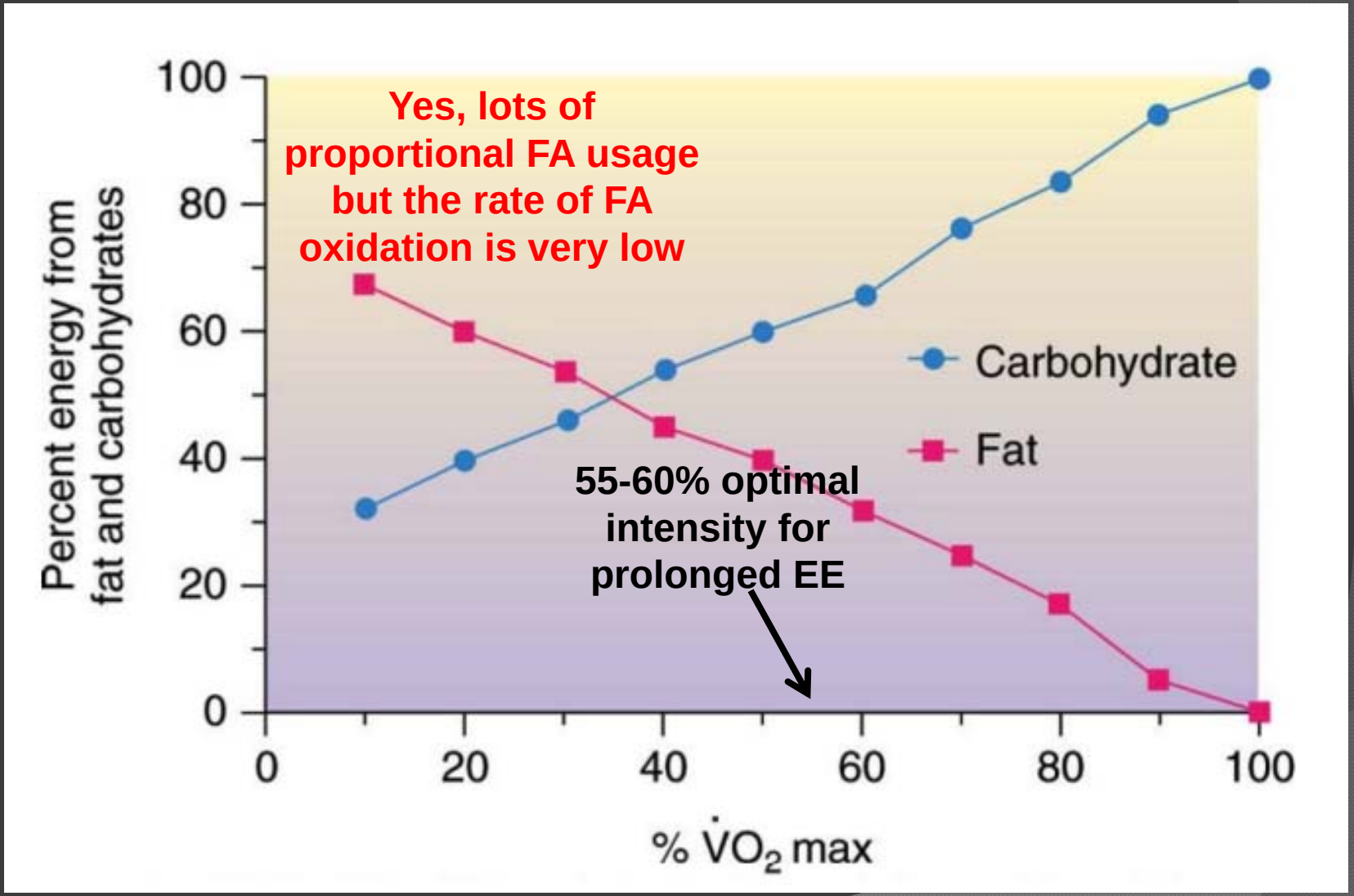
A counterintuitive assumption/misconception

Exercise Duration and Fuel Selection



- During prolonged exercise there is a shift from CHO metabolism toward fat metabolism
- The rate of FFA oxidation is relatively low at long-durations

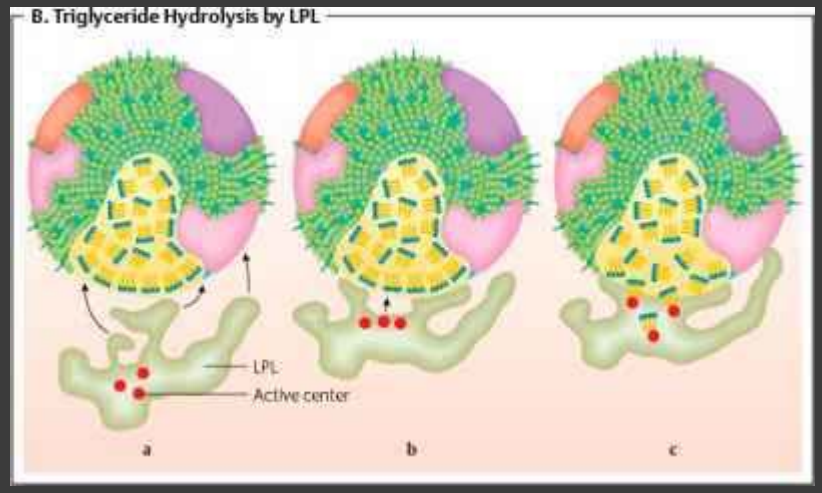
Exercise Intensity and Fuel Selection

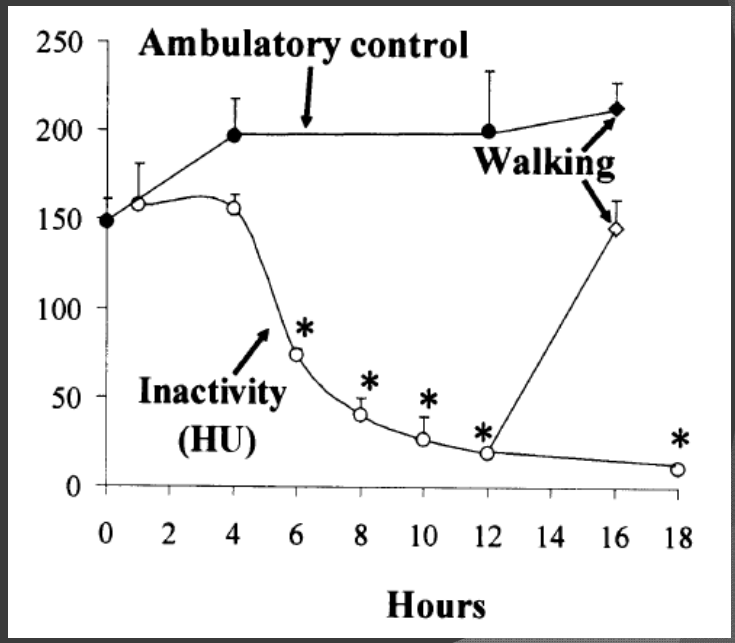


Powers & Howley 2009

Lipoprotein Lipase Activity

Restriction of physical activity (e.g., sedentary or sitting time) has been reported to result in a 10-fold decrease in lipoprotein lipase activity in red oxidative muscle fibers and in adipose tissue. This transiently increases TG and decreases HDL-C





Bey 2003
Hamilton 2003
Katamarzyk & Church 2009

Key Research Findings
1989-2014

- Exercise-induced TAG-lowering is acute, in that it manifests after just a single bout of exercise and is not the result of repeated exercise sessions (i.e., training), and short-lived, as it is readily reversed when exercise is withdrawn (i.e., detraining).

- Numerous studies have confirmed this initial hypothesis: the magnitude of the decrease in plasma TAG concentration after a single exercise session and after training is the same (i.e., 15–50%).

- These observations suggest that chronic exercise does not have an equally sustainable effect on plasma TAG concentration, i.e., beyond that attributed to acute exercise; hence exercise should be performed on a regular and uninterrupted basis to maintain hypoTG.

- An apparent energy expenditure threshold, more exercise does not seem to result in greater decreases in fasting plasma TAG concentrations although it may produce a somewhat longer-lived effect.

Annuzzi 1997
Zhang 2007
Ferguson 1998

- The magnitude of TAG-lowering in response to a single bout of exercise of the same duration and relative intensity is similar in *obese and lean subjects*, and *men and women* but greater in trained than untrained subjects

Gill 2004, 2002

- 400-500 kcal of aerobic exercise performed 12–16 h prior to a meal seems to produce the most dramatic and consistent decrease in postprandial lipemia (TG and TGRL's)

  *400-500 kcal = ~ 4-5 mile run or 6-8 mile walk

Peddie 2012
Maraki 2010
Burns 2005
Shannon 2005

- Delayed-onset hypotriacylglycerolemia in the basal state, 1 day after a single bout of endurance exercise is due to *augmented efficiency VLDL-TAG removal* from the circulation, likely mediated by the secretion of fewer but TAG-richer VLDL particles from the liver;

Exercise-induced changes in skeletal muscle lipoprotein lipase are more likely a contributing rather than the primary factor of TAG-lowering.

Magkos 2009

- The exercise-induced increase in basal VLDL-TAG clearance rate plateaus at 40%, whereas the threshold of energy that needs to be expended during endurance exercise lies near or above 500–600 kcal.

Resistance exercise is more potent than endurance exercise in this respect.

Magkos 2009

- The type of endurance exercise, i.e., cycling or running, does not appear to affect the VLDL-TAG metabolism response to exercise, despite differences in muscle recruitment and substrate oxidation rates during these two types of activity.

Magkos 2006
Tsekouras 2007
Achten 2003

Exercise and Postprandial Lipemia/TG

Response to fatty meals







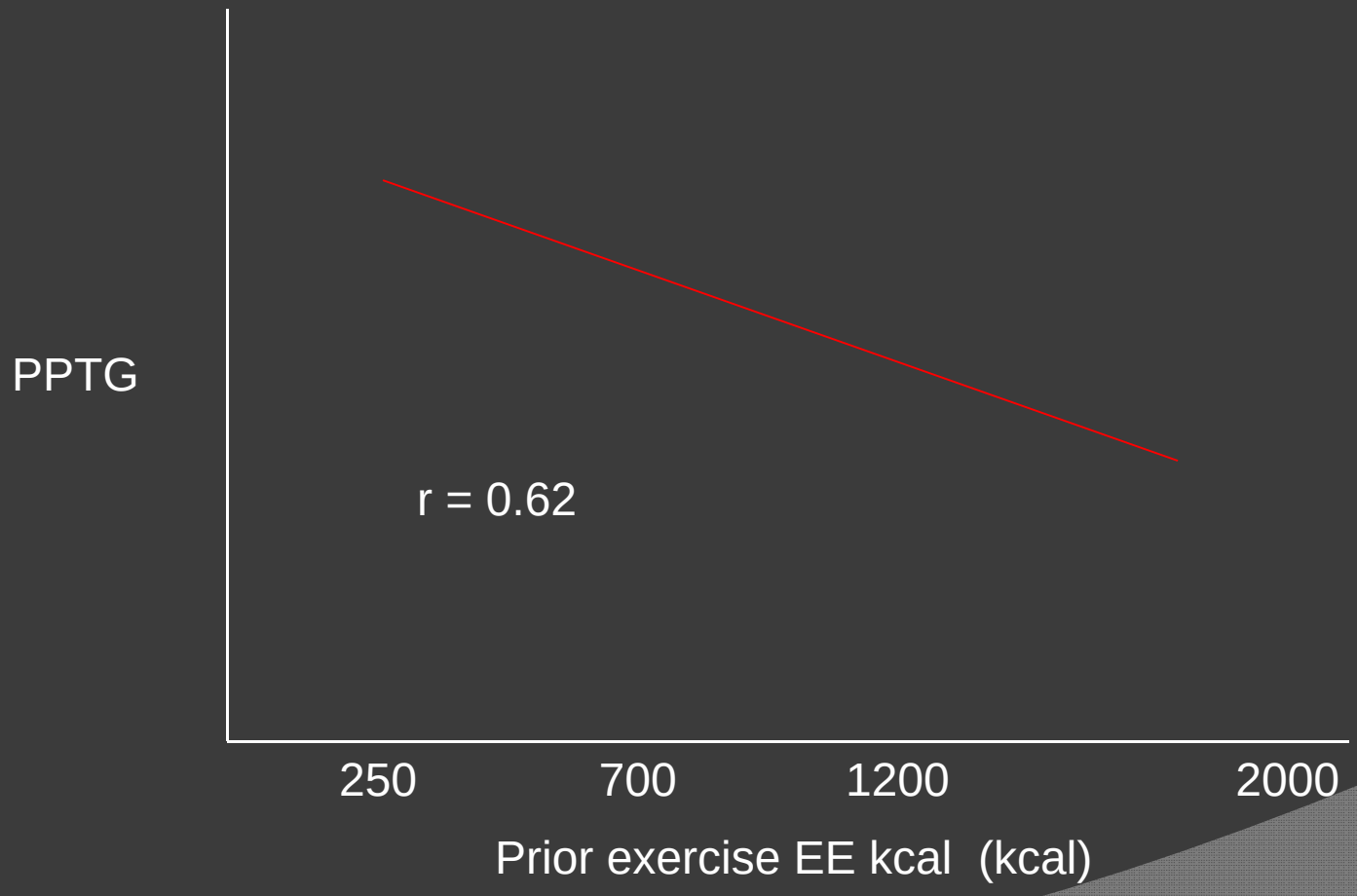
Fat load (12 - 22 grams) and/or
glycemic load

+

Caffeine load (40-200 milligrams)

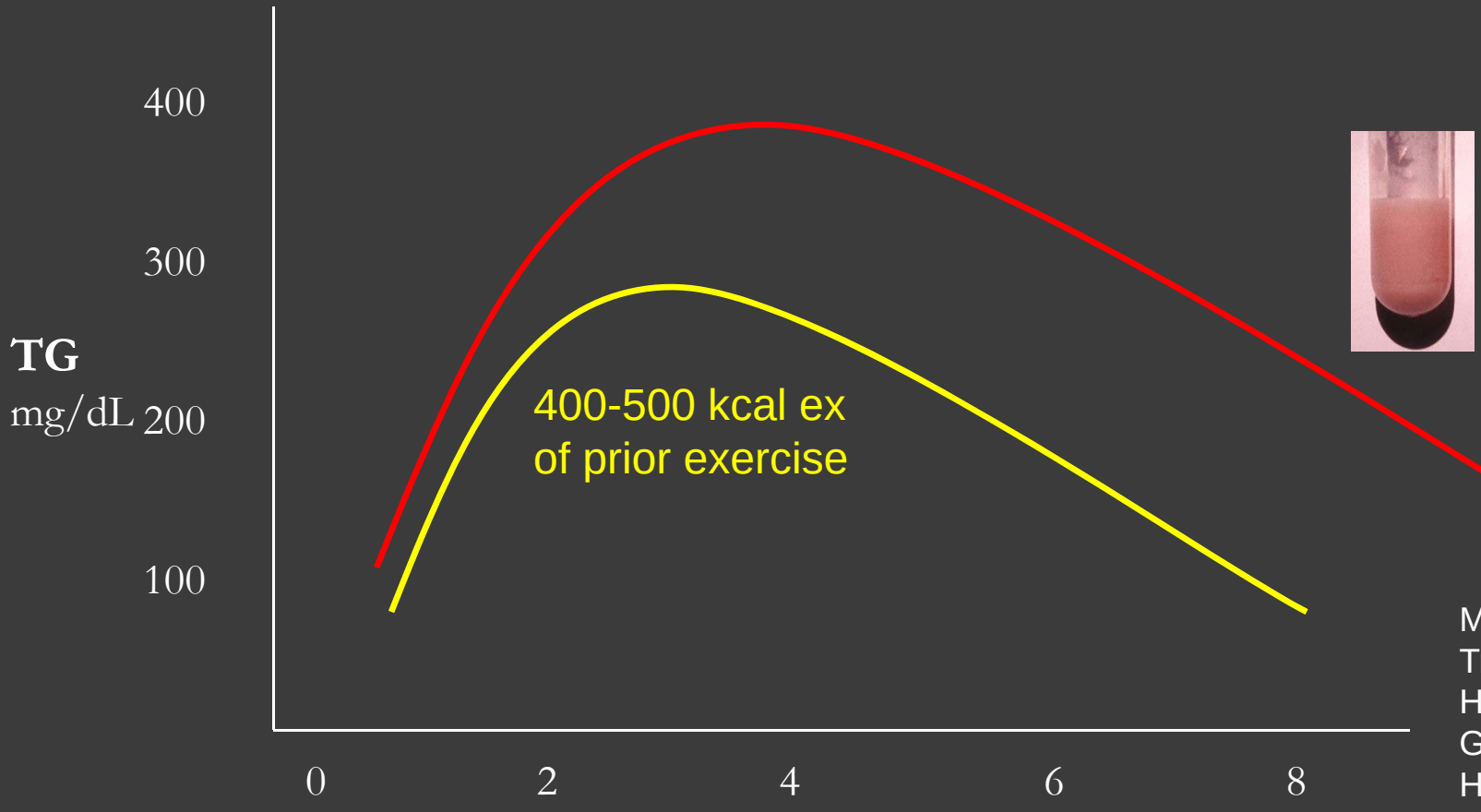
Quantitative Review of Exercise and PPTG

38 effects from 555 subjects, 28 studies



Petitt D & Cureton K Metabolism. 2003;4:418

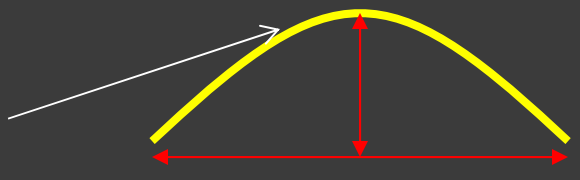
Preprandial Exercise and Postprandial Lipemia



Maraki 2013
Trombold 2013
Hashimoto 2013
Gabriel 2013
Ho 2011
Mestek 2011
Farah 2010
Magkos 2009
Smith 2004
Petitt 2003
Thomas 2000
Zhang 1998

Postprandial Lipemia (TG) Issues

- TG time/area under the curve is greater with T2D, visceral ob, & MetSyn



- Decreased arterial endothelial function
- Decreased HDL-C response
- Increased chylomicron, & IDL- VLDL remnant exposure

Maraki 2013
Napolitano 2013
Nakajima, 2012
Wojczynski, 2011
Giannattasio, 2005
Wang, 2011
Hajer, 2008
Kris-Etherton, 2007
Nestel, 2001
Whitman, 1998
Zhang, 1998

Exercise plus n-3 fatty acids: Additive effect on postprandial lipemia

Smith BK et. al. Metabolism 2004;53:1365 (Univ. of Kansas)

N = 10 healthy males (25yrs)

Supplementation consisted of 4.0 g of n-3FA per day for 5 weeks.

Results: TG peak ↓ 38% by n-3FA supplementation and 50% by the combination of exercise and n-3FA supplementation.

When compared with the exercise trial, the TG-AUC_T during the combined trial was significantly lower.

Exercise: 40%

n-3FAs: 42%

Ex + n3: 58%

The chronic effects of fish oil with exercise on postprandial lipaemia and chylomicron homeostasis in insulin resistant viscerally obese men

Clark K et.al. *Nutrition & Metabolism* 2012, 9:9 Perth Aust.

- 29 men with metabolic syndrome were randomly assigned to take fish oil or placebo for four weeks, before undertaking an additional 12 week walking program.
- Supervised **walking sessions, 3-5 X week @ 474 kcal per session**
- 4 fish oil capsules (providing a total of 1000 mg EPA and 700 mg DHA) or four placebo tabs/day with meals. **1.7g n3**

Results: Combining fish oil and exercise resulted in a significant further reduction in the fasting apo B48 concentration, concomitant with attenuation of fasting TAG concentrations and the postprandial TAGIAUC response - ↓ **22%.**

✓ **An effective therapeutic strategy for the chylomicronemia in subjects with MetS is the combination of chronic, regular exercise and a relatively low dose of fish oil.**

The chronic effects of fish oil with exercise on postprandial lipaemia and chylomicron homeostasis in insulin resistant viscerally obese men

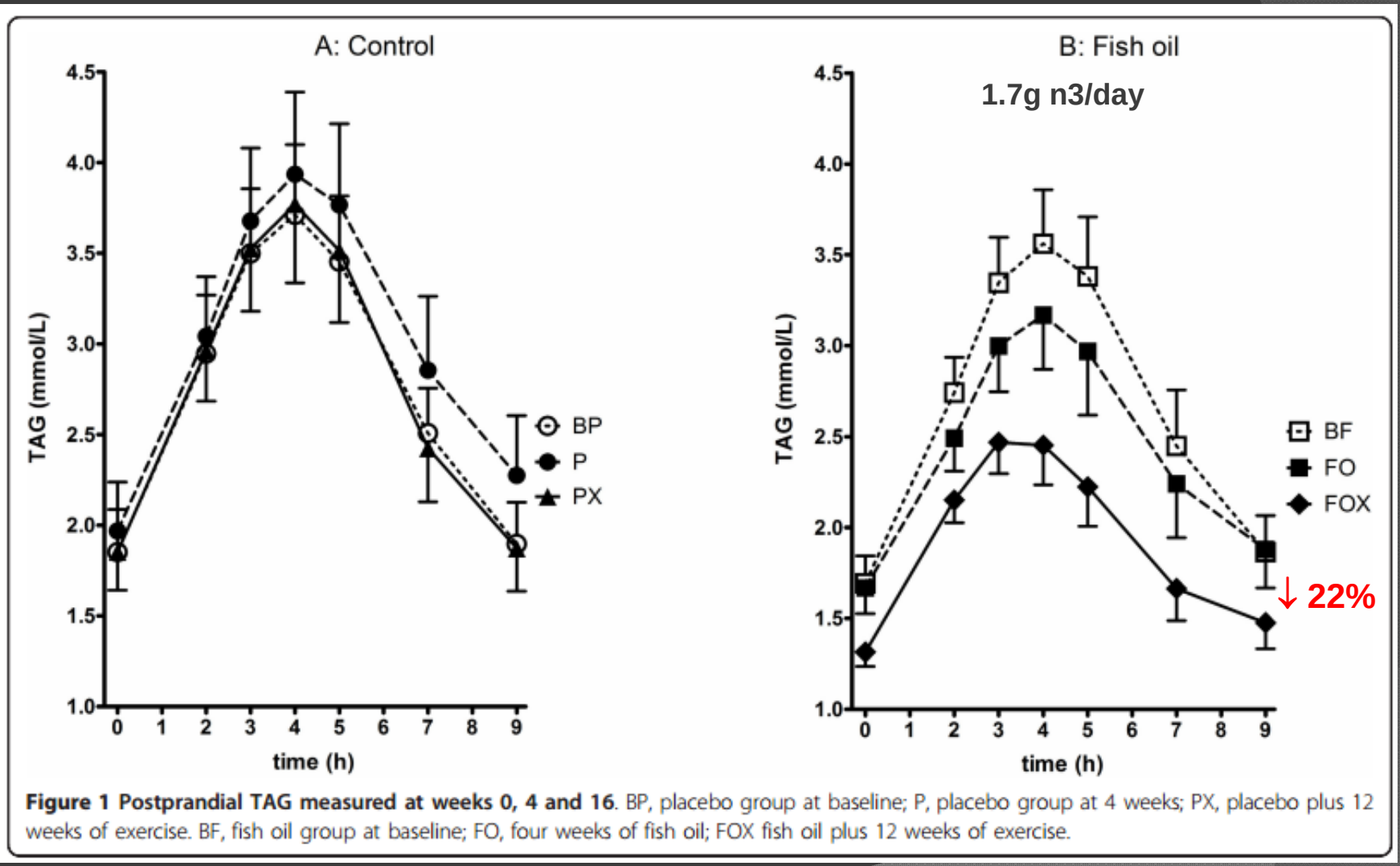


Figure 1 Postprandial TAG measured at weeks 0, 4 and 16. BP, placebo group at baseline; P, placebo group at 4 weeks; PX, placebo plus 12 weeks of exercise. BF, fish oil group at baseline; FO, four weeks of fish oil; FOX fish oil plus 12 weeks of exercise.

Clark 2012

✓ We therefore conclude that an effective therapeutic strategy for the chylomicronemia in subjects with MetS is the combination of chronic, regular exercise and a relatively low dose (~2g) of fish oil.

Karin Clark *Nutrition & Metabolism* 2012, 9:9

Overall Characteristics of Exercise Quantity Required to Reduce Postprandial Lipemia

- Total exercise energy expenditure volume (kcal) in a single session appears to be more important than exercise intensity
- Ideal acute exercise volume is: ≥ 50 min or ≥ 400 kcal (minimum 45 minutes)
- Continuous or interval exercise of equal total kcal have similar TG-AUC effects (*e.g., 10 4-min bouts vs 1 40-min bout*)
- Ideal timing of exercise prior to fatty/glycemic meal is 8-12 hrs (6-24 hr range)
- The magnitude of postprandial TG reduction ranges from 25-50%
- The TG reduction is relatively short-lived (24-36 hrs)
- ↑ PPTG response is greatest when ≥ 50g of fat are consumed although several studies demonstrated response at lower intake values

Summary

- Exercise training programs (eg. 3-4 months of aerobic activity 5-7 days a week) appear to reduce plasma TG 4-37%
- Single exercise session TG reductions range from 15-50%
- The acute TG response to a 400 kcal dose of exercise appears to be limited to 24-36 hours
- Postprandial TG and TGRL response to high fat (and high glycemic) meals is attenuated by the volume and timing of prior exercise (8-12 hours earlier, ~400 kcal PA)


Sara Novenson



August 23, 2014

Title :Current & Future Triglyceride Pharmaceuticals

Harold Bays MD, FTOS, FACC, FACE, FNLA
L-MARC Research Center
Louisville, KY

HEART

Study Questions Fat and Heart Disease Link

By ANAHAD O'CONNOR MARCH 17, 2014, 5:00 PM 466 Comments



Smokey Bones Bar & Fire Grill/PRNewsFoto

A new study questions the relationship between heart disease and saturated fat.

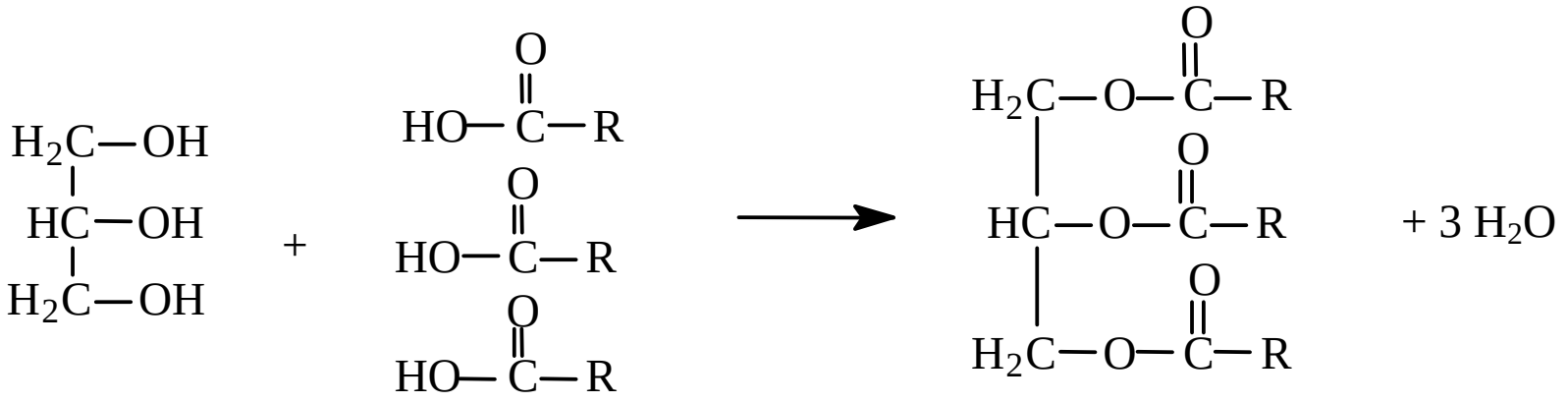
E-MAIL
FACEBOOK
TWITTER
SAVE

Many of us have long been told that saturated fat, the type found in meat, butter and cheese, causes heart disease. But a large and exhaustive new analysis by a team of international scientists found no evidence that eating saturated fat increased heart attacks and other cardiac events.

Fats = solid triglycerides
Oils = liquid triglycerides



Triglycerides



Glycerol 3 Fatty Acids Triglyceride

Types of Fatty Acids

Saturated Fats:

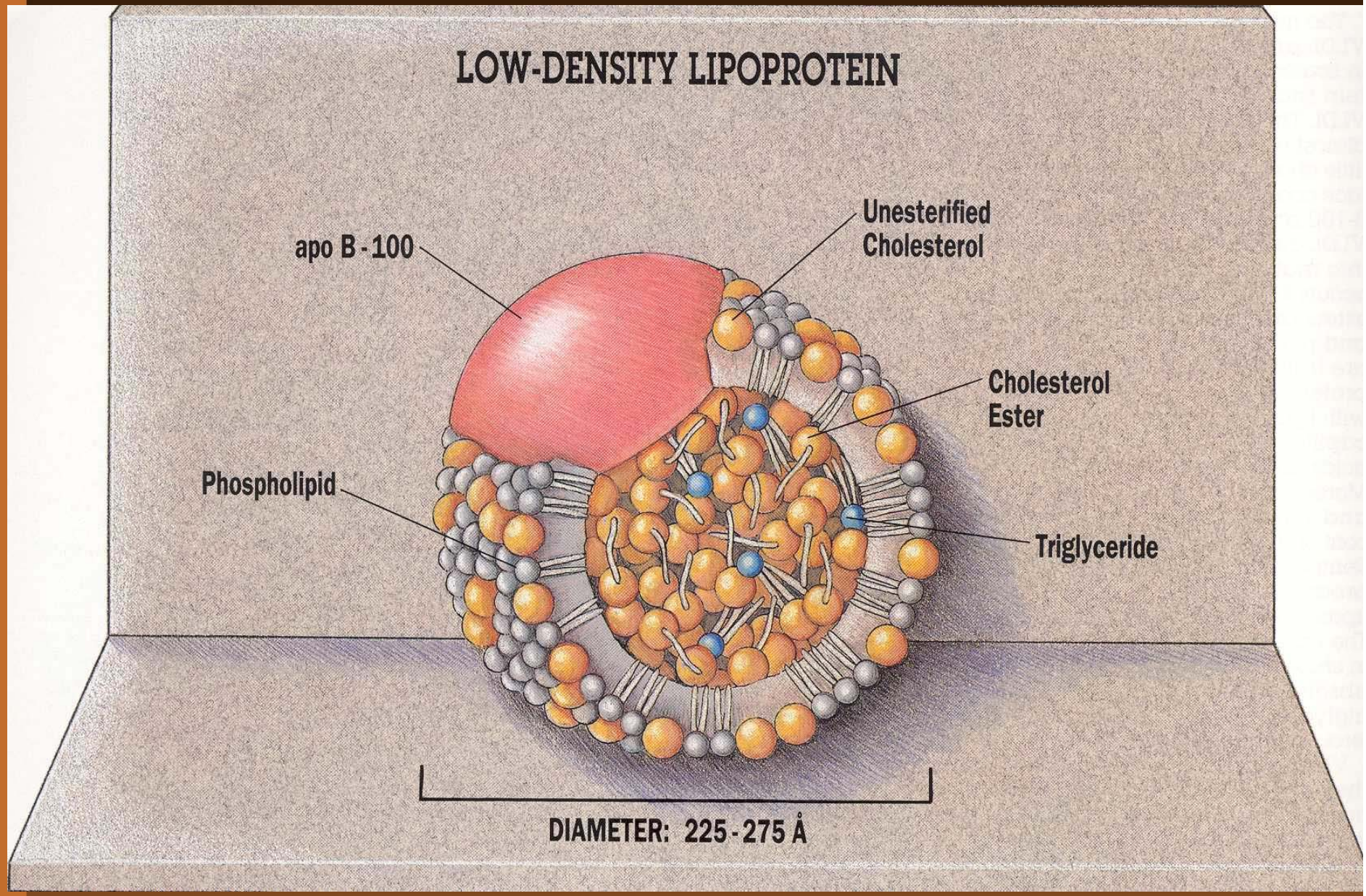
- Fully hydrogenated (no double bonds).
- From meat, dairy products, certain plant oils (palm, coconut).
- Usually solid at room temperature.

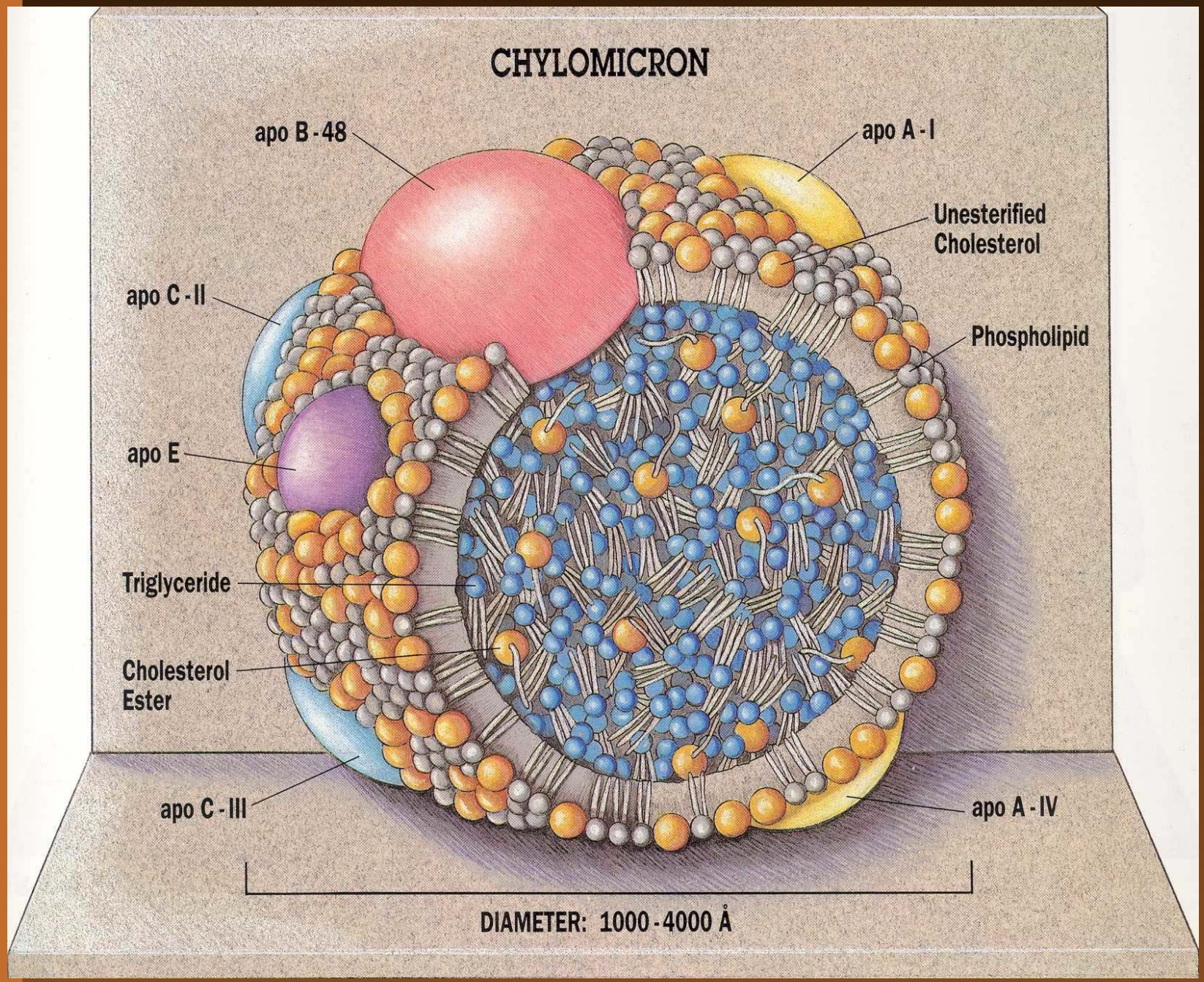


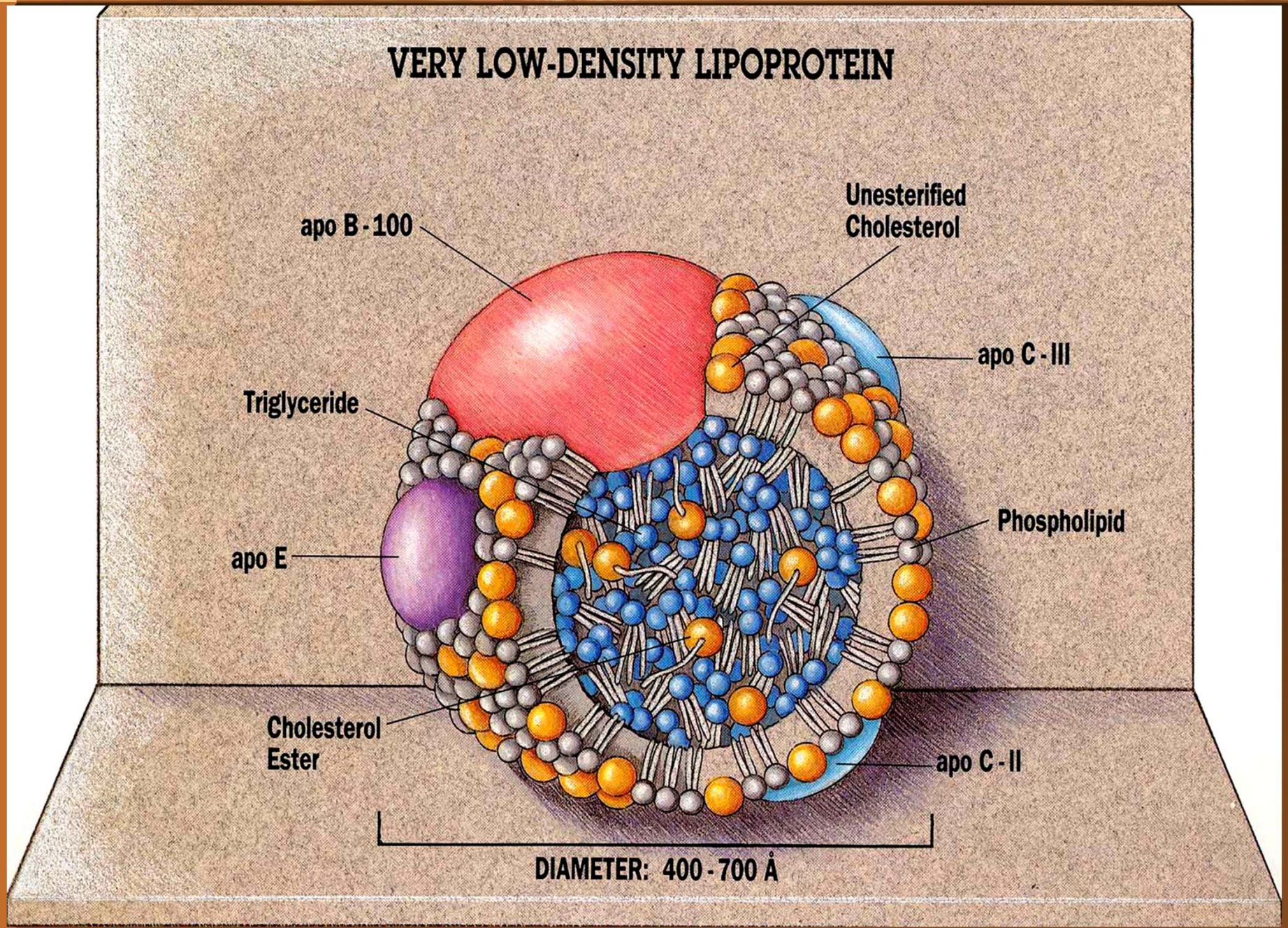
Unsaturated fats

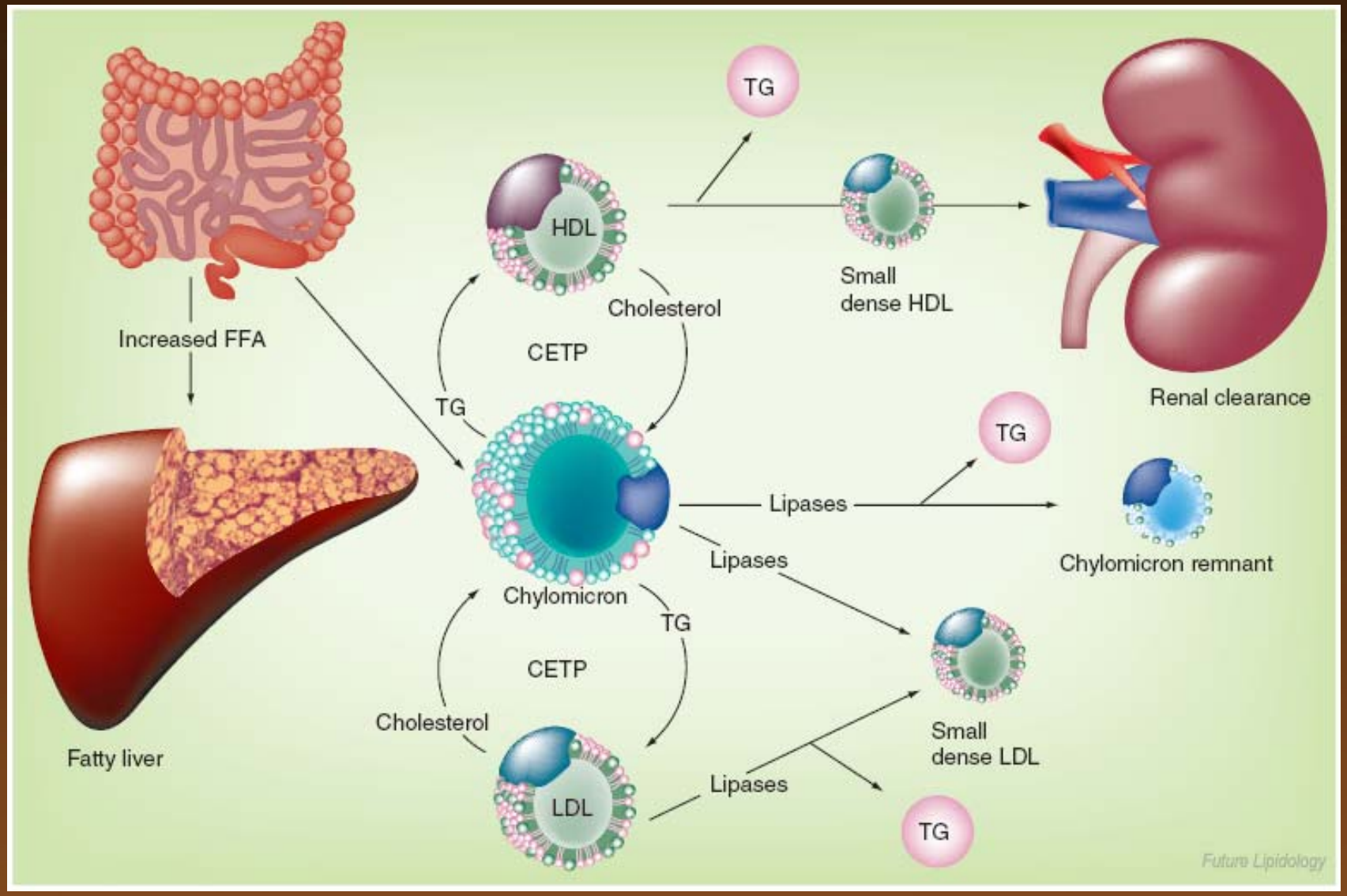
- Not fully hydrogenated (some double bonds).
  - Monounsaturated (one alkene unit) or polyunsaturated (several alkene units).
  - Mostly *cis*-alkenes
- From fish, oily fruits & vegetables, nuts, certain plant oils (soybean, corn, canola, olive, sunflower).
- Often oily rather than solid.
- Tend to oxidize in air and become rancid.



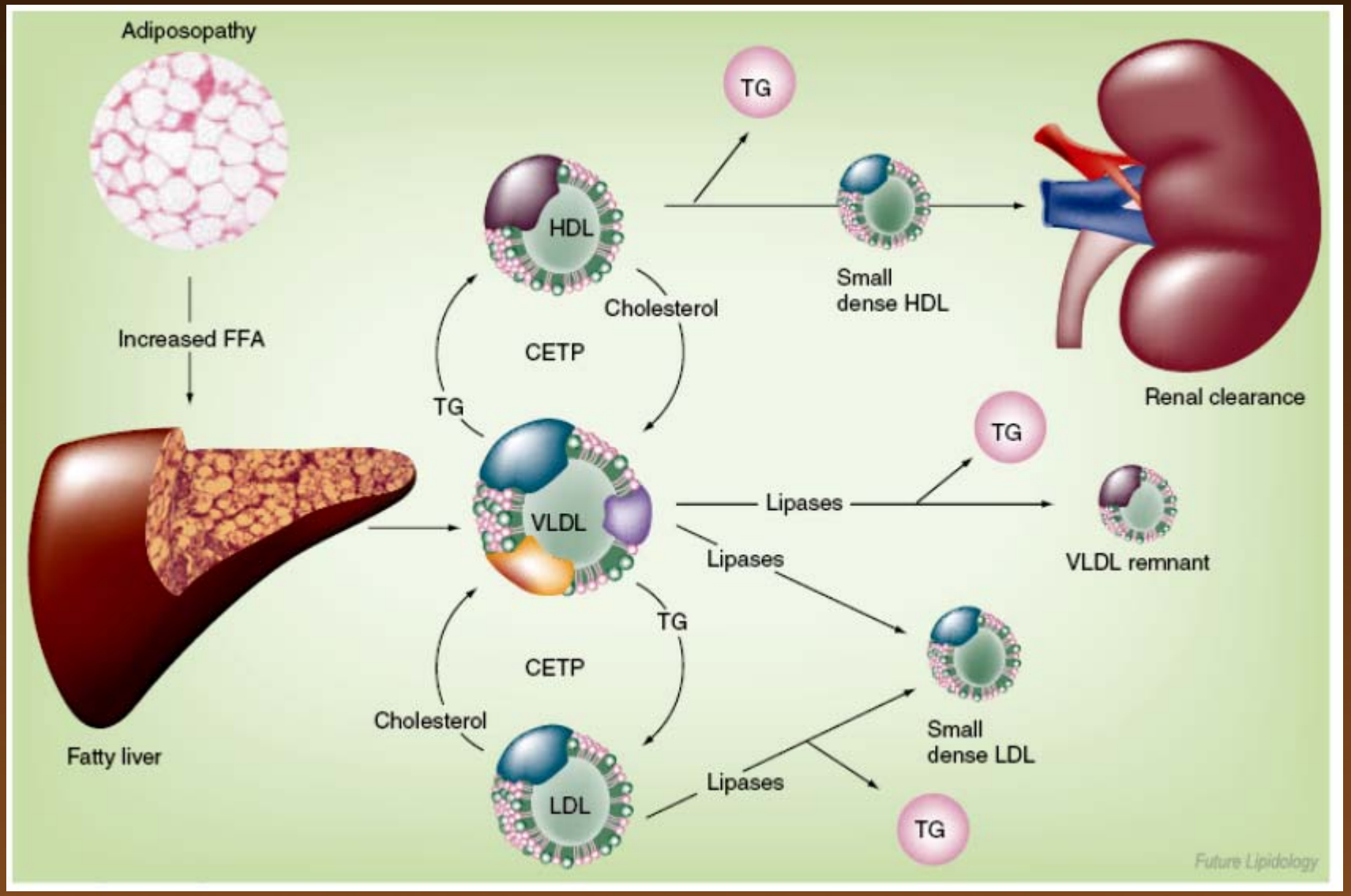

LOW-DENSITY LIPOPROTEIN
apo B-100
Unesterified Cholesterol
Cholesterol Ester
Phospholipid
Triglyceride
DIAMETER: 225-275 Å


CHYLOMICRON
apo B-48
apo A-I
Unesterified Cholesterol
apo C-II
Phospholipid
apo E
Triglyceride
Cholesterol Ester
apo C-III
apo A-IV
DIAMETER: 1000-4000 Å


VERY LOW-DENSITY LIPOPROTEIN
apo B - 100
Unesterified Cholesterol
apo C - III
Triglyceride
Phospholipid
apo E
Cholesterol Ester
apo C - II
DIAMETER: 400 - 700 Å



Bays H, Ballantyne C. *Future Lipidology.* 2006;1(4):389-420



Bays H, Ballantyne C. *Future Lipidology.* 2006;1:389-420;
Bays H, et al. *Expert Rev Cardiovasc Ther.* 2005;3:789-820.

Introduction / Outline

- Omega-3 fatty acids
- DGAT inhibitors
- Apo CIII inhibitors

Statins Reduce CVD Events in HTG Patients
(HTG Subgroup Data)

Trial (Subgroup, mg/dL) (Drug)	Risk difference vs placebo		P-value	
	Main Study	Subgroup	Main Study	Subgroup
WOSCOPS (TG ≥148) (Pravastatin)	**–31%**	**–32%**	**<0.001**	**0.003**
CARE (TG ≥144) (Pravastatin)	**–24%**	**–15%**	**0.003**	**0.07**
PPP Project (TG ≥200) (Pravastatin)	**–23%**	**–15%**	**<0.001**	**0.029**
4S (TG >159, HDL-C <39) (Simvastatin)	**–34%**	**–52%**	**<0.001**	**<0.001**
JUPITER (TG ≥150) (Rosuvastatin)	**–44%**	**–21%**	**<0.001**	**NS**
CTT (TG >177) (Various)	**–21%**	**–24%**	**<0.001**	**<0.001**

Median follow-up: ≥5 yrs.

CARE=Cholesterol and Recurrent Events Trial; CTT=Cholesterol Treatment Trialists; JUPITER=Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin; NS=not significant; PPP=Prospective Pravastatin Pooling; 4S=Scandinavian Simvastatin Survival Study; WOSCOPS=West of Scotland Coronary Prevention Study. Ballantyne CM et al. *Circulation*. 2001;104:3056-51. CTT Collaborators. *Lancet*. 2005;366:1267-78. Maki KC et al. *J Clin Lipidol*. 2012;6:413-26.

Risk Difference vs Placebo of HTG Subgroups

Large-scale, Primary and Secondary CVD Prevention Trials

Trial (drug)	Primary endpoint: entire cohort (P)	Lipid subgroup criterion	Primary endpoint: subgroup post-hoc (P)
HHS (gemfibrozil)	–34% (<0.02)	TG >204 mg/dL LDL-C/HDL-C ratio >5.0	–72% (0.005)
BIP (bezafibrate)	–9% (0.26)	TG ≥200 mg/dL	–39.5% (0.02)
VA-HIT (gemfibrozil)	–22% (0.006)	TG ≥150 mg/dL	–27% (0.01)
FIELD (fenofibrate)	–11% (0.16)	TG ≥204 mg/dL HDL-C <40 mg/dL (men) or <50 mg/dL (women)	–27% (0.005)
ACCORD (fenofibrate)	–8% (0.32)	TG ≥204 mg/dL HDL-C ≤34 mg/dL	Prespecified –31% (<0.05)
JELIS (EPA)	–19% (0.011)	TG ≥150 mg/dL HDL-C <40 mg/dL	–53% (.043)
AIM-HIGH (niacin)	+2% (0.79)	TG ≥200 mg/dL HDL-C <32 mg/dL	–36% (0.032)

ACCORD=Action to Control Cardiovascular Risk in Diabetes; AIM-HIGH=Atherothrombosis Intervention in MetS with Low HDL/High TG: Impact on Global Health Outcomes; BIP=Bezafibrate Infarction Prevention; FIELD=Fenofibrate Intervention and Event Lowering in Diabetes; HHS=Helsinki Heart Study; JELIS=Japan EPA Lipid Intervention Study; VA-HIT=Veterans Affairs HDL Intervention Trial.

Guyton JR et al. *J Am Coll Cardiol*. 2013;62:1580-4. Maki KC, Bays HE, Dicklin MR. *J Clin Lipidol*. 2012;6:413-26.

Omega-3 fatty acids

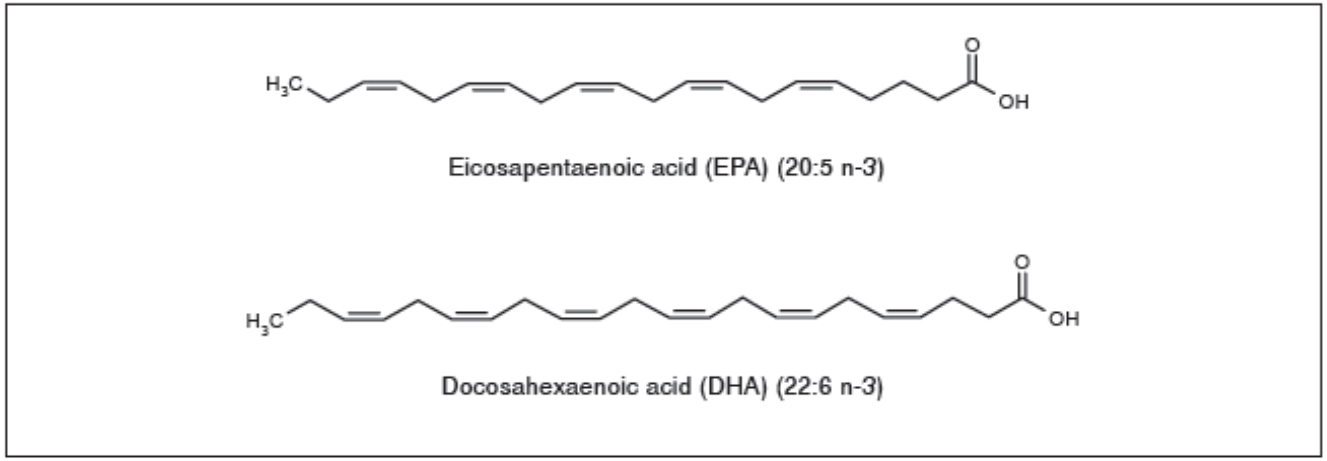


Fig. 7. Chemical structures of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The omega-3 EPA has five double bonds, while DHA has six double bonds, with the first double bond being three carbons from the methyl ("omega") end.

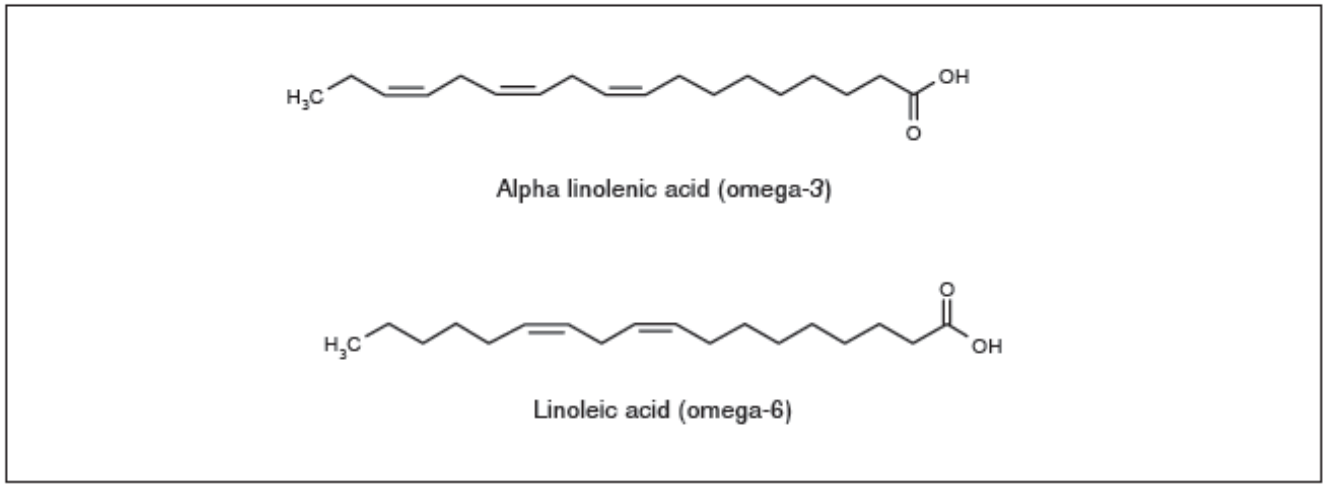


Fig. 8. Comparison of omega-3 and omega-6 fatty acids. Omega-3 fatty acids have a double bond three carbons from the methyl end, while omega-6 fatty acids have a double bond six carbons from the methyl ("omega") end.

Bays HE. Drugs of Today 2008, 44(3): 205-246

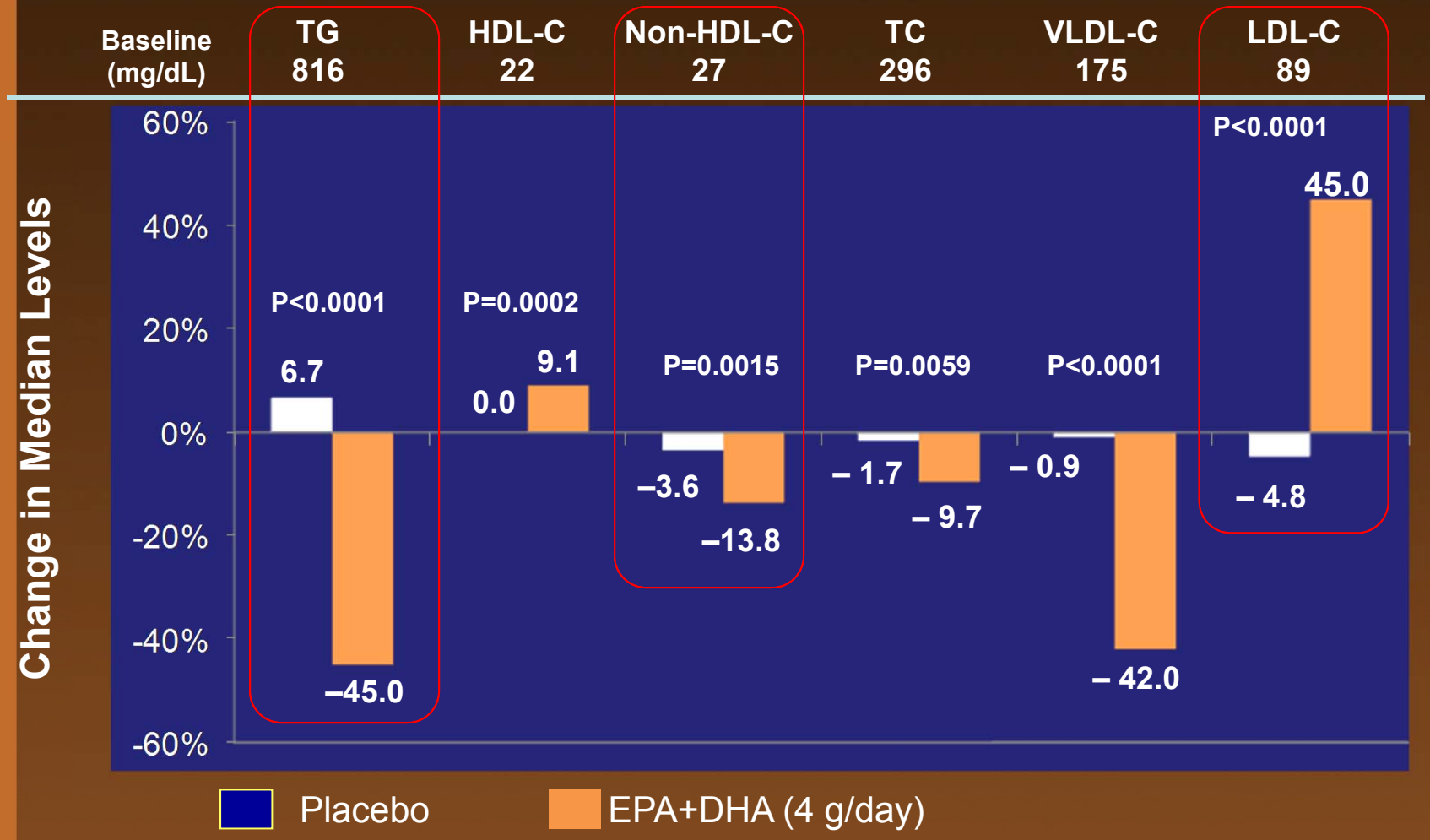
Table X: Approximate levels of eicosapentaenoic acid and docosahexaenoic acid in dry-heat cooked fish (2, 109, 142).*

Fish	EPA plus DHA (mg/100 g eaten)
Salmon Atlantic wild	1,840
Salmon Atlantic farmed	2,150
Salmon Chinook	1,740
Salmon Coho wild	1,060
Salmon Coho farmed	1,280
Herring Atlantic	2,000
Herring Pacific	2,130
Mackerel Pacific and jack	1,850
Mackerel Atlantic	1,200
Mackerel king	400
Halibt Atlantic and Pacific	470
Halibut Greenland	1,180
Tuna bluefin	1,500
Tuna yellowfin	280
Tuna skipjack	300
Bluefish	990
Pollock Alaskan	120***
Cod Atlantic	160
Cod Pacific	280
Sablefish (black cod)**	1,790
Bass sea	760
Bass freshwater	760
Whitefish	1,610
Trout rainbow wild	990
Trout rainbow farmed	1,150

DHA = docosahexaenoic acid (22:6 n-3); EPA = eicosapentaenoic acid (20:5 n-3). *Cooked fish (dry heat) often has less omega-3 fatty acid content than raw fish: 100 g of fish would be approximately 4 ozs, which would be a bit larger than a deck of playing cards or cassette tape. The amount of omega-3 fatty acids varies considerably in the same type of fish, depending on the environment and location. **Sablefish or "black cod" is not part of the codfish family. ***Alaskan Pollock is the fish used in many fast-food restaurants, where it is usually battered and fried.

Bays HE. Drugs of Today 2008, 44(3): 205-246

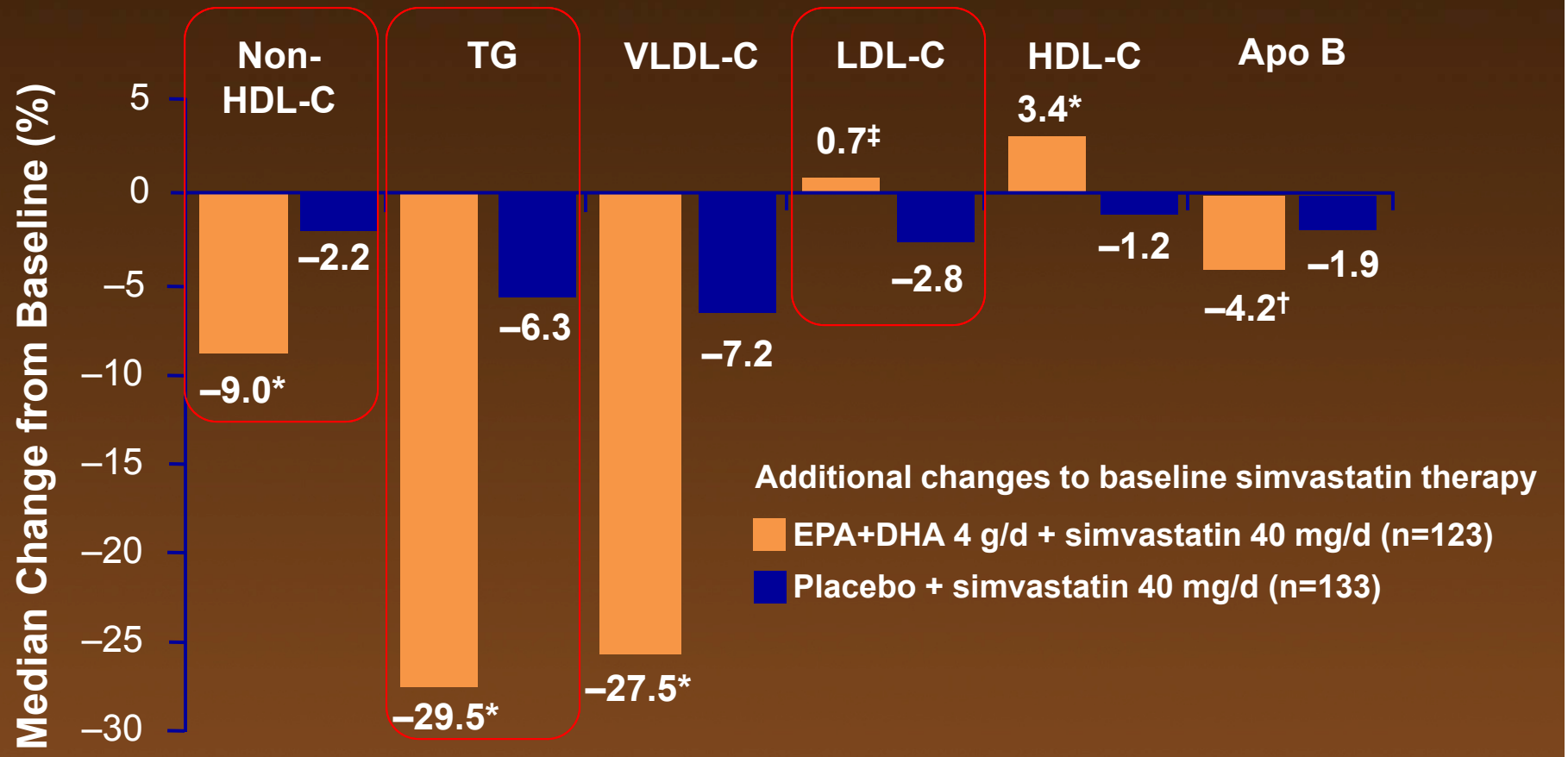
EPA+DHA and Lipid Levels in Patients with TG >500 mg/dL



Pooled analysis (N=82).

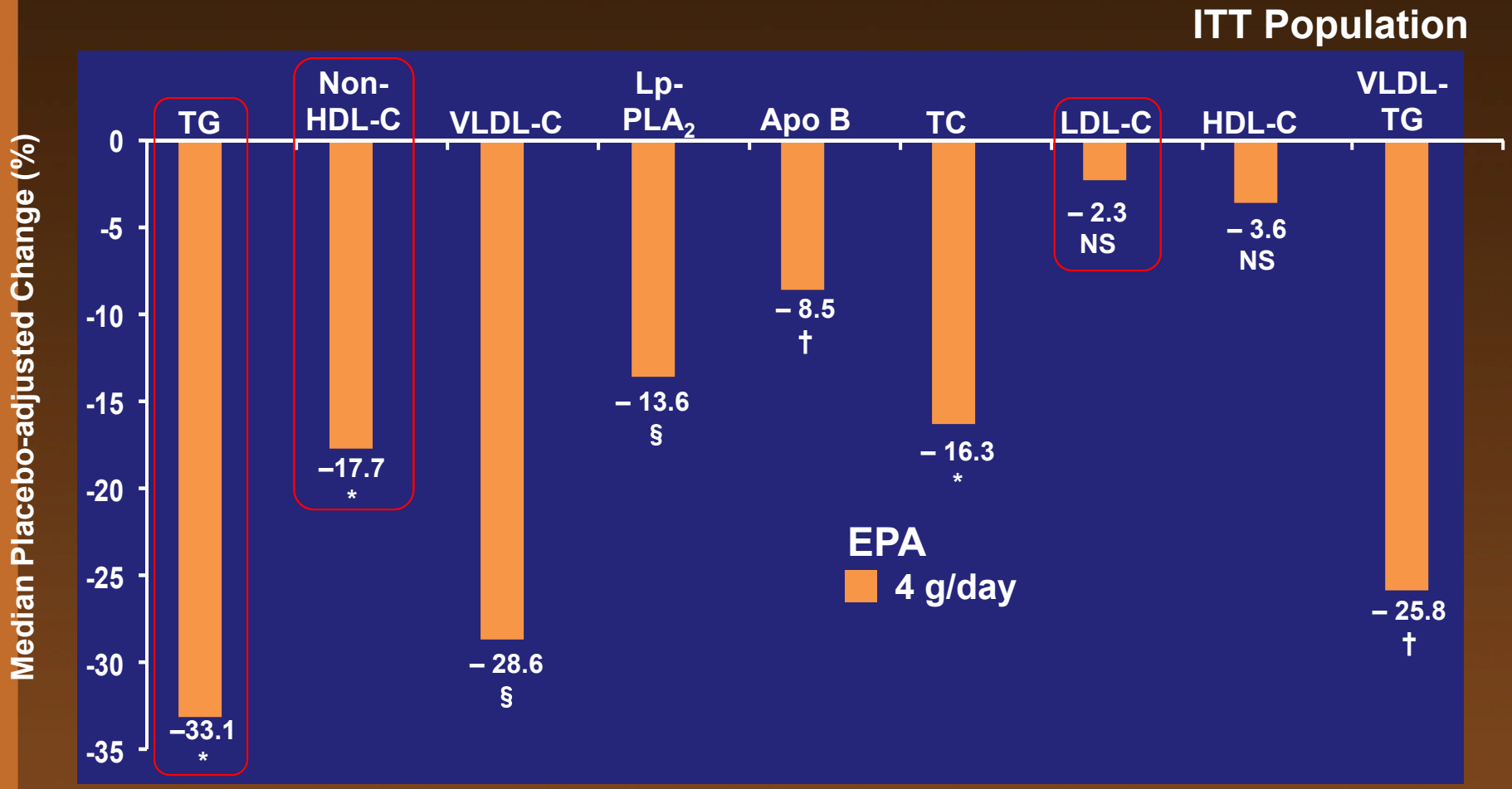
Harris WS et al. *J Cardiovasc Risk* 1997;4:385-91; Pownall HJ et al. *Atherosclerosis* 1999;143:285-97.

Statin + (EPA+DHA): COMBOS Primary and Secondary Efficacy Results



*P<0.0001 between groups. †P=0.0232 between groups. ‡P=0.0522 between groups.
COMBOS=Combination of Prescription Omega-3 with Simvastatin.
Davidson MH et al. *Clin Ther*. 2007;29:1354-67.

MARINE Study: EPA Median Placebo-adjusted Change from Baseline for Efficacy Endpoints



*P<0.0001. †P<0.01. §P<0.001. NS = P≥0.05.

TG >500 mg/dL

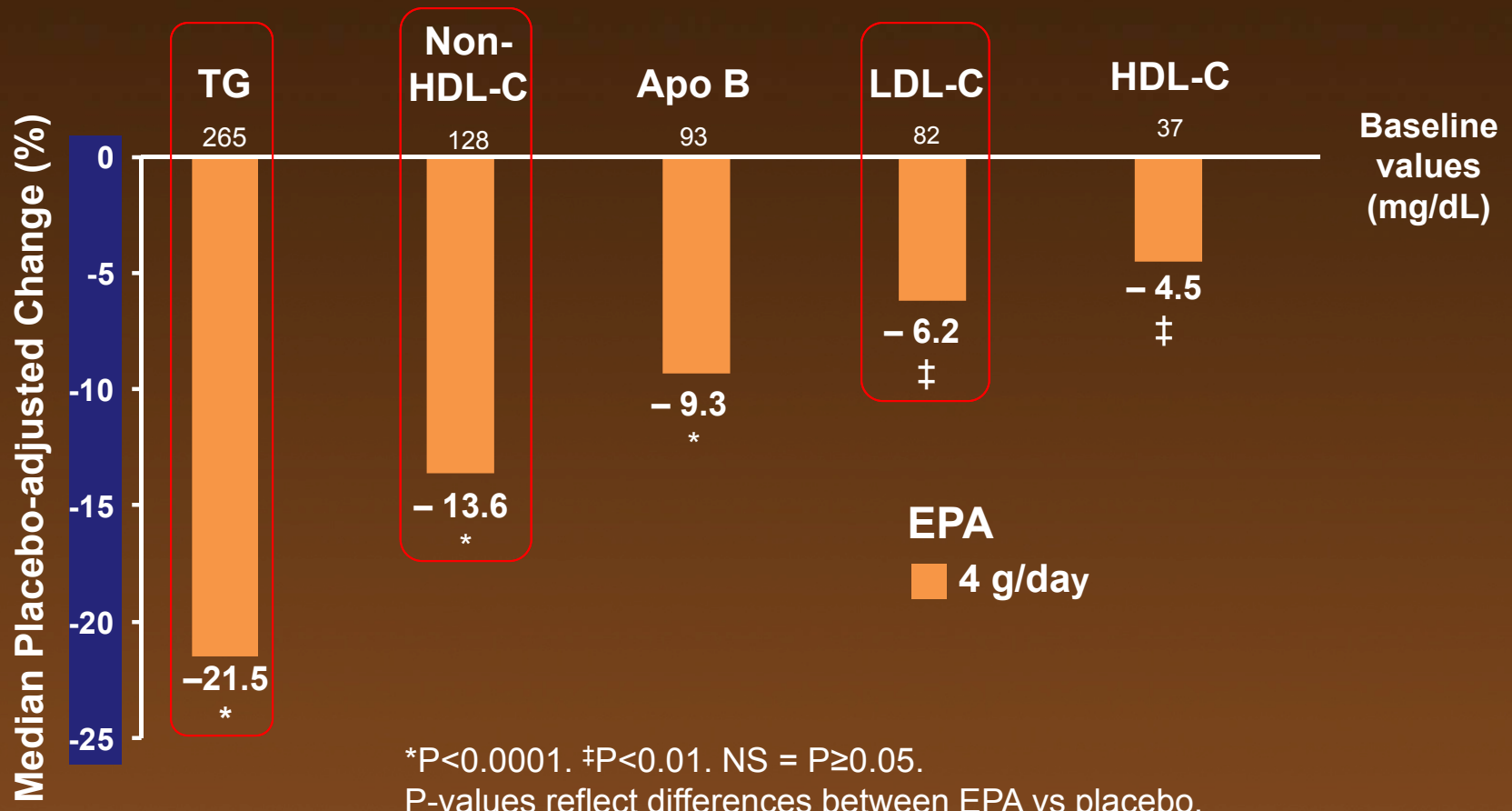
P-values reflect differences between EPA vs placebo.

ITT=intention to treat; Lp-PLA=lipoprotein-associated phospholipase A;
MARINE= Multi-center, Placebo-controlled, Randomized, Double-blind, 12-week Study with an Open-label Extension.

Bays HE et al. *Am J Cardiol*. 2011;108:682-90.

ANCHOR Study: EPA-based Changes in Lipid Endpoints

TG ≥200 and <500 mg/dL



*P<0.0001. ‡P<0.01. NS = P≥0.05.
P-values reflect differences between EPA vs placebo.

12-week trial in high-risk statin-treated patients (N=702) with residually ↑TG levels (≥200 and <500 mg/dL) despite LDL-C control (≥40 and <100 mg/dL). ANCHOR=Effect of AMR101 (Ethyl Icosapentate) on Triglyceride (Tg) Levels in Patients on Statins With High Tg Levels (≥200 and <500 mg/dL). Ballantyne CM et al. *Am J Cardiol*. 2012;110:984-92.

Selected OM-3 CVD Outcome Studies

	GISSI-P[1-2]	ORIGIN[3]	JELIS[4]	REDUCE-IT[5] (Ongoing)
OM-3 Type/dose	**EPA/DHA 1 g/day[2]**	**EPA/DHA 1 g/day**	**EPA 1.8 g/day**	**EPA 4 g/day**
Population	Italian	International	Japanese	International
N	11,324	12,536	18,645	~8,000
Gender	85% male	65% male	31% male	Accrual ongoing
Risk Profile	Recent MI (≤3 mos; median 16 days)	High CV risk, and IFG, IGT, or T2DM	80% 1° prev; TC ≥6.5 mM; excl MI ≤6 mos prior	TG >150 mg/dL +CHD or ↑CHD risk
Follow-up	3.5 years	6.2 years (median)	4.6 years (mean)	4–6 years (planned)
Statin Use	**Minimal**	53–55%	100% (sim or prav)	All on statins (LDL-C ≤goal)
Primary End Point	Tot. mort, NF CVD	CV death	MACE	MACE
Result	**RRR 10% (P=0.05) / 15% (P=0.023)**	**HR=0.98 P=0.72**	**RRR 19% (no minimum TG level) P=0.011**	**NA (Power 15% RRR)**

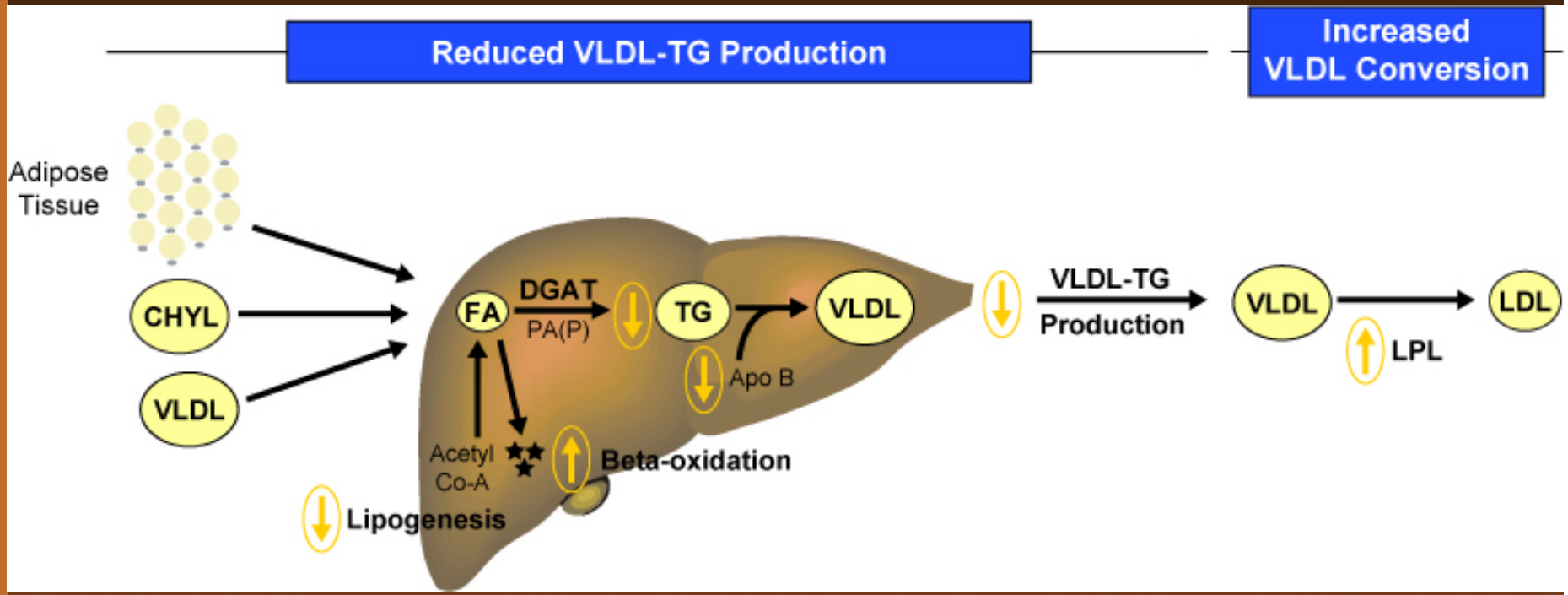
Low-dose OM-3 doesn't ↓CVD in statin-era. Mid-dose OM-3 does ↓CVD
--STRENGTH trial just started w/ EPA/DHA (FFA) in TG 200–500 mg/dL--

excl=excluded; GISSI= Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; IFG=impaired fasting glucose; IGT=impaired glucose tolerance; MACE=major adverse cardiac event; mos=months; ORIGIN=Outcome Reduction with an Initial Glargine Intervention; pbo=placebo; prev=prevention; REDUCE-IT=Reduction of Cardiovascular Events with EPA-Intervention Trial; RR=relative risk; RRR=relative risk reduction.

1. GISSI-Prevenzione Investigators. *Lancet*. 1999;354:447-55. 2. www.trialresultscenter.org/study4440-GISSI-P.htm. 3. ORIGIN Investigators. *N Engl J Med*. 2012;367:309-18. Similar lack of benefit with Risk and Prevention Trial 4. Yokoyama M et al. *Lancet*. 2007;369:1090-8. 5. http://www.clinicaltrials.gov.

Introduction / Outline

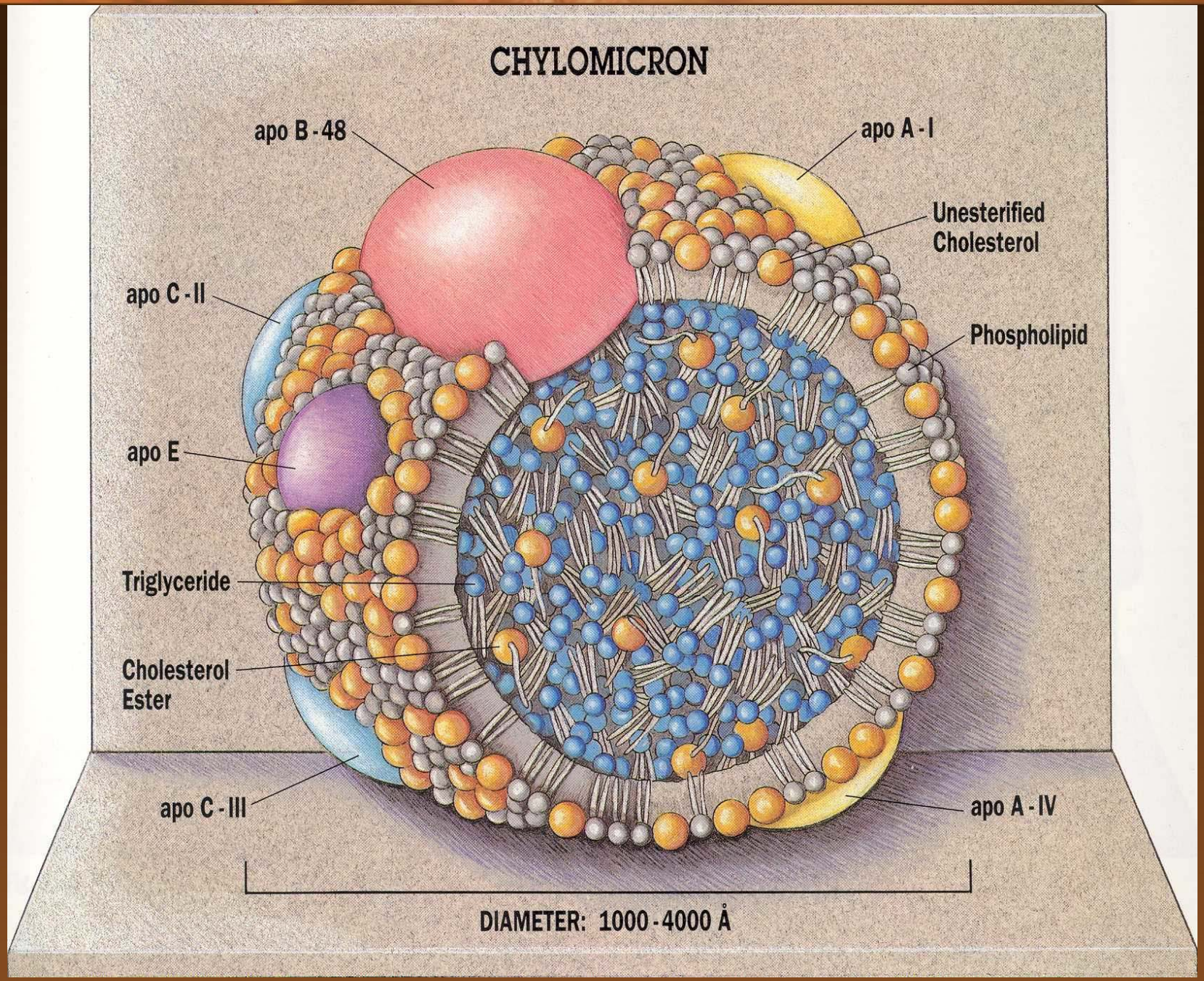
- Omega-3 fatty acids
- DGAT inhibitors
- Apo CIII inhibitors

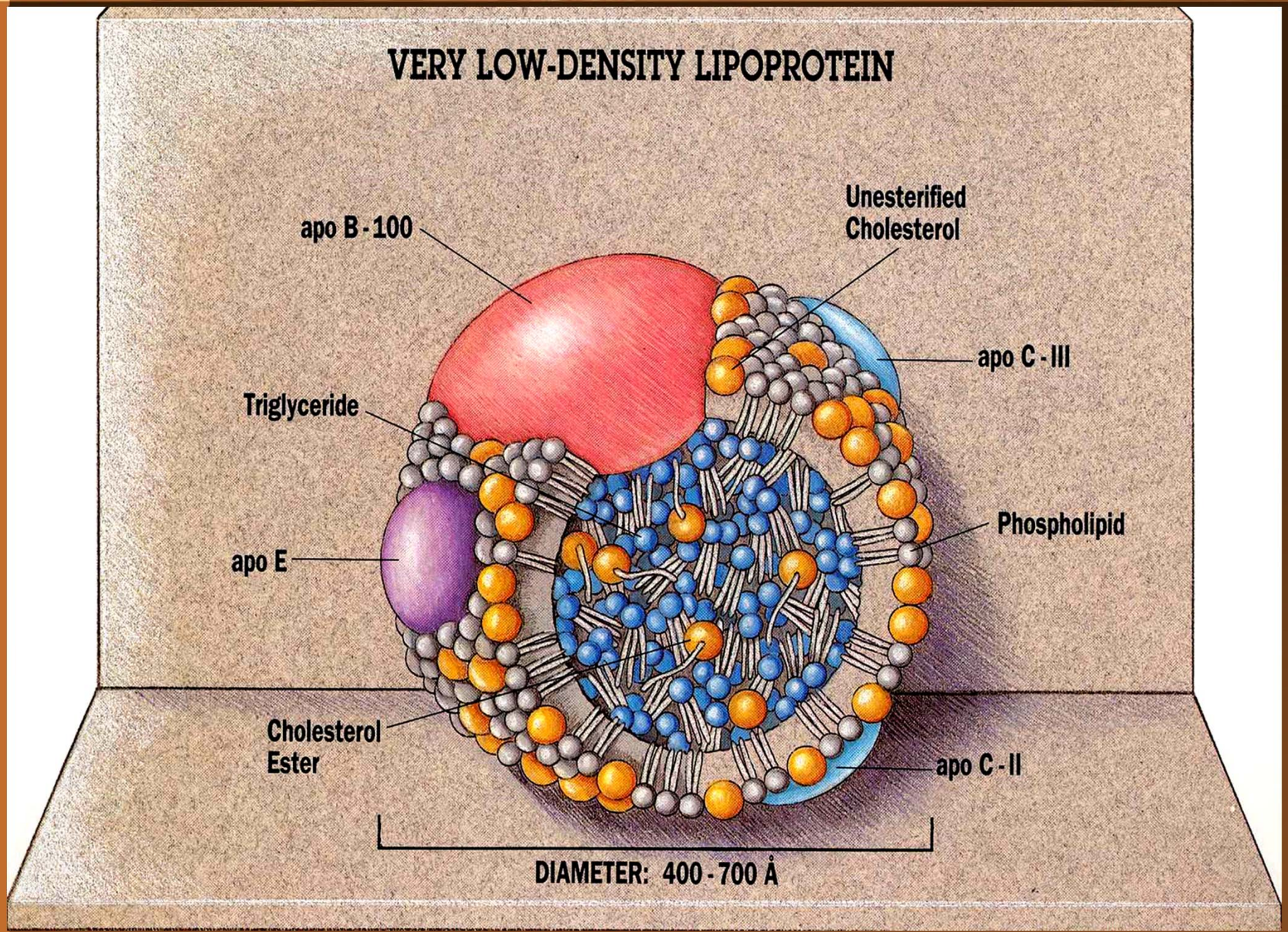


Harris WS, Bulchandani D. Curr Opin Lipidol 2006;17:387-393
Bays HE. *Expert Rev. Cardiovasc. Ther. 6(3), 391–409 (2008)*

Introduction / Outline

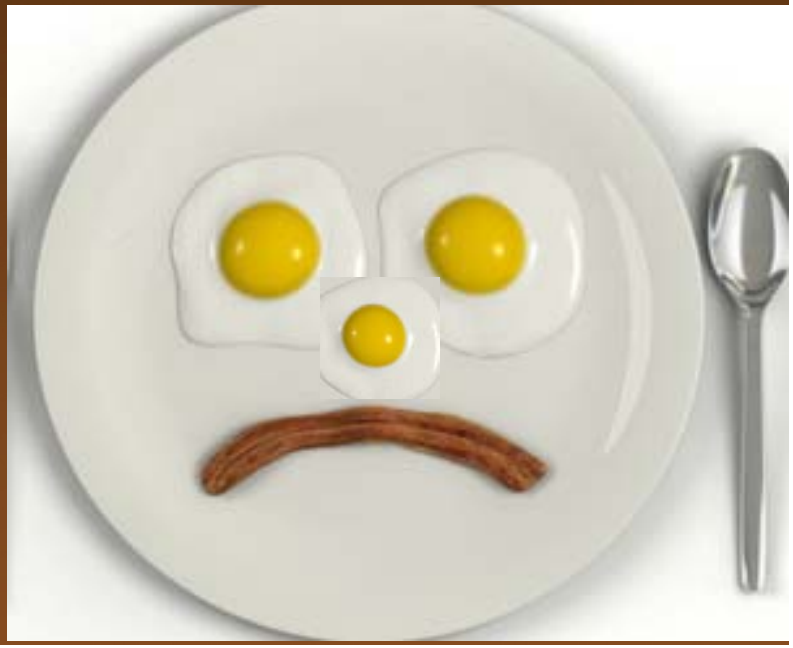
- Omega-3 fatty acids
- DGAT inhibitors
- Apo CIII inhibitors


CHYLOMICRON
apo B - 48
apo A - I
Unesterified Cholesterol
apo C - II
Phospholipid
apo E
Triglyceride
Cholesterol Ester
apo C - III
apo A - IV
DIAMETER: 1000 - 4000 Å


VERY LOW-DENSITY LIPOPROTEIN
apo B-100
Unesterified Cholesterol
apo C-III
Triglyceride
Phospholipid
apo E
Cholesterol Ester
apo C-II
DIAMETER: 400-700 Å

ApoCIII

- Apolipoprotein C-III (ApoC-III) is a small protein that resides on various lipoproteins
- Inhibits lipoprotein/hepatic lipases
- Impairs hepatic uptake of triglyceride (TG)-rich lipoproteins (such as lipoprotein remnants)
- Generally promotes hypertriglyceridemia.
- May contribute to insulin resistance
- May contribute to atherosclerosis.



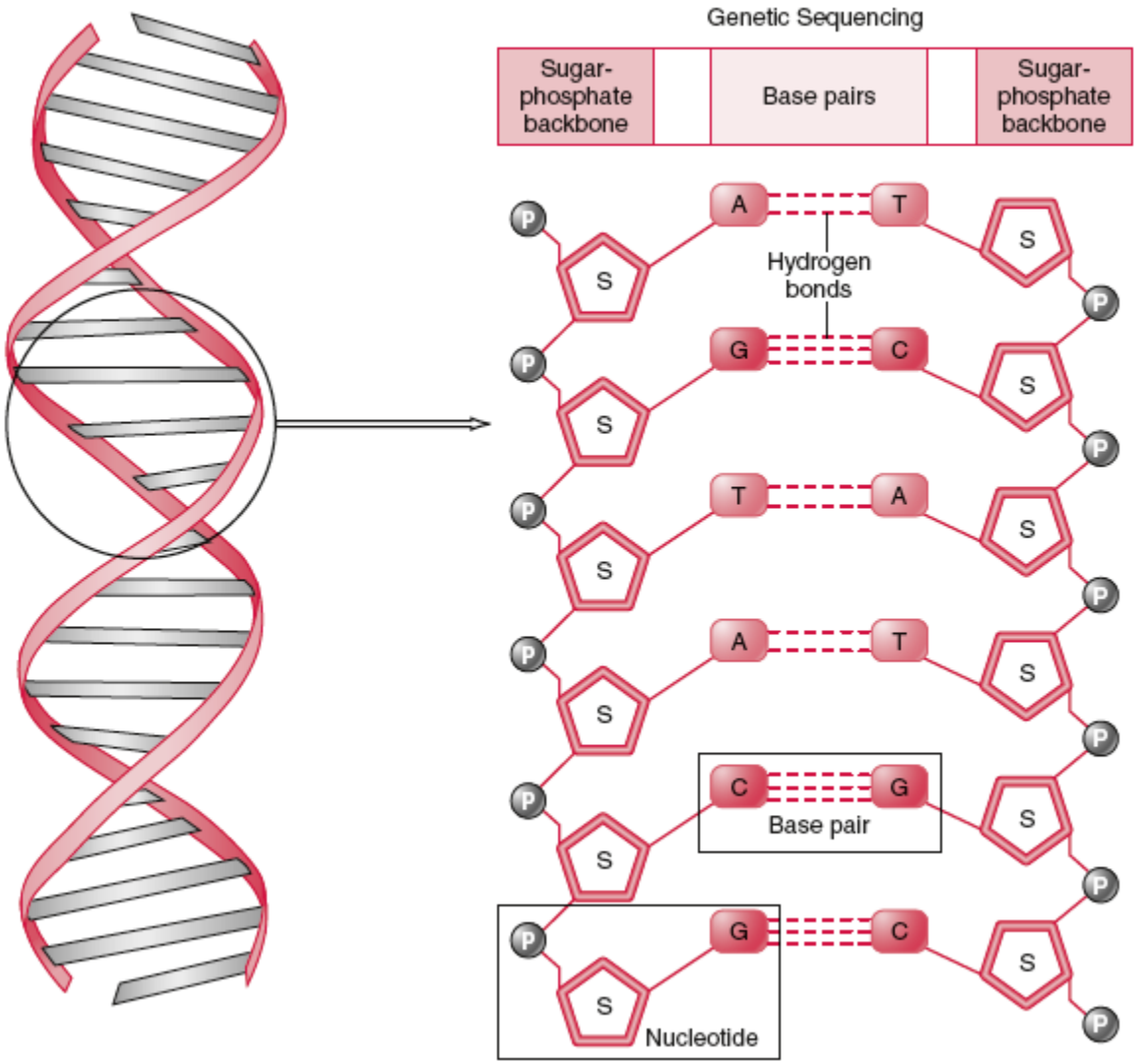


FIGURE 44-12 Simplifi ed fi gure of deoxyribonucieic acid (DNA) sequencing which constitutes a gene. DNA is a nuclear genetic helix molecule that encodes the “blueprint” information for constructing cellular components. A nucleotide is composed of a sugar (pentose), phosphate backbone, and a nitrogen-containing heterocylic base (purine or pyrimidine). Sequences of nucleotides forming nucleic acids are illustrated by DNA. Genes are strands of DNA that contain coding sequences which determine what and when functional proteins are translated, and thus determine what and when inherited traits are expressed.

Bays H. Chapter 44: Investigational Agents Affecting Atherogenic Lipoproteins. Clinical Lipidology: A Companion to Braunwald's Heart Disease, by Christie Ballantyne MD. ISBN-13: 978-1-4160-5469-6 ISBN-10: 1-4160-5469-3 Saunders. Dec 2008; 530-543.

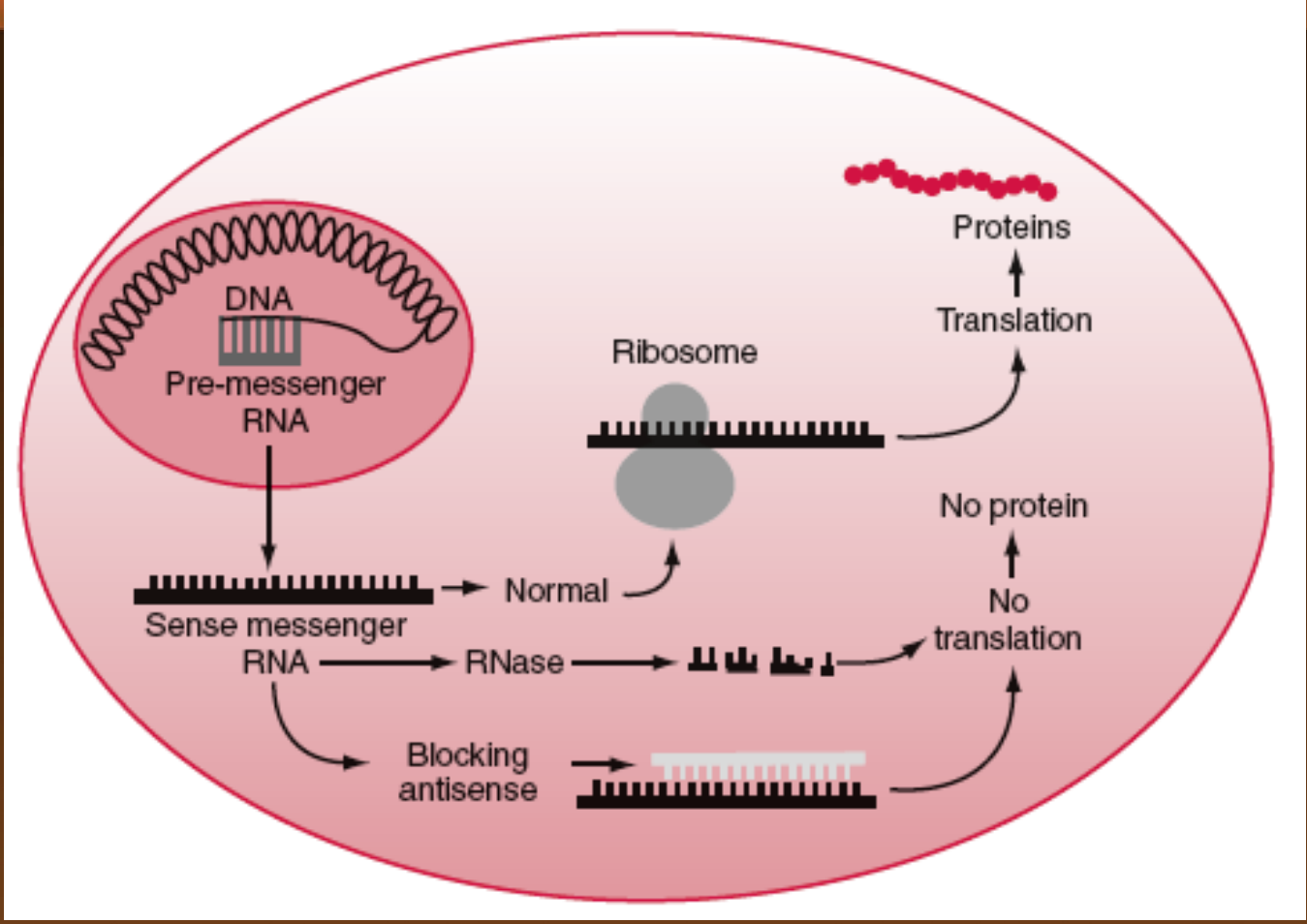


FIGURE 44-13 Antisense disruption of protein translation. One strand of the dual-stranded DNA represents the "sense" genetic code sequence, while the other paired strand represents "antisense" genetic coding. During transcription, the antisense DNA strand serves as a template for the formation of single-stranded messenger ribonucleic acids (mRNA), which is termed "sense." Sense mRNA migrate from the nucleus into the cytosol where ribosomes "translate" the genetic information for protein production. Antisense agents block target sense mRNA, impairing its associated protein translation and production.

Bays H. Chapter 44: Investigational Agents Affecting Atherogenic Lipoproteins. Clinical Lipidology: A Companion to Braunwald's Heart Disease, by Christie Ballantyne MD. ISBN-13: 978-1-4160-5469-6 ISBN-10: 1-4160-5469-3 Saunders, Dec 2008: 530-543



August 23, 2014

Title :Current & Future Triglyceride Pharmaceuticals

Harold Bays MD, FTOS, FACC, FACE, FNLA
L-MARC Research Center
Louisville, KY

MANAGEMENT OF DYSLIPIDEMIA IN CHRONIC KIDNEY DISEASE: A REVIEW OF CURRENT KDIGO GUIDELINES

EDGAR V. LERMA, MD, FNLA

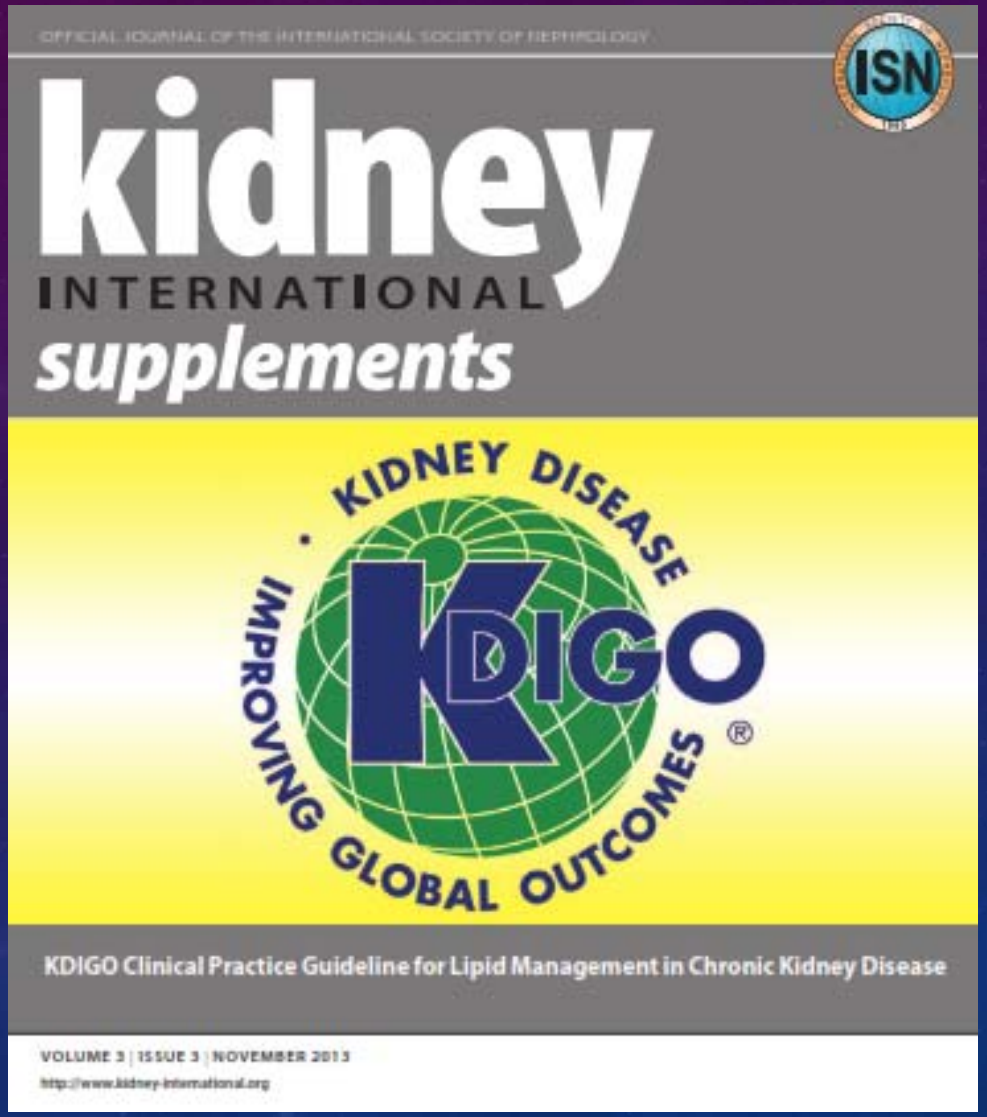
CLINICAL PROFESSOR OF MEDICINE

UNIVERSITY OF ILLINOIS AT CHICAGO COLLEGE OF MEDICINE

ADVOCATE CHRIST MEDICAL CENTER

CHICAGO, IL

AUGUST 23, 2014 SATURDAY


OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY
ISN
kidney
INTERNATIONAL
supplements
KIDNEY DISEASE
IMPROVING GLOBAL OUTCOMES
KDIGO
KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease
VOLUME 3 | ISSUE 3 | NOVEMBER 2013
http://www.kidney-international.org

- Systematic reviews of **RCTs**
- Systematic reviews for **6 TOPICS OF INTEREST**
  - **Lipid Lowering Agents**
  - **Diet or Lifestyle Modifications**
  - **Drug Interactions**
  - **Changes in LDL by Statins**
  - **Adverse Events from Statins + Fibrates**
  - **Frequency of Lipid Testing**

Appendix Table 1. **GRADE Criteria Used for Grading the Strength of Recommendation in the KDIGO Lipid Guideline**

Grade Level*	Implications		
	Patients	**Clinicians**	**Policymakers**
1 ("We recommend")	Most persons in this situation would—and only a small proportion would not—want the recommended course of action.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
2 ("We suggest")	Most persons in this situation would—but many would not—want the recommended course of action.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with his or her values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

GRADE = Grading of Recommendations Assessment, Development and Evaluation; KDIGO = Kidney Disease: Improving Global Outcomes.
* Within each recommendation, the strength of recommendation is indicated as Level 1, Level 2, or Not Graded. The additional category "Not Graded" was used to provide guidance on the basis of common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations about monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements but are not meant to be interpreted as being stronger recommendations than level 1 or 2 recommendations.

Appendix Table 2. **GRADE Criteria Used for Grading the Overall Quality of Evidence in the KDIGO Lipid Guideline**

Letter Grade	Quality of Evidence	Meaning
A	High	We are confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain and often will be far from the truth.

GRADE = Grading of Recommendations Assessment, Development and Evaluation; KDIGO = Kidney Disease: Improving Global Outcomes.

CLINICAL RELEVANCE OF RATING GUIDELINE RECOMMENDATIONS

LEVEL1	**WE RECOMMEND**	**Most patients should receive the recommended course of action**
LEVEL 2	**WE SUGGEST**	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision appropriate for them.
NOT GRADED		Usually provides guidance based on common sense or where the issue does not allow adequate application of evidence

QUALITY OF SUPPORTING EVIDENCE

A 1A (STRONGEST)

B

C

D 2D (WEAKEST)

Annals of Internal Medicine | REVIEW

Lipid-Lowering Therapy in Persons With Chronic Kidney Disease

A Systematic Review and Meta-analysis

Ashish Upadhyay, MD; Amy Earley, BS; Jenny L. Lamont, MS; Shana Haynes, DHSc, MS; Christoph Wanner, MD; and Ethan M. Balk, MD, MPH

Background: Lipid-lowering therapy is not widely used in persons with chronic kidney disease (CKD) despite a high burden of dyslipidemia and cardiovascular disease in this population.

Purpose: To synthesize evidence examining the effect of lipid-lowering therapy on clinical outcomes in persons with CKD.

Data Sources: MEDLINE, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews from January 2000 through November 2011.

Study Selection: Randomized, controlled trials (RCTs) comparing lipid-lowering therapy with control treatment in persons with CKD, including subgroup analyses of trials in the general population.

Data Extraction: Abstracts were screened and data were extracted on study methodology, population, interventions, cardiovascular and kidney outcomes, and adverse events. Data were extracted by one author and confirmed by another. Study quality was determined by consensus. Random-effects model meta-analyses were performed.

Data Synthesis: 18 RCTs, all in adults, met the eligibility criteria. Five RCTs involved CKD populations, and 13 were CKD subgroup analyses from trials in the general population. Sixteen RCTs examined statins, and 2 examined statins plus ezetimibe. Lipid-lowering therapy does not improve kidney outcomes but decreases the risk for cardiac mortality (pooled risk ratio [RR] from 6 trials, 0.82 [95% CI, 0.74 to 0.91]; $P < 0.001$), cardiovascular events (including revascularization) (pooled RR from 9 trials, 0.78 [CI, 0.71 to 0.86]; $P < 0.001$), and myocardial infarction (pooled RR from 9 trials, 0.74 [CI, 0.67 to 0.81]; $P < 0.001$). Significant benefit was also seen for all-cause mortality but was limited by a high degree of heterogeneity. No benefit was found for other cardiovascular outcomes. Rates of adverse events were similar between intervention and comparator groups.

Limitations: Lack of data in children, heterogeneity among reviewed studies, and the possibility of selective reporting of outcomes and adverse events.

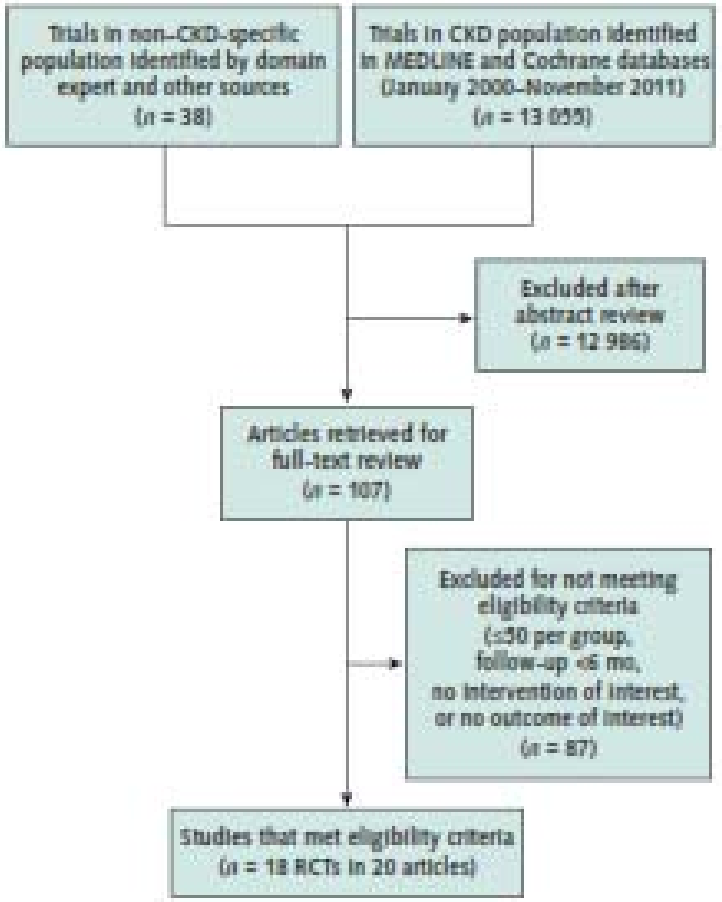
Conclusion: Lipid-lowering therapy decreases cardiac death and atherosclerosis-mediated cardiovascular events in persons with CKD.

Primary Funding Source: Kidney Diseases: Improving Global Outcomes.

Ann Intern Med. 2012;157:251-262. www.annals.org

For author affiliations, see end of text.

Figure 1. Summary of evidence search and selection.



CKD = chronic kidney disease; RCT = randomized, controlled trial.

CLINICAL GUIDELINE | Annals of Internal Medicine

Lipid Management in Chronic Kidney Disease: Synopsis of the Kidney Disease: Improving Global Outcomes 2013 Clinical Practice Guideline

Marcello Tonelli, MD, SM, and Christoph Wanner, MD, for the Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group Members*

Description: The Kidney Disease: Improving Global Outcomes (KDIGO) organization developed a clinical practice guideline in 2013 on lipid management and treatment of all adults and children with chronic kidney disease (CKD). All forms of CKD are included (non–dialysis-dependent, dialysis-dependent, and kidney transplant recipients).

Methods: The KDIGO Lipid Guideline Development Work Group defined the scope of the guideline, gathered evidence, determined topics for systematic review, and graded the quality of evidence that had been summarized by an evidence review team. Searches of the English-language literature were conducted through August 2011 and supplemented by targeted searches through June 2013. Final modification of the guidelines was informed by the KDIGO Board of Directors and a public review process involving registered stakeholders.

Recommendations: The full guideline includes 13 recommendations; a key element was the recommendation for statin or statin with ezetimibe treatment of adults aged 50 years or older with estimated glomerular filtration rates less than 60 mL/min/1.73 m^2 but not treated with long-term dialysis or kidney transplantation. This synopsis focuses on 8 recommendations pertinent to assessment of lipid status and treatment with a statin-based regimen in adults.

Ann Intern Med. 2014;160:182-189. www.annals.org

For author affiliations, see end of text.

* For a list of the members of the KDIGO Lipid Guideline Development Work Group, see the **Appendix** (available at www.annals.org).

This article was published online first at www.annals.org on 10 December 2013.

Annals of Internal Medicine
ESTABLISHED IN 1927 BY THE AMERICAN COLLEGE OF PHYSICIANS

From: Lipid Management in Chronic Kidney Disease: Synopsis of the Kidney Disease: Improving Global Outcomes 2013 Clinical Practice Guideline

Ann Intern Med. 2014;160(3):182-189. doi:10.7326/M13-2453

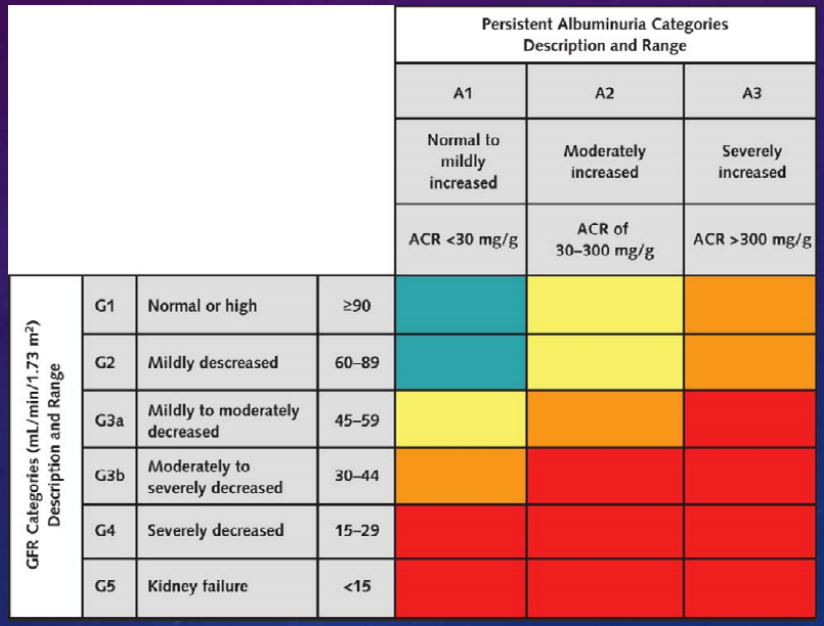


Figure Legend:

Prognosis of CKD chronic kidney disease by GFR and albuminuria categories: KDIGO 2012.

Chronic kidney disease is defined as abnormalities of kidney structure or function, present for >3 mo, with implications for health. Chronic kidney disease is classified based on cause, GFR category (G1–G5), and albuminuria category (A1–A3), abbreviated as CGA. Green means low risk (if no other markers of kidney disease, no CKD), yellow means moderately increased risk, orange means high risk, and red means very high risk. ACR = albumin–creatinine ratio; GFR = glomerular filtration rate.

Date of download: 7/5/2014

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- Dyslipidemia is common but ***not universal*** in persons with CKD.

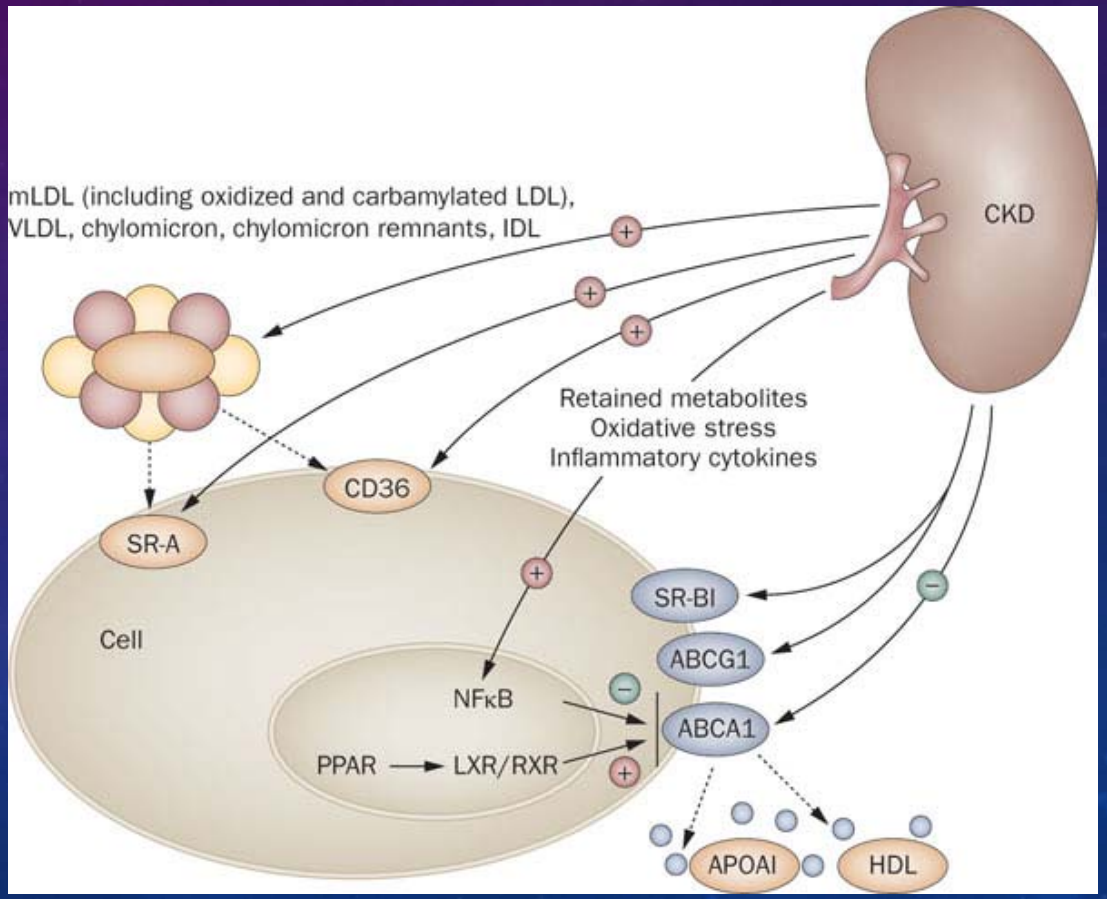
MECHANISMS OF DYSLIPIDEMIA IN CKD

Table 3 Mechanisms of Dyslipidemia in Chronic Kidney Disease

Protein	Change	Effect on Plasma Lipids or LP
ApoA-1	↓	↓ HDL
LCAT	↓	↓ HDL-C, HDL-2/HDL-3
CETP	↑	↓ HDL-C
ACAT	↑	↑ VLDL-C, ↓ HDL-C
LPL	↓	↑ Trig (↑ delipidation of VLDL and CM)
VLDL receptor	↓	↑ VLDL, Trig
Hepatic lipase	↓	↑ IDL, CM remnants, HDL-TG, Trig, LDL-TG
LRP	↓	↑ IDL, CM remnants
ApoCII/CIII ratio	↓	↑ Trig (↑ LPL activity)
Pre-β HDL	↑	↑ Trig (↑ LPL activity)

Adapted from Vaziri (4).

↓ = decreases; ↑ = increases; ACAT = acyl-CoA (cholesterol acyl) transferase; Apo = apoprotein; CETP = cholesterol ester transferase protein; CM = chylomicron; DGAT = acyl-CoA diglycerol acyl transferase; HDL = high-density lipoprotein; HDL-C = high-density lipoprotein cholesterol; HDL-TG = high-density lipoprotein triglyceride; IDL = intermediate-density lipoprotein; LCAT = lecithin cholesterol acyl transferase; LDL-TG = low-density lipoprotein triglyceride; LP = lipoproteins; LPL = lipoprotein lipase; LRP = low-density lipoprotein receptor-related protein; Trig = triglyceride; VLDL = very-low-density lipoprotein; VLDL-C = very-low-density lipoprotein cholesterol; VLDL-TG = very-low-density lipoprotein triglyceride.



- CKD causes a **PROFOUND DYSREGULATION OF LIPOPROTEIN METABOLISM**
  - **Decreased HDL-C**
  - **Increased TGs**

PREVALENCE OF DYSLIPIDEMIAS IN CKD

Table 1. Lipid Abnormalities by Target Population (Approximate Percentage)

	Total Cholesterol >240 mg/dl	LDL Cholesterol >130 mg/dl	HDL Cholesterol <35 mg/dl	Triglycerides >200 mg/dl
General population*	20	40	15	15
CKD Stages 1 to 4†				
With nephrotic syndrome‡	90	85	50	60
Without nephrotic syndrome‡	30	10	35	40
CKD Stage 5†				
Hemodialysis	20	30	50	45
Peritoneal dialysis	25	45	20	50

Reproduced and modified with permission from Kasiske.[20]

* *Data from National Health and Nutrition Examination Survey (NHANES) III and the Framingham Offspring Study.*[54,55]

† *Data extracted from multiple observational studies Kasiske.*[20]

‡ *Nephrotic proteinuria was defined as >3 g of total protein excretion in 24 hours.*

CKD, chronic kidney disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

MAJOR DETERMINANTS OF DYSLIPIDEMIA IN CKD

- GFR
- DM
- Proteinuria
- Immunosuppressive Agents
- Method of Renal Replacement
- Co-morbidity
- Nutritional Status

Kasiske BL, Am J Kidney Dis 1998; 32: S: 5142-5156

1. ASSESSMENT OF LIPID STATUS IN ADULTS WITH CKD

INITIAL EVALUATION OF THE LIPID PROFILE

- To establish the diagnosis of severe hypercholesterolemia or hypertriglyceridemia

INITIAL EVALUATION OF THE LIPID PROFILE

- To establish the diagnosis of severe hypercholesterolemia or hypertriglyceridemia
- To potentially rule out a ***remediable (secondary cause)*** if dyslipidemia is present

Table 2. **Secondary Causes of Dyslipidemia***

Medical Conditions

- The nephrotic syndrome
- Hypothyroidism
- Diabetes
- Excessive alcohol consumption
- Liver disease

Medications

- 13-cis-retinoic acid
- Anticonvulsants
- Highly active antiretroviral therapy
- Diuretics
- β-Blockers
- Androgens
- Oral contraceptives
- Corticosteroids
- Cyclosporine
- Sirolimus

* Reproduced from reference 30.

NO DIRECT EVIDENCE THAT MEASUREMENT OF LIPID STATUS WILL IMPROVE OUTCOMES

- The precise level of serum or plasma lipids that should trigger referral to a specialist are not supported by evidence - BUT

EXCEPTIONS TO THE RULE

- **Fasting triglyceride level > 1000 mgs/dL or LDL cholesterol level > 190 mgs/ dL** should prompt consideration of (or specialist referral for) further evaluation.

1.1: In adults with NEWLY IDENTIFIED CKD (including those treated with chronic dialysis or kidney transplantation), we recommend EVALUATION WITH A LIPID PROFILE (TOTAL CHOLESTEROL, LDL-CHOLESTEROL, HDL-CHOLESTEROL, TRIGLYCERIDES). (1C)

1: WE RECOMMEND. Most patients should receive the recommended course of action.

C: LOW QUALITY OF EVIDENCE. The true effect may be substantially different from the estimate of the effect.

- Because the association between LDL cholesterol and adverse clinical outcomes is weaker in persons with CKD than in the general population, ***the value of measuring LDL cholesterol to assess prognosis is uncertain.***

1.2: In adults with CKD (including those treated with chronic dialysis or kidney transplantation), FOLLOW-UP MEASUREMENT OF LIPID LEVELS IS NOT REQUIRED FOR THE MAJORITY OF PATIENTS. (NOT GRADED)

NOT GRADED: was used, typically to provide guidance based on common sense or where the topic does not allow adequate application of evidence.

- There is no direct evidence that routine follow-up of lipid levels improves clinical outcomes or adherence to lipid-lowering therapy.

However, some patients may prefer to know their lipid levels during follow-up or may respond favorably to such knowledge (for example, with better adherence to recommended statin use) – **NOT GRADED**

- However, the ***clinical benefits of statin treatment*** (including lower risk for myocardial infarction [MI], stroke, and peripheral vascular events) are proportional to ***baseline coronary risk*** rather than baseline LDL cholesterol.

- **HIGHER CARDIOVASCULAR RISK** (rather than elevated LDL cholesterol levels) is now the ***primary indication*** to initiate or adjust lipid-lowering treatment in CKD patients
  - Follow-up monitoring of LDL cholesterol (after an initial measurement) may not be required for many patients.

Glasziou PP, et al. Ann Intern Med 2008; 148: 656-661.

KEY POINTS

- Dyslipidemia is common in people with CKD but ***LDL-C DOES NOT RELIABLY DISCRIMINATE*** between those at low or high risk of CV events.
- Clinicians ***SHOULD MEASURE THE LIPID PROFILE AT INITIAL PRESENTATION*** with CKD.
- ***FOLLOW-UP OF THE LIPID PROFILE or LDL-C IS NOT REQUIRED*** unless the results would change management.

Table 3. **Examples of Situations in Which Measuring Cholesterol Levels May or May Not Change Patient Management**

Patient Characteristics	Is the Patient Already Receiving Statin?	Would Measuring Cholesterol Levels Change Management?
Man aged 55 y with eGFR of 35 mL/min/1.73 m^2	Yes	No; patient is already receiving a statin
Man aged 55 y with eGFR of 35 mL/min/1.73 m^2	No	No; statin is already indicated based on recommendation 2.1.1
Man aged 55 y with eGFR of 75 mL/min/1.73 m^2 and ACR of 1100 mg/g	No	No; statin is already indicated based on recommendation 2.1.2
Man aged 45 y with eGFR of 35 mL/min/1.73 m^2 who is a smoker and has diabetes and hypertension	No	No; statin is already indicated based on recommendation 2.1.3 because predicted 10-y risk for coronary death or MI is >10% regardless of cholesterol level
Man aged 45 y with eGFR of 35 mL/min/1.73 m^2 who is a nonsmoker without diabetes or hypertension	Yes	No; patient is already receiving a statin
Man aged 45 y with eGFR of 35 mL/min/1.73 m^2 who is a nonsmoker without diabetes or hypertension	No	Yes; patient's predicted 10-y risk for coronary death or MI could vary from 5% to 20% based on cholesterol level. This would change the decision to prescribe a statin based on recommendation 2.1.3.
Man aged 35 y with eGFR of 35 mL/min/1.73 m^2 who is a nonsmoker without diabetes or hypertension	No	No; patient's predicted 10-y risk for coronary death or MI is <10% regardless of cholesterol level

ACR = albumin–creatinine ratio; eGFR = estimated glomerular filtration rate; MI = myocardial infarction.

THE OTHER SIDE OF THE STORY

Giving People the Benefit of the Doubt

WHY DO OTHER GUIDELINES EMPHASIZE REGULAR MONITORING OF LDL-CHOLESTEROL?

Why do other guidelines emphasize regular monitoring of LDL-cholesterol?

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



KDIGO

2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

David C. Goff, Jr, Donald M. Lloyd-Jones, Glen Bennett, Sean Coady, Ralph B. D'Agostino, Sr, Raymond Gibbons, Philip Greenland, Daniel T. Lackland, Daniel Levy, Christopher J. O'Donnell, Jennifer Robinson, J. Sanford Schwartz, Susan T. Shero, Sidney C. Smith, Jr, Paul Sorlie, Neil J. Stone and Peter W.F. Wilson

Circulation. published online November 12, 2013;

Why do other guidelines emphasize regular monitoring of LDL-cholesterol ?

ACC/AHA workgroup:

- (1) A lipid panel should be done 4-12 weeks after initiation of statin therapy to determine a patients adherence.
- (2) Down titrating statin dose due to unacceptable adverse effects when taking the recommended intensity of statin therapy (decide on new prescriptions and intensity of therapy).

KDIGO work group:

- random variation in TC on a single measurement is -0.8 to +0.8 mmol/l (-30 to +30 mg/dl)

KDIGO

2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

Recommendations	NHLBI Grade
Treatment Targets	
1. The panel makes no recommendations for or against specific LDL–C or non-HDL–C targets for the primary or secondary prevention of ASCVD.	N (No recommendation)

Use moderate intensity statin therapy
Avoid high intensity statin therapy

Heart Failure and Hemodialysis	
1. The Expert Panel makes no recommendations regarding the initiation or discontinuation of statins in patients with NYHA class II–IV ischemic systolic heart failure or in patients on maintenance hemodialysis.	N (No Recommendation)

2. PHARMACOLOGICAL CHOLESTEROL-LOWERING TREATMENT IN ADULTS

- To maximize the ratio of benefits to harms and costs, ***FUTURE CORONARY RISK*** is considered an important potential determinant of the decision to prescribe cholesterol lowering treatment

- In the general population, **LDL cholesterol** is widely used as a proxy for future risk because LDL cholesterol levels are ***strongly and independently associated with risk for atherosclerotic events.***

Lewington S, et al. Lancet 2007; 37): 1829-1839

WHICH CKD PATIENTS SHOULD RECEIVE PHARMACOLOGICAL CHOLESTEROL-LOWERING TREATMENT?

LDL CHOLESTEROL IS NOT SUITABLE FOR ASSESSING CORONARY RISK IN PERSONS WITH CKD

- Although higher levels of LDL cholesterol are associated with higher risk, dialysis patients with the lowest levels of LDL cholesterol and total cholesterol are also at very high risk for all-cause an cardiovascular mortality, likely because of confounding by inflammation and malnutrition

- Among persons with non–dialysis-dependent CKD, **the magnitude of the excess risk associated with increased LDL cholesterol levels** decreases at lower eGFRs.

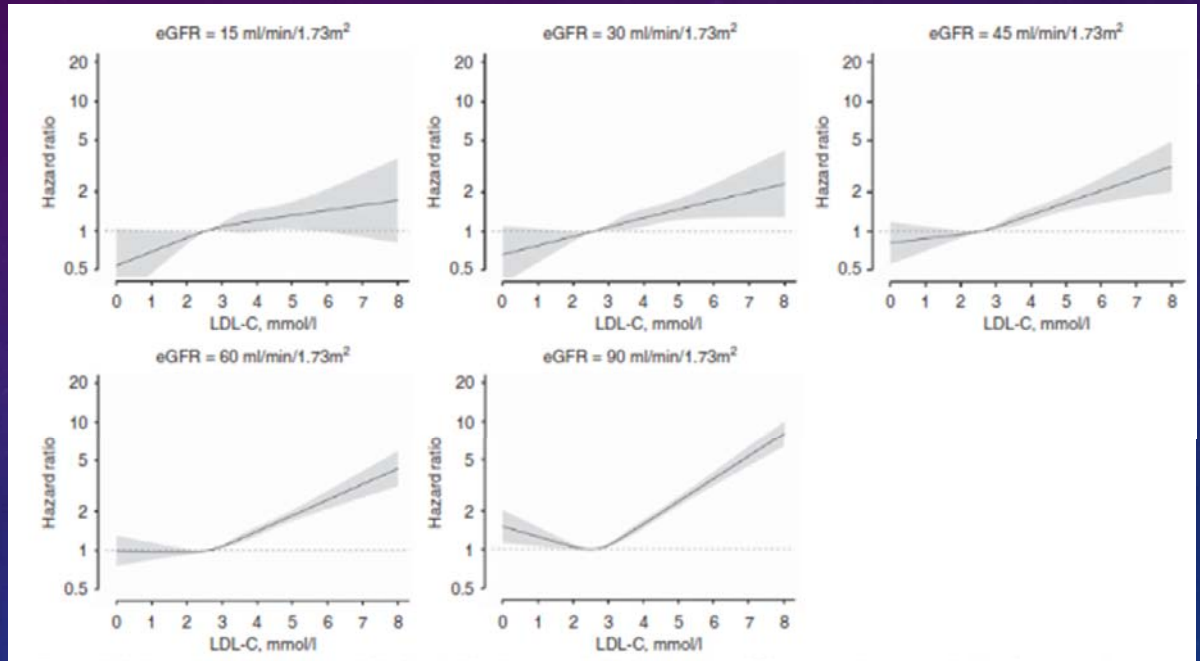


Figure 1 | Adjusted relation between LDL-C and HR of myocardial infarction by eGFR as a continuous variable. Data are adjusted hazard ratios for MI during a median follow-up period of 48 months. Data are from 836,060 participants in the Alberta Kidney Disease cohort and have been adjusted for age, sex, diabetes, hypertension, Aboriginal status, socioeconomic status, proteinuria categories, statin use, and the Charlson comorbidities (cancer, cerebrovascular disease, congestive heart failure, chronic pulmonary disease, dementia, metastatic solid tumor, MI, liver disease, hemiplegia/paraplegia, peptic ulcer disease, peripheral vascular disease, and rheumatic disease). eGFR, estimated glomerular filtration rate; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction. Reproduced from Tonelli M, Muntner P, Lloyd A, *et al.* Association between LDL-C and Risk of Myocardial Infarction in CKD. *J Am Soc Nephrol* 2013; 24: 979-986 with permission from American Society of Nephrology[22] conveyed through Copyright Clearance Center, Inc; accessed http://jasn.asnjournals.org/content/24/6/979.long

- The weaker and potentially misleading association between LDL cholesterol and coronary risk among those with lower levels of kidney function (who are at the highest absolute risk for coronary events) argues against the use of LDL cholesterol for identifying CKD patients who should receive pharmacologic cholesterol-lowering treatment.

CORONARY RISK: 10-YEAR INCIDENCE OF CORONARY DEATH OR NON-FATAL MI

- CKD patients > 50 years (± DM or previous MI): consistently > 10%
- CKD patients ≤ 50 years (w/o DM or previous MI): low

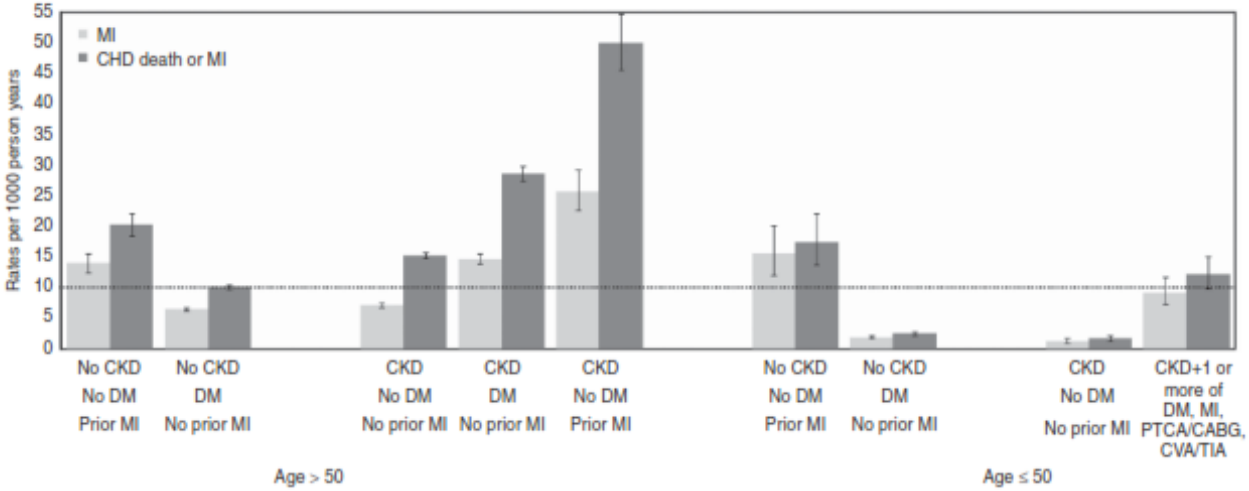


Figure 2 | Future 10-year coronary risk based on various patient characteristics. Data are unadjusted rates from 1,268,029 participants in the Alberta Kidney Disease cohort. CKD refers to eGFR 15-59.9 ml/min/1.73 m^2 or with proteinuria. CABG, coronary artery bypass grafting; CHD, coronary heart disease; CKD, chronic kidney disease; CVA, cerebrovascular accident; DM, diabetes mellitus; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; TIA, transient ischemic attack.

Appendix Table 4. **Risk for Coronary Death or Nonfatal MI, by Age and eGFR***

Characteristic	10-Year Probability of Coronary Death or Nonfatal MI (95% CI), %		
	Overall	Men	Women
Age >40 y	14.9 (14.6–15.3)	17.4 (16.9–17.9)	12.7 (12.3–13.1)
eGFR G3a–G4	19.3 (18.8–19.8)	23.4 (22.6–24.2)	16.4 (15.8–17.0)
eGFR G1–G2	9.7 (9.3–10.0)	12.0 (11.4–12.6)	6.7 (6.3–7.2)
Age >50 y	17.3 (17.0–17.7)	20.2 (19.6–20.8)	14.8 (14.3–15.3)
eGFR G3a–G4	19.9 (19.4–20.4)	24.3 (23.4–25.2)	16.9 (16.3–17.5)
eGFR G1–G2	12.9 (12.4–13.4)	15.2 (14.5–16.0)	9.7 (9.0–10.5)
Age 40–50 y	3.2 (2.9–3.6)	4.7 (4.2–5.4)	1.6 (1.2–2.0)
eGFR G3a–G4	4.7 (3.7–6.0)	5.9 (4.3–8.1)	3.6 (2.5–5.3)
eGFR G1–G2	3.0 (2.6–3.3)	4.6 (4.0–5.3)	1.2 (0.9–1.6)

eGFR = estimated glomerular filtration rate; MI = myocardial infarction.
* Data are unadjusted rates from 1 268 029 participants in the Alberta Kidney Disease Network cohort. Persons with diabetes, MI, and other cardiovascular disease were included. Data do not apply to persons who had kidney transplantation.

- Available evidence argues against the use of LDL cholesterol to identify patients with CKD who should receive cholesterol-lowering treatment and suggests focusing instead on the ***absolute risk for coronary events***.

HOW SHOULD THE DOSE OF PHARMACOLOGICAL CHOLESTEROL LOWERING TREATMENT BE DETERMINED IN CKD PATIENTS?

CKD PATIENTS ARE AT HIGH RISK FOR MEDICATION RELATED ADVERSE EVENTS

- Decreased **Renal Excretion**
- Frequency of **Polypharmacy** ~ Drug Interactions
- Increased Prevalence of **Comorbidities** in the CKD population

Table 1. **Recommended Doses of Statins in Adults With Chronic Kidney Disease***

Statin	eGFR G1–G2	eGFR G3a–G5, Including Patients Receiving Dialysis or Who Had a Kidney Transplant
Lovastatin	Any dose approved for GP	ND
Fluvastatin	Any dose approved for GP	80†
Atorvastatin	Any dose approved for GP	20‡
Rosuvastatin	Any dose approved for GP	10§
Simvastatin/ ezetimibe	Any dose approved for GP	20/10‖
Pravastatin	Any dose approved for GP	40
Simvastatin	Any dose approved for GP	40
Pitavastatin	Any dose approved for GP	2

eGFR = estimated glomerular filtration rate; GP = general population; ND = not done.

* All doses are mg/d. All statins may not be available in all countries. Lower doses than those used in major trials of statins in chronic kidney disease populations may be appropriate in Asian countries. Note that 40 mg of rosuvastatin daily is not recommended for use in patients with chronic kidney disease G1–G2 who did not have transplants because it may increase the risk for adverse renal events. Cyclosporine inhibits the metabolism of certain statins, resulting in higher blood levels.

† Data based on Assessment of Lescol in Renal Transplantation trial.

‡ Data based on Die Deutsche Diabetes Dialyse Studie.

§ Data based on A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events.

‖ Data based on the Study of Heart and Renal Protection trial.

Table 5 **Clinical Pharmacokinetics of Statins**

	Rosuva	Atorva	Simva	Lova	Prava	Fluva
T 1/2, h	20.8	15–30	2–3	2.9	1.3–2.8	0.5–2.3
Urinary excretion, %	10	<2	13	10	20	6
CYP-3A4 metabolism	No	Yes	Yes	Yes	No	No
CYP metabolism	2CY9	3A4	3A4	3A4	sulfation	2CY9

Adapted from Blum (31).

Atorva = atorvastatin; CYP = cytochrome P450; CYP-3A4 = cytochrome p450-3A4; Fluva = fluvastatin; Lova = lovastatin; Prava = pravastatin; Rosuva = rosuvastatin; Simva = simvastatin; T 1/2 = half life.

2.1.1: In adults aged >/= 50 years with eGFR > 60 ml/min/1.73 m2 but not treated with chronic dialysis or kidney transplantation (GFR categories G3a-G5), we recommend TREATMENT WITH A STATIN or STATIN/ EZETEMIBE COMBINATION. (1A)

1: WE RECOMMEND. Most patients should receive the recommended course of action.

A: HIGH QUALITY OF EVIDENCE. The Work Group is confident that the true effect lies close to that of the estimate of the effect.

2.1.2: In adults aged >/= 50 years with CKD and eGFR > 60 ml/min/1.73 m2 (GFR categories G1-G2), we recommend TREATMENT WITH A STATIN. (1B)

1: WE RECOMMEND. Most patients should receive the recommended course of action.

B: MODERATE QUALITY OF EVIDENCE: The true effect is likely to be close to the estimate of the effect, but there is a possibility that is substantially different.

2.2: In adults aged 18-49 years with CKD but not treated with chronic dialysis or kidney transplantation, we suggest STATIN TREATMENT in people with one or more of the following: (2A)

- Known coronary disease (myocardial infarction or coronary revascularization)
- DM
- Prior Ischemic CVA
- Estimated 10-year incidence of coronary death or non-fatal myocardial infarction > 10%

2: WE SUGGEST. Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with his or her values and preferences.

A: HIGH QUALITY OF EVIDENCE. The Work Group is confident that the true effect lies close to that of the estimate of the effect.

2.3.1: In adults with DIALYSIS-DEPENDENT CKD, we suggest that statins or statin/ ezetemibe combination NOT BE INITIATED. (2A)

2: WE SUGGEST. Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with his or her values and preferences.

A: HIGH QUALITY OF EVIDENCE. The Work Group is confident that the true effect lies close to that of the estimate of the effect.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Atorvastatin in Patients with Type 2 Diabetes Mellitus Undergoing Hemodialysis

Christoph Wanner, M.D., Vera Krane, M.D., Winfried März, M.D., Manfred Olschewski, M.Sc., Johannes F.E. Mann, M.D., Günther Ruf, M.D., and Eberhard Ritz, M.D., for the German Diabetes and Dialysis Study Investigators*

4D STUDY (DIE DEUTSCHE DIABETES DIALYSE STUDIE)

- **Multicenter**
- **Double blind RCT**
- **1255 Dialysis patients**
- **Atorvastatin 20 daily vs placebo**
- **At least 4 years**

4D STUDY (DIE DEUTSCHE DIABETES DIALYSE STUDIE)

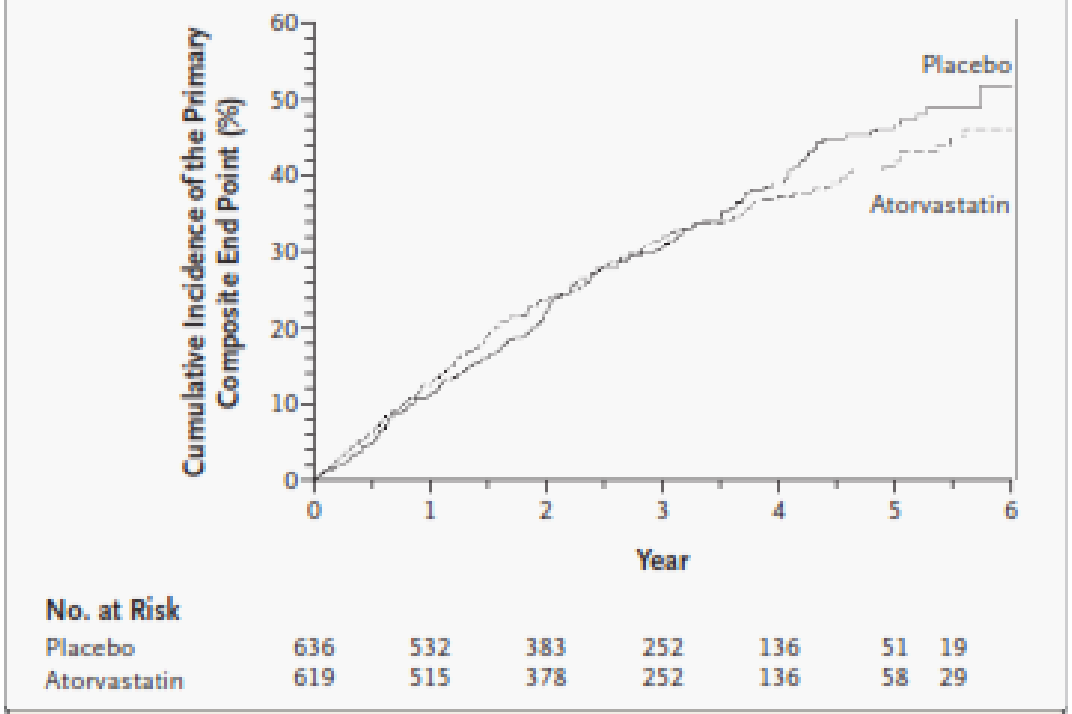


Figure 3. Estimated Cumulative Incidence of the Composite Primary End Point.

Table 2. Rates of Primary and Secondary End Points.[a]

End Point	Placebo Group (N=636)	Atorvastatin Group (N=619)	RR (95% CI)	P Value
	no. (%)			
Primary	243 (38)	226 (37)	0.92 (0.77–1.10)	0.37
Death from cardiac causes	149 (23)	121 (20)	0.81 (0.64–1.03)	0.08
Sudden death	83 (13)	77 (12)		
Fatal myocardial infarction	33 (5)	23 (4)		
Death due to congestive heart failure	24 (4)	17 (3)		
Death after interventions to treat coronary heart disease	4 (0.6)	3 (0.5)		
Other death due to coronary heart disease	5 (0.8)	1 (0.2)		
Nonfatal myocardial infarction	79 (12)	70 (11)	0.88 (0.64–1.21)	0.42
Silent	50 (8)	41 (7)		
Nonsilent	35 (6)	33 (5)		
Fatal stroke	13 (2)	27 (4)	2.03 (1.05–3.93)	0.04
Ischemic	7 (1)	18 (3)		
Hemorrhagic	5 (0.8)	3 (0.5)		
Other (not classified)	1 (0.2)	6 (1)		
Nonfatal stroke	32 (5)	33 (5)	1.04 (0.64–1.69)	0.89
Secondary				
All cardiac events combined	246 (39)	205 (33)	0.82 (0.68–0.99)	0.03
Death from cardiac causes	149 (23)	121 (20)		
Nonfatal myocardial infarction	79 (12)	70 (11)		
PTCA	45 (7)	34 (5)		
CABG	30 (5)	24 (4)		
Other interventions to treat coronary heart disease	0	1 (0.2)		
All cerebrovascular events combined	70 (11)	79 (13)	1.12 (0.81–1.55)	0.49
Stroke	44 (7)	59 (10)	1.33 (0.90–1.97)	0.15
Ischemic	33 (5)	47 (8)		
Hemorrhagic	8 (1)	5 (1)		
Other (not classified)	6 (1)	10 (2)		
TIA or PRIND	31 (5)	26 (4)		
Death from all causes	320 (50)	297 (48)	0.93 (0.79–1.08)	0.33
Death from causes other than cardiovascular or cerebrovascular disease	158 (25)	149 (24)	0.95 (0.76–1.18)	0.62
Fatal infection	68 (11)	60 (10)		
Fatal cancer	19 (3)	17 (3)		
Other	71 (11)	72 (12)		

[a] The total number of patients reaching the primary end point does not equal the sum of the numbers for each component of the primary end point, because only the first event per patient is included in the primary end point. Thus, a patient who had a stroke and a myocardial infarction was counted once in the primary end point, but appears in the separate totals for stroke and myocardial infarction. RR denotes relative risk, CI confidence interval, CABG coronary-artery bypass grafting, TIA transient ischemic attack, and PRIND prolonged reversible ischemic neurologic deficit.

4D STUDY (DIE DEUTSCHE DIABETES DIALYSE STUDIE)

- Atorvastatin had **NO EFFECT** on the single components of the **PRIMARY ENDPOINT** (Composite of Cardiac Death, Non-fatal MI and Non-fatal CVA) with the exception of FATAL CVA (RR 2.03)
  - Although the SECONDARY ENDPOINT (Combined Events) WAS DECREASED (RR 0.82), NOT ALL COMBINED CEREBROVASCULAR EVENTS (RR 1.12) or TOTAL MORTALITY (RR 0.93)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rosuvastatin and Cardiovascular Events in Patients Undergoing Hemodialysis

Bengt C. Fellström, M.D., Ph.D., Alan G. Jardine, M.D., Roland E. Schmieder, M.D., Hallvard Holdaas, M.D., Ph.D., Kym Bannister, M.D., Jaap Beutler, M.D., Ph.D., Dong-Wan Chae, M.D., Ph.D., Alejandro Chevaile, M.D., Stuart M. Cobbe, M.D., Carola Grönhagen-Riska, M.D., Ph.D., José J. De Lima, M.D., Ph.D., Robert Lins, M.D., Ph.D., Gert Mayer, M.D., Alan W. McMahon, M.D., Hans-Henrik Parving, M.D., D.M.Sc., Giuseppe Remuzzi, M.D., Ola Samuelsson, M.D., Ph.D., Sandor Sonkodi, M.D., Ph.D., D. Sci., Gultekin Süleymanlar, M.D., Dimitrios Tsakiris, M.D., Ph.D., Vladimir Tesar, M.D., Ph.D., Vasil Todorov, M.D., Ph.D., Andrzej Wiecek, M.D., Ph.D., Rudolf P. Wüthrich, M.D., Mattis Gottlow, M.Sc., Eva Johnsson, M.D., Ph.D., and Faiez Zannad, M.D., Ph.D., for the AURORA Study Group*

AURORA (A STUDY TO EVALUATE THE USE OF ROSUVASTATIN IN SUBJECTS ON REGULAR DIALYSIS: AN ASSESSMENT OF SURVIVAL AND CARDIOVASCULAR EVENTS)

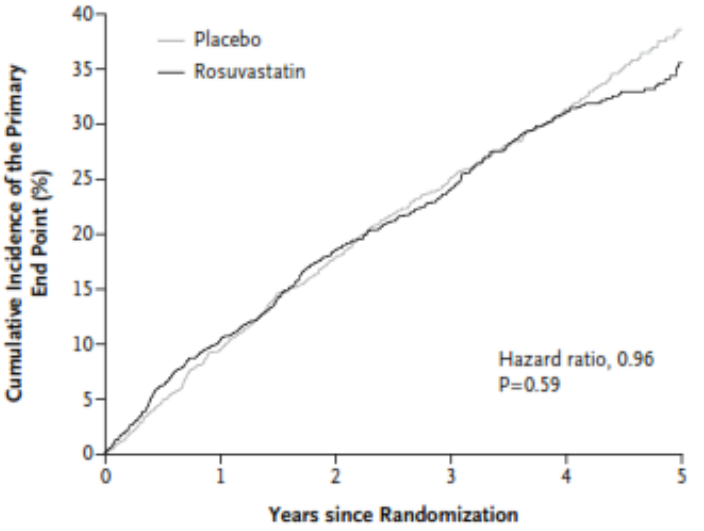


Figure 2. Kaplan–Meier Curves for the Primary End Point in the Two Study Groups.

The primary end point was the first major cardiovascular event.

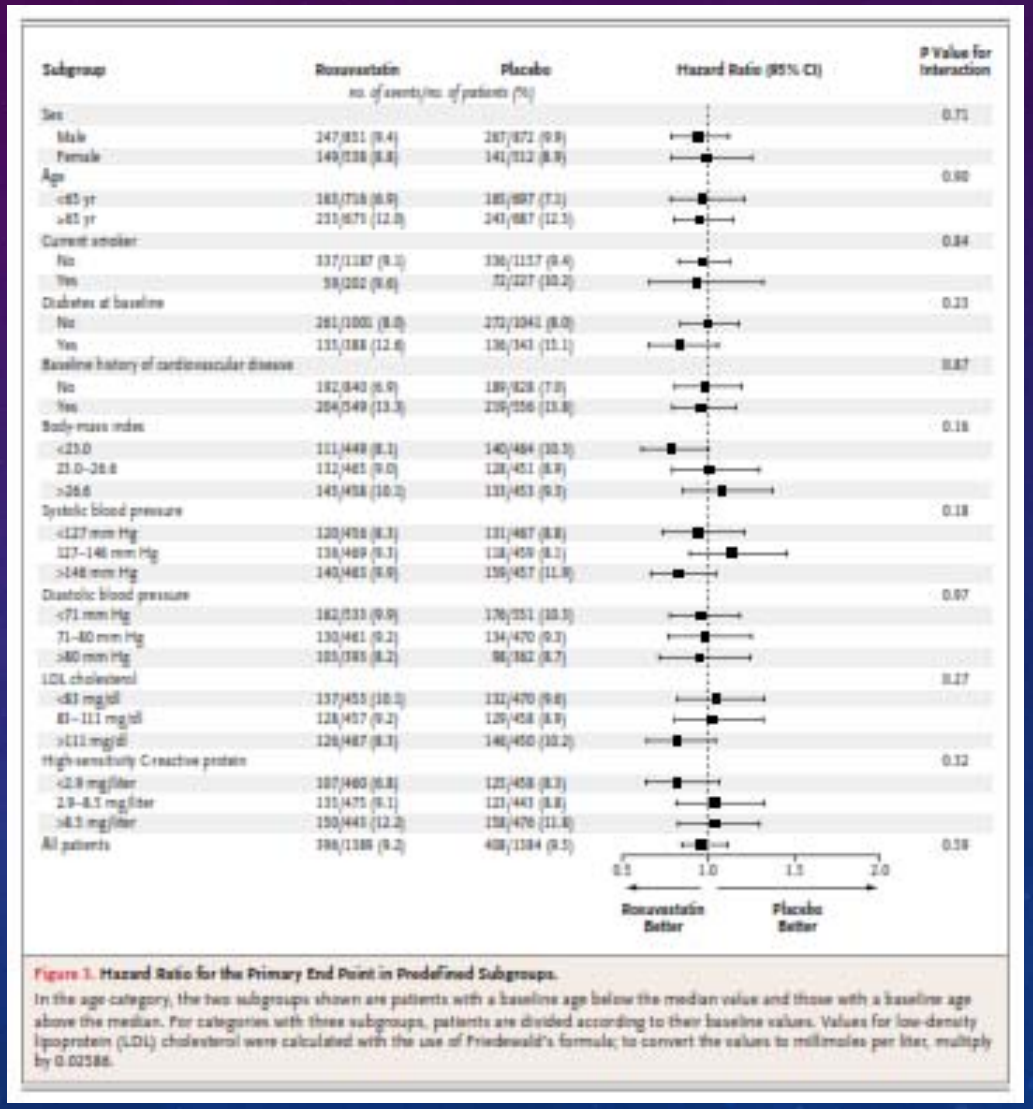


Figure 3. Hazard Ratio for the Primary End Point in Predefined Subgroups.

In the age category, the two subgroups shown are patients with a baseline age below the median value and those with a baseline age above the median. For categories with three subgroups, patients are divided according to their baseline values. Values for low-density lipoprotein (LDL) cholesterol were calculated with the use of Friedewald's formula; to convert the values to millimoles per liter, multiply by 0.02586.

AURORA (A STUDY TO EVALUATE THE USE OF ROSUVASTATIN IN SUBJECTS ON REGULAR DIALYSIS: AN ASSESSMENT OF SURVIVAL AND CARDIOVASCULAR EVENTS)

- **International**
- **Double blind RCT**
- **2776 Dialysis Patients**
- **Rosuvastatin 10 daily vs Placebo**
- **Mean of 3.8 years**

AURORA (A STUDY TO EVALUATE THE USE OF ROSUVASTATIN IN SUBJECTS ON REGULAR DIALYSIS: AN ASSESSMENT OF SURVIVAL AND CARDIOVASCULAR EVENTS)

- The COMBINED ENDPOINT of Death from CV Causes (Non-fatal MI or Non-fatal CVA) was **NOT REDUCED.**
- Rosuvastatin **DID NOT DECREASE the risk of individual components of the PRIMARY ENDPOINT nor of ALL-CAUSE MORTALITY.**

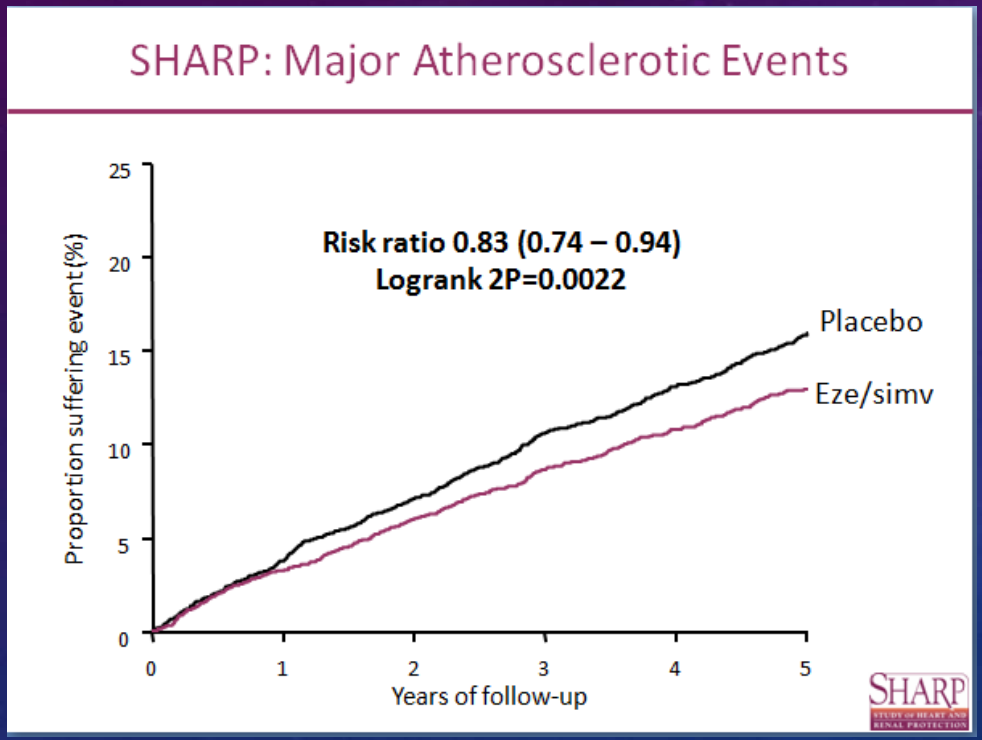
The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial

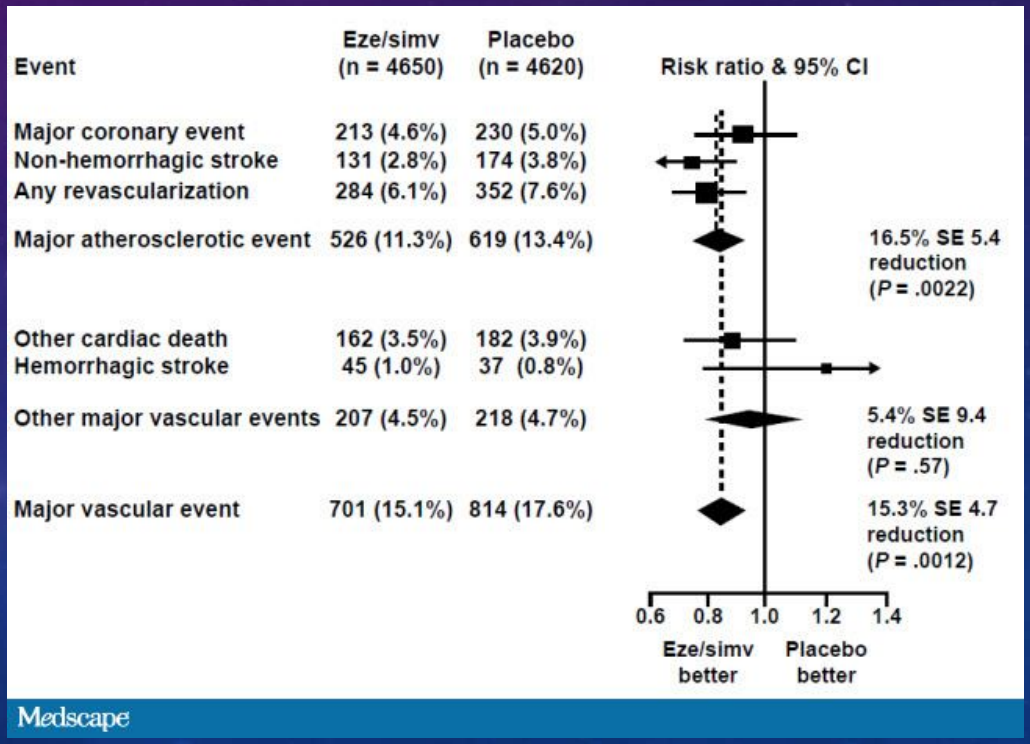
*Colin Baigent, Martin J Landray, Christina Reith, Jonathan Emberson, David C Wheeler, Charles Tomson, Christoph Wanner, Vera Krane, Alan Cass, Jonathan Craig, Bruce Neal, Lixin Jiang, Lai Seong Hooi, Adeera Levin, Lawrence Agodoa, Mike Gaziano, Bertram Kasiske, Robert Walker, Ziad A Massy, Bo Feldt-Rasmussen, Udom Krairittichai, Vuddidhej Ophascharoensuk, Bengt Fellström, Hallvard Holdaas, Vladimir Tesar, Andrzej Wiecek, Diederick Grobbee, Dick de Zeeuw, Carola Grönhagen-Riska, Tanaji Dasgupta, David Lewis, William Herrington, Marion Mafham, William Majoni, Karl Wallendszus, Richard Grimm, Terje Pedersen, Jonathan Tobert, Jane Armitage, Alex Baxter, Christopher Bray, Yiping Chen, Zhengming Chen, Michael Hill, Carol Knott, Sarah Parish, David Simpson, Peter Sleight, Alan Young, Rory Collins, on behalf of the SHARP Investigators**

SHARP (STUDY OF HEART AND RENAL PROTECTION)

- **International**
- **Double blind RCT**
- **9270 patients with CKD**
  - **3023 patients (33%) on dialysis**
  - **6247 patients (67%) with mean eGFR ~ 27**
- **Simvastatin 20 daily + Ezetemibe 10 daily vs. Placebo**
- **4.9 years**

SHARP (STUDY OF HEART AND RENAL PROTECTION)





SHARP (STUDY OF HEART AND RENAL PROTECTION)

- Combination therapy led to a **SIGNIFICANT 17% RR REDUCTION OF PRIMARY OUTCOME of major atherosclerotic events (Coronary death, MI, Non-hemorrhagic CVA or any revascularization)**
  - **BUT IN THE SUBGROUP OF 3023 DIALYSIS PATIENTS, THE RISK OF PRIMARY OUTCOME WAS NOT REDUCED.**

2.3.2: In patients ALREADY RECEIVING statins or statin/ezetemibe combination AT THE TIME OF DIALYSIS INITIATION, we suggest that these agents BE CONTINUED. (2C)

2: WE SUGGEST. Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with his or her values and preferences.

C: LOW QUALITY OF EVIDENCE. The true effect may be substantially different from the estimate of the effect.

SHARP (STUDY OF HEART AND RENAL PROTECTION)

- 2141 (34%) of CKD patients who were not on dialysis at baseline but went on dialysis during the study
  - **Overall benefit** was observed

2.4: In adult KIDNEY TRANSPLANT RECIPIENTS, we suggest TREATMENT WITH A STATIN (2B)

2: WE SUGGEST. Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with his or her values and preferences.

B: MODERATE QUALITY OF EVIDENCE: The true effect is likely to be close to the estimate of the effect, but there is a possibility that is substantially different.

ALERT: ASSESSMENT OF FLUVASTATIN IN RENAL TRANSPLANTATION

Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial

*Hallvard Holdaas, Bengt Fellström, Alan G Jardine, Ingar Holme, Gudrun Nyberg, Per Fauchald, Carola Grönhagen-Riska, Søren Madsen, Hans-Hellmut Neumayer, Edward Cole, Bart Maes, Patrice Ambühl, Anders G Olsson, Anders Hartmann, Dag O Solbu, Terje R Pedersen, on behalf of the Assessment of LEscol in Renal Transplantation (ALERT) Study Investigators**

ALERT: ASSESSMENT OF FLUVASTATIN IN RENAL TRANSPLANTATION

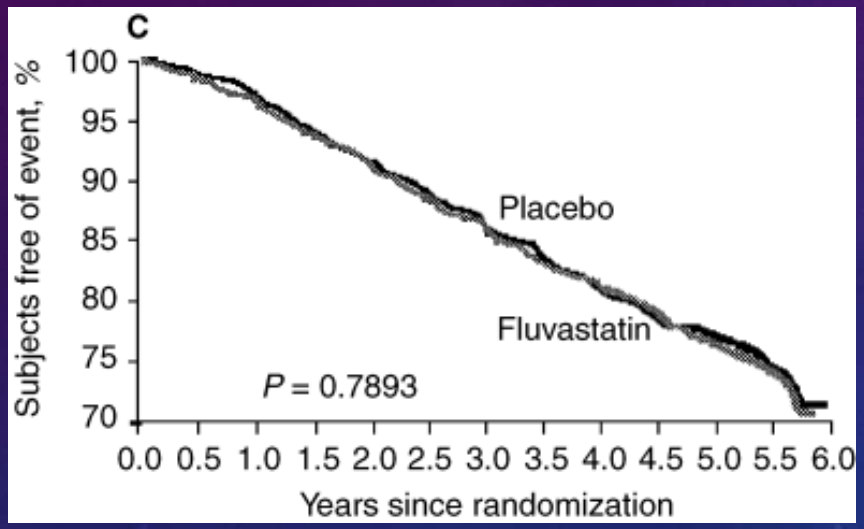
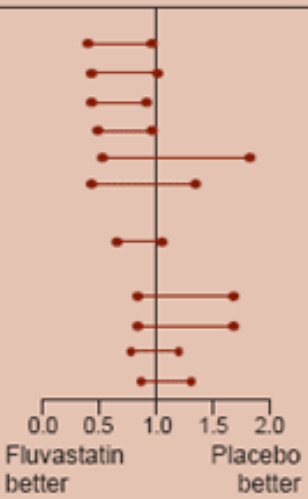


Table 3

Endpoints in the ALERT Trial of Fluvastatin Therapy in Renal Transplant Recipients[70]

Endpoint	*P*	Risk Ratio (95% CI)
Cardiac death	.031	0.62 (0.40-0.96)
Definite nonfatal MI	.050	0.68 (0.40-1.00)
Cardiac death or definite nonfatal MI	.005	0.65 (0.48-0.88)
Cardiac death or definite or probable nonfatal MI	.032	0.72 (0.54-0.97)
CABG	.932	1.03 (0.58-1.81)
PCI	.357	0.80 (0.49-1.30)
Cardiac death or definite or probable nonfatal MI, CABG/PCI (MACE)	.139	0.83 (0.64-1.06)
Fatal or nonfatal cerebrovascular events*	.391	1.16 (0.83-1.63)
Noncardiovascular deaths	.288	1.20 (0.86-1.67)
All-cause death	.848	1.02 (0.81-1.30)
Graft loss or doubling of serum creatinine	.369	1.10 (0.89-1.36)



ALERT = Assessment of Lescol in Renal Transplantation; CI = confidence interval; MI = myocardial infarction; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; MACE = major adverse coronary events. *Fatal or nonfatal stroke, transient ischemic attack, reversible ischemic neurologic deficit, subarachnoid hemorrhage. Adapted with permission from Holdaas H, et al. *Lancet* 2003;361:2024-2031.

ALERT: ASSESSMENT OF FLUVASTATIN IN RENAL TRANSPLANTATION

- 2102 Kidney transplant patients
- 30-75 yo
- Fluvastatin 40-80 mgs daily vs Placebo

ALERT: ASSESSMENT OF FLUVASTATIN IN RENAL TRANSPLANTATION

- 17% REDUCTION IN PRIMARY OUTCOME (Coronary death or Non-fatal MI) ~ **NOT SIGNIFICANT**
- **35% REDUCTION in cardiac death or definite non-fatal MI**
  - UNBLINDED EXTENSION STUDY: **SIGNIFICANT DECREASE IN ORIGINAL PRIMARY OUTCOME (after 6.7 years of follow up)**

KEY POINTS

- ***CORONARY RISK IS SUFFICIENTLY HIGH*** to justify prescription of statins in people aged ≥ 50 with non-dialysis dependent CKD or a kidney transplant.
- ***CORONARY RISK*** in people aged < 50 years with non-dialysis dependent CKD ***IS LOWER***, but the presence of additional CV risk factors may increase risk to justify statin prescription.

KEY POINTS

- Patients with dialysis-dependent CKD ***SHOULD NOT BE INITIATED*** on statin or statin/ezetemibe treatment, given the ***lack of evidence*** that such treatment is beneficial.
- Physicians should be alert to the ***POSSIBILITY OF TOXICITY*** resulting from substances that increase blood levels of statins

DRUG INTERACTIONS

Medscape® www.medscape.com

CYP 1A2	CYP 2C9	CYP 2C19	CYP 2D6	CYP 2E1	CYP 3A4
Acetaminophen	Alprenolol	Diazepam	Amitriptyline	Acetaminophen	Amiodarone
Caffeine	Diclofenac	Ibuprofen	Codeine	Ethanol	**Atorvastatin**
Theophylline	**Fluvastatin**	Mephenytoin	Debrisoquine	Halothane	Clarithromycin
	Hexobarbital	Methylphenobarbital	Flecainide		Cyclosporine
	Phenytoin	Omeprazole	Imipramine		Diltiazem
	Rosuvastatin	Phenytoin	Metoprolol		Erythromycin
	Tolbutamide	Proguanyl	Nortriptyline		Itraconazole
	Warfarin	**Rosuvastatin**	Pherexiline		Ketoconazole
			Propafenone		Lacidipine
			Propranolol		**Lovastatin**
			Sparteine		Mibefradil
			Thioridazine		Midazolam
			Timolol		Nefazodone
					Nifedipine
					Protease inhibitors
					Quinidine
					Sildenafil
					Simvastatin
					Terbinafine
					Verapamil
					Warfarin

Source: Adapted from reference 13.

Abbreviation used: CYP, cytochrome P.
*Statins metabolized by CYP 450 isoenzymes are printed in boldface type.

Source: J Am Pharm Assoc © 2006 American Pharmacists Association

Annals of Internal Medicine
Established in 1927 by the American College of Physicians

From: Lipid Management in Chronic Kidney Disease: Synopsis of the Kidney Disease: Improving Global Outcomes 2013 Clinical Practice Guideline

Ann Intern Med. 2014;160(3):182-189. doi:10.7326/M13-2453

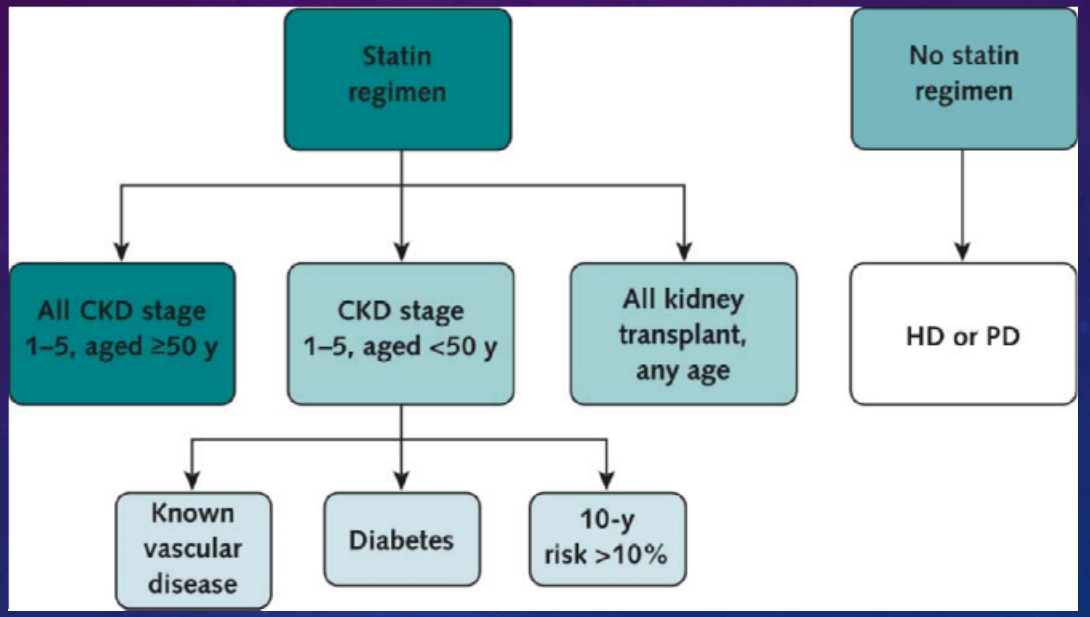


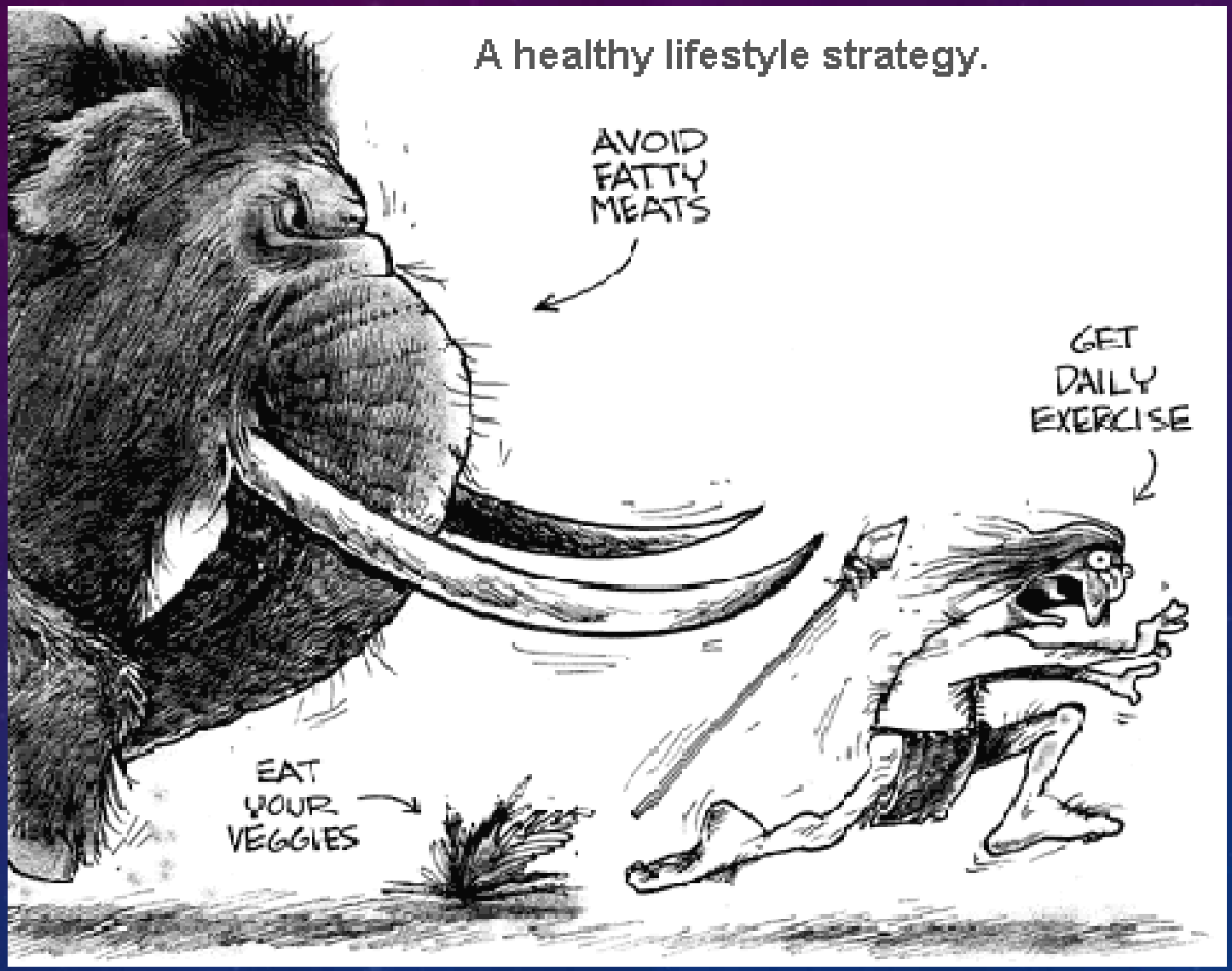
Figure Legend:

Algorithm for cholesterol-lowering treatment in persons with CKD.

Boxes represent recommendations about whether to prescribe a statin regimen. Boxes with dark and medium green fill represent strong recommendations; lighter green and white boxes represent weak recommendations. Recommended statin regimens are shown in Table 1 and include statin monotherapy or statin/ezetimibe for those with CKD stage 3a to 5 and statin monotherapy for all other CKD populations. CKD = chronic kidney disease; HD = hemodialysis; PD = peritoneal dialysis.

Date of download: 7/5/2014

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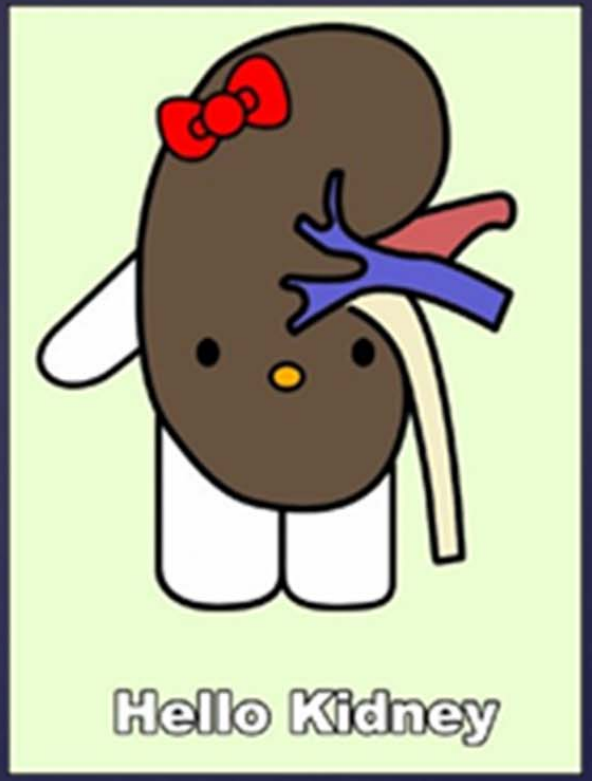

A healthy lifestyle strategy.
AVOID FATTY MEATS
GET DAILY EXERCISE
EAT YOUR VEGGIES








Hello Kidney


Hello Kidney


ThankYou
Merci
Salamat
Kop
Tack
Hvala
Xie
Gra
kun
Dhanyavad
Khopjai
Kruthagnathalu
Arigatou
Dhonnobaad
Asante
Dhan
daa
Hain
ederim
Or
Shukriya
Kun
Euxaristo
Danke
dank
Terima
Enkosi
Fyrir
Blagodariya
Nandree
Gracias
Gomapsupnida
Grazzi
raibh
krap
Dakujem
Daw
Waad
Dhanyavaadaalu
Dank
Takk
Gamsahapnida
Te ekkür
Dekuju/Dekujeme
Diolch
Kiitos
Sheun
umesc
Shnorhakalutiun
Kasih
Mamnoon
Todah
Shokriya
Ngiyabonga
Dziękuję
Shokrun
Spaas
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al
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Go
Grazie
Falemínderit
Dhanyavaad

A Teaching Affiliate of Harvard Medical School

Metabolic Syndrome: Diabetes/Pre-diabetic state

Paul L. Huang, MD, PhD
Professor of Medicine, Harvard Medical School
Director, MGH Cardiac Metabolic Syndrome Program

August 23, 2014
National Lipid Association
Clinical Updates

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Presentation Outline

Topics

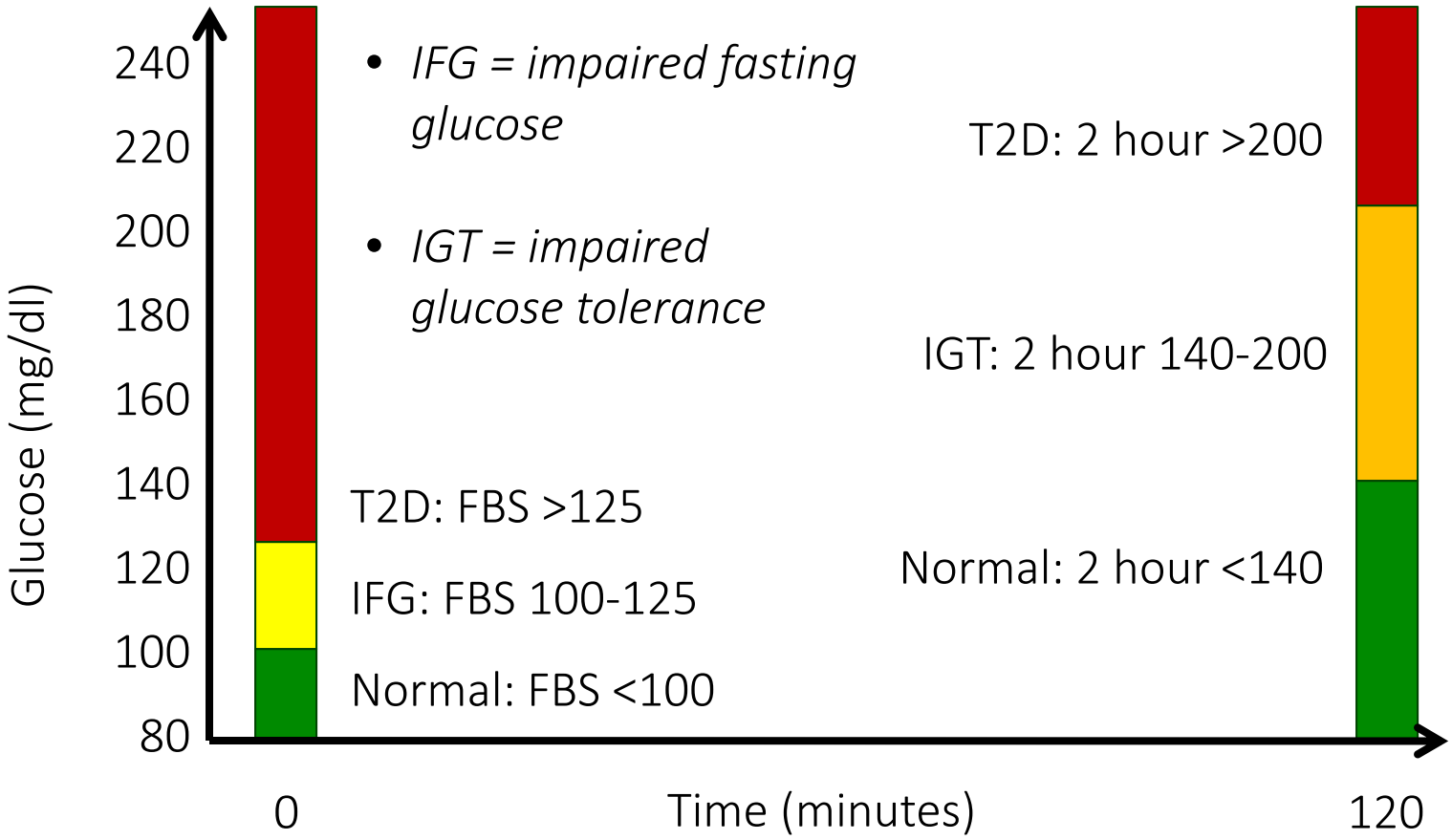
- Definitions and criteria:
  Diabetes, pre-diabetes, and metabolic syndrome
- Atherogenic dyslipidemia
- Pathophysiology of insulin resistance
- Diabetes and ACC/AHA 2013 treatment guidelines
- Residual cardiovascular risk: high TG and low HDL
- Diabetogenicity of statins

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Definitions and criteria

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Glucose tolerance test (GTT)



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Diagnostic criteria

	Normal	Pre-diabetes	Diabetes
Fasting BS	<100	100-125	>125
2-hour BS	<140	140-200	>200
HbA1c	<5.7	5.8-6.4	>6.5

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Metabolic syndrome

Metabolic syndrome is present if 3 out of 5 diagnostic criteria are present:

- Abdominal obesity: waist > 40” (men) or 35”(women)
- Hypertension: BP > 130/85
- Hypertriglyceridemia: TG > 150 mg/dl
- Low HDL cholesterol: HDL < 40 (men) or 50 (women)
- Hyperglycemia: FBS > 100 mg/dl

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Metabolic syndrome

Epidemiology

- > 50 million in the US have metabolic syndrome
- Prevalence > 30% over age 50

Risks

- Risk of diabetes increases 5-fold
- Risks of heart attack and stroke increase 2-fold

Concept

- Clustering of risk factors occurs because of shared pathophysiology and mechanisms

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Atherogenic dyslipidemia

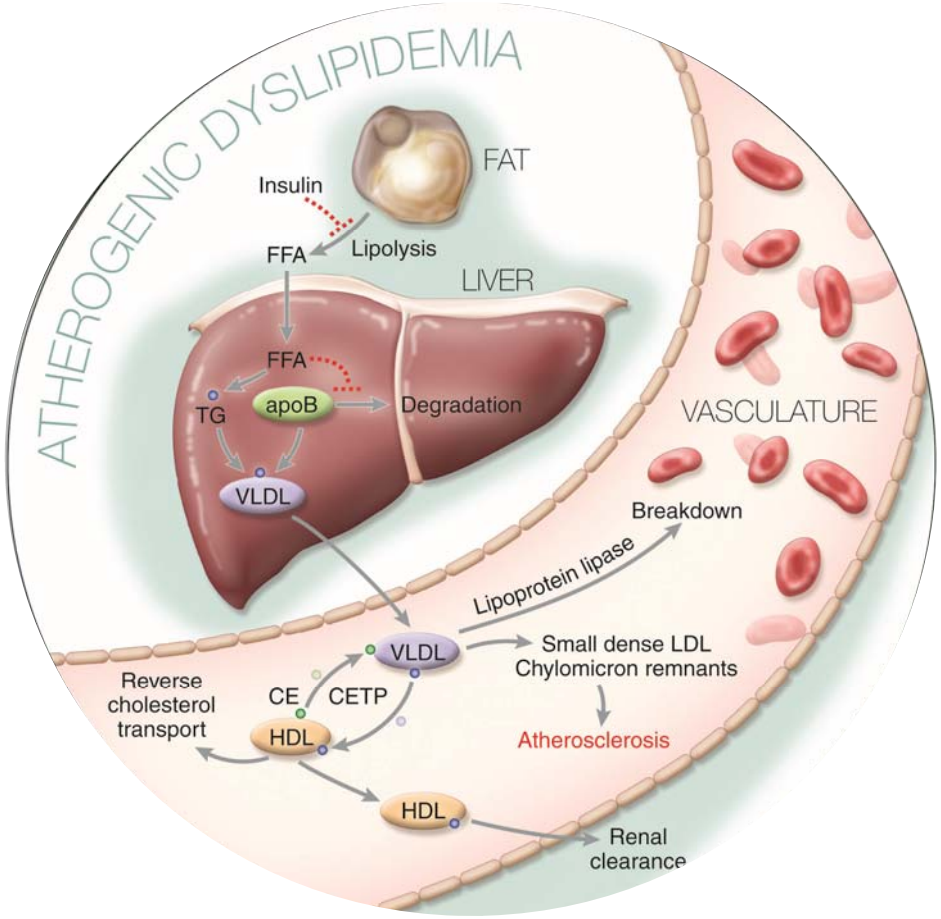
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Atherogenic dyslipidemia

Elevated TG

Low HDL

Small, dense LDL particles



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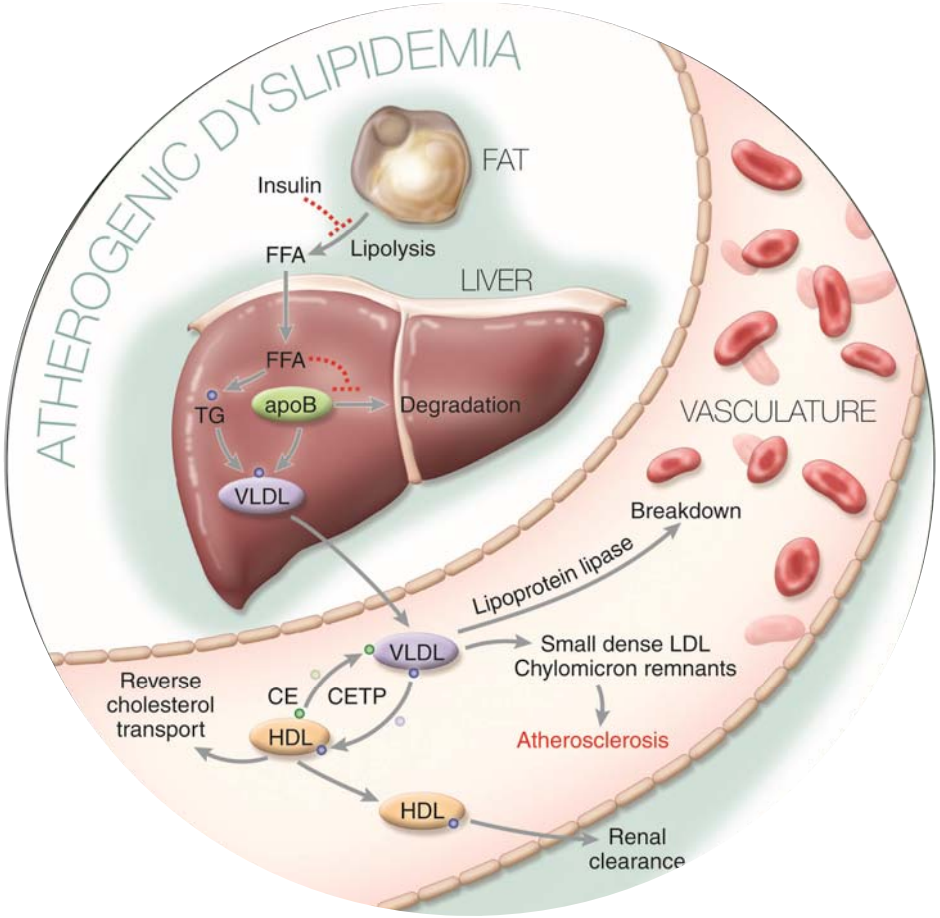
Atherogenic dyslipidemia

Increased VLDL production

- Increased lipolysis in adipocytes: ↑FFA
- FFA used as substrate to synthesize TG
- FFA block PI3K-dependent degradation of apoB100

Decreased VLDL clearance

- Lipoprotein lipase



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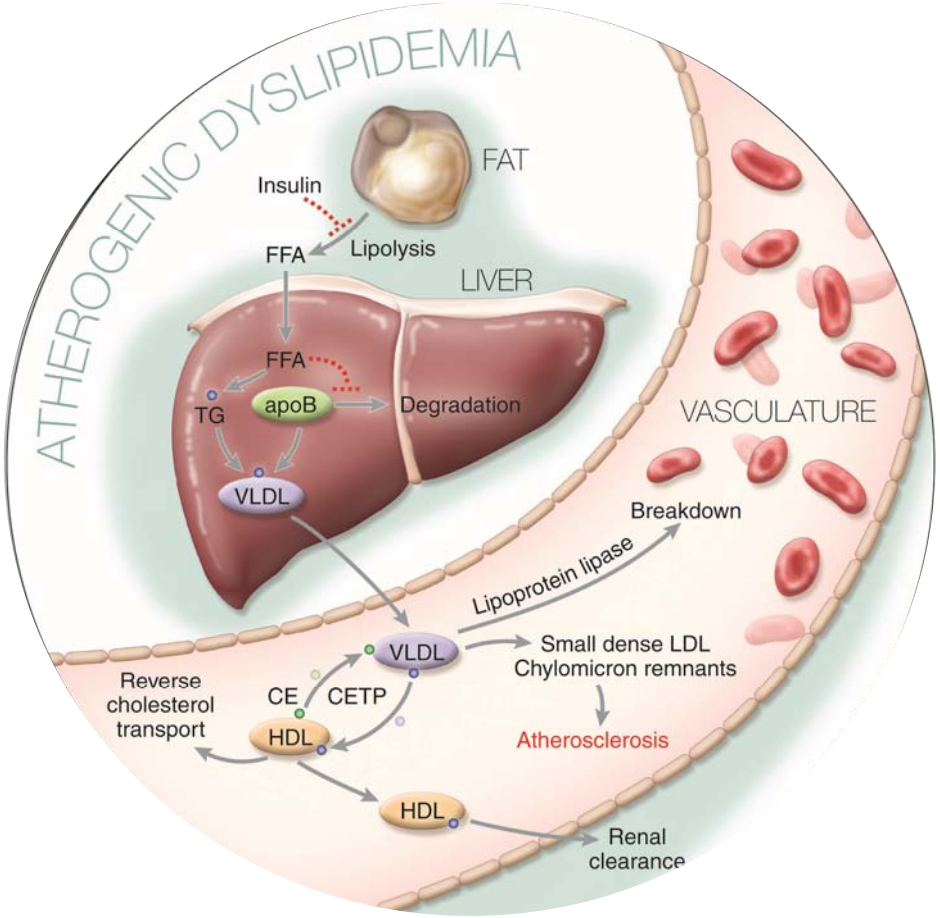
Atherogenic dyslipidemia

Less functional HDL

- TG in VLDL exchanged for cholesteryl esters in HDL by CETP
- TG-enriched HDL, increased clearance

Atherogenic VLDL

- Remnant lipoproteins
- Small dense LDL particles



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Insulin resistance

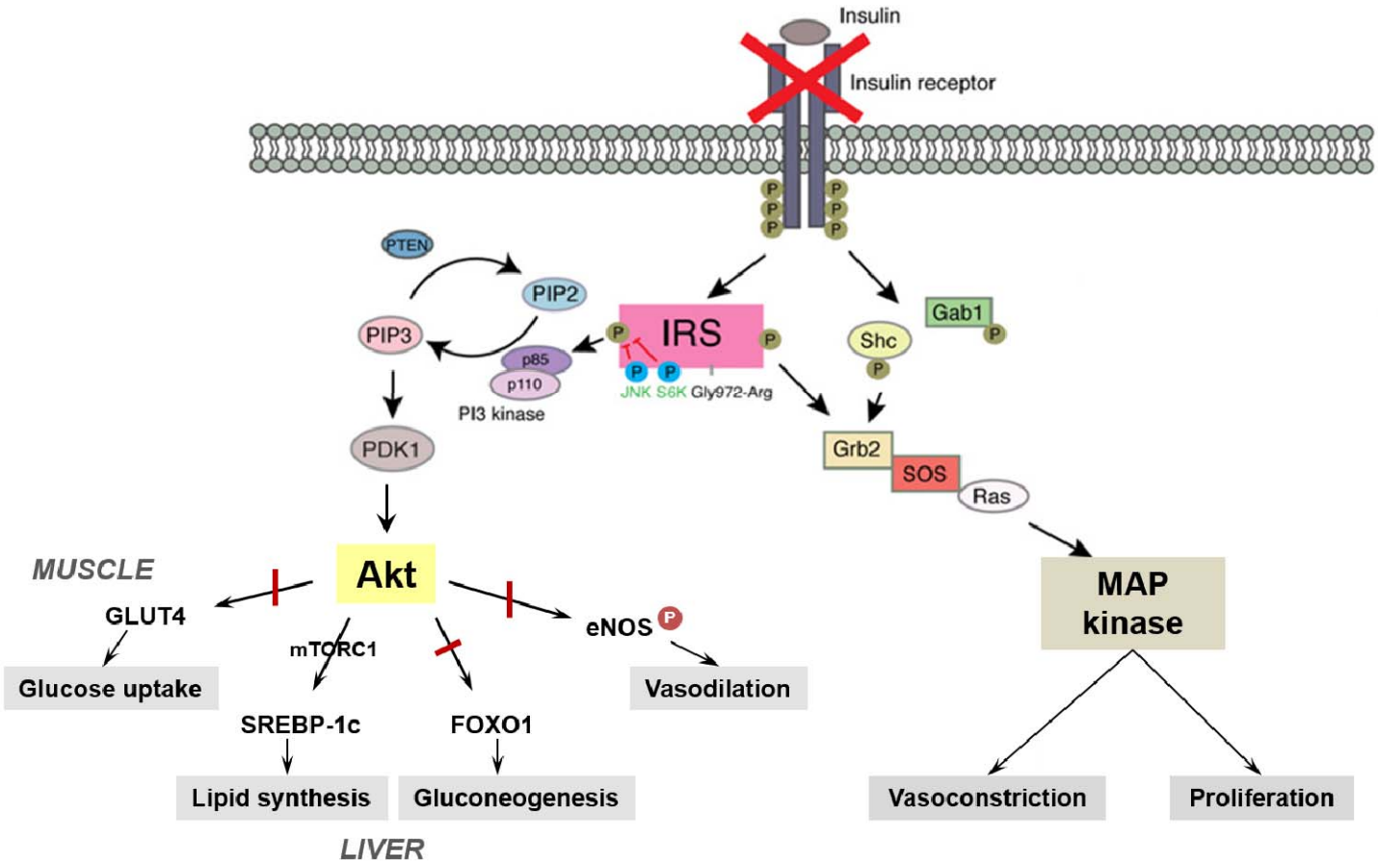
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Insulin signaling

- Diabetes and metabolic syndrome are associated with ***hyperinsulinemia***, to compensate for insulin resistance
- Insulin resistance is ***selective***; some signaling pathways are diminished, others are not
- Some disease pathogenesis is because of hyperinsulinemia-driven, unaffected pathways:
  - MAPK vs. Akt in vasculature: more vasoconstriction and less vasodilation
  - Decreased hepatic and skeletal muscle glucose regulation with persistent lipogenesis

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Insulin signaling and selective resistance



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New targets suggested by pathophysiology

Targets involved in persistent hepatic lipogenesis

- mTORC1, which mediates lipogenesis, bypassing normal Akt regulation
- SREPB-1c, transcription factor involved in expression of lipogenic genes

Targets involved in mitochondrial beta-oxidation

- Enzymes involved in beta oxidation, such as VLCAD, LCAD are regulated by S-nitrosylation
- Activity of LCAD is regulated by sirtuins

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Diabetes and ACC/AHA 2013 treatment guidelines

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New ACC/AHA guidelines

Four subgroups may benefit from statins:

1. Established ASCVD
2. LDL > 190 mg/dl
3. Ten year risk of ASCVD > 7.5%
4. Type 1 or type 2 diabetes

Concepts

- Paradigm shift away from LDL-based goals
- Risk calculator controversial

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Statins reduce CVD in diabetes

Study	n (T2D)	Intervention	Outcome
Heart Protection Study (HPS)	5963	Simva 40	25% reduction
Collaborative Atorvastatin Diabetes Study (CARDS)	2800	Atorva 10	37% reduction, early termination
Atorvastatin Study for Prevention of CHD Endpoints (ASPEN)	2410	Atorva 10	No significant difference
Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-LLA)	2226	Atorva 10	25% reduction
Lescol Intervention Prevention (LIPS)	303	Fluva 80	51% reduction
Treating to New Targets (TNT)	1501	Atorva 10/80	13.8% vs. 17.9%
Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT)	4162	Prava 40 Atorva 80	5.5% absolute RR with atorva 80

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Meta-analysis of statins in diabetes

Cholesterol Treatment Trials Collaborators

- Meta-analysis of 14 randomized trials
- n = 18,686 with diabetes (1466 T1D; 17,220 T2D)
  n = 71,370 without diabetes
- Mean follow-up 4.3 years
- 9% reduction in all-cause mortality per mM (39 mg/dl) drop in LDL
- 21% reduction in major CVD events per mM drop in LDL

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Residual cardiovascular risk: high TG and low HDL

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Residual risk associated with HDL and TG

HDL

- Epidemiologic studies show HDL is strong, independent inverse predictor of CVD risk
- CETP inhibitor trials show dissociation between HDL raising and CVD reduction
- Functionality of HDL (e.g. reverse cholesterol transport) as well as absolute level of HDL is important

TG

- Extreme hypertriglyceridemia is risk for pancreatitis and should be treated

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ApoC3, triglycerides, and CHD

TG and HDL Working Group, NHLBI (n=110,970)

- identified apoC3 mutations that affect TG levels
- apoC3 loss of function mutations lower TG by 39% and CHD risk by 40%

NEJM 2014; 371: 22

Copenhagen, two studies (total n=75,725)

- association between TG and CHD risk
- apoC3 loss of function mutations lower TG by 44%, vascular disease by 41%, CHD by 36%

NEJM 2014; 371: 32

Niacin

Effects on lipid profile

- Lowers TG by 10-30%
- Increases HDL by 10-40%
- Lowers LDL by 5-20%

Effects on CVD

- Multiple studies confirm niacin lowers CVD
- Niacin may increase blood glucose levels
- ARBITER: niacin added to statin reduces carotid IMT after 12 months (n=167)

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Niacin

AIM-HIGH Study (n=3414, 1/3 with T2D)

- Niacin increased HDL and lowered TG c/w statins alone
- Niacin did not affect CVD endpoint at 2 years
- Study stopped early due to lack of efficacy

NEJM 2014; 371: 290 and NEJM 2011; 365: 2255

HPS-2-THRIVE Study (n= 25,673, 1/3 with T2D)

- No reduction in CVD endpoints
- Increased adverse events in niacin group: new diabetes, infection, and bleeding

NEJM 2014; 371: 203

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Fibrate monotherapy

Gemfibrozil

- Monotherapy reduces CVD, including in T2D

Benzafibrate (BIP Trial)

- Monotherapy has no benefit on CVD outcome
- No difference in mortality, but reduced endpoints in subgroup with high TG

Fenofibrate Intervention and Event Lowering in Diabetes (FIELD)

- Monotherapy reduces total CVD events but not coronary events or mortality
- Benefit greatest in metabolic syndrome and high TG

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Fibrate with statins

ACCORD Study

- Action to Control Cardiovascular Risk in Diabetes
- Fenofibrate plus simvastatin compared with simvastatin alone
- Primary outcome: nonfatal MI, stroke, or CVD mortality not significantly different
- Prespecified subgroup analysis indicates benefit for
  - men, and
  - those with high TG and low HDL

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Diabetogenicity of statins

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Statin therapy and risk of T2D

JUPITER trial

- Rosuvastatin 20 daily for 1.9 years
- Significant increase 3.0% vs. 2.4% in incident T2D
- Increased A1c

WOSCOPS trial

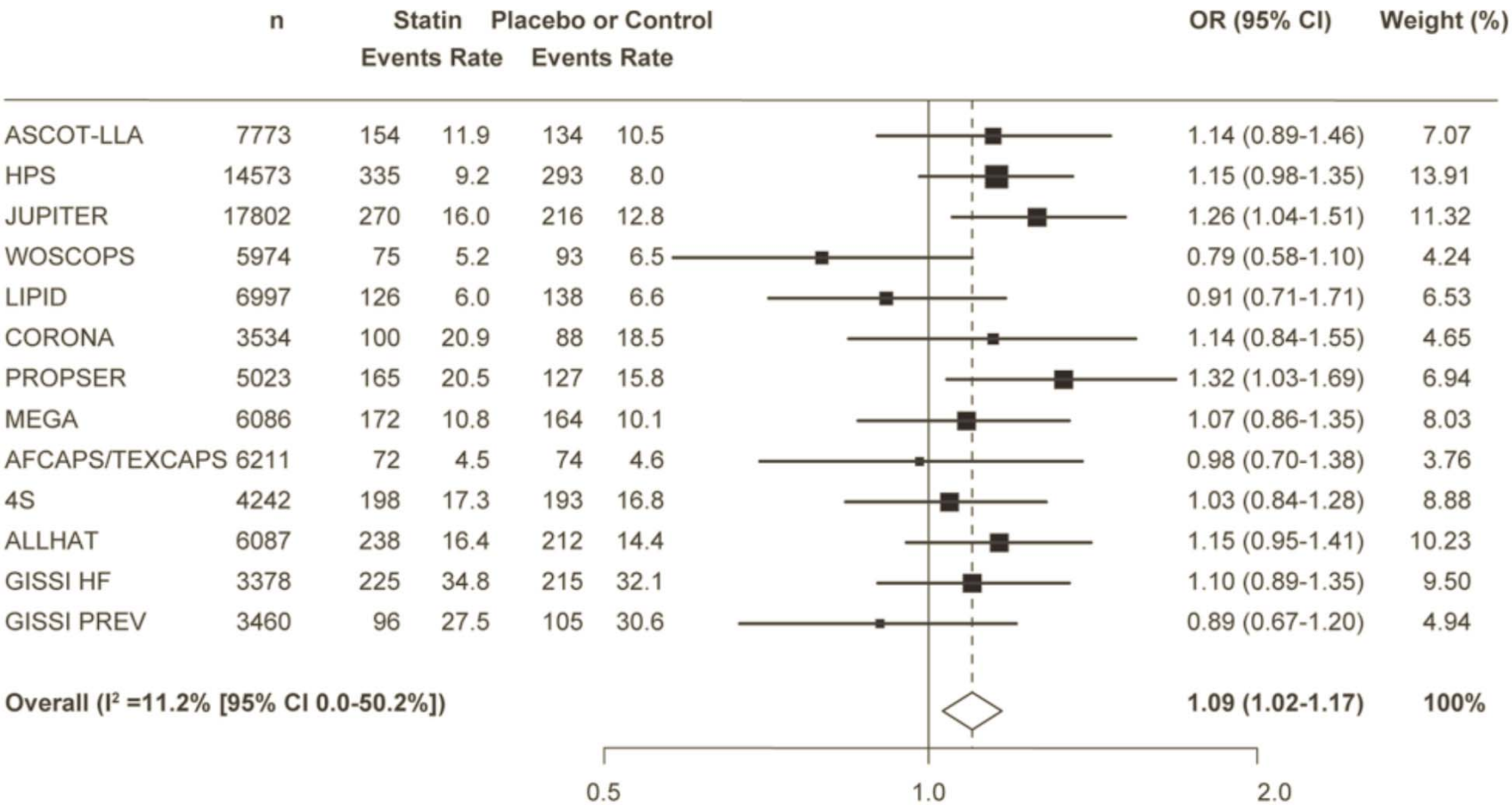
- Pravastatin decreased hazard of T2D by 30%

Meta-analysis of 13 trials

- 91,140 patients without diabetes
- 9% increased risk of T2D over 4 years
- Effect is dose related and varies between statins

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Statin therapy and risk of T2D



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Statins and risk of T2D

- Analysis of risk of developing T2D and CVD risk reduction by statins supports use of statins
- On average, treatment of 255 patients with statins for 4 years results in one additional case of T2D, while preventing 5.4 CVD events in those same 255 patients
- Number needed to harm for intensive-dose statin therapy for one year is 498 for new T2D; number needed to treat is 155 to prevent CVD events
- For new ACC/AHA guidelines, benefits significantly outweigh the risks of developing T2D

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Summary and

Take home messages

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Summary

- Atherogenic dyslipidemia consists of high TG, low HDL, and small dense LDL particles
- Insulin resistance affects some pathways, but not others
- Statins reduce CVD events in those with T2D (both primary and secondary prevention)
- Residual CVD risk from low HDL or high TG may be treated with fibrates
- Risk of developing T2D from statin is outweighed by benefit of CVD reduction

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Take-home messages (1)

STATINS

- Statins have been proven to reduce CVD events in T2D
- Risk of developing T2D from statin is outweighed by benefit of CVD reduction

FIBRATES

- Fenofibrate added to statin reduces residual CVD risk
- Fibrate monotherapy reduces CVD events in diabetes, especially with high TG and metabolic syndrome

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Take-home messages (2)

NIACIN

- AIM-HIGH and HSP2-THRIVE
  - did not show further reduction in CVD events when added to statins
  - showed increased adverse events
- Niacin has roles
  - to reduce LDL in statin-intolerant patients
  - to reduce TG in fibrate-intolerant patients
  - in treatment of FH

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Discussion

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Insulin Resistance and PCOS: A not uncommon reproductive disorder

Joyce L. Ross, MSN, CRNP, CS, FNLA, FPCNA
Diplomate Accrediation Council for Clinical Lipidology
President Preventive Cardiovascular Nurses Association
Consultative Education Specialist, Cardiovascular Risk Intervention
University of Pennsylvania Health System– Retired
Philadelphia, Pennsylvania
jlr@joycerossnp.com

Case Study
18 year old college freshman

- SA presents to the cardiovascular risk intervention program for evaluation and treatment recommendations for her elevated triglyceride (TG) level
- She is heading off to college and was recently placed on birth control pills
- Reports that she has been generally healthy, although has ongoing issues with her irregular periods and problems with controlling her weight

Case Study Continued

- Only medication at presentation is her new birth control pill which contains estrogen
- She reports only intermittent exercise now, but had played sports in her freshman and sophomore years in high school
- She follows no specific diet and reports that most of her family members are over weight and that it “runs in the family”

Other Health History

- Denies HTN, DM, thyroid disease
- Reports some intermittent joint and muscle problems, nothing ever diagnosed
- Gets H/A's a few times per week, takes tylenol with good effect
- Ongoing issues with acne which is followed by a dermatologist
- Is annoyed by some unusual hair growth on her face, feels that it looks like sideburns and hair is heavier than her friends above the lip
- No cardiovascular s/s but has family history of premature heart disease

Laboratory results

- PCP had blood work scheduled for 2 weeks prior to her appointment which is a 2 month follow-up after starting her OC.
- The labs were found to be very different from her normal ranges, especially her lipids and he felt they were likely a lab error.
- When repeat labs were completed with little change she was referred for evaluation and treatment recommendations.
- Total Chol. = 270, TGs = 620, HDL = 30, Non HDL = 240
- No direct LDL drawn, Glucose 119 which she now remembers has been in this area over many years, liver & kidney function WNL

Physical Examination

- Pleasant and alert young woman, in no apparent distress
- Height = 5’2”, weight = 168, BMI = 31
- Waist circumference = 36”
- Blood pressure = 136/88
- Normal cardiac and respiratory exam
- Skin: multiple skin tags, acne to face and neck, hirsutism
- Abdominal exam unremarkable
- No other remarkable physical findings noted

Differential Diagnosis

- PCOS
- Hypertriglyceridemia
- Metabolic Syndrome
- Obesity
- Cushing's Syndrome

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- No cardiovascular s/s but has family history of premature heart disease

Laboratory results

- Her primary care provider had blood work drawn prior to her visit. She had labs 2 weeks prior after the birth control pills started and he felt they were likely wrong. When new labs were received he referred her for evaluation
- Total Chol. = 270 TGs = 620

  HDL = 30 Non HDL = 240 No direct LDL drawn, Glucose 119 which she now remembers has been in this area over many years, liver & kidney function WNL

Physical Examination

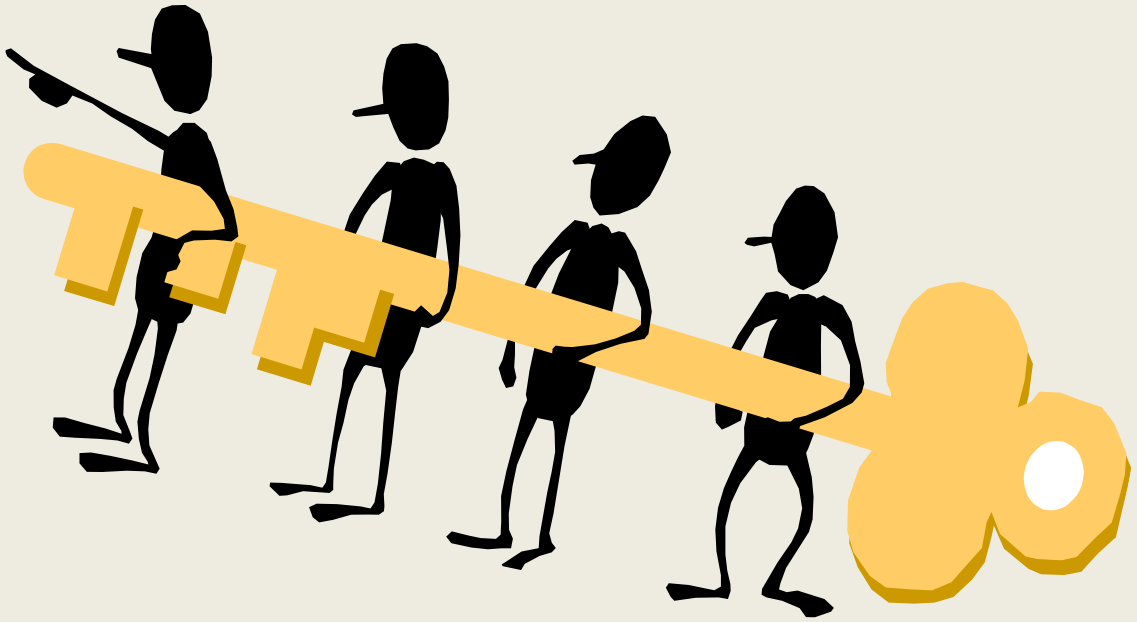
- Pleasant and alert young woman, in no apparent distress
- Height = 5’2”, weight = 168, BMI = 31
- Waist circumference = 36”
- Blood pressure = 136/88
- Normal cardiac and respiratory exam
- Skin: multiple skin tags, acne to face and neck, hirsutism
- No other remarkable physical findings

Diagnosis

- PCOS yes
- Hypertrygliceridemia yes
- Metabolic Syndrome yes
- Obesity yes

Can make presumptive diagnosis all of the above but will need to clarify some studies and add others

Management of PCOS



It’s a team approach !

Case Study
19 year old college freshman

- Dyslipidemia
- Impaired glucose
- High Blood Pressure
- Birth control pills
  - birth control pill that contained estrogen
- irregular periods
- Weight/obesity
- Exercise
- Acne
- Unusual hair growth on her face

- Diagnosis:
  - PCOS
  - Metabolic Syndrome
  - Dyslipidemia
  - Obesity

- Treatment Plan
  - Lifestyle Management
  - Hormonal Intervention

Approaches to Therapy for PCOS is similar to that of Metabolic Syndrome

I. Lifestyle modification (weight loss, increased activity)
II. Treat existing risk factors
   a) BP control, smoking cessation
   b) LDL-C < 70 mg/dl (non HDL-C < 100) reasonable in CHD patients; LDL-C < 100 mg/dL reasonable for high risk primary prevention patients
III. Insulin sensitizing therapies (metformin, TZD) in non-diabetic subjects
   a) Reasonable if impaired fasting glucose
   b) May be reasonable if A1C 6 – 6.5%

IV. The major difference is the addition of hormonal contraception for the patient with PCOS

TZD = Thiazolidinediones

The Future for SA

- Marriage
- Children
- Menopause
- Post-Menopause



PCOS: Changing Paradigm
Reproductive vs Metabolic Issues

Younger

- Menstrual problems
- Hirsutism
- Contraception
- Mental health
- Infertility
- Prevention of Sequelae

Older

- Infertility
- Quality of life issues
- Type 2 diabetes
- Cardiovascular disease
- Cancers

Slide courtesy of Mimi Secor, MS, M.Ed, FNP-BC, FAANP

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PCOS and Pregnancy Risks: Obesity is a "Ticking Time Bomb" for Reproductive Health

- Infertility: 40% female/PCOS
- Spontaneous Abortion /SAB, (25-73%)
- Gestational Diabetes (3 x increased risk)
- Preeclampsia/Hypertension



Slide courtesy of Mimi Secor, MS, M.Ed, FNP-BC, FAANP

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Polycystic Ovary Syndrome

Robert A Wild MD,MPH,PHD, FNLA

Diplomate American Board of Clinical Lipidology

Executive Board NLA

Professor Ob/Gyn & Clinical Lipidology

The University of Oklahoma Health Sciences Center

Medicine

OUTLINE

- Prevalence
- Signs and symptoms
- Major competing clinical issues
- Non metabolic therapies
- Metabolic therapies



ANDROGEN EXCESS



10% of all women

30% of some subgroups

Prevalence of Androgen Disorders in Clinical Practice

- **Acne**
  - most teens
  - ~25% 35yrs-menopause
- **Hirsutism**
  - Upper lip ~35% reproductive years
  - Chin and facial ~8-10%
- **Androgenic Alopecia**
  - 23-87% all men and women
- **Congenital Adrenal Hyperplasia**
  - Afflicts 1/14,000
  - Alaskans, American Indians, Hispanics, Ashkenazi Jews, Yugoslavians

PCOS

- Presents -elevated triglyceride (TG) level
- Recently placed on ‘birth control pills ‘
- Irregular periods problems controlling her weight
- Acne & Hirsutism

- Cosmetic
- Fertility
- Cardiometabolic
- Endometrial Cancer

PCOS

- Intermittent exercise
- No specific diet
- Family members overweight
- Fam. Hx premature CVD
- Cardiometabolic

PCOS

- Chol 270 mg/dL,TGs 620 mg/dL , HDL 30 mg/dL
- nonHDL Cholesterol 240 mg/dL
- CMP nl. , Glucose 119 mg/dL
- Cardiometabolic

PCOS

- BMI 31
- Waist = 36 “ Caucasian
- BP 136/88
- Skin tags, acanthosis nigricans, hirsutism
- CMP nl. Glucose 119 mg/dL
- Cardiometabolic
- Cosmetic

Androgen Excess: Why Identify?

- Treat presenting Sxs
- Avoid exacerbation of clinical/sub-clinical condition
- Reduce the psychosocial Impact
- Diminish progression of masculinization
- Minimize related long-term health effects

Why Identify Androgen Excess?

- Rule out ovarian or adrenal tumor, Cushing's Syndrome
- Infertility
- Interrupt continuum of disease progression
  - Hypertension
  - Diabetes
  - ASCVD
  - Endometrial Cancer

Think Androgens



PCOS Diagnostic Challenge

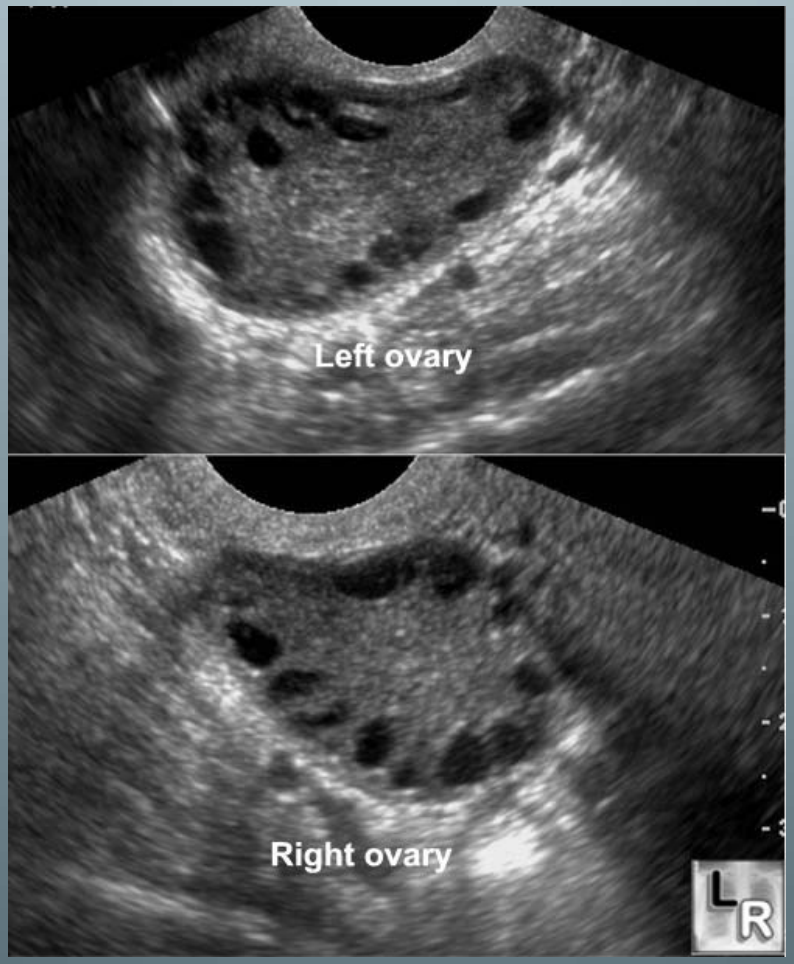


- Varied Individual Responses
  - Level of androgen
  - Target organ sensitivity
  - Labs don't correlate
- Exogenous Androgen
  - Anticonvulsants
  - Danazol
  - Androgenic progestins
  - Anabolic steroids
  - Ace inhibitors

Laboratory Findings in Women With Androgen Excess

Proportion	Androgen Production	[Plasma]	MCR
1/3	↑	↑	↑
1/3	↑	↑	Normal
1/3	↑	Normal	↑

Polycystic Ovaries



Criteria for PCOS
2 of 3

androgen excess –clinical or biochemical

irregular menstrual intervals ,<21 or >36days

polycystic ovaries by vaginal ultrasound

½ obese

PCOS

- Presents -elevated triglyceride (TG) level
- Recently placed on ‘birth control pills ‘
- Irregular periods problems controlling her weight
- Acne & Hirsutism

- **Cosmetic**
- **InfertilityContraception**
- **Cardiometabolic**
- **Endometrial Cancer**
- **Mood disorders**

PCOS - Cosmetic

- Other meds?
- A higher estrogenic 35 mcg, lower androgenic progestin OC works best
- Progestin only
- Prevents endometrial cancer
- Spironolactone,Finasteride, combinations
  Takes 6-9 mos.
- 5 alpha reductase in hair follicles
- Contraceptive need?
- Laser, electrolysis, shaving ,plucking

Time Required for Improvement

- Acne
  - 2-8 weeks, decrease new lesions
  - One year
  - Multifactorial
    - Androgen driven sebum production
    - inflammatory
- Hirsutism
  - 3-4 mos. Slower the growth
  - 6-12 mos. to decrease area coverage, darkness, thickness & stiffness
- Alopecia
  - 2-6 weeks, reduced shedding, healthier
  - 6-24 mos. partial regrowth

PCOS Hirsutism Treatment : Skin and Hair Manifestations

- Local Methods
  - Acne
    - Anti-bacterials
    - Retinoic acid
    - OTC
  - Alopecia
    - Minoxidil
    - Dark hair spray
    - Styling
    - wig
- Hirsutism
  - Plucking
  - Bleaching
  - Depilatory
  - Waxing
  - Shaving
  - Electrolysis

PCOS -Pharmacological treatments

- Androgen antagonists: almost always necessary: except acne
- Choice
  - OC (that decrease free T)
  - Spironolactone
  - OC + S
  - Metformin
  - Finasteride
  - GnRHa
  - Flutamide

PCOS Fertility



- Ovulation induction
  - Clomiphene, aromatase inhibitors, metformin
  - Gestational diabetes , toxemia, prematurity, stillborn, NICU admissions, childhood obesity, metabolic syndrome in adulthood
- Menopause
  - Weight gain, central obesity , atherosclerosis
  - Menses regulate
  - Contraception
- Post Menopause
  - Diabetes , CHD, Stroke
  - Earlier mortality

PCOS Mood Disorders

- PCOS Quality of Life Inventory
  - Cronin et al 1998 JCEM 83(6):1976-87
  - Becks Depression Inventory
- Depression and Anxiety assessment
- Weight neutral medication alternatives

PCOS - Cardiometabolic

- Metabolic syndrome
  - Diabetes Screen, Treatment
    - 2 hr. pp. glucose
    - At risk any age
    - Most common reason for hypertriglyceridemia
    - Metformin,Glitazones
  - Lifestyle Management

    Weight loss readiness

    Stages of change

    Depression screen

    Nutritionist

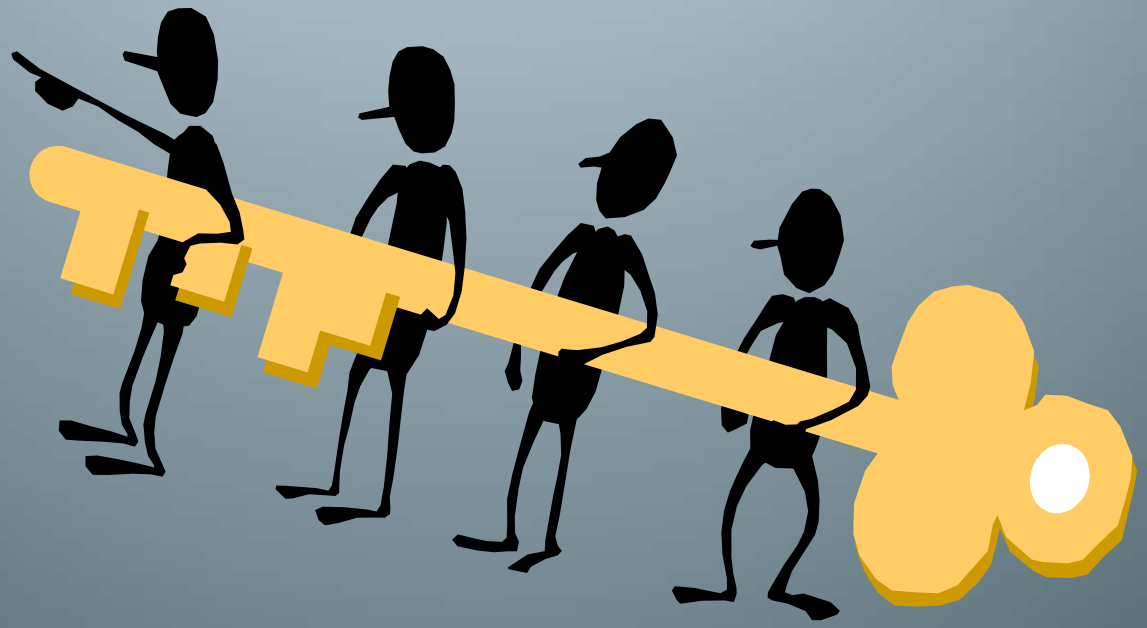
Hypertriglyceridemia

- Metabolic Syndrome
  - Statins, Fish Oil, Fibrates
    - Category x, category C
  - Contraception
- Genetic Disorders of Triglycerides
  - Chylomicronemia
    - Lipoprotein lipase deficiency
    - Apo CII deficiency
  - Familial combined dyslipidemia
    - Overproduction of Apo B-100
  - Familial hypertriglyceridemia
    - Large VLDL particles
    - Minimal ↑ CAD risk
  - Type III dyslipidemia

Take Home

- Androgen excess : Multi-system
- Long term consequences CVD, Diabetes, Cancer
- Select therapy to decrease androgenicity
- One androgen manifestation - look for others
- Diagnose early - treat continually
- One ounce of prevention = 1 lb of cure

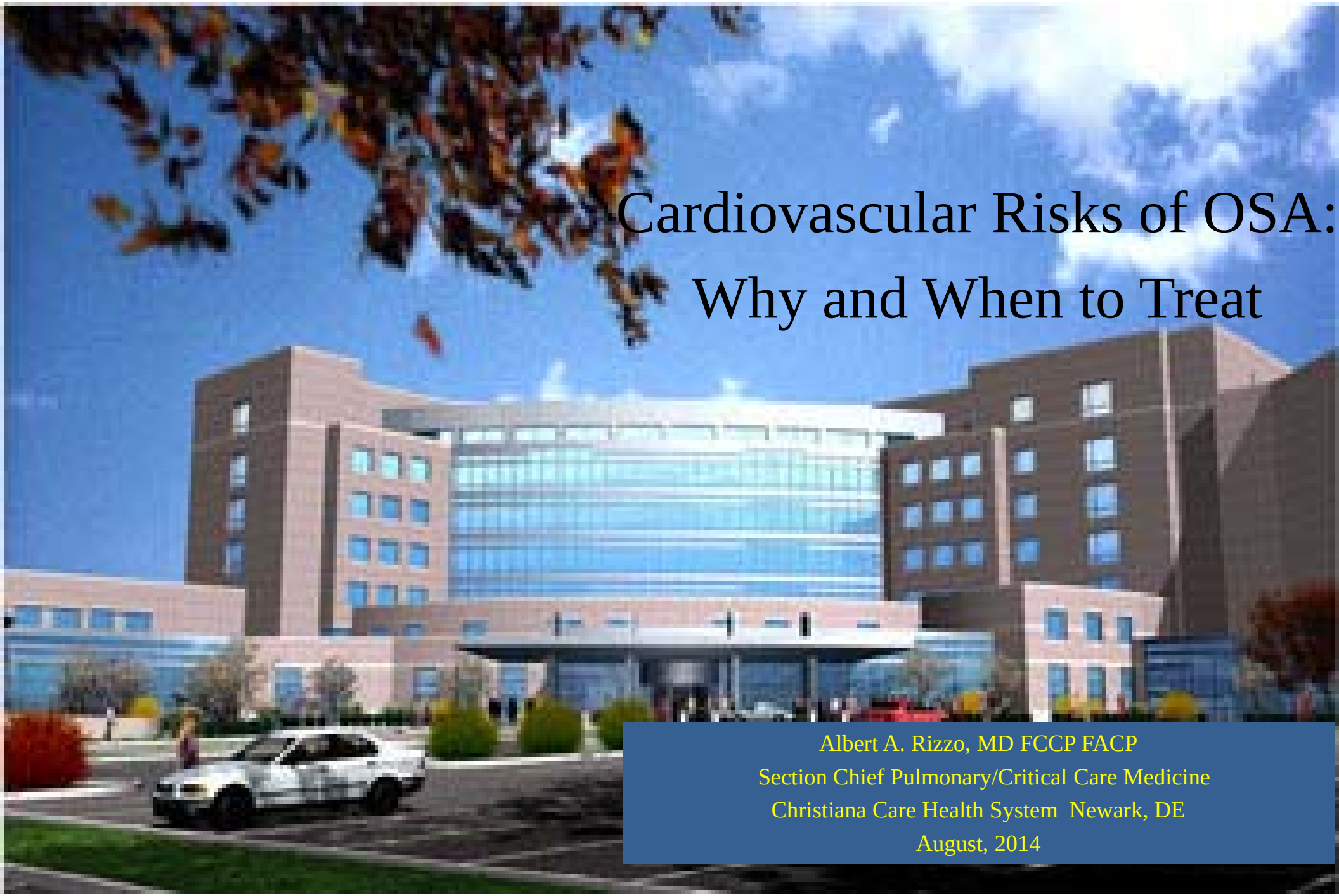
Management of PCOS



It’s a team approach !

References

- Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society Wild, R.A. JCEM 95(5):2038-2049
- Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline Legro , R. JCEM 98(12);4565-4592
- Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group Fauser,B.C.; Tarlatzis,B.C.; Rebar,R.W.; Legro,R.S.; Balen,A.H.; Lobo,R.; Carmina,E.; Chang,J.; Yildiz,B.O.; Laven,J.S.; Boivin,J.; Petraglia,F.; Wijeyeratne,C.N.; Norman,R.J.; Dunaif,A.; Franks,S.; Wild,R.A.; Dumesic,D.; Barnhart,K. Fertil Steril 97(1) 28-38



Cardiovascular Risks of OSA: Why and When to Treat

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Section Chief Pulmonary/Critical Care Medicine
Christiana Care Health System Newark, DE
August, 2014

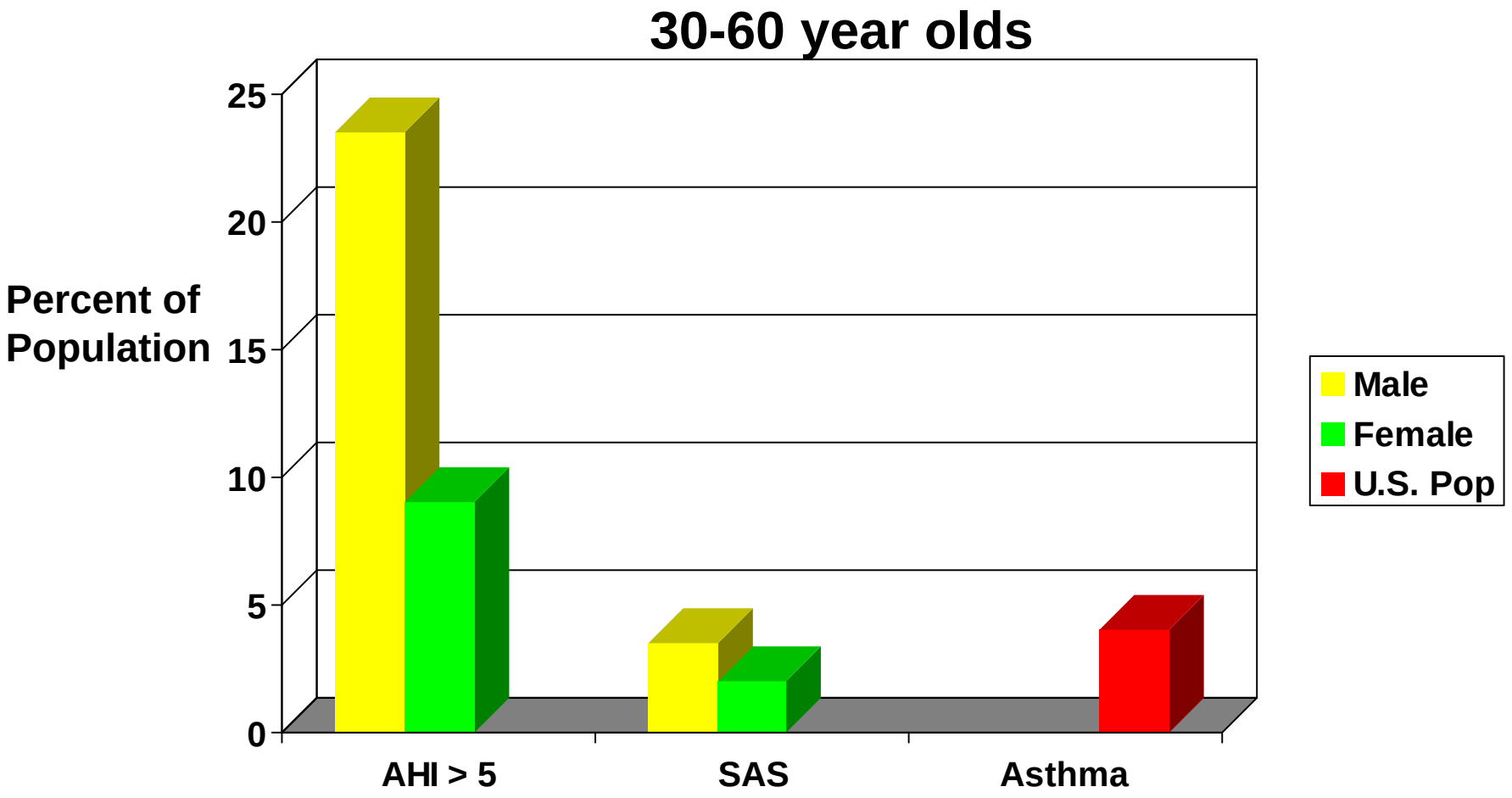
Sleep Apnea



Obstructive Sleep Apnea Presentation Outline

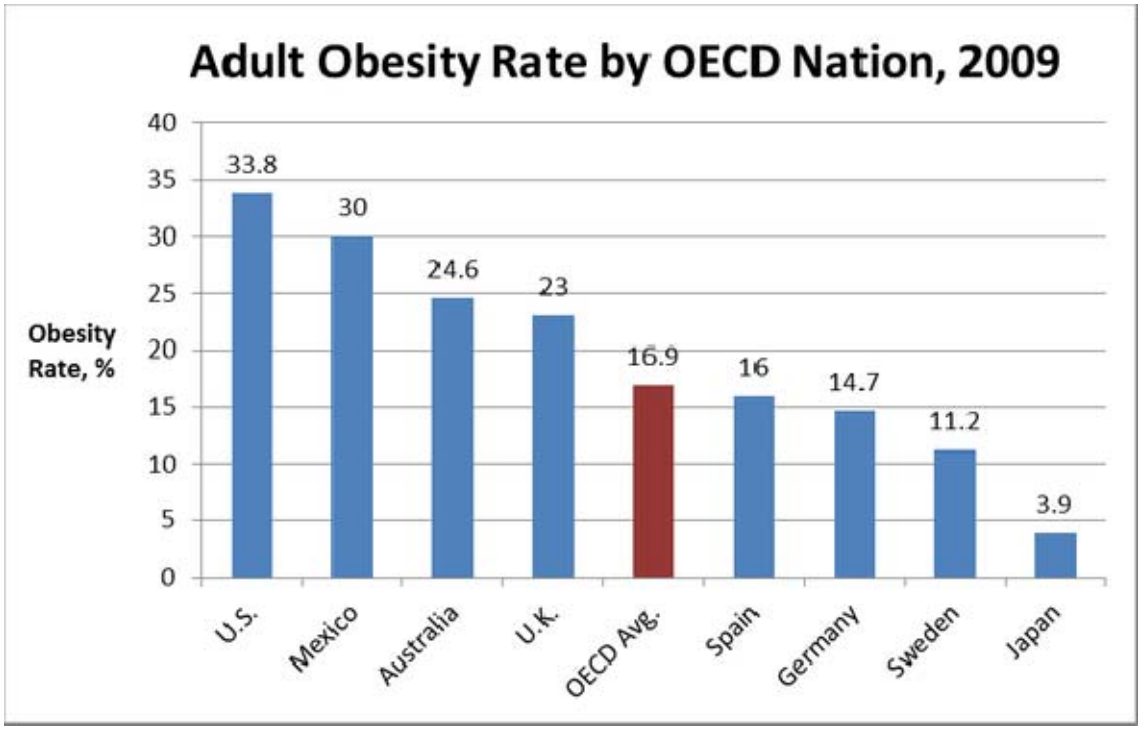
- Epidemiology and Definition
- Pathophysiology
- The relationship to cardiovascular disease
- Diagnosis
- Treatment Modalities

Prevalence of Sleep Apnea

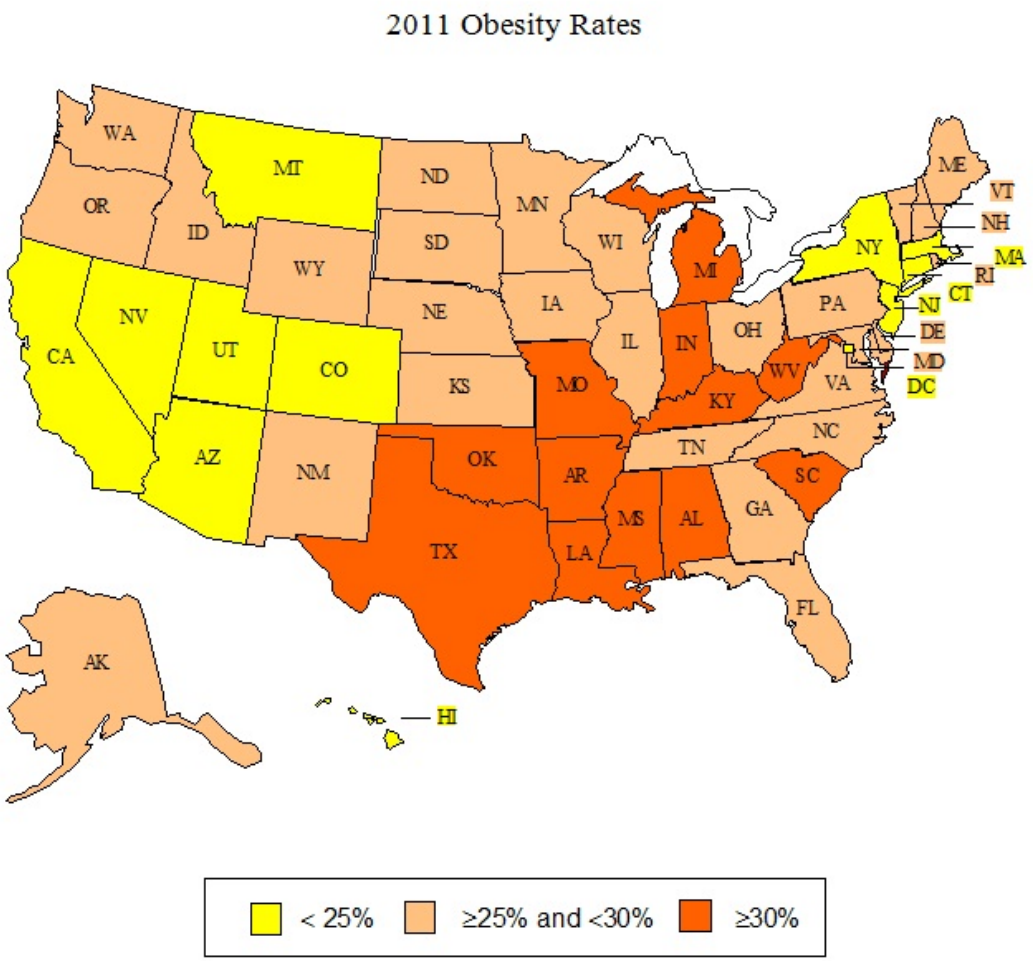


Adapted from Young T et al. N Engl J Med 1993;328.

The Obesity Epidemic



The Obesity Epidemic



The issue

- Obstructive sleep apnea is characterized by recurrent collapse of the upper airway during sleep resulting in intermittent hypoxia and frequent arousals.
- OSA is associated with cardiovascular morbidity and mortality

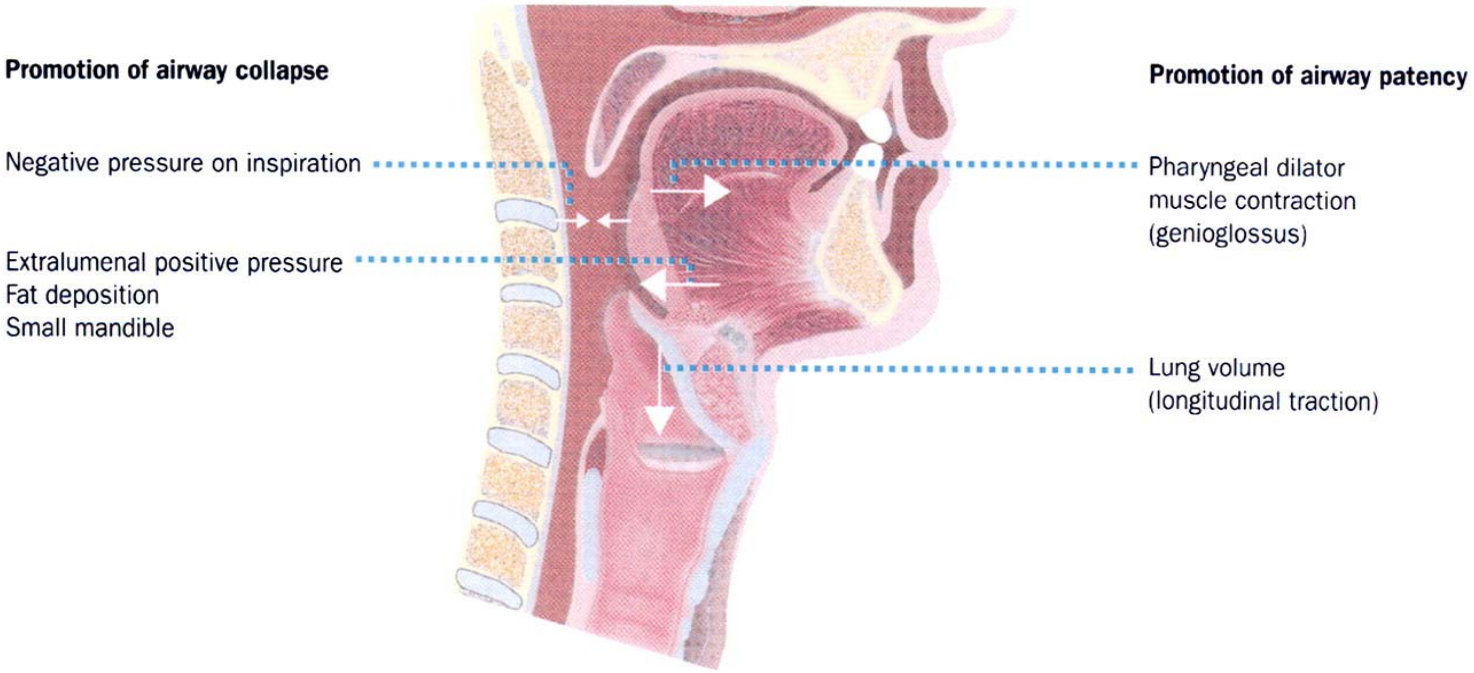


Figure 1. A sagittal section of a normal pharyngeal airway with the major variables contributing to airway patency/collapse shown. Reprinted by permission from Reference 2.

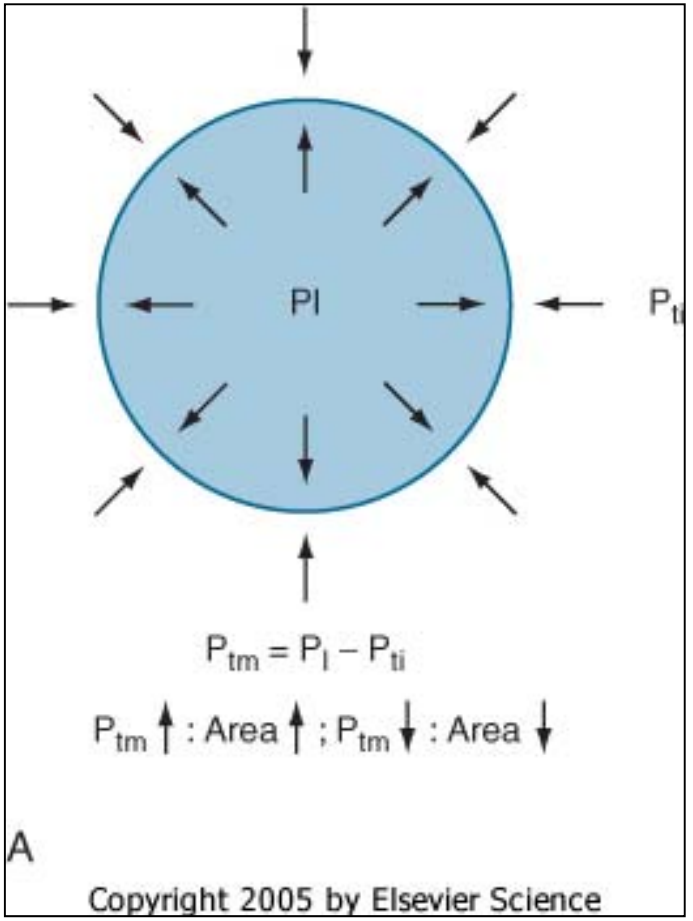
Am J Respir Crit Care Med,
http://www.atsjournals.org/doi/abs/10.1164/rccm.200412-1631SO

Published in: David P. White; *Am J Respir Crit Care Med* **2005,** 172, 1363-1370.
DOI: 10.1164/rccm.200412-1631SO
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Upper Airway Patency

- Ptm = Pl – Pti
  - Increased Ptm = increased area of airway
  - Decreased Ptm = decreased area of airway
- Patency is determined by a balance between the action of the upper airway dilator muscles and negative intraluminal pressure.



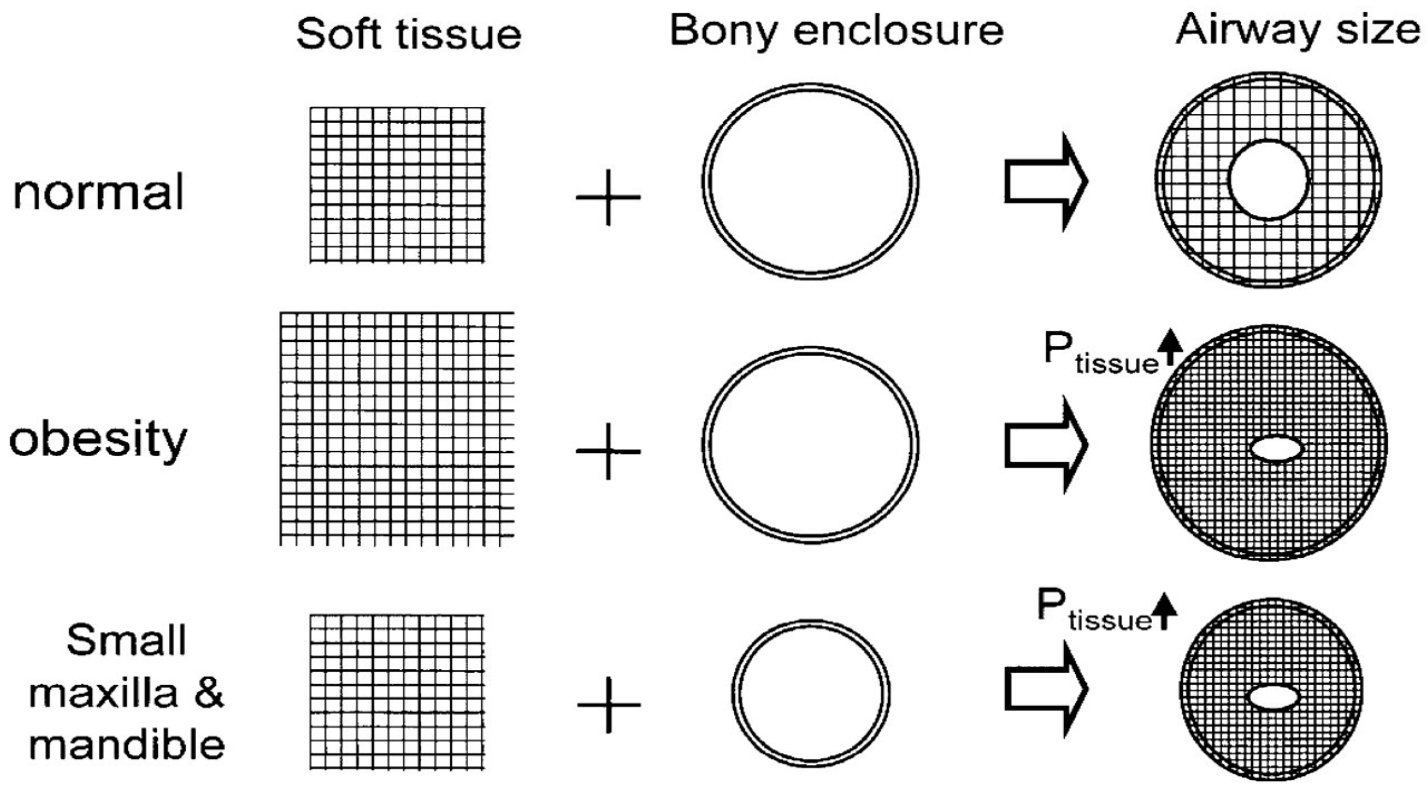


Figure 2. A schematic representation of the interaction between soft tissue and the upper airway bony enclosure and their combined affect on airway size. Reprinted by permission from Reference 14.

Am J Respir Crit Care Med,
http://www.atsjournals.org/doi/abs/10.1164/rccm.200412-1631SO

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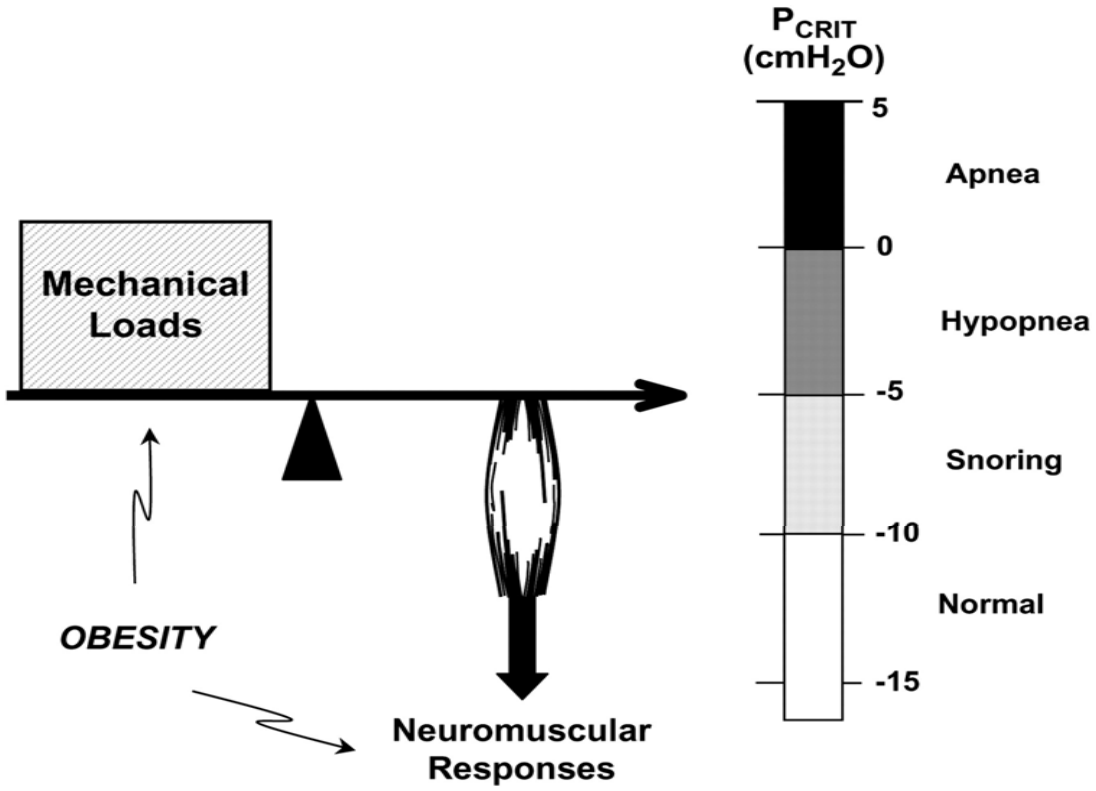
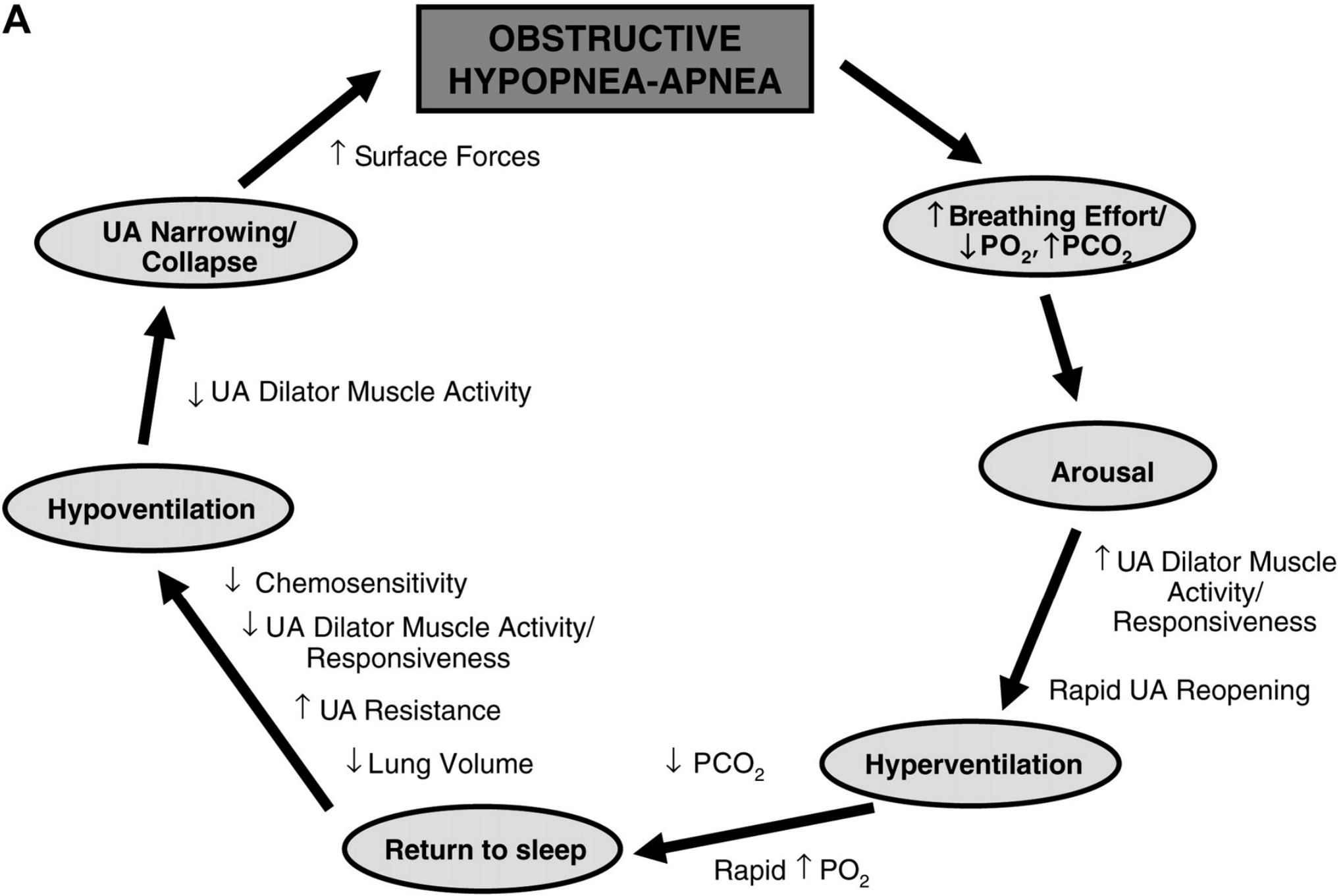


Figure 1. Obesity and the modulation of upper airway collapsibility and sleep apnea susceptibility. Upper airway collapsibility during sleep is represented by the critical pressure (Pcrit), which spans a range from health (negative) to disease (positive). Pcrit is determined by the mechanical loads imposed by boney structures and soft tissues on the pharynx, and are offset by neuromuscular responses to airway obstruction. Obesity can influence passive mechanical loads and neuromuscular control, thereby modulating upper airway collapsibility and sleep apnea susceptibility. *See* text for details.

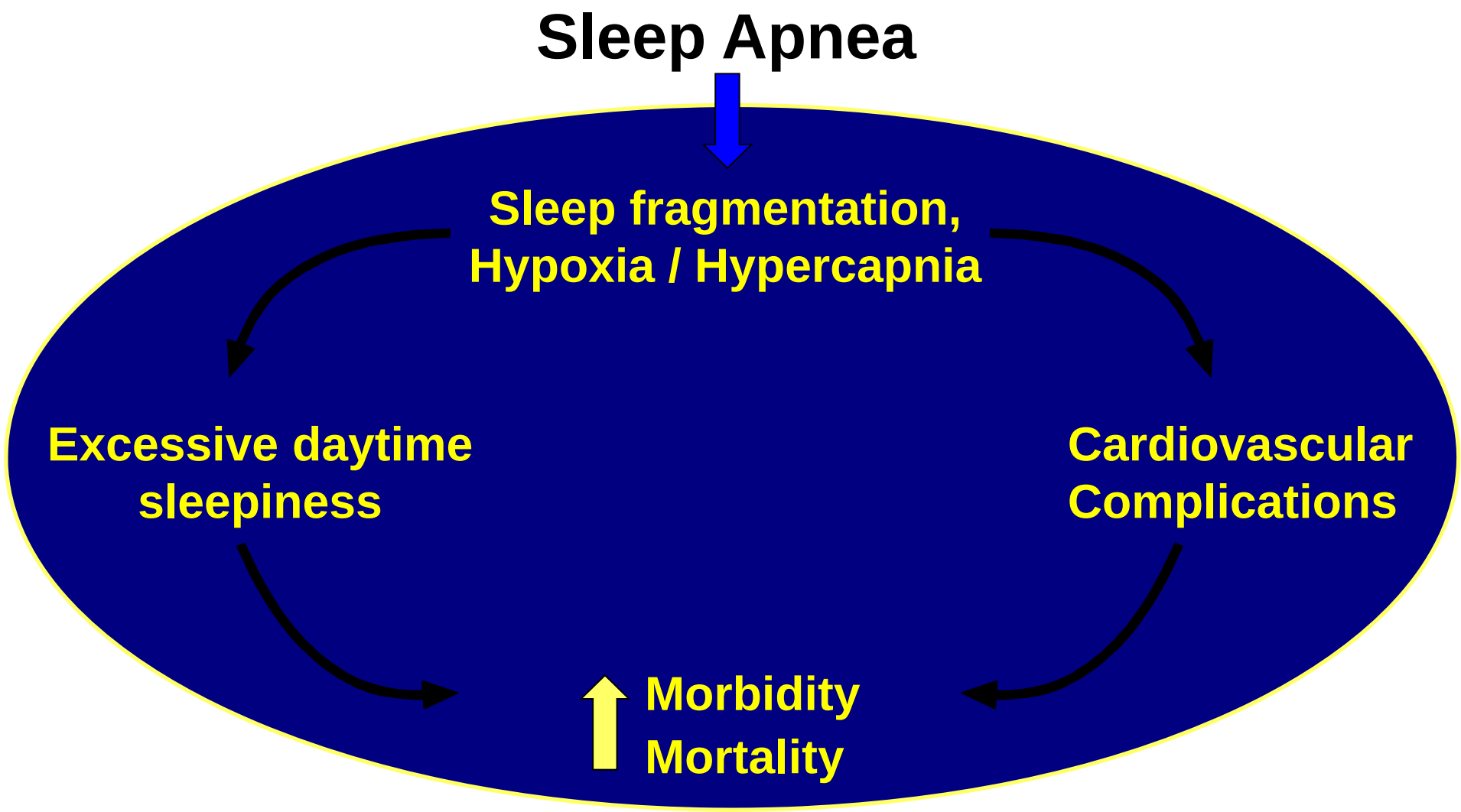
Proc Am Thorac Soc,
http://www.atsjournals.org/doi/abs/10.1513/pats.200708-137MG

Published in: Alan R. Schwartz; Susheel P. Patil; Alison M. Laffan; Vsevolod Polotsky; Hartmut Schneider; Philip L. Smith; *Proc Am Thorac Soc* **2008,** 5, 185-192.
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A
OBSTRUCTIVE HYPOPNEA-APNEA
↑ Surface Forces
UA Narrowing/ Collapse
↑ Breathing Effort/ ↓PO2, ↑PCO2
↓ UA Dilator Muscle Activity
Arousal
Hypoventilation
↑ UA Dilator Muscle Activity/ Responsiveness
↓ Chemosensitivity
↓ UA Dilator Muscle Activity/ Responsiveness
Rapid UA Reopening
↑ UA Resistance
↓ Lung Volume
↓ PCO2
Hyperventilation
Return to sleep
Rapid ↑ PO2

Clinical Consequences



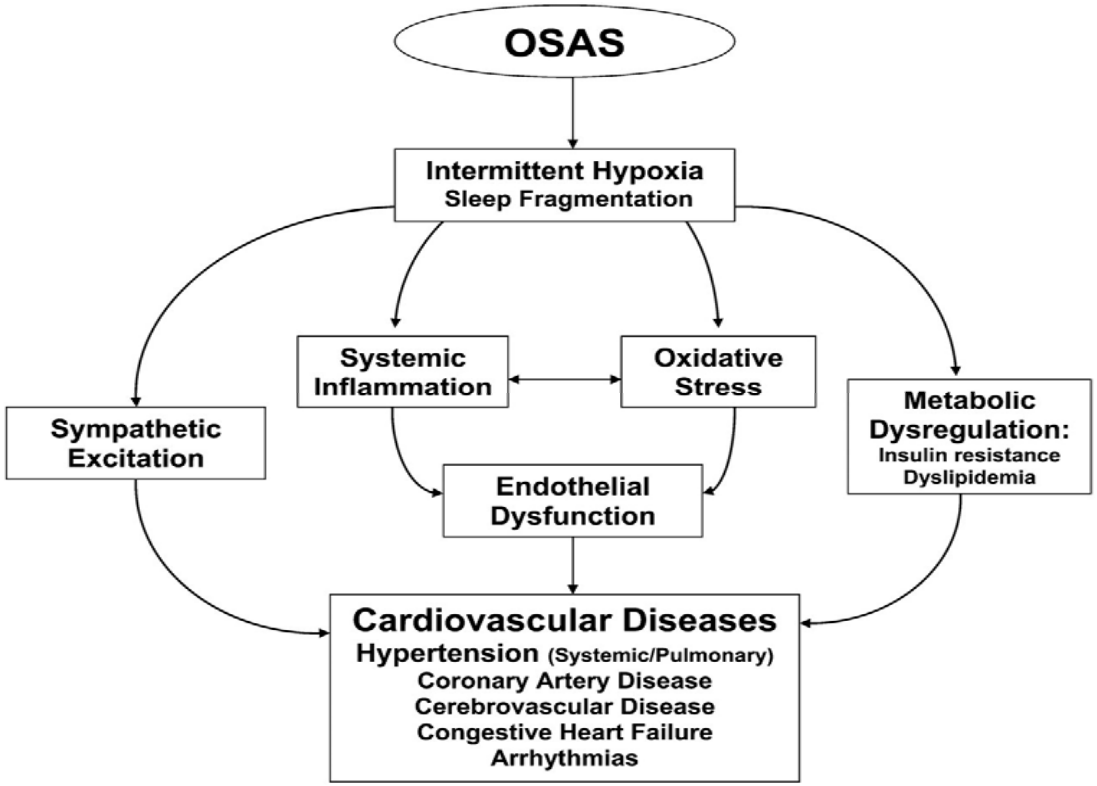


Figure 2. Mechanisms associated with intermittent hypoxia/sleep fragmentation in obstructive sleep apnea contributing to cardiovascular diseases. The intermittent hypoxia and sleep fragmentation associated with obstructive sleep apnea syndrome (OSAS) result in a variety of responses, including increased sympathetic nervous system activity, systemic inflammation, oxidative stress, and metabolic dysregulation, the latter involving insulin resistance and disordered lipid metabolism. Inflammation and oxidative stress produce endothelial dysfunction, and the various mechanisms combine to promote the development of atherosclerosis and cardiovascular disease.

Am J Respir Crit Care Med,
http://www.atsjournals.org/doi/abs/10.1164/rccm.200903-0347PP

Published in: Walter T. McNicholas; *Am J Respir Crit Care Med* **2009,** 180, 692-700.
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The Associations with OSA

- Hypertension
- CAD
- Stroke
- Heart Failure
- Atrial fibrillation
- Metabolic Syndrome

Mechanisms for OSA to interact with Cardiovascular Diseases and the Metabolic Syndrome

- Increased pro-inflammatory cytokines and C-reactive protein
- Higher leptin and chemerin levels in OSA
- Lower levels of adiponectin in OSA
- Effects on Fatty Acid Binding proteins
- Effects on VEGF and sCD40 may promote atherosclerosis
- Atherosclerosis, arterial stiffness, correlations with pulse wave velocity
- Reactive oxygen species, increased levels of adhesion molecules and coagulation factors

Mechanisms of Cardiovascular Complications

- Increased sympathetic activity
- Oxidative stress
- Systemic inflammation
- Insulin resistance
- Endothelial dysfunction
- Dysregulation of lipid metabolism and dyslipidemias and potential mediator of accelerated atherogenesis

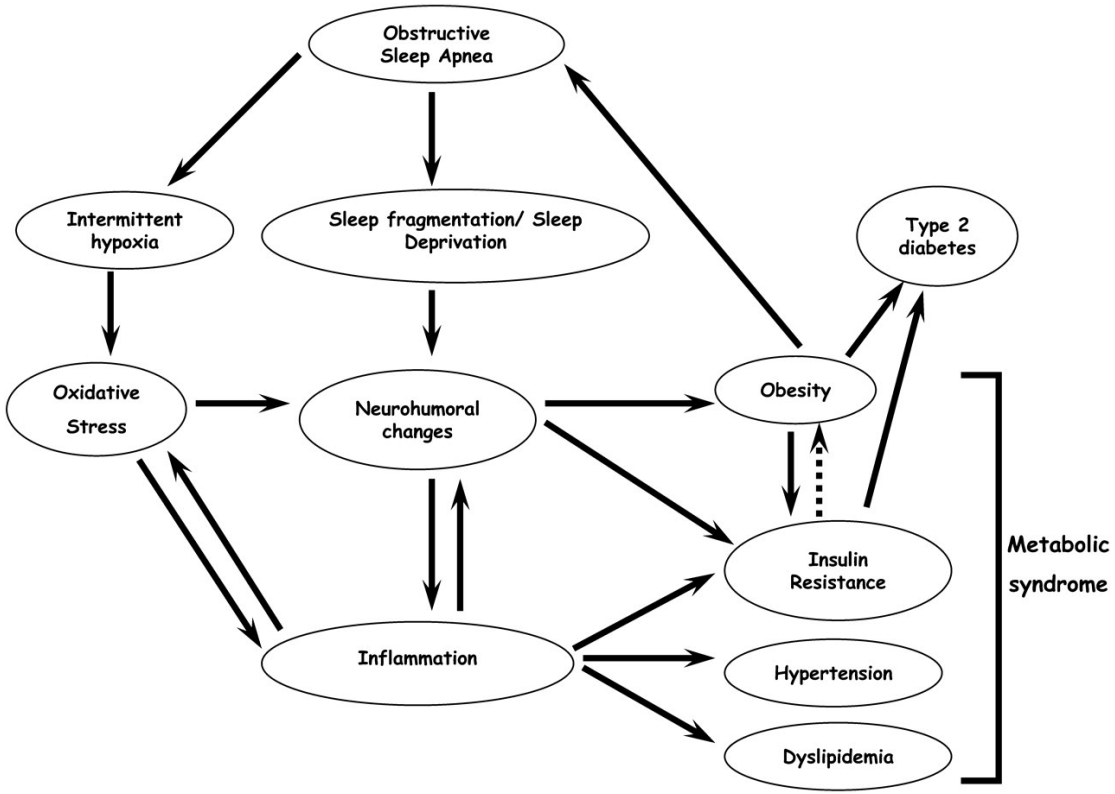


Figure 1. Possible mechanistic links between obstructive sleep apnea, metabolic syndrome, and type 2 diabetes.

Proc Am Thorac Soc,
http://www.atsjournals.org/doi/abs/10.1513/pats.200708-139MG

Published in: Esra Tasali; Mary S. M. Ip; *Proc Am Thorac Soc* **2008,** 5, 207-217.
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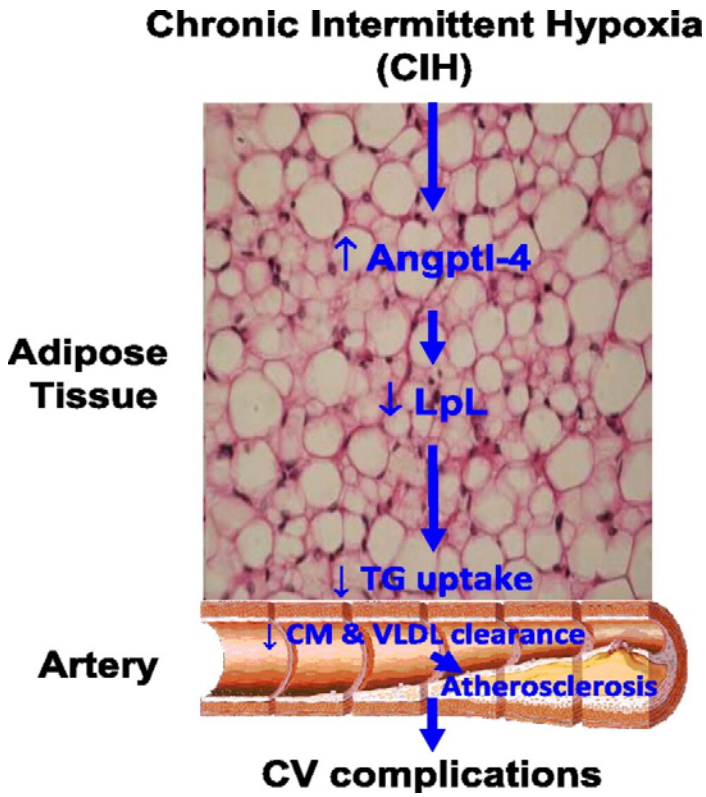


Figure 1. Effects of chronic intermittent hypoxia (CIH) on lipoprotein clearance. CIH inhibits triglyceride-rich lipoprotein clearance (chylomicrons [CM] and very-low-density lipoprotein [VLDL]) by activating angiopoietin-like protein-4 (Angptl-4), a potent inhibitor of lipoprotein lipase (LpL) in the adipose tissue. The decrease in the LpL activity, an enzyme that is anchored at the capillary endothelium, promotes a significant decrease in the hydrolysis of triglycerides into free fatty acids from CM and VLDL particles. The consequence of the LpL inhibition is the prolonged circulation of CM and VLDL in the bloodstream that may favor the progression of atherosclerosis.

Am J Respir Crit Care Med,
http://www.atsjournals.org/doi/abs/10.1164/rccm.201105-0837ED

Published in: Luciano Drager; Vsevolod Polotsky; *Am J Respir Crit Care Med* **2011,** 184, 288-290.
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Diagnosis: History

- Snoring
- Nocturnal gasping and choking
  - Ask bed partner (witnessed apneas)
- Automobile or work related accidents
- Personality changes or cognitive problems
- Mood disturbances
- Fatigue/non-refreshing sleep
- Excessive daytime sleepiness (Epworth, Berlin, Stanford)

Sleep Apnea: Is Your Patient at Risk? NIH Publication, No 95-3803.

STOP BANG

- Snoring
- Tired
- Observed apnea
- High Blood Pressure
- BMI over 35
- Age over 50
- Neck circumference > 17 in m, 16 in f
- Gender male
- Score 3 or more yes's = high risk

Sleep Apnea Risk Factors

- Obesity
- Increasing age
- Male gender
- Anatomic abnormalities of upper airway
- Family history
- Alcohol or sedative use
- Smoking
- Associated conditions

Associated Conditions at High-Risk for OSA

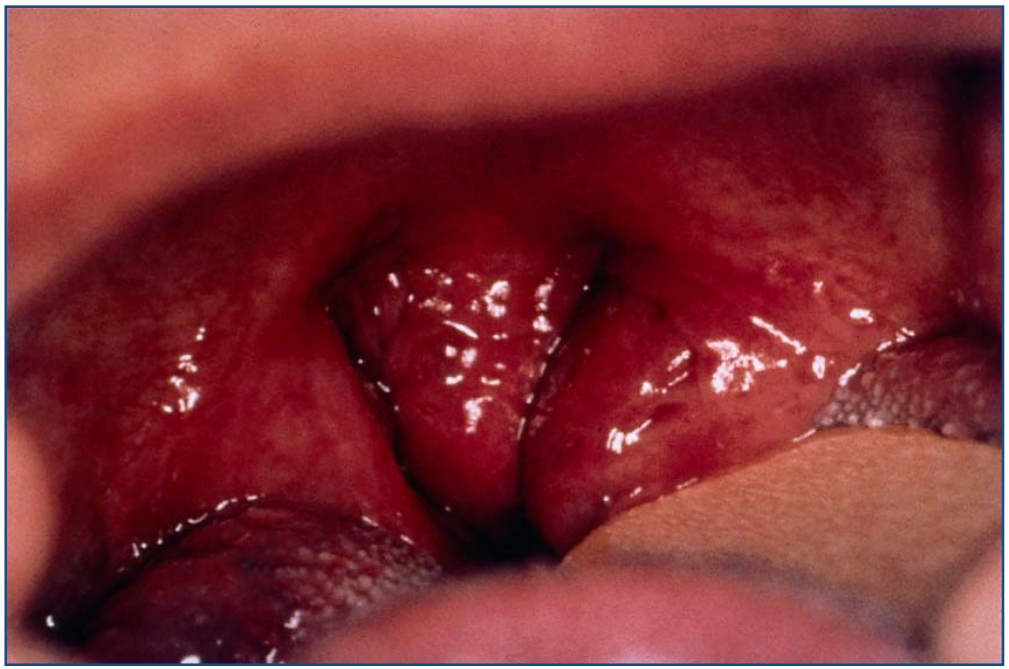
- Obesity
- CHF
- Atrial fibrillation
- Refractory hypertension
- Type 2 Diabetes
- CVA
- Nocturnal dysrhythmias
- Pulmonary hypertension
- High risk driving populations (commercial truckers)
- Pre-op Bariatric Surgery

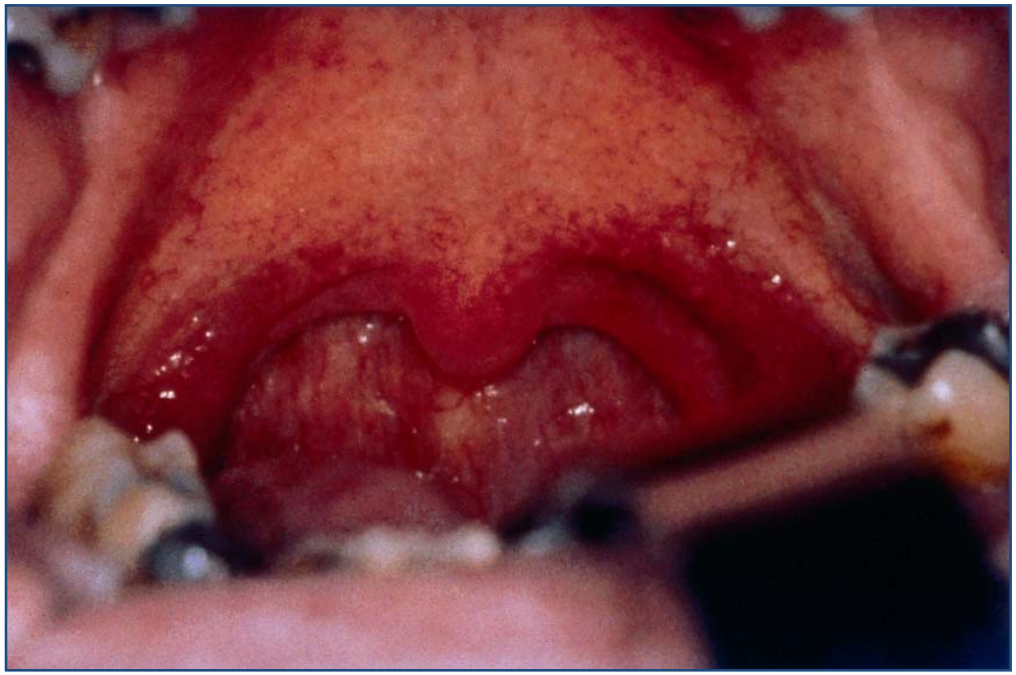
Diagnosis: Physical Examination

- BMI > 32
- Upper body obesity / thick neck

  $\geq$ 17” males, $\geq$ 16” females
- Macroglossia
- Mallampati Score
- Obvious airway abnormality

Exam: Tonsillar Hypertrophy





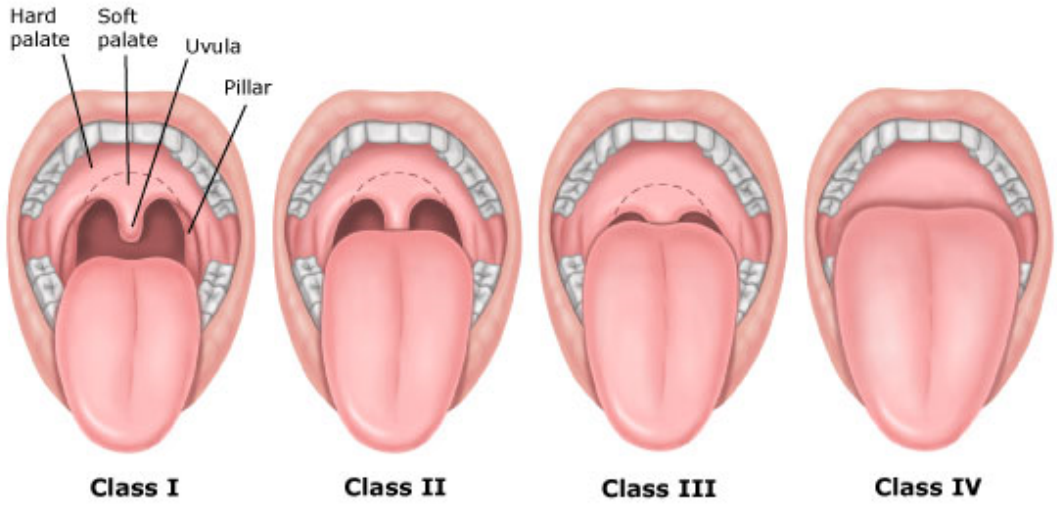
Shepard JW Jr et al. Mayo Clin Proc 1990;65.

Physical Examination



Guilleminault C et al. Sleep Apnea Syndromes. New York: Alan R. Liss, 1978.

Mallampati Classification



Consequences: Cognitive and Neurobehavioral Deficits

- Cognition
- Memory
- Sustained attention/vigilance
- Divided attention
- Executive functioning

Consequences:
Excessive Daytime Sleepiness

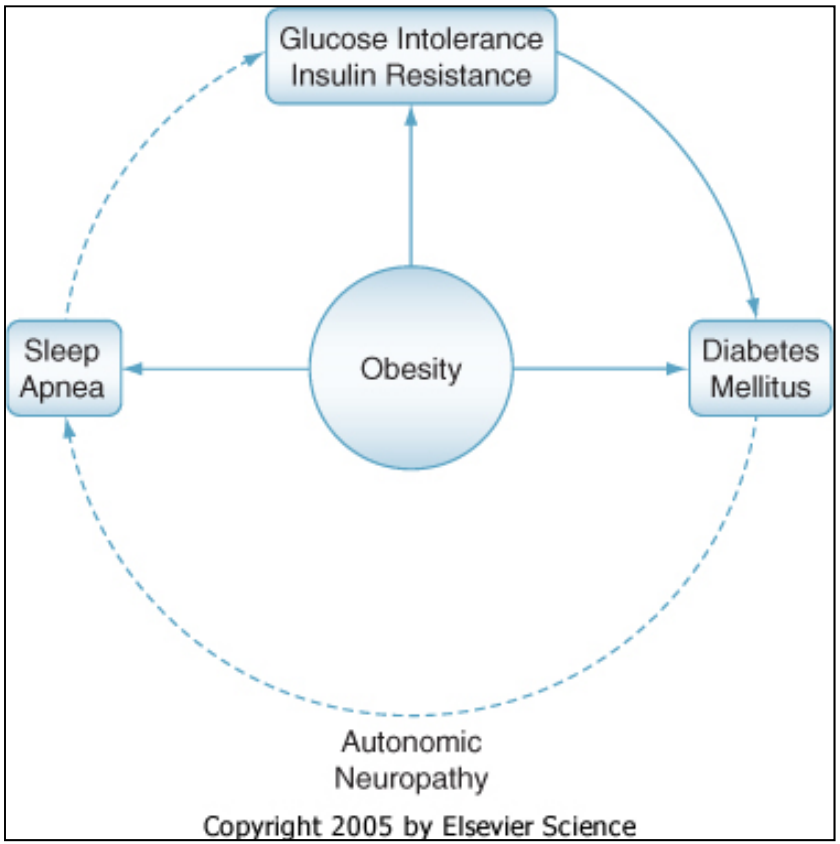
- Increased motor vehicle crashes
- Increased work-related accidents
- Poor job performance
- Depression
- Family discord
- Decreased quality of life

Consequences: Cardiovascular

- Systemic hypertension
- Cardiac arrhythmias
- Myocardial ischemia
- Cerebrovascular disease
- Pulmonary hypertension / cor pulmonale

Consequences: Metabolic

- Glucose intolerance
- Insulin resistance
- Type II diabetes mellitus



What Test Should be Used?

- In-laboratory, attended full night polysomnography
  - Split night studies
- Home diagnostic systems
  - Sleep, Cardiovascular, Oximetry, Position, Effort, Respiratory
  - High pre-test probability



Figure 1. A 30-s episode of obstructive apnea occurring during REM sleep is demonstrated. Note the increasing ventilatory effort across the episode indicating its obstructive nature. Also note the sequelae of the episode: arousal from sleep and intermittent hypoxia.

Proc Am Thorac Soc,
http://www.atsjournals.org/doi/abs/10.1513/pats.200510-116JH

Published in: David P. White; *Proc Am Thorac Soc* **2006,** 3, 124-128.
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Measures of Sleep Apnea Frequency

- Apnea = cessation of airflow for at least 10 secs
- Hypopnea = abnormal resp event lasting at least 10 secs associated with a 30% reduction in thoracoabdominal movement or airflow compared to baseline and at least 4% decrease in O2 saturation
  - Apnea Index = # apneas per hour of sleep
  - Apnea / Hypopnea Index (AHI)= # apneas + hypopneas per hour of sleep
  - AHI < 5, normal, 5-15 mild, 15-30 moderate, > 30 severe
- Respiratory disturbance index (RDI) = AHI for Medicare;
  - For others, RDI = # apneas + hypopneas + RERA's per hour of sleep

CMS coverage for CPAP

- AHI > 15 events/hr with a minimum of 30
- AHI > 5 and < 14 events/hr with any of the following
  - Hypertension
  - History of Stroke
  - Ischemic Heart Disease
  - Excessive Daytime Sleepiness
  - Impaired cognition
  - Insomnia
  - Mood disorders

Treatment Goals

- Reduce mortality and morbidity
- Improve quality of life
- The challenge is that not all patients appreciate both goals when confronted with options for treatment vs non-treatment

Therapeutic Approach

- Risk counseling
  - Motor vehicle crashes
  - Job-related hazards
  - Judgment impairment
  - Cardiovascular risks in increased MI, CVA, death
- Treatment Modalities
  - Behavioral
  - PAP
  - Oral Appliances
  - Surgical
  - Adjuncts

Behavioral Interventions

- Encourage patients to:
  - –Lose weight (15% : 30% ???)
  - –Avoid alcohol and sedatives
  - –Avoid sleep deprivation
  - –Avoid supine sleep position
  - –Stop smoking

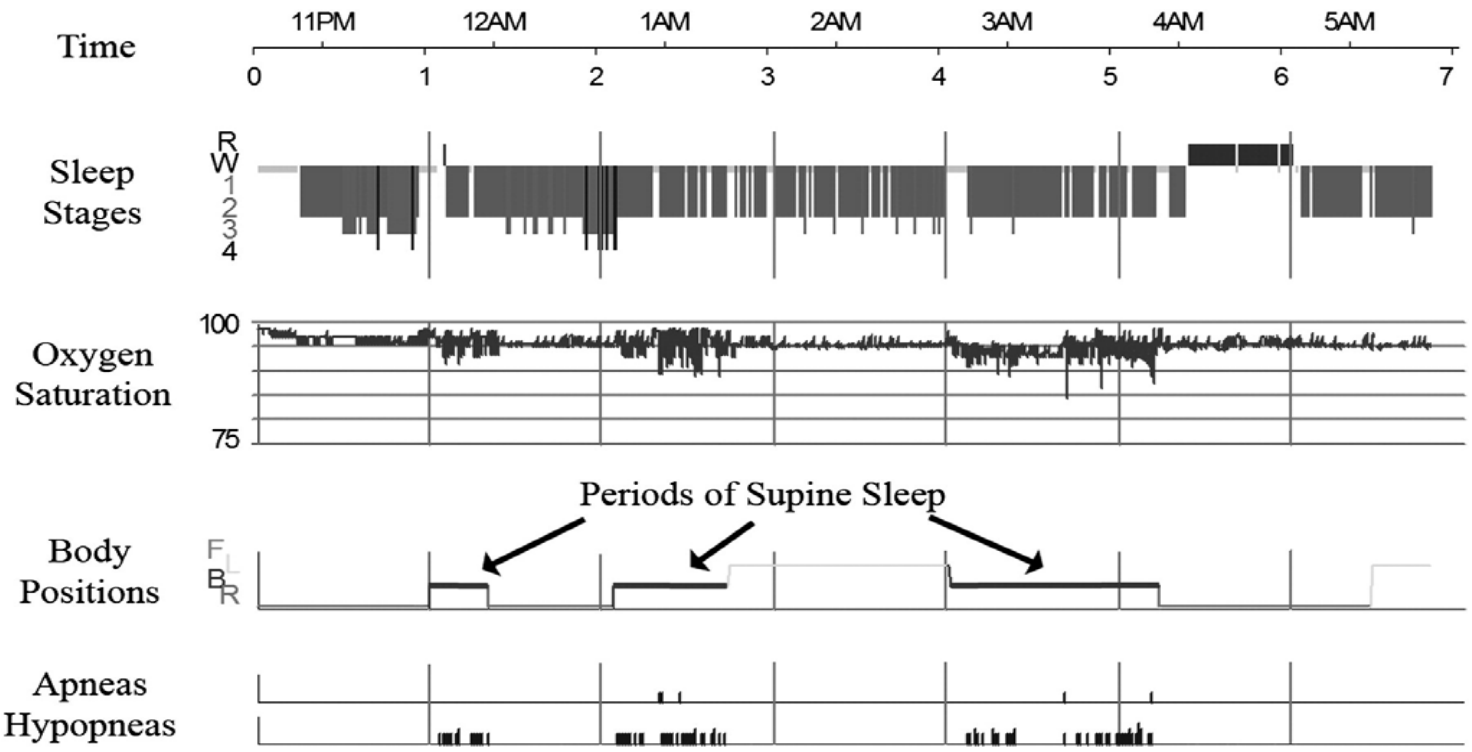


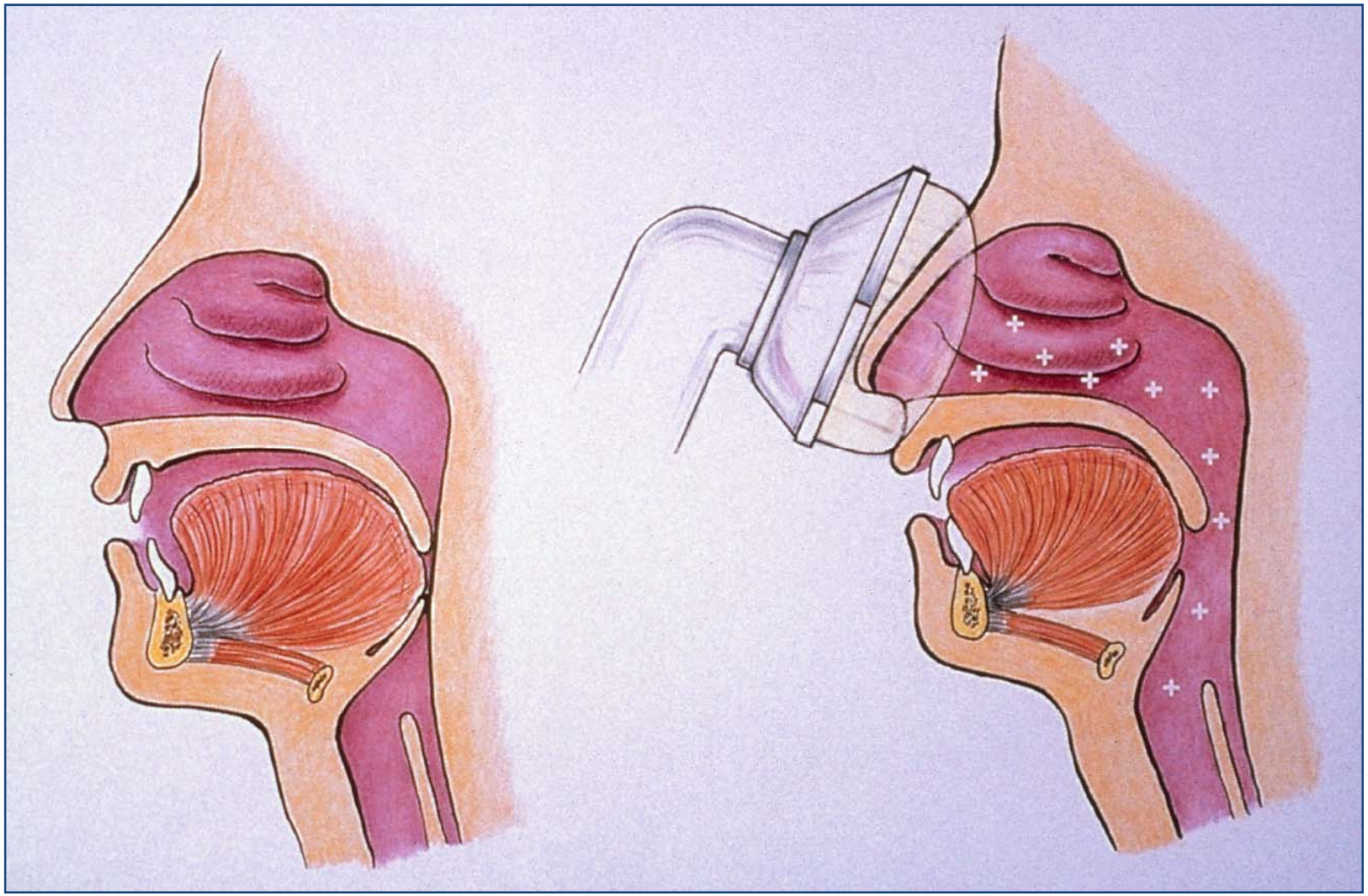
Figure 2. Positional obstructive sleep apnea. Polysomnogram showing obstructive apneas and hypopneas occurring only during periods of supine sleep. Abbreviations for sleep stages: R = REM sleep; W = awake; 1 = stage 1 non-REM sleep; 2 = stage 2 non-REM sleep; 3 = stage 3 non-REM sleep; 4 = stage 4 non-REM sleep. Abbreviations for body position: F = front; B = back; L = left; R = right.

Proc Am Thorac Soc,
http://www.atsjournals.org/doi/abs/10.1513/pats.200707-104MG

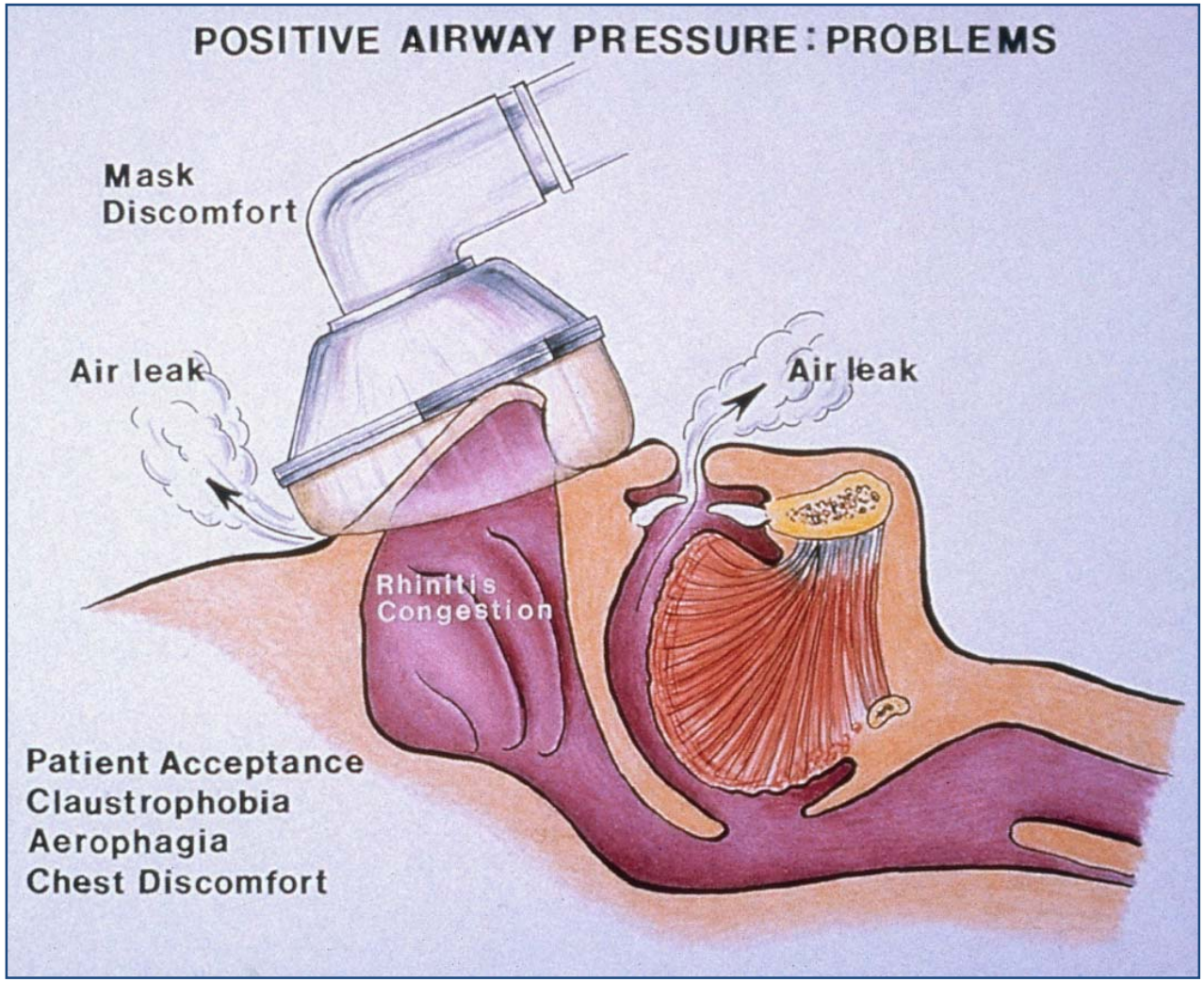
Published in: Andrew S. L. Chan; Richard W. W. Lee; Peter A. Cistulli; *Proc Am Thorac Soc* **2008,** 5, 179-184.
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Positive Airway Pressure



Positive Airway Pressure: Problems



Adverse Effects of PAP

- Nasal
  - Rhinorrhea, nasal congestion, oronasal dryness, epistaxis
- Mask
  - Skin abrasion/rash, conjunctivitis from air leak
- Noise
- Flow related: chest discomfort; aerophagia; sinus discomfort; claustrophobia; difficulty exhaling; barotrauma
- Partner intolerance/inconvenience

CPAP Compliance

- Patient report: 75%
- Objectively measured use

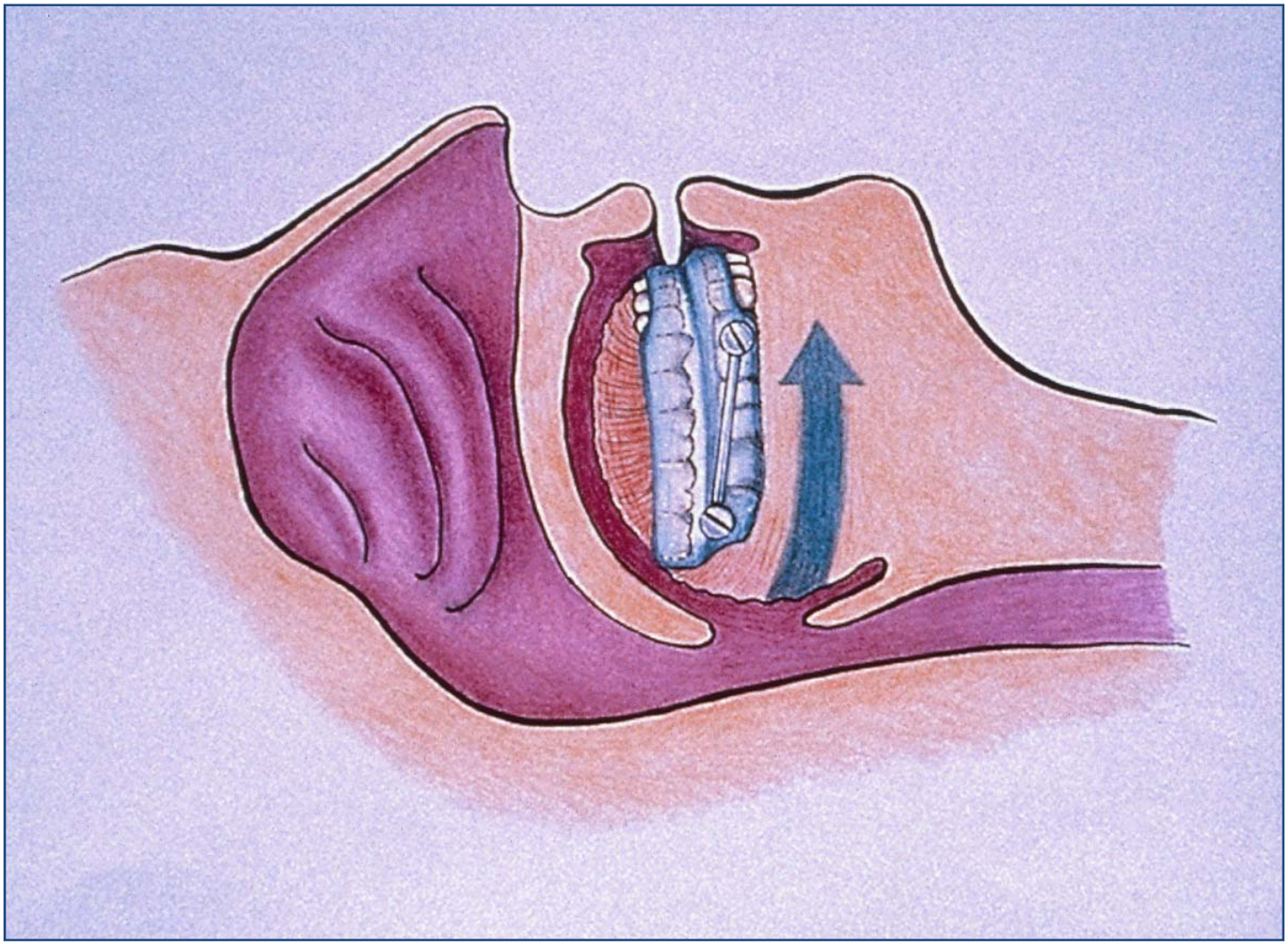
  $\geq$ 4 hrs for $\geq$ 5 nights / week: 46%

- Asthma medicine compliance: 30%
- Medicare compliance = > 4 hrs, > 70% of the nights during a 30 day consecutive period

Strategies to Improve Compliance

- EDUCATION (pre, post, throughout)
- Machine-patient interfaces
  - Masks
  - Nasal pillows
  - Chin straps
- Humidifiers
- Ramp
- Desensitization
- Bi-level pressure

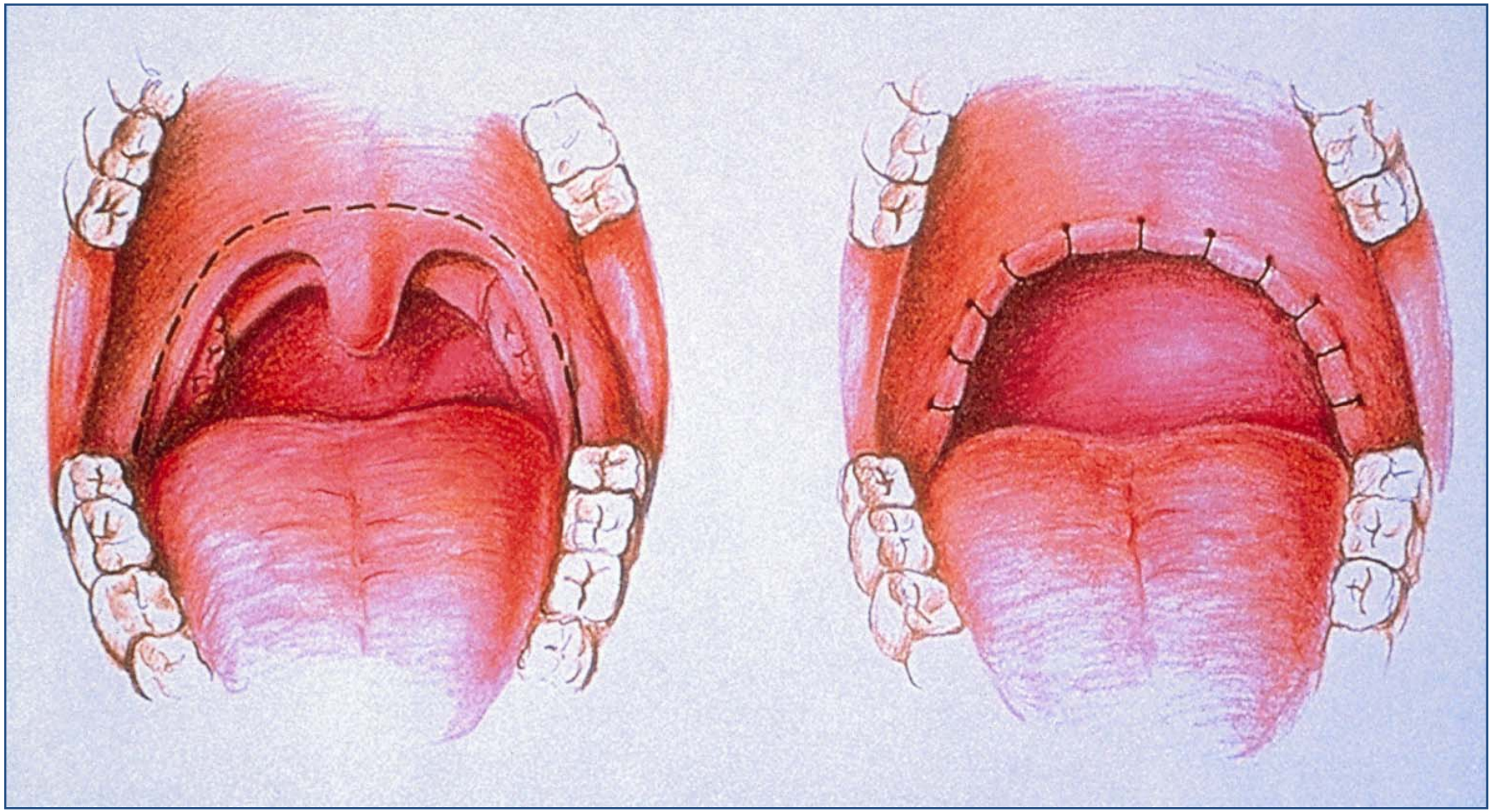
Oral Appliance: Mechanics



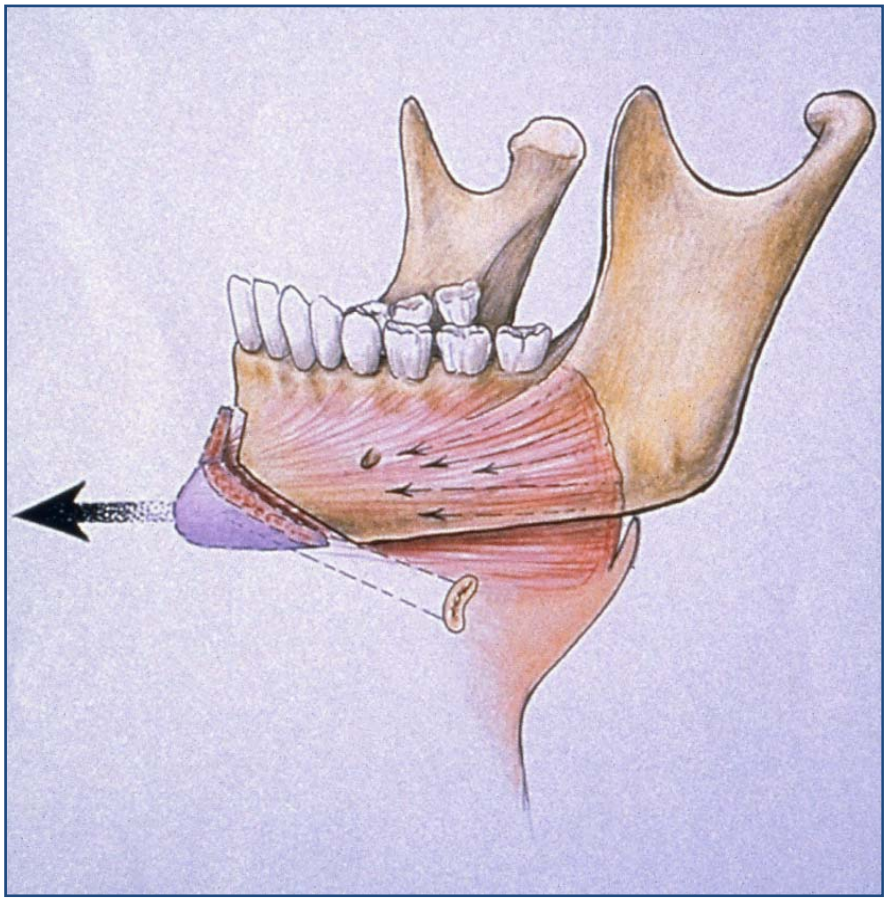
Oral Appliances

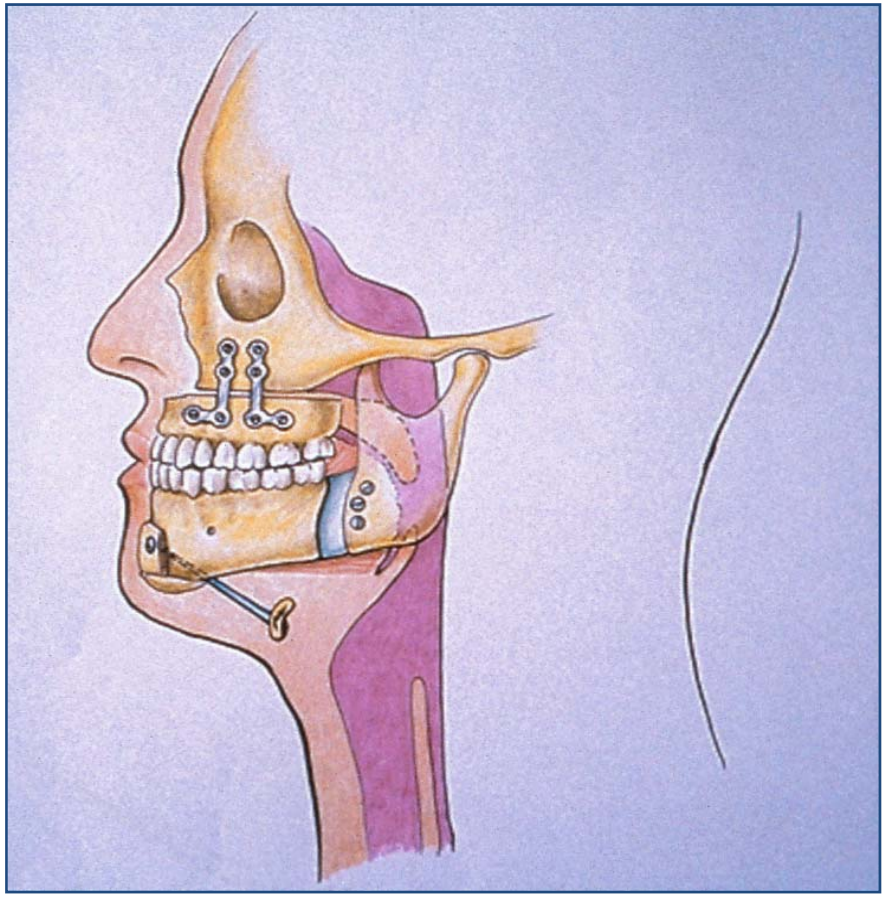
- Efficacy
  - Variable; may cure mild disease and can reduce AHI by 30-50% in more severe disease
- Side effects
  - TMJ discomfort, dental misalignment, and salivation

Uvulopalatopharyngoplasty (UPPP)



Staged Surgical Procedures





Treatment Adjuncts

- Supplemental O2
  - Not a primary therapy; reduces hypoxia during apneas
  - May prolong apneas
  - May reduce arrhythmias
- Pharmacologic
  - Modafinil/Armodafinil
  - Nasal steroids/antihistamines
- Nasal Valves
- Hypoglossal nerve stimulation

Chronic Care Management

- Risk counseling
- Behavior modification
- Monitor symptoms and compliance
  - Monitor weight and blood pressure
  - Ask about recurrence of symptoms
  - Evaluate CPAP use and side effects

Sleep Apnea: Is Your Patient at Risk? NIH Publication No.95-3803.

Obstructive Sleep Apnea Presentation Summary

- Epidemiology and Definition
  - 2-5% of the population; recurrent collapsibility of the upper airway during sleep leading to intermittent hypoxia and arousals
- Pathophysiology
  - The intermittent hypoxia, intra-thoracic pressure swings result in increased sympathetic activity and alteration in inflammatory processes and lipid metabolism.
- The relationship to cardiovascular disease and the metabolic syndrome
  - Association exists with increased cardiovascular events include MI's, CVA's, refractory hypertension and dysrhythmias.
- Diagnosis
  - Home sleep testing in those with high predictive positivity
  - In-lab study in the presence of co-morbidities.
- Treatment Modalities
  - CPAP as a first line approach coupled with behavioral modifications. Oral appliances are increasing in popularity. New advances include neuro-stimulation of oropharyngeal muscles. Surgery is less popular.

Why and When to Treat?
Take Home Message

- OSA is a **common, under-diagnosed despite being easily diagnosed and treatable** disease that leads to increased cardiovascular events when under-appreciated and untreated.
- The history and physical can identify **risk factors** for OSA. The presence and severity of OSA requires testing either in the home setting or in the sleep lab.
- **Treatment should be pursued in all** identified patients and includes CPAP as a first line choice and will require education of the patient and persistent efforts to improve compliance with **CPAP or seek alternative treatments**.

Questions?



Thank You

Adherence: *Patient Barriers, Provider Barriers, and Strategies for Improving Adherence*

Lynne T Braun, PhD, CNP, FAHA, FNLA, FAAN
Professor of Nursing, Nurse Practitioner
Rush University Medical Center

Rush is a not-for-profit health care, education and research enterprise comprising Rush University Medical Center, Rush University, Rush Oak Park Hospital and Rush Health.

Adherence

- WHO (2001):
  - The extent to which a person's behavior (taking medications, following a diet and/or executing lifestyle changes) corresponds with agreed recommendations from a healthcare provider

http://apps.who.int/medicinedocs/en/d/Js4883e/6.html

Why the concern over non-adherence?

- ½ of the 3.2 billion annual prescriptions in the U.S. are not taken as prescribed.
- Patients with chronic conditions adhere only to 50-60% of medications as prescribed.
- Approximately 125,000 deaths per year in the U.S. are due to medication non-adherence.
- 33-69% of medication-related hospital admissions are due to poor adherence.
- Total cost of non-adherence in the US is estimated at $100-300 billion each year.

Bosworth HB et al, *Am Heart J* 2011;162:412-424.

Factors That Place Patients at Risk of Nonadherence

- Cost of medication
- Concern over adverse effects
- Complexity of medication regimen
- Taking multiple medications
- “Silent” conditions
- Forgetfulness



- **Perceived lack of communication with provider**
- Suboptimal provider/patient relationship
- **Low level of health literacy** *(~ 90 million US adults)*
- **Transitional care**
- Depression/cognitive impairment

Table 3. Self-Reported Reasons for Primary Nonadherence (n = 73)

Did not pick up cholesterol medication due to/because...	% Yes (n)
General concerns about medication	63.0 (46)
Decided to try lifestyle modification	63.0 (46)
Fear of side effects	53.4 (39)
Did not think medication was needed	38.9 (28)
Did not believe condition was life threatening	34.7 (25)
Fear of drug interactions	16.4 (12)
Already took too many medications and did not want to take any more	16.4 (12)
Financial hardship	12.3 (9)
Did not understand why provider prescribed medication	11.0 (8)
Did not understand purpose of medication	8.2 (6)
Did not think medication would be effective for condition	6.9 (5)
Inconvenient dosing regimen	4.1 (3)
Change in health insurance/drug benefit	2.7 (2)

Harrison TN et al., *Am J Managed Care* 2013;19:e133-e139.

Provider-Related Factors That May Impact Adherence

- Failure to provide adequate explanations of benefits/adverse effects of medications
- Ineffective communication with the patient
- Prescribing complex drug regimens
- Neglecting to consider cost issues
- Neglecting to communicate among patient's various providers
- Lack of time, lack of time, lack of time!

What is health literacy?

"The degree to which individuals have the capacity to obtain, process and understand basic health information and services needed to make appropriate health decisions."

Source: Healthy People 2010

Health Literacy

- Questions evaluated by Chew LD et a., 2008:
  - *How confident are you filling out forms by yourself?*
  - *How often do you have someone help you read hospital materials?*
  - *How often do you have problems learning about your medical condition because of difficulty reading hospital materials?*
- By responding to these questions, 32.9% reported inadequate health literacy:
  - 16.9% reported needing help reading medical material
  - 17.1% reported having problems learning about their medical condition
  - 29.6% were not confident completing health forms alone

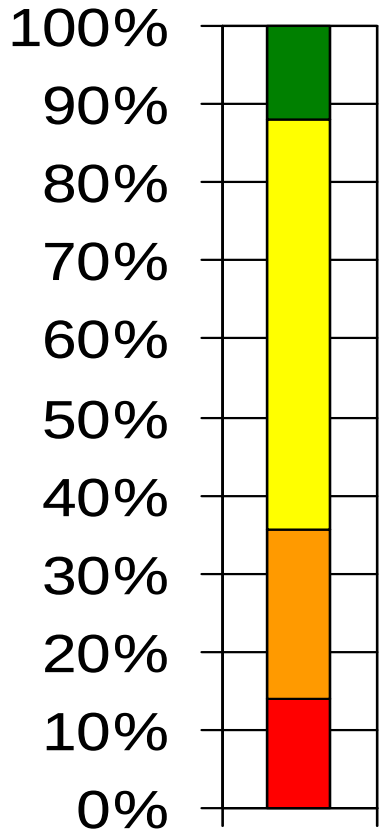
Harrison TN et al., *Am J Managed Care* 2013;19:e133-e139.

So what?

- Annual health care costs for those with low literacy skills are **4 X higher** than those with higher literacy skills
- Poor patient compliance and medical errors may be based on poor understanding of health care information.
- Pts with low health literacy and chronic diseases have **less knowledge** of their disease and treatment and fewer self-management skills than literate patients
- Pts with low literacy skills were observed to have a 50% increased risk of hospitalization, compared with pts who had adequate literacy skills.

NPSF
National Patient Safety Foundation®

Health Literacy in America: Results from the National Assessment of Adult Literacy (NAAL)



12% Proficient: Define medical term from complex document, Calculate share of employee's health insurance costs

53% Intermediate: Determine healthy weight from BMI chart, Interpret prescription and over-the-counter drug labels

22% Basic: Understand simple patient education handout

14% Below Basic: Circle date on appointment slip, Understand simple pamphlet about pre-test instructions

Recognize Red Flags:
"Need-to-knows" for support staff too!

- Seeking help only when illness is advanced
- Making excuses
- Becoming angry/demanding or quiet/passive
- Difficulty explaining concerns or no questions
- Frequently missed appointments, tests
- Non-adherence *(may not be able to read/understand a medication bottle)*
- "I forgot my glasses" or "I' ll bring this home so I can discuss it with my family."
- Intake forms incomplete
- Medication review - looking vs reading
- *Patients may feel shame which prevents them from seeking help*


DELETE COOKIES?!
gegen-den-strich.com
FERNANDEZ

Burden of Changes in Pill Appearance for Patients Receiving Generic CV Medications after MI

- Generic prescription drugs made by different manufacturers may vary in color or shape.
- Purpose: To determine whether persistent use of generic drugs among post MI patients is associated with inconsistent appearance of their meds.
- Design: Nested case-control study
  - Cases: discontinued their index drug for at least 1 mo.
  - Controls: continued treatment
- Controls and cases were matched on therapeutic class, number of dispensings before nonpersistence, age, and sex.



Simvastatin 20 mg



Kesselheim et al., *Ann Intern Med* 2014;161:96-103.

Burden of Changes in Pill Appearance for Patients Receiving Generic CV Medications after MI

- Results:
  - 29% of patients (3286 of 11,513) had a change in pill shape or color.
  - Statins had the most changes in appearance.
  - Odds of nonpersistence in case patients increased by 34% after a change in pill color and 66% after a change in pill shape.

RUSH

"The biggest barrier is realizing it is not just about reading and writing about health. It is a social issue. We must assume that everyone has some limited health literacy. An estimated 88% of adults– almost all of us- do not have the health literacy skills to proficiently interact with the healthcare system."

Andrew Pleasant, PhD,
Assistant Professor at Rutgers University
Director of Health Literacy and Communication

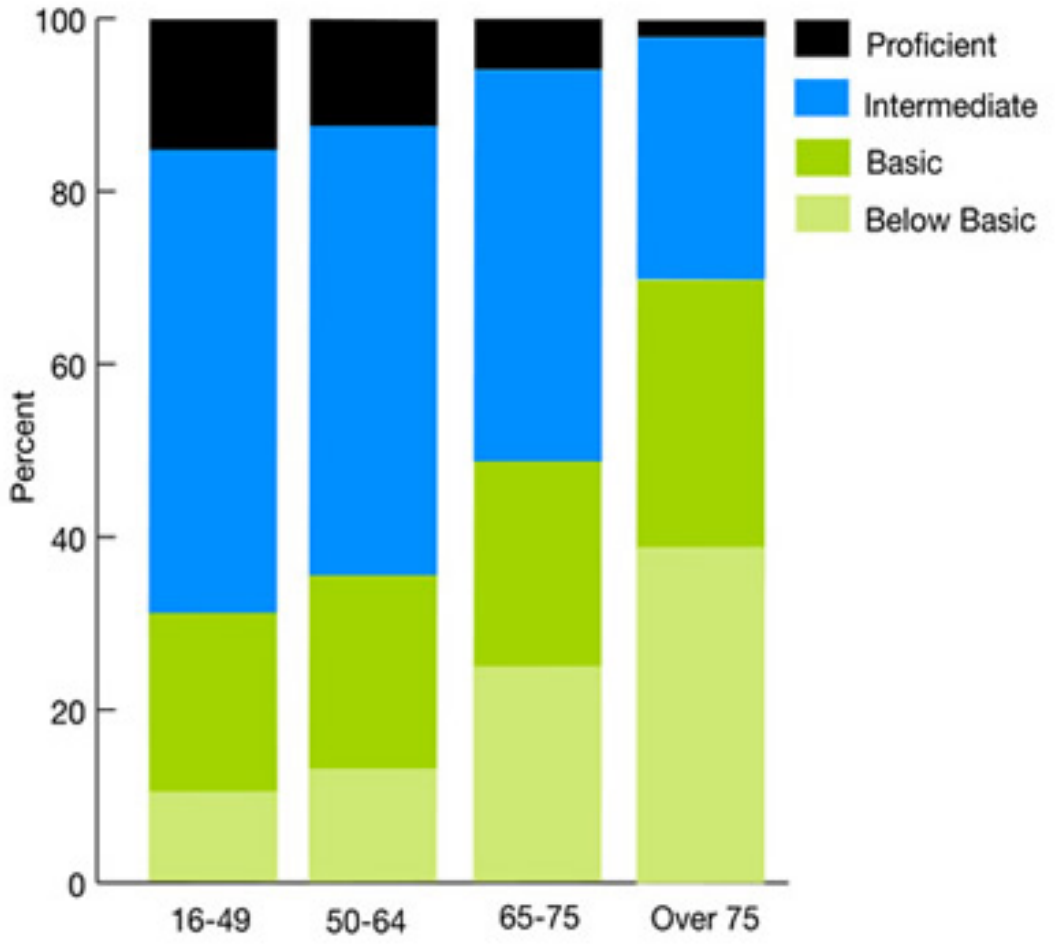
I never know what he says after I leave his office. It's like he's talking Russian. I try to follow what he's saying, but he talks too fast and uses words that mean nothing to me. I don't want him to think I'm stupid...I'm not stupid. I may be old and slow, but I'm not stupid.

L.P.I., 91 years old

College graduate and fluent reader

(personal communication, Feb. 14, 2009)

Adults at each health literacy level, by age



National Assessment of Adult Literacy, Health Literacy Component, 2003.

RUSH

The main problem with communication is the assumption that it has occurred.

George Bernard Shaw

Rush is a not-for-profit health care, education and research enterprise comprising Rush University Medical Center, Rush University, Rush Oak Park Hospital and Rush Health.

Strategies

- *Create a shame-free environment.*
- All staff should be made aware of literacy issues.
- Speak slowly to foster a patient-centered approach.
- Use plain, nonmedical language.
- Use supplemental materials with visual images, video, and audio sources to improve recall.
- Limit the amount of information and repeat it.

Strategies

- Use teach-back to confirm patient understanding
- Reinforce education with follow-up phone calls/visits
- Use teach-back with telephone instructions
- Create a collaborative environment to encourage questions
- Enlist the aid of the patient's family or friends: 2nd pair of eyes and ears who can reinforce & clarify later

Pictures, videos to reinforce information: helpful for physiologic concepts

Date: 03-15-06 Name: Jane Doe GMH# 01234567

Names of Pills	What It's For	Morning/ Breakfast	Afternoon/ Lunch	Evening/ Dinner	Night/ Bedtime
Lisinopril 20 mg 1 pill once a day	Blood Pressure 				
Simvastatin (Zocor) 40 mg 1 pill at bedtime	Cholesterol 				
Metformin 500 mg 2 pills twice a day	Diabetes/ Sugar 				
Gabapentin (Neurontin) 300 mg 1 pill every 8 hours	Nerve Pain 				
Aspirin EC 81 mg 1 pill once a day	Heart 				

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S. Kripalani et al. / Patient Education and Counseling 66 (2007) 368–377

Shared Decision-Making

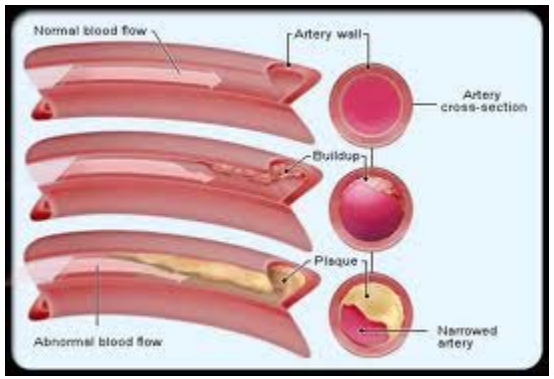
- Follow a patient-centered approach to care that involves the patient in the decision-making process.
- Engage in a clinician–patient discussion before initiating treatment, e.g, statin therapy for primary prevention in patients with lower ASCVD risk.
- The ACC/AHA cholesterol guidelines recommend not only the risk calculation, but also the clinician–patient review of risk and the decision to take a statin.
- The more empowered patients feel, the more likely they will be motivated to manage their condition and adhere to medications.

Shared Decision-Making

- Age is a major contributor to the ASCVD risk calculation.
- A 65-year-old man and a 71-year-old woman with optimal risk factors have a >7.5% 10-year risk.
- Clinical judgment, statin safety issues, and consideration of patient preferences inform the treatment plan.
- Prescription of a statin is not automatic.
- Treatment plan is a comprehensive approach to risk reduction using current lipid panel, the ASCVD risk calculator, and incorporates addressing all modifiable risk factors.

Educating the Patient

- Assess patient's need for information (verbal explanation, written materials)
- Specifically relate the reason for prescribing a lipid modifying agent to an individual patient's condition:
  - Recent cardiac event
  - Diabetes as CAD equivalent
  - Presence of CAC
  - High LDL + family history



Educating the Patient

- Address the importance of 3 forms of therapy to modify lipids and reduce CHD risk:
  - Heart-healthy diet
  - Regular physical activity
  - Medication





- Stress the “life-saving, event prevention” nature of statins for high-risk patients

Address Potential Adverse Effects



- Patients hear/read about them.
- Discuss the potential for muscle aches and describe how muscle aches feel (statins).
- Inform patients about flushing with niacin and how to avoid it.
- Tell patients you <u>want</u> to be called if they believe they are experiencing an adverse effect.
- Assure patients that you will check safety labs when you check a lipid panel.
- Explain that although statins are one "class" of drugs, they are very different from one another; a problem with one doesn't usually mean every statin should be avoided.

Assess Adherence During Each Appointment

- “In the past 2 weeks, what percent of your cholesterol medicine would you say you have taken?”
- (If less than 100%)……..”What is the main reason you might miss your medication?”



Family Support; Patient's Beliefs; Patient/Provider Relationship

- Engage family members (spouses, significant others, children)
  - Explain the importance of treatment adherence.
- Acknowledge patient's beliefs and preferences.
- Emphasize "partnership" between provider (or clinic team) and the patient.
- Key: provider/patient relationship; establish a collaborative process for problem-solving.
- Patients must know they can ask any question.
- Praise patients for achieving treatment goals.

Involve Nurses, Pharmacists, Other Members of the Healthcare Team

- Telephone follow-up
- Interim appointments
- Monitoring of prescription refills





Reminder Systems; Change Medication to Improve Adherence

- Patient initiated: Phone/watch alarms
- Connect medication-taking to other tasks
- Periodic nurse phone calls
- Forgetting to take statin in evening or at bedtime → switch to long-acting statin



Motivational Interviewing

- Useful for patients who are resistant to treatment regimens (don't like to take medication, don't think their condition is severe enough, they are too busy or stressed)
- MI doesn't rely on information sharing or advice giving; not confrontational, forceful or authoritarian
- Shaped by an understanding of what triggers change



Butterworth SW, JMCP 2008;14:S21-S25.

Motivational Interviewing

- Express empathy: "*It's not easy making all of these changes.*"
- Roll with resistance: "*You don't want to take the medicine anymore. You feel fine.*"
- Elicit-provide-elicit → find out what the patient knows, fill in the gaps, correct misconceptions, explore how this will fit into the patients lifestyle

Motivational Interviewing

- Support autonomy: *"Of course it's your decision. If you elect to try this medication, I assure you that I will monitor any side effects and alter the dose or the medication.*
- Explore ambivalence: "*Let's talk about the pros and cons of taking medication for your lipids.*"
- Developing a plan of action: *"So what's the next step for you? What do you think you are willing to do for your health right now?"*

Case Scenario



- 59-year-old male cardiac transplant patient with vasculopathy referred to NP lipid specialist by cardiologist for LDL of 167 mg/dL
- Presumably, lipid management included simvastatin 80 mg (yikes!) and ezetimibe 10 mg daily
- Patient also had chronic renal insufficiency
- A few months ago, patient was hospitalized for an unrelated problem
- After careful review by NP and pharmacist, the patient last refilled his statin the month prior to hospitalization
- NP reinstituted statin (atorvastatin 10 mg daily)

Conclusion

- Poor medication adherence contributes to sub-optimal clinical benefits.
- Poor medication adherence has many causes related to the patient, provider, and healthcare system.
- Poor health literacy and inadequate patient/provider/clinic communication are significant causes of medication non-adherence.
- The solution is 1) early recognition of non-adherence, and 2) a sustained, coordinated effort by the entire healthcare team to prevent and address non-adherence.

NLA Resource

- Patient Adherence Toolkit: https://www.lipid.org/practicetools/tools/adherence

Genetic Causes of Elevated Triglycerides

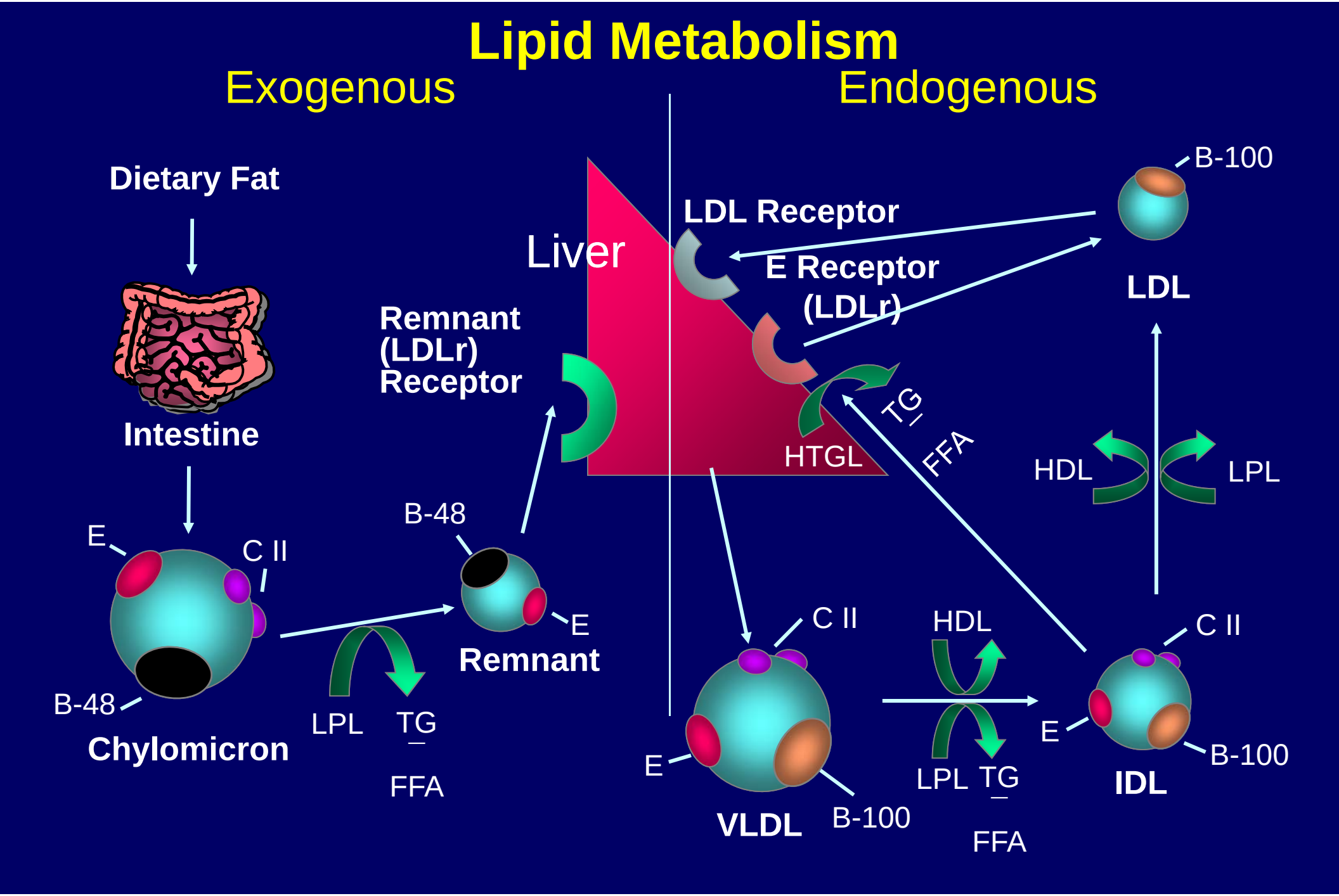
Alan S. Brown, MD FACC FNLA FAHA
Director, Division of Cardiology
Advocate Lutheran General Hospital
Park Ridge, IL
Director, Midwest Heart Disease Prevention Center

Case

- 62 y/o female referred to the Lipid Clinic by nephrologist for elevated TG
- History of resistant HTN on 4 meds for BP, no lipid meds , vitamin D
- BP 162/98 P 56 Exam otherwise unremarkable
- TC 286 HDL 50 LDL 126 TG 550
- All other chemistry is normal except mild elevation in LFT’s
- What is your diagnosis?

Rule out Secondary Causes of Elevated Triglyceride

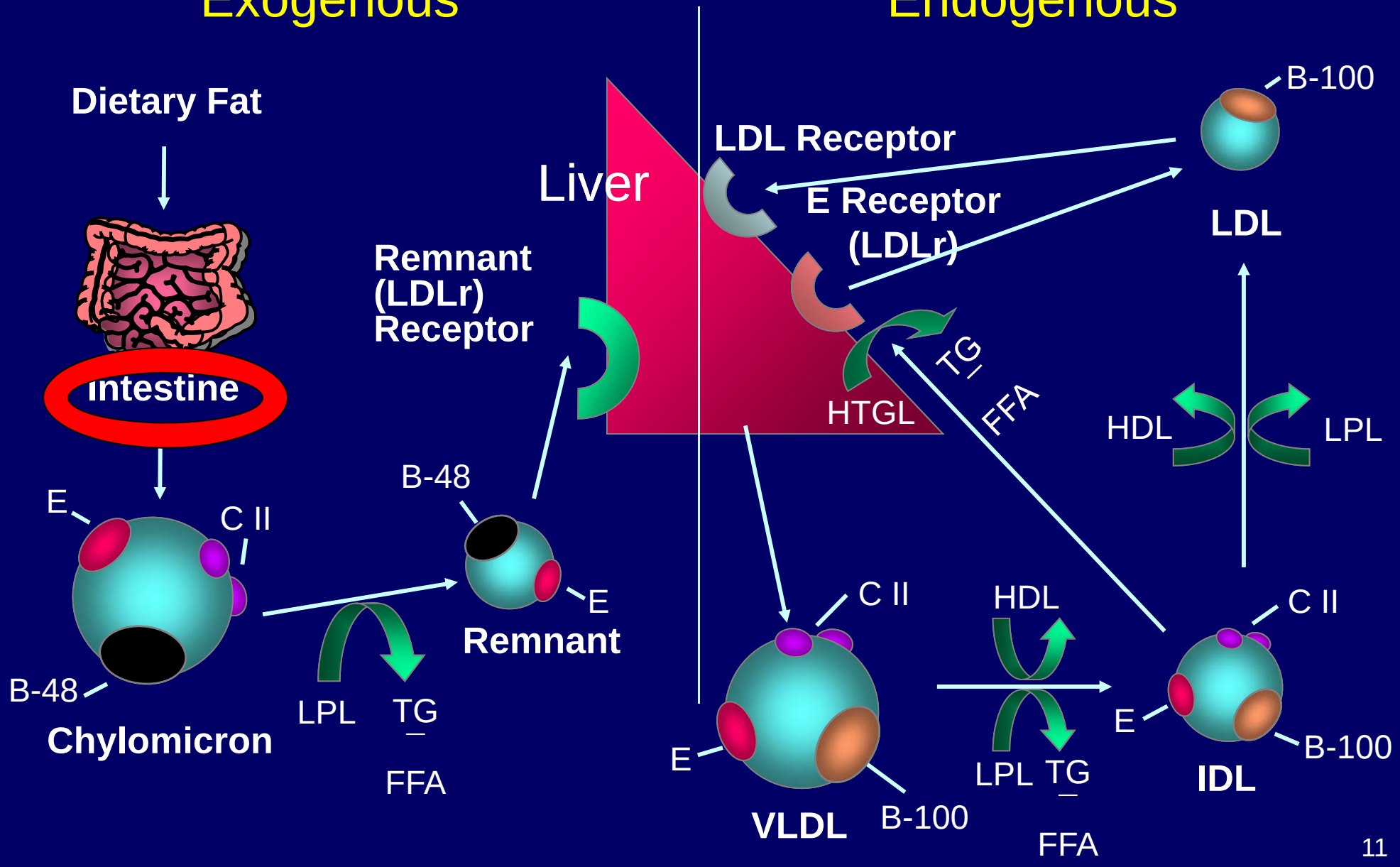
- Obesity
- Metabolic syndrome/insulin resistance
- DM
- Alcohol
- Estrogen,corticosteroids,protease inhibitors,retinoids, some beta blockers,cyclosporin
- Pregnancy
- Bulemia


Lipid Metabolism
Exogenous
Endogenous
Dietary Fat
Intestine
Liver
Remnant
(LDLr)
Receptor
LDL Receptor
E Receptor
(LDLr)
B-100
LDL
HTGL
TG
FFA
HDL
LPL
E
C II
B-48
Chylomicron
LPL
TG
FFA
B-48
E
Remnant
C II
E
VLDL
B-100
HDL
LPL
TG
FFA
C II
E
B-100
IDL

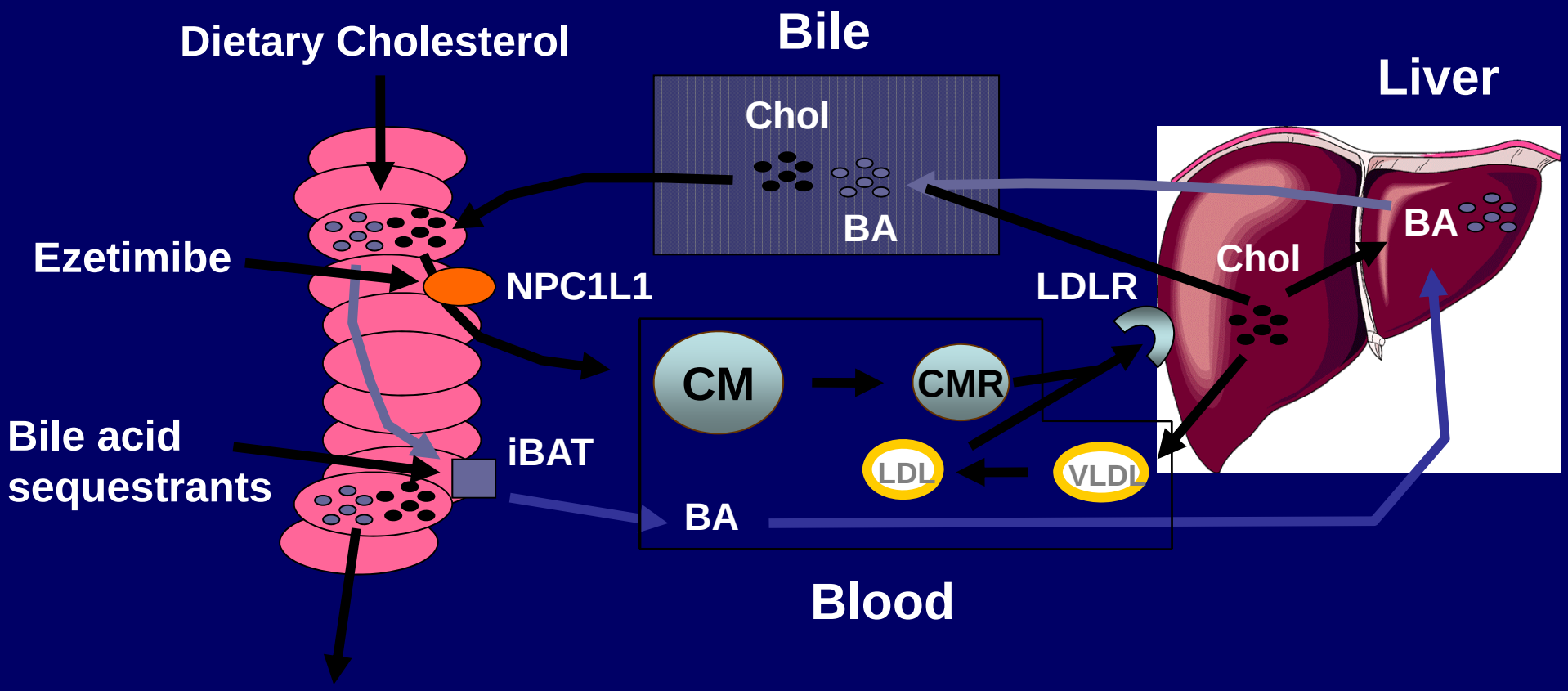
Apolipoproteins

apoA-I	HDL structural protein; LCAT(Lecithin cholesterol acyl transferase) activator;Enhances reverse cholesterol transport
apoA-II	HDL structural protein; Hepatic Lipase activation
apoA-IV	Triglyceride metabolism; LCAT activator;
apoB-100	Structural protein of all Lipoproteins except HDL Binding to LDL receptor
apoB-48	
apoC-I	Inhibit Lipoprotein binding to LDL Receptor; LCAT activator
apoC-II	Lipoprotein lipase (LpL) activator
apoC-III	LpL inhibitor; antagonizes apoE
apoE	B/E receptor ligand *E2:IDL; *E4: Diet Responsivity

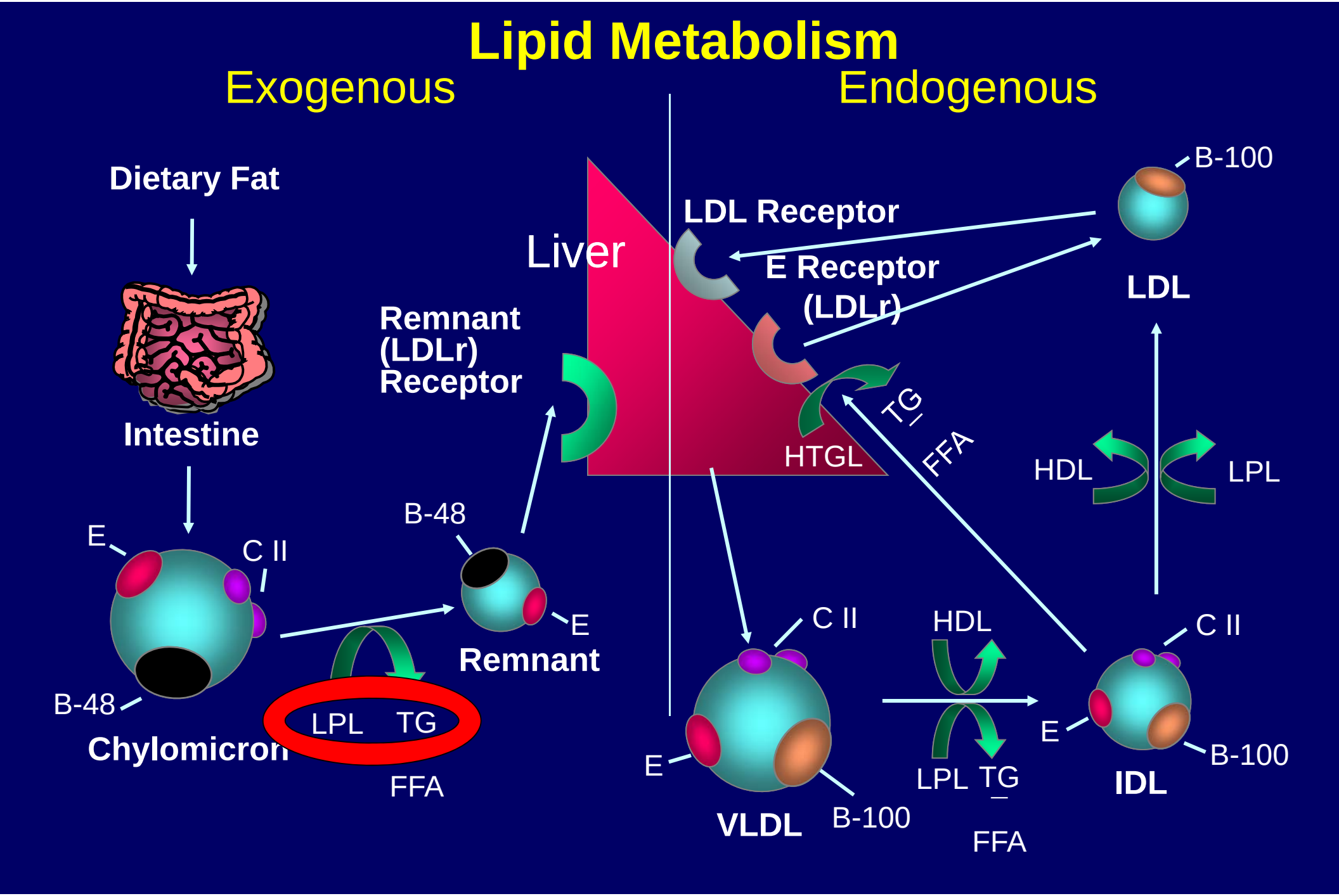
Lipid Metabolism



Intestinal Absorption of Cholesterol and Bile Acids Influences Lipoprotein Metabolism



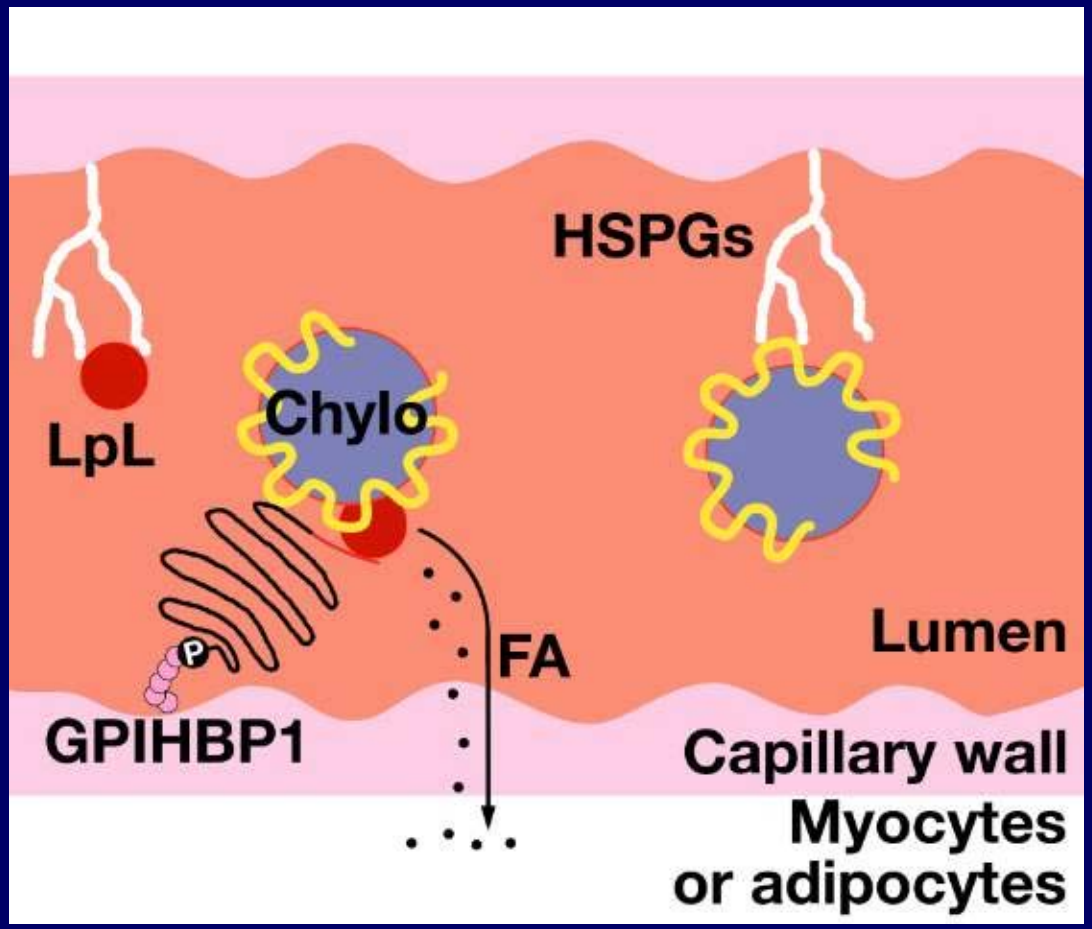
Rader DJ, Nature Medicine 2001; 7:1282-1284


Lipid Metabolism
Exogenous
Endogenous
Dietary Fat
Intestine
Liver
Remnant
(LDLr)
Receptor
LDL Receptor
E Receptor
(LDLr)
B-100
LDL
HTGL
TG
FFA
HDL
LPL
E
C II
B-48
Chylomicron
LPL
TG
FFA
B-48
E
Remnant
C II
E
VLDL
B-100
HDL
LPL
TG
FFA
C II
E
B-100
IDL

Lipoprotein Lipase

- Breaks down triglycerides from TG rich lipoproteins into FFAs
- Activated by Apo CII
- Inhibited by Apo CIII
- Secreted into the interstitium by adipocytes and myocytes
- Requires transport to the lumen by GPIHBP1 (glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1)

The role of GPIHBP1 (glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1) in transporting lipoprotein lipase (LpL) into the capillary lumen



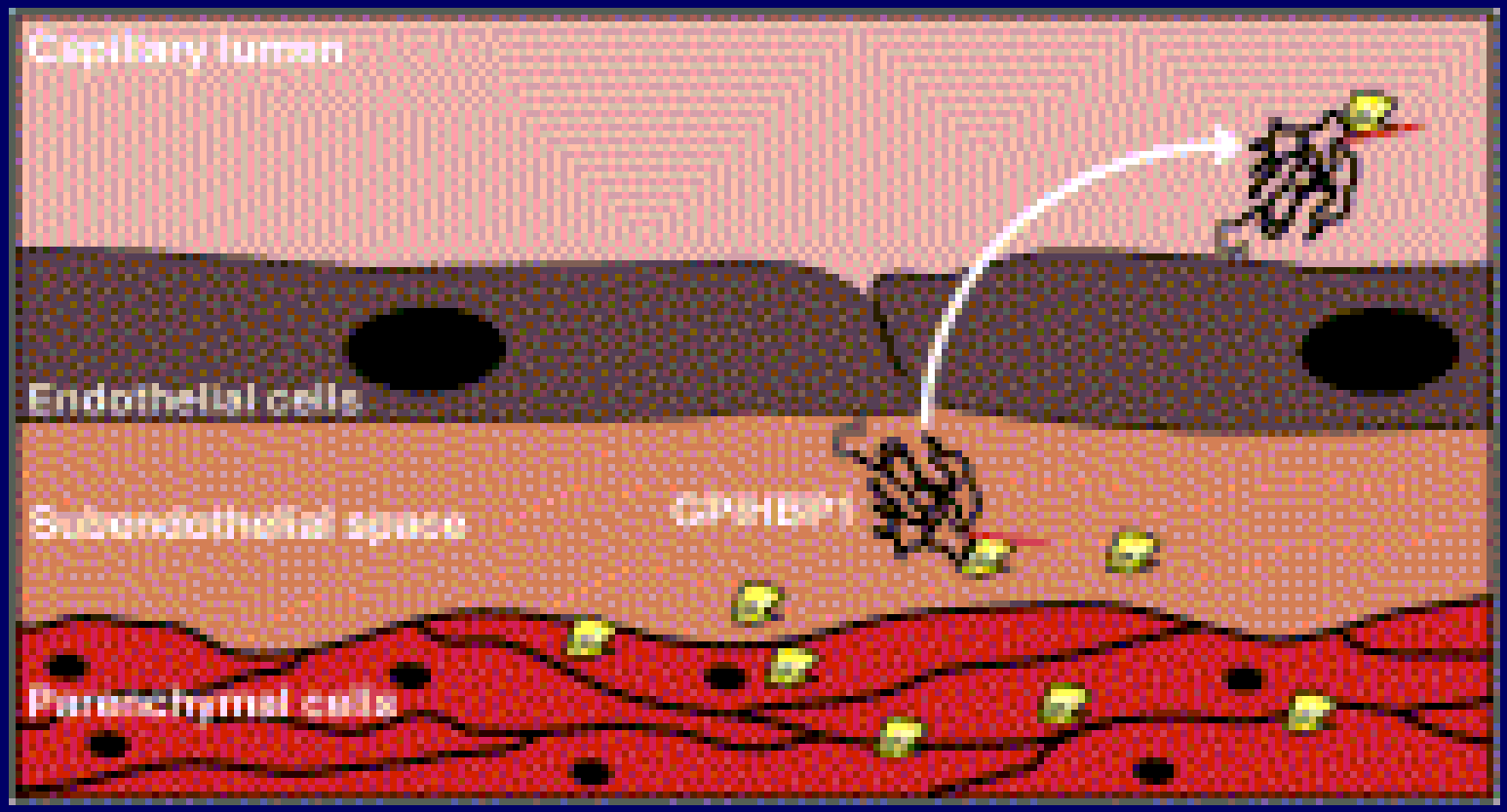
HPSGs=
Heparan sulphate
Proteoglycans

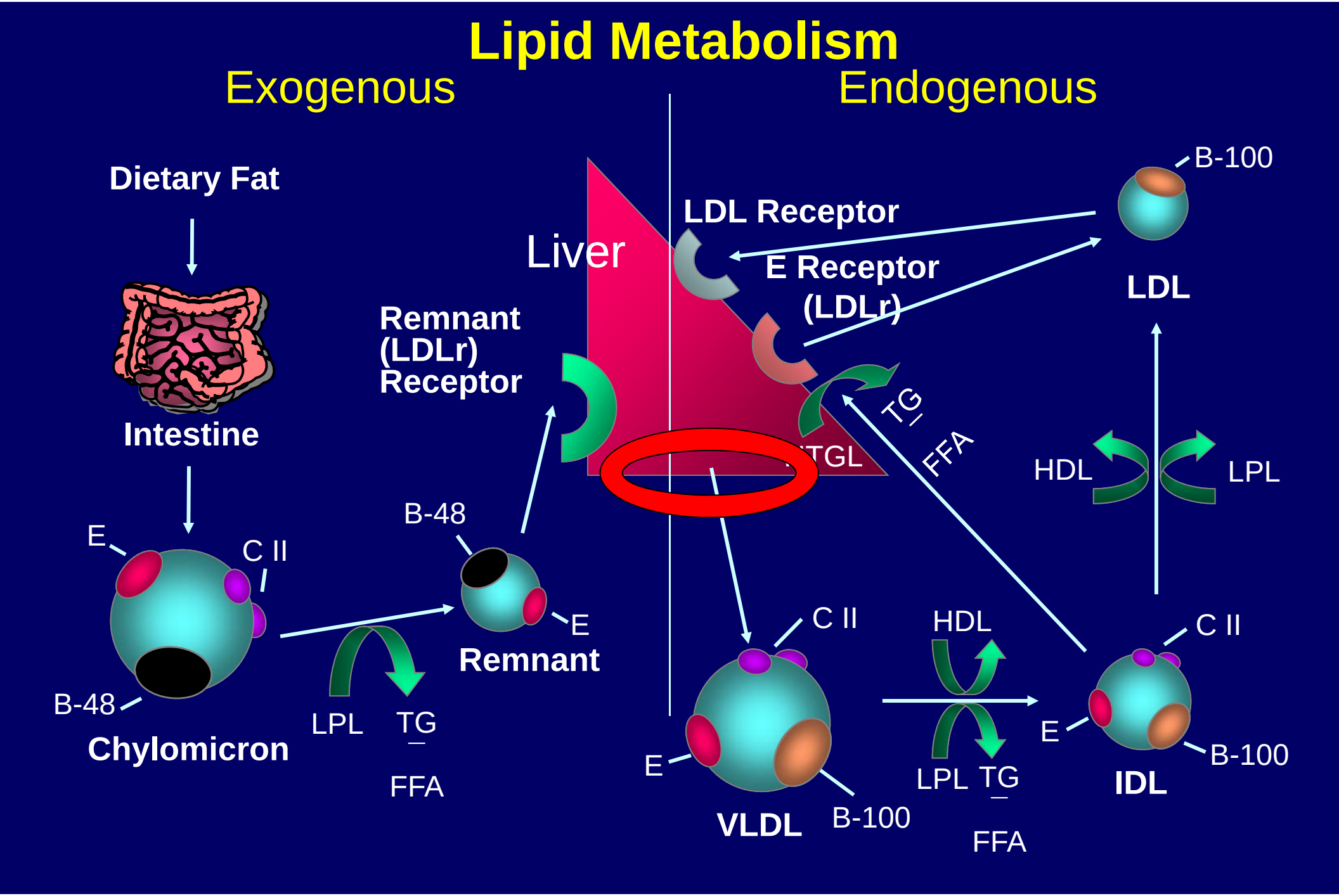
FA=fatty acid

LpL= Lipoprotein
Lipase

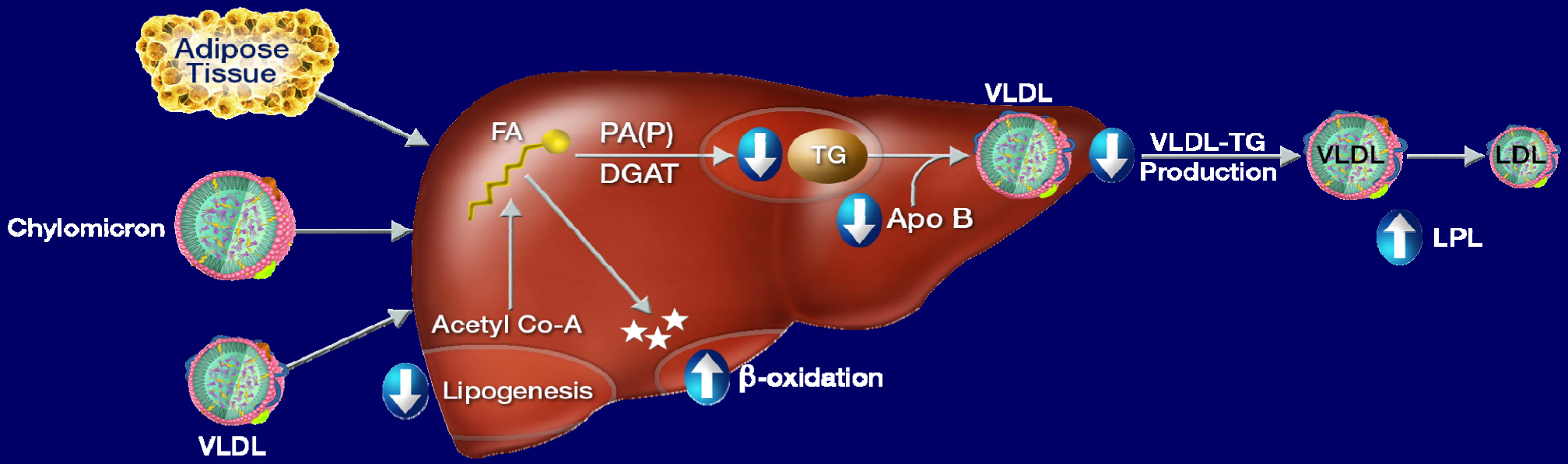
Chylo=Chylomicrons

Lipoprotein Lipase Movement to the Capillary Lumen




Lipid Metabolism
Exogenous
Endogenous
Dietary Fat
Intestine
Liver
Remnant (LDLr) Receptor
LDL Receptor
E Receptor (LDLr)
B-100
LDL
TG
FFA
HDL
LPL
TGL
E
C II
B-48
Chylomicron
LPL
TG
FFA
B-48
E
Remnant
C II
E
VLDL
B-100
HDL
LPL
TG
FFA
C II
E
B-100
IDL

VLDL Packaging in the liver



DGAT=diacylglycerol acyltransferase; PA(P)=phosphatidic acid phosphatase/phosphohydrolase.

Adapted from Bays HE et al. *Expert Rev Cardiovasc Ther.* 2008;6(3):391-409.

Genetic Dyslipidemias

- Disorders affecting LDL
- Disorders affecting Triglycerides
- Low HDL disorders
- Low LDL disorders
- Lp(a)

Classification of Lipoprotein Disorders (Frederickson / Levy / Lees)

	I	IIa	IIb	III	IV	V
Lipoprotein	CM	LDL	LDL+ VLDL	Remnants	VLDL	CM+ VLDL
TG	⇑⇑	N	⇑	⇑	⇑	⇑⇑
Xanthomas	eruptive	tendon	none	palmar tubero-eruptive	none	eruptive
Clinical	pancreatitis	CHD	CHD	CHD	none	pancreatitis
Etiology	LPL apoC-II	LDLR	unknown	apoE2	unknown	unknown
Name	FCS	FH	± FCH	FD	FEHTG	MHTG

Genetic Disorders	Defect
Hyperchylomicronemia	Lipoprotein Lipase, CII
Familial	
Hypercholesterolemia	LDL-Receptors
Defective Apo B	Apo B
Combined Hyperlipidemia	Apo B Overproduction
Dysbetalipoproteinemia	Apo E2:E2 + FCH
Hypertriglyceridemia	Enlarged VLDL
Hypoalphalipoproteinemia	Apo AI, HDL
Lp (a)	Lp (a)

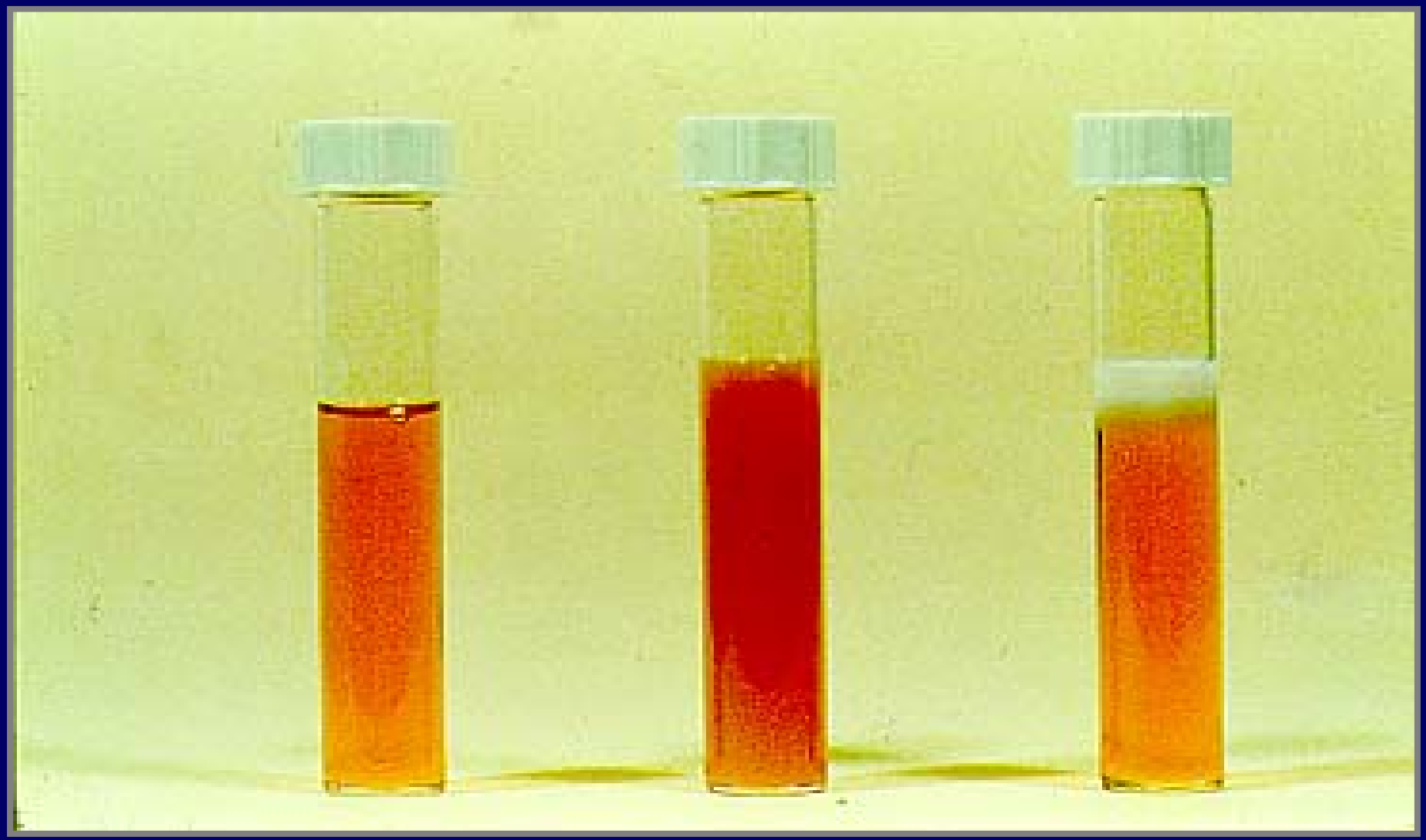
Genetic Disorders of LDL

- Familial hypercholesterolemia (FH)
  - Heterozygous
  - Homozygous
- Familial defective Apo B-100
- PCSK9 abnormality
- Hereditary Sitosterolemia (Can mimic physical findings of FH)
- Physical findings of
  - Corneal arcus
  - Extensor tendon xanthomas
  - Achilles xanthomas

Genetic Disorders of Triglycerides

- Chylomicronemia
  - Lipoprotein lipase deficiency
  - Apo CII deficiency
- Familial combined dyslipidemia
  - Overproduction of Apo B-100
- Familial hypertriglyceridemia
  - Large VLDL particles
  - Minimal ↑ CAD risk
- Type III dyslipidemia

Clues to Lipid Abnormalities by Serum Examination



Tuberoeruptive Xanthomas in Hypertriglyceridemia

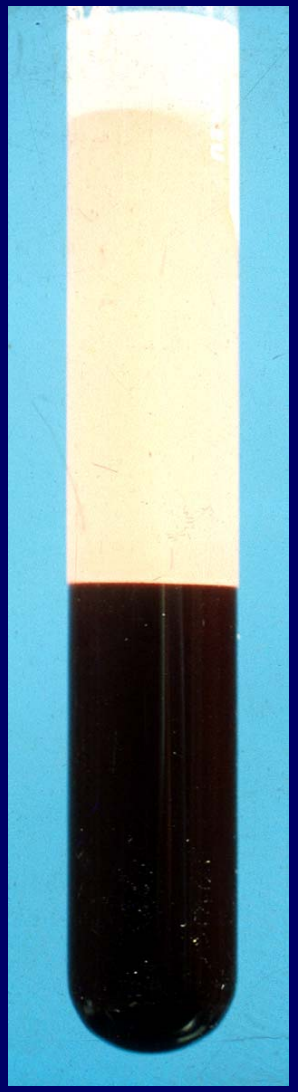


Tuberoeruptive Xanthomas in Chylomicronemia

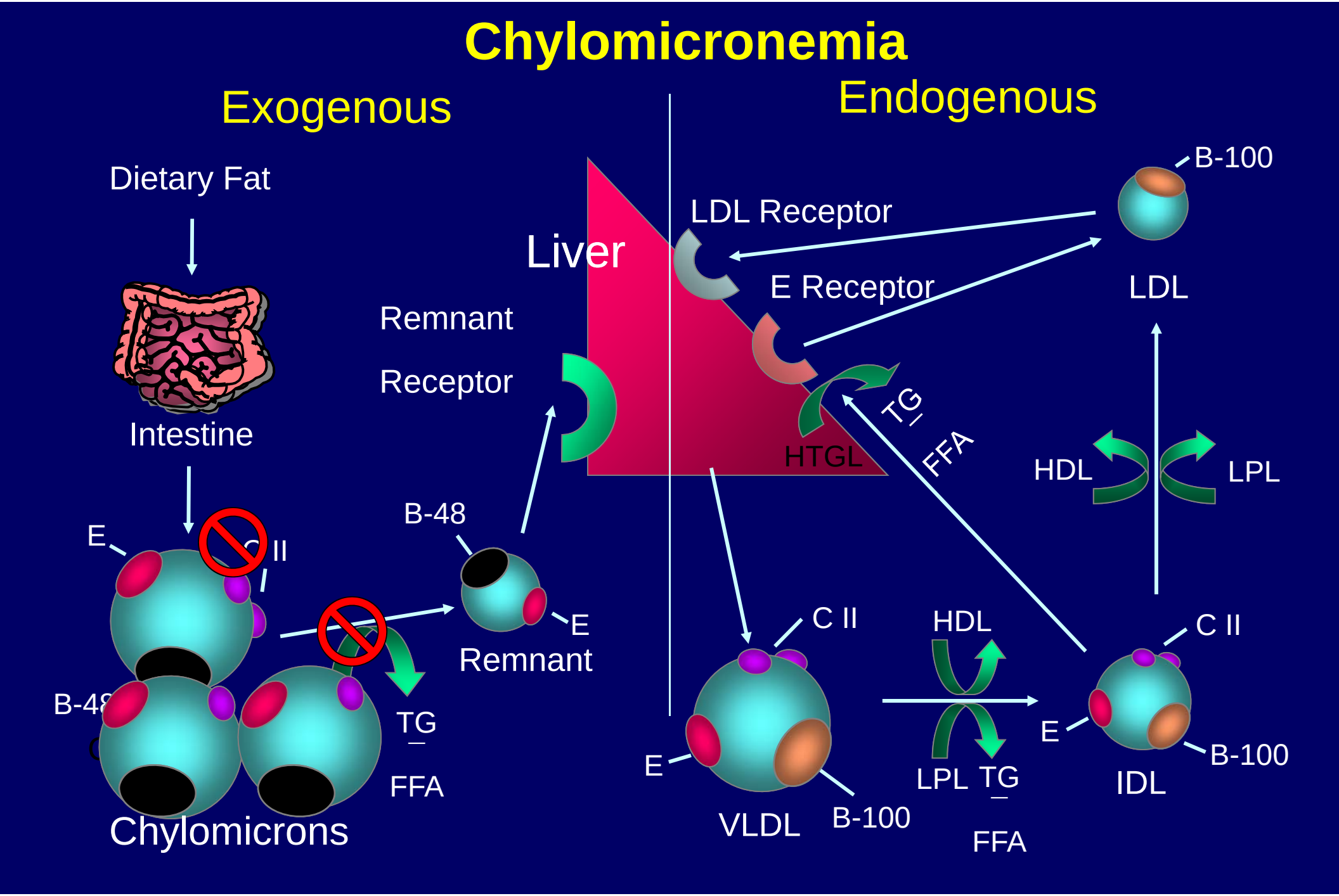


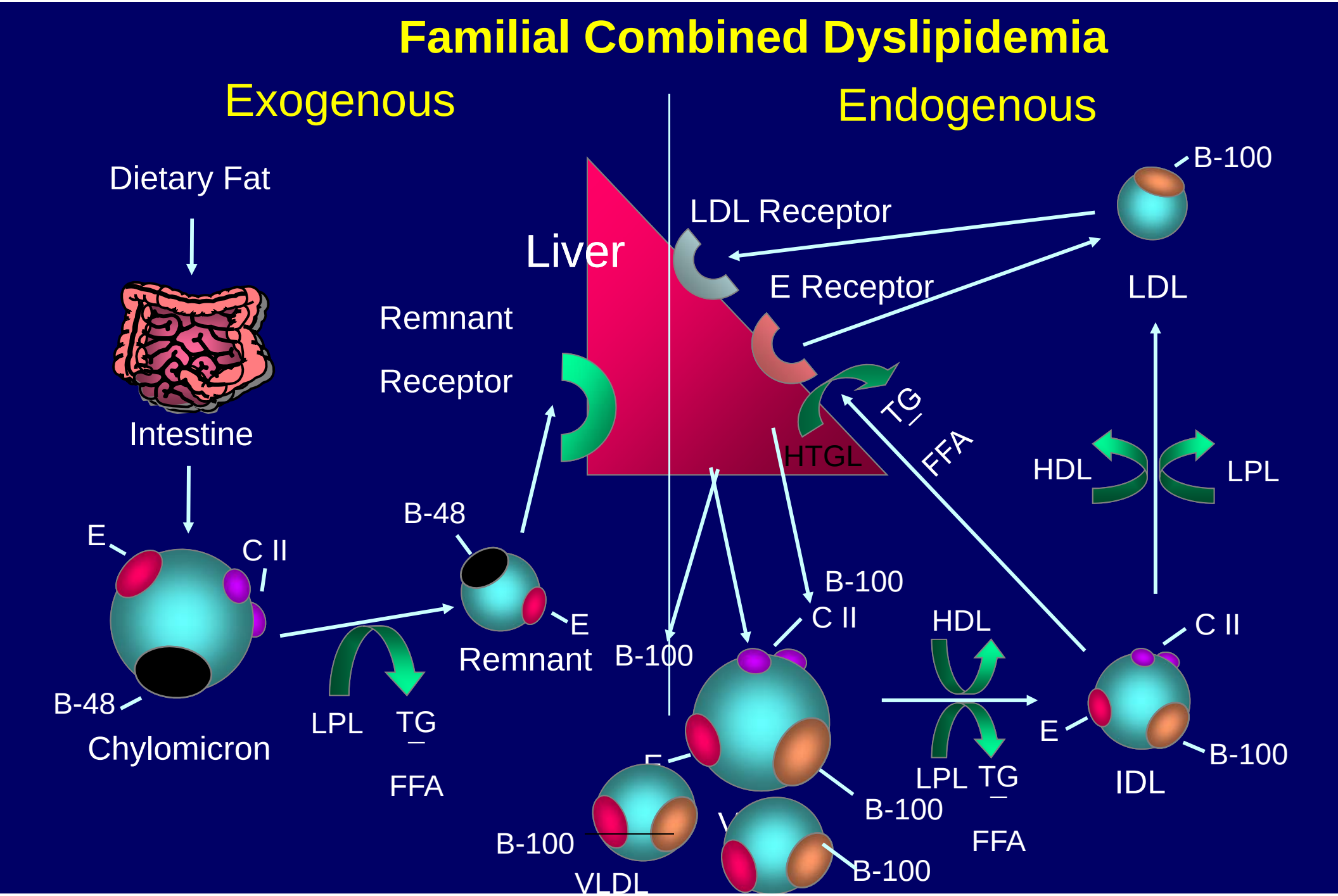
Lipemia Retinalis





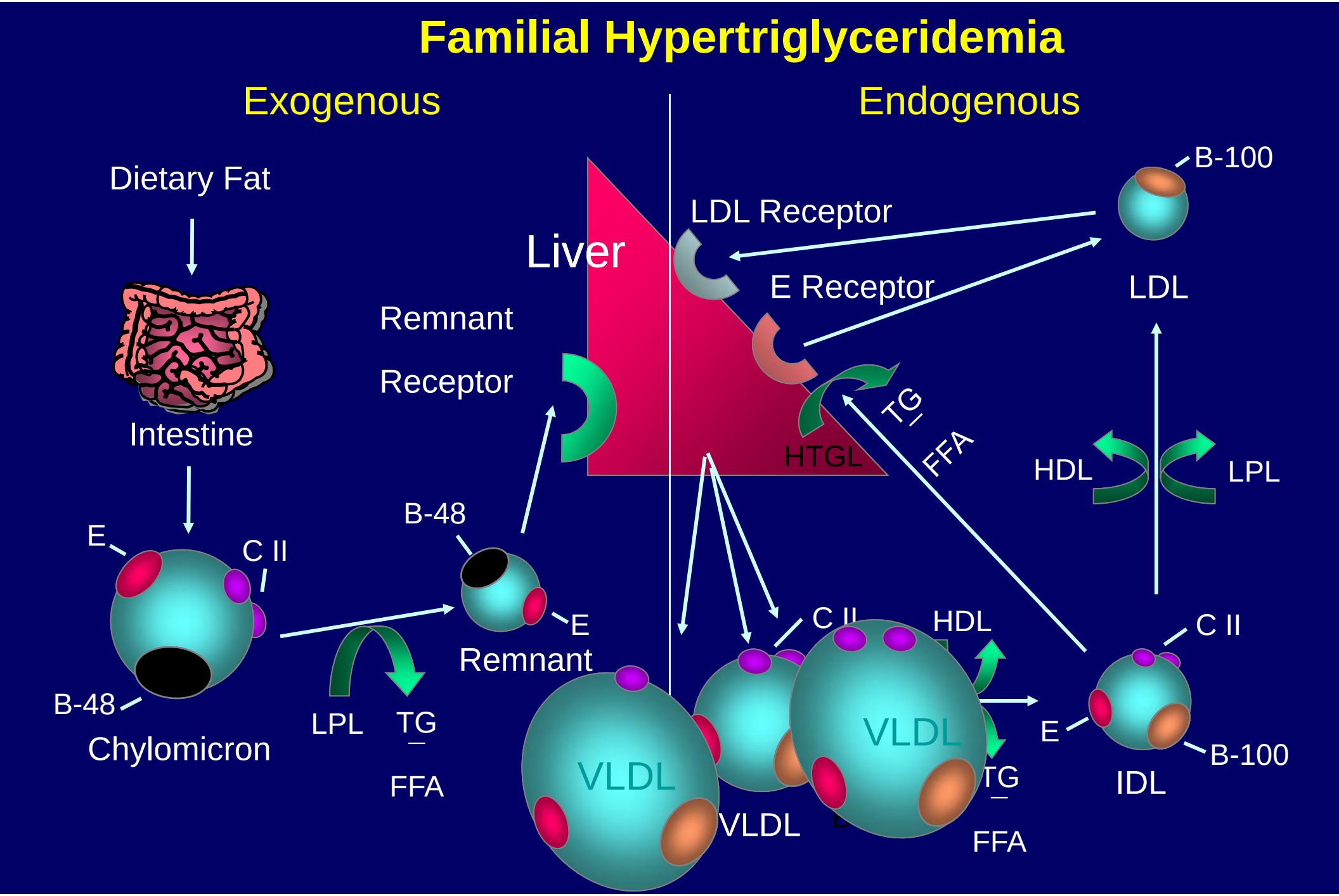
TG = 8000 mg/dL


Chylomicronemia
Exogenous
Endogenous
Dietary Fat
Intestine
Liver
Remnant
Receptor
LDL Receptor
E Receptor
B-100
LDL
HTGL
TG
FFA
HDL
LPL
E
C II
B-48
Remnant
Chylomicrons
TG
FFA
VLDL
B-100
HDL
LPL
TG
FFA
IDL
C II
E
B-100


Familial Combined Dyslipidemia
Exogenous
Endogenous
Dietary Fat
Intestine
Liver
Remnant
Receptor
LDL Receptor
E Receptor
B-100
LDL
HTGL
TG
FFA
HDL
LPL
E
C II
B-48
Chylomicron
LPL
TG
FFA
B-48
E
Remnant
B-100
C II
B-100
B-100
VLDL
B-100
HDL
LPL
TG
FFA
E
C II
B-100
IDL

Familial Combined Hyperlipidemia

- Use Non-HDL cholesterol or Apo B rather than LDL
- Apo B/LDL > 1.0
- Autosomal Dominant/Family Screening/Valuable
- Evaluate Lp (a), homocysteine

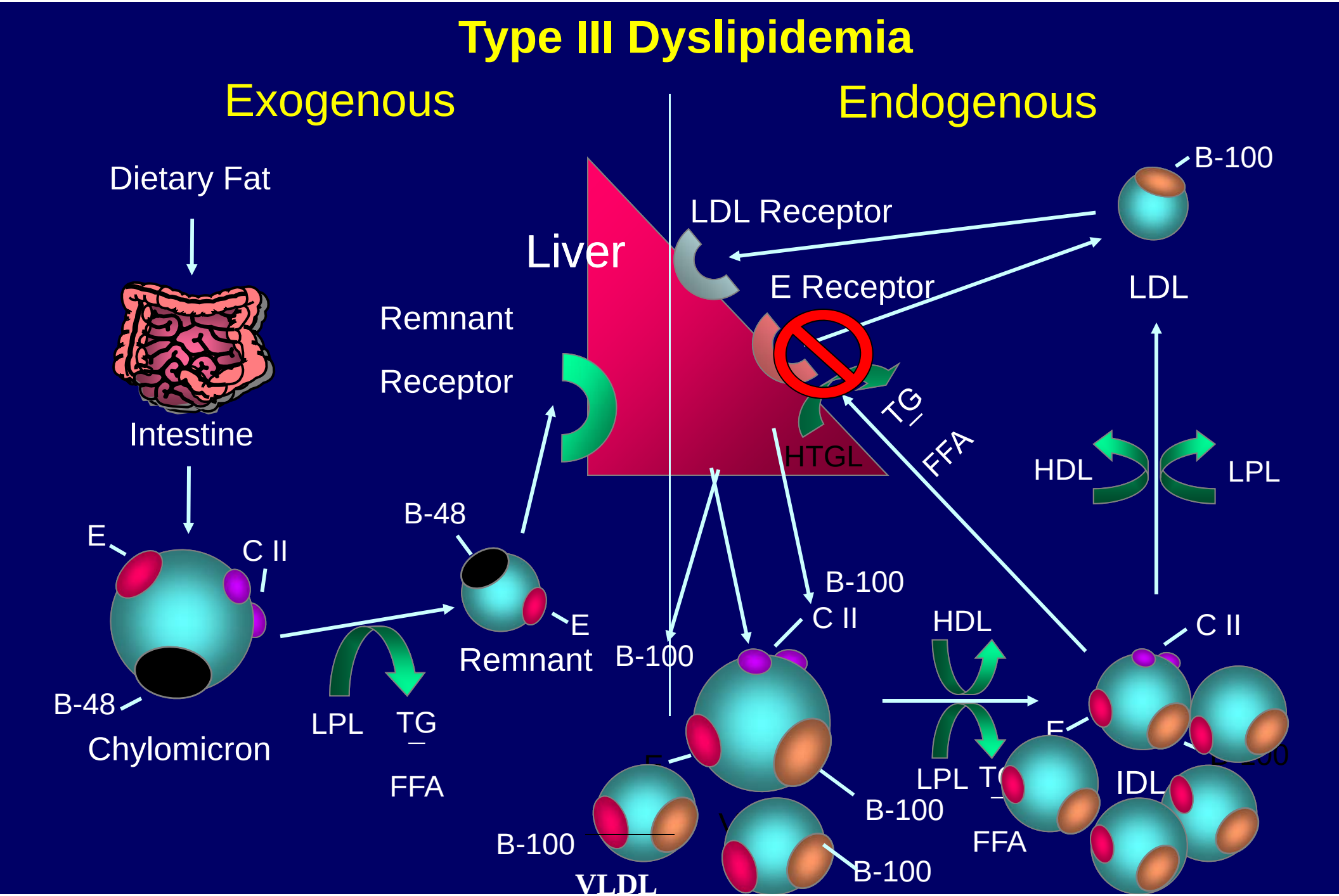

Familial Hypertriglyceridemia
Exogenous
Endogenous
Dietary Fat
Intestine
Liver
Remnant
Receptor
LDL Receptor
E Receptor
B-100
LDL
HTGL
TG
FFA
HDL
LPL
E
C II
B-48
Chylomicron
LPL
TG
FFA
B-48
E
Remnant
VLDL
VLDL
C II
HDL
VLDL
TG
FFA
E
C II
B-100
IDL

Familial Hypertriglyceridemia

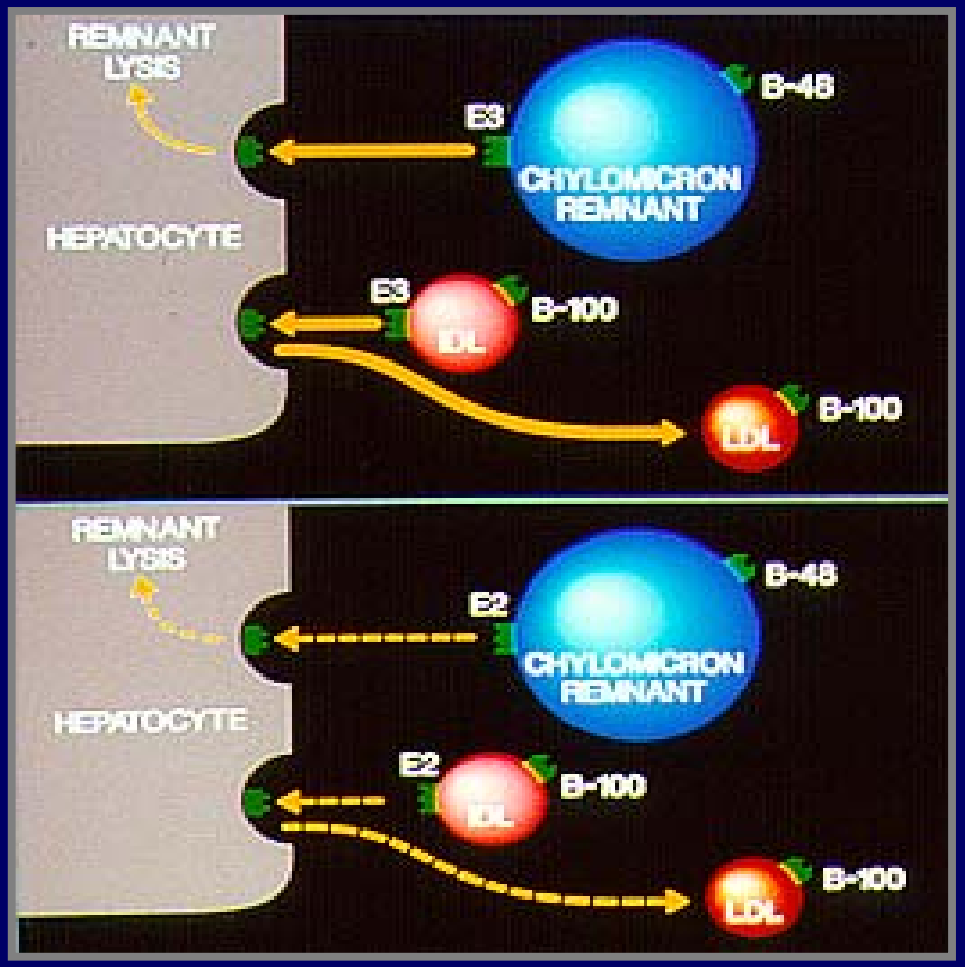
- Family member has hypertriglyceridemia only
- Apo B/LDL < 1.0
- HDL usually low
- CHD risk only slightly above average

Type III Dyslipidemia

- Extremely rare (1:10,000)
- Combination of familial combined dyslipidemia and Apo E2/E2 phenotype
- ↑ risk for CAD
- Extremely diet sensitive
- Orange palmar creases
- Palmar xanthomas


Type III Dyslipidemia
Exogenous
Endogenous
Dietary Fat
Intestine
Liver
Remnant
Receptor
LDL Receptor
E Receptor
HTGL
TG
FFA
B-100
LDL
HDL
LPL
E
C II
B-48
Chylomicron
LPL
TG
FFA
B-48
E
Remnant
B-100
C II
B-100
B-100
B-100
VLDL
HDL
LPL
TG
FFA
C II
IDL

Apo-E Isoforms and Type III Hyperlipidemia



Features of Apo-E2 Homozygosity

- 1 % incidence in population
- Total cholesterol and LDL cholesterol
- VLDL Cholesterol
- 1:50 people homozygous for Apo-E2 develop type III hyperlipidemia
- Coincident second defect in lipoprotein metabolism required for Type III Hyperlipidemia to develop
- Hypothyroidism, obesity, estrogen deficiency or glucose intolerance may result in expression of Type III Hyperlipidemia

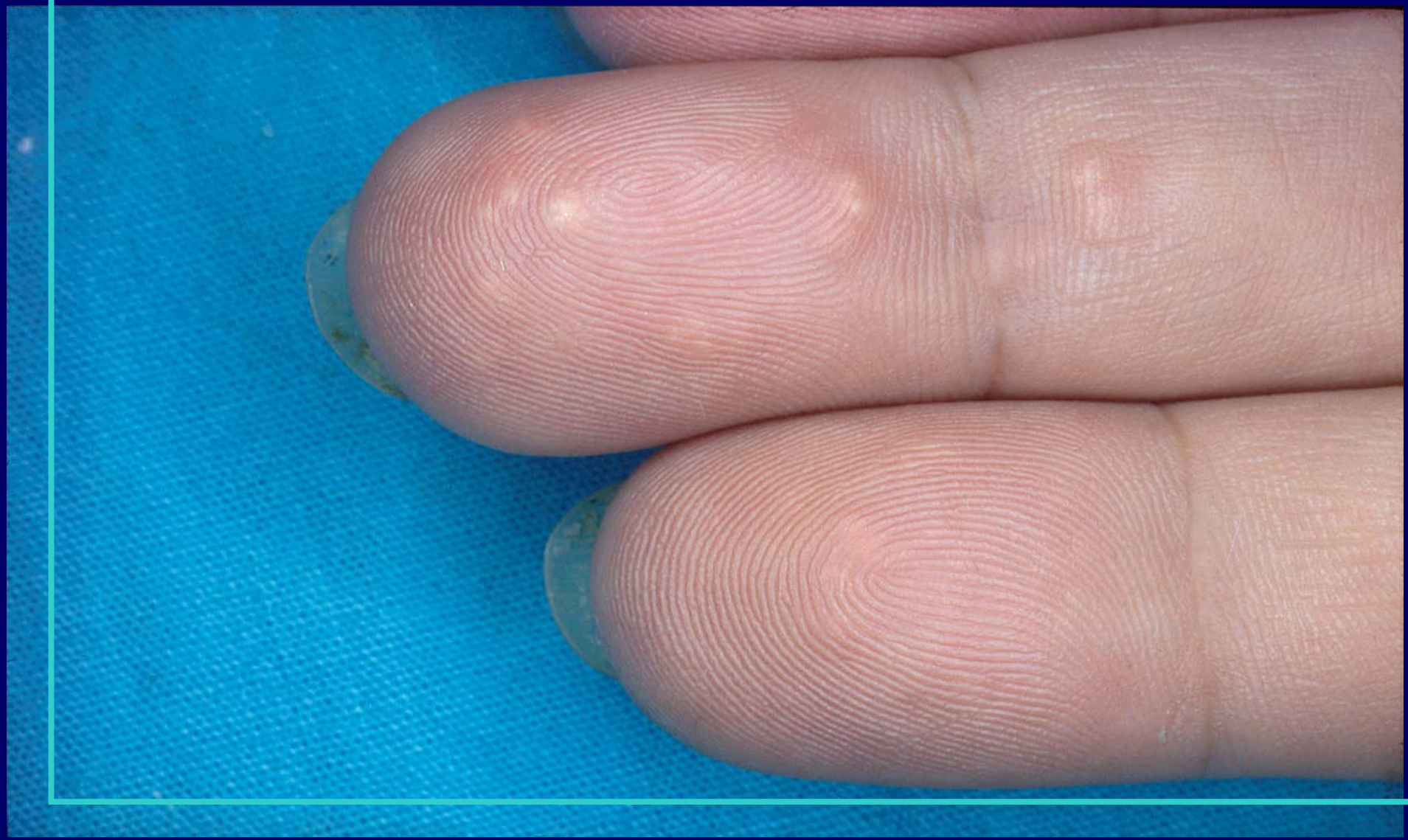
Orange Palmar Creases in Type III



Tubero-Eruptive Xanthomata-Dysbetalipoprotenemia



Palmar xanthomas in Type III



Palmar Xanthomas in Type III (Dysbetalipoproteinemia)



Genetic Disorders	Defect
Hyperchylomicronemia	Lipoprotein Lipase, CII
Familial	
Hypercholesterolemia	LDL-Receptors
Defective Apo B	Apo B
Combined Hyperlipidemia	Apo B Overproduction
Dysbetalipoproteinemia	Apo E2:E2 + FCH
Hypertriglyceridemia	Enlarged VLDL
Hypoalphalipoproteinemia	Apo AI, HDL
Lp (a)	Lp (a)

Patient Case-Is Diabetes the Only Reason for High Triglycerides or Could there be another Genetic Cause

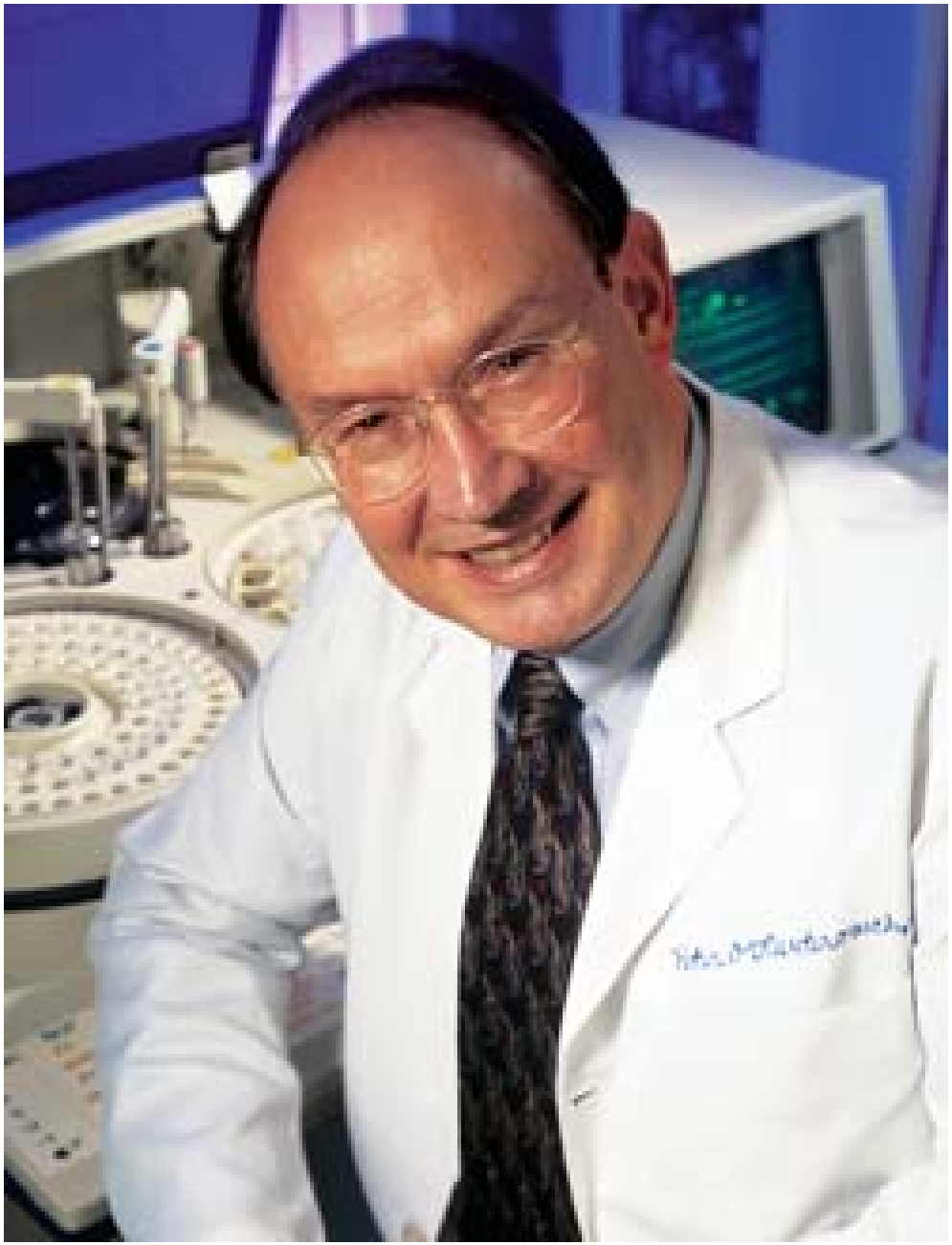
Michael Miller, MD, FACC, FAHA, FNLA

Professor of Medicine, Epidemiology & Public Health

University of Maryland School of Medicine

Baltimore, MD

- Peter Kwiterovich, Jr, MD



- Cord Blood to Diagnose FH
- Early Studies of Sitosterolemia
- HyperapoB (PNAS 1980- Citation Classic)

INTRODUCTION: Genetic Causes of HTG

Common

- Familial combined hyperlipidemia (FCH)
  - Variable ↑TG and cholesterol genetic defects in lipoprotein metabolism
- Familial hypertriglyceridemia (FHT)
  - ↑TG levels only, related to ↑ hepatic VLDL production and/or polygenic vs environmental ↓ lipoprotein lipase (LPL) activity

Rare

- Familial dysbetalipoproteinemia (Fredrickson Type III)
- LPL deficiency
- Apo C-II deficiency
- GPIHBP1 deficiency
- Others

Bays HE. In: Kwiterovich PO Jr, ed. *The Johns Hopkins Textbook of Dyslipidemia*. 1st ed. Lippincott Williams & Wilkins;2010:245-57.

Secondary Causes of HTG

- **Ethanol** intake (especially chronic or acute excess)
- Physical Inactivity
- **Central adiposity**
- **Insulin resistance**/Metabolic Syndrome/Pre-diabetes
- **Diabetes Mellitus** (especially w/ poor glycemic control)
- **Hypothyroidism**
- Nephrotic syndrome
- Medications:
  - **Oral estrogen**, tamoxifen
  - **Glucocorticoids**
  - **Antiretrovirals**
  - **Isotretinoin**
  - Phenothiazines and some second-generation antipsychotics
  - Nonselective beta-blockers, thiazide diuretics

Bays HE. In: Kwiterovich PO Jr, ed. *The Johns Hopkins Textbook of Dyslipidemia*. 1st ed. Lippincott Williams & Wilkins;2010:245-57.

IR & DM Induced Hypertriglyceridemia



Insulin Resistance

↑ FFA

DGAT

TG TG TG TG TG

CE

Glycerol

VLDL

Liver

TG

CETP

CE

HDL

Apo A-I

TG

HTGL

HDL

Apo A-I

Small, dense HDL

VLDL

Apo B-100

TG

CETP

CE

HTGL

LDL

Apo B-100

TG

LDL

Apo B-100

Small, dense LDL

Miller M, et al. *Circulation.* 2011;123:2292-2333

Original Article

Null Mutation in Hormone-Sensitive Lipase Gene and Risk of Type 2 Diabetes

A null mutation in the gene encoding hormone-sensitive lipase causes type 2 diabetes and results in small adipocytes, lipolysis, insulin resistance, and secondary inflammation of white adipose tissue.

N Engl J Med
Volume 370(24):2307-2315
June 12, 2014



The NEW ENGLAND JOURNAL of MEDICINE

Case Report: New Onset HTG

58-yr-old W: HTN

Episodes of hypoglycemia & RUQ pain

PMH:

Blurry vision and nausea, both relieved following food consumption.

(-) no hx DM, dyslipidemia, or (+) FH

Diet: vegetarian +/- ETOH

Exercise: physically active MD

PSH: s/p cholecystectomy.

Case History: New Onset HTG

- Meds:
- metoprolol succinate 50 mg bid
- aspirin 81mg
- amlodipine 5 mg
- Lisinopril 20 mg

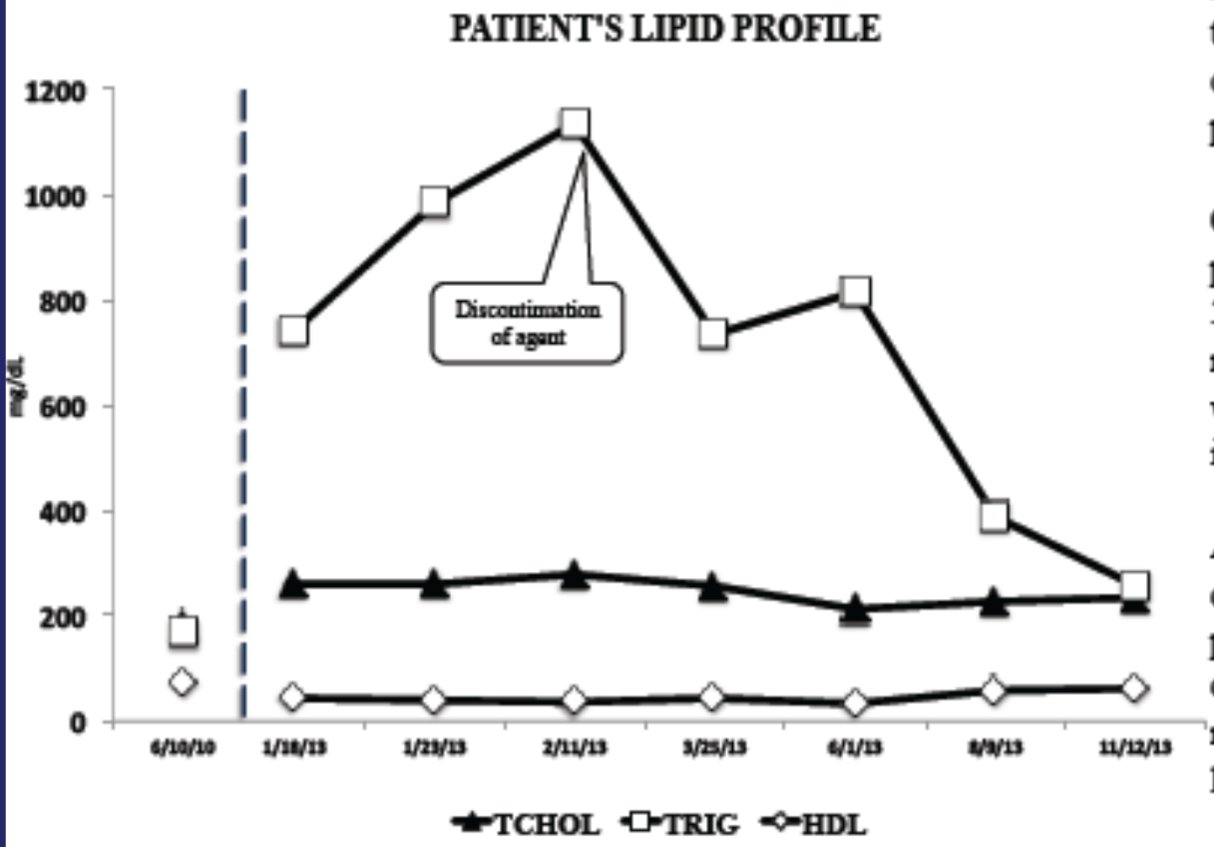
Physical examination

Mild abdominal tenderness and a palpable liver edge

(-) palmer streaking

(-) xanthomas

Case History: TG Levels

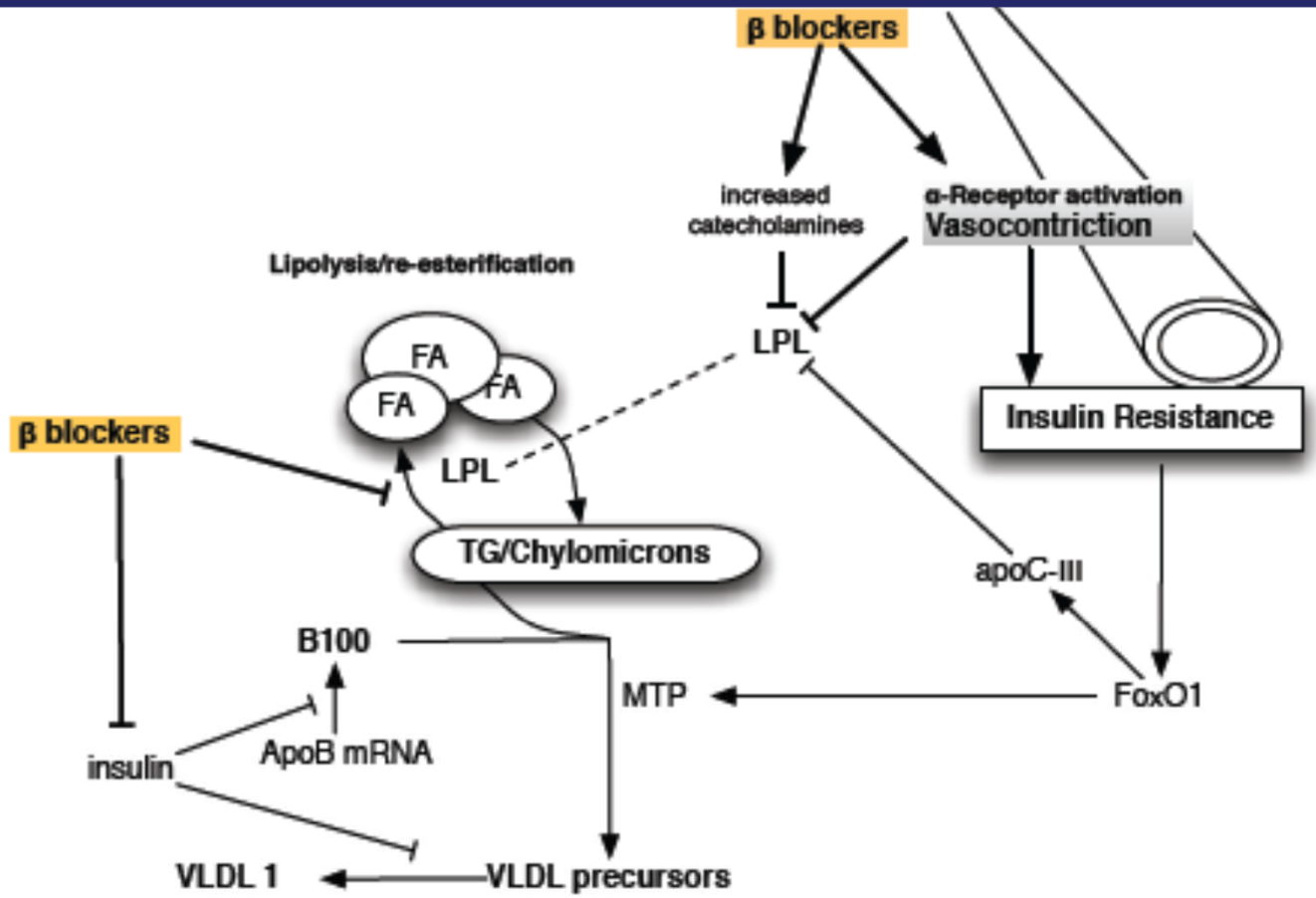


Laboratory testing revealed an elevated serum triglyceride (TG) level of 743 mg/dL and 1133 mg/dL on repeat testing. Her TG level three years prior to presentation was 169 mg/dL.

Other tests performed excluded presence of acute pancreatitis, uncontrolled diabetes (hemoglobin A_1C 5.3 mmol/L), and multiple myeloma. Magnetic resonance imaging (MRI) of the abdomen with and without intravenous contrast did not reveal evidence of intra-abdominal pathology.

At a subsequent clinic visit, metoprolol was discontinued. Over the course of five months, the patient had repeat TG testing, which showed a rapid decline in TG level. During this time, the patient did not have changes in weight, dietary habits, or activity level from baseline.

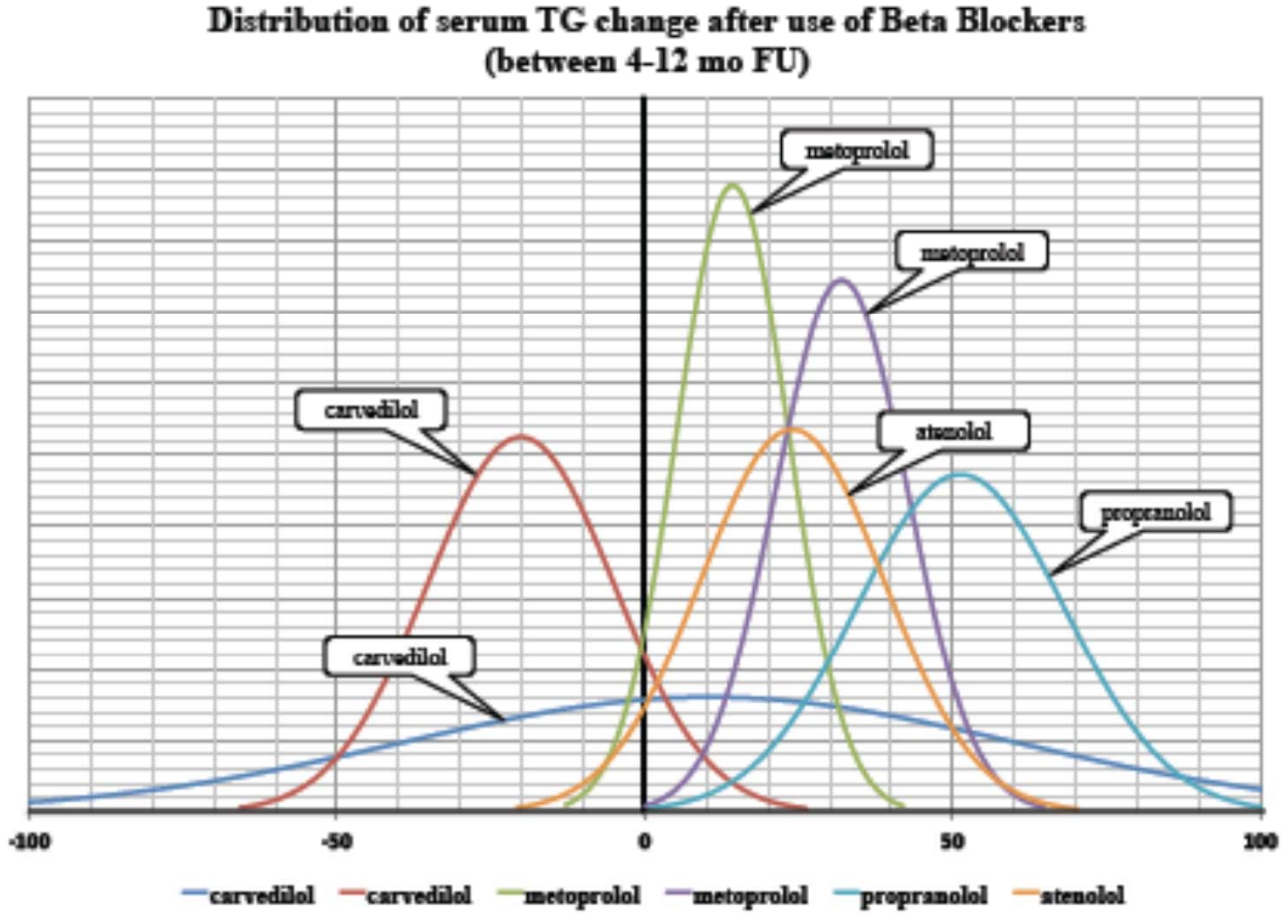
Case History



Mechanism of β blocker induced hTG. There are two plausible mechanisms behind β blocker induced hTG. **A)** insulin resistance. Direct relationship have been shown *de novo*. Patients on β blockers have increased insulin levels and decreased clearance. **B)** lipoprotein lipase (LPL) inhibitions. There is a direct link between inactive LPL and hTG, as seen in familial hTG.

Case Report

Effects of different β-blocking agents on serum TG levels in previous studies. Non-specific β blockers or those without intrinsic sympathomimetic activity may increase serum TG levels.



VAP- Results

TC 223

LDL Direct 116

HDL 66 mg/dL

VLDL-C 41 (H) <30 mg/dL

Triglycerides 159

Non-HDL 156

Lp(a) Cholesterol 8.0

IDL Cholesterol 30 (H) <20 mg/dL

Remnant (IDL+VLDL3) 54 (H) <30 mg/dL

ApoE 2/3

Effects of Nutrition Practices on Triglyceride Lowering

Nutrition Practice	TG-Lowering
Weight loss (5% to 10% of body weight)	20%
Implement a Mediterranean-style diet vs a low-fat diet	10–15%
Add marine-derived PUFA (EPA/DHA) (per gram)	5–10%
Decrease carbohydrates	
1% Energy replacement with MUFA/PUFA	1–2%
Eliminate *trans* fats	
1% Energy replacement with MUFA/PUFA	1%

Miller M, et al. *Circulation.* 2011;123:2292-2333

Treatment Recommendations

- Discontinued Metoprolol
- Low carb diet
- Aerobic activity
- ETOH restriction
- Omega-3 capsules 4 gm daily

Summary Slide

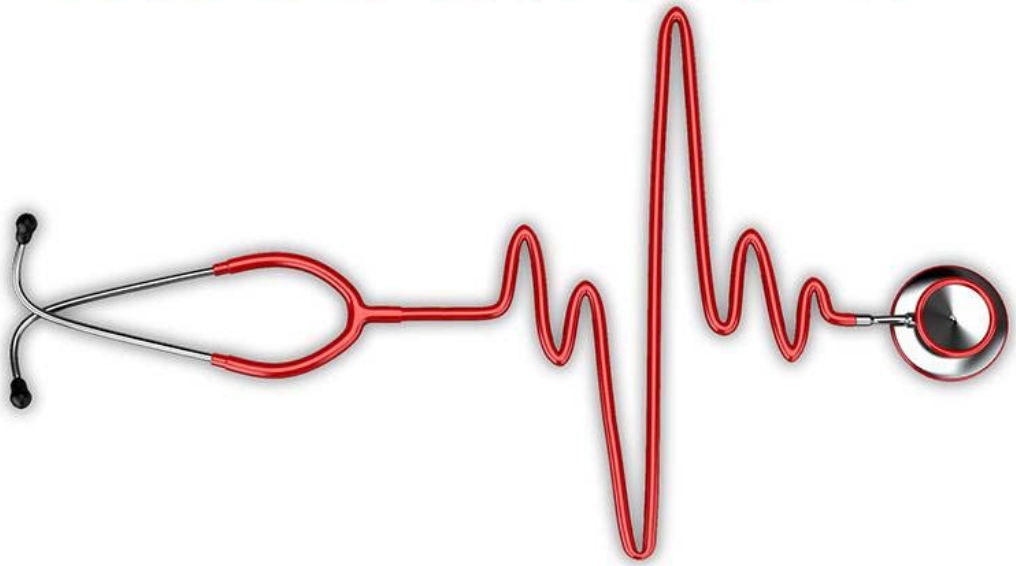
- Genetic and Metabolic Factors contribute to HTG
- New onset HTG should alert possibility of recent change in lifestyle or medications

Take Home Message Slide

- Diabetes is not the only reason for high TG
- Underlying genetic predisposition may be present

THE POSITIVE EMOTIONS PRESCRIPTION
TO PREVENT AND REVERSE HEART DISEASE

HEAL YOUR HEART



MICHAEL MILLER, MD,
with CATHERINE KNEPPER

Patient Case – The South Asian Patient

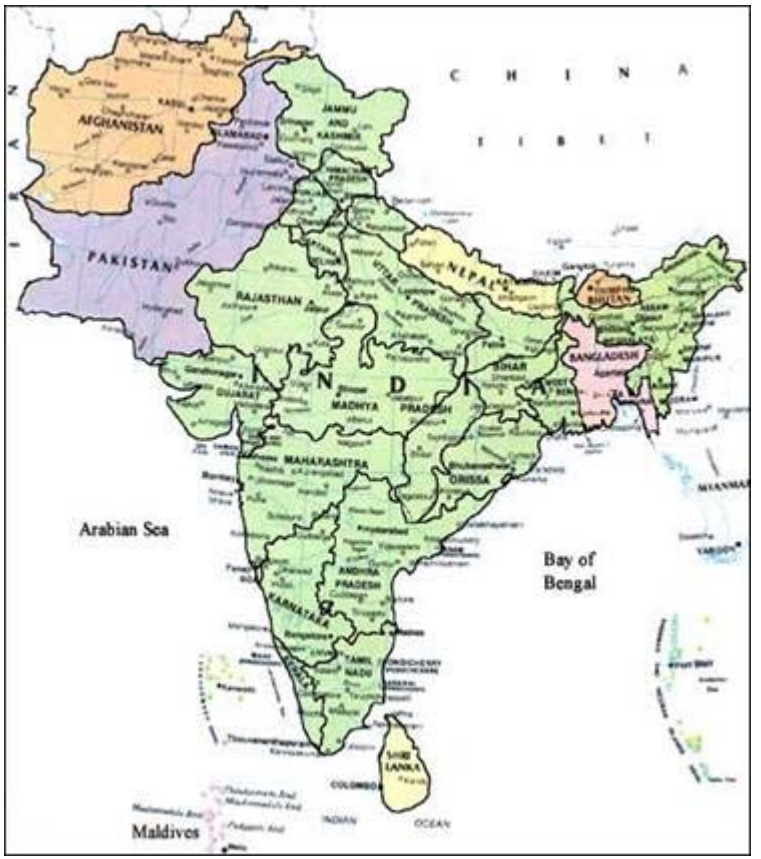
National Lipid Association
Fall Clinical Update

Shoeb J. Sitafalwalla, MD
Medical Director
South Asian Cardiovascular Center

Advocate Lutheran General Hospital
Inspiring medicine. Changing lives.

South Asian Defined

- Asian Indian
- Pakistani
- Bangladeshi
- Sri Lankan
- Nepalese



Advocate Lutheran General Hospital

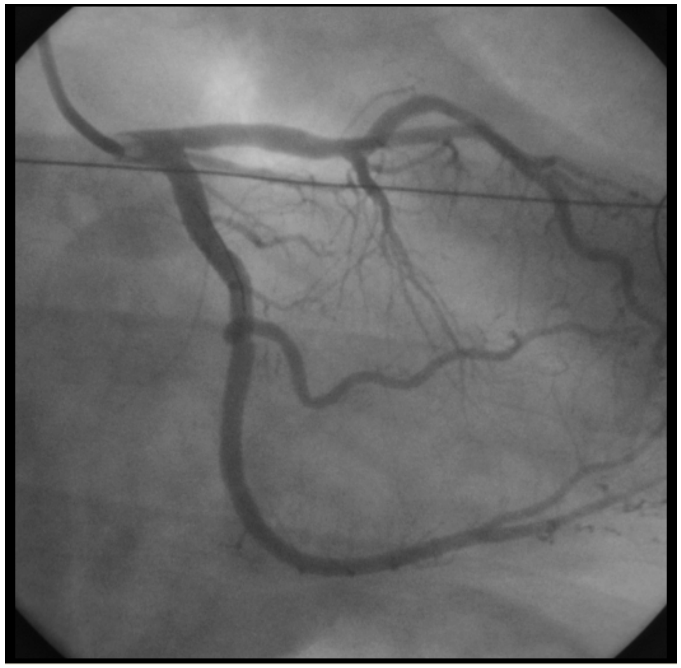
A NOT so uncommon story…

- 33 year old gentleman
- No past medical history, no tobacco, no alcohol
- Not obese with a BMI = 24
- New father with a 4 month old son
- Wife works as a nurse
- Family History: father died at 64 of a heart attack
- Presents with chest pain while driving his son to the pediatrician

Before

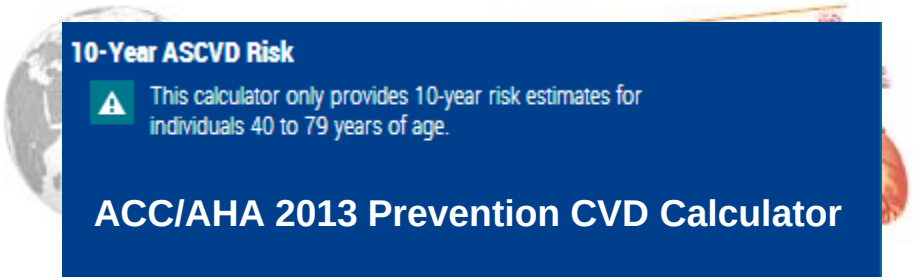


After



Framingham Risk Calculator

- **Age: 33 years old**
- **Gender: Male**
- **Total Cholesterol: 190 mg/dl**
- **HDL: 30 mg/dl**
- **Smoker: NO**
- **SBP: 130 mm Hg**

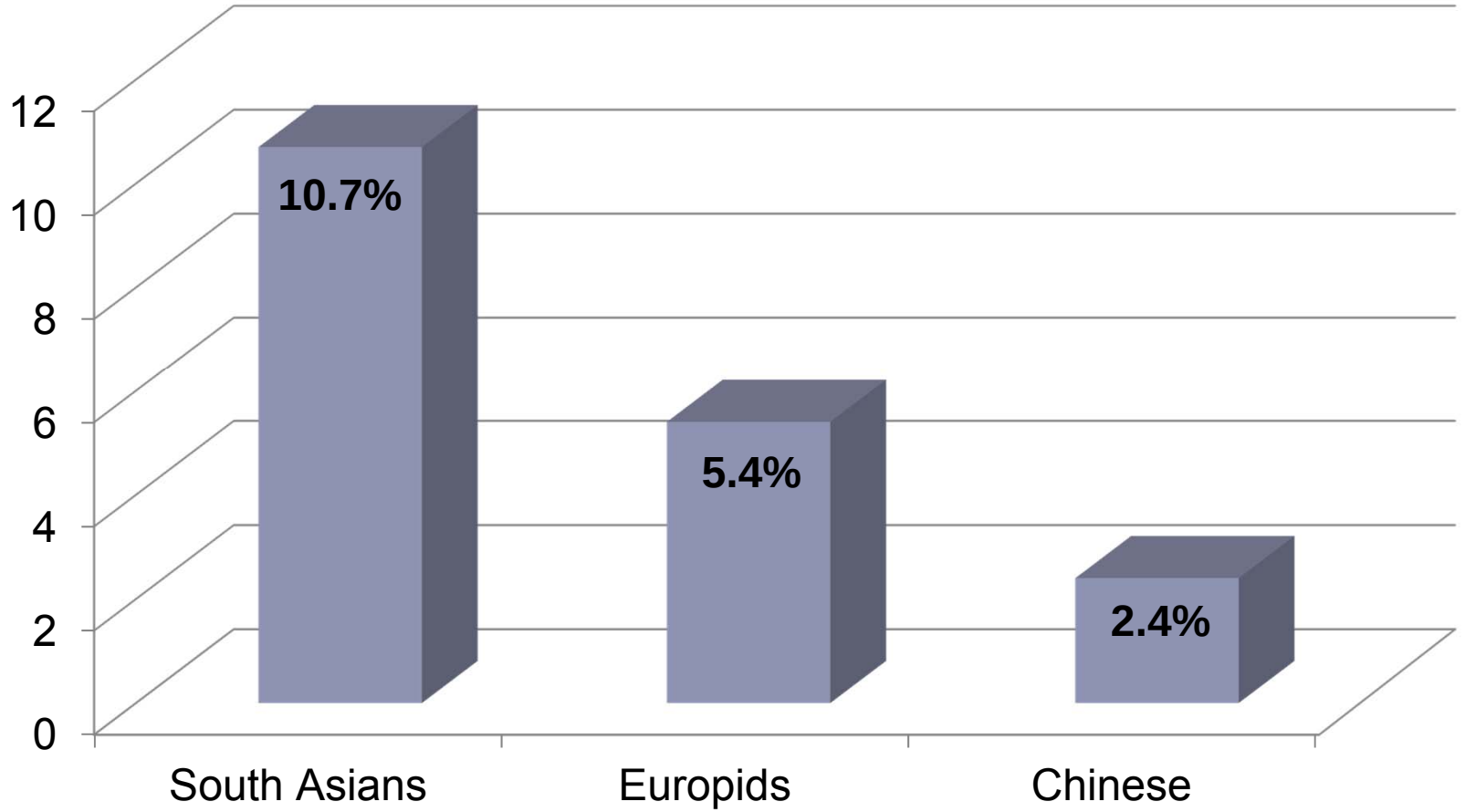


Total Risk over 10 years of having a heart attack: 1%!!!!!!

Advocate Lutheran General Hospital

Narasimhan et al, Cardiology In Review 2012

Prevalence of Cardiovascular Disease



Advocate Lutheran General Hospital

SHARE Study, Lancet 2000

Mortality from Ischemic Heart Disease in the United States

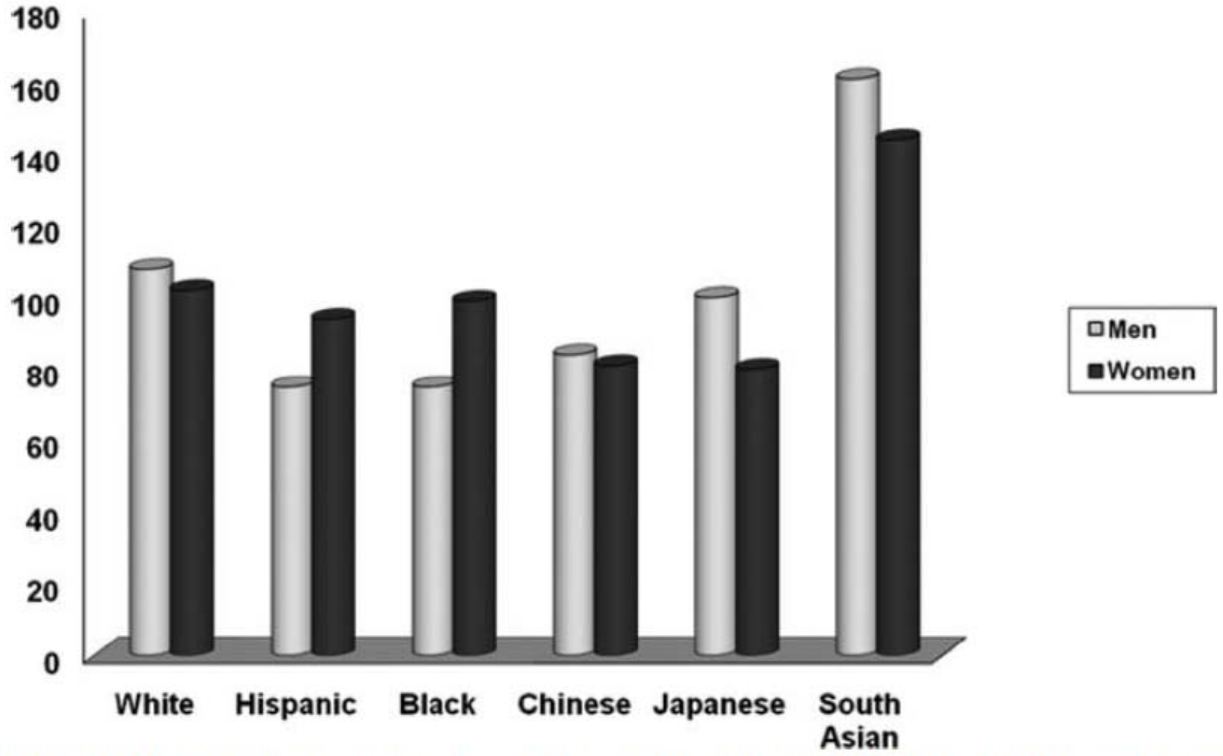
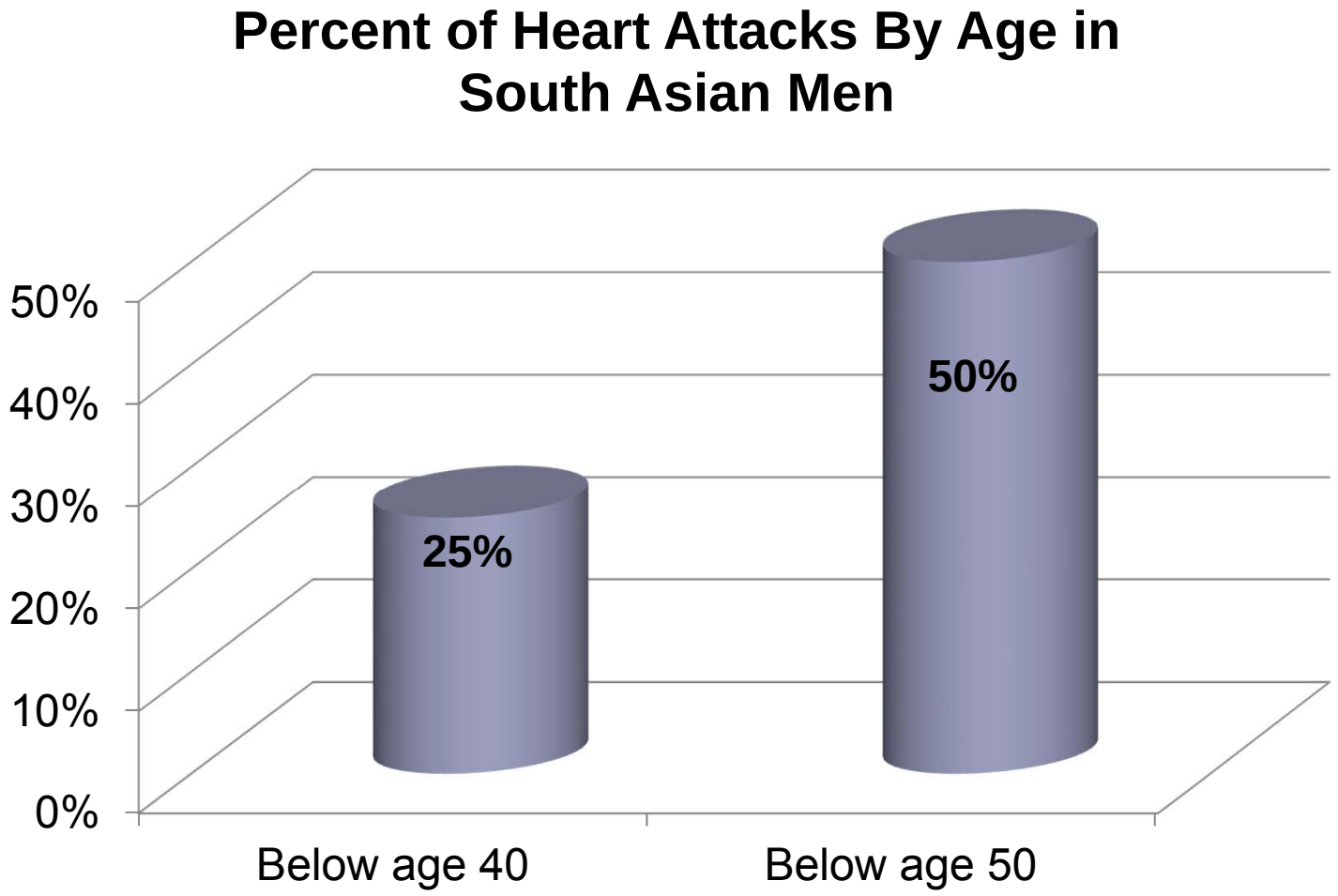


FIGURE 2. Mortality of different ethnic groups from ischemic heart disease. Reprinted with permission from *Ann Epidemiol* 2004;14:499–506.

Advocate Lutheran General Hospital

Narasimhan et al, Cardiology In Review 2012

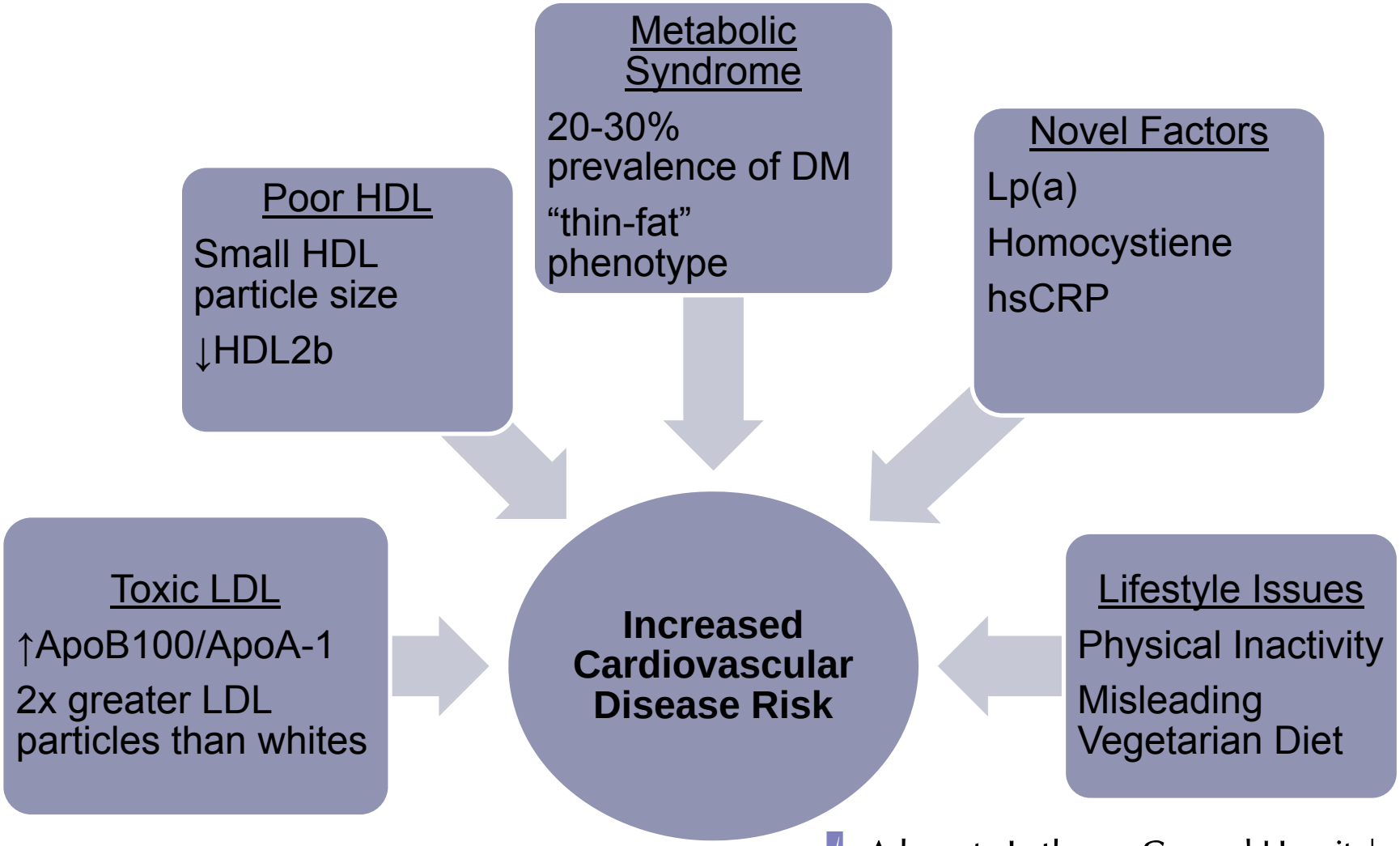
Younger and Sicker



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Sharma et al, Vascular Health & Risk Management, 2005

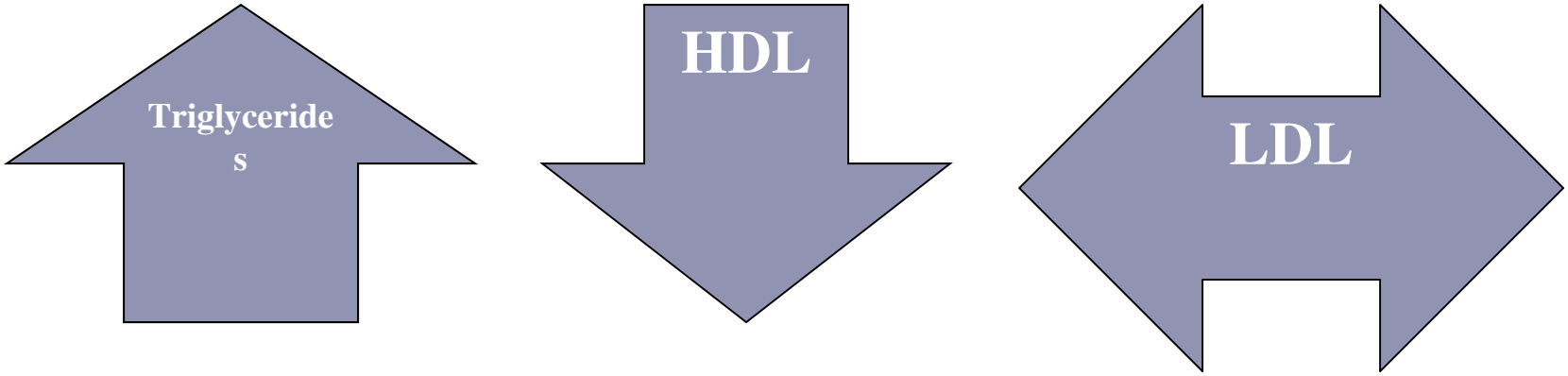
The Perfect Storm



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Gupta et al, Circulation 2006

The Classic South Asian Lipid Profile



	SHARE				SABRE							
Factor (mg/dl)	*South Asian*	European	Chinese	p	*South Asian Men*	European Men	African Caribbean Men	p	*South Asian Women*	European Women	African Caribbean Women	p
Total Cholesterol	***211.77***	184.6	183.69	0.0001	***228.2***	232	208.8	0.002	***220.4***	232	216.6	<0.001
LDL	***128.7***	123.63	122.46	0.03	***n/a***	n/a	n/a	n/a	***n/a***	n/a	n/a	n/a
HDL	***38.56***	46.41	46.41	0.0001	***42.5***	46.4	54.1	<0.001	***54.1***	61.9	61.9	<0.001
Triglycerides	***174.44***	145.96	158.42	0.005	***159.4***	132	97.4	<0.001	***124***	115	97.4	<0.001

Table 1. Compiled lipid data from Study of Health Assessment and Risk in Ethnic groups (SHARE) and Relationship Between Metabolic Risk Factors and Incident Cardiovascular Disease in Europeans, South Asians, and African Caribbeans [Southall and Brent Revisited] (SABRE) Studies.3,5 Data from SABRE Study was converted from mmol/L to mg/dl.

The Gap

NICE National Institute for Health and Care Excellence

Lipid modification

Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease

Issued: May 2008 last modified: March 2010

NICE clinical guideline 67
guidance.nice.org.uk/cg67

Introduction

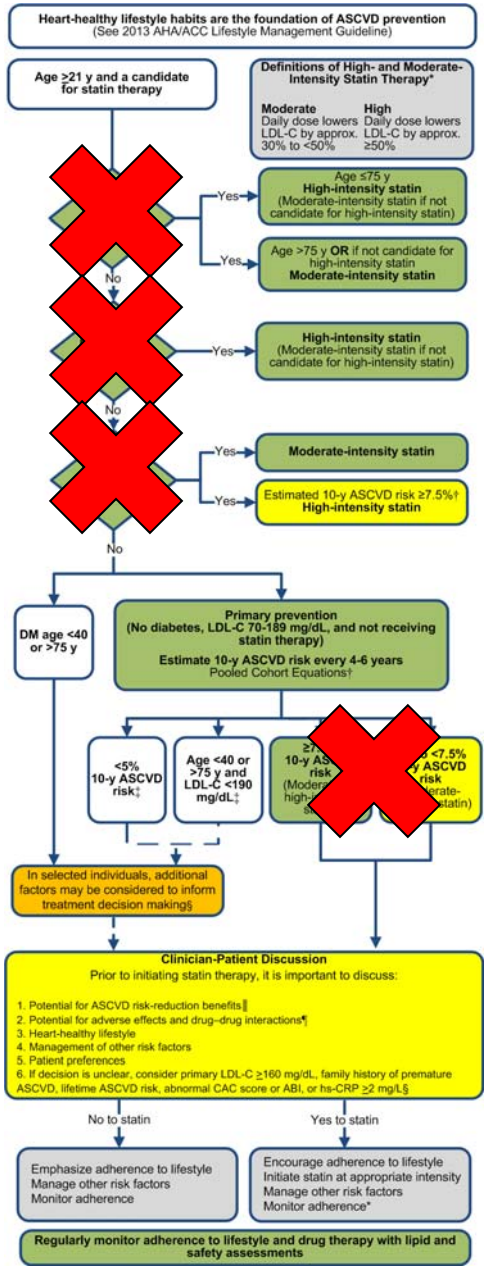
App
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Cardiovascular disease (CVD) is the leading cause of death in England and Wales. In 2005, CVD was the cause of one in three deaths, accounting for 124,000 deaths; 39,000 of those who died were younger than 75[i]. For every one fatality, there are at least two people who have a major non-fatal CVD event.

CVD predominantly affects people older than 50 and age is the main determinant of risk. Apart from age and sex, three modifiable risk factors – smoking, raised blood pressure and raised cholesterol – make a major contribution to CVD risk, particularly in combination. These account for 80% of all cases of premature coronary heart disease (CHD)[ii]. The risk of a future CVD event can be calculated from these risk factors and people at highest risk can be identified. There are also major identifiable population groups at particular risk. CVD is strongly associated with low income and social deprivation, the lifetime burden is greater in women because of their longevity and their increased risk of stroke over the age of 75[iii]. South Asian men are more likely to develop CVD at a younger age. Family history of premature CHD identifies an important group that contains people with a genetic predisposition.

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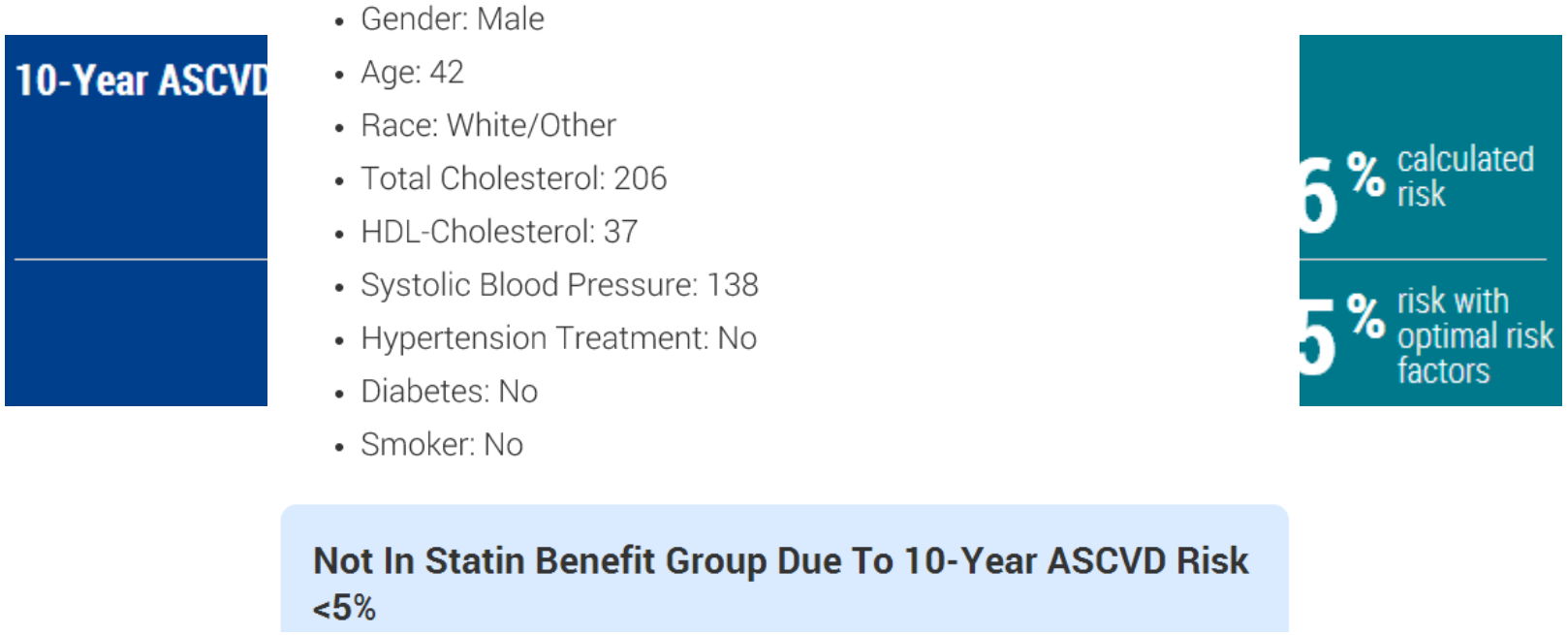
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Another not so uncommon story…

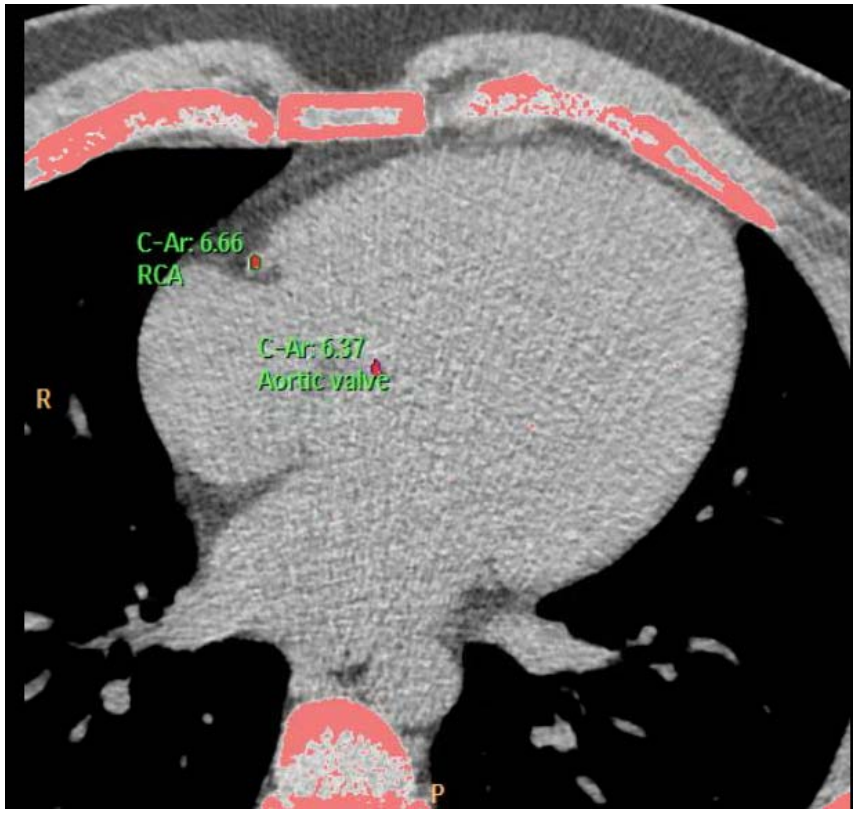
- 42 year old South Asian male
- Two young children and a wife
- Brother recently admitted for chest pain and mother with premature heart disease
- Total Cholesterol = 206 mg/dl
- LDL = 129 mg/dl
- HDL = 37 mg/dl
- Triglycerides = 199 mg/dl

Went to his Primary Care Physician

- Placed on 1000mg of Omega 3 Fish Oil
- Told to eat a heart healthy diet



SACC Evaluation



- Positive Coronary Calcium Score (132.37)
- MESA Database
  - Arterial age of 76
  - Modified risk of 30% over 10 years

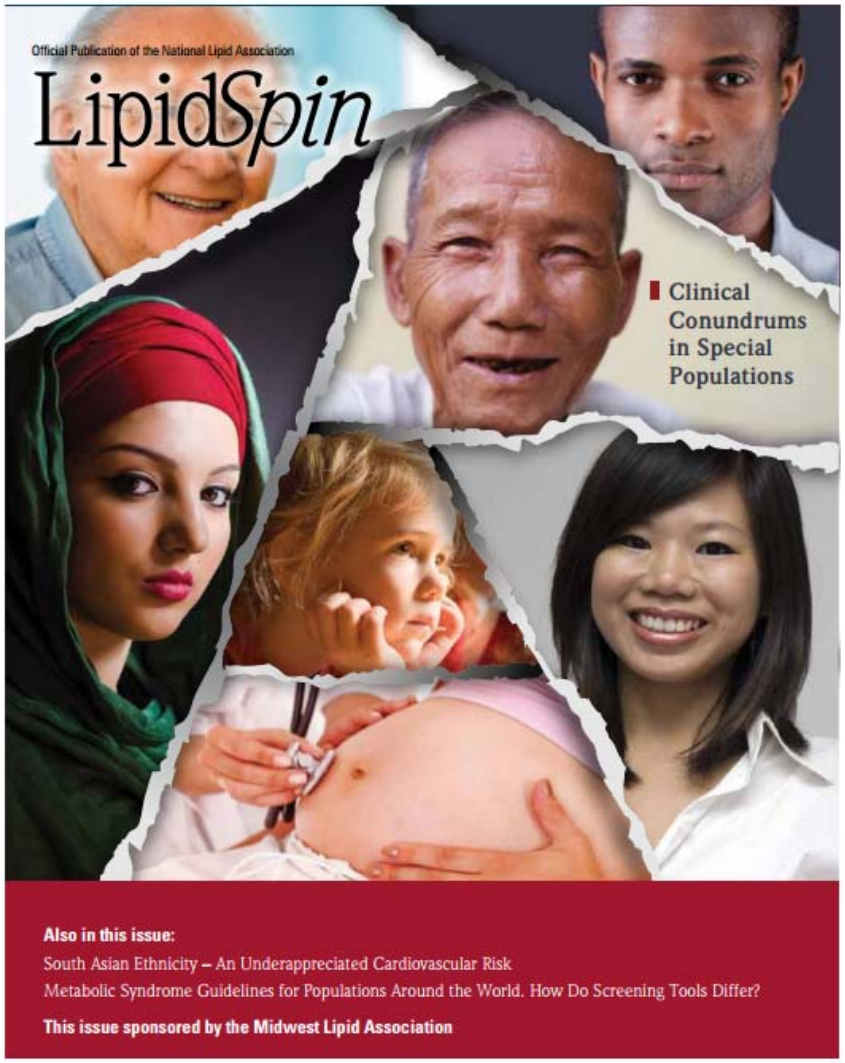
2.6% → 30%

Consider when evaluating South Asian CV risk

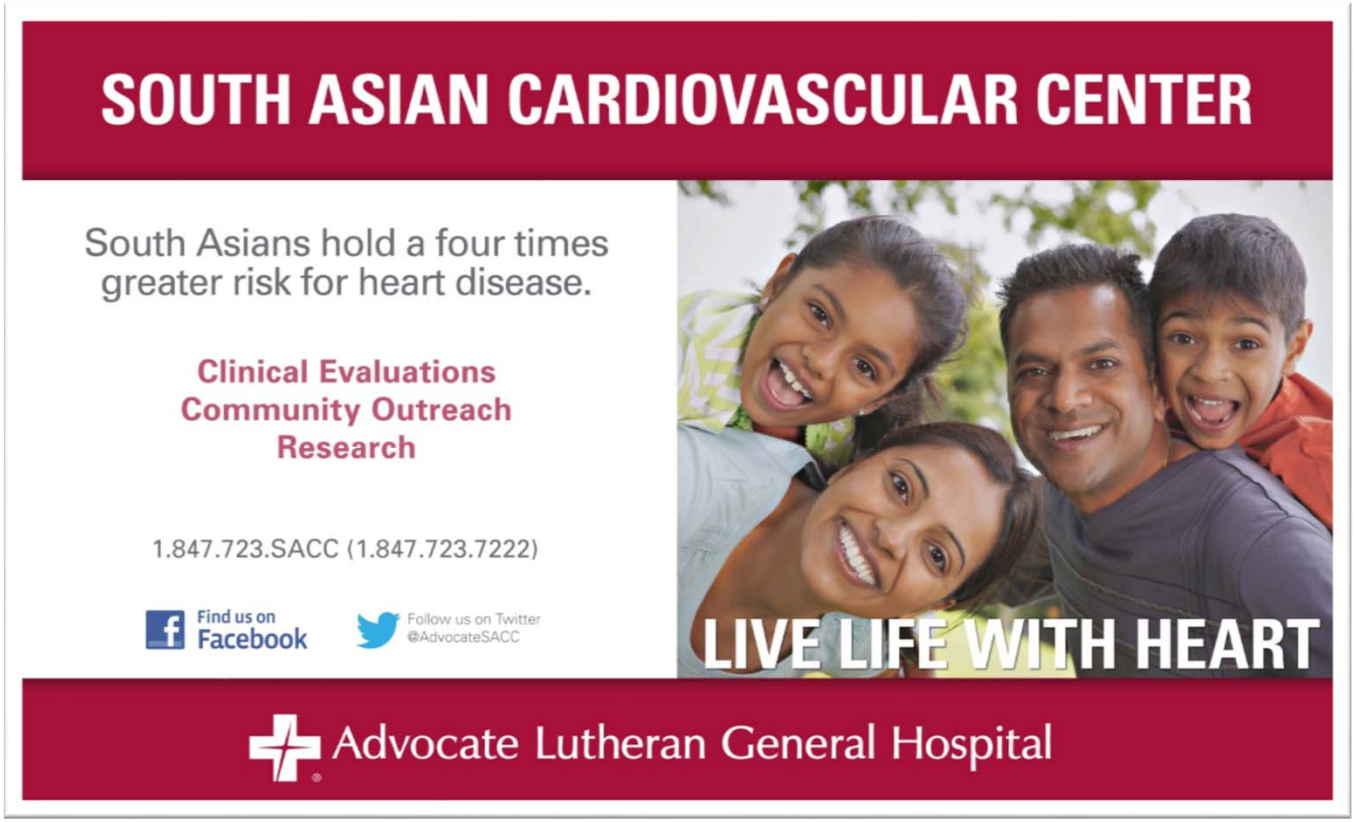
- Traditional Risk Factor Factors
- HgBa1c
- Lp(a)
- hsCRP
- Homocystiene
- ApoB/ApoA
- Coronary Calcium Score



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Thank You

Advocate Lutheran General Hospital

Hypertriglyceridemia in Children

Don P. Wilson, M.D., FNLA
Fellow, American Board of Clinical Lipidology
Director, Pediatric Cardiovascular Risk Prevention Clinic
Pediatric Endocrinology
Cook Children's Medical Center
Fort Worth, Texas

INTRODUCTION

Plasma Triglycerides (TG):

- **Are a measure of circulating triglyceride-rich lipoproteins (TRL) and their metabolic remnants.**

- **Are derived either from the diet or produced by the liver.**

Although genetic disorders that cause hyperTG are rare, significant elevations in plasma TG concentration are becoming increasingly recognized in children:

- **Who are sedentary**
- **Are overweight or obese**
- **Consume a high fat, high CHO diet**
- **For whom medications are prescribed for a variety of conditions**

In addition, there are a number of pediatric conditions that are commonly associated with hyperTG.

Common Secondary Causes of Dyslipidemia	
Condition	Screening Tests
Hypothyroidism	Free T4, TSH
Liver Diseases	CMP
Kidney Diseases	CMP / UA
Diabetes Mellitus	CMP / UA / Fasting or Random Glucose / HgbA1c
Obesity / Insulin Resistance	CMP / Fasting Glucose and Insulin
Medications	Corticosteroids, beta-blockers, bile acid resins, retinoids, oral estrogens (not transcutaneous), tamoxifen, protease inhibitors (especially ritonavir), sirolimus, asparaginase / prednisone combination therapy for ALL.

CMP=Comprehensive Metabolic Profile; UA=Urinalysis

DEFINITIONS

Abnormal serum triglyceride levels for children are generally classified on the basis of cutoff points suggested in AAP and AHA guidelines.

American Heart Association Guidelines for Primary Prevention of Atherosclerotic Cardiovascular Disease Beginning in Childhood. Circulation. 2003; 107:1562-1566.

Clinical Definition of Plasma Triglyceride Concentration			
Organization	Interpretation	nmol/L	mg/dL
2001 NCEP ATP III			
	Normal	<1.7	<150
	Borderline High	1.7-2.3	150-199
	High	2.3-5.6	200-499
	Very High	>5.6	≥500
2012 Endocrine Society			
	Normal	<1.7	<150
	Mild	1.7-2.3	150-199
	Moderate	2.3-11.2	200-999
	Severe	11.2-22.4	1000-1999
	Very Severe	>22.4	≥2000
2014 National Lipid Association			
	Normal	<1.7	<150
	Borderline High	1.7-2.3	150-199
	High	2.3-5.6	200-499
	Very High	>5.6	≥500
AAP /AHA			
0-9 years of age	Acceptable		<75 mg/dL
	Borderline		75-99 mg/dL
	High		>100 mg/dL
10-19 years of age	Acceptable		<90 mg/dL
	Borderline		90-129 mg/dL
	High		>130 mg/dL

NCEP=National Cholesterol Education Program Adult Treatment Panel III;
AAP= American Academy of Pediatrics; AHA= American Heart Association

Modified from: www.thelancet.com/diabetes-endocrinology Published online December 23, 2013 http://dx.doi.org/10.1016/S2213-8587(13)70191-8

Distribution of Triglycerides for Males and Females 5-19 years of age

Mean concentration of triglycerides (mg/dL) in males and females 5-19 years of age.						
Percentile	Males			Females		
	5-9 yrs	10-14 yrs	15-19 yrs	5-9 yrs	10-14 yrs	15-19 yrs
50th	48	58	68	57	68	64
75th	58	74	88	74	85	85
90th	70	94	125	103	104	112
95th	85	111	143	120	120	126
Adapted from the Lipid Research Clinic Pediatric Prevalence Study.						

Tamir I, Heiss G, Glueck CJ, Christensen B, Kwiterovich P, Rifkind B. Lipid and lipoprotein distributions in white children ages 6–19 yrs: the Lipid Research Clinics Program Prevalence Study. J Chronic Dis. 1981; 34(1):27–39

NHANES - 1999 to 2006

The prevalence of triglyceride levels > 150 mg/dL among all youths 12 to 19 years of age was 10.2%.

- **Boys 11.4%**
- **Girls 8.8%**

US Department of Health and Human Services, Centers for Disease Control and Prevention. Prevalence of abnormal lipid levels among youths: United States, 1999–2006. Morbidity and Mortality Weekly Report. 2010; 59:2.

Weight Category	TG >150 mg/dL
Normal (BMI 5th - 85th %)	5.9%
Overweight (BMI 85th - 94th %)	13.8%
Obese (BMI ≥ 95th %)	24.1%
Race / Ethnicity	
White, non-Hispanic	12.1%
Hispanic	9.3%
Black, non-Hispanic	3.7%

US Department of Health and Human Services, Centers for Disease Control and Prevention. Prevalence of abnormal lipid levels among youths: United States, 1999–2006. Morbidity and Mortality Weekly Report. 2010; 59:2.

NHANES -1999 to 2008

Triglyceride Levels in Children 12 to 19 Years of Age				
TG Concentration	**Normal**	**Mild-Mod**	**High**	**Missing**
Triglyceride Levels (mg/dL)	**<150**	**150-499**	**> 500**	
Sample (n)	2872	316	3	57
Weighted to US population (n)	29,168,008	3,464,483	59,946	465,332
Weighted % for each category	88.0%	10.5%	0.2%	1.4%
Abbreviations: NHANES, National Health and Nutrition Examination Survey.				

Christian JB, et al. Prevalence, Characteristics, and Risk Factors of Elevated Triglycerides in US Children. Clinical Pediatrics 2011; 50(12):1103-1109.

ETIOLOGY

Hypertriglyceridemia in childhood can be classified as:

- **Genetic**
- **Acquired**
- **Genetic and Acquired**

ETIOLOGY

Genetic abnormalities of triglyceride metabolism (LPL, APOC2, APOA5, LMF1,GPIHBP1 and GPD1), are rare and generally diagnosed soon after birth.

Copenhagen General Population Study

Subjects: >70,000 Adults Age: >20 years			Multigenic* and Small-Effect Variants							Can be Monogenic**					
% Popn	26%	46%	28%							0.1%					
Triglycerides															
mmol/L	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
mg/dL	<88	88-177	177-797							797-1329					
HyperTg			<-------- Mild to High -------->							<---------- Severe ---------->					
Risk			Increase in CVD							Chylomicronemia Pancreatitis CVD Risk Less Likely					

*LPL, APOA5, GCKR, APOB, LMF1, GPIHBP1, CREBH1, APOC2, APOE
**LPL, APOC2, APOA5, LMF1, GPIHBP1 AND GPD1

Modified from: Hegele, RA et al. The polygenic nature of hypertriglycerideaemia: implications for definitions, diagnosis, and management. www.thelancet.com/diabetes-endocrinology. Published online December 23, 2013 http://dx.doi.org/10.1016/S2213-8587(13)70191-8

CLASSIFICATION

Historically disorders that cause hyperTG have been classified by the electrophoretic patterns of lipoprotein fractions (Fredrickson Classification).

The polygenic nature of most hyperTG states, however, precludes a meaningful classification based on genetic mutations.

Diagnosis	Fredrickson Classification	Primary Lipid Change	Primary Lipoprotein Change	Genetics
Familial Hyperchylomicronemia	Type 1	↑TG	↑Chylomicrons	**Monogenic**; autosomal recessive due to 2 mutant alleles of *LPL, APOC2, APOA5, LMF1, GPIHBP1*, or *GPD1*; presentation mainly in pediatric or early adulthood.
Familial Hypercholesterolemia	Type 2A	↑TC	↑LDL	Monogenic; autosomal codominant; heterozygous form results from 1 mutant allele of *LDLR*, *APOB*, or *PCSK9*; homozygous form results from 2 mutant alleles of these genes or of *LDLRAP1* (recessive).
Familial Combined Hyperlipoproteinemia	Type 2B	↑TC, ↑TG	↑VLDL, ↑LDL	**Polygenic**; high GRS* for hypertriglyceridemia; excess of rare variants in hypertriglyceridemia-associated genes; high GRS for LDL cholesterol.
Dysbetalipoproteinemia	Type 3	↑TC, ↑TG	↑IDL	**Polygenic**; high GRS for hypertriglyceridemia; excess of rare variants in hypertriglyceridemia-associated genes; *APOE E2/E2* homozygosity; or heterozygous rare mutations in *APOE*.
Primary Hypertriglyceridemia	Type 4	↑TG	↑VLDL	**Polygenic**; high GRS for hypertriglyceridemia; excess of rare variants in hypertriglyceridemia-associated genes.
Mixed Hypertriglyceridemia	Type 5	↑TC, ↑TG	↑VLDL, ↑Chylomicrons	**Polygenic**; high GRS for hypertriglyceridemia; excess of rare variants in hypertriglyceridemia-associated genes, with higher burden of risk alleles than for hyperlipoproteinemia type 4.

*GRS=polygenic genetic risk score

Adapted from: Hegele RA. Plasma lipoproteins: genetic influences and clinical implications. Nat Rev Genet 2009; 10:109-21.

Risk Factors for HyperTG in Childhood

In clinical practice hyperTg is most commonly encountered in children and adolescents who are:

- **Obese (BMI $\geq$ 95th %)**
- **Insulin resistance, clinically manifest by the presence of acanthosis nigricans, impaired or elevated fasting glucose, hypertension, and in girls, polycystic ovarian syndrome (PCOS)**

Risk Factor Tracking

Risk Factor	Tracking *	Comments
Obesity	Yes	BMI>99th %; 100% Obese as an adult BMI 95th – 99th %; 85% Obese as an adult
Risk Factor Clustering**	Yes	Insulin resistance Elevated triglycerides Reduced HDL-C Elevated blood pressure

* Childhood into Adulthood
** Obesity and Metabolic Syndrome

Adapted from: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, & National Heart, Lung, and Blood Institute, (2011). Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics, 128 Suppl 5, S213-56.

Clinical Manifestations

Clinical Manifestations of hyperTG

- **Pancreatitis**
- **Premature Cardiovascular Disease**

Pancreatitis

Pancreatitis is the most frequent acute complication described in individuals with severe hyperTG.

The literature suggests that fasting levels of TG > 500 mg/dL increases the risk of pancreatitis, although data to support the exact level of TG that precipitates pancreatitis is lacking.

Pancreatitis

Brunzell found that triglyceride-induced pancreatitis occurred at plasma levels >2000 mg/dl, but not if levels were maintained <2000 mg/dL.

He, therefore, recommended that TG <1000 mg/dL be used as a threshold for preventing pancreatitis.

Brunzell JD, Bierman EL. Med Clin North Am 66(2)455-68,1982.
Sandhu S et al. Lipids in Health and Disease 10:157,2011.

HyperTG and CVD Risk

Although the consequences of atherosclerotic CVD are seen only rarely in children, the early pathophysiological changes in arteries begin soon after birth and accelerate during adolescence.

HyperTG and Lifetime CVD Risk

There is evidence to suggest that elevated TG levels in childhood may be associated with atherosclerotic risk and subsequent cardiovascular events in adulthood.

Sarwar N, et al. Triglyceride and risk of coronary heart disease. Circulation 115; 450 - 458, 2007.

Frontini MG, Srinivasan SR, Xu J, Tang R, Bond MG, Berenson GS. Usefulness of childhood non-high density lipoprotein cholesterol levels versus other lipoprotein measures in predicting adult subclinical atherosclerosis: the Bogalusa Heart Study. Pediatrics 2008;121:924-9.

HyperTG and Lifetime CVD Risk

The Bogalusa Heart Study found that serum concentrations of TG, total cholesterol (TC), and LDL cholesterol in children and young adults (aged 2 to 39 years) were associated with lesions in the coronary arteries and aorta at autopsy.

Berenson GS, Srinivasan SR, Bao W, Newman WP III, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults: the Bogalusa Heart Study. N Engl J Med.1998;338: 1650-1656.

HyperTG and Lifetime CVD Risk

The lifetime role of TG in atherogenic particle formation is supported by gene variants associated with classic hypertriglyceride phenotypes (IIb,III,IV,and V), whose expression is increased by hepatic fat deposition and insulin resistance.

HyperTG and Lifetime CVD Risk

The association of lifetime TG lowering providing protection from CVD is evident in recent studies on loss of function APOC-III mutations.

As compared with non-carriers, carriers of any of four APOC3 mutations had:

- **↓ Triglyceride levels (39%)**
- **↓ LDL cholesterol levels (16%)**
- **↓ APOC3 levels (46%)**
- **↑ HDL cholesterol levels (22%)**

The risk of coronary heart disease was reduced 40%.

The New England Journal of Medicine 2014;371:22-31.

HyperTG and Lifetime CVD Risk

TG, non-HDL-C, apoB and apoB:apoA-I ratio all predict carotid IMT after more than 20 years of follow-up.

Non-HDL-Cholesterol is superior to TG.

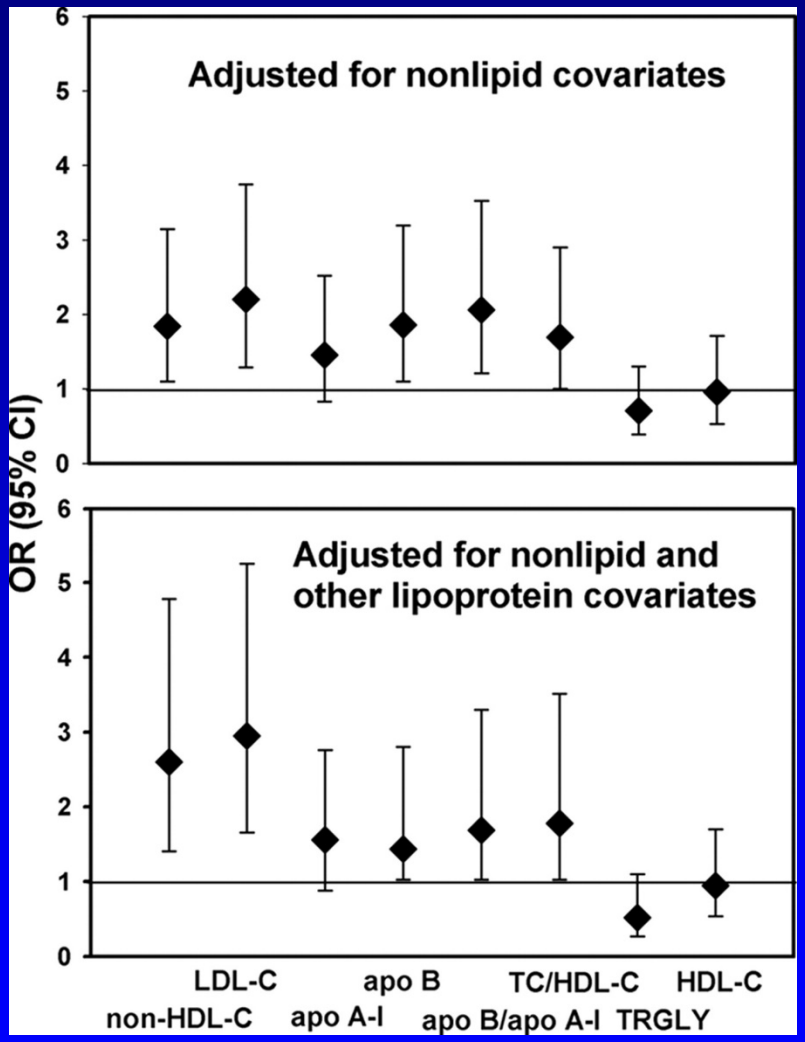
Circulation 2010;122:2514-20.
Pediatrics 2008;121:924-9.

HyperTG and Lifetime CVD Risk

Thus the combined effects of genetic and environmental factors, beginning before birth, promote insulin resistance and associated dyslipidemia, leading to early adult disease.

Nature Reviews Cardiology 2013;10:648-61.
Diabetologia 2006;49:755-65.
Journal of the International Association for the Study of Obesity 2000;24:330-9.
Journal of Clinical Lipidology 2013;7:65-81.

ORs and 95% CI for having excess adulthood carotid IMT (top versus bottom 9 deciles) by childhood lipoprotein measures (top versus bottom 3 quartiles) in the Bogalusa Heart Study cohort.



Frontini M G et al. Pediatrics 2008;121:924-929

©2008 by American Academy of Pediatrics

PEDIATRICS®

HyperTG and Lifetime CVD Risk

Similar to adult meta-analysis, adjustment for established risk factors attenuate the association of TG with CVD evident in young adults with carotd IMT thickening.

Circulation 2007;115:450-8.

HyperTG and Lifetime CVD Risk

- Pediatric studies rely on surrogate markers, not hard end points.
- The prolonged time between initial detection of hyperTg and a CVD event.
- HyperTG is generally accompanied by atherogenic particles, best measured by non HDL-cholesterol, making direct causality difficult to prove.

Treatment of Hypertriglyceridemia

TG (mg/dL)	Normal	Mild-Moderate	High	Severe
	<150	**150-499**	**500-999**	**>1000**
Goal	Health Maintenance	CVD Risk Prevention	Avoid Pancreatitis	
Rx Target	TG < 150	Non HDL-C < 130	Triglycerides < 150	
Diet				
Fat*	25-30%	25-30%	15-30%	<10-15%
CHO*	55-60%	Avoid Excessive Consumption		
TG Lowering Rx				
	None	Consider statin as 1st line therapy	Consider Fibrate;O3FA;Niacin	Usually ineffective

* % of daily kcal/EER

TREATMENT
Acquired HyperTG

Individuals with acquired disorders, such as obesity and diabetes, should be encouraged to maintain a healthy weight as well as restrict excessive calories, fat and refined carbohydrate in their diet.

TREATMENT
Lifestyle Modifications

Depending upon the clinical context, lifestyle modifications can collectively decrease plasma triglyceride concentrations by up to 60%.

Int. J. Obes. Relat. Metab. Disord. 21 (Suppl. 1), S5-S9 (1997).
Am. J. Clin. Nutr. 56, 320-328 (1992).

TREATMENT
Acquired HyperTG

Alcohol and medications known to increase triglycerides, such as estrogens and glucocorticoids, should be avoided if possible.

Drug Therapy for HyperTG

Table 3. Summary of Dyslipidemic Agent Use by Triglyceride Levels and Age using i3 InVision Data Mart Database

TG Levels (mg/dL)	Niacin (%)[a]	Statin (%)[a]	Fibric Acid (%)[a]	Lovaza (%)[a]	No Treatment
Total	n = 120	n = 433	n = 126	n = 42	n = 64 578
<150	73.3	50.4	10.3	35.7	80.9
150-499	26.7	46.2	65.9	45.2	18.7
500+	0	3.5	23.8	19.1	0.3
5-11 years	n = 0	n = 51	n = 2	n = 4	n = 14 983
<150	0	66.7	0	25.0	84.5
150-499	0	33.3	100.0	75.0	15.3
500+	0	0	0	0	0.2
12-19 years	n = 120	n = 382	n = 124	n = 38	n = 49 595
<150	73.3	48.2	10.5	36.8	79.8
150-499	26.7	47.9	65.3	42.1	19.8
500+	0	3.9	24.2	21.0	0.4

[a]The sum of the percentages may not equal 100% because of rounding, and/or patients may be counted more than once if they have used more than one dyslipidemic agent.

Triglycerides >150 mg/dl
5-11 years of age = 0.1%
12-19 years of age = 0.7%

Jennifer B. Christian, Maneesh X. Juneja, Amy M. Meadowcroft, Spencer Borden and Kimberly A. Lowe. Prevalence, Characteristics, and Risk Factors of Elevated Triglyceride Levels in US Children. CLIN PEDIATR 2011 50(12): 1103-1109.

Drug Therapy for HyperTG

Table 4. Summary of Triglyceride Levels by Dyslipidemic Agent Use and Age using i3 InVision Data Mart Database

	TG Levels (mg/dL), Total (%)[a]			TG Levels (mg/dL), 5-11 years (%)[a]			TG Levels (mg/dL), 12-19 years (%)[a]		
	<150	150-499	500+	<150	150-499	500+	<150	150-499	500+
Total	n = 52587	n = 12414	n = 257	n = 12699	n = 2308	n = 32	n = 39888	n = 10106	n = 225
Niacin	0.2	0.3	0	0	0	0	0.2	0.3	0
Statin	0.4	1.6	5.8	0.3	0.7	0	0.5	1.8	6.7
Fibric acid	0	0.7	11.7	0	0.1	0	0	0.8	13.3
Lovaza	0	0.2	3.1	0	0.1	0	0	0.2	3.6
No treatment	99.4	97.5	84.0	99.7	99.1	100.0	99.3	97.1	81.8

[a]The sum of the percentages may not equal 100% because of rounding, and/or patients may be counted more than once if they have used more than one dyslipidemic agent.

Jennifer B. Christian, Maneesh X. Juneja, Amy M. Meadowcroft, Spencer Borden and Kimberly A. Lowe. Prevalence, Characteristics, and Risk Factors of Elevated Triglyceride Levels in US Children. CLIN PEDIATR 2011 50(12): 1103-1109.

TREATMENT
Severe HyperTG

While lipid lowering medications are generally not effective, triglycerides can be substantially lowered by restricting dietary fat to <15% of the total daily caloric intake.

Effective treatment requires strict, life-long adherence to a very low fat diet.

TREATMENT
Severe HyperTG

Adequate intake of linoleic acid and fat soluble vitamins (A, D, E, and K) should be monitored.

Supplemental medium chained triglycerides (MCT) may be beneficial in providing additional calories and improving compliance.

Novel Therapies for Treatment of HyperTG

Several novel therapies for treatment of hyperTG are in development.

These agents increase clearance or reduce the production of TRLs.

Agent	Target	Secretion	Catabolism	Expected mean reduction in TG
Dual PPAR α/δ agonist	Liver, Muscle, Adiocytes	Decreased	Increased	30
CETP inhibitor	Plasma	=	Increased	20
MTP inhibitor	Liver, Enterocyte	Decreased	=	30
DGAT-1 inhibitor	Liver, Enterocyte, Adipocytes	Decreased	=	40
DGAT-2 inhibitor	Liver	Decreased	=	40
ANGPTL inhibitor	Muscle, Adipocytes	=	Increased	40
ApoB antisense	Liver	Decreased	=	30
ApoC-III antisense	Liver	=	Increased	40
PCSK9 inhibitor	Liver	Uncertain	Increased	15
LPL gene replacement	Muscle, Adipocytes	=	Increased	40

Modified from: Hegele, RA et al. The polygenic nature of hypertriglycerideaemia: implications for definitions, diagnosis, and management. www.thelancet.com/diabetes-endocrinology Published online December 23, 2013 http://dx.doi.org/10.1016/S2213-8587(13)70191-8

Novel Therapies for Treatment of HyperTG

Their clinical efficacy, cost-effectiveness, and indications, especially in children, are yet to be established.

Hypertriglyceridemia in Children Summary

Although monogenic causes are rare, significant elevations in plasma TG concentration are becoming increasingly recognized in children.

Hypertriglyceridemia in Children Summary

Obesity and insulin resistance, the most common cause of hyperTG in children, are frequently associated with high levels of TG, a low HDL-C and small dense LDL-C.

Non HDL-C is a clinically useful tool to measure these atherogenic particles.

Hypertriglyceridemia in Children Summary

Severe hyperTG (>1000 mg/dL) may cause acute pancreatitis, while mild to moderate elevations (150-499 mg/dL) may increase risk of premature CVD.

Triglycerides & Pregnancy

- Robert A Wild MD,MPH,PHD
- Professor Ob/Gyn , Clinical Lipidology
- Oklahoma University Health Sciences Center
- VA Medical Center, Oklahoma City
- Past President SWLA,
- Executive Committee NLA
- ABCL Board

The University of Oklahoma Health Sciences Center

OU Medicine

Triglycerides & Pregnancy



OUTLINE

- Implications of dyslipidemia in pregnancy
- Pre-Pregnancy screening and CVD risk management
- Lipids in Pregnancy
  - Normal changes
  - Abnormal changes
  - Pathological disorders
- Post Pregnancy Considerations

PRE PREGNANCY

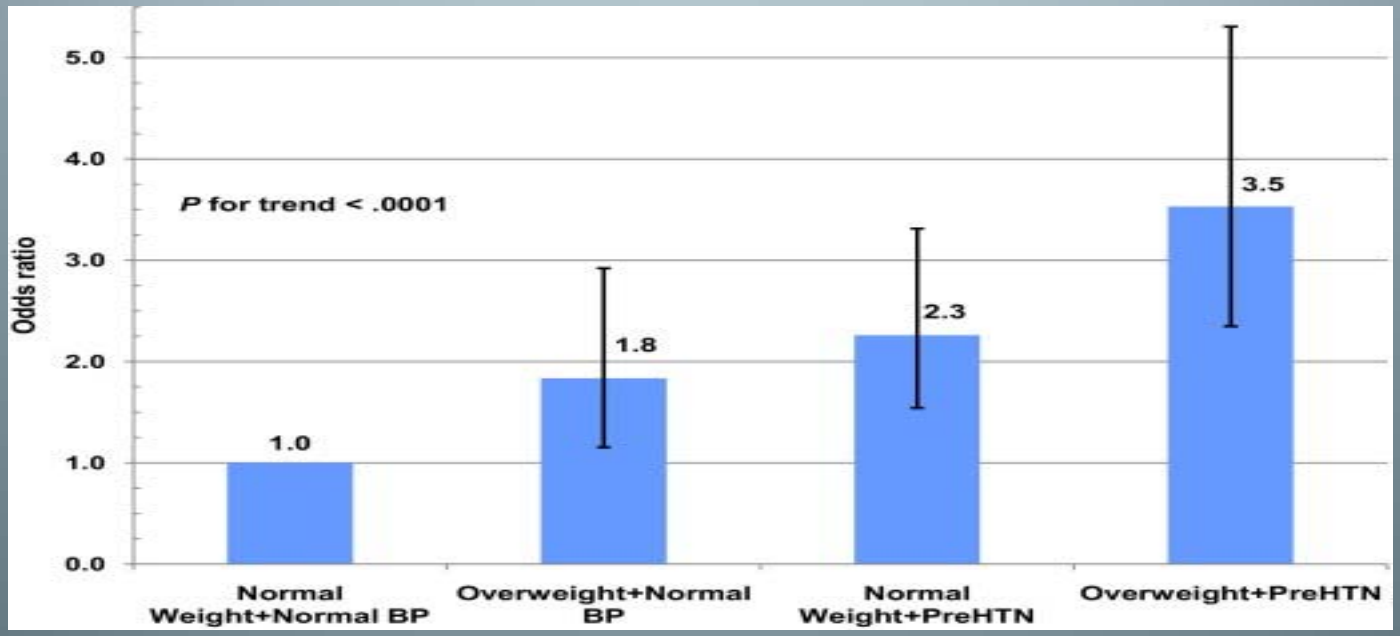
Prevalence of CVD Risk Factors Among Women of Reproductive Ages, 20–44, 1999–2008

	%(95% CI)
Diabetes	2.4(2.0-2.9)
Hypertension	7.7(6.9-8.5)
Obesity - BMI category (Kg/m^2)	
<25	**Only 42.4(40.3-44.5)!!!!**
25-<30	25.9(24.3-27.7)
30-<35	16.2(15.0-17.6)
≥35	25.4(23.6-27.2)
Tobacco Use	25.4(23.6-27.2)
C K Disease	2.9(2.4-3.5)

NHANES 1999-2012

N=3,380 Kaiser Permanente

Risk of hypertensive disorders of pregnancy



Pre-pregnancy cardiometabolic and inflammatory risk factors and subsequent odds of a hypertensive disorder in pregnancy

Hedderson,MM et al 2012 Am J Obstet Gynecol 207(1);68

How well do we screen?
N=3,015 National repr sample

- 61% of women reported Gyn or Ob visit in past year
  - regardless of income - lack of time is why they can't go to the doctor
- More women than men forgo health care because of cost
- Largest burden is with the uninsured
  - Work place feasibility, sick leave, child care, no transportation
- **Rates of screening Lipids**
  - **58% 18-44yo , 78% 45-64 yo**
- Lower than for bp screening

2013 Kaiser W Health Survey May 2014

Missed opportunities for preventive health care

- Women's Health care **"Patchwork quilt with gaps"**
- National Health Interview Survey
  - Of Women ages 18-64
    - 15% seen by general medical physicians
    - 62% Gynecologists alone
    - 23% both

    Those seen by GYN receive more counseling and preventive services

Ehrenthal, DB Curr Opin Cardiol 2013

Missed opportunities for preventive health care

- (2 health care plans - 3.6 million members)
  - New DX hypertension
- **Hypertension recognized < 1/3 in course of care!**
- Dx ½ as likely by Ob/Gyn
- Rural setting obese women more likely to have counseling for CVD risk reduction
- **< 70% had lipid screening**, nutrition counsel, weight management - **regardless of specialty!**

Ehrenthal,DB Curr Opin Cardiol 2013

Missed opportunities for preventive health care

- Recent Title X clinic screening for CVD risk
  - Protocol driven
  - Majority of women in need of referral for hypertension,diabetes,dyslipidemia, smoking and dyslipidemia received them
- However **few women were able to complete the referrals or participated in risk reduction strategies**
- A better understanding of barriers to referral care among low-income women is needed!

Ehrenthal,DB Curr Opin Cardiol 2013

Missed opportunities for preventive health care

- Majority of Ob/Gyns go beyond reproductive care
  - knowledge , skill deficits, liability concerns, barriers of practice structure - difficulty getting 1^{O} care referrals !
- More Ob/Gyns likely to recommend follow up testing for diabetes than primary care physicians (Internists, Fam Med, DO)
- Nearly all primary care providers screen for CVD risk
- 70% of Ob/Gyns screen consistently
- **Limited knowledge about Preeclampsia and future CVD risk - all specialties!**

Ehrenthal,DB Curr Opin Cardiol 2013

Pg. rates for women 25-29 have not changed!

Rates for women in their 30s to 40s have increased!

National Vital Statistics Reports

Volume 60, Number 7 June 20, 2012

Estimated Pregnancy Rates and Rates of Pregnancy Outcomes for the United States, 1990–2008

by Stephanie J. Ventura, M.A., Sally C. Curtin, M.A., Joyce C. Abma, Ph.D., Division of Vital Statistics; and Stanley K. Henshaw, Ph.D., The Guttmacher Institute

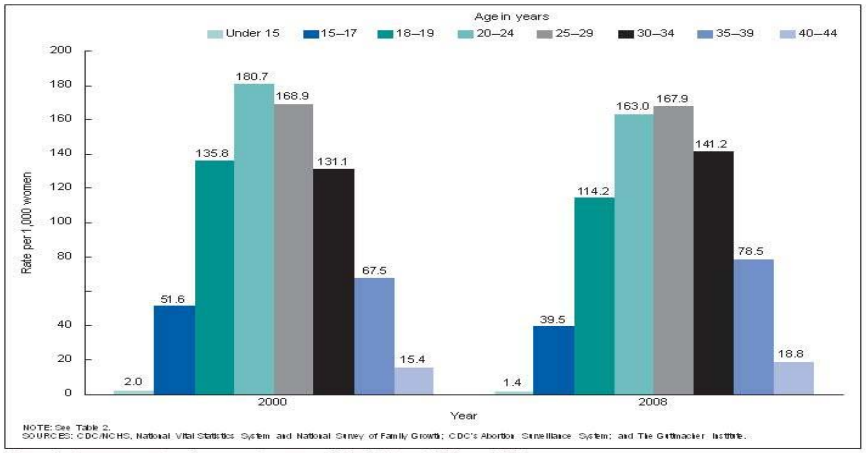


Figure 1. Pregnancy rates, by age of woman: United States, 2000 and 2008

Childbearing and Obesity in Women: Weight Before, During, and After Pregnancy

- **US women 35-44 yo - greatest increase in prevalence of obesity in past 45 yrs!**
  - **Associated Hypertriglyceridemia!**
- **45% of women begin Pg. overweight or obese**
  - **Up from 24% in 1983!**
- **43% of PG women gain more weight than is recommended**
- **Maternal overweight and obesity most common hi-risk OB condition**
  - **Gestational diabetes, hypertensive disorders, newborn macrosomia , perinatal complications**

Gunderson, E Obstet Gynecol Clin North Am 2009 36(2) : 317-28

Fertility and Dyslipidemia Window of Opportunity

- Maximum fertility both genders is 23 yrs.
- By Age 32 it begins to decline
- This is a wonderful opportunity (9 years) for Preventing CVD risk in Pg or for their offspring by lifestyle and/or meds – **in motivated people!**
- It takes time to affect change and CVD Risk Factors
  - Obesity (low HDL , Hi TG, high nonHDL Cholesterol)
  - Dyslipidemia
  - Smoking
  - BP

Fetal Considerations

When does metabolic syndrome begin?

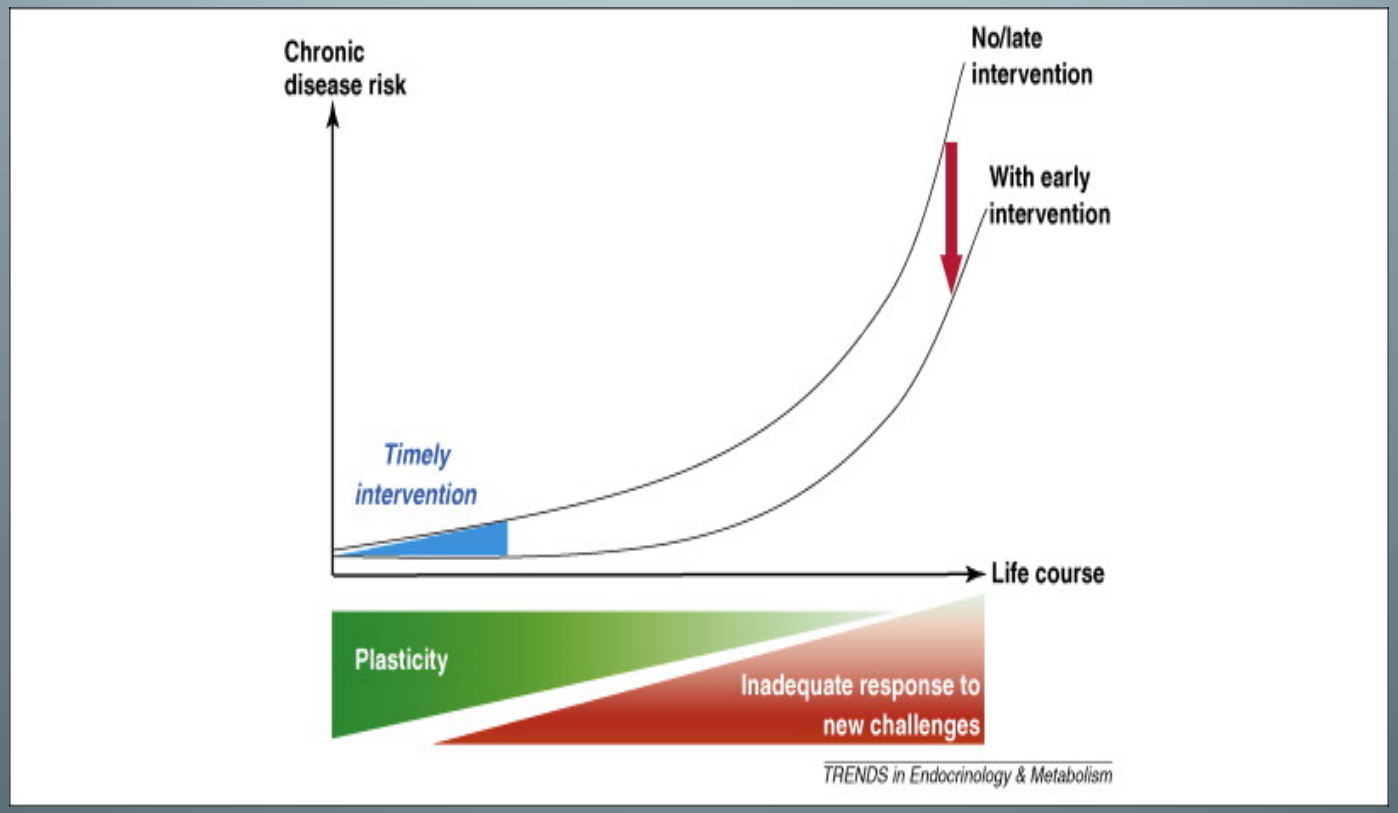


Lipid Changes in Pg. and CVD

- Controlling diabetes pre-pregnancy reduces fetal cardiac anomalies
- Dyslipidemia – Historically considered physiologic with little clinical relevance and not routinely measured!
  - Increased fatty streaks in aortas of 6 mos. old fetuses of mothers with hypercholesterolemia
  - FELIC study - maternal dyslipidemia associated with increase aortic atherosclerosis in normo-cholesterolemic children
- New Zealand While Rabbits - diet induced maternal dyslipidemia - dose dependent fetal and postnatal atherogenesis , maternal cholestyramine reduced it
- Murine Model supportive
  - – multiple animal models similar story
- Double blind studies have not been performed
  - **Ethics, feasibility, horizon**

Palinski W Circulation. 2014;129:2066-2077

Chronic Non Communicable Disease



Hanson, M. Progress in Biophysics and Molecular Biology 106 (2011) 272e280

Fetal Developmental Programming

- Pre-Pregnancy
  - Genetic, metabolic , smoking , maternal, paternal
- Pregnancy
  - Malnutrition, stress, chemicals, steroids, cardiomyopathy , preeclampsia , gestational diabetes , smoking, Met Syndrome, gestational hyperlipidemia , obesity , IUGR , LGA , placental function, hypoxia
  - **Fetal epigenetic changes - DNA methylation**
- Post Pregnancy
  - Genetics, lifestyle risk
    - Immune response , inflammation, endothelial dysfunction,
    - atherogenesis
- Adult Phenotype at different genetic set points – cardio-metabolic disease with Obesity and Metabolic Syndrome

Palinski W Circulation. 2014;129:2066-2077

Lipids & Atherogenesis Dynamic

- Pg increased permeability of vascular endothelium by small molecules
  - Increased by diabetes
  - Active transport mechanisms of lipids to fetus
- Different in different stages of Pg.
- Fetus shunts fat early in gestation depending upon liver maturity
- Pericardial fat in fetus early
  - later liver shunts it to protect the brain

Gunitilake,R Abstract 2014 OUHSC Annual Research Day

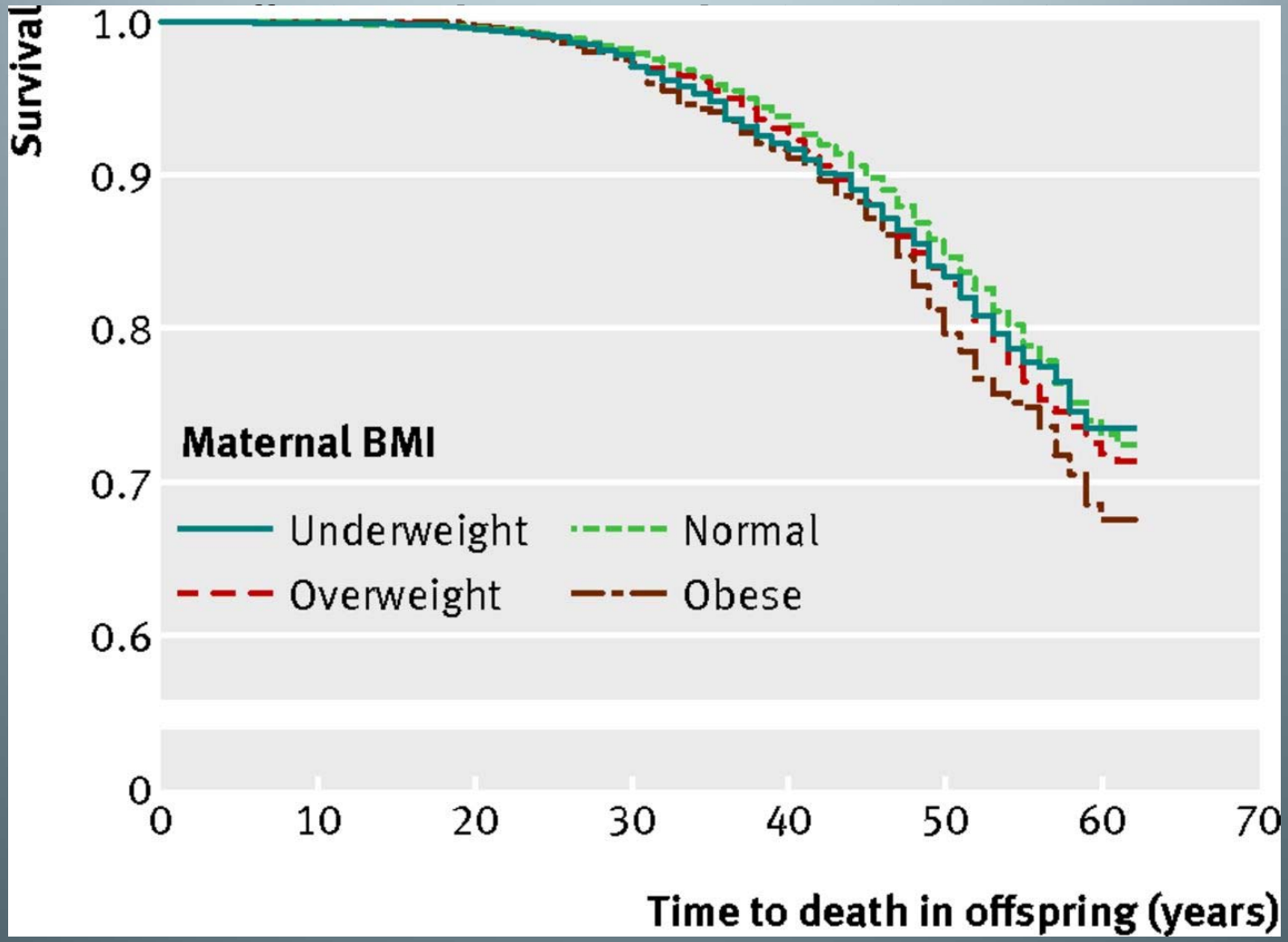
Palinski W Circulation. 2014;129:2066-2077

BMI & Fetal Outcomes

- Even modest increases in maternal BMI were associated with increased risk of fetal death, stillbirth, neonatal death, perinatal death, and infant death.
- Weight management guidelines for women who plan pregnancies should take these findings into consideration to reduce the burden of fetal deaths, stillbirths, and infant deaths.

JAMA. 2014;311(15):1536-1546.

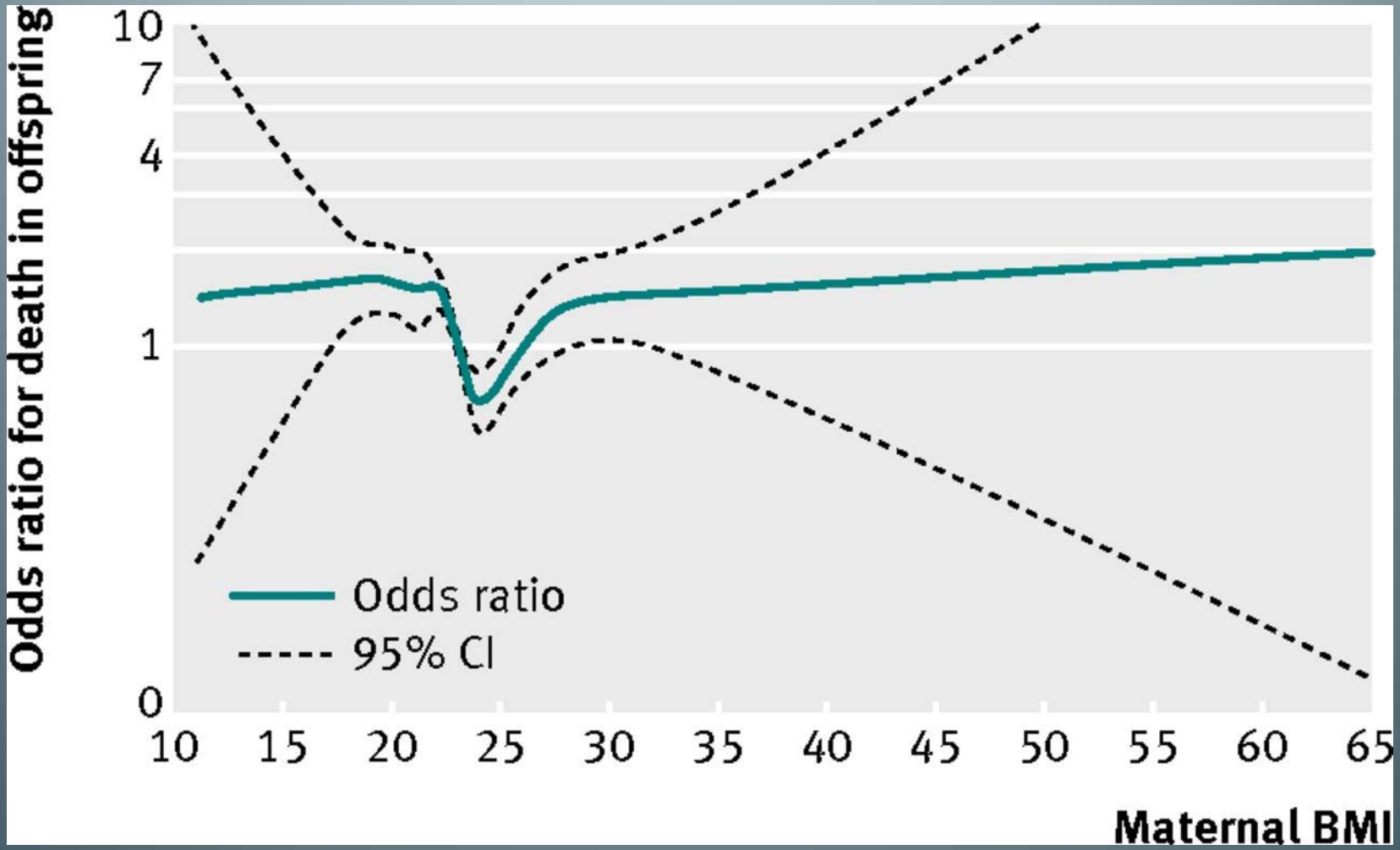
Kaplan-Meier curves for death rates in offspring according to maternal BMI category showing increased adjusted all cause premature mortality in offspring of obese mothers (BMI >30).



Reynolds R M et al. BMJ 2013;347:bmj.f4539

Maternal obesity during pregnancy and premature mortality from cardiovascular event in adult offspring: follow-up of 1 ,323 ,275 person years

Non-linear relation of maternal BMI with mortality in offspring, showing that odds of offspring death was more among mothers with low or high BMI before pregnancy compared with mothers with BMI of 23. Offspring aged 34-61



Reynolds R M et al. BMJ 2013;347:bmj.f4539

Maternal obesity during pregnancy and premature mortality from cardiovascular event in adult offspring: follow-up of 1, 323, 275 person years

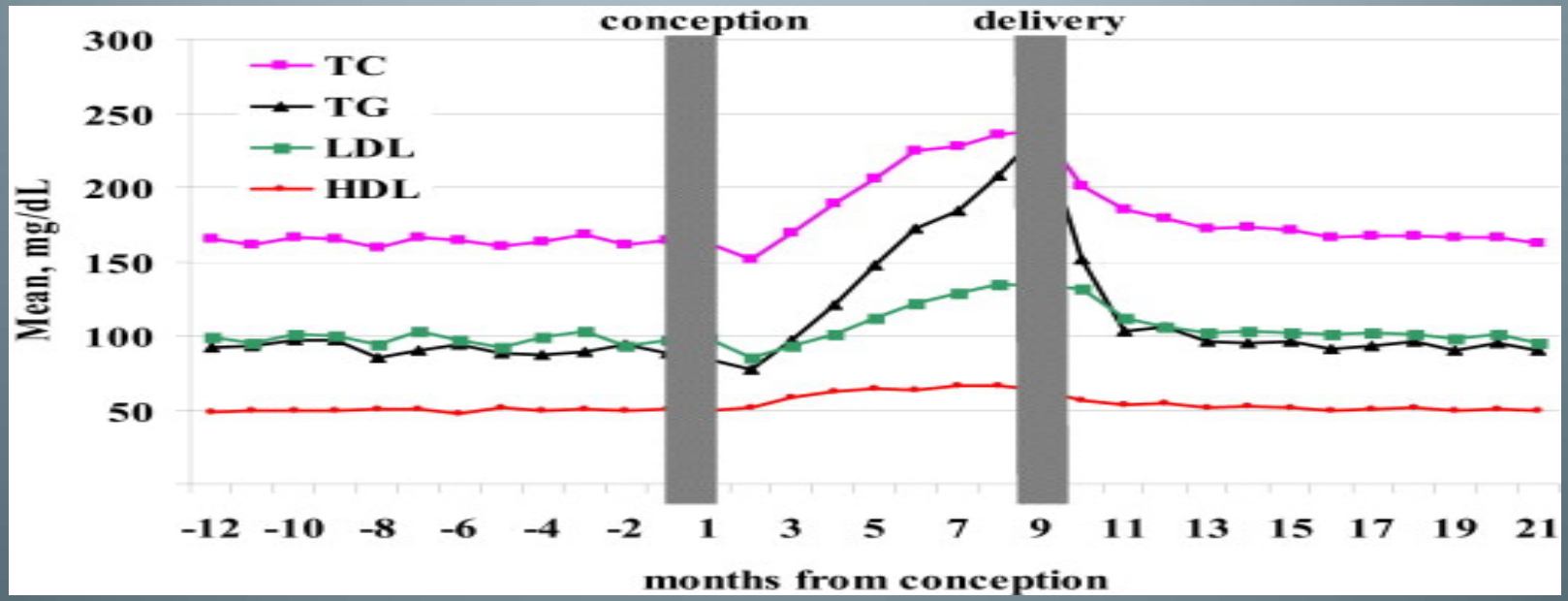
Cardiometabolic outcomes of Offspring at age 32 by quartile of maternal pre Pg weight and weight gain both during Pg

- BMI\Waist
- TG
- Blood Pressure
- Insulin resistance

Hochner,H. et al 2012
Circulation 125(11):1381
2012

Mother

TC,TG,HDL, LDL 1 yr. before, during and 1 year after Pg. n=8,700



Wiznitzer. Lipids in pregnancy. Am J Obstet Gynecol 2009;201;483 e1-8

Lipids in Pregnancy

- Pharmacological amounts Estrogens increase TGs by stimulating hepatic production of VLDL and inhibiting hepatic and adipose lipoprotein lipase
- Progesterone apposes these actions
- E/P and VEGF, TNF alpha (and other cytokines and inflammatory factors) are important contributors of Insulin Resistance
- Pregnancy is a STRESS TEST

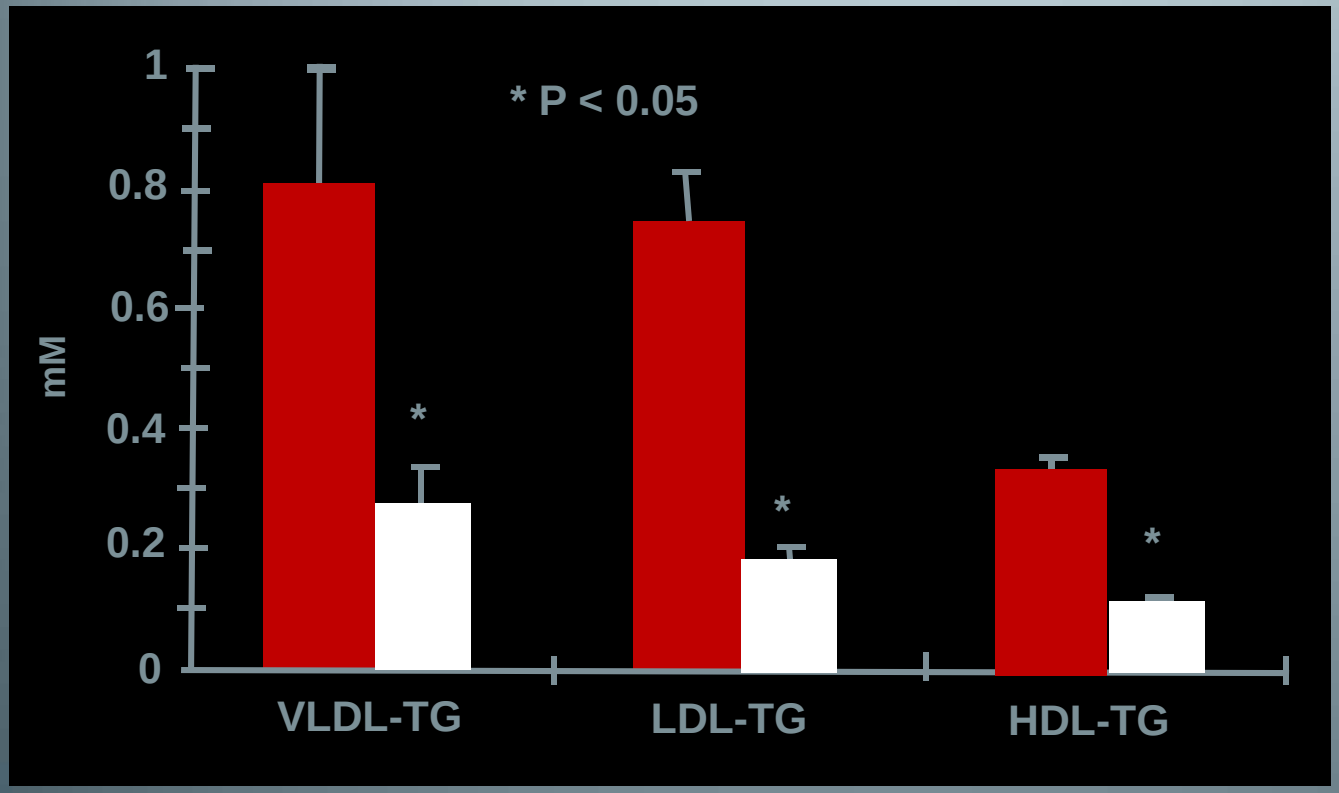
Wiznitzer,A Amer J Obstet Gynecol 2009

Lipids in Pregnancy

- Lipids vary during Pg. initial decrease then a nadir during first trimester followed by gradual increase and peak before delivery
- **Hi Levels of TGs are associated with an increased risk for preeclampsia and gestational diabetes (n=1,209)**
- Hyperlipidemia is common in 2nd ½ of PG as physiologically required mechanism to maintain stable fuel for fetus
  - **Likely pathologic indicating a metabolic syndrome**

Wiznitzer. Lipids in pregnancy. Am J Obstet Gynecol 2009;201;483 e1-8

Triglycerides in Pregnancy



Plasma lipoprotein TG in women at then 3rd trimester of pregnancy (red) and at post-lactation .

Under non-pregnant conditions the TG content in HDL and LDL are low compared to VLDL. **In nl Pg women there is a significant increase in TG in all lipoprotein fractions**.

Herrera E. Eur J Clin Nutr 2000;54:Suppl 1 S47-S51

Small low-density lipoproteins and vascular cell adhesion molecule-1 are increased in association with hyperlipidemia in preeclampsia

- Preeclampsia is characterized by endothelial dysfunction prompted by increase in TG and FFAs.
- Smaller LDL can induce endothelial dysfunction
- TG, Apo B, small LDL increased in preeclampsia
- VCAM1 (indicator of endothelial dysfunction) increased - not associated with particles
- Are changes from ApoB or LDL?

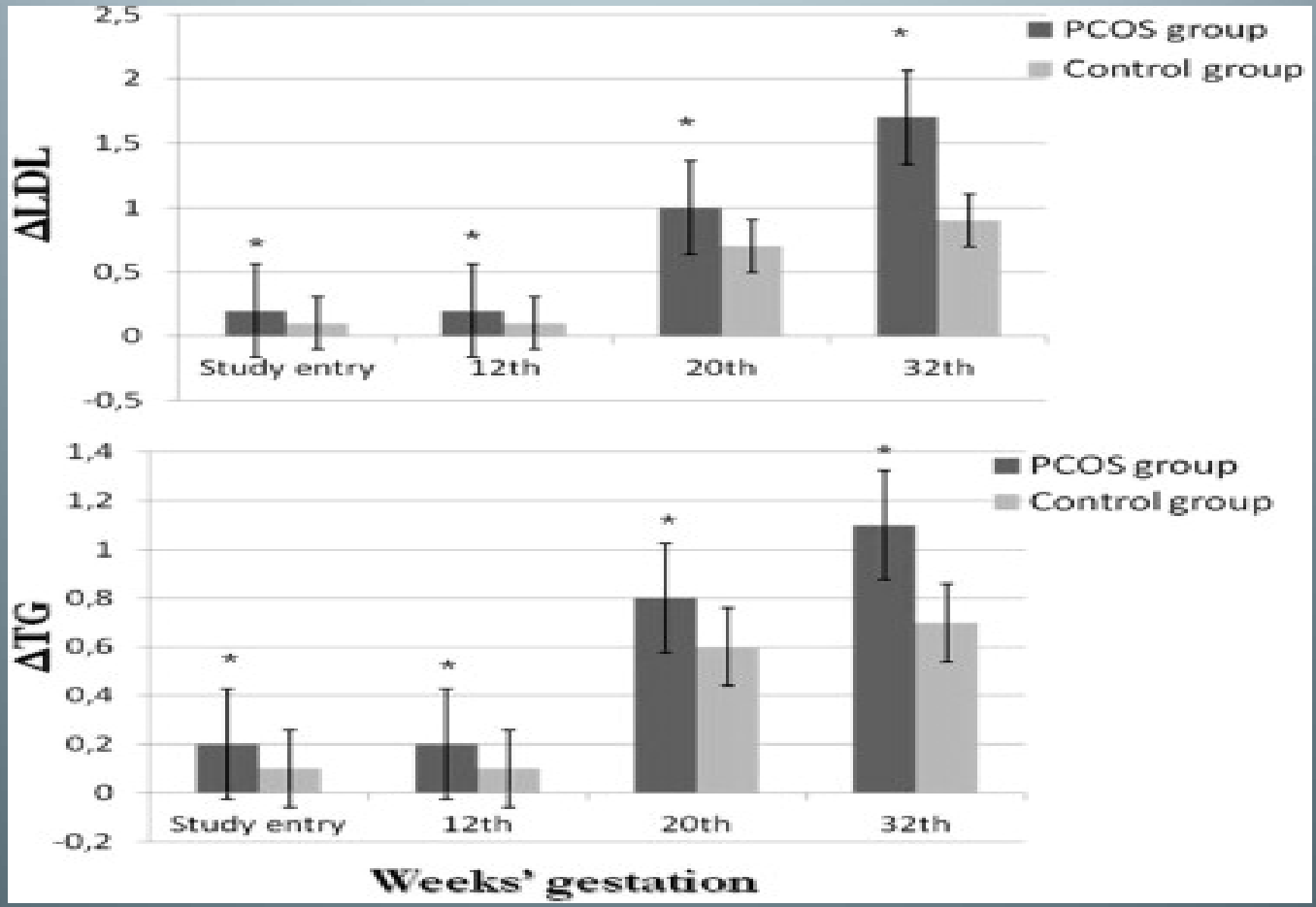
Hubel, C.A. 1989 Am J Obstet Gynecol161(4):1025

Dyslipidemia and Preeclampsia & Gestational Diabetes

- Endothelial dysfunction – some indication secondary to oxidative stress and decreased release of prostacyclin
- Altered lipoprotein lipase, enhanced endothelial uptake of FAs, esterified to TG
  - Metabolic syndrome
  - Gestational diabetics - higher TG

Wiznitzer, A Amer J Obstet Gynecol 2009

Lipid profile in non-obese pregnant women with polycystic ovary syndrome: A prospective controlled clinical study n=300



Adverse Pg. Outcomes
PCOS=32% Control 11.3%

Palumbo,S et al 2014 Steroids

Lipid Changes in Pg

- Trig and Cholesterol usually not > 332 and 337 mg/dL
- Extreme values can occur (Trig>1000 mg/dL)
  - Pre-existing, coexistent medical disorders
  - Co-existent Pg. disorders, limited to gestational period (DM,PET) , supra-physiologic, dysbetalipoproteinemia, partial LPL deficiency and Apo E3/3 phenotype

Basaran,A 2009 Reproductive Science 16 (5):531

Lipid levels with medical conditions

- Hypothyroidism, OH consumption, LMW Heparin, glucocorticoids, psychotropic meds, kidney disease, lipodystrophy
- Effects not well characterized
- Observed hyperlipidemia is independent of Diabetic status ….

Toescu,V 2004 Clin Sci 106(1):93

Gestational Diabetes…Any degree of glucose intolerance with onset of first recognition during pregnancy – Triglyceride Connection

- Most with GDM have glucose intolerance that begins in pregnancy
- Some have Type 2 DM unrecognized prior
- 10% with GDM have circulating islet-cell antibodies &/or HLADR3 or DR4….increase risk for Type 1 post delivery (exact risk unknown)

Mauricio, et al Diabetes Metab Rev 1996;12:275
**Ferber, et al Clin Endo Metab 1999;84:2342*

Gestational Diabetes
Oral Hypoglycemic Agents

- Primary effect is to enhance insulin secretion
- As of 2014, ACOG has not supported use of oral agents over insulin in pregnancy- Widely used however!
- In US major objection is/was the theoretical risk of:
  - Congenital fetal anomalies
  - Fetal macrosomia
  - Neonatal hypoglycemia
- Emergence of a new generation of agents has lead to a re-examination of this issue: Glyburide & Metformin
- No evidence of harm - both cross the placenta

Gestational Diabetes

Glyburide

- A second generation sulfonylurea
- MOA: Increases insulin secretion & decreases insulin resistance by lowering glucose toxicity
- Onset of action 4 hrs, duration of action 10 hrs.
- Cross the placenta (minimal?)
- Category B drug
- Effects on fetus unknown

Metformin & GDM2

- **Safety profile of metformin (class B) in the first trimester and apparent lack of teratogenicity has been well documented.**
- **Prematurity?**
- **A follow-up study is currently underway to assess the offspring of the women enrolled in the MIG trial at 2 years of age.**

Glyburide or Metformin vs. Insulin for GDMA2

- Advantages for oral treatment of GDMA2
- Lower cost and Improved Compliance
- 1 vial of 10cc of Regular insulin=$37.99
- 1 vial of 10cc of NPH insulin=$37.99
- A box of 100 syringes=$19.00
- 30 day supply of glyburide or metformin (max dose)=$4.00 at Walmart
- or $43.99 at Walgreen's

Hypertensive Disorders in Pregnancy Triglyceride Connection

Categories

- Those with HTN who become pregnant
- Those who develop HTN disorders during pregnancy

Classes

- Chronic hypertension
- CHTN with superimposed preeclampsia
- Gestational hypertension
- **Preeclampsia**
- **Eclampsia**
- Transient hypertension

Effects of Selected Drugs

Drug	**Triglycerides**
• OH	INCREASED
• ESTROGEN	
• GLUCOCORTICOIDS	
• BBLOCKERS	
• VALPROATE	
• SERTALINE	
• ISORETENOID	
• CYCLOSPORIN,TACROLIMUS,ETC	

Chylomicronemia

- Hi VLDL & Chylomicrons (V)
- TG > 1000 (usually > 2000 mg/dL)
- Risk for pancreatitis
- Clinical features
  - Eruptive xanthoma peripheral neuropathy
  - Hepatosplenomegaly Dyspnea
  - Lipemia retinalis Memory loss/dementia
  - Abdominal pain without pancreatitis

Severe Hypertriglyceridemia

- Reduce fat calories (15%)
- Insulin therapy (acute insulin infusion)
- TPN
- Omega 3 – fatty acids (4-10g/d) - 20-45% reduction
  - Fish Oil (840 mg/1 gram capsule) TG> 500 mg/dL
  - Gemfibrozil 600mg bid or Fenofibrate 145-200
    - Class C
- Goal :
  - Trigs < 400 mg/dL to prevent pancreatitis

Hypertriglyceridemia

case series

MCTG 10-30g/day

Topical sunflower oil 1tblsp subcut

Niacin

Gene therapy

Plasma-pheresis

Goldberg,A.S. 2012 JCEM 97(8):2589

Post Partum

Preeclampsia vs. no – 1 yr. P. Partum!

	Preeclampsia (n = 70)	Normo tensive (n = 70)	
Weight (kg)	77.3 (20.2)	71.8 (14.7)	< .01
BMI (kg/m^2)	29.0 (7.0)	26.0 (5.0)	< .01
BMI (kg/m^2), n (%)			
< 25 (healthy)	23 (32.9)	34 (48.6)	< .05
25-30 (overweight)	20 (28.6)	23 (32.9)	
> 30 (obese)	27 (38.6)	13 (18.6)	
Wt gain – pre to Post	1.83 (3.58)	0.59 (2.18)	< .05
Systolic	120.0 (11.9)	111.3 (9.3)	< .01
Diastolic	81.5 (10.3)	72.7 (8.1)	< .01
Insulin (pmol/L)	63.6 (55.2)	44.7 (27.9)	< .05
HOMA	1.18 (1.02)	0.83 (0.52)	< .05
Total cholesterol (mmol/L)	4.69 (0.85)	4.30 (0.76)	< .01
Triglycerides (mmol/L)	97	85	NS
HDL cholesterol (mmol/L)	56.7	58	NS
LDL cholesterol (mmol/L)	105	92	< .01
NonHDL cholesterol	124	108	<.01
Microalbumin/creatinine (mg/mmol)	0.80 (0.40, 2.68)	0.51 (0.40, 0.90)	< .01

Smith 2009

Childbearing and Obesity in Women: Weight Before, During, and After Pregnancy

- Weight tends to be retained or increases after Pg. on in to the next one
- Overweight and obese women 6xs more likely to exceed weight gain recommendations in Pg.
  - – - these women are predisposed to higher post partum weight gain and retention after Pg.
- 13% to 20% of women are 5 kg or more above their preconception weight by 1 year postpartum!

Gunderson,E.P. Ostet Clin NA 2009

Preterm delivery
Later maternal CVD risk

- Health and Aging and Body Composition Study
- CVD more prevalent in those with preterm infant
- ODDs for CVD among mothers who delivered a pre-term low birth weight infant were 3.31 xs higher

Catov, J.M. 2007 Epidemiology 18(6):733

Childbearing and Obesity in Women: Weight Before, During, and After Pregnancy

- Weight gain and overweight during midlife are strong independent predictors of CVD particularly among women
- Weight gain and overweight during midlife are strong independent predictors of Met Syndrome , Type II DM and early mortality

Hubert,H.B. 1983 Circulation 67:968
Willet,W.C. 1995 JAMA (273):461
Colditz,G.A. 1995 Ann Intern Med (122):481
Ford,E.S. 1997 Am J Epidem (146):214

Cardiovascular consequences of having preeclampsia/eclampsia: Systematic reviews and Meta-analyses Case/Control & Cohort Studies

- ODDS for CVD 2.48 Case/Control
- ODSS for CVD 2.3 Cohort

- ODDS for CVD 2.28 Case/Control
- ODDS for CVD 1.76 Cohort

Sarak,D. Amer Heart Journal 2008
Brown,MC Er J Epidemiol 2013

When does metabolic syndrome begin?

***Gestational Diabetes - 10 yr. Risk

Type 2 DM = 39%

Hypertension = 10.3%

Dyslipidemia = 27%

Hi Risk in Pg. vs. Low Risk (**Odds=7x higher!**)

BMI > 30 Kg/m^2

Glucose > 90 mg/dL

Insulin > 7.8 mUI^{-1}

Triglycerides >212 mg/dL

HDL<62 mg/dL

Systolic BP > 105 mmHg

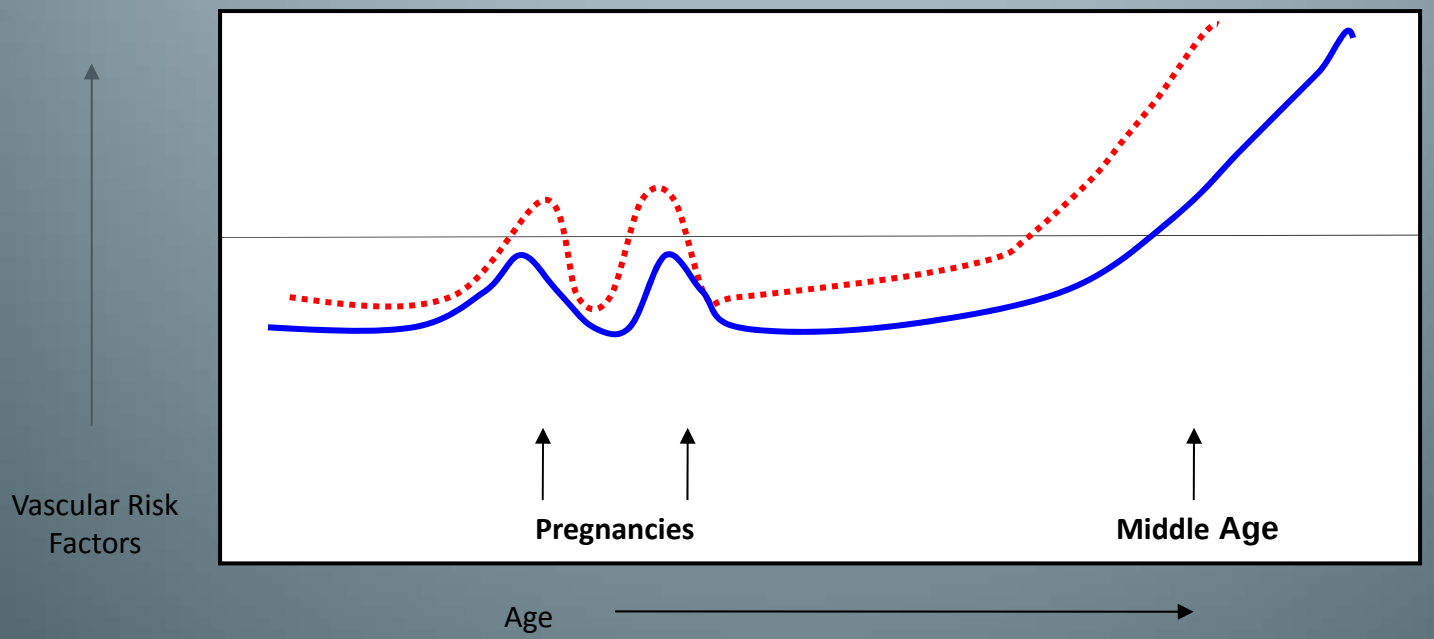


Bardin A Nutrition and Diabetes 2013 e72

Take Home Message(s)

Excursions into Metabolic Syndrome During Pregnancy





Sattar & Greer, 2002;. Adapted from Deborah Ehrenthal, MD, FACP

Take Home Message(s)

- Screen , Dx & Treat
  - before
  - during
  - and after Pg.
  - Break the viscous generational cycle

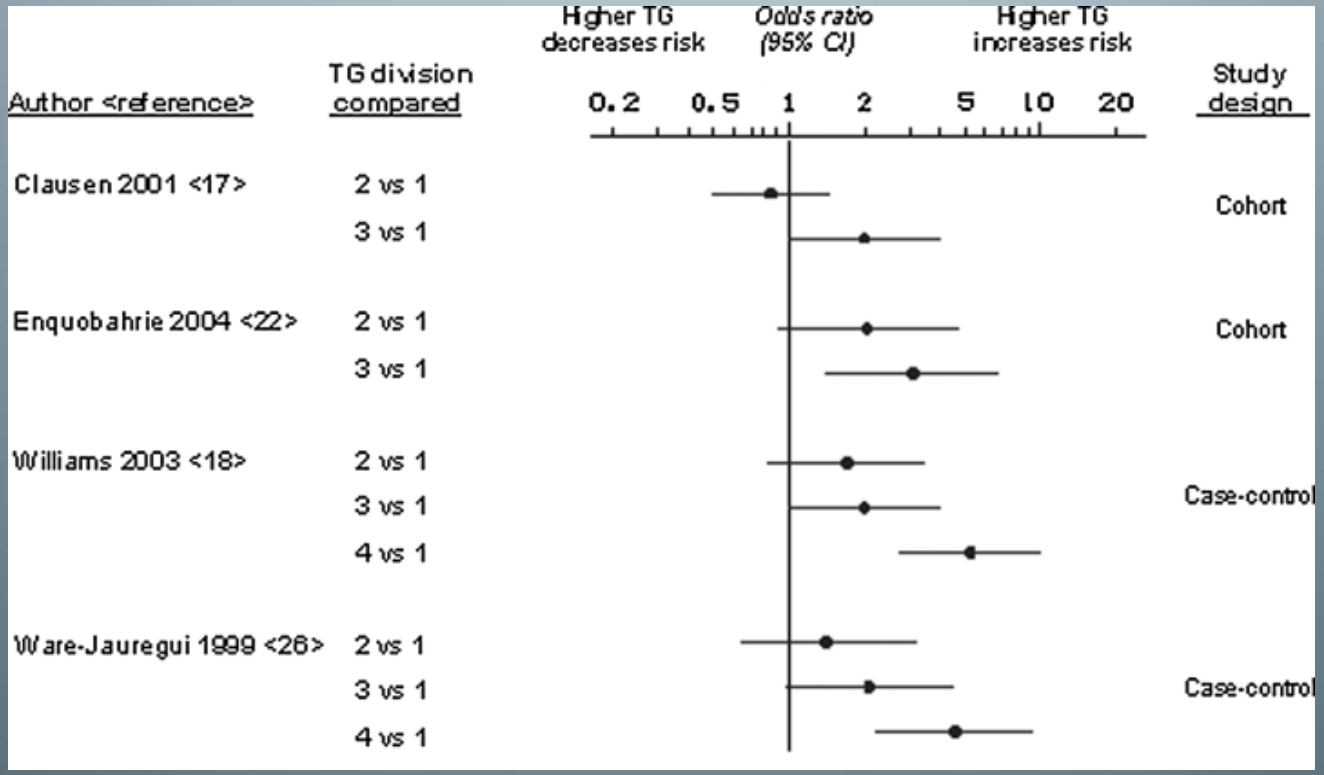
Cardiovascular Risk Factors During Women's Reproductive Years

- Traditional
  - Smoking , Diabetes , hi BP , Dyslipidemia , Inactivity
- Reproductive Risks
  - PCOS , Infertility , Adverse PG Outcomes (preterm delivery low birth weight , hypertensive disorders, gestational diabetes)
- Behavioral Risks
  - Physical Inactivity, poor diet , obesity, lactation
- Be Pro-Active! –
  - DO WHAT YOU CAN DO to reduce the Epigenetic Burden for generations to come!

CVD and Programming Research Agenda

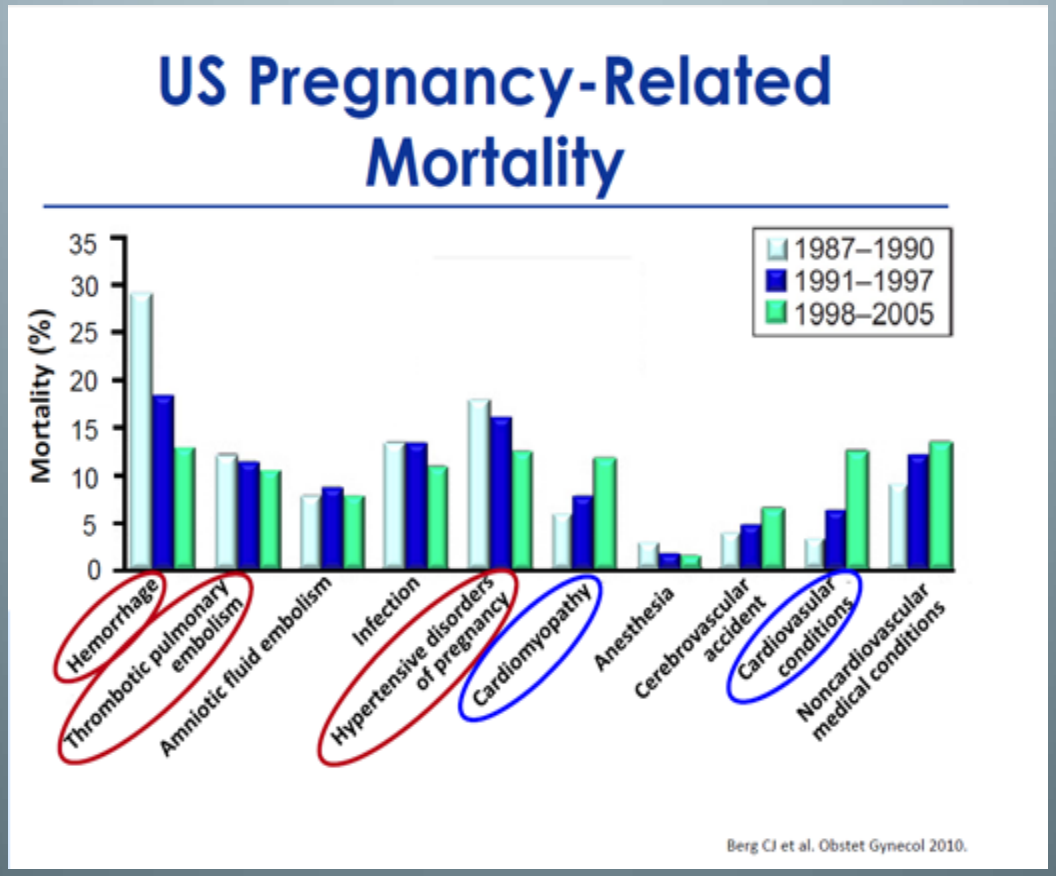
Which of the CVD risk factors during pregnancy or maternal dysmetabolic conditions are actually responsible for developmental programming?	**Epidemiological associations between risk factors of developmental programming and offspring CVD Demonstration of causality in experimental models of specific risk factors**
Can pathogenic programming by specific risk factors be prevented?	Dietary and drug interventions in experimental models
How effective is conventional prevention or treatment before pregnancy?	Prospective studies on offspring of mothers treated under existing guidelines before or during pregnancy
How effective are safe dietary interventions during pregnancy?	Clinical trials
How safe are current cholesterol-lowering, anti-inflammatory, or antioxidant drugs during pregnancy?	Critical review of case reports Epidemiology Clinical trials
What is the relative contribution of developmental programming to offspring CVD compared with genetic susceptibility and postnatal risk factors?	Epidemiology focusing on specific maternal risk factors and postnatal lifestyle Animal studies
What fetal cells/tissues/organs are programmed?	Identification of epigenetic changes in tissues of humans and experimental animals
What epigenetic mechanisms affect CVD mechanisms or manifestations in offspring?	Association studies in humans Studies testing causality of specific mechanisms in experimental models
Does maternal immunomodulation influence developmental programming in humans?	Initially, retrospective studies only

Brief overview of maternal triglycerides as a risk factor for pre-eclampsia



BJOG: An International Journal of Obstetrics & Gynaecology
Volume 113, Issue 4, pages 379-386, 17 MAR 2006 DOI: 10.1111/j.1471-0528.2006.00889.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1471-0528.2006.00889.x/full#f1

PRE-ECLAMPSIA KILLS



Hypertriglyceridemia late pregnancy associated with small dense low-density lipoproteins & large buoyant high-density lipoproteins n= 36 Hispanics 35-36 weeks and postpartum

- TG = 218, Cholesterol 234, ApoB 130 mg/dL
- 97% classified is pattern B or Intermediate
- Predominance of small dense LDL was associated with TGs
- HDL 2 mass was increased

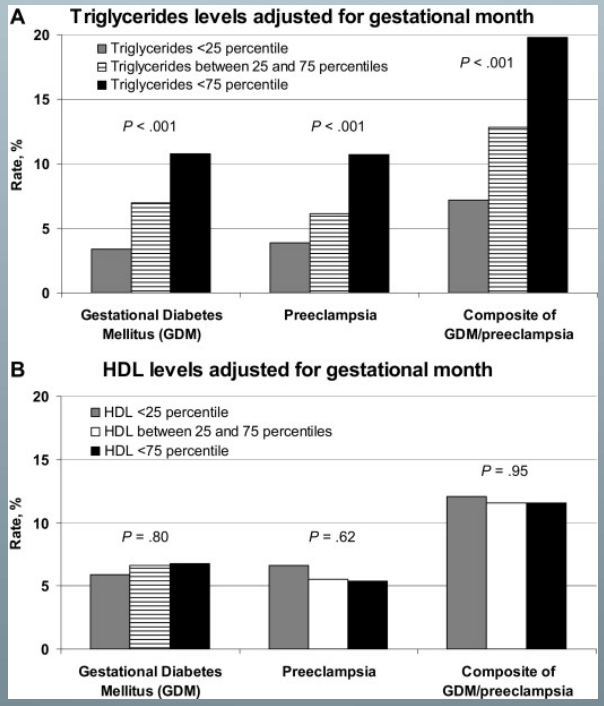
Silliman,K. Metabolism 1994

Low-density lipoprotein particle size decreases during **normal pregnancy** in association with triglyceride increases

- Uncomplicated nonsmoking Pg. women without metabolic disorder
- LDL diameter decreased with advancing gestation 16-20 wks. evident vs. 5-12 weeks
- 70% pattern B
- LDL diameter was inversely correlated with TG, ApoB and cholesterol (r-.6)
- All changes were reversed post partum

Hubel,C.A. JSGI 1998

Association of lipid levels during gestation with preeclampsia and gestational diabetes mellitus: a population-based study



Wiznitzer, A. Amer J Obstet Gynecol 2009

Glyburide & Gestational Diabetes

- Langer 2000: only RCT of 404 patients, demonstrated similar efficacy of glyburide & insulin in glucose control & pregnancy outcome.
- Conway 2004: retrospective study of 75 patients, found glyburide was useful in achieving glycemic control.
- Jacobson 2005: retrospective study of 584 patients found similar efficacy between glyburide & insulin, but higher rates of preeclampsia and phototherapy in the glyburide group.

Parity and cardiovascular disease risk among older women: how do pregnancy complications mediate the association?

- Health and Aging and Body Composition Study
- N=540 47% AA
- Nulliparous women less CVD than Parrous (185 vs. 30%)
- After adjustment for perinatal complications – toxemia, lbw,preterm,stillbirth
- ODDS for CVD among Parrous women 1.95 (1.03,3.7)
- With complications CVD prevalence 2.67 times higher

Catov , J.M. Ann Epidemiol 2008



Common Diagnoses In Ob/Gyn That Increase Lifetime Cardiovascular Disease (CVD) Risk

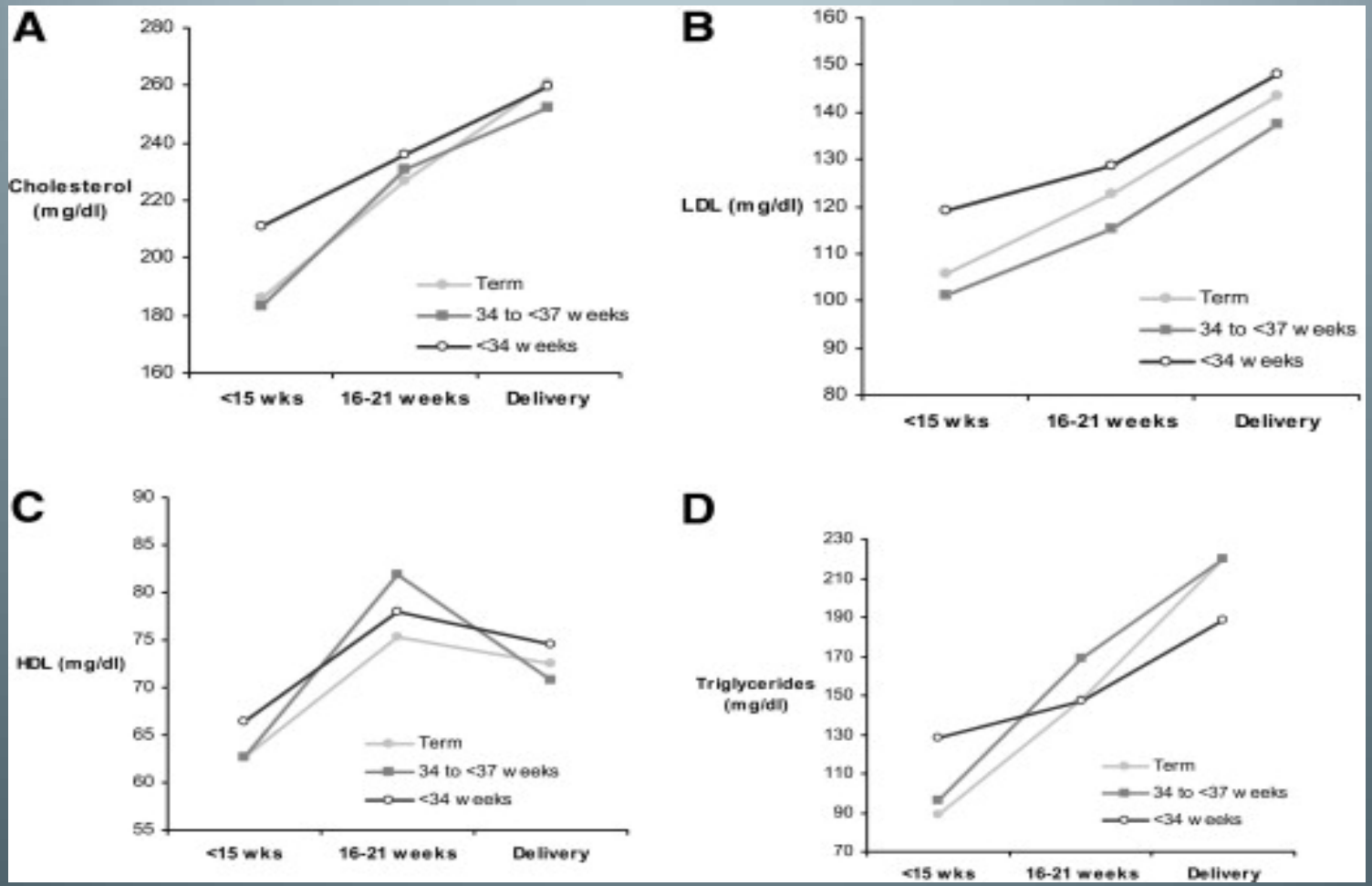


- Pregnancy-induced Hypertension, Gestational Diabetes (GDM), Polycystic Ovary Syndrome (PCOS), premature delivery
- Hypertension (HTN), Diabetes, Hyperlipidemia
- Smoking, Overweight/Obesity, Unhealthy Diet, Lack of Exercise



Source: Mosca 2011, Wild 2010

Early pregnancy lipid concentrations and spontaneous preterm birth



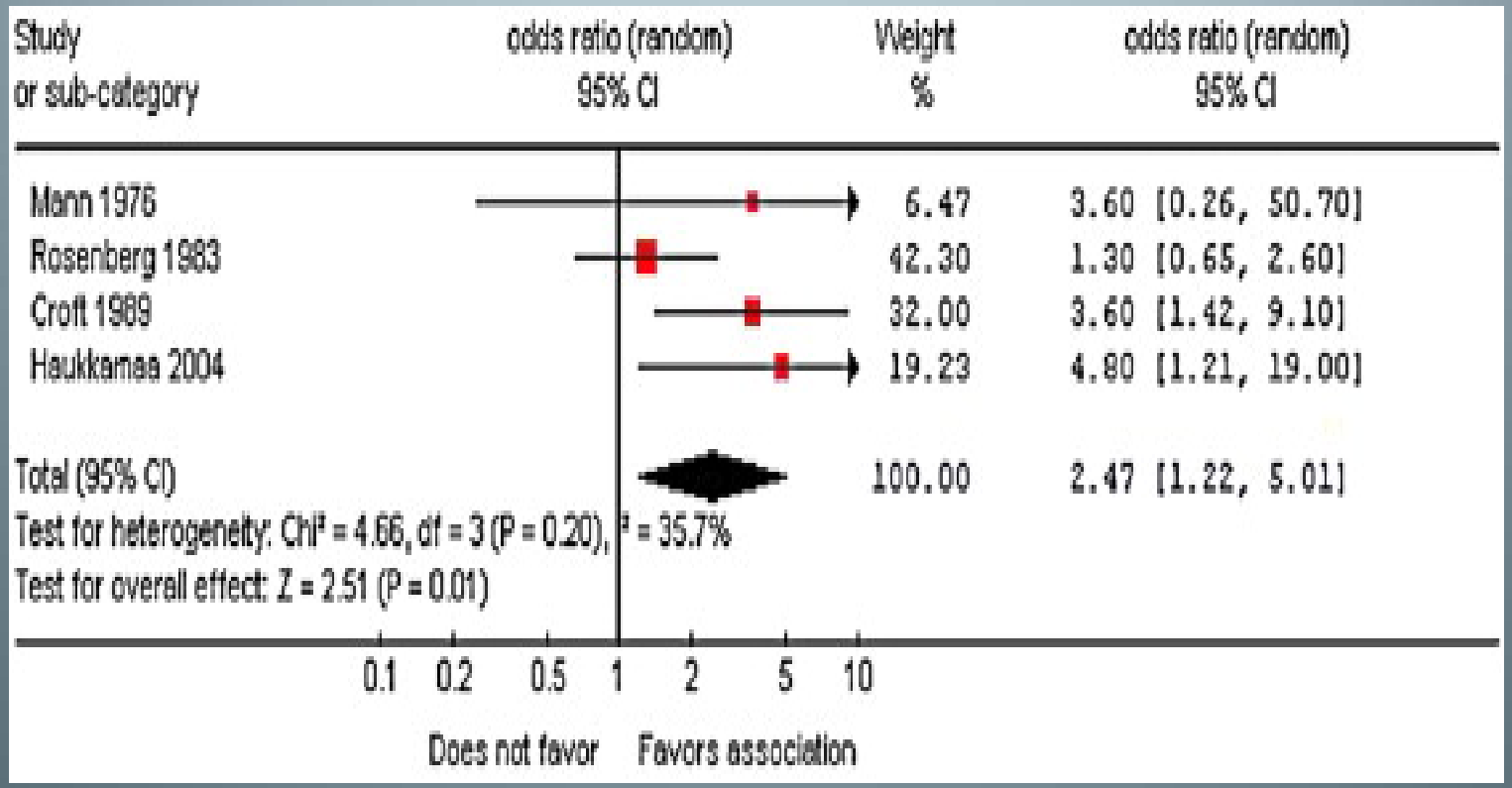
Catow, JM AJOG 2007

Lipoprotein particles in preeclampsia: susceptibility to oxidative modification women with preeclampsia vs. normal PG women

- Pre-eclamptic women Higher TG and LDL
- Conjugated diene production & shorter lag time for LDL and HDL in pre-eclamptic women
- HDL and LDL particles more susceptible to oxidative modification and plasma concentration of LDL particles not HDL particles were increased in Pre-eclamptics

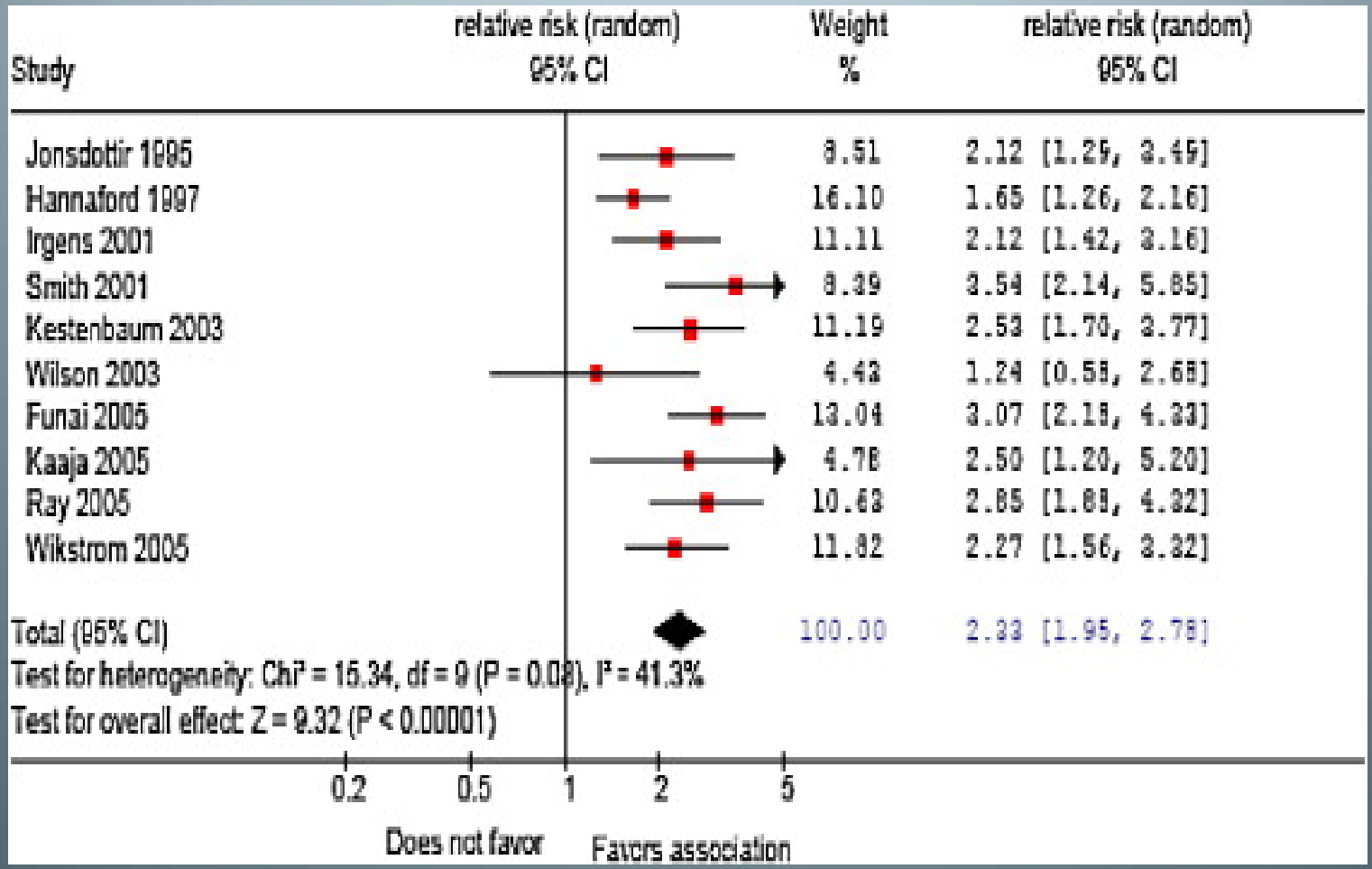
Wakatsuki,A. Obstet Gynecol 2000

Cardiovascular sequelae of preeclampsia/eclampsia: A systematic review and meta-analyses Case/Control Studies



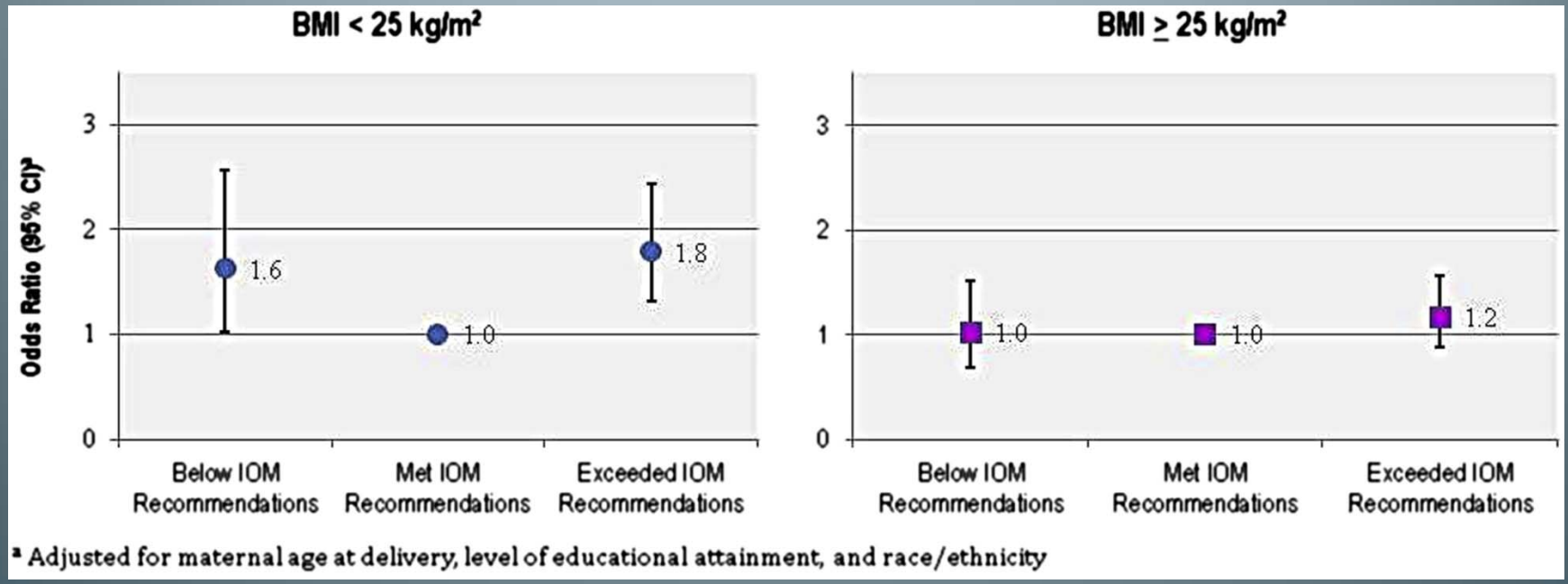
Sarak,D. Amer Heart Journal 2008

Cardiovascular sequelae of preeclampsia/eclampsia: A systematic review and meta-analyses Cohort Studies



Sarak,D. Amer Heart Journal 2008

Maternal gestational weight gain and offspring risk for childhood overweight or obesity



N=4,145 women offspring 2-5 yrs. Sridhar, SB Am J Ob/Gyn 2014

Diabetes in Pregnancy Dietary Care

- Nutritional counseling ideal
- 30kcal/kg/day
- Pre-pregnant weight
- Most appropriate diet not established…
- Carbohydrate 60%
- Protein 20%
- Fat 20%
- Saturated 10%
- Unsaturated 10%

ANTIHYPERTENSIVES CONSIDERED SAFE IN PREGNANCY

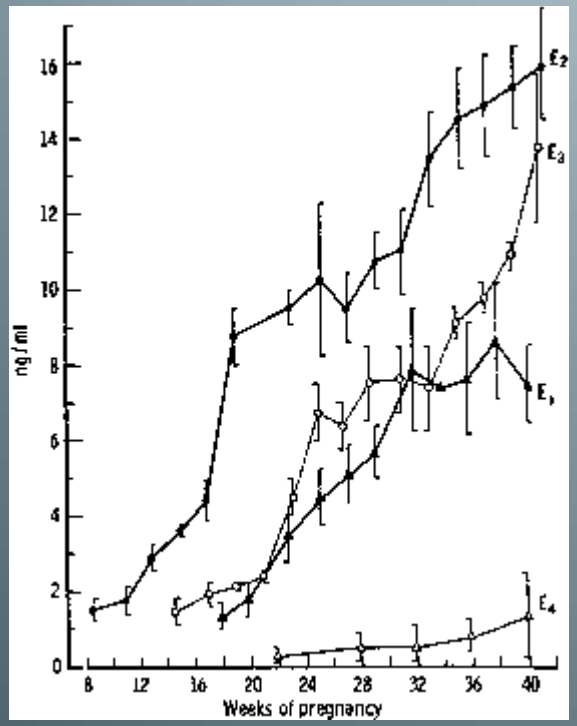
- Methyldopa (Aldomet) 250-1000 mg qid
- Labetolol (Nomodyne) 100-1200 mg bid
- Nifedipine (Procardia) 10-30 mg tid
- Nifedipine (Procardia XL) 30-60 mg qd
- Hydralazine (Apresoline) 10-75 mg qid
- Minoxidil (Loniten) 5-10 mg qd
- Clonidine (Catapres) 0.1-0.2 mg bid

MEDICATIONS
THAT CAUSE HYPERTENSION in PG

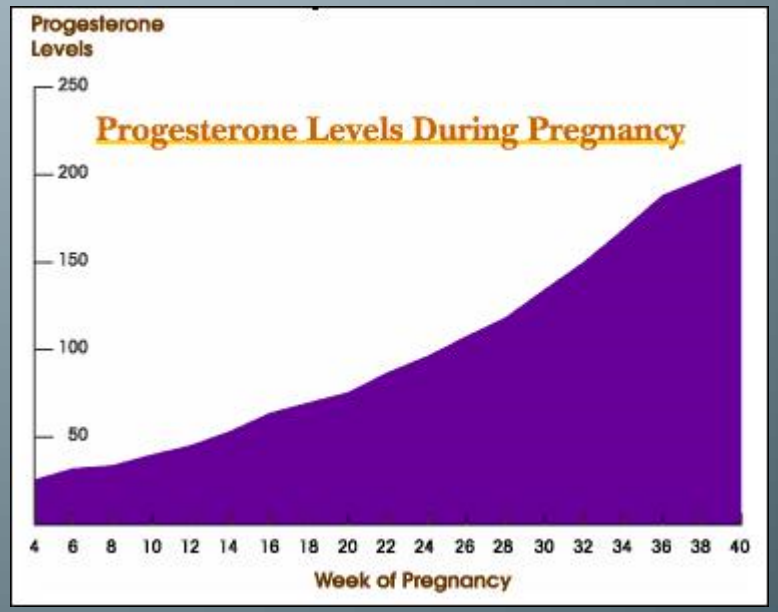
- Corticosteroids
- Cyclosporine
- Contraceptives
- Amphetamines
- Sympathomimetics
- Ephedrine
- Cocaine!

Sex Steroids Levels in Pg.

Estrogen



Progesterone



Gestation and Lipids

- **First 2/3 gestation mother anaerobic state, increasing her fat depots**
  - **hyper-phagia and enhanced lipogenesis**

- **Last 1/3 mother switches to catabolic state.**
  - **Glucose most abundant nutrient crossing the placenta**
  - **causes maternal hypoglycemia despite an increase in**
  - **gluconeogenesis**

- **Adipose tissue lipolytic activity increases –raised FFA and glycerol reach liver, increase in hepatic production of TG, more circulating VLDLs.**

- **Enhanced CETP enriched LDL and HDL with TG**

Herrera E. Eur J Clin Nutr 2000;54:Suppl 1 S47-S51

Gestation and Lipids

- **Glycerol also a gluconeogenic substrate saving amino acids for the fetus**

- **Fasting conditions, FA, via beta-oxidation are converted into ketone bodies - easily cross the placenta and metabolized by the fetus**

- **Enhanced liver production of VLDL-TG together with decreased adipocyte LPL , increased plasma CETP & hepatic lipase cause both an increment in ldl particles and particle TG**

- **Maternal TG do not cross the placenta, but are hydrolyzed by LPL releasing FA to the fetus.**

Herrera E. Eur J Clin Nutr 2000;54:Suppl 1 S47-S51

Gestation and Lipids

- **Changes in lipid metabolism during Pg promote accumulation of maternal fat stores in early and mid Pg and enhance mobilization in late Pg**
- **Cholesterol is used by placenta for steroid synthesis, and fatty acids for placental oxidation and membrane formation**
- **Anabolic phase in preparation for rapid fetal growth in late PG**

Basaran 2009

Gestation and Lipids

- **A third mechanism by which maternal hypertriglyceridemia benefits offspring is its contribution to milk synthesis in preparation for lactation**

- **With decreased adipocyte LPL , TG more available to breasts. Around parturition rapid increases in LPL expression and activity in mammary glands.**
  - **Due to both increased prolactin and insulin levels and a specific enhancement in mammary gland insulin sensitivity**

- **Mammary induction of LPL facilitates clearing of maternal TG for milk synthesis. Essential FA from the diet become available to the nursing infant.**

Herrera E. Eur J Clin Nutr 2000;54:Suppl 1 S47-S51

Gestational Diabetes Prevalence

- US: 2-5% (1.4-14%)
- NA & Hispanic>AA>Caucasian
- Increasing in all groups*
- Increased maternal age
- Obesity
- Varies worldwide & among racial/ethnic groups

**Getahun, et al Am J Obstet Gynecol 2008;198:525*

Lipoprotein Changes in T2DM

- Triglyceride –rich lipoproteins
  - Increased particle number
  - Increased postprandial concentrations
  - Triglyceride enriched and cholesterol enriched particles
- LDL
  - Increased particle number
  - Small dense particles
- HDL
  - Decreased particle number
  - Changes in particle composition

Mazzone 2008

OBJECTIVES

- Clinical Lipidologist will become familiar with the **implications of Dyslipidemia/TG before, during and after Pregnancy**
- Clinical lipidologist will become familiar with **Obstetrical considerations of dyslipidemia/TG in PG and the consequences**
- Clinical Lipidologist will be able to describe principles of **Dyslipidemia management during gestation**
- Clinical Lipidologist will be familiar with **strategies for reducing long term CVD risk for women who plan who are or recently have been Pregnant (PG)**

Total and Rate of Weight Gain by Pre-Pg BMI

Pre Pg. BMI	BMI (Kg/m^2)WHO	Total Range(lbs)	Rates 2nd ▲ LBS/week	and 3rd ▲ LBS/week
Underweight	<18.5	28-40	0.51(0.44-0.58)	1(1-1.3)
NL weight	18.5-24.9	25-35	0.42(0.35-0.5)	1(0.8-1)
Overweight	25.0-29.9	15-25	0.28(0.23-0.33)	0.6(0.5-0.7)
Obese	≥30	11-20	0.22(0.17-0.27)	0.5(O.4-0.6)

Assumes 0.5-2Kg(1.1-4.4lbs) weight gain in first ▲

Provisional NL BMI twins 37-54lbs,overweight 31-50lbs,obese 25-42lbs

Slide title

Presentation

The University of Oklahoma Health Sciences Center

Medicine

Evolution of Cardiovascular Disease in the HIV patient

Robert S. Rosenson, MD, FNLA
Professor of Medicine
Director, Cardiometabolic Disorders
Mount Sinai Heart
Mount Sinai School of Medicine
New York, NY

47 y Latino Referred for Evaluation of Chest Tightness and Exercise Intolerance

- Several months of chest tightness, palpitations and fatigue with moderately-intense activity
- HIV infection 1998; Treatment delayed 1999
- Chronic infections with genital herpex simplex and hepatitis B
- AV nodal reentry tachycardia – S/P ablation
- Treatment with dolutegravir, abacavir/lamivudine/tenofovir

Diagnostic Studies

- Echocardiogram – mild to moderate hypocontractility of apex/apical septum;
  LVEF = 48%; reduced LV compliance
- Stress echocardiogram – no inducible ischemia
- Holter – isolated APBs
- FBG 102 mg/dL, Cr 1.61 mg/dL (eGFR 55.8 mL/min/1.73 m^2, ALT 27 U/L, TSH 1.54 µIU/mL
- NMR LipoProfile
  TC 171 mg/dL, HDL-C 27 mg/dL, TG 409 mg/dL
  Non-HDL-C
  LDL-P 1579 nmol/L, HDL-P 22 µmol/L
- Lp(a) 175 mg/dL

Objectives

- Discuss the evolution in cardiovascular disease in HIV patients
- Review lipoprotein abnormalities associated with HIV infection and HAART therapy and their importance in cardiovascular risk assessment.
- Discuss the limitations of current lipid modifying therapy in HIV patients

Cardiovascular Complications in HIV Pre-ART Era

Dilated Cardiomyopathy

- Prevalence 10-30% based on echocardiographic, observational and autopsy studies[1]
- Associated with significantly reduced CD4 T-cell count[1]
- Poor prognosis than those without DCM (101 days (95% CI: 42-146) vs. 472 days (95% CI: 383-560)[2]
- Pathogenesis:
  - Direct infection by HIV
  - Opportunistic infections (toxoplasmosis)
  - Mitochondrial dysfunction by non-nucleoside reverse transcriptase inhibitors (NNRTI)
  - Circulating toxins
  - Toxicity of alcohol, illicit or self-prescribed substances
  - Nutritional disorders

1. Rerkpattanapipat P, et al Arch Intern Med 2000;160:602-608, 2. Currie PF, et al. BMJ 1994;309:1605-1607, 3. Prendergast BD. Heart 2003;89:793-800

Cardiovascular Complications in HIV Pre-ART Era

Pericardial Disease

- Frequency between 5% and 46% with incidence of 11-17% per year[1,2]
- Associated with significantly reduced CD4 T-cell count[1]
- Pathogenesis:
  - Opportunistic infections
  - Malignacy

Post-ART Era:

- Control of herpes virus 8 and Epstein-Barr virus infection, which are both associated with HIV-related tumors, have contributed to the reduced incidence of pericardial effusion in HIV-infected patients in recent years

[1]Heidenreich PA, et al. Circulation 1995;92:3229-3234, [2]Resteppo CS, et al. Radiographics 2006;26:213-231.

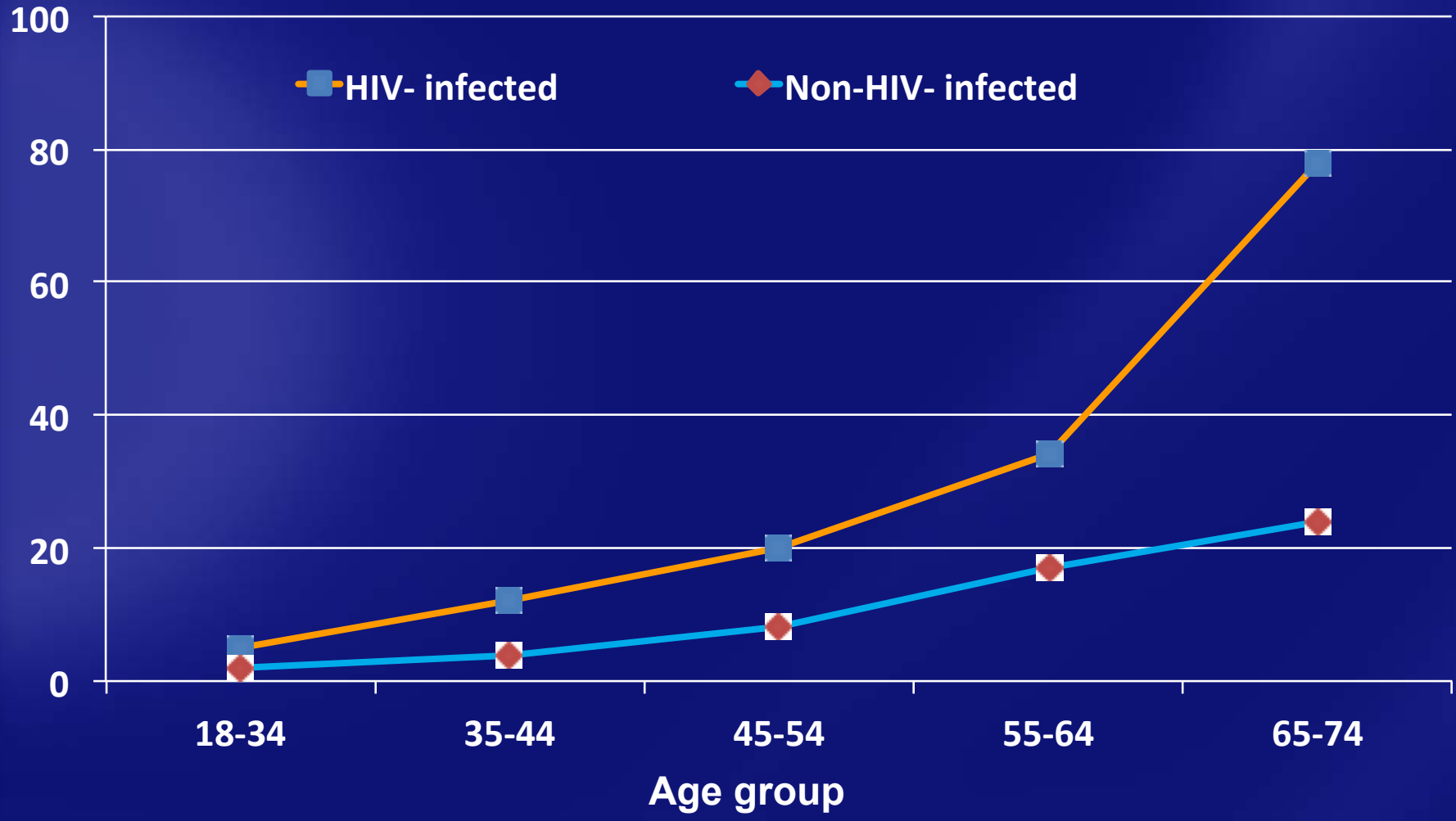
Cardiovascular Complications in HIV Pre-ART Era

Pulmonary Arterial Hypertension (PAH)

- Prevalence 1/200 HIV-infected patients vs 1/200,000 in general population[1]
- Devastating, progressive disease assoicated with severe cardiac impairment, poor quality of life, right ventricular failure and death
- Occurs in HIV-infected patients without predisposing risk factors such as intravenous durg use, thromboembolic disease or pulmonary infection
- More common in young men (mean age 32 y)
- Pathology of HIV-associated PAH shares similarities with PAH of different etiologies[2]
- Prevalence has not changed in ART era. Risk associated with drug use, homosexulaity and hemophilia[1]

1. Speich R, et al Chest 1991;100:1268-71, 2. Limsukon A, et al. Mt Sinai J Med 2006;73:1037-44,
3. Rerkpattanapipat P, et al Arch Intern Med 2000;160:602-608

MI Rates in HIV- and Non-HIV-Infected Patients

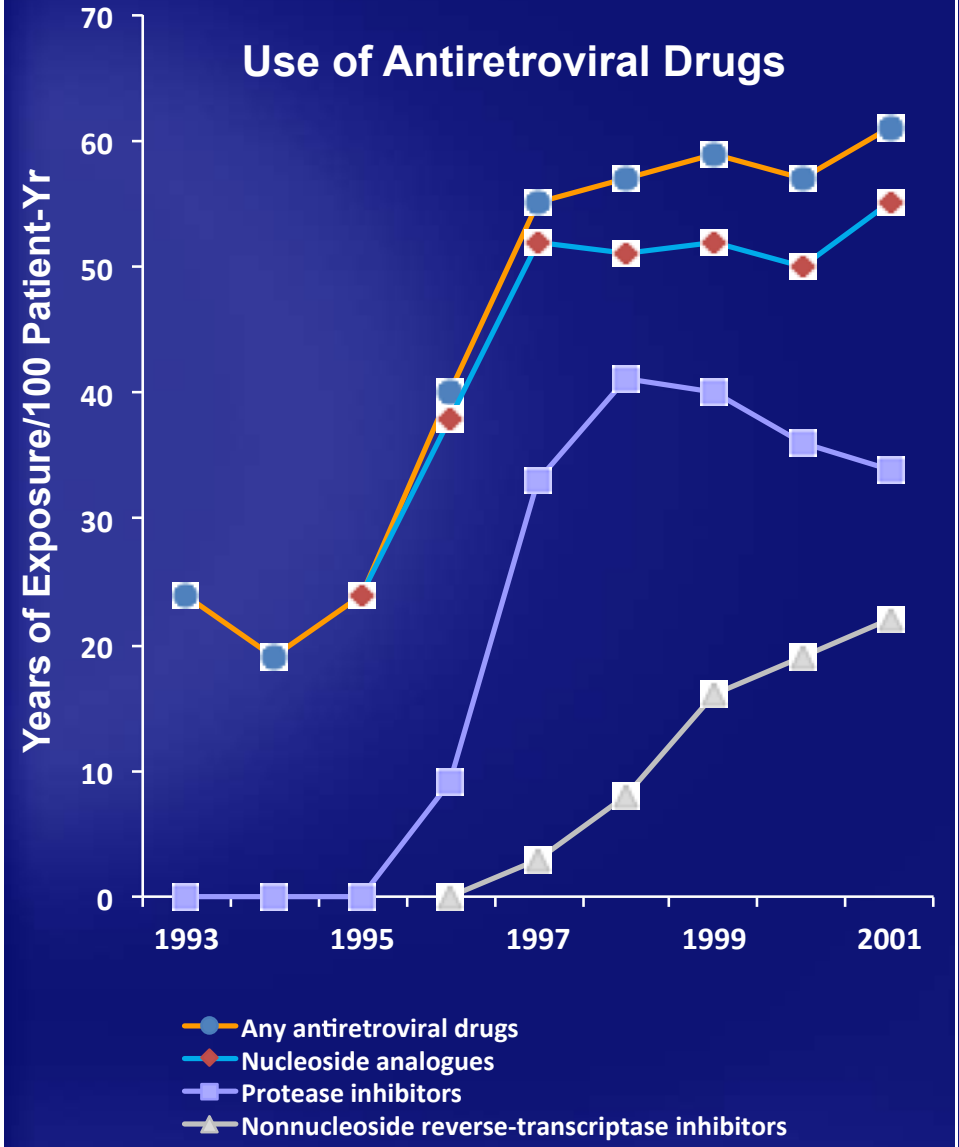


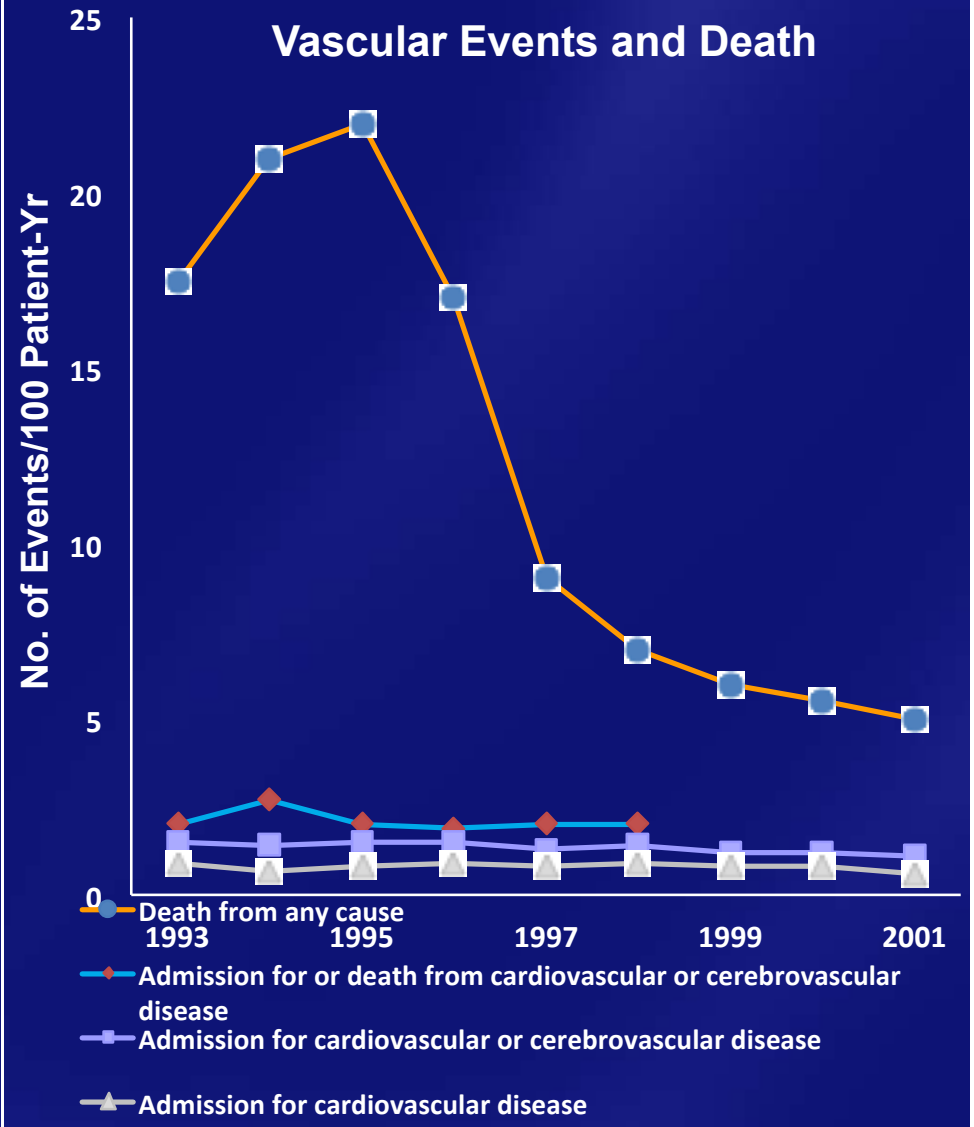
Schambelan M, et al. Circulation 2008;118:e48-e53.

Anti-Retroviral Therapies

- Non-nucleoside reverse transcriptase inhibitors (NNRTI)
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Protease inhibitors (PI)
- Fusion Inhibitor
- Integrase Inhibitors
- CCR5 Anatagonist

Changes in Antiretroviral Drug Use and Vascular Events





Bozzette SA, et al. N Engl J Med. 2003;348:702-710.

Risk of Events Related to Exposure to Antiretroviral Drugs

Antiretroviral Drug or Combination	All Cause Death		Admission for CVD or CVAD or All Cause Death	
	HR (95% CI)*	P-Value*	HR (95% CI)*	P-Value*
NRTI	0.67 (0.62 – 0.72)	<0.001	0.69 (0.64 – 0.74)	<0.001
PI	0.54 (0.47 – 0.61)	<0.001	0.56 (0.49 – 0.64)	<0.001
NNRTI	0.62 (0.50 – 0.77)	<0.001	0.62 (0.50 – 0.76)	<0.001
NA + PI	0.36 (0.32 – 0.41)	<0.001	0.38 (0.34 – 0.44)	<0.001
NA + NNRTI	0.41 (0.33 – 0.52)	<0.001	0.42 (0.34 – 0.53)	<0.001

*Comparing events related to exposure for 24 months vs 0 months
NRTI = nucleoside reverse-transcriptase inhibitor; PI = protease inhibitor; NA = nucleoside analogue
NNRTs = nonnucleoside reverse-transcriptase inhibitor
CVD = cardiovascular disease; CVAD = cerebrovascular disease

Bozzette SA, et al. N Engl J Med. 2003;348:702-710.

Factors That Potentially Influence Cardiovascular Risk in HIV Patients

Increase Cardiovascular Risk	Decrease Cardiovascular Risk
Dyslipidemia, insulin resistance, body habitus changes associated with HIV itself and certain components of ART	Control of viral replication with ART improves endothelial function
High rates of other cardiovascular risk factors, in particular smoking	Current antiretroviral regimens have more favorable effects on metabolic parameters and morphological changes than earlier regimens
Prolongation of survival: Older patients are intrinsically at greater cardiovascular risk	ART reduces inflammatory markers and immune activation
	HIV providers more aggressive about modification of ART or initiation of lipid-lowering therapies

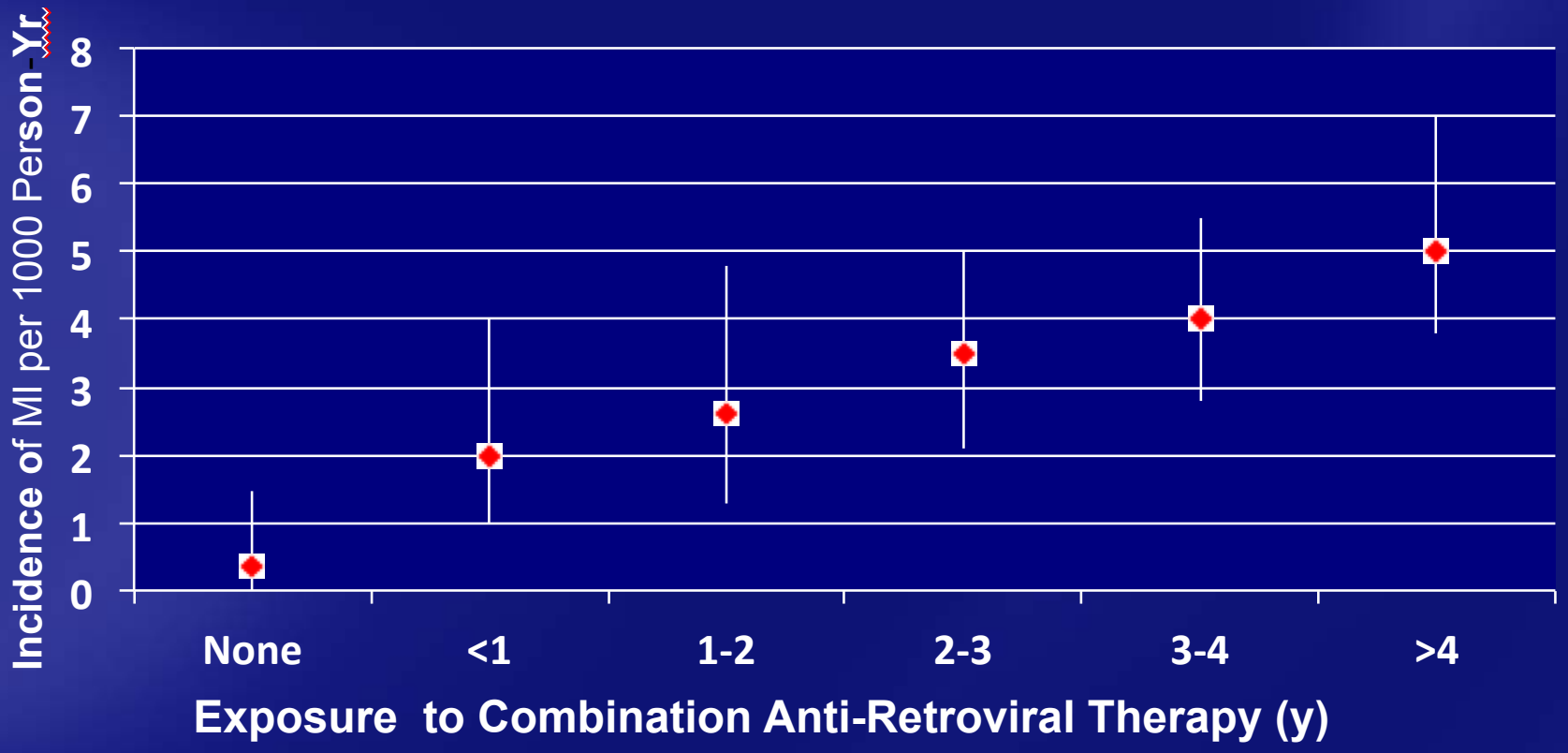
Currier JS, et al. Circulation 2008;118:e29-e35.

Predictors of Coronary Artery Stenosis 50% Among HIV-Infected ART-Treated Men

Variable	Minimally Adjusted Risk §		Model Adjusted for CAD Risk Factors¶	
	RR (95% CI)	p-Value	RR (95% CI	p-Value
Current HIV RNA level > copies/mL	1.26 (0.76-2.10)	0.37	1.43 (0.84-2.43)	0.187
Duration of HAART use	1.09 (1.02-1.17)	0.007	1.09 (1.02-1.17)	0.007
History of AIDS	1.49 (0.92-2.41)	0.103	1.40 (0.82-2.26)	0.170
Current CD4+ T cell count	1.01 (0.93-1.09)	0.002	0.80 (0.69-0.94)	0.0005

§ Adjusted for age, race, CT scanning center and cohort before or after 2001.
¶Adjusted for age, race CT scanning center, cohort, and CHD risk factors, SBP, antihypertensive medications, diabetes medication use, fasting glucose, total and HDL-C levels, use of lipid lowering agents, BMI and pack years of cigarette smoking

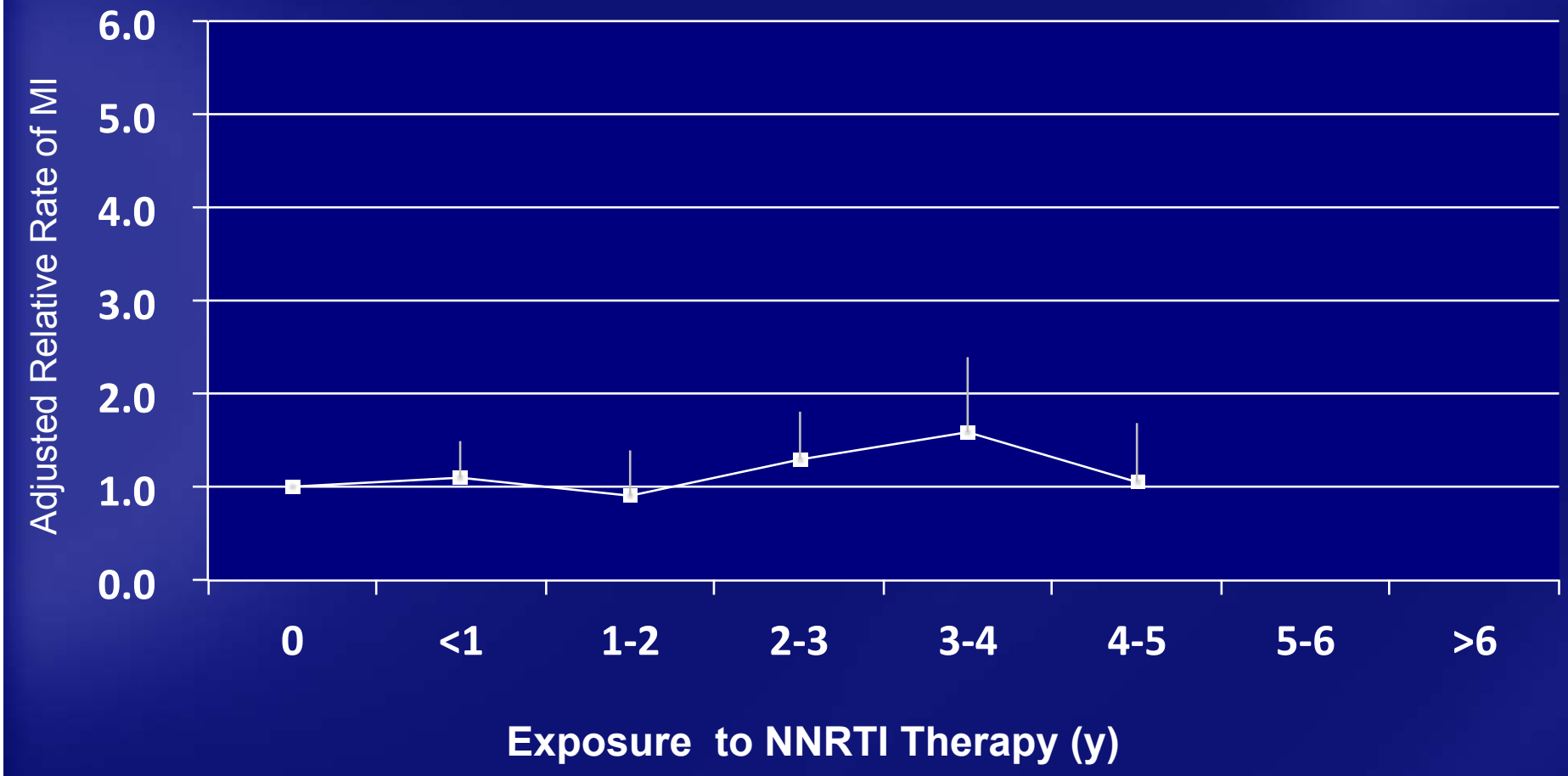
Incidence of MI with Exposure to Combination Antiretroviral Therapy



# events	3	9	14	22	31	47
# person-years	5714	4140	4801	5847	7220	8477

The Data collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group*
N Eng J Med. 2003;349:1993-2003.

Risk of MI with Exposure to NNRTIs

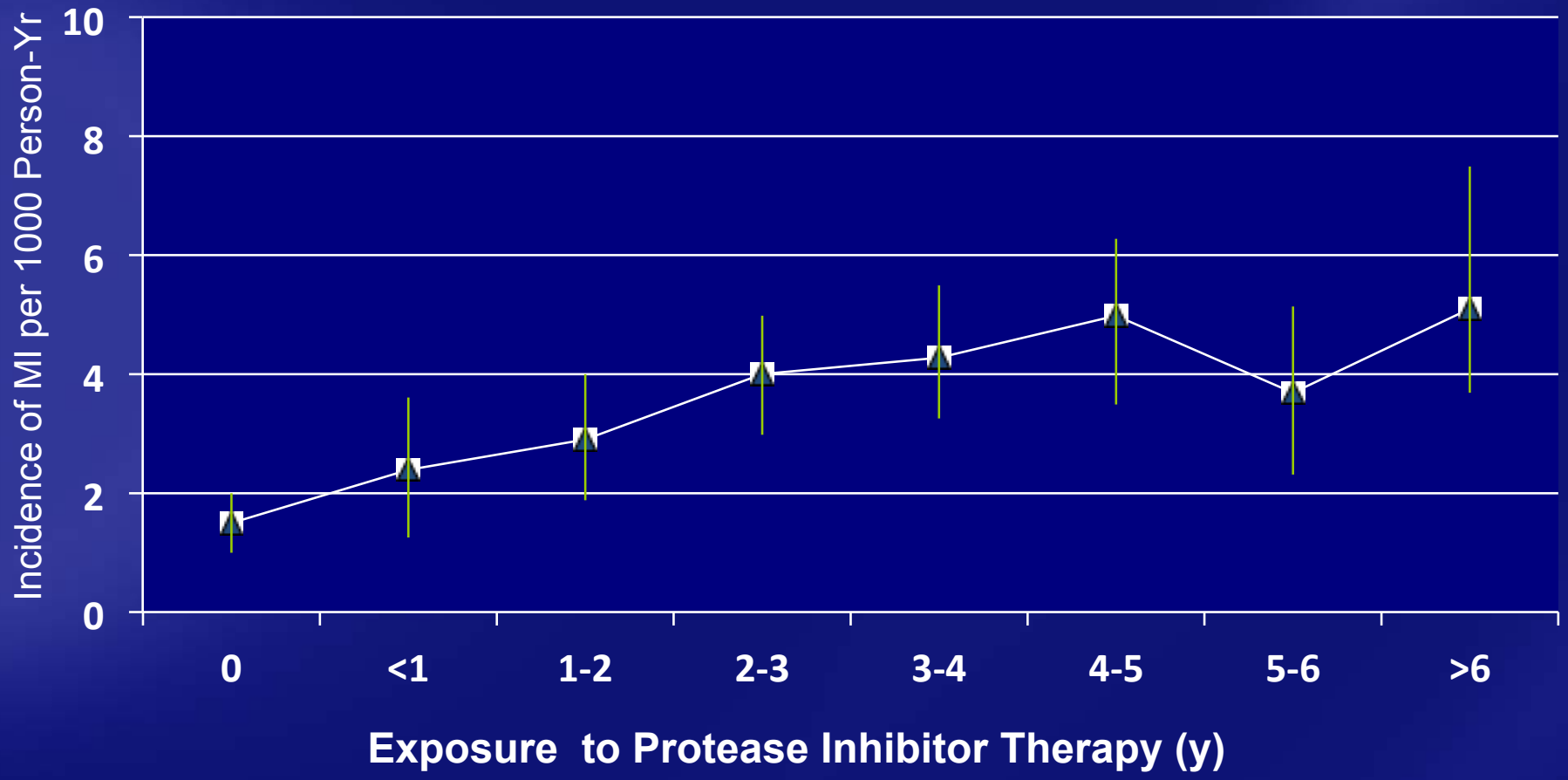


DAD Study Group. N Eng J Med. 2007;356:1723-1735.

Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

- Delavirdine (DLV)
- Efavirenz (EFV)
- Etravirine (ETR)
- Nevirapine (NVP)
- Rilpivirine (RPV)

Risk of MI with Exposure to Protease Inhibitors

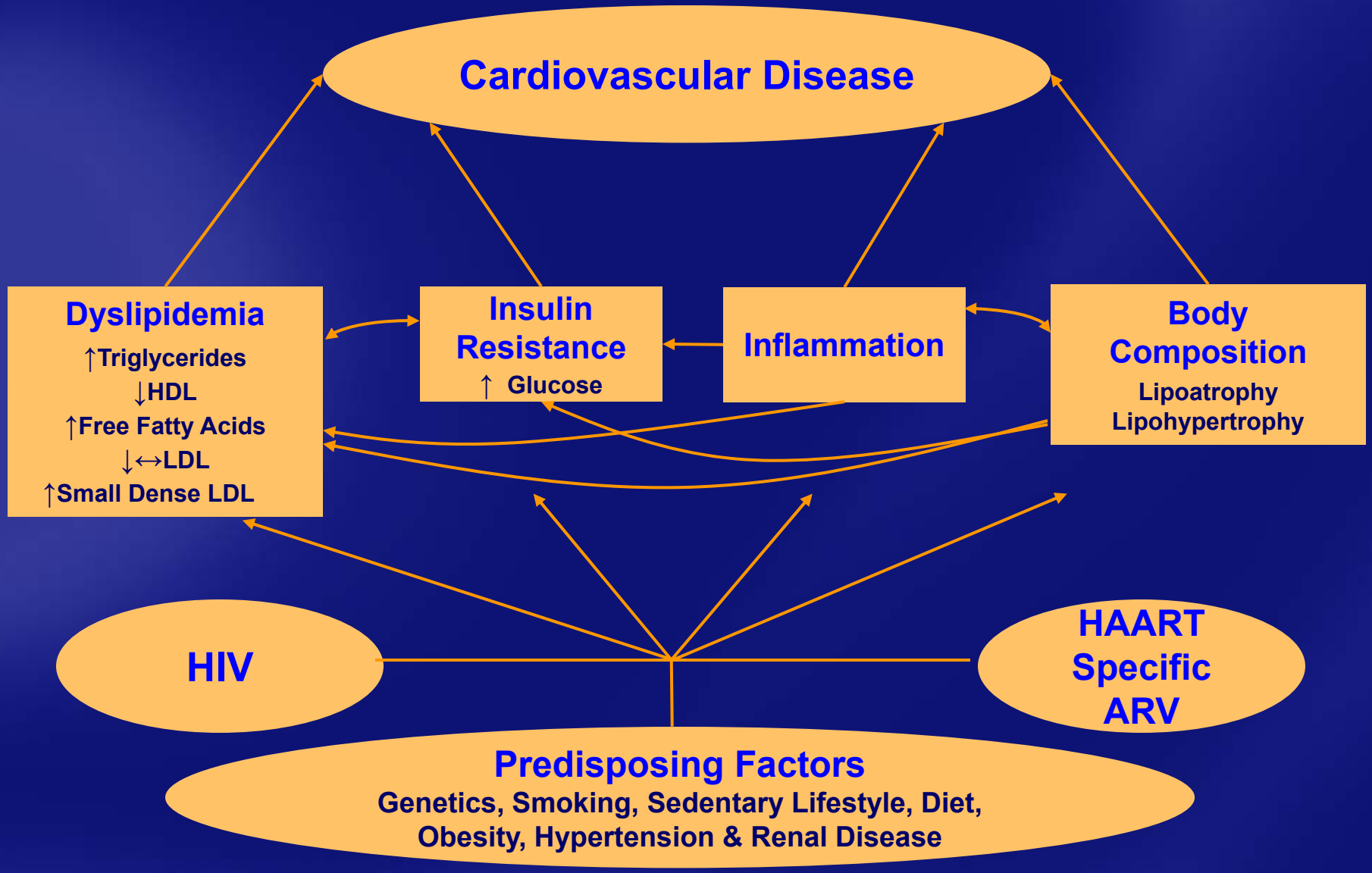


DAD Study Group. N Eng J Med. 2007;356:1723-1735.

Protease Inhibitors

- Atazanavir (ATV)
- Darunavir (DRV)
- Fosamprenavir (FPV)
- Indinavir (IDV)
- Lopinavir/ritonavir (LPV/rKaletra)
  (boosting agent)
- Nelfinavir (NFV)
- Ritonavir (RTV)
- (used as a pharmacokinetic boosting agent)
- Saquinavir (SQV)
- Tipranavir (TPV)

CVD in HIV: Risk Factors in Post-ART Era



Grunfeld C, et al. Circulation 2008;118:e20-e28.

Increased Mortality in HIV–Infected Subjects with High Baseline sCD14 Levels

Biomarker	<25th Percentile(Reference)	25th – 49th Percentile OR (95% CI)	*P*	50th – 74th Percentile OR (95% CI)	*P*	≥74th Percentile OR (95% CI)	*P*
sCD14 ($\times 10^6$ pg/mL)							
N (case patients/control subjects)	10/46	16/39		21/35		27/28	
Univariate	1.0	2.1 (0.8–5.7)	.12	3.3 (1.3– 8.6)	.01	6.0 (2.2–16.1)	<.001
Adjusted—risk factors[a]	1.0	2.8 (0.8–10.0)	.10	2.7 (.8–9.0)	.11	8.0 (2.0–31.9)	.003

Sandler NG, et al. JID 2011;203:780-9

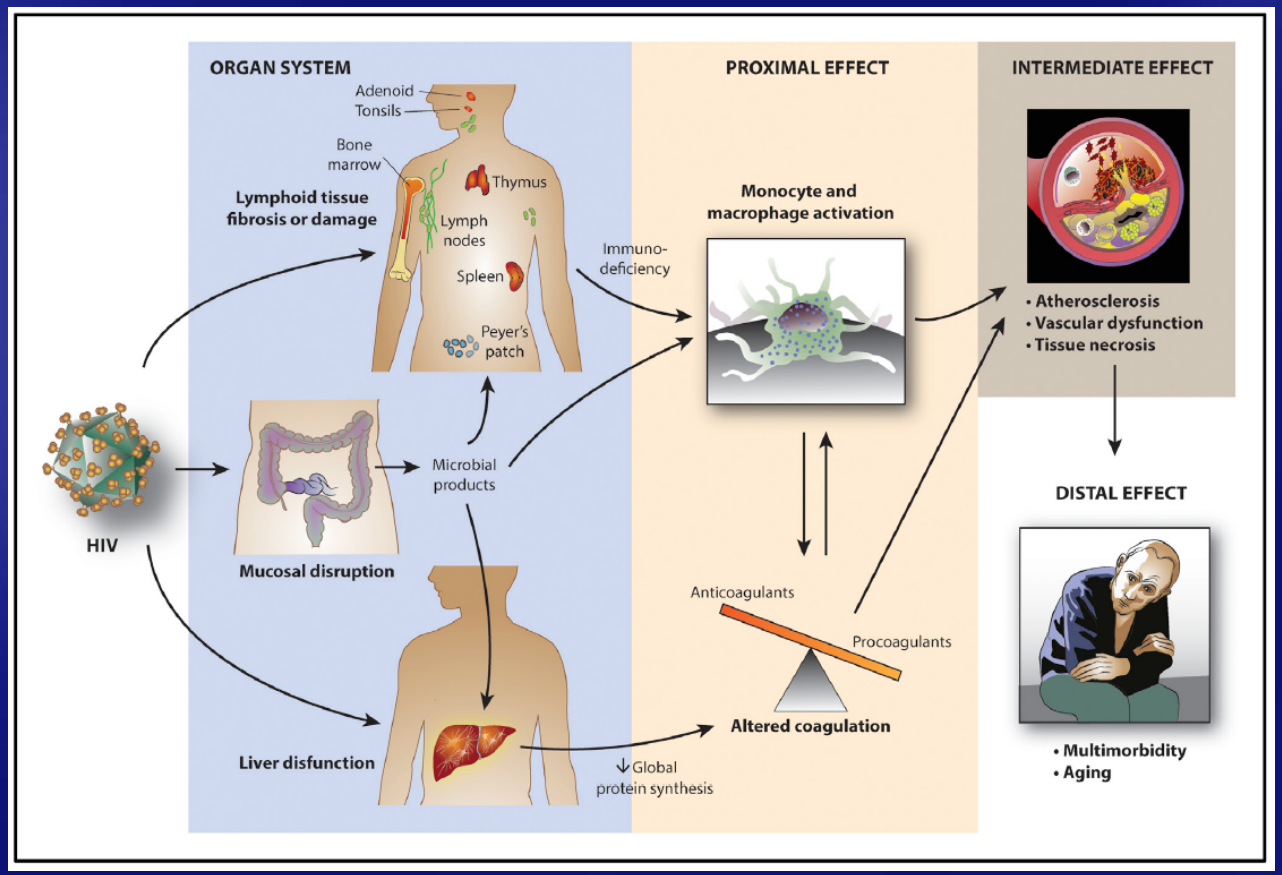
Association Between Inflammatory Macrophage Markers and Measures of Subclinical Carotid Artery Disease

Women's Interagency HIV Study

	Any Carotid Artery Lesion			Distensibility ($10^{-6} \times N^{-1} \times m^2$)		
	Odds Ratio	95% CI	*P* Value	B	95% CI	*P* Value
Individual inflammatory macrophage markers, per each standard deviation						
Among entire study population (n=256)						
Gal-3BP	1.48*	1.01, 2.15*	0.04*	−1.44*	−2.28, −0.61*	<0.001*
sCD163	1.85*	1.21, 2.83*	0.005*	−0.05	−1.26, 1.15	0.93
sCD14	1.49*	1.04, 2.12*	0.03*	−1.11*	−2.10, −0.12*	0.03*

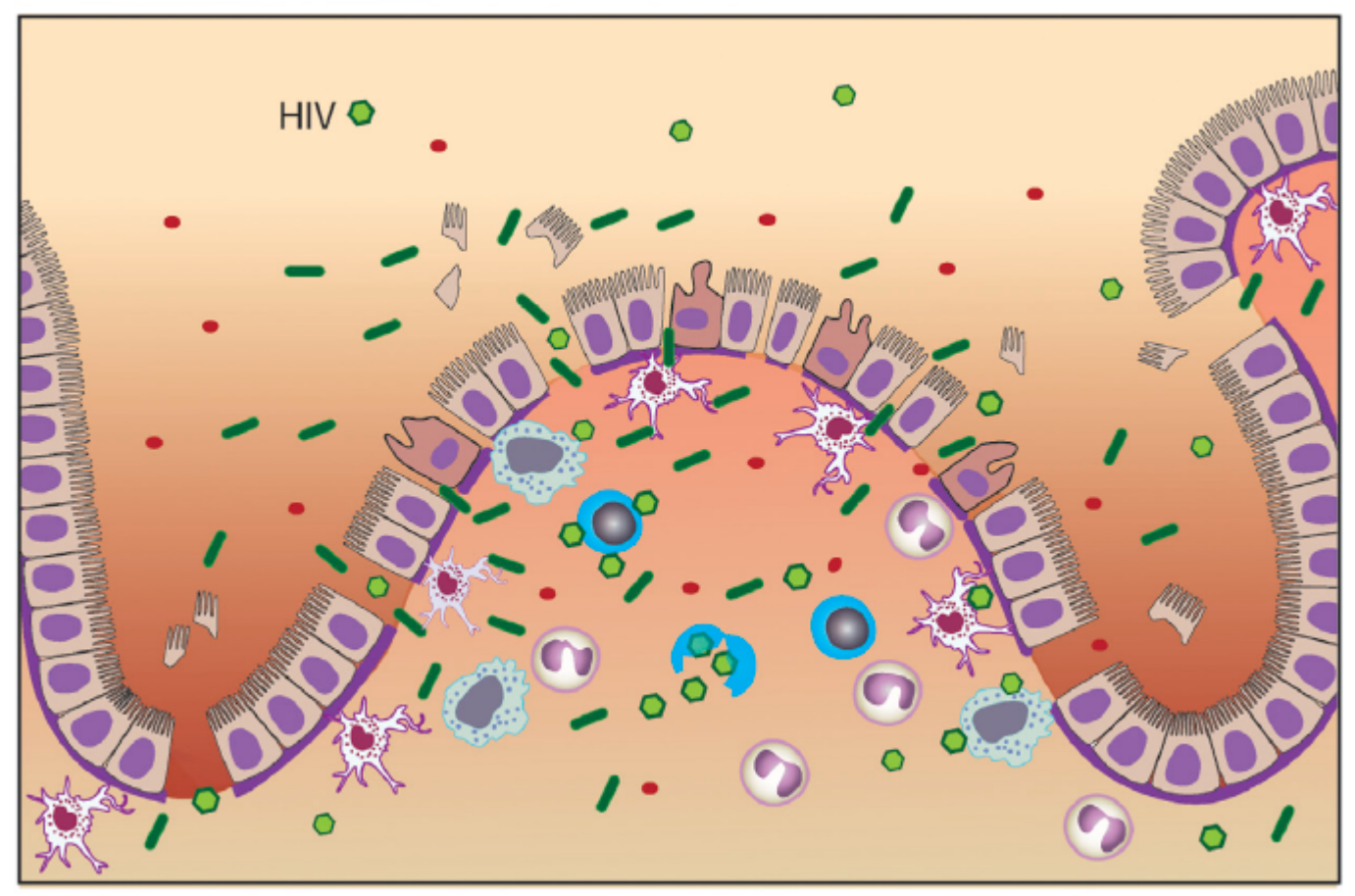
Shaked I, et al. *Arterioscler Thromb Vasc Biol* 2014;34:1085-92

Pathogenesis of Inflammation-Associated Disease in HIV-Infected Adults



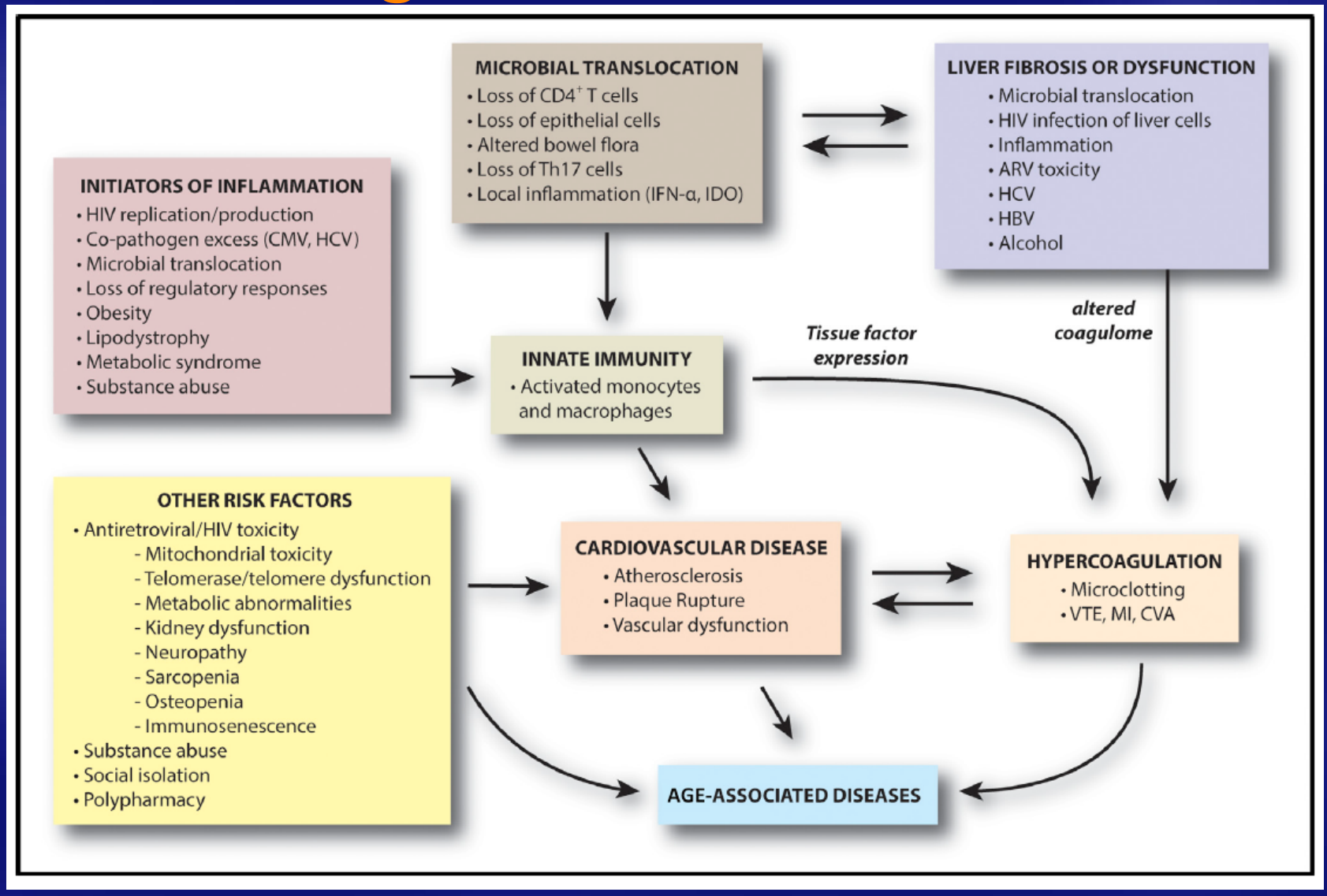
Deeks S, et al. Immunity. 2013;39:633-45

Impact of HIV on Gut Mucosa



Deeks S, et al. Immunity. 2013;39:633-45

Impact of HIV on Inflammation, Coagulation, and Health



Deeks S, et al. Immunity. 2013;39:633-45

Changes in Lipids and Lipoproteins After 24 Weeks of Antiretroviral Therapy

Lipids, Lipoproteins	NRTIs + Efavirenz (PI-Sparing)	NRTIs + Lopinavir/ritonavir (NNRTI-Sparing)	Efavirenz + Lopinavir/ritonavir (NRTI-Sparing)	P_{KW}
Total-C, mg/dL	18* (3 – 29)	21* (6 – 57)	65* (6 – 57)	<0.001
Triglycerides, mg/dL	22 (-49 – 79)	72* (-1 – 186)	83* (11 – 164)	0.051
Direct LDL-C, mg/dL	6 (-5 – 24)	7 (-8 – 19)	26* (11 – 54)	<0.001
HDL-C, mg/dL	9* (5 – 15)	3# (-1 – 13)	11* (7 – 17)	0.053
VLDL-P, nmol/L	13 (-16.6 – 33.4)	26.3* (2.8 – 60.3)	48.3* (14.2 – 84.4)	
LDL-P, nmol/L	64 (-65 – 167)	135# (-115 – 312)	414* (120 – 740)	0.003
Small LDL-P, nmol/L	101 (-162 – 207)	127 (-162 – 357)	371 (-9 – 720)	0.039
HDL-P, µmol/L	5.3*	5.1*	8.3*	0.069

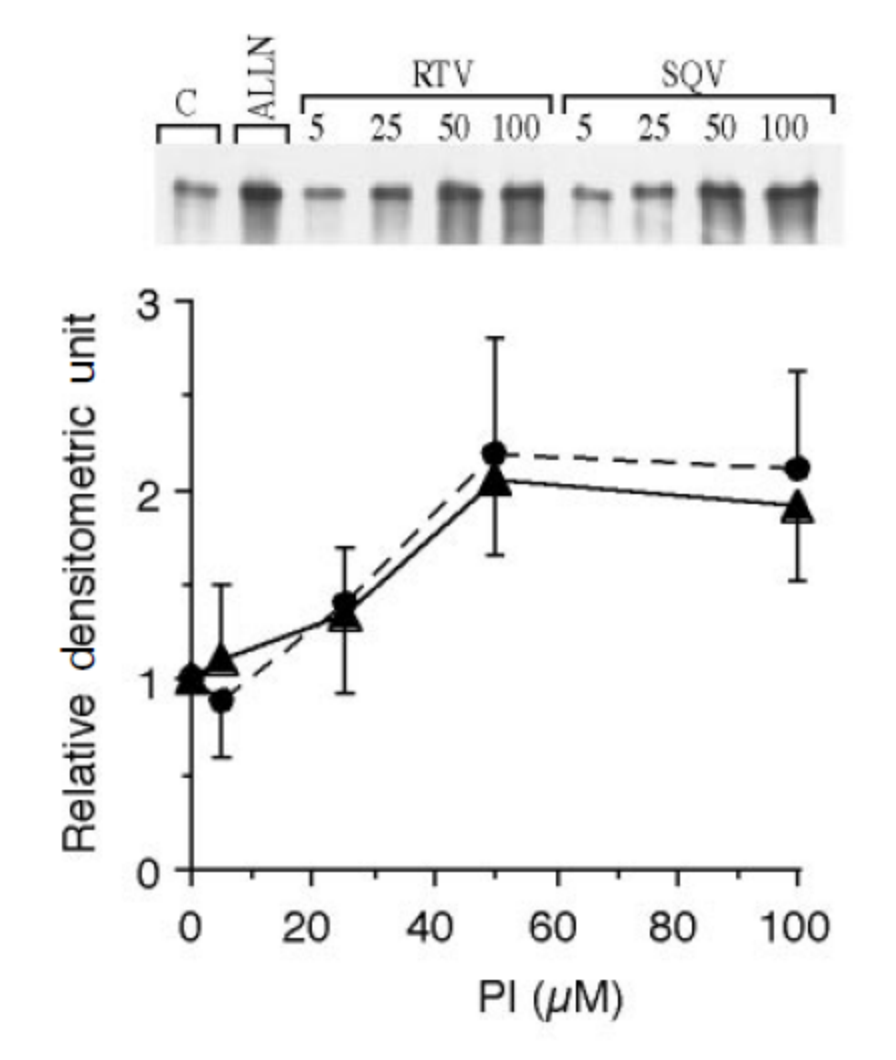
All values are medians (interquartile ranges) ; C (eg, LDL-C) = cholesterol, P (eg, LDL-P) = particle number
**p<0.01 compared to baseline, Wilcoxon signed rank probability test*
#0.01≤p<0.05 compared to baseline, Wilcoxon signed rank probability test

N Eng J Med. 2003;349:1993-2003.

Mechanisms for ART-Induced Lipoprotein Abnormalities

- Interference with ApoB proteasomal degradation
- Increased ApoC-III containing lipoproteins due to overproduction and impaired clearance
- Reduced lipoprotein lipase activity due to visceral adiposity (lipodystrophy), insulin resistance and acute phase response due to opportunistic infections

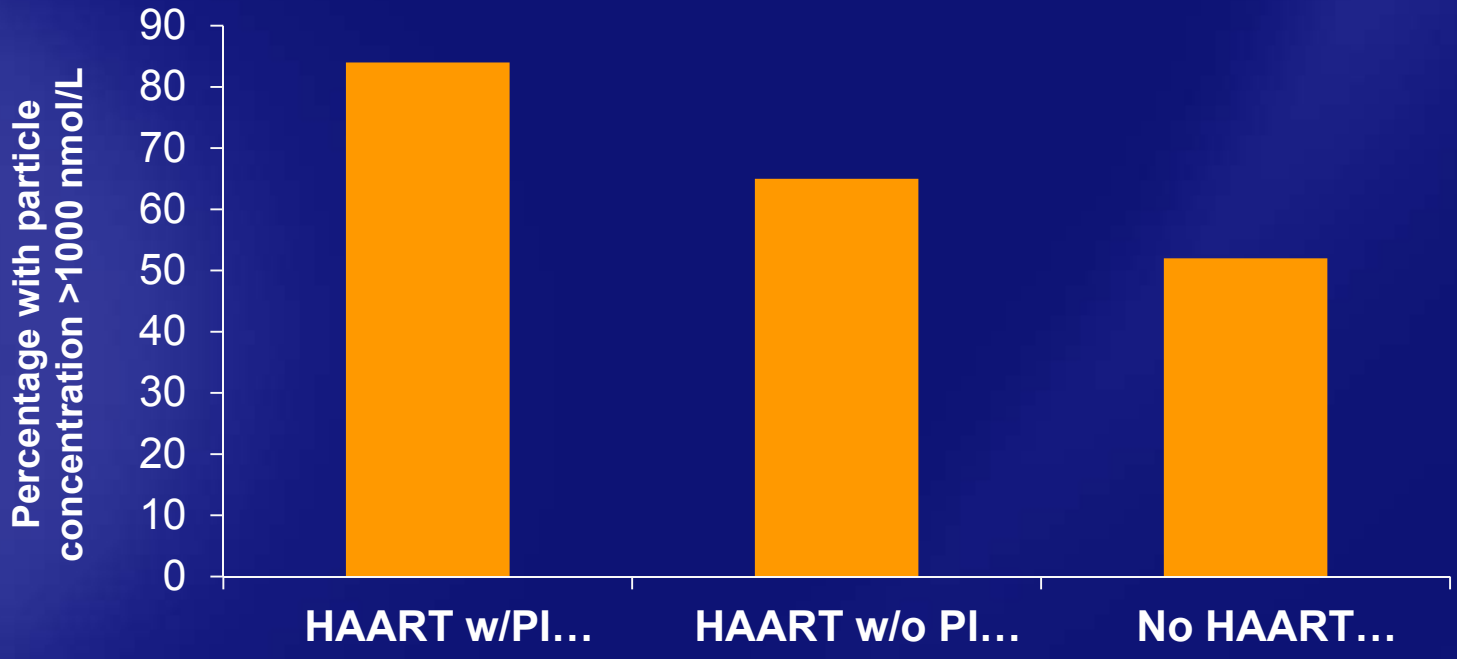
HIV Protease Inhibitor Protect ApoB Degradation by the Proteasome



PI treatment results in accumulation of cellular ApoB and ubiquitin-associated ApoB in HepG2 cells

Liang J-S, et al. Nat Med 2001;7:1327-31

Elevated LDL Particle Number in HIV-Infected Ethnic Minorities

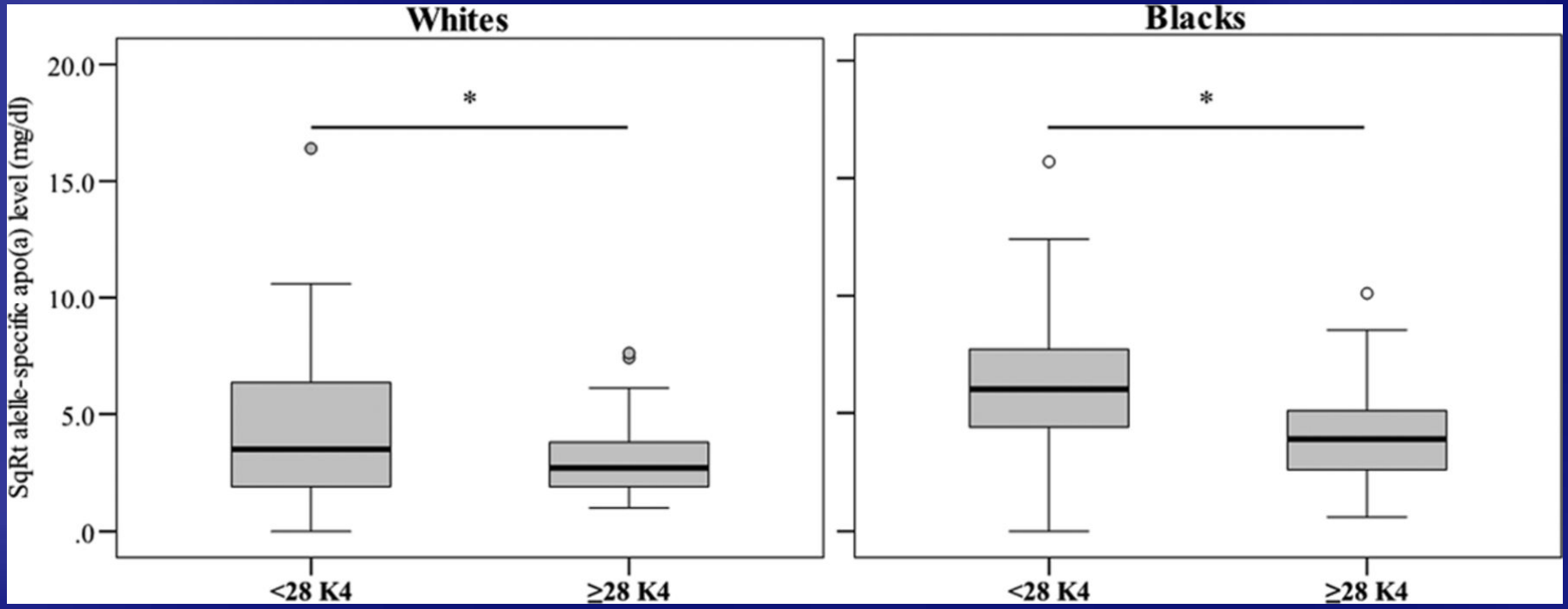


- **Participants recruited from a RCT of a dietary supplement to manage HIV-related dyslipidemia**
- **Cohort was 64% male; 92% African American**

Swanson B et al, J Clin Lipidol 2009;3:379-381

Lipoprotein (a) and HIV Disease Activity

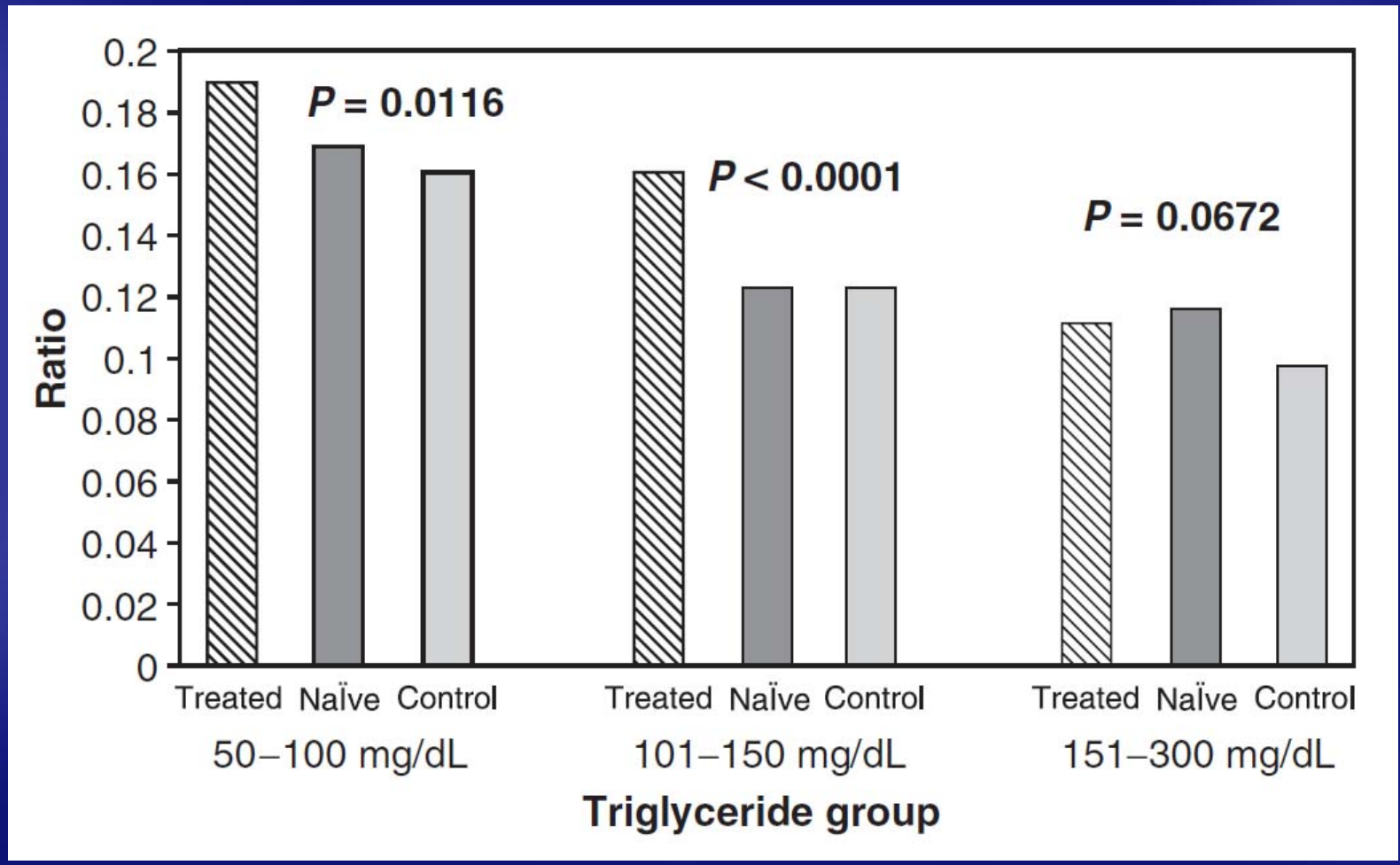
Allele-specific apo(a) Levels for Smaller apo(a) sizes (<28 kringle [K] 4 repeats)



**P*<0.001.

Enkhmaa et al. Arterioscler Thromb Vasc Biol 20143;33:387-92

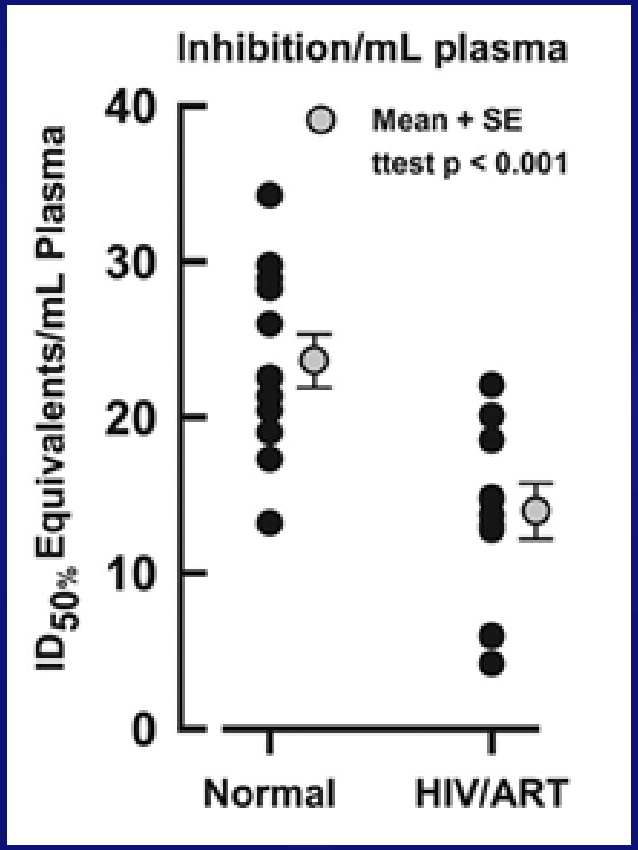
ApoC-III Triglyceride-Rich Lipoproteins are Elevated in HIV+ Men Treated with ART



Rimland D, et al. HIV Medicine 2005;6:326-33

Reduced HDL Functionality in HIV/ART

Inhibitory potency of each patient's plasma needed to achieve 50% inhibition of hepatic CE uptake



Gillard BK, et al. *Arterioscler Thromb Vasc Biol* 2013;33:1714-21

Drug Interactions – PI and Statins

Drug	PI	Effect on PI on Statin Levels	Recommendation
Lovastatin	All	Significant ↑ Levels	Contraindicated
Simvastatin	All	Significant ↑ Levels	Contraindicated
Pravastatin	DRV/r	AUC ↑	Use lowest dose
	LPV/r	AUC ↑	No adjustment
	SQV/r	AUC ↓ 47-50%	No adjustment
Pitavastatin	All	AUC ↑ 31%	No adjustment
Rosuvastatin	ATV/r	AUC ↑ 300%	Dosage ≤10 mg/d
	LPV/r	AUC ↑ 108%, Cmax ↑ 366-700%	Dosage ≤10 mg/d
	DRV/r	AUC ↑ 48%, Cmax ↑ 139%	Dosage ≤10 mg/d

Kellick KA, et al. J Clin Lipidol 2014;8:S30-S46

Drug Interactions – PIs and Statins

Drug	PI	Effect on PI on Statin Levels	Recommendation
Atorvastatin	ATV/r	↑ Levels	Lowest dosage
	DRV/r	AUC ↑ 400%	Dosage ≤20 mg/d
	FPV/r	AUC ↑ 400%	Dosage ≤20 mg/d
	FPV	AUC ↑ 130-153%	Dosage ≤20 mg/d
	SQV/r	AUC ↑ 79%	Dosage ≤20 mg/d
	LPV/r	AUC ↑ 488%	Lowest dosage
	TPV/r	AUC ↑ 836%	Do not use

Kellick KA, et al. J Clin Lipidol 2014;8:S30-S46

Drug Interactions – NNRTIs and Statins

Drug	NNRTI	Effect on NNRTI on Statin Levels	Recommendation
Lovastatin	Efavirenz	Significant ↑ levels	Contraindicated
	Etravirine	↓ lovastatin levels	---
Simvastatin	Nevirapine	↓ simvastatin levels	---
Pravastatin	Efavirenz	AUC ↓ 44%	Adjustment based on lipid levels
	Etravirine	No significant effect	No adjustment
Fluvastatin	Etravirine	↑ Fluvastatin possible	Cautious use
Rosuvastatin	Etravirine	No significant effect	No adjustment
Pitavastatin	Efavirenz Etravirine Nevirapine Rilpivirine	No data	No recommendation

Kellick KA, et al. J Clin Lipidol 2014;8:S30-S46

Fixed Combination ARTs

- Abacavir-lamivudine (ABC/3TC)
- Abacavir-lamivudine-zidovudine (ABC/3TC/ZDV) Trizivir
- Efavirenz-tenofovir-emtricitabine (EFV/TDF/FTC)
- Elvitegravir-cobicistat-tenofovir-emtricitabine (EVG/COBI/TDF/FTC)
- Tenofovir-emtricitabine (TDF/FTC)
- Rilpivirine-emtricitabine-tenofovir (RPV/FTC/TDF)
- Zidovudine-lamivudine (ZDV/3TC)

Lipid Changes in Comparator Studies of 3 Commonly Used ART Therapies

	Elvitegravi, Cobicstat, Emtricitabine Tenofovir (N=701)		**Efavirenz/emtricitabine/tenofovir (N=352)**		**ATV + RTV +** Emtricitabine/ tenofovir	
	Baseline	Wk 96	Baseline	Wk 96	Baseline	Wk 96
	mg/dL	% Change	mg/dL	% Change	mg/dL	% Change
TC	166	+12	161	+20	168	+11
LDL-C	100	+12	97	+17	101	+13
HDL-C	43	+7	43	+9	42	+6
TG	122	+8	121	+17	132	+25

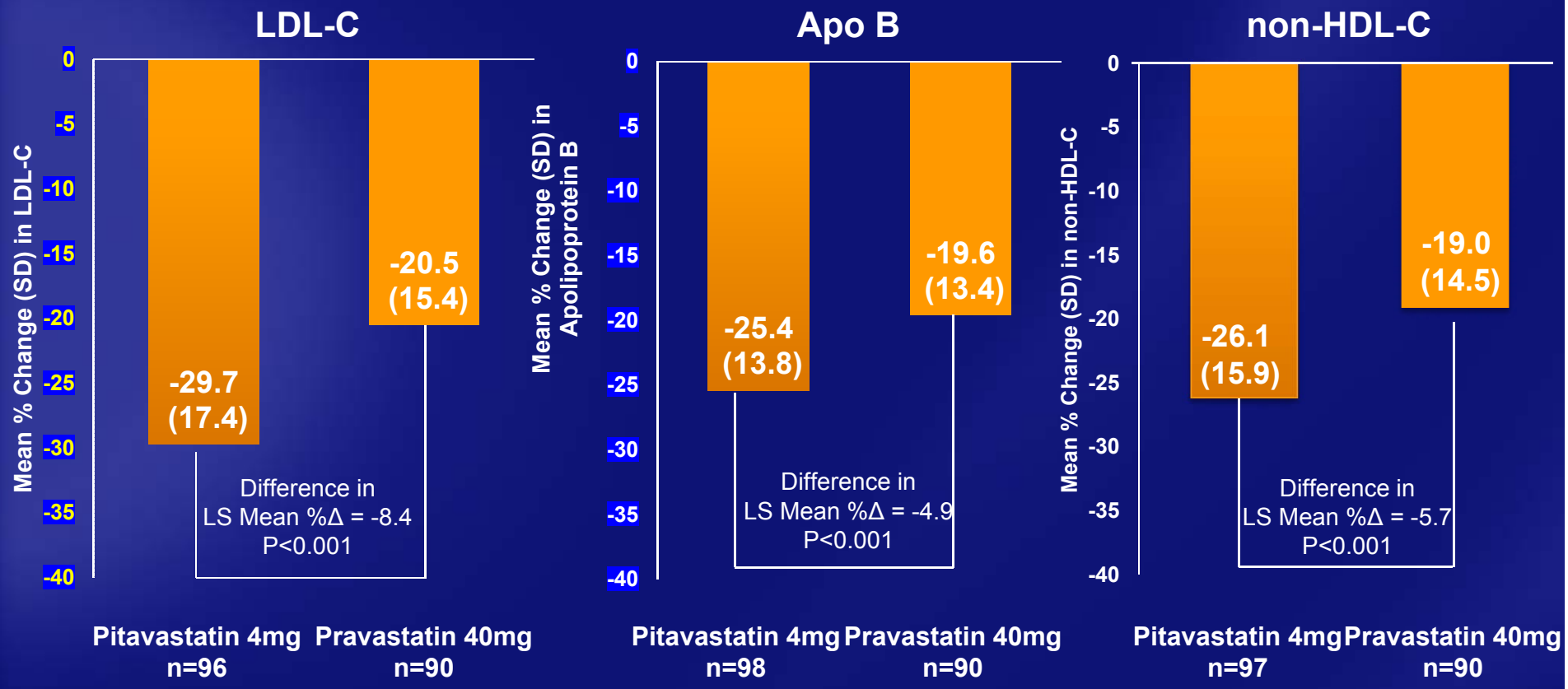
Product circular

Commonly Used Combination ART and Interactions with Statins

- Emtricitabine/tenofovir
  - No reported interactions
- Efavirenz/emtricitabine/tenofovir
  - Simvastatin ↓AUC 68% (62-73)
  - Atorvastatin ↓ AUC 43% (34-50)
  - Pravastatin ↓ AUC 44% (26-57)
- Elvitegravir, cobicstat, emtricitabine, tenofovir
  - Lovastatin, Simvastatin (contraindication)
  - Atorvastatin ↑ levels (start lowest dose, titrate carefelly
  - Rosuvastatin – No interaction

Ref – Product circulars

HIV-Infected Individuals: Mean Percent Change from Baseline to Week 52 in LDL-C, ApoB, non-HDL-C (INTREPID)



Sponseller CA, et al. CROI 2014, poster presented

INTREPID: Change from Week 0 to 52 in HIV-1 RNA Viral Load, CD4 Cell Count, and hs-CRP

Parameter	Pitavastatin 4 mg (n=98)	Pravastatin 40 mg (n=90)	P-value[b]
	Mean Change from Baseline (SD)		
HIV-1 RNA viral load, log copies[a]	0.03 (0.4)	0.07 (0.4)	0.81
CD4 count, cells/mm^3	-8.3 (124.0)	36.5 (157.5)	0.18
hsCRP, mg/L	-1.2 (6.5)	-1.1 (14.4)	0.08

[a]n= 97 for pitavastatin

[b]p-values from ANCOVA model of LS mean percent change from baseline

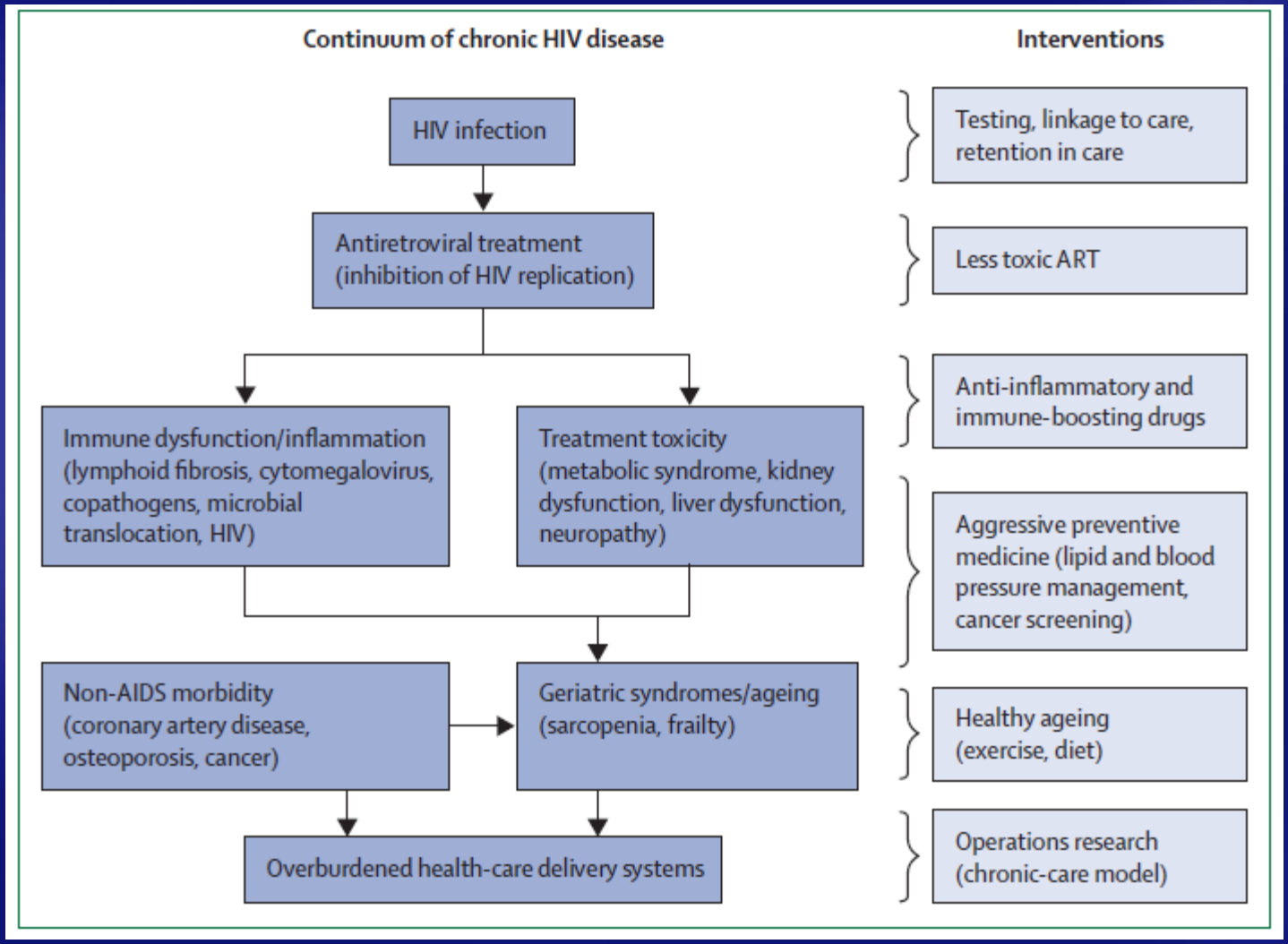
Sponseller CA, et al. CROI 2014, poster presented

REPRIEVE Trial

- NIH initiated multi-center randomized, placebo-controlled trial of pitavastatin 4 mg daily to prevent CVD events in HIV-infected individuals ≥40 years of age with LDL-C <130 mg/dL
- 6,500 individuals who have no current indication for a statin
- Thus, exclusions include patients with establsihed atherosclerotic CVD and diabetes.
- Primary endpoint: Major adverse cardiovascular events (MACE)
- Follow-up 5 years

NIH request for application –clinical sites

HIV Infection As A Chronic Disease



Deeks SG, et al. Lancet 2013;382:1525-33

Conclusions

- ART therapy has changed HIV-infection into a chronic illness characterized by high rates of atherosclerotic CVD disease
- The major contributing causes of CVD in ART-treated HIV patients includes inflammation, overproduction of apoB-containing lipoproteins, dysfunctional HDL and insulin resistance
- Risk reduction with statins is complicated by statin associated adverse muscle events with NNRTIs and drug interactions with PIs.
- Newer apoB-lowering therapies may be important in reducing residual risk in statin-ART treated HIV patients.