Application of New Lipid Guidelines to Clinical Practice: Evidence and Controversies

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Wexner Medical Center

Disclosures

- Advisory Board: Akcea Pharmaceuticals

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Case

- 42 y/o LAF is referred to you for evaluation of dyslipidemia
  - Referred for mixed dyslipidemia with abnormal LFTs
    - January: TC 205 TG 175 HDL 32 LDL 138
      - Started atorvastatin, 40 mg once daily
    - April: TC 144 TG 140 HDL 30 LDL 96
      ALT 78 AST 85 atorvastatin stopped
- FH: father had an MI at age 58
- SH: no tobacco, social EtOH, sedentary job
- PMH: Metabolic Syndrome x 10 years

Case
Labs

- May: *presents to your clinic off meds*
  - Lipids back to baseline: TC 200 TG 175 HDL 32 LDL 133
  - ALT 44 AST 53
- What do you do now?
  - Does this person need to be on a lipid lowering medication?
  - Review of medical records finds labs from ten years prior:
    - ALT 14 AST 18
    - TC 195 TG 125 HDL 41 LDL 129

Who Should be Treated with Lipid Lowering Agents?

- 42 y/o LAF with LDL 133 & abnormal LFTs
- 53 y/o whose LDL was “under control” and “passed” a recent stress test
- A 51 y/o who died of “natural causes” with a massive heart attack
- A 50 y/o who denied classic symptoms because she is a woman




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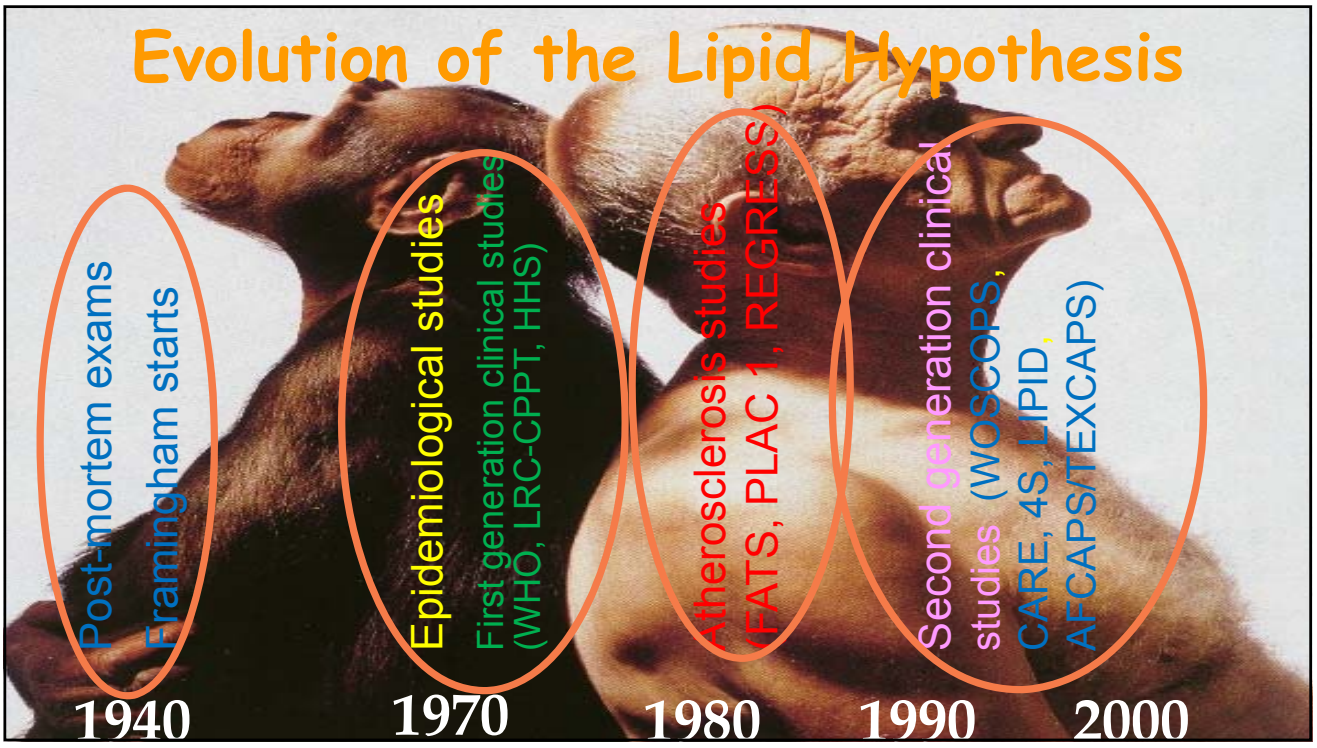


Dyslipidemia and Cardiovascular Disease

Key Announcements of 1988

NCEP ATP I

NCEP Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. Arch Intern Med 1988;148:36-69

Syndrome X

Reaven, Gerald M: Banting Lecture, 48th Annual Scientific Sessions ADA & "Role of Insulin Resistance in Human Disease" *Diabetes* 1988;*37:1495-1607*

Atherogenic Lipoprotein Phenotype: Pattern A & B

Austin MA, Breslow JL, Hennekens CH, Buring JE, Willett WC, Krauss RM. Annual Meeting AHA: Low Density Lipoprotein Subclass Patterns and Risk for Myocardial Infarction JAMA 1988;260:1917-1921

NHLBI & Cholesterol Guidelines

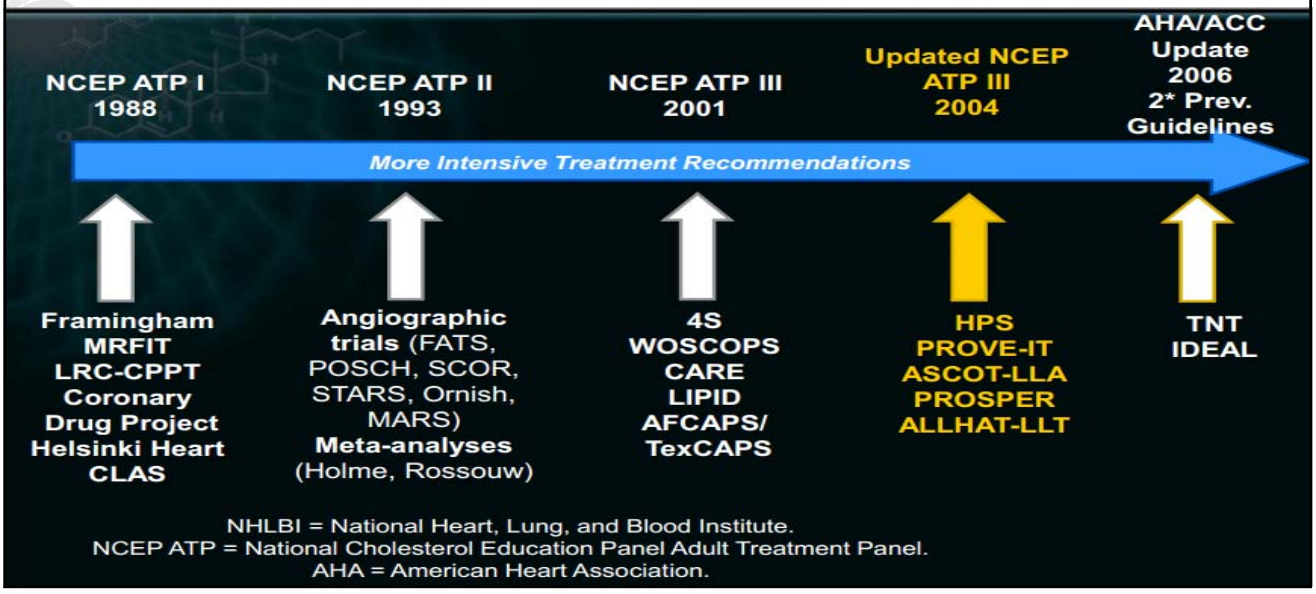
ATP history

The Adult Treatment Panel (ATP) of the National Cholesterol Education Program (NCEP) issued evidence-based sets of guidelines on cholesterol management

Their mandate was to update the guidelines when substantive evidence existed to merit revision

- ATP I: published 1988
- ATP II: published 1993
- ATP III: published 2001
- ATP IV was convened in 2008
  - Modified to be a clinical practice guideline developed under the NHLBI partnership model

Evolution of NHLBI Supported Guidelines
The Evidence Base



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2013: IAS Guidelines

ACC/AHA Guidelines

no change in AACE Guidelines

2014: NLA Guidelines

Stone NJ, et al.
2013 ACC/AHA Blood Cholesterol Guideline

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

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

Circulation. June 24, 2014

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

- In 2008, the NHLBI initiated the guidelines* by sponsoring rigorous systematic evidence reviews for each topic by expert panels convened to develop critical questions (CQs), interpret the evidence and craft recommendations.

*CPGs (clinical practice guidelines) for assessment of CV risk, lifestyle modifications to reduce CV risk, and management of blood cholesterol, overweight and obesity in adults

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

- In response to the 2011 report of the Institute of Medicine on the development of trustworthy clinical guidelines, the NHLBI Advisory Council (NHLBAC) recommended that the NHLBI focus specifically on reviewing the highest quality evidence and *partner* with other organizations to develop recommendations

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

- Accordingly, in June 2013 the NHLBI initiated collaboration with the ACC and AHA to work with other organizations to complete and publish the 4 guidelines* and make them available to the widest possible constituency.
- **Recognizing that the expert panels did not consider evidence beyond 2011 (except as specified in the methodology), the ACC, AHA and collaborating societies plan to begin updating these guidelines starting in 2014.**

*adult lipids, pediatric lipids, HTN & obesity

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

- Guidelines attempt 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 events.

Circulation. 2014; 129: S49-S73.

What's new in the 2013 ACC/AHA guideline…?

1. Focus on ASCVD Risk Reduction:

- Based on a comprehensive set of data from RCTs that identified 4 clinical groups on which they rec we focus efforts to reduce ASCVD events in secondary and primary prevention.
- Identifies high-intensity and moderate-intensity statin therapy for use in secondary and primary prevention.

What Are the "4 Statin Benefit Groups "?
they are a form of risk stratification

Introduced identification of 4 Statin Benefit Groups in which the potential for an ASCVD risk reduction benefit clearly exceeds the potential for adverse effects in adults with:

1. Individuals with clinical ASCVD
2. Individuals with primary elevations of LDL–C ≥190 mg/dL
3. Individuals age 40 to 75 with DM with LDL-C 70-189 mg/dL
4. Individuals without clinical ASCVD or diabetes who are age 40-75 with LDL-C 70-189 mg/dL and an estimated 10-year ASCVD risk of 7.5% or higher

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What's new in the 2013 ACC/AHA guideline…?

2. A New Perspective on LDL–C and/or Non-HDL–C Treatment Goals

- The Expert Panel was unable to find RCT evidence to support continued use of specific LDL–C and/or non-HDL–C treatment targets.
- The appropriate intensity of statin therapy should be used to reduce ASCVD risk in those most likely to benefit.
  - *The idea here is to start with the dose that is most likely to get LDL to therapeutic range*
- Nonstatin therapies do not provide acceptable ASCVD risk reduction benefits compared to their potential for adverse effects in the routine prevention of ASCVD.

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What's new in the 2013 ACC/AHA guideline…?

3. Global Risk Assessment for Primary Prevention

- This guideline recommends use of the new Pooled Cohort Equations to estimate 10-year ASCVD risk in both white and black men and women.
- By more accurately identifying higher risk individuals for statin therapy, the guideline focuses statin therapy on those most likely to benefit.
- It also indicates, based on RCT data, those high-risk groups that *may not* benefit.
- Before initiating statin therapy, this guideline recommends a discussion by clinician and patients.

What's new in the 2013 ACC/AHA guideline…?

4. Safety Recommendations

- This guideline used RCTs to identify important safety considerations in individuals receiving treatment of blood cholesterol to reduce ASCVD risk.
- Using RCTs to determine statin adverse effects facilitates understanding of the net benefit from statin therapy.
- Provides expert guidance on management of statin-associated adverse effects, including muscle symptoms.

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What's new in the 2013 ACC/AHA guideline…?

5. Role of Biomarkers and Noninvasive Tests

- In selected individuals who are not in one of the 4 statin benefit groups, and for whom a decision to initiate statin therapy is otherwise unclear, additional factors may be considered to inform treatment decision making.

What's new in the 2013 ACC/AHA guideline…?

5. Role of Biomarkers and Noninvasive Tests

- These factors include:
  - primary LDL–C ≥160 mg/dL or other evidence of genetic hyperlipidemias,
  - family history of premature ASCVD with onset <*55 years of age* in a first degree male relative or <*65 years of age* in a first degree female relative
  - high-sensitivity C-reactive protein (hsCRP) >2 mg/L *(note units)*
  - CAC score ≥300 Agatston units or ≥75 percentile for age, sex, and ethnicity
  - ankle-brachial index <0.9,
  - elevated lifetime risk of ASCVD.
- Additional factors may be identified in the future.

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What's new in the 2013 ACC/AHA guideline…?

6. Future Updates to the Blood Cholesterol Guideline

Future updates will build on this foundation to provide expert guidance on the management of complex lipid disorders and incorporate refinements in risk stratification based on critical review of emerging data. CQs for future guidelines could examine:

1. the treatment of hypertriglyceridemia;
2. use of non-HDL-C in treatment decision-making;
3. whether on-treatment markers such as Apo B, Lp(a), or LDL particles are useful for guiding treatment decisions;
4. the best approaches to using noninvasive imaging for refining risk estimates to guide treatment decisions;
5. how lifetime ASCVD risk should be used to inform treatment decisions and the optimal age for initiating statin therapy to reduce lifetime risk of ASCVD;
6. subgroups of individuals with heart failure or undergoing hemodialysis that might benefit from statin therapy;

Specific Questions

CQ1: What is the evidence for LDL-C and non-HDL-C goals for the secondary prevention of ASCVD?

- The Expert Panel reviewed 19 RCTs to answer CQ1.
- Although supported conceptually by an extrapolation of observational studies and observational data from RCTs, *no data were identified regarding treatment or titration to a specific LDL–C goal in adults with clinical ASCVD*.
- The majority of studies confirming the efficacy of cholesterol reduction in improving clinical outcomes in patients with clinical ASCVD used a single fixed-dose statin therapy to lower LDL–C levels.

Specific Questions

CQ1: What is the evidence for LDL-C and non-HDL-C goals for the secondary prevention of ASCVD?

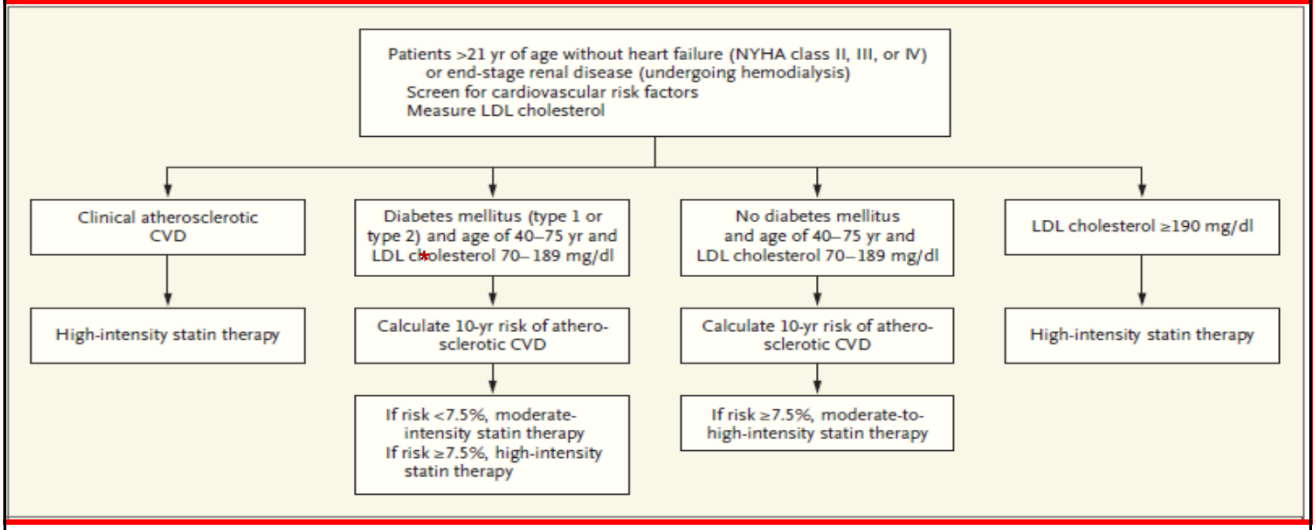
- The Expert Panel was unable to find any RCTs ***that evaluated titration of all individuals in a treatment group to specific*** LDL–C targets <100 mg/dL or <70 mg/dL.
  - Nor were any RCTs comparing 2 LDL–C treatment targets identified.
  - ***No statin RCTs reporting on-treatment non-HDL–C levels were identified.***

What does that mean?

Studies generally evaluate the effect of single doses as opposed to a "treat-to-target" approach

In the past we have extrapolated from these data to a treat-to-target approach. This did not address the fact that not everyone gets to target, even with the highest doses of medication

2013 ACC/AHA Guidelines



*date does not support combining risk for those type 1 diabetes and type 2 diabetes

Limitations of the 2013 ACC/AHA Guidelines

- Clinical judgement required in pts, for whom RCT evidence is insufficient
  - How many of our patients are represented by clinical trial data?
- Younger adults< 40 yrs with <7.5% ASCVD risk for 10 yrs may have high lifetime risk.
  - Clinical trial data does not include those <35-40 y/o
- Type 1 diabetes considered equivalent to type 2 diabetes
- Other special groups not addressed: HIV pts, rheumatological pts, IBD pts, CKD pts, etc
- The panel did not just consider RCTs but also Systematic Reviews & meta analysis of RCTs were taken into consideration.

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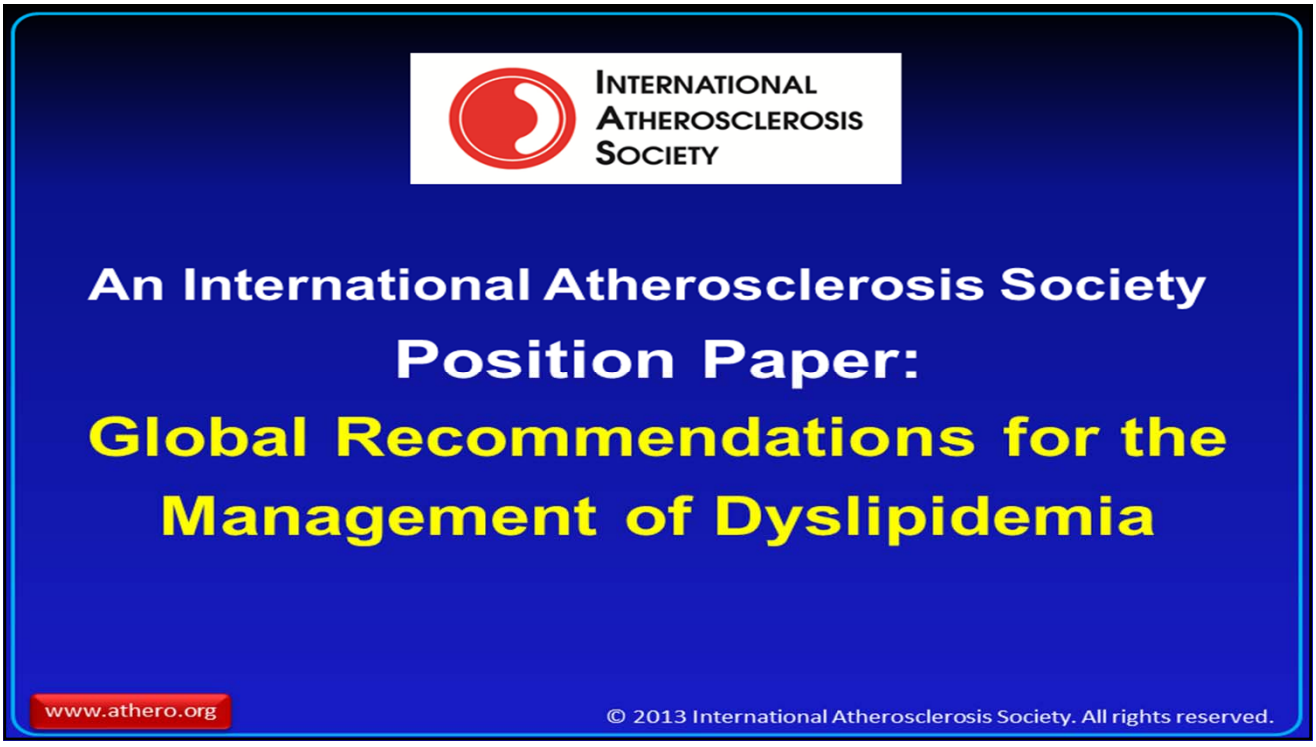

INTERNATIONAL ATHEROSCLEROSIS SOCIETY

Innovations-1

- International position paper based on multiple lines of evidence
- Identification of non-HDL-cholesterol (non-HDL-C) as a major form of atherogenic cholesterol
- Definition of atherogenic cholesterol as either LDL-cholesterol (LDL-C) or non-HDL-C
- Definition of optimal levels of atherogenic cholesterol (both LDL-C and non-HDL-C) for primary and secondary prevention

www.athero.org

INTERNATIONAL ATHEROSCLEROSIS SOCIETY

Innovations-2

- Assigning priority to long-term risk categories over short-term risk
- Adjustment of risk estimation according to baseline risk of different nations or regions
- Primary emphasis on lifestyle intervention; secondary emphasis on drug therapy

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Optimal Levels of LDL-C and Non-HDL-C for Primary Prevention

- Optimal levels
  - LDL-C < 100 mg/dL (2.6 mmol/L)
  - Non-HDL-C < 130 mg/dL (3.4 mmol/L)
- Optimal levels not goals of therapy
- Cholesterol-lowering goals determined by clinical judgment

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Identifying Persons at Long-term Risk for ASCVD

- Long-term risk takes precedence over short-term risk for decisions about dyslipidemia intervention
- Long-term risk = risk to age 80 years

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Secondary Prevention: Achieving an Optimal Atherogenic Cholesterol Level

- The optimal LDL-C in patients with established ASCVD is < 70 mg/dL (1.8 mmol/L) (or non-HDL-C of < 100 mg/dL [2.6 mmol/L])
- Most patients with ASCVD deserve maximal statin therapy when it is tolerated
- To achieve an LDL-C < 70 mg/dL (1.8 mmol/L) some patients will require add-on drugs to statins (i.e. ezetimibe and/or bile acid resins)

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Secondary Prevention: Intolerance to High-Dose Statins

- In patients who cannot tolerate high-dose statins, an alternative is to combine a moderate dose of statin with either ezetimibe or bile acid-binding resin

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IAS: Summary

- Published prior to presentation of ACC/AHA Guidelines
  - Identified goals of therapy (LDL cholesterol & nonHDL-C)
    - Individualize goals based on clinical judgement
  - Emphasized life time risk
  - Introduced QRISK® lifetime CV risk calculator
  - Rec combination therapy if intolerant to high dose statin or not attaining goal

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How Do We Apply This To Our Patients?

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2016: new consensus conference will be convened

AACE Lipid Guidelines

- Clinical Practice Guideline (CPG) last updated in 2012
- Type 2 Diabetes CPG last updated 2016: retained the concept of targets
  - Does not address type 1 diabetes
  - Retained TG> 500 as a primary target of therapy
  - Encouraged combination therapy if needed to get to target
- pdf & ppt files: https://www.aace.com/publications/algorithm

AACE Lipid Targets for Patients With Type 2 Diabetes

	High-risk patients (T2D but no other major risk and/or age <40 years)	Very-high-risk patients (T2D plus ≥1 major ASCVD risk[a] or established ASCVD)
LDL-C (mg/dL)	<100	<70
Non-HDL-C (mg/dL)	<130	<100
Triglycerides (mg/dL)	<150	<150
TC/HDL-C	<3.5	<3.0
Apo B (mg/dL)	<90	<80
LDL-P (nmol/L)	<1,200	<1,000

Abbreviations: AACE = American Association of Clinical Endocrinologists; Apo B = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density-lipoprotein cholesterol; LDL-C = low-density-lipoprotein cholesterol; LDL-P = low-density-lipoprotein particle; TC = total cholesterol; T2D = type 2 diabetes.

[a] Hypertension, family history of ASCVD, low HDL-C, smoking.

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Presented May 2, 2014 at NLA Annual Scientific Sessions

www.lipid.org

Conceptual Framework for Formulation of NLA Expert Panel Recommendations

- Various guidelines and recommendations have been issued in the last few years that contain material differences.
- An NLA Expert Panel was formed to prepare a set of consensus recommendations intended to inform, not replace, clinical judgment regarding dyslipidemia management.
- The NLA Expert Panel recommendations for Patient-Centered Management of Dyslipidemia were prepared after a comment period to allow input and advice to be obtained from other experts and organizations.
  - A *patient-centered* approach dictates that clinical judgment take into account the circumstances, objectives, and preferences of each individual patient.

Conceptual Framework (continued)

- 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).
- 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.

Conceptual Framework (continued)

- 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.

Part 2: published in 2015

1. Lifestyle therapies–nutrition and exercise/physical activity
2. Groups with special considerations that span the lifespan from children to seniors and from pregnancy to menopause
3. Ethnic groups including Hispanics/Latinos, African Americans (AAs), South Asians (SAs), and American Indians (AIs)/Alaska Natives (ANs)
4. Groups with increased ASCVD risk, including patients with human immunodeficiency virus (HIV), rheumatologic disease, and those with high residual risk despite statin and lifestyle therapies
5. Strategies to improve patient outcomes centered on improving adherence and maximizing team-based collaborative care

Journal of Clinical Lipidology, November 2015

NLA: Summary

- Recommend screening every 5 years starting at age 20
- Focus on patient centered therapy
- Emphasize risk stratification over life time
- Emphasize the value of having treatment goals
- Emphasize nonHDL-C as primary target over LDL-C
  - more predictive of ASCVD
  - no additional cost when do standard lipid panel
  - can be done nonfasting
- Can initiate with moderate dose statin and titrate to goal
- Consider combination therapy as needed

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

Statin Regimens

The 2013 ACC/AHA guidelines recommend either a high-intensity or moderate-intensity statin regimen in patients who have an elevated ASCVD risk (≥ 7.5%) for primary prevention of CVD

High-Intensity Statin Therapy

- Atorvastatin 80 mg (40 mg less preferred)
- Rosuvastatin 20-40 mg

Moderate-Intensity Statin Therapy

- 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

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- PMH: Metabolic Syndrome x 10 years
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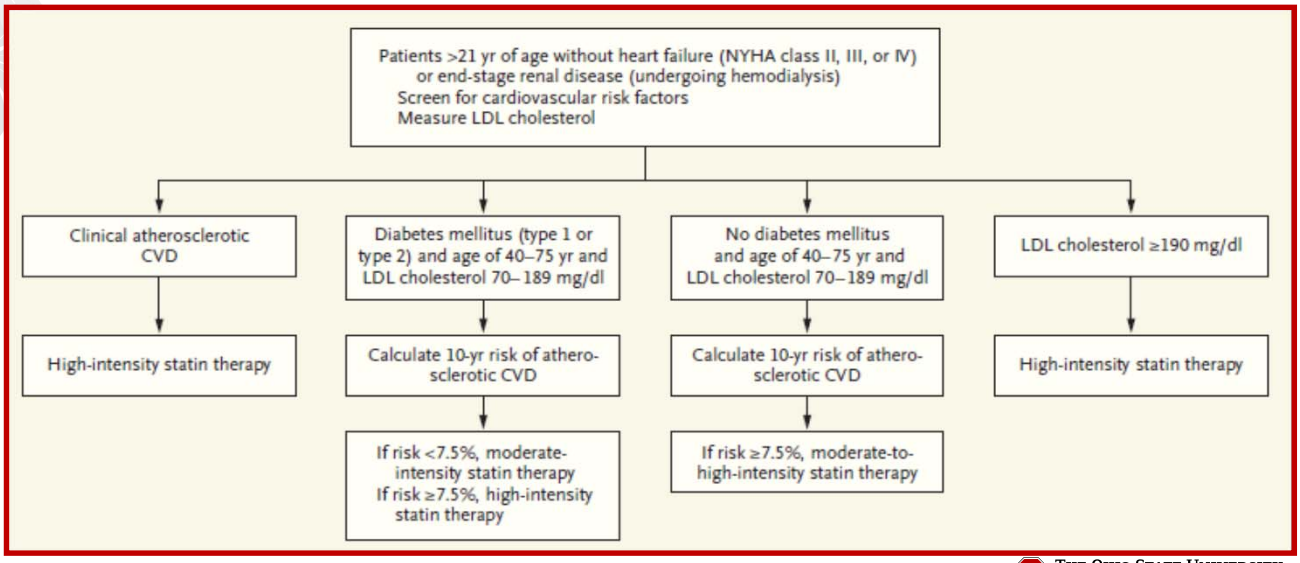
2013 ACC/AHA Guidelines



NEJM; online before print: Nov/2013

Risk Calculators

- Framingham Risk calculator
  - http://cvdrisk.nhlbi.nih.gov/
- Pooled Cohort Risk calculator
  - http://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx
- QRISK® lifetime CV risk calculator
  - BMJ 2008;336:1475-82.

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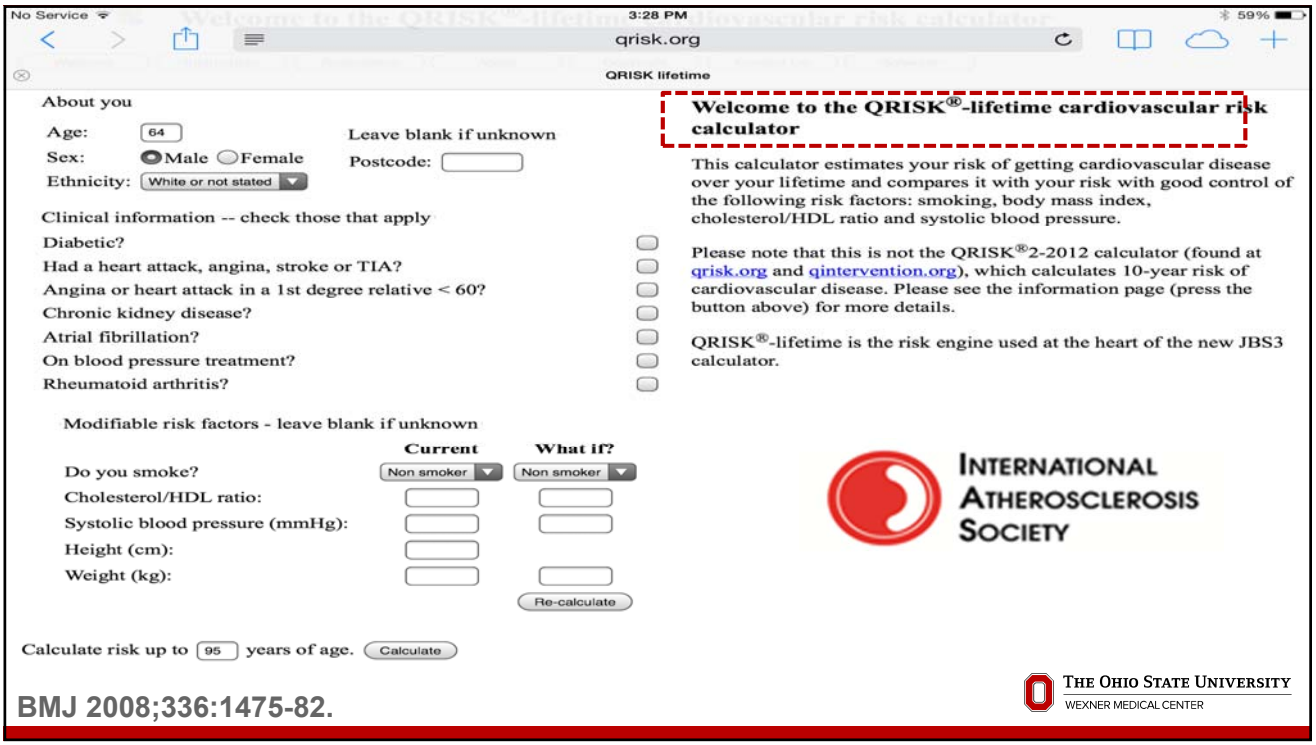
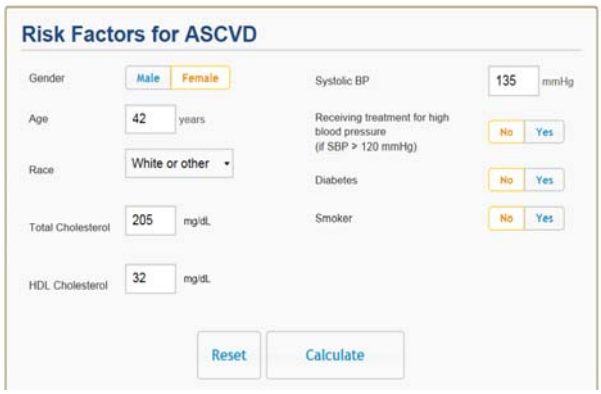


BMJ 2008;336:1475-82.

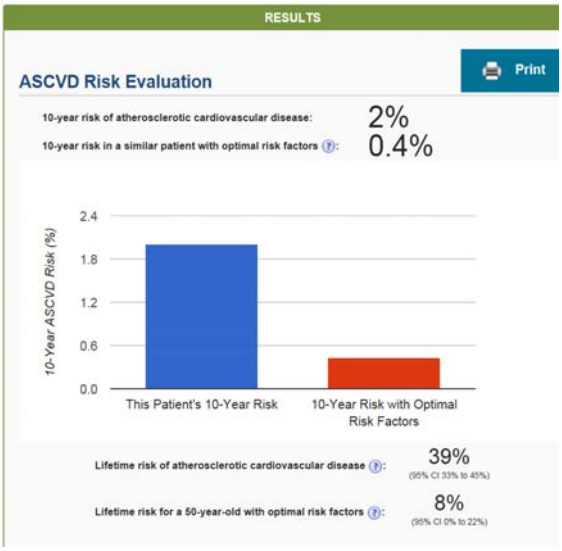
Case: Dyslipidemia with Abnormal LFTs

Pooled Cohort Risk Assessment Equations

Predicts 10-year risk for a first atherosclerotic cardiovascular disease (ASCVD) event



http://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx



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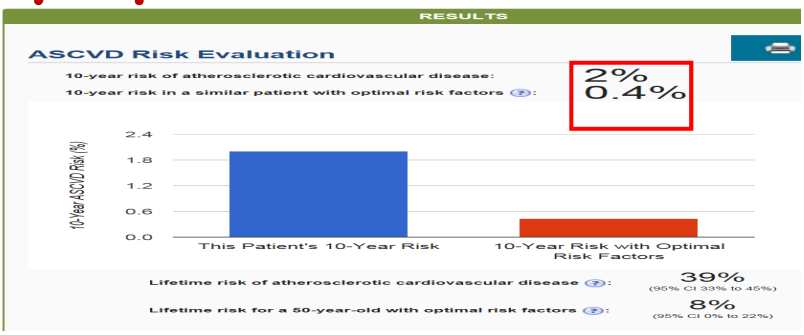

ASCVD Risk Interpretation

This patient is at LOW 10-year risk (< 7.5%) for atherosclerotic cardiovascular disease (ASCVD)

In individuals not receiving cholesterol-lowering drug therapy, recalculate the 10-year ASCVD risk every 4 to 6 years (assuming age 40-75 years, no clinical ASCVD or diabetes, and LDL 70-189 mg/dL)

http://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx

Summary: NLA

- Begin Screening Adults at age 21
- Identify High Risk Groups
- Calculate life time risk
- Individualize targets of therapy
  - Lifestyle management remains the foundation
  - Consider alternate risk factors
  - consider risk of life long therapy with moderate or high dose

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2016: new consensus conference will be convened
why?

New since 2011

New agents for Familial Hypercholesterolemia

Longacting: weekly-monthly injections

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New Lipid Lowering Agents

How do we incorporate these into the guidelines?

- very long acting
- more potent than high intensity statins

Lomitapide	December 2012
Mipomersen	January 2013
Alirocumab	July 2015
Evolocumab	August 2015

Summary

- The new Guidelines from 2013/4 all allow for personalized therapeutic targets
- Differences between the guidelines:
  - Evidence base utilized
  - Role of LDL-C vs nonHDL-C
  - Role of specific targets
  - Risk calculators

❖ The next update is already in process because the new agents have provided substantive new data to mandate updating the guidelines

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Questions?

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What is the Data?

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2013 ACC/AHA Approach to LDL

Clinical Trial Data Supporting LDL lowering without therapeutic targets

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Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials

*Cholesterol Treatment Trialists' (CTT) Collaboration**

Lancet 2010; 376: 1670–81
Published Online November 9, 2010
DOI:10.1016/S0140-6736(10)61350-5

See Comment page 1622
See Articles page 1658

*Collaborators are listed at the end of the paper
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ctt@ctsu.ox.ac.uk
or
National Health and Medical Research Council (NHMRC) Clinical Trial Centre, Mallett

Summary

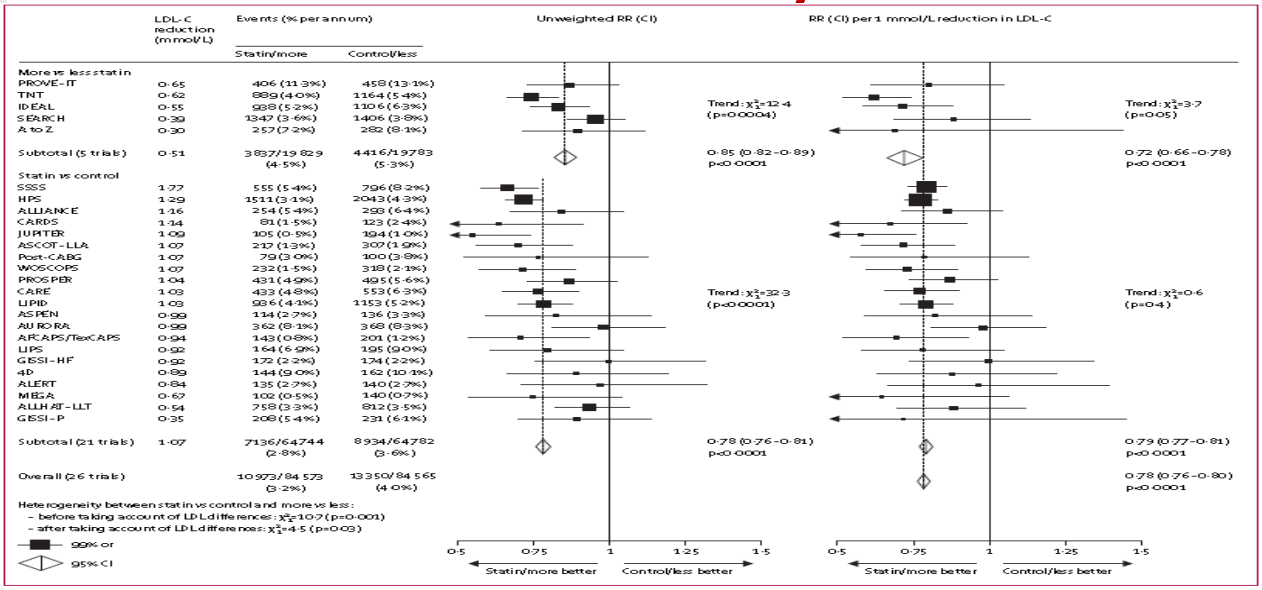
Background Lowering of LDL cholesterol with standard statin regimens reduces the risk of occlusive vascular events in a wide range of individuals. We aimed to assess the safety and efficacy of more intensive lowering of LDL cholesterol with statin therapy.

Methods We undertook meta-analyses of individual participant data from randomised trials involving at least 1000 participants and at least 2 years' treatment duration of more versus less intensive statin regimens (five trials; 39 612 individuals; median follow-up 5·1 years) and of statin versus control (21 trials; 129 526 individuals; median follow-up 4·8 years). For each type of trial, we calculated not only the average risk reduction, but also the average risk reduction per 1·0 mmol/L LDL cholesterol reduction at 1 year after randomisation.

Findings In the trials of more versus less intensive statin therapy, the weighted mean further reduction in LDL cholesterol at 1 year was 0·51 mmol/L. Compared with less intensive regimens, more intensive regimens produced a highly significant 15% (95% CI 11–18; p<0·0001) further reduction in major vascular events, consisting of separately significant reductions in coronary death or non-fatal myocardial infarction of 13% (95% CI 7–19; p<0·0001), in coronary revascularisation of 19% (95% CI 15–24; p<0·0001), and in ischaemic stroke of 16% (95% CI 5–26; p=0·005). Per 1·0 mmol/L reduction in LDL cholesterol, these further reductions in risk were similar to the proportional reductions in the trials of statin versus control. When both types of trial were combined, similar proportional reductions in major vascular events per 1·0 mmol/L LDL cholesterol reduction were found in all

	Number of patients	Treatment comparison (mg per day)	Median follow-up in survivors (years)*	Baseline LDL-C (mmol/L)	LDL-C difference at 1 year (mmol/L)	Women (%)	Diabetes (%)	Prior CHD (%)	Other vascular disease (%)†	No prior vascular disease (%)‡
More versus less statin										
PROVE-IT	4162	A80 vs P40	2·1	2·62§	−0·65	911 (22%)	734 (18%)	4162 (100%)	328 (8%)	0
A to Z	4497	S40 then S80 vs placebo then S20	2·0	2·09§	−0·30	1100 (24%)	1059 (24%)	4497 (100%)	479 (11%)	0
TNT	10 001	A80 vs A10	5·0	2·52	−0·62	1902 (19%)	1501 (15%)	10 001 (100%)	1537 (15%)	0
IDEAL	8888	A40–80 vs S20–40	4·8	2·64§	−0·55	1702 (19%)	1069 (12%)	8888 (100%)	971 (11%)	0
SEARCH	12 064	S80 vs S20	7·0	2·50	−0·39	2052 (17%)	1267 (11%)	12 064 (100%)	1062 (9%)	0
Subtotal (5 trials)	39 612	NA	5·1‖	2·53‖	−0·51‖	7667 (19%)	5630 (14%)	39 612 (100%)	4377 (11%)	0
Statin versus control										
SSSS	4444	S20–40 vs placebo	5·4	4·88	−1·77	827 (19%)	202 (5%)	4444 (100%)	126 (3%)	0
WOSCOPS	6595	P40 vs placebo	4·8	4·96	−1·07	0	76 (1%)	338 (5%)	193 (3%)	6096 (92%)
CARE	4159	P40 vs placebo	5·0	3·58	−1·03	576 (14%)	586 (14%)	4159 (100%)	0	0
Post-CABG	1351	L40–80 vs L2·5–5	4·3	4·02	−1·07	102 (8%)	116 (9%)	1351 (100%)	37 (3%)	0
AFCAPS/TexCAPS	6605	L20–40 vs placebo	5·2	3·89	−0·94	997 (15%)	155 (2%)	10 (<1%)	9 (<1%)	6586 (>99%)
LIPID	9014	P40 vs placebo	6·0	3·88	−1·03	1516 (17%)	782 (9%)	9014 (100%)	905 (10%)	0
GISSI-P	4271	P20 vs no treatment	2·0	3·92	−0·35	587 (14%)	582 (14%)	4271 (100%)	179 (4%)	0
LIPS	1677	F80 vs placebo	3·9	3·42	−0·92	271 (16%)	202 (12%)	1677 (100%)	142 (8%)	0
HPS	20 536	S40 vs placebo	5·4	3·38	−1·29	5082 (25%)	5963 (29%)	13 386 (65%)	8865 (43%)	3161 (15%)
PROSPER	5804	P40 vs placebo	3·3	3·79	−1·04	3000 (52%)	623 (11%)	1881 (32%)	1026 (18%)	3254 (56%)
ALLHAT-LLT	10 355	P40 vs usual care	4·9	3·76	−0·54	5051 (49%)	3638 (35%)	1188 (11%)	1788 (17%)	8037 (78%)
ASCOT-LLA	10 305	A10 vs placebo	3·3	3·44	−1·07	1942 (19%)	2527 (25%)	15 (<1%)	1435 (14%)	8860 (86%)
ALERT	2102	F40 vs placebo	5·5	4·14	−0·84	715 (34%)	396 (19%)	400 (19%)	241 (11%)	1702 (81%)
CARDS	2838	A10 vs placebo	4·1	3·03	−1·14	909 (32%)	2838 (100%)	9 (<1%)	97 (3%)	2738 (96%)
ALLIANCE**	2442	A10–80 vs usual care	4·7	3·80	−1·16	434 (18%)	540 (22%)	2442 (100%)	162 (7%)	0
4D**	1255	A20 vs placebo	4·0	3·25	−0·89	578 (46%)	1255 (100%)	630 (50%)	666 (53%)	344 (27%)
ASPEN**	2410	A10 vs placebo	4·0	2·93	−0·99	811 (34%)	2410 (100%)	578 (24%)	302 (13%)	1663 (69%)
MEGA**††	8214	P10–20 vs usual care	5·0	4·05	−0·67	5547 (68%)	1686 (21%)	42 (<1%)	53 (<1%)	8119 (99%)
JUPITER**	17 802	R20 vs placebo	2·0	2·70	−1·09	6801 (38%)	76 (<1%)	0	0	17 802 (100%)
GISSI-HF**	4574	R10 vs placebo	4·2	3·06	−0·92	1032 (23%)	1196 (26%)	1797 (39%)	4574 (100%)	0
AURORA**	2773	R10 vs placebo	4·6	2·58	−0·99	1050 (38%)	731 (26%)	659 (24%)	743 (27%)	1663 (60%)
Subtotal (21 trials)	129 526	NA	4·8‖	3·70‖	−1·07‖	37 828 (29%)	26 580 (21%)	48 291 (37%)	21 543 (17%)	70 025 (54%)
Total (26 trials)	169 138	NA	4·9‖	NA	NA	45 495 (27%)	32 210 (19%)	87 903 (52%)	25 920 (15%)	70 025 (41%)

CTT: Effects on any Major Vascular Event in Each Study



Cholesterol Treatment Trialist Collaboration
Conclusion

- "The primary goal for patients at high risk for occlusive vascular events should be to achieve the largest LDL cholesterol reduction possible without materially increasing myopathy risk."

Lancet. 2010;376:1670-1681

Is There a Role for non-HDL-C?

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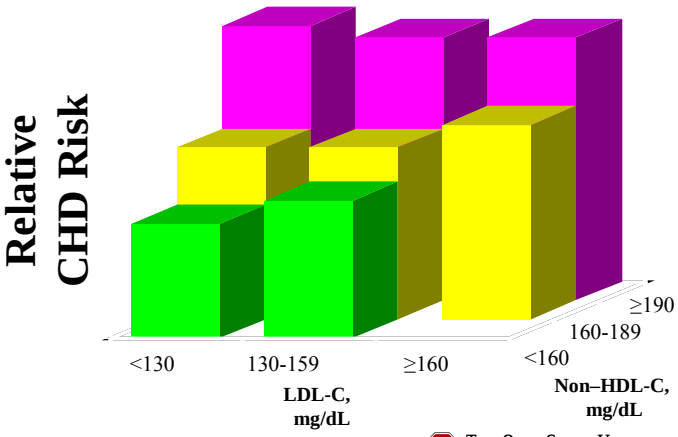
Best Targets

- Candidates for the best target of lipid lowering therapy to prevent CHD
  - LDL-C
  - non-HDL-C
  - Apo B
  - LDL-P

Non-HDL-C Is Superior to LDL-C in Predicting CHD Risk

- Within non–HDL-C levels, no association was found between LDL-C and the risk for CHD
- In contrast, a strong positive and graded association between non–HDL-C and risk for CHD occurred within every level of LDL-C
- Non–HDL-C is a stronger predictor of CHD risk than LDL-C



Liu J, et al. *Am J Cardiol.* 2006;98:1363-1368.

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EPIC-Norfolk

Beyond Low-Density Lipoprotein Cholesterol

Respective Contributions of Non–High-Density Lipoprotein Cholesterol Levels, Triglycerides, and the Total Cholesterol/High-Density Lipoprotein Cholesterol Ratio to Coronary Heart Disease Risk in Apparently Healthy Men and Women

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Jean-Pierre Després, PHD,*‡ Prediman K. Shah, MD,§ John J. P. Kastelein, MD, PHD,‖
Nicholas J. Wareham, MBBS, PHD,# S. Matthijs Boekholdt, MD, PHD,¶ Kay-Tee Khaw, MBBCHIR**
Québec, Québec, Canada; Los Angeles, California; Amsterdam, the Netherlands; and Cambridge, United Kingdom

Objectives This study was designed to test the hypothesis that at any low-density lipoprotein cholesterol (LDL-C) level, other lipid parameters such as non–high-density lipoprotein cholesterol (HDL-C) levels, triglyceride (TG) levels, and the total cholesterol (TC)/HDL-C are still associated with an increased coronary heart disease (CHD) risk.

Background Although LDL-C is considered to be the primary target of lipid-lowering therapy, other parameters of the lipoprotein-lipid profile may more closely associated with CHD risk.

Methods In the EPIC (European Prospective Investigation Into Cancer and Nutrition)-Norfolk prospective population study, 21,448 participants without diabetes or CHD between age 45 and 79 years were followed for 11.0 years. A total of 2,086 participants developed CHD during follow-up.

Results Among individuals with low LDL-C levels (<100 mg/dl), after adjustment for age, sex, smoking, systolic blood pressure, waist circumference, physical activity, and hormone replacement therapy (in women), those with non–HDL-C >130 mg/dl had a hazard ratio (HR) for future CHD of 1.84 (95% confidence interval [CI]: 1.12 to 3.04) when compared with those with non–HDL-C levels <130 mg/dl. In a similar model, individuals with TG levels >150 mg/dl had an HR of 1.63 (95% CI: 1.02 to 2.59) when compared with those with TG levels <150 mg/dl, and individuals with a TC/HDL-C ratio >5 had an HR of 2.19 (95% CI: 1.22 to 3.93) when compared with those with a TC/HDL-C ratio <5.

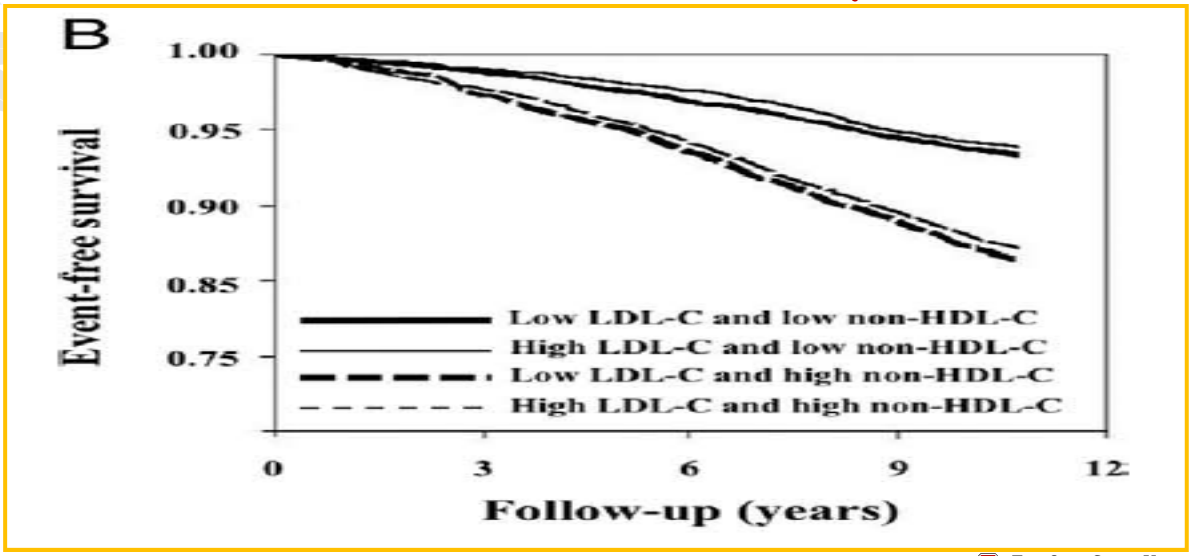
Conclusions In this prospective study, independently of their plasma LDL-C levels, participants with high non–HDL-C levels, high TG levels, or with an elevated TC/HDL-C ratio were at increased CHD risk. CHD risk assessment algorithms as well as lipid targets of lipid-lowering trials may also need to consider other easily available parameters such as non–HDL-C. (J Am Coll Cardiol 2010;55:35–41)

EPIC-Norfolk Study

- Non-HDL-C was the best predictor of future CHD over the 11 year follow-up
- Non-HDL-C HR 2.39
- LDL-C HR 1.22
- TG HR 1.14 (mean TG 159)
- TC/HDL HR 1.19 (mean HDL 45)

J Am Coll Cardiol 2010;55:35-41

EPIC-Norfolk Study



J Am Coll Cardiol 2010;55:35–41

Best Targets

- Candidates for the best target of lipid lowering therapy to prevent CHD
  - LDL-C
  - non-HDL-C
  - Apo B
  - LDL-P

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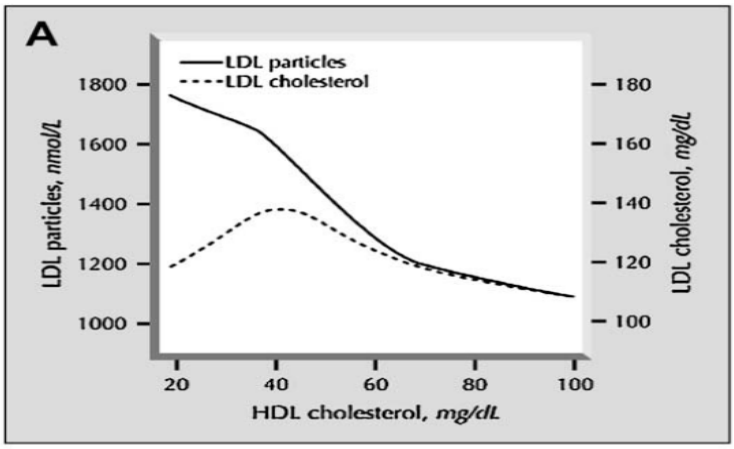
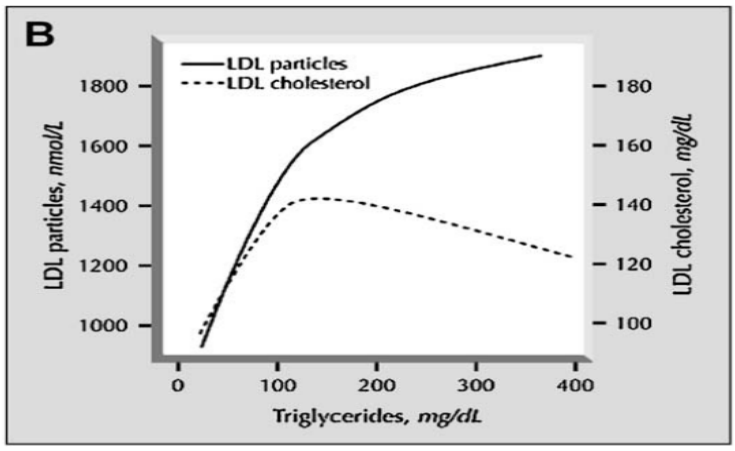
LDL-C and LDL-P Discordance



Current Atherosclerosis Reports;2004;6;385

LDL-C and LDL-P Discordance

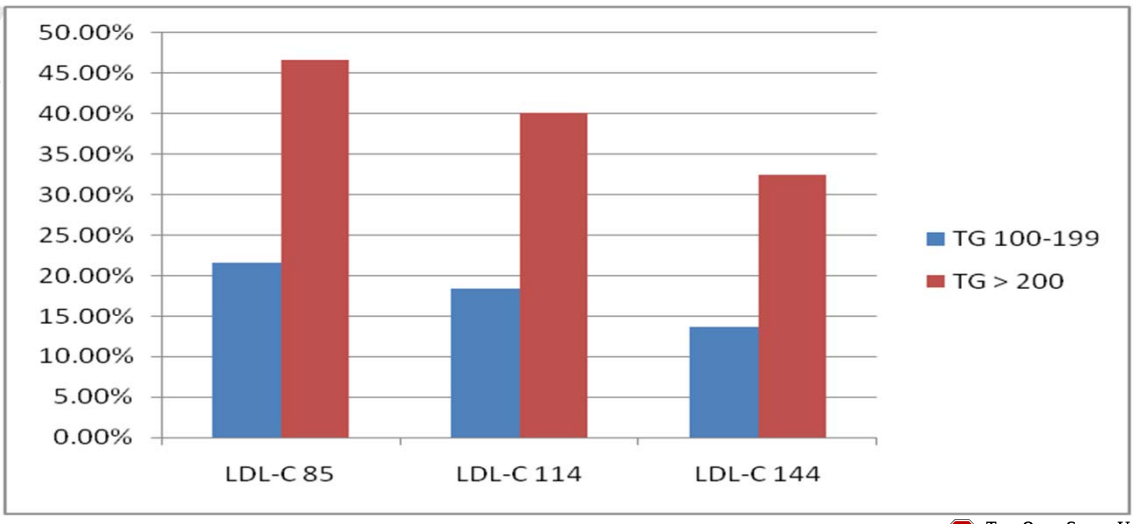


Current Atherosclerosis Reports;2004;6;385

Non-HDL-C

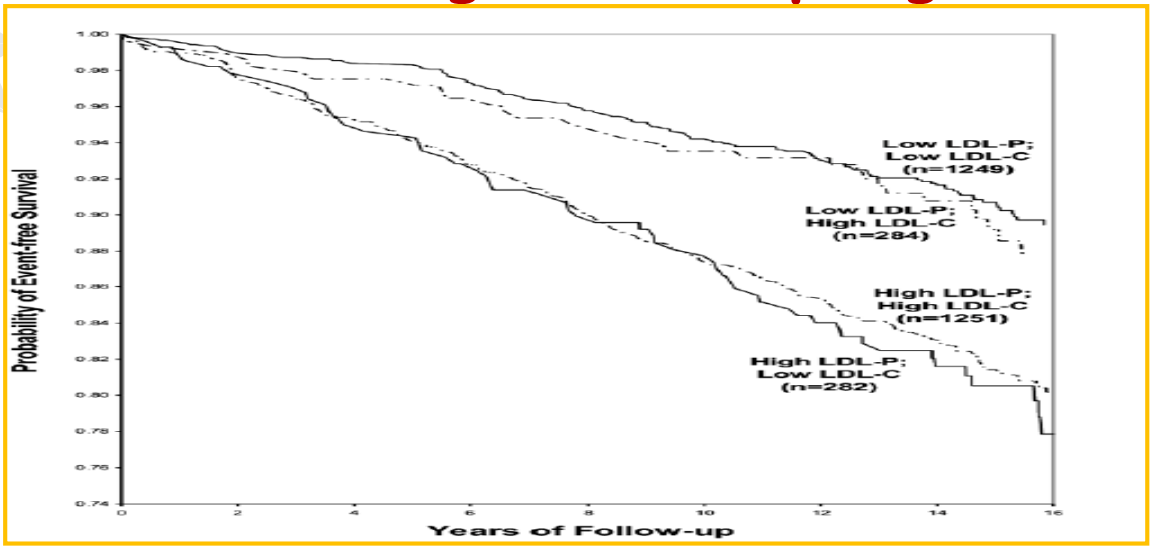
- Within a given LDL-C category, non-HDL-C rises proportional to TG levels.
- Given an LDL-C of 115, **with TG> 200**
  - LDL-P is 40% higher (1652 vs 1179)
  - Non-HDL-C is 31% higher (168 vs 128)
- The lower the LDL-C the more discordant is the LDL-P
  - *High LDL-P means many small particles*

LDL-P Percent Discordance



Journal of Clinical Lipidology; vol 1, no 6, Dec 2007

Framingham Offspring



Journal of Clinical Lipidology; vol 1, no 6, Dec 2007

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Apo B vs LDL-P

High concordance between Apo B and LDL-P of 78.9%

- LDL-P was more strongly associated with risk:
  - VAHIT
  - Women's Health Study 2002.
- Apo B was more strongly associated with risk:
  - Framingham Offspring 2007
  - Women's Health Study 2007
- Heart Protection Study
  - both biomarkers were equal in risk prediction

Clinical Chemistry 59;5;2013;764

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Apo B vs LDL-P

- On review of 25 studies, the risk prediction of Apo B and LDL-P are comparable.
- When the markers are discordant, LDL-P more often is a stronger predictor of risk based on the magnitude of the HR and statistical strength.

Clinical Chemistry 59;5;2013;764

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LDL Particle Number Measures as Targets of Therapy

Biomarker		Population	Percentile Equivalent Concentration			
			<5th	20th	50th	80th
LDL-C	(mg/dL)	Framingham [1]	<75	100	130	160
ApoB	(mg/dL)		<60	80	100	120
			< 850	1100	1400	1800
NMR LDL-P	(nmol/L)	MESA [2]	< 800	1000	1300	1600

Organization	Proposed Targets of Therapy		
	Very High Risk	High Risk	Moderate Risk
American Diabetes Association / American College of Cardiology Foundation Consensus Statement [3]	Apo B <80	ApoB <90	NA
American Association for Clinical Chemistry Lipoproteins & Vascular Diseases Working Group Recommendations [1]	Apo B or LDL-P < 20th Percentile (see above)		ApoB or LDL-P < 50th Percentile
American Association of Clinical Endocrinologists Guidelines for Management of Dyslipidemia [4]	Apo B <80	Apo B<90	NA
American Association of Clinical Endocrinologists 2013 Comprehensive Diabetes Management Consensus Statement [8]	Apo B < 80 LDL-P < 1000		ApoB < 90 LDL-P < 1200
National Lipid Association Expert Recommendations [5]	Option Apo B or LDL-P < 5th Percentile	Apo B or LDL-P < 20th Percentile	Apo B or LDL-P < 50th Percentile
Canadian Cardiovascular Society Guidelines [6]	ApoB <80		NA
ESC/EAS Guidelines for the Management of Dyslipidaemias [7]	Apo B<80	Apo B <100	NA

1. Contois JH et al. *Clin Chem.* 2009;55:407-419.
2. Otvos et al. *J Clin Lipidol* 2011;5:105-13.
3. Brunzell JD et al. *J Am Coll Cardiol*. 2008;51:1512-1524.
4. Jellinger PS et al. *Endocr Pract*. 2012;18(Suppl 1):1-78.
5. Davidson MH et al. *J Clin Lipidol*. 2011;5:338-367.
6. Genest J et al. *Can J Cardiol*. 2009;25:567-579.
7. Reiner Ž, et al. *Eur Heart Journal*. 2011;32:1769–1818.
8. Garber AJ, et al. *Endocr Pract* 2013;19(Suppl 2):1-48.

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What About Triglycerides?

Syndrome X 1988 → 2001: Metabolic Syndrome

"Metabolic Disturbances Commonly Cluster in Patients with Cardiovascular Disease"

…even without diabetes mellitus

- Resistance to Insulin-stimulated Glucose Uptake
- Hyperinsulinemia
- Hypertension
- Glucose Intolerance
- Increased VLDL-Triglycerides
- Decreased HDL-Cholesterol

Reaven, Gerald M: "Role of Insulin Resistance in Human Disease". *Diabetes* (1988) *37:1495-1607*

High TG/Low HDL

- TG/HDL > 3.5 = insulin resistance
- Epidemiology identifies the following risk cut points:
  - TG > 150 mg/dL
  - HDL < 40 mg/dL (<50 for women)
- **Intervention Studies show benefit when baseline:**
  - **TG > 200 mg/dL**
  - **HDL < 35-40 mg/dL**

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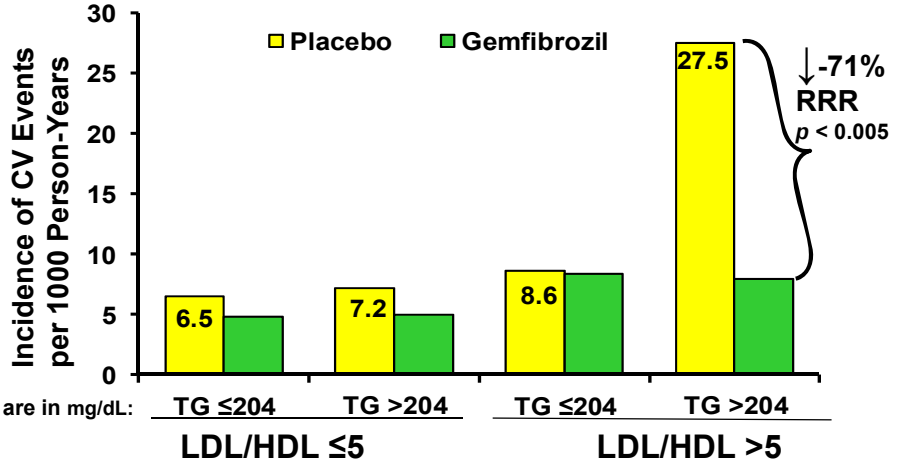
Helsinki Heart Study*: Marked Reduction of CHD Events in Patients With High TG (>204) & High LDL/HDL Ratio

OVERALL 34% Reduction in CAD events (p<0.02)

N=4,081 men
(40-55yrs)
non-HDL-C
>200

Baseline
TChol 289
TG.....176
HDL-C.....47
LDL-C.....189
Non-HDL.242



*Helsinki Heart Study: a primary prevention study
Manninen V, Tenkanen P, Koskinen Pet al. Circulation. 1992;85:37-45

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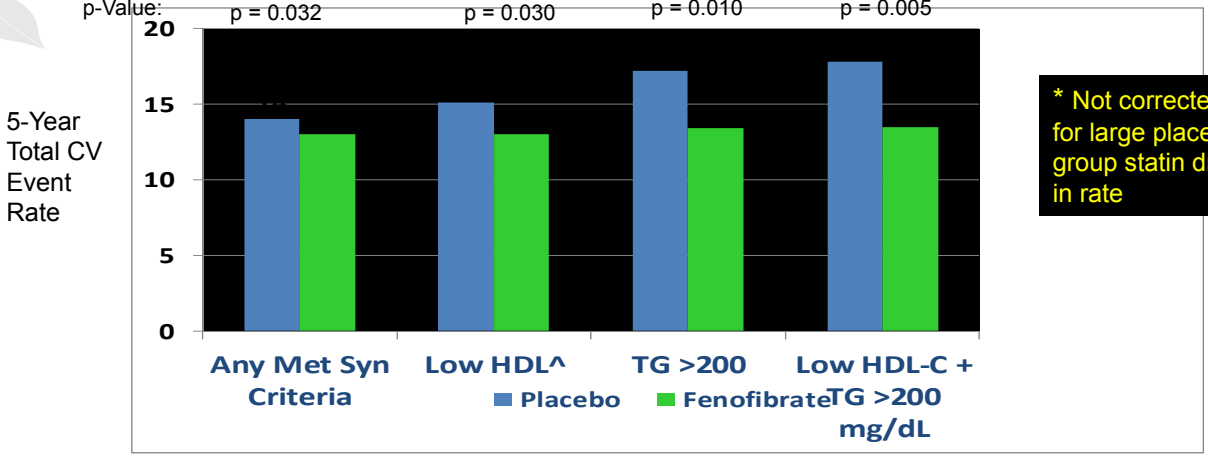
FIELD: Highest Therapeutic Benefit of Fenofibrate Seen in Patients with Elevated TG and Low HDL-Cholesterol

	Any Met Syn Criteria	Low HDL^	TG >200	Low HDL-C + TG >200 mg/dL
Risk Reduction*:	11%	12%	23%	27%
Hazard Ratio*:	0.89	0.88	0.88	0.73
(95%) CI:	(0.80-0.99	(0.75-0.99	(0.63-0.94	(0.58-0.91
p-Value:	p = 0.032	p = 0.030	p = 0.010	p = 0.005



* Not corrected for large placebo group statin drop-in rate

^Low HDL: <40 mg/dL (men) & <50 mg/dL (women)

Scott R, O'Brien R, Fulcher G et al. Diabetes Care 2009;32:493-498

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ACCORD-Lipid Trial

baseline TG = 162 mg/dL

- Lipid Trial question: whether a statin plus a fibrate would reduce CVD compared to statin monotherapy, in T2DM pts at high risk for CVD disease. Observed F/U: 4 to 8 years (mean 4.7 years)
- Baseline: TC 175; TG 162; HDL-C 38; LDL-C 100; Non-HDL 137
- All 5,518 on Simvastatin, mean 22.3 mg/d, randomized to Fenofibrate (54-160mg) or Placebo

	Fenofibrate (N=2,765)		Placebo (N=2,753)			
Primary Outcome:	n of Events	Rate (%/yr)	n of Events	Rate (%/yr)	HR (95% CI)	p Value
Major Fatal or Nonfatal Cardiovascular Event	291	2.24	310	2.41	0.92 (0.79 - 1.08)	0.32

ACCORD-Lipid showed that addition of fenofibrate to statin resulted in an 8% RRR as a NS trend in the primary outcome; a negative trial

The ACCORD Study Group, NEJM. 2010; 362:1563-1574

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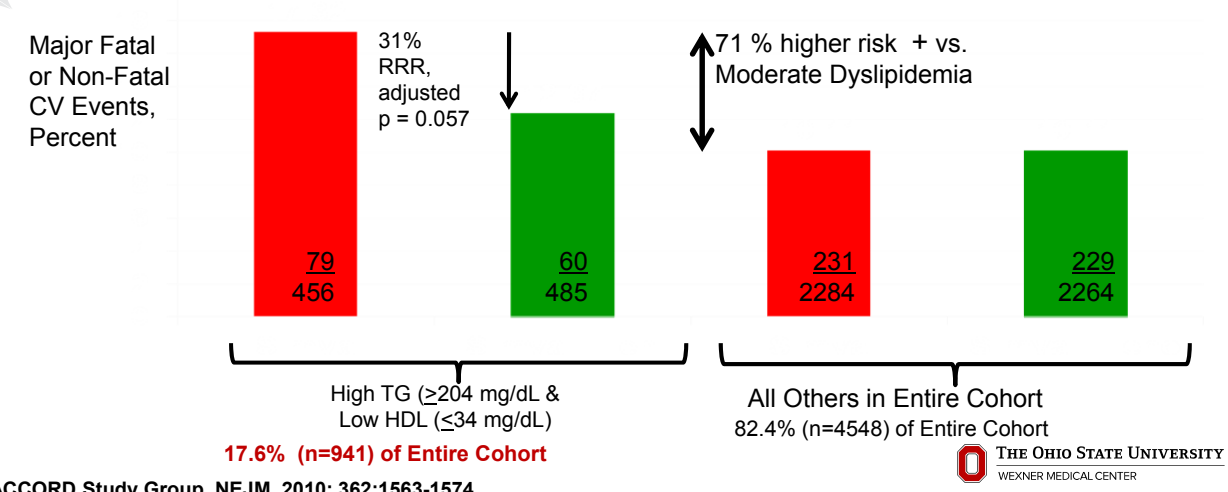
ACCORD-LIPID: Primary Outcomes of Pre-Specified Subgroups: High TG & Low HDL-C vs. All Others in Entire Cohort

The entire effect (benefit) associated with fenofibrate treatment was confined to High TG/Low HDL subgroup comprising <18% of ACCORD-LIPID trial population.



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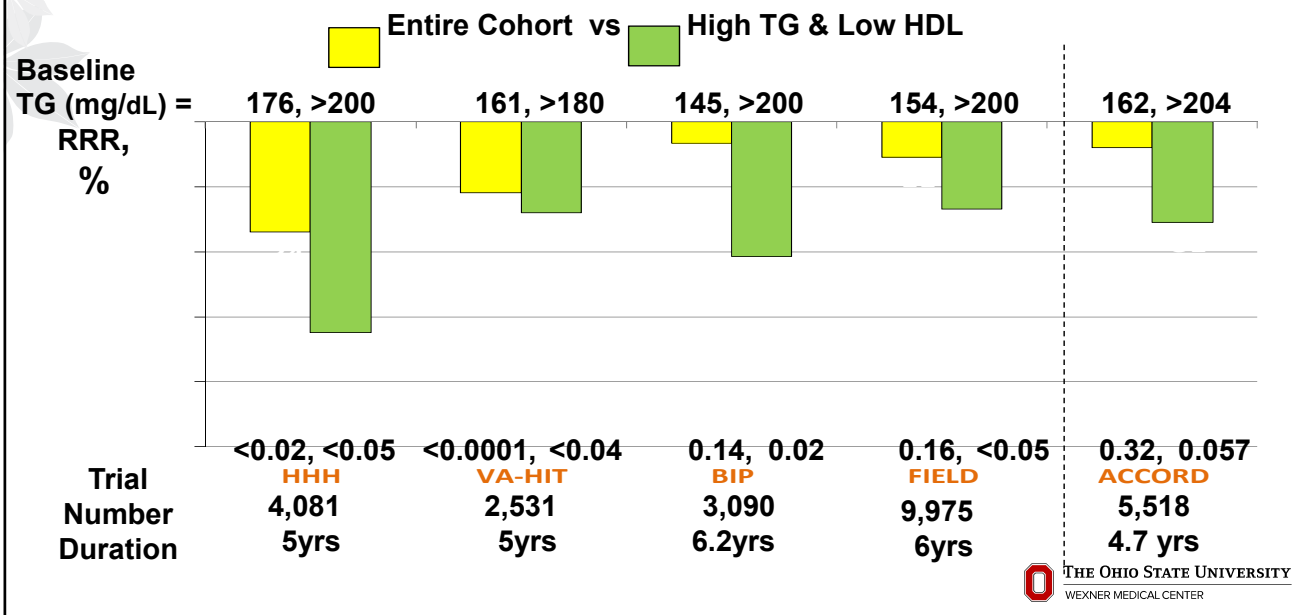
The ACCORD Study Group, NEJM. 2010; 362:1563-1574

Cardiovascular Event Risk Reduction in Large Monotherapy Fibrate Clinical Trials, Relative to ACCORD study



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How Have We Been Doing Under the Prior Guidelines?

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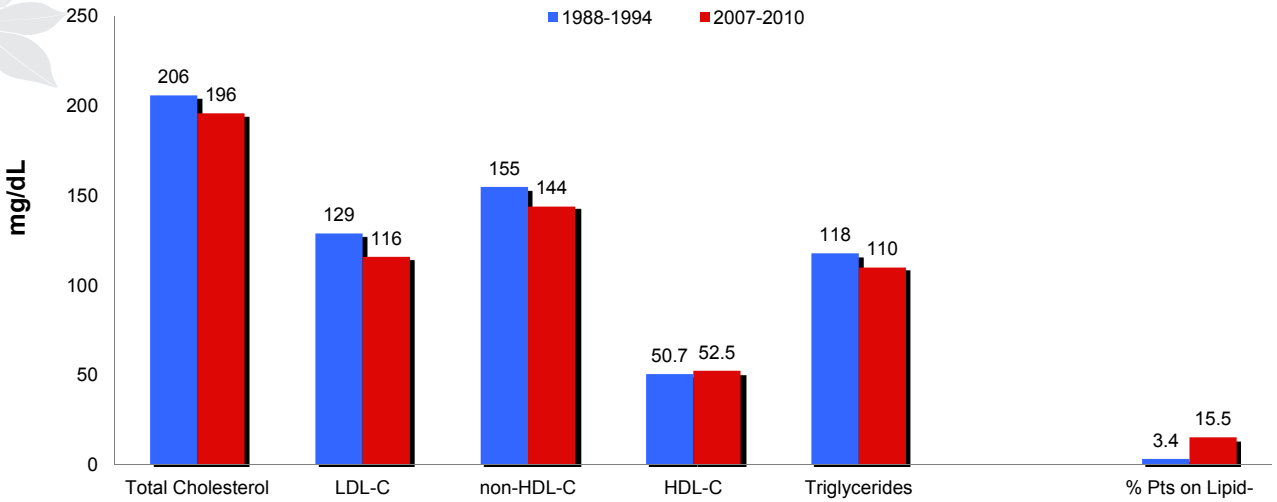
Trends in Lipids and Lipoproteins in U.S. Adults, NHANES 1988-2010



all: P<0.001

Carroll MD, et al. *JAMA*. 2012;308:1545-54

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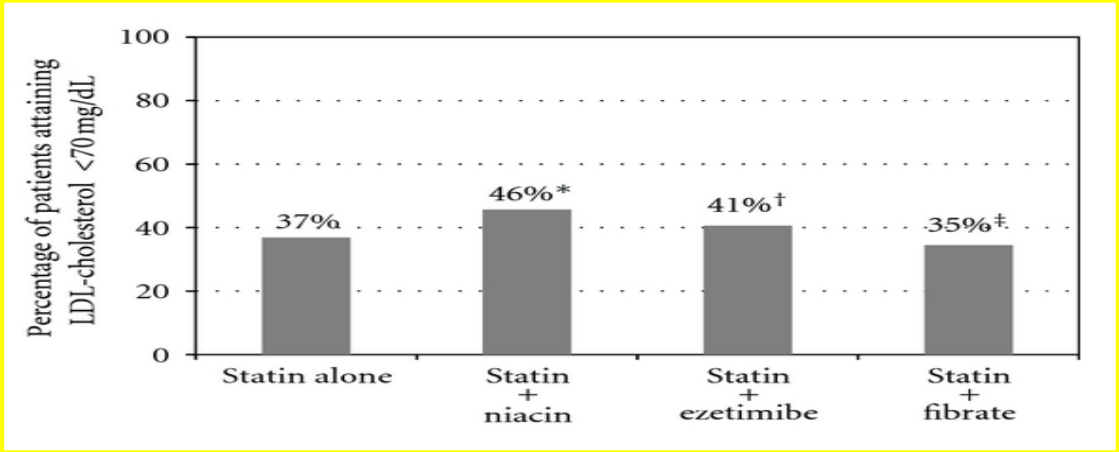
Use of Lipid-Lowering Medications and the Likelihood of Achieving Optimal LDL-C Goals in CAD Patients



Karalis DG, et al. *Cholesterol* 2012;2012:861-924

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Presented May 2, 2014 at NLA Annual Scientific Sessions

NATIONAL LIPID ASSOCIATION

NLA Recommendations for Patient-Centered Management of Dyslipidemia

Part 1 -- Final

www.lipid.org

NATIONAL LIPID ASSOCIATION

NLA Expert Panel Members

Terry A. Jacobson, MD (Co-Chair)
Matthew K. Ito, PharmD (Co-Chair)
Harold E. Bays, MD
W. Virgil Brown, MD
Edward A. Gill, MD
Scott M. Grundy, MD, PhD
Peter H. Jones, MD
Kevin C. Maki, PhD
James M. McKenney, PharmD
Carl E. Orringer, MD
Robert A. Wild, MD, PhD
Don P. Wilson, MD

Conceptual Framework for Formulation of NLA Expert Panel Recommendations

- Various guidelines and recommendations have been issued in the last few years that contain material differences.
- An NLA Expert Panel was formed to prepare a set of consensus recommendations intended to inform, not replace, clinical judgment regarding dyslipidemia management.
- The NLA Expert Panel recommendations for Patient-Centered Management of Dyslipidemia were prepared after a comment period to allow input and advice to be obtained from other experts and organizations.
  - A *patient-centered* approach dictates that clinical judgment take into account the circumstances, objectives, and preferences of each individual patient.

Conceptual Framework (continued)

- 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).
- 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.

Conceptual Framework (continued)

- 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.

Part 2

- Part 2 of the NLA Recommendations for Patient-Centered Management of Dyslipidemia is in development and will cover the following topics:
  - Lifestyle therapies
  - Groups with special considerations
    - Children, adolescents, pregnant women, and older patients
    - Gender and ethnic differences
    - Patients with congestive heart failure (CHF)
    - Patients with human immunodeficiency virus (HIV)
    - Patients with selected chronic inflammatory states and immune disorders
    - Patients with residual risk despite statin therapy
  - Strategies to assist with patient adherence
  - Team-based collaborative care

Usefulness of Treatment Goals

- The NLA Expert Panel's consensus view is that treatment goals are useful as means to ensure that the aggressiveness of therapy to lower atherogenic cholesterol is matched to absolute risk for an event, and to facilitate effective communication between patients and clinicians while maximizing long-term adherence to the treatment plan.
- The strategy of treating patients to a specific level of LDL-C or non-HDL-C has not been tested in any of the large trials assessing ASCVD morbidity or mortality.
  - However, results from RCTs that have employed various methods for lowering atherogenic cholesterol (pharmacotherapy, diet, ileal bypass surgery) have indicated that lower on-treatment levels have been consistently associated with lower absolute risk for an ASCVD event, and generally align with results from observational studies suggesting a log-linear relationship between levels of atherogenic cholesterol and absolute ASCVD event risk.

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 (covered later).
- 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)
  - Re-screen in 5 years, or with changes in risk factors (including weight gain), co-morbidities, new secondary causes of dyslipidemia, premature ASCVD events in first degree relatives, or other changes, based on clinical judgment
- Otherwise, institute therapies and monitoring as outlined in the subsequent slides.

Targets of Therapy – Atherogenic Cholesterol

- Atherogenic cholesterol (non-HDL-C and LDL-C) levels are the primary targets of therapy. Non-HDL-C is listed first because the panel consensus was that it is a better primary target than LDL-C.
  - Non-HDL-C is more predictive of ASCVD risk than LDL-C in observational studies, and with regard to changes or on-treatment levels in clinical trials.
  - When non-HDL-C and LDL-C are discordant, risk is more closely aligned with non-HDL-C.
  - Non-HDL-C testing is universally available, requires no additional cost, and may be obtained in the non-fasting state.

High or Very High Risk Patient Groups

- Quantitative risk scoring is not necessary for initial risk assessment in patients with the following conditions*:
  - Diabetes mellitus, type 1 or 2
  - Chronic kidney disease, Stage ≥3B
  - LDL-C ≥190 mg/dL - severe hypercholesterolemia phenotype, which includes FH
  - ASCVD

*Patients in these categories are all at ***high*** or ***very*** *risk* for an ASCVD event and should be treated accordingly.

Sequential Steps in ASCVD Risk Assessment

1. Identify patients with either ***very high risk*** **or** ***high risk*** conditions.*

   Very High Risk

   a. ASCVD
   b. Diabetes mellitus with ≥2 other major ASCVD risk factors or end organ damage[1]

   High Risk

   a. Diabetes mellitus with 0-1 other major ASCVD risk factors
   b. Chronic kidney disease Stage 3B or 4[2]
   c. LDL-C ≥190 mg/dL (severe hypercholesterolemia phenotype)

2. Count major ASCVD risk factors
   a. If 0-1 and no other major indicators of higher risk, assign to ***low risk*** category. Consider assigning to a higher risk category based on other known risk indicators, when present.
   b. If ≥3 major ASCVD risk factors are present, assign to ***high risk*** category.

3. If 2 major ASCVD risk factors, ***risk scoring*** should be considered and additional testing may be useful for some patients.
   a. If quantitative risk scoring reaches the high risk threshold,[3] assign to ***high risk*** category.
   b. Consider assigning to ***high risk*** category if other risk indicators are present based on additional testing (see later slide).
   c. If, based on above steps, no indication is present to assign to ***high risk***, assign to ***moderate risk*** category.

*Further risk assessment is not required after identifying the highest applicable risk level.

Criteria for ASCVD Risk Categories

Risk Category	Criteria
Low	▪ 0-1 major ASCVD risk factors ▪ Consider other risk indicators, if known
Moderate	▪ 2 major ASCVD risk factors ▪ Consider quantitative risk scoring ▪ Consider other risk indicators

High	▪ ≥3 major ASCVD risk factors
	▪ Diabetes mellitus (type 1 or 2)
	  ▪ 0-1 other major ASCVD risk factors, and
	  ▪ No evidence of end organ damage
	▪ Chronic kidney disease Stage 3B or 4
	▪ LDL-C ≥190 mg/dL (severe hypercholesterolemia)
	▪ Quantitative risk score reaching the high risk threshold

Very High	▪ ASCVD
	▪ Diabetes mellitus (type 1 or 2)
	  ▪ ≥2 other major ASCVD risk factors or
	  ▪ Evidence of end organ damage

Treatment Goals and Levels to Consider Drug Therapy According to Risk Category

Risk Category	Treatment Goal	Consider Drug Therapy
	Non-HDL-C mg/dL LDL-C mg/dL	
Low	<130 <100	≥190 ≥160
Moderate	<130 <100	≥160 ≥130
High	<130 <100	≥130 ≥100
Very High	<100 < 70	≥100 ≥ 70

For patients with ASCVD or diabetes mellitus, consideration should be given to use of moderate or high intensity statin therapy, irrespective of baseline atherogenic cholesterol levels.

Risk Indicators (Other Than Major ASCVD Risk Factors) That Might Be Considered For Risk Refinement[1]

1. A severe disturbance in a major ASCVD risk factor, such as multi-pack per day smoking, or strong family history of premature CHD
2. Indicators of subclinical disease, including coronary artery calcium
   - ≥300 Agatston units[2] is considered *high risk*
3. LDL-C ≥160 and/or non-HDL-C ≥190 mg/dL
4. High-sensitivity C-reactive protein ≥2.0 mg/L[3]
5. Lipoprotein (a) ≥50 mg/dL (protein) using an isoform insensitive assay
6. Urine albumin / creatinine ratio ≥30 mg/g

Drug Therapies – Important Considerations

- Patient-centered therapy: before initiation of pharmacotherapy, the clinician should have a discussion with the patient about treatment objectives and potential ASCVD risk reduction, as well as the potential for adverse effects, interactions with other medications, and patient preferences.
- When pharmacotherapy is to be used for lowering atherogenic cholesterol, moderate or high intensity statin therapy should be the first-line agent. Starting with a moderate dose and titrating as necessary to achieve treatment goals is a reasonable approach.
  - An alternate drug (bile acid sequestrant, cholesterol absorption inhibitor, fibric acid or nicotinic acid) may be considered in those with contraindications or intolerance to statin therapy

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