USING NONTRADITIONAL RISK MARKERS IN THE ERA OF THE 2013 ACC/AHA LIPID GUIDELINES

Atherosclerosis is a metabolic disease

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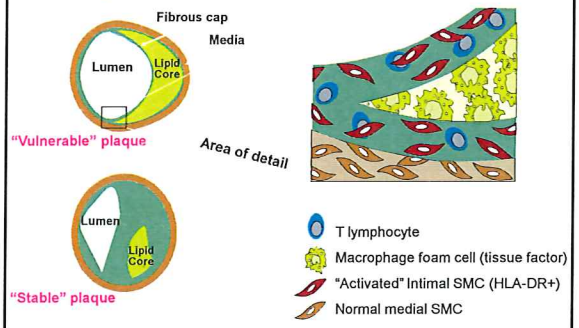
(0 is number zero)

No conflicts whatsoever to report.

Characteristics of Plaques Prone to Rupture From Inflammation and LDL*



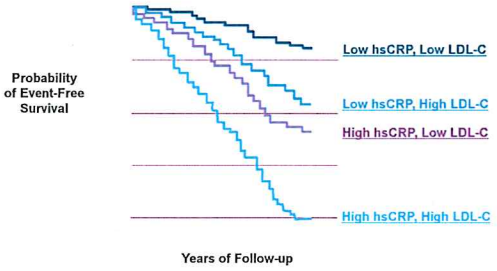
*Libby P. *Circulation*. 1999; 91:2844-2850.

HIGH SENSENSITIVITY C–REACTIVE PROTEIN (hs-CRP)

- A MARKER OF INFLAMMATION: CRP AND hsCRP ARE SAME PROTEIN.
- MAY BE ANOTHER RISK FACTOR AND PLAY A ROLE IN PLAQUE FORMATION.
- MAY PREDICT HIGH RISK ACUTE CORONARY SYNDROME.
- MAY INDICATE PATIENTS MOST LIKELY TO RESPOND TO STATINS.
- ASSOC. WITH ⇑ELEMENTS OF METAB. SYNDR.
- STATINS SHOWN TO REDUCE CRP.
  - EZETIMIBE ACCENTUATES THIS EFFECT.*
- NEED STATIN DOSE RESPONSE CURVE.
- LDL LOWERING IS STILL THE GOLD STANDARD.

First Coronary Event*

Women's Survival Rates



Tumor Necrosis Factor-α (TNF-α)*

- TNF-α also Tissue Necrosis Factor-α.
- Increased in acute and chronic inflammation.
- An inflammatory cytokine (cell-signaling protein).
- Inflammation and TNF-α are linked to development of atherosclerosis and Type 2 diabetes mellitus.
- TNF-α is a surrogate marker of atherosclerosis risk.
- There is interest in possible TNF-α blockade as a possible management of cardiovascular risk.

*Popa C, et al. J Lipid Res 2007;48:751-762.

CHD CHARACTERISTICS OF WOMEN

- Once MI occurs, women do worse. In-hospital mortality of women < 50 is twice that of men (6.1 vs 2.9%).*
- CHD in the young woman appears to be in an especially malignant form.
- Arterial inflammation probably different.
  - High levels of TNF-alpha receptors significant only in women in Nurses' Health Study vs men in Health Professionals Follow-up Study†
- Aggressive statin use and LDL lowering appear essential in the young woman with CHD.

Lipoprotein (a) [Lp(a)] as Surrogate or Independent CV Risk Marker

- Lp(a) is an LDL particle with a glycoprotein [apolipoprotein (a)], linked to the apoB of LDL by a disulfide bond.*
- Apo(a) is structurally similar to plasminogen but is antifibrinolytic.*
- Apo(a) is a multiple pleated structure (Kringles) with Lp(a) level inversely related to number of Kringle repeats.†
- Lp(a) has dsecreased LDL receptor affinity (statins ineffective) and catabolism is renal with renal excretion.*
- Lp(a) assembly from newly synthesized LDL occurs in liver and Lp(a) is increased in familial hypercholesterolemia.*

*Thompson GR and Seed M. Heart 2014;100:534-535.
†Clarke R, et al. N Engl J Med 2009;361:2518-2528.

Lipoprotein (a) [Lp(a)] as Surrogate or Independent CV Risk Marker

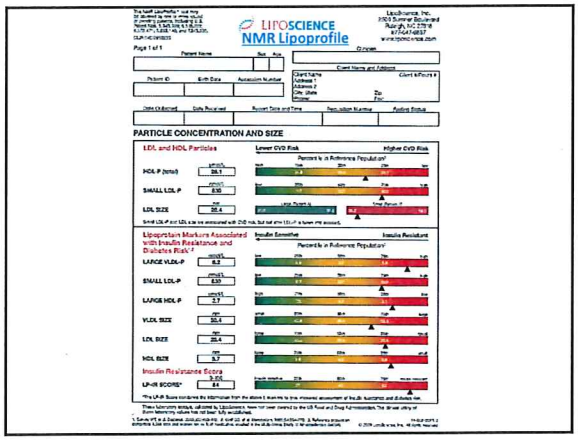
- Lp(a) associated with increased calcific aortic valve disease* and progression of stenosis to replacement.†
- Lp(a) predicts development of diabetic retinopathy.^
- Lp(a) is more susceptible to oxidation; it is also thrombogenic, promotes inflammation and increases foam cell formation.# Lp(a)↑ causes CAD↑ and PAD↑.•
- In JUPITER on rosuvastatin 20 mg/d, Lp(a) independently determined residual risk but relative risk reduction with rosuvastatin was similar with Lp(a) high or low.&
- There is evidence of benefit from Lp(a)↓; trials needed.@

*Cao J, et al. Arterioscler Thromb Vasc Biol 2016;36:1003-1009.
†Gurdasani D, et al. Arterioscler Thromb Vasc Biol 2012;32:3058-3065.
‡Capoulade R, et al. J Am Coll Cardiol 2015;66:1236-1246.
^Jae-Seung Y, et al. J Clin Lipidol 2016;10:426-433.
‡Emerging Risk Factors Collaboration. JAMA 2009;302: 412-423.
*Khera AV, et al. Circulation 2014;129:635-642.
#Kronenberg F. Circulation 2014;129:619-621.

APOLIPOPROTEIN (Apo) ANALYSIS AS SURROGATE MARKERS OF CV RISK

- Apo A.
  - The major structural protein of HDL.
  - Consideration has been made for possible value as a surrogate.
  - ApoA-1_{Milano} beneficial and can result in CHD plaque reduction.*
- Apo B.
  - Specific analysis instead of LDL-C has been evaluated.
  - Apo B may offer additional prediction of CV risk such as for coronary atherosclerosis with lower levels of plasma total cholesterol (e.g. cholesterol <265 mg/dL.†

*Nissen SE, et al. JAMA 2003;290:2292-2300.
†Whayne TF. Atherosclerosis 1981;39:411-424.


LIPOSCIENCE
NMR Lipoprofile
PARTICLE CONCENTRATION AND SIZE

GLYCEROL KINASE (GK) DEFICIENCY

- GK deficiency rarely diagnosed and involves X-linked recessive gene in isolation or in association with development/dystrophy problems.*
- Relevance to clinician is when hypertriglyceridemia fails to respond to any Rx, suspect GK deficiency.
- Usual plasma triglycerides (TG) assay depends on glycerol production by enzymatic reaction and subsequent spectrophotometric assay.
- Clarify by analysis of TG by Liposcience NMR.

*Whayne TF. J KY Med Assoc 2011;109:89-91.

OTHER ADVANCED LIPOPROTEIN TESTING*

- Berkeley (California): Gradient Gel Electrophoresis.
  - Determines distribution of LDL size phenotype by proprietary segmented polyacrylamide gradient gels.
  - Separates lipoproteins in a gradient gel based on size and, to a lesser extent, the charge on the lipoproteins.
  - Pattern A: large LDL; Pattern B: small dense LDL.
- Vertical Autoprofile (VAP): Density Gradient Ultracentrifugation (Birmingham, Alabama).
  - Measures relative distribution of cholesterol within various lipoprotein (Lp) subfractions.
  - Quantifies cholesterol content of Lp subclasses.
    - VLDL, IDL, LDL, Lp(a), and HDL.

*Mora S. Circulation 2009;119;2396-2404.

SUPPORT FOR LOWER LDL: LIPID RESEARCH CLINICS (LRC)

OVER 7.4 YEARS, MAJOR CORONARY EVENTS REDUCED BY 19% WITH P = 0.05.*

*Lipid Research Clinics. JAMA 1984;251:365-374.

SUPPORT FOR LOWER LDL: PROGRAM ON THE SURGICAL CONTROL OF THE HYPERLIPIDEMIAS (POSCH)*

- Between 1975 and 1983, 838 survivors of single MI entered into study which ended in 1990.*
  - 417 patients to Rx/diet/control group.
  - 421 patients to diet/partial ileal bypass intervention group.
    - Apparent zero surgical mortality in the first 57 patients.†
- All POSCH post 5 yr. mort./ath. endpts. favorable.*
  - Mort. from CHD/nonfatal MI: 157 vs. 105 (P<0.001).
  - Nonfatal MI: 109 vs. 68 (P<0.001).
  - CABG or PTCA: 201 vs. 106 (P<0.001).
  - Onset of PVD: 93 vs. 68 (P=0.02).
- POSCH: LDL 37.7% lower and HDL 4.3% higher.*

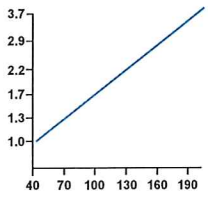
*Buchwald H. Arch Intern Med 1998;158:1253-1261.
†Buchwald H. Ann Surg 1990;212:318-329.

SUPPORT FOR LOWER LDL: PROVE-IT; JUPITER

- SUBSTUDY OF ACS PATIENTS IN PROVE-IT SHOWED THAT SUBGROUPS OF LDL < 40 mg/dl AND LDL 40-60 mg/dl HAD EVEN FEWER MAJOR CARDIAC EVENTS.†
- THE JUPITER STUDY SHOWED SIGNIFICANTLY FEWER CV EVENTS IN THE GROUP ATTAINING LDL < 50 mg/dl WITTHOUT ⇑ ADVERSE EVENTS.*

†Wiviott SD, et al. J Am Coll Cardiol 2005;46:1411-1416.
*Hsia J, et al. J Am Coll Cardiol 2011;57:1666-1675.

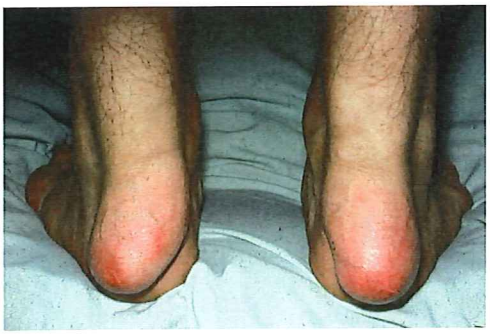
Log-Linear Relationship Between LDL Levels (LDL remains the gold standard of CV risk) and Relative Risk for CHD



- This relationship is consistent with a large body of epidemiologic data and data available from clinical trials of LDL-C–lowering therapy. Goal for high CV risk is LDL < 70 mg/dl.
- These data suggest that for every 30 mg/dL change in LDL, the relative risk for CHD is changed in proportion by about 30%.
- The relative risk is set at 1.0 for LDL = 40 mg/dL.

LDL-C = low-density lipoprotein cholesterol; CHD = coronary heart disease.

Reprinted with permission from Grundy SM, Cleeman JI, Merz CNB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation. 2004;110:227–239; http://ww.com.



Key Statin Pleiotropic Effects*

- Improved endothelial motor dysfunction.
- Increased fibrinolysis (via ⇓ PAI-1).
- Favorable modulation of immune function.
- Antithrombotic properties-decreased platelet aggregation.
- Decreased metalloproteinase activity with decreased macrophage activity
- Anti-inflammatory effects.
- Increased nitric oxide.

*Davignon J. Curr Ath Reports. 2004;6:27-35.

Summary of 2013 ACC/AHA Rx of Blood Cholesterol Guidelines*

- CV risk focused on 4 groups that appear to benefit from a statin.
  1. Established clinical CV disease.
  2. Documented LDL-C ≥ 190 mg/dL.
  3. Presence of DM in patient aged 40-75 yrs without clinical CV disease and LDL-C 70-189 mg/dL.
  4. Absence of Clinical CV disease or DM, LDL-C 70-189 mg/dL, and estimated 10-yr CV risk ≥ 7.5%.
- Goal is to use high-dose statin to attain a "significant" LDL-C reduction of ≥50% from the untreated baseline without specifying a specific LDL-C target.
- Estimation of 10-yr CV risk by internet cohort equations.

*Stone NJ et al. J Am Coll Cardiol 2014;63:2889-2934.

CONFLICTS OF INTEREST

- *British Med J** reported in 2013 that 8 of 15 panelists of 2013 ACC/AHA were conflicted.

ORGANIZATIONS NOT ACCEPTING 2013 ACC/AHA

- International Atherosclerosis Society (2014) recommended optimal LDL <70mg/dl for sec. prevention.
- Natl. Lipid Assoc.^ and Amer. Assoc. of Clin. Endocrinologists# are opposed to removing LDL goals as recommended by 2013 ACC/AHA.
- In 2011, Eur. Soc. Cardiol. and Eur. Atheroscler. Soc. published treatment targets, either/or, as LDL < 70 mg/dL for very high CV risk patient or a ≥50% decrease in LDL of high CV risk patient.+

*Lenzer J. *BMJ*. 2013;347:f6989.
^Jacobsen TA. J Clin Lipidol 2014;8:473-488.
#Miller N. Internal Medicine News, Jan 2014, page 14.
+ESC/EAS Guidelines. Eur Heart J 2011;32:1769-1818

LDL: TARGETED VS. TAILORED APPROACH

- Change to tailored approach advocated with contention that benefit of LDL lowering not established.*
- LDL lowering as a targeted approach has much support from LRC, LDL apheresis, POSCH, quantitative coronary angiography, hypobetalipoproteinemia, statin outcomes studies.#
- Acceptance of risk modification of CV disease still not widespread as standard of care. Why confuse the practitioner with idea of quantum change needed?+

*Hayward RA and Krumholz HM. Circ Cardiovasc Qual Outcomes. 2012;5:2-5.
#Whayne TF Jr. Angiology 2012 June 25 [doi:10.1177/0003319712451115].
+Whayne TF Jr. Cardiology News 2012;10:30.

HDL: GOOD, BUT CAN BE BAD

- HDL reverse transport appears beneficial.
- Inflammation et al. (eg myeloperoxidase mediated oxidation) can change HDL structure and impair HDL function.#
- Increasing HDL is not a guarantee of CV benefit.
- No routine diagnostic assays of HDL function.
- Statins not ↑HDL well; after 1 year, HDL may fall below starting baseline with atorvastatin.

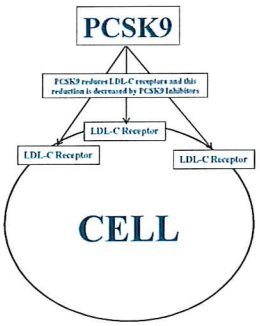
#Fisher EA, et al. Arterioscler Thromb Vasc Biol 2012;32:2813-2820

PROPROTEIN CONVERTASE SUBTILISIN-LIKE/KEXIN TYPE 9 (PCSK9) ANTIBODY

- Normal function of PCSK9 is to decrease LDL receptor levels by binding to the receptor; i.e. negative feedback.
- With LDL receptors bound by PCSK9, increase LDL results.
- A monoclonal antibody to PCSK9 can be highly specific and result in up to a 72% decrease in LDL.*
- Idea for possible monoclonal antibody for PCSK9:
  - PCSK9 loss-of-function mutations that resulted in ↓LDL.
  - PCSK9 gain-of-function mutations that resulted in ↑LDL.
- Administration is subcutaneous every 2 or 4 weeks.
- GAUSS-3 (reported at ACC 2016): Confirmed true atorvastatin intolerance and also a psychosomatic component as well as the markedly increased potency of evolocumab vs. ezetimibe in lowering LDL.

*McKenney J et al. J Am Coll Cardiol 2012;59:2344-2353.

Mechanism of PCSK9 Inhibitors.



PCSK9 INHIBITORS IN ACUTE CORONARY SYNDROME*

- PCSK9 INCREASES IN ACUTE CORONARY SYNDROME (ACS).
- PCSK9 INHIBITION IN (ACS) MAY BENEFIT MORE THAN JUST LDL REDUCTION BY THE FOLLOWING IN THE ACS PATIENT:
  - ANTI-INFLAMMATORY EFFECTS.
  - ANTIPLATELET EFFECTS.
  - DIRECT PLAQUE STABILIZATION.
- FURTHER STUDIES + TIMING INDICATED.

*Navarese EP, et al. Ann Intern Med 2016;164:600-607.

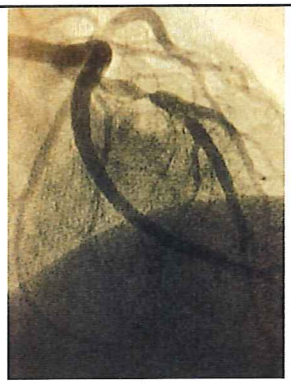
How Low is Too Low?

- Epidemiologic studies show that people with naturally low LDL-C levels have improved longevity[1]
- Newborn human infant has LDL-C of approximately 30 mg/dL[2]
- Some findings suggests that LDL-C level of 25 mg/dL would be sufficient to nourish body with cholesterol [2]
- How Low is Too Low --- UNKNOWN

1. O'Keefe JH et al. *J Am Coll Cardiol.* 2004;43: 2142–6
2. Brown MS, Goldstein JL. *Science.* 1986; 232: 34–47

PATIENT OF MINE FROM TOLUCA, MÉXICO

- A 32 yo Mexican male with acute myocardial infarction (STEMI) involving LAD artery.
- Atorvastatin 80 mg per day prescribed in hospital before cath. and stent placement.
- Referred to me for consultation and follow up; on the atorvastatin, LDL-C 131 mg/dL.
- Ezetimibe decreased the LDL-C to 100 mg/dL.
- Alirocumab 75 mg sc q 2 weeks added and after approximately 3-4 weeks, LDL-C 75 mg/dL; significant further LDL-C decrease expected.
- Working full time in construction.



Patient RI. LAD lesion. Very aggressive LDL lowering and essentially no angina. (never forget that atherosclerosis is a metabolic disease)

CONCLUSIONS

- Women have increased mortality from coronary artery disease (CAD) when CHD develops <age 50 and inflammatory status appears increased.
- High sensitivity C-reactive protein (hsCRP) is the most useful clinical marker of inflammation; TNFα for research.
- Nontraditional risk markers: value in selective situations.
- LDL is still the gold standard of cardiovascular (CV) risk and it is essential to make it the target of treatment.
- The treatment of HDL might be the next major focus in the reduction of cardiovascular risk but problems lurk.
- Failure to treat and decrease LDL in a patient with high primary or secondary CV risk, without a specific reason, is malpractice.