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.

HIGH SENSITIVITY 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.
- EZEIMMIVE ACCENTUATES THIS EFFECT.*
- NEED STATIN DOSE RESPONSE CURVE.
- LDL LOWERING IS STILL THE GOLD STANDARD.

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.


Characteristics of Plaques Prone to Rupture From Inflammation and LDL*

First Coronary Event*

Women's Survival Rates

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 receptor 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 (Kringle) with Lp(a) level inversely related to number of kringle repeats.*
- Lp(a) has decreased 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 Seld M. Heart 2014;100:534-535.

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.*

*Thompson GR and Seld M. Heart 2014;100:534-535.

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.
  - Apo A-1↑ 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.

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.


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 Autoprobe (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.

SUPPORT FOR LOWER LDL: LIPID RESEARCH CLINICS (LRC)

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


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

- 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. mortality endpoints 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.*


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 WITHOUT ‡ ADVERSE EVENTS.*


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.
**Key Statin Pleiotropic Effects**

- Improved endothelial motor dysfunction.
- Increased fibrinolysis (via $\Delta$ 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.


**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 $\geq$ 130 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 $\geq$ 7.5%.
- Goal is to use high-dose statin to attain a "significant" LDL-C reduction of $\geq$50% from the untreated baseline without specifying a specific LDL-C target.
- Estimation of 10-yr CV risk by internet cohort equations.


**CONFLICTS OF INTEREST**

- *British Med* $^*$ 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 $\geq$50% decrease in LDL of high CV risk patient.$^*$


**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, FOSCH, 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?+$^*$

*$^*$Hickman Y et al. Atheroscler Thromb Vasc Biol 2012;32:2183-2189

**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.$^*$


**PROPROTEIN CONVERTASE SUBTILISIN-LIKE/KEKIN 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 2015): Confirmed true atorvastatin intolerance and also a psychosomatic component as well as the markedly increased potency of evolocumab vs. ezetimibe in lowering LDL.$^*$

**Mechanism of PCSK9 Inhibitors.**

**PCSK9**

1. PCSK9 binds LDL-C receptor
2. PCSK9 inhibitor
3. LDL-C receptor
4. LDL-C

**CELL**

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**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.


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**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 suggest that LDL-C level of 25 mg/dL would be sufficient to nourish body with cholesterol \(^2\)
- How Low is Too Low --- UNKNOWN


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**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.

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**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.

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