New Markers of Cardiovascular Risk

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Requirements for Novel Risk Factors

• Shown in multiple prospective studies to predict future CV events.

• Provide independent information on risk or prognosis.

• Easy to measure in a cost-effective manner in outpatient settings.

• Accepted if reduction of the biomarker leads to reduced vascular risk
Emerging Novel Biomarkers

• No additive value over and above Framingham risk scoring except hsCRP.

• Few are supported by commercial assays.

• Lowering plasma levels of any of these biomarkers, including hsCRP, does not lower vascular risk.

• They provide important insights into the pathophysiology of atherothrombosis.

Ridker et al, Circulation.2004;109[suppl V]:IV-6 - IV-19
Lp(a) as a RF in Atherosclerosis (ASO)

• The ATP III guidelines:
  - Lp(a) is an “emerging” lipid RF for CVD.

• The National Cholesterol Education Program:
  - At high risk of CAD plasma Lp(a):
    * Is increased in ~37% of US population
  - At low risk:
    * Lp(a) is increased in only 14%.
Clinical Perspective Studies

• Lp (a) and CHD:
  - Metaanalysis of 27 prospective studies.
  - Atherosclerosis Risk in Communities (ARIC) Study
    Sharrett et al, Circulation. 2001;104:1108-1113
  - Non Additive to Framingham Risk Score and Lipid Screening.
The predictive strength of Lp(a) for CHD was evaluated.

10-years FU of 12,339 middle-aged participants free of CHD.

725 CHD events occurred.

Lp(a) was associated with modest risk ratio.

Much higher RR in women than men.

Less risk in blacks than in whites.

Sharrett et al, Circulation.2001;104:1108-1113
**Interaction between Lp(a) and other RFs**

- PROCAM Study [788 males, 35-65 y, FU 10 ys]:
  - RR of CAD event:
  * At Lp(a) ≥ 20 mg/dL is 2.7
  * Compared to men with <20 mg/dL.
  - Risk is most prominent with:
    * LDL ≥ 160 mg/dL (RR 2.6)
    * HDL < 35 mg/dL (RR 8.3)
    * Hypertension (RR 3.2)

Stable effort angina:
- Prospective cohort (1216 pts)
- Examined with CAG
- FU 6.7 y.
- Total mortality: 16.4%

Lp(a) ≥ 300 mg/L:
- 30% of the study population
- Independent predictor for death.

Lp(a) >300 mg/L:
- Poor prognosis.

Lp(a): Prognosis in Primary Prevention

- Remains uncertain

- Important marker in individuals with markedly elevated risk caused by diabetes or hyperlipidemia

- has greater benefit in certain high risk groups as premature ATS and CRF.
Against use of Lp(a) in clinical practice

- Poor standardization of commercial assays
- Few interventions lower Lp(a) except niacin
- No evidence that lowering Lp(a) lowers vascular risk

Marcovina et al, Clinical Chemistry. 2003; 49(11): 1785-1796
Role of Homocysteine in Vascular Disease

• Meta-analysis of 30 studies.

• (5073 CAD & 1113 stroke events)

• After adjustment for known CVD risk factors, a 25% lower homocysteine was associated with a lower risk of:

  * CAD 11% (smaller than anticipated).
  
  * Stroke 19%.

Homocysteine Screening

• Not recommended in recent guidelines.

• Folate supplementation:
  - Decreases predictive value of homocysteine
  - Reduces homocysteine levels ~25%,
  - Addition of vit. B\textsubscript{12} reduces another 7%
  - Inexpensive and safe
  - Used without screening.

Wilson et al, JAMA. 2002;288:2042-2043
Wald et al, Arch Intern Med. 2001;161:695-700
Who to screen?

• Premature ASO dis and absent convent RFs.

• Unexplained venous thrombosis.

• AHA recommend screening in:
  - Malnutrition, malabsorption,
  - Hypothyroidism,
  - CRF,
  - SLE,
  - Medications: niacin, theophylline, MTX, L-dopa.

Circulation 1999; 99:178-
• Adipocyte-derived peptide

• Regulation of:
  - Insulin sensitivity
  - Lipid oxidation

• Anti-atherogenic properties

• High plasma Adiponectin:
  - Lower risk of MI in men
  - Independent of inflammation and glycemia

Matching factors included age, smoking status. Multivariable adjustment included matching factors, BMI, family history of MI, history of DM and HTN, alcohol intake, and physical activity. Biomarkers were added to the model as continuous variables. RR of MI associated with doubling of adiponectin levels after sequential adjustment for LDL-C, HDL-C, TG, HbA1c, and CRP levels.


- High plasma adiponectin concentrations are associated with lower risk of MI in men.
Myeloperoxidases (MPO):
- Leukocyte-derived heme peroxidase.
- Generates chlorinating oxidants as hypochlorous acid (HOCL)
- Potent proatherogenic properties:
  * LDL-C oxidation.
  * Metalloproteinase activation.
  * eNO consumption.
In 547 pts with ACS:
- MPO levels predict increased risk for subsequent CV events.

**MPO:** 222 µg/ L (1st tertile), 223 to 350 µg/ L (2nd tertile), and >350 µg/ L (3rd tertile). **Event rates between tertiles were significant at 72 hours (P<0.001), 30 days (P<0.001), and 6 months FU (P<0.001).**

*Baldus et al. Circulation.* 2003;108:1440-
Predictive value of MPO for incidence of death and nonfatal MI according to TnT serum levels “CAPTURE Trial”

- In pts with TnT <0.01 µg/ L:
  - Elevated MPO significantly increased cardiac risk (adjusted hazard ratio 7.48; \( P=0.001 \)).
  - In conjunction with TnT, MPO identified 95% of all adverse events

*Baldus et al. Circulation. 2003;108:1440*
Markers in Myocardial Ischemia

• Ischemia-modified albumin (IMA):
  - Sensitive & early biochemical marker of M ischemia.
  - N-terminal of albumin is a binding site for transitional metals as cobalt.
  - In presence of ischemia:
    * Hypoxia, acidosis, free-radical
    * Decrease the binding capacity to exogen cobalt
    * Occurs within mins after the onset of AM ischemia
In 208 pts presenting with symptoms of acute chest pain, IMA is highly sensitive for the diagnosis of MI ischaemia.

Sensitivity of IMA for ischaemic chest pain was 82%. IMA with cTnT or ECG, had 90% and 92% respectively. All 3 tests identified IHD in 95% of pts.

Strong evidence of proatherogenic role of ROS.

Trials of antioxidant vitamins:
- Ineffective in reducing coronary events.
Trials of Antioxidant Vitamins

• Negative trials may be due to:
  - No well-accepted marker of oxidative stress:
    * Allows therapy to be targeted
    * Efficacy of ttt to be followed.
  - Correct antioxidants that:
    * Penetrate the cell membrane
    * Have long-lasting effect
    * Are not yet available.
Circulating ox-LDL is a sensitive marker of CAD

- Impossible to distinguish whether ox-LDL elevations are a cause or a result of ASO.

- No study has prospectively examined the usefulness of ox-LDL as a RF for the subsequent development of ATS in healthy subjects.
Cellular antioxidant enzyme:
  - Central role in the control of (ROS)
  - May protect against ATS

In pats with CAD:
  - ↓ activity of red-cell glutathione peroxidase 1:
    - Independently associated with ↑ risk of CV events

↑ glutathione peroxidase 1 activity might ↓ risk of CV events.

Blankenberg et al. N ENG J MED.2003; 349(17):1605-1613
The risk of CV events: was inversely associated with increasing quartiles of glutathione peroxidase 1 activity (P<0.001)

Blankenberg et al. N ENG J MED 2003; 349(17):1605-1613