Use of Emerging Risk Factors: Why and On Whom

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Brief Background

- NCEP-I guidelines increased the clinical usefulness of total cholesterol (TC) testing by partitioning the measurement into lipoprotein components (VLDL-C, LDL-C, HDL-C).
- Numerous recent research suggests that partitioning these major lipoprotein components further (VLDL, LDL and HDL subfractions), Lp(a), lipoprotein density/particle size, apolipoproteins (A and B) enhances their association with CAD.
- NCEP-III guidelines identified Emerging Risk Factors for the assessment of CAD risk.
- Technological analytical advances in the laboratory measurements of Emerging Risk Factors simplifies total risk assessment and can be directly quantitated rapidly and reliably.

QUESTION

- Does the partitioning of the major lipoprotein components show better association with the CAD process than the standard lipid panel?

- Does the partitioning of the major lipoprotein components show better predictability of the CAD than the standard lipid panel?

CASE I

- Double-blind study of 226 male CCF patients (mean age = 52 y.o.) who had cineangiography performed.
- 26 standardized sites were evaluated by two cardiologist for the degree of obstruction and mean scores were tabulated. The most severe coronary stenosis score was used to categorized each patient's severity of disease and placed into one of 4 groups: Control Gr. (0%) n = 21; Gr. II (1-50%, mean = 22%) n = 33; Gr. III (51-99%, mean = 89%) n = 68; Gr. IV (100%) n = 104.
- Data were analyzed by analysis of variance, covariance and correlation analysis.
- From: Naito HK; *Annals of NY Academy of Sciences* 454:230-238 (1985)

Case 1 Results

- Analysis of Variance and Covariance: comparing mean values among the 4 groups:

– TC	Not significant
– TG	Not significant
– LDL-C	Not significant
– HDL-C	Not significant
– HDL_3-C	Not significant
– Apo A-II	P = 0.01
– HDL_2-C	P = 0.001
– Apo A-I	P = 0.001
– Apo B	P = 0.001

Case I Results (Cont.)

- Correlation Coefficient

– VLDL-C	r = 0.02	P = 0.80
– HDL_3-C	r = 0.02	P = 0.80
– Apo A-II	r = 0.03	P = 0.50
– TG	r = 0.11	P = 0.21
– HDL-C	r = - 0.13	P = 0.05
– TC	r = 0.14	P = 0.04
– LDL-C/HDL-C	r = 0.16	P = 0.02
– LDL-C	r = 0.16	P = 0.02
– LDL-C/TC	r = - 0.20	P = 0.002
– Apo B	r = 0.42	P = 0.001

Case 1 Results (Cont.)

– Apo A-I	r = - 0.50	P = 0.001
– HDL_2-C	r = - 0.58	P < 0.001
– Apo A-I/Apo B	r = - 0.62	P < 0.001
– HDL_2-C/HDL-C	r = - 0.64	P < 0.001
– HDL_2-C/HDL_3-C	r = - 0.67	P < 0.001

Case 2

- Double-blind study of 134 male CCF patients who had cineangiography performed (subset study)
- Data were analyzed using Receiver Operating (ROC) Characteristic Curve
- SENSITIVITY = probability that, given the presence of CAD, the abnormal test results indicate the presence of the disease
- SPECIFICITY = probability that, given the absence of CAD the test results exclude the disease

- From: Naito, HK; *J Clin Immunoassay* 9:11-20 (1986)

Case 2 Results

Marker	Cutoff Pt.	Sensitivity	Specificity
TC	224 mg/dL	63%	67%
HDL-C	44 mg/dL	71%	73%
HDL-C/TC	0.194	71%	87%
Apo A-I	148 mg/dL	86%	67%
LDL-C/HDL_2-C	10	76%	93%
Apo A-I/B	1.325	87%	80%
HDL_2-C	14 mg/dL	81%	93%
HDL_2/HDL_3	0.545	89%	93%
HDL_2/HDL	0. 353	90%	93%

Summary

- This cineangiographic study suggests that by partitioning the measurement of the major classes of lipoproteins into their subfractions and apolipoprotein components can:
  - enhance the correlation with the increasing degree of coronary artery obstruction (substantially better than the standard lipid profile)
  - enhance the prediction of the severity of the coronary artery disease with greater sensitivity and specificity (better than the standard lipid profile)

Recommendations

- The clinical use of Emerging Risk Factors should not be use for generalized screening.
- They should be used selectively for a better estimate of the absolute risk for CAD in the high-risk patient:
  - Symptomatic patients with documented CAD, CABAG, stent implant, abnormal lipid profile
  - Asymptomatic patients with positive history for premature CHD and with a normal lipid profile
  - Patients with diabetes mellitus or metabolic syndrome
- In addition, use of Emerging Risk Factors should be encouraged for basic and clinical research.
- Every effort should be made to develop standardization programs to help ensure the accuracy of testing of these advanced analytical techniques.

Closing Thoughts

- On an individual basis, nearly half of the MI patients have normal lipid profile[1]. Doing the standard lipid panel does not provide an accurate view for CHD risk assessment.
- Using the Emerging Risk Factors can provide more comprehensive estimate of absolute risk. As an example, Superko and Hecht[2] showed that simply adding LDL-subclasses increased the diagnostic yeild from 55% to 84% for subclinical CAD in asymptomatic patients.
- Analytical technology is now available to readily do Emerging Risk Factors. It's selective use should not be denyied.

- [1]Ridker P, In: Handbook of Electrophoresis. AACC Press, p. 65-75, (2000)
- [2]Superko R and Hecht H, *Amer J Cardiol* 88:260-4 (2001)