

Emerging Themes in Lipid Metabolism: Insights for CVD and Diabetes

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CVD – The Startling Statistics

- CVD affects approximately 121.5 million Americans (2016)
 - CHD is most common form of heart disease
 - CVD often results in heart attack
- Dyslipidemia affects more than 95 million Americans
- Healthcare costs exceed \$351.2 billion in 2014 to 2015

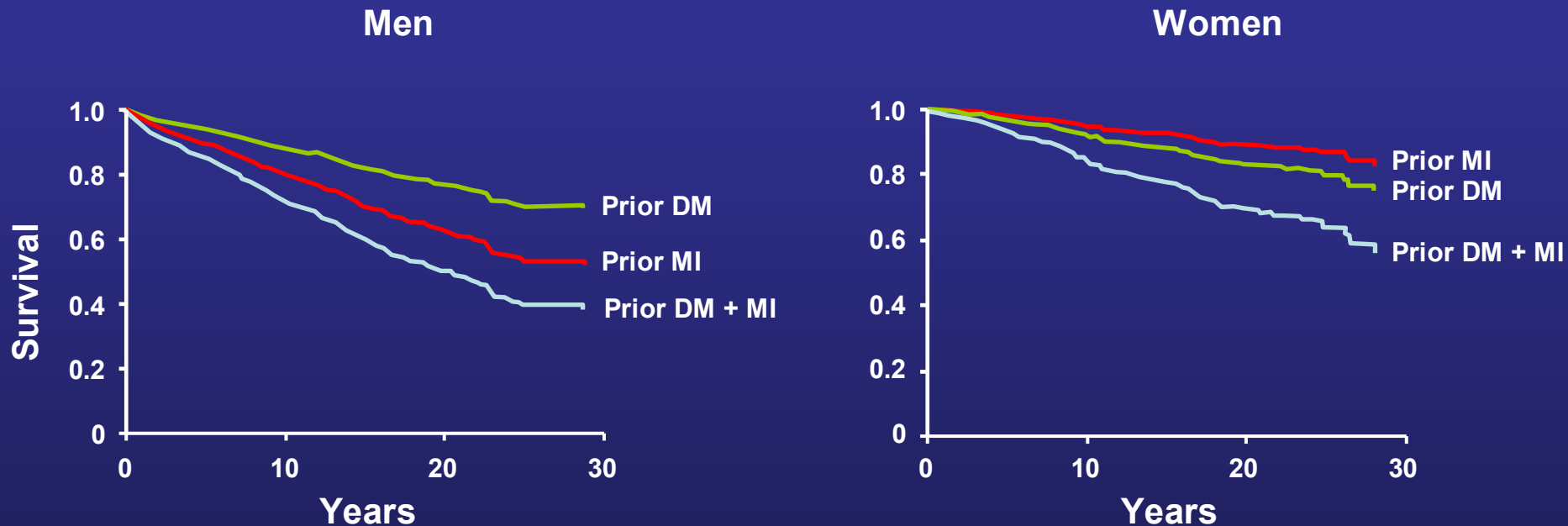
Diabetes and CVD

- Current estimates show that:
 - More than 30.3 million Americans have diabetes¹
 - Prevalence* will increase 165% by 2050²
- Diabetes is a CHD risk equivalent²
 - Associated with ↑ prevalence of CV risk factors (atherogenic dyslipidemia, hypertension)
- *Up to 68% of diabetic patients will die of CVD*

1. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2017. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Dept of Health and Human Services; 2017.

2. ADA website. Available at: <http://www.diabetes.org>. Accessed Oct 6, 2004. 2. Boyle JP et al. *Diabetes Care*. 2001;24:1936-1940. 3. AHA. *Heart Disease and Stroke Statistics—2004 Update*. Dallas, TX: AHA

Coronary Mortality in Patients With and Without Diabetes Mellitus¹



Adjusted for age, study year, body mass index, systolic blood pressure, total cholesterol, and smoking.

DM = diabetes mellitus; MI = myocardial infarction.

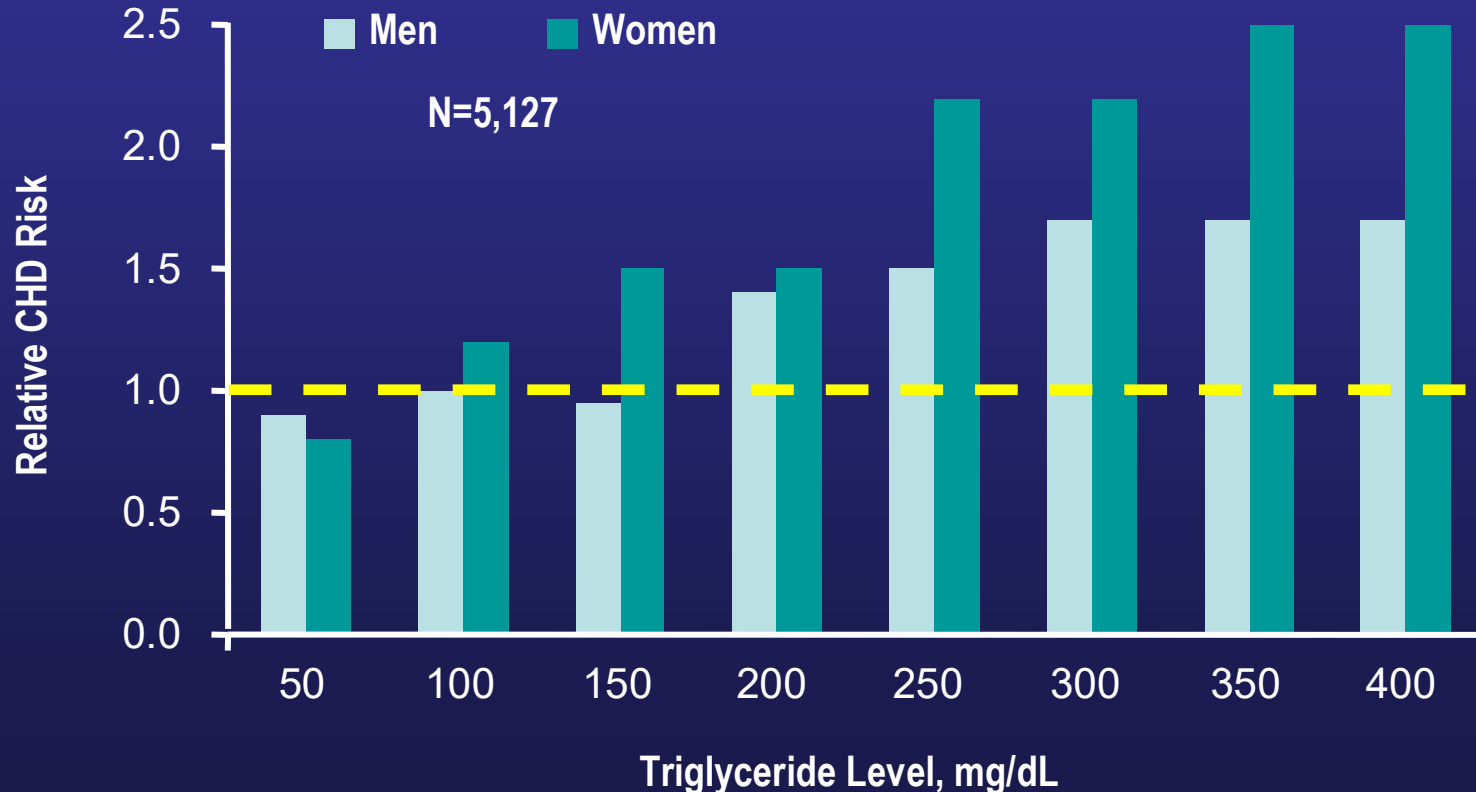
1. Hu G et al. *J Am Coll Cardiol.* 2005;45:1413–1418.

Mechanisms for Atherosclerosis

- Influx (LDL, TG)
- Inflammation (Cytokines, Lp(a))
- Efflux (pre-beta 1 HDL)

CHD Risk Increased With Elevated Triglyceride Levels: The Framingham Heart Study¹

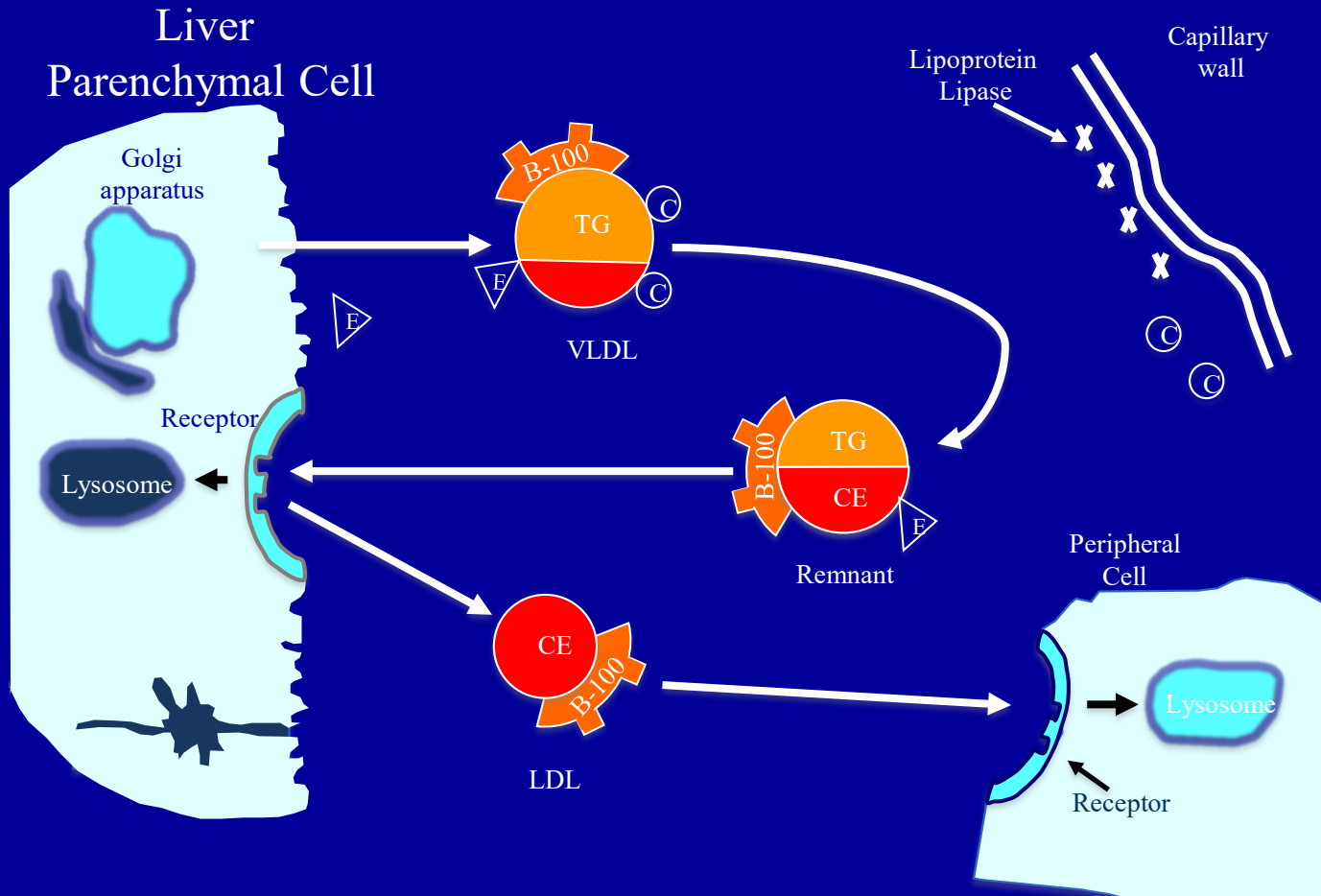
In a univariate analysis, the relationship between serum triglycerides and subsequent development of CAD was significant for all correlations in women, but only for the 30-year data in men.



CAD = coronary artery disease.

1. Castelli WP. *Am J Cardiol.* 1992;70:3H-9H.

Metabolism of VLDL and LDL



Isolated Elevation of LDL

Genetic:

- Familial hypercholesterolemia
- Ligand-defective apoB100
- PCSK-9 gain of function
- ARH (Autosomal recessive hypercholesterolemia)
- Cyp 7-alpha deficiency
- LAL (Lysosomal acid lipase deficiency)

Secondary

- Hypothyroidism
- Early nephrosis
- Cholestasis
- Multiple myeloma
- Phytosterolemia

Secondary Causes of Hypertriglyceridemia

- Secondary causes of hypertriglyceridemia
- Diabetes/Insulin resistance/obesity
- Insulinopenia
- Alcohol
- Medications- tacrolimus, sirolimus, steroids, other
- Fructose

Emerging Therapy: PCSK9

- Proprotein convertase subtilisin/kexin type 9 binds to LDL receptors and increases their degradation, thus reducing the removal rate of LDL
- Gain of function mutations result in increased levels of LDL-C
- Loss of function mutations result in very low LDL-C

Mechanisms for Atherosclerosis

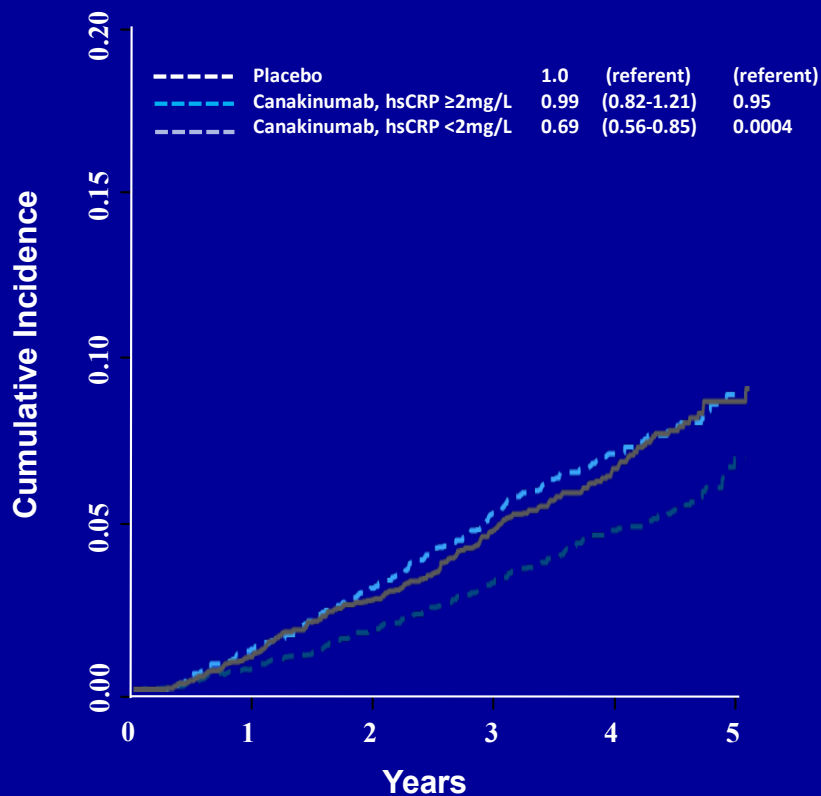
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Chylomicrons in the Immune Defense

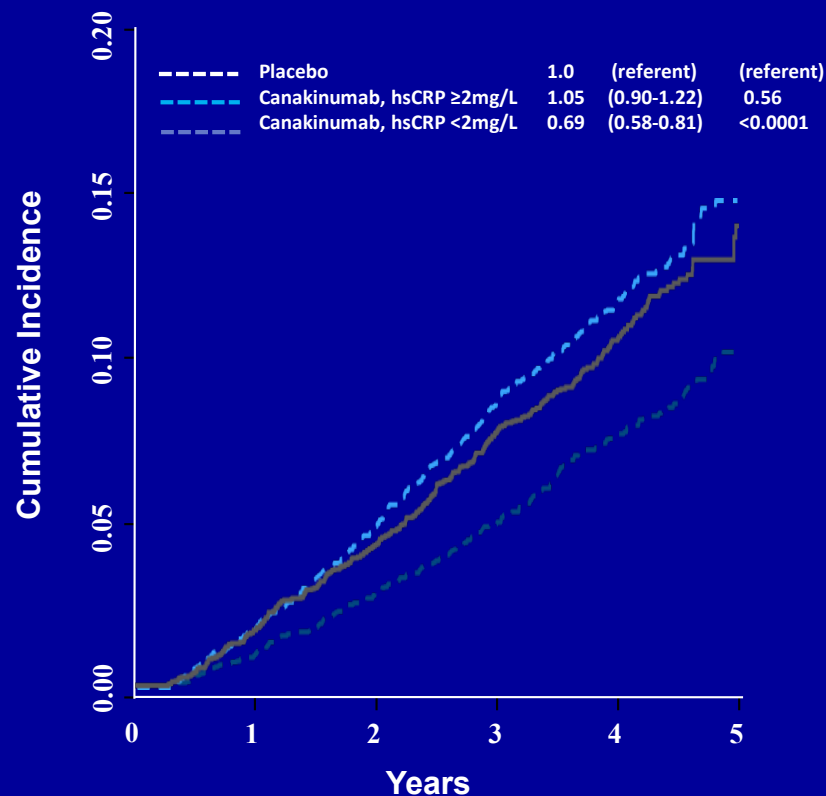
- Individuals with low triglyceride levels have greater mortality from sepsis
- Raising triglyceride levels improves survival
- Chylomicrons sequester endotoxins: the role of the thoracic duct
- ApoB-48 inhibits quorum sensing by *Staphylococcus aureus*
- Chylomicrons increase leukocyte activation

CANTOS : 31% Reduction in Cardiovascular Mortality and All-Cause Mortality Among Participants with Robust Inhibition of the Inflammatory Response

CANTOS - Cardiovascular Mortality



CANTOS - All Cause Mortality

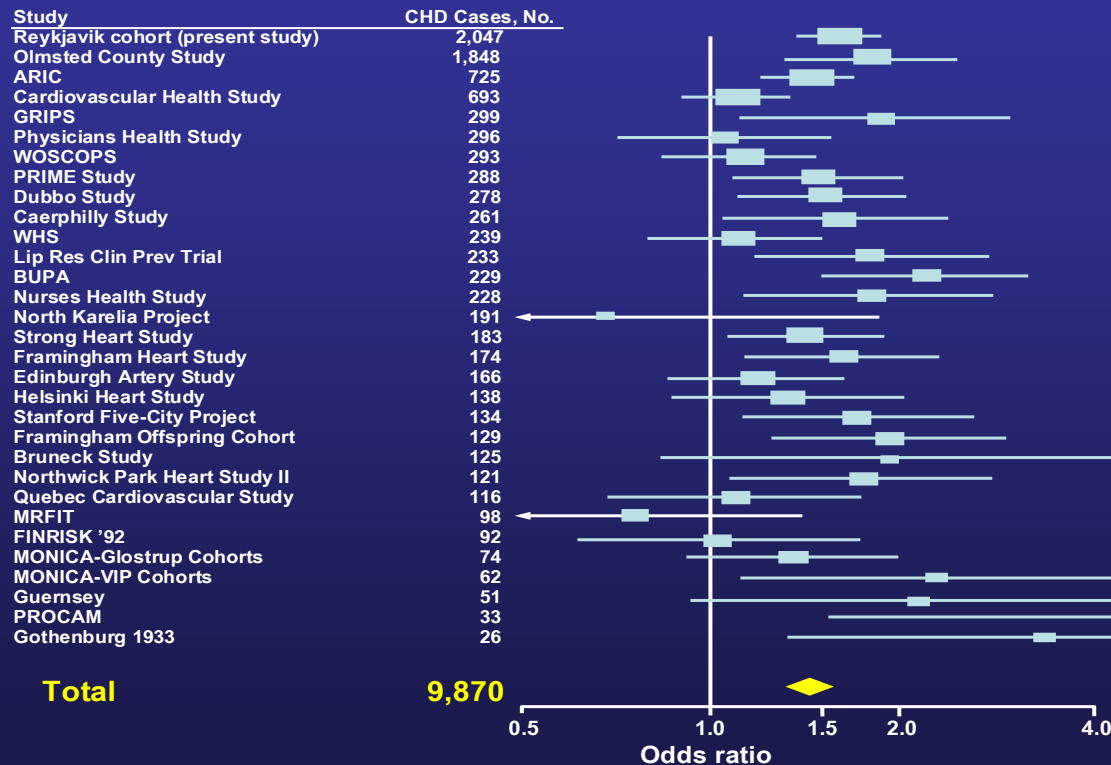


**35 - 40% reductions in hsCRP and IL-6
No change in LDLC**

Lp(a)

- When elevated Lp(a) is associated with the atherogenic lipoprotein profile (low HDL₂, elevated dense LDL, IDL, dense VLDL and VLDL), the increased risk is 25.
- If two or more non-lipid risk factors are also present (hypertension, diabetes, cigarette smoking, or high total homocysteine) the increased risk is 122.

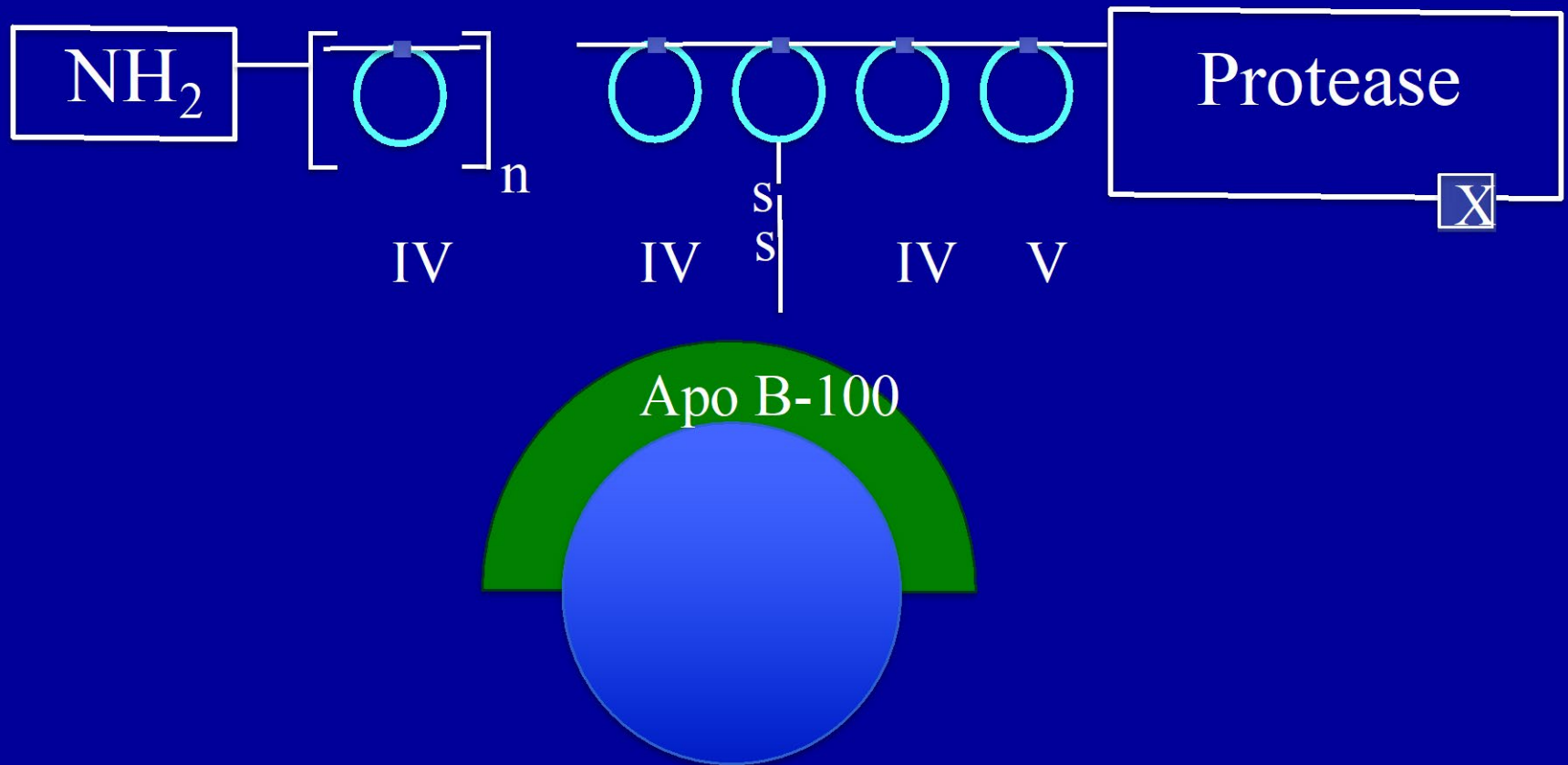
High Lp(a) Levels Were Associated With Increased CHD Risk: Meta-Analysis Results¹



Odds ratios for CHD (top third vs bottom third of the baseline Lp(a) distribution) in each of 31 published prospective studies of Lp(a) in general populations. Lp(a) = lipoprotein(a)

1. Bennett A et al. *Arch Intern Med.* 2008;168:598–608.

Lp(a) Lipoprotein



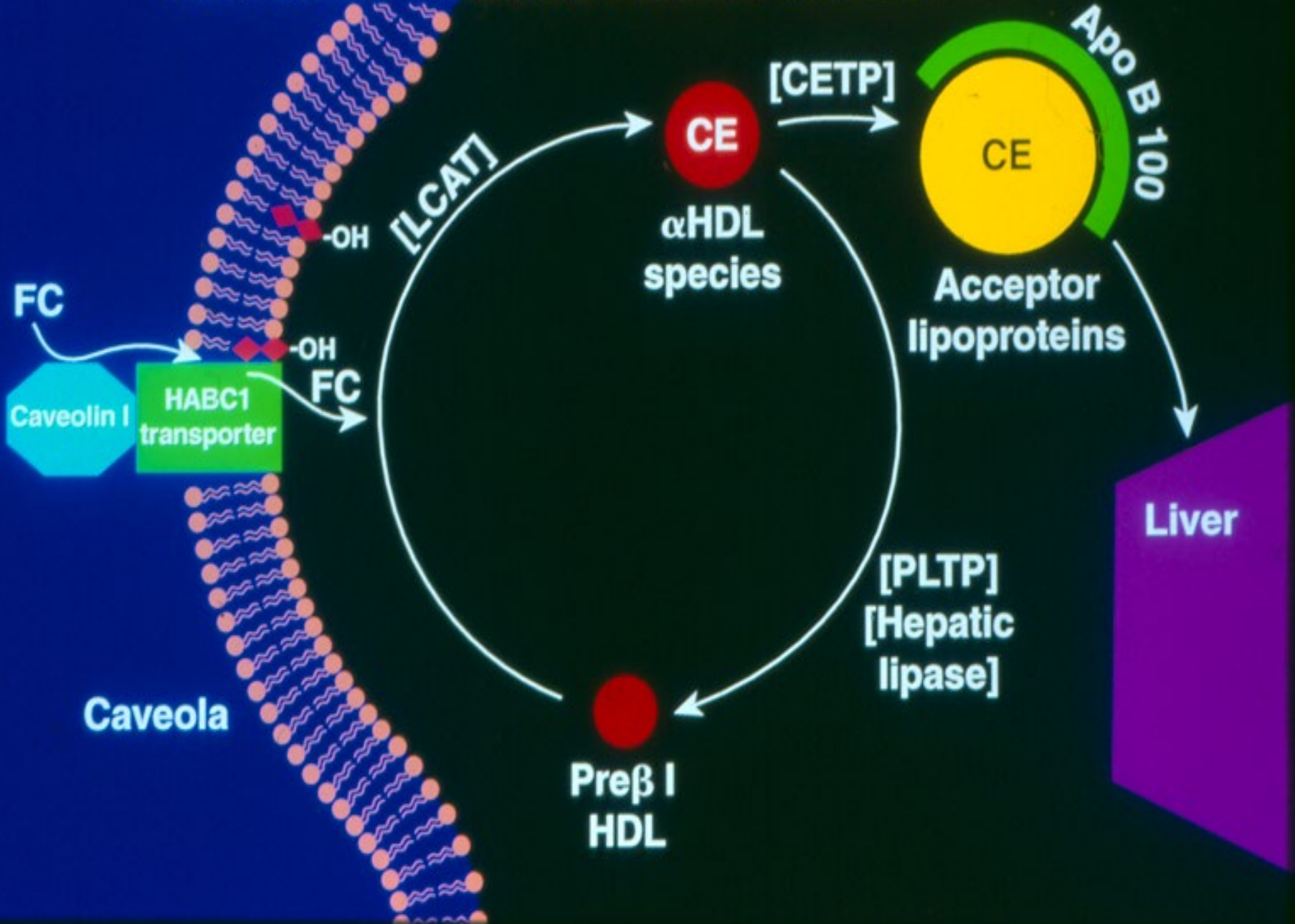
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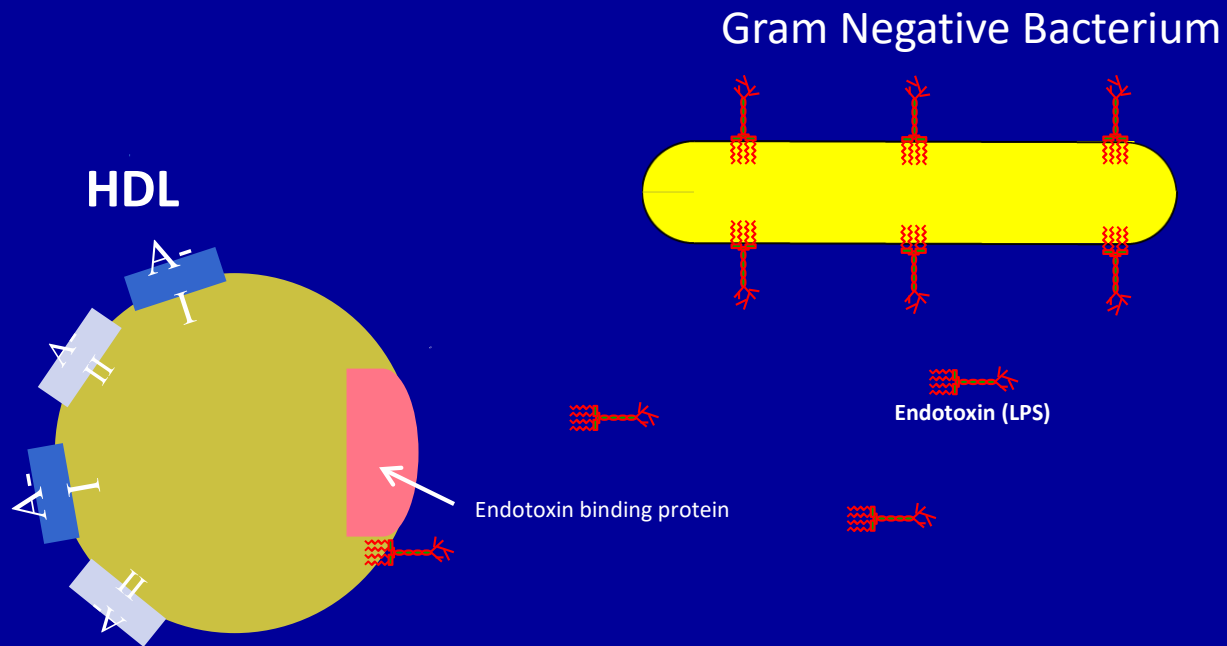
HDL: The Changing Landscape

- Total HDL cholesterol levels do not reflect risk in many individuals
- HDL can vary two-fold in its ability to promote efflux
- The ability to efflux cholesterol from the artery wall can vary widely
- The level of prebeta-1 HDL is an independent indicator of the rate of efflux
- Prebeta-1 HDL is a powerful and independent indicator of risk of MI
- Many other properties of HDL may be of importance to risk

REVERSE CHOLESTEROL TRANSPORT



HDL Sequesters Endotoxins



Thank You Questions?

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