Emerging Themes in Lipid Metabolism: Insights for CVD and Diabetes

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September 24, 2019
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 diabetes\(^1\)
  – Prevalence* will increase 165% by 2050\(^2\)
• Diabetes is a CHD risk equivalent\(^2\)
  – Associated with \(\uparrow\) prevalence of CV risk factors
    (atherogenic dyslipidemia, hypertension)
• \textit{Up to 68\% of diabetic patients will die of CVD}


Coronary Mortality in Patients With and Without Diabetes Mellitus\textsuperscript{1}

Adjusted for age, study year, body mass index, systolic blood pressure, total cholesterol, and smoking.
DM = diabetes mellitus; MI = myocardial infarction.
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 Study\textsuperscript{1}

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.

\textsuperscript{1}Castelli WP. \textit{Am J Cardiol.} 1992;70:3H–9H.
Metabolism of VLDL and LDL

Liver Parenchymal Cell

Golgi apparatus

Receptor

Lysosome

VLDL

TG

CE

LDL

Remnant

Peripheral Cell

Lysosome

Receptor

Capillary wall

Lipoprotein Lipase
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

Ridker PM. Circulation 2018
Lp(a)

• When elevated Lp(a) is associated with the atherogenic lipoprotein profile (low HDL$_2$, 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 Results

<table>
<thead>
<tr>
<th>Study</th>
<th>CHD Cases, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reykjavik cohort (present study)</td>
<td>2,047</td>
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<tr>
<td>Olmsted County Study</td>
<td>1,848</td>
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<td>ARIC</td>
<td>725</td>
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<td>Cardiovascular Health Study</td>
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<td>GRIPS</td>
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</tr>
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<td>Physicians Health Study</td>
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</tr>
<tr>
<td>WOSCOPS</td>
<td>293</td>
</tr>
<tr>
<td>PRIME Study</td>
<td>288</td>
</tr>
<tr>
<td>Dubbo Study</td>
<td>278</td>
</tr>
<tr>
<td>Caerphilly Study</td>
<td>261</td>
</tr>
<tr>
<td>WHS</td>
<td>239</td>
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<td>Lip Res Clin Prev Trial</td>
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<td>BUPA</td>
<td>229</td>
</tr>
<tr>
<td>Nurses Health Study</td>
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</tr>
<tr>
<td>North Karelia Project</td>
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</tr>
<tr>
<td>Strong Heart Study</td>
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</tr>
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</tr>
<tr>
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<td>166</td>
</tr>
<tr>
<td>Helsinki Heart Study</td>
<td>138</td>
</tr>
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<td>Stanford Five-City Project</td>
<td>134</td>
</tr>
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<td>Bruneck Study</td>
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</tr>
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</tr>
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<tr>
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<td>PROCAM</td>
<td>33</td>
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<td>Gothenburg 1933</td>
<td>26</td>
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</tbody>
</table>

Total: 9,870

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)

Lp(a) Lipoprotein

NH₂

[ ]

n

IV

IV

SS

IV

V

Protease

Apo B-100

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Mechanisms for Atherosclerosis

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- Efflux (pre-beta 1 HDL)
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
HDL Sequesters Endotoxins

Gram Negative Bacterium

Endotoxin (LPS)

Endotoxin binding protein
Thank You

Questions?

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