“Thinkings” on Lipids: Genetics, apoB, HDL, and PCSK9 inhibition

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Human genetics is leading to identification of new pathways and to smarter and faster development of new medicines
Lipoproteins and CAD

LDL
TG, CE
TG-rich lipoproteins
Lp(a)

HDL
CE

A-I

?
ApoB-lipoproteins are biomarkers of CAD risk

Clinical trait  Association with CAD  Lipoprotein class

LDL cholesterol  ↑

Triglycerides  ↑

Lipoprotein(a)  ↑
ApoB-containing lipoproteins are causally related to coronary disease.
Evidence for the causality of apoB-lipoproteins to CAD risk

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<th>Trait</th>
<th>LDL</th>
<th>TRLs</th>
<th>Lp(a)</th>
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<td>Epidemiology</td>
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<td>Human Genetics</td>
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<td>Randomized Trials</td>
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Inherited Syndromes of Extremes of LDL-C: Story of PCSK9

- Loss of function mutations in PCSK9
- Gain of function mutations in PCSK9

Frequency (%)
LDL Receptor Function and Life Cycle
The Role of PCSK9 in the Regulation of LDL Receptor Expression
Impact of an PCSK9 mAb on LDL Receptor Expression
PCSK9 Inhibitors

- Alirocumab and Evolocumab
- SQ injection biweekly or monthly
- Indications:
  - Patients with heterozygous familial hypercholesterolemia on maximally tolerated statin therapy with inadequate plasma LDL levels
  - Patients with a history of CHD with inadequate plasma LDL levels

- Cardiovascular outcome trials ongoing
Lipoproteins and Coronary Disease

Remaining unmet medical needs in treatment of dyslipidemia
Triglyceride-rich lipoproteins are causally related to coronary disease.
ApoC-III inhibits LPL and TG-rich remnant uptake.
ApoC-III as a novel therapeutic target
Lipoprotein lipase is a nodal pathway for new therapeutic development.
HDL-C does not appear to be causally associated with CAD
CETP inhibition raises HDL-C levels… but doesn’t reduce CV events
ApoA-I promotes macrophage cholesterol efflux and reverse cholesterol transport.
Genetics, Lipoproteins and CAD: Implications for new therapies

- TG, CE
- LDL
- TG-rich lipoproteins
  - Lp(a)

? ->

- A-I
- CE
- HDL