Background 1 – What is Known
- Premenopausal women are protected from CVD vs. men of the same age; risk is similar to that of men ten years younger.
- Protection is lost in post-menopausal years.
- CVD risk has been attributed in part to increased LDL cholesterol in post-menopause.
- Estrogen (and estrogen-progestin) therapy increase CVD risk in older post-menopausal women, but may be protective if instituted earlier.

Background 2 – What is Not Known
- To what extent does increased LDL-C explain the increase in CVD risk in post-menopause?
- Is there evidence that estrogen effects on lipids and lipoproteins reverse atherogenic changes in post-menopause?
LDL has been the primary focus of CVD risk reduction

LDL-C reduction (mmol/L) vs. Major coronary events

CTT Collaborators. Lancet 366:1267, 2005

LDL-C is just one component of an LDL particle

Apoprotein B (ApoB)

Cholesterol
Phospholipids
Triglycerides

LDL-C vs. LDL-Particles (LDL-P) and CVD Risk

Cumulative incidence of cardiovascular events in subgroups with concordant or discordant levels of LDL-C and LDL-P


LDL Metabolism – Traditional Model

Liver
lipolysis, lipid and apoprotein transfers

VLDL
Remnants (IDL)
LDL

Eisenberg et al., Biochim Biophys Acta 326: 361-377, 1973
LDL particles comprise a spectrum of subclasses with differing cholesterol content and CVD risk:

- Large LDL: more cholesterol/particle
- Medium LDL
- Small and very small (sdLDL): less cholesterol/particle

Berneis and Krauss, JLR 43:1155, 2002

Origin of LDL subclasses:

Adapted from Berneis and Krauss, JLR 43:1155, 2002

Lipoprotein subclasses: High-resolution separation and direct quantitation by ion mobility:


Standard LDL-C assay is a measure of remnant particles as well as "true" LDL:

N=748 men and women not using hormones

In stepwise regression, 48% of variance in LDL-C explained by IDL, 2% by LDL particles.
Atherogenic Dyslipidemia of Metabolic Syndrome

**Definition**
- Elevated triglycerides (VLDL remnants)
- Reduced HDL cholesterol
- LDL-C normal, but increase in sdLDL particles

**Prevalence**
- ~ 20% in persons with ≥1 CVD risk factor
- ~ 30% in diabetics with ≥1 CVD risk factor

For small LDL particles, LDL-C level misrepresents the number of LDL particles

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Small dense (sd)-LDL-C but not large buoyant (lb)-LDL-C predicts CHD

Hoogeveen et al., ATVB 34:1069, 2014

sdLDL-C predicts CHD even when LDL-C < 100 mg/dl

Hoogeveen et al., ATVB 34:1069, 2014
Why are sdLDL associated with increased CVD risk?

- Reduced LDL receptor binding – longer plasma residence time
- Greater arterial proteoglycan binding
- Greater oxidative susceptibility
- Association with other risk biomarkers:
  - Reduced HDL, increased remnants
  - Insulin resistance
- Atherogenic components
  - Oxidized lipids
  - ApoCIII

ApoC-III

- Small exchangeable apolipoprotein (MW 10,800) found in all lipoprotein classes
- ApoCIII in apoB-containing lipoproteins is associated with CHD risk
- Reduces lipolysis and receptor-mediated clearance of apoB-containing lipoproteins
- Increases arterial proteoglycan binding of apoB-containing lipoproteins
- Direct pro-inflammatory properties
- Human apoCIII deficiency associated with reduced atherosclerosis
- Anti-sense oligo for apoCIII in phase 3 studies

Risk for developing coronary heart disease is associated with “LDL” containing apo-CIII

“LDL” apoCIII is mainly in remnants and small LDL fractions

Mendivil et al., Circulation 124:2065, 2011

Data from Krauss et al., J. Lipid Res 53: 540, 2012
ApoCIII has a key pathologic role in atherogenic dyslipidemia

Reduced hepatic remnant uptake

Increased artery binding & direct inflammatory effects

Non-Fasting Triglyceride and CHD Risk
Women’s Health Study

Both remnant particles and medium/small LDL are associated with increased CVD & total mortality on statin therapy (JUPITER)


Odds ratio for 1mmol/L change

Remnant cholesterol

Remnant cholesterol is associated with increased CHD risk


n=75,513 participants; 11,984 IHD cases

Remnant cholesterol*

HDL cholesterol

LDL cholesterol

*Estimated by total C - LDLC - HDLC


* p < 0.05


n=26,330 women (19,983 fasting; 6,347 nonfasting)


Conclusions(1)
- Greater age-related increases in LDL cholesterol in women vs. men are mainly due to atherogenic remnant lipoprotein particles.
- These particles reach levels higher than those in men in the post-menopausal years.
- Thus, remnant lipoprotein particles may contribute to increased CVD risk in older women and loss of premenopausal CVD protection compared to men of similar age.
- Hormone therapy in post-menopause reduces LDL cholesterol but this is not accompanied by a decrease in remnants and there is an increase in sdLDL particles.
- Smaller HDL particles are increased by hormones; add to levels of large HDL that increase slightly with age.

Conclusions (2)
- Age-related increases in apoCIII in women vs. men, beginning in pre-menopausal years, may contribute to increased levels of atherogenic lipoproteins.
- Therapies aimed at reducing apoCIII levels (e.g. newer PPAR agonists and anti-sense oligonucleotides) may have particular benefit for reducing CVD risk in post-menopausal women.
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