HDL plays no role in the pathogenesis of atherosclerosis

Børge G Nordestgaard
Professor, Chief Physician, MD, DMSc

Conflict of Interest Disclosure
Consultancies or talks sponsored by AstraZeneca, Merck, Omthera, Sanofi-Aventis, Regeneron, ISIS Pharmaceuticals, Aegerion, Dezima, Fresenius, B Braun, Kaneka, Pfizer, Amgen, Lilly, Kowa, Denka Seiken
Two weavers promise an Emperor a new suit of clothes that is invisible to those who are unfit for their positions, stupid, or incompetent.
The good cholesterol

Brain washed

Lay press HDL

Medical textbooks

Low HDL protects against heart disease

A HDL level above 60 is good!
Main focus on LDL cholesterol

- LDL receptor – Goldstein & Brown
- Oxidized LDL – Steinberg
- Statins – Endo, 4S trial and others
- European guidelines – LDL only
- American guidelines – LDL mainly
Next focus on HDL cholesterol

- Strong epidemiology – all studies
- Animal studies
- The ”HDL mafia”
- Big Pharma
- But then…

HDL-C $\uparrow$ → CVD $\uparrow$
Drug targets based on genetic evidence

LDL-C

Lp(a)

HDL-C ?

Remnant-C / TG

Nordestgaard Eur Society Cardiology Congress 2011
Clinical focus on lipoproteins for CVD prevention

Epidemiology
Clinicians
Trials
"Postprandial"

Nobel prize 85 & statins

4S trial

Genetics & "failed" HDL trials

Remnants
TGs

Nordestgaard 2014
Evidence for risk factors causing atherosclerotic disease?

<table>
<thead>
<tr>
<th></th>
<th>LDL↑</th>
<th>Many other risk factors</th>
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<tbody>
<tr>
<td>Epidemiology</td>
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<td>√</td>
<td>FH + SNPs</td>
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<td>Many models</td>
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<tr>
<td>Mechanism</td>
<td>√</td>
<td>Understood</td>
</tr>
<tr>
<td>Intervention</td>
<td>√</td>
<td>Statin trials</td>
</tr>
</tbody>
</table>

Nordestgaard 2015
Randomized trial vs. Mendelian randomization

Randomization methods

Placebo

Drug: (lipo)protein levels ↑ or ↓

Confounders evenly distributed

Cardiovascular disease ↓ or ↑

Random distribution of alleles

Normal allele

Allele: (lipo)protein levels ↓ or ↑

Confounders evenly distributed

Cardiovascular disease ↓ or ↑

Reverse causation
Triglycerides

- HDL
- LDL
- Remnants

**HDL cholesterol**

**LDL cholesterol**

**Remnant or VLDL cholesterol**

*total cholesterol minus LDL-C minus HDL-C*

*no direct assay available yet*
Copenhagen General Population Study
Lipoprotein cholesterol, mmol/L

<table>
<thead>
<tr>
<th>Triglycerides, mmol/L</th>
<th>N</th>
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<tr>
<td>&lt; 1</td>
<td>2309</td>
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<tr>
<td>1 – 2</td>
<td>6040</td>
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<td>2 – 3</td>
<td>3023</td>
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<td>3 – 4</td>
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<td>4 – 5</td>
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<td>≥ 5</td>
<td>477</td>
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Remnant
LDL
HDL

Triglycerides, mg/dL

<table>
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<th>Observations, No.</th>
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<tbody>
<tr>
<td>4564</td>
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<tr>
<td>7355</td>
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<td>2298</td>
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<td>652</td>
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<td>212</td>
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<td>141</td>
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</table>

Remnant
LDL
HDL

**Trend**

Freiberg, Nordestgaard 2011
Remnants
Evidence for lipoproteins causing atherosclerotic disease?

<table>
<thead>
<tr>
<th></th>
<th>LDL↑</th>
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<td>√</td>
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<td>√</td>
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<tr>
<td>Animal models</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Mechanism</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Intervention</td>
<td>√</td>
<td>(√)</td>
</tr>
</tbody>
</table>

Many studies
Remnant hyperlipidemia
Many models
Similar to LDL
More needed

Nordestgaard 2015
Copenhagen General Population Study (CGPS)

N=15,000

37 yrs follow-up

No losses to follow-up 1977-2014

Copenhagen City Heart Study (CCHS)

N=110,000+

10 yrs follow-up

Copenhagen
Nonfasting triglycerides, mmol/L

Fraction of population

27% 46%

27%

0.1%

Reference  In extreme groups

Nordestgaard & Varbo, Lancet 2014; 384: 626-635
Copenhagen City Heart Study and Copenhagen General Population Study

Myocardial infarction

N = 96,394 (Events = 3,287)

Nonfasting triglycerides, mmol/L

Hazard ratio (95% CI)

Nordestgaard & Varbo, Lancet 2014; 384: 626-635
Copenhagen City Heart Study and Copenhagen General Population Study

Ischemic Heart Disease
N = 93,410 (Events = 7,183)

Hazard ratio (95%CI)

Mainly fasting triglycerides, mmol/L

Emerging Risk Factors Collaboration
JAMA 2009

Coronary Heart Disease
N = 302,430 (Events = 12,785)

In deciles

Nordestgaard & Varbo, Lancet 2014; 384: 626-635

In extreme groups

Nonfasting triglycerides, mmol/L

Mainly fasting triglycerides, mmol/L
Nonfasting triglycerides, mmol/L

Copenhagen City Heart Study and Copenhagen General Population Study

Ischemic Stroke
N = 97,442 (Events = 2,994)

Nordestgaard & Varbo, Lancet 2014; 384: 626-635

Mainly fasting triglycerides, mmol/L

Emerging Risk Factors Collaboration
JAMA 2009

Ischemic Stroke
N = 173,312 (Events = 2,534)

In quintiles

In extreme groups
All-cause mortality

N = 98,515 (Events = 14,547)

In extreme groups

Nordestgaard & Varbo, Lancet 2014; 384: 626-635

Nonfasting triglycerides, mmol/L
Mendelian randomization hypotheses

Lipoprotein \leftrightarrow \text{Genotype} \leftrightarrow \text{Cardiovascular Disease Risk}

1. established but causal?
2. effect size? pleiotropic effects?
3. statistical power?

Causality: Instrumental Variable Analysis
Remnant cholesterol (mmol/L)
- <0.4
- 0.4-0.6
- 0.6-0.7
- 0.7-1.1
- >1.1

HDL cholesterol (mmol/L)
- >2.0
- 1.7-2.0
- 1.4-1.7
- 1.2-1.4
- <1.2

CCHS+CGPS
N=57,000

Hazard ratio for IHD
- <0.4
- 0.4-0.6
- 0.6-0.7
- 0.7-1.1
- >1.1

Varbo et al. JACC 2013; 61: 427-36
Remnant cholesterol↑
Plasma: observational
Genetic: causal
Remnant↑ / HDL-C↓
Plasma
Genetic

HDL cholesterol↓
Plasma
Genetic

LDL cholesterol↑
Plasma
Genetic

N=66,000 CCHS+CGPS+CIHDS

Varbo et al JACC
2013; 61: 427-36

Hazard ratio for IHD per 1mM ↑or↓

15 selected genetic variants
Triglycerides $\uparrow$
Genetic unadjusted
Genetic LDL+HDL adjust

HDL cholesterol $\downarrow$
Genetic unadjusted
Genetic LDL+TG adjust

LDL cholesterol $\uparrow$
Genetic unadjusted
Genetic TG+HDL adjust

Effect size ($\beta$) for CAD per 1SD $\uparrow$ or $\downarrow$

N=87,000 CARDIoGRAM
Do et al Nat Genet 2013; 45: 1345-52

Genome wide 185 SNPs

22,000 CAD
Loss-of-Function Mutations in \textit{APOC3} and Risk of Ischemic Vascular Disease


Loss-of-Function Mutations in \textit{APOC3}, Triglycerides, and Coronary Disease

The TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute*
Ischemic vascular disease

<table>
<thead>
<tr>
<th>N alleles</th>
<th>N total</th>
<th>N events</th>
<th>Risk estimate</th>
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</thead>
<tbody>
<tr>
<td>0 APOC3</td>
<td>75,465</td>
<td>10,770</td>
<td>0.59</td>
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<tr>
<td>1 APOC3</td>
<td>260</td>
<td>27</td>
<td></td>
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<tr>
<td>0 TG and HDL Working Group</td>
<td>110,472</td>
<td>33,889</td>
<td>0.60</td>
</tr>
<tr>
<td>1</td>
<td>498</td>
<td>113</td>
<td></td>
</tr>
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<td>0 APOC3</td>
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<td>1 APOC3</td>
<td>498</td>
<td>113</td>
<td></td>
</tr>
<tr>
<td>0 PCSK9</td>
<td>64,492</td>
<td>10,665</td>
<td>0.90</td>
</tr>
<tr>
<td>1 PCSK9</td>
<td>1,697</td>
<td>250</td>
<td></td>
</tr>
</tbody>
</table>

Triglycerides, mmol/L

Hazard ratio (95% CI)

LDL cholesterol, mmol/L

Hazard ratio (95% CI)

Nordestgaard & Varbo, Lancet 2014; 384: 626-635
Nordestgaard & Varbo, Lancet 2014; 384: 626-635
HDL cholesterol
### Evidence for lipoproteins causing atherosclerotic disease?

The table below summarizes the evidence for lipoproteins in the context of atherosclerosis from various biological perspectives.

<table>
<thead>
<tr>
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<th>LDL↑</th>
<th>TG↑ &amp; Remnants↑</th>
<th>Low HDL</th>
</tr>
</thead>
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<td><strong>Epidemiology</strong></td>
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<td>√</td>
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<td>√</td>
<td>?</td>
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<tr>
<td><strong>Intervention</strong></td>
<td>√</td>
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Nordestgaard 2015
Elevated HDL Cholesterol Is a Risk Factor for Ischemic Heart Disease in White Women When Caused by a Common Mutation in the Cholesteryl Ester Transfer Protein Gene (Circulation. 2000;101:1907-1912.)

Birgit Agerholm-Larsen, MSc, PhD; Børge G. Nordestgaard, MD, DMSc; Rolf Steffensen, MD; Gorm Jensen, MD, DMSc; Anne Tybjærg-Hansen, MD, DMSc

Common Cholesteryl Ester Transfer Protein Mutations, Decreased HDL Cholesterol, and Possible Decreased Risk of Ischemic Heart Disease

The Copenhagen City Heart Study

Implications are that increased HDL levels may in certain situations be not protective, but rather associated with increased IHD risk.

Hepatic Lipase Mutations, Elevated High-Density Lipoprotein Cholesterol, and Increased Risk of Ischemic Heart Disease

The Copenhagen City Heart Study

Rolf V. Andersen, MSC, PHD,* Hans H. Wittrup, MD, PHD,* Anne Tybjærg-Hansen, MD, DMSc,†§ Rolf Steffensen, MD,‡ Peter Schnohr, MD,§ Børge G. Nordestgaard, MD, DMSc*§
Association of Loss-of-Function Mutations in the Lipid and...
Hepatic Lipase, Genetically Elevated High-Density Lipoprotein, and Risk of Ischemic Cardiovascular Disease

*(J Clin Endocrinol Metab 94: 1264–1273, 2009)*

Trine Holm Johannsen, Pia R. Kamstrup, Rolf V. Andersen, Gorm B. Jensen, Henrik Sillese, Anne Tybjærg-Hansen, and Børge G. Nordestgaard

LCAT, HDL Cholesterol and Ischemic Cardiovascular Disease: A Mendelian Randomization Study of HDL Cholesterol in 54,500 Individuals

*(J Clin Endocrinol Metab 97: E248–E256, 2012)*

Christiane L. Haase, Anne Tybjærg-Hansen, Abbas Ali Qayyum, Jesper Schou, Børge G. Nordestgaard, and Ruth Frikke-Schmidt

Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study


*Lancet 2012; 380: 572–80*
Evidence for lipoproteins causing atherosclerotic disease?

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<td>(✓)</td>
<td>None</td>
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</table>

Nordestgaard 2013
Reverse cholesterol transport?

HDL + cholesterol

Human evidence?

Evolution?
Causal factor with variation

Longterm monitoring

Glucose $\uparrow$

TG $\uparrow$

Remnants $\uparrow$

HgbA1c $\uparrow$

HDL $\downarrow$

Nordestgaard et al. Current Drug Targets, 2009, 10, 328-335
Evidence for lipoproteins causing atherosclerotic disease?

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<thead>
<tr>
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<th>LDL↑</th>
<th>TG↑ &amp; Remnants↑</th>
<th>Low HDL</th>
<th>HDL functionality</th>
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<td>(√)</td>
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<td>Intervention</td>
<td>√</td>
<td>(√)</td>
<td>None</td>
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</table>

Present | Future | The past?
HDL hypothesis

Remnant cholesterol

HDL functionality
HDL-C for risk prediction
<table>
<thead>
<tr>
<th>SCORE-HDL</th>
<th>Non_Smoker</th>
<th></th>
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<th></th>
<th>Smoker</th>
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<tr>
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<td>Without HDL: 9.1</td>
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<td>HDL 0.8: 11.6</td>
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<td></td>
<td></td>
<td>HDL 1.0: 10.4</td>
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<td>HDL 1.4: 8.5</td>
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<td>HDL 1.8: 7.2</td>
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<td>Without HDL: 5.1</td>
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<td>HDL 0.8: 6.6</td>
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<td>HDL 0.8: 4.4</td>
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<td>HDL 1.0: 4.9</td>
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<td>Total Cholesterol (mmol/l)</td>
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<td>8</td>
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</tbody>
</table>
Copenhagen General Population Study

2003-2008: 46092 individuals without CVD, diabetes or statin use
6.8 years of follow-up

Proportion classified as high CVD mortality risk

≥5%, Men 40-65

≥5%, Women 40-65

Martin Mortensen, Afzal, Nordestgaard, Falk. Eur Heart J 2015; in press
Copenhagen General Population Study

Reclassification across 5% 10-year risk of fatal CVD Using SCORE-HDL instead of SCORE

Fatal CVD

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Non-cases</th>
<th>Combined</th>
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</thead>
<tbody>
<tr>
<td>NRI, %</td>
<td>-16</td>
<td>+4</td>
<td>-12</td>
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</table>

Fatal CVD + nonfatal MI or stroke

<table>
<thead>
<tr>
<th></th>
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<th>Non-cases</th>
<th>Combined</th>
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</thead>
<tbody>
<tr>
<td>NRI, %</td>
<td>-9</td>
<td>+4</td>
<td>-5</td>
</tr>
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</table>
"GOOD" = innocent

BAD

UGLY

HDL

LDL

Remnant
Hans Christian Andersen's fairytale: The Emperor's New Clothes

HDL supporters

HDL

"HDL mafia"

Borge

"HDL mafia"
Rebellious