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
Rebellious
Hans Christian Andersen’s fairy tale: The Emperor's New Clothes

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

Low HDL protects against heart disease

Medical textbooks

Lay press

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↑
→ CVD↑

The NEW ENGLAND JOURNAL of MEDICINE 2007

Effects of Torcetrapib in Patients at High Risk for Coronary Events

Philip J. Barter, M.D., Ph.D., Mark Caulfield, M.D., M.B., B.S., Mats Eriksson, M.D., Ph.D., Scott M. Grundy, M.D., Ph.D., John J.P. Kastelein, M.D., Ph.D., Michel Komajda, M.D., Jose Lopez-Sendon, M.D., Ph.D., Lori Mosca, M.D., M.P.H., Ph.D., Jean-Claude Tardif, M.D., David D. Waters, M.D., Charles L. Shear, Dr.P.H., James H. Revkin, M.D., Kevin A. Buhr, Ph.D., Marian R. Fisher, Ph.D., Alan R. Tall, M.B., B.S., and Bryan Brewer, M.D., Ph.D., for the ILLUMINATE Investigators*
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

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><strong>Epidemiology</strong></td>
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<tr>
<td><strong>Genetics</strong></td>
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<td>FH + SNPs</td>
</tr>
<tr>
<td><strong>Animal models</strong></td>
<td>✓</td>
<td>Many models</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>✓</td>
<td>Understood</td>
</tr>
<tr>
<td><strong>Intervention</strong></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 ↓

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>
</tr>
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<tbody>
<tr>
<td>&lt; 1</td>
<td>2309</td>
</tr>
<tr>
<td>1 – 2</td>
<td>6040</td>
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<td>2 – 3</td>
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<td>3 – 4</td>
<td>1294</td>
</tr>
<tr>
<td>4 – 5</td>
<td>527</td>
</tr>
<tr>
<td>≥ 5</td>
<td>477</td>
</tr>
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Observations, No.

<table>
<thead>
<tr>
<th>Cholesterol, mmol/L (mg/dL)</th>
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<tbody>
<tr>
<td>Remnant</td>
</tr>
<tr>
<td>LDL</td>
</tr>
<tr>
<td>HDL</td>
</tr>
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</table>

N =

Remnant
LDL
HDL

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

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<thead>
<tr>
<th></th>
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<tr>
<td>Epidemiology</td>
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<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Intervention</td>
<td>✓</td>
<td>(✓)</td>
</tr>
</tbody>
</table>

Nordestgaard 2015
Copenhagen City Heart Study (CCHS)

Copenhagen General Population Study (CGPS)

N=15,000
37 yrs follow-up

N=110,000+
10 yrs follow-up

No losses to follow-up 1977-2014

Copenhagen
Copenhagen City Heart Study and Copenhagen General Population Study

**Myocardial infarction**

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

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)

Hazard ratio (95%CI)

In extreme groups

In deciles

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

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

Hazard ratio (95%CI)

In extreme groups

Nonfasting triglycerides, mmol/L

In quintiles

Mainly fasting triglycerides, mmol/L

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

Emerging Risk Factors Collaboration
JAMA 2009

Ischemic Stroke
N = 173,312 (Events = 2,534)
Nonfasting triglycerides, mmol/L

Copenhagen City Heart Study and Copenhagen General Population Study

All-cause mortality

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

In extreme groups

Hazard ratio (95%CI)

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

Lipoprotein ↔ Cardiovascular Disease Risk

Genotype

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

Causality: Instrumental Variable Analysis
Remnant cholesterol
mmol/L

Hazard ratio for IHD

<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

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
Triglycerides↑
Genetic unadjusted
Genetic LDL+HDL adjust

HDL cholesterol↓
Genetic unadjusted
Genetic LDL+TG adjust

LDL cholesterol↑
Genetic unadjusted
Genetic TG+HDL adjust

Effect size (β) for CAD per 1SD ↑or↓

 Genome wide 185 SNPs

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

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


Loss-of-Function Mutations in 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

#### APOC3

- **Jørgensen et al. NEJM 2014**
  - 0 alleles: 75,465, 10,770 events, Risk estimate 0.59
  - 1 allele: 260, 27 events

- **TG and HDL Working Group NEJM 2014**
  - 0 alleles: 110,472, 33,889 events, Risk estimate 0.60
  - 1 allele: 498, 113 events

#### PCSK9

- **CGPS & CCHS**
  - 0 alleles: 64,492, 10,665 events, Risk estimate 0.90
  - 1 allele: 1,697, 250 events

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

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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 Tybjaerg-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 Tybjaerg-Hansen, MD, DMSc,†§ Rolf Steffensen, MD,‡ Peter Schnohr, MD,§ Børge G. Nordestgaard, MD, DMSc*§

JACC Vol. 41, No. 11, 2003

June 4, 2003:1972–82
Association of Loss-of-Function Mutations in the Lipoprotein Lipase Gene

“...I think HDL is a bystander; I don’t think it has anything to do with risk.”

—ANNE TYBJÆRG-HANSEN, COPENHAGEN UNIVERSITY HOSPITAL

Ruth Friis

work gives HDL a role in lowering blood pressure. “I think HDL is a lipid transporter in the blood,” Rader says, “and that it is involved in the ‘risk’ of heart disease.”

Borge G. Nordestgaard

and Maria C. Hobbs agree that HDL is important in the prevention of heart disease, but they disagree about its role in risk assessment.

Amar A. Ridker

says that so many people have bought into this idea that statins have all these magical properties,” he says, “but Rader, who is dubious that the drugs have halting the trial early because of ‘unequivocal evidence of benefit.’”

Ridker will elaborate on the results of the study at a cardiology meeting in November. An outspoken CRP proponent, he holds a patent on a method of measuring CRP in the blood. Hobbs, who disagrees with Ridker’s perspective, thinks he is picking an easy target by focusing on people with LDL values of up to 130, because he “is talking about LDLs that are still high” compared with “our ancestors,” she says. Pushing LDL to lower levels in this group, she believes, may explain why

Peter Schach

that markers in the blood are inversely related to risk of ischemic heart disease, and that this is due to heterozygous mutations from the CHS (Copenhagen Heart Study), a 31-year follow-up of the Copenhagen population study for loss of function of IHD.

Anne Tybjerg-Hansen

Conclusions

Ruth Friis agrees that HDL is important in lowering blood pressure. “I think HDL is a lipid transporter in the blood,” Rader says, “and that it is involved in the ‘risk’ of heart disease.”

Borge G. Nordestgaard and Maria C. Hobbs agree that HDL is important in the prevention of heart disease, but they disagree about its role in risk assessment.

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


Evidence for lipoproteins causing atherosclerotic disease?

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Nordestgaard 2013
Reverse cholesterol transport?

HDL + cholesterol

Human evidence?

Evolution?
Causal factor with variation

Glucose $\uparrow$

TG $\uparrow$

Remnants $\uparrow$

HgbA1c $\uparrow$

HDL $\downarrow$

Longterm monitoring

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

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<td>Genetics</td>
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<td>(√)</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

Present | Future | The past?
HDL hypothesis

Remnant cholesterol

HDL functionality
HDL-C for risk prediction
SCORE-HDL

Non_Smoker

Smoker

Without HDL: 5.1
HDL 0.8: 6.6
HDL 1.0: 5.9
HDL 1.4: 4.9
HDL 1.8: 4.1

Without HDL: 9.1
HDL 0.8: 11.6
HDL 1.0: 10.4
HDL 1.4: 8.5
HDL 1.8: 7.2

Without HDL: 4.4
HDL 0.8: 5.6
HDL 1.0: 5.0
HDL 1.4: 4.1
HDL 1.8: 3.5

Without HDL: 5.5
HDL 0.8: 7.0
HDL 1.0: 6.3
HDL 1.4: 5.1
HDL 1.8: 4.3

Without HDL: 4.6
HDL 0.8: 6.1
HDL 1.0: 5.4
HDL 1.4: 4.3
HDL 1.8: 3.5

Without HDL: 5.1
HDL 0.8: 6.8
HDL 1.0: 6.0
HDL 1.4: 4.6
HDL 1.8: 3.6

Without HDL: 3.6
HDL 0.8: 4.6
HDL 1.0: 4.2
HDL 1.4: 3.4
HDL 1.8: 2.8

Without HDL: 4.7
HDL 0.8: 6.6
HDL 1.0: 5.9
HDL 1.4: 4.6
HDL 1.8: 3.6

Systolic Blood Pressure (mmHg)

Total Cholesterol (mmol/l)
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

Percent

SCORE
SCORE-HDL

Martin Mortensen, Afzal, Nordestgaard, Falk. Eur Heart J 2015; in press
Reclassification across 5% 10-year risk of fatal CVD
Using SCORE-HDL instead of SCORE

Fatal CVD

<table>
<thead>
<tr>
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<th>Inappropriate</th>
<th>Appropriate</th>
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<tbody>
<tr>
<td>Cases</td>
<td>-16</td>
<td>+4</td>
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<tr>
<td>Non-cases</td>
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<td>+4</td>
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<tr>
<td>Combined</td>
<td>-12</td>
<td>0</td>
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</tbody>
</table>

NRI, %  
p value

|                | 0.002         | <0.0001     | 0.02         |

Fatal CVD + nonfatal MI or stroke

<table>
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<th>Appropriate</th>
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<tbody>
<tr>
<td>Cases</td>
<td>-9</td>
<td>+4</td>
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<tr>
<td>Non-cases</td>
<td>+4</td>
<td>+4</td>
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<tr>
<td>Combined</td>
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</table>

NRI, %  
p value

|                | <0.0001       | <0.0001     | <0.0001      |

Copenhagen General Population Study
Hans Christian Andersen's fairytale: The Emperor's New Clothes

HDL supporters

"HDL mafia"

HDL

Borge

"HDL mafia"
Rebellious