ApoC3, risk factor, pathophysiology and target

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NLA New Orleans May 2016
Disclosures
Anne Tybjærg-Hansen
Professor of Clinical Biochemistry and Translational Molecular Cardiology

None
History – ApoCIII: 47 years old and even more interesting

Adapted from Ginsberg and Brown ATVB 2011
ApoCIII, a component of VLDL and an inhibitor of lipoprotein lipase

Studies of the Proteins in Human Plasma Very Low Density Lipoproteins*

(Received for publication, April 17, 1969)

W. Virgil Brown, Robert I. Levy, and Donald S. Fredrickson

INHIBITION OF LIPOPROTEIN LIPASE BY AN APOPROTEIN OF HUMAN VERY LOW DENSITY LIPOPROTEIN

W. Virgil Brown and M.L. Baginsky

Vol. 46, No. 2, 1972 BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS
Triglyceride-rich lipoproteins

- VLDL production
- Chylomicron lipolysis
- Liver uptake
- TRL

ApoC-III

APOB

APOCIII

Cholesterol

Triglycerides
Relative Risk Estimates for Non-HDL ApoCIII (per 5mg/dL)

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sacks et al. (2000)</td>
<td>1.60 (0.78, 3.32)</td>
<td>32.26</td>
</tr>
<tr>
<td>Gerber et al. (2003)</td>
<td>4.42 (2.14, 9.15)</td>
<td>32.27</td>
</tr>
<tr>
<td>Onat et al. (2003)</td>
<td>2.98 (1.01, 8.76)</td>
<td>19.38</td>
</tr>
<tr>
<td>Mendivil et al. (2011)</td>
<td>1.48 (0.44, 5.02)</td>
<td>16.09</td>
</tr>
<tr>
<td>Overall (I-squared = 34.8%, p = 0.203)</td>
<td>2.48 (1.42, 4.32)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Triglyceride-rich lipoproteins

APOB

Cholesterol

Triglycerides

APOCIII
Genetics suggest reduced risk of ischemic cardiovascular disease
A Null Mutation in Human APOC3 Confers a Favorable Plasma Lipid Profile and Apparent Cardioprotection

Toni I. Pollin¹, Coleen M. Damcott¹, Haiqing Shen¹, Sandra H. Ott¹, John Shelton¹, Richard B. Horenstein¹, Wendy Post², John C. McLenithan¹,³, Lawrence F. Bielak⁴, Patricia A. Peyser⁴, Braxton D. Mitchell¹, Michael Miller¹, Jeffrey R. O’Connell¹, and Alan R. Shuldiner¹,³

Any coronary artery calcification: RX vs. RR: OR 0.35 (95%CI: 0.21 – 0.60)

Pollin TI et al. Science 2008; 322: 1702–1705
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*
**APOC3 loss-of-function mutations**

<table>
<thead>
<tr>
<th></th>
<th>No. of participants</th>
<th>No. of events</th>
<th>Triglycerides</th>
<th>Theoretically predicted risk</th>
<th>Observed risk</th>
<th>P-value</th>
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<tbody>
<tr>
<td><strong>Ischemic vascular disease</strong></td>
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<tr>
<td>Any mutation</td>
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<tr>
<td>Wildtype</td>
<td>75,465</td>
<td>10,770</td>
<td>1</td>
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<td>0.75</td>
<td>0.5</td>
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<tr>
<td>All heterozygotes</td>
<td>260</td>
<td>27</td>
<td>0.5</td>
<td>$2 \times 10^{-54}$</td>
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<td>0.75</td>
<td>$2 \times 10^{-54}$</td>
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<td>7,537</td>
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</tbody>
</table>

*Jørgensen NEJM 2014;371:32-41*
Ischemic vascular disease

**APOC3**

- **Jørgensen et al**
  - NEJM 2014
  - N alleles: 0
  - N total: 75,465
  - N events: 10,770
  - Risk estimate: 0.59

- **Crosby et al**
  - TG and HDL Working Group
  - NEJM 2014
  - N alleles: 1
  - N total: 110,472
  - N events: 33,889
  - Risk estimate: 0.60

<table>
<thead>
<tr>
<th>Triglycerides, mmol/L</th>
<th>Hazard ratio (95% CI)</th>
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<tr>
<td>0</td>
<td>0.0</td>
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<tr>
<td>1</td>
<td>-44%</td>
</tr>
<tr>
<td>2</td>
<td>-39%</td>
</tr>
</tbody>
</table>

Adapted from Nordestgaard & Varbo, Lancet 2014; 384: 626-635
Triglyceride-rich remnant lipoproteins

Nonfasting state:
Chylomicron remnants
VLDL
IDL

APOB

APOCIII

Cholesterol
Triglycerides
Copenhagen City Heart Study (CCHS)

N=15,000
37 yrs follow-up
No losses to follow-up 1977-2014

Copenhagen General Population Study (CGPS)

N=100,000+
10 yrs follow-up
Nonfasting triglycerides, mmol/L

Copenhagen General Population Study
N = 84,224

Mild-to-moderately elevated triglycerides
Often multigenic

27%

Severely elevated triglycerides
Can be monogenic

0.1%

Hegele et al. Lancet Diabetes Endocrinol 2013 Dec 23
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

All-cause mortality

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

In extreme groups

Nordestgaard & Varbo, Lancet 2014; 384: 626-635
54% reduction in major CVD event per 1 mmol/L triglyceride reduction

Fibrate trials

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

- HDL
- LDL
- Remnants

Clinical use: Cholesterol

- HDL cholesterol
- LDL cholesterol
- Remnant cholesterol

Alternative: Apo A1

- ApoB
- or non-HDL cholesterol
Remnant cholesterol

total cholesterol minus LDL-C minus HDL-C
no direct automated assay available yet
Nonfasting remnant cholesterol, mmol/L

Copenhagen General Population Study

N = 84,224

Fraction of population

34% 45% 21%

Nonfasting remnant cholesterol, mmol/L

Nordestgaard & Varbo, 2014
LDL Remnants

Plasma

Inflammation

Macrophage

FFA + Monoacylglycerol

Remnants

Chylomicron

Foam cells

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

Cholesterol

Triglycerides

Intima
Reverse causation?

Lifestyle confounding?
Genetics suggest causality
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
Mendelian randomization hypotheses

Causality: Instrumental Variable Analysis

Lipoprotein - Genotype - Cardiovascular Disease Risk

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

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

CCHS+CGPS+CIHDS
N=68,000

Varbo et al. JACC 2013;61:427-436
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
15 selected genetic variants
Hazard ratio for IHD per 1mM ↑or↓
1.0 2.0 4.0
12,000 IHD
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↓

N=87,000 CARDioGRAM
Do et al Nat Genet 2013; 45: 1345-52
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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<tbody>
<tr>
<td>APOC3</td>
<td>0</td>
<td>75,465</td>
<td>10,770</td>
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<td>0</td>
<td>110,472</td>
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<tr>
<td></td>
<td>1</td>
<td>498</td>
<td>113</td>
</tr>
</tbody>
</table>

Triglycerides, mmol/L

Hazard ratio (95% CI)

Adapted from Nordestgaard & Varbo, Lancet 2014; 384: 626-635
Extreme Nonfasting Remnant Cholesterol vs Extreme LDL Cholesterol as Contributors to Cardiovascular Disease and All-Cause Mortality in 90,000 Individuals from the General Population

Anette Varbo,1,2,4 Jacob J. Freiberg,1,2,4 and Børge G. Nordestgaard1,2,3,4*

Increased Remnant Cholesterol Explains Part of Residual Risk of All-Cause Mortality in 5,414 Patients with Ischemic Heart Disease

Anne-Marie K. Jepsen,1,2 Anne Langsted,1,2 Anette Varbo,1,2 Lia E. Bang,2,3 Pia R. Kamstrup,1,2 and Børge G. Nordestgaard1,2*
97,962 nonfasting samples
Copenhagen General Population Study and the Copenhagen City Heart Study combined

~90,000 individuals from CGPS & CCHS combined

<table>
<thead>
<tr>
<th>Remnant cholesterol (mmol/L)</th>
<th>Participants (No.)</th>
<th>Events (No.)</th>
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</thead>
<tbody>
<tr>
<td>Ischemic heart disease</td>
<td></td>
<td></td>
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<tr>
<td>&lt;0.50</td>
<td>28 569</td>
<td>995</td>
</tr>
<tr>
<td>0.50–0.99</td>
<td>37 163</td>
<td>2153</td>
</tr>
<tr>
<td>1.00–1.49</td>
<td>11 803</td>
<td>835</td>
</tr>
<tr>
<td>≥1.50</td>
<td>53 555</td>
<td>452</td>
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<table>
<thead>
<tr>
<th>LDL cholesterol (mmol/L)</th>
<th>Participants (No.)</th>
<th>Events (No.)</th>
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<tbody>
<tr>
<td>Ischemic heart disease</td>
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<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>32 626</td>
<td>1295</td>
</tr>
<tr>
<td>3–3.99</td>
<td>31 422</td>
<td>1651</td>
</tr>
<tr>
<td>4–4.99</td>
<td>14 699</td>
<td>1029</td>
</tr>
<tr>
<td>≥5</td>
<td>41 443</td>
<td>460</td>
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</table>

<table>
<thead>
<tr>
<th>Myocardial infarction</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td>&lt;0.50</td>
<td>29 321</td>
<td>316</td>
</tr>
<tr>
<td>0.50–0.99</td>
<td>38 641</td>
<td>868</td>
</tr>
<tr>
<td>1.00–1.49</td>
<td>12 360</td>
<td>342</td>
</tr>
<tr>
<td>≥1.50</td>
<td>56 455</td>
<td>196</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Myocardial infarction</th>
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<tbody>
<tr>
<td>&lt;3</td>
<td>33 650</td>
<td>399</td>
</tr>
<tr>
<td>3–3.99</td>
<td>32 561</td>
<td>634</td>
</tr>
<tr>
<td>4–4.99</td>
<td>15 348</td>
<td>462</td>
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<tr>
<td>≥5</td>
<td>44 048</td>
<td>227</td>
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<table>
<thead>
<tr>
<th>All-cause mortality</th>
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<tr>
<td>&lt;0.50</td>
<td>28 900</td>
<td>1963</td>
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<tr>
<td>0.50–0.99</td>
<td>37 752</td>
<td>4090</td>
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<tr>
<td>1.00–1.49</td>
<td>12 196</td>
<td>1393</td>
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<tr>
<td>≥1.50</td>
<td>55 900</td>
<td>675</td>
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<tr>
<th>All-cause mortality</th>
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<tr>
<td>&lt;3</td>
<td>34 201</td>
<td>2835</td>
</tr>
<tr>
<td>3–3.99</td>
<td>31 609</td>
<td>2808</td>
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<tr>
<td>4–4.99</td>
<td>14 606</td>
<td>1714</td>
</tr>
<tr>
<td>≥5</td>
<td>40 222</td>
<td>764</td>
</tr>
</tbody>
</table>

~90,000 individuals from CGPS & CCHS combined

Myocardial Infarction

~90,000 individuals from CGPS & CCHS combined

5414 patients with ischemic heart disease

Calculated remnant cholesterol

Survival in patients with ischemic heart disease

≥1 mmol/L
n = 1443 (27%)
Deaths = 404

<1 mmol/L
n = 3971 (73%)
Deaths = 915

Log-rank: P = 9 × 10⁻⁶
HR (95% CI): 1.3 (1.2–1.5)
Corrected HR: 1.8 (1.4–2.4)

5414 patients with ischemic heart disease

• Can the associated reduction in LDL cholesterol explain the reduction in risk?

• Could the contribution of LDL cholesterol to risk be masked by statin treatment?
Discovery cohorts

Jørgensen et al. (CCHS)
Noncarriers 10,292
APOC3 mutation 41 -42% $p = 6 \times 10^{-9}$

Crosby et al. (ESP)
Noncarriers 3,701
APOC3 mutation 33 -39% $p = 6 \times 10^{-9}$

Pollin et al. (HAPI)
Noncarriers 763
APOC3 mutation 39 -46% $p = 4 \times 10^{-13}$

p = 0.001

Triglycerides % of noncarrier level

LDL cholesterol % of noncarrier level

Jørgensen et al. NEJM 2014;371:32-41
Crosby et al. NEJM 2014;371:22-31
Pollin et al. Science 2008;322:1702-1705
### APOC3 metaanalysis: Remnant cholesterol

<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort</th>
<th>Participants</th>
<th>Difference (%)(95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pollin et al.</td>
<td>HAPI</td>
<td>802</td>
<td>-46 (-58, -33)</td>
<td>7</td>
</tr>
<tr>
<td>Pollin et al.</td>
<td>AFCS excl HAPI</td>
<td>698</td>
<td>-47 (-56, -38)</td>
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<tr>
<td>Tachmazidou et al.</td>
<td>MANOLIS</td>
<td>1,267</td>
<td>-41 (-53, -29)</td>
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<tr>
<td>Jørgensen et al.</td>
<td>CCHS+CGPS</td>
<td>75,725</td>
<td>-44 (-50, -39)</td>
<td>35</td>
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<td>Crosby et al.</td>
<td>ESP</td>
<td>3,734</td>
<td>-39 (-52, -26)</td>
<td>6</td>
</tr>
<tr>
<td>Crosby et al.</td>
<td>Replication</td>
<td>41,671</td>
<td>-39 (-47, -31)</td>
<td>17</td>
</tr>
<tr>
<td>Crawford et al.</td>
<td>NHANES</td>
<td>7,603</td>
<td>-51 (-89, -14)</td>
<td>1</td>
</tr>
<tr>
<td>Natarajan et al.</td>
<td>Biolmage</td>
<td>6,395</td>
<td>-44 (-53, -35)</td>
<td>14</td>
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<tr>
<td>Overall: Fixed-effect</td>
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<td>-43 (-47, -40)</td>
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<tr>
<td>Overall: Random-effect</td>
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% lower remnant cholesterol in APOC3 loss-of-function heterozygotes vs noncarriers
### APOC3 metaanalysis: LDL cholesterol

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<td>6,502</td>
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<td>2 (-8, 11)</td>
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<td></td>
<td>-5 (-8, -1)</td>
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</table>

**% lower LDL cholesterol in APOC3 loss-of-function heterozygotes vs noncarriers**
Can the associated reduction in LDL cholesterol explain the reduction in risk?

Could the contribution of LDL cholesterol to risk be masked by statin treatment?
Influence of statin treatment on lipid levels

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean (±SE)</th>
<th>Δ (%)</th>
<th>P</th>
<th>Mean (±SE)</th>
<th>Δ (%)</th>
<th>P</th>
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<tbody>
<tr>
<td><strong>All participants</strong></td>
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<tr>
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<td>1x10^{-51}</td>
<td>-3%</td>
<td>0.06</td>
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<tr>
<td><strong>Statin corrected</strong></td>
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<td>-4%</td>
<td>0.008</td>
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<td><strong>Non-statin participants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Noncarriers</td>
<td>68,419</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterozygotes</td>
<td>244</td>
<td>-44%</td>
<td>2x10^{-49}</td>
<td>-3%</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Jørgensen AB et al. submitted
Mediation analysis

APOC3 loss-of-function mutations (R19X, IVS2+1G>A, A43T)

- 43% lower remnant cholesterol
- 4% lower LDL cholesterol

Mediated % of the reduced risk

- 37% (95%CI: 31-43%)
- 54% (95%CI: 45-62%)
- 1% (95%CI: 0-2%)
- 2% (95%CI: 0-3%)

41% reduced risk of ischemic vascular disease
36% reduced risk of ischemic heart disease

Jørgensen AB et al. submitted
Genetics suggest a new drug target
Targeting APOC3 in the Familial Chylomicronemia Syndrome

Daniel Gaudet, M.D., Ph.D., Diane Brisson, Ph.D., Karine Tremblay, Ph.D., Veronica J. Alexander, Ph.D., Walter Singleton, M.D., Steven G. Hughes, M.B., B.S., Richard S. Geary, Ph.D., Brenda F. Baker, Ph.D., Mark J. Graham, M.S., Rosanne M. Crooke, Ph.D., and Joseph L. Witztum, M.D.

Genetic disorder characterized by severe hypertriglyceridemia and recurrent pancreatitis due to a deficiency in lipoprotein lipase. Lack of efficient therapies except extreme fat restriction or \textit{LPL} gene replacement.
Study overview

• 3 patients homozygous or compound heterozygous for severe loss-of-function mutations in LPL (triglycerides 16-24 mmol/L; P207L or G188E)

• ISIS 304801 AntiSense Oligo (ASO) to APOC3 mRNA 300mg once weekly as s.c. injection for 13 weeks
Nonfasting triglycerides, mmol/L

Copenhagen General Population Study
N = 84,224

Fraction of population

Mild-to-moderately elevated triglycerides
Often multigenic

Severely elevated triglycerides
Can be monogenic

27% 46%

27% 0.1%

Hegele et al. Lancet Diabetes Endocrinol 2013 Dec 23
Effect of ISIS 304801 ASO 300mg once weekly as s.c. injection for 13 weeks
Plasma triglyceride metabolism and the role of apoCIII.

A Normal sources and metabolism of triglycerides

Dietary fat → Liver → Intestine → Chylomicron → VLDL

APOC3 regulates TG metabolism by inhibiting an LPL-dependent pathway and one or more LPL-independent pathways.

B Familial chylomicronemia syndrome

Loss-of-function mutations in LPL render the LPL-dependent pathway inefficient.

C Familial chylomicronemia syndrome with antisense therapy

Reduction of APOC3 levels liberates the LPL-independent pathway and thereby lowers TG levels.

TRL remnant removal

Normal TG levels (<150 mg/dl)

Chylomicronemia (TG, >880 mg/dl)

Reduced TG levels (250–500 mg/dl)

Randomized double-blind placebo-controlled, dose-ranging, phase 2 study to evaluate ISIS 304801 in untreated patients with fasting triglyceride levels between 350 mg/dL (4.0 mmol/L) and 2000 mg/dL (22.6 mmol/L) (monotherapy cohort), as well as in patients receiving stable fibrate therapy who had fasting triglyceride levels between 225 mg/dL (2.5 mmol/L) and 2000 mg/dL (fibrate cohort).
Nonfasting triglycerides, mmol/L

- **Mild-to-moderately elevated triglycerides**
  - Often multigenic
  - 27%

- **Severely elevated triglycerides**
  - Can be monogenic
  - 0.1%

Copenhagen General Population Study

N = 84,224

Hegele et al. Lancet Diabetes Endocrinol 2013 Dec 23
Changes from Baseline in Levels of Apolipoprotein C-III and Triglycerides

Mean percent reduction (± SEM) in apoCIII-apoB, apoCIII-apoA-I, and apoCIII-Lp(a) in the volanesorsen monotherapy group with 100, 200, and 300 mg/dose volanesorsen treatment.

Xiaohong Yang et al. J. Lipid Res. 2016;57:706-713

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Summary slides
Triglyceride-rich remnant lipoproteins

APOB

Remnant cholesterol

APOCIII

Triglycerides
## APOC3 metaanalysis: Remnant cholesterol

<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort</th>
<th>Participants</th>
<th>Difference (%) (95% CI)</th>
<th>Weight (%)</th>
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</thead>
<tbody>
<tr>
<td>Pollin et al.</td>
<td>HAPI</td>
<td>802</td>
<td>-46 (-58, -33)</td>
<td>7</td>
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<tr>
<td>Pollin et al.</td>
<td>AFCS excl HAPI</td>
<td>698</td>
<td>-47 (-56, -38)</td>
<td>12</td>
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<tr>
<td>Tachmazidou et al.</td>
<td>MANOLIS</td>
<td>1,267</td>
<td>-41 (-53, -29)</td>
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<tr>
<td>Jørgensen et al.</td>
<td>CCHS+CGPS</td>
<td>75,725</td>
<td>-44 (-50, -39)</td>
<td>35</td>
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<tr>
<td>Crosby et al.</td>
<td>ESP</td>
<td>3,734</td>
<td>-39 (-52, -26)</td>
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<td>Crosby et al.</td>
<td>Replication</td>
<td>41,671</td>
<td>-39 (-47, -31)</td>
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<tr>
<td>Crawford et al.</td>
<td>NHANES</td>
<td>7,603</td>
<td>-51 (-89, -14)</td>
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<tr>
<td>Nataraj et al.</td>
<td>BiolImage</td>
<td>6,395</td>
<td>-44 (-53, -35)</td>
<td>14</td>
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<tr>
<td><strong>Overall: Fixed-effect</strong></td>
<td><strong>I^2 = 0%, p = 0.92</strong></td>
<td></td>
<td><strong>-43 (-47, -40)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Overall: Random-effect</strong></td>
<td></td>
<td></td>
<td><strong>-43 (-47, -40)</strong></td>
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</tr>
</tbody>
</table>

% lower remnant cholesterol in APOC3 loss-of-function heterozygotes vs noncarriers
Ischemic vascular disease

<table>
<thead>
<tr>
<th>N alleles</th>
<th>N total</th>
<th>N events</th>
<th>Risk estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>75,465</td>
<td>10,770</td>
<td>0.59</td>
</tr>
<tr>
<td>1</td>
<td>260</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>110,472</td>
<td>33,889</td>
<td>0.60</td>
</tr>
<tr>
<td>1</td>
<td>498</td>
<td>113</td>
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</table>

Adapted from Nordestgaard & Varbo, Lancet 2014; 384: 626-635
Changes from Baseline in Levels of Apolipoprotein C-III and Triglycerides

History – ApoCIII: 47 years old and even more interesting

Adapted from Ginsberg and Brown ATVB 2011
ApoCIII, direct proatherogenic role?

- Increased binding to proteoglycans
- Increases monocyte binding to cultured endothelial cells via stimulation of VCAM-1
5414 patients with ischemic heart disease
5414 patients with ischemic heart disease

Measured remnant cholesterol was 0.40 mmol/L (95% CI 0.39–0.41 mmol/L) higher per 1 mmol/L higher calculated remnant cholesterol. 

\( P < 0.001, \ R^2 = 0.74, \ n = 5414 \)

5414 patients with ischemic heart disease

**Diagram:**

- **Y-axis:** HR for all-cause mortality
- **X-axis:** Calculated remnant cholesterol (mmol/L)

**Graph Details:**

- Three lines representing different cholesterol levels.
- Each line shows an increasing trend with higher cholesterol levels.

**Reference:**

5414 patients with ischemic heart disease