New biologics for the treatment of atherosclerosis and the safety thereof

Derick Raal
FCP(SA), FRCP, FRCPC, Cert Endo, MMED, PHD

Head, Division of Endocrinology & Metabolism
Director, Carbohydrate and Lipid Metabolism Research Unit
Faculty of Health Sciences, University of the Witwatersrand
Presenter Disclosure Information

Frederick J. Raal

FCP(SA), FRCP, FRCPC, Cert Endo, MMed(Wits), PhD

*Professor Raal has received research grants, honoraria, or consulting fees for professional input and/or delivered lectures from Pfizer Pharmaceuticals, Merck, Sanofi, Regeneron, Amgen and The Medicines Company.*
Decline in deaths from cardiovascular disease in relation to scientific advances

- **1954**: First open-heart procedure developed (Gibbon)
- **1958**: Coronary arteriography developed (Sones)
- **1961**: Risk factors defined
- **1961**: Coronary care unit developed (Julian)
- **1962**: First β-blocker developed (Black)
- **1969**: First description of CABG (Favolaro)
- **1961**: Coronary care unit developed (Julian)
- **1972**: NHBPEP
- **1976**: First HMG CoA reductase inhibitor described (Endo)
- **1972**: NHBPEP
- **1976**: First implantable cardioverter defibrillator developed (Mirowski)
- **1979**: Coronary angioplasty developed (Grunfeld)
- **1985**: TIMI 1
- **1985**: GISSI and ISIS-Z
- **1986**: Superiority of primary PCI vs fibrinolysis in acute MI noted
- **1992**: SAVE
- **1993**: Efficacy of drug-eluting vs bare-metal stents determined
- **1993**: Superiority of primary PCI vs fibrinolysis in acute MI noted
- **1993**: Efficacy of drug-eluting vs bare-metal stents determined
- **2002**: Benefit of cardiac resynchronization therapy in heart failure shown to be effective
- **2002**: Efficacy of drug-eluting vs bare-metal stents determined
- **2007**: Left ventricular assist device as destination therapy in advanced heart failure shown to be effective
- **2009**: Genomwide association in early onset MI described
- **2009**: Deep gene sequencing for responsiveness to CV drugs performed
- **2009**: Genomwide association in early onset MI described
- **2009**: Deep gene sequencing for responsiveness to CV drugs performed
Cardiovascular disease is the leading cause of death worldwide

- 1 in every 2.4 deaths
- > 17 million people worldwide every year

Murray CJL, Lopez AD, eds. The Global Burden of Disease; Boston: Harvard School of Public Health; 1996
Atherosclerosis

Hypertension

Smoking

Obesity

Diabetes mellitus

DYSLIPIDAEMIA
Cholesterol, particularly LDL-cholesterol is the pivotal risk factor for atherosclerosis.
Relative concentration of ApoB containing lipoproteins in normolipidaemic individuals

- LDL
- VLDL
- IDL remnants
- Lipoprotein(a)

Ference et al. Eur Heart J 2017;38:2459-2472
INTERHEART: Nine modifiable risk factors predict 90% of acute myocardial infarction

N = 30 000
(262 sites across 52 countries)

LDL/HDL
Current smoking
Diabetes
Hypertension
Abdominal obesity
Psychosocial

Fruit & veg daily
Exercise
Alcohol intake

Odds Ratio

Salim Yusuf  Lancet  2004;364: 937-52
Relation between proportional reduction in incidence of major CAD and vascular events and mean absolute reduction in LDL cholesterol at 1 year

N= 170 000 subjects from 26 statin trials

For every 1 mmol/L reduction in LDL cholesterol there is:

a) a 21-24% reduction in major CAD or vascular events

b) a 12% reduction in overall mortality
### “Residual Risk”

<table>
<thead>
<tr>
<th>Study</th>
<th>With CVD</th>
<th>No CVD</th>
<th>RRR with statin (%)</th>
<th>RRR with statin (events/1000 person years)</th>
<th>Residual risk despite statin (events/1000 person years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPS</td>
<td>18</td>
<td>33</td>
<td>14</td>
<td>64</td>
<td>19</td>
</tr>
<tr>
<td>CARDS</td>
<td>No CVD</td>
<td>37</td>
<td>9</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>ASPEN</td>
<td>18</td>
<td>3</td>
<td>14</td>
<td>66</td>
<td>26</td>
</tr>
<tr>
<td>CTTC</td>
<td>20</td>
<td>27</td>
<td>15</td>
<td>61</td>
<td>21</td>
</tr>
</tbody>
</table>

**STATINS ARE EFFECTIVE IN CAD PREVENTION BUT DO NOT ELIMINATE THE RISK**
Atherosclerosis

- LDL – cholesterol/remnant deposition
- Thrombosis
- Stenosis through wound healing (fibrosis)

Tailored therapy in atherosclerotic cardiovascular disease

Known atherosclerotic cardiovascular disease

↓

High intensity statin +/- ezetimibe

“Residual Cholesterol Risk”

LDL-C high
Lp(a)/ hsCRP low

Additional LDL-C reduction

“Residual Inflammatory Risk”

LDL-C low
Lp(a)/ hsCRP high

Additional inflammation reduction

“Residual Thrombotic Risk”

LDL-C low
Lp(a)/ hsCRP high

Additional antiplatelet & anticoagulant therapy

Ridker P, ESC Barcelona 2017
Reduction in LDL-C in FH with combination lipid-lowering therapy

Adapted from Nordestgaard B.G. et al. *Eur Heart J* 2013;34:3478-3490 and Hovingh G.K et al. *Eur Heart J* 2013;34, 962–971
Proportion of FH patients on LDL-C targets for different treatment goals

Pijlman AH, Atherosclerosis 2010;209:189-94
Emerging therapies for severe hypercholesterolaemia

- While statins and ezetimibe constitute first-line therapy, they provide less than optimal LDL-C reduction in severe FH
- in particular HoFH requires combination therapy: high-dose statin, ezetimibe, with or without apheresis

<table>
<thead>
<tr>
<th>Therapies for severe FH:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>New therapies</strong></td>
</tr>
<tr>
<td>- Mipomersen (apoB inhibitor)</td>
</tr>
<tr>
<td>- Lomitapide (MTP inhibitor)</td>
</tr>
<tr>
<td>- PCSK9 inhibitors</td>
</tr>
<tr>
<td><strong>Emerging therapies</strong></td>
</tr>
<tr>
<td>- PPAR delta agonists</td>
</tr>
<tr>
<td>- Acetyl CoA carboxylase inhibitor (Gemcabene)</td>
</tr>
<tr>
<td>- ACL/AMP kinase modulator (ETC-1002 or Bempedoic acid)</td>
</tr>
<tr>
<td>- <strong>ANGPTL3 inhibitors</strong></td>
</tr>
<tr>
<td>- Others e.g. CETP-inhibitors, probucol</td>
</tr>
<tr>
<td>- AAV-8 LDLR gene replacement therapy</td>
</tr>
</tbody>
</table>

Stein EA, Raal FJ. Curr Cardiol Reports 2015;17:1-11
In 2003 Marianne Abifadel from Lebanon described two gain-of-function mutations in the PCSK9 gene which resulted in a FH phenotype.

First subjects treated with PCSK9 mAb in SAD studies

First MAD phase 1b trials with PCSK9 mAb started including FH, non-FH, statin Rx

Phase 2 trials in-progress published for REGN727 including FH, Q2W/Q4W dosing

Phase 2 trials published for AMG145 including HoFH, Statin intol, Q2W/Q4W

Phase 3 trials complete for 2 mAbs, BLA* filed and CVD outcome trials started

Early data on CVD benefit

Marketing approval USA/Europe


1st publications MAD in FH, nonFH on statin or diet

*BLA – Biologics licensing application; SAD – single ascending dose, MAD – multiple ascending dose

# Pharmaceutical approaches targeting PCSK9

<table>
<thead>
<tr>
<th>Approach</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Compound</th>
<th>Development stage</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>mAbs</td>
<td>Highly selective</td>
<td>IV or subcutaneous admin.</td>
<td><strong>Alirocumab</strong>/ REGN7272/SAR236553</td>
<td>FDA approved July 24, 2015</td>
<td>Sanofi/Regeneron</td>
</tr>
<tr>
<td></td>
<td>Less dosing frequencies</td>
<td>High cost</td>
<td><strong>Evolocumab</strong>/ AMG145</td>
<td>FDA approved Aug 27, 2015</td>
<td>Amgen</td>
</tr>
<tr>
<td></td>
<td>No serious adverse reactions</td>
<td>Short shelf life</td>
<td><strong>Bococizumab</strong>/ RN-316/PFO4950615</td>
<td>Development stopped in Nov 2016</td>
<td>Pfizer/Genetech</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RG7652(MPSK3169A)</td>
<td>Phase II</td>
<td>Genentech/Roche</td>
</tr>
<tr>
<td>Mimetic peptides</td>
<td>Highly selective</td>
<td>Injection administration</td>
<td><strong>SX-PCK9</strong> EGF-A peptide</td>
<td>Preclinical</td>
<td>Serometrix</td>
</tr>
<tr>
<td></td>
<td>Easier production than mAbs</td>
<td></td>
<td></td>
<td>Preclinical</td>
<td>Merck &amp; Co</td>
</tr>
<tr>
<td>Adnectin</td>
<td>Selective</td>
<td>Short half-life</td>
<td><strong>BMS-962476</strong></td>
<td>Phase I completed</td>
<td>BMS-Adnexus</td>
</tr>
<tr>
<td></td>
<td>Easier &amp; less costly production than mAbs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>siRNA</td>
<td>Highly selective</td>
<td>IV or subcutaneous admin.</td>
<td><strong>Inclisiran</strong> ALN-PCS (IV)</td>
<td>Phase I completed</td>
<td>Alnylam Pharmaceuticals; Medicines Company</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ALN-PCSsc (sub)</td>
<td></td>
<td>Phase II recruiting</td>
<td></td>
</tr>
<tr>
<td>Small molecules</td>
<td>Oral administration</td>
<td>Less selective</td>
<td><strong>SBC-1 &amp; SBC-1</strong></td>
<td>Preclinical completed</td>
<td>Shifa Biomedical Corp</td>
</tr>
<tr>
<td></td>
<td>Low cost</td>
<td>Greater likelihood of side effects</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Catabolism of LDL, the role of PCSK9 and antibody to PCSK9

- LDL
- Endocytosis
- LDL receptor
- Endosome
- Lysosome
- Clathrin-coated vesicle
- Hepatocyte
- Nucleus
  -↑SREBP
- Endoplasmic reticulum
- Golgi apparatus
- PCSK9 processing/export

Mean percent change from baseline in LDL-C values among healthy volunteers in single-dose studies

Subcutaneous administration of Alirocumab

Mean change from baseline in LDL-C (%)

-70 -60 -50 -40 -30 -20 -10 0 10 20

Study Day

1 2 4 8 11 15 22 29 43 84 85 106

Placebo 50 mg 100 mg 150 mg 250 mg
### PCSK9 Inhibitor CVD Outcomes Trials

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Evolocumab</th>
<th>Alirocumab</th>
<th>Bococizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amgen</td>
<td>Sanofi / Regeneron</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Trial</td>
<td>FOURIER</td>
<td>ODYSSEY outcomes</td>
<td>SPIRE I SPIRE II</td>
</tr>
<tr>
<td>Sample size</td>
<td>27,500</td>
<td>17,000</td>
<td>17,000 9,000</td>
</tr>
<tr>
<td>Patients</td>
<td>MI, stroke or PAD</td>
<td>4052 wks post-ACS</td>
<td>High risk of CV event</td>
</tr>
<tr>
<td>Statin</td>
<td>Atorva ≥20 mg or equiv</td>
<td>Evid.-based med Rx</td>
<td>Lipid-lowering Rx</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>≥1.8</td>
<td>≥1.8</td>
<td>1.8-2.6  ≥2.6</td>
</tr>
<tr>
<td>PCSK9i Dosing</td>
<td>Q2W or Q4W</td>
<td>Q2W</td>
<td>Q2W</td>
</tr>
<tr>
<td>Endpoint</td>
<td>1º: CV death, MI stroke, revasc. or hosp for UA Key 2º: CV death, MI or stroke</td>
<td>CHD death, MI, ischaemic stroke, or hospital for UA</td>
<td>CV death, MI, stroke, or urgent revasc.</td>
</tr>
<tr>
<td>Recruitment status</td>
<td>Completed June 2015</td>
<td>Completed Dec 2015</td>
<td>Discontinued</td>
</tr>
<tr>
<td>Completion</td>
<td>ACC 2017</td>
<td>2017/2018</td>
<td>2017/2018</td>
</tr>
</tbody>
</table>
Primary endpoint

27,564 high-risk, stable patients with established CV disease

Hazard ratio 0.85
(95% CI, 0.79-0.92)
P<0.0001

Months from Randomization

CV Death, MI, Stroke, Hosp for UA or Cor revasc

Placebo

Evolocumab

Pharmacokinetics and pharmacodynamics of evolocumab: changes in PCSK9 and LDL-C levels in response to evolocumab

Model predicted time course of LDL-C after multiple evolocumab doses

Small interfering RNA (siRNA) targeted to PCSK9: Mechanism of action

INCLISIRAN

Hepatic ASP receptor

5’ GalNAc

GalNAc

GalNAc

3’

siRNA

Long DNA

Cytoplasm

AGO2

RISC

RISC assembly

Target mRNA recognition

Cleaved sense strand

Recycled RISC-siRNA activated complex

Target mRNA cleavage

Sense strand

Antisense strand

Target mRNA

INCLISIRAN

Hepatic ASP receptor

Change in LDL-Cholesterol level in single-dose cohorts with Inclisiran

Inter-individual LDL-C lowering response to Inclisiran

Phase 2 Study

Placebo group at day 180

Two-dose 300 mg Inclisiran group at day 180

Change from baseline in LDL-C (mmol/L)

Placebo group

Two-dose 300 mg Inclisiran group

Mean 1.66 mmol/L
LDL levels in FH
From a lethal disorder to a manageable dyslipidaemia

Adapted from Kastelein JJP. Nat Rev Cardiol. 2014;11:629-631
Tailored therapy in atherosclerotic cardiovascular disease

Known atherosclerotic cardiovascular disease

↓

High intensity statin +/- ezetimibe

“Residual Cholesterol Risk”

LDL-C high
Lp(a)/ hsCRP low

Additional LDL-C reduction

“Residual Inflammatory Risk”

LDL-C low
Lp(a)/ hsCRP high

Additional inflammation reduction

“Residual Thrombotic Risk”

LDL-C low
Lp(a)/ hsCRP high

Additional antiplatelet & anticoagulant therapy

IMPROVE-IT: Ezetimibe 6% RR
FOURIER/SPIRE: PCSK9 inhibition Q2W 15% RRR

Ridker PM, Eur Heart J 2016;37:1720-22
Cholesterol crystals induce local and systemic inflammation

Experimental studies

Monocytes and macrophages
Volume expansion
Intima perforation

Human studies

Carotid artery
Coronary artery
Systemic effects

Activation of inflammasome - “clinical utility”

- NLRP3 inflammasome
  - IL-1β
  - TNF
  - IL-6
  - hsCRP

Target:
- Canakinumab
- Anakinra
- Colchicine

Converter:
- Tocilizumab

Distributor:
- Low-Dose Methotrexate

Biomarker:
- Vascular Risk
  - High: $>3$
  - Intermediate: $1-3$
  - Low: $<1$

Ridker PM et al, *Circulation* 2012;126:2739-2748
CANTOS: dose-dependent effects on inflammatory biomarkers and lipids (38 months)

Patient change from baseline (median)

Placebo SC q 3 nth
Canakinumab 50mg SC q 3 mth
Canakinumab 150mg SC q 3 mth
Canakinumab 300mg SC q 3 mth
CANTOS: greater risk reduction among those with greater hsCRP reduction (MACE+)

- Cumulative incidence (%)
- Follow-up years

**Graph: CANTOS Study**

- Placebo
- Canakinumab (on treatment hsCRP < median)
- Canakinumab (on treatment hsCRP ≥ median)

**Table:**

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 (referent)</td>
<td>referent</td>
</tr>
<tr>
<td>0.95 (0.84-1.08)</td>
<td>0.47</td>
</tr>
<tr>
<td>0.73 (0.63-0.83)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

**HR 0.73**

- 95% CI 0.63-0.83
- p = 0.0001

for those with reductions in hsCRP ≥median at 3 mths (1.8 mg/dL)
## CANTOS: additional outcomes (per 100 person years of exposure)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Placebo (N=3347)</th>
<th>50 mg (N=2170)</th>
<th>150 mg (N=2284)</th>
<th>300 mg (N=2263)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any SAE</td>
<td>12.0</td>
<td>11.4</td>
<td>11.7</td>
<td>12.3</td>
<td>0.43</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>0.24</td>
<td>0.30</td>
<td>0.37</td>
<td>0.52</td>
<td>0.002</td>
</tr>
<tr>
<td>Any infection</td>
<td>2.86</td>
<td>3.03</td>
<td>3.13</td>
<td>3.25</td>
<td>0.12</td>
</tr>
<tr>
<td>Fatal infection</td>
<td>0.18</td>
<td>0.31</td>
<td>0.28</td>
<td>0.34</td>
<td>0.9/0.02*</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>0.23</td>
<td>0.27</td>
<td>0.28</td>
<td>0.30</td>
<td>0.49</td>
</tr>
<tr>
<td>Any malignancy</td>
<td>1.88</td>
<td>1.75</td>
<td>1.69</td>
<td>1.72</td>
<td>0.31</td>
</tr>
<tr>
<td>Fatal malignancy</td>
<td>0.64</td>
<td>0.55</td>
<td>0.50</td>
<td>0.31</td>
<td>0.0007</td>
</tr>
<tr>
<td>Arthritis</td>
<td>3.32</td>
<td>2.15</td>
<td>2.17</td>
<td>2.47</td>
<td>0.002</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>1.67</td>
<td>1.21</td>
<td>1.12</td>
<td>1.30</td>
<td>0.04</td>
</tr>
<tr>
<td>Gout</td>
<td>0.80</td>
<td>0.43</td>
<td>0.35</td>
<td>0.37</td>
<td>0.0001</td>
</tr>
<tr>
<td>ALT &gt;2x normal</td>
<td>1.4</td>
<td>1.9</td>
<td>1.9</td>
<td>2.0</td>
<td>0.19</td>
</tr>
<tr>
<td>Bilirubin &gt;2x normal</td>
<td>0.8</td>
<td>1.0</td>
<td>0.7</td>
<td>0.7</td>
<td>0.34</td>
</tr>
</tbody>
</table>

* P-value for combined Canakinumab doses vs. placebo

Tailored therapy in atherosclerotic cardiovascular disease

Known atherosclerotic cardiovascular disease

High intensity statin +/- ezetimibe

“Residual Cholesterol Risk”
LDL-C high
Lp(a)/ hsCRP low
Additional LDL-C reduction

“Residual Inflammatory Risk”
LDL-C low
Lp(a)/ hsCRP high
Additional inflammation reduction

“Residual Thrombotic Risk”
LDL-C low
Lp(a)/ hsCRP high
Additional antiplatelet & anticoagulant therapy

IMPROVE-IT: Ezetimibe 6% RR
FOURIER/SPIRE: PCSK9 inhibition Q2W 15% RRR

CANTOS

Ridker PM, Eur Heart J 2016;37:1720-22
Evidence base for Lp(a) as an independent, causal, genetic risk factor for ASCVD

Epi/Meta-analyses

Adjustment for age and sex only
Nonfatal MI and coronary death
9318 cases

Risk ratio (95% CI)

Usual Lp(a) Geometric mean mg/dL

Mendelian Randomisation

Multivariable and KIV-2 adjusted

Lp(a) mg/dL

Hazard Ratio (95% CI)

< 5
0.8 1 2 4

P > 0.002

Genome-wide association

Odds ratio for coronary disease

Geometric mean Lp(a) (mg/dL)

0 Variant alleles
1 Variant allele
2 Variant alleles

0 25 50 75 100 125

0.0 1.0 2.0 4.0 8.0

Erqou et al. JAMA 2009;302:412-23
Kamstrup et al. JAMA 2009;301:2331-9
Clarke et al. NEJM 2009;361:2518-28
Lp(a) has \( \frac{1}{4} \) effect of LDL-cholesterol on ASCVD risk but the effect is 3 fold greater per mmol/L cholesterol.
Comparison of cumulative effects of Lp(a) and LDL-C on CVD

Exome. CHD consortium 2017, in press
Changes in Lp(a) and LDL-C with equivalent effects on CVD

1.0 mmol/L lifetime lower LDL-C

50% reduction in lifetime risk of CHD

90 – 100 mg/dL lifetime lower Lp(a)

- Reconciles epidemiologic and Mendelian randomisation studies
- Explains failure of lowering Lp(a) in niacin, CETP and PCSK9 randomised trials
- Informs the optimal design of RCTs for potent Lp(a) lowering agents

Ference B et al. Exome. CHD consortium 2017, in press
Phase 2 IONIS-APO(a) Rx Study - mean change in Lp(a) in placebo and patients with Lp(a) 50-175 mg/dL and >175 mg/dL

Fasting Lp(a), mean % change from baseline (± SEM)

Placebo

Cohort B (50-175 mg/dL)

Cohort A (> 175 mg/dL)

Treatment period (days)
"chronic inflammatory fibroproliferative process which is excessive and in its excess, this protective response has become a disease state."

75th Percentile of CAC score in women (A) and men (B) across populations

CAC scores by age for US MESA and Tsimane populations

## CAD in the Tsimane Tribe

**Total (n=705)**

### Anthropometry

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of men (%)</td>
<td>50 (0.5)</td>
</tr>
<tr>
<td>Mean weight (kg)</td>
<td>58.4 (9.9)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>155.7 (7.8)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.1 (3.5)</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>22.1 (8.2)</td>
</tr>
</tbody>
</table>

### Physiology

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>116.0 (12.5)</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>73.4 (10.0)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>65.9 (9.3)</td>
</tr>
</tbody>
</table>

### Lipids

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>3.9 (0.8)</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>2.4 (0.7)</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.0 (0.2)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.2 (0.5)</td>
</tr>
<tr>
<td>ApoA (mg/dL)</td>
<td>126.0 (84.9)</td>
</tr>
<tr>
<td>ApoB (mg/dL)</td>
<td>97.2 (41.5)</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>22.0 (13.9)</td>
</tr>
<tr>
<td>hs-CRP (mg/dL)</td>
<td>3.7 (3.2)</td>
</tr>
</tbody>
</table>
Tuberculosis is also a disease that has a strong inflammatory component. It is associated with:

- Influx of macrophages and T cells
- High levels of inflammatory cytokines
- Elevated CRP

However, treatment of this "inflammatory disease" is the elimination of *Mycobacterium tuberculosis*, the root cause.
Likewise, in atherosclerosis, inflammation is a consequence of LDL retention in the sub-endothelial space, not the cause.

The most successful treatment of atherothrombotic vascular disease in humans is therefore to address the root cause, namely LDL-cholesterol!
LDL cholesterol is essential for the development of atherosclerosis. Other factors are “accelerating factors”.

**ACCELERATING FACTORS**
- Smoking
- Hypertension
- Diabetes
- Obesity
- Inflammation

LDL-Cholesterol

Atherosclerotic plaque development

Plaque expansion and acute CV event
Can we go too low?
Lower LDL-C is better

Patients divided by quartile of baseline and by treatment arm

Achieved LDL-C (mmol/L)

Cardiovascular death, MI, or stroke

P<0.0001

Q1 Q2 Q3 Q4

Q1 Q2 Q3 Q4

Placebo Evolocumab

Clinical Efficacy and Safety of Achieving Very Low LDL Levels with the PCSK9 Inhibitor Evolocumab in the FOURIER Outcomes Trial

RP Giugliano, TR Pedersen, AV Keech, PS Seever, JG Park, and MS Sabatine, for the FOURIER Steering Committee & Investigators

Presented at ESC, Barcelona, August 2017
Published in the Lancet 2017;390;1962-1971
Achieved LDL-C at 4 weeks

**Median [IQR] LDL-C at 4 weeks**

- **Evolocumab** 0.8 (mmol/L [0.5-1.2] 32 mg/dL [21-45]
- **Placebo** 2.2 mmol/l [1.9-2.7] 87 mg/dL 2.24 mmol/L [74-104]

<table>
<thead>
<tr>
<th>LDL (mmol/L)</th>
<th>Evolocumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.8</td>
<td>99.6%</td>
<td>0.4%</td>
</tr>
<tr>
<td>1.3-1.8</td>
<td>96.5%</td>
<td>3.5%</td>
</tr>
<tr>
<td>1.3-1.8</td>
<td>41%</td>
<td>59%</td>
</tr>
<tr>
<td>1.8-2.6</td>
<td>10%</td>
<td>90%</td>
</tr>
<tr>
<td>≥2.6</td>
<td>9.6%</td>
<td>90.4%</td>
</tr>
</tbody>
</table>
LDL-C over time

LDL-C at 4 weeks in mmol/L

Mean LDL-C (mmol/L)

- <0.5
- 0.5-1.3
- 1.3-1.8
- 1.8-2.6
- ≥2.6

Weeks after randomisation

Giugliano RP, ESC Congress 2017, Barcelona August 2017
CV death, MI or stroke

<table>
<thead>
<tr>
<th>LDL-C (mmol/L) at 4 weeks</th>
<th>Adj HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.5</td>
<td>0.69 (0.56-0.85)</td>
</tr>
<tr>
<td>0.5-1.4</td>
<td>0.75 (0.64-0.86)</td>
</tr>
<tr>
<td>1.3-1.8</td>
<td>0.87 (0.73-1.04)</td>
</tr>
<tr>
<td>1.8-2.6</td>
<td>0.90 (0.78-1.05)</td>
</tr>
<tr>
<td>≥2.6</td>
<td>referent</td>
</tr>
</tbody>
</table>

P = 0.0001

Giugliano RP, ESC Congress 2017, Barcelona August 2017
Safety events - 1

Adj P-values for trend >0.10 for each comparison

LDL-C (mmol/L) at 4 weeks

- <0.5
- 0.5-1.3
- 1.3-1.8
- 1.8-2.6
- >2.6

Giugliano RP, ESC Congress 2017, Barcelona August 2017
Safety events - 2

LDL-C (mmol/L) at 4 weeks

- <0.5
- 0.5-1.3
- 1.3-1.8
- 1.8-2.6
- >2.6

% pts

Neurocog  AST/ALT↑  CK↑  Non-CV death  Hemor stroke

Giugliano RP, ESC Congress 2017, Barcelona August 2017
Does reducing LDL cholesterol to low and very low levels have safety concerns?

- In Fourier, reduction of LDL-C with evolocumab to a median of 0.78 mmol/L, with nearly 6,000 patients <0.65 mmol/L and 2500 patients below 0.5 mmol/L, was not associated with any major safety concerns such as haemorrhagic stroke, cognitive impairment or cataracts.

- Safety and benefit data for very low LDL-C based on increased LDL clearance via upregulation of the LDL receptor (statins, ezetimibe and PCSK9 inhibition) suggest eliminating a lower limit for LDL-cholesterol.

Based on current evidence the real safety concern is under treatment of LDL-C, not too low LDL-C!
A quarter of a century of treating LDL-C

High is bad
Average is not good
Lower is better
Even lower is even better
Lowest is best
HEART ATTACKS
Gone with the Century?
Cholesterol year score and the threshold for CHD

Concept of lifetime cumulative LDL-C exposure and vascular risk

Adapted from Horton et al. J Lipid Res. 2009;50:S172-S177
The mean age at the time of randomization in the statin trials was 63 years
### Comparative CHD risk reduction of earlier and later LDL-C lowering

<table>
<thead>
<tr>
<th>Lower LDL-C</th>
<th>Meta-analysis</th>
<th>Sample size (N)</th>
<th>OR (95% CI)</th>
<th>P diff.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 mmol/L</td>
<td>Genetic studies</td>
<td>312,321</td>
<td>0.46 (0.41-9.51)</td>
<td>8.4x10^{-19}</td>
</tr>
<tr>
<td></td>
<td>Statin trials</td>
<td>169,138</td>
<td>0.76 (0.74-0.78)</td>
<td></td>
</tr>
<tr>
<td>0.5 mmol/L</td>
<td>Genetic studies</td>
<td>212,321</td>
<td>0.67 (0.64-0.72)</td>
<td>8.4x10^{-19}</td>
</tr>
<tr>
<td></td>
<td>Statin trials</td>
<td>169,138</td>
<td>0.87 (0.86-0.88)</td>
<td></td>
</tr>
<tr>
<td>0.25 mmol/L</td>
<td>Genetic studies</td>
<td>312,321</td>
<td>0.82 (0.80-0.85)</td>
<td>8.4x10^{-19}</td>
</tr>
<tr>
<td></td>
<td>Statin trials</td>
<td>169,138</td>
<td>0.93 (0.93-0.94)</td>
<td></td>
</tr>
<tr>
<td>0.125 mmol/L</td>
<td>Genetic studies</td>
<td>312,321</td>
<td>0.91 (0.89-0.92)</td>
<td>8.4x10^{-19}</td>
</tr>
<tr>
<td></td>
<td>Statin trials</td>
<td>169,138</td>
<td>0.96 (0.96-0.97)</td>
<td></td>
</tr>
</tbody>
</table>
# Expected lifetime risk reduction with 50% reduction in LDL-C beginning in early adulthood

<table>
<thead>
<tr>
<th>Baseline LDL-C mmol/L</th>
<th>LDL-C mmol/L after 50% reduction</th>
<th>RR for CHD&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Relative reduction in lifetime risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.5</td>
<td>3.25</td>
<td>0.08</td>
<td>92%</td>
</tr>
<tr>
<td>5.0</td>
<td>2.5</td>
<td>0.14</td>
<td>86%</td>
</tr>
<tr>
<td>4.0</td>
<td>2.0</td>
<td>0.21</td>
<td>79%</td>
</tr>
<tr>
<td>3.5</td>
<td>1.75</td>
<td>0.26</td>
<td>64%</td>
</tr>
<tr>
<td>3.0</td>
<td>1.5</td>
<td>0.31</td>
<td>69%</td>
</tr>
<tr>
<td>2.5</td>
<td>1.25</td>
<td>0.38</td>
<td>62%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Based on an expected 54% reduction in lifetime risk of ASCVD per mmol/L reduction in LDL-C
Importance of Early Treatment

Age (years)

Age of intervention

Age at which clinical horizon is reached
Conclusions

- Biologics including PCSK9 inhibitors are very promising, and potentially the most effective, approach to further reducing LDL-cholesterol, the cause of atherosclerosis.
- Two large CVD outcome trials are completed or soon to be completed with the Amgen (evolocumab) and Sanofi (alirocumab) monoclonal antibodies and no significant adverse effects have emerged so far.
- “Residual risk” may well be the result of treating “too little, too late”.
- Earlier intervention and more aggressive LDL-cholesterol reduction is pivotal for effective treatment and prevention of atherosclerosis.