Prof. John Chapman, MD, PhD, DSc

- Director of the Dyslipidemia and Atherosclerosis Research Unit of the National Institute for Health and Medical Research (INSERM) at the Pitié-Salpêtrière Hospital in Paris
- Associate European Editor of “Arteriosclerosis, Thrombosis and Vascular Biology” and of “Pharmacology and Therapeutics”
- President of the European Atherosclerosis Society
CVS-European Postgraduate School
in Cardiology
Prague 2011

WHAT NEXT
IN CVD PREVENTION?

M. John Chapman  Ph.D., D.Sc., FESC
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Hôpital de la Pitié-Salpetriere,
Paris, France

President, European Atherosclerosis Society
INTERHEART : RF for first MI

High Global CV Risk

Accelerated Atherosclerosis and CVD

Apo B / Apo AI

1. Smoking
2. Diabetes
3. Hypertension
4. Abdominal Obesity
5. Psychosocial Stress
6. Vegetables and Fruit Consumption Daily
7. Exercise
8. Alcohol Intake
9. Daily

On-treatment LDL-C & CHD Events in Statin Trials

Lowering LDL-C:HDL-C Ratio to approx 1:1 stops Atherosclerosis progression

IVUS Trials: REVERSAL, CAMELOT, ACTIVATE, ASTEROID

BUT......
Residual Cardiovascular Risk in Prospective Intervention Trials

Chapman et al, Pharmacol Therap, 2010
BUT......
Obésité: fléau mondial

En France:
1 personne sur 3 en surpoids ou obèse
20 Millions en surpoids
6 Millions d’obèses

Obépi 2009
WHO Prediction of Worldwide Prevalence of TYPE 2 DIABETES in 2025

Le Monde, 2001
Pathophysiology of Type 2 Diabetes, Metabolic Syndrome and Premature Vascular Disease

- Positive Energy Balance
  - Adipose Fat accumulation
  - Portal FFA
  - VLDL production
- Mixed Dyslipidemia
- Adipose Fat accumulation
- Glucose AGE
  - IL6, IL8
  - TNFα
  - Angio II
  - Leptin
  - PAI-1
  - Adiponectin
- Insulin resistance
  - Inflammation
  - Oxidative Stress
  - Microangiopathy
  - Atherosclerosis
- Hyperglycemia
- Hypertension
Mixed Dyslipidemia

**TG-rich LPs**
- Chylos, VLDL
- Remnants
  - Fasting
  - Nonfasting

**Chronic Inflammation, Premature Atherosclerosis and CHD**

**HDL-C**
- Apo AI

**Small Dense LDL**
- Apo B
Factors Contributing to Elevated Triglyceride Levels

<table>
<thead>
<tr>
<th>High Triglyceride Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity/overweight</td>
</tr>
<tr>
<td>Physical inactivity</td>
</tr>
<tr>
<td>Cigarette smoking</td>
</tr>
<tr>
<td>Excess alcohol intake</td>
</tr>
<tr>
<td>High carbohydrate diet</td>
</tr>
<tr>
<td>Type 2 diabetes, renal failure, underactive thyroid</td>
</tr>
<tr>
<td>Certain drugs</td>
</tr>
<tr>
<td>Genetic factors</td>
</tr>
</tbody>
</table>

NCEP III=National Cholesterol Education Program Adult Treatment Panel III
Metabolic Basis of low HDL-C in Type 2 Diabetes and Metabolic Syndrome with insulinoresistance

**Diagram Explanation**

- **Liver**
  - Increase in **FFA**
  - Production of **TG-rich VLDL-1**
  - CE increase, TG decrease

- **Adipose Tissue**
  - Increase in **TG**
  - Increase in **HSL**
  - Increase in **FFA**
  - Increase in **INSULIN**

- **CETP**
  - CE increase, TG decrease

- **HDL**
  - CE increase, TG increase
  - HDL decrease

- **Small dense LDL**
  - TG decrease, CE increase

- **Kidney**
  - AI, AII
  - Decrease in **HDL**
  - TG decrease

- **In Vivo Observations**
  - Small dense LDL
  - HSL increase
  - FFA increase
  - INCREASE in TG
Cardiovascular Disease Prevention: The Unmet Need

- Metabolic disease
- CHD patients
- Mixed hyperlipidemia
- Hypercholesterolemia (FH)
- Renal Disease
Unmet Therapeutic Needs in Atherogenic Dyslipidemia

- Statin intolerance; pharmacogenomically-determined hyporesponse (OATP1B1) to statins

Responses:
- 1) anti-PCSK9 biologics
- 2) new potent statins, poorly metabolised, low dose, polypharmacy
- 3) MTP inhibitors, low dose, combination therapy
- 4) Anti-sense oligonucleotides (apo(a) ; apoB )
HDL: New Perspectives

QUANTITY
HDL-C / Apo AI

QUALITY
Particle structure
Lipidome, Proteome
Functionality

Abnormal Metabolism and Defective Function of HDL in Diabetic High TG/Low HDL Dyslipidemia

Oxidative stress

Liver

Chronic low-grade inflammation

IL-6

SAA (CRP)

A-I

PON1

HL

TG

Functionally deficient HDL

↓ Cholesterol efflux capacity
↓ Antioxidative activity
↓ Anti-inflammatory activity
↓ Antiapoptotic activity
↓ Vasodilatory activity

Mixed Dyslipidemia

TG-rich LPs
Chylos, VLDL + Remnants
- Fasting
- Nonfasting

Chronic Inflammation,
Premature Atherosclerosis
and CHD

HDL-C
Apo AI

Small Dense LDL
Apo B
Proposed algorithm for management of elevated TG and/or low HDL-C in high-risk patients at LDL-C goal

Patient at LDL-C goal\(^1\) WITH
\[
\begin{align*}
\text{TG} & \geq 1.7 \text{ mmol/L} \\
\text{and/or} \\
\text{HDL-C} & < 1.0 \text{ mmol/L}
\end{align*}
\]

- Intensify lifestyle management
- Address secondary causes
- Check compliance

Insufficient improvement?\(^2\)

- Consider adding niacin or a fibrate\(^3\)
- Consider intensifying LDL-C lowering\(^4\)

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Atheroprotective & Vasculoprotective Actions of HDL

- Reverse Cholesterol Transport
- Cellular Cholesterol Efflux
- Anti-Infectious Activity
- Anti-Thrombotic Activity
- Anti-Inflammatory Activity
- Anti-Apoptotic Activity
- Anti-Oxidative Activity
- Anti-proteolytic activity
- Endothelial Repair; Vasodilation
- Innate immune system

Cholesterol efflux capacity, HDL Function and Atherosclerosis

- Khera et al, NEJM 2011, 364: 127-135

- “Cholesterol efflux capacity from macrophages has a strong inverse association with both carotid IMT and the likelihood of angiographic CAD, independently of HDL-cholesterol”
# HDL-C Raising Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Effect on HDL-C</th>
<th>Effect on LDL-C</th>
<th>Effect on Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niacin</td>
<td>15%–35% ↑</td>
<td>5%–25% ↓</td>
<td>20%–40% ↓</td>
</tr>
<tr>
<td>Fibrates</td>
<td>1%–20% ↑</td>
<td>up to 10% ↓</td>
<td>20%–50% ↓</td>
</tr>
<tr>
<td>Statins</td>
<td>1%–15% ↑</td>
<td>18%–55% ↓</td>
<td>7%–30% ↓</td>
</tr>
</tbody>
</table>
Cholesteryl Ester Transfer Protein (CETP)

VLDL or Chylomicron Remnant

Cholesteryl Ester

Apo AI

HDL

Apo B

Apo E

CETP

TG

CE

Triglyceride
The **dal-HEART Program**

dalcetrapib HDL Evaluation, Atherosclerosis & Reverse cholesterol Transport

The **dal-HEART Program** hypothesis: enhancing HDL efficacy through CETP modulation will treat the underlying disease of atherosclerosis and will attenuate CV risk

<table>
<thead>
<tr>
<th>dalOUTCOME S</th>
<th>dal-VESSEL²</th>
<th>dal-PLAQUE³</th>
<th>dal-PLAQUE²⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>15,600 patients recently hospitalized for ACS</td>
<td>450 patients with CHD or CHD risk equivalent</td>
<td>130 patients with CHD</td>
<td>900 patients with CAD</td>
</tr>
<tr>
<td>To evaluate the effect of dalcetrapib on CV outcomes</td>
<td>To evaluate the effect of dalcetrapib on endothelial function and blood</td>
<td>To evaluate the effect of dalcetrapib on inflammation, plaque size and burden, measured by PET/CT and MRI</td>
<td>To evaluate the effect of dalcetrapib on atherosclerotic disease progression, assessed by IVUS and carotid B-mode ultrasound</td>
</tr>
</tbody>
</table>

**RECRUITMENT COMPLETE**

**pressure, measured by FMD and ABPM**
Cardiovascular Disease Prevention: The Unmet Need

- Metabolic disease
- CHD patients
- Mixed hyperlipidemia
- Hypercholesterolemia (FH)
- Renal Disease