The importance of Lipid Residual Risk in Cardiometabolic Disease After Statin Treatment

Memorial Lecture
Fernandez-Cruz Foundation

Prof. JC Fruchart
Residual vascular risk – our definition

The significant residual risk of macrovascular events and microvascular complications which persists in most patients despite current standards of care including achievement of low-density lipoprotein (LDL-C) goal and intensive control of blood pressure and blood glucose

Endorsed by the Members of R³i International Steering Committee
Why should we be concerned about Residual Vascular Risk today?
Residual macrovascular risk remains high in patients at LDL-C goal

Lowering LDL-C by 1 mmol/L (approx 40 mg/dL) with statins reduces major coronary events by 23%, leaving CV residual risk of 77%

Residual vascular risk is critically important in diabetics

- **Diabetic Retinopathy**: Leading cause of blindness in adults. 24,000 new cases p.a. in US.
- **Diabetic Nephropathy**: Leading cause of end-stage renal disease in adults. 44% new cases p.a.
- **Diabetic Neuropathy**: Leading cause of non-traumatic limb amputations. 60% new cases p.a.
- **Stroke**: 2 to 4-fold increase in cerebrovascular disease and stroke.
- **Cardiovascular Disease**: 8 out of 10 diabetic patients die from cardiovascular events. 5-10 years reduction in life expectancy.

Economic burden of microvascular complications

**Nephropathy**

Annual cost
US$ 933 million (UK)
US$ 15.0 billion (USA)


**Retinopathy**

Annual cost
Euros 3.51 billion (Germany)


**Peripheral neuropathy**

Annual cost
US$ 10.1 billion (USA)

Multifactorial interventions (including statins) fail to prevent microvascular disease in ± 50% of patients with T2DM$^{1,2}$

**STENO-2 Study:** Despite intensive treatment with OAD, antiHT, LLD + diet and lifestyle, after mean follow-up of 13.3 years still:

- **51%** progression of retinopathy
- **25%** development of nephropathy
- **55%** progression of peripheral neuropathy

Alarming worldwide epidemic of diabetes

World
2007 = 246 million
2025 = 380 million
Increase 55%

What is the role of atherogenic dyslipidemia in Residual Vascular Risk?
Defining atherogenic dyslipidemia

- Atherogenic dyslipidemia is characterized by¹:
  - Low levels of HDL-C
  - Elevated triglycerides

- Common in patients with established cardiovascular disease²

- Typical in patients with type 2 diabetes or metabolic syndrome

- Implicated in the pathogenesis of diabetic microvascular disease

Elevated triglycerides increase macrovascular residual risk independent of LDL-C

**PROVE IT-TIMI 22 study:** Despite achieving LDL-C <70 mg/dL (1.8 mmol/L) with high-dose statins, patients with TG ≥200 mg/dL (2.3 mmol/L) show a 56% increase in the risk of death, MI or ACS¹

Low HDL-C increases macrovascular residual risk independent of LDL-C

**PROCAM study:** Low HDL-C is an independent predictor of CHD risk even when LDL-C is low.

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HDL-C is an important contributor to MACROvascular residual risk

**TNT study:** CV event rate was reduced by 39% in the highest HDL-C quintile compared with the lowest (HR: 0.61, 95% CI: 0.38-0.97) even in patients with low LDL-C (<70 mg/dL or 1.8 mmol/L)¹

Today’s challenge

How can we reduce the significant Residual Risk of fatal and non-fatal macro- and micro-vascular events in patients already receiving today’s best care?
R³i offers you the unique opportunity to respond to this challenge through:

- **RESEARCH** creating the evidence on which to base better intervention strategies

- **EDUCATION** to translate current and future knowledge into improved daily patient care

- **ADVOCACY** to include this evidence in guidelines and treatment protocols
The $R^3i$ is an...

- Academic
- Worldwide
- Multidisciplinary
- Research Driven
- Education Focused
- Public Advocacy
- Non-profit Foundation
What is the mission of the R³i?

To reduce the significant residual risk of MACROvascular events and MICROvascular complications that persist in most patients despite receiving current standard-of-care including achievement of low-density lipid (LDL-C) goal and intensive control of blood glucose and blood pressure.
How will we achieve our mission?

By:

▪ Providing an academically stimulating environment
▪ Engaging the global and local healthcare community
▪ Gaining a commitment to vigorous action
▪ Increasing knowledge and awareness of physicians, patients and policy makers worldwide

We will improve and extend the lives of millions of people worldwide
R³i: A worldwide, academic, multidisciplinary Foundation

- Led by a Board of Trustees and an International Steering Committee of 20 members

- Engaged in three major areas of activity
  - Research
  - Education
  - Advocacy
R³i: International Steering Committee

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Harvard School of Public Health, Boston, USA

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Cliniques Universitaires Saint-Luc, Brussels, Belgium

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▪ Professor Jesus Millàn Nuñez-Cortés
  University Hospital Gregorio Marañón, Madrid, Spain

▪ Professor Jorge Plutzky
  Harvard Medical School, Boston, USA

▪ Professor Robert S. Rosenson
  University of Michigan, Ann Arbor, USA

▪ Professor Bart Staels
  Pasteur Institute, Lille, France

▪ Professor Rody Sy
  Mandaluyong City, Philippines

▪ Professor Paul Valensi
  Paris-Nord University, Bondy, France

▪ Professor Christoph Wanner
  University Hospital Würzburg, Würzburg, Germany

▪ Professor Gerald Watts
  University of Western Australia, Perth, Australia

▪ Professor Alberto Zambon
  University of Padua, Padua, Italy

▪ Professor Paul Zimmet
  International Diabetes Institute, Caulfield, Australia

▪ Professor Jun-ren Zhu
  Fundan University, Shanghai, China
**R³i: Organization and programs**

**R³i Organization**

- **International Steering Committee**: 3 officers and 20 Scientific Members
- **National Steering Committees**
- **National Faculties**

**Residual Risk Reduction Programs**

- **Research**
  - Worldwide epidemiological surveys
- **Education**
  - Global educational programs, CME, website, conferences, webinars
- **Advocacy**
  - Publications, guidelines, treatment algorithms

**Interaction with Healthcare Community**

*: Cardiology, diabetology, lipidology, endocrinology, ophthalmology, nephrology, epidemiology, basic science
R³i: National organizations

- R³i National Steering Committees
  - Take part in the design of global R³i projects
  - Define and implement national R³i activity plan in collaboration with R³i Faculty members

- R³i National Faculties
  - Disseminate R³i medical education programs to Primary Care Physicians
R³i: National organizations
R³i Research: the REALIST studies

- Two global epidemiological studies
  - Involving a large number of countries around the world
  - Conducted by Harvard Medical School
  - MACROvascular epidemiological study
    - to establish the risk of macrovascular events attributable to high TG and/or low HDL-C in patients optimally treated according to current standard of care
  - MICROvascular epidemiological study
    - to establish the risk of microvascular complications attributable to high TG and/or low HDL-C in patients with T2D optimally treated according to current standard of care
Macrovascular Risk Associated with Atherogenic Dyslipidemia In Patients with Heart Disease: Initial REALIST Study Results
To determine whether low HDL-C or elevated TG levels are associated with a significant risk of coronary events in patients at goal for LDL-C (≤3.4 mmol/L or 130 mg/dL)
MACROvascular Study

**Cases:**
- Adult male and female patients with a first or subsequent coronary event (acute coronary syndrome including MI)
- LDL-C ≤3.4 mmol/L (130 mg/dL)
- With or without statin therapy

**Controls**
- Patients free of coronary events
- Hospitalized for other reasons
- LDL-C ≤3.4 mmol/L (130 mg/dL)
- Treated or not for elevated LDL-C

**Matched for:**
- Age
- Gender
- Diabetes status
- LDL-C levels (<70 mg/dL, 70 ≤ LDL-C <100 mg/dL, 100 ≥ LDL-C ≤130 mg/dL)
## Patients’ Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>170</td>
<td>175</td>
</tr>
<tr>
<td>Male (%)</td>
<td>75</td>
<td>48</td>
</tr>
<tr>
<td>White (%)</td>
<td>88</td>
<td>75</td>
</tr>
<tr>
<td>Age</td>
<td>66</td>
<td>66</td>
</tr>
<tr>
<td>Total CHOL (mg/dL – mmol/L)</td>
<td>139 – 3.6</td>
<td>160 – 4.1</td>
</tr>
<tr>
<td>LDL-C (mg/dL – mmol/L)</td>
<td>73 – 1.9</td>
<td>87 – 2.2</td>
</tr>
<tr>
<td>HDL-C (mg/dL – mmol/L)</td>
<td>37 – 1.0</td>
<td>47 – 1.2</td>
</tr>
<tr>
<td>TG (mg/dL – mmol/L)</td>
<td>147 – 1.6</td>
<td>136 – 1.5</td>
</tr>
<tr>
<td>Lipid lowering drugs at admission (%)</td>
<td>48</td>
<td>26</td>
</tr>
</tbody>
</table>
Each Higher TG Quintile Represents a Coronary Risk Increase of 20%

Categorical and linear measures of TG effect on CHD risk, with matching for LDL-C, age, race, gender
Each Lower HDL-C Quintile Represents a Coronary Risk Reduction of 40%

Categorical and linear measures of HDL effect on CHD risk, with matching for LDL-C, age, race, gender.
Synergistic Impact of High TG and Low HDL-C on Coronary Risk
Greater than the sum of their individual effects

<table>
<thead>
<tr>
<th>HDL quintile</th>
<th>TG quintile</th>
<th>(22-72]</th>
<th>(72-102]</th>
<th>(102-133]</th>
<th>(133-190]</th>
<th>(190-838]</th>
</tr>
</thead>
<tbody>
<tr>
<td>(53-94]</td>
<td>1.0</td>
<td>1.0</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>(42-53]</td>
<td>1.2</td>
<td></td>
<td>1.3</td>
<td>1.4</td>
<td>1.5</td>
<td>1.6</td>
</tr>
<tr>
<td>(36-42]</td>
<td>1.4</td>
<td>1.7</td>
<td></td>
<td>2.0</td>
<td>2.5</td>
<td>3.0</td>
</tr>
<tr>
<td>(30-36]</td>
<td>1.7</td>
<td>2.2</td>
<td>3.0</td>
<td></td>
<td>4.1</td>
<td>5.5</td>
</tr>
<tr>
<td>(7-30]</td>
<td>2.0</td>
<td>2.3</td>
<td>4.5</td>
<td>6.7</td>
<td></td>
<td>10.2</td>
</tr>
</tbody>
</table>

10 X increase in risk
Initial Findings of the Macrovascular Residual Risk Study: Conclusions

- Confirmation of these initial results sought globally in REALIST Study

- Confirmation of synergistic impact of high TG and low-HDL-C could motivate new emphasis or lowering TG and raising HDL-C
  - New efforts to improve diet, increase exercise and lose weight
  - Revising pharmaceutical strategies
To determine whether low HDL-C or elevated TG levels are associated with a significant residual risk of microvascular complications after adjustment for other risk factors in patients with type 2 diabetes at near goal for LDL-C.
## Lipid Profiles and Microvascular Complications

**Controls versus patients with diabetic nephropathy**

<table>
<thead>
<tr>
<th></th>
<th>Cases N = 127</th>
<th>Controls N = 190</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>91 ± 23</td>
<td>89 ± 23</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>43 ± 14</td>
<td>47 ± 13</td>
<td>0.0097</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>181 ± 85</td>
<td>144 ± 83</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

**Controls versus patients with diabetic retinopathy**

<table>
<thead>
<tr>
<th></th>
<th>Cases N = 68</th>
<th>Controls N = 190</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>93 ± 23</td>
<td>89 ± 23</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>45 ± 12</td>
<td>47 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>179 ± 97</td>
<td>144 ± 83</td>
<td>0.0047</td>
</tr>
</tbody>
</table>
These preliminary data suggest that both nephropathy and retinopathy are associated with elevated TG and/or low HDL-C in patients with type 2 diabetes at goal for LDL-C.

Additional data are currently being collected worldwide.

Once available, analysis of the full set of data will be performed.

Confirmation of the link between atherogenic dyslipidemia and microvascular complications could lead to changes in:

- The way we assess the microvascular risk of our patients
- The way we treat them
Recommendations of the R3i to improve management of residual vascular risk

- Initiate lifestyle modification as a first step
- Normalize HbA$_{1c}$ and blood pressure
- Improve achievement of lipid goals. Addition of a fibrate, niacin or omega 3 fatty acids to statin therapy may be useful. Clinical outcomes studies of combinations are in progress.
- Intervene earlier in the disease process with lifestyle modification and drug therapy
“Lower is better”?  
- Lowering LDL threshold from 100 to 70 mg/dL has brought additional reduction in macrovascular disease, especially in high-risk patients (TNT)  
- Has no impact on microvascular disease reported so far  
- Does not wipe out the HDL-related macrovascular RR with Atorvastatin (recent TNT analyses) but not with pitavastatin.

HDL- or HDL/TG-targeted therapy?  
- CETP inhibition: dead-end street?  
- Rimonabant tackling HDL/TG via abdominal obesity: tolerance issues  
- Niacin: hot flushes? Tolerance of new PG inhibitor?  

Fibrates most logical choice as add-on therapy or in combination with statins
Nicotinic Acid

Nicotinic Acid is the most potent drug currently available to raise HDL cholesterol.
Mechanism of Action of Nicotinic Acid on HDL Cholesterol
Improvement of tolerability and efficacy of nicotinic acid is currently assessed in combination trials

- **Adverse effects with monotherapy**
  - Flushing
    - Commonest side-effect: 18%\(^1\)
  - Increases blood glucose and may reduce insulin sensitivity\(^2\)
    - May lead to new-onset diabetes in people with metabolic syndrome\(^3\)

- **Ongoing trials are exploring the benefits and safety of combination therapy**
  - AIM-HIGH: nicotinic acid + statin\(^4\)
  - HPS2-THRIVE: nicotinic acid + laropiprant\(^5\)

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5 – HPS2-THRIVE: www.clinicaltrials.gov/Show/NCT00461...
Atherogenic dyslipidemia and PPARα Receptors
PPARα discovery elucidates fibrates mechanism of action
Effects of PPARα activated on lipid metabolism
PPAR transcriptional activation
The PPARα-RXR complex recognizes genes carrying its response element: the PPRE.
Fibrates regulate lipid metabolism…

… by controlling the expression of PPARα target genes

**PPARα activators lower small dense LDL**

**Diagram:**
- **VLDL poor in apo C-III**
  - TG
  - CETP
  - Cholesteryl ester
- **Large buoyant LDL**
  - LDL receptor
- **VLDL rich in apo C-III**
  - Cholesteryl ester
  - CETP
- **LDL**
  - CETP
  - TG
  - Small dense LDL
- **Macrophage**

**References:**
PPARα and HDL metabolism

PPARα regulates 6 key genes involved in HDL metabolism
PPARα and reverse cholesterol transport

PPAR α activators increase cholesterol efflux and induce reverse cholesterol transport

Activated PPARα

Free cholesterol

Esterified cholesterol

↑ HDL rich in Apo A-I and Apo A-II

↑ ABCA-1

ABCG-1

↑ cholesterol efflux

Peripheral cell

↑ LPL

HDL

Pre β-HDL

LCAT

PLTP

SR-B1

cholesterol catabolism and elimination

Macrophage cholesterol trafficking

**LDL**

- LAL
- CE $\rightarrow$ FC
- early endosome

**SM + FC**

- ABCA1/G1

**CHOLESTEROL EFFLUX**

**β-oxidation**

- CPT-I
- mitochondria
- FA

**ACAT1**

- NCEH

**FOAM CELL FORMATION**

Chinetti-Gbaguidi G., Fruchart J.C., Staels B. et al., *J. lipid Res.*, 2005, 46, 2717-2725
PPARα induces NPC1, NPC2 and MLN64 gene expression in primary human macrophages
PPAR\(\alpha\) leads to cholesterol plasma membrane enrichment in macrophage foam cells

Control  
Bezafibrate

Fold increase of cholesterol oxidase accessibility

Cholesterol trafficking in macrophages

Activated PPARα

Lysosome

NPC1
NCP2
MLN64

Lipoproteins

ABCA1
ABCG1

ApoAI

Liver

Pre β-HDL

HDL

Fruchart J.C., Duriez P., "Drugs of Today", 2006, 42, 39-64
Effects of PPARα activated on vascular inflammation
PPARs in the vascular wall

PPARα and vascular inflammation

PPARα activators reduce inflammation and thrombogenesis by interfering with NFκB and AP-1 transcription factors.

Inhibition of NFκB-RE activation

↓ MMP, VCAM, TF... gene expression

Inhibition of AP-1 activation

PPARα overall vascular effects

- Thrombosis
- Plaque stability
- Vasoconstriction
- Cell migration
- Inflammatory response
- Cholesterol efflux
- Foam cell formation
- Cell recruitment and activation

- MMP-9, TXS, PAF, TF
- ET-1, MMPs, Ets-1, TXS
- TNFα, Interleukins, CRP, COX-2, VCAM-1, TF, Fibrinogen, sPLA₂
- ABCA1, SR-BI, CD36, SR-A

PPARα improves vascular function

PPARα overall vascular effects

Thrombosis
- Plaque stability
- MMP-9, TXS, PAF, TF

Vasoconstriction
- Cell migration
- ET-1, MMPs, Ets-1, TXS

Inflammatory response
- TNFα, Interleukins, CRP, COX-2,
  - VCAM-1, TF, Fibrinogen, sPLA2

Cholesterol efflux
- Foam cell formation
- ABCA1, SR-BI, CD36
  - SR-A

PPARα improves vascular function

Cell recruitment and activation
- MPC-1, CCR2, VCAM-1, ICAM-1, chemokines

Clinical benefits of PPARα activated by fibrates
Cardiometabolic risk
Dyslipidemia traditional risk factor

LDL-C is a well known risk factor.

But even with LDL-C brought within the normal range...there is still high residual cardiovascular risk.

So, what about triglycerides, low HDL-C, small dense LDL-C particles?
Dyslipidemia of Type 2 Diabetes and Metabolic Syndrome

Most Common Lipid Profile in Patients with Coronary Artery Disease (60%)

± LDL
Small, dense LDL

HDL-C

TG

Metabolic Syndrome
FCHL
Type 2 Diabetes
Polycystic ovarian syndrome
PPARα activation effects on CV risk factors and surrogate markers

Lipids
- ApoA1
- HDL
- TG
- LDL density

Vascular Function
- Flow mediated vasodilation

Coagulation
- Fibrinogen
- Tissue Factor

Inflammation
- ICAM1
- CRP
Lipid-Related Residual Risk
Atherogenic lipid profile

➢ Less benefits of statins in patients with
  ▪ Low HDL (4S, LIPID, CARE, WOSCOPS, AFCAPS/TexCAPS, HPS, TNT)
  ▪ Elevated TG
  ▪ Metabolic syndrome (WOSCOPS)
  ▪ Type 2 diabetes (ALLHAT-LLT, ASCOT-LLA)

➢ Atherogenic Lipid Profile commonly found in patients with MetS, prediabetes and diabetes
  ▪ Low HDL
  ▪ Elevated TG
  ▪ Preponderance of small, dense LDL particles

Statins address the LDL-related risk but not the other components of lipid risk
Reducing the Lipid-Related Residual Risk
Efficacy of fibrates, PPAR\(\alpha\) agonists

**HHS**
- Reduction of 34% of CHD events

**SAFARI trial**
- Additional effects of simvastatin/fenofibrate on all parameters of lipid risk, including LDL, HDL, TGs

**VA-HIT**
- Reduction of CV events (However, safety problems when gemfibrozil associated with statins)

**FIELD trial**
- Significant reduction of CV and CHD events when silent myocardial infarction is taken into account
- Reduction of microvascular disease
  - first demonstration of reduction of microvascular disease with lipid-modifying therapy so far
- Safety of combination with statins demonstrated

**ACCORD trial**
- Expected benefits of combination on both macro- and microvascular disease
1. Macrovascular outcomes
n=9,795 patients with T2DM
## FIELD Trial Outcomes

### Primary outcome
- First occurrence of nonfatal MI or CHD death

### Secondary outcomes
- **Total CVD events***
  - MI, stroke, CVD death, coronary and carotid revascularisation
- Coronary & peripheral revascularisation
- Stroke
- CHD deaths
- CVD deaths
- Total mortality

*Principal outcome for subgroup analyses

### Tertiary outcomes
- Progression of renal disease
- Laser treatment for diabetic retinopathy
- Non-fatal cancers
- Vascular & neuropathic amputations
- Hospitalisation for angina pectoris
- Hospital admissions
FIELD Trial
Significant absolute benefits and harms per 1000 persons treated over 5 years

- Nonfatal MI: P=0.01
- Total CVD: P=0.035
- Revasc: P=0.04
- ACS: P=0.003
- Amputation: P=0.011
- Laser Eye: P=0.0003
- Ur alb: P<0.002
- Pancreatitis: P=0.03
- Pulmonary embolism: P=0.02

macrovascular
microvascular
### FIELD Trial
Effects of fenofibrate according to MS features *

<table>
<thead>
<tr>
<th>MS feature</th>
<th>Placebo</th>
<th><strong>Fenofibrate</strong></th>
<th>ARR</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low HDLc</td>
<td>15.10%</td>
<td><strong>13.00%</strong></td>
<td>2.10%</td>
<td><strong>0.85</strong></td>
<td>0.74-0.97</td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td>TG&gt;150 mg/dL</td>
<td>15.40%</td>
<td><strong>13.60%</strong></td>
<td>1.80%</td>
<td><strong>0.88</strong></td>
<td>0.76-1.01</td>
<td><strong>0.07</strong></td>
</tr>
<tr>
<td>High waist</td>
<td>13.30%</td>
<td><strong>12.10%</strong></td>
<td>1.20%</td>
<td>0.9</td>
<td>0.79-1.03</td>
<td>0.13</td>
</tr>
<tr>
<td>Elevated BP</td>
<td>14.90%</td>
<td><strong>13.50%</strong></td>
<td>1.40%</td>
<td>0.89</td>
<td>0.80-1.00</td>
<td>0.06</td>
</tr>
<tr>
<td>Low HDLc + TG &gt; 200 mg/dL</td>
<td>17.80%</td>
<td><strong>13.50%</strong></td>
<td><strong>4.30%</strong></td>
<td><strong>0.74</strong></td>
<td>0.59-0.92</td>
<td><strong>0.01</strong></td>
</tr>
</tbody>
</table>

*ARR = Absolute Risk reduction; HR = Hazard Ratio

NNT=22
Patients with atherogenic dyslipidaemia benefited the most from fenofibrate treatment

Number needed to treat (NNT) to prevent one CV event in patients with T2D and atherogenic dyslipidaemia treated with fenofibrate: 23

2. Microvascular outcomes - pre-specified endpoints

<table>
<thead>
<tr>
<th>Laser therapy</th>
<th>progression of nephropathy</th>
<th>Amputations</th>
</tr>
</thead>
<tbody>
<tr>
<td>progression of retinopathy</td>
<td>albuminuria, eGFR</td>
<td>nontraumatic</td>
</tr>
</tbody>
</table>
Type 2 Diabetes and vascular complications
Lessons from the STENO 2 Study

Microvascular Complications
Despite an intensive treatment with OAD, antiHT, LLA + diet and lifestyle program, after a mean follow-up of 7.8 years still*:

34%: development of retinopathy
20%: development of nephropathy
50%: progression of peripheral neuropathy

Macrovascular Complications

*Cardiovasculaire death, MI, stroke, revascularisation, amputation

Diabetes and Eye

Intraocular damages

- Damaged cells lining walls of small blood vessels
- Blocked capillaries
- Increased levels of growth factors like VEGF
- Proliferative changes (bleeding, retinal detachment and blindness)
- Macular oedema (reduced reading and functional vision)
- Retinopathy
FIELD: Effects on Microvascular and Peripheral Vascular Disease

- Retinopathy needing laser therapy: 30% risk reduction, P<0.001
- Albumin Excretion Rate: 15% risk reduction, P=0.002
- Non-Traumatic Amputation: 38% risk reduction, P=0.01

Effects independent of the degree of glycemic control (HbA1c), Blood Pressure or concomitant medications!
Diabetes and Eye - FIELD and ACCORD Studies

Main Study findings

<table>
<thead>
<tr>
<th>Finding</th>
<th>Percentage</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First laser overall</td>
<td>-31%</td>
<td>0.0002</td>
</tr>
<tr>
<td>For maculopathy</td>
<td>-31%</td>
<td>0.002</td>
</tr>
<tr>
<td>For proliferative retinopathy</td>
<td>-30%</td>
<td>0.015</td>
</tr>
<tr>
<td>Total laser therapies</td>
<td>-37%</td>
<td>0.0003</td>
</tr>
<tr>
<td>All laser - primary</td>
<td>-49%</td>
<td>0.0002</td>
</tr>
<tr>
<td>Progression of retinopathy</td>
<td>-40%</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Diabetes and Eye - FIELD Study

Characteristics of fenofibrate effects on the eye

**Unique** as no other lipid modifying agent has been shown to significantly alter these clinically important effects of diabetes on the eye.

**Broad-based** as the benefits are reported across both types of diabetic retinopathy, in patients with and without retinopathy as baseline.

**Additive** to blood pressure and glycaemic control.

**Achieved rapidly** within eight months of starting treatment and increasing throughout the five years of the study.

Diabetes and Eye - FIELD Study
Clinical application - 5 years treatment with fenofibrate

With pre-existing retinopathy
Avoid first laser : NNT = 17
16 fewer multiple laser events per 100 Rx

Without known prior eye disease
Avoid first laser : NNT = 90
2,8 fewer multiple laser events per 100 Rx

FIELD Trial
Need for retinal laser therapy

Cumulative risk (%)

All retinopathy

HR 0.69 (95% CI 0.56-0.84) p=0.0002

Years after randomisation

Cumulative risk (%)

Number at risk

Placebo 4900 4784 4674 4559 4485 2524 837
Fenofibrate 4895 4797 4706 4626 4515 2540 845
Macrovascular Outcomes

ACCORD LIPID
**ACCORD Lipid**

31% reduction in events in patients with atherogenic dyslipidemia

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Simvastatin + Fenofibrate</th>
<th>Simvastatin + Placebo</th>
<th>Hazard ratio (95% CI)</th>
<th>p value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>10.5 (2765)</td>
<td>11.3 (2753)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Triglyceride – HDL-C combination</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>TG ≥204 mg/dL + HDL-C ≤34 mg/dL</td>
<td>12.4 (485)</td>
<td>17.3 (456)</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>All others</td>
<td>10.1 (2264)</td>
<td>10.1 (2284)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 20 patients with type 2 diabetes and atherogenic dyslipidemia needed to be treated for 5 years to prevent one CV event

1. Results reinforce the residual risk hypothesis

2. The combination of fenofibrate and simvastatin is safe

3. Lower incidence of micro and macroalbuminuria with fenofibrate-simvastatin

4. Residual risk attributable to atherogenic dyslipidemia was lower with the combination of fenofibrate and simvastatin
Meta-analysis of fibrate treatment of dyslipidemia

Both statins and fibrates should have an important role in the management of diabetes mellitus to prevent vascular complications.