Press Release aux USA sur une Etude Scientifique à l’USJ

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Professeur Associé en Médecine
Service de Cardiologie
Hôtel Dieu de France
Effect of Ezetimibe/Atorvastatin Combination on Oxidized LDL-Cholesterol in Patients With CAD or CAD Equivalent

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Données Connues Avant l’Etude
Risk of CAD according to LDL and HDL
20+ years of studies:
Patients with smaller LDL size have greater CHD risk at any given level of LDL-C.

Lower risk
130 mg/dL
Large LDL (Pattern A)

Higher risk
130 mg/dL
Small LDL (Pattern B)

But they also have more particles!
Stages of Atherosclerosis

LUMEN

LDL

INTIMA

MEDIA
Stages of Atherosclerosis

- **LUMEN**
- **LDL**
- **OXIDIZED LDL**
- **INTIMA**
- **Lp-PLA$_2$**
- **LYSO-PC OxF A**
- **MEDIA**
- **ADHESION MOLECULES**
Stages of Atherosclerosis

- **LUMEN**
- **MEDIA**
- **INTIMA**

**Components:**
- Oxidized LDL
- Lp-PLA₂
- Lyso-PC OxFA

**Cell Types:**
- Monocytes
- Macrophage
- Foam cell

**Processes:**
- Adhesion molecules
- Monocytes
- Cytokines

**Plaque formation**
Stages of Atherosclerosis

LUMEN

LDL petit

LDL Large

INTIMA

Oxidized LDL

Lyso-PC OxFA

LyP-PLA₂

MEDIA

Adhesion molecules

Monocytes

Cytokines

Foam cell

Macrophage

Plaque formation
Stages of Atherosclerosis

LUMEN

MEDIA

INTIMA

Cytokines

Plaque formation

Monocytes

Foam cell

Macrophage

Adhesion molecules

Lp-PLA₂

Lyso-PC OxFA

Oxidized LDL
oxLDL and oxLDL/HDL ratio are the best predictors of CAD

<table>
<thead>
<tr>
<th>Biological marker</th>
<th>Unadjusted odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>1.20 (0.93–1.56)</td>
</tr>
<tr>
<td>LDL</td>
<td>1.90 (1.44–2.51)</td>
</tr>
<tr>
<td>Lp-PLA2</td>
<td>2.02 (1.54–2.66)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>2.34 (1.79–3.05)</td>
</tr>
<tr>
<td>Total cholesterol/HDL</td>
<td>6.12 (4.56–8.20)</td>
</tr>
<tr>
<td>1/HDL</td>
<td>6.61 (4.93–8.86)</td>
</tr>
<tr>
<td>Oxidized LDL</td>
<td>8.26 (6.15–11.11)</td>
</tr>
<tr>
<td>Oxidized LDL/HDL</td>
<td>13.92 (10.07–19.23)</td>
</tr>
</tbody>
</table>

OR = odds ratio.

Johnston et al. Am J Cardiol 2006;97:640-645
Effect of Ezetimibe/Atorvastatin Combination on Oxidized LDL-Cholesterol in Patients With CAD or CAD Equivallent

Rabih Azar, Georges Badaoui, Antoine Sarkis, Mireille Azar, Hermine Aydanian, Serge Harb, Guy Achkouty and Roland Kassab

- Presented on March 14, 2010 at the Meeting of the American College of Cardiology in Atlanta, USA
- J Am Coll Cardiol March 2010 (abstract)
- Am J Cardiol July 2010 (manuscript)
- Sponsored by Pharmaline
Médicament testé dans l’étude

- L’ezetimibe : un nouveau médicament qui diminue l’absorption du LDL par l’intestin.

- Les effets de l’ezetimibe sur le LDL oxydé n’ont pas encore été investigués et demeurent inconnus
Hypothèse De L’Etude

L’Ezetimibe diminue le LDL oxydé chez des patients coronariens qui sont déjà traités une statine à dose optimale.
Design de l’Étude

• Prospective
• Randomisée
• Contrôlée par Placebo
• Double Aveugle
• 100 Patients coronariens
ox-LDL significantly decreased in the ezetimibe group but did not change in the placebo group. Baseline values are similar between the 2 groups. Final levels are lower in the ezetimibe group compared to the placebo group (p = 0.02).
Correlation Between the Changes in ox-LDL and Total LDL
Summary of Results: Effects of Atorvastatin and Ezetimibe on Various Lipid Parameters

<table>
<thead>
<tr>
<th></th>
<th>LDL</th>
<th>Large LDL</th>
<th>Small dense LDL</th>
<th>Particle size</th>
<th>HDL</th>
<th>VLDL</th>
<th>Ox-LDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>More potent statin</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td></td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Ezetimbe</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

The changes induced by statin are quantitative and **qualitative**
The Changes induced by ezetimibe are only quantitative
Ezetimibe reduces ox-LDL levels

*Am J Cardiol* 2010; 106: 193–197

*MedWire News*: Adding ezetimibe to atorvastatin decreases levels of oxidized low-density lipoprotein (ox-LDL) cholesterol in patients with coronary heart disease (CAD) or an equivalent condition, research shows.

"Ox-LDL level correlates with the vulnerability of atherosclerotic lesions," say Rabih Azar and colleagues from Hôtel Dieu de France Hospital in Beirut, Lebanon.

"Reduction of ox-LDL level by ezetimibe therapy may thus be considered a possible marker of plaque stabilization."
Ezetimibe reduces ox-LDL levels

Am J Cardiol 2010; 106: 993–997

MedWire News: Adding ezetimibe to atorvastatin decreases levels of oxidized low-density lipoprotein (ox-LDL) cholesterol in patients with coronary heart disease (CAD) or an equivalent condition, research shows.

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"Reduction of ox-LDL level by ezetimibe therapy may thus be considered a possible marker of plaque stabilization."

The team randomly assigned 100 patients with CAD or equivalent (diabetes, stroke, peripheral vascular disease) to receive atorvastatin 40 mg/day plus either ezetimibe 10 mg/day or placebo. Most patients had previously been taking statins, and had relatively low cholesterol levels.

After 8 weeks of treatment, patients taking ezetimibe had a larger average reduction in LDL cholesterol than those taking placebo, of 20% versus 10%. This was due to ezetimibe causing a larger reduction in levels of large, buoyant LDL, relative to placebo, with levels falling by 24% versus 10%.

"Thus, the change in lipid profile obtained by ezetimibe was mainly quantitative, while that observed by statins was quantitative and qualitative," say Azar et al.

Other studies have reported that ezetimibe reduces the largest subgroup of LDL. A study in healthy men, recently reported by MedWire News, showed that ezetimibe added to simvastatin also increased levels of small, dense LDL, resulting in an overall shift toward a more atherogenic profile.

In the current study, however, the two treatment groups had comparable falls in small, dense LDL, and ezetimibe also caused a significant reduction in ox-LDL levels, from 51 to 46 U/l, whereas these did not significantly change with placebo (50 to 51 U/l).

Changes in ox-LDL correlated with changes in LDL cholesterol and the large, buoyant LDL subfraction, but not with small, dense LDL, high-density lipoprotein, or LDL particle size.

The researchers say that small, dense LDL is most prone to oxidization. But the current findings suggest that if patients have fairly well-controlled lipid levels and low levels of small, dense LDL then large, buoyant LDL may be oxidized instead.

Large, buoyant LDL should therefore be "a target of therapy," in such patients, concludes the team in the American Journal of Cardiology.

MedWire (www.medwire-news.md) is an independent clinical news service provided by Current Medicine Group, a trading division of Springer Healthcare Ltd; 2010

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Messages
Closing the Gap in LDL-C Goal Attainment
Dr. Robert Vacek, Chief Scientific Officer, Piescorus-Heart Institute, Brought to you by Vacek & Co., Inc.
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Articles: Clinical Pharmacology for July 12, 2010
Today we found, sorted, and summarized:
6 new articles from 100 contributor journals scanned today (see the list)
Lipid-Altering Efficacy of Ezetimibe/Simvastatin 10/20 mg Compared to Rosuvastatin 10 mg in High-Risk Patients with and without Type 2 Diabetes Mellitus Inadequately Controlled Despite Prior Statin Monotherapy
Cardiovascular Drug Reviews
Sildenafil and Simpatozine Combination Therapy in Patients with Pulmonary Hypertension
Undergoing Ventilator Support
The Journal of Heart Valve Disease
Improvement of endothelial damage and regeneration indexes in patients with coronary artery disease after 4 weeks of statin therapy
Atherosclerosis
Effect of HMG-CoA reductase inhibitors on vascular cell apoptosis: Beneficial or detrimental
Atherosclerosis
Evolution of the lipid lowering ability, anti-inflammatory effects and clinical safety of intensive therapy with Zhibi, a Chinese traditional medicine
Atherosclerosis
Diurnal blood pressure variation, risk categories and antihypertensive treatment
Hypertension Research

Top Read Articles This Month
1. New oral anticoagulant drugs in cardiovascular disease
2. Effect of Ezetimibe/Simvastatin Combination on Cholesterol in Patients with Coronary Artery Disease
3. Dronedarone for the treatment of atrial fibrillation and atrial flutter: approval and efficacy

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1. New oral anticoagulant drugs in cardiovascular disease
   Thrombosis and Haemostasis

2. Effect of Ezetimibe/Atorvastatin Combination on Oxidized Low Density Lipoprotein Cholesterol in Patients With Coronary Artery Disease or Coronary Artery Disease Equivalent
   The American Journal of Cardiology

3. Dronedarone for the treatment of atrial fibrillation and atrial flutter: approval and efficacy
   Vascular Health and Risk Management
Conclusions

• Il est possible au Liban, de mener des études scientifiques innovantes

• Depuis que nous avons commencé nos projets de recherche à l’HDF en 2001, notre unité de recherche a réussi à présenter les résultats de plusieurs études au congrès de l’American College of Cardiology ou American Heart Association en
  • 2003
  • 2004
  • 2005
  • 2008
  • 2010

• Ceci est bien au-delà des autres institutions dans les pays Arabes ou d’autres institutions Libanaises (exemple : L’AUB qui bénéficie de moyen de recherche beaucoup plus important n’a présenté qu’en 2008)