Fibrates and Nicotinic Acid: Where did it all go wrong?

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Disclosures

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Fibrates and nicotinic acid have potentially beneficial effects on all plasma lipoprotein fractions.
## Effects of fibrates and nicotinic acid on plasma lipids

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Fibrates</th>
<th>Nicotinic Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma TG</td>
<td>↓ 35 – 40%</td>
<td>↓ 25 – 35%</td>
</tr>
<tr>
<td>HDL-C</td>
<td>↑ 2 – 15%</td>
<td>↑ 15 – 25%</td>
</tr>
<tr>
<td>LDL-C</td>
<td>↑ 5% - ↓ 15%</td>
<td>↓ 5% - 15%</td>
</tr>
<tr>
<td>Lp(a)</td>
<td></td>
<td>↓ 20 – 30%</td>
</tr>
</tbody>
</table>
But the results of CV clinical outcome trials with both fibrates and nicotinic acid have been mixed.

Both agents have failed to reduce the risk of having a cardiovascular event when used in clinical trials of patients being treated with statins.
## Human Clinical Endpoint Studies with Fibrates

<table>
<thead>
<tr>
<th></th>
<th>Fibrate</th>
<th>On a statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO</td>
<td>clofibrate</td>
<td>No</td>
</tr>
<tr>
<td>HHS</td>
<td>gemfibrozil</td>
<td>No</td>
</tr>
<tr>
<td>VA-HIT:</td>
<td>gemfibrozil</td>
<td>No</td>
</tr>
<tr>
<td>BIP</td>
<td>bezafibrate</td>
<td>No</td>
</tr>
<tr>
<td>FIELD:</td>
<td>fenofibrate</td>
<td>No</td>
</tr>
<tr>
<td>ACCORD:</td>
<td>fenofibrate</td>
<td>Yes</td>
</tr>
</tbody>
</table>
## Human Clinical Endpoint Studies with Fibrates

<table>
<thead>
<tr>
<th>Fibrates</th>
<th>Trial Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WHO:</strong></td>
<td>clofibrate</td>
</tr>
<tr>
<td><strong>HHS:</strong></td>
<td>gemfibrozil</td>
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</tr>
<tr>
<td><strong>ACCORD:</strong></td>
<td>fenofibrate</td>
</tr>
</tbody>
</table>
But while BIP with bezafibrate and FIELD and ACCORD with fenofibrate failed to achieve their primary endpoints, treatment with these fibrates significantly reduced ASCVD events in people with elevated plasma triglyceride and low HDL-C, especially if associated with obesity.
So, what are the effects of fibrates in subgroups with elevated plasma triglyceride, low HDL-C and obesity in the fibrate trials?
Helsinki Heart Study

A randomized, placebo-controlled trial of gemfibrozil in people with elevated levels of non-HDL-C

Treatment with gemfibrozil produced a significant 34% reduction in the incidence of nonfatal MI and CHD death

Helsinki Heart Study: Total population

The reduction in events in this trial were even greater in people with elevated plasma TG, low HDL-C and higher BMI.
Helsinki Heart Study: effects of baseline TG on CHD Events

Manninen et al, Circulation, 1992
Helsinki Heart Study: effects of baseline TG on response to treatment

Manninen et al, Circulation, 1992
Helsinki Heart Study: effects of baseline TG on response to treatment

Total population

TG ≤ 200 mg/dl

TG > 200 mg/dl

Manninen et al, Circulation, 1992
Helsinki Heart Study: effects of baseline HDL-C on CHD events

Manninen et al, Circulation, 1992
Helsinki Heart Study: effects of baseline HDL-C on response to treatment

- Total population
  - HDL-C ≥ 40 mg/dl: 34%
  - HDL-C < 40 mg/dl: 44%
  - HDL-C ≥ 40 mg/dl: 23%

Manninen et al, Circulation, 1992
Helsinki Heart Study: effects of BMI on response to treatment

Tenkanen et al, Circulation, 1995
Helsinki Heart Study: effects of BMI on response to treatment

Tenkanen et al, Circulation, 1995
Helsinki Heart Study: combined effects of BMI and dyslipidemia on CHD events

Tenkanen et al., Circulation, 1995
Helsinki Heart Study: combined effects of BMI and dyslipidemia on CHD events

Tenkanen et al, Circulation, 1995
BIP Study

A randomized, placebo-controlled trial of bezafibrate in people with manifest ASCVD.

Treatment with bezafibrate produced a non-significant 9% reduction in the incidence of nonfatal MI and CHD death.

BIP Study Group, Circulation, 2000;102:21-7
BIP Study: Total population

CHD events/1000

Total population

P 9%
B

BIP Study Group, Circulation, 2000;102:21-7
But there was a significant reduction in events in people with features of the metabolic syndrome
BIP Study: effects of baseline TG on response to treatment

BIP Study Group, Circulation, 2000;102:21-7
BIP Study: effects of baseline TG on response to treatment

BIP Study Group, Circulation, 2000;102:21-7
## BIP Study: Impact of bezafibrate on outcome of patients with Metabolic Syndrome

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>All patients (n = 1470)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>0.67</td>
</tr>
<tr>
<td>Any myocardial infarction</td>
<td>0.71</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>0.74</td>
</tr>
<tr>
<td>Total death</td>
<td>0.9</td>
</tr>
</tbody>
</table>

### BIP Study: Influence of bezafibrate on outcome in patients with 4-5 features of the Metabolic Syndrome

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Patients with augmented features of metabolic syndrome (n = 575)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>0.66</td>
</tr>
<tr>
<td>Any myocardial infarction</td>
<td>0.65</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>0.44</td>
</tr>
<tr>
<td>Total death</td>
<td>0.76</td>
</tr>
</tbody>
</table>

FIELD Study

A randomized, placebo-controlled trial of fenofibrate in people with type-2 diabetes

Treatment with fenofibrate produced a non-significant 11% reduction in the incidence of nonfatal MI and CHD death

FIELD Study: Result in Total Population

But there was a significant reduction in events in people with elevated levels of plasma triglyceride
FIELD Study: effects of baseline TG on CHD Events

- Normal TG, normal HDL-C
- High TG, low HDL-C

FIELD Study: effects of baseline TG on response to treatment

FIELD Study: effects of baseline TG on response to treatment

ACCORD Study

The lipid arm of the ACCORD study was randomized, placebo-controlled trial of fenofibrate in statin-treated people with type-2 diabetes.

Treatment with fenofibrate produced a non-significant 8% reduction in the incidence of nonfatal MI and CHD death.
ACCORD Study: Results in Total Population

But, again, there was a significant reduction in events in people with the combination of high plasma triglyceride and low HDL-C
ACCORD Study: effects of baseline TG and HDL-C on response to treatment

- Total population
  - CHD events/1000: P = 8%

- TG > 204 mg/dl, HDL-C < 34 mg/dl
  - CHD events/1000: P

ACCORD Study: effects of baseline TG and HDL-C on response to treatment

Subgroup analyses of fibrate studies

<table>
<thead>
<tr>
<th>Trial (treatment)</th>
<th>Primary endpoint:</th>
<th>Lipid subgroup criteria (mg/dL)</th>
<th>Primary endpoint: Subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACCORD Lipid</strong> (fenofibrate)</td>
<td>-8% (p=0.32)</td>
<td>TG ≥ 200 + HDL-C ≤ 34</td>
<td>-31% (p=0.05)</td>
</tr>
<tr>
<td><strong>FIELD</strong> (fenofibrate)</td>
<td>-11% (p=0.16)</td>
<td>TG ≥ 200 + Low HDL-C</td>
<td>-27% (p=0.005)</td>
</tr>
<tr>
<td><strong>BIP</strong> (bezafibrate)</td>
<td>-7.3% (p=0.24)</td>
<td>TG ≥ 200</td>
<td>-39.5% (p=0.02)</td>
</tr>
<tr>
<td><strong>Helsinki Heart Study</strong></td>
<td>-34% (p=0.02)</td>
<td>TG &gt; 200</td>
<td>-56% (p&lt;0.005)</td>
</tr>
</tbody>
</table>
Conclusions from Fibrate Trials

There is a consistent finding in the fibrate trials of a reduction in ASCVD events in people with high TG and low HDL-C, whether or not they are treated with a statin.

There is a clear need to conduct a trial with fibrates in such a population.
Niacin
Rationale for using niacin

- Niacin increases the level of HDL-C by up to 30%
- It reduces the level of plasma triglyceride by up to 30%
- It reduces the level of LDL-C by about 15%
- Given as monotherapy, niacin reduces CV events
- Given in combination with a statin, niacin promotes regression of atherosclerosis as assessed by measuring carotid intima-media thickness

Taylor et al. NEJM 2009; 361:2113-2122
Niacin reduces CV events: results from secondary prevention studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment(s)</th>
<th>Duration (y)</th>
<th>Efficacy results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Drug Project (CDP)</td>
<td>Nicotinic acid</td>
<td>5</td>
<td>Nonfatal MI ↓27%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15</td>
<td>Stroke/TIA ↓24%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total mortality ↓11%</td>
</tr>
<tr>
<td>Stockholm Ischaemic Heart Disease study (IHD)</td>
<td>Nicotinic acid + clofibrate</td>
<td>5</td>
<td>Total mortality ↓26%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IHD mortality ↓36%</td>
</tr>
</tbody>
</table>

Niacin promotes regression of atherosclerosis

ARBITER-6 HALTS

This trial in statin treated patients compared the effects of ezetimibe (added to the statin to achieve further lowering of LDL-C) with those of niacin (added to the statin to achieve not only additional lowering of LDL-C but also raising of HDL-C).
Change from Baseline in Mean cIMT

- Niacin
- Ezetimibe

P = 0.003

Taylor et al. NEJM 2009; 361:2113-2122
But niacin has not been shown to reduce clinical cardiovascular events in statin-treated patients?
AIM HIGH: Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes

3300 patients

- Men and women
- Aged ≥45 years
- Established vascular disease and atherogenic dyslipidemia (low HDL-C and high triglycerides)

Primary End Point

- Composite of CHD death, nonfatal MI, ischemic stroke, or hospitalization for high-risk ACS with objective evidence of ischemia

Key Secondary End Points

- Composite of CHD death, nonfatal MI, or ischemic stroke

Simvastatin ≥40 mg + ER niacin 2 g

Simvastatin ≥40 mg

4-year follow-up

clinicaltrials.gov/ct/show/NCT00120289
This was an event driven trial designed to have an 85% power to detect a 25% reduction in cardiovascular events.

It was calculated that a sample size of 3400 participants followed for 2.5 - 7 years would generate the required 800 primary events.

However, the study was terminated early on the basis of futility at which time there had been about 550 primary events.
AIM-HIGH

- The on-treatment difference in HDL-C levels between the two groups was only 4 mg/dL.
- The on-treatment difference in plasma TG levels between the two groups was ?? mg/dL.
- The on-treatment difference in LDL-C level between the two groups was 5 mg/dL.

AIM-HIGH

From population studies, these on-treatment lipid levels in the two groups predict a CV event rate in the niacin group approximately 8% lower than in the placebo group.

Note: A predicted 8% lower event rate is only about one third the predicted 25% reduction on which the power calculations were based.
This trial did not have the power to detect an 8% reduction in events.

So, whatever, conclusions are drawn from this trial, it did NOT test the hypothesis that treatment with niacin reduces CV risk in statin-treated patients.
AIM-HIGH

But:

In a subgroup (n = 439) of participants with TGs ≥200 mg/dl and HDL-C <32 mg/dl, there was a 36% reduction in events (p = 0.032).

HPS2—THRIVE: Treatment of HDL to Reduce the Incidence of Vascular Events

25,000 patients
- Men and women
- Aged 50-80 years
- History of MI, stroke, or PAD
- ~7,000 patients with diabetes
- Coordinating centers in UK, China, and Scandinavia

Primary End Point
- MI, stroke, revascularization procedures

Statin therapy to optimal LDL-C level
- ER-Niacin + Laropiprant
- Placebo

4-year follow-up

clinicaltrials.gov/ct2/show/NCT00461630
This study tested the effects of niacin in statin-treated people in whom the LDL-C had been already reduced to very low levels and in whom the level of HDL-C was not low.
Baseline LIPID Levels

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD) baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg/dL</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>128 (22)</td>
</tr>
<tr>
<td>Direct-LDL</td>
<td>63 (17)</td>
</tr>
<tr>
<td>HDL</td>
<td>44 (11)</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>125 (74)</td>
</tr>
</tbody>
</table>

# Effects of ER niacin/laropiprant on lipid levels

<table>
<thead>
<tr>
<th>Year of FU</th>
<th>LDL-C (mg/dL)</th>
<th>HDL-C (mg/dL)</th>
<th>Triglyceride (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-12</td>
<td>6</td>
<td>-35</td>
</tr>
<tr>
<td>4</td>
<td>-7</td>
<td>6</td>
<td>-31</td>
</tr>
<tr>
<td>STUDY AVERAGE</td>
<td>-10</td>
<td>6</td>
<td>-33</td>
</tr>
</tbody>
</table>

The authors concluded that these changes in LDL-C and HDL-C would have been expected to reduce the risk of having a major vascular event by about 10%, which is compatible with the observed result.
Effect of ERN/LRPT on MAJOR VASCULAR EVENTS

Risk ratio 0.96 (95% CI 0.90 – 1.03)
Logrank P=0.29

HPS2-THRIVE

Serious Adverse Effects

- Increased risk of myopathy among patients in China
- Increase in risk of GI bleeding
- Increased risk of strokes
- Increase risk of infections

HPS2-THRIVE

Serious Adverse Effects

Over 4 years, ER niacin/laropiprant caused serious adverse effects in approximately 30 patients per 1000
It should be noted that the absence of a positive result in HPS2-THRIVE does not refute the hypothesis that there would have been significant beneficial effects had there been greater reductions in levels of LDL-C and/or greater increases in HDL-C.
Conclusions from Niacin Trials

While the results of AIM-HIGH and THRIVE do not exclude the possibility of beneficial effects of niacin in statin-treated patients, in the absence of a trial showing benefit, niacin will most likely disappear as a therapy to reduce ASCVD.
Conclusions

In the light of the recent trials with niacin, it is likely that the use of this agent will decline and probably disappear completely.

The future of fibrates will depend on results of a trial to be conducted in people with elevated TG and low HDL-C. If such a trial provides results comparable to the subgroup analyses of the previous fibrate trials, it is likely that the use of these agents will greatly increase.