Comments on HPS2-THRIVE

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Comments on HPS2-THRIVE
Treatment of HDL to Reduce the Incidence of Vascular Events

1. Lipid-targeted therapies – what should be added to statins?
2. Niacin – the first lipid-modifying drug - what have we learnt?
3. Comments on HPS2-THRIVE analysis
4. Comparison between AIM-HIGH and HPS2-THRIVE
Lipid-targeted Therapies - What should be added to statins in patients with high vascular risk?

- **NPC1L1** (Ezetimibe*)
- **CETP inhibition** (Anacetrapib*, Evacetrapib*)
- **Reconstituted HDLs**
- **ApoA1 modulation**

Further LDL-C ↓

Combined LDL-C ↓ HDL-C ↑

HDL-C ↑

- **PCSK9 inhibition** (Monoclonal Ab*)
- **ApoB-100 Antisense oligonucleotides**
- **Niacin/Laropiprant***
- **CETP inhibition** (Anacetrapib*, Evacetrapib*)

*Clinical outcome trials ongoing
Effect of HDL on monocyte adhesion to TNFα-stimulated endothelial cells

Role of HDL function versus HDL cholesterol levels?
Different effects of HDL from patients with CAD on inflammatory activation

Niacin – the first lipid-modifying drug

1955  Niacin (vitamin B3) - first antidyslipidemic agent  (>50 years of clinical use)

1975  Coronary Drug Project  
(1,119 patients on niacin)

2003  Discovery of niacin receptor (GPR109A)

2009  Coadministration of DP₁ antagonist laropiprant reduces flushing  (1,455 patients)
Proposed model of niacin-associated adverse skin effects

Dunbar RL, Gelfand JM. *J Clin Invest* 2010;120: 2651-5
Withdrawal of active ER-Niacin/laropiprant before randomization:

For any medical reason: 25.4 %
- Skin (11.3. %)  
  (Pruritus, rash, flashing)
- GI symptoms (5.5%)

Withdrawal in randomized treatment phase:

- Skin symptoms (5.1 vs. 1.2 %)  
  (mostly pruritus)
- GI symptoms (3.6 vs. 1.6 %)  
  (upper and lower GI)

Approximately 2/3 of patients can tolerate ER-Niacin/laropiprant therapy
Comments on HPS2-THRIVE: Safety analyses

Myopathy increased: 62/69 (0.5%) vs. 10/12 (0.1%)

Rhabdomyolysis: 7 (0.05%) vs. 3 (0.02%)

Severe liver disease (3x ULN + bilirubin ≥2x ULN): 15 (0.1%) vs. 18 (0.1%)

FDA approved label change for simvastatin:
"Patients of Chinese descent should not receive simvastatin 80 mg with cholesterol-modifying doses of niacin-containing products. Caution is recommended when such patients are treated with simvastatin 40 mg or less in combination with cholesterol-modifying doses of niacin-containing products."

Largely in patients with Chinese descent

Caution in patients with Chinese descent (myopathy)
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2011  AIM-HIGH Study

2013  Clinical outcome data of HPS2-THRIVE
Comparison of AIM-HIGH and HPS2-THRIVE

AIM-HIGH trial
(N Engl J Med 2011)

- Pre-randomisation phase with niacin (1.5/2g) exclusion: 20.1%
- Aiming to have similarly low LDL-C in both treatment groups
  LDL: -5.5%, HDL: +13.2%
- More patients on high-dose statin and ezetimibe in control-group
- Randomization (n): 1718 vs. 1696 patients
- Mean FU - 3 years (556 events)

HPS2-THRIVE trial

- Pre-randomisation phase with ER-niacin (2g)/laropiprant exclusion: 25.4%
- No further adjustment of LDL-C levels after randomization
  LDL: -20%; HDL + 17%
- Addition of laropiprant (Antagonist of PGD2 receptor DP1)
- Randomization (n): 12838 vs. 12835 patients
- Mean FU - 4 years (? events)

HPS2-THRIVE clinical outcome data (presentation expected in 2013)
Thank you
(I) HDL-C raising can be due to increased production and/or reduced catabolism

(1) apoA-I (lipid-free)

(2) ABCA-1 expression

(3) CETP inhibition

(4) SR-BI inhibition