Preventive Cardiology

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Conflicts of Interest
Speaker/advisor/research grant for Actelion, Sanofi, Servier, Toshiba
TOPIC 1 ➔ SIGNIFY

TOPIC 2 ➔ SOLID-TIMI 52

TOPIC 3 ➔ ODYSSEY
  FH I / FH III / COMBO II / LONG TERM

/f inhibition

Lp-PLA$_2$

PCSK9
Study design

**Population**

- ≥ 55 years, stable CAD (With at least one other CV risk factor (including angina CCS class ≥ II))
- Without clinical heart failure (LVEF > 40%)
- HR ≥ 70 bpm

Ivabradine 7.5 mg bid

- Matching placebo, bid

Run-in 14 to 30 days

Ivabradine 5, 7.5, or 10 mg bid according to heart rate (target 55-60 bpm) and tolerability

Every 6 months

Study design

Population

- ≥ 55 years, stable CAD (With at least one other CV risk factor (including angina CCS class ≥ II))
- Without clinical heart failure (LVEF >40%)
- HR ≥ 70 bpm

Primary composite end point:
Cardiovascular death or nonfatal myocardial infarction

- Primary analysis: Ivabradine versus placebo on primary end point
- Prespecified analysis: in patients with angina CCS class ≥ II on primary end point

Patients and follow-up

Preventive Cardiology

19,102 patients randomized

Ivabradine (n=9550)
- 235 had incomplete follow-up
  - 231 withdrew consent
  - 3 lost to follow-up
  - 1 medical reason

Placebo (n=9552)
- 230 had incomplete follow-up
  - 199 withdrew consent
  - 1 lost to follow-up

9550 analyzed
- 6037 with angina
- 3513 with no angina

9552 analyzed
- 6012 with angina
- 3540 with no angina
Mean heart rate reduction

Mean reduction = 9.7 bpm
95% CI [-10.0 ; -9.5]

Placebo

Ivabradine
Primary composite end point

Ivabradine n=654 (3.03% PY)  
HR = 1.08 [95% CI 0.96-1.20]  
P=0.20

Placebo n=611 (2.82% PY)
Incidence of selected adverse events (n=19,083)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Ivabradine (n=9539) % (n)</th>
<th>Placebo (n=9544) % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic bradycardia</td>
<td>7.9 (757)</td>
<td>1.2 (110)</td>
</tr>
<tr>
<td>Asymptomatic bradycardia</td>
<td>11.0 (1047)</td>
<td>1.3 (126)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5.3 (508)</td>
<td>3.8 (362)</td>
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<tr>
<td>Phosphenes</td>
<td>5.4 (512)</td>
<td>0.5 (52)</td>
</tr>
</tbody>
</table>
Effect of Ivabradine on symptoms (angina population: CCS class ≥ II, n=12,049)

Improvement in CCS class at M3

Elective revascularization
Ivabradine 2.8%  Placebo 3.5%
HR 0.82 (p=0.058)

P<0.01

Patients (%)

Improvement in CCS class Worsening in CCS class at M3

Ivabradine Placebo

24.8  19.4

0.31  0.55
Primary composite end point
(angina population: CCS class ≥II, n=12 049)

Ivabradine n=459 (3.37% PY)
HR = 1.18 [95% CI 1.03-1.35]

Placebo n=390 (2.86% PY)

$P=0.018$

Numbers at risk

<table>
<thead>
<tr>
<th></th>
<th>Ivabradine</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>6037</td>
<td>5869</td>
<td>5712</td>
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<tr>
<td>5712</td>
<td>5428</td>
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<td>227</td>
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<tr>
<td>227</td>
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</tbody>
</table>

Time from randomization (months)

Patients with event (%)

ESC CONGRESS
BARCELONA 2014

www.escardio.org/esc2014

#esccongress
TOPIC 1 ➔ SIGNIFY /$_f$ inhibition

TOPIC 2 ➔ SOLID-TIMI 52 Lp-PLA$_2$

TOPIC 3 ➔ ODYSSEY PCSK9
   FH I / FHIII / COMBO II / LONG TERM
Lipoprotein- associated Phospholipase A2 (Lp-PLA2): Background

- **Lumen**: Native LDL carrier of Lp-PLA2
- **Intima**: Oxidized LDL substrate for Lp-PLA2
- **Leukocyte**: Sustained Inflammation, Necrotic Core Expansion

Lp-PLA$_2$ activity and risk of CV outcomes

79,036 participants, 32 prospective studies

Adjusted for age, sex, diabetes and baseline history of vascular disease

Lp-PLA$_2$ Studies Collaboration. *Lancet* 2010;375:1536-44
Darapladib Phase III Clinical Programme

ACS patients (NSTE- or STE-ACS) with high-risk features*

Randomization ≤30 days from hospitalization with ACS

Randomization to Darapladib or Placebo

n= 13,026 (2.5 year median follow-up)

* High-risk criteria (≥1 of the following): age ≥60 years, diabetes mellitus requiring Rx, eGFR 30-59 ml/min/1.73 m2, polyvascular disease, HDL <40 mg/dl (STABILITY only), tobacco use (STABILITY only), or prior MI (SOLID-TIMI 52 only)
SOLID TIMI 52: Lp-PLA₂ inhibition in ACS

High-risk* patients ≤30 days post-ACS: UA, NSTEMI or STEMI

Total N 13,026

Guideline-recommended background Rx, including statins and antiplatelet drugs

Randomized 1:1 Double-blind

Darapladib (160mg daily)

Placebo (daily)

Median f/u 2.5y

Primary Endpoint: CHD Death, Non-fatal MI, or Urgent Coronary Revascularization for Myocardial Ischemia

* Must have met ≥1 enrichment criteria
Primary endpoint: CHD death, MI or urgent coronary revascularization

HR 1.00 (95% CI 0.91-1.09)
P=0.93
TOPIC 1 ➔ SIGNIFY

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TOPIC 3 ➔ ODYSSEY

FH I / FH II / COMBO II / LONG TERM

/\_f inhibition

Lp-PLA\_2

PCSK9
PCSK9 – A novel target to lower LDL

Monoclonal AB
## PCSK9 Inhibitors in development

<table>
<thead>
<tr>
<th>Investigational Product</th>
<th>Company</th>
<th>Stage of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monoclonal antibodies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alirocumab (SAR236553, REGN727)</td>
<td>Sanofi (Regeneron)</td>
<td>Phase III</td>
</tr>
<tr>
<td>AMG 145</td>
<td>Amgen</td>
<td>Phase III</td>
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<tr>
<td>PF-0490615 (RN316)</td>
<td>Pfizer (Rinat)</td>
<td>Phase IIb</td>
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<td>LY3015014</td>
<td>Lilly</td>
<td>Phase I</td>
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<tr>
<td><strong>PCSK9 synthesis inhibitor/siRNA</strong></td>
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<tr>
<td>Alnylam</td>
<td>ALN-PCS02</td>
<td>Phase I</td>
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<tr>
<td>Bristols Myers Squibb/Adnexus</td>
<td>BMS-962476 (Adnectin)</td>
<td>Phase I</td>
</tr>
<tr>
<td><strong>Small molecule</strong></td>
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<tr>
<td>Serometrix</td>
<td>SX-PCK9</td>
<td>Preclinical</td>
</tr>
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Overview of studies presented at ESC-2014 from the ODYSSEY Phase 3 Programme

**HeFH population**

- **ODYSSEY FH I** (NCT01623115; EFC12492)
  - LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
  - n=486; 18 months

- **ODYSSEY FH II** (NCT01709500; CL1112)
  - LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
  - n=249; 18 months

**HC in high CV-risk population**

- **ODYSSEY LONG TERM** (NCT01507831; LTS11717)
  - LDL-C ≥70 mg/dL
  - n=2,341; 18 months

- **ODYSSEY COMBO II** (NCT01644188; EFC11569)
  - LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
  - n=720; 24 months

Add-on to max tolerated statin (± other LLT)
ODYSSEY LONG TERM Study Design

HeFH or High CV-risk patients
On max-tolerated statin ± other lipid-lowering therapy
LDL-C ≥ 1.81 mmol/L [70 mg/dL]

Double-blind treatment (18 months)

n=1553

Alirocumab 150 mg Q2W SC
(single 1-mL injection using prefilled syringe for self-administration)

n=788

Placebo Q2W SC

Assessments

W0 W4 W8 W12 W16 W24 W36 W52 W64 W78

Follow-up (8 weeks)

86% (2011/2341) completed 52 weeks (both treatment arms)
26.1% (405/1553 alirocumab) and 25.6% (202/788 placebo) had completed 78 weeks by time of this analysis
Mean treatment duration: 65 weeks (both treatment arms)

Primary efficacy endpoint

Pre-specified analysis
Efficacy: All Patients To W52
Safety: Baseline-W78
(all patients at least W52)

ClinicalTrials.gov identifier: NCT01507831.
Alirocumab maintained consistent LDL-C reductions over 52 weeks.

Achieved LDL-C Over Time
All patients on background of maximally-tolerated statin ± other lipid-lowering therapy

**Purpose:**

*Intention-to-treat (ITT) analysis*

**Graph:**

- **Placebo**
  - 3.1 mmol/L (118.9 mg/dL)
  - 3.2 mmol/L (123.0 mg/dL)

- **Alirocumab**
  - 1.3 mmol/L (48.3 mg/dL)
  - 1.4 mmol/L (53.1 mg/dL)
Post-hoc adjudicated cardiovascular TEAEs† safety analysis (at least 52 weeks for all patients in ongoing study)

Kaplan-Meier Estimates for Time to First Adjudicated Major CV Event
Safety Analysis (at least 52 weeks for all patients continuing treatment, including 607 patients who completed W78 visit)

Cox model analysis:
HR=0.46 (95% CI: 0.26 to 0.82)
Nominal p-value = <0.01

Mean treatment duration: 65 weeks
SIGNIFY: Lowering heart rate by $/f$ inhibition with ivabradine in stable CAD patients without clinical heart failure does not reduce risk of CV death or nonfatal MI

SOLID-TIMI 52: Lp-PLA2 inhibition by Darapladip failed to reduce cardiovascular events in patients after ACS

ODYSSEY: PCSK9 inhibition by alirocumab efficiently reduces LDL-C in addition to maximally tolerated statin therapy. A post-hoc safety analysis showed a lower rate of adjudicated major CV events.
Spotlight
ENVIRONMENT AND THE HEART
Where cardiology comes together