Role of PCSK9 Inhibitors in Diabetes: Indications for Use and Avoiding Misuse

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Overview Talk

• Review of pathogenesis of atherosclerosis and residual risk
• In patients with diabetes need to go beyond LDL biomarker and assess non-HDL cholesterol
• Review of PCSK9 Inhibitors and their role in reducing LDL in patients with diabetes
• Impact of PCSK9 inhibitors on glucose levels in diabetics
• Avoiding misuse of PCSK9 inhibitors
Pathogenesis of Atherosclerosis

- Atherosclerosis is a DIFFUSE DISEASE driven by inflammation, atherogenic lipoproteins and in the acute phase platelet aggregation.
- Serial angiographic studies reveal culprit lesion of a future acute MI often does not cause significant stenosis.
- A multi biomarker strategy is needed for better risk factor stratification.

Libby, NEJM 2013

Plaque can cause outward expansion of the artery wall which accommodates the growth of the plaque and minimizes luminal narrowing.

Luminal stenosis occurs late in the process of atherosclerosis.

Angiography is an assessment of luminal narrowing.

Libby, NEJM 2013
Medical Management = PCI

- Landmark clinical trials such as COURAGE show that medical treatment of chronic angiographically defined CAD has the same outcome as percutaneous coronary intervention
- The cornerstone of medical management of CAD is treatment of dyslipidemia.

**Key Finding:**
- Intensive lipid-lowering treatment with atorvastatin for 18 months reduced progression of coronary atherosclerosis compared with pravastatin in CAD patients

Better Biomarkers are needed to address Residual Risk

Residual CVD Risk in Statin vs Placebo Trials
Many CHD Events Still Occur in Statin-Treated Patients

25-40% CVD Reduction Leaves High Residual Risk

**Residual risk:** Due to increased triglycerides, elevated Lp(a), other untreated risk factors

**IMPROVE-IT Study**

Residual risk: Due to increased triglycerides, elevated Lp(a), other untreated risk factors

Cannon et al NEJM 2015
The Lipid Profile Is Different In Patients With Diabetes

- Increase in triglycerides
- Decrease in HDL cholesterol
- Predominance of small dense LDL particles and increased number of particles


From Sanofi LPS Investigator meeting Slides.

Even LDL Particles of the Same Size can Differ in Cholesterol Content

Adapted from Otvos JD, Jayarajah E, Cromwell, WC. AJC 2002;90(8A):22i-29i
Beyond LDL Cholesterol in Diabetics

- LDL-C: amount of cholesterol in LDL particles
- LDL-P: number of LDL particles
- Apo-B: reflection of number of atherogenic particles
- Non-HDL: (Total cholesterol - HDL) amount of cholesterol in atherogenic particles
- Low HDL and high TG are associated with higher LDL-P
  - If triglycerides are high there will be less space for cholesterol and it may take more LDL particles to carry a given amount of cholesterol

Atherosclerosis is a Gradient Driven Process

LDL particle number (LDL-P), as opposed to size, is a key driver of atherogenic plaque formation

- After adjustment for LDL-P concentration, particles subclass and size do not impact outcomes

References:
1. Fredricson et al. JAMA 1987; 259: 1183
MESA: LDL-P and LDL-C Discordance Relations with Incident CVD Events (n=319)

Follow-up (years)
0 1 2 3 4 5 6
Cumulative Incidence
0.02
0.04
0.06

LDL-P > LDL-C
Concordant
LDL-P < LDL-C

LDL-C underestimates LDL-attributable risk
LDL-C overestimates LDL-attributable risk

MetSyn
LDL-C
LDL-P
54%
104
1372
33%
117
1249
16%
130
1117
mg/dL nmol/L


PCSK9 Regulates LDLR Turnover Through Increased Intracellular Degradation

LDL (hepatic)
PCSK9
Vesicle
Endosome
Lysosome
Degradation
Fusion
Fusion
Endocytosis
ARH
Secretion

LIPID & METABOLIC
Blocking PCSK9 Activity Inhibits Intracellular Degradation of LDLR

Odyssey Trial Results

Figure 2. Calculated LDL Cholesterol Levels over Time (Intention-to-Treat Analysis).

Calculated LDL cholesterol levels are shown in milligrams per deciliter (left axis) and millimoles per liter (right axis). Values above the data points indicate least-squares mean absolute LDL cholesterol levels, and values below the data points indicate least-squares mean percentage changes from baseline. Values below the chart indicate the number of patients with LDL cholesterol values available for the intention-to-treat analysis at each time point; those include levels measured while the study drug was being taken and, in the case of patients who discontinued the study drug but returned to the clinic for assessments, after the study drug was discontinued. Missing data were accounted for with the use of a mixed-effects model with repeated measures. For statin therapy, the maximum tolerated dose was the highest dose associated with an acceptable side-effect profile. LLT denotes lipid-lowering therapy.
Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>Individuals with DM (N=838)</th>
<th>Individuals without DM (N=1503)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alirocumab 150 mg Q2W (n=559)</td>
<td>Placebo (n=279)</td>
</tr>
<tr>
<td>Age, years</td>
<td>61.7 (9.6)</td>
<td>61.0 (10.1)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>327 (58.5)</td>
<td>144 (51.6)</td>
</tr>
<tr>
<td>Race, white, n (%)</td>
<td>477 (85.3)</td>
<td>237 (84.9)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>32.0 (6.2)</td>
<td>32.7 (5.7)</td>
</tr>
<tr>
<td>HeFH, n (%)</td>
<td>38 (6.8)</td>
<td>20 (7.2)</td>
</tr>
<tr>
<td>Diabetes and ≥2 other risk factors, n (%)</td>
<td>315 (56.4)</td>
<td>168 (60.2)</td>
</tr>
<tr>
<td>Prior CHD†, n (%)</td>
<td>302 (54.0)</td>
<td>147 (52.7)</td>
</tr>
</tbody>
</table>

- Values are mean (SD), unless otherwise stated; † Diagnosis by invasive or non-invasive testing
- BMI, body mass index; CHD, coronary heart disease; DM, diabetes mellitus; HeFH, heterozygous familial hypercholesterolemia; SD, standard deviation

Significant Reductions in Secondary Lipid Parameters at Week 24
## Baseline Lipid Profile

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<tr>
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<th>Individuals with DM (N=838)</th>
<th>Individuals without DM (N=1503)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline lipids, mg/dL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calculated LDL-C</td>
<td>116.7 (36.3) n=559</td>
<td>117.2 (36.4) n=279</td>
</tr>
<tr>
<td>HDL-C</td>
<td>48.3 (11.3)</td>
<td>48.8 (12.5)</td>
</tr>
<tr>
<td>Triglycerides, median (IQR)</td>
<td>153.1 (111.5–214.0)</td>
<td>149.6 (105.0–208.0)</td>
</tr>
<tr>
<td>Non–HDL-C</td>
<td>151.0 (41.9)</td>
<td>149.5 (43.1)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>199.3 (43.2)</td>
<td>198.1 (43.7)</td>
</tr>
<tr>
<td>Lp(a), median (IQR)</td>
<td>18.6 (5.7–49.0)</td>
<td>17.1 (5.4–58.0)</td>
</tr>
<tr>
<td>Apo B</td>
<td>101.7 (25.9)</td>
<td>99.9 (26.3)</td>
</tr>
<tr>
<td>Apo A1</td>
<td>146.2 (24.4)</td>
<td>146.3 (26.6)</td>
</tr>
</tbody>
</table>

- Values are mean (SD), unless otherwise stated;
- Apo A1: apolipoprotein A1; Apo B: apolipoprotein B; IQR, interquartile range; SD, standard deviation
Figure 1. Low-Density Lipoprotein (LDL) Cholesterol Levels.
LDL cholesterol was measured in both the OSLER-1 and OSLER-2 trials at 12, 24, and 48 weeks and in the OSLER-1 trial at 4 and 36 weeks. Shown are median values with 95% confidence intervals in the two studies. Values for the baseline measurement were obtained before randomization into a parent study. The dashed lines indicate that patients were receiving either evolocumab or placebo during the period from baseline to enrollment into OSLER. In the chart below the graph, the absolute and percentage reductions in the LDL level in the evolocumab group are compared with those in the standard-therapy group and are presented as means. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

Figure 2. Cumulative incidence of Cardiovascular Events.
Included among the cardiovascular events were death, myocardial infarction, unstable angina requiring hospitalization, coronary revascularization, stroke, transient ischemic attack, and hospitalization for heart failure. Cardiovascular events were reported in 29 of 28% patients in the evolocumab group (Kaplan-Meier 1-year event rate, 0.95%) and in 31 of 1489 patients in the standard-therapy group (Kaplan-Meier 1-year event rate, 2.18%). The inset shows the same data on an expanded y-axis. The P value was calculated with the use of a log-rank test.
OSLER: Effect of Evolocumab on Other Lipid Parameters at 1 Year

Error bars represent standard error.
Data in parentheses represent interquartile ranges.
Week 52 vs baseline:
* P < 0.0001; † P < 0.001; ‡ P < 0.01; ‡ P < 0.05
Evolocumab vs placebo:
§ P< 0.0001; ¶ P< 0.001

Lipid-lowering efficacy of the PCSK9 inhibitor evolocumab (AMG 145) in patients with type 2 diabetes: a meta-analysis of individual patient data

Interpretation Evolocumab markedly reduces atherogenic lipoproteins in patients with type 2 diabetes, an effect that is consistent across subgroups and similar to that seen in patients without type 2 diabetes. Results from ongoing cardiovascular outcome trials of PCSK9 inhibitors will provide additional data to inform the use of these drugs in patients with type 2 diabetes.
Figure 1

33 citations identified and screened

8 from MEDLINE
25 from Embase

8 duplicates removed

26 records screened

20 excluded

8 were not clinical trials
12 were of phase 1 or 2 clinical trials that were shorter or longer than 12 weeks

5 full-text articles assessed for eligibility

2 included

1 TURINO limited to patients with homozygous familial hypercholesterolaemia
1 GENDEL limited to patients with diabetes

3 studies included in the meta-analysis

1 with combination therapy (LAPLACE-2)\(^1\)
1 with patients with homozygous familial hypercholesterolaemia (TURINO)\(^1\)
1 with patients with diabetes (GENDEL)\(^1\)

Figure 2

2532 patients in three phase 3 studies of evolocumab were randomly assigned and received at least one dose of investigational drug.

Combination therapy
1896 patients in the LAPLACE-2 trial\(^2\)
552 assigned to placebo plus any statin
223 assigned to ezetimibe plus atorvastatin
1121 assigned to evolocumab plus any statin

Patients with heterozygous familial hypercholesterolaemia
379 patients in the RUTHERFORD-2 trial\(^3\)
509 assigned to placebo
230 assigned to evolocumab

Statin-intolerant patients
307 patients in the GAUSS-2 trial\(^4\)
102 assigned to ezetimibe
205 assigned to evolocumab

413 patients with type 2 diabetes
73 assigned to ezetimibe
240 assigned to evolocumab

2139 patients with type 2 diabetes
72 assigned to ezetimibe
250 assigned to evolocumab
1796 assigned to evolocumab
T2DM and Loss of Function PCSK9 Mutations

T2DM prevalence amongst 3363 black subjects with and without PCSK9 mutations

<table>
<thead>
<tr>
<th>Non-carriers</th>
<th>PCSK9142X and PCSK9679X carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>% subjects with T2DM</td>
<td>18</td>
</tr>
</tbody>
</table>

P = 0.26

T2DM prevalence amongst 9524 white subjects with and without PCSK9 mutations

<table>
<thead>
<tr>
<th>Non-carriers</th>
<th>PCSK99461 carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>% subjects with T2DM</td>
<td>8</td>
</tr>
</tbody>
</table>

P = 0.68


T2DM and PCSK9 Mutations

Association between PCSK9-pR46L variant and type 2 diabetes risk and incidence*

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>T-allele frequency</th>
<th>OR or HR (95%CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 Diabetes Case-Control Analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal Glucose controls</td>
<td>2207</td>
<td>2.15%</td>
<td>0.81</td>
<td>(0.56-1.17)\textsuperscript{a}</td>
</tr>
<tr>
<td>Type 2 diabetes cases</td>
<td>1469</td>
<td>1.97%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2 Diabetes Incidence Analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-diabetic participants</td>
<td>4280</td>
<td>2.09%</td>
<td>0.34</td>
<td>(0.11-1.07)\textsuperscript{b}</td>
</tr>
<tr>
<td>Incident type 2 diabetes cases</td>
<td>184</td>
<td>0.83%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Data are n unless otherwise indicated

\textsuperscript{a}OR from a logistic regression model adjusted for age, sex, and BMI

\textsuperscript{b}HR from a Cox regression model adjusted for age, sex, and BMI at baseline

Diabetologica 2015; 58:2051-5
### Evolocumab: Incidence of glycemic changes

<table>
<thead>
<tr>
<th>Initial Phase 2/3 Studies</th>
<th>Open-label Year 1 Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Control (%)</td>
</tr>
<tr>
<td>Median study exposure (mo)</td>
<td>3.2</td>
</tr>
<tr>
<td>Baseline normoglycemia and impaired fasting glucose (FBG&lt;1.2%mg/Dl)</td>
<td>N=1796 1.7</td>
</tr>
</tbody>
</table>

Incidence of new onset diabetes

| Baseline normoglycemia (FBG <100mg/dL) | N=1234 0.6 | N=2161 0.5 | N=831 1.4 | N=1633 1.1 |
| Baseline impaired fasting glucose (100%FBG<126mg/dL) | N=564 4.1 | N=1159 4.6 | N=403 5.2 | N=645 6.3 |

From FDA EMDAC Briefing Document

### Alirocumab: Change in fasting plasma glucose

<table>
<thead>
<tr>
<th>Placebo-Controlled pool</th>
<th>Ezetimibe-controlled pool</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline fasting plasma glucose (mg/dL)</td>
<td>Placebo</td>
</tr>
<tr>
<td>N=117 110.8 (34.2)</td>
<td>N=2316 109.5 (31.2)</td>
</tr>
</tbody>
</table>

Mean Change (SD) from baseline to

<table>
<thead>
<tr>
<th>Last on-treatment</th>
<th>Placebo</th>
<th>Alirocumab</th>
<th>Placebo</th>
<th>Alirocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=1136 4.3 (31.3)</td>
<td>N=2238 3.8 (30.3)</td>
<td>N=589 3.2 (28.8)</td>
<td>N=820 2.8 (24.6)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Worst (highest) on-treatment</th>
<th>Placebo</th>
<th>Alirocumab</th>
<th>Placebo</th>
<th>Alirocumab</th>
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<tbody>
<tr>
<td>N=1136 16.8 (35.4)</td>
<td>N=2238 17.0 (35.7)</td>
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<td>N=820 11.9 (26.6)</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Week 52 (placebo)/ Week 24 (ezetimibe)</th>
<th>Placebo</th>
<th>Alirocumab</th>
<th>Placebo</th>
<th>Alirocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=969 2.4 (29.6)</td>
<td>N=1930 2.8 (27.3)</td>
<td>N=496 2.9 (24.4)</td>
<td>N=727 1.5 (23.0)</td>
<td></td>
</tr>
</tbody>
</table>

From FDA EMDAC Briefing Document
PCSK9 Inhibitors

- Currently 2 PCSK9 inhibitors on the market
  - Repatha/ Evolocumab (Amgen)
  - Praluent/Alirocumab (Sanofi/Regeneron)
- FDA indication for these agents are:
  “approved for use in addition to diet and maximally-tolerated statin therapy in adult patients with:
  1. Heterozygous familial hypercholesterolemia
  2. Homozygous familial hypercholesterolemia
  3. or clinical atherosclerotic cardiovascular disease such as heart attacks or strokes, who require additional lowering of LDL cholesterol.”
- Outcome Trials Pending

Avoiding Misuse

- PCSK9 inhibitors do not yet have cardiovascular outcome data to support their use in diabetics for primary prevention
- All trials of PCSK9 inhibitors have been conducted on top of baseline statin therapy.
- Long term data on the impact of PCSK9 inhibitors on glucose levels in diabetics and pre-diabetics not known
Conclusions

1. In patients with diabetes need to look beyond LDL C for better cardiovascular risk factor stratification as they often have elevated triglycerides, non-HDL cholesterol/LDL P

2. PCSK9 inhibitors reduce LDL cholesterol and have favorable safety profile
   - LDL-C reductions in those with diabetes were similar to those without diabetes

3. PCSK9 inhibitors lower non HDL cholesterol, Lp(a) and maybe an important tool in reducing residual risk

4. PCKS9 inhibitors appear to have no impact on blood glucose levels (but duration of follow up is limited)

5. Outcome data pending on PCSK9 inhibitors