A Risky Game of Jeopardy:

*Optimizing Statin Therapy is the Correct Answer*

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Disclosures

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Objectives

• Discuss recent RCT data on the efficacy of non-statin therapies among ASCVD patients.
• Maximizing available statin therapy (and adherence) as the first step.
• Remaining issues (inter-individual variability in treatment response, cost, how to identify best candidates).
Recent RCT Data on Non-Statin Use in ASCVD Patients
IMPROVE-IT: ASCVD risk reduction post-ACS
Ezetimibe + simvastatin vs. simvastatin monotherapy

- Addition of ezetimibe to simvastatin 40 mg resulted in additional 16.9 mg/dL reduction in LDL-C and 7% RRR/2% ARR in ASCVD events. No significant adverse events noted,
Trial Design

27,564 high-risk, stable patients with established CV disease (prior MI, prior stroke, or symptomatic PAD)

Screening, Lipid Stabilization, and Placebo Run-in
High or moderate intensity statin therapy (± ezetimibe)

LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL

RANDOMIZED DOUBLE BLIND

Evolocumab SC
140 mg Q2W or 420 mg QM

Placebo SC
Q2W or QM

Follow-up Q 12 weeks
Primary Endpoint

Hazard ratio 0.85
(95% CI, 0.79-0.92)
P < 0.0001

CV Death, MI, Stroke, Hosp for UA, or Cor Revasc

Months from Randomization

0% 2% 4% 6% 8% 10% 12% 14% 16%

0 6 12 18 24 30 36

Placebo

Evolocumab

14.6%
12.6%
CV Death, MI, or Stroke

<table>
<thead>
<tr>
<th>LDL-C (mM)</th>
<th>Adj HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.5</td>
<td>0.69 (0.56-0.85)</td>
</tr>
<tr>
<td>0.5-1.3</td>
<td>0.75 (0.64-0.86)</td>
</tr>
<tr>
<td>1.3-1.8</td>
<td>0.87 (0.73-1.04)</td>
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<tr>
<td>1.8-2.6</td>
<td>0.90 (0.78-1.04)</td>
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<tr>
<td>≥ 2.6</td>
<td>referent</td>
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P = 0.0001
Safety Events - 2

% pts

Adj P-values for trend >0.10 for each comparison

LDL-C (mM) at 4wks

- <0.5
- 0.5-1.3
- 1.3-1.8
- 1.8-2.6
- ≥2.6

Neurocog | AST/ALT↑ | CK↑ | Non-CV death | Hem stroke

Giugliano RP, ESC Congress 2017, Barcelona 8/28/2017
Components of the primary outcome

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>Anacetrapib (N=15225)</th>
<th>Placebo (N=15224)</th>
<th>Rate Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants with events (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Coronary death</td>
<td>388 (2.5)</td>
<td>420 (2.8)</td>
<td>0.92 (0.80–1.06)</td>
<td>0.25</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>669 (4.4)</td>
<td>769 (5.1)</td>
<td>0.87 (0.78–0.96)</td>
<td>0.007</td>
</tr>
<tr>
<td>Coronary death or MI</td>
<td>934 (6.1)</td>
<td>1048 (6.9)</td>
<td>0.89 (0.81–0.97)</td>
<td>0.008</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>1081 (7.1)</td>
<td>1201 (7.9)</td>
<td>0.90 (0.83–0.97)</td>
<td>0.01</td>
</tr>
<tr>
<td>Major coronary event</td>
<td>1640 (10.8)</td>
<td>1803 (11.8)</td>
<td>0.91 (0.85–0.97)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Major coronary event: Coronary death, MI or coronary revascularization

No significant evidence of differential proportional effects among 23 pre-specified subgroup categories

CANTOS: Primary Cardiovascular Endpoint (MACE)

Placebo SC q 3 months
Canakinumab 150/300 SC q 3 months

HR 0.85
95% CI 0.76-0.96
P = 0.007

39% reduction in hsCRP
No change in LDL-C
15% reduction in MACE

The 150mg group met multiplicity adjusted thresholds for formal statistical significance for both the primary and secondary cardiovascular endpoints.
Residual Inflammatory Risk: Addressing the Obverse Side of the Atherosclerosis Prevention Coin
Ridker PM. Eur Heart J 2016;37:1720-22

Known Cardiovascular Disease
LDL 150 mg/dL (3.8 mmol/L)
hsCRP 4.5 mg/L
High Intensity Statin

“Residual Cholesterol Risk”
LDL 110 mg/dL (2.8 mmol/L)
hsCRP 1.8 mg/L
Additional LDL Reduction

“Residual Inflammatory Risk”
LDL 70 mg/dL (1.8 mmol/L)
hsCRP 3.8 mg/L
Additional Inflammation Reduction

IMPROVE-IT: Ezetimibe 6% RRR
FOURIER/SPIRE: PCSK9 Inhibition q2 weeks 15% RRR
No Prior Proof of Concept
Maximizing Statin Intensity and Adherence as the First Step
Excluded 7,284 not meeting 1 major or 2 minor risk factors

Excluded 241,213 with LDL-C <70mg/dL and non-HDL-C <100 mg/dL

Excluded 228,535 for other reasons (not on moderate-intensity statin, TGs >400, ESRD, acute liver disease, FH)

631,855 patients with clinically evident ASCVD

624,571 ASCVD patients

383,358 ASCVD patients

154,823 ASCVD patients

73,626 (47.5%) on moderate-intensity statin therapy
77,180 (49.9%) on high-intensity statin therapy
1340 (0.9%) on moderate-intensity statin therapy + ezetimibe
2677 (1.7%) on high-intensity statin therapy + ezetimibe

41% with statin non-adherence

Estimates based on cost of $2.00 per day for 10 mg tablet of ezetimibe.

- **A**: Annual cost of starting all FOURIER-eligible patients on evolocumab.
- **B**: Cost of titrating every patient on moderate intensity statin to high-intensity statin and initiating every patient on ezetimibe who was not on ezetimibe.
- **C**: Annual cost of initiating evolocumab in patients with LDL-C levels >70 mg/dL after B.
- **D**: Total cost of titrating statin and ezetimibe plus initiating evolocumab in patients with LDL-C levels >70 mg/dL.

Total net annual savings associated with evolocumab therapy in all patients (A) minus the annual cost associated with titrating every patient to high-intensity statin therapy (if not on one) and the cost associated with initiation of ezetimibe (if patient is not on it) (B+C) plus the annual cost of evolocumab among those with LDL-C >70 mg/dL (D).
Remaining Issues
Variation in Response to Statin Therapy

- JUPITER trial participants receiving rosuvastatin 20 mg
  - Marked inter-individual variability in response to therapy
  - 10.8% no reduction in LDL-C, 43% >0 to <50%, 46% >50%
  - Reduction in ASCVD events greatest in those with greatest % reduction in LDL-C

Variability in response to Bococizumab

The SPIRE 1 and SPIRE 2 Cardiovascular Outcomes Trials: Confirmation of Wide Individual Variability in Percent LDLC Reduction

14 weeks

52 weeks

Cost Associated with PCSK9i

Annual increase in health care expenditure = $120 billion

*Total US health care expenditure on drugs in 2015: $329 billion

*Total US health care spending in 2015: $2.8 trillion
How to Maximize Net ASCVD Benefit of Non-Statin Therapies?
ARR 2.2%, NNT 45

ARR 6.3%, NNT 16

Conclusions

- Multiple novel non-statin therapies have shown efficacy in improving CV outcomes in patients with clinical ASCVD.
- Variation in response to therapy and cost remain important issues.
- Evidence-based statin therapy use and improvement in statin adherence may decrease the need for some of these therapies.
- There remains a need to identify which subgroups of ASCVD patients derive the most benefit from non-statin therapies based on net ASCVD benefit and cost-effectiveness.