Utilizing Quantitative Data to Optimize Benefits of Non-Statin Therapies in Patients with ASCVD

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Disclosures

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CTT meta-analysis LDL-C & CVD event reduction

Statins (5 years), ezetimibe (7 years), PCSK9mAbs (11-26 months)


Applied FOURIER inclusion criteria to LONG TERM ODYSSEY LONGTERM/ASCVD*

- LDL-C 120 → 48 mg/dl (3.2 → 1.3 mmol/L)
- LDL-C 122 → 48 mg/dl (3.2 → 1.3 mmol/L)
- FOURIER ASCVD 92 → 30 mg/dl (2.4 → 0.8 mmol/L)


- Applied FOURIER inclusion criteria to LONG TERM ODYSSEY LONGTERM/ASCVD*
FOURIER 2.2 years vs SPIRE-2 1 year MACE

FOURIER baseline LDL-C mean 92 mg/dl (2.4 mmol/L)
Mean 60 mg/dl LDL-C ↓

SPIRE-2 baseline) mean LDL-C 134 mg/dl (3.5 mmol/L)
Mean 59 mg/dl LDL-C ↓ @6 months

Largest absolute CVD risk reduction benefit in high risk patients with higher LDL-C levels

Risk curve concept

IFG, impaired fasting glucose; MS, metabolic syndrome
Giugliano, R et al. Presented at European Society of Cardiology Congress 2017; Barcelona, Spain
Determining When to Add Nonstatin Therapy
A Quantitative Approach

Jennifer G. Robinson, MD, MPH, Roeland Huijgen, MD, PhD, Kausik Ray, MBCoD, MD, MPH, Jane Persons, PhD, John J.P. Kastelein, MD, PhD, Michael J. Pennica, PhD

ABSTRACT

BACKGROUND Costs and uncertainty about the benefits of nonstatin therapies limit their use.

OBJECTIVES The authors sought to identify patients who might benefit from the addition of a nonstatin to background statin therapy.

METHODS We performed systematic reviews of subgroup analyses from randomized trials and observational studies with statin-treated participants to determine the number needed to treat (NNT) to prevent 1 ASCVD event over 5 years for each patient group and to allow comparisons with 5-year cost analyses.

RESULTS The 10-year ASCVD risk is at least 30% (very high risk) for statin-treated participants with clinical ASCVD and comorbidities, and 20% to 29% (high risk) for those with ASCVD without comorbidities or who have heterozygous familial hypercholesterolemia. Adding ezetimibe to reduce low-density LDL-C by 20% would provide a 5-year NNT = 50 for very high-risk patients with LDL-C = 130 mg/dl or for high-risk patients with LDL-C = 190 mg/dl, and an NNT = 30 for very high-risk patients with LDL-C = 160 mg/dl. Adding a PCSK9 monoclonal antibody to lower LDL-C by at least 50% would provide an NNT = 50 for very high-risk and high-risk patients with LDL-C = 70 mg/dl, and an NNT = 30 for very high-risk and high-risk patients with an LDL-C = 130 mg/dl.

CONCLUSIONS Adding ezetimibe or PCSK9 monoclonal antibodies to maximally tolerated statin therapy may be cost effective in very high-risk and high-risk patients, depending on baseline LDL-C levels. (J Am Coll Cardiol 2016;68:2412-21) © 2016 by the American College of Cardiology Foundation.
Very high risk – CVD “plus”

>30% 10-year ASCVD risk ON statin therapy in RCTs

- Clinical ASCVD + Diabetes
- Clinical ASCVD + Familial hypercholesterolemia (FH)
- Clinical ASCVD + Poorly controlled risk factors
- Clinical ASCVD + Chronic kidney disease
- Recent acute coronary syndrome (<3 months)
- Clinical ASCVD with polyvascular disease*
- Clinical ASCVD + Age $\geq$ 65 years*
- Clinical ASCVD + multiple recurrent events**
- Clinical ASCVD + elevated lipoprotein (a)**

CVD PLUS = Very high risk (≥30% 10-year ASCVD risk)
5-year NNT to prevent 1 ASCVD event

<table>
<thead>
<tr>
<th>Initial LDL-C</th>
<th>Ezetimibe LDL-C ↓20%</th>
<th>PCSK9 mAb LDL-C ↓50%</th>
<th>PCSK9 mAb ↓65%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>190 mg/dl</strong> (4.9 mmol/L)</td>
<td>32</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td><strong>160 mg/dl</strong> (4.1 mmol/L)</td>
<td>38</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td><strong>130 mg/dl</strong> (3.4 mmol/L)</td>
<td>47</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td><strong>100 mg/dl</strong> (2.6 mmol/L)</td>
<td>61</td>
<td>25</td>
<td>19</td>
</tr>
<tr>
<td><strong>70 mg/dl</strong> (1.8 mmol/L)</td>
<td>88</td>
<td>35</td>
<td>27</td>
</tr>
</tbody>
</table>

Reasonable NNT thresholds: Physicians: NNT < 50   Patients: NNT <30

Clinical ASCVD without high risk characteristics
(no diabetes/high risk characteristics and primary LDL-C <190 mg/dl)

Primary prevention familial hypercholesterolemia (FH)
(heterozygous; no clinical ASCVD; age >40 years)

<table>
<thead>
<tr>
<th>Initial LDL-C</th>
<th>20%</th>
<th>50%</th>
<th>65%</th>
</tr>
</thead>
<tbody>
<tr>
<td>190 mg/dl</td>
<td>48</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>160 mg/dl</td>
<td>57</td>
<td>23</td>
<td>18</td>
</tr>
<tr>
<td>130 mg/dl</td>
<td>71</td>
<td>28</td>
<td>22</td>
</tr>
<tr>
<td>100 mg/dl</td>
<td>92</td>
<td>37</td>
<td>28</td>
</tr>
<tr>
<td>70 mg/dl</td>
<td>131</td>
<td>53</td>
<td>40</td>
</tr>
</tbody>
</table>
MODERATE RISK 10-<20% 10-year ASCVD risk
Primary prevention LDL-C <190 mg/dl††
(with or without diabetes)

<table>
<thead>
<tr>
<th>Initial LDL-C</th>
<th>20%</th>
<th>35%</th>
<th>50%</th>
<th>65%</th>
</tr>
</thead>
<tbody>
<tr>
<td>190 mg/dl</td>
<td>97</td>
<td>55</td>
<td>39</td>
<td>30</td>
</tr>
<tr>
<td>160 mg/dl</td>
<td>115</td>
<td>66</td>
<td>46</td>
<td>35</td>
</tr>
<tr>
<td>130 mg/dl</td>
<td>141</td>
<td>81</td>
<td>57</td>
<td>44</td>
</tr>
<tr>
<td>100 mg/dl</td>
<td>184</td>
<td>105</td>
<td>74</td>
<td>57</td>
</tr>
<tr>
<td>70 mg/dl</td>
<td>263</td>
<td>150</td>
<td>105</td>
<td>81</td>
</tr>
</tbody>
</table>
## Cost effectiveness – Based on 2016 ICER analysis

<table>
<thead>
<tr>
<th>NNT 10-14</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Very high risk individuals with LDL-C &gt; 190 mg/dl (4.9 mmol/L) or LDL-C &gt; 160 (4.1 mmol/L) mg/dl if &gt; 65% LDL-C reduction</td>
</tr>
<tr>
<td>No discount /≈ $150,000 QALY</td>
</tr>
</tbody>
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<thead>
<tr>
<th>NNT 21-28</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Very high risk patients with LDL-C &gt; 100 mg/dl (2.6 mmol/L)</td>
</tr>
<tr>
<td>• High risk patients with LDL-C &gt; 130 mg/dl (3.4 mmol/L)</td>
</tr>
<tr>
<td>Depending on discount</td>
</tr>
<tr>
<td>Discount ≈ 50% (≈ $7700/year) /≈ $150,000 QALY</td>
</tr>
<tr>
<td>Discount ≈ 60% (≈ $5400/year) /≈ $100,000 QALY</td>
</tr>
<tr>
<td>Discount ≈ 77% (≈ $3200/year) /≈ $50,000 QALY</td>
</tr>
<tr>
<td>Discount ≈ 85% (≈ $2200/year) to avoid exceeding growth targets US healthcare costs</td>
</tr>
</tbody>
</table>

Cost per quality adjusted life year (QALY) gained over 5 years of treatment (assuming undiscounted acquisition cost of $14,000/year and 50% relative risk reduction with PCSK9 mAb\(^{32}\)). All costs in US dollars.

### Very high risk
- **Statin intolerant CVD “Plus”**
- **CVD + FH**
  - LDL-C $\geq 100-130^*$ mg/dl (2.6-3.4 mmol/L) consider Ezetimibe or PCSK9 mAb

### High risk
- **Statin intolerant CVD**
- **FH**
  - LDL-C $\geq 130$ mg/dl (3.4 mmol/L)
  - Consider PCSK9 mAb
  - LDL-C $\geq 190$ mg/dl (4.9 mmol/L) Consider Ezetimibe

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**NNT Calculator in development for US CVD & statin-treated patients; calibrate for other countries**

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The "rule of thumb" categories of patients who are likely to experience an atherosclerotic cardiovascular disease (ASCVD) risk reduction benefit from additional low-density lipoprotein cholesterol (LDL-C)-lowering therapy, considering both clinical and cost perspective (assuming no adverse events). mAb = monoclonal antibody; NNT = number needed to treat.