Ezetimibe in Prevention of Cerebro- and Cardiovascular Events in Middle- to High-Risk, Elderly (75 Years Old or Over) Patients With Elevated LDL-Cholesterol: A Multicenter, Randomized, Controlled, Open-Label Trial (EWTOPIA 75)

Discussant
Jennifer G. Robinson, MD, MPH
Professor, Departments of Epidemiology & Medicine
Director, Prevention Intervention Center
University of Iowa
Iowa City, Iowa

Late-breaking clinical trials session
November 10, 2018 Chicago, IL, USA
Proportional reduction in major vascular/cardiovascular events in randomized trials of statins, ezetimibe, and PCSK9 monoclonal antibodies for the magnitude LDL-C reduction

**EWTOPIA** 75 mean age 81 year, 75% women
- Ezetimibe vs usual care
- LDL-C 1 year 126 vs 144 mg/dl
  - (3.2 vs 3.72 mmol/L)
  - ↓18 mg/dl (0.47 mmol/L) = ↓13%
- MACE HR 0.66 (95% CI 0.50-.86)
  - MACE=2%/y

- CTT MVE RRR ↓22%/1 mmol/L
  - Expected RR 10%

**MEGA** mean age 58 year, 69% women
- Pravastatin 10-20 (mean 8.3) mg vs usual care
- LDL-C 1 year 128 vs 154 mg/dl
  - (3.30 vs 3.97 mmol/L)
  - ↓26 mg/dl (0.67 mmol/L)
- CVE HR 0.74 (0.59-.94)
  - 10-y ASCVD risk ≈ 5%

- CTT Expected RR 15%

Total mortality in primary prevention RCTs

**EWTOPIA – Ezetimibe vs UC**

- **HR (95% CI)**
  - 70–97 y: 0.80 (0.62-1.04) p=0.090
  - 50–59 y: 0.80 (0.60-1.04) P=0.10

**MEGA – Pravastatin vs UC**

- **HR (95% CI)**: 0.72 (0.51-1.01) P=0.055

**JUPITER – Rosuvastatin 10 mg vs placebo**

<table>
<thead>
<tr>
<th>Baseline CRP &gt;2.0 mg/L</th>
<th>LDL-C 1y 55 vs 110 mg/dl (1.42-2.85 mmol/L)</th>
<th>↓55 mg/dl (1.43 mmol/L)</th>
<th>~7% 10-y ASCVD risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hazard ratio (HR) (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70–97 y</td>
<td>0.80 (0.62-1.04) p=0.090</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–59 y</td>
<td>0.80 (0.60-1.04) P=0.10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusions

- LDL-C lowering from ezetimibe in Japanese older adults without CVD
  - LDL-C ↓ efficacy about expected %, but greater than expected CVD reduction
    - Chance?
    - Open-label design?
    - Genetic? Japanese have different genetic polymorphisms NPC1L1
      - ? Different effect on plaque regression/stabilization
        - Japanese PRECISE-IVUS: LDL-C ↓10 mg/dl 9-12 months
        - PAV regression atorvastatin/ezetimibe 78% vs atorvastatin alone 58%
          - Older adults different?
  - Statins may be more effective ↓ total mortality
  - Need primary prevention LDL-C lowering trials in other populations aged ≥75 years
    - Ongoing STAREE NCT02099123 end 2022
      - Australia Age ≥70 y: N=18,000 Atorvastatin 40 mg vs placebo
    - USA NIH RFA-AG-19-020