Further cardiovascular OUTcomes Research with PCSK9 Inhibition in subjects with Elevated Risk Outcomes by age and sex


for the FOURIER Steering Committee & Investigators
Disclosures

Recipient of research grants and consulting fees from Amgen and Pfizer Inc.
Trial Design

27,564 stable patients with CV disease (prior MI, stroke or PAD) age 40-85 years; additional CV risk factor(s)

Screening, Placebo Run-in, & Lipid Stabilization
Effective statin therapy (atorva ≥20 mg or ≈ statin dose ± 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 median 26 months

### Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years, mean (SD)</strong></td>
<td>63 (9)</td>
</tr>
<tr>
<td><strong>Male sex (%)</strong></td>
<td>75</td>
</tr>
<tr>
<td><strong>Type of cardiovascular disease (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>81</td>
</tr>
<tr>
<td>Stroke (non-hemorrhagic)</td>
<td>19</td>
</tr>
<tr>
<td>Symptomatic PAD</td>
<td>13</td>
</tr>
<tr>
<td><strong>Cardiovascular risk factor (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>80</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>37</td>
</tr>
<tr>
<td>Current cigarette use</td>
<td>28</td>
</tr>
</tbody>
</table>

Median time from most recent event ~3 yrs; ~¼ within 1 yr
Summary of Effects of PCSK9i Evolocumab

- ↓ LDL-C by 59% down to a median of 30 mg/dl
- ↓ CV outcomes in patients on statin
- Safe and well-tolerated

Evolocumab (median 30 mg/dl, IQR 19-46 mg/dl)

Placebo

59% reduction
P<0.00001

Absolute ↓ 56 mg/dl

KM Rate (%) at 3 Years

HR 0.85 (0.79-0.92) P<0.0001

HR 0.80 (0.73-0.88) P<0.0001

Sabatine MS et al. NEJM 2017;376:1713-22
Analyses by Age and Sex
Rationale

There is evidence that the benefits of lipid-lowering with statins may be attenuated in the elderly population and concerns have been expressed about the risk benefits in women versus men.

Observations in clinical practice demonstrate that despite evidence for the overall benefits of lipid-lowering, elderly patients and women are frequently undertreated.
Methods

- Efficacy analyses were conducted in the ITT population based on time from randomization to the first event.

- Hazard ratios and 95% confidence intervals were generated with the use of Cox proportional hazards models with stratification factors (screening LDL and region) as covariates.

- Analyses by age and sex were a prespecified subgroup analysis for the FOURIER trial

- Tests for subgroup heterogeneity were conducted by including an interaction term in the model.

- Given the exploratory nature of the analysis, a P value <0.05 was considered significant.
## Baseline Characteristics by Age Quartile

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Q1 &lt;56y (N=7122)</th>
<th>Q2 56 - ≤63y (N=7154)</th>
<th>Q3 &gt;63 - ≤69y (N=7055)</th>
<th>Q4 &gt; 69y (N=6233)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs) mean</td>
<td>50.8</td>
<td>60.0</td>
<td>66.4</td>
<td>74.2</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>80%</td>
<td>77%</td>
<td>75%</td>
<td>69%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Weight (kg) - mean</td>
<td>89.4</td>
<td>86.5</td>
<td>84.4</td>
<td>80.1</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Type of atherosclerosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>86%</td>
<td>81%</td>
<td>80%</td>
<td>77%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Non-hemorrhagic stroke</td>
<td>15%</td>
<td>20%</td>
<td>20%</td>
<td>24%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>9%</td>
<td>15%</td>
<td>14%</td>
<td>14%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>74%</td>
<td>82%</td>
<td>81%</td>
<td>84%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>35%</td>
<td>41%</td>
<td>36%</td>
<td>35%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Current cigarette use</td>
<td>45%</td>
<td>39%</td>
<td>18%</td>
<td>9%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>High intensity statin use</td>
<td>75%</td>
<td>73%</td>
<td>67%</td>
<td>62%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Median lipid measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol - mg/dl</td>
<td>94</td>
<td>93</td>
<td>91</td>
<td>90</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Total cholesterol - mg/dl</td>
<td>169</td>
<td>169</td>
<td>167</td>
<td>166</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>HDL cholesterol - mg/dl</td>
<td>41</td>
<td>43</td>
<td>46</td>
<td>48</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Triglycerides - mg/dl</td>
<td>145</td>
<td>139</td>
<td>129</td>
<td>121</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Lipoprotein(a) - nmol/liter</td>
<td>38</td>
<td>36</td>
<td>37</td>
<td>37</td>
<td>0.57</td>
</tr>
</tbody>
</table>
## Baseline demographics by sex

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Male (N=20795)</th>
<th>Female (N=6769)</th>
<th>P- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – yr, mean</td>
<td>62.0</td>
<td>64.1</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Weight – kg, mean</td>
<td>88.1</td>
<td>76.7</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Type of atherosclerosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>84%</td>
<td>71%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Non-hemorrhagic stroke</td>
<td>7%</td>
<td>27%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>13%</td>
<td>15%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>79%</td>
<td>85%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>35%</td>
<td>40%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Current cigarette use</td>
<td>29%</td>
<td>25%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>High intensity statin use</td>
<td>69%</td>
<td>69%</td>
<td>0.94</td>
</tr>
<tr>
<td>Median lipid measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol - mg/dl</td>
<td>91</td>
<td>95</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Total cholesterol - mg/dl</td>
<td>165</td>
<td>176</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>HDL cholesterol - mg/dl</td>
<td>42</td>
<td>49</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Triglycerides - mg/dl</td>
<td>133</td>
<td>134</td>
<td>0.16</td>
</tr>
<tr>
<td>Lipoprotein(a) - nmol/liter</td>
<td>34</td>
<td>51</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>
Similar Absolute Reduction in LDL-C with Evolocumab Regardless of Age

Q1 <56y, Q2 56-≤63y, Q3 >63-≤69y, Q4 >69y
Similar Absolute Reduction in LDL-C with Evolocumab Regardless of Patient Sex

At week 48
- LDL male: 60 mg/dl
- LDL female: 55 mg/dl
The efficacy of evolocumab stratified by age

FOURIER Primary endpoint
(CVD, MI, stroke, hosp for UA, coronary revasc)

Overall 0.85 (0.79, 0.92)
Female 0.81 (0.69, 0.95)
Male 0.86 (0.80, 0.94)
Age quartile 1 0.83 (0.72, 0.96)
Age quartile 2 0.88 (0.76, 1.01)
Age quartile 3 0.82 (0.71, 0.95)
Age quartile 4 0.86 (0.74, 1.00)
Overall 0.85 (0.79, 0.92)

p interaction 0.908
Primary endpoint stratified by age quartile

- Age Q1-Evomab
- Age Q2-Evomab
- Age Q3-Evomab
- Age Q4-Evomab
- Age Q1-Placebo
- Age Q2-Placebo
- Age Q3-Placebo
- Age Q4-Placebo

ARR. Q1 2.98  NNT 34
Q4 2.04  NNT 49
The efficacy of evolocumab stratified by age

FOURIER Key Secondary endpoint
CV death, MI or stroke

<table>
<thead>
<tr>
<th>Age quartile</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.74 (0.61, 0.89)</td>
</tr>
<tr>
<td>2</td>
<td>0.83 (0.69, 1.00)</td>
</tr>
<tr>
<td>3</td>
<td>0.78 (0.65, 0.94)</td>
</tr>
<tr>
<td>4</td>
<td>0.82 (0.69, 0.98)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.80 (0.73, 0.88)</td>
</tr>
</tbody>
</table>

p interaction 0.813
Secondary endpoint stratified by age quartile

- Age Q1-Evomab
- Age Q2-Evomab
- Age Q3-Evomab
- Age Q4-Evomab
- Age Q1-Placebo
- Age Q2-Placebo
- Age Q3-Placebo
- Age Q4-Placebo

ARR Q1 2.64  NNT 38
Q4 2.48  NNT 40

Values:
- Age Q4-Placebo: 12.41%
- Age Q4-Evomab: 9.93%
- Age Q3-Placebo: 9.50%
- Age Q3-Evomab: 9.33%
- Age Q2-Placebo: 8.84%
- Age Q2-Evomab: 7.71%
- Age Q1-Placebo: 7.57%
- Age Q1-Evomab: 6.69%
The efficacy of evolocumab stratified by sex

FOURIER Primary endpoint
(CVD, MI, stroke, hosp for UA, coronary revasc)

Hazard ratio (95% CI)

Male
0.86 (0.80, 0.94)

Female
0.81 (0.69, 0.95)

Overall
0.85 (0.79, 0.92)

p interaction 0.477
Primary endpoint stratified by sex

ARR male. 1.82. NNT 55
female. 2.66 NNT 38
The efficacy of evolocumab stratified by sex

FOURIER Key Secondary endpoint
CV death, MI or stroke

Hazard ratio (95% CI)

- Male: 0.81 (0.73, 0.90)
- Female: 0.74 (0.61, 0.90)
- Overall: 0.80 (0.73, 0.88)

p interaction 0.436
Secondary endpoint stratified by sex

ARR male 1.78. NNT 56
female 2.69. NNT 37
Adverse events by age quartile and treatment allocation

All Adverse events

Serious adverse events

Discontinuations

% placebo
evolocumab
Adverse events by sex and treatment allocation

All adverse events

- Male: 73%
- Female: 83%

Serious adverse events

- Male: 4%
- Female: 7%

Discontinuations

- Male: 3%
- Female: 7%
Summary and Conclusion

The results of the FOURIER Trial clearly demonstrate that in both sexes and across a wide age range of patients with established CV disease, the efficacy of evolocumab in reducing CV events is maintained.

Despite some differences in reporting of adverse events in men and women, and across the age range, there were no differences in those reported by those assigned evolocumab or placebo.

The current results provide new evidence that lowering LDL-cholesterol with evolocumab confers CV outcome benefits irrespective of age and sex.