Early initiation of PCSK9 inhibitor therapy versus placebo in patients with acute coronary syndrome: a systematic review and meta-analysis

G.B. Justino¹, L.B. Justino¹, M.E. Muller¹, A.V. Rocha², A. Mazetto³, R. Cardoso⁴, T.M. Leucker⁵

¹Federal University of Santa Catarina, Department of Medicine, Florianopolis, Brazil
²University of Miami Leonard M. Miller School of Medicine, Department of Public Health Sciences, Miami, United States of America
³Nove de Julho University, Department of Medicine, Sao Paulo, Brazil
⁴Brigham and Women’s Hospital, Heart and Vascular Center, Division of Cardiovascular Medicine, Boston, United States of America
⁵The Johns Hopkins University School of Medicine, Department of Medicine, Division of Cardiology, Baltimore, United States of America

Funding Acknowledgements: None.

Background: In patients with stable atherosclerotic cardiovascular disease (ASCVD) and prior atherosclerotic events, PCSK9 inhibitors (PCSK9i) have shown a 50-60% reduction in LDL-C from baseline, on a background of high-intensity or maximally tolerated statin therapy, leading to a 15% relative reduction in the incidence of major adverse cardiovascular events. However, less is known about the impact of PCSK9i initiation acutely in the setting of an acute coronary syndrome (ACS).

Purpose: To assess the efficacy of early initiation of PCSK9i therapy in lipid parameters among patients presenting with ACS.

Methods: We performed a systematic review and meta-analysis comparing PCSK9i with placebo in the setting of ACS, added to guideline directed high-intensity or maximally tolerated statin therapy. Inclusion was restricted to randomized controlled trials (RCTs) with initiation of PCSK9i or placebo within 1 week of presentation or percutaneous coronary intervention for ACS. PubMed, EMBASE, and Cochrane Central were searched. The systematic review and meta-analysis followed Cochrane and PRISMA recommendations.

Results: Six RCTs with a total of 996 patients were included, of whom 503 (50.5%) received PCSK9i. Mean follow-up ranged from 4 to 52 weeks. Mean time from presentation to administration of first dose ranged from 3.6 hours to 6.5 days. LDL-C levels were significantly lower at follow-up in the PCSK9i group (mean difference [MD] -44 mg/dL; 95% CI -54.3 to -33.8 mg/dL; p<0.001; Figure 1A). Lp(a) was also significantly decreased with PCSK9i therapy (MD -24.0 nmol/L; 95% CI -43.0 to -4.9 nmol/L; p=0.01; Figure 1B). Similarly, total cholesterol (MD -49.2 mg/dL; 95% CI -84.0 to -5.4 mg/dL; p<0.001) and triglycerides (MD -19 mg/dL; 95% CI -50.6 to -8.2 mg/dL; p=0.001) were significantly reduced with PCSK9i therapy, respectively. HDL-C was marginally increased in this same group (MD 2.5 mg/dL; 95% CI 0.9 to 4.2 mg/dL; p=0.003).

Conclusions: In patients with ACS, early initiation of PCSK9i, in addition to statin therapy, leads to a significant reduction in LDL-C and Lp(a) as compared with placebo. Whether the differences in these lipoproteins translate into a reduction in clinical endpoints is yet to be determined.

Figure 1A. LDL-C was significantly reduced with PCSK9 inhibitor therapy relative to placebo (mg/dL).
Figure 1B. Lp(a) was significantly reduced with PCSK9 inhibitor therapy relative to placebo (nmol/L).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean PCSK9</th>
<th>Mean Placebo</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVOPACS 2019</td>
<td>69.8</td>
<td>97.2</td>
<td>24.0%</td>
<td>2019</td>
</tr>
<tr>
<td>Okada 2020 (1)</td>
<td>85.1</td>
<td>43.3</td>
<td>49 37.2%</td>
<td>2020</td>
</tr>
<tr>
<td>EVMS 2020</td>
<td>85.9</td>
<td>96</td>
<td>95.1 104.5%</td>
<td>2020</td>
</tr>
<tr>
<td>HUYGENS 2022</td>
<td>84.5</td>
<td>91.2</td>
<td>80 106.5%</td>
<td>2022</td>
</tr>
<tr>
<td>PACMAN-AMI 2022 (1)</td>
<td>58</td>
<td>86.9</td>
<td>126 103.9%</td>
<td>2022</td>
</tr>
</tbody>
</table>

Total (95% CI) 426 439 100.0% -23.95 [-42.98, -4.93]

Heterogeneity: Tau² = 270.90; Chi² = 10.80, df = 4 (P = 0.03); I² = 63%

Test for overall effect: Z = 2.47 (P = 0.01)

Footnotes
(1) Lp(a), mmol/L=2.18×Lp(a), mg/dL=3.83