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PCSK9 Inhibitors in Secondary Prevention – An Opportunity for Personalized Therapy

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Recommended Citation

Board C, Kelly MS, Shapiro MD, Dixon DL. PCSK9 inhibitors in secondary prevention – an opportunity for personalized therapy. *J Cardiovasc Pharmacol.* 2020;75(5):410-420. <https://doi.org/10.1097/FJC.0000000000000809>

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PCSK9 Inhibitors in Secondary Prevention – An Opportunity for Personalized Therapy

Comments

This is a pre-copy-editing, author-produced PDF of an article accepted for publication in *Journal of Cardiovascular Pharmacology*, volume 75, issue 5, in 2020 following peer review. The definitive publisher-authenticated version is available online at <https://doi.org/10.1097/FJC.0000000000000809>.

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1 PCSK9 inhibitors in secondary prevention – an opportunity for personalized therapy

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22 **Short Title:** PCSK9 inhibitors in secondary prevention

23 **Funding:** none

24 **Disclosures:** Michael Shapiro is on advisory board for Regeneron

25 **Abstract:** Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of
26 death worldwide. Low-density lipoprotein cholesterol (LDL-C) is the primary cause of
27 ASCVD and reducing LDL-C levels with statin therapy significantly reduces ASCVD risk;
28 however, significant residual risk remains. Two monoclonal antibodies (mAbs), alirocumab
29 and evolocumab, that target proprotein convertase subtilisin/kexin-type 9 (PCSK9), reduce
30 LDL-C levels by up to 60% when used in combination with statins and significantly reduce
31 the risk of recurrent ASCVD events in both stable secondary prevention and acute
32 coronary syndrome populations. Pre-specified analyses of recent randomized controlled
33 trials have shed light on how best to prioritize these therapies to maximize their value in
34 select high risk groups. These data have also informed recent clinical practice guidelines
35 and scientific statements resulting in an expanded role for PCSK9-mAbs compared to
36 previous guidelines, albeit there are notable differences between these recommendations.
37 Ongoing research is exploring the long-term safety of PCSK9-mAbs and their role in the
38 acute setting as well as patients without prior myocardial infarction or stroke. Novel
39 therapies that inhibit PCSK9 synthesis via small interfering RNA, such as inclisiran, are
40 also in development and may reduce LDL-C levels similar to PCSK9-mAbs but with less
41 frequent administration. Nonetheless, the PCSK9-mAbs are a breakthrough therapy and
42 warrant consideration in very-high risk patients who are most likely to benefit. Such a
43 personalized approach can help to ensure cost-effectiveness and maximize their value.

44

45 **Key Words:** PCSK9, alirocumab, evolocumab, inclisiran, low-density lipoprotein
46 cholesterol

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48

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50 **Background**

51 Atherosclerotic cardiovascular disease (ASCVD) continues to be the leading cause
52 of death worldwide.¹ In the United States (US), the Center for Disease Control and
53 Prevention (CDC) reports cardiovascular mortality rates are actually increasing despite
54 decades of decline.² The principal factor in the development and progression of ASCVD is
55 low-density lipoprotein cholesterol (LDL-C).³ Thus, reducing LDL-C levels through lifestyle
56 modification and lipid-lowering therapies are effective means of reducing ASCVD risk.⁴
57 Statins are the cornerstone lipid-lowering therapy in ASCVD prevention as they have been
58 shown to not only significantly reduce LDL-C levels but also ASCVD events and
59 cardiovascular (CV) mortality, across a wide range of populations.³ Despite statin therapy,
60 residual ASCVD risk remains, especially in select high risk groups with additional risk-
61 enhancing factors. While there are numerous drivers of residual CV risk, one approach to
62 addressing it focuses on further reduction of LDL-C levels beyond what is achievable with
63 maximally tolerated statin therapy alone.

64 In 2015, the US Food and Drug Administration (FDA) approved two fully human
65 therapeutic monoclonal antibodies (mAbs), alirocumab and evolocumab, for use in
66 combination with statin therapy to lower LDL-C levels. Alirocumab and evolocumab inhibit
67 proprotein convertase subtilisin/kexin-type 9 (PCSK9), a protein primarily expressed in
68 hepatocytes, but also found in endothelial and smooth muscle cells, kidney mesenchymal
69 cells, intestinal ileum, embryonic brain telencephalon neurons, and colon epithelia.⁵ From a
70 physiological perspective, PCSK9 binds to LDL receptors on the hepatocyte and facilitates
71 the intracellular degradation and compartmentalization of LDL receptors resulting in
72 decreased availability of LDL receptors and increased circulation of LDL-C in the plasma.
73 Because PCSK9 targets highly specific proteins, such as LDL receptors, it is an ideal
74 therapeutic target.⁶

75 The mechanism by which PCSK9-mAbs reduce LDL-C levels involves the binding
76 of the mAb to circulating PCSK9, which disrupts the binding of PCSK9 to LDL receptors on
77 the hepatocyte surface (Figure 1). Under normal physiological circumstances, the lifespan
78 of LDL receptors is approximately 20 hours, and each recycles to the hepatocyte cell
79 surface for several hundred rounds of receptor-mediated endocytosis.⁷ Thus, PCSK9-
80 mAbs interfere with the normal LDL receptor recycling loop and increases the recycling of
81 LDL receptors to facilitate the removal of LDL-C from the plasma resulting in lower LDL-C
82 levels. Both PCSK-mAbs have demonstrated high affinity and specificity for PSCK9.^{8,9}
83 They are each formulated as subcutaneous injections and self-administered either bi-
84 weekly or once-monthly, depending on patient preference. To date, both alirocumab and
85 evolocumab are generally well tolerated with injection site reactions being the most
86 frequently reported adverse effect.¹⁰

87 Since FDA approval in 2015, two randomized, placebo-controlled trials have
88 demonstrated that both alirocumab and evolocumab significantly reduce LDL-C levels (up
89 to 60%), and more importantly, reduce the risk of recurrent CV events in patients receiving
90 maximally tolerated statin therapy with prior myocardial infarction (MI) or ischemic
91 stroke.^{11,12} Additional prespecified analyses from these trials have provided important
92 insights regarding which subjects are most likely to benefit from these novel therapies.
93 This consideration is important due to ongoing debates around the cost-effectiveness of
94 these agents.¹³ In this review, we will discuss the evidence supporting a personalized
95 approach to the use of PCSK9-mAbs, outline areas of uncertainty, and what the future
96 may hold for this therapeutic class.

97

98

99

100 **Cardiovascular Outcome Trials**

101 Both alirocumab and evolocumab have been evaluated in large, multi-center,
102 randomized controlled trials that evaluated their effects on CV events and other key CV
103 endpoints. An overview of the trials' design and key findings is important given subsequent
104 analyses of these data have provided significant guidance regarding which patients benefit
105 most from PCSK9-mAbs (Table 1).

106 The Further Cardiovascular Subjects with Elevated Risk (FOURIER) trial¹¹
107 evaluated the safety and efficacy of evolocumab in 27,564 subjects with stable ASCVD,
108 defined as a history of MI, ischemic stroke, or symptomatic peripheral artery disease
109 (PAD), already taking optimized statin therapy (at least atorvastatin 20 mg or equivalent)
110 with a LDL-C ≥ 70 mg/dL or non-high-density lipoprotein cholesterol (non-HDL-C) ≥ 100
111 mg/dL. The primary outcome was a composite of major adverse cardiovascular events
112 (MACE), including CV death, MI, fatal or stroke, hospitalization for unstable angina, or
113 coronary revascularization. The incidence of the primary outcome was significantly lower in
114 subjects randomized to evolocumab (9.8%) compared to placebo (11.3%) (HR: 0.85; 95%
115 CI, 0.79-0.92) with a number needed to treat (NNT) of 74. Evolocumab was also
116 associated with reduction in the key secondary outcomes with significant reductions in MI
117 (HR: 0.73; 95% CI, 0.65-0.82), stroke (HR: 0.79; 95% CI, 0.66-0.95), and coronary
118 revascularization (HR: 0.78; 95% CI, 0.71-0.86). Injection-site reactions (2.1%) vs placebo
119 (1.6%) were the only nominally significant adverse event in this trial ($P < 0.001$).

120 The Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome
121 (ODYSSEY-OUTCOMES) trial¹² evaluated alirocumab in 18,924 subjects with recent (1 to
122 12 months) acute coronary syndrome (ACS) prior to enrollment on background high-
123 intensity statin therapy with an LDL-C ≥ 70 mg/dL, non-HDL-C ≥ 100 mg/dL, or
124 apolipoprotein B (apoB) ≥ 80 mg/dL. The primary outcome was a composite of death from

125 coronary heart disease, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina
126 requiring hospitalization. The incidence of the primary outcome was significantly lower in
127 subjects randomized to alirocumab (9.5%) compared to placebo (11.1%) (HR: 0.85; 95%
128 CI, 0.78-0.93) with an NNT of 63. Key secondary outcomes in favor of alirocumab versus
129 placebo included any coronary heart disease event (death from coronary heart disease,
130 nonfatal MI, unstable angina requiring hospitalization, and ischemia-driven coronary
131 revascularization procedure) (HR: 0.88; 95% CI, 0.81-0.95), major coronary heart disease
132 event (coronary heart disease and nonfatal MI) (HR: 0.88; 95% CI, 0.80-0.96), any CV
133 event (death from CV causes, nonfatal MI, unstable angina requiring hospitalization,
134 ischemia-driven coronary revascularization procedure, or nonfatal ischemic stroke) (HR:
135 0.87; 95% CI, 0.81-0.94), and composite of death from any cause, nonfatal MI, or nonfatal
136 ischemic stroke (HR: 0.86; 95% CI, 0.79-0.93). Injection-site reactions occurred more
137 frequently in alirocumab-treated subjects (3.8%) compared to placebo (2.1%) (P<0.001).

138

139 **Evidence Supporting the Use of PCSK9-mAbs in Select Populations**

140 Multiple prespecified analyses of FOUREIR and ODYSSEY-OUTCOMES have
141 provided important insights as to the specific populations and factors that clinicians may
142 consider when identifying those most likely to benefit from alirocumab or evolocumab.
143 These data also informed recent clinical practice guidelines and scientific statements, and
144 reshaped the conversation around the cost-effectiveness of these therapies.

145

146 *Polyvascular disease*

147 It is important to note that ASCVD includes a broad range of vascular diseases,
148 including significant atherosclerosis in the coronary, cerebrovascular, and/or peripheral
149 arterial territories.¹ A higher degree of atherosclerotic burden may be expected to impart

150 an increased risk of future ASCVD events. Thus, analysis of the benefits of PCSK9-mAbs
151 in subjects with polyvascular ASCVD may be useful to determine which subjects are at
152 highest risk and most likely to benefit from PCSK9-mAbs. While the primary endpoints of
153 both FOURIER and ODYSSEY-OUTCOMES focused primarily on coronary and
154 cerebrovascular events, subjects with pre-existing peripheral arterial disease (PAD) were
155 included in FOURIER and a subset of subjects had baseline PAD in ODYSSEY-
156 OUTCOMES.

157 Among the FOURIER study population, 13.2% of subjects had PAD at baseline and
158 the majority (58.7%) of these subjects had a previous MI or stroke, in addition to PAD.¹¹
159 Subjects with PAD at baseline were more likely to demonstrate renal insufficiency,
160 diabetes mellitus (DM), and smoke at baseline. In a post-hoc analysis¹⁴ of the FOURIER
161 trial evaluating the efficacy of evolocumab by PAD at baseline, evolocumab significantly
162 reduced the risk of the primary endpoint in both groups (PAD and no PAD) compared to
163 placebo. Both the relative risk reduction (RRR) and absolute risk reduction (ARR) were
164 lower in patients with PAD treated with evolocumab versus placebo (RRR=21%:
165 ARR=3.5%) compared to subjects without PVD (RRR=14%; ARR=1.6%). The secondary
166 composite endpoint of CV death, MI, or stroke occurred less frequently in subjects with
167 PAD receiving evolocumab (9.5%) vs placebo (13%). Furthermore, major adverse limb
168 events (MALE), including acute limb ischemia, urgent peripheral revascularization, and
169 major amputations, were also assessed in the post-hoc analysis. Overall MALE rates were
170 low (<1% in the entire study population) yet were lower among subjects receiving
171 evolocumab compared to placebo in the overall study cohort (0.27% vs 0.45%; HR: 0.58;
172 95% CI, 0.38-0.88). In subjects with PAD, MALE occurred at a higher frequency (1.5%
173 evolocumab vs 2.4% placebo) and evolocumab was associated with lower risk of MALE
174 (HR: 0.63; 95% CI, 0.39-1.03). Given that MALE was higher among subjects with PAD at

175 baseline, these subjects are at higher risk of ASCVD as well as MALE and seemed to
176 benefit most from further LDL-C lowering with evolocumab.

177 A prespecified analysis of ODYSSEY-OUTCOMES assessed risk of MACE by
178 presence of mono- or poly-vascular disease.¹⁵ Monovascular disease was defined as
179 coronary artery disease (CAD), while polyvascular disease was defined as ASCVD in two
180 vascular areas (coronary plus cerebrovascular or peripheral arterial) or all three ASCVD
181 sites (coronary, cerebrovascular, and peripheral arterial disease) among the 18,924
182 subjects in the ODYSSEY-OUTCOMES trial. Overall, 91.8% of study subjects exhibited
183 monovascular ASCVD, 7.4% exhibited polyvascular disease of two vascular sites, and
184 0.8% manifested polyvascular disease in all three major vascular distributions. Notably,
185 subjects with ASCVD in three sites were older, had lower rates of high-intensity statin use,
186 exhibited greater LDL-C and Lp(a) levels at baseline, and were more likely to smoke.
187 Similar to the results of the overall study population, alirocumab was associated with lower
188 rates of the primary endpoint compared to placebo in those with monovascular disease
189 (HR: 0.85; 95% CI, 0.77-0.93) and an ARR of 1.4% between treatment groups.

190 Rates of the primary endpoint were higher in subjects with atherosclerosis at two
191 sites (coronary and either cerebrovascular or peripheral arterial) than subjects with
192 monovascular disease.¹⁵ However, there was no statistically significant reduction with
193 evolocumab among subjects with CAD and PAD (HR: 0.93; 95% CI, 0.67-1.30) or those
194 with CAD and cerebrovascular disease (HR: 0.87; 95% CI, 0.63-1.19). The ARR
195 associated with alirocumab among subjects with CAD and evidence of vascular disease at
196 an additional site was 1.9%. Subjects with vascular disease at all three sites (CAD,
197 cerebrovascular, and PAD), had the highest rates of MACE and alirocumab was
198 associated with a lower rate of MACE (26.8%) compared to placebo (39.7%) despite a
199 non-significant reduction in the primary outcome (HR: 0.64; 95% CI, 0.35-1.12). The ARR

200 (13%) was greatest among this group of subjects with diffuse ASCVD and the NNT was 8.
201 Similarly, all-cause mortality was significantly reduced among this group of subjects with
202 polyvascular disease treated with alirocumab (5.6%) vs placebo (21.8), (HR: 0.23; 95% CI,
203 0.08-0.68).

204

205 *Previous Myocardial Infarction*

206 A majority of subjects (81%) met FOURIER inclusion criteria by previous MI, with a
207 median 3.4 years from most recent MI.¹¹ A prespecified analysis of FOURIER sought to
208 evaluate whether evolocumab would produce a greater ASCVD risk reduction among
209 subjects considered at elevated risk.¹⁶ As such, subjects were stratified by time since most
210 recent MI, number of previous MI events, as well as presence of residual multivessel CAD
211 from the larger FOURIER study. Subjects with two or more previous MIs, multivessel CAD,
212 or an MI within the previous two years exhibited higher rates of the primary MACE
213 endpoint compared to those with one previous MI, no multivessel CAD, or an MI occurring
214 more than 2 years ago. Each high-risk sub-group, except recent MI, were more likely to be
215 male and had higher rates of PAD and hypertension. All three high-risk groups were more
216 frequently prescribed high-intensity statin. For each high-risk subgroup, evolocumab was
217 associated with an RRR of 18 to 21% and an ARR between 3.4% and 3.7% across the
218 high-risk groups compared to placebo. From this analysis, subjects with recent MI, multiple
219 MI events, or residual multivessel CAD represent a group with elevated ASCVD risk
220 despite statin treatment who appear to derive greater absolute risk reduction with the
221 addition of a PCSK-mAb.

222

223 *Coronary Artery Bypass Graft Surgery*

224 A prespecified analysis of ODYSSEY OUTCOMES sought to determine the benefit
225 of alirocumab stratified by prior CABG.¹⁷ For this analysis, three subgroups were identified;
226 no previous CABG (89.3%), CABG following the index ACS event (5.4%), and CABG prior
227 to index event (5.3%). Those with prior CABG were older, more likely to be male, had
228 lower utilization of high-intensity statins, and had higher baseline LDL-C, apoB, and Lp(a)
229 levels compared to the other CABG sub-groups. Across all three CABG sub-groups,
230 alirocumab was associated with lower rates of the primary composite MACE outcome
231 compared to placebo but appeared to have the greatest risk reduction among those with
232 prior CABG (24.5% versus 30.9%, HR: 0.77; 95% CI, 0.61-0.98). Additionally, rates of CV
233 death were lower among subjects treated with alirocumab (5.6%) compared to placebo
234 (9.2%), with an ARR of 3.6% (HR: 0.61; 95% CI, 0.38-0.97).

235

236 *Diabetes mellitus*

237 A prespecified analysis of ODYSSEY-OUTCOMES assessed the efficacy of
238 evolocumab according to DM status at baseline.¹⁸ Among the total study population,
239 28.8% of subjects had confirmed DM at baseline and 43.6% had prediabetes. Achieved
240 LDL-C values were similar among subjects receiving placebo or alirocumab across all
241 three sub-groups. The primary endpoint occurred at higher rates in subjects with DM and
242 prediabetes compared to normal glucose in both the placebo and alirocumab groups.
243 Among subjects with normal glucose, the primary endpoint occurred in 7.3% in alirocumab
244 and 8.5% in placebo groups (HR: 0.85; 95% CI, 0.70-1.03). In the subgroup of subjects
245 with prediabetes, the primary endpoint occurred in 8.0% and 9.2% of subjects in the
246 alirocumab and placebo groups, respectively (HR: 0.86; 95% CI, 0.74-1.00). Note, both the
247 normal glucose and prediabetes subjects treated with alirocumab experienced an ARR of
248 1.2% compared to placebo. In the subgroup of subjects with DM, event rates occurred in

249 14.1% and 16.4% of subjects in the alirocumab and placebo groups, respectively (HR:
250 0.84; 95% CI, 0.74-0.97). It is noteworthy that the corresponding ARR of 2.3% was nearly
251 double that of normal or prediabetes subgroups.

252 Risk of new-onset DM is a concern associated with statin therapy, although likely a
253 greater risk to those with pre-existing risk factors for developing DM (e.g.,
254 overweight/obese, family history).¹⁹ A prespecified safety analysis of the ODYSSEY-
255 OUTCOMES trial evaluated the risk of developing new-onset DM associated with
256 alirocumab.¹⁸ In subjects with normal glucose status at baseline, 3.0% of subjects treated
257 with alirocumab and 2.4% of subjects treated with placebo developed DM. In the
258 prediabetes subgroup, the rates of new-onset DM were 13.8% for alirocumab and 15.3%
259 for placebo. From this subgroup analysis, it appears that subjects with DM are at increased
260 risk for subsequent ASCVD following an ACS event, with a greater risk reduction when
261 treated with alirocumab. For subjects at risk of developing DM, alirocumab does not
262 appear to increase the risk of new-onset DM.

263 An analysis from the FOURIER trial reported similar findings in a prespecified
264 analysis of DM status.²⁰ Among the study subjects, 40% had DM and the rest were
265 categorized as non-DM, although a majority of these subjects (62.6%) met criteria for
266 prediabetes. Risk of the primary composite MACE endpoint was lower among subjects
267 with DM treated with evolocumab (HR: 0.83; 95% CI, 0.75-0.93) and in those without DM
268 (HR: 0.87; 95% CI, 0.79-0.96), similar to the findings of the ODYSSEY-OUTCOMES sub-
269 group analysis.¹⁸ Additionally, the ARR was greater among subjects with DM compared to
270 those without DM (2.7% vs 1.6%, respectively). The risk of new-onset DM was not
271 increased with evolocumab among subjects without DM at baseline, including those with
272 prediabetes.

273 Although both trials^{11,12} were of relatively short duration (less than 3 years), a large
274 proportion of subjects with DM at baseline were included in both trials. Results of these
275 subgroup analyses suggest PCSK9-mAbs result in a greater risk reduction in subjects with
276 DM without increasing the risk of new-onset DM, even in subjects with prediabetes. These
277 results contrast to Mendelian randomization studies that suggest that genetic variants in
278 PCSK9, used as a surrogate for therapeutic PCSK9-mAbs, were associated with
279 increased risk of DM.^{21,22} It is important to note that both of CV outcome trials were of
280 relatively short duration and longer follow-up of patients on PCSK9-mAbs will be critical to
281 assess their impact on the future development of DM.

282

283 *Chronic Kidney Disease*

284 Similar to DM, coronary heart disease is the leading cause of death in individuals
285 with chronic kidney disease (CKD).²³ Benefits of evolocumab on MACE by CKD status
286 was assessed in a post-hoc analysis of the FOURIER trial.²⁴ Information on kidney
287 function was available for nearly all subjects (99.96%) and subjects were categorized by
288 eGFR calculated by CKD-EPI equation. A majority of subjects (54.6%) had stage 2 CKD,
289 16.1% had stage 3 CKD or lower, and 29.3% had preserved renal function. Subjects with
290 at least stage 3 CKD were more likely to have hypertension and DM, higher baseline TG
291 and Lp(a) values, more likely to be treated with a renin-angiotensin-aldosterone inhibitor,
292 but less likely to be receiving antiplatelet agents. Stage 3 CKD or higher was associated
293 with an increased risk of MACE (HR: 1.36; 95% CI, 1.20-1.54) compared to normal kidney
294 function, while no increased risk was seen in subjects with stage 2 CKD compared to
295 preserved renal function.

296 Primary event rates by CKD status demonstrated that for each subgroup, treatment
297 with evolocumab was associated with a lower risk of the primary endpoint at 30 months.²⁴

298 For subjects with at least stage 3 CKD, a primary endpoint occurred in 14.6% and 16.1%
299 of subjects treated with evolocumab and placebo, respectively (HR: 0.89; 95% CI, 0.76-
300 1.05). Subjects with preserved renal function treated with evolocumab also experienced
301 fewer primary events (10.0%) versus placebo (12.2%) (HR: 0.82; 95% CI, 0.71-0.94).
302 Subjects with preserved function were found to have the greatest ARR (2.2%) with
303 evolocumab, while those with at least stage 3 CKD had the lowest ARR (1.5%) for the
304 primary endpoint; however, greater ARR was seen in patients with at least stage 3 CKD for
305 the key composite secondary endpoint (CV death, MI, or stroke) compared to preserved
306 renal function. No significant differences in changes to renal function were noted between
307 the placebo group according to baseline kidney function. Although associated with a lower
308 ARR for the primary outcome, subjects with worse renal function had the highest rates of
309 MACE and appeared to benefit most from evolocumab when assessed for the key
310 secondary endpoint of CV death, MI, or stroke. Given the apparent renal safety of
311 evolocumab, those with previous ASCVD and additional risk factors, such as CKD, are
312 likely to derive larger risk reductions than subjects without additional risk factors.

313

314 *Elevated Lp(a) Levels*

315 Lipoprotein(a) is an LDL-like particle synthesized by the liver that contains an
316 apoB molecule and apolipoprotein (a) [apo(a)].²⁵ Elevated Lp(a) levels are strongly
317 associated with an increased risk of ASCVD and calcific aortic stenosis.^{26,27} A meta-
318 analysis of 27 randomized controlled trials found PCSK9-mAbs reduce Lp(a) levels by
319 21.9% (95% CI, -24.3 to -19.5).²⁸ However, it remains unclear whether reduction in Lp(a)
320 with drug therapy reduces CV event rates as this has yet to be evaluated in a prospective,
321 randomized controlled trial.

322 In a prespecified analysis of the FOURIER trial, investigators sought to assess the
323 relationship between evolocumab, Lp(a) levels, and CV events.²⁹ The median Lp(a) at
324 baseline was 37 nmol/L (IQR 13-165), while the quartile with the highest baseline Lp(a)
325 had a mean value of 216.0 nmol/L. By week 48, Lp(a) had been reduced by 26.9% with
326 evolocumab, with greater absolute reductions seen in the highest Lp(a) quartile. In
327 subjects with baseline Lp(a) values at or below the median, evolocumab was associated
328 with a non-significant reduction of the composite primary endpoint (HR: 0.93; 95% CI,
329 0.80-1.08). In subjects with Lp(a) levels above the median baseline value, event rates
330 were significantly lower with evolocumab compared to placebo (HR: 0.77; 95% CI, 0.67-
331 0.88). Stratifying subjects by Lp(a) also identified a significant reduction in the composite
332 CV outcome among subjects with baseline Lp(a) above 120 nmol/L (HR: 0.75; 95% CI,
333 0.64-0.88), while the risk reduction was less in subjects with baseline Lp(a) below 120
334 nmol/L (HR: 0.89; 95% CI, 0.79-1.01). An exploratory analysis also assessed the
335 relationship between achieved LDL-C and Lp(a) and suggested greater risk reduction in
336 subjects achieving both LDL-C and Lp(a) levels below the median value. In total, it
337 appears that subjects with ASCVD and elevated Lp(a) are at higher risk for subsequent CV
338 events and may derive greater risk reduction with PCSK9-mAbs. Whether lowering Lp(a)
339 reduces ASCVD risk remains unknown, but this exploratory analysis suggests that
340 achieving low levels of both Lp(a) and LDL-C may offer greater CV risk reduction.

341

342 **Clinical Practice Guidelines and Scientific Statements**

343 In light of recent clinical outcome data from FOURIER and ODYSSEY-
344 OUTCOMES, clinical practice guidelines and scientific statements from various
345 professional organizations were updated in 2018 and 2019. It is clear from these

346 recommendations that clinicians should individualize treatment decisions to ensure
347 PCSK9-mAb use is targeted at patients most likely to benefit.

348
349 *2018 American College of Cardiology/American Heart Association/Multi-society*
350 *Cholesterol Guideline*

351 This guideline stratified subjects with clinical ASCVD into two groups: 1) not at very-
352 high risk and 2) at very high risk (Table 2).⁴ By definition, very-high risk includes patients
353 with clinical ASCVD with multiple major ASCVD events or who have had one major
354 ASCVD event and have other high-risk conditions. This approach embodies the concept of
355 individualizing the use of PCSK9-mAbs to those at the highest risk who are most likely to
356 benefit.

357 The guideline recommends adding ezetimibe to maximally tolerated statin therapy
358 for patients at very high-risk with an LDL-C threshold of 70 mg/dL or greater before
359 considering a PCSK9-mAb.⁴ This decision was based on several factors. Cost-
360 effectiveness was a major consideration as ezetimibe is an oral, once-daily tablet that is
361 available as a generic, while PCSK9 inhibitors are fully human mAbs with an average
362 wholesale price of approximately \$14,000/year at the time the guideline was being
363 developed. Thus, for the first time, the writing committee added a value statement
364 indicating that PCSK9-mAbs were not deemed cost-effective in patients with ASCVD or
365 familial hypercholesterolemia (FH). Additionally, ezetimibe is administered orally, which
366 may be preferred by many patients and observational data suggests that upwards of 58%
367 of patients receiving a high-intensity statin plus ezetimibe will achieve an LDL-C below 70
368 mg/dL.³⁰ Therefore, from a practical perspective, a trial of ezetimibe is reasonable before
369 considering a PCSK9-mAb and is sometimes required by third party payers before a prior
370 authorization for a PCSK9-mAb will be approved.

371 As for other groups, including patients with ASCVD who are not at very high-risk
372 and primary prevention groups with or without DM, there are no recommendations to
373 consider PCSK9-mAbs in any case. The use of PCSK9-mAbs is recommended as an
374 option for patients with severe hypercholesterolemia (LDL-C \geq 190 mg/dL) but only after
375 receiving maximally tolerated statin and ezetimibe. The value of PCSK9-mAbs for patients
376 with FH was deemed uncertain at mid-2018 prices.

377

378 *2019 Consensus Statement from the National Lipid Association*

379 Following release of the 2018 ACC/AHA/Multi-Society Cholesterol Guideline, the
380 average wholesale price for alirocumab and evolocumab was reduced by 60%.³¹ The
381 authors of this statement carefully reviewed subgroup analyses of FOURIER and
382 ODYSSEY-OUTCOMES to identify groups of patients where alirocumab and evolocumab
383 would be of reasonable value based on the lower price.³¹ This evaluation was performed
384 by considering the net benefit from LDL-C lowering according to the ARR and NNT based
385 on estimates for LDL-C reductions of 20%, 50%, and 65% with PCSK9-mAbs. Accordingly,
386 the authors determined that PCSK9-mAbs were of reasonable (<US\$100,000 per quality
387 adjusted life year [QALY]) or high (<US\$50,000 per QALY) value in select higher risk
388 groups according to 2019 prices (Table 2). Additionally, the authors determined that the 5-
389 year NNT ranged from 21 to 28 among these high-risk groups, further supporting the value
390 of alirocumab and evolocumab in these groups.

391

392 *2019 European Society of Cardiology/European Atherosclerosis Society Guidelines for the*
393 *Management of Dyslipidemias*

394 Similar to US Guidelines, the European Dyslipidemia Guidelines continue to support
395 the initial use of maximally tolerated statin and ezetimibe before considering a PCSK9-

396 mAb.³² Similar to the US Guideline, PCSK9-mAbs are recommended in subjects who are
397 at very-high risk, although this is defined slightly differently (Table 2). The very-high risk
398 category not only includes patients with established ASCVD, but also those who have DM
399 with target organ damage, at least three risk factors, or early diagnosis; as well as subjects
400 with severe CKD, a calculated SCORE $\geq 10\%$ for 10-year risk of fatal CV disease, and
401 subjects with FH and additional risk factors. Whereas the US Guidelines recommend
402 PCSK9-mAbs primarily for those with established ASCVD, the European Guidelines allow
403 consideration for their use in very-high risk primary prevention patients. One factor that
404 may have informed the decision to more broadly recommend PCSK9-mAbs was the need
405 to have more potent LDL-C lowering to achieve the lower LDL-C goal (<55 mg/dL) that the
406 European Guidelines committee established for very-high risk secondary and primary
407 prevention subjects and very-high risk subjects with DM or FH.

408 Issues related to cost-effectiveness are discussed in detail in the European
409 Guideline.³² The cost-effectiveness of generically available statins and ezetimibe is
410 reaffirmed, while the cost-effectiveness of PCSK9-mAbs is linked to a variety of high-risk
411 patient groups based on lower prices. Importantly, the guideline notes the evidence gaps
412 for determining the cost-effectiveness of lipid-lowering treatments, including the need for
413 more precise risk estimation scores to better target intervention needs and longer-term
414 studies that would help provide more precise cost-effectiveness estimates.

415

416 **Remaining Questions and Ongoing Clinical Trials**

417 *Long-Term Safety of PCSK9-mAbs*

418 There is limited long-term safety data with PCSK9-mAbs as FOURIER and
419 ODYSSEY-OUTCOMES were limited to a median 2.2 and 2.8 years of follow-up,
420 respectively. The Open-Label Study of Long-Term Evaluation Against LDL-C (OSLER-1)

421 trial was initiated in 2011 to help address this concern.³³ Subjects enrolled in OSLER-1
422 were randomized to standard of care or evolocumab 420 mg monthly for one year, then
423 subjects could opt-in to the all-evolocumab period and receive evolocumab for four
424 additional years. Of the 1,324 subjects originally enrolled in OSLER-1, long-term (up to 5
425 years) safety results were available for 1,255 of these subjects. The mean \pm standard
426 deviation (SD) for age was 57 ± 12 years and 53% were female. A consistent LDL-C
427 reduction of approximately 56% was maintained over the study period. Importantly, there
428 were no significant differences between groups for adverse event rates and no neutralizing
429 antibodies were detected with evolocumab use.

430 Currently, a multicenter, open-label extension study of the FOURIER trial
431 (clinicaltrials.gov, [NCT03080935](https://clinicaltrials.gov/ct2/show/study/NCT03080935)) is ongoing to provide extended long-term safety data in
432 subjects who completed the FOURIER trial. Subjects will have laboratory assessments at
433 day 1, week 12, and every 6 months thereafter. This study will enroll 1600 subjects and
434 continue for approximately 5 years. The primary endpoint is incidence of adverse events.
435 The anticipated study completion date is 2022 and it will provide valuable data regarding
436 the long-term safety of evolocumab.

437

438 *PCSK9-mAb Use in the Acute Setting*

439 Early initiation of high-intensity statin therapy during the acute MI phase
440 demonstrated significant reductions in CV events and mortality.³⁴ However, the addition of
441 a PCSK9-mAb to background statin therapy during this acute MI phase has only recently
442 been explored.

443 Trankle, et al.³⁵ randomized 20 subjects with type 1 non-ST-elevation myocardial
444 infarction (NSTEMI) and an LDL-C >70 mg/dL despite high-intensity statin therapy to either
445 a single dose of alirocumab 150 mg or placebo within 24 hours of presentation. The

446 primary endpoint was change in LDL-C at 14 days. The median baseline LDL-C was 98
447 mg/dL and 91 mg/dL in the placebo and alirocumab groups, respectively. At 72 hours,
448 subjects receiving placebo experienced a very modest reduction in LDL-C to 94 mg/dL,
449 while those receiving alirocumab achieved an LDL-C level of 73 mg/dL ($P<0.02$). At 14
450 days, the LDL-C in the placebo group was 90 mg/dL, while the LDL-C in the alirocumab
451 group was further reduced to 28 mg/dL ($P<0.001$). Secondary endpoints included changes
452 in high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), interleukin-10 (IL-10),
453 and tumor necrosis factor α (TNF- α), but there were no significant differences for between-
454 group changes.

455 Koskinas, et al.³⁶ published a larger trial, Evolocumab for Early Reduction of LDL-
456 cholesterol Levels in Patients with Acute Coronary Syndromes (EVOPACS), involving 308
457 subjects hospitalized for non-ST-elevation ACS with symptom onset <72 hours or ST-
458 elevation myocardial infarction with symptom onset <24 hours who had elevated LDL-C,
459 regardless of background lipid-lowering therapy. Participants were randomized to either
460 evolocumab 420 mg or matching placebo, along with atorvastatin 40 mg. Interestingly,
461 78.2% of subjects were not receiving statin therapy at baseline. Those randomized to
462 evolocumab had a 77.1% reduction in LDL-C by week eight and 95.7% achieved an LDL-C
463 <70 mg/dL, while the placebo group achieved only a 35.4% reduction in LDL-C and only
464 37.6% achieved an LDL-C <70 mg/dL. Similar to the findings reported by Trankle, et al.³⁵,
465 the change in hsCRP and other inflammatory markers were not significantly different
466 between groups. Adverse event rates were similar between the two groups.

467 While both studies demonstrated the feasibility of initiating a PCSK9-mAb during the
468 acute MI phase, it remains unknown if this early initiation would lead to a reduction in CV
469 events. The ODYSSEY-OUTCOMES trial¹² enrolled post-ACS subjects 1 to 12 months
470 from their index event, but only one-third of the participants were randomized less than two

471 months from the index event. However, the greatest relative risk reduction (HR 0.83; 95%
472 CI, 0.71 to 0.96) was observed in this group, suggesting there may be greater benefit with
473 earlier initiation of PCSK9-mAbs.

474

475 *PCSK9-mAb Use in Subjects Without Prior MI or Stroke*

476 While there is clear evidence supporting the use of alirocumab and evolocumab in
477 secondary and post-ACS populations, it is unknown if these agents can reduce CV events
478 in subjects without prior MI or stroke. The Effect of Evolocumab in Subjects at High
479 Cardiovascular Risk Without Prior Myocardial Infarction or Stroke (VESALIUS-CV) trial is a
480 randomized, double-blind, placebo-controlled, multicenter study seeking to answer this
481 question (clinicaltrials.gov, [NCT03872401](https://clinicaltrials.gov/ct2/show/study/NCT03872401)). The trial has a co-primary outcome of 3-point
482 (coronary heart disease death, MI, or ischemic stroke) and 4-point (coronary heart disease
483 death, MI, or ischemic stroke, any ischemia-driven arterial stroke) MACE. Eligible subjects
484 include adults aged 50 to 75 years with an LDL-C \geq 100 mg/dL or non-HDL-C \geq 130 mg/dL
485 at screening, after at least 4 weeks of optimized lipid-lowering therapy, evidence of
486 significant CAD, cerebrovascular disease, PAD, or DM, and at least one additional high-
487 risk feature. Importantly, those with a prior MI, stroke, or CABG will be excluded.
488 Participants will be randomized to placebo or evolocumab 140 mg b-weekly for a minimum
489 of four years. The anticipated study completion date is 2024. If the use of evolocumab
490 improves cardiovascular outcomes in this population, it may dramatically increase the
491 number of patients eligible for PCSK9-mAb therapy.

492

493 *Silencing PCSK9 with Inclisiran*

494 While initial approaches to modulating PCSK9 have focused on the use of mAbs to
495 inhibit the function of PCSK9, inclisiran targets PCSK9 synthesis via small interfering RNA

496 (siRNA) (Figure 1). Inclisiran is a long acting synthetic siRNA conjugated to triantennary
497 *N*-acetylgalactosamine carbohydrates (GalNAC) which bind hepatocyte expressed
498 asialoglycoprotein receptors.³⁷ Once inside the hepatocyte, inclisiran targets specifically,
499 and hence, silences the *PCSK9* messenger RNA (mRNA) by preventing its translation. As
500 a result, PCSK9 synthesis is dramatically reduced. Since plasma concentration of PCSK9
501 is markedly decreased, LDL receptors are maximally expressed, resulting in significant
502 LDL-C reduction. One advantage of inclisiran compared to PCSK9-mAbs is the potential
503 for a longer duration of action requiring less frequent administration.³⁸

504 In the phase 2 Trial to Evaluate the Effect of ALN-PCSSC (i.e., inclisiran) Treatment
505 on LDL-C (ORION-1)³⁹, subjects with an LDL-C ≥ 70 mg/dL (presence of clinical ASCVD)
506 or LDL-C ≥ 100 mg/dL (absence of clinical ASCVD) on maximally tolerated statin were
507 randomized to one of eight groups: single dose of inclisiran (200, 300, or 500 mg) or
508 placebo, or two doses of inclisiran on day 1 and day 90 (100, 200, or 300 mg) or placebo.
509 The primary endpoint was change in LDL-C from baseline to day 180, which ranged from
510 27.9% to 41.9% (single dose) and 35.5% to 52.6% (two doses). These LDL-C reductions
511 were statistically significant for all comparisons versus placebo ($P < 0.001$). The greatest
512 reduction in LDL-C was found with the two 300 mg doses of inclisiran as nearly 50% of
513 these individuals achieved an LDL-C below 50 mg/dL at day 180. Adverse events with
514 inclisiran included injection site reactions (5%), hepatic injury (rare), and development of
515 antidrug antibodies (only one patient).

516 The efficacy of inclisiran is highly durable as it reduces LDL-C by 54% when
517 administered as 300 mg on day 1, 90, and then every six months.⁴⁰ Additionally, in the
518 ORION-11 trial (clinicaltrials.gov, [NCT03400800](https://clinicaltrials.gov/ct2/show/study/NCT03400800)), an exploratory composite endpoint of
519 CV death, cardiac arrest, non-fatal MI, or stroke occurred in 63 patients (7.8 percent) in the
520 inclisiran group compared to 83 patients (10.3 percent) in the placebo group.⁴⁰ Thus,

521 despite differences in mechanism of action, it appears that inclisiran produces similar
522 reductions in LDL-C as PCSK9-mAbs and may also produce similar reductions in major
523 CV events. The ongoing ORION-4 trial (clinicaltrials.gov, [NCT03705234](https://clinicaltrials.gov/ct2/show/study/NCT03705234)) is evaluating the
524 effect of inclisiran on CV outcomes and is expected to be completed in 2024.

525

526 **Conclusion**

527 In less than two decades since the discovery of PCSK9, there are two approved
528 therapeutic agents that target plasma PCSK9 and significantly reduce LDL-C. Moreover,
529 both PCSK9-mAbs demonstrated improvement in CV outcomes in randomized controlled
530 trials. These trials also demonstrate that individuals at very-high risk of ASCVD events
531 garner the greatest benefit with these therapies. The use of PCSK9-mAbs appears most
532 cost-effective in this high-risk population as well. It remains to be seen, however, if these
533 therapies will be utilized in lower-risk patients or ever be considered for use as a
534 monotherapy option. Ongoing safety extension trials may provide further evidence that
535 maintaining very low levels of LDL-C via pharmacologic intervention is indeed safe and
536 maximizes ASCVD risk reduction. New developments with novel approaches to
537 antagonizing PCSK9, such as siRNA therapies, will only enhance our ability to sustain
538 significant reductions in LDL-C levels with a lower medication burden and possibly
539 improved adherence.

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696 **Figure 1. Approaches to Modulating PCSK9**

697 Compares the mechanism of action for PCSK9-mAb (A) and siRNA (B) approaches to
698 modulating PCSK9. Both result in increased presence of LDL-R on the hepatocyte surface
699 by either inhibiting the functionality of PCSK9 (A) or turning off PCSK9 synthesis (B).

700 Abbreviations: LDL-P, low-density lipoprotein particle; LDL-R, low-density lipoprotein

701 receptor; mAb, monoclonal antibody; PCSK9, proprotein convertase subtilisin/kexin type 9;

702 siRNA, small interfering RNA

703

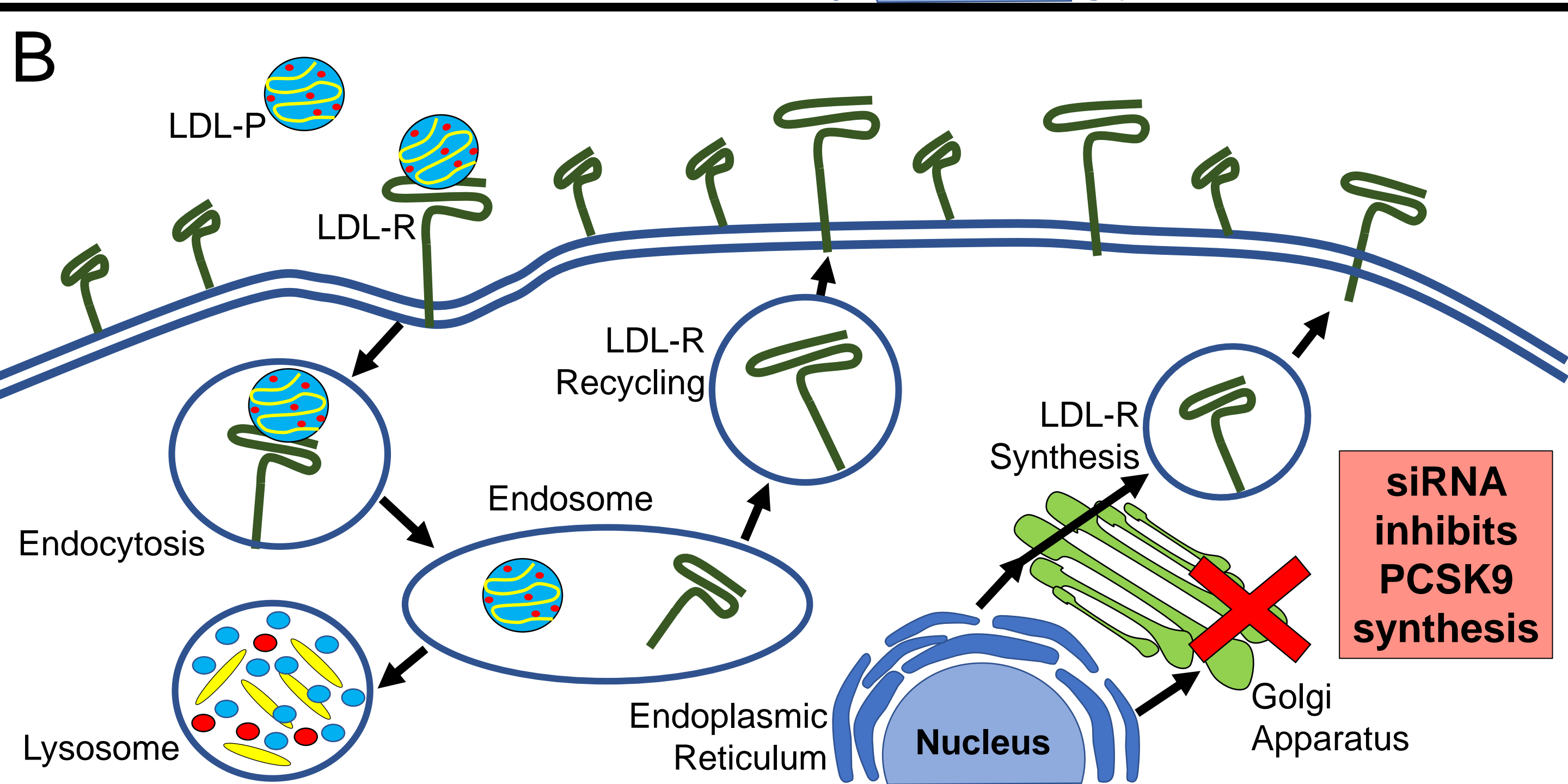
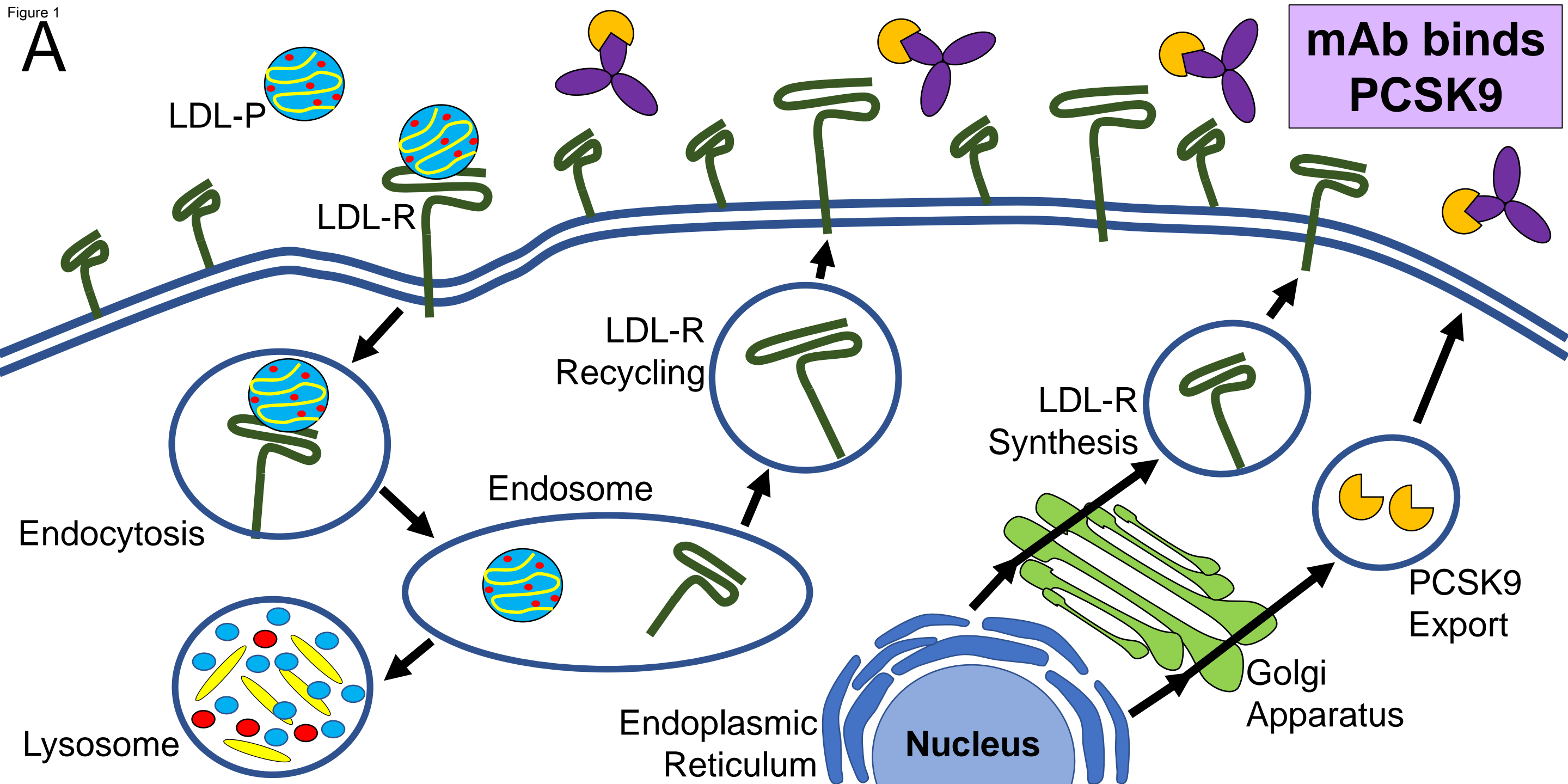


Table 1. Baseline Characteristics of PCSK9-mAb Cardiovascular Outcome Trials

Characteristic	FOURIER ¹¹	ODYSSEY-OUTCOMES ¹²
Intervention	Evolocumab 140 mg SC every two weeks or 420 mg SC every four weeks	Alirocumab 75 mg SC every two weeks Dose-adjusted, per protocol, to maintain LDL-C levels between 25 and 50 mg/dL
Median study duration, years	2.2	2.8
Mean age, years	62.5	58.5
White	85%	79%
Female sex	25%	25%
Hypertension	80%	65%
Diabetes mellitus	36%	29%
Prior myocardial infarction	81%	*19%
Prior stroke	19%	3.2%
High-intensity statin	69%	100%
Ezetimibe use	2.9%	5.3%
LDL-C, mg/dL	92	92
* All patients enrolled had an index acute coronary syndrome but only 19% had a prior myocardial infarction LDL-C, low-density lipoprotein cholesterol; SC, subcutaneous		

Table 2. Comparison of Recommendations for PCSK9-mAb Use

Recommendations	2018 ACC/AHA/Multi-Society Guideline	2019 NLA PCSK9 Value Statement	2019 EAS/ESC Guideline
Risk category definitions	<p>Very-high risk ASCVD</p> <ul style="list-style-type: none"> Multiple major ASCVD events Single ASCVD event with multiple high-risk conditions 	<p>Extremely-high risk</p> <ul style="list-style-type: none"> ≥40% 10-year ASCVD risk <p>Very-high risk</p> <ul style="list-style-type: none"> 30-39% 10-year ASCVD risk <p>High risk</p> <ul style="list-style-type: none"> 20-29% 10-year ASCVD risk cardiometabolic risk factors 	<p>Very-high risk</p> <ul style="list-style-type: none"> ASCVD ± FH FH with other major risk factor Chronic kidney disease with eGFR <30 ml/min/1.73m² DM and target organ damage, ≥3 major risk factors, or duration of T1DM >20 years 10-year risk of fatal CVD ≥10%
Use in Patients with Clinical ASCVD	<p>Very-high risk ASCVD and LDL-C ≥70 mg/dL on maximal statin PLUS ezetimibe.</p> <p>Using a PCSK9 inhibitor before ezetimibe is considered low value.</p>	<p>Extremely-high risk and LDL-C ≥70 mg/dL</p> <p>Very-high risk and LDL-C ≥ 100 mg/dL on maximal statin ± ezetimibe</p> <p>High risk with LDL-C ≥130 mg/dL on maximal statin ± ezetimibe</p>	<p>Very-high risk with LDL-C ≥ 55 mg/dL on maximal statin PLUS ezetimibe</p>
Use in Patients Without Clinical ASCVD	<p>HeFH and LDL-C ≥100 mg/dL on maximal statin PLUS ezetimibe.</p> <p>Baseline LDL-C ≥ 220 mg/dL and current LDL-C ≥130 mg/dL on maximal statin PLUS ezetimibe.</p>	<p>High risk and LDL-C ≥ 130 mg/dL on maximal statin ± ezetimibe</p>	<p>Very-high risk with LDL-C ≥ 55 mg/dL on maximal statin PLUS ezetimibe</p>
<p>ACC/AHA= American College of Cardiology/American Heart Association; ASCVD= atherosclerotic cardiovascular disease; CVD= cardiovascular disease; DM= diabetes mellitus; ESC/EAS= European Society of Cardiology/European Atherosclerosis Society; HeFH= heterozygous familial hypercholesterolemia; LDL-C= low-density lipoprotein cholesterol; NLA= National Lipid Association</p>			