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PCSK9 Inhibitors in Secondary Prevention – An Opportunity for Personalized Therapy

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

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

Background

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

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

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

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

Cardiovascular Outcome Trials

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

The Further Cardiovascular Subjects with Elevated Risk (FOURIER) trial[11] evaluated the safety and efficacy of evolocumab in 27,564 subjects with stable ASCVD, defined as a history of MI, ischemic stroke, or symptomatic peripheral artery disease (PAD), already taking optimized statin therapy (at least atorvastatin 20 mg or equivalent) with a LDL-C ≥70 mg/dL or non-high-density lipoprotein cholesterol (non-HDL-C) ≥100 mg/dL. The primary outcome was a composite of major adverse cardiovascular events (MACE), including CV death, MI, fatal or stroke, hospitalization for unstable angina, or coronary revascularization. The incidence of the primary outcome was significantly lower in subjects randomized to evolocumab (9.8%) compared to placebo (11.3%) (HR: 0.85; 95% CI, 0.79-0.92) with a number needed to treat (NNT) of 74. Evolocumab was also associated with reduction in the key secondary outcomes with significant reductions in MI (HR: 0.73; 95% CI, 0.65-0.82), stroke (HR: 0.79; 95% CI, 0.66-0.95), and coronary revascularization (HR: 0.78; 95% CI, 0.71-0.86). Injection-site reactions (2.1%) vs placebo (1.6%) were the only nominally significant adverse event in this trial (P<0.001).

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

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

Evidence Supporting the Use of PCSK9-mAbs in Select Populations

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

Polyvascular disease

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

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

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

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

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

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

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

Previous Myocardial Infarction

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

Coronary Artery Bypass Graft Surgery

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

Diabetes mellitus

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

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

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

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

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

Chronic Kidney Disease

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

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

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

Elevated Lp(a) Levels

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

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

Clinical Practice Guidelines and Scientific Statements

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

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

2018 American College of Cardiology/American Heart Association/Multi-society Cholesterol Guideline

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

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

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

2019 Consensus Statement from the National Lipid Association

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

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

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

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

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

Remaining Questions and Ongoing Clinical Trials

Long-Term Safety of PCSK9-mAbs

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

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

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

PCSK9-mAb Use in the Acute Setting

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

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

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

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

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

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

PCSK9-mAb Use in Subjects Without Prior MI or Stroke

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

Silencing PCSK9 with Inclisiran

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

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

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

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

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

Conclusion

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

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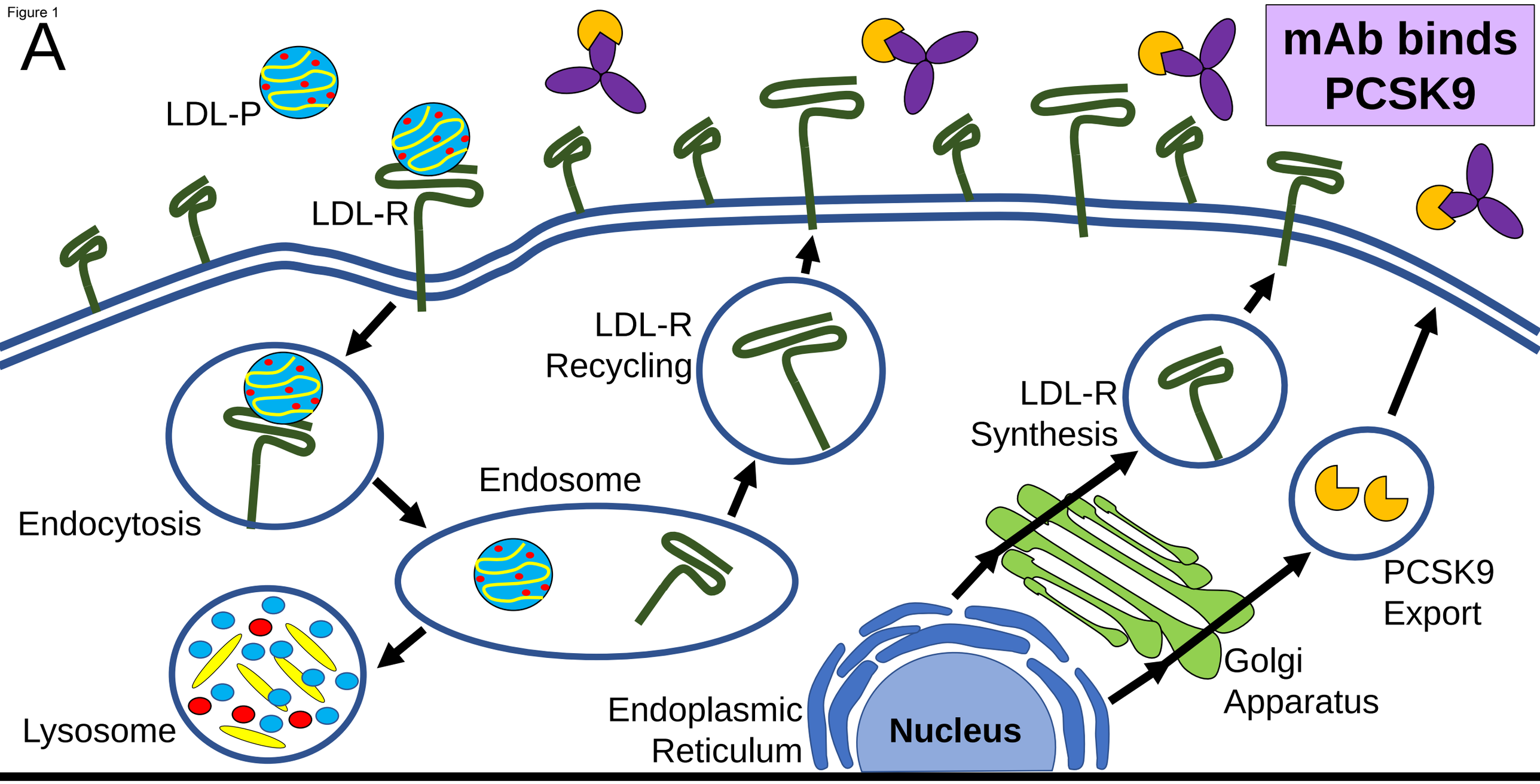
Figure 1. Approaches to Modulating PCSK9

Compares the mechanism of action for PCSK9-mAb (A) and siRNA (B) approaches to modulating PCSK9. Both result in increased presence of LDL-R on the hepatocyte surface by either inhibiting the functionality of PCSK9 (A) or turning off PCSK9 synthesis (B). Abbreviations: LDL-P, low-density lipoprotein particle; LDL-R, low-density lipoprotein receptor; mAb, monoclonal antibody; PCSK9, proprotein convertase subtilisin/kexin type 9; siRNA, small interfering RNA

Figure 1

A


mAb binds PCSK9
LDL-P
LDL-R
LDL-R Recycling
Endocytosis
Endosome
Lysosome
Endoplasmic Reticulum
Nucleus
LDL-R Synthesis
Golgi Apparatus
PCSK9 Export

B

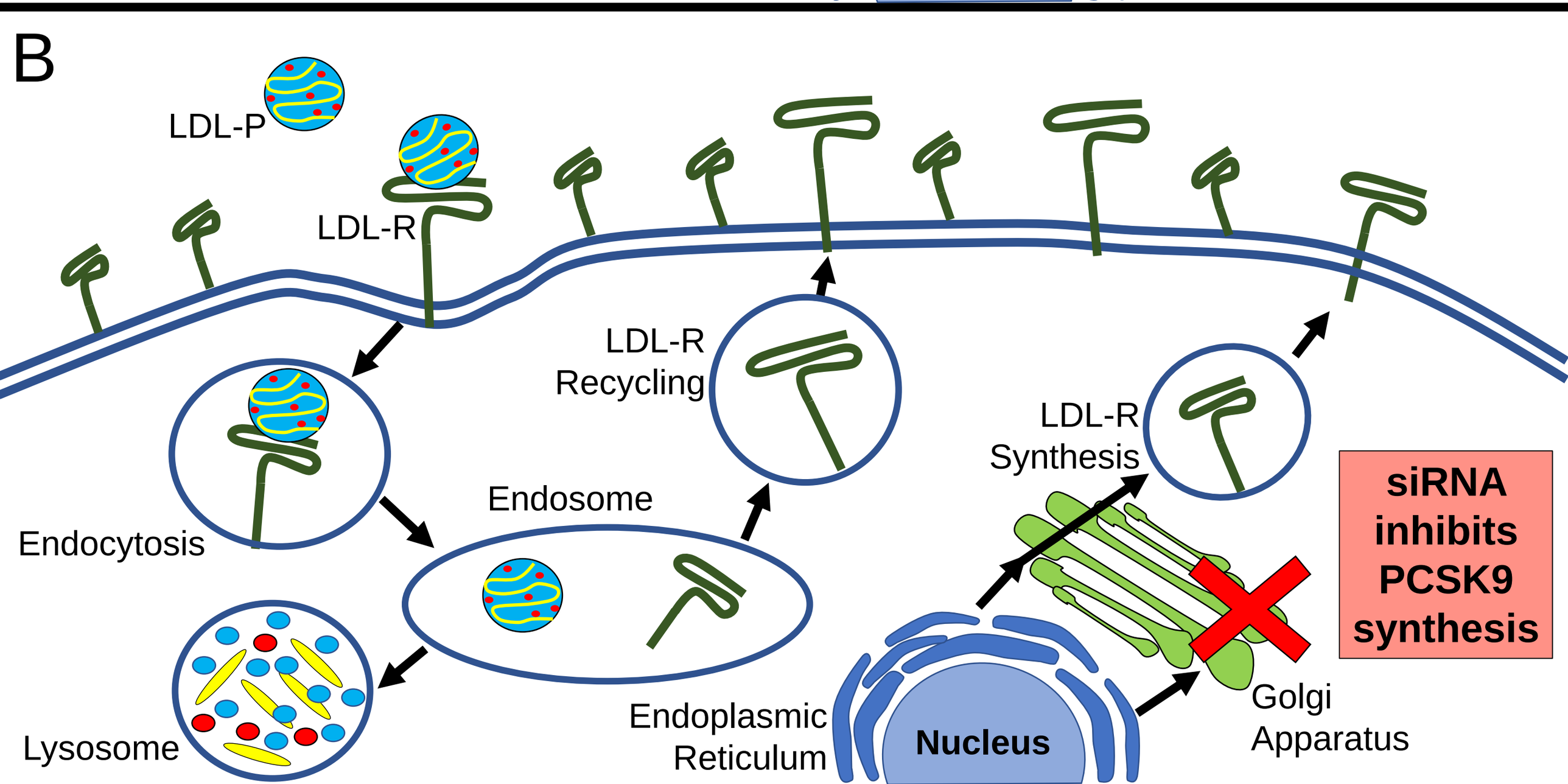

LDL-P
LDL-R
LDL-R Recycling
Endocytosis
Endosome
Lysosome
Endoplasmic Reticulum
Nucleus
LDL-R Synthesis
Golgi Apparatus
siRNA inhibits PCSK9 synthesis

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	**Very-high risk ASCVD** • Multiple major ASCVD events • Single ASCVD event with multiple high-risk conditions	**Extremely-high risk** • ≥40% 10-year ASCVD risk **Very-high risk** • 30-39% 10-year ASCVD risk **High risk** • 20-29% 10-year ASCVD risk • cardiometabolic risk factors	**Very-high risk** • ASCVD ± FH • FH with other major risk factor • Chronic kidney disease with eGFR <30 ml/min/1.73m^2 • 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 <u>with</u> Clinical ASCVD	**Very-high risk ASCVD** and LDL-C ≥70 mg/dL on maximal statin PLUS ezetimibe. Using a PCSK9 inhibitor before ezetimibe is considered low value.	**Extremely-high risk** and LDL-C ≥70 mg/dL **Very-high risk** and LDL-C ≥ 100 mg/dL on maximal statin ± ezetimibe **High risk** with LDL-C ≥130 mg/dL on maximal statin ± ezetimibe	**Very-high risk** with LDL-C ≥ 55 mg/dL on maximal statin PLUS ezetimibe
Use in Patients <u>Without</u> Clinical ASCVD	**HeFH** and LDL-C ≥100 mg/dL on maximal statin PLUS ezetimibe. **Baseline LDL-C ≥ 220 mg/dL** and current LDL-C ≥130 mg/dL on maximal statin PLUS ezetimibe.	**High risk** and LDL-C ≥ 130 mg/dL on maximal statin ± ezetimibe	**Very-high risk** with LDL-C ≥ 55 mg/dL on maximal statin PLUS ezetimibe

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