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Enhancing the Value of PCSK9 Monoclonal Antibodies by Identifying Patients Most Likely to Benefit

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National Lipid Association Statement

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Introduction

HMG-CoA reductase inhibitors (statins) remain the foundation of lipid-lowering therapy to reduce atherosclerotic cardiovascular disease (ASCVD) risk.[1,2] Two classes of nonstatin medications, the cholesterol absorption inhibitor (i.e., ezetimibe) and the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibiting monoclonal antibodies (mAbs) [i.e., alirocumab and evolocumab], have been shown to reduce ASCVD events when added to background statin therapy.[3-7] Recent guidelines and statements from several professional organizations have provided recommendations for the use of these therapies in clinical practice, including some consideration of their value.[8-11] However, significant reductions in the prices of the PCSK9 mAbs have occurred since the release of the 2018 Guideline on the Management of Blood Cholesterol by the American College of Cardiology (ACC), American Heart Association (AHA), the National Lipid Association (NLA) and other groups (referred to subsequently as the 2018 Cholesterol Guideline), that may impact their clinical utilization. This **NLA statement** provides updated guidance to the clinician for enhancing the value of alirocumab and evolocumab in clinical practice based on the most updated costs of these agents.

Background

Ezetimibe is now generic in many countries, resulting in easier overall access to this medication. On the other hand, the initial wholesale acquisition cost of greater than $14,000 per year for PCSK9 mAbs has limited their use in the United States.[12-14] The 2018 Cholesterol Guideline considered PCSK9 mAbs to be of low value [$\geq$$150,000 per quality adjusted life year (QALY) as defined by the ACC/AHA[15]; all in US dollars] and uncertain value for severe hypercholesterolemia at mid-2018 US acquisition prices.[1] Similarly, cost analyses to date have found PCSK9 mAbs to be of low value $\geq$US$150,000 per QALY) or close to low value without substantial discounting.[1,16-25]

Cost-effectiveness analyses are intended to provide information to patients, clinicians, healthcare systems and policy makers to facilitate decisions that will ensure that whatever resources are available are used as effectively as possible to improve health.[26] Cost effectiveness analyses have wide ranges of value depending on the population risk and other assumptions. Analyses supported by the manufacturers of evolocumab and alirocumab have found that PCSK-9 mAb therapy with discounting approaches reasonable cost-effectiveness (≈$100,000 per QALY) when low density lipoprotein cholesterol (LDL-C) levels are ≥100 mg/dl in very high-risk patients, or when a subsequent reduction in nonfatal cardiovascular events, including revascularization, are considered.[18,21] In contrast, a recent analysis using more conservative assumptions regarding reduction in incident myocardial infarction, stroke and cardiovascular death found that discounting to $2656 per year would be needed to approach a reasonable value of $100,000 per QALY in patients with a recent myocardial infarction whose LDL-C was ≥100 mg/dl.[27]

Because the manufacturers of alirocumab and evolocumab are in the process of substantially reducing acquisition prices, these drugs could now provide better value in selected patient groups.[28,29] Based on an analysis of a trial in patients with recent acute coronary syndrome on intensive statin therapy, ODYSSEY OUTCOMES, the manufacturers of alirocumab first adjusted the acquisition price (wholesale price plus discounts) for one purchaser to the price point set by the Institute for Clinical and Economic Review (ICER) for cost effectiveness in higher risk ASCVD patients with LDL-C ≥100 mg/dl at $4500 to $8000 per year.[12] The manufacturers of evolocumab and alirocumab subsequently announced they would reduce the list price by about 60% to $5850 per year. [30,31]

Even at reduced prices, PCSK9 mAbs would still be low value (>$150,000/QALY) for many of the ASCVD patients with LDL-C ≥70 mg/dl that were enrolled in the evolocumab and alirocumab cardiovascular outcomes trials according to the ICER analyses.[16,27,32] However, there are likely subgroups of patients in these trials where PCSK9 mAbs could provide reasonable (<$100,000/QALY) or even high

(<$50,000/QALY) value. Recently developed methods can be applied to evidence emerging from the evolocumab and alirocumab cardiovascular outcomes trials to identify patient subgroups most likely to benefit from PCSK9 mAb therapy. Robinson et al have suggested that consideration of the absolute risk reduction (ARR), or net benefit, from LDL-C lowering therapy could inform considerations of cost-effectiveness.[33] Net benefit is a function of the absolute risk of ASCVD, and the magnitude of low-density lipoprotein cholesterol (LDL-C) reduction. ARR is reflected in the number-needed-to-treat (NNT) to prevent one ASCVD event. NNT is simply the inverse of the ARR. This analysis found that with sufficient discounting, PCSK9 mAbs could be a reasonable (<$100,000 per QALY) or even good (<$50,000 per QALY) value in selected groups of patients with familial hypercholesterolemia (FH) and/or ASCVD depending on their expected NNTs for their level of ASCVD risk and LDL-C on maximal statin therapy.

NNTs also were used to inform the 2017 European PCSK9 statement.[10] Although cost effectiveness was not addressed in the European statement, acquisition costs in Europe have been much lower than the initial US acquisition price.

Robinson et al in 2018 updated their analysis after publication of several subgroup analyses from the evolocumab cardiovascular outcomes trial, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Patients with Elevated Risk (FOURIER).[34] The 2018 analysis suggested that patients can be grouped into 3 clinically meaningful phenotypes, based on ASCVD burden and activity, control of cardiometabolic risk factors, and baseline LDL-C level, where alirocumab and evolocumab with substantial discounting can be considered a reasonable value (<$100,000 per QALY) based on expected NNTs [**Figure 1**]. This **NLA Statement** builds on these previous analyses in order to provide guidance for clinicians to identify patient groups in which PCSK9 mAbs could be considered a reasonable to good value.

Methods for Identifying More Cost-effective Patient Subgroups

In populations with FH or ASCVD and statin intolerance, a previous ICER analysis found that with discounting, 5-year NNTs of 21-28 resulted in reasonable value (ie, <$100,000/QALY)[32] [**Table 1**]. It can be extrapolated that patients with 50% lower NNTs would experience high value (<$50,000/QALY).

Calculating NNT

NNT reflects the ARR from the relative reduction in ASCVD risk from drug therapy and the absolute ASCVD risk of the patient. NNT is calculated as 1/ARR. The magnitude of LDL-C reduction depends on the baseline LDL-C level and LDL-C lowering efficacy, and predicts the average reduction in the relative risk of ASCVD. From the Cholesterol Treatment Trialists (CTT) meta-analysis of individual data from more than 25 statin cardiovascular outcome trials, a 38.7 mg/dl (1 mmol/L) reduction in LDL-C is associated with a 22% reduction in incident major vascular events.[35]

Although the 95% confidence intervals for the reduction of major cardiovascular events observed in the FOURIER and ODYSSEY OUTCOMES overlapped with the CTT statin meta-analysis, the point estimates for the relative risk reductions were somewhat attenuated in the trials overall. However, in ODYSSEY OUTCOMES the relative risk reduction point estimate when baseline LDL-C was ≥100 mg/dl was similar to that observed in the CTT meta-analysis.[7,35] A meta-analysis of statin, ezetimibe, and PCSK9 mAb cardiovascular outcomes trials suggests this may be due to a loss of cardiovascular and total mortality benefits when LDL-C levels are <100 mg/dl in statin-treated patients.[36] Therefore when LDL-C levels are <100 mg/dl, the relative ASCVD risk reductions from evolocumab observed in the stable ASCVD population in FOURIER, where the mean baseline LDL-C level on maximal statin therapy was 92 mg/dl, may be preferred for estimating NNTs over the longer term.

Patients with Familial Hypercholesterolemia (FH) or Severe Hypercholesterolemia (SH)

If left untreated, patients with heterozygous familial hypercholesterolemia (HeFH) have a ≥20-fold higher ASCVD risk than otherwise similar normocholesterolemic individuals.[37-41] Patients with LDL-C ≥190 mg/dl without a diagnosis of HeFH are at 5-fold increased ASCVD risk. Prospective data have shown that LDL-C lowering therapy started in adolescence or early adulthood and continued long term largely ameliorates this excess risk.[39,41] Nonetheless, in small contemporary HeFH cohorts, despite statin therapy (with and without ezetimibe), extrapolated 10-year ASCVD risk is about 45% in those with clinical ASCVD or with coronary artery calcium >100 Agatston units.[33,42,43] Primary prevention HeFH patients and those with severe untreated LDL-C elevations ≥220 mg/dl with risk factors also remain at high risk despite statin therapy.[1,33,43-46]

In the US, high intensity statin therapy, or the maximally tolerated statin intensity, is recommended for adult men and non-pregnant/non-lactating women with primary severe hypercholesterolemia (LDL-C ≥190 mg/dl or ≥4.9 mmol/L).[1] Patients with HeFH also may benefit from adding a nonstatin to further reduce LDL-C and prevent ASCVD events.[1,10] According to the 2018 Cholesterol Guideline, HeFH patients with ASCVD, especially in the presence of additional high-risk conditions, are considered at very high risk of future clinical ASCVD events.[1] In such patients, when LDL-C remains ≥70 mg/dl while on maximally tolerated statin therapy, adding ezetimibe is reasonable. Adding a PCSK9 is reasonable if LDL-C remains ≥70 mg/dl on maximally tolerated statin and ezetimibe therapy in those patients as well. In primary prevention HeFH, the addition of ezetimibe to maximally tolerated statin is reasonable if a <50% reduction in LDL-C occurs or LDL-C remains ≥100 mg/dl. A PCSK9 mAb may be reasonable if LDL-C remains ≥100 mg/dl despite maximally tolerated statin and ezetimibe therapy.

The 2018 Cholesterol Guideline also identified a group of patients with severe elevations in LDL-C ≥220 mg/dl who do not meet the diagnostic criteria for HeFH as potential candidates for PCSK9 mAbs due their high cholesterol-attributable ASCVD risk. They recommend that in patients without a diagnosis

of HeFH with an untreated LDL-C ≥220 mg/dl (≥5.7 mmol/L), a PCSK9 mAb may be reasonable if LDL-C remains ≥130 mg/dl despite maximally tolerated statin and ezetimibe therapy.

In patients with severe, potentially fatal genetic disorders such as HeFH, the cost-effectiveness of therapy is not typically a major consideration. However, since the relative risk reduction of major vascular events is proportional to the absolute LDL-C reduction achieved with pharmacotherapy, there is greater event reduction from treating individuals with higher starting ASCVD risk and higher LDL-C levels. Conversely, LDL-C lowering therapy for lower risk individuals with lower LDL-C may have low value. Notably, when discounted to about $5400/year, PCSK9 inhibitor therapy that lowers LDL-C by 65% over 5 years provides a high value for secondary prevention in HeFH patients or primary severe hypercholesterolemia with untreated LDL-C ≥220 mg/dl (SH ≥220 mg/dl) with ASCVD and LDL-C levels ≥100 mg/dl despite maximal statin and ezetimibe therapy, and a reasonable value when LDL-C levels are closer to 70 mg/dl (**Table 2**). Adding a PCSK9 mAb likely provides similar value in HeFH or SH ≥220 mg/dl patients with coronary artery calcium >100 Agatston units.

For primary prevention HeFH or SH ≥220 mg/dl patients, PCSK9 mAb therapy should be a high value when LDL-C levels are ≥190 mg/dl on maximal statin/ezetimibe therapy, and a reasonable value when LDL-C levels are closer to 100 mg/dl, especially if risk factors are present (**Table 2**). The value of PCSK9 mAbs may be further enhanced when considering the large relative reduction in the risk of subsequent ASCVD events when substantial reduction in LDL-C occurs and treatment begins earlier in life.[46]

Patients with ASCVD

Systematic Review

Two authors (JGR and MBJ) performed an updated systematic review of publications from the PCSK9 mAb cardiovascular outcomes trials through January 20, 2019 for this **NLA Statement**. Methods

are described in the **Supplement**, along with an overview of the FOURIER and ODYSSEY OUTCOMES trials.[6,7] FOURIER included patients with stable ASCVD, and ODYSSEY OUTCOMES included patients within 1 year of an acute coronary event. All patients were receiving moderate or high intensity statin therapy. Ten-year ASCVD risks were extrapolated from the annualized rates of myocardial infarction, stroke and cardiovascular death for patients in the subgroups receiving placebo in the FOURIER trial. Rates in stable ASCVD patients may be more relevant to long-term considerations of risk and benefit in ASCVD patients than rates extrapolated from patients with acute coronary syndromes, where relative ASCVD risk increases more in the first year than in subsequent years.[3,7]

When subgroups were sorted according to 10-year ASCVD risk of <30%, 30-39% and ≥40% in the control group, 3 clinical phenotypes began to emerge based on ASCVD burden and control of the cardiometabolic risk factors: **Extremely High**, **Very High**, and **High Risk** (**Figure 1; Table 3; Supplement**).

Extremely High Risk patients (≥40% 10-year ASCVD risk on maximal statin therapy have either):

(A) An extensive or active burden of ASCVD ((ie, polyvascular ASCVD which affects all 3 vascular beds – coronary, cerebrovascular and peripheral arterial; clinical peripheral arterial disease in addition to coronary and/or cerebrovascular disease; a clinical ASCVD event with multi-vessel coronary artery disease defined as ≥40% stenosis in ≥2 large vessels; or recurrent myocardial infarction within 2 years of the initial event) in the presence of adverse or poorly controlled cardiometabolic risk factors; **OR**

(B) Extremely high-risk elevations in cardiometabolic factors with less extensive ASCVD (ie, HeFH, diabetes, LDL-C ≥100 mg/dl, less than high intensity statin therapy, chronic kidney disease, poorly controlled hypertension, high sensitivity C-reactive protein >3 mg/L, or metabolic syndrome, usually occurring with other extremely high or very high risk characteristics) (see **Supplement** for references), usually with other adverse or poorly controlled

cardiometabolic risk factors present. Patients with ASCVD and HeFH or SH ≥220 mg/dl are an additional group of extremely high risk patients, with >45% 10-year ASCVD risk despite statin therapy.[1,33] Statin-treated HeFH patients with coronary artery calcium score >100 Agatston units also have about a >45% 10-year ASCVD risk despite statin therapy.[43]

Very High Risk patients (30-39% 10-year ASCVD risk on maximal statin therapy) have:

(1) **Less extensive clinical ASCVD** (ie, no polyvascular ASCVD, no clinical peripheral arterial disease, a prior ASCVD event ≥2 years prior, and no coronary artery bypass grafting) **AND**

(2) **Adverse or poorly controlled cardiometabolic risk factor(s)** including age ≥65 years, current smoking, chronic kidney disease, lipoprotein(a) ≥37 nmol/L, high sensitivity C-reactive protein 1-3 mg/L, metabolic syndrome with a history of myocardial infarction, ischemic stroke, or symptomatic peripheral arterial disease, usually in the presence of other adverse or poorly controlled cardiometabolic risk factors.

High Risk (<30% 10-year ASCVD risk) includes 2 groups of patients:

(A) High-risk ASCVD patients have:

(1) **Less extensive ASCVD AND**

(2) **Well-controlled cardiometabolic risk factors** (ie, no diabetes, nonsmoker, on high intensity statin with LDL-C <100 mg/dl, blood pressure <140/90 mm Hg, and C-reactive protein <1 mg/dl)

(B) Primary prevention HeFH or SH ≥220 mg/dl have:

(1) **No clinical ASCVD or CAC <100** Agatston units **AND**

(2) **Poorly controlled cardiometabolic risk factor(s)** as discussed above.

Acute Coronary Syndrome Patients

Patients with an acute coronary syndrome are at greater risk of a recurrent ASCVD event in the subsequent year.[3,7] However, after 1 year their 10-year ASCVD risk would then be that of their chronic ASCVD status. A patient with an incident acute coronary syndrome who experiences a subsequent ASCVD event within 2 years would then be considered extremely high risk.

Identifying LDL-C Thresholds for Considering PCSK9 mAb Therapy

Similar LDL-C lowering efficacy of approximately 60-65% is observed for alirocumab 150 mg every 2 weeks and evolocumab 140 mg every 2 weeks or 420 mg every 4 weeks.[4,6,47] Alirocumab 75 mg every 2 weeks up-titrated to 150 mg/dl every 2 weeks when LDL-C remains >50 mg/dl lowers LDL-C by about 50%.[36] Ezetimibe lowers LDL-C by an average of 13-24% added to background statin therapy.[1,3,48] NNTs can be estimated based on absolute risk, baseline LDL-C, and average percent reduction for an LDL-C lowering therapy, with examples provided in **Table 5**. To facilitate clinical decision-making, these data also can be used to identify LDL-C thresholds at which PCSK9 mAbs therapy that lowers LDL-C by 65% would provide a reasonable value (<US$100,000/QALY) with discounting for the 3 patient risk phenotypes based on extent of ASCVD and cardiometabolic risk factors (**Figure 1**). These 3 groups are: (1) Extremely high-risk ASCVD patients with LDL-C $\geq$70 mg/dl, Very high risk ASCVD patients with LDL-C $\geq$100 mg/dl, and high-risk patients with LDL-C $\geq$130 mg/dl. Patient groups where PCSK9 mAbs provide a good value (<$50,000/QALY) can also be identified, which have NNTs of about 10-14, about half that of the NNTs of 21-28 that are associated with a reasonable value of ≈$100,000/QALY. (**Table 6**).

More Benefit When LDL-C $\geq$100 mg/dl

Cardiovascular and total mortality were not reduced in the FOURIER trial or in the ODYSSEY OUTCOMES trial when baseline LDL-C levels were <100 mg/dl.[6,7] Nor were reductions in mortality observed in the longer duration trials of moderate versus high intensity statins, or the IMPROVE-IT trial

with ezetimibe.[3,49,50] A meta-analysis of statin, ezetimibe, and PCSK9 mAb trials found that total and cardiovascular mortality were reduced only in those trials where the mean baseline LDL-C levels were ≥100 mg/dl.[36] Total and cardiovascular mortality were reduced progressively more the higher the mean baseline LDL-C levels (**Figure 2**), as were myocardial infarction, revascularization, and major cardiovascular events. This suggests that the greatest relative risk reductions from LDL-C lowering will occur when LDL-C levels are ≥100 mg/dl, and that cost-effectiveness will be greater in this patient group.

Comparison to 2018 Cholesterol Guideline Very High Risk ASCVD Category

The systematic review of the PCSK9 mAb and statin randomized trials performed for this **NLA Statement** identified several very high- or extremely high-risk patient subgroups that were not included in the 2018 Cholesterol Guideline definition of very high risk ASCVD patients (**Table 4**).[1] The **NLA Statement** systematic review included subgroups from the high versus moderate intensity statin trials, which included a broader definition of coronary heart disease beyond acute myocardial infarction or acute coronary syndromes, and also identified the importance of concurrent peripheral arterial disease and other ASCVD, angina with documented ischemia, and an extremely high risk time interval for recurrent events (ie, recurrent myocardial infarction <2 years). Additional very high risk cardiometabolic risk factors also were identified in the **NLA Statement** systematic review (ie, less than high intensity statin therapy, elevated lipoprotein(a) level, poorly controlled hypertension, metabolic syndrome, elevated C-reactive protein). The **NLA Statement** also identifies two groups of patients with LDL-C levels ≥130 mg/dl as High Risk patient groups that also might experience reasonable value from PCSK9 mAb therapy: (1) ASCVD with well-controlled risk factors and (2) primary prevention HeFH or SH LDL-C ≥220 mg/dl patients with additional risk factors.

Conversely, the systematic review conducted for this **NLA Statement** did not identify some patient subgroups that were included in the 2018 Cholesterol Guideline very high-risk patient category

(**Table 4**): Controlled hypertension without other cardiometabolic risk factors or a history of heart failure). Indeed, New York Heart Association Class III or IV heart failure patients were excluded from both of the PCSK9 mAb cardiovascular outcomes trials.[6,7]

If the 2018 Cholesterol Guideline very high-risk classification is used, cost-effectiveness should be improved if a treatment threshold of LDL-C is ≥100 mg/dl is used.

Ezetimibe Step Therapy

Due to considering PCSK9 mAb therapy low value for ASCVD patients and uncertain value for severe hypercholesterolemia patients due to pricing at the time of their writing, as well as noting that some patients have a greater than expected LDL-C reduction when treated with ezetimibe, the 2018 Cholesterol Guideline recommends consideration of adding ezetimibe when the LDL-C remains ≥70 mg/dl despite maximally tolerated statin therapy.[1] Once ezetimibe is added and the LDL-C still remains ≥70 mg/dl, it is reasonable to add a PCSK9 mAb in ASCVD patients and may be reasonable to add a PCSK9 mAb therapy in those with severe hypercholesterolemia.

However, the recommendation for ezetimibe step therapy prior to initiating a PCSK9 inhibitor may be subject to individual consideration in certain very or extremely high-risk patients for several reasons. First, some ASCVD patients may experience a modest ASCVD risk reduction from adding ezetimibe, such as those with baseline LDL-C <100 mg/dl or lower 10-year ASCVD risk (**Table 5).** For example, the calculated 5-year NNTs range from 131 to 56 when LDL-C levels are close to 70 mg/dl as 10-year ASCVD risk increases from 20% to 45%. Even for patients with very high 10-year ASCVD risk of 30%, 5-year NNT is 88 when LDL-C is close to 70 mg/dl, 61 when LDL-C is close to 100 mg/dl, and 47 when LDL-C is close to 130 mg/dl. These calculations used the 22% relative risk reduction per 1 mmol/L reduction in LDL-C observed in the Cholesterol Treatment Trialists meta-analysis.[35] These estimated NNTs can be compared to estimates calculated for the IMPROVE-IT trial, which added ezetimibe to

moderate intensity background statin therapy in patients with acute coronary syndromes with baseline LDL-C levels of on average 70 mg/dl and a mean 24% reduction in LDL-C.[3] A *post hoc* analysis of IMPROVE-IT grouped participants by the number of high risk characteristics in addition to recent acute coronary syndromes (heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, prior coronary artery bypass grafting, peripheral arterial disease, estimated glomerular filtration rate <60, or current smoking).[51] Those with 3 or more high risk characteristics had an extrapolated 10-year ASCVD risk of approximately 50% in the placebo-statin group, and an approximately 42% 10-year ASCVD risk in the ezetimibe-statin group. This 8% absolute risk reduction over 10 years converts to a 5-year NNT of 25. In the group with 2 high risk characteristics, extrapolated 10-year ASCVD risk was approximately 28% in the placebo-statin group and 25% in the ezetimibe-statin group; the 5-year NNT is 66. Both NNTs derived from IMPROVE-IT are consistent with conclusions from our analysis, which used a 20% reduction in LDL-C and found more clinically meaningful benefits in the extreme risk patients. LDL-C reductions of 18-20% were more commonly observed in trials of statin-treated participants with higher baseline LDL-C levels.[48]

Second, the response to ezetimibe is highly variable.[52,53] For those patients responding in the lower range of efficacy for ezetimibe, the smaller magnitude of LDL-C reduction may therefore result in less than expected ASCVD risk reduction and larger NNTs. However, since some patients may experience above average LDL-C lowering response to ezetimibe, a trial of ezetimibe is reasonable as recommended by the 2018 Cholesterol Guideline.

Third, ezetimibe cost-effectiveness depends on acquisition cost, which may vary despite its generic status in the US. A cost-effectiveness analysis modeling a population of patients with acute myocardial infarction and LDL-C ≥70 mg/dl found that the addition of ezetimibe at an acquisition cost of $1411 per year cost US$81,000/QALY compared to statin alone, based on the reduction in incident ASCVD events.[20] If ezetimibe is available at $304 per year, the cost of adding ezetimibe is

$18,600/QALY. The cost-effectiveness of ezetimibe is likely better for the very high or extremely high risk patient groups identified in for this **NLA Statement**, although such analyses are not yet available.

Fourth, and most importantly, addition of ezetimibe may result in fewer very high and extremely high-risk patients being eligible for PCSK9 mAb therapy because their LDL-C falls slightly below the 70 mg/dL (or 100 mg/dL) threshold for considering PCSK9 mAb therapy. Their ASCVD risk would remain substantially elevated despite the addition of ezetimibe, and they may benefit from further LDL-C reduction. For example, an extremely high-risk ASCVD patient with 45% 10-year ASCVD risk treated with ezetimibe who sustains a 25% LDL-C reduction of 90 mg/dl to 68 mg/dl. Based on IMPROVE-IT, a 10% reduction in ASCVD risk would be expected over the long term.[3] Thus, after ezetimibe treatment the 10-year ASCVD risk would be 40%, a level of risk that is still extremely high. Indeed, this is what was observed in IMPROVE-IT, which showed a 34% risk of ASCVD over 7 years in the placebo-statin group, [51] extrapolating to an approximately 42% 10-year ASCVD risk despite the addition of ezetimibe. Thus, if an LDL-C of 70 mg/dl is used as a strict threshold for considering the addition of a PCSK9 inhibitor, this patient might be considered to no longer be a candidate for a PCSK9 mAb, despite being likely to benefit from additional ASCVD risk reduction from additional LDL-C lowering.

In sum, in patients whose ASCVD risk remains very or extremely high despite maximizing statin therapy, or if LDL-C levels are <100 mg/dl, or a less than expected response to ezetimibe occurs, it may be more cost effective and clinically efficacious to initiate a PCSK9 mAb rather than ezetimibe to maximize relative risk reduction from further LDL-C lowering. On the other hand, it is reasonable to consider adding ezetimibe per the 2018 Cholesterol guidelines in such patients to determine if the patient achieves a larger than expected reduction in LDL-C from the ezetimibe. Clinical judgement is warranted in such situations.

Shared Decision-Making

The 2018 Cholesterol Guideline recommends that clinicians and patients engage in shared decision-making by when considering the addition of ezetimibe or a PCSK9 mAb to maximal statin and lifestyle therapy.[1] Considerations in shared decision-making include the potential for an ASCVD risk reduction benefit, response to ezetimibe or PCSK9 mAb therapy, the potential for adverse effects, patient preferences regarding pill versus injection, costs, and medication burden, all of which may also influence adherence.[1,54]

Clinicians may consider an NNT = 50 as the break-point to be considered reasonable, while patients may consider an NNT = 30 to be reasonable.[55] Notably, patients in the groups identified in this **NLA Statement** (**Figure 1**) for whom PCSK9 mAbs can provide reasonable value with discounting, are likely to also consider treatment with PCSK9 mAbs beneficial based on NNT <30.

Because some patients have a greater than expected response to adding ezetimibe, it is reasonable to add ezetimibe before proceeding to a PCSK9 inhibitor as per the guidelines. For some patients, however, especially at the lower levels of LDL, and who obtain the average LDL reduction from ezetimibe, it may be more clinically efficacious to proceed directly to a PCSK9 inhibitor.

Limitations

Cost-effectiveness analyses have numerous limitations including heterogeneous populations studied, dependence of short-term outcomes to extrapolate long-term outcomes, and simplified model assumptions that may not accurately reflect the complex clinical setting.[26] This Statement addresses some of these limitations by separately considering event rates in patient subgroups in randomized trials rather than the trial as a whole, and limiting the horizon of benefit to 5 years. The focus on "hard" ASCVD events of myocardial infarction, stroke and cardiovascular death provides a consistent endpoint for comparison across trials, regions and time. The ASCVD endpoint provides a conservative estimate of benefit. Greater absolute benefit, and lower NNTs, would occur if (1) additional endpoints such as

revascularization or unstable angina hospitalizations were included, or if (2) longer time horizon were considered.

Tables 2 and **5** were presented with the intent of providing examples of average NNTs expected for specific 10-year absolute ASCVD risk levels (e.g., 45%, 30%, and 20%) given baseline LDL-C level in order to compare average percent LDL-C reductions for ezetimibe versus PCSK9 mAbs. However, a range of event rates was observed for the patient subgroups included in each risk phenotype (**Figure 1**). In addition, patient response to LDL-C lowering therapies may vary, impacting the degree of LDL-C lowering. Thus, patients at higher ASCVD risk experiencing greater LDL-C lowering efficacy would be anticipated to have lower NNTs than expected from these **Tables**, and therefore experience greater cost-effectiveness from added LDL-C lowering therapy. Conversely, those at lower ASCVD risk or experiencing less LDL-C lowering efficacy would be anticipated to have higher NNTs, with lesser cost-effectiveness from therapy.

Although annualized event rates from the placebo groups were used to extrapolate 10-year ASCVD risk, this assumption is consistent with the linear rates observed in follow-up of patients with chronic ASCVD treated with statins over a period of 5-7 years.[49,50] The convention of 10-year ASCVD risk is intended to compare to risk categories used in the 2018 Cholesterol Guideline.[1] However, the estimate of benefit as reflected in NNT was calculated for a 5-year time period.

Cost-effectiveness also depends on the assumptions of the modeling. Importantly, we have used conservative analyses by ICER that used incident ASCVD events and demonstrated several groups of patients that where PCSK9 mAbs would have reasonable to high value at pricing of approximately $5500/year. The value of PCSK9 mAbs would be anticipated to be higher when prevention of subsequent events, revascularization, or lifetime perspectives are considered.[56]

An Unmet Need

In a retrospective analysis of >12,000 patients, prescribed a PCSK9 mAb between August 2015 and December 2017, the mean baseline LDL-C was 150 mg/dl, and 63% had LDL-C levels ≥130 mg/dl.[57] Over 75% had at least one ACC clinical pathway comorbidity or 2018 Cholesterol Guideline high risk characteristic in addition to ASCVD. Therefore, there are significant numbers of high, very, high and extremely high-risk patients who could benefit from further lowering LDL-C, and for whom PCSK9 mAb therapy would provide reasonable or even high levels of cost-effectiveness.

Conclusions

Many more patients with HeFH, SH LDL-C≥220 mg/dl, or ASCVD could benefit from use of PCSK9 mAbs, especially those with LDL-C ≥100 mg/dl on maximally tolerated statin/ezetimibe therapy who are more likely to experience reductions in cardiovascular and total mortality as well as nonfatal ASCVD events from additional LDL-C lowering. Although cost-effectiveness informs only part of the decision-making process, substantial reductions in acquisition costs for PCSK9 inhibitors in late 2018 and early 2019 have favorably affected economic considerations for PCSK9 mAb therapy for many patients.

Based on our analyses, consideration of ASCVD risk phenotypes and LDL-C thresholds may facilitate identification of patients for whom PCSK9 mAbs can provide reasonable or even high value. The 3 groups of patients **on maximally tolerated statin therapy** where reasonable cost-effectiveness (<$100,000 per QALY) might be expected are:

(1**) Extremely high risk ASCVD patients** (extensive burden of or active ASCVD, or ASCVD with extremely high burden of adverse or poorly controlled risk cardiometabolic risk factors including HeFH or SH LDL-C ≥220 mg/dl) with **LDL-C ≥70 mg/dl**

(2) **Very high risk ASCVD patients** (less extensive ASCVD and poorly controlled cardiometabolic risk factors) with **LDL-C ≥100 mg/dl**, and

(3) **High risk patients** with **LDL-C ≥130 mg/dl**: (1) less extensive ASCVD and well-controlled risk factors or (2) primary prevention HeFH or SH ≥220 mg/dl with poorly controlled risk factors.

Because some patients receive a greater than expected response to adding ezetimibe, it is reasonable to add ezetimibe before proceeding to a PCSK9 inhibitor as per the 2018 Cholesterol Guideline. For some very high and extremely high-risk patients, however, especially at the lower levels of LDL-C, or with below average LDL-C reduction from ezetimibe, it may be more clinically efficacious to proceed directly to a PCSK9 inhibitor. This information can inform shared decision-making.

It is hoped that this assessment of the value of PCSK9 inhibitors following recent price reduction will improve access to PCSK9 mAbs for patient groups with the greatest likelihood of improved clinical outcomes and cost-effectiveness.

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Table 1. Number of nonfatal and fatal ASCVD events that need to be prevented over 5-years and approximate cost per quality adjusted life-year (QALY), assuming undiscounted acquisition cost of $14,000/year and 50% relative risk reduction with PCSK9 mAb. All costs US dollars.

From Robinson JG et al. *J Am Coll Cardiol.* 2016;68:2412-2421; Tice JA et al. *JAMA Intern Med*. 2016;176:107-108

5-year NNT 10-14	No discount ($14,000/year) /≈ $150,000 QALY (Poor value)
5-year NNT 21-28	Discount ≈ 50% (≈ $7700/year) /$150,000 QALY (Low value) Discount ≈ 60% (≈ $5400/year) /$100,000 QALY (Reasonable value) Discount ≈ 77% (≈ $3200/year) /$50,000 QALY (High value) Discount ≈ 85% (≈ $2200/year) to avoid exceeding growth targets US healthcare costs

Table 2. Estimated cost-effectiveness of PCSK9 mAbs discounted to $5400/year that reduce LDL-C by 60-65% in patients with heterozygous familial hypercholesterolemia (HeFH) or severe hypercholesterolemia (SH) with LDL-C ≥220 mg/dl assuming a 50% reduction in subsequent ASCVD events

ON MAXIMALLY TOLERATED STATIN & EZETIMIBE THERAPY		
	High value (<$50,000/QALY)	**Reasonable value** (<$100,000/QALY)
5-year NNT	14	28
Secondary prevention		
FH or SH ≥220 mg/dl with clinical ASCVD (ASCVD risk likely similar when coronary artery calcium >100 Agatston units)	LDL-C ≥100 mg/dl	LDL-C ≥70 mg/dl
Primary prevention		
FH or SH ≥220 mg/dl with risk factor(s)*	LDL-C ≥190 mg/dl)	LDL-C >100 mg/dl

* Age >35 years, male sex, obesity, hypertension, smoking, lipoprotein (a) ≥50 mg/dl, low HDL-C <35 mg/dl[1,2]

Table 3. Patient characteristics that identify **Extremely high, Very high**, and **High** risk patient phenotypes based on subgroup analyses identified in a systematic review of PCSK9 mAB and statin randomized trials (see **Supplement** for references), and from observational data from HeFH populations[3,4]

ON HIGH OR MODERATE INTENSITY STATIN THERAPY	
Burden and activity of clinical ASCVD	**Adverse or poorly controlled cardiometabolic risk factors**
Extremely high burden (≥40% 10-y ASCVD risk)* • Polyvascular clinical ASCVD (coronary heart disease†, ischemic stroke, and symptomatic peripheral arterial disease**) • Symptomatic peripheral arterial disease** in addition to a coronary heart disease† or ischemic stroke • A clinical ASCVD event (coronary heart disease†, stroke, or symptomatic peripheral arterial disease**) with multi-vessel coronary artery disease defined as ≥40% stenosis in ≥2 large vessels • Recurrent myocardial infarction within 2 years Very high burden (30-39% 10-year ASCVD risk) • Recent acute coronary syndrome (only if no prior event within 2 years) • Coronary heart disease† and ischemic stroke without symptomatic peripheral arterial disease** • Coronary artery bypass grafting High burden (20-29% 10-year ASCVD risk) • Coronary heart disease† only • Ischemic stroke only • Symptomatic peripheral arterial disease only** • Acute coronary syndrome with no subsequent ASCVD event after 2 years	Extremely high risk (≥40% 10-y ASCVD risk)* • Heterozygous familial hypercholesterolemia with clinical ASCVD or coronary artery calcium >100 • History of myocardial infarction, ischemic stroke, or symptomatic peripheral arterial disease** with at least one of: o Diabetes o LDL-C ≥100 mg/dl o Less than high intensity statin therapy o High sensitivity C-reactive protein >3 mg/L • Poorly controlled hypertension and clinical ASCVD Very high risk (30-39% 10-year ASCVD risk)* Clinical ASCVD and one or more of: • Age ≥65 years • Chronic kidney disease • Lipoprotein(a) ≥37 nmol/L • High sensitivity C-reactive protein 1-3 mg/L • Metabolic syndrome with a history of myocardial infarction, ischemic stroke, or symptomatic peripheral arterial disease** • Smoking

* Majority had at least 1 additional adverse or poorly controlled cardiometabolic risk factor

† Clinically evident coronary heart disease includes myocardial infarction, history of angina with objective evidence of coronary artery disease (electrocardiographic, positive stress test, wall motion abnormality on ultrasound, coronary angiographic evidence of significant atherosclerotic lesions), or prior revascularization including coronary artery bypass grafting or percutaneous coronary intervention)

** Symptomatic peripheral arterial disease as evidenced by intermittent claudication with ankle-brachial index (ABI) < 0.85, or peripheral arterial revascularization procedure, or amputation due to atherosclerotic disease

Table 4. 2018 AHA/ACC Cholesterol Guideline Very High Risk ASCVD Risk patient classification

From Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary. *A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.* 2018.

(1) Multiple major ASCVD events	
OR	
(2) One major ASCVD event and multiple high-risk conditions	
Major ASCVD events	High-risk conditions
• Recent acute coronary syndrome (ACS) • History of myocardial infarction • History of ischemic stroke • Symptomatic peripheral arterial disease	• Age ≥65 years • Heterozygous familial hypercholesterolemia • History of prior coronary artery bypass grafting or percutaneous coronary intervention • Hypertension • Chronic kidney disease (15-59 mL/min/1.73 m^2) • Current smoking • Persistently elevated LDL-C ≥100 mg/dl despite maximally tolerated statin therapy and ezetimibe • History of heart failure

Table 5. Examples of 5-year NNT estimates for 20, 50 or 65 percent reductions in LDL-C for various LDL-C levels for patients at various levels of 10-year ASCVD risk based on the presence of ASCVD or familial hypercholesterolemia and other high risk characteristics (Supplemental Table 2): (A) at an extremely high risk of 45% 10-year ASCVD risk, (B) at a very high risk of 30% 10-year ASCVD risk, and (C) at a high risk of 20% 10-year ASCVD risk; Color-coded for reasonable NNT thresholds for **physicians NNT < 50** and **patients NNT <30** based on Steel N. *BMJ.* 2000; 320:1446-1447.

(A) Extremely high risk (45% 10-year ASCVD risk

Initial LDL-C	Ezetimibe LDL-C ↓20%	PCSK9 mAb LDL-C ↓50%	PCSK9 mAb LDL-C ↓65%
190 mg/dL (4.9 mmol/L)	21	8	6
160 mg/dL (4.1 mmol/L)	24	10	7
130 mg/dL (3.4 mmol/L)	30	12	9
100 mg/dL (2.6 mmol/L)	39	16	12
70 mg/dL (1.8 mmol/L)	56	28*	22*

(B) Very high risk (30% 10-year ASCVD risk)

Initial LDL-C	Ezetimibe LDL-C ↓20%	PCSK9 mAb LDL-C ↓50%	PCSK9 mAb LDL-C ↓65%
190 mg/dL (4.9 mmol/L)	32	13	10
160 mg/dL (4.1 mmol/L)	38	15	12
130 mg/dL (3.4 mmol/L)	47	19	15
100 mg/dL (2.6 mmol/L)	61	25	19
70 mg/dL (1.8 mmol/L)	88	43*	33*

(C) High risk (20% 10-year ASCVD risk)

Initial LDL-C	Ezetimibe LDL-C ↓20%	PCSK9 mAb LDL-C ↓50%	PCSK9 mAb LDL-C ↓65%
190 mg/dL (4.9 mmol/L)	48	19	15
160 mg/dL (4.1 mmol/L)	57	23	18
130 mg/dL (3.4 mmol/L)	71	28	22

100 mg/dL (2.6 mmol/L)	92	37	28
70 mg/dL (1.8 mmol/L)	131	65*	50*

*2-year relative risk reduction for FOURIER CTT endpoint from Sabatine MS et al. N Engl J Med. 2015;372:1500-1509.
ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; DM, diabetes mellitus; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; NNT, number needed to treat; mAb, monoclonal antibody; PCSK9, proprotein convertase subtilisin/kexin type 9.

Adapted from Robinson JG et al. *J Am Coll Cardiol.* 2016;68:2412-2421.; Robinson J, Watson K. Identifying patients for nonstatin therapy. *Rev Cardiovasc Med* 2018;19(suppl 1):S1-S8

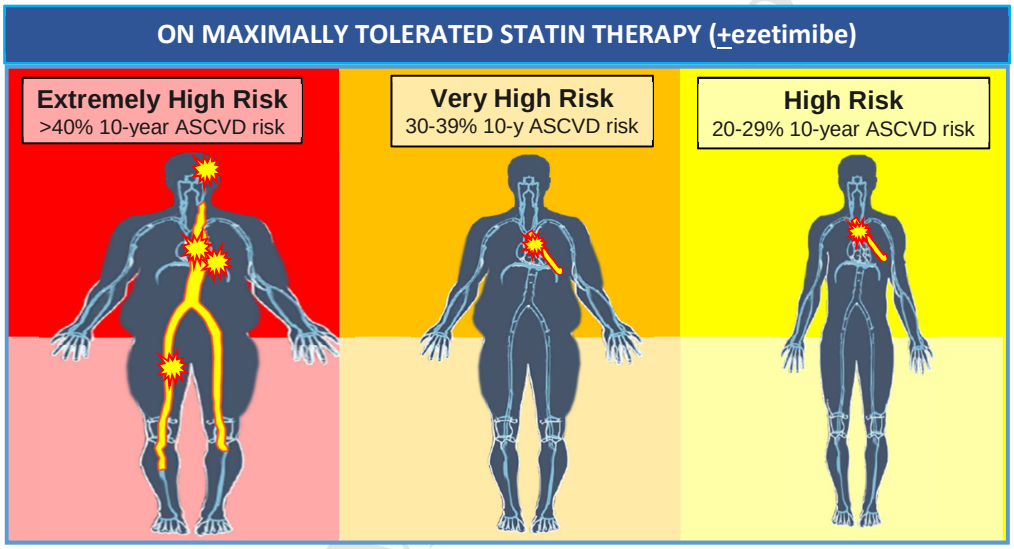
Table 6. Cost-effectiveness of PCSK9 mAbs discounted to $5400/year that reduce LDL-C by 65% in patients with ASCVD assuming a 50% reduction in subsequent ASCVD events

	Good value (<$50,000/QALY)	**Reasonable value** (<$100,000/QALY)
5-year NNT	**10**	**21**
ASCVD 45% 10-y ASCVD risk		LDL-C 70 mg/dl
ASCVD 30% 10-y ASCVD risk	LDL-C 100 mg/dl	
ASCVD 20% 10-y ASCVD risk	LDL-C 190 mg/dl	LDL-C 100 mg/dl

1. Pérez de Isla L, Alonso R, Mata N, et al. Predicting Cardiovascular Events in Familial Hypercholesterolemia: The SAFEHEART Registry. *Circulation.* 2017;135:2133-2144.
2. Paquette M, Baass A. Predicting cardiovascular disease in familial hypercholesterolemia. *Current Opinion in Lipidology.* 2018;29(4):299-306.
3. Robinson J, Huijgen R, Ray K, Persons J, Kastelein J, Pencina M. Determining when to add nonstatin therapy: A quantitative approach. *J Am Coll Cardiol.* 2016;68:2412-2421.
4. Miname MH, Bittencourt MS, Nasir K, Santos RD. Subclinical coronary atherosclerosis and cardiovascular risk stratification in heterozygous familial hypercholesterolemia patients undergoing statin treatment. 2019;30(2):82-87.

Figure 1. Groups of patients in whom PSCK9 mAbs may provide reasonable value (<US$100,000/QALY) based on extent of ASCVD and presence of cardiometabolic risk factors and LDL-C thresholds on maximally tolerated statin therapy ± ezetimibe. Refer to **Table 3** for listing of types of events and risk factors.

(Adapted from Robinson J, Watson K. Identifying patients for nonstatin therapy. *Rev Cardiovasc Med* 2018;19(suppl 1):S1-S8)

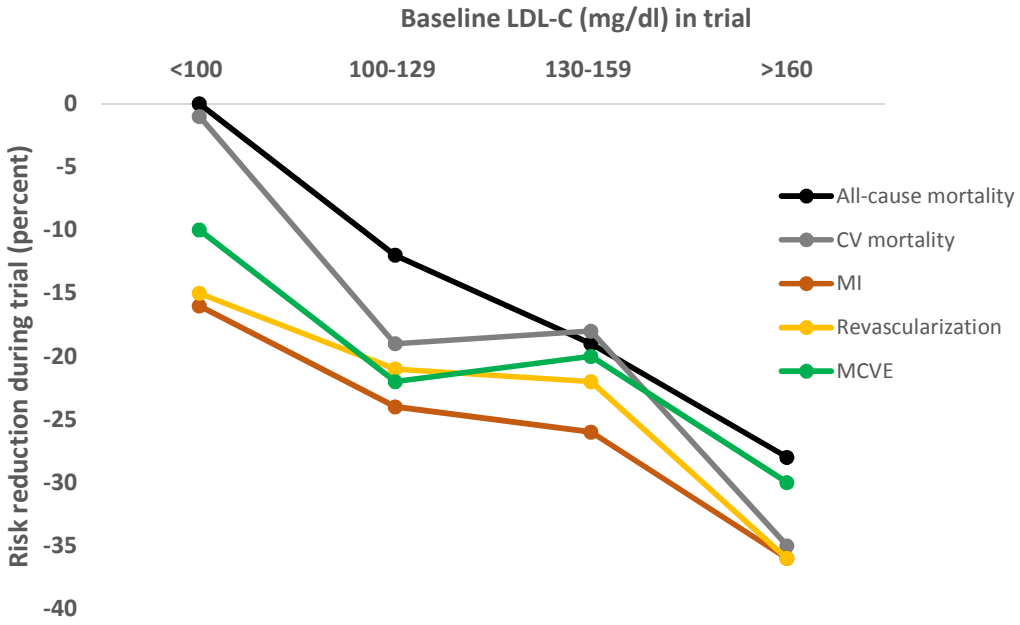


Extensive or active burden of ASCVD Usually with poorly controlled cardiometabolic risk factors	**Less extensive ASCVD & Poorly controlled cardiometabolic risk factors**	**Less extensive ASCVD & Well controlled risk factors**
Less extensive ASCVD & Extremely high risk cardiometabolic risk factors		**HeFH/SH LDL-C≥220 mg/dl & Poorly controlled cardiometabolic risk factors**
LDL-C ≥70 mg/dl	**LDL-C ≥100 mg/dl**	**LDL-C ≥130 mg/dl**

ASCVD	Atherosclerotic cardiovascular disease
HeFH	Heterozygous familial hypercholesterolemia
LDL-C	Low-density lipoprotein cholesterol
SH LDL-C ≥ 220 mg/dl	Severe primary hypercholesterolemia with LDL-C ≥220 mg/dl

Figure 2. Progressively greater reductions in the risk of all-cause and cardiovascular mortality, myocardial infarction, revascularizations, and major cardiovascular events (MCVE) for progressively higher baseline LDL-C levels in randomized trials of statins, ezetimibe, and PCSK9 mAbs

Data from Navarese EP, Robinson JG, Kowalewski M, et al. Association between baseline LDL-C level and total and cardiovascular mortality after LDL-C lowering: A systematic review and meta-analysis. *JAMA.* 2018;319(15):1566-1579.



Highlights:

- Initial pricing limited uptake of highly effectively PCSK9 monoclonal antibodies.
- Recent price reductions call for new guidance in this NLA Statement.
- Value assessment may improve access to PCSK9 mAbs for appropriate patient groups.