

## Scientific Statement

# Enhancing the value of PCSK9 monoclonal antibodies by identifying patients most likely to benefit. A consensus statement from the National Lipid Association



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**Abstract:** Acquisition costs and cost-effectiveness have limited access and recommendations to use proprotein convertase subtilisin/kexin type 9 (PCSK9)-inhibiting monoclonal antibodies (mAbs). Recently, prices were reduced by 60% for alirocumab and evolocumab. This statement systematically reviewed subgroup analyses from statin and PCSK9 mAb trials to identify higher risk groups for which PCSK9 mAbs at the new price could be considered a reasonable (<US\$100,000 per quality adjusted life year [QALY]) or high (<US\$50,000 per QALY) value. In patients at extremely high risk, with a high burden of atherosclerotic cardiovascular disease (ASCVD) or ASCVD with multiple poorly controlled or adverse risk factors, PCSK9 mAbs can provide reasonable value when low-density lipoprotein cholesterol (LDL-C) is  $\geq 70$  mg/dL. In patients at very high risk (ASCVD without peripheral arterial disease and lower levels of poorly controlled risk factors), PCSK9 mAbs provide a reasonable

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value when LDL-C levels are  $\geq 100$  mg/dL. High-risk patients (less-extensive ASCVD with well-controlled risk factors) may experience reasonable value when LDL-C levels are  $\geq 130$  mg/dL. Patients with heterozygous familial hypercholesterolemia or severe hypercholesterolemia with untreated LDL-C levels  $\geq 220$  mg/dL also should experience reasonable or high value from PCSK9 mAbs when LDL-C is  $\geq 100$  mg/dL for primary prevention and  $\geq 70$  mg/dL for secondary prevention.  
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## Introduction

3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (statins) remain the foundation of lipid-lowering therapy to reduce atherosclerotic cardiovascular disease (ASCVD) risk.<sup>1,2</sup> Two classes of nonstatin medications, the cholesterol absorption inhibitor (ie, ezetimibe) and the pro-protein convertase subtilisin/kexin type 9 (PCSK9) inhibiting monoclonal antibodies (mAbs) (ie, alirocumab and evolocumab), have been shown to reduce ASCVD events when added to background statin therapy.<sup>3–7</sup> 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.<sup>8–11</sup> 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, the National Lipid Association (NLA), and other groups (referred to subsequently as the 2018 Cholesterol Guideline), which 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.<sup>12–14</sup> 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/American Heart Association<sup>15</sup>; all in U.S. dollars) and uncertain value for severe hypercholesterolemia (SH) at mid-2018 U.S. acquisition prices.<sup>1</sup> Similarly, cost analyses to date have found PCSK9 mAbs to be of low value  $\geq \$150,000$  per QALY or close to low value without substantial discounting.<sup>1,16–25</sup>

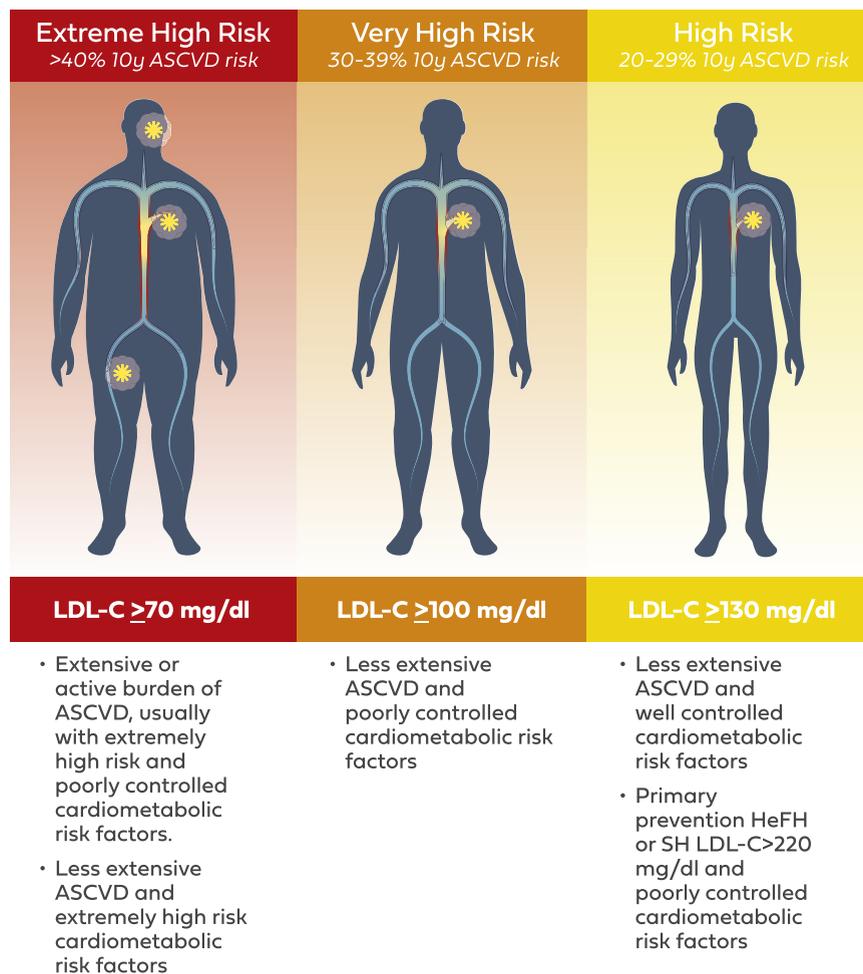
Cost-effectiveness analyses are intended to provide information to patients, clinicians, health care systems, and policy makers to facilitate decisions that will ensure that whatever resources are available are used as effectively as possible to improve health.<sup>26</sup> Cost-effectiveness analyses 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 PCSK9 mAb therapy with discounting approaches reasonable cost-effectiveness ( $\approx$  US\$100,000 per QALY) when low-density lipoprotein cholesterol (LDL-C) levels are  $\geq 100$  mg/dL in very-high-risk patients or when a subsequent reduction in nonfatal cardiovascular events, including revascularization, are considered.<sup>18,21</sup> In contrast, a recent analysis using more conservative assumptions regarding reduction in incident myocardial infarction, stroke, and cardiovascular death found that discounting to US\$2656 per year would be needed to approach a reasonable value of US\$100,000 per QALY in patients with a recent myocardial infarction whose LDL-C was  $\geq 100$  mg/dL.<sup>27</sup>

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.<sup>28,29</sup> 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 patients with ASCVD with LDL-C  $\geq 100$  mg/dL at \$4500 to \$8000 per year.<sup>12</sup> The manufacturers of evolocumab and alirocumab subsequently announced they would reduce the list price by about 60% to \$5850 per year.<sup>30,31</sup>

Even at reduced prices, PCSK9 mAbs would still be of low value ( $> \$150,000$ /QALY) for many of the patients with ASCVD with LDL-C  $\geq 70$  mg/dL who were enrolled in the evolocumab and alirocumab cardiovascular outcomes trials according to the ICER analyses.<sup>16,27</sup> 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 outcome 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.<sup>32</sup> Net benefit is a function of the absolute risk of ASCVD and the magnitude of 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 high ( $< \$50,000$  per QALY) value in selected groups of patients



**Figure 1** Groups of patients in whom PCSK9 mAbs may provide reasonable value (<\$100,000/QALY) based on extent of ASCVD and presence of cardiometabolic risk factors and LDL-C thresholds on maximally tolerated statin therapy  $\pm$  ezetimibe. Refer to Table 3 for listing of types of events and risk factors. ASCVD, atherosclerotic cardiovascular disease; QALY, quality-adjusted life year; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; mAbs, monoclonal antibodies; SH, severe hypercholesterolemia. (Adapted from Robinson J, Watson K. Identifying patients for nonstatin therapy. *Rev Cardiovasc Med* 2018;19(suppl 1):S1–S8).

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.<sup>10</sup> Although cost-effectiveness was not addressed in the European statement, acquisition costs in Europe have been much lower than the initial U.S. acquisition price.

Robinson et al in 2018 updated their analysis after publication of several subgroup analyses from the evolocumab cardiovascular outcomes trial and Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Patients with Elevated Risk (FOURIER).<sup>33</sup> The 2018 analysis suggested that patients can be grouped into 3 clinically meaningful phenotypes, based on ASCVD burden and activity, control of

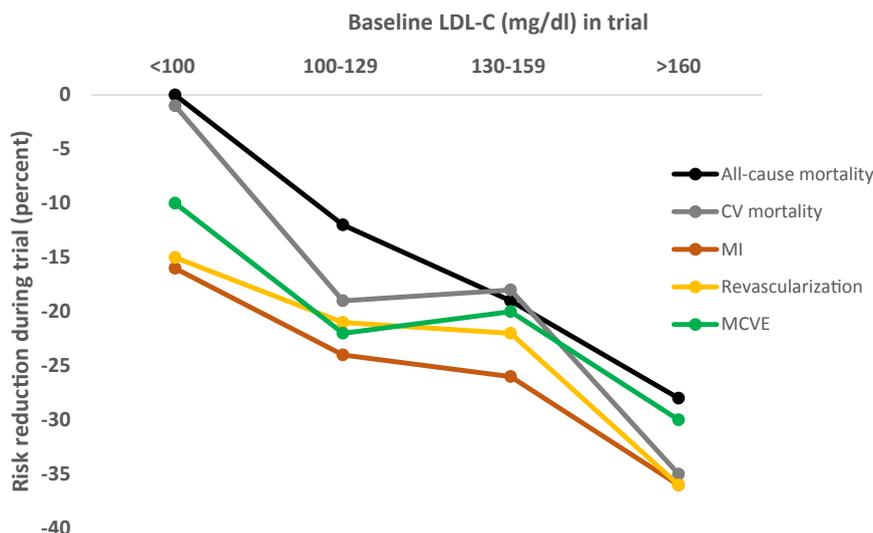
**Table 1** Number of nonfatal and fatal ASCVD events that need to be prevented over 5-y and approximate cost per quality-adjusted life year, assuming undiscounted acquisition cost of \$14,000/y and 50% relative risk reduction with PCSK9 mAb

5-y NNT 10–14	No discount (\$14,000/y)/ $\approx$ \$150,000 QALY (low value)
5-y NNT 21–28	Discount $\approx$ 50% ( $\approx$ \$7700/y)/ $\approx$ \$150,000 QALY (low value)
	Discount $\approx$ 60% ( $\approx$ \$5400/y)/ $\approx$ \$100,000 QALY (reasonable value)
	Discount $\approx$ 77% ( $\approx$ \$3200/y)/ $\approx$ \$50,000 QALY (high value)
	Discount $\approx$ 85% ( $\approx$ \$2200/y) to avoid exceeding growth targets U.S. health care costs

ASCVD, atherosclerotic cardiovascular disease; PCSK9, proprotein convertase subtilisin/kexin type 9; mAbs, monoclonal antibodies; NNT, number needed to treat; QALY, quality-adjusted life year.

All costs U.S. 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.



**Figure 2** Progressively greater reductions in the relative risk of all-cause and cardiovascular mortality, myocardial infarction (MI), 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. LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; mAbs, monoclonal antibodies.

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 (Fig. 1). This NLA statement builds on these previous analyses 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)<sup>16</sup> (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.<sup>34</sup>

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  $\geq 100$  mg/dL was similar to that observed in the CTT meta-analysis.<sup>34</sup> A meta-analysis of statin, ezetimibe, and PCSK9 mAb cardiovascular outcome trials suggests this may be because of a loss of cardiovascular and total mortality benefits when LDL-C levels are <100 mg/dL in statin-treated patients (Fig. 2).<sup>35</sup> 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 long term when LDL-C levels are <100 mg/dL.

### Patients with familial hypercholesterolemia or severe hypercholesterolemia

If left untreated, patients with heterozygous FH (HeFH) have a  $\geq 20$ -fold higher ASCVD risk than otherwise similar normocholesterolemic individuals.<sup>1,36–39</sup> Patients with primary SH and LDL-C  $\geq 190$  mg/dL without a diagnosis of HeFH are at 5-fold increased ASCVD risk. The risk of patients with SH and LDL-C >220 mg/dL have ASCVD risk more similar to that of patient with HeFH. Prospective data have shown that LDL-C-lowering therapy started in adolescence or early adulthood and continued long term largely ameliorates this excess risk.<sup>37,38,40</sup> However, in small contemporary HeFH cohorts with clinical ASCVD, extrapolated 10-year ASCVD risk is about 45% despite statin therapy (with or without ezetimibe).<sup>32,41,42</sup> Some data also suggest HeFH patients with coronary artery

calcium (CAC) >100 Agatston units also have about a 45% 10-year ASCVD risk.<sup>41</sup> In the presence of risk factors, primary prevention patients with HeFH and those with severe untreated LDL-C elevations of ≥220 mg/dL also remain at high risk despite statin therapy.<sup>1,32,42-44</sup>

In the United States, high-intensity statin therapy, or the maximally tolerated statin intensity, is recommended for adult men and nonpregnant/nonlactating women with primary SH when LDL-C ≥190 mg/dL or ≥4.9 mmol/L.<sup>1</sup> Patients with HeFH also may benefit from adding a nonstatin to further reduce LDL-C and prevent ASCVD events.<sup>1,10</sup> 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.<sup>1</sup> In such patients, when LDL-C remains ≥70 mg/dL while on maximally tolerated statin therapy, adding ezetimibe is reasonable. Adding a PCSK9 mAb is reasonable if LDL-C still remains ≥70 mg/dL on maximally tolerated statin and ezetimibe therapy. In primary prevention patients with 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. Adding a PCSK9 mAb may be reasonable if LDL-C remains ≥100 mg/dL despite maximally tolerated statin and ezetimibe therapy in primary prevention HeFH as well.

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 because of 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, because the relative risk reduction of major vascular events is proportional to the absolute LDL-C reduction achieved with pharmacotherapy, there is greater relative and absolute risk 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 lower value. Notably, when discounted to about \$5400/y, PCSK9 inhibitor therapy that lowers LDL-C by 65% over 5 years provides a high value for secondary prevention in patients with HeFH or primary SH with untreated LDL-C ≥220 mg/dL (SH LDL-C ≥ 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 LDL-C ≥ 220 mg/dL patients with CAC >100 Agatston units.

For primary prevention patients with HeFH or SH LDL-C ≥220 mg/dL, 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.

**Patients with ASCVD**

**Systematic review**

Two authors (J.G.R. and M.B.J.) performed an updated systematic review of publications from the PCSK9 mAb cardiovascular outcome trials through January 20, 2019, for this NLA statement. Methods are described in Supplement, along with an overview of the FOURIER and ODYSSEY OUTCOMES trials.<sup>6,7</sup> FOURIER included patients with

**Table 2** Estimated cost-effectiveness of PCSK9 mAbs discounted to \$5400/y that reduce LDL-C by 60% to 65% in patients with heterozygous familial hypercholesterolemia or severe hypercholesterolemia with LDL-C ≥220 mg/dL assuming a 50% reduction in subsequent ASCVD events

On maximally tolerated statin and ezetimibe therapy		
	High value (<\$50,000/QALY)	Reasonable value (<\$100,000/QALY)
5-y NNT	≤14	≤28
Secondary prevention		
FH or SH LDL-C ≥220 mg/dL with clinical ASCVD (ASCVD risk likely similar when CAC was >100 Agatston units)	LDL-C ≥100 mg/dL	LDL-C ≥70 mg/dL
Primary prevention		
FH or SH LDL-C ≥ 220 mg/dL with risk factor(s) <sup>*</sup>	LDL-C ≥190 mg/dL	LDL-C ≥100 mg/dL

FH, familial hypercholesterolemia; SH, severe hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; PCSK9, proprotein convertase subtilisin/kexin type 9; mAbs, monoclonal antibodies; NNT, number needed to treat; QALY, quality-adjusted life year.

<sup>\*</sup>Age >35 y, male sex, obesity, hypertension, smoking, lipoprotein (a) ≥50 mg/dL, low HDL-C <35 mg/dL.<sup>1,2</sup>

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 patients with ASCVD may be more relevant to long-term considerations of risk and benefit in patients with ASCVD than rates extrapolated from patients with acute coronary syndromes, where relative ASCVD risk increases more in the first year than in the subsequent years.<sup>3,7</sup>

When subgroups were sorted according to 10-year ASCVD risk of <30%, 30% to 39%, and  $\geq 40\%$  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 (Fig. 1; Table 3; Supplement).

Extremely high-risk patients ( $\geq 40\%$  of 10-year ASCVD risk on maximal statin therapy) have either of the following:

- (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 multivessel coronary artery disease defined as  $\geq 40\%$  stenosis in  $\geq 2$  large vessels; or recurrent myocardial infarction within 2 years of the initial event) in the presence of adverse or poorly controlled cardiometabolic risk factors.
- (B) Extremely high-risk elevations in cardiometabolic factors with less-extensive ASCVD (ie, HeFH, diabetes, LDL-C  $\geq 100$  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-risk 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 LDL-C  $\geq 220$  mg/dL are an additional

**Table 3** Patient characteristics that identify extremely high-risk, very-high-risk, 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<sup>3,4</sup>

On high- or moderate-intensity statin therapy

Burden and activity of clinical ASCVD

Extremely high burden ( $\geq 40\%$  10-y ASCVD risk)<sup>\*</sup>

- Polyvascular clinical ASCVD (coronary heart disease<sup>†</sup>, ischemic stroke, and symptomatic peripheral arterial disease<sup>‡</sup>)
- Symptomatic peripheral arterial disease<sup>‡</sup> in addition to a coronary heart disease<sup>†</sup> or ischemic stroke
- A clinical ASCVD event (coronary heart disease<sup>†</sup>, stroke, or symptomatic peripheral arterial disease<sup>‡</sup>) with multivessel coronary artery disease defined as  $\geq 40\%$  stenosis in  $\geq 2$  large vessels
- Recurrent myocardial infarction within 2 y

Very high burden (30%–39% 10-y ASCVD risk)

- Recent acute coronary syndrome (only if no prior event within 2 y)
- Coronary heart disease<sup>†</sup> and ischemic stroke without symptomatic peripheral arterial disease<sup>‡</sup>
- Coronary artery bypass grafting

High burden (20%–29% 10-y ASCVD risk)

- Coronary heart disease<sup>†</sup> only
- Ischemic stroke only
- Symptomatic peripheral arterial disease only<sup>‡</sup>
- Acute coronary syndrome with no subsequent ASCVD event after 2 y

Adverse or poorly controlled cardiometabolic risk factors

Extremely high risk ( $\geq 40\%$  10-y ASCVD risk)<sup>\*</sup>

- Heterozygous familial hypercholesterolemia with clinical ASCVD or coronary artery calcium  $> 100$
- History of myocardial infarction, ischemic stroke, or symptomatic peripheral arterial disease<sup>‡</sup> with at least one of the following:
  - Diabetes
  - LDL-C  $\geq 100$  mg/dL
  - Less than high-intensity statin therapy
  - High-sensitivity C-reactive protein  $> 3$  mg/L
- Poorly controlled hypertension and clinical ASCVD

Very high risk (30%–39% 10-y ASCVD risk)<sup>\*</sup>

Clinical ASCVD and one or more of:

- Age  $\geq 65$  y
- Chronic kidney disease
- Lipoprotein(a)  $\geq 37$  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<sup>‡</sup>
- Smoking

ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; mAbs, monoclonal antibodies; HeFH, heterozygous familial hypercholesterolemia.

<sup>\*</sup>Majority had at least 1 additional adverse or poorly controlled cardiometabolic risk factor.

<sup>†</sup>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.

<sup>‡</sup>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.

group of extremely high-risk patients, with ≥45% 10-year ASCVD risk despite statin therapy (see above). Statin-treated HeFH patients with CAC score >100 Agatston units also have about a 45% 10-year ASCVD risk despite statin therapy.<sup>41</sup>

Very-high-risk patients (30%–39% 10-year ASCVD risk on maximal statin therapy) have the following:

- (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)
- (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.

The high-risk category (<30% 10-year ASCVD risk) includes the following 2 groups of patients:

- (A) High-risk patients with ASCVD have the following:
- (1) Less-extensive ASCVD
  - (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 patients with HeFH or SH LDL-C ≥ 220 mg/dL have the following:
- (1) No clinical ASCVD or CAC <100 Agatston units
  - (2) Poorly controlled cardiometabolic risk factor(s).

**Patients with acute coronary syndrome**

Patients with acute coronary syndrome are at greater risk of a recurrent ASCVD event in the subsequent year.<sup>3,7</sup> By year 2, 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% to 65% is observed for alirocumab 150 mg every 2 weeks and evolocumab 140 mg every 2 weeks or 420 mg every 4 weeks.<sup>4,6,45</sup> Alirocumab 75 mg every 2 weeks uptitrated to 150 mg/dL every 2 weeks when LDL-C remains >50 mg/dL lowers LDL-C by about 50%.<sup>37</sup> Ezetimibe lowers LDL-C by an average of 13% to 24% added to background statin therapy.<sup>46</sup> NNTs can be estimated based on absolute risk, baseline LDL-C, and average percent

**Table 4** Examples of 5-y NNT estimates for 20, 50, or 65 percent reductions in LDL-C for various LDL-C levels for patients at various levels of 10-y ASCVD risk based on the presence of ASCVD or familial hypercholesterolemia and other high-risk characteristics

(A) Extremely high risk (45% 10-y 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*

ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; NNT, number needed to treat; mAb, monoclonal antibody; PCSK9, proprotein convertase subtilisin/kexin type 9.

Color coded for high value (5-y NNT ≤14; <\$50,000/QALY) in green, reasonable value (5-y NNT 15-28; >\$50,000 to <\$100,000/QALY) in yellow, considered reasonable for physicians; NNT <50 in light green, and reasonable by patients; NNT <30 in light gold.<sup>47</sup>

\* 2-y relative risk reduction for FOURIER CTT end point from Sabatine MS et al. *N Engl J Med.* 2015; 372:1500–1509.

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 5** Cost-effectiveness of PCSK9 mAbs discounted to \$5400/y that reduce LDL-C by 65% in patients with ASCVD

	High value (<\$50,000/QALY)	Reasonable value (<\$100,000/QALY)
5-y NNT	≤14	≤28
ASCVD ≥40% 10-y ASCVD risk	LDL-C ≥130 mg/dL	LDL-C ≥70 mg/dL
ASCVD 30-39% 10-y ASCVD risk	LDL-C ≥190 mg/dL	LDL-C ≥100 mg/dL
ASCVD 20-29% 10-y ASCVD risk	NA	LDL-C ≥130 mg/dL

ASCVD, atherosclerotic cardiovascular disease; QALY, quality-adjusted life year; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; mAbs, monoclonal antibodies; NNT, number needed to treat.

reduction for an LDL-C-lowering therapy, with examples provided in Table 4. To facilitate clinical decision-making, these data also can be used to identify LDL-C thresholds at which PCSK9 mAb therapy that lowers LDL-C by 65% would provide a reasonable value (<USD 100,000/QALY) with discounting for the 3 patient risk phenotypes based on extent of ASCVD and cardiometabolic risk factors (Fig. 1). These 3 groups are (1) extremely high-risk patients with ASCVD with LDL-C ≥70 mg/dL, (2) very-high-risk patients with ASCVD with LDL-C ≥100 mg/dL, and (3) high-risk patients with LDL-C ≥130 mg/dL. Patient groups where PCSK9 mAbs provide a high 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 5).

### More benefit when LDL-C ≥100 mg/dL

Cardiovascular mortality 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.<sup>6,7</sup> Nor were reductions in mortality observed in the longer

duration trials of moderate- vs high-intensity statins or the IMPROVE-IT trial with ezetimibe.<sup>3,48,49</sup> A meta-analysis of statin, ezetimibe, and PCSK9 mAb trials found that total mortality and cardiovascular mortality were reduced only in those trials where the mean baseline LDL-C levels were ≥100 mg/dL.<sup>35</sup> Total mortality and cardiovascular mortality were reduced progressively more the higher the mean baseline LDL-C levels (Fig. 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 with 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-risk or extremely high-risk patient subgroups that were not included in the 2018 Cholesterol Guideline definition of very-high-risk patients with ASCVD (Tables 3 and 6).<sup>1</sup> This NLA statement systematic review included subgroups from the high- vs

**Table 6** The 2018 AHA/ACC Cholesterol Guideline very-high-risk ASCVD risk patient classification

(1) Multiple major ASCVD events or (2) One major ASCVD event and multiple high-risk conditions	
Major ASCVD events	High-risk conditions
<ul style="list-style-type: none"> <li>Recent acute coronary syndrome (ACS)</li> <li>History of myocardial infarction</li> <li>History of ischemic stroke</li> <li>Symptomatic peripheral arterial disease</li> </ul>	<ul style="list-style-type: none"> <li>Age ≥65 y</li> <li>Heterozygous familial hypercholesterolemia</li> <li>History of prior coronary artery bypass grafting or percutaneous coronary intervention</li> <li>Hypertension</li> <li>Chronic kidney disease (15–59 mL/min/1.73 m<sup>2</sup>)</li> <li>Current smoking</li> <li>Persistently elevated LDL-C ≥100 mg/dL despite maximally tolerated statin therapy and ezetimibe</li> <li>History of heart failure</li> </ul>

ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; AHA, American Heart Association; ACC, American College of Cardiology.

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*, *J Am Coll Cardiol* 2019; 73(24):3168-3209.

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 were also 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 2 groups of patients with LDL-C levels  $\geq 130$  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 patients with HeFH or SH LDL-C  $\geq 220$  mg/dL 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 6): Controlled hypertension without other cardiometabolic risk factors or a history of heart failure. New York Heart Association Class III or IV heart failure patients were excluded from both of the PCSK9 mAb cardiovascular outcomes trials.<sup>6,7</sup>

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

### Ezetimibe step therapy

Due to considering PCSK9 mAb therapy of low value for patients with ASCVD and uncertain value for patients with SH, because of 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  $\geq 70$  mg/dL despite maximally tolerated statin therapy.<sup>1</sup> Once ezetimibe is added and the LDL-C still remains  $\geq 70$  mg/dL, it is reasonable to add a PCSK9 mAb in patients with ASCVD and it may be reasonable to add a PCSK9 mAb therapy in those with SH.

However, the recommendation for ezetimibe step therapy before initiating a PCSK9 inhibitor may be subject to individual consideration in certain very-high-risk patients or extremely high-risk patients for several reasons. First, some patients with ASCVD 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 4). 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 CTT meta-analysis.<sup>34</sup> These estimated NNTs can be compared with 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.<sup>3</sup> 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  $\geq 75$  years, diabetes mellitus, prior stroke, prior coronary artery bypass grafting, peripheral arterial disease, estimated glomerular filtration rate <60, or current smoking).<sup>50</sup> 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% ARR 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% to 20% were more commonly observed in trials of statin-treated participants with higher baseline LDL-C levels.<sup>46</sup>

Second, the response to ezetimibe is highly variable.<sup>49,51</sup> 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, because 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 United States. A cost-effectiveness analysis modeling a population of patients with acute myocardial infarction and LDL-C  $\geq 70$  mg/dL found that the addition of ezetimibe at an acquisition cost of \$1411 per year cost USD \$81,000/QALY compared with statin alone, based on the reduction in incident ASCVD events.<sup>20</sup> 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-risk 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-risk 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 still benefit from further LDL-C reduction. For example, an extremely high-risk patient with ASCVD 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.<sup>3</sup> 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.<sup>50</sup> The risk reduction from adding ezetimibe extrapolates to a 42% 10-year ASCVD risk. 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 judgment is warranted in such situations.

## Shared decision-making

The 2018 Cholesterol Guideline recommends that clinicians and patients engage in shared decision-making when considering the addition of ezetimibe or a PCSK9 mAb to maximal statin and lifestyle therapy.<sup>1</sup> 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 vs injection, costs, and medication burden, all of which may also influence adherence.<sup>52</sup>

Clinicians may consider an NNT = 50 as the break point to be considered reasonable, whereas patients may consider an NNT = 30 to be reasonable.<sup>47</sup> Notably, patients in the groups identified in this NLA statement (Fig. 1) for whom PCSK9 mAbs can provide reasonable value with discounting are likely to also consider treatment with PCSK9 mAbs beneficial based on an 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 mAb as per the guidelines. For some patients, however, especially at the lower levels of LDL-C, or who obtain the average LDL-C reduction from ezetimibe, it may be more clinically efficacious to proceed directly to a PCSK9 mAb.

## 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.<sup>26</sup> 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 end point for comparison across trials, regions, and time. The ASCVD end point provides a conservative estimate of benefit. Greater absolute benefit, and lower NNTs, would occur if (1) additional end points such as revascularization or unstable angina hospitalizations were included or if (2) longer time horizon were considered.

Tables 2 and 4 were presented with the intent of providing examples of average NNTs expected for specific 10-year absolute ASCVD risk levels (eg, 45%, 30%, and 20%), given baseline LDL-C level to compare average percent LDL-C reductions for ezetimibe vs PCSK9 mAbs. However, a range of event rates was observed for the patient subgroups included in each risk phenotype (Fig. 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 to 7 years.<sup>48,53</sup> The convention of 10-year ASCVD risk is intended to compare to risk categories used in the 2018 Cholesterol Guideline.<sup>1</sup> 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, although we based our considerations on conservative analyses by ICER that used incident ASCVD events, we were still able to demonstrate that PCSK9 mAbs would have a reasonable to high value at pricing of approximately \$5400/y in several groups of patients. The value of PCSK9 mAbs would be anticipated to be higher when prevention of subsequent events, revascularization, or lifetime perspectives are considered.<sup>54</sup>

## 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  $\geq$  130 mg/dL.<sup>55</sup> 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-risk, very-high-risk, and extremely

high-risk patients who could benefit from further lowering of 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  $\geq 220$  mg/dL, or ASCVD could benefit from use of PCSK9 mAbs, especially those with LDL-C  $\geq 100$  mg/dL on maximally tolerated statin/ezetimibe therapy who are more likely to experience reductions in cardiovascular mortality 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 mAbs 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 following are the 3 groups of patients on maximally tolerated statin therapy where reasonable cost-effectiveness (<\$100,000 per QALY) might be expected:

- (1) Extremely high-risk patients with ASCVD (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  $\geq 220$  mg/dL) with LDL-C  $\geq 70$  mg/dL.
- (2) Very-high-risk patients with ASCVD (less-extensive ASCVD and poorly controlled cardiometabolic risk factors) with LDL-C  $\geq 100$  mg/dL, and
- (3) High-risk patients with LDL-C  $\geq 130$  mg/dL: (1) less-extensive ASCVD and well-controlled risk factors or (2) primary prevention HeFH or SH LDL-C  $\geq 220$  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 mAb as per the 2018 Cholesterol Guideline. For some very-high-risk and extremely high-risk patients, however, especially at the lower levels of LDL-C, or with a 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 after 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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## Supplementary data

Supplementary data related to this article can be found online at <https://doi.org/10.1016/j.jacl.2019.05.005>.

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